3(e)-Phenyl-*trans*-decalin 2(a)-Mesylate (40). To 3(e)-phenyl-*trans*-2(a)-decalol (36) (0.69 g, 0.003 mol) in 10 ml of anhydrous C_5H_5N, cooled in an ice bath, was added methanesulfonyl chloride (0.69 g, 0.006 mol) to afford 0.70 g (80%) of 40: mp 115°; nmr ($CDCl_3$) 4.80 (m, 1 H, $W_{1/2}$ = 7 Hz, C-2 CH). *Anal.* ($C_{17}H_{24}O_3S$) C, H.

General Procedure for Preparation of Isopropyl Analogs. The amine salt was converted to the free amine by the use of a strong base ion-exchange column (Amberlite IRA-400) or by adding the amine salt to a saturated NH_3–$CHCl_3$ solution, filtering the ammonium salt, and evaporating the solvent to yield the free amine. The free amine was dissolved in absolute EtOH containing 5% MeOH and to this solution was added a 4 *M* excess amount of Me_2CO. The solution was subjected to hydrogenation over Adams platinum catalyst at 32 psi at 25° for 12 hr. The catalyst and the solvent were removed to afford the isopropyl analog as the free amine, which was dissolved in Et_2O. The hydrochloride salt was prepared by the addition of saturated HCl–Et_2O solution to the etheral solution. The salt was removed by filtration and recrystallized from the appropriate solvent.

2(e)-Isopropylamino-3(e)-phenyl-*trans*-decalin Hydrochloride (5). This compound was recrystallized from Me_2CO–hexane, mp 117°. *Anal.* ($C_{19}H_{30}ClN$) C, H, N.

2(a)-Isopropylamino-3(e)-phenyl-*trans*-decalin Hydrochloride (6). The compound was recrystallized from CH_3CN, mp 295–300°. *Anal.* ($C_{19}H_{30}ClN$) C, H, N.

2(e)-Isopropylamino-3(a)-phenyl-*trans*-decalin Hydrochloride (7). This compound was recrystallized from $CHCl_3$, mp 280°. *Anal.* ($C_{19}H_{30}ClN$) C, H, N.

2(a)-Isopropylamino-3(a)-phenyl-*trans*-decalin Hydrochloride (8). This compound was recrystallized from C_6H_6–EtOAc, mp 227°. *Anal.* ($C_{19}H_{30}ClN$) C, H, N.

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Conformational Aspects of Systems Related to Acetylcholine. 5. Syntheses of the *dl*-2(e)-Methyl-, *dl*-3(e)-Methyl-, and *dl*-2(e),3(e)-Dimethyl-3(a)-trimethylammonium-2(a)-acetoxy-*trans*-decalin Halides

Edward E. Smissman* and George R. Parker†

The Department of Medicinal Chemistry, School of Pharmacy, The University of Kansas, Lawrence, Kansas 66044.
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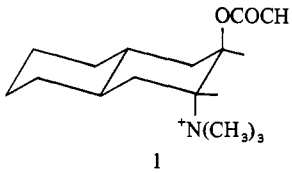
The syntheses of the *dl*-2(e)-methyl-, *dl*-3(e)-methyl-, and *dl*-2(e),3(e)-dimethyl-3(a)-trimethylammonium-2(a)-acetoxy-*trans*-decalin halides (5–7) are described. These three compounds were assayed for their muscarinic activity and as substrates for AChE.

In previous reports from these laboratories, the synthesis and testing of conformationally rigid analogs of acetylcholine (ACh) in the *trans*-decalin series and the *trans*-decahydroquinoline series were discussed.[1-4] These compounds were prepared in an attempt to determine the conformational requirements for ACh at the muscarinic, nicotinic, and esterase receptor sites. The compounds having the acetoxy and the ammonium functions in a staggered conformation, **1** and **2**, were substrates for acetylcholineesterase (AChE)



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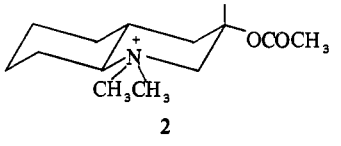
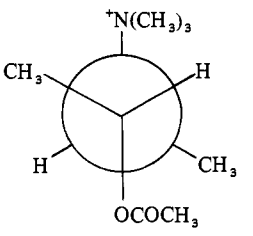


2

while the compounds in a gauche conformation did not undergo significant hydrolysis with AChE. The diaxial analog in the decalin series, **1**, also exhibited the greatest amount of muscarinic activity in the series. Similar studies[5,6] with systems incapable of a truly staggered conformation show maximum activity with the partial eclipse conformations having a dihedral angle ~120° rather than with the total eclipse conformation having a dihedral angle ~0° with respect to the acetoxy and quaternary nitrogen.

Cocolas, *et al.*,[7] have proposed a model for muscarinic and hydrolytic sites which is dependent on a tight three-dimensional fit of cholinergic molecules between the agonist and hydrolytic sites. This proposal is similar to that of Chothia[8] who has based his receptor site conformational preferences on crystallographic studies.[9-12]

The postulates offered by the above authors are not in agreement with the observations previously reported from this laboratory.[1,3] With *dl-erythro*- and *dl-threo*-α,β-di-



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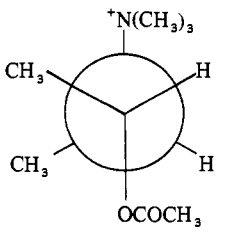

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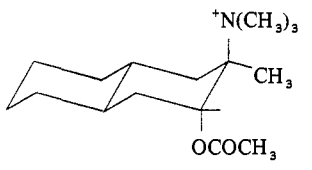
methylacetylcholines (**3** and **4**) muscarinic activity of **3** was markedly greater than that of **4** while the erythro isomer **3**

†Taken in part from the dissertation presented by G. R. Parker, Nov 1970, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy Degree.

was not a substrate for AChE but the threo isomer **4** was hydrolyzed. The decalin analog **1** possessed less muscarinic activity than **3** and greater activity than **4**; however, **1** was a better substrate for AChE than **4**. These results were explained on the necessity of having a dihedral angle of ~180° between the functional groups for both muscarinic activity and hydrolysis by AChE. The lower muscarinic activity of the threo isomer 4 was attributed to the steric hindrance necessary to place the functional groups in a staggered conformation and the inability of the erythro isomer 3 to undergo hydrolysis was assumed to be due to the inability of the molecule to interact with the enzyme because of the steric effects of the methyl groups when the acetoxy and quaternary nitrogen are in a staggered conformation.

In an attempt to investigate this hypothesis the 3(a)-trimethylammonium-2(a)-acetoxy-*trans*-decalin halides with 2(e)-methyl-, 3(e)-methyl-, and 2(e),3(e)-dimethyl groups (**5**, **6**, and **7**) were prepared. These compounds represent sterically rigid analogs of the *erythro*- and *threo*-α,β-dimethylacetylcholines (**8–10**).



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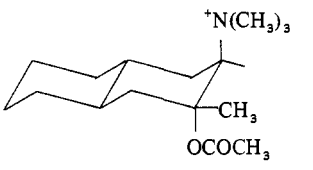

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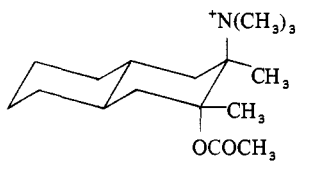

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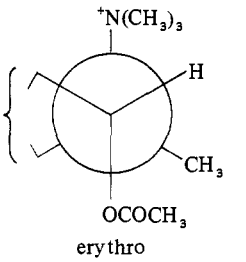
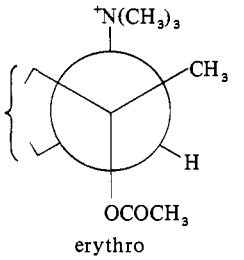


erythro

8



erythro

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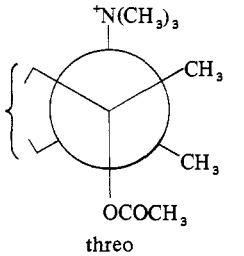


threo

10

The starting material for the preparation of the 3(e)-methyl- and 2(e)-methyl compounds, **5** and **6**, was 2-methyl-Δ^2-*trans*-octalin (**11**).[13] When treated with the pseudohalogen iodoisocyanate, **11** gave the trans addition product **12**. This type of reaction has previously been shown to occur in a trans manner[14] with the isocyanate function adding at the most substituted carbon.[15,16] The isocyanate **12** was not isolated but was converted to the corresponding carbamate **16** by treatment with methanol in order to determine the steric course of the reaction. The nmr spectrum of **16** showed a multiplet at δ 4.7 ($W_{1/2}$ = 6 cps) which is consistent with an equatorial methine proton at C-2 (Scheme I).

Acid hydrolysis of **12** afforded the iodoamine hydrochloride **13** which on treatment with base cyclized to the aziridine **14**. When heated in glacial acetic acid, **14** opened in a trans-diaxial manner to yield the amino acetate **15**. The nmr spectrum of **15** had a triplet at δ 3.3 (J = 6 cps) which is consistent with an equatorial proton at C-2. Compound **15** was converted to the desired compound **5** by reductive methylation to the tertiary amine followed by treatment with methyl iodide to afford the quaternary system.

Compound **11** could be converted to the epoxide **17** either by treatment with peroxy acids or by formation of the bromohydrin followed by treatment with base. The epoxide **17** was opened by allowing it to react with anhydrous dimethylamine to give 2(e)-methyl-3(a)-dimethylamino-2(a)-*trans*-decalol (**18**). The equatorial methine proton at C-3 was observed to have a triplet at δ 3.6 (J = 4 cps) when the amino group was quaternized with methyl iodide. The desired product **6** was obtained by acetylation of the hydroxyl function and formation of the quaternary nitrogen utilizing methyl iodide. The corresponding chloride was obtained by ion exchange.

The trans-diaxial opening of 2,3-dimethyl-2,3-epoxy-*trans*-octalin (**19**)[17] by azide ion[18] afforded a route to 2(e),3(e)-dimethyl-3(a)-trimethylammonium-2(a)-acetoxy-*trans*-decalin chloride (**7**) (Scheme II). The purity of the epoxide **19** obtained by Henbest, *et al.*,[17] has been questioned by Rickborn and Murphy.[19] They reported that the Henbest synthesis contains 25% *cis*-decalin; however, their claims could not be substantiated in this laboratory.

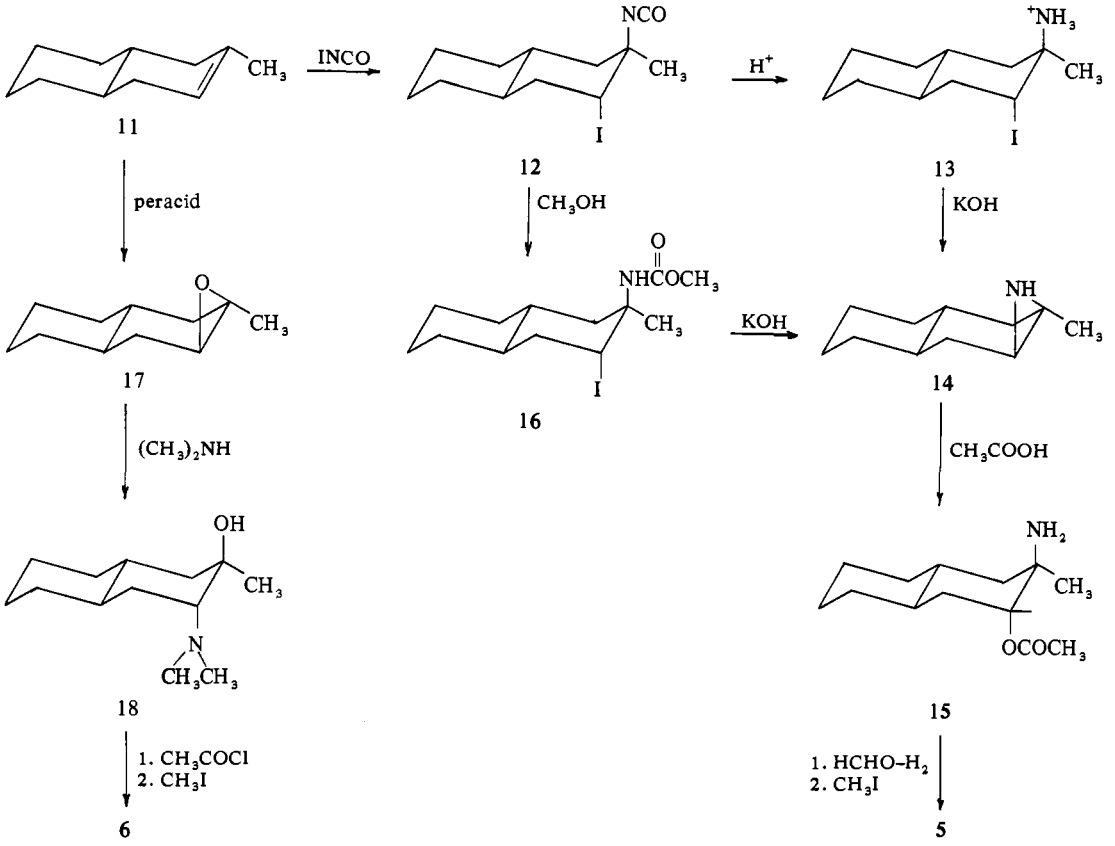
The steric course of azide opening of the epoxide **19** could not be ascertained by the use of nmr as employed with the monomethyl compounds since no methine protons are present. Epoxide openings, in general, proceed in a trans-diaxial manner.[20–23] Opening *via* a carbonium ion during azide formation would be expected to yield a mixture of axial and equatorial isomers. Thin-layer chromatography and nmr spectroscopy indicated only one compound to be present. Catalytic reduction of the azide **20** afforded the amine **21** which was converted to the desired compound **7** by reductive methylation, acetylation, and quaternization. The nmr spectrum of each compound in this sequence contained only two carbon-methyl groups which would be inconsistent with the added presence of an equatorial nitrogen function and thus substantiates a trans-diaxial opening.

Biological Results. The muscarinic activity was assayed in five guinea pig ileum preparations[24] using the cumulative dose-response technique.[25]

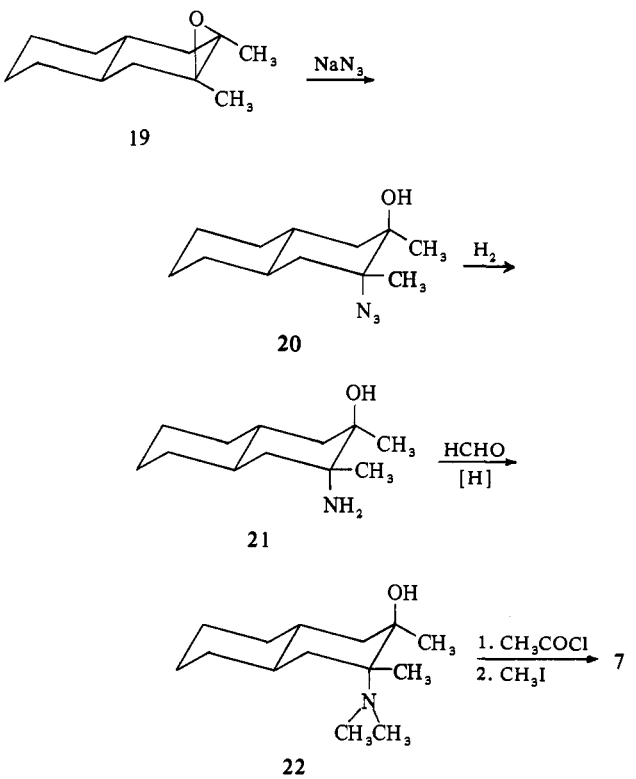
The 2,3-dimethyl compound **7** was found to be the most effective of the three compounds tested as a muscarinic agonist. The activity was 50 times less than acetylcholine (ACh) (pD_2 = 4.6 against pD_2 of ACh = 6.3).[25] The activity of **6** was 50% less than **7** (pD_2 = 4.3) and compound **5** had the lowest activity (pD_2 = 4.0). All three compounds increased the effect of ACh in concentrations of 1.0×10^{-6}–$2.1 \times 10^{-5} M$ and partially blocked the effect of ACh and histamine in concentrations of 1.0×10^{-5}–$1.0 \times 10^{-4} M$, with compound **7** showing the greatest blocking effect.

The effect of **5**, **6**, and **7** on blood pressure was followed in acute experiments on three cats (wt, 2–3 kg) anesthetized with pentobarbital (35 mg/kg, ip). The compounds were administered *via* the *vena jugularis* and the blood pressure was registered with a Statham pressure transducer P23AA on a Beckman Dynograph RB from the left *arteria femoralis*. The animals were breathing normally. Before treatment the blood pressure in the three cats varied between 130 and 150 mm. Doses (iv) of 0.1, 0.4, and 2.0 mg/kg were administered. Compounds **6** and **7** gave a 30–50-mm fall in blood pressure, at the dose of 2.0 mg/kg, which lasted for 1 hr. Compound **5** at the same dose lowered the blood pres-

Scheme I



Scheme II



sure 20–30 mm. No significant response was noted at the lower doses.

The hydrolysis rates were obtained using true acetylcholinesterase.[3] Compound **6** was hydrolyzed at a rate approximately 600 times less than ACh while **5** was 1000 times less and **7** did not act as a substrate. The biological results tend to support the general hypothesis that structural requirements are more specific in approaching the esterase active site than the muscarinic site.

Experimental Section‡

2-Methyl-*trans*-Δ²-octalin (11). This compound was prepared in 75% yield by the method of Ruzickas, *et al.*,[13] from *trans*-2-decalone. Glc utilizing LAC 446 indicated 10% of 2-methyl-*trans*-Δ¹-octalin to be present. Distillation on an annular still enriched the sample in the desired compound but no attempt was made to remove the last traces of the Δ¹ olefin.

2(e)-Methyl-3(a)-iodo-2(a)-carbomethoxyamino-*trans*-decalin (16). To a slurry of 25.4 g (0.100 mol) of I_2 and 20.0 g (0.130 mol) of freshly prepared AgOCN in 200 ml of anhydrous Et_2O at 0° was added 15.0 g (0.1000 mol) of the olefin **11**. The solution was stirred at 25° for a minimum of 5 hr or until the I_2 color diminished. The mixture was filtered through Celite 545 and the solvent removed from the filtrate to give crude iodoisocyanate **12**. The iodoisocyanate was added to 200 ml of anhydrous MeOH containing a small amount of LiOMe and the mixture refluxed for 4 hr. On cooling, the solution was poured into an ice-H_2O mixture containing a trace of $NaHSO_3$. The solution was extracted with Et_2O, and the Et_2O was washed with aqueous NaCl and dried (Na_2SO_4). The solvent was removed to yield 9.0 g (25%) of a white powder which recrystallized (Me_2CO), mp 137–139°. The nmr ($CDCl_3$) δ 4.7 ($W_{1/2}$ = 6 cps) indicates an equatorial methine proton at C-3.

Anal. ($C_{13}H_{22}NO_2I$) C, H, N.

2-Methyl-2,3-imino-*trans*-decalin (14). A. To a solution of 200 ml of KOH (1.5 *N*) in MeOH was added 7.0 g (0.02 mol) of the carbamate **16**. This solution was refluxed for 4 hr after which time

‡Melting points were obtained on a calibrated Thomas-Hoover Unimelt and are corrected. Ir data were recorded on Beckman IR-8 and IR-10 spectrophotometers. Nmr data were recorded on Varian Associates A-60 or A-60A spectrometers using tetramethylsilane or sodium 3-(trimethylsilyl)-1-propane sulfonate as internal standards. If not specified, the spectral data are consistent with the assigned structure. Glc data were obtained on F & M 810 or Beckman GC4 chromatographs. Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind., and on an F & M 185 C, H, N analyzer, University of Kansas.

the solution was cooled and poured into 75 ml of saturated NaCl solution. This solution was extracted with hexane, and the hexane layer was washed with H_2O and extracted with 10% HCl. The HCl solution was washed with hexane and made alkaline with dilute NaOH, and the aqueous solution was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O and dried ($MgSO_4$), and the solvent was removed to yield 0.34 g (10%) of an oil, bp 100–102° (1 mm).

Anal. ($C_{11}H_{19}N$) C, H, N.

B. To a solution of 6 *N* HCl was added the crude adduct **12** obtained by treating 15.0 g (0.100 mol) of the octalin **11** with I_2 and fresh AgOCN. This solution was stirred at 25° for 24 hr. The Et_2O and most of the H_2O were removed to produce a dark solid. The solid was placed in 2 *N* methanolic KOH and refluxed for 3 hr. The solution was extracted with Et_2O and the Et_2O solution was extracted with 10% HCl. The acid solution was washed with Et_2O and then made alkaline with dilute NaOH. The aqueous solution was extracted with $CHCl_3$, and the $CHCl_3$ extract was washed with H_2O and dried ($MgSO_4$). The solvent was removed to yield 5.7 g (34%) of an oil which was identical with the oil obtained in A.

3(e)-Methyl-3(a)-amino-2(a)-acetoxy-*trans*-decalin (15). To 75 ml of glacial AcOH was added 3.3 g (0.02 mol) of the iminodecalin **14**. This solution was refluxed for 72 hr. After cooling the solution was made alkaline with 10% NaOH and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O until neutral and dried ($MgSO_4$). The solvent was removed to yield 1.0 g (22%) of a golden oil which crystallized on standing, mp 270–272°. The nmr ($CDCl_3$) δ 3.3 (t, J = 6 cps) indicated an equatorial methine proton at C-2.

Anal. ($C_{13}H_{23}NO_2$) C, H, N.

3(e)-Methyl-3(a)-trimethylammonium-2(a)-acetoxy-*trans*-decalin Iodide (5). To a solution of 1.0 g (4.0 mmol) of **15** in 150 ml of absolute EtOH was added 2 ml (0.02 mol) of 37% formalin and 1.0 g of 10% Pd/C catalyst. This solution was placed under H_2 at 30 psi for 24 hr. The solvent was removed and EtOH was added and removed three times to remove excess formalin to afford an oil. The oil was dissolved in $CHCl_3$ and dried ($MgSO_4$). The solvent was removed to yield 1.1 g of an oil which was insoluble in Et_2O and appeared to be the formate salt. The oil was redissolved in $CHCl_3$ and washed with dilute NaOH. The solution was washed with H_2O and dried ($MgSO_4$), and the solvent was removed to afford 0.95 g (85%) of a colorless oil. The oil was dissolved in 10 ml of MeI and allowed to stand for 48 hr at 25°. The excess MeI was removed to produce a tan solid. Recrystallization (EtOH–Et_2O) yielded 0.4 g (26%) of a tan solid, mp 192–194°.

Anal. ($C_{16}H_{30}NO_2I$) C, H, N.

2-Methyl-2,3-epoxy-*trans*-decalin (17). A. Bromohydrin Method. To a solution of 29.5 g (0.17 mol) of NBS, 8.0 g (0.20 mol) of H_2SO_4, 10 ml of H_2O, and 150 ml of dioxane at 0° was added 25.0 g (0.17 mol) of 2-methyl-Δ^2-*trans*-octalin (**11**) with stirring. The solution was allowed to warm to 25°, stirred for 12 hr, and extracted with Et_2O several times. The Et_2O extracts were washed with 10% aqueous NaOH and H_2O and dried ($MgSO_4$). The solvent was removed to afford a brown liquid which was slowly added to a 1.5 *N* solution of KOH in MeOH with stirring at 25°. After the precipitate (KBr) was stirred for 2 hr, it was removed by filtration, the solution extracted with Et_2O, and the extract washed with H_2O until the washings were neutral. The Et_2O solution was dried ($MgSO_4$) and the solvent removed to yield a golden oil. Chromatography on silica gel, utilizing $CHCl_3$ as the eluent, gave 23.2 g (85%) of a clear liquid: bp 60° (5 mm); n^{25}D 1.4820; nmr ($CDCl_3$) δ 2.95 (d, J = 5 cps, methine proton at C-3).

Anal. ($C_{11}H_{18}O$) C, H.

B. Peracid Method. To a solution containing 17.3 g (0.1 mol) of *m*-chloroperbenzoic acid in anhydrous CH_2Cl_2 (NaOAc buffer) was added 15.0 g of **11** with stirring. After the slow addition the mixture was maintained at 4° for 12 hr. A precipitate formed and was removed by filtration. The filtrate was washed with 10% $NaHSO_3$, 10% $NaHCO_3$, saturated NaCl, and H_2O in succession. The solution was dried ($MgSO_4$) and the solvent removed to yield a golden oil which on chromatography as in A afforded a colorless liquid in 86% yield which was identical with that obtained by the bromohydrin method.

2(e)-Methyl-3(a)-dimethylamino-2(a)-*trans*-decalol (18). To a steel reaction vessel was added 8.3 g (0.05 mol) of 2-methyl-2,3-epoxy-*trans*-decalin and 40 ml of dimethylamine (liquified by cooling). The vessel was sealed and heated at 100° for 48 hr. After cooling the vessel was opened and the excess dimethylamine was allowed to evaporate leaving a brown solid. The solid was dissolved in Et_2O and the solution washed with H_2O and extracted with 10% HCl. The acid solution was washed with $CHCl_3$ and neutralized with 10% NaOH which produced a white precipitate. The solid and the solution were extracted with $CHCl_3$ and the organic layer was washed with H_2O and dried ($MgSO_4$). The solvent was removed to yield a cream-colored solid which was recrystallized (EtOH–H_2O) to give 7.9 g (78%) of white needles, mp 119–120°.

Anal. ($C_{13}H_{25}NO$) C, H, N.

2(e)-Methyl-3(a)-trimethylammonium-2(a)-*trans*-decalol Iodide. To 1.0 g (5.0 mmol) of the dimethylamino-*trans*-decalol **18** in 25 ml of Et_2O was added 10 ml of MeI and the mixture was allowed to stand 12 hr. White needles were collected and recrystallized (*i*-PrOH–Et_2O) to afford 1.0 g (60%) of white needles, mp 161–163°. The nmr (D_2O) δ 3.6 (t, $J_{ee,ea}$ = 4 cps) indicates an equatorial methine proton at C-3.

Anal. ($C_{14}H_{28}NOI$) C, H, N.

2(e)-Methyl-2(a)-dimethylamino-2(a)-acetoxy-*trans*-decalin. A solution of 4.2 g (0.02 mol) of the decalol **18** and 10.0 g (0.130 mol) of AcCl in 150 ml of CH_2CN was refluxed for 3 hr. On cooling, the mixture was washed with 10% NaOH and H_2O and dried ($MgSO_4$). The solvent was removed to afford 4.7 g (94%) of a cream-colored solid. The picrate was formed, mp 182–184°, to afford a crystalline derivative.

Anal. ($C_{21}H_{30}N_4O_9$) C, H, N.

2(e)-Methyl-3(a)-trimethylammonium-2(a)-acetoxy-*trans*-decalin Chloride (6). A mixture of 1.0 g (0.40 mmol) of the acetate of **18** and 5 ml of MeI in 35 ml of Et_2O was allowed to stand for 24 hr at 25°. The volatile materials were removed to afford a brown solid. The solid was dissolved in MeOH and stirred with Dowex 1-X8 (50–100 mesh) ion-exchange resin in the chloride form for 48 hr. The solvent was removed from the supernatant to give a golden oil which crystallized (Me_2CO–Et_2O) to yield 700 mg (58%) of colorless cubes, mp 174–176°.

Anal. ($C_{16}H_{30}NO_2Cl$) C, H, N.

2,3-Dimethyl-2,3-epoxy-*trans*-decalin (19). This compound was prepared by the method of Henbest, *et al.*,[17] in an 18% overall yield.

2(e),3(e)-Dimethyl-3(a)-azido-2(a)-*trans*-decalol (20). A solution of 3.1 g (0.017 mol) of the epoxy decalin **19**, 13 g (0.20 mol) of NaN_3, and 10.6 g (0.20 mol) of NH_4Cl in 100 ml of EtOH and 30 ml of H_2O was refluxed for 30 hr. The mixture was cooled and extracted with Et_2O; the Et_2O extract was washed with saturated aqueous $NaHCO_3$ and H_2O and dried ($MgSO_4$). The solvent was removed to yield 2.7 g (71%) of a liquid: bp 88–90° (1 mm); n^{25}D 1.4773.

2(e),3(e)-Dimethyl-3(a)-amino-2(a)-*trans*-decalol (21). To a solution containing 1.40 g (0.062 mol) of the azidodecalol **20** in EtOH was added 0.75 g of PtO_2. Hydrogenation was allowed to proceed at 50 psi until no further pressure drop occurred. The mixture was filtered and the solvent removed from the filtrate to yield an oil. The oil was dissolved in $CHCl_3$ and extracted with 10% HCl. The acid solution was washed with $CHCl_3$ and neutralized with dilute NaOH. The aqueous solution was extracted with $CHCl_3$; the extract was washed with H_2O and dried ($MgSO_4$). The solvent was removed to afford 8.2 g (66%) of a white solid, mp 62–65°.

Anal. ($C_{12}H_{23}NO$) C, H, N.

2(e),3(e)-Dimethyl-3(a)-dimethylamino-2(a)-*trans*-decalol (22). The procedure used is essentially that used in the preparation of **5**. The amino decalol **21** (2.0 g, 0.010 mol) yielded 1.7 g (75.5%) of an oil which crystallized (CH_3CN), mp 188–190°.

Anal. ($C_{14}H_{27}NO$) C, H, N.

2(e),3(e)-Dimethyl-3(a)-dimethylamino-2(a)-acetoxy-*trans*-decalin. Acetylation of **22** was performed in a similar method to that used in the preparation of **6**. The decalol **22** (4.5 g, 0.020 mol) gave 4.2 g (79%) of cream-colored crystals (petroleum ether, bp 60–68°), mp 170–172°.

Anal. ($C_{16}H_{29}NO_2$) C, H, N.

2(e),3(e)-Dimethyl-3(a)-trimethylammonium-2(a)-acetoxy-*trans*-decalin Chloride (7). The methylation of 2(e),3(e)-dimethyl-3(a)-dimethylamino-2(a)-acetoxy-*trans*-decalin MeI and the conversion to the corresponding chloride were performed in the same manner as utilized in the preparation of **6**. Using 1.0 g (0.004 mol) of the dimethylamino compound, 1.05 g (89%) of cream-colored crystals (EtOH–Et_2O) was obtained, mp 223–225°.

Anal. ($C_{17}H_{32}NO_2Cl$) C, H, N.

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Cyclobutane Analogs of Acetyl-γ-homocholine†

Joseph G. Cannon,* Youlin Lin,

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.
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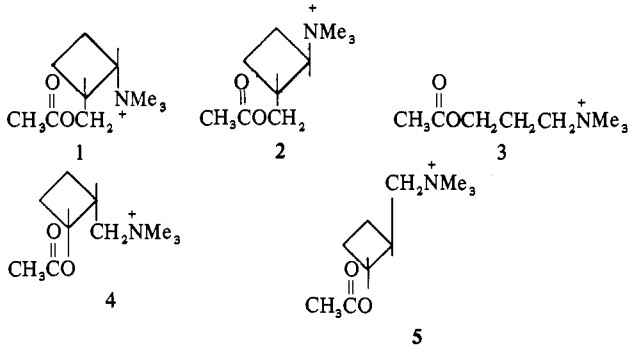
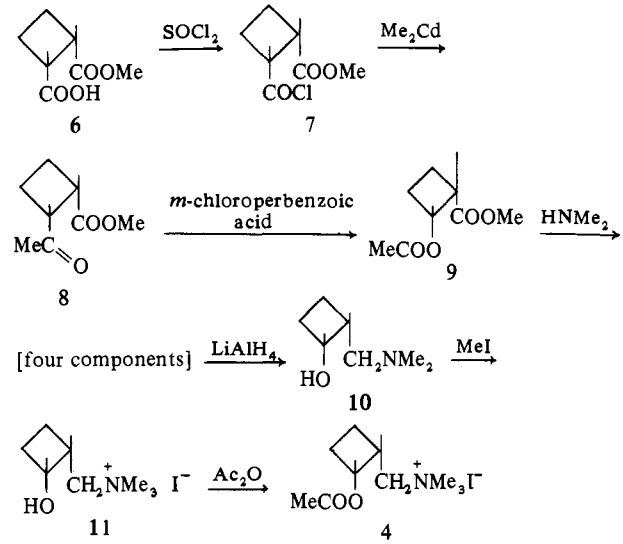
Cis and trans isomers of cyclobutane analogs of acetyl-γ-homocholine have been prepared in which the acetoxy group is attached directly to the cyclobutane ring and the quaternary nitrogen function is separated from the ring by a methylene group. The conversion of a cyclobutanecarbonyl chloride moiety 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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