10.31; N, 12.23. Found: C, 62.77; H, 5.42; Cl, 10.14; N, 11.98.

7-Chloro-2-dimethylamino-5-phenyl-3H-1,4-benzodiazepine (VI).—To 4.5 g. (14.25 mmoles) of III dissolved in 75 ml. of chloroform was added 9 ml. of phosphorous trichloride. The mixture was maintained at reflux for 1 hr. and then was extracted twice with water. The aqueous extracts were made basic with saturated sodium carbonate solution and were extracted with ether. The ether was evaporated on a steam bath under reduced pressure. The residue, after recrystallization from absolute ethanol, gave 3.3 g. (78%) of material m.p. 178–179°, ν_{max}^{Nujol} 1602 (s), 1573 (w), 1462, 1455, 1420, 1400, 1390, 1330, 1310, 1295 cm.$^{-1}$; $\lambda_{max}^{95\%\ ethanol\ (pH\ 1)}$ 251 mμ (ε 3200).

Anal. Calcd. for $C_{17}H_{16}ClN_3$: C, 68.56; H, 5.42; Cl, 11.91; N, 14.11. Found: C, 68.32; H, 5.64; Cl, 12.03, 12.04; N, 13.82.

The same compound, as shown by mixture melting point and infrared spectrum, was obtained in 60% yield when V was subjected to the methyl iodide–sodium hydride procedure described earlier.

Structural Changes and Anticholinergic Activity in a Class of Tropic and α-Methyltropic Acid Derivatives

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As a continuation of the studies on α-methyltropic acid carried out in our laboratories, the optically active isomers of tropine α-methyltropate were synthesized.[1] The replacement of the α-hydrogen atom with a methyl group in the tropate moiety allowed the isolation of stable optically active forms,[1] which were pharmacologically investigated. (−)-Tropine α-methyltropate was shown to be twice as active as atropine in antagonizing the acetylcholine-induced contraction in isolated gut.[2] This result prompted us to investigate the relationship between the pharmacological activity and certain structural changes in a series of tropic and α-methyltropic acid derivatives.

We first investigated the relation of optical activity and anticholinergic action. In order to answer the question whether molecular asymmetry is essential for such activity, tropine α-hydroxymethyl tropate,[3] devoided of optical activity because of the presence of two hydroxymethyl groups on the α-carbon atom, was studied. Furthermore, we investigated the influence of the basic moieties of the molecules on the anticholinergic activity. For this purpose, some tropoyl and α-methyltropoyl derivatives of 3- and 8-methyl-3,8-diazabicyclo[3.2.1]octane were prepared by Cignarella, *et al.*[4,5] The tropoyl and α-methyltropoyl derivatives of N-methylpiperazine have also been synthesized in the course of the present investigation.

Pharmacology. Methods.—The calculated amount of the products, dissolved in a fixed volume of saline (0.2 ml.), was added to the oxygenated Tyrode solution of the bath chamber, in which the isolated rat intestine was suspended, 1 min. before the introduction of acetylcholine. The recorded effects were evaluated as % reduction of the contractile response elicited by acetylcholine. Dose–response curves were found to be sufficiently parallel to allow a direct comparison of potency. To indicate the anticholinergic activity, the concentration of each compound that reduces the contractile effect of acetylcholine by 50% was recorded.

Results

Compound II (A, R = CH_2OH) was found to possess marked anticholinergic activity although quantitatively it was less effective than atropine. In the 8-methyl-3,8-diazabicyclo[3.2.1]octane amides (IV-V), the racemic tropoyl derivative (IV) was 4 to 5 times less effective than the racemic α-methyltropyl derivative (V). As previously reported,[4] the anticholinergic activity of V was found to reside in the (−) isomer Va, which is twice as active as the racemic form, thus indicating a close parallelism with the behavior of tropine α-methyltropate[2] (III). More detailed *in vivo* investigations on compound Va are still in progress and will be reported elsewhere; however, it may already be mentioned that Va appears twice as active as atropine in preventing methacholine-induced hypersalivation when orally administered to mice.

The N-methylpiperazine amides of tropic and α-methyltropic acids (VII, VIII, VIIIa) showed weak anticholinergic activity. The ratio of equally effective doses of racemic VIII and of the (−) isomer (VIIIa) was 3:2, which suggests a greater activity of the (±) isomer; however, these results seem scarcely significant because of the low activity of the products. The racemic tropoyl amide (VII) is about 3 times more effective than the corresponding α-methyltropoyl derivative (VIII).

Finally, (±)-3-methyl-8-α-methyltropoyl-3,8-diazabicyclo[3.2.1]octane (VI), which differs from V by having the substituents on 3- and 8-nitrogen reversed, was found to be about 9 times less active than V as an anticholinergic agent.

Discussion

In contrast with a hypothesis of Cushny,[6] the presence of an asymmetric carbon atom in atropine is not essential for parasympatholytic activity. In fact, the disappearance of the center of asymmetry in II reduces the activity only a little. This result agrees with the statement of Kreitmair[7] that optically inactive tropine benzylate has anticholinergic properties. On the other hand, the anticholinergic activity of the present *dl* derivatives of α-methyltropic acid is due to the (−) isomer.

The basic moiety of the compounds tested seems to determine the degree of anticholinergic activity. In fact, when tropine is replaced by 8-methyl-3,8-diazabicyclo[3.2.1]octane and, especially, when replaced

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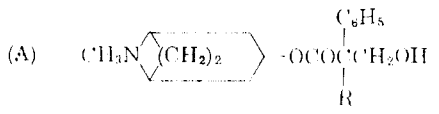
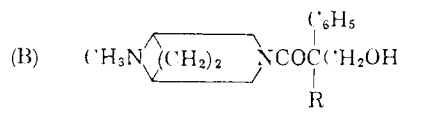
TABLE I

(A)



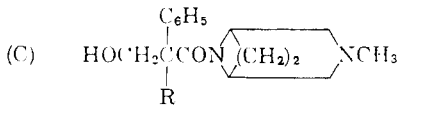
Compd.	Isomer	R	Ref.	*In vitro* activity,[a] (γ/ml.)	Relative potency
I	± Atropine			0.016	100
II		CH_2OH	3	.025	64
III	(±)	CH_3	1	.018	89
IIIa	(−)	CH_3	1	.008	200
IIIb	(+)	CH_3	1	.300	5

(B)



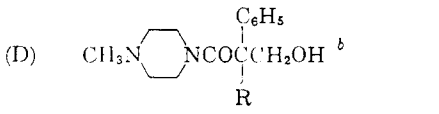
IV	(±)	H	4	0.180	9
V	(±)	CH_3	4	.040	40
Va	(−)	CH_3	4	.020	80
Vb	(+)	CH_3	4	>10	0

(C)



VI	(±)	CH_3	5	0.350	5

(D)



VII[c]	(±)	H	...	0.190	8
VIII[d]	(±)	CH_3	...	.600	3
VIIIa[e]	(−)	CH_3	...	.400	4

[a] Concentration able to reduce to 50% the contractile response of isolated intestine to acetylcholine. [b] These compounds were prepared starting from N-methylpiperazine by a procedure similar to that described[4,5] for IV–VI. [c] Yield, 48%; m.p. 102–103° (Et_2O). *Anal.* Calcd. for $C_{14}H_{20}N_2O_2$: C, 67.74; H, 8.12; N, 11.28. Found: C, 67.92; H, 8.27; N, 10.92. [d] Yield, 68%; m.p. 225–228° (HCl salt) (EtOH). *Anal.* Calcd. for $C_{15}H_{23}ClN_2O_2$: N, 9.37; Cl, 11.86. Found: N, 9.02; Cl, 12.06. [e] Yield, 55%; m.p. 213–215° (HCl salt) (EtOH). *Anal.* Calcd. for $C_{15}H_{23}ClN_2O_2$: N, 9.37; Cl, 11.86. Found: N, 9.51; Cl, 11.91. $[\alpha]D^{20}$ −45.4° (*c* 1, H_2O).

by N-methylpiperazine or by 3-methyl-3,8-diazabicyclo[3.2.1]octane, a decrease in activity was observed.

As far as a comparison of the anticholinergic activity in the tropoyl and α-methyltropoyl series is concerned, α-methyltropoyl amides are more active than the corresponding tropoyl derivative in the 8-methyl-3,8-diazabicyclo[3.2.1]octane series (B), but are less active in the N-methylpiperazine series (D).

The weak anticholinergic activity of (±)-3-methyl-8-α-methyltropoyl-3,8-diazabicyclo[3.2.1]octane (VI) may be correlated with the lack of structural similarity with the active isomer V. This result offers an indirect support for the assumed[4] pharmacological analogy of 8-methyl-3,8-diazabicyclo[3.2.1]octane (parent compound of V) and tropane.

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Steroidal Heterocycles. X.[1] Steroidal[3,2-*d*]pyrimidines and Related Compounds

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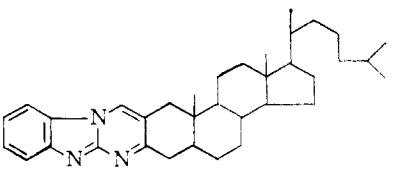
As part of our continuing program on the synthesis of steroidal heterocycles, we have prepared a series of steroidal[3,2-*d*]pyrimidines. Prior to our initial report in the field of steroidal heterocycles,[2] no steroidal pyrimidines had been reported.[3] Subsequently, several other groups have reported on steroidal[3,2-*d*]-pyrimidines.[4]



Our method for preparing the steroidal[3,2-*d*]pyrimidines employed the same intermediates, the 2-hydroxymethylenesteroids, as used previously with other steroidal heterocycles.[2,5,6] These intermediates were converted to the corresponding steroidal pyrimidines by the procedure of Baumgarten, *et al.*,[7] or a modification of this method. With this procedure, the pyrimidine ring was formed from the 2-hydroxymethylenesteroids and an amidine hydrochloride. Triethylamine was generally the catalyst employed and ethanol was usually the solvent. Baumgarten, *et al.*,[7] reported yields of 23–43% in their preparation of nonsteroidal pyrimidines. Our yields generally ran lower, but with the aid of chromatography, the steroidal pyrimidines could be isolated readily. 17β-Hydroxy-2-hydroxymethylene-5α-androstan-3-one (**1**) and acetamidine hydrochloride gave 17β-hydroxy-5α-androstano[3,2-*d*]-2′-methylpyrimidine (**2**). A side product was isolated from the acid-soluble part of the reaction mixture and shown to be 2-aminomethylene-17β-hydroxy-5α-androstan-3-one (**3**).

Similarly, when 17β-hydroxy-2-hydroxymethylene-17β-methyl-5α-androstan-3-one (**4**) was treated with acetamidine and formamidine hydrochlorides, the pyrimidines **5** and **6**, respectively, were obtained. The enamine **7** was isolated from the reaction mixture from

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