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N-Dimethylation of β-Phenylethylamine Derivatives

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Abstract □ Direct *N*-methylation of 3,4-dimethoxyphenethylamine, 4-methoxyphenethylamine, tyramine, and 3-methoxytryamine, by refluxing each compound with a mixture of formaldehyde and formic acid in the presence of dimethylformamide, to the corresponding *N*-dimethyl derivative in 45–86% yield is reported. The synthesis of macromerine from normetanephrine by a two-step methylation, using diazomethane and formaldehyde–formic acid mixture, is also reported.

Keyphrases □ *N*-Dimethylation—aromatic primary amines in dimethylformamide using formaldehyde–formic acid □ β-Phenylethylamines and β-phenylethanolamines, *N,N*-dimethyl derivatives—as potential metabolites of levodopa □ Macromerine—synthesis, two-step methylation using diazomethane and formaldehyde–formic acid

Levodopa (L-3,4-dihydroxyphenylalanine) is used extensively in the treatment of Parkinson's disease. In spite of marked improvements in many patients, some adverse reactions, including psychotic symptoms such as confusion, hallucination, and agitation, have been noted (1, 2). *N,N*-Dimethyl-3,4-dimethoxy-β-hydroxy-β-phenethylamine (macromerine), a possible metabolite of levodopa, was reported to be hallucinogenic when tested in squirrel monkeys (3). A number of alkaloids, including *N,N*-dimethyl-3,4-dimethoxyphenethylamine, *N,N* - dimethyl - 3 - methoxytyramine, *N,N* - dimethyltyramine (hordenine), *N*-methyl-3,4-dimethoxy-β-hydroxy-β-phenethylamine (normacromerine), and macromerine have been isolated from cactus plants (4–7).

The possibility that such compounds may be formed in the human or animal body as metabolites of levodopa or 3,4-dihydroxyphenethylamine (dopamine) prompted the search for a relatively simple method of *N*-methylation of β-phenylethylamine and β-phenylethanolamine derivatives. The preparation of *N*-methylated derivatives of β-phenylethylamine and the ring-substituted compounds was reported previously (8). This method involves several steps, starting with the corresponding aldehyde, and is very time consuming. Methods for methylating aliphatic amino alcohols and amino mercaptans using formaldehyde and formic acid were described (9, 10), and a modified method for preparing *N,N*-dimethyl derivatives of other amino alcohols or amino mercaptans in 90–100% yield was published (11). This method has been modified to include a reaction medium, dimethylformamide, and extended to the *N*-methylation of β-phenylethylamine derivatives.

An attempt to identify these compounds as metabolites of levodopa in Parkinson's disease is in progress.

EXPERIMENTAL[1]

Materials—3,4-Dimethoxyphenethylamine (I) and its hydrochloride (I*a*), 4-methoxyphenethylamine (II), tyramine (III), 3-methoxytyramine (IV), normetanephrine hydrochloride (V), octopamine hydrochloride (VI), dimethylformamide[2], formaldehyde (35%)[3], formic acid (88%), ethyl acetate, ether, and methanol[4] were used.

Methylations—N,N-*Dimethyl-3,4-dimethoxyphenethylamine* (*VII*) —To 220 mg. (1 mmole) of I*a* taken in a 10-ml. round-bottom flask,

[1] All melting points were taken on a Fisher-Johns hot-stage melting-point apparatus and are uncorrected. Microanalyses were performed by PCR, Inc., Gainesville, Fla. TLC was done on silica gel G (E. Merck, Darmstadt, Germany) in two solvent systems: Solvent A, *n*-butanol–acetic acid–water (4:1:1); and Solvent B, isopropanol–10% ammonia–water (8:1:1) (12). GLC was performed in a Barber-Colman model 15 gas chromatograph provided with an ionization detector system (radium source). A glass U-tube (1.83 m. × 4 cm.) containing 12% C_6-diethylene glycol succinate on Anakrom ABS 60–70 mesh (Analabs, Inc., North Haven, Conn.), preconditioned at 200° for 72 hr. with nitrogen flowing at the rate of 100 ml./min. and maintained at 200° with an external argon pressure of 20 p.s.i. (flow rate at exit 98 ml./min.), was used as a polar column. A nonpolar column of 15% Apiezon L on 100–120-mesh Gas Chrom Q (Applied Science Laboratories, State College, Pa.), preconditioned at 255° for 144 hr. with nitrogen flowing at the rate of 66 ml./min. and maintained at 255° with an external argon pressure of 30 p.s.i. (flow rate 50 ml./min.) was also used for analyses.

[2] Sigma Chemical Co., St. Louis, Mo.

[3] E. Merck & Co., Rahway, N. J.

[4] Mallinckrodt Chemical Works, St. Louis, Mo.

84 mg. (1 mmole) of sodium bicarbonate and 5 ml. of dimethylformamide were added; while the flask was kept cooled in ice, a mixture of 0.22 ml. of 88% formic acid (5 mmoles) and 0.42 ml. of 35% formaldehyde (5 mmoles) was added slowly. The mixture was heated gently on a heating mantle until the vigorous evolution of carbon dioxide subsided and then was refluxed with a water condenser for 5 hr. The solution was cooled and added to 15 ml. of cold water, made alkaline with solid sodium hydroxide (pH ~ 8), and extracted three times with 25-ml. portions of ethyl acetate. The combined ethyl acetate layer was washed twice with 30 and 25 ml. each of water, and the organic phase was dried (sodium sulfate) and filtered through glass wool. Finally, the ethyl acetate was evaporated in a flash evaporator. A light-yellow oil (184 mg., 92%) was obtained.

This oil (69.5 mg.) was converted to the hydrochloride by adding a solution of 10% concentrated hydrochloric acid in methanol and evaporating the solution to dryness when tiny chalk-white crystals were formed. The crystals were recrystallized from methanol–ether to yield 65.5 mg. (80%) of VII-hydrochloride (overall yield 72%), m.p. 196–198° [lit. (8) m.p. 197°]. GLC of this compound as the free amine on diethylene glycol succinate and Apiezon L showed only one peak in each case with retention times of 4.5 and 6.3 min., respectively. When I was used as the starting material, the sodium bicarbonate was excluded from the reaction mixture and the proportions of formic acid and formaldehyde were reduced by one-half. A similar yield was obtained.

N,N-*Dimethyl-4-methoxyphenethylamine* (*VIII*)—To 1.52 g. (10 mmoles) of II, 30 ml. of dimethylformamide, 1.1 ml. of 88% formic acid (25 mmoles), and 2.1 ml. of 35% formaldehyde (25 mmoles) were added and refluxed for 5 hr. The solution was added to water containing sodium hydroxide (pH ~ 10) and extracted three times with ethyl acetate; on evaporation of the ethyl acetate, 1.87 g. of a colorless oil (104%) was obtained. A portion of this dimethylamine (98.0 mg.) was converted to the hydrochloride, as already described, to yield 101.6 mg. (overall yield 86%) of white crystals, m.p. 175–176° [lit. (8) m.p. 176.5°].

N,N-*Dimethyl-3-methoxytyramine* (*IX*)—The hydrochloride of IV (95.6 mg., 0.5 mmole), 0.5 mmole sodium bicarbonate, and 2.5 mmoles each of formaldehyde and formic acid were mixed with 5 ml. of dimethylformamide. The mixture was refluxed for 5 hr., cooled, added to 15 ml. of water containing 20 ml. of 0.5 *M* sodium borate buffer (pH 10), and extracted three times with 25-ml. portions of ethyl acetate. After drying (sodium sulfate) and evaporating the solvent, 84.0 mg. (92%) of a light-yellow oil was obtained. This oil was partially purified by chromatography on 10 g. of magnesium silicate[5] by eluting with 125 ml. of ethyl acetate and 50 ml. of chloroform–methanol (2:1) when 71.8 mg. of colorless oil was obtained. A portion of the oil (33.0 mg.) was dissolved in ethyl acetate and kept at −18° for several days when 27.5 mg. of shining flat white crystals, m.p. 94–96°, was obtained. This compound gave a green color with ferric chloride, indicating the presence of a phenolic group, and no pink color with ninhydrin, indicating the absence of a primary amino group. TLC of this compound (IX) gave spots with an R_f value lower than IV (0.22 *versus* 0.44) in Solvent A and higher than IV (0.50 *versus* 0.33) in Solvent B. GLC on diethylene glycol succinate and Apiezon L gave only a single peak in each case with retention times of 7.5 and 6.75 min., respectively.

Anal.—Calc. for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.74; H, 8.76; N, 7.11.

The remaining oil (free base, 38.0 mg.) was converted to the hydrochloride and recrystallized from methanol–ether to yield 45.5 mg. (100%) of crystals, m.p. 191–192° [lit. (5) m.p. 190–191°]. The overall yield of the *N,N*-dimethyl hydrochloride derivative was 70%.

Anal.—Calc. for $C_{11}H_{18}ClNO_2$: C, 57.02; H, 7.83; N, 6.04. Found: C, 56.77; H, 7.75; N, 6.14.

N,N-*Dimethyltyramine* (*Hordenine*) (*X*)—Compound III (5.488 g.) was similarly converted to the *N,N*-dimethyl derivative and extracted from borate buffer with ethyl acetate to give 4.142 g. (63%) of oil, part of which (1.116 g.) was crystallized from benzene–petroleum ether to yield 0.648 g. (58%) of white flaky crystals, m.p. 116–117° [lit. (13) m.p. 117–118°]. The mother liquor and the rest of the free amine (3.494 g.) were converted to the hydrochloride, decolorized with activated charcoal, and crystallized from methanol–ether. Fine needle-shaped crystals (1.914 g., 55%; overall yield, 45%), m.p. 181–183° [lit. (8) m.p. 181°], were obtained.

Macromerine Hydrochloride (*XI*)—One hundred milligrams of V dissolved in methanol was treated with an ethereal solution of diazomethane until the solution was yellow. The solvent and excess diazomethane were evaporated under nitrogen and the free amine was extracted from borate buffer with ethyl acetate. The residue (80 mg.) was *N*-methylated as before with formaldehyde–formic acid. The dimethylamine was converted to the hydrochloride, decolorized with charcoal, and crystallized from methanol–ether to yield 58 mg. (overall yield 52%) of needle-shaped crystals, m.p. 162–163° [lit. (14) m.p. 163–164°]. Compound XI had the same R_f value as authentic macromerine in both Solvents A and B.

Attempts to N-Methylate V and VI—Methylation of 440.7 mg. of V analogously yielded 403.0 mg. of yellow oil, which had an R_f value lower than V (0.23 *versus* 0.43) on TLC in Solvent A and higher than V in Solvent B (0.45 *versus* 0.40). It gave a green color with ferric chloride and no pink color with ninhydrin. The *N*-methylated free amine or its hydrochloride was not obtained in crystalline form, so the product is only tentatively identified as the *N,N*-dimethyl derivative of V.

Compound VI (81.5 mg.) was methylated similarly to yield 67.6 mg. of yellow oil, which had an R_f value lower than VI in Solvent A (0.33 *versus* 0.63) and higher than VI in Solvent B (0.50 *versus* 0.45). The methylated product gave a brown color with ferric chloride and no color with ninhydrin. Attempts to crystallize the *N*-methylated free base or the hydrochloride were unsuccessful, so the identification of the derivative as *N,N*-dimethyloctopamine is only tentative.

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