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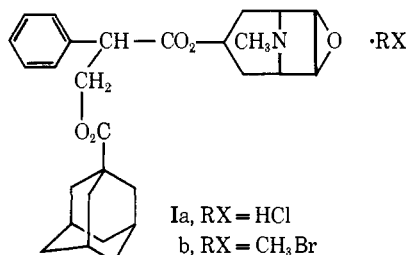
1-Adamantanecarboxylic Acid Ester of Scopolamine

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A few years ago it was found¹ that the esters of scopolamine were powerful anticholinergics. One of these, scopolamine pivalate hydrochloride, was found to be very effective as a topical antiperspirant.² In order to assess the influence of the rigid structure the 1-adamantanecarboxylic acid ester of scopolamine (I) has now been made.



Both the hydrochloride (Ia) and the methobromide (Ib) were found to be powerful anticholinergics. They markedly dilated mouse pupils when injected intraperitoneally at doses of 20% of their LD₅₀'s. Ia had an LD₅₀ of 562 mg/kg and Ib, 56 mg/kg.³ Further testing is desirable to determine their minimum effective doses and to evaluate the degree of usefulness of Ia as an antiperspirant.

Experimental Section⁴

1-Adamantanecarboxylic Acid Ester of Scopolamine Hydrochloride (Ia).—1-Adamantanecarbonyl chloride was prepared from 12.6 g (0.07 mole) of the acid and 30 ml of SOCl₂. After removing the excess SOCl₂ under reduced pressure and purging with C₆H₆, the crude acid chloride was dissolved in 10 ml of C₆H₆ and added to a suspension of 19.22 g (0.05 mole) of dried scopolamine hydrobromide in 50 ml of dry pyridine under N₂. The solid was dissolved by warming and the mixture was allowed to stand overnight at room temperature. The mixture was basified with aqueous Na₂CO₃ and extracted (Et₂O). The Et₂O solution was washed (H₂O, saturated NaCl), dried (Na₂SO₄), and evaporated under reduced pressure. The gummy free base was dis-

(1) R. B. Moffett and B. D. Aspergren, *J. Amer. Chem. Soc.*, **78**, 3448 (1956).

(2) F. S. K. MacMillan, H. H. Reller, and F. H. Synder, *J. Invest. Dermatol.*, **43**, 363 (1964).

(3) For the method see R. B. Moffett, A. R. Hanze, and P. H. Seay, *J. Med. Chem.*, **7**, 178 (1964), Table I, footnote a.

(4) Melting points were taken in capillary tubes with a partial immersion thermometer. Calibration of the apparatus against standard compounds showed no need for correction. IR spectra were obtained on both compounds and nmr on the hydrochloride. These were in accordance with the proposed structures. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for these elements or functions were within $\pm 0.4\%$ of theoretical.

solved in 500 ml of absolute Et₂O and acidified with ethereal HCl giving 27.5 g of white solid hydrochloride. Recrystallization from 150 ml of *i*-PrOH yielded 19.6 g (78%) of white crystals, mp 218–221° dec. *Anal.* (C₂₃H₃₆ClNO₅) C, H, Cl, N.

The Methobromide Ib.—Free base was liberated from 5.02 g (0.01 mole) of the above hydrochloride with Na₂CO₃ and extracted (Et₂O). The Et₂O solution was washed (H₂O, saturated NaCl) and evaporated under reduced pressure. To the gummy free base in 25 ml of cold EtCOMe was added 10 ml of cold MeBr. The flask was stoppered, clamped and allowed to stand at room temperature for 3 days. The quaternary salt was collected, washed (EtCOMe and Et₂O), and dried yielding 5.5 g (98%) of white crystals, mp 226.5–227.5° dec. *Anal.* (C₂₃H₃₅BrNO₅) C, H, Br, N.

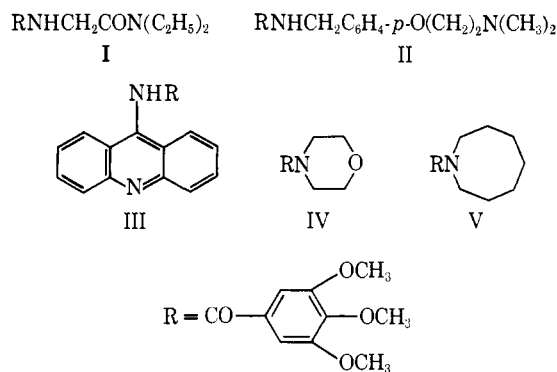
Structure-Activity Studies of 3,4,5-Trimethoxybenzamides. I. Variation of the Amine Function

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Various types of biological activity have been reported for 3,4,5-trimethoxybenzamides. The simplest member of the series, 3,4,5-trimethoxybenzamide, was found to have hypotensive effects and to potentiate the effects of phenobarbital.¹ Trimeglamide² (I) has been reported to possess hypnotic activity. Tigan (II) is well known as an antiemetic. Compound III has been reported³ to have hypotensive activity and to potentiate muscle contraction. Vargha, *et al.*,⁴ have synthesized a series of trimethoxybenzamides. A study⁵ on one of these, N-(3,4,5-trimethoxybenzoyl)tetrahydro-1,4-oxazine (IV), has shown it to possess interesting tranquilizing properties. Compound V, however, reportedly possesses antidepressant activity.⁶ The effect of IV on spontaneous activity of mice was compared with its effect on muscle function using the rotarod.⁵ A comparison of the effective dose for depression of activity to that required for rotarod effects gives a measure of the selectivity of drug action. One would want to



(1) P. C. Dandiya, P. K. Sharma, and M. K. Menon, *Indian J. Med. Res.*, **50**, 750 (1962).

(2) G. Cronheim, J. T. Gourzis, and I. M. Tockes, *Science*, **128**, 1570 (1958).

(3) A. Pimenta, J. E. Murad, and D. P. Lenza, *Therapie*, **17**, 1189 (1962).

(4) J. Borsy, B. Dumbovich, L. Vargha, and L. Farkas, Hungarian Patent 147,687 (1960); *Chem. Abstr.*, **53**, 7950 (1963).

(5) J. Borsy, *Arch. Intern. Pharmacodyn.*, **126**, 426 (1960).

(6) M. Gibaldi, S. Feldman, and T. R. Bates, *J. Pharm. Sci.*, **57**, 709 (1968).