4. Series of mercury derivatives have been prepared from di-*n*-propyl-, di-*n*-butyl-, methylethyl- and benzylethylanilines.

5. The conversion $RHgX \longrightarrow R_2Hg$ has also been accomplished in all these cases by means of sodium iodide.

EVANSTON, ILLINOIS

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY, NO. 594]

A STUDY OF SOME OF THE REACTIONS OF 3-HYDROXY-6-AMINOTOLUENE AND OF CERTAIN OF ITS DERIVATIVES[1,2]

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Since this *o*-amino-*m*-cresol is an industrial by-product, it seemed desirable to investigate it somewhat more fully as a possible source of useful intermediate or final products.

Because of its *p*-aminophenol structure, the first line of attack consisted in the synthesis of derivatives analogous to various well-known synthetic drugs, but none of these products have been subjected as yet to pharmacological examination. It is hoped that, since *m*-cresol is a somewhat stronger antiseptic than phenol, and the toluidines are less toxic than aniline, there may be some advantages in these new products, although Heubner[3] and Rhode[4] have pointed out that the analogous derivatives of *o,o*-dimethyl-*p*-phenetidine are all inferior therapeutically to those of *p*-phenetidine itself.

The simple phenacetin homolog, 3-ethoxy-6-acetylaminotoluene, is somewhat more soluble in water than phenacetin. The most soluble derivative of this type prepared in the course of the work was the 3-hydroxy-ethoxy-6-acetylaminotoluene, which structurally resembles "Pertonal," a drug stated by Cow[5] to be far less toxic than phenacetin, and as antipyretic to possess a much feebler but longer continued action. Like salicylyl-*p*-phenetidide, the corresponding salicylylaminocresol derivative was too resistant to hydrolysis to hold out much promise as a medicament. "Malakin" is the trade name under which salicylal-*p*-phenetidine has been marketed. It is stated to be a good analgesic, but too difficultly soluble in water. We synthesized the aminocresol analog and the corre-

[1] Presented in abstract before the Organic Division, at the Swampscott Meeting of the American Chemical Society, September, 1928.

[2] This investigation was made possible through the generous assistance of the Verona Chemical Co., North Newark, N. J., who, through their Chief Chemist, Dr. Jacob Ehrlich, supplied us with the necessary raw material. We take this opportunity of expressing our thanks to both of them.—M. T. B.

[3] Heubner, *Biochem. Z.*, **93**, 395 (1919).

[4] Rhode, *Ber. deut. pharm. Ges.*, **31**, 271 (1921).

[5] Cow, *J. Pharmacol.*, **12**, 343 (1919).

sponding hydroxy derivative, but they are likewise but very slightly soluble in water.

Bender[6] and also Chattaway and Orton[7] have shown that acetylated anilines, when treated with hypochlorous acid, give chloro-amino derivatives which are unstable when the positions ortho or para to the nitrogen are either of them unoccupied, and that heating, alone or in solution, causes the halogen to migrate from the nitrogen to the ring. In the case of 3-ethoxy-6-acetyl-aminotoluene, when we applied Bender's method of treatment with hypochlorite, the product was a stable dichloride which lost no halogen when hydrolyzed by concentrated hydrochloric acid and was identified as the 2,4-dichloro-3-ethoxy-6-acetylaminotoluene by ethylation of the 2,4-dichloro-3-hydroxy-6-acetylaminotoluene. Further, the saponification product gave a stable hydrochloride, which would scarcely have been the case if the halogen had been adjacent to the amino group.

Staedel and Kolb[8] have shown that the action of hypochlorous acid on aminocresol hydrochloride yields the toluquinonechlorimide, but we found that excess of hypochorous acid converted the acetylaminocresol into 2,4-dichlorotoluquinone-6-acetimide, the structure of which was proved by its oxidation to 2,4-dichlorotoluquinone and its reduction to the 2,4-dichloro-6-acetylaminocresol, the structures of both of which have been established by Raiford.[9]

The reason for this 2,4-disubstitution is apparently the orienting influence of both the methyl and hydroxy (or ethoxy) groups toward these positions while only the acetylamino group tends to direct the halogen to Position 5. The chlorination thus follows the same course as in *m*-cresol itself.

Nitration of 3-hydroxy-6-acetylaminotoluene gave the 2,4-dinitro derivative. With the 3-acetoxy-6-acetylaminotoluene, nitration yielded the 5-nitro-acetylamino acetate, unless the reaction was carried out in such a way that some hydrolysis of the acetoxy group occurred, in which event the 3-hydroxy-2,4-dinitro derivative was also formed.

In the case of the 3-ethoxy-6-acetylaminotoluene, nitration in glacial acetic acid solution resulted in a mixture of approximately 85–90% of the 4-nitro derivative with 10–15% of the 5-nitro isomer. That the isomer formed in larger amount was the 4-nitro derivative was proved by the formation of 3-ethoxy-4-nitrotoluene by elimination of the acetylamino group, as well as by its other properties.

For these 6-acetylaminotoluenes, then, the hydroxyl group in Position 3 directs the entering nitro groups to 2 and 4. When the hydroxyl is ethylated, the 4-nitro is the chief product, with only a small quantity of

[6] Bender, *Ber.*, **19**, 2272 (1886).

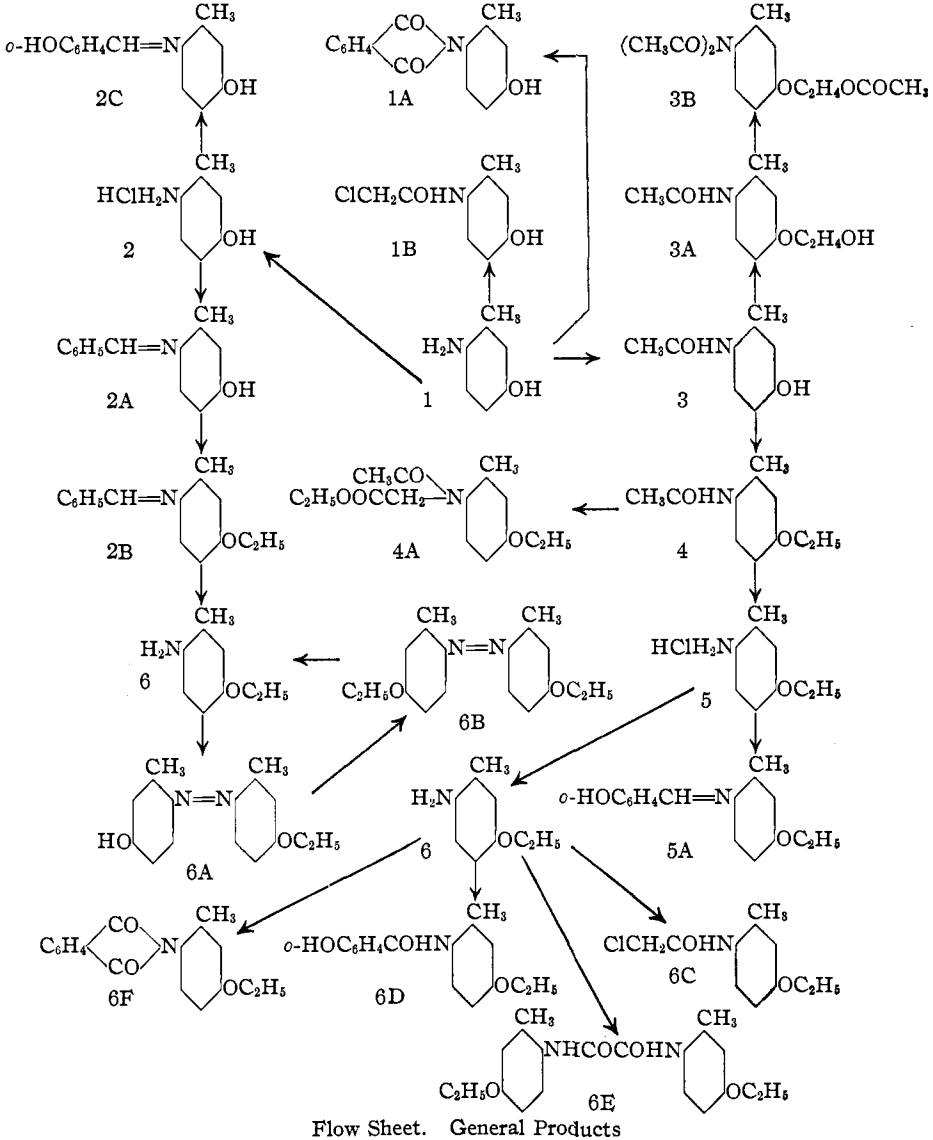
[7] Chattaway and Orton, *J. Chem. Soc.*, **75**, 1046 (1899).

[8] Staedel and Kolb, *Ann.*, **259**, 218 (1890).

[9] Raiford, *Am. Chem. J.*, **46**, 417 (1911).

the 5-nitro isomer. But when the hydroxyl is acetylated, the nitro group enters Position 5 practically exclusively.

Nitration of 3-ethoxy-6-acetylaminotoluene with stronger acid, under the same conditions employed for the preparation of the 2,3-dinitro derivative from phenacetin,[10] gave similar results with the 3-ethoxy-6-acetylaminotoluene, the product being the 4,5-dinitro derivative.



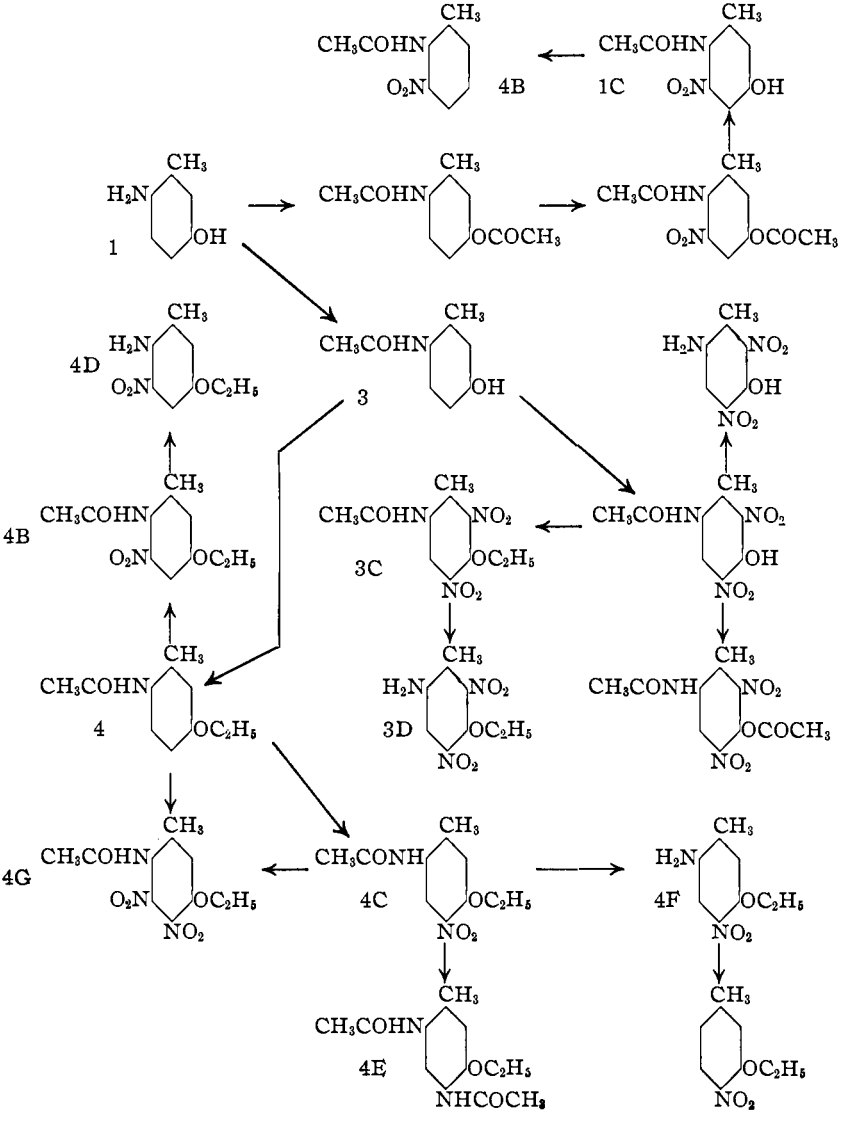
Flow Sheet. General Products

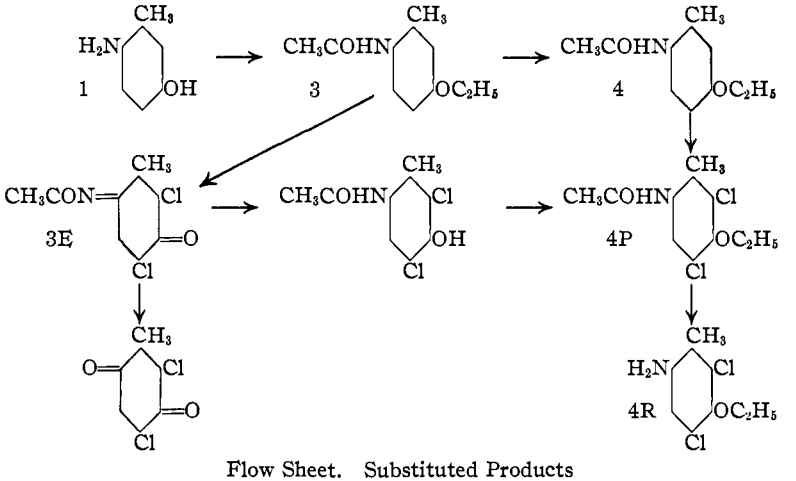
[10] Blanksma, *Rec. trav. chim.*, **27**, 49 (1908).

The synthetic work is presented diagrammatically in the Flow Sheets.

Experimental Part

3-Hydroxy-6-aminotoluene Hydrochloride.—After boiling the crude aminocresol (100 g.) with dilute hydrochloric acid (200 cc. of concentrated acid + = 400 cc. of water) until dissolved, the solution was digested for an hour with Norite (40 g.) and filtered hot. As the clear red filtrate cooled, it deposited square, greenish plates whose color faded somewhat on drying. Recrystallized from dilute (1:2) hydrochloric acid, colorless plates were obtained, soluble in water or alcohol, which began darkening above





Flow Sheet. Substituted Products

250° and decomposed at about 290° (uncorr.); yield, about 80%. It was prepared first by Staedel and Kolb,[11] by the reduction of the nitrocresol with tin and hydrochloric acid.

This salt was used as our initial material, rather than the free base, because of its greater stability and the ease with which it could be obtained practically pure.

3-Hydroxy-6-benzalaminotoluene.—To a solution of the aminocresol hydrochloride (10 g.) in water (100 cc.), containing some sodium bisulfite (0.1 g.) to prevent oxidation, there was added an equimolar amount (6.62 g.) of benzaldehyde and slightly more (105%) than the calculated quantity of an aqueous solution of sodium acetate. The mixture was shaken vigorously and frequently during two hours. The pale, tan-colored flocculent precipitate of the crude benzal derivative was crystallized from benzene, alcohol or dilute acetic acid. From benzene it separated in needles, from the other solvents in blades, both forms melting at 135.5° (corr.); yield, practically that calculated.

Anal. Calcd. for $C_{14}H_{13}ON$: C, 79.60; H, 6.20. Found: C, 79.45; H, 6.02.

It proved to be easier to get a pure benzal derivative from the hydrochloride of the aminocresol than from the aminocresol itself. Fusion of this benzal derivative with sulfur gave a resin from which no thiazole could be isolated.

3-Hydroxy-6-salicylalaminotoluene.—When a mixture of 10 g. of 3-hydroxy-6-aminotoluene hydrochloride, 0.5 g. of sodium bisulfite, 7.6 g. of salicylaldehyde and 200 cc. of water was vigorously shaken, a voluminous yellow precipitate separated. An aqueous solution of sodium acetate (6 g. of $C_2H_3O_2Na$) was added and the mass again vigorously agitated, when its color changed rapidly from yellow to a reddish orange. The precipitate was collected, washed with water and dried; yield, practically that calculated. Recrystallized from 60% alcohol, it formed red blades, m. p. 92.5° (corr.), soluble in alcohol, ether, benzene or acetic acid, nearly insoluble in water.

Anal. Calcd. for $(C_{14}H_{13}O_2N)_4 \cdot C_2H_6O$: C, 72.95; H, 6.13. Found: C, 72.97; H, 6.19.

[11] Staedel and Kolb, *Ann.*, **259**, 217 (1890).

These analytical results indicate the presence of alcohol of crystallization. The product was therefore recrystallized from carbon tetrachloride until the m. p. remained constant at 111–111.5° (corr.).

Anal. Calcd. for $C_{14}H_{13}O_2N$: C, 73.99; H, 5.77. Found: C, 73.35, 73.30; H, 5.75, 5.75.

Long drying of these crystals at 105° caused some decomposition. Fusion of this compound with sulfur failed to yield any thiazole.

3-Hydroxy-6-acetylaminotoluene.—A solution of 5 g. of the aminocresol in 150 cc. of water was added to one of 10 cc. of acetic anhydride in 2 cc. of glacial acetic acid, the mixture heated to boiling and filtered hot. Ten g. of Norite was added to the filtrate, which was evaporated on the steam-bath to half its volume, filtered and the filtrate allowed to cool. Radiating clusters of leaflets separated, m. p. 80.5° (corr.); yield, 65–70%. This is the mono-hydrate obtained previously by Staedel and Kolb,[11] who carried out the acetylation by the action of acetic anhydride upon the dry base, a less convenient method of preparation. It loses its water above 110° with formation of the anhydrous amide, m. p. 125°.

Its formation is in agreement with the observation of Lumière and Barbier[12] that the acetylation of aminophenols by acetic anhydride in the presence of water gives only the amide.

3-Hydroxy-6-chloro-acetylaminotoluene was prepared by following the procedure used by Jacobs and Heidelberger[13] for the production of the chloro-acetamide of *p*-aminophenol. The crude product (m. p. 121°; yield, 15%) was recrystallized from a benzene–alcohol (95:5) mixture, until the m. p. remained constant at 133–133.5° (corr.). The pure compound formed pale brownish, irregular plates, soluble in alcohol or hot water but only slightly soluble in benzene.

Anal. Calcd. for $C_9H_{10}O_2NCl$: C, 54.16; H, 5.05. Found: C, 53.91; H, 5.17.

Phthal-*p*-hydroxy-*o*-tolil.—A mixture of 3-hydroxy-6-aminotoluene (10 g.), phthalic anhydride (12.1 g.) and benzene (100 cc.) was refluxed for an hour, the solvent then distilled off, the residual gummy mass dissolved in hot 95% alcohol (20 cc.) and the solution cooled. The crystals so obtained were recrystallized from 50% acetic acid, in the presence of Norite, and finally from 95% alcohol. The pure compound formed colorless, fine, short needles, m. p. 204° (corr.); yield, 33%.

Anal. Calcd. for $C_{15}H_{11}O_3N$: C, 71.14; H, 4.38. Found: C, 70.90; H, 4.48.

3-Acetyloxy-6-acetylaminotoluene.—After refluxing for an hour a mixture of 100 g. of the aminocresol with 100 cc. of glacial acetic acid, 10 g. of fused sodium acetate and 85 g. of acetic anhydride were added and the refluxing was continued for another hour. The excess of acid (100–125 cc.) was distilled off, 300 cc. of water and 20 g. of Norite added to the residue, the mixture boiled vigorously for a short time and filtered. As the filtrate cooled, long colorless needles separated which were purified by recrystallization from water and then melted at 127.5–128° (corr.); yield, 75%.

Anal. Calcd. for $C_{11}H_{13}O_3N$: C, 63.77; H, 6.28. Found: C, 63.96; H, 6.15.

Nitration of this compound yielded the 5-nitro-acetylamino acetate, unless the reaction was carried out in such a way as to cause some hydrolysis of the acetoxy group, when the 2,4-dinitro-acetylamino *m*-cresol was formed also.

[12] Lumière and Barbier, *Bull. soc. chim.*, [3] **33**, 783 (1905).

[13] Jacobs and Heidelberger, THIS JOURNAL, **41**, 458 (1919).

It dissolved in ether. In water it was less soluble than the hydroxyacetylaminotoluene, but more so than *m*-aminocresol itself. In dilute alkali it dissolved but slowly to a yellow solution which, when neutralized with hydrochloric acid and concentrated, gave the mono-acetyl derivative in a yield almost equal to that calculated. Its aqueous or alcoholic solution was not colored by the addition of ferric chloride.

The same product was obtained by the action of acetic anhydride upon the hydroxyacetylaminotoluene.

2,4-Dichlorotoluquinone-6-acetimide.—A cooled aqueous solution of calcium hypochlorite was poured into an ice cold solution of 3-hydroxy-6-acetylaminotoluene (20 g.) in glacial acetic acid (50 cc.) as long as it caused a precipitate. This yellowish-gray deposit, which gradually became brown and resinous, was collected, washed, dried and extracted with hot carbon tetrachloride. As these extracts cooled, crystals separated which, after repeated crystallization from ether, formed long, yellowish needles, m. p. 159–159.5° (corr.); yield of pure product, 25%.

Anal. Calcd. for $C_9H_7O_2NCl_2$: C, 46.59; H, 3.04. Found: C, 46.20; H, 3.03.

2,4-Dichlorotoluquinone.—The above toluquinone acetimide (1 g.), after standing for an hour with cold dilute chromic acid mixture, was distilled with steam. The quinone which passed over, when crystallized from 30% alcohol, formed golden scales, m. p. 104° (corr.), thus agreeing in crystalline form and m. p. with the reports of Southworth[14] and of Raiford,[15] who prepared the compound in other ways.

2,4-Dichloro-3-hydroxy-6-acetylaminotoluene.—Reduction of the dichlorotoluquinone acetimide was accomplished by passing a slow stream of sulfur dioxide through its suspension in dilute alcohol until the yellow color was discharged. The mixture was warmed with sufficient alcohol to effect solution and filtered hot. As the filtrate cooled, short, colorless needles separated, m. p. 212–212.5° (corr.). Raiford,[15] who prepared the compound by acetylation of the dichloro-aminocresol, found a m. p. of 204–207° (uncorr.) on an impure product.

Anal. Calcd. for $C_9H_9O_2NCl_2$: C, 46.20; H, 3.88. Found: C, 46.29; H, 3.92.

3-Hydroxy-5-nitro-6-acetylaminotoluene.—The nitro-acetylaminocresyl acetate described beyond was warmed below 70° with a potassium carbonate solution (1 g. of anhydrous potassium carbonate to 20 cc. of water) until all was dissolved. The resultant red solution was neutralized immediately and carefully with acetic acid and the solution cooled. The greenish-yellow blades which separated were removed, and addition of a few drops of acetic anhydride to the red mother liquor discharged the color and separated a few more of the crystals; total yield, 62%. Recrystallized from 30% alcohol, this product formed greenish-yellow plates, m. p. 188.5° (corr.). Mixed with the initial nitro-acetate, the m. p. was lowered to 150–155°.

Anal. Calcd. for $C_9H_{10}O_4N_2$: C, 51.45; H, 4.80. Found: C, 51.24; H, 4.82.

Treated with strong mineral acids, this amide formed red, viscous oils and gums and no simple hydrolysis was realized.

The use of caustic in place of carbonated alkali in the initial hydrolysis caused deeper seated changes and decomposition, accompanied by the evolution of ammonia.

3-Acetyloxy-5-nitro-6-acetylaminotoluene.—The acetylaminocresyl acetate (15 g.)

[14] Southworth, *Ann.*, **168**, 270 (1873).

[15] Raiford, THIS JOURNAL, **36**, 670 (1914).

was added in small portions to a solution of 15 cc. of fuming nitric acid (sp. gr. 1.6) in 25 cc. of acetic anhydride, while the temperature was maintained below 5°. After the addition of all the acetate, the mixture was left in the freezing mixture for an hour. Crushed ice (300 g.) was then added and the mixture allowed to warm up gradually to laboratory temperature. The fine, yellow precipitate of crude nitro derivative amounted to a yield of 93%. Recrystallized from 50% acetic acid, it formed pale tan blades, m. p. 190–190.5° (corr.).

Anal. Calcd. for $C_{11}H_{12}O_5N_2$: C, 52.38; H, 4.76. Found: C, 52.52; H, 4.90.

The properties of this compound are quite different from those of the 3-acetyloxy-2-nitro-6-acetylaminotoluene described by Brand and Zoller.[16]

In the mother liquors some 3-hydroxy-2,4-dinitro-6-acetylaminotoluene was found, the amount being small unless the nitration was carried out in such manner as to cause considerable hydrolysis of the acetoxy group.

3-Hydroxy-2,4-dinitro-6-aminotoluene.—The dinitro-acetylaminocresol (1 g.) was boiled with concentrated hydrochloric acid (20 cc.) and water (30 cc.) until all was dissolved. The solution was decolorized with Norite, the filtrate from which yielded irregular, pale yellow plates on cooling. These plates lost hydrochloric acid gradually when heated and decomposed very rapidly at 200°.

Anal. Calcd. for $C_7H_7O_5N_3 \cdot HCl$: Cl, 14.20. Found: Cl, 14.34.

The free base was obtained by neutralizing with ammonia the mother liquors from the above hydrochloride and then adding a slight excess of acetic acid. The base precipitated as a red powder, which crystallized from 50% alcohol in blood-red blades, m. p. 166.5–167.5° (corr.). Nietzki and Ruppert,[17] who prepared this compound by the nitration of amino-cresotinic acid (CH_3,OH,COOH,NH_2 = 1,3,4,6), gave its m. p. as 160°. It is but slightly soluble in water.

Anal. Calcd. for $C_7H_7O_5N_3$: C, 38.54; H, 3.24. Found: C, 38.57; H, 3.60.

3-Hydroxy-2,4-dinitro-6-acetylaminotoluene.—The acetylaminocresol (30 g.) was dissolved in the minimum quantity of glacial acetic acid and added dropwise to a well-cooled mixture of fuming nitric (sp. gr. 1.5) (45 g.) and glacial acetic (15 g.) acids, at such a rate that the temperature was maintained below 5°. After this addition had been completed, the mixture was left in the ice pack for two hours longer and was then poured upon 200 g. of crushed ice. The crude dinitro derivative separated as a yellow powder (yield, 50%), which was removed, washed with water and crystallized from glacial acetic acid, when it formed twinned orange-yellow plates, melting with decomposition at 231° (corr.), somewhat soluble in water.

Anal. Calcd. for $C_9H_9O_6N_3$: C, 42.37; H, 3.56. Found: C, 42.53; H, 3.62.

This method is a modification of that used by Reverdin and Crépieux[18] for the nitration of *o*-acetotoluidide.

By a different method, employing an acetylamino-*m*-cresotinic acid as initial material, Nietzki and Ruppert[19] have prepared this same compound and record an uncorrected m. p. of 225°.

[16] Brand and Zoller, *Ber.*, **40**, 3332 (1907).

[17] Nietzki and Ruppert, *ibid.*, **23**, 3479 (1890).

[18] Reverdin and Crépieux, *ibid.*, **33**, 2498 (1900).

[19] Nietzki and Ruppert, *ibid.*, **23**, 3478 (1890).

3-Acetyloxy-2,4-dinitro-6-acetylaminotoluene.—After refluxing for four hours a solution of 0.7 g. of the dinitro-acetylaminocresol and a small amount of fused sodium acetate in 5 cc. of glacial acetic acid and 5 cc. of acetic anhydride, the mixture was cooled, diluted with 10 cc. of water, 0.5 g. of Norite added, the refluxing continued for another hour and the mixture filtered hot. As the filtrate cooled, yellowish-green needles separated which were crystallized from 50% alcohol and then melted at 170–170.5° (corr.); yield of pure product, 75%.

Anal. Calcd. for $C_{11}H_{11}O_7N_3$: C, 44.44; H, 3.73. Found: C, 44.40; H, 3.80.

The product was only slightly soluble in water, and its aqueous solution was not colored by the addition of ferric chloride. Nietzki and Ruppert[17] recorded a m. p. of 175° for a diacetyl derivative prepared by the action of acetic anhydride upon the dinitro-aminocresol but gave no analytical figures.

3-Ethoxy-4-nitrotoluene.—The ethoxynitrotoluidine (1 g.) was dissolved in boiling alcohol (20 cc.) and diazotized by adding slightly more than the calculated amount of sulfuric acid and then introducing slowly into the interior of the liquid, by means of a funnel tube, the calculated amount of nitrite dissolved in the minimum quantity of water. The mixture was boiled for five minutes, cooled, concentrated under reduced pressure and the gummy residue distilled with steam. The yellow solid carried over by the steam, crystallized from petroleum ether, gave tan needles (0.3 g.), m. p. 51–51.5°. Staedel and Kolb,[20] who prepared this compound from the silver salt of the nitrocresol and ethyl iodide reported a m. p. of 50–51°.

3-Ethoxy-6-aminotoluene.—When 3-ethoxy-6-benzalaminotoluene (100 g.) was mixed with dilute (50 cc. of concentrated acid to 600 cc. of water) hydrochloric acid, and the mixture distilled with steam as long as benzaldehyde came over, 70% of the calculated amount of aldehyde was collected. The red solution remaining in the distilling flask was neutralized with the calculated amount of sodium hydroxide and a red oil separated, which was collected and distilled, the major fraction coming over at 253–255° as a pale yellow oil which slowly darkened; yield, 83%.

Anal. Calcd. for $C_9H_{13}ON$: C, 71.50; H, 8.67. Found: C, 71.42; H, 8.46.

The compound was only very slightly soluble in water. Staedel and Kayser[21] obtained the same compound by reduction of the corresponding nitrocresyl ether, but merely stated that it resembled in general the corresponding *o*-cresol derivative and was volatile with steam. They also prepared and analyzed its oxalate.

Hydrochloride.—Colorless, large, flat plates, which began to decompose above 200° and melted finally at 212° (corr.); soluble in water or in alcohol.

Anal. Calcd. for $C_9H_{13}ON \cdot HCl$; Cl, 18.90: Found, 18.94.

3-Ethoxy-6-benzalaminotoluene.—One mole (10 g.) of 3-hydroxy-6-benzalaminotoluene was ground up with 1.05 moles (1.1 g.) of sodium hydroxide and 2.5 cc. of 95% alcohol. The heat evolved was sufficient to drive off the water and alcohol, leaving a greenish-gray powder. This powder was mixed with 20 cc. of 95% alcohol and 1.5 moles (7.8 cc.) of ethyl bromide, and the mixture refluxed for three hours, after which the alcohol and excess ethyl bromide were evaporated, 100 cc. of water was added to the residue, the heavy red oil which separated was removed and the residual liquid extracted with 20 cc. of benzene to recover the rest of this oil. The oil was washed carefully

[20] Staedel and Kolb, *Ann.*, **259**, 224 (1890).

[21] Staedel and Kayser, *ibid.*, **217**, 219 (1883).

(to avoid emulsions) thrice with 0.5 *N* sodium hydroxide solution and then with water to remove the alkali. The washed oil was diluted with benzene (100 cc.), the solution dried over anhydrous sodium sulfate and distilled under diminished pressure, collecting the fraction of b. p. 212–217° (20 mm.); yield, 80%. The product was a bright yellow oil which gradually turned red on standing. It was soluble in alcohol, ether or benzene but not in water or alkalies.

Anal. Calcd. for $C_{16}H_{17}ON$: C, 80.30; H, 7.17. Found: C, 79.66, 79.58; H, 7.17, 7.15.

The same product was obtained when the ethylation was effected with ethyl sulfate instead of ethyl bromide.

The sodium salt of the aminocresol was dried thoroughly at 100–110°, the dry powder stirred slowly into the calculated amount of ethyl sulfate, the mixture heated at 100° for three hours, then diluted with water, the heavy oil separated and treated as described above; yield, 50%, of a product boiling at 210–217° (20 mm.). No thiazole was obtained when this benzal derivative was fused with sulfur.

3-Ethoxy-6-salicylaminotoluene.—When a mixture of 10 g. of 3-ethoxy-6-aminotoluene hydrochloride, 5 g. of sodium acetate, 100 cc. of water and 6.5 g. of salicylaldehyde was shaken vigorously, a heavy, yellow oil separated. This was removed and distilled under reduced pressure, collecting the fraction of b. p. 237–238° (16 mm.). On long standing this fraction crystallized in yellow blades which were purified by dissolving them in an ether-alcohol (4:1) mixture and allowing the solvent to evaporate spontaneously. The yellow solid obtained was readily freed from mother liquor by pressing and melted at 48.5° (corr.).

Anal. Calcd. for $C_{16}H_{17}O_2N$: C, 75.28; H, 6.72. Found: C, 75.50; H, 6.57.

Attempts to prepare a thiazole by fusion of this salicylal derivative with sulfur proved unsuccessful.

3-Ethoxy-6-acetylaminotoluene.—A mixture of 5 g. of the acetylaminocresol, 1.5 g. of sodium hydroxide, 3 cc. of ethyl bromide and 150 cc. of 95% alcohol was refluxed for ten hours, the alcohol then distilled off, the residue dissolved in the minimum quantity of hot 20% alcohol, the solution filtered and the filtrate cooled. The crystals which separated, after repeated recrystallization and decolorization, appeared as glistening, colorless needles, m. p. 118.5° (corr.); yield, 80–85%. Kayser[22] and Staedel and Kayser,[21] both of whom prepared it by direct acetylation of the aminocresol ethyl ether, gave the m. p. of this compound as 114°.

The solubility of phenacetin itself in 100 parts of water at 25° is stated as 0.077 part,[23] whereas this homolog dissolves to the extent of 0.28 part.

Anal. Calcd. for $C_9H_{11}O_2N$: C, 68.37; H, 7.83. Found: C, 68.36; H, 7.84.

Attempts to oxidize this toluene derivative to the corresponding benzoic acid by the action of potassium permanganate, either alone or in the presence of magnesium sulfate, proved unsuccessful; nor could we convert it into the corresponding benzaldehyde by Bornemann's[24] modification of the Étard reaction.

[22] Kayser, *Ber.*, **15**, 1135 (1882).

[23] U. S. Pharmacopoeia, 10th Revision, **1926**.

[24] Bornemann, *Ber.*, **17**, 1462 (1884).

A similar lack of success attended our efforts to convert it into the 2-methyl-5-ethoxy-indole by the action of sodium ethylate or amylate in a reducing atmosphere, according to the method by which Madelung[25] obtained indoles from the acetyl, benzoyl and oxalyl derivatives of *o*-toluidine. Our products were only intractable tars from which no pure compounds were isolated.

3-Ethoxy-6-chloro-acetylaminotoluene.—To a solution of 15 g. of chloro-acetyl chloride in 30 cc. of benzene, there was added slowly 20 g. of 3-ethoxy-6-aminotoluene in 30 cc. of benzene. After a vigorous stirring of the crystal paste, the benzene (and hydrogen chloride) was evaporated, leaving a yield of crude amide about equal to that calculated. By crystallization from dilute acetic acid, the pure compound was secured in colorless, short, matted needles, m. p. 140.5–141° (corr.).

Anal. Calcd. for $C_{11}H_{14}O_2NCl$: C, 58.03; H, 6.20. Found: C, 57.87; H, 6.16.

When this compound was heated with aluminum chloride, following the method of Stollé,[26] no oxindole was obtained, although Stollé accomplished this cyclization with chloro-acetyl-*o*-toluidide.

3-Ethoxy-6-salicylylaminotoluene.—When a benzene (20 cc.) solution of salicylic acid (4.6 g.) was added to a simple solution of 3-ethoxy-6-aminotoluene (5 g.) in benzene (30 cc.), and the flask shaken vigorously, the salt separated immediately. Phosphorus oxychloride (4 cc.) was added and the mixture refluxed as long as hydrogen chloride was evolved. The benzene was evaporated and the residue washed with hot water to remove the phosphoric acid. The soft, resinous mass remaining was dissolved in alcohol. Addition of water (50%) to this alcoholic solution, precipitated the crude amide (4 g.). As repeated crystallization from 75% acetic acid failed to give a colorless product, it was dissolved in 1 *N* sodium hydroxide, the alkaline solution digested with Norite for thirty minutes, filtered, the amide reprecipitated by saturating the filtrate with carbon dioxide, the precipitate washed, dried and recrystallized from alcohol. It was thus obtained in fine, colorless needles, m. p. 153.4–154° (corr.).

Anal. Calcd. for $C_{16}H_{17}O_3N$: C, 70.82; H, 6.32. Found: C, 70.74; H, 6.19.

Oxal-*p*-ethoxy-*o*-toluidide.—If a mixture of 10 g. of 3-ethoxy-6-aminotoluene with 5 cc. of ethyl oxalate was refluxed gently for two hours, or until no more condensate dripped back from the condenser, and was then cooled, it congealed to a cake of the crude toluidide (m. p. 200°); yield, 8.5 g., or 72%. Recrystallized from a 1:1 alcohol–benzene mixture, it yielded long, colorless needles, m. p. 205° (corr.), soluble in alcohol, benzene or ether, but not in water.

Anal. Calcd. for $C_{20}H_{24}O_4N_2$: C, 67.39; H, 6.79. Found: C, 67.45; H, 6.95.

As a by-product there was isolated what appeared to be the substituted oxanilic acid ester but the amount was too small for satisfactory purification and identification.

Experiments designed to transform this toluidide into the 5,5′-diethoxydiindyl, by the method of Madelung,[25] yielded only decomposition products.

Phthal-*p*-ethoxy-*o*-tolil.—A solution of 5 g. of 3-ethoxy-6-aminotoluene and 5 g. of phthalic anhydride in 25 cc. of benzene was refluxed for an hour. As the solution

[25] Madelung, *Ber.*, **45**, 1128 (1912).

[26] Stollé, *J. prakt. Chem.*, [2] **105**, 137 (1923).

cooled, crystals separated which were recrystallized from 80% alcohol until colorless needles were obtained of the constant m. p. 140.5° (corr.); yield, 75%.

Anal. Calcd. for $C_{17}H_{15}O_3N$: C, 72.57; H, 5.38. Found: C, 72.07; H, 5.27.

Ethyl (2-Methyl-4-ethoxyphenyl)-acetylglycinate.—To a solution of 12 g. of 3-ethoxy-6-acetylaminotoluene in 50 cc. of dry benzene, there was added 1.5 g. of metallic sodium and the mixture was refluxed until the sodium had all reacted. At thirty to sixty-minute intervals three portions of ethyl chloro-acetate were added, amounting in all to 10 g., after which the mixture was refluxed for two to three hours longer, cooled, 10 cc. of water added to dissolve the salt formed, the benzene layer separated, the aqueous layer extracted twice more with benzene, the benzene extracts united, dried with anhydrous sodium carbonate and distilled, at first under atmospheric and finally under reduced pressure. A yellow, viscous oil was obtained, b. p. about 210° (15 mm.) which, after repeated rectification, yielded a fraction, b. p. 210–212.5° (22 mm.); yield, 10 g. or 60%.

Anal. Calcd. for $C_{15}H_{21}O_4N$: C, 64.51; H, 7.58. Found: C, 64.25; H, 7.34.

The above procedure is similar to that employed by Paal and Otten[27] for the production of ethyl acetanilido-acetate.

According to a recent German patent,[28] it should be possible to condense such a glycine to an indoxyl and to oxidize this indoxyl to the corresponding indigo but, although we followed the patent specifications closely, this result could not be realized.

2,4-Dichloro-3-ethoxy-6-aminotoluene.—The acetyl derivative (10 g.) was hydrolyzed by refluxing it for four hours with 2 *N* hydrochloric acid. There resulted a yellow, granular precipitate with red supernatant solution. Sufficient hot water was added to bring all into solution and the color was removed by digesting the solution with Norite. As the filtrate from this Norite cooled, it deposited long, colorless blades of the hydrochloride, which lost hydrochloric acid slowly and turned pinkish. They began to darken at 220° and melted at 244° (corr.).

Anal. Calcd. for $C_9H_{11}ONCl_2 \cdot HCl$: Cl, 13.82. Found: Cl, 13.78.

The free amine was obtained by the addition of solid ammonium carbonate to a solution of the above hydrochloride and was purified by crystallization from 20% alcohol. It formed irregular plates and scales, m. p. 83° (corr.).

Anal. Calcd. for $C_9H_{11}ONCl_2$: C, 49.11; H, 5.04. Found: C, 49.44, 49.43; H, 5.18, 5.16.

2,4-Dichloro-3-ethoxy-6-acetylaminotoluene.—Bender's[6] procedure for the chlorination of acetanilide was modified as follows.

A hypochlorite solution was prepared from 127 g. (one mole) of calcium hypochlorite and 84 g. (one mole) of sodium bicarbonate in 1 liter of water, which was agitated frequently during three or four hours, then left overnight and finally filtered. This filtrate was added gradually to a cold solution of 10 g. of 3-ethoxy-6-acetylaminotoluene in 30 cc. of glacial acetic acid as long as it caused a precipitate. This required about 200 cc. The amorphous precipitate was crystallized from 50% acetic acid until its

[27] Paal and Otten, *Ber.*, **23**, 2594 (1890).

[28] Badische Anilin- und Soda Fabrik, German Patent 188,436 (1907); *Friedländer*, **4**, 514.

m. p. remained constant at 162.5–163° (corr.); yield, 10 g. or 75%. The product was soluble in alcohol, benzene or acetic acid, but dissolved very slightly in water.

Anal. Calcd. for $C_{11}H_{13}O_2NCl_2$: C, 50.40; H, 5.00. Found: C, 50.23; H, 5.08.

The same product was obtained by the action of sodium ethoxide and ethyl iodide upon 3-hydroxy-2,4-dichloro-6-acetylaminotoluene.

3-Ethoxy-4-nitro-6-aminotoluene.—When the acetyl derivative of this compound (1 g.) was boiled in 6 *N* hydrochloric acid until solution was complete and this solution was then allowed to cool, colorless plates of the hydrochloride separated which began to darken at 240° and decomposed at 249°. This salt was better defined and more stable than the 5-nitro isomer.

Anal. Calcd. for $C_9H_{12}O_3N_2 \cdot HCl$: Cl, 15.24. Found: Cl, 15.28.

Neutralization of the mother liquors yielded the free base, which crystallized from 30% alcohol in dark red, columnar form, m. p. 86–87° (corr.).

Anal. Calcd. for $C_9H_{12}O_3N_2$: C, 55.09; H, 6.17. Found: C, 54.91; H, 6.23.

3-Ethoxy-4-nitro-6-acetylaminotoluene.—A solution of 20 g. of the acetylamino cresyl ether in the minimum amount of glacial acetic acid was added very slowly to a well-cooled solution of 20 g. of fuming (sp. gr. 1.5) nitric in 20 cc. of glacial acetic acid, so that the temperature never rose above 0°. After standing for two hours at 0°, the mixture was poured upon 200 g. of crushed ice, the yellow precipitate collected (yield, 55%), washed, dried and recrystallized from 95% alcohol, when it formed yellow plates, m. p. 192.5–193° (corr.).

Anal. Calcd. for $C_{11}H_{14}O_4N_2$: C, 55.47; H, 5.93. Found: C, 55.62; H, 5.93.

The mother liquor from these crystals contained also the 5-nitro isomer (m. p. 160°) to the extent of 10–15% of the total yield. It was separated from the 4-nitro form by fractional crystallization from 20% alcohol, in which solvent the 4-nitro derivative is the less soluble.

The 5-nitro derivative separated in this reaction was identical in all respects with that prepared by the ethylation of the 5-nitro-acetylamino-cresol.

3-Ethoxy-5-nitro-6-aminotoluene.—The acetyl derivative of this base was hydrolyzed easily by concentrated hydrochloric acid, forming a red solution from which but little of the hydrochloride separated. The small amount obtained appeared in tan-colored fibers which began to darken above 200°, resinified at about 220°, and decomposed at about 240°.

Anal. Calcd. for $C_9H_{12}O_3N_2 \cdot HCl$: Cl, 15.34. Found: Cl, 14.87.

This salt was rapidly hydrolyzed by water to the free base, which crystallized from 30% alcohol in long orange-red needles, m. p. 101–101.5° (corr.).

Anal. Calcd. for $C_9H_{12}O_3N_2$: C, 55.09; H, 6.17. Found: C, 54.93; H, 6.31.

3-Ethoxy-5-nitro-6-acetylaminotoluene.—Metallic sodium (0.3 g.) was dissolved in absolute alcohol (20 cc.), the nitro-acetylaminocresol (1 g.) was added, followed by ethyl iodide (5 cc.), and the mixture was refluxed until its color changed from red to yellow (about two hours). Water (20 cc.) and Norite (1 g.) were added, the mixture boiled for ten minutes and filtered hot. As the filtrate cooled the crude ethoxy derivative separated in yellow needles which melted at 160° (corr.) after recrystallization from 50% alcohol; yield of crude product, 85%.

Anal. Calcd. for $C_{11}H_{14}O_4N_2$: C, 55.47; H, 5.93. Found: C, 55.56; H, 5.88.

By crystalline form, color and mixed m. p., this compound was proved to be identical with the 5-nitro derivative prepared by direct nitration of the ethoxyacetylaminotoluene.

The failure of our attempts to reduce this nitro derivative to the amine is in agreement with the observations of Bogert and Taylor[29] on the reduction of 3-nitro-4-acetylaminophenetole, and is in further support of the assumption that the nitro is adjacent to the acetylamino group.

3-Ethoxy-2,4-dinitro-6-aminotoluene.—The acetyl derivative of this compound (1 g.) was refluxed for three hours with 6 *N* hydrochloric acid (30 cc.) and Norite (1 g.), and filtered hot. The hydrochloride of the base separated, as the filtrate cooled, in pale yellow, rectangular plates which began to darken above 140° and decomposed at 195–197°.

Anal. Calcd. for $C_9H_{11}O_5N_3 \cdot HCl$: Cl, 12.77. Found: Cl, 12.85.

The mother liquors from the hydrochloride, when treated with ammonia, precipitated the free base as a yellow, flocculent solid which crystallized from 10% alcohol in short, yellow needles, m. p. 96–97° (corr.).

Anal. Calcd. for $C_9H_{11}O_5N_3$: C, 44.82; H, 4.60. Found: C, 44.70; H, 4.70.

3-Ethoxy-2,4-dinitro-6-acetylaminotoluene.—The dinitro-acetylaminocresol (5 g.) was ground in a mortar with anhydrous sodium carbonate (2.5 g.) and a little water (0.5 cc.). The brownish red triturate, after thorough drying, was heated with ethyl sulfate (5 cc.) at 140° for an hour, then cooled, water (50 cc.), alcohol (20 cc.) and Norite (1 g.) were added, the mixture was boiled for a short time and filtered hot. As the filtrate cooled, the ethoxy derivative separated. It was collected and crystallized from 50% alcohol, when it appeared in long, pale yellow needles, m. p. 167–167.5° (corr.); yield, 76% (2.5 g.), calculated on unrecovered cresol, since 30% of the initial material was recovered by acidification of the mother liquors from the crude product.

Anal. Calcd. for $C_{11}H_{13}O_5N_3$: C, 46.65; H, 4.63. Found: C, 46.89; H, 4.74.

3-Ethoxy-4,5-dinitro-6-acetylaminotoluene was prepared by the direct nitration of the ethoxy-acetyltoluidide, by the method of Blanksma,[10] for the analogous phenacetin derivative, following the modifications later suggested by Bogert and Taylor;[29] yield 67%. It crystallized from 95% alcohol in pale yellowish, fine needles, m. p. 257–258° (corr.).

The same product was obtained by subjecting the ethoxy-4-nitro-acetyltoluidide to a similar treatment; yield, 85%. It was insoluble in water and only slightly soluble in alcohol or glacial acetic acid.

Anal. Calcd. for $C_{11}H_{13}O_6N_3$: C, 46.68; H, 4.63. Found: C, 46.54; H, 4.74.

3-Ethoxy-4,6-diacetylaminotoluene.—When 2 g. of the 4-nitro-ethoxyacetotoluidide was reduced with stannous chloride in hydrochloric acid solution until the yellow color of the solution was discharged, and the tin was then precipitated by hydrogen sulfide, the filtrate darkened so rapidly in the air that the excess of acid was neutralized with sodium carbonate and 5 cc. of acetic anhydride was added; yield of crude product, 57%. It crystallized from 10% alcohol in colorless, short, matted needles, m. p. 200–200.5° (corr.).

Anal. Calcd. for $C_{13}H_{18}O_3N_2$: C, 62.40; H, 7.25. Found: C, 62.09; H, 7.47.

3-Ethoxy-3'-hydroxy-6,6'-azotoluene.—To the solution of the diazonium chloride obtained by diazotizing at 0° 20 g. of 3-ethoxy-6-aminotoluene, there was added a cold

[29] Bogert and Taylor, THIS JOURNAL, **49**, 1578 (1927).

solution of 11.5 g. of *m*-cresol and 15.5 g. of hydrated sodium carbonate in 100 cc. of water. After standing overnight, the tarry precipitate became crystalline. It was removed, washed, dried and crystallized from benzene, when it appeared in long brownish spikes, m. p. 132.5° (corr.); yield, 60%.

Anal. Calcd. for $C_{16}H_{18}O_2N_2$: C, 71.09; H, 6.71. Found: C, 71.15; H, 6.71.

3,3'-Diethoxy-6,6'-azotoluene.—To 300 cc. of absolute alcohol in which 3 g. of metallic sodium had been dissolved, there was added 25.5 g. of 3-ethoxy-3'-hydroxy-6,6'-azotoluene, followed by 25 g. of ethyl bromide. The mixture was allowed to stand overnight and was then refluxed for six hours. The crystals which separated as the solution cooled were ground up in water, to remove all sodium salts, dried and crystallized from benzene. The compound separated in yellow, granular crystals, m. p. 149–149.5° (corr.); yield, 62%.

Anal. Calcd. for $C_{18}H_{22}O_2N_2$: C, 72.46; H, 7.44. Found: C, 72.61; H, 7.60.

3-Hydroxyethoxy-6-acetylaminotoluene.—After dissolving 5 g. of metallic sodium in 200 cc. of absolute alcohol, the solution was well cooled and 35 g. of the acetylaminocresol hydrate was gradually stirred in until all was dissolved. To this solution there was added 20 g. (125% of that calculated) of ethylene chlorohydrin. The mixture was left for twelve hours in a closed vessel at laboratory temperature and was then refluxed for six hours, the alcohol distilled off, 200 cc. of water added to the residue and the mixture again evaporated. A resinous oil separated and gradually congealed. It was treated with hot 95% alcohol, filtered from the sodium chloride and the filtrate as it cooled deposited crystals. By concentration of the mother liquor a second crop of crystals was obtained. Addition of acetone to this second mother liquor precipitated a third crop. These various lots of crystals were combined and recrystallized. From acetone small granular crystals were secured; from water rhomboidal striated plates and blades; yield of purified product, 25%. Both forms melted at 117–117.5° (corr.).

Anal. Calcd. for $C_{11}H_{15}O_3N$: C, 63.16; H, 7.23. Found: C, 62.92; H, 7.11.

In one hundred parts of water at 25° it dissolved to the extent of 4.35 parts.

3-Acetyloxyethoxy-6-diacetylaminotoluene.—The 3-hydroxyethoxy-6-acetylaminotoluene (3.5 g.) and a little sodium acetate were dissolved in acetic anhydride (3 cc.), the excess of anhydride distilled off, the residual solid dissolved in the minimum quantity of hot 30% alcohol, the solution cooled and the crystals which separated recrystallized from the same solvent. The product appeared as fine, colorless needles, m. p. 117° (corr.). Mixed with some of the initial hydroxyethoxy derivative (m. p. 117–117.5°, corr.), the m. p. was 95–109°.

Anal. Calcd. for $C_{15}H_{19}O_5N$: C, 61.42; H, 6.52. Found: C, 61.52; H, 6.58.

Summary

1. 3-Hydroxy-6-aminotoluene has been studied as a possible source of useful intermediate or final products.

2. Since it is a homolog of *p*-aminophenol, various new derivatives have been prepared, analogous structurally to such well-known drugs as Phenacetin, Pertonal, Malakin and the like, but the pharmacological properties of these new products have not been determined as yet.

3. Chlorination and nitration of both the hydroxy and the corresponding ethoxy derivatives have been investigated, as well as the reduction products of the nitro derivatives.

4. In the course of the research many new compounds have been synthesized and many old ones prepared by new methods.

5. It was discovered that the benzalamino derivatives of these *p*-aminophenol types offered a very satisfactory form in which to ethylate the phenolic hydroxyl group.

NEW YORK, N. Y.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

LOCAL ANESTHETICS DERIVED FROM 2-(BETA-HYDROXYETHYL)-PIPERIDINE

BY C. S. MARVEL AND R. S. SHELTON

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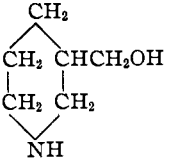
Recently Sandborn and Marvel[1] have prepared the *p*-aminobenzoates of certain N-alkyl derivatives of β-piperidylcarbinol and have found that their monohydrochlorides have a strong local anesthetic action combined with a low toxicity. The close structural relation between β-piperidylcarbinol (3-hydroxymethylpiperidine) (I) and 2-(β-hydroxyethyl)-piperidine (II) suggested that similar derivatives of this second amino alcohol might have desirable pharmacological action.



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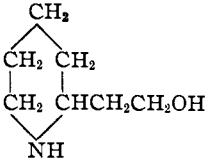

II

The starting material for the preparation of these compounds is α-picoline. By the procedure of Ladenburg[2] this with formalin gave 2-(β-hydroxyethyl)-pyridine, which was reduced to the piperidine derivative by means of sodium and alcohol.[3] The nitrogen atom was alkylated by treatment with the corresponding alkyl halide, following the general method used to alkylate β-piperidylcarbinol.[4] These tertiary amino alcohols were treated with *p*-nitrobenzoyl chloride to give the corresponding ester hydrochlorides, which were in turn reduced catalytically by means of hydrogen and the platinum catalyst of Adams and Shriner[5] to the amino ester hydrochlorides. This reduction gave the best product when glacial acetic acid was used as a solvent. When alcohol was used as a solvent a colorless product was obtained at first but on standing it turned red. When

[1] Sandborn and Marvel, THIS JOURNAL, **50**, 563 (1928).

[2] Ladenburg, *Ber.*, **43**, 2378 (1910).

[3] Ladenburg, *Ann.*, **301**, 129 (1898).

[4] Ref. 1, p. 566.

[5] Adams and Shriner, THIS JOURNAL, **45**, 2171 (1923).