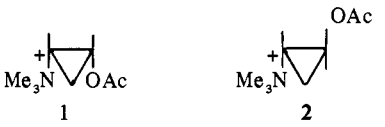
1,2-Disubstituted Cyclopropane and Cyclobutane Derivatives Related to Acetylcholine†

Joseph G. Cannon,* Arvind B. Rege, T. Lee Gruen,
Division of Medicinal Chemistry, College of Pharmacy

and John Paul Long
Department of Pharmacology, College of Medicine, The University of Iowa, Iowa City, Iowa 52240. *Received July 3, 1971*

As a means of extending the study of steric aspects of ACh with respect to nicotinic and muscarinic receptors, a series of cis- and trans-1,2-substituted cyclopropane and cyclobutane analogs of acetyl γ-homocholine and 4-acetoxy-*n*-butyltrimethylammonium has been prepared. These small ring products are also analogs of *cis*- and *trans*-ACTM (1 and 2), the latter of which is an extremely potent muscarinic agonist. Test data revealed a considerable degree of nicotinic effect for certain of the cyclopropane-derived compounds; none of the products demonstrated muscarinic effects. These results are difficult to rationalize on the basis of current theories of ACh stereochemistry and cholinergic receptor site topography, and suggest that none of these theories is adequate.

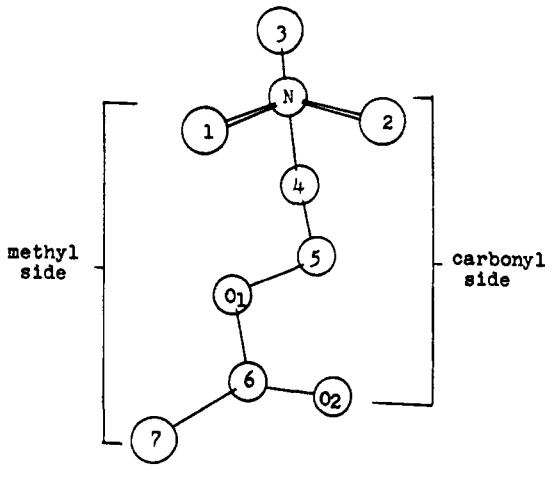
Prior communications[1-3] have reported preparation, cholinergic effects, and absolute configuration of cyclopropane analogs **1** and **2** (*cis*- and *trans*-"ACTM"). The extremely potent muscarinic activity and complete lack of



1 **2**

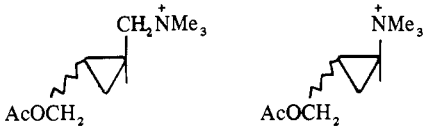
nicotinic agonist effect of (+)–(*S*)–(*S*)–**2**, coupled with the muscarinic and nicotinic inactivity of (±)–**1**, casts doubt upon the validity of the proposals of Archer and coworkers[4] that nicotinic action of ACh is referable to a "cisoid" conformation of the molecule.

Chothia and Pauling[5,6] have concluded that the experimental data on **1** and **2** are consistent with their proposal that the conformation of ACh relevant to both nicotinic and muscarinic receptors is the same–gauche with respect to C 4 and 5, structure **3**–but that different portions of the molecule interact with nicotinic and with muscarinic receptors. These workers further proposed that the essential structure for muscarinic agonists is the quaternary N and a Me group, constituting the so-called "methyl side," and that the essential structure for nicotinic agonists is the quaternary N and a carbonyl group, constituting the "carbonyl side." A sterically unhindered C=O side is required for nicotinic activity, and a sterically unhindered Me side is required for muscarinic activity. Shefter and Triggle[7] have challenged the Me side–carbonyl side hypothesis and have cited experimental data which they view as being inconsistent with it.



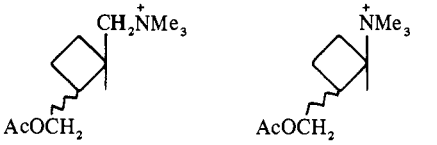
3: Proposed[6] conformation of acetylcholine

In the work reported herein, parallel series of cyclopropane and cyclobutane homologs (**4–11**) of the rigid ACh analogs **1** and **2** were prepared.



4, cis
5, trans

6, cis
7, trans



8, cis
9, trans

10, cis
11, trans

The range of possible distances between the quaternary head and the ester oxygens in these series of compounds varies considerably, and there is more flexibility and less conformational restriction in these systems than in *cis*- and *trans*-ACTM (**1**, **2**). It was speculated that biological test data on these compounds might be correlated with conformational aspects of the systems, so as to permit further evaluation of current theories for explaining acetylcholine's nicotinic and muscarinic activities. Compounds **4**, **5**, **8**, and **9** are semirigid analogs of 4-acetoxybutyltrimethylammonium (**12**) which was reported by Lands and Cavallito[8] to be muscarinically 1/700 as active as ACh and 0.05 as active a nicotinic agonist.

Compounds **6**, **7**, **10**, and **11** are semirigid analogs of acetyl γ-homocholine **13** which has been described in the older literature[9,10] as being less active a nicotinic and a muscarinic agent than ACh. The age of these studies and

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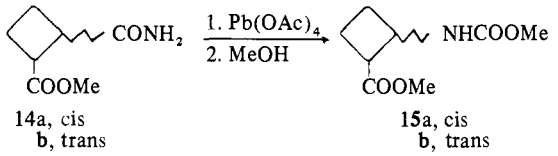
$CH_3COO(CH_2)_4\overset{+}{N}Me_3$ $CH_3COO(CH_2)_3\overset{+}{N}Me_3$

12 13

the absence of convincing recent quantitative data on acetyl γ-homocholine in the literature suggested that **6**, **7**, **10**, and **11** merited investigation. No attempt was made to resolve any of the products.

Preparation of compounds in both the cyclopropane and the cyclobutane series began with the appropriate *cis*- or *trans*-1,2-dicarboxylic acids or a simple derivative thereof and, for the most part, followed classic synthetic routes.

Attempts to place an N function on the ring by application of the Hofmann hypohalite reaction to cis and trans half ester-half amides in both the cyclopropane and the cyclobutane series failed. In some instances, mixtures of the starting ester-amide and of the 1,2-dicarboxylic acid hydrolysis product were recovered; occasionally, no identifiable material could be isolated. The cyclobutanecarboxamides **14**a and **b** were smoothly rearranged to *N*-cyclobutylcarbamate derivatives **15**a and **b** with $Pb(OAc)_4$, by modifications of procedures of Acott, *et al.*,[11] and of Baumgarten and Staklis.[12] It has been proposed[12,13] that these Pb(IV)-induced reactions proceed *via* a nitrene intermediate in a manner similar to the Hofmann hypohalite reaction.



14a, cis
b, trans

15a, cis
b, trans

Therefore, retention of configuration at the migrating origin would be expected, as in the Hofmann reaction. Et_3N was added to the reaction mixtures to speed the reactions, presumably by breaking the amide-$Pb(OAc)_3$ intermediate complex.

The $Pb(OAc)_4$ method failed when it was applied in the cyclopropanecarboxamide series; under vigorous conditions, no identifiable material could be isolated, and under milder conditions starting material was recovered. Ouellette and coworkers[14,15] reported that $Pb(OAc)_4$ decomposes alkyl- and arylcyclopropanes under conditions of prolonged heating. Mihailovic and Cekovic[16] found that treatment of cyclopropyl carbinol with $Pb(OAc)_4$ gives rise to a series of some 12 products, some, the result of ring opening.

cis- and *trans*-2-Carbomethoxycyclopropylcarbonyl chlorides were converted to the respective 2-carbomethoxycyclopropyl carbamates *via* Curtius reactions.

Pharmacology. The muscarinic activity was evaluated using guinea pig ilea from animals weighing 200-300 g. The terminal portion of the ileum, 3-5 cm in length, was removed, threaded at both ends and superfused with Tyrode's solution oxygenated with 95% O_2-5% CO_2 at 37°. The superfusion rate was 3-4 ml/min. Drugs were injected directly into the superfusate in volumes of not more than 0.1 ml.

Nicotinic activity was evaluated using the rectus abdominis muscle of the frog (*Rana pipiens*). The muscle was dissected as described by Burn.[17] It was superfused with frog Ringer's solution oxygenated with 95% O_2-5% CO_2 at room temp. The method of administration was as described above.

The activity relative to ACh was determined by comparing the activity of the compounds with the dose-response curve for ACh. Each compound was evaluated 3 times on each preparation and 4-6 preparations were used for each compound. Table I shows the average activity relative to ACh.

Table I. Nicotinic-Muscarinic Agonist Effects of Cyclopropane and Cyclobutane Derivatives

Compound no.	Muscarinic effect[a]	Nicotinic effect[b]
4	1/6666	1/200
5	1/6666	1/200
6	1/608	1/18
7	1/981	1/8
8	<1/10,000	1/200
9	<1/10,000	1/200
10	1/6666	1/1600
11	1/958	1/1600

[a]Superfused guinea pig ileum. ACh = 1. All responses were blocked by atropine (0.2 μg/ml). [b]Superfused frog rectus abdominis preparation. ACh = 1. All responses were blocked by curare (1 μg/ml).

The cholinergic inertness of the entire cyclobutane series (**8**-**11**) and of the cyclopropane analogs 4 and **5** of 4-acetoxybutyltrimethylammonium (**12**) contrasts strikingly with the appreciable nicotinic activities shown by **6** and **7**, the *cis*- and *trans*-cyclopropane analogs of acetyl γ-homocholine. These nicotinic effects become enigmatic when it is noted that the corresponding cyclobutane analogs **10** and **11** were inert. It is difficult to reconcile these biological differences between the cyclopropane and the cyclobutane analogs on conformational or other stereochemical grounds, or upon other chemical bases. The relatively small differences in nicotinic potencies between the *cis*- and *trans*-cyclopropane quaternaries (approximately a factor of 2) is consistent with the observation that nicotinic agonists in general show lower indices of stereospecificity than do muscarinic agonists.

These biological data add little to understanding the stereochemistry of ACh relative to nicotinic and muscarinic receptors; indeed, they seem further to becloud the entire problem.

Experimental Section‡

(±)-*trans*-2-Carbomethoxycyclopropanecarbonyl Chloride (16b). *trans*-Cyclopropane-1,2-dicarboxylic acid, monomethyl ester[18] (22 g, 0.15 mole) and 50 ml of $SOCl_2$ were refluxed gently for 12 hr. The excess $SOCl_2$ was removed under reduced pressure and the last traces were removed by azeotroping with C_6H_6. The residual oil was distilled through a Vigreux column: bp 50-52° (1.5 mm); yield, 19.8 g (80%). *Anal.* ($C_6H_7ClO_3$) C, H, Cl.

(±)-*trans*-2-Carbomethoxy-*N*,*N*-dimethylcyclopropanecarboxamide (19). Anhyd Me_2NH was slowly passed into a stirred soln of 19.8 g (0.121 mole) of 16b in 100 ml of dry C_6H_6, with intermittent cooling. The reaction was assumed to be complete when no more heat was evolved upon addn of Me_2NH. The reaction mixt was filtered and C_6H_6 was evapd from the filtrate under reduced pressure to leave a liq residue which was distd through a Vigreux column: bp 80-86° (0.4 mm); yield, 17.6 g (84%). *Anal.* ($C_8H_{13}NO_3$) C, H, N.

(±)-*trans*-1-Dimethylaminomethyl-2-hydroxymethylcyclopropane (20). To 12.5 g (0.33 mole) of LAH in 250 ml of dry Et_2O was added 13.7 g (0.08 mole) of 19 in 50 ml of dry Et_2O over 2 hr, then the mixt was refluxed with stirring for 2 hr. The cooled reaction mixt was treated with 12.5 ml of H_2O, followed by 12.5 ml of 15% NaOH, and finally with 37.5 ml of H_2O. The solid which sepd was collected on a filter and washed with Et_2O. The combined filtrates

‡All boiling points are uncorrected. Melting points were determined in open glass capillaries using a Thomas-Hoover Uni-Melt apparatus, and are corrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and Hufmann Laboratories, Wheatridge, Colo. Where analyses are indicated only by symbols of the elements, the analytical results for those elements were within ±0.4% of the theoretical value. Differential thermal analyses (dta) were determined with a DuPont 900 Differential Thermal Analyzer.

were dried (Na_2SO_4) and evapd under reduced pressure to yield an oil which was distd through a Vigreux column: bp 54° (0.1 mm); yield, 7.6 g (75%). *Anal.* ($C_7H_{15}NO$) C, H, N.

(±)-*trans*-1-Dimethylaminomethyl-2-acetoxymethylcyclopropane (21). A mixt of 6 g (0.047 mole) of **20** and 20 ml of Ac_2O was heated gently for 0.5 hr. After cooling, 200 ml of dry Et_2O was added and the ethereal soln was treated with anhyd HCl. The supernatant was decanted from the solid which formed, and this solid was washed with Et_2O and dissolved in 10% NaOH. This soln was extd with five 20-ml portions of Et_2O. The combined exts were dried (Na_2SO_4) and volatiles were removed under reduced pressure to leave a liq residue which was distd through a Vigreux column: bp 56° (0.65 mm); yield, 6.0 g (75%). *Anal.* ($C_9H_{17}NO_2$) C, H, N.

(±)-*trans*-1-Dimethylaminomethyl-2-acetoxymethylcyclopropane Methobromide (5). Excess anhyd MeBr was passed at room temp into a soln of 1 g (0.006 mole) of **21** in 40 ml of *i*-PrOH. After 0.5 hr the *i*-PrOH was removed under reduced pressure to leave a hygroscopic solid which was recrystd from anhyd Me_2CO and collected in a dry box: mp 91–92°; yield, 1.3 g (84%). *Anal.* ($C_{10}H_{20}BrNO_2$) C, H, Br, N.

(±)-*cis*-2-Carboxy-*N,N*-dimethylcyclopropanecarboxamide (22). To excess anhyd Me_2NH, maintd at −20 to 0°, was added 10 g (0.089 mole) of *cis*-cyclopropane-1,2-dicarboxylic anhydride.[19] The reaction mixt was stirred at this temp for 2 hr, then the excess Me_2NH was evapd, and the solid residue was dissolved in 5% $NaHCO_3$. This soln was extd with three 20-ml portions of Et_2O, acidified with concd HCl, and extd with $CHCl_3$. Removal of the $CHCl_3$ under reduced pressure gave a solid which was recrystd from Me_2CO: mp 141–142°; yield, 8.8 g (63%). *Anal.* ($C_8H_{13}NO_3$) C, H, N.

(±)-*cis*-1-Dimethylaminomethyl-2-hydroxymethylcyclopropane (23). A 1-l. round-bottom flask contg 15 g (0.40 mole) of LAH and 400 ml of purified (distd from LAH) THF was attached to a Soxhlet extractor whose thimble was charged with 16 g (0.102 mole) of **22**, and the apparatus was cycled for 96 hr. The cooled reaction mixt was treated with 15 ml of H_2O, 15 ml of 15% NaOH, and 45 ml of H_2O, and was filtered. The solid on the filter was extd with Et_2O. The combined Et_2O–THF soln was dried (Na_2SO_4) and then was evapd under reduced pressure to leave a liq which was distd through a Vigreux column: bp 36° (0.5 mm); yield, 11 g (83%). *Anal.* ($C_7H_{15}NO$) C, H, N.

(±)-*cis*-1-Dimethylaminomethyl-2-acetoxymethylcyclopropane (24). Excess AcCl was slowly added to a stirred soln of 8.5 g (0.066 mole) of **23** in 100 ml of anhyd Et_2O. After 1 hr, the Et_2O layer was decanted from the ppt which formed and the ppt was dissolved in excess 5% $NaHCO_3$. This soln was extd with eight 30-ml portions of Et_2O. After drying, Et_2O was removed from the combined exts under reduced pressure to leave a liq which was distd through a Vigreux column: bp 52.5° (0.25 mm); yield, 9.5 g (85%). *Anal.* ($C_9H_{17}NO_2$) C, H, N.

(±)-*cis*-1-Dimethylaminomethyl-2-acetoxymethylcyclopropane Methobromide (4). Compd **24** (1 g, 0.006 mole) in 25 ml of EtOAc was treated with MeBr as described for **5**: yield, 1.4 g (83%); mp 139–140.5° (Me_2CO). *Anal.* ($C_{10}H_{20}BrNO_2$) C, H, Br, N.

(±)-*trans*-2-Carbomethoxycyclopropanecarboxamide (25). Anhyd NH_3 was passed into a soln of 41 g (0.253 mole) of **16b** in 250 ml of C_6H_6 until no more solid formed. The reaction mixt was cooled and the ppt was collected on a filter. The ppt was refluxed with 200 ml of Me_2CO and this mixture was filtered. Evapn of the filtrate under reduced pressure left a solid which was recrystd from Me_2CO to yield 27 g (75%) of product, mp 102–103°. *Anal.* ($C_6H_9NO_2$) C, H, N.

(±)-*trans*-Methyl *N*-(2-Carbomethoxycyclopropyl)carbamate (17b). A mixt of 33 g (0.203 mole) of **16b**, 18.2 g (0.280 mole) of NaN_3, and 250 ml of anhyd toluene was refluxed with stirring for 24 hr, or until an ir spectrum of the reaction mixt indicated a band (2300 cm^{-1}) for the isocyanate product. MeOH (30 ml) was then added to the cooled reaction mixt and it was stirred for 10 hr at room temp. The mixt was filtered, and the filtrate was evapd under reduced pressure to leave a liquid residue which was distd through a Vigreux column: bp 104° (0.25 mm); yield, 28 g (80%). The distillate was induced to cryst at Dry Ice–Me_2CO temp: mp 68–70°. *Anal.* ($C_7H_{11}NO_4$) C, H, N.

(±)-*trans*-(2-Hydroxymethylcyclopropyl)methylamine (26). To 5 g (0.132 mole) of LAH in 200 ml of purified THF was added 5 g (0.029 mole) of **17b** in 100 ml of THF, and the mixt was refluxed and stirred for 96 hr. After cooling, the reaction mixt was treated with 5 ml of H_2O, 5 ml of 15% NaOH, and 15 ml of H_2O, then was filtered. The solid on the filter was washed with THF, and the combined filtrates were dried (Na_2SO_4). Removal of the THF under reduced pressure left an oil which was distd through a "short path" apparatus: bp 51° (0.5 mm); yield, 1.4 g (48%).

To an Et_2O soln of 0.1 g (0.001 mole) of **26** was added an Et_2O soln of 0.19 g (0.0005 mole) of di-*p*-toluoyl-*d*-tartaric acid (Aldrich Chemical Co.). The ppt which formed was recrystd from Me_2CO–Et_2O: mp 124–125°. *Anal.* ($C_{30}H_{40}N_2O_{10}$) C, H, N.

(±)-*trans*-(2-Hydroxymethylcyclopropyl)dimethylamine (27). CH_2O soln (7.8 ml of 37%; 2.9 g, 0.034 mole) was slowly added to a stirred soln of 1.8 g (0.018 mole) of **26** in 3.1 g (0.058 mole) of 90% HCOOH. The mixt was intermittently heated at 95° for 16 hr. After cooling, 40 ml of 4 *N* HCl was added and the resulting soln was concd under reduced pressure. The residue was dissolved in 10% NaOH, and this soln was extd with five 20-ml portions of $CHCl_3$. The combined exts were dried (Na_2SO_4) and evapd under reduced pressure to leave an oil which was distd through a "short path" apparatus: bp 43–45° (0.15 mm); yield, 1.4 g (68%).

To a soln of 1.1 g (0.096 mole) of **27** in anhyd Et_2O was added excess MeI. After 0.25 hr, the solid MeI salt **28** which sepd was collected on a filter and recrystd from Me_2CO–Et_2O: mp 120–122°; yield, 1.95 g (79%). *Anal.* ($C_7H_{16}INO$) C, H, I, N.

(±)-*trans*-2-Acetoxymethylcyclopropyltrimethylammonium Iodide (7). A mixt of 0.5 g (0.019 mole) of **28** and 15 ml of Ac_2O was heated under reflux for 3 hr. After cooling, 200 ml of Et_2O was added, causing sepn of a solid which was collected on a filter, washed with Et_2O, and recrystd from Me_2CO–Et_2O: mp 141–143°; dta mp 145°; yield, 0.41 g (70%). *Anal.* ($C_9H_{18}INO_2$) C, H, I, N.

(±)-*cis*-2-Carbomethoxycyclopropanecarbonyl Chloride (16a). *cis*-Cyclopropane-1,2-dicarboxylic acid, monomethyl ester[20] (33.8 g, 0.234 mole) in 40 ml of $SOCl_2$ was refluxed gently for 6 hr. The excess $SOCl_2$ was removed under reduced pressure and the remaining traces of $SOCl_2$ were azeotroped with C_6H_6. The residual oil was distd through a Vigreux column: bp 56–58° (0.75 mm); yield, 34.6 g (91%). *Anal.* ($C_6H_7ClO_3$) C, H, Cl.

(±)-*cis*-Methyl *N*-(2-Carbomethoxycyclopropyl)carbamate (17a). The procedure utilized for **17b** was employed, utilizing 8 g (0.049 mole) of **16a** and 3.5 g (0.054 mole) of NaN_3 in 150 ml of toluene. The cooled reaction mixt was filtered, and volatiles were removed from the filtrate under reduced pressure. Addn of Et_2O to the oily residue induced formation of a solid which was recrystd from Et_2O at Dry Ice–Me_2CO temp: yield, 5.5 g (67%); mp 89.5–91°. *Anal.* ($C_7H_{11}NO_4$) C, H, N.

(±)-*cis*-(2-Hydroxymethylcyclopropyl)methylamine (29). Compd 17a (6.8 g, 0.039 mole) was reduced as described for **26**, utilizing 6 g (0.158 mole) of LAH and 200 ml of anhyd THF: bp 55–58° (0.10 mm); yield, 1.1 g (28%).

The product was characterized as its di-*p*-toluoyl-*d*-tartrate salt as described for **26**: mp 128–129° (Me_2CO–Et_2O). *Anal.* ($C_{30}H_{40}N_2O_{10}$) C, H, N.

(±)-*cis*-(2-Hydroxymethylcyclopropyl)dimethylamine (30). Compd **29** (0.8 g, 0.008 mole) was methylated as described for **27**, utilizing 8.4 ml (3.2 g, 0.037 mole) of 37% CH_2O and 3.5 g (0.067 mole) of 90% HCOOH: yield, 0.55 g (61%); bp 41° (0.10 mm).

An Et_2O soln of 0.50 g (0.004 mole) of **30** was treated with excess MeI, and the solid, **31**, which septd was recrystd from Me_2CO–Et_2O: mp 103–104°; yield, 0.68 g (61%). *Anal.* ($C_7H_{16}INO$) C, H, I, N.

(±)-*cis*-2-Acetoxymethylcyclopropyltrimethylammonium Iodide (6). Compd 31 (0.68 g, 0.0025 mole) was acetylated with 15 ml of Ac_2O as described for **7**, and the product was recrystd from Me_2CO–Et_2O to yield 0.47 g (62%) of crystals: mp 116–117°; dta mp 120°. *Anal.* ($C_9H_{18}INO_2$) C, H, I, N.

(±)-*cis*-2-Carboxy-*N,N*-dimethylcyclobutanecarboxamide (32). To 53.56 g (1.2 mole) of anhyd Me_2NH, cooled to −10°, was added with stirring 50 g (0.4 mole) of *cis*-cyclobutane-1,2-dicarboxylic anhydride (Aldrich Chemical Co.). The reaction mixt was stirred at −10° for 0.25 hr then was allowed to come to room temp. The crude amide salt was dissolved in 5% $NaHCO_3$ and the soln was extd several times with Et_2O. The aq soln was taken to pH 2 with 10% HCl and was extd repeatedly with $CHCl_3$. The combined $CHCl_3$ exts were dried (Na_2SO_4), and the $CHCl_3$ was removed under reduced pressure to leave a white solid which was recrystd from Me_2CO: mp 116–119°; yield, 23.8 g (35%). *Anal.* ($C_8H_{13}NO_3$) C, H, N.

(±)-*cis*-1-Dimethylaminomethyl-2-hydroxymethylcyclobutane (33). To a suspension of 3 g (0.0795 mole) of LAH in 400 ml of purified THF was added 4.1 g (0.024 mole) of **32** in 150 ml of purified THF over 2 hr, then the reaction mixt was refluxed for 12 hr. The mixt was treated with wet Et_2O then with 20 ml of H_2O, filtered, and the solid which was collected was extd with THF. The combined org portions were evapd under reduced pressure to leave a liquid residue which was taken up in Et_2O and dried (Na_2SO_4). This soln was filtered and the Et_2O was removed to leave a liq which was distd through a Vigreux column: bp 33° (0.2 mm); yield, 1.9 g (56%). *Anal.* ($C_8H_{17}NO$) C, H, N.

(±)-*cis*-1-Dimethylaminomethyl-2-acetoxymethylcyclobutane (34). Compd 33 (0.9 g, 0.0063 mole) was added dropwise to a stirred soln of 1.49 g (0.019 mole) of AcCl in 5 ml of anhyd Et_2O. The pptd amine HCl was washed with anhyd Et_2O and a small portion of it was recrystd from MeOH–Et_2O: mp 138.5–140.5°. *Anal.* ($C_{10}H_{20}ClNO_2$) C, H, N.

The remainder of the amine HCl was dissolved in H_2O, and this soln was made basic in the cold with Na_2CO_3, and was extd repeatedly with Et_2O. The combined exts were dried ($MgSO_4$), and Et_2O was removed to leave a liq which was distd through a "short path" apparatus: bp 43° (0.1 mm); yield, 0.444 g (38%). *Anal.* ($C_{10}H_{19}NO_2$) C, H, N.

(±)-*cis*-1-Dimethylaminomethyl-2-acetoxymethylcyclobutane Methiodide (8). MeI (1 g, 0.007 mole) was added dropwise to a stirred soln of 0.4 g (0.0022 mole) of 34 in 5 ml of Et_2O. The pptd MeI salt was washed with anhyd Et_2O and recrystd from abs EtOH to afford 0.4 g (57%) of product: mp 122–125°. *Anal.* ($C_{11}H_{22}INO_2$) C, H, I, N.

(±)-*trans*-Cyclobutane-1,2-dicarboxylic Acid Monomethyl Ester (35). A mixt of 28.2 g (0.162 mole) of dimethyl *trans*-cyclobutane-1,2-dicarboxylate,[21] 40.58 g (0.252 mole) of *trans*-cyclobutane-1,2-dicarboxylic acid (Aldrich Chemical Co.), and 7 ml of concd HCl was heated under reflux until homogeneity was attained. The soln was cooled to 100°, 9 g of anhyd MeOH was added, and the mixt was heated at 120° for 2 hr. An addl 3.7 g of MeOH was added and the mixt was again heated at 120° for 2 hr. Anhyd Et_2O was added to the cooled reaction mixt; the Et_2O layer was sepd and dried ($MgSO_4$). The soln was filtered and volatiles were removed from the filtrate under reduced pressure to leave a liq residue which was fractionated through a Vigreux column. The dimethyl ester (22.9 g), bp 60° (0.6 mm), was followed by the monomethyl ester 35: bp 102° (0.6 mm); yield of 35, 21.75 g (49%). *Anal.* ($C_7H_{10}O_4$) C, H.

(±)-*trans*-2-Carboxy-*N,N*-dimethylcyclobutanecarboxamide (36). A mixt of 20 g (0.127 mole) of 35 and 17 g (0.38 mole) of anhyd Me_2NH was heated in a bomb at 65° for 24 hr. Excess Me_2NH was allowed to evap, and the residue was taken up in 5% $NaHCO_3$. This soln was washed with Et_2O, taken to pH 2.0 with 10% HCl, and extd repeatedly with $CHCl_3$. This ext was dried ($MgSO_4$) and filtered, and volatiles were removed under reduced pressure from a steam bath. Upon treatment of the liq residue with Et_2O, the material solidified and was recrystd from Et_2O: mp 80–81°; yield, 13 g (60%). *Anal.* ($C_8H_{13}NO_3$) C, H, N.

(±)-*trans*-1-Dimethylaminomethyl-2-hydroxymethylcyclobutane (37). Compd 36 (28.75 g, 0.168 mole) was reduced with 18 g (0.474 mole) of LAH in 1 l. of purified THF, as described for 33: bp 40–42° (0.05 mm); yield, 15.1 g (63%). *Anal.* ($C_8H_{17}NO$) C, H, N.

(±)-*trans*-1-Dimethylaminomethyl-2-acetoxymethylcyclobutane (38). Compd 37 (3.2 g, 0.0225 mole) was treated with 4.5 g (0.057 mole) of AcCl as described for 34. The HCl salt was recrystd from MeOH–Et_2O: mp 139.5–140.5°; yield, 3 g (61%). *Anal.* ($C_{10}H_{20}ClNO_2$) C, H, Cl, N.

The HCl salt was dissolved in 5% Na_2CO_3 and this soln was repeatedly extd with Et_2O. The combined exts were dried (K_2CO_3), and the Et_2O was removed under reduced pressure to leave a liq which was distd through a Vigreux column: bp 38–40° (0.1 mm); yield, 2.3 g (56%). *Anal.* ($C_{10}H_{19}NO_2$) C, H, N.

(±)-*trans*-1-Dimethylaminomethyl-2-acetoxycyclobutane Methiodide (9). MeI (2.13 g, 0.015 mole) was added cautiously to 1 g (0.0054 mole) of 38, and the mixt was warmed gently for 1 hr. The yellow solid which formed was washed with anhyd Et_2O and was recrystd from abs EtOH to yield 1.3 g (74%) of product: mp 113–115°. *Anal.* ($C_{11}H_{22}INO_2$) C, H, N.

(±)-*cis*-Cyclobutane-1,2-dicarboxylic Acid Monomethyl Ester (39). *cis*-Cyclobutane-1,2-dicarboxylic anhydride (10 g, 0.08 mole) was refluxed with 40 g (1.25 mole) of anhyd MeOH for 3 hr. The cooled reaction mixt was taken up in 100 ml of Et_2O and dried ($MgSO_4$), and volatiles were removed under reduced pressure to leave a liq residue which was distd through a Vigreux column: bp 114–116° (0.5 mm); yield, 11.6 g (92%). *Anal.* ($C_7H_{10}O_4$) C, H.

(±)-*cis*-2-Carbomethoxycyclobutanecarboxamide (14a). $SOCl_2$ (17.5 g, 0.14 mole) was added dropwise to 11.5 g (0.072 mole) of 39 and the reaction mixt was stirred at room temp for 3 hr. The excess $SOCl_2$ was removed at 45° under reduced pressure to leave a liquid which was distd through a Vigreux column to give 12.4 g (89%) of the acid chloride 40: bp 69° (0.1 mm).

Compd 40 (12 g, 0.068 mole) in 50 ml of Me_2CO was treated with 2.3 g (0.136 mole) of anhyd NH_3. The resulting mixt was filtered and the Me_2CO was removed from the filtrate under reduced pressure. The liq residue was treated with Et_2O; a solid formed which was recrystd from MeOH–Et_2O to yield 8 g (82%) of material: mp 91–92°. *Anal.* ($C_7H_{11}NO_3$) C, H, N.

(±)-*cis*-Methyl *N*-(2-Carbomethoxycyclobutyl)carbamate (15a). $Pb(OAc)_4$ (58 g, 0.13 mole) was added to a soln of 12 g (0.0765 mole) of 14a in 435 ml of C_6H_6 and 140 ml of MeOH. The reaction mixt was stirred at room temp for 0.25 hr, then was heated at 65° for 4 hr. It was cooled to 55° and enough Et_3N was added to decompose the amide–$Pb(OAc)_3$ complex (as indicated by decoloration of the dark brown reaction mixt). An addl 140 ml of MeOH was added and the reaction mixt was heated at 65° for 4 hr. Et_2O was added to the cooled reaction mixt until no more solid sepd, the mixt was filtered, and the filtrate was washed twice with H_2O and twice with satd Na_2CO_3 and dried ($MgSO_4$). The soln was filtered and Et_2O was removed from the filtrate to leave a liq residue which was distd through a "short path" apparatus: bp 87–89° (0.3 mm); yield, 8.95 g (63%). *Anal.* ($C_8H_{13}NO_4$) C, H, N.

(±)-*cis*-(2-Hydroxymethylcyclobutyl)methylamine (41). Compd 15a (7 g, 0.0375 mole) was reduced with 7 g (0.184 mole) of LAH in 700 ml of purified THF as described for 33. The product was distd through a "short path" apparatus: bp 53–57° (0.45 mm); yield, 3 g (70%). The product was characterized as its di-*p*-toluoyl-*d*-tartrate salt as described for 26: mp 172.5–173.5° (abs EtOH). *Anal.* ($C_{32}H_{44}N_2O_{10}$) C, H, N.

(±)-*cis*-(2-Hydroxymethylcyclobutyl)dimethylamine (42). CH_2O soln (2 ml of 37%; 0.74 g, 0.0247 mole) was added dropwise to a soln of 2.28 g (0.02 mole) of 41 in 2.3 ml (2.024 g, 0.044 mole) of 88% HCOOH, and the reaction mixt was heated slowly to 90°. Heating was contd such that gas evoln could be controlled; when it subsided the reaction mixt was heated at 95–100° for 8 hr. The cooled reaction mixt was dissolved in H_2O and was taken to pH 2 with 4 *N* HCl. It was then taken to dryness under reduced pressure, the residue was dissolved in H_2O, and the free base was liberated with concd NaOH. This mixt was extd with Et_2O, the ext was dried (K_2CO_3), and the Et_2O was removed under reduced pressure to leave a liq which was distd through a "short path" apparatus: bp 40–43° (0.4 mm); yield, 1 g (39%).

A mixt of 1 g (0.00775 mole) of 42, 4 g (0.028 mole) of MeI, and 30 ml of MeOH was stirred at room temp for 1 hr, then was refluxed for 1 hr. Most of the MeOH was removed under reduced pressure and the product was pptd with Et_2O; it was recrystd from MeOH–Et_2O to yield 1.5 g of the MeI salt 43: mp 238–239° dec. *Anal.* ($C_8H_{18}INO$) C, H, I, N.

(±)-*cis*-2-Acetoxymethylcyclobutyltrimethylammonium Iodide (10). A mixt of 1.05 g (0.0038 mole) of 43 and 11.67 g (0.115 mole) of Ac_2O was refluxed at 100° for 16 hr. Et_2O was added to the cooled reaction mixt until pptn was complete, and the crude product was recrystd from EtOH–Et_2O to afford 0.7 g (58%) of material: mp 149–150°. *Anal.* ($C_{10}H_{20}INO_2$) C, H, I, N.

(±)-*trans*-2-Carbomethoxycyclobutanecarboxamide (14b). $SOCl_2$ (13.41 g, 0.118 mole) was added dropwise to 8.9 g (0.056 mole) of 35 and the reaction mixt was refluxed at 75–80° for 3 hr. Excess $SOCl_2$ was removed at 45° under reduced pressure, the residue was taken up in Me_2CO, and 2 g (0.118 mole) of anhyd NH_3 was introduced into the soln. The soln was filtered and Me_2CO was removed from the filtrate under reduced pressure to leave a liq residue which was treated with Et_2O. The solid which sepd was recrystd from MeOH–Et_2O to yield 5 g (56%) of material: mp 98–100°. *Anal.* ($C_7H_{11}NO_3$) C, H, N.

(±)-*trans*-Methyl *N*-(2-Carbomethoxycyclobutyl)carbamate (15b). Compd 14b (12.35 g, 0.0786 mole) was treated with 69.61 g (0.157 mole) of $Pb(OAc)_4$ in 432 ml of C_6H_6 and 148 ml of MeOH as described for 15a. The crude product was distd through a "short path" apparatus, bp 110° (0.5 mm), to yield 11.1 g (76%) of product. *Anal.* ($C_8H_{13}NO_4$) C, H, N.

(±)-*trans*-(2-Hydroxymethylcyclobutyl)methylamine (44). Compd 15b (5 g, 0.063 mole) was reduced with 5 g (0.132 mole) of LAH in 900 ml of THF as described for 33. The product was distd through a "short path" apparatus, bp 59–61° (0.075 mm), to afford 2.45 g (80%) of material. It was characterized as its di-*p*-toluoyl-*d*-tartrate salt as described for 26: mp 186–187° (abs EtOH). *Anal.* ($C_{32}H_{44}N_2O_{10}$) C, H, N.

(±)-*trans*-(2-Hydroxymethylcyclobutyl)dimethylamine (45). Compd 44 (3.1 g, 0.027 mole) was treated with 3 ml of 88% HCOOH (2.64 g, 0.0574 mole) and 2.62 ml of 37% CH_2O soln (0.97 g, 0.0323 mole) as described for 42. The product was distd through a "short path" apparatus, bp 52° (0.075 mm), to yield 2.5 g (72%) of material.

A mixt of 2 g (0.014 mole) of MeI, 0.5 g (0.00388 mole) of 45, and 15 ml of anhyd MeOH was stirred at room temp for 1 hr then

was refluxed for 1 hr. Most of the solvent was removed from the reaction mixt, and the residue was treated with Et_2O. The pptd crude product was recrystd from MeOH-Et_2O to yield 0.63 g (60%) of the MeI salt 46. *Anal.* ($C_8H_{18}INO$) C, H, I, N.

(±)-*trans*-2-Acetoxymethylcyclobutyltrimethylammonium Iodide (11). Compd 46 (0.45 g, 0.00166 mole) was treated with 5 g (0.049 mole) of Ac_2O as described for 10. The product was recrystd from EtOH-Et_2O to yield 0.3 g (58%) of material, mp 104–105°. *Anal.* ($C_{10}H_{20}INO_2$) C, H, I, N.

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dl-α-[4-Cycloalkyl(cyclohexen-1-yl)]alkanoic Acids and Derivatives as Antiinflammatory and Antiarthritic Compounds

Michel Vincent,* Georges Remond,
Chemical Research Division

and Jean-Claude Poignant

Pharmacological Research Division, Science Union et Associés, Groupe de Recherches des Laboratoires Servier, 92-Suresnes, France.

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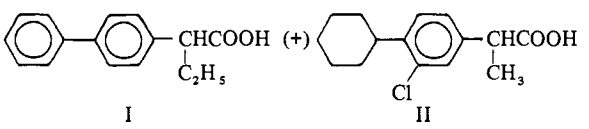
The Reformatsky reaction followed by dehydration gave 6 esters of the title compounds. These esters furnished a total of 16 corresponding acids, amides, and hydroxamic acids which were submitted to antiinflammatory assays. *dl*-α-[(4-Cyclohexyl)cyclohexen-1-yl]propionic acid was a potent adjuvant arthritis inhibitor and was selected for toxicological studies before clinical trials.

A large number of analgetic-antiinflammatory arylacetic acids have been reported. Among them, *p*-butoxyphenylacethydroxamic acid,[1] 4-allyloxy-3-chlorophenylacetic acid,[2] and α-(4-isobutylphenyl)acetic and -propionic acids[3] have been selected for a clinical use after extensive pharmacological studies. Moreover, α-(4-biphenylyl)butyric acid (I) is an active antiartherosclerotic drug,[4] and its dimethylaminoethanol salt is a good analgetic.[5] The most active antiinflammatory agents in these series were prepared by Shen, *et al.*[6,7] After an extensive synthetic and pharmacological study, the *d* isomer of 2-(*p*-cyclohexyl-*m*-chlorophenyl)-propionic acid (II) appeared as unsurpassed by any other nonsteroidal agent in the granuloma assay and in the carrageenin edema assay.



I II

We have found that several *dl*-α-[4-cycloalkyl(cyclohexen-1-yl)]alkanoic acids and derivatives (III) retained an interesting and above all antiarthritic activity, although one of their rings was completely, and the other one was partially saturated.

The compounds III were prepared following Scheme I. A 4-cycloalkylcyclohexanone (IV) was treated by the Reformatsky reaction with an α-bromo ester. The crude cis-trans mixture of hydroxy esters (V) so obtained was dehydrated with P_2O_5,[8] providing a β-unsaturated ester (III, X = OEt) (method A). This last derivative was either saponified (method B), furnishing an acid (III, X = OH), or treated with $HONH_2$ (method D), thus producing an hydroxamic acid (III, X = NHOH). Several compounds of structure III were prepared from III (X = OH) by condensing its acid chloride (III, X = Cl) with an alcohol or an amine (method C).

In structure III, the position of the double bond was ambiguous, because the dehydration of V could produce either an α- or a β-unsaturated ester. Therefore, the β-unsaturated nonconjugated structure of all derivatives III was ascertained by ir and uv spectrophotometry.[9] We also confirmed these results in one case, by synthesizing the conjugated α-unsaturated derivative VI in an unambiguous way, and by comparing it with its β-unsaturated isomer 7 (see Experimental Section).

The stereochemistry of the compounds III was ambiguous but has not been studied yet. The homogeneity of all the tested compounds was established by glc and tlc. The intermediates (III, X = OEt) and the test compounds (III) are listed in Tables I and II, respectively.