

TABLE I

Compound ^a	M. p., °C. (corr.)	Formula	Nitrogen, %	
			Calcd.	Found ^b
2-N ⁴ -Acetylsulfanilamidopyridine	226-227	C ₁₃ H ₁₃ N ₃ O ₃ S	14.42	14.60
2-Sulfanilamidopyridine	190-191	C ₁₁ H ₁₁ N ₃ O ₂ S	16.86	16.68
3-N ⁴ -Acetylsulfanilamidopyridine	272-275 dec.	C ₁₃ H ₁₃ N ₃ O ₃ S	14.42	14.14
3-Sulfanilamidopyridine	248-251 dec.	C ₁₁ H ₁₁ N ₃ O ₂ S	16.86	16.61
5-N ⁴ -Acetylsulfanilamido-2-acetylaminopyridine	288-291 dec.	C ₁₅ H ₁₅ N ₄ O ₄ S	16.09	15.81
5-Sulfanilamido-2-aminopyridine	210-211	C ₁₁ H ₁₂ N ₄ O ₂ S	21.20	20.94
3-N ⁴ -Acetylsulfanilamidoquinoline	250-253 dec.	C ₁₇ H ₁₅ N ₃ O ₃ S	12.31	12.23
3-Sulfanilamidoquinoline	185-186 dec.	C ₁₅ H ₁₃ N ₃ O ₂ S	14.04	14.20
5-N ⁴ -Acetylsulfanilamidoquinoline ^c	256-258	C ₁₇ H ₁₅ N ₃ O ₃ S	12.31	12.52
5-Sulfanilamidoquinoline ^c	228-230	C ₁₅ H ₁₃ N ₃ O ₂ S	14.04	14.15
6-N ⁴ -Acetylsulfanilamidoquinoline ^c	285-287	C ₁₇ H ₁₅ N ₃ O ₃ S	12.31	12.12
6-N ⁴ -Acetylsulfanilamidoquinoline hydrochloride	238-240	C ₁₇ H ₁₆ ClN ₃ O ₃ S	11.12	11.06
6-Sulfanilamidoquinoline ^c	202-204	C ₁₅ H ₁₃ N ₃ O ₂ S	14.04	13.86
8-N ⁴ -Acetylsulfanilamidoquinoline ^{c,d}	193-194	C ₁₇ H ₁₅ N ₃ O ₃ S	12.31	12.02
8-Sulfanilamidoquinoline ^{c,d}	194-195	C ₁₅ H ₁₃ N ₃ O ₂ S	14.04	13.87

^a Nomenclature according to Crossley, Northey and Hultquist, *THIS JOURNAL*, **60**, 2217 (1938). ^b Dumas. ^c Previously prepared by Bobranski.² ^d Previously prepared by A. D. Choudhury, *et al.*, *J. Ind. Chem. Soc.*, **14**, 733 (1937).

chloric acid. After refluxing for twenty minutes, the reaction mixture was diluted with water and made basic with ammonium hydroxide. It was recrystallized from ethanol; yield, 0.67 g. (75%).

5-N⁴-Acetylsulfanilamido-2-acetylaminopyridine.—Using the same procedure as above, 3.0 g. of 5-amino-2-acetylaminopyridine and 4.0 g. of acetyl sulfanilyl chloride gave 6.0 g. (94%) of crude 5-N⁴-acetylsulfanilamido-2-acetylaminopyridine. This was converted to 5-sulfanilamido-2-aminopyridine by the same procedure used below for 3-sulfanilamidoquinoline.

3-Sulfanilamidoquinoline.—3-Aminoquinoline (2.5 g.) and acetylsulfanilyl chloride (4.0 g.) were dissolved in 30 cc. of dry pyridine. After heating for two hours on the steam-bath, the reaction mixture was poured into 400 cc. of cold water. The product separated as a white crystalline mass weighing 5.4 g. when dry. For analysis a small

amount was washed successively with water and ethanol and dried at 100°. One gram of the crude acetyl compound was boiled for a half hour with 25 cc. of 12% hydrochloric acid. Upon cooling and neutralizing with ammonium hydroxide, the sulfonamide was obtained; yield 0.8 g. (91%). It was recrystallized from ethanol.

Summary

An improved method of preparation of the 5, 7, and 8-aminoquinolines as well as the preparation of certain sulfanilamido derivatives of pyridine and quinoline amines is described.

The results obtained by Bobranski² are confirmed.

NEW YORK, N. Y.

RECEIVED OCTOBER 31, 1939

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

Amines Related to 2,5-Dimethoxyphenethylamine.¹ I

By RICHARD BALTZLY AND JOHANNES S. BUCK

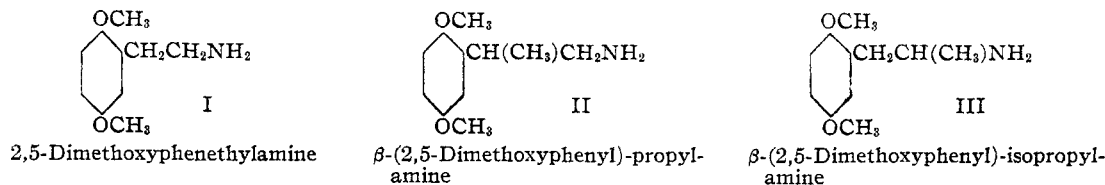
Preliminary pharmacological work has indicated that some amines containing the 2,5-dimethoxyphenyl group show activity comparable with that of similar phenolic amines, and also that they probably will be active orally. It therefore became important to prepare, for pharmacological examination, as complete a series as possible of amines (as hydrochlorides) containing the 2,5-dimethoxyphenethyl grouping, the optimal C-C-N side chain being present in all cases.

(1) This work is part of a joint research being carried out in collaboration with a pharmacological group at the above laboratories.

Six series of 2,5-dimethoxyphenethylamines were prepared, in each series the primary, secondary, tertiary and quaternary compounds being made. Included in the series are the analogs of practically all the known pharmacologically active amines containing the phenethyl group (that is, containing the C-C-N side chain).

The present paper deals with the preparation and properties of the amines with no hydroxyl group in the side chain. One hydrochloride has been described previously.

The formulas of the primary amines are



The syntheses of the first primary amine (I) and of the corresponding secondary amine have been described.² The starting material for the β -phenylpropylamine (II) was obtained by a Reformatzky reaction (2,5-dimethoxyacetophenone and ethyl bromoacetate). The remaining stages of the synthesis paralleled those of the first amine. The 2,5-dimethoxy- α -methylhydrocinnamic acid required for the third, β -phenylisopropylamine, was obtained by two methods, (a) by condensation of 2,5-dimethoxybenzaldehyde with ethyl α -bromopropionate, followed by reduction, and (b) by condensation of 2,5-dimethoxybenzaldehyde with diethyl malonate, followed by reduction, methylation, saponification and decarboxylation. Inaccessibility of the starting aldehyde deterred the authors from using the Claisen condensation with ethyl propionate, as this condensation in similar cases is wasteful and troublesome. The method of Bogert and Davidson³ also was avoided, as in the authors' hands it gave discouraging results with dialkoxybenzaldehydes.

Secondary amines were obtained from the primary amines by the method of Decker.^{2,4} The tertiary amines were prepared from the primary (or, better, secondary) amines by an adaptation of the Eschweiler reaction. Quaternary chlorides were obtained by the action of silver chloride on the methiodides of the tertiary amines.

Experimental

2,5-Dimethoxybenzaldehyde (gentisic aldehyde dimethyl ether) was prepared by the Gattermann method.⁵ Amine hydrochlorides were all recrystallized, until pure, from absolute alcohol-ether mixture, sometimes with the addition of ethyl acetate. The solubilities of the hydrochlorides are all very similar, the compounds being readily soluble in water, alcohol, and methanol, and practically insoluble in less polar solvents. The melting points were determined on material dried for several hours at 100° *in vacuo*. All melting points are corrected.

2,5-Dimethoxyphenethylamine Hydrochloride.—The amine has been described previously.² The hydrochloride, made by the addition of absolute alcoholic hydrogen chlo-

ride to an ether solution of the amine, forms lustrous leaflets, melting at 139°.

Anal. Calcd. for $C_{10}H_{16}O_2NCl$: C, 55.15; H, 7.41. Found: C, 55.19; H, 7.37.

2,5-Dimethoxyphenethylmethylamine Hydrochloride.—This has been described previously.²

2,5-Dimethoxyphenethyltrimethylammonium Chloride.—The above primary amine was converted into the tertiary amine by a modified Eschweiler reaction.^{6,7,8} Nine grams of primary amine, 40 cc. of 36% formaldehyde solution and 0.1 cc. formic acid were heated for three hours at 125° in a sealed tube. The tertiary amine, b. p. 159° (23 mm.), was isolated in good yield and converted into the hydrochloride by adding alcoholic hydrogen chloride to the ether solution. The hydrochloride forms small, colorless plates, melting at 148°, and is rather hygroscopic.

Anal. Calcd. for $C_{12}H_{20}O_2NCl$: C, 58.63; H, 8.21. Found: C, 58.79; H, 8.25.

2,5-Dimethoxyphenethyltrimethylammonium Chloride.—The foregoing tertiary amine was converted, in ether solution, into the methiodide, which was filtered off, dissolved in water, and allowed to stand with silver chloride. After filtration, evaporation *in vacuo* and recrystallization, the chloride forms very hygroscopic lustrous plates, melting at 184–185°.

Anal. Calcd. for $C_{13}H_{22}O_2NCl$: C, 60.06; H, 8.54. Found: C, 60.28; H, 8.79.

2,5-Dimethoxy- β -methylcinnamic Acid.—2,5-Dimethoxyacetophenone and ethyl bromoacetate were condensed by the Reformatzky method, using a zinc-copper alloy. The resulting β -hydroxybutyric ester was dehydrated by phosphorus oxychloride to the β -methylcinnamic ester,^{9,10} which was distilled, b. p. 140–143° (1.0 mm.). Saponification yielded the acid which crystallized from aqueous alcohol in slender prisms, melting at 113.5°.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.83; H, 6.35. Found: C, 64.82; H, 6.69.

β -(2,5-Dimethoxyphenyl)-butyric Acid.—The ester described above was reduced (platinum oxide and hydrogen) and then saponified. The resulting acid forms irregular crystals from ether-petroleum ether, melting at 79°.

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.27; H, 7.20. Found: C, 64.62; H, 7.40.

β -(2,5-Dimethoxyphenyl)-butyramide.—The foregoing acid was heated in a stream of ammonia, at 220–230°, for two hours. Recrystallized from benzene the amide forms columnar prisms melting at 121°.

(6) Cf. Decker and Becker, *ibid.*, **45**, 2404 (1912); *Ann.*, **395**, 342 (1913).

(7) For an alternative method see Buck, Baltzly and Ide, *This Journal*, **60**, 1789 (1938).

(8) The adaptation of Clarke and Gillespie, *ibid.*, **55**, 4571 (1933), appears to give some substitution with certain dimethoxy derivatives.

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

(10) Cf. Woodruff and Pierson, *This Journal*, **60**, 1075 (1938).

(2) Buck, *This Journal*, **54**, 3661 (1932).

(3) Bogert and Davidson, *ibid.*, **54**, 334 (1932).

(4) Decker and Becker, *Ann.*, **395**, 362 (1913).

(5) Kauffmann and Burr, *Ber.*, **40**, 2352 (1907).

Anal. Calcd. for $C_{12}H_{17}O_2N$: C, 64.54; H, 7.68. Found: C, 64.76; H, 7.88.

β - (2,5 - Dimethoxyphenyl) - propylamine Hydrochloride.—The amine was obtained from the amide, in 45% yield, by the usual Hofmann procedure, using sodium hypochlorite. It boiled at 114° (1.0 mm.) and was converted into the hydrochloride by adding alcoholic hydrogen chloride to the ether solution. After recrystallization the hydrochloride forms fine, colorless, felted needles melting at 149 – 150° .

Anal. Calcd. for $C_{11}H_{15}O_2NCl$: C, 56.99; H, 7.83. Found: C, 57.11; H, 8.03.

β - (2,5 - Dimethoxyphenyl) - propylmethylamine Hydrochloride.—The above primary amine was converted into the hydriodide of the secondary amine (m. p. 131°) by the Decker method (v. s.). The base, liberated from the hydriodide, was converted directly into the hydrochloride, which crystallizes in fine, colorless needles, melting at 146° .

Anal. Calcd. for $C_{12}H_{19}O_2NCl$: C, 58.63; H, 8.21. Found: C, 58.82; H, 8.07.

β - (2,5 - Dimethoxyphenyl) - propyldimethylamine Hydrochloride.—The tertiary amine may be prepared from the primary amine (or, better, from the secondary amine) by the Eschweiler methylation (v. s.). The amine was purified as the hydrochloride, which forms slender prisms, melting at 182 – 183° .

Anal. Calcd. for $C_{13}H_{21}O_2NCl$: C, 60.06; H, 8.54. Found: C, 60.33; H, 8.60.

β - (2,5 - Dimethoxyphenyl) - propyltrimethylammonium Chloride.— β - (2,5 - Dimethoxyphenyl) - propyldimethylamine (above) was treated with methyl iodide in ether solution to give the quaternary iodide (*i. e.*, the methiodide). Silver chloride converted the iodide (m. p. 139°) into the required chloride, which crystallizes in hygroscopic slender prisms. It forms a stable monohydrate, melting at 92° . After thorough drying, the chloride melts at 159 – 161° with discoloration.

Anal. Calcd. for $C_{14}H_{23}O_2NCl$: C, 61.37; H, 8.84. Found: C, 61.48; H, 9.18.

Diethyl 2,5-Dimethoxybenzylmalonate.—Diethyl malonate was condensed with 2,5-dimethoxybenzaldehyde in the presence of piperidine.¹¹ Saponification of a portion yielded an acid crystallizing in faint yellow leaflets from alcohol-benzene mixture. The acid melts at 183° (dec.). Kauffmann and Burr⁶ prepared this acid by another method and gave the m. p. as 188° (dec.).

Anal. Calcd. for $C_{12}H_{12}O_6$: C, 57.12; H, 4.80. Found: C, 57.10; H, 5.13.

Diethyl 2,5-Dimethoxybenzylmalonate.—Catalytic reduction of the preceding ester yielded a nearly colorless oil, which was identified by saponifying a portion. The acid obtained, recrystallized from benzene, gave rhombic prisms melting at 156.5° (dec.).

Anal. Calcd. for $C_{12}H_{14}O_6$: C, 56.68; H, 5.55. Found: C, 57.03; H, 5.43.

2,5-Dimethoxybenzylmethylmalonic Acid.—The foregoing ester was methylated in the usual way (methyl iodide and sodium ethylate) and the product saponified. The re-

sulting acid after crystallization from hexane forms fine, colorless crystals, melting at 143° (dec.).

Anal. Calcd. for $C_{13}H_{16}O_6$: C, 58.19; H, 6.02. Found: C, 58.35; H, 5.87.

α -Methyl-2,5-dimethoxyhydrocinnamic Acid.—This was obtained by heating the corresponding malonic acid (above) at 150° . After crystallization from ether-hexane mixture it forms a cream-colored powder melting at 59.5° .

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.27; H, 7.20. Found: C, 64.39; H, 7.14.

α -Methyl-2,5-dimethoxyhydrocinnamide.—The amide was obtained by heating the corresponding hydrocinnamic acid (above) in a stream of ammonia at 220 – 230° for two hours. Recrystallized from benzene it forms a finely crystalline powder melting at 99° .

Anal. Calcd. for $C_{12}H_{17}O_2N$: C, 64.54; H, 7.68. Found: C, 64.58; H, 7.91.

The same amide was prepared, in poor yield by condensing ethyl bromopropionate with 2,5-dimethoxybenzaldehyde (Reformatsky method with ordinary zinc), dehydrating the resulting ester with phosphorus oxychloride, reducing the unsaturated ester catalytically, and then saponifying, and, finally, amidating the acid produced. The dehydration with phosphorus oxychloride or the subsequent distillation resulted in extensive polymerization, the yield of unsaturated ester being only about 20%.

β -(2,5-Dimethoxyphenyl)-isopropylamine Hydrochloride.—The Hofmann reaction on the foregoing amide was carried out as usual except that the amide was added dissolved in dioxane to the hypochlorite solution.¹² The yield of distilled amine (b. p. 137 – 140° (3 mm.)) was 70%. The hydrochloride, prepared in the usual way (v. s.), crystallizes in fine prisms melting at 117.5° .

Anal. Calcd. for $C_{11}H_{15}O_2NCl$: C, 56.99; H, 7.83. Found: C, 57.25; H, 7.89.

The same hydrochloride was also prepared, in very poor yield, by the catalytic reduction, in strongly acid alcohol, of 2,5-dimethoxynitropropenylbenzene.¹³ The compound was isolated via the hydriodide, which forms prismatic needles, m. p. 138° .

Anal. Calcd. for $C_{11}H_{15}O_2NI$: C, 40.86; H, 5.62. Found: C, 40.94; H, 5.94.

β - (2,5 - Dimethoxyphenyl) - isopropylmethylamine Hydrochloride.—The primary amine (v. s.) was readily converted into the secondary amine by the Decker method.⁶ The hydrochloride crystallizes in needle prisms, melting at 98.5° .

Anal. Calcd. for $C_{12}H_{19}O_2NCl$: C, 58.63; H, 8.21. Found: C, 58.52; H, 8.46.

β - (2,5 - Dimethoxyphenyl) - isopropyldimethylamine Hydrochloride.—The tertiary amine, b. p. 118 – 121° (0.5 mm.), was obtained by the Eschweiler methylation (v. s.) of the primary amine. The hydrochloride forms needles melting at 138 – 139° .

(12) The use of dioxane to dissolve amides (using about one-third of the volume of the hypochlorite solution) greatly improves matters in cases where the amide is of low solubility. Cf. Woodruff and Conger, *THIS JOURNAL*, **60**, 465 (1938).

(13) Kauffmann, *Ber.*, **50**, 630 (1917).

(11) Cf. Knoevenagel, *Ber.*, **31**, 2585 (1898).

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.

TUCKAHOE, NEW YORK

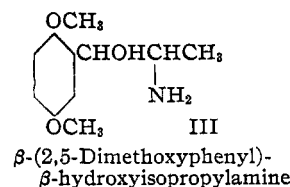
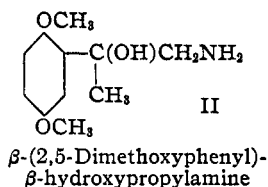
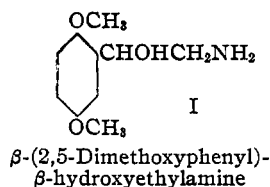
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Amines Related to 2,5-Dimethoxyphenethylamine.¹ II

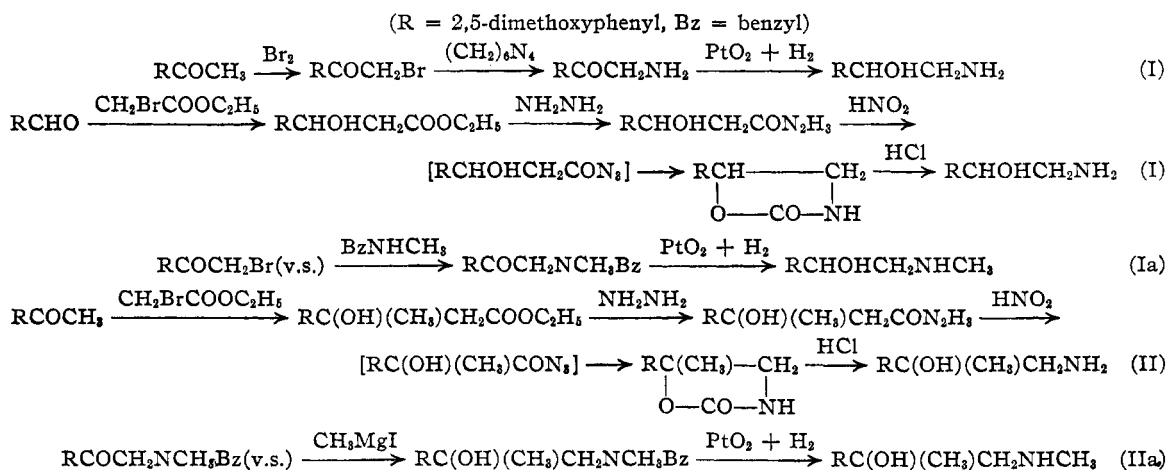
BY RICHARD BALTZLY AND JOHANNES S. BUCK

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: