ate (2 g., VIIa, $R_1 = R_3 = H$; $R_2 = OMe$, prepared by treating an aqueous solution of the bromide with 10% perchloric acid and recrystallizing the precipitate from ethanol, m.p. 174–175°) was dissolved in 200 ml. of water, and treated over the course of 2 hr. at 90° with 10 g. of zinc dust and 15 ml. of 60% perchloric acid in small portions. The yellow color of the solution faded to a final water-white. Excess zinc was removed by filtration and the filtrate was cooled. The precipitated white solid was filtered, dissolved in a small volume of methanol, and poured into 5% NaOH solution. The base was extracted with ether. The dried ether solution was treated with dry hydrogen bromide and the precipitated salt was recrystallized from ethanol to give 0.5 g. of VIIIb, m.p. 225–228°. This material, by thin layer chromatography, contains none of the higher melting, less soluble *syn-cis* epimer VIIIa.

Sodium–Liquid Ammonia Reduction of VIIa.—A solution of 0.5 g. of quaternary bromide VIIa ($R_1 = R_3 = H$; $R_2 = OMe$) in 10 ml. of methanol was poured into a mixture of ice and 5% NaOH solution. The precipitated base was extracted with 100 ml. of ether, and the dried ether layer was added to a mixture of 400 ml. of liquid ammonia and 10 ml. of *t*-butyl alcohol. The resulting clear solution was treated with stirring at reflux (−33°) with very small pieces of clean sodium until the solution turned blue (3 min.). Methanol (5 ml.) was then added immediately to discharge the blue color (to avoid Birch reduction of the aromatic ring). The ammonia was allowed to evaporate, 20 ml. of water was added, and the ether phase was separated and dried. Thin layer chromatography of this solution showed a major spot for the *syn-cis* epimer VIIIa, R_f 0.40, and a very weak spot (R_f 0.44) corresponding to the *anti-cis* epimer VIIIb.

***cis*- and *trans*-1-(*m*-Methoxyphenylacetyl)-octahydro-1-pyrindine (XI).**—A solution of 13.65 g. (0.075 mole) of *m*-methoxyphenylacetic acid and 20 ml. of thionyl chloride in 200 ml. of benzene was refluxed for 1 hr., then concentrated to a yellow oil under reduced pressure. The oil was dissolved in 50 ml. of benzene and added dropwise at 0° with rapid stirring to a mixture of 7.5 g. (.059 mole) of the octahydro-1-pyrindine, 45 ml. of benzene and 48 ml. of 12% NaOH solution. After stirring overnight at room temperature, the benzene layer was separated, washed with 5% NaOH solution, water, 2 *N* HCl, and water. The solution was dried and concentrated to 16 g. of an orange oil.

Prepared as above from reportedly "pure" *cis*- and *trans*-octahydro-1-pyrindines, the total crude XIa and XIb both showed 2 clear spots by thin layer chromatography (R_f 0.8 and 0.9; solvent ethyl acetate), the faster of which was the major spot in the *trans* compound and the slower of which was the major spot in the *cis* compound. Extensive chromatography on alumina (Merck neutral) afforded pure samples of both amides. Both products were eluted with ether, the *trans* compound came off the column first. From this work, it was estimated that the reportedly pure *trans*-octahydro-1-pyrindine actually contained *ca.* 10% of the *cis*, and the reportedly pure *cis* base contained *ca.* 25% of the *trans* isomer.

Lithium Aluminum Hydride Reductions of Amides IV, VI, XIa, and XIb.—The amide in ether was treated with excess lithium aluminum hydride and the mixture was stirred overnight. The reaction mixture was decomposed cautiously by the slow addition of the minimum amount of water. After stirring for several hours, the granular white slurry was filtered, and the filtrate was treated with dry hydrogen bromide. The precipitated salt was filtered and recrystallized from 2-propanol. The IXa hydrobromides (*cis*) prepared from IV and Xa were identical by melting point (153–154°), infrared spectrum, and thin layer chromatography. The IXb hydrobromides (*trans*) prepared from VI and Xb were identical by the same criteria (m.p. 169–170°).

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Notes

Reaction of 6-Chloro-2-chloromethyl-4-phenylquinazoline 3-Oxide with Dimethylamine

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The reaction of 2-chloromethyl-4-phenylquinazoline 3-oxides with amines has been the subject of considerable recent study.[1–5] Both Sternbach, *et al.*,[2] and Bell[5] have reported that reaction of 2-chloromethyl-4-phenylquinazoline 3-oxides with secondary amines gives only the "normal" quinazoline product in which the chloro atom was replaced by the secondary amine. We have confirmed this simple replacement when 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide was allowed to react with either diethylamine or piperidine. On the other hand, when the secondary amine employed was dimethylamine, two reaction products were obtained. The simple replacement product, 6-chloro-2-dimethylaminomethyl-4-phenylquinazoline 3-oxide (II),[1] and the rearranged product, 7-chloro-2-dimethylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide, (III) were both obtained.

To prove the structure of III, 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide (IV)[1] was methylated with sodium hydride and methyl iodide; III resulted in 83% yield.

A similar alkylation procedure converted 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine (V)[1] to 7-chloro-2-dimethylamino-5-phenyl-3H-1,4-benzodiazepine (VI). The latter compound was also prepared by deoxygenation of III. The spectral properties of III were markedly similar to IV but dissimilar to I and II.[2,6]

N-Alkylation of IV was also carried out with sodium hydride and benzyl chloride, allyl bromide, and methoxymethyl chloride. Cyclohexyl bromide, cyclohexyl iodide, propargyl bromide, ethyl bromoacetate, and ethyl chloroacetate failed to give the desired N-alkylated product.

(1) L. H. Sternbach, S. Kaiser, and E. Reeder, *J. Am. Chem. Soc.*, **82**, 475 (1960).

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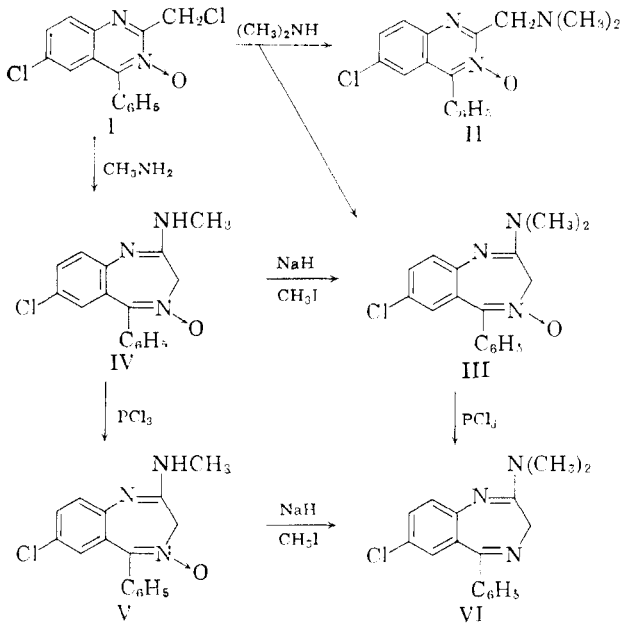
(6) The ultraviolet spectrum of IV as reported[7] could be reproduced in 95% ethanol. It was found that the six-membered ring structure could be differentiated from the seven-membered ring structure easily if the spectra were determined by solution of the compound in 5 ml. of 95% ethanol diluted to 50 ml. with 0.1 *N* HCl.

(7) L. H. Sternbach, B. A. Koechlin, and E. Reeder, *J. Org. Chem.*, **27**, 4671 (1962).



The products obtained by alkylation of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine (IV) with methyl iodide, allyl bromide, and methoxymethyl chloride retained the essential central nervous system (CNS) profile of chlorodiazepoxide (IV) on the basis of a behavioral test in mice.[8] The potencies of all these compounds were of the same order of magnitude as noted in this type of test. Benzylation, however, resulted in a product whose CNS activity was greatly diminished. In preventing the tonic hind leg extension in audiogenic seizure mice[9] and in antagonizing the aggressive behavior in isolated mice,[10] again the four compounds were effective at comparable doses (see Table I).

TABLE I

	Mouse p.o. LD_{50}, mg./kg.	Mouse p.o. Isolated mice	ED_{50} mg./kg., Audiogenic seizure
IV	680	15	4.4
N-Methyl-IV	400	15	5.5
N-Benzyl-IV	>1000	No significant CNS activity at doses tested (up to 1000 mg./kg. P.O.)	
N-Allyl-IV	>1000	15	2.7
N-Methoxymethyl-IV	1000	10	5.0

Experimental[11]

6-Chloro-2-dimethylaminomethyl-4-phenylquinazoline 3-Oxide (II) and 7-Chloro-2-dimethylamino-5-phenyl-3H-1,4-benzodiazepine 4-Oxide (III).—To 47.0 g. of dimethylamine (1.05 moles) dissolved in 120 ml. of ice-cooled methanol was added 20.0 g. (65.5 mmoles) of 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide (I).[6] The reaction mixture was allowed to stand at room temperature for 2 hr. The precipitated material was filtered and after recrystallization from acetonitrile gave 4.0 g.(19.4%) of II, m.p. 133–133.5°, lit.[2] 133–134°, ν_{max}^{Nujol} 1482 (s), 1300 (s) cm.$^{-1}$; $\lambda_{max}^{95\%\ ethanol\ (pH\ 1)}$ 265 mμ (ε 34,500), 232.5 (24,000).

Anal. Calcd. for $C_{17}H_{16}ClN_3O$: C, 65.07; H, 5.14; Cl, 11.30; N, 13.39. Found: C, 64.84; H, 5.29; Cl, 11.45; N, 13.40.

The reaction mixture deposited III after standing overnight in a refrigerator. Recrystallization from ethanol afforded 1.7 g. (8.25%) of product, m.p. 204.5–205.5°, ν_{max}^{Nujol} 1605 (s), 1584(m), 1470, 1452, 1382, 1280 cm.$^{-1}$; $\lambda_{max}^{95\%\ ethanol\ (pH\ 1)}$ 251 mμ (ε 36,000); $\lambda_{inf}^{95\%\ ethanol\ (pH\ 1)}$ 305 mμ (ε 10,000).

Anal. Calcd. for $C_{17}H_{16}ClN_3O$: C, 65.07; H, 5.14; Cl, 11.30; N, 13.39. Found: C, 65.22; H, 5.36; Cl, 11.31, 11.29; N, 13.35.

6-Chloro-2-piperidinomethyl-4-phenylquinazoline 3-Oxide.—This compound was prepared using the procedure for II. Recrystallization from absolute ethanol gave 73.5% yield, m.p. 140.5–142.5°, $\lambda_{max}^{95\%\ ethanol\ (pH\ 1)}$ 262 mμ (ε 34,700), 238 (19,000); ν_{max}^{Nujol} 1607 (w), 1548 (w), 1309 (m), 1288 (m), cm.$^{-1}$.

Anal. Calcd. for $C_{20}H_{20}ClN_3O$: C, 67.88; H, 5.70; Cl, 10.02; N, 11.88. Found: C, 67.86; H, 5.64; Cl, 9.99, 9.93; N, 11.74.

6-Chloro-2-diethylamino-4-phenylquinazoline 3-Oxide.—This compound was prepared using the procedure for II. Recrystallization from acetonitrile gave a 59% yield, m.p. 183.5–184° dec., ν_{max}^{Nujol} 2600 (m, shoulder), 2450 (s), 2400 (m, shoulder) 1600 (w), 1595 (w), 1550 (w), 1480, 1440, 1420, 1390, 1355, 1330, 1320, 1300, 1225 cm.$^{-1}$; $\lambda_{max}^{95\%\ ethanol\ (pH\ 1)}$ 263 mμ (ε 33,600), 238 (10,800).

Anal. Calcd. for $C_{19}H_{20}ClN_3O$: C, 60.32; H, 5.60; Cl, 9.37; N, 11.11. Found: C, 60.53; H, 5.57; Cl, 8.71; N, 11.12.

7-Chloro-2-dimethylamino-5-phenyl-3H-1,4-benzodiazepine 4-Oxide (III) by Methylation of 7-Chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-Oxide (IV).—To 15.0 g. (50 mmoles) of IV[2], dissolved in an ice-cooled mixture of 200 ml. of toluene and 200 ml. of dimethylformamide was added 8.1 g. (169 mmoles) of a 50% dispersion of sodium hydride in oil. Hydrogen evolution ceased after 1 hr. and then 7.1 g. (50 mmoles) of methyl iodide was added rapidly. The resulting voluminous precipitate was removed by filtration. Further addition of 0.5 g. of methyl iodide discharged the yellow color of the reaction mixture completely. Ice was added, and the organic phase was separated and diluted with ether. On standing, 8.85 g. (56.7%) m.p. 201–204.5°, precipitated. This material was identical with that prepared from I and dimethylamine as shown by mixture melting point and ultraviolet and infrared spectra. The ether–toluene mother liquor was evaporated and the residue was washed with Skellysolve B. Recrystallization afforded 2.45 g. of material. The total yield was 77.5%.

7-Chloro-2-benzylmethylamino-5-phenyl-3H-1,4-benzodiazepine 4-Oxide.—This compound was prepared *via* the above methylation procedure using benzyl chloride. Recrystallization from 1-butanol gave a 65% yield, m.p. 204–204.5°, ν_{max}^{Nujol} 1604 (s), 1582 (s), 1520 (w), 1458, 1440, 1390, 1360, 1300 cm.$^{-1}$; $\lambda_{max}^{95\%\ ethanol\ (pH\ 1)}$ 253 mμ (ε 33,400); $\lambda_{inf}^{95\%\ ethanol\ (pH\ 1)}$ 307 mμ (ε 9600).

Anal. Calcd. for $C_{23}H_{20}ClN_3O$: C, 70.85; H, 5.17; Cl, 9.10; N, 10.78. Found: C, 71.01, 70.93; H, 5.25, 5.45; Cl, 8.93, 8.94; N, 10.52.

7-Chloro-2-allylmethylamino-5-phenyl-3H-1,4-benzodiazepine 4-Oxide.—This compound was prepared *via* the methylation procedure using allyl bromide in place of methyl iodide. Recrystallization from isopropyl alcohol gave a 73% yield, m.p. 126–126.5°, $\nu_{max}^{CHCl_3}$ 1635 (w), 1602 (s), 1580 (s), 1450, 1435, 1400, 1380, 1276 cm.$^{-1}$; $\lambda_{max}^{95\%\ ethanol\ (pH\ 1)}$ 253 mμ (ε 32,800); $\lambda_{inf}^{95\%\ ethanol\ (pH\ 1)}$ 307 mμ (ε 9200).

Anal. Calcd. for $C_{19}H_{18}ClN_3O$: C, 67.15; H, 5.34; Cl, 10.44; N, 12.27. Found: C, 67.24; H, 5.34; Cl, 10.45; N, 12.34.

7-Chloro-2-(methoxymethyl)methylamino-5-phenyl-3H-1,4-benzodiazepine 4-Oxide.—This compound was prepared by the same procedure using methoxymethyl chloride in place of methyl iodide. Recrystallization from absolute ethanol gave a 64% yield, m.p. 139–140°, ν_{max}^{Nujol} 1605 (s), 1582 (s), 1460, 1440 1380, 1310, 1295, 1285 cm.$^{-1}$; $\lambda_{max}^{95\%\ ethanol\ (pH\ 1)}$ 250 mμ (ε 32,800); $\lambda_{inf}^{95\%\ ethanol\ (pH\ 1)}$ 307 mμ (ε 9600).

Anal. Calcd. for $C_{18}H_{18}ClN_3O_2$: C, 62.88; H, 5.28; Cl,

(8) These evaluations were carried out by Dr. J. A. Gylys of the Department of Pharmacology of the Warner-Lambert Research Institute. The procedure employed was that developed by S. Irwin, M. Slabok, P. L. Debiase, and W. M. Govier, *Arch. Intern. Pharmacodyn.*, **118**, 358 (1959).

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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.$^{-1}$; $\lambda_{max}^{95\% \text{ ethanol (pH 1)}}$ 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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