Anal. ($C_{26}H_{22}O_5$) C, H. **8-Benzyloxywarfarin** was obtained from 4-hydroxy-8-benzyloxycoumarin in 67% yield, mp 165–166° (from Et_2O). *Anal.* ($C_{26}H_{22}O_5$) C, H.

6-Hydroxywarfarin.—A mixture of 6-benzyloxywarfarin (10 g) and 1.46 g of 10% Pd–C (60 g/mole) in 100 ml of 90% EtOH was shaken for 2 hr under H_2 pressure of 3.16 kg/cm². The catalyst was removed by filtration, and the solvent was evapd *in vacuo*. The residue was recrystd from $CHCl_3$;[12] yield 4.8 g (61.5%), mp 219–220°. *Anal.* ($C_{19}H_{16}O_5$) C, H.

Likewise, **7-hydroxywarfarin** was prepared from 7-benzyloxywarfarin in 77% yield, mp 208–210° (from $CHCl_3$[12]). *Anal.* ($C_{19}H_{16}O_5$) C, H. **8-Hydroxywarfarin** was prepared from 8-benzyloxywarfarin in 60% yield, mp 189–191° (from $CHCl_3$[12]). *Anal.* ($C_{19}H_{16}O_5$) C, H.

4,5-Dihydroxycoumarin.—2,6-Dihydroxyacetophenone (15.2 g) and Et_3N (21 g) were mixed with stirring in 500 ml of dry PhH and cooled in an ice bath. EtOCOCl (21.7 g) in 100 ml of dry PhH was added dropwise, while the temp was maintained at 0–5°. After addn of the reactants, the mixture was stirred and allowed to warm to room temp for 0.5 hr, then filtered. $(EtO)_2CO$ (12 g) and NaH (15 g, 50% in mineral oil) were added to the filtrate and the mixture was stirred and slowly distd for 8 hr. Dry PhH was added to the mixture periodically to maintain the reaction vol. The mixture was cooled and poured slowly into a mixture of 1000 g of ice in excess HCl. EtOAc was added to the mixture to dissolve the ppt. After phase separation the organic solvents were evapd *in vacuo*. The residue was dissolved in 200 ml of 10% NaOH, stirred at room temp for 4 hr, and then acidified with HCl and the product collected by filtration. The 4,5-dihydroxycoumarin was crystd from EtOH, yielding 9.5 g (60%), mp 218°.

In like manner, **4,6-dihydroxycoumarin** was synthesized from 2,5-dihydroxyacetophenone in 75% yield and crystd from EtOH, mp 300° (dec >290°). **4,7-Dihydroxycoumarin** was similarly prepared from 2,4-dihydroxyacetophenone and crystd from EtOH (25% yield), mp 282°; and **4,6,7-trihydroxycoumarin** from 2,4,5-trihydroxyacetophenone[13] in 40% yield, mp above 300° (undetd) (from MeOH).

5-Hydroxywarfarin.—4,5-Dihydroxycoumarin (1.78 g), benzalacetone (3.0 g), and Et_3N (0.073 ml)[14] were stirred and refluxed in 75 ml of H_2O for 8 hr. The mixture was cooled, 75 ml of satd $NaHCO_3$ added, and the mixture extd (Et_2O). The H_2O layer was made acidic with HCl, and the product collected by filtration. The 5-hydroxywarfarin was crystd from Me_2CO–H_2O and from PhH, mp 166° (70% yield). *Anal.* ($C_{19}H_{16}O_5$) C, H.

6,7-Dihydroxywarfarin was synthesized in 65% yield from 4,6,7-trihydroxycoumarin, mp 221–222° (from $CHCl_3$[12]). *Anal.* ($C_{19}H_{16}O_6$) H; C: calcd 67.05; found 64.73.[15]

4′,6-Dihydroxywarfarin, mp 256° [(from $CHCl_3$) *Anal.* ($C_{19}H_{16}O_6$) C, H], and **4′,7-dihydroxywarfarin,** mp 237° [(from $CHCl_3$[12]) *Anal.* ($C_{19}H_{16}O_6$) C, H], were prepared as above from the appropriate dihydroxycoumarins and *p*-hydroxybenzalacetone.

3′-Hydroxywarfarin was prepared from *m*-hydroxybenzalacetone and 4-hydroxycoumarin as above, mp 188–189° (from $CHCl_3$[12]). *Anal.* ($C_{19}H_{16}O_5$) H; C: calcd 70.36; found 69.35.[15]

2,3-Dihydro-2-methyl-4-phenyl-5-oxo-γ-pyrano[3,2-c][1]benzopyran.—2-Methyl-4-phenyl-5-oxo-α-pyrano[3,2-*c*][1]benzopyran (4 g) was suspended in 100 ml of 95% EtOH and 5 ml of AcOH with 100 mg of 10% Pd–C. The mixture was shaken with H_2 (3.16 kg/cm²) for 4 hr at room temp. The catalyst was removed by filtration and the solvent evapd *in vacuo*. The product was crystd from MeOH; mp 188–189°, yield, 90%. The pmr spectrum showed 16 H atoms with the assignments fitting the desired compd.

(12) All hydroxywarfarins, except 5-hydroxywarfarin, were purified by dissolving in a minimum of Me_2CO, then adding at least 6 vol of $CHCl_3$ and removing the Me_2CO by boiling. The products crystd from the cooled $CHCl_3$ soln.

(13) M. B. Knowles (to Eastman Kodak Co.), U. S. Patent 2,763,691, Sept 18, 1956 [*Chem. Abstr.*, **51**, 8791 (1957)].

(14) It was critical that the Et_3N concn be 5 mole % (based on the coumarin derivative concn) when condensing di- or trihydroxycoumarins with benzalacetone. Too much base prevented condn.

(15) This compd was chromatographically pure and gave a satisfactory ir spectrum. A change in crystal structure near the mp suggested a fair amount of solvation.

Conformationally Rigid Neurotransmitters. Acetylcholine Analogs in the Bicyclo[2.2.2]octane System[1a,b]

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Steric and electronic effects have long been offered as at least partial explanations for differences in biological activity of variously substituted analogs of acetylcholine (ACh).[2] Hypotheses delineating the architectural features of the cholinergic receptor have been based on such observations of activity. Conformational aspects of ACh and its analogs have been studied in solution[3a-c] and in the solid state[3d-i] and extended Hückel theory calculations[3j,k] have been applied in attempts to determine the conformational aspects of the cholinergic receptor.

Work in rigid systems, designed to represent various conformations of cholinergic agents, *e.g.*, cyclopropane,[4a,b] tropane,[4c] *trans*-decalin,[4d,e] cyclohexane,[4f,g] cyclopentane,[4h] and isoquinuclidine,[4i] has produced some evidence concerning conformational aspects of the cholinergic drug–receptor interaction. In most cases evidence has been accumulated supporting an extended or transoid conformation of ACh in the drug–receptor complex at the muscarinic receptor and in the enzyme–substrate interaction of AChE, although not without some exceptions.[5] Evidence in the dioxolane series also supports a maximum $N^+ \rightarrow O$ distance at the muscarinic site.[6a-d]

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(1) (a) A preliminary account of this work was presented to the 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968, Abstract M-2. (b) This work was supported in part by the National Institute of Mental Health, U. S. Public Health Service, under Grant MH-13,514. (c) Mead Johnson Undergraduate Research Award participant, 1966–1967.

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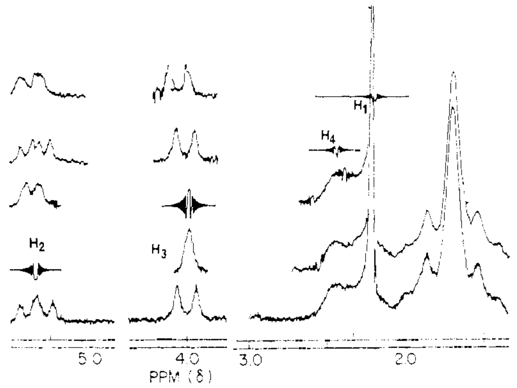


Figure 1.—Partially decoupled nmr spectrum of **1** in CD_3OD.

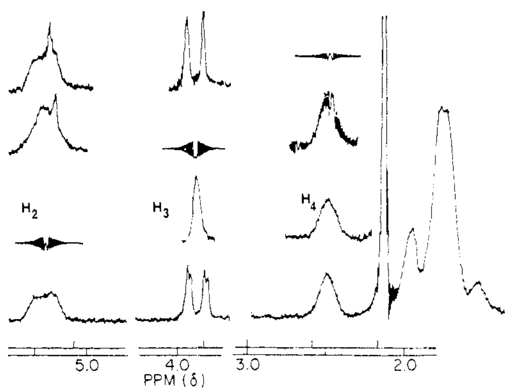
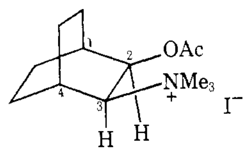
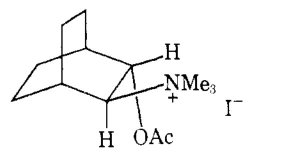


Figure 2.—Partially decoupled nmr spectrum of **2** in CD_3OD.

We wish to report preparation of the *cis*- and *trans*-3-trimethylammonium-2-acetoxybicyclo[2.2.2]octane iodides, **1** and **2**. These compounds represent semirigid analogs of a fully eclipsed conformation ($\theta_{N^+,O^*} \sim 0°$) and an eclipsed conformation ($\theta_{N^+,O^*} \sim 120°$) of ACh, respectively.



1



2

Preparation of these ACh derivatives proceeded from the isomeric *cis*- and *trans*-3-dimethylamino-2-hydroxybicyclo[2.2.2]octanes. The cis amino alcohol[7] was converted into **1** by acetylation followed by quaternization with MeI. The trans compound was available from 2,3-epoxybicyclo[2.2.2]octane[8] which was opened by nucleophilic addition of Me_2NH. A product of trans stereochemistry has been reported by similar opening with NH_3.[9] Acetylation and quaternization completed the sequence to **2**.

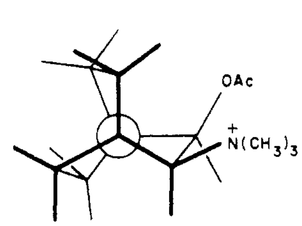
Because introduction of the sterically bulky $^+NMe_3$ cation could bring about considerable distortion of the bicyclo[2.2.2]octane ring system, the nmr spectra were examined by spin-decoupling experiments to gain information concerning the conformation in solution. Small deviations from D_{3h} symmetry have been reported in some 1-substituted bicyclo[2.2.2]octanes,[10a-d] indicating some distortion is present in some bicyclo[2.2.2]octane systems in the solid state.

In **1**, a broadened triplet at δ 5.33 is observed for H_2 and a doublet for H_3 at 4.00, $J_{3,2} = 7$ Hz. On the basis of decoupling experiments (Figure 1) the coupling constants were resolved to $J_{1,2} = 4.5$ Hz, $J_{2,3} = 7$ Hz, $J_{2,4} < 1$ Hz, $J_{3,4} \simeq 0$ Hz, consistent with dihedral angles[11] of $\theta_{2,3} \simeq 25°$, $\theta_{1,2} \simeq 45°$, $\theta_{3,4} \simeq 75°$, as an indication of the average conformation. These approximate angles are consistent with a conformation in which the $^+NMe_3$ moves away from the C-5–C-6 bridge relieving steric interaction with it. The angles, based on coupling constants, give a qualitative representation of the average conformation and not a quantitative one.[11] Some credence is given this model since in a related rigid model, *cis*-*N*-methylbicyclo[2.2.2]octyl[2,3-*d*]-oxazolidin-2-one, where $\theta_{2,3} \simeq 0°$, $J_{2,3} = 9.5$ Hz.[7]

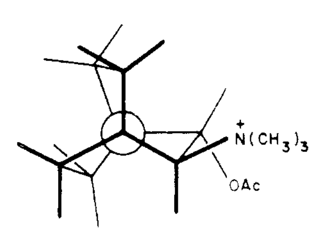
In the trans compound only a broadened multiplet for H_2 at δ 5.23 of $W_h \simeq 12$ Hz and a doublet of doublets at 3.88 δ for H-3, $J_{3,2} = 6.5$ and $J_{3,4} = 1$ Hz, are observed, and readily assigned on the basis of decoupling experiments (Figure 2). Further attempts to resolve the signal of H-2, *e.g.*, decoupling H_1 failed. The additional line broadening of H-2 may be caused by $^1H-^{14}N$ coupling,[12,3a] or by long-range coupling, *e.g.*, between H-2 and an H-6 proton which makes a "*W*" conformation with it.[13,14]

The relatively large coupling constant $J_{2,3}$ is best explained by also invoking steric repulsion of $^+NMe_3$ away from the C-5–C-6 bridge. Models show $\theta_{2,3} \simeq 145°$, and $\theta_{1,2} \simeq \theta_{2,3} \simeq 75°$. This conformation is consistent with the nmr spectrum. It results in moving the AcO and $^+NMe_3$ groups closer than 120° from each other, approaching 95–100°, which may relieve additional Pitzer strain due to the partial eclipsed conformation.

These calculations and conformations at best provide information concerning a preferred conformation, and may in no particular manner reflect any analogy to the drug–receptor interaction, nor exclude other possible conformations in solution.



1.



2.

Biological Results.—Compounds **1** and **2** were screened for muscarinic activity utilizing strips of rabbit ileum suspended in Tyrode's solution and compared to

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ACh. *trans*-3-Trimethylammonium-2-acetoxybicyclo-[2.2.2]octane iodide (**2**) showed muscarinic activity at 1.1×10^{-4} *M* equivalent to 3×10^{-7} *M* ACh chloride, equipotent molar concentration equal to 370. This activity was blocked by atropine, and not by hexamethonium. Repeated experiments at close intervals gave reproducible dose-response curves. These data indicate the activity of **2** is muscarinic, not nicotinic, and provides no evidence for ACh-releasing activity.[6c] Compound **1** showed no muscarinic activity at concentrations up to 10^{-3} *M*. The difference in activity of **1** and **2** is compatible with the hypothesis that the muscarinic receptor is most complementary to a transoid arrangement of the AcO function and the quaternary ammonium head.

Both the cis and trans analogs are substrates for eel AChE. Hydrolysis rates were *ca.* 0.33% ACh ($K_m = 4.3 \times 10^{-4}$) for **1** and 13.6% ACh for **2** ($K_m = 1.2 \times 10^{-3}$); K_m for ACh = 1.2×10^{-4}.[15,16] Both also were inhibitors of eel AChE showing $K_i = 1.0 \times 10^{-5}$ for **1** and 1.8×10^{-5} for **2**, indicating each is more tightly bound to the enzyme than the substrate, ACh, but not nearly as active as competitive inhibitors like physostigmine ($K_i = 4.25 \times 10^{-8}$).[16]

The activity of the trans compound **2**, being a better substrate for AChE by some 40-fold, is more consistent with an eclipsed conformation of the AcO group and quaternary ammonium head ($\theta \simeq 120°$) of ACh analogs in the enzyme-substrate complex of eel AChE than the totally eclipsed conformation. Dreiding models indicate considerable flexibility in the molecule allowing θ to vary from *ca.* 95 to 145°. The upper limit of this range is consistent with the conformation suggested by Chothia and Pauling[17] for the AChE site, on the basis of X-ray data. However, since there is some flexibility in molecular models of the compounds, no absolute analogy can be made. In addition speculation concerning these results and the conformation of ACh at its site on AChE may be misleading because of possible allosteric interactions of the bicyclooctane analogs at sites adjacent to the esteratic site. However, the comparison of cis and trans analogs, **1** and **2**, suggests the latter is a more suitable model for the ACh-AChE interaction than the former.

Experimental Section[18]

***cis*-3-Trimethylammonium-2-acetoxybicyclo[2.2.2]octane Iodide (1).**—A mixture of 618 mg (3.0 mmoles) of *cis*-3-dimethylamino-2-hydroxybicyclo[2.2.2]octane · HCl,[7] 20 ml of pyridine, and 10 ml of Ac_2O was allowed to stand overnight. Excess reactants were removed utilizing a rotary evaporator 20 ml of aq 3% HCl was added, and the mixture allowed to stand at room temp for 20 min. The aq soln was washed with $CHCl_3$, made alk with aq 10% NaOH, and extd 3 times with EtOAc. The combined organic exts were washed with H_2O, satd NaCl and dried ($MgSO_4$), and the solvent was removed, affording a yellow oil.

The yellow oil was dissolved in 5 ml of Me_2CO, 5 ml of MeI added, and the solution was allowed to stand at room temp for 5 hr. The solvent was removed, and the residue crystd from EtOAc-MeOH affording 385 mg (36%): mp 206-208°; nmr (D_2O), δ 5.50 (HCOAc, broadened triplet, line separation *ca.* 7 Hz), 3.75 (HCN^+, broadened doublet, $J_{32} = 6.5$ Hz, $J_{34} = 0$-1 Hz), 3.30 [$(H_3C)_3N^+$, singlet], 2.32 (H_3CCOO, singlet), 2.45 (H-4 methine, multiplet, W_h *ca.* 10 Hz), 1.5-2.2 (CH_2-CH envelope). *Anal.* ($C_{13}H_{24}INO_2$): C, H, N.

***trans*-3-Trimethylammonium-2-acetoxybicyclo[2.2.2]octane Iodide (2).**—Crude 2,3-epoxybicyclo[2.2.2]octane,[8] 3.40 g (27 mmoles), obtained from the reaction of bicyclo[2.2.2]oct-2-ene (Chemical Samples Co., Columbus, Ohio) and *m*-$ClC_6H_4CO_3H$, was heated with 33.8 g (0.75 mole) of anhyd $HNMe_2$ in 50 ml of C_6H_6 in a stainless steel autoclave at 160° for 3 days. After cooling to 0° the autoclave was opened, and the contents were removed by washing the bomb with several portions of C_6H_6. C_6H_6 and excess $HNMe_2$ were removed on a rotary evaporator, and the residue was dissolved in aq 10% HCl, washed with C_6H_6, made alk with aq 10% NaOH, and extd with several portions of C_6H_6. The combined org exts were dried ($MgSO_4$) and the solvent removed (vac) affording 1.70 g (37%) of a brown viscous liquid which was not further purified.

The crude trans amino alcohol was acetylated and allowed to react with MeI as described for the cis compound affording colorless needles: mp 209-210° (MeOH-EtOAc); nmr (D_2O), δ 5.17 (HCOAc, multiplet, W_h = *ca.* 12 Hz), 3.73 (HCN^+, doublet of doublets, $J_{32} = 6.5$ Hz, $J_{34} = 0$-1 Hz), 3.17 [$(H_3C)_3N^+$, singlet], 2.12 (H_3CCOO, singlet), 2.42 (H-4 methine multiplet, W_h = *ca.* 7 Hz), 1.5-2.2 (CH_2-CH envelope). *Anal.* ($C_{13}H_{24}INO_2$): C, H, N.

Enzyme-catalyzed hydrolyses of the compounds and their inhibition of ACh hydrolysis were determined at pH 7.2 using a Radiometer TTT-1 Titrator pH-Stat. Eel AChE (Sigma, type III) was used in the presence of 0.160 *M* NaCl, 0.002 *M* $MgCl_2$, and 0.05% bovine serum albumin. Inhibitor concns were 5×10^{-6} and 5×10^{-7} *M*. Reaction rates were determined at 25° and were linear. A computer program was used to determine K_m and K_i.

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Antimalarials Related to Aminopyrocatechol Dialkyl Ethers. Conformational Effects[1,2]

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Many of the common antimalarial agents, particularly the polynuclear types such as chloroquine, may function biologically *via* an intercalation of the drug with DNA.[3] The basic amino side chain of this type of antimalarials interacts ionically with the phosphoric acid groups of the complementary strands of DNA

(1) This work was supported by the U. S. Army Medicinal Research and Development Command under Contract No. DA-49-193-MD-2900. This is Contribution No. 829 from the Army Research Program on Malaria.

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