methyl alcohol was added. After refluxing for an hour the methyl alcohol was distilled from a water-bath. The crude xanthogenic ester obtained by treating the residue with water weighed 16.0 g. The crude product was dissolved in hot methyl alcohol and filtered. By cooling the filtrate in an ice–salt-bath 14.3 g. of pure product was obtained, m.p. 172°.

Reaction with Trimethylamine.—A cold solution of 14.5 g. of 5-β-bromoethyl-5-*n*-butylbarbituric acid in 125 cc. of absolute alcohol was carefully mixed with a cold solution of 13.3 g. of trimethylamine in 65 cc. of absolute alcohol. After standing two days in the ice-box and a month at room temperature no crystals had separated. After distillation to dryness under diminished pressure and crystallization from *n*-butyl alcohol 13 g. of product melting at 245–50° and decomposing at 255° were obtained. Crystallization of this from ethyl alcohol yielded 11 g. melting at 250–251° with slight decomposition. The bromine is precipitated directly from water solution.

Summary

1. Some comparisons are made with respect to the relative ease with which urea, thiourea and benzamidine condense with an α-alkyl-α-carbethoxy-γ-butyric lactone and an alkylmalonic ester to yield compounds related to pyrimidine.

2. A tentative mechanism for the reaction is proposed which is based partly on the isolation of two types of intermediates.

3. The replacement of bromine in the β-position to the barbituric acid nucleus proceeds smoothly. The β-amino group is quantitatively diazotized to the hydroxy compound without rearrangement.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF J. T. BAKER CHEMICAL CO.]

Some Urethans of Phenolic Quaternary Ammonium Salts

BY JOHN H. GARDNER AND JOSEPH R. STEVENS

Stevens and Beutel[1] have demonstrated the pronounced physostigmine activity of certain 3-alkyl-4-dimethylaminophenol dimethylurethan methiodides. A new series of *p*-aminophenol derivatives with other groups in the 3-position has now been prepared and shown to be physiologically active. Similar derivatives of 5-hydroxy-1,2,3-trimethylindoline and of 6- and 8-hydroxy-1-methyl-1,2,3,4-tetrahydroquinoline have also been prepared and found to be active. The properties of the dimethylurethan hydrochlorides are summarized in Table I and those of the methiodides in Table II.

Pharmacological measurements were made in the laboratory of The Wm. S. Merrell Co., through the courtesy of Dr. Robert S. Shelton, or in the laboratory of Dr. F. O. Zillessen of Easton, Pennsylvania. For a preliminary evaluation, the toxicities were determined. These were stated as LD_{50}, in mg./kg., in mice by intravenous injection. Of the meta-substituted *p*-dimethylaminophenol derivatives, the methoxy compound was by far the most toxic (LD_{50} 1.3 mg./kg.), but the greatest toxicity of the series was shown by 8-hydroxy-1-methyl-1,2,3,4-tetrahydroquinoline dimethylurethan methiodide (0.24 mg./kg.).

Experimental

General Procedure.—For the preparation of the aminophenols, the phenols were coupled with diazotized sulfanilic acid, and the azo dye was reduced with sodium hydrosulfite with or without being isolated. The aminophenols were methylated with methyl iodide in the presence of sodium carbonate and the resulting quaternary salt was subjected to destructive distillation in vacuum. In the preparation of 4-dimethylamino-3-methoxyphenol, it was found better to decompose the quaternary salt under reflux in vacuum. The dimethylaminophenols were converted into the dimethylurethan hydrochlorides by the general procedure of Stevens and Beutel.[1] In some cases it was necessary to boil the dimethyl urethans with excess methyl iodide in acetone for several days. The indoline and quinoline dimethylurethan salts were obtained in a similar way. For illustration the preparation of 4-dimethylamino-3-isopropoxyphenol and its derivatives is described in detail.

Resorcinol Mono- and Di-isopropyl Ethers.—The monoether has been used previously in another connection[2] but its preparation has not been described. These ethers were prepared by the general method for the preparation of resorcinol mono-alkyl ethers of Klarmann, Gatyas and Shternov.[3] Resorcinol mono-isopropyl ether, yield, 27.1%, b. p. 122–125° under 3.5 mm.

Anal. Calcd. for $C_9H_{12}O_2$: C, 71.1; H, 7.9. Found: C, 71.43; H, 7.96.

Resorcinol di-isopropyl ether, yield, 11.5%, b. p. 89.5–95° under 3 mm.

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.2; H, 9.3. Found: C, 74.2; H, 9.13.

4-Amino-3-isopropoxyphenol.—To a solution of 19.1 g. of sulfanilic acid, 6.5 g. of sodium carbonate monohydrate and 6.2 g. of sodium nitrite in 75 ml. of water, cooled to 2° by adding ice, 25 ml. of concentrated hydrochloric acid was added and then enough sodium nitrite to give a blue color on starch-potassium iodide paper after a minute. Urea was added to destroy the excess nitrous acid and the solution was then poured into a cold solution of 15.2 g. of resorcinol mono-isopropyl ether in 80 ml. of 10% sodium hydroxide. The mixture was allowed to stand about two hours until no test for diazo compound was obtained with an alkaline solution of β-naphthol. It was then acidified with hydrochloric acid, chilled in the refrigerator, filtered and the precipitate washed with water. The dye was dried in a vacuum at 50°. Yield was 28.4 g. (93.4%).

The dye was dissolved in a mixture of 190 ml. of water and 26 ml. of 50% sodium hydroxide. To the solution 44.5 g. of sodium hydrosulfite was added with stirring. The temperature rose to 60° and the solution became light green. It was then neutralized to a brilliant yellow end point with glacial acetic acid, chilled in the refrigerator and the light brown crystals were filtered out and dried in

(1) I. R. Stevens and R. H. Beutel, THIS JOURNAL, **63**, 308 (1941).

(2) H. H. Hodgson, R. J. H. Dyer and H. Clay, *J. Chem. Soc.*, 629 (1934).

(3) E. Klarmann, L. W. Gatyas and V. A. Shternov, THIS JOURNAL, **53**, 3397 (1931).

TABLE I

4-Dimethylamino-3-R-phenol dimethylurethan hydrochloride	M. p., °C.	Formula	Analyses,[a] % Calcd.	Found	Calcd.	Found
Methoxy	162–164	$C_{12}H_{19}O_3N_2Cl$	N, 10.2	10.2	Cl, 12.9	12.85
Isopropoxy	153–154	$C_{14}H_{23}O_3N_2Cl$	C, 55.54	55.40	H, 7.60	7.48
Chloro	137.5–138.5	$C_{11}H_{16}O_2N_2Cl_2$	C, 47.3	47.15	H, 5.7	5.65
Phenyl	163.5–164	$C_{17}H_{21}O_2N_2Cl$	C, 63.65	63.45	H, 6.55	6.67
Cyclohexyl	167–168	$C_{17}H_{27}O_2N_2Cl$	C, 62.48	62.30	H, 8.27	8.50
3-Ethyl-5-methyl	133–134	$C_{14}H_{23}O_2N_2Cl$	C, 58.61	59.00	H, 8.03	7.80
Dimethylurethan of hydrochloride						
5-Hydroxy-1,2,3-trimethylindoline	173.5–174.5	$C_{14}H_{21}O_2N_2Cl$	C, 59.05	59.2	H, 7.38	7.19
6-Hydroxy-1-methyl-1,2,3,4-tetrahydroquinoline	162.5–164	$C_{13}H_{19}O_2N_2Cl$	C, 57.67	57.35	H, 7.02	6.97
8-Hydroxy-1-methyl-1,2,3,4-tetrahydroquinoline	107–109	$C_{13}H_{19}O_2N_2Cl$	C, 57.67	57.65	H, 7.02	7.09

[a] All analyses by Dr. V. B. Fish of this Laboratory.

TABLE II

4-Dimethylamino-3-R-phenol dimethylurethan methiodide	M. p., °C.	Formula	LD_{50} mg./kg.	Analyses, % Calcd.	Found	Calcd.	Found
Methoxy	169.5–170	$C_{13}H_{21}O_3N_2I$	1.3	C, 41.05	41.25	H, 5.51	5.27
Isopropoxy	177 dec.	$C_{15}H_{25}O_3N_2I$	2.5	C, 44.2	44.15	H, 6.13	6.19
Chloro	133–133.5	$C_{12}H_{18}O_2N_2ClI$	7.8	C, 37.4	37.35	H, 4.7	4.75
Phenyl	166–167	$C_{18}H_{23}O_2N_2I$	28	C, 50.70	50.70	H, 5.40	5.51
Cyclohexyl	169–172	$C_{18}H_{29}O_2N_2I$	7.2	C, 50.00	49.95	H, 6.71	6.74
3-Ethyl-5-methyl	129–131	$C_{15}H_{25}O_2N_2I$	33	N, 7.14	7.14	I, 32.40	32.42
Dimethylurethan of methiodide							
5-Hydroxy-1,2,3-trimethylindoline	187.5–191.5	$C_{15}H_{23}O_2N_2I$	15	C, 46.15	46.3	H, 5.90	5.89
6-Hydroxy-1-methyl-1,2,3,4-tetrahydroquinoline	190–195 dec.	$C_{14}H_{21}O_2N_2I$	33	C, 44.68	44.70	H, 5.59	5.56
8-Hydroxy-1-methyl-1,2,3,4-tetrahydroquinoline	153.5–154	$C_{14}H_{21}O_2N_2I$	0.24	C, 44.68	44.55	H, 5.59	5.61

a vacuum desiccator over sulfuric acid. Yield was 12.1 g. (72.4%), darkening at 83°, melting 130–142° with much decomposition.

Anal. Calcd. for $C_9H_{13}O_2N$: C, 64.7; H, 7.8; N, 8.4. Found (cor. for ash): C, 64.6; H, 7.62; N, 8.23; ash, 5.49.

4-Dimethylamino-3-isopropoxyphenol.—To a solution of 11.5 g. of 4-amino-3-isopropoxyphenol in 300 ml. of absolute alcohol, 35 g. of anhydrous sodium carbonate and 30 ml. of methyl iodide was added. The solution was boiled under reflux for twenty-one hours. It was then filtered while hot and the filtrate evaporated to incipient crystallization. The solution was then chilled and the crystals filtered out and dried in a vacuum desiccator over sulfuric acid. The quaternary ammonium salt so obtained was subjected to destructive distillation under 2 mm. pressure, with the bath temperature slowly rising from 270 to 300° as the distillation proceeded. The distillate was taken up in 10% sodium hydroxide and ether, and the layers separated. The alkaline layer was washed twice with ether. The ether layer, on evaporation, left 0.2 g. of a red oil. The alkaline layer was acidified with 10% sulfuric acid and neutralized with sodium bicarbonate solution. The mixture was then extracted three times with ether; the combined ether extracts evaporated, and the residue dried over sulfuric acid in a vacuum desiccator. The yield of brown crystals was 4.9 g. (36.4%), m. p. 96–98°.

Anal. Calcd. for $C_{11}H_{17}O_2N$: C, 67.70; H, 8.72; N, 7.18. Found: C, 67.75; H, 8.63; N, 7.05, 7.02.

4-Dimethylamino-3-isopropoxyphenol Dimethylurethan Hydrochloride.—A solution of 4.4 g. 4-dimethylamino-3-isopropoxyphenol and 5 ml. of dimethylcarbamyl chloride in 15 ml. of dry pyridine was heated on the steam-bath for twenty-four hours. It was then poured into water and 10% sodium hydroxide was added until the mixture was alkaline to phenolphthalein. Then 20 ml. of 2% sodium hydroxide was added in excess. The mixture was extracted three times with ether and the combined ether extracts were washed twice with water. The ether was distilled and the residue dried by heating in a boiling water-bath under 2 mm. pressure. The residue was dissolved in anhydrous ether and the hydrochloride was precipitated by saturating with hydrogen chloride gas. This was purified by solution in absolute alcohol and fractional precipitation with anhydrous ether. A red oil separated first, then some orange, waxy crystals and finally white crystals. The last were dried in vacuum at 61°. The yield was 2.4 g. (35.2%) m. p. 153–154°

4-Dimethylamino-3-isopropoxyphenol Dimethylurethan Methiodide.—A solution of 2 g. of 4-dimethylamino-3-isopropoxyphenol dimethylurethan hydrochloride in 15 ml. of water was made alkaline with ammonia and extracted twice with ether. The combined ether extracts were washed with water and the ether distilled. The residue was dried in vacuum as before and dissolved in 10 ml. of acetone and 5 ml. of methyl iodide was added. After standing for two days, the crystals which formed were filtered out and dried. These were treated with boiling acetone to dissolve most of the colored impurities, the mixture cooled and filtered. After recrystallization from absolute alcohol there were obtained 0.65 g. of white crystals, m. p. 177° with decomposition. The acetone and alcohol mother liquors yielded 1.3 g. of somewhat less pure material. Total yield was 1.95 g. (72.3%).

***m*-1-Cyclohexenylanisole.**—To a Grignard reagent prepared from 33.5 g. of *m*-bromoanisole and 5.2 g. of magnesium, 20 g. of cyclohexanone was added during a half hour. After boiling an additional half hour, 50 ml. of 20% hydrochloric acid was added. The ether layer was separated, washed with 5% hydrochloric acid, 10% sodium hydroxide and finally with water. After drying over dried magnesium sulfate, it was distilled, and redistilled over 1 g. of sodium bisulfate. After solution in ether, it was washed twice with dilute sodium hydroxide and with water, dried over magnesium sulfate and distilled. The yield was 11.3 g. (33.8%), b. p. 285–290°.

***m*-Cyclohexylanisole.**—The *m*-1-cyclohexenylanisole was reduced catalytically in the presence of palladium; yield was 9.5 g. (83.5%), b. p. 148–152° under 7 mm.

Anal. Calcd. for $C_{13}H_{18}O$: C, 82.11; H, 9.47. Found: C, 81.15; H, 10.02.

m-Cyclohexylphenol.—The *m*-cyclohexylanisole was dissolved in a mixture of 90 ml. of glacial acetic acid and 45 ml. of constant boiling hydrobromic acid and boiled for fourteen hours. It was then poured into water and the mixture extracted three times with ether. The ether extract was washed with a saturated sodium bicarbonate solution and extracted twice with a 5% and once with a 10% solution of potassium hydroxide. The ether extract yielded 4.6 g. of unchanged *m*-cyclohexylanisole.

The alkaline solution was acidified with hydrochloric acid and extracted twice with ether. The ether extract was evaporated to dryness and the resulting crystalline mass dried in a vacuum desiccator over sulfuric acid; yield was 4.3 g. (94.8% based on the *m*-cyclohexylanisole consumed), m. p. 52°.

Anal. Calcd. for $C_{12}H_{16}O$: C, 81.82; H, 9.09. Found: C, 81.60, 81.50; H, 9.27, 9.31.

***as*-Methyl-*p*-anisylhydrazine.**—*p*-Anisidine was methylated with methyl sulfate by the procedure of Späth and Brunner,[4] but in much larger amounts. The product was a mixture of *p*-anisidine with mono- and dimethyl-*p*-anisidine. For the preparation of the nitrosamine, 160 g. of the mixture was treated with 172 ml. of concentrated hydrochloric acid and 600 g. of ice was added. A solution of 83 g. of sodium nitrite in 300 ml. of water was added slowly until the solution gave a persistent test for nitrous acid on starch–potassium iodide paper. After stirring an hour, the mixture was filtered and the nitrosamine washed with water until the washings were colorless. The yield was 62.5 g., m. p. 45–45.5°.

For reduction, a suspension of 108 g. of zinc dust in 165 ml. of water was cooled to 10° in an ice-bath and a solution of 62.5 g. of the nitrosamine in 108 ml. of glacial acetic acid was added during three hours, with stirring. After stirring in the cold two more hours, the mixture was heated to boiling and filtered while hot. The filter cake was washed with 500 ml. of 5% hydrochloric acid in small portions. After cooling, 50% sodium hydroxide was added to the filtrate until the zinc hydroxide dissolved. The oily layer was separated and the aqueous layer extracted twice with ether. The combined water-insoluble material was dried over potassium carbonate, the ether evaporated and the residue distilled under reduced pressure; yield, 41.4 g., boiling range 120.5 to 134.5° under 6.5 mm. Späth and Brunner give 135–139° under 10 mm.

5-Methoxy-1,2,3-trimethylindole.—A solution of 20 g. of *as*-methyl-*p*-anisylhydrazine in 200 ml. of water and a minimum of glacial acetic acid was nearly decolorized with Nuchar W. On adding 30 ml. of methyl ethyl ketone, the mixture became turbid and an oil soon separated. After two and a half hours, the mixture was extracted three times with ether, and the ether distilled and the residue dried by heating in a boiling water-bath under 18 mm. pressure for a half hour. The residue was treated with 60 ml. of 15% sulfuric acid in alcohol. After the first violent reaction had subsided, the mixture was heated on the boiling water-bath a half hour. It was then poured into water and the resulting precipitate washed free of acid. Yield was 15.9 g. (63.8%), m. p. 93–95°, dried over calcium chloride in a vacuum. Crystallization from Skellysolve D did not change the melting point.

Anal. Calcd. for $C_{12}H_{15}ON$: C, 76.3; H, 7.9. Found: C, 76.6, 76.1; H, 7.9, 7.8.

5-Hydroxy-1,2,3-trimethylindole.—A mixture of 7.4 g. of 5-methoxy-1,2,3-trimethylindole, 25 ml. of glacial acetic acid and 25 ml. of 48% hydrobromic acid was boiled seven hours, poured into water and filtered. The precipitate was washed free of acid; yield was 6.4 g. (93.6%). After purification by crystallization from alcohol, or better, by sublimation under 3 mm. pressure with the bath at 148°, m. p. 144.5–146°.

Anal. Calcd. for $C_{11}H_{13}ON$: C, 75.43; H, 7.43; N, 8.00. Found: C, 75.40; H, 7.12; N, 8.09.

5-Hydroxy-1,2,3-trimethylindoline.—A mixture of 8.2 g. of 5-hydroxy-1,2,3-trimethylindole and 25 g. of mossy tin was boiled with 35 ml. each of concd. and of 20% hydrochloric acid until all of the tin had dissolved. After dilution with water, the tin was precipitated with hydrogen sulfide, the solution filtered and the filtrate made just alkaline to Brilliant Yellow with ammonia. The precipitate was dried over calcium chloride in vacuum; yield was 4 g. (48.5%), m. p. 104.5–108°. For analysis, a portion was sublimed in vacuum; m. p. 107–109°.

Anal. Calcd. for $C_{11}H_{15}ON$: C, 74.58; H, 8.47. Found: C, 74.1, 74.2; H, 8.65, 8.60.

8-Hydroxy-1-methyl-1,2,3,4-tetrahydroquinoline.—8-Hydroxyquinoline was reduced by the method of Bedall and Fischer,[5] and the product was methylated by the method of Fischer.[6]

6-Hydroxy-1-methyl-1,2,3,4-tetrahydroquinoline.—6-Hydroxyquinoline methiodide was reduced in the usual way with tin and hydrochloric acid; yield was 31–49%, m. p. 111–112°.

Anal. Calcd. for $C_{10}H_{13}ON$: C, 73.62; H, 7.98; N, 8.59. Found: C, 73.55; H, 7.96; N, 8.51, 8.57.

Summary

1. A new series of 3-substituted-4-dimethylaminophenol dimethylurethan methiodides showing physostigmine activity has been prepared.

2. A group of hydroxyindoline and tetrahydroquinoline dimethylurethan methiodides showing similar activity has been prepared.

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(4) E. Späth and O. Brunner, *Ber.*, **58**, 522 (1925).

(5) K. Bedall and O. Fischer, *ibid.*, **14**, 1368 (1881).

(6) O. Fischer, *ibid.*, **16**, 714 (1883).