Journal of Medicinal and Pharmaceutical Chemistry

VOL. 2, No. 1 (1960)

Note

Derivatives of *N*-Methylpiperidine*

ANDREW LASSLO and PAULINE D. WALLER, *Department of Pharmacology, Division of Basic Health Sciences, Emory University, Atlanta 22, Georgia*

Introduction

The hallucinatory effects induced by the benzilic acid ester of 1-methyl-3-hydroxypiperidine (JB–336, Lakeside Laboratories, Milwaukee, Wisconsin) suggested that simple esters of *N*-alkyl-3-hydroxypiperidines with sterically hindered ester linkages be evaluated for psychotomimetic properties. Since Meyer[1] has shown that ethyl trimethylacetate does not respond to ammonolysis due to steric hindrance, the trimethylacetate ester of 1-methyl-3-hydroxypiperidine was synthesized.

The occurrence of psychic side-reactions during the administration of meperidine (ethyl 1-methyl-4-phenylhexahydroisonicotinate)[2] led us to the synthesis of its diethylamide analogue, following—in general—the same train of thought as in our work with cocaine.[3]

Dr. Carl C. Pfeiffer and Miss Elizabeth H. Jenney's preliminary tests disclosed LD50–s in the neighbourhood of 550 mg/kg for the former, and 175 mg/kg for the latter compound (in mice, intraperitoneally). The preliminary evaluations indicated that both compounds exert effects upon the central nervous system; the latter induced typical 'Straub-tail' characteristics in mice.

Methods and Results

1-Methyl-3-hydroxypiperidine (*I*). A solution of 3-hydroxypiperidine (50·0 g, 0·494 mole), aqueous 88 per cent formic acid

* This investigation is supported by USPHS Research Grant No. M-2072 from the National Institute of Mental Health.

(71·8 g, 1·372 moles of HCOOH), and aqueous 37 per cent formaldehyde (48·8 g, 0·602 mole of HCHO) was refluxed for 35·5 h. With the reaction mixture cooled by means of an ice-water bath, 28 ml of concentrated hydrochloric acid was added. The reaction mixture was subsequently subjected to reduced pressure (21 mm) at 100°, for 45 min; the viscous residue was dissolved in 13 ml water and the aqueous solution rendered alkaline with potassium hydroxide and extracted with ethyl ether. The ether extracts were dried over anhydrous potassium carbonate and filtered, the ether was removed on the steam bath, and the residue fractionated under reduced pressure. The pure product (39·2 g, 69 per cent yield) distilled at 81·0–85·0°/17 mm ($n_D^{20·5}$ 1·4747), in accordance with the literature.[4] The hydrochloride was obtained by treating the base with anhydrous hydrogen chloride in anhydrous ethyl ether; upon recrystallization from ethanol-ethyl acetate the colourless crystals melted at 146·0–147·0° (uncorr.).

Trimethylacetyl chloride (*II*). A mixture of trimethylacetic acid (50·0 g, 0·490 mole) and anhydrous ethyl ether (10 ml) was gradually added to thionyl chloride (68·4 g, 0·575 mole) cooled to −5°, at a rate maintaining the temperature below 0°. The mixture was allowed to warm gradually to room temperature and was subsequently refluxed at 53–68° for 45 min. Then, the reaction mixture was fractionated at atmospheric pressure; the pure product distilled at 102·0–104·0° (26·5 g, 45 per cent yield) in accordance with the literature.[5]

1-Methyl-3-(trimethylacetoxy)piperidine hydrochloride (*III*). Trimethylacetyl chloride (13·1 g, 0·109 mole) in anhydrous benzene (85 ml) was gradually added to a mixture of (I) (12·5 g, 0·109 mole), anhydrous sodium carbonate (23·1 g, 0·218 mole), and anhydrous benzene (400 ml), with vigorous stirring. The reaction mixture was subsequently refluxed for 2¼ h and allowed to cool to room temperature. After filtration, the filtrate was dried over anhydrous sodium sulphate, filtered, and the benzene removed under reduced pressure (maximum pot temperature 55°). The crude reaction product, a dark brown liquid (10·9 g, 50 per cent yield), was dissolved in anhydrous ethyl ether, the solution was filtered through Celite and treated with anhydrous hydrogen chloride. The salt was recrystallized from ethanol-ethyl acetate; the fine white crystals melted at 207·6–208·4° (uncorr.).

Anal. Calcd. for $C_{11}H_{22}ClNO_2$: C, 56·03; H, 9·41; Cl, 15·04; N, 5·94 per cent. Found: C, 56·15; H, 9·59; Cl, 15·2; N, 5·85 per cent.*

1-Methyl-4-phenyl-4-(N,N-*diethylcarboxamido)piperidine hydrochloride* (*IV*). Meperidine was converted to 1-methyl-4-phenylpiperidine-4-carboxylic acid by means of Jahns' hydrolysis with aqueous barium hydroxide.[6] To 11·6 g (0·053 mole) of the acid, thionyl chloride (104·8 g, 0·881 mole) was added, the mixture was heated gradually to reflux temperature, and the resulting solution was refluxed for 15 min. The excess thionyl chloride was removed under reduced pressure (maximum pot temperature 40°). The residual thionyl chloride was removed by azeotropic distillation under reduced pressure with two 400 ml portions of anhydrous benzene. Then 400 ml of anhydrous benzene was introduced into the reaction vessel, and the solid acid chloride was finely dispersed with mechanical agitation. To this dispersion diethylamine (38·8 g, 0·530 mole) was gradually added at room temperature. Subsequently, the mixture was stirred vigorously for 3·5 h at about 53°, allowed to stand overnight at room temperature, and stirred vigorously for 8 additional hours at about 53°. Upon cooling, the reaction mixture was treated with aqueous 40 per cent sodium hydroxide, and the base was extracted with benzene. The combined benzene extracts were dried over a mixture of anhydrous sodium sulphate and magnesium sulphate, filtered, and the benzene was removed under reduced pressure. The base was purified by filtering its solution in anhydrous ethyl ether through Celite, removing the ether on the steam bath, and filtering the hot residue through the filter aid. The base solidified upon cooling (10·8 g, 68 per cent yield). It was converted to the hydrochloride by treating it with anhydrous hydrogen chloride in anhydrous ethyl ether. The salt crystallized from ethyl acetate as colourless crystals and melted at 173·0–175·0° (uncorr.).

Anal. Calcd. for $C_{17}H_{27}ClN_2O$: C, 65·68; H, 8·76; Cl, 11·41; N, 9·01 per cent. Found: C, 65·81; H, 8·75; Cl, 11·42; N, 9·12 per cent.

* All analyses by Drs. G. Weiler and F. B. Strauss, Oxford, England.

(*Received 20 November, 1959*)

References

[1] Meyer, H. *Mh. Chem.* **27,** 36 (1906)
[2] Goodman, L. S. and Gilman, A. *The Pharmacological Basis of Therapeutics,* p. 264. Second Edition, 1955. New York; Macmillan
[3] Jordan, S. E., Lasslo, A., Livingston, H. L., Alperin, H. and Gersing, A. *Arch. int. Pharmacodyn.* **115,** 452 (1958)
[4] Biel, J. H., Friedman, H. L., Leiser, H. A. and Sprengeler, E. P. *J. Amer. chem. Soc.* **74,** 1487 (1952)
[5] Butlerow, A. *Ann.* **173,** 373 (1875)
[6] Jahns, E. *Arch. Pharm., Berl.* **229,** 680 (1891)