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Cyclobutane Analogs of Acetyl-γ-homocholine†

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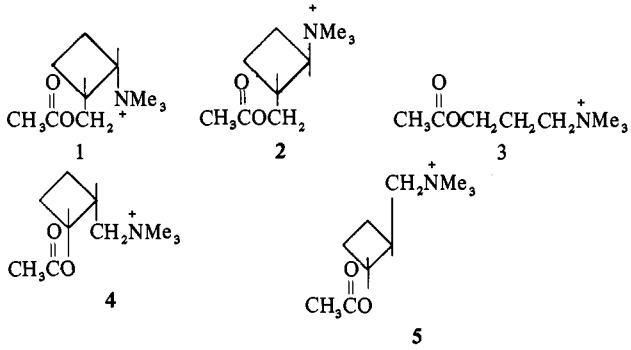
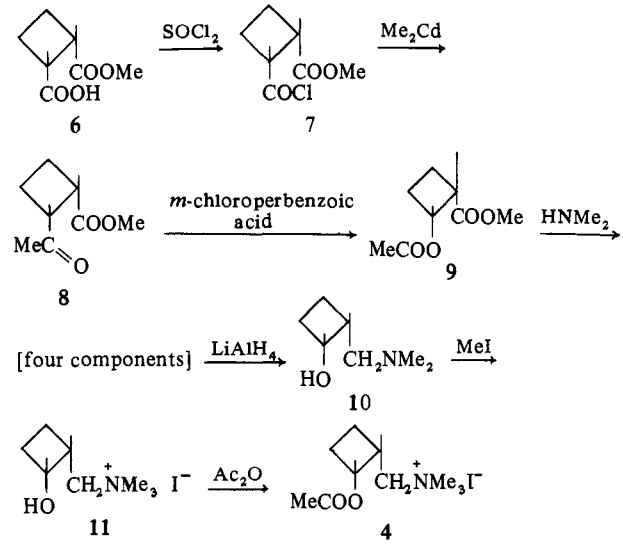
Cis and trans isomers of cyclobutane analogs of acetyl-γ-homocholine have been prepared in which the acetoxy group is attached directly to the cyclobutane ring and the quaternary nitrogen function is separated from the ring by a methylene group. The conversion of a cyclobutanecarbonyl chloride moiety into the corresponding cyclobutylmethyl ketone has been studied, and several methods have been attempted and evaluated. The Baeyer–Villiger reaction has been successfully applied to isomeric methylcyclobutyl ketones as an integral step in the preparation of the final products. The acetyl-γ-homocholine congeners exhibited almost no muscarinic activity.

A prior communication[1] described preparation and muscarinic screening of the conformationally restricted analogs **1** and **2** of acetyl-γ-homocholine (**3**). The present work describes the preparation of **4** and **5**, isomers of **1** and **2** in which the acetoxy group is attached directly to the ring and the quaternary group is on the methylene side chain. *cis*-Cyclobutane-1,2-dicarboxylic acid anhydride and *trans*-cyclobutane-1,2-dicarboxylic acid served as starting materials for **4** and **5**, respectively, as indicated in Schemes I and II.



The *trans*-keto acid **15** could be prepared best by the two-step procedure shown in Scheme II; the methyl ester **27** of this acid was also preparable by treatment of **13** with dimethylcadmium, as for the cis isomer (**7** → **8**, Scheme I), or by use of methylaluminum dichloride. Treatment of **7** (Scheme I) with ethoxymagnesium malonic ester gave the expected product, the cis isomer of **14** (**28**). However, either acid- or base-catalyzed hydrolysis of the β-ketomalo-

Scheme I. Preparation of *cis*-(2-Acetoxycyclobutylmethyl)trimethylammonium Iodide (**4**)



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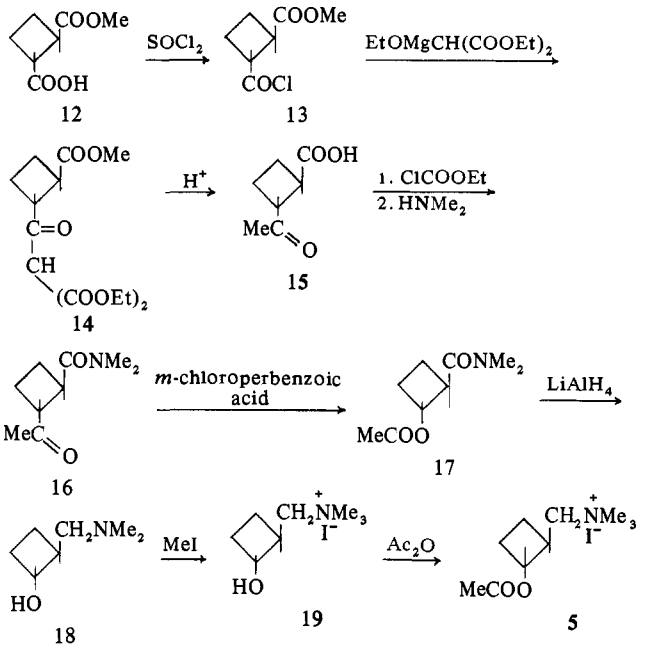
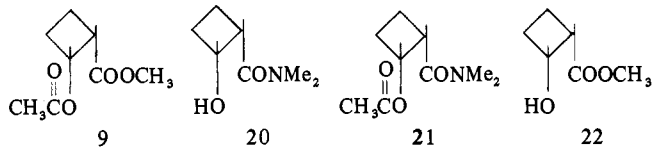
Scheme II. Preparation of *trans*-(2-Acetoxycyclobutylmethyl)trimethylammonium Iodide (5)



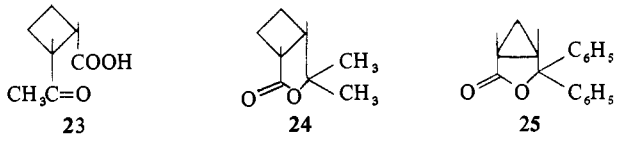
nate derivative **28** resulted in epimerization to the trans system.

Treatment of compound **9** (Scheme I) with anhydrous dimethylamine gave a four-component mixture which, on the basis of infrared data, was assumed to consist of **9**, **20**, **21**, and **22**. This mixture was reduced with $LiAlH_4$ which con-



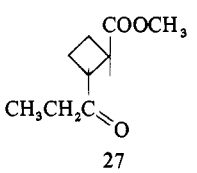
verted both **20** and **21** into the desired amino alcohol **10**, which was easily separable from the nonbasic products of the reduction of **9** and **22**.

An attempt to prepare **23** by treatment of *cis*-cyclobutane-1,2-dicarboxylic acid anhydride with dimethylcadmium resulted in predominant formation of the γ lactone **24**, together with a minor amount (5%) of the desired product **23**.



Spectral and elemental analytical data supported this assigned structure for **24**. In addition, Augustine and Pinto[2] reported formation of the cyclopropane γ lactone **25** from a reaction of *cis*-cyclopropane-1,2-dicarboxylic acid anhydride with a phenyl Grignard reagent.

trans-2-Carbomethoxycyclobutanecarbonyl chloride (**13**) was converted into the ethyl ketone **26** with diethylzinc. However, a Baeyer-Villiger reaction on **26** gave rise to a two-component mixture which could not be separated well.



Isomeric homogeneity of all products was verified by tlc data, using several solvent systems. Spectral (ir, nmr) data for all intermediates and final compounds were consistent with the proposed structures.

Pharmacology. Compounds **4** and **5** were evaluated for muscarinic activity in a superfused guinea pig ileum preparation.[1] The trans isomer **5** was 1/5000 as active as acetylcholine, and the cis isomer **4** was 1/40,000 as active. The effects of both were blocked by atropine but not by C-6. These compounds were even less active than the isomeric systems **1** and **2** which were reported[1] to be 1/6666 and 1/958 as active, respectively, as acetylcholine. Barrass, *et al.*,[3] have reported that acetyl-γ-homocholine (**3**) is 1/50 as active as acetylcholine in the guinea pig ileum. Muscarinic inactivity seems to be an inexplicable property of acetylcholine congeners based upon the cyclobutane ring system, as compared to analogous systems derived from cyclopropane.

Experimental Section

Boiling points are uncorrected. Melting points were determined in open glass capillaries using a Thomas-Hoover Uni-Melt apparatus and are corrected. Infrared spectra were obtained on a Beckman IR-10 instrument. Nuclear magnetic resonance spectra were recorded with a Varian Associates T-60 instrument using TMS as the internal reference. Elemental analyses were performed by Huffman Laboratories, Wheatridge, Colo., and Galbraith Laboratories, Knoxville, Tenn. Where analyses are indicated by symbols of the elements, the analytical results were within ±0.4% of the theoretical values.

cis-**2-Carbomethoxycyclobutanecarbonyl Chloride (7).** A mixture of 7.9 g (0.05 mol) of *cis*-cyclobutane-1,2-dicarboxylic acid, monomethyl ester 6,[1] and 12 g (0.1 mol) of $SOCl_2$ was stirred at room temperature for 1 hr and then was heated at 55° for 0.5 hr. Unreacted $SOCl_2$ was removed under reduced pressure and the residual liquid was distilled through a Vigreux column: bp 130–132° (22 mm); yield, 8.6 g (96%). *Anal.* ($C_7H_9ClO_3$) C, H, Cl.

cis-**2-Carbomethoxycyclobutyl Methyl Ketone (8).** To an ice-salt cooled (−5°) ether solution containing 0.035 mol of dimethylcadmium, prepared *in situ* according to procedures of Pinson and Friess[4] and of Cason,[5] was slowly added 8.80 g (0.05 mol) of 7, and the mixture was stirred and kept at −5° for 6 hr. The organometallic solution was then treated with excess 10% HCl, and the aqueous phase which separated was extracted with ether. The combined organic solutions were washed with 5% $NaHCO_3$ and water and dried (Na_2SO_4). Removal of the solvent gave a liquid residue which, after distillation at 120–134° (22 mm), was found by tlc and vpc to be a two-component mixture, with the major component present to the extent of 85%. This mixture was chromatographed on silica and eluted with C_6H_6. Evaporation of the eluent and distillation of the residue gave pure **8**: bp 113–115° (12 mm); yield, 3.12 g (40%). *Anal.* ($C_8H_{12}O_3$) C, H.

Methyl *cis*-**2-Acetoxycyclobutanecarboxylate (9).** A mixture of 8.8 g (0.056 mol) of **8**, 13.6 g (85% purity, 0.0672 mol) of *m*-chloroperbenzoic acid, and 85 ml of $CHCl_3$ was stirred at room temperature for 45 hr. The precipitated *m*-chlorobenzoic acid was removed by filtration and the filtrate was washed with 10% NaOH and then with water. The dried (Na_2SO_4) organic phase was evaporated under reduced pressure, leaving a liquid residue which was distilled through a Vigreux column: bp 114–116° (12 mm); yield, 8.0 g (83%). *Anal.* ($C_8H_{12}O_4$) C, H.

Aminolysis of Methyl *cis*-**2-Acetoxycyclobutanecarboxylate (9).** The ester was stirred in a bomb with a fivefold molar excess of anhydrous dimethylamine at room temperature for 20 hr or at 100° for 8 hr. Unreacted dimethylamine was evaporated at room temperature, and the residue was distilled giving MeOH, acetamide, and a liquid, bp 122–125° (16 mm), which was shown (vpc) to consist of four components: ir (film) 1725–1735 (ester C=O), 1640 (amide C=O), and 3450–3600 cm^{-1} (OH). This material was employed in subsequent steps without further purification.

cis-**2-Dimethylaminomethylcyclobutanol (10).** The crude mixture of products obtained from aminolysis of **9** (23.3 g) was refluxed for 8 hr with 15.2 g (0.4 mol) of $LiAlH_4$ in 300 ml of THF The cooled reaction mixture was treated with a mixture of 250 ml of THF and 250 ml of water. The solid which separated was collected on a filter and washed with THF. THF was removed from the combined filtrates under reduced pressure, and the residual water solution was acidified with 2% HCl, washed with ether, and basified with 10% NaOH. The resulting aqueous solution was extracted repeatedly with $CHCl_3$ and ether. The combined extracts were dried

(Na_2SO_4) and the solvents were removed under reduced pressure to give a liquid residue which was distilled through a "short path" apparatus: bp 97–98° (12 mm); yield, 2.9 g. *Anal.* ($C_7H_{15}NO$) C, H, N.

cis-(2-Hydroxycyclobutylmethyl)trimethylammonium Iodide (11). A mixture of 0.6 g (0.0046 mol) of **10**, 5 g (0.035 mol) of MeI, and 10 ml of anhydrous MeOH was refluxed for 2 hr. Volatiles were removed under reduced pressure and the residue, upon addition of ether, deposited a yellow solid which was recrystallized from MeOH–ether: mp 73–76°; yield, 0.79 g (63%). *Anal.* ($C_8H_{18}INO$) C, H, I, N.

cis-(2-Acetoxycyclobutylmethyl)trimethylammonium Iodide (4). A mixture of 1.1 g (0.004 mol) of **11** and 4.08 g (0.04 mol) of Ac_2O was heated at 95° for 15 hr. Ether was added to the cooled reaction mixture until precipitation was complete, and the precipitate was recrystallized from MeOH–ether to yield 0.81 g (64%) of product, mp 96–98°. *Anal.* ($C_{10}H_{20}INO_2$) C, H, I, N.

trans-2-Carbomethoxycyclobutanecarbonyl Chloride (13). A solution of 15.8 g (0.1 mol) of *trans*-cyclobutane-1,2-dicarboxylic acid monomethyl ester **12**[1] in 38 ml (60 g, 0.5 mol) of $SOCl_2$ was heated under gentle reflux for 3 hr. Unreacted $SOCl_2$ was removed under reduced pressure and the residual liquid was distilled through a Vigreux column: bp 106–108° (16 mm); yield, 15.9 g (90%). *Anal.* ($C_7H_9ClO_3$) C, H, Cl.

Diethyl *trans*-2-Carbomethoxycyclobutanecarbonylmalonate (14). This was prepared by a method of Loeffler, *et al.*[6] Ethoxymagnesium malonic ester was prepared *in situ* by refluxing a mixture of Mg turnings (1.12 g, 0.046 g-atom), 2.5 ml of anhydrous EtOH, 7.36 g (0.046 mol) of diethyl malonate, and 15 ml of C_6H_6. When all of the Mg had dissolved, 7.1 g (0.04 mol) of **13** in 10 ml of C_6H_6 was added dropwise to the refluxing mixture. and refluxing was continued for 15 hr. The cooled reaction mixture was acidified with 10% HCl and the resulting mixture was extracted repeatedly with ether. The combined extracts were dried (Na_2SO_4), the solvent was removed and the residue was distilled through a Vigreux column: bp 127–129° (0.15 mm); yield, 8.7 g (73%). *Anal.* ($C_{14}H_{20}O_7$) C, H.

trans-2-Acetylcyclobutanecarboxylic Acid (15). Compound **14** (7.1 g, 0.0237 mol) was refluxed gently with 40 ml of 20% HCl and 10 ml of AcOH for 12 hr. Water (100 ml) was added to the cooled reaction mixture and the solution was extracted with ether. The extracts were dried (Na_2SO_4) and were evaporated under reduced pressure. Fractional distillation of the liquid residue through a Vigreux column gave AcOH and 1.7 g (51%) of **15**, bp 105–108° (0.2 mm). *Anal.* ($C_7H_{10}O_3$) C, H.

trans-2-Acetyl-*N*,*N*-dimethylcyclobutanecarboxamide (16). Compound **15** (5.68 g, 0.04 mol) and 4.6 g (0.045 mol) of triethylamine in 25 ml of $CHCl_3$ were cooled to −70° and to this was added dropwise with stirring 4.9 g (0.045 mol) of ethyl chloroformate in 12 ml of $CHCl_3$. The mixture was stirred at −70° for 4 hr. Formation of the mixed anhydride was monitored by ir of the reaction mixture: 1810, 1750 (anhydride C=O), and 1705 cm^{-1} (ketone C=O). Maintaining the reaction temperature at −70°, 20 g (0.44 mol) of anhydrous dimethylamine was added slowly and the mixture was stirred for 6 hr. The cold bath was then removed and unreacted dimethylamine evaporated at room temperature. The resulting $CHCl_3$ solution was washed with 10% HCl and water and dried (Na_2SO_4). Removal of the solvent under reduced pressure left a liquid residue which was distilled through a "short path" apparatus, bp 75–78° (0.02 mm). This distillate was chromatographed on silica gel and eluted with $CHCl_3$ and, after removal of the solvent, was redistilled: bp 71–73° (0.02 mm); yield, 1.9 g (28%). *Anal.* ($C_9H_{15}NO_2$) C, H, N.

trans-2-Acetoxy-*N*,*N*-dimethylcyclobutanecarboxamide (17). This was prepared in the manner described for **9**, using 5.5 g (0.032 mol) of **16** and 8.7 g (85% purity, 0.042 mol) of *m*-chloroperbenzoic acid. The crude product was distilled: bp 87–90° (0.05 mm); yield, 3.42 g (56%). *Anal.* ($C_9H_{15}NO_3$) C, H, N.

trans-2-Dimethylaminomethylcyclobutanol (18). To an ice-cooled slurry of 1.9 g (0.05 mol) of $LiAlH_4$ in 20 ml of purified THF was added dropwise with stirring 3.3 g (0.017 mol) of **17** in 25 ml of purified THF. The mixture was then refluxed with stirring for 8 hr. The cooled reaction mixture was treated with a mixture of 25 ml of THF and 25 ml of water. The solid which separated was collected on a filter and washed with THF. THF was removed from the combined filtrates under reduced pressure and the residual aqueous solution was extracted repeatedly with $CHCl_3$ and ether. The combined extracts were dried (Na_2SO_4) and volatiles were removed under reduced pressure to give a liquid residue which was distilled through a "short path" apparatus: bp 88–90° (12 mm); yield, 0.65 g (31%). *Anal.* ($C_7H_{15}NO$) C, H, N.

trans-(2-Hydroxycyclobutylmethyl)trimethylammonium Iodide (19). This was prepared as described for **11**, using 5 g (0.035 mol) of MeI and 0.6 g (0.0046 mol) of **18**. The product was recrystallized from MeOH–ether: mp 99–101°; yield, 1.12 g (89%). *Anal.* ($C_8H_{18}INO$) C, H, I, N.

trans-(2-Acetoxycyclobutylmethyl)trimethylammonium Iodide (5). This was prepared as described for **4**, using 1.0 g (0.00369 mol) of **19** and 3.8 g (0.0369 mol) of Ac_2O. The product was recrystallized from MeOH–ether to give 0.32 g (28%) of crystals, mp 131–133°. *Anal.* ($C_{10}H_{20}INO_2$) C, H, I, N.

trans-2-Carbomethoxycyclobutyl Methyl Ketone (27). Method A. This was the method described for **8**, beginning with the trans isomer **13**: yield, 46%; bp 99–101° (12 mm). *Anal.* ($C_8H_{12}O_3$) C, H.

Method B. A procedure of Adkins and Scanley[7] was utilized. To a stirred mixture of 16.5 g (0.093 mol) of **13** in 50 ml of C_6H_6 at 10–15° under N_2 was added slowly 20 g (0.18 mol) of methylaluminum dichloride (K & K) as a 35% solution in C_6H_6. The reaction mixture was stirred at room temperature for 2 hr and then was run slowly from the bottom of the reaction flask into 200 ml of ice-cold water, with stirring under N_2. The C_6H_6 layer which separated was washed with 5% $NaHCO_3$ and water and dried (Na_2SO_4). Removal of the solvent gave a liquid residue which was chromatographed on silica gel and eluted with C_6H_6. The solvent was removed from the eluate and the residue was distilled: bp 99–101° (12 mm); yield, 6.5 g (45%). An ir spectrum (film) of this material was superimposable upon a similar spectrum of the product from method A.

Diethyl *cis*-2-Carbomethoxycyclobutanecarbonylmalonate (28). This was prepared from 7.9 g (0.0447 mol) of **7**, 1.26 g (0.051 g-atom) of Mg turnings, 2.8 ml of anhydrous EtOH, and 8.1 g (0.05 mol) of diethyl malonate in 18 ml of C_6H_6, as described for **14**: bp 134–136° (0.1 mm); yield, 9.8 g (73%). *Anal.* ($C_{14}H_{20}O_7$) C, H.

Hydrolysis of Diethyl *cis*-2-Carbomethoxycyclobutanecarbonylmalonate (28). Acid Hydrolysis. The reaction was carried out as described for **15** using 35 g (0.117 mol) of **28**, 200 ml of 20% HCl, and 100 ml of AcOH. The product was distilled, bp 105–108° (0.2 mm), to provide 5.7 g (34%) of material whose ir (film) and nmr (CCl_4) were identical with those of **15**.

Base Hydrolysis. A mixture of 21 g (0.07 mol) of **28** and 400 ml of 5% NaOH was stirred at room temperature for 24 hr. The reaction mixture was then acidified with 10% HCl and extracted repeatedly with ether. The combined extracts were washed with water and dried (Na_2SO_4). Removal of the ether under reduced pressure left a liquid residue which was distilled at 105–108° (0.2 mm) to give 1.2 g (12%) of material whose ir and nmr characteristics were identical with those of an authentic sample of **15**.

Reaction of *cis*-Cyclobutane-1,2-dicarboxylic Acid Anhydride with Dimethylcadmium. Dimethylcadmium[4] (0.035 mol) in ether was added slowly to 6.3 g (0.05 mol) of *cis*-cyclobutane-1,2-dicarboxylic acid anhydride in 40 ml of anhydrous ether. The mixture was stirred for 1 hr under reflux and then was cooled in an ice slurry, and 60 ml of 10% HCl was added. The aqueous layer was separated and extracted with ether; the combined organic layers were extracted with 5% $NaHCO_3$ and the ether solution was reserved as solution A. The $NaHCO_3$ soln was acidified with 10% HCl and extracted with ether. This extract was dried (Na_2SO_4) and volatiles were removed to leave a liquid residue which was distilled through a "short path" apparatus to afford 0.38 g (5%) of *cis*-2-acetylcyclobutanecarboxylic acid (**23**), bp 101–103° (0.05 mm). *Anal.* ($C_{12}H_{10}O_3$) C, H.

Solution A was washed with water and dried (Na_2SO_4). Volatiles were removed under reduced pressure and the residual liquid was distilled through a Vigreux column, bp 93–95° (3.5 mm), to afford 2.7 g (38%) of the cis γ lactone **24**. *Anal.* ($C_8H_{12}O_2$) C, H.

Methyl *trans*-2-Propionylcyclobutanecarboxylate (26). Compound **13** (10.6 g, 0.06 mol) was treated with diethylzinc (3.7 g, 0.03 mol) according to a procedure of Wiberg and Williams:[8] yield, 7.0 g (68%); bp 124–126° (12 mm). *Anal.* ($C_9H_{14}O_3$) C, H.

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