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Physiologically Active Secondary Amines. β-(o-Methoxyphenyl)-isopropyl-N-methylamine and Related Compounds

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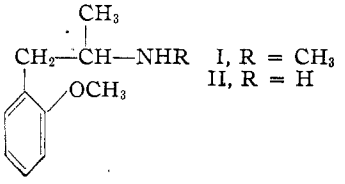
Fourteen secondary amines related to β-(o-methoxyphenyl)-isopropyl-N-methylamine (Orthoxine) have been prepared. Some of these have been separated into their diastereoisomeric forms, and one into its optical isomers. Several of these compounds possess a high order of bronchodilator and/or local anesthetic activity as indicated by pharmacological and preliminary clinical studies. An improved method is described for the preparation of aralkyl alkyl ketones by condensing an arylaldehyde with the requisite nitroparaffin in toluene using an azeotropic distillation procedure to force the reaction to completion, followed by a two-phase reductive hydrolysis.

During recent years, studies in these laboratories[1-7] have been directed toward the separation of the various pharmacological activities of sympathomimetic amines with the objective of preparing bronchodilator compounds which possessed the desirable properties of ephedrine or epinephrine but lacked the normally attendant undesirable side effects such as pressor and central nervous system stimulating properties. Considerable progress in this direction was realized with the finding[8-10] that β-(o-methoxyphenyl)-isopropyl-N-methylamine[11]



I, R = CH_3
II, R = H

(I) possessed promising oral bronchodilator activity without exhibiting any significant effect on the blood pressure or central nervous system. Since that time work has continued on the investigation of related compounds, and the present paper reports a number of secondary amines structurally related to I.

Efforts to prepare I by catalytic hydrogenation of β-(o-methoxyphenyl)-β-hydroxyisopropyl-N-methylamine by the method of Rosenmund and Karg[12] were not successful. Synthesis through the intermediate o-methoxyphenylacetone was studied in some detail. Preparation of this ketone from o-propenylanisole *via* the corresponding glycol[14] resulted in relatively low yields of the desired ketone and, moreover, the process was cumbersome. The most satisfactory procedure involved the condensation of o-anisaldehyde with nitroethane in toluene, with concomitant removal of water, azeotropically, to complete the reaction. This was followed by a two-phase chemical reductive hydrolysis to the desired o-methoxyphenylacetone.[15] The latter was then subjected to reductive amination with methanolic methylamine. Using a variety of amines a series of related secondary amines was prepared as shown in Table I.

In order to prepare a number of longer chain secondary alkylamines a variety of methods were studied for the preparation of β-(o-methoxyphenyl)-isopropylamine (II) from the corresponding substituted phenylacetone. Catalytic hydrogenation of the oxime using Adams platinum oxide or Raney nickel in the presence of ammonia gave a yield of 73% of the desired compound (II). When o-methoxyphenylacetone was subjected to the Leuckart reaction following the procedure of Crossley and Moore,[18] the primary amine (II) was formed in a 58% yield. Attempts at catalytic debenzylation of β-(o-methoxyphenyl)-isopropyl-N-benzylamine using palladium–charcoal have been unsuccessful. In this connection it is interesting that similar debenzylation attempts with the corresponding dibenzylamine caused the removal of only one benzyl group. When the procedure of Alexander and Misegades[19] was used, in which ammonium chloride was added to the ketone–ammonia mixture to decrease secondary amine formation, there was obtained a mixture of 40% of primary amine and 13% of secondary amine. This secondary amine, bis-[β-(o-methoxyphenyl)-isopropyl]-amine, could be obtained in good yield from o-methoxyphenyl-

(1) E. H. Woodruff and T. W. Conger, THIS JOURNAL, **60**, 465 (1938).

(2) E. H. Woodruff and E. Pierson, *ibid.*, **60**, 1075 (1938).

(3) E. H. Woodruff, J. P. Lambooy and W. E. Burt, *ibid.*, **62**, 922 (1940).

(4) E. H. Woodruff, *ibid.*, **64**, 2859 (1942).

(5) N. Levin, B. E. Graham and H. G. Kolloff, *J. Org. Chem.*, **9**, 380 (1944).

(6) R. V. Heinzelmann, H. G. Kolloff and J. H. Hunter, THIS JOURNAL, **70**, 1386 (1948).

(7) R. V. Heinzelmann, B. D. Aspergren and J. H. Hunter, *J. Org. Chem.*, **14**, 906 (1949).

(8) B. E. Graham, G. F. Cartland and E. H. Woodruff, *Ind. Eng. Chem.*, **37**, 149 (1945).

(9) B. E. Graham and M. H. Kuizenga, *J. Pharmacol.*, **94**, 150 (1948).

(10) J. J. Curry, J. E. Fuchs and S. E. Leard, *J. Allergy*, **20**, 104 (1949).

(11) This compound has been assigned the trade name Orthoxine by The Upjohn Company.

(12) K. W. Rosenmund and E. Karg, *Ber.*, **75**, 1854 (1942). Since our attempt, Zenitz, Macks and Moore[13] have also reported lack of success using this method with related compounds.

(13) B. L. Zenitz, E. B. Macks and M. L. Moore, THIS JOURNAL, **70**, 955 (1948).

(14) D. G. Thomas, unpublished data. See Tarbell, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., pp. 26–27; A. Wacek, *Ber.*, **77**, 85 (1944).

(15) R. V. Heinzelmann, U. S. Patent 2,557,051. This procedure is an improvement over that reported by Hoover and Hass[16] for the corresponding *p*-isomer; their condensation was carried out in alcohol (yield of nitroölefin, 59%) and the isolated nitroölefin reduced in an aqueous acid medium (over-all yield, 35%). However, using the present procedure the yield of ketone is more than twice that obtained by the Hoover and Hass method. It is interesting to note that Hass, Susie and Heider[17] reported little or no phenylacetone when a two-phase (benzene–water) reduction was tried.

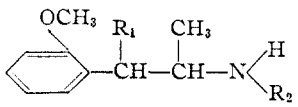
(16) F. W. Hoover and H. B. Hass, *J. Org. Chem.*, **12**, 501 (1947).

(17) H. B. Hass, A. G. Susie and R. L. Heider, *ibid.*, **15**, 8 (1950).

(18) F. S. Crossley and M. L. Moore, *ibid.*, **9**, 529 (1944).

(19) E. R. Alexander and A. L. Misegades, THIS JOURNAL, **70**, 1315 (1948).

TABLE I



R_1	R_2	B.p., °C.	B.p., Mm.	M.p., °C. HCl	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
H	CH_3 (*d,l*-form)	125	15	129–131[a]	$C_{11}H_{18}ClNO$	61.24	61.16	8.41	8.37		
H	CH_3 (*d*-form)	125	15	139–141	$C_{11}H_{18}ClNO$	[b]					
H	CH_3 (*l*-form)	125	15	139–140	$C_{11}H_{18}ClNO$	[b]					
H	$CH(CH_3)_2$	126	10	173.5–174.5	$C_{13}H_{22}ClNO$	64.04	64.00	9.10	8.94	5.75	5.72
H	C_6H_{13}	125	0.03	116–117	C_1 $H_{28}ClNO$	67.23	67.52	9.87	9.82	12.40[k]	12.41[k]
H	$C_{12}H_{25}$	185	1.0	85–87	$C_{22}H_{40}ClNO$	71.41	71.27	10.90	10.79	9.58[k]	9.64[k]
H	$C_6H_5CH_2$	207–210	19	130[c]	$C_{17}H_{22}ClNO$						
H	S—CH=CH—CH=C—CH_2	143–148	0.2	171–172	$C_{15}H_{20}ClNOS$	60.50	60.57	6.77	6.68	4.71	5.44
H	O—CH=CH—CH=C—CH_2			132–133	$C_{15}H_{20}ClNO_2$	63.93	63.96	7.15	7.16	12.58[k]	12.58[k]
H	$C_6H_5CH_2CH_2CH_2$	180	2.0	157–158	$C_{19}H_{26}ClNO$	71.34	71.15	8.19	8.25	4.38	4.53
H	*o*-$CH_3OC_6H_4$—CH_2CHCH_3	192	2.0	254–256[d]	$C_{20}H_{28}ClNO_2$	68.65	68.68	8.06	7.90	4.00	4.25
H	*o*-$CH_3OC_6H_4$—CH_2CHCH_3	194	1.5	214–215[e]	$C_{20}H_{28}ClNO_2$	68.65	68.46	8.06	8.00	4.00	3.97
OH	CH_3			193	$C_{11}H_{18}ClNO_2$	57.01	57.10	7.83	7.77	6.04	6.04
OH	$CH(CH_3)_2$			247–248	$C_{13}H_{22}ClNO_2$	60.10	60.44	8.54	8.42	5.39	5.35
$(C_6H_5)_2CH$—$CH(CH_3)$—$NHCH_3$[f]		123–130	0.9	188–189	$C_{16}H_{20}ClN$	73.40	73.37	7.70	7.64	5.35	5.49
o-CH_3O—$C_6H_{10}CH_2CH(CH_3)NHCH_3$[j]		60–77	0.25	156.5–157.5[g]	$C_{11}H_{24}ClNO$	59.57	59.43	10.91	10.70	6.32	6.77
o-CH_3O—$C_6H_{10}CH_2CH(CH_3)NHCH_3$[j]		60–77	0.25	114–115[h]	$C_{11}H_{24}ClNO$	59.57	59.53	10.91	10.71	6.32	6.60

[a] The published m.p.[3] of 137–138° is incorrect. [b] Prepared from pure racemic Orthoxine having the analysis shown: see Table III. [c] Reported,[3] 130–131° when prepared by a different method. [d] High melting diastereoisomer. [e] Low melting diastereoisomer. [f] This compound does not contain an *o*-methoxyl group. Prepared by reductive amination of α,α-diphenylacetone (*Org. Syntheses*, **29**, 38 (1949)). [g] High melting diastereoisomer. Calcd.: Cl, 15.99. Found: Cl 15.94. [h] Low melting diastereoisomer. Calcd.: Cl, 15.99. Found: Cl, 16.14. [j] Cyclohexyl derivatives. [k] Chlorine.

acetone by reductive amination with either β-(*o*-methoxyphenyl)-isopropylamine or half a molecular equivalent of alcoholic ammonia. It was isolated in two diastereoisomeric modifications, one of which crystallized during filtration from the catalyst and subsequent solvent removal. This appeared to be a solvated form of the free base, from which the alcohol could be removed by warming *in vacuo*, or even by exposing to the air. The hydrochloride of this latter diastereoisomer was extremely insoluble in water and a number of salts were prepared in an effort to increase its solubility. The lactate was found to be about seventeen times as soluble as the hydrochloride.

The resolution of I was carried out by reaction with *d*-tartaric acid and conversion of the separated diastereoisomeric tartrates to the corresponding hydrochlorides. The pharmacology of these optical isomers, which are quite different in their physiological action, will be reported elsewhere.

Compound I was converted to the corresponding cyclohexyl compound by catalytic hydrogenation in glacial acetic acid using Adams platinum catalyst. The uptake of hydrogen was slow but complete. Two diastereoisomeric modifications were isolated by fractional crystallization of their hydrochlorides.

A number of these compounds show bronchodilator activity comparable to or greater than that of I.[20] Several of them also exhibit a high order of local anesthetic activity. For example, bis-[β-(*o*-methoxyphenyl)-isopropyl]-amine lactate (m.p. 140.5–142°) has a cocaine index of about 200 and a procaine index of approximately 50.[21]

(20) The bronchodilator activity of these compounds was studied under the direction of B. E. Graham and Dr. Milton J. VanderBrook of our Pharmacology Department, and will be published by them.

(21) The local anesthetic activity of some of these compounds was evaluated under the direction of Dr. W. B. Bass and Dr. Milton J. VanderBrook of our Pharmacology Department. A paper covering a portion of their work will appear shortly.

Experimental[22]

o-Methoxy-α-bromopropiophenone.—One hundred and forty-seven grams (0.895 mole) of *o*-methoxypropiophenone[23] was dissolved in 500 cc. of chloroform and with stirring 144 g. (0.9 mole) of bromine in 250 cc. of chloroform was added over a period of 1.5 hours with cooling to 20°. The solution was allowed to stir an additional 2 hours at room temperature, after which air was bubbled through it for 30 minutes. The amber solution was washed with water, sodium bicarbonate, then water, and dried. The pale green solution was stored in the refrigerator until use. The yield was about 80%.

The bromoketone could be used in this form for the next step, but somewhat better yields were obtained if the chloroform was removed, the oil dissolved in toluene which was then chilled in Dry Ice and petroleum ether added. On scratching, the bromoketone came out as pale green crystals, melting below 40°; yield about 50%.

o-Methoxy-α-methylaminopropiophenone.—Without any further purification the above crystalline bromoketone (45.5 g., 0.187 mole) in 150 cc. of chloroform was stirred vigorously at 35–40° and a solution of 15 g. (0.48 mole) of methylamine in 60 cc. of water was added dropwise over a 30-minute period. Stirring was continued an additional 1.5 hours at that temperature. The chloroform layer was washed three times with water, dried and the solvent removed *in vacuo*. The residue was dissolved in ether which was poured into cold ethereal hydrogen chloride. The resulting yellowish gum soon set to a solid. Two recrystallizations from absolute alcohol gave 8.5 g. of beautiful long white needles, m.p. 175–177°.

Anal. Calcd. for $C_{11}H_{16}ClNO_2$: C, 57.51; H, 7.02; N, 6.10. Found: C, 57.29; H, 6.94; N, 6.02.

The filtrates yielded an additional 9 g. of white crystals; total yield 41%.

The β-Hydroxy-β-(o-methoxyphenyl)-isopropyl-N-methylamine.—The free base of the aminoketone, b.p. 152–153° at 13 mm., was hydrogenated in the presence of Raney nickel at 140° and 3000 lb. hydrogen pressure. The hydrogen uptake stopped at the carbinol stage.

Hydrogenation of the aminoketone hydrochloride in glacial acetic acid using active palladium–charcoal in the Parr apparatus resulted in the carbinol as before. Removal

(22) Melting points are uncorrected. Analyses are by W. A. Struck and staff of our Microanalytical Laboratory.

(23) W. H. Hartung, J. C. Munch, E. Miller and F. Crossley, THIS JOURNAL, **53**, 4155 (1931).

of the solvent and recrystallization of the resulting crystals from absolute alcohol gave very large tablets, m.p. 193°.

Anal. Calcd. for $C_{11}H_{18}ClNO_2$: C, 57.01; H, 7.83; N, 6.04. Found: C, 57.10; H, 7.77; N, 6.04.

When the above hydrogenation was repeated at 50° but with the addition of 0.075 cc. of 70% perchloric acid[12] the hydrogen uptake was only 60% that required for the formation of the carbinol. Hydrogenation of the carbinol under these conditions resulted at the end of 16 hours in the uptake of half the hydrogen required for the formation of the isopropylamine.

1-(o-Methoxyphenyl)-2-nitropropene-1. (a) Method of Hoover and Hass.[16]—Following the published procedure for the corresponding *p*-isomer, on a half-mole scale, a first crop of 40 g. (42%) of crystalline nitroölefin was obtained. Two fractional distillations of the residue yielded 18.4 g. of *o*-anisaldehyde and an additional 16.5 g. (17%) of the nitropropene; yield 59%, conversion 80%. Using methanol as solvent the yield was 59.7%; conversion, 74%.

(b) Modified Procedure.—Sixty-eight grams (0.5 mole) of *o*-anisaldehyde and 37.5 g. (0.5 mole) of nitroethane were dissolved in 100 cc. of benzene and 10 cc. of *n*-butylamine was added. The flask was fitted with a reflux condenser and water separator and the mixture was heated under reflux until the collection of water ceased. The solvent was removed *in vacuo* and the light brown oil remaining was fractionally distilled; the main fraction was again subjected to fractional distillation, and the resulting main crop (b.p. 144° at 1.5 mm.) crystallized almost at once on seeding with a crystal of nitroölefin. Recrystallization from alcohol or petroleum ether gave long yellow needles, m.p. 51–52°. The approximate refractive index in the supercooled molten state was $n^{20}D$ 1.61.

The above experiment was repeated using toluene and xylene as solvents. The effect of the boiling point of the solvent on the reaction rate is indicated in Table II.

TABLE II

PREPARATION OF 1-(*o*-METHOXYPHENYL)-2-NITROPROPENE-1

Solvent	Time (hr.) for removal of H_2O 50% of theory	100% of theory	Yield of nitroölefin, %
Benzene	1.5	20.0	91
Toluene	1.1	5.25	80
Xylene	0.75	5.0	93

***o*-Methoxyphenylacetone. (a) From Distilled Nitroölefin.**—Two hundred and fifty grams (1.3 moles) of 1-(*o*-methoxyphenyl)-2-nitropropene-1, 500 g. of powdered iron (30 mesh), 1000 cc. of water and 5 g. of $FeCl_3$ were heated under reflux with efficient stirring, and 500 cc. of concentrated hydrochloric acid was dripped in over a period of 7.5 hours. The resulting mixture was subjected to steam distillation until 12 liters had collected. The distillate was extracted with ether, the ether dried and removed, leaving a pale yellow oil which was distilled, b.p. 128–131° at 14 mm., $n^{20}D$ 1.5240, yield 176 g. (83%).

The semicarbazone was recrystallized from 50% alcohol, m.p. 157–159°.

(b) Using Undistilled Nitroölefin.—The conditions for optimum yields have been studied quite extensively and the following procedure was found to be the most satisfactory. In parallel experiments it was found that the yield of ketone was increased about 8% by not removing the toluene prior to reduction, and this procedure was adopted for subsequent runs.

Two hundred and seventy-two grams (2.0 moles) of *o*-anisaldehyde, 180 g. (90% pure, 2.2 moles of pure $C_2H_5NO_2$) of nitroethane, 400 cc. of toluene and 40 cc. of *n*-butylamine were added in that order to a flask equipped with reflux condenser and water separator. The solution was heated under reflux until the water stopped collecting One mole of water had collected after 45 minutes and 2.1 moles after 4 hours. The solution was transferred to a 5-liter, three-necked flask, equipped with a very efficient high speed stirrer, two condensers and a dropping funnel. To this flask were added 1000 cc. of water, 400 g. of iron (40 mesh) and 8 g. of $FeCl_3$. With vigorous agitation the suspension was heated almost to boiling and 720 cc. of concentrated hydrochloric acid was added over a 2-hour period causing the mixture to reflux actively. Heating and stirring were continued an additional 30 minutes. The flask was then adapted for steam distillation and 25 liters of steam distillate was collected. The toluene layer was removed, the aqueous layer extracted with toluene and the combined toluene layers were agitated for 30 minutes with 52 g. (0.5 mole) of sodium bisulfite in 1 liter of water to remove traces of aldehyde. The toluene layer was washed with water and the solvent removed to yield 238 g. (73%) of *o*-methoxyphenylacetone, $n^{20}D$ 1.5250, of sufficient purity for reductive amination reactions.

The yield of ketone was found to be fairly constant as long as the above iron–acid ratio was maintained. Varying the ratio in either direction caused a drop in yield.

β-(o-Methoxyphenyl)-isopropyl-N-methylamine Hydrochloride.—Eighty-two grams (0.5 mole) of the above ketone was placed in a Parr hydrogenation bottle, and 0.5 g. of Adams platinum oxide catalyst and 17 g. (0.55 mole) of methylamine in 150 cc. of absolute methanol were added. Hydrogenation was carried out at three atmospheres pressure. After an induction period of an hour the hydrogenation was complete in from 1 to 3 hours. The solvent was removed *in vacuo*, a small volume of benzene added and likewise removed *in vacuo*. The base was dissolved in acetone and with stirring and cooling below 10° hydrogen chloride gas was bubbled in until the suspension was just acid. After stirring for an hour in an ice-bath the white crystals were filtered off, washed with cold acetone and dried. They had the properties indicated in Table I; yield, based on *o*-methoxyphenylacetone, 90%. If recrystallization was necessary it was best carried out by dissolving the crystals in 0.75 part of boiling isopropyl alcohol, adding 5 parts of acetone and chilling.

***o*-Methoxyphenylacetoneoxime.**—This compound was prepared by the procedure used by Hoover and Hass[16] for the corresponding *p*-methoxy isomer. After two recrystallizations from 50% alcohol the white crystals melted at 80–81°.

β-(o-Methoxyphenyl)-isopropylamine. (a) From the Oxime.—Seventeen and eight-tenths grams (0.1 mole) of the above oxime was hydrogenated in a Parr apparatus in 200 cc. of absolute ethanol containing 6.0 g. (0.4 mole) of ammonia, using Adams platinum oxide or Raney nickel as the catalyst. Hydrogenation required about 16 hours. The solvent was removed and the product was distilled; b.p. 118° at 12.5 mm.,[1] yield 24 g. (73%).

(b) Leuckart Reaction.—To a three-necked, 2-liter flask, fitted with a dropping funnel, a thermometer reaching to the bottom, a stirrer and a Friedrich condenser arranged for downward distillation was added 315 cc. of 28% aqueous ammonia. To this stirred solution was added dropwise 264 cc. of 90% formic acid. The stirrer was removed and the solution was heated gradually over a 2- to 3-hour period to 160°, the temperature being regulated so that fairly rapid distillation took place. After cooling to 110°, 164 g. (1.0 mole) of *o*-methoxyphenylacetone was added and the mixture heated at 160–170° for 5 hours. At the end of 2 hours the upper layer of the distillate was returned to the reaction. After standing overnight the homogeneous solution was heated 2 hours more. It was then cooled to 70°, 360 cc. of concentrated hydrochloric acid was added dropwise and the mixture heated for 6 hours under reflux and allowed to stand overnight. The suspension was diluted with 600 cc. of water and extracted with benzene. The aqueous layer was basified, extracted with benzene and the residue from the benzene distilled under an atmosphere of nitrogen; b.p. 118–122° at 11 mm.,[1] yield 95 g. (58%).

(c) Procedure of Alexander and Misegades.[19]—Forty-nine and two-tenths grams (0.3 mole) of *o*-methoxyphenylacetone, 20 g. of ammonium chloride, 225 cc. of absolute alcohol saturated with ammonia and 25 cc. of aqueous ammonia were added to 0.2 g. of prereduced Adams platinum oxide catalyst in water. The suspension was hydrogenated in a Parr apparatus at three atmospheres hydrogen pressure. Hydrogenation was very slow, being 90% complete in 45 hours. The catalyst was removed by filtration, and the filtrate heated under reflux for an hour to remove ammonia. Acidification to congo red paper gave a white precipitate which was filtered off. The filtrate was concentrated to a paste, which was dissolved in water and extracted with benzene. The aqueous layer and the white precipitate above were basified, extracted with benzene and the residue from the benzene was distilled. The first fraction, b.p. 118–120° at 11 mm.,[1] represented the primary amine and amounted to 19.5 g. (40%). The second fraction, b.p.

TABLE III

SALTS CORRESPONDING TO HIGH MELTING HYDROCHLORIDE OF BIS-[β-(o-METHOXYPHENYL)-ISOPROPYL]-AMINE

Salt	Melting point, °C.	Solubility in H_2O, %	Recrystallizing solvent	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Nicotinate	156–158	0.48	Isopropyl alc.–ether	$C_{26}H_{32}N_2O_4$	71.53	71.52	7.39	7.39	6.46	6.43
Nitrate	168–169	.08	Isopropyl alc.	$C_{20}H_{28}N_2O_5$	63.75	64.05	7.50	7.44	7.44	7.62
Acetylsalicylate	110–111	.25	Ethanol–ether–petroleum ether	$C_{29}H_{35}NO_6$	70.56	70.41	7.15	7.11	2.84	2.92
Glycolate	166.5–167	1.44	Isopropyl alc.	$C_{22}H_{31}NO_5$	67.84	67.10	8.02	8.10	3.60	3.57
Lactate	156.5–157	1.75	Isopropyl alc.	$C_{23}H_{33}NO_5$	68.46	68.51	8.24	8.21	3.47	3.67

TABLE IV

SALTS CORRESPONDING TO LOW MELTING HYDROCHLORIDE OF BIS-[β-(o-METHOXYPHENYL)-ISOPROPYL]-AMINE

Salt	Melting point, °C.	Solubility in H_2O, %	Recrystallizing solvent	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Sulfate	188.5–189.5	0.74	Isopropyl alc.–ether	$C_{20}H_{29}NO_6S$	58.37	58.60	7.10	6.99	3.40	3.70
Nicotinate	155.5–157	0.55	Isopropyl alc.	$C_{26}H_{32}N_2O_4$	71.53	71.62	7.39	7.29	6.46	6.36
Pyruvate	145–146	1.2	Isopropyl alc.–ether	$C_{23}H_{31}NO_5$	68.80	68.89	7.75	7.71	3.49	3.43
Levulinate	99.5–100	>5	Isopropyl alc.–ether	$C_{25}H_{33}NO_5$	70.23	70.38	7.78	7.66	3.26	3.26
Maleate	135–135.5	0.23	Isopropyl alc.–ether	$C_{24}H_{31}NO_6$	67.11	67.39	7.28	7.32	3.26	3.45
Acetate	106–107.5	1.8	Acetone	$C_{22}H_{31}NO_4$	70.71	71.12	8.37	8.28	3.75	3.76
Benzoate	161.5–162.5	0.06	Isopropyl alc.	$C_{27}H_{33}NO_4$	74.45	74.71	7.64	7.70	3.22	3.20
Lactate	140.5–142	5	Isopropyl alc.	$C_{23}H_{33}NO_5$	68.46	68.35	8.24	8.40	3.47	3.45

185–192° at 2.0 mm., represented secondary amine; yield 6.5 g. (13%).

β-(o-Methoxyphenyl)-isopropyl-N-γ-phenylpropylamine.[24]—This compound resulted from the reductive alkylation of o-methoxyphenylisopropylamine with cinnamaldehyde, using Adams platinum oxide as catalyst. Two molecular equivalents of hydrogen were absorbed. The distilled base was converted to the hydrochloride in ethanol–ethyl acetate. Recrystallization from this mixture gave a white product having the properties reported in Table I.

β-(o-Methoxyphenyl)-isopropyl-N-hexylamine.[24]—Thirty-three grams (0.2 mole) of o-methoxyphenylisopropylamine and 16.5 g. (0.1 mole) of n-hexyl bromide were dissolved in 100 cc. of benzene and the solution heated under reflux for 18 hours. The benzene solution was washed with water, dried and the solvent was removed *in vacuo*. The oil obtained by distillation, b.p. 125–129° at 0.03 mm., was dissolved in ethyl acetate and treated with ethanolic hydrogen chloride. The solid product was recrystallized from this combination to yield white crystals having the properties indicated in Table I.

β-(o-Methoxyphenyl)-isopropyl-N-dodecylamine.[24]—The above procedure was followed using n-dodecyl bromide. The hydrochloride, formed in ethanol and ethyl acetate, was found to be appreciably soluble in ether and benzene, and quite insoluble in water. It was recrystallized from acetone, to give a product with the properties indicated in Table I.

Bis-[β-(o-methoxyphenyl)-isopropyl]-amine.—Eighty-two and one-half grams (0.5 mole) of o-methoxyphenylisopropylamine and 82.0 g. (0.5 mole) of o-methoxyphenylacetone in 200 cc. of absolute methanol were subjected to catalytic hydrogenation in a Parr apparatus at three atmospheres pressure, using 0.5 g. of Adams platinum oxide as the catalyst. Hydrogenation was complete in 5 hours. The solution was warmed, filtered from the catalyst causing the deposition of crystals of the high melting diastereoisomer. The solvent was removed and the entire product distilled *in vacuo*, b.p. 200° at 3.0 mm., yield 116 g. (75%), $n^{20}D$ 1.5500.

The above oil was dissolved in 100 cc. of hot methanol and chilled to precipitate 60 g. of the high melting diastereoisomer. A portion of this was converted to the hydrochloride in isopropyl alcohol. The latter was recrystallized from 75% alcohol to give beautiful white crystals having the properties indicated in Table I. The solubility of this salt in water was about 0.1%.

Other salts prepared, their melting points and water solubilities and the recrystallizing solvents are given in Table III.

The filtrate from the high melting diastereoisomer was concentrated to an oil which was converted to the hydrochloride in isopropyl alcohol. The crude hydrochloride was extracted with a large volume of boiling isopropyl alcohol, the undissolved high melting diastereoisomer filtered off and ether added to the filtrate to precipitate the more soluble form. This process was repeated one or two times more till the product had the melting point indicated in Table I.

The hydrochloride, m.p. 214–215°, was converted to the free base in ether and a slight excess of 85% lactic acid was added. After chilling, crystals of the lactate were deposited which were recrystallized from a small volume of isopropyl alcohol. Its properties and those of related salts are given in Table IV.

Resolution of β-(o-Methoxyphenyl)-isopropyl-N-methylamine (I).—One hundred and seventy-nine grams (1.0 mole) of I base ($n^{20}D$ 1.5188), prepared from pure I hydrochloride and distilled, and 150 g. (1.0 mole) of d-tartaric acid were dissolved in 1 liter of methanol and 2 liters of acetone at the boil. After chilling overnight there were obtained 90 g. of white crystals, m.p. 118–123.5°. To the filtrate was added an additional 1.3 liters of acetone and the solution was again chilled, causing 68 g. more of crystals, m.p. 112–118°, to deposit. The combined 158 g. was recrystallized several times by dissolving in 2.5 parts of hot methanol, adding 5 parts of acetone and allowing the solution to stand at room temperature. The product was l-β-(o-methoxyphenyl)-isopropyl-N-methylamine d-tartrate.

The filtrate from the 158 g. of crystals above was concentrated to give a thick oil which on scratching set up to a semi-solid mass of crystals. These were recrystallized several times by dissolving in 4 parts of absolute ethanol at the boil and allowing to stand at room temperature, and once from 30 parts of isopropyl alcohol. The product was d-β-(o-methoxyphenyl)-isopropyl-N-methylamine d-tartrate.

The above tartrates were converted to the free bases which were dissolved in 10 parts of acetone and with cooling in ice and stirring one part of ether containing a molecular equivalent of hydrogen chloride was added dropwise. The hydrochlorides precipitated out in pure form.

Table V gives the properties of the tartrates and hydrochlorides.

TABLE V

PROPERTIES OF I TARTRATES AND HYDROCHLORIDES

	l-I d-Tartrate	l-I Hydrochloride	d-I d-Tartrate	d-I Hydrochloride
Melting point, °C.	129–131	139.2–140.2	121–122.2	139.1–140
Specific rotation in 2% aqueous solution $[\alpha]^{28}D$	+4.25°	−14.25°	+20.75°	+13.80°

β-(o-Methoxycyclohexyl)-isopropyl-N-methylamine.—I base was obtained from the pure hydrochloride and distilled. This base (17.9 g., 0.1 mole) was dissolved in 150 cc. of

(24) Prepared by B. D. Aspergren of these laboratories.

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., $n^{20}D$ 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 compounds[24] and to W. H. Maroney for technical assistance.

KALAMAZOO, MICHIGAN

[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

BY R. V. HEINZELMAN AND B. D. ASPERGREN

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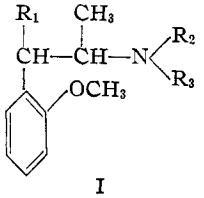
Eighteen tertiary amines or quaternary salts related to β-(o-methoxyphenyl)-isopropyl-N-methylamine have been prepared. Some of these possess notable bronchodilator and local anesthetic activity.

The present paper reports a continuation of our study[1] 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



I

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_3Cl 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-[β-(o-methoxyphenyl)-isopropyl]-amine[1] (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-[β-(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-[β-(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.

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

(2) J. F. Kerwin, T. F. Herdegen, R. Y. Heisler and G. E. Ullyot, *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.