Derivatives of 7-Oxabicyclo[2.2.1]hept-5-ene and 7-Oxabicyclo[2.2.1]heptane. Synthesis, Transformations, and Stereochemistry Using Nmr Methods (1)

Wendel L. Nelson and David R. Allen

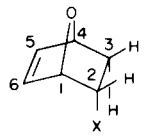
School of Pharmacy, University of Washington, Seattle, Washington 98195

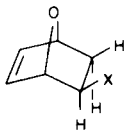
Received January 27, 1972

Synthesis and stereochemistry of various *endo*-2- and *exo*-2-substituted-7-oxabicyclo[2.2.1]-hept-5-enes and -heptanes are described. The nmr spectra of several derivatives are reported and discussed. Use is made of this data to allow determination of the stereochemical integrity of the system. Facile chromatographic separation methods were found for *endo*- and *exo*-2-substituted-7-oxabicyclo[2.2.1]hept-5-enes and -heptanes.

In association with some work related to preparation of analogs of muscarine, it was necessary to prepare *endo*- and *exo*-2-substituted derivatives of 7-oxabicyclo[2.2.1]-hept-5-ene and heptane. An essential element of this work was the determination of the stereochemistry at C-2, and to analyze possible isomerization in these systems under the conditions of the various reactions performed. In addition, it was necessary to find a suitable method for separation of gram quantities of various *endo*- and *exo*-2-substituted derivatives, and a monitoring system for the separation. Facile chromatographic separation methods have been found for various derivatives, and nmr data has been exceedingly useful in monitoring these separations.

Routinely the mixture of *endo*- and *exo*-2-carbomethoxy-7-oxabicyclo[2.2.1]hept-5-enes, **1** and **2**, was prepared by the Diels-Alder addition of furan to methyl acrylate, which is reported to occur in poor yield at reflux for several weeks (2) or at 40° for one month (3). In our hands, yields over more than 50% of a non-equilibrium (4) mixture of **1** and **2** were obtained under conditions at room temperature and up to a two month reaction time. This *endo:exo* ratio was determined to be 6:1 by nmr methods, and glpc data obtained onthis reduced mixture.





1 X = COOMe
3 X = COOH
5 X = $CONHNH_2$
7 X = NHCOMe
9 X = N(Me)COMe

2 X = COOMe
4 X = COOH
6 X = $CONHNH_2$
8 X = NHCOMe
10 X = N(Me)COMe

Tarbell (3) has reported successful isolation of the *endo* acid **3**, at the expense of *exo* isomer **4**, by chromatography of the saponification mixture on alumina. Considerable losses were encountered during chromatography, probably in part due to the reversible nature of the preparation method. Using the mixture of esters, we were able to separate **1** and **2** using silver nitrate impregnated silica gel (6,7). However, on standing a single ester afforded a mixture of **1** and **2**, due to instability of the adducts (8,9), requiring use of the single ester within a few days.

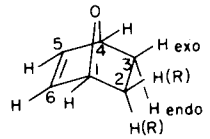
Separation of the esters allowed for complete analysis of the nmr spectra of the isomers. Considerable differences were noted (Table I and Figure 1). The signal most useful in following the separation was the OMe ester singlet observed at 3.63 δ (for **1**) and 3.71 δ (**2**). These methyl resonances occur at different field strengths, and at field strengths in opposite relationship to each other than reported by Ouelette (2).

Solvent effects are responsible for this difference. We recorded spectra in deuteriochloroform and Ouelette recorded data in the reaction mixture of furan and methyl acrylate. Repeating his experiment showed this to be true, as the *endo*- isomer is predominant in early stages of the reaction and other signals consistent with a preponderance of **1** were observed.

Choosing carefully controlled conditions, it was possible to perform many of the standard transformations on the esters separately, *e.g.*, saponification, hydrazide formation and Curtius rearrangement. In each case, the stereochemical integrity of the products could be demostrated from the nmr spectra which indicated no isomerization at C-2. Alternatively separation of these *endo*- and *exo*-2-substituted compounds could be accomplished at later stages using silica gel column chromatography without

TABLE I

Chemical Shifts and Coupling Constants for 2-Substituted-7-oxabicyclo[2.2.1]hept-5-enes (a)



Compound	δ $H_{2\text{-}endo}$	δ $H_{2\text{-}exo}$	δ $H_{3\text{-}exo}$	δ $H_{3\text{-}endo}$	δ H_1	δ H_4	δ H_5	δ H_6	Others
1 *endo*-$COOCH_3$		3.17 quintet $J_{2,3\text{-}exo} = 8$ $J_{2,1} = 4$ $J_{2,3\text{-}endo} = 4$	2.09, m, 8 peaks $J_{gem} = 10$ $J_{3,4} = 4$ $J_{3,2\text{-}exo} = 8$	1.55, dd $J_{gem} = 10$ $J_{3,2\text{-}exo} = 4$	5.16 d, broadened $J_{1,2\text{-}exo} = 4$ $J_{1,6} \cong 0$	5.00 d, broadened $J_{4,3\text{-}exo} = 4$ $J_{4,5} \cong 0$	6.21, dd $J_{5,6} = 6$ $J_{5,4} = 2$	6.43, dd $J_{6,5} = 6$ $J_{6,1} = 2$	3.63 (OCH_3)
2 *exo*-$COOCH_3$	2.43, dd $J_{2,3\text{-}endo} = 8$ $J_{2,3\text{-}exo} = 4$		2.16, dt $J_{gem} = 12$ $J_{3,4} = 4$ $J_{3,2\text{-}endo} = 4$	1.57, dd $J_{gem} = 12$ $J_{3,2\text{-}endo} = 8$	5.18 s, broadened $J_{1,2\text{-}endo} \cong 0$ $J_{1,6} \cong 0$	5.06 d, broadened $J_{4,3\text{-}exo} = 4$ $J_{4,5} \cong 0$	6.37 s, broadened		3.71 (OCH_3)
3 *endo*-COOH		3.17 quintet $J_{2,3\text{-}exo} = 8$ $J_{2,1} = 4$ $J_{2,3\text{-}endo} = 4$	2.13, m, 8 peaks $J_{gem} = 10$ $J_{3,4} = 4$ $J_{3,2\text{-}exo} = 8$	1.55, dd $J_{gem} = 10$ $J_{3,2\text{-}exo} = 4$	5.23 d, broadened $J_{1,2\text{-}exo} = 4$ $J_{1,6} \cong 2$	5.06 d, broadened $J_{4,3\text{-}exo} = 4$ $J_{4,5} \cong 2$	6.28, dd $J_{5,6} = 6$ $J_{5,4} \cong 2$	6.45, dd $J_{6,5} = 6$ $J_{6,1} = 2$	8.81 (COOH)
4 *exo*-COOH	2.45, dd $J_{2,3\text{-}endo} = 8$ $J_{2,3\text{-}exo} = 4$		2.15, dt $J_{gem} = 12$ $J_{3,4} = 4$ $J_{3,2\text{-}endo} = 4$	1.57, dd $J_{gem} = 12$ $J_{3,2\text{-}endo} = 8$	5.23 s, broadened $J_{1,2\text{-}endo} \cong 0$ $J_{1,6} \cong 0$	5.10 d $J_{4,3\text{-}exo} = 4$ $J_{4,5} \cong 0$	6.35 s, broadened W/2 = 4		8.85 (COOH)
5 *endo*-$CONHNH_2$		3.10, quintet $J_{2,3\text{-}exo} = 9$ $J_{2,1} = 5$ $J_{2,3\text{-}endo} = 5$	2.13, m, 8 peaks $J_{gem} = 11$ $J_{3,4} = 5$ $J_{3,2\text{-}exo} = 9$	1.68, dd $J_{gem} = 11$ $J_{3,2\text{-}exo} = 5$	5.22 d, broadened $J_{1,2\text{-}exo} = 4$ $J_{1,6} \cong 2\text{-}3$	5.15 d, broadened $J_{4,3\text{-}exo} = 4$ $J_{4,5} \cong 2\text{-}3$	6.35, dd $J_{5,6} = 6$ $J_{5,4} = 3$	6.43, dd $J_{6,5} = 6$ $J_{6,1} = 3$	7.50 (NH) 3.95 (NH_2)
6 *exo*-$CONHNH_2$	2.18, dd $J_{2,3\text{-}endo} = 8$ $J_{2,3\text{-}exo} = 4$		2,00, m	1.62, dd $J_{gem} = 11$ $J_{3,2\text{-}endo} = 8$	5.06 s, broadened $J_{1,2\text{-}endo} \cong 0$ $J_{1,6} \cong 0$	5.10 d, broadened $J_{4,3\text{-}exo} = 4$ $J_{4,5} \cong 0$	6.40 s, broadened W/2 = 3		7.50 (NH) 3.85 (NH_2)
7 *endo*-$NHCOOCH_3$		4.29, quintet $J_{2,3\text{-}exo} = 8$ $J_{2,3\text{-}endo} = 4$ $J_{2,1} = 4$	2.35, m, 8 peaks $J_{gem} = 12$ $J_{3,2\text{-}exo} = 8$ $J_{3,4} = 4$	0.90, dd $J_{gem} = 12$ $J_{3,2\text{-}exo} = 4$	5.03 d, broadened $J_{1,2\text{-}exo} = 4$ $J_{1,6} \cong 2$	4.97 d, broadened $J_{4,3\text{-}exo} = 4$ $J_{4,5} \cong 2$	6.35, dd $J_{5,6} = 6$ $J_{5,4} = 2$	6.60, dd $J_{6,5} = 6$ $J_{6,1} = 2$	4.77 (NH) 3.68 (OCH_3)
8 *exo*-$NHCOOCH_3$	3.83, dd $J_{2,3\text{-}endo} = 8$ $J_{2,3\text{-}exo} = 3$		1.37, m, 8 peaks $J_{gem} = 12$ $J_{3,4} = 5$ $J_{3,2\text{-}endo} = 3$	1.86, dd $J_{gem} = 12$ $J_{3,2\text{-}endo} = 8$	4.78 s, broadened $J_{1,2\text{-}endo} \cong 0$ $J_{1,6} \cong 0$	5.03 d, broadened $J_{4,3\text{-}exo} \cong 5$ $J_{4,5} \cong 0$	5.68 s, broadened		5.68 (NH) 3.68 (OCH_3)

(a) Spectra are recorded in deuteriochloroform. Chemical shifts are given in δ, coupling constants in Hz.

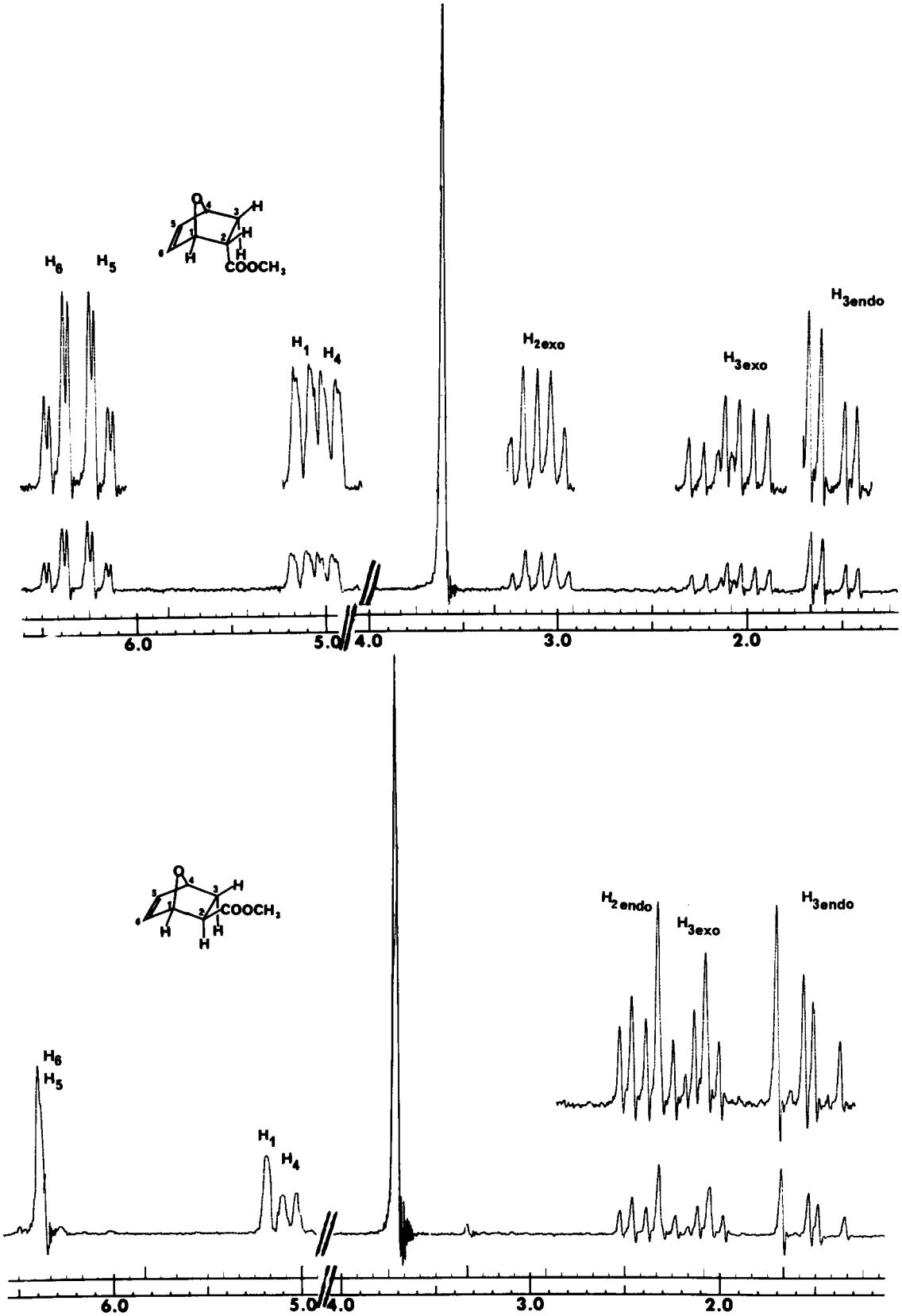
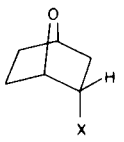


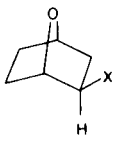
Figure 1. 60 MHz nmr spectra of *Endo*- and *exo*-2-carbomethoxy-7-oxabicyclo[2.2.1]hept-5-ene, **1** and **2**.

resorting to the silver nitrate method for separation of the esters, which was reproduced erratically.

In a similar fashion, the corresponding saturated esters, (**11** and **12**) prepared by catalytic reduction of the mixture of **1** and **2**, were separated by silica gel column chromatography without isomerization of C-2. Esters **11** and **12** allowed the preparation of a series of similar derivatives in which the stereochemistry at C-2 could be monitored by nmr.

In only a single case was considerable isomerization noted. Aminolysis with dimethylamine of the mixture of **11** and **12** could be controlled to give various mixtures of *endo* amide **17** and *exo* amide **18**, depending on reaction time. Conversion of the individual ester to the acid, its acyl halide, followed by treatment with dimethylamine maintained the stereochemistry at C-2, while heating (100°) a mixture of the ester with dimethylamine and a trace of dimethylamine hydrochloride afforded a preponderance of **18**, especially over reaction periods of three or more days. This process afforded a convenient method of increasing the amount of *exo* material available for further transformation.





11	X = COOMe	**12**	X = COOMe
13	X = COOH	**14**	X = COOH
15	X = $COONHNH_2$	**16**	X = $COONHNH_2$
17	X = $CONMe_2$	**18**	X = $CONMe_2$
19	X = NHCOOMe	**20**	X = NHCOOMe
21	X = NHMe	**22**	X = NHMe
23	X = NMe_2	**24**	X = NMe_2

Data from the nmr spectra of various *endo*- and *exo*-2-substituted-7-oxabicyclo[2.2.1]hept-5-enes are given in Table I. Considerable differences in chemical shifts and multiplicity were noted, protons of the OMe esters **1** and **2**, for H_2, H_3-*endo* and H_3-*exo*. Differences are also noted for bridgehead protons H_1 and H_4, and vinyl proton H_5 and H_6.

The H_2 protons in the *endo* and *exo* series show considerable differences in chemical shifts and multiplicity. A quintet, resulting from two overlapping triplets was observed for H_2-*exo* (in **1**) at 3.17 δ and a quartet for H_2-*endo* (in **2**) is seen at 2.43 δ. The large difference in chemical shifts (0.72 δ) is probably the result of a deshielding effect of the 7-oxygen on the *exo* proton in **1**, with respect to its effect on the *endo* proton in **2**, and/or a difference in shielding effect of the olefinic bond on H_2-*endo* (in **2**) or H_2-*exo* (in **1**). The former explanation is quite consistent with a difference noted in saturated esters **11** and **12**, although it is much smaller (0.28 δ). The difference in multiplicity results from $J_{2\text{-}endo,1} \cong 0$, consistent with a torsion angle measurement of *ca.* 90°, resulting in a quartet for H_2-*endo* in **2**, and a quintet for H_2-*exo* in **1** resulting from $J_{2\text{-}exo,1} \cong J_{2\text{-}exo,3\text{-}endo} \cong (1/2)\, J_{2\text{-}exo,3\text{-}exo}$.

The C-3 protons also show differences in chemical shifts between H_3-*exo* and H_3-*endo* of 0.6 δ, with the *exo* proton being downfield, also most likely an effect of the 7-oxygen atom producing a deshielding effect. Multiplicity differences are a result of $J_{3\text{-}endo,4} \cong 0$, as well as torsion angle dependent coupling constants.

Bridgehead protons H_1 and H_4 show differences in multiplicity based on torsion angle dependent $J_{1,2}$ and $J_{3,4}$ coupling constants, and perhaps a difference in chemical shifts due to a deshielding effect of the *endo*-carboxyl group on H_1, since it is found downfield from H_4. Decoupling of H_2 readily allowed distinguishing of H_1 from H_4. This technique is especially valuable in the *endo* cases where no great differences exist in multiplicity of H_1 and H_4.

H_5 and H_6 have different chemical shifts in **1**, and each is seen as a quartet of an ABX, with H_6 is tentatively assigned downfield, evidently due to a deshielding effect of the *endo*-carboxyl group. In decoupling experiments, it was not possible to decouple H_1 leaving H_4, and the assignment is made analogous to H_1 being downfield from H_4.

In various derivatives similar differences are noted between analogous sets of protons, especially in the carbonyl derivatives (acids **3** and **4** and hydrazides **5** and **6**), which is most helpful demonstrating that no isomerization at the 2 position occurred during saponification or hydrazinolysis.

In the Curtius rearrangement product, the spectra show some additional changes. The downfield chemical shift of H_1 with respect to H_4 is not consistent in *exo*-carbamate **8**, and H_3-*exo* and H_3-*endo* show large differences in chemical shifts when compared to the corresponding protons in *endo*-carbamate **7**. H_3-*endo* is shifted upfield to 0.90 δ in **7** compared to 1.86 δ in *exo*-carbamate whereas H_3-*exo* is downfield (2.35 δ) with respect to *exo*-analog (1.37 δ). The result is most likely a result of a combination of factors, including the adjacent C-N bond and perhaps an effect of the carbonyl group in a preferred rotomer, as well as other factors mentioned (oxygen bridge and double bond).

In the saturated analogs, some useful similar differences are noted. Consistently the chemical shift differences between H_2-*exo* and H_2-*endo* are noted, although the signal H_2-*exo* is sometimes seen as a multiplet (see Experimental). This difference is likewise useful in determining the stereochemistry at C-2.

The nmr spectra of amides **17** and **18** showed different

sets of N-Me groups for each isomer (2 peaks each), as well as differences for H_2 and H_3 protons. Both are useful in determining the degree of isomerization at C-2.

The separations and use of nmr spectral data will allow for further studies on other derivatives in these systems.

EXPERIMENTAL

Melting points were obtained on a calibrated Thomas-Hoover Unimelt melting point apparatus and are corrected. Infrared spectra were recorded on Beckman IR-5A and IR-20 spectrophotometers. Nmr spectra were determined with Varian A-60 and T-60 spectrometers using tetramethylsilane (TMS) and sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as internal standards. In nmr descriptions the following notations are used: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, and m = multiplet. Mass spectra were recorded on an AEI MS-9 spectrometer with a Digital Equipment Corporation PDP-12 computer attachment. Gas-liquid partition chromatography was performed on a Hewlitt-Packard 5752 chromatograph, hydrogen flame detector, helium carrier gas at a flow rate of 50 ml. per minute. All columns were 1.88 meters long and 0.317 cm in diameter. Microanalyses were conducted by Dr. G. Weiler and Dr. F. B. Strauss, Oxford, England.

Endo- and *exo*-2-carbomethoxy-7-oxabicyclo[2.2.1]hept-5-ene (**1** and **2**).

A mixture of 30.0 g. (0.35 mole) of freshly distilled furan and 21.5 g. (0.41 mole) of methyl acrylate (Eastman Organic) was allowed to stand at room temperature for one to two months or alternately under low reflux for 2 weeks or longer. Excess reactants were removed *in vacuo* and the residue vacuum distilled affording 22.0 g. (50%) of a mixture of esters (6:1 *endo:exo*) as shown by reduction and glpc experiments, b.p. 60°/0.15 torr [lit. (2) b.p. 50°/0.10 torr].

A 3.0 g. sample of this mixture was chromatographed on 100 g. of silica gel impregnated with 20% silver nitrate, using approximately 1.5 l. of chloroform as eluent. The silica gel was prepared using an aqueous or acetonitrile solution of silver nitrate, followed by evaporation of the solvents and activation at 110° to Brockmann activity I. The separation was monitored by nmr spectroscopy of the fractions from the column. This separation afforded 2.1 g. of pure *endo* ester, **1**, in the first 500 ml., a small amount of mixed esters in the next 300 ml. and 0.50 g. of pure *exo* ester in the next 700 ml., ir (neat) **1** 3.30 and 3.37, 5.75, 6.96, 7.41, 7.57, 8.27, 8.48, 9.48, 9.77, 10.12, 11.19, 11.77, 12.60, 13.20, 14.07, 14.29, 15.08 μ; nmr (deuteriochloroform) Table I, Figure 1; **2** ir (neat) 3.35, 5.75, 7.09, 7.38, 7.60, 7.91, 9.11, 9.77, 11.55, 12.46, 13.12, 15.10 μ; nmr (deuteriochloroform) Table I, Figure 1.

Endo- and *exo*-2-carboxy-7-oxabicyclo[2.2.1]hept-5-ene (**3** and **4**).

To 5.0 g. (32.4 mmoles) of the mixture of *endo-* and *exo*-2-carbomethoxy-7-oxabicyclo[2.2.1]hept-5-ene (**1** and **2**) was added 20 ml. of 10% aqueous sodium hydroxide solution. The mixture was stirred at room temperature for 24 hours, then acidified with concentrated hydrochloric acid and continuously extracted with ether for 24 hours. The ether was dried (magnesium sulfate), and evaporated affording 4.5 g. (98%) of this mixture of crude acids, which solidified on standing.

The acids, 4.5 g. of the mixture, were chromatographed on 180 g. of alumina (Woelm neutral activity I, deactivated with 16 ml. of 10% aqueous acetic acid) using petroleum ether as eluent. The elution with a 5% ether/petroleum ether mixture (b.p. 30°) affording 1.0 g. of pure *endo* acid **3** in the first 1000 ml. The *exo* isomer, **4**, was eluted with 1000 ml. of 1:1:methanol:ether affording 0.25 g. Both acids (**3** and **4**) were oils; the *endo* acid, **3**, solidified on standing, m.p. 96-98° [lit. (2) m.p. 98-99°]; ir (neat) **3** 3.30, 5.85, 7.05, 7.60, 7.80, 8.15, 8.45, 8.70, 9.11, 9.85, 10.80, 11.10, 11.50, 12.23, 12.42, 13.35, 13.12 μ; nmr (deuteriochloroform) Table I; **4** ir (neat) 3.30, 5.80, 7.05, 7.60, 7.80, 8.10, 8.45, 9.13, 9.65, 9.85, 10.80, 11.10, 11.50, 12.41, 14.13 μ; nmr (deuteriochloroform) Table I.

Endo- and *exo*-2-carboxy-7-oxabicyclo[2.2.1]hept-5-ene hydrazide (**5** and **6**).

A mixture of 60 g. (0.39 mole) of 6:1 *endo-* and *exo*-2-carbomethoxy-7-oxabicyclo[2.2.1]hept-5-ene (**1** and **2**) and 50 g. of 99% hydrazine hydrate was refluxed for 3 hours. Excess hydrazine hydrate was azeotroped from the reaction mixture with 95% ethanol affording 60 g. (100%) of crude hydrazide, which solidified on standing.

The hydrazide mixture was chromatographed on a 300 g. silica gel column packed by slurry method with a 1:40:methanol:chloroform mixture. Ten g. of mixed hydrazide were added to the column. A Gilson automatic fraction collector was used to collect 180 ml. fractions. The first 2500 ml. of eluent was recycled. From the next 1.3 l., 1.60 g. of pure *exo* hydrazide **6** was obtained, then a mixture of isomers in the next 2.5 l. and finally 2.30 g. of pure *endo* hydrazide **5**, m.p. 120-121°, with elution with 2.0 l. of a 1:4:methanol:chloroform mixture. The hydrazides (**5** and **6**) were separately recrystallized from ethyl acetate; ir (potassium bromide) **5** 3.05, and 3.30, 6.25, 6.65, 6.90, 7.40, 7.55, 7.80, 8.00, 8.70, 8.85, 9.15, 9.55, 9.80, 10.10, 10.85 (broad), 11.60, 12.51, 14.50 (broad) μ; nmr (deuteriochloroform) Table I.

Anal. **5** Calcd. for $C_7H_{10}N_2O_2$: C, 54.54; H, 6.54; N, 18.17. Found: C, 54.45; H, 6.59; N, 18.08.

Hydrazide **6**, m.p. 119°, ir (potassium bromide) 3.05 and 3.32 (aliphatic C-H and N-H stretching), 6.20 (hydrazide C=O stretching), 6.65, 6.97, 7.25, 7.47, 7.62, 8.90, 9.53, 9.87, 10.90 (broad), 11.60, 12.10, 12.55, 19.50 (broad) μ; nmr (deuteriochloroform) Table I.

Anal. **6** Calcd. for $C_7H_{10}N_2O_2$: C, 54.54; H, 6.54; N, 18.17. Found: C, 54.42; H, 6.62; N, 18.00.

Endo- and *exo*-2-(*N*-carbomethoxyamino)-7-oxabicyclo[2.2.1]hept-5-ene (**7** and **8**).

A solution of hydrazide **5**, 3.6 g. (19.5 mmoles), in 25 ml. of water was cooled to 0° in an ice-salt bath. Concentrated hydrochloric acid, 3 ml. and 30 ml. of chloroform were added to the stirring (magnetic) solution followed by the dropwise addition of 2.5 g. (41.5 mmoles) of sodium nitrite, dissolved in 10 ml. of water, at such a rate to avoid a temperature rise of more than 10°. The two phase mixture was immediately partitioned. The aqueous layer was extracted with chloroform, 3 x 15 ml. The chloroform extracts were combined, washed with 30 ml. of aqueous 10% sodium bicarbonate solution, dried (magnesium sulfate), and evaporated (35°). The crude azide and 30 ml. of absolute methanol were refluxed for 3 hours, and the methanol evaporated and the residue sublimed (90°/0.15 torr) affording 2.65 g. (80%) of **7**, m.p. $\leqslant$ 35°, ir (warm NaCl plate) 3.00 and 3.35, 5.90, 6.50, 6.90, 7.39, 8.00, 8.40, 8.95, 9.42, 9.82, 10.81, 11.05, 11.63, 12.12, 12.85, 13.79 μ; nmr (deuteriochloroform) Table I.

The *exo* carbamate **8**, an oil, was prepared in 85% yield by a method analogous to **7**; (neat) 3.00, 3.32, 3.39, 5.85, 6.55, 6.90, 7.40, 7.90, 8.00, 8.39, 8.78, 8.90, 9.45, 9.79, 9.93, 10.25, 10.68,

11.00, 11.45, 11.63, 12.55, 12.82, 14.15, 14.45; nmr (deuteriochloroform) Table I.

Endo- and *exo*-2-(*N*-methyl-*N*-carbomethoxy)-7-oxabicyclo[2.2.1]-hept-5-ene (**9** and **10**).

Carbamate **7**, 1.0 g. (5.4 mmoles), and 0.59 g. (21 mmoles) 50% sodium hydride dispersion in mineral oil (washed with petroleum ether) were suspended in 25 ml. anhydrous dimethylformamide (distilled from Drierite^{R}) under nitrogen. The mixture was stirred (magnetic) for 15 minutes followed by the dropwise addition of 3.0 g. of iodomethane over a 5 minute period. The stirred mixture was maintained under a positive nitrogen pressure overnight, filtered (sintered glass funnel, water suction), and transferred to a separatory funnel containing 30 ml. of water. The aqueous mixture was extracted with ether, 4 x 30 ml. The ether extracts were combined, washed once with water, dried (magnesium sulfate), and evaporated affording 0.70 g. (78%) of **9**. The crude carbamate was vacuum distilled with a Kontes microdistillation apparatus; ir (neat) 3.30, 5.85, 6.45, 6.89, 7.45, 8.37, 8.63, 9.60, 9.80, 10.80, 11.05, 11.40, 12.50, 13.00 μ; nmr (deuteriochloroform) Table I.

Mass spectrum (70 ev) m/e calcd. for $C_9H_{13}NO_3$, 183.0895; Found: 183.0895.

The *exo* carbamate, **10**, was prepared in 95% yield by the method analogous to **9**; ir (neat) 3.32 and 3.39, 5.89, 6.90, 7.12, 7.46, 7.62, 7.95, 8.25, 8.40, 8.60, 8.85, 9.15, 9.45, 9.75, 10.05, 11.05, 11.62, 12.00, 12.55, 14.20, 15.25 μ; nmr (deuteriochloroform) Table I.

Mass spectrum (70 ev) m/e calcd. for $C_9H_{13}NO_3$, 183.0895; Found: 183.0895.

Endo- and *exo*-2-carbomethoxy-7-oxabicyclo[2.2.1]heptane (**11** and **12**).

A mixture of unsatured esters (**1** and **2**) 10.0 g. (65 mmoles) was dissolved in 100 ml. of 90% ethanol and hydrogenated (0.5 g. 10% palladium on carbon) at 35 psi. About 4 hours was required for hydrogen uptake. The solution was filtered (Celite) and evaporated. The residue was chromatographed on a 300 g. of silica gel (Merck) column and eluted with 8.0 l. of a mixture of 1:6:ether: petroleum ether (b.p. 30-60°). In the first 5.5 l., 5.1 g. of *endo* ester (**11**) was obtained, followed by 1.5 g. of a mixture of esters, predominantly *endo*, in the next 1.0 l., followed by 1.5 g. of pure *exo* ester (**12**) in the final 1.5 l. Both esters (**11** and **12**) were oils.

Fractions were analyzed by glpc using 5% SE-30 silicon gum rubber on Chromosorb W operated isothermally at 160°. The retention times were 2.1 minutes for *endo* ester **11** and 2.7 minutes for *exo* ester **12**. The ratio of esters prior to separation was 6:1 *endo:exo*; ir (neat) **11** 3.35, 5.75, 6.90, 7.00, 7.39, 7.60, 7.65, 7.96, 8.35, 9.02, 9.30, 9.47, 9.75, 10.00, 10.15, 10.70, 10.87, 11.32, 11.80, 12.10, 12.50, 12.73, and 13.30 μ; nmr (deuteriochloroform) **11** δ 4.65 (s, broad, 2, H_1 and H_4), 3.68 (s, 3, $-OCH_3$), 2.93 (m, 1, $H_{2\text{-}exo}$), 2.0-0.95 (m, 6, $-CH_2$); ir (neat) **12**, 3.35, 5.75, 6.95, 7.39, 7.65, 7.86, 8.25, 9.39, 9.60, 9.96, 10.65, 10.87, 11.12, 11.53, 12.30, 12.57, 13.25, 15.10 μ; nmr (deuteriochloroform) **12** δ 4.73 (d, broad, 2, H_1 and H_4), 3.70 (s, 3, $-OCH_3$), 2.65 (dt, overlapping appearing as a quintet, 1, $H_{2\text{-}endo}$, $J_{2\text{-}exo,3\text{-}exo}$ = 8 Hz, $J_{2\text{-}exo,3\text{-}endo}$ = 4 Hz), 2.50-1.5 (m, 5, $-CH_2$-), 1.30 (dd, 1, $H_{3\text{-}endo}$, J_{gem} = 12 Hz, $J_{3\text{-}endo,2\text{-}exo}$ = 4 Hz).

Endo- and *exo*-2-carboxy-7-oxabicyclo[2.2.1]heptane (**13** and **14**).

To 1.5 g. (9.6 mmoles) of *endo*-2-carbomethoxy-7-oxabicyclo-[2.2.1]heptane, **11**, was added 25 ml. of 5% aqueous sodium hydroxide solution. The solution was stirred at room temperature for 1 hour and extracted with chloroform, 3 x 25 ml. The alkaline layer was acidified with 6% aqueous hydrochloric acid and again extracted with chloroform, 3 x 25 ml. The chloroform extracts were combined, dried (magnesium sulfate) and concentrated affording 1.0 g. (90%) of pale yellow oil which was sublimed (60°/0.15 torr). The sublimed acid was recrystallized from a benzene-hexane mixture, m.p. 76-77° [lit. (3) 78-79°]; ir (neat) 3.35, 5.87, 7.19, 7.69, 8.45, 10.95, 12.20, 12.90, 14.10 μ; nmr (deuteriochloroform) δ 4.68 (s, broad, 2, H_1 and H_4, W/2 = 18.5 Hz), 2.93 (dt, overlapping appearing as a quintet, 1, $H_{2\text{-}exo}$), 1.68 (m, 6, $-CH_2$-).

An analogous procedure was used to prepare *exo* acid **14** (80%), m.p. 76-77°; ir (potassium bromide) 3.35, 5.87, 7.05, 7.40, 7.61, 7.80, 8.09, 8.41, 9.41, 9.68, 9.99, 10.43, 10.85, 11.53, 11.87, 12.35, 12.55, 12.75, 15.25 μ; nmr (chloroform) δ 4.78 (s, broad, 2, H_1 and H_4, W/2 = 18 Hz), 2.65 (dd, 1, $H_{2\text{-}endo}$, $J_{2\text{-}endo,3\text{-}endo}$ = 8 Hz, $J_{2\text{-}endo,3\text{-}exo}$ = 4 Hz), 2.40-1.30 (m, 6, $-CH_2$-).

Endo- and *exo*-2-carboxy-7-oxabicyclo[2.2.1]heptane hydrazide (**15** and **16**).

A mixture of 2.0 g. (12.8 mmoles) of *endo*-2-carbomethoxy-7-oxabicyclo[2.2.1]heptane (**13**) and 3.03 g. (94.0 mmoles) of 99% hydrazine hydrate was refluxed for 15 minutes. Ethanol, 50 ml., was added and refluxing continued for an additional 45 minutes. The excess reactants were removed under reduced pressure and the residue was dissolved in chloroform, dried (magnesium sulfate), passed through a column of 5.0 g. of neutral alumina (Woelm) and concentrated affording 2.0 g. (95%) of **15** as a yellow oil; ir (neat) 3.00 and 3.30, 6.13, 6.60, 6.75, 7.30, 7.59, 7.94, 8.41, 8.60, 9.00, 9.50, 9.70, 10.05, 10.82, 11.20, 11.63, 11.92, 12.22, 12.72, 15.10 μ; nmr (deuteriochloroform) δ 8.07 (s, broad, 1, NH), 4.63 (s, broad, 2, H_1 and H_4), 4.01 (s, broad, 2, NH_2), 2.86 (m, 1, $H_{2\text{-}exo}$), 2.05-1.20 (m, 6, $-CH_2$-).

Mass spectrum (70 ev) m/e calcd. for $C_7H_{12}N_2O_2$, 156.0898. Found: 156.0910.

The *exo* hydrazide, **16**, was prepared as described for **15** (85%), m.p. 118°; ir (potassium bromide) 3.02 and 3.35 (aliphatic C-H and N-H stretching), 6.12 (hydrazide C=O stretching), 7.19, 7.81, 8.01, 8.31, 8.65, 8.81, 9.37, 9.61, 10.05, 10.67, 11.17, 11.75, 12.35, 12.87, 13.05, 15.00 μ; nmr (deuteriochloroform) δ 4.69 (s, broad, 2, H_1 and H_4), 3.80 (m, broad, 3, NH-NH_2), 2.60 (m, 1, $H_{2\text{-}endo}$), 2.0-1.0 (m, 6, $-CH_2$-).

Mass spectrum (70 ev) m/e calcd. for $C_7H_{12}N_2O_2$, 156.0898. Found: 156.0899.

Endo- and *exo*-2-(*N*,*N*-dimethylcarboxamido)-7-oxabicyclo[2.2.1]-heptanes (**17** and **18**).

A. Ester Aminolysis.

A mixture of 3.09 g. (19 mmoles) of *endo* and *exo* saturated esters (**11** and **12**), prepared by reduction of the 6:1 mixture of esters **1** and **2**, 25 ml. of anhydrous dimethylamine (b.p. 6°), and 15 mg. of dimethylamine hydrochloride were sealed in a cooled (dry ice-acetone bath) Parr bomb. The bomb was heated in a 125° oil bath for 1 to 3 days, depending on the proportion of *exo* amide desired. Longer runs produced a greater proportion of the *exo* amide. After cooling, the bomb was opened and the excess dimethylamine was allowed to evaporate. The residue was partitioned between chloroform and aqueous 5% sodium hydroxide solution. The aqueous layer was extracted with three additional portions of chloroform. The extracts were combined, dried (sodium sulfate) and evaporated affording 2.10 g. (65%) of a mixture of amides. The alkaline layer was acidified with aqueous 6% hydrochloric acid and extracted with several portions of chloroform. These extracts, when combined, dried (sodium

sulfate), and evaporated, afforded 0.50 g. of mixed acids.

A 2.0 g. portion of the amide mixture was chromatographed on a 300 g. of silica gel column using chloroform as eluent, and a Gilson automatic fraction collector to collect 180 ml. fractions. Elution was complete with 15 l. of chloroform affording 480 mg. of pure *endo* amide, **17**, as oil and 580 mg. of pure *exo* amide, **18**, also an oil. This separation was readily followed by glpc using a 5% SE-30 silicon gum rubber on a chromasorb W column, operated isothermally at 200°. The retention times were 1.3 minutes for the *endo* amide (**17**) and 2.0 minutes for the *exo* amide (**18**).

B. Acid Chloride Aminolysis.

The respective carboxylic acids (**13** and **14**) could be converted individually, or as a mixture, to their respective halides using an excess of thionyl chloride in benzene. In a typical experiment, 0.80 g. (5.6 mmoles) of mixed acids (**13** and **14**) were dissolved in 25 ml. of anhydrous benzene (Na wire) followed by the addition of 5 ml. of thionyl chloride. The mixture was refluxed on a steam bath for 1 hour, after which the excess reactants were removed under reduced pressure. The residue was dissolved in 25 ml. of benzene and 25 ml. of cold anhydrous dimethylamine added cautiously. The mixture was allowed to stand for 30 minutes and then 10 ml. of 5% aqueous sodium hydroxide was added and the mixture partitioned. The benzene solution was concentrated under reduced pressure, after which the residue was dissolved in 25 ml. of water and continuously extracted for 24 hours with ether. The ether extract was dried (sodium sulfate) and evaporated under reduced pressure to leave 0.70 g. (73%) of crude mixed amides, **17** and **18**. The mixture of amides was then chromatographed on silica gel, as described in A; ir (neat) **17**, 3.35, 6.10, 6.20, 7.15, 7.55, 7.75, 7.90, 8.35, 8.70, 8.90, 9.47, 9.70, 9.85, 10.03, 10.75, 11.05, 11.30, 11.85, 12.20, 13.35, 15.15 μ; nmr (deuteriochloroform) δ 4.66 (s, broad, 2, H_1 and H_4), 3.12 and 2.99 [s, 6, $N(CH_3)_2$], 3.35-2.85 (m, under N-CH_3 peaks, 1, $H_{2\text{-}exo}$), 2.35-0.95 (m, 6, -CH_2-).

Anal. Calcd. (**17**) for $C_9H_{15}NO_2$: C, 63.87; H, 8.93; N, 8.28. Found: C, 63.80; H, 8.96; N, 8.24.

Ir (neat) **18**, 3.35, 6.10, 6.67, 7.10, 7.47, 7.72, 7.86, 8.27, 8.65, 8.85, 9.41, 9.65, 9.81, 9.97, 10.67, 11.00, 11.25, 11.67, 12.10, 12.78, 12.33, 14.37, 15.10 μ; nmr (deuteriochloroform) δ 4.78 (dd, distorted, 1, H_1), 4.65 (dd, distorted, 1, H_4), 3.01 and 2.96 [s, 6, $N(CH_3)_2$], 2.80 (m, 1, $H_{2\text{-}endo}$), 2.35-1.40 (m, 6, -CH_2-).

Anal. Calcd. (**18**) for $C_9H_{15}NO_2$: C, 63.87; H, 8.93; N, 8.28. Found: C, 64.04; H, 9.09; N, 8.22.

Endo- and *exo*-2-(*N*-carboethoxyamino)-7-oxabicyclo[2.2.1]heptane (**19** and **20**).

A solution of hydrazide **15**, 1.69 g. (11 mmoles), in 25 ml. of 50% aqueous acetic acid was cooled to 0° in an ice-salt bath. A solution of 0.90 g. (13 mmoles) of sodium nitrite in 10 ml. of water was added dropwise with rapid stirring (magnetic). After addition, the mixture was maintained at 0° for an additional 45 minutes. Water and ether were added and the mixture partitioned. The aqueous layer was extracted with three additional portions of ether. The extracts were combined, washed twice with cold water, twice with aqueous 10% potassium bicarbonate solution, dried (magnesium sulfate), and concentrated (bath temperature 35°) affording a yellow oil, crude azide, ir (neat) 4.65 μ.

The crude acyl azide in 20 ml. of absolute ethanol was refluxed for 45 minutes and then concentrated. The crude carbamate was dissolved in chloroform, dried (sodium sulfate), and the solvent evaporated affording 1.72 g. (98%) pale yellow oil; ir (neat), 3.00 and 3.35, 5.85, 6.55, 6.91, 6.89, 7.30, 7.65, 8.00, 8.45, 9.02, 9.12, 9.95, 10.15, 10.75, 11.07, 11.49, 11.79, 12.10, 12.80, 13.25 μ; nmr (deuteriochloroform) δ 5.73 (s, broad, 1, NH), 4.60 (s, distorted, 2, H_1 and H_4), 4.72 (q, 2, ester -CH_2-, J = 7 Hz), 2.32 (dd, distorted, 1, $H_{2\text{-}exo}$), 2.10-0.85 (m, 6, -CH_2-), 1.26 (t, 3, ester CH_3, J = 7 Hz).

Mass spectrum (70 ev) m/e calcd. for $C_9H_{15}NO_3$, 185.1051. Found: 185.1056.

Carbamate **20** was prepared as described for **19** (70%); ir (neat) 3.00 and 3.35, 8.85, 6.55, 6.80, 7.29, 7.70, 7.87, 8.00, 8.39, 8.79, 9.13, 9.30, 9.61, 9.98, 10.45, 10.70, 10.80, 11.20, 11.60, 11.90, 12.30, 12.80 μ; nmr (deuteriochloroform) δ 5.00 (m, broad, 1, NH), 4.63 (s, broad, 1, H_1), 4.38 (s, broad, 1, H_4), 4.13 (q, 2, ester -CH_2-, J = 7 Hz), 2.02 (dd, 1, $H_{2\text{-}endo}$, $J_{2\text{-}endo,3\text{-}endo}$ = 12 Hz, $J_{2\text{-}endo,3\text{-}exo}$ = 8 Hz), 1.78-1.00 (m, 6, -CH_2-), 1.27 (t, 3, ester -CH_3, J = 7 Hz).

Endo- and *exo*-2-(*N*-methylamino)-7-oxabicyclo[2.2.1]heptane (**21** and **22**).

To a suspension of 1.20 g. (31.7 mmoles) of lithium aluminum hydride in 250 ml. of freshly distilled tetrahydrofuran (from calcium hydride) was added dropwise a solution of 1.80 g. (9.2 mmoles) of carbamate **19** dissolved in 20 ml. of anhydrous tetrahydrofuran. The mixture was stirred at room temperature for 24 hours and then 2 ml. of aqueous 40% Rochelle salt solution was added dropwise to destroy the excess lithium aluminum hydride. After suction filtration and drying (sodium sulfate) the solvent was evaporated affording 1.10 g. (97%) of a pale yellow oil which was not further purified; ir (neat) 3.00, 3.35, 3.45 and 3.55, 6.90, 7.40, 7.89, 8.25, 8.80, 9.35, 9.70, 9.90, 10.00, 10.75, 11.21, 12.20 μ; nmr (deuteriochloroform) δ 4.45 (dd, overlapping, appearing as a t, 2, H_1 and H_4, $J_{1,2\text{-}exo} \cong J_{1,6} \cong J_{4,3\text{-}exo} \cong J_{4,5\text{-}exo} \cong$ 4-5 Hz), 3.63 (s, broad, 1, NH), 3.10 (dt, overlapping appearing as a quintet, 1, $H_{2\text{-}exo}$, $J_{2\text{-}exo,3\text{-}exo}$ = 8 Hz, $J_{2\text{-}exo,3\text{-}endo}$ = 4 Hz, $J_{2\text{-}exo,1}$ = 4 Hz), 2.36 (s, 3, NCH_3), 2.20-1.20 (m, 5, CH_2), 0.95 (dd, 1, $H_{3\text{-}endo}$, J_{gem} = 12 Hz, $J_{3\text{-}endo,2\text{-}exo}$ = 4 Hz).

Mass spectrum (70 ev) calcd. m/e for $C_7H_{13}NO$, 127.0996. Found: 127.0996.

The *exo* amine, **22**, was obtained in a 70% yield by a similar process as that used for **21**; ir (neat), 3.35, 3.43, 3.45, 6.75, 6.87, 7.35, 7.69, 7.90, 8.20, 8.32, 8.80, 9.07, 9.35, 9.70, 10.03, 10.45, 10.60, 10.79, 11.17, 11.69, 11.95, 12.30, 12.70, 13.10 μ; nmr (deuteriochloroform) δ 4.55 (s, distorted 2, H_1 and H_4), 3.75 (s, broad, 1, NH), 2.75 (dd, 1, $H_{2\text{-}endo}$, $J_{2\text{-}endo,3\text{-}endo}$ = 8 Hz, $J_{2\text{-}endo,3\text{-}exo}$ = 4 Hz), 2.40 (s, 3, NCH_3), 2.27-0.85 (m, 6, -CH_2-).

Mass spectrum (70 ev) m/e calcd. for $C_7H_{13}NO$, 127.0996. Found: 127.1004.

Endo- and *exo*-2-(*N*,*N*-dimethylamino)-7-oxabicyclo[2.2.1]heptane (**23** and **24**).

To a solution of 500 mg. (3.8 mmoles) of secondary amine **21** in 50 ml. of ethanol was added 500 mg. of catalyst (10% palladium on carbon) and 5.0 g. of 37% aqueous formalin solution. Hydrogenation was performed at 35 psi initial pressure for 4 hours, followed by filtration (Celite) to remove the catalyst. Acetic acid, 3 ml., was added to the ethanol solution to prevent volatilization of the amine during evaporation of the solvents. The residue was mixed with 15 ml. of 10% aqueous sodium hydroxide solution and extracted with ethyl ether, 3 x 25 ml. The extracts were combined, dried (sodium sulfate) and evaporated (bath 35°) affording 450 mg. (85%) of a colorless oil; ir (neat) 3.30, 3.45, 3.53 and 3.57, 6.85, 7.20, 7.40, 7.90, 8.25, 8.35, 8.50, 8.71, 9.00, 9.43, 9.60, 10.00, 10.75, 10.95, 11.32, 11.85, 12.21, 12.95, 13.30 μ; nmr (deuteriochloroform) δ 4.45 (s, distorted 2, H_1 and H_4), 3.65 (m, 1, $H_{2\text{-}exo}$), 2.53-1.0 (m, 6, -CH_2-), 2.19 [s, 6,

$N(CH_3)_2$].

Mass spectrum (70 ev) m/e calcd. for $C_8H_{15}NO$, 141.11531. Found: 141.11512.

The corresponding quaternary ammonium iodide was prepared using iodomethane in ethyl acetate, m.p. 262-268° (acetone-methanol).

Anal. Calcd. for $C_9H_{18}INO$: C, 38.17; H, 6.40; N, 4.95. Found: C, 38.38; H, 6.33; N, 4.92.

The *exo* amine, **24**, was prepared by a procedure analogous to **23** in a 60% yield; ir (neat) 3.35, 3.45 and 3.58, 7.22, 7.32, 7.53, 8.90, 8.30, 8.55, 8.67, 8.85, 9.10, 9.27, 9.56, 9.97, 10.20, 10.67, 11.19, 11.75, 12.05, 12.40, 12.85, 14.23 μ; nmr (deuteriochloroform) δ 4.45 (s, broad, 2, H_1 and H_4), 2.37 (dd, 1, $H_{2\text{-}endo}$, $J_{2\text{-}endo,3\text{-}endo}$ = 8 Hz, $J_{2\text{-}endo,3\text{-}exo}$ = 4 Hz), 2.10 [s, 6, $N(CH_3)_2$, 1.68-0.85 (m, 6, CH_2).

The quaternary ammonium salt was prepared using iodomethane, m.p. 205-206° (acetone-methanol).

Anal. Calcd. for $C_9H_{18}INO$: C, 38.17; H, 6.40; N, 4.95. Found: C, 38.45; H, 6.58; N, 4.83.

REFERENCES

(1) This investigation was supported by a Public Health Service Research Grant (NS-08121) from the National Institute of Neurological Diseases and Stroke, by the University of Washington Graduate School Research Fund, and by a Public Health Service Research Career Development Award (1-K4-GM-70,023) from the National Institute of General Medical Sciences. Taken in part from the dissertation presented by D. R. Allen, to the Graduate School, University of Washington, in partial fulfillment of the Ph.D. degree requirements, August, 1971.

(2) R. J. Ouellette, A. Rosenblum, and G. Booth, *J. Org. Chem.*, **33**, 4302 (1968).

(3) M. P. Kunstman, D. S. Tarbell, and R. L. Autrey, *J. Am. Chem. Soc.*, **84**, 4115 (1962).

(4) An equilibrium ratio of *ca.* 1:1:*endo-exo* has been determined in various solvents (2) and for the 2-carbomethoxybicyclo-[2.2.1]hept-5-enes (5).

(5) R. J. Ouelette and G. E. Booth, *J. Org. Chem.*, **30**, 423 (1965).

(6) N. H. Andersen and D. D. Syrdal, *Phytochemistry*, 1325 (1970).

(7) A. S. Gupta and S. Dev, *J. Chromatogr.*, **20**, 43 (1970).

(8) R. B. Woodward and H. Baer, *J. Am. Chem. Soc.*, **70**, 1161 (1948).

(9) J. A. Berson and R. Swidler, *ibid.*, 75, 1721 (1953).