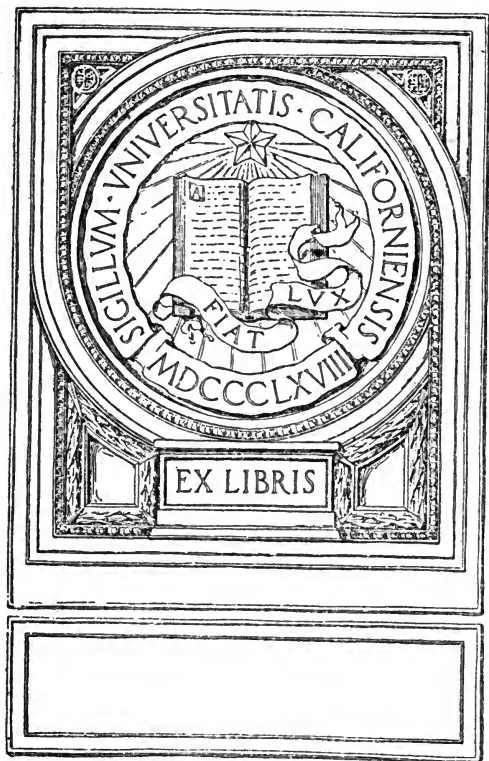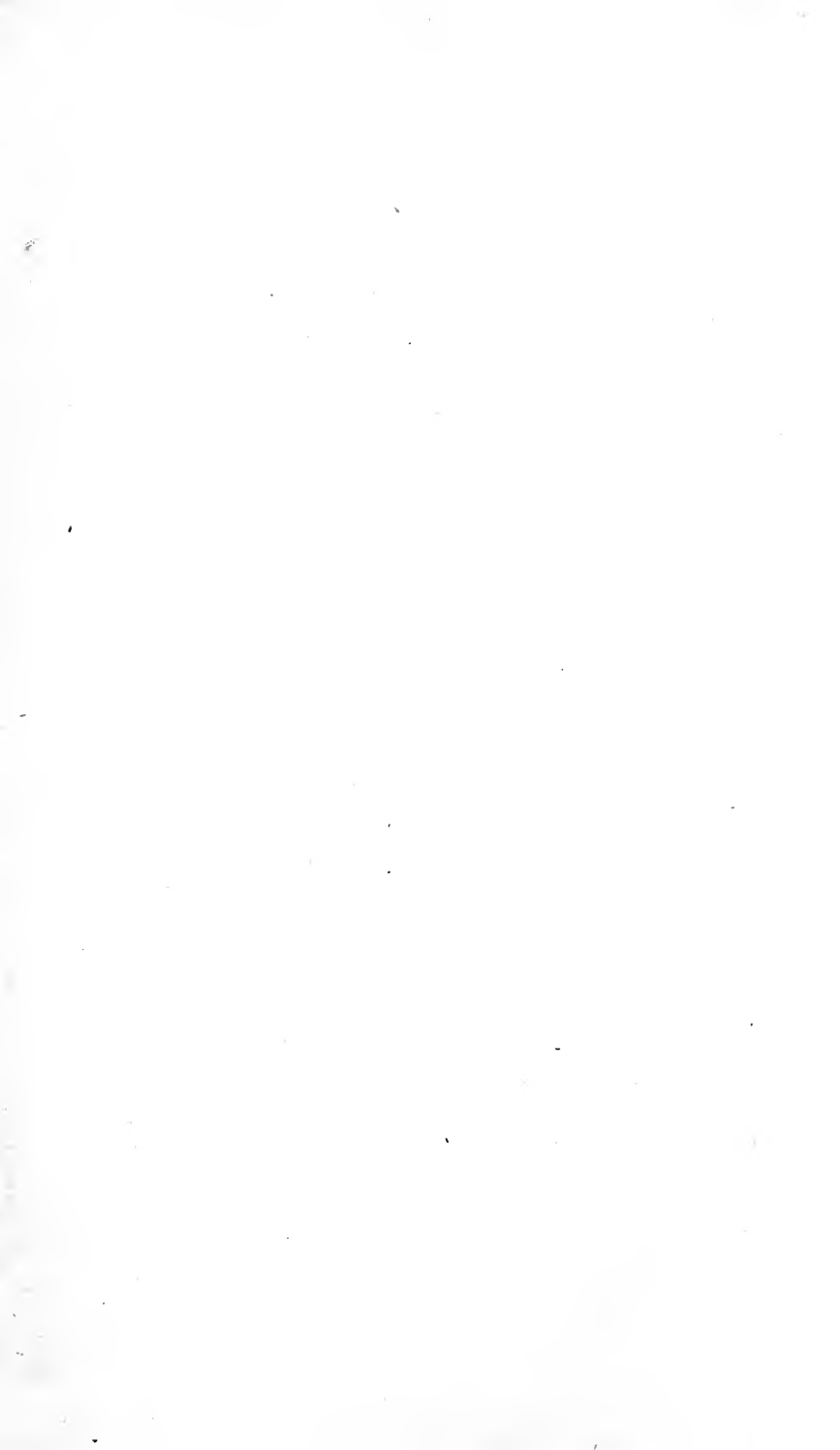# INDUSTRIAL CHEMISTRY

BEING A SERIES OF VOLUMES GIVING A COMPREHENSIVE SURVEY OF

THE CHEMICAL INDUSTRIES

INDUSTRIAL CHEMISTRY

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THE CHEMICAL INDUSTRIES

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ORGANIC MEDICINAL CHEMICALS

(*SYNTHETIC AND NATURAL*)

BY

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AND

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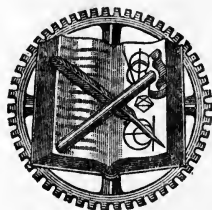
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GENERAL PREFACE

THE rapid development of Applied Chemistry in recent years has brought about a revolution in all branches of technology. This growth has been accelerated during the war, and the British Empire has now an opportunity of increasing its industrial output by the application of this knowledge to the raw materials available in the different parts of the world. The subject in this series of handbooks will be treated from the chemical rather than the engineering standpoint. The industrial aspect will also be more prominent than that of the laboratory. Each volume will be complete in itself, and will give a general survey of the industry, showing how chemical principles have been applied and have affected manufacture. The influence of new inventions on the development of the industry will be shown, as also the effect of industrial requirements in stimulating invention. Historical notes will be a feature in dealing with the different branches of the subject, but they will be kept within moderate limits. Present tendencies and possible future developments will have attention, and some space will be devoted to a comparison of industrial methods and progress in the chief producing countries. There will be a general bibliography, and also a select bibliography to follow each section. Statistical information will only be introduced in so far as it serves to illustrate the line of argument.

Each book will be divided into sections instead of chapters, and the sections will deal with separate branches of the subject in the manner of a special article or monograph. An attempt will, in fact, be made to get away from

the orthodox textbook manner, not only to make the treatment original, but also to appeal to the very large class of readers already possessing good textbooks, of which there are quite sufficient. The books should also be found useful by men of affairs having no special technical knowledge, but who may require from time to time to refer to technical matters in a book of moderate compass, with references to the large standard works for fuller details on special points if required.

To the advanced student the books should be especially valuable. His mind is often crammed with the hard facts and details of his subject which crowd out the power of realizing the industry as a whole. These books are intended to remedy such a state of affairs. While recapitulating the essential basic facts, they will aim at presenting the reality of the living industry. It has long been a drawback of our technical education that the college graduate, on commencing his industrial career, is positively handicapped by his academic knowledge because of his lack of information on current industrial conditions. A book giving a comprehensive survey of the industry can be of very material assistance to the student as an adjunct to his ordinary textbooks, and this is one of the chief objects of the present series. Those actually engaged in the industry who have specialized in rather narrow limits will probably find these books more readable than the larger textbooks when they wish to refresh their memories in regard to branches of the subject with which they are not immediately concerned.

The volume will also serve as a guide to the standard literature of the subject, and prove of value to the consultant, so that, having obtained a comprehensive view of the whole industry, he can go at once to the proper authorities for more elaborate information on special points, and thus save a couple of days spent in hunting through the libraries of scientific societies.

As far as this country is concerned, it is believed that the general scheme of this series of handbooks is unique, and it is confidently hoped that it will supply mental

munitions for the coming industrial war. I have been fortunate in securing writers for the different volumes who are specially connected with the several departments of Industrial Chemistry, and trust that the whole series will contribute to the further development of applied chemistry throughout the Empire.

SAMUEL RIDEAL.

PREFACE

THE section of the British Chemical Industry concerned with the manufacture of Synthetic Medicinal Chemicals calls for most earnest attention. It is unnecessary here to discuss its importance, which becomes ever greater with the advance of our knowledge.

Creditable as was the accomplishment of British chemists during the war in supplying within a short space of time most of the important synthetic medicinal chemicals, these manufactures were not in every case established on an economic basis. In order to do this, it is of outstanding importance to perfect processes so that the most economical methods are used and the best possible yields obtained; and such perfection can only be attained by zealous work on the part of men with knowledge.

It is hoped that the material here collected will prove of value to chemists engaged in this work, as well as to those responsible for the education of the men whose task in the era which is dawning will be the application of chemical science to industry.

No attempt has been made to deal with all the known synthetic remedies, very many of which are non-essential, and of yet others too little is known to permit a true judgment of their value. Similarly, reference has been omitted to very numerous processes which do not seem capable of practical application. "Blocking" patents, when referred to, are not described in detail.

The authors recognise the incompleteness of some of the descriptions given. To this shortcoming limitations

of space have contributed, but chiefly it is due to the insufficiency of published accounts.

The various chemicals dealt with are for the most part grouped in sections according to their therapeutic uses. Such an arrangement is considered by the authors to be the most convenient, though this classification is superficial and rests on little or no scientific foundation.

The authors wish most gratefully to acknowledge assistance given by H.M. Explosives Department of the Ministry of Munitions for an account of the manufacture of ether; to the Royal Society's Committee for various processes worked out in the Universities; and to the following engineering firms who have supplied photographs and drawings of plant: Messrs. E. Barbet et Cie., W. J. Fraser & Co., Manlove Alliot & Co., and The Standard Chemical Engineering Co. Acknowledgments are also due to Ullmann's "Enzyklopædie," from which the authors have received assistance, and to the authors of very many other standard works, notably to Prof. Cushny and Dr. Cain.

<div style="text-align: right">M. B.
F. H. C.</div>

November, 1920.

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INTRODUCTION

In the thirteenth century Roger Bacon wrote in his treatise, " Of the Secret Works of Art and Nature," that " a person who is perfectly acquainted with the manner which Nature observes in her operations will be able not only to rival but to surpass her." In another place in his writings we read : " By a dexterous application of the knowledge of the properties of bodies and the methods of Nature many things may be produced more surprising than all the pretended magic has ever effected." It was some six centuries after Roger Bacon had written this that Wöhler first built up urea in the laboratory and so prepared artificially a substance identical with that produced in nature. During the century which has elapsed since that achievement chemists have not only succeeded in rivalling the medicinal agents produced by nature, but have been able vastly to improve upon them. As a result the ordinary practice of medicine to-day is to a large extent dependent upon the products of synthetic chemistry. Roger Bacon's remarkable prophecy that discovery would come from a study of the methods of Nature has been strangely verified in this field of research. The discovery of many substances of use in medicine, as, for instance, antipyrine, eucaine, homatropine, epinine, and aspirin, was the direct result of attempts, based on a knowledge of the chemical constitution of natural substances, to improve upon them or to cheapen them. It is true, nevertheless, that chance discovery has revealed valuable physiological properties of many of the synthetic compounds which

are now of great importance in medicine ; for instance, the
purgative action of phenolphthalein was accidentally dis-
covered from its employment in " ear-marking " wines,
and the antipyretic properties of acetanilide were revealed
hrough the action of a laboratory boy in mistaking it for
naphthalene—a discovery which led to that of other and
better antipyretics.   Chance discovery may in the future dis-
close valuable physiological properties possessed by some of
the many thousands of organic compounds which have been
prepared during the past fifty years.   But just as the
discovery of these numerous substances has resulted from
earnest attempts to extend and perfect our theoretical
conceptions of chemical constitution and change, so also will
most of the future discoveries in medicinal chemistry result
from a study of body metabolism and pathological change
in health and disease.   Our perfect pharmacopœia can only
evolve as we make progress in knowledge of the correlation
between chemical constitution, physical properties, and
physiological action.   The theoretical concepts of the
nature of physiological processes are as yet in the making,
but in the past two decades such progress has been made as
to give confident expectation for the future.

There is a very long road for both chemists and physio-
logists to traverse before they can set up reasonable working
hypotheses.   It may be necessary first that chemists and
mathematicians should succeed in deducing from chemical
constitution the exact physical properties of a substance.
Certainly, if that consummation were reached the pharma-
cologist would be in a better position to unravel the mysteries
of physiological action.   For the present it may be said of
our knowledge that it shows enough remarkable cases of
relationship between chemical constitution and physiological
action to encourage and assist the chemist in his search for
new and useful drugs, and to suggest the importance of his
working in close association with the pharmacologist.

A practically useful result from an attempt to improve
on the naturally occurring cocaine is the synthesis of alpha-
and beta-eucaine, both of which possess valuable local

anæsthetic action similar to that possessed by cocaine. Cocaine has been shown to possess the following constitution :

$$CH_2—CH——CHCOOCH_3$$
$$NCH_3 \quad CHOCOC_6H_5$$
$$CH_2—CH——CH_2$$
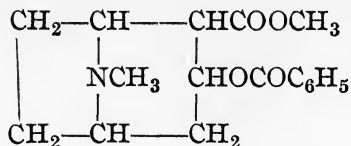
The preparation of substances with like grouping led to the production of alpha-eucaine, but this was found unfortunately to exercise greater irritating effect on the tissues. Further research revealed the substance known as beta-eucaine, which is less irritant than alpha-eucaine and less toxic than cocaine itself, and consequently preferable to the latter. The similarity between the constitution of alpha- and beta-eucaines and that of cocaine is clearly shown from their formulæ :

$$(CH_3)_2—C———CH_2 \qquad (CH_3)_2—C——CH_2$$
$$N—CH_3 \quad C\langle{COOCH_3 \atop OCOC_6H_5} \qquad NH \quad CHOCOC_6H_5$$
$$(CH_3)_2—C———CH_2 \qquad CH_3—CH—CH_2$$
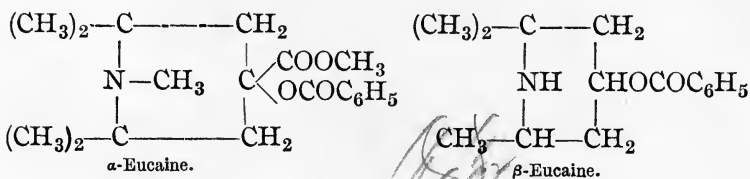
α-Eucaine.   β-Eucaine.

Beta-eucaine is now commonly employed to replace cocaine, to which it is in many respects preferable.

A classic example of modern research for therapeutic remedies is that for means of combating diseases such as sleeping sickness and syphilis, which are caused by the presence of protozoan parasites in the blood and tissues. The most successful of the remedies which have been discovered as the result of this work are the organic arsenic compounds.

In the course of research inorganic arsenic compounds were found readily to destroy such parasites *in vitro*, but only under conditions which were found to be also destructive to the host. Ehrlich and his colleagues, with well-known success, directed researches with the object of discovering derivatives which would be destructive to the parasite and

harmless to the host. Their work was rendered additionally complicated by the fact that surviving organisms which have been subjected to these parasiticides acquire some degree of immunity in succeeding generations.

Atoxyl, sodium-arsanilate

$$NH_2 \left\langle \bigcirc \right\rangle - As \overset{ONa}{\underset{OH}{\lessgtr O}}$$
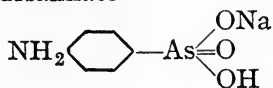
was the first substance introduced for this purpose. It was found to be very effective for the treatment of sleeping sickness, but the frequent cases of blindness which resulted from its use made necessary the search for other and better medicaments.

Ehrlich showed that atoxyl exercised much greater influence *in vivo* than *in vitro*, and from the known reducing action of the body tissues he was led to postulate the view that this difference is due to the formation within the organism of trivalent arsenic derivatives, by reduction of the pentavalent arsenic in atoxyl. This led to a search among trivalent organic arsenic compounds for one which is directly toxic to the parasites, as arsenious acid is, and yet possesses the low toxicity to the host exhibited by atoxyl.

Finding that certain dyes possessed parasiticidal properties and at the same time selectively stained the living protozoa, he therefore supposed that it might be possible to find an arsenic compound which in analogy with these dyes would attach itself to the parasites and not to the tissues of the host. A careful technique of testing his synthetic compounds both *in vitro* and in living rats and mice was set up, and a very large number of substances were thus submitted to test, especially dyes and new organic compounds. In this manner Ehrlich was finally led to select salvarsan and neosalvarsan as the remedies most nearly approaching the ideal.

$$\underset{\text{Salvarsan.}}{\overset{\text{As = As}}{H_2N\bigcirc \quad \bigcirc NH_2}} \qquad \underset{\text{Neosalvarsan.}}{\overset{\text{As = As}}{H_2N\bigcirc \quad \bigcirc -NH-CH_2-SO_2Na}}$$
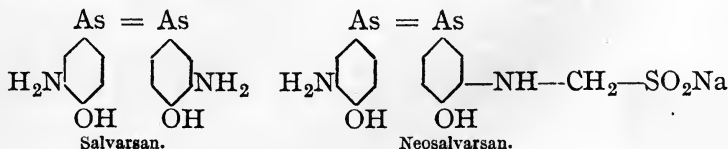
This choice was not made until a very large number of substances had been tested. Some of the dyes which were thus discovered to be fatal to protozoan parasites are now finding practical application in medicine. In particular methylene blue, malachite green, trypan red, scarlet red, and acriflavine are being employed. Acriflavine has proved to be of greater value for the destruction of bacteria than for that of protozoa, and has been most successfully employed in the treatment of gonorrhœa as well as in surgery. Thus is being introduced a new and important type of medication with dyes.

The advance in our knowledge of the chemical constitution of active substances secreted by the body, especially that of the so-called hormones, secreted by the ductless glands, indicates another and extremely important direction in which progress may confidently be looked for. So far the preparation of the pure active hormones has been accomplished only in the case of two of the glands. The first to be discovered was adrenaline, the principle of the suprarenal gland. This discovery has led to extended researches upon other amines which have a like action, and was the starting-point of a most important chapter of bio-chemistry.

Adrenaline: $OH\langle\rangle CHOH—CH_2NHCH_3$:   is   now OH

manufactured synthetically as well as prepared from the suprarenal glands of oxen and sheep. Since the synthetically produced racemic compound is less active than its *lævo*. constituent it is resolved on a manufacturing scale and the more active stereo-isomeride employed.

In their researches on amines allied to adrenaline, Barger and Dale have shown that physiological properties somewhat similar to those of adrenaline are exhibited by the amines derived by loss of CO_2 from certain amino acids, such as tyrosine and leucine, and that this type of activity is shown in varying degrees by a series of amines intermediate in structure between them and adrenaline. The greatest activity is possessed by those having two phenolic hydroxyl

groupings in the 3·4 position relative to a side chain consisting of two carbon atoms and bearing the amino group.   Also of importance amongst substances of this type is histamine, beta-iminazolyl-ethylamine, which has a very powerful physiological action of a different type.

$$\begin{matrix} NH—CH \\ | \qquad\qquad \\ CH=N \end{matrix} \Big\rangle C—CH_2—CH_2—NH_2$$
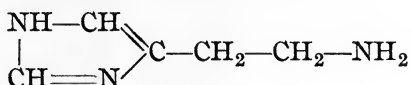
This base is derived from histidine, which is an amino acid, by the loss of CO_2.   Histamine has become of great interest in bio-chemistry and it has been recently suggested that it is one of the active constituents of the pituitary gland.   It results from the putrefaction of animal tissues and is also present in extract of ergot.   Since histidine, from which it is derived, is a constituent part of most body proteins, its production in minute quantity by biochemical change is not inconceivable.   Like adrenaline it is now manufactured synthetically.

A more recent discovery is thyroxin, the hormone of the thyroid gland.   The value of this gland in therapeutics has been known since 1891, but not till the year 1917 was the isolation of the active principle by Kendall reported. Not only has the purified crystalline substance been rendered available for therapeutic use, but its constitution has been determined.   Kendall states it to be a tri-hydro-tri-iodo· hydro-β-indole-propionic acid, and assigns to it the following formula :

$$\begin{matrix} IH \\ IH \\ IH \end{matrix} \bigcirc = C—CH_2—CH_2COOH \\ \qquad\qquad CO \\ H \quad NH$$
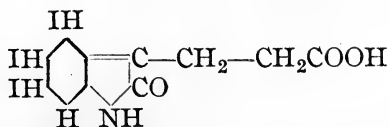
It is related to tryptophane, an amino acid, produced by the hydrolysis of proteins, which seems to play a special and peculiar part in nutriment, its absence from the diet having been found to be accompanied by loss of weight and ultimate death.   This is significant when we bear in mind the remarkable effects on metabolism produced by thyroxin

itself. The latter in small doses exercises a remarkable influence upon the rate of body metabolism, which rate is of fundamental importance in all bio-chemical change. There seems, therefore, hardly any finality to the power over the body mechanism which may be acquired by the aid of chemistry. In this connection it is the chemist's object to place in the hands of those who practise medicine the most perfect armoury for their combat with disease. What has been achieved so far must be regarded as merely indicating the road.

Section I.—NARCOTICS AND GENERAL ANÆSTHETICS

The following chapter deals with the method of preparation of the principal synthetic substances which have found general use in medicine for their action upon the central nervous system.

In every case the practical requirement is either that of a sedative or the promotion of sleep, whether it be of a temporary character as in the case of volatile anæsthetics such as ether or chloroform, or of a more lasting character such as the sleep produced by veronal. From remote times opium and alcohol have been used for this purpose, and while both are retained for use in medicine, they have been largely supplanted by later discoveries of chemical substances possessing less disadvantages than those of opium and alcohol.

Most of these substances, however, exert other actions besides that on the central nervous system, and the search for the ideal narcotic which is free from any by-effects must still be continued. Many interesting theories relating to narcotic action have been advanced, but no satisfactory generalisation has been adduced as to the nature of the chemical groupings which bring about the change in the circulation of blood in the brain that results in sleep.

Substances containing ethyl groups are generally more narcotic than those containing methyl, and less depressant than those containing higher alkyl groupings. The substitution of hydrogen by halogen, especially chlorine, increases the action in many instances.

8

ETHER—ethylic ether, sulphuric ether, $C_2H_5.O.C_2H_5$. 74.
—Ether is made by the dehydration of alcohol with sulphuric
acid. The technique of this method has been well developed
by the Explosives Department, Ministry of Munitions,
through whose courtesy we are enabled to give an account,
necessarily abbreviated, of the process for manufacturing
ether as carried out at H.M. factories, Pembrey and Gretna.

The plant, which has a productive capacity of 25 tons of
ether per 24 hours, is largely covered by the patents of
Barbet, to whom the illustrations given are to be attributed.
The process is smooth running and continuous, and in essence
consists of passing ethyl alcohol vapour through a heated
mixture of sulphuric acid and ethyl sulphuric, or sulphonic,
acid, $C_2H_5HSO_4$, whereby the elements of water are ab-
stracted.

$$C_2H_5.OH + H_2SO_4 = C_2H_5HSO_4 + H_2O$$
$$C_2H_5HSO_4 + C_2H_5OH \rightarrow (C_2H_5)_2O + H_2SO_4$$
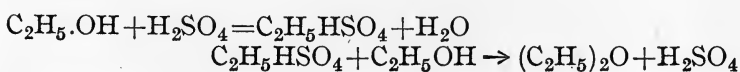
The issuing vapours, consisting of ether, alcohol, and water,
are separated into their constituents, by means of very
carefully designed fractionating and analysing columns.

During a period in which over 5000 tons of ether were
produced, the efficiency of the process averaged 94·3 %,
100 tons of ether requiring 131·2 tons of 100 % alcohol
(142·6 tons of 92 % alcohol); 124·3 tons of 100 % alcohol
being required according to theory.

The plant, which is by Barbet, is illustrated in Figs.
1 and 2. The still, or reaction vessel, is constructed of mild
steel plates and is lined with lead. It is 9 ft. 2 ins. diameter
by 11 ft. 6 ins., is insulated and contains a steam coil of
$1\frac{1}{2}$ ins. lead piping 5 ft. 2 ins. high and 3 ft. 8 ins. diameter,
and an open lead coil of 3 ins. diameter provided with $\frac{3}{8}$ in.
holes by which the alcohol vapour is admitted. The cover,
of copper plate, is provided with (1) an inspection hole ;
(2) a manhole ; (3) a vapour outlet pipe $6\frac{1}{2}$ ins. diameter in
a copper turret provided with a baffle plate ; (4) connection
for alcohol vapour pipe ; (5) connections for steam pipe ; (6)
connections for acid pipes ; (7) thermometer tube.

The fractionating column is made of copper and consists of eleven sections joined and bolted together, each section,
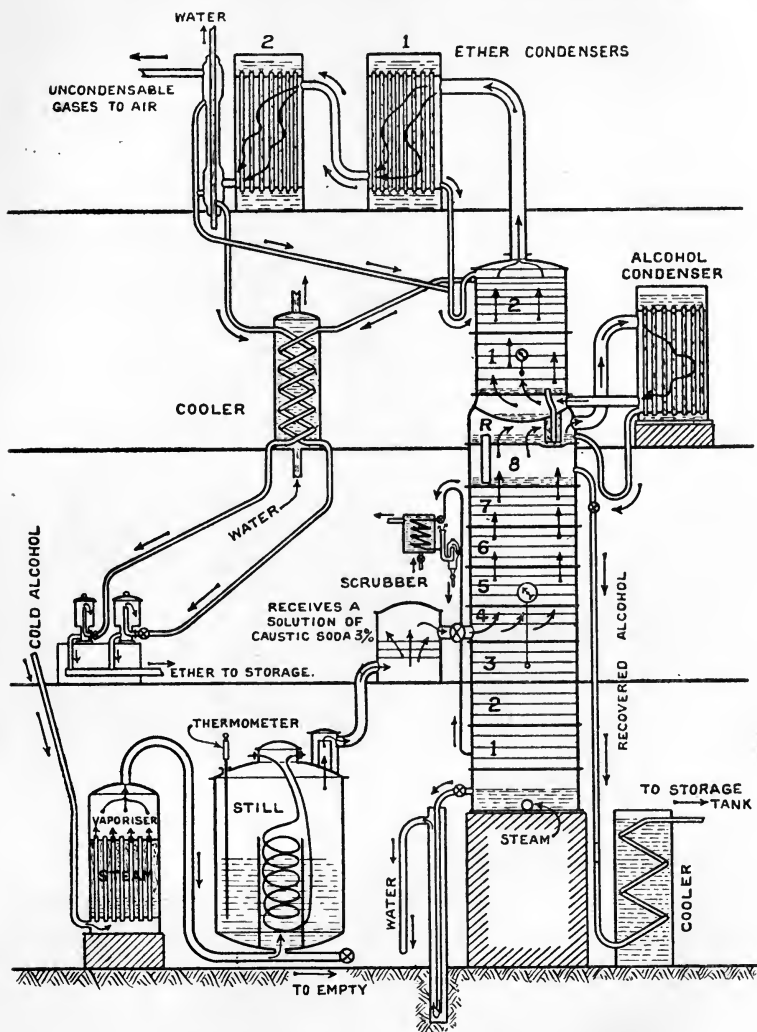
FIG. 1.—Ether production and rectification plant.—Barbet.

with the exception of the bottom and reducing sections, fitted into trays containing calottes and drip pipes. A diagram of a section is shown in Fig. 2. The reducing

section contains a tray with drip pipes only and divides the column into two parts.

(*a*) The lower part, 22 ft. high by 5 ft. 3 ins. diameter, consists of 22 trays and comprises the portion of the column from which recovered alcohol is drawn off.

(*b*) The upper part, 7 ft. 4 ins. high by 4 ft. 10 ins., consists of 11 trays and con-tains the "Ether Zone" from which rectified ether is with-drawn.

In the reducing section below the plate is a $6\frac{1}{2}$ ins. copper pipe for con-veying vapours to the alcohol condenser and a $3\frac{1}{4}$ ins. copper pipe for conveying liquid from the alcohol condenser. Above the plate is a $6\frac{1}{2}$ ins. copper pipe for conveying va-pours from the alcohol condenser to the upper part of the column. A $3\frac{1}{2}$ ins.

FIG. 2.—Section of fractionating column.

copper pipe leads from the top of the column to the ether condensers, and a $1\frac{1}{2}$ ins. pipe with cock from the third tray to the ether cooler.

The three condensers, one for alcohol and two for ether, made of copper, 3 ft. 9 ins. diameter by 7 ft. 7 ins. high, are of the tubular, water-cooled, surface type. Each contains 492 tubes of $1\frac{1}{2}$ ins. external diameter by about 6 ft. long.

The vaporiser, 8 ft. 8 ins. high by 2 ft. diameter, is constructed of mild steel plates and is built in two sections. The bottom section contains 151 steam-heated mild steel

tubes, $\frac{5}{8}$ in. internal diameter. A $1\frac{1}{2}$ ins. alcohol feed pipe enters this section near the bottom. The top section contains a baffle plate and is fitted with a cover with a 3 ins. outlet pipe, on which an atmospheric relief pipe is provided. The vaporiser is also fitted with a steam pressure gauge, steam safety valve, gauge glass, and thermometer fittings. A tee-piece is provided on the outlet pipe, one branch leading through a 3 ins. lead pipe to the alcohol feed coil in the still, the other to the fractionating column.

The process.—With one part by volume of sulphuric acid (78 % by weight) are mixed two parts by volume of undenatured alcohol (92 % by weight), and 2600 gallons of the mixture are pumped into the still. This is heated up, and at the same time steam is turned on to the alcohol vaporiser, being so regulated that liquid alcohol does not appear in the gauge glass. When the temperature in the still reaches 105° a small supply of alcohol vapour is admitted, and this quantity is gradually increased as the temperature rises. When at 121°, the steam is shut off, the heat of reaction being sufficient to take the temperature to 128° at which it is maintained throughout. The issuing vapours, consisting of ether, 50 % by volume, alcohol 30 % by volume, and water 20 % by volume, are bubbled through a 2 % solution of caustic soda in the scrubber, and then pass to the fractionating column, entering between the ninth and tenth trays from the bottom. The lower portion of the column has previously been heated, and at the time the vapours commence to pass over, the trays are laden with hot water. The temperature in the alcohol condenser is allowed to rise to 50° and is kept at this by regulation of the water supply. As is to be seen from the diagram of a section of the column, the vapours, in ascending from tray to tray, bubble through condensed liquor. Recovered alcohol, containing 5 % of ether, is drawn off at the bottom of the eighth section, to the recovered alcohol cooler, from which it is pumped up to the alcohol storage tank which supplies the vaporiser. The alkaline scrubber liquor, which contains some alcohol, is passed into the column at the foot of the

fourth section, and the liquor which is run off at the bottom of the fractionator is free from both alcohol and ether.

The rectified ether is withdrawn from the "ether zone," at the third tray from the top of the column, and runs through the cooler to a storage tank.

A certain quantity of ether, termed the "heads," and containing compounds of lower boiling point, such as methyl ether, and dissolved gases, is drawn from the jacketed tube connected to the second ether condenser, and may be collected separately. It can be mixed with rectified ether to form Methylated Ether (s.g. 0·717).

The quantities of materials and steam consumed per 2240 lbs. of ether produced are as follows :—

Alcohol (92 %), 1·426 ton.
Caustic soda, 0·0014 ton.
Sulphuric acid (100 %), 0·0012 ton.
Water, 9000 gallons.
Steam, 6000 lbs. using fresh alcohol ; and 10,000 lbs. using
    recovered liquors.

Labour, One chargeman and 4 labourers for 20,000 gallons per week.

A suitable plant for rectifying ether is illustrated in Fig. 3. The ether enters through a preheating coil A in the middle section of the column and passes by the drip pipes through the lower section to the steam coil.

Ether for anæsthetic purposes is required (British Pharmacopœia) to have a specific gravity of 0·720 to 0·722 at 15·5°. It should not commence to distil below 34·5° and must leave no residue on evaporation. Ether is used for producing general anæsthesia by inhalation in minor surgical and dental operations. It has a less depressing action than chloroform upon the heart, vessels, and respiratory centre. When taken internally it acts as a stimulant and carminative. So-called methylated ether is made from methylated spirit. It has a somewhat lower boiling point, due to the presence of methyl ethyl ether. Methyl ethyl ether is superior to ethyl ether when employed as a spray for producing local anæsthesia in minor surgery. For this purpose ether, however, is
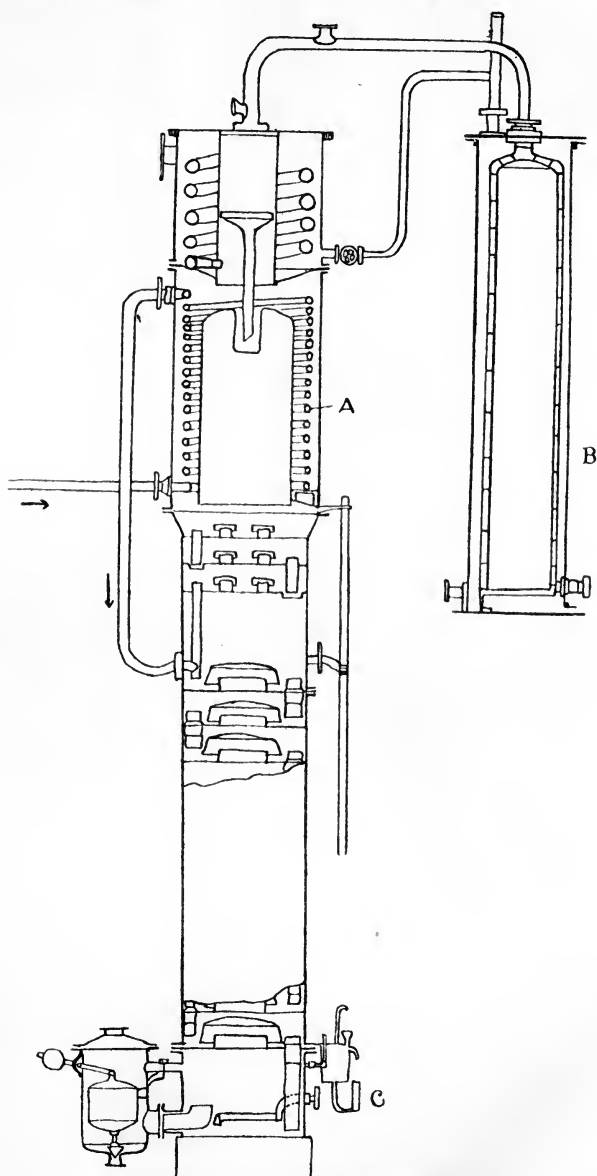
FIG. 3.—Rectifier for ether purification.

less efficient than ethyl chloride, besides being more objectionable to the operator.

Ether is a valuable solvent and is employed in the manufacture of fine chemicals, for which purpose pure ethyl ether is to be preferred to methylated ether.

METHYLAL—methylene dimethyl ether, $CH_2\Big\langle\begin{matrix}OCH_3\\OCH_3\end{matrix}$ 76.—

Methylal is prepared by the following procedure : A mixture of $2\frac{1}{2}$ parts of methyl alcohol, containing 1 % of anhydrous hydrochloric acid and 1 part of paraformaldehyde, is heated under a reflux condenser at 40°–50° for six hours, and then allowed to stand overnight. The acidity is neutralised by the addition of lime and the mixture is then fractionally distilled. Methylal is a colourless volatile liquid, s.g. 0·855, B.P. 42°. It is readily soluble in water and neutral to litmus. Methylal is used as an inhalation anæsthetic ; also, mixed with oil or glycerin, as a local anæsthetic. It is said to be an antidote to strychnine.

PARALDEHYDE, $C_6H_{12}O_3$. 132.—Paraldehyde is produced by the polymerisation of acetaldehyde. Acetaldehyde is an intermediate compound in the manufacture of acetic acid from acetylene or ethyl alcohol. It is also recoverable from the first runnings of alcohol distillation in the fermentation industry. Acetylene is to be regarded as the chief economic source ; from it acetaldehyde is prepared by passing the gas into a violently agitated suspension of mercuric oxide in sulphuric acid. The process has been the subject of a large number of patents. A useful account of the procedure as carried out at Shawinigan Falls, Quebec, will be found in the *Canadian Chem. J.* 1919, **3**, 258.

The polymerisation of acetaldehyde is conducted as follows : 500 lbs. of acetaldehyde are placed in an earthenware or lead-lined vessel provided with a stirrer and an efficient ice- or brine-cooled condenser. One cubic centimetre of hydrochloric acid, s.g. 1·18, is added. After a time, the length of which is dependent upon the initial temperature, a vigorous reaction sets in, the aldehyde boiling and being refluxed. When this slows down a further similar quantity of acid is

added, which starts the reaction afresh, and the same procedure is repeated until no further heat is developed. The maximum degree of polymerisation has then been attained, and the liquid is neutralised by washing with water and sodium bicarbonate, dried with anhydrous potassium carbonate and fractionally distilled, a very efficient rectifying and analysing column being required. Unchanged acetaldehyde passes over first and is mixed with the batch next to be polymerised, as is also an intermediate fraction which consists of a mixture of aldehyde and paraldehyde.

The fraction distilling at 123°–125° consists of pure paraldehyde ; a colourless mobile liquid, having a characteristic odour, and neutral in reaction towards litmus. B.P. 124°, M.P. 10°. When mixed with potassium hydrate solution, 6 %, no colour should be developed within two hours.

Paraldehyde is a valuable sedative and hypnotic. It produces quiet and refreshing sleep and does not depress the heart's action. It is largely used in the insomnia of mania, melancholia and other mental, and also cardiac, diseases. It has a marked action on the kidneys, increasing the flow of urine.

ACETOPHENONE or **Hypnone** — phenyl methyl ketone, $C_6H_5COCH_3$. 120.—Acetophenone is prepared (*see Ber.* **30,** 1769 [1897]) by the following method :

$$C_6H_6+CH_3COCl \rightarrow C_6H_5COCH_3+HCl$$
$$78 \qquad 78\cdot4 \qquad 120 \qquad 36\cdot4$$
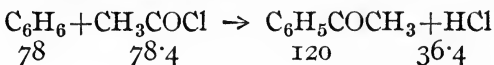
Two parts of sublimed aluminium chloride powder are covered with 1·6 parts of dry carbon bisulphide in a jacketed iron still provided with a stirrer and a reflux condenser. Cold brine is circulated through the jacket and the mixture stirred, whilst a mixture of 1·3 parts of acetyl chloride and 1·5 parts of dry thiophene-free benzol is added slowly, through a pipe reaching below the level of the liquid. A vigorous reaction ensues, and is kept under control by regulating the rate of flow of the mixture. When all has been added and the evolution of gaseous hydrochloric acid has slowed down, steam is passed into the jacket in place of the brine, and the

mixture boiled for half an hour. It is then cooled and run out on to a stirred mixture of crushed ice and water. The lower layer consists of acetophenone dissolved in carbon disulphide. It is separated, washed free from acid, dried, the solvent removed and the acetophenone purified by distillation *in vacuo*.

Acetophenone forms colourless crystals, m.p. 20°. The commercial product is often a liquid. It boils at 201°, is insoluble in water, but readily dissolved by alcohol.

Like many other ketones it possesses fairly strong hypnotic properties. Its homologue phenylethyl ketone has a more powerful action, but is not commonly employed. The urethanes and sulphones (*see* pp. 32–48) are generally regarded as safer hypnotics for general use.

ETHYL CHLORIDE — KELENE — C_2H_5Cl. 64·4. — Two methods are in use for the manufacture of ethyl chloride, one (the older) involving the use of a high-pressure lead-lined autoclave. The descriptions that follow are based on those given in Ullmann's *Encyclopedia der Technischen Chemie.*

(1) Molecular quantities of 94 % alcohol and hydrochloric acid (sp.gr. 1·16, or higher gravity if available) are mixed in a jacketed autoclave homogeneously lined with lead. Heat is applied, the temperature being raised slowly, in the course of 3 hours, to 120°, at which it is maintained for a further 2–4 hours, that is, until the pressure no longer increases. The reaction mixture is then cooled to 60° and the vapours are led through towers in which they are washed successively with water, caustic soda solution, and concentrated sulphuric acid. The ethyl chloride is finally condensed in an earthenware coil cooled to −10° by means of circulating cold brine, and led into a jacketed and cooled receiver.

(2) Seventy-five parts by weight of alcohol, 200 parts of hydrochloric acid (sp.gr. 1·16, or higher gravity if available), and 64 parts of calcium chloride are added to 200 parts of the residue, adjusted to sp.gr. 1·208, of a previous operation, such residue being contained in an earthenware still set in a water bath. The still is provided with a vertical outlet pipe,

which condenses and returns the unchanged alcohol vapour. The ethyl chloride vapours pass through a series of wash towers, successively containing water, acid sodium bichromate solution, caustic soda, and concentrated sulphuric acid, and condensed in a brine-cooled earthenware coil. The whole system is maintained under a slight positive pressure during operation.

Heat is applied slowly, the temperature being raised until ethyl chloride is seen, through a suitably placed sight glass, to be evolved. The distillation is so conducted that a regular flow of distillate is secured, the operation taking 8–9 hours, in which time 70–72 parts of ethyl chloride are obtained.

Of the residue in the still 200 parts are left for the next operation, the gravity being adjusted to 1·208 by addition of water. The remainder is neutralised with lime and the calcium chloride recovered by evaporation.

Ethyl chloride is a neutral, colourless, volatile, inflammable liquid distilling at 12·5° and having a sp.gr. at 0° of 0·921. Latent heat of vaporisation 100. It may safely be stored in metal vessels able to withstand a gauge pressure of 15 lbs. per sq. in.

It is employed as an ethylating agent in synthetic processes. In medicine it is used for producing local anæsthesia. Its effectiveness for this purpose results from its action as a refrigerant, due to its low boiling-point. It is also employed as a general inhaled anæsthetic for minor operations, being quick in its action and leaving no after effects. In point of safety it is said to stand between ether and chloroform.

Small quantities of ethyl chloride present in chloroform are believed to improve the anæsthetic qualities of the latter. When made from methylated alcohol, ethyl chloride contains methyl chloride unless separated therefrom by careful fractionation.

ETHYL BROMIDE C_2H_5Br.   109.—The following method, based on that given by Weston (*Trans. J. C. S.* 1915, **107**, 1489), is satisfactory and economical.

Twenty parts of ice are added to 625 parts of sulphuric acid (sp.gr. 1·84) contained in a jacketed enamelled or lead-lined still provided with a stirrer, and fitted to a condenser ; after cooling this mixture, 276 parts of absolute alcohol are added. During addition of the alcohol the mixture is well stirred and the temperature kept below 40°. The mixture is allowed to stand overnight, after which are added 618 parts of coarsely powdered anhydrous sodium bromide. The stirring is now started and steam admitted cautiously to the jacket. The temperature is raised slowly and steadily until ethyl bromide commences to distil. The distillation is conducted gently, the temperature being increased only when the flow of ethyl bromide from the condenser slows down. Attached to the end of the condenser is an adaptor dipping below the surface of a layer of water which is kept in the receiver. No frothing occurs if the heating is carefully conducted. When the evolution of ethyl bromide has ceased, sodium carbonate is added to the liquid in the receiver until the mixture is slightly alkaline after agitation. The aqueous layer is then separated from the heavier layer of ethyl bromide and evaporated down, when a quantity of sodium bromide is recovered. The ethyl bromide layer is washed, once by churning with water in a lead-lined agitator, and then with successive quantities of concentrated sulphuric acid, until the acid is no longer coloured, and until the specific gravity at 15·5° exceeds 1·45. The sulphuric acid is used, with the exception of the first washing, for making up the reaction mixture for a succeeding batch.

The product is finally rectified in earthenware, enamelled, or silica apparatus. Yield, 550–560 parts.

Ethyl bromide is a colourless, inflammable, strongly refractive liquid having a pleasant ethereal odour. B.p. 38°–39° ; sp.gr. 1·453–1·457/15°.

It is a local and general anæsthetic, similar to chloroform, but more rapid in its action, and is occasionally used in conjunction with it. It produces anæsthesia rapidly and is useful in minor surgery and in dental operations. In inexperienced hands, however, ethyl bromide must be

regarded as a dangerous agent, as the respiration is paralysed at about the same time as the reflexes, so that the zone of safety is very narrow.

CHLOROFORM $CHCl_3$. 119·4.—For the manufacture of chloroform there are many methods of industrial importance. Chief among them are those in which bleaching powder reacts with alcohol or acetone ; but in addition to these, chloroform is made through chloral hydrate prepared from chlorine and alcohol. It is also made by an electrolytic process and by the reduction of carbon tetrachloride.

Manufacture from Alcohol.—The best published description of the method of manufacturing chloroform from alcohol and bleaching powder is that given by Frerichs (*J. Ind. & Eng. Chem.*, 1912, **iv.** 345 and 406). He describes the process as it was being carried out in an American factory, and as it was modified as the result of his own experimental work.

By the original process for making 100 parts of pure chloroform 1440 parts of 35 % bleaching powder, and 72–73 parts of 100 % alcohol were consumed. By the modified method the corresponding figures were 977 parts of 33·3 % bleaching powder and 69·5 parts of 100 % alcohol. The essential difference between the two methods is that whereas as originally carried out the whole of the bleaching powder was mixed with the aqueous alcohol before the heating was commenced, by the modified process the bleaching powder was added gradually to the hot dilute alcohol. This modification was based on the observation that the yield of chloroform obtained by heating chloral hydrate, which may be assumed to be an intermediate in the formation of chloroform from alcohol with lime, is greatest if the materials are mixed at the boiling-point of their aqueous solutions.

$$2C_2H_5OH + 8Ca(OCl)_2 \rightarrow 2CCl_3CHO + 3Ca(OH)_2 + 5CaCl_2 + H_2O$$
$$\underset{92}{} \quad \underset{1303}{}$$
$$\swarrow$$
$$2CHCl_3 + Ca(HCOO)_2 + 2Ca(OH)_2 + 5CaCl_2 + 2H_2O$$
$$\underset{239}{}$$
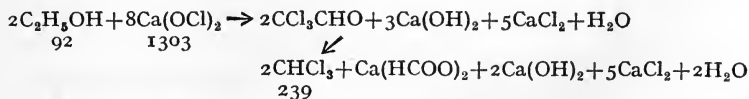
A general design of the plant is illustrated in Fig. 4. The vessels A and B are constructed of wrought or

cast-iron, the condenser of copper and the receivers of galvanised iron.

Ninety-six gallons of alcohol (94 % w/v) are diluted with 360 gallons of water in the reaction vessel B. The equivalent of 1500 lbs. of bleaching powder, 35 %, is charged into the agitator A and stirred with 750 gallons of water. The diluted alcohol is then heated to boiling by direct steam,
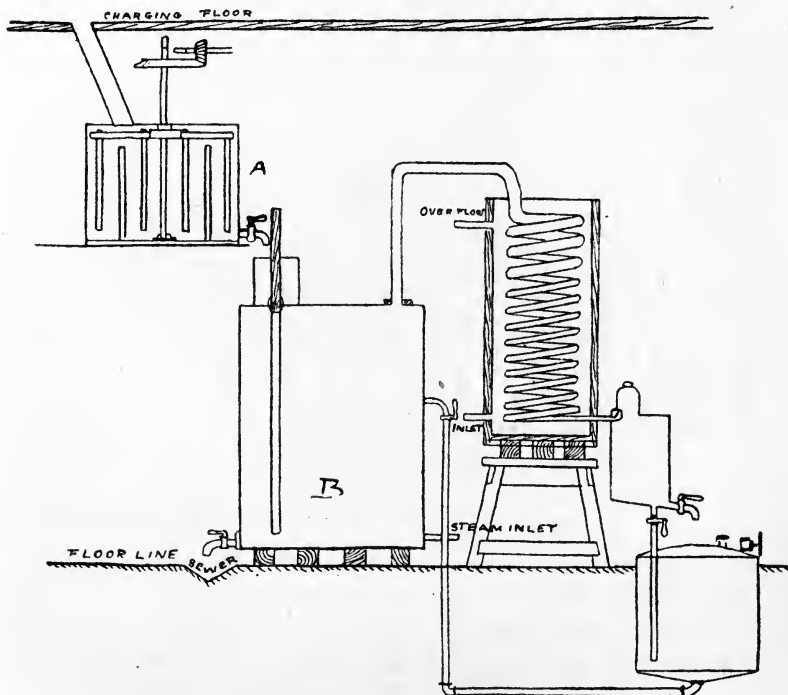
Fig. 4.—Production of chloroform from alcohol.

and the bleaching powder mixture added gradually, at such a rate that, without further addition of heat, a steady stream of chloroform, which is mixed with some alcohol, distils over. When all the bleaching powder has been added, distillation is continued, about 480 gallons of diluted alcohol being obtained, in addition to the chloroform, in each operation.

This 480 gallons of dilute alcohol is used, together with

fresh alcohol, to produce a further quantity of 20 % alcohol for making up the charge for the second operation, which is carried out in exactly the same way.

The following are the results given for a series of six operations carried out as above :—

Operation.	Bleaching powder.			Eng. gallons alcohol 94%.	Chloroform, s.g. 1·48.
	Weight.	Per cent. Cl.	Equal to lbs. at 35%.		
1	1694	31	1500	96	125
2	1694	31	1500	12	147
3	1694	31	1500	12	159
4	1694	31	1500	12	158
5	1694	31	1500	12	153
6	1694	31	1500	12	159

Not counting the first two days, in which the previous charges have no influence upon the yield, the average consumption, for making 100 lbs. of chloroform was 952 lbs. of 35 % bleaching powder. A record of a thirty-three days' run with 6 units of plant showed a yield of 30,675 lbs. of pure chloroform from 299,525 lbs. of 35 % bleaching powder and 2753 gallons of 94 % alcohol.

The amount of steam consumed was 2 tons for 100 lbs. of chloroform produced.[1]

Manufacture from Acetone.—Bleaching powder (35 %), 1400 lbs., is mixed with 700 gallons of water in an iron mixer fitted with rousing gear, and the mixture is transferred to an iron reaction vessel of 2000 gallons capacity fitted with stirring gear, steam and water inlets, and connected through a long stillhead to an effective condenser. The sludge is kept stirred and is heated to 45°, steam then being shut off. Acetone, 122 lbs., mixed with an equal volume of water, is next added, in the course of 10–15 minutes. The heat evolved by the reaction raises the temperature to about 60°, and chloroform distils over. When the rate of evolution commences to slow down,

[1] Baskerville and Hamor, *J. Ind. & Eng. Chem.*, **iv.**, 212, 278, 362, 422, 499, 571.
Dott, *J. Soc. Chem. Ind.*, **27**, 6, 271.

additional heat is applied and the distillation carried on until the condensate no longer contains oily drops of chloroform.

The plant designed by Meyer is illustrated in Fig. 5. In the iron mixer A the bleach and water are mixed. B is the reaction vessel, and C the acetone container. D is a condenser, E a washer and F the receiver.

The condensate of crude chloroform is then separated from the upper layer of water, and set aside for further purification. The aqueous layer is returned to the reaction vessel.

The above quantities yield about 105 parts of crude chloroform. The yield is stated in Ullmann's *Encyclop. der Tech. Chem.* to be 100 parts of chloroform from 600 parts of 35 % bleaching powder and 57 parts of acetone.

The relative economic advantage of using one or other of these methods depends, of course, on the prices of bleaching powder, acetone, and alcohol, and it may happen that at different periods or in different countries either method may be the cheaper.

Manufacture by Electrolytic Process (Rev. d. Prod. Chim. 3, 309).—A 20 % solution of NaCl is heated at 100° in a leaden still and is kept agitated by means of carbon spatulas which at the same time serve as anodes for a 5–6 amp. current. Acetone is introduced into the bottom of the still and is acted upon by the chlorine, forming a compound— probably trichloracetone—which is decomposed by the action of the caustic soda produced, giving chloroform.

The yield is stated to be 85 % of the theoretical.

Manufacture from Carbon Tetrachloride.—Chloroform is also manufactured from carbon tetrachloride, by reducing this with iron powder and weak acid, or with zinc and hydrochloric acid (*Chem. Rev.* 1896, 88), but it may be doubted whether a product of pharmaceutical quality is as yet obtainable from this source.

Manufacture from Chlorinated Alcohol or Chloral.— According to D. R. P. 129237, chlorine is passed into cold stirred alcohol until the density has reached 1·32, or (*J. Chem.*
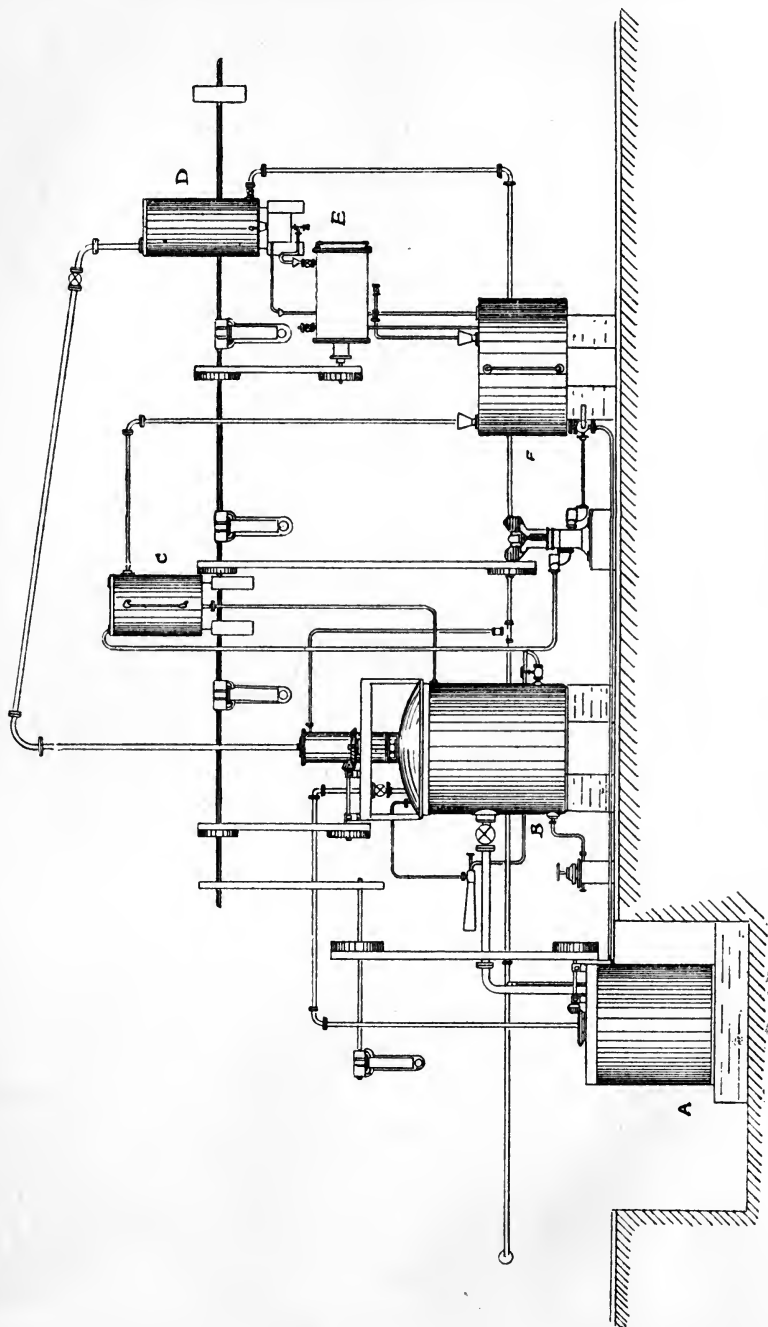
Fig. 5.—Chloroform manufacture from acetone.

Ind. Tokyo, 1918, **21**, 219) until the two layers which form are almost equal in volume. One hundred parts of the chlorinated product are added to a mixture of 500 parts of bleaching powder, 100 parts of slaked lime, and 2000 parts of water. Heat is applied, and the chloroform slowly distilled over. It is stated that 95–98 parts of chloroform are yielded by 100 parts of alcohol.

By whichever process described above chloroform is produced, it requires considerable further treatment to render it pure enough for medicinal purposes. Absolute freedom from aldehyde, ketone, phosgene, carbon tetrachloride or like impurity must be secured by agitating it successively with sulphite or thiosulphate, an oxidising agent such as bichromate, sulphuric acid and an alkali. A suitable
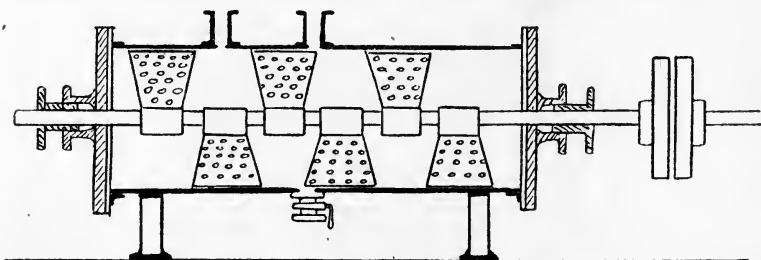
FIG. 6.—Washer for chloroform purification.

washer is shown in Fig. 6. It should be lead-coated throughout. The chloroform is finally dried and distilled by careful fractionation and the constant boiling fraction is alone employed.

To the freshly distilled chloroform the amount of absolute alcohol required to reduce the gravity to 1·485–1·487 must be added as a preservative.

Pure chloroform may be produced directly from pure chloral hydrate by the action of caustic alkali.

Chloroform is a colourless, refractive, volatile liquid, sp.gr. 1·4988, but as commonly sold admixed with 2 % of alcohol, 1·485–1·487 ; b.p. 61·2°. It must withstand the stringent tests of the B.P. and U.S.P. if employed for pharmaceutical purposes. No colour should be given when 20 c.c. are shaken with 15 c.c. of conc. H_2SO_4 and 4 c.c. of

40 % formaldehyde. In order to make it withstand this test great care is required to avoid contamination with any organic matter such as cork or grease, and the alcohol employed as a preservative must be carefully selected.

CHLORAL HYDRATE $CCl_3CH(OH)_2$. 165·4.—Until the commencement of the present century the chlorination of alcohol to chloral hydrate was carried out in glass containers, in which 25 kg. of absolute alcohol were slowly chlorinated,
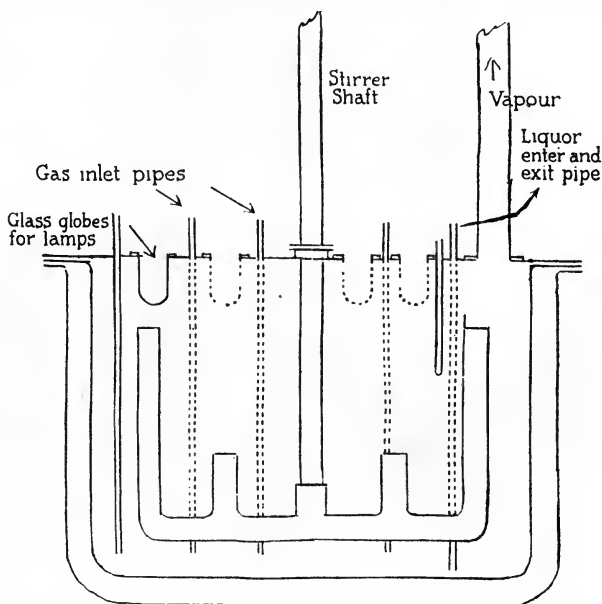
FIG. 7.—Sectional sketch of chlorinating vessel

first in the cold, then with temperature gradually increasing to 90°–95°, an operation taking 6–8 weeks, day and night. This procedure was naturally very costly, and necessitated much labour and supervision.

As carried out by D. R. P. 198422, homogeneously lead-lined jacketed vessels of 200–500 litres capacity, coated internally with porcelain tiles, are employed, fitted with stirring gear, a jacket, and internal coils, through which either cold brine, water or steam can be passed, and numerous

chlorine distributing tubes. The vessel illustrated (Fig. 7) is suitable for chlorinations generally. It is fitted with globes for electric lamps, employed for accelerating the reaction. The vessel is filled to two-thirds of its capacity with alcohol. Liquid chlorine may be employed, being distributed in fine drops. The apparatus is kept under slight pressure, and several vessels may be arranged in series, so that no chlorine is lost. The operation is finished in 3–5 days of 24 hours. On the first day the temperature of the alcohol is kept at 20°–25°; and it is slowly raised to 50°–60° during the second day, the specific gravity after 48 hours being 35°–40° Bé. Finally, the temperature is raised to 95°, the operation usually being finished when the specific gravity reaches 49° Bé.

Reactions:

$$CH_3CH_2OH \rightarrow CH_2Cl\text{---}CHCl\text{---}OH \rightarrow CH_2ClCHClOC_2H_5$$
$$CHCl_2CHClOC_2H_5 \rightarrow CHCl_2CH{<}^{OH}_{OC_2H_5} \rightarrow CCl_3CH{<}^{OH}_{OC_2H_5}$$
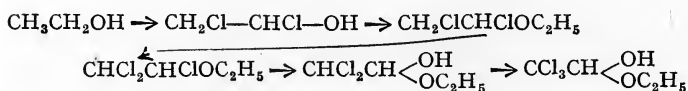
Chloral alcoholate is the main constituent of the reaction mixture at the end of the operation (*A.* **279**, 293; **A. ch. 10,** 3320). Volatile chlorinated by-products containing ethyl chloride are recovered from the exit vapours by condensation in stoneware towers.

The reaction mixture is allowed to cool, when part of the chloral alcoholate crystallises out. An equal volume of sulphuric acid, sp. gr. 1·84, is added in the cold, and the mixture gradually distilled. Ethyl chloride distils off first, HCl gas being also evolved. Between 70° and 90° ethyl alcohol passes over, and from 90° chloral commences to distil.

The crude chloral is neutralised with calcium carbonate and distilled from a lead-lined still, the vapours passing through a heated vessel containing lumps of limestone before being condensed.

The distilled chloral is converted into chloral hydrate by the gradual addition, with cooling and stirring, of water, 12·2 parts of which are required by 100 parts of chloral.

The resulting material is recrystallised from benzol or petroleum ether.

Colourless rhomboidal crystals having a penetrating aromatic odour and an unpleasant bitter taste. M.p. 50°; b.p. 94·4°–96·7°. Readily soluble in water, alcohol, glycerine, ether, and chloroform. When shaken with 20 parts by weight of concentrated sulphuric acid no colour should be developed within one hour. An aqueous solution should be neutral to litmus, and should give no precipitate on addition of silver nitrate solution.

Chloral hydrate was introduced into medicine as an hypnotic in 1869 by Liebreich. It quickly produces a natural and placid sleep, but is not suitable for insomnia caused by pain. It is employed in cases of acute mania and delirium tremens, in asthma and whooping cough, and is of great value in midwifery.

It is reduced in the body to trichlorethyl alcohol, which is eliminated in the form of a compound with glycuronic acid.

CHLORALOSE (Chloral Glucose—Glucochloral)

$$C_8H_{11}O_6Cl_3. \quad 309·4$$
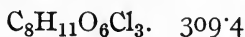
—Chloralose is prepared (*Ber.* **22**, 1051) by heating together for 2 hours at 100° equal quantities of distilled chloral and anhydrous glucose. Steam is then blown through the reaction mixture, to remove unchanged chloral, and, after cooling, the mixture of chloralose and para-chloralose is filtered off. These compounds are separated by fractional crystallisation from hot alcohol, when the para-chloralose, being the less soluble, separates first; or (*Bl.* [3] **9**, 17) by treatment with hot ether, which removes para-chloralose, after which the chloralose may be finally purified by crystallisation from hot water or alcohol. Colourless crystals, possessing a bitter, disagreeable taste ; m.p. 186°–187° (para-chloralose, m.p. 227°). Sparingly soluble in water (0·65 parts in 100), soluble in 31 parts of 91 % alcohol, and in 125 parts of ether. Chloralose is employed as a hypnotic and sedative in the insomnia of phthisis and mania. It is said to act more like morphine and to possess a greater toxicity than chloral hydrate, but patients are said to become rapidly habituated to its use.

CHLORAL FORMAMIDE (Chloralamide)

$$CCl_3CH(OH)NHCHO. \quad 192\cdot4.$$

—Formamide, 45 parts (for preparation, *see J. Amer. Chem. Soc.* **40,** 793), is added, with stirring, to cooled, freshly distilled chloral, 147·4 parts. Combination takes place with evolution of heat. The mixture sets, on cooling, to a solid crystalline mass of chloral formamide. (D. R. P. 50586; E. P. 7391/1886.)

$$CCl_3CHO + HC\!\!\underset{NH_2}{\overset{O}{\diagdown\!\!\diagup}} \rightarrow CCl_3\overset{OH}{\overset{|}{CH}}-NHCHO$$

$$\text{147·4} \qquad \text{45} \qquad\qquad \text{192·4}$$
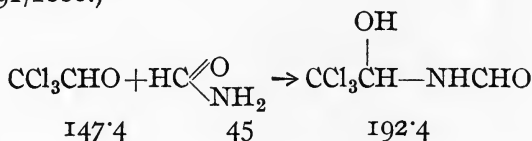
The product is purified by recrystallising it from dilute alcohol. The solution must not be heated above 48°, as at higher temperatures chloral formamide is reconverted into chloral and formamide.

An alternative method of preparation is by heating together chloralammonia, prepared by passing dry ammonia gas into a solution of chloral in benzene or ether, and ethyl formate.

$$CCl_3CH\!\!\underset{NH_2}{\overset{OH}{\diagdown\!\!\diagup}} + HCOOC_2H_5 \rightarrow CCl_3CH\!\!\underset{NHCHO}{\overset{OH}{\diagdown\!\!\diagup}} + C_2H_5OH$$

$$\text{164·4} \qquad\qquad \text{74} \qquad\quad \text{192·4} \qquad\qquad \text{46}$$
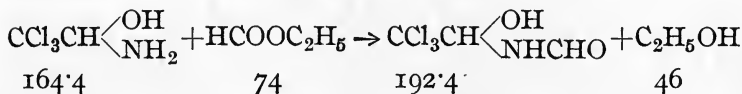
Colourless odourless crystals; m.p. 114°–115°. Soluble in 21 parts of water at 20° and in 2 parts of 90 % alcohol. The aqueous solution should be neutral to litmus, and no immediate turbidity should be produced on the addition of silver nitrate solution.

Chloralamide is a hypnotic possessing analgesic as well as sedative properties. Its action is similar to, but slower than, that of chloral hydrate, than which it is said to be less irritant to the stomach. It is claimed that it has less influence on the heart than chloral hydrate, but this claim has not been substantiated.

BUTYLCHLORAL HYDRATE (Trichlorobutyraldehyde hydrate) $CH_3\cdot CHCl\cdot CCl_2\cdot CH(OH)_2$ (193·4) is prepared by the action of chlorine on paraldehyde in a similar manner to that by which chloral is produced from alcohol.

The operation is carried out in a lead or porcelain-lined vessel provided with stirring gear, with a jacket and internal coils through which either cold brine, hot and cold water, or steam can be circulated, and with chlorine distributing tubes.

Chlorination is commenced at −5°, and the temperature is not allowed to rise above 0° until complete absorption occurs. Thereafter it is raised by increments of 5° up to 90°, whenever appreciable quantities of chlorine are seen to be escaping with the hydrochloric acid vapour. The time occupied by the whole operation depends largely, of course, upon chlorine distribution and upon the efficiency of the stirring; also, in the earlier stages, upon the adequacy of the cooling. It is advisable that the chlorination should be uninterrupted, as the longer the time taken the larger is the quantity of the tarry condensation products that are formed. When sufficiently chlorinated, the reaction product is subjected to steam distillation. Butylchloral hydrate passes over, and is collected and recrystallised from water. Pearly white crystals; m.p. 78°. The odour is pungent and somewhat fruitlike, and should not be acrid. It should not afford a brown colour when shaken or gently warmed with concentrated sulphuric acid, and should be free from hydrochloric acid and chloride ions. It dissolves in 44 parts of cold, and readily in hot, water. Readily soluble in alcohol, glycerine and oils.

Butylchloral hydrate is employed sometimes as a hypnotic, in this respect being similar to but less efficient than chloral hydrate. It is analgesic and especially recommended for the relief of facial neuralgia, and in the treatment of tic douloureux.

CHLORETONE (Trichloro tertiary-butyl alcohol) (acetone-chloroform)

$$CH_3\diagdown\,C\diagup OH$$
$$CH_3\diagup\,\,\diagdown CCl_3$$
177·4
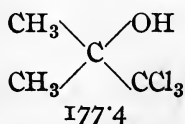
To a mixture of 500 parts of dry acetone and 1000 parts of chloroform, cooled to below 0° and continuously

stirred, are added gradually, over a period of $2\frac{1}{2}$ days, 325 parts of finely powdered caustic potash. After being allowed to stand at room temperature for a further $1\frac{1}{2}$ days with intermittent stirring the mass is filtered and the residue washed with acetone. The combined filtrate and washings are distilled ; unchanged chloroform and acetone are recovered, and the fraction passing over between 165° and 172° is collected separately and shaken with water. Crystallisation sets in, and when this is complete the solid is filtered off and recrystallised from a mixture of alcohol and water (*J. pr. Chem.* **37,** 362). It is extremely volatile even at ordinary temperatures, and requires to be dried with great care to avoid loss.

White glistening crystals having a camphoraceous odour and taste ; m.p., when anhydrous, 96°–97°. Soluble in 125 parts of water ; in $\frac{2}{3}$ part of 90 % alcohol.

Chloretone has an action similar to that of chloral hydrate on the central nervous system, and is used in the treatment of insomnia, vomiting, and spasmodic conditions, being less liable to irritate the stomach. It is employed as an introductory to general anæsthesia, excitement and nausea being thereby lessened. It is a mild local anæsthetic and possesses antiseptic properties. Both chloretone and its condensation product with chloral

$$\left((CH_3)_2 = C \big\langle \begin{matrix} CCl_3 \\ OCHOCCl_3 \end{matrix} \quad \text{m.p. } 65° \right)$$

are said to be efficient preventives of sea-sickness.

THE SULPHONE HYPNOTICS.

Sulphones of the type :—

$$\begin{matrix} R_1SO_2 \\ R_2SO_2 \end{matrix} \big\rangle C \big\langle \begin{matrix} R_3 \\ R_4 \end{matrix}$$
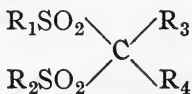
possess remarkable narcotic properties when the radicles are alkyl groups of which at least two are ethyl. The physiological activity of an equal concentration of these

compounds increases according as two, three, or four of
these radicles are ethyl groups. Sulphonal is a substance
of the above formula, in which R_1 and R_2 are ethyl groups,
R_3 and R_4 being methyl. In Trional there are three, and
in Tetronal four, ethyl radicles.

According to Meyer, the physiological effect of the three
substances may be expressed by the ratio :—

Sulphonal	.	.	.	.	6
Trional	.	.	.	.	13
Tetronal	.	.	.	.	18

SULPHONAL (Diethyl-sulphone-dimethyl-methane)

$$C_2H_5SO_2 \diagdown \diagup CH_3$$
$$C$$
$$C_2H_5SO_2 \diagup \diagdown CH_3$$

0·228
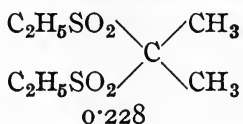
Sulphonal is prepared by condensing ethyl mercaptan
with acetone,

$$2C_2H_5SH + CO(CH_3)_2 \rightarrow (C_2H_5S)_2C(CH_3)_2 + H_2O$$
$$124 \qquad 58 \qquad 164$$
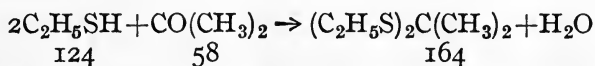
and the resulting acetone ethyl mercaptol is oxidised to
the sulphone, sulphonal.

Preparation of Ethyl Mercaptan C_2H_5SH.—Ethyl mer-
captan is made by the interaction of potassium, or sodium,
hydrogen sulphide, KHS or NaHS, with sodium ethyl
sulphate or with ethyl chloride (Rengault, *Ann.* **34**, 25).

Two parts by volume of 99 % alcohol are added to a
mixture of 1 part by volume of sulphuric acid (sp.gr. 1·84)
and 1 part of 20 % fuming sulphuric acid, the temperature
being kept below 70°. The mixture is allowed to cool
overnight, diluted with crushed ice, and poured on to a
mixture of ice and a solution containing 8 parts by weight
of sodium carbonate crystals, with stirring. More sodium
carbonate is added if necessary, and the neutral solution is
concentrated until a crust of salt forms on the surface. On
cooling, most of the sodium sulphate separates out, and is
filtered off. The filtrate, measuring about 3 volumes, is
mixed with a solution of potassium sulphide, prepared by

saturating with H_2S a solution of 1·6 parts by weight of KOH in 3 parts by volume of water. The mixture is gradually heated, and the ethyl mercaptan distilled over. It is freed from ethyl sulphide by treatment with concentrated NaOH solution, in which ethyl mercaptan dissolves. Any undissolved oil is separated, after which the mercaptan is reprecipitated by addition of acid.

Mercaptan may also be prepared from ethyl chloride by the following method. A solution of potassium (or sodium) hydrogen sulphide is treated with ethyl chloride in a jacketed autoclave, fitted with a stirrer and connected to a condenser. Slightly more than one molecule of ethyl chloride is required, some alcohol also being added to facilitate reaction. The mixture is gently warmed, with continuous stirring, to 50°–60°, and maintained at this temperature until the titration of test portions with acid, using methyl orange as indicator, shows the reaction to be completed. The ethyl mercaptan, which is mixed with alcohol and some diethyl sulphide, is distilled over, converted into its sodium salt, after which the alcohol and diethyl sulphide are removed by a second distillation, and reprecipitated by the addition of acid, as mentioned above.

Ethyl mercaptan boils at 36°; it is nearly insoluble in water.

Preparation of Acetone Ethyl Mercaptol

$$\begin{matrix} C_2H_5S \\ C_2H_5S \end{matrix} \Big\rangle C(CH_3)_2. \quad 164.$$
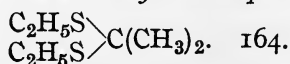
(*Ber.* **19**, 2803). One part of acetone is mixed with $2\frac{1}{2}$ parts of ethyl mercaptan (20 % excess) and the mixture treated with dry hydrogen chloride, the temperature being kept, by cooling, below 25°. The condensation may be facilitated by the presence of anhydrous calcium chloride, which serves to remove the water formed by the reaction. When saturated with HCl the mixture is left to stand overnight; then washed with water. The mercaptol layer is dried over $CaCl_2$ and fractionally distilled. Unchanged ethyl mercaptan passes over first, the mercaptol distilling at 190°–191°.

I.

3

Oxidation of Acetone Ethyl Mercaptol to Sulphonal (*Ber.* **19**, 280).—To acetone ethyl mercaptol, 164 parts, are added, with violent agitation, 5000 parts of a 5 % solution of potassium permanganate. The mixture warms itself as oxidation proceeds. Solid potassium permanganate is added from time to time, to maintain the concentration, until, in all, about 420 parts have been used. Stirring is continued until the permanganate has been practically all consumed, after which the temperature is raised to boiling, the solution decolorised, if necessary, by addition of sodium bisulphide, and filtered. From the filtrate sulphonal separates on cooling, and is filtered off and purified by recrystallisation from aqueous alcohol.

By another method sulphonal is made from ethylidene diethyl sulphone, acetaldehyde taking the place of acetone.

Acetaldehyde (b.p. 21°) 44 parts, (1 molecule), is mixed with ethyl mercaptan 124 parts, ($2\frac{1}{4}$ mols.), when interaction occurs with the evolution of heat. Anhydrous zinc chloride is added, with good cooling. After standing for some time the mercaptol is separated from the layer of aqueous zinc chloride, and is washed with water, dried, and distilled ; b.p. 185°–187°. The mercaptol is oxidised with potassium permanganate solution to the corresponding sulphone $CH_3CH(SO_2C_2H_5)_2$ in the same way as before, and this is converted into sulphonal by boiling an alcoholic solution of the sodium salt with methyl iodide.

$$(C_2H_5SO_2)_2CCH_3Na + CH_3I \rightarrow (C_2H_5SO_2)_2C(CH_3)_2 + NaI.$$
$$236142228150$$
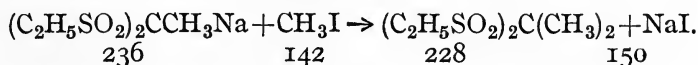
Sulphonal forms colourless, odourless, almost tasteless prismatic crystals. It dissolves in 400 parts of cold, and in 15 parts of boiling, water. It is readily soluble in alcohol, 1 in 80, and in chloroform. M.p. 125·5°. The aqueous solution should be neutral in reaction, and should not give the reactions of chlorides or sulphates. The solution in boiling water should be free from odour, showing absence of mercaptan and mercaptol. The aqueous solution (10 c.c.) should not be immediately decolorised after addition of a

drop of potassium permanganate. Its physiological properties are compared to those of other sulphones, p. 36.

TRIONAL (Methyl sulphonal. Diethyl-sulphone-ethyl methyl methane)

$$C_2H_5SO_2 \diagdown \diagup CH_3$$
$$\qquad\qquad C$$
$$C_2H_5SO_2 \diagup \diagdown C_2H_5$$
$$242$$
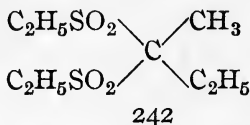
Methyl ethyl ketone and ethyl mercaptan are condensed to the mercaptol, which is oxidised in the same way as has been described under "Sulphonal" (D. R. P. 49073). The conditions to be observed are materially the same. Ethyl methyl-ketone-ethyl mercaptol ; b.p. 198°–203°.

Alternatively, the ethylidene diethyl sulphone

$$CH_3CH(SO_2C_2H_5)_2,$$

described under "Sulphonal," may be ethylated, by treatment with sodium ethylate and ethyl iodide in absolute alcohol, when trional is afforded. The ethylation is stated not to proceed well, much substance remaining unchanged. Trional is a white crystalline powder, which melts at 76·5°. It dissolves in 400 parts of cold water, giving a neutral solution ; it is readily soluble in alcohol. Trional should comply with the same tests as sulphonal for absence of impurities.

TETRONAL (Ethyl sulphonal—Diethyl-sulphone-diethyl methane)

$$C_2H_5SO_2 \diagdown \diagup C_2H_5$$
$$\qquad\qquad C$$
$$C_2H_5SO_2 \diagup \diagdown C_2H_5$$
$$256$$
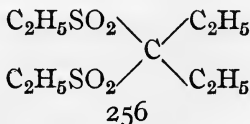
Ethyl mercaptan, 7 parts, is mixed with 5 parts of diethyl ketone ; the mixture is cooled with ice and saturated with dry HCl. Condensation is completed in a few hours and the mercaptal is then washed with water and distilled ; b.p. 225°–230°. It is oxidised to the sulphone, tetronal, in the manner described under "Sulphonal." (D. R. P. 49366 ; E. P. 12563/1888.)

Tetronal crystallises in silvery leaflets ; m.p. 85° C. It

dissolves in 500 parts of cold water, and in 12 parts of 90 % alcohol. It should comply with the same exclusive tests as sulphonal.

The three sulphone methanes described above, when administered in therapeutic doses, produce sleep without noticeable effect on the circulation and respiration. Sulphonal is the most generally used ; trional is next in importance ; tetronal is but little used. The action of sulphonal is more slowly established than that of trional, probably on account of its lesser solubility. The low solubility of the sulphones renders them somewhat uncertain in their action.

Hypnotic action is not exhibited by disulphones which do not contain ethyl groups. Thus dimethyl-sulphonedimethyl-methane $(CH_3)_2C(SO_2CH_3)_2$ is without hypnotic action.

Dimethyl-sulphone-ethyl·methyl methane

$$\begin{array}{c} C_2H_5 \\ CH_3 \end{array}\!\!\Big\rangle C(SO_2CH_3)_2$$

has a slight hypnotic action ; whilst sulphonal

$$(CH_3)_2C(SO_2C_2H_5)_2$$

and the isomeric dimethyl - sulphone - diethyl - methane $(C_2H_5)_2C(SO_2CH_3)_2$ possess a considerable and equal hypnotic effect.

DERIVATIVES OF UREA.

The constitution of a large number of compounds of significance in biochemistry includes the carbamic acid grouping. The *Narcotics*, which are esters and derivatives of carbamic acid, comprise a very important class. The physiological activity of these urethanes is traceable chiefly to their physical properties and to the presence of ethyl groups, and is not commonly attributed to the carbamic residue. Ethyl urethane, methylpropylcarbinylurethane, tertiary amyl urea, diethyl malonyl urea, etc., constitute a series of hypnotics, the commercially important members of which are here described.

The action of adalin and veronal seems to be confined to

the central nervous system, and they are consequently preferred to all other hypnotics when sleep alone is sought.

URETHANE (Ethyl carbamate) $CO{<}{NH_2 \atop OC_2H_5}$. 89.—Urethane can be prepared from ethyl chloroformate by the action of ammonia, or by the interaction of urea nitrate, or urea chloride, or isocyanic acid, with alcohol.

1. *From Ethyl chloroformate.*—Ethyl chloroformate is made—

(*a*) (D. R. P. 117624) By the interaction of molecular proportions of phosgene and antipyrine in benzene solution. A double compound is formed, which, treated with absolute alcohol, is dissociated into antipyrine hydrochloride and ethyl chloroformate.

$$C_{11}H_{12}ON_2COCl_2 + C_2H_5OH \rightarrow C_{11}H_{12}ON_2HCl + CO{<}{Cl \atop OC_2H_5}$$
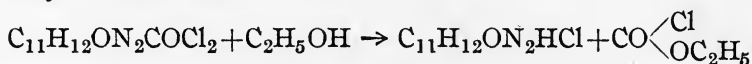
(*b*) (D. R. P. 251805) To 250 parts of a 20 % solution of phosgene in ether are added gradually, with cooling, 23 parts of absolute alcohol diluted with some ether, followed by 54 parts of technical monomethyl aniline in an equal volume of ether. After the reaction is completed the solution is shaken out with dilute acid to remove the methyl aniline, dried, and fractionally distilled.

(*c*) Phosgene is passed slowly into ethyl alcohol cooled by a freezing mixture, the reaction mixture is poured into a little water, dried, and distilled.

Ethyl chloroformate distils at 93°.

To obtain urethane from ethyl chloroformate, the latter is added, with vigorous stirring, to an excess of 0·880 ammonia, cooled to 10°–15° by external cooling. (*Ann.* **10,** 284.)

$$CO{<}{Cl \atop OC_2H_5} + 2NH_3 \rightarrow CO{<}{NH_2 \atop OC_2H_5} + NH_4Cl$$
$$108{\cdot}4 \qquad 0{\cdot}34 \qquad 0{\cdot}89 \qquad 53{\cdot}4$$
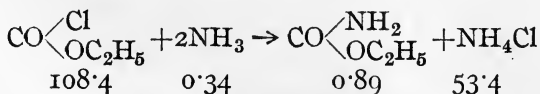
It may also be prepared by passing ammonia gas into an ethereal solution of ethyl chloroformate. The reaction mixture is evaporated to remove excess of ammonia, and the urethane extracted with ether, and, after removal of

the solvent, distilled *in vacuo.* B.p. 172° at 760 mm. ; m.p. 48°.

(2) *From Potassium Isocyanate* (Folim, *Am. Chem. J.* **19**, 341).—Five parts of potassium isocyanate are dissolved in sufficient warm 50 % alcohol to give a clear solution. This is added slowly to a concentrated alcoholic solution of hydrochloric acid, containing excess of acid. The mixture is allowed to stand for 24 hours, neutralised with barium carbonate, filtered, and freed from alcohol by distillation under reduced pressure. From the residual liquid urethane is extracted with ether. Yield, 60 % of the theoretical.

$$CO=NH+C_2H_5OH \rightarrow CO\diagup^{NH_2}_{OC_2H_5}$$
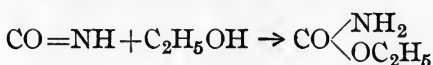
(3) *From Carbamic chloride* (*Ann.* **244**, 40).—Carbamic chloride (prepared by the action of phosgene on ammonium chloride) is added slowly to an excess of absolute alcohol.

The reaction mixture is treated with water, and the urethane extracted with ether. A quantitative yield is said to be afforded by this method.

Urethane forms colourless, odourless crystals, m.p. 48°, possessing a peculiar " cool " taste. It dissolves in 2 parts of water, and in 1 part of alcohol 90 %. A 10 % aqueous solution should give no reaction for chloride or nitrate.

Urethane is employed as a mild narcotic. Compared with chloral hydrate it has little action on the blood pressure and does not affect the heart. It is especially suitable for children. It is oxidised in the system to carbon dioxide and urea.

HEDONAL (Methylpropylcarbinyl urethane)

$$^{C_3H_7}_{CH_3}\diagup CHOCONH_2, \quad 131.$$

Methylpropylcarbinyl urethane (hedonal) has an hypnotic action twice as powerful as that of urethane. It is said to have no action on the circulation or respiration, and to be useful in insomnia.

According to D. R. P. 114396, methylpropylcarbinol, 20 parts, is mixed with 28 parts of urea nitrate, and the

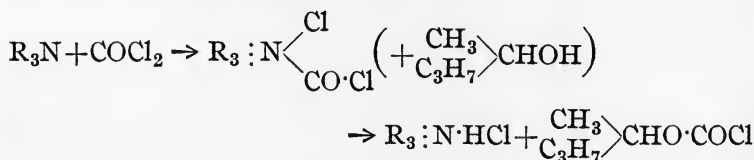mixture heated in a closed vessel under pressure for 5–6 hours at 125°–130°. When cold a small quantity of water is added to the mass, and the oily liquid which separates is isolated from the aqueous solution. On standing it solidifies, and is purified by recrystallisation from light petroleum. An alternative method of preparation is by the action of ammonia on methylpropylcarbinyl chlorocarbonate $\genfrac{}{}{0pt}{}{CH_3}{C_3H_7}$>CHOCOCl (D. R. P. 120863). The chlorocarbonic ester may be obtained (D. R. PP. 117624, 118536, 118537) by combining phosgene with a molecular proportion of a tertiary base, such as antipyrine or dimethylaniline. The resulting double compound is treated, in benzene or ether solution, with a molecular proportion of the alcohol, in this case methylpropylcarbinol, when the hydrochloride of the base and the chlorocarbonic ester are produced. The former is washed out with dilute hydrochloric acid, the solvent removed, and the ester distilled.

$$R_3N + COCl_2 \rightarrow R_3 : N\genfrac{<}{}{0pt}{}{Cl}{CO \cdot Cl}\left(+ \genfrac{}{}{0pt}{}{CH_3}{C_3H_7}\text{>CHOH} \right)$$

$$\rightarrow R_3 : N \cdot HCl + \genfrac{}{}{0pt}{}{CH_3}{C_3H_7}\text{>CHO} \cdot COCl$$

Five parts of methylpropylcarbinyl chlorocarbonate ester dissolved in 10 parts of benzene are treated, whilst being cooled and stirred, with 20 % aqueous ammonia (2 mols.) and agitated until the odour of the ester has disappeared. After standing for one hour the benzene layer is isolated and the benzene distilled off, when the urethane is obtained. (*Cf.* also D. R. PP. 120864 and 120865.)

$$\genfrac{}{}{0pt}{}{CH_3}{C_3H_7}\text{>CHOCOCl} + 2NH_3 \rightarrow \genfrac{}{}{0pt}{}{CH_3}{C_3H_7}\text{>CHOCONH_2} + NH_4Cl$$
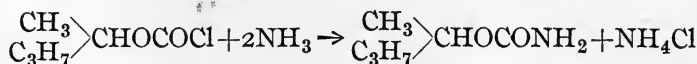
A white crystalline powder, having a faint aromatic odour and taste. M.p. 74° ; b.p. 215°.

Slightly soluble in cold water, readily soluble in alcohol, ether, chloroform, and other organic solvents.

Hedonal is used as an hypnotic in cases of insomnia due

to mental overwork, or nervous excitement due to neurasthenia or hysteria. It is stated to have a greater hypnotic effect than ethyl carbamate, and its use to be unattended by deleterious after-effects.

ADALIN (Bromodiethylacetyl urea)

$$(C_2H_5)_2CBrCONH \cdot CONH_2. \quad 237.$$

In considering the manufacture of the important narcotics of this group the preparation of the intermediate substance, diethylmalonic ester, and from it of diethylacetic acid, will first be described. The group includes, besides adalin, veronal or diethylbarbituric acid, proponal or dipropylbarbituric acid, luminal or phenylethylbarbituric acid.

Malonic Ester $CH_2{<}^{COOC_2H_5}_{COOC_2H_5}$ 160 (*see Amer. Journ. of Science*, **26**, 269 (1908)).—Monochloroacetic acid, 200 parts, is mixed with water, 50 parts, and neutralised by the addition of 300 parts of crystallised sodium carbonate. The solution is heated to 80° and poured, with rapid stirring, into a solution of 125 parts of sodium cyanide in 250 parts of water, heated to 90°–95°, and, after the reaction has subsided, the mixture is boiled for several minutes. It is then cooled and neutralised with sulphuric acid, using logwood paper as an indicator. The separated salt is filtered off, and the filtrate evaporated to dryness *in vacuo* at 60°. The salt is washed with 200 parts of 94 % alcohol, filtered, the filtrate added to the residue obtained from the evaporation, warmed and again filtered. The solid is washed with a further similar quantity of alcohol, and the two alcoholic filtrates are combined and evaporated under diminished pressure. The dry residue is mixed with 600 parts of absolute alcohol, 10 parts by weight of sulphuric acid (sp.gr. 1·84) added, the mixture cooled to below 0°, and saturated with dry hydrochloric acid gas. After standing for 2 hours the solution is boiled for 2 hours, then cooled and filtered. The solid is washed with 100 parts of absolute alcohol, which is then mixed with the previous filtrate. The mixture is boiled, and the vapour of 700 parts of absolute alcohol passed through it, in 3–4 hours.
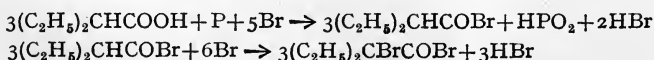
Part of the alcohol is then distilled off, and the residue, after cooling, poured on to ice. The ethyl malonate is extracted with ether, washed with an alkaline carbonate, dried with calcium chloride, and distilled *in vacuo*, after removal of the solvent. A yield of 85–88 % is claimed by this method. B.p. 198°.

Diethylmalonic Ester $(C_2H_5)_2C \begin{subarray}{l} \diagup COOC_2H_5 \\ \diagdown COOC_2H_5 \end{subarray}$ 216.—Sodium, 23 parts, is dissolved in absolute alcohol, treated with ethyl malonate, 1 molecule, 160 parts, and slightly more than 1 molecule of dry ethyl iodide or ethyl bromide. The mixture is refluxed until neutral, the alcohol is distilled off, the cooled residue treated with water, and the monoethyl malonic ester extracted and rectified. The second ethylation is brought about by a repetition of this process under identical conditions, whereby diethyl malonic ester is produced. B.p. 195°–205°.

Diethylacetic Acid $(C_2H_5)_2CHCOOH$. 116.—One molecule of diethylmalonic ester is heated with an aqueous solution of 2 molecules of caustic soda until neutral to phenolphthalein, or until the alkalinity to this indicator no longer decreases. The alcohol is distilled off, the residue cooled and treated, whilst stirring, with an amount of concentrated hydrochloric acid equivalent to the caustic soda employed. An oil separates which presently solidifies, and consists of diethylmalonic acid. This is filtered off and recrystallised from benzene, after which it should melt sharply at 121°.

It is converted into diethylacetic acid by heating to 180° *in vacuo* in an oil-jacketed still provided with stirring gear and a condenser. After the evolution of CO_2 is complete the temperature is raised until the diethylacetic acid distils over.

Bromodiethylacetyl Bromide.—Diethylacetic acid is treated with phosphorus and bromine according to Volhard's well-known method (*Ann.* **242**, 141).

$$3(C_2H_5)_2CHCOOH + P + 5Br \rightarrow 3(C_2H_5)_2CHCOBr + HPO_2 + 2HBr$$
$$3(C_2H_5)_2CHCOBr + 6Br \rightarrow 3(C_2H_5)_2CBrCOBr + 3HBr$$

The components are reacted at as low a temperature as possible, 50°–60°, and the resulting acid bromide is isolated from the hypophosphorous acid and freed from hydrobromic acid by aspirating through it a current of dried air or carbon dioxide.   Lastly it is distilled *in vacuo*.

Bromodiethylacetyl urea (D. R. P. 225710).—Pure bromo-diethyl acetyl bromide, 258 parts, is mixed with dry powdered urea, 122 parts, and the mixture allowed to remain at atmospheric temperature for 12 hours, with intermittent stirring, after which it is heated on a water-bath at 60°–70° for 3 hours.   When cold, the reaction product is powdered, treated with water, and sodium bicarbonate added until alkaline.   The undissolved material consists of bromodiethylacetyl urea, and is filtered off, washed, and dried, after which it is recrystallised.   In view of the fact that on heating with water it loses HBr, giving diethyl hydantoin $(C_2H_5)_2C\begin{subarray}{l} CO-NH \\ | \\ NH-CO \end{subarray}$ (m.p. 181°) (*Ber. d. deutsch. pharm. Ges.* **21**, 96 (1912)), crystallisation is best carried out in an anhydrous solvent, such as benzene, or ligroin, but it may be crystallised from alcohol.

Many alternative methods of preparation have been protected, of which the following is a summary :—

From bromodiethylcyanamide $(C_2H_5)_2CBrCO\cdot NH\cdot CN$ by hydrolysis with concentrated sulphuric acid (D. R. P. 225710).

By the bromination of diethylacetyl urea (D. R. P. 225710).

Oxidation of bromodiethyl thiourea with $KMnO_4$ (D. R. P. 225710).

From bromodiethylacetyl phenyl carbamate (D. R. P. 225710).

By heating bromodiethylacetyl isourea methyl ether with HCl (D. R. PP. 240353 and 243223).

By the action of HCNO on bromodiethylacetamide (D. R. P. 249906).

By treating bromodiethylacetyl carbamide chloride with ammonia (D. R. P. 249906).

By treating bromodiethyl acetyl cyanate with ammonia (D. R. P. 271682).

By interaction of bromodiethyl acetamide and carbamic chloride (D. R. P. 262148).

Adalin is a colourless, crystalline powder, m.p. 115°–116°, containing 35·8 % Br. It is slightly soluble in cold water, and in cold benzol or ligroin, and readily soluble in alcohol or acetone.

Adalin is a mild and promptly acting sedative, the use of which is associated with no unpleasant sequelæ. It is employed as a sedative in cases of neurasthenia, hysteria, and insomnia, and for mental disorders.

VERONAL (Barbitone — diethylbarbituric acid — diethyl malonyl urea) $(C_2H_5)_2C\begin{matrix} CO-NH \\ CO-NH \end{matrix}CO$. $C_8H_{12}N_2O_3$. 184.— This useful hypnotic has attained great commercial importance. A very large number of patents cover its preparation. The two methods which are of greatest technical importance are described in some detail; the others are merely enumerated.

(1) *By the Condensation of Diethylmalonic ester and Urea* (D. R. P. 146496).—For the preparation of diethylmalonic ester, *see* "Adalin," p. 40. Sodium, 32 parts (3 mols.), is dissolved in absolute alcohol (600 parts), and to the cooled solution 40 parts of dry urea and 100 parts (1 mol.) of diethylmalonic ester are added. The mixture is heated under pressure in an autoclave at 100°–110° for 4–5 hours. After cooling, the sodium salt of diethylbarbituric acid is filtered off and the filtrate reheated, when a further crop may be obtained.

The sodium-veronal is dissolved in water and the solution acidified with hydrochloric acid. The product is filtered off and crystallised from water, a decolourising agent, such as vegetable charcoal, being employed if necessary.

By a modification of the above process, which is said (*J. Amer. Chem. Soc.* **40**, 725) to afford higher yields,

anhydrous methyl alcohol is employed in place of ethyl alcohol.

$$(C_2H_5)_2C{<}^{COOC_2H_5}_{COOC_2H_5} + {}^{NH_2}_{NH_2}{>}CO$$
$$216 \qquad\qquad 60$$

$$\rightarrow (C_2H_5)_2C{<}^{CO-NH}_{CO-NH}{>}CO + 2C_2H_5OH$$
$$184$$
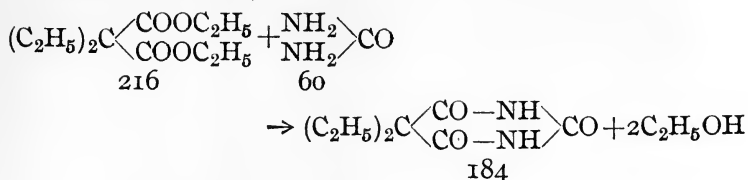
(2) *From Diethyl-cyanoacetic Ester* (D. R. PP. 156384, 156385).—46 parts of sodium are dissolved in 800 parts of absolute alcohol, and, after cooling, 70 parts of powdered urea and 169 parts of diethyl-cyanoacetic ester added, and the mixture refluxed for 3 hours. The alcohol is then distilled off, the residue dissolved in water, extracted with ether, neutralised with concentrated hydrochloric acid, and the precipitated iminodiethyl malonyl urea purified by recrystallisation from water. M.p. 195°.

$$(C_2H_5)_2C{<}^{CN}_{COOC_2H_5} + {}^{NH_2}_{NH_2}{>}CO$$
$$169 \qquad\qquad 60$$

$$\rightarrow (C_2H_5)_2C{<}^{\overset{\displaystyle NH}{\overset{\|}{C}}-NH}_{CO-NH}{>}CO + C_2H_5OH$$
$$183$$
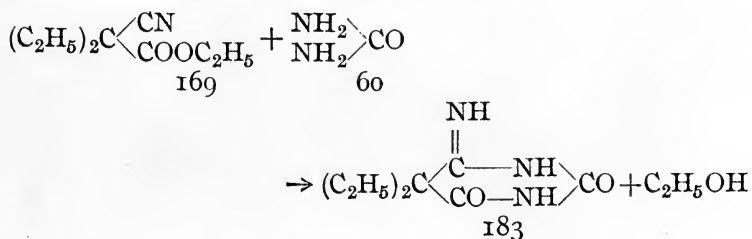
100 parts of iminodiethyl malonyl urea are dissolved in 500 volumes of 3·3 N-hydrochloric acid, and the solution is boiled for a short time. Diethyl barbituric acid crystallises out on cooling, and is filtered off and recrystallised from water. The acid filtrate may be used, after raising the concentration again to 3·3 N, for the hydrolysis of a further quantity of the imino acid.

$$(C_2H_5)_2C{<}^{\overset{\displaystyle NH}{\overset{\|}{C}}-NH}_{CO-NH}{>}CO \rightarrow (C_2H_5)_2C{<}^{CO-NH}_{CO-NH}{>}CO + NH_4Cl$$
$$183 \qquad\qquad\qquad 184$$
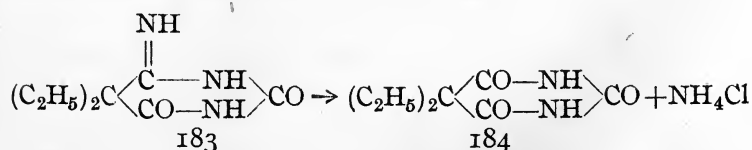
(3) *From Diethylmalonyl Chloride and Urea* (D. R. PP.

146949, 182764).—Diethyl malonic acid (1 mol.) is warmed gently with phosphorus pentachloride ($2\frac{1}{8}$ mol.), the diethylmalonyl chloride is separated from phosphorus oxychloride, and purified by distillation. B.p. 197°. (*Ber.* **35**, 854).

Diethylmalonyl chloride, 3 parts, is mixed with 1·9 parts of finely powdered dried urea and heated for 20 hours at 90°–100°. Hydrochloric acid is evolved, and finally there remains a solid mass which, on crystallisation from hot water, affords pure veronal (D. R. P. 146949).

$$(C_2H_5)_2C\underset{196·8}{\overset{\textstyle COCl}{\underset{\textstyle COCl}{<}}} + \underset{60}{\overset{\textstyle NH_2}{\underset{\textstyle NH_2}{>}}}CO \rightarrow (C_2H_5)_2C\underset{184}{\overset{\textstyle CO-NH}{\underset{\textstyle CO-NH}{<}}}CO$$
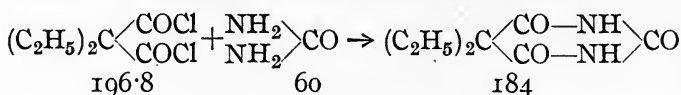
Veronal forms colourless, odourless crystals, possessing a faintly bitter taste ; m.p. 191°. It is sparingly soluble in cold water (1 in 160), more readily in hot water, and fairly soluble in aqueous solutions of alkalis ; it dissolves (1 in $8\frac{1}{2}$) in 90% alcohol.

Veronal-sodium, known as Medinal, is readily soluble in water, and is consequently a useful form for administration, especially per rectum. Veronal is one of the most widely used synthetic hypnotics, on account of its relatively low toxicity and comparative freedom from harmful by-effects. It produces quiet, deep sleep within an hour of administration. Large doses cause death. It is of little value where there is pain and in such cases it is of advantage to administer aspirin at the same time. When taken internally, 62 % is said to be eliminated unchanged, and subsequently to be found in the urine.

Veronal and its homologues can also be made from the following substances :

C-Monoalkylbarbituric acid by alkylation (D. R. P. 144432).

Dialkylmalonic esters, urea, acyl urea, or alkyl urea, and alcoholates, alkali metals, alkaliamides, or disodium-cyanamide (D. R. PP. 147278, 147279, 147280, 178935).

2:4-diimino-5-dialkyl-6-oxypyrimidine with acids (D. R. PP. 158592, 162657, 168405 (158581), 180669).

Dialkylated 2-thio-4·6-dioxypyrimidines (D. R. PP. 162219, 165649, 172404).

Dialkylthiobarbituric acids (D. R. P. 170907).

5-dialkyl-2-thio-4-imino-6-oxypyrimidines (A. P. 751724 ; D. R. P. 173241).

Dialkylmalonyl chloride and biuret (D. R. PP. 162220 ; 183857).

Dialkylmalonyl halides and allophanic esters (D. R. P. 177694).

Dialkylmalonamic acid ester (D. R. PP. 162280, 182045, 163200, 171294).

Dialkylmalonyl diurethanes (D. R. PP. 171992, 172886, 172885, 179946, 183628).

Dialkylmalonyl diamides and carbonic esters (D. R. PP. 163136, 169406, 168407).

Dialkylmalonyl diamides and phosgene (D. R. P. 167332).

Cyanodialkylacetyl urea (D. R. P. 165225).

5-dialkyl-4·6-diamino-2-oxy-(D. R. P. 166448), or 4·6-triamino-pyrimidines (D. R. PP. 165692, 165693).

Pyrimidine derivatives from dialkylcyaonacetic ester, malonic esters, etc., with dicyandiamides or guanylurea (D. R. PP. 158591, 170586, 165223, 180119, 187990).

CC-dialkyl 2-arylimino and 2-arylhydrazine barbituric acid (D. R. PP. 166266, 172979).

CC-dialkyl mono- di-, tri-iminobarbituric acids (D. R. P. 175592).

Guanyldiethyl barbituric acid (D. R. P. 17147).

Dialkylmalonuric acid amides (D. R. P. 174178).

5 - Diethyl - 2·4 - diamino - 6 - oxypyrimidine (D. R. P. 180669).

Diethylmalonyl guanidine (D. R. PP. 189076, 201244).

Diethylmalonic acid tetraalkyl diureides (D. R. P. 193446).

Dialkylmalonyl halogenides and isourea alkyl ethers (D. R. P. 249907).

Diethylmalonamide and oxalyl chloride (D. R. PP. 2254570, 227321).

Use of calcium carbide as condensing agent (D. R. P. 185963).

Hydrolysis of thiobarbituric acids (dialkylmalonic esters or thiourea) (D. R. P. 182764).

Preparation of dialkylthiobarbituric acids (D. R. PP. 234012, 235801).

From dialkyliminobarbituric acid (ex guanidine and dialkylmalonic ester) (D. R. P. 235802).

Monoalkylbarbituric acids (urea and monoalkylmalonic esters) (D. R. P. 146948).

Ureides of dialkylacetic acid, by treating a mixture of dialkyl malonic acid and urea with fuming H_2SO_4 and heating the product, ureidodialkylmalonic acid. CO_2 and dialkylacetyl urea result (D. R. P. 144431).

From allophanic esters or biuret and diethylmalonic ester (D. R. P. 183857).

Dialkylmalonhalides and allophanic esters (D. R. P. 177694).

From dialkylmalonuric acid amide (from cyandialkyl acetyl urea) (D. R. P. 174178).

From halogen substituted iminodialkylpyrimidines (D. R. P. 217946).

From dialkylthiobarbituric acids (D. R. P. 179907).

Disodio cyanamide as condensation medium (D. R. P. 178935).

From dialkylmalonicdiaryl esters and guanidine (D. R. P. 231887).

Dialkylmalonamic esters by alkylation of malonamic esters (D. R. P. 182045).

BROMURAL (α-Monobromoisovaleryl urea)

$$\begin{array}{c} CH_3 \\ CH_3 \end{array}\!\!\!\!> CH—CHBr—CO—NH—CO—NH_2. \quad 223.$$
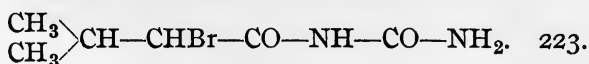
Two parts of α-bromoisovaleryl bromide are intimately mixed with 1 part of perfectly dry, finely powdered urea. The urea passes gradually into solution, the mixture attaining, without the application of external heat, a temperature of about 70°. It is maintained at this temperature until

the odour of the acid bromide is no longer perceptible, for which several hours are required. After cooling, the mass is powdered and treated with sodium bicarbonate solution, to remove hydrobromic acid and some α-bromisovaleric acid which is formed. The product is then dried and crystallised from toluene, from which it separates in leaflets, melting at 149° (D. R. P. 185962).

Colourless tasteless crystals, sparingly soluble in cold water, easily in ether, alcohol, and alkalis.

Bromural is employed as a hypnotic in nerve cases, and is stated not to possess the harmful by-effects of veronal. It is claimed that sleep is produced without the circulation or respiration being markedly affected. It does not, however, bring about the desired effects in cases of insomnia in which pain, cough, angina pectoris, or delirium exists.
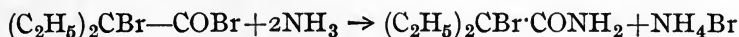
NEURONAL (Diethylbromoacetamide) $(C_2H_5)_2CBrCONH_2$ 194.—Neuronal is prepared (D. R. P. 158220) by dissolving bromodiethylacetyl bromide in ether and passing in ammonia gas to saturation.

$$(C_2H_5)_2CBr—COBr + 2NH_3 \rightarrow (C_2H_5)_2CBr \cdot CONH_2 + NH_4Br$$

The product is filtered off, washed with water to remove ammonium bromide, dried, and recrystallised from petroleum ether.

Alternatively, the acid halide is allowed to flow, with cooling and stirring, into an excess of aqueous ammonia.

A colourless crystalline compound containing 41 % of bromine. Sparingly soluble in water.

Neuronal was introduced as a hypnotic and sedative, and is said to have a very rapid action and to serve well in conditions of excitement and nervous irritability. It has no cumulative effect and the patient does not become habituated to its use, but it is said to cause depression.

Section II.—NATURALLY OCCURRING ALKALOIDS AND THEIR DERIVATIVES

NOTWITHSTANDING the many rivals to morphine which organic chemistry has provided of late, none has supplanted it. For its value in allaying pain, morphine is probably still to be regarded as superior to every other drug. However, the danger of inducing the habit of taking morphine and the other disadvantages of its use are serious drawbacks, and with the advance of knowledge of pharmacology it must be regarded as probable that by the combined use of antipyretic and narcotic synthetic drugs, morphine and its analogues will ultimately be replaced.

As the methods of manufacture of the different alkaloids may conveniently be considered jointly, the present section deals with the alkaloids in common use, with the exception of cocaine, which is treated separately with the local anæsthetics in the next section.

The isolation of alkaloids from plant materials follows to a certain extent the same lines whatever the nature of the alkaloid, but some being more prone to hydrolysis than others require expensive low-boiling solvents for their extraction; while many, as for instance strychnine and quinine, may be boiled with water with relative impunity, so that they are extracted by less expensive methods.

Speaking generally, the procedure is to remove by means of a solvent the bases present in the plant, leaving the sugar, starch, protein, and pectenous matter unextracted. Fats, if present, accompany the bases; chlorophyll may or may not do so, according to the solvent. The solvents employed are very numerous; alcohol, fusel oil, benzene, solvent naphtha,

ether, and petroleum being variously employed according to the circumstances. If benzene, solvent naphtha, or petroleum is used it is necessary to set free the bases in the plant by treatment with lime or alkali, since the alkaloids are present in combination with weak acids and are as a rule insoluble in this condition in these solvents. Many suitable extraction plants for use with volatile solvents have been designed. That illustrated in Fig. 8, by the Standard Chemical Engineering Co., is economical as regards heat consumption and solvent losses. It is constructed on the principle of the well-known Soxhlet extraction, the solvent refluxing from the condenser into the material packed in the upper part of the lower vessel. The extract percolates through into the lower half of this vessel, from which it is vaporised to the condenser, leaving the extract.

FIG. 8.—Extraction plant—Fischer type.

The solvent is next extracted with dilute acid; in some cases it is unnecessary first to distil away any of the solvent, but usually the greater part is first removed. The weak acid extract is frequently concentrated *in vacuo* before neutralisation, and thus is obtained in very crude form the

total alkaloid of the plant, admixed with a certain amount of sugar and so forth. Fat is removed at this stage by extraction with benzene or petroleum, in which the salts of the alkaloid are not soluble. The further treatment and the long and tedious separation and purification of the alkaloids must be varied not only with each kind of material,

FIG. 9.—Extraction of aqueous liquids with light solvents.

but with every batch, and requires great skill and experience and extremely careful workers.

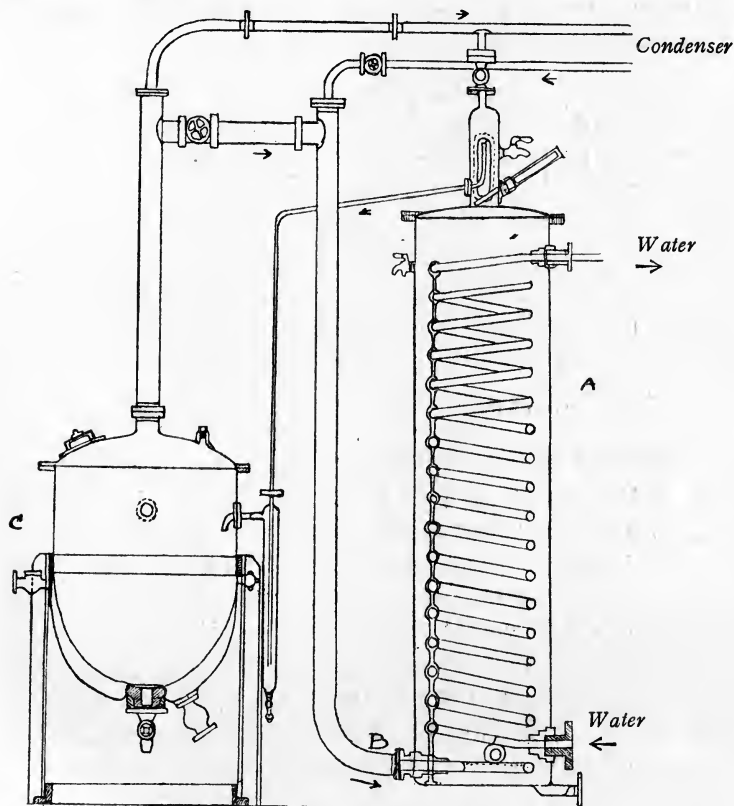For the extraction of an aqueous liquid with ether, petrol or other light immiscible solvent the apparatus shown in Fig. 9 is suitable. The liquid to be extracted is placed in A, which is fitted with an efficient cooling coil. The

solvent enters at B either as a liquid or vapour and overflows into the still C, from which the extract is finally removed.

MORPHINE $C_{17}H_{19}O_3N$. 285.—By the assiduous work of many chemists the constitution of morphine has been in the main elucidated; there remains, however, a choice to be made between several formulæ which explain satisfactorily its known reactions. Of those formulæ, the two following are of chief importance :
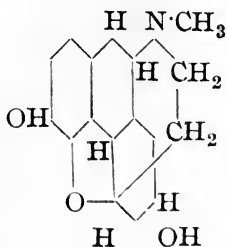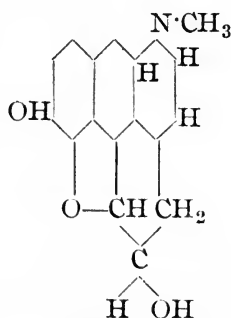
Knorr's formula.   Pschorr's formula.

Morphine is obtained from opium, the dried latex or sap of the unripe fruit of *Papaver somniferum*, the opium poppy, which is cultivated in Asia Minor, Persia, India, and China. Twenty-five alkaloids have so far been isolated from opium, the most important, medicinally, being morphine, next to which comes codeine. Smyrna opium, which comprises the bulk of that employed for manufacturing purposes, contains 9–12 % of morphine, 0·3–1·0 % of codeine, and 4–6 % of narcotine. The recorded alkaloidal content of India, Persian, and Chinese opium is as follows :—

Opium.	Per cent. morphine.	Per cent. narcotine.
Indian	3·2–8·6	3·1–7·1
Persian	6–8	5–7
Chinese	4·3–11·2	1·6–6·6

For the extraction of the alkaloids the opium is worked down to a thin paste with calcium chloride solution and then

extracted with warm water. By this treatment the morphine and other bases are converted into their respective hydrochlorides, whilst the acids with which they were combined in the drug, such as meconic acid, are precipitated as insoluble calcium salts. The insoluble matter is separated by means of a filter press or suction filter, and to prevent oxidation sodium sulphite is added to the filtrate, which is then concentrated, preferably *in vacuo*, to the consistency of a thin syrup. Addition is then made of a concentrated sodium acetate solution, which precipitates *narcotine* and *papaverine*. These are filtered off, a small proportion of alcohol is added and the *morphine* is precipitated from the warmed filtrate by the careful addition of lime in presence of ammonium chloride or by the addition of caustic soda. It is allowed to stand and is removed by filtration. The filtrate is extracted, after cooling, with benzene or chloroform, whereby *codeine* is removed. It is isolated by extraction with acid and regenerating and crystallising as base from water.

The crude morphine is freed from traces of codeine by washing it with benzene. It is then mixed with thrice its weight of boiling water and treated with the exact quantity of 25 % hydrochloric acid required for neutralisation. To prevent atmospheric oxidation the solution is covered with a layer of petroleum. Morphine hydrochloride crystallises out on cooling, is filtered off, recrystallised from water till pure, and dried at atmospheric temperature. From an aqueous solution of the pure hydrochloride, pure morphine may be obtained by precipitation with ammonia.

Anhydrous morphine melts at 230°. It is soluble in 5000 parts of water at 15°, in 500 parts at 100°, in 300 parts of cold 90 % alcohol, and in 30 parts of boiling alcohol. It dissolves in 200 parts of chloroform and is only very slightly soluble in ether, ethyl acetate, or benzene.

0·2 gram of morphine should form a clear solution in 4 c.c. of caustic potash solution (5 % w/w). A solution of 0·1 gram morphine in 10 c.c. of 10 % hydrochloric acid should afford no red coloration with ferric chloride solution (absence of meconates).

Treated with concentrated sulphuric acid morphine should dissolve to a colourless solution.

SALTS OF MORPHINE

Morphine hydrochloride $C_{17}H_{19}O_3N \cdot HCl + 3H_2O$. 375·4.—White, lustrous, silky needles. Dissolves in 24 parts of water, giving a neutral solution. It should contain 75·5 % of anhydrous morphine. It may best be crystallised from water or dilute alcohol; the presence of ammonium sulphite is of assistance in preventing coloration.

Morphine Acetate $C_{17}H_{19}O_3N$, $CH_3COOH + 3H_2O$. 399. —For the preparation of this salt 10 parts of pure powdered morphine are mixed with 30 parts of hot water and 7 parts of 30 % acetic acid. The solution is filtered hot and evaporated *in vacuo* at 50° to 20 parts. It is cooled, seeded with a crystal of morphine acetate and kept in a cold place. Access of air should be prevented, by a layer of petroleum or by other means. Morphine acetate crystallises out and is dried at atmospheric temperature.

A light, white, crystalline powder. Dissolves in 3 parts of water to a solution which becomes perfectly clear on addition of a small quantity of acetic acid. To obtain the salt completely soluble in water it is necessary to crystallise it from a slight excess of acetic acid and to dry with great caution.

Morphine acetate should contain at least 71 % of morphine.

Morphine Sulphate $(C_{17}H_{19}O_3N)_2$, $H_2SO_4 + 5H_2O$. 758. —Forms colourless acicular crystals, soluble in 21 parts of water. It is prepared in the same way as morphine hydrochloride and is crystallised from water in the presence of ammonium sulphite.

Morphine Tartrate $(C_{17}H_{19}O_3N)_2$, $C_4H_6O_6 + 3H_2O$, 774, is prepared by dissolving morphine in the theoretical quantity of tartaric acid in water, from which it separates on cooling as a white crystalline powder, soluble in 10 parts of water. Excess of tartaric acid must be avoided because the acid

tartrate which is then produced is sparingly soluble and separates with the neutral tartrate on cooling.

Morphine possesses the power simultaneously to exercise a depressant, narcotic action on the brain and a stimulating action on the spinal cord. It is also analgesic, slows the respiration, but has little effect on the circulation.

It is widely employed as an hypnotic, being usually administered by hypodermic injection of one of its salts. Morphine acts more quickly than opium, and is less likely to disturb the digestion or to cause headache and nausea.

Codeine $C_{18}H_{21}O_3N$. 299.—
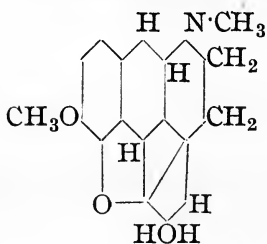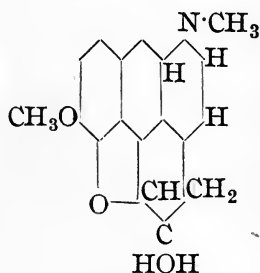
Knorr's formula.   Pschorr's formula.

Codeine is a methyl ether of morphine. It occurs in opium in amounts varying from 0·1 % to 3·0 % and is isolated therefrom in the way already described (*see* Morphine).

Much of the codeine of commerce, however, is prepared synthetically by the methylation of morphine.

The following methylating agents have been proposed :

Methyl iodide (*Compt. Rend.* **92**, 1140, 1228 ; **93**, 67, 217, 591).

Salts of methyl sulphuric acid (D. R. P. 39887).

Nitrosomethyl urethane, or diazomethane, (D. R. PP. 92789, 95644, 96145).

Dimethyl sulphate (D. R. P. 102634).

Methyl phosphate (D. R. P. 107225).

Methyl nitrate (D. R. P. 108075).

p-toluene sulphon nitrosomethyl amide (D. R. P. 224388).

Methyl sulphite (D. R. P. 214783).

Methyl benzene (or toluene), sulphonate (D. R. P. 131980).

(1) *Employing Dimethyl Sulphate* (D. R. P. 102634).—Morphine, 100 parts, is dissolved in a solution of 8·7 parts of sodium in 700 parts of methyl alcohol, and the solution treated with 41·6 parts of dimethyl sulphate and gently warmed. Sodium methyl sulphate separates, and is filtered off. The filtrate is freed from methyl alcohol by distillation, the residue dissolved in water, made alkaline with ammonia, and the codeine extracted with benzene, from the solution in which it is obtained, after removal of the bulk of the solvent, in small glistening crystals.

(2) *From Nitroso Methyl Urethane.*—A 33 % aqueous methylamine solution is reacted in the cold with methyl (or ethyl) chloroformate.
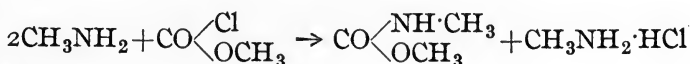
$$2CH_3NH_2 + CO{<}^{Cl}_{OCH_3} \rightarrow CO{<}^{NH \cdot CH_3}_{OCH_3} + CH_3NH_2 \cdot HCl$$
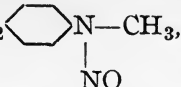
The reaction mixture is extracted with ether, and the extract distilled. B.p. 158°. On treatment with sodium nitrite and sulphuric acid, nitroso methyl urethane

$$CO{<}^{\overset{\displaystyle NO}{\overset{\displaystyle |}{N{-}CH_3}}}_{OCH_3}$$
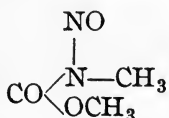
is formed (*R. Trav. Chim.* **7**, 353; **9**, 139), and is extracted with ether.

According to D. R. P. 95644, 285 grams of morphine and 132 grams of nitroso methyl urethane are dissolved in 1000 grams of methyl alcohol. With stirring, a solution of 50 grams of KOH in 800 grams of methyl alcohol is slowly added. The methyl alcohol is then distilled off, and the codeine extracted from the residue with benzol and purified by recrystallisation.

(3) *From Diazomethane.*—Diazomethane is prepared by warming 1 volume of nitroso methyl urethane with 1·2 volumes of a 25 % solution of KOH in methyl alcohol (*Ber.* **27**, 1888; **28**, 856), and is evolved in the form of a yellow gas, which is absorbed in dry ether. It can also be made from

p-nitrophenylnitrosomethylamine $NO_2\langle\underset{\underset{\overset{|}{NO}}{}}{}\rangle N{-}CH_3$, which

decomposes, on treatment with alkali, into diazomethane and sodium p-nitrophenate.

Morphine, 1 molecule, dissolved in absolute methyl alcohol, is allowed to flow into a cooled ethereal solution of diazo methane. When evolution of nitrogen has ceased, and the colour has disappeared, the solvent is distilled off and the codeine purified. (D. R. P. 92789.)

$$C_{17}H_{18}O_2N{\cdot}OH + CH_2{\langle}\overset{N}{\underset{N}{\|}} \rightarrow C_{17}H_{18}O_2N{\cdot}OCH_3 + N_2$$
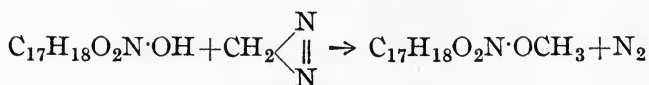
Codeine forms small glistening crystals; m.p. 155°. Soluble in 80 parts of cold, and in 24 parts of boiling, water; in 12 parts of benzene, 2 parts of chloroform, 58 parts of ether, and in 2 parts of 90 % alcohol.

Codeine should dissolve without colour formation in cold concentrated sulphuric acid. A saturated aqueous solution should not be coloured blue by ferric chloride, and should gradually afford, on acidification with hydrochloric acid and treatment with ferric chloride and dilute potassium ferricyanide, only a dirty green, but no blue, colour (absence of morphine).

Codeine Phosphate $C_{18}H_{21}O_3N{\cdot}H_3PO_4 + 2H_2O$. 433.— Codeine phosphate is the most soluble salt of codeine and is the form in which the alkaloid is most usually administered. It is prepared by neutralising codeine with the calculated quantity of 25 % phosphoric acid and adding 90 % alcohol to the solution, when the phosphate is precipitated as a white crystalline powder.

Codeine phosphate dissolves in 4 parts of water at ordinary temperature and in 200 parts of 90 % alcohol. The aqueous solution possesses a feebly acid reaction to litmus. It should answer the tests prescribed for codeine.

Codeine is used to stop, or lessen, glycosuria in diabetes; in the treatment of irritant coughs; for abdominal and ovarian pain, and as a mild hypnotic.

Codeine Hydrochloride $C_{18}H_{21}O_3N \cdot HCl \cdot 2H_2O$, 371·4, forms a white crystalline powder soluble in 20 parts of water.

Codeine Sulphate $(C_{18}H_{21}O_3N)_2H_2SO_45H_2O$, 678·6, may be obtained in fine needles by crystallisation from water, in which it is very soluble. It readily loses its water of crystallisation.

APOMORPHINE $C_{17}H_{17}O_2N$.   267.
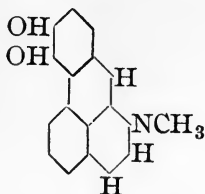
Apomorphine is derived from morphine by abstraction of the elements of water.

The best published method of preparation is still that of the discoverers of this substance (Matthieson & Wright, *Annalen*, 1870, Suppl. **7**, 170, 177), but by it very indifferent yields may be obtained.

Morphine, 1 part, is heated under pressure with 10 parts of 25 % HCl for 2–3 hours at 140°–150°. When cold, the solution is treated with a slight excess of sodium bicarbonate, and extracted with ether, benzene or chloroform, air being excluded. The apomorphine is obtained, as hydrochloride, when the resulting solution is agitated with concentrated hydrochloric acid, and the salt is purified by recrystallisation from water.

Apomorphine hydrochloride $C_{17}H_{17}NO_2 \cdot HCl\frac{1}{2}H_2O$, occurs as small white or greyish-white needle-shaped crystals, soluble in 60 parts of cold water and in 50 parts of alcohol, 90 %. On exposure to air and light it turns green.

The aqueous solution (1 : 100) should be neutral to litmus, or only faintly acid, and almost colourless. Apomorphine hydrochloride is soluble in 5 parts of alcohol. It is a non-irritant emetic and is the most reliable drug known for this purpose. It is usually administered hypodermically, but may be given by the mouth also. It takes effect promptly

(2 or 3 minutes) without production of much preceding nausea or unpleasant by-effects. It acts as a stimulant of the central nervous system, particularly of the vomiting centre of the medulla oblongata.

NARCOTINE $C_{22}H_{23}O_7N$. 413.—The mixture of narcotine and papaverine precipitated by sodium acetate from the solution of the hydrochlorides of the mixed alkaloids from opium (see Morphine) is treated with oxalic acid solution in sufficient quantity to form the acid oxalates. Narcotine acid oxalate dissolves, papaverine acid oxalate remains mostly undissolved and is filtered off. The narcotine is precipitated from the filtrate by ammonia and is purified by recrystallisation of the alkaloid from alcohol.

Colourless needles; m.p. 176°. Insoluble in water, soluble in 100 parts of cold alcohol, in 170 parts of ether, and in 22 parts of benzene. Readily soluble in chloroform and in hot alcohol. Narcotine possesses no narcotic properties; it is little used in medicine, but is sometimes given as a substitute for quinine, as an antiperiodic in ague.

It is employed for the preparation of *cotarnine*, which it affords on oxidation.

COTARNINE $C_{12}H_{15}O_4N$. 239.

$$CH_2\!\!\begin{array}{c}O\\O\end{array}\!\!\begin{array}{c}CH_2\\ \\CHO\end{array}\!\!CH_2-NH-CH_3$$
$$\underset{OCH_3}{|}$$
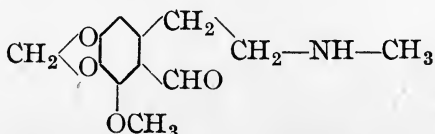
Cotarnine is obtained by oxidising narcotine with nitric acid, opianic acid being produced at the same time (Anderson, *Ann.* **86**, 187(1853)). One part of narcotine is dissolved in 8 parts of water and 2·8 parts of nitric acid (sp.gr. 1·4) and the mixture warmed to 49°. When nitrous fumes have ceased to be evolved, the solution is cooled and filtered; the cotarnine is precipitated by the addition of caustic alkali solution, and purified by recrystallisation from benzene, or by conversion into the hydrochloride. (*Ann.* **86**, 187.)

Small needles, m.p. 132°, readily soluble in alcohol or ether, sparingly soluble in water.

Cotarnine Hydrochloride $C_{12}H_{14}O_3NCl + 2H_2O$, is employed in medicine under the name "Stypticine."

A pale yellow, crystalline powder, soluble in water and alcohol. It is used as an internal styptic, principally for arresting uterine hæmorrhage. It acts directly on the uterus, causing contraction.

Cotarnine Phthalate, employed for the same purpose, is known as "Styptol."

HYDRASTINE $C_{21}H_{21}O_6N$.   383.
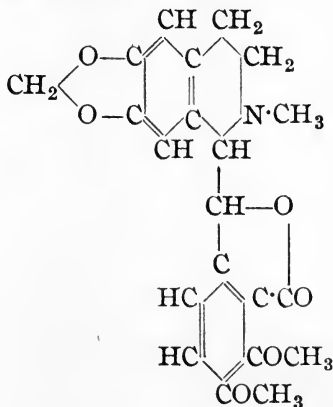
Hydrastine is prepared from the root of *Hydrastis Canadensis*, or Golden Seal, a plant which is indigenous to North America and is to a small extent cultivated there. The dried rhizomes and rootlets contain 2·5 to 4·0 % of hydrastine, 3–4 % of berberine, and a small quantity of canadine. The powdered root is extracted exhaustively with hot water, acidified with acetic acid, or with alcohol. The extract is evaporated *in vacuo* to a thin syrup. Two to three volumes of 20 % sulphuric acid are added, when crystalline berberine acid sulphate separates. The crude sulphate is filtered off and dissolved in the minimum quantity of boiling water ; the hot solution is mixed with an equal volume of alcohol, and concentrated sulphuric acid to the amount of 1/50th the volume of the solution is added. Berberine acid sulphate $C_{20}H_{17}O_4N \cdot H_2SO_4$ crystallises out and is filtered off. The filtrates from the berberine

sulphate are freed from alcohol and made alkaline with ammonia, when hydrastine is precipitated. This is filtered off and purified by crystallisation, first from ethyl acetate and then from a mixture of chloroform and alcohol. The alkaloid when pure melts at 133° and is colourless ; a yellow colour usually indicates the presence of canadine or berberine, but the last trace of colour can only be removed by repeated purification.

An alternative method of removing berberine is to dissolve the alkaloid in ether or toluene, filter off the insoluble berberine and subsequently to extract the base from the solvent with dilute acid.

Hydrastine acid oxalate and hydrastine acid tartrate may be recrystallised from hot water, and being but sparingly soluble in cold water they may usefully be employed in alternative methods of purification, especially for the removal of canadine, which is apt to remain associated with hydrastine.

Hydrastine Hydrochloride $C_{21}H_{21}O_6N \cdot HCl$, 419·4, is prepared by passing dry hydrochloric acid gas into an ethereal solution of the base, or by drying down an alcoholic solution of the salt obtained by neutralisation.

Hydrastine hydrochloride is a white or very pale yellow hygroscopic crystalline powder, melting at 116°, readily soluble in water, alcohol and in chloroform.

Hydrastine is poisonous in large doses. It resembles strychnine in increasing reflex irritability. If injected it causes contraction of the uterus, and has been used as an ecbolic to induce premature labour. *See, Ber.* (1886), **19**, 2798; *C. & D.* (1901), **59**, 152; *Arch. Pharm.* (1888), **226**, 329.

HYDRASTININE $C_{11}H_{13}O_3N$. 207.
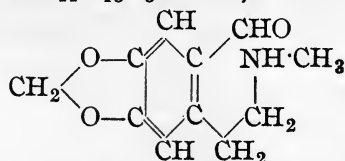
Hydrastinine does not occur naturally, but is prepared by the oxidation of hydrastine, or from narcotine through cotarnine.

From Hydrastine.—Hydrastinine is obtained from hydrastine as follows (*Ber.* (1887), **20**, 88) :—10 parts of hydrastine are heated with a mixture of 25 parts of water and 50 parts by vol. of nitric acid (sp.gr. 1·3), at 50°–60°, until a test-portion ho longer gives a precipitate when treated with ammonia. The solution is then cooled, made slightly alkaline with caustic alkali, the hydrastinine extracted with chloroform or with ether, and the solvent removed. The base is then recrystallised from light petroleum and ether.

The hydrochloride is prepared by neutralising an alcoholic solution of the base with hydrochloric acid and may be crystallised from alcohol.

From Narcotine.—Cotarnine is first prepared (see method given on page 59) and is reduced to hydrocotarnine by adding sodium amalgam to a solution of the base in dilute hydrochloric acid. The reaction proceeds almost quantitatively (*Ber.* **24**, 2734).

Cotarnine.

Hydrocotarnine.   Hydrohydrastinine.
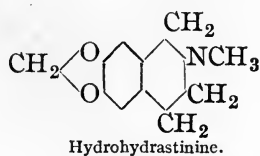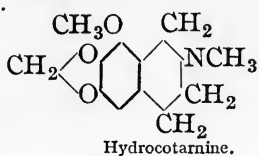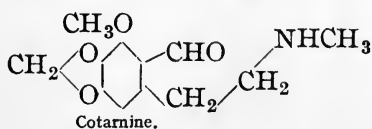
HYDROHYDRASTININE is prepared from hydrocotarnine according to the method of Pyman and Remfry (*Trans. J. Chem. Soc.* **101**, 1601) : 120 parts of crude hydrocotarnine are dissolved in 450 volumes of dry fusel oil (b.p. 122°–132°). To one-third of the solution, heated to boiling, are added 180 parts of sodium. When this has melted the remainder of the solution is added in the course of 20 minutes, when the temperature rises to 155°–160°. Dry fusel oil, 2500 parts, is run in, in a constant stream, in the course of 100 minutes, by which time nearly all the sodium has dissolved. The solution is then cooled, separated from unchanged sodium, and washed with dilute caustic soda to

remove phenolic bases. The hydrocotarnine is then extracted with hydrochloric acid, the acid solution made alkaline and shaken out with chloroform. After removal of the solvent the residue is dissolved in 300 parts of alcohol and the solution made slightly acid by addition of 30 % hydrobromic acid. On standing, 65–70 parts of hydrohydrastinine hydrobromide crystallise out.

Hydrohydrastinine is then treated in dilute sulphuric acid solution with a solution of potassium bichromate and thus oxidised to hydrastinine (*Ber.* (1887), **20**, 2403).

Another synthesis of hydrastinine is described by Decker (D. R. P. 234850). Homopiperonylamine is converted to its formyl derivative which, when heated with phosphoric oxide, yields 6 : 7-methylenedioxy-3 : 4-dihydro *iso* quinoline. The latter on treatment with methyl iodide gives hydrastinine.

Methylenedioxy - ω - nitrostyrol $CH_2 \underset{O}{\overset{O}{<}} \bigcirc CH=CHNO_2$,
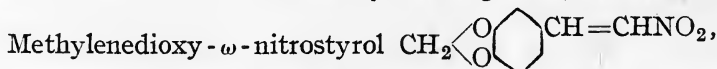
a condensation product of piperonal and nitromethane, 75 parts, is dissolved in a mixture of 300 parts of alcohol and 300 parts of acetic acid. Zinc dust, 150 parts, is gradually added, and after reduction is complete the zinc is filtered off. The filtrate is treated with a further quantity, 600 parts, of a mixture of equal volumes of alcohol and acetic acid, and then, gradually, with 1800 parts of 4 % sodium amalgam. After cooling, 800 parts of water are added, and unchanged homopiperonal-oxime allowed to crystallise out. The filtrate from this is made alkaline with caustic soda and the base (homopiperonylamine) extracted with a solvent and distilled. B.p. 145° at 17 mm. (D. R. P. 245523).

From this is prepared formyl homopiperonylamine (*Ber.* **41**, 2752) by heating the formate at 160°–170°.

To obtain hydrastinine, 10 parts of formyl homopiperonylamine are dissolved in 70 parts of toluol and boiled with 15 parts of phosphorus pentoxide. The resulting insoluble

product, $CH_2 \underset{O}{\overset{O}{<}} \bigcirc \overset{\overset{CH}{\big|}}{\underset{\underset{CH_2}{\big|}}{\bigcirc}} \overset{N}{\underset{CH_2}{}}$, is filtered off, dissolved in 40
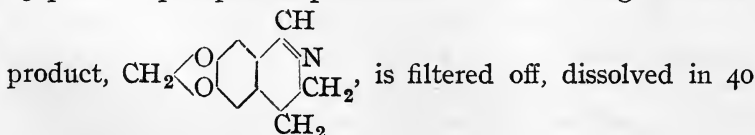
parts of xylene and boiled with 8 parts of dimethyl sulphate. On cooling, hydrastinine methyl sulphate separates. (D. R. P. 234850.)

A further partial synthesis has been effected, employing berberine as the initial material (D. R. P. 241136). Benzyldihydroberberine, prepared (D. R. P. 179212) from berberine chloride and benzyl magnesium bromide, 50 parts, is dissolved in 300 volumes of alcohol and 350 volumes of concentrated hydrochloric acid. The solution is boiled, and treated with 150–200 parts of tinfoil. Heating is continued for 5–10 hours, whereupon the tin double salt of the resulting base, benzyltetrahydroberberine, separates. This is filtered off and digested with ammonium sulphide solution in excess. The undissolved base is filtered off, dried, and extracted with chloroform. (M.p. 163°–165°.)

Benzyltetrahydroberberine, 100 parts, is heated with 100 volumes of methyl iodide, for 4–5 hours at 100°. The methiodide which results is washed with alcohol, added (60 parts) to 200 volumes of 50 % alcohol in which 40 parts of freshly precipitated silver oxide are suspended. After digestion at 50° for a half-hour the silver iodide is filtered off, the solution concentrated till an oil separates, treated with 35 parts of " stick " potash, and boiled for some time. After cooling, the crystalline product is filtered off, washed with cold alcohol and recrystallised from this solvent. (M.p. 121°–122°.)

The base (2 parts) is dissolved in 4 volumes of glacial acetic acid which has been distilled over sodium bichromate, and a solution of 1·5 parts of this salt in 15 volumes of 50 % acetic acid added at once. The mixture is kept at 90° for 2 hours, or until completely green. After addition of a little alcohol to complete reduction of the bichromate, water is added, and sodium carbonate until alkaline. A reddish gum separates and is removed. On heating, chromium oxide is precipitated, and is filtered off. The filtrate is made strongly alkaline with caustic soda and the hydrastinine extracted with ether, from which it is subsequently obtained by evaporation. The yield is said to be 78 %.

Hydrastinine forms white crystals (m.p. 117°) which are readily soluble in alcohol, ether, benzene and light petroleum ; they dissolve in water to form an alkaline solution which is fluorescent.

Hydrastinine hydrochloride is the salt employed in medicine, and forms faintly yellow needles readily soluble in water and showing a blue fluorescence in dilute solution.

It exerts a powerful action on the uterus, causing rhythmic contraction, and for this purpose is to be regarded as of greater value than hydrastine.

EMETINE $C_{29}H_{40}O_4N_2$. 480.—The chief source of emetine is the root of *Psychotria Ipecacuanha*, a plant indigenous to South America and cultivated in Selangor, Federated Malay States. The root from the latter source is known as " Johore " ipecacuanha ; that from Brazil is marketed under the names of " Rio," " Matto Grosso," or " Minas," whilst from Colombia is derived another species of ipecacuanha, *Psychotria acuminata*, the root of which is commonly sold as Carthagena ipecacuanha. Brazilian and Johore roots contain up to 2·5 % of total alkaloids, in the ratio, approximately, of emetine 72, cephæline 26, and psychotrine 2 ; whilst Carthagena ipecacuanha contains up to 2·0 % of alkaloid in the proportion—emetine 40, cephæline 57, and psychotrine 3. Two other alkaloids have been found in ipecacuanha, emetamine and psychotrine O-methylether.

For the preparation of emetine the Brazilian or Johore root is preferably employed. The drug is thoroughly powdered and extracted with hot alcohol. The later stages of the extraction proceed only slowly and may be accelerated by a very cautious addition of alkali. When the root has been exhausted, the combined alcoholic extracts are acidified with hydrochloric acid, and the alcohol distilled off. The residue is diluted with water, filtered from fat, etc., and made alkaline with ammonia ; the alkaloids are then extracted with chloroform or ether. Before the removal of the solvent the extract is freed from cephæline by treatment with caustic soda solution, in which it is soluble. The remaining emetine

is extracted with hydrobromic acid and purified by recrystallisation in the form of hydrobromide and as hydrochloride from water. Emetine base cannot be crystallised; it is readily soluble in alcohol, ether, acetone and chloroform, less so in benzene or petroleum. When dry the amorphous base melts at 74°.

Emetine Hydrobromide $C_{29}H_{40}O_4N_2 \cdot 2HBr + 4H_2O$, 714, crystallises in long slender needles sparingly soluble in water and less soluble in dilute hydrobromic acid. It has not a characteristic melting point, but fuses between 245° and 265°.

Emetine Hydrochloride $C_{29}H_{40}O_4N_2 \cdot 2HCl \cdot 7H_2O$, 679, crystallises in white powdery needles, soluble in 8 parts of water at 18°, less soluble in the presence of free hydrochloric acid. Soluble in alcohol and chloroform. It has not a characteristic melting point, but melts between 235° and 255°.

Preparation of Emetine from Cephæline.—Cephæline not being of use in medicine, may be utilised for the preparation of a further quantity of emetine by the process of methylation. The cephæline is recovered as alkaloid from the caustic soda solution which results from the purification of emetine as described above. For this purpose sodium bicarbonate is added and the mixture extracted with chloroform. The residue, after removing chloroform by distillation, is dissolved in hydrochloric acid, 5 %, and allowed to crystallise; the cephæline hydrochloride is then filtered off and converted to base with sodium carbonate and extracted with chloroform. The dried chloroform extract is dissolved (Fig. 10), in a solution of $\frac{1}{10}$th its weight of sodium in 10 times its weight of dry fusel oil (boiling at 130°–140°), $\frac{4}{10}$ths its weight of anhydrous sodium methyl sulphate is then added and the mixture boiled under a reflux condenser for two hours. By extracting the fusel oil with dilute hydrochloric acid, emetine and unchanged cephæline are obtained as hydrochlorides and are separated as described above. (*J. Chem. Soc.*, **1913**, 1620.) (Eng. Pats. 14677 and 17483.)

The methylation of cephæline may also be conveniently

effected by the use of nascent diazo-methane (D. R. P. 298678).

Emetine has a strong local constricting effect upon blood
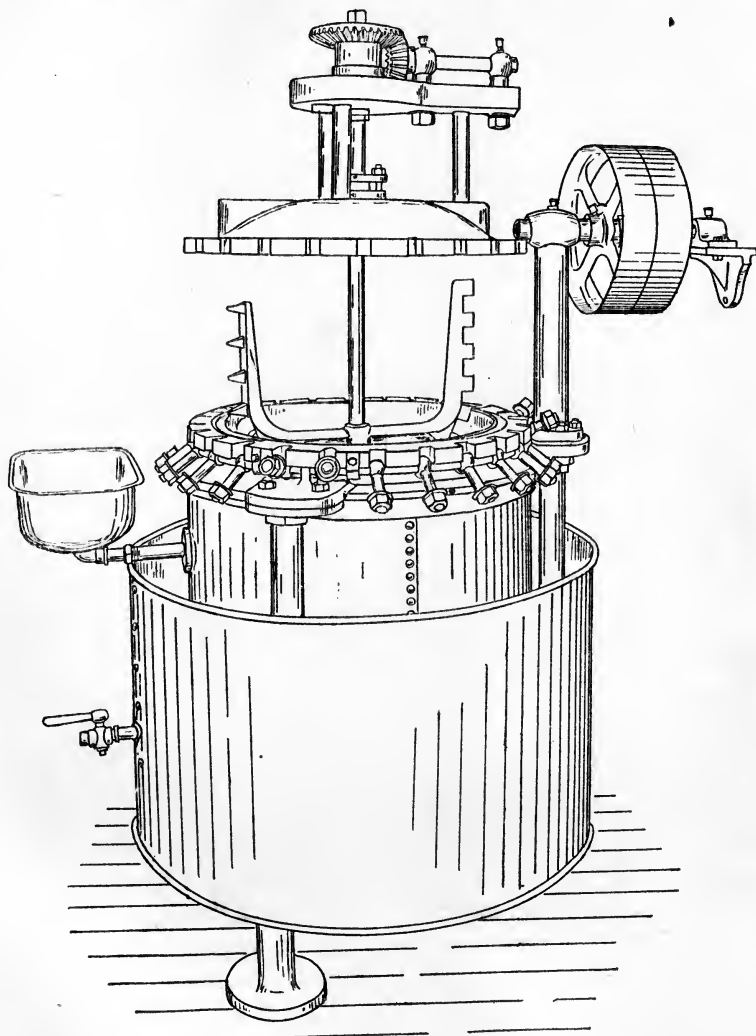

FIG. 10.—Reaction vessel for alkylation.

vessels and powerful irritant action when taken internally, promoting copious salivary secretion and vomiting. It is

employed as expectorant and emetic. It has a wider application in the treatment of amœbic dysentery, for which purpose the hydrobromide or hydrochloride may be injected hypodermically, or the insoluble double bismuth iodide may be administered internally.

HYOSCYAMINE AND ATROPINE $C_{17}H_{23}O_3N$.   289.

$$CH_2-CH-\!\!-\!\!-CH_2$$
$$\quad\quad|\quad\quad\quad\quad|$$
$$\quad N-CH_3\quad CH-O-CO-CH\!\!<^{CH_2OH}_{C_6H_5}$$
$$\quad\quad|\quad\quad\quad\quad|$$
$$CH_2-CH-\!\!-\!\!-CH_2$$
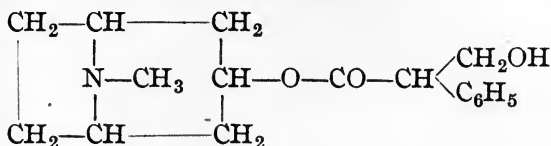
Atropine is the optically inactive mixture of dextro- and lævo-hyoscyamine. Lævo-hyoscyamine alone occurs in nature. The best source of hyoscyamine is a variety of henbane indigenous in Egypt, Soudan and India, known as *Hyoscyamus muticus*, in the various parts of which it has been shown to be present in the following proportions: leaves $1\cdot4$ %; stems $0\cdot6$ %; seeds $0\cdot87-1\cdot34$ %. Atropine is also manufactured from the root of *Scopolia carniolica*, in which hyoscyamine is present to the extent of $0\cdot43-0\cdot51$ %; and from *Atropa belladonna*, the leaves of which contain, on the average, $0\cdot4$ %, and the roots $0\cdot5$ %, of hyoscyamine. Many other solanaceous plants of the *Datura* species contain these alkaloids, in varying, and smaller, amounts, often associated with hyoscine or scopolamine.

The drug should be dried immediately after collection and should be extracted as soon as possible, as the alkaloid content gradually diminishes on keeping.

For the manufacture of atropine and hyoscyamine the drug is powdered and extracted, in a copper extractor, by percolation with hot alcohol (S.V.M.), until free from alkaloid. The alcohol is removed from the extract by distillation, preferably under somewhat diminished pressure, and the syrupy extract is allowed to flow, in a thin stream, and with good stirring, into very dilute ($0\cdot5-1\cdot0$ %) acid, hydrochloric or sulphuric. The aqueous portion is separated from undissolved resinous matter, etc., and is further freed from impurity by being shaken out with petrol. It is then made neutral,

or faintly alkaline, by addition of ammonia solution, and set aside for a time, when a quantity of resinous material is precipitated and removed. An excess of ammonia is then added, whereby the alkaloids are precipitated. They are extracted by shaking out with chloroform, and are finally freed from resinous and other impurity by being dissolved out of the chloroform extract with dilute acid, reprecipitated with ammonia, and again extracted into chloroform. The solvent is removed by distillation ; and the treatment of the mixed alkaloids, consisting mainly of *l*-hyoscyamine, with a little atropine, and possibly hyoscine, varies as hyoscyamine or atropine is required.

The alkaloid is converted by neutralisation with the required quantity of oxalic acid into the oxalate $(B)_2H_2C_2O_4$ (*see Trans. Chem. Soc.* (1912), **101**, 946).

This is recrystallised from water until it has the melting point of pure *l*-hyoscyamine oxalate (176°). The base is then obtained by dissolving the oxalate in water, making alkaline with ammonia and extracting with chloroform. After removing the solvent, the neutral sulphate is prepared and crystallised from alcohol or moist acetone.

Lævo-Hyoscyamine Sulphate

$$(C_{17}H_{23}O_3N)_2H_2SO_4 + 2H_2O. \quad 712.$$

White, slender, hygroscopic needles. M.p. 206°, $[a]_D -21°$. Dissolves in 0·5 part of water and in 4·5 parts of 90 % alcohol ; very slightly soluble in chloroform. The aqueous solution is neutral in reaction, and should afford no precipitate with platinic chloride solution (absence of foreign alkaloids). Hyoscyamine sulphate should give no colour with concentrated sulphuric acid.

Atropine Sulphate $(C_{17}H_{23}O_3N)_2 \cdot H_2SO_4$. 676.—The crude alkaloid, together with that regenerated from the mother liquors after the removal of *l*-hyoscyamine oxalate, is racemised by dissolving 52 parts in 520 volumes of 95 % alcohol containing 4·16 parts of sodium hydroxide (*loc. cit.*). The solution is allowed to stand, at room temperature, until it shows no optical activity, after which it

is neutralised with oxalic acid, the alcohol is removed, and the oxalate recrystallised from water until a melting point of 196°–197° is obtained. From this the base is regenerated and converted into the sulphate, as described above in the case of hyoscyamine.

Atropine sulphate is a white crystalline powder. M.p. 194°. It dissolves in 0·4 part of water, and in 4 parts of 90 % alcohol. The aqueous solution is neutral in reaction, and should be optically inactive.

No colour should be imparted by the salt to sulphuric acid.

Three cubic centimetres of a 1 in 60 solution should yield no precipitate when mixed with 1 c.c. of ammonia solution (10 %).

Atropine $C_{17}H_{23}O_3N$, 289, is prepared by regenerating the base from the pure oxalate and crystallising from aqueous alcohol.

Atropine crystallises in colourless acicular crystals. M.p. 115·5°. It dissolves in 450 parts of water at 25° and in 87 parts at 80°; in 3 parts of 90 % alcohol and in 1 part of chloroform. It should be optically inactive and no colour should be developed on treatment with sulphuric acid.

Atropine and *l*-hyoscyamine are employed chiefly to dilate the pupil of the eye and paralyse the accommodation. The former effect is due to paralysis of the motor nerve terminations in the circular muscle of the iris ; the latter by the action of the alkaloid on the nerve endings in the ciliary muscle. The two alkaloids have qualitatively the same action, but pure *l*-hyoscyamine has about fifty times the mydriatic power of atropine.

Atropine is frequently administered hypodermically with morphine, to counteract the undesirable effects of the latter. It is given hypodermically also, to diminish the sweating of phthisis, in spasmodic asthma, narcotic poisoning, etc.

Hyoscyamine is generally used in the form of its hydrobromide or sulphate.

HYOSCINE OR SCOPOLAMINE $C_{17}H_{21}O_4N$.   303.

$$\begin{array}{c} CH_2OH \\ C_6H_5 \end{array}\!\!\!\!> CH-CO-OCHCH\!-\!\!-\!CH_2$$

N-CH_3 CH—

CH-CH-CH_2

——O——

King.

or

$$\begin{array}{c} CH_2OH \\ C_6H_5 \end{array}\!\!\!\!> CH-CO-OCH-CH\!-\!\!-\!CH_2$$

NCH_3 CH_2

CH-CH—·—CH

O

Hess.
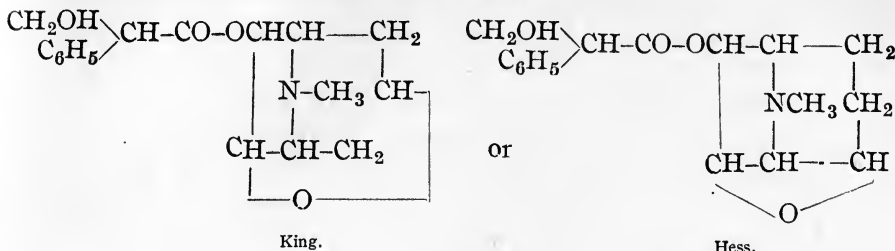
Naturally occurring hyoscine is a combination of lævo-tropic acid with inactive oscine. It is found, mostly in conjunction with hyoscyamine, in many species of *Datura*. In *D. arborea*, *D. fastuosa*, and *D. metel*, the alkaloid consists chiefly of hyoscine ; whilst *D. stramonium* contains princi-pally hyoscyamine, with some hyoscine. It is present also in *Scopolia* and *Hyoscyamus* species, for instance in *Scopolia japonica* and *Hyoscyamus niger*.

Datura metel is probably the most readily available source of hyoscine. The powdered drug is extracted with hot alcohol and the crude alkaloids are isolated in the same way as has been described under *hyoscyamine*, except that sodium bicarbonate is employed, instead of ammonia, for liberating the bases. The alkaloid is neutralised exactly with hydrobromic acid and the solution of the hydrobromide concentrated. The salt which crystallises out on cooling is separated and purified by recrystallisation from water, until of constant melting point.

Hyoscine Hydrobromide $C_{17}H_{21}O_4NHBr\!-\!3H_2O$.   438. —Colourless transparent crystals, which dissolve in 4 parts of water and in 14 parts of 90 % alcohol. Hyoscine hydro-bromide loses 12·3 % of moisture at 100°.

The pure lævo- hydrobromide melts, when anhydrous, at 193° and has a specific rotation of $[a]_D\!-\!22\cdot7°$ (for the hydrated salt). The commercial product is often mixed with inactive hyoscine (m.p. 181°) and has a lower melting point and rotation.

The aqueous solution should be neutral in reaction to litmus, but is frequently slightly acid.

The salt should afford only a faint yellow colour with sulphuric acid. Hyoscine is a valuable hypnotic and sedative, employed in treatment of all forms of violent mania and cerebral excitement. In conjunction with morphine it is administered hypodermically as an anæsthetic prior to an operation. Very little chloroform is required. This treatment is becoming extensively employed in childbirth, and is known as " Twilight Sleep."

Hyoscine also produces mydriasis and paralysis of accommodation ; the effect is obtained more quickly than with hyoscyamine or atropine but is not so lasting.

HOMATROPINE (Mandelyl tropeine) $C_{16}H_{21}O_3N$.   275.

$$CH_2—CH——CH_2$$
$$| \qquad | \qquad |$$
$$NCH_3 \quad CHOCOCH(OH)C_6H_5$$
$$| \qquad |$$
$$CH_2—CH——CH_2$$
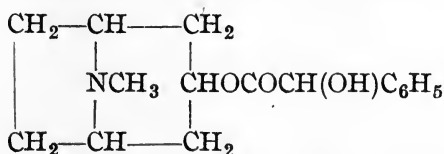
Homatropine is prepared by condensing together mandelic acid and tropine. Tropine is obtained by boiling crude atropine or hyoscyamine sulphate for some hours with an excess of dilute sulphuric or hydrochloric acid or of baryta.

The solution is neutralised, concentrated, and made alkaline by addition of caustic soda, and the base is then shaken out with chloroform and purified by distillation under diminished pressure. B.p. 141° at 3–5 mm.

Fig. 11 illustrates the type of oil-jacketed vacuum still suited for this operation ; the twin receiver is utilised for separating the fractions. The condenser water must be kept at 65° to prevent solidification of the tropine.

The condensation is carried out as follows (*see* D. R. P. 95853, also *Trans. Chem. Soc.*, **95**, 1020).

One molecular equivalent of tropine, 14·2 parts, is mixed with an equivalent of mandelic acid, 13·6 parts, and the mixture heated at 130° in a stream of dry hydrogen chloride, for 7 hours. The product is treated with ammonia and the base extracted with chloroform. It is extracted

from this solution with hydrobromic acid, and the neutral solution of the hydrobromide is concentrated and allowed to crystallise. The separated crystals are purified by recrystallisation from water or alcohol. The base, regenerated

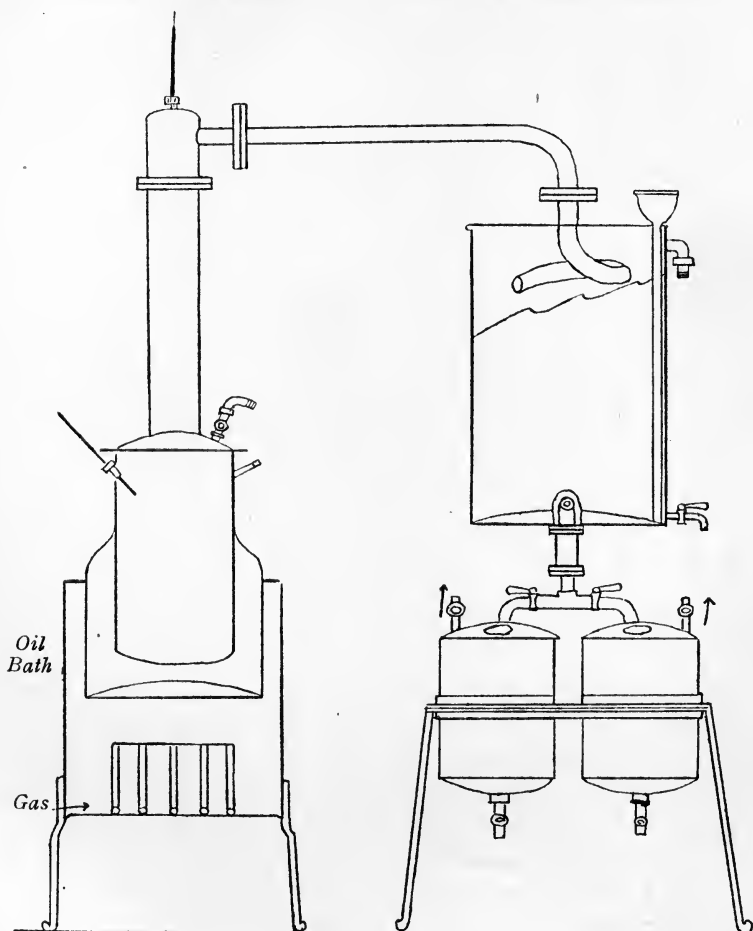FIG. 11.—Vacuum Still, oil-jacketed.

from the purified hydrobromide and crystallised from alcohol, melts at 96°.

Homatropine Hydrobromide $C_{16}H_{21}O_3NHBr$. 356. —Small colourless rhombic prisms. M.p. 214°. Soluble in 6 parts of water, and in 18 parts of 90 % alcohol.

The solutions are neutral to litmus. A 2 % solution should yield no precipitate on the cautious addition of 5 % ammonia solution. Homatropine does not give the Vitali reaction : 0·1 gram of the salt is added to 5 drops of nitric acid and evaporated to dryness in a porcelain dish, when the residue should not be coloured violet upon the addition of a drop of alcoholic potash solution (absence of atropine, etc.).

Homatropine is employed as a mydriatic. It dilates the pupil more rapidly than atropine, and the effects disappear in about a quarter of the time. It is also less toxic than atropine.

THE ALKALOIDS OF CINCHONA BARK

From the various species of cinchona bark which have been investigated, more than twenty alkaloids have been isolated, of which quinine, quinidine, cinchonidine, and cinchonine are medicinally the most important. The variety of cinchona official in the British Pharmacopœia is *Cinchona succirubra*, a " red " cinchona bark, which is cultivated in Java and India. For the manufacture of quinine and associated alkaloids, however, bark from the species *C. ledgeriana* and hybrids of this with *C. succirubra* are mainly employed, these containing higher percentages of alkaloid, of which a larger proportion is quinine.

From figures given in the yearly report of the Dutch Government Cinchona Undertakings, 1904, the average quantities of quinine, cinchonidine, and cinchonine plus amorphous alkaloids contained in the various species cultivated in Java are as follows :—

Species.	Quinine.	Cinchonidine.	Cinchonine + amorphous alkaloids.
	per cent.	per cent.	per cent.
C. ledgeriana . . .	7	0·5	1·25
Hybrid of C. ledgeriana and C. succirubra .	5·5	0·5	2·8
C. succirubra . . .	1·6	1·5	3·4

The bulk of the world's quinine supply is derived from Java cinchona, though an important quantity is now manufactured, under Government auspices, in India.

QUININE $C_{20}H_{24}O_2N_2$. 324.—The method of manufacture of quinine is as follows :

The bark is sun dried, powdered, and ground up with 30 % of its weight of sifted slaked lime and 90 % of a 5 % caustic soda solution. The mixture is extracted in steam-
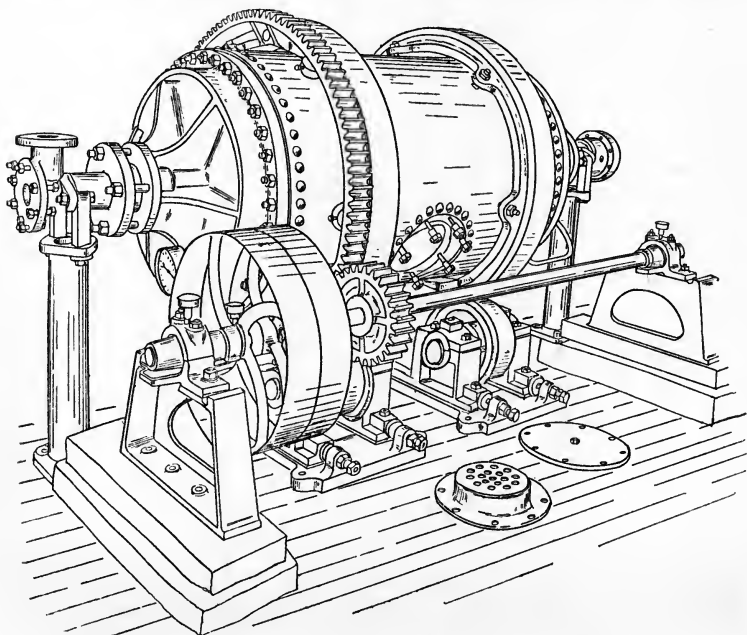
Fig. 12.—Steam-heated ball mill. Manlove.

heated rotating ball mills (Fig. 12), or some other type of vessel provided with powerful stirrers, with hot, high boiling petroleum, which dissolves out the alkaloids. The selection of a suitable petroleum oil possessing good solvent properties is a matter of importance. After several hours the mechanism is stopped and the oil solution separated as completely as possible by decantation. It is replaced by a further quantity, three extractions being made in all. The combined extracts are agitated in a lead-coated washer (Fig. 13) at 90°–100°,

with a 0·45 % aqueous sulphuric acid solution, sufficient in quantity to form the neutral sulphates. The oil is separated whilst the solution is hot, and is used for extracting further quantities of bark. From the aqueous solution, after adjusting the acidity, quinine sulphate crystallises out on cooling. It is purified by being recrystallised from water, using animal charcoal as a decolouriser, until sufficiently free from cinchonidine and cinchonine. Quinine alkaloid is obtained by dissolving the sulphate in 30–40 volumes of water containing sulphuric acid and allowing the solution to flow, with stirring, into a slight excess of dilute sodium carbonate or ammonia. The amorphous precipitate
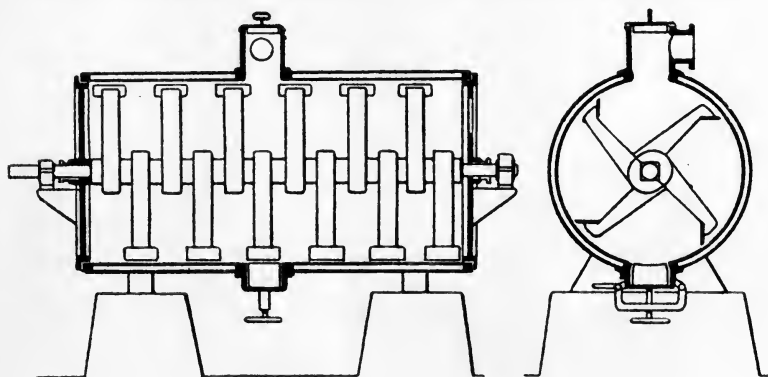
FIG. 13.—Lead-coated washer.

is filtered off, washed until free from sodium or ammonium salts, and dried, first in a centrifugal machine, and subsequently in a dark drying room at a temperature not exceeding 30°.

Quinine is a white granular powder containing about 10 % of water. When anhydrous it melts at 175°. It is sparingly soluble in water (1 in 1700 at 15° and 1 in 900 at 100°). It is more soluble in ammonia solution and less soluble in fixed alkali solutions than in water. It is soluble (1 in 1) in ether. The anhydrous base dissolves in 25 parts of ether, in 2 parts of chloroform, and in 200 parts of benzene.

Quinine Sulphate $(C_{20}H_{24}O_2N_2)_2H_2SO_4 + 7\frac{1}{2}H_2O$. 881.

—The neutral sulphate is the most extensively used salt of quinine. It is commonly sold in the form of light, colourless, silky, needle-shaped crystals, which effloresce in dry air ; but a denser form is occasionally required consisting of larger crystals. Both forms readily lose part of their water of crystallisation if exposed to the air.

Quinine sulphate dissolves in 800 parts of water at 15°, in 25 parts at 100° ; in 6 parts of boiling, and in 100 parts of cold, 90 % alcohol. It is required to comply with the following tests for freedom from cinchonidine and cinchonine.

Ether test : Dissolve 4 grams of the quinine sulphate in 120 c.c. of boiling water. Cool the solution slowly to 50°, with frequent stirring. Separate by filtration the purified quinine sulphate which has crystallised out. Evaporate the filtrate to 10 c.c., and when cool add 5 c.c. of solution of ammonia (sp.gr. 0·959) and 10 c.c. of pure ether, and shake. Set aside in a cool place for 24 hours. Collect the crystals, which consist of cinchonidine and cinchonine together with some quinine, on a tared filter, wash with a little dry ether, dry at 100° and weigh. The weight should be not more than 0·12 gram.

Ammonia test : Two grams of quinine sulphate, dried at 50° for 2 hours, are mixed with 20 c.c. of water, kept with occasional agitation at 60°–65° during 30 minutes, then cooled to 15° and kept at this temperature for 2 hours with occasional agitation. It is then filtered and 5 c.c. of the filtrate measured into a dry test tube. According to the United States Pharmacopœia, 7 c.c. of ammonia (0·958 at 25°) added all at once should produce a clear solution, whilst the German Pharmacopœia stipulates that a clear solution should be produced by 4 c.c. of ammonia of the same strength.

The other most generally used salts of quinine are :

Quinine bisulphate $C_{20}H_{24}O_2N_2H_2SO_4+7H_2O$. 548.

Quinine hydrochloride $C_{20}H_{24}O_2N_2HCl+2H_2O$. 396·4.

Quinine bihydrochloride $C_{20}H_{24}O_2N_22HCl+3H_2O$. 451.

Quinine hydrobromide $C_{20}H_{24}O_2N_2HBr+H_2O$. 423.

Quinine phosphate $(C_{20}H_{24}O_2N_2)_2H_3PO_4+8H_2O$. 890.

All these salts are readily prepared by dissolving quinine in the respective acids, and may be crystallised from water.

Quinine is administered most frequently as a prophylactic against malaria and as a cure for this disease, against which it has for long been regarded as a specific. It possesses antipyretic properties, apparently by direct action on the tissues, and finds much application in general medicine on this account. In small doses it acts as a bitter stomachic and tonic, causing increased secretion of gastric juice in the alimentary canal, with consequent improved appetite and digestion. For this purpose it is often prescribed in the form of a double compound with iron—iron and quinine citrate.

CINCHONIDINE $C_{19}H_{22}ON_2$. 294.—Cinchonidine, together with some quinine, cinchonine, and other alkaloids, remains in the liquors from which quinine sulphate has crystallised. The alkaloids are precipitated by addition of alkali, dried, and extracted repeatedly with small quantities of ether or chloroform, by which treatment cinchonidine, quinidine, and quinine are dissolved out, leaving behind the more sparingly soluble cinchonine. The solution is agitated with hydrochloric acid and the alkaloids converted into their neutral hydrochlorides. The aqueous solution of these is treated with sodium potassium tartrate solution, whereby the cinchonidine is precipitated, mixed with a little quinine, as tartrate. This is separated, treated with aqueous alkali, and the base filtered off and dried *in vacuo* at 40°–45° It is then washed with absolute ether until it no longer affords a green colouration when treated with chlorine water and ammonia solution (thalleioquin reaction) and is purified finally by recrystallisation from alcohol.

Cinchonidine forms colourless leaflets, or prisms. M.p. 206·5°. It dissolves in 188 parts of ether (sp.gr. 0·720), in 16·3 parts of 97 % alcohol, and in 300 parts of 50 % alcohol. It is very slightly soluble in water ; dissolves readily in chloroform. It is not fluorescent in dilute sulphuric acid.

The salts of cinchonidine most commonly employed are cinchonidine hydrobromide ($C_{19}H_{22}ON_2 \cdot HBr + H_2O$), 393; cinchonidine acid hydrobromide ($C_{19}H_{22}ON_2 2HBr + 2H_2O$), 492; and cinchonidine sulphate (($C_{19}H_{22}ON_2)_2H_2SO_4 3H_2O$), 740.

Cinchonidine is used as a substitute for quinine, having a similar, though weaker, action.

CINCHONINE $C_{19}H_{22}ON_2$. 294.—This alkaloid occurs in most species of cinchona.

The crude cinchonine, which remains undissolved on treating with ether or chloroform the alkaloids precipitated from the quinine sulphate mother liquors (*see* Cinchonidine), is recrystallised from alcohol, adding charcoal to decolourise the solution.

Cinchonine forms rhombic prisms. M.p. 264°, $[a]_D +229°$ in dry alcohol. It is very sparingly soluble in water, dissolves in 370 parts of ether (sp.gr. 0·730), in 280 parts of chloroform, in 126 parts of alcohol (sp.gr. 0·852) at 20°.

Cinchonine does not give the thalleioquin reaction and is not fluorescent in dilute sulphuric acid solution. The fact that it is very sparingly soluble in ether and forms a sparingly soluble hydriodide distinguishes it from quinine.

Cinchonine sulphate ($(C_{19}H_{22}ON_2)_2H_2SO_4 + 2H_2O$, 722, is employed in medicine as a substitute for quinine, to which it is preferred by some, but it is much weaker in its action. The dehydrated salts are soluble in chloroform (80 parts), (distinction from quinine and quinidine sulphates).

QUINIDINE $C_{20}H_{24}O_2N_2$. 324.—Quinidine is isomeric with quinine, with which it is associated in various species of cinchona. Quinidine remains dissolved in the liquors from which cinchonidine tartrate has been precipitated (*see* Cinchonidine) and is precipitated from a not too concentrated solution, as the sparingly soluble hydriodide, by addition of potassium iodide solution. The precipitate is treated with ammonia solution, the base dissolved in acetic acid, and the solution decolourised by treatment with charcoal. The quinidine is reprecipitated with ammonia and recrystallised from boiling alcohol.

Anhydrous quinidine melts at 171·5° and is soluble in 35 parts of ether and in 26 parts of alcohol (80 %) at 20°. It is readily soluble in chloroform, sparingly soluble in light petroleum and in water.

Quinidine Sulphate $(C_{20}H_{24}O_2N_2)_2H_2SO_4+2H_2O$.   782. —White silky crystals, soluble in 200 parts of cold water.

When a solution of 0·5 gram dissolved in 10 c.c. of water at 60° is treated with 0·5 gram of potassium iodide, cooled, kept for one hour and filtered, the filtrate should afford no precipitate with ammonia solution (absence of cinchonidine, cinchonine, etc.).

THE ALKALOIDS OF *STRYCHNOS* SPECIES

STRYCHNINE $C_{21}H_{22}O_2N_2$.   334.—Strychnine and Brucine are found in various species of *Strychnos* indigenous to the East Indies and India, the seeds of two of which are employed as a source of these alkaloids, *i.e. Strychnos Ignatii* and *Strychnos Nux-Vomica*. The former contain 2·0 to 2·5 % of total alkaloid, two-thirds of which is said to be strychnine, and the remainder brucine ; in the latter species, although the total alkaloid content is slightly more (2·5 to 3·0 %), somewhat less than one-half of it consists of strychnine. The seeds of a third species, *S. Tieute*, found in Java, contain about 1·5 % of strychnine with only traces of brucine. The beans, on account of their rough, horny nature, cannot readily be powdered, and before they can be subjected to extraction, may best be disintegrated by one of the following methods :—

(1) By steaming under pressure in a boiler.

(2) By passing through suitable rolls, after being softened by a preliminary steeping in hot water.

(3) By powdering in a ball mill after gentle roasting.

The first method is the one generally preferred. The magma thus obtained is made alkaline by treatment with milk of lime and extracted, in a vessel provided with powerful beaters, with hot solvent naphtha. The solution obtained is extracted whilst hot with 5 % sulphuric acid sufficient to

form the neutral sulphates. On cooling, strychnine sulphate, mixed with some brucine sulphate, crystallises out, whilst most of the brucine sulphate, which is more soluble, remains in solution, together with a portion of the strychnine.

The crude crystalline strychnine sulphate is dissolved in hot water, and the alkaloid set free by addition of sodium carbonate solution and recrystallised from alcohol until free from brucine.

Alternatively, the total alkaloid may be precipitated from the solution of the mixed sulphates, washed with successive portions of 25 % alcohol, which extracts most of the brucine, and the strychnine finally obtained pure by crystallisation from 80 % or 90 % alcohol.

Translucent, colourless, rhombic prisms. M.p. 265°.

Very slightly soluble in water or ether ; dissolves in 170 parts of 90 % alcohol, in 250 parts of 70 % alcohol, and in 6 parts of chloroform.

Strychnine should dissolve in concentrated sulphuric acid without colour formation ; it should not be coloured on treatment with cold concentrated nitric acid (absence of brucine).

The more important salts are :—

Strychnine Hydrochloride $C_{21}H_{22}O_2N_2 \cdot HCl + 2H_2O$. 406·4. Soluble in 35 parts of water.

Strychnine Nitrate $C_{21}H_{22}O_2N_2 \cdot HNO_3$. 397. Soluble in 63 parts of water.

Strychnine Sulphate $(C_{21}H_{22}O_2N_2)_2 \cdot H_2SO_4 + 5H_2O$. 856. Dissolves in 48 parts of water.

Strychnine is used in medicine chiefly as a gastric, cardiac, and general tonic. In medicinal doses it slows the heart, raises the blood pressure, and exerts a tonic action upon the digestive organs. It increases peristalsis and is a frequent ingredient of medicine for the cure of chronic constipation. Strychnine has a powerful stimulant action on the central nervous system and is consequently useful in the treatment of reflex or functional paralysis.

BRUCINE $C_{23}H_{26}O_4N_2$. 394.—In order to obtain brucine the alkaloids remaining in the mother liquors after the
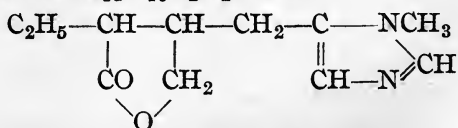
separation of strychnine are converted into the neutral oxalates. These are dried, and extracted at a low temperature with absolute alcohol, whereby strychnine oxalate is dissolved out. The residual brucine oxalate is dissolved in hot water, and after decolourisation with charcoal, the alkaloid is precipitated, dried and extracted with cold acetone, or absolute alcohol. Strychnine being very sparingly soluble, much of it is thus removed. The brucine is finally purified by being recrystallised from dilute (25 %) alcohol until free from strychnine. Alternatively, the total mixed alkaloids obtained from the mother liquors after removal of the strychnine are dried, and the brucine is extracted by treatment with cold acetone, and purified as above by recrystallisation from dilute alcohol.

From this solvent brucine crystallises out in colourless transparent monoclinic crystals containing 4 molecules of water. When anhydrous it melts at 178°. Sparingly soluble in water, readily soluble in acetone and in chloroform; the hydrated compound dissolves in 20 parts of 90 % alcohol.

The absence of strychnine can be proved by warming the alkaloid at 90° with nitric acid (sp.gr. 1·05) until the red colour has disappeared, by which treatment the brucine is destroyed. On making the solution alkaline, extracting it with a mixture of chloroform and ether, and treating the residue, after evaporation of the solvent, with concentrated sulphuric acid and a trace of solid potassium bichromate, strychnine, if present, is revealed by the formation of an intense purple violet colouration, passing from red to yellow.

Brucine is little used in medicine. It resembles strychnine in its physiological action but possesses approximately only one-eighth the toxicity of the latter alkaloid. It also differs from strychnine in having a more powerful curare-like action.

PILOCARPINE $C_{11}H_{16}O_2N_2$.   208.

$$C_2H_5{-}CH{-}CH{-}CH_2{-}C{-\!-\!-}NCH_3$$
$$\underset{\displaystyle \searrow O \swarrow}{\underset{\displaystyle \overset{|}{CO}\quad \overset{|}{CH_2}}{}}\qquad \underset{\displaystyle CH{-}N}{\overset{\displaystyle \|}{}}{\searrow}CH$$
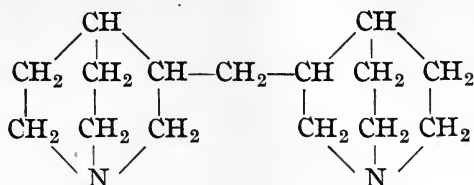
Pilocarpine is a constituent of the leaves of *Pilocarpus*

jaborandi, and *Pilocarpus microphyllus*, plants indigenous to South America. In recent years the so-called jaborandi of commerce has consisted almost entirely of the latter variety. The quantities of crystalline pilocarpine nitrate yielded by samples of *P. jaborandi* and *P. microphyllus* examined by Paul and Cownley (*Pharm. J.* 1896, **IV.**, **3**, 1) were 0·67 % and 0·45 % respectively. For the isolation of the alkaloid powdered jaborandi leaves are exhausted with hot alcohol, the alcohol is distilled off and the residue dissolved in ammoniacal spirit, the solution filtered and again freed from alcohol. It is then poured while hot into heated 1 % hydrochloric acid and allowed to stand during a few days for resin to separate. The pilocarpine is extracted with chloroform from the aqueous extract, after rendering alkaline with ammonia. The chloroform is then removed by distillation and the residual alkaloid is dissolved in a small quantity of alcohol and the solution made acid with nitric acid. A crystal of pilocarpine nitrate is added and the solution allowed to stand until crystallisation is complete. The separated crystals are filtered off and purified by recrystallisation from alcohol.

Pilocarpine Nitrate $C_{11}H_{16}O_2N_2 \cdot HNO_3$, 271, is the salt most commonly used in medicine. It forms white prismatic crystals. M.p. 177°, $[a]_D + 81° - 83°$; soluble in 6–7 parts of water and in 146 parts of alcohol (95 %) at 15°. Addition of ammonia to an aqueous solution of the salt should not afford a precipitate.

Pilocarpine Hydrochloride $C_{11}H_{16}O_2N_2 \cdot HCl$, 244·4, forms white powdery crystals from alcohol. It is very soluble in water and has a hygroscopic tendency. M.p. 203°–204°. Pilocarpine is a powerful diaphoretic and sialogogue. It produces persistent sweating and salivation and is prescribed in the dropsy of Bright's disease, in uræmia, and to remove pleural and peritoneal effusion. It is an antidote in belladonna poisoning, and is a common constituent of lotions and ointments used to increase the growth of hair. It has a depressant action on the heart and requires to be used with caution in cardiac cases.

SPARTEINE $C_{15}H_{26}N_2$.   234.

$$\begin{array}{c} CH \\ \diagup \quad | \quad \diagdown \\ CH_2 \quad CH_2 \quad CH-CH_2-CH \quad CH_2 \quad CH_2 \\ | \quad\quad | \quad\quad | \quad\quad\quad\quad\quad | \quad\quad | \quad\quad | \\ CH_2 \quad CH_2 \quad CH_2 \quad\quad\quad CH_2 \quad CH_2 \quad CH_2 \\ \diagdown \quad | \quad \diagup \quad\quad\quad\quad \diagdown \quad | \quad \diagup \\ N \quad\quad\quad\quad\quad\quad N \end{array}$$

Sparteine is obtained from " broom tops;" the herbaceous branches of the broom, *Cytisus scoparius*, gathered in the spring just before flowering.   Broom tops yield 0·23 to 0·68 % of sparteine, according to the time of collection, being richest in March, and poorest in August, after flowering.

For the extraction of the alkaloid the ground drug, without previous drying, is macerated in the cold for 3 or 4 days with $\dfrac{N}{2}$ dilute sulphuric acid.   The extracts are combined, carefully neutralised, and concentrated to a syrupy consistency.   The mixture is then made alkaline and steam distilled, when the sparteine, being volatile, passes over.   The distillate is neutralised to methyl orange, or iodeosin, with sulphuric acid and evaporated to dryness. The sparteine sulphate so obtained is crystallised, first from water, then from alcohol (50 %).

Sparteine   sulphate $C_{15}H_{26}N_2 \cdot H_2SO_4 5H_2O$.   422.— Colourless prismatic crystals.   When   anhydrous, melts at 136°–138°.   Dissolves in 0·5 part of water, and in 5 parts of 90 % alcohol.   The solutions are lævo-rotary, having $[a]_D$ −22·1°.

No colour should be yielded with sulphuric or nitric acid.   Sparteine sulphate is a cardiac tonic and diuretic. It slows and strengthens the pulse, this action being more rapid but less persistent than that of digitalis.

ESERINE   OR   PHYSOSTIGMINE $C_{15}H_{21}O_2N_3$.   275.— Eserine occurs, associated with eseramine and physovenine, in the seeds (Calabar beans or Ordeal beans) of *Physostigma venenosum*, Balfour, a plant indigenous to West Africa.   The ripe seeds contain about 0·15 to 0·30 % of ether soluble alkaloids.

For the preparation of eserine the crushed beans are exhausted with hot 90 % alcohol. The extract, after removal of the alcohol, is poured while hot, with violent stirring, into 0·1 % sulphuric acid ; it is then allowed to stand until cold and filtered from fat, etc. To the clear aqueous solution is added a slight excess of sodium bicarbonate, and the alkaloid is extracted with ether. The ether is concentrated to a low bulk and shaken into dilute sulphuric acid. The acid extract is separated from the ether and the aqueous liquid carefully neutralised. An excess of sodium salicylate is then added by which eserine salicylate is precipitated. It is purified by repeated crystallisations from alcohol.

Eserine Salicylate $C_{15}H_{21}O_2N_3 \cdot C_7H_6O_3$. 413.—The most stable and convenient salt of eserine is the salicylate, which is made as described above or by neutralising an ethereal solution of the alkaloid with a solution of salicylic acid in the same solvent, when it is precipitated as a crystalline powder. The crystallised salt is dried *in vacuo.*

Colourless acicular crystals. M.p. 186°–187°. Soluble in 130 parts of cold water and in 15 parts of alcohol (90 %).

Eserine Sulphate $(C_{15}H_{21}O_2N_3)_2H_2SO_4$. 648.—Physostigmine sulphate is prepared by exactly neutralising the ethereal solution of the base with a solution of sulphuric acid in absolute alcohol and evaporating the liquid *in vacuo* as quickly as possible.

White, deliquescent, needle-shaped crystals (m.p. 145°), which afford a neutral aqueous solution. It readily turns pink on exposure and is less stable than the salicylate or hydrobromide.

Eserine Hydrobromide $C_{15}H_{21}O_2N_3 \cdot 2HBr$, 437, forms white needle-shaped crystals from alcohol. It is readily soluble in water and is not deliquescent. M.p. 224°–226°.

Salts of physostigmine are employed to contract the pupil of the eye, in ciliary paralysis, glaucoma, etc., in painful affections of the eye, and to break down adhesions due to iritis, its use being alternated with that of atropine. Physostigmine is also used as an antidote in cases of strychnine poisoning.

COLCHICINE $C_{22}H_{25}O_6N$. 399.—Colchicine is obtained from the seeds and corms of *Colchicum autumnale*, the autumn crocus or meadow saffron ; it also occurs in other species of *Colchicum* and *Merendera*. The ripe seeds contain from 0·3 % to 0·8 % of colchicine ; the corms from 0·11 % to 0·4 %.

For the preparation, the seeds are extracted with hot 90 % alcohol. The extract is freed from spirit and diluted with water, filtered from fat, and shaken out repeatedly with chloroform. The solvent is removed by distillation, the residue dissolved in water, filtered, and the colchicine again shaken out with chloroform. The chloroform extract is concentrated until it is nearly viscous, treated with a small quantity of absolute alcohol, warmed till homogeneous and kept at below 0° until crystallisation is complete. The product which separates consists of chloroform-colchicine $C_{22}H_{25}O_6N+2CHCl_3$. After being filtered off it is boiled with water, whereby the chloroform is split off, and the aqueous solution of colchicine thus obtained is evaporated to dryness *in vacuo*. The mother liquors from the chloroform-colchicine are concentrated, and by repetition of the above treatment a further quantity is obtained. (*See Monatshefte*, 1883, **4**, 162 ; 1886, **7**, 557 ; 1888, **9**, 1, 865.) An alternative method is based on the power of tannic acid to precipitate colchicine. The aqueous solution obtained by dilution of the alcoholic extract may be fractionally precipitated with this reagent. A small first fraction is rejected, similarly a third fraction. The second and main fraction is well washed, decomposed by treatment with lead oxide and the colchicine extracted by alcohol.

A yellowish amorphous powder, soluble in chloroform, alcohol, or water, slightly soluble in ether. M.p. 143°–147°. Neutral to litmus.

Colchicine Salicylate $C_{22}H_{25}O_6N \cdot C_7H_6O_3$. 537.— Colchicine is used in medicine mostly in the form of its salicylate, which forms a faintly yellow crystalline powder. It is used as a remedy for gout, in which it relieves the pain and inflammation. The galenical extracts of the seeds,

however, find wider employment than does the isolated alkaloid.

ACONITINE $C_{34}H_{47}O_{11}N$. 645.—Aconitine is obtained from the root of *Aconitum Napellus*, a plant cultivated in Britain, France, and other temperate countries. A variety grown in Japan, *A. uncinatum*, var. *japonicum*, affords japaconitine, an alkaloid closely allied to, but not identical with, aconitine.

European aconite root, from *A. Napellus*, contains 0·4 % to 0·6 % of alkaloids; other varieties contain smaller quantities.

For the isolation of aconitine the powdered root is extracted, by percolation at a moderate temperature, with alcohol acidified with tartaric acid. The extract is freed from alcohol, which is removed by distillation *in vacuo*, and treated with water sufficient in amount to throw out, in a filterable form, fat, resin, etc. After several days' standing, the aqueous portion is separated by filtration and freed from last traces of resin by agitation with petroleum ether. The alkaloid is then precipitated with sodium carbonate solution, extracted with ether and purified by conversion into its hydrobromide, which is recrystallised in neutral condition from water until of constant melting point. The alkaloid may be obtained by precipitation with ammonia from the solution of the pure salt, and is crystallised from methyl alcohol.

Aconitine crystallises in colourless rhombic crystals. M.p. 197°–198°. It is soluble in 726 parts of water, 37 parts of absolute alcohol, 40 parts of ether, 5·5 parts of benzene, and is almost insoluble in petroleum ether; it is readily soluble in chloroform.

Aconitine hydrobromide $C_{34}H_{47}O_{11}N \cdot HBr + 2\frac{1}{2}H_2O$ (from water). When heating is commenced at 160°, it sinters at 164°, and melts at 180°.

Aconitine first stimulates and then depresses the respiratory centre, and in toxic doses produces death by respiratory failure. It is antipyretic and slows the action of the heart.

It is applied externally, embodied in an ointment, to relieve acute nervous pain, such as that of acute rheumatism and gout and of trigeminal neuralgia. Internally it relieves pain and high temperature and is useful in acute local inflammations, such as those of pneumonia, peritonitis, painful neuralgic affections, etc.

Section III.—NATURAL AND SYNTHETIC LOCAL ANÆSTHETICS

COCAINE is closely allied to atropine inasmuch as it yields on hydrolysis ecgonine, a carboxylic acid derivative of tropine, the hydrolytic product of atropine,

$$
\begin{array}{ccc}
CH_2-CH & -\!\!\!-\!\!\!- & CH{\cdot}COOH \\
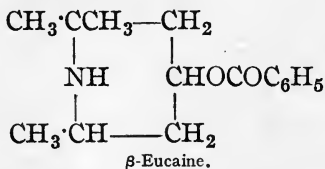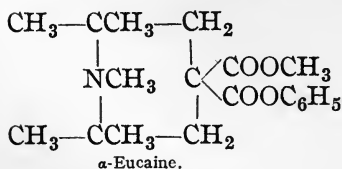| & | & | \\
& NCH_3 & CH{\cdot}OH \\
| & | & | \\
CH_2-CH & -\!\!\!-\!\!\!- & CH_2 \\
& \text{Ecgonine.} &
\end{array}
\qquad
\begin{array}{ccc}
CH_2-CH & -\!\!\!-\!\!\!- & CH_2 \\
| & | & | \\
& NCH_3 & CHOH \\
| & | & | \\
CH_2-CH & -\!\!\!-\!\!\!- & CH_2 \\
& \text{Tropine.} &
\end{array}
$$
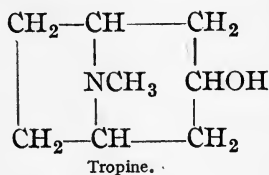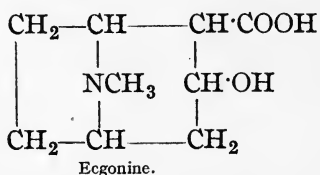
Cocaine is of chief importance for its local action in paralysing sensory nerve endings, particularly those conveying pain and touch.

A study of the chemical constitution of cocaine has been completely successful in leading chemists to produce other substances possessing like anæsthetic action. a-Eucaine was the first substance of this type introduced, but was quickly superseded by β-eucaine, which is less toxic than either the former or cocaine.

$$
\begin{array}{ccc}
CH_3-CCH_3-CH_2 \\
| \quad | \\
NCH_3 \quad C\!\!<^{COOCH_3}_{COOC_6H_5} \\
| \quad | \\
CH_3-CCH_3-CH_2 \\
\text{a-Eucaine.}
\end{array}
\qquad
\begin{array}{ccc}
CH_3{\cdot}CCH_3-CH_2 \\
| \quad | \\
NH \quad CHOCOC_6H_5 \\
| \quad | \\
CH_3{\cdot}CH-\!\!\!-\!\!\!-CH_2 \\
\text{β-Eucaine.}
\end{array}
$$

These discoveries led to others, for instance the alkamine esters stovaine and alypine. A certain chemical resemblance

of these alkamine esters to cocaine is shown by their constitutional formulæ:

$$
\begin{array}{ll}
CH_3 & CH_3 \\
| & | \\
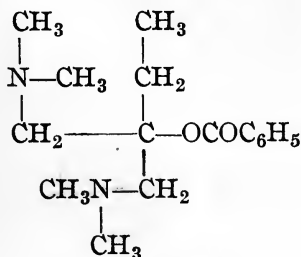N—CH_3 & CH_2 \\
| & | \\
CH_2———COCOC_6H_5 \\
& | \\
& CH_3
\end{array}
$$

Stovaine.

$$
\begin{array}{ll}
CH_3 & CH_3 \\
| & | \\
N—CH_3 & CH_2 \\
| & | \\
CH_2———C—OCOC_6H_5 \\
& | \\
CH_3N—CH_2 \\
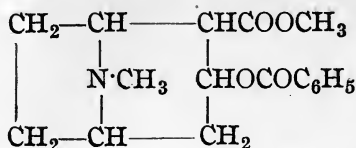| \\
CH_3
\end{array}
$$
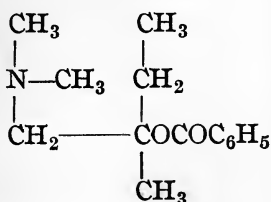
Alypine.

A new series of local anæsthetics, derivatives of amino benzoic acid, has, however, been introduced, and these do not bear any marked chemical resemblance to cocaine. Some of these compounds have attained considerable importance; the simplest of them is ethyl para-aminobenzoate, anæsthesine, but of greater importance is its diethylamino derivative known as novocaine.

New orthoform, the methyl ester of aminohydroxy benzoic acid, is another useful anæsthetic of this class, and an improvement on this is the diethyl glycocoll derivative of *p*-amino-methyl salicylate known as nirvanine.

The respective merits of these local anæsthetics are to be judged not merely by their anæsthetic action, but partly by their solubility and stability during sterilisation by boiling, and especially by the general toxicity and local irritant action. The following interesting table of comparison is taken from Cushny's *Text-book of Pharmacology*.

	Toxicity.	Anæsthetic action.	Irritant action.
Cocaine	1	1	+
Eucaine	0·4	1	++
Stovaine	0·6	1	++
Alypine	0·9—1·25	1	++++
Novocaine . . .	0·3—0·5	0·1	Absent
Nirvanine . . .	0·3—0·7	0·4	++

COCAINE (Benzoyl methyl ecgonine)$C_{17}H_{21}O_4N$.   303.

$$
\begin{array}{lll}
CH_2-CH & \!\!\!\!-\!\!\!\!- & CHCOOCH_3 \\
\ | & \ N\cdot CH_3 & CHOCOC_6H_5 \\
CH_2-CH & \!\!\!\!-\!\!\!\!- & CH_2
\end{array}
$$

Cocaine is obtained from the leaves of various species of *Erythroxylon*. Three kinds of coca leaves occur in commerce : (1) *Erythroxylon Coca*, Lamarck, Huanuco or Bolivian Coca ; (2) *E. Truxillense*, Rusby, Truxillo or Peruvian Coca, also cultivated in Ceylon ; (3) *E. Spruceanum*, Burck, Java Coca. In addition to the foregoing species, many varieties of *Erythroxylon* exist, a few of them only containing significant proportions of cocaine. The percentage of alkaloids present in commercial coca leaves varies from 0·6 to 2·4, Java leaves containing the highest amount. Associated with cocaine are a number of other alkaloids : cinnamyl-cocaine, the chief constituent of the Java leaves ; a- and β-truxilline, cocamine or isatropyl-cocaine, and benzoyl-ecgonine, which possess, with cocaine, the common property of affording ecgonine on hydrolysis, together with benzoic, cinnamic, or truxillic acids. Tropacocaine, another important constituent, when hydrolysed, gives pseudo-tropine, a stereo-isomeride of tropine, and benzoic acid. Ecgonine can be converted into cocaine, by methods to be described ; pseudo-tropine cannot.

Crude Cocaine.—In order to save freight and to eliminate the risk of deterioration to which the leaves are subject, the alkaloids are commonly, though not always, extracted in the country of origin, and imported into Europe under the name of " crude " cocaine, which may consist either of the bases themselves, or of their hydrochlorides. " Crude " cocaine, from South America, is an extremely variable article and frequently is heavily adulterated. Purchase on assay even is attended by risk, as the same keg may contain material of greatly varying purity.

The preparation of crude cocaine is believed to be carried out in South America by extracting the finely ground leaves

with dilute sulphuric acid. The acid extract is made alkaline with sodium carbonate and the liberated alkaloids are dissolved in petroleum. From this they are re-extracted into dilute sulphuric acid and reprecipitated with soda, the precipitate being washed with water, pressed, and dried. (*C. and D.* 1912, **80**, 51.)

Java cocaine, from which a very large proportion of the world's supply of pure cocaine is now obtained, is manufactured as follows : the leaves are dried in a well-ventilated but cool place and, after powdering in a disintegrator, are mixed with from 3 to 5 % of slaked lime and sufficient water to afford a stiff paste. The mixture is placed in a jacketed iron vessel provided with good stirring facilities and is extracted, at a temperature of 80°–100°, with a petroleum fraction distilling at 200°–250° ; or, in the cold, with benzene or solvent naphtha.

The oil solution after separation is agitated with dilute hydrochloric acid, sufficient in amount to extract the bases in the form of their hydrochlorides. The aqueous solution is then either neutralised and evaporated down, the salts being crystallised out, or is treated with sodium carbonate, whereby the crude cocaine alkaloids are precipitated.

Pure Cocaine.—Although it is possible to purify cocaine by crystallisation of the hydrochlorides of the mixed alkaloids, this procedure has been found to be tedious and uneconomic ; the proportions of the associated alkaloids vary considerably, and Java cocaine, as has already been stated, consists mainly of the cinnamyl derivative. The technical method of manufacture consists of hydrolysing the alkaloids to methyl ecgonine, or to ecgonine, and reconverting the purified methyl-ecgonine or ecgonine into cocaine by benzoylation, or esterification and benzoylation respectively. Hydrolysis to methyl-ecgonine may be effected by boiling with hydrochloric acid in methyl alcohol under a reflux condenser. For complete hydrolysis the hydrochlorides of the alkaloids are dissolved in water, the solution is made acid with hydrochloric acid to the extent of about 0·2 % and heated for one hour in an enamelled or silver-lined autoclave to 150°,

whereby the methyl group, as well as the benzoyl, cinnamyl, truxillyl, etc., radicles are split off. The resulting solution is filtered, after cooling, from the liberated acids and evaporated to dryness. Ecgonine hydrochloride is thus obtained, associated at times with some pseudotropine hydrochloride. It is washed with alcohol or acetone and the base isolated by treatment with sodium carbonate and extraction, after drying, with hot alcohol. It is purified by crystallisation from the same solvent, from which it separates in colourless prisms, containing 1 molecule of water, and melting at 198°, or by crystallisation of its barium salt.

Methylation.—The pure ecgonine is converted into its methyl ester, by heating with methyl alcohol and hydrochloric or sulphuric acid, or by employing sodium methyl sulphate, and the ester, after liberation from its salt, is extracted with chloroform and cleaned by distillation in a high vacuum.

Benzoylation.—Distilled methyl-ecgonine dissolved in benzene is mixed with a small excess of benzoyl chloride, and the mixture heated at its boiling point under a reflux condenser. The cocaine hydrochloride obtained on cooling is converted to base and is purified by recrystallisation from alcohol. The hydrochloride is then re-formed and recrystallised from mixtures of alcohol and light petroleum or ether. Recrystallisation must be repeated, if necessary, until the pharmacopœial tests of purity are complied with, since associated impurities are apt to possess dangerous toxic properties.

Several other methods have been proposed for the conversion of ecgonine into cocaine :—

Ecgonine is benzoylated by heating with benzoic anhydride or benzoyl chloride, or by heating the hydrochloride with benzoyl chloride, and the resulting benzoyl ecgonine esterified by boiling with methyl iodide and one molecular proportion of sodium in methyl alcohol solution. (Liebermann and Giesel, *Ber.* 1888, **21**, 3196), (D. R. P. 46702.)

The conversion is carried out in one operation, whereby ecgonine is heated together with methyl iodide and benzoic anhydride under pressure. (Merck, *Ber.* 1885, **18**, 2953.)

The hydrolysis of crude cocaine to ecgonine has been

carried out by boiling with an excess of hydrochloric acid (sp.gr. 1·1–1·2) (D. R. P. 46702), and by boiling for an hour with 60 times its weight of 7 % hydrochloric acid (Greshoff, *Pharm. Weckbl.* 1907, **44**, 961). De Jong, criticising the latter procedure, has stated that under these conditions decomposition results. (*Chem. Weckbl.* 1907, **5**, 645.)

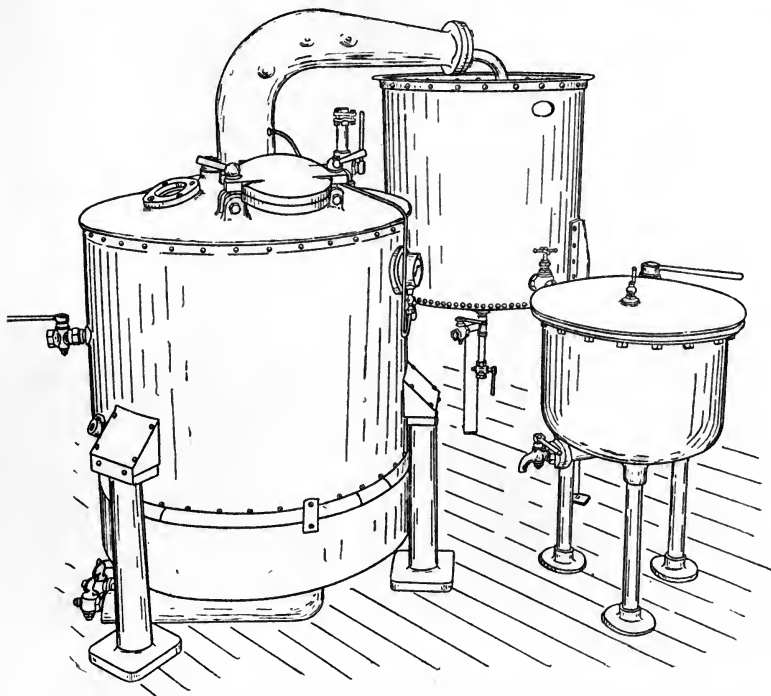Tests : A solution of 0·1 gram in 5 c.c. of water, acidified

FIG. 14.—Vacuum Still for Methyl-ecgonine.

with 3 drops of dilute sulphuric acid (10 % w/w) is mixed with 3 drops of decinormal potassium permanganate solution, when the colour should not disappear in half an hour (U. S. P.). For this test to be complied with it is necessary that every trace of organic solvent should have been removed.

A solution of 0·1 gram of cocaine hydrochloride in 80 c.c. of water is treated carefully, without shaking, with 2 c.c. of a mixture of 9 volumes of water and 1 volume of 10 %

ammonia solution; no turbidity should form within one hour. On then scratching the sides of the vessel with a glass rod a crystalline precipitate (cocaine) should be thrown down, the supernatant liquor remaining clear.

Cocaine hydrochloride should melt at 180°–186° (B. P.), 183° (P. G.), 186° (Fr. Codex). It should be perfectly colourless, and should afford a bright, neutral solution in water.

This salt of cocaine is the one most generally employed in medicine. It is largely used for producing local anæsthesia in minor operations and in dental practice. Given internally, or in small hypodermic doses, it acts as a nerve stimulant, restorative, and tonic. The mental exhilaration it produces often conduces to the formation of the " cocaine habit," which is even more unfortunate than the " morphia habit " in its results.

TROPACOCAINE (Benzoyl pseudotropine) $C_{15}H_{19}O_2N$. 245.

$$CH_2—CH—CH_2$$
$$|\quad\quad|\quad\quad|$$
$$\quad NCH_3\quad CHOCOC_6H_5$$
$$|\quad\quad|\quad\quad|$$
$$CH_2—CH—CH_2$$
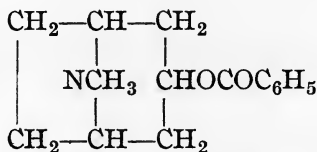
Tropacocaine was discovered in Java coca leaves (Giesel, *Ber.* 1891, **24**, 2336) and has since been found to be present in Peruvian coca (Hesse, *J. prakt. Chem.* 1902, **66**, 401). Its isolation from crude cocaine is a matter of difficulty; hence it is technically prepared from tropine. Tropine is boiled with sodium amyloxide in amyl alcohol, prepared by dissolving sodium in dry amyl alcohol. By this treatment it is converted, to a large extent, into its stereoisomeride, ψ-tropine (Willstäter, *Ber.* **29**, 936).

The base thus obtained is distilled *in vacuo* and crystallised from a mixture of benzene and light petroleum. About 65 % of pseudotropine (m.p. 108°) is obtained, and 35 % of a mixture of tropine and pseudo-tropine, which is mixed with the next batch of tropine to be converted. It is benzoylated in the same way as has been described under cocaine (Barrowcliff and Tutin, *J.C.S.* 1909, **95**, 1970),
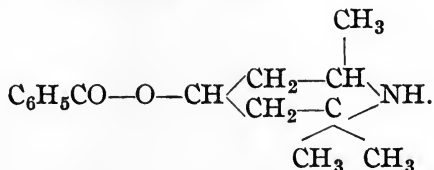
and the resulting tropacocaine hydrochloride purified by recrystallisation from petroleum. M.p. 271° (Willstäter); 283° (Barrowcliff and Tutin).

Tropacocaine hydrochloride forms colourless crystals readily soluble in water. It should withstand permanganate to the same extent as does cocaine hydrochloride, when the same test is applied.
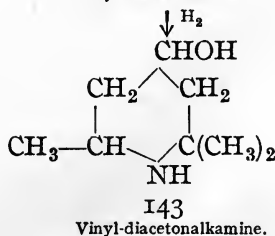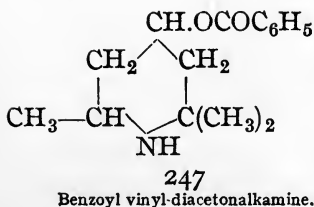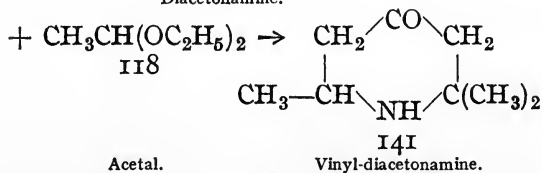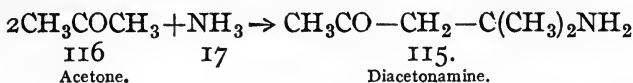
Tropacocaine is employed as a local anæsthetic and closely resembles cocaine in its action. It is said to possess only one-half the toxicity of cocaine and to produce less dilation of the pupil of the eye. Anæsthesia sets in more rapidly and is more prolonged than in the case of cocaine.

In lumbar anæsthesia tropacocaine is indicated as the most reliable and least dangerous of the drugs in use.

BETA-EUCAINE (Benzamine) (Benzoylvinyl-diaceton-alkamine). $C_{15}H_{21}O_2N$. 247.

$$C_6H_5CO-O-CH\Big\langle\begin{matrix}CH_2-CH\\CH_2-C\end{matrix}\Big\rangle NH.$$

with CH_3 above and $CH_3\ CH_3$ below.

Beta-eucaine is prepared according to the following series of reactions

$$2CH_3COCH_3 + NH_3 \rightarrow CH_3CO-CH_2-C(CH_3)_2NH_2$$

$$116 \qquad 17 \qquad\qquad 115.$$

Acetone. Diacetonamine.

$$+ CH_3CH(OC_2H_5)_2 \rightarrow CH_2\Big\langle\begin{matrix}CO\\ \end{matrix}\Big\rangle CH_2$$

$$118$$

$$CH_3-CH\Big\langle\begin{matrix}\\NH\end{matrix}\Big\rangle C(CH_3)_2$$

Acetal.   141
                    Vinyl-diacetonamine.

$$\downarrow H_2$$

$$CHOH$$

$$CH_2\Big\langle\ \Big\rangle CH_2$$

$$CH_3-CH\Big\langle\begin{matrix}\\NH\end{matrix}\Big\rangle C(CH_3)_2$$

143
Vinyl-diacetonalkamine.

$$CH.OCOC_6H_5$$

$$CH_2\Big\langle\ \Big\rangle CH_2$$

$$CH_3-CH\Big\langle\begin{matrix}\\NH\end{matrix}\Big\rangle C(CH_3)_2$$

$\xleftarrow{C_6H_5COCl}$

247
Benzoyl vinyl-diacetonalkamine.

Diacetonamine (see Everest, *J.C.S.* **115**, 588 (1919)). —Acetone (1160 parts) and anhydrous calcium chloride (200 parts) are introduced into a water-cooled, jacketed enamelled vessel provided with a reflux condenser (to prevent loss of acetone during the introduction of ammonia), a stirrer, and an inlet tube leading below the surface of the liquid. Ammonia gas (from a cylinder) is passed in as rapidly as absorbed, until 200 parts have been added. Heat is developed during the addition of the ammonia, and care must be taken that no loss of acetone is caused thereby. The addition of the ammonia occupies about nine days, after which the reaction mixture is allowed to stand for a further nine days, being intermittently stirred. The layers are then separated, the lower one, consisting of aqueous calcium chloride, being removed. Dry air is then passed rapidly for several hours through the amine layer, whereby a large proportion of the excess of ammonia is removed. The amount of oxalic acid required for the formation of the acid oxalate is determined (by titration with standard oxalic acid) ; this quantity is dissolved in alcohol (S.V.M.), three times the volume of the reaction mixture being employed, and the amine then poured slowly into the acid solution, the whole being well agitated, and the temperature kept below 50°. The mixture is then distilled, until the temperature reaches 75°, when a small amount of acetone, mixed with alcohol, is recovered. The solid ammonium oxalate which separates is filtered off while hot and washed with hot alcohol. The filtrates deposit, on cooling, diacetonamine acid oxalate in a crystalline condition. It is collected, washed with alcohol, and dried. From the total mother liquors a considerable further quantity of product is obtained by distillation at water-bath temperature, allowing the residue to remain for about 24 hours in the cold, collecting the crystals which separate, and washing them with alcohol. About 800 parts of diacetonamine acid oxalate are obtained ; 600 parts from the first deposition, and about 200 parts from the liquors and by extraction of the acid residues. M.p. 125°–127°.

I.

Vinyl-diacetonamine Oxalate (*see* E. P. 101738 of 1916, King, Mason and Schryver).—Diacetonamine acid oxalate, 800 parts, is mixed with alcohol (S.V.M.), 2400 parts, and acetal, 1600 parts, and the mixture boiled for 8 hours in a vessel provided with a reflux condenser. While still warm, the crystalline vinyl-diacetonamine oxalate is separated by filtration, and a further crop is obtained after concentration of the mother liquor. Yield, 85–90 %.

The product is purified, and separated from unchanged diacetonamine acid oxalate, etc., by washing with hot 95 % alcohol until a dried sample melts at 184°–185°.

As an alternative method of purification 600 parts of crude vinyl-diacetonamine oxalate are dissolved in 1500 parts of boiling water ; 900 parts of caustic soda are dissolved in 1000 parts of water and about one-half of the solution is added to the solution of the vinyl compound and the precipitated sodium oxalate, if any, is filtered off. The vinyl-diacetonamine base is precipitated in the filtrate by the addition of the remainder of the sodium hydrate solution and is removed by extraction with a solvent, such as ether. The solvent is distilled off, the residual base amounting to about 350–400 parts.

Preparation of Vinyl-diacetone-alkamine.—The following process is based on a method communicated to the Royal Society Committee by Professor R. Robinson of Liverpool University.

Vinyl-diacetonamine oxalate, 280 grams, or an equivalent quantity of the base, is dissolved in boiling amyl alcohol, 2000 grams, and 175 grams of sliced sodium added, in quantities of 10 to 20 grams at a time, at such a rate that the mixture keeps boiling. This operation can be effected in a metal vessel provided with a long tube as a reflux condenser, and a side tubulure for the introduction of the sodium. Shaking must be vigorous and continuous throughout. The product of a number of such reactions is mixed and boiled in a vessel provided with a reflux condenser, until the base extracted from a test-portion has the correct melting point, 137°–138°. This operation may take from 30–40 hours.

A current of steam is then blown through the mixture, when amyl alcohol and the alkamine distil over. The layer of the former is separated and washed with dilute hydrochloric acid, which is then used to neutralise the aqueous portion of the distillate. The solution of the vinyl-diacetone-alkamine hydrochloride is evaporated to dryness and purified by washing with acetone. Yield, 295 grams.

The base obtained by dissolving a portion of the hydrochloride in water and precipitating it with soda should melt at 137°–138°. If the melting point is incorrect the material requires to be purified, either by preparing the free base and recrystallising it from benzene, or by recrystallisation of the hydrochloride from alcohol and water.

Benzoylation of vinyl-diacetone-alkamine hydrochloride. —A mixture of equal weights of benzoyl chloride and vinyl-diacetone-alkamine hydrochloride is heated at 130°–140° (internal temperature) for 2 hours and then at 160° until evolution of fumes of hydrogen chloride is no longer noticeable. The pasty mass is stirred from time to time. The whole operation takes about 3 hours. After cooling somewhat, the solid mass is digested with a small quantity of hot water and crushed. When cold it is filtered, and washed with successive small amounts of cold water until the colour has been removed. It is then dried and washed with ether or benzene to remove benzoic acid. The beta-eucaine hydrochloride is then recrystallised from water till pure.

Beta-eucaine Hydrochloride (Benzamine Hydrochloride) $C_{15}H_{21}O_2N\cdot HCl$, 283·4, is a fine white crystalline powder. The melting point has been given as 268°, but Pickard has shown that the pure salt, when heated in a capillary tube sealed at both ends, melts at 278°. It is soluble in 12 parts of 90 % alcohol, and in 40 parts of water; the aqueous solution should be perfectly bright and colourless. It should also dissolve without change of colour in concentrated sulphuric and nitric acids.
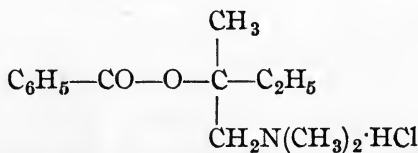
Beta-eucaine Lactate (Benzamine lactate)

$$C_{15}H_{21}O_2N \cdot C_3H_6O_3. \quad 337.$$
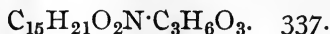
For the preparation of this salt the hydrochloride is dissolved in hot water and the base liberated by addition of twice the theoretical quantity of caustic soda. When cold it is extracted by ether and the ethereal solution dried with anhydrous potassium carbonate. Lactic acid is dissolved in ether, to a 40 % solution, and dried over anhydrous sodium sulphate. Slightly less than the theoretical quantity (1 molecule) of this is added, with stirring, to the ethereal solution of the base. After two hours' standing the lactate has completely separated and is filtered off and washed with dry ether and dried.
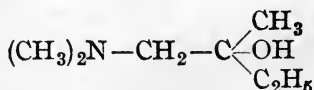
The salt is a white, odourless, crystalline powder, soluble in 4 parts of water and in 8 parts of alcohol, giving clear and colourless solutions. The lactate is more usually employed than the hydrochloride, on account of its more ready solubility in water.

Beta-eucaine is a powerful local anæsthetic, similar in action to cocaine but less toxic, somewhat weaker, and devoid of the stimulating properties of the latter. Further, it neither dilates the pupil nor contracts the blood vessels as does cocaine. Beta-eucaine is especially useful for ophthalmic purposes. It is usually administered in a 2 % aqueous solution. Solutions of the salts can be sterilised by boiling, without undergoing decomposition.

STOVAINE (Benzoyl dimethylaminodimethylethylcarbinol hydrochloride). $C_{14}H_{21}O_2N \cdot HCl.$ 271·4.

$$C_6H_5-CO-O-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle CH_2N(CH_3)_2 \cdot HCl}{|}}{C}}-C_2H_5$$

Dimethylaminodimethylethylcarbinol

$$(CH_3)_2N-CH_2-C\diagup^{CH_3}_{\diagdown C_2H_5}^{OH}$$

One molecule of monochloracetone (prepared by direct chlorination of acetone—D. R. P. 68039) is treated, in absolute ether, with one molecule of magnesium ethyl bromide. The resulting magnesium compound is decomposed with ice and the monochlorodimethylethylcarbinol extracted and distilled (Tiffeneau, *Compt. Rend.* **134**, 775). This is next heated with 2 molecular proportions of 30 % dimethylamine solution at 180° for 3 hours. The solution is then neutralised and evaporated to dryness, the salt treated with concentrated alkali, and the dimethylaminodimethylethylcarbinol extracted with a solvent and separated from recovered dimethylamine by distillation (D. R. P. 169746).

By another method (D. R. P. 169819) dimethylaminoacetone, prepared from monochloracetone and dimethylamine, is treated with magnesium ethyl bromide in anhydrous ether solution. A vigorous reaction ensues, the ether boils, and a white powder separates. The addition of the dimethylaminoacetone occupies about 3 hours. The reaction mixture is allowed to stand for 4–6 hours and is decomposed, after adding powdered ice, with sufficient nitric acid to render the solution acid. The ether layer is separated and the acid layer concentrated *in vacuo* as far as possible. The residue is treated with concentrated alkali solution and the liberated base extracted with ether or benzene, and, after drying, distilled *in vacuo*. (B.p. 57° at 23 mm., 140° at 760 mm.)

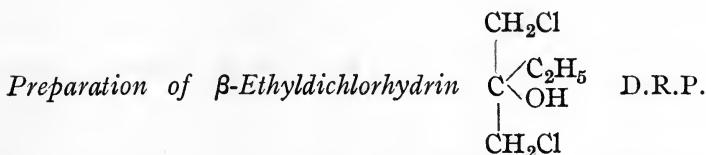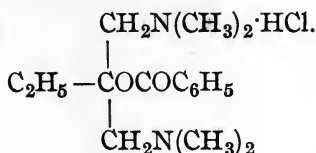*Benzoylation of Dimethylaminodimethylethylcarbinol.*— One hundred parts of the distilled base are mixed with a solution of 115 parts of benzoyl chloride dissolved in 200 parts of benzol. Heat is developed, and the hydrochloride of the benzoylated base separates. After boiling for some time the reaction mixture is cooled, and the crystals are filtered off, washed with cold benzol and recrystallised from absolute alcohol, or by dissolving in the minimum amount of methyl alcohol and mixing with an equal volume of acetone.

Stovaine is sold in the form of small colourless, glistening, scaly crystals. M.p. 175°. It is very soluble in water, and the solution can be sterilised by boiling without

decomposition taking place. It is readily soluble in alcohol and almost insoluble in ether. It is neutral to litmus.

Stovaine is a lumbar anæsthetic said to possess only one-half the toxicity of cocaine. It differs physiologically from cocaine in that it dilates the blood vessels instead of contracting them, and, further, seems to have a tonic effect upon the heart. Hence the vascular system is said to escape all the harmful effects produced by cocaine.

ALYPINE (Benzoyl tetra-methyldiaminodimethylethylcarbinol hydrochloride) $C_{16}H_{26}O_2N_2 \cdot HCl$.   314·4.

$$\begin{array}{c} CH_2N(CH_3)_2 \cdot HCl. \\ | \\ C_2H_5 - COCOC_6H_5 \\ | \\ CH_2N(CH_3)_2 \end{array}$$

Preparation of β-Ethyldichlorhydrin
$$\begin{array}{c} CH_2Cl \\ | \\ C{<}^{C_2H_5}_{OH} \\ | \\ CH_2Cl \end{array}$$
D.R.P.

168941.—48 parts of magnesium are treated with a mixture of 218 parts of ethyl bromide and 300 parts of absolute ether. To the resulting solution of magnesium ethyl bromide are added, slowly and with careful cooling and good stirring, 254 parts of symmetrical dichloracetone, $CH_2Cl-CO-CH_2Cl$, dissolved in an equal quantity of absolute ether. The mixture is allowed to stand overnight and is then poured on to powdered ice. Dilute sulphuric acid is added in quantity sufficient to dissolve the precipitated magnesia, after which the ether layer is separated, washed, and dried, and the ethyldichlorhydrin, after removal of the solvent, distilled *in vacuo*. B.p. 77° at 15 mm.

Tetra-methyldiaminodimethylethylcarbinol

$$\begin{array}{c} CH_2N(CH_3)_2 \\ | \\ C_2H_5 - C - OH \\ | \\ CH_2N(CH_3)_2 \end{array}$$
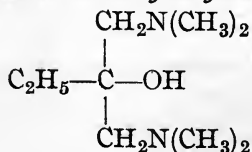
D. R. P. 173610.—157 parts of β-ethyldichlorhydrin are treated with a solution of 180 parts of dimethylamine in water, and the mixture is heated in an autoclave for 3 hours at 180°. The resulting solution is made slightly acid with hydrochloric acid and extracted with ether, to remove unchanged β-ethyldichlorhydrin, after which it is evaporated to dryness. The residue is covered with a layer of ether and is treated with concentrated caustic soda solution and with solid caustic soda to saturation. The liberated bases, dimethylamine and tetra-methyldiaminodimethylethylcarbinol, are taken up by the ether. The ether and dimethylamine are removed and the residual base distilled *in vacuo*. B.p. 87° at 17 mm.

Benzoyl tetra-methyldiaminodimethylethylcarbinol D. P. R. 173631.—The method given for the benzoylation consists in treating 147 parts of the base, mixed with crushed ice, with 200 parts of 20 % caustic soda solution and 140·5 parts of benzoyl chloride, added in equivalent amounts, in small quantities at a time, stirring being continuous and efficient. The temperature is kept at 0° by the addition of ice. When benzoylation is complete, the benzoylated base is extracted with a solvent and converted into its hydrochloride by neutralising with an alcoholic solution of hydrochloric acid. The solution is evaporated to dryness and the hydrochloride purified by recrystallisation from acetone.

It seems probable that the benzoylation could be more simply carried out by treating the carbinol derivative with a molecular quantity of benzoyl chloride, as in the case of cocaine, when alypine hydrochloride should directly result.

Alypine hydrochloride is a white crystalline hygroscopic powder, melting at 169°. It is soluble in water and in alcohol. The aqueous solution is neutral in reaction. It should be protected from air.

It is a local anæsthetic having an action similar to that of cocaine, than which it is stated to be less toxic. It is also said not to produce disturbance of the accommodation.
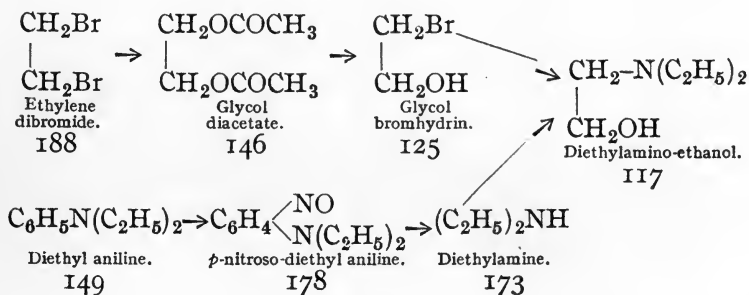
NOVOCAINE (*p*-aminobenzoyldiethylamino-ethanol hydrochloride) $NH_2\langle\ \rangle CO - O - CH_2 - CH_2 - N(C_2H_5)_2HCl$. 272·4.—Novocaine can be prepared, according to D. R. P.

179,629, by condensing *p*-nitrobenzoyl chloride with ethylene chlorhydrin, and treating the resulting *p*-nitrobenzoyl-chlorethanol with diethylamine. The product, *p*-nitro-benzoyldiethylamino-ethanol, is then reduced to novocaine with tin and hydrochloric acid.

By D. R. P. 194748, *p*-nitrobenzoylchlorethanol is first reduced and the *p*-aminobenzoylchlorethanol condensed with diethylamine to novocaine.

The researches carried out under the direction of the Royal Society's Committee, shortly after the commencement of the war, indicated the best method to consist in first preparing diethylamino-ethanol, which is reacted with *p*-nitrobenzoyl chloride, the resulting compound being then reduced to novocaine.

The following are the steps by which diethylamino-ethanol is prepared :

$$
\begin{array}{cccc}
CH_2Br & CH_2OCOCH_3 & CH_2Br & \\
| \;\; \rightarrow & | \;\; \rightarrow & | \;\; \searrow & CH_2-N(C_2H_5)_2 \\
CH_2Br & CH_2OCOCH_3 & CH_2OH & | \\
\text{Ethylene} & \text{Glycol} & \text{Glycol} & \nearrow \;\; CH_2OH \\
\text{dibromide.} & \text{diacetate.} & \text{bromhydrin.} & \text{Diethylamino-ethanol.} \\
188 & 146 & 125 & 117
\end{array}
$$

$$
C_6H_5N(C_2H_5)_2 \rightarrow C_6H_4\!\!\!\begin{array}{c} NO \\ \diagdown N(C_2H_5)_2 \end{array} \rightarrow (C_2H_5)_2NH
$$

Diethyl aniline.   *p*-nitroso-diethyl aniline.   Diethylamine.
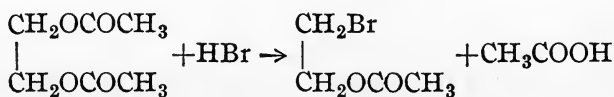149   178   173

Preparation of Glycol bromhydrin.—Ethylene, prepared either by the usual method from alcohol and syrupy phosphoric acid, or by passing alcohol vapour through a tube containing alumina heated at 320°–360°, is passed into bromine and the resulting ethylene dibromide purified by fractional distillation.

Ethylene dibromide, 188 parts (1 mol.), glycol diacetate, 146 parts (1 mol.), and coarsely powdered potassium acetate, 206 parts (rather more than 2 mols.), are well mixed together in a vessel provided with a reflux condenser and a powerful stirrer, and is heated in an oil bath. The temperature of the bath is slowly raised to about 150°, when ethylene dibromide

begins to boil vigorously. After about an hour very little liquid is refluxing and the temperature is raised to 200° and kept at this point for $1\frac{1}{2}$ hours, the total time of heating being about $2\frac{1}{2}$–3 hours, stirring being continuous. The reflux is then replaced by a direct condenser, to which a receiver is attached, and the system evacuated to 10 mm. The temperature is raised finally to 210°, and maintained at this until no more liquid distils over. The distillate consists of glycol diacetate, acetic acid, and ethylene dibromide. It is redistilled under ordinary pressure and collected in three portions: (1) 135°–180°, (2) 180°–190°, (3) above 190°.

Fraction (1) is refractionated with a column, distillation being interrupted when the thermometer reaches 170°. The distillate (acetic acid and ethylene dibromide) is treated with water and neutralised with potash, ethylene dibromide and potassium acetate being recovered. The residue is mainly glycol diacetate, used in the next stage of the reaction. Fraction (3) on redistillation affords a further quantity of glycol diacetate. Yield, 80–85 % of theory.

The glycol diacetate is converted into glycol bromacetate by the action of hydrogen bromide, according to the equation

$$\begin{array}{l} CH_2OCOCH_3 \\ | \\ CH_2OCOCH_3 \end{array} + HBr \rightarrow \begin{array}{l} CH_2Br \\ | \\ CH_2OCOCH_3 \end{array} + CH_3COOH$$

Hydrogen bromide, 81 parts, prepared from bromine and moist red phosphorus and dried over calcium chloride, is passed into 146 parts of glycol diacetate. This operation may be carried out in a closed earthenware still suitable for being maintained under slight pressure of the gas. If working on a large scale a stirrer is advantageous. The brominated liquor is allowed to remain overnight, after which any uncombined hydrogen bromide is removed, by blowing or aspirating a current of air through the liquid, and absorbed in a fresh charge of glycol diacetate. The liquor is then distilled, to remove acetic acid, employing a fractionating

column and heating up to 125°. The distillate is refractionated once.

The glycol bromacetate without further purifying is boiled for 3 hours, a reflux condenser being fitted, with 70 parts by volume of absolute methyl alcohol, when hydrolysis to glycol bromhydrin and methyl acetate occurs.

$$\begin{array}{ccc} CH_2Br & & CH_2Br \\ | & +CH_3OH \rightarrow | & +CH_3COOCH_3 \\ CH_2OCOCH_3 & & CH_2OH \end{array}$$
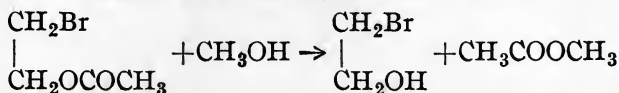
The liquid is then distilled, using a column, and the methyl acetate and excess of methyl alcohol are removed. The residue is distilled, the fraction 146°–150°, consisting of glycol bromhydrin, is reserved. Anything boiling above 150° consists chiefly of glycol bromacetate and is mixed with the next batch to be hydrolysed. Yield, 76 % of theory (from glycol diacetate).

An alternative method for the preparation of glycol bromhydrin, which seems to possess practical possibilities, has been described by Read and Williams, *J.C.S.* **111**, 240 (1917).

Washed ethylene is passed into an ice-cold solution of 7·2 grams of bromine in 500 c.c. of water. After complete absorption of the bromine a fresh portion, equal to the first, is added, with frequent and vigorous agitation, until a total weight of 200 grams of bromine has reacted. The lower layer of ethylene dibromide which is formed during the process is separated, washed with water, and dried over sodium sulphate. Yield, 88 grams. After neutralising the sodium carbonate and saturating the aqueous layer with common salt, the ethylene bromhydrin is extracted from it by shaking with two successive quantities of 100 c.c. of ether ; from the extract, dried over sodium sulphate, the ether is distilled. The bulk of the residual liquid—yield, 85 grams —distils between 145° and 149°. It consists of glycol bromhydrin.   54·4 % of the bromine is converted into ethylene bromhydrin and 37·5 % into ethylene dibromide. The remainder is found as hydrobromic acid, which should be recoverable.

Preparation of Diethylamine.—From diethylaniline: Diethylaniline, 50 parts, dissolved in 148 parts of hydrochloric acid (sp.gr. 1·12) diluted with 75 parts of water, is diazotised with a solution of 32 parts of sodium nitrite in 52 parts of water, the temperature being kept at 0°. The reaction mixture is allowed to stand for a short time, then run slowly into a boiling solution of 85 parts of caustic soda in 2000 parts of water, contained in a vessel provided with a condenser and receiver. Diethylamine is distilled off and is collected in an excess of hydrochloric acid. The boiling is continued for 45 minutes after all the nitroso body has been added.

The solution of diethylamine hydrochloride is then evaporated to dryness and the dry salt gently warmed with strong alkali solution (40 % NaOH) when the diethylamine which is liberated is distilled over and obtained pure by one further rectification. B.p. 55°–56°; yield, 75 % of theory.

A promising alternative method for the preparation of diethylamine is based on D. R. P. 105870.

Toluene para-sulphonamide is ethylated by heating with two molecules of caustic soda in aqueous solution and two molecules of ethyl chloride, in an autoclave at 80°–90°. Ethylation takes place, a diethyl compound being formed.

$$CH_3\langle\ \rangle SO_2NH_2 + 2C_2H_5Cl + 2NaOH$$
$$\rightarrow CH_3\langle\ \rangle SO_2N(C_2H_5)_2 + 2NaCl + 2H_2O$$
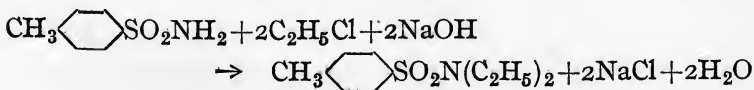
This, on heating with chlorsulphonic acid, is decomposed into toluene sulphonchloride and diethylamine sulphonic acid

$$CH_3\langle\ \rangle SO_2N(C_2H_5)_2 + SO_2\langle^{OH}_{Cl}$$
$$\rightarrow CH_3\langle\ \rangle SO_2Cl + SO_2\langle^{OH}_{N(C_2H_5)_2}$$
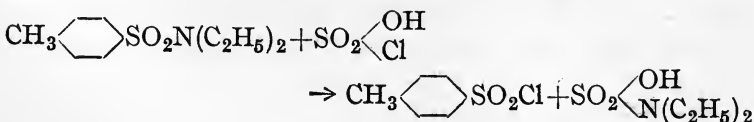
from which diethylamine is obtained by distillation with alkali. 227 parts of toluene parasulphondiethylamide are mixed with 130 parts of chlorsulphonic acid and heated

for 2–3 hours at 130°–150°. After cooling, toluene sulphon-chloride is extracted with a solvent (petroleum, benzene, or ether), the residue dissolved in water, made alkaline with caustic soda liquor, and distilled, whereupon diethylamine passes over and is absorbed in hydrochloric acid.
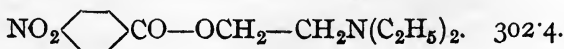
Preparation of Diethylaminoethanol

$$OH-CH_2-CH_2N(C_2H_5)_2.$$

—438 parts (2 mols.) of diethylamine are placed in a vessel provided with a stirrer, an efficient reflux condenser, and a tap funnel, through which 375 parts (1 mol.) of glycol bromhydrin are gradually added, the rate of addition being such that gentle spontaneous ebullition takes place. Stirring is continued for some time after the glycol bromhydrin has all been added, and the reaction mixture is allowed to cool. The product consists of the hydrobromides of diethyl-amine and diethylaminoethanol, together with some diethylamine. Concentrated soda liquor (containing 140 parts of NaOH) is added and the mixture stirred until all the solid has passed into solution. The upper layer, consisting of diethylamine and diethylaminoethanol, is separated and dried over solid caustic soda. The lower aqueous layer is extracted twice with ether.

The mixture of bases is fractionally distilled, and separated into diethylamine (b.p. 55°–58°) and diethyl-aminoethanol (b.p. 158°–163°). The residue boiling above 163° contains a little diethylaminoethyl acetate and is hydrolysed by boiling with methyl alcohol and the diethyl-aminoethanol separated by distillation. Yield, 84 % of theory.

Para-nitrobenzoyl chloride is prepared by oxidising para-nitro-toluene by boiling sodium bichromate and sulphuric acid, and treating the resulting para-nitro-benzoic acid with PCl_5. The product is fractionally separated by distillation into phosphorus oxychloride and para-nitro-benzoyl chloride.

Para-nitrobenzoyldiethylaminoethanol

$$NO_2\langle\ \rangle CO-OCH_2-CH_2N(C_2H_5)_2.\quad 302\cdot4.$$

117 parts (1 mol.) of diethylaminoethanol are mixed with 185·4 parts (1 mol.) of *p*-nitro-benzoyl chloride. The reaction, which takes place spontaneously, is completed by heating the mixture for 2 hours at 120°. The solid product consists of the hydrochloride of *p*-nitrobenzoyl diethylaminoethanol.

Para-aminobenzolydiethylaminoethanol (novocaine base). 236.—The product of the above reaction is dissolved in water and concentrated hydrochloric acid, 800 parts, and treated gradually with 240 parts of granulated tin, the temperature being kept at 35°–40°. After reduction is completed the solution is freed from tin with H_2S and filtered. It is made alkaline with sodium carbonate, when the base separates as an oil which presently crystallises. The mass is separated and recrystallised from dilute alcohol, from which crystals containing 2 molecules of water and melting at 51° are obtained.

These are filtered off and neutralised with one molecule of hydrochloric acid. The salt obtained on evaporation crystallises from alcohol in needles melting at 156°.

Novocaine is a white, odourless, crystalline powder, soluble in an equal weight of water, giving a neutral solution. It possesses a prompt and powerful local anæsthetic action when injected subcutaneously. It is non-toxic and has no irritant action on living tissues. It is particularly useful in dental practice.

ANÆSTHESINE, ethyl *p*-amino-benzoate

$$NH_2\underset{}{\bigodot}COOC_2H_5. \quad 165.$$
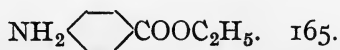
—One molecular proportion of para-nitro-benzoic acid, prepared by oxidising pure para-nitro-toluene, is dissolved in one molecule of concentrated aqueous caustic soda, and the solution added slowly to $1\frac{1}{4}$ mols. of crystallised sodium sulphide heated at 100°. The mixture is then boiled for 2 hours, the vapours being condensed and refluxed (cf. D. R. P. 139568). The resulting solution is poured into $3\frac{1}{2}$ mols. of diluted hydrochloric acid, and the SO_2 expelled by boiling. After filtering, sodium acetate, $1\frac{1}{2}$ mols., is added. The para-amino-benzoic acid crystallises out on cooling. M.p. 186°–187°.

It is esterified in the usual manner by heating with alcohol and a mineral acid. The solution is neutralised, excess of alcohol distilled off, water added, and the ethyl ester filtered off and recrystallised from alcohol.

According to D. R. P. 147552, 10 parts of ethyl *p*-nitro benzoate are mixed with 65 parts of 40 % sodium bisulphite solution and 200 parts of water, and heated until all has passed into solution, which takes place in from $\frac{1}{2}$–1 hour. The solution is evaporated down, or salted out, when the sodium salt of ethyl N-sulpho-*p*-aminobenzoate is obtained ($COOC_2H_5\langle\quad\rangle NHSO_3Na$). This, when warmed with concentrated hydrochloric acid, gives SO_2 and ethyl *p*-aminobenzoate.

Anæsthesine is a white crystalline powder. M.p. 90°–91°. It is almost insoluble in water, soluble in alcohol or ether and olive oil. Solutions in oil may be sterilised without decomposition.
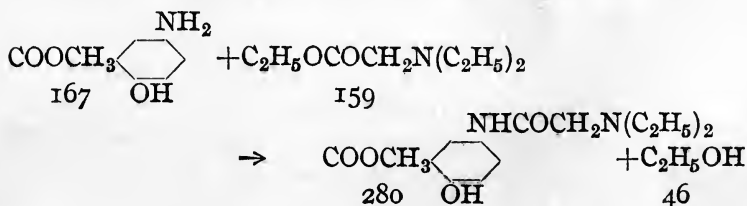
Anæsthesine was introduced as a local anæsthetic, as a substitute for orthoform. Unlike that of cocaine, its action is purely local, not penetrating the mucous membranes.

It is employed as a dusting powder or in an ointment for anæsthetising wounded surfaces, such as burns, and for allaying the pain of ulcerative stomatitis, also in tuberculosis and malignant ulceration of the larynx and other regions.

NIRVANINE (Diethylglycocoll *p*-aminomethyl salicylate)

$$COOCH_3\langle\quad\rangle \overset{\displaystyle NH-CO\cdot CH_2N(C_2H_5)_2}{\underset{\displaystyle OH}{}} \qquad 280.$$
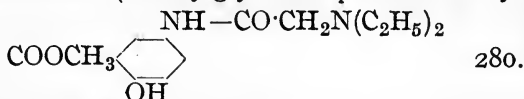
Several methods for the preparation of nirvanine have been protected, of which the best would seem to be the one covered by D. R. P. 108027, in which methyl *p*-amino salicylate and diethylglycocoll-ethyl ester are condensed.

$$COOCH_3\overset{\displaystyle NH_2}{\underset{\displaystyle OH}{\langle\quad\rangle}} + C_2H_5OCOCH_2N(C_2H_5)_2$$
$$167\quad \qquad\qquad 159$$

$$\rightarrow \quad COOCH_3\overset{\displaystyle NHCOCH_2N(C_2H_5)_2}{\underset{\displaystyle OH}{\langle\quad\rangle}} + C_2H_5OH$$
$$ 280\quad\qquad\qquad 46$$

Methyl p-*amino salicylate*—For the preparation of *p*-aminosalicylic acid (D. R. P. 96853) 30 kg. of meta-nitrobenzoic acid are dissolved in 250 kg. of sulphuric acid (sp.gr. 1·84) and treated, at 50°–80°, in the course of about 4 hours, with 45–50 kg. of zinc dust. After standing for 10 hours the reaction mixture is poured on to ice, and the amido salicylic acid sulphate filtered off and recrystallised from hot water. M.p. 334°. It is esterified in the usual manner by boiling with methyl alcohol containing sulphuric acid, and the ester isolated, after removal of excess of methyl alcohol, by adding water and sodium carbonate. M.p. 96°.

Diethylglycocoll ester—Chloracetic acid, 9·4 parts (1 mol.), dissolved in water, 5 parts, is added to 15 parts of diethylamine, with stirring. The mixture is allowed to stand for 24 hours, after which an excess of HCl is added and the solution evaporated to dryness. A mixture of diethylamine hydrochloride and diethylglycocoll hydrochloride is obtained. It is treated when dry with 40 volumes of absolute alcohol and HCl gas is passed in to the point of saturation. After standing overnight the mixture is distilled in order to remove excess of alcohol, and the residue is dissolved in water and made alkaline with sodium carbonate solution. The bases are extracted with ether and the solution is dried over anhydrous sodium sulphate and fractionally distilled. Diethylamine is first recovered, mixed with ether, from which it may be extracted with a further quantity of chloracetic acid and the diethyl glycocoll ethyl ester is obtained as a fraction boiling at 177°.

Condensation of diethylglycocoll ester and p-*amido methyl salicylate* (D. R. P. 108027).—5 parts of *p*-amido methyl salicylate and 2·5 parts of diethylglycocoll ester are mixed and heated together for several hours at 150°–160°, until evolution of alcohol can no longer be detected. The reaction product is then dissolved in water, and made alkaline with sodium carbonate. The solution is now acidified with acetic acid, the nirvanine base extracted with ether and converted into the hydrochloride, which is the salt commonly employed.

According to D. R. P. 106502, methyl *p*-aminosalicy-late is condensed, in benzene solution, with chloracetyl chloride, and the resulting methyl *p*-chloracetylamino salicylate converted into nirvanine by heating with diethylamine. By a variation of this method, D. R. P. 108871, *p*-aminosalicylic acid is reacted with chloracetyl chloride, and the product treated with diethylamine, when diethylglycocoll *p*-aminosalicylic acid is produced and is converted into nirvanine by esterification with methyl alcohol and HCl.

Nirvanine forms small white prisms, readily soluble in water. M.p. 185°. It is employed as a local anæsthetic in surgical and dental operations. It has less toxicity than cocaine and about half its anæsthetic action.

Section IV.—ANTIPYRETICS AND ANALGESICS.

PRIOR to the introduction of synthetic remedies, quinine and aconitine were the chief active drugs employed in reducing high temperature. The introduction of the synthetic remedies of this class, which are now so well known, has made it possible to attain this therapeutic object without the ill effects attendant on the use of substances as toxic as aconitine.

Salicin, a glucoside of salicylic alcohol occurring in the bark of the willow, has also been employed for this purpose, thus leading to the use of salicylic acid, the first of the synthetic coal tar derivatives introduced into medicine. The methyl and phenyl esters and acetyl derivative of salicylic acid later came into use ; the last mentioned, under the name aspirin, being now more widely employed than any other drug of this class.

Antipyrine, which was introduced in 1884, has proved of great value on account of its positive action, but as this is frequently accompanied by collapse, other and safer substances of the type of phenacetin have found wide acceptance. The first of these to be introduced was acetanilide. They are said to owe their activity to the formation of simple derivatives of para-aminophenol in the tissues. If this happens rapidly there is a tendency to collapse and the antipyretic action is too quickly over. Consequently, those members of this class which decompose gradually in the blood, such as phenacetin and lactophenin, are preferred to acetanilide and exalgin, which are regarded as dangerous. Phenacetin is the para-ethoxyl derivative of acetanilide ; the methyl, propyl and butyl members of the series have been

examined pharmacologically and found inferior to phenacetin. The N-ethyl derivative of phenacetin is said to be superior to phenacetin.

The drugs of this class remove the symptoms of disease rather than its cause and their use as curative agents has been questioned.

They are effective in reducing pain, and because of value in headache and in relieving rheumatic and neuralgia pain, they are much sought by the public apart from medical advice, not infrequently with untoward effects.

ACETANILIDE (antifebrin) C_8H_9ON.   135.

$$C_6H_5NH \cdot COCH_3$$
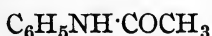
The method given by Muller, *Chem. Zeit.* **36** (1912), 1050, 1055, described in detail by Cain in *The Manufacture of Intermediate Products for Dyes*, page 51, is not suitable for manufacturing acetanilide of pharmaceutical quality, as the product, on account of the high temperature attained (240°) and the length of time of heating, about 80 hours, is highly coloured and difficult to purify.   It is found better to mix together the whole of the ingredients, 500 lb. of aniline and 500 lb. of glacial acetic acid, in a steam jacketed enamelled still of 150 gallons capacity, and to heat the mixture at a temperature of 120°–125°, the heating being so regulated that practically no vapour passes over into the condenser.   The progress of the acetylation is followed, after the lapse of 8–9 hours, by diazotising a portion of the reaction mixture, coupling with an alkaline solution of β-naphthol or R-salt, and measuring the colour intensity, which indicates the quantity of aniline unchanged.   When the test is negative, in 10–12 hours, vacuum is applied and as much acetic acid recovered as will readily distil off at 120°.

The residue is then blown into 200 gallons of water and allowed to cool.   The crude acetanilide which separates is centrifuged, the filtrate being employed to receive a further batch from the still.   The acetanilide is recrystallised from boiling water, of which about 1000 gallons will be required,

using a good, decolourising charcoal. From the filtered solution pure acetanilide crystallises out on cooling. It is separated by means of a centrifuge, washed with a little water and dried in a warm room. The liquors are used for the recrystallisation of further batches of crude acetanilide.

Acetanilide forms colourless, glistening plates, m.p. 113°–114°. It dissolves in 190 parts of cold, in 18 parts of boiling, water; in 12 parts of 60 % alcohol, and in 4 parts of 90 % alcohol. The solutions are neutral to litmus.

Colourless solutions should be afforded in concentrated sulphuric and nitric acids, and a sample should leave no residue on ignition. Acetanilide is a powerful antipyretic and is useful for treatment of the high temperatures of typhoid fever, phthisis, acute rheumatism, and smallpox. It acts as an analgesic in neuralgia and other nerve affections.

METHYLACETANILIDE OR EXALGIN $C_9H_{11}ON$. 149.

$$C_6H_5NCH_3COCH_3$$

Exalgin may be prepared according to the method given in *Ber.* **10**, 328. Four parts of acetanilide are added to 25 parts of anhydrous xylene containing 1 part of granulated sodium. The mixture is heated at 130°, with continuous stirring, for 2–3 hours. The sodium salt of acetanilide is formed and separates in the form of a white gelatinous mass. After cooling, a slight excess of methyl iodide is added; reaction sets in spontaneously, and is carried to completion by gentle heating. The mixture of methylacetanilide and sodium iodide is filtered off, washed with water, which removes the latter substance, and recrystallised from boiling water. In this solvent it is apt to form supersaturated solutions, which require seeding with a crystal to induce crystallisation.

It may also be made by the interaction of pure mono-methyl aniline with acetyl chloride or acetic anhydride.

Exalgin crystallises in colourless prismatic needles. M.p. 101°. It is soluble in 50 parts of cold water, in 2 parts of 90 % alcohol, and in 4 parts of 60 % alcohol.
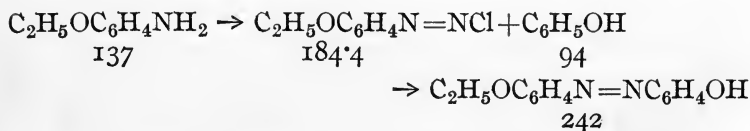
Exalgin resembles acetanilide in its action; it is employed as an analgesic, in neuralgia and toothache.

PHENACETIN (acetphenetidine) $C_{10}H_{13}O_2N$.   179.

$$C_2H_5O\langle\ \rangle NH \cdot CO \cdot CH_3.$$
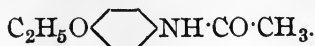
Phenacetin is prepared either by the acetylation of para-phenetidine $C_2H_5OC_6H_4NH_2$, or by ethylating *p*-acetamino-phenol $OHC_6H_4NHCOCH_3$.
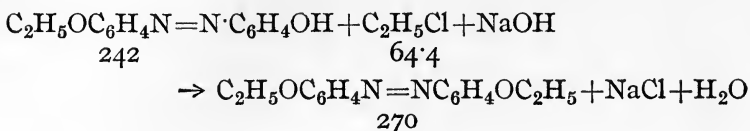
p-**Phenetidine** can be prepared either by the reduction of para-nitrophenetol, produced by the ethylation of para-nitrophenol, or it may be formed by the reduction of *p:p'*-diethoxyazobenzol $OC_2H_5\langle\ \rangle N = N\langle\ \rangle OC_2H_5$. The latter process will be given first, after which will be described various technical methods for preparing para-nitrophenol, and for its conversion into *p*-nitrophenetol and *p*-phenetidine respectively.

From Phenetidine.—Preparation of p-p'-*diethoxyazobenzol and its reduction to* p-*phenetidine.*—The process consists, in essence, in the conversion of 1 mol. of phenol and 1 mol. of phenetidine into 2 mols. of phenetidine. 13·7 kilos of para-phenetidine are dissolved in 200 litres of water and 37·5 kilos of 20 % hydrochloric acid. The mixture is maintained below $+6°$, and diazotised with a solution of 6·3 kgs. of sodium nitrite dissolved in 50 litres of water. The diazo solution is then allowed to flow, with stirring, into a solution of 9·5 kgs. of phenol and 20 kgs. of sodium carbonate, cryst. in 350 litres of water. In the course of an hour *p*-ethoxy-*p*-oxyazobenzol separates, in quantitative yield. M.p. 104·5°.

$$C_2H_5OC_6H_4NH_2 \rightarrow C_2H_5OC_6H_4N{=}NCl + C_6H_5OH$$
$$\quad\ 137 \qquad\qquad\quad 184·4 \qquad\qquad 94$$
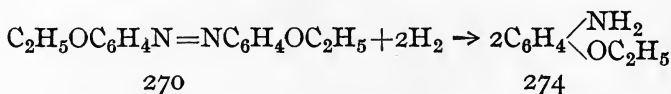$$\rightarrow C_2H_5OC_6H_4N{=}NC_6H_4OH$$
$$242$$

24·2 kilos (1 mol.) of *p*-ethoxy-*p*-oxyazobenzol are dissolved in 100 litres of alcohol containing 4 kilos (1 mol.) of caustic soda and heated, in a lead-lined autoclave, at 90°–100°, for 5–6 hours, with 7 kilos ($1\frac{1}{10}$ mol.) of ethyl chloride. After cooling, the *p-p*-diethoxyazobenzol is

filtered, the filtrate being used in another operation. M.p. of diethoxyazobenzol, 156°.

$$C_2H_5OC_6H_4N=N\cdot C_6H_4OH+C_2H_5Cl+NaOH$$
$$242 \qquad\qquad 64\cdot4$$
$$\rightarrow C_2H_5OC_6H_4N=NC_6H_4OC_2H_5+NaCl+H_2O$$
$$270$$

Ten kilos of *p-p*-diethoxyazobenzol are mixed with 50 kgs. of 20 % hydrochloric acid and reduced with 6 kilos of granulated tin. When all has dissolved, the reaction liquor is made alkaline with caustic soda solution and the *p*-phenetidine distilled over by means of superheated steam (160°–180°). (*See* D. R. P. 48543.)

$$C_2H_5OC_6H_4N=NC_6H_4OC_2H_5+2H_2 \rightarrow 2C_6H_4{\displaystyle \diagdown}{NH_2 \atop OC_2H_5}$$
$$270 \qquad\qquad\qquad 274$$

Preparation of p-*phenetidine from* p-*nitrophenol.*—p-*Nitrophenol* OH$\langle\ \rangle$NO$_2$ is now prepared technically by heating with caustic alkali solution or lime, para-chlornitrobenzene Cl$\langle\ \rangle$NO$_2$, which is a product of the nitration of chlorbenzol. It can be readily obtained pure by distillation.

Particulars of the older method, by which phenol is nitrated directly, are given by Barnett (*Coal Tar Dyes and Intermediates*, p. 25). A mixture of the ortho- and para-isomerides is formed, and separated by distillation in superheated steam, ortho-nitrophenol being volatile, para-nitrophenol non-volatile.

Para-nitrophenol can also be prepared (D. R. P. 91314) by condensing phenol with para-toluene sulphonchloride to CH$_3\langle\ \rangle$SO$_2$OC$_6$H$_5$, which, on nitration, affords the *p*-nitrophenyl ester of *o*-nitrotoluene-*p*-sulphonic acid CH$_3\langle\ \rangle$SO$_2$O$\langle\ \rangle$NO$_2$. This compound, on heating with NO$_2$ caustic soda solution, is resolved into para-nitrophenol and ortho-nitrotoluene-para-sulphonic acid.

Ethylation of p-*Nitrophenol.*—139 parts (1 mol.) of para-nitrophenol are dissolved in 400 parts of 10 % caustic soda solution and the mixture is introduced into a lead-coated, steam-jacketed autoclave provided with an efficient stirrer. Ethyl chloride, 70 parts ($1\frac{1}{10}$ mol.), is introduced, and the mixture heated under pressure at 90°–100° for 7–8 hours. The *p*-nitrophenetol is filtered off after cooling, washed first with 5 % caustic soda solution, to remove any unchanged *p*-nitrophenol, and then with water. It is passed on for reduction in the next stage without being dried.

Reduction of p-*Nitrophenetol to* p-*Phenetidine.*—This operation is carried out in a similar way to that of the reduction of nitrobenzene to aniline, with iron and hydrochloric acid. A cast-iron still is employed, which is provided with stirring gear, a manhole for the introduction of the materials, and a pipe for admitting live steam.

A mixture of 1000 parts of *p*-nitrophenetol, 2000 parts of water, and 60 parts of hydrochloric acid (sp.gr. 1·14) is introduced into the vessel and heated by direct steam to about 60°. With continuous stirring 100 lbs. of iron turnings are introduced, followed by a further 900 lbs. in portions over a period of 3–4 hours. The temperature is then raised gradually to about 90°, at which it is maintained until the reduction is completed. The whole operation occupies about 8 hours. Heating and stirring are then stopped, and the supernatant aqueous liquor siphoned off from the iron-ironoxide-phenetidine sludge. A portion of the liquor is utilised for a further reduction ; the remainder is either discarded—the amount of phenetidine contained in it being very small—or, if a separate steam generator is employed, is vaporised and used either in the heating up of another charge or in the removal of the phenetidine from the sludge. This is effected by distillation in a current of superheated steam, at 160°–180°, at which temperature phenetidine is readily volatilised. It distils over as a clear colourless oil, which is separated mechanically from the aqueous layer of the distillate.

The reduction of *p*-nitrophenetol may also be carried out

by means of sodium sulphide, the reaction proceeding according to the following equations.   (D. R. P. 139568.)

$$R \cdot NO_2 + Na_2S + H_2O \rightarrow R \cdot NH_2 + Na_2SO_3 \text{ (at 110°)}$$
$$4R \cdot NO_2 + 6Na_2S + 7H_2O \rightarrow 4R \cdot NH_2 + 3Na_2S_2O_3 + 6NaOH$$
(at lower temperatures).
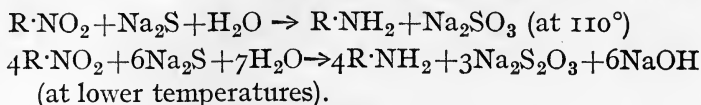
Crystallised sodium sulphide ($Na_2S \cdot 10H_2O$), $2\frac{1}{2}$ parts, is fused in a jacketed iron vessel, provided with a stirrer and a reflux condenser, and heated to boiling point (108°– 110°). Nitrophenetol, 1 part, is added, and the mixture vigorously boiled. The reduction is complete when a test portion, after acidification with hydrochloric acid, affords no extract to ether. The phenetidine may either be distilled with superheated steam, or separated mechanically from the sulphite liquor and purified by direct distillation *in vacuo*. (Fig. 15.)

This method of reduction is more costly, in materials, than the one with iron and acid, but the isolation of the product is attended by fewer mechanical difficulties.

Acetylation of p-*Phenetidine*.—The preparation of acet-*p*-phenetidine (phenacetin) is similar to that of acetanilide. Equal weights of distilled phenetidine and glacial acetic acid are heated together at the boiling point of the mixture in an enamelled or silver-lined still until the diazo test shows that it is free from unchanged amine, which should be in about 10 hours. As much of the excess of acetic acid as will distil over *in vacuo* at about 120° is then recovered and the residue dissolved in boiling water, from which, after treatment with charcoal, filtering, and cooling, greyish-tinted crystals of phenacetin separate. These are centrifuged, and washed with water. It is purified by recrystallisation from boiling water or from 60 % alcohol, using animal charcoal to decolourise, and adding a little SO_2 to the filtered solution, to prevent oxidation during crystallisation.

From p-*Acetaminophenol*.—*Preparation of para-acetaminophenol*.—The preparation of para-aminophenol by the reduction of para-nitrophenol, using tin and hydrochloric acid,

has been described by Paul (*Zeits. angew. Chem.* 1896, **9**, 594). A cheaper method is to employ sodium sulphide. One part of *p*-nitrophenol is boiled with 3 parts of crystallised sodium sulphide for an hour, when reduction is complete. The
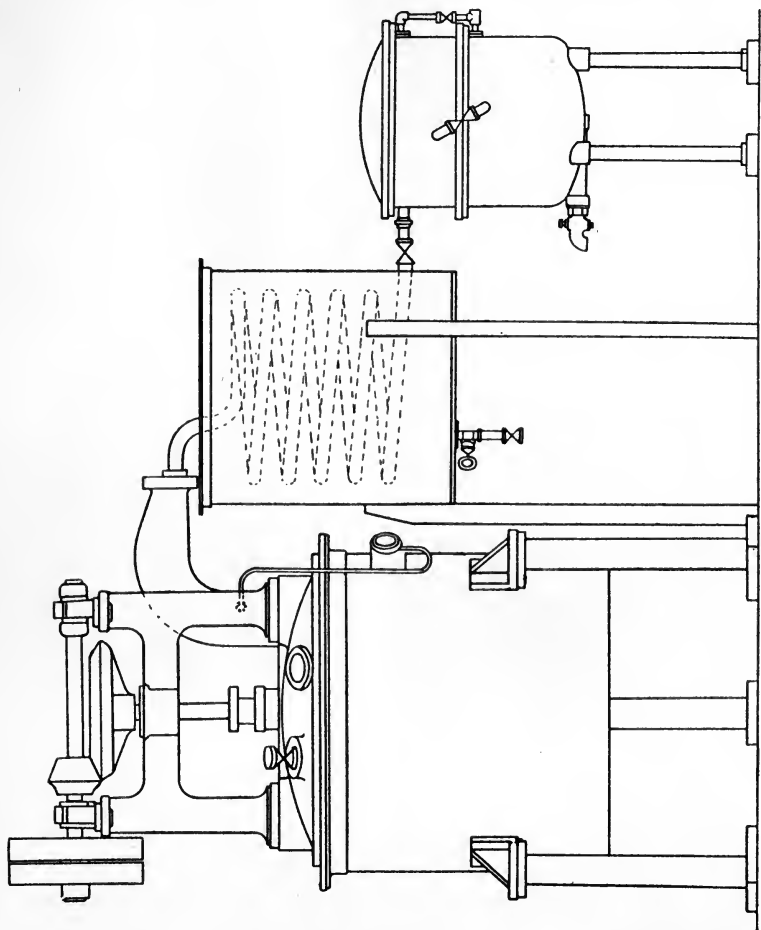

Fig. 15.—Vacuum Still with stirrer for phenetidine. Manlove.

product is poured, with stirring, into a slight excess, 5 parts, of hydrochloric acid solution (sp.gr. 1·14). The mixture is heated to boiling point and filtered. On cooling, *p*-amino-phenol hydrochloride crystallises out and is separated. The filtrate, after being concentrated until salt commences

to separate, affords on cooling a further small crop of the hydrochloride.

Another method for the preparation of *p*-aminophenol consists in reducing para-nitrosophenol, also with sodium sulphide.

p-*Nitrosophenol.*—In a wooden vat provided with an efficient stirrer is prepared a solution of 520 lb. of sodium nitrite in 100 galls. of water. This is cooled to +5° by the addition of ice and to it added slowly, simultaneously, and in equivalent quantities, a cold solution of 560 lb. of phenol in 56 lb. of water, and 400 lb. of sulphuric acid conc., diluted with 800 parts of ice. The temperature is kept between 4° and 7° by the addition of ice. After the addition is completed stirring is continued for an hour, after which 10 cwt. of salt is dissolved in the solution. The precipitated nitrosophenol is then centrifuged or strained off and washed with salt solution. It is reduced by being added gradually to a stirred mixture of 15 cwt. of sodium sulphide cryst. and 120 galls. of water. The temperature during addition of the nitrosophenol is not allowed to rise above 30°; after all has been added it is raised to 70°. The reduction liquor is then allowed to flow, with stirring, into 160 galls. of 25 % hydrochloric acid. The solution, which contains *p*-aminophenol hydrochloride, is filtered, after cooling, and the base precipitated by addition of soda ash. It is pressed off, washed with water, and purified by dissolving it in hot diluted sulphuric acid, from which crystals of pure aminophenol sulphate separate on cooling. This salt is only sparingly soluble in cold water. The filtrate, after addition of more sulphuric acid, is employed for dissolving a further quantity of the base.

Acetylation of p-*Aminophenol.*—An amount of the crystallised hydrochloride or sulphate containing 100 parts of *p*-aminophenol is mixed with water and the quantity of soda ash necessary to liberate the base is added. The mixture is well stirred, cooled to 10°, and 100 parts of acetic anhydride (100 %) added, in small quantities at a time, the temperature being kept at about 10° by the addition

of ice.   Stirring is continued for an hour after the anhydride has all been added, after which the precipitate of para-acetaminophenol is centrifuged off and washed with a little water or salt solution.   The filtrates are neutralised with sodium carbonate, and any base that is precipitated reacetylated with another batch.   The liquors may be evaporated down and the acetic acid recovered.

The acetaminophenol should be practically colourless and should melt at $167°$–$169°$.

Ethylation of p-*acetaminophenol.*—A quantity of moist *p*-acetaminophenol, containing 151 parts of the dry material (1 mol.), 120 parts of ethyl bromide ($1\frac{1}{10}$ mol.), 40 parts of caustic soda (1 mol.), and 400 parts of alcohol (S.V.M.), and recovered alcohol from a previous batch are refluxed together for 8 hours.   Excess of ethyl bromide and alcohol are then distilled off and the residue dissolved out in boiling water.   The solution, after filtration, is allowed to cool. Phenacetin crystallises out, a pinkish-grey product, and is centrifuged off.   From the liquors alcohol is recovered by distillation, and they are then evaporated down for the recovery of sodium bromide.

The crude phenacetin is purified by a further crystallisation from water, or from 90 % alcohol (S.V.M.), charcoal and SO_2 being employed as decolourising agents.

Phenacetin is usually sold in the form of white glistening crystalline scales.   M.p. $134°$.   It dissolves in 1700 parts of water, when cold, and in 50 parts of boiling water.   In cold 90 % alcohol, it is soluble to the extent of 1 in 21 ; and in cold 60 % alcohol, 1 in 100.

Phenacetin should dissolve without the formation even of a transitory colour in concentrated sulphuric acid.   A mixture of 0·3 gram with 1 c.c. of alcohol and 3 c.c. of water should not acquire a red colour on boiling with 1 drop of $\frac{N}{10}$ iodine solution (absence of phenetidine).   No residue should be left after ignition of a sample.

Phenacetin is a most widely used antipyretic and analgesic, and has a notable freedom from injurious action.

It does not produce nausea, and has but a slight depressant action. Phenacetin is administered for the relief of pain in neuralgia, rheumatism, locomotor ataxia, etc., and as an antipyretic in influenza and in fevers generally.

LACTOPHENIN (Lactyl phenetidine).

$$C_2H_5O\langle\quad\rangle NH(COCHOHCH_3). \quad 209.$$

The following methods of preparation of this substance have been described : by heating phenetidine lactate (D. R. P. 70250); by condensing lactamide with p-phenetidine (D. R. P. 81539) ; by treating with sodium acetate the condensation product of p-phenetidine and a-brompropionyl bromide (D. R. P. 85212) ; and by ethylating lactyl p-aminophenol (D. R. P. 90595). Of these the first is the only one likely to be employed in practice.

Ten kilos of phenetidine lactate are heated slowly to 180° in an enamelled vessel, *in vacuo*, and maintained at this temperature until water is no longer evolved. The reaction mixture is poured into 200 litres of water, which is boiled until solution is complete. Charcoal is employed to de-colourise the solution, from which, after filtration and cooling, the lactyl p-phenetidine crystallises out. If still coloured it is recrystallised from dilute alcohol, again with the use of charcoal. Lactophenin is a white crystalline powder. M.p. 117°–118°. It dissolves in 55 parts of boiling, and is sparingly soluble in cold, water.

The solution in pure sulphuric acid should be colourless. Lactophenin should give no reaction for para-phenetidine, which is tested for by boiling 5 c.c. of a solution in 25 % alcohol with 1 drop of $\frac{N}{10}$ iodine solution, when no red coloura-tion should be developed.
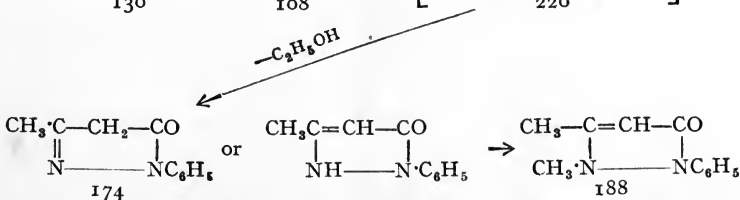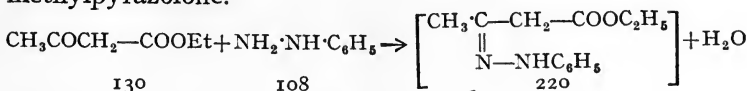
Lactophenin is antipyretic and analgesic, similar in action to phenacetin but stated to have a more marked hypnotic action and not to affect either the circulation or the respira-tion. It is employed in migraine, erysipelas, nervous headache, and the neuralgia of influenza. It is stated to attain its maximum activity in a very short time,

owing to its being, to a large extent, absorbed from the stomach.

ANTIPYRINE (Phenazone, analgesin), 1 phenyl- 2.3 dimethyl- 5-pyrazolone $C_{11}H_{12}ON_2$.   188.

$$
\begin{array}{c}
C_6H_5 \\
| \\
N \\
\diagup\diagdown \\
CH_3 \cdot N \quad CO \\
| \qquad | \\
CH_3-C=CH
\end{array}
$$
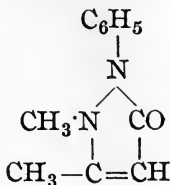
Antipyrine is prepared by condensing acetoacetic ester with phenyl hydrazine, and methylating the resulting 1·3 phenyl-methylpyrazolone.

$$
CH_3COCH_2-COOEt + NH_2 \cdot NH \cdot C_6H_5 \rightarrow \left[\begin{array}{c} CH_3 \cdot C-CH_2-COOC_2H_5 \\ \| \\ N-NHC_6H_5 \end{array} \right] + H_2O
$$

130   108   220

$-C_2H_5OH$

$$
\begin{array}{ccc}
CH_3 \cdot C-CH_2-CO & CH_3C=CH-CO & CH_3-C=CH-CO \\
\| \qquad\qquad | & \quad | \qquad\quad | & \quad | \qquad\qquad | \\
N\!-\!\!-\!\!-\!\!-\!NC_6H_5 \;\; or & NH\!-\!\!-\!\!-\!\!N \cdot C_6H_5 \;\rightarrow & CH_3 \cdot N\!-\!\!-\!\!-\!NC_6H_5 \\
174 & & 188
\end{array}
$$

D. R. P. 26429 ; E. P. 3097/1884 ; *Ber.* **16**, 2597, **17**, 549, 2037, **25**, 759 ; *Ann.* **238**, 147.

It has also been made, in one operation, by condensing equivalent quantities of acetoacetic ester and methyl-phenyl hydrazine $C_6H_5NH \cdot NHCH_3$ (D. R. P. 40377), but the yields afforded by this method are stated to be small.

Another patented process consists of condensing phenyl hydrazine with β-chloropropionic acid, to phenyldihydropyrazolone
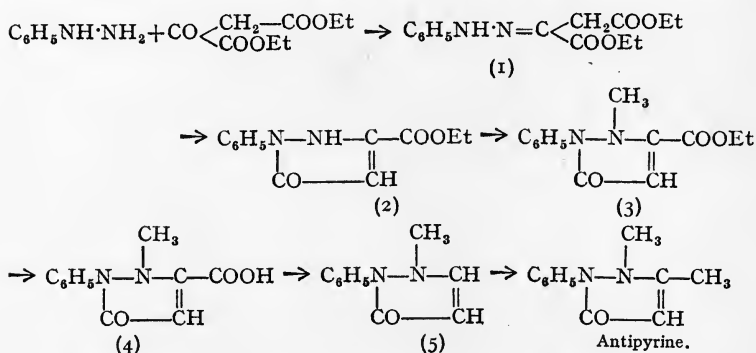
$$
\begin{array}{c}
C_6H_5N \\
NH\diagup\diagdown CO \\
| \qquad\quad | \\
CH_2-CH_2
\end{array}
$$
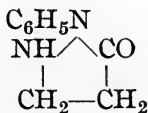
and oxidising this with mercuric oxide to phenylpyrazolone

$$
\begin{array}{c}
C_6H_5N \\
NH\diagup\diagdown CO \\
| \qquad\quad | \\
CH=CH
\end{array}
$$
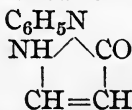
which affords antipyrine when methylated (D. R. P. 53834).

Protection was refused for a method whereby antipyrine was claimed to be formed in one operation, by heating under pressure a mixture of phenyl hydrazine, acetoacetic ester, sodium methyl sulphate, sodium iodide, and methyl alcohol containing a little hydriodic acid.

According to D. R. P. 69883, 1-phenyl-2-methyl-5-pyrazolone can be obtained by combining phenyl hydrazine and oxalacetic ester, methylating the product (phenylpyrazolone carbonic acid ester), saponifying and splitting off carbon dioxide ; alternatively the condensation product (2) is saponified, CO_2 split off, and the resulting body methylated.

$$C_6H_5NH \cdot NH_2 + CO \begin{subarray}{l} CH_2-COOEt \\ COOEt \end{subarray} \rightarrow C_6H_5NH \cdot N = C \begin{subarray}{l} CH_2COOEt \\ COOEt \end{subarray}$$

(1)

$$\rightarrow C_6H_5N-NH-C-COOEt \rightarrow C_6H_5N-\overset{CH_3}{\underset{\mid}{N}}-C-COOEt$$
$$\underset{CO----CH}{\mid \quad \quad \parallel} \quad \quad \underset{CO----CH}{\mid \quad \quad \parallel}$$

(2)   (3)

$$\rightarrow C_6H_5N-\overset{CH_3}{\underset{\mid}{N}}-C-COOH \rightarrow C_6H_5N-\overset{CH_3}{\underset{\mid}{N}}-CH \rightarrow C_6H_5N-\overset{CH_3}{\underset{\mid}{N}}-C-CH_3$$
$$\underset{CO----CH}{\mid \quad \parallel} \quad \quad \underset{CO----CH}{\mid \quad \parallel} \quad \quad \underset{CO----CH}{\mid \quad \parallel}$$

(4)   (5)   Antipyrine.

From Phenyl Hydrazine and Acetoacetic Ester (*see* D. R. P. 26429).—Pure acetoacetic ester, 120 kgs., mixed with 12 kgs. of 85 % alcohol, is allowed to flow, with cooling and stirring, into 100 kgs. of phenyl hydrazine which has been freshly distilled *in vacuo* and dissolved in benzene. The reacting substances are in practically equivalent proportions, the phenyl hydrazine being in very slight excess. It is stated that an excess of either is detrimental ; if of the ester, a yellow-coloured pyrazolone is produced which gives rise to an antipyrine that becomes coloured by the action of light ; if of phenyl hydrazine, the required condensation product is oxidised to a *bis*-phenylmethylpyrazolone. The mixture is boiled for a short time under a reflux, the solvent then distilled off and the residue is allowed to cool, when a crystalline mass of 1-phenyl-3-methyl-5-pyrazolone separates. It is dissolved in hot water, filtered from coloured impurities,

allowed to crystallise, and recrystallised from alcohol. M.p. 127°.

The phenyl-methyl-pyrazolone is methylated with methyl chloride or methyl bromide in methyl alcoholic solution, at 90°–100°, a slight excess of the methylating agent being employed. This operation is conducted under pressure in an autoclave fitted with stirring gear. After distilling off the alcohol the reaction product is dissolved in water, made slightly alkaline with sodium hydroxide solution, the alcohol and unchanged methylating agent are recovered, and the antipyrine is extracted with benzene. It is purified by recrystallisation, first from benzene, then from water, charcoal being employed to decolourise the solutions.

Antipyrine is sold in the form of colourless crystalline scales or as a white powder. It is odourless, and possesses a slightly bitter taste. M.p. 113°.

Soluble in $1\frac{1}{4}$ parts of water, very readily also in alcohol, chloroform, and benzene. The aqueous solution should be neutral to litmus and should not be affected by hydrogen sulphide solution.

Antipyrine is a valuable analgesic and antipyretic. It is employed in neuralgia, gout, rheumatism, and other painful affections, and is used to reduce temperature in febrile disease.

It is stated to be a good uterine sedative; also to relieve sickness. Antipyrine should not be administered to subjects of cardiac weakness, on account of its depressant effect. To counteract this it is frequently prescribed in conjunction with caffeine.

Combinations with antipyrine which have found considerable acceptance are antipyrine salicylate—*salipyrine*, and chloral and antipyrine—*hypnal*.

PYRAMIDON (4 - dimethylamino-1-phenyl-2.3-dimethyl pyrazolon) $C_{13}H_{17}ON_3$. 231.

$$C_6H_5$$
$$|$$
$$N$$
$$CH_3 \cdot N \diagup \diagdown CO$$
$$| \qquad |$$
$$CH_3 \cdot C \!=\! CN(CH_3)_2$$
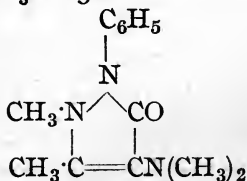
Pyramidon is obtained by the following series of reactions:—
Antipyrine is converted into its nitroso derivative, which is
reduced to the corresponding amino compound. This is
methylated, either by treatment with a methyl halide, or
by condensation with chloracetic acid followed by subse-
quent elimination of CO_2.

$$
\begin{array}{ccc}
\underset{\underset{CH_3C=CH}{\overset{CH_3N\diagup^{\diagdown}CO}{|}}}{\overset{\overset{C_6H_5}{|}}{\overset{N}{|}}}
& \rightarrow &
\underset{\underset{CH_3C=C\cdot NO}{\overset{CH_3N\diagup^{\diagdown}CO}{|}}}{\overset{\overset{C_6H_5}{|}}{\overset{N}{|}}}
\end{array}
$$

$$
\begin{array}{ccc}
\rightarrow \quad
\underset{\underset{CH_3\cdot C=C\cdot NH_2}{\overset{CH_3\cdot N\diagup^{\diagdown}CO}{|}}}{\overset{\overset{C_6H_5}{|}}{\overset{N}{|}}}
& \rightarrow &
\underset{\underset{CH_3\cdot C=CN(CH_3)_2}{\overset{CH_3\cdot N\diagup^{\diagdown}CO}{|}}}{\overset{\overset{C_6H_5}{|}}{\overset{N}{|}}}
\end{array}
$$
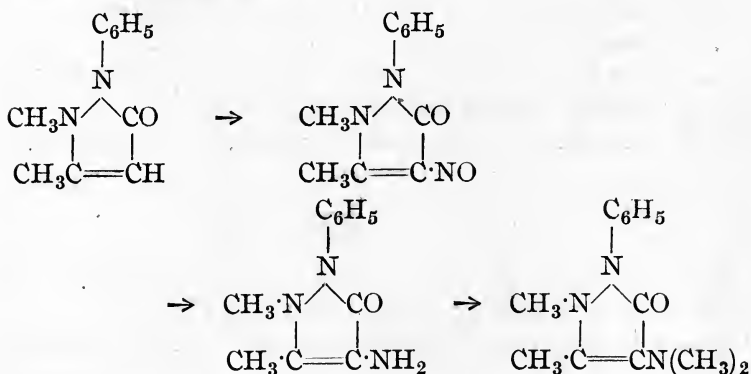
Nitroso-antipyrine is prepared (*Ann.* **238**, 212) by dis-
solving antipyrine in one molecular proportion of dilute
aqueous hydrochloric acid and treating, whilst cooling and
stirring, with the calculated quantity (1 mol.) of sodium
nitrite. The nitroso compound separates as a green crystal-
line precipitate, which is filtered off.

Nitroso-antipyrine is slightly soluble in water, alcohol, or
chloroform ; it dissolves in acids, and is reprecipitated on
neutralisation. On heating it decomposes at 200°.

Amino-antipyrine (D. R. P. 71261)

$$
\underset{\underset{CH_3\cdot C=C\cdot NH_2}{\overset{CH_3\cdot N\diagup^{\diagdown}CO}{|}}}{\overset{\overset{C_6H_5}{|}}{\overset{N}{|}}}
$$
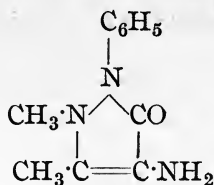
Nitroso-antipyrine, 100 parts, is suspended in a mixture of
100 parts of water, 500 parts of alcohol, and 200 parts of
10 % acetic acid and reduced by the gradual addition of zinc
dust. The temperature is kept below 40° by cooling.

When the nitroso body has all disappeared and the solution remains only slightly coloured, 48 parts of benzaldehyde, dissolved in 200 parts of 10 % acetic acid containing 20 % alcohol, are added, when the benzylidene compound of amino-antipyrine separates. After standing for some time the crystals are filtered off, washed first with 50 % alcohol, then with water acidified with acetic acid (to remove the zinc acetate), and dried. The product is recrystallised from alcohol, from which it separates in the form of yellow, shining leaflets. M.p. 173°.

The benzylidene compound is decomposed into benzaldehyde and amino-antipyrin hydrochloride by agitation with dilute hydrochloric acid and benzene. The acid layer is separated, neutralised, and concentrated ; then, after cooling, made alkaline with sodium carbonate and extracted with benzene or toluene, which removes the base.

Amino-antipyrine   crystallises   in   yellow   needles. M.p. 109°.

Methylation of Amino-antipyrine.—(a) *With methyl iodide* (D. R. P. 90959).—According to the patent specification 1 kg. of amido-antipyrine is heated for 1 hour at 90° with 1 kg. of methyl alcohol and 1 kg. of methyl iodide. The alcohol is distilled off, and the residue dissolved in water, made alkaline, and extracted with benzene. The solvent is distilled off and the pyramidon recrystallised from light petroleum.

In D. R. P. 111724 it is stated that in carrying out the methylation as above the quaternary methiodide is always produced together with the required tertiary base. This is converted into pyramidon by either of the following methods :—

(1) 10 parts of dimethylamino-phenylpyrazolone methiodide are heated under pressure with 40 parts of alcohol at 140° for 1 day. After cooling, any unchanged methiodide is filtered off and the pyramidon extracted, after removal of alcohol and alkalisation, with benzene.

(2) The methiodide is heated with an equivalent quantity of sodium acetate, in aqueous solution, at 150°–160° for 1 day.

Alcohol may be used by preference, the reaction being carried out at 140°. The pyramidon is extracted with benzene as above. It is to be noted in connection with this methylation, that considerably less than the theoretical quantity (2 mols.) of methyl iodide is stated to be used. At the same time it seems unlikely that, at the temperature given, methyl alcohol would act as a methylating agent.

(b) *With chloracetic acid* (D. R. P. 144393).—9·45 kgs. of chloracetic acid are dissolved in 25 litres of water, and gradually neutralised with 16·8 kgs. of sodium carbonate cryst. Amino-antipyrine, 10·15 kgs., is then added, and the mixture boiled, under a reflux condenser, for 2 hours. It is then cooled to 20° and treated with 2·37 kgs. of chloracetic acid, 4·3 kgs. of sodium carbonate, and 2·1 kgs. of sodium bicarbonate, and boiled for a further 2 hours.

The completion of the reaction is ascertained by the following tests :

Absence of amino-antipyrine.—A small test portion is diluted with water, cooled with ice, and treated first with HCl and then with sodium nitrite solution. Excess of nitrous acid is destroyed by the addition of urea, and the solution then added to an alkaline aqueous solution of R salt, when only a faint red colouration, or none, should be produced.

Test for absence of the monoacetic acid derivative.— Several cubic centimetres of the solution are made faintly acid with acetic acid, heated to 50° and extracted with chloroform, in which any mono-compound will be dissolved and obtained on evaporation of the solvent.

$$C_{11}H_{11}N_2O \cdot NH_2 + 2CH_2ClCOONa$$
$$\rightarrow \quad C_{11}H_{11}N_2O \cdot N \Big\langle {CH_2COOH \atop CH_2COOH} + 2NaCl$$
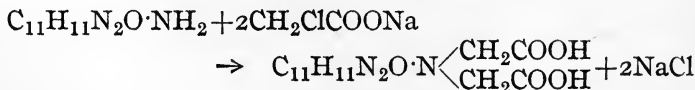
The total reaction mixture is now transferred to an enamelled autoclave, treated with 2·85 kgs. of 24 % hydrochloric acid (3¾ mols.) and heated for 10–12 hours at 120°

to 140°. Considerable pressure is present after cooling, owing to the liberation of CO_2.

$$C_{11}H_{11}N_2O \cdot N{<}{CH_2COOH \atop CH_2COOH} \quad \rightarrow \quad 2CO_2 + C_{11}H_{11}N_2O \cdot N{<}{CH_3 \atop CH_3}$$

After cooling, 25 kgs. of caustic soda are added, when a mass of white crystals separates. These are filtered off and the filtrate extracted three times with benzene. The crystals also are dissolved in the benzene, the solution is dried over potassium carbonate and the solvent distilled off. The pyramidon thus obtained is purified by recrystallisation from light petroleum.

As a modification of the above method 1 molecular proportion of amino-antipyrine, $2\frac{1}{2}$ mols. of chlor- or brom-acetic acid and $2\frac{1}{2}$ mols. of crystallised sodium acetate are heated together for 2 hours at 100°, followed by 1 hour at 120°. The mixture is then diluted with 2–3 volumes of water, treated with $3\frac{1}{2}$ mols. of sulphuric acid, and saturated with salt, when the diacetic acid derivative comes out in the form of a thick, gummy syrup. This is separated, and boiled with 1 mol. of sulphuric acid and 6 vols. of water, until evolution of CO_2 has ceased. The pyramidon is then precipitated, as in the former example, by saturating the solution with caustic soda.

Pyramidon is a white, or yellowish-white, crystalline powder. M.p. 108°. It dissolves in 11 parts of cold water, and is readily soluble in alcohol, ether, and benzene.

Pyramidon is antipyretic and analgesic, like antipyrine, and is effective in smaller doses. It is claimed to be comparatively free from harmful action on the blood, heart, or kidneys.

It is employed in acute febrile conditions incident to typhoid fever, pneumonia, and erysipelas; also in treatment of high temperature caused by tuberculosis. It has also been used in asthma of reflex origin.

BENZOIC ACID $C_7H_6O_2$. 122.—(C_6H_5COOH). Benzoic acid is formed during the production of benzaldehyde from toluene (*see* Barnett, *Coal Tar Dyes and Intermediates*, p. 79), and the commonly employed method of manufacture is as follows :—

Chlorine passed through lead pipes, is bubbled through rectified toluene heated to 110°, in an earthenware-lined or lead-lined cast-iron vessel, until it possesses, at 15°, a specific gravity of 1·35. The product consists mainly of benzotrichloride $C_6H_5CCl_3$, admixed with some benzal chloride $C_6H_5CHCl_2$. Iron must be carefully excluded from the apparatus, as ferric chloride acts as a catalyst and causes the chlorine to enter the nucleus, with formation of chlorotoluenes. It is necessary that both toluene and chlorine should be dry, since moisture also facilitates nuclear substitution. The hydrochloric acid which is evolved and volatilised toluene are condensed in earthenware condensers and washing towers.

Under the above conditions it is not necessary to employ a carrier, for which phosphorus trichloride has been recommended, or to conduct the chlorination in ultra-violet light, though the latter procedure is said to be advantageous in accelerating the reaction.

Sixty kgs. of benzotrichloride are added to 200 kgs. of milk of lime, containing 34 kgs. of CaO, and 20 grams of iron powder, in a cast-iron vessel, fitted with stirring gear and connected to a condenser. The mixture is heated by direct steam to 50°, at which point the temperature rises spontaneously; the water and benzaldehyde commence to distil and are allowed to reflux. When the reaction commences to slow down, direct steam is again applied, and the benzaldehyde is distilled away.

The operation takes 9–10 hours. The residual liquid is filtered, transferred to a wooden vat fitted with a stirrer, and acidified with hydrochloric acid to precipitate the benzoic acid. This is filtered off after cooling and purified by recrystallisation from water, or by sublimation after drying. In Fig. 16 is shown a plant for the sublimation of benzoic acid.

Another method for the preparation of benzoic acid, based on the formation and oxidation of benzyl alcohol, is given in E. P. 116348/1917. Toluene, 92 parts by weight, is chlorinated at its boiling point until the density

at 15° is 1·11, the bulk of the product being at this stage benzyl chloride. It is then boiled, in an iron vessel provided with a reflux condenser, for 2 hours, with a quantity of lime or caustic soda equivalent to the chlorine used, *e.g.* 400 parts of 20 % caustic soda. A solution of sodium or calcium hypochlorite, *e.g.* 2030 parts of calcium hypochlorite solution containing 7 % of available chlorine, is added in the course of 3 hours, and stirring is continued for a further 3 hours,
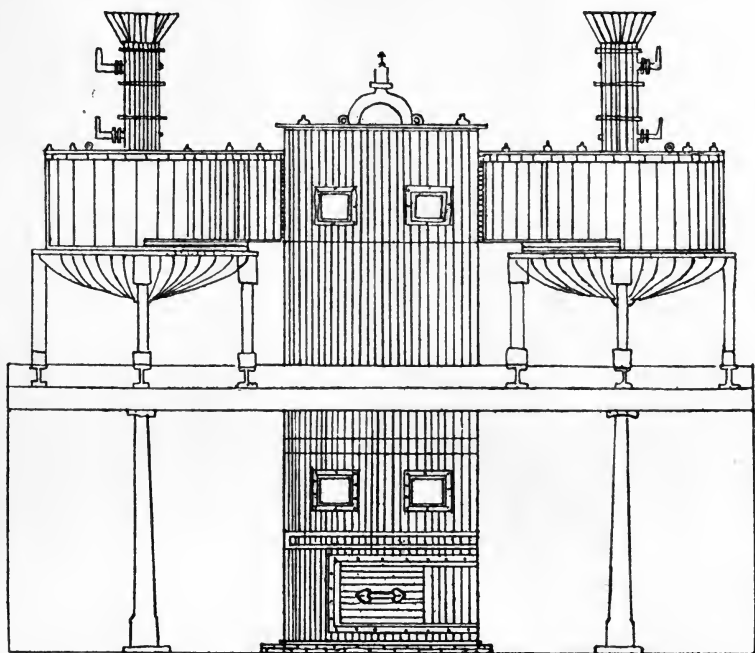
FIG. 16.—Benzoic acid sublimer.

after which the mixture is distilled until free from toluene. The residual alkali benzoate solution is filtered, and the benzoic acid precipitated with hydrochloric acid, dried and volatilised. The important object to attain in manufacturing benzoic acid for pharmaceutical purposes is freedom from chloro compounds.

Benzoic acid forms colourless, feathery, almost odourless crystals, melting at 121·4°. It is soluble in 390 parts of

cold, and in 12 parts of boiling water ; in 12 parts of benzene, and in $2\frac{3}{4}$ parts of 90 % alcohol. It should be free from chloro compounds, detected by igniting a portion with chlorine-free lime or calcium carbonate, dissolving the residue in nitric acid and adding silver nitrate solution. A solution in pure concentrated sulphuric acid should not become darker than light brown on warming, and the colour of 2 drops of 1 % potassium permanganate solution should not be immediately destroyed by 0·2 gram of the acid suspended in 10 c.c. of water.

Benzoic acid is employed as a disinfecting expectorant in cases of phthisis and chronic bronchitis ; also in chronic cystitis, to acidify and disinfect alkaline and decomposing urine. It is excreted partly as hippuric acid but partly unchanged. It is frequently administered in the form of its sodium or ammonium salt, since these are less irritating to the alimentary canal. The acid also possesses antipyretic properties, and is prescribed in acute rheumatism.

SALICYLIC ACID $\underset{}{\langle\ \rangle}\overset{\text{OH}}{\text{COOH}}$ (orthohydroxybenzoic acid). 138.—For the preparation of salicylic acid, sodium phenate is combined with carbon dioxide, forming sodium phenyl carbonate, which, on heating, is converted into sodium salicylate.

$$C_6H_5ONa + CO_2 \rightarrow C_6H_5OCOONa \rightarrow C_6H_4{<}{\overset{OH}{_{COONa}}}$$

The operations comprise :—
(1) The preparation of dry sodium phenate.
(2) Carbonation and conversion to sodium salicylate.
(3) The separation and purification of salicylic acid.

It is essential that the sodium phenate should be finely powdered and that it should be absolutely free from moisture. As, when hot, it readily oxidises in the presence of air, it is advisable to conduct the operation of drying and powdering in a shallow vacuum pan fitted with powerful stirring gear, similar to that shown in Figs. 17 and 18. In order to obviate the risk of the dried phenate absorbing moisture

when handled, it is desirable to carry out the drying and powdering in a vessel so constructed that the dried product can be transferred, without exposure, to the vessel in which the carbonation is to be conducted. The most suitable type of plant for the latter purpose is a horizontal jacketed steel autoclave, provided with powerful rotating stirrers which scrape the sides (Figs. 19 and 20). An inlet pipe for
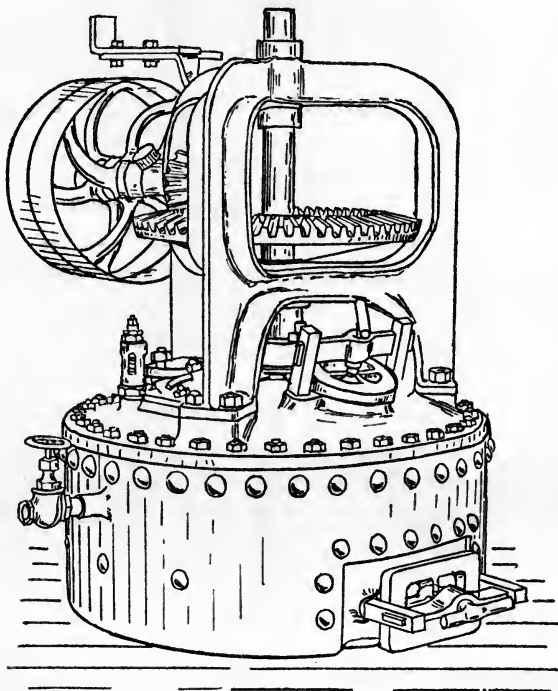
FIG. 17.—Vacuum dryer.

the introduction of the carbon dioxide is required ; also an outlet to a condenser and receiver (provided with a sight glass) which is connected with a vacuum pump, so that the phenate may be submitted to a final drying before carbonation commences. Either cold water or steam at 60 lbs. pressure can be circulated through the jacket.

Phenol is dissolved in the calculated quantity (1 mol.) of 40 % caustic soda solution and the mixture introduced

into the vacuum pan, in which it is evaporated to dryness *in vacuo*, the stirrers being kept continuously in motion.
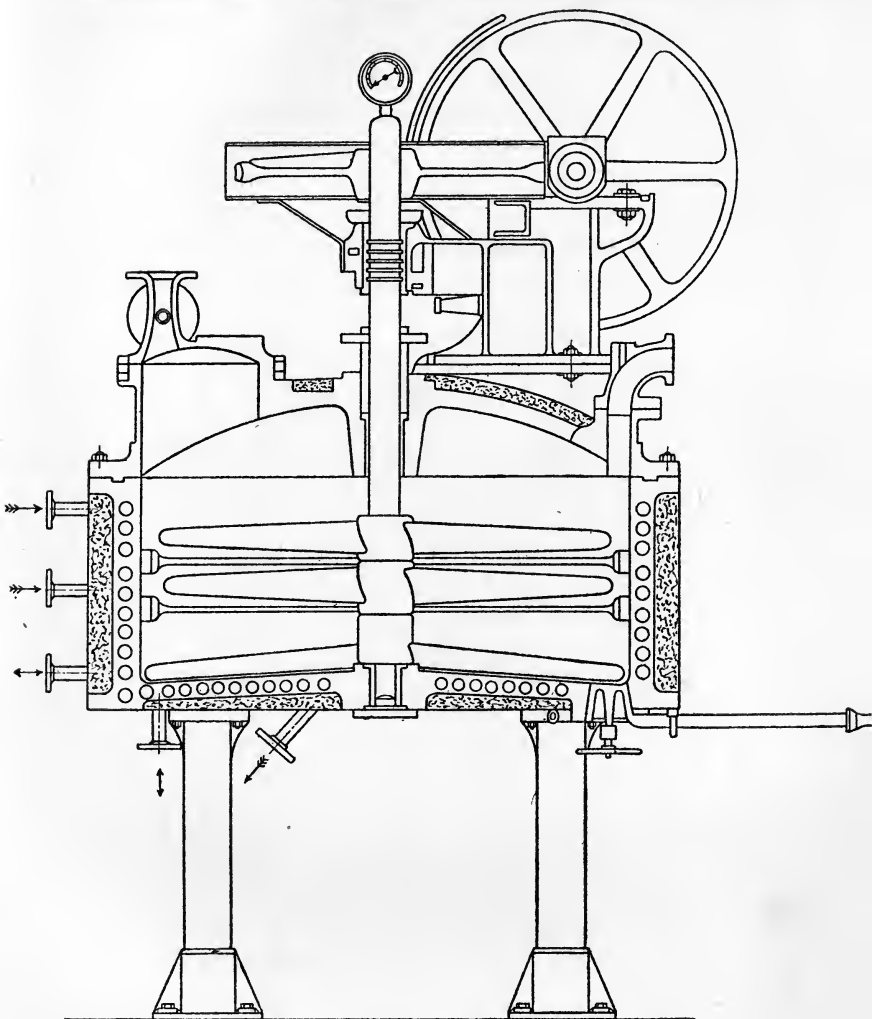
FIG. 18.—Vacuum dryer and carbonator.

Heating, to a temperature of 120°–130°, is continued for about an hour after the condensation of water has ceased. The sodium phenate is now in the form of a fine powder and is

transferred while still hot to the autoclave, the latter is rendered vacuous and the stirrer started ; the vacuum valve is then closed and dry carbon dioxide is introduced. Absorption takes place rapidly, with rise of temperature. The gas is passed in until the gauge shows a positive pressure of 3 atmospheres. Steam is then turned on and the temperature raised to 120°–130°, more gas being introduced to maintain the pressure. Heating is continued for 3 hours after absorption is complete, after which time it is stopped and the cold water circulated again, to reduce the temperature somewhat. The excess of CO_2 is used in the carbonation
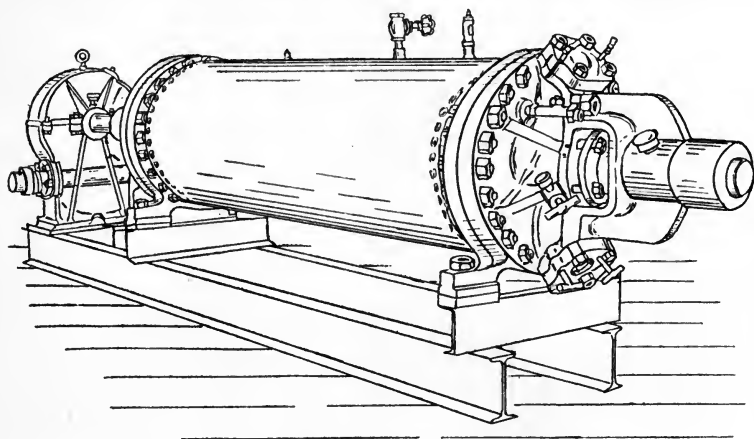
FIG. 19.—High-pressure autoclave for carbonating.

of a charge in another autoclave. Water is added and the solution of sodium salicylate pumped out, filtered, and transferred to a wooden vat with stirrer. The salicylic acid is precipitated by addition of acid, centrifuged off and dried. The crude acid, which is light brown in colour, is purified by distillation, either with superheated steam (*Ber.* (1875), **8**, 537) or with air. In the latter case the acid is heated in a shallow still provided with a stirrer, or in shallow trays, to a temperature of about 140°–150°. A current of air, preheated to the same degree, is blown through and over the stirred mass and thence into a suitable condensing chamber, in which provision is made for removing the heat ; also for filtering
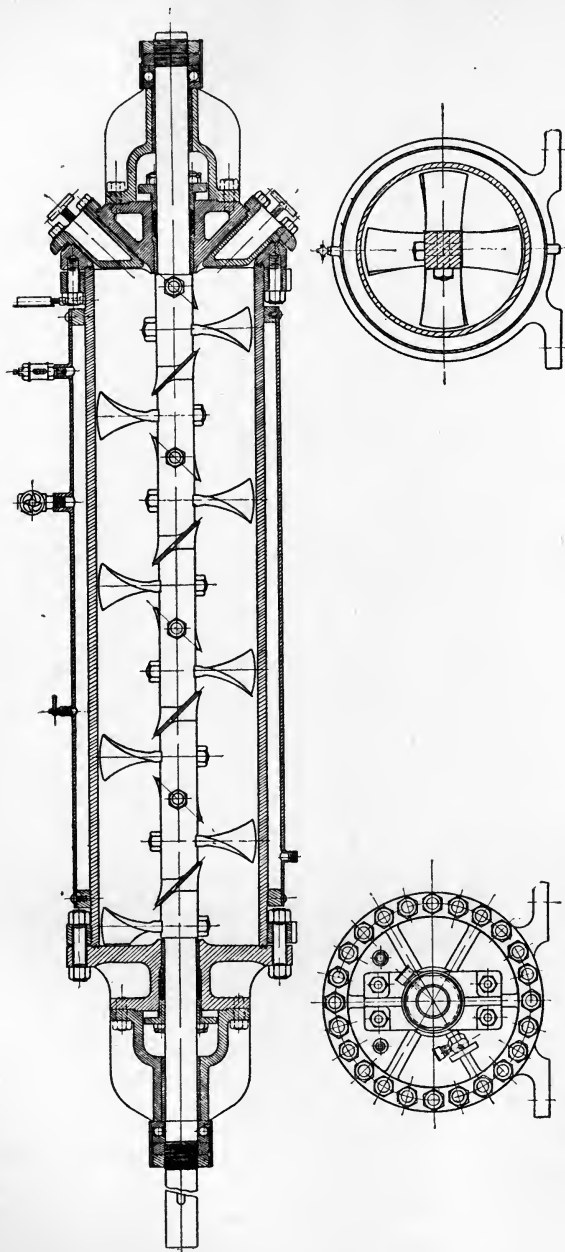
FIG. 20.—Horizontal M.S. steam jacketed agitator for carbonating.   Fraser.

out the last portions of salicylic acid flakes from the air (*see* D. R. PP. 10167, 29939, 38742). A ball mill designed for the production of dry sodium phenate is described in E. P. 105614/1916, and its use in E. P. 105611/1916. Five per cent. of sodium sulphite is added to the sodium phenate solution and the temperature of drying is given as 250°–280°. The product is cooled *in vacuo*. (*See also* E. P. 105612/1916 for the manufacture of salicylic acid.) In E. P. 105613/1916 is described a method for the purification of the crude sodium salicylate solution (1 in 9), whereby it is first pumped through a column containing granulated zinc, and then, at a temperature of 80°–100°, passed through a tower containing a mixture of 5 % of zinc and 95 % of decolourising charcoal. The liquor passing from the tower is stated to yield, on acidification, pure white salicylic acid. According to E. P. 274/1901, D. R. P. 133500, sodium phenate may be replaced by the product of the fusion of sodium benzene sulphonate (200 kgs.) with sodium hydroxide (111 kgs.).

Salicylic acid is sold in the form of colourless, light, matted needles, or somewhat heavier prismatic crystals. M.p. 157°.

It dissolves in 500 parts of water at 20° ; in 12 parts at 100°. Soluble in $3\frac{1}{2}$ parts of 90 % alcohol ; in 55 parts of chloroform and in 2 parts of ether.

A filtered sample of the aqueous solution, when evaporated to dryness, should afford a perfectly white residue. One part of the acid should dissolve without colouration in 6 parts of pure sulphuric acid. If 1 gram be dissolved in 20 c.c. of cold 10 % sodium carbonate solution, the liquid shaken with ether, and the ether be allowed to evaporate spontaneously, the residue, if any, should be free from the odour of phenol. An alcoholic solution of salicylic acid (10 %) should be unaffected by the addition of silver nitrate solution, after the addition of a few drops of nitric acid, indicating the absence of chlorides. Salicylic acid is both antiseptic and antipyretic. It is a specific in acute rheumatism, is used as a lotion in pruritis and some forms of eczema, and as an injection in the dysenteric diarrhœa of children. It is a

constituent of dusting powders and, dissolved in collodion, is employed as a solvent for corns and warts.

Of the salts of salicylic acid that are used in medicine, the action of which is dependent on the salicylic radicle alone, the sodium salt only needs attention.

Sodium Salicylate $C_6H_4\begin{matrix}\diagup OH \\ \diagdown COONa\end{matrix}$ 160.—When preparing sodium salicylate it is necessary to ensure that the materials are perfectly pure and free from even traces of metals such as iron, and to work in porcelain, nickel, silver, or glass-enamelled apparatus. 16·5 parts of pure salicylic acid and 10 parts of pure sodium bicarbonate, both free from iron, are intimately mixed in a porcelain edge runner, with a little water, to a thick paste. It is advisable to grind the acid with the water and to add the bicarbonate in portions, in order to prevent undue frothing. After most of the carbon dioxide has been evolved the mixture is evaporated to dryness *in vacuo*, at a temperature not exceeding 50°–60°. The dried sodium salicylate is powdered and sifted, or, if flaky crystals are required, is recrystallised from hot alcohol, with the addition of some ether. A slight excess of salicylic acid should always be employed, as alkaline solutions acquire a brown colour on evaporation.

The sodium salicylate of pharmacy is met with in the form of white, lustrous, pearly scales, or as a white amorphous powder. It dissolves in 1 part of water, in 5 parts of 90 % alcohol, and in 30 parts of absolute alcohol. The aqueous (10 %) solution is neutral or faintly acid to litmus, and should be perfectly bright. The salt should dissolve without effervescence and without colouration in pure sulphuric acid. An aqueous solution (10 %) should not be affected by hydrogen sulphide solution and should not give the reactions for chloride, sulphate, or sulphite. Sodium salicylate is less irritating than salicylic acid, whilst its greater solubility is often advantageous. It is prescribed in acute rheumatism, for which it is specific, and is useful in influenza, diabetes, sciatica, and acute tonsilitis. It is used as an antipyretic in pneumonia, typhoid fever, and all pyrexial affections. It

is also an effective antiseptic for fermentative dyspepsia, and increases the acidity of the urine.

Methyl salicylate $C_6H_4{<}^{OH}_{COOCH_3}$ 152.—Methyl salicylate is the main constituent of the oil of *Gaultheria procumbens* (Wintergreen), of which it comprises about 99 %. The volatile oil of *Betula lenta* (sweet birch) contains 99·8 % of methyl salicylate.

It is prepared synthetically by esterifying salicylic acid with methyl alcohol.

According to Ullmann (*Enzyclopæd. der Tech. Chem.*), 2 parts of salicylic acid, 2 parts of methyl alcohol, and 1 part of concentrated sulphuric acid are boiled together, the esterification mixture being worked up in the usual way by distillation.

Methyl salicylate boils at 219°–221°, and has a specific gravity of 1·185 to 1·90 at 15·5°. It is readily soluble in alcohol, ether, and chloroform. Very slightly soluble in water.

It is administered internally, in acute rheumatism and sciatica. It is employed as a liniment or ointment for external application to the joints and limbs. It is a good antiseptic and a frequent constituent of dentifrices.

Methyl salicylate is stated to be better for external application than oil of wintergreen, as it does not, like the latter, produce an eruption.

ACETYLSALICYLIC ACID (Aspirin) $C_6H_4{<}^{OCOCH_3 \ (1)}_{COOH \quad (2)}$ 180. —No trustworthy method for the preparation of aspirin appears yet to have been published.

It was first obtained, in a very impure state, as indicated by the low melting point (118°), by Kraut (*Ann.* **150,** 9), by the action of acetyl chloride upon salicylic acid and on sodium salicylate.

Bayer applied for a patent, No. 10563 and 10581 of 1898, but acceptance of this was declined, no doubt on account of the previous publication referred to. In this patent application salicylic acid and acetic anhydride were caused to interact

at temperatures below 160°, and it was stated that acetyl chloride could be employed in place of the anhydride. According to a method given by Ullmann (*Enzyclopæd. der Tech. Chem.*), 138 kgs. of salicylic acid are dissolved in 120 kgs. of acetic anhydride, and 500 grams of concentrated sulphuric acid added. The mixture is heated at 50°-60°, and the temperature taken up gradually to 90°. The mass is stirred whilst being allowed to cool and, when cold, the acetylsalicylic acid is filtered off, and washed, first with ice water and then with toluol. The acetic acid and unused acetic anhydride are distilled off from the mother liquors and salicylic acid recovered from the residue.

The work of Tsakalotos and Hörsch (*Bull. Soc. Chim.* [IV] **17**, 186 (1915)) serves to indicate the conditions under which the acetylation can best be carried out. Studying the velocity of the formation of acetylsalicylic acid by the action of acetic anhydride on salicylic acid in benzene solution these workers found the reaction to be one of the second order, the velocity being multipliable by 2·2 for each rise of 10°. The temperatures at which observations were made were 25°, 30° and 50°. At 90° it was found that a secondary change occurred, at an appreciable velocity, whereby the aspirin was converted into salicylosalicylic acid, with liberation of acetic anhydride, an irreversible reaction.

$$2C_6H_4{<}{OCOCH_3 \atop COOH} \rightarrow O{<}{C_6H_4COOH \atop COC_6H_4OH}+(CH_3CO)_2O$$
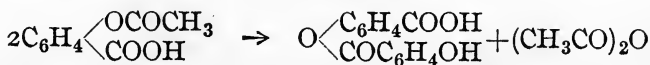
Using equimolecular quantities of the reacting materials in a dilute benzene solution (*ca.* 1 %) at 25°, equilibrium was reached in 24 hours, when, calculated from the titrations given, 94 % of the theoretical amount of acetylsalicylic acid had been produced under the conditions referred to, while at 50° in $3\frac{1}{2}$ hours only 86 % of conversion had taken place. In order to obtain complete conversion an excess of acetic anhydride is required and the temperature and time of reaction must be adjusted to the lowest practical limits. The presence of iron salts must be rigidly excluded, as this not only produces colour by interaction with salicylic acid,

but brings about catalytically the production of compounds in which the aceto group $COCH_3$ has entered the nucleus.

The aspirin is filtered from the acetylation mixture, dried, and recrystallised from dilute alcohol or other solvent.

Acetylation with Acetyl Chloride.—The acetylation of salicylic acid may also be carried out with acetyl chloride ; it is a matter for careful determination according to price whether this reagent or acetic anhydride is the more economical to use. The employment of the chloride is dominated by similar considerations to those discussed in connection with the anhydride. Contamination by metals such as iron or aluminium must be rigorously excluded, lest Friedel-Kraft's condensation be induced, and the working temperature must be kept as low as is practicable. Further, it is necessary to use a relatively large excess of the acetylating agent, as the reaction—

$$CH_3COCl + C_6H_4OH\text{--}COOH \rightleftarrows C_6H_4OCOCH_3\text{--}COOH + HCl$$
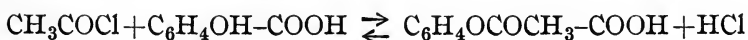
is reversible.

The reaction is carried out in a good enamelled, tiled, or earthenware-lined, jacketed still provided with a manhole for charging, a thermometer, a glass or earthenware pipe through which the acetyl chloride is introduced, with an earthenware or lead condenser, a receiver for the distillate (acetyl chloride), and a scrubber containing a solvent, such as acetic acid or high boiling petrol, for freeing the hydrogen chloride vapours as far as possible from acetyl chloride before being passed into an absorption tower.

The still is charged with 138 parts (1 mol.) of salicylic acid, to which are added 50 parts of glacial acetic acid and 200 parts of acetyl chloride (*ca.* $2\frac{1}{2}$ mols.). The still is heated up gently, steam being shut off as soon as the reaction is seen to be proceeding vigorously. Much HCl is evolved, and acetyl chloride commences to pass slowly over. As soon as a slackening is noticed the steam is applied again, the temperature being raised gradually to 60°. When the reaction has nearly ceased, the temperature is raised slowly to 70° in order to free the reaction mixture

as far as possible from acetyl chloride. The application of
a slight vacuum towards the finish greatly facilitates this.
When distillation has ceased, the still content is blown out
into enamelled pans and left until crystallisation is complete.
The crystallised mass is then centrifuged, washed with a
small quantity of solvent, and dried at 30°–40° until practi-
cally free from volatile acid.

Crystallisation of Aspirin.—A wide choice of solvents
for the purification of aspirin can be exercised according to
the circumstances. Benzene, ethyl or methyl acetate,
chloroform, ethyl or methyl alcohol, may each be employed.
It is important that high temperature should be avoided,
in order to prevent the production of salicylosalicylic acid,
which affects the product detrimentally. (*Bull. Soc. Chem.*
(1918) (IV.) **23**, 16.)

Tsakalotos and Hörsch (*ibid.* (1914), **15**, 743) have shown
that cold water, in which aspirin is soluble only to the extent
of 1 in 400, exerts an extremely slight hydrolysing action,
which, however, is enormously increased by the presence of
mineral acids, and to some extent by acetic acid.

A useful method of crystallisation is to dissolve the acid,
which must be quite free from mineral acid, and as free as
possible from acetic acid, in methyl or ethyl alcohol at a
moderate temperature and to throw it out of solution by the
addition of cold water.

Acetylsalicylic acid crystallises, when quite pure, in
small symmetrical rhombic plates ; though it is more
frequently met with in the form of more or less irregularly
shaped needles. Much discussion has taken place regarding
the melting point of pure aspirin. This can be made to
vary considerably, by altering the rate of heating ; but
under the conditions prescribed by the British Pharma-
copœia it may be taken as 134°–135°. It dissolves in 400
parts of cold water, and in 5 parts of 90 % alcohol.
0·1 gram treated with 5 c.c. of alcohol and diluted with
20 c.c. of water should not be coloured violet on the addition
of 1 drop of ferric chloride solution (absence of salicylic
acid). Volatile (acetic) acid should be absent as indicated

by a strip of moistened blue litmus paper, suspended in a closed bottle above a sample of the powdered substance, not becoming reddened within 20 minutes.

Acetylsalicylic acid is now probably the most generally used analgesic and antipyretic. Its action is similar to that of salicylic acid and the salicylates, and it does not irritate the stomach, to a large extent passing through it undecomposed. It is absorbed from the duodenum, where it is slowly hydrolysed, and it is said to be due to its gradual absorption in this way that it does not exhibit the cumulative toxic action of salicylic acid.

Calcium acetylsalicylate

$$\left(C_6H_4 \diagup{}^{OCOCH_3}_{COO}\right)_2 Ca + 2H_2O. \quad 434.$$
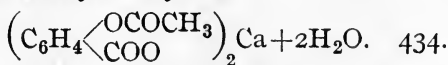
The preparation of this compound is attended with some difficulty on account of the readiness with which it hydrolyses and the consequent necessity for avoiding heat as well as that of preventing contamination by iron.

The following methods of procedure have been protected by patents :—

(*a*) Calcium acetate, 80 parts, dissolved in 240 parts of cold water, is added to a cold solution of 180 parts of acetylsalicylic acid in 1500 parts of methyl alcohol. Calcium acetylsalicylate crystallises out and is filtered off, washed with methyl alcohol, and dried. (E. P. 4053/1912. D. R. PP. 253924, 255673.)

(*b*) Acetylsalicylic acid, 1 kg., is rubbed up with 2 kgs. of water, and 350 grams of precipitated, iron-free, calcium carbonate added, with stirring. When evolution of CO_2 is at an end, the solution is filtered as quickly as possible and mixed with 3 to 4 volumes of methyl alcohol. The calcium salt crystallises out, and is filtered, washed with methyl alcohol, and dried at a low temperature. (D. R. P. 251333.)

(*c*) Acetylsalicylic acid, 180 parts, and anhydrous calcium chloride, 56 parts, are dissolved in 2000 parts of anhydrous methyl alcohol. A solution of 17 parts of NH_3 in methyl alcohol is added, whereupon the calcium acetylsalicylate crystallises out. (D. R. P. 275038.)

(*d*) Equivalent quantities of acetylsalicylic acid and dry sifted hydrated lime, Ca(OH)₂, are intimately mixed. The mixture is moistened with a small amount of a suitable solvent, and the whole triturated until a dried sample of the solid is found to be completely soluble in water. The solvent is then removed by filtration, and the calcium acetylsalicylate dried, powdered, and, if necessary, extracted with small quantities of dry ether until neutral, after which it is dried again. Suitable solvents are stated to be methyl alcohol, methylethyl ketone, methyl or ethyl acetate, methyl or ethyl formate, amyl acetate, and ethyl alcohol. (E. P. 100343/1916 ; D. R. PP. 27668, 286691, 287661.)

Calcium acetylsalicylate is a white crystalline powder, which dissolves in 6 parts of water. It should be neutral in reaction to litmus, and practically free from salicylic acid.

It is employed in the treatment of rheumatism, of influenza, of catarrhs, and neuralgia, and generally as an analgesic. It is stated also to be efficacious in cases of obstinate diarrhœa.

Sodium acetylsalicylate (D. R. P. 270326).—180 parts of finely powdered acetylsalicylic acid are mixed intimately with 55 parts of powdered anhydrous sodium carbonate and 150 parts of ethyl acetate. The mixture is ground in a mill for some hours, until a test portion dissolves completely in water, without evolution of CO_2. The product is then filtered off, washed with ether, and dried *in vacuo*.

The lithium salt may be similarly prepared. It has been specially recommended for treatment of rheumatism.

Section V.—ORGANIC ANTISEPTICS AND DISINFECTANTS

A very large variety of substances (antiseptics) possess the property of inhibiting the growth of bacteria, and many of these possess also the property of killing them (disinfectants). There are numerous inorganic substances not coming within the scope of this volume which act powerfully in these respects. Such, for instance, are boric acid, hydrogen peroxide, mercury, zinc, bismuth and silver salts, the hypochlorites and the free halogens. Others to be classed among the organic substances with which we are concerned are dealt with in different sections of this book ; such are exemplified by quinine, benzoic and salicylic acids, ether and chloroform, etc.

Disease germs may need to be attacked by a disinfectant in widely different circumstances ; they may be on a superficial wound, a diseased skin lesion, a mucous surface, or in the intestines, veins or tissues, and the agent suitable in one of these cases is not necessarily suitable in the others.

Simple estimates of germicidal action made *in vitro* have proved misleading as to the practical value of the agent. In testing antiseptics it is necessary to choose methods which are in conformity with the purpose for which they are to be used as regards considerations of concentration, temperature, and above all of the medium. Dakin has shown that in a medium composed of a mixture of blood serum and muscle extract very different results are obtained from those *in which* water is employed.

In a mixture of blood serum and muscle extract hydrogen peroxide possesses negligible value as a disinfectant,

while the activity of sodium hypochlorite in this medium is much greater than in defibrinated blood. He has also pointed out that a likely explanation of the deep-seated action of chlorine antiseptics is due to the formation of chloramine groupings in the amino-acid residue of the proteins.

The cells of a body surface may become poisoned by a particular disinfectant, so that healing is retarded, or again the curative action of the blood may be weakened by damage to the leucocytes by the disinfectant. (Recent experimentation has been largely directed to the discovery of substances which differentiate between the protoplasm of the host and that of its invading microbe;) forms of protoplasm differ in their affinities for dyes, and dyes have already been discovered which exert powerful germicidal action, as instanced by the flavine antiseptics.) There is, therefore, reason to hope that great improvements upon the older methods of disinfection are at hand. In the present section various phenolic antiseptics are classed together, as are also the halogen disinfectants. Other than this, but little chemical classification of these substances is possible.

PHENOL (carbolic acid) C_6H_5OH. 94.—Phenol is manufactured technically by fusing benzene-monosulphonic acid with caustic soda. Another method, however, has been protected (E. P. 25555/1912), whereby monochlorobenzene is heated under a pressure of 200–300 atmospheres, at 300°, with 4 molecular proportions of 15 to 20 % caustic soda. A 96 % yield of pure phenol is obtained.

Preparation of Benzenesulphonic acid (*see* Cain, *Manufacture of Intermediate Products for Dyes*, p. 101).—The sulphonation of benzene is performed in a closed, cast-iron, steam-jacketed vessel, fitted with a helical stirrer having a speed of 180 revolutions per minute (Grandmougin, *Rev. Prod. Chim.* (1916), **19**, 373). The lid is supplied with a thermometer pipe, a reflux condenser, and a charging hole. The vessel is fitted with a valve at the bottom for running out the finished batch. It is charged with 225 kilos of sulphuric acid (100 %) and 100 kilos of benzene. The

stirrer must be kept running constantly. The temperature rises to 60°–70° and is then raised further by turning steam into the jacket so as to keep the benzene gently boiling. At the end of seven to eight hours the benzene should have disappeared and the product should be completely soluble in water.

Alternatively, the vessel may be charged with 260 kilos of 98 % acid and 40 kilos of benzene. The remaining 60 kilos are added as the temperature ceases to rise, and finally the temperature is raised to 80°.

In D. R. P. 113784, 100 parts of benzene are heated with 250 parts of an acid sodium sulphate, $NaH_3(SO_4)_2$, prepared by treating sodium bisulphate with sulphuric acid (66° Bé.). The reaction mixture is diluted with water, and neutralised with milk of lime, and filtered from gypsum, the filtrate constituting a solution of sodium benzenesulphonate.

Sodium Benzenesulphonate.—The mixture obtained as above by the sulphonation of 100 kilos of benzene is run into 300 litres of water contained in a lead-lined vat fitted with a stirrer and a perforated-lead steam-coil, and nearly neutralised with milk of lime (about 140 kilos of lime and 700 litres of water). Complete neutralisation is effected by adding precipitated calcium carbonate obtained from the next operation. The whole is heated to boiling, about 450 litres of cold water are added so as to render the calcium sulphate easily filterable, and it is filtered through a filter press at about 60°. The calcium sulphate is well washed, the wash liquors being used to dilute the next sulphonation mixture or to slake the lime. The filtrate, which contains calcium benzenesulphonate, is stirred and sodium carbonate added until a filtered sample gives no further precipitate with the alkali; about 70 kilos of sodium carbonate are required. The precipitated calcium carbonate is allowed to settle, the clear liquid separated by decantation or filtration, evaporated and finally dried. Drum dryers are used in America for this purpose. About 230–235 kilos of sodium benzenesulphonate are obtained from 100 kilos of benzene. Instead of sodium carbonate the sulphate may

be used in the above operation, and, further, the correct amounts of lime and sodium sulphate may be added to the diluted sulphonation mixture (U. S. P. 1207798).

As an alternative method the sulphonation mixture from 100 kilos of benzene is poured into a lead-lined tank (25 cm. deep) fitted with an agitator, and containing about 250 litres of water and 150 kilos of anhydrous sodium sulphate. On cooling, the sodium benzenesulphonate is centrifuged or filtered. The separation is rather slow and it is necessary to have a large surface for this purpose. About 180 square metres are required for 1 ton of benzene. The product contains about 84 % of the sodium salt and the yield is about 210–220 kilos, but can be increased with good working. The filtrate from the separation may be used (U. S. P. 1179415) to acidify the sodium phenoxide from the fusion. Sodium carbonate may be used instead of the sulphate ; in U. S. P. 1191880 the phenol from the sodium phenoxide is liberated by means of carbon dioxide and the sodium carbonate so formed employed to neutralise the sulphonation mixture.

Fusion with Sodium hydroxide.—This is done in an open cast-iron pan fitted with an agitator and heated by gas. Local overheating must be avoided, as this gives rise to the formation of thiophenol. Two hundred and twenty kilos of sodium hydroxide (90 % NaOH) are placed in the pan, 20 litres of water added, and the mixture is heated to 290°. Two hundred and eighty kilos of sodium benzene sulphonate are slowly added, care being taken that the temperature does not drop but rises gradually to 300°. When the addition is finished, the temperature may be raised to 315°–330°, but must not go beyond 340°. The reaction proceeds fairly rapidly and the mass finally becomes fluid and homogeneous. The fusion takes 3–4 hours as a rule. It is now run, while still fluid, into cold water, three parts of the latter being used for one part of sodium hydroxide employed. The temperature of the water rises to nearly 100°, and the solution has a density of 27° Bé. The sodium phenoxide is thus dissolved whilst most of the

sodium sulphite separates in the anhydrous condition. The whole is filtered and the sulphite is mixed with water at 85° and filtered again, the wash waters being added to the solution phenoxide. This solution is treated with sulphuric acid (about 190 kilos of 50° Bé.) until it is neutral to litmus, and after a few hours the phenol, which forms as a yellowish oily layer on the top of the aqueous solution, is separated. By allowing the aqueous solution to crystallise, sodium sulphate is obtained, which can be again used in the process.

The phenol is washed with water and distilled in a vacuum. A silver or silver-plated copper coil may be used.

The yield by the " salting out " method is 82–83 %. By the liming method 85 % can be obtained.

Phenol, or carbolic acid, forms small, colourless, deliquescent crystals, which have a tendency to acquire a pink tinge on exposure to air and light; whilst synthetic phenol turns yellow to brown. It is soluble in 12 to 13 parts of water, and is very readily soluble in alcohol, ether, and other organic solvents.

The melting point should be not less than 38·8° (102° F.); synthetic phenol usually fusing at 40·5°. B.p. 178°–182°.

Ten parts liquefied by the addition of 1 part of water should form a clear liquid with 3 to 4 parts of water, and be completely dissolved by 120 parts of water.

One volume of phenol liquefied by the addition of 10 % of water should form a clear liquid when mixed with 1 vol. of glycerine, and not be rendered turbid when 3 vols. of water are added (freedom from cresylic acid).

Phenol acts as an antiseptic, a disinfectant, and a local anæsthetic. Externally, when undiluted, it is powerfully caustic ; as a lotion it is applied for eczema, ulcers, carbuncles, ringworm and other parasitic skin diseases. It is given internally as an intestinal and gastric antiseptic, in phthisis, bronchitis, whooping-cough, and as a prophylactic in scarlet fever. A solution of sodium phenate is used as an antiseptic mouth-wash.

SALOL (phenylsalicylate) $C_6H_4\!\!<^{OH}_{COOC_6H_5}$. 214.—According to D. R. P. 38973, salol is prepared by the action of phenol and phosphorus oxychloride upon salicylic acid or sodium salicylate,

$$2C_6H_4\!\!<^{OH}_{COONa} + 2C_6H_5OH + POCl_3$$
$$\quad 320 \qquad\qquad 188 \qquad 153$$
$$\rightarrow 2C_6H_4\!\!<^{OH}_{COOC_6H_5} + NaPO_3 + NaCl + 2HCl$$
$$428$$
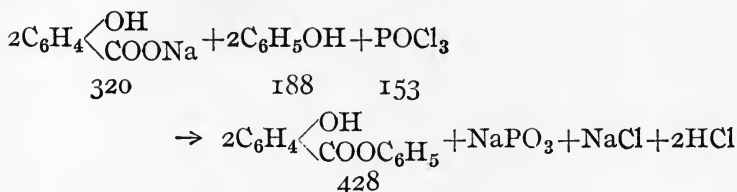
or by using sodium phenate in place of phenol,

$$2C_6H_4\!\!<^{OH}_{COONa} + 2C_6H_5ONa + POCl_3$$
$$\rightarrow 2C_6H_4\!\!<^{OH}_{COOC_6H_5} + NaPO_3 + 3NaCl$$
$$428$$
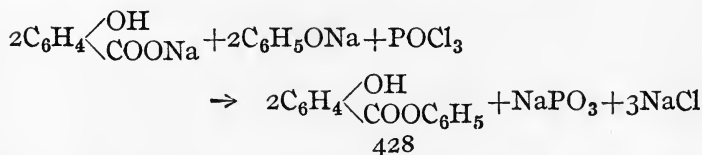
By an addition to the above patent, D. R. P. 43713, benzol or toluol may be used as a diluent or vehicle in the above reactions, sodium or potassium acid sulphate being employed as dehydrating agent. When employing salicylic acid, phenol, and $POCl_3$, these substances are mixed in the proportions required by the equation and the mixture is heated, in an enamelled still (Fig. 21), at 120°–130° for 2 hours. The vessel is provided with a reflux condenser, and provision is made for taking away the HCl fumes that are evolved. After the reaction mixture has cooled, the upper layer is separated and agitated with sodium carbonate solution until free from salicylic acid. It is then washed with water, dried with calcium chloride, distilled under a vacuum of 10 mm. and obtained pure and in crystalline form by crystallisation from 60 % alcohol.

It has been stated that it is preferable to use sodium salicylate and sodium phenate in carrying out the above reaction, as the formation of phosphoric esters is thereby inhibited.

By another process, D. R. P. 31984, phosgene is employed as a condensing agent in place of phosphorus oxychloride.

Fifty kilos of sodium phenate and 80 kilos of sodium salicylate (anhydrous) are mixed in a cast-iron vessel provided with stirring gear and a steam jacket or internal coils, and
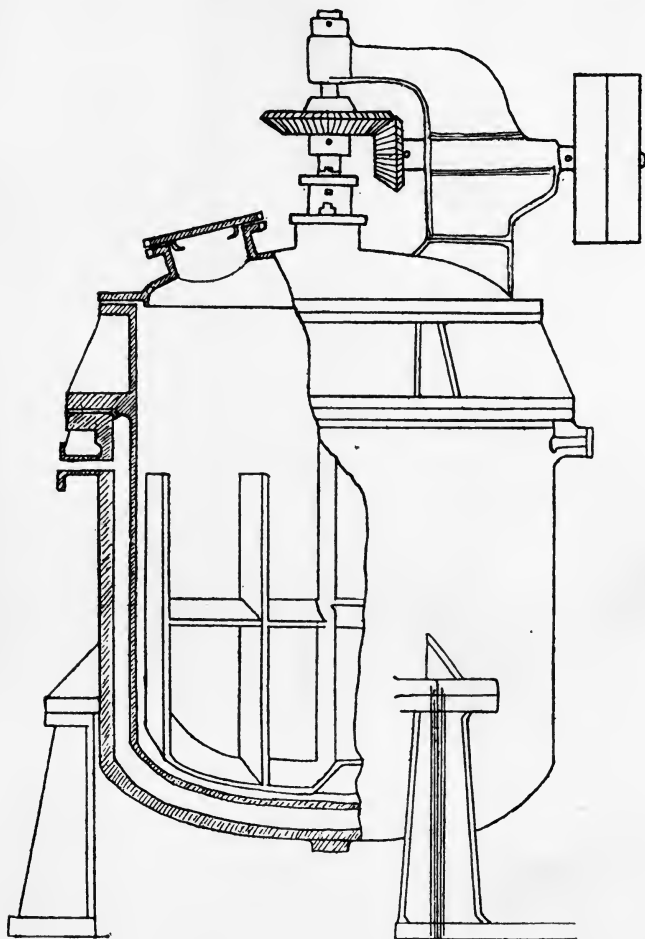
FIG. 21.—Enamelled still.

phosgene is introduced. Heat is developed, a vigorous reaction taking place. It is completed by gentle heating, after which the salol is distilled over in steam and recrystallised from dilute alcohol.

$$C_6H_5ONa + C_6H_4{<}^{OH}_{COONa} + COCl_2$$
$$\quad 116 \qquad\qquad 160 \qquad\quad 99$$

$$\rightarrow \ C_6H_4{<}^{OH}_{COOC_6H_5} + 2NaCl + CO_2$$
$$\qquad\qquad\qquad 214$$
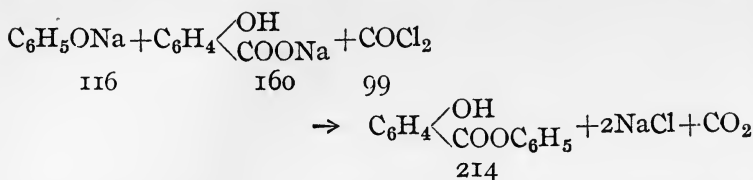
Salol forms colourless translucent crystals, possessing a characteristic odour. M.p. 42°–43°.

It is insoluble in cold water; dissolves in 12 parts of 90 % alcohol; very soluble in ether, chloroform and most organic solvents.

When shaken with 50 times its weight of water and filtered, the filtrate should not afford the reactions of chlorides or sulphates; nor give a violet or blue colouration on treatment with ferric chloride solution (absence of phenol and of salicylic acid).

Salol is antipyretic and antiseptic; it is used largely as an intestinal and urinary disinfectant. It is stated to pass unchanged through the stomach, but to be decomposed in the small intestine into its components, phenol and salicylic acid.

Salol has been recommended in dyspepsia, intestinal fermentation, intestinal tuberculosis, in acute and chronic rheumatism, and in cholera, typhoid fever, and smallpox. It has also been applied externally to wounds and employed as a constituent of antiseptic mouth-washes.

RESORCINOL (*m*-dihydroxy-benzene) 110.—
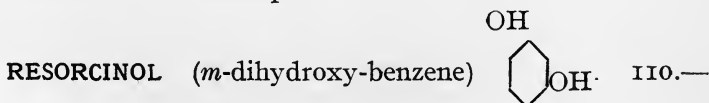
Resorcinol is manufactured by fusing benzene-*m*-disulphonic acid with caustic soda. The following description is given by Mühlhaüser (*Dingl. Polyt. J.* (1887), **263**, 154), and is taken from Cain (*Manufacture of Intermediate Products for Dyes*, p. 127).

Preparation of Benzenemonosulphonic acid.—Three hundred kilos of sulphuric acid, 67° Bé., and 60 kilos of pure benzene are placed in a cast-iron jacketed vessel of 400 litres capacity fitted with stirrer and a lead reflux condenser,

the mixture well stirred and warmed to about 80°. The pipe between the reflux condenser and the vessel should feel only slightly warm to the hand. The process is carried on for 10 hours, when monosulphonation should be complete.

*Preparation of Salt of Benzene-*m-*disulphonic acid.*—Next day the above batch is blown into a cast-iron oil-jacketed vessel of 800 litres capacity, fitted with a stirrer and an ordinary lead condenser ; 85 kilos of dry ground sodium sulphate are added, the stirrer is kept going, and the oil bath heated to 240°. After about 4 hours the contents of the vessel will have reached the temperature of about 225° and are kept at this point for about 8 hours. During the first period of heating benzene distils over and sulphur dioxide is evolved. On the following day the contents of the vessel are blown into 1500 litres of water contained in a vat of 3000 litres capacity, and neutralised with sifted slaked lime made from 200 kilos of quicklime. In order to render the calcium sulphate easily filterable about 800 litres of cold water are added to the boiling mixture, which is then filtered through a filter press. The press cake is boiled up with about 1500 litres of water, cold water being added as before, and again filtered. The combined filtrates are evaporated to about 2000 litres and then treated in a vat with 6 to 10 kilos of sodium carbonate, to convert the calcium salt into the sodium salt. The calcium carbonate is filtered off by means of a filter press and the filtrate evaporated in two evaporating pans, 1500 litres capacity, provided with stirrers, until it is thick enough to stop the stirrers. The moist salt is then completely dried in drying pans, being continually stirred with an iron rake, and the dry powder is ground and sieved. Yield 200 kilos.

Fusion.—Two hundred and fifty kilos of solid caustic soda are put into a cast-iron vessel (600 litres) fitted with stirrer, and heated by direct fire ; 10 kilos of water are added and the mixture is heated until no skin is formed on the surface and the crusts forming on the sides have also melted (270°). The stirrer is started and 125 kilos of the dry sodium salt are added within about half an hour, care being taken that the

mass does not froth over. This can be regulated by stopping and restarting the stirrer. The foaming gradually ceases and the melt acquires an oily appearance ; it becomes yellow and then brown. When no further reaction appears to be taking place (8–9 hours), the mass is scooped out on to iron trays, where it solidifies on cooling.

Extraction.—The broken-up cakes are added to 500 litres of water in a 1500 litre earthenware vessel and made just acid with hydrochloric acid (7 to 8 carboys). When the sulphur dioxide has been driven off, the solution is blown into an extraction apparatus consisting of a closed vessel (2000 litres) fitted with a stirrer, a separator (2000 litres), and a container for the solvent (500 litres). It is extracted four times with amyl alcohol, 100 litres being used for each extraction. The solution and amyl alcohol are mixed together for about 30 minutes and then blown into the separator, which is a cylinder with a pointed end. After settling for an hour the aqueous solution is run back into the extractor. The solution of resorcinol in amyl alcohol is first heated to about 100° with indirect steam and then steam is passed in to drive over the solvent. When only water is being condensed, the resorcinol solution is run into an enamelled drying pan, where the water is evaporated.

Purification.—The resorcinol is purified by distillation in a vacuum. The contents of the drying pan are transferred to a copper still (75 litres capacity) and heated, at first without vacuum being applied. A little water and phenol pass over first. At about 190° the pressure is reduced to 130 mm. and the resorcinol distilled over. About 20–23 kilos of pure resorcinol are obtained from 125 kilos of the disulphonate.

Ether may be used in place of amyl alcohol for the extraction.

Resorcinol forms white, or nearly white, glistening needle-shaped or prismatic crystals. One hundred parts of water dissolve 86·4 parts at 0°, 147 parts at 12·5°, and 228·6 parts at 30°. It is very readily soluble in alcohol and in ether. M.p. 118°–119°. B.p. 276°.

The aqueous solution should be colourless and should yield no precipitate when treated with lead acetate (absence of catechol). No odour of phenol should be emitted when the concentrated aqueous solution is gently heated. The aqueous solution should not give a red colour with a pine splinter nor afford an odour of benzoquinone when warmed with ferric chloride (absence of quinol).

Resorcinol is a powerful antiseptic. It is employed as a spray (1 to 2 %) in diphtheria and whooping-cough, in ointments (5 to 10 %) in the treatment of skin diseases, and in lotions for removing dandruff from the scalp. Internally it is prescribed in diarrhœa and gastric affections. It exercises a very depressant action on the heart.

MONOACETYL-RESORCINOL (Euresol) $C_6H_4{<}^{OH}_{OCOCH_3}$ 152.
—Ten kilos of resorcinol (D. R. P. 103857) are mixed with 2·2 litres of acetic anhydride and 1·8 litres of glacial acetic acid, and heated for $1\frac{1}{2}$ hours at 40°, followed by an hour's heating at 45°. Excess of acetic anhydride is then destroyed by careful addition of water, and the acetic acid removed completely by distillation *in vacuo* and with the aid of a current of carbon dioxide. Pure resorcinol monoacetate remains. It is completely soluble in caustic alkali and distils at 283°.
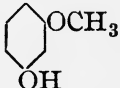
Alternatively, 5 kilos of resorcinol dissolved in 7·5 litres of glacial acetic acid are treated with 3·5 litres of acetyl chloride, with good cooling. The mixture is finally warmed for an hour at 40° and worked up as in the previous example.

According to D. R. P. 281099, 8 parts of resorcinol are mixed with $7\frac{1}{2}$ parts of acetic anhydride and 2 parts of glacial acetic acid and the mixture heated on the water bath for several hours. Acetic acid is then distilled off in a vacuum, and a current of slightly superheated steam is passed, *in vacuo*, over the residue, which is heated at 100°, until it is free from any unpleasant smell.

Euresol is a thick, honey-like, yellow liquid, which is fairly soluble in water, and readily soluble in acetone. It should possess a saponification value agreeing with that

required by the monoacetate of resorcinol, and should be readily soluble in cold dilute caustic soda (freedom from resorcin diacetate).

Euresol possesses an antiseptic action similar to that of resorcinol, but milder and more lasting, the phenol being only gradually liberated. It is said to be useful in acne, scrofula, chilblains, and particularly in the treatment of alopecia and seborrhœa.

GUAIACOL (pyrocatechol monomethyl ether)

124.—Guaiacol occurs in beechwood tar, of which it constitutes the fraction distilling at 200°–205°. It is prepared synthetically according to the following reactions :

o-nitrophenol. → o-nitroanisol. → o-anisidine. → → Guaiacol.
139   153   123   124
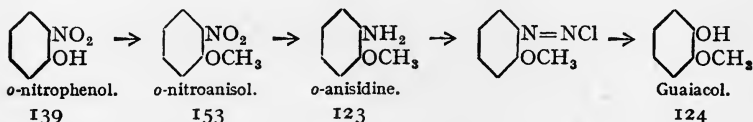
Preparation of o-nitroanisol.—The following account of the preparation of o-nitroanisol by the methylation of o-nitrophenol is given by Jansen (*Chem. Zeit.* (1913), **12**, 171 ; *Zeits. Farb. Ind.* (1913), **12**, 247).

Eighty-three kilos of caustic soda solution (37° Bé.), 180 litres of water, and 75·5 kilos of o-nitrophenol are placed in a cast-iron steam-jacketed pan and evaporated to a thick paste. On cooling, the whole sets to a thick cake (162 kilos). One hundred and sixty kilos of this are transferred to a jacketed autoclave fitted with a stirrer, and 60 kilos of anhydrous sodium carbonate and 90 kilos of methyl alcohol are added. The autoclave is closed, and 51·5 kilos of methyl chloride are led in. The stirrer is kept going slowly for about 12 hours. Steam is blown into the jacket until a temperature of 90°–100° is recorded, whereby the autoclave is kept uniformly at a moderate temperature. Next day the pressure is released, the autoclave opened, and the contents are transferred to a still fitted with a stirrer. About 100 litres of water are added and the whole is distilled until water alone

passes over. The residue is run into a reservoir half filled with hot water and left for a day. The water is then drawn off and the oil washed in a separator with dilute hydrochloric acid. Sixty kilos of o-nitroanisol are obtained, and 20 kilos of salt residue, from which more oil can be extracted by distillation. (Cain, *Intermediate Products for Dyes*, p. 94.) It can also be prepared from o-chloronitro-benzene (Brand, *J. pr. Chem.* (1903), ii. **67**, 145).

One hundred grams of o-chloronitro-benzene are dissolved in 200 c.c. of methyl alcohol and a solution of 40 grams of potassium hydroxide in 200 c.c. of water and 300 c.c. of methyl alcohol is added. The mixture is boiled under a reflux condenser for about 26 to 31 hours, after which the greater part of the alcohol is distilled off. Steam is now blown in and any unchanged o-chloronitro-benzene, together with some o-nitroanisol, is obtained in the first 20 grams of oil which passes over. The remainder of the distillate consists of o-nitro-anisol. The fraction containing the o-chloronitro-benzene is used again in the next operation.

Preparation of ortho-anisidine.—The reduction of o-nitro-anisol to o-anisidine can be carried out either with iron and hydrochloric acid or with sodium sulphide, and is effected in the same way as has been described for the reduction of *p*-nitrophenetol to *p*-phenetidine (p. 118).

Guaiacol from o-anisidine (see D. R. PP. 95339; 167211). —Twelve kilos of o-anisidine are dissolved in 27 kilos of sulphuric acid (36° Bé.) and 24 kilos of water, mixed with 50 kilos of ice and diazotised with a freshly prepared solution, which must be absolutely free from chloride, of 7·5 kilos of sodium nitrite in 30 kilos of water. The temperature is not allowed to exceed 8°.

The mixture is allowed to stand until nitrite can no longer be detected. A solution is prepared containing 40 kilos of copper sulphate cryst., 40 kilos of ammonium sulphate, 20 kilos of sodium sulphate, 80 litres of water, and 60 kilos of sulphuric acid (36° Bé.), and heated to 105°. In the course of 2½ to 3 hours the diazo solution is allowed to flow into this, the temperature being maintained at 105°. Water and

guaiacol distil over and are collected. When all has been added, steam is blown in and distillation is continued until no more guaiacol passes over. The distillate, which measures about 125 litres, is made alkaline, in a copper vessel, with 12 kilos of caustic soda (36° Bé.) and distilled by indirect steam until the condensate is perfectly clear. As the distillate contains some guaiacol, due to dissociation of the sodium salt, it is used again in the next operation. The alkaline guaiacol solution is now acidified by the addition of 15 kilos of sulphuric acid (36 °Bé.), the guaiacol distilled over by indirect steam, and separated mechanically from the distillate. The aqueous layer is mixed with the guaiacol distillate obtained in a subsequent operation.

The copper-ammonium sulphate solution can be employed for the conversion of 8 to 9 charges of diazotised anisidine, after which the copper is precipitated by the addition of iron and recovered. The yield is said to be practically quantitative. Care must be taken that no metallic copper is present during the conversion.

The separated guaiacol contains 2–3 % of water and crystallises only partially. It is purified by distillation from an enamelled iron or silvered copper vessel, after being dried over 0·3 to 0·5 % of anhydrous sodium carbonate. A silver condenser and a glass or earthenware receiver are employed.

GUAIACOL CARBONATE (duotal) $\bigcirc O—CO—O\bigcirc$ 274.
$\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad\quad OCH_3\quad\quad OCH_3$

—Guaiacol carbonate was first prepared by the action of phosgene on guaiacol, or an alkali salt of guaiacol (D. R. P. 58129).

$$2C_6H_4\big\langle{}^{OH}_{OCH_3} + COCl_2 \;\rightarrow\; \big(C_6H_4\big\langle{}^{OCH_3}_{O}\big)_2 CO + 2HCl$$
$$\quad 248 \quad\quad\quad 99 \quad\quad\quad\quad\quad 274$$

$$2C_6H_4\big\langle{}^{ONa}_{OCH_3} + COCl_2 \;\rightarrow\; \big(C_6H_4\big\langle{}^{OCH_3}_{O}\big)_2 CO + 2NaCl$$
$$\quad 292 \quad\quad\quad 99 \quad\quad\quad\quad\quad 274$$
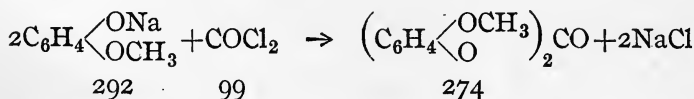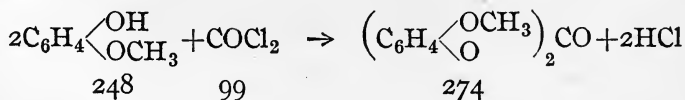
Several general methods of carrying out the preparation

are given. In one instance, 2 molecular equivalents of guaiacol and 1 equivalent of phosgene dissolved in benzene are heated together under pressure at 150°.

Equivalent quantities of guaiacol and caustic soda are dissolved in water and phosgene led in until the reaction liquor is neutral to litmus. The carbonate, which is insoluble in water, separates, and is filtered off, washed and crystallised from alcohol. Small yields are afforded, however. Another method consists in dissolving two molecular equivalents of the phenol in toluene or benzene, treating with the necessary amount of sodium for the formation of the sodium salt, and then adding, with stirring, one equivalent of phosgene dissolved in the same solvent. Reaction takes place without the application of heat. After it is completed the solvent is removed by direct or steam distillation, the guaiacol carbonate washed with water and recrystallised from alcohol. As a variation of this procedure sodium guaiacolate may be first prepared, by evaporation of its aqueous solution, dried thoroughly, and powdered, suspended in benzol and treated with phosgene as above.

A more recent method, D. R. P. 99057, consists in combining guaiacol with ethyl or methyl chloroformate (prepared by the action of alcohol on phosgene) in accordance with the following equations :

$$CO{<}^{OCH_3}_{Cl} + C_6H_4{<}^{ONa}_{OCH_3} \rightarrow CO{<}^{OCH_3}_{OC_6H_4OCH_3} + NaCl$$
$$94\cdot4 146 182$$

$$2CO{<}^{OCH_3}_{OC_6H_4OCH_3} \rightarrow \left(C_6H_4{<}^{OCH_3}_{O}\right)_2 CO + CO(OCH_3)_2$$
$$364 274 90$$

$$\text{or } CO{<}^{OCH_3}_{OC_6H_4OCH_3} + C_6H_4{<}^{OH}_{OCH_3}$$
$$182 124$$

$$\rightarrow \left(C_6H_4{<}^{OCH_3}_{O}\right)_2 CO + CH_3OH$$
$$274 32$$
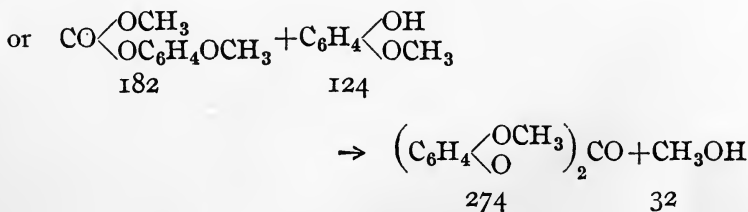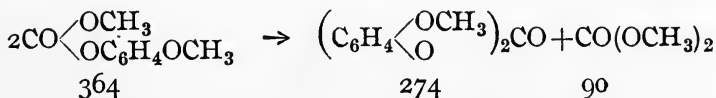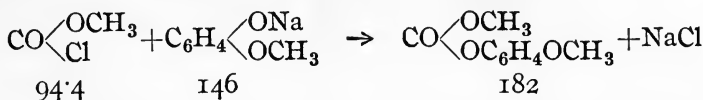
Two equivalents of guaiacol are dissolved in toluene and treated with one equivalent of sodium. The conversion into sodium guaiacolate is completed by boiling, after which the solution is cooled and treated, whilst being stirred, with one equivalent of ethyl chloroformate. The solvent is removed by distillation and the residue heated up to 140°, so long as any distillate is afforded. After cooling, the product is washed with water and recrystallised from alcohol.

In place of chloroformic ester, diethyl or dimethyl carbonate may be employed.

$$2C_6H_4{<}^{OCH_3}_{OH} + (C_2H_5O)_2CO$$

$$248 \qquad 118$$

$$\rightarrow \left(C_6H_4{<}^{OCH_3}_{O}\right)_2 CO + 2C_2H_5OH$$

$$274 \qquad 92$$
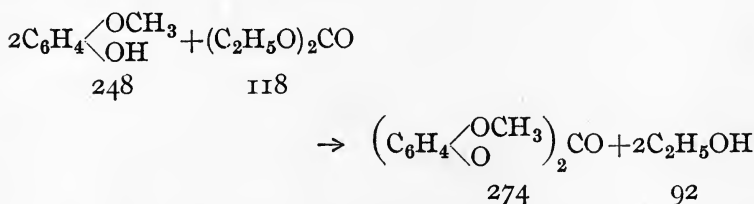
Guaiacol carbonate is a white crystalline powder, without taste or odour. M.p. 84°. It is insoluble in water ; dissolves in 70 parts of cold 90 % alcohol. The alcoholic solution should afford no green colouration when treated with ferric chloride solution (absence of guaiacol). No weighable residue should be left on ignition.

Guaiacol carbonate is employed as an intestinal antiseptic. It is largely administered in cases of phthisis, and, particularly, of rheumatoid arthritis, for which it has been highly recommended.

POTASSIUM GUAIACOL SULPHONATE (" Thiocol ")

$$SO_3K{-}C_6H_3{<}^{OH}_{OCH_3}. \qquad 242.$$
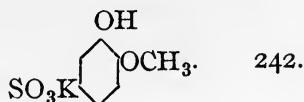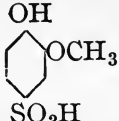
According to the patent specification, D. R. P. 132645, molecular quantities of guaiacol and of concentrated sulphuric acid are heated together at a temperature not exceeding 80° until a test portion forms a clear solution in water. After cooling, the sulphonation mixture is diluted with water, neutralised with potassium carbonate, and the solution
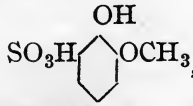
saturated with potassium chloride, whereby the potassium salt of the sulphonic acid is salted out.

The sulphonation of guaiacol is preferably, however, carried out at 30°–60°, and the product, after conversion into the normal calcium salt, is treated with lime ($\frac{1}{2}$ mol. CaO : 1 mol. guaiacol), or the corresponding amount of calcium chloride in ammoniacal solution. The resulting solution rapidly deposits colourless prismatic crystals of basic calcium guaiacol-4-sulphonate, the salt of the 5-sulphonic acid remaining in solution.

The separation may also be effected by means of the lead salts. A hot solution of the normal lead salts, when treated with lead acetate corresponding to $\frac{1}{2}$ mol. of PbO, gives a white precipitate which at the boiling temperature contains only the lead salt of guaiacol-4-sulphonic acid. This is filtered off, and on cooling the filtrate the basic salt of guaiacol-5-sulphonic acid is obtained. Rising (*Ber.* (1906), **39,** 3688) employed 105 % of the theoretical quantity of sulphuric acid and heated at 70° for 15 hours. The sulphonation mixture was diluted with water and excess of guaiacol removed by distillation with steam, 6·5 % being recovered. Sulphuric acid was then removed by treatment with baryta, and the filtered solution neutralised with potash and concentrated. A crop of heavy crystals of the 4-sul-

phonate was obtained, the filtrate from which

was evaporated to dryness and extracted with boiling alcohol, from which potassium guaiacol-5-sulphonate crystallised on cooling. Under the above conditions 57 % of the 4-sulphonic acid and 43 % of the 5-sulphonic acid were found to be formed. Thiocol was originally believed to be

a salt of guaiacol-6-sulphonic acid , but

was shown by Paul (*Ber.* (1906), **39, 2772**) to be mainly potassium guaiacol-5-sulphonate. The following methods,

by which, it is claimed, a product consisting mainly of the guaiacol-5-sulphonate is formed, were then protected (D.R.P. 212389).

(1) Finely powdered guaiacol carbonate is gradually stirred into a slight excess of sulphuric acid (66° Bé.), when the temperature rises to 60°. The mixture is allowed to stand until a test portion dissolves clear in water, after which it is diluted with water and the guaiacol-5-sulphonic acid carbonate decomposed by heating at 100°. Excess of sulphuric acid is removed by baryta or calcium carbonate, and the potassium salt prepared in the usual way.

Alternatively, the sulphonation mixture is diluted with a little ice, when the sulphonic acid carbonate
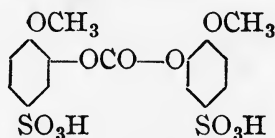
separates as a mass of needle-shaped crystals. It is filtered off, washed with a little concentrated hydrochloric acid and dried at a low temperature. M.p. 115°–117°. The aqueous solution evolves CO_2 on heating, yielding guaiacol-5-sulphonic acid.

(2) One kilo of acetylguaiacol is dissolved in 1 kilo of acetic anhydride, and 1 kilo of sulphuric acid (66° Bé.) is added gradually, with cooling and stirring. After standing for some hours, until the reaction product dissolves completely in water, an equal volume of water is added and the acetic acid removed by steam distillation. The aqueous solution is then neutralised with barium carbonate and the potassium salt of guaiacol-5-sulphonic acid prepared from the resulting barium salt.

The guaiacol-4-sulphonic acid obtained as a by-product in the manufacture of thiocol may be reconverted into guaiacol by heating with phosphoric or sulphuric acids (D. R. P. 250380). Twenty kilos of sodium guaiacol sulphonate are mixed with 100 kilos of 24 % phosphoric acid and the mixture concentrated until the boiling point is over

140°. Superheated steam is then blown in, when the guaiacol distils over. In place of phosphoric acid, sulphuric acid of b.p. 135° may be employed.

The thiocol obtained by any of the above methods is purified, if coloured, by recrystallisation from water, employing vegetable charcoal as a decolourising agent.

Thiocol is a colourless, crystalline powder, neutral, or faintly alkaline to litmus. It is readily soluble in water, slightly so in cold alcohol. It is important that the salt for therapeutic use should be free from the 4-sulphonate. Concentrated nitric acid, added to a 10 % aqueous solution, should afford only a red colour. If the 4-sulphonic acid is present a yellow precipitate of dinitroguaiacol, m.p. 122°, is obtained. Ammoniacal calcium or barium chlorides, added to the aqueous solution, should afford no white precipitate.

Thiocol is employed for the same purposes as guaiacol. It possesses the advantages of being comparatively tasteless, non-toxic, and of exercising no disturbing action on the digestion. It is claimed to be useful in treatment of diseases of the respiratory tract, incipient tuberculosis, and in certain forms of diarrhœa.

$$CH_3$$
THYMOL (*iso*-propyl-*m*-cresol) $OH\bigcirc$ 150.—Thymol
$$CH(CH_3)_2$$
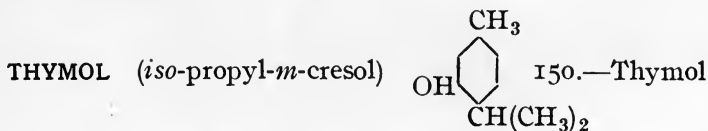
occurs in the volatile oil from *Ptychotis ajowan* (fruits) (50–60 %) ; *Monarda punctata* (50–60 %) ; *Mosula japonica* (42 %) ; *Thymus vulgaris* (20–50 %) ; *Carum copticum.*

It is prepared in Britain and India from *Carum copticum ;* in Germany also it is said to be made from this source. In America, however, it is made from *Monarda punctata,* the phenol content of the oil of which has been improved by cultivation to over seventy per cent.

Thymol is isolated from the volatile oil by shaking the latter with an equal volume of warm sodium hydroxide solution (sp.gr. 1·33) and after several hours the mixture is diluted with 2–3 volumes of hot water. The aqueous portion, which contains the thymol in solution, in the form of its

sodium salt, is separated and acidified. The precipitated thymol is dried and rectified by distillation. The fraction which distils at 220°–235° is seeded with a crystal of pure thymol and set aside in a cold place. The crystallised thymol is separated by filtration and purified by recrystallisation from petroleum ether.

Thymol forms large, colourless, translucent rhombic prisms, having a characteristic odour and a burning taste. M.p. 50°–51°. B.p. 230°. It is sparingly soluble in water (1 in 1500), is very readily soluble in alcohol, ether and chloroform, and dissolves in 6 parts of petrol-ether. The aqueous extract should be neutral, and not coloured violet by ferric chloride (absence of phenol). Addition of bromine water to the extract should produce a milky turbidity, but not a crystalline precipitate. Thymol should volatilise, without leaving a residue, at the temperature of a steam bath.

Thymol is a powerful antiseptic. It is employed as an intestinal antiseptic in diarrhœa and typhoid, and as an ointment or soap in the treatment of parasitic skin diseases ; also as an inhalant in laryngitis. Like carbolic acid, it has local anæsthetic properties. It is also employed to destroy intestinal worms.

BETA-NAPHTHOL (beta-monohydroxy-naphthalene)

144.
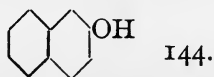
—β-naphthol is prepared by the fusion of sodium naphthalene-β-sulphonate with caustic soda. The following account of its manufacture is taken from Cain's *The Manufacture of Intermediate Products for Dyes*, pages 166 and 204. One hundred kilos of naphthalene are melted, heated to 160°, and 100 kilos of sulphuric acid (66° Bé.) gradually added, the temperature being kept constant. The mixture is maintained at this temperature for a further 3 hours and is then heated at 170° for an hour and subsequently at 180° for the same time. Three or four kilos of naphthalene distil over. The reaction is finished when a sample dissolves

completely in water. The product is blown into 2500 litres of water, neutralised with 50–60 kilos of lime, filtered, and the calcium salt converted into the sodium salt by treating the filtrate with about 40 kilos of sodium carbonate, filtering, and evaporating to crystallising point. The sodium salt of the β-acid separates out, whilst the salt of the α-acid remains in the mother liquor. It is simpler, however, to salt out the acid, after pouring it into 2500 litres of water, by adding salt or sodium sulphate, or by neutralising with about 40 kilos of sodium carbonate. The sodium salt obtained in this way is filtered in a filter press and dried, preferably in a vacuum dryer. The yield is about 160–165 kilos (Grandmougin, *Rev. Prod. Chim.* (1917), **20**, 197).

One hundred kilos of caustic soda are melted with 20 litres of water, and at 200°, 160 kilos of sodium naphthalene β-sulphonate are gradually added. The temperature is then raised to 280°–300° and the fusion is complete in 5 to 6 hours. The liquid mass is then run into 2000 litres of water, and hydrochloric acid, about 100 kilos, added sufficient to liberate the naphthol, but not to decompose the sodium sulphite.

Alternatively, the sodium β-naphthoxide is allowed to settle out on the surface of the fusion mixture and then separated, when the mixture of sodium hydroxide and sodium sulphite may be used for neutralising the sulphonation mixture (E. P. 2300/1883). The naphthol is filtered in a filter press, dried, and distilled in a vacuum. The first runnings are separated from the main distillate and about 10–15 % of the weight of naphthol remains behind as tar. Yield 80 kilos. By another method (F. P. 469040) sodium naphthalene-β-sulphonate, 46 parts, is treated in an autoclave with 50 parts of sodium hydroxide, 40° Bé., for 10–20 hours at 300°–330°. The β-naphthol is separated, after cooling, as described above. It has been stated also (*Ber.* (1914), **47**, 3160) that 10 % sodium hydroxide at 300° will effect the conversion. Distillation by means of superheated steam may also be employed for the purification of β-naphthol.

It is obtained finally in the form required for pharmaceutical purposes by crystallisation from dilute alcohol.

Beta-naphthol is marketed in the form of almost white crystalline laminæ, or as a nearly white crystalline powder. M.p. 122°. B.p. 286° at atmospheric pressure.

It is very sparingly soluble in water, and dissolves in 2 parts of alcohol (90 %). On account of its susceptibility to light it should be kept in the dark; and it should also be as far as possible protected from air.

The solution in aqueous alcohol should be neutral in reaction towards litmus. A cold saturated aqueous solution should not afford a violet colour with calcium hypochlorite solution (absence of alpha-naphthol). A method for determining the alpha-naphthol content of beta-naphthol is given in the *Journ. Soc. Chem. Ind.* vol. xvi., p. 295.

When ignited, no weighable residue should be left; complete solution should be effected in 50 parts of 10 % aqueous ammonia, and the solution should not have a deeper colour than pale yellow.

Beta-naphthol is employed internally as an intestinal antiseptic, and externally, in the form of ointment, for the treatment of eczema and parasitic skin diseases. It is prescribed in typhoid and intestinal dyspepsia, and in summer diarrhœa of children. Prolonged administration, especially of large doses, may lead to nephritis.

CHLORAMINE-T (sodium toluene *p*-sulphonchloramine) $CH_3 \langle \rangle SO_2NNaCl + 3H_2O$. 281·4.—The use of this substance as a disinfectant was introduced recently by Dakin and his colleagues. A method for its preparation has been described in some detail by Inglis (*J.S.C.I.* (1918), **37,** 288 T). Toluene was the starting point, being converted into toluene-*p*-sulphonic acid, the sodium salt of which, when treated with phosphorus pentachloride, afforded toluene-*p*-sulphonchloride. This substance, however, is a cheap and plentiful by-product obtained in the production of saccharin (see this), in connection with which its manufacture is described.

Inglis converted toluene-*p*-sulphonchloride into toluene

p-sulphonamide by interaction with a large excess of 0·880 ammonia in a pressure vessel (100 c.c. of ammonia to 100 grams of sulphonchloride), the reaction taking place spontaneously, with considerable evolution of heat.

$$C_6H_4\begin{array}{c}CH_3\\SO_2Cl\end{array}+2NH_3 \rightarrow C_6H_4\begin{array}{c}CH_3\\SO_2NH_2\end{array}+NH_4Cl$$

$$190{\cdot}4 \qquad 34 \qquad\qquad 171 \qquad 53{\cdot}4$$
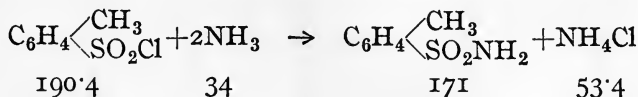
In practice, the use of diluted ammonia, in an open vessel, is found to be possible, whilst only a small excess is required. Into an iron vessel provided with an efficient stirrer are introduced 320 parts of 6 % aqueous ammonia solution (*ca.* 7 % excess), to which are added 100 parts of toluene-*p*-sulphonchloride. Stirring is continued until a filtered sample of the solid develops no acidity on being boiled with water. The toluene *p*-sulphonamide is then filtered off by means of a centrifugal machine and washed with water. The liquor, which contains ammonium chloride, is alkalised with lime and distilled, in order to recover the ammonia.

The method given by Inglis (*loc. cit.*) for the conversion of toluene-*p*-sulphonamide into chloramine-T is carried out as follows : Toluene-*p*-sulphonamide, 171 parts (1 mol.), is added to 525 parts of a 2N solution of sodium hypochlorite (1·05 mol.) containing 40 parts of caustic soda (1 mol.), and is dissolved by gentle warmth. On cooling, the sodium toluene *p*-chlorsulphonamide (chloramine-T) separates as a mass of colourless crystals. It is filtered off, washed with a little brine, recrystallised from twice its weight of hot water, being allowed to cool without stirring, and dried finally at 35°–40°.

$$C_6H_4\begin{array}{c}CH_3\\SO_2NHNa\end{array}+NaOCl \rightarrow C_6H_4\begin{array}{c}CH_3\\SO_2NClNa\end{array}+NaOH$$

$$193 \qquad\qquad\qquad 227{\cdot}4$$
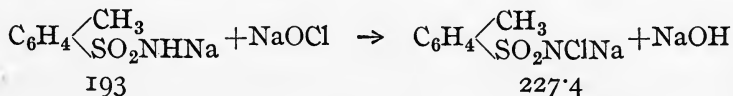
The filtrate from the crude chloramine-T, which is saturated with the salt, and contains the whole of the caustic soda taken, is used for a subsequent operation, being mixed with 1 molecular proportion of sodium hypochlorite and

employed for converting into chloramine-T a further mole-
cular equivalent of toluene-*p*-sulphonamide. The filtrate
from the recrystallisation of the chloramine-T is used
repeatedly for the same purpose until too highly coloured.
The chloramine-T contained in the liquors which can no
longer be used, is recovered in the form of toluene-*p*-sulphon-
amide by treatment with sodium bisulphite, together with
acid to neutralise any free caustic soda present.

$$C_6H_4 {<}^{CH_3}_{SO_2NClNa} + NaHSO_3 + H_2O$$

$$227 \cdot 4 \qquad 104$$

$$\rightarrow \quad C_6H_4 {<}^{CH_3}_{SO_2NH_2} + NaCl + NaHSO_4$$

$$171$$
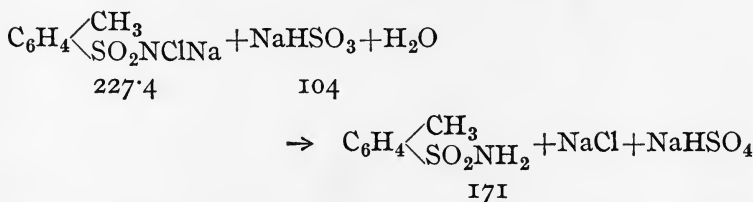
Chloramine-T forms colourless needles, possessing a
characteristic chlorous odour. It dissolves in 15 parts of
cold, and is readily soluble in hot, water. The solution is
neutral to phenolphthalein, and may be boiled without
decomposition.

A weighed quantity, dissolved in water, treated with
potassium iodide and hydrochloric acid, and titrated with
standard thiosulphate solution, should be found to contain
not less than 12·3 % of active chlorine. A perfectly bright
solution (10 %) should be formed in normal saline (0·9 %
NaCl).

Chloramine-T is a powerful disinfectant and has been
used with success in the treatment of practically all external
infectious conditions of the body, and for disinfecting the
nose, throat, and mouth, and the uterine and urethral
passages.

Chloramine-T has been extensively used, during the war,
for the treatment of wounds. It possesses a very high
germicidal coefficient and is superior in many respects to
the commonly employed organic germicides, phenol, iodo-
form, lysol, etc. It is comparable in efficiency with sodium
hypochlorite, but possesses over this substance the advan-
tages of certainty of composition and complete stability.

Dichloramine-T (toluene-*p*-sulphondichloramine)

$$CH_3 \langle \quad \rangle SO_2NCl_2. \quad 239 \cdot 8.$$
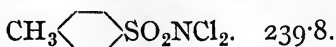
—This substance was first prepared by Chattaway (*Trans. Chem. Soc.* (1905), **87**, 145), two methods being employed. In the one, chlorine was passed through a solution of toluene-*p*-sulphonamide in caustic soda ; in the other an alkaline solution of toluene-*p*-sulphonamide was added to an excess of a saturated solution of bleaching powder, and the dichloramine precipitated by acidification with acetic acid.

A modification of the latter method is most suited for technical application. One may start with either sodium toluene-sulphonchloramine (*see* under chloramine-T) or toluene-*p*-sulphonamide ; in the former case one molecular equivalent, in the latter case two, of hypochlorite will be required.

$$C_6H_4 \langle {}^{CH_3}_{SO_2NNaCl} + NaClO + 2HCl$$
$$227 \cdot 4$$
$$\rightarrow C_6H_4 \langle {}^{CH_3}_{SO_2NCl_2} + 2NaCl + H_2O$$
$$239 \cdot 8$$

$$C_6H_4 \langle {}^{CH_3}_{SO_2NHNa} + 2NaClO + 3HCl$$
$$193$$
$$\rightarrow C_6H_4 \langle {}^{CH_3}_{SO_2NCl_2} + 3NaCl + 2H_2O$$
$$239 \cdot 8$$
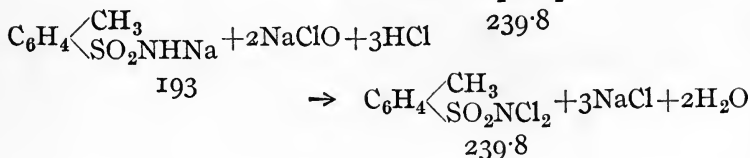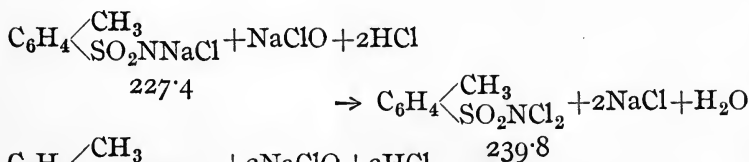
Chloramine-T, 281·4 parts (1 mol.), is dissolved in water, 2800 parts, mixed with 500 parts of 2N sodium hypochlorite solution (1 mol.) and cooled to 0°. Hydrochloric acid is added, with stirring, the amount required being 2 molecular proportions, in addition to the quantity necessary to neutralise the alkalinity of the hypochlorite solution. Dichloramine-T is precipitated in the form of a white powder, and is filtered off, washed with water, and dried at atmospheric temperature.

It may be obtained in the form of yellow-tinted, heavy, acicular crystals by recrystallisation from chloroform or carbon tetrachloride.

Dichloramine-T is a white or faintly yellow-tinted crystalline powder. It is almost insoluble in water, but readily soluble in most organic solvents, except petroleum, in few of which, however, is it stable.

A weighed quantity dissolved in glacial acetic acid and treated with potassium iodide and titrated with standard thiosulphate solution should show a content of not less than 29·0 % of active chlorine.

Dichloramine-T is usually employed dissolved in chlorinated eucalyptol, or " chlorcosane," a chlorinated paraffin wax (*B. M. J.*, 12th January, 1918).

It should form a bright solution in these solvents, which are the best Dakin could find for preparing a stable solution suitable for practical use.

Oily solutions of dichloramine-T are employed for nasopharyngeal disinfection, and in the treatment of infected wounds, of boils and carbuncles, etc. Applied in this way dichloramine-T has a greater and more prolonged germicidal action than that of any other compound. It possesses the power of being able to dissolve dead tissues, and does not coagulate protein, so that a deep-seated sterilisation of the wound is ensured.

HALAZONE (*p*-dichlorsulphonamino-benzoic acid)

$$COOH \langle \ \rangle SO_2NCl_2. \quad 269\cdot8.$$
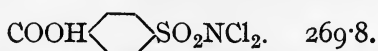
—The preparation of halazone was first described by Dakin and Dunham (*Brit. Med. J.*, 26th May, 1917). Toluene *p*-sulphonamide is oxidised to *p*-sulphonamino-benzoic acid, and this, dissolved in caustic soda, is chlorinated by passing through it a current of chlorine gas. A more convenient method consists in treating it with sodium hypochlorite and hydrochloric acid.

$$\underset{171}{CH_3C_6H_4SO_2NH_2} \ \rightarrow \ \underset{201}{COOHC_6H_4SO_2NH_2}$$

$$\underset{201}{COOHC_6H_4SO_2NH_2} + 2NaOCl + 2HCl$$
$$\rightarrow \ \underset{269\cdot8}{C_6H_4 \langle \genfrac{}{}{0pt}{}{COOH}{SO_2NCl_2}} + 2NaCl + 2H_2O$$
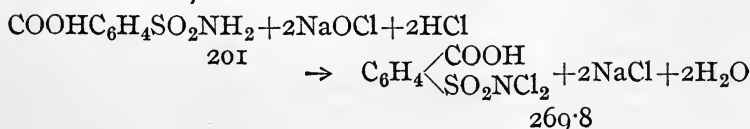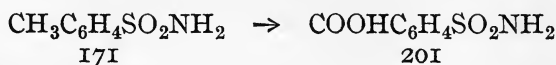
One hundred parts of toluene-*p*-sulphonamide are added to a mixture of 250 parts of sodium bichromate, 370 parts of concentrated sulphuric acid, and 600 parts of water, and the whole boiled for an hour. After cooling, the crude sulphonamino-benzoic acid is filtered off, washed with water, and dissolved in hot diluted caustic soda. The solution is filtered and whilst still hot the acid is reprecipitated by addition of hydrochloric acid, separated by filtration, and well washed.

One hundred parts of sulphonamino-benzoic acid are dissolved in 500 parts of N/1 caustic soda (1 mol.), the solution cooled to 0° and mixed with 500 parts of 14·9 % sodium hypochlorite, or its equivalent (2 mols.).

With continued stirring and cooling are added 500 parts of 2N hydrochloric acid *plus* the quantity necessary to neutralise the alkalinity of the hypochlorite solution. The temperature is kept below 5° throughout. The halazone, which is precipitated as a light, white, crystalline powder, is filtered off, washed with water, and dried at atmospheric temperature.

Halazone is a white, chalky powder, insoluble in water. M.p. 213°. It dissolves in cold sodium carbonate or bicarbonate, from which it is reprecipitated unchanged by acid.

Halazone contains 26·2 % of active chlorine ; 0·1 gram dissolved in glacial acetic acid and treated with potassium iodide should require from 14·8 to 14·9 c.c. of decinormal thiosulphate solution for combination with the liberated iodine.

Halazone was introduced as a water sterilising agent, being for this purpose extraordinarily efficacious. Its germicidal power is such that at a concentration of 1 in 300,000 it destroys the organisms of cholera, typhoid, coli, and dysentery, even in heavily contaminated water, in about 30 minutes.

Halazone is usually mixed with dry sodium carbonate, sodium bicarbonate, or borax, and made up into tablet form.

TRIBROMPHENOL (bromol)

OH
Br⟮　⟯Br
Br
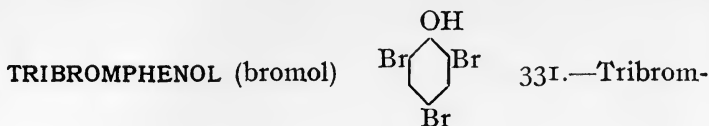
331.—Tribrom-

phenol can be prepared (*Ann.* **137,** 209) by dropping bromine into cooled, stirred phenol.

$$C_6H_5OH + 3Br_2 \rightarrow C_6H_2Br_3OH + 3HBr$$

$$94 480 331 243$$
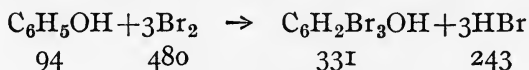
Theoretical quantities are used, and the completion of the reaction is hastened by warming. A hard, yellow, crystalline mass is obtained. It is crushed, washed with water until neutral, and dissolved in an equal weight of hot alcohol. The solution is filtered, and water is added, just short of the point of forming a permanent turbidity. The tribromphenol crystallises out on cooling in the form of long, fine needles.

Tribromphenol is colourless to faintly yellow. M.p. 95°. It is soluble in 2 parts of 90 % alcohol, insoluble in water ; dissolves in caustic alkali solution.

Tribromphenol possesses considerable antiseptic properties. It is employed mainly in the form of its bismuth salt.

Bismuth tribromphenolate (Xeroform).—Thirty kilos of tribromphenol are dissolved in 150 litres of water containing 4 kilos of sodium hydroxide, and 12 kilos of bismuth nitrate are added to the solution (D. R. P. 78889). The reaction product is filtered, washed and extracted with alcohol, to remove free tribromphenol. The extracted substance is stated to yield, after drying, 50 % of Bi_2O_3 on ignition. The commerical product, however, yields from 57 to 61 per cent. of bismuth oxide (*Squire Compend. B. P.*). This corresponds to the formula

$$C_6H_2Br_3OBi(OH)_2 + \tfrac{1}{2}Bi_2O_3 \text{ (requires } 57\cdot4 \text{ \% } Bi_2O_3)$$

To produce this compound two equivalents of bismuth nitrate are required for one equivalent of tribromphenol,

whereas, according to the figures given above, rather less than one equivalent is employed (even supposing the bismuth nitrate to be calculated as anhydrous), and a considerable proportion of the tribromphenol must be recovered. These facts suggest that different proportions of the ingredients are, or could advantageously be, used.

Bismuth tribromphenolate is a yellow powder, insoluble in water and in alcohol. It should yield on ignition, as stated above, 57 to 61 per cent. of bismuth oxide.

It is a non-irritating antiseptic, and is employed as a dressing for wounds and in the treatment of ulcers.

IODOFORM CHI_3. 394.—Iodoform is prepared by the action of iodine on an alkaline solution of diluted alcohol or acetone, and also by the electrolysis of a solution of potassium iodide in dilute alcohol.

From alcohol and iodine: A solution of 32 parts of potassium carbonate in 80 parts of water and 16 parts of 95 % alcohol is warmed to 70° and treated gradually, whilst stirring, with 32 parts of powdered iodine. Iodoform separates as a yellow crystalline powder, and, after the solution has become completely decolourised, is filtered off, washed with water and dried at atmospheric temperature. The filtrate is treated with 2–3 parts of potassium bichromate and 16–24 parts of concentrated hydrochloric acid, and then neutralised, after which are added 32 parts of potassium carbonate, 16 parts of 95 % alcohol, and 6 parts of iodine, when, on warming at 70°, a further quantity of iodoform is produced (Rother, *Jahresbericht*, 1894, 317).

Beilstein recommends the following proportions in place of the above :—7·5 parts potassium carbonate ; 50 parts of water ; 8 parts of 94 % alcohol ; 10 parts of iodine ; the operation being carried out in the same way as before.

From acetone and iodine : One hundred parts of iodine are dissolved in 320 parts of warmed 10 % caustic soda solution. After cooling, 20 parts of acetone are introduced, followed by 100 parts of powdered iodine. Caustic soda liquor is added, in small amounts at a time, until the iodine has disappeared. When cold, the iodoform is filtered off.

The filtrate is treated with 20 parts of acetone, acidified with hydrochloric acid, and then made alkaline again with caustic alkali. The two operations are repeated until the addition of acid no longer gives a precipitate of iodine. Then, by careful addition of a hypochlorite solution and of caustic soda a further precipitation of iodoform is obtained. Total yield 180 parts. It is purified by recrystallisation from alcohol.

By electrolysis: According to D. R. P. 29771, 50 kilos of potassium iodide are dissolved in 300 kilos of water and 30 kilos of 96 % alcohol. The solution is electrolysed whilst warm, CO_2 being led in.

Elbs (*Electrolytic Preparations*) gives a process in more detail. Electrodes of platinum gauze (anode) and foil (cathode) are employed, and a current density of 1 to 3 amps. per 100 sq. cm. The electrolyte consists of 20 grams of sodium carbonate (anhydrous), 20 grams of potassium iodide, 50 c.c. of 96 % alcohol in 200 c.c. of water. It is heated at 50°–70° and a current of CO_2 passed through, between the anode and cathode, whilst electrolysis proceeds. The correct rate of passage of the CO_2 is recognised by the solution being maintained at a light to dark yellow colour ; if it should become brown from the separation of free iodine the stream of gas is interrupted for a time. The iodine is filtered off, washed with water, and dried at ordinary temperature, the solution being used again after the addition of fresh quantities of alcohol and potassium iodide. A current efficiency of 80 % may thus be obtained.

A careful study of the process was made by Foerster and Meves (*J. pr. Chem.* (1897), 256, 354). An anode of platinum was employed, and a cathode of lead, the latter being enveloped in parchment paper. The electrolyte consisted of 400 c.c. of an aqueous solution containing 60 grams of potassium iodide, 20 grams of sodium carbonate (anhydrous) and 80 c.c. of 96 % alcohol. The temperature was maintained at 60°–65° and CO_2 was passed in. The optimum current density was found to be 1 amp. per 100 sq. cm., when a current efficiency of 95–97 % was obtained. At

2 amps. the efficiency was 80–93 % ; at 3 amps. it fell to 73–79 %.

The following equations have been given to represent the formation of iodoform :—

$$C_2H_5OH + 5I_2 + H_2O \rightarrow CHI_3 + CO_2 + 7HI$$
$$C_2H_5OH + 4I_2 + H_2O \rightarrow CHI_3 + HCOOH + 5HI$$

Iodoform is supplied in the form of small, lemon-yellow, hexagonal crystals, and as a crystalline powder. It possesses a characteristic odour and taste. M.p. 115°. It is very sparingly soluble in water ; dissolves in 120 parts of 90 % alcohol, in 14 parts of chloroform, and in 7 parts of ether.

When treated with water 1 : 10 and filtered, the filtrate should be colourless, possess no bitter taste, yield only a faint opalescence with silver nitrate, and be unaffected by barium nitrate solution. It should also be neutral in reaction. Iodoform is required to dissolve completely in chloroform and the solution should be bright. A turbidity usually indicates the presence of moisture.

Iodoform is a very generally used antiseptic and deodorant. It has also local anæsthetic properties. Internally it is administered in cancer, to relieve the pain, and as a suppository in chronic prostatis, hæmorrhoids, and anal fissure. Externally it is applied to burns, and to cleanse foul ulcers and sores of venereal origin.

TETRA-IODO-PYRROL (iodol).

$$
\begin{array}{c}
\text{IC—CI} \\
\parallel \quad \parallel \\
\text{IC} \quad \text{CI} \qquad 571. \\
\diagdown\diagup \\
\text{NH}
\end{array}
$$
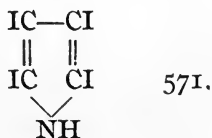
—One part of pyrrol is stirred with 150 to 300 parts of water containing 2·4 parts of caustic soda. An aqueous solution containing 15 parts of iodine and 20 parts of sodium iodide is then added, until the liquid is slightly brown (contains free iodine). The precipitate is filtered off, washed, and dissolved in alcohol. The alcoholic solution is decolourised by boiling with animal charcoal, filtered, and

treated with water, when the iodol is reprecipitated (D. R. P. 35130).

Iodol forms a light-brown powder, having a faint odour. It is insoluble in water, dissolves in 18 parts of 90 % alcohol, in $1\frac{1}{2}$ parts of ether, and in 150 parts of chloroform.

It should contain no free iodine, and a filtered aqueous extract should not afford a reaction with silver nitrate solution.

Iodol is employed as a substitute for iodoform. It is devoid of objectionable smell and is stated to be less poisonous than the latter substance.

IODIPIN (iodised sesamé oil).—Iodipin may be taken as a typical representative of a class of iodised unsaturated fats. It is sold in mixtures containing varying amounts (5 %, 10 %, and 20 %) of iodine.

According to the original patent specification, D. R. P. 96495, 10 kilos of sesamé oil are treated at 40°–50°, whilst being stirred, with a solution of 1·3 kilos of iodine monochloride in 10 litres of alcohol. The iodised fat is washed several times with warm alcohol and dried *in vacuo* at 50°. The product yielded by taking the above proportions is stated to contain 7·5 % of iodine.

By a variation of the above method a mixture of 170 grams of potassium nitrite and 166 grams of potassium iodide is treated with the theoretically necessary quantity of concentrated hydrochloric acid,

$$2KNO_2 + KI + 4HCl \rightarrow ICl + 3KCl + 2H_2O + 2NO$$

and one litre of alcohol is added. The precipitated potassium chloride is filtered off, and the solution used, in the manner described above, for the iodisation of 1 kilo of sesamé oil.

Hydriodic acid can also be used for the iodisation (D. R. P. 135835). Sesamé oil is treated, at 5° to 10°, with gaseous hydriodic acid ; by this method products containing up to 30 % of iodine can be obtained. A further method is given by D. R. P. 159748. Into a well-stirred mixture of 5 kilos of sesamé oil, 2 litres of water, and 300 grams of finely-powdered iodine, sulphur dioxide is passed, until the iodine

I   12

colour has nearly disappeared. By this process - a fat containing 5 % of iodine is obtained. According to the quantity of iodine they contain iodipin preparations varying from a pale straw-coloured oily liquid to a yellowish-brown viscous fluid are obtained. They are insoluble in water and in alcohol (90 %), but dissolve in all proportions of ether and of chloroform.

Iodipin is employed, by oral or by hypodermic administration, in syphilis and syphilitic affections; also in gonorrhœal rheumatism, bronchial asthma, bronchitis, emphysema and pleurisis. It is stated to be well tolerated and to produce no iodism or depression.

SOZOIODOL (di-iodo-phenol-*p*-sulphonic acid)

$$C_6H_2 {\overset{\displaystyle I_2}{\underset{\displaystyle SO_3H}{<}} OH} \qquad 426.$$
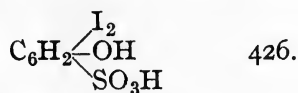
—Di-iodo-phenol-*p*-sulphonic acid is prepared by the action of iodine upon phenol-para-sulphonic acid. Potassium iodide and potassium iodate with acid may be used to generate the iodine, when the sparingly soluble potassium salt is directly obtained; or a mixture of sodium iodide and sodium hypochlorite and acid, when either the product may be precipitated as the insoluble barium salt, or the solution may be evaporated if the sodium salt is required.

(1) $3C_6H_4{<}{\overset{OH}{\underset{SO_3K}{}}} + 4KI + 2KIO_3 + 6HCl$

$$\rightarrow 3C_6H_2I_2{<}{\overset{OH}{\underset{SO_3K}{}}} + 6KCl + 6H_2O$$

(2) $C_6H_4{<}{\overset{OH}{\underset{SO_3H}{}}} + 2NaI + 2NaOCl + HCl$

      '174   300

$$\rightarrow C_6H_2I_2{<}{\overset{OH}{\underset{SO_3Na}{}}} + 3NaCl + 2H_2O$$

      448
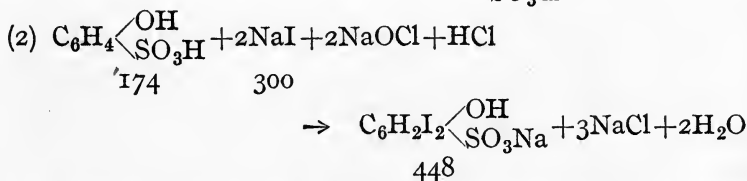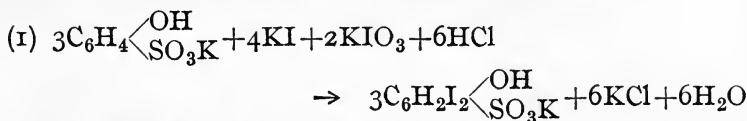
Another process (D. R. P. 45226) consists of acting upon a solution of the potassium salt of phenol-*p*-sulphonic acid with iodine mono-chloride, when a mixture of the mono- and di-phenol-*p*-sulphonic acids is obtained,

$$(3)\ 2C_6H_4\!\!<^{OH}_{SO_3H} + 3ICl \rightarrow C_6H_2\!\!<^{I_2}_{SO_3K}\!\!{}^{OH} + C_6H_3\!\!<^{I}_{SO_3K}\!\!{}^{OH} + 3HCl$$
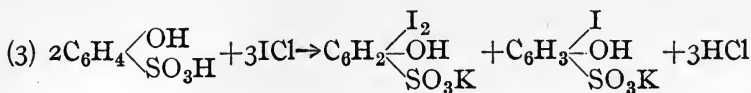
Of these the second method is the one likely to be employed in practice, and this only, therefore, will be described.

To a solution of 17·4 parts (1 mol.) of phenol-*p*-sulphonic acid in 100 parts of water containing 30 parts (2 mols.) of sodium iodide, are added, with continuous stirring, the equivalent of 100 c.c. of a 14·9 % solution of sodium hypochlorite (2 mols.), followed by the calculated quantity of 5N. hydrochloric acid required to furnish one molecular equivalent of acid and to neutralise the free alkali contained in the hypochlorite solution. The neutral reaction mixture, in which the sozoiodol is contained as sodium salt, is treated according to the salt which is required. Potassium, zinc, or mercury salts, all of which are sparingly soluble, can be prepared by double decomposition. The sodium salt is obtained by concentration of the solution, and crystallisation; whilst the free acid is prepared by precipitating the insoluble barium salt by treatment with barium chloride, and decomposing this with the necessary amount of sulphuric acid. Di-iodo-phenol-*p*-sulphonic acid is a white crystalline powder, soluble in water.

Sodium di-iodo-phenol-*p*-sulphonate dissolves in 14 parts of water. Potassium di-iodo-phenol-*p*-sulphonic acid dissolves in 100 parts of water. Mercury di-iodo-phenol-*p*-sulphonate (mercury sozoiodol) is an orange-yellow amorphous powder, insoluble in water but soluble in sodium-chloride solution.

Sozoiodol and its salts are used as disinfectants, chiefly locally, in nasal and pharyngeal disorders, and in parasitic skin infections. The mercury salt has been employed in syphilis and psoriasis, by hypodermic injection of its solution in aqueous sodium chloride.

ARISTOL (di-iodo-thymol) $C_6H_2I\!\!<^{CH_3}_{OI}\!\!{}^{C_3H_7}$—A solution of
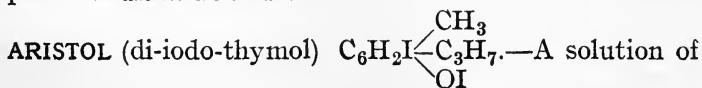
five kilos of thymol in 10 litres of water containing 1·2 kilos of caustic soda is added, at 15°–20°, with good stirring, to a solution of 6 kilos of iodine and 9 kilos of potassium iodide in 10 litres of water.

A voluminous dark reddish-brown precipitate is formed ; it is filtered off, washed with water, and dried at atmospheric temperature (D. R. P. 49739). The compound may also be prepared by the action of sodium or calcium hypochlorite, and acid, upon a solution of sodium thymolate containing a soluble iodide.

$$C_6H_3{<}{\overset{\displaystyle CH_3}{\underset{\displaystyle ONa}{C_3H_7}}}+2NaOCl+2NaI+3HCl$$
$$172 \qquad\qquad 300$$
$$\rightarrow \quad C_6H_2I{<}{\overset{\displaystyle CH_3}{\underset{\displaystyle OI}{C_3H_7}}}+5NaCl+2H_2O$$
$$402$$
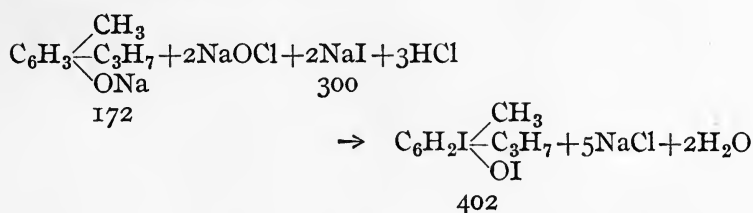
Aristol is a bulky, bright-yellowish, or reddish-yellow powder, possessing a slight odour resembling that of iodoform. It is insoluble in water, slightly soluble in alcohol, readily soluble in ether and chloroform. A filtered aqueous extract should be neutral to litmus and should not give a blue colour with starch solution, indicating absence of free iodine. Twenty c.c. of water shaken with 0·1 gram and filtered should not afford more than a faint opalescence on the addition of nitric acid and silver nitrate solutions.

Aristol is used as a substitute for iodoform. It has been employed with success in ulcerating lupus, pyrrhœa, and syphilitic ulcers, in the form of a 10 % ointment or as a dusting powder. A solution (10 %) in flexible collodion is applied in poisonous eczema.

Loretin (iodo-8-oxyquinoline-5-sulphonic acid)

351.
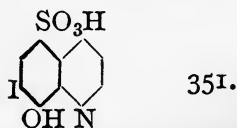
—One part of 8-oxyquinoline (*see* chinosol) is dissolved,

at below 0°, in 6 to 8 parts of fuming sulphuric acid. After being allowed to stand for 24 hours the mixture is poured on to crushed ice. A copious precipitate is obtained in the form of fine needles. This consists of 8-oxyquinoline-5-sulphonic acid. It is filtered off and may be purified by recrystallisation from dilute hydrochloric acid. Forty parts of the acid are dissolved in a boiling solution of 12 parts of potassium carbonate and 27·5 parts of potassium iodide in 350 to 400 parts of water. With constant stirring and uninterrupted boiling are added, in four or five separate portions, 46·8 parts of bleaching powder (25 %). Boiling is continued for 15 to 20 minutes after addition of the bleaching powder is completed. A thick yellow paste results. This is cooled in an ice and salt mixture, and, with good stirring and at a low temperature, 100 vols. of hydrochloric acid (sp.gr. 1·025) are added, followed by 45 vols. of concentrated hydrochloric acid. A homogeneous red paste is obtained, which consists of the calcium salt of iodo-oxyquinoline-sulphonic acid. After being allowed to stand overnight it is filtered off and washed with cold water. The free acid is obtained as a heavy, yellow powder, by acidification with hydrochloric acid (D. R. P. 72942).

Loretin has been employed, mainly in the form of its bismuth salt, as an iodoform substitute.

SAJODIN (calcium iodo-behenolate) $(C_{22}H_{41}O_2I)_2Ca$. 970.—References D. R. PP. 180087, 186214, 180622, 187449, 187822. Five hundred grams of orucic acid (obtained from rape seed oil) are treated with 330 grams of powdered sodium iodide, and 600 c.c. of glacial acetic acid which has been saturated with dry hydrogen chloride. The mixture is warmed at 40°–50° for 2–3 days, with continuous stirring. It is then diluted with water, and the mono-iodo-behenolic acid extracted with benzene. The benzene solution is washed, first with aqueous sulphurous acid, to remove traces of iodine, and then with water, until the washings no longer react with silver nitrate solution. The solvent is then removed *in vacuo* at a low temperature, the residue consisting of mono-iodo-behenolic acid.

Twenty-five parts of crystallised calcium chloride are dissolved in 120 parts by weight of hot 92 % alcohol, and the solution saturated with gaseous ammonia. A further 130 parts of alcohol are added, after which the mixture is cooled. To it is added, in a thin stream, with good stirring, a solution of 44 parts of mono-iodo-behenolic acid in 120 parts of alcohol. The calcium salt separates in the form of a thick white precipitate. It is filtered off and washed, first with alcohol, then with water, until the washings are free from chloride ; finally it is again washed with alcohol and dried *in vacuo*.

Sajodin is a white, neutral, tasteless powder, almost insoluble in water and alcohol. It is stable if protected from white light, under the influence of which it slowly becomes yellow. It contains about 26 % of iodine.

Sajodin is administered internally in treatment of syphilis.

TETRA-IODO-PHENOL-PHTHALEIN (Nosophen).

$$C(C_6H_2I_2OH)_2$$
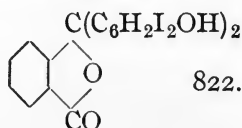
822.

—The preparation of this compound has been described by Orudoff and Mahood (*J. Am. Chem. Soc.* (1918), **40**, 941), the method being similar to that given in the original patent specification, D. R. P. 85930.

Thirty parts of phenol-phthalein are dissolved in 500 volumes of 2N. caustic soda. The solution is mechanically stirred and to it is added, in the course of half an hour, a solution of 100 parts of iodine and 120 parts of potassium iodide in 500 parts of water. The reaction mixture is stirred for 8 hours, after which it is carefully neutralised with 2N. acetic acid. The resulting greyish-white precipitate is filtered off. It is redissolved in 2 % alkali and reprecipitated with acetic acid, being now a pale yellow colour. After the precipitate has been again dissolved in 2 % alkali, the solution is strongly acidified with hydrochloric acid, and steam blown

in until the precipitate has coagulated. After cooling and filtration, the solid is washed with water until free from chloride and dried at atmospheric temperature. Yield 87 %.

It is purified by recrystallisation, first from acetone and then from a mixture of acetone and alcohol, from which it is obtained in the form of colourless microscopic crystals which melt at 270°–272°.

According to D. R. P. 85930, thirty parts of phenol-phthalein are dissolved in 100 parts of water containing 40 parts of caustic soda. At a temperature not exceeding 20° is added a solution of 100 parts of iodine and 120 parts of potassium iodide in 400 parts of water. The solution is strongly cooled and neutralised with hydrochloric acid, when an amorphous yellow-brown precipitate is obtained. This is filtered off and purified by being dissolved in chloroform and reprecipitated by the addition of ligroin.

It has also been prepared by the electrolysis of an alkaline solution of phenol-phthalein containing the equivalent amount of potassium iodide. Tetra-iodo-phenol phthalein is an odourless powder, insoluble in water, soluble in chloroform and in ether.

It has been employed, externally, as a substitute for iodoform, and, internally, as an intestinal antiseptic.

FORMALDEHYDE $H \cdot COH$. 30.—Formaldehyde is usually prepared as a solution in water. Its solution is variously termed Formalin, Formol, Methanal and Liquor formaldehyde. It is prepared technically by the oxidation of methyl alcohol, derived from wood spirit, although attempts have been made to obtain it from methane (D. R. PP. 109014, 286731) and from carbon monoxide (U.S. Patent 1302016, 29/4/19).

The oxidation of methyl alcohol is carried out by passing its vapour mixed with air over a catalyst heated at about 450°. The main reaction is expressed by the equation

$$2CH_3OH + O_2 \rightarrow 2HCHO + 2H_2O + 60 \cdot 4 \text{ Cal.}$$

though at the same time a portion of the methyl alcohol is probably decomposed pyrogenetically into formaldehyde and hydrogen,

$$CH_3OH \rightarrow HCHO + H_2$$

Under the influence of high temperature some of the formaldehyde is decomposed into CO and H_2, of which a part may become oxidised to CO_2 and water.

The reaction is, as shown by the equation, exothermic, and, once started, no further application of heat is required.

The conditions which require to be observed in order that good yields shall be obtained have been worked out by Orloff (*J. russ. phys. chem. Ges.* **39,** 855, 1023, 1404 (1908) ; **40,** 796 (1909), and by Le Blanc and Plaschke (*Zeits. Elektrochem.* **17,** 55 (1911)). The methyl alcohol should be at least 90 % in strength ; 100 % being better. It should contain not more than 1 % of acetone. The highest conversion, employing a copper catalyst, is obtained when for 1 part of methyl alcohol 0·39 part of oxygen is taken ; the smallest loss of methyl alcohol when 0·315 part of oxygen is employed. The corresponding figures, using a silver catalyst, are 0·459 and 0·314. The optimum temperature of the interior of the catalyst is 450°, this being regulated by adjustment of the rate of flow of the methyl alcohol-air mixture, or the proportion of methyl alcohol contained in it. The depth of the catalyst is of importance ; when silver gauze 100 mesh was employed, 70 millimetres was found to be the best (le B. and P.). Using copper, Orloff recommends a depth of 120 mm.

The catalytic chamber is the most important part of the apparatus, and a brief description of the one employed by Orloff may advantageously be given. It consists of 169 copper tubes, 800 mm. long, external diam. 19 mm., thickness of wall 17 mm., arranged in circles (1+8+16+24+32 +40+48) set in two copper plates, the whole being enclosed in a, preferably copper, box having on the one side a tube through which the air-methyl alcohol mixture is introduced, on the other an exit for the formaldehyde-nitrogen vapour. Inside each tube is set one of glass, 300 mm. long, internal diameter 14·75 mm. Each glass tube contains a roll of copper 120 mm. long, made of gauze of 15×15 meshes per square cm. A device for igniting the gases, in order to start the reaction, is provided and may consist of an electrically
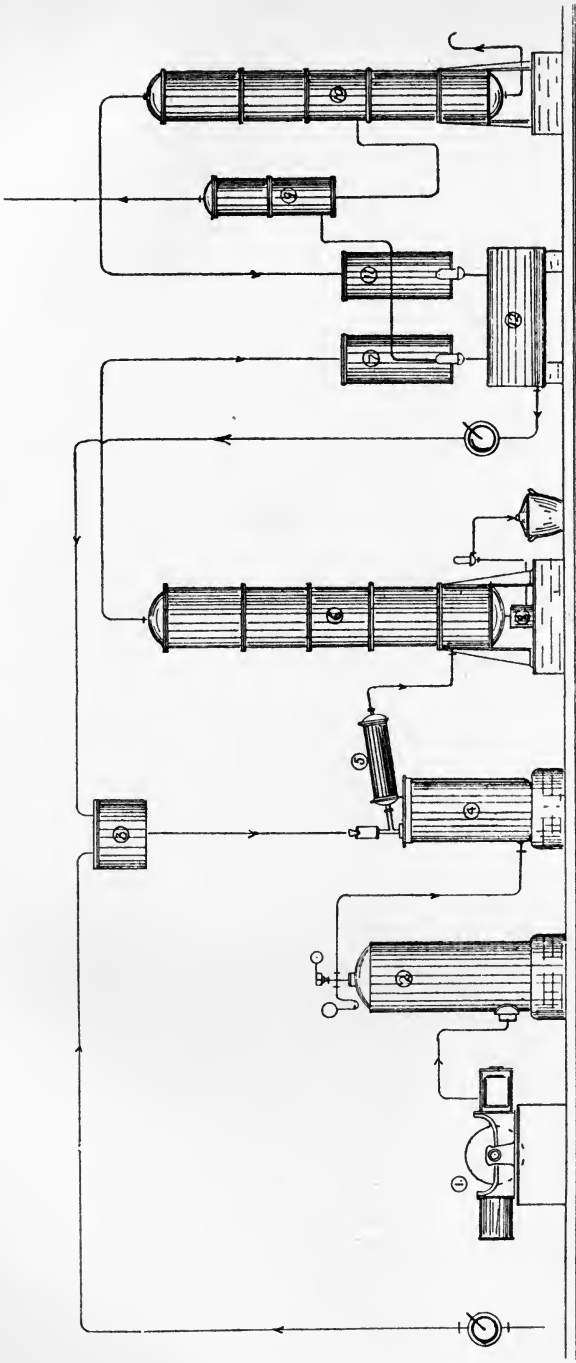
FIG. 22.—Formaldehyde plant.

heated wire. A catalyst of this size consumes 170 kilos of methyl alcohol in 10 hrs., affording 255 kilos of formaldehyde 38 %. A diagram of a plant for the manufacture of formaldehyde is given (Fig. 22).

Air is compressed by a pump (1) into a reservoir (2). Methyl alcohol stored in (3) flows down into the carburettor (4), in which it is maintained at a constant level, and is warmed by means of a closed steam coil. Air is blown into it from the air reservoir, through a perforated coil. The temperature is regulated so that the ratio of oxygen to alcohol in the vapour is as 0·31 to 0·32 : 1. The mixture then passes into the catalyst chamber (5) in which, after being started by ignition, the reaction proceeds without further addition of heat. The temperature maintained in the catalyst chamber is 450°. The issuing vapours pass into the fractionating column (6) in which 38–40 % formaldehyde is condensed, the methyl alcohol passing over, together with the waste gases, into a condenser (7). In this is condensed the greater part of the excess of methyl alcohol, which runs into (12), a store tank from which it can be pumped up into (3). The gases, which still contain some methyl alcohol, pass into a gas scrubber (9), in which they are washed with water. The washings are then fractionated in the fractionating column (10), the methyl alcohol being condensed in (11) and run into the store tank (12).

X   Commercial formaldehyde solution contains 35–40 % of formaldehyde, and 10–15 % of methyl alcohol. It has a specific gravity of 1·079 to 1·018.

The acidity should not exceed 0·23 % w/v, calculated as formic acid. Heavy metals, sulphate and chloride should be absent, and 5 c.c. should leave no weighable residue on ignition.

Formaldehyde solution is a powerful antiseptic, disinfectant and deodorant. Diluted with water (50 to 100 vols.) it is used as a general antiseptic, and with 400–500 vols. as a mouth wash and gargle.

It has been employed, by intravenous injection and as an inhalant, in pulmonary phthisis.

HEXAMINE (urotropine, hexamethylenetetramine), $(CH_2)_6N_4$. 140. Also known as cystamine, aminoform, and formin.

Hexamethylenetetramine is produced by the condensation of formaldehyde and ammonia, in accordance with the following equation :

$$6HCHO + 4NH_4OH \rightarrow (CH_2)_6N_4 + 10H_2O$$
$$180 \qquad 140 \qquad\qquad 140 \qquad 180$$
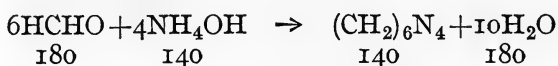
Formaldehyde solution, containing 180 parts of formaldehyde, *e.g.* 473 parts of a 38 % solution, is treated with 140 parts of ammonium hydrate, for instance, 700 parts of a 20 % solution, until the solution is slightly alkaline, using rosolic acid as indicator. The mixture is allowed to stand, more ammonia being added if necessary, for several hours, until the alkalinity is shown, by successive titrations with N/100 acid, to remain constant. The solution is filtered and then boiled down in an enamelled vessel, preferably under diminished pressure, to a thick paste. The crystals are filtered off, by means of a centrifugal machine or vacuum filter, freed from colour by washing with alcohol, and dried. It is then recrystallised from water or alcohol until pure. Hexamine forms colourless, odourless crystals, which dissolve in rather more than an equal weight of water, and in 8 parts of 90 % alcohol. It does not melt on heating, but sublimes at a temperature of about 260°. The aqueous solution should be perfectly bright and should be free from iron (potassium ferrocyanide solution), heavy metals (sulphuretted hydrogen), chlorides or sulphates, ammonium salts (Nessler solution), and para-formaldehyde, the latter reducing Nessler solution (potassium mercuriciodide) to metallic mercury. No residue should be left on ignition.

Hexamine is a urinary antiseptic, owing its action to the liberation of formaldehyde, which occurs in acid fluids. It is not so effective, therefore, *per se*, if the urine is alkaline. Hexamine has been found to give excellent results in cystitis and typhoid bacilluria ; also as a prophylactic against the nephritis of scarlatina.

It is not a solvent for uric acid.

PROFLAVINE (3·6 diamino-acridine sulphate)

$$NH_2 \underset{N}{\overset{CH}{\bigcirc\bigcirc\bigcirc}} NH_2 \quad H_2SO_4. \quad 307.$$
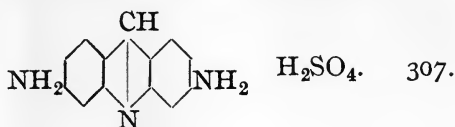
—The following reactions are involved in the formation of this compound :—

Aniline $(C_6H_5NH_2)$ + formaldehyde (HCHO)
$\rightarrow$ anhydro-formaldehyde aniline $(CH_2NC_6H_5)_3$

$(CH_2NC_6H_5)_3 + 3C_6H_5NH_2$

$\rightarrow$ methylene-diphenyl-diamine $3CH_2 \overset{NHC_6H_5}{\underset{NHC_6H_5}{\big\langle}}$
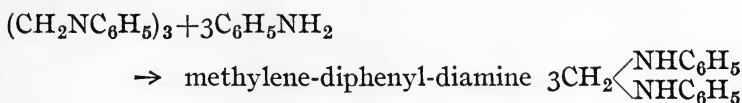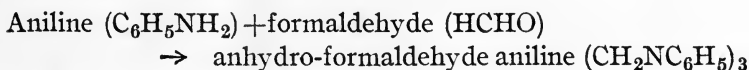
This compound undergoes rearrangement to

$$NH_2 \big\langle \ \ \big\rangle CH_2 \big\langle \ \ \big\rangle NH_2$$

p-p-diamino-diphenyl-methane.

Nitration affords $NH_2 \underset{NO_2}{\big\langle \ \ \big\rangle} - CH_2 - \underset{NO_2}{\big\langle \ \ \big\rangle} NH_2$, 2 : 2
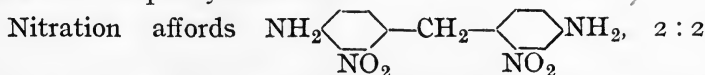
dinitro 4 : 4 diamino-diphenyl-methane, which, on reduction and heating, yields 3·6 diamino-hydro-acridine

$$NH_2 \underset{NH_2}{\big\langle \ \ \big\rangle} CH_2 \underset{NH_2}{\big\langle \ \ \big\rangle} NH_2 + HCl \rightarrow NH_2 \big\langle \ \ \big\rangle \overset{CH}{\underset{N}{\big|}} \big\langle \ \ \big\rangle NH_2$$
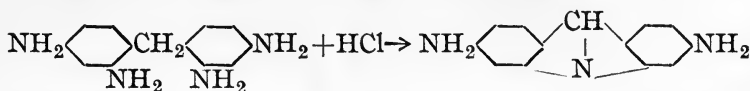
which readily changes to 3·6 diamino-acridine—" proflavine."

Aniline, 93 parts (1 mol.), is dissolved in 5 volumes of 96 % alcohol (S.V.M.) and the solution cooled and stirred whilst 120 parts of 40 % formaldehyde solution (1 mol.) are gradually added. After the addition is completed, stirring is continued until the odour of formaldehyde has disappeared, when a second molecular portion of aniline, 93 parts, is added. The mixture is boiled, using a reflux condenser, for 2 hours, to complete the formation of methylene-diphenyl-diamine.

Aniline hydrochloride (1 mol.), 130 parts, is then added,

and boiling continued for a further 12 hours. The alcohol is distilled off, the residue made alkaline with caustic soda and the excess of aniline removed by distillation with (superheated) steam. The residual oil, which consists of *p-p*-diamino-diphenyl-methane, is then purified by solution in dilute hydrochloric acid and reprecipitation with dilute alkali. The base is filtered off, washed and dried.

The nitration, reduction and conversion are carried out, according to D. R. P. 230412, in the following manner : Twenty-five kilos of *p-p*-diamino-diphenyl-methane are dissolved in 500 kilos of sulphuric acid (66° Bé.), cooled to 0° and nitrated with 54 kilos of a mixture of sulphuric and nitric acids containing 16 kilos of HNO_3 (100 %), the temperature being kept below 5°. The whole is allowed to stand for a further 2 to 3 hours, at 8°–10°, then run out on to ice, and neutralised with caustic soda liquor. Ammonia solution is added, to precipitate the base, which is centrifuged and washed with water. The product, without being dried, is dissolved in 24 kilos of hydrochloric acid (sp.gr. 1·18) and heated to 50°, when 54 kilos of granulated tin are added. A vigorous reaction ensues, the temperature rising to 110°. The resulting solution is transferred to an autoclave and heated to 135° for 4 hours. After cooling, the resulting crystalline tin double compound of 3·6 diamino-acridine is dissolved in 500 litres of boiling water, the solution neutralised with caustic soda and then made alkaline with sodium carbonate solution. After cooling, the precipitate, which consists of tin oxide and diamino-acridine, is filtered off and the latter compound removed by repeated extractions with boiling water, from which it crystallises on cooling in shining orange to brown-coloured leaflets. The product is filtered off and either dried and used for the manufacture of acriflavine or converted into proflavine sulphate, which is effected by dissolving in a slight excess of hot dilute sulphuric acid and allowing to crystallise.

Proflavine sulphate separates in dark red or reddish-brown crystals, which dissolve in about 100 parts of cold water.

A solution which remains perfectly bright for 24 hours should be afforded in 500 parts of normal saline solution (0·9 % NaCl). Tin and other metals should be absent, and a sample of 0·5 gram should afford no weighable ash on ignition in air.

Proflavine sulphate is a valuable germicide and antiseptic. It is employed in the form of a 0·1 % or 0·2 % solution, and as an ointment. A wide employment in the treatment of surface wounds was attained during the war, and an increasingly extensive use for it is being found in the treatment of gonorrhœa, by urethral or vaginal injection.

ACRIFLAVINE (2–6 diamino-acridinium metho-chloride)

$$NH_2 \diagup \diagdown \overset{\text{CH}}{\diagup} \diagup \diagdown NH_2 \cdot HCl. \qquad 296.$$

$$\underset{\substack{\text{N} \\ \text{CH}_3 \ \text{Cl}}}{}$$
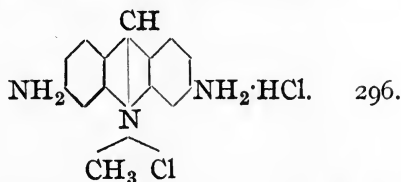
—Acriflavine is prepared, according to D. R. P. 243085, in the following manner. Five kilos of 3·6 diamino-acridine (*see* proflavine, p. 188) are acetylated by boiling with 13 kilos of acetic anhydride and 1·25 kilos of anhydrous sodium acetate, until no diazo reaction is given by a test sample. Thirty-five litres of water are added and the solution boiled, filtered, and allowed to crystallise. The crystals are filtered off, dissolved in hot water, and treated with 8 litres of ammonia solution. The 3·6 diacetyl-diamino acridine is filtered off when cold, washed and dried.

Four kilos of the acetyl compound are dissolved in 40 kilos of nitro-benzol, at 180°. At a slightly lower temperature, *i.e.* 175°, 3·3 kilos of methyl *p*-toluenesulphonate are added and, after cooling, the separated crystals are filtered off. They consist of the methyl toluene-sulphonate compound

$$CHCO_3NH \diagup \diagdown \diagup \diagdown NHCOCH_3$$

$$\underset{\substack{\text{N} \\ \text{CH}_3 \ \text{SO}_2\text{C}_6\text{H}_4\text{CH}_3}}{}$$
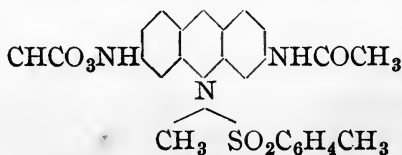
5·45 kilos of this are boiled for several hours with a mixture of 17·5 litres of concentrated hydrochloric acid and 17·5 litres of water. On cooling, the hydrochloride of 3·6 diamino-acridinium metho-chloride, "acriflavine," crystallises out and is filtered off and dried.

Acriflavine crystallises in dark red shining crystals, which dissolve in 5 parts of cold water.

A 0·2 % solution in normal saline should be perfectly clear after 24 hours. Proflavine should be absent, as indicated by 100 c.c. of a 0·4 % solution remaining unclouded for 10 minutes upon addition of 10 c.c. of N. caustic soda solution.

Tin and other heavy metals must be undetectable, and no weighable residue must be left after ignition in air of 0·5 gram.

Acriflavine is employed in the same concentration and for the same purposes as proflavine, to which it has a similar action.

MALACHITE GREEN
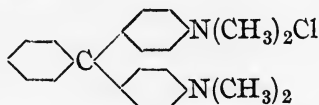
364·4.

—The following account of the preparation of this substance is taken from Cain and Thorpe's *Synthetic Dyestuffs*, p. 270.

Thirty-five grams of dimethylaniline and 14 grams of benzaldehyde are mixed with 31·5 grams of concentrated hydrochloric acid and the mixture heated, under a reflux condenser, for 24 hours, at 100°. The mass is made alkaline with caustic soda, after which traces of benzaldehyde and of dimethylaniline are removed by a current of steam. On pouring into 1 litre of water the leuco base separates in the form of hard granules. It is filtered off, washed free from alkali, and an estimation made of the moisture content. It is oxidised as follows: Ten grams of leuco base (dry weight) are melted by a current of steam. Hydrochloric acid, containing 2·7 grams of HCl, and 4 grams of acetic acid in 2½ to 3 litres of water are added, and a thin paste

containing 7·5 grams of pure lead peroxide is allowed to flow in, with stirring, which is continued for 2 hours after the addition is complete.   Unchanged lead peroxide is then filtered off ;   the filtrate is heated to boiling point and treated with sodium sulphate, to remove the lead.   After filtration the solution is again raised to boiling point and the base is precipitated with caustic soda solution.   After cooling, it is filtered off, washed, dried, and purified by being dissolved in light petroleum and filtered from impurities, after which the petrol is distilled off by means of a current of steam.

The hydrochloride has been employed as an antiseptic, in the treatment of wounds.

CHINOSOL (8-hydroxyquinoline sulphate) $\left(\overset{OH\ N}{\underset{}{\bigcirc\bigcirc}}\right)_2 H_2SO_4.$
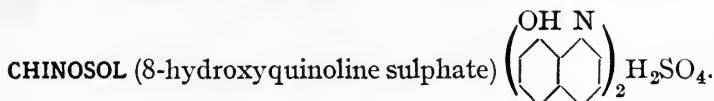
388.—Chinosol was originally supposed to be potassium ortho-hydroxyquinoline sulphonate, but was subsequently found, when prepared according to the patent specifications D.R.P. 88520 and E. P. 1409/1896, to be a mixture of δ-hydroxy-quinoline sulphate and potassium sulphate.

Ortho-hydroxyquinoline is made by gently boiling, for 3–4 hours, a mixture of 7 parts of ortho-nitrophenol, 15 parts of ortho-aminophenol hydrochloride, 25 parts of glycerine and 20 parts of sulphuric acid.   The reaction mixture is diluted with water, made alkaline, and the ortho-oxyquino-line distilled over in steam (Skraup, *Ber.* **16,** 713).   M.p. 73°–74°.

According to D. R. P. 88520, E. P. 1409/1896, twenty-nine kilos of ortho-oxyquinoline are dissolved in 120 kilos of alcohol.   To the solution are gradually added, with good stirring, 25 kilos of finely-powdered potassium pyrosulphate.   The mixture is boiled for 10 hours, employing a reflux condenser, and, after cooling, the product, chinosol, is filtered off.

This was believed, as stated above, to consist of the potassium salt of an oxyquinoline sulphonic acid, but was proved subsequently to be a mixture of the neutral sulphate

and potassium sulphate. For preparing the neutral sulphate in a pure state, the following method was patented (D. R. P. 187943 ; E. P. 11725/1906) :

To a solution of 29 parts of *o*-oxyquinoline in 100 parts of 96 % alcohol are added 10·6 parts of sulphuric acid (65·5° Bé.). The neutral sulphate separates, is filtered off and dried at a low temperature.

Prepared by this method chinosol is a yellowish crystalline powder. M.p. 175°–177°. It is very soluble in water, sparingly soluble in alcohol, and insoluble in ether.

Chinosol is a powerful antiseptic, and is claimed to be stronger in this respect than mercuric chloride, but is only a relatively feeble germicide, its great value being due to its strong inhibiting action on the growth of bacteria. It possesses marked analgesic power, but should be diluted down when used in the form of powder, as otherwise local irritation and swelling may ensue. Chinosol is non-toxic, does not coagulate albumen or injure mucous tissues.

TANNIC ACID DERIVATIVES

Several tannic acid derivatives are employed as intestinal antiseptics. Because the acid itself is irritating to the stomach, and is to a large extent decomposed or absorbed before reaching the intestine, efforts have been made to produce combinations of it with other substances, to render it non-irritating to the stomach ; which combinations become broken up in the intestines, so that the astringent effect of the tannic acid is exerted where required.

TANNALBEN (albumen tannate).—Tannalben is a compound of tannic acid and egg albumen. It is prepared by mixing 10 parts of a 10 % aqueous solution of egg albumen with 6·5 parts of a 10 % aqueous solution of tannic acid.

The precipitate which is formed is separated by filtration, washed with water until the washings react only faintly with ferric chloride solution, dried and powdered, and heated at 126° for 6 hours (E. PP. 6140 and 13281 of 1896).

Tannalben is a light-brown, odourless and tasteless powder, containing about 50 % of tannic acid. It is practically insoluble in water and in alcohol, but dissolves gradually in alkaline fluids, which resolve it into its constituents.

One gram of tannalben, digested for 4 hours at 40° with 0·1 gram of pepsin, 50 c.c. of water, and 1·5 grams of dilute hydrochloric acid (12·5 %), leaves a residue which, after washing with 30 c.c. of water and drying at 100°, should weigh not more than 0·5 gram.

Tannalben is employed as an intestinal astringent. It is unaffected by gastric secretions but is digested by the pancreatic fluids. It is useful in diarrhœa, especially in that of children, and in phthisis.

TANNOFORM (methylene ditannin) $(C_{14}H_9O_9)_2CH_2$. 656. —Tannoform, as its name indicates, is a compound derived from tannic acid and formaldehyde.

Five kilos of tannin are dissolved (D. R. P. 88082) in hot water, 10 kgs. of 30 % formaldehyde are then added, followed by concentrated hydrochloric acid so long as a precipitate is produced.

This is filtered off by means of a filter press, washed well with cold water, and dried at a moderate temperature.

The same substance is stated (D. R. P. 93593) to be obtained by heating tannin and formaldehyde together for several hours in an autoclave, at 100°.

Tannoform is a voluminous reddish powder, odourless, tasteless. It is insoluble in water, but dissolves in alcohol and in alkaline liquids. It is used externally in skin diseases, such as eczema, and as an application to wounds. Internally, it is administered in chronic intestinal catarrh.

Other derivatives of tannic acid used for the same purposes are: Diacetyl-tannin or Tannigen $C_{14}H_8O_9(COCH_3)_2$, and Tannocol, a combination of tannic acid with gelatine.

Santalol and its Derivatives

Sandalwood oil is obtained by steam distillation under pressure from the wood of *Santalum album*, L., in which it is present to the extent of 2·5 to 6·0 %.

The East Indian oil only is official in the British Pharmacopœia. It is a pale-yellow, oily liquid, having a characteristic odour and possessing a specific gravity of 0·975 to 0·980 ; it is required to form a clear solution in six times its volume of 70 % alcohol.

The oil is *lævo*-rotatory and has an optical rotation of −16° to −20° in a tube of 100 mm. length. Not less than 90 % of alcohols, calculated in terms of santalol, should be present. This is determined by acetylating a portion of the oil and determining the saponification value of the acetylated product.

Sandalwood oil is employed extensively in gonorrhœa ; it is a stimulating disinfectant to the mucous membranes of the bladder and urethra.

SANTALOL (articol) $C_{15}H_{23}OH$. 220.—For the preparation of santalol, 6 kilos of sandalwood oil are saponified by boiling for 2–3 hours with 0·6 kilo of potassium hydroxide in 2 kilos of 90 % alcohol. The solvent is then removed by distillation and the santalol distilled over in a current of superheated steam. The first portion of the distillate is set aside if it possesses an objectionable odour, and added to the following batch. Yield, 75–80 % of the weight of oil taken. (D. R. PP. 110485, 116815.)

Santalol is an effective urinary antiseptic and is stated not to cause disturbance of the stomach and kidneys, whereas sandalwood oil may do so at times. It is employed in gonorrhœa and cystitis.

On account of the unmistakable and unforgettable odour of sandalwood oil and santalol, which has become universally associated with the disease gonorrhœa, odourless derivatives of santalol have been a practical requirement and several of these have been introduced into medicine.

SANTALOL CARBONATE (D. R. P. 187254) $(C_{15}H_{23}O)_2CO.$ 466.—Two hundred parts of sandalwood oil are treated with 100 parts of phenyl carbonate and 2 parts of powdered caustic soda, and the mixture heated under reduced pressure. At 140° separation of phenol commences and is completed at 175°. The residue, which consists of almost pure santalol carbonate, is washed with water, and can be purified by distillation in steam.

$$2C_{15}H_{23}OH + (C_6H_5O)_2CO \rightarrow (C_{15}H_{23}O)_2CO + 2C_6H_5OH$$

Santalol carbonate is a yellow, oily liquid, almost tasteless and odourless.

It is broken up in the intestine into santalol and has therefore the same antiseptic action as the latter.

ALLOSAN (santalyl allophanate) $C_{15}H_{23}OCONHCONH_2.$ 306. (D. R. P. 204922).—To a solution of 1·59 kilos of carbamic chloride (2 mols.) in 11 kilos of benzol, are added 2·2 kilos of santalol, with efficient stirring and good cooling. After several hours' standing, the benzol is removed by distillation, the product washed with petroleum and recrystallised from a mixture of benzol and petroleum.

$$C_{15}H_{23}OH + ClCONH_2 \rightarrow C_{15}H_{23}OCONH_2 + HCl$$
<div align="center">Santalyl carbamate.</div>

$$C_{15}H_{23}OCONH_2 + ClCONH_2 \rightarrow C_{15}H_{23}OCONH \cdot CO \cdot NH_2 + HCl$$
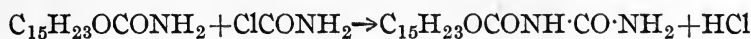
Six kilos of the benzol employed in the above example may be replaced with advantage by 2·5 kilos of dimethylaniline, which combines with the hydrogen chloride formed by the reaction. The mixture, after standing for several hours, is filtered, and the filtrate washed with dilute sulphuric or hydrochloric acid, to remove any remaining dimethylaniline, after which the solvent is distilled off, and the product purified as before.

Allosan forms white crystals which are tasteless. It is soluble in organic solvents, insoluble in water.

ALMOST any drug which acts as a skin irritant will cause evacuation of the bowel, but in the medicinal sense a purgative is an irritant which acts only upon the intestine. The substances employed in medicine are for the most part crude vegetable products. Even in those cases in which the chief active principle can be separated, preference is generally given to the cruder total extract or resin because more satisfactory action is obtained from it.

The principal chemical investigations that have been made in this connection concern the anthraquinone derivatives. Aloes, cascara, rhubarb and senna each contain hydroxy-methyl-anthraquinones. The glucosides of emodin and chrysophanic acid are purgatives ; the probable formulæ of these two anthraquinone derivatives are as follows :—

CH₃ O OH

OH

O OH

Emodin.

CH₃ O OH

O OH

Chrysophanic acid.
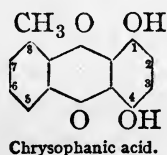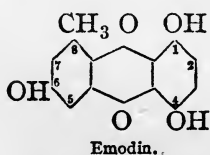
An investigation of the synthetic homologous tri-hydroxy anthraquinones has shown that the position of the hydroxy groups considerably affects the activity. Anthrapurpurin, 1.2.7 trihydroxy-anthraquinone, was found to be more active than the 1.2.6, this more active than the 1.2.3, and this more so than the 1.2.4. The tetra-hydroxy and hexahydroxy-anthraquinones were found less active than the 1.2.3 tri-hydroxy derivative. The presence of methyl groups appears to have a very uncertain influence.

Phenol-phthalein is the only synthetic purgative which is

in practical use on a large scale ; the discovery of its physiological action was accidental.

The ideal purgative has yet to be found, there being great need of research of this kind

ALOIN (barbaloin) $C_{16}H_{18}O_7 \cdot 3H_2O$.   376.—Aloin, or barbaloin, is a derivative of tetra-hydroxy-methyl-anthraquinone, and according to Robinson and Simonsen (*T. Chem. Soc.* (1909), **95**, 1087), may probably be represented by the formula :—

$$CO\text{-}O\text{-}CH_2$$
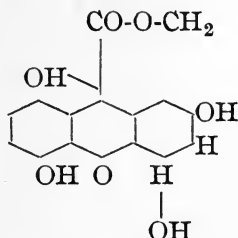
It yields on oxidation aloe-emodin, a tri-hydroxy-methyl anthraquinone, showing its near relationship to emodin derived from rhubarb and to chrysophanic acid derived from araroba.

Aloin is prepared from Curaçoa or Barbadoes aloes, the desiccated juice of the leaves of *Aloe vera*, L., and *Aloe chinensis*, Steud. Curaçoa aloes varies considerably in colour and consistency, from a stiff yellowish-brown paste to a deep brown or almost black, hard solid. It has a comparatively smooth surface when fractured. Several tests can be applied in order to distinguish the Barbadoes from the African (Natal or Cape) aloes, which do not yield an aloin of the same composition. These other aloins are named respectively Socaloin, Nataloin and Capaloin.

If a particle of Barbadoes aloes be treated with concentrated nitric acid a red colour should be produced, which changes to green. Cape aloes gives a green colour, whilst Natal aloes affords a permanent crimson colour.

No blue colouration should be produced when the vapour of nitric acid is blown over powdered aloes which has been previously moistened with sulphuric acid.

Not less than 70 % of the aloes should be soluble in water and it should dissolve almost completely in a mixture of 90 % alcohol with one half its volume of water.

On ignition the quantity of ash should not exceed 3·0 %.

For the preparation of aloin powdered Barbadoes aloes is dissolved in 9 to 10 times its weight of boiling water. The solution is acidified with sulphuric acid, allowed to cool and filtered from resinous matter. The bright filtrate is neutralised and evaporated down *in vacuo* (Fig. 23) until it has a volume of about one gallon for each five pounds of aloes taken. It is then allowed to cool, a few crystals of aloin are added and it is allowed to stand. When crystallisation is completed, the crystals which have separated are filtered off, and washed with a small quantity of diluted alcohol. They are recrystallised from dilute ethyl alcohol, or from methyl alcohol. The yield is, according to the quality, 10 to 20 per cent. of the weight of aloes taken.

Barbaloin is a bright yellow crystalline powder possessing a bitter taste. It dissolves in 120 parts of cold water and in 18 parts of 90 % alcohol. In hot water and alcohol it is readily soluble. The solutions are neutral. After dehydration at 100° barbaloin melts at 147°.

Cold nitric acid (sp. gr. 1·42) gives a cherry-red colouration (distinction from Socaloin, Nataloin, and Capaloin). Copper sulphate gives a bright yellow colour with a dilute aqueous solution ; this when mixed with a few drops of a concentrated solution of sodium chloride gives a red colour, and on adding a little alcohol the colour becomes violet (distinction from Nat- and Cap-aloin).

Absence of emodin is shown by shaking a quantity of aloin with benzene (10 vols.), when the benzene solution should not impart more than a faint pink colour to an equal volume of 5 % ammonia when shaken with it. Aloin is a bitter tonic, and purgative, acting chiefly on the large intestine. It is a good tonic cathartic in habitual constipation and in that associated with anæmia and amenorrhœa. Administered by an enema it is a vermifuge. It is also an emmenagogue.

CASCARA SAGRADA.—Cascara Sagrada is the name given to the dried barks of *Rhamnus purshiana*, *R. frangula*, and
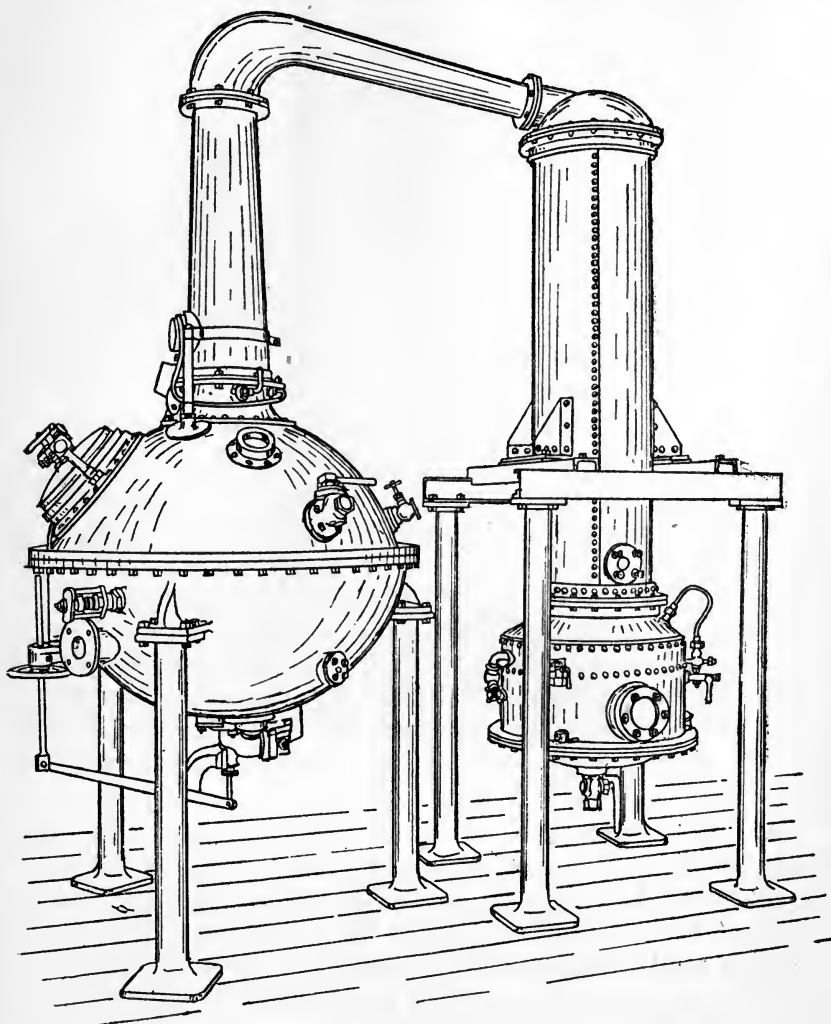
FIG. 23.—Vacuum still for concentration of extracts.

R. Californicus. It is a valuable tonic laxative, acting principally on the large intestine. It is especially useful in

obstinate and habitual constipation, for which it is given, usually in the form of extract in pills, or as a fluid preparation, in such a continuous manner that a normal condition is gradually brought about.

Extract of Cascara Sagrada.—The bark, in No. 20 powder, is exhausted by percolation with distilled water, and the extract evaporated to dryness *in vacuo.*

Liquid Extract of Cascara.—Five parts of cascara bark are exhausted by percolation with distilled water and the percolate evaporated to 3 parts ; one part of alcohol (90 %) mixed with an equal weight of distilled water is added, the whole being made up to 5 parts by the addition, if necessary, of more water. Isolation, in a pure state, of the constituent or constituents to which the physiological activity of the drug is due has not yet been effected, but anthraquinone derivatives allied to emodin are known to be present. An exhaustive chemical examination of the constituents of cascara extract was made by Jowett, and presented in a paper to the American Pharmaceutical Association, 1904. The active principle was found to be contained almost exclusively in an ethyl acetate solution of that portion of a water extract that is precipitated by lead sub-acetate, but all attempts to obtain a pure substance from it were unsuccessful.

This active extract was obtained in the following way. The powdered bark was exhausted thoroughly with hot alcohol, and the solvent removed by distillation. The dried extract was mixed with water, and filtered from fatty matter. The filtrate was extracted with chloroform, which removed emodin and an isomeride, treated with lead acetate solution and filtered from the resulting precipitate. Lead subacetate solution was added to the filtrate, and the bulky red substance, which was precipitated, collected, and washed well with water. It was then suspended in water and decomposed with sulphuretted hydrogen. The filtrate from the lead sulphide was concentrated as far as possible by evaporation in a vacuum. The syrupy residue was mixed with sawdust, dried, and extracted with hot ethyl acetate. On removing the solvent a dark-red residue was obtained, and this was

found by physiological tests to contain the active properties of the drug.

RHUBARB.—The official rhubarb " root " consists of the erect rhizomes of *Rheum palmatum*, Linn., *Rheum officinale*, Baill., and probably other species, and is obtained from China and Thibet. The best root is derived from the province of Shensi. It is dried in the sun. The English cultivated rhubarb, *R. officinale*, is less active as a purgative.

Rhubarb is cathartic and astringent, the purgative effect preceding the astringent, so that its use is indicated in diarrhœa when an aperient is needed. In small doses it is a stomachic tonic. It is non-irritant and is suitable for increasing the effect of other cholagogues and cathartics.

In pharmacy several extracts are employed. **Extract of Rhubarb** is a dried extract made by exhausting the drug with 60 % alcohol, and concentrating the extract to dryness.

Infusion of Rhubarb is made by infusing 1 part of rhubarb, cut into thin slices, with 20 parts of distilled water for 15 minutes.

Concentrated Solution of Rhubarb.—Ten parts of rhubarb root are percolated with 20 % alcohol to yield 20 parts.

A recent investigation of the constituents of rhubarb root has been made by Tutin and Clewer (*T. Chem. Soc.* (1911), **99,** 946). Three constituents only were found which possess a purgative action : aloe-emodin, hydroxy-methyl dihydroxy-anthraquinone $C_{14}H_5O_2(OH)_2 \cdot CH_2OH$, present to the extent of 0·16 % ; chrysophanic acid, dihydroxy-methyl-anthra-quinone $CH_3 \cdot C_{14}H_5O_2(OH)_2$, (0·49 %), both of which are distinctly purgative, though not very active ; and a non-glucosidic resin (10·4 %), which appears to be the chief purgative principle.

0·1 gram of this possessed a much more pronounced purgative action than the same weight of aloe-emodin or of chrysophanic acid, although it represented a much smaller weight of the drug. This resin was obtained in the following manner : the drug was exhausted with hot alcohol, and the extract freed from solvent and boiled out with water. The

aqueous portion was extracted first with ether, whereby cinnamic acid, rhein, emodin methyl-ether, and chryoso-phanic acid emodin, aloe-emodin, etc., were removed, and then with amyl alcohol. The first amyl alcoholic extract was deprived of solvent by evaporation under reduced pressure, the residue dissolved in alcohol and the solution mixed with an equal volume of chloroform. A dark-coloured resin was precipitated, which, as described above, was found to be the main active principle of rhubarb.

EXODIN (diacetyl-rufigallic acid tetra-methyl ester)

$$C_{12}H_2(CO)_2(OCH_3)_4(OCOCH_3)_2$$

Rufigallic acid, hexa-hydroxy-anthraquinone
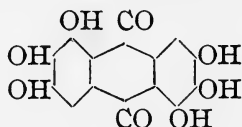
is produced by heating gallic acid with sulphuric acid (*Ann.* **19**, 204). Methylation is brought about (*Ber.* **10**, 885) by heating with excess of methyl iodide in the presence of 4 equivalents of caustic potash in aqueous methyl alcoholic solution, for 3–4 hours at 120°–130° under pressure. A red, insoluble, powdery mass is obtained, and after being filtered off is recrystallised from ethyl acetate, from which it separates in shining gold leaflets. This substance is tetra-methoxy-dihydroxy-anthraquinone $C_{12}H_2(CO)_2(OH)_2(OCH_3)_4$. It is insoluble in ether and water, dissolves with difficulty in boiling alcohol; is easily soluble in acetic acid and ethyl acetate.

The acetylation is carried out as follows:—Five kilos of the above product are boiled for $\frac{3}{4}$ hour, under a reflux condenser, with 20 kilos of glacial acetic acid and 1·25 kilos of powdered anhydrous sodium acetate. After being cooled to 60°–80° the reaction mixture is poured into 18 kilos of water and left to stand for a day or two. The crystalline diacetyl compound which separates is filtered off and re-crystallised, from alcohol, benzene, or acetic acid (D. R. P. 151724). M.p. 180°–190°. It is stated to be a mild laxative

CHRYSAROBIN.—Chrysarobin is the name given to the crystalline residue which results from the extraction of Goa powder. Goa powder or araroba is a concretion found in cavities in the tree trunk of *Andira araroba*. It is imported from Brazil. For the preparation of chrysarobin, the powdered material is extracted with hot benzene or hot chloroform and the extract dried. A yield of upwards of 50 per cent. is to be expected from a Goa powder of satisfactory quality. It consists of a mixture of chrysophanic acid (dihydroxy-methyl-anthraquinone) and its ethers. It is a crystalline yellow powder, soluble in chloroform and benzene and partially dissolved by alcohol and by ether.

It is chiefly used as a parasiticide and is employed in ointments for ringworm, acne, psoriasis, alopœcia, etc.

SENNA.—The leaves and fruits of *Cassia acutifolia* (Alexandrian senna) and of *Cassia angustifolia* (Tinnevelly or East Indian senna) have an extremely high value as laxatives. The active principles have not been completely identified, but rhein and aloe-emodin have been found. It therefore probably owes its activity to anthraquinone derivatives. Its activity is more readily destroyed than that of rhubarb or cascara and its preparations require to be made with particular care in consequence.

The infusion, extract, and confection, in all of which powdered leaf is used, are prepared according to the methods officially described in the pharmacopœias.

An examination of the constituents of the leaves has been made by Tutin (*T. Chem. Soc.* (1913), **103,** 2006).

COLOCYNTHIN, the principle of Colocynth.—Colocynth is the dried pulp of the fruit of *Citrullus Colocynthis*, Schrader, freed from its seeds. It is imported from Asia Minor. Smyrna, Spain, Mogador, Egypt and Cyprus, also from Persia.

In commerce the Turkish and Spanish varieties are most frequently met with, both of which have been peeled after drying. The Mogador fruit is larger and unpeeled ; the Persian colocynth is peeled before drying and presents, consequently, a shrunken appearance.

A boiled and cooled aqueous decoction of the pulp should yield no blue colouration with starch solution. Between 9 and 12 per cent. of ash should be afforded on ignition.

Colocynth pulp is an intensely bitter substance and acts as a very powerful cathartic. It is dangerous in large doses and is not commonly prescribed alone but in small doses in conjunction with other purgative principles.

The active principle, colocynthin, a glucoside to which the formula $C_{56}H_{84}O_{23}$ has been ascribed, when treated with acids is hydrolysed to a sugar and colocynthein, which is said to be even more irritant than colocynthin.

Colocynthin is obtained from an extract of the pulp, prepared with weak alcohol. This is dried and extracted with cold water. The filtered extract is treated with lead acetate solution, and filtered again from the precipitate which is produced. The filtrate is freed from lead by means of sulphuretted hydrogen, and, after removal of excess of the latter, is precipitated with tannic acid. The precipitate is washed with water and decomposed, in alcoholic solution, with lead oxide (precipitated). The filtered solution is freed from lead, decolourised with animal charcoal, and evaporated to dryness *in vacuo*. The resulting product is washed with anhydrous ether. It consists of a yellow, amorphous, bitter-tasting mass, easily soluble in water and alcohol ; insoluble in ether.

It possesses a powerful purgative action, and has been employed for hypodermic administration.

JALAP.—The official jalap consists of the dried tubers of *Ipomœa purga*, Hayne. It is mostly imported from Vera Cruz, but is cultivated also in India and Jamaica. The active principles have not been isolated from the resinous extract.

Evaluation of Jalap.—A weighed quantity (10 gms.) of jalap is digested at a gentle heat for 24 hours with twice its weight of alcohol (90 %), transferred to a percolator and percolated with alcohol until nothing further is dissolved. The alcoholic solution is precipitated by addition of water, the alcohol distilled, the residue transferred whilst still hot

to a dish, cooled, and the supernatant liquor removed. The resin is washed with hot water, dried and weighed. It should weigh not less than 0·9 nor more than 1·1 gram (B.P.).

Jalap should not afford more than 6 % of ash on ignition.

Jalap, employed either as the powdered drug or in the form of an extract, is a powerful cathartic, operating at times painfully, and is a common constituent of pills. It is especially serviceable in dropsy and cerebral congestion.

Extract of Jalap is made according to the directions of the Pharmacopœias. One part of coarsely-powdered jalap is extracted first with 5 parts of 90 % alcohol, then with 10 parts of distilled water, and the two residues are combined into one extract. One hundred pounds of jalap yield about 50 lbs. of extract.

Jalap Resin is extracted from jalap by exhausting the powdered rhizome with alcohol (90 %), pouring the hot extract with stirring into water, separating the oily resin and purifying by washing it with hot water. It is best dried in a vacuum cupboard, but may be dried over a steam bath. After cooling it is pulverisable. Jalap resin or Jalapin is a grey-brown friable substance, possessing a slight characteristic taste and an irritating smell. It is easily soluble in alcohol, dissolves in 50 parts of petrol ether and in 10 parts of ether. Further, it dissolves completely in acetic acid, baryta and caustic potash. The active principle of jalap has not been isolated. Power and Rogerson (*J. Am. Chem. Soc.* (1901), **32**, 80) found the resin to be of very complex composition. Extracts were prepared, employing consecutively different solvents, and physiologically tested, with the following results :—

(1) The petroleum extract had no effect.

(2) The ether extract produced prompt but not severe purgation.

(3) The chloroform extract caused repeated purgation lasting 48 hours.

(4) The ethyl acetate action was similar in its action to the chloroform extract, purgation lasting 24 hours.

(5) The alcohol extract produced repeated and violent purgation.

From this it is presumed that the purgative action is not due to any single or well-defined constituent.

SCAMMONY RESIN.—*Scammony resin* is obtained by extracting with hot alcohol the root of *Convolvulus Scammonia*. Most of the solvent is removed by distillation, after which the hot concentrated solution is poured into water, which precipitates the resin. The resin is repeatedly washed with hot water, separated and dried *in vacuo* or in an open steam pan. Mexican scammony resin—the gum-resin afforded by the root of *Ipomœa orizabensis*—closely resembles genuine scammony resin in its chemical and physical properties and physiological action, but is not identical. Both these resins have a similar action to that of jalap resin, being energetic hydragogue cathartics. They are valuable when brisk action is needed, as in severe dropsy and in cerebral congestion. They also act as anthelmintics to round worms and tape worms.

Scammony resin is met with in greenish-grey, or brownish-green, translucent brittle lumps, with more or less sharp edges, and breaking with a shining fracture. It is, in contradistinction to jalap resin, almost completely soluble in ether. The acid value should be 14·6, the ester value 171·0, and the saponification value 185·6. It should yield not more than 1·0 % of ash.

Virgin Scammony is a gum resin obtained by incision of the living root of *Convolvulus Scammonia*. It is derived chiefly from Asia Minor and constitutes brown, dark-grey, or brownish-black, irregular masses, or circular cakes, which break with a glossy resinous fracture. It forms with water a greenish emulsion (distinction from scammony resin). When treated with ether, at least 70 % should be dissolved.

Aleppo scammony has an acid value of 8·2, an ester value of 172, and a saponification value of 180·2. Not more than 3·0 % of ash should be left on ignition.

Power and Rogerson (*T. Chem. Soc.* (1912), **101**, 398)

have found these resins of scammony to be exceedingly complex in character. Though similar in their general characteristics they are not perfectly identical. They appear to consist to a large extent of the glucosides and rhamnosides of jalapinolic acid $C_{15}H_{30}(OH)COOH$ and its methyl ester. The resin from Mexican scammony root, *Ipomœa orizabensis*, on the other hand, differs from them very considerably. Amongst other differences may be mentioned the fact that it affords on hydrolysis a methylpentoside differing from rhamnose.

Podophyllin.—Podophyllin is the resin obtained from the dried rhizome and roots of *Podophyllum peltatum*, a plant which grows wild in North America. It is an active cholagogue, and, in ¼ gr. doses, acts as a powerful purgative.

Although the American species only is official in the British Pharmacopœia, Dunstan and Henry (*T. Chem. Soc.* (1898), **73**, 209) have shown that the constituents of the Indian species, *P. emodi*, are identical with, though in different proportion to, those of *P. peltatum ;* furthermore, *P. emodi* contains a higher percentage of resin. The chief active principles in these two varieties are *podophyllo-toxin* $C_{15}H_{14}O_6 \cdot 2H_2O$ and a podophyllo-resin. The former, however, is unsuitable as a medicinal substitute for podophyllin resin on account of its intensely irritating action, whilst the use of the resin constituent seemed to present no advantage over the drug as generally employed ; other constituents are podophyllo-quercitin and picropodophyllin. The latter is isomeric with podophyllo-toxin and has been given the following probable formula by Dunstan and Henry (*T. Chem. Soc.* (1898), **73**, 209) :—
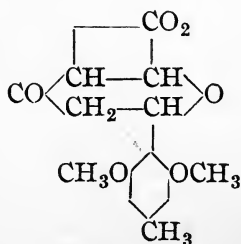
Picropodophyllin.

Podophyllin resin is prepared by extracting the powdered root with hot alcohol, concentrating the extract, and pouring it into cold acidified water with vigorous stirring ; the temperature should be kept low and ice employed, if necessary, to prevent coagulation of the precipitate. The precipitated resin is filtered off, washed and dried at a low temperature.

Podophyllin resin is a light yellow powder. It is sparingly soluble in water, almost completely soluble in alcohol (90 %) and in ammonia solution. The quantity insoluble in alcohol should not exceed five per cent.

More than 50 % of the resin should be soluble in cold chloroform. Not more than 1 % of ash should be left on ignition.

The resins from *P. emodi* and *P. peltatum* may be distinguished by the following test. Six grains of the resin are mixed with 1 fluid dram of dilute alcohol and 8 to 10 drops of caustic potash solution (6·2 % KOH). The resin of *P. peltatum* affords a deep yellow solution on shaking, that of *P. emodi* a semi-solid gelatinous mass.

$$\textbf{PHENOL-PHTHALEIN (purgen)} \quad \begin{array}{c} C(C_6H_4OH)_2 \\ \diagup \diagup \diagdown O \\ CO \end{array} \quad 318.\text{—}$$
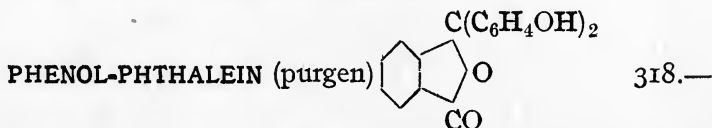
Baeyer's original method (*Ann.* (1880), **202**, 69) still remains the only one published which deals with the preparation of phenol-phthalein.

$$C_6H_4\diagdown_{CO}^{CO}\diagup O + 2C_6H_5OH \;\rightarrow\; C_6H_4\diagdown_{CO}^{C-(C_6H_4OH)_2}\diagup O + H_2O$$
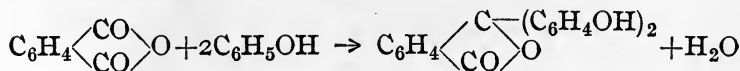
A solution of 250 grams of phthalic anhydride in 200 grams of concentrated sulphuric acid is prepared with careful heating. It is cooled to 115°, and treated with 500 grams of phenol, and the mixture is then heated at 115°–120° for 10–12 hours, care being taken that the temperature does not exceed 120°. The melt is then poured into boiling water, and the excess of phenol removed by steam

distillation. The granular yellow solid is extracted with dilute caustic soda, which dissolves out the phenol-phthalein, leaving behind a by-product, phthalein anhydride. After cooling, the liquid is filtered, acidified with acetic acid, mixed with a few drops of hydrochloric acid, and left to stand for 24 hours. The crude phenol-phthalein, a sandy-yellow powder, is then filtered off and dried. To purify it for pharmaceutical use it must be crystallised. Ten parts of the air-dried crude product are boiled under reflux for $1\frac{1}{2}$ hours with 60 parts of absolute alcohol and 5 parts of dry animal charcoal. The mass is filtered while still hot, the charcoal being washed with 20 parts of boiling alcohol. The combined filtrates are concentrated to two-thirds their original volume, and treated with water ; the milky liquid deposits, on standing, crystals of phenol-phthalein mixed with a gummy impurity. To remove this, the alcoholic solution is added to water, in the proportion of 40 grams to 320 c.c., the mixture is vigorously shaken, and after standing for a short time separated quickly from the precipitated resin. The solution is then heated, when the milkiness disappears, a white crystalline powder being precipitated. This is filtered off, washed with water, and dried at a low temperature. A further quantity is obtained by removal by distillation of the alcohol from the filtrate. The yield is given as 75 %, calculated from the weight of phthalic anhydride employed.

Phenol-phthalein forms a white powder, almost insoluble in water ; readily soluble in alcohol. M.p. 250°–253°. It dissolves completely in sodium or potassium hydroxide solution.

Phenol-phthalein is employed in medicine as an aperient, and is the only synthetic purgative which has found wide acceptance. Its action is maintained mildly for several days. This is explained by the fact that it is absorbed in the blood and excreted by the bile duct into the gut again.

Tetrachlorophenol-phthalein exerts a similar action to that of phenol-phthalein itself.

Section VII.—VASO-CONSTRICTORS AND VASO-DILATORS

THE usual products of tissue metabolism exercise a dilator action on the blood vessels ; this action is balanced partly by sympathetic nerve reflexes, but also by a substance secreted by the supra-renal gland (adrenaline) which exerts a very powerful constrictor action. This has been termed by Barger and Dale sympathomimetic action. The elucidation of the chemical constitution of adrenaline pointed the way to the preparation of other substances of analogous constitution which possess like action. Adrenaline has the constitution :

$$OH\underset{OH}{\underset{|}{\diamondsuit}}CH(OH)—CH_2—NH—CH_3$$
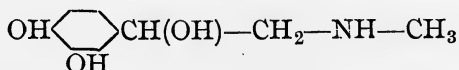
If the hydroxyl group of the side chain is substituted by hydrogen, the compound (epinine) has a like though weaker action, and is also used in medicine.

During an investigation of the substances responsible for the well-known pressor action of ergot, what may be regarded as a parent substance of adrenaline, para-hydroxy-phenyl-ethylamine (tyramine) $OH\underset{OH}{\diamondsuit}—CH_2CH_2NH_2,$ proved to have similar physiological properties. Following this discovery many other amines were found to act in this way. Of most especial value and importance is β-iminazolyl-ethylamine (histamine), also present in ergot.

Ergot has long been employed in medicine for its pressor action and, strangely, it yields, in addition to the two substances referred to above, an alkaloid of complex consti-tution (as yet unknown) which also acts powerfully as a

vaso-constrictor ; this, as well as the bases, tyramine, hista-mine and adrenaline, are dealt with more fully in the follow-ing pages.

The nitrites exert an opposite (vaso-dilator) action on the arteries ; they also are here described. Organic nitric esters act similarly to nitrites on the blood vessels through becoming reduced to nitrites in the tissues ; thus nitro-glycerin acts similarly to, but more slowly than, amyl nitrite.

ERGOTOXINE $C_{35}H_{41}O_6N_5$. 627.—Ergotoxine is the physiologically active alkaloid of ergot—the mycelium of a fungus, *Claviceps purpurea*, which is developed on, and takes the place of, the growing ovary of the rye plant, *Secale cornutum*.

The principal commercial varieties of ergot are derived from Russia, Spain, Germany and Austria. Ergot should be hard and dry, flexible and damp specimens being inferior. It should be kept dry, and not longer than a year owing to its liability to be destroyed by weevils.

For the preparation of ergotoxine powdered ergot is completely extracted with ether and the ether extract is concentrated to an oily residue, which is extracted with aqueous 0·5 per cent. tartaric acid solution. The filtered acid extract is shaken out with ether and rendered alkaline with sodium carbonate, and the precipitated alkaloid (amounting to 0·2 to 0·25 % of the drug) is extracted with ether. The ether extract is washed and dried at a low temperature. It is dissolved in methyl alcohol, wherefrom ergotinine crystallines. The filtrate from this, which con-tains the ergotoxine, is dissolved in 3 parts of acetic acid, the solution is diluted to 300 parts, filtered, and treated with 100 parts of an aqueous solution containing 1 part of anhy-drous $NaSO_4$. The sparingly soluble ergotoxine sulphate crystallises out, whilst ergotinine remains in solution. The sulphate is purified by recrystallisation. Another suitable salt for the purification process is the phosphate, which may be crystallised from 80 per cent. alcohol.

An alternative method of preparation is as follows :—An alcoholic extract of ergot is prepared and the solvent

removed by distillation. The residue is extracted with light petroleum to remove fat, etc., dissolved in ethyl acetate and shaken with citric acid solution. Sodium bromide is added, when the sparingly soluble hydrobromides are precipitated and are filtered off.

The mixed hydrobromides are dissolved in dilute caustic soda, and the solution extracted with ether, which dissolves out the ergotinine, mixed with a little ergotoxine. The ether is removed and the ergotinine crystallised from absolute alcohol, from which it separates in long needles.

Ergotinine can be converted into ergotoxine by boiling it with dilute acetic or phosphoric acid in dilute alcohol. The liquor from which the ergotinine has been extracted is neutralised, made alkaline with sodium carbonate, and shaken out with ether. The residue left after evaporation of the ether, together with that from the ergotinine mother liquors, is dissolved in 80 % alcohol and treated with a slight excess of phosphoric acid dissolved in alcohol. Ergotoxine phosphate separates out on standing and is filtered off and recrystallised from 90 % alcohol.

Ergotoxine Phosphate $C_{35}H_{41}O_6N_5 \cdot H_3PO_4 \cdot H_2O$ is the most readily prepared salt of ergotoxine. It forms an almost white crystalline powder. M.p. 186°–187°. It dissolves in 14 parts of boiling, or 313 parts of cold, 90 % alcohol; with cold water it gives a colloidal solution.

Ergotoxine hydrochloride, sulphate and oxalate are crystallisable.

Ergotoxine Alkaloid is a white amorphous powder. M.p. 160°–162°. It is almost insoluble in water; easily soluble in alcohol, ether and in boiling benzene. It is a carboxylic acid derivative and forms the lactone, ergotinine.

Ergotoxine exerts a powerful action upon the tissues and causes rhythmic contraction of the uterus. It does not possess all the characteristic actions of ergot extracts, which owe their activity also to the presence of *p*-hydroxyphenylethylamine (tyramine) and β-iminazolyl-ethylamine (histamine). Barger and Carr (*Trans.* (1907), 337), Kraft (*Arch. der Pharm.* (1906), 244, 336).

ERGOTININE $C_{35}H_{39}O_5N_5$, 609, is the lactone of ergotoxine, from which it may be derived by treatment with boiling methyl alcohol or by the action of acetic anhydride. It is crystallised from absolute alcohol, from which it separates in long needles, or from ether. M.p. 219°–220°. It is readily soluble in acetone, ethyl-acetate and benzene, less so in alcohol (1 in 290 parts) and in ether (1 in 1000 parts). It does not form crystalline salts.

A solution in methyl- or ethyl-alcohol slowly undergoes decomposition. A solution in acetic or phosphoric acid undergoes gradual conversion into the salt of ergotoxine.

Ergotinine does not exert any notable physiological action.

Other active substances from ergot are p-hydroxy-phenyl-ethylamine OH$\langle$ $\rangle$CH$_2$CH$_2$NH$_2$, which has been synthesised and introduced into medicine under the name of tyramine, and β-iminazolyl-ethylamine or 4-β-amino-ethyl-glyoxaline (histamine)

$$CH\begin{array}{c} {}^{\diagup}NH\text{---}CH \\ {}\qquad\quad\| \\ {}_{\diagdown}N\text{---}C\cdot CH_2\text{---}CH_2\text{---}NH_2 \end{array}$$
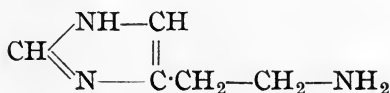
These bases were isolated from ergot extract by Barger and Dale (*Trans. Chem. Soc.* (1909), **95**, 1125 and (1910), **97**, 2592), also by Kutscher (*Zeits. Physiol.* (1910), **24**, 163).

Of the bases enumerated above, ergotoxine causes contraction of the uterus, rise of blood pressure, and gangrene of the cock's comb ; p-hydroxy-phenyl-ethylamine causes uterine contraction and rise of blood pressure; β-iminazolyl-ethylamine produces a very rapid rise of blood pressure, also contraction of the uterus, Ergotinine has, when unchanged in the system, only a very slight action, but is liable to be converted into the physiologically active ergotoxine.

TYRAMINE (*p*-hydroxy-phenyl-ethylamine)

$$OH\langle\ \rangle CH_2CH_2NH_2. \quad 137.$$
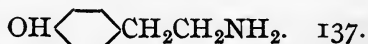
—Tyramine was isolated from ergot extract by Barger and

Dale, and is present in putrefactive animal matter. It may be derived from tyrosine by loss of CO_2 :—

$$OH\langle\bigcirc\rangle CH_2CH\langle^{COOH}_{NH_2}$$
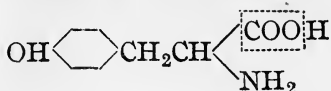
Several methods of preparing it synthetically have been put forward.

(1) Benzyl cyanide is reduced to phenyl-ethylamine, and this compound is benzoylated, nitrated, reduced, diazotised and hydrolysed :—

$$\bigcirc_{CH_2CN} \rightarrow \bigcirc_{CH_2CH_2NH_2} \rightarrow \bigcirc_{CH_2CH_2NH\cdot COC_6H_5}$$

$$\rightarrow \bigcirc^{NO_2}_{CH_2CH_2NHCOC_6H_5} \rightarrow \bigcirc^{NH_2}_{CH_2CH_2NHCOC_6H_5} \rightarrow \bigcirc^{OH}_{CH_2CH_2NH_2}$$
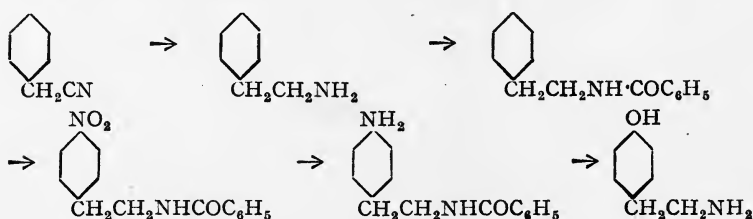
(2) Anisic aldehyde is condensed with ethyl-acetate, using sodium, and the product is subsequently boiled with alcoholic potash. The methoxy-phenyl-propionic acid thus produced is converted into its chloride, by the action of phosphorus pentachloride, and thence into its amide, with gaseous ammonia. Thence to p-methoxy-phenyl-ethylamine, from which the methoxy group is split off by treatment with hydrobromic or hydriodic acid under pressure.

(3) Anisic aldehyde is condensed with nitro-methane to form β-nitro-p-methoxy-styrene, which is reduced to p-methoxy-phenyl-ethylamine and the methoxy group split off as under method (2).

HISTAMINE (β-iminazolyl-ethylamine, 4-β-amino-ethyl-glyoxaline) $CH\langle^{NH—CH}_{N——C\cdot CH_2\cdot CH_2\cdot NH_2}$ III.—Histamine
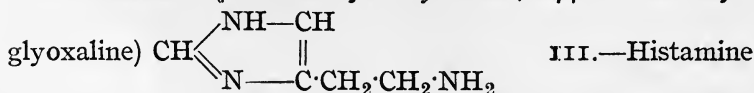
was first isolated by Barger and Dale from ergot extract. It may be obtained from histidine—

$$CH\langle^{NH—CH}_{N——C\cdot CH_2}\overset{COOH}{\underset{CH\cdot NH_2}{|}}$$
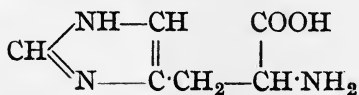
an amino acid which occurs as a product of hydrolysis of many albumens, notably, in considerable amount, of hæmoglobin.

Histidine itself has been synthesised by Pyman (*Trans. Chem. Soc.* **99,** 1086 (1911) ; **109,** 186 (1916)). The same investigator has also effected a direct synthesis of histamine, starting with diamino-acetone hydrochloride (*Trans. Chem. Soc.* **99,** 668 (1911)), and has succeeded, in collaboration with Ewins, in obtaining a 25 % yield of histamine from histidine by heating the latter with hydrochloric acid (*Trans. Chem. Soc.* **99,** 339 (1911)). The synthetic methods of preparing histidine, however, involve many steps, and it is possible that it is best prepared technically by the hydrolysis of hæmoglobin.

It is claimed, in D. R. P. 252873, that good yields of pure histamine can be obtained from the products of the hydrolysis of blood. One kilo of blood is hydrolysed by boiling with 4 kgs. of 25 % sulphuric acid for 16–20 hours. Excess of the acid is removed by treatment with baryta, and the solution concentrated to 700 c.c. The amino acids which separate on cooling contain no histidine and are filtered off. The filtrate is mixed with 500 c.c. of alcohol and evaporated to dryness, and the residue then macerated with 1 litre of alcohol, when about 80 grams of amino acids, histidine free, pass into solution and are removed by filtration. The residual mass is dried *in vacuo*. It weighs about 420 grams, and contains (estimated from the yield of histamine it affords) about 120 to 140 grams of histidine.

This is treated according to D. R. P. 252872, in which a solution of 10 grams of histidine hydrochloride in 800 c.c. of water is fermented at 37°–39°, with 5 c.c. of an autolysate from 15 grams of thymus gland in 100 c.c. of water, or with a pure culture obtained therefrom (D. R. P. 256116). The fermentation is allowed to continue until the quantity of histamine present, estimated by conversion into its picrate, no longer increases, and is usually completed in 5 to 6 days, when 1 part of the above solution should give 0·018 to 0·019 part of histamine picrate, an amount almost corresponding to a theoretical yield.

The solution of histamine may then be treated with picric acid, the picrate filtered off, recrystallised (m.p. 228°), and converted into the hydrochloride by treating with the required quantity of hydrochloric acid, shaking out the picric acid with a solvent, such as ether, and then evaporating to dryness. A kilogram of blood should afford 107 grams of histamine hydrochloride.

Alternatively, D. R. P. 252874, the solution after fermentation is acidified with hydrochloric acid and evaporated to a syrup, which is made alkaline, and mixed with sufficient anhydrous sodium sulphate to give a pulverisable mass after powdering. This is extracted with hot chloroform, from which, after concentration and on cooling, the histamine separates in crusts.

A method of fermentation is described in D. R. P. 250110, whereby decomposing pancreas is employed. The process is stated to occupy seven weeks. The histamine is purified by conversion into its mercury salt, from which it is regenerated by H_2S. One hundred parts of histidine hydrochloride are said to yield 60 parts of histamine hydrochloride.

ADRENALINE (epinephrine, adrenine, suprarenine)

OH

$\begin{matrix} \text{OH} \end{matrix}$ 183.

CHOH·CH$_2$·NHCH$_3$
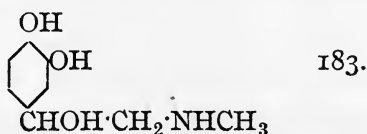
Adrenaline is the active principle of the suprarenal gland, from which it was first isolated in a pure state by Takamine (*Amer. Journ. Pharm.* (1901), **73**, 523), though Abel had previously obtained it in impure form. The naturally occurring base is the lævo-stereoisomeride, which has about twice the activity—judged by the augmentation of the blood pressure—of the synthetically obtained racemic substance. The synthetic lævo-base obtained from the latter is identical in all respects with the natural active principle.

Preparation of the Glands.—Minced fresh suprarenal glands of the ox or sheep, containing about 0·2 per cent. of adrenaline, are exhausted by successive extractions with

boiling acidified water, a little zinc dust being added.
The filtered extract is evaporated down *in vacuo* at 50°
to a syrupy condition ; it is then mixed with several volumes
of ethyl or methyl alcohol and may be treated with lead
acetate solution until this reagent produces no further pre-
cipitation.   The filtrate from this (after being freed from
lead by H_2S if lead acetate has been added) is evaporated
in a current of CO_2, or *in vacuo*, to a syrupy consistence, a
layer of paraffin is added and then an excess of concentrated
ammonia solution.   A crystalline precipitate of adrenaline
gradually forms ; it is filtered off, washed successively with
water, alcohol and ether, and dried in a vacuum over
concentrated sulphuric acid.   It can be purified further
by solution in dilute hydrochloric acid and reprecipita-
tion with ammonia.   To prevent oxidation it is useful to
keep sulphites present during the above operations.   The
crude base may be purified by being ground up with a
strong solution of oxalic acid in 90 per cent. alcohol, which
leaves inorganic impurities behind ; these are filtered off
and the adrenaline is precipitated with ammonia.

A large number of processes for preparing adrenaline
synthetically have been devised ; of them the following is
of chief technical value.   The starting out materials are
pyrocatechol and chloracetyl chloride (or chloracetic acid
and phosphorus oxychloride) and the synthesis is effected
according to the following scheme :—

Pyrocatechol.   Chloraceto-catechol.

Amino-methyl-acetocatechol (adrenalone).   *r*-adrenaline.
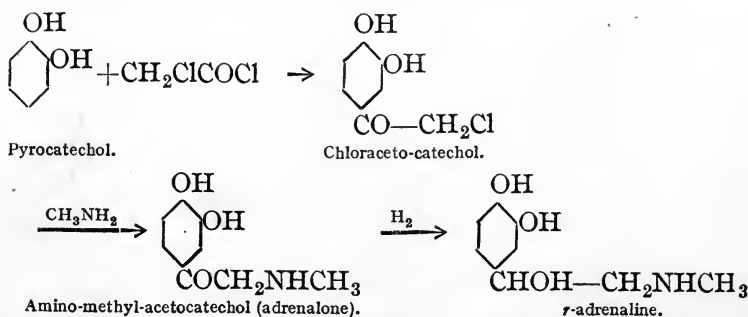
Chloraceto-catechol (D. R. P. 71312).—Pyrocatechol, 10
parts, is mixed with chloracetyl chloride, 8 parts, and

the mixture carefully heated until evolution of HCl has commenced, when the reaction completes itself. The chloraceto-catechol which is thus produced is recrystallised from water, employing charcoal as a decolourising agent, and is obtained in the form of colourless needles. M.p. 173°.

Bromaceto-catechol may be prepared similarly, by employing bromacetyl bromide or bromacetyl chloride. M.p. 170°.

Methylamino-acetocatechol   OH

OH

$\dot{C}O\cdot CH_2NHCH_3$ (D. R. P.
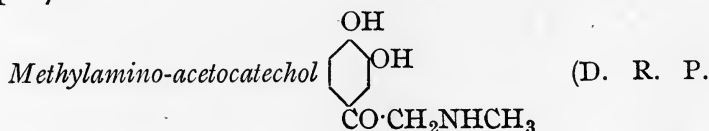
152814).—Finely powdered chloraceto-catechol, 1 part, is suspended in 1 volume of alcohol, and 1 part of aqueous 60 % methylamine solution added. Heat is developed and the methylamine salt of the chlor-dioxy ketone is formed. This is gradually converted, on maintaining the solution at a moderate temperature, into methylamino-acetocatechol, which separates as a crystalline precipitate. This, after standing for 1 hour, is filtered off and washed with cold alcohol. It is purified by dissolving it in dilute hydrochloric acid and carefully treating the solution with ammonia, when a small quantity of amorphous impurity separates and is filtered off before the bulk of the base is precipitated.

Methylamino-acetocatechol forms clear yellow crystals, which on heating colour at 200° and decompose at 230°.

The hydrochloride crystallises from alcohol in colourless leaflets, which decompose on heating at 240°.

Reduction of Methylamino-acetocatechol to Adrenaline (D. R. P. 157300).—One part of methylamino-acetocatechol is dissolved in 30 parts of hot water containing the calculated quantity ($\frac{1}{2}$ mol.) of sulphuric acid. The solution is heated on a water bath and to it are added 1 part of a 1 % solution of mercuric sulphate and 1 part of aluminium foil The mixture is heated and stirred for 3–4 hours, during which time the base which separates is brought into solution by successive and careful additions of sulphuric acid. When the

reduction is finished, any excess of acid, and the alumina, are precipitated by exact neutralisation with baryta, filtered off, and the solution evaporated to dryness *in vacuo*. The sulphate of the methylamino-ethanol-catechol is obtained as an amorphous mass. This is dissolved in water, and made alkaline with ammonia, when the adrenaline is precipitated as a crystalline powder, which is filtered off.

r-**Adrenaline Hydrochloride** is prepared (D. R. P. 202169) by moistening the base with absolute alcohol and dissolving in absolute alcohol containing the theoretically necessary quantity of hydrogen chloride. The hydrochloride crystallises out on standing and is filtered off, washed with ether, and recrystallised from absolute alcohol.

Colourless crystals. M.p. 157°. Readily soluble in water.

Resolution of *r*-Adrenaline into lævo- and dextro-Adrenaline.—According to D. R. P. 222451 fifty grams of racemic adrenaline are moistened with absolute methyl or ethyl alcohol and treated with an alcoholic solution of 43 grams of dextro-tartaric acid. The alcohol is removed *in vacuo* at 35°–40° and the tartrate dried. The salt is ground up with methyl alcohol, whereupon the tartrate of dextro-adrenaline dissolves. The lævo-adrenaline *d*-tartrate is then purified by being recrystallised from 95 % methyl alcohol, until it has a melting point of 149°. The liquors from the above preparation, which contain the dextro-adrenaline, are freed from alcohol, the residue is dissolved in water and the *d*-adrenaline recovered by precipitation with ammonia. It may then be racemised (D. R. P. 220355) by dissolving 15 parts in 135 c.c. of normal hydrochloric acid and 150 c.c. of water, and heating the solution at 80°–90° until it has become optically inactive (2–3 hours). The base is then precipitated with ammonia and reconverted into the *d*-tartrate. Organic acids, such as tartaric and oxalic acids, can also be employed for the racemisation of *d*-adrenaline (D. R. P. 223839).

A modification of the above method of resolving racemic adrenaline is given in D. R. P. 269327. *r*-adrenaline, 182

parts, is dissolved, together with 150 parts of dextro-tartaric acid, in 1000 parts of hot methyl alcohol. Lævo-adrenaline *d*-tartrate crystallises out on cooling, and, after several days' standing, is filtered off and purified by being twice recrystallised from methyl alcohol.

Other methods of preparing *r*-adrenaline are :—

(1) Diacetyl-proto-catechuic aldehyde (I) on condensation with nitro-methane in feebly alkaline aqueous solution yields β-hydroxy-β-3 : 4-diacetoxy-phenyl-nitro-ethane (II). When this is mixed with the calculated quantity of formaldehyde and reduced by zinc and acetic acid, β-hydroxy-β-3 : 4-diacetoxy-phenyl-ethyl-methylamine (III) is formed, from which adrenaline is obtained on removal of the acetyl groups.
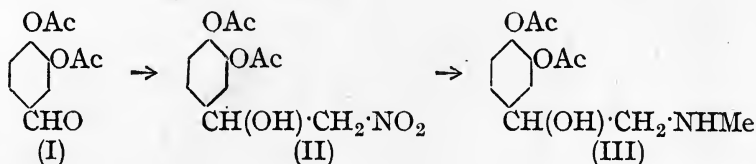
(N. Nagai, Jap. Pats. 32440, 32441 (1918).)

(2) From proto-catechuic aldehyde cyanhydrin (D. R. P. 220355) by reduction to $OH\langle\ \rangle CHOH \cdot CH_2NH_2$ and OH

methylation of this.

(3) From the methylene-dioxyphenyl-ethylene-halogenhydrins, by treatment with PCl_5, then with water and methylamine (D. R. PP. 209962, 216640, 209609).

(4) By D. R. PP. 185598 and 189483, a catechol ether, such as veratrol, is combined with phthalyl-glycyl chloride, giving the corresponding ether of phthalimido-acetocatechol. This, on treatment with hydrochloric acid in glacial acetic acid solution, is hydrolysed into phthalic acid and amino-aceto-catechol, which can be made to yield adrenaline by methylation and reduction.

Racemic adrenaline is a white crystalline powder, which decomposes at 230° C. Lævo-adrenaline forms small white acicular crystals.

M.p. 212° with decomposition. $[\alpha]_D -53°$ (in dilute hydrochloric acid). Sparingly soluble in cold water, insoluble in alcohol and in ether. Soluble in dilute acids and caustic alkali.

The aqueous solution, particularly when alkaline, rapidly absorbs oxygen from the air, becoming pink, red and eventually brown, this constituting a delicate reaction for the identification of adrenaline in small amounts.

The chief crystalline salt is the acid tartrate. The racemic base forms a crystalline hydrochloride and oxalate, but the corresponding salts of the lævo modification are amorphous.

Adrenaline acts by constricting the blood vessels, causing a large rise of blood pressure. It also stimulates the vagus centre, with slowing of the heart, and has a direct and tonic effect on the heart muscle. When administered subcutaneously very small doses produce a marked vasoconstrictor effect.

It is chiefly used locally in hæmorrhage and in catarrhal and congestive conditions. Its vaso-constrictor action is employed also to intensify the effects of local anæsthetics by retarding the circulation in the affected part, thus hindering the dilution of the anæsthetic by too rapid absorption in the blood stream.

ADRENALINE SUBSTITUTES.—Numerous amines have an action more or less resembling that of adrenaline (Barger and Dale, *J. Physiol.* (1910), **41**, 19). Three, all closely related to adrenaline in structure, have been recommended as substitutes but have not found wide application.

ARTERENAL *r*-3 : 4-dihydroxy - phenyl - ethanol - amine, $(OH)_2C_6H_3 \cdot CH(OH) \cdot CH_2NH_2$, m.p. 191° (hydrochloride, m.p. 141°), is said to be about half as active as *l*-adrenaline.

HOMORENON (ω-ethylamino-3 : 4-dihydroxy-acetophenone) $(OH)_2C_6H_3 \cdot CO \cdot CH_2 \cdot NH \cdot C_2H_5$ affords a crystalline hydrochloride, m.p. 260°, and it has a much weaker action than adrenaline.

EPININE (3 : 4-dihydroxy-phenyl-ethyl-methylamine)

$$(OH)_2C_6H_3 \cdot CH_2 \cdot CH_2 \cdot NH \cdot CH_3$$
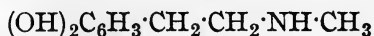
M.p. 188°–189° (Pyman, *Trans. Chem. Soc.* (1910), **97**, 272), is intermediate in action between the two former bases.

ETHYL NITRITE—$C_2H_5NO_2$.—Ethyl nitrite is employed in medicine in the form of an alcoholic solution, known as " Spiritus Ætheris Nitrosi." The B.P. requires the solution to contain 1·5 to 2·6 % of ethyl nitrite, and the U. S. P. 4·0 %.

It can be prepared by either of the following methods.

(*a*) Forty parts by volume of sulphuric acid (sp. gr. 1·84) are added to 120 parts of water, followed, after cooling, by a mixture of 85 vols. of alcohol (90 %) and 85 parts of water. The mixture is cooled to 0°, when a filtered solution of 100 parts of sodium nitrite in 280 parts of water is added drop by drop, the temperature being kept below +5°. When all has been added, the liquid portion is decanted from crystals of sodium sulphate, and transferred to a cooled separator, in which the ethyl nitrite layer is separated. It is washed, first with 20 parts of ice-cold water, then with 15 parts of water containing 0·6 part of sodium carbonate (monohydrate), and dried, after careful separation, by agitation with 3 parts of anhydrous potassium carbonate. It is then mixed with a weighed amount of alcohol and diluted to the required strength.

(*b*) One hundred parts by volume of sulphuric acid (1·84 sp. gr.) are added to 1000 vols. of alcohol (90 %), followed by 125 vols. of nitric acid (sp. gr. 1·4), with cooling and stirring. One hundred parts of copper turnings are then added and the mixture gently distilled, the commencing temperature being 77°. The receiver contains 1000 vols. of 90 % alcohol, which is cooled to 0°. Distillation is continued until the volume in the receiver has increased to 1600 parts ; the contents of the still are then allowed to cool, when 25 vols. more of nitric acid are added, after which distillation is resumed, and continued until a further 100 parts of distillate have been collected.

The product is then assayed (see below) and diluted with

alcohol until it contains 2·66 % by weight of ethyl nitrite (B. P.).

Spirit of nitrous ether B. P. has a sp. gr. of 0·823–0·840 at 15°. When freshly prepared it is neutral in reaction towards litmus, but gradually develops acidity on keeping. This instability shows itself in some degree under all conditions of storage and is accompanied by loss of ethyl nitrite.

Ten c.c. of the spirit, mixed with 5 c.c. of normal sodium hydroxide solution and 5 c.c. of water, assumes a yellow colour which should not become brown within 12 hours (freedom from aldehydes).

Ten c.c. should not require more than 0·2 c.c. of $N/1$ alkali for neutralisation.

Assay : A quantity of about 30 grams of the spirit, which has been previously shaken with 0·5 gram of potassium bicarbonate, is transferred to a graduated 100 c.c. measuring flask, and is accurately weighed. It is then diluted to 100 c.c. with alcohol (95 %) and thoroughly mixed. A measured quantity of 10 c.c. of this solution is introduced into a nitrometer filled with saturated brine. Ten c.c. of 10 % potassium iodide solution are introduced, followed by 10 c.c. of $N/1$ sulphuric acid. The volume of gas evolved is read off when it has become constant, usually within 30 to 60 minutes. The number of c.c. of gas is multiplied by 0·307, and the product divided by one-tenth of the original weight of the ethyl nitrite solution taken. At the standard temperature and pressure the quotient will represent the percentage of ethyl nitrite in the liquid.

Ethyl nitrite solution is stimulant, diuretic, diaphoretic and antipyretic. It is used in dropsy of renal origin, and in asthma, angina pectoris and dysmenorrhœa.

AMYL NITRITE (Isoamyl Nitrite) $C_5H_{11}ONO$. 117.— Amyl nitrite is prepared by distilling amyl alcohol with nitrous acid. Thirty parts of the mixture of isomeric amyl alcohols, obtained by fermentation, distilling between 127·7° and 132·2°, are dissolved in 30 parts of concentrated sulphuric acid. To the cold solution are added, with stirring, 26 parts

of potassium nitrite (or 21 parts of sodium nitrite) mixed with 15 parts of water. The mixture is then slowly heated, when amyl nitrite distils over. The distillate is washed, first with sodium carbonate solution, then with sodium bisulphite, finally with water, dried over calcium chloride, and rectified. The U. S. P. requires a content of about 80 % of amyl nitrite.

By another method (*Ber.* (1886), **19,** 915) a concentrated aqueous solution of 35 parts of sodium nitrite is treated with 44 parts of amyl alcohol, and the mixture cooled to 0°. With efficient stirring and cooling 43 vols. of hydrochloric acid (sp. gr. 1·19) are added, the temperature being maintained at 0°. The oil is then separated, washed, dried and distilled, amyl nitrite passing over at 94°–98°. Yield 53 parts.

An alternative method of preparation consists in dissolving 30 parts of amyl alcohol in 30 parts of concentrated sulphuric acid, adding 6 parts of copper turnings, 30 parts of concentrated nitric acid, and 15 parts of water, and distilling the mixture as above.

Amyl nitrite is a pale yellow volatile liquid. The British Pharmacopœia requires that 70 % should distil between the temperatures of 90° and 100°. Many other pharmacopœias (Dutch, Japanese, Russian, German, etc.) state that it boils at 97° to 99°. To meet this requirement it is necessary to start from an amyl alcohol mixture having a closer range of boiling point than that given above.

The specific gravity at 15·5° should be 0·870 to 0·880.

Amyl nitrite is insoluble in water ; soluble in alcohol, chloroform and ether.

A mixture of 1·5 c.c. silver nitrate solution, 1·5 c.c. alcohol (pure), and a few drops of ammonia solution, when gently warmed with 1 c.c. of amyl nitrite, should not turn brown or black.

It must not become turbid when cooled to 0° (absence of water).

Five c.c. should not decolourise a solution containing 1 c.c. N./1 KOH, 10 c.c. of water, and a drop of phenolphthalein, when shaken with it.

Estimation : When 5 c.c. of a 5 % solution of amyl nitrite in alcohol (90 %) is shaken intermittently for 5 minutes, in a nitrometer containing saturated brine solution, with 5 c.c. of a 20 % solution of potassium iodide and 5 c.c. of 10 % sulphuric acid, and the liquid in the two limbs of the nitrometer is adjusted to the same level, not less than 30 c.c. of gas (nitrogen), adjusted to N. T. P. should be yielded (B.P.). The number of c.c. of gas multiplied by 5 gives the weight in milligrams of amyl nitrite present.

Amyl nitrite is an antispasmodic, and a restorative in cardiac failure during chloroform or nitrous oxide anæsthesia. It is much used in angina pectoris, where a rapid fall of arterial tension is required ; in epilepsy, neuralgia, migraine, and seasickness ; also in spasmodic asthma and in hepatic, intestinal and renal colic.

It is administered by inhalation ; and internally, dissolved in alcohol and diffused through water by the aid of tragacanth powder. In cases of Bright's disease, where prolonged administration is required, it is advisable to employ an amyl nitrite that has been prepared from pure amyl alcohol.

NITROGLYCERIN (Trinitrin, Glonoin)

$$CH_2ONO_2 \cdot CHONO_2 \cdot CH_2ONO_2. \quad 227.$$
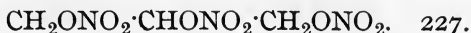
—As the preparation of nitroglycerin on the commercial scale is dealt with in a book on " Explosives " in this series, a brief account only will here be given.

Six parts of a mixture of nitric acid (1·5 sp. gr.) and oleum, and having the approximate composition H_2SO_4 58 % ; HNO_3 41 % ; H_2O 1·0 %, are placed in a lead vessel provided with cooling coils, and are agitated by compressed air. One part of glycerin is introduced, through an aluminium rose, in the form of a fine spray, the rate of addition being so regulated that the temperature is maintained at about 22°. The water in the cooling coils is maintained under a slight vacuum, so that in case of leakage through corrosion none can enter the nitration mixture. A modern type of nitrator is described in E. P. 15893/1911.

When all the glycerin has been added, the mixture is cooled to 15°. The nitroglycerin, which separates as a layer on the surface of the acid, is displaced into a washer by running in, at the bottom of the vessel, waste acid from a previous charge. The nitrator is allowed to remain filled with the waste acid until required again for use. Nitrogen oxides evolved during the operation are carried away to a stoneware condensing tower and absorbed in water. The nitroglycerin is washed, in wide and shallow tanks, thrice with water at 18°, four times with a $3\frac{1}{2}$ % solution of sodium carbonate, and finally twice with water at 30°.

Nitroglycerin is a colourless or pale yellow oil, specific gravity 1·6. It is very slightly soluble in water, dissolves readily in alcohol and is miscible with ether or chloroform. When shaken with water the latter should not acquire an acid reaction. Nitroglycerin explodes with great violence on percussion. It is employed in medicine in the form of a 10 % solution in alcohol.

Nitroglycerin is a vaso-dilator, employed chiefly in angina pectoris associated with aortic diseases. It reduces arterial tension in Bright's disease, and acts as a diuretic and diminishes the albuminuria. Its action is similar to that of amyl nitrite, but is slower and more prolonged. It is employed also in spasmodic asthma and in headache or neuralgia if associated with pallor.

ERYTHROL TETRANITRATE (tetranitrin)

$$CH_2ONO_2$$
$$|$$
$$(CHONO_2)_2 \qquad 302.$$
$$|$$
$$CH_2ONO_2$$
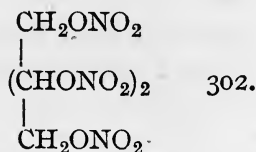
—The preparation of erythrol tetranitrate is based on a method given by Stenhouse (*Ann.* (1849), **70**, 226).

One part of powdered erythrol is added, with good stirring and in small quantities at a time, to strongly cooled nitric acid (sp. gr. 1·5), $4\frac{1}{2}$ parts. The temperature is not allowed to rise above 0°. When all has dissolved, 9 parts

of concentrated sulphuric acid are added, and the mixture allowed to stand, when the tetranitro compound crystallises out. After several hours it is filtered off, on asbestos, washed with ice-cold water until the washings are free from sulphate ions, and recrystallised from hot alcohol.

Erythrol tetranitrate is a colourless crystalline solid. M.p. 61. It is sparingly soluble in water ; readily soluble in alcohol. The solutions should be quite neutral. It is stable if kept in a dark and cool place, but if exposed to warmth and especially sunlight it rapidly decomposes. Care should be exercised in handling this substance as it explodes on percussion.

Tetranitrin is a vaso-dilator ; it is comparable in action to nitroglycerin, having, however, a less marked but more prolonged activity.

MANNITOL HEXANITRATE (hexanitrin)

$$CH_2ONO_2 \cdot (CHONO_2)_4 \cdot CH_2 \cdot ONO_2. \quad 452.$$
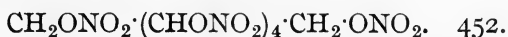
—One part of finely powdered mannitol is gradually treated, with stirring, with 5 parts of nitric acid (sp. gr. 1·5). When all has dissolved, the solution is cooled to 0° and 10 parts of concentrated sulphuric acid are added. After standing for an hour the separated crystals of mannitol hexanitrate are filtered off, and washed, first with cold water, then with warm sodium carbonate solution. They are finally recrystallised from alcohol (Sokolow, *Journ. d. Russ. Chem. Ges.* **11,** 136). According to Strecker (*Ann.* **73,** 62), one part of powdered mannitol is rubbed with just sufficient nitric acid (1·5 sp. gr.) completely to dissolve it. The solution is then treated alternately with nitric and sulphuric acids until $4\frac{1}{2}$ parts of the former and $10\frac{1}{2}$ parts of the latter have been added. A hard mass of crystals is obtained. They are filtered off, washed with cold water, partially dried and crystallised from alcohol.

The nitro-sulphuric acid mixture affords, when diluted with ice, a further quantity of mannitol hexanitrate.

Mannitol hexanitrate crystallises in colourless silky needles. It is almost insoluble in water, is fairly soluble in

alcohol, and readily soluble in ether. It explodes on percussion, and therefore requires to be handled with care. It is employed as a vaso-dilator in a similar manner to erythrol tetranitrate. Its action is said to be more prolonged, but milder than that of erythrol tetranitrate.

Section VIII.—DIURETICS AND URIC ACID SOLVENTS

None of the drugs available for increasing the flow of urine can be regarded as satisfactorily meeting the requirements of medical practice. Theobromine, theophylline and caffeine are the substances in commonest use for this purpose.

Since these are derivatives of uric acid and it is for the elimination of uric acid that such drugs are most frequently required, the objection to them in this connection is obvious.

The hormone secreted by the posterior lobe of the pituitary gland exerts a very marked diuretic action. The chemical nature of the substance so secreted is not yet determined, and when this is achieved it is not improbable that the knowledge so acquired will materially assist the chemist in the search for an ideal diuretic substance.

Of drugs which act as solvents of uric acid piperazine and atophan have given greatest satisfaction ; the former is a solvent *in vitro* for uric acid but does not appear to act satisfactorily in dissolving uric acid gravel and calculi. Atophan increases the amount of uric acid eliminated by the urine in a manner as yet unexplained.

CAFFEINE (1 . 3 . 7 trimethyl-xanthine)

$$
\begin{array}{l}
\overset{(1)}{CH_3 \cdot N} - \overset{(6)}{CO} \\
\quad |_{(2)} \quad |_{(5)} \;_{(7)} \diagup CH_3 \\
\quad CO \quad C - N \diagdown_{(8)} \; +H_2O \quad 212. \\
\quad |_{(3)} \quad \|_{(4)} \;_{(9)} \diagup CH \\
CH_3 \cdot N - C - N
\end{array}
$$
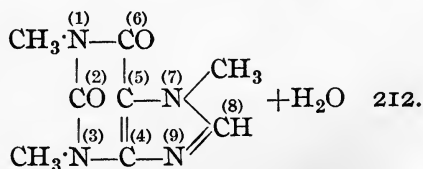
—Caffeine is manufactured from natural sources as well as

synthetically; the former consist of soiled tea or tea-dust and the by-product from the preparation of "caffeine-free" coffee extracts, whilst synthetically it is obtained, as are the closely allied compounds, theobromine and theophylline, from uric acid, by the following reactions, of which numerous modifications have been devised.

(1)

$$
\begin{array}{l}
\text{NH—CO} \\
\text{CO\quad C—NH} \\
\text{NH—C—NH}
\end{array}\!\!\!\!>\!\!\text{CO} \quad \xrightarrow{(CH_3CO)_2O} \quad
\left(
\begin{array}{l}
\text{NH—CO} \\
\text{CO—C—NH·COCH}_3 \\
\text{NH—C—NH·COCH}_3
\end{array}
\right)
$$

Uric acid.   Diacetyl-diamino-uracil.

$$
\rightarrow
\begin{array}{l}
\text{NH—CO} \\
\text{CO\quad C—NH} \\
\text{NH—C——N}
\end{array}\!\!\!\!>\!\!\text{C—CH}_3
\quad \xrightarrow{\text{Methylation}} \quad
\begin{array}{l}
\text{CH}_3\text{—N—CO} \\
\text{CO\quad C—N} \\
\text{CH}_3\text{—N—C—N}
\end{array}\!\!\!\!>\!\!
\begin{array}{l}\text{CH}_3\\ \\ \text{C—CH}_3\end{array}
$$

8-methyl xanthine.   1.3.7.8-tetra-methyl xanthine.

$$
\xrightarrow{SO_2Cl_2}
\begin{array}{l}
\text{CH}_3\text{—N—CO} \\
\text{CO\quad C—N} \\
\text{CH}_3\text{—N—C—N}
\end{array}\!\!\!\!>\!\!
\begin{array}{l}\text{CH}_3\\ \\ \text{C—CCl}_3\end{array}
\quad \xrightarrow{H_2O} \quad
\begin{array}{l}
\text{CH}_3\text{—N—CO} \\
\text{CO\quad C—N} \\
\text{CH}_3\text{—N—C—N}
\end{array}\!\!\!\!>\!\!
\begin{array}{l}\text{CH}_3\\ \\ \text{CH}\end{array}
$$

Trichlor-8-methyl caffeine.   Caffeine.

(2)

$$
\begin{array}{l}
\text{NH—CO} \\
\text{CO\quad C—NH} \\
\text{NH—C—NH}
\end{array}\!\!\!\!>\!\!\text{CO}
\quad \xrightarrow{HCHO} \quad
\begin{array}{l}
\text{NH—CO} \\
\text{CO\quad C——N} \\
\text{NH—C—NH}
\end{array}\!\!\!\!>\!\!
\begin{array}{l}\text{CH}_2\text{OH}\\ \\ \text{CO}\end{array}
$$

Uric acid.   7-hydroxy methylene uric acid.

$$
\xrightarrow[\text{KOH}]{CH_3I}
\begin{array}{l}
\text{CH}_3\text{—N—CO} \\
\text{CO\quad C—N} \\
\text{CH}_3\text{—N—C—NH}
\end{array}\!\!\!\!>\!\!
\begin{array}{l}\text{CH}_2\text{OH}\\ \\ \text{CO}\end{array}
\quad \xrightarrow{Sn + HCl} \quad
\begin{array}{l}
\text{CH}_3\text{—N—CO} \\
\text{CO\quad C——N} \\
\text{CH}_3\text{—N—C—NH}
\end{array}\!\!\!\!>\!\!
\begin{array}{l}\text{CH}_3\\ \\ \text{CO}\end{array}
$$

1.3-dimethyl-7-hydroxy-methylene uric acid.   1.3.7-trimethyl uric acid.

1.3.7-trimethyl uric acid is also obtained by the direct methylation of uric acid. Treated with phosphorus oxychloride it gives 8-chloro-caffeine, from which caffeine is obtained on reduction.

$$
\begin{array}{l}
\text{CH}_3\text{—N—CO} \\
\text{CO\quad C—N} \\
\text{CH}_3\text{—N—C—N}
\end{array}\!\!\!\!>\!\!
\begin{array}{l}\text{CH}_3\\ \\ \text{CCl}\end{array}
\quad \xrightarrow{HI} \quad \text{Caffeine.}
$$
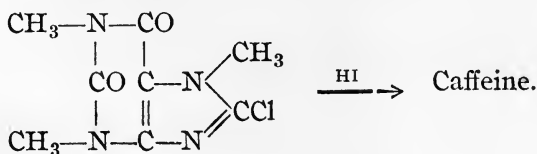
Probably the first method only is employed commercially for making caffeine from uric acid. Amongst other advantages it possesses, diacetyl-diamino-uracil, one of the intermediate compounds, lends itself readily to conversion into the important substance theophyllin (or theocin). The second involves two more operations, and includes two reductions with expensive reducing agents.

Caffeine is also manufactured by Traube's method, by which dimethyl urea (or dimethyl guanidine) and cyanacetic ester constitute the starting out materials. This is more economical than Fischer's earlier process, which started from ethyl malonate and dimethyl urea.

Traube's synthesis :—

1 . 3-dimethyl-4-amino-2 . 6-dioxy pyrimidine.

1 . 3-dimethyl-2 . 6-dioxy
4 . 5-diamino pyrimidine.

Caffeine
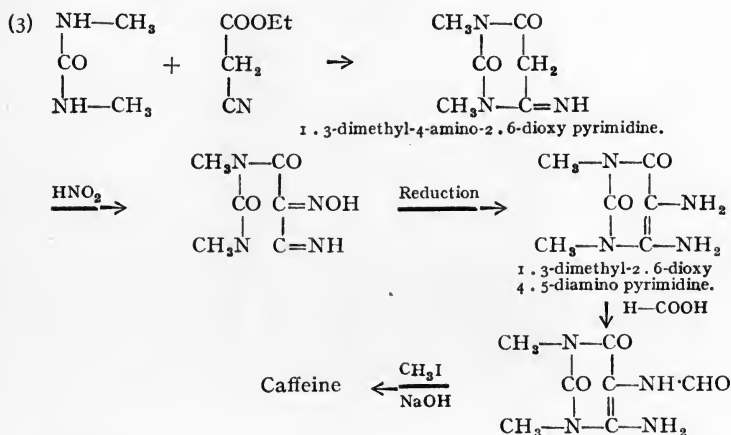
Dimethyl guanidine can be used in place of dimethyl urea, the C=NH group being subsequently converted into C=O by hydrolysis.

Dimethyl urea is prepared by distilling potassium isocyanate with potassium methyl-sulphate and treating the resulting methyl-isocyanate with methylamine, or with water.

$$CH_3N{=}C{=}O + CH_3NH_2 \;\rightarrow\; CO{<}^{NHCH_3}_{NHCH_3}$$

$$2CH_3NCO + H_2O \;\rightarrow\; CO{<}^{NHCH_3}_{NHCH_3} + CO_2$$
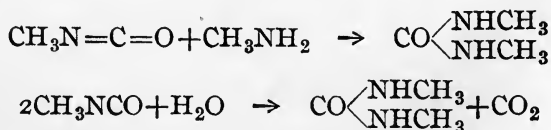
Guanidine is now made from calcium cyanamide *via* dicyano diamide, which is prepared from calcium carbide (D. R. P. 222552), and is methylated by means of dimethyl sulphate (*Arch. Pharm.* (1909), **247**, 466).

Extraction of Caffeine from Tea.—Tea dust is extracted with boiling water. The extract is treated with lead acetate solution so long as a precipitate is formed, and, after filtration and removal of the excess of lead from the filtrate, is evaporated to small bulk. On cooling, the caffeine crystallises out. It is filtered off, and purified by recrystallisation from water, employing charcoal as a decolourising agent. Or the extract may be evaporated to dryness on a film evaporator (Fig. 24) and the dried material extracted with ether from which the caffeine crystallises.

Alternatively, the powdered tea is mixed with one quarter its weight of slaked lime, and exhausted with 80 % alcohol. The extract is freed from alcohol by distillation, the residue is diluted with water, separated from fat, concentrated, and allowed to crystallise.

For recrystallising caffeine, alcohol, benzene, or chloroform may be used in place of water.

Preparation from Uric Acid (D. R. P. 121224) :

8-*methyl-xanthine*

$$
\begin{array}{c}
\text{NH--CO} \\
|\qquad | \\
\text{CO}\quad \text{C--NH} \\
|\qquad \| \qquad\quad \diagdown \text{C--CH}_3 \\
\text{NH--C----N} \diagup
\end{array}
$$
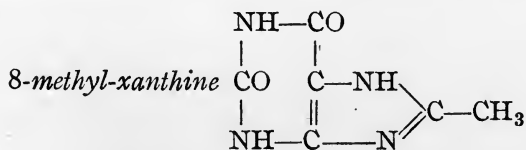
—One part of uric acid is boiled with 10 parts of acetic anhydride for 80 hours, or is heated under pressure at 180°–185° with 5–6 parts of anhydride, or is boiled for 40–45 hours with 10 parts of acetic anhydride and 0·5 part of pyridine at atmospheric pressure. After cooling, the product is filtered off. It is boiled with water, in which any diacetyl diamino-uracil which has not been converted into 8-methyl-xanthine will dissolve. After filtration the insoluble 8-methyl-xanthine is washed with alcohol.
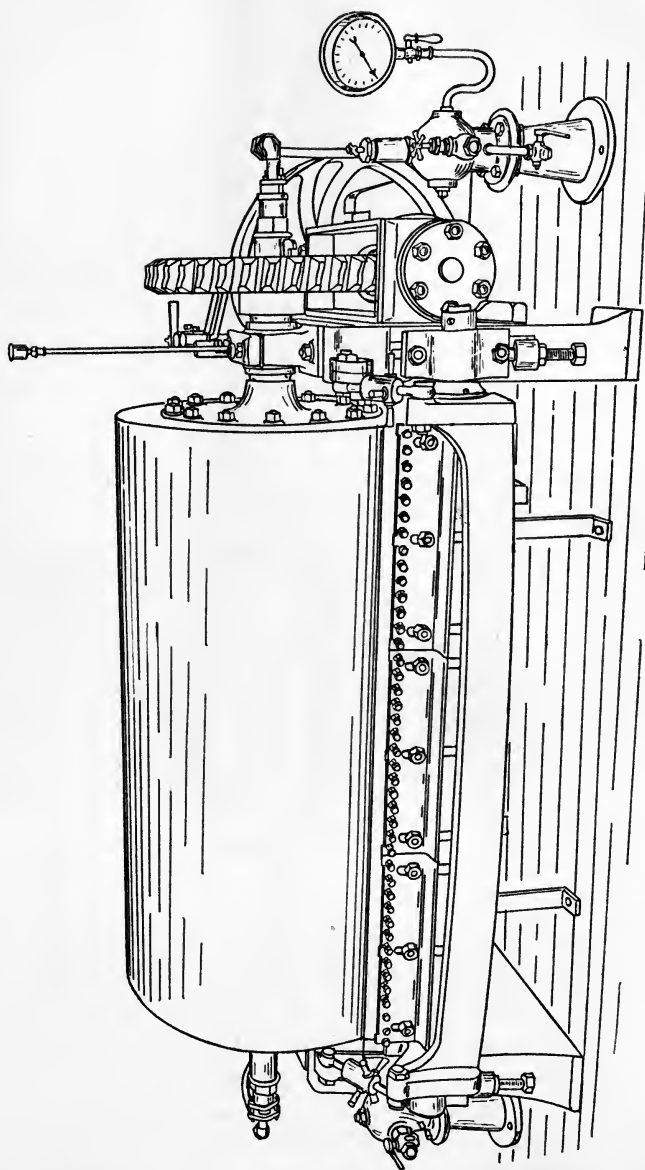
FIG. 24.—Film evaporator for concentration of tea extract.

1 . 3 . 7 . 8-*tetra-methyl-xanthine* (8-methyl-caffeine).

$$CH_3—N—C$$
$$\begin{array}{cc} | & | \end{array} \quad CH_3$$
$$CO \quad C—N{<}$$
$$\begin{array}{cc} | & || \end{array} {>}C—CH_3$$
$$CH_3—N—C—N$$
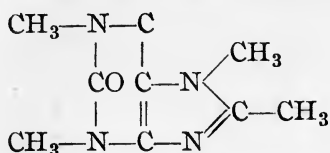
—Ten parts of 8-methyl-xanthine are dissolved in 10·5 vols. of 2N. sodium hydroxide, mixed with 12 parts of methyl chloride and heated in an autoclave for 7 hours at 80°. On cooling, the 8-methyl-caffeine crystallises out in the form of fine needles.

It dissolves in 1·6 parts of boiling water, is easily soluble in hot chloroform, and fairly readily soluble in alcohol, benzene, acetone, and ethyl acetate.

8-trichloromethyl-caffeine

$$CH_3—N—CO$$
$$\begin{array}{cc} | & | \end{array} \quad CH_3$$
$$CO \quad C—N{<}$$
$$\begin{array}{cc} | & || \end{array} {>}C—CCl_3$$
$$CH_3—N—C—N$$
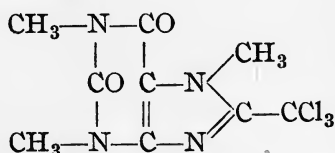
(D. R. P. 146714).—One hundred parts of 8-methyl-caffeine are dissolved in 500 vols. of chloroform and the solution is cooled to 0°. At this temperature are added, with constant stirring, 270 parts of sulphuryl chloride (SO_2Cl_2). When the addition is complete, and hydrogen chloride has ceased to be evolved, the chloroform is distilled off and the product purified by recrystallisation from ethyl acetate.

Alternatively, direct chlorination of the chloroform solution can be effected. 8-trichloro-methyl-caffeine melts at 182°–184°.

Caffeine from 8-trichloro-methyl-caffeine (D. R. P. 151133).—One part of 8-trichloro-methyl-caffeine is boiled under reflux with 10 parts of water until the acidity required by the following equation is developed :—

$$—N{<}\begin{array}{c}CH_3 \\ C—CCl_3\end{array} +2H_2O \; \rightarrow \; —N{<}\begin{array}{c}CH_3 \\ CH\end{array} +3HCl+CO_2$$
$$—N{/} \qquad\qquad\qquad —N{/}$$
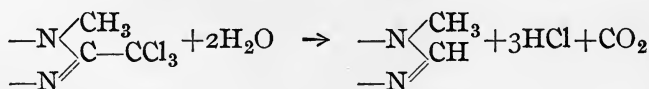
The solution is then evaporated and the caffeine, which

crystallises out after cooling, filtered off, washed, and re-crystallised.

Alternatively, one part of dry 8-trichloro-methyl-caffeine is mixed with one part of anhydrous oxalic acid and the mixture heated for several hours at 150°–180°. After cooling, the reaction product is powdered, dissolved in chloroform, filtered and distilled to dryness. The residue is recrystallised from ethyl acetate.

Preparation from Dimethyl-urea:

Ethyl cyanacetate CN—CH$_2$—COOC$_2$H$_5$ (*Amer. Jour. of Sci.* (1908), **26,** 275).—Two hundred parts of monochloracetic acid are treated with 50 parts of water and 300 parts of sodium carbonate cryst. with stirring. The reaction is endothermic, causing the mass to freeze, and may be hastened by circulating water at atmospheric temperature round the vessel. The solution of sodium chloracetate is then poured as quickly as possible into a solution of 165 parts of potassium cyanide (98 %) in 250 parts of water, which is maintained at a temperature of 100°–110°. After the addition is complete the solution is boiled for 5 minutes to complete the reaction. After cooling, the solution is made faintly acid with sulphuric acid, employing logwood paper as the indicator. The precipitated salts, sodium and potassium sulphates and chlorides, are filtered off, and the filtrate, which contains cyanacetic acid, is concentrated as far as possible under reduced pressure at 70°–80°. The salts are washed with 300 vols. of 96 % alcohol and filtered, when the alcoholic filtrate is mixed with the cyanacetic acid residue. The mixture is well agitated, filtered, and the insoluble matter washed with 100 parts of alcohol. The combined alcoholic solutions are then freed from solvent by distillation under reduced pressure at 50°–60°.

The residue consists chiefly of cyanacetic acid, with some ester and a little alkali cyanacetate. Pure cyanacetic acid may be obtained by extraction with hot chloroform, from which it crystallises well. For the preparation of the ester the crude acid is mixed with 100 vols. of absolute alcohol and 5 vols. of sulphuric acid (1·84). The mass is

esterified by heating the mixture to boiling and passing through it, during $2\frac{1}{2}$–3 hours, the vapour of 500 vols. of absolute alcohol. The ester is then purified by extraction in the usual way, washing, and rectifying *in vacuo.*

The yield is stated to be 92–93 %.

Condensation of Ethyl-cyanacetate and Dimethyl-urea

to

$$CH_3—N—CO$$
$$| \quad |$$
$$CO \quad CH$$
$$| \quad ||$$
$$CH_3—N—C—NH_2$$
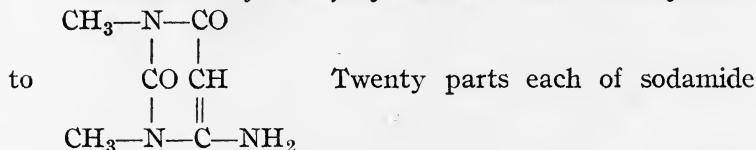
Twenty parts each of sodamide and dry dimethyl-urea are thoroughly mixed, and treated with 20 parts of xylene. With efficient stirring and good cooling are added 20 parts of ethyl-cyanacetate. After the main reaction is over, the mixture is heated for several hours at 100°–120°.

After cooling, the product is carefully treated with water, the xylene removed, and the 1 . 3-dimethyl-2 . 6-dioxy-4-amino-pyrimidine precipitated with acid (D. R. P. 165561). Instead of sodamide, sodium in absolute alcohol may be used (D. R. P. 134984), or sodium in xylene (D. R. P. 165562).

1 . 3-*dimethyl*-2 . 6-*dioxy*-4-*amino*-5-*isonitroso-pyrimidine*

$$CH_3—N—C=O$$
$$| \quad |$$
$$CO \quad C—NOH$$
$$| \quad ||$$
$$CH_3—N—C—NH_2$$
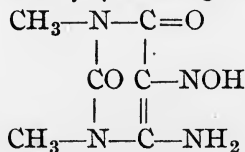
The above compound is dissolved in hot water containing the theoretically necessary quantity (1 mol.) of sodium nitrite. Dilute acetic acid is then added, when the solution becomes red-coloured and the isonitroso derivative commences to crystallise out. After standing for about 24 hours crystallisation is complete and the liquor is almost colourless (*Ber.* (1900), 3052).

Reduction to 1 . 3-dimethyl-2 . 6-dioxy-4 . 5-dia-

mino-pyrimidine

$$CH_3—N—C=O$$
$$| \quad |$$
$$CO \quad C—NH_2$$
$$| \quad ||$$
$$CH_3—N—C—NH_2$$

According to Traube's
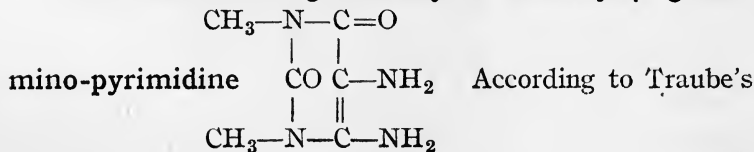
original method, this was carried out by boiling with ammonium sulphide solution. It is stated by D. R. P. 161493 to be better effected by the following procedure.

Five parts of the isonitroso compound are rubbed up with 50 to 100 parts of 20 % sulphuric acid, and the mixture gradually treated with 5 parts of zinc dust. The temperature is maintained, by cooling, at between 20° and 30°. The red colour of the isonitroso body gradually disappears, whilst white crystals of the sulphate separate. Water is added after the reduction is finished, the mixture is filtered and the zinc residue washed thoroughly with hot water. The combined filtrates are freed from zinc, by treatment with sodium carbonate, and evaporated to dryness. The base is extracted from the residue with chloroform or some other suitable solvent. M.p. 209°. It is stated that this reduction can also be effected with iron, and according to D. R. P. 166267 it is carried out electrolytically.

1 . 3-*dimethyl*-2 . 6-*dioxy*-4-*amino*-5-*formylamino pyri-*

$$\text{—C—NH—CHO}$$
midine   ‖   The formyl compound of the base
$$\text{—C—NH}_2$$

thus obtained is prepared by digesting the diamine with several times its weight of 90 per cent. formic acid at its boiling point. The resulting substance melts at 252°. If necessary it is purified by recrystallisation from water. It is dried before further treatment.

$$
\begin{array}{l}
\text{CH}_3\text{N—CO} \\
\quad | \qquad | \\
\text{Conversion of} \quad \text{CO} \quad \text{C—NH—CHO} \quad \text{into caffeine—} \\
\quad | \qquad ‖ \\
\text{CH}_3\text{N—C—NH}_2
\end{array}
$$
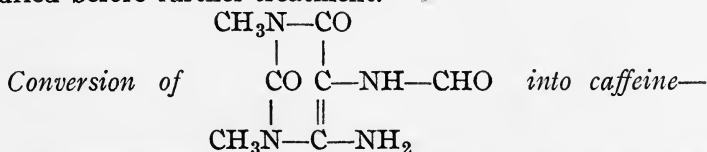
The completely dry formyl compound is dissolved in absolute alcohol containing one molecular equivalent of sodium ethylate, the quantity of alcohol employed being such that the resulting sodium salt remains dissolved in the hot solution ; a slight excess of methyl iodide is added and the mixture refluxed for several hours. On then concentrating the solution caffeine separates in long silky needles.

By another series of reactions urea is condensed with cyanacetic ester to 2.6-dioxy-4-aminopyrimidine (E. P. 22126/1904), which is converted first into the isonitroso, then into the diamido compound. This, on methylation, (D. R. P. 148208) yields 1.3-dimethyl-2.6-dioxy-4-amino-5-formylamino pyrimidine (see above).

Caffeine crystallises with one molecule of water in fine, colourless, silky acicular crystals, which possess a bitter taste.

It dissolves in one part of boiling, and in 68 parts of cold, water; in 7 of chloroform and in 40 of alcohol (90 %). In ether it is only sparingly soluble (1 in 400).

Caffeine loses its water of crystallisation at 100° and then melts at 132°–133°. It dissolves without colour in sulphuric and nitric acids. The aqueous solution should be neutral to litmus and should give no precipitate with mercuric potassium iodide solution. The cold saturated aqueous solution should not become turbid with chlorine water, nor become coloured on the addition of ammonia solution.

Caffeine acts on the kidneys (increasing the flow of urine), and on the muscles and heart; also on the central nervous system. The stimulant action of tea and coffee is due to it. It is employed in medicine as a heart tonic and diuretic. It is frequently given in the form of *caffeine citrate*, a mixture with citric acid which is soluble in 32 parts of water, or in combination with sodium salicylate or sodium benzoate, both of which increase its solubility in water.

Theophylline or **Theocine.** (1.3-di-methyl-xanthine).

$$
\begin{array}{l}
CH_3N\!-\!CO \\
\quad |\quad\; | \\
\quad CO\;\; C\!-\!NH \\
\quad |\quad\; \| \qquad\qquad CH + H_2O \quad 198. \\
CH_3N\!-\!C\!-\!-\!N
\end{array}
$$
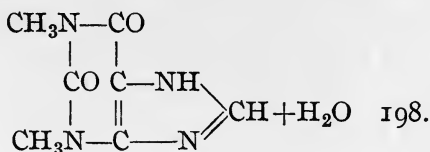
Theophylline occurs naturally in small amounts in the tea plant, *Camellia Thea*, in association with caffeine. That used in medicine, however, is exclusively prepared synthetically, from uric acid, urea, guanidine, or their methylated derivatives.

(1) **From uric acid :** 1 . 3 . 7 . 8-tetra-methyl-xanthine (*see* Caffeine), on exhaustive chlorination, gives a tetrachlor-tetramethyl-xanthine, which affords theophylline on hydrolysis :—

(2) **From diacetyl-diamino-uracil,** by the following steps :—

(3) **From dimethyl urea and cyanacetic ester.**—The procedure is the same as in the case of caffeine, except that the methylating agent is omitted in the final stage ; the conversion of 1.3 - dimethyl - 4 - amino - 5 - formylamido - 2.6 - dioxy-pyrimidine into theophylline being effected with potash.

The same compound is obtained as stated under Caffeine, p. 239, by condensing urea with cyanacetic ester and methylating the 4-amino-5-formylamido-2 . 6-dioxy pyrimidine.

Method I.

Chlorination of 1 . 3 . 7 . 8-*tetramethyl-xanthine to* 1 : 3-*dimethyl-7-dichloromethyl-8-trichloromethyl-xanthine*

$$\begin{array}{c} CH_3—N—CO \\ |\ \ \ | \qquad CH_2Cl \\ CO\ \ C—N \\ |\ \ \ || \qquad C—CCl_3 \\ CH_3—N—C—N \end{array}$$
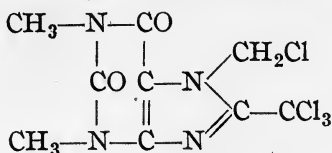
Two methods of procedure are given in D. R. P. 146715.

(*a*) One part of tetramethyl-xanthine (8-methyl-caffeine) is dissolved in 8 parts of nitrobenzene, heated at 90°–100°, and chlorinated until no more chlorine is absorbed. Chlorine in solution is removed by a current of air, and the nitrobenzene is distilled off *in vacuo*, the product being recrystallised from hot alcohol. It melts at 204°–205°.

(*b*) Ten parts of 8-methyl-caffeine are suspended in 50 parts of nitrobenzene containing a trace of iodine, and 36 parts of sulphuryl chloride are gradually added, with stirring. After a short time the suspended solid dissolves, heat being evolved. The solution is allowed to remain at room temperature for several hours, after which it is heated for two hours at 100°. The nitrobenzene is removed by steam-distillation. After cooling, the solid product is filtered off and purified by recrystallisation from alcohol.

Conversion of tetrachloro-8-methyl-xanthine into Theophylline (D. R. P. 151133).—One part of the tetrachloro compound is boiled under a reflux condenser with 10 parts of water until no more formaldehyde is evolved, and until the acidity of the solution has increased in accordance with the equation—

$$-N\begin{subarray}{l} CH_2Cl \\ C—CCl_3 \end{subarray} +3H_2O \ \rightarrow\ \begin{subarray}{l} -NH \\ -N \end{subarray}CH+CO_2+HCHO+4HCl$$
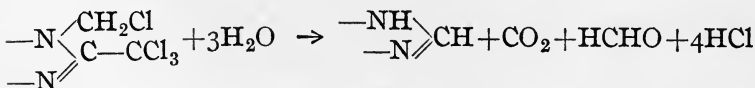
The acidity is neutralised with alkali, and, on cooling, theophylline crystallises out. The yield is stated to be quantitative.

I.   16

Method II.

4 . 5-*diacetyl-diamino-uracil*

$$\begin{array}{c} NH-CO \\ |\quad\quad| \\ CO\quad C-NH-COCH_3 \\ |\quad\quad|| \\ NH-C-NH-COCH_3 \end{array}$$

(D. R. P. 126797).—Ten parts of uric acid are boiled for
15 hours with 30 parts of acetic anhydride and 5 parts of
pyridine. The solid reaction-product is filtered off and
boiled with 30 parts of water. The diacetyl-diamino-uracil
passes into solution; 8-methyl-xanthine remains undissolved,
and is filtered off. The filtrate is concentrated, and on
cooling, the desired product crystallises out in colourless
needles.

4 . 5-*diamino-2 . 6-dioxy-pyrimidine*

$$\begin{array}{c} NH-CO \\ |\quad\quad| \\ CO\quad C-NH_2 \\ |\quad\quad|| \\ NH-C-NH_2 \end{array}$$
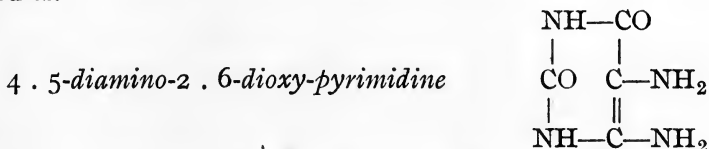
Fifteen parts of diacetyl-diamino-uracil are boiled gently for
15 minutes with 100 volumes of 50 % caustic alkali solution.
After cooling, the clear solution is diluted with 300 vols. of
water and treated with an excess of sulphuric acid, when the
sparingly soluble sulphate of 4 . 5-diamino-2 . 6-dioxy-pyrimi-
dine is precipitated.

4-*amino*-5-*formylamido*-2 . 6-*dioxy-pyrimidine*

$$\begin{array}{c} NH-CO \\ |\quad\quad| \\ CO\quad C-NH-CHO \\ |\quad\quad|| \\ NH-C-NH_2 \end{array}$$
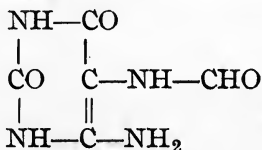
The sulphate, after being dried, is mixed with one mole-
cular equivalent of sodium formate and boiled with 10–15
parts by weight of 90 per cent. formic acid. Solution first
occurs, followed by the gradual formation of a precipitate.
After cooling and dilution with water the product is filtered
off, and purified by recrystallisation from water, or by dis-
solving in dilute alkali and reprecipitating with acid.

1 . 3 - *dimethyl* - 4 - *amino* - 5 - *formylamido* - 2 . 6 - *dioxy* -

$$
\begin{array}{c}
CH_3-N-C \\
| \quad | \\
CO \quad C-NH-CHO \\
| \quad \| \\
CH_3-N-C-NH_2
\end{array}
$$

pyrimidine   CO C—NH—CHO.—Eighty-five parts of the
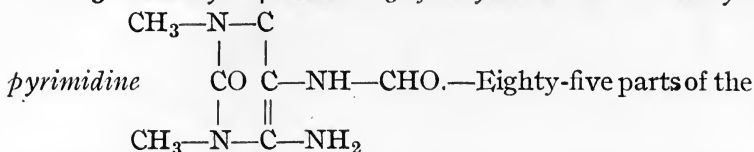
monoformyl compound are dissolved in 1050 parts of normal caustic soda and 300 parts of water, and treated, at 30°–40°, with efficient agitation, with 160 parts of methyl iodide. When this has for the most part disappeared, the reaction mixture is acidified with acetic acid and evaporated to small bulk. The dimethylated body, which crystallises out on cooling, is purified by recrystallisation from water (D. R. P. 148208).

$$
\begin{array}{c}
CH_3N-CO \\
| \quad | \\
CO \quad C-NH-CHO \\
| \quad \| \\
CH_3-N-C-NH_2
\end{array}
$$

Conversion of   CO C—NH—CHO   *into Theophylline*
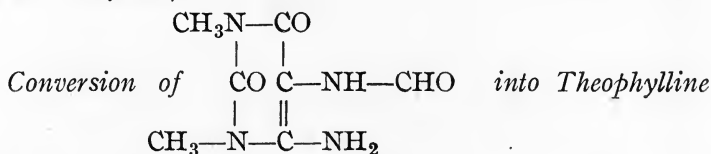
(D. R. P. 138444).—Ten parts of the dimethylated mono-formyl compound are warmed at 90°–100° with a mixture of 10 parts of 30 % caustic soda and 100 parts of water. After cooling, the solution is saturated with salt, or with caustic soda, when the sodium salt of theophylline crystallises out. After filtration the base is obtained from it by neutralisation with acid, and is purified by recrystallisation from water.

Alternatively, a solution of 3 % alcoholic potash (100 parts) or of potassium (2·1 parts) in alcohol (100 parts) may be employed. In these cases the potassium salt of theophylline crystallises out on cooling.

Method III.

From Urea and Cyanacetic Ester.—Preparation of 4-amino-2 . 6-dioxy-pyrimidine

$$
\begin{array}{c}
NH-CO \\
| \quad | \\
CO-CH \\
| \quad \| \\
NH-C-NH_2
\end{array}
$$
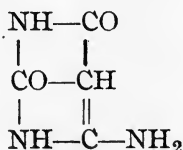
Cyanacetic ester, 113 parts, is dissolved in 2260 parts of absolute alcohol containing 46 parts of sodium. Urea, 58 parts, is then added and the mixture boiled under reflux for several hours. The solution is then neutralised, the alcohol distilled off and the residue dissolved in water. The base is precipitated by addition of acetic acid and is filtered off. Sodium or sodamide in xylene may be used instead of sodium in alcohol.

The conversion of this compound successively into the iso-nitroso
$$\begin{array}{c} -C-NOH \\ \| \\ -C-NH_2 \end{array}$$
, diamino
$$\begin{array}{c} -C-NH_2 \\ \| \\ -C-NH_2 \end{array}$$
, and formyldiamino
$$\begin{array}{c} -C-NH-CHO \\ \| \\ -C-NH_2 \end{array}$$
compounds is performed in the manner described under caffeine for the 1.3-dimethyl derivative (p. 237). The methylation of the last-named body and the conversion of the dimethyl compound into theophylline have been described above.
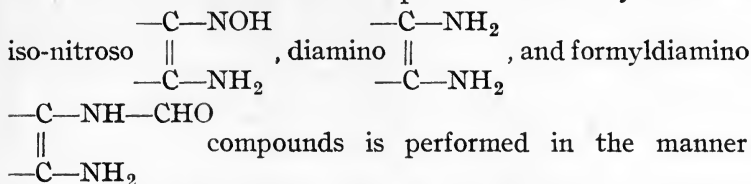
Theophylline forms colourless crystalline needles containing one molecule of water, which is lost at 110°. The anhydrous substance melts at 268°. It is soluble in 190 parts of cold water, and in 80 parts of 90 % alcohol. It dissolves readily in ammonia and alkalis.

Theophylline is used as a diuretic, mostly in the form of a double compound of its sodium salt with sodium acetate. It is indicated in all forms of dropsy in which the functions of the kidneys are not too seriously impaired by the disease. Theophylline is a less powerful stimulant than caffeine, but is more active as a diuretic than either caffeine or theobromine.

THEOBROMINE (3.7-dimethyl-xanthine)

$$\begin{array}{c} NH-C=O \\ | \quad\quad | \quad\quad\quad CH_3 \\ CO \quad C-N< \\ | \quad\quad \| \quad\quad CH \\ CH_3N-C-N \end{array}$$ 180.
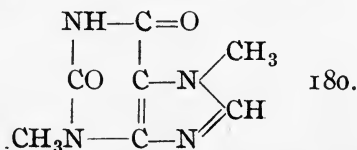
—Theobromine is contained in the seeds, both in the shells and the endocarp, of the cocoa plant, *Theobroma Cacao*, from

which it is extracted commercially. It is probable that the entire present demand is, or could be, economically met from this natural source.

Extraction from Cocoa Beans.—This is effected in essentially the same way as has been described for caffeine. Cocoa beans, which contain from 1 to 2 per cent. of the alkaloid, are pressed as free as possible from fat, ground to a fine powder, mixed with one-half their weight of sifted slaked lime, and exhausted with 80 % alcohol. The extract is acidified with hydrochloric acid and the alcohol removed by distillation. The residue is diluted with water, freed from fat, concentrated to small bulk, and made alkaline with ammonia, whereby the theobromine is precipitated. It is filtered off and purified by recrystallisation from boiling water, or from 80 % alcohol.

Theobromine can be synthesised, however, by modifications of the methods that have been described under *Caffeine* and *Theophylline*. The starting point may be either uric acid, urea or monomethylated urea, or guanidine.

A few examples are given :—

From Uric Acid—

From Methyl, or Methylacetyl, Urea (Traube).

(3)
$$
\begin{array}{ccc}
\text{HN—COCH}_3 & \text{COOEt} & \text{HN—CO} \\
| & | & | \quad | \\
\text{CO} \;\;+\;\; \text{CH}_2 & \rightarrow & \text{CO CH} \\
| & | & | \quad \| \\
\text{CH}_3\text{NH} & \text{CN} & \text{CH}_3\text{N—C—NH}_2
\end{array}
$$

Methyl-acetyl urea.   3-methyl-4-amino
                                   pyrimidine.

$$
\begin{array}{ccc}
\text{HN—CO} & \text{HN—CO} & \text{HN—CO} \\
| \quad | & | \quad | & | \quad | \\
\rightarrow \;\; \text{CO C—NOH} \;\; \rightarrow & \text{CO C—NH}_2 \;\; \rightarrow & \text{CO C—NH—CHO} \\
| \quad \| & | \quad \| & | \quad \| \\
\text{CH}_3\text{N—C—NH}_2 & \text{CH}_3\text{N—C—NH}_2 & \text{CH}_3\text{N—C—NH}_2
\end{array}
$$

                    3-methyl 4.5-diamino
                    pyrimidine.

Theobromine. ←——Methylation.——

$$
\begin{array}{c}
\text{HN—CO} \\
| \quad | \\
\text{CO C—NH} \\
| \quad \| \qquad \diagdown\!\!\!\diagup\text{CH} \\
\text{CH}_3\text{N—C——N}
\end{array}
$$

                    3-methyl-xanthine.
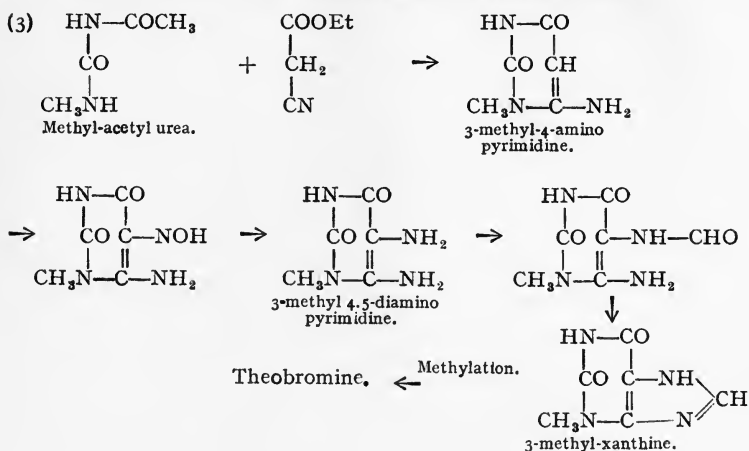
Of these the only one that will be given in detail is that *via* hydroxymethylene uric acid, of which an example has not previously been furnished. It is not intended to imply, however, that this would be the most economical method of synthetically preparing theobromine.

Preparation from Uric Acid

7-hydroxymethylene uric acid

$$
\begin{array}{c}
\text{NH—CO} \\
| \quad\quad | \\
\text{CO C——N}\diagup^{\text{CH}_2\text{OH}} \;\; +\text{H}_2\text{O} \;\; \text{(E. P. 20447/1898).} \\
| \quad\; \| \qquad\diagdown_{\text{CO}} \\
\text{NH—C—NH}
\end{array}
$$
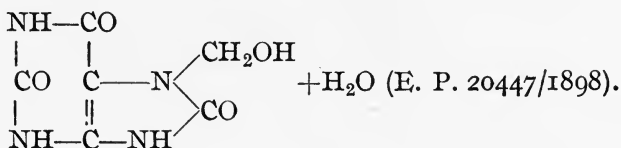
—One part of uric acid is dissolved, by the aid of gentle warmth, in 15 parts of water and 1 part ($2\frac{1}{2}$ mols.) of 80 % caustic potash. The solution is cooled, mixed with 1·6 parts of 40 % formaldehyde, and allowed to stand for about 24 hours. It is then acidified with hydrochloric acid, agitated with charcoal and quickly filtered. On standing, oxymethylene uric acid crystallises out. It is filtered off, washed with alcohol and dried.

3-methyl-7-oxymethylene-uric acid

$$
\begin{array}{c}
\text{NH---CO} \\
\quad | \quad\quad | \\
\text{CO} \quad \text{C----N}\diagup^{\text{CH}_2\text{OH}}_{\diagdown\text{CO}} \\
\quad | \quad\quad \| \\
\text{CH}_3\text{---N---C---NH}
\end{array}
$$
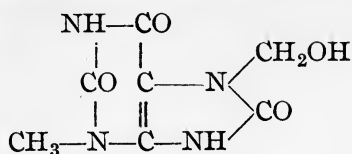
(E. P. 3300/1899).

Fifteen parts of 7-oxymethylene uric acid are dissolved in 50 parts of twice normal potassium hydroxide solution ($1\frac{1}{4}$ mols.) and 50 parts of water. Methyl iodide, 13 parts by volume, is added and the mixture heated in an autoclave for 2 hours at 80°–90°, with stirring. On cooling, some 3-methyl-uric acid crystallises out. This is separated and converted into 3-methyl-7-oxymethylene uric acid by treatment with formaldehyde. The filtrate is evaporated *in vacuo*, and on neutralisation 3-methyl-7-oxymethylene uric acid separates, and is collected.

It is stated that the same product is obtained when 1 part of potassium urate, 5·5 parts of 40 % formaldehyde, 7·5 parts (by vol.) of methyl iodide, and 7·8 parts of water are heated together in an autoclave at 90° for 2 hours.

3 . *7-dimethyl-uric acid*

$$
\begin{array}{c}
\text{NH---CO} \\
\quad | \quad\quad | \\
\text{CO} \quad \text{C----N}\diagup^{\text{CH}_3}_{\diagdown\text{CO}} \\
\quad | \quad\quad \| \\
\text{CH}_3\text{N---C---NH}
\end{array}
$$
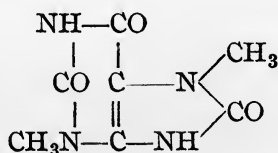
(E. P. 1678/1899).

One part of 3-methyl-7-oxymethylene uric acid is dissolved in 8 parts of concentrated hydrochloric acid, cooled to, and maintained at, 0°, treated with 5 to 6 parts of granulated tin, and stirred. When the evolution of hydrogen has become sluggish, after about 20 hours, the reaction is accelerated by the introduction of gaseous hydrogen chloride. After about 40 hours any undissolved tin is separated and the liquid is diluted with water, when 3.7-dimethyl uric acid

is precipitated. It is filtered off and purified by solution in ammonia, treatment with charcoal, and reprecipitation.

3 . 7-*dimethyl-chloroxanthine* (*chlorotheobromine*)

$$\begin{array}{c}
NH{-}CO \\
|\quad\ | \qquad CH_3 \\
CO\ \ C{-}N{<} \\
|\quad\ \| \qquad CCl \\
CH_3N{-}C{-}N{/}
\end{array}$$
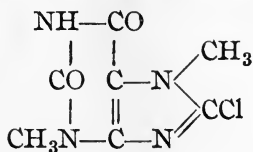
(*see* E. P. 5949/1898).

One part of anhydrous 3.7-dimethyl uric acid is added to 5 parts of phosphorus oxychloride, and the mixture heated, with stirring, at 130°–140° for 3–4 hours. The excess of $POCl_3$ is then distilled off, and the residue dissolved in 5 parts of alcohol, boiled for 2–3 hours and allowed to cool. Chlorotheobromine crystallises out on cooling, a further portion being obtained by evaporation of the solvent from the filtrate. It is purified by solution in dilute alkali, and reprecipitation after decolourisation with charcoal.

Theobromine from chlorotheobromine (E. P. 5949/1898).—One part of chlorotheobromine is heated with $\frac{1}{2}$ part of phosphonium iodide and 8 parts of hydriodic acid (sp. gr. 1·96). After 15–20 minutes a clear solution is obtained. This is distilled to dryness, the residue treated with water, and the solution neutralised. The theobromine is filtered off and recrystallised from boiling water.

Theobromine is a white crystalline powder, which sublimes without melting at 290°. It is soluble in 1700 parts of cold water, or in 5000 parts of alcohol (90 %). It dissolves in both acids and alkali.

Its physiological action resembles that of caffeine, but it is without action on the central nervous system.

Theobromine is employed medicinally as a diuretic and cardiac stimulant, and is usually administered in the form of the soluble double compound of its sodium salt with sodium salicylate (*diuretin*). Another soluble derivative is *urocitral* (theobromine sodium citrate).

PIPERAZINE—Diethylene-diamine $NH{<}\genfrac{}{}{0pt}{}{CH_2{-}CH_2}{CH_2{-}CH_2}{>}NH$
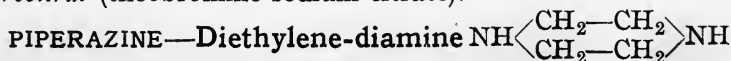
86.—Piperazine is manufactured according to the following reactions. Diphenyl-piperazine is first prepared by treating ethylene dibromide with aniline in the presence of an alkali :

$$2C_2H_4Br_2 + 2C_6H_5NH_2 + 2Na_2CO_3$$

$$\rightarrow \quad C_6H_5N\langle{}^{CH_2-CH_2}_{CH_2-CH_2}\rangle NC_6H_5 + 4NaBr + 2CO_2 + 2H_2O$$
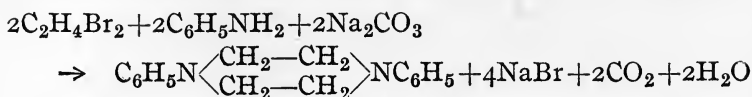
This is converted into its dinitroso compound or into a dinitro-disulphonic acid,

$$C_6H_5N\langle{}^{CH_2-CH_2}_{CH_2-CH_2}\rangle NC_6H_5 + 2HNO_2$$

$$\rightarrow \quad NO-C_6H_4N\langle{}^{CH_2-CH_2}_{CH_2-CH_2}\rangle N \cdot C_6H_4-NO + 2H_2O$$

$$\text{or } C_6H_5N\langle{}^{CH_2-CH_2}_{CH_2-CH_2}\rangle NC_6H_5$$

$$\rightarrow SO_3HC_6H_4N(CH_2)_4NC_6H_4SO_3H$$

$$\rightarrow \quad \{{}^{NO_2}_{SO_3H}\rangle C_6H_3N\langle{}^{CH_2}_{CH_2}\}_2$$
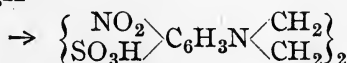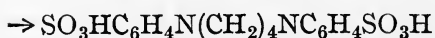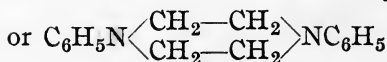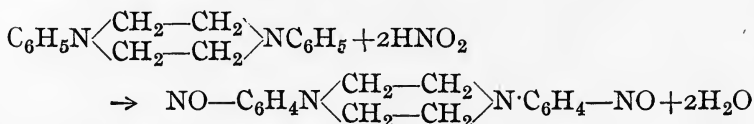
both of which, on distillation with alkali, afford piperazine.

Diphenyl-piperazine (Bischoff, *Ber*. **22**, 1778).—A mixture of 188 parts of ethylene dibromide, 93 parts of aniline and 106 parts of powdered anhydrous sodium carbonate is heated together with stirring at 150° for several hours. The reaction mixture is extracted with hot water, to dissolve out sodium bromide, steam is blown through to remove unchanged materials, and the diphenyl-piperazine is filtered off, and washed. Yield 90 %.

Dinitroso-diphenyl-piperazine—Diphenyl-piperazine, 238 parts, is warmed with thrice its weight of 22 per cent. hydrochloric acid, or an equivalent quantity, and the mixture is then maintained at 4°–5°, with continual stirring, whilst an aqueous solution containing the equivalent of 138 parts of 100 % sodium nitrite is slowly added. After the addition is completed the reaction mixture is allowed to stand in the cold for several hours, when the hydrochloride of the dinitroso-diphenyl-piperazine is filtered off.

Piperazine.—According to the method given in D. R. P. 60547, one part by weight of the dinitroso-diphenyl-piperazine

(hydrochloride) is distilled with 3 parts of a 25 % solution of caustic soda until the distillate no longer affords a precipitate with picric acid. Steam is blown through towards the end of the distillation, if necessary. The distillate is neutralised with hydrochloric acid, concentrated to small bulk and allowed to crystallise, when piperazine dihydrochloride $\{(CH_2)_2NH\}_2 2HCl + H_2O$ is obtained, and separated. The base is formed by treating the hydrochloride with a concentrated solution of caustic soda, and on saturating with solid caustic soda it separates as an oil. This is carefully removed and mixed with the correct quantity of water for the formation of the hexa-hydrate, and on stirring and cooling crystallisation ensues ; the crystals are filtered off and dried, under diminished pressure, over lime or caustic soda.

According to D. R. P. 83524, dinitroso-diphenyl-piperazine can be split up by boiling with strong mineral acids, or with acetic acid.

By another method, D. R. P. 59222, sulphur dioxide is employed, the resulting addition product being resolved, by heating with hydrochloric acid, into aminophenol disulphonic acid and piperazine hydrochloride, thus :

$$NQC_6H_4N(CH_2)_4NC_6H_4NO + 4H_2SO_3$$
$$\rightarrow \ 2C_6H_2 \begin{cases} OH \\ NH_2 \\ (SO_3H)_2 \end{cases} + HN(CH_2)_4NH$$
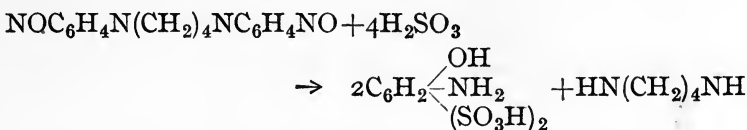
Ten kilos of dinitroso-diphenyl-piperazine are suspended in 300 litres of water and a rapid current of sulphur dioxide passed in until all is dissolved. Twenty-two kilos of hydrochloric acid of 23° Bé. are then added and the solution concentrated to one half its volume. On cooling, part of the amino-phenol-disulphonic acid crystallises out in the form of needles, the remainder, together with piperazine hydrochloride, remaining in solution. After filtration, the liquid portion is made alkaline with 70 kilos of 33 per cent. caustic soda, and treated with superheated steam until the distillate ceases to contain piperazine. The distillate is treated as before for the isolation of the base.

Instead of dinitroso-diphenyl-piperazine, dinitro-diphenyl-piperazine-disulphonic acid can be employed for generating piperazine (D. R. P. 63618). Ten kilos of diphenyl-piperazine are dissolved in a mixture of 10 kilos of concentrated sulphuric acid and 10 kilos of fuming sulphuric acid and heated at 150° until a test portion is completely soluble in alkali. The mixture is then cooled to 0° and nitrated with a mixture of 6 kilos of 88 % nitric acid and 6 kilos of sulphuric acid (66° Bé.). After nitration is complete the mixture is run on to 600 kilos of water and ice, and the solution neutralised with calcium carbonate. The filtrate, after removal of calcium sulphate, is boiled with 6 kilos of sodium carbonate cryst. and, after filtering off the calcium carbonate, evaporated to dryness. The residue is added to a concentrated solution containing 10 kilos of sodium hydrate, and the piperazine distilled over.

Yet another alternative method of preparation starts with an aryl-sulphon-chloride or sulphonamide and ethylene-diamine or ethylene-dibromide respectively (D. R. P. 70055).

$$2C_2H_4Br_2 + 2RSO_2NH_2 + 2NaOH$$
$$\rightarrow (RSO_2N)(CH_2)_4(NSO_2R) \rightarrow (CH_2)_4(NH)_2 + 2RH, \text{ etc.}$$

$$(CH_2NH_2)_2 + 2RSO_2Cl$$

$$\rightarrow \quad \begin{array}{l} CH_2\text{—}NH{\cdot}SO_2R \\ | \\ CH_2\text{—}NH.SO_2R \end{array} \quad (+C_2H_4Br_2 + 2NaOH)$$

$$\rightarrow \quad \begin{array}{c} SO_2R \\ | \\ CH_2\text{—}N\text{—}CH_2 \\ | \qquad\quad | \\ CH_2\text{—}N\text{—}CH_2 \\ | \\ SO_2R \end{array} \quad \rightarrow (CH_2)_4(NH)_2 + 2RH, \text{ etc.}$$
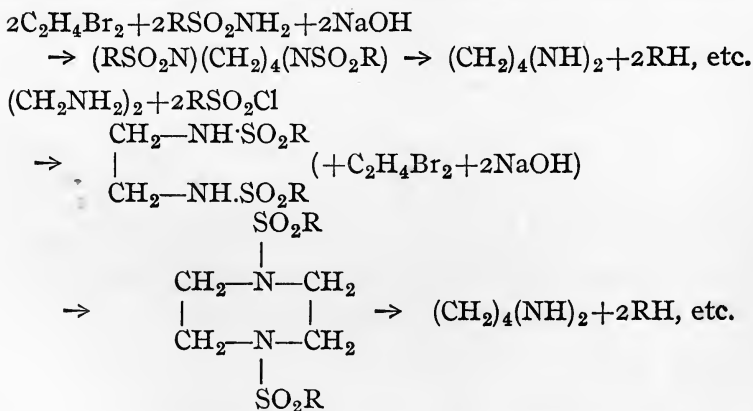
Dibenzene-disulphon-ethylene-diamide.—A solution of six kilos of ethylene-diamine in 25 litres of water is treated alternately in small portions at a time, with 35·7 kilos of benzene-sulphon-chloride and 8 kilos of sodium hydrate in 25 litres of water, shaking or stirring being continuous. Dibenzene-disulphon-ethylene-diamide is obtained.

Dibenzene-disulphon-piperazide.—Benzene sulphonamide (33·2 kilos) and ethylene dibromide (37·6 kilos) are dissolved in 250 kilos of 96 % alcohol, boiled and treated gradually with 40 kilos of 20 per cent. caustic soda.   Heating is continued until the solution is neutral, when a further 37·6 kilos of ethylene dibromide (or the corresponding quantity of ethylene dichloride) and 40 kilos of 20 per cent. caustic soda are added and the mixture again boiled until neutral.   After cooling, the dibenzene-disulphon-piperazide is filtered off, and washed with (1) alcohol, (2) water, (3) dil. caustic soda, (4) water.

The same compound is obtained by treating the dibenzene-disulphon-ethylene-diamide obtained in the first example with ethylene-dihalide and caustic soda in alcoholic solution.

Hydrolysis of Dibenzene-disulphon-piperazide.—This may be effected either by hydrochloric or sulphuric acid (D. R. P. ₇0056) or with chlorsulphonic acid (D. R. P. 100232).

Ten kilos of dibenzene-disulphon-piperazide are mixed with 50 kilos of water and 50 kilos of 10–20 % hydrochloric acid and heated in an autoclave at 200°–250° for six hours. After cooling, the benzene is separated and, on evaporation, piperazine acid sulphate is obtained.

Or, one molecular equivalent of the piperazide is heated with two equivalents of chlorsulphonic acid at 130°. The resulting mass is powdered, after cooling, and introduced into water.   Benzene sulphonchloride separates as an oil, and is removed, whilst the aqueous solution is distilled with alkali, when piperazine is obtained.

$$C_6H_5SO_2N(CH_2)_4NSO_2C_6H_5 + 2SO_3HCl$$
$$\rightarrow \quad 2C_6H_5SO_2Cl + (SO_3HN)_2(CH_2)_4$$
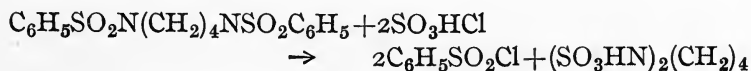
Piperazine crystallises with 6 molecules of water in colourless crystals which melt at 44°. It absorbs carbon dioxide with avidity. When anhydrous, piperazine fuses at 104° and distils at 145°.

It is extremely soluble in water, the solution having a strongly alkaline reaction.   It should give no reaction for

ammonium salts, chlorides or sulphates, and should sublime without leaving a residue.

Piperazine is used to prevent the formation of renal and vesical calculi, and for the relief of irritation of the bladder due to excess of uric acid in the urine, in cases of chronic gout, rheumatism, etc.

The urine of patients to whom piperazine has been administered has been found to contain more uric acid than if untreated ; this effect being more marked if sodium citrate or sodium bicarbonate has also been given.

ATOPHAN (2-phenyl-quinoline-4-carboxylic acid)

$$\text{COOH}$$

249.
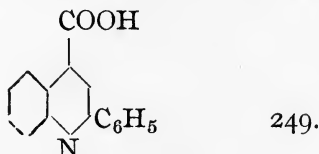
—Atophan was first made by Doebner and Giesecke, in 1887 (*Ann.* **242**, 290), by the following reaction :

$$\underset{93}{C_6H_5NH_2} + \underset{88}{\overset{\overset{\displaystyle CH_3}{|}}{CO—COOH}} + \underset{106}{CHOC_6H_5}$$

$$\rightarrow \quad C_6H_4 \underset{N}{\overset{C}{\diagdown}} \overset{\overset{\displaystyle COOH}{|}}{\underset{C—C_6H_5}{\diagdown}} \begin{matrix} CH \\ \| \end{matrix} + 2H_2O + H_2$$

249
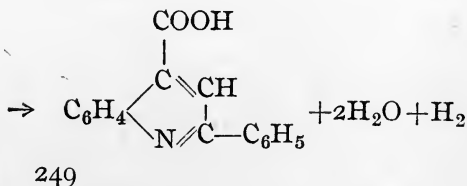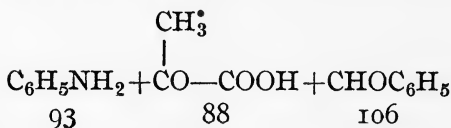
Equimolecular proportions of benzaldehyde and pyruvic acid (prepared by the distillation of tartaric acid, alone (*Ann.* **172**, 142) or (*Ber.* **14**, 321) with potassium bisulphate) are dissolved in cold absolute alcohol. A solution of one molecular equivalent of aniline, also in absolute alcohol, is gradually added. Heat is developed, and the reaction is brought to completion by boiling the mixture, under reflux, for 3 hours. On cooling, crystals of 2-phenyl-4-quinoline carboxylic acid separate and are filtered off, dissolved in

sodium hydroxide solution, separated from an insoluble impurity, reprecipitated with acid, and recrystallised from dilute alcohol.   Yield 53 %.

A variation of this method, proposed in D. R. P. Anmeldung, 20870, consists in gradually adding 1 molecular proportion of pyruvic acid to a boiling alcoholic solution of benzylidene aniline (1 mol.), afterwards refluxing for some time and separating the product as above.

An alternative process, in which isatin is the starting out material, was discovered by Pfitzinger (*J. f. prakt. Chim.* (1897), **56**, 292).

$$C_6H_4\diagdown\!\!\!\!\overset{CO}{\underset{NH}{}}\!\!\!\!\diagup CO + CH_3COC_6H_5$$

$$\qquad 147 \qquad\qquad 120$$

$$\rightarrow\quad C_6H_4\diagdown\!\!\!\!\begin{array}{c} \overset{COOH}{|}\\ C=CH \\ | \quad | \\ N=C-C_6H_5 \end{array} + H_2O$$

$$249$$
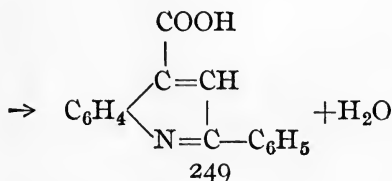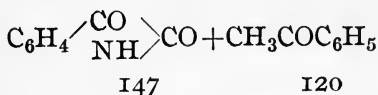
Isatin, 15 grams, acetophenone, 22·5 grams, alcohol, 122 c.c., and 33 % potassium hydroxide, 60 c.c., are boiled together, under a reflux condenser for 6 hours.   The alcohol is then distilled off, excess of acetophenone is removed by steam distillation, and the residue, after cooling, is extracted with ether to remove impurities.   The aqueous solution is freed from ether, cooled, and carefully acidified, whilst being stirred, with dilute hydrochloric acid.   After 12 hours the yellow precipitate is filtered off, washed with water, and dissolved in sodium carbonate.   The solution is diluted to 750 c.c. and, after 50 grams of salt have been dissolved in it, allowed to stand for 36 hours.   During this period a coloured impurity is precipitated.   This is filtered off, and the atophan precipitated by careful acidification.   It is finally purified by two recrystallisations from alcohol, employing charcoal as a decolourising agent.   Yield 65 %.

A similar method is given by D. R. P. 287304.

Fifteen kilos of isatin are mixed with 12 kilos of aceto-phenone and 60 kilos of 33 % aqueous caustic potash and heated at 90°–100° for 8 hours, with good stirring. The reaction mixture is then diluted with water and filtered. The filtrate is carefully treated with acetic acid so long as a precipitate of a reddish-brown flocculent material is produced. This is removed by filtration, and the atophan precipitated by addition of the correct quantity of acetic acid. The yield is stated to be almost quantitative.

Atophan is a colourless crystalline substance, melting at 209°. It is insoluble in cold, and nearly so in hot, water. It is easily soluble in ether and in hot alcohol. It dissolves readily in cold alkalis, with formation of salts, and also, on warming, in dilute acids.

Atophan and its derivatives stimulate the action of the kidneys ; it slightly increases the flow of urine and greatly increases the excretion of uric acid. It is prescribed in acute gout and other renal diseases.

PARATOPHAN, 6-methyl-2-phenyl-4-quinoline-carboxylic acid, and its ethyl ester (novatophan) are recently introduced derivatives of atophan the value of which is not fully established.

SECTION IX.—ORGANO-METALLIC COMPOUNDS

THE use in medicine of substances in which atoms of the metallic elements are directly linked to carbon atoms is restricted to a very small number of compounds, chiefly derivatives of arsenic. Ionisable salts of antimony, arsenic, bismuth, iron, lead, manganese, silver and zinc are employed therapeutically for various purposes, but prior to the introduction of salvarsan little importance had been attained by any of the so-called organo-metallic compounds. The discovery that sodium arsanilate acts more powerfully as a parasiticide in the body than in the test-tube led Ehrlich and his associates to the most important of modern discoveries in chemico-therapeutics—salvarsan, in which there is a double arsenic linkage, the arsenic being in the trivalent form. The danger and difficulty of administering organic arsenic compounds have been reduced by the improvements on salvarsan which have already been introduced; further progress in this direction may still be expected.

Iron plays a definite and important part in body metabolism, being essential to life, and a constituent of hæmoglobin; but no readily available form of its administration has yet been introduced.

p-AMINO-PHENYLARSINIC ACID (arsanilic acid)

$$NH_2$$

217.—
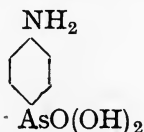
$$AsO(OH)_2$$

This acid, the sodium salt of which is employed in medicine under the names "Atoxyl" and "Soamin," was first prepared

by Béchamp (*Bull. Soc. Chim.* (1863), **5**, 518), who, however, considered it to possess the configuration $\langle\ \rangle$NHAsO(OH)$_2$, a supposition not corrected until 1907, when Ehrlich and Bertheim demonstrated Béchamp's compound to be *p*-amino-phenyl-arsinic acid.

Kober and Davis (*J. Amer. Chem. Soc.* (1919), **41**, 451) recommend the following method of preparation.

One litre of 76 % technical arsenic acid is concentrated to 100 % by heating at 120°–140° for 12–15 hours, then cooled, and stirred into 1400 c.c. of dry, ice-cold aniline. The arsenate so formed (aniline : acid, 3 : 2) is ground to a powder, stirred at 160° until molten, and finally heated under a reflux condenser for 1 to 1½ hours at 160°–170°, and for 1 hour at 180°–185°. After cooling somewhat, 450 c.c. of N/1 sodium hydroxide are added, the unchanged aniline is separated and the aqueous layer is shaken with kaolin or kieselguhr, and filtered. The clear solution is then treated with 100 c.c. of 6N. hydrochloric acid, and as much more as is found to be necessary to effect complete precipitation of the *p*-amino-phenyl-arsinic acid.

The almost solid mass is then filtered and washed with cold water. The sodium salt is prepared by neutralising the acid (1 mol.) with sodium carbonate (½ mol.) or sodium hydroxide (1 mol.) and recrystallising it from 50 % aqueous alcohol.

Should it be necessary to evaporate or boil aqueous solutions of sodium arsanilate, they should be made alkaline by the addition of a second molecule of caustic soda, as otherwise considerable hydrolysis results (*Ber.* (1914), **47**, 363).

SODIUM *p* - **AMINO-PHENYL- ARSINATE** (" Atoxyl " or "Soamin ") $C_6H_4\langle{}^{NH_2}_{AsO(OH)(ONa)}+5H_2O$, 329, forms colourless crystals, soluble in 5 parts of water, giving a solution that is neutral to litmus. It dissolves in alcohol, 1 in 125. It contains 22·8 % of arsenic. The toxicity of " atoxyl " to mammals is about one-fortieth that of arsenious acid.

Aqueous solutions become more toxic on keeping, due to decomposition.

"Atoxyl" was introduced into medicine for the treatment of trypanosomiasis, and it was soon employed in syphilis, relapsing fever, anæmia, and skin diseases. Cases of blindness, however, were frequently experienced, and since the introduction of salvarsan the use of atoxyl has been greatly reduced. It is of interest as being an important intermediate in the manufacture of salvarsan.

ARSENO-PHENYL-GLYCINE

$$As{=}As$$

COOHCH$_2$NH   NHCH$_2$COOH
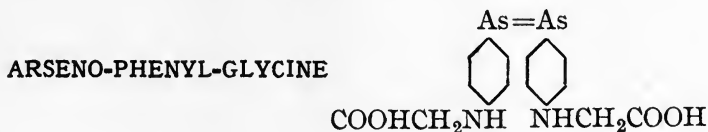
Arseno-phenyl-glycine, introduced by Ehrlich, was the first trivalent organic arsenic compound introduced. On account of its low toxicity and high trypanocidal power it constituted an important advance on atoxyl. It is prepared by the reduction of phenyl-glycine arsanilic acid.

*Phenyl-glycine-*p-*amino-phenyl-arsinic acid*

NH·CH$_2$·COOH

AsO(OH)$_2$
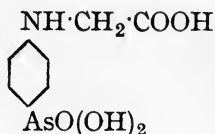
Sodium arsanilate, 27·5 parts, is dissolved in 80 parts of hot water. A solution of 16 parts of mono-chloracetic acid in 20 parts of water is added and the mixture boiled for 6–8 hours. On cooling, the phenyl-glycine-arsanilic acid crystallises out and is filtered off and freed from any unchanged arsanilic acid by treatment with dilute hydrochloric acid.

$$C_6H_4{<}^{NH_2}_{AsO(OH)ONa}+CH_2ClCOOH$$

$$\rightarrow C_6H_4{<}^{NH\cdot CH_2-COOH}_{AsO(OH)_2}+NaCl$$
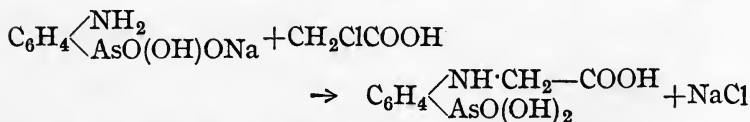
Arseno-phenyl-glycine.—

Two hundred grams of phenyl-glycine arsanilic acid are

dissolved in 4 litres of hot water and added to a solution of 2 kilos of sodium hydrosulphite in 10 litres of water containing 600 c.c. of 10N. caustic soda and 1 kilo of crystallised magnesium chloride, from which the precipitated magnesia has been removed by filtration. The mixture is warmed for $\frac{3}{4}$ hour on a gently boiling water bath. The precipitate of arseno-phenyl-glycine which has separated is filtered off after cooling, washed with cold water, and purified by being dissolved in dilute hot sodium carbonate solution and reprecipitated with acetic acid.

The sodium salt $As_2(C_6H_4NHCH_2COONa)_2$, named " spirarsyl," is readily soluble in water, giving a neutral solution.

It has a high trypanocidal power combined with low toxicity, but is inferior to salvarsan.

Salvarsan, kharsivan, arsenobillon. 3 . 3'-diamino-4 . 4'-dihydroxy-arsenobenzene

$$HClNH_2 \overset{OH\ OH}{\underset{As=As}{\bigcirc\ \bigcirc}} NH_2HCl \cdot 2H_2O. \quad 475.$$
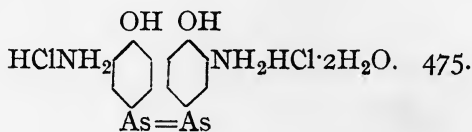
—Salvarsan is prepared by reduction, generally with sodium hydrosulphite, of 3-nitro-4-hydroxy-phenyl-arsinic acid, and the various modifications of the original method of manufacture deal with different means of obtaining the latter substance.

These are :—

(1) Nitration of *p*-oxy-phenyl-arsinic acid (D.R.P. 224953), which is obtained either by heating phenol and arsenic acid (D.R.P. 205616) or by diazotisation of *p*-amino-phenyl-arsinic acid and replacement of the diazo- by the hydroxy- group (*Trans. C. S.* (1908), **93**, 1895, and *Ber.* (1908), **41**, 1678, 1854).

$$\overset{OH}{\underset{AsO(OH)_2}{\bigcirc}} \rightarrow \overset{OH}{\underset{AsO(OH)_2}{\bigcirc}}NO_2$$
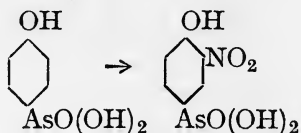
(2) By nitration of oxalyl-amino-phenyl-arsinic acid, and boiling the product with alkali, when the NH·CO·COOH group is replaced by OH(D.R.P. 31969), with the elimination of oxalic acid and ammonia.
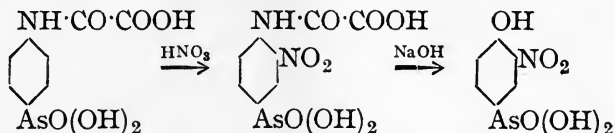
(3) By nitration of *p*-chlorophenyl-arsinic acid, prepared by treating diazotised para-chloraniline with sodium arsenite (Bart's reaction, D.R.PP. 250264, 254345), after which by digestion with alkali the Cl atom is replaced by OH.
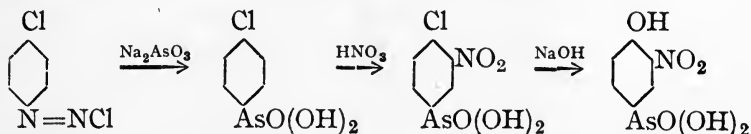
D.R.P. 245536).

(4) Ortho-nitrophenol is coupled with diazotised sulphanilic acid and the resulting azo-compound
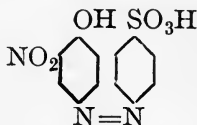
is reduced to 1-amino-3-nitro-4-hydroxy-benzene, into which the arsinic acid radicle is introduced, by Bart's reaction, in place of the amino group (D.R.P. 258059). This process is unsatisfactory, however, as in the case of *meta*-nitroamines the reaction between the diazo compound and sodium arsenite gives rise only to very small yields of the required arsinic acid (Jacobs, Heidelberger, and Rolf, *J. Am. Chem. Soc.* (1918), **40**, 1580).

(5) From *p*-dimethylamino-phenyl-arsinic acid.

The specific reducing agent by which nitro-hydroxyphenyl-arsinic acid is converted into salvarsan is, as stated above, sodium hydrosulphite. According to D.R.P. 271894

the operation is successfully effected by hypophosphorous and hydriodic acids, employed together.

(1) **Preparation of Para-hydroxyphenyl-arsinic acid**

OH

AsO(OH)$_2$
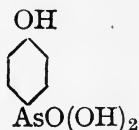
Phenol, 94 parts, and crystallised arsenic acid, 151 parts, are mixed and heated together with stirring for 4 hours at 150°. The resulting mass is extracted with 1000 parts of hot water, and the filtered solution evaporated as far as possible under diminished pressure. The residue is repeatedly extracted with acetone. After removal of the solvent the crude arsinic acid is obtained as an oil which gradually solidifies. Conant (*J. Amer. Chem. Soc.* (1919), **41**, 431) employs a 10 % excess of arsenic acid and heats at 147°–157° for 3 hours. The aqueous solution of the crude acid is filtered from tar, treated with barium hydroxide until the brown colour begins to change to pink, and then extracted with ether to remove tarry matter. More baryta is then added until a test portion, after rendering it alkaline and filtering, shows the presence of barium ions. The solution is then made just alkaline with sodium hydroxide and filtered. The barium is removed by treatment with sodium sulphate and the filtrate evaporated to a syrup. Sulphuric acid is added until the red colour changes to yellow, and the impurities which separate are filtered off. The filtrate is neutralised with soda and evaporated to dryness, when a mixture of sodium sulphate and sodium *p*-hydroxyphenyl-arsinate is obtained. This can be nitrated directly, or the latter compound may be extracted with boiling alcohol and crystallised. Yield 21·5 %.

Alternatively, the syrupy residue containing the *p*-hydroxy-phenyl arsinic acid can be treated as follows (E.P. 6322/1915). Eighty parts are dissolved in 80 parts of warm water and the solution neutralised, after cooling, with a solution of 16 parts

of caustic soda in 80 parts of water. After filtration from some separated impurities the filtrate is concentrated and allowed to crystallise. Sixty parts of crude sodium *p*-hydroxy-phenyl arsinate are obtained. It may be purified by dissolving in 120 c.c. of boiling water, and adding 250 parts of absolute alcohol. After cooling, 30 parts of pure sodium *p*-hydroxyphenyl-arsinate crystallise out, a further 5 parts being obtained by concentration of the mother liquors.

By another method (see *Trans. C. S.* (1908), **93**, 1895) 329 parts of sodium para-amino-phenyl-arsinate ($+5H_2O$) are dissolved in 1000 parts of water containing 300 parts of 10N. hydrochloric acid and diazotised, at 0°–5°, with sodium nitrite, 69 parts (100 %) dissolved in 100 parts of water. After standing for an hour the solution is gradually heated up to 100°, and then, when evolution of nitrogen has ceased, partially neutralised with 100 c.c. of 10N. sodium hydroxide, but left still just acid to congo red, and evaporated, under reduced pressure, to dryness. The residue is powdered, re-dried if necessary, and extracted with boiling acetone. The solvent is partially removed from the extract and, after cooling, *p*-hydroxyphenyl-arsinic acid crystallises out. M.p. 173°–174°.

It may be purified by recrystallisation from glacial acetic acid. It is readily soluble in water and alcohol.

Nitration of p-*hydroxyphenyl-arsinic acid to* 3-*nitro*-4-*hydroxyphenyl-arsinic acid* $\underset{\text{AsO(OH)}_2}{\overset{\text{OH}}{\bigcirc}}NO_2$ (D.R.P. 224953).—Sodium para-oxyphenyl-arsinate, dried at 80°, 144 parts, is added, in small portions at a time, to 450 parts by vol. of concentrated sulphuric acid, which is kept at 0°. A mixture of 39 parts by vol. of nitric acid (sp. gr. 1·4) and 39 parts by vol. of concentrated sulphuric acid is then added, at the same temperature, with constant stirring. When addition of the nitrating acid is complete, the mixture is allowed to stand for some time and the temperature to rise to 10°. It is then poured on to 2250 grams of ice, and after

12 hours' standing in the cold the precipitated 3-nitro-4-hydroxyphenyl-arsinic acid is filtered off.

(2) **Oxanil-4-arsinic acid**

$$\overset{\text{NH·CO·COOH}}{\underset{\text{AsO(OH)}_2}{\bigcirc}}$$
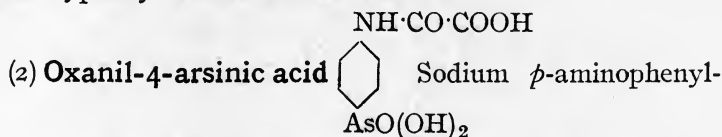
Sodium *p*-aminophenyl-

arsinate ($+5H_2O$), 347 parts, is mixed thoroughly with 378 parts of crystallised oxalic acid. The mixture is heated, with constant stirring, at 120°–130°, until the bulk of the water has been removed and the mass, which at first melted, has resolidified. The temperature is then raised slowly to 160° and heating continued until the mass is again solid and in powder form. After cooling it is treated with 3000 parts of water, 390 vols. of hydrochloric acid (sp. gr. 1·12) are added, and the mixture is stirred for half an hour. The solid oxanil-4-arsinic acid is then filtered off, purified by recrystallisation from water, and thoroughly dried. Alternatively it may be purified by dissolving in normal caustic soda solution and reprecipitation, after being filtered, with hydrochloric acid.

3-nitro-4-arsinic acid

$$\overset{\text{NH·CO·COOH}}{\underset{\text{AsO(OH)}_2}{\bigcirc}}{}^{\text{NO}_2}$$

and *3-nitro-4-amino-*
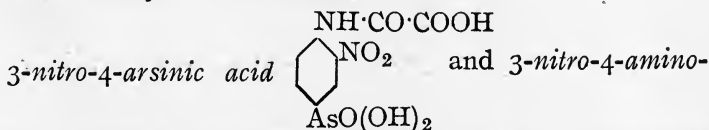
phenyl-arsinic acid.—The dried oxanil-arsinic acid, 115·6 parts, is dissolved in 300 vols. of concentrated sulphuric acid at 0°–5°. A mixture of 26 vols. of nitric acid (sp. gr. 1·4) and 26 vols. of sulphuric acid is added, with stirring, the temperature being kept at or below 5°. The mixture is allowed to stand for some time after the addition is completed and is then poured into 1500 parts of cold water, when the nitro-oxanil-arsinic acid separates as a crystalline paste. The whole is heated to boiling, a clear yellow solution being obtained. Boiling is continued until the acidity increases no further, and the mixture is cooled, when 3-nitro-4-amino-phenyl-arsinic acid crystallises out in sulphur-coloured needles, which are only sparingly soluble in cold water. It is filtered off and washed with cold water.

Ten kilos are dissolved (D. R. P. 235141) in 60 litres of caustic potash (36° Bé.) and the solution heated at 80°, until a portion is shown by test to be free from substances containing an amino group. After cooling, the solution is made acid to congo red, with hydrochloric acid, when 3-nitro-4-hydroxyphenyl-arsinic acid is precipitated.

Alternatively the 3-nitro-4-oxanil-arsinic acid is separated by filtration and heated, as above, with caustic alkali solution.

By another protected process (D.R.P. 232879) the urethane of *p*-amino-phenyl-arsinic acid, prepared by condensing the acid with ethyl-chloro-carbonate, is nitrated and treated as is the oxalyl compound.

(3) **4-Chlorophenyl-arsinic acid** $\begin{matrix} Cl \\ \bigcirc \\ AsO(OH)_2 \end{matrix}$ This compound is prepared from para-chloraniline by Bart's reaction (D. R. P. 250264).

$$ClC_6H_4N = NCl + As \begin{matrix} OH \\ (ONa)_2 \end{matrix}$$
$$\rightarrow ClC_6H_4AsO \begin{matrix} OH \\ ONa \end{matrix} + NaCl + N_2$$
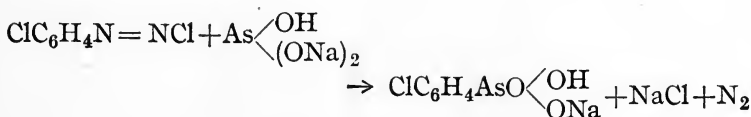
Para-chloraniline, 0·74 part, is dissolved in 10 parts of water and 2 parts of hydrochloric acid (sp. gr. 1·16), and diazotised at 10° with the required amount of sodium nitrite. The diazo solution is then mixed with 2 parts of sodium arsenite dissolved in 5 parts of water. The mixture is made alkaline and gently heated. When the evolution of nitrogen has ceased, the reaction mixture is filtered from tarry impurity and the para-chlorophenyl-arsinic acid precipitated by the addition of hydrochloric acid. According to the British specification (E. P. 568/1911), 3 parts of sodium arsenite dissolved in 5 parts of water and 1 part of 96 % alcohol are employed, and the mixture heated to 70°.

In a subsequent patent (D. R. P. 268172) copper is employed as a catalyst, 50 parts of copper paste being added

to a solution of 51 parts of sodium arsenite in 150 parts of water and 60 parts of 40 % caustic soda. D. R. P. 264924, dealing with the preparation of phenyl-arsinic acid from aniline by the Bart method, utilises, as the catalyst, freshly prepared cuprous oxide, precipitated from alkalised copper nitrate by glucose. Cobalt, nickel, and silver and their salts have been proposed as catalysts, as well as copper.

Jacobs, Heidelberger and Rolf (*J. Am. Chem. Soc.* (1918), **40**, 1580), in carrying out the Bart reaction, convert the diazo-compounds into the iso-diazo salts by pouring into an excess of caustic soda at 0°. The arsenite is then added and the reaction mixture heated at 60°–70° until the evolution of nitrogen has ceased.

(4) From dimethyl-amino-phenyl-arsinic acid

$$N(CH_3)_2$$

$$AsO(OH)_2$$
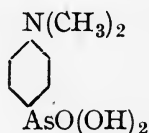
(D. R. P. 200065).—A mixture of 15 parts of dimethyl aniline and 25 parts of arsenious chloride is heated at 100° for 2 hours, and is then poured in 300–400 parts of cold water. Excess of aqueous caustic soda is added until the *p*-dimethyl-amino-phenyl arsenious oxide is dissolved. After removing unchanged dimethylaniline by extraction with light petroleum, an excess of 30 % hydrogen peroxide is added and *p*-dimethyl-amino-phenyl-arsinic acid precipitated with acetic acid.

4-dimethyl-amino-3-nitro-phenyl-arsinic acid

$$N(CH_3)_2$$
$$NO_2$$

$$AsO(OH)_2$$
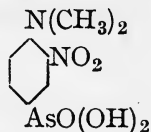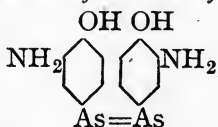
(F. P. 449373).—One hundred parts of dry dimethyl-amino-phenyl-arsinic acid are dissolved at below 15° in 250 parts of concentrated sulphuric acid and nitrated with a mixture of 35 parts of nitric acid (sp. gr. 1·49)

and 150 parts of sulphuric acid, the temperature being kept below 15°. After standing for some time the reaction mixture is poured on to ice, the yellow precipitate filtered off, washed, dissolved in aqueous sodium carbonate solution and reprecipitated, after filtration, by very dilute mineral acid. It may be further purified by crystallisation from hot water.

Conversion of dimethyl-amino-nitro-phenyl-arsinic acid to 3-nitro-4-hydroxyphenyl-arsinic acid (Fr. Pat. 451078).— Five hundred parts of the nitro-acid are dissolved in a solution of 500 parts of caustic potash in 1500 parts of water and the mixture maintained at 80°–90° until it becomes nearly solid. Ice-cold water (2000 parts) and concentrated hydrochloric acid are added successively, the precipitate is dissolved in hot water, and the filtered solution treated with sodium acetate (1 mol.) and animal charcoal. It is filtered again and acidified with hydrochloric acid, when 3-nitro-4-oxyphenyl-arsinic acid separates either in yellow, rhombohedral plates, or in tufts of almost colourless needles.

Reduction of Nitro-hydroxyphenyl-arsinic acid to Sal-varsan NH_2⟨⟩⟨⟩NH_2 (with OH OH above and As=As below).—The preparation of salvarsan by the reduction of 3-nitro-4-hydroxyphenyl-arsinic acid with sodium hydrosulphite in one operation is thus described by Kober (*J. Amer. Chem. Soc.* (1919), **41**, 442).

Magnesium chloride, 220 grams, is dissolved in 5500 cc. of distilled water, and sodium hydrosulphite, 1100 grams, quickly added, with stirring. To this solution are then added, with stirring, 85 grams of crude 3-nitro-4-hydroxyphenyl-arsinic acid dissolved in 290 c.c. of 2N. sodium hydroxide and diluted with 1700 c.c. of water. The mixture is allowed to stand at room temperature, or it is slowly warmed in a water bath at 40°, until the suspension, which consists mostly of impurities, besides a little of the salvarsan base, has separated. The mixture is then rapidly filtered through hard paper, or alundum ware. The weight of the residue

rarely exceeds 3 to 4 grams, or 4 to 5 per cent. of the total yield.

The clear yellow filtrate is then digested at 50°–60° for 2 to 2½ hours, during which time the salvarsan base, 3 . 3'-diamino-4 . 4'-dihydroxy-arsenobenzene, separates out as a yellow precipitate.

The above differs from Ehrlich and Bertheim's method (*Ber.* (1912), **45**, 756) only in respect of the filtration, which these workers omitted. The precipitate is filtered off, washed with water at 0°, and pressed. By Ehrlich and Bertheim's process it is dissolved in anhydrous methyl alcohol, 725 c.c. for the above quantities, and treated with 0·75 mol. of hydrogen chloride dissolved in methyl alcohol. Ether is added to the filtered solution, whereby salvarsan hydrochloride is precipitated. It is filtered off quickly, washed with ether, and dried in an inert atmosphere, such as CO_2, or *in vacuo*, at 65°.   Yield (E. & B.) 82 %.

Kober, *loc. cit.*, considers that the very variable toxicity of salvarsan, of which 50 per cent. of that manufactured in America fails to pass the prescribed physiological tests, may be attributable to impurities concomitant with this methyl alcohol-ether treatment.   He suspends washed base in 400 c.c. of distilled water at 0° and dissolves it by addition of 150 c.c. of 2N. caustic soda.   The alkaline solution is filtered through an alundum anærobic filter, and 150 c.c. of 1 : 1 hydrochloric acid at 0° are added to the clear filtrate.   This precipitates the base and redissolves it as the dihydrochloride.   The solution is diluted with distilled water at 0° to bring the total volume to 1700 c.c. It is then allowed to flow, slowly and with stirring, into a mixture, cooled to 0°, of 1625 c.c. of pure concentrated hydrochloric acid and 1625 c.c. of water.   Salvarsan dihydrochloride is precipitated as a greyish-white precipitate. It is filtered, and dried *in vacuo* at a low pressure, in presence of calcium chloride and solid caustic soda.   After 12 hours or more, hydrogen is introduced, to equalise the pressure, and the salvarsan is ground and further dried until of constant weight.   Yield 75 %.

From Fargher and Pyman's work (*Trans. C. S.* (1920), **117**, 372), Kober's purification is of doubtful value. Commercial salvarsan contains 1 to 3 per cent. of sulphur, which occurs, at least in part, in the form of a sulphamo-group $NH—SO_3H$. When obtained free from sulphur salvarsan is less readily soluble and therefore less suited for clinical use.

The following method of reduction has also been employed (D.R.P. 271894). Twenty parts of 3-nitro-4-hydroxyphenyl-arsinic acid are mixed with 100 vols. of 25 % hypophosphorous acid solution and 70 vols. of glacial acetic acid, and the mixture heated on the water bath with stirring and in absence of air. Dinitro-dihydroxy-arseno-benzol separates out as a yellow crystalline precipitate. After about an hour's heating 12 parts of potassium iodide are added. A vigorous reaction takes place, and the precipitate passes into solution, which acquires a faint yellow colour. After cooling it is poured into 150 vols. of concentrated hydrochloric acid, and the mixture is saturated with HCl gas. The dihydrochloride of salvarsan separates out and is filtered off, washed successively with concentrated hydrochloric acid, alcoholic hydrochloric acid and ether, and dried *in vacuo*.

By a variation of the procedure the reduction solution is poured into 600 vols. of alcohol, when the hypophosphite of the base is precipitated as a yellowish-white powder. This is converted into hydrochloride, base, or sodium salt, as desired. Prepared in this manner salvarsan is less soluble in water or methyl-acohol than when reduced by the previously described method.

Electrolytic Reduction of 3-nitro-4-hydroxyphenyl-arsinic acid. (D. R. P. 270568.)—Fifty parts of 3-nitro-4-oxyphenyl-arsinic acid are dissolved in 150 parts of water and 12·5 parts (1 mol.) of potassium carbonate. This is placed in the cathode chamber of an electrolytic cell, the anode chamber containing a 10 to 20 % solution of potassium carbonate. Lead electrodes are employed, and the cathode liquor is well stirred. A current of 10 to 25 amps. per 100 sq. cm. is employed, and it is recommended that a stream of CO_2 be passed through the liquor during electrolysis.

The current is passed until the solution is, as far as it can be, decolourised. The resulting salvarsan is precipitated, with sulphuric acid, as the sulphate. It is claimed that the product afforded by this electrolytic method of reduction possesses a lower degree of toxicity.

If electrolysed in an acid solution 3 . 3'-dinitro-4 . 4'- dihydroxy - arseno - benzene is produced. This may be reduced further, to salvarsan, by electrolysis in an alkaline solution.

The reduction of 3-nitro-4-hydroxyphenyl-arsinic acid can also be effected in stages. By employing sodium amalgam, or ferrous sulphate and caustic soda, 3-*amino*-4-*hydroxyphenyl-arsinic acid* is obtained. This is reduced further, by the action of sulphurous acid in the presence of hydriodic acid, to 3-*amino*-4-*hydroxyphenyl-arsenious oxide*, which is converted into salvarsan by reduction with hypophosphorous acid used in conjunction with hydriodic acid. No advantage can be claimed for this mode of procedure. Another direct method of reduction depends upon the formation of hydrosulphurous acid *in situ.* (E. P. 21421/1914.)

One hundred grams of 3-nitro-4-hydroxyphenyl-arsinic acid are dissolved in 500 c.c. of water containing a sufficient quantity of soda to produce a neutral solution, 50 grams of zinc chloride or acetate are then added, followed successively by a concentrated aqueous solution of 100 grams of sodium sulphite, glacial acetic acid, 150 c.c., and zinc dust, 200 grams, the emulsion being thoroughly stirred. Five hundred c.c. of hydrochloric acid (18 %) are then added very slowly, the temperature being between 25° and 35°. The resulting clear solution is warmed to 50° and treated gradually with a further 570 c.c. of 18 % hydrochloric acid. After 20–30 minutes the solution is filtered rapidly and the filtrate treated with magnesium sulphate, when salvarsan sulphate is precipitated. It is claimed that the presence of sulphurous acid prevents the reduction going beyond the arsenobenzene stage to primary arsine.

Salvarsan, which is the dihydrochloride of diamino-dihydroxy-arseno-benzene, is a pale yellow powder, soluble in 5

parts of water. Its solution has a strongly acid reaction. The solubility is increased by certain impurities which accompany it. It is moderately soluble in methyl, sparingly soluble in ethyl alcohol, and almost insoluble in acetone, ether, or glacial acetic acid. On account of the readiness with which salvarsan undergoes change in air, with formation of highly toxic impurities, it is preserved in sealed tubes in an atmosphere of an inert gas.

When heated, salvarsan hydrochloride does not melt; it darkens at 160° and begins to char about 180°.

When perfectly pure the dihydrochloride is practically colourless. The appearance, however, is no criterion of physiological purity, as very light-coloured preparations have been found on occasion to be extremely toxic. Theoretically salvarsan dihydrochloride, if anhydrous, should contain 34·2 % of arsenic; if it contains $2H_2O$, 31·6 %.

Ewins (*Trans. C. S.* (1916), **109**, 1355) found from 30·4 % to 31·45 % of arsenic in four commercial samples examined. Kober (*loc. cit.*) considers that no justification exists for assuming the commercial product to contain two molecules of water, and that, as made by the patented method, it contains instead one molecule of methyl alcohol. Samples prepared by Kober's method (see above) appear to have contained from one to rather more than two molecules of water, and afforded from 30·3 % to 32·89 % of arsenic. But Fargher and Pyman found that salvarsan if precipitated from methylic alcohol solution with ether contains no combined organic solvent, though if precipitated with acetone from methyl-alcohol it contains one molecule of acetone.

All batches of salvarsan, neo-salvarsan, etc., made in this country and in the United States are required to satisfy physiological tests of freedom from toxicity, carried out by a public authority, before they are allowed to be issued.

Salvarsan, neo-salvarsan, galyl, and luargol, are the most powerful drugs so far available for combating syphilis. They are specific for primary and secondary syphilis, and in many cases have been used with success even in hereditary syphilis and in tertiary para-syphilitic conditions.

Not only syphilis but other diseases attributable to *spirillosa*, such as yaws, frambœsia, and (probably) pernicious anæmia are beneficially treated by arsenic administered in the arsenobenzol form.

Salvarsan is administered by intravenous or intramuscular injection, a solution being employed which is prepared by treating the salt with sufficient caustic soda to precipitate the base and redissolve it as the di-sodium salt.

To avoid the inconvenience of this procedure the sodium salt of salvarsan was prepared and is marketed in the form of a yellowish powder, which is readily soluble in water.

Sodium Salvarsan (E. P. 15931/1912).—Six grams of salvarsan dihydrochloride are mixed with 60 c.c. of strongly cooled methyl alcohol and the mixture treated with 5·05 c.c. of 10N. caustic soda solution, with stirring. To the solution are added 1·2 gram of sodium formaldehyde-sulphoxylate dissolved in 3 c.c. of water, and the mixture is then poured into a mixture of 300 c.c. of methyl alcohol and 240 c.c. of pure ether. The sodium salt is precipitated, and is filtered off, washed with ether, and dried *in vacuo* over sulphuric acid. All these operations are carried out in absence of air.

NEO-SALVARSAN (sodium 3 : 3'-diamino-4 : 4'-dihydroxy-arseno-benzene-N-methylene-sulphinate)

$$NH_2\bigodot\ \bigodot NH{\cdot}CH_2O{\cdot}SONa$$
$$OH\quad OH$$
$$As{=}As$$
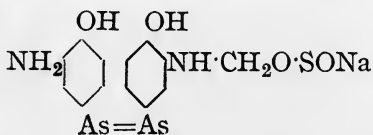
The inconvenience involved in the preparation of salvarsan solution for injection led Ehrlich to search for a soluble neutral derivative which would not possess the same disadvantages. The methylene-sulphinate, prepared by treating the salvarsan base with sodium formaldehyde sulphoxylate, proved the most satisfactory of the substances made and tested, and was named Neo-salvarsan.

Twenty-five parts of salvarsan dihydrochloride are dissolved in 250 parts of water and mixed at room

temperature with a solution of 25 parts of sodium formaldehyde-sulphoxylate in 250 parts of water. After one hour 80 parts of a 10 % solution of sodium carbonate are added, when a clear solution is formed. Addition of 100 parts by vol. of 12 % hydrochloric acid then precipitates the methylene-sulphinic acid derivative of salvarsan, containing one CH_2SO_2H group. In order to make neo-salvarsan—the sodium salt of the acid thus obtained—20 parts of the acid are suspended in 70-80 parts of water, and brought into solution with the aid of 20 parts of twice normal sodium hydroxide. The solution is then allowed to flow, with stirring, in a thin stream into 1000 parts by vol. of alcohol. The sodium salt is precipitated, and is filtered off, washed with cold water, and dried *in vacuo*. (D. R. P. 24576.)

Acetone also may be used as a precipitant, or the aqueous solution of the sodium salt may be evaporated to dryness under diminished pressure. According to D. R. P. 260235 neo-salvarsan having a lower toxicity can be prepared by operating in alcohol solution. Methyl and ethyl alcohol, glycol, and glycerol are cited.

Thirty-one parts of sodium formaldehyde-sulphoxylate dissolved in 50 parts of water are added to a solution of 50 parts of salvarsan base in 200 parts of ethylene-glycol. After five minutes the solution is neutralised with sodium carbonate, and allowed to flow into a large quantity of alcohol, alcohol and ether, or acetone, when neo-salvarsan is precipitated. Neo-salvarsan can also be prepared directly from 3-nitro-4-hydroxyphenyl-arsinic acid. One part of this is dissolved in 5 parts of water and 3·8 parts of 4 % caustic soda, and warmed with 2 parts of sodium-formaldehyde-sulphoxylate dissolved in 10 parts of water, when a yellow precipitate of the free sulphinic acid is gradually formed (D. R. P. 260235). When this no longer continues to increase in amount, it is filtered off, washed with water, and converted into the sodium salt in the way described above. By another variation, 10 parts of 3-amino-4-hydroxyphenyl-arsinic acid are dissolved in 100 parts of water containing 2·3 parts of sodium carbonate

and the solution mixed with one of 20 parts of sodium formaldehyde-sulphoxylate in 100 parts of water. Normal hydrochloric acid, 41 parts, is then added, and the mixture digested for several hours at 40°–60°. After cooling, the sulphoxylic acid is precipitated by acidification with dilute sulphuric acid.

Neo-salvarsan is a pale yellow powder which is readily soluble in water, affording a neutral solution. It contains usually about 20 % of arsenic. It is used for the same purposes as salvarsan, having a very similar physiological action. It is becoming the more extensively used drug on account of its greater solubility and the consequent greater ease with which the solution for injection may be prepared.

Co-ordination Compounds of Salvarsan and Neo-salvarsan.—Compounds of salvarsan with copper, silver, gold, platinum, mercury, palladium, iridium, ruthenium, and osmium, in which the arsenobenzene enters into combination with one or two molecular proportions of the metallic salt in such a way that the metal is held in a non-ionisable condition, were discovered by Ehrlich and Karrer (*Ber.* (1915), **48**, 1634). The combination is a general one and is manifested by organic arsenious oxides and arsines as well as by all arsenoaryls.

Recent German communications indicate that certain of these new substances, notably the co-ordination compounds of salvarsan and neo-salvarsan with silver salts, possess high therapeutic value, the ratio of the toxic dose to the efficient dose being very much greater than in the case of the parent arsenobenzene compound.

Silver Salvarsan (D. R. P. 270253).—One part of salvarsan dihydrochloride is dissolved in 10 parts of methyl alcohol and the solution treated with a methyl alcoholic solution of 0·36 part (1 mol.) of silver nitrate. Addition of ether precipitates the co-ordination compound, which is easily soluble in water, methyl alcohol and glycerol.

A compound containing two molecular proportions of silver is prepared exactly as the above, but with employment of 0·72 part (2 mols.) of silver nitrate.

Silver Neo-salvarsan (D. R. P. 268221).—Three parts of neo-salvarsan are dissolved in the smallest possible quantity of water and treated with 0·77 part of silver nitrate dissolved in 20 parts of water. The solution is then poured into a mixture of alcohol and ether, when silver neo-salvarsan is precipitated. Copper, gold, and other metallic derivatives are prepared similarly. A copper co-ordination compound is also produced when a mixture of molecular proportions of sodium-3-amino-4-hydroxyphenyl arsinate and cupric chloride in aqueous solution is reduced with sodium hydrosulphite. Reduction of the arsinic acid to the arsenobenzene compound, and formation of the co-ordination complex proceed consecutively, and the copper compound, which is only sparingly soluble in water, is precipitated. It is very soluble in dilute hydrochloric acid, and also in sodium hydroxide.

LUARGOL (3 : 3'-diamino-4 : 4'-dihydroxy-arsenobenzene silver bromide antimonyl sulphate)

$$(C_{12}H_{12}O_2N_2As_2)_2AgBr-SbO(H_2SO_4)_2$$

Luargol is a co-ordination compound of a more complex type, containing non-ionisable antimony as well as silver. It was introduced by Danysz, who prepared it in the following manner (E. P. 104497/1917).

One hundred grams of salvarsan dihydrochloride are dissolved in 2500 c.c. of distilled water, and the solution is agitated for 2–3 hours, at 15°–20°, with 43 grams (1 mol.) of freshly precipitated silver bromide. Antimony trichloride (1 mol.) 52 grams, is then added, and dissolved by warming the solution, which is then treated with 30 grams of citric acid dissolved in 100 c.c. of water. Addition of 50 grams of pure concentrated sulphuric acid dissolved in 250 c.c. of water then precipitates luargol.

Luargol is an orange-yellow powder containing 20·6 % As ; 7·4 % Ag ; 5·52 % Br ; and 8·19 % Sb.

It is insoluble in water, and for injection purposes is dissolved in sodium hydroxide solution (0·4 gram NaOH to 1 gram luargol). Luargol has been found to be very effica-

cious in treatment of *Trypanasoma surra* and *Tr. gambiense,* and for sleeping sickness and syphilis.

Disodio Luargol (Poulenc) is readily soluble in water, and is a convenient form of administration of this drug.

GALYL (4 : 4′ dihydroxy-arsenobenzene-3 : 3′-phosphamic acid).

$$
\begin{array}{c}
\text{OH} \qquad\qquad\qquad \text{OH} \\
\overset{\displaystyle\bigcirc}{}\text{NH}\diagup\text{PO·OH}\diagdown\text{NH}\overset{\displaystyle\bigcirc}{} \\
\text{As}=\!=\!=\!=\!=\!=\!=\text{As}
\end{array}
\quad\text{or}\quad
\begin{array}{c}
\text{OH} \qquad\qquad \text{OH} \\
\text{NH}\diagup\text{PO·OH}\diagdown\text{NH} \\
\text{As} \qquad\qquad \text{As} \\
\| \qquad\qquad \| \\
\text{As} \qquad\qquad \text{As} \\
\text{NH}\diagdown\text{PO·OH}\diagup\text{NH} \\
\text{OH} \qquad\qquad \text{OH}
\end{array}
$$
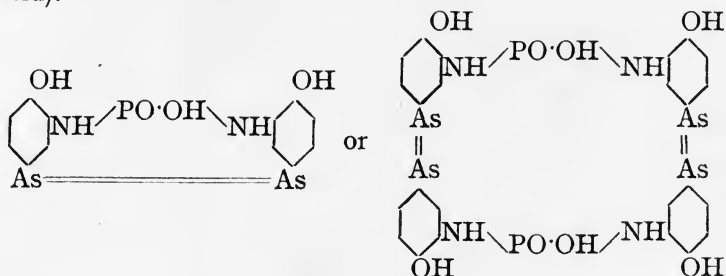
Galyl is prepared (E. P. 9234/1915) by condensing 3-amino-4-hydroxyphenyl-arsinic acid with phosphorus oxychloride, and reducing the resulting phosphamic acid with sodium hydrosulphite. It was introduced by Mouneyrat.

3-Amino-4-hydroxyphenyl-arsinic acid
$$
\begin{array}{c}
\text{OH} \\
\overset{\displaystyle\bigcirc}{}\text{NH}_2 \\
\text{AsO(OH)}_2
\end{array}
$$
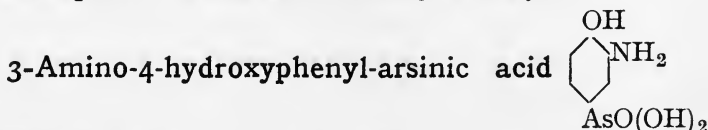
Mouneyrat (E. P. 3087/1915) prepared this compound by the electrolytic reduction of 3-nitro-4-hydroxyphenyl-arsinic acid.

Twenty grams of the nitro-acid are dissolved in 400 c.c. of normal caustic soda and the solution placed in the cathode compartment of an electrolytic cell, the anode liquor being 15 % caustic soda solution. The negative electrode is mercury, the positive electrode nickel. The cell is cooled by immersion in cold water. A current of 2 amps. at $3\frac{1}{2}$–4 volts is passed until a filtered portion of the cathodic liquor no longer affords a precipitate when treated with an excess of hydrochloric acid. About 5 hours is required. The solution is then allowed to stand for 24 hours, and neutralised exactly, to methyl orange, with hydrochloric acid. After cooling to 0° the precipitated acid is filtered off and purified

by dissolving in dilute hydrochloric acid, decolourising with animal charcoal, and reprecipitating by neutralisation with alkali.

It can also be prepared (E. P. 13485/1910) by dissolving 3-nitro-4-hydroxyphenyl-arsinic acid, 31·6 grams, in 600 c.c. of methyl alcohol, adding 840 grams of 4 % sodium amalgam, and digesting at 60°–80° until the evolution of gas has ceased. Part (450–500 c.c.) of the solvent is then distilled off, the residue mixed with 120 c.c. of water, and acidified with 150 c.c. of hydrochloric acid (sp. gr. 1·19). After standing for 12 hours the solution is filtered from impurities, boiled with charcoal, filtered, and neutralised with 52 c.c. of 10N. caustic soda, when the bulk of the amino acid is precipitated.

Jacobs, Heidelberger and Rolf (J. Amer. Chem. Soc. (1918), 40, 1580) effect the reduction with ferrous sulphate in the following manner. Ferrous sulphate, 440 grams, is dissolved in about 1320 c.c. of water, the solution chilled well, and treated, with vigorous stirring or shaking, in absence of air, with 25 % sodium hydroxide solution, until the mud reacts strongly alkaline to litmus paper. A solution of 58·4 grams of 3-nitro-4-hydroxyphenyl-arsinic acid in dilute caustic soda solution (1 mol.) is then added, and the mixture vigorously agitated for five minutes, without heating. The whole is then filtered and the ferric hydroxide mud washed with water. The filtrate is acidified with acetic acid, when the amino acid crystallises out. Yield 80 %.

4 : 4′-Dihydroxy-arseno-benzene-3 : 3′-phosphamic acid.—" Galyl," 3-amino-4-hydroxyphenyl-arsinic acid, 23.3 grams, is dissolved in 300 c.c. of water and 90 c.c. of caustic soda (36° Bé.). To the solution are added 350 c.c. of 90 % alcohol, after which are introduced at 0°, with cooling and stirring, 27 c.c. of phosphorus oxychloride. The liquor is then neutralised by the addition of 18 c.c. of caustic soda (36° Bé.) and poured into a solution of 100 grams of crystallised magnesium chloride and 500 grams of sodium hydrosulphite in 1800 c.c. of water. The mixture is heated for 4 hours at 50°, after which the phosphamic acid is precipitated, filtered off, washed, and can be converted into the sodium salt by

being dissolved in sodium carbonate and poured into alcohol. It is dried *in vacuo* over sulphuric acid.

ORGANIC ANTIMONY COMPOUNDS.—Although most of the antimony analogues of the organic arsenicals have been prepared, none has yet been discovered that approaches in specific therapeutic effect the arsenic compounds of the salvarsan type. So far, only one antimony preparation, sulphoform, has retained a position in medicine.

SULPHOFORM (Triphenyl-stibine sulphide) $(C_6H_5)_3SbS$. 383.—Sulphoform is prepared by treating triphenyl-stibine dichloride, or dibromide, with ammonium sulphide.

Thirty parts of sliced sodium are covered with 100 parts of dry benzene, in a cast-iron vessel provided with a reflux condenser, stirring gear, and a jacket through which can be circulated either cooling water or steam. The mixture is warmed to about 70°, when a solution of 40 parts of distilled antimony chloride and 60 parts of monochlorbenzene in 100 parts of benzene is allowed to flow in, at such a rate that, without further application of heat, the benzene is kept gently boiling by the heat evolved by the reaction. If it becomes violent the addition is suspended, and cold water circulated through the jacket. When all has been added, the mixture is boiled for several hours to complete the interaction. After cooling, the solution is filtered from sodium chloride and unchanged sodium, and the benzene removed by distillation. The residue, which solidifies, consists mainly of triphenyl-stibine, together with a little diphenyl-stibine chloride and phenyl-stibine dichloride. It is dissolved in light petroleum and treated, whilst being cooled and stirred, with bromine (1 mol.). Triphenyl-stibine bromide $(C_6H_5)_3SbBr_2$ separates out in crystals. M.p. 216°.

It may be purified by recrystallisation from glacial acetic acid.

$$3C_6H_5 + SbCl_3 + 6Na \rightarrow (C_6H_5)_3Sb + 6NaCl$$
$$(C_6H_5)_3Sb + Br \rightarrow (C_6H_5)_3SbBr_2$$
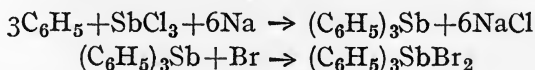
Triphenyl-stibine sulphide.—Ten parts of triphenyl-stibine bromide are dissolved in 160 parts of a cold alcoholic

solution of ammonia, saturated at room temperature. The solution is filtered and treated, whilst being stirred, with purified hydrogen sulphide until a permanent faint yellow colouration is obtained. The precipitated crystals are filtered off, washed successively with alcohol and petroleum, and air-dried.

Sulphoform forms white needles, fusing at 119°–120°. It is readily soluble in benzene, chloroform, and acetic acid, sparingly so in alcohol, and very slightly soluble in ether, petroleum ether, or olive oil. Sulphoform is employed in treatment of skin diseases such as eczema, psoriasis, and seborrhœa.

PROTEIN COMPOUNDS CONTAINING SILVER.—Silver compounds are employed in medicine to produce caustic, astringent, germicidal, and antiseptic effects. For creating caustic and astringent effects silver nitrate is preferred, as the organic compounds of silver are lacking in caustic properties. This salt, however, coagulates protein, which is undesirable when it is necessary to create antiseptic conditions. Irritation is thereby caused and the penetration of the germicide is lessened.

It has been found that soluble compounds containing silver, in which the metal is non-ionised, are produced by digesting the insoluble compounds which silver salts and proteins form when interacted with solutions of albumoses. The resulting bodies possess the antiseptic and germicidal action of silver nitrate and are relatively non-irritant, as they do not coagulate protein. They are used for treatment of affections of the sensitive mucous membranes of the urethra, the eye, ear, nose, and throat.

Protargol is the most generally used of these silver protein compounds; it contains 8·3 % Ag. Others that may be mentioned are argyrol, 30 % Ag.; argonin, 4·2 % Ag.; albargin, 15·0 % Ag.

PROTARGOL. (E. P. 18478/1897).—A concentrated aqueous solution containing 4·4 parts of protalbumose is stirred into a solution of 1 part of silver nitrate in 1·5 parts of water. The precipitate thus obtained is filtered, washed with water,

and without being previously dried is introduced into a warm solution of 5 parts of deutero albumose in 4·5 parts of water. On heating at 95° for some time a clear solution results ; this is evaporated to dryness under reduced pressure.

Protargol is a light-brown powder, soluble in 2 parts of water. It should be kept in well-stoppered amber bottles.

A 1 per cent. aqueous solution should give no precipitate with alkalis, sodium chloride, or ammonium sulphide solutions. The solution yields the biuret reaction when mixed with an equal volume of 10 per cent. caustic alkali and a drop or so of dilute copper sulphate solution. On ignition a residue of about 8 % of metallic silver should be obtained. Protargol is successfully employed in treatment of gonorrhœa and gonorrhœal ophthalmia. It is a powerful antiseptic and germicide.

ARGONIN (E. P. 22191/1894 ; D. R. P. 82951).—Three kilos of the sodium salt of casein, containing no free alkali, are mixed with 300 grams of silver nitrate, and the mixture dissolved in hot water. The solution is then evaporated to dryness *in vacuo*, when a white solid is obtained which is soluble in water, giving a neutral reaction. As an alternative method of procedure the aqueous solution is poured into alcohol, when the argonin is precipitated.

Argonin contains about 4 per cent. of silver. It is used in the treatment of gonorrhœa and in ophthalmic practice.

ORGANIC MERCURY COMPOUNDS.—The great value and efficiency of inorganic mercury compounds in the treatment of syphilis and as antiseptics have stimulated a vast amount of research in order to discover organic compounds of the metal which should have equal or greater antisyphilitic properties, and which should be free from the many disadvantages possessed by mercury itself and its inorganic derivatives. Mercuric salts, such as mercuric chloride, have an extremely high bactericidal power. Their use, however, is limited by their high toxicity and the property they possess of coagulating albumen, which causes them to be extremely irritant. A further drawback is that solutions of mercury

salts must not be brought into contact with metallic instruments, which otherwise will be attacked, and coated with metallic mercury.

Mercurous salts and mercury itself are insoluble in water or other media, and are therefore non-toxic. Their physiological action depends, in all probability, upon the gradual formation from them of soluble mercuric compounds. Relatively large doses have to be administered in order to register the required therapeutic effect, and it not infrequently happens that a dose that for the majority of patients is normal will produce in some, in whose metabolism, presumably, the oxidation to mercuric derivatives takes place with abnormal rapidity, the symptoms of mercury poisoning.

Further, the administration of these insoluble compounds, usually effected by intramuscular injection, is often accompanied by severe local pain. Remarkably slight success, however, has attended the efforts to discover organic mercury derivatives which are therapeutically effective and yet devoid of the effects mentioned.

Many compounds, soluble in water or an alkali, in which the mercury is non-ionised, have been successively introduced into medicine, but almost without exception their use has been ephemeral.

Mercury salicylate, almost the first of this class of compound to be employed, still remains unsuperseded ; it finds, however, only a limited use. Others that may be mentioned are : Mercury succinimide $(C_2H_4(CO)_2N)_2Hg$ (Hydrargol) ; Asurol, a double compound of mercury salicylate and sodium hydroxyisobutyrate ; Hydrargyrol, mercury phenol-parasulphonate ; Asterol, a double salt of Hydrargyrol with ammonium tartrate ; and Afidol, the sodium salt of oxymercury ortho-toluic acid, the last named substance being employed as the active constituent of a disinfectant soap.

MERCURY SALICYLATE $C_6H_4{<}^{O-}_{COO}{>}Hg$.   336.—One molecular equivalent of salicylic acid, 138 parts, is mixed with freshly precipitated mercuric oxide, 216 parts (1 mol.) and 500 parts of 1 % acetic acid solution. The

mixture is heated at 90°–100°, with continuous stirring, until the red colour of the mercuric oxide has disappeared. The resulting white amorphous precipitate is filtered off, washed with water, and dissolved in 10 % caustic soda solution, about 400 parts (1 mol.) of which will be required. After filtration the clear filtrate is treated, whilst being stirred, with dilute acetic acid, when the mercury salicylate is precipitated. It is filtered, washed, and dried, in absence of light, at a low temperature. Mercury salicylate is a white, or pinkish-white, powder, insoluble in water and in alcohol. It dissolves to a clear solution, from which it is reprecipitated unchanged by acetic acid.

Mercury salicylate does not answer the tests distinctive of mercury salts. It gives no precipitate when treated with ammonium sulphide or hydrogen sulphide.

It should afford no residue on ignition, and should contain not less than 57·4 % of mercury.

It is an antiseptic and antisyphilitic. It is employed internally, being well tolerated by the stomach, and does not set up salivation. Occasionally, however, gastro-intestinal irritation is produced, even when administered by intramuscular injection. Externally it is used as a dusting powder, in treatment of syphilitic sores and certain other diseases of the skin.

Mercury Succinimide $\begin{array}{c} CH_2CO \\ | \\ H_2CO \end{array}\Big\rangle N\text{–}Hg\text{–}N\Big\langle \begin{array}{c} COCH_2 \\ | \\ COCH_2 \end{array}$ 376.
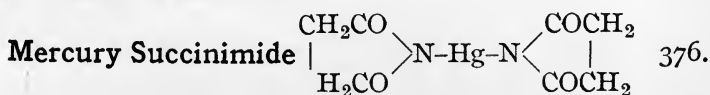
—Succinimide, 19·8 parts (2 mol.), is dissolved in 40 parts of 20 % sodium hydrate solution and treated with a concentrated aqueous solution containing 31·8 parts of mercuric acetate (1 mol.). The precipitate which is formed is dissolved by boiling, as much more water being added as is necessary, the solution filtered and cooled, when mercury succinimide crystallises out.

Alternatively, 19·8 parts of succinimide are heated at 100°, whilst being stirred, with 21·6 parts of freshly precipitated mercuric oxide and 100 parts of water, until the red colour has disappeared. Boiling water is then

added until the white precipitate has dissolved, the solution filtered and allowed to cool and crystallise.

Mercury succinimide is a white crystalline powder, soluble in 28 parts of cold water. The aqueous solution does not precipitate albumen, but the mercury is ionised, and reacts to hydrogen sulphide, iodides, and alkalis. Mercury succinimide is employed in syphilis, administered by hypodermic injection. It has also been employed, with good result, in pulmonary tuberculosis.

Section X.—THE DIGITALIS GROUP, SKIN IRRITANTS, GLUCOSIDES, AND NEUTRAL PRINCIPLES

In the present chapter active natural glucosides are dealt with, of chief importance among which is the group of heart tonics generally classified under digitalis. The plants commonly employed in medicine in this connection are digitalis, strophanthus, and squill, but others in less use contain similar active glucosides: black hellebore, *Convallaria majalis, Apocynum cannabinum,* may be mentioned, but there are many others. The chemical examination of these herbs has not been satisfactorily completed, though much work has been done, especially upon digitalis. The fact remains, even in this case, that the most satisfactory medicament is the unpurified tincture of the drug, although the latter is notoriously variable in its activity and subject to rapid deterioration. To meet this difficulty, physiologically standardised tinctures of digitalis, strophanthus and squill are usually employed. The method of physiological standardisation employed is based upon the determination of the minimum lethal dose to a frog. Such a criterion is obviously empirical and unsatisfactory, and there is need of greater knowledge of the chemical constituents of these drugs and the methods of administering them.

The therapeutic use of skin irritants dates from very early times; they are valuable in the relief of pain. Very little is known of the rationale of their action. In addition to cantharidin and oil of mustard, which are referred to in this chapter, *Rhus toxicodendron,* or poison ivy, capsicum, and euphorbia are employed, and many other plants possess this property.

Cantharidin and capsicum exert very marked blistering

action upon the skin. $\beta\beta$-dichlorodiethyl sulphide, employed as a lethal " gas " in the war under the name of " mustard gas," possesses this blistering property in greater degree than any other known substance.

Digitalis and its Principles

The official digitalis of the British Pharmacopœia consists of the dried leaves of *Digitalis purpurea*, L., collected from plants of the second year's growth, as they are commencing to flower, but the time of collection does not greatly affect their activity.   Other species of digitalis are active, especially the wild Spanish variety.

Digitalis is a cardiac and circulatory stimulant and tonic, also a diuretic.   It increases the strength of the cardiac contractions and reduces the pulse rate without diminishing tension, acting directly on the heart muscle.   It is of great value as a heart stimulant in acute pneumonia, and in mitral disease.

It is used as a diuretic in cardiac and renal dropsy.

In Great Britain the infusion and tincture are chiefly employed.   They should be prepared from carefully dried leaves.   Moist leaves rapidly lose their activity.

Infusion of Digitalis is prepared from digitalis leaves. To 60 grains of leaves, in No. 20 powder, are added 20 fl. oz. of boiling distilled water.   The mixture is strained after being infused for 15 minutes.

Tincture of Digitalis is prepared by percolating $2\frac{1}{2}$ parts of dried digitalis leaves with 60 % alcohol, to yield 20 parts.

The preparation of the following partly purified principles, which occur in commerce, will be described.

(1) Digitalin Nativelle (crystallised digitalin).
(2) Digitalin Homolle (French digitalin).
(3) Digitalin Germanicum (German digitalin).
(4) Digitalin Verum (Kiliani).
(5) Digitoxin.
(6) Gitalin (Kraft).

DIGITALIN NATIVELLE.— One   thousand   grams   of

powdered digitalis leaves are mixed with 100 grams of a solution of 250 grams of neutral lead acetate in a litre of water. After 24 hours the mass is extracted with 50 % alcohol. The extract is treated with a saturated aqueous solution containing 40 grams of sodium bicarbonate, freed from alcohol by distillation, and concentrated until it weighs 2000 grams. When quite cold it is diluted with an equal volume of water. The precipitate is collected, suspended in 100 grams of 80 % alcohol, heated to boiling and treated with 10 grams of lead acetate. After cooling, the liquor is filtered, mixed with 50 grams of powdered animal charcoal, freed from alcohol, evaporated to dryness, and the dry residue powdered. It is extracted exhaustively with hot chloroform, and, on removal of the solvent, crude digitalin is obtained. It is purified by being dissolved in 100 grams of 90 % alcohol, treating the solution with 10 grams of purified charcoal and a concentrated aqueous solution containing 1 gram of lead acetate, boiling for 10 minutes, filtering, and washing the solid portion with alcohol. From the combined filtrate and washings the alcohol is removed completely, and the residue is extracted with ether, in order to remove fat. It is then taken up in 8 parts of hot 90 % alcohol, and the solution mixed, after being cooled, with 4 parts of ether and 8 parts of water. On standing, digitalin crystallises out in loose white glistening needles.

Digitalin Nativelle is sparingly soluble in water and ether, dissolves easily in chloroform. It is stated to consist largely of digitonin, which is devoid of " digitalis " action, but to contain at times much digitoxin.

DIGITALIN HOMOLLE (amorphous digitalin).—One hundred parts of powdered leaves are moistened with 1000 parts of water, and slowly exhausted, cold, in a percolator, until 3000 parts of percolate have been obtained.

This is treated with 250 parts of lead acetate, and the filtrate from the resulting precipitate freed from lead by treatment with 40 parts of crystallised sodium carbonate and 20 parts of sodium ammonium phosphate. After filtration, the liquor is precipitated with 40 parts of tannic

acid. The moist tannate is intimately mixed with 25 parts of powdered litharge and 50 parts of purified animal charcoal, after which it is dried. The dried mass is extracted with 90 % alcohol, which dissolves out the digitalin compounds. The solvent is distilled off, and the residue washed with water, after which it is redissolved in alcohol (90 %), filtered, and the solvent again removed. The residue is extracted with chloroform, and, on distilling off the latter, after filtering, the digitalin is obtained.

A yellowish-white amorphous powder, possessing a peculiar aromatic odour. It is soluble in alcohol and chloroform, and almost insoluble in water and ether. It is stated to consist mainly of digitalin, with some digitoxin.

DIGITALIN GERMANICUM.—German digitalin is prepared from the seeds of *Digitalis purpurea*, not from the leaves. An alcoholic extract is made, and is treated with lead acetate solution. The filtrate is freed from lead by means of disodium hydrogen phosphate. Digitalin is precipitated in combination with tannic acid, and the tannate, after being washed, decomposed with litharge or zinc oxide. The solution is evaporated to dryness, and the residue purified by crystallisation from dilute methyl alcohol. German digitalin is stated to consist principally of digitalein, with some digitalin and digitonin. It is readily soluble in water and almost insoluble in chloroform.

DIGITALIN VERUM.—One part of German digitalin is dissolved in 4 parts of 95 % alcohol. Five parts of ether (·720) are added, and the mixture is allowed to stand in a closed vessel for 24 hours. An estimation is made of the quantity of solid dissolved in the clear supernatant solution, and this, after decantation, is concentrated under reduced pressure until the total weight is 1·6 times that of the dissolved portion.

Water, 2·4 times the weight of the dissolved substance, is added, and, on standing, digitalin gradually separates. It is filtered off, washed with 10 % alcohol, then with water, and finally dried at a moderate temperature.

Digitalin Verum is a white amorphous powder.

M.p. 217° It dissolves in 1000 parts of water, and 100 parts of 50 % alcohol. It is insoluble in ether and chloroform.

DIGITOXIN $C_{34}H_{54}O_{11}$.—Digitalis leaves are lixiviated with cold water, filtered, pressed, and extracted with 50–60 % alcohol. The alcoholic solution is precipitated with lead acetate, excess of lead being removed from the filtrate by means of ammonia. The lead-free filtrate is concentrated under reduced pressure. Crude digitoxin slowly crystallises out from the residue. It is collected, dried, and redissolved in chloroform, from which it is obtained again in a pure form on distilling off the solvent. After being washed with ether it is purified finally by crystallisation from 80 % alcohol.

Digitoxin crystallises in pearly plates or needles, melting at 240°. It is readily soluble in alcohol, less soluble in chloroform, very sparingly in ether, and insoluble in water.

Digitoxin is the most toxic of the constituents of digitalis, and is cumulative in its action. Its sparing solubility and the narrow difference between the therapeutic and the toxic dose militate against its practical value. The presence of other glucosides of digitalis increases its solubility.

Digitalin Nativelle is also said to be a dangerous preparation on account of the presence of digitoxin.

GITALIN $C_{28}H_{48}O_{10}$.—Powdered digitalis leaves are extracted with cold water and the decoction is precipitated, first with lead acetate, and then with sodium phosphate solution. The clear filtrate is then treated with tannic acid and the collected precipitate is decomposed with zinc oxide, and extracted with methyl alcohol. The extract is carefully dried, dissolved in water and extracted with chloroform. Gitalin crystallises from the concentrated chloroform extract.

Gitalin is a glucoside which affords digitoxose and anhydrogitaligenin on hydrolysis. It has m.p. 150°–155°, is soluble in 600 parts of water, and readily dissolved by most organic solvents. It is said to possess to a greater degree than any other of the digitalis preparations the characteristic medicinal action of digitalis. Digitalis

Homolle and Digitalis Verum are also valued in clinical practice.

Digitalin dissolves in concentrated hydrochloric or sulphuric acid, giving a golden-yellow solution, the colour in the latter case changing rapidly to blood-red. On adding to the solution whilst still yellow a drop of either nitric acid, ferric chloride, or bromine water, a brilliant purple colouration is produced.

Digitoxin does not give the colour reaction of digitalin with concentrated sulphuric acid.

If when dissolved in acetic acid, to which has been added 1 % of a 5 % solution of ferric sulphate, there is poured sulphuric acid containing the same quantity of ferric sulphate so as to form a layer beneath it, a blue colour is gradually developed in the acetic acid, whilst the sulphuric acid remains colourless. None of the other digitalis compounds affords this reaction.

STROPHANTHUS AND STROPHANTHIN.—The strophanthus seeds of commerce consist of a mixture derived from different species. Officially the dried ripe seeds of *Strophanthus Kombé* are specified : actually the *S. Kombé* seeds of commerce commonly are mixed with those of *S. hispidus*, *S. gratus*, etc.

Strophanthus Kombé seeds yield from 3 to 4 % of ash. If a section of the seed be immersed in a mixture of 8 parts of sulphuric acid (1·84), and 2 parts of water, a deep green colour rapidly appears in the albumen surrounding the embryo, to which the colour rapidly extends. The galenical preparation of strophanthus—the tincture—is more widely employed than its active principle—strophanthin, though the latter exhibits the characteristic action of the drug and is soluble.

Tincture of Strophanthus.—One part of strophanthus seeds in No. 30 powder is percolated with alcohol, 70 %, until 20 parts are obtained, and diluted with alcohol of the same strength, to yield 40 parts.

Assay.—A measured quantity of 50 c.c. of the tincture is diluted with 50 c.c. of water and the alcohol removed by

distillation. The filtered aqueous liquid, after being shaken with chloroform, is digested for 1 hour on a water bath with dilute sulphuric acid ; after cooling, the turbid liquid is agitated with 3 successive small quantities of chloroform. The chloroform extracts are transferred to a tared flask, the solvent removed by distillation, the residue of strophanthidin dried below 60° and weighed. The percentage of strophanthidin found when divided by 0·365 gives the percentage of strophanthin present.

S. Kombé contains 2·3 % of strophanthin ; *S. hispidus* 1·5 to 3·5 % ; *S. gratus* about 3·6 %.

STROPHANTHIN.—The strophanthin from seeds of different botanical species is said to differ both physiologically and chemically. The explanation probably lies in the fact that, as prepared technically, the product is not a pure substance, but a mixture of glucosides, the proportions in the mixture as obtained from seeds of different species, and possibly even from the same variety at different times, exhibiting variations.

Strophanthin may be prepared by the following method :—

The powdered seeds are defatted with petroleum ether or carbon disulphide, and extracted with alcohol. The solvent is removed from the extract by distillation, and the residue taken up with water. The filtered solution is treated with tannic acid, when the glucosides are precipitated in combination with this substance. The precipitate is collected, washed with water, mixed with an excess of basic lead acetate, and dried at a gentle heat. The dry mass is extracted with alcohol, the extract freed from lead by hydrogen sulphide and evaporated. The residue is crystallised from methyl alcohol, or is dissolved in alcohol and precipitated by ether.

Hefter and Sachs (*Biochem. Zeits.* (1912), **40**, 83) proceed as follows :—

An alcoholic extract of the seeds is prepared, and the alcohol removed by distillation. The residue is treated with water and the aqueous solution purified by precipitation

with lead acetate. The filtrate is freed from excess of lead and evaporated to a syrup in the presence of an excess of calcium carbonate. The calcium carbonate is filtered off and the glucoside precipitated by the addition of a large excess of ammonium sulphate. It is purified by repeatedly being dissolved in alcohol and reprecipitated by ether.

By this procedure practically identical glucosides have been obtained from *S. Kombé* and *S. hispidus*, the only difference noted being a slight one in the optical rotation. By extracting the calcium carbonate precipitate, obtained as above, with hot water, a crystalline glucoside was obtained from seeds of the *Kombé* plant. It possessed very similar physiological action to that of the amorphous glucosides, differing only inasmuch as it possessed a slight hæmolytic action ; and, like them, it yielded strophanthidin on hydrolysis. Optical rotation $[a]_D + 28 \cdot 7°$. Strophanthin is met with as a pale yellow amorphous powder or in the form of microscopic white crystals. M.p. (anhydrous), 170°.

It is readily soluble in water and alcohol, and is practically insoluble in chloroform, ether, petrol-ether, and carbon disulphide. No close agreement as to the empirical formula of strophanthin has been reached, but it is regarded generally to be $C_{40}H_{50}O_{16}$.

The solution is dextro-rotatory ; Hefter and Sachs (*loc. cit.*) give $[a]_D + 11 \cdot 87°$ for the glucoside from the *Kombé* plant, and $[a] + 13 \cdot 9°$ for that from *S. hispidus*.

Strophanthin from *S. gratus* is sparingly soluble in water (1 : 100 at 15°), fuses at 187°–188°, and is lævo-rotatory.

Ouabain, the active principle of *Acocanthera Schimperi* (Oliv.), is identical with strophanthin from *S. gratus*.

Strophanthus is a cardiac tonic. It acts more energetically on the heart than on the vessels, whereas digitalis acts on the vessels as much as, or even more than, on the heart. Strophanthus is therefore preferred in cases in which arterial tension is already high, as digitalis increases it. Strophanthus is valuable in mitral regurgitation, accompanied by cardiac insufficiency. It acts with greater rapidity than

digitalis, being very soluble and diffusible, and is more useful than the latter in promptly stimulating sudden cases of cardiac failure. It is not cumulative, and, unless there be gastro-intestinal catarrh, has no tendency to produce digestive disturbances.

SQUILL.—Squill is the sliced dried bulb of *Urginea Scilla* (Steinh.) ; it is obtained from the coast of the Mediterranean.

Dried squill is very hygroscopic ; it should be kept thoroughly dry in order to preserve its medicinal activity unimpaired. No active principle suitable for use in medicine has been isolated from squill. The chief preparations employed are the tincture and the acetic acid extract.

Tincture of Squill is prepared by macerating bruised squill, 1 part, with 5 parts of 60 % alcohol, and straining. *Acetum Scillæ* results from macerating squill, 1 part, acetic acid, 1 part, and water, 3·2 parts.

The active principle (scillain, scillitoxin) is a non-nitrogenous glucoside.

For its isolation, the disintegrated dried drug is digested for 1–2 days with water, the extract is treated with lead acetate, and after removal of excess of lead, the filtrate is precipitated with tannic acid. The precipitate is washed with water, treated with alcohol and zinc oxide and evaporated to dryness.

The dried mixture is extracted with boiling alcohol, and from the extract, after removal of the solvent by distillation, the glucoside is obtained. The product is a yellow, amorphous powder, possessing a bitter taste. It is readily soluble in alcohol ; sparingly so in water, ether and chloroform. It possesses a similar physiological action to that of digitalin. Kopaczewski (*Compt. rend.* (1914), **158**, 1520) isolated from *Scilla maritima* an active principle which he named *Scillitin*. It melted at 152°-154°, and was not obtained crystalline.

Squill is a stimulant expectorant, and a diuretic and cardiac tonic. It increases the secretion of the bronchial mucous membrane, and is used, with other expectorants, in

chronic bronchitis with scanty secretion. It is too irritant for use in acute bronchitis. Squill increases the force of the heart more than either digitalis or strophanthus; it slows the heart more, and causes more constriction of the coronary vessels. It is preferred in cases where the blood pressure requires to be raised.

SALICIN $C_6H_{11}O_5 \cdot O \cdot C_6H_4 \cdot CH_2OH$.—Salicin is a glucoside of ortho-hydroxy-benzyl-alcohol, and is found in the bark of various species of *Salix, e.g., S. pentandra, S. helix, S. præcox. S. nigra* yields about 0·7 % of salinigrin, which is the glucoside of meta-hydroxy-benzaldehyde.

To prepare salicin the powdered bark is extracted with boiling water, the extract is concentrated *in vacuo* and purified by precipitation with lead acetate. After filtration, excess of lead is removed from the filtrate, which is then made neutral with ammonia and concentrated to a syrup. On standing, salicin slowly crystallises out. It is purified by recrystallisation from water, employing charcoal as a decolourising agent. A second crystallisation, from alcohol, may be given if necessary.

Salicin forms colourless, tabular, or slender acicular crystals, possessing very little taste. M.p. 200°.

It dissolves in 28 parts of water and in 82 parts of alcohol (90 %). The aqueous solution is neutral towards litmus.

Salicin is an antipyretic, antiperiodic, tonic and bitter stomachic. It is better tolerated by the stomach, and is less depressant, than sodium salicylate, by which, however, it has been largely replaced in medicine. Salicin has been recommended as a prophylactic against influenza, and for its cure.

CANTHARIDIN $C_{10}H_{12}O_4$. 196.—Cantharidin is the active principle of the beetle, *Cantharis vesicatoria*, which is found in Spain, France, Russia, Sicily and Hungary, also of *Mylabris phalerata* (Chinese cantharides), and other species of Mylabris. The dried beetles contain, according to the species, from 0·6 to 1·0 % of cantharidin.

The cantharidin is extracted from the crushed beetles with a solvent, a little hydrochloric or acetic acid being

added to liberate the cantharidin from its salts. Benzene and acetone are satisfactory and cheap solvents to employ. The residue, after removing the solvent from the extract, is treated with petrol-ether, in which cantharidin is insoluble, to remove fatty substances ; it is then crystallised from chloroform, alcohol or glacial acetic acid.

Another method of procedure is afforded by D. R. P. 233467. Thirty kilos of the powdered insects are mixed with 6 litres of absolute alcohol, containing 25 % of dry hydrogen chloride, and the mixture allowed to stand at below 50°, with frequent agitation. It is then extracted with a boiling mixture of 5 vols. of benzene and 2·5 vols. of petrol-ether (b.p. 50°–90°). After extraction, the solvent is removed at the lowest possible temperature, and the mixture dissolved in a hot mixture of 1 vol. of absolute alcohol and 9 vols. of petroleum ether. The cantharidin crystallises out after cooling.

[With regard to this process it may be remarked that, cantharidin being a carboxylic acid, it would seem likely that the foregoing procedure would result in part of it, at any rate, being transformed into its ethyl ester.]

Cantharidin forms white, crystalline scales. M.p. 218°.

It is very slightly soluble in water, but dissolves in alkalis, forming salts ; it is soluble in 1150 parts of cold alcohol, 55 parts of chloroform, and in 700 parts of ether (rect.).

It should dissolve without change of colour in concentrated sulphuric acid, from which it is precipitated unchanged on dilution with water. Cantharidin is a powerful vesicant, or blistering agent. It is employed for treatment of deep-seated inflammations, such as in pleuritis, pericarditis, pneumonia, sciatica, etc. ; internally, in small doses, it is diuretic and aphrodisiac.

OIL OF MUSTARD.—Oil of mustard consists of not less than 92 per cent. of allyl isothiocyanate C_3H_5CNS. It is derived from the dried seeds of *Brassica nigra* by distillation. The latter contain a glucoside, senigrin, which is hydrolysed to allyl isothiocyanate and a sugar.

Allyl isothiocyanate may be produced synthetically by

interaction of allyl iodide and potassium thiocyanate. Molecular quantities of the two latter are dissolved in alcohol and water to make a clear solution and boiled, using a reflux condenser, for several hours. The reaction mixture is gently distilled to remove alcohol, water is added, and the oil separated. Oil of mustard is a skin irritant employed as a rubifacient and counter-irritant in the relief of pain. Prolonged application causes vesication.

THIOSINAMIN (allyl thio-carbamate) $C_3H_5NH \cdot CS \cdot NH_2$, 116, is derived from allyl isothiocyanate by the action of alcoholic ammonia. It forms white crystals soluble in water, 1 in 18, and in alcohol, 1 in 2. It is employed usually in conjunction with sodium salicylate to reduce fibrous ankylosis of joints and for the removal of fibroid tissues.

LECITHIN.—Lecithin is a choline compound of stearyl-glycero-phosphoric acid ; it is a common constituent of animal cells and of the seeds of plants. It is of the class of substances, extracted by alcohol from cells, generally termed lipoids. Lipoids containing phosphorus are called phosphatides or phospholipines.

Lecithin is chiefly prepared from egg yolk, but processes have been protected for extracting it from beans and peas and from the sprouts of germinating wheat.

Preparation of Lecithin from Yolk of Egg.—The first practical method for the isolation of lecithin in a reasonably pure form was given by Bergell (*Ber.* (1900), **42**, 2584).

The yolks (approx. 2·2 kilos) of about 150 eggs are mechanically separated and extracted for 6 hours by boiling with 10 litres of 96 % alcohol. The solution is cooled slowly to 0°, and treated with an alcoholic solution containing 40 grams of cadmium chloride. After being allowed to stand for several hours, the crystalline precipitate is filtered off, washed with 96 % alcohol, air dried, and extracted with ether. It is then refluxed with eight times its weight of 80 % alcohol and treated with the correct quantity (about 25 grams) of ammonium carbonate in concentrated solution, until the liquor has a distinct alkaline reaction, and the filtrate from a test portion is found to be free from cadmium.

It is then filtered whilst hot, and the filtrate cooled to
—10°. The lecithin, in the form of a treacly substance,
separates during several hours' standing. It is isolated by
decantation, washed by decantation with cold alcohol, dis-
solved in a small quantity of chloroform, reprecipitated
with acetone, and the precipitate filtered off and dried
in vacuo. A further quantity is obtained from the alcoholic
solution, by distilling off the alcohol, shaking out the
residue with chloroform, and, after washing the chloroform
solution with water, precipitating the lecithin contained
in it with acetone.

Yet more is obtained from the ether extract of the
cadmium precipitate. This is freed from cadmium with
ammonium carbonate, the lecithin isolated by freezing out,
and purified by precipitation with acetone from its solution
in chloroform. The total yield is 5 % of the weight of the
egg yolk.

Several methods have been protected by which the use
of cadmium chloride is avoided.

In D. R. P. 223593, ethyl acetate is employed as a solvent.
One hundred kilos of egg yolk are shaken, at 15°, with
500 kilos of ethyl acetate. The solvent layer is then
separated, filtered, and concentrated, the distillate being
used for another extraction of the yolk. This is repeated
until the ethyl acetate comes away colourless. The residue,
after removal of the solvent, is dried *in vacuo* until free from
solvent. It is obtained in the form of a powder, which
contains 35–40 % of lecithin, and is free from cholesterin.

A pure lecithin is obtained by dissolving the crude
product in warm ethyl acetate (40°–70°), from which it
crystallises out on cooling. 100 kilos of egg yolk yield
9–10 kilos of the purified lecithin.

In D. R. P. 260886 it is pointed out that lecithin is
unstable at temperatures higher than 50°. One hundred
kilos of yolk of egg are shaken for 3 hours, at atmospheric
temperature, with 100 kilos of methyl alcohol. After
standing overnight, the solvent layer is filtered, and the
residue extracted again in the same way with 100 kilos of

methyl alcohol. The combined extracts are separated from the fat which comes out on standing, concentrated under reduced pressure, and the residue is dried.

The purification of crude lecithin is carried out, according to D. R. P. 291494, by washing twice, by prolonged agitation, with acetone containing 10–15 % of water, and to which 0·5 to 1·0 % of sodium bicarbonate has been added, and then with pure acetone until it attains a waxy consistency, after which it is dried *in vacno* at a low temperature. A tasteless and odourless product is obtained by this procedure.

By D. R. P. 261212, one hundred kilos of egg yolk are mixed with 500 litres of 96 % alcohol and shaken for 24–48 hours, at ordinary temperature. The solution, after separation and filtration, is mixed with one third its volume of a 1 % to 2 % solution of sodium chloride. The lecithin separates in a gelatinous layer, mainly on the surface of the solution, during a long period of standing, after which it is filtered off and dried at 30°.

19–20 kilos of this product (stated to be pure lecithin) are yielded by 100 kilos of egg yolk.

The Extraction of Lecithin from Seeds.—(*a*) *From Wheat Embryo* (D. R. P. 179591): Four parts of wheat embryo, dried at 70°, are deprived of fat by exhaustion with 20 parts of petrol-ether (b.p. 55°–57°). The mass is freed from solvent and extracted completely with 10 parts of hot alcohol (95 %). A clear brown honey-like syrup, which contains lecithin together with proteid matter, etc., separates. Part of the alcohol is removed by distillation, and the residue is diluted with water until the alcohol content is 70 %. Alcohol (70 %) is added, if necessary, so that one part of extractive (estimated by evaporation of an aliquot portion) is dissolved in 10 parts. The solution is warmed and treated with a hot 10 % solution of barium chloride so long as a precipitate continues to be produced. After cooling, the crude lecithin which is precipitated is collected and purified by solution in 5 parts of chloroform, filtration from insoluble matter, and removal of the solvent, preferably *in vacuo*.

(*b*) *From Peas and Beans* (D. R. PP. 200253, 210013):

One hundred kilos of dried shelled peas are boiled for 4 hours with 150 to 200 litres of 96 % alcohol. The extract, after filtration, is concentrated to one half its volume, and water added to reduce the alcohol content to 85 %. On standing, the lecithin, which is only sparingly soluble in alcohol of this strength, separates out as a gelatinous mass. This is separated, washed with a little cold 96 % alcohol in order to remove last traces of fatty and bitter principles, and dried *in vacuo*. 1 to 1½ kilos are afforded by 100 kilos of peas.

The lecithin from plants, however, seems not to be identical with that of animal origin.

Lecithin is a translucent, yellow or yellowish-white, hygroscopic, waxy solid. It is completely soluble in chloroform.

Lecithin is employed to improve general conditions in neurasthenia, and generally as a nerve tonic. Bain (*Lancet*, April 6, 1912) states that lecithin is a valuable drug in anæmia and debility ; it acts as a metabolic stimulus. Its good effect on the nervous system is attributable to improvement in general nutrition and not to its being a good "brain-food." Its most striking effect is on the blood, red and white corpuscles (especially lymphocytes) and hæmoglobin being all increased. With phytin (plant lecithin), on the other hand, unsatisfactory results were obtained.

α- AND β-GLYCEROPHOSPHORIC ACID

$$
\begin{array}{ccc}
CH_2O \cdot PO(OH)_2 & & CH_2OH \\
| & & | \\
CHOH & \text{and} & CHO \cdot PO(OH)_2 \\
| & & | \\
CH_2OH & & CH_2OH
\end{array}
$$
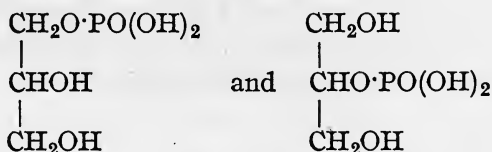
The following salts of glycerophosphoric acid are employed, as well as the acid itself, in medicine : sodium, calcium, potassium, magnesium and iron glycerophosphates. The sodium salt, moreover, is met with in two varieties, a handsomely crystalline compound containing 5 molecules of water of crystallisation, and a syrup containing 50 % or 75 % of anhydrous sodium glycerophosphate.

Two isomeric glycerophosphoric acids, α and β, can exist,

$$
\begin{array}{ccc}
\text{CH}_2\text{O·PO(OH)}_2 & & \text{CH}_2\text{OH} \\
| & & | \\
\text{CHOH} & \text{and} & \text{CHO·PO(OH)}_2 \\
| & & | \\
\text{CH}_2\text{OH} & & \text{CH}_2\text{OH} \\
\alpha\text{-glycerophosphoric acid.} & & \beta\text{-glycerophosphoric acid.}
\end{array}
$$

of which the α variety, containing an asymmetric carbon atom, can exist in two stereo-isomeric forms, lævo and dextro.

"Natural" glycerophosphoric acid, derived from egg lecithin, exhibits optical rotation, therefore must consist, at least partially, of the α acid.

Two processes are employed technically for the synthesis of glycerophosphoric acid. One consists in heating glycerine and phosphoric acid together at a temperature of $100°$–$105°$ and has been shown to afford mainly the α acid; by the other method mono-sodium phosphate is heated with two molecular proportions of glycerol, and the resulting diglyceryl ester hydrolysed with sodium hydroxide.

$$
\begin{aligned}
\text{NaO·PO(OH)}_2 + 2\text{C}_3\text{H}_8\text{O}_3 \;\rightarrow\;\; & \text{NaO·PO(OC}_3\text{H}_7\text{O}_2)_2 \\
\rightarrow\;\; & (\text{NaO})_2\text{PO·O·C}_3\text{H}_7\text{O}_2
\end{aligned}
$$

A considerable portion of a crystalline sodium salt is obtainable by this process, and this has been shown to be sodium β-glycerophosphate. The liquor from which no further quantity of this crystalline salt can be obtained, constitutes the liquid sodium glycerophosphate of commerce, whilst the other salts, calcium, magnesium, iron, etc., and the acid itself, are most generally prepared from the product of the interaction of phosphoric acid and glycerin.

Another method (E. P. 2883 of 1912) consists in heating monochlorohydrin, $\text{C}_3\text{H}_6\text{O}_2\text{Cl}$, with phosphoric acid.

Pure α-glycerophosphoric acid has been prepared (King and Pyman, *Trans. C. S.* **105**, 1253) by the interaction of α-monochlorohydrin and trisodium phosphate, and the pure β acid by the interaction of α-dichlorohydrin with phosphoryl

chloride, converting the product, bis-*s*-dichloro-iso-propyl phosphoric acid, into its calcium salt,

$$\{(CH_2Cl)_2 : CHO\}_2 \, PO-O\cdot Ca\cdot O\cdot PO\{O\cdot CH : (CH_2Cl)_2\}_2-4H_2O$$
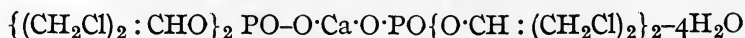
and hydrolysing this by boiling with sodium carbonate solution, when sodium β-glycerophosphate is produced.

Preparation from Glycerine and Phosphoric Acid.— A mixture of 25 parts of glycerine and 30 parts of 66 % phosphoric acid (sp. gr. 1·70) is heated at 105°. Power and Tutin (*Trans. Chem Soc.* (1905), 249) heated for 24 hours (three periods of 8 hours) ; Prunier (*Bull. Soc. Chim.* (1907), [4] 1046) heated equal weights of glycerine and 60 % acid at 110° for 70–80 hours. The reaction mass should be stirred, in order to prevent local overheating. The product is blown into 600 parts of water containing 30 parts of slaked lime, and stirred until neutral. The solution is filtered, through a filter press, at 16°–18°, at which temperature the calcium salt is most soluble, and the residue washed with water until the washings no longer afford a precipitate when heated to 100°. The combined filtrates, which contain the calcium glycerophosphate in solution, are neutralised (to phenol-phthalein) with a solution of glycerophosphoric acid, and evaporated nearly to dryness, preferably under diminished pressure. After cooling, alcohol is added, and the whole filtered. The filtrate contains the excess of glycerine and any colouring matter that has been produced. The alcohol and glycerine are recovered by distillation and used again.

The calcium glycerophosphate is washed with a little alcohol and dried. In order to obtain the free acid, from which the other salts are prepared, a weighed quantity of the calcium salt, in which the percentage of calcium has been accurately determined, is mixed with water and treated with the theoretically required amount of sulphuric acid. After filtration from the precipitated calcium sulphate, a solution of barium glycerophosphate is added, exactly sufficient to precipitate, as barium sulphate, the dissolved sulphate ions. The filtered solution is then concentrated to sp. gr. 1·127, if glycerophosphoric acid itself is required, or

neutralised with precipitated ferric hydroxide, magnesia, or potash. Addition, before or during neutralisation, of the quantity of oxalic acid necessary to combine with the calcium still remaining in the solution, will result in the removal of this impurity. The respective salts are then obtained by evaporation.

Preparation from Sodium Dihydrogen Phosphate and Glycerine.—According to Poulenc Frère's original patented method (D. R. P. 208700), by which crystalline sodium β-glycerophosphate is prepared, 1 molecular equivalent of sodium dihydrogen phosphate and 2 equivalents of glycerin are heated *in vacuo*.

$$O=P\begin{cases}OH\\OH\\ONa\end{cases} +2C_3H_8O_3 \quad \rightarrow \quad O=P\begin{cases}OC_3H_7O_2\\OC_3H_7O_2+2H_2O\\ONa\end{cases}$$
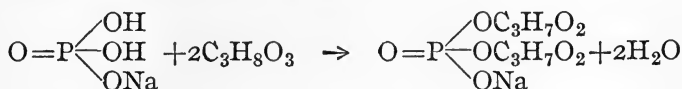
The resulting product, sodium diglycero-phosphate, is hydrolysed by being boiled with sodium hydroxide solution.

$$O=P\begin{cases}OC_3H_7O_2\\OC_3H_7O_2+NaOH\\ONa\end{cases} \rightarrow \quad O=P\begin{cases}OC_3H_7O_2\\ONa\\ONa\end{cases} +C_3H_8O_3$$
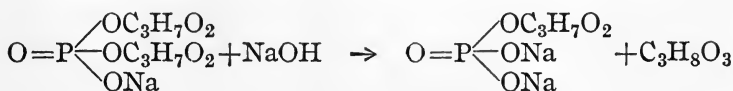
The solution is then concentrated and, after cooling, sodium glycerophosphate crystallises out. By a variation of the above, ammonium acid phosphate is used in place of the sodium salt.

No details are furnished in the specification as to the temperature, or time of heating. These are supplied, however, by Wulfing, who evades the above patent by employing, instead of sodium dihydrogen phosphate, a mixture of disodium hydrogen phosphate and meta-phosphoric acid (D. R. P. 205579).

One part of glacial metaphosphoric acid is mixed with 1·4 parts of disodium hydrogen phosphate and 3·2 parts of glycerine. The mixture is heated under a vacuum of about 50 mm., and the temperature gradually raised from 120 to 210°, at which it is kept until a test portion gives a negative reaction for phosphoric acid. The reaction mixture

is then hydrolysed with caustic soda. The composition of the metaphosphoric acid employed in this example is given as $Na = 14.04\%$; HPO_3 (free) $= 31.68\%$; HPO_3 (combined) $= 52.8\%$; $H_2O = 2.4\%$.

In a subsequent patent (D. R. P. 217553), in which a further variation is described, it is stated that the temperature given above is unnecessarily high, and that the reaction can be carried out advantageously at 145°. One hundred parts of meta-phosphoric acid and 17 parts of sodium hydrate are mixed with 60 parts of water and 100 parts of glycerin (sp. gr. 1·23) and heated *in vacuo*. The water distils over at 70°, and at 125° solution is complete. The reaction is finished at 145°, when the product is treated as before.

The reaction mixture, after hydrolysis, contains, as seen from the equations, sodium glycerophosphate together with a molecular equivalent of glycerine. This requires to be recovered, and by doing so the subsequent crystallisation of the salt is facilitated. This is effected by concentrating, *in vacuo*, to a syrup, and boiling out with strong alcohol, in which the glycerine dissolves. After separation of the alcohol-glycerine layer, the residue is set aside to crystallise, and allowed to stand until the process is complete. Crystals and liquid are then separated by centrifugal action or hydraulic pressure. The former are purified by recrystallisation from water ; the latter is adjusted to the required strength and marketed as "Sodium glycerophosphate liquor," 50 % or 75 %.

Another process that has been proposed (D. R. P. 242422) for the production of glycerophosphoric acid consists in generating phosphoric acid *in situ* by treating calcium phosphate with sulphuric acid and heating the mixture with glycerine.

Section XI.—OTHER SUBSTANCES OF INTEREST—PITUITARY AND THYROID EXTRACTS, VITAMINES, SACCHARIN

PREPARATIONS of pituitary and thyroid glands exhibit marked pharmacological properties, and their medicinal application has acquired outstanding importance compared to that of the preparations of other animal glands, such as duodenal gland, thymus gland, ovaries, testicles, and brain and spinal cord, to none of which can so far be ascribed characteristic physiological effects.

The wide application of pituitary extract in obstetrics and of thyroid in the treatment of myxœdema and cretinism was thought to call for a reference to the methods of preparation of these substances, albeit that we have but little chemical knowledge of them.

The latter statement also applies to the vitamines or accessory food substances, the present state of our knowledge of which is derived almost exclusively from physiological as distinct from chemical experiments. Their use in medical treatment and dietetics is very rapidly gaining ground.

Saccharin, on the other hand, is a substance of which the chemistry is well known, but which is entirely without physiological action apart from its intensely sweet taste. Its use as a sweetening agent where sugars are contra-indicated gives it a place of importance in medicine despite its inactivity.

PITUITARY GLAND.—The pituitary gland of mammals—a small ductless gland situated at the base of the brain—contains in its posterior or infundibular lobe a substance which exerts powerful physiological activity. The anterior lobe, or hypophysis, is not possessed of the same action, but

exercises an obscure controlling action upon development and metabolism.

The infundibular portions of the glands of sheep, oxen, or pigs possess similar activity. Any of these sources of the glands may therefore be employed in the preparation of the extract. The gland being an exceedingly small one, ox glands repay best the labour of dissection. The dried, dissected whole gland is occasionally administered internally to improve metabolism, but its administration is not attended with any obvious results. On the other hand, extracts of the posterior lobe injected intramuscularly or intravenously exercise a pronounced action on many organs, causing prolonged rise in blood pressure and a strengthening of heart beat. They also stimulate peristalsis, diuresis, contraction of the uterus, milk secretion, etc. See Oliver and Schafer (*Journ. Phys.* xviii. p. 277); Magnus and Schafer (*Ibid.* xxvii.); Dale (*Biochem. Journ.* iv. p. 427).

Extract of Pituitary Gland.—The finely minced fresh or dried posterior lobe in weighed amount is added to distilled water acidified by acetic acid—0·5 %, the temperature is raised to the boiling point, and the boiling continued for ten minutes. This operation may best be done in a hard-glass flask. The solution is set aside to cool and allowed to stand for at least twenty-four hours, care being taken to exclude bacteria. It is then filtered, made up to the required volume, again sterilised by heating to 90°, and allowed to stand. The process is a perfectly simple one and, under conditions of ordinary care, little or no loss of activity takes place. It is important to avoid the alkaline condition, traces of hydrogen peroxide will cause a loss of activity, and a rapid loss of activity will also occur if organisms be allowed to develop in the solution, or if proteolytic enzymes or other hydrolytic agencies be at work.

Proposals have been made to precipitate albuminous matter by the addition of uranium acetate or dialysed iron, but these constitute no improvement and are apt to result in a loss of activity possible through adsorption of the active substance by the precipitate.

No chemical method of testing the activity of the extract has been devised, nothing being known of the chemical nature of the active ingredient, which, however, can be removed from the extract by dialysis and appears to be of a comparatively simple nature. The extract is made in different strengths ; a solution representing 20 % of its weight of fresh gland is that commonly employed. It is not official in the British Pharmacopœia, but the United States Pharmacopœia includes an extract. This is standardised by a physiological method, to represent about 13 % of fresh gland. The physiological standard there proposed is that 1 c.c. diluted 20,000 times with Ringer's solution has the same activity on the isolated uterus of the virgin guinea pig as a 1 in 20,000,000 solution of Histamine hydrochloride. It has, however, been pointed out that this standard is unsuitable and considerably below that of commercial solutions in common use. The above method is based on the method published by Dale and Laidlaw (*Journal of Pharmacology*, iv. 75), who, however, adopt as their standard an extract prepared from perfectly fresh infundibular substance, which has been preserved and sterilised in sealed glass phials. Under such conditions they find the extract has great stability.

The determination by means of the contraction of the uterus of the virgin guinea pig has been found a more accurate method of evaluation than methods dependent upon the action on the blood pressure or on diuresis.

Pituitary extract is used chiefly in medicine as a remedy for secondary weakness of uterine contraction, and is of special value in assisting labour at child-birth. It is employed in surgical shock and collapse after severe operations and serious loss of blood, also to restore activity to the paralytically distended bowel in certain conditions and to produce diuresis. Paradoxically it controls the diuresis of *Diabetes insipidus*. For a few hours after a full dose has been administered further doses have no effect.

THYROID GLAND.—The thyroid gland is a ductless gland situated in the throat ; its secretions are essential to normal metabolism. Various diseases result from the failure of this

gland to function properly. On the other hand, an excessive thyroid secretion appears to be at least a factor in the causation of exophthalmic goitre or Graves' disease. Thyroid deficiency is generally met by the administration of the gland itself, but an extract may be prepared which has the same effect. The dried gland, however, is characterised by great stability, and consequently but little advantage is gained by the use of an extract.

The glands are generally obtained from the sheep ; in this species one pair of the small glands, known as the parathyroid glands, is incorporated in the lobes, and these are stated to secrete a substance which acts powerfully upon the nervous system. To prepare the dried thyroid the total gland is dissected from the surrounding fat and tissues, minced and salted. It is then carefully and thoroughly dried, either in a current of warm air or in a vacuum cupboard, at a temperature not exceeding 40°. The dried glands are finely powdered. They are commonly administered in tablet or cachet form.

The active principle being a substance containing a considerable percentage of iodine, the activity of the gland may be tested by a determination of the combined iodine content, which should be about 0·2 %.

The British Pharmacopœia gives a method for the preparation of a Liquor Thyroidei, and the British Pharmaceutical Codex one for an Extractum Thyroidei. They are simple pharmaceutical processes which do not call for comment. Recently Kendall (*Journ. Biolog. Chem.* xxxix. 125 and xl. 265) has isolated from the thyroid a pure crystalline substance, Thyroxin, possessing the characteristic physiological activity of the glands ; the following is the method of preparation.

Preparation of Thyroxin.—Fresh or desiccated thyroid gland is treated in an enamelled vessel for 24 hours with hot 5 % aqueous sodium hydrate solution. The insoluble soaps are separated by filtration, and the filtrate acidified after being cooled. The precipitate thus formed comprises 1 % of the total weight of the fresh glands used, and contains 26 % of iodine. It is redissolved in caustic soda and

reprecipitated with hydrochloric acid. It is then air-dried, dissolved in alcohol 95 % and made neutral to litmus with sodium hydroxide. The solution is then filtered and the filtrate treated with a hot concentrated aqueous solution of baryta; after a further filtration a small quantity of sodium hydrate is added, and carbon dioxide passed through. The precipitated barium and sodium carbonates are removed and the alcohol distilled, the last traces being removed by evaporation in an open dish. The residue is acidified with hydrochloric acid, the precipitate filtered off and dissolved in alkaline (NaOH) alcohol. The solution is next treated with carbon dioxide, and after removing the sodium carbonate the alcohol is again removed by distillation. On standing the mono-sodium salt of thyroxin separates. It is subjected to further precipitation by a repetition of the above treatment and by being several times dissolved in alkaline alcohol and precipitated with acetic acid. By this method, 6550 pounds of fresh hog's thyroid gland yielded 33 grams of thyroxin.

The following formula has been assigned by Kendall to thyroxin :
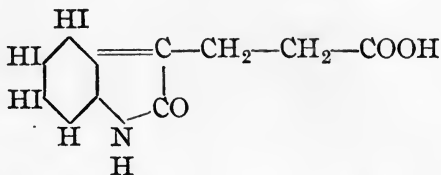
It is a colourless, odourless, crystalline substance, existing in four distinct forms, the keto—m.p. 250°, the enol—m.p. 204°, open ring—m.p. 225°, and a tautomeric form—m.p. 216°. It contains 65 % of iodine ; it is insoluble in aqueous solutions of all acids. With alkali hydroxides it forms dibasic salts, with alkali carbonates monobasic salts. Its acetyl and dimethyl derivatives have been prepared and the presence of an indol ring recorded ; the constitutional formula given above requires further confirmation.

Thyroid medication is chiefly employed in the treatment of diseases resulting from deficient conditions of the

thyroid gland, for instance in myxœdema and cretinism ; the dried substance in tablets or cachets is generally employed. The administration is continued often for long periods, and frequently throughout life.

The myxœdematous patients possess generally a uniform metabolic rate which is about 40 % below normal. Administration of 1 mg. of thyroxin has been shown to produce, in an adult weighing 150 lbs., an increase of 2 % in the metabolic rate. The curve of this response is approximately a straight line between 30 % below normal to 15–20 % above normal metabolic rate, and it is possible by such medication to maintain the metabolic rate at any desired figure between these limits, over periods of time measured in years.

Thyroxin is not essential to life, and in its complete absence the fundamental chemical reactions occur and life is maintained, but the flexibility of energy output is limited to a narrow range. It has been found that in the winter months the thyroid glands of oxen, sheep and pigs contain less thyroxin, as measured by the iodine content, than in summer, and this is held to be attributable to the fact that the greater amount of energy required to be exerted during cold weather to maintain body temperature, causes a wearing out of the thyroid reserves, consumption being greater than production. With the advent of the warmer seasons the reverse process sets in and the thyroxin store is again built up.

VITAMINES.—Vitamines are substances—the existence of three is recognised with certainty—whose presence in the dietary is essential for proper nutrition, and whose absence, if prolonged, gives rise to serious disease, such as rickets, scurvy, and beri-beri. Little is known as to their chemical nature ; in fact, no vitamine has yet been isolated in a state approaching purity. Recognition of the vitamine principle arose out of a study of the etiology of beri-beri. This disease is endemic among populations whose main article of diet is rice. The arrival in the East of modern milling machinery brought about a great increase in the number of cases, and in 1897 evidence was brought forward,

by Eijkmann, that beri-beri was related to the kind of rice consumed. Statistics were collected showing the incidence of beri-beri in the Dutch East Indian prison establishments. Different gaols, owing to different situations and local customs, were supplied with different kinds of rice. In thirty-seven prisons red rice was employed, and only one of these developed cases of beri-beri ; in thirteen prisons in which a mixture of red and white rice was given, six of them developed the disease ; whilst of fifty-one prisons where white rice alone was eaten, in no fewer than thirty-six was beri-beri developed.

In 1907–8 Fraser and Stanton carried out experiments in which disturbing factors, such as the possibility of the conveyance of an infection, were eliminated or were adequately controlled. One half of a gang of 300 Javanese labourers was fed on white rice and the other half on parboiled rice. In about three months cases of beri-beri began to occur among those fed on white rice, whilst no sign of the disease appeared amongst the others. The conditions were then reversed, and again the disease developed only among the party partaking of white rice Continuing their researches these investigators showed that the disease is caused by the deficiency in polished rice of a substance, contained in the outer layers, that is removed in the milling process. This substance was found to be soluble in water and alcohol. It is stable in neutral or acid solutions, but is destroyed by alkali. Heating at 120° for 2 hours completely destroys it.

It was soon shown that vitamines were not contained only in rice polishings, but were present in many other substances of vegetable and animal origin. Funk, Edie, and others proved their existence in yeast, milk, and bran ; the list has been extended to include wheat, oats, nettles, blood, yolk of eggs, cabbage, potatoes, meat, and other substances.

Three classes of vitamine, having different actions, are now recognised. The antineuritic vitamine, which prevents and cures polyneuritis, or beri-beri, is known as the **Water-soluble B vitamine**. It occurs in greatest quantity in rice

polishings, wheat embryo, and yeast, and is present also in lean meat, milk, egg yolk, cabbage, potatoes, etc.

Another, known as **Fat-soluble A,** is anti-rachitic, that is to say, its presence in the dietary is essential if the development of rickets in children is to be prevented. This body is contained, in largest amount, in cod liver oil, butter, and yolk of egg ; to a lesser extent in wheat embryo and cabbage, and to a certain degree in lean meat, potatoes, yeast, and wheat bran. Beef suet and arachis oil also contain it in small amount, and have recently been recommended as constituents of artificial cream, for feeding infants when the natural article is unobtainable.

The third of the vitamines at present recognised possesses anti-scorbutic activity, and is known as **Antiscorbutic;** it prevents the onset of scurvy. It is present in fresh vegetable foodstuffs and fruit juice—lime juice particularly may be mentioned. This antiscorbutic vitamine is less stable than the others ; it is rapidly decomposed when the foodstuffs in which it is contained are heated, and even when they are kept too long. The Water-soluble B or anti-neuritic, and the Fat-soluble A, or anti-rachitic, vitamines are apparently permanently stable at atmospheric temperature, and are only slowly destroyed by heating at 100°. As to the chemical nature of the vitamines, nothing is known with certainty. Drummond and Funk, in an examination of the phosphotungstate precipitate containing the anti-neuritic vitamine, found it to contain choline and nicotinic acid in considerable amount. This led Williams to test the curative action of certain pyridine derivatives on polyneuritic pigeons. He found 2-hydroxy-pyridine, 2.4.6, and 2.3.4 trihydroxy pyridines to be definitely curative. 2-hydroxy-pyridine was obtained in two tautomeric forms, to which the following formulæ were ascribed [structure]OH and [structure]O.

One only of these (the latter) is anti-neuritic. The corresponding forms of 3-hydroxy-pyridine and the anhydrous forms of methyl-pyridone, trigonelline, and betaine, were

found also to possess curative effects on polyneuritic birds. Similarly, nicotinic acid was obtained in a tautomeric form with a betaine structure and this, too, was anti-neuritic. Williams expresses the opinion that the curative properties of the vitamine fractions of yeast and rice polishings are due in part to the presence of this isomeric form of nicotinic acid, or a polymeride or simple derivative of it. Further work on these lines is awaited with interest.

Water-soluble B vitamine extract is made by extracting rice polishings with hot alcohol (90 %), concentrating under reduced pressure, treating the residue with water, removing the separated fat, and adjusting the aqueous portion to a finite strength. Stanton (private communication) macerates the polishings with cold 10 % alcohol which has been acidified with hydrochloric acid, filters, and concentrates the extract under reduced pressure, at as low a temperature as possible. The extract, to which is added 10 % of alcohol as a preservative, is adjusted so that one part by volume equals two parts of rice polishings.

Preparations which are freer from inactive extractive matter can be obtained (see U. S. P. 1235198) by extracting a suitable organic foodstuff with dilute alcohol, and removing the alcohol by distillation under reduced pressure. The aqueous solution is treated with lead acetate and basic lead acetate, filtered, the filtrate freed from lead and evaporated *in vacuo* to dryness. Further purification may be effected by precipitating the vitamine with either tannin, silver nitrate, phospho-molybdic, or phosphotungstic acids, and decomposing the precipitates by appropriate means.

Williams (*Phillipine J. Sci.* (1916), **11,** 49) mixes the air-dried phosphotungstic acid precipitate with excess of baryta, and extracts with water. The extract is freed from barium and sulphuric acid, neutralised with nitric acid, concentrated under reduced pressure, and then treated with silver nitrate. The precipitated purine bases are separated and a further quantity of silver nitrate, and sufficient barium hydroxide

to produce a permanent precipitate, added to the solution. The precipitate is decomposed with hydrogen sulphide and filtered, barium is removed as sulphate, and the solution then concentrated and treated with twice its volume of alcohol. A precipitate forms which has but slight anti-neuritic properties. The filtrate from this yields on evaporation a substance with highly curative powers.

Vitamine from brewers' yeast is prepared (U. S. P. 1173317) by digesting washed and pressed brewers' yeast for 36 hours at 37·5°. The mass is filtered, and the filtrate treated with about 50 grams per litre of Fuller's earth. The mixture is shaken and treated with about 1 % of N/1 hydrochloric acid, to assist settling. The sediment is filtered, washed with dilute acid, and dried *in vacuo* over sulphuric acid. The vitamines contained in the yeast extract are almost completely absorbed by the Fuller's earth. The product is administered without further treatment.

SACCHARIN (gluside, *o*-benzoyl-sulphonimide)

$$\text{C}_6\text{H}_4 \underset{\text{SO}_2}{\overset{\text{CO}}{\diagdown\diagup}} \text{NH.} \quad 183.$$
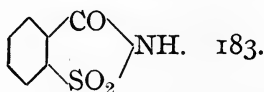
The preparation of saccharin by the method technically employed can be resolved into three stages.

(1) Preparation and purification of toluene-ortho-sulphonchloride.

(2) Preparation and purification of toluene-ortho-sulphonamide.

(3) Oxidation of ortho-toluene-sulphonamide to saccharin.

These will be considered in some detail, and following this will be given a *résumé* of other processes for obtaining saccharin which have been proposed.

Preparation of Toluene-ortho-sulphonchloride.— (*a*) *By the sulphonation of toluene with sulphuric acid :* The original patentees, Fahlberg and List, give the following description of the method employed for sulphonating toluene (E. P. 6626 of 1885) :—" Toluene may be treated with fuming sulphuric acid in the cold state or it is heated

with hydrated sulphuric acid of 66° Bé. to a temperature not rising above the boiling point of water. In applying hydrated sulphuric acid the reaction takes place more smoothly than with fuming acid and without any boiling over."

A quantitative study of the sulphonation of toluene with sulphuric acid made by Holleman and Caland (*Ber.* (1911), 44, 2504), showed that the higher the temperature the smaller is the proportion of toluene-ortho-sulphonic acid in the mixture of isomerides that is formed. It was found best to sulphonate at 0°, and most economical to employ two parts by weight of sulphuric acid (96–100 %) to each part of toluene. Under these conditions the sulphonation mixture contains 39·5 to 40 % of ortho–, 3·5 to 4·0 % of meta–, and 56 to 57 % of para-toluene-sulphonic acids. By employing 6 parts of sulphuric acid the proportion of ortho-acid is increased to 45 %, and with a large excess, *i.e.*, 41·5 parts of 94 % H_2SO_4, to 51·5 %.

The components are mixed in a cast-iron vessel provided with a powerful stirrer and cooling coils, or in a horizontal jacketed autoclave, maintained at 0°, and stirred until a test-portion dissolves completely in water. The velocity of sulphonation would probably be accelerated by adding infusorial earth until the mass is pasty (D. R. P. 71556), or powdered animal charcoal (D. R. P. 74639), whereby the incorporation of the hydrocarbon with the acid is greatly facilitated. The sulphonation mixture is run into cold water, contained in a wooden vat, and is neutralised with milk of lime. After filtering off the calcium sulphate the sodium salt is prepared by treating the solution with sodium carbonate, separating the calcium carbonate, and evaporating to dryness.

Several methods have been proposed for the separation of the isomeric acids formed. In E. P. 10955/1895, this is effected by crystallisation of the magnesium salts, when magnesium toluene-para-sulphonate separates first. The zinc salts have also been employed (E. P. 17,401/1896). In E. P. 15778/1890 the sulphonation mixture is diluted with ice until the concentration of the sulphuric acid, 6 parts of

which are employed to 1 of toluene, is 66 % w/w. The para- acid is only sparingly soluble in acid of this strength, and crystallises out. According to E. P. 16299/1903, 400 parts of toluene are sulphonated at 16°–17° with 1435 parts of sulphuric acid, the operation being completed in 10 hours. Three hundred parts of water are added, when, on standing, 675 parts of para-acid crystallise out. This is separated, and a further 80 parts of water are added to the filtrate. The ortho-acid then crystallises out, 390 parts being obtained.

Economy is effected by separating the isomers, when employing this method of sulphonation, as thereby phosphorus pentachloride is saved in the following stage, namely, that of chlorinating the para compound. The toluene contained in the acid filtrate from the ortho-acid in E. P. 16299/1903 can be regenerated by heating to 160° and blowing in superheated steam, when the sulphonic acid is decomposed. The separated toluene-para-sulphonic acid is resolved into toluene and sulphuric acid by the same means.

Toluene-sulphonchloride :—Fahlberg and List (*loc. cit.*) prepared the sulphonchloride by mixing the dried sodium salts, in a lead-lined iron vessel, with phosphorus pentachloride, or, preferably, with phosphorus trichloride followed by treatment with chlorine. The temperature is regulated by cooling. Phosphorus oxychloride is then removed by distillation, after which the sulphonchloride is allowed to cool. Crystals of the para-chloride separate out and are removed by filtration. The liquid filtrate is then cooled to 0°, when a further crop of para-chloride separates and is removed.

Holleman and Caland (*loc. cit.*) mixed the dried sodium toluene-sulphonates with a two-thirds weight of phosphorus pentachloride and a one-fifth weight of phosphorus oxychloride. The reaction was completed by heating to 130°–140° for $\frac{3}{4}$ hour, after which the $POCl_3$ was distilled off and the residue added slowly to a large quantity of ice.

In E. P. 11078/1898 a variation is described whereby sodium toluene-ortho-sulphonate, 39 kilos, is mixed with

50 kilos of carbon bisulphide and 3 kilos of phosphorus, and chlorine, 18 kilos, passed in to saturation.

$$2C_6H_4 \underset{SO_3Na}{\overset{CH_3}{<}} + P + 5Cl \rightarrow 2C_6H_4 \underset{SO_2Cl}{\overset{CH_3}{<}} + 2NaCl + PO_2Cl$$
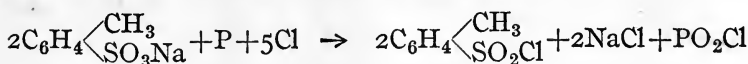
The solvent is then distilled off and the residue of toluene-sulphonchloride converted into amide by treatment with aqueous ammonia. Magnesium toluene-ortho-sulphonate, 250 kilos (see above), is converted into toluene-sulphonchloride (E. P. 14390/1901) by slowly adding it to 1250 kilos of chlorsulphonic acid, the temperature being maintained at 15°–18°. After standing for a few hours the mixture is poured on to 1000 kilos of ice and the ortho-toluene-sulphonchloride separated.

(b) *By sulphonation with chlorsulphonic acid :*—Sulphuric acid for the sulphonation of toluene has been completely superseded by chlorsulphonic acid, whereby the ortho- and para-toluene-sulphonchlorides are obtained in one operation.

$$C_6H_5CH_3 + 2SO_2 \cdot OH.Cl \rightarrow C_6H_4 \underset{SO_2Cl}{\overset{CH_3}{<}} + HCl + H_2SO_4$$

$$\quad 92 \qquad 2(116 \cdot 4) \qquad \qquad 190 \cdot 4 \quad 36 \cdot 4 \quad 98$$
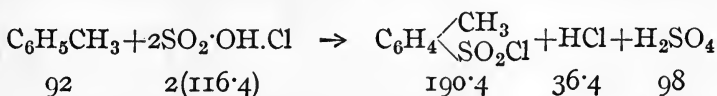
This great improvement was introduced by Monnet (E. P. 25273/1894). Into 400 kilos of chlor-sulphonic acid, cooled to 0°, there are run slowly, with constant stirring, 100 kilos of toluene, the temperature of the mass being never allowed to rise above 5°. When all the toluene has been added, the mixture is constantly stirred for 12 hours in order to complete the reaction, the temperature being maintained between ˙0° and 5°. The mass is then poured on to ice, when the sulphonchlorides separate in the form of a liquid oily layer containing some solidified para-chloride. They are separated by decanting off the upper aqueous layer.

The sulphonation is carried out in a cast-iron vessel, provided with a powerful stirrer and a cooling jacket through which circulates cold brine. The vessel, which must be a closed one, requires an inlet tube for the admission of the toluene, and an exit pipe through which the hydrogen

chloride vapour is led away, either to an absorption tower or to a chlorsulphonic acid plant, in which it is re-combined with sulphuric anhydride. The proportion of chlorsulphonic acid to toluene may advantageously be increased to 5 : 1. The greater excess of acid results in a higher yield of sulphonchlorides, and the choice of the most economical proportions must be governed by the respective costs of the ingredients. An improvement in the after-treatment of the sulphonation mixture is made (D. R. P. 224386) by diluting with saturated hydrochloric acid until the sulphuric acid mixture has a specific gravity of about 50° Bé. At this concentration the sulphonchlorides are comparatively insoluble and separate as a layer on the surface of the acid. The temperature must be kept down as near as possible to 5°. The hydrogen chloride liberated from the hydrochloric acid solution and that formed by the decomposition of the excess of chlorsulphonic acid is absorbed in a tower. A considerable quantity of HCl is saved by this procedure, and a stronger residual sulphuric acid results. From this acid toluene held in the form of sulphonic acid can be regenerated (see above).

The mixture of the ortho- and para-toluene-sulphonchlorides, which contains doubtless also a small proportion of meta-chloride, is partially separated by freezing out. Holleman and Calland (*loc. cit.*) have shown the melting point of pure ortho-chloride to be +10°, that of pure para-chloride +67°, and that a eutectic mixture of the two is formed which melts at +3·5°, and has the composition ortho- 87·5 %, para- 12·5 %. In practice it is possible to obtain by freezing an oil containing 85 % of toluene-ortho-sulphonchloride.

From 100 parts of toluene about 110 parts of ortho-chloride (85 %) are obtainable, together with 70–75 parts of para-chloride.

Preparation of Toluene-ortho-sulphonamide.—For the conversion of toluene-ortho-sulphonchloride into the amide, ammonia gas, ammonia solution, and ammonium carbonate have been employed.

$$C_6H_4{\overset{CH_3}{\underset{SO_2Cl}{<}}} + 2NH_4OH \rightarrow C_6H_4{\overset{CH_3}{\underset{SO_2NH_2}{<}}} + NH_4Cl + 2H_2O$$

$$\qquad 190\cdot4 \qquad 70 \qquad\qquad\qquad 171 \qquad 53\cdot4 \qquad 36$$

$$C_6H_4{\overset{CH_3}{\underset{SO_2Cl}{<}}} + (NH_4)_2CO_3$$

$$\qquad\qquad \rightarrow C_6H_4{\overset{CH_3}{\underset{SO_2NH_2}{<}}} + NH_4Cl + CO_2 + H_2O$$
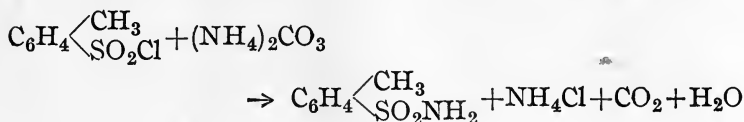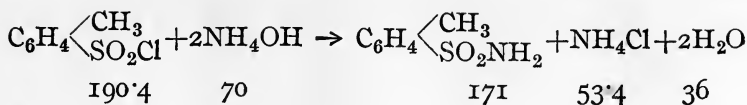
Fahlberg and List (*loc. cit.*) recommended ammonium carbonate. The sulphon-chloride is mixed with the theoretically required proportion of ammonium carbonate and the pasty mass subjected to the action of steam. The resulting product is treated with water, whereby the ammonium chloride is dissolved out, the residual solid being the sulphonamide.

An alternative method, based on E. P. 3930 of 1895, consists of adding toluene-sulphonchloride gradually to an equal quantity of 20 % ammonia, which is cooled by being surrounded with ice, or by brine coils. The reaction is completed by warming, after which the toluene-sulphonamide is filtered off and washed with water.

Purification of Toluene-ortho-sulphonamide.—The crude product, as made from a properly frozen-out oil, contains not less than 85 % of ortho-amide nor more than 15 % of para-amide. It has been shown by McKie (*Trans. C. S.* (1818), 799), that the two amides form a eutectic mixture having the composition 60 % para- and 40 % ortho-amide. One hundred parts of the crude amide containing 15 % of para-, therefore, can theoretically be separated into 75 parts of 100 % ortho-amide and 25 parts of eutectic mixture containing 60 % of para-amide. It is dissolved in the theoretically required quantity of normal caustic soda solution, filtered from impurity, and treated, whilst being stirred, with acid sufficient to precipitate 75 % of the amide in solution (see E. P. 22726 of 1894). Stirring is continued for some time in order to promote the attainment of equilibrium, or the solution is heated, when most of the precipitated amide passes into solution, from which it crystallises again

on cooling. The product is a nearly pure toluene-ortho-sulphonamide.

In place of acid, ammonium chloride may be added, when amide is precipitated with liberation of ammonia (E. P. 848 of 1903),

$$C_6H_4\!\!\!<^{CH_3}_{SO_2NHNa} + NH_4Cl + H_2O$$

$$\rightarrow C_6H_4\!\!\!<^{CH_3}_{SO_2NH_2} + NaCl + NH_4OH$$
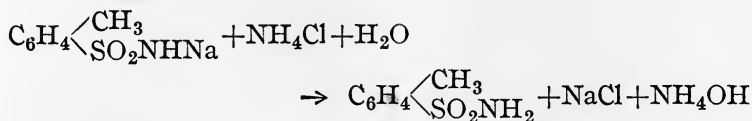
This permits of the employment of the filtrate containing ammonium chloride obtained from the manufacture of the crude toluene-sulphonamide.

According to E. P. 6198/1894 the separation of the toluene-ortho-sulphonamide can be brought about by crystallisation of the sodium salts; or by following E. P. 848/1903, by fractional precipitation with a magnesium salt, when the magnesium toluene-ortho-sulphonamide is precipitated first. The eutectic mixture of amides, obtained by neutralisation of the liquors from which the ortho-amide has been filtered, can be treated (D. R. P. 133919) with chlorsulphonic acid, when the toluene-sulphonchlorides are reformed. The bulk of the para-chloride is then removed by freezing, and the ortho-chloride reconverted into amide.

Another method of partially separating these amides consists in fractionally crystallising the sodium salts from water, when much of the para- salt separates first, allowing a further quantity of ortho-amide to be precipitated from the filtrate. The amide as thus obtained contains 90–95 % of ortho-amide and 5–10 % of para-amide.

Oxidation of Toluene-ortho-sulphonamide.—The oxidation of the ortho-amide to saccharin is usually carried out by means of potassium or sodium permanganate, though calcium and ammonium permanganate have also been recommended. Varied and conflicting statements as to the conditions under which the oxidation is best carried out are to be found in the patent literature, and careful

sifting of the evidence is required in order to arrive at a procedure likely to be productive of good results.

Fahlberg and List give no particulars whatever as to temperature, concentration, quantity of permanganate employed. The following equation represents the reaction, in their view :—

$$C_6H_4\!\!<^{SO_2NH_2}_{CH_3}+K_2Mn_2O_8$$
$$\quad 171 \qquad\qquad 316$$
$$\rightarrow\ C_6H_4\!\!<^{SO_2}_{CO}\!\!>NK+KOH+2MnO_2+2H_2O$$
$$\qquad\qquad 221$$
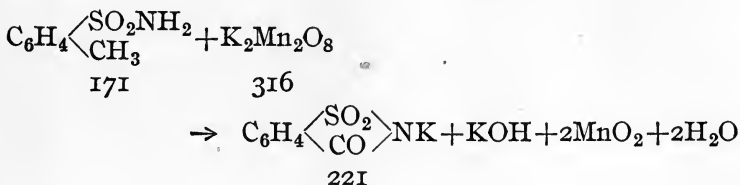
They say it is necessary to neutralise, during the progress of the reaction, the alkali that is formed. In *Ber.* **21**, 243, they state that in acid solutions ortho-sulphobenzoic acid is formed ; in neutral solutions saccharin together with ortho-sulphobenzoic acid ; and in alkaline solutions ortho-sulphamino-benzoic acid. Hauff, in E. P. 3680 of 1898, states that if the oxidation is carried out according to Fahlberg's method and neutralising agents are added, no saccharin is obtained ; but that if, on the contrary, the sulphonamide be dissolved in alkali, to form the compound $C_6H_4\!\!<^{CH_3}_{SO_2NHNa}$, and oxidised with permanganate without the addition of neutralising agents, larger yields (80–90 %) of saccharin are afforded.

Theoretically, 1·89 parts of potassium permanganate are required to oxidise 1 part of toluene-sulphonamide to saccharin. Hauff employed 2·57 parts, and in E. P. 4525/1900 2·5 parts are given. In E. P. 3563/1903, however, it is stated that better results are obtained by using permanganate insufficient to oxidise the whole of the amide, and 1·5 parts are used, part of the amide being recovered unchanged.

E. P. 4525/1900 is specific on the points of temperature and dilution. It is stated that, using a concentration of 1 of amide in 15, the temperature should be kept between 40°

and 50°, whilst at a dilution of 1 in 60 a temperature of 90°–95° is desirable. Solid permanganate is employed according to this patent.

High dilutions are disadvantageous on account of the loss of saccharin by reason of its solubility.

The best conditions based upon the above published accounts are as follows : One molecular equivalent of toluene sulphonamide, 171 parts, is dissolved in 1 equivalent of caustic soda, 40 parts, and 2565 parts of water, contained in a lead-lined vessel. At a temperature of 40°–50° are added, with stirring, and in small quantities at a time, 256 parts of potassium permanganate. The addition of the permanganate is spread out over the whole period of the oxidation. When completed, and when the colour of the permanganate has nearly disappeared, the excess is destroyed by addition of sodium hydrogen sulphide and the solution filtered from the precipitated manganese compound, which is washed with water until addition of acid to the filtrate no longer produces a precipitate of saccharin.

The combined filtrate and washings is cooled to 15°–18° and made neutral, to methyl orange, with hydrochloric acid. The excess of toluene-sulphonamide is thereby precipitated, and is filtered off. The filtrate is treated with hydrochloric acid exactly equivalent to the amount of para-amide present in the amide taken for oxidation (E. P. 1164 of 1897). In place of hydrochloric (or sulphuric) acid saccharin itself may be used (E. P. 22787/1891). By this treatment the para-sulphonamido-benzoic acid which has been formed by oxidation of the para-amide, being a much weaker acid than saccharin, is precipitated. From the filtrate, saccharin is precipitated by addition of a further quantity of hydrochloric acid and is filtered off, washed with cold water and dried at a moderate temperature (35°–40°). A further small quantity can be obtained by saturating the filtrate with salt.

Electrolytic Oxidation of Toluene-sulphonamide.— In E. P. 8661/1895 the oxidation of toluene-sulphonamide by passing a current of electricity through its solution, in an alkali, is proposed.

A more promising method is described (E. P. 9322/1803), in which potassium permanganate is employed as a carrier of the electrolytic oxygen.
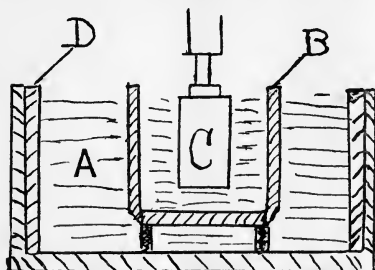
A is a vat furnished with a lining of lead, tin, or other conducting substance (D) not capable of affecting the reagents. This lining forms the cathode. Inside the vat is a vessel B of porous porcelain in which is suspended a lead, or lead-coated iron, sheet C, which constitutes the anode, and is fixed to the shaft of an agitator.

According to the conditions given, 0·9 kilo of potassium permanganate is dissolved in 13 litres of 10 % sodium hydroxide solution, or in potassium hydrate or baryta, and the volume made to 40 litres with water. Another solution is prepared containing 2 kilos of ortho-amide and 500 grams of caustic soda in 12 litres of water.

The permanganate solution is placed in B, 4 litres of the amide solution are added, and the whole is heated to 40°–50°, when a current of 300 amps. at below 2 volts is passed through it. After 2 hours, 1800 c.c. of the amide solution are added, and this addition is renewed every hour. The temperature is maintained for an hour after the last addition, after which the current is arrested, the permanganate destroyed, and the saccharin isolated in the usual manner.

It will be noted that this oxidation was carried out in the presence of a large excess of caustic alkali, which Fahlberg and others have shown to be conducive to the formation of sulphamido-benzoic acid at the expense of the saccharin, and that a small yield only of the latter is to be expected.

Probably, however, by observance of the conditions set out in connection with the oxidation by means of permanganate, an electrolytic oxidation, with the aid of a carrier such as permanganate, could be successfully carried out.

Other Methods of Synthesis of Saccharin.—Brief reference is given only to the more important of the other methods that have been proposed for obtaining saccharin. None of them has competed commercially with the toluene-chlorsulphonic acid process.

1. Fahlberg (E. P. 10955/1895) :—

$$\underset{SO_2OH}{\overset{CH_3}{\bigcirc}} \rightarrow \underset{SO_2OH}{\overset{COOH}{\bigcirc}} \rightarrow \underset{SO_2OH}{\overset{COOR}{\bigcirc}}$$

$$\rightarrow \underset{SO_2Cl}{\overset{COOR}{\bigcirc}} \rightarrow \underset{SO_2NH_2}{\overset{COOR}{\bigcirc}} \rightarrow \overset{CO}{\underset{SO_2}{\bigcirc}}\!\!\!>\!NH$$

2. Basler (D. R. P. 80713/1893) :—

$$\underset{SH}{\overset{COOH}{\bigcirc}} \rightarrow \underset{SH}{\overset{COCl}{\bigcirc}} \rightarrow \underset{SH}{\overset{CONH_2}{\bigcirc}} \rightarrow \overset{CO}{\underset{SO_2}{\bigcirc}}\!\!\!>\!NH$$
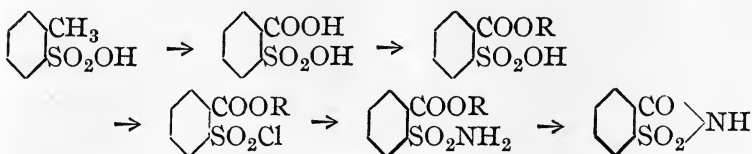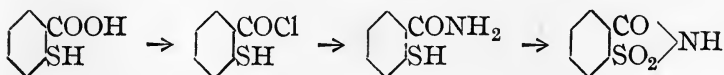
3. Cerckel (E. P. 15493/1896) : Ortho-cresol, heated under pressure with ammonium thiocyanate, gives toluene-ortho-sulphonamide.

4. A number of patents deal with the preparation of toluene-ortho-sulphinic acid, and its conversion into saccharin.

E. PP. 26139/1896; 23047/1897; 12871/1900; 7288/1906; 13054/1906; 13055/1906, deal with the following reactions :

$$\underset{NH_2}{\overset{CH_3}{\bigcirc}} \rightarrow \underset{N=NAc.}{\overset{CH_3}{\bigcirc}}$$

$$\rightarrow \underset{N=NSO_3H}{\overset{CH_3}{\bigcirc}} \rightarrow \underset{SO_2H}{\overset{CH_3}{\bigcirc}} \quad \begin{array}{l}\text{toluene-ortho-}\\\text{sulphinic acid.}\end{array}$$
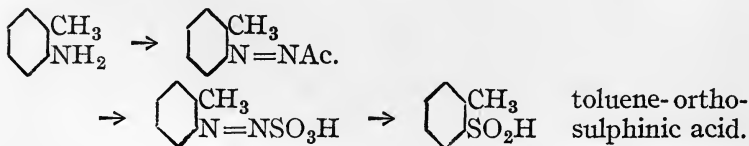
Ortho-toluene-sulphinic acid is converted into toluene-*o*-sulphonchloride (E. PP. 4525/1900; 10356/1906) or directly into toluene-*o*-sulphonamide (E. P. 12585/1900).

5. Lastly may be mentioned the conversion of ortho-sulphonamido-benzoic acid, which is formed to a varying extent as a by-product during the oxidation, and which can be obtained in quantitative yield by oxidising in a strongly alkaline solution, into saccharin. By E. P. 1164/1897, 10

kilos of *o*-sulphamido-benzoic acid are dissolved in 40 kilos of 98 % alcohol, 2 kilos of concentrated sulphuric acid are added, and the mixture boiled under a reflux condenser for several hours. The alcohol is then distilled off and the residue poured into cold water, when ethyl-ortho-sulphamido-benzoate separates as an oil which quickly solidifies. The ester is then heated at 100°–110° with constant stirring, ethyl alcohol is split off, with the formation of saccharin.

By another method, E. P. 19629/1899, 40 kilos of ortho-sulphamido-benzoic acid are introduced slowly, with good stirring, into 120 kilos of 20 % fuming sulphuric acid, care being taken that the temperature does not rise above 40°. The clear solution is allowed to stand, at ordinary temperature, for 24 hours, after which it is poured upon a mixture of 300 kilos of ice and 100 kilos of water. Saccharin is precipitated, and filtered off. Yield, 95 %.

According to E. P. 7199/1900 the ortho-sulphonamido-benzoic acid is heated in alcoholic solution with dry powdered sodium acid sulphate, or sodium pyro-sulphate. A mixture of saccharin and its ester is said to be formed, which, on solution in caustic soda and acidification with acid, affords a yield of over 95 % of saccharin.

Saccharin is a white crystalline powder, possessing an extremely sweet taste. It dissolves in 400 parts of cold water, in 28 parts of boiling water, and in 38 parts of alcohol. It is readily soluble in alkalis or alkali carbonates, with formation of salts. M.p. 220°.

Saccharin should contain not less than 97 % of *o*-benzoyl-sulphonimide (for method of estimation see Richmond and Hill, *J. S. C. I.* (1918), **37**, 246 T). It should form a clear solution when treated with sodium bicarbonate and water (absence of toluene-sulphonamide).

No carbonisable impurities should be present, as shown by a solution of 0·2 gram in 10 c.c. of pure sulphuric acid warmed at 50° not showing a brown colour in 10 minutes.

Ammonium salts should be absent, and no weighable residue should be left after ignition of 0·5 gram.

Saccharin should form a clear solution in aeceton.

Absence of ortho-sulphonamido-benzoic acid is shown by the acidity of the filtered solution obtained after shaking 1 gram of saccharin with 10 c.c. of water for 1 hour at 20°, which should not be appreciably greater than that calculated for a 0·3 % solution of saccharin.

Saccharin is used as a substitute for sugar and is prescribed in cases of diabetes and hepatic disease, also in corpulence. It is also employed to disguise the taste of nauseous drugs.

INDEX

THE END

INDUSTRIAL CHEMISTRY

Being a Series of Volumes Giving a Comprehensive Survey of

THE CHEMICAL INDUSTRIES

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