Stereochemistry of Pyrrolidine Addition to Bicyclo[2.2.2]oct-2-ene-2-carbonitrile[1]

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In the reaction of pyrrolidine with bicyclo[2.2.2]oct-2-ene-2-carbonitrile (**1**) the product is shown to be exclusively *trans*-3-pyrrolidinobicyclo[2.2.2]octane-2-carbonitrile (**2**). The configuration is established by hydrolyzing **1** to the acid hydrochloride under epimerizing conditions which afford exclusively *trans*-3-pyrrolidinobicyclo-[2.2.2]octane-2-carboxylic acid hydrochloride (**11**) and reconverting this substance exclusively to **2** via the amide. The configuration of **11** is established with the aid of nmr spectra of model compounds: *trans*-3-aminobicyclo-[2.2.2]octane-2-carboxylic acid hydrochloride (**15**) and *cis*-3-aminobicyclo[2.2.2]octane-2-carboxylic acid hydrochloride (**17**). The apparent coupling constants ($J_{2,3}$) for **11** and **15** are identical and the corresponding constant for **2** is close to the same value, while $J_{2,3}$ for **17** is almost exactly the value expected for the *cis* configuration in which the dihedral angle is 0°.

In continuing studies directed toward synthesis of bicyclic acid derivatives of potential interest as anticancer agents,[4] it became desirable to study possible routes to a bicyclo[2.2.2]octane-2-carbonitrile containing a tertiary amino group as a model for a nitrogen mustard derivative. An obvious means of achieving this end appeared to be addition of pyrrolidine to bicyclo[2.2.2]oct-2-ene-2-carbonitrile (**1**). Such a reaction is clearly analogous to cyanoethylation,[5] which appears in general to be reversible.[6,7] Kinetic data obtained by Ogata and Okano[8] agree with addition of the amine *via* rate-determining nucleophilic attack on the β carbon of an acrylonitrile, followed by a rapid intramolecular proton shift. Furthermore, Michael-type additions afford products varying from pure *trans* isomer through mistures to pure *cis* isomer, with the former being the one generally isolated.[9]

These considerations suggest the possible production of two epimeric adducts when pyrrolidine is added to **1**: *trans*-3-pyrrolidinobicyclo[2.2.2]octane-2-carbonitrile (**2**), and *cis*-3-pyrrolidinobicyclo[2.2.2]octane-2-carbonitrile (**3**). The mechanism study cited above implies that **2** should be more readily produced than **3**; and the reversible character of the addition reaction, coupled with implied greater thermodynamic stability of **2** (Fisher–Hirschfelder models), likewise favors predominance of **2** over **3** in the product (Chart I).

Two successful syntheses were developed for preparation of **1** (Chart I). The over-all yields were comparable, but the first sequence was both more economical and more readily adaptable to large-scale synthesis. Method A begins with addition of chloromaleic anhydride to 1,3-cyclohexadiene to give *cis*-2-chlorobicyclo-[2.2.2]oct-5-ene-2,3-dicarboxylic anhydride (**4**),[10] hydrogenation of which afforded *cis*-2-chlorobicyclo[2.2.2]-octane-2,3-dicarboxylic anhydride (**5**). This was then converted into bicyclo[2.2.2]oct-2-ene-2-carboxylic acid (**6**) by a typical dehalogenative decarboxylation (fragmentation).[4,11,12] Conversion of **6** into an acid chloride, which was at once treated with ammonium hydroxide solution, afforded bicyclo[2.2.2]oct-2-ene-2-carboxamide (**7**), which was dehydrated to **1** by refluxing with thionyl chloride.

Method B involves initial addition of propiolaldehyde to 1,3-cyclohexadiene to give bicyclo[2.2.2]octa-2,5-diene-2-carboxaldehyde (**8**), selective hydrogenation of which gave bicyclo[2.2.2]oct-2-ene-2-carboxaldehyde (**9**). Oximation[13] of **9** afforded bicyclo[2.2.2]oct-2-ene-2-carboxaldoxime (**10**), dehydration[14] of which produced **1**.

The reaction of **1** with pyrrolidine was followed by glpc (at several temperatures), and only a single sharp peak was observed under all conditions, indicating the production of but one of the two possible isomers (**2** and **3**). Proof of configuration of this adduct as **2** was obtained in part by hydrolysis to a carboxylic acid hydrochloride (**11**) (under conditions conducive to epimerization,[15] which was then converted into its amide (**12**); and finally **12** was dehydrated to the nitrile, which proved to be identical with the original **2** (nmr and infrared spectra, glpc). At no stage in these operations was it possible to detect other than one isomer, even in the crude reaction products. Thus either no epimerization has taken place in the sequence, **2** → **11** → **12** → **2** (Chart II), or an even number of epimerizations, which are necessarily total, has occurred. The probability of the latter happening is vanishingly small, and hence it may be inferred that the configuration of the nitrile (**2**) and that of the acid hydrochloride (**11**) are the same.

The remainder of the configuration proof for **2** comes from preparation of model compounds for comparative nmr study and is supported by the nmr spectrum of **2** itself. By using milder conditions than given by Petrov[16] for the addition of dimethyl fumarate to 1,3-cyclohexadiene more than twice the yield of *trans*-2,3-dicarbomethoxybicyclo[2.2.2]octane (**13**) was obtained. Half saponification gave *trans*-3-carbometh-

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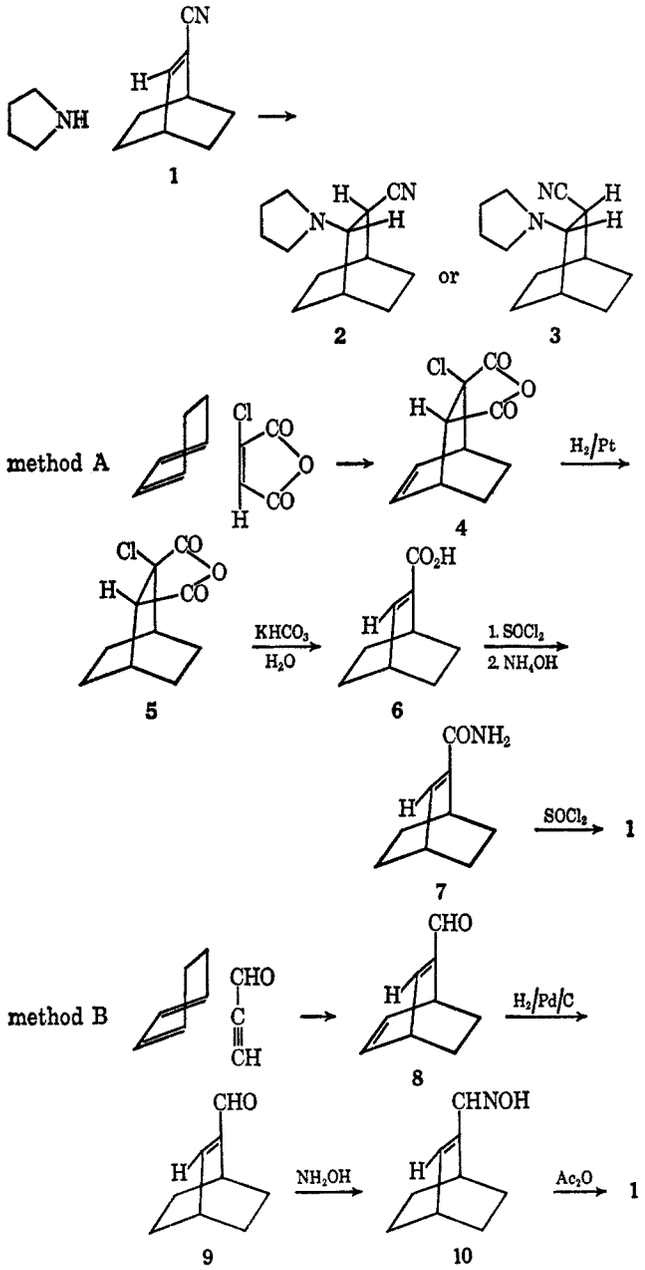
CHART I
SYNTHESES OF 2 AND 1

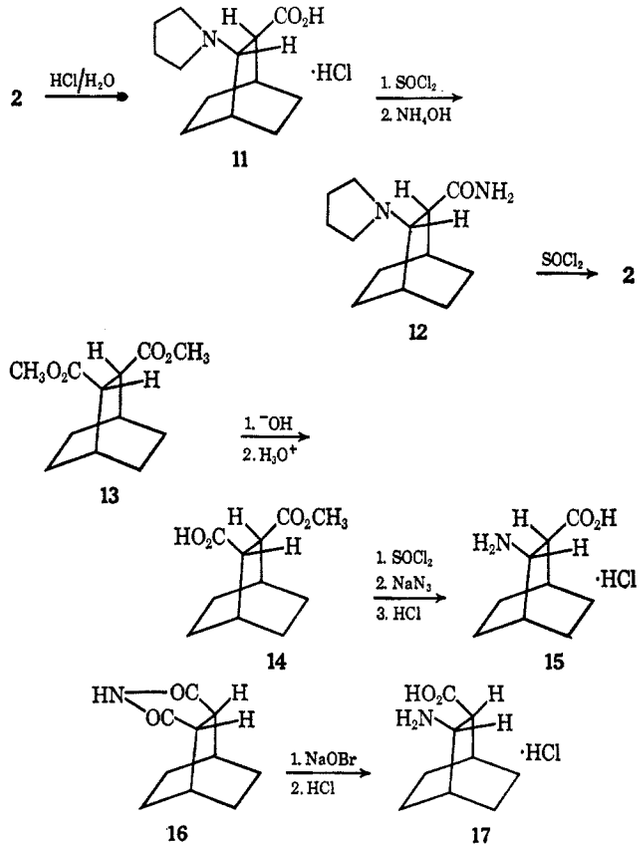


oxybicyclo[2.2.2]octane-2-carboxylic acid (**14**), which was converted *via* the Curtius reaction ("wet" method)[17] to *trans*-3-aminobicyclo[2.2.2]octanecarboxylic acid hydrochloride (**15**) (Chart II).

The second model compound was prepared from *cis*-bicyclo[2.2.2]octane-2,3-dicarboximide[18-21] (**16**) *via* the Hofmann rearrangement[22] which affords *cis*-3-aminobicyclo[2.2.2]octane-2-carboxylic acid hydrochloride (**17**). That **15** and **17** are indeed *cis–trans* isomers is clear from the fact that they afford different *p*-toluenesulfonamides (Experimental Section) and display different coupling constants ($J_{2,3}$). The configurations must be as assigned, and involve no epimerization (or an even number of epimerizations in the preparation of **15**), or they are reversed (and involve an odd number of epimerizations in the preparations of both **15** and **17**) (Chart II).

The conversion of **16** to **17** can admit of but one epimerization (*cis* to *trans*, *via* enolization). If this occurs, any common enolizations in the sequence **13** → **15** should favor *trans* products, leaving only the reaction of **14** with thionyl chloride as a potential reverse (*trans* to *cis*) epimerization. Although epimerization of this general type has been reported,[23] the nmr spectra of **15** and **17** suggest over-all retention of configurations in both reaction sequences. Thus, while the (apparent) coupling constants for the *trans* 2,3 protons in **15** and the *cis* 2,3 protons in **17** are somewhat larger than those predicted by the Karplus equation,[24] they agree with the values given by Williamson and Johnson's revised expression[25] in which $J = 10$ cps when the dihedral angle is 0° (*cis* in the present system) and $J = 4$ cps when the angle is 120° (*trans* in the present system). Thus for **17**, $J_{2,3} = 10.3 \pm 0.2$ cps, and for **15**, $J_{2,3} = 6.3 \pm 0.2$ cps. The latter value is identical with the value for $J_{2,3}$ for **11**, which strongly supports a *trans* configuration for **11**. Since it has already been inferred that the configuration for **2** is the same as that for **11**, the value $J_{2,3} = 5.1 \pm 0.2$ for **2** confirms the *trans* configuration for the adduct of pyrrolidine and **1**. Thus, the only isomer observed in the conjugate addition of pyrrolidine to bicyclo[2.2.2]oct-2-ene-2-carbonitrile has the *trans*

CHART II
AMINO ACID SYNTHESES



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configuration, in keeping with inferences drawn from kinetics of the cyanoethylation reaction[8] and the examination of Fisher–Hirschfelder models, the only unusual observation being the failure to detect by any method a measurable amount of the epimeric *cis* isomer.

Experimental Section[26-29]

cis-2-Chlorobicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic Anhydride (4).[10]—A solution of 58.0 g (0.73 mol) of 1,3-cyclohexadiene and 96.0 g (0.73 mol) of chloromaleic anhydride in 100 ml of ethyl acetate was refluxed overnight. The solvent and unreacted starting material were removed by water pump distillation and the product was sublimed at 100° (1 mm) to give 114.0 g (73.9%), mp 176–178°, of a colorless waxy solid, mp 187–189° (after five sublimations at 100° and 1 mm).

Anal. Calcd for $C_{10}H_9ClO_3$: C, 56.49; H, 4.27; Cl, 16.66. Found: C, 56.82; H, 4.47; Cl, 16.53.

cis-2-Chlorobicyclo[2.2.2]octane-2,3-dicarboxylic Anhydride (5).—A solution of 59.8 g (0.28 mol) of *cis*-2-chlorobicyclo-[2.2.2]oct-5-ene-2,3-dicarboxylic anhydride (4) in 100 ml of ethyl acetate was hydrogenated at 3 atm with 0.5 g of Adams platinum dioxide catalyst. After filtration and removal of ethyl acetate, sublimation at 100° (1 mm) gave 58.0 g (96.2%) of a colorless waxy solid, mp 201–203°.

Anal. Calcd for $C_{10}H_{11}ClO_3$: C, 55.96; H, 5.17; Cl, 16.52. Found: C, 56.04; H, 5.23; Cl, 16.35.

Bicyclo[2.2.2]oct-2-ene-2-carboxylic Acid (6).—A solution of 10.4 g (0.104 mol) of potassium bicarbonate in 40 ml of water was added to 11.0 g (0.052 mol) of *cis*-2-chlorobicyclo[2.2.2]octane-2,3-dicarboxylic anhydride (5). The resulting solution was heated at 100° for 1 hr, cooled, and acidified with concentrated hydrochloric acid, and then cooled in a refrigerator for 1 hr. The white solid was filtered, washed with water, and dried *in vacuo*. A white crystalline solid (14.80 g, 61.7%), mp 90–91°, was obtained. Recrystallization from water–ethanol raised the melting point to 93–94°.

Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.88; H, 7.94.

Bicyclo[2.2.2]oct-2-ene-2-carboxamide (7).—A 4.6-g (0.03 mol) sample of bicyclo[2.2.2]oct-2-ene-carboxylic acid (6) was refluxed for 1 hr with 46 ml of thionyl chloride, the excess of which was distilled, and the residual acid chloride was cooled in ice and treated dropwise with 50 ml of ice-cooled 28% ammonium hydroxide solution. After cooling and filtration, the white solid was washed with water and dried *in vacuo*, giving 1.4 g (31%), mp 128–132°, of a white crystalline solid, mp 140–141° (after three recrystallizations from water–ethanol).

Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.50; H, 8.61; N, 9.12.

Bicyclo[2.2.2]oct-2-ene-2-carbonitrile (1).—A 4.6-g (0.03 mol) sample of bicyclo[2.2.2]oct-2-ene-2-carboxamide (7) was refluxed for 24 hr with 46 ml of thionyl chloride, the excess of which was removed using a water pump; distillation gave 3.4 g (84%) of a colorless oil, bp 40–46° (0.3 mm). The oil darkens on standing and should be stored under refrigeration in a dark bottle.

Anal. Calcd for $C_9H_{11}N$: C, 81.15; H, 8.33; N, 10.52. Found: C, 80.51; H, 8.24; N, 10.28.

Bicyclo[2.2.2]octa-2,5-diene-2-carboxaldehyde (8).—A solution of 39.0 g (0.490 mol) of 1,3-cyclohexadiene and 23.5 g (0.435 mol) of propiolaldehyde was stirred at room temperature for 1 week. Reaction progress was followed by observation of the decrease in triple bond absorption (2140 cm^{-1}) in the infrared spectrum. Distillation of the reaction mixture gave 38.6 g (66.0%) of a colorless liquid, bp 84–85° (20 mm). Nmr analysis showed the aldehyde proton at τ 0.52, the vinyl proton at 2.76 (quartet), two unconjugated vinyl protons at 3.68 (triplet), bridgehead protons at 5.76 and 6.25, and the remaining protons in an envelope centered about 8.80 (deuteriochloroform solvent).

Anal. Calcd for $C_9H_{10}O$: C, 80.54; H, 7.51. Found: C, 80.40; H, 7.32.

Bicyclo[2.2.2]oct-2-ene-2-carboxaldehyde (9).—Hydrogen (0.10 mol) was added to 13.4 g (0.1 mol) of bicyclo[2.2.2]octa-2,5-diene-2-carboxaldehyde (8) in 100 ml of ethyl acetate with 0.3 g of 5% palladium-on-carbon catalyst. After filtration and removal of ethyl acetate, distillation gave 10.1 g (74.1%) of a colorless liquid, bp 86–89° (20 mm). Nmr analysis showed the aldehyde proton at τ 0.52, the conjugated vinyl proton at 2.76 (quartet), bridgehead protons at 6.80 and 7.20, and the remaining protons in an envelope centered about 8.73 (deuteriochloroform solvent).

Bicyclo[2.2.2]oct-2-ene-2-carboxaldoxime (10).—A solution of 1.0 g (0.0074 mol) of bicyclo[2.2.2]oct-2-ene-2-carboxaldehyde (9), 1.0 g (0.014 mol) of hydroxylamine hydrochloride, 6 ml of pyridine, and 6 ml of absolute alcohol was refluxed for 24 hr, then poured into an evaporating dish and the was solvent removed in a current of air. The residue was taken up in ether and washed with 5% hydrochloric acid solution. The ether solution was dried over magnesium sulfate; after filtration and removal of ether, 0.59 g (53%), mp 88.5–90.0°, of a white solid, mp 89–90° (after three recrystallizations from ethanol), was obtained.

Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.51; H, 8.54; N, 9.34.

Bicyclo[2.2.2]oct-2-ene-2-carbonitrile (1).—A solution of 0.64 g (0.0042 mol) of bicyclo[2.2.2]oct-2-ene-2-carboxaldoxime (10) and 4 ml of acetic anhydride was refluxed for 24 hr, then carefully poured into 15 ml of cold water. The aqueous solution was extracted with ether; the ether solution was then washed with 10% sodium carbonate solution and dried over magnesium sulfate. After filtration and removal of ether, the remaining liquid was purified by evaporative distillation at 100° (1 mm) to give 0.30 g (53%) of a colorless liquid whose infrared spectrum was superimposable on that of 1 obtained by dehydration of bicyclo[2.2.2]-oct-2-ene-2-carboxamide (7).

***trans*-3-Pyrrolidinobicyclo[2.2.2]octane-2-carbonitrile (2) and/or *cis*-3-Pyrrolidinobicyclo[2.2.2]octane-2-carbonitrile (3).**—A 7.98-g (0.06 mol) sample of bicylo[2.2.2]oct-2-ene-2-carbonitrile (1) was refluxed for 24 hr with 8.52 g (0.12 mol) of pyrrolidine, the excess of which was removed by distillation, and the residual dark brown liquid was dissolved in 5% hydrochloric acid solution and then extracted with ether. After basification with 28% ammonium hydroxide solution, the aqueous phase was extracted with ether. The ether extract was dried over magnesium sulfate and filtered; after removal of the ether, distillation gave 7.00 g (57.2%) of a colorless liquid at 90–94° (0.1 mm). Glpc analyses using a silicone oil 200 on Haloport-F column at 130 and 150° and a silicone gum rubber on Chromosorb P column at 140 and 160° each showed a single sharp peak. Glpc analysis (silicone gum rubber column at 140°) of the reaction mixture at room temperature showed peaks corresponding to starting materials and the isomer isolated from the refluxing reaction mixture (see above). There was no indication of a second isomer.

Nmr analysis showed the proton α to the nitrile group at τ 7.72 (a pair of quartets with unresolved fine structure, splitting by the proton α to the pyrrolidino group is 5.1 ± 0.2 cps.). The five protons α to the pyrrolidino nitrogen appeared in a poorly resolved group centered about τ 7.48 (deuteriochloroform solvent); picrate, mp 234–235° dec.

Anal. Calcd for $C_{13}H_{20}N_2$: C, 76.42; H, 9.87. Found: C, 76.32; H, 9.90.

Anal. Calcd for $C_{19}H_{23}N_5O_7$: C, 52.65; H, 5.35; N, 16.16. Found: C, 52.60; H, 5.25; N, 16.30.

***trans*-3-Pyrrolidinobicyclo[2.2.2]octane-2-carboxylic acid Hydrochloride (11).**—A solution of 4.90 g (0.024 mol) of *trans*-2-pyrrolidinobicyclo[2.2.2]octane-2-carbonitrile (2) and/or *cis*-3-pyrrolidinobicyclo[2.2.2]octane-2-carbonitrile (3) and 8 ml of concentrated hydrochloric acid was refluxed for 24 hr. The solution was evaporated to dryness and triturated with 100 ml of hot *n*-butyl alcohol. Evaporation of the butanol gave 5.95 g (95.4%), mp 232–236°, of a white crystalline solid, mp 240–241° dec (after recrystallization from absolute alcohol). Nmr analysis showed the proton α to the carboxyl group at τ 7.21 (quartet, splitting by the proton α to the pyrrolidino group is 6.3 ± 0.2 cps, which is the same as that for *trans*-3-amino-bicyclo[2.2.2]-octane-2-carboxylic acid (15) and splitting by the bridgehead

(26) Boiling and melting points are uncorrected.

(27) Microanalyses by Spang Microanalytical Laboratory, Ann Arbor, Mich. Infrared spectra obtained from Nujol mulls (solids) or liquid films, Perkin-Elmer Model 21 infrared spectrometer. Nmr spectra (Varian A-60) were obtained by Mr. F. Parker and Mr. G. Schütze of this department (internal tetramethylsilane, 60 Mc).

(28) Mr. R. Pietcher of Varian Associates, Pittsburgh, Pa., kindly ran a spectrum of II using an HA-100 Varian spectrophotometer system.

(29) The following materials were obtained from Hi-Laboratory, Whitmore Lake, Mich.: 1,3-cyclohexadiene, propiolaldehyde, α-chloroacrylonitrile, and *cis*-bicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic anhydride.

proton is 2.4 ± 0.2 cps). The five protons α to the pyrrolidino nitrogen appeared downfield in a wide poorly resolved group centered about τ 6.60 (deuterium oxide solvent).

Anal. Calcd for $C_{13}H_{22}ClNO_2$: C, 60.10; H, 8.54; Cl, 13.65; N, 5.39. Found: C, 60.07; H, 8.49; Cl, 13.66; N, 5.40.

***trans*-3-Pyrrolidinobicyclo[2.2.2]octane-2-carboxamide (12).**—A 4.60-g (0.018 mol) sample of *trans*-3-pyrrolidinobicyclo[2.2.2]-octane-2-carboxylic acid hydrochloride (**11**) was stirred at room temperature for 24 hr with 46 ml of thionyl chloride, the excess of which was distilled, and the residual acid chloride was cooled in ice and treated dropwise with 50 ml of ice-cooled 28% ammonium hydroxide solution. After dilution with water, the solution was extracted with ether. The ether extract was dried over magnesium sulfate, filtered, and, after removal of the ether, gave 1.93 g (49.1%) of a white solid, mp 155–159°. Two recrystallizations from absolute alcohol raised the melting point to 165.0–165.5°.

Anal. Calcd for $C_{13}H_{22}N_2O$: C, 70.23; H, 9.97; N, 12.60. Found: C, 70.01; H, 9.92; N, 12.58.

***trans*-3-Pyrrolidinobicyclo[2.2.2]octane-2-carbonitrile (2).**—A 1.93-g (0.0087 mol) sample of *trans*-3-pyrrolidinobicyclo-[2.2.2]octane-2-carboxamide (**12**) was heated at 45° for 38 hr with 20 ml of thionyl chloride, the excess of which was distilled, and the residual light brown liquid was added to 5% sodium hydroxide solution, and then this solution was extracted with ether. The ether extract was dried over magnesium sulfate and filtered; after removal of the ether, distillation gave 3.81 g (80.1%) of a colorless liquid, bp 91–95° (0.1 mm). The infrared and nmr spectrum of this liquid are superimposable on those of the adduct of bicyclo[2.2.2]oct-2-ene-2-carbonitrile (**1**) and pyrrolidine. Their glpc retention times were identical using a silicone oil 200 on Haloport-F column at 130 and 150° and a silicone gum rubber on Chromosorb P column at 140 and 160°.

***trans*-3-Carbomethoxybicyclo[2.2.2]octane-2-carboxylic Acid (14).**—A solution of 41.0 g of potassium hydroxide pellets in 350 ml of absolute methanol was slowly added to a well-stirred solution of 125.0 g (0.553 mol) of *trans*-2,3-dicarbomethoxybicyclo-[2.2.2]octane (**13**)[30] in 350 ml of absolute methanol. The stirring was continued at room temperature for 24 hr, and then 1.2 l. of water was added and the resulting solution extracted twice with 600-ml portions of ether. The ether extracts were dried over magnesium sulfate, filtered, and, after removal of the ether, gave 3.7 g of recovered **13**. The aqueous phase was acidified with concentrated hydrochloric acid, then extracted with ether. The ether extract was dried over magnesium sulfate, filtered, and, after removal of the ether, gave 110.5 g (94.2%), mp 97–100°, of a white crystalline solid, mp 102.0–103.5° (after two recrystallizations from water–ethanol).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.12; H, 7.72.

***trans*-3-Aminobicyclo[2.2.2]octane-2-carboxylic acid Hydrochloride (15).**—A 5.1-g (0.024 mol) sample of *trans*-2-carbomethoxybicyclo[2.2.2]octane-3-carboxylic acid (**14**) was refluxed for 1 hr with 25 ml of thionyl chloride, the excess of which was distilled, and the residual acid chloride was dissolved in 60 ml of acetone, then cooled in ice. A solution of 1.7 g of sodium azide in 4.5 ml of water was added dropwise to the ice-cooled solution and, after stirring for 1 hr, 120 ml of water was added and the resulting solution extracted with ether. The ether extract was dried over magnesium sulfate and filtered; after removal of the ether, the remaining azide was refluxed overnight in 12 ml of dry xylene. This solution was cooled in an ice bath and 25 ml of concentrated hydrochloric acid was added. After refluxing overnight, the solution was evaporated in an air stream, water was added, and the solution extracted with ether. The aqueous phase was evaporated in an air stream and dried *in vacuo* giving 3.0 g (61%), mp 213–225°, of a creamy white solid, mp 225–230° dec (after recrystallization from water–ethanol). Nmr analysis showed the proton α to the carboxyl group at τ 7.34 (quartet; splitting by the proton α to the amino group is 6.3 ± 0.2 cps and splitting by the bridgehead proton is 2.4 ± 0.2 cps). The proton α to the amino group appeared at τ 6.12 (quartet, splitting by the proton α to the carboxyl group is 6.3 ± 0.2 cps and splitting by the bridgehead proton is 2.4 ± 0.2 cps) (deuterium oxide solvent); *p*-toluenesulfonamide, mp 176–177°.

Anal. Calcd for $C_9H_{16}ClNO_2$: C, 52.55; H, 7.84; Cl, 17.24; N, 6.81. Found: C, 52.51; H, 7.86; Cl, 17.29; N, 6.72.

Anal. Calcd for $C_{16}H_{21}NO_4S$: C, 59.43; N, 6.55; N, 4.33; S, 9.90. Found: C, 59.35; H, 6.58; N, 4.40; S, 9.88.

***cis*-3-Aminobicyclo[2.2.2]octane-2-carboxylic Acid Hydrochloride (17).**—A sample of 1.62 g (0.01 mol) of bromine was slowly added to an ice-cooled solution of 5.03 g of potassium hydroxide pellets in 45 ml of water; 1.79 g (0.01 mol) of *cis*-bicyclo[2.2.2]octane-2-dicarboximide (**16**)[21] was slowly added and the resulting solution heated at 60° for 2 hr. After cooling, the solution was acidified with concentrated hydrochloric acid and evaporated to dryness. The crude solid was triturated with cold water (leaving unreacted **16**), evaporated to dryness, triturated with hot *n*-butyl alcohol (leaving inorganic salts), and then the butanol was evaporated to dryness. The residual solid was recrystallized from absolute alcohol to give 0.51 g (24.8%) of a white crystalline solid, mp 227–230°. Nmr analysis showed the proton α to the carboxyl group at τ 6.82 (quartet, splitting by the proton α to the amino group is 10.3 ± 0.2 cps and splitting by the bridgehead proton is 2.4 ± 0.2 cps). The proton α to the amino group appeared at τ 6.22 (quartet, splitting by the proton α to the carboxyl group is 10.3 ± 0.2 cps and splitting by the bridgehead proton is 2.4 ± 0.2 cps) (deuterium oxide solvent); *p*-toluenesulfonamide, mp 159°.

Anal. Calcd for $C_{16}H_{21}NO_4S$: C, 59.43; H, 6.55; N, 4.33; S, 9.90. Found: C, 59.27; H, 6.59; N, 4.40; S, 9.94.

Registry No.—**1**, 14948-74-4; **2**, 16317-18-3; picrate of **2**, 16317-19-4; **4**, 16317-20-7; **5**, 16317-21-8; **6**, 16317-22-9; **7**, 16317-23-0; **8**, 16317-24-1; **9**, 16317-25-2; **10**, 16317-26-3; **11**, 16317-27-4; **12**, 16317-28-5; **14**, 16317-29-6; **15**, 16317-30-9; *p*-toluenesulfonamide of **15**, 16394-36-8; **17**, 16317-32-1; *p*-toluenesulfonamide of **17**, 16317-31-0; pyrrolidine, 123-75-1.

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