

APPLICATION OF BREDT'S RULE
TO BRIDGED BICYCLIC SYSTEMS

by

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ABSTRACT

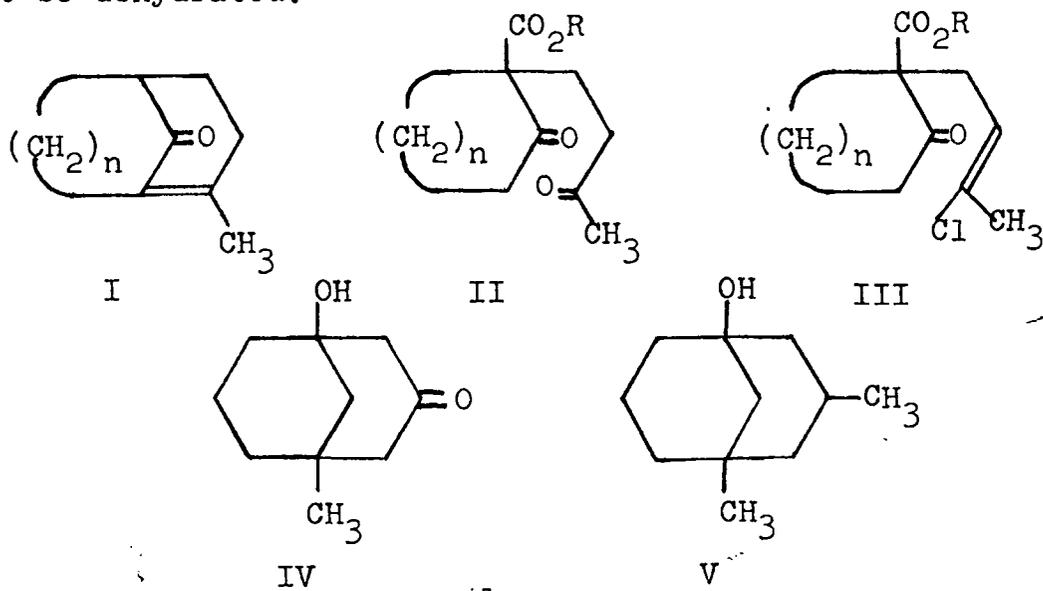
Bicyclo[3.2.1]octan-2-one was prepared by Demjanov rearrangement of endo-2-aminomethylbicyclo[2.2.1]octane and subsequent oxidation of the resultant alcohols. Dieckmann condensation of ethyl β -(3-carbethoxycyclohexyl)propionate produced 3-carbethoxybicyclo[3.3.1]nonan-2-one. Hydrolysis and decarboxylation of this β -ketoester afforded bicyclo[3.3.1]nonan-2-one.

Bicyclo[3.2.1]octan-2-one and bicyclo[3.3.1]nonan-2-one were subjected to base-catalyzed deuterium exchange. It was shown that exchange did not occur at the bridgehead position of the octanone. However, the bridgehead hydrogen of bicyclo[3.3.1]nonan-2-one was sufficiently acidic to permit deuterium exchange. Thus, a violation of Bredt's rule was indicated in the case of the nonanone.

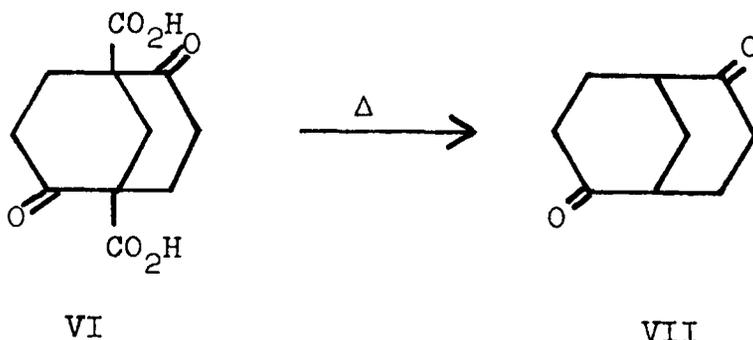
INTRODUCTION

According to Bredt's rule,^{1,2} the existence of certain bridge polycyclic compounds with carbon-carbon double bonds at the bridgehead is prohibited. The rigidity of the ring system conflicts with the geometrical requirements for the formation of such a double bond. This rule is qualitative and has no validity for large-ring systems.

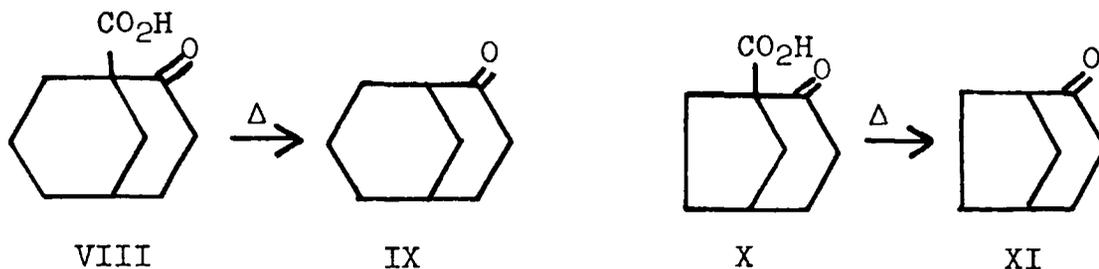
Efforts have been made to determine the limits of applicability of Bredt's rule. Prelog and co-workers³ were able to prepare and isolate I, a member of the bicyclo[n.3.1] series, from II or III only when n was greater than or equal to 5. Similarly, IV was found to be extraordinarily resistant to dehydration⁴ and V could not be dehydrated.⁵



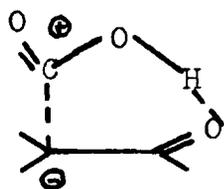
Seemingly contradictory evidence is gained from the successful decarboxylation of VI, a member of the bicyclo[3.3.1]nonane system, by Meerwein and Schürmann.⁶



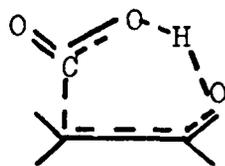
Since the decarboxylation of β -ketoacids is usually thought to involve the formation of an enol, a violation of Bredt's rule is implied. It should be mentioned that Ferris and Miller⁷ have successfully decarboxylated VIII and X at 145° and 260°, respectively. They have



proposed a mechanism which involves transition state A rather than an enolic transition state B. The temperature at which decarboxylation occurred was found to be dependent on the degree of overlap between the sp^3



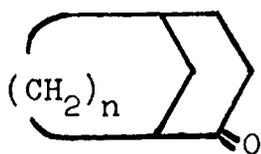
A



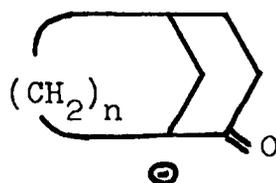
B

orbital of the developing carbanion and the p orbital of the adjacent carbonyl group. Thus, according to this explanation, Bredt's rule was not violated. The application of Bredt's rule to the bicyclo[3.3.1]nonane system has also been discussed by Schaefer and Lark.⁸

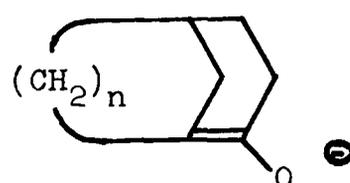
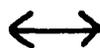
Because the validity limits would probably differ for the two categories, Fawcett² distinguished between violation of Bredt's rule by isolable compounds and infractions by transient intermediates. Base-catalyzed deuterium exchange at the bridgehead position by bicyclic ketone XII would constitute evidence for the latter, since the acidity of the bridgehead hydrogen depends on the stability of the enolate anion XIII. If the constraints of the bridged ring system were such that the



XII



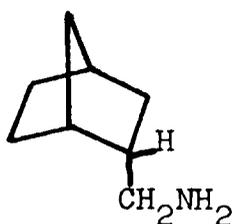
XIIIa



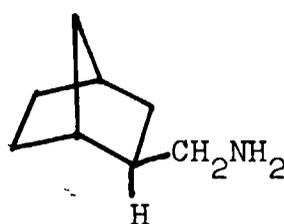
XIIIb

pair of electrons associated with the bridgehead carbanion were held in an sp^3 orbital, effective overlap with the p orbitals of the keto group could not take place. Thus, resonance form XIIIb could not be an important contributor and the bridgehead hydrogen would not be expected to be appreciably acidic. Consequently, if exchange does occur at the bridgehead, the ring system must be sufficiently flexible to permit at least partial double bond character between C_1 and C_2 . On this premise and with the intention of extending the knowledge of the validity limits of Bredt's rule, the preparation and base-catalyzed deuterium exchange of bicyclo[3.2.1]octan-2-one (XI) and bicyclo[3.3.1]nonan-2-one (IX) were undertaken.

Bicyclo[3.2.1]octan-2-one (XI) and the related isomeric alcohols have been prepared in a variety of ways. Alder and co-workers⁹ obtained a mixture of bicyclic octanols¹⁰ by ring expansion of endo-2-aminomethylbicyclo[2.2.1]heptane (XIVa) under nitrosative deamination conditions (Demjanov rearrangement). Oxidation of these alcohols yielded a mixture of ketones; the major product was bicyclo[3.2.1]octan-2-one (XI).

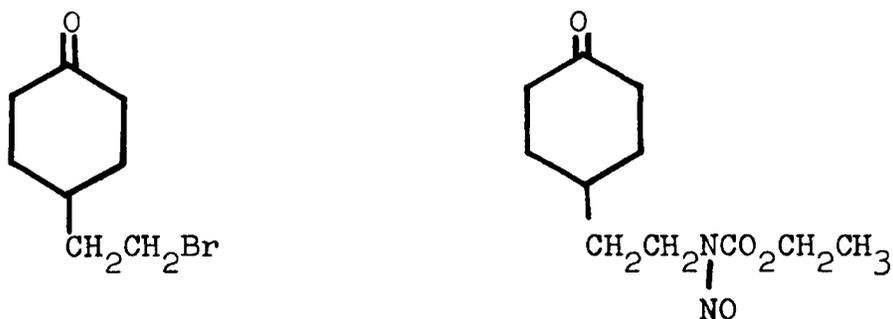


XIVa



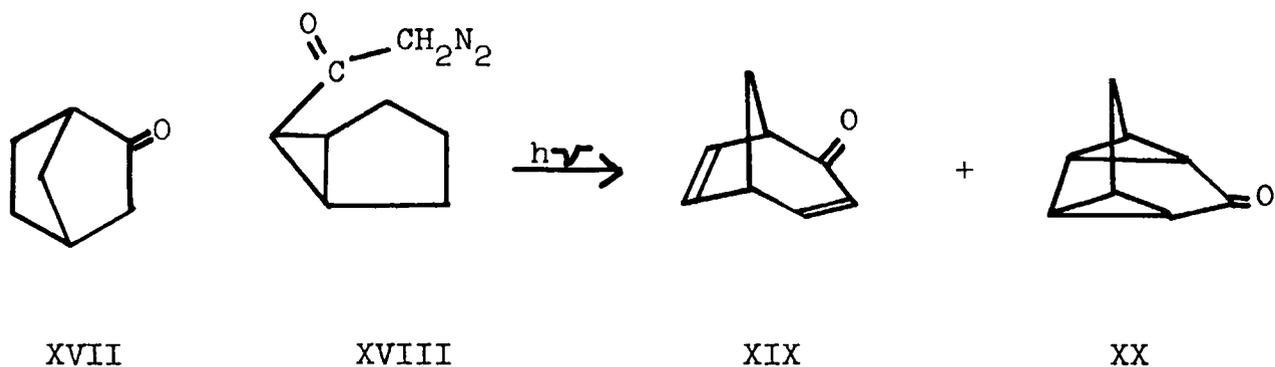
XIVb

Although bicyclo[3.2.1]octan-2-one (XI) and the corresponding alcohol were neither the desired nor the expected products, they were obtained by Newman and Yu¹¹ in poor yield by treating 4-(β -bromoethyl)-cyclohexanone (XV) with lithium in dry diethyl ether. The octanone has also been obtained in moderate yield by treatment of N-nitroso-N-carbethoxy-2-(4'-ketocyclohexyl)ethylamine (XVI) with potassium carbonate in methanol and methylene chloride.¹²

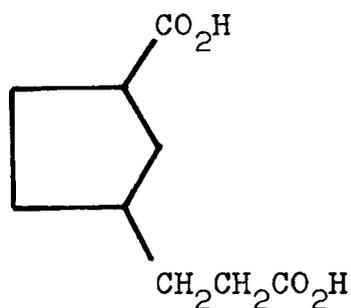


Sauers and Tucker¹³ obtained bicyclo[3.2.1]octan-2-one (XI), bicyclo[3.2.1]octan-3-one (XXXIX) and a variety of nine-carbon ketones by ring enlargement of norcamphor (XVII) with diazomethane. Photolysis of endo-6-diazomethylketobicyclo[3.1.0]hex-2-ene (XVIII) has been shown by Freeman and Kuper¹⁴ to give a mixture of bicyclo[3.2.1]octan-3,6-dien-2-one (XIX) and a tetracyclic octanone (XX) in moderate yield. The bicyclic dienone, the major

product, was readily saturated to yield bicyclo [3.2.1]-octan-2-one (XI).

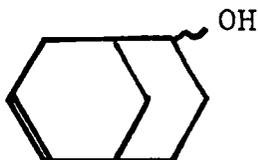


In preparation for their decarboxylation studies, Ferris and Miller^{7(b)} synthesized 1-carxybicyclo [3.2.1]-octan-2-one (X) from 3-(3'-carboxycyclopentyl) propanoic acid (XXI) by cyclization of the corresponding diacid chloride with triethylamine and subsequent hydrolysis of the resultant acid chloride of X. The yield was poor. As previously mentioned, decarboxylation of X gave bicyclo [3.2.1]octan-2-one (XI).



Interest in non-classical carbonium ions and carbonium ion rearrangements has prompted a number of previously unmentioned studies involving the bicyclo-[3.2.1]oct-2-yl or bicyclo[3.2.1]oct-3-en-2-yl systems. Several different schemes^{11, 15-21} leading to alcohols or acetates which could be converted readily to bicyclo-[3.2.1]octan-2-one have been developed.

The second of the two ketones under consideration, bicyclo[3.3.1]nonan-2-one (IX), was prepared by Meerwein and co-workers²² in 1922. Dione VII was reduced to the corresponding diol with sodium amalgam.

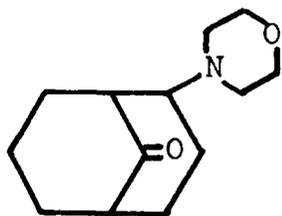


XXII

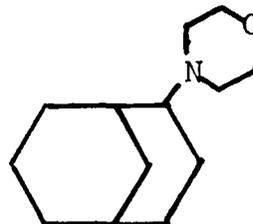
Unsaturated alcohol XXII was obtained by a partial dehydration of the diol with 38% sulfuric acid. Catalytic hydrogenation, followed by oxidation with chromic acid, afforded the desired ketone IX.

Bicyclo[3.3.1]nonan-2-one (IX) has been synthesized²³ by a scheme using 2-N-morpholinobicyclo[3.3.1]nonan-9-one (XXIII).²⁴ Wolff-Kishner reduction afforded

XXIV. Subsequent preparation and pyrolysis of the amine oxide gave olefin XXV. Selenium dioxide oxidation of XXV in dioxane and water gave the allylic alcohol XXVI.



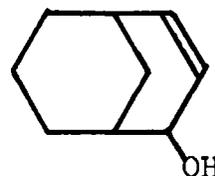
XXIII



XXIV



XXV

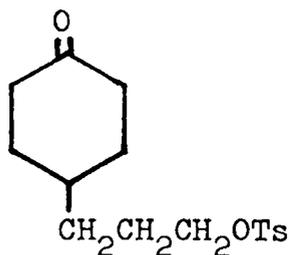


XXVI

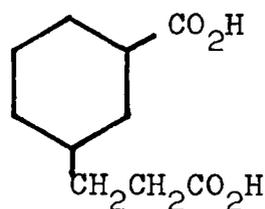
The desired ketone (IX) was obtained after catalytic reduction of the carbon-carbon double bond and oxidation of the resultant saturated alcohol with chromium trioxide in pyridine.

Bicyclic amine XXIV has been used also by Hartmann²⁵ in a synthesis of ketone IX. Treatment of XXIV with mercuric acetate in 10% acetic acid, followed by hydrolysis of the resultant enamine, gave bicyclo-[3.3.1]nonan-2-one (IX) in 56% yield.

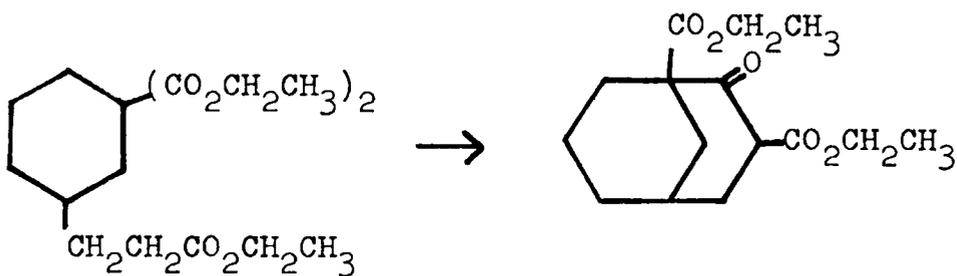
Various substituted cyclohexanes have served as precursors to bicyclo[3.3.1]nonan-2-one (IX). The action of the *t*-butoxide ion in tetrahydrofuran on 4-(γ -tosyloxypropyl)cyclohexanone (XXVII) produced IX in 42% yield.²⁶ Pyrolysis of the barium²⁷ or magnesium²⁵ salt of diacid XXVIII has also given the desired ketone in 31 (isolated as the semicarbazone) and 42% yield, respectively. Dieckmann condensation of XXIX with sodium hydride produced XXX in 21% yield.^{7(a)} Hydrolysis and decarboxylation of XXX under mild conditions gave VIII. As previously mentioned, VIII afforded ketone IX when heated at 145° for thirty minutes.



XXVII



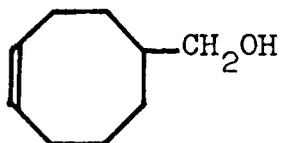
XXVIII



XXIX

XXX

Solvolysis of the brosylate²⁸ or tosylate²⁹ of 4-cyclooctene-1-methanol (XXXI) in buffered acetic acid has served as an approach to the bicyclo[3.3.1]non-2-yl system. The solvolysis product afforded ketone IX upon lithium aluminum hydride reduction of the acetate and oxidation of the resultant alcohol. Cope²⁸ has also developed a satisfactory synthesis of bicyclo[3.3.1]nonan-2-ol using the enamine of cyclohexanone.



XXXI

RESULTS AND DISCUSSION

Bicyclo[3.2.1]octan-2-one (XI), having been selected as a suitable compound for use in this study of the validity limits of Bredt's rule, was prepared according to a modification of the method described by Alder.⁹ Other synthetic routes described below were investigated. Figure 1 summarizes this work. Alder's procedure, although virtually free of experimental difficulties, was not fully satisfactory because the final product was found to be a mixture of isomeric bicyclic octanones. However, since it was possible to identify the components of the mixture and to estimate their relative amounts, the product which was obtained was deemed acceptable for deuterium exchange studies.

A Diels-Alder reaction between cyclopentadiene and acrylonitrile produced a mixture of endo- and exo-2-cyanobicyclo[2.2.1]hept-5-ene (XXXII a and b) in quantitative yield. For preliminary work, the isomers were not separated. Rather, XXXII was converted directly to 2-aminomethylbicyclo[2.2.1]heptane (XIV a and b) in good yield by high-pressure hydrogenation of the Diels-Alder product with Raney nickel serving as catalyst.

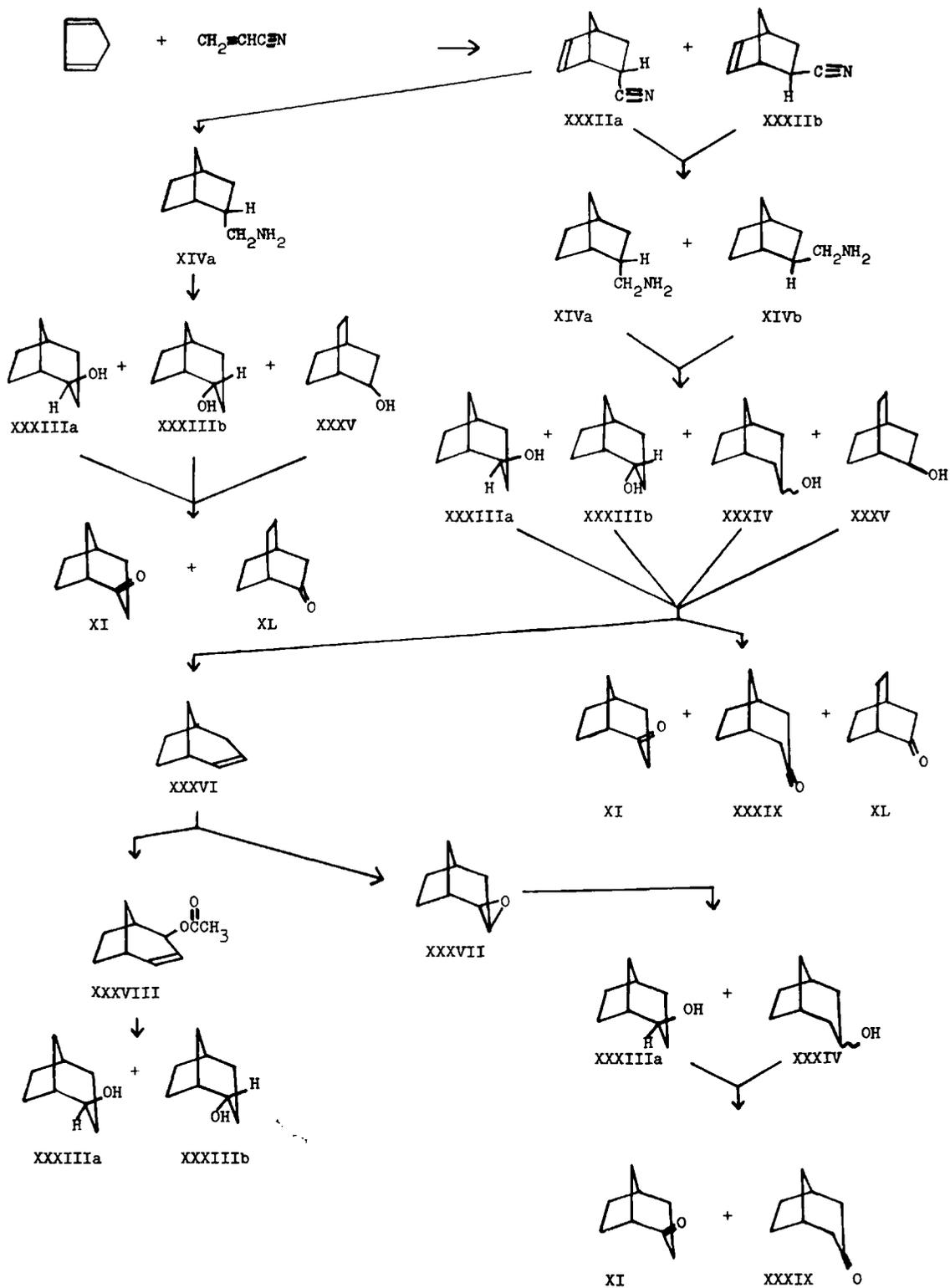


Figure 1 -- Synthesis of Bicyclo[3.2.1]octan-2-one

Alternatively, the carbon-carbon double bond in XXXII was reduced with palladium on powdered charcoal in a Parr hydrogenation apparatus. Lithium aluminum hydride reduction of the saturated nitrile afforded a mixture of XIV a and b in moderate yield.

In preparation for a Demjanov rearrangement, methylamine XIV, a mixture of isomers, was converted to its hydrochloride with concentrated hydrochloric acid. Dissolution of the hydrochloride in water was followed by diazotization with sodium nitrite and acetic acid at reflux temperature. After alkaline hydrolysis, the reaction mixture was steam distilled. Analysis of the product by vapor phase chromatography (v.p.c.) revealed the presence of four major components. The peaks corresponding to these components were in a cluster. The relative peak areas, given in the order in which the peaks appeared, were approximately 2:2:4:1. On the basis of Alder's⁹ work, it was reasonable to assume that the principal components of this mixture were octanols XXXIII a and/or b, XXXIV and XXXV. Oxidation of the rearrangement product with chromium trioxide and acetic acid was carried out in good yield. As expected, the oxidation product was shown by v.p.v. to be a mixture.

It has been demonstrated³⁰ that bicyclo[3.2.1]-oct-2-ene (XXXVI) can serve as a precursor to the exo isomer of bicyclo[3.2.1]octan-2-ol (XXXIIIa) and hence to the corresponding ketone XI. In order to investigate this promising route, the olefin (XXXVI) was prepared. The mixture of alcohols obtained by Demjanov rearrangement was acetylated by means of acetyl chloride in pyridine. Pyrolysis of the resultant acetates gave olefin XXXVI in moderate yield. The product showed only one peak upon v.p.c. analysis. It should be noted that pyrolysis of the acetates corresponding to XXXIIIa, XXXIIIb, and XXXIV would give the same olefin (XXXVI). The olefin resulting from the acetate of XXXV would give bicyclo[2.2.2]oct-2-ene, which might be expected to decompose via a reverse Diels-Alder reaction when heated. The single peak in the v.p.c. of the product would indicate either that the two olefins had the same retention time or that bicyclo[2.2.2]oct-2-ene had decomposed as predicted.

Bicyclo[3.2.1]oct-2-ene (XXXVI) was epoxidized with peracetic acid in chloroform. Reduction of the resultant epoxide (XXXVII) with lithium aluminum hydride afforded a product which was not homogeneous, as shown by v.p.c.

Since reduction of the epoxide (XXXVII) appeared to give more than one alcohol, another approach to attaining the desired product was attempted. Selenium dioxide oxidation of olefin XXXVI in acetic anhydride gave acetate XXXVIII, which was not isolated. Catalytic hydrogenation of the double bond and hydrolysis of the ester group produced a three-component mixture. One component was tentatively identified as bicyclo[3.2.1]-octane; the others appeared to be XXXIIIa and XXXIIIb. Although the selenium dioxide oxidation route apparently would have led to pure bicyclo[3.2.1]octan-2-one (XI), it was judged to be an unsatisfactory method of preparing an appreciable quantity of the desired ketone.

Alder's⁹ procedure, with modification, was repeated using pure endo-2-cyanobicyclo[2.2.1]hept-2-ene (XXXIIIa) obtained by fractional distillation of the Diels-Alder product. Catalytic reduction afforded endo-2-aminomethylbicyclo[2.2.1]heptane (XIVa). Nitrosative deamination (Demjanov rearrangement) at room temperature³¹ led to a mixture of products, some of which proved to be organonitrites. Therefore reduction with lithium aluminum hydride was necessary in order to obtain the desired octanols. Analysis by v.p.c. revealed the presence of three major components in the approximate ratio 1:1:8.

Preparation and crystallization of the p-nitrobenzoate derivatives, followed by recovery of the alcohol by hydrolysis, failed to yield a single, isomer-free product.

At this point, sufficient information was available to permit identification of the major products obtained by the epoxide route, the selenium dioxide oxidation route, and Alder's⁹ method. It may be recalled that a cluster of four peaks was seen in the chromatograph of the product obtained by Demjanov rearrangement of XIV a and b. The peak with the shortest retention time (Peak A) was shown by comparative v.p.c. studies to be identical with one of the two peaks noted for the product obtained by the selenium dioxide oxidation route and with the major peak noted for the product obtained via the epoxide. Thus, this component would appear to be exo-bicyclo[3.2.1]octan-2-ol (XXXIIIa). This peak was also seen in the chromatograph of the product obtained by Demjanov rearrangement of XIVa. The second peak to appear (Peak B) was seen only in the chromatographs of the products obtained directly from the Demjanov rearrangement. The third peak (Peak C) was seen distinctly in all the chromatographs except the one for the product obtained by the epoxide route and was therefore taken to be endo-bicyclo[3.2.1]octan-2-ol

(XXXIIIb). The remaining peak (Peak D) was distinct only in the first-mentioned chromatograph, but appeared to be present as a shoulder in the chromatograph of the alcohol obtained via the epoxide.

Oxidation of the mixture of alcohols obtained from XIVa afforded a ketonic product in good yield. Although oxidation of three alcohols must lead to at least two ketones, only one sizable peak with a long retention time (Peak E) was seen upon v.p.c. analysis. A sample of bicyclo[2.2.2]octanone (XL), provided by Leland S. Endres, was found to have a retention time identical to that for the major ketone resulting from oxidation of the alcohols obtained via the epoxide and to that for the material showing Peak E. As previously mentioned, the product obtained from oxidation of the alcohols resulting from XIV a and b was a mixture. Preparative v.p.c. and attempted preparation of 2,4-dinitrophenylhydrazones revealed that the small peaks with short retention times did not correspond to carbonyl compounds. Only the two peaks with longer retention times proved to arise from ketones. Thus, it appeared that the ketone (XXXIX) arising from alcohol XXXIV could be separated by v.p.c. from the desired ketone XI, whereas ketone XL arising from XXXV could

not be separated. It was concluded that the identification of Peak B with bicyclo[2.2.2]octan-2-ol (XXXV) and Peak D with bicyclo[3.2.1]octan-3-ol (XXXIV) was justified. These conclusions were confirmed by the work of Berson.^{10, 32}

An abundance of the ketones obtained by oxidation of the Demjanov rearrangement product made it expedient to use the product obtained in this manner for the deuteration studies. Preparative v.p.c. was employed in order to remove some minor impurities. Thus, a mixture consisting of bicyclo[3.2.1]octan-2-one (XI) (90-93%) and bicyclo[2.2.2]octanone (XL) (7-10%) was subjected to deuterium exchange. A maximum of 1.98 atoms of deuterium per molecule was obtained even when the ketone mixture was heated for 48 hours at 225° in sodium deuterioxide-deuterium oxide solution. The significance of this result will be discussed later.

Bicyclo[3.3.1]nonan-2-one (IX), the second ketone selected for deuterium exchange, was prepared by Dieckmann condensation of an appropriate diester (XLI) and subsequent hydrolysis and decarboxylation of the Dieckmann product (XLII). The availability of substituted aromatic compounds which could be converted to the necessary diester and interest in the Dieckmann condensation for

its own sake prompted the selection of this synthetic approach. The preparation of bicyclo[3.3.1]nonan-2-one (IX) is outlined in Figure 2.

m-Nitrobenzaldehyde (XLIII), a suitable and readily available starting material, was converted to m-nitrocinnamic acid (XLIV) in good yield by condensation with malonic acid in pyridine with piperidine serving as catalyst. Acid-catalyzed esterification of XLIV afforded ethyl m-nitrocinnamate (XLV) in moderate yield. Alternatively, ester XLV was prepared in excellent yield from m-nitrobenzaldehyde (XLIII) by base-catalyzed condensation with ethyl hydrogen malonate. This would appear to be an excellent method for the direct preparation of an α , β -unsaturated ester from an aldehyde.

Catalytic reduction of XLV produced ethyl m-aminohydrocinnamate (XLVI), which could not be distilled satisfactorily because of its tendency to polymerize when heated. Crude XLVI was converted to its diazonium salt by means of sodium nitrite and hydrochloric acid. Subsequent treatment of the diazonium salt of XLVI with aqueous cuprous cyanide solution yielded ethyl m-cyanohydrocinnamate (XLVII). This Sandmeyer reaction proceeded in 52% yield. Ethyl m-carbethoxyhydrocinnamate (XLVIII) was prepared readily by reacting XLVII with ethanol and sulfuric acid.

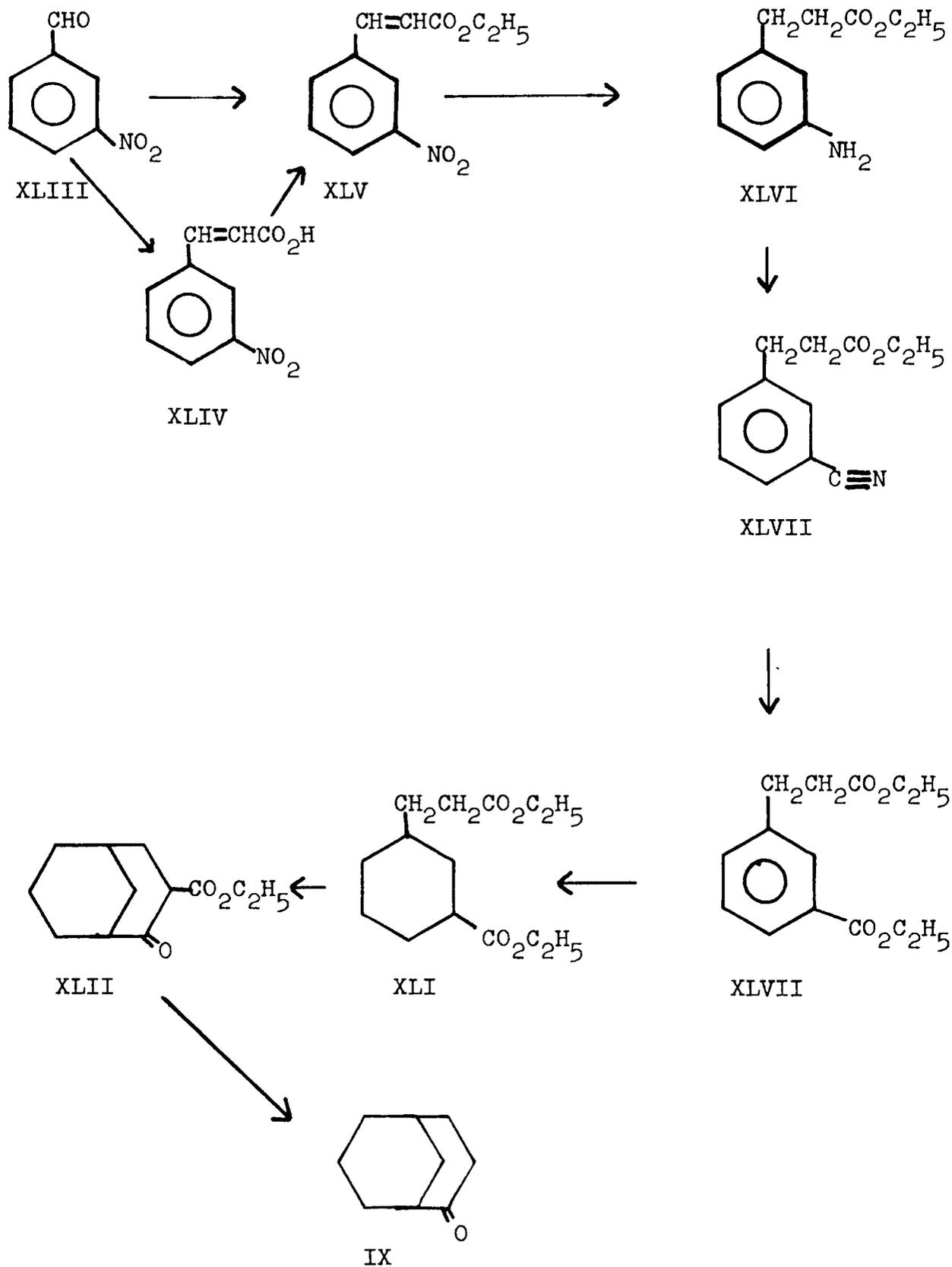


Figure 2 -- Synthesis of Bicyclo[3.3.1]nonan-2-one

The reduction of aromatic diester XLVIII to the corresponding cyclohexane derivative XLI was brought about without difficulty by low-pressure hydrogenation. Rhodium on powdered alumina proved to be an effective catalyst. Although only the cis-diaxial form of diester XLI could undergo a Dieckmann condensation, the fact that diester XLI was a mixture of cis and trans isomers was of no concern. The carbon atom in the cyclohexane ring to which the carbethoxy group was attached was expected to epimerize under the basic Dieckmann condensation conditions to give a predominance of the thermodynamically more stable cis isomer.

A cyclic high-dilution apparatus was employed for the Dieckmann condensation of ethyl β -(3-carbethoxycyclohexyl)propionate (XLI). Potassium t-butoxide served as base; xylene was the solvent. Hydrolysis and decarboxylation of the resultant β -ketoester (XLII) with a mixture of acetic acid, hydrochloric acid and water afforded the desired ketone (IX) in 34% yield based on the amount of XLI used. Preparation, crystallization, and hydrolysis of the semicarbazone gave very pure bicyclo[3.3.1]nonan-2-one (IX). This material was subjected to deuterium exchange in sodium deuterioxide-deuterium oxide solution under the conditions described

for bicyclo[3.2.1]octan-2-one (XI). The deuterated product had 18.60 atom % excess deuterium or 2.61 atoms of deuterium per molecule. An n.m.r. spectrum confirmed that exchange had taken place at the bridgehead position.

It may be concluded from this work that the bridgehead hydrogen in bicyclo[3.3.1]nonan-2-one (IX) is sufficiently acidic for deuterium exchange to occur at that position. In contrast, the corresponding hydrogen in bicyclo[3.2.1]octan-2-one (XI) is not acidic and therefore not subject to deuterium exchange. Since even a small contribution by enolate anion resonance form XIIIb might be expected to make exchange of the bridgehead hydrogen possible, it is apparent that no double bond character can exist between C_1 and C_2 in bicyclo[3.2.1]octan-2-one (XI). On the other hand, the ability of the nonanone (IX) to exchange at three positions indicates that some double bond character is permitted between C_1 and C_2 in that system. In other words, Bredt's rule is not violated in the case of bicyclo[3.2.1]octan-2-one (XI), whereas an infraction is indicated by the behavior of bicyclo[3.3.1]nonan-2-one (IX).

The importance of these conclusions to the work of Ferris and Miller^{7(b)} should be noted. The fact that deuterium exchange did not occur at the bridgehead

position of bicyclo[3.2.1]octan-2-one (XI) even under vigorous conditions would confirm their hypothesis that decarboxylation of a β -ketoacid can occur without the involvement of enol formation.

EXPERIMENTAL

General

Melting points were determined in capillary tubes with a Mel-Temp apparatus and are uncorrected.

Infrared spectra were determined on a Perkin-Elmer Infracord spectrophotometer calibrated against polystyrene. Nuclear magnetic resonance (n.m.r.) spectra were determined in carbon tetrachloride on a Varian Model A-60 (60 Mc.) instrument; tetramethylsilane was used as an external standard for all n.m.r. spectra.

Microanalyses were performed by C. F. Geiger of Ontario, California. Deuterium analyses were performed by Josef Nemeth of Urbana, Illinois.

High-pressure hydrogenations were done by Dr. James Berry and co-workers at the Agricultural Biochemistry High Pressure Laboratory of the University of Arizona.

Analytical vapor phase chromatography (v.p.c.) was carried out on a Model 609 F and M Flame Ionization chromatograph. An Aerograph Research instrument with a Varian recorder was used for preparative v.p.c. work. Relative peak areas were determined either by cutting

out the peaks and weighing them or by means of a Disc Integrator. The columns which were used are described below. The letter associated with each description is employed throughout the text to identify specific columns.

- A. 12' x 1/4" 20% Carbowax 20M on 30/60 Gas-chrom R at 180°.
- B. 10' x 1/4" 20% tri- β -(cyanoethoxy)-propane (TCEP) on 30/60 NAW Chromosorb P at 150°.
- C. 5' x 1/4" 20% Carbowax 20M on 50/60 fire-brick at 100°.
- D. 12' x 3/8" + 12' x 1/4" 20% Carbowax 20M on 30/60 Gas-chrom R at 195° and 30 p.s.i. of helium.

Synthesis and Deuteration of Bicyclo[3.2.1]octan-2-one

2-Cyanobicyclo[2.2.1]hept-5-ene

Dicyclopentadiene was heated until the monomer, cyclopentadiene, began to distill from it. The diene was distilled through a Vigreux column directly into a flask containing 532 g. (10.0 mole) of acrylonitrile and a few crystals of hydroquinone. Throughout the reaction, the contents of the receiver were cooled with

an ice bath and stirred by means of a magnetic bar. Distillation was continued until more than 662 g. (10.0 mole) of cyclopentadiene had been added. After the addition was complete, stirring was continued with cooling for two hours and at room temperature for an additional eighteen hours. The clear, colorless, liquid product was distilled under vacuum through a Vigreux column. The material which was collected had b.p. $79-88^{\circ}/12$ mm. (lit.^{9(b)} b.p. $84-89^{\circ}/13$ mm.). The yield was quantitative. A portion of the adduct resulting from a repetition of this preparation was distilled through a spinning-band column in order to separate the endo isomer from its exo counterpart. Analysis by v.p.c. on a Carbowax column (A) revealed that the fraction with b.p. $82-88^{\circ}/12$ mm. contained only 7-8% of the exo isomer. Re-distillation gave pure endo-2-cyanobicyclo[2.2.1]hept-5-ene (XXXIIa), which is a colorless, low-melting solid with b.p. $87-88^{\circ}/12$ mm. (lit.^{9(c)} b.p. $88.0^{\circ}/12$ mm.).

Catalytic Hydrogenation of 2-Cyanobicyclo [2.2.1] hept-5-ene

2-Cyanobicyclo[2.2.1]hept-5-ene (XXXIIa and b) (49.9 g.; 0.418 mole) was dissolved in 150 ml. of 95% ethanol and reduced at room temperature in a Parr hydrogenation apparatus. Palladium on charcoal (10%) served

as the catalyst; the initial tank pressure was 50 p.s.i. After one hour, hydrogen absorption had ceased. The catalyst was removed by gravity filtration, fresh catalyst was added, and hydrogenation was resumed for a short time in order to ensure complete reduction. The second portion of catalyst was removed by filtration and the ethanol was taken off by means of a solvent stripper. This procedure was repeated several times. The combined residues were distilled under vacuum through a spinning-band column. The product, which was obtained in an overall yield of 90%, is a colorless, low-melting solid with b.p. 84-87°/12 mm. (lit.^{9(b)} b.p. 97°/19 mm.).

2-Aminomethylbicyclo[2.2.1]heptane

Method A. A slurry of 22.8 g. (0.601 mole) of lithium aluminum hydride in 800 ml. of anhydrous diethyl ether was prepared in a dry flask. The contents of the vessel were cooled to 0° by means of an ice-salt bath and then stirred while 48.4 g. (0.400 mole) of 2-cyanobicyclo[2.2.1]heptane in 120 ml. of anhydrous ether was added dropwise. After the addition was complete, the reaction mixture was stirred vigorously at room temperature for three hours. The resultant complex and unreacted lithium aluminum hydride were decomposed by the cautious

addition of 40 ml. of ice water followed by 40 ml. of 50% sodium hydroxide. After an hour of vigorous stirring, an additional 30 ml. of water was added to complete the hydrolysis. The large, white granules which formed were removed by suction filtration and washed with several portions of ether. The ether washings were combined with the filtrate and the solvent was removed by means of a solvent stripper. The residue was distilled through a spinning-band column at reduced pressure. The amine (39.6 g.; 79.0%) was collected at 64-69°/12 mm. (lit.^{9(c)} b.p. 67-71°/12 mm.).

Method B. 2-Cyanobicyclo[2.2.1]hept-5-ene (XXXII a and b) (ca. 1200 g.; 10.0 mole) was dissolved in sufficient ammonia-saturated 100% ethanol to make a 30-40% (by volume) solution. This solution was divided into several portions and Raney nickel (W-2), which had been prepared according to the method of Mozingo,³³ was added to each. Hydrogenation of each portion was carried out in a high pressure bomb at 60° for twelve hours at approximately 2000 p.s.i. of hydrogen. The bulk of the catalyst was removed by filtration; a second filtration using Hyflo Super Cel was required. Ethanol was removed from the combined product solutions with a solvent stripper. Distillation through a spinning-band column

at aspirator-pump pressure afforded 1076 g. (8.6 mole; 86%) of the amine, which showed b.p. 88-89°/32-34 mm. The pure endo-2-cyanobicyclo[2.2.1]hept-5-ene (XXXIIa), obtained by fractional distillation of the Diels-Alder product, was also reduced in this manner.

Bicyclic Octanols by Demjanov Rearrangement

Method A. The procedure of Alder and Reubke^{9(d)} was employed. To 62.8 g. (0.502 mole) of a mixture of exo- and endo-2-aminomethylbicyclo[2.2.1]heptane (XIV a and b) was added with stirring 55 ml. of concentrated hydrochloric acid. Cooling with an ice bath was necessary. The amine hydrochloride thus formed was dissolved in 440 ml. of distilled water and the solution was heated to boiling. Sodium nitrite (43.3 g.; 0.629 mole) in 150 ml. of water was added cautiously with vigorous stirring. The addition of 40 ml. of glacial acetic acid followed. After nearly an hour of stirring, 75 ml. of 50% sodium hydroxide was added to make the reaction mixture strongly alkaline. Stirring and reflux were continued for three hours more. Exhaustive steam distillation was carried out by forcing steam from an external source through the reaction mixture. After the distillate was poured into 150 ml. of diethyl ether, sufficient

sodium chloride was added to saturate the aqueous layer. The layers were separated and the aqueous layer was extracted further with two 100 ml. portions of ether. The ether extracts were combined and dried over anhydrous magnesium sulfate. After removal of the drying agent by filtration, the solvent was taken off by distillation at atmospheric pressure through a short Vigreux column. The yield of crude product was 46.9 g. (74.4%). Several repetitions of this procedure gave yields ranging from 69 to 87%. After one sublimation at reduced pressure, the white, crystalline product had m.p. 168-172.5° (lit.^{9(b)} m.p. 183°). Analysis of the sublimed product by v.p.c. on a tri- β -(cyanoethoxy)-propane (TCEP) column (B), revealed that the product was a mixture of four components with long retention times and two minor components with short retention times (see Results and Discussion).

Method B. The procedure described by Youssef, Baum and Walborsky³¹ was followed. The amine hydrochloride was prepared by the addition of 50 g. of concentrated hydrochloric acid to cold endo-2-aminomethylbicyclo[2.2.1]-heptane (XIVa) (62.5 g.; 0.499 mole). The addition of 180 ml. of water and 60 ml. (1.0 mole) of glacial acetic acid followed. The mixture was cooled to 5°

by means of an ice-salt bath. This temperature was maintained and the mixture was stirred while a solution of sodium nitrite (69.0 g.; 1.00 mole) in 120 ml. of water was added dropwise over a period of four hours. Stirring was continued overnight at room temperature. Hydrolysis was presumably completed by heating the reaction mixture for 1.5 hours after the addition of 81 ml. of 50% sodium hydroxide. Steam distillation was carried out. It was observed that the organic portion of the distillate was a yellow liquid and not the expected white solid. The distillate was poured into 200 ml. of diethyl ether and sufficient sodium chloride was added to saturate the aqueous layer. After separation of the layers, the aqueous solution was extracted with 700 ml. of ether divided into seven or eight portions. The combined ether extracts were washed with cold, saturated, aqueous sodium bicarbonate and dried with anhydrous magnesium sulfate. Following collection of the drying agent by filtration, the solvent was taken off at aspirator-pump pressure on a rotary evaporator. The product, which was a yellow slurry, gave an infrared spectrum (in carbon tetrachloride) with a broad peak centered at 3400 cm.^{-1} and also absorption at 1600 , 1640 and 1740 cm.^{-1} These

findings might indicate that the yellow slurry consisted of alcohols, organic nitrites³⁴ and acetates.

The product mixture was refluxed for five hours in the presence of aqueous potassium hydroxide. This procedure resulted in a diminution of the peak at 1740 cm.^{-1} in the infrared spectrum, but did not affect the peaks at 1600 and 1640 cm.^{-1} . Liberation of the alcohol was finally achieved by treatment with lithium aluminum hydride, as suggested by the work of Soffer and co-workers.³⁵ To a slurry consisting of 23 g. (0.60 mole) of lithium aluminum hydride and 400 ml. of anhydrous diethyl ether was added a solution of the alcohol-nitrite mixture in 125 ml. of anhydrous ether. The hydride slurry was stirred and cooled throughout the addition. After the addition was complete, stirring was continued at room temperature for 24 hours. The mixture was cooled again with an ice bath and hydrolyzed by means of carefully added water (68.4 ml.) and 50% sodium hydroxide (22.8 g.). After two more hours of stirring, the white precipitate was removed by suction filtration and washed with several portions of diethyl ether. All ether solutions were combined, dried over anhydrous magnesium sulfate and freed of drying agent by filtration. Removal of the solvent at aspirator-pump pressure on a rotary evaporator

gave 41.4 g. (65.7%) of crystalline product. The infrared spectrum (in carbon tetrachloride) revealed the presence of only the alcohol, as expected. Analysis by v.p.c. on a TCEP column (B) showed the product to be composed of three compounds with long retention times and several minor components with short retention times (see Results and Discussion). After repeated crystallization from pentane, the product had m.p. 170-174° (sealed capillary) (lit.^{9(d)} m.p. 183°).

The p-nitrobenzoate derivatives were prepared by treating 7.0 g. (0.055 mole) of the crude alcohol mixture dissolved in 35 ml. of dry pyridine with 16.7 g. (0.0898 mole) of p-nitrobenzoyl chloride dissolved in 125 ml. of dry pyridine. Several crystallizations from either absolute ethanol or methanol, followed by one or more crystallizations from pentane, gave long, creamy-white needles which melted at 77.2-78.1° (lit.¹⁵ m.p. 80.0-80.4° for the derivative of endo-bicyclo[3.2.1]octan-2-ol). The yield of crude product was quantitative, but the recovery after purification was only 21-27%.

The alcohols were recovered by hydrolysis of the purified ester according to the procedure described by Youssef, Baum and Walborsky.³¹ The yield of alcohol was quantitative. Analysis by v.p.c. on a TCEP column (B)

revealed that the product was still a mixture of three components with long retention times. The components with short retention times were no longer present.

Acetylation of the Demjanov Rearrangement Product

After sublimation, the mixture of bicyclic octanols (10.0 g.; 0.0792 mole) obtained by Demjanov rearrangement of exo- and endo-2-aminomethylbicyclo [2.2.1]heptane (XIV a and b) was dissolved in 50 ml. of dry pyridine. The solution was cooled in an ice bath while 10 ml. (10 g.; 0.14 mole) of freshly distilled acetyl chloride was added dropwise with stirring. After addition was complete, the reaction mixture was stirred at room temperature for 3.5 hours and then poured into 40 ml. of cold water to dissolve the pyridinium hydrochloride which had precipitated. Extraction was effected with three 20 ml. portions of diethyl ether. The combined ethereal extracts were washed first with four small portions of 10% hydrochloric acid solution to remove the pyridine and then with 20 ml. of 15% potassium carbonate solution and 25 ml. of saturated sodium chloride solution. The ether solution was dried over anhydrous magnesium sulfate and filtered. The solvent was removed at aspirator-pump pressure and the product was distilled through a

spinning-band column under reduced pressure. The fraction with b.p. 75-79°/4-6 mm. (lit.³¹ b.p. 52-54°/2.5 mm. for endo-bicyclo[3.2.1]octyl-2-acetate) showed carbonyl absorption in the infrared at 1740 cm.⁻¹ (film). The weight of this fraction was 9.7 g. (73%).

Bicyclo [3.2.1] oct-2-ene

The mixture of acetates (104.8 g.; 0.624 mole) obtained by acetylation of the Demjanov rearrangement product was passed in a nitrogen atmosphere through a helix-packed glass tube encased by an oven maintained at a temperature of 450°. The esters were admitted into the tube from a pressure-equalizing addition funnel at the rate of one drop every six to ten seconds. The receiver was cooled in a Dry Ice-acetone bath. The product was poured into 150 ml. of pentane. The pentane solution was washed first with 25 ml. of cold water, then with three 40 ml. portions of cold, saturated sodium bicarbonate solution and finally with 40 ml. of cold, saturated sodium chloride solution. Anhydrous magnesium sulfate was employed as a drying agent. After removal of the solid by filtration, the pentane was taken off by distillation at atmospheric pressure. The olefinic product was distilled through a spinning-band column under reduced pressure. The

waxy, colorless, solid product had b.p. $71-72^{\circ}/80-85$ mm. (lit.^{9(b)} m.p. 133°); it melted at $51-52^{\circ}$ (sealed capillary) (lit.^{9(b)} m.p. 47°). The yield was 35.5 g. (52.6%). The product decolorized a solution of bromine in carbon tetrachloride and showed infrared absorption (in carbon tetrachloride) at 1640 cm.^{-1} . Analysis by v.p.c. on a Carbowax column (C) revealed the presence of only one compound, presumably bicyclo[3.2.1]oct-2-ene (XXXVI).

Distillation of the olefin left a sizable dark residue which bore the sweet odor of the acetates. Passing this material through the pyrolysis tube a second time gave an additional small quantity of olefin.

Epoxidation of Bicyclo[3.2.1]oct-2-ene

The procedure which was employed has been described by Sauers, How and Feilich.³⁰ Bicyclo[3.2.1]oct-2-ene (XXXVI) (4.0 g.; 0.037 mole) was dissolved in 35 ml. of chloroform and cooled to 0° in an ice-salt bath. This temperature was maintained while 13.5 ml. of 40% peracetic acid solution (Becco) in which 0.48 g. of anhydrous sodium acetate had been dissolved was added dropwise with stirring over a period of fifteen minutes. After the addition was complete, stirring was continued for two hours at 0° and

for four more hours at room temperature. The chloroform solution was then washed with three 20 ml. portions of cold 10% potassium hydroxide solution and with 20 ml. of cold water. The solution was dried over anhydrous magnesium sulfate. After separation of the drying agent by filtration, the solvent was removed at aspirator-pump pressure. The product was sublimed under reduced pressure with heat supplied by an oil bath held at 80°. The yield of epoxide (XXXVII) was 3.0 g. (65%). The white, crystalline product had m.p. 132-136° (lit.³⁰ m.p. 129-133; m.p. 136-138° after preparative v.p.c.) and gave an n.m.r. spectrum like that described by Sauers and co-workers.³⁰

exo-Bicyclo[3.2.1]octan-2-ol

The procedure of Sauers, How and Feilich³⁰ was employed. Into a cold, stirred slurry of 1.2 g. (0.030 mole) of lithium aluminum hydride in 20 ml. of anhydrous diethyl ether was introduced slowly a solution of 2.0 g. (0.016 mole) of the epoxide (XXXVII) of bicyclo[3.2.1]-oct-2-ene (XXXVI) in 7 ml. of anhydrous ether. This mixture was stirred at room temperature for 24.75 hours. Cold water (3.5 ml.) was added cautiously to decompose the complex which had formed. Stirring was continued

for 2.5 hours, by which time the solid in the reaction flask had become white. The precipitate was collected on a funnel and washed with ether. The washings were combined with the filtrate before anhydrous magnesium sulfate was added to dry the solution. After removal of the solid by filtration, the ether was taken off at aspirator-pump pressure. The residue was sublimed under reduced pressure from an oil bath maintained at ca. 90°. A white, crystalline solid weighing 1.5 g. (74%) was obtained. The product had m.p. 187.5-189° (lit.³⁰ m.p. 196.7-197.1°). The infrared and n.m.r. spectra confirmed that the product was the expected alcohol. However, analysis by v.p.c. on a TCEP column (B) revealed the presence of one major component and at least one minor component with long retention times (see Results and Discussion).

Bicyclo[3.2.1]octan-2-ol by Selenium Dioxide Oxidation

Route

A solution of 4.0 g. (0.037 mole) of bicyclo-[3.2.1]oct-2-ene (XXXVI) in 45 ml. of acetic anhydride was added at a moderate rate to a stirred slurry of 4.4 g. (0.040 mole) of selenium dioxide in 10 ml. of acetic anhydride. When the addition was complete, the

mixture was heated with an oil bath until the temperature of the contents of the reaction vessel exceeded 120° . After the temperature began to decrease spontaneously, stirring and heating at $100-110^{\circ}$ were continued for an additional 22.5 hours. The mixture was cooled to room temperature and filtered in order to remove the dark metallic selenium which had formed. The filtrate was poured with stirring into 100 ml. of water; this mixture was allowed to stand at room temperature for several hours. Subsequently, exhaustive steam distillation was carried out. The distillate, which had the unpleasant odor characteristic of many selenium compounds, was poured into 75 ml. of pentane. Sufficient sodium chloride was added to saturate the aqueous layer and the layers were separated. Further extraction was done with three 50 ml. portions of pentane. The combined pentane extracts were washed twice with 50 ml. portions of saturated sodium bicarbonate solution and once with 40 ml. of saturated sodium chloride solution. The pentane solution was dried over anhydrous magnesium sulfate and filtered.

The pentane solution was stirred and refluxed in the presence of freshly prepared Raney nickel (W-2) for seven hours. The highly pyrophoric nickel was

removed by gravity filtration and the pentane solution was again dried with anhydrous magnesium sulfate. After removal of the drying agent by filtration, the solvent was taken off by distillation at atmospheric pressure. The product no longer had a disagreeable odor. Its weight was 3.6 g. (57%). An infrared spectrum (in carbon tetrachloride) showed the expected carbonyl absorption at 1745 cm.^{-1} arising from the acetate grouping, but gave no evidence of a carbon-carbon double bond. Apparently, the treatment with Raney nickel had reduced the double bond, although no hydrogen gas was supplied during the reflux.

The product, which presumably was the saturated acetate, was dissolved in 25 ml. of 95% ethanol. This mixture was added to a solution of 11.2 g. of potassium hydroxide in 30 ml. of water, and the resultant was heated to the boiling point. After eighteen hours of stirring and reflux, the reaction mixture was cooled to room temperature and poured into 50 ml. of pentane. The layers were separated. The aqueous layer was extracted with two more 50 ml. portions of pentane. The combined pentane extracts were dried over anhydrous magnesium sulfate. After collection of the drying agent by filtration, the solvent was removed at aspirator-pump pressure. The product was sublimed at reduced pressure with heat supplied

by an oil bath maintained at 60°. Only a minute quantity of material was obtained.

The material which was the first to sublime had m.p. 117-129° and gave an infrared spectrum (in carbon tetrachloride) characteristic of a hydrocarbon. A short retention time was demonstrated when the material was subjected to v.p.c. analysis on a TCEP column (B). It is reasonable that this material was chiefly bicyclo-[3.2.1]octane (lit.³⁶ m.p. 139.5-141°), which could have arisen from reduction of unoxidized starting olefin.

Continuation of the sublimation procedure yielded material which showed a broad peak centered at 3400 cm.⁻¹ in its infrared spectrum (in carbon tetrachloride). Analysis by v.p.c. on a TCEP column (B) revealed the presence of at least two components, both of which had retention times which corresponded to the retention times of the compounds obtained directly from the Demjanov rearrangement. Presumably this material was principally the desired endo- and exo-bicyclo[3.2.1]-octan-2-ol (XXXIII a and b), although it showed m.p. 125-137° (lit.³¹ m.p. 182-183° for the endo alcohol).

Bicyclo[3.2.1]octan-2-one

The procedure described by Youssef, Baum, and Walborsky³¹ was followed. The product (41.4 g.; 0.328 mole) obtained from the Demjanov rearrangement of endo-2-aminomethylbicyclo[2.2.1]heptane (XIVa) was dissolved in 112 ml. of glacial acetic acid. After this mixture had been cooled to 0° by means of an ice water bath, a solution of 25.8 g. (0.258 mole) of chromium trioxide in 125 ml. of glacial acetic acid and 15.8 ml. of water was added dropwise. The mixture was stirred for 24 hours at room temperature after all the oxidant had been added. Subsequently, the mixture was stirred for one hour at the temperature of a hot water bath. The mixture was cooled, poured into water, and extracted with 100 ml. portions of pentane until a 2,4-dinitrophenylhydrazone could not be formed from two consecutive extracts. The combined extracts were neutralized with solid sodium carbonate and dried with anhydrous magnesium sulfate. The solid materials were removed by filtration and the solvent was taken off at reduced pressure on a rotary evaporator. The yield was 32 g. (80%). Analysis of the crude ketonic product by v.p.c. on a Carbowax column (A) revealed the presence of several minor components with short retention

times. The one major fraction (see Results and Discussion) was collected (Column D). The white, crystalline product thus obtained had m.p. 119.0-123.5° (lit.³¹ m.p. 127-129°) and showed strong carbonyl absorption at 1730 cm.⁻¹ in the infrared (in carbon tetrachloride).

In order to obtain samples for comparative v.p.c. studies, this oxidation procedure was repeated on a portion of the alcohols obtained from the Demjanov rearrangement of the mixture of exo- and endo-2-aminomethylbicyclo[2.2.1]heptane (XIV a and b) and on a portion of the alcohols obtained by reduction of the epoxide (XXXVII) of bicyclo[3.2.1]oct-2-ene (XXXVI).

Deuteration of Bicyclo[3.2.1]octan-2-one

Method A. In a thick-walled glass tube was placed 0.500 g. (0.00402 mole) of the ketone obtained by preparative v.p.c., 0.031 g. (0.000457 mole) of sodium ethoxide, 5.0 ml. of 99.5% deuterium oxide and 2.0 ml. of ethanol-d (prepared by treating ethyl orthoformate with deuterium oxide). The tube was sealed carefully and heated at 100° for one week. The tube and its contents were first cooled to room temperature and then placed in a Dry Ice-acetone slush before the tube was opened. The contents of the tube were poured into 100 ml. of cold pentane. The

solution was washed with two 25 ml. portions of ice water and dried over anhydrous magnesium sulfate. After separation of the drying agent by filtration, the solvent was removed by distillation at atmospheric pressure through a short Vigreux column. When almost all the pentane had been removed, the residue was transferred to a Metroware sublimation apparatus and sublimed at aspirator-pump pressure with heat supplied by an oil bath maintained at 90° . The product had 16.15 atom % excess deuterium or 1.94 atoms of deuterium per molecule. A second sample, heated at 100° for 18 days, had 16.30 atom % excess deuterium or 1.96 atoms of deuterium per molecule. Whereas the n.m.r. spectrum of the non-deuterated ketone showed a broad peak centered at 7.9τ , there was no peak in this region in the spectrum of the deuterated ketone.

Method B. In a thick-walled glass tube was placed 0.502 g. (0.00404 mole) of the ketone obtained by preparative v.p.c. and 10 ml. of a 0.01 N solution of sodium deuterioxide in 99.5% deuterium oxide. The tube was sealed and heated at 225° in an oven for 48 hours. The deuterated ketone was isolated in a manner identical to that described for Method A. The product had 16.50 atom % excess deuterium or 1.98 atoms of deuterium per molecule.

Synthesis and Deuteration of Bicyclo[3.3.1]nonan-2-one

m-Nitrocinnamic Acid

A solution of 15.1 g. (0.100 mole) of m-nitrobenzaldehyde (XLIII) in 50 ml. of dry pyridine and 0.5 ml. of piperidine was heated to 80° by means of a hot water bath. To this solution was added with stirring 13.5 g. (0.128 mole) of malonic acid dissolved in 50 ml. of dry pyridine. After the addition was complete, stirring was continued at 85-95° for five hours. The reaction mixture was cooled to room temperature and poured in 100 ml. of water. Concentrated hydrochloric acid was added until the mixture became slightly acidic. The precipitate was collected by suction filtration and washed with dilute hydrochloric acid solution. After the precipitate had been transferred to a beaker, sufficient saturated sodium bicarbonate solution was added to dissolve the solid. The basic solution was filtered in order to remove any remaining solids, such as unreacted m-nitrobenzaldehyde. The filtrate was acidified with concentrated hydrochloric acid in order to precipitate the desired product. The resultant mixture was cooled in an ice bath and filtered with suction. The filter cake was washed with water and

then dried over calcium chloride in a vacuum desiccator. The cream-colored product (XLIV) weighed 16.9 g. (86.0%) and had m.p. 204-205° (lit.³⁷ m.p. 201°).

Ethyl *m*-Nitrocinnamate

A slurry of *m*-nitrocinnamic acid (XLIV) (64.0 g.; 0.331 mole) in 500 ml. of benzene and 250 ml. of 100% ethanol was treated with 25 ml. of concentrated sulfuric acid. The mixture was stirred and heated to reflux. After these conditions had been maintained for five hours, 300 ml. of solvent was removed by distillation. The residue was cooled slightly and poured into ice water. After neutralization of the mixture was achieved with sodium bicarbonate, the layers were separated. The aqueous layer was extracted with several portions of diethyl ether. The ether extracts were combined with the benzene solution and the resultant mixture was dried over anhydrous magnesium sulfate. After removal of the drying agent by filtration, the solvent was taken off by means of a solvent stripper. After a single crystallization from 100% ethanol, the product (XLV) melted at 72.0-73.5° (lit.³⁸ m.p. 78-79°). The yield was 56.7 g. (77.3%).

Ethyl Hydrogen Malonate

A modification of the procedure described by Strube³⁹ was employed. To a stirred solution of 20 g. (0.12 mole) of diethyl malonate in 80 ml. of absolute ethanol was added a solution of 7.0 g. of potassium hydroxide in 80 ml. of absolute ethanol. The rate of addition was such that one-half hour was required to complete the procedure. Stirring was continued at room temperature for two more hours. Then the mixture was allowed to stand undisturbed overnight. The white platelets which had formed were dissolved by heating the mixture to reflux. The hot solution was immediately filtered with the aid of suction through an oven-warmed funnel. A small amount of an unidentified solid was collected on the funnel. The filtrate was cooled in an ice water bath to facilitate reprecipitation of the desired potassium ethyl malonate. The shiny platelets were recovered by suction filtration and washed with a small amount of absolute diethyl ether. Concentration of the mother liquor yielded an additional crop of crystals. The combined crops were dried in a vacuum desiccator. The yield was 16.9 g. (83%).

A solution of 16.9 g. of potassium ethyl malonate in 10.6 ml. of water was cooled to 5° with an ice water bath.

Concentrated hydrochloric acid (8.5 ml.) was added at such a rate that the temperature of the reaction mixture did not exceed 10° . After the addition was complete, the potassium chloride which had precipitated was removed by suction filtration. The filter cake was washed with 20 ml. of diethyl ether. The filtrate was extracted with four 20 ml. portions of ether; these extracts were combined with the ether used to wash the filter cake. Anhydrous magnesium sulfate was utilized as a drying agent. After removal of the solid by filtration, the solvent was taken off at reduced pressure. This procedure afforded 12.6 g. (96%) of ethyl hydrogen malonate, which was used immediately without further purification or characterization.

Condensation of Ethyl Hydrogen Malonate with *m*-Nitrobenzaldehyde

A modification of the procedure described by Galat⁴⁰ was employed. Ethyl hydrogen malonate (11 g.; 0.084 mole), *m*-nitrobenzaldehyde (XLIII) (8.5 g.; 0.056 mole), 28 ml. of dry pyridine and 0.7 ml. of piperidine were combined in a dry flask. For six hours, this mixture was stirred and heated by means of a bath maintained at $80-90^{\circ}$. Subsequently the solution was cooled to room

temperature and filtered with suction in order to remove some unidentified solid material. A portion of the solvent was removed at reduced pressure on a rotary evaporator. Crystals formed readily when the concentrated solution was cooled in an ice water bath. The product was collected by suction filtration. Further concentration of the mother liquor yielded additional crops of crystals. A single crystallization from 100% ethanol, followed by drying over calcium chloride in a vacuum desiccator, gave long, yellow needles with m.p. 69-71.5° (lit.³⁸ m.p. 78-79°). Additional crystallizations from ethanol afforded almost white crystals which had m.p. 72-72.9°. The yield of product, ethyl m-nitrocinnamate (XLV), was 10 g. (82%).

Catalytic Reduction of Ethyl m-Nitrocinnamate

Ethyl m-nitrocinnamate (XLV) (716 g.; 3.24 mole) was dissolved in 3 ml. of 100% ethanol and the catalyst, 5% rhodium on charcoal, was added. Hydrogenation was carried out in a high-pressure bomb for 24 hours at pressures ranging from 200 to 500 p.s.i. of hydrogen. Hydrogen absorption occurred quite readily and the temperature rose spontaneously to 50-60°. The catalyst was removed by gravity filtration. Decolorizing carbon was

added and the mixture was subjected to suction filtration with the aid of Hyflo Super Cel. The solvent was removed at aspirator-pump pressure on a rotary evaporator. The yield of crude product was 622 g. (99.5%). An attempt to distill a portion of the product through a spinning-band column at reduced pressure was only moderately successful because the product, ethyl m-aminohydrocinnamate (XLVI), tended to polymerize when heated. However, distillation did afford some of the desired product, which had b.p. 128-130°/1 mm. and $n_D^{21.5}$ 1.5350. An infrared spectrum (film) showed a cluster of peaks centered at 3400 cm.^{-1} , carbonyl absorption at 1735 cm.^{-1} , and a broad peak centered at 1610 cm.^{-1} . An n.m.r. spectrum displayed a complex multiplet centered at 3.3 τ (4 protons), a quartet centered at 6.0 τ (2 protons), a broad singlet at 6.4 τ (2 protons), a complex multiplet centered at 7.4 τ (4 protons), and a triplet centered at 8.9 τ (3 protons).

Anal. Calcd. for $\text{C}_{11}\text{H}_{15}\text{NO}_2$: C, 68.37; H, 7.83; N, 7.25. Found: C, 67.97; H, 7.77; N, 7.57.

Also collected was a small fraction which had b.p. 100-110°/1 mm. The infrared and n.m.r. spectra of this fraction indicated that it was composed principally of ethyl β -(3-aminocyclohexyl)propionate.

Ethyl m-Cyanohydrocinnamate

The method of Marvel and McElvain,⁴¹ with modifications, was employed in the preparation of cuprous cyanide. A mixture of cupric sulfate (78.0 g.; 0.351 mole) and 250 ml. of water was stirred and heated by means of a heating mantle until the solution was hot, but not boiling. Stirring and heating were maintained while a solution of 16.5 g. (0.158 mole) of sodium bisulfite and 11.0 g. (0.275 mole) of sodium hydroxide in 125 ml. of water was added at a moderate rate. After the mixture had been cooled to room temperature, the liquid was decanted, leaving solid cuprous chloride in the flask. The white precipitate was washed several times by suspension in water and subsequent decantation of the liquid after the solid had settled. Finally the cuprous chloride was suspended in 125 ml. of water while 40.5 g. (0.826 mole) of sodium cyanide in 75 ml. of water was added. The flask and its contents were cooled in an ice bath during this addition. The clear, colorless solution of cuprous cyanide was stored in a refrigerator until needed. This reagent was found to be satisfactory after as long as six days of storage.

The Sandmeyer reaction was conducted in a manner similar to that described by Clarke and Read.⁴² Ethyl m-aminohydrocinnamate (XLVI) (50.0 g.; 0.259 mole) was cooled in an ice bath and stirred while 62.5 ml. of concentrated hydrochloric acid and sufficient cracked ice to keep the temperature between 0 and 5° were added concomitantly. Diazotization was effected when a solution of 19.0 g. (0.275 mole) of sodium nitrite in 50 ml. of water was added rapidly with stirring. Cracked ice was supplied as needed. The resultant mixture gave a positive starch iodide test. Neutralization was achieved by the rapid addition of dry sodium bicarbonate. The color of the solution changed from yellow to green when neutrality was reached. The cold, neutral diazonium salt solution was added immediately and rapidly to a 3-l., round-bottomed flask which contained a vigorously stirred mixture of the cuprous cyanide solution and 65 ml. of toluene. Cracked ice was added as required in order to keep the temperature of the reaction mixture below 5°. After about one-third of the diazonium salt solution had been added, an orange-brown complex formed and nitrogen gas was given off. After the addition was complete, stirring was continued at 0° for one-half hour and then at room temperature for five or six hours. Finally, stirring was stopped and the

mixture was heated to 50-60° by means of a hot water bath. The heat source was removed and the mixture was allowed to stand overnight. After the aqueous layer had been siphoned off, it was extracted with two or three 100 ml. portions of benzene. The benzene extracts were combined with the toluene solution before anhydrous magnesium sulfate was added. The drying agent was removed by filtration and the solvents were taken off on a rotary evaporator.

Doubling the quantities used in this preparation led to a decrease in yield. Therefore, it was necessary to repeat this procedure several times on the scale described in order to obtain the desired quantity of product. The combined residues were distilled under reduced pressure through a spinning-band column. The clear, nearly colorless, liquid product (XLVII) which was obtained in an overall yield of 51.6%, had b.p. 133-136°/1.5 mm. and n_D^{21} 1.5129. An infrared spectrum (film) revealed nitrile absorption at 2240 cm.^{-1} and strong carbonyl absorption at 1740 cm.^{-1} . An n.m.r. spectrum showed a multiplet centered at 2.7 τ (4 protons), a quartet centered at 6.1 τ (2 protons), a complex multiplet centered at 7.4 τ (4 protons) and a triplet centered at 8.9 τ (3 protons).

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.95; H, 6.45; N, 6.90. Found: C, 71.30; H, 6.64; N, 6.90.

A sizable fraction with b.p. $74^{\circ}/0.6$ mm. was also obtained from this reaction. This material was identified as ethyl hydrocinnamate.

Ethyl *m*-Carbethoxyhydrocinnamate

A modification of the procedure of Adams and Thal⁴³ was used. To a solution of ethyl *m*-cyanohydrocinnamate (XLVII) (36.0 g.; 0.177 mole) in 42.3 ml. of 95% ethanol was added 18.8 ml. of concentrated sulfuric acid. This mixture was heated to reflux with an oil bath and stirred at that temperature for twenty hours. When the reaction mixture was cooled to room temperature, solid ammonium sulfate formed. The liquid layer was decanted into 50 ml. of water in a separatory funnel. Benzene (ca. 125 ml.), after having been used to wash the solid residue, was also poured into the separatory funnel. The water layer was drawn off. The organic material was washed again with a 25 ml. portion of water and then transferred to a round-bottomed flask. Absolute ethanol (50 ml.) and 2.5 ml. of concentrated sulfuric acid were added. This mixture was stirred and heated to reflux. After three hours at reflux, about 150 ml.

of solvent was removed by distillation. No water was detected in the distillate. This procedure was carried out in order to ensure complete esterification. The concentrated mixture was cooled in ice and then washed with three 25 ml. portions of cold, saturated sodium bicarbonate solution and one 25 ml. portion of saturated sodium chloride solution. Filtration through a cone of anhydrous sodium sulfate served to dry the solution. The remaining solvent was removed by distillation at atmospheric pressure through a short Vigreux column. The product (XLVIII), obtained in 77.8% yield, was subjected to simple distillation and showed b.p. 150-155°/2 mm. (lit.²⁷ b.p. 170°/4.5 mm.).

Catalytic Reduction of Ethyl *m*-Carbethoxyhydrocinnamate

A solution of ethyl *m*-carbethoxyhydrocinnamate (XLVIII) (142 g.; 0.568 mole) in approximately 1 l. of 100% ethanol was divided into five nearly equal portions. Hydrogenation of each portion was carried out in a Parr apparatus with approximately 3 g. of 5% rhodium on alumina serving as catalyst. The initial hydrogen pressure was 60 p.s.i.; heat was supplied by a lamp. After twelve hours, the catalyst was removed by filtration and the solvent was taken off on a rotary evaporator at

reduced pressure. After recombination of the five portions, the product, ethyl β -(3-carbethoxycyclohexyl)propionate (XLI), was distilled at reduced pressure through a spinning-band column. The clear, colorless, liquid product had b.p. 123-124.5°/1 mm. (lit.²⁷ b.p. 135°/ 1.5 mm.) and weighed 122 g. (84%).

Bicyclo[3.3.1]nonan-2-one

A carefully dried, 2-l. Morton flask fitted with a cyclic high-dilution apparatus and a high-speed stirrer was flushed with dry nitrogen. A nitrogen atmosphere was maintained throughout the procedure. Approximately 700 ml. of dry xylene was placed in the flask and then 70 ml. of it was removed by distillation in order to ensure dryness. The contents of the flask were cooled slightly while 13.3 g. (0.340 mole) of freshly cut potassium and 87.5 ml. (0.647 mole) of dry t-butyl alcohol were added with stirring. Excess alcohol was removed by distillation. Reflux and stirring were continued while the addition of 35 g. (0.14 mole) of ethyl β -(3-carbethoxycyclohexyl)propionate (XLI) in 100 ml. of dry xylene from a Hershberg funnel was carried out at the rate of 2-4 drops per minute. Reflux was terminated

three hours after the addition of diester was complete. When the reaction mixture had cooled to room temperature, 22 ml. of glacial acetic acid was added slowly. The acidified mixture was stirred for several hours. Nitrogen flow was discontinued and sufficient water was added to dissolve the potassium acetate which had formed. The aqueous layer was separated and extracted with three 100 ml. portions of xylene. The combined xylene extracts were washed with water and sodium bicarbonate solution, dried and filtered. The solvent was removed by distillation at aspirator-pump pressure. To the residue was added ten times its volume of a mixture which consisted of 5.0 parts of glacial acetic acid, 1.15 parts of concentrated hydrochloric acid and 1.5 parts of water. After 22 hours of reflux and stirring, the reaction mixture was cooled to room temperature, saturated with solid ammonium sulfate and extracted exhaustively with diethyl ether. The combined extracts were washed with saturated sodium bicarbonate solution until neutrality was achieved. The ether solution was dried over anhydrous magnesium sulfate and filtered. The solvent was removed by distillation at atmospheric pressure through a short Vigreux column. Sublimation of the residue gave 6.5 g. (34%) of the ketone (IX), which melted at 124-133.5° (lit.^{7(a)};²² m.p. 135-137°, 150°).

The semicarbazone, m.p. 183.5-184.5° (lit.²² m.p. 180-181°), was prepared. Pure ketone, m.p. 134-136.5°, was obtained after hydrolysis of the semicarbazone by steam distillation from oxalic acid solution.

Anal. Calcd. for C₉H₁₄O: C, 78.21; H, 10.21.
Found: C, 78.05; H, 10.40.

Pure β -ketoester (XLII) which had b.p. 109-112.5°/2.5 mm. and $n_D^{25.5}$ 1.5045, could be obtained by distillation of the condensation product. The product showed infrared absorption (film) at 1605, 1650 and 1710 cm.⁻¹ An n.m.r. spectrum revealed a peak at -2 τ corresponding to the enol proton.

Anal. Calcd. for C₁₂H₁₈O₃: C, 68.54; H, 8.63.
Found: C, 68.66; H, 8.78.

Deuteration of Bicyclo[3.3.1]nonan-2-one

In a thick-walled glass tube was placed 0.258 g. (0.00187 mole) of bicyclo[3.3.1]nonan-2-one (IX) and 10 ml. of a 0.01 N solution of sodium deuterioxide in 99.5% deuterium oxide. The tube was sealed and heated at 225° in an oven for 48 hours. The deuterated ketone was isolated in a manner identical to that described for deuterated bicyclo[3.2.1]octan-2-one. The product had 18.60 atom % excess deuterium or 2.61 atoms of deuterium

per molecule. A comparison of the n.m.r. spectra of the deuterated and non-deuterated ketones showed that exchange had occurred at the positions adjacent to the carbonyl group.

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