

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF MICHIGAN, ANN ARBOR, MICHIGAN]

 β -Bromo Acids. I. Stereochemistry and Mechanism of the Hydrobromination of α,β -Unsaturated Cyclohexenecarboxylic Acids^{1,2}BY WYMAN R. VAUGHAN AND RONALD CAPLE³

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Cyclohexene-1-carboxylic acid (I), *trans*-1,4,5,6,7,8,9,10-octahydronaphthalene-2-carboxylic acid (II) (*trans*- Δ^2 -octalin-2-carboxylic acid), and bicyclo[3.2.1]oct-2-ene-2-carboxylic acid (III) have been hydrobrominated under various polar conditions. The initial product in each case is kinetically controlled. The data are interpreted as support for a multistep process in which carbon-bromine bond formation is rate determining and subsequent "ketonization" of the resultant "acid-enol" is structure determining. Isomerization of the initially kinetically controlled product to a thermodynamically more favorable configuration may occur by facile reversal of the last step, and in the cases of II and III the initially formed *axial* carbon-bromine bond may be replaced by the thermodynamically more favorable *equatorial* carbon-bromine bond. Structural assignments in the hydrobromides of the unsaturated acids are made on the basis of n.m.r. spectra. Comparison with the two hydrobromides of cyclohexene-1-carboxylic acid, of previously determined configurations, provides unequivocal reference data.

Previous work in this laboratory^{4,5} has strongly suggested that the addition of hydrogen halides to α,β -unsaturated acids is a kinetically controlled process which may be followed by a slower, thermodynamically controlled epimerization at the α -carbon. In the case of *cis*-2-bromocyclohexanecarboxylic acid (Ia) it was shown that bromide ion added to a glacial acetic acid solution failed to epimerize Ia,⁵ and in other cases halide ion induced epimerization was ruled out on steric grounds.^{4,5} Thus the most obvious course for epimerization is *via* the acid-enol, as has been suggested.^{4,5}

However, the true nature of the hydrobromination process remains in doubt. Thus Gould⁶ suggests π -complex formation at the ethylenic bond to account for the predominantly *trans*-hydrohalogenation,⁵ whereas Dewar⁷ has suggested recently that 1,4-addition to the conjugated system of the unsaturated acids is more reasonable. With this we concur, and testing of this hypothesis was one of the original purposes of the present research.

The observations that tiglic and angelic acids (*cis*- and *trans*-2,3-dimethylacrylic acids, respectively) give the same hydrobromide⁸ but different hydriodides^{9,10} suggested to us that rate control, and possibly structure also, might be a function of carbon-halogen bond formation involving a resonance-stabilized carbonium ion previously generated by protonation of the unsaturated acids on the doubly bound oxygen. Thus the structure of the resultant halo acid would be the result of competition between stereoselective "ketonization" of the consequent "acid-enol" and rotation about the C $^{\alpha}$ -C $^{\beta}$ bond, followed by stereoselective ketonization of the new conformer, in effect as suggested by Dewar.⁷ Rotation about the same bond in

the carbonium ion is not entirely ruled out but seems less probable in view of the π -character in this bond. Since this phase of the problem is essentially independent of the mechanism of hydrohalogenation and is the object of another study currently in progress in this laboratory, we have confined the present study to cyclic systems in which any rotation about the C $^{\alpha}$ -C $^{\beta}$ bond is inhibited.

In addition to cyclohexene-1-carboxylic acid (I), two additional α,β -unsaturated acids were selected as substrates for hydrobromination: *trans*-1,4,5,6,7,8,9,10-octahydronaphthalene-2-carboxylic acid (II, *trans*- Δ^2 -octalin-2-carboxylic acid), and bicyclo[3.2.1]oct-2-ene-2-carboxylic acid (III). The steric requirements of I and II for *trans*-hydrobromination are essentially the same, regardless of the direction of attack, but those of III are strikingly different, and in both II and III the rigidity of the fused ring systems is such as to enable determination of initial configurations of the hydrobromides. For although the stereochemistry of hydrobromination of the α,β -unsaturated cyclohexenecarboxylic acid system has been shown to be *trans*, neither the kinetics of addition nor its precise geometry have been examined, and the choice of II should permit direct comparison with I while the choice of III should permit examination of steric effects not present in the simpler system; *e.g.*, the ethano bridge should inhibit approach from one side of the cyclohexene ring system more than do the two *axial* hydrogen atoms in the corresponding positions in I and II.

Both I and II were known compounds, but III was not; and in the course of developing a practicable synthesis for III, a modification of conditions for the cyanohydrin synthesis of α,β -unsaturated acids was devised and applied to the preparation of II from *trans*-2-decalone. The synthesis of bicyclo[3.2.1]octan-2-one (IV) was carried out according to reported procedures, and its conversion to III is described below.

The usual methods of cyanohydrin formation failed with IV, and the method finally adopted proved to be generally applicable, as shown both by its application to the preparation of II and by almost quantitative conversion of cyclohexanone to cyclohexanone cyanohydrin in appreciably less time than required by the conventional bisulfite method. Details are given in the Experimental.

The cyanohydrin of IV (V) was not stable but

(1) Presented before the Division of Organic Chemistry, 146th National Meeting of the American Chemical Society, Denver, Colo., Jan. 19-24, 1964.

(2) Abstracted from the Ph.D. Dissertation of R. Caple, The University of Michigan, 1964.

(3) National Science Foundation Cooperative Fellow, 1962-1964.

(4) W. R. Vaughan and K. M. Milton, *J. Am. Chem. Soc.*, **74**, 5623 (1952).

(5) W. R. Vaughan, R. L. Craven, R. Q. Little, Jr., and A. C. Schoenthaler, *ibid.*, **77**, 1594 (1955).

(6) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1959, pp. 519-520.

(7) M. J. S. Dewar and R. C. Fahey, *J. Am. Chem. Soc.*, **85**, 2245, 2248 (1963).

(8) R. Fittig and A. Pugenstrecker, *Ann.*, **195**, 108 (1879).

(9) J. Wislicenus and H. P. Talbot, *ibid.*, **313**, 228 (1900).

(10) W. G. Young, R. T. Dillon, and H. J. Lucas, *J. Am. Chem. Soc.*, **51**, 2528 (1929).

readily decomposed into IV; however, this provided the useful information that the rather drastic acidic conditions used in its preparation did not induce rearrangement. The acetate of V (VI) served both for its isolation and identification, as well as for its conversion to bicyclo[3.2.1]oct-2-ene-2-carbonitrile (VII). The absence of a proton signal downfield from the methylene and methine envelope of signals in the n.m.r. spectrum of VI provides conclusive evidence that VI possesses no secondary acetoxy substituent, thus confirming the absence of rearrangement.

Pyrolysis of VI at 450° affords VII, and, while elimination is not complete at this temperature, higher temperatures afford increasing amounts of benzonitrile. Unaltered VI can be recovered and recycled, and the resultant VII shows but one vinyl proton in its n.m.r. spectrum (422 c.p.s.¹¹), along with approximately three allylic protons (180–130 c.p.s.). Analysis by gas-liquid phase (v.p.c.) chromatography indicates that VI is a single substance, and the infrared spectrum of VI possesses a strong nitrile band at 2280 cm.⁻¹ and a strong conjugated ethylenic band at 1635 cm.⁻¹.

Before adoption of the pyrolysis of VI as the method of preparation of VII a number of attempts were made to dehydrate V, and useful information was obtained by application of the conventional thionyl chloride-pyridine procedure. Distillation of the product of such dehydration afforded two fractions in about equal quantities, each of which was shown by v.p.c. analysis to consist of two components. The lower boiling fraction comprised VII and the isomeric bicyclo[2.2.2]octene-1-carbonitrile (VIII), while the higher boiling fraction consisted of two isomeric chloro nitriles, 2-chlorobicyclo[3.2.1]octane-2-carbonitrile (IX) and 2-chlorobicyclo[2.2.2]octane-1-carbonitrile (X). The infrared spectrum of X lacks absorption for an ethylenic system, and its n.m.r. spectrum has a signal at 258 c.p.s.¹¹ attributable to a proton attached to a chlorine-bearing carbon atom, but no signal for a proton α to nitrile. The alternative 2-equatorial-chlorobicyclo[3.2.1]octane-1-carbonitrile structure may be ruled out by the results of basic hydrolysis which afforded only III and bicyclo[2.2.2]octene-1-carboxylic acid¹² (XI), identified by comparison with an authentic sample (v.p.c. of methyl ester, XI').

The ratio III:XI was 3:7, whereas that of IX:X was 1:9 (v.p.c. analysis, methyl esters of III and XI prepared by diazomethane treatment). This change in composition may be attributed to incomplete dehydrochlorination of X, presumably attributable to less favorable structural and electronic characteristics. The methyl ester of XI (XI') is ultraviolet inactive, and its n.m.r. spectrum shows two vinyl protons (375 and 338 c.p.s.¹¹). Thus the major chloro nitrile is indeed X and not the alternative [3.2.1] isomer.

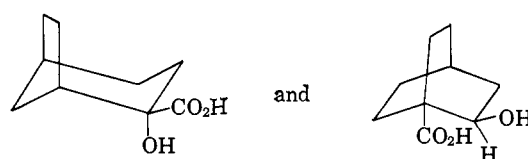
The ratio of unsaturated nitriles VII and VIII (9:1) is unchanged by acid-catalyzed methanolysis to give the methyl esters of III and XI (III' and XI'). Since v.p.c. analysis does indeed permit resolution of the isomeric III' and XI', the purity of III prepared by the acetate pyrolysis route can be established, as can the purity of its precursor VII, since the pres-

ence of its isomer VIII can similarly be established, and since no isomeric contaminant in III can be tolerated in a study of the present type, it is essential that a check on its purity be possible.

Conversion of VII, prepared by acetate pyrolysis, to III' was accomplished by acid-catalyzed methanolysis without demonstrable isomerization, and the infrared spectrum of III' possesses bands characteristic of an α,β -unsaturated ester at 1725 and 1650 cm.⁻¹ while its ultraviolet spectrum possesses λ_{\max} 228 m μ (ϵ 7730). The n.m.r. spectrum likewise is in agreement with the assigned structure: one vinyl proton (412 c.p.s.) and three allylic protons (200–135 c.p.s.).¹¹

Conversion of VII to III led to a difficultly purified product; hence methanolysis followed by saponification of III' was adopted, and the resultant III was readily recrystallized. Reconversion of III to III' (diazomethane) affords a product identical in all respects with the original III', and III has physical characteristics appropriate to its assigned structure: λ_{\max} 224 m μ (ϵ 8340), one vinyl proton (400 c.p.s.),¹¹ and bands in the infrared spectrum at 1695 and 1640 cm.⁻¹.

One further experiment was carried out in connection with the behavior of the cyanohydrin of IV (V). A sample of V was subjected to reaction in aqueous methanol-sulfuric acid whereupon a complex mixture of products was obtained which could be separated into two fractions, the first of which proved to consist of a large number of components, and the second of which proved to consist of two components. The infrared spectrum of the latter was consistent with that of a hydroxy ester mixture, and the mixture was not affected by treatment with Jones reagent (*cf.* Experimental). Hydrolysis of the methyl esters afforded a crude mixture of hydroxy acids which resisted purification by fractional crystallization, but which analyzed for a mixture of hydroxy acids which most reasonably may be assigned the structures

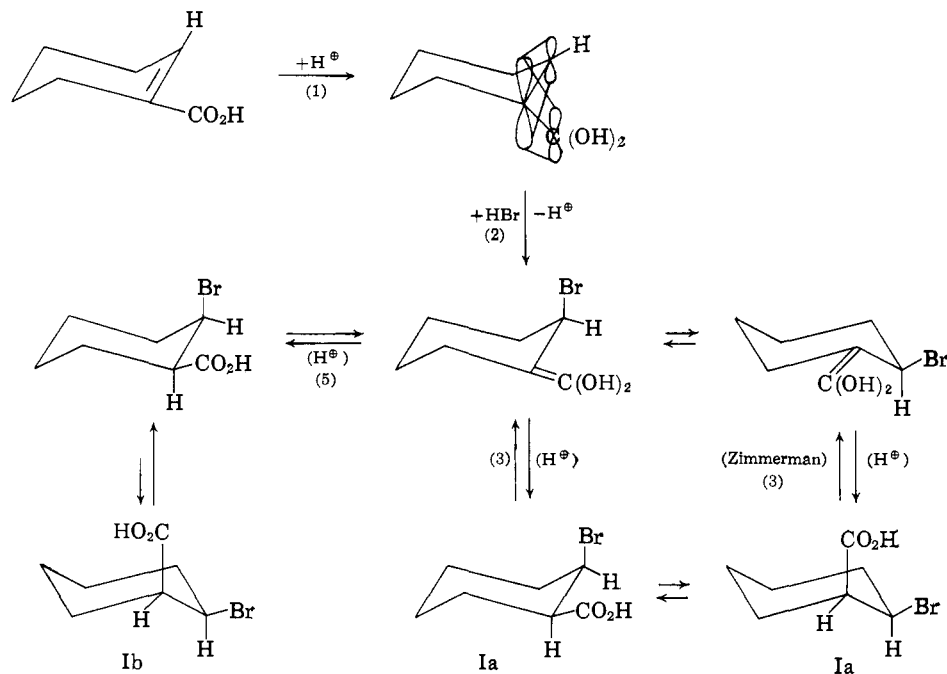


Support for this structural assignment comes from an inspection of Dreiding models of V and the acid derived therefrom which suggests that the equatorial orientation for the nitrile and carboxyl groups is preferred. Since cyanohydrin formation is reversible, thermodynamic principles should govern the structure of the product; thus, acid-catalyzed hydrolysis of V should afford the unrearranged α -hydroxy acid, while rearrangement of this compound should lead exclusively to the bicyclo[2.2.2]octane system.

Reaction Kinetics in Glacial Acetic Acid.—It was our intent to examine the kinetics of hydrobromination of all three unsaturated acids, but II proved to be too insoluble in glacial acetic acid at temperatures compatible with satisfactory measurement. However, a competition experiment involving I and II (*cf.* Experimental) demonstrated that, as was expected, the rates of hydrobromination of these two compounds in glacial acetic acid are about the same.

(11) All n.m.r. spectra obtained using a 60 Mc. Varian A-60 instrument, with internal tetramethylsilane reference.

(12) P. Scheiner, Ph.D. Dissertation, The University of Michigan, 1961, p. 93.

CHART I
 HYDROBROMINATION OF I


Actual pseudo-first-order rate constants for hydrobromination of I and III in glacial acetic acid were obtained by following the disappearance of conjugated acid absorption in the ultraviolet spectrum as a function of time, and consequently only such reactions as result in essentially irreversible removal of conjugated acid were determined, *i.e.*, production of the kinetically controlled product even though this might not be the product actually isolated.

Since relatively high concentrations of hydrogen bromide appear to be essential, kinetic measurements were made first with "30%" hydrogen bromide, as supplied by the manufacturer. Unfortunately the exact concentration of hydrogen bromide varies from lot to lot, and, in addition, storage without measurable change in concentration is difficult. Consequently the data assembled in Table V report the results of but one run involving I and two runs (each with a different lot of reagent) involving III. Each lot of reagent was also diluted as indicated, and additional pseudo-first-order constants were calculated.

While the most striking feature of these data is the enormous difference in rates of hydrobromination of I and III, it is of interest to note that within each series from a specific lot of reagent the pseudo-first-order rate constant varies with the $3/2$ power of the dilution factor (*e.g.*, $1/2$, $3/4$) for the hydrogen bromide reagent solution. The single exception is in the case of added lithium bromide for which the measured constant is somewhat *smaller* than expected on the basis of such variation, suggesting that bromide ion as such is probably not the attacking reagent in the rate-controlling step.

It is apparent that the behavior of these systems is quite different from that reported for hydrobromination of simple ethylenic compounds, albeit not in glacial acetic acid.^{13,14} The large variation in rate from

one compound to another argues against any rate-controlling proton-transfer process and in favor of rate-controlling carbon-bromine bond formation and the suggested individual steps are outlined in Charts I and II.

Stereochemistry.—(In the following discussion the configurations of the hydrobromides of II and III are assigned in accordance with the facts presented in the next section of this paper).

The hydrobromination of I was first re-examined, and it was found that at 100° and 90 min. reaction time (100% reaction) 75% *trans* and 25% *cis* addition occurred, whereas after 24 hr. under the same conditions the product (again 100% reaction) consisted of 5% *trans* adduct and 95% *cis* adduct. Thus the *cis* adduct is the thermodynamically more favorable one, and its appearance is most readily explained by reversal of step 3. Consequently it follows that conclusions concerning kinetic control of the initial addition are correct and that the stereochemistry of the initial product is governed by steric control of ketonization.

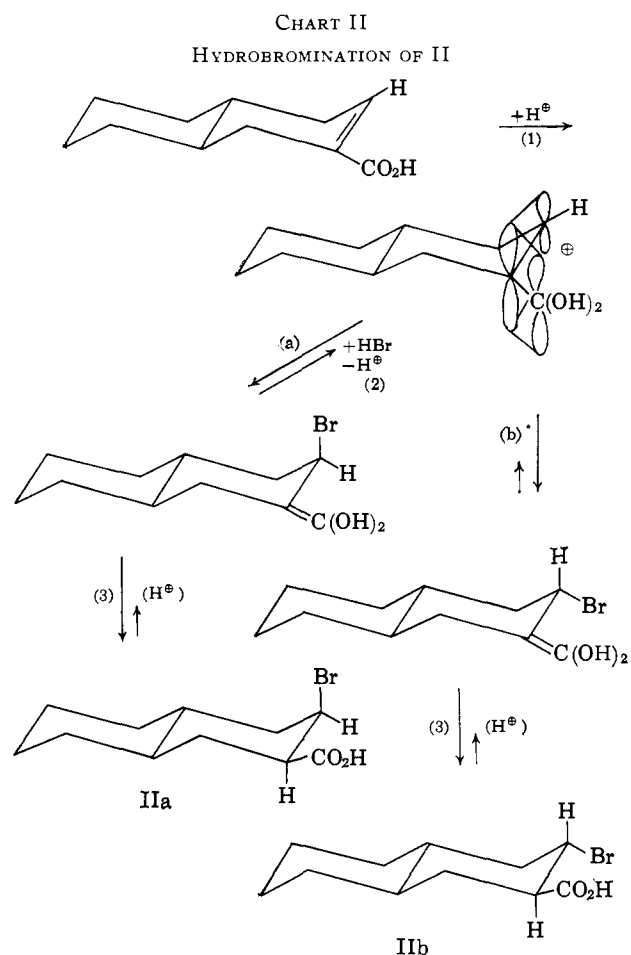
If the incoming bromine assumes an equatorial position, the situation becomes analogous to those described by Zimmerman¹⁵ in which 1-cyclohexylidene enols ketonize stereoselectively to give the thermodynamically less favorable epimer.

With I, however, it is not possible to determine the precise mode of entry of bromine. It could enter equatorially in the first place, or it could enter axially and the resultant enol experience a conformational flip prior to ketonization; or it could enter axially and ketonize immediately. This situation dictated our choice of II as a stereochemically equivalent substrate which could not undergo the conformational

(13) F. R. Mayo and J. J. Katz, *J. Am. Chem. Soc.*, **69**, 1339 (1947); F. R. Mayo and M. G. Savoy, *ibid.*, **69**, 1348 (1947) (approximately third order in hydrogen halide).

(14) Y. Pocker, F. Naso, and G. Tocchi, Abstracts, 144th Meeting of the American Chemical Society, Los Angeles, Calif., April 1-5, 1963, p. 50M (second order in hydrogen halide).

(15) H. E. Zimmerman, *J. Am. Chem. Soc.*, **81**, 3644 (1959), and previous papers cited therein.



Note that $k_a > k_b$; but $K_b > K_a$; see text for stereochemistry of step 3.

flip, thus affording a means of ruling out such a process as a necessary step in the addition process. Under comparable conditions (20 hr., 100°) hydrogen bromide adds to II with the bromine appearing axially (Chart II) at the 3-position, and the same product is obtained upon addition of hydrogen bromide to II in toluene (6 hr. at 25°). The carboxyl group appears equatorially; thus this group occupies the thermodynamically more favorable position, and a new question is posed: is this thermodynamic control, or is it the consequence of the stereochemistry of the system?

This question cannot be answered unequivocally with the evidence at hand, for it can be argued either that the bulk of the axial bromine is more effective than the 4,9-diaxial hydrogens in screening approach by the proton carrier to C-2 or that the 4,9-diaxial hydrogens do indeed dominate but a rapid epimerization ensues. However, the absence of any transient isomer, even in the early stages of the reaction, can be used as an argument against the latter alternative. Thus, until evidence to the contrary is forthcoming, the similarity to open chain systems (in which *trans* hydriodination as a consequence of the bulk of the halogen appears to control the stereochemistry^{9,10}) suggests support for the former alternative.

Prolonged heating of the reaction of II with hydrogen bromide affords an epimer of the original adduct in which the bromine is oriented equatorially (Chart II). If IIb is produced directly from the equatorial bromo enol, the process would appear to be a real

violation of Zimmerman's principle, which would predict the axial orientation for the carboxyl group. However, the rather drastic conditions necessary for reorientation of bromine from the initially axial position to equatorial (reversal of (a) in Chart II) clearly are such as to promote epimerization (reversal of last step) of any carboxyl group which had assumed the axial orientation as a consequence of kinetic control of the ketonization step.

Although accurate kinetic data for the hydrobromination of II was not obtained, for reasons noted above, the reaction occurs qualitatively at about the same rate as with I. Thus, since the energy requirements for a conformational flip may reasonably be expected to be appreciably less than for a proton-transfer reaction, it is not possible with the present data to decide between the first two alternatives for the production of Ia, but the initial attack can be unequivocally described as axial. Whether or not a conformational flip intervenes, steric control of ketonization, either by 3,5-diaxial hydrogen (4,9-interaction in the decalin system) or axial bromine, accounts for the configuration of the product.

Perhaps the most significant feature of the work with II is the specific preference shown for axial attack by bromine in the rate-determining step. This would appear to be a clear-cut case of stereoelectronic control, as proposed by Corey and Sneen,¹⁶ and it is particularly interesting in that the process here is nucleophilic. To be sure, there is no axial methyl group to offer more resistance to such axial attack, as there is in the Corey and Sneen cases, but this preference appears to be a dominant characteristic of the hydrobromination reaction, as will be emphasized in the case of III wherein a major barrier to axial approach is present. In the case of II the production of but one isomer at short reaction time (and only one other at longer time) appears to rule out a π -complex⁶ as an intermediate, since at least some epimeric material at short time would be expected if a π -complex is involved because protonation of the π -bond should be possible from either side of II with about equal facility.

The strong preference for axial attack by bromine is emphasized in the hydrobromination of III. If attack were equatorial, no striking change in reaction rate from that observed for I (and by implication, II) would be expected. But axial approach is more strongly inhibited than in the Corey and Sneen cases by the ethano bridge, and this is reflected in identical kinetic behavior on dilution and a very much smaller pseudo-first-order rate constant. The course of the reaction was followed by v.p.c. analysis of the methyl esters of the component acids as a function of time, an approximate plot of the observations being displayed in Fig. 1. Potentially there are four geometric isomers to be expected from the hydrobromination of III, two in which bromine at C₃ is axial and two in which it is equatorial, with axial and equatorial carboxyl groups corresponding to each orientation of bromine. It is clear from Fig. 1 that three of these are actually formed: one appears early in the reaction (IIIa) and rapidly disappears; another appears in greater percentage at the same observation time (IIIb) and does not completely disappear; and a third appears in

(16) E. J. Corey and R. A. Sneen, *J. Am. Chem. Soc.*, **78**, 6269 (1956).

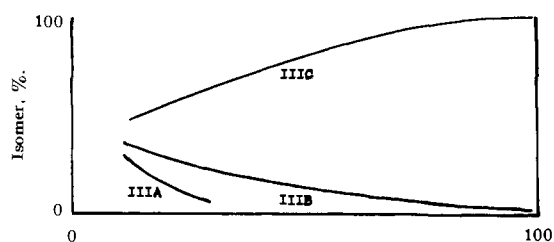


Figure 1.

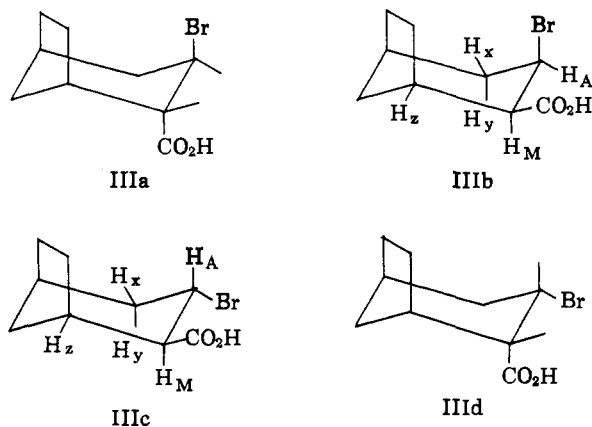


Fig. 2.—Hydrobromides of III.

still greater concentration at the initial observation time (IIIc) and continues to increase so that ultimately it constitutes the major reaction product.

The isolation of IIIc was straightforward, and by resorting to addition of hydrogen bromide to III in toluene IIIb could be prepared and separated from traces of IIIc. Under these conditions IIIa also appeared in the early stages of the reaction but disappeared as the reaction went to completion.

The configurations of IIIb and IIIc are deduced from data presented in the next section, but thus far we have been unable to isolate a pure sample of IIIa. However, a mixture consisting of IIIa with IIIb as the only demonstrable impurity (microanalysis, and v.p.c. of methyl esters) has been obtained. Discounting lines manifestly arising from IIIb, the n.m.r. spectrum of the mixture clearly differs from those of IIIb and IIIc (Table I), and the structure and configuration of IIIa may be inferred both from these data and as argued in the sequel.

The carboxyl group of IIIa must be axially oriented if a chair conformation obtains, since IIIb and IIIc both possess equatorial carboxyl groups, and its bromine may be either axial or equatorial. That the former is more reasonable follows from the fact that IIIa is formed early in the reaction (acetic acid or toluene) and disappears, and in the toluene reaction only IIIb, whose bromine is axial, remains. It would appear that IIIa and IIIb are the kinetically favored products and that IIIa is epimerized to IIIb under conditions such that the axial orientation of bromide is undisturbed (toluene solution). Thus the "missing" isomer (IIIc) must possess axial carboxyl and equatorial bromine. Its failure to appear is analogous to the failure to observe the corresponding hydrobromide of II: conditions sufficiently severe to reorient the initially axial bromine equatorially are drastic enough to permit thermodynamic control of the stereochemistry at C-2.

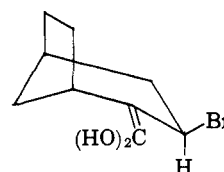


Fig. 3.—Initial acid-enol XII.

The foregoing evidence and argument suggest the following sequence of events in the hydrobromination of III, subsequent to initial protonation of the carboxyl. The carbonium ion is attacked axially by hydrogen bromide at C-3 leading to the acid-enol XII (Fig. 3). Both IIIa and IIIb may be formed from XII, whose structure suggests that distortion resulting from repulsions between bromine and the ethano bridge lead to a quasi-boat form for XII. Under such conditions both Fisher-Hirschfelder and Dreiding models of XII reveal hindrance to approach by a proton carrier from below (*i.e.*, *trans* to bromine); consequently, equatorial proton transfer is relatively easier than in the corresponding situation in II. Thus either IIIa is the kinetically favored product, which rapidly epimerizes to IIIb owing to severe crowding in IIIa, or both IIIa and IIIb are produced at comparable rates from XII, with epimerization of IIIa proceeding at a relatively rapid rate.

The conversion of IIIb to IIIc occurs more readily in acetic acid than in toluene for two reasons. The first is inhibition of reversal of carbon-bromine bond formation by the more inimical medium (toluene) for carbonium ions; and the second is enhanced inhibition of axial hydrogen bromide approach by its more effective solvation by acetic acid, which increases the steric requirements of the attacking species.

The conclusions to be reached on the basis of this investigation are: (1) hydrobromination of α,β -unsaturated acids in glacial acetic acid, and very likely in nonpolar solvents as well, involves rapid and reversible protonation of the doubly bound oxygen of the carboxyl group, followed by rate-determining reaction in which the C $^{\beta}$ -bromine bond is formed, this being difficultly reversible; (2) bromine enters a cyclohexene-1-carboxylic acid system axially to give an acid-enol; (3) a conformational flip (or rotation, in the case of an open chain acid) may occur at this stage; (4) ketonization of the acid-enol will occur in such a manner that the incoming proton is oriented *trans* to the bromine unless serious steric inhibition to such approach by the proton carrier is present or unless reaction conditions are such as to permit thermodynamic control of the resulting structure; (5) if conditions are sufficiently drastic, the initial axial orientation of the bromine, which normally governs the stereochemistry at C $^{\beta}$, may be altered to equatorial, in which case the orientation of the carboxyl will be governed strictly by thermodynamic principles; (6) it is not unreasonable to assume that reorientation of the initially axial bromine may involve complete reversal of the reaction sequence to the original unsaturated acid; but this is not necessary to account for the process, since simple ionization of the β -bromine can lead to the observed phenomena if the medium is conducive to such ionization and bromide ion remains the most effective nucleophile present. In favorable

TABLE I
 N.M.R. DATA FOR α -PROTONS

Compd.	Proton ^a	Position ^b	Frequency ^c	Splitting pattern ^d	Coupling constants in c.p.s. ^e						
					J_{AM}	J_{AX}	J_{AY}	J_{MA}	J_{MX}	J_{MY}	J_{MZ}
Ia ^f	H _A	e	288	1:3:3:1 ^g	~2.5	~2.5	~2.5				
	H _M	a	157	1:1:?:?:1:1 ^h				~2.5	~2.5	~10.5	
Ib ^f	H _A	a	249	1:1:2:2:1:1	11.0	4.0	11.0				
	H _M	a	167	1:1:2:2:1:1				11.0 multiplet partially obscured			
IIa ⁱ	H _A	e	303	1:3:3:1	~2.5	~2.5	~2.5				
	H _M	a	177	1:1:?:?:1:1 ^h				~2.5	~2.5	~11	
IIb ⁱ	H _A	a	257	1:1:2:2:1:1	11.5	4.0	11.5				
	H _M	a	176	1:1:2:2:1:1				11.5	4.0	11.5	
IIIa	H _A	e ^j	260	Multiplet ^k							
	H _M	e ^j	179	Multiplet							
IIIb ^{f,l,m}	H _A	e	284	1:1:2:2:1:1 ^g	6.0	~1-2	~4-6				
	H _M	a	177	1:1:1:1				6.0			2.0
IIIc ^f	H _A	a	257	1:1:2:2:1:1	11.0	6.0	11.0				
	H _M	a	169	1:1:1:1				11.0			2.0

^a H_A α to bromine; H_M α to carboxyl. ^b a = axial; e = equatorial. ^c Chemical shift in c.p.s. from internal tetramethylsilane ref.; Varian A-60 (60 Mc.) instrument. ^d Ratio of peak areas. ^e H_X, H_{X'} equatorial; H_Y, H_Y, axial; H_Z bridgehead. Values are correct to ± 0.2 c.p.s. unless ~ is indicated. The J -values represent observed splittings and represent *apparent* rather than established coupling constants. ^f CDCl₃ solvent. ^g Poorly resolved. ^h Ratio uncertain, center peaks larger. ⁱ F₂CCO₂H solvent. ^j The designation e is for convenient reference; it is unlikely that the normal chair form obtains. ^k The apparent coupling constants are ~ 10 c.p.s. suggesting quasi-diaxial relationships with adjacent protons, e.g., H_M, as would obtain in a quasi-boat conformation. ^l CS₂ solvent used for observing fine structure; change in chemical shift less than 5 c.p.s. ^m A signal at 142 c.p.s., representing ~ 4 protons, appears in this spectrum, while in IIIc it appears at ~ 96 c.p.s.

cases the original unsaturated acid can conceivably be formed by direct dehydrobromination.

Assignment of Configurations.—The configurations of the two hydrobromides of I have been unequivocally determined,⁵ and consequently Ia and Ib may serve as reference compounds for the various hydrobromides from II and III. In addition, the assignment of the carboxyl group of IIIc to the equatorial position was made on the basis of hydrogenolysis (palladium catalyst) of the methyl ester IIIc' which afforded the same product (XIII) as obtained by hydrogenation of III, followed by diazomethane esterification. Subsequent treatment of XIII with refluxing methanolic sodium methoxide failed to alter it in any way; thus the ester group in XIII and the carboxyl group in IIIc must occupy the thermodynamically more favorable position.

It is to be noted that nonpolar addition of hydrogen to the double bond of III occurs from the side opposite to that of carbon-bromine bond formation, for whereas the latter is stereoelectronically controlled, the former is a consequence of the purely steric situation which an examination of Dreiding models shows to favor the observed approach.

Support for the over-all configurational assignments is to be found in examination of n.m.r. data (Table I). The protons α to bromine (H_A) and to carboxyl (H_M) produce signals downfield from other protons in the systems,¹⁷ and when they are equatorially oriented they resonate farther downfield than when they are axially oriented.¹⁸⁻²⁰ Furthermore, independently resolved multiplets afford information by way of the coupling constants as to the dihedral angle between protons on adjacent carbon atoms.^{21,22} A comparison

of the recorded data for the hydrobromides of II and III with Ia or Ib indicates by way of the chemical shifts, splitting patterns, and coupling constants that the assignments of configurations for the H_A and H_M protons is correct and hence that the over-all configurational assignments are justified.

It is worth mentioning that the methylene envelope in the n.m.r. spectrum of Ia is less complex than in that of Ib, and, while the chemical shift for the H_M proton is appropriate for preferentially equatorial carboxyl, the total spectrum appears to be a weighted average^{23,24} of the spectra of the two chair conformations which must be in dynamic equilibrium with each other. In Ib the system appears to be more nearly fixed in the more stable diequatorial conformation.

It should be noted that the data for IIIb are consistent only with a chair conformation, and hence the deshielding of the four protons in the ethano bridge must be attributed to bromine which in a Fisher-Hirschfelder model is in actual contact with the bridge. Thus there is further support for the axial orientation of bromine in IIIb.

Finally the n.m.r. spectrum of IIIa deserves comment. As argued previously, IIIa necessarily possesses an axial carboxyl group, if a chair conformation obtains. However, neither the chemical shifts nor the apparent coupling constants are in consonance with the *trans* bromine/carboxyl diaxial chair conformation, although the splitting patterns and apparent coupling constants suggest the appropriate proton environment for a *trans* bromo/carboxyl boat conformation. The acute situation for axial bromine noted in IIIb has disappeared (no deshielding of the ethano bridge protons) in consonance with this hypothesis, which is reasonable since the diaxial conformation would lead to severe nonbonded interactions both with bromine (ethano bridge) and with carboxyl (methano bridge), and thus favor the boat conformation.

(17) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1954, Chapter 4.

(18) L. M. Jackman, *ibid.*, Chapter 7.

(19) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Am. Chem. Soc.*, **80**, 6098 (1958).

(20) J. N. Shoolery and M. T. Rogers, *ibid.*, **80**, 5126 (1958).

(21) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

(22) F. A. L. Anet, *Can. J. Chem.*, **39**, 789 (1961).

(23) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, Chapter 14.

(24) H. Finegold and H. Kwart, *J. Org. Chem.*, **27**, 2361 (1962).

3-Bromobicyclo[3.2.1]octan-2-one (XIV).—In the course of attempting to establish the orientation of bromine in IIIc, the ketone IV was brominated under conditions expected to afford thermodynamic control (equatorial bromine),²⁵ and the product XIV was examined with the aid of n.m.r. spectroscopy. The proton (H_A , α to bromine) gives rise to a 1:1:1:1 quartet centered at 292 c.p.s.¹¹ with apparent coupling constants $J_{AX} = 8.0 \pm 0.4$ c.p.s., $J_{AY} = 12.0 \pm 0.4$ c.p.s.²⁴ The data support observations made on certain α -acetoxy ketones by Williamson and Johnson.²⁶

Bridgehead Protons in the Bicyclo[3.2.1]octane System.—The examples collected in Table II are arranged in order of increasing deshielding for H_Z (the C_1 -bridgehead proton). The linear (and cylindrical)

TABLE II
CHEMICAL SHIFTS FOR BICYCLO[3.2.1]OCTANE
BRIDGEHEAD PROTONS

Compd.	C_2 -Substituent	H_Z^a (c.p.s.) ¹¹
XIII	e -CO ₂ H	135
VII	Δ^2 -CN	155
XIV	$=O^b$	155 ^c
IV	$=O$	158
VI	$-OCOCH_3^d$	165
	$-CN$	
III	Δ^2 -CO ₂ H	174
III'	Δ^2 -CO ₂ CH ₃	177

^a H_Z is bridgehead proton on C-1. ^b Equatorial bromine on C-3. ^c Assignment of 155 c.p.s. signal to H_Z made on basis of IV, which is unequivocal. A second single proton signal is observed at 185 c.p.s. This is tentatively assigned to the *endo* proton on C-6 which is susceptible to deshielding by bromine. ^d Configuration uncertain.

π -electron system of an α,β -unsaturated nitrile (VII) is not a particularly effective deshielding agent, and the keto group (XIV and IV) is about equivalent. If, as might be expected, the nitrile group in VI has entered the system equatorially, the position of the H_Z signal in VI may be unaffected, but the combined effects of acetoxy and nitrile groups on C-2 may well account for the net deshielding, regardless of orientation. Consequently it is not possible to use this information for configurational assignment.

Experimental²⁷

Reaction of I with Hydrogen Bromide (30%) in Acetic Acid.—Samples of I⁶ were allowed to react at 100° with 30% hydrogen bromide-glacial acetic acid, and the resulting products were converted to methyl esters (diazomethane) and analyzed by v.p.c., comparison being made with authentic samples of Ia and Ib' (below). Data are presented in Table IV.

Methyl *cis*-2-Bromocyclohexanecarboxylate (Ia).—The methyl ester of *cis*-2-bromocyclohexanecarboxylic acid² was formed in the same manner as the *trans* isomer. A v.p.c. analysis indicated about 5% of the *trans* isomer present.

Anal. Calcd. for C₈H₁₃BrO₂: C, 43.46; H, 5.93; Br, 36.14. Found: C, 43.60; H, 6.00; Br, 36.10.

(25) E. J. Corey, *Experientia*, **9**, 329 (1953); *J. Am. Chem. Soc.*, **75**, 2301 (1953); **76**, 175 (1954).

(26) K. L. Williamson and W. S. Johnson, *ibid.*, **83**, 4623 (1961).

(27) (a) All melting and boiling points are uncorrected. (b) Microanalyses are by Spang Microanalytical Laboratory, Ann Arbor, Mich. (c) All infrared spectra were run neat or as Nujol mulls on a double beam Perkin-Elmer Model 21 infrared spectrophotometer using sodium chloride optics. (d) The ultraviolet spectra were obtained using a double beam Model 11 Cary recording spectrophotometer and absolute ethanol as the solvent. (e) The vapor phase chromatograms were all obtained from an F and M Model 500, programmed temperature gas chromatograph. The LAC-446 column referred to has a crosslinked diethylene glycol adipate liquid phase. (f) The nuclear magnetic spectra were run by Dr. G. Caple, Florida State University, Tallahassee, Fla., and Mr. B. E. Wenzel, University of Michigan, Ann Arbor (*cf.* footnote 11).

TABLE III
VAPOR PHASE CHROMATOGRAPHY DATA^a

Compound		Temp., °C.
Ia'	Methyl <i>cis</i> -2-bromocyclohexanecarboxylate	170
Ib'	Methyl <i>trans</i> -2-bromocyclohexanecarboxylate	170
II'	Methyl <i>trans</i> - Δ^2 -octalin-2-carboxylate	200
III'	Methyl bicyclo[3.2.1]oct-2-ene-2-carboxylate	170
IIIb'	Methyl <i>axial</i> -3-bromobicyclo[3.2.1]octane- <i>equat.</i> -2-carboxylate	205
IIIc'	Methyl <i>equat.</i> -3-bromobicyclo[3.2.1]octane- <i>equat.</i> -2-carboxylate	205
IV	Bicyclo[3.2.1]octan-2-one	150
V	Bicyclo[3.2.1]octan-2-one cyanohydrin	175
VI	2-Acetoxybicyclo[3.2.1]octane-2-carbonitrile	190
VII	Bicyclo[3.2.1]oct-2-ene-2-carbonitrile	160
X	2-Chlorobicyclo[2.2.2]octane-1-carbonitrile	190
XIII'	Methyl bicyclo[3.2.1]octane- <i>exo</i> -2-carboxylate	170

^a F and M Model 500 programmed vapor fractometer using 10% LAC-446.

TABLE IV

Time	Reaction, %	% <i>cis</i> isomer (net <i>trans</i> add.)	% <i>trans</i> isomer (net <i>cis</i> add.)
1 90 min.	100	75	25
2 24 hr.	100	5	95

Methyl *trans*-2-Bromocyclohexanecarboxylate Ib.—An ethereal solution of *trans*-2-bromocyclohexanecarboxylic acid² was methylated with diazomethane and ether removed under slight vacuum. A v.p.c. analysis indicated about 1% of the *cis* isomer.

Anal. Calcd. for C₈H₁₃BrO₂: C, 43.46; H, 5.93; Br, 36.14. Found: C, 43.63; H, 6.12; Br, 36.20.

***trans*- β -Decalone Cyanohydrin.**—To 100 g. (0.66 mole) of *trans*- β -decalone²⁸ in 600 ml. of methanol in a 2-l. flask fitted with a reflux condenser and mechanical stirrer was added 102 g. (0.99 mole) of concentrated sulfuric acid, followed immediately by the addition of 97 g. (1.98 moles) of sodium cyanide in a saturated water solution at such a rate as to produce refluxing. After completion of the addition, the reaction mixture, which turned reddish brown, was stirred for 4 hr. at room temperature. The mixture was then acidified with concentrated sulfuric acid and stirred for another hour. Ether, 500 ml., was added and after stirring for a short time was decanted from the dark residue. The residue was washed several more times with ether and the combined ether solutions, after filtering, were washed thoroughly with water saturated with sodium chloride, dried over anhydrous magnesium sulfate, and the ether removed under vacuum. The crude product remaining, 113 g. (97%), exhibited only a trace of unreacted ketone in the infrared spectrum. Upon distillation, b.p. 113–117° (0.1 mm.), of a small sample the cyanohydrin partially decomposed to starting ketone, although Chaudry³⁰ reported a purification by distillation, b.p. 113° (6 mm.). Three recrystallizations from 40–60° petroleum ether gave a crystalline solid, m.p. 115–116°. Hüchel³¹ reported a melting point of 108°, but there is a question of epimers.

Anal. Calcd. for C₁₁H₁₇NO: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.50; H, 9.50; N, 7.61.

***trans*- Δ^1 and Δ^2 -Octalin-2-carbonitriles.**—Crude *trans*- β -decalone cyanohydrin (100 g., 0.56 mole) was dissolved in 250 ml. of dry ether in a 1-l. flask fitted with a mechanical stirrer, dropping funnel, and condenser, cooled in an ice-salt bath, and 121 g. (1.13 moles) of 2,6-lutidine was added. With rapid stirring and continued cooling, 133 g. (1.12 moles) of thionyl chloride was added dropwise over a period of 90 min., and stirring was continued at room temperature for 8 hr. The ether and excess thionyl chloride were removed by heating at 60° in an oil bath after

(28) Prepared by oxidation of *trans*- β -decalol (Columbia Organic Chemicals Co., Inc., Columbia, S. C.) with 2.67 *M* Jones reagent²⁹; yield 99%; semicarbazone m.p. 192.5–193.5°, reported 192° dec. (I. M. Heilbron, "Dictionary of Organic Compounds," Vol. 3, Oxford University Press, New York, N. Y., 1953, p. 142).

(29) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(30) N. A. Chaudry, R. D. Desai, and G. S. Sahariya, *Proc. Indian Acad. Sci.*, **11A**, 139 (1940).

(31) W. Hüchel and F. Wiebke, *Ber.*, **59**, 2843 (1926).

removing the condenser. Heating and stirring were continued, after adding 100 g. more of 2,6-lutidine, at 100° for 90 min. After cooling, 200 ml. of a 10% hydrochloric acid solution was added to the dark, hardened residue, followed by the addition of 250 ml. of ether. The mixture was stirred to break up the larger particles and filtered. The residue was washed with two more 250-ml. portions of ether. The combined dark brown filtrates were washed twice with 10% hydrochloric acid, and then with water, dilute sodium bicarbonate, and more water. The combined ether extracts were dried over anhydrous magnesium sulfate and the ether removed under vacuum. Distillation of the dark liquid residue gave, after a small forerun, 57 g. (62%), b.p. 70–80° (0.1 mm.), n_D^{25} 1.5028, of a mixture of a 70:30 ratio of α,β -unsaturated nitriles (infrared) as determined by v.p.c., LAC-446, 190°. Chaudry³⁰ reported only the Δ^2 -isomer, b.p. 145° (6 mm.), upon dehydration with thionyl chloride and pyridine.

Anal. Calcd. for $C_{11}H_{15}N$: C, 81.93; H, 9.38; N, 8.69. Found: C, 81.69; H, 9.43; N, 8.74.

trans- Δ^2 -Octalin-2-carboxylic Acid (II).—To 45 g. (0.28 mole) of *trans- Δ^1 -* and *Δ^2 -octalin-2-carbonitriles* were added slowly with stirring in an ice bath 31 g. (0.30 mole) of concentrated sulfuric acid and 31 g. (1.7 moles) of water. The solution was heated to 110° with stirring for 6 hr. when an additional 31 g. (0.30 mole) of concentrated sulfuric acid was added and heating continued at 110° for 12 hr. After cooling, the solution was made alkaline with 500 ml. of a 10% potassium hydroxide solution, and diluted to 2.5 l., whereupon all the salts went into solution. Extraction with ether of the basic solution and work-up produced only a trace of the corresponding amide and no unreacted nitrile. Acidification of the alkaline solution with excess concentrated hydrochloric acid gave a curdy, white precipitate which was extracted with ether. The ether solution was dried over anhydrous magnesium sulfate and the ether removed under vacuum. The crude product, 48 g. (95%), consisted of an 80:20 ratio of α,β -unsaturated acids (infrared) as indicated by a v.p.c. analysis of the methyl esters (below). A fractional recrystallization from absolute ethanol produced the major isomer present in a purity of 98%, m.p. 142–143°, reported³⁰ 146°.

Anal. Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.13; H, 8.84.

Methyl trans- Δ^2 -Octalin-2-carboxylate (II').—A small sample of *trans- Δ^2 -octalin-2-carboxylic acid* was methylated with diazomethane; n_D^{25} 1.4963.

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.00; H, 9.37.

trans-axial-3-Bromodecalin-equat-2-carboxylic Acid (IIa).—This isomer may be formed readily in two ways: (a) A 0.50-g. sample of II (2.8 mmoles) was dissolved in 25 ml. of reagent toluene. The toluene solution was saturated with hydrogen bromide at room temperature by continuously passing a slow stream of anhydrous hydrogen bromide through it for 6 hr. At the end of this time the toluene was removed under vacuum, and the infrared spectrum indicated roughly 75% reaction. Only one bromo acid could be recovered by recrystallizing from benzene; 0.40 g. (55%), m.p. 163.5–164.5°.

(b) A 1.0-g. (5.6 mmoles) sample of II was placed in a test tube and 20 ml. of 30% hydrogen bromide in acetic acid added. The tube was sealed and heated at 100° for 20 hr. After removal of acetic acid and hydrogen bromide under vacuum with mild heating, a quantitative yield of crude crystalline product remained, possessing no unsaturated character in the infrared spectrum. A careful recrystallization from benzene produced only one bromo acid, m.p. 163.5–164.5°, although the crops obtained from the mother liquor could not be purified above a melting range of 145–155°. Attempts to determine the ratio of isomers in the crude product by v.p.c. of the corresponding methyl esters failed owing to the large amount of decomposition products observed during analysis. Admixture with the bromo acid from route (a) showed no depression in melting point and the two acids have identical infrared and nuclear magnetic resonance spectra.

Anal. Calcd. for $C_{11}H_{17}BrO_2$: C, 50.68; H, 6.56; Br, 30.53. Found: C, 50.75; H, 6.44; Br, 30.54.

trans-equat-3-Bromodecalin-equat-2-carboxylic Acid (IIb).—This isomer was formed as in procedure (b) for the *axial-equatorial* isomer except that heating at 100° was lengthened to 8 days. A quantitative yield of crude bromo acids was again obtained. However, the only product which could be isolated melted at 176.5–177.5°. The second crops again melted low. The infra-

red and nuclear magnetic resonance spectra differed from the *axial-equatorial* bromo acid. An attempt to determine the extent of epimerization *via* v.p.c. again was not feasible owing to decomposition during analysis.

Anal. Calcd. for $C_{11}H_{17}BrO_2$: C, 50.68; H, 6.56; Br, 30.53. Found: C, 50.56; H, 6.50; Br, 30.40.

2-endo-Aminomethylbicyclo[2.2.1]heptane Hydrochloride.—The following one-step procedure is a modification of Alder's³² two-step procedure. Bicyclo[2.2.1]hept-5-ene-*endo*-2-carbonitrile³³ (140 g., 1.18 moles) was dissolved in 400 ml. of methanol saturated with ammonia at 0°, 30 g. of W-2 Raney nickel catalyst was added, and hydrogenation carried out at 60° and 1800 lb. pressure for 24 hr. The catalyst was filtered off and the methanol removed under vacuum. The remaining free amine was dissolved in 400 ml. of a 3 *N* hydrochloric acid solution and extracted with ether to remove unreacted nitrile. Yields based on recovered nitrile varied from 80–90%. The aqueous solution of 2-*endo*-aminomethylbicyclo[2.2.1]heptane hydrochloride was carried directly to next step.

Bicyclo[3.2.1]octan-2-one (IV).—The hydrochloride prepared in the preceding section was converted to IV by treatment with nitrous acid, followed by oxidation according to Alder's procedure.³²

Bicyclo[3.2.1]octan-2-one Cyanohydrin (V).—A 310-g. (2.5 moles) sample of IV was dissolved in 1.2 l. of methanol in a 3-necked, 3-l. round-bottom flask fitted with a condenser, dropping funnel, and mechanical stirrer. Concentrated sulfuric acid (382 g., 3.8 moles) was added at room temperature as fast as was permissible, followed immediately by 368 g. (7.5 moles) of sodium cyanide in a saturated water solution at such a rate as to maintain refluxing. The solution was stirred during the addition and vigorously for 4 hr. at room temperature after the addition. A white precipitate of sodium cyanide formed during the mixing and the clear solution gradually turned dark as the reaction proceeded. At the end of 4 hr. the mixture was acidified with concentrated sulfuric acid and the stirring at room temperature continued for 1 hr. Then 1 l. of ether was added, the mixture stirred, and the ether-methanol solution decanted from the precipitate which was again washed with 1 l. of ether. The combined ether washings were filtered, washed with 600 ml. of water saturated with sodium chloride, dried over anhydrous magnesium sulfate, and the solvent removed under vacuum. A brownish red oil of crude bicyclo[3.2.1]octan-2-one cyanohydrin (340 g., 90%) remained. A small sample was recrystallized 5 times from petroleum ether to give a white solid melting at 121–125°, suspiciously close to that observed for the original ketone, 125–127°. The infrared spectrum exhibited, in addition to characteristic cyanohydrin bands, a weak carbonyl absorption which could not be eliminated by further recrystallizations. The v.p.c. retention time was identical with that of bicyclo[3.2.1]octan-2-one. Sublimation of the crude cyanohydrin also produced more ketone as indicated by the infrared spectrum. A carbon-hydrogen analysis was slightly high in both elements, reflecting the presence of a small amount of ketone. The instability of the cyanohydrin explained why all prior attempts at this conversion failed. Bicyclo[3.2.1]octan-2-one cyanohydrin was characterized as the acetate VI (below).

2-Acetoxybicyclo[3.2.1]octane-2-carbonitrile (VI).—The crude cyanohydrin from 400 g. (3.2 moles) of IV was dissolved in 800 ml. of pyridine at 0° and 800 g. (7.85 moles) of acetic anhydride was added with shaking.³⁴ The solution was heated on a steam bath with occasional shaking for 3 hr. and allowed to stand at room temperature for 3 hr. more. The resulting red solution was poured into 1 l. of a 25% hydrochloric acid-ice mixture whereupon an oil separated. The aqueous mixture was extracted with ether and washed repeatedly with dilute hydrochloric acid, followed by water, dilute sodium bicarbonate, and more water. The ether extract was dried over anhydrous magnesium sulfate and solvent removed under vacuum. Vacuum distillation of the residue gave 466 g. (75%) of the acetate, b.p. 113–116° (0.5 mm.), n_D^{25} 1.4746. A v.p.c. analysis showed the acetate to be 100% pure.

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.40; H, 7.77; N, 7.26. Found: C, 68.49; H, 7.73; N, 7.39.

(32) K. Alder, K. Heimbach, and R. Reubke, *Chem. Ber.*, **91**, 1516 (1958).

(33) Hi Lab, Whitmore Lake, Mich.

(34) R. L. Shriner, R. G. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 212.

Bicyclo[3.2.1]oct-2-ene-2-carbonitrile.—A 400-g. (2.25 moles) sample of VI was slowly passed through a 50-cm. pyrolysis tube fitted with glass helices over a period of 24 hr. at a temperature of $450 \pm 10^\circ$. An extremely slow flow of nitrogen was continuously passed through the column and the pyrolyzed products were collected in an ice-salt trap at the bottom. The column was flushed with benzene at the end of pyrolysis. The recovered products were taken up in 800 ml. of ether and washed repeatedly with water and then with dilute sodium bicarbonate to remove the acetic acid. The ether solution was dried over anhydrous magnesium sulfate and the solvent removed under vacuum. The dark residue was distilled at 1.5 mm. and yielded 200 g. of product contaminated with a much more volatile forerun. Further distillation at 0.5 mm. produced 80 g. of unpyrolyzed acetate which was recycled through the pyrolysis column and work-up repeated. A careful fractional distillation of the crude distillates produced, in addition to a forerun, b.p. 64° (4 mm.), which had an infrared spectrum identical with that of benzonitrile; 30 g. of unreacted acetate; 165 g. (64%) of bicyclo[3.2.1]oct-2-ene-2-carbonitrile, b.p. $67\text{--}69^\circ$ (1.5 mm.), $n_D^{23.5}$ 1.4809. A v.p.c. analysis indicated a purity of greater than 97%.

Anal. Calcd. for $C_9H_{11}N$: C, 81.15; H, 8.33; N, 10.52. Found: C, 80.95; H, 8.44; N, 10.90.

Methyl Bicyclo[3.2.1]oct-2-ene-2-carboxylate (III').—To 150 g. (1.12 moles) of bicyclo[3.2.1]oct-2-ene-2-carbonitrile in 500 ml. of methanol and 75 ml. of water in a 2-l. round-bottom flask fitted with a condenser and mechanical stirrer was added 450 g. of concentrated sulfuric acid. The solution was stirred vigorously and refluxed for 2 hr.; an additional 250 g. of sulfuric acid was added and heating was continued for 5 hr. Methanol, 500 ml., was then added and stirring was continued at room temperature. After 12 hr. about half of the methanol was removed under vacuum and 1 l. of ether was added. The ether solution was washed repeatedly with water saturated with sodium chloride, dried over anhydrous magnesium sulfate, and solvent removed under vacuum. Distillation of residue produced 118 g. (71%), b.p. 65° (1 mm.), $n_D^{23.5}$ 1.4746, λ_{max} 228 $m\mu$ (ϵ 7725), of 99% purity (v.p.c.).

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.25; H, 8.50. Found: C, 72.03; H, 8.35.

Bicyclo[3.2.1]oct-2-ene-2-carboxylic Acid (III).—To 90 g. (0.54 mole) of methyl bicyclo[3.2.1]oct-2-ene-2-carboxylate in 200 ml. of ethanol was added 200 ml. of a 50% potassium hydroxide solution and the mixture was refluxed with continuous stirring for 48 hr. Excess ethanol was removed under vacuum, 100 ml. of water was added, and the basic solution was extracted with ether to remove any neutral products. The basic solution was then carefully acidified with concentrated hydrochloric acid, producing a white oily precipitate. This precipitate was removed by extraction with ether, dried over anhydrous magnesium sulfate, and ether removed under vacuum. A 90% yield, based on recovered methyl ester, of a gummy white solid remained. Recrystallization from $30\text{--}60^\circ$ petroleum ether produced a white solid, m.p. $46.0\text{--}47.5^\circ$, λ_{max} 224 $m\mu$ (ϵ 8340). Methylation with diazomethane of a small sample and check *via* v.p.c. indicated the acid to be 100% pure.

Anal. Calcd. for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.97; H, 8.02.

Thionyl Chloride-Pyridine Dehydration of V.—To a solution of 15.0 g. (0.1 mole) of crude V in 10 ml. of dry ether and 19.8 g. (0.25 mole) of pyridine in a 100-ml. flask fitted with a stirrer, condenser, drying tube, and cooled in an ice bath, was added 23.8 g. (0.20 mole) of thionyl chloride over a period of 30 min.³⁸ The solution was then stirred continuously at 100° for 12 hr. The condenser was then removed and heating continued to drive off ether and excess thionyl chloride. After cooling, 50 ml. of a 25% hydrochloric acid solution was added and the dark brown solution extracted with ether. The solution was dried over anhydrous magnesium sulfate and the ether removed under vacuum. The dark, vile-smelling liquid remaining was carefully distilled, yielding two fractions, 8.0 g., b.p. $67\text{--}69^\circ$ (1 mm.), and 6.0 g., b.p. $130\text{--}135^\circ$ (1 mm.). The first fraction gave a good α,β -unsaturated nitrile infrared spectrum, but a v.p.c. analysis indicated two products in a ratio of 90:10. The main peak corresponded to an authentic sample of VII, but further purification by fractional distillation proved difficult. Methanolysis of the mixture according to the previous procedure produced a 90:10 ratio of the corresponding methyl esters. The gas phase re-

teution time of the major peak was again identical with that of a sample of III' and the minor peak corresponded to an authentic sample of methyl bicyclo[2.2.2]oct-2-ene-1-carboxylate (XI').¹² An attempted purification by recrystallization of the corresponding acids failed as indicated by methylation with diazomethane and v.p.c. analysis.

The second fraction gave a saturated nitrile spectrum in the infrared and positive Beilstein test. The crude product also consisted of a 90:10 ratio of products (v.p.c.); five recrystallizations from $90\text{--}100^\circ$ petroleum ether, followed by a sublimation at 1 mm., gave a white waxy solid, m.p. $123\text{--}126^\circ$, which v.p.c. analysis showed to be a mixture of a 95:5 ratio (*cf.* XI, below).

Treatment of 5 g. of the original mixture of the chloronitriles with 50 ml. of a 50% ethanol solution saturated with potassium hydroxide and refluxing for 15 hr. produced, after acidification with hydrochloric acid and extraction with ether, an acid-amide mixture possessing some carbon-carbon double bond character as indicated by the infrared spectrum. The mixture was refluxed for 5 hr. in 50 ml. of methanol and 25 ml. of concentrated sulfuric acid. After work-up, 2.5 g. of a fraction, b.p. 65° (1 mm.), and less than 1 g. of a fraction, b.p. $95\text{--}100^\circ$ (1 mm.), were recovered. The second fraction gave a positive Beilstein test and was undoubtedly the corresponding chloro esters. The first fraction consisted of a mixture of unsaturated methyl esters in a ratio of 70:30, the major isomer corresponding to XI', and the minor isomer to III'. Basic hydrolysis produced the acids in the same ratio.

2-Chlorobicyclo[2.2.2]octane-1-carbonitrile (XI): *Anal.* Calcd. for $C_9H_{12}ClN$: C, 63.74; H, 7.08; N, 8.26. Found: C, 63.93; H, 7.13; N, 8.72.

Direct Hydrolysis of V.—The crude V from 5 g. (0.04 mole) of IV was dissolved in 25 ml. of methanol, 5 ml. of water, and 25 g. of concentrated sulfuric acid. The solution was refluxed for 8 hr., cooled, and extracted with ether. The ether, after being washed with water and dried over anhydrous magnesium sulfate, was removed *in vacuo*. Distillation produced two sweet-smelling fractions: 2.5 g., b.p. $48\text{--}51^\circ$ (0.5 mm.), and 3.0 g., b.p. $88\text{--}92^\circ$ (0.5 mm.). A v.p.c. analysis of the first fraction indicated it to consist of a prohibitive number of components. The infrared spectrum showed a broad carbonyl band but lacked any carbon-carbon double bond, nitrile, or hydroxyl absorptions. The second fraction consisted of two peaks (LAC-446, 160°) in a 60:40 ratio and the infrared spectrum was consistent with an hydroxy ester. The hydroxy esters were not oxidized upon treatment with 2.67 *M* Jones reagent.²⁹

The corresponding hydroxy acids were formed by hydrolysis of 1 g. of the methyl esters by refluxing for 3 hr. in 10 ml. of an 80% ethanol solution containing 3 g. of potassium hydroxide. The neutral products were removed by ether extraction, the solution acidified with dilute hydrochloric acid, and again extracted with ether. Drying and removal of the ether left a white, crude product possessing an hydroxy acid infrared spectrum. Five recrystallizations, however, from pentane and ether, did not raise the melting point beyond $126\text{--}136^\circ$. The analysis is consistent with an hydroxy acid mixture.

Anal. Calcd. for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.59; H, 8.33.

Bicyclo[3.2.1]octane-equat-2-carboxylic Acid (XIII).—Bicyclo[3.2.1]oct-2-ene-2-carboxylic acid (0.50 g., 3.3 mmoles) was dissolved in 10 ml. of ethyl acetate and hydrogenated with 100 mg. of platinum dioxide at 3 atm. The catalyst was removed by filtration through Celite and solvent removed under vacuum, leaving a quantitative yield of a gray mass. Four sublimations at 45° (0.5 mm.) gave a crystalline white solid, m.p. $63\text{--}65^\circ$.

Anal. Calcd. for $C_9H_{12}O_3$: C, 70.08; H, 9.16. Found: C, 70.05; H, 9.15.

Methyl Bicyclo[3.2.1]octane-equat-2-carboxylate (XIII').—Methylation of an ethereal solution of bicyclo[3.2.1]octane-equat-2-carboxylic acid with diazomethane produced the corresponding methyl ester. A v.p.c. analysis using several columns and temperatures indicated the presence of only one component. A few drops of the methyl ester were dissolved in 10 ml. of absolute methanol and a small piece of clean metallic sodium was added. The resulting cloudy solution was refluxed for 24 hr., the condenser being protected with a calcium chloride drying tube. The solution was then neutralized with a drop of hydrochloric acid and most of the methanol removed under vacuum, causing sodium chloride to precipitate. The v.p.c. retention time of the recovered methyl ester was unchanged.

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 71.39; H, 9.59. Found: C, 71.19; H, 9.39.

axial-3-Bromobicyclo[3.2.1]octane-axial-2-carboxylic Acid (IIIa and IIIb).—A 250-mg. sample of III in 25 ml. of toluene was treated with hydrogen bromide at -60° for ca. 15 min. After sealing, the reaction tube was allowed to warm up and stand at room temperature for 3 weeks. After recooling and opening, the tube was allowed to come to room temperature over a 4-day period after which solvent was removed under aspirator pressure. A benzene solution of the residue was clarified with Norit and then evaporated to dryness, the residue being repeatedly recrystallized from heptane; m.p. 101–104°.

Anal. Calcd. for $C_9H_{13}BrO_2$: C, 46.36; H, 5.63; Br, 34.29. Found: C, 46.38; H, 5.52; Br, 34.41.

axial-3-Bromobicyclo[3.2.1]octane-equat-2-carboxylic Acid (IIIb).—A 0.50-g. (3.3 mmoles) sample of III was dissolved in 30 ml. of reagent toluene in a tube and saturated with anhydrous hydrogen bromide in a Dry Ice trap. The tube was sealed and allowed to stand at room temperature for 8 days. An infrared spectrum of the crude product after the toluene was removed indicated about 50% reaction. Three recrystallizations from a 90–100° petroleum ether–benzene mixture gave 0.20 g. (26%) of a white crystalline solid, m.p. 142.0–143.5°.

Anal. Calcd. for $C_9H_{13}BrO_2$: C, 46.36; H, 5.63; Br, 34.29. Found: C, 46.40; H, 5.60; Br, 34.40.

Methyl axial-3-Bromobicyclo[3.2.1]octane-equat-2-carboxylate (IIIb').—Methylation of IIIb with diazomethane produced a single bromo ester as indicated by v.p.c.

Anal. Calcd. for $C_{10}H_{15}BrO_2$: C, 48.60; H, 6.12; Br, 32.33. Found: C, 48.69; H, 6.12; Br, 32.20.

equat-3-Bromobicyclo[3.2.1]octane-equat-2-carboxylic Acid (IIIc).—A 5.0-g. (0.033 mole) sample of III was heated at 100° with 50 ml. of 30% hydrogen bromide in acetic acid in a sealed tube for 3 days. The excess hydrogen bromide and acetic acid were removed under vacuum by mild heating. Three recrystallizations from a 90–100° petroleum ether–benzene mixture gave 4.46 g. (62%) of a white crystalline solid, m.p. 154–155°.

Anal. Calcd. for $C_9H_{13}BrO_2$: C, 46.36; H, 5.63; Br, 34.29. Found: C, 46.40; H, 5.62; Br, 34.20.

Methyl equat-3-Bromobicyclo[3.2.1]octane-equat-2-carboxylate (IIIc').—Methylation of IIIc produced the corresponding methyl ester of a purity greater than 99% (v.p.c.).

Anal. Calcd. for $C_{10}H_{15}BrO_2$: C, 48.60; H, 6.12; Br, 32.33. Found: C, 48.86; H, 6.17; Br, 32.12.

Partial hydrogenolysis of 0.5 g. of the methyl ester in 25 ml. of methanol over 1 g. of 5% palladium-on-carbon at atmospheric pressure for 6 days produced, after removal of catalyst and solvent, a saturated methyl ester which could not be distinguished by v.p.c. from methyl bicyclo[3.2.1]octane-equat-2-carboxylate. The hydrogenolysis proceeded to about 50% completion.

equat-3-Bromobicyclo[3.2.1]octan-2-one (XIV).—To 9.0 g. (0.072 mole) of bicyclo[3.2.1]octan-2-one in 150 ml. of dry ether and 80 ml. of glacial acetic acid was added dropwise 12.0 g. (0.075 mole) of bromine in 135 ml. of glacial acetic acid.^{16,25} The solution was refluxed for 30 hr. during which time the dark color of bromine disappeared. After cooling, 200 ml. of ether was added and the ethereal solution washed with water and dilute sodium bicarbonate. The recovered product, after drying over anhydrous magnesium sulfate and removing the ether under vacuum, was a yellowish oil and a very strong lachrymator. After an initial rough distillation, a careful fractional distillation gave 4.0 g. (27%) of a center cut, b.p. 92–94° (0.1 mm.). Then, after standing at room temperature for 7 days, the yellow liquid began

to crystallize. When solidification was complete the solid was recrystallized three times from a 30–60° petroleum ether–benzene mixture, yielding a white crystalline solid, m.p. 57.0–58.5°.

Anal. Calcd. for $C_8H_{11}BrO$: C, 47.31; H, 5.46; Br, 39.35. Found: C, 47.20; H, 5.34; Br, 39.40.

Kinetic Determinations.—The pseudo-first-order rate constant for hydrogen bromide addition in acetic acid was determined by following the decrease in absorbance at λ_{max} in the ultraviolet spectrum for the α,β -unsaturated acid in question. The dependence on reagent concentration was determined by dilution with glacial acetic acid.

Since it was necessary to run the reactions in sealed ampoules (each containing 40.0 ± 0.3 mg. of sample in 2.0 ± 0.1 ml. of hydrogen bromide–acetic acid reagent), each point was of necessity an individual reaction. The rate constant was determined as an average from a series of determinations, using the same lot of reagent for any given series.

Initial time was taken as the moment of immersion in the thermostated bath and quenching was achieved by immersion in an acetone–Dry Ice slush. The contents of each ampoule was first diluted to 100 ml. and then 2.0 ± 0.1 ml. of the new solution was diluted to 25 ml. with absolute ethanol. Suitable blanks and precisely determined initial absorbance for the substrates were employed.² Data are collected in Table V.

TABLE V
KINETICS OF HYDROBROMINATION

Compound (temp., °C.)	$k \times 10^3$, ^a min. ⁻¹	Half-life, min.	System ^b
I (35 ± 0.2)	7.86 ± 0.41	88	30% HBr–HOAc
	2.79 ± .23	248	1/2(30% HBr–HOAc)
III ^c (100 ± 0.2)	2.99 ± .22	231	30% HBr–HOAc
	1.07 ± .06	648	1/2(30% HBr–HOAc)
III ^d (100 ± 0.2)	4.03 ± .13	172	30% HBr–HOAc
	2.61 ± .32	265	3/4(30% HBr–HOAc)
	1.13 ± .09	613	1/2(30% HBr–HOAc) ^e

^a Pseudo-first-order rate constant. ^b Stock samples of "30% hydrogen bromide" in glacial acetic acid as supplied by Distillation Products. Fractions represent dilutions with glacial acetic acid. Further dilution resulted in nonlinear plots. ^c First sample of HBr–HOAc as supplied by manufacturer. ^d Second sample of HBr–HOAc as supplied by manufacturer. ^e Two molar equivalents of lithium bromide added.

Relative Rate by Competition for trans- Δ^2 -Octalin-2-carboxylic Acid (II).—Equimolar quantities of I and II, 0.81 and 0.82 mmole, respectively, were sealed in a 10-mm. test tube containing 2 ml. of 30% hydrogen bromide. Heating and swirling in a steam bath for almost 10 min. was required for dissolution. The sealed tube was then allowed to stand at room temperature for 2 hr. after which the tube was opened and the acetic acid quickly removed with mild heating under vacuum. The crude product was methylated with diazomethane and subjected to a programmed v.p.c. analysis (LAC 100–150°). That the reaction had proceeded to about 85% completion for both I and II was indicated by the same molar ratio of I to the *cis*- and *trans*-hydrobromides of I (Ia and Ib) as for II to a single octalin hydrobromide (undoubtedly IIa). The octalin hydrobromide decomposed readily to give II at higher column temperatures and came off as a broad band with the column temperatures used.