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NOMENCLATURE

Preparations are listed under the names which are used commonly for the compounds. For the convenience of those who wish to make a complete survey of the literature on any preparation, the *Chemical Abstracts* **indexing name** for each compound is given as a subtitle when that name differs from the title of the preparation.

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Organic Syntheses invites the submission of preparations of compounds which are of general interest or which illustrate useful synthetic methods. Preparations are welcomed particularly from those who have had occasion to work out the optimum conditions of preparation. The directions should be written in the style employed in the latest volume of *Organic Syntheses*. Full details for all steps should be included, and the range of yields should be reported rather than the maximum yield obtainable. Two copies of the directions should be sent to the Secretary. Additions, corrections, and improvements to previously published preparations are likewise welcomed.

ACROLEIN ACETAL AND β-ETHOXYPROPIONALDEHYDE ACETAL

(**Acrolein,** diethyl acetal, and **propionaldehyde, β-ethoxy-,** diethyl acetal)

$$CH_2{=}CHCHO \xrightarrow[HCl]{C_2H_5OH} CH_2{=}CHCH(OC_2H_5)_2 + C_2H_5OCH_2CH_2CH(OC_2H_5)_2$$

Submitted by F. P. Pingert.
Checked by Nathan L. Drake and W. Mayo Smith.

1. Procedure

A mixture of 158 g. (5.6 moles) of acrolein (Note 1) and 450 ml. of absolute alcohol (Note 1) is placed in a 1-l. Florence flask. The neck of the flask is closed by a plug of cotton,[1] and the flask is then immersed up to its neck in an ice bath containing about 1.5 kg. of ice. When the temperature of the mixture is about 0°, 50 ml. of absolute alcohol containing 2 g. of hydrogen chloride is added with swirling. The temperature is apt to rise very rapidly. The flask is clamped firmly in place and left 48–60 hours; the ice is allowed to melt and is not renewed.

The contents of the flask are transferred to a 1.5-l. round-bottomed flask, 0.5–1 g. of copper carbonate is added, and the liquid is fractionally distilled *in vacuo* with the aid of a Fenske column (Fig. 1) (Notes 2 and 3). The following fractions are collected.

Below 45°/24 mm.	Acrolein and alcohol (Note 4)
45°/24 mm.	Acrolein acetal (Note 5)
80–84°/21 mm.	β-Ethoxypropionaldehyde acetal (Note 6)

The yield of acrolein acetal is 89–108 g. (24–30%), and of β-ethoxypropionaldehyde acetal, 104–132 g. (21–26%) (Note 7).

---

[1] *Org. Syntheses,* **20,** 9 (1940).

2. Notes

1. The commercial products are used. The stabilizer in acrolein is not removed.

2. This design of a Fenske[2] fractionating column (Fig. 1) consists essentially of a packed glass tube (*A*) which is provided with two heat-insulating jackets (*B* and *C*) and a total reflux variable take-off head (*D*, *E*, and *F*). It is constructed of Pyrex glass and filled with single helix copper spirals.[3] Although the dimensions are probably not critical, trial and error have proved this particular design to be efficient, rugged, and well adaptable to numerous laboratory separations. Mixtures of compounds boiling from about 0° to 400° at 1 to 760 mm. have been fractionated successfully by means of this column.

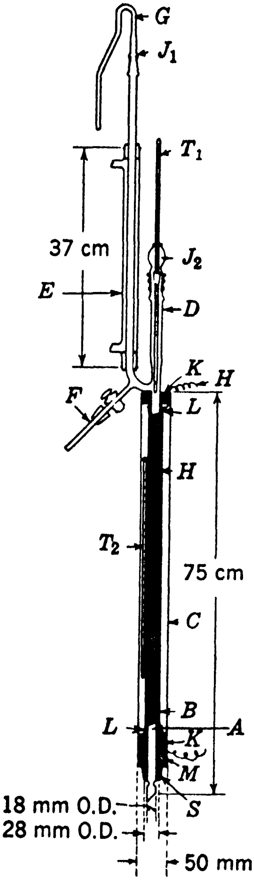

FIG. 1.

The heating element (*H*) consists of about 165 turns of No. 24 B & S gauge nichrome wire wound onto the jacket (*B*) directly or, preferably, over strands of asbestos string glued longitudinally to this jacket (*B*)—an arrangement that prevents side-slipping and short-circuiting of the individual wire loops. The central jacket (*B*) should not be omitted, and *the heating element should not be wound directly onto the column* (*A*) *itself.* This would be poor economy, as it would largely defeat the purpose of maintaining a heat gradient throughout the column and would introduce the hazard of cracking by local overheating, particularly in work under reduced pressure. The cork spacers (*L* and *K*) between the jackets must be carefully fitted with the aid of sandpaper and a rasp, since the whole weight of the column is supported by the outer jacket. If this adjustment is not made with precision and care, a single bump of a superheated distilland may shatter the column. If replacement of the cork spacers becomes necessary, the apparatus need not be torn down, but the new spacers may be sawed diametrically and the halves cemented after appropriate fitting. The outer jacket (*C*) may be replaced by pipe insulation, but glass is preferable in experimental work.

---

[2] Whitmore and Lux, *J. Am. Chem. Soc.*, **54**, 3448 (1932).

[3] *Org. Syntheses*, **20**, 96 (1940).

The heating element is connected to a 110-volt line through a rheostat (such as a 140-ohm, 3-ampere resistor), and the temperature is adjusted with the aid of two thermometers (T_1 and T_2), a reasonable differential, depending upon the materials to be distilled, being allowed.

The water condenser (*E*) should be sufficiently large to permit a high rate of reflux; with high-boiling substances it may be advantageous to cool with air or with steam. An attachment (*G*) provides for vacuum distillation with the aid of a glass Y and pressure tubing. An all-glass head[2] is more elegant but not so flexible. Ground-glass joints at J_1 and J_2 are convenient but not essential.

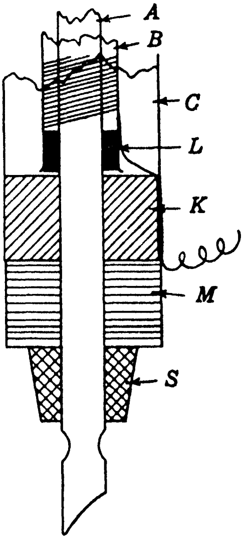

FIG. 2.

Details of the lower end of the column are shown in Fig. 2. *S* is a rubber stopper to fit the still pot, and *L* and *K* are cork stoppers. The outer jacket (*C*) ends at the bottom of *K*. *M* is a stack of asbestos disks which serve as a bumper between the stoppers *S* and *K;* they are indispensable for operation under reduced pressure. The disks are easily removable and provide for flexibility in the choice of stopper sizes. Still pots of 250 ml. to 12 l. can be attached to this column.

3. By taking advantage of the relatively high vapor pressure of the fore-run, the acrolein acetal may be collected practically automatically, as follows. The stopcock at *F* is closed, and the

pressure is reduced to 25 mm. No heat is supplied to the still pot, and the cooling water is adjusted to minimum flow. The forerun escapes at *G* and is collected, if desirable, in suitable traps. When evaporation ceases (4–5 hours), stopcock *F* is opened, the flow of cooling water is increased sharply, the heating jacket is adjusted to 45° (at T_2), and the still pot is heated gently with low-pressure steam. After suitable adjustment of the reflux and take-off rates at *F*, the acrolein acetal distils without further attention. It is convenient to do this overnight. The cutting of fractions is automatic, inasmuch as the higher-boiling β-ethoxypropionaldehyde acetal will not come over under these conditions and distillation simply ceases. An oil bath is needed to distil the higher fraction. Though some loss may be incurred in this shortcut procedure, it is more than offset by the economy in operator's attention and the higher purity of the product.

4. The recovered acrolein and alcohol fractions may be used in subsequent runs after suitable drying.

5. Other boiling points of acrolein acetal are 40°/18 mm. and 52°/36 mm.

6. Other boiling points for β-ethoxypropionaldehyde acetal are 78°/14 mm. and 92°/32 mm.

7. Among the advantages of this procedure over an alternative synthesis [4] are the following. The material is obtained in one step by a method which obviates most of the disagreeable features of the older two-step procedure. The overall yield by the older method is at best 25% and falls off badly if the hydroxide is not meticulously dry. Furthermore, the acrolein acetal prepared by the dehydrohalogenation of β-chloropropionaldehyde acetal [5] does not keep well, whereas samples of the product obtained by this procedure showed no discoloration and no change in boiling point on storage in an ice chest for 18 months. Only a faint odor of acrolein was noted at the end of that period.

3. Methods of Preparation

These have been recently summarized.[4]

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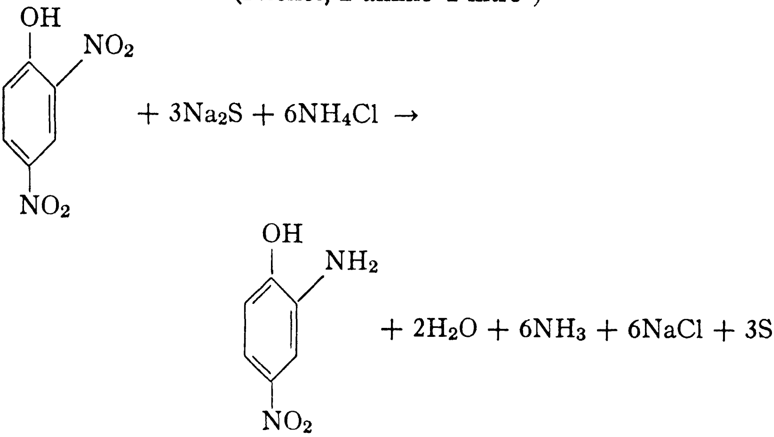
[4] *Org. Syntheses* Coll. Vol. **2**, 17 (1943).

[5] *Org. Syntheses* Coll. Vol. **2**, 137 (1943).

2-AMINO-4-NITROPHENOL

(Phenol, 2-amino-4-nitro-)



Submitted by W. W. Hartman and H. L. Silloway.
Checked by H. R. Snyder and J. Wayne Kneisley.

1. Procedure

In a 5-l. three-necked flask, suspended over a steam bath, are placed 300 g. (1.63 moles) of technical 2,4-dinitrophenol and 2.5 l. of water. The flask is fitted with an efficient stirrer, a reflux condenser, and a thermometer which dips below the surface of the mixture. After the stirrer has been started, 600 g. (11.6 moles) of ammonium chloride and 100 ml. of concentrated aqueous ammonia (about 28%) are added, and the mixture is heated to 85°. The steam is turned off, and the mixture is allowed to cool. When the temperature reaches 70° (Note 1), 700 g. (5.4 moles) of 60% fused sodium sulfide is added in portions of about 100 g. at 5-minute intervals. After two or three such additions the temperature of the reaction mixture reaches 80–85°; it is kept in this range either by adding the remaining portions of sodium sulfide at 10-minute intervals or by wrapping the flask with a wet cloth and continuing the additions at 5-minute intervals. After all the sodium sulfide has been added, the reaction mixture is heated at 85° for 15-minutes and then filtered through a heated 6-in. Büchner funnel (Note 2).

The hot filtrate is transferred to a 5-l. round-bottomed flask and cooled overnight by a stream of cold water. The mixture is filtered, and the crystals are pressed nearly dry. The solid is dissolved in 1.5 l. of boiling water, and the solution is acidified with glacial acetic acid (about 100 ml. is required, Note 3). The solution is heated with 10 g. of Norite, filtered hot, and cooled to 20°. The brown crystals are collected and dried for several hours in an oven at 65° or in a vacuum desiccator (Note 4). The yield of 2-amino-4-nitrophenol melting at 140–142° is 160–167 g. (64–67%). If a purer product is desired, the crude substance is recrystallized from 1.5 l. of hot water; 147–153 g. (58–61%) of material melting at 142–143° is obtained.

2. Notes

1. If the reaction is run at temperatures below 70° it is impossible to obtain a pure product even after several recrystallizations.

2. The Büchner funnel is preheated by inverting it over a steam bath and passing a lively current of steam through it for at least 10 minutes. During the filtration, suction is applied gently and at intervals to avoid excessive cooling by evaporation in the lower part of the funnel. If the filtration is not performed rapidly and carefully, the crude product will crystallize in the funnel. The filtration can be omitted, but the presence of insoluble materials complicates the next step by making it difficult to determine when solution of the crude product is complete.

3. The amount of acid required varies with dryness of the filter cake. The acidification can be followed by observing the color of a thin layer of the solution splashed against the side of the container. The color changes from dark red to olive brown at the end point. Both colors are so deep that they are not easily distinguished except when thin layers are viewed. After the end point is observed, an additional 10 ml. of acetic acid is added.

4. Unless properly dried the substance will melt at 80–90°, owing to the presence of water of crystallization.

3. Methods of Preparation

2-Amino-4-nitrophenol has been prepared by the partial reduction of 2,4-dinitrophenol chemically [1-5] and electrolytically,[6] and by the action of sulfuric acid on 3-nitroazidobenzene.[7]

BENZOYLACETANILIDE

(Acetanilide, α-benzoyl)

$$C_6H_5COCH_2CO_2C_2H_5 + C_6H_5NH_2 \rightarrow C_6H_5COCH_2CONHC_6H_5 + C_2H_5OH$$

Submitted by CHARLES J. KIBLER and A. WEISSBERGER.
Checked by R. L. SHRINER and FRED W. NEUMANN.

1. Procedure

A 250-ml. three-necked, round-bottomed flask is fitted with a dropping funnel, a mechanical stirrer, and a steam-jacketed column (15–20 cm. long) terminating in a still head. The still head carries a thermometer and is connected to a condenser set for downward distillation. In the flask are placed 42.2 g. (0.22 mole) of ethyl benzoylacetate [1] (Note 1) and 50 ml. of dry xylene, and the flask is immersed in an oil bath. The bath is heated to 145–150°, stirring is begun, and 18.2 ml. (18.6 g., 0.20 mole) of

---

[1] Laurent and Gerhardt, *Ann.*, **75**, 68 (1850).
[2] Post and Stuckenberg, *Ann.*, **205**, 72 (1880).
[3] Auwers and Rohrig, *Ber.*, **30**, 995 (1897).
[4] Pomeranz, Ger. pat. 289,454 [*Frdl.*, **12**, 117 (1914–1916)].
[5] Gershzon, *J. Applied Chem.* (*U.S.S.R.*), **9**, 879 (1936) [*C.A.*, **30**, 7554 (1936)].
[6] Hofer and Jacob, *Ber.*, **41**, 3196 (1908).
[7] Kehrmann and Idzkowska, *Ber.*, **32**, 1066 (1899).

BENZOYLACETANILIDE

[1] *Org. Syntheses*, **23**, 35 (1943).

aniline is added dropwise during 30 minutes. About 5 minutes after the addition has begun, the temperature in the still head rises to 75–78° as alcohol begins to distil. Approximately 12–14 ml. of distillate (Note 2) is collected in a 25-ml. graduate in about 1 hour; the end of the reaction is indicated by the fall of the temperature in the still head.

The reaction flask is removed from the oil bath, and the solution is poured into a 250-ml. beaker to crystallize; 10 ml. of benzene is used to rinse out the flask. When crystallization sets in, 50 ml. of petroleum ether (b.p. 35–55°) is added to the warm mixture with manual stirring. After the mixture has been chilled in an ice bath, the product is filtered by suction and washed with 100 ml. of a 1 : 1 petroleum ether-benzene mixture. It is then removed from the funnel, stirred into a slurry with 100 ml. of the mixed solvent, filtered, and again washed with 50 ml. of the solvent. These washings remove the bulk of the color, and a powdery white product remains. After standing overnight in a warm place, the product weighs 35.5–36.5 g. (74–76%) and melts at 104–105°. It may be purified further by recrystallization from benzene (3.7 ml. per g.). The yield of colorless benzoylacetanilide melting at 106–106.5° cor. is 32–34 g.

2. Notes

1. The ethyl benzoylacetate, aniline, and xylene should be redistilled before use. It is necessary that the flask and reagents be free from moisture. Impure starting materials and particularly traces of acids lower the yields. The submitters obtained 82–83% yields of benzoylacetanilide by using Eastman xylene (histological).

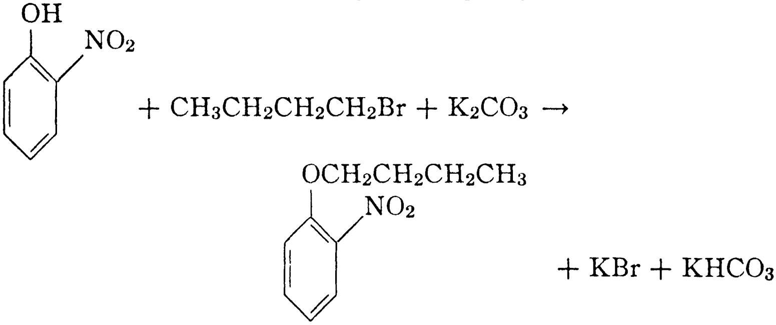
2. The distillate consists of a mixture of xylene and alcohol. By adding 100 ml. of water, the xylene layer can be separated and measured. Of 14 ml. of distillate, about 3.5 ml. is xylene and the balance, 10.5 ml. (89% of the theoretical amount), is alcohol.

3. Methods of Preparation

Benzoylacetanilide has been made by heating aniline and methyl benzoylacetate in an autoclave at 150° [2] and by heating the anil $C_6H_5NHCOCH_2C(=NC_6H_5)C_6H_5$ with dilute acid.[2]

o-n-BUTOXYNITROBENZENE

(Ether, butyl *o*-nitrophenyl)



Submitted by C. F. H. Allen and J. W. Gates, Jr.
Checked by W. E Bachmann and G. Dana Johnson.

1. Procedure

A mixture of 28 g. (0.2 mole) of *o*-nitrophenol (Note 1), 30 g. (0.22 mole) of *n*-butyl bromide, 28 g. (0.2 mole) of anhydrous potassium carbonate, and 200 ml. of dry acetone in a 1-l. round-bottomed flask is refluxed on a steam bath for 48 hours (Note 2). At the end of this time the acetone is distilled from the mixture, 200 ml. of water is added to the residue, and the product is extracted with two 100-ml. portions of benzene. The combined benzene extracts are washed with three 100-ml. portions of 10% sodium hydroxide, the benzene is removed by distillation at ordinary pressure, and the residual oil is distilled under reduced pressure. The yield of product boiling at 118–121°/1 mm. (Note 3) is 29–31 g. (75–80%) (Notes 4 and 5).

---

[2] Knorr, *Ann.*, **245**, 372 (1888).

2. Notes

1. A technical grade of *o*-nitrophenol was used; the yield is no better with the pure material. In place of *n*-butyl bromide, a corresponding amount (36.8 g.) of the iodide can be used with no change in yield.

2. The checkers shook the flask occasionally during the first 1.5 hours in order to prevent caking of the contents.

3. The boiling point is 126–129° at 2 mm. and 171–172° at 19 mm.

4. Other nitrophenyl ethers can be prepared in a similar manner and in essentially the same yields. When the size of the run was increased to 2 moles, the yields were increased to 85–90%. The hexyl derivatives require 72 hours for reaction.

The boiling points of some ethers prepared by the present procedure are as follows: *m*-*n*-butoxynitrobenzene, 120–124°/2 mm.; *p*-*n*-butoxynitrobenzene, 150–154°/5 mm.; *p*-isopropoxynitrobenzene, 283–286°/760 mm.; *o*-*n*-hexoxynitrobenzene, 145–148°/1 mm.; *p*-*n*-hexoxynitrobenzene, 170–174°/5 mm.

5. The alkoxyanilines are obtained readily by reduction of the alkoxynitrobenzenes in alcohol in the presence of Raney nickel catalyst.[1] The boiling points of some of these are as follows: *m*-*n*-butoxyaniline, 120–124°/2 mm.; *p*-*n*-butoxyaniline, 135–138°/5 mm.; *p*-isopropoxyaniline, 145–147°/20 mm.; *p*-*n*-hexoxyaniline, 155–158°/5 mm.

3. Methods of Preparation

The present procedure, which avoids the preparation of the salts of the phenols, is of general utility. It was first used by Claisen[2] for allyl ethers. *o*-*n*-Butoxynitrobenzene has been prepared in a similar manner previously.[3] The *m*-nitro- and *p*-nitrobutoxybenzenes have been obtained by alkylation of the phenol salts.[4,5] The corresponding amines have been prepared previously by reduction of the nitro compounds by means of iron and water [3] and by stannous chloride and hydrochloric acid.[5]

---

[1] *Org. Syntheses*, **22**, 9 (1942).

[2] Claisen and Eisleb, *Ann.*, **401**, 39, 59 (1913).

n-BUTYLBENZENE

(Benzene, butyl-)

$$C_6H_5Br + 2Na + n\text{-}C_4H_9Br \rightarrow n\text{-}C_4H_9C_6H_5 + 2NaBr$$

Submitted by R R Read, L. S. Foster, Alfred Russell, and V. L. Simril.
Checked by C F. H. Allen and James Van Allan.

1. Procedure

A dry, 3-l., three-necked, round-bottomed flask (Notes 1 and 2) is fitted with an efficient reflux condenser (Note 3) protected by a drying tube, a dropping funnel, and a thermometer which extends well into the reaction mixture (Note 4); the flask is arranged so that it can be cooled externally (Note 5). In the flask is placed 161 g. (7 gram atoms) of sodium cut into shavings 1–2 mm. in thickness (Notes 6 and 7); the sodium is just covered with dry ether (about 300 ml.) (Note 8). A mixture of 411 g. (321 ml., 3 moles) of *n*-butyl bromide and 471 g. (315 ml., 3 moles) of bromobenzene (Note 9) is added slowly from the dropping funnel over a period of about 2.5 hours, the temperature being kept as near 20° as possible; the mass acquires a bluish color.

After the flask and contents have been allowed to stand at room temperature for 2 days with occasional shaking, the liquid is decanted (Note 10). Three hundred milliliters of methanol is then added carefully, and the mixture is refluxed on a steam bath

[3] Li and Adams, *J. Am. Chem. Soc.*, **57**, 1567 (1935).

[4] Hodgson and Clay, *J. Chem. Soc.*, **1933**, 661.

[5] Gutekunst and Gray, *J. Am. Chem. Soc.*, **44**, 1742 (1922).

for 4 hours. Then 800 ml. of water is added to dissolve the salt, and the hydrocarbon layer is separated and added to the decanted liquid. The aqueous layer is extracted once with 250 ml. of ether (Note 11), and the combined hydrocarbon fraction, decanted solution, and ether extract are dried over 40 g. of calcium chloride. Most of the ether is removed on a steam bath, and the residual liquid is distilled through an electrically heated, jacketed column (Note 12). The fraction which boils at 180–182.5°/750 mm. is collected as *n*-butylbenzene (Notes 13 and 14); the yield is 261–281 g. (65–70%) (Note 15).

2. Notes

1. The size of the pieces of sodium, the control of temperature, and the use of an electrically heated, jacketed fractionating column are important factors in the successful preparation of the compound.

2. A copper flask and copper condenser reduce the hazard from breakage but are not essential and are less convenient with the quantities indicated.

3. Unless the reaction gets out of hand, the only function of the condenser is to prevent loss of ether. If the temperature gets above 30°, the reaction becomes violent and cannot be controlled by a single condenser.

4. A thermometer on which the scale is well above the surface of the reaction mixture is advisable; one reading from −50° to 50° is convenient.

5. The temperature range is critical. Below 15° reaction is extremely slow, but in time a vigorous reaction suddenly sets in and blows a good part of the reactants out through the condenser. Above 30° the reaction gets out of hand (Note 3).

6. This is a very tedious task. It is best accomplished by flattening the usual bars of sodium with a hammer and cutting the flattened strips with scissors. Alternatively the sodium, in 1-lb. lots, can be rolled under a heavy lawn roller (Read and Foster).

7. If the sodium is too thick, much of it fails to react, whereas

sodium "sand" reacts very vigorously but gives poor yields of the desired product.

8. Larger runs require more ether. The ether may be dried over calcium chloride and used directly.

9. The *n*-butyl bromide and bromobenzene need not be redistilled.

10. Read and Foster recommend extracting the residue with benzene, using an automatic extractor.

11. Although this extract contains but 2–3 g. of hydrocarbon, its use facilitates drying later on and reduces loss through an occasional imperfect separation of layers.

12. A column such as the Whitmore-Lux or Fenske column (p. 2, Fig. 1) provided with an electrically heated jacket is essential.

13. Alternatively, a crude fraction boiling at 160–185° is collected; on redistillation, the product which boils at 181–184° is collected (Read and Foster).

14. The fore-run amounts to about 45 g. The residue is largely biphenyl. Small additional amounts of product can be secured by combining these fractions from several runs and refractionating.

15. Without a heated column, the yield drops to 221 g. (54%).

3. Methods of Preparation

n-Butylbenzene has been prepared by the action of sodium (*a*) on benzyl chloride or bromide and *n*-propyl bromide without diluents,[1] or (*b*) on *n*-butyl bromide and bromobenzene without a solvent [2] or in benzene; [3] by a Clemmensen reduction of *n*-butyrophenone; [4] and by the action of benzylmagnesium chloride on *n*-propyl *p*-toluenesulfonate.[5] Other procedures do not appear to be of preparative value.

[1] Radziszewski, *Ber.*, **9**, 261 (1876).

[2] Read and Foster, *J. Am. Chem. Soc.*, **48**, 1606 (1926).

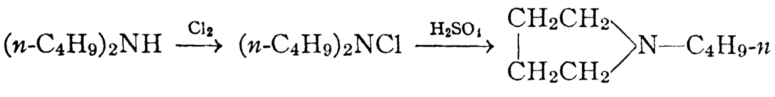
[3] Balbiano, *Ber.*, **10**, 296 (1877); *Gazz. chim. ital.*, **7**, 343 (1877).

[4] Clemmensen, *Ber.*, **46**, 1839 (1913).

[5] Gilman and Beaber, *J. Am. Chem. Soc.*, **47**, 523 (1925).

1-*n*-BUTYLPYRROLIDINE

(Pyrrolidine, 1-butyl-)



$$(n\text{-}C_4H_9)_2NH \xrightarrow{Cl_2} (n\text{-}C_4H_9)_2NCl \xrightarrow{H_2SO_4} \left.\begin{matrix}CH_2CH_2\\ | \\ CH_2CH_2\end{matrix}\right> N{-}C_4H_9\text{-}n$$

Submitted by George H. Coleman, Gust Nichols, and Ted F. Martens.
Checked by C. F. H. Allen and J. Van Allan.

1. Procedure

This preparation must be carried through the ring closure without interruption.

The apparatus is arranged as in Fig. 3. In a bottle of about 1.5-l. capacity are placed 64.5 g. (0.5 mole) of di-*n*-butylamine,[1] 350 ml. of ligroin (Note 1), and 350 ml. of 3 *N* sodium hydroxide (Note 2). The bottle is fitted with an inlet tube which passes only 1 in. through the stopper. The mixture is cooled in an ice bath (Note 3), and chlorine from a cylinder is passed in under pressure (Note 4). The bottle is kept in the ice bath and is shaken during the addition to aid in absorption of the gas. The rate of shaking and the valve on the chlorine cylinder are so regulated that the pressure as indicated on the manometer is maintained between 100 and 150 mm. (Note 5). The addition of the chlorine is continued until the white fumes of the hydrochloride, which form when chlorine comes in contact with the amine vapor, disappear, and the non-aqueous layer takes on a greenish yellow color, due to a slight excess of chlorine. This indicates that chlorination is complete (Note 6).

The ligroin solution of the chloramine is separated from the aqueous layer in a chilled, short-stemmed 1-l. separatory funnel and washed successively with 50 ml. of ice-cold 3 *N* sodium hydroxide (Note 7), 50 ml. of ice water, and 50 ml. of cold 2 *N* sulfuric acid. The ligroin solution becomes nearly colorless. The chloramine is extracted from the solution with sulfuric acid in the following manner. An ice-cold mixture of 200 ml. of concentrated sulfuric acid (sp. gr. 1.84) and 80 ml. of water is allowed to stand in contact with the ligroin solution for 10 minutes *without* shaking, then for 20 minutes *with* occasional shaking; the mixture is kept cool by immersion in an ice bath. After separation from the acid layer, the ligroin is extracted with two 60-ml. portions of cold concentrated sulfuric acid. The combined sulfuric acid extracts are used for ring closure (Note 8). The ligroin, which contains not more than a trace of chloramine, is discarded.

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[1] *Org. Syntheses* Coll. Vol. **1,** 202 (1941).

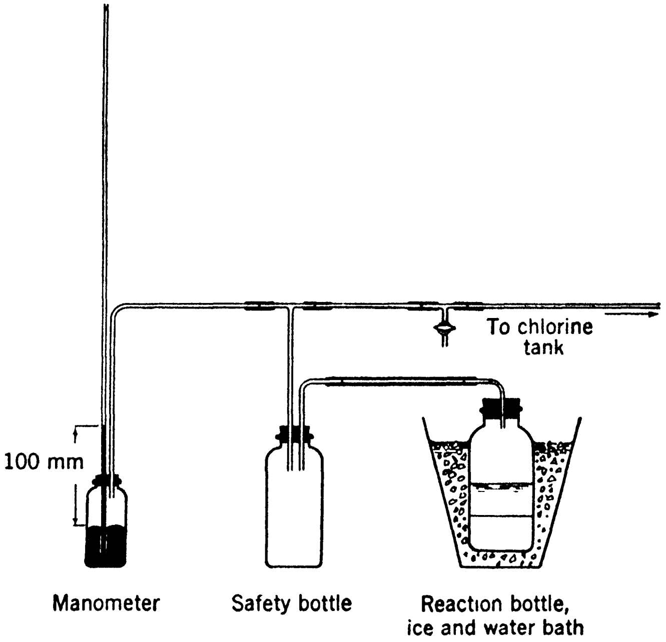

FIG. 3.

A 1-l. wide-mouthed Erlenmeyer flask, fitted with a propeller-type stirrer and a thermometer, is set in an oil bath. A mixture of 40 ml. of concentrated sulfuric acid and 10 ml. of water is placed in the flask, the oil bath is heated to 120°, and the cold sulfuric acid solution of the chloramine is allowed to flow into the heated acid from the short-stemmed separatory funnel (Note 9). The addition, which requires 30–40 minutes (Note 10), is carried out at such a rate that the temperature of the reaction mixture in the flask is dropped from 120° rapidly to 95° by the addition of the cold chloramine solution, and thereafter at such a rate that the temperature of the reaction mixture remains at 90–100°, preferably at 95°. The reaction is exothermic, and the rise in temperature is controlled by the addition of the cold chloramine solution. To avoid an undue rise in temperature after the last addition of the chloramine, the oil bath is removed, and the flask and contents are allowed to come to room temperature.

A 5-l. flask is fitted with a separatory funnel and arranged for steam distillation.[2] Two liters of crushed ice is placed in the flask, and the sulfuric acid solution, cooled to 0°, is slowly added. The amines are then liberated (Note 11) by adding cold concentrated sodium hydroxide solution (650 g. in 1.5 l. of water) through the separatory funnel. The amines are steam-distilled and collected in a solution of 100 ml. of concentrated hydrochloric acid (sp. gr. 1.19) and 200 ml. of water (Note 12). Distillation is continued until all amine has passed over, as indicated by a negative test with litmus paper. About 2 l. of distillate is usually required.

The amine hydrochloride solution is evaporated nearly to dryness on a steam bath (Note 13) and transferred with about 300 ml. of water to a 1-l. three-necked flask equipped with a stirrer,[3] separatory funnel, and condenser. The stirrer is started, and the acid solution is cooled to 0° by immersing the flask in an ice bath. The amines are liberated by adding slowly 100 g. of sodium hydroxide dissolved in 250 ml. of water.

Hinsberg separation. To this solution, which should be cold (5–8°), is now added 23 g. of benzenesulfonyl chloride,[4] and the mixture is stirred vigorously for 30 minutes. The separatory funnel is replaced by a stopper bearing a thermometer, and the contents of the flask are warmed to 40° and stirred until the odor of the acid chloride is no longer noticeable. This usually requires about a half hour. The 1-*n*-butylpyrrolidine is separated (Note 14) from the non-volatile di-*n*-butylbenzenesulfonamide by steam distillation, the amine being collected in dilute acid (Note 12) as before. The acid solution is then evaporated to dryness, and the amine is liberated by adding 20% sodium hydroxide solution until the aqueous layer turns red litmus blue. The amine is extracted by one 200-ml. portion of ether, and the ethereal solution is dried over 15–20 pellets of potassium hydroxide. After the ether has been distilled from the decanted solution, the residue is distilled from an oil bath. The yield of 1-*n*-butylpyrrolidine boiling at 154–155°/758 mm. is 44–51 g. (70–80%); n_D^{27} 1.437 (Note 15).

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[2] *Org. Syntheses*, **22**, 10, Fig. 1 (1942).

[3] *Org. Syntheses* Coll Vol. **1**, 33, Fig 2B (1941).

[4] *Org. Syntheses* Coll. Vol. **1**, 84 (1941).

2. Notes

1. Any fraction boiling within the range 60–90° may be used.

2. This is obtained by dissolving 42 g. of sodium hydroxide in 350 ml. of water.

3. All equipment, the solutions, and the chloramine solution should be kept ice-cold to prevent decomposition during the preparation. Apparatus may be stored in a refrigerator.

4. As the addition of chlorine is started, the stopper in the reaction bottle is loosened momentarily and the chlorine is allowed to replace most of the air in the system.

5. As the chlorine passes initially into the bottle, the pressure rises rapidly. Shaking greatly increases the rate of absorption, and the pressure drops. The chlorine valve is then regulated so as to maintain the proper pressure with shaking. One hundred millimeters was selected as the approximate pressure, since the rate of chlorination under this pressure is satisfactory.

6. A large excess of chlorine is undesirable and may result in greatly decreased yields. The time required varies widely, being dependent upon the chlorine pressure maintained and the vigor of the shaking. The checkers found that 20 minutes was ample under their conditions; the submitters reported that 60–90 minutes was required.

7. If the green color, due to excess chlorine, is not removed by one washing, the operation is repeated as many times as may be necessary.

8. The sulfuric acid layers are transferred directly into the 500-ml. short-stemmed separatory funnel to be used in the next step. The solution, which usually has a light brown color, should be cold and well mixed before the ring-closure operation. The ratio of acid to water is important, and only the amounts specified should be used.

9. The funnel and contents may be supported over the reaction flask during the addition without cooling.

10. The rate of addition should be as rapid as possible provided that the proper temperature is maintained. Deviation of more than 5° from the optimum reaction temperature of 95° results in reduced yields.

11. This reaction is vigorous, and the solution of alkali should be added slowly while the flask is shaken gently with a rotary motion.

12. An adapter (rubber connector and glass tube) from the lower end of the condenser should extend below the surface of the absorbing acid in the receiver. To reduce fuming, a 3- to 4-mm. layer of ligroin is placed over the acid solution. The acid solution may be stirred occasionally.

13. Use of reduced pressure considerably diminishes the time required.

14. The amine can be separated from the sulfonamide by extracting both with ether, drying this extract over solid potassium hydroxide, and fractionating. The pyrrolidine distils smoothly, but the yield is slightly lower.

15. Several other pyrrolidines of this series can be prepared by the same general method. The temperature required for ring closure and the percentage yield of pyrrolidine vary with the different amines used. The following temperatures are given as approximately correct for the ring closure of the N-chloro derivatives of the amines listed. With lower-boiling pyrrolidines, incomplete separation from the ether may result in lower yields.

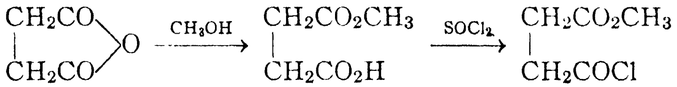
AMINE	OPTIMUM TEMPERATURE	PYRROLIDINE FORMED
Methyl-*n*-butyl	100–110°	1-Methylpyrrolidine
Ethyl-*n*-butyl	110–115°	1-Ethylpyrrolidine
n-Propyl-*n*-butyl	80–85°	1-*n*-Propylpyrrolidine
Methyl-*n*-amyl	90–100°	1,2-Dimethylpyrrolidine
Ethyl-*n*-amyl	80–90°	1-Ethyl-2-methylpyrrolidine
Methyl-*n*-octyl	60–70°	1-Methyl-2-*n*-butylpyrrolidine

3. Methods of Preparation

1-*n*-Butylpyrrolidine can be prepared also by heating the corresponding N-bromoamine in concentrated sulfuric acid[5] and by the catalytic reduction of N-butylpyrrole.[6] The procedure described is adapted from the preparation reported in earlier work[7] in less detail.

β-CARBOMETHOXYPROPIONYL CHLORIDE

(Propionic acid, β-(chloroformyl)-, methyl ester)



$$\begin{array}{l}CH_2CO\\ |\\ CH_2CO\end{array}\!\!>O \xrightarrow{CH_3OH} \begin{array}{l}CH_2CO_2CH_3\\ |\\ CH_2CO_2H\end{array} \xrightarrow{SOCl_2} \begin{array}{l}CH_2CO_2CH_3\\ |\\ CH_2COCl\end{array}$$

Submitted by JAMES CASON.
Checked by C. F. H. ALLEN and C V. WILSON.

1. Procedure

A. *Methyl hydrogen succinate.* A mixture of 400 g. (4 moles) of succinic anhydride (Note 1) and 194 ml. (4.8 moles) of methanol (Note 2) in a 1-l. round-bottomed flask is refluxed on a steam bath. After about 35 minutes the mixture is swirled frequently until it becomes homogeneous (this requires 15–30 minutes); the flask is then half immersed in the steam bath for an additional 30–25 minutes (Note 3).

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[5] Britton, U. S. pat. 1,607,605 [*C.A.*, **21**, 249 (1927)].

[6] Ochiai, Tsude, and Yokoyama, *Ber.*, **68**, 2293 (1935).

[7] Coleman and Goheen, *J. Am. Chem. Soc.*, **60**, 730 (1938).

The excess methanol is removed by distillation *in vacuo* (water pump) from a steam bath, and the residual liquid is poured into an 18- to 25-cm. evaporating dish which is cooled in a shallow pan of cold water. As the half ester crystallizes, it is stirred and scraped off the dish in order to prevent formation of a solid cake. After being dried to constant weight in a vacuum desiccator (5–8 days), the product weighs 502–507 g. (95–96%) and melts at 57–58° (Notes 4 and 5).

B. *β-Carbomethoxypropionyl chloride.* In a 1-l. flask (Note 6) bearing a reflux condenser are placed 264 g. (2 moles) of methyl hydrogen succinate and 290 ml. (4 moles) of thionyl chloride (Note 7), and the solution is warmed in a bath at 30–40° for 3 hours (Note 8). The condenser is replaced by a modified Claisen still head, the excess thionyl chloride is removed on a steam bath *in vacuo*, and the β-carbomethoxypropionyl chloride is distilled (Notes 9 and 10). The yield of colorless product is 270–278 g. (90–93%), b.p. 92–93°/18 mm. (Notes 11 and 12).

2. Notes

1. Eastman's succinic anhydride (m. p. 115–116°) was used.

2. Synthetic methanol was used. Since this anhydrous alcohol is hygroscopic, partially filled bottles that have been opened intermittently in the laboratory should be rejected.

3. Thirty minutes is allowed if solution resulted after 15 minutes of swirling; 25 minutes if 30 minutes was needed for homogeneity.

The time factor is very important. In one run in which the mixture was heated for a total of 55 minutes, a product was obtained which was shown by titration to contain about 6% of anhydride. Longer heating than that specified increases the yield of diester. Any change in quantity of materials used may necessitate a new set of conditions in order to obtain the maximum yield.

4. The checkers prefer the following procedure, which can be carried through in one day. A suspension of approximately one-half of the crude product in 750 ml. of carbon disulfide is

warmed on a steam bath; two layers form, in which some solid remains in suspension. This is dissolved by the addition of 350 ml. of ether. The whole is chilled to 0°, and the solid is filtered by suction. The other half of the crude product is now dissolved in this filtrate, the solution is again chilled to 0°, and the solid is filtered. The combined yield of acid ester, m.p. 57–58°, is 438–449 g. (83–85%). A further 32–37 g. (6–7%) of less pure material (m.p. 56–57°) can be obtained by concentrating the filtrate to half its volume and chilling to 0°.

5. The product, which is sufficiently pure for the next step, contains at least 98% methyl hydrogen succinate as shown by titration or distillation through an 18-in. Podbielniak-type column.

6. Equipment with ground-glass joints is used throughout.

7. Eastman's thionyl chloride (b.p. 75–76°) was used. The checkers obtained equivalent yields of the choride by using only 20% excess of thionyl chloride. The mixture was heated for 1 hour at 40°, allowed to stand overnight, and heated again for 2 hours at 40°.

8. Since hydrogen chloride is evolved, it is advisable to work in a hood or employ a gas trap.[1]

9. An electric heating mantle * is convenient.

10. Other boiling points are 85.5–87°/13 mm. and 89–90°/15 mm. The use of as low a pressure as possible is advisable, since the substance tends to lose methyl chloride and form succinic anhydride.

11. The submitter obtained the same yield when phosphorus pentachloride was used instead of thionyl chloride. Consistent results were obtained with the former reagent only when the acid chloride was distilled at pressures below 3 mm. (b.p. 58–59°/2.5 mm.).

12. Ethyl hydrogen adipate and ethyl hydrogen sebacate may be converted to the corresponding ester acid chlorides by this procedure in about the same yields. Distillation should be carried out rapidly at a pressure of 4 mm. or lower.

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[1] *Org. Syntheses* Coll. Vol. 2, 4 (1943).

* Such as supplied by the Glas-Col Apparatus Company, Terre Haute, Indiana.

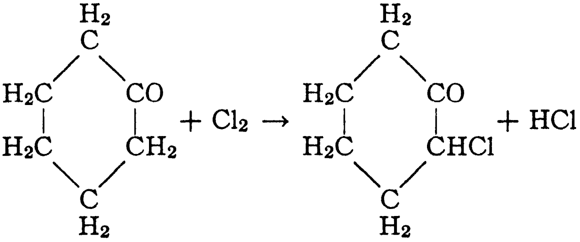
3. Methods of Preparation

Methyl hydrogen succinate has been prepared by heating succinic acid with methyl succinate,[2] by treating ethyl succinate with sodium methoxide,[3] and by heating succinic anhydride with methanol.[4,5,6]

β-Carbomethoxypropionyl chloride has been prepared from methyl hydrogen succinate by the use of thionyl chloride[6] or phosphorus pentachloride.[5]

2-CHLOROCYCLOHEXANONE

(Cyclohexanone, 2-chloro-)



Submitted by M. S. Newman, M. D. Farbman, and H. Hipsher.
Checked by C. S. Hamilton and C. W. Whitehead.

1. Procedure

In a 3-l., three-necked, round-bottomed flask, fitted with a gas inlet tube reaching almost to the bottom, a sealed mechanical stirrer (Note 1), and a gas outlet tube connected to a mercury valve (Note 2), are placed 294 g. (3 moles) of cyclohexanone (Note 3) and 900 ml. of water. After the reaction vessel has been swept out with chlorine, the gas outlet tube is connected to the mercury valve, the flask is cooled in an ice bath, the stirrer is started, and 215 g. (slightly more than 3 moles) of chlorine is bubbled in as rapidly as the gas is absorbed (about 45 minutes) (Note 4).

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[2] Fourneau and Sabetay, *Bull. soc. chim.*, (4) **45**, 841 (1929).

[3] Komnenos, *Monatsh.*, **32**, 77 (1911).

[4] Bone, Sudborough, and Sprankling, *J. Chem. Soc.*, **85**, 539 (1904).

[5] Cason, *J. Am. Chem. Soc.*, **64**, 1107 (1942).

[6] Ruggli and Maeder, *Helv. Chim. Acta*, **25**, 943 (1942).

The heavier chlorocyclohexanone layer is separated and combined with three 150-ml. ether extracts of the aqueous phase, and washed with 150 ml. of water and then with 200 ml. of saturated sodium chloride solution. After filtration (gravity) through anhydrous sodium sulfate the ether is removed and the residue vacuum-distilled in a modified Claisen flask. The fraction (300–340 g.) boiling below 100° at 10 mm. (Note 5) is collected (Note 6). This material is then fractionated carefully under reduced pressure by means of a 42-in. modified Vigreux column (heated) with a total condensation variable takeoff head (Note 7). The yield of 2-chlorocyclohexanone boiling at 90–91°/14–15 mm. is 240–265 g. (61–66%) (Notes 8 and 9).

2. Notes

1. A large propeller-type stirrer is satisfactory. The blades should be pitched to drive the liquid upwards, and the propeller should be located just below the surface of the liquid to provide splashing. The checkers used a glycerol-lubricated rubber-tube seal.[1]

2. The mercury valve consists of a tube dipping about 0.5 in. into some mercury in a vented test tube. This allows the reaction to be carried out under a slight pressure of chlorine. The checkers found a water valve to be more satisfactory. The outlet tube was made to dip about 7 in. into water in a vented glass tube. A trap (125-ml. suction flask) was placed between the water valve and the reaction flask to prevent water from being sucked into the reaction mixture.

3. The checkers used Eastman's cyclohexanone boiling at 154–156°. The submitters report that the Practical grade gives just as good yields.

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[1] *Org. Syntheses*, **21**, 40 (1941).

4. Careful control of the temperature is unnecessary as approximately the same results are obtained when the temperature is allowed to rise to about 50° or is kept below 20°. However, at the lower temperature a greater amount of cyclohexanone is recovered.

5. Or below 110°/13 mm., or 92°/4 mm.

6. This preliminary purification is advisable prior to careful fractionation.

7. The head used was similar to that described by Turk and Matuszak[2] except for the stopcock which was of the variety described by Newman.[3]

8. This material shows a long flat at 23.2° cor. in a time-temperature cooling curve. It can be stored in a refrigerator in paraffin-covered stoppered bottles for long periods of time without discoloration.

9. About 15–40 g. (5–13%) of cyclohexanone, b.p. 52°/14–15 mm., is recovered.

3. Methods of Preparation

2-Chlorocyclohexanone can be prepared by chlorinating cyclohexanone in glacial acetic acid as the solvent,[4] by passing chlorine into a mixture of cyclohexanone[5] or cyclohexanol[6] and water in the presence of powdered calcium carbonate, by the electrochemical chlorination of cyclohexanone in hydrochloric acid,[7] by the action of monochlorourea in acetic acid on the ketone,[8] and by the oxidation of 2-chlorocyclohexanol.[9]

[2] Turk and Matuszak, *Ind. Eng. Chem., Anal. Ed.*, **14**, 72 (1942).

[3] Newman, *Ind. Eng. Chem., Anal. Ed.*, **14**, 902 (1942).

[4] Bartlett and Rosenwald, *J. Am. Chem. Soc.*, **56**, 1992 (1934).

[5] Kotz and Grethe, *J. prakt. Chem.*, (2) **188**, 487 (1909).

[6] Ebel, *Helv. Chim. Acta*, **12**, 9 (1929); Bouveault and Chereau, *Compt. rend.*, **142**, 1086 (1906); Meyer, *Helv. Chim. Acta*, **16**, 1291 (1933); Vavon and Mitchovitch, *Bull. soc. chim.*, (4) **45**, 961 (1929).

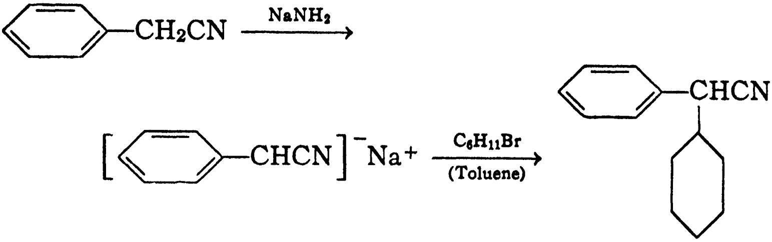
[7] Szper, *Bull. soc. chim.*, (4) **51**, 653 (1932).

[8] Godchot and Mousseron, *Bull. soc. chim.*, (4) **51**, 361 (1932).

[9] Detoeuf, *Bull. soc. chim.*, (4) **31**, 178 (1922).

α-CYCLOHEXYLPHENYLACETONITRILE

(Cyclohexaneacetonitrile, α-phenyl)



Submitted by Evelyn M. Hancock and Arthur C. Cope.
Checked by Nathan L. Drake and W. Mayo Smith.

1. Procedure

A 1-l. three-necked flask is equipped with a mercury-sealed stirrer, an inlet tube, and a reflux condenser which is connected through a soda-lime tube to a gas-absorption trap.[1] The apparatus is dried in an oven and assembled rapidly to exclude moisture; it is advisable to set up the apparatus in a hood to vent ammonia which may escape by accident. The flask is cooled in a Dry Ice-trichloroethylene bath, and 200 ml. of anhydrous (refrigeration grade) ammonia is introduced through the inlet tube from an ammonia cylinder which is either inverted or equipped with a siphon tube. Just before the apparatus is assembled, 8.1 g. (0.35 gram atom) of sodium is cut, weighed, and kept under kerosene in a small beaker. The Dry Ice bath is removed, the inlet tube is replaced by a rubber stopper, and a crystal of hydrated ferric nitrate (about 0.2 g.) is added. A small (about 5-mm.) cube of the sodium is cut, blotted rapidly with filter paper, and added quickly to the liquid ammonia. The solution is stirred until the blue color disappears, after which the remainder of the sodium is added in narrow, thin strips about as rapidly as it can be cut and blotted, while the solution is stirred vigorously (Note 1). After the solution has turned from blue to gray, the flask is swirled by hand until the blue flecks of sodium which have spattered onto the upper part of the flask are washed into the solution.

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[1] *Org. Syntheses* Coll. Vol. 2, 4 (1943).

The flask is again cooled in the Dry Ice bath, and 41 g. (0.35 mole) of benzyl cyanide (Note 2) is added during about 10 minutes through a dry dropping funnel. The Dry Ice bath is removed, and the clear solution is stirred for about 15 minutes, after which 200 ml. of dry sulfur-free toluene (Note 3) and 25 ml. of anhydrous ether are added dropwise through the funnel while the ammonia evaporates. The solution is allowed to stand or is warmed in a water bath until it comes to room temperature; the ammonia may be vaporized at any rate which does not cause gas to escape through the mercury seal on the stirrer. The remainder of the ammonia is removed by turning off the water in the reflux condenser, warming the flask in a hot water bath, and distilling most of the ether (and ammonia) through the reflux condenser.

A fresh drying tube is attached to the reflux condenser, the cooling water is turned on, and to the warm solution is added 65.2 g. (0.4 mole) of bromocyclohexane (Note 4) during approximately 20 minutes. The reaction is vigorous and may require cooling. Refluxing is continued by heating the mixture in an oil bath for 2 hours. The reaction mixture is cooled and washed with 300 ml. of water. The aqueous layer is extracted with two 50-ml. portions of benzene, and the combined benzene and toluene solutions are washed with two 50-ml. portions of water and distilled from a 500-ml. modified Claisen flask under reduced pressure. The yield of α-cyclohexylphenylacetonitrile boiling at 174–176°/13 mm. (Note 5) is 45–53 g. (65–77%); the distillate solidifies to a crystalline mass which has a melting point of 50–53.5°. The nitrile can be recrystallized from commercial pentane with approximately 15% loss; it then melts at 56–58°.

2. Notes

1. Vigorous stirring and addition of the sodium in small pieces decrease the time required for complete conversion of the sodium into sodamide.

2. Redistilled benzyl cyanide[2] was used, b.p. 108–110°/13 mm.

3. The toluene (Merck reagent grade) was kept dry by storage over sodium wire. Dry thiophene-free benzene may be used instead but is less convenient because it freezes when added to the liquid ammonia solution.

4. Bromocyclohexane obtained from the Eastman Kodak Company was dried over calcium chloride and redistilled.

5. Another boiling point is 165–167°/9 mm.

3. Methods of Preparation

α-Cyclohexylphenylacetonitrile has been prepared by treating the sodium derivative obtained from benzyl cyanide and sodamide with bromocyclohexane in benzene[3] and in ether.[4]

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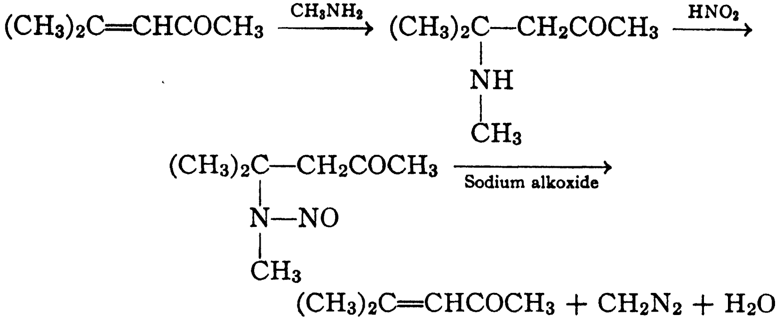
[2] *Org. Syntheses* Coll. Vol. **1**, 107 (1941).

[3] Venus-Danilova and Bol'shukon, *J. Gen. Chem.* (*U.S.S.R.*), **7**, 2823 (1937) [*C.A.*, **32**, 2925 (1938)].

[4] Vasiliu, *Bul. Soc. Chim. România*, **19A**, 75 (1937) [*C.A.*, **33**, 4207 (1939)].

DIAZOMETHANE

(Methane, diazo-)



$$(CH_3)_2C{=}CHCOCH_3 \xrightarrow{CH_3NH_2} (CH_3)_2\underset{\substack{|\\ NH\\ |\\ CH_3}}{C}{-}CH_2COCH_3 \xrightarrow{HNO_2}$$

$$(CH_3)_2\underset{\substack{|\\ N{-}NO\\ |\\ CH_3}}{C}{-}CH_2COCH_3 \xrightarrow[\text{Sodium alkoxide}]{} (CH_3)_2C{=}CHCOCH_3 + CH_2N_2 + H_2O$$

Submitted by C. Ernst Redemann, F. O. Rice, R. Roberts, and H. P. Ward.
Checked by Nathan L. Drake, Charles M. Eaker, Robert K. Preston, and W. Mayo Smith.

1. Procedure

A. *N-Nitroso-β-methylaminoisobutyl methyl ketone.* In a 2-l. three-necked flask, fitted with a mechanical stirrer, a thermometer, and a dropping funnel, is placed 250 ml. (2.1 moles) of 30% aqueous methylamine (Note 1). The flask is surrounded by an ice bath, and the stirrer is started. When the temperature of the solution has dropped to 5°, 196 g. (2 moles) of mesityl oxide is added through the dropping funnel at such a rate that the temperature remains below 20° (Notes 2 and 3). After the mesityl oxide has been added, the mixture is allowed to stand without cooling for 30 minutes.

The solution is then cooled to 10° by means of the ice bath, and 125 ml. of glacial acetic acid is added through the dropping funnel at such a rate that the temperature remains below 15°; then an additional 75 ml. of the acid is added rapidly.

The ice bath is removed, and 300 ml. of 8 *N* sodium nitrite

(Note 4) is added in 20–30 minutes to the stirred solution, which is kept at 25–35° by intermittent cooling with the ice bath. Stirring is then discontinued, and the mixture is allowed to stand for 6 hours or longer (Note 5).

The oily layer is separated from the aqueous layer, the aqueous layer is extracted with two 200-ml. portions of ether, and the combined extracts and oil are dried over calcium chloride. The drying agent is removed by filtration, and the ether is distilled on a water bath; finally, all low-boiling material is removed from the mixture on a boiling water bath under the lowest pressure obtainable with a water pump (Note 6). The nitrosoaminoketone which remains in the flask is sufficiently pure for the preparation of diazomethane (Note 7). The yield is 221–257 g. (70–80% based on mesityl oxide).

If a purer product is desired for other purposes, the nitrosoaminoketone is distilled at low pressure (see *Caution*). The substance boils at 119°/5 mm., at 111°/3 mm., or at 101°/1.5 mm.

CAUTION

Only a small quantity of the nitrosoaminoketone should be distilled at a time. It is reported that the substance occasionally undergoes violent decomposition. If the distillation is carried out, the operator should be protected by a suitable screen or plate of safety glass (Note 8).

B. *Diazomethane. Sodium isopropoxide method* (Note 9).

CAUTION

Diazomethane is very toxic; its preparation should be carried out only in a well-ventilated hood. Individuals differ in their susceptibility; some develop symptoms similar to asthma from very small concentrations, whereas others notice no ill effects from much larger quantities. The use of a safety screen is also recommended.

Thirty milliliters of a solution of sodium isopropoxide, prepared from 1 g. of sodium and 100 ml. of isopropyl alcohol, is placed in a 250-ml. Claisen flask arranged for heating in a water bath. The flask is provided with a dropping funnel, a condenser, and a receiver cooled in a Dry Ice bath; this receiver is connected to a second one containing 20 ml. of anhydrous ether; the inlet tube of the second receiver should dip below the surface of the ether.

The water bath is heated to 70–75°, and one half of a solution, prepared by dissolving 15.8 g. (0.1 mole) of N-nitroso-β-methylaminoisobutyl methyl ketone in a mixture of 80 ml. of anhydrous ether and 12 ml. of isopropyl alcohol, is added through the dropping funnel at a rate slightly greater than that of distillation. When the separatory funnel is empty, an additional 15 ml. of the solution of sodium isopropoxide is added; the remainder of the solution of nitroso compound is then added as before. Anhydrous ether is then added gradually through the dropping funnel until the condensing ether becomes colorless. The diazomethane comes over with the ether as a golden yellow distillate. The process can be continued until all the nitrosoaminoketone has been decomposed. The yield of diazomethane, which varies with the purity of the nitrosoaminoketone, is 1.9–2.5 g. (45–60%).

C. *Diazomethane. Sodium cyclohexoxide method* (Note 10). A solution of sodium cyclohexoxide is prepared from 4 g. of sodium and 100 ml. of cyclohexanol (Note 11) in a 2-l. flask; the cyclohexanol is heated to boiling under reflux to speed up the formation of the alkoxide. As soon as the sodium has disappeared, heating is discontinued and the condenser is removed. When solid begins to separate from the solution, the mixture is stirred with a stout rod to prevent the formation of a hard cake. The flask is surrounded by an ice bath, and, when the temperature of the mixture has dropped to 10°, 300 ml. of dry ether and a solution of 49 g. (0.33 mole) of N-nitroso-β-methylaminoisobutyl methyl ketone dissolved in 600 ml. of dry ether are added. The flask is connected to a 25-cm. fractionating column and an efficient water-cooled condenser (Note 12). The delivery end of the condenser should be connected to an adapter which dips below the surface of 50 ml. of ether contained in a 1-l. Erlenmeyer flask immersed in an ice bath. The mixture is heated by a water bath whose temperature is maintained at 50–55°. Distillation is continued until the condensing ether is colorless; usually 700–750 ml. of distillate containing 10–11 g. (77–84% yield) (Note 13) of diazomethane is collected (Notes 14 and 15). The diazomethane-ether solution may be purified further with only slight loss by drying over potassium hydroxide pellets (Note 16) and redistillation through a fractionating column.

2. Notes

1. Methylamine is available from several manufacturers. The Commercial Solvents Corporation and Rohm and Haas Company offer an aqueous solution containing 30% to 33% of amine. Solutions of other strengths are satisfactory if appropriate quantities are employed. The amine solution may be prepared from the hydrochloride by adding slowly 210 ml. of 10 *N* sodium hydroxide solution to an ice-cold solution of 142 g. (2.1 moles) of methylamine hydrochloride in 250 ml. of water. The resulting solution is used without further treatment.

2. The mesityl oxide should be freshly distilled.

3. The length of time needed for this addition varies with the efficiency of the cooling bath; a period of 30 minutes to 1 hour is usually required.

4. The nitrite solution is very nearly saturated. The sodium nitrite need not be of C.P. grade; if it is less pure, appropriate allowance must be made when the solution is prepared.

5. It is preferable to allow the mixture to stand overnight; care should be taken, however, that its temperature does not exceed 35° at any time.

6. The pressure should not be above 30 mm.; a pressure of 20 mm. is desirable.

7. Because of the low cost of the starting materials and the stability in storage of the nitrosoaminoketone, this substance is an excellent intermediate for preparing diazomethane. One of the submitters (Redemann) reports that a sample of the crude material was kept in the laboratory in a brown bottle for

more than 2 years without evident decomposition; the trace of acetic acid remaining in the ketone tends to stabilize it.

8. One of the submitters (Redemann) reports that he has never experienced difficulty during distillation of this ketone.

9. Submitted by F. O. Rice, R. Roberts, and H. P. Ward.

10. Submitted by C. Ernst Redemann.

11. The cyclohexanol may be replaced by benzyl alcohol. Benzyl alcohol is reported to give a slightly increased rate of formation of diazomethane and a slightly more concentrated ethereal solution; however, the over-all yield is somewhat lower. If only a small amount of diazomethane is wanted, concentrated aqueous sodium hydroxide may replace the solution of the alkoxide of cyclohexanol. The yield under these conditions is 40–50%.

12. A column with smooth packing or smooth inner surface should be used; rough surfaces catalyze the decomposition of diazomethane. A column helps to remove mesityl oxide.

13. The diazomethane content of the ethereal solution may be determined by the method described previously.[1]

14. A solution of diazomethane in dry ether may be stored in a smooth flask or bottle in a refrigerator for several weeks. Since slow decomposition of the diazomethane occurs, the concentration of the solution should be checked before use.

15. Other alkyl diazo compounds can be prepared readily by the same general method with some alterations because of the lower volatility of the higher homologs.[2]

16. Pellets are recommended because their smooth surface causes little decomposition of diazomethane.

3. Methods of Preparation

Diazomethane has been prepared from nitrosomethylurea,[1] from nitrosomethylurethane,[3,4] and from a mixture of chloroform and hydrazine hydrate by reaction with potassium hydroxide.[5] The methods described are adapted from the work of Kenner.[6,7]

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[1] *Org. Syntheses* Coll. Vol. **2**, 165 (1943).

[2] Adamson and Kenner, *J. Chem. Soc.*, **1937**, 1551.

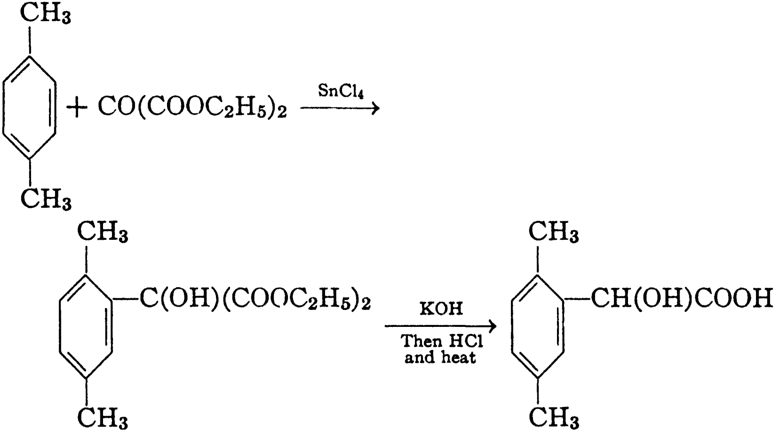
[3] v. Pechmann, *Ber.*, **27**, 1888 (1894); **28**, 855 (1895).

[4] Meerwein and Burneleit, *Ber.*, **61**, 1845 (1928).

Two recent reviews of the reactions and uses of diazomethane have appeared.[8,9]

2,5-DIMETHYLMANDELIC ACID

(Mandelic acid, 2,5-dimethyl-)



Submitted by J. L. Riebsomer and James Irvine.
Checked by H. R. Snyder and R. L. Rowland.

1. Procedure

A. *Ethyl 2,5-dimethylphenylhydroxymalonate.* One hundred and seventy-four grams (1 mole) of ethyl oxomalonate (Note 1) and 265 g. (2.5 moles) of *p*-xylene are mixed in a 1-l. three-necked flask equipped with a good stirrer, a dropping funnel, and a calcium chloride drying tube. Suitable precautions are taken to exclude moisture from the reaction mixture. While the mixture is cooled in an ice-water bath and stirred vigorously, 325 g.

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[5] Staudinger and Kupfer, *Ber.*, **45**, 505 (1912).

[6] Jones and Kenner, *J. Chem. Soc.*, **1933**, 363.

[7] Adamson and Kenner, *J. Chem. Soc.*, **1935**, 286; **1937**, 1551.

[8] Smith, *Chem. Revs.*, **23**, 193 (1938).

[9] Eistert, *Z. angew. Chem.*, **54**, 99, 124 (1941).

(1.25 moles) of anhydrous stannic chloride is added dropwise from the funnel. After the addition is complete, the cooling bath is removed and stirring is continued for 3 hours. The reaction mixture is poured with stirring into about 300 g. of cracked ice containing 50 ml. of concentrated hydrochloric acid. On standing this mixture separates into two layers. Two hundred milliliters of ether is added, and the ether layer is washed with 100-ml. portions of water until the wash water is free from chlorides. The ether solution is dried with anhydrous sodium sulfate and distilled. After removal of the ether and the excess of reagents (Note 2), the fraction boiling at 154–156°/5 mm. is collected. The yield of 2,5-dimethylphenylhydroxymalonic ester is 144.5–160 g. (51.5–57%).

B. *2,5-Dimethylmandelic acid.* A mixture prepared from 140 g. (0.5 mole) of 2,5-dimethylphenylhydroxymalonic ester and a cold solution of 140 g. of potassium hydroxide in 560 ml. of water in a 1-l. round-bottomed flask is warmed on a steam bath for 5 hours. The alkaline solution is cooled and extracted with one 100-ml. portion of ether to remove any material not soluble in alkali. The alkaline solution is acidified with 300 ml. of concentrated hydrochloric acid and then warmed on a steam bath and stirred for 2 hours (or until there is no further evidence that carbon dioxide is escaping). The mixture is cooled, the oily layer is extracted with ether, the ethereal solution is dried with anhydrous sodium sulfate, and the ether is distilled under partial vacuum (Note 3). The oily residue is crystallized from benzene. The yield of 2,5-dimethylmandelic acid melting at 116.5–117° is 55–63 g. (63–70%) (Note 4).

2. Notes

1. The ethyl oxomalonate must be of good quality. It has been found possible to use nitrogen peroxide (now available in cylinders from the du Pont Company) in the preparation of this reagent. The general conditions are the same as in the previous method in *Organic Syntheses*[1] except that the generating flask

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[1] *Org. Syntheses* Coll. Vol. 1, 266 (1941).

containing arsenious oxide and nitric acid is replaced with a cylinder of nitrogen peroxide. This method is much more satisfactory.

2. The excess *p*-xylene can be recovered easily.

3. It is important to avoid long heating after removal of the ether. The mandelic acid tends to react with itself.

4. This general method has been applied to the synthesis of a variety of alkyl-substituted mandelic acids.[2]

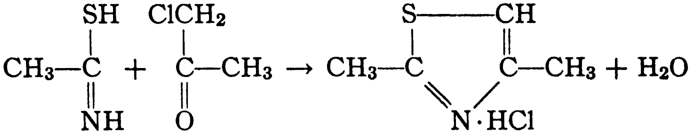
3. Methods of Preparation

2,5-Dimethylmandelic acid has been prepared by the procedure described above;[2] and by the reaction between 2,5-dimethylphenylmagnesium bromide and chloral, followed by alkaline hydrolysis.[3]

2,4-DIMETHYLTHIAZOLE

(Thiazole, 2,4-dimethyl-)

$$CH_3CONH_2 + P_2S_5 \rightarrow CH_3CSNH_2$$



Submitted by George Schwarz.
Checked by C. S. Hamilton and Edward J. Cragoe, Jr.

1. Procedure

In a 2-l. round-bottomed flask provided with a reflux condenser is placed 200 ml. of dry benzene (Note 1). A mixture of

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[2] Ando, *J. Chem. Soc. Japan*, **56**, 745 (1935) [*C.A.*, **29**, 7960 (1935)]; Riebsomer, Irvine, and Andrews, *J. Am. Chem. Soc.*, **60**, 1015 (1938); *Proc. Indiana Acad. Sci.*, **47**, 139 (1938); Riebsomer, Baldwin, Buchanan, and Burkett, *J. Am. Chem. Soc.*, **60**, 2974 (1938); Riebsomer, Stauffer, Glick, and Lambert, *J. Am. Chem. Soc.*, **64**, 2080 (1942).

[3] Savarian, *Compt. rend.*, **146**, 297 (1908) [*C.A.*, **2**, 1443 (1908)].

300 g. (5.08 moles) of finely divided acetamide and 200 g. (0.9 mole) of powdered phosphorus pentasulfide is prepared quickly and transferred immediately to the flask. To this is added 20 ml. of a mixture of 400 ml. (4.97 moles) of chloroacetone (Note 2) and 150 ml. of dry benzene. The exothermic reaction is started by careful heating in a water bath. The water bath is removed, and the remainder of the chloroacetone-benzene mixture is introduced gradually through the reflux condenser (Notes 3 and 4). When all the chloroacetone has been added and reaction is no longer apparent, the mixture is refluxed on the water bath for 30 minutes.

About 750 ml. of water is added to the mixture with shaking. After 30 minutes the mixture is poured into a separatory funnel, and the reddish upper layer containing the benzene with some impurities is discarded. The lower layer is made alkaline (Note 5) by the addition of 5 *N* sodium hydroxide or potassium hydroxide, and the crude thiazole, which separates as a black upper layer, is removed with ether, and the aqueous lower layer is extracted with five 120-ml. portions of ether. The combined ethereal extracts are dried over anhydrous sodium sulfate and filtered through glass wool. The ether is removed by distillation from a steam bath (Note 6), and the residual oil is fractionated at atmospheric pressure; the fraction boiling at 140–150° is collected and redistilled. The yield of 2,4-dimethylthiazole boiling at 143–145° (Note 7) is 210–230 g. (41–45% based on the phosphorus pentasulfide).

2. Notes

1. Commercial benzene is satisfactory after being dried over calcium chloride and distilled.

2. Commercial chloroacetone is distilled, and the fraction boiling at 116–122° is used.

3. The progress of the reaction is controlled by the portions of chloroacetone added. If too much is added at once the reaction may become too vigorous. Portions of 20 ml. are safe. Toward the end of the reaction, larger portions may be added.

4. As soon as the reaction has begun, the mixture becomes a gray-black oily liquid.

5. The alkalinity of the deeply colored solution can be tested with phenolphthalein paper. The edges of the wetted paper become visibly red. One should be sure to test the aqueous solution and not the separated thiazole floating on top of the liquid.

6. The thiazole is hygroscopic and should be protected from moisture.

7. Reported boiling points are 144–145.5°/719 mm.[1] and 143°.[2] No 2,4-dimethyloxazole (b.p. 108°) was obtained during the distillation.

3. Methods of Preparation

2,4-Dimethylthiazole has been prepared from chloroacetone and thioacetamide,[1] but forming the required thioacetamide in the reaction mixture is to be preferred since no additional manipulation is involved. The method here described is substantially that of E. Merck.[2] Other substituted thiazoles can be prepared by practically the same method.[2] 2,4-Dimethylthiazole has been obtained by dry distillation of 2-methylthiazyl-4-acetic acid,[3] and also by heating 2,4-dimethylthiazole-5-carboxylic acid with calcium oxide.[4]

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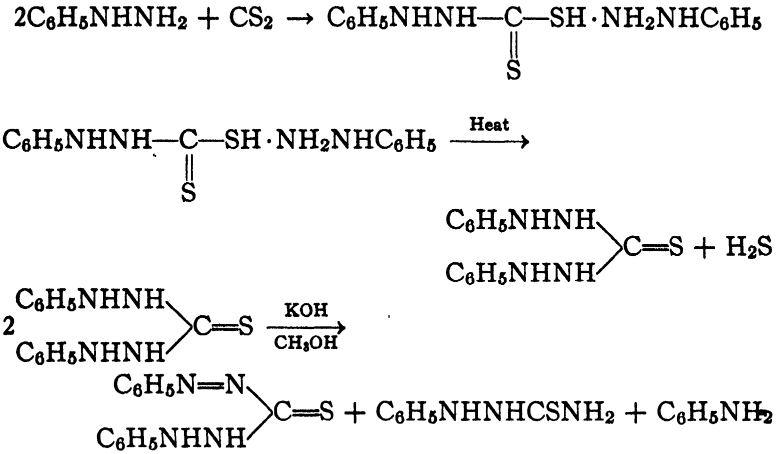
[1] Hantzsch, *Ann.*, **250**, 265 (1889).

[2] E. Merck, Ger. pat. 670,131 [*C.A.*, **33**, 2909 (1939)].

[3] Steude, *Ann.*, **261**, 41 (1891).

[4] Rubleff, *Ann.*, **259**, 266 (1890).

DITHIZONE



Submitted by John H. Billman and Elizabeth S. Cleland.
Checked by Lee Irvin Smith and Burris D. Tiffany.

1. Procedure

A. *Phenylhydrazine salt of β-phenyldithiocarbazic acid.* In a 1-l. three-necked flask, fitted with a mechanical stirrer, a condenser, and a dropping funnel, is placed a solution of 128 ml. (1.3 moles) of pure redistilled phenylhydrazine in 600 ml. of ordinary ether. To the vigorously stirred mixture, 52 ml. (0.86 mole) of carbon disulfide is added in the course of 30 minutes (Note 1). After the mixture has been stirred for an additional 30 minutes, the precipitate is filtered with suction, washed with 50 ml. of ether, and spread on filter paper for 15–20 minutes to allow evaporation of the ether. The yield of the salt is 181–185 g. (96–98%).

B. *Diphenylthiocarbazide.* The above salt is transferred to a 1-l. beaker, and, while it is continuously stirred by hand (Note 2), it is heated (Hood) in a water bath maintained at 96–98° (Note 3). After about 10–15 minutes the material softens to a taffylike mass, becomes yellow, foams, and evolves hydrogen sulfide. After about 20–30 minutes ammonia is evolved. When a distinct odor of ammonia is *first detected* (Note 4), the beaker is removed from the bath, placed in a pan of cold water for 1 minute (Note 5), and then surrounded immediately by cracked ice. About 150 ml. of absolute alcohol is added, the mixture is warmed slightly to loosen the mass, and the taffylike material is stirred until it is transformed into a granular precipitate. After the mixture has stood at room temperature for 1 hour, the precipitate is collected on a Büchner funnel and washed with 50 ml. of absolute alcohol (Note 6). The yield of crude diphenylthiocarbazide is 100–125 g. (60–75% based on phenylhydrazine) (Note 7).

C. *Dithizone.* The crude diphenylthiocarbazide is added to a solution of 60 g. of potassium hydroxide in 600 ml. of methanol in a 1-l. round-bottomed flask. The flask is immersed in a boiling water bath, and the mixture is *refluxed* for exactly 5 minutes (Note 8). The red solution is cooled with ice water and filtered by gravity. Ice-cold 1 *N* sulfuric acid (900–1100 ml.) is added to the filtrate, which is stirred vigorously by means of a mechanical stirrer, until the solution is just acid to Congo red paper (Note 9). The blue-black precipitate is filtered with suction and washed with 50 ml. of cold water (Note 10). The crude carbazone is dissolved in 500 ml. of 5% sodium hydroxide solution, the mixture is filtered with suction, and the filtrate is cooled in an ice bath and acidified immediately with ice-cold 1 *N* sulfuric acid (about 650 ml. is required) until it is just acid to Congo red paper. The precipitate is filtered with suction and then washed by transferring it to a 2-l. beaker and stirring it thoroughly with 1.6–1.8 l. of cold water. The mixture is filtered, and the process of washing is repeated until there is no trace of sulfate in the washings (Note 11). After air has been drawn through the precipitate on the Büchner funnel for 20–30 minutes, the solid is dried in an oven at 40°. The product at this stage weighs 63–85 g. For purification, a portion of 5–10 g. of the carbazone is placed in the thimble of a Soxhlet extractor (Note 12), covered with ether, allowed to stand for 1 hour, and then extracted for 1.5 hours. The material in the thimble is transferred immediately to a beaker, stirred with 50 ml.

of ether, and the mixture is filtered with suction until most, but not all, of the liquid is removed. The wet product is then dried by pressing it between filter papers. The yield of pure dithizone (diphenylthiocarbazone) which decomposes sharply at a temperature between 165° and 169° is 43–54.8 g. (50–64% based on phenylhydrazine) (Note 13).

2. Notes

1. A precipitate is formed immediately upon addition of the carbon disulfide; the mixture becomes warm, and the temperature soon approaches the boiling point. The temperature is maintained just below the boiling point; cooling with ice water may be necessary to keep it there. As the carbon disulfide is added, the mixture soon becomes pasty, then more fluid, and finally pasty again.

2. A heavy glass rod, bent or flattened at the bottom, serves as an efficient stirrer.

3. Care must be taken that the temperature of the bath does not exceed 98°. If the material remains above 98° for a long period of time and/or if it is not immediately cooled after removal from the water bath, the product decomposes violently after standing for 10–15 minutes.

4. Ammonia can be detected by means of litmus paper before the odor is noticeable, but the heating should be continued until there is a *distinct* odor of ammonia (but no longer). The yield depends upon the rapidity with which the heating is stopped after the first sign of ammonia is detected.

5. The mass may be olive-green or brown while hot, but it becomes light brown on cooling.

6. The precipitate is almost pure white. More diphenylthiocarbazide crystallizes from the red alcoholic filtrate and washings, if they are allowed to evaporate slowly. When the mixture is allowed to stand for some time before it is filtered, the amount of precipitate is increased and that of the material left in the filtrate is decreased.

7. Diphenylthiocarbazide does not have a sharp melting

point. The compound is reported to become green at 130° and melt at 150° to a dark green liquid which decomposes on further heating.

8. The solution is heated until it is definitely boiling; then it is allowed to boil for 5 minutes only. If the solution is boiled for a longer time, the yield of product is decreased.

9. When the end point is reached, the mother liquor is no longer red but colorless.

10. Care should be exercised in handling this precipitate or suspensions of it. If any of it is spilled or splashed, it should be removed at once, for it dries to a light, fine powder which is readily scattered; it dyes the skin black and other material pink.

11. Four or five washings are usually necessary.

12. The Soxhlet extractor used by the submitters had a capacity of 85 ml. to the top of the siphon tube. The size of the thimble was 33 by 80 mm.

13. The pure compound is completely soluble in chloroform.

3. Methods of Preparation

This method of preparation is a modification of the method used by Emil Fischer.[1] Similar methods have been described by H. Fischer,[2] Wertheim,[3] and Grummitt and Stickle.[4]

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[1] E. Fischer, *Ann.*, **190**, 118 (1878); **212**, 316 (1882).

[2] H. Fischer and Leopoldi, *Wiss. Veröffentl. Siemens-Konzern*, **12**, 44 (1933) [*C.A.*, **27**, 3418 (1933)].

[3] Wertheim, *Organic Chemistry Laboratory Guide*, 2nd ed., p. 504, P. Blakiston's Son & Co.

[4] Grummitt and Stickle, *Ind. Eng. Chem., Anal. Ed.*, **14**, 953 (1942).

ETHYL BENZALMALONATE

(Malonic acid, benzal-, diethyl ester)

$$C_6H_5CHO + CH_2(COOC_2H_5)_2 \xrightarrow{\substack{\text{Piperidine}\\ \text{benzoate}}} C_6H_5CH{=}C(COOC_2H_5)_2 + H_2O$$

Submitted by C. F. H. Allen and F. W. Spangler.
Checked by R. L. Shriner and Fred W. Neumann.

1. Procedure

In a 1-l. round-bottomed flask, which is fitted with a Clarke-Rahrs column [1] with a unit for removing water and surmounted by a reflux condenser, are placed 100 g. (0.63 mole) of ethyl malonate (Note 1), about 72–76 g. of commercial benzaldehyde (Note 2), 2–7 ml. of piperidine (Note 3), and 200 ml. of benzene. The mixture is refluxed vigorously in an oil bath at 130–140° until no more water (total, 12–13 ml.) is collected; this operation requires 11–18 hours. After the mixture has been cooled, 100 ml. of benzene is added and the solution is washed with two 100-ml. portions of water, with two 100-ml. portions of 1 *N* hydrochloric acid, and then with 100 ml. of a saturated solution of sodium bicarbonate. The aqueous wash solutions are shaken with a single 50-ml. portion of benzene, the benzene extract is added to the original organic layer, and the organic solution is dried with 30 g. of anhydrous sodium sulfate. After the benzene has been removed under reduced pressure on a steam bath, the residue is distilled under reduced pressure from a 250-ml. modified Claisen flask [2] well wrapped with asbestos. The yield of colorless ethyl benzalmalonate boiling at 140–142°/4 mm. (Note 4) is 137–142 g. (89–91%) (Note 5).

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[1] *Org. Syntheses*, **24**, 72 (1944). The column can be purchased from the Precision Optical Company, Rochester, New York.

[2] *Org. Syntheses*, **22**, 11, Fig. 2 (1942).

2. Notes

1. B.p. 94–96°/16 mm. The checkers used redistilled ethyl malonate.

2. Commercial benzaldehyde which contains 2–8% of benzoic acid is eminently satisfactory. The acid content is determined (conveniently by titration of a sample in neutral ethanol with standard alkali), and a quantity of aldehyde containing 70 g. (0.66 mole) of benzaldehyde is used. The checkers used 76 g. of commercial benzaldehyde which contained 8% of benzoic acid. If pure benzaldehyde is employed, then 2 g. of benzoic acid should be added.

It has been shown [3] that piperidine salts and not the free base act as the catalyst in the Knoevenagel reaction. The checkers obtained only a 71% yield with benzaldehyde containing less than 0.2% of benzoic acid.

3. The amount of piperidine that is employed depends on the benzoic acid content of the aldehyde; it should be slightly in excess of that required to neutralize the benzoic acid. About 1.2 ml. of piperidine per gram of acid is satisfactory.

4. Another boiling point is 179–181°/10 mm. The boiling points reported for ethyl benzalmalonate vary widely. The temperature observed depends on the degree of superheating and the rapidity of distillation.

5. Methyl benzalmalonate (b.p. 143–146°/2 mm., 169–171°/10 mm.) can be prepared in the same manner and in the same apparatus in yields of 90–94%.

3. Methods of Preparation

Ethyl benzalmalonate has been prepared by the esterification of benzalmalonic acid in the presence of concentrated sulfuric acid; [4] by the action of benzal chloride on sodiomalonic ester; [5] by the condensation of benzaldehyde and malonic ester in the presence of hydrogen chloride,[6,7] acetic anhydride,[8] or alcoholic piperidine or ammonia;[9] and by the action of phenylmagnesium bromide on hydroxymethylenemalonic ester.[10]

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[3] Kuhn, Badstubner, and Grundmann, *Ber.*, **69**, 98 (1936).

[4] Stuart, *J. Chem. Soc.*, **47**, 158 (1885).

[5] Avery and Bouton, *Am. Chem. J.*, **20**, 510 (1898).

ETHYL (1-ETHYLPROPENYL)-METHYLCYANOACETATE

(3-Pentenoic acid, 2-cyano-3-ethyl-2-methyl-, ethyl ester)

$$(C_2H_5)_2C{=}C(CN)COOC_2H_5 \xrightarrow{NaOC_2H_5} [CH_3CH{=}C(C_2H_5)C(CN)COOC_2H_5]^-Na^+ \xrightarrow{CH_3I} CH_3CH{=}C(C_2H_5)C(CH_3)(CN)COOC_2H_5$$

Submitted by Evelyn M. Hancock and Arthur C. Cope.
Checked by H. R. Snyder and J. H. Saunders.

1. Procedure

A solution of sodium ethoxide is prepared from 9.2 g. (0.40 mole) of freshly cut sodium and 400 ml. of absolute alcohol (Note 1) in a 1-l. three-necked flask fitted with a dropping funnel, a thermometer, a mercury-sealed stirrer, and a condenser protected by a drying tube (Note 2). To the stirred solution, which is kept at −5° (conveniently by partially immersing the flask in a Dry Ice bath), 72.4 g. (0.40 mole) of ethyl (1-ethylpropylidene)-cyanoacetate (p. 46) is added dropwise from the funnel during 8–10 minutes. After the mixture has been stirred for an additional 20 minutes at −5°, 62.5 g. (0.44 mole) of methyl iodide is added from the dropping funnel as rapidly as possible. The flask is heated immediately with a strong flame which is withdrawn just as the solution reaches the boiling point. The alkylation is vigorous, but the flask is not cooled unless loss of material through

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[6] Claisen, *Ber.*, **14**, 348 (1891).

[7] Claisen and Crismer, *Ann.*, **218**, 131 (1883).

[8] Knoevenagel, *Ber.*, **31**, 2591 (1898); Gravel, *Nat. canadien*, **57**, 181 (1931) [*C.A.*, **28**, 169 (1934)].

[9] Ger. pat. 97,734 [*Frdl.*, **5**, 906 (1898–1900)].

[10] Reynolds, *Am. Chem. J.*, **44**, 314 (1910).

the reflux condenser appears imminent (Note 3). After the spontaneous reaction has subsided, the solution is refluxed until a piece of red litmus paper dipped into the liquid and subsequently moistened shows a neutral reaction (15–30 minutes).

The solution is cooled and diluted with 1 l. of water, and the ester layer is separated. The aqueous layer is extracted with four 50-ml. portions of benzene, and the combined ester and benzene extracts are washed with two 25-ml. portions of water and then distilled from a 500-ml. modified Claisen flask. The fraction (about 75 g.) which is collected at 95–118°/10 mm. is shaken mechanically for 4 hours with 100 ml. of 20% sodium bisulfite solution (Note 4). The ester layer is separated, the aqueous layer is extracted with three 25-ml. portions of benzene, and the combined ester and benzene extracts are washed with 25 ml. of water. The product remaining after removal of the benzene is distilled under reduced pressure from a 250-ml. modified Claisen flask or through a Widmer column. The yield of ester boiling at 112–113°/8 mm. is 63.5–68 g. (81–87%).

2. Notes

1. Commercial absolute alcohol is dried with sodium and ethyl phthalate[1] and redistilled. The checkers obtained a considerably lower yield in a run employing alcohol dried over magnesium methoxide.

2. The various pieces of apparatus are dried in an oven and assembled rapidly in order to exclude moisture.

3. Excessive cleavage (alcoholysis) of the product is avoided by carrying out the alkylation rapidly. This procedure minimizes the time during which the product is in contact with sodium ethoxide.

4. This treatment removes ethyl (1-ethylpropylidene)-cyanoacetate as a water-soluble sodium bisulfite addition product (p. 46).

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[1] *Org. Syntheses* Coll. Vol. 2, 155 (1943).

3. Methods of Preparation

The above procedure illustrates a general method for preparing homologous ethyl (dialkylvinyl)-alkylcyanoacetates by the alkylation of ethyl alkylidenecyanoacetates.[2]

ETHYL (1-ETHYLPROPYLIDENE)-CYANOACETATE

(2-Pentenoic acid, 2-cyano-3-ethyl-, ethyl ester)

$$(C_2H_5)_2CO + CH_2(CN)COOC_2H_5 \xrightarrow[CH_3COOH]{CH_3COONH_4} (C_2H_5)_2C{=}C(CN)COOC_2H_5 + H_2O$$

Submitted by Arthur C. Cope and Evelyn M. Hancock.
Checked by H. R. Snyder and J. H. Saunders.

1. Procedure

In a 500-ml. round-bottomed flask attached to a modified Dean and Stark constant water separator [1] (Note 1) which is connected to a reflux condenser are placed 67.8 g. (0.60 mole) of ethyl cyanoacetate (Note 2), 56.8 g. (0.66 mole) of diethyl ketone (Note 3), 9.2 g. (0.12 mole) of ammonium acetate, 30 g. (0.48 mole) of glacial acetic acid, and 100 ml. of benzene. The flask is heated in an oil bath at 160–165°, and the water which distils out of the mixture with the refluxing benzene is removed from the separator at intervals. Refluxing is continued for 24 hours (several hours after the separation of water has ceased) (Note 4).

The solution is cooled and washed with three 25-ml. portions of 10% sodium chloride solution, after which the benzene is removed by distillation under reduced pressure. The residue is transferred to a 1-l. bottle, a solution of 78 g. (0.75 mole) of commercial sodium bisulfite in 310 ml. of water is added, and the

[2] Cope and Hancock, *J. Am. Chem. Soc.*, **60**, 2903 (1938).

ETHYL (1-ETHYLPROPYLIDENE)-CYANOACETATE

[1] Cope, Hofmann, Wyckoff, and Hardenbergh, *J. Am. Chem. Soc.*, **63**, 3452 (1941).

mixture is shaken on a mechanical shaker for 2 hours. The turbid solution is diluted with 500 ml. of water and extracted with three 50-ml. portions of benzene. The extracts are discarded (Note 5). The bisulfite solution is then cooled in an ice bath, and an ice-cold solution of 32 g. (0.8 mole) of sodium hydroxide in 130 ml. of water is added dropwise with mechanical stirring. The ester which separates is extracted at once with four 25-ml. portions of benzene (Note 6). The benzene solution is washed with 50 ml. of 1% hydrochloric acid, dried for a short time over 20 g. of anhydrous sodium sulfate, filtered into a 250-ml. modified Claisen flask, and distilled under reduced pressure. The yield of ester boiling at 123–125°/12 mm. (Note 7) is 65.4–75 g. (60.5–68%) (Notes 8, 9, and 10).

2. Notes

1. Another suitable separator is described in *Organic Syntheses*.[2] Any continuous water separator which will return the benzene to the reaction mixture may be used.

2. Commercial ethyl cyanoacetate (Dow Chemical Company) was redistilled before use; b.p. 93–94°/12 mm.

3. Diethyl ketone was either purchased from the Eastman Kodak Company and redistilled, or prepared by passing propionic acid slowly over a mixture of manganous oxide and clay plate chips in a tube furnace at 420–440°;[3] the apparatus was similar to one described in *Organic Syntheses*.[4] When prepared by this method the ketone was distilled, dried over potassium carbonate, and redistilled; b.p. 100–101°.

4. The water layer (20–25 ml.) contains some acetic acid and acetamide, the acetamide being formed from the ammonium acetate catalyst.

5. Extraction of the aqueous solution removes ethyl cyanoacetate from the aqueous solution of the sodium bisulfite addition product of ethyl (1-ethylpropylidene)-cyanoacetate.

6. The unsaturated ester is regenerated when the bisulfite is neutralized with sodium hydroxide. The solution is kept cold

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[2] *Org. Syntheses*, **23**, 38 (1943).

[3] Sabatier and Mailhe, *Compt. rend.*, **158**, 831 (1914).

[4] *Org. Syntheses* Coll. Vol. **2**, 389 (1943).

during neutralization and extraction, and but little excess sodium hydroxide is used in order to prevent hydrolytic cleavage of the ester to diethyl ketone and ethyl cyanoacetate.

7. Other boiling points are 135–137°/25 mm. and 88–89°/1 mm.

8. A number of ketones have been condensed with ethyl cyanoacetate by this procedure. Reactive ketones such as aliphatic methyl ketones and cyclohexanone condense with ethyl cyanoacetate much more rapidly and give better yields of alkylidene esters. It is advantageous with such ketones to use a lower ratio of ammonium acetate-acetic acid catalyst.[1]

9. The sodium bisulfite purification step may be omitted, and the alkylidene ester purified directly by distillation. Care must be taken to separate the product from ethyl cyanoacetate by fractionation through a moderately efficient column. Purification through the bisulfite addition compound is recommended for alkylidene cyanoacetic esters derived from ketones containing four and five carbon atoms, but not for the higher homologs.

The checkers obtained a slightly higher yield by the method employing fractional distillation (64% vs. 60.5%) but the quality of the product appeared to be slightly inferior (n_D^{25} 1.4645 vs. 1.4649).

10. A trace of a water-soluble white solid may cause the distillate to be slightly turbid. It may be removed by washing the product with water and redistilling.

3. Methods of Preparation

The above procedure is a very slight modification of a recently described[1] general method for condensing ketones with ethyl cyanoacetate. Ethyl (1-ethylpropylidene)-cyanoacetate also has been prepared by condensing diethyl ketone with ethyl cyanoacetate in the presence of piperidine or acetic anhydride and zinc chloride,[5] or piperidine and anhydrous sodium sulfate in a pressure bottle at 100°.[6]

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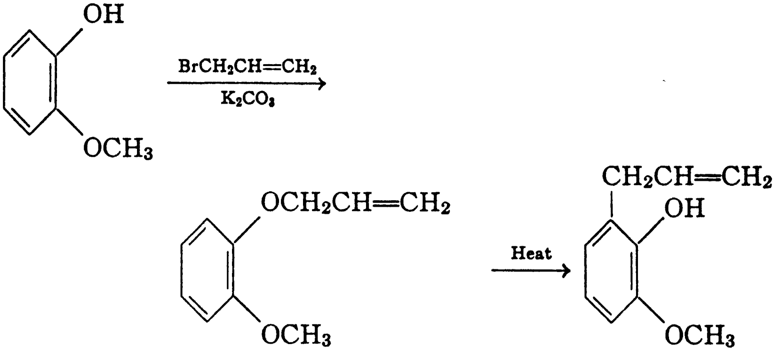
[5] Birch and Kon, *J. Chem. Soc.*, **1923**, 2448.

[6] Cowan and Vogel, *J. Chem. Soc.*, **1940**, 1528.

o-EUGENOL



Submitted by C. F. H. Allen and J. W. Gates, Jr.
Checked by W. E. Bachmann and N. C. Deno.

1. Procedure

A. *Guaiacol allyl ether.* A mixture of 63 g. (0.5 mole) of guaiacol, 66 g. (0.55 mole) of allyl bromide,[1] 70 g. of anhydrous potassium carbonate (0.5 mole), and 100 ml. of dry acetone in a 500-ml. round-bottomed flask is refluxed on a steam bath for 8 hours and cooled. The mixture is diluted with 200 ml. of water and extracted with two 100-ml. portions of ether. The combined extracts are washed with two 100-ml. portions of 10% sodium hydroxide (Note 1) and dried with 50 g. of anhydrous potassium carbonate. After removal of the solvent, the residual oil (Note 2) is distilled under reduced pressure. The yield of guaiacol allyl ether boiling at 110–113°/12 mm. is 66–75 g. (80–90%).

B. *o-Eugenol.* The allyl ether (70 g.) is cautiously (Note 3) brought to boiling in a 500-ml. round-bottomed flask, refluxed for 1 hour, and cooled. The oil is dissolved in 100 ml. of ether (Note 4), and the solution is extracted with three 100-ml. portions of 10% sodium hydroxide. The combined alkaline extracts are then acidified with 100 ml. of concentrated hydrochloric acid diluted with 100 ml. of water, and the mixture is extracted with three 100-ml. portions of ether. The combined ether extracts are dried with 50 g. of anhydrous sodium sulfate and evaporated, and the residual oil is distilled under reduced pressure. The yield of *o*-eugenol boiling at 120–122°/12 mm. (Note 5) is 56–63 g. (80–90%).

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[1] *Org. Syntheses* Coll. Vol. 1, 27 (1941).

2. Notes

1. A small amount of guaiacol may be recovered by acidifying the alkaline wash and extracting with ether.

2. When this crude guaiacol allyl ether was rearranged without prior distillation, the yields of *o*-eugenol were about 10% lower than those obtained with the distilled ether.

3. This rearrangement is sometimes quite vigorous and needs little heat once it is started. Dimethylaniline is said to be a good solvent for use in this type of rearrangement.[2]

4. Benzene may be substituted for ether throughout.

5. Other boiling points are 250–251°/760 mm., 125°/14 mm., and 115°/9 mm.

3. Methods of Preparation

Guaiacol allyl ether has been prepared from guaiacol, alcoholic potassium hydroxide, and allyl iodide;[3] or from guaiacol, allyl bromide, and potassium carbonate in acetone.[4,5] *o*-Eugenol has been prepared by the rearrangement of guaiacol allyl ether;[4,5] from 3-methoxy-2-allyloxybenzaldehyde by heating to 210°,[6] and from 3-methoxy-2-allyloxybenzoic acid by heating above 110°.[7]

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[2] Tarbell, *Org. Reactions*, **2**, 24 (1944).

[3] Marfori, *Annali di chimica e di farmacologia*, (5), **12**, 115; *Jahresb.*, **1890**, 1196.

[4] Claisen and Eisleb, *Ann.*, **401**, 52 (1913).

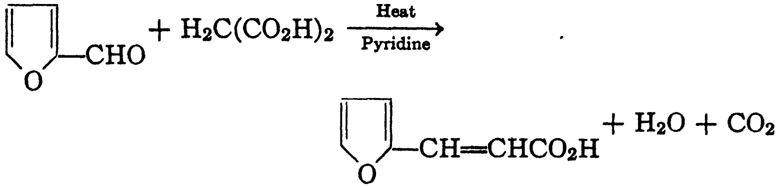
[5] Claisen, *Ber.*, **45**, 3161 (1912); Ger. pat. 268,099 [*Chem. Zentr.*, **1914** I, 308; *Frdl.*, **11**, 181 (1912–1914)].

[6] Claisen and Eisleb, *Ann.*, **401**, 112, 114 (1913).

[7] Claisen, *Ann.*, **418**, 117 (1919).

FURYLACRYLIC ACID

(2-Furanacrylic acid)



Submitted by S. Rajagopalan and P. V. A. Raman.
Checked by C. S. Hamilton and R. A. Alberty.

1. Procedure

In a 1-l. round-bottomed flask fitted with a reflux condenser are placed 192 g. (166 ml., 2 moles) of freshly distilled furfural (Note 1), 208 g. (2 moles) of malonic acid (Note 2), and 96 ml. (1.2 moles) of pyridine (Note 3). The flask is heated on a boiling water bath for 2 hours, and the reaction mixture is cooled and diluted with 200 ml. of water. The acid is dissolved by the addition of concentrated aqueous ammonia, the solution is filtered through a fluted filter paper, and the paper is washed with three 80-ml. portions of water. The combined filtrates are acidified with an excess of diluted (1 : 1) hydrochloric acid with stirring. The mixture is cooled by running water and then allowed to stand in an ice bath for at least 1 hour. The furylacrylic acid is filtered, washed with four 100-ml. portions of water, and dried. The yield of practically colorless needles melting at 141° is 252–254 g. (91–92%). If a purer product is desired, recrystallization is best effected from dilute alcohol (Note 4). On slow cooling of the solution, needles melting at 141° separate.

2. Notes

1. Commercial furfural is subjected to a single distillation; b.p. 160–161°.

2. Commercial malonic acid is dried at 100° for 2 hours and stored in a stoppered bottle.

3. The pyridine, which may be a commercial grade, is dried over sticks of potassium hydroxide for a few hours and filtered.

4. A convenient procedure is to dissolve the acid in a slight excess of 50% alcohol, reflux the solution with charcoal (5 g. per 100 g. of acid) for 5–10 minutes, and filter through a fluted filter in a preheated funnel. Any solid material that separates toward the later stages is redissolved by the addition of a few drops of alcohol. The residue is thoroughly washed with boiling water. The hot solution is then diluted with cold water until crystals separate, heated to boiling, cooled slowly, and allowed to stand in a refrigerator for several hours. When the mother liquors are used for subsequent batches, the usual loss (2–3%) by recrystallization is more than halved.

3. Methods of Preparation

The acid has been prepared through the Perkin reaction,[1] by the condensation of furfural with malonic acid in the presence of pyridine,[2] and, on a large scale, by the modified Perkin procedure of Johnson.[3]

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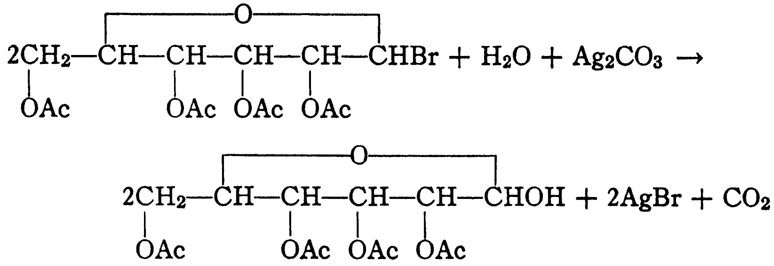
[1] Marckwald, *Ber.*, **10**, 357 (1877); Gibson and Kahnweiler, *Am. Chem. J.*, **12**, 314 (1890).

[2] Dutt, *J. Indian Chem. Soc.*, **1**, 297 (1925); Kurien, Pandya, and Surange, *J. Indian Chem. Soc.*, **11**, 824 (1934) [*C.A.*, **29**, 3325 (1935)].

[3] Johnson, *Org. Syntheses*, **20**, 55 (1940).

β-*d*-GLUCOSE-2,3,4,6-TETRAACETATE

(*d*-Glucose, 2,3,4,6-tetraacetate of β-)



$$2\underset{\text{OAc}}{\text{CH}_2}-\text{CH}-\underset{\text{OAc}}{\text{CH}}-\underset{\text{OAc}}{\text{CH}}-\underset{\text{OAc}}{\text{CH}}-\text{CHBr} + \text{H}_2\text{O} + \text{Ag}_2\text{CO}_3 \rightarrow$$

$$2\underset{\text{OAc}}{\text{CH}_2}-\text{CH}-\underset{\text{OAc}}{\text{CH}}-\underset{\text{OAc}}{\text{CH}}-\underset{\text{OAc}}{\text{CH}}-\text{CHOH} + 2\text{AgBr} + \text{CO}_2$$

Submitted by Chester M. McCloskey and George H. Coleman.
Checked by C. S. Hamilton, Robert Angier, and Ivan Baumgart.

1. Procedure

A solution of 82.2 g. (0.2 mole) of acetobromoglucose[1] (Note 1) in 125 ml. of dry acetone (Note 2) in a 250-ml. flask is cooled to 0° in an ice bath. To the cold solution is added 2.3 ml. of water and then 46.5 g. (0.17 mole) of silver carbonate (Note 3) in small portions in the course of 15 minutes. The mixture is shaken well during the addition and for 30 minutes longer (Note 4). The mixture is then warmed to 50–60° and filtered. The mass of silver salts is washed with 65 ml. of dry acetone (Note 5), removed from the funnel, warmed in a flask with 65 ml. more of acetone, filtered, and washed again on the funnel.

The combined filtrates are concentrated under reduced pressure in a 500-ml. filter flask (Note 6) until most of the solution is filled with crystals. The mixture is warmed to dissolve the crystals, the solution is poured into a 600-ml. beaker, and an equal volume of absolute ether and a similar volume of ligroin are added. The resulting solution is cooled in a freezing mixture with gentle stirring. The crystals of the tetraacetate form quickly and after about 10 minutes are filtered and air-dried. The crystals so obtained melt at 132–134° (Note 7). If a purer product is required, the product is dissolved in acetone, and ether and ligroin are added to the solution in the manner described. The yield of once-crystallized product melting at 132–134° is 52–56 g. (75–80%).

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[1] *Org. Syntheses*, **22**, 1 (1942).

2. Notes

1. The acetobromoglucose which was used had a melting point of 87–88°.

2. The acetone was dried over calcium chloride.

3. The silver carbonate should be freshly prepared and finely ground. Silver carbonate can be prepared by the addition of a solution of sodium carbonate (53 g. in 600 ml. of water) to one of silver nitrate (172 g. in 2 l. of water). This is a very slight excess of the silver nitrate. The sodium carbonate solution is added slowly (10 minutes), and the reaction mixture is stirred vigorously with a mechanical stirrer. The silver carbonate is filtered, washed with a little acetone to facilitate drying, and then air-dried. All operations are carried out in dim light.

4. At the end of this time, evolution of carbon dioxide should no longer be appreciable. The time required for the reaction depends largely on the agitation of the silver carbonate. In large runs mechanical stirring is required.

5. Anhydrous chemicals are used throughout as the presence of any appreciable amount of water interferes with the crystallization of the tetraacetate.

6. The solution is not heated during the concentration, and thus the temperature is maintained below that of the room by the evaporation of the solvent. If a capillary is used it should be equipped with a drying tube.

7. *β-d*-Glucose-2,3,4,6-tetraacetate (2,3,4,6-tetraacetyl-*β-d*-glucose) decomposes slightly on prolonged standing and after one to two months has a melting range of 5–8 degrees. Such material can be purified by recrystallization.

3. Methods of Preparation

β-d-Glucose-2,3,4,6-tetraacetate has been prepared usually by the hydrolysis of acetobromoglucose.[2]

m-HYDROXYBENZALDEHYDE

(Benzaldehyde, *m*-hydroxy-)

$$m\text{-}NO_2C_6H_4CHO \xrightarrow[HCl]{SnCl_2} m\text{-}NH_2C_6H_4CHO\cdot(SnCl_4)_x \xrightarrow[HCl]{NaNO_2}$$

$$(m\text{-}ClN_2C_6H_4CHO)_2\cdot SnCl_4 \xrightarrow[Heat]{H_2O} m\text{-}HOC_6H_4CHO$$

Submitted by R. B. WOODWARD.
Checked by C. S. HAMILTON and RAYMOND J. ANDRES.

1. Procedure

A solution of 450 g. (2 moles) of powdered stannous chloride dihydrate (Note 1) in 600 ml. of concentrated hydrochloric acid in a 3-l. beaker provided with an efficient mechanical stirrer is cooled in an ice-salt bath. When the temperature of the solution has fallen to 5°, the ice bath is removed, and 100 g. (0.66 mole) of *m*-nitrobenzaldehyde (Note 2) is added in one portion. The temperature rises slowly at first, reaching 25–30° in about 5 minutes. As it then rises rapidly to about 100° the ice-salt bath is again placed around the beaker. Stirring must be vigorous or the reaction mixture may be forced out of the beaker (Note 3). During the reaction the *m*-nitrobenzaldehyde dissolves, and an almost clear red solution is obtained. The solution is cooled with very slow stirring (Note 4) in an ice-salt mixture for 2.5 hours. The orange-red paste of the stannichloride of *m*-aminobenzaldehyde (Note 5) is filtered on a sintered glass funnel (Note 6).

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[2] Fischer and Delbruck, *Ber.*, **42**, 2776 (1909); Georg, *Helv. Chim. Acta*, **15**, 924 (1932); Hendricks, Wulf, and Liddel, *J. Am. Chem. Soc.*, **58**, 1998 (1936); McCloskey, Pyle, and Coleman, *J. Am. Chem. Soc.*, **66**, 349 (1944).

A suspension of the material in 600 ml. of concentrated hydrochloric acid is stirred mechanically in a 3-l. beaker which is set in an ice-salt bath. A solution of 46 g. of sodium nitrite in 150 ml. of water in a 250-ml. dropping funnel fixed with its stem below the surface of the suspension is added slowly while the temperature of the mixture is kept at 4–5° (Note 7). After the addition is completed (in approximately 80 minutes), stirring in the ice-salt bath is continued for 1 hour to crystallize completely the stannichloride of the diazonium salt. The reddish brown salt is filtered on a sintered glass funnel (Note 6).

The damp salt is added cautiously in small portions to 1.7 l. of boiling water in a 4-l. beaker in the course of 40 minutes. During the reaction, the water lost by vaporization is replaced (Note 8). The solution is treated with 4 g. of Norite, boiled a few minutes, and filtered hot. The red filtrate is kept in an icebox for 12–16 hours; during this time scratching is employed occasionally to induce crystallization (Note 9). The yield of orange crystals melting at 99–101° is 48–52 g. (59–64%). A solution of this product in about 1 l. of boiling benzene is treated with Norite, filtered, and concentrated to 300 ml. On cooling, 41–45 g. (51–56%) of light tan crystals melting at 101–102° is obtained (Note 10).

2. Notes

1. A chemically pure grade of stannous chloride ($SnCl_2 \cdot 2H_2O$) should be used. Lower yields are obtained with technical stannous chloride.

2. A practical grade of *m*-nitrobenzaldehyde (m.p. 52–55°) was used by the submitters. The checkers used Eastman's *m*-nitrobenzaldehyde (m.p. 57–58°).

3. Less satisfactory yields are obtained when the reaction is moderated by the addition of the *m*-nitrobenzaldehyde in several portions.

4. Stirring must be very slow since gradual cooling is necessary in order to obtain particles large enough to permit fairly rapid filtration.

5. The exact formula of the *m*-aminobenzaldehyde stannichloride is not known.

6. As a substitute for the sintered-glass funnel, a large Büchner funnel provided with an asbestos fiber mat under the filter paper will serve. The asbestos mat can be washed and used repeatedly.

7. Best results are obtained by keeping the temperature during diazotization at 4–5°. Below 0° the speed of diazotization is greatly decreased, and above 5° the diazonium salt begins to decompose.

8. Concentrating the solution below 1.7 l. results in markedly decreased purity.

9. If scratching does not succeed in inducing crystallization, a small portion of the solution may be removed and evaporated for seed.

10. According to the submitter, further purification can be effected by sublimation: the material is placed in the bottom of a Pyrex desiccator which is then evacuated and placed on a steam bath overnight. The mat of interwoven needles can be removed easily. One crystallization from benzene gives 37–40 g. (47–49%) of needles melting at 103–104°.

3. Methods of Preparation

m-Hydroxybenzaldehyde has been made by reduction of *m*-hydroxybenzoic acid with sodium amalgam in weak acid solution;[1] by oxidation of the arylsulfonic ester $ArSO_2OC_6H_4CH_3$ with manganese dioxide and sulfuric acid to the corresponding derivative of *m*-hydroxybenzaldehyde $ArSO_2OC_6H_4CHO$ and hydrolysis of the latter with concentrated sulfuric acid;[2] from *m*-dichloromethylphenyl benzoate by heating with water and calcium carbonate under a pressure of 4–5 atmospheres.[3] The present method is derived from that of Tiemann and Ludwig[4] and is similar to the procedure for the preparation of *m*-chlorobenzaldehyde.[5]

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[1] Sandmann, *Ber.*, **14**, 969 (1881).

[2] Ger. pat. 162,322 (*Chem. Zentr.*, **1905** II, 726).

[3] Raschig, Ger. pat. 233,631 [*Chem. Zentr.*, **1911** I, 1388; *Frdl.*, **10**, 163 (1910–1912)].

ISOBUTYRAMIDE

$$(CH_3)_2CHCOOH \xrightarrow{SOCl_2} (CH_3)_2CHCOCl \xrightarrow{NH_3} (CH_3)_2CHCONH_2$$

Submitted by R. E. KENT and S. M. MCELVAIN.
Checked by C. R. NOLLER and D. FRAZIER.

1. Procedure

A. *Isobutyryl chloride.* A 1-l. three-necked flask is equipped with a 250-ml. dropping funnel, an efficient stirrer sealed with a glycerol-lubricated rubber tube,[1] and an efficient condenser (Note 1). The water supplied to the condenser is cooled to 0°, and the flask is cooled in a large water bath. The apparatus is set up in a hood, and a gas-absorption trap[2] is attached to the top of the condenser.

In the flask is placed 542 g. (4.55 moles) of thionyl chloride; to this is added dropwise, and with rapid stirring, 352 g. (4 moles) of isobutyric acid (Note 2). A vigorous evolution of hydrogen chloride and sulfur dioxide takes place. When all the acid has been added, the water bath is heated to 80° and is kept at this temperature for 30 minutes. Stirring is continued throughout the heating. The reaction mixture is then distilled through a 30-cm. Vigreux column by means of an oil bath heated on a hot plate (Note 3). The fore-run boiling up to 89° weighs 44 g. The isobutyryl chloride which is collected at 89–93° weighs 351 g. The residue weighs 49 g. On combining the fore-run and residue

[4] Tiemann and Ludwig, *Ber.*, **15**, 2045 (1882); see also Rieche, *Ber.*, **22**, 2348 (1889); Ger. pat. 18,016 [*Frdl.*, **1**, 586 (1888)]; Subak, *Monatsh.*, **24**, 167 (1903).

[5] *Org. Syntheses* Coll. Vol. **2**, 130 (1943).

ISOBUTYRAMIDE

[1] *Org. Syntheses*, **21**, 40 (1941).

[2] *Org. Syntheses* Coll. Vol. **2**, 4 (1943).

and redistilling slowly, an additional 33 g. of isobutyryl chloride is obtained; the total yield is 384 g. (90%). Redistillation gives a faintly yellow product boiling at 90–92° (Notes 4 and 5).

B. *Isobutyramide.* In a 3-l. flask, equipped with an efficient stirrer and a 500-ml. dropping funnel, and surrounded by an ice-salt freezing mixture, is placed 1.25 l. of cold concentrated aqueous ammonia (about 28%). To this 318 g. (3 moles) of isobutyryl chloride is added dropwise with rapid stirring at such a rate that the temperature of the reaction mixture does not rise above 15°, and the evolution of white fumes (mostly ammonium chloride) does not become vigorous. Stirring is continued for 1 hour after the addition of the acid chloride is finished.

The flask is heated by steam in a large can, and the reaction mixture is evaporated to dryness under reduced pressure (Note 6). The dry residue of ammonium chloride and isobutyramide is boiled 10 minutes with 2 l. of dry ethyl acetate, and the boiling solution is filtered quickly through a fluted filter paper on a large hot funnel. The residue on the filter is extracted in the same way with two 1-l. portions of ethyl acetate. The combined ethyl acetate extracts are cooled to 0°, and the crystalline amide which separates is removed by filtration. The filtrate is concentrated to about 300 ml. and chilled, and a second crop of amide is collected (Notes 7 and 8). The two crops of isobutyramide are combined and dried, first in an oven at 70° for 3 hours and then in a vacuum desiccator. The yield of glistening white needles melting at 127–129° is 203–215 g. (78–83%) (Note 9). This material is suitable for the preparation of isobutyronitrile.

2. Notes

1. A Friedrichs condenser is recommended. This efficient condenser has an inner cooling coil around which the vapors pass and condense. The submitters used rubber stoppers throughout.
2. Eastman's Technical grade of isobutyric acid was distilled, and the fraction boiling at 151–153° was used.
3. The submitters used an electrically heated oil bath.
4. When 5 moles of thionyl chloride and 4 moles of isobutyric

acid were used, the yield on the first distillation was 83%, and redistillation of the fore-run gave an additional 7%. There was practically no high-boiling material.

5. The submitters obtained the same percentage yields in runs four times as large.

6. The steam can should be large enough to contain the entire reaction flask; otherwise the evaporation is very slow.

7. If the mixture of amide and ammonium chloride is not thoroughly dry, the ethyl acetate removed at this point will contain water and must be dried and redistilled before further use.

8. The filtrate from the second crop of amide may be evaporated to dryness and the residue crystallized from a mixture of ethyl acetate and ligroin (60–68°). It is profitable to work up this third crop of amide only when the mother liquors from several runs are combined.

9. The submitters obtained the same percentage yield in runs twice as large.

3. Methods of Preparation

Isobutyramide has been prepared by the action of concentrated aqueous ammonia on isobutyryl chloride[3] or methyl isobutyrate;[4] by distillation of ammonium isobutyrate[5] or a mixture of isobutyric acid and potassium thiocyanate.[6] Hydrolysis of isobutyronitrile also results in the formation of isobutyramide.[7]

[3] Aschan, *Ber.*, **31**, 2348 (1898).

[4] Meyer, *Monatsh.*, **27**, 43 (1906).

[5] Hofmann, *Ber.*, **15**, 982 (1882)

[6] Letts, *Ber.*, **5**, 671 (1872).

[7] de Hoffmann and Barbier, *Bull. soc. chim. Belg.*, **45**, 565 (1936) [*C.A.*, **31**, 919 (1937)].

ISOBUTYRONITRILE

$$(CH_3)_2CHCONH_2 \xrightarrow{P_2O_5} (CH_3)_2CHCN + H_2O$$

Submitted by R. E. KENT and S. M. MCELVAIN.
Checked by C. R. NOLLER and D. FRAZIER.

1. Procedure

To 308 g. (2.1 moles) of phosphorus pentoxide (reagent grade) in a 3-l. round-bottomed flask is added 174 g. (2 moles) of finely powdered, dry isobutyramide (Note 1). The flask is tightly stoppered, and the two dry solids are thoroughly mixed by shaking. The flask then is attached to a water-cooled condenser set for downward distillation; a 500-ml. suction flask connected to the condenser by a rubber stopper is a convenient receiver. A calcium chloride tube is attached to the side arm of the receiver, and the receiver is surrounded by crushed ice. The reaction flask is heated for 8–10 hours in an electrically heated oil bath maintained at 200–220°. The nitrile starts to distil almost at once. The reaction mixture becomes a thick, brown syrup which foams considerably toward the end of the distillation. The time of reaction may be cut to 1–2 hours by connecting the distillation system to an aspirator and intermittently removing the nitrile under reduced pressure (Note 2). Very little additional nitrile can be obtained by further heating of the reaction mixture.

The contents of the receiver are transferred to a 500-ml. modified Claisen flask,[1] 10–15 g. of phosphorus pentoxide is added (Note 3), and the product is distilled from an oil bath held at 145–155°. After only a few drops of fore-run, the main fraction distils at 99–102°/740 mm. The yield is 96–120 g. (69–86%). The product is colorless when first distilled but acquires a yellow tint after standing a few days. If it is again distilled from phosphorus pentoxide or Drierite, it boils at 101–103° and remains colorless; n_D^{25} 1.3713.

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[1] *Org. Syntheses* Coll. Vol. 1, 130 (1941).

2. Notes

1. The amide must be thoroughly dry or immediate reaction will take place with considerable generation of heat, and the yield will be lowered owing to the failure to obtain proper mixing of the reactants. If the amide is not finely powdered the yield of nitrile falls off sharply.

2. The yield is not altered by this procedure if care is taken not to evaporate the nitrile in the receiver. Keeping the flask surrounded by crushed ice and using a Dry Ice-acetone safety trap between the receiver and aspirator will guard against such loss.

3. When phosphorus pentoxide is added to isobutyronitrile, the liquid sets to a semi-solid gel which is difficult to transfer from a flask. Hence, the addition of one to the other should be made only in the flask from which the distillation is to be made.

3. Methods of Preparation

Isobutyronitrile has been prepared by a number of catalytic vapor-phase reactions at elevated temperatures: isobutylamine over copper [2] or nickel,[3] isobutyramide over alumina,[4] a mixture of ammonia and isobutyraldehyde over thorium dioxide,[5] and a mixture of ammonia and isobutyl alcohol over copper.[6] Isobutyronitrile also has been obtained by decarboxylation of 2-methyl-2-cyanopropanoic acid [7] and from the reaction of isobutyric acid with potassium thiocyanate.[8] The above procedure is a modification of the method used by Walter and McElvain.[9]

[2] Mailhe and de Godon, *J. pharm. chim.*, (7) **16**, 225 (1917) (*Chem. Zentr.*, **1918**, I, 819).

[3] Mailhe and de Godon, *Bull. soc. chim.*, (4) **21**, 288 (1917).

[4] Boehmer and Andrews, *J. Am. Chem. Soc.*, **38**, 2504 (1916).

[5] Mailhe, *Compt. rend.*, **166**, 216 (1918).

[6] Hara and Komatsu, *Mem. Coll. Sci. Kyoto Imp. Univ.*, **8A**, 241 (1925) [*C.A.*, **19**, 3248 (1925)].

[7] de Hoffmann and Barbier, *Bull. soc. chim. Belg.*, **45**, 565 (1936) [*C.A.*, **31**, 919 (1937)].

[8] Letts, *Ber.*, **5**, 671 (1872).

[9] Walter and McElvain, *J. Am. Chem. Soc.*, **56**, 1615 (1934).

MALONONITRILE

$2NCCH_2CONH_2 + POCl_3 \rightarrow 2CH_2(CN)_2 + HPO_3 + 3HCl$

Submitted by ALEXANDER R. SURREY.
Checked by C. F. H. ALLEN and J. VAN ALLAN.

1. Procedure

In a 12-l. three-necked, round-bottomed flask, fitted with a powerful stirrer (Note 1) and a reflux condenser, are placed 1260 g. (15 moles) of cyanoacetamide,[1] 1 kg. of salt (Note 2), and 5 l. of ethylene dichloride. After the mixture has been stirred rapidly for 15 minutes, 800 ml. (8.75 moles) of phosphorus oxychloride is added and the mixture is refluxed for 8 hours in an oil bath (Note 3). After the mixture has been cooled to room temperature, it is filtered and the solid is washed with 500 ml. of ethylene dichloride. The solvent is distilled from the combined filtrates in a 12-l. flask, and the residual crude nitrile is decanted into a 1-l. flask (Note 4) from any solid that may have separated. A fractionating column, condenser, and fractionating receiver are attached, and the malononitrile is distilled under reduced pressure. The fraction boiling at 113–118°/25 mm. weighs 570–654 g. (57–66%) (Note 5). This material may be freed from a small amount of phosphorus oxychloride which is present by redistillation. After a fore-run of about 5 ml., the malononitrile distils smoothly at 92–94°/8 mm.

2. Notes

1. A heavy motor-driven stirrer is advisable, because frequently the solid that separates contains some viscous material that makes stirring difficult.

2. The addition of salt gives a lighter-colored, granular solid that can be easily removed by filtration and washed.

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[1] *Org. Syntheses* Coll. Vol. 1, 179 (1941).

3. The reaction can be done in a hood, or the hydrogen chloride which is evolved can be absorbed in a gas trap.[2]

4. Ground-glass equipment is advisable. The fractionating column is the standard modified Claisen type.

5. The submitter obtained a 70–72% yield at this point in a run of this size and 80% yields in small runs. He also obtained yields of the same order by using a mixture of phosphorus oxychloride and a small amount of phosphorus pentachloride.

3. Methods of Preparation

The methods of preparation have already been given,[3] except for this new modification of the submitter.[4]

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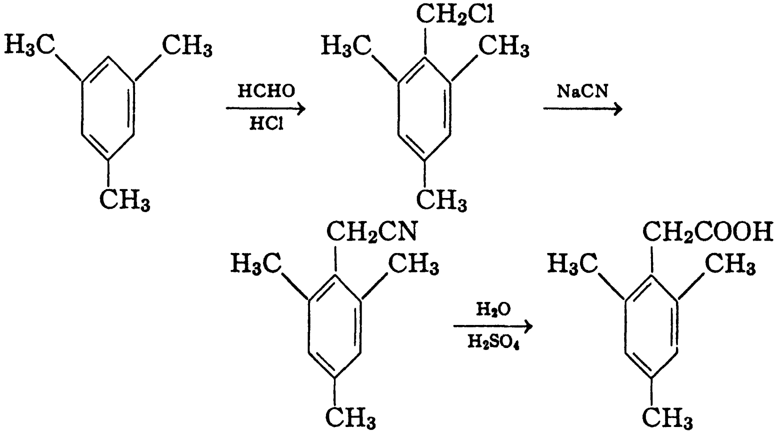
[2] *Org. Syntheses* Coll. Vol. **2**, 4 (1943).

[3] *Org. Syntheses* Coll. Vol. **2**, 379 (1943).

[4] Surrey, *J. Am. Chem. Soc.*, **65**, 2471 (1943).

MESITYLACETIC ACID

(α-Toluic acid, 2,4,6-trimethyl-)



Submitted by Reynold C. Fuson and Norman Rabjohn.
Checked by W. E. Bachmann, E. L. Jenner, and G. Dana Johnson.

1. Procedure

A. *α²-Chloroisodurene.* In a 2-l. round-bottomed flask, equipped with a sealed mechanical stirrer (Note 1), a gas inlet tube, and a reflux condenser, are placed 200 g. (1.66 moles) of mesitylene, 1 l. of concentrated hydrochloric acid, and 63 ml. (0.84 mole) of formaldehyde solution (concentration, 37%) (Note 2). Hydrogen chloride is introduced below the surface of the mixture (Note 3), which is stirred vigorously and heated in a water bath kept at 55°. These conditions are maintained throughout the reaction, which requires a total of 5.5 hours. At the halfway point, an additional 63 ml. (0.84 mole) of formaldehyde solution is added (Note 4).

After the mixture has been cooled to room temperature (Note 5), it is extracted with three 300-ml. portions of benzene. The combined benzene extracts are washed successively with water, dilute sodium hydroxide, and water, dried over calcium chloride, and filtered. The mixture is distilled through a still head under reduced pressure; the pressure is reduced only slightly while the benzene is distilling. The yield of α^2-chloroisodurene boiling at 130–131°/22 mm. is 155–170 g. (55–61%) (Note 6); the distillate solidifies to a crystalline mass which melts at 37°.

B. *Mesitylacetonitrile.* In a 1-l. three-necked flask, fitted with a mechanical stirrer, a reflux condenser, and a dropping funnel, are placed 77 g. (1.57 moles) of sodium cyanide, 110 ml. of water, and 160 ml. of alcohol. The flask is heated in a boiling water bath, and the contents are stirred until all the sodium cyanide is dissolved. Then 152 g. (0.90 mole) of α^2-chloroisodurene is added slowly, and stirring and heating are continued for 3 hours.

The reaction mixture is allowed to cool to about 40° (Note 7) and extracted with three 300-ml. portions of benzene. The benzene solution is washed well with water, dried over calcium chloride, filtered, and distilled under slightly reduced pressure to remove all the benzene. The residue is then distilled *in vacuo* from a Claisen flask with a wide-bore side arm. The yield of mesitylacetonitrile boiling at 160–165°/22 mm. is 128–133 g. (89–93%) (Note 8). This product is sufficiently pure for the next step. When recrystallized from petroleum ether, it melts at 79–80°.

C. *Mesitylacetic acid.* To 900 ml. of water in a 3-l. three-necked flask is added 750 ml. of concentrated sulfuric acid.When the mixture has cooled to about 50°, 127 g. (0.80 mole) of mesitylacetonitrile is added (Note 9), and the mixture is refluxed and stirred mechanically for 6 hours. At the end of this period, a large amount of mesitylacetic acid has precipitated from the solution. The contents of the flask are cooled and poured into 3 l. of ice water. The acid is collected on a Büchner funnel and washed well with water. A solution of the acid in dilute alkali is boiled with Norite, and the acid is precipitated from the filtered solution by acidifying with dilute hydrochloric acid. The mesitylacetic acid is collected on a filter, washed well with water, and dried in an oven at about 80°. The yield of mesitylacetic acid melting at 163–166° is 123 g. (87%). After recrystallization from dilute alcohol or ligroin, the acid melts at 167–168°.

2. Notes

1. The checkers used an Ace Tru-bore stirrer. This convenient sealed stirrer, which owes its seal to the snug fit between a ground-glass section of the stirrer shaft and a ground-glass bearing, can be obtained from the Ace Glass Company, Vineland, New Jersey.

2. Commercial formalin was used. This aqueous-methanolic solution contains 37% formaldehyde by weight. It is sometimes called "40% formalin" because 100 ml. of the solution contains 40 g. of formaldehyde.

3. The hydrogen chloride is introduced at such a rate that the bubbles form a little faster than they can be counted.

4. The yield of monochloromethyl compound seems to be improved slightly by adding the formalin in two portions instead of introducing the entire amount at the beginning of the reaction.

5. If the reaction mixture is cooled to too low a temperature, the chloromethyl derivatives will solidify. It is much easier to carry out the extractions while the mixture is still liquid.

6. The residue consists chiefly of α^2,α^4-dichloropentamethylbenzene. The fraction boiling at 131–200°/22 mm. is collected and recrystallized from petroleum ether; m.p. 105°.

7. If the reaction mixture is allowed to cool much below this temperature, it will solidify in the flask.

8. This method has been applied successfully to the preparation of 2,4,6-triethylphenylacetonitrile (b.p. 127°/3–4 mm.; yield, 72%); durylacetonitrile (m.p. 80–81°; yield, 75%); and isodurylacetonitrile (m.p. 74–75°; yield, 74%).

9. If the mesitylacetonitrile has not been purified by distillation, or if it is added to a boiling solution of sulfuric acid, the reaction mixture has a tendency to become very dark.

3. Methods of Preparation

α^2-Chloroisodurene can be prepared by the action of chloromethyl ether on mesitylene in the presence of stannic chloride[1] or acetic acid.[2] The procedure described is based on that of Nauta and Dienske.[3]

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[1] Sommelet, *Compt. rend.*, **157**, 1443 (1913).

Mesitylacetonitrile can be prepared by the action of potassium cyanide on α^2-chloroisodurene [4] or by treating α^2-chloroisodurene with cuprous cyanide in the presence of pyridine.[5] The procedure described is based upon the method for the preparation of benzyl cyanide from benzyl chloride.

Mesitylacetic acid has been prepared from 2,4,6-trimethylacetophenone by treatment with yellow ammonium sulfide and hydrolyzing the resulting amide with alkali,[6] by the dry distillation of 2,4,6-trimethylmandelic acid,[7] by heating 2,4,6-trimethylphenylglyoxylic acid with hydriodic acid and red phosphorus,[8] and by treating mesitylacetonitrile with potassium hydroxide.[4]

[2] Vavon and Bolle, *Compt. rend.*, **204**, 1826 (1932).

[3] Nauta and Dienske, *Rec. trav. chim.*, **55**, 1000 (1936).

[4] Hoch, *Compt. rend.*, **192**, 1464 (1931).

[5] Newman, *J. Am. Chem. Soc.*, **59**, 2472 (1937).

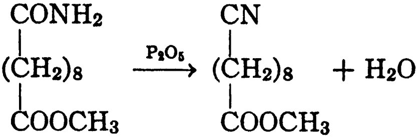
[6] Claus, *J. prakt. Chem.*, (2) **41**, 508 (1890); Willgerodt, *J. prakt. Chem.*, (2) **80**, 185 (1909); Willgerodt and Merk, *J. prakt. Chem.*, (2) **80**, 193 (1909).

[7] Meyer and Molz, *Ber.*, **30**, 1274 (1897).

[8] Dittrich and Meyer, *Ann.*, **264**, 140 (1891).

METHYL ω-CYANOPELARGONATE

(Pelargonic acid, θ-cyano-, methyl ester)



$$\underset{\mathrm{COOCH_3}}{\overset{\mathrm{CONH_2}}{(\mathrm{CH_2})_8}} \xrightarrow{\mathrm{P_2O_5}} \underset{\mathrm{COOCH_3}}{\overset{\mathrm{CN}}{(\mathrm{CH_2})_8}} + \mathrm{H_2O}$$

Submitted by W. S. Bishop.
Checked by C. F. H. Allen and J. Van Allan.

CAUTION

Tetrachloroethane is toxic; the operations should be conducted in a hood.

1. Procedure

In a 1.5-l. Erlenmeyer flask to which is attached a reflux condenser, 190 g. (0.88 mole) of methyl sebacamate (p. 71) is dissolved in 200 ml. of boiling tetrachloroethane. The solution is allowed to cool to 40–50° (Note 1), 95 g. (0.67 mole) of phosphorus pentoxide is added (Note 2), and the mixture is stirred well by means of a glass rod. The mixture is heated in an oil bath to 120° (thermometer in oil), and a second 95-g. portion of phosphorus pentoxide is added. After the mixture has been heated at 145° for 30 minutes with occasional hand stirring, the liquid is decanted. The residue is heated at 145° with 200 ml. of tetrachloroethane for 30 minutes with occasional stirring, and the liquid is decanted. This process is repeated once. The combined extracts are placed in a 1-l. flask, and most of the solvent is distilled under the reduced pressure of a water pump. The residue is transferred to a 300-ml. flask, and the remainder of the solvent is removed (Note 3). When no more distillate comes over, the receiver is changed, the water pump is replaced by an oil pump, and the residue is fractionated (Note 4). The yield of methyl ω-cyanopelargonate boiling at 121–124°/1 mm. (Note 5) is 119–124 g. (69–71%).

2. Notes

1. The slush that results on cooling is easily mixed with the phosphorus pentoxide.

2. The phosphorus pentoxide is weighed rapidly on a piece of paper, from which it can be slid quickly into the flask.

3. About 550–560 ml. of tetrachloroethane is recovered. Ground-glass equipment is preferable for the distillations.

4. There is no fore-run. At 1 mm., the thermometer reads about 118° when the first drop appears at the end of the side tube of the distilling flask. There is a 5- to 6-g. fraction, b.p. 124–135°/1 mm., and some residue.

5. Other boiling points are 154°/5 mm. and 170°/14 mm.

3. Methods of Preparation

Methyl ω-cyanopelargonate has also been prepared by esterification of ω-cyanopelargonic acid with methyl sulfate [1] or methanol.[2] The procedure described appears in the recent literature.[1,3]

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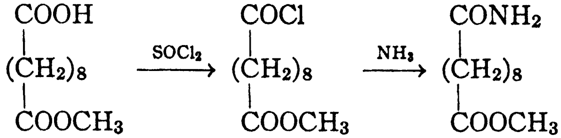
[1] Biggs and Bishop, *J. Am. Chem. Soc.*, **63**, 944 (1941).

[2] Biggs, U. S. pat. 2,339,072 [*C.A.*, **38**, 3990 (1944)].

[3] Bishop, U. S. pat. 2,277,033 [*C.A.*, **36**, 4636 (1942)].

METHYL SEBACAMATE

(Sebacamic acid, methyl ester)



$$\begin{array}{c}\mathrm{COOH}\\ |\\ (\mathrm{CH_2})_8\\ |\\ \mathrm{COOCH_3}\end{array} \xrightarrow{\mathrm{SOCl_2}} \begin{array}{c}\mathrm{COCl}\\ |\\ (\mathrm{CH_2})_8\\ |\\ \mathrm{COOCH_3}\end{array} \xrightarrow{\mathrm{NH_3}} \begin{array}{c}\mathrm{CONH_2}\\ |\\ (\mathrm{CH_2})_8\\ |\\ \mathrm{COOCH_3}\end{array}$$

Submitted by W. S. Bishop.
Checked by C. F. H. Allen and J. Van Allan.

1. Procedure

A. *ω-Carbomethoxypelargonyl chloride.* A mixture of 216 g. (1 mole) of methyl hydrogen sebacate (Note 1) and 147 g. (1.24 moles) of thionyl chloride in a 2-l. round-bottomed flask attached by a standard ground-glass joint to an upright condenser is refluxed on a steam bath for 5 hours. The condenser is then replaced by a still head having a modified side arm, and the unused thionyl chloride is removed. The residual ω-carbomethoxypelargonyl chloride is suitable for the next step. If a purer product is desired it is distilled under reduced pressure. The yield of ester chloride boiling at 158–160°/10 mm. is 194–201 g. (83–86%).

B. *Methyl sebacamate.* Two and one-half liters of concentrated aqueous ammonia (about 28%) in a 4-l. beaker or enameled pot (Note 2) is stirred vigorously with an off-center stirrer and chilled to 8° in a cooling bath. The crude chloride from part A is added slowly from a dropping funnel to the solution which is kept below 8° throughout the addition. A vigorous reaction takes place, and methyl sebacamate precipitates immediately. After the addition has been completed, the product is filtered by suction and washed with 200 ml. of cold water. After 3 days' drying in a vacuum desiccator, the methyl sebacamate weighs 200–204 g. (93–95%) and melts at 72–74° (Note 3).

2. Notes

1. Methyl hydrogen sebacate (b.p. 168–170°/3 mm.) was prepared by the checkers in yields of 52–61% from sebacic acid and methanol by the procedure described for the ethyl analog.[1] The ethyl ester can be used to obtain ethyl sebacamate. The preparation of the acid chloride from ethyl hydrogen sebacate is mentioned in Note 12, page 21.

2. A variety of enameled-steel pots known as bain-marie is available from the American Specialty Company, Rochester, New York.

3. The yield is no higher with the distilled chloride.

3. Methods of Preparation

These compounds are described only in the recent literature.[2,3]

[1] *Org. Syntheses* Coll. Vol. **2**, 276 (1943).

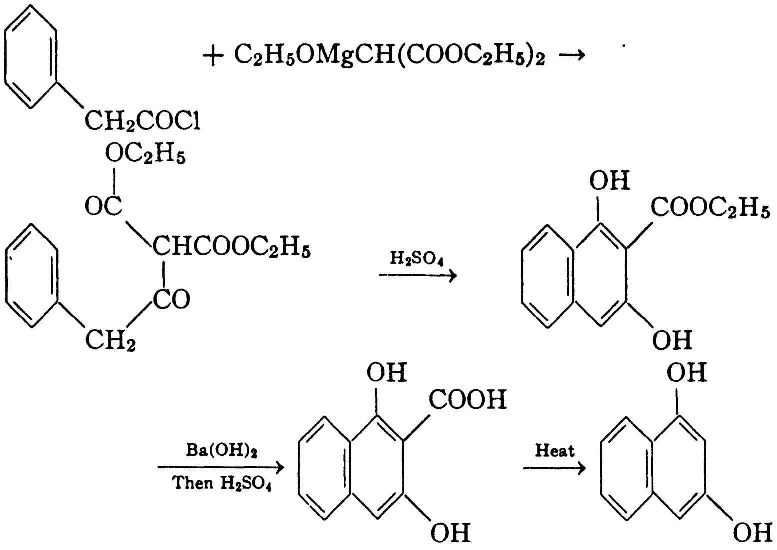
[2] Biggs and Bishop, *J. Am. Chem. Soc.*, **63**, 944 (1941).

[3] Bishop, U. S. pat. 2,277,033 [*C.A.*, **36**, 4636 (1942)].

NAPHTHORESORCINOL

(1,3-Naphthalenediol)

$$C_2H_5OH + Mg + CH_2(COOC_2H_5)_2 \rightarrow C_2H_5OMgCH(COOC_2H_5)_2 + H_2$$


CH₂COCl
+ C₂H₅OMgCH(COOC₂H₅)₂ →
OC₂H₅
OC
CHCOOC₂H₅
CO
CH₂
H₂SO₄
OH
COOC₂H₅
OH
Ba(OH)₂
Then H₂SO₄
OH
COOH
OH
Heat
OH
OH

Submitted by Karl Meyer and Henry S. Bloch.
Checked by H. R. Snyder and Curtis W. Smith.

1. Procedure

A. *Ethyl phenylacetylmalonate.* A 1-l. three-necked, round-bottomed flask is equipped with a dropping funnel (Note 1) and a reflux condenser provided with a calcium chloride tube. Before the apparatus is assembled, it is washed in the following manner with absolute alcohol which has been prepared in a distilling flask (Note 2). Ninety milliliters of the anhydrous ethanol is distilled through the dropping funnel into the apparatus, used for rinsing, and discarded. In the reaction flask are placed 12.5 g. (0.52 atom) of magnesium turnings, 1 ml. of carbon tetrachloride

(Note 3), and 40 g. (0.25 mole) of malonic ester (Note 3); then 90 ml. of absolute alcohol is distilled into the dropping funnel and transferred to the flask. The reaction is started by heating and is controlled by applying an ice bath when the condenser begins to flood. When the reaction has subsided, 40 g (0.25 mole) more of malonic ester is added at one time. After this reaction has subsided, the flask is cooled slightly, 180 ml. of dry ether is added, and the reaction mixture is heated on a steam bath for 1 hour. Then 88 g. (74 ml., 0.57 mole) of phenylacetyl chloride, diluted with 90 ml. of dry ether, is added slowly (in about 30 minutes) from the dropping funnel in portions at such a rate that the vigorous reaction subsides between additions. When the addition has been completed, the flask is warmed for 10 minutes on a steam bath. After the mixture has been cooled, 100 ml. of water is added dropwise in about 30 minutes. The oily layer is washed with two 100-ml. portions of water and dried over sodium sulfate, and the ether is removed by distillation under reduced pressure (water pump). The crude phenylacetylmalonic ester (87 ml.) which remains is a reddish, somewhat viscous oil.

B. *Ethyl 1,3-dihydroxy-2-naphthoate.* In a 1-l. flask 1 volume (87 ml.) of the crude ester is added in one lot to 3 volumes (261 ml.) of concentrated sulfuric acid without cooling, and the solution is allowed to stand for about 1 week (Note 4). The whole mixture, including any precipitate which may have formed, is poured slowly with stirring into a mixture of 1 kg. of ice and 500 ml. of water (Note 5); the solid yellow ester is filtered with suction, washed with a small amount of cold water, pressed in the filter for 30 minutes with a rubber dam, and finally dried in a vacuum desiccator. The yield of ester melting at 80° is 58–68 g. (50–59%, based on the malonic ester used).

Recrystallization of 50 g. of the ester from 300 ml. of 70% alcohol (Note 6) yields 45 g. of yellow, needlelike crystals melting at 82°.

C. *1,3-Dihydroxy-2-naphthoic acid.* In a 1-l. three-necked, round-bottomed flask, fitted with a mechanical stirrer, nitrogen inlet tube, and a condenser carrying a separatory funnel attached by means of a notched cork, is placed 20.9 g. (0.09 mole) of the recrystallized ester dissolved in 300 ml. of dioxane. The apparatus is flushed with nitrogen, the solution is stirred and heated on a steam bath, and a solution of 40 g. (0.13 mole) of barium hydroxide octahydrate in 500 ml. of water is added in the course of 1 hour. Heating and stirring are continued for 3 hours. The precipitated barium salt, which may vary in color from yellow to greenish gray, is filtered from the hot solution and transferred immediately to a cool (25°) solution of 11 ml. of concentrated sulfuric acid in 185 ml. of water in a 500-ml. three-necked, round-bottomed flask fitted with a nitrogen inlet tube, a mechanical stirrer, and a condenser. The mixture is stirred in an atmosphere of nitrogen for 5 minutes without heating (Note 7). The precipitate is removed by filtration, washed with a small amount of distilled water, transferred to a beaker, and extracted with two 100-ml. portions of hot absolute alcohol. To the warm filtrate is added 200 ml. of water, and the solution is allowed to cool in an ice bath for 2 hours. The yield of the crude acid which is obtained by filtration as a fine, yellow powder melting at 135° (Note 8) is 16.5 g. (90%).

D. *Naphthoresorcinol.* In a 200-ml. three-necked, round-bottomed flask, equipped with a nitrogen inlet tube, a stirrer, and a condenser, is placed 65 ml. of water; the water is then boiled to expel dissolved oxygen. To the boiling water is added 16.5 g. of the crude acid (Note 9), and the mixture is boiled with stirring for 2 hours in an atmosphere of nitrogen. The water is decanted from any pasty residue; the residue is boiled with 35 ml. of water for 2 hours, and the supernatant liquid is decanted through a filter and combined with the first solution. Just enough sodium hydrosulfite (about 0.3 to 0.5 g.) is added to decolorize the red solution, 15 g. of sodium chloride is dissolved in the solution, and the mixture is allowed to stand at 5° for 24 hours. The naphthoresorcinol precipitates first as an oil, which solidifies to a reddish solid on further cooling, and then as colorless or slightly yellow plates. The yield is 7.0–7.3 g. (54–56%). After standing over calcium chloride in a vacuum desiccator for 1 day, the white or slightly yellow plates melt at 119–122° and the reddish solid melts at 110–118°.

To 100 ml. of hot water are added 3.5 g. of the reddish solid, just enough sodium hydrosulfite to remove the red coloration, and 0.3 g. of Norite. The mixture is filtered, 7 g. of sodium chloride is dissolved in the filtrate, and the solution is allowed to stand in a closed container at 5° for 24 hours. The yield of naphthoresorcinol, which separates as large, nearly transparent plates melting at 122–124° (Note 10), is 2.6 g. (75% recovery).

2. Notes

1. In order to measure the volume of alcohol to be used, an equal volume of water (90 ml.) is placed in the dropping funnel and a label is pasted at the level of the water. The funnel is then emptied and carefully dried.

2. A liter of commercial absolute alcohol is dried by means of sodium and ethyl phthalate [1] in a 2-l. distilling flask equipped with a reflux condenser. A short section of rubber tubing closed by a screw clamp is attached to the side arm of the flask. In the next step the condenser is set for downward distillation.

3. The carbon tetrachloride, ether, and malonic ester are dried over anhydrous magnesium sulfate. The malonic ester is distilled before use.

4. The yield of ethyl 1,3-dihydroxy-2-naphthoate is decreased to 45% if the sulfuric acid solution is allowed to stand for only 2 days.

5. After about 25 ml. of the sulfuric acid solution has been added, the mixture is stirred until a yellow solid separates. Precipitation of the main portion of the product then occurs very smoothly as the remainder of the sulfuric acid solution is added.

6. The ester may be recrystallized also by solution in dioxane and precipitation by water.

7. An alternative procedure consists in decomposing the barium salt with hydrochloric acid. However, in the checkers' hands this procedure did not yield a barium-free product.

8. The submitters obtained the pure acid as follows: To 0.5 g. of the crude acid was added 200 ml. of boiling water, and the mix-

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[1] *Org. Syntheses* Coll. Vol. 2, 155 (1943).

ture was heated for an instant to effect solution and filtered immediately. The filtrate was cooled by vigorous shaking in an ice bath. Addition of 1 ml. of concentrated hydrochloric acid to the solution caused the separation of crystals, which were collected after 30 minutes' additional cooling in ice, washed with ice water, and dried in vacuum over phosphorus pentoxide. The recovery of material melting in the range of 138.5–140.5° to 146.5° was 62%.

9. The solid has a tendency to assume a semi-plastic consistency, but the size of the mass decreases as decarboxylation occurs.

10. If part of the material separates as an oil and solidifies, the appearance of the product may be poor, although the melting point is 122–124°. Separation as an oil may be prevented by slow cooling with shaking and seeding. An alternative procedure for final purification of naphthoresorcinol consists in sublimation at 120–130°/5×10^{-4} mm.

3. Methods of Preparation

Naphthoresorcinol has been prepared by heating 1-amino-3-hydroxy-4-naphthalenesulfonic acid or its salt in water or slightly acidic solution[2] and by cyclization of ethyl phenylacetylmalonate[3] or of ethyl phenylacetoacetate.[4] Phenylacetylmalonic ester has been prepared by condensing phenylacetyl chloride and malonic ester in ether with sodium.[3]

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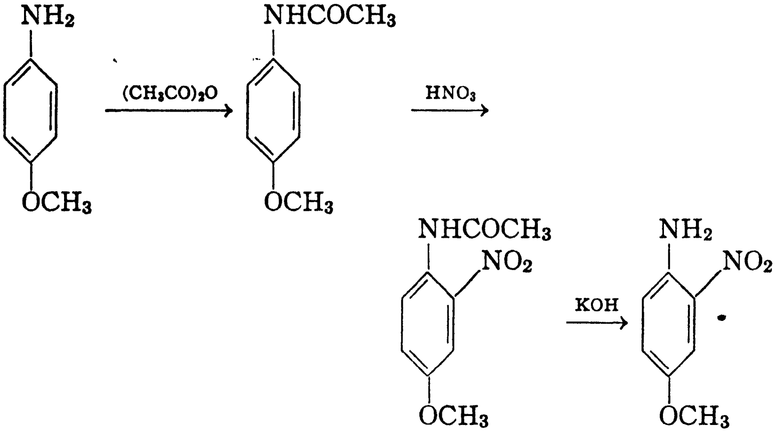
[2] Friedlander and Rudt, *Ber.*, **29**, 1609 (1896); Ger. pat. 84,990 [*Frdl.*, **4**, 229 (1894–1897)]; Ger. pat. 87,429 [*Frdl.*, **4**, 584 (1894–1897)]; Ger. pat. 90,096 [*Frdl.*, **4**, 585 (1894–1897)].

[3] Metzner, *Ann.*, **298**, 374 (1897); Wagreich, Roberts, and Harrow, *Chemist-Analyst*, **31**, 59 (1942).

[4] Soliman and West, *J. Chem. Soc.*, **1944**, 53.

2-NITRO-4-METHOXYANILINE

(*p*-Anisidine, 2-nitro-)



Submitted by Paul E. Fanta and D. S. Tarbell.
Checked by W. E. Bachmann and N. C. Deno.

1. Procedure

A. *2-Nitro-4-methoxyacetanilide.* In a 2-l. three-necked, round-bottomed flask equipped with a mechanical stirrer and a thermometer are placed 123 g. (1 mole) of *p*-anisidine (Note 1), 300 ml. of glacial acetic acid, and 217 ml. of water. Stirring is started, and, when the *p*-anisidine has dissolved, 350 g. of ice is added. When the temperature reaches 0–5°, 103 ml. (1.1 moles) of acetic anhydride is added all at once with rapid stirring. Within several seconds the contents of the flask set to a crystalline mass and the temperature rises to 20–25°. The flask is heated on a steam bath until the crystalline material dissolves and is then cooled with stirring to 45°, at which temperature crystals begin to separate. An ice bath is applied, and 100 ml. (55% excess) of concentrated nitric acid (sp. gr. 1.42) is added all at once. The temperature rises rapidly to 70° and soon begins to fall. By suitable adjustment of the cooling bath the temperature is maintained at 60–65° for 10 minutes and then brought down to 25° in the course of 10 minutes (Note 2).

The solution is chilled overnight in an ice chest, and the precipitated yellow crystals are collected on a 19-cm. Büchner funnel. The crystals are washed with 270 ml. of ice-cold water and pressed as dry as possible with a rubber dam. The filter cake can be dried (Note 3) in air or in a vacuum desiccator over calcium chloride and soda lime. The yield of 2-nitro-4-methoxyacetanilide melting at 116–116.5° is 158–168 g. (75–79%).

B. *2-Nitro-4-methoxyaniline.* A mixture of 160 g. of 2-nitro-4-methoxyacetanilide and 250 ml. of cold Claisen's alkali (Note 4) in a 2-l. beaker is stirred and warmed on a steam bath for 15 minutes; it first becomes liquid and then sets to a thick, red paste. After the addition of 250 ml. of hot water the mixture is stirred and digested on a steam bath for an additional 15 minutes and then cooled to 0–5°. The product is collected on a 19-cm. Büchner funnel, washed with three 160-ml. portions of ice-cold water, and pressed as dry as possible with a rubber dam. The yield of vacuum-dried product melting at 122.5–123° is 122–4 g. (95–97%).

2. Notes

1. Eastman Kodak Company's Practical grade of *p*-anisidine was used.

2. In a run in which the mixture was allowed to cool spontaneously from 65° the product became dark.

3. Drying is unnecessary if the 2-nitro-4-methoxyacetanilide is used in step B. The material may be recrystallized with 97% recovery from dilute aqueous alcohol (2 ml. of 95% alcohol and 4 ml. of water per gram). The product so obtained melts at 116.5–117°.

4. Claisen's alkali is prepared by dissolving 88 g. of potassium hydroxide in 63 ml. of water, cooling, and diluting to 250 ml. with methanol.

3. Methods of Preparation

2-Nitro-4-methoxyacetanilide has been prepared by the nitration of *p*-acetaniside.[1] The procedure described for the nitration is essentially that used by Lothrop.[1d]

2-Nitro-4-methoxyaniline has been prepared by heating nitrohydroquinone dimethyl ether with aqueous ammonia; [2] by heating the tetramethylammonium salt of 3-nitro-4-aminophenol; [3] by the hydrolysis of 2-nitro-4-methoxyacetanilide [1a] with alcoholic potassium hydroxide [1b, 1c] or hydrochloric acid; [1d] and by the hydrolysis of the *p*-toluenesulfonamide,[4] the 3-nitrobenzenesulfonamide,[5] the 3-nitro-*p*-toluenesulfonamide,[5] and the acetyl derivative of the *p*-toluenesulfonamide [6] of 2-nitro-4-methoxyaniline with concentrated sulfuric acid.

NITROSOBENZENE

$$C_6H_5NO_2 \xrightarrow[NH_4Cl]{Zn} C_6H_5NHOH \xrightarrow[H_2SO_4]{Na_2Cr_2O_7} C_6H_5NO$$

Submitted by GEORGE H. COLEMAN, CHESTER M. MCCLOSKEY, and FRANK A. STUART.
Checked by W. E. BACHMANN, N. C. DENO, and R. F. EDGERTON.

1. Procedure

A mixture of 250 ml. (2.44 moles) of nitrobenzene (Notes 1 and 2) and a solution of 150 g. of ammonium chloride in 5 l. of water in a 5-gal. crock (Note 3) is stirred vigorously (Note 4), and 372 g. (5.15 moles) of zinc dust (90% zinc) is added in small portions over a period of 5 minutes. About 5 minutes after the addition of the zinc, the main reaction occurs and the temperature rises. When the temperature reaches about 65°, enough ice is added to the stirred mixture to bring the temperature down to 50–55° (Note 5). Twenty minutes after the addition of zinc was started, the solution is filtered through a 24-cm. Büchner funnel and the zinc oxide residues are washed with 3 l. of boiling water. The filtrate and washings are combined in a 6-gal. crock (Note 6) and cooled immediately (Note 7) by the addition of enough ice to bring the temperature to 0° to −2° and leave at least 1 kg. of ice unmelted.

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[1] (*a*) Hinsberg, *Ann.*, **292**, 249 (1896); (*b*) Reverdin, *Ber.*, **29**, 2595 (1896); *Jahresb.*, **1896**, 1156; *Bull. soc. chim.*, (3) **17**, 115 (1897); (*c*) Hata, Tatematsu, and Kubota, *Bull. Chem. Soc. Japan*, **10**, 425 (1935) [*C.A.*, **30**, 1056 (1936)]; (*d*) Lothrop, *J. Am. Chem. Soc.*, **64**, 1698 (1942).

[2] Scheidel, Ger. pat. 36,014 [*Frdl.*, **1**, 221 (1888)].

[3] Hahle, *J. prakt. Chem.*, (2) **43**, 66 (1891).

[4] Reverdin, *Ber.*, **42**, 1525 (1909); Simonov, *J. Gen. Chem.* (*U.S.S.R.*), **10**, 1580 (1940) [*C.A.*, **35**, 2870 (1941)].

[5] Reverdin and de Luc, *Ber.*, **45**, 352 (1912).

[6] Reverdin and de Luc, *Ber.*, **43**, 3461 (1910).

To this cold solution or suspension of β-phenylhydroxylamine, a cold solution of sulfuric acid (750 ml. of concentrated acid and sufficient ice to bring the temperature down to −5°) is added with stirring. An ice-cold solution of 170 g. of sodium dichromate dihydrate in 500–750 ml. of water is added as rapidly as it can be poured into the mixture, which is stirred or swirled (Note 8). After 2 to 3 minutes, the straw-colored precipitate of nitrosobenzene is collected on a Büchner funnel and washed with 1 l. of water (Note 9).

The crude nitrosobenzene is steam-distilled (Note 10), and the distillate is collected in a receiver cooled by ice (Note 11). The nitrosobenzene is finely ground in a mortar, transferred to a Büchner funnel, and washed with water until the washings are no longer brown. After it has been sucked as dry as possible on the filter the nitrosobenzene is pressed between layers of filter paper (or other porous paper). One or two changes of paper may be necessary. The yield of nitrosobenzene melting at 64–67° is 128–138 g. (49–53%) (Notes 12 and 13). If a purer product is desired, the crude nitrosobenzene can be recrystallized from a small amount of alcohol with good cooling, and the product dried over calcium chloride at atmospheric pressure.

2. Notes

1. Commercial nitrobenzene of good quality is satisfactory.

2. Contact with nitrobenzene, phenylhydroxylamine, and nitrosobenzene or prolonged breathing of the vapors should be avoided.

3. The checkers used a 12-l. round-bottomed flask.

4. Vigorous stirring is necessary in order to prevent the zinc dust from caking on the bottom of the crock. The submitters employed two mechanically driven stirrers in order to keep the zinc dust in suspension. The checkers used a single paddle stirrer successfully.

5. At higher temperatures secondary reactions take place.

6. The checkers used a 22-l. round-bottomed flask.

7. Since β-phenylhydroxylamine decomposes on standing, the filtrate should be cooled as soon as the filtration is completed, and the oxidation to nitrosobenzene should be carried out immediately. An excess of ice should be present since the oxidation reaction is exothermic and the temperature of the solution should still be near 0° after the oxidation. At higher temperatures oxidation products other than nitrosobenzene are produced.

8. It is important to add the dichromate solution rapidly in order to obtain a good yield of easily filterable product. In a run in which the dichromate solution was added over a period of 25 minutes, only a 10% yield of nitrosobenzene was obtained.

9. This product is stable for about a week if kept at 0°.

10. Connections should be of glass since cork and rubber are attacked readily. Since nitrosobenzene decomposes at the elevated temperature, it should be steam-distilled as rapidly as possible. If several runs are made, not more than four or five should be combined for distillation. A Hopkins still head is effective for preventing contamination.

The nitrosobenzene condenses to a green liquid which solidifies to a white solid. Care should be taken that the solid does not clog the condenser. Distillation is stopped when yellow oily material appears in the condenser.

11. Cooling of the receiver is necessary because the nitrosobenzene has a very high vapor pressure at room temperature.

12. Yields as high as 65–70% have been obtained in smaller runs.

13. Nitrosobenzene can be kept at room temperature in a closed container for 1–2 days. Over longer periods it should be stored at 0°.

3. Methods of Preparation

Nitrosobenzene can be prepared by the oxidation of aniline with permonosulfuric acid [1] or peracetic acid [2] and by the oxidation of β-phenylhydroxylamine,[3] which is prepared by the reduction of nitrobenzene.

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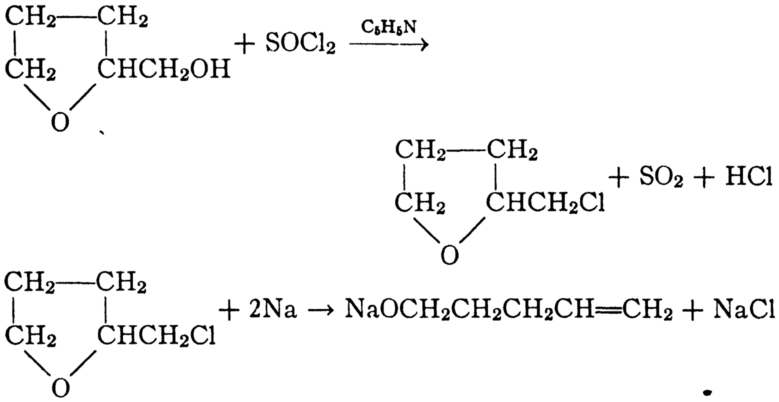
[1] Caro, *Z. angew. Chem.*, **11**, 845 (1898).

[2] D'Ans and Kneip, *Ber.*, **48**, 1144 (1915).

[3] Bamberger, *Ber.*, **27**, 1555 (1894); Parsons and Bailar, *J. Am. Chem. Soc.*, **58**, 268 (1936).

4-PENTEN-1-OL



$$NaOCH_2CH_2CH_2CH{=}CH_2 + H_2O \rightarrow HOCH_2CH_2CH_2CH{=}CH_2 + NaOH$$

Submitted by L. A. BROOKS and H. R. SNYDER.
Checked by NATHAN L. DRAKE and W. MAYO SMITH.

1. Procedure

A. *Tetrahydrofurfuryl chloride.* In a 2-l. three-necked flask, fitted with a mechanical stirrer, a dropping funnel, and a thermometer, are placed 408 g. (4 moles) of freshly distilled tetrahydrofurfuryl alcohol (Note 1) and 348 g. (4.4 moles) of pyridine. To the rapidly stirred mixture which is cooled in an ice bath, 500 g. (4.2 moles) of freshly distilled thionyl chloride (Note 1) is added from the dropping funnel at the rate of 3–5 drops per second. When one-third to one-half of the thionyl chloride has been added, a pasty crystalline mass begins to separate and the temperature begins to rise rapidly. The temperature should not be allowed to go above 60°. As more thionyl chloride is added the mass redissolves and a dark brown liquid forms. When the addition is complete, the bath is removed and the mixture is stirred for 3–4 hours. The liquid (or the slurry, if some crystallization has occurred) is poured into a beaker (Note 2) and extracted seven times with 500-ml. portions of ether (Note 3); the ether extracts are decanted and combined. The ether is removed by distillation, and the residue is washed three times with 100-ml. portions of water, dried over anhydrous magnesium sulfate, and distilled under reduced pressure. The yield of tetrahydrofurfuryl chloride boiling at 41–42°/11 mm. (47–48°/15 mm.) is 354–360 g. (73–75%).

B. *4-Penten-1-ol.* A 2-l. three-necked flask containing 112 g. (4.87 moles) of powdered sodium (Note 4) under 700 ml. of anhydrous ether is fitted with a mechanical stirrer, a separatory funnel, and a reflux condenser with a drying tube. A few milliliters (2–3) of a mixture of 300 g. (2.5 moles) of tetrahydrofurfuryl chloride and 300 ml. of anhydrous ether is added to the rapidly stirred suspension. A vigorous reaction occurs, and the solution turns blue. The remainder of the solution of the chloride is then added dropwise over a period of 5 hours, during which time the flask is cooled in an ice bath (Note 5). When the addition is complete, stirring is continued for 2 hours. The suspension is decanted from any sodium that remains (Note 6) into a dry beaker and decomposed with sufficient ice water to give two liquid layers. The ether layer is separated and dried over magnesium sulfate. After the removal of the ether by distillation on a steam cone, the residue is distilled. The yield of 4-penten-1-ol boiling at 134–137° is 161–178 g. (76–83%).

2. Notes

1. Undistilled commercial thionyl chloride and Eastman Practical tetrahydrofurfuryl alcohol may be used, but the yields are slightly lower (65–70%).

2. The checkers found it easier to separate the ethereal extract from the residue when the mixture was in a large separatory funnel.

3. The yield will be low if extraction is incomplete. It is advisable to stir with a heavy glass rod and break up any lumps that have formed.

4. The powdered sodium is prepared under hot xylene [1] with the aid of a Hershberg stirrer; [2] the xylene is decanted and replaced with ether.

5. The ice bath is not used until the reaction has definitely started.

6. Occasionally a little sodium is left on the bottom of the flask. This is destroyed with alcohol and the flask is washed with ice water.

3. Methods of Preparation

Tetrahydrofurfuryl chloride has been prepared from the alcohol and thionyl chloride [3] or phosphorus trichloride. 4-Penten-1-ol has been prepared from tetrahydrofurfuryl bromide or chloride and magnesium or sodium.[4-6]

p-PHENYLAZOBENZOIC ACID

(Benzoic acid, *p*-phenylazo-)

$$C_6H_5NO + H_2NC_6H_4COOH \rightarrow C_6H_5N{=}NC_6H_4COOH + H_2O$$

Submitted by Harry D. Anspon.
Checked by W. E. Bachmann and N. C. Deno.

1. Procedure

Fifty-four grams (0.39 mole) of *p*-aminobenzoic acid is dissolved in 390 ml. of warm glacial acetic acid in a 1-l. Erlenmeyer flask. The solution is cooled to room temperature, 42 g. (0.39 mole) of nitrosobenzene (p. 80) is added, and the mixture is shaken until the nitrosobenzene dissolves. The flask is stoppered, and the solution is allowed to stand for 12 hours at room temperature. The product begins to crystallize after about 15 minutes.

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[1] *Org. Syntheses*, **20**, 8 (1940).

[2] *Org. Syntheses* Coll. Vol. **2**, 117 (1943).

[3] Kirner, *J. Am. Chem. Soc.*, **52**, 3251 (1930).

[4] Paul, *Bull. soc. chim.*, (4) **53**, 424 (1933); (5) **2**, 745 (1935).

[5] Robinson and Smith, *J. Chem. Soc.*, **1936**, 196.

[6] Gambert, Linstead, and Rydon, *J. Chem. Soc.*, **1937**, 1972.

The *p*-phenylazobenzoic acid is collected on a Büchner funnel (Note 1) and washed with acetic acid and with water. The yield of air-dried acid melting at 245–247° cor. is 62 g. (70%). By recrystallization from 95% alcohol (60 ml. per g.) the acid is obtained as orange-gold plates which melt at 248.5–249.5° cor.; the yield is 54 g. (61%).

2. Notes

1. The solution is not cooled below room temperature before filtering; cooling below 20° brings down impurities.

3. Methods of Preparation

The method employed here is essentially the one described by Angeli and Valori.[1]

p-PHENYLAZOBENZOYL CHLORIDE

(Benzoyl chloride, *p*-phenylazo-)

$$C_6H_5N{=}NC_6H_4CO_2H + SOCl_2 \rightarrow C_6H_5N{=}NC_6H_4COCl + HCl + SO_2$$

Submitted by George H. Coleman, Gust Nichols, Chester M. McCloskey, and Harry D. Anspon.
Checked by W. E. Bachmann and N. C. Deno.

1. Procedure

Fifty grams (0.22 mole) of recrystallized *p*-phenylazobenzoic acid (p. 86) (Note 1) and 50 g. (0.47 mole) of anhydrous sodium carbonate (Note 2) are placed in a 1-l. flask and thoroughly mixed by shaking. To this mixture is added 250 ml. (3.5 moles) of thionyl chloride (Note 3); a reflux condenser with a drying tube is fitted to the flask, and the mixture is refluxed for 1.5 hours (Note 4). A condenser is set for distillation, and as much as possible of the thionyl chloride is distilled on a steam bath (Note 5).

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[1] Angeli and Valori, *Atti accad. Lincei*, **22**, I, 132 (1913) [*C.A.*, **7**, 2223 (1913)].

The acid chloride is dissolved by refluxing with 500 ml. of 90–100° ligroin, and the hot solution is decanted from the sodium carbonate onto a fluted filter. This process is repeated with three 150-ml. portions of ligroin. The combined filtrates are concentrated to 500 ml., filtered if necessary, and cooled to 0°. The acid chloride is collected on a Büchner funnel and pressed as dry as possible. It is washed twice with 30–60° petroleum ether and stored in a vacuum desiccator over phosphorus pentoxide and paraffin shavings (Note 6). The yield of orange-red crystals melting at 94.5–95.5° is 48 g. (89%).

2. Notes

1. The checkers found that 50 g. of unrecrystallized acid gave 45 g. of acid chloride melting at 92–94°. When this was recrystallized from 90–100° petroleum ether (10 ml. per g.), 41.5 g. of orange-red crystals melting at 94.5–95.5° was obtained. The over-all yield of pure acid chloride on the basis of unrecrystallized acid is the same. The use of unrecrystallized acid has an advantage in that the volume of solvent required for recrystallization of the acid chloride is much less than for the acid.

2. The use of sodium carbonate is unusual. It is claimed that the sodium carbonate prevents decomposition and tar formation during the reaction.

3. The checkers used Eastman Kodak Company's best grade of thionyl chloride.

4. Refluxing should be carried out under a hood or in an apparatus provided with a gas trap.[1]

5. About 170 ml. of good thionyl chloride can be recovered.

6. The acid chloride holds the petroleum ether tenaciously. About a week is required for complete removal of the petroleum ether.

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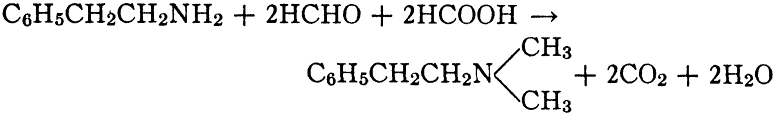
[1] *Org. Syntheses* Coll. Vol. 1, 97 (1941).

3. Methods of Preparation

p-Phenylazobenzoyl chloride (azoyl chloride) has been prepared by the action of thionyl chloride on the acid.[2,3] The method used is a modification of that of Ladenburg, Fernholz, and Wallis.[3]

β-PHENYLETHYLDIMETHYLAMINE

(Phenethylamine, N,N-dimethyl-)



$$C_6H_5CH_2CH_2NH_2 + 2HCHO + 2HCOOH \rightarrow C_6H_5CH_2CH_2N\begin{matrix}\diagup CH_3\\ \diagdown CH_3\end{matrix} + 2CO_2 + 2H_2O$$

Submitted by Roland N. Icke and Burnett B. Wisegarver with Gordon A. Alles.
Checked by H. R. Snyder and James H. Saunders.

1. Procedure

To 51.2 g. (1 mole) of 90% formic acid in a 500-ml. round-bottomed flask (Note 1), cooled in running tap water, is added slowly 24.2 g. (0.2 mole) of β-phenylethylamine.[1] To the resulting clear solution are added 45 ml. (0.6 mole) of formaldehyde solution (concentration, 37%) (Note 2) and a small boiling-stone. The flask is connected to a reflux condenser and is placed in an oil bath which has been heated to 90–100°. A vigorous evolution of carbon dioxide begins after 2 or 3 minutes, at which time the flask is removed from the bath until the gas evolution notably subsides (15–20 minutes); then it is returned to the bath and heated at 95–100° for 8 hours.

[2] Reich, *Biochem. J.*, **33**, 1001 (1939).

[3] Ladenburg, Fernholz, and Wallis, *J. Org. Chem.*, **3**, 294 (1938).

β-PHENYLETHYLDIMETHYLAMINE

[1] *Org. Syntheses*, **23**, 71 (1943).

After the solution has been cooled, 100 ml. of 4 *N* hydrochloric acid is added and the solution is evaporated to dryness under reduced pressure (water pump) from a water bath; the receiver is cooled in an ice bath. The pale yellow syrupy residue (or crystalline solid) is dissolved in 60–75 ml. of water, and the organic base is liberated by the addition of 50 ml. of 18 *N* sodium hydroxide solution. The upper (organic) phase is separated, and the lower (aqueous) phase is extracted with two 30-ml. portions of benzene. The combined organic base and benzene extracts are dried over 10 g. of anhydrous granular potassium carbonate (Note 3). After the benzene has been distilled slowly under slightly reduced pressure from a 125-ml. Claisen flask, the pressure is lowered further, and the product is distilled. The yield of colorless β-phenylethyldimethylamine boiling at 97–98°/22 mm. (Note 4) is 22–24.7 g. (74–83%) (Note 5).

2. Notes

1. A flask of this size is used because of the tendency of the solution to froth during the gas evolution. Frothing usually is not bad with this amine but is quite bothersome when the higher aliphatic amines (decylamine to octadecylamine) are methylated.

2. U.S.P. formaldehyde was used. The commercial aqueous-methanolic solution contains 37% formaldehyde by weight. It is sometimes called "40% formalin" because 100 ml. of the solution contains 40 g. of formaldehyde.

3. If complete separation of the benzene extracts from the aqueous solution is difficult, it is advantageous to dry the benzene solution roughly over 10 g. of the anhydrous potassium carbonate and to decant the resulting clear solution into another flask where it may be dried over 5 g. of fresh drying agent. The spent drying agent is rinsed with 15–20 ml. of benzene, and the rinsings are added to the main solution.

4. Another boiling point is 66–68°/6 mm. If the product is distilled through a short column (12–15 cm.) packed with glass helices, it boils constantly at 98°/22 mm. The recovery is somewhat lower when a column is used.

The product gives a negative carbylamine test and hence contains no significant amount of unchanged primary amine.

5. This methylation procedure is quite generally satisfactory for simple primary and secondary amines. For methylation of a secondary amine only half as much formaldehyde is required, although a larger amount does no harm. The submitters also have prepared, in uniformly good yields, benzyldodecylmethylamine (b.p. 180–182°/4 mm.) from benzyldodecylamine, and α-amylhexyldimethylamine (b.p. 115°/16 mm.) from α-amylhexylamine. It is reported [2] that the reaction can be successfully applied to the methylation of butylamine, benzylamine, tetramethylenediamine, piperidine, and α-phenyl-α-aminobutyric acid.

3. Methods of Preparation

The procedure given above is an adaptation of the methylation method first used by Sommelet and Ferrand [3] and developed more fully by Clarke, Gillespie, and Weisshaus.[2] β-Phenylethyldimethylamine has been prepared from β-phenylethylamine by alkylation with dimethyl sulfate; [4] by the reaction of β-phenylethylamine and of N-methyl-β-phenylethylamine with formaldehyde; [5] by catalytic reduction of phenylacetonitrile in the presence of dimethylamine; [6] by the reaction of dimethylamine with β-phenylethyl chloride [7,8,9] and with β-phenylethyl bromide; [9] and by the reaction of phenylacetaldehyde with dimethylamine.[10]

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[2] Clarke, Gillespie, and Weisshaus, *J. Am. Chem. Soc.*, **55**, 4571 (1933).

[3] Sommelet and Ferrand, *Bull. soc. chim.*, (4) **35**, 446 (1924).

[4] Johnson and Guest, *J. Am. Chem. Soc.*, **32**, 761 (1910).

[5] Decker and Becker, *Ber.*, **45**, 2404 (1912); *Ann.*, **395**, 344 (1913).

[6] Buck, Baltzly, and Ide, *J. Am. Chem. Soc.*, **60**, 1789 (1938).

[7] Barger, *J. Chem. Soc.*, **95**, 2193 (1909).

[8] Tiffeneau and Fuhrer, *Bull. soc. chim.*, (4) **15**, 173 (1914).

[9] v. Braun, *Ber.*, **43**, 3209 (1910).

[10] Ger. pat. 291,222 [*Frdl.*, **12**, 802 (1914–1916)].

PHENYLPROPARGYL ALDEHYDE

(Propiolaldehyde, phenyl-)

$$C_6H_5CH{=}CHCHO \xrightarrow{Br_2} C_6H_5CHBrCHBrCHO \xrightarrow{K_2CO_3}$$

$$C_6H_5CH{=}CBrCHO \xrightarrow{HC(OC_2H_5)_3}$$

$$C_6H_5CH{=}CBrCH(OC_2H_5)_2 \xrightarrow{KOH}$$

$$C_6H_5C{\equiv}CCH(OC_2H_5)_2 \xrightarrow[H_2SO_4]{H_2O} C_6H_5C{\equiv}CCHO$$

Submitted by C. F. H. Allen and C. O. Edens, Jr.
Checked by C. D. Heaton and C. R. Noller.

1. Procedure

A. *α-Bromocinnamic aldehyde.* A mixture of 44 g. (0.33 mole) of cinnamic aldehyde and 167 ml. of acetic acid in a 500-ml. three-necked, round-bottomed flask, surrounded by a cold water bath and fitted with a stirrer, reflux condenser, and dropping funnel, is stirred vigorously while 17.1 ml. (53.5 g., 0.33 mole) of bromine is added. This is followed by the addition of 23 g. (0.17 mole) of anhydrous potassium carbonate. When the evolution of gas has ceased, the mixture is refluxed for 30 minutes, then cooled and poured into 435 ml. of water in a 1-l. flask; a lower, reddish layer of crude α-bromoaldehyde separates. The flask is stoppered, cooled under running water, and shaken vigorously. The resulting granular solid is filtered with suction and dissolved without drying by warming with 220 ml. of 95% alcohol. After the addition of 50 ml. of water, the solution is warmed until it becomes clear and is then set aside to crystallize at room temperature and finally in a refrigerator. α-Bromocinnamic aldehyde separates as nearly colorless needles, which are filtered with suction, rinsed with 17 ml. of 80% alcohol, and air-dried. The yield of product melting at 72–73° is 52–60 g. (75–85%) (Note 1).

B. *α-Bromocinnamic aldehyde acetal.* In a 250-ml. flask are placed 45 g. (0.21 mole) of α-bromocinnamic aldehyde, 50 ml.

(0.3 mole) of ethyl orthoformate,[1] 40 ml. of absolute ethanol, and 0.5 g. of ammonium chloride. After the mixture has been refluxed for 30 minutes, it is transferred to a modified Claisen flask,[2] and the low-boiling constituents are removed at atmospheric pressure and a bath temperature up to 150° (Note 2). The yield of acetal boiling at 146–149°/5 mm. and with n_D^{22} 1.5500 is 50–52 g. (82–86%).

C. *Phenylpropargyl aldehyde acetal.* A solution of 20.7 g. (0.25 mole) of potassium hydroxide in 200 ml. of absolute ethanol is added to 50 g. (0.18 mole) of α-bromocinnamic aldehyde acetal in a 500-ml. flask. The mixture is refluxed for 1.5 hours and poured into a 3-l. separatory funnel containing 1.5 l. of water. The oil which separates is extracted with three 170-ml. portions of chloroform, and the combined chloroform extracts are washed with three 75-ml. portions of water and then dried over 15 g. of anhydrous sodium sulfate. The chloroform is removed by distillation, and the residual oil is distilled from a modified Claisen flask. The yield of phenylpropargyl aldehyde acetal boiling at 153–156°/19 mm. is 28–31 g. (80–86%).

D. *Phenylpropargyl aldehyde.* Twenty-nine grams (0.14 mole) of the acetal is added to 140 ml. of water containing 10 ml. of concentrated sulfuric acid, and the mixture is heated on a steam bath with occasional shaking for 30 minutes. The aldehyde is then steam-distilled and extracted from the distillate with two 250-ml. portions of ether. The ethereal solution is dried over 20 g. of anhydrous sodium sulfate, the solvent is removed, and the residue is distilled from a 100-ml. modified Claisen flask. The yield of phenylpropargyl aldehyde boiling at 114–117°/17 mm. and with n_D^{25} 1.6032 is 13–15 g. (70–81%).

2. Notes

1. The same percentage yield is obtained in runs three times as large.

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[1] *Org. Syntheses* Coll. Vol. **1**, 258 (1941).

[2] *Org. Syntheses* Coll. Vol. **1**, 130 (1941).

2. Both the reaction and the distillation can be carried out in the same flask.

3. Methods of Preparation

The procedure given for the preparation of phenylpropargyl aldehyde is a modification of Claisen's directions[3] in part due to Kalff.[4] The monobromocinnamic aldehyde was described by Zincke.[5] Other methods of possible preparative value for the acetal are the interaction of sodium phenylacetylene,[6-9] or the Grignard reagent from phenylacetylene,[10, 11] and ethyl orthoformate.

[3] Claisen, *Ber.*, **31**, 1020 (1898).

[4] Kalff, *Rec. trav. chim.*, **46**, 594 (1927).

[5] Zincke and Hagen, *Ber.*, **17**, 1815 (1884).

[6] Moureu and Delange, *Compt. rend.*, **133**, 106 (1901).

[7] Moureu and Delange, *Bull. soc. chim.*, (3) **31**, 1329 (1904).

[8] Brachim, *Bull. soc. chim.*, (3) **35** 1165 (1906).

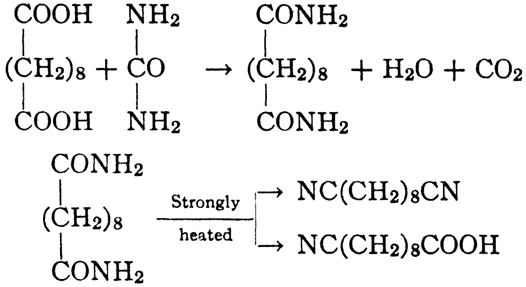
[9] Charon and Dugoujon, *Compt. rend.*, **137**, 126 (1903).

[10] Moureu and Delange, *Compt. rend.*, **138**, 1341 (1904).

[11] Moureu and Delange, *Bull. soc. chim.*, (3) **31**, 1332 (1904).

SEBACONITRILE AND ω-CYANOPELARGONIC ACID

(Sebaconitrile and θ-cyanopelargonic acid)



$$\begin{array}{c}\text{COOH}\\|\\(\text{CH}_2)_8\\|\\\text{COOH}\end{array} + \begin{array}{c}\text{NH}_2\\|\\\text{CO}\\|\\\text{NH}_2\end{array} \rightarrow \begin{array}{c}\text{CONH}_2\\|\\(\text{CH}_2)_8\\|\\\text{CONH}_2\end{array} + \text{H}_2\text{O} + \text{CO}_2$$

$$\begin{array}{c}\text{CONH}_2\\|\\(\text{CH}_2)_8\\|\\\text{CONH}_2\end{array} \xrightarrow[\text{heated}]{\text{Strongly}} \left\{\begin{array}{l}\rightarrow \text{NC(CH}_2)_8\text{CN}\\ \rightarrow \text{NC(CH}_2)_8\text{COOH}\end{array}\right.$$

Submitted by B. S. Biggs and W. S. Bishop.
Checked by C. F. H. Allen and J. Van Allan.

1. Procedure

A. *Sebaconitrile.* A 3-l. three-necked flask (Note 1), equipped with a mechanical stirrer (Notes 2 and 3) and a thermometer which dips into the liquid, is heated in an oil bath to 160°. In the flask are placed 505 g. (2.5 moles) of commercial sebacic acid (Note 4) and 180 g. (3 moles) of urea (Note 5), and the melt is heated with stirring for 4 hours at about 160° (Note 6). The oil bath is removed, the surplus oil is wiped off, the flask is insulated (Note 7), and the temperature is then raised, as rapidly as foaming permits, to 220° by means of a triple burner and wire gauze. It is important to continue the stirring for at least 5 minutes after 220° is attained; otherwise the mass will foam over during the subsequent distillation.

The stirrer is then replaced by a short still head connected to a long (90-cm.) air condenser and receiver (Note 8), and the product is distilled at atmospheric pressure as long as any distillate is obtained. The temperature of the vapor rises gradually to 340°. The distillate, which consists chiefly of water, dinitrile, acid nitrile, and sebacic acid, is poured into a large (2-l.) separatory funnel and, after the addition of 500 ml. of ether (Note 9), is extracted three times with 650-ml. portions of 5% ammonium carbonate (Note 10). The crude dinitrile which remains after the removal of the ether is distilled *in vacuo;* after a small fore-run (20–25 ml.) the main product is collected at 185–188°/12 mm. (Note 11). The yield of sebaconitrile is 190–200 g. (46–49%) (Note 12).

B. *ω-Cyanopelargonic acid.* The combined ammoniacal extracts are heated nearly to boiling in a large enameled pot or 4-l. beaker and neutralized to phenolphthalein with concentrated hydrochloric acid (about 120 ml.) (Note 13). A hot solution of 400 g. of barium chloride is then added slowly with stirring, and the hot solution is filtered from the precipitated barium sebacate (Note 14) through a fluted filter paper or "Shark Skin" filter paper (Note 15) on a 20-cm. Büchner funnel. The barium salt of the cyano acid that separates on cooling is filtered on the same sized funnel and dissolved in 1 l. of hot water, and the solution is acidified to litmus with concentrated hydrochloric acid (about 30 ml.). The cyano acid separates as a clear oil. The filtrate from which the barium salt was filtered is acidified likewise to litmus with concentrated hydrochloric acid (about 50 ml.). The two oils are combined. The cyano acid is washed by decantation with three 200-ml. portions of hot water, separated completely from water, and dried in a vacuum desiccator over calcium chloride. The yield of ω-cyanopelargonic acid melting at 48–49° is 146–155 g. (32–34%) (Note 16).

2. Notes

1. Ground-glass equipment is preferable, since the final temperature is high enough to decompose rubber or cork stoppers.

2. The stirrer is a bent glass rod that will break up the foam produced.

3. Attention is called to the powerful but compact compressed-air stirrer, Catalog No. 9224, of the A. H. Thomas Com-

pany. When a compressed-air line is available, such a stirrer is preferable to an electric motor.

4. Commercial grades of sebacic acid (m.p. 127–130°) and urea (m.p. 132–134°) were used; pure sebacic acid (m.p. 132–133°) gives only a slightly (13%) higher yield. Since the acid is light and bulky, it is convenient to melt it in an enameled pot (p. 72, Note 2) and pour the liquid into the preheated flask.

5. It is important to use the amount of urea which is specified. When 2 moles of urea per mole of sebacic acid was employed, the yield of sebaconitrile was only 27%.

6. At the end of this time the product consists almost entirely of sebacamide, which may be isolated if desired.

7. This insulation is easily accomplished by wrapping with asbestos rope, starting at the neck and winding as far down the bulge of the flask as possible. After the flask is clamped in place on the wire gauze, asbestos paper is bent around to enclose the bottom. Magnesia can also be used.

8. If the condenser is short, it is advisable to have a second receiver with a reflux condenser attached, because some dinitrile may be carried through by uncondensed steam. A water-cooled condenser should not be placed ahead of the first receiver, however, since the distillate contains some solid products (sebacic acid and products from urea).

9. Although not absolutely essential, the ether facilitates the operation. Benzene is not satisfactory.

10. Ammonium hydroxide (about 3%) is equally satisfactory. The aqueous extracts are saved.

11. Another boiling point is 201–203°/16 mm.

12. The submitters obtained 410–450 g. (50–55%) in runs twice this size.

13. The checkers used a *p*H meter and neutralized to *p*H 7.8.

14. This amounts to 43–45 g.

15. S & S "Shark Skin" filter paper has "high wet-strength" and a high resistance to acids and alkalies.

16. If the cyano acid obtained from the precipitated barium salt is worked up separately, it melts at 51–52°.

3. Methods of Preparation

Sebaconitrile has been obtained by heating sebacic acid in a stream of ammonia,[1] and from sebacamide by pyrolysis [2,3] or by dehydration with phosphorus pentachloride [4] or phosphorus oxychloride.[5] Sebacamide has been prepared from ethyl sebacate [6] or sebacyl chloride and ammonia,[7] and by heating sebacic acid with urea [2,3,8] or ammonium thiocyanate.[9]

[1] Greenewalt and Rigby, U. S. pat. 2,132,849 [*C.A.*, **33**, 178 (1939)].

[2] Biggs and Bishop, *J. Am. Chem. Soc.*, **63**, 944 (1941).

[3] Biggs, U. S. pat. 2,322,914 [*C.A.*, **38**, 118 (1944)].

[4] Phookan and Krafft, *Ber.*, **25**, 2252 (1892).

[5] Wilcke, U. S. pat. 1,828,267 [*C.A.*, **26**, 735 (1932)].

[6] Rowney, *Ann.*, **82**, 123 (1852).

[7] Aschan, *Ber.*, **31**, 2350 (1898).

[8] D'Alelio and Reid, U. S. pat. 2,109,941 [*C.A.*, **32**, 3419 (1938)].

[9] Ssolonina, *J. Russ. phys. chem. Ges.*, **28**, 558 (1896).

SUBJECT INDEX

(This cumulative index comprises material from Volumes 20 through 25 of this series; for previous volumes see Collective Volumes 1 and 2.)

Names in small capital letters refer to the titles of individual preparations. A number in ordinary bold-face type denotes the volume. A number in bold-face italics refers to a page which gives preparative directions for substances formed either as principal products or as by-products; numbers in ordinary type indicate pages on which a compound or a subject is mentioned in connection with other preparations. For example, Acetone cyanohydrin, **20**, 42, ***43***, indicates that acetone cyanohydrin is mentioned on page 42, and that directions for its preparation are given in detail on page 43, of Volume 20.

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