

glacial acetic acid and hydrogenated at three atmospheres pressure in a Parr apparatus. Three 0.5-g. portions of Adams platinum oxide catalyst were added during the 72 hours needed to complete the hydrogenation. The solvent was removed and the oil treated with excess alkali and extracted with ether, and distilled; b.p. 60–77° at 0.25 mm., n_D^{20} 1.4640, yield 75%.

The mixture of diastereoisomers was converted to the hydrochloride in ethanol and ether. On chilling a crystalline product was obtained, m.p. 129–140°. This was recrystallized several times by dissolving in isopropyl alcohol, adding ethyl acetate and allowing to stand at room temperature, to yield white crystals, m.p. 156.5–157.5°, having the analysis indicated in Table I.

The filtrate from the high melting diastereoisomer above along with filtrates obtained in its recrystallization yielded a solid which was recrystallized from a mixture of isopropyl alcohol, ethyl acetate and ether to give a product, m.p. 100–106°. Several recrystallizations from ethyl acetate gave white crystals, m.p. 114–115°, having the analysis indicated in Table I.

Acknowledgment.—The author is grateful to B. D. Aspergren for preparing three of these compounds²⁴ and to W. H. Maroney for technical assistance.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

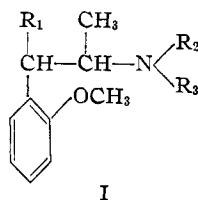
Physiologically Active Amines. Tertiary Amines and Quaternary Salts Related to β -(*o*-Methoxyphenyl)-isopropyl-N-methylamine

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Eighteen tertiary amines or quaternary salts related to β -(*o*-methoxyphenyl)-isopropyl-N-methylamine have been prepared. Some of these possess notable bronchodilator and local anesthetic activity.

The present paper reports a continuation of our study¹ of amines related to β -(*o*-methoxyphenyl)-isopropyl-N-methylamine. Included is a group of tertiary amines of the general formula I, wherein R_1 is either H or OH, R_2 is alkyl or aralkyl and R_3



is substituted alkyl or aralkyl. Two of these were converted to the corresponding quaternary salts. In several cases the methoxy group was located in the para position or omitted.

The compounds in which R_1 is H were prepared from the corresponding secondary amines by alkylation with R_3 Cl or ethylene oxide in the presence of sodium carbonate with or without solvent. Yields were generally good when R_2 was methyl but dropped noticeably when R_2 was isopropyl. The series in which R_1 is OH was prepared by alkylation of benzylmethylamine with the requisite α -bromopropiophenones, and reduction of the resulting aminopropiophenones either catalytically or with lithium aluminum hydride. The quaternary salts were prepared from the corresponding secondary or tertiary amines using excess methyl iodide in the presence of sodium carbonate.

In view of the high order of bronchodilator and local anesthetic activities of bis- $[\beta$ -(*o*-methoxyphenyl)-isopropyl]-amine¹ (II), synthesis of some related tertiary amines was of particular interest. In an attempt to increase the solubility of II it was alkylated to form the corresponding β -hydroxyethylamine. The latter was then converted to

bis- $[\beta$ -(*o*-methoxyphenyl)-isopropyl]-N- β -chloroethylamine hydrochloride whose adrenolytic activity was compared with that of Dibenamine and β -(*p*-methoxyphenyl)-isopropyl-N-benzyl-N- β -chloroethylamine hydrochloride.² When II was heated in benzene under reflux with sodamide for 4 hours, β -chloroethyl *p*-toluenesulfonate added and heating continued for an additional 4 hours only starting material was recovered. When the secondary amine in alcohol was treated with ethylene oxide, even at the boiling point of the mixture, only small amounts of the hydroxyethylamine were obtained which were difficult to separate from the starting material. Similar results were obtained using ethylenechlorohydrin at 80–100°, either with or without benzene as a solvent and in the presence of sodium carbonate at 135° without solvent. However, when ethylenechlorohydrin was added in excess, dropwise, to the secondary amine over a period of 6 hours the hydroxyethylamine was obtained in about 32% yield. The yield was increased to 50% when the amine, ethylenechlorohydrin and sodium carbonate were mixed and rapidly heated to 160°. On treatment of the hydroxyethylamine with thionyl chloride in benzene, there was obtained the desired bis- $[\beta$ -(*o*-methoxyphenyl)-isopropyl]-N- β -chloroethylamine hydrochloride.

A number of these compounds are potent bronchodilators and some also possess considerable local anesthetic activity.³ The chloroethylamine III has a low order of adrenolytic activity.

Acknowledgment.—The authors are grateful to R. B. Howard for the preparation of two of these compounds.

(2) J. F. Kerwin, T. F. Herdegen, R. Y. Heisler and G. E. Ulliot, *ibid.*, **72**, 3983 (1950).

(3) These compounds were studied pharmacologically under the direction of M. J. Vander Brook, B. E. Graham and W. B. Bass of our Department of Pharmacology, and will be reported by them.

(1) For the previous paper in this series, see R. V. Heinzelman, *THIS JOURNAL*, **75**, 921 (1953).

form, both products melted at 182–184°. ^d The picrate melts at 145–147°. *Anal.* Calcd. for $C_{26}H_{30}N_4O_8$: C, 59.32; H, 5.74; N, 10.64. Found: C, 59.58; H, 5.64; N, 10.74. ^e n_D^{25} 1.5455. ^f For the picrate. The hydrochloride, m.p. 106–107°, did not analyze well. Sulfate, m.p. 178–180°. *Anal.* Calcd. for $C_{21}H_{21}NO_6S$: C, 59.27; H, 7.35; N, 3.30; S, 7.54. Found: C, 59.41; H, 7.17; N, 3.44; S, 7.69. ^g The free base has a n_D^{20} 1.5529. The picrate melts at 127–128°. *Anal.* Calcd. for $C_{24}H_{28}N_4O_8S$: C, 54.12; H, 5.30; N, 10.52. Found: C, 54.03; H, 5.03; N, 6.09. ^h The free base is a solid, m.p. 67°. *Anal.* Calcd. for $C_{24}H_{27}NO$: N, 4.05. Found: N, 4.12. ⁱ Base melts 84–85°. *Anal.* Calcd. for $C_{22}H_{21}NO_3$: C, 73.91; H, 8.74; N, 3.91. Found: C, 74.13; H, 8.69; N, 3.96. Made from high melting diastereoisomeric secondary amine hydrochloride. ^j Calcd.: Cl, 11.02. Found: Cl, 11.21.

Experimental⁴

β -(*o*-Methoxyphenyl)-isopropyl-N-benzyl-N-methylamine.—One hundred and sixty-one grams (0.9 mole) of β -(*o*-methoxyphenyl)-isopropyl-N-methylamine base¹ and 160 g. (1.5 moles) of sodium carbonate were heated with stirring at 120° and 116 g. (0.92 mole) of benzyl chloride was added over the period of an hour. Heating was continued for an additional 2 hours during which time the temperature rose to 130°. After standing overnight the product was treated with water and stirred vigorously with benzene. The benzene layer was washed with water and extracted with aqueous 20% hydrochloric acid. Three layers were produced and the two lower layers were basified and the alkaline suspension was extracted with benzene. The benzene was washed with water and dried, and the solvent removed *in vacuo*.

The pale amber base was dissolved in 300 cc. of ethyl acetate, the solution chilled to –10° and with stirring a cold solution of 37.5 g. of hydrogen chloride in 80 cc. of isopropyl alcohol and 50 cc. of ether was added over 45 minutes. More ether (300 cc.) was then added and the suspension was kept cold and stirred for 3 hours after which the white crystals were removed by filtration. They represented 217 g., m.p. 157.5–159°. Addition of 200 cc. more ether to the filtrate yielded a second crop of 14.5 g., m.p. 157–158°, total yield 85%.

The above crystals were dissolved in 0.75 parts of boiling alcohol, the solution filtered and poured into 5 parts of ethyl acetate. When the stirred suspension had reached 15° five parts of ether was added and the slurry chilled overnight. After filtering and washing the crystals with ether the product melted at 158.5–160°, recovery 225 g., 97.5%.

β -Hydroxy- β -(*o*-methoxyphenyl)-isopropyl-N-benzyl-N-methylamine.—Twenty-four and three-tenths grams (0.1 mole) of *o*-methoxy- α -bromopropiophenone¹ was dissolved in 100 cc. of ether and with cooling 24.2 g. (0.2 mole) of benzylmethylamine was added dropwise. The solution was allowed to warm to room temperature and after standing overnight the benzylmethylamine hydrobromide was filtered off, and the ether layer dried.

Without isolating the amino compound the above ether solution was subjected to reduction by means of lithium aluminum hydride in the conventional manner.⁵ The resulting base was dissolved in ethyl acetate and ethanolic hydrogen chloride was added. The gummy hydrochloride was recrystallized from isopropyl alcohol and ether to give a product with the properties indicated in Table I.

β -(*o*-Methoxyphenyl)-isopropyl-N-dimethylamine Methiodide.—Seventeen and nine-tenths grams (0.1 mole) of β -(*o*-methoxyphenyl)-isopropyl-N-methylamine¹ and 5.3 g. (0.05 mole) of finely ground anhydrous sodium carbonate were stirred vigorously and 42.6 g. (0.3 mole) of methyl iodide was added dropwise. Solid material began to form before all the methyl iodide had been added. The mixture was heated under reflux for a few minutes and allowed to stand overnight. The product was recrystallized from ethanol and ethyl acetate and then from ethanol to give crystals having the properties shown in Table I.

(4) Melting points were taken in a capillary and are uncorrected. Analyses are by W. A. Struck and staff of our Microanalytical Laboratory.

(5) R. F. Nystrom and W. G. Brown, *THIS JOURNAL*, **69**, 1197 (1947).

Bis- β -(*o*-methoxyphenyl)-isopropyl-N- β -hydroxyethylamine. A. From the High Melting Diastereoisomeric Secondary Amine Hydrochloride¹. (a).—One hundred and one grams (0.3 mole) of bis- β -(*o*-methoxyphenyl)-isopropylamine was placed in a three-necked flask and with good agitation was warmed to about 75° and 52 g. (0.6 mole) of ethylenechlorohydrin was added over a six-hour period. The mixture had deposited crystals of the hydrochloride of the secondary amine by this time and heating was continued overnight at 90°.

The reaction mixture was treated with aqueous alkali, extracted with benzene, the solvent removed and the product distilled. The first fraction of 35 g., b.p. 203–206° at 3 mm., n_D^{20} 1.5488, represented starting material. The second portion, weighing 31.7 g., b.p. 215–225° at 2 mm., n_D^{20} 1.5514, consisted mainly of the desired product. It could be caused to crystallize by treatment with petroleum ether; m.p. 84–85°.

(b).—A somewhat better procedure was carried out as follows: Twenty-five grams (0.075 mole) of bis- β -(*o*-methoxyphenyl)-isopropylamine, 6.5 g. (5.3 cc., 0.075 mole) of ethylenechlorohydrin and 10.6 g. of powdered anhydrous sodium carbonate were stirred and heated rapidly to 160° over a free flame. Refluxing gradually decreased over 1.25 hours but did not quite stop. The light brown suspension was allowed to cool and 200 cc. of Skelly "C" was added to dissolve out the organic material. The residue weighed 21 g. and was suspended in water to give 9.5 g. (36%) of the hydrochloride of the secondary amine, m.p. 247–249°. The Skelly filtrate was charcoaled and concentrated to 50 cc. Crystals soon began to form. On chilling there was obtained 13 g. (49%) of white crystals, m.p. 82–85°. This on recrystallization from 50 cc. of Skelly "C" gave 12 g. of white crystals, m.p. 84–86.5°.

A sample of the above free base was dissolved in isopropyl alcohol and treated with ethereal hydrogen chloride. On chilling, white crystals formed which were recrystallized twice from isopropyl alcohol and ether. The product, m.p. 125.5–126°, had the analysis indicated in Table I. It could also be recrystallized from methylchloroform or methyl ethyl ketone.

B. From the Low Melting Diastereoisomeric Secondary Amine Hydrochloride.—Thirty grams (0.095 mole) of distilled bis- β -(*o*-methoxyphenyl)-isopropylamine base was treated exactly as in example (b) above, using proportionate amounts of reagents. The temperature remained at about 160° for 30–40 minutes after which refluxing decreased and the temperature rose to 180–190°.

After the reaction product had cooled, 200 cc. of Skelly "C" was added and the suspension filtered. Weight of residue, 15.1 g. (calcd. 14.8 g., based on the 12 g. of Na_2CO_3 used). The light amber filtrate was charcoaled to give a yellow solution which was concentrated till all the solvent had been removed, giving an amber oil, wt. 30 g. The oil was distilled, giving a forerun of starting material weighing 9 g., and a second viscous fraction boiling at 188–195° at 0.05 mm., and weighing 14 g., n_D^{20} 1.5540. This material gives a solid hydrochloride in isopropyl alcohol which, however, appears to be too hygroscopic to isolate.

Bis- β -(*o*-methoxyphenyl)-isopropyl-N- β -chloroethylamine.—The free base, m.p. 84–85°, from A above (20 g., 0.056 mole) was dissolved in 250 cc. of benzene and, with stirring, dry hydrogen chloride gas was passed in till the solution was almost saturated. The clear solution was brought to a boil and, with stirring, a solution of 10 g. (50% excess) of thionyl chloride in 100 cc. of benzene was added over a 10-minute period. After 1 hour of refluxing the solution was clear and practically colorless. On allowing to cool the product precipitated as fine white crystals weighing 23 g., m.p. 165–166°. Concentration of the filtrate to a small volume and addition of ether yielded an additional 2.8 g. of similar melting point. This represents more than the theoretical yield, probably due to solvent of crystallization.

The combined material above was dissolved in 200 cc. of isopropyl alcohol, decolorized with charcoal, filtered and allowed to cool. On standing at room temperature there was deposited 20.4 g. (88% yield) of white crystals, m.p. 167–168° after drying under high vacuum at 75°. The analysis is given in Table I.

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