8-Methylisobornyl Trifluoroacetate (9b) and Trifluoroacetic Acid. A mixture of 831 mg (3.15 mmol) of trifluoroacetate **9b** and 75 mg (0.67 mmol) of trifluoroacetic acid was heated at 100° for 24 hr. The mixture was hydrolyzed and dehydrated in the usual manner to yield 321 mg of a mixture containing 74% of 8-methylcamphene (**5**) and 26% of 9- and 10-methylcamphenes (**7** and **8**).

Registry No.—**3**, 56906-70-8; **5**, 54382-52-4; **6**, 54382-53-5; **7**, 54345-89-0; **9b**, 56817-46-0; **10**, 56817-47-1; **11**, 3751-96-0; **12**, 56906-71-9; **13**, 56817-48-2; **14**, 56817-49-3; **15**, 56817-50-6; **16a**, 56817-51-7; **17**, 56906-72-0; **19**, 56817-52-8; 8-bromomethylcamphene, 6090-21-7; *exo,exo*-2,3-dimethyl-*endo*-3-(2-hydroxymethyl)-*endo*-2-norbornanol, 56817-53-9; 10-hydroxymethylcamphene, 56817-54-0; potassium cyanide, 151-50-8; 8-methylcamphor, 56817-55-1; trifluoroacetic anhydride, 407-25-0; (−)-isoborneol, 10334-13-1; (+)-camphene, 5794-03-6; trichloroacetic acid, 76-03-9; 10-hydroxymethylisoborneol, 56817-56-2; methanesulfonyl chloride, 124-63-0.

References and Notes

(1) Abstracted from part of the thesis submitted by E. J. E. in partial fulfillment of the requirements for the Ph.D. degree, Purdue University, June 1972.
(2) W. R. Vaughan, J. Wolinsky, R. R. Dueltgen, S. Grey, and F. Seichter, *J. Org. Chem.*, **35**, 400 (1970).
(3) See J. Wolinsky, R. L. Marhenke, and R. Lau, *Synth. Commun.*, **2**, 165 (1972), for references to the synthesis of the santalenes.
(4) See G. E. Gream, C. F. Pincombe, and D. Wege, *Aust. J. Chem.*, **27**, 603 (1974), for the isolation of the 8-methylcamphenes from the lead tetraacetate oxidation of bornane-2-carboxylic acid.
(5) The configurations of **5** and **6** are tentatively assigned on the basis of the C-9 and C-10 methyl shifts which appear at 1.13 and 1.18 ppm for **6** and at 0.97 and 0.99 ppm for **5**. The syn C-8 methyl in **6** should reduce the anisotropic shielding of the C-9 and C-10 methyl groups by the carbon–carbon double bond and result in a downfield shift from the corresponding methyl signals of *anti*-**5** and camphene (1.02 and 1.05 ppm).
(6) J. E. Mc Murry, *J. Org. Chem.*, **36**, 2826 (1971).
(7) The proportion of **6** in the recovered olefin rose to 14%.
(8) W. R. Vaughan and D. M. Teegarden, *J. Am. Chem. Soc.*, **96**, 4902 (1974).
(9) J. J. Ritter and G. Vlases, *J. Am. Chem. Soc.*, **64**, 583 (1942).
(10) J. Wolinsky, D. R. Dimmel, and T. W. Gibson, *J. Org. Chem.*, **32**, 2087 (1967).
(11) (a) E. J. Corey, S. W. Chow, and R. A. Scherrer, *J. Am. Chem. Soc.*, **79**, 5773 (1957); (b) *J. Am. Chem. Soc.*, **81**, 6305 (1959).
(12) J. Wolinsky, R. L. Marhenke, and E. J. Eustace, *J. Org. Chem.*, **38**, 1428 (1973).
(13) See G. L. Hodgson, D. F. MacSweeney, and T. Money, *J. Chem. Soc., Perkin Trans. 1*, 2113 (1973), for the selective dehydration of 8- and 9-substituted isoborneol derivatives to β-santalene and epi-β-santalene.
(14) All melting and boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Infracord. NMR spectra were measured with a Varian Associates A-60 spectrometer. Optical rotations were measured with a Zeiss polarimeter. Mass spectra were determined by the Purdue University Spectral Service employing a Hitachi RMU-6A spectrometer. Microanalyses were performed by Dr. C. S. Yeh and associates.
(15) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedom, *J. Chem. Soc.*, **39** (1946).
(16) A. T. Blomquist, R. J. Himics, and J. D. Meador, *J. Org. Chem.*, **33**, 2462 (1968).

Bicyclic Amino Alcohols. The Isomeric 2-Dimethylaminomethyl-3-hydroxymethylbicyclo[2.2.1]hept-5-enes

Wendel L. Nelson,* David S. Freeman, and Raman Sankar

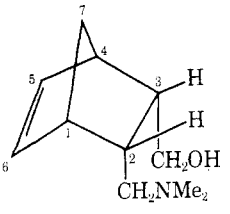
Department of Pharmaceutical Sciences, University of Washington, Seattle, Washington 98195

Received May 1, 1975

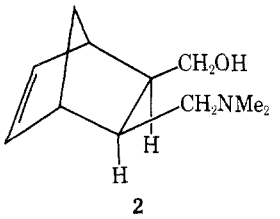
Preparation of the four isomeric 2-dimethylaminomethyl-3-hydroxymethylbicyclo[2.2.1]hept-5-enes is reported and characterization of the stereochemistry of each by NMR techniques is discussed. The cis isomers (**1** and **2**) were prepared from the cyclopentadiene–maleic anhydride Diels–Alder adduct, by reaction with dimethylamine, followed by reduction with $LiAlH_4$. The trans compounds (**3** and **4**) were prepared from appropriate adducts of cyclopentadiene and fumaric acid derivatives. Stereochemistry was assigned by NMR spin–spin decoupling techniques and use made of the anisotropic effects of the 5,6 unsaturation on the C-2 or C-3 methylene protons and on H-2, H-3.

Derivatives of amino alcohols in bicyclic systems have provided a number of interesting structures useful for the study of conformational and steric aspects of the action of drugs related to neurotransmitters, especially acetylcholine and its congeners. Previously, derivatives of the 2-alkylamino-3-hydroxybicyclo[2.2.2]octanes[1-3] and of boranes[4,5] have been reported. More recently, analogs of cholinergic drugs have been studied in semirigid butane systems, e.g., from *cis*- and *trans*-1-dimethylaminomethyl-2-hydroxymethylcyclopropane[6] and certain *cis*- and *trans*-2-butenes.[7]

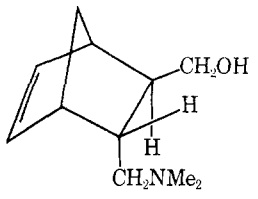
We have prepared isomeric 2-dimethylaminomethyl-3-hydroxymethylbicyclo[2.2.1]hept-5-enes (**1**–**4**) to provide



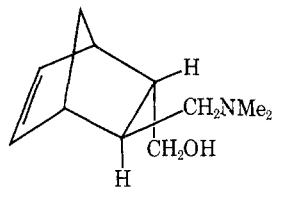
1



2



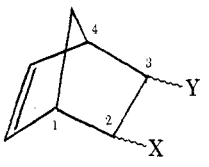
3



4

precursors for preparation of analogs of a muscarinic ganglionic stimulant, McN-A-343.[7,8] In this paper the synthesis of these amino alcohols is reported and facile characterization of the stereochemistry of each is demonstrated by use of NMR spectroscopic techniques.

Our initial efforts were concerned with the preparation of the three isomeric 2,3-di(hydroxymethyl)bicyclo[2.2.1]hept-5-enes (**8**, **11**, and **14**), available from the Diels–Alder adducts of cyclopentadiene with maleic anhydride or with dimethyl fumarate. Endo anhydride **5**, the kinetic product of the former addition,[9] was readily converted at 190° to a mixture of anhydrides from which exo anhydride **6** was obtained by crystallization.[10] 2-*endo*-3-*exo*-Dicarbomethoxybicyclo[2.2.1]hept-5-ene (**7**) was prepared by the



cis

	C-2	C-3
8	X = *endo*-CH_2OH	Y = *endo*-CH_2OH
9	X = *endo*-CH_2OH	Y = *endo*-CH_2OCNH–C$_6$H$_4$–Cl
10	X = *endo*-CH_2OTs	Y = *endo*-CH_2OCNH–C$_6$H$_4$–Cl
11	X = *exo*-CH_2OH	Y = *exo*-CH_2OH
12	X = *exo*-CH_2OH	Y = *exo*-CH_2OCNH–C$_6$H$_4$–Cl
13	X = *exo*-CH_2OTs	Y = *exo*-CH_2OCNH–C$_6$H$_4$–Cl

trans

14	X = *endo*-CH_2OH	Y = *exo*-CH_2OH
15	X = *endo*-CH_2OH	Y = *exo*-CH_2OCNH–C$_6$H$_4$–Cl
16	X = *endo*-CH_2OTs	Y = *exo*-CH_2OCNH–C$_6$H$_4$–Cl
17	X = *exo*-CH_2OH	Y = *endo*-CH_2OCNH–C$_6$H$_4$–Cl
18	X = *exo*-CH_2OTs	Y = *endo*-CH_2OCNH–C$_6$H$_4$–Cl

method of Koch.[11] The isomeric cis hydroxymethyl compounds 8 and 11 and trans hydroxymethyl compound 14 were then prepared by hydride reduction.

Since our interests in this system ultimately required carbamate derivatives of the bicyclic amino alcohols as potential muscarinic, ganglionic stimulants, we converted the diols into mono-*N*-(4-chlorophenyl)carbamates. These carbamate derivatives (**9, 12, 15, 17**) were also advantageous because they are relatively inert to functionalizing the other hydroxyl group and can be readily removed by $LiAlH_4$ reduction, thus facilitating the preparation of other esters of the amino alcohols.

The cis diols, **8** and **11**, were readily converted to their monocarbamate esters, **9** and **12**, then to the corresponding tosylates, **10** and **13**. Attempted displacement of the tosylate group with dimethylamine failed, even at 80°, probably partly owing to steric hindrance to approach presented by the cis carbamate ester adjacent to the tosylate in this system.

Even though this process failed, the same transformations were attempted in the trans series because it was thought that the lack of an adjacent cis substituent would present less steric hindrance to the displacement. Diol **14** was converted to a mixture of monocarbamates (**15** and **17**), which were partially separated by column chromatography.

The NMR spectra were extremely useful in monitoring this separation. As noted previously in bicyclo[2.2.1]hept-5-enes, an exo proton at H-2 (or H-3) is downfield from one in the endo position on the same carbon in the skeleton.[12] This shielding effect of the 5,6 double bond on endo protons and slight deshielding effects for exo protons have been noted in related systems.[13] Even the methyl esters derived from anhydrides **5** and **6**, and of **7**, show different methyl resonances, with the exo ester group being downfield.[14,15]

Early chromatographic fractions contained primarily the 3-*endo*-methylene carbamate, **17**, as evidenced by the doublets at δ 3.90 and 3.64 assigned to methylenes at C-3 and C-2, respectively (Figure 1). Decoupling of H-3 at δ 1.95 and H-2 at δ 1.2 confirmed these assignments. As expected the exo methine proton H-3 is downfield from the endo methine proton, H-2.

Later fractions showed two additional methylene doublets, one further downfield at δ 4.17 and one upfield at δ 3.40 assigned to methylenes at C-3 and C-2 in compound **15**. Decoupling experiments performed on a nearly pure fraction of **15** confirmed these assignments.

It is therefore readily apparent that the compound hav-

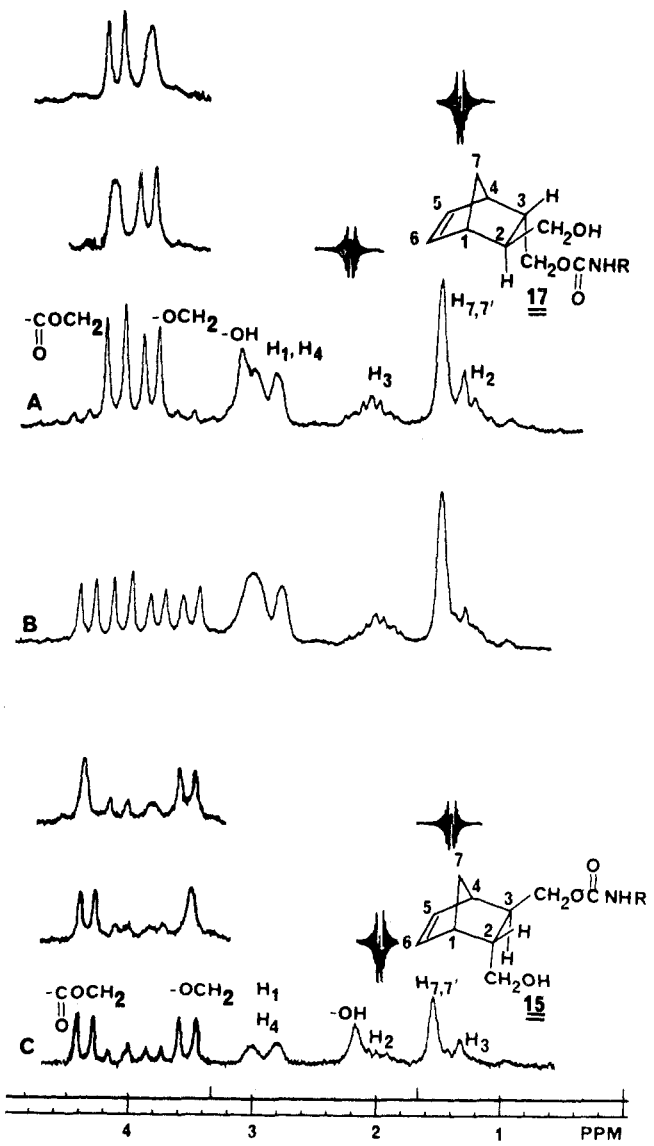
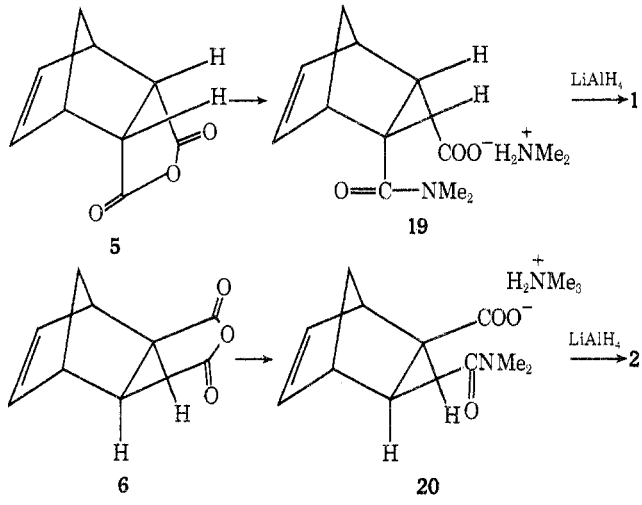


Figure 1. Portions of the 60-MHz ($CDCl_3$) NMR spectra of fractions from the chromatographic separation of **17** from **15**: A, early fraction containing nearly pure **17**; B, fraction containing nearly equal amounts of **17** and **15**; C, last fraction containing mostly **15**.

ing the methylene adjacent to the carbamate further downfield in the NMR would have the *exo*-*N*-(4-chlorophenyl)carbamoyloxymethylene substituent at C-3. Consequently, the hydroxymethylene group would be in the endo position and further upfield. These assignments are consistent with the spectrum for the later eluted compound, **15**.

The purified carbamate **17** was converted to its tosylate ester and displacement attempted with dimethylamine. After an attempt to displace the tosyl group under mild conditions failed, more drastic conditions of temperature and time were attempted, 100° in a bomb for 3 days. Only *N*,*N*-dimethyl-*n*′-(4-chlorophenyl)urea, a result of aminolysis of the carbamate ester, was isolated. This scheme was abandoned.

A more direct method was found for preparation of the desired bicyclic amino alcohols. The isomeric endo and exo anhydrides (**5** and **6**) were converted to the salts of the corresponding monoamide monocarboxylic acids (**19** and **20**) using excess dimethylamine. Attempted isolation of the



5 19 6 20

free amide acids by neutralization of the salts with hydrochloric acid resulted in re-formation of the anhydrides.

Direct $LiAlH_4$ reduction on the salts produced the desired amino alcohols. In this reduction, usually only amino alcohols were isolated. However, in the reduction of **20** small amounts of the diamine were formed, as evidenced by obtaining a small amount of the bis quaternary ammonium salt after reaction with methyl iodide. The diamine is the result of attack of dimethylamine on an aldehyde intermediate in the hydride reduction.

Preparation of the trans compounds **3** and **4** was pursued by a similar procedure. This process required preparation of the two possible isomeric monoamide monoesters of the Diels–Alder adduct of a furmaric acid derivative and cyclopentadiene (**27** and **28**). It was believed that this could be readily accomplished by an appropriate choice of the sequence of synthetic steps.

We expected the reaction of the Diels–Alder adduct of cyclopentadiene and fumaryl chloride (**24**) with 1 equiv of methanol to provide a mixture of monoester monoacid chlorides **25** and **26** consisting primarily of exo ester **25**. This strategy is consistent with other reports concerning steric preferance for attack at an exo position over the endo one in related bicyclic systems.[16-18]

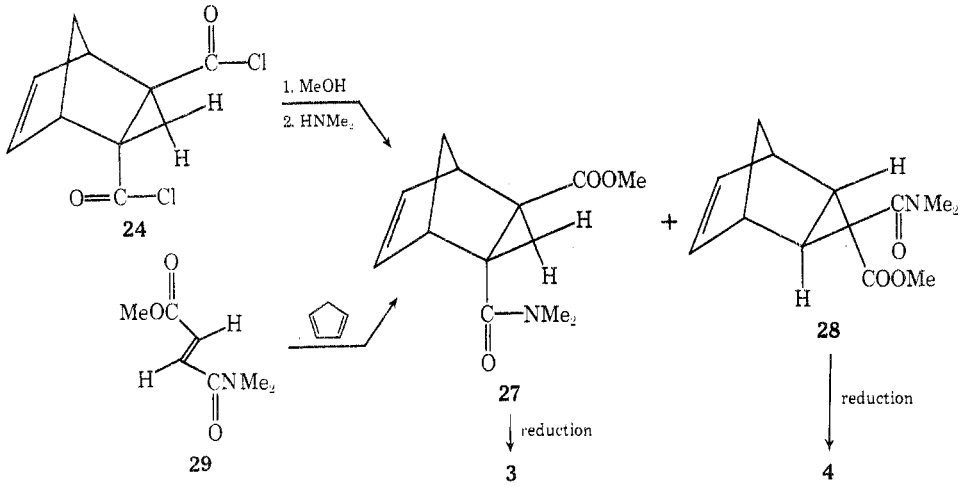
From diacyl chloride **24** was obtained a 2:1 ratio of exo ester **25** to endo ester **26**. Subsequent reaction of this mixture with dimethylamine afforded a similar ratio of **27** to **28**.

We also reasoned that the Diels–Alder addition of cyclopentadiene to the methyl ester of *N*,*N*-dimethylfumaramic acid (**29**) would afford primarily exo amide **28** based on steric effects (bulkier amide function) and/or electronic effects.[19,20] Although this process was successful, affording a 1:2 ratio of **27** to **28**, there appears to be no real consistencies in the prediction of exo:endo ratio of products obtained from the addition of α,β-difunctional dienophiles to cyclopentadiene. Predictions based on steric size and/or electronic considerations have provided variable results.[19-22]

Separation of **27** and **28** was readily accomplished by column chromatography using ether as eluent and NMR spectra to monitor the process. As previously noted in 2-*endo*-3-*exo*-dicarbomethoxybicyclo[2.2.1]hept-5-ene (**7**), the exo ester methyl group is consistently downfield from the endo one.[14,15] Similar results have been noted in the 2-exo and 2-endo methyl esters of 7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid.[13] In this case, the MeO groups were at δ 3.66 for the endo ester (exo amide) of **28** and δ 3.73 for the exo ester (endo amide) of **27**.

Hydride reduction of the individual ester amides, **27** and **28**, afforded amino alcohols **3** and **4**, respectively. Double irridiation of the NMR signals of the methine multiplets due to H-2 and H-3 confirmed the stereochemical assignments. Irradiation of the downfield exo proton, H-3 in compound **4**, caused collapse of the two downfield multiplets of the hydroxymethylene protons into essentially two doublets. Correspondingly, irradiation of the upfield signal of the endo C-3 methine proton in **3** causes collapse of the hydroxymethylene multiplets into two doublets, J_{gem} = 10 Hz.

In both trans amino alcohols (**3** and **4**) the hydroxymethylene protons were observed as two separate multiplets,



24 29 27 28 3 4

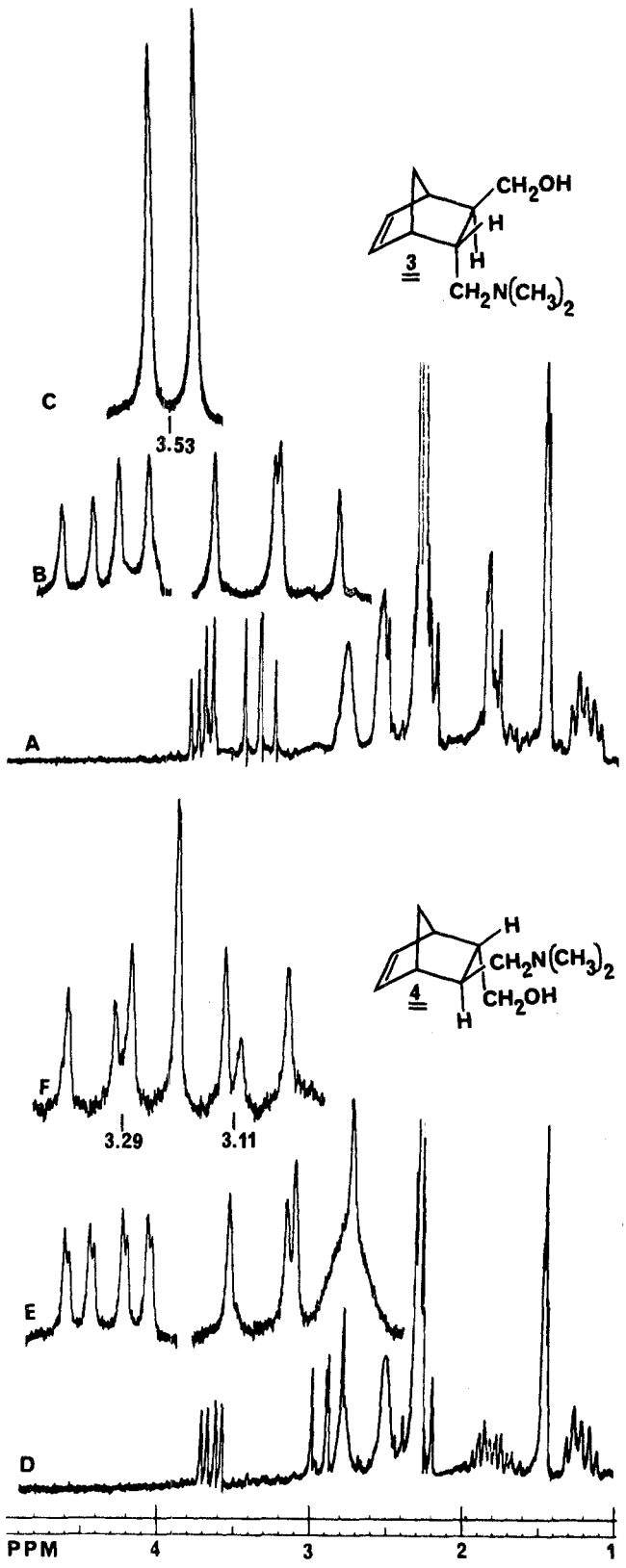


Figure 2. Portions of the 100-MHz NMR spectra of amino alcohols **3** and **4**: A, amino alcohol **3**, 1000-Hz sweep width, in $CDCl_3$; B, 250-Hz sweep width expansion of CH_2OH protons, in $CDCl_3$; C, 250-Hz sweep width expansion of CH_2OH in acetone-d_6–D_2O (9:1); D, amino alcohol **4**, 100-Hz sweep width, in $CDCl_3$; E, 250 Hz sweep width expansion of CH_2OH protons, in $CDCl_3$; F, 250-Hz sweep width expansion of CH_2OH protons, in acetone-d_6–D_2O (9:1).

$J_{gem} \simeq$ 9–10 Hz (Figure 2). Additional vicinal coupling constants of J = 10–11 and 4–5 Hz were observed. These protons are diastereotopic, being adjacent to an asymmetric center; thus a difference in chemical shift is not unexpected. However, the observation of different vicinal coupling constants suggests a conformational preference. Models show one or more conformations where intramolecular hydrogen bonding between the hydroxyl and amine moieties accommodate the observed differences in coupling constants.

Changes observed in polar solvents are consistent with this explanation. In hydroxylic solvents, methanol or acetone–water (9:1), the hydroxymethylene protons in **3** have identical chemical shifts and collapse into a doublet at δ 3.53, J = 7.5 Hz (Figure 2). In the spectrum of **4** in acetone–water (9:1), these protons appear as overlapping quartets at δ 3.29 and 2.11, J_{gem} = 10 and J_{vic} = 8 Hz, indicating different chemical shifts, but averaged coupling constants indicating no conformational preference. However, in the presence of less water, 5% in acetone, these changes are not complete, as evidenced by quartets at δ 3.32 and 3.05, J_{gem} = 9.5, J_{vic} = 6.5 and 8 Hz.

Of the cis compounds only endo compounds **1** showed behavior in $CDCl_3$ similar to the trans compounds. However, in polar solvents the multiplets due to the CH_2OH in **1** and **2** do not change significantly, probably because of stronger intramolecular hydrogen bonding.

The preparation of amino alcohols **1–4** will allow for further work related to semirigid cholinergic ligands, which will be the subject of another publication.

Experimental Section

Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are corrected. Infrared spectra were recorded on a Beckman IR-5A spectrophotometer. NMR spectra were recorded using Varian A-60, T-60, and HA-100 spectrometers using tetramethylsilane as internal standard. Notations used in the NMR descriptions are s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet. Mass spectra were obtained on the SRI-Biospect mass spectrometer operated in the CI mode using methane as carrier gas. Microanalyses were performed by F. B. Strauss, Oxford, England, and Schwarzkopf Microanalytical Laboratory, Woodside, N.Y.

2-*endo*-3-*endo*-Bicyclo[2.2.1]hept-5-enedicarboxylic Anhydride (5). Anhydride **5** was prepared as described by Kloetzel,[9] and was obtained in 94% yield as needles, mp 164–166° (benzene–petroleum ether, bp 30–60°) (lit.[9] mp 164–165°).

The dimethyl ester was prepared from **5** using MeOH and a catalytic quantity of BF_3-Et_2O and was obtained as an oil: NMR (CCl_4) δ 6.15 (t, unsymmetrical, 2, H_5 and H_6, $J_{allylic}$, $J_{6,1}$, and $J_{5,4}$ = 1.5 Hz), 3.57 (s, 6, OCH_3), 3.23 (m, 2, H_2 and H_3, W_h = 4 Hz), 3.10 (m, 2, H_1 and H_4, W_h = 6 Hz), 1.37 (m, 2, 2 H_7, W_h = 4 Hz).

2-*exo*-3-*exo*-Bicyclo[2.2.1]hept-5-enedicarboxylic Anhydride (6). This compound was prepared in 49% yield from **5** by the method of Craig,[10] mp 141–143° (benzene) (lit.[10] mp 142–143°).

The dimethyl ester was prepared from **6**, using MeOH and a catalytic quantity of BF_3-Et_2O, and was obtained as an oil: NMR (CCl_4) δ 6.22 (t, unsymmetrical, 2, H_5 and H_6, $J_{allylic}$, $J_{6,1}$, and $J_{5,4}$ = 2 Hz), 3.67 (s, 6, OCH_3), 3.12 (m, 2, H_1 and H_4, W_h = 5 Hz), 2.62 (d, 2, H_2 and H_3, $J_{2,1}$ ($J_{3,4}$) = 2 Hz), 2.14 (d, 1, H_7-syn, J_{gem} = 9 Hz), 1.50 (dt, 1, $H_{7\text{-anti}}$, $J_{7,1} = J_{7,4}$ = 2, J_{gem} = 9 Hz).

2-*endo*-3-*exo*-Dicarbomethoxybicyclo[2.2.1]hept-5-ene (7).[11] Reaction of dimethyl fumarate with cyclopentadiene followed by distillation produced **7** in 71% yield, obtained as an oil: bp 80–85° (1 mm) [lit.[23] bp 119–120° (4 mm)]; NMR ($CDCl_3$) δ 6.22 (dd, 1, H_6, $J_{6,1}$ = 3, $J_{6,5}$ = 6 Hz), 6.00 (dd, 1, H_5, $J_{5,4}$ = 2, $J_{5,6}$ = 6 Hz), 3.70 (s, 3, exo $COOCH_3$), 3.62 (s, 3, endo $COOCH_3$), 3.1–3.4 (m, 2, H_2 and H_4), 3.07 (m, 1, H_1), 2.58 (d, 1, H_3, $J_{3,2}$ = 4 Hz), 1.2–1.8 (m, 2, 2 H_7).

2-*endo*-3-*endo*-Di(hydroxymethyl)bicyclo[2.2.1]hept-5-ene (8). To 100 mg (2.6 mmol) of $LiAlH_4$ in 25 ml of anhydrous Et_2O was added dropwise, with stirring, a solution of 200 mg (0.95 mmol) of the dimethyl ester of **5** in 10 ml of Et_2O. The reaction was refluxed for 24 hr and after cooling was carefully treated with H_2O. The white solid was removed by suction filtration and

washed with EtOAc, and the combined organic filtrate was dried (Na_2SO_4). The solvent was removed by rotary evaporation to yield 145 mg (99%) of a colorless oil which solidified upon standing: mp 79–82°; infrared (neat) 2.98 (s), 3.24 (w), 3.36, 6.10 (w), 6.90, 7.45, 7.98, 8.07 (w), 8.28 (w), 8.56, 9.00 (br), 9.57 (s), 9.76 (s), 10.14, 10.35 (w), 10.93, 11.26, 11.80 (w), 12.11 (w), 12.33 (w), 12.84, 13.47, and 13.84 (br); NMR ($CDCl_3$) δ 6.05 (t, unsymmetrical, 2, H_5 and H_6, $J_{allylic}$, $J_{6,1}$, and $J_{5,4}$ = 2 Hz), 4.00 (s, 2, OH), 3.2–3.8 (m, 4, OCH_2), 2.77 (m, 2, H_1 and H_4, W_h = 8 Hz), 2.3–2.7 (m, 2, H_2 and H_3), 1.40 (t, unsymmetrical, 2, 2 H_7, $J_{7,1}$ and $J_{7,4}$ = 1.5 Hz).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.84; H, 9.05.

2-*endo*-Hydroxymethyl-3-*endo*-*N*-(4-chlorophenyl)carbamoyloxymethylbicyclo[2.2.1]hept-5-ene (9). To a stirred solution of 1.90 g (12.3 mmol) of diol **8** in 100 ml of anhydrous Et_2O was added dropwise a solution of 1.70 g (11.0 mmol) of 4-chlorophenyl isocyanate in 20 ml of Et_2O. The reaction mixture was stirred at room temperature for 2 days and the Et_2O removed by rotary evaporation. The residue was dissolved in benzene and the insoluble *N,N'*-di(4-chlorophenyl)urea removed by suction filtration. The carbamate, **9**, was crystallized from a benzene–petroleum ether (bp 30–60°) mixture to yield 1.60 g (48%) of white crystals: mp 117–119°; infrared (KBr) 2.88, 3.03, 3.18 (w), 3.22, 3.33, 5.85 (s), 6.24, 6.47 (s), 6.70, 7.11, 7.46 (w), 7.52, 7.62, 7.78, 7.90 (w), 8.09 (s), 8.51 (w), 8.94 (w), 9.14, 9.38, 9.52, 9.73, 9.90, 10.05 (w), 10.70 (w), 10.96 (w), 11.22, 12.10, 13,00, 13.51, 13.92, and 14.60 μ; NMR ($CDCl_3$) δ 7.32 (s, 4, ArH), 7.11 (s, 1, NH), 6.18 (t, unsymmetrical, 2, H_5 and H_6, $J_{allylic}$, $J_{6,1}$, and $J_{5,4}$ = 1.5 Hz), 3.98 (d, 2, ester OCH_2, $J_{H,3}$ = 7 Hz), 3.40 (d, 2, OCH_2, $J_{H,2}$ = 5 Hz), 2.94 (m, 2, H_1 and H_4, W_h = 7 Hz), 2.50 (m, 2, H_2 and H_3, W_h = 11 Hz), 2.10 (s, broad, 1, OH, W_h = 7 Hz), 1.2–1.7 (m, 2, 2 H_7).

Anal. Calcd for $C_{16}H_{18}NO_3Cl$: C, 62.44; H, 5.89; N, 4.55. Found: C, 62.68; H, 5.65; N, 4.60.

2-*endo*-Tosyloxymethyl-3-*endo*-*N*-(4-chlorophenyl)carbamoyloxymethylbicyclo[2.2.1]hept-5-ene (10). To a cold (4°) solution of 200 mg (0.55 mmol) of alcohol **9** in 3 ml of anhydrous pyridine was added 200 mg (1.04 mmol) of *p*-TsCl. The reaction mixture was stored at 4° for 2.5 days and then diluted with 40 ml of ice water. This mixture was extracted with Et_2O (4 × 20 ml) and the combined Et_2O extract washed with aqueous 1 *N* HCl and with H_2O. After drying ($MgSO_4$) the Et_2O was removed by rotary evaporation to yield 300 mg (98%) of a light brown oil which was used without further purification: infrared 2.95, 3.18 (w), 3.24, 3.33, 5.82 (s), 6.24, 6.52 (s), 6.70, 6.88 (w), 7.13, 7.38 (s), 7.66, 7.77, 8.18 (s), 8.41, 8.50 (s), 8.80 (w), 8.95, 9.13, 9.45 (br), 9.88, 10.50 (br, s), 11.20, 11.56, 12.10 (br), 12.89, 13.47, 14.24 (w), 14.60, 14.92, and 15.18 μ; NMR ($CDCl_3$) δ 7.82 and 7.32 (two d, 4, Ts-ArH, J = 8 Hz), 7.30 (s, 4, ArH), 6.97 (s, 1, NH), 6.18 and 5.96 (two dd, 2, H_5 and H_6, $J_{6,1}$ and $J_{5,4}$ = 3, $J_{5,6}$ = 6 Hz), 3.5–4.1 (m, 4, $TsOCH_2$ and ester OCH_2), 2.90 (m, 2, H_1 and H_4, W_h = 8 Hz), 2.3–2.7 (m, 2, H_2 and H_3, overlapping signals), 2.43 (s, 3, $ArCH_3$), 1.2–1.6 (m, 2, 2 H_7).

2-*endo*-(*N,N*-Dimethylcarboxamido)-3-*endo*-carboxybicyclo[2.2.1]hept-5-ene Dimethylamine Salt (19). To a cold (0°), stirred solution of 2.00 g (12 mmol) of anhydride **5** in 75 ml of Et_2O was added 1.40 g (31 mmol) of anhydrous $(CH_3)_2NH$. The reaction mixture was stirred at 0° for 1 hr and then stirred at room temperature overnight. The white precipitate was collected by suction filtration and washed with Et_2O to yield 3.00 g (97%) of a white solid: mp 100–105° dec; infrared (KBr) 2.90, 3.17, 3.38, 6.20 (s), 6.33 (s), 6.70 (w), 6.85 (w), 7.14 (s), 7.46 (w), 7.79 (w), 7.88, 8.05, 8.22, 8.70, 9.45 (w), 9.70, 11.10, 11.69 (w), 11.86 (w), 12.42, 13.47, 14.04, and 14.81 μ; NMR (D_2O) δ 6.38 (dd, 1, H_6, $J_{6,5}$ = 6, $J_{6,1}$ = 3 Hz), 5.98 (dd, 1, H_5, $J_{5,6}$ = 6, $J_{5,4}$ = 3 Hz), 4.74 (s, 2, $-^+NH_2$), 3.32 (m, 2, H_1 and H_4, overlapping signals), 3.17 (m, 2, H_2 and H_3, overlapping signals), 2.97 and 2.80 [two s, 6, amide $N(CH_3)_2$], 2.73 [s, 6, $-^+N(CH_3)_2$], .38 (m, unsymmetrical, 2, 2 H_7, $J_{7,1}$ and $J_{7,4}$ = 1.5 Hz).

Anal. Calcd for $C_{13}H_{22}N_2O_3$: C, 61.39; H, 8.72; N, 11.01. Found: C, 61.13; H, 8.50; N, 11.39.

2-*exo*-(*N,N*-Dimethylcarboxamido)-3-*exo*-carboxybicyclo[2.2.1]hept-5-ene Dimethylamine Salt (20). To a stirred, water–ice bath cooled solution of 800 mg (4.9 mmol) of anhydride **6** in 50 ml of Et_2O was added 1.40 g (31 mmol) of anhydrous $(CH_3)_2NH$. The reaction mixture was allowed to stand at room temperature overnight. The white precipitate was collected by suction filtration and washed with Et_2O to yield 1.22 g (98%) of the salt **20**, mp 81–84°, although it was sometimes obtained as an oil: infrared (KBr) 2.90 (s), 3.37 (s), 3.57, 6.25 (s), 6.70, 7.20 (s), 7.75 (w), 7.92, 8.54, 8.73, 9.02, 9.45 (w), 9.72, 9.92 (w), 11.09, 11.92, 12.13 (w), 12.61, 13.23, 13.94 (s), and 14.58 μ; NMR (D_2O) δ 6.32 (t, unsymmetrical, 2, H_5 and H_6, $J_{allylic}$, $J_{6,1}$, and $J_{5,4}$ = 2 Hz), 4.77 (s, 2, $-^+NH_2$), 3.03 and 2.88 [two s, 6, amide $N(CH_3)_2$], 2.73 [s, 6, $^+N(CH_3)_2$], 2.67 and 2.92 (two m, 2, H_1 and H_4, overlapping signals), 2.05 and 2.20 (two m, 2, H_2 and H_3, W_h = 4 Hz), 1.2–1.7 (m, 2, 2 H_7).

Anal. Calcd for $C_{13}H_{22}N_2O_3$: C, 61.39; H, 8.72; N, 11.01. Found: C, 61.05; H, 8.52; N, 10.95.

2-*endo*-Dimethylaminomethyl-3-*endo*-hydroxymethylbicyclo[2.2.1]hept-5-ene (1). To 2.00 g (53 mmol) of $LiAlH_4$ in 150 ml of anhydrous THF was added dropwise, with stirring, a solution of 1.90 g (7.5 mmol) of **19** in THF. The reaction mixture was refluxed for 3 days and after cooling was carefully treated with H_2O. The white solid was removed by suction filtration and washed with THF, and the combined filtrate was dried (Na_2SO_4). The THF solvent was removed by rotary evaporation to give an oil which solidified upon standing. Recrystallization from benzene provided 0.70 g (52%) of white, granular crystals: mp 94–96°; infrared (KBr) 3.1–3.6 (br), 3.14, 3.38 (s), 3.52, 6.85, 7.34 (w), 7.48, 7.81, 7.98, 8.23, 8.54, 8.92 (w), 9.06, 9.58 (s), 9.90, 10.97, 11.15 (w), 11.70 (w), 11.87, 12.18, 12.52, 12.89, 13.50 (w), and 13.94 μ (s); NMR ($CDCl_3$) δ 6.82 (s, broad, 1, OH), 6.03 (t, unsymmetrical, 2, H_5 and H_6, $J_{allylic}$, $J_{6,1}$, and $J_{5,4}$ = 2 Hz), 3.50 (dd, 1, OCH, J_{gem} = 11.5, $J_{H,3}$ = 2.5 Hz), 3.18 (dd, 1, OCH', J_{gem} = 11.5, $J_{H',3}$ = 10.5 Hz), 2.72 (m, 2, H_1 and H_4, overlapping signals), 2.46 (m, 2, H_2 and H_3, overlapping signals), 2.07–2.42 [overlapping signals, 8, NCH_2 and $N(CH_3)_2$], 1.41 (t, 2, 2 H_7, $J_{7,1}$ and $J_{7,4} \simeq$ 1.5 Hz). In acetone-d_6–D_2O (9:1), the CH_2OH signals appear at δ 3.40 (dd, 1, OCH, J_{gem} = 11.5, $J_{H,3}$ = 4 Hz) and 3.15 (dd, 1, OCH, J_{gem} = 11.5, $J_{H,3}$ = 10.5 Hz). Chemical shifts and coupling constants for other protons are similar to those observed in $CDCl_3$. Mass spectrum (methane, CI), 182 (M + 1).

Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.57; N, 7.73. Found: C, 72.89; H, 10.43; N, 7.77.

The methiodide salt was prepared, mp 214–216° dec (MeOH–Et_2O).

Anal. Calcd for $C_{12}H_{22}INO$: C, 44.59; H, 6.86; N, 4.33. Found: C, 44.30; H, 6.89; N, 4.39.

2-*exo*-Dimethylaminomethyl-3-*exo*-hydroxymethylbicyclo[2.2.1]hept-5-ene (2). To 800 mg (21 mmol) of $LiAlH_4$ in 60 ml of anhydrous THF was added dropwise, with stirring, a solution of 620 mg (2.4 mmol) of amine salt **20** in 30 ml of THF. The reaction mixture was refluxed for 60 hr and after cooling was carefully treated with H_2O. The white solid was removed by suction filtration and washed with THF. The combined THF filtrate was dried (Na_2SO_4) and rotary evaporated to give 300 mg (68%) of a light brown oil: infrared (neat) 2.90 (s), 3.33 (s), 6.78 (s), 7.06, 7.14, 7.50, 7.70 (w), 7.96, 8.08, 8.50 (w), 8.86 (w), 9.24 (w), 9.61 (w), 10.32 (s), 10.63, 11.18 (s), 11.45, 13.17, 13.80, and 14.38 μ; NMR ($CDCl_3$) δ 6.20 (t, 2, H_5 and H_6, $J_{allylic}$, $J_{6,1}$, and $J_{5,4}$ = 2 Hz), 5.28 (s, broad, 1, OH, W_h = 20 Hz), 3.60 (m, unsymmetrical, 2, OCH_2, $J_{H,3}$ = 6 Hz), 2.1–2.8 (m, 2, NCH_2, overlapping signals), 2.43 (m, 2, H_1 and H_4, W_h = 7 Hz), 2.27 [s, 6, $-N(CH_3)_2$], 1.5–2.0 (m, 2, H_2 and H_3, overlapping signals), 1.1–1.5 (m, 2, 2 H_7, overlapping signals). In CD_3OD the CH_2OH signals appear at δ 3.60 (m, 2, OCH_2), and in acetone-d_6–D_2O (9:1) at δ 3.62 (m, complex, 2, OCH_2). Chemical shifts and coupling constants for other protons are similar to those observed in $CDCl_3$.

A sample of crude amine was allowed to react with methyl iodide. Two salts were obtained, a small amount of the bis quaternary salt, mp 265–266° dec, and the methiodide of the amino alcohol, mp 180–182° dec (MeOH–Et_2O). Samples of the amine were also purified by chromatographing on silica gel, eluting with EtOAc–methanol: mass spectrum (methane CI), 182 (M + 1).

Anal. Calcd for $C_{12}H_{22}INO$: C, 44.59; H, 6.86; N, 4.33. Found: C, 44.83; H, 7.11; N, 4.49.

2-*endo*-3-*exo*-Di(hydroxymethyl)bicyclo[2.2.1]hept-5-ene (14). The trans diol **14** was prepared in a manner similar to preparation of cis diol **8** using 1.00 g (4.8 mmol) of diester **7**, 500 mg (13 mmol) of $LiAlH_4$, and 150 ml of anhydrous Et_2O. This procedure afforded 720 mg (98%) of colorless oil: infrared (neat) 2.95 (s), 3.23 (w), 3.35 (s), 3.44, 6.10, 6.38 (w), 6.98 (br), 7.28, 7.48, 7.85 (w), 7.98 (w), 8.23 (w), 8.40 (w), 8.57 (w), 8.88, 9.13, 9.42 (s), 9.74 (br, s), 10.08, 10.22, 11.07 (w), 11.28 (w), 11.92 (w), 12.35 (w), 12.93 (w), and 13.93 μ (s); NMR ($CDCl_3$) δ 6.25 and 6.00 (two dd, 2, H_5 and H_6, $J_{6,1}$ and $J_{5,4}$ = 3, $J_{5,6}$ = 6 Hz), 4.06 (s, broad, 2, 2 OH, W_h = 9 Hz), 2.9–3.9 (m, 4, OCH_2, overlapping signals), 2.84 (m, 1, H_1, W_h = 8 Hz), 2.60 (m, 1, H_4, W_h = 7 Hz), 1.7–2.1 (m, 1, H_2), 1.43 (m, 2, 2 H_7, W_h = 5 Hz), 1.0–1.5 (m, 1, H_3, overlapping signals).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.80; H, 9.20.

2-*endo*-Hydroxymethyl-3-*exo*-*N*-(4-chlorophenyl)carba-

moyloxymethylbicyclo[2.2.1]hept-5-ene (15) and 2-*exo*-Hydroxymethyl-3-*endo*-*N*-(4-chlorophenyl)carbamoyloxymethylbicyclo[2.2.1]hept-5-ene (17). To a stirred solution of 2.10 g (14 mmol) of cis diol **14** in 20 ml of anhydrous Et_2O was added dropwise a solution of 2.00 g (13 mmol) of 4-chlorophenyl isocyanate in 25 ml of Et_2O. The reaction mixture was stirred at room temperature for 8 hr and the Et_2O removed by rotary evaporation. The residue was redissolved in benzene and the insoluble *N,N'*-di(4-chlorophenyl)urea removed by suction filtration. The benzene was removed by rotary evaporation to give 3.80 g (95%) of a brown oil consisting of the dicarbamate of **14** and monocarbamates **15** and **17**.

A 1.9-g sample of this mixture was chromatographed on a 4.5 × 50 cm column of silica gel (400 g) using a benzene–Et_2O (3:2) mixture as eluent. The fractions collected between 100 and 300 ml of eluted solvent contained 450 mg of the dicarbamate ester of **14**, 170 mg of nearly pure isomer **17** obtained between 1600 and 1700 ml eluent, 180 mg of a 3:1 mixture of **17:15** between 1700 and 1760 ml, 500 mg of a 1:1 mixture of **17** and **15** between 1760 and 1880 ml, and 50 mg of nearly pure isomer **15** between 1880 and 1940 ml of eluted solvent. The purification was monitored by NMR spectroscopy. After rotary evaporation, the fractions containing **17** collected were colorless oils which solidified upon standing: mp 99–100°; infrared (KBr) **17**, 2.91, 3.00, 3.19 (w), 3.23, 3.33, 5.86 (s), 6.24, 6.46 (s), 6.70, 6.80 (w), 7.11, 7.63, 7.77, 8.05 (s), 8.50 (w), 8.92 (w), 9.14, 9.40 (s), 9.87, 10.13 (w), 11.03 (w), 11.28 (w), 12.10, 12.92, 13.89, and 14.59 μ; NMR ($CDCl_3$) δ 7.50 (s, 1, NH), 7.32 (s, 4, ArH), 6.28 and 6.03 (two dd, 2, H_5 and H_6, $J_{6,1}$ and $J_{5,4}$ = 3, $J_{5,6}$ = 6 Hz), 3.90 (d, 2, $COOCH_2$, $J_{H,3}$ = 8 Hz), 3.64 (d, 2, OCH_2, $J_{H,2}$ = 7 Hz), 2.94 (s, broad, 1, OH, W_h = 7 Hz), 2.85 and 2.66 (two m, 2, H_1 and H_4, W_h = 8 Hz), 1.7–2.2 (m, 1, H_3), 1.43 (m, 2, 2 H_7, W_h = 5 Hz), 1.0–1.5 (m, 1, H_2, overlapping signals with H_7). Compound **15** was never obtained totally free of **17**: infrared (KBr) **15**, 2.92, 3.07, 3.13 (w), 3.20 (w), 3.25, 3.35, 5.87 (s), 6.22, 6.45, 6.70, 6.81 (w), 7.11, 7.61, 7.98, 8.50 (w), 8.92 (w), 9.13, 9.35, 9.42, 9.87, 10.14, 10.90 (w), 11.00 (w), 11.29 (w), 12.00, 12.96, 13.90, and 14.58 μ; NMR ($CDCl_3$) δ 7.30 (s, 4, ArH), 7.04 (s, broad, 1, NH, W_h = 7 Hz), 6.0–6.4 (m, 2, H_5 and H_6), 4.17 (d, 2, $COOCH_2$, $J_{H,3}$ = 7 Hz), 3.40 (d, 2, OCH_2, $J_{H,2}$ = 8 Hz), 2.88 and 2.70 (two m, 2, H_1 and H_4, W_h = 8 Hz), 2.08 (s, broad, 1, OH, W_h = 6 Hz), 1.7–2.1 (m, 1, H_2, overlapping signals with OH), 1.50 (m, 2, 2 H_7, W_h = 5 Hz), 1.0–1.5 (m, 1, H_3, overlapping signals with H_7).

Anal. Calcd for $C_{16}H_{18}NO_3Cl$ (17): C, 62.44; H, 5.89; N, 4.55. Found: C, 62.02; H, 6.17; N, 4.94.

2-*exo*-Tosyloxymethyl-3-*endo*-*N*-(4-chlorophenyl)carbamoyloxymethylbicyclo[2.2.1]hept-5-ene (18). The trans tosylate **18** was prepared in the same manner as cis tosylate **10** using 170 mg (1.55 mmol) of alcohol **17**, 200 mg (1.04 mmol) of *p*-TsCl, and 3 ml of anhydrous pyridine to yield 200 mg (79%) of tosylate **18** as a light brown oil which was used without further purification: infrared (neat) 2.96, 3.06 (w), 3.27, 3.35, 5.79 (s), 6.25, 6.53, 6.70, 6.96, 7.13, 7.36, 7.65, 7.77 (w), 8.19 (s), 8.42, 8.50 (s), 8.95 (w), 9.14, 9.38, 9.88, 10.10 (w), 10.50 (s), 11.26 (w), 11.46 (w), 11.57 (w), 12.08 (s), 12.29, 12.73, 13.01, 13.40, 14.23 (s), 14.60, and 15.06 μ; NMR ($CDCl_3$) δ 7.80 and 7.32 (two d, 4, TsArH, J = 8 Hz), 7.30 (s, 4, ArH), 7.18 (s, 1, NH), 6.0–6.4 (m, 2, H_5 and H_6), 3.5–4.2 (m, 4, $TsOCH_2$ and ester OCH_2, overlapping signals), 2.80 and 2.63 (two m, 2, H_1 and H_4, W_h = 7 Hz), 2.44 (s, 3, $ArCH_3$), 1.8–2.2 (m, 1, H_3), 1.40 (m, 2, 2 H_7, W_h = 6 Hz), 1.1–1.7 (m, 1, H_2, overlapping signals with H_7).

Reaction of Dimethylamine with 2-*exo*-Tosyloxymethyl-3-*endo*-*N*-(4-chlorophenyl)carbamoyloxymethylbicyclo[2.2.1]hept-5-ene (18). To a cold (4°) solution of 200 mg (0.43 mmol) of tosylate **18** in 20 ml of benzene was added 700 mg (15.5 mmol) of anhydrous $(CH_3)_2NH$. This reaction mixture was heated in a bomb at 100° for 3 days, after which the cooled benzene solution was decanted from the insoluble residue. The benzene and excess $(CH_3)_2NH$ were removed by rotary evaporation to give a brown oil which was crystallized and recrystallized from $CHCl_3$ yielding white needles. These crystals were identified as *N,N*-dimethyl-*N'*-(4-chlorophenyl)urea by ir and NMR spectroscopy, mp 170–172° (lit.[24] 170–171°).

2-*endo*-3-*exo*-Di(chloroformyl)bicyclo[2.2.1]hept-5-ene (24). Cyclopentadiene was distilled from pyrolysis of the dimer into a stirred, water–ice bath cooled solution of 150 g (0.98 mol) of fumaryl chloride[25] in 100 ml of anhydrous Et_2O. The distillation was continued for 8 hr to allow approximately 77 g (1.2 mol) of cyclopentadiene to distil into the reaction solution. The reaction mixture was stirred at room temperature overnight and then the Et_2O was removed by rotary evaporation. The residue was vacuum distilled, yielding 122 g (57%) of a colorless oil, bp 60–62° (0.2–0.3 mm) [lit.[23] 114–118° (11 mm)].

2-*endo*-Chloroformyl-3-*exo*-carbomethoxybicyclo[2.2.1]hept-5-ene (25) and 2-*exo*-Chloroformyl-3-*endo*-carbomethoxybicyclo[2.2.1]hept-5-ene (26). To a stirred, water–ice bath cooled solution of 60.0 g (0.27 mol) of acid chloride **24** in 100 ml of benzene was added dropwise a solution of 8.7 g (0.27 mol) of MeOH in 100 ml of benzene. The reaction mixture was stirred at room temperature overnight and then the benzene was removed by rotary evaporation. The residue was vacuum distilled to yield 48.5 g (83%) of a colorless oil consisting of a mixture of acid chloride esters **25** and **26** (2:1 **25:26**), as shown by NMR. This mixture was used without further purification: bp 80–82° (0.2–0.4 mm); infrared (neat) 3.24 (w), 3.32, 3.45 (w), 5.57 (s), 5.78 (s), 6.98, 7.30, 7.51, 7.64, 7.91, 8.03, 8.28, 8.35, 8.48, 8.98, 9.37, 9.78 (s), 10.04 (w), 10.19 (w), 10.78 (w), 11.02, 11.29, 11.65, 11.92 (w), 12.15, 12.71, 12.94, 13.50, 14.33, and 14.64 μ; NMR ($CDCl_3$) δ 6.0–6.6 (m, 2, H_5 and H_6), 3.0–4.0 (m, 4, H_1, H_2, H_3, and H_4, overlapping signals for isomeric mixture), 3.78 and 3.70 (two s, 3, exo OCH_3 and endo OCH_3 protons from isomeric mixture), 2.73 (m, 1, endo H_3, W_h = 8 Hz), 1.64 (m, 2, 2 H_7, W_h = 8 Hz).

***trans*-β-Carbomethoxy-*N,N*-dimethylacrylamide (29).** To a stirred, water–ice bath cooled solution of 78.0 g (0.52 mol) of *trans*-β-carbomethoxyacrylyl chloride, prepared by the method of Lutz,[26] in 100 ml of benzene was added dropwise a solution of 50.0 g (1.10 mol) of anhydrous $(CH_3)_2NH$ in 100 ml of benzene. The reaction mixture was stirred at room temperature overnight and then treated with 200 ml of H_2O. The organic phase was separated and washed consecutively with portions of aqueous 1 *N* HCl, H_2O, aqueous 0.5 *M* Na_2CO_3, and H_2O. After drying ($MgSO_4$) the benzene was removed by rotary evaporation and the residue vacuum distilled. The first fraction of the distillate solidified in the condenser (dimethyl fumarate) followed by 5.5 g (7%) of amide **29** collected as a colorless oil: bp 76–80° (0.2–0.3 mm); infrared (neat) 3.30, 3.38, 5.80 (s), 6.10 (br, s), 6.70, 6.97, 7.16 (s), 7.63 (s), 7.81 (s), 8.34, 8.51, 8.76, 9.43 (w), 9.68, 9.91, 10.25, 10.70, 11.33 (w), 11.62 (w), 12.12 (w), 13.11, 14.22, and 14.58 μ (w); NMR ($CDCl_3$) δ 7.48 and 6.76 (two d, 2, H_α and H_β, $J_{\alpha,\beta}$ = 14 Hz), 3.83 (s, 3, OCH_3), 3.17 [s, broad, 6, $N(CH_3)_2$, W_h = 9 Hz].

Anal. Calcd for $C_7H_{11}NO_3$: C, 53.59; H, 7.05; N, 8.91. Found: C, 53.23; H, 6.84; N, 8.75.

2-*endo*-(*N,N*-Dimethylcarboxamido)-3-*exo*-carbomethoxybicyclo[2.2.1]hept-5-ene (27) and 2-*exo*-(*N,N*-Dimethylcarboxamido)-3-*endo*-carbomethoxybicyclo[2.2.1]hept-5-ene (28). A. Diels–Alder Addition of 29 with Cyclopentadiene. Cyclopentadiene was added to a stirred solution of 4.8 g (30 mmol) of amide ester **29** in 50 ml of benzene. The distillation from cyclopentadiene dimer was continued for 50 min to allow approximately 8.0 g (120 mmol) of cyclopentadiene to distil into the reaction solution. The reaction mixture was stirred at room temperature overnight and then the benzene was removed by rotary evaporation. The residue was vacuum distilled, affording 5.4 g (80%) of a yellow oil consisting of a mixture of the isomeric amide esters **27** and **28** (2:1 **28:27**) as shown by NMR, bp 107–112° (0.1 mm).

A 3.4-g sample of this mixture was chromatographed on a 2.5 × 33 cm silica gel column using Et_2O as eluent. The fractions collected between 250 and 325 ml of eluted solvent contained 1.7 g of the pure exo amide endo ester **28**, 0.6 g of mixed isomers between 325 and 375 ml, and 0.5 g of pure endo amide exo ester **27** between 375 and 500 ml of eluted solvent. The purification was monitored by NMR spectroscopy. Both purified isomers **27** and **28** were obtained as colorless oils.

B. Reaction of 25 and 26 with Dimethylamine. To a stirred, water–ice bath cooled solution of 21.0 g (0.47 mol) of anhydrous $(CH_3)_2NH$ in 50 ml of benzene was added dropwise a solution of 45.0 g (0.21 mol) of the mixture of acid chlorides, **25** and **26**, in 75 ml of benzene. The reaction mixture was stirred at room temperature overnight and the white precipitate which formed removed by suction filtration. The benzene was removed from the filtrate by rotary evaporation and the residue vacuum distilled affording 18.5 g (40%) of a colorless oil consisting of a mixture of isomeric amide esters **27** and **28** (2:1 **27:28**), bp 130–132° (0.3 mm).

A 3.0-g sample of this mixture was chromatographed on silica gel as previously described, providing 0.40 g of pure exo amide endo ester **28** and 1.0 g of pure endo amide exo ester **27**: infrared (neat), **28**, 2.84 (w), 3.23 (w), 3.37, 5.78 (s), 6.10 (s), 6.68, 6.88, 6.97, 7.07, 7.13, 7.38, 7.49, 7.65, 7.90 (s), 8.30 (s), 8.51, 8.70, 8.95, 9.40 (br), 9.75, 10.00, 10.99, 11.52, 11.85 (w), 12.48 (w), 12.68 (w), 12.97 (w), 13.80, 14.06, and 14.57 μ; NMR ($CDCl_3$), **28**, δ 6.38 and 6.13 (two dd, 2, H_5 and H_6, $J_{6,1}$ and $J_{5,4}$ = 3, $J_{5,6}$ = 6 Hz), 3.66 (s, 3,

$COOCH_3$), 3.5–3.7 (m, 1, H_3, overlapping signals with $COOCH_3$), 2.8–3.4 (m, 3, H_1, H_2, and H_4, overlapping signals), 3.15 and 3.00 [two s, 6, $N(CH_3)_2$], 1.92 (d, unsymmetrical, 1, H_7, J_{gem} = 9 Hz), 1.40 (d, unsymmetrical, 1, H_7, J_{gem} = 9 Hz); infrared (neat), **27**, 2.84 (w), 3.24 (w), 3.37, 5.79 (s), 6.10 (s), 6.67, 6.88, 6.97, 7.08, 7.13, 7.36, 7.48, 7.67, 7.90 (s), 8.04, 8.25, 8.38, 8.53 (s), 8.71 (s), 9.00, 9.42, 9.76, 9.98, 10.52, 10.75, 11.20, 11.61, 11.88 (w), 12.18, 12.68 (w), 13.35, 13.76, 14.17, and 14.55 μ; NMR ($CDCl_3$), **27**, δ 6.38 and 6.05 (two dd, 2, H_5 and H_6, $J_{6,1}$ and $J_{5,4}$ = 3, $J_{5,6}$ = 7 Hz), 3.73 (s, 3, $COOCH_3$), 3.4–3.7 (m, 1, H_2, overlapping signals), 2.9–3.4 (m, 3, H_1, H_3, and H_4, overlapping signals), 3.20 and 2.97 [two s, 6, $N(CH_3)_2$], 1.3–1.9 (m, 2, 2 H_7).

Anal. Calcd for $C_{12}H_{17}NO_3$ (**28**): C, 64.55; H, 7.67; N, 6.27. Found: C, 64.47, H, 7.74; N, 6.38.

Anal. Calcd for $C_{12}H_{17}NO_3$ (**27**): C, 64.55; H, 7.67; N, 6.27. Found: C, 64.31; H, 7.69; N, 6.46.

2-*exo*-Dimethylaminomethyl-3-*endo*-hydroxymethylbicyclo[2.2.1]hept-5-ene (4). To a stirred solution of 7.00 g (35 mmol) of $NaAlH_2(OCH_2CH_2OCH_3)_2$ (70% solution in benzene, Red-al, Aldrich) in 75 ml of anhydrous benzene was added dropwise a solution of 1.00 g (4.5 mmol) of amide ester **28** in 25 ml of benzene. The reaction mixture was refluxed for 24 hr and after cooling was slowly treated with 150 ml of aqueous 2.5 N NaOH. The organic phase was separated and the aqueous layer extracted with $CHCl_3$ (3 × 50 ml). The combined organic extract was washed with H_2O, dried ($MgSO_4$), and rotary evaporated to yield 0.60 g (74%) of a light yellow oil: infrared (neat) 2.90 (br), 3.23 (w), 3.34 (s), 3.46, 3.52, 3.58, 6.12 (w), 6.37 (w), 6.83 (s), 7.27, 7.47, 7.69 (w), 7.97, 8.23, 8.50, 8.57, 8.68, 8.88 (w), 9.06, 9.17, 9.42 (s), 9.70 (s), 10.98 (w), 11.08 (w), 11.25 (w), 11.98, 12.54 (w), 12.90, 13.23 (w), and 13.93 μ (s); NMR (100 MHz) ($CDCl_3$) δ 6.20 and 5.94 (two dd, 2, H_5 and H_6, $J_{6,1}$ and $J_{5,4}$ = 3, $J_{5,6}$ = 6 Hz), 4.50 (s, broad, 1, OH, W_h = 5 Hz), 3.62 (ddd, 1, OCH, $J_{H,3}$ = 4, J_{gem} = 9.5, J_w = 0.5 Hz), 2.87 (t, 1, OCH′, $J_{H',3}$ = 11, J_{gem} = 9.5 Hz), 2.77 (m, 1, H_4, W_h = 8 Hz), 2.50 (m, 1, H_1, W_h = 8 Hz), 2.22–2.36 [overlapping signals, 8, NCH_2 and $N(CH_3)_2$], 1.82 (m, 1, H_3, W = 19 Hz), 1.46 (m, 2, 2 H_7, W_h = 4 Hz), 1.16 (m, 1, H_2, W = 20 Hz). In acetone-d_6–D_2O (9:1), the CH_2OH signals appear at δ 3.29 (dd, 1, OCH, J_{gem} = 10, $J_{H,3}$ = 8 Hz) and 3.11 (dd, 1, OCH′, J_{gem} = 10, $J_{H',3}$ = 8 Hz). In acetone-d_6–D_2O (19:1), the CH_2OH signals appear at δ 3.32 (dd, 1, OCH, J_{gem} = 9.5, $J_{H,3}$ = 6.5 Hz) and 3.05 (dd, 1, OCH′, J_{gem} = 9.5, $J_{H',3}$ = 8 Hz). Chemical shifts and coupling constants for other protons are similar to those observed in $CDCl_3$. Mass spectrum (methane-CI) 182 (M + 1).

For an analytical sample, the methiodide salt was prepared, mp 148–150° (MeOH–Et_2O).

Anal. Calcd for $C_{12}H_{22}INO$: C, 44.59; H, 6.86; N, 4.33. Found: C, 44.31; H, 6.90; N, 4.11.

2-*endo*-Dimethylaminomethyl-3-*exo*-hydroxymethylbicyclo[2.2.1]hept-5-ene (3). Amino alcohol **3** was prepared in a manner similar to compound **4** using 3.50 g (17 mmol) of $NaAlH_2(OCH_2CH_2OCH_3)_2$ (70% solution in benzene, Red-al), 0.54 g (2.4 mmol) of amide ester **27**, and 75 ml of anhydrous benzene. This procedure provided 0.40 g (91%) of amino alcohol **3** as a light yellow oil: infrared (neat) 2.90 (br), 3.36 (s), 3.58, 6.86, 7.28 (w), 7.48, 7.95, 8.22, 8.58, 8.70, 8.92 (w), 9.13, 9.40, 9.62 (s), 9.80, 11.74 (w), 12.00, 12.38, 12.91, and 14.96 μ (s); NMR (100 MHz) ($CDCl_3$) δ 6.23 and 5.94 (two dd, 2, H_5 and H_6, $J_{6,1}$ and $J_{5,4}$ = 3, $J_{5,6}$ = 6 Hz), 4.82 (s, 1, OH), 3.69 (dd, 1, OCH, $J_{H,3}$ = 5, J_{gem} = 9 Hz), 3.30 (t, 1, OCH′, $J_{H',3}$ = 11, J_{gem} = 9 Hz), 2.75 (m, 1, H_1, W_h = 8 Hz), 2.52 (m, 1, H_4, W_h = 8 Hz), 2.26–2.31 [overlapping signals 8, NCH_2 and $N(CH_3)_2$], 1.80 (m, 1, H_2), 1.47 (m, 2, 2 H_7, W_h = 4 Hz), 1.20 (m, 1, H_3, W = 18 Hz). In CD_3OD the OCH_2 protons appear at δ 3.53 (d, 2, OCH_2, $J_{H,3}$ = 7.5 Hz). Chemical shifts and coupling constants for other protons are similar to those observed in $CDCl_3$. Mass spectrum (methane CI), 182 (M + 1).

For an analytical sample, the methiodide salt was prepared, mp 180–182° (MeOH–Et_2O).

Anal. Calcd for $C_{12}H_{22}INO$: C, 44.59; H, 6.86; N, 4.33. Found: C, 44.20; H, 6.87; N, 4.08.

Acknowledgments. This investigation was supported in part by a U.S. Public Health Service Career Development Award (5-K4-GM-70,023) to W.L.N. from the National Institute of General Medical Sciences. We acknowledge support of D.S.F. by the American Foundation for Pharmaceutical Education through the Josiah Kirby Lilly Memorial Fellowship, 1972–1974.

Registry No.—**1**, 56679-25-5; 1 methiodide, 56689-38-4; **2**, 56679-26-6; **2** methiodide, 56679-27-7; **2** bis quaternary salt, 56679-28-8; **3**, 56711-26-3; **3** methiodide, 56760-97-5; **4**, 56711-27-4; **4** methiodide, 56711-28-5; **5**, 129-64-6; **5** dimethyl ester, 39589-98-5; **6**, 2746-19-2; **6** dimethyl ester, 7184-07-8; **7**, 3014-58-2; **8**, 699-97-8; **9**, 56679-29-9; **10**, 56679-30-2; **14**, 699-96-7; **15**, 56711-29-6; **17**, 56711-30-9; **18**, 56711-31-0; **19**, 56679-32-4; **20**, 56679-34-6; **24**, 4582-21-2; **25**, 56679-35-7; **26**, 56711-32-1; **27**, 56679-36-8; **28**, 56711-33-2; **29**, 23743-87-5; dimethyl fumarate, 624-49-7; cyclopentadiene, 542-92-7; 4-chlorophenyl isocyanate, 104-12-1; *p*-toluenesulfonyl chloride, 98-59-9; dimethylamine, 124-40-3; *trans*-β-carbomethoxyacrylyl chloride, 17081-97-9.

References and Notes

(1) W. L. Nelson, *J. Heterocycl. Chem.*, **5**, 231 (1968).
(2) W. L. Nelson and R. S. Wilson, *J. Med. Chem.*, **14**, 169 (1971).
(3) A. H. Beckett and R. E. Reid, *Tetrahedron*, **28**, 5555 (1972).
(4) A. H. Beckett, N. T. Lan, and G. R. McDonough, *Tetrahedron*, **25**, 5693 (1969).
(5) A. H. Beckett, N. T. Lan, and G. R. McDonough, *Tetrahedron*, **25**, 5689 (1969).
(6) J. G. Cannon, A. B. Rege, T. L. Gruen, and J. P. Long, *J. Med. Chem.*, **15**, 71 (1972).
(7) W. L. Nelson, D. S. Freeman, P. D. Wilkinson, and F. F. Vincenzi, *J. Med. Chem.*, **16**, 506 (1973).
(8) A. P. Roszkowski, *J. Pharmacol. Exp. Ther.*, **132**, 156 (1961).
(9) M. Kloetzel, *Org. React.*, **4**, 9 (1948).
(10) D. Craig, *J. Am. Chem. Soc.*, **73**, 4889 (1951).
(11) H. Koch, *Monatsh. Chem.*, **93**, 1343 (1962).
(12) D. R. Arnold, D. J. Trecker, and E. B. Whipple, *J. Am. Chem. Soc.*, **87**, 2596 (1965).
(13) W. L. Nelson and D. R. Allen, *J. Heterocycl. Chem.*, **9**, 561 (1972).
(14) R. Noyori, Y. Kumagi, and H. Takaya, *J. Am. Chem. Soc.*, **96**, 634 (1974).
(15) D. S. Freeman, Ph.D. Thesis, University of Washington, 1974.
(16) H. C. Brown in "Hydroboration", W. A. Benjamin, New York, N.Y., 1962, p 126; H. C. Brown, *Chem. Eng. News*, **45**, 87 (February 13, 1967).
(17) J. K. Stille and F. M. Sonnenberg, *Tetrahedron Lett.*, 4587 (1966).
(18) G. D. Sargent, *Q. Rev., Chem. Soc.*, **20**, 301 (1966).
(19) C. S. Rondestvedt, Jr., and C. D. Ver Nooy, *J. Am. Chem. Soc.*, **77**, 4878 (1955).
(20) C. S. Rondestvedt, Jr., and J. C. Wygant, *J. Org. Chem.*, **17**, 975 (1952).
(21) H. P. Braendlin, A. Z. Zielinski, and E. J. McBee, *J. Am. Chem. Soc.*, **84**, 2109 (1962).
(22) H. Christol, A. Donche, and F. Pleuat, *Bull. Soc. Chim. Fr.*, 1315 (1966).
(23) A. T. Blomquist and E. C. Winslow, *J. Org. Chem.*, **10**, 149 (1945).
(24) A. V. Logan and N. R. Odell, *Weeds*, **2**, 135 (1953).
(25) U. Eisner, J. A. Elvidge, and R. P. Linstead, *J. Chem. Soc.*, 1501 (1951).
(26) R. E. Lutz, *J. Am. Chem. Soc.*, **52**, 3423 (1930).