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Small Ring Analogs of Acetylcholine. Synthesis and Absolute Configurations of Cyclopropane Derivatives[1a]

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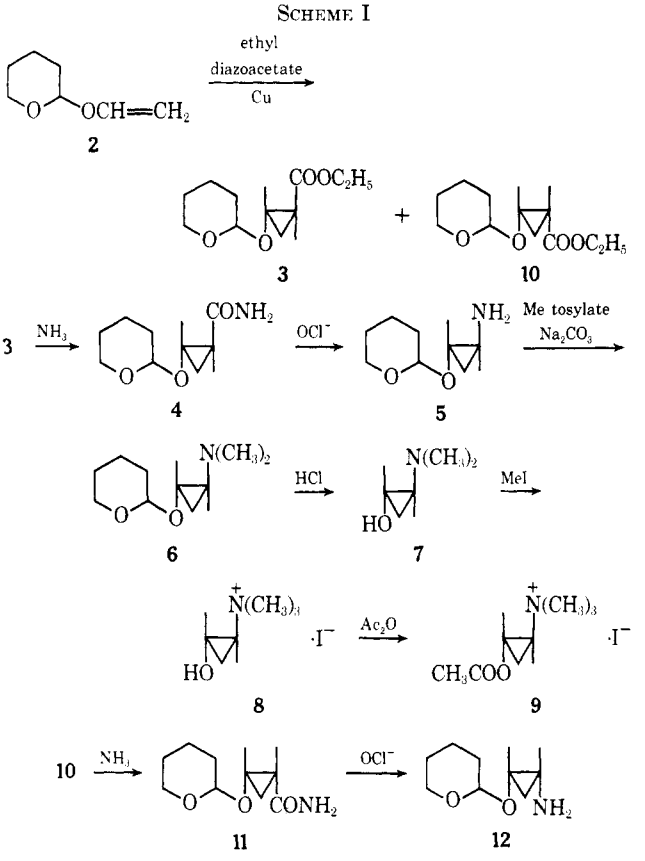
Conformational rigidity has been conferred upon the OCCN portion of acetylcholine by incorporation of the C atoms into a cyclopropane ring. *trans*-2-Acetoxycyclopropyltrimethylammonium iodide has been prepared from an olefinic starting material, 2-vinyloxytetrahydropyran; assignment of the trans configuration to the 1,2-disubstituted cyclopropane systems was based upon literature precedent and upon nmr data, and was confirmed by X-ray crystallographic analysis. Resolution of one of the racemic intermediates in the reaction sequence was achieved, which permitted preparation of both enantiomers of the final product. X-Ray crystallographic analysis has demonstrated that the muscarinically active (+)-*trans*-2-acetoxycyclopropyltrimethylammonium iodide possesses the same absolute configuration as the muscarinically active enantiomers of acetyl-β-methylcholine and muscarine.

Earlier communications have presented preliminary reports of the synthesis[2] of (+)- and (−)-*trans*-2-acetoxycyclopropyltrimethylammonium iodide **9** and the details of the cholinergic effects and enzymatic hydrolysis rates[3] of the two isomers. Herein are presented the details of synthesis of (+)- and (−)-**9** (outlined in Scheme I), and assignments of absolute configurations to the enantiomers.

The 2-tetrahydropyranyl moiety was utilized to mask the cyclopropanol group which is highly susceptible to ring-opening and other undesirable reactions.[4] This protecting group is stable in neutral and basic media, and is easily cleaved under very mild acidic conditions.[5] 2-Vinyloxytetrahydropyran (**2**) reacted with ethyl diazoacetate to give a mixture of the *cis*- and *trans*-cyclopropane isomers (**10** and **3**) which were separable by distillation. The configurational assignments at this stage were tentative and were based upon the expected predominance of the sterically favored trans isomer in reactions of this type.[6] Vpc analysis of the crude reaction mixture indicated a ratio of *trans*-**3** to *cis*-**10** of 45:1. Attempts to modify this ring-closure reaction to attain larger proportions of the cis isomer failed, as did efforts to photoisomerize the trans isomer to cis.[7]

The trans isomer **3** could be converted into the amide **4** either with anhyd NH_3 in ethylene glycol or by use of *n*-BuLi and liq NH_3;[8] while the *n*-BuLi method afforded lower yields than the ethylene glycol method, it

SCHEME I



permitted a less tedious, less time-consuming work-up. Ammonolysis of the cis ester **10** by the ethylene glycol method (Chart I) gave rise to an amide which could not be obtained analytically pure. Both the trans amide **4** and its cis isomer **11** underwent the Hofmann hypohalite reaction to form the trans and cis primary amines **5** and **12**. The cis amine **12** did not yield a satisfactory analysis for all elements, although spectral data supported its structure. The use of the reaction sequence in Scheme I as a route to the cis isomer of structure **9** was concluded to be unpromising and was abandoned.

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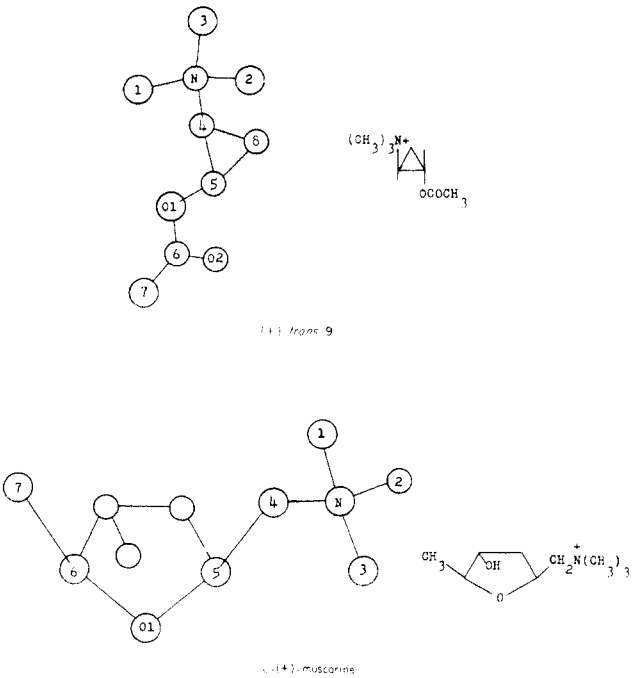

Figure 1.—Absolute configurations of muscarinically active compounds. Structural representation for (+)-*trans*-**9** adapted from Chothia and Pauling.[11]

The nmr spectrum of the cis primary amine **12** showed a sharp singlet at δ 1.7, which integrated for 2 protons and was assigned to the NH_2 group. The trans isomer **5** showed a sharp singlet at δ 1.4 which integrated for 2 protons and was assigned to the NH_2 group. The NH_2 group of cyclopropylamine exhibits a sharp singlet at δ 1.83.[9] The positions of the chemical shifts of the NH_2 protons of the cis and trans isomers **12** and **5** support the configurational assignments, since intramolecular H bonding involving the NH_2 group, which may be expected to be stronger in the cis isomer than in the trans, has been reported[10] to produce a downfield shift. Crystallographic studies[11] have proved the correctness of these assignments of geometry to the cis-trans isomers.

The tetrahydropyranyl group was removed from **6** under mild conditions to afford a quantitative yield of (±)-*trans*-2-dimethylaminocyclopropanol (**7**) which was resolved with *l*-tartaric acid. Each enantiomer of **7** was converted into the final structure **9**.

The (+) enantiomer of **9**, which exhibits powerful muscarinic effects,[3] has been shown by X-ray crystallographic analysis to have the S−S absolute configuration[11] (Figure 1). Models indicate that conformations are possible in which the train of atoms in (+)-*trans*-**9**, C1, C2, C3; N; C4; C5; O1; C6; C7 superimpose perfectly upon C1, C2, C3; N; C4; C5; O1; C6; C7 of L-(+)-muscarine (Figure 1), the muscarinically active stereoisomer.[12] The absolute configuration of (+)-*trans*-**9** is the same as that of the corresponding asymmetric center of the muscarinically potent acetyl (+)-(*S*)-β-methylcholine.[13] The conformation suggested[11] for (+)-*trans*-**9** "relevant to muscarinic receptors" differs from a conformation for "receptor-bound" acetylcholine proposed by Belleau and Puranen.[14] Data are not yet available which would permit selection one of these conformations over the other.

Experimental Section[15]

2-(2-Tetrahydropyranyloxy)ethyl chloride (**1**) was prepared in 80% yield by the method of Frearson, *et al.*:[16] bp 103–104° (25 mm); n^{27}D 1.4528 [lit.[16] bp 93° (20 mm); n^{20}D 1.4580].

2-Vinyloxytetrahydropyran (**2**).—A 1-l. flask was charged with 509 g (9.1 moles) of KOH, and the system was connected to a source of reduced pressure (H_2O aspirator). The flask was maintained at 175–180° while 279 g (1.69 moles) of **1** was added dropwise over 2 hr, while maintaining a gentle flow of air through the apparatus. After addition was complete, stirring was continued at 170–180° for 1.5 hr, then at 195–200° for 1 hr, and finally at 215–220° for 0.5 hr. A total of 195 g of colorless liquid distilled. The residue in the reaction vessel was taken up in H_2O and was extracted with Et_2O. The extract was added to the distillate, the combined organic phases were dried (K_2CO_3) and concentrated at atm pressure, and the residue was distilled through a column packed with Berl saddles to yield 122.7 g of a colorless liquid, bp 55–56° (25 mm). The pot residue was distilled to afford of 37.6 g of starting material **1**; yield of **2** (based upon amount of **1** recovered), 66%. Distillation of **2** through a spinning band column gave a center fraction: bp 60° (21 mm); n^{25}D 1.4413. *Anal.* ($C_7H_{12}O_2$) C, H.

Ethyl *cis*- and *trans*-2-(2-Tetrahydropyranyloxy)cyclopropanecarboxylate (**10** and **3**).—Ethyl diazoacetate (185 g, 1.62 moles, Aldrich Chemical Co.) in 180 g (1.40 moles) of **2** was added dropwise to a stirred mixture of 3.5 g of Cu powder (Matheson, Coleman, and Bell, purified) and 58 g (0.45 mole) of **2** at 125–130° over 5.5 hr. After addition was complete, stirring was continued at 150–160° for 0.5 hr. The reaction mixture was cooled to room temp and was filtered. The combined filtrates from two such reactions were distilled through a Vigreux column; the fraction bp 54–114° (3 mm), amounting to 507 g, was distilled through a spinning band column. The fraction bp 73–74° (1 mm), consisting of the cis isomer **10** was homogeneous by vpc: yield, 9.0 g (1.3%); n^{30}D 1.4572; ir (film) 1720 cm^{-1} (C=O). *Anal.* ($C_{11}H_{18}O_4$) C, H.

The fraction bp 92–94° (1 mm) consisted of 433 g (62%) of trans isomer **3**: n^{30}D 1.4531; ir (film) 1725 cm^{-1} (C=O). *Anal.* ($C_{11}H_{18}O_4$) C, H. This material demonstrated a different vpc retention time than the bp 73–74° fraction, and was homogeneous.

***trans*-2-(2-Tetrahydropyranyloxy)cyclopropanecarboxamide** (**4**). **Method A.**—Anhydrous NH_3 was passed into a stirred mixture of 543 g (2.5 moles) of **3** and 3.8 l. of ethylene glycol at room temp for 62 hr. Removal of the NH_3 and ethylene glycol under reduced pressure at a temp not exceeding 75° gave 476 g of a light yellow-orange solid which was treated with 500 ml of C_6H_6 on a steam bath. The resulting soln was filtered, to the filtrate was added 2.5 l. of anhyd Et_2O, which resulted in separation of a light yellow-orange crystalline solid which was collected on a filter. Dilution of the filtrate with 500 ml of heptane caused a light yellow oil to separate, which was discarded. The organic soln, upon standing overnight, deposited crystals which were collected on a filter. This filtrate was again dild with 500 ml of heptane; the oil which sepd was removed; and the organic layer deposited an additional crop of crystals upon standing; total yield, 258 g (55%). This material was sufficiently pure for

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(15) Melting points were determined in open capillaries on a Thomas-Hoover Uni-Melt apparatus and are corrected. Boiling points are uncorrected. Ir spectra were recorded on Beckman IR5-A and IR-10 instruments, and nmr spectra on a Varian Associates A-60 instrument (Me$_4$Si). Optical rotations were determined on a Zeiss circular scale polarimeter. Gas chromatograms were obtained using an F & M Model 500 instrument with a Model 1609 flame ionization detector, using He as the carrier. Where analyses are indicated only by symbols of the elements, the analytical results for those elements were within ±0.4% of the theoretical value.

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subsequent steps. A small portion of it was recryst repeatedly from EtOAc: mp 92.5–93.5°; ir (KBr) 1620 ("amide II"), 1655 ("amide I"), 3190 (NH_2), and 3360 cm^{-1} (NH_2). *Anal.* ($C_9H_{15}NO_3$) C, H, N.

Method B.—To a stirred mixture of 75 ml of liquid NH_3 and 25 ml of purified THF was added in a slow stream 0.1 mole of *n*-BuLi in hexane (Alpha Inorganics, Inc.); a copious white ppt formed. Compound **3** (20.8 g 0.097 mole) in an equal vol of THF was added dropwise with stirring; the white ppt dissolved. After stirring 4 hr, the excess NH_3 was removed at room temp, the reaction mixture was poured into an ice–H_2O slush, and the resulting soln was extracted repeatedly with Et_2O. Evaporation of the Et_2O left a light yellow gum which was chromatographed in C_6H_6 on neutral alumina and eluted with Et_2O–MeOH (9:1). The solid material from the eluate was recryst from EtOAc to yield 4.6 g (26%) of white crystals: mp 118–120°; ir ($CHCl_3$) of the product of method B was superimposable upon a similar spectrum of the product of method A.

***cis*-2-(2-Tetrahydropyranyloxy)cyclopropanecarboxamide (11).**—Method A, described for the trans isomer **4**, was employed, using 10.8 g (0.05 mole) of **10** and 900 ml of ethylene glycol. Removal of the ethylene glycol from the reaction mixture left a yellow solid residue which was treated with 275 ml of EtOAc on a steam bath. On filtration and cooling overnight, this soln deposited 5.7 g of colorless crystals, the mother liquor yielded additional crystals; total yield, 6.8 g (72%). Repeated successive recrystallizations from EtOAc, C_6H_6, and Me_2CO and column chromatography on silica gel afforded colorless crystals: mp 180–181°; ir (KBr) 1615 ("amide II"), 1660 ("amide I"), 3185 (NH_2), and 3350 cm^{-1} (NH_2). *Anal.* ($C_9H_{15}NO_3$) C, H; N: calcd, 7.56; found, 8.07.

***trans*-2-(2-Tetrahydropyranyloxy)cyclopropylamine (5).**—A mixture of 250 g (1.35 moles) of **4** and a soln of 101 g (1.4 moles) of Cl_2 and 285 g (7.1 moles) of NaOH in 3.24 l. of H_2O was stirred at room temp for 0.5 hr, then at 50–60° for 19 hr. The reaction mixture was saturated with K_2CO_3 and extracted several times with Et_2O. An orange-yellow liquid which separated from the Et_2O extracts was removed, and the Et_2O phase was dried (K_2CO_3) and concentrated under reduced pressure. The residual liquid was distilled through a Vigreux column, bp 69–72° (0.8 mm), to yield 140 g (67%) of a colorless liquid. For characterization, a small portion of this material was distilled through a spinning band column, bp 67° (1.3 mm). Glc indicated that this distillate was homogeneous: $n^{25}D$ 1.4698; ir (film) 3300 (NH_2) and 3375 cm^{-1} (NH_2); nmr (CCl_4) δ 1.4 (s, 2H).

A phenylthiourea derivative was recrystd repeatedly from EtOH, mp 160–161°. *Anal.* ($C_{15}H_{20}N_2O_2S$) C, H, N, S.

***cis*-2-(2-Tetrahydropyranyloxy)cyclopropylamine (12).**—A soln of 2.3 g (0.03 mole) of Cl_2, 6.3 g (0.16 mole) of NaOH, and 4.5 g (0.02 mole) of **11** in 58 ml of H_2O was stirred at room temp for 0.5 hr, then at 60–65° for 21 hr. The reaction mixture was saturated with K_2CO_3 and extracted repeatedly with Et_2O, the combined extracts were dried (Na_2SO_4) and filtered, and the Et_2O was removed. The light yellow residue was distilled: bp 58–59° (4.2 mm); yield, 2.8 g (73%) of a colorless liquid; $n^{30}D$ 1.4779; ir (film) 3300 (NH_2) and 3370 cm^{-1} (NH_2); nmr (CCl_4) δ 1.7 (s, 2H). *Anal.* ($C_8H_{15}NO_2$) H, N; C: calcd, 61.12; found, 63.45.

A phenylthiourea derivative was recrystd from anhyd EtOH, mp 167.5–168°. *Anal.* ($C_{15}H_{20}N_2O_2S$) C, H; N: calcd, 9.58; found, 10.82; S, calcd, 10.97; found, 12.85.

A benzamide derivative was recryst repeatedly from C_6H_6, mp 162–163°. *Anal.* ($C_{15}H_{19}NO_3$) H; C: calcd, 68.94; found, 71.18.

***trans*-2-(2-Tetrahydropyranyloxy)cyclopropyldimethylamine (6).**—A mixture of 190 ml of anhyd MeOH, 31.8 g of anhyd Na_2CO_3, and 19.1 g (0.12 mole) of **5** was stirred under reflux for 10 min, then 45.2 g (0.24 mole) of methyl *p*-toluenesulfonate in 190 ml of anhyd MeOH was added dropwise with stirring over 21 hr. After addition was complete, stirring and refluxing were continued for 7.25 hr, the reaction mixture was allowed to cool to room temp and was filtered. The solid which collected on the filter was washed with 3 portions of anhyd Et_2O; the washings were added to the filtrate, which caused sepn of additional solid which was removed by filtration. The combined filtrate and Et_2O washings were concentrated under reduced pressure to give a light yellow liquid which was distd through a Vigreux column: bp 54–61° (0.6 mm); yield, 7.0 g (31%). A MeI salt of this product was recryst from Me_2CO–EtOAc, mp 133.0–134.5° dec, when introduced into the melting point bath at 128°. *Anal.* ($C_{11}H_{22}INO_2$) C, H, I.

(±)-*trans*-2-Dimethylaminocyclopropanol (7).—A soln of 19.5 g (0.105 mole) of **6** in 230 ml of 3% HCl was stirred at room temp for 9 hr. The reaction mixture was washed several times with Et_2O, then was satd with K_2CO_3 while immersed in an ice bath. The resulting mixture was extracted repeatedly with Et_2O, the combined extracts were dried (Na_2SO_4), and the solvent was removed under reduced pressure to leave a light yellow liquid which was distd through a "short path" apparatus, bp 58–60° (3 mm). This distillate was redistd through a Vigreux column, collecting the fraction at bp 54° (2 mm): yield, 10.4 g (98%); $n^{30}D$ 1.4428.

A bifumarate salt of **7** was recrystd twice from EtOAc, mp 114–117.5°. *Anal.* ($C_9H_{15}NO_5$) C, H, N.

Resolution of (±)-*trans*-2-Dimethylaminocyclopropanol (7).—To 14.7 g (0.1 mole) of *l*-tartaric acid in 1.18 l. of anhyd EtOH and 1.78 l. of EtOAc was added 9.9 g (0.1 mole) of (±)-**7** in 600 ml of anhyd EtOH. After cooling for 36 hr, the crystals which separated were collected on a filter, the mother liquor was reserved as solution A. The crystals were recrystd 4 times from EtOH–EtOAc, then once from MeCN–*i*-PrOH, mp 170–171° dec. *Anal.* ($C_9H_{17}NO_7$) C, H, N. A soln of this material (2.1 g) in 25 ml of H_2O was saturated with K_2CO_3 and was extracted repeatedly with Et_2O. The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure, and the residual liquid was distd through a "short path" apparatus: bp 54–55° (3.0 mm); yield, 0.6 g $[\alpha]^{25}D$ −70.1° (*c* 3.9, H_2O). An ir spectrum of this material (film) was superimposable upon one of (±)-**7**.

Solution A was concentrated under reduced pressure to 1.1 l. Anhyd EtOH (350 ml) and 100 ml of EtOAc were added and the resulting soln was permitted to stand at room temp for 1 day, resulting in separation of crystals. Additional crops of crystals were obtained by successive additions to the filtrate of 100-ml portions of EtOAc. The combined crops were recryst from MeCN and from anhyd EtOH, mp 123–124° dec. *Anal.* ($C_9H_{17}NO_7$) C, H, N. The free base was liberated as described for the (−) isomer: bp 53° (2.4 mm); yield, 0.6 g; $(\alpha)^{25}D$ +59.2° (*c* 3.6, H_2O). An ir spectrum (film) of this material was superimposable upon one of (±)-**7**.

(−)-*trans*-2-Trimethylammoniumcyclopropanol Iodide (8).—A soln of 0.5 g (0.005 mole) of (−)-**7** and 2.0 g (0.014 mole) of MeI in 15 ml of anhyd MeOH was stirred at room temp for 40 min and at reflux for 20 min. The solid which separated was collected on a filter, diln of the filtrate with EtOAc and Et_2O resulted in separation of additional solid. The combined solids were recrystd from anhyd MeOH to give 0.6 g (54%) of crystals: mp 250–253° dec; $[\alpha]^{25}D$ −13.5° (*c* 2.1, H_2O). *Anal.* ($C_6H_{14}INO$) C, H, I, N.

(+)-*trans*-2-Trimethylammoniumcyclopropanol Iodide (8).—Using the procedure described for (−)-**8**, 0.4 g (0.004 mole) of (+)-**7** yielded a solid which was recryst from anhyd MeOH to afford 0.5 g (51%) of crystals: mp 254–255° dec; $[\alpha]^{25}D$ +14.2° (*c* 1.9, H_2O). *Anal.* ($C_6H_{14}INO$) C, H, I, N.

(−)-*trans*-2-Acetoxycyclopropyltrimethylammonium Iodide (9).—A mixture of 0.564 g (0.002 mole) of (−)-**8** and 6.0 g (0.06 mole) of Ac_2O was stirred on a steam bath for 13 hr. The cooled reaction mixture was diluted with 400 ml of anhyd Et_2O, the solid which sepd was collected on a filter, washed with anhyd Et_2O, and recrystd repeatedly from EtOAc–MeOH to yield 0.25 g (43%) of a light tan solid: mp 173–175.5°; $[\alpha]^{30}D$ −89° (*c* 1.01 H_2O). *Anal.* ($C_8H_{16}INO_2$) C, H, I, N.

(+)-*trans*-2-Acetoxycyclopropyltrimethylammonium Iodide (9).—The procedure described for (−)-**9** was carried out on 0.495 g (0.002 mole) of (+)-**8**, to yield 0.196 g (34%) of an almost colorless solid: mp 172–174°; $[\alpha]^{30}D$ +93.2° (*c* 1.13, H_2O). *Anal.* ($C_8H_{16}INO_2$) C, H, I, N.

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