

Anal. Calcd. for $C_{13}H_{22}O_2NCl$: C, 60.06; H, 8.54. Found: C, 60.17; H, 8.39.

β - (2,5 - Dimethoxyphenyl) - isopropyltrimethylammonium Chloride.—The preceding tertiary amine was converted, in ether solution, into the methiodide (m. p. 142°), which on treatment with silver chloride gave the quaternary chloride. After crystallization, the chloride forms very hygroscopic, tiny, colorless prisms. After thorough drying (finally at 120° *in vacuo*) it melts at 203°.

Anal. Calcd. for $C_{14}H_{24}O_2NCl$: C, 61.37; H, 8.84. Found: C, 61.63; H, 8.81.

The authors wish to thank Mr. W. S. Ide for the many micro-analyses carried out during this work, and Dr. C. W. Ferry for the preparation

of considerable amounts of 2,5-dimethoxybenzaldehyde.

Summary

As part of a series of 2,5-dimethoxyphenylalkyl- and alkanolamines, 2,5-dimethoxyphenethylamine hydrochloride, β -(2,5-dimethoxyphenyl)-propylamine hydrochloride and β -(2,5-dimethoxyphenyl)-isopropylamine hydrochloride, together with the corresponding secondary and tertiary amine hydrochlorides and the quaternary chlorides, have been prepared.

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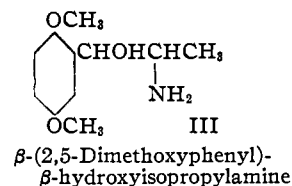
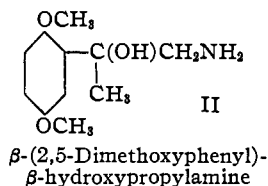
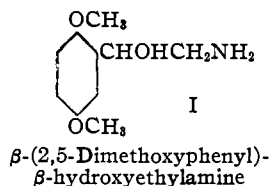
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[CONTRIBUTION FROM THE BURROUGHS WELLCOME & CO. U. S. A. EXPERIMENTAL RESEARCH LABORATORIES]

Amines Related to 2,5-Dimethoxyphenethylamine.¹ II

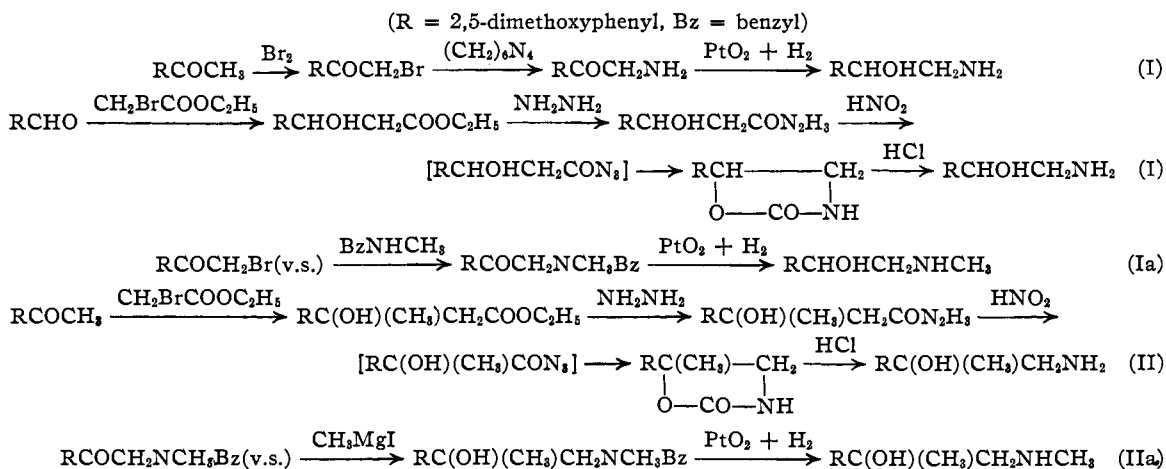
BY RICHARD BALTZLY AND JOHANNES S. BUCK

The work described below is a continuation made. The primary amines have the formulas



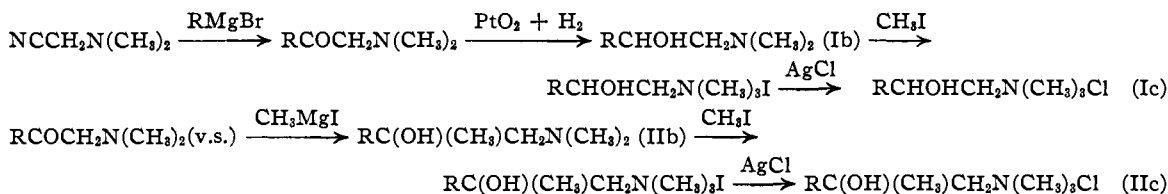
and completion of that described in Part I.² The amines have the same structure as in the previous work but possess, in addition, a β -hydroxy group. As before, the primary, secondary, tertiary and quaternary compounds were

Secondary amines are denoted by "a," tertiary by "b," and quaternary salts by "c." The primary and secondary hydroxyethylamines and hydroxypropylamines (I, Ia, II, IIa) were prepared by the following series of reactions:



(1) This work is part of a joint research being carried out in collaboration with a pharmacological group at the above laboratories.
(2) Baltzly and Buck, *THIS JOURNAL*, **62**, 161 (1940).

The corresponding tertiary amines and quaternary salts were prepared as follows:



The primary amine of the third (hydroxyisopropylamine) series (III) was prepared by Hartung's³ method, by the reduction of α -isonitroso-2,5-dimethoxypropiofenone. The secondary amine (IIIa) and the tertiary amine (IIIb) were prepared, by a method similar to that of Hyde, Browning and Adams,⁴ from α -bromo-2,5-dimethoxypropiofenone. From the tertiary amine, the quaternary chloride was prepared, via the methiodide.

It is assumed, pending further investigation, that the hydroxyisopropylamine group (III, IIIa, IIIb, IIIc) has the ephedrine, rather than the ψ -ephedrine, configuration. The relatively high melting points and the methods of preparation support this view.

Experimental

β -(2,5-Dimethoxyphenyl)-hydracrylic Hydrazide.—2,5-Dimethoxybenzaldehyde and ethyl bromoacetate were condensed by the Reformatsky method^{5,6} to give ethyl β -(2,5-dimethoxyphenyl)-hydracrylate. This ester, obtained in 80% yield, is a viscous yellow oil, b. p. 164–167° (1.0 mm.). The ester was converted into the hydrazide, which, crystallized from alcohol-benzene mixture, formed glossy needles melting at 161.5°.

Anal. Calcd. for $\text{C}_{11}\text{H}_{16}\text{O}_4\text{N}_2$: C, 54.97; H, 6.72. Found: C, 55.19; H, 6.80.

5-(2,5-Dimethoxyphenyl)-oxazolidone-2.—Prepared by the Curtius⁷ rearrangement from the hydrazide (v. s.) this crystallizes from benzene in colorless needles, m. p. 107°.

Anal. Calcd. for $\text{C}_{11}\text{H}_{14}\text{O}_4\text{N}$: C, 59.17; H, 5.87. Found: C, 59.38; H, 5.80.

β -(2,5-Dimethoxyphenyl)- β -hydroxyethylamine Hydrochloride (I).—Cleavage of the preceding oxazolidone⁷ by cold concd. hydrochloric acid gave the desired amine hydrochloride. It forms fine colorless needles melting at 158.5°, and is very soluble in water, readily soluble in hot alcohol, moderately soluble in cold alcohol, sparingly soluble in ethyl acetate, and practically insoluble in non-polar solvents. Similar solubilities are shown by the other hydroxyamine hydrochlorides of this series, which may be crystallized conveniently from absolute alcohol solution by the addition of ether or ethyl acetate or both.

Anal. Calcd. for $\text{C}_{10}\text{H}_{16}\text{O}_3\text{NCl}$: C, 51.37; H, 6.91. Found: C, 51.24; H, 6.92.

(3) Hartung, U. S. Patent 1,989,093.

(4) Hyde, Browning and Adams, *THIS JOURNAL*, **50**, 2287 (1928).

(5) Cf. Lindenbaum, *Ber.*, **50**, 1270 (1917).

(6) Cf. Woodruff and Pierson, *THIS JOURNAL*, **60**, 1075 (1938).

(7) Cf. Schroeter, German Patent 220,852.

This amine also may be prepared by the reduction of 2,5-dimethoxyphenacylamine hydrobromide, prepared from 2,5-dimethoxyphenacyl bromide and hexamethylenetetramine by the procedure of Mannich and Hahn.⁸ Hydrobromic acid was used for the hydrolysis so as to obtain a homogeneous hydrohalide. The amino ketone hydrobromide so prepared forms yellowish prisms, melting at 195° (dec.).

Anal. Calcd. for $\text{C}_{10}\text{H}_{14}\text{O}_2\text{NBr}$: C, 43.46; H, 5.11. Found: C, 43.60; H, 5.31.

2,5-Dimethoxyphenacylmethylbenzylamine.—2,5-Dimethoxyphenacyl bromide was added as a solid to twice its equivalent amount of methylbenzylamine⁹ in absolute ether, with occasional shaking. After standing overnight, the methylbenzylamine hydrobromide formed was filtered off and the amino ketone precipitated as hydrochloride by the addition of absolute alcoholic hydrogen chloride. The hydrochloride forms a light yellow oil which soon crystallizes. On recrystallization (absolute alcohol-ether) it forms nearly colorless prisms melting at 167.5°.

Anal. Calcd. for $\text{C}_{13}\text{H}_{22}\text{O}_2\text{NCl}$: C, 64.38; H, 6.61. Found: C, 64.36; H, 6.73.

β -(2,5-Dimethoxyphenyl)- β -hydroxyethylmethylamine Hydrochloride (Ia).—The foregoing amino ketone hydrochloride is readily reduced (PtO₂ and hydrogen) in alcohol solution, yielding the desired amine hydrochloride, the benzyl group being eliminated as toluene.¹⁰ The hydrochloride crystallizes in fine, felted needles, melting at 151.5°.

Anal. Calcd. for $\text{C}_{11}\text{H}_{18}\text{O}_2\text{NCl}$: C, 53.31; H, 7.33. Found: C, 53.62; H, 7.43.

β -(2,5-Dimethoxyphenyl)- β -hydroxypropylmethylamine Hydrochloride (IIa).—2,5-Dimethoxyphenacylmethylbenzylamine (v. s.), liberated from the hydrochloride, was dried, in ethereal solution, over potassium carbonate. The ether solution was added to an excess of methylmagnesium iodide. The reaction mixture was worked up as usual and the base liberated by ammonia, extracted with ether, the ether dried over potassium carbonate, and the hydrochloride precipitated by adding alcoholic carbonate chloride. The hydrochloride formed an uncrystallizable yellow sirup, probably due to a certain amount of dehydration. The sirup was reduced catalytically (reaction rather slow) and the desired amine hydrochloride isolated from the solution. It forms silky needles, melting at 158–159°.

(8) Mannich and Hahn, *Ber.*, **44**, 1542 (1911).

(9) Prepared by catalytic reduction of benzylidenemethylamine. Zauschirm, *Ann.*, **245**, 279 (1888); cf. Emde, *Arch. Pharm.*, **247**, 351 (1909).

(10) The reductive removal of the N-benzyl group (mentioned in British Patent 318,488) is a very useful and convenient reaction, especially when, as in the present case, the method of Hyde, Browning and Adams (*loc. cit.*) proves unmanageable. The same process might profitably be used for the secondary amine (IIa). Reductive removal of O-benzyl groups is a familiar procedure.

Anal. Calcd. for $C_{12}H_{20}O_3NCl$: C, 55.05; H, 7.71. Found: C, 55.11; H, 7.94.

β - Methyl - β - (2,5 - dimethoxyphenyl) - hydracrylic Acid.—2,5-Dimethoxyacetophenone was condensed with ethyl bromoacetate (zinc-copper alloy); after the usual washings, saponification and acidification gave the hydroxy acid, which crystallizes from benzene-petroleum ether in platelets, melting at 121–122°.

Anal. Calcd. for $C_{12}H_{16}O_5$: C, 59.98; H, 6.72. Found: C, 60.17; H, 6.77.

β - Methyl - β - (2,5 - dimethoxyphenyl) - hydracrylic Hydrazide.—The preparation of this hydrazide gave considerable trouble, due to the tendency of the compounds in this series to dehydrate when distilled or subjected to acids. Finally it was found that a 27% yield of hydrazide (reckoned on the starting ketone) could be obtained by treating the crude washed, but not distilled, ester from the Reformatsky reaction with hydrazine hydrate in alcohol. Nothing isolable was obtained when the ester was distilled or prepared from the acid. After considerable purification, the hydrazide was obtained as needles, m. p. 112°.

Anal. Calcd. for $C_{12}H_{18}O_4N_2$: C, 56.66; H, 7.14. Found: C, 56.83; H, 7.24.

5 - Methyl - 5 - (2,5 - dimethoxyphenyl) - oxazolidone-2.—The oxazolidone was obtained in excellent yield from the hydrazide, by the Curtius rearrangement.⁷ It crystallizes from benzene in colorless prisms, melting at 159°.

Anal. Calcd. for $C_{12}H_{18}O_4N$: C, 60.74; H, 6.38. Found: C, 60.91; H, 6.66.

β - (2,5 - Dimethoxyphenyl) - β - hydroxypropylamine Hydrochloride (II).—The preceding oxazolidone was dissolved in concd. hydrochloric acid. After the evolution of carbon dioxide had ceased, excess acid was removed under reduced pressure at around room temperature. The yield of the amine salt is practically quantitative, but if higher temperatures are used other products make their appearance. The hydroxyamine salt, after recrystallization, forms flat-sided prisms, melting at 174°.

Anal. Calcd. for $C_{11}H_{18}O_3NCl$: C, 53.31; H, 7.33. Found: C, 53.57; H, 7.39.

2,5 - Dimethoxyphenacyldimethylamine.—Bromohydroquinone dimethyl ether¹¹ was converted into the Grignard reagent and dimethylaminoacetonitrile¹² added. The reaction mixture was decomposed with acid, the ether layer separated, and the base liberated by ammonia. After extraction with ether, the extract was washed, dried, and treated with alcoholic hydrogen chloride. The hydrochloride so obtained, after recrystallization, forms nearly colorless prisms, m. p. 171° (dec.).

Anal. Calcd. for $C_{12}H_{18}O_3NCl$: C, 55.48; H, 6.99. Found: C, 55.76; H, 7.17.

β - (2,5 - Dimethoxyphenyl) - β - hydroxyethyl dimethylamine Hydrochloride (Ib).—This hydrochloride is readily obtained by the reduction (PtO_2 and hydrogen), in alcohol solution, of the above amino ketone hydrochloride. When recrystallized, it forms fine, colorless, needle-like prisms melting at 155°.

(11) Noelting and Werner, *Ber.*, **23**, 3246 (1890).

(12) Von Braun, *ibid.*, **40**, 3933 (1907).

Anal. Calcd. for $C_{12}H_{20}O_3NCl$: C, 55.05; H, 7.71. Found: C, 55.28; H, 7.98.

β - (2,5 - Dimethoxyphenyl) - β - hydroxyethyltrimethylammonium Chloride (Ic).—The methiodide of the foregoing tertiary amine was prepared in the usual way, and converted into the chloride by silver chloride. It forms slender prisms, melting at 185–186°.

Anal. Calcd. for $C_{13}H_{22}O_3NCl$: C, 56.60; H, 8.05. Found: C, 56.33; H, 7.99.

β - (2,5 - Dimethoxyphenyl) - β - hydroxypropyldimethylamine Hydrochloride (IIb).—This tertiary amine was prepared by the action of methylmagnesium iodide on 2,5-dimethoxyphenacyldimethylamine (v. s.) and was converted into the hydrochloride by alcoholic hydrogen chloride. It forms stout, almost colorless rhombs, melting at 176.5°.

Anal. Calcd. for $C_{13}H_{22}O_3NCl$: C, 56.60; H, 8.05. Found: C, 56.58; H, 7.76.

β - (2,5 - Dimethoxyphenyl) - β - hydroxypropyltrimethylammonium Chloride (IIc).—The quaternary salt was prepared from the preceding tertiary amine via the methiodide and silver chloride. After recrystallization it forms stout, colorless prisms, melting at 213.5°.

Anal. Calcd. for $C_{14}H_{24}O_3NCl$: C, 57.99; H, 8.33. Found: C, 58.06; H, 8.63.

α - Isonitroso - 2,5 - dimethoxypropiofenone.—2,5-Dimethoxypropiofenone¹³ was converted into the isonitroso compound by Hartung's⁸ method. After recrystallization from benzene-heptane mixture, the compound forms pale yellow leaflets, melting at 97–98°.

Anal. Calcd. for $C_{11}H_{18}O_4N$: C, 59.17; H, 5.87. Found: C, 59.25; H, 5.86.

β - (2,5 - Dimethoxyphenyl) - β - hydroxyisopropylamine Hydrochloride (III).—The above isonitroso compound was readily reduced by palladized charcoal in absolute alcohol containing hydrogen chloride. The product crystallizes in columnar prisms, melting at 175–176° (dec.).

Anal. Calcd. for $C_{11}H_{18}O_3NCl$: C, 53.31; H, 7.33. Found: C, 53.42; H, 7.34.

2,5 - Dimethoxy - α - methylaminopropiofenone.—2,5-Dimethoxy- α -bromopropiofenone was prepared by bromination of 2,5-dimethoxypropiofenone in chloroform solution (*cf.* 5). The bromo ketone was added to a large excess of methylamine in absolute ether. After standing overnight at 0°, the precipitated methylamine hydrobromide was filtered off, and the filtrate evaporated to dryness under reduced pressure, at room temperature or below. The residue was dissolved in ether and absolute alcoholic hydrogen chloride added. The hydrochloride still contains some methylamine salts, which are removed by repeated recrystallization. The pure amino ketone hydrochloride forms colorless prisms melting at 172–173° (dec.).

Anal. Calcd. for $C_{12}H_{18}O_3NCl$: C, 55.48; H, 6.99. Found: C, 55.48; H, 7.22.

β - (2,5 - Dimethoxyphenyl) - β - hydroxyisopropylmethylamine Hydrochloride (IIIa).—Catalytic reduction of the foregoing amino ketone hydrochloride yielded the

(13) Johnson and Hodge, *This Journal*, **25**, 1014 (1913).

desired hydroxyamine hydrochloride, which crystallizes in fine, colorless needles, m. p. 170°.

Anal. Calcd. for $C_{12}H_{20}O_3NCl$: C, 55.05; H, 7.71. Found: C, 55.33; H, 7.91.

2,5 - Dimethoxy - α - dimethylaminopropiophenone.—The method of Hyde, Browning and Adams⁴ gave very good results in this case. It was necessary, in order to remove dimethylamine completely, to wash the ether solution of the base with water. The tertiary amino ketones of this type are reasonably stable. The hydrochloride crystallizes in slender, practically colorless prisms, melting at 154–156° (dec.).

Anal. Calcd. for $C_{13}H_{20}O_3NCl$: C, 57.00; H, 7.37. Found: C, 56.89; H, 7.57.

β - (2,5 - Dimethoxyphenyl) - β - hydroxyisopropylidimethylamine Hydrochloride (IIIb).—Catalytic reduction of the preceding α -dimethylaminopropiophenone gave the desired compound. The hydrochloride crystallizes in fine, colorless needles, melting at 198° (dec.).

Anal. Calcd. for $C_{13}H_{22}O_3NCl$: C, 56.60; H, 8.05. Found: C, 56.52; H, 8.25.

β - (2,5 - Dimethoxyphenyl) - β - hydroxyisopropyltrimethylammonium Chloride (IIIc).—The methiodide, prepared from the above tertiary base, was converted into

the chloride by the silver chloride method. After recrystallization, the chloride forms fine, colorless, felted needles, melting at 221–223° (dec.).

Anal. Calcd. for $C_{14}H_{24}O_3NCl$: C, 57.99; H, 8.33. Found: C, 58.08; H, 8.62.

Melting points are all corrected. Those for the hydrochlorides were determined on material dried *in vacuo* at 100° for several hours. The authors wish to make the same acknowledgments to Mr. W. S. Ide and Dr. C. W. Ferry as were made in Part I.

Summary

The projected series of 2,5-dimethoxyphenyl-alkyl- and alkanolamines has been completed by the preparation of the alkanolamines, β -(2,5-dimethoxyphenyl)- β -hydroxyethylamine hydrochloride, β -(2,5-dimethoxyphenyl)- β -hydroxypropylamine hydrochloride, and β -(2,5-dimethoxyphenyl)- β -hydroxyisopropylamine hydrochloride, together with the corresponding secondary and tertiary amine hydrochlorides and the quaternary chlorides.

TUCKAHOE, NEW YORK

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[CONTRIBUTION FROM THE SYPHILIS DIVISION OF THE DEPARTMENT OF MEDICINE, JOHNS HOPKINS MEDICAL SCHOOL, BALTIMORE, MARYLAND, AND THE UNITED STATES PUBLIC HEALTH SERVICE, WASHINGTON, D. C.]

A Modified Bart Reaction

By G. O. DOAK

Indirect methods for preparing sulfonic and sulfamido substituted arsonic acids are tedious and give low yields. Although Oneto¹ recently has succeeded in preparing *p*-sulfophenyl- and *p*-sulfamidophenylarsonic acids by means of the Bart reaction, in this Laboratory this method failed with the corresponding *m*- and *o*- compounds. The alcoholic Bart reaction described by Scheller² has received but scant attention in the literature.^{3a,b} When this modification proved successful in this Laboratory with both *p*- and *m*-sulfamidophenylarsonic acids, it was extended to include other arsonic acids, difficult to prepare by the customary Bart procedure. It was found that while anilines substituted in the ring by nitro, carboxy, or sulfamido groups gave excellent results, the reaction failed with 2,6- and 3,5-dimethylanilines. It also failed with metanilic acid. When applicable, the method gave higher

yields, was less time consuming, and gave a product more easily purified than the customary Bart procedure.

Experimental Part

The amine, 0.1 mole in 250 cc. absolute alcohol with 10 g. of sulfuric acid and 28 g. arsenous chloride cooled to 0°, was diazotized with a saturated aqueous solution of the calculated amount of sodium nitrite, using starch-iodide paper to protect the end-point. Then, and not before, 1 g. of cuprous bromide⁴ was added, the mixture thoroughly stirred, warmed to 60° until no more nitrogen was evolved, and then distilled with steam. The separated arsonic acid was recrystallized.

***p*-Sulfamidophenylarsonic Acid.**—This compound was obtained in 57% yield from sulfanilamide, crystallizing from water in small needles.

Anal. Calcd. for $C_6H_8NO_5SAs$: As, 26.7. Found: As, 26.8.

***m*-Sulfamidophenylarsonic Acid.**—*m*-Aminobenzenesulfonamide, 0.2 mole, gave 32.7 g. (58% yield) of *m*-sulfamidophenylarsonic acid, which crystallized from water in warty aggregates. When placed in a bath at 215° and the temperature slowly raised, it melted at 218–219°, but

(1) Oneto, *THIS JOURNAL*, **60**, 2058 (1938); **61**, 2105 (1939).

(2) Scheller, French Patent 624,028, *Chem. Zentr.*, **98**, II, 229 (1927).

(3) (a) Steinkopf, *J. prakt. Chem.*, **128**, 68 (1930); (b) Cherline and Iacoubovitch, *Bull. soc. chim.*, [5] **1**, 1367 (1934).

(4) Cuprous bromide was found to give slightly better yields than the cuprous chloride as recommended by Scheller.