to Dr. C. A. de Bock and Dr. W. T. Goedemans for supplying and discussing the biological data and to colleagues and coworkers of the analytical department, especially to Miss M. E. van der Heeden, for measurements and interpretation of the spectra.

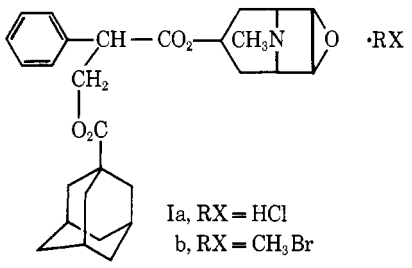
1-Adamantanecarboxylic Acid Ester of Scopolamine

ROBERT BRUCE MOFFETT

Research Laboratories of The Upjohn Company, Kalamazoo, Michigan 49001

Received March 27, 1969

A few years ago it was found[1] 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.



Ia, RX = HCl
b, RX = CH_3Br

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 LD_{50}'s. Ia had an LD_{50} 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 Section[4]

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 $SOCl_2$. After removing the excess $SOCl_2$ under reduced pressure and purging with C_6H_6, the crude acid chloride was dissolved in 10 ml of C_6H_6 and added to a suspension of 19.22 g (0.05 mole) of dried scopolamine hydrobromide in 50 ml of dry pyridine under N_2. The solid was dissolved by warming and the mixture was allowed to stand overnight at room temperature. The mixture was basified with aqueous Na_2CO_3 and extracted (Et_2O). The Et_2O solution was washed (H_2O, saturated NaCl), dried (Na_2SO_4), and evaporated under reduced pressure. The gummy free base was dissolved in 500 ml of absolute Et_2O 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.* ($C_{28}H_{36}ClNO_5$) C, H, Cl, N.

The Methobromide Ib.—Free base was liberated from 5.02 g (0.01 mole) of the above hydrochloride with Na_2CO_3 and extracted (Et_2O). The Et_2O solution was washed (H_2O, 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 Et_2O), and dried yielding 5.5 g (98%) of white crystals, mp 226.5–227.5° dec. *Anal.* ($C_{29}H_{38}BrNO_5$) C, H, Br, N.

(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 ±0.4% of theoretical.

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

W. A. SKINNER, J. KENNEDY, J. DEGRAW, AND H. JOHNSON

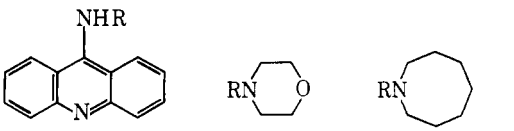
Department of Pharmaceutical Chemistry, Stanford Research Institute, Menlo Park, California 94025

Received February 12, 1969

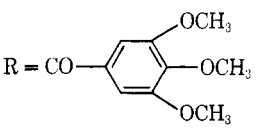
Various types of biological activity have been reported for 3,4,5-trimethoxybenzamides. The simplest member of the series, 3,4,5-trimethoxybenzamide, was found to have hypotensive effects and to potentiate the effects of phenobarbital.[1] Trimeglamide[2] (I) has been reported to possess hypnotic activity. Tigan (II) is well known as an antiemetic. Compound III has been reported[3] to have hypotensive activity and to potentiate muscle contraction. Vargha, *et al.*,[4] have synthesized a series of trimethoxybenzamides. A study[5] 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

$RNHCH_2CON(C_2H_5)_2$ I

$RNHCH_2C_6H_4$-*p*-$O(CH_2)_2N(CH_3)_2$ II



III IV V



(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.*, **58**, 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).