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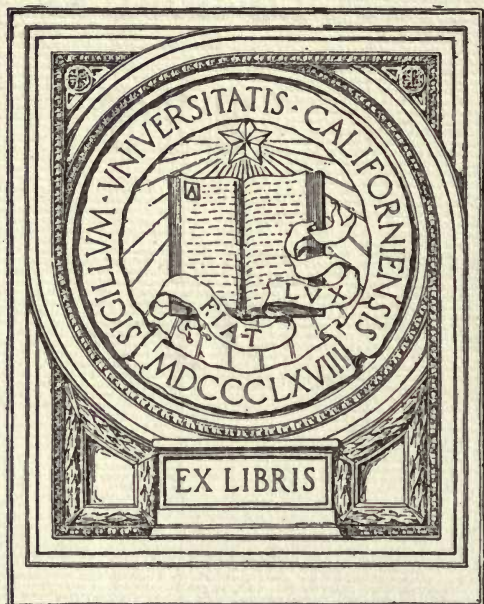
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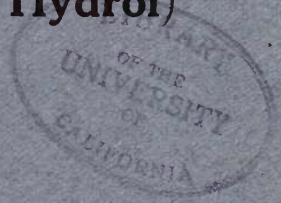
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**Some New Condensations with Para-  
para-bis (Dimethylamino)-Benzo-  
hydrol (Michler's Hydrol)**



**DISSERTATION**

SUBMITTED IN PARTIAL FULFILLMENT OF THE RE-  
QUIREMENTS FOR THE DEGREE OF DOCTOR OF  
PHILOSOPHY IN THE FACULTY OF PURE  
SCIENCE OF COLUMBIA UNIVERSITY

BY  
**AARON RUDERMAN, B.S., M.A.**

1922

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AUGUST 1960

UNIVERSITY OF COLUMBIA

# Some New Condensations with Para-para-bis (Dimethylamino)-Benzohydrol (Michler's Hydrol)

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AARON RUDERMAN, B.S., M.A.,

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DISSERTATION

Exchange

YARON RUDERMAN, B.S., M.A.

TO THE MEMORY

OF

MY FATHER

502086

## ACKNOWLEDGMENT

The author desires to express his indebtedness to Professor Marston Taylor Bogert, who suggested this work and under whose direction it was carried out. Whatever merit this research may have is due to his constructive criticism and invaluable assistance.



## SOME CONDENSATION REACTIONS WITH PARA-PARA-BIS (DIMETHYLAMINO)-BENZOHYDROL (MICHLER'S HYDROL)

### Introductory

Fosse<sup>1</sup> has shown that *p*-substituted secondary aromatic alcohols, including Michler's hydrol, condense with one of the methylene hydrogens in compounds containing the  $-\text{CO}-\text{CH}_2-\text{CO}-$  grouping, with elimination of a molecule of water and the insertion of the alcohol residue in place of the hydrogen removed.

Inasmuch as the hydrogen of the imino group in imides of dibasic acids often behaves in a way recalling that of the hydrogen in reactive methylenes similar to the above (for example, compare the Gabriel imide reactions with those of malonic ester), it was thought of interest to test this experimentally, particularly in view of the fact that Möhlau and Heinze<sup>2</sup> found it impossible to effect such condensation with any amides except urea, and that Reitzenstein and Breuning<sup>3</sup> have reported that the hydrol reacts with isatin (an isomer of phthalimide) by removal of nuclear and not of imide hydrogen. The experiments of Möhlau and his co-workers<sup>4</sup> have indicated, further, that the hydrol condenses with primary or secondary aromatic amines in alcoholic solution with formation of the corresponding leucauramines. Kern<sup>5</sup> and Noelting,<sup>6</sup> using conc. sulfuric acid

<sup>1</sup> Fosse, *Chem. Zentr.*, 1907, I, 1696; *C. A.*, 2, 823, 2387, 2689 (1908); *Ann. chim. phys.*, [8] 18, 400, 503, 531 (1909); *Bull. soc. chim.*, [4] 7, 229 (1910); *Compt. rend.*, 150, 179 (1910); *Ann. chim. phys.*, [9] 13, 118, 154 (1920); *C. A.*, 15, 1711 (1921).

<sup>2</sup> Möhlau and Heinze, *Ber.*, 35, 359 (1902).

<sup>3</sup> Reitzenstein and Breuning, *Ann.*, 272, 257 (1910).

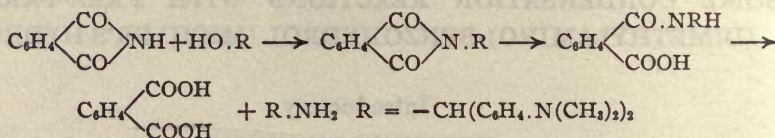
<sup>4</sup> Möhlau and others, *Ber.*, 33, 799 (1900); 34, 882, 3384 (1901); 35, 359 (1902).

<sup>5</sup> Kern, *Ger. pat.*, 27,032, 1883.

<sup>6</sup> Noelting, *Ber.*, 24, 3127, 3136, 3139 (1891).

as solvent, noted that the reaction then follows a different course, nuclear hydrogen being removed and not that of the amine groups, the products being triphenylmethane derivatives and not leucauramines. This difference in behavior is somewhat akin to that of benzaldehyde and aniline which yield benzal-aniline in alcoholic solution, but diamino-triphenylmethane in presence of mineral acid.

On dissolving phthalimide and the hydrol in alcohol and warming the solution, a condensation product was obtained, crystallizing in greenish-yellow plates, m. p. 186.7° (corr.). This gave phthalic acid and leucauramine on hydrolysis with dil. mineral acid, and on warming with dil. potassium hydroxide solution added the elements of water with formation of the amidic acid. Boiling the latter with dil. hydrochloric acid split it into phthalic acid and leucauramine.



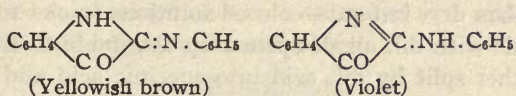
These facts justify the conclusion that the hydrol residue is in union with nitrogen and not with carbon in this product.

When conc. sulfuric acid was substituted for alcohol as solvent in this reaction, and the solution was warmed at 100°, a colorless product was obtained on precipitation with alkali, which proved to be a labile form of the compound (m. p. 186.7°) mentioned above, and into which it changed slowly on standing, or more rapidly when heated. On dissolving the colored form in sulfuric acid and precipitating rapidly by alkali, a colorless oil separated which soon congealed to the yellow form again.

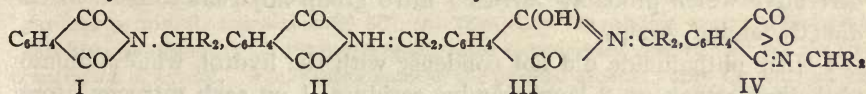
Phthalimide contains the 2 chromophoric carbonyl groups attached to the benzene nucleus just as they are arranged on one side of the anthraquinone formula, but with an imino group on the other side instead of a second benzene nucleus. A similar relationship exists between the isomeric isatin and phenanthraquinone. Phthalimide is colorless, whereas isatin is a deep yellowish-red. Anthraquinone is clear light yellow, but phenanthraquinone is orange. The arrangement of the carbonyl groups in isatin is, therefore, of greater chromophoric effect than that in phthalimide. Those auxochromes which have the most potent bathochromic action in the anthraquinone group,  $\text{NHAr} > \text{NAlkyl} > \text{NH}_2$ , appear to be the ones with greatest influence also in the phthalimide molecule, since the amino-phthalic acid derivatives generally show decided color (yellow). Acylation of the amino group of course discharges this color, since the acylamino group is not ordinarily an auxochrome.

Kauffmann and Beisswenger<sup>7</sup> found that 3-amino-phthalimide exists in 2 tautomeric forms, one yellow with green fluorescence, and the other colorless with violet fluorescence. Such tautomerism might be explained conceivably by assuming a migration of hydrogen from the imino group to an adjacent carbonyl, giving a  $-C(OH) : N-$  structure. Such an hypothesis, however, scarcely can apply to the *p*-alkyloxy phthalanils,  $C_6H_4-(CO)_2N.C_6H_4.OR$ , which Pitui and Abati<sup>8</sup> report as also occurring in colored (yellow) and colorless modifications, and these investigators, recognizing the fact, conclude that this difference cannot be accounted for on the basis of difference in chemical structure, but may be due to a dimorphism similar to that of benzophenone.

Although but one form of isatin is known, Pummerer<sup>9</sup> has succeeded in producing aniline derivatives of the 2 tautomeric structures,



If the tautomeric forms of phthalyl leucauramine observed by us are similarly related structurally, the colorless modification would be represented by Formula I, and the colored by Formula II or III—



On the basis of these structures, one would expect Formula I to represent the more stable (colored), rather than the less stable (colorless) tautomer.

There remains the further possibility that the colored form may be related to the colorless as indicated in Formulas I and IV. This is a change of linking of the type postulated by Baly and Desch<sup>10</sup> in aceto-acetic compounds, and by Stewart<sup>11</sup> in ethyl pyruvate, a kind of tautomerism which they have termed "isorropesis," and to which they have attributed the property of selective absorption. If then Formula IV is a correct representation of the colored modification, we are dealing with a compound possessing absorption bands in the visible part of the spectrum which are due to isorropesis.

In favor of Formula IV it may be remarked that it contains a  $:C:N-$  grouping, resembling the chromophore of the Schiff bases. On the other hand, it has been found in the case of the quinophthalones<sup>12</sup> that the first

<sup>7</sup> Kauffmann and Beisswenger, *Ber.*, **36**, 2495 (1903).

<sup>8</sup> Pitui and Abati, *ibid.*, **36**, 996 (1903).

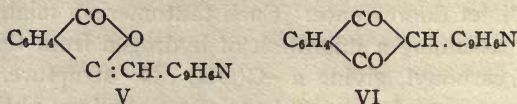
<sup>9</sup> Pummerer, *ibid.*, **44**, 338 (1911).

<sup>10</sup> Baly and Desch, *J. Chem. Soc.*, **87**, 766 (1905).

<sup>11</sup> Stewart, *ibid.*, **89**, 489 (1906).

<sup>12</sup> Eibner and others, *Ber.*, **35**, 2297 (1902); **37**, 3008, 3011, 3019 (1904); etc.

product is the unsymmetrical form V, which changes to the symmetrical V at higher temperatures, or when treated with sodium ethylate.



In the formation of phthaleins and related types, phthalic anhydride condenses preferably also to unsymmetrical compounds.

Finally, although phthalimide itself exists in but one form, to which the symmetrical structure I is usually assigned, substituted phthalimides are known for which the unsymmetrical form IV is preferred.<sup>13</sup>

In the case of succinimide, the condensation with the hydrol was carried out only in alcoholic solution, and a succinyl-leucauramine obtained which was colorless when dry, but gave colored solutions (violet to blue) in alcohol. Hydrolysis with dil. alkali opened up the imide to the amidic acid, which was further split by dil. acid into succinic acid and leucauramine.

Oxidized by lead dioxide in acid solution, both phthalyl-leucauramine and the corresponding amidic acid gave carbinols, the  $-\text{CH}$  grouping changing to  $-\text{C}(\text{OH})-$ ; whereas, with nitrous acid, there resulted a dinitro derivative which probably carries 1 nitro group adjacent to each of the dimethylamino groups.

4-Nitro-phthalimide did not condense with the hydrol, while 3-amino-phthalimide took up 2 leucauramine residues, 1 on each nitrogen atom.

Both phthalimidine and phthalide failed to react with the hydrol in alcoholic solution; but when the phthalide and hydrol were fused together, the phthalide exchanged both hydrogens of its methylene group for leucauramine radicals, giving a product which probably possesses the structure

$\text{O} \cdot \text{CO} \cdot \text{C}_6\text{H}_4 \cdot \overline{\text{C}(\text{CHR})_2}$ , and is colored (pink) in acid solution, but is colorless in alkali. The behavior of the phthalimidine was quite unexpected, since it contains the methylene group of phthalide and the imino of phthalimide.

Saccharin, which differs from phthalimide only in containing an  $\text{SO}_2$  group in place of one of the carbonyl groups of the latter, seems to react with the hydrol only to the extent of salt formation, since the addition of either one to a dil. alcoholic solution of the other gives immediately a deep blue color, and in fact this may be used as a delicate test for the presence of small amounts of saccharin.

Dehydrothio-*p*-toluidine condenses smoothly with 1 mole of the hydrol in alcoholic solution.

Möhlau and Klopper<sup>14</sup> observed that 2 moles of hydrol united with 1

<sup>13</sup> Hoogewerf and v. Dorp, *Rec. trav. chim.*, 13, 93 (1894). v. d. Meulen, *ibid.*, 15, 286, 323 (1896); etc.

<sup>14</sup> Möhlau and Klopper, *Ber.*, 32, 2146 (1899).

of benzoquinone (with elimination of 2 moles of water), whereas with  $\alpha$ -naphthoquinone the union occurred with equal moles. In the case of  $\beta$ -naphthoquinone, and of phenanthraquinone, no condensation took place. They concluded, therefore, that *p*-quinones condense with the hydrol, but *o*-quinones do not. Our own experiments do not bear out this conclusion, for we have tried in vain to cause the hydrol to react with anthraquinone in either alcohol or conc. sulfuric acid; nor would alizarin react in the latter solvent at 100°, although under similar conditions, the hydrol condenses readily with phenols and phenolic ethers;<sup>15</sup>  $\alpha$ - and  $\beta$ -amino-anthraquinones were equally unreactive in alcoholic solution.

Möhlau and Heinze<sup>2</sup> state that their attempts to condense the hydrol with acid amides were unsuccessful, except in the case of urea, which united with 2 moles of this secondary alcohol. We have found, further, that negative results are obtained also with thio-urea and with the cyclic benzoylene-urea (2,4-dihydroxy-quinazoline).

### Experimental

Michler's hydrol was prepared by oxidizing the corresponding bis(-dimethylamino)-diphenylmethane with lead dioxide, as recommended by Möhlau and Heinze;<sup>2</sup> yield of crude product, 85%. To avoid formation of large amounts of tar in the recrystallization of this crude material, it was found advantageous to dissolve about 150 g. in a liter of gasolene previously warmed to 80–85°, and then allow the solution to cool. Instead of gasolene, benzene may be employed at the same temperature, but with double the concentration of hydrol. The melting point of the purified product varied for different lots from 96–98° (uncorr.). The figures given in the literature run from 96° to 102°.

Production of the hydrol by the action of sodium amalgam upon an alcoholic solution of the ketone<sup>2</sup> proved unsatisfactory, because of the frequent incompleteness of the reduction and consequent difficulties of purification.

The lead dioxide employed was precipitated by adding a solution of bleaching powder to one of lead acetate, and was standardized by titration with sodium thiosulfate in presence of a dil. acetic acid solution of potassium iodide.

**Succinyl-leucauramine**,  $((\text{CH}_3)_2\text{N} \cdot \text{C}_6\text{H}_4)_2\text{CH} \cdot \text{N} \cdot \text{CO} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CO}$ .—A solution of 5 g. of succinimide (1 mole) and 13 g. (1 mole) of hydrol in 200 cc. of alcohol was boiled gently for 10 hours. On cooling, a few crystals of the condensation product separated. More were recovered on concentration. Recrystallized from alcohol, the substance was obtained in nearly colorless minute needles, melting at 151° (corr.), which darkened on standing; yield, approximately 50%. It is soluble also in hot methyl alcohol or hot benzene.

*Analyses.* Calc. for  $\text{C}_{21}\text{H}_{25}\text{O}_2\text{N}_3$ : N, 11.96. Found: 12.09, 12.22.

**Succinyl-dinitro-leucauramine**, prepared from the above by the action of nitrous acid, in the same way as the corresponding phthalimide derivative described beyond, crystallized from alcohol as a yellowish-brown powder, melting with decomposition at 94° to 96°; yield, about 90%.

*Analyses.* Calc. for  $\text{C}_{21}\text{H}_{23}\text{O}_6\text{N}_5$ : N, 15.87. Found: 15.61, 15.95.

***p,p'*-Bis(dimethylamino)-benzohydril-succinamic Acid**,  $((\text{CH}_3)_2\text{N} \cdot \text{C}_6\text{H}_4)_2\text{CH} \cdot \text{NH} \cdot \text{CO} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{COOH}$ .—Five g. of succinyl-leucauramine was warmed for 2 hours at 100°

<sup>15</sup> Ger. pats., 58,483, 64,217, 64,306, 66,072, 67,429, 72,898, 76,931, 79,320.

with 10 cc. of a dilute (about 10%) potassium hydroxide solution, but a clear solution was not obtained. Water (300 cc.) was added, therefore, the mixture boiled, filtered, the filtrate neutralized with dil. acid and worked up as described beyond for the analogous phthalamidic compound. The crude product was crystallized from water containing 10 to 15% of alcohol, and minute colorless needles were obtained. These melted at 170°, and on standing gradually assumed a pale slaty color.

*Analyses.* Calc. for  $C_{21}H_{27}O_3N_3$ : N, 11.39. Found: 11.14, 11.30.

Phthalyl-leucauramine,  $((CH_3)_2N.C_6H_4)_2CH.N.CO.C_6H_4.CO$ .—The requisite phthalimide was prepared by the method of Dunlap,<sup>16</sup> by fusing a mixture of equimolar amounts of phthalic anhydride and urea, and was obtained in a yield of 97%; m. p., 233.5° (corr.).

A solution of 10 g. of phthalimide (1 mole) and 18 g. (1 mole) of the hydrol, in 300 cc. of alcohol, was boiled gently for 10 hours, and then cooled. Seventeen g. of greenish-yellow leaflets separated from the cold solution, and 4 g. more was recovered by concentrating the mother liquor, making the total yield 80%. The purified compound melted at 186.7° (corr.), and crystallized in greenish-yellow prisms or leaflets.

*Analyses.* Calc. for  $C_{26}H_{25}O_2N_3$ : C, 75.18; H, 6.27; N, 10.52. Found: C, 74.88, 75.30; H, 6.21, 6.36; N, 10.70, 10.70.

The substance is soluble in cold acetone, difficultly soluble in ether or ligroin, and dissolves in alcohol, ethyl acetate, carbon disulfide, or benzene, at their boiling-points. As phthalimide is difficultly soluble in either carbon disulfide or benzene, it may be separated thus from its hydrol condensation product. When dry hydrogen chloride is passed into an anhydrous ether solution of the new compound, a greenish precipitate separates which is probably the mono-hydrochloride. On further addition of hydrogen chloride, this precipitate loses its color, presumably through formation of the di-hydrochloride. The latter dissolves in water to form a green solution of the same color as given by the original phthalyl-leucauramine when dissolved in dil. hydrochloric acid.

When conc. sulfuric acid was substituted for the alcohol in the above reaction and the solution was warmed at 100° for several hours and then cooled, a colorless product separated on neutralization with alkali, which proved to be a labile form of the compound obtained from alcoholic solution. Yield, about 18–20%. It dissolves more readily than the stable form in alcohol, acetone or benzene. After long standing in alcoholic solution, greenish-yellow crystals of the stable form separate. The same change ensues slowly when the dry substance is left in the open; heat accelerates the transformation. When the colorless modification was heated, it melted at about 90°, changed to the greenish-yellow form and resolidified. This resolidified product, crystallized from alcohol, showed the correct melting point (186.7°) for the stable form. When it was dissolved in conc. sulfuric acid, or even in the dil. acid, a colorless or but faintly colored solution resulted, from which rapid addition of alkali precipitated a colorless oil. This oil congealed to a yellow solid, which gradually assumed the greenish-yellow characteristic of the stable form.

Phthalyl-leucauramine Carbinol,  $((CH_3)_2N.C_6H_4)_2C(OH).N.CO.C_6H_4.CO$ .—Twenty g. of phthalyl-leucauramine was dissolved in a mixture of 160 cc. of water and 12 cc. of conc. hydrochloric acid, and 1 liter of water and 10 cc. of glacial acetic acid were added. The mixture was stirred vigorously while 30 g. of 40% lead dioxide paste, in about 150 cc. of water, was added gradually. The stirring was continued for an hour longer, when a solution of 16 g. of sodium sulfate was poured in, to remove the lead. On making the filtrate alkaline, only a small amount of precipitate was formed. The lead sulfate

<sup>16</sup> Dunlap, *J. Am. Chem. Soc.*, **18**, 333 (1896).

precipitate, therefore, was boiled with dil. hydrochloric acid (50 cc. of conc. acid to 300 cc. of water), and the mixture filtered hot. As the solution cooled some lead sulfate crystallized and was removed. The filtrate from this was precipitated with dil. sodium hydroxide solution, and the carbinol extracted from this precipitate by hot alcohol. It was recrystallized from either alcohol or acetone, and dissolved also in chloroform, but not appreciably in ether. It formed nearly colorless crystals, melting at  $176^{\circ}$  (corr.); yield, 60%.

*Analyses.* Calc. for  $C_{25}H_{25}O_3N_3$ : N, 10.11. Found: 10.34, 10.23.

**Dinitro-phthalyl-leucauramine.**—Five g. of phthalyl-leucauramine was dissolved in 30 cc. of dil. (1:1) hydrochloric acid, and an aqueous solution of sodium nitrite (4 moles) run in slowly as long as it caused the separation of precipitate. The nitrite must be added very carefully, so that the temperature does not rise to the point where excessive formation of nitrogen oxides occurs, or the yield of nitro derivative will be diminished. The brown precipitate was collected and crystallized from alcohol, or from glacial acetic acid, and then appeared as a yellowish-brown solid, melting with decomposition at  $104^{\circ}$ ; yield, 90%. It gave no Liebermann reaction for nitroso groups, and was free from halogen.

*Analyses.* Calc. for  $C_{25}H_{23}O_6N_5$ : N, 14.32. Found: 14.08, 14.02.

An effort to secure the same product was made by dissolving the phthalyl-leucauramine in conc. sulfuric acid, adding a mixture of conc. sulfuric and conc. nitric acids at  $-5^{\circ}$  to  $0^{\circ}$ , and finally pouring the mixture into ice water. Some phthalimide separated, but saturation of the filtrate with sodium carbonate precipitated only unchanged initial material.

Reduction of the dinitro derivative with tin and hydrochloric acid yielded brown oils difficult to handle, which were not further investigated.

*o,o'*-Dinitro-*p,p'*-bis(dimethylamino) diphenylmethane was prepared according to the directions of Pinnow<sup>17</sup> in a yield of 86%; it melted at  $188^{\circ}$  (uncorr.); Pinnow gives  $191.5^{\circ}$ . Twenty g. of this product was suspended in 600 cc. of water and sufficient hydrochloric acid added to give a clear solution. Twenty-six g. of lead dioxide paste (40%), mixed with 100 cc. of water, was stirred in and the oxidation continued for an hour at laboratory temperature; the mixture was then heated to  $60^{\circ}$  to complete the reaction, and on dilution with water, the original diphenylmethane compound separated unaltered. In view of this result, it seemed profitless to attempt the oxidation of the dinitro-phthalyl-leucauramine.

*p,p'*-Bis(dimethylamino)-benzohdryl-phthalamidic Acid,  $((CH_3)_2N.C_6H_4)_2CH.NH.CO.C_6H_4.COOH$ .—Fifty g. (1 mole) of phthalyl-leucauramine was covered with 50 cc. of a dil. (about 10%) aqueous potassium hydroxide solution (slightly over 1 mole), and the mixture heated at  $100^{\circ}$  for about half an hour, at the end of which time the solid was nearly all dissolved. Longer heating caused evolution of ammonia, due probably to the separation of leucauramine and the hydrolysis of the latter to hydrol and ammonia. Water was added to the alkaline solution and then dil. sulfuric acid to neutralization. As the precipitate formed was soluble either in acid or alkali, it was found advisable not to overrun the neutral point. This point was easily detected by the sudden change in color. The colorless precipitate dissolved readily in methyl or ethyl alcohol, chloroform or acetone, but proved very difficultly soluble in carbon tetrachloride or gasolene. On recrystallization from alcohol, colorless needles were obtained, which melted with decomposition at  $163.8^{\circ}$  (corr.); yield, 90%.

*Analyses.* Calc. for  $C_{25}H_{27}O_3N_3$ : N, 10.07. Found: 10.03, 10.14.

Some of this amidic acid was dissolved in dil. hydrochloric acid and the solution

<sup>17</sup> Pinnow, *Ber.*, 27, 3161 (1894).

heated at 100° for an hour. The solution was then diluted and cooled. Phthalic acid separated and was filtered out. The filtrate was then made alkaline and leucauramine precipitated. Similar results were secured when the original phthalyl-leucauramine was saponified with dil. (20%) hydrochloric acid at 100°, without separation of the intermediate amidic acid.

**Oxidation of the Amidic Acid.**—Five g. (1 mole) of the amidic acid was dissolved in 40 cc. of water and 3 cc. of conc. hydrochloric acid, and a solution of 5 cc. of glacial acetic acid in 200 cc. of water poured in. This solution was stirred vigorously while 6 g. (1 mole) of lead dioxide paste (40%), suspended in 50 cc. of water, was added slowly. The stirring was continued for half an hour longer, and the lead then precipitated by dil. sulfuric acid. The lead sulfate was removed and washed with dil. hydrochloric acid, the washings being combined with the original filtrate. The united filtrate and washings were made alkaline, and the desired carbinol thereby precipitated. It was purified by crystallization from dil. acetone, and then formed a brownish solid, melting at 187° (corr.), and soluble also in alcohol; yield, 75%.

*Analyses.* Calc. for  $((\text{CH}_3)_2\text{N.C}_6\text{H}_4)_2\text{C}(\text{OH}).\text{NH.CO.C}_6\text{H}_4.\text{COOH}$ : N, 9.70. Found: 9.48, 9.75.

**Michler's Hydrol and Phthalimidine.**—The phthalimidine was prepared from phthalimide in the usual way,<sup>18</sup> and melted at 150° (uncorr.). Five g. (1 mole) of this imidine and 30.5 g. (3 moles) of the hydrol were heated with 250 cc. of alcohol and a few drops of glacial acetic acid for a day at 100°, but no condensation occurred and the initial materials were recovered unchanged.

**Di-bis(dimethylamino)-benzohydril-phthalide,**  $([(\text{CH}_3)_2\text{N.C}_6\text{H}_4]_2\text{CH})_2:\text{CC}_6\text{H}_4\text{COO}$ .—Phthalide and the hydrol were mixed in the proportion of one mole of the former to two of the latter, a few drops of glacial acetic added, and the mixture was heated at 100° for 6 to 8 hours, giving a blue, pasty mass which solidified on cooling. This solid was pulverized and extracted with boiling alcohol, to recover unchanged phthalide and hydrol. The insoluble residue was crystallized from a mixture of 1 part of gasolene and 2 parts of xylene, and then formed reddish-brown prismatic crystals, melting at 201° (corr.), which were but slightly soluble in alcohol, ethyl acetate, acetone, carbon tetrachloride, benzene, aniline or gasolene, and somewhat more soluble in hot xylene; yield, about 10%. The same compound resulted when the phthalide and hydrol were present in equimolar proportions, and no monobenzohydril derivative was encountered.

*Analyses.* Calc. for  $\text{C}_{44}\text{H}_{46}\text{O}_2\text{N}_4$ : C, 78.99; H, 7.30; N, 8.77. Found: C, 78.84, 78.63; H, 7.32, 7.20; N, 8.79, 8.85.

With acids, the compound turns pink; but the color is discharged on addition of alkali, and the freshly separated compound is practically colorless. In alcoholic solution, the phthalide and hydrol do not interact at the boiling point of the mixture. The phthalide used in these experiments was prepared by hydrolysis of nitroso-phthalimidine,<sup>18</sup> and melted at 73° (corr.).

**Michler's Hydrol and 4-Nitro-phthalimide.**—Equimolar amounts of the two were dissolved in alcohol and the solution boiled for 10 hours on a steam-bath. The solution turned blue, but the hydrol and imide were recovered from the solution unaltered.

**3-Leucauraminyl-phthalyl-leucauramine,**  $((\text{CH}_3)_2\text{N.C}_6\text{H}_4)_2\text{CH.NH.C}_6\text{H}_3(\text{CO})_2\text{N.CH}(\text{C}_6\text{H}_4.\text{N}(\text{CH}_3)_2)_2$ .—0.87 g. (1 mole) of 3-amino-phthalimide and 3 g. (2 moles) of hydrol were dissolved in 35 cc. of alcohol containing a few drops of glacial acetic acid, and the solution boiled gently for 10 hours. As the mixture cooled, a small amount of tar separated, and more began to come out on further concentration. The

<sup>18</sup> Graebe, *Ann.*, 247, 291 (1888); *Ber.*, 17, 2598 (1884).



alcoholic solution, therefore, was treated with dil. hydrochloric acid, and the clear solution precipitated by neutralization with alkali. The dried precipitate amounted to 3 g. Boiling with alcohol appeared to decompose it slowly with formation of tar, as noted above, but crystallization from acetone yielded greenish-yellow plates, melting at 219–220° (corr.), analysis of which showed that both the amino and the imide groups had reacted with the hydrol.

*Analyses.* Calc. for  $C_{42}H_{48}O_2N_6$ : C, 75.78; H, 6.77. Found: C, 75.61, 76.09; H, 7.05, 7.11.

The product is difficultly soluble in petroleum ether, but rather readily soluble in benzene, and a mixture of the two may be used as a crystallizing medium, but is not so satisfactory as acetone. Its solutions are not fluorescent, although those of the initial amino-phthalimide are. The pale color of the solid substance is also noteworthy, and is in harmony with its leucauramine structure.

Michler's Hydrol and Saccharin yielded no condensation product when the two were heated together in equimolar proportion in alcoholic solution, with or without the addition of small amounts of glacial acetic acid. It was observed, however, that when the two substances were brought together even in very dilute alcoholic solution, a deep blue color resulted, presumably due to the formation of a quinoid salt of the hydrol, and this reaction appears to be a delicate test for either compound. The color is discharged by sulfur dioxide and restored by addition of the component originally present in the smaller amount. The corresponding ketone (Michler's ketone) and hydrocarbon give no such color reaction when saccharin is added to their alcoholic solutions.

Michler's Hydrol and Anthraquinone.—No condensation was effected either in alcoholic solution or in conc. sulfuric acid.

Michler's Hydrol and Alizarin.—In conc. sulfuric acid solution, no condensation occurred.

Michler's Hydrol and Amino-anthraquinones.—The condensation was attempted in alcoholic solution, with both  $\alpha$ - and  $\beta$ -amino-anthraquinone, and failed in both cases.

Michler's Hydrol and Thio-urea.—Möhlau and Heinze,<sup>2</sup> report that the hydrol condenses in alcoholic solution with urea, but our experiments with thio-urea were less successful. We dissolved 2 moles of the hydrol and 1 mole of thio-urea in alcohol, and boiled the solution gently for 8 hours. There was no indication of any change, so more thio-urea (3 moles) was added and the boiling resumed, but we failed to accomplish any condensation.

Michler's Hydrol and Benzoylene-urea did not condense in alcoholic solution.

*p,p'*-Bis(dimethylamino)-benzohydryl-dehydrothio-*p*-toluidine,  $CH_3.C_6H_4 \begin{array}{c} \diagup S \diagdown \\ \diagdown N \diagup \end{array} C.$

$C_6H_4.NH.CH(C_6H_4.N(CH_3)_2)_2$ .—Five g. (1 mole) of dehydrothio-*p*-toluidine and 5.5 g. (1 mole) of the hydrol were dissolved in 250 cc. of alcohol and the solution was boiled gently on the steam-bath. The original blue color of the solution was almost completely discharged after a half hour's boiling and a faint fluorescence appeared, while a straw-yellow precipitate separated from the hot solution, the amount increasing as the boiling was continued. When this precipitate no longer increased in amount, the solution was cooled and filtered, and a further crop of crystals recovered by concentration of the mother liquor. The crude product was purified by crystallization from benzene, washed with acetone, to remove any adhering dehydrothio-*p*-toluidine, and then appeared as a pale yellow micro-crystalline solid, melting at 190–191° (corr.), moderately soluble in alcohol or in benzene, and difficultly soluble in acetone or ether; yield, 75%.

*Analyses.* Calc. for  $C_{31}H_{32}N_4S$ : C, 75.60; H, 6.50. Found: C, 75.94; H, 6.55.

### Summary

1. *p,p'*-Bis(dimethylamino)-benzohydrol, better known as Michler's hydrol, condenses with the imides of succinic and phthalic acids to succinyl- and phthalyl-leucauramines, which can be hydrolyzed by alkali to the corresponding amidic acids. The results of the condensation were the same whether carried out in conc. sulfuric acid or in alcoholic solution.

2. Phthalyl-leucauramine exists in a labile, colorless (m. p. 90°), and a stable, greenish-yellow, modification (m. p. 186.7°), which are interconvertible.

3. These acyl leucauramines yield the corresponding carbinols when oxidized by lead dioxide, or give dinitro derivatives when treated with nitrous acid.

4. Phthalimidine and the hydrol do not condense in alcoholic solution.

5. Phthalide reacts with two moles of the hydrol.

6. 3-Amino-phthalimide also condenses with 2 moles of hydrol, one entering the amino and the other the imide group. 4-Nitro-phthalimide, on the other hand, does not react.

7. The hydrol is a delicate reagent for detecting saccharin in alcoholic solution, giving a deep blue coloration even in dilute solutions.

8. Dehydrothio-*p*-toluidine condenses readily with the hydrol in alcoholic solution.

9. Anthraquinone, its  $\alpha$ - or  $\beta$ -amino derivative, alizarin, thio-urea or benzoylene-urea, fails to react with the hydrol, under the conditions of our experiments.

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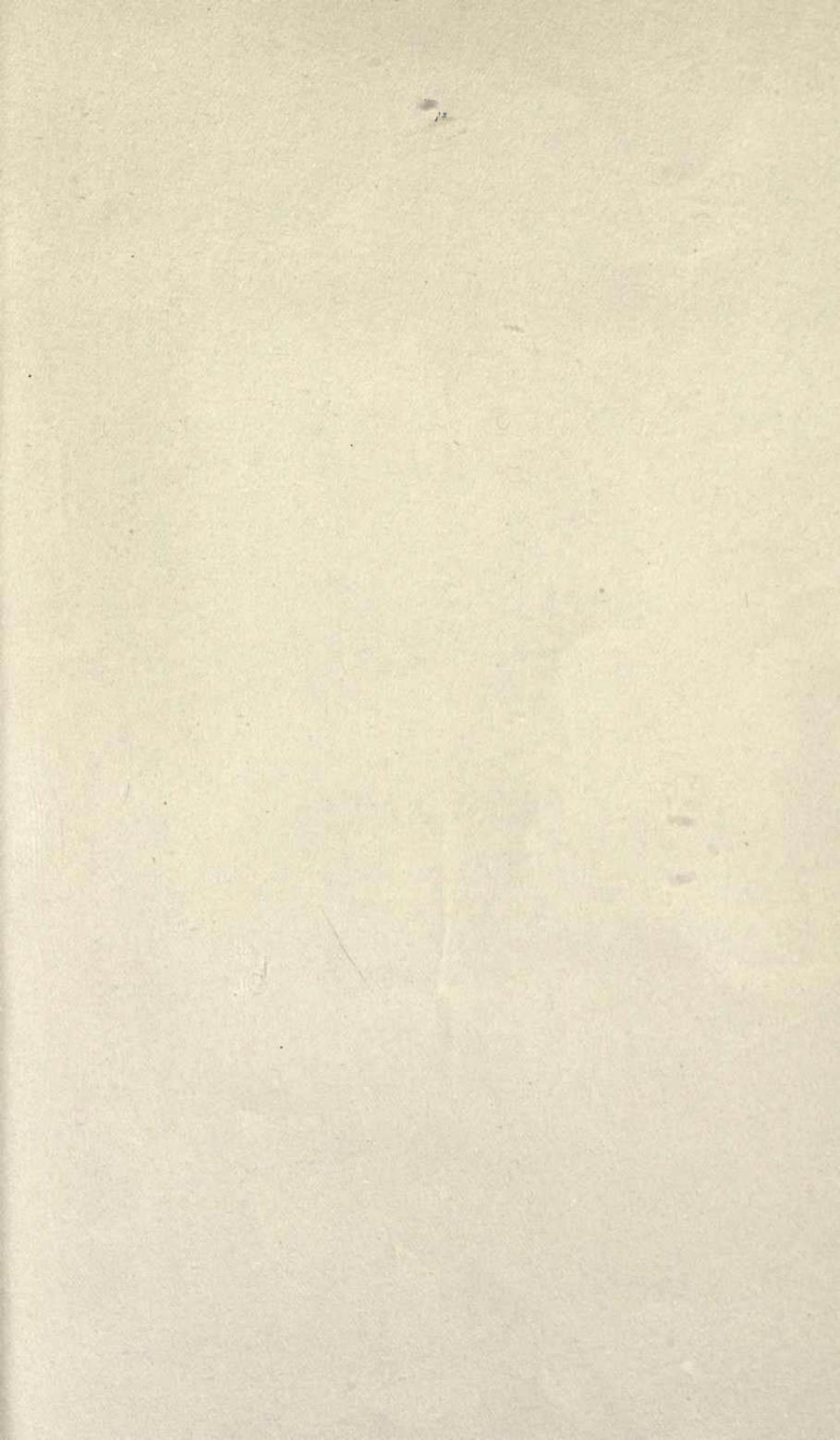
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