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Note

An Hydroxylamine Analogue of Methantheline with Mydriatic Activity*

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Methantheline bromide, β-diethylaminoethyl 9-xanthenecarboxylate methobromide, is one of the most useful parasympatholytic agents.[1] In view of earlier evidence that the pharmacological activity of some derivatives of hydroxylamine is comparable with that of chemically related amines,[2] it was decided to make one or more hydroxylamine analogues of methantheline bromide.

N-Methoxy-*N*-methyl-β-aminoethyl 9-xanthenecarboxylate methiodide has been prepared and examined pharmacologically. Unexpectedly, attempts to prepare the related methiodide and methobromide of *N*-ethoxy-*N*-ethyl-β-aminoethyl 9-xanthenecarboxylate have not proved successful, although the intermediate *N*-ethoxy-*N*-ethyl-β-aminoethyl 9-xanthenecarboxylate could be made readily.

N-Methoxy-*N*-methyl-β-aminoethyl 9-xanthenecarboxylate and *N*-ethoxy-*N*-ethyl-β-aminoethyl 9-xanthenecarboxylate were prepared by interaction of 9-xanthenecarbonyl chloride[3] with *N*-2-hydroxyethyl-*N*-methoxy-methylamine[4] and *N*-2-hydroxyethyl-*N*-ethoxy-*N*-ethylamine,[5] respectively.

These basic esters were yellow oils which formed crystalline hydrobromides. The picrate and methiodide of *N*-methoxy-*N*-methyl-β-aminoethyl 9-xanthenecarboxylate were prepared by standard procedures. Similar attempts to prepare the methiodide and methobromide of *N*-ethoxy-*N*-ethyl-β-aminoethyl 9-

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xanthenecarboxylate gave products which did not show correct analyses for the expected products. We have been unable to carry this study any further and currently have no explanation for these findings.

Dr. C. A. Stone and Mr. Sam McKinney of the Merck Institute for Therapeutic Research, West Point, Pennsylvania have found that *N*-methoxy-*N*-methyl-β-aminoethyl 9-xanthenecarboxylate methiodide exhibits an atropine-like action in mice, as does methantheline bromide. The new compound caused dilation of the pupils of mice receiving the drug, either intravenously or orally. The dose required to dilate the pupil 10 micrometer units, intravenously, was 0·11 mg/kg and, orally, 83 mg/kg. These results indicate that the new product is about half as active as methantheline bromide in mice when tested in the same way. The onset and duration of action of both substances were similar.

The toxicity of *N*-methoxy-*N*-methyl-β-aminoethyl 9-xanthenecarboxylate methiodide was similar to that of methantheline bromide. The intravenous LD_{50}'s as determined from data based on five or six dose levels with ten mice per level were:

Compound	LD_{50}, mg of ion/kg
Methantheline bromide	11·6 (11·1 to 12·0)
N-methoxy-*N*-methyl-β-aminoethyl 9-xanthenecarboxylate methiodide	13·8 (13·0 to 14·6)

The signs noted were similar with both compounds and included exophthalmos, coarse body tremors, and jumping, kicking convulsions. Death occurred within one or two minutes after administration.

Experimental

N-*Methoxy*-N-*methyl-β-aminoethyl 9-xanthenecarboxylate.* *N*-Hydroxyethyl-*N*-methoxy-*N*-methylamine[4] (12 g, 0·114 mole) in benzene (30 ml) was added to 9-xanthenecarbonyl chloride[3] (20 g, 0·082 mole) in benzene (40 ml). The mixture was heated under reflux for two hours, then the benzene was removed *in vacuo*. To the heavy oil which remained, was added sodium bicarbonate solution; the insoluble ester was extracted with ether. The ether solution was dried (Na_2SO_4 anhyd.) and then fractionated. An

oil with b.p. 174–180°/0·6 mm was obtained; yield 19 g (74 per cent); redistilled, b.p. 170–172°/0·5 mm.

Hydrobromide. The hydrobromide was prepared in ether with anhydrous hydrobromic acid and recrystallized several times from ethyl acetate, m.p. 102–104°.

Anal. Calcd. for $C_{18}H_{20}BrNO_4$: C, 54·83; H, 5·11; Br, 20·27; N, 3·55. Found: C, 54·54; H, 5·16; Br, 19·92; N, 3·39.

Picrate. The picrate was prepared in ether and recrystallized from ethanol, m.p. 91–93°.

Anal. Calcd. for $C_{24}H_{22}N_4O$: C, 53·12; H, 4·08; N, 10·33. Found: C, 53·22; H, 4·25; N, 10·73.

Methiodide. The methiodide was prepared in ether solution with methyl iodide and recrystallized from ethanol, m.p. 114°.

Anal. Calcd. for $C_{19}H_{22}INO_4$: C, 50·12; H, 4·87; I, 27·87; N, 3·05. Found: C, 50·07; H, 4·82; I, 27·89; N, 3·44.

N-*Ethoxy*-N-*ethyl*-β-*aminoethyl 9-xanthenecarboxylate.* This ester was prepared from *N*-hydroxyethyl-*N*-ethoxy-*N*-ethylamine[5] by a method similar to that described above for *N*-methoxy-*N*-methyl-β-aminoethyl 9-xanthenecarboxylate, b.p. 173–176°/0·1 mm; yield, 64 per cent.

Anal. Calcd. for $C_{20}H_{23}NO_4$: C, 70·36; H, 6·79; Found: C, 70·05; H, 6·65.

Hydrobromide. The hydrobromide was prepared in ether with dry hydrogen bromide, and recrystallized from a mixture of ethyl acetate and ether, m.p. 115–118°.

Anal. Calcd. for $C_{20}H_{24}BrNO_4$: C, 56·88; H, 5·73; Br, 18·93; N, 3·32. Found: C, 56·86; H, 5·53; Br, 19·18; N, 3·66.

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