New Compounds: Preparation of Oxime Esters from 1-Azabicyclo[4.4.0]decane-4-one

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Abstract □ The synthesis of two new oxime esters is described. Preliminary results of pharmacological tests are also reported.

Keyphrases □ Oxime esters—synthesis from 1-azabicyclo[4.4.0]-decane-4-one, pharmacological evaluation as anticholinergic agents □ Anticholinergic agents, potential—synthesis, pharmacological evaluation of oxime esters from 1-azabicyclo[4.4.0]decane-4-one

Many of the presently available anticholinergic compounds possess an esteratic function. Recently, it was shown that the esteratic function is not absolutely essential (1). Numerous modifications have been studied, and recent reports indicated that esters derived from appropriate oximes possess anticholinergic activity (2). A greater activity in the tropane derivatives was reported relative to 1-methyl-4-piperidine. This was explained partially on the basis of a greater rigidity of the tropane system.

It was also reported (3–5) that the esters of amino-alcohols with a bridgehead nitrogen possess anticholinergic activity. It appeared that oximino esters derived from bridgehead nitrogen compounds might have some merit. 1-Azabicyclo[4.4.0]decane-4-one was prepared and derivatized to two oxime esters, 4-(benzoyloximino)-1-azabicyclo[4.4.0]decane and 4-(xanthene-9-acyloximino)-1-azabicyclo[4.4.0]decane. These oximino esters should possess the rigidity of a bicyclic system as well as characteristics of oximino esters which may be responsible for the activity.

Preliminary pharmacological testing was performed on isolated rabbit ileum.

EXPERIMENTAL

1-Azabicyclo[4.4.0]decane-4-one—The synthetic procedure employed was described by Rhodes and Soine (3). The initial synthesis commenced with bromobenzene. During the course of the work, the intermediate ethyl(2-pyridyl) acetate became commercially available; subsequent syntheses began with this intermediate.

1-Azabicyclo[4.4.0]decane-4-oxime—The oxime was prepared by the method described by Vogel (6). Characteristic IR bands for the oxime and carbon–hydrogen analytical data substantiated the structure: IR bands at 6.02 and 6.22 μ; m.p. 162–163°.

4-(Benzoyloximino)-1-azabicyclo[4.4.0]decane—This compound was prepared from 1-azabicyclo[4.4.0]decane-4-oxime (0.84 g., 0.005 mole) and benzoyl chloride (0.70 g., 0.005 mole) in anhydrous benzene. The reaction period was 48 hr., at which time the benzene was removed. Upon addition of a 3% solution of sodium bicarbonate, an oily layer separated. The oily layer was extracted into benzene and dried. The desired compound was identified as the methyl iodide: IR bands at 5.70–5.85 and 6.0–6.2 μ.

4-(Xanthene-9-acyloximino)-1-azabicyclo[4.4.0]decane—This compound was prepared using 1-azabicyclo[4.4.0]decane-4-oxime (0.84 g., 0.005 mole) and xanthene-9-acyl chloride (12 g., 0.005 mole) in anhydrous benzene. The conditions for isolation were analogous to the benzoate. The desired product was identified as the methyl iodide salt: IR bands at 5.70–5.85 and 6.0–6.2 μ.

Table II—Relative Potencies of Esters Derived from 1-Azabicyclo[4.4.0]decane-4-oxime

Compound	Effect	Relative Potency Compared with Atropine Sulfate
Benzoate	Cholinomimetic	—
Xanthene-9-acyl	Anticholinergic	1/46

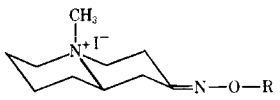
REFERENCES

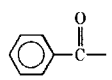
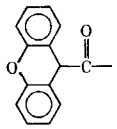
(1) R. B. Barlow, "Introduction to Chemical Pharmacology," Wiley, New York, N. Y., 1955, p. 154.

(2) M. M. Kochhar, R. G. Brown, and J. N. Delgado, *J. Pharm. Sci.*, **54**, 393(1965).

(3) H. J. Rhodes and T. O. Soine, *J. Amer. Pharm. Ass., Sci. Ed.*, **45**, 746(1956).

Table I—Physical Constants and Analytical Data



R	Recrystallized from	Melting Point[a]	Empirical Formula	Analysis, %[b] Calc.	Found
	Ethanol–isopropyl ether	152.5–153°	$C_{17}H_{23}IN_2O_2$	C, 48.93 H, 5.56	C, 49.12 H, 6.20
	Isopropyl alcohol Isopropyl ether	171.5–172°	$C_{24}H_{27}IN_2O_3$	C, 55.60 H, 5.25	C, 55.48 H, 5.42

[a] All melting points were taken on a Thomas-Hoover capillary melting-point apparatus and are uncorrected. [b] Carbon–hydrogen analyses were conducted by Schwarzkopf Microanalytical Laboratory, Woodside, NY 11377

(4) R. E. Counsell and T. O. Soine, *ibid.*, **49**, 289(1960).

(5) L. H. Sternbach and S. Kaisen, *J. Amer. Chem. Soc.*, **74**, 2219 (1952).

(6) A. I. Vogel, "Practical Organic Chemistry," Longmans, New York, N. Y., 1948, p. 345.

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COMMUNICATIONS

NMR Evidence for Self-Association of Theophylline in Aqueous Solution

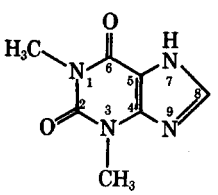
Keyphrases ☐ Theophylline, association in aqueous solution—determination, NMR spectroscopy ☐ Dimers, theophylline—in aqueous solution, NMR spectroscopy ☐ NMR spectroscopy—determination, theophylline self-association ☐ Association, theophylline—aqueous solution

Sir:

In 1957, Guttman and Higuchi (1) observed that the partition coefficient of theophylline between water and an organic phase remained unaltered (at ~23) over a concentration range (in the aqueous phase) of 2.3–28 × 10^{-3} *M*. This observation and the assumption that theophylline would exist only as the monomer in the nonaqueous phase (chloroform, 90%; isooctane, 10%) led them to conclude that: "for all practical purposes the partition coefficient of theophylline remains a constant over the concentration range studied, indicating the absence of association tendencies." In this respect, theophylline was unique; all the other xanthines examined, including several theophylline derivatives, were found to associate. The idea that theophylline does not self-associate in aqueous solution appears to have been generally accepted (2–5).

We present NMR spectroscopic evidence showing that theophylline does, in fact, associate in aqueous solution. This communication is part of a larger NMR investigation of the various association properties of xanthines.

The high-resolution 100-MHz. NMR spectrum of a 0.004 *M* D_2O solution of theophylline (I) has three



I

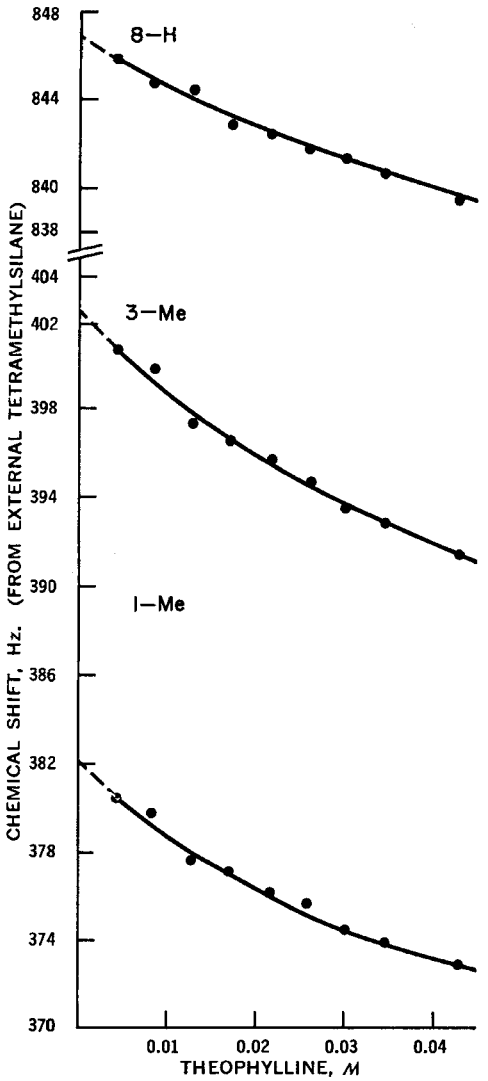


Figure 1—*Concentration dependence of theophylline proton chemical shifts at 30° in D_2O.*

signals of relative intensities, 1:3:3, at about 846, 401, and 380 Hz. (from external tetramethylsilane), corresponding to the proton at C-8 and to the 3- and 1-