The α,α′ Annelation of Cyclic Ketones. Synthesis of Bicyclo[3.2.1]octane Derivatives

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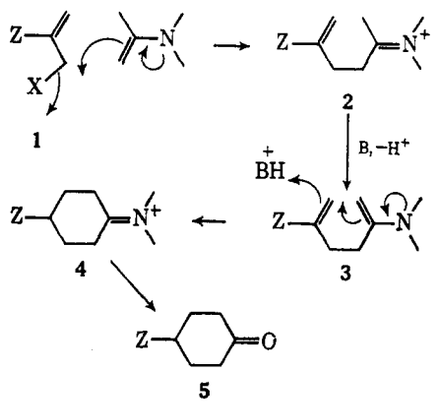
Reaction of cyclopentanone enamine with ethyl α-(1-bromomethyl)acrylate affords ethyl bicyclo[3.2.1]octan-8-one-3-*endo*-carboxylate. The reaction generally follows a pathway including alkylation and proton transfer to re-form an enamine, followed by Michael reaction. The preparation of *trans*-diaxial bicyclo[3.2.1]octanone diesters from γ-bromomesaconic ester and benzobicyclo[3.2.1]octanones from indanone is described. Proof of stereochemistry of these molecules reflects upon the mechanism of the reaction and provides interesting intermediates for further study.

Bridged bicyclic ring systems such as bicyclo[3.2.1]-octane or bicyclo[3.3.1]nonane continually serve as basic structural frames in investigations of conformational analysis[1] and carbonium-ion research.[2] Although there are numerous entries into these systems, the previously available methods often placed severe limitations upon the nature, quantity, distribution, and stereochemistry of their functionality.[3] The development of the α,α′-annelation procedure, described earlier[4] and elaborated here, provides a unique pathway for the construction of a wide variety of bicyclic systems having otherwise unobtainable functionality and stereochemistry. This paper discusses the development, mechanism, and some of the limitations of the synthesis involving the bicyclo[3.2.1]octane system.

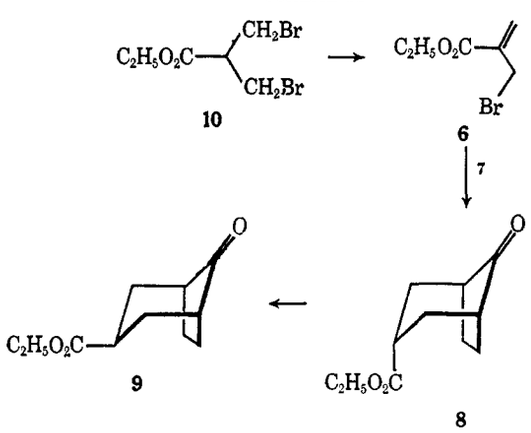
With the mildness and proven utility of the Stork enamine procedure in affecting both alkylation by allylic halides as well as by the Michael addition reaction,[5] speculation led to the possibility of causing the enamine of a ketone to react with a single reagent capable of serving sequentially as both an alkylation and Michael addition agent. In a structure having the appropriate distribution of functionality, a double bond could both serve to activate the leaving group as well as to provide conjugation with an electron-withdrawing function to provide the Michael acceptor moiety. The basic structure corresponding to this design is **1** where X is some leaving group and where Z is some electronegative function. Condensation of the annelation agent **1** with a ketone enamine would afford a substituted cyclohexanone by the process **1** → **5** (Scheme I). It is clear that one is allowed considerable latitude in the type and distribution of functionality in either enamine or annelating agent in this sequence.

SCHEME I



Ethyl α-bromomethylacrylate (**6**)[6] is one of the simplest substances capable of serving as an α,α′-annelation agent. Condensation of **6** with the pyrrolidine enamine of cyclopentanone (**7**)[5] in refluxing acetonitrile afforded an 80% yield of *endo*-3-carbethoxybicyclo[3.2.1]octan-8-one (**8**) (Scheme II). The axial or

SCHEME II



endo configuration of the ester function was established by the facile isomerization of keto ester **8** to a new *exo* ester **9** by sodium ethoxide in ethanol. This result indicated that, in the Michael stage of the reaction, the transition state assumed a chairlike conformation of the developing ring and that a concerted or kinetic protonation of the formed enolate occurred from the least

(1) (a) W. D. K. Macrosson, J. Martin, and W. Parker, *Tetrahedron Lett.*, 2589 (1965); (b) G. Eglington, J. Martin, and W. Parker, *J. Chem. Soc.*, 1243 (1965); (c) W. A. C. Brown, G. Eglington, J. Martin, W. Parker, and G. A. Sim, *Proc. Chem. Soc.*, **57** (1964); (d) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 296; (e) H. O. House, P. P. Wickam, and H. C. Muller, *J. Amer. Chem. Soc.*, **84**, 3139 (1962); (f) H. O. House, H. C. Muller, C. G. Pitt, and P. P. Wickam, *J. Org. Chem.*, **28**, 2407 (1963); (g) A. A. Youssef, M. E. Baum, and H. M. Walborsky, *J. Amer. Chem. Soc.*, **81**, 4709 (1959).

(2) (a) C. S. Foote and R. B. Woodward, *Tetrahedron*, **20**, 687 (1964); (b) H. L. Goering and M. F. Sloan, *J. Amer. Chem. Soc.*, **83**, 1397 (1961).

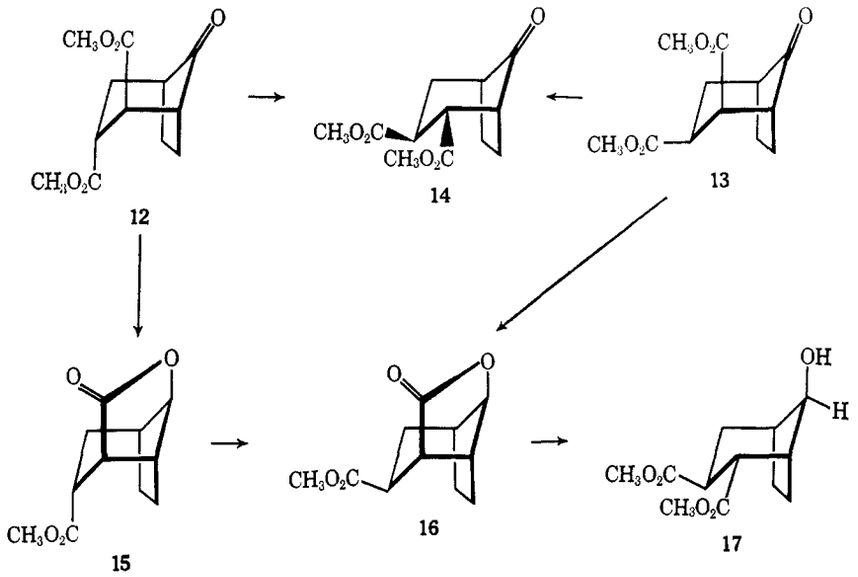
(3) (a) A. C. Cope, D. L. Nealy, P. Scheiner, and G. Wood, *J. Amer. Chem. Soc.*, **87**, 3130 (1965); (b) J. A. Marshall and D. J. Schaeffer, *J. Org. Chem.*, **30**, 3642 (1965); (c) A. C. Cope and M. E. Synerholm, *J. Amer. Chem. Soc.*, **72**, 5228 (1950); (d) J. Martin, W. Parker, and R. A. Raphael, *J. Chem. Soc.*, 289 (1964); (e) S. Julia, *Bull. Soc. Chim. Fr.*, 780 (1954); (f) G. Stork and H. K. Landesman, *J. Amer. Chem. Soc.*, **78**, 5129 (1956); (g) J. P. Schaefer, J. C. Lark, C. A. Flegal, and L. M. Honig, *J. Org. Chem.*, **32**, 1372 (1967); (h) D. M. Bailey, J. E. Bowers, and C. D. Gutsche, *ibid.*, **28**, 610 (1963); (i) E. Buchta and S. Billenstein, *Naturwissenschaften*, **51**, 383 (1964); (j) K. Alder and R. Reubke, *Chem. Ber.*, **91**, 1525 (1958); (k) C. W. Jefford, *Proc. Chem. Soc.*, **64** (1963).

(4) R. P. Nelson and R. G. Lawton, *J. Amer. Chem. Soc.*, **88**, 2884 (1966).

(5) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *ibid.*, **85**, 207 (1963).

(6) A. F. Ferris, *J. Org. Chem.*, **20**, 780 (1955).

SCHEME III



hindered side of the molecule.[7] It is this stereochemical result which greatly enhances the synthetic utility of this annelation process. Further, the sequence clearly defines the mechanism and stereochemical preference of this type of Michael reaction. Obviously the alkylating agent must reside axially with regard to the cyclopentanone ring during the Michael process and certain aspects of this feature of the reaction become important in the construction of bicyclononanone systems.

The preparation of the unsaturated bromo ester **6** is somewhat inefficient and it is our usual practice to utilize its precursor, ethyl β,β'-dibromoisobutyrate (**10**).[6] Triethylamine dehydrohalogenation *in situ* provided the bromo ester **6** which resulted in the same *endo*-bicyclic ester **8**.

The question of the exact sequence of steps in the annelation synthesis becomes important when one has an annelation agent which is unsymmetrical. Although the proposed alkylation–Michael pathway appeared most plausible, two alternate routes, (A) an N-alkylation–Claisen rearrangement–Michael[8] route and (B) an SN2′–Michael route could not be eliminated. Although the SN2′ pathway is not common, the possibility of its occurrence with **6** is enhanced by the increased electrophilicity of the double bond caused by conjugation with the ester function. Thus, route B could also be looked upon as a Michael–elimination–Michael process. In contrast to more complex reagents, all of the three pathways give the same product using starting material **6**.

Dimethyl γ-bromomesaconate (**11**) was easily prepared by N-bromosuccinimide reaction with mesaconic ester.[9] The structure contains the requisite alkylation and Michael addition sites and an extra ester function which serves as a means to determine additional features of the reaction. Reaction of the bromo diester with the pyrrolidine enamine of cyclopentanone (**7**) in acetonitrile afforded, after hydrolysis of the imine salt, a 51% yield of a major isomer, dimethyl bicyclo[3.2.1]octan-8-one-2-*exo*,3-*endo*-dicarboxylate (**12**) contaminated with a small quantity (<5%) of an inseparable minor isomer later determined to be the 2-*exo*,3-*exo* diester (**13**). Treatment of the diesters with sodium methoxide in methanol afforded a single new isomer (**14**) (Scheme III) which clearly must have both ester functions in the more stable equatorial positions (2-*endo*,3-*exo*).

Sodium borohydride reduction[10] of octanones **12** and **13** gave two γ-lactone esters directly which could be separated by chromatography. There was also obtained a trace quantity of unlactonized alcohol, presumably the C_8 epimer. The facile formation of the γ-lactones **15** and **16** indicated the axial (*exo*) orientation of the 2-carbomethoxy function in both the major and minor isomers. The major isomer was confirmed as **12** by the *t*-butoxide–*t*-butyl alcohol isomerization of the γ-lactone of the major isomer (**15**) to the minor isomer γ-lactone **16**. Methoxide–methanol opened the lactone and isomerized both ester functions to give **17**. Consequently, the relative stereochemistry of the ester functions in the major isomer is *trans* and in the least stable diaxial position.

The stereoselectivity of the reaction in this case eliminates the other two considered pathways. If either alternate path A or B occurred, both possible diastereomeric intermediates **18** and **19** would be expected and the final product should, therefore, consist of a mixture of **12** and **20** (Scheme IV). The ratio of these products would only depend upon a subtle conformation orientation of enamine and ester fragments in the Claisen rearrangement of route A or in the SN2′ step of route B. The absence of significant quantities of **20** in the product indicates the C-alkylation–Michael pathway is preferred in this case.[11] Nevertheless, the C-alkylation–Michael pathway is not unique, and the exact path or paths vary with the structure. An example of an al-

(7) (a) F. Johnson and S. K. Malhotra, *J. Amer. Chem. Soc.*, **87**, 5492 (1965); (b) S. K. Malhotra and F. Johnson, *ibid.*, **87**, 5493 (1965).

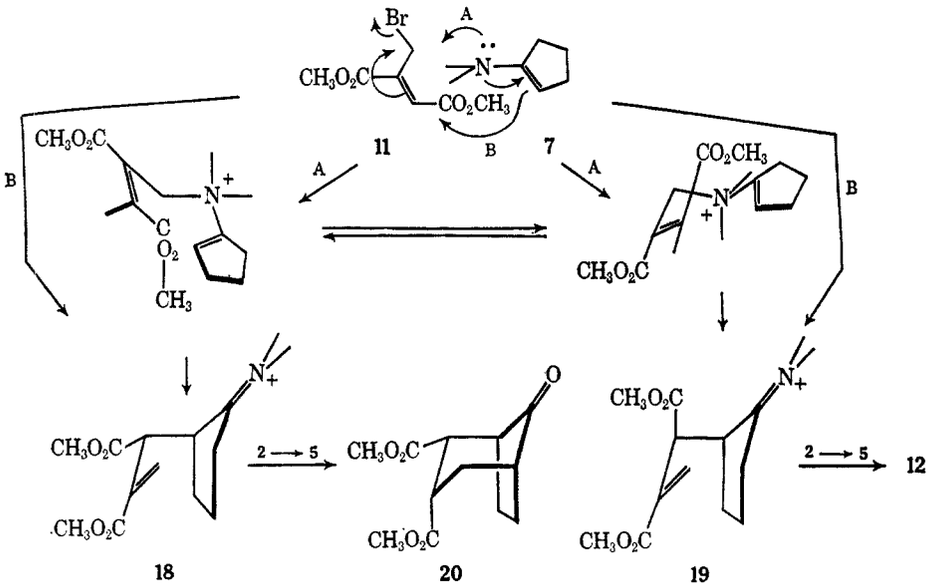
(8) See J. Szmuszkovicz in "Advances in Organic Chemistry: Methods and Results," Vol. 4, R. A. Raphael, E. Taylor, and H. Wynberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p 26.

(9) N. R. Campbell and J. H. Hunt, *J. Chem. Soc.*, 1176 (1947).

(10) A. C. Cope, J. M. Grisar, and P. E. Peterson, *J. Amer. Chem. Soc.*, **82**, 4299 (1960).

(11) The intermediate C-alkylation product has been isolated in the condensation of cyclohexanone enamine and dimethyl γ-bromomesaconate. These studies will be detailed in a future paper.

SCHEME IV



ternate mechanistic route arose in the synthesis of the strained benzobicyclo[3.2.1]octanone system.

Reaction of the homopiperidine enamine of 2-indanone (**21**) with dimethyl γ-bromomesaconate (**11**) in acetonitrile gave a 10% yield of ring-closed product. The homopiperidine enamine was chosen because this particular enamine had previously been found to give the largest amounts of C-alkylated products with a variety of alkylating agents.[12]

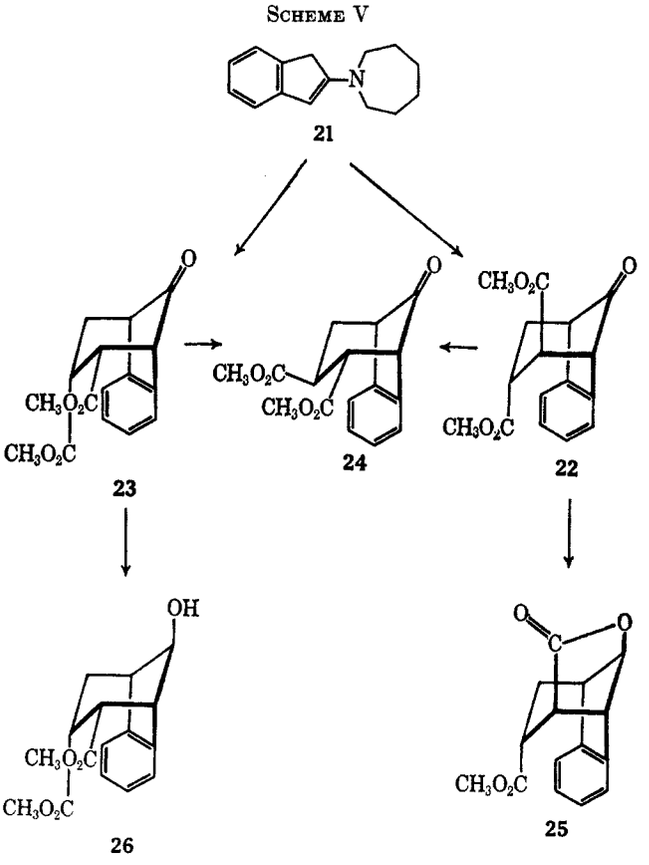
Proton magnetic resonance (pmr) analysis of the product indicated the presence of two isomers since there were four ester methyls at τ 6.21, 6.30, 6.83, and 6.89. The fact that two of the ester absorptions occurred at such high field led to the conclusion that both isomers possessed an *axial* 3-carbomethoxy function which was strongly shielded by the aromatic ring. Separation of the mixture yielded an equal quantity of both crystalline isomers. The isomer assigned structure **22** possessed a single absorption at τ 2.76 for the aromatic protons (methoxyls at 6.21 and 6.83), whereas isomer **23** had the aromatics as multiplets at 2.59 and 2.81 (methoxyls at 6.30 and 6.89). The anisotropic effect of the equatorial 2-carbomethoxy function in **23** on a portion of the aromatic ring accounts for the aromatic multiplets observed. The shielding effect of the aromatic ring on the equatorial ester methoxyl of **23** is also apparent.

Confirmation of this spectral assignment was obtained by chemical techniques used with compound **12**. Treatment of either isomer **22** or **23** with sodium methoxide–methanol afforded a single new isomer **24** (Scheme V) having methyl ester absorptions at τ 6.25 and 6.48. When the isomer **22** was caused to react with sodium borohydride, a γ-lactone (**25**) was formed, whereas borohydride reduction of the isomer **23** gave only alcohol **26**. These data clearly assigned the structures.

Mechanistically, the observed stereochemistry of the two products can be explained by the N-alkylation–rearrangement–Michael route, the S_N2'–Michael route, or by a process involving the normal C-alkylation–Michael route combined with either of these alternate routes.

(12) A. T. Blomquist and E. J. Moriconi, *J. Org. Chem.*, **26**, 3761 (1961).

SCHEME V



Both the enamine and α-(1-haloalkyl)-unsaturated derivative are able to include many diverse features and the α,α′-annelation procedure provides a general method for the construction of a wide variety of cyclic structures in a single step and under mild conditions. The stereochemistry and conformation of bicyclo[3.3.1]nonan-9-ones[4] constructed by this process as well as the synthesis of tricyclic, tetracyclic, and spiro systems will be developed in later publications.

Experimental Section

Infrared (ir) spectra were taken using a Perkin-Elmer Model 237 spectrophotometer and were determined as thin films or in chloroform solution. Pmr spectra were determined for deuteriochloroform solutions with a Varian A-60 spectrophotometer using tetramethylsilane as an internal reference: s, singlet; d, doublet; t, triplet; q, quadruplet; quint, quintuplet; m, multiplet. Chemical shifts are reported using the τ scale. Melting points were determined in open capillary tubes unless stated otherwise, using a Thomas–Hoover capillary melting point apparatus and are uncorrected. Microanalysis were performed by the Spang Microanalytical Laboratory, Ann Arbor, Mich. Mass spectral analysis were performed by the Morgan Schaeffer Corp., Montreal, Que.

Ethyl Bicyclo[3.2.1]octan-8-one-3-*endo*-carboxylate (8).—To a solution of 1.01 g (0.0074 mol) of the pyrrolidine enamine of cyclopentanone[5] (7) and 0.82 g (0.0080 mol) triethylamine in 10 ml of acetonitrile (dried over calcium hydride) was added dropwise with stirring 2.03 g (0.0074 mol) ethyl β,β'-dibromoisobutyrate[6] dissolved in 10 ml of dry acetonitrile. Heat was generated upon addition and, as the solution turned reddish brown, a solid precipitated. The reaction mixture was heated at reflux for 3.5 hr. Hydrolysis of the iminium ion was accomplished by the addition of 5 ml of 5% aqueous acetic acid followed by a 0.5-hr reflux period. The reaction mixture was cooled and an equal volume of water was added. The aqueous mixture was then extracted several times with ether and the combined extracts were washed with 5% aqueous hydrochloric acid, saturated aqueous sodium bicarbonate, and saturated aqueous sodium chloride. The resulting ethereal solution was dried over anhydrous magnesium sulfate. Filtration and evaporation of the ether yielded 1.34 g of a pale yellow oil which distilled at 83–88° (0.05 mm). The product consisted of a single isomer as shown by glpc analysis using a 5-ft 20% SE-30 (silicone) column maintained at 200°. Spectral properties follow: ir ($CHCl_3$) 1749, 1726, 1375, 1076, 1040 cm^{-1}; pmr ($CDCl_3$) τ 5.82 (2 H, q), 7.09 (1 H, m), 7.34 (2 H, m), 7.59 (1 H, m), 7.99 (3 H, m), 8.15 (4 H, s), 8.70 (3 H, t).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.30; H, 8.16.

Ethyl Bicyclo[3.2.1]octan-8-one-3-*exo*-carboxylate (9).—9 was prepared by sodium ethoxide epimerization of the *endo* compound. To a solution of 0.012 g (0.0005 g-atom) of sodium in 25 ml of dry ethanol was added with stirring 0.16 g (0.0008 mol) of *endo* compound 8 in 10 ml of ethanol. The reaction mixture was heated at reflux for 1 hr, allowed to cool, and neutralized with 10 ml of 5% aqueous acetic acid. An equal volume of water was added and the resulting mixture was extracted several times with ether. The combined extracts were washed with saturated aqueous sodium bicarbonate and saturated sodium chloride and then dried over anhydrous magnesium sulfate. Filtration and evaporation of the ether yielded 0.12 g of yellow oil. Kugelrohr distillation at 100–110° (bath temperature) (0.1 mm) gave a product consisting of predominately one isomer as shown by pmr analysis. Spectral properties follow: ir ($CHCl_3$) 1765, 1748, 1726, 1453, 1378, 1125, 1105, 1055, 1030 cm^{-1}; pmr ($CDCl_3$) τ 5.94 (2 H, q), 6.49 (1 H, quint), 7.80–8.45 (10 H, broad overlapping multiplets), 8.78 (3 H, t).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.36; H, 8.32.

Dimethyl γ-Bromomesaconate (11).—11 was prepared using the general route designed by Campbell and Hunt.[9] To a solution of 100 g (0.633 mol) of dimethyl mesaconate in 140 ml of carbon tetrachloride was added 133 g (0.633 mol) of N-bromosuccinimide and 5.50 g of benzoyl peroxide. The mixture was irradiated with an incandescent lamp and heated with a heating mantle to maintain a constant reflux. The reaction period was 2 hr. The reaction mixture was cooled and washed repeatedly with water to remove the succinimide. The carbon tetrachloride layer was dried with anhydrous magnesium sulfate, filtered, and rid of solvent under aspirator vacuum. The resulting light green oil was fractionated yielding 116 g (76.9%) of bromo ester 11, bp 123–124° (5 mm) [lit.[9] ethyl ester bp 72° (0.1 mm)]. Spectral properties follow: ir ($CHCl_3$) 3020, 2960, 1725, 1635, 1280 cm^{-1}; pmr ($CDCl_3$) τ 3.18 (1 H, s), 5.30 (2 H, s), 6.10 (3 H, s), 6.19 (3 H, s).

Anal. Calcd for $C_7H_9O_4Br$: C, 35.47; H, 3.79; Br, 33.71. Found: C, 36.07, 35.92; H, 3.83, 3.85; Br, 33.78.

Dimethyl Bicyclo[3.2.1]octan-8-one-2,3-dicarboxylate (12.)—To a solution of 16.9 g (0.123 mol) of the pyrrolidine enamine of cyclopentanone (7) in 90 ml of acetonitrile (dried over calcium hydride) was added dropwise with stirring 29.4 g (0.123 mol) of dimethyl γ-bromomesaconate (11). Heat was generated as the bromo ester was added and the solution turned orange-brown. The reaction mixture (under nitrogen) was maintained at reflux for 2 hr using a heating mantle. Hydrolysis of the resulting iminium ion was effected through the addition of 10 ml of 5% aqueous acetic acid, followed by an additional reflux period of 1 hr. The reaction mixture was processed in the same manner as was used to obtain 8. Evaporation of the ether solvent yielded 21.8 g of an orange viscous oil which exhibited no carbon–carbon double-bond absorptions in the ir. Fractionation of the crude oil gave 15.3 g (51.6%) of dimethyl bicyclo[3.2.1]octan-8-one-2-*exo*,3-*endo*-dicarboxylate (12) with a trace of 13, bp 161–164.5° (1.8 mm). The product appeared to consist of a major isomer as shown by glpc analysis using a 6-ft, 6% LAC-728 (adipate ester) column maintained at approximately 250°. Spectral properties follow: ir ($CHCl_3$) 1747, 1725, 1260, 1175, 1025 (three peaks) cm^{-1}; pmr ($CDCl_3$) τ 6.20 (3 H, s), 6.27 (3 H, s), 8.10 (4 H, m), 7.76 (1 H, m), 7.38 (3 H, m), 6.88 (1 H, m); mass spectrum *m/e* peak at 240.

Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 60.16; H, 6.82.

The 2,4-dinitrophenylhydrazone of 12 was prepared using the procedure of Vogel.[13] The orange-yellow hydrazone was recrystallized from methanol–chloroform yielding purified crystals, mp 206–207°.

Anal. Calcd for $C_{18}H_{20}N_4O_8$: C, 51.53; H, 4.80; H, 13.33. Found: C, 51.58; H, 4.88; H, 13.30.

Epimerization of Dimethyl Bicyclo[3.2.1]octan-8-one-2-*exo*,3-*endo*-dicarboxylate (12) with Sodium Methoxide.—A solution of 6.02 g (0.0251 mol) of dimethyl bicyclo[3.2.1]octan-8-one 2-*exo*,3-*endo*-dicarboxylate and 1.35 g (0.0249 mol) of sodium methoxide in 50 ml of methanol (dried with magnesium) was heated at reflux (heating mantle) for 1.5 hr. The reaction mixture was processed in the same manner as that used to obtain 9. Evaporation of solvent yielded 4.22 g (70.0%) of brown oil which solidified on standing. Recrystallization of the crude crystals from ether gave 3.73 g of white solid, mp 92–94°. Spectral properties follow: ir ($CHCl_3$) 1745, 1730, 1320, 1250 cm^{-1}; pmr ($CDCl_3$) τ 6.30 (3 H, s), 6.71 (q), 7.47 (m), 7.77 (m), 8.10 (m).

Anal. Calcd for $C_{12}H_{16}O_5$: C, 59.49; H, 6.71. Found: C, 59.35; H, 6.60.

Methyl Bicyclo[3.2.1]octan-8-ol-2-carboxy-3-*endo*-carboxylate γ-Lactone (15) and -3-*exo*-carboxylate γ-Lactone (16).—To a cooled (ice bath) solution of 0.205 g (0.855 mmol) of dimethyl bicyclo-[3.2.1]octan-8-one 2,3-dicarboxylate (12) in 12 ml of methanol was added slowly 0.0337 g (0.880 mmol) of sodium borohydride. The reaction was allowed to stand with occasional stirring at room temperature for 30 min. An approximately equal volume of water was added and the aqueous methanol solution was extracted with ether. The combined ether extracts were dried over anhydrous magnesium sulfate. Evaporation of solvent yielded 0.170 g of crude slightly yellow oil whose ir spectrum possessed the characteristic γ-lactone carbonyl absorption at 1785 cm^{-1}. Column chromatography of 1.52 g of oil, prepared in an analogous experiment over 80 g of silicic acid absorbant using 5% ether in benzene as eluent, yielded 0.302 g of a major γ-lactone (15) followed by 0.0367 g of a minor epimeric γ-lactone (16). There was also obtained C_8 epimeric alcohol.

The major γ-lactone (15) [Kugelrohr 200° (1 mm)] had the following spectral properties: ir ($CHCl_3$) 1785, 1730, 1310, 1150 (three peaks), 1025 cm^{-1}; pmr ($CDCl_3$) τ 6.21 (3 H, s), 5.22 (1 H, t), 6.82 (1 H, m), 7.21 (2 H, m), 7.67 (2 H, m), 8.25 (4 H, m).

Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85, H, 6.71. Found: C, 62.96; H, 6.76.

The minor γ-lactone (16) had the following spectral properties: ir ($CHCl_3$) 1780, 1730, 1150, 1015 (three peaks) cm^{-1}; pmr ($CDCl_3$) τ 6.25 (3 H, s), 5.22 (1 H, m), 7.07 (m), 7.65 (m), 8.17 (m).

The epimeric alcohol (C_8) had the following spectral properties: ir ($CHCl_3$) 3610 (s), 3450 (b), 1730, 1260 cm^{-1}; pmr ($CDCl_3$) τ 6.34 (6 H, s), 6.78 (2 H, m), 8.25 (m).

(13) A. I. Vogel, "A Textbook of Practical Organic Chemistry," 3rd ed, John Wiley & Sons, Inc., New York, N. Y., 1962, p 344.

Attempted Epimerization of Methyl Bicyclo[3.2.1]octan-8-ol-2-Carboxy-3-carboxylate γ-Lactone (15) with Sodium Methoxide.—To a solution containing 0.0020 g (0.00087 g-atom) of sodium metal dissolved completely in 1 ml of methanol was added 0.0459 g (0.219 mmol) of γ-lactone (**15**). An additional 1 ml of methanol was used as a transfer agent. The mixture was heated in an oil bath to maintain reflux for 0.5 hr. Cooling of the mixture followed by processing as in the epimerization of ketone **8** yielded 0.0449 g (84.9%) of clear oil. The ir spectrum of the crude oil lacked the γ-lactone carbonyl absorption at 1785 cm^{-1}. Alcohol **17** had the following spectral properties: ir ($CHCl_3$) 3610 (s), 3475 (b), 2960, 1730, 1250 cm^{-1}.

Epimerization of Methyl Bicyclo[3.2.1]octan-8-ol-2-carboxy-3-carboxylate γ-Lactone (15) with Potassium *t*-Butoxide.—A solution of 0.110 g (0.476 mmol) of pure γ-lactone **15** and 0.012 g (0.099 mmol) of potassium *t*-butoxide in 4 ml of *t*-butyl alcohol (dried over calcium hydride) was stirred at room temperature for 2 hr. Neutralization of the solution with 5% acetic acid followed by processing as in the procedure used for the epimerization of ketone **8** yielded 0.108 g of oil which contained approximately 18% epimerized material **16** by pmr analysis. The pmr spectrum revealed that the previous ester methyl absorption at τ 6.21 had shifted to 6.25. Spectral properties follow: ir ($CHCl_3$) 1780, 1730, 1150, 1015 (three peaks) cm^{-1}; pmr ($CDCl_3$) τ 5.22 (1 H, m), 6.25 (3 H, s), 6.83 (m), 7.07 (m), 7.65 (m), 8.17 (m).

Dimethyl 6,7-Benzobicyclo[3.2.1]octan-8-one-2,3-dicarboxylates (22 and 23).—To a solution of 8.16 g (0.0422 mol) of the homopiperidine enamine of 2-indanone (**21**)[12,14] in 50 ml of acetonitrile was added 10.0 g (0.0422 mol) of bromomesaconate (**11**). Nitrogen was swept over the reaction mixture throughout the bromo ester addition and during the subsequent 3-hr reflux period. Triethylamine (3 ml, 0.04 mol) was added and the mixture was heated at reflux for another hour. The imine salt was hydrolyzed using 10 ml of 5% acetic acid followed by an additional reflux period of 12.5 hr. Processing of the reaction as in the preparation of keto ester **8** followed by evaporation of solvent gave 6.88 g of brown oil. Fractionation of the oil yielded 1.30 g (10.9%) of dimethyl 6,7-benzobicyclo[3.2.1]octan-8-one-2,3-dicarboxylates (**22** and **23**), bp 168–172° (0.35 mm). The pmr analysis indicated two compounds. The remaining oil was chromatographed over 65 g of acid-washed silicic acid using ether–benzene as eluent. Keto diester **22** (0.275 g) was the first isomer eluted from the column in 4% ether–benzene with keto diester **23** (0.446 g), mp 109.5–111°, being removed with 10% ether–benzene.

Keto diester 23 had the following spectral properties: ir ($CHCl_3$) 3020, 1765, 1740, 1200, 1025 cm^{-1}; pmr ($CDCl_3$) τ 2.59, 2.81 (4 H, m), 6.12 (m), 6.30 (3 H, s), 6.63 (m), 6.89 (ester methyl superimposed on multiplet), 71.6 (m), 7.75 (m).

Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.68; H, 5.50.

Keto diester 22 had the following spectral properties: ir ($CHCl_3$) 3010, 1775, 1740, 1280 cm^{-1}; pmr ($CDCl_3$) τ 2.76 (4 H, s), 5.88 (1 H, m), 6.21 (3 H, s), 6.28 (1 H, m), 6.66 (m), 6.83 (3 H, s), 7.11 (m), 7.42 (m).

Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.60; H, 5.55.

Epimerization of Dimethyl 6,7-Benzobicyclo[3.2.1]octan-8-one-2-*exo*,3-*endo*-dicarboxylate (22) with Sodium Methoxide.—To a solution of 0.005 g (0.0002 g-atom) of sodium metal dissolved completely in 2 ml of methanol (dried with magnesium) under nitrogen was added 0.100 g (0.35 mmol) of keto diester **22**. The solution was maintained at reflux using an oil bath for 0.75 hr during which time the solution turned wine red. The reaction mixture was cooled and processed as in the epimerization of bicyclononanone **8**. Evaporation of solvent yielded 0.0813 g (81.3%) of yellow oil which solidified to give white crystals. Recrystallization from ether followed by vacuum drying over concentrated sulfuric acid gave 0.0377 g of purified material, mp 143.5–144.5° (**24**). Spectral properties follow: ir ($CHCl_3$) 3020, 1775, 1740, 1260, 1100 cm^{-1}; pmr ($CDCl_3$) τ 2.72 (4 H, m), 6.25 (3 H, s), 6.48 (3 H, s), 6.55 (m), 6.69 (m), 7.78 (m).

Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.78; H, 5.46.

Epimerization of Dimethyl 6,7-Benzobicyclo[3.2.1]octan-8-one-2-*endo*,3-*endo*-dicarboxylate (23) with Sodium Methoxide.—In 2 ml of methanol (dried with magnesium) was dissolved 0.005 g (0.0002 g-atom) of sodium metal. To the sodium ethoxide–methanol solution was added 0.0871 g (0.300 mmol) of keto diester **23**. The reaction mixture was heated at reflux for 0.75 hr using an oil bath, cooled, and processed as in the epimerization of dimethyl 6,7-benzobicyclo[3.2.1]octan-8-one-2-*exo*,3-*endo*-dicarboxylate (**22**). Evaporation of solvent gave 0.0607 g (69.6%) of yellow oil which yielded 0.0270 g (44.5%) of white crystals of keto ester **24** upon treatment with ether.

Methyl 6,7-Benzobicyclo[3.2.1]octan-8-ol-2-carboxy-3-*endo*-carboxylate γ-Lactone (25).—To 1.5 ml of methanol was added 0.133 g (0.464 mmol) of keto diester **22**. The resulting solution was treated with 0.0190 g (0.505 mmol) of sodium borohydride which caused a color change in the solution from colorless to yellow. After the solution was allowed to stand at room temperature for 0.5 hr, the reaction was processed as in the reduction of keto diester **12** giving 0.132 g (100% recovery) of a yellow oil. The product consisted of γ-lactone [–C(=O)–, 1785 cm^{-1}] contaminated with unlactonized alcohol [3700, 3620 (sharp), 3330 (broad) cm^{-1}]. More γ-lactone was not formed after heating at 170° for 1.75 hr. Spectral properties follow: ir ($CHCl_3$) 1785, 1730, 1170 cm^{-1}; pmr (major peaks of crude oil) ($CDCl_3$) τ 2.84 (s), 2.91 (s), 5.82 (1 H, t), 6.83 (3 H, s).

Dimethyl 6,7-Benzobicyclo[3.2.1]octan-8-ol-2-*endo*,3-*endo*-dicarboxylate (26.)—A cooled solution (~15°) of 0.148 g (0.513 mmol) of keto diester **23** in 1.5 ml of methanol was treated with 0.0228 g (0.603 mmol) of sodium borohydride. After the reaction mixture ceased bubbling, it was allowed to stand at room temperature for 0.5 hr. Processing as in the reduction of **12** yielded 0.151 g (100%) of oil which solidified on standing (mp 124–124.5°). Ir analysis indicated the presence of an alcohol function [3650 (sharp), 3520 (broad) cm^{-1}]. However, no γ-lactone had formed. Spectral properties follow: ir ($CHCl_3$) 3650 (sharp), 3520 (broad), 3040, 1265, 1200 cm^{-1}; pmr ($CDCl_3$) τ 2.74 (s on m) and 2.93 (m) [4 H], 5.75 (1 H, t), 6.38 (3 H, s), 6.61 (m), 6.99 (3 H, s superimposed on m), 7.55 (m).

Registry No.—**8**, 19530-66-6; **9**, 19530-67-7; **11**, 19530-68-8; **12**, 19530-69-9; **12** (2,4-dinitrophenylhydrazone), 19530-70-2; **13**, 19530-71-3; **14**, 10560-30-2; **15**, 10555-66-5; **16**, 10555-67-6; **17**, 19530-74-6; **22**, 19545-03-0; **23**, 19530-75-7; **24**, 19530-76-8; **25**, 19530-77-9; **26**, 19545-04-1.

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