of Alder and co-workers[16] and hydrogenated to 2-*exo*-bromonorbornane-2-*endo*-carboxylic acid (m.p. 131–132°, reported[16] m.p. 134°) in the presence of acetic acid and platinum oxide catalyst; infrared absorption maxima: 10.45(m), 10.60(s), 10.70(s), 11.08(s), 11.32(s), 11.79(m), 12.38(m), 12.87(m), 13.08(m), 13.72(s) and 15.32(m) $\mu$.

**Hydrogenolysis of 2-*exo*-Bromonorbornane-2-*endo*-carboxylic Acid (I, R = OH).**—One-fourth gram of 2-*exo*-bromonorbornane-2-*endo*-carboxylic acid was dissolved in an ice-cold solution of 0.5 g. of potassium hydroxide in 25 ml. of methanol and hydrogenated[21] in the presence of palladium–charcoal catalyst at 3 atm. pressure. The catalyst was removed by filtration and the solvent was distilled under reduced pressure. The residue was taken up in 10 ml. of water and acidified with concentrated hydrochloric acid. The precipitated norbornane-2-*endo*-carboxylic acid (m.p. 58–60°) was recrystallized from pentane, m.p. 65–66° (reported[4] m.p. 65–66°).

**2-*exo*-Bromo-2-*endo*-carbomethoxynorbornane (I, R = $OCH_3$).** (a) **From I (R = Cl).**—A solution of 25 g. of 2-*exo*-bromonorbornane-2-*endo*-carbonyl chloride in 100 ml. of cold methanol was allowed to stand for one hour at room temperature and the solvent was removed by distillation under reduced pressure on the steam-bath. The residue was taken up in ether, washed with saturated sodium bicarbonate solution and dried superficially by shaking for several minutes with anhydrous magnesium sulfate. Distillation of the ether solution gave 22.0–23.2 g. (90–95%), b.p. 97–99° (5 mm.), $n^{24.5}D$ 1.5043; infrared absorption maxima: 10.33(w), 10.54(w), 10.63(m), 10.87(m), 11.33(w), 11.58 (w), 11.77(w), 12.12(w), 12.35(w), 12.80(w), 13.08(w), 13.30(w), 14.45(m) and 14.55(m) $\mu$.

*Anal.* Calcd. for $C_9H_{13}BrO_2$: C, 46.37; H, 5.62. Found: C, 46.42; H, 5.36.

(b) **From I (R = OH).**—One gram of 2-*exo*-bromonorbornane-2-*endo*-carboxylic acid was dissolved in ether and esterified with an excess of diazomethane in ether. When the evolution of nitrogen had subsided the solution was distilled under reduced pressure. The distillate (1.0 g.) boiled at 120–121° (28 mm.), $n^{25}D$ 1.5041.

**Hydrogenolysis of 2-*exo*-Bromo-2-*endo*-carbomethoxynorbornane (I, R = $OCH_3$).**—Reduction of 2-*exo*-bromo-2-*endo*-carbomethoxynorbornane with hydrogen in the presence of methanol, palladium chloride and calcium carbonate or with zinc and acetic acid by the procedures employed for the reduction of compound I (R = $NH_2$) gave 2-*endo*-carbomethoxynorbornane (III, R = $OCH_3$), b.p. 70–71° (5 mm.), $n^{24.5}D$ 1.4630 (reported[15] b.p. 82° (15 mm.)).

Saponification of the debrominated ester by refluxing for one hour with 20% aqueous potassium hydroxide solution and subsequent acidification with concentrated hydrochloric acid gave norbornane-2-*endo*-carboxylic acid (m.p. 65–66° from pentane).

**2-*exo*-Bromo-1-carbomethoxynorbornane (II, R = $OCH_3$).**—An excess of ethereal diazomethane (from 21.5 g. of N-methyl-N-nitroso-*p*-toluenesulfonamide) was added dropwise to a solution of 10.5 g. of 2-*exo*-bromonorbornane-1-carboxylic acid in 250 ml. of ether. Distillation of the solution after the reaction had subsided gave 10.9 g. (98%), b.p. 117–118° (5 mm.), $n^{24.5}D$ 1.5055; infrared absorption maxima: 10.18(m), 10.25(m), 10.32(s), 10.59(s), 10.71(m), 11.01(m), 11.79(m), 12.18(w), 12.45(m), 13.05(m) and 13.39(m) $\mu$.

*Anal.* Calcd. for $C_9H_{13}BrO_2$: C, 46.37; H, 5.62. Found: C, 46.25; H, 5.72.

**Hydrogenolysis of 2-*exo*-Bromo-1-carbomethoxynorbornane (II, R = $OCH_3$).**—Reduction of this ester by either of the procedures employed for compound I (R = $NH_2$) gave, after saponification with 20% aqueous potassium hydroxide solution and acidification with concentrated hydrochloric acid, norbornane-1-carboxylic acid (m.p. 111–112° from pentane).

**Hydrogenolysis of 2-*exo*-Bromonorbornane-1-carboxylic Acid (II, R = OH).**—An ice-cold solution of 21.9 g. of 2-*exo*-bromonorbornane-1-carboxylic acid and 16.8 g. of potassium hydroxide in 200 ml. of water was hydrogenated at 3–4 atm. pressure in the presence of palladium–charcoal catalyst. The absorption of hydrogen was complete in one hour and the catalyst was removed by filtration. The filtrate was acidified with concentrated hydrochloric acid, the precipitate was filtered off, washed with a little cold water and dried over calcium chloride *in vacuo*. The crude product (12.8 g., m.p. 109–111°) was purified by sublimation[8,9] *in vacuo* to give 12.2 g. (87%) of norbornane-1-carboxylic acid, m.p. 111–112°.

SOMERVILLE, N. J.

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(21) L. F. Fieser and W. T. Huang, THIS JOURNAL, 75, 4837 (1953).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF DELAWARE]

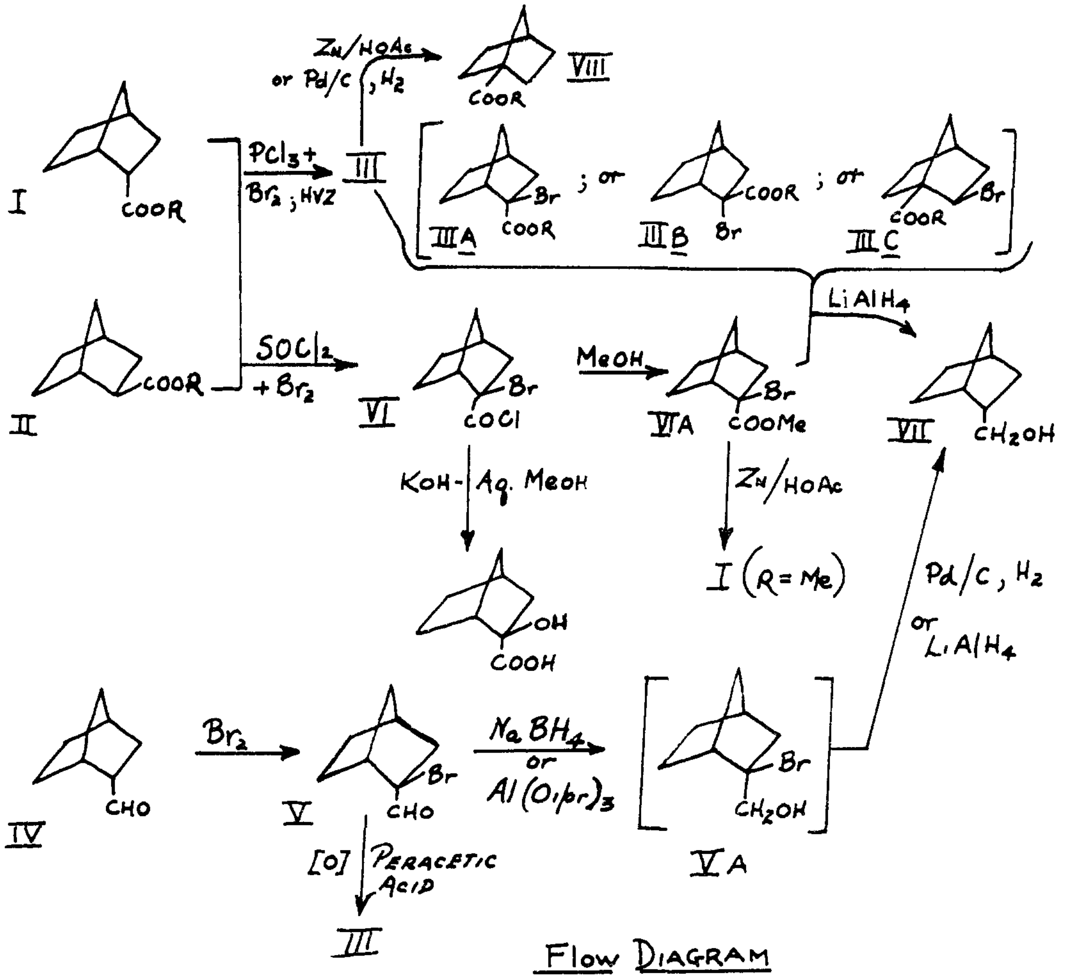
# The Course of Bromination in Bicyclo[2.2.1]heptanecarboxylic Acids; the Observation of Rearrangement During a Reduction of β-Bromoacids

BY HAROLD KWART AND GEORGE NULL

RECEIVED JUNE 18, 1958

The bromination of both *exo*- and *endo*-norbornane-2-carboxylic acids produced the identical bromoacid derivative using $PCl_3$ and Hell–Volhard–Zelinsky conditions. Bromination in thionyl chloride solution yielded an isomeric bromoacid derivative. The rearranged structure IIIc is assigned to the former and structure VI (R = H) to the latter on the basis of evidence of hydrogenolysis with palladium-charcoal-hydrogen, zinc-acetic acid, and lithium aluminum hydride and, finally, decisive evidence deduced from nuclear magnetic resonance measurements. Reversal of Wagner–Meerwein rearrangement is established for the course of $LiAlH_4$ hydrogenolysis of III. The higher rate of formation of the product on bromination of the *endo*-acid I is correlated with the greater ease of abstraction of an *exo* (equatorial) proton in the formation of the enolic intermediate in the bromination reaction. The hydrogenolysis reaction with zinc in acetic acid which involves the same intermediate apparently exhibits the same preference for equatorial attack. The formation of the rearranged bromoacid IIIc has also been noted to occur in good yield on direct bromination in the absence of $PCl_3$, $SOCl_2$ or any extraneous solvent. The ready solvolysis of the bromine in the bromoacid chloride of IIIa has been observed during attempts to prepare the pure bromoacid of IIIa. These and other results have been considered in a discussion of the factors that produce Wagner–Meerwein rearrangement of the IIIa bromoacid derivatives.

In the course of studies on the bromination of the *endo*- and *exo*-norbornane-2-carboxylic acids, hydrogenolysis of the common bromination product III under a variety of conditions was explored as a possible means of establishing the stereochemistry of the reaction. Treatment of the methyl ester of III with zinc and acetic acid furnished the norbornane-1-carboxylic ester (VIII) in good yield. Reduction of the ester III with lithium aluminum hydride, on the other hand, furnished the *endo*-2-methylolnorbornane (VII). These results permit two alternative interpretations: (a) either that hydrogenolysis with zinc–acetic acid had led to rearrangement, or (b) that carbon skeleton rearrangement had occurred in both the bromination and the lithium aluminum hydride



Flow Diagram

reduction. Our initial interpretation of the course of reaction was the former and our preliminary communication[1] of these results was based on this premise.

An article which appeared almost simultaneously with our communication by Alder, Hartmann and Roth[2] cast some doubt on this interpretation, however. These authors had prepared by Diels–Alder condensation of $\alpha$-bromoacrylic acid and cyclopentadiene a bromacid assigned the structure of IIIa which differed in its properties from the common bromination product of I and II whose structure we had inferred as IIIa. Subsequently, the possibility that rearrangement had accompanied the bromination step was independently advanced by Boehme[3] on the basis of studies with the related amide. We were therefore led to reinvestigate the problem of the structure of the bromination product, with the result that unequivocal evidence for the course of the reactions as indicated on the accompanying flow diagram now has been obtained.

## Results and Discussion

**Structure of the Bromination Products on the Course of Bromination.**—The common bromination product III was treated with lithium aluminum hydride in the manner of Eliel and co-workers who have studied the hydrogenolysis of the halogen atom in the reduction of haloacids.[4] The result of brief reaction appeared to be a very difficultly separable mixture of the bromohydrin and carbinol. Overnight stirring in the presence of excess reducing agent served to complete the hydrogenolysis and resulted in a good yield of pure carbinol readily identified as the *endo*-2-methylolnorbornane (VII) by infrared comparison with the products of reduction of I and II with lithium aluminum hydride and mixed melting points of the *p*-nitrobenzoate derivatives. However, when hydrogenolysis of the bromoacid III was undertaken with hydrogen and palladium–charcoal catalyst[5] or with zinc and acetic acid according to well known procedures, the rearranged norbornane-1-carboxylic acid (VIII, R = H) was isolated in high conversion.[6] It was obvious that rearrangement had accompanied only one of the hydrogenolysis reactions, either with the lithium aluminum hydride or the metallic reductions. Appropriate mechanistic arguments could be advanced to justify either conclusion. A choice between these alternatives was first attempted on

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[1] H. Kwart and G. Null, THIS JOURNAL, **80**, 248 (1958).

[2] K. Alder, R. Hartmann and W. Roth, *Ann.*, **613**, 6 (1958).

[3] W. R. Boehme, THIS JOURNAL, **80**, 4740 (1958).

[4] (a) E. L. Eliel, C. Herrmann and J. T. Traxler, *ibid.*, **78**, 1193 (1956); (b) E. L. Eliel and J. T. Traxler, *ibid.*, **78**, 4049 (1956).

[5] L. F. Fieser and W. T. Huang, *ibid.*, **75**, 4837 (1953).

[6] The norbornane-1-carboxylic acid, the highest melting of the monocarboxylic acids in this series, was identified by comparison with a sample kindly provided by Dr. W. von E. Doering of Yale University.

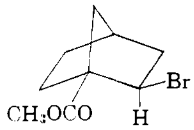
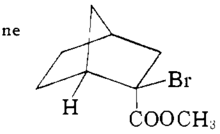
the basis of an examination of the bromination reaction with closely related norbornane derivatives. When the *endo*-aldehyde IV was brominated, presumably *via* an analogous enolic intermediate, a bromoaldehyde V was produced in good yield. Mild reduction of V with sodium borohydride or aluminum isopropylate, conditions which do not ordinarily afford hydrogenolysis of α-bromocarbonyl compounds, gave a bromohydrin (Va) which could now be reduced with palladium or zinc reagents to the *endo*-carbinol, VII. The bromoaldehyde V thus has the *endo*-aldehyde configuration. When V was subjected to oxidation at room temperature with peracetic acid the bromoacid that resulted in high yield was identified as the HVZ product III. On this basis, therefore, it could be surmised that III has the structure IIIa, if the assumption was made that no rearrangement took place under the mild reaction conditions by which the transformation from V was accomplished. On the other hand, if Wagner–Meerwein rearrangement had taken place here, the unusual ease with which this step occurred would require explanation.

Moreover, the conclusions to be derived from these experiments were not considered definitive on other grounds. It could be argued that, while the palladium or zinc reagents did not effect rearrangement of the bromohydrin, the ability to rearrange may be specifically a property of the α-bromocarbonyl when steric requirements for the Wagner–Meerwein are being met. Corey and Sneen,[7] for example, have discussed a mechanism for hydrogenolysis with zinc and acetic acid involving the intermediate formation of enol which is based on observations in systems (α-bromocyclohexanones) where Wagner–Meerwein rearrangements do not generally occur with great ease. Furthermore, since it has been fairly well established[4a] that the halohydrin is intermediate in the hydrogenolysis of α-haloacids with $LiAlH_4$, the demonstration that the bromohydrin possessing the structure of Va underwent hydrogenolysis with $LiAlH_4$ to yield the *endo*-carbinol VII suggests the possibility that $LiAlH_4$ had not rearranged the bromoacid III when it reduced it to VII.

In the hope of resolving these contradictions we undertook an extensive examination of the possible influence of reaction conditions on the course of bromination. The HVZ reaction undoubtedly proceeds *via* the formation of the acid chloride or anhydride which possesses far more readily enolizable carbonyl functions than the acid. Consequently, the acid chloride of I was prepared and subjected to bromination under comparable conditions of temperature but in more dilute solution than prescribed for the HVZ reaction. A liquid bromoacid chloride VI was obtained which could not readily be freed of a persistent colored impurity. When this product was compared with the bromoacid chloride prepared from III by reaction with hot thionyl chloride in the familiar manner it proved to be entirely different. The latter was a solid, m.p. 51–53°, readily recrystallizable from hydrocarbon solvents. Both bromoacid chlorides led to different derivatives, the methyl esters being distinguished by infrared and the amides by melting and mixed melting points.

Again, the bromoacid chloride VI could conceivably have had any of the three alternative structures IIIa, IIIb or IIIc (OR = Cl). Studies on hydrogenolysis with $LiAlH_4$ and palladium or zinc reagents were therefore undertaken to establish a distinction. Reduction of the ester with zinc–acetic acid resulted in the *endo*-ester I in contrast to III which formed the rearranged bridgehead ester VIII (R = methyl). On the other hand, when the methyl ester VIa was treated with $LiAlH_4$ under the reaction conditions previously applied to this derivative of III, the identical carbinol VII was obtained. Once again, therefore, the assignment of structure (to III or VI) was clouded by a choice based on the possible occurrence of rearrangement in one of the hydrogenolysis steps. It might have been argued reasonably (a) that the bromoacid derivatives of VI possessed the structure IIIc and had reverted to the same acid derivative as a result of rearrangement during hydrogenolysis with both $LiAlH_4$, palladium and zinc reagents, or (b) that VI had the epimeric structure IIIb and failed to undergo Wagner–Meerwein rearrangement with any of the hydrogenolysis reagents because the *endo*-bromine did not possess the steric requirements for participation by neighboring carbon.[8] Apparently, a satisfactory decision among the alternatives could only be achieved by use of a physical method. A unique solution was secured by resorting to the nuclear magnetic resonance spectra of the methyl ester of III and VIa.

TABLE OF NUCLEAR MAGNETIC RESONANCE DATA AND INTERPRETATION

| | Observed Proton Resonances[a] | | | |
|---|---|---|---|---|
| Compd. | Peak position c.p.s.[b] | Relative area under peak | Identification of distinguishable hydrogen atoms | Assigned structure |
| III (R = $CH_3$) | −121 | 6 | Ring methylene |  |
| | − 97 | 3 | Bridge and bridgehead | |
| | − 39 | 3 | -O methyl | |
| | − 20 | 1 | Bromo-methinyl | |
| VIa | −133 | 6 | Ring methylene |  |
| | − 93 | 4 | Bridge and bridgehead | |
| | − 37 | 3 | -O methyl | |

[a] See Experimental section for measurement method. [b] Displacements measured in cycles per second from the water proton resonance at approx. 25°.

As will be noted in the accompanying table of n.m.r. data the two compounds III and VIa are readily distinguishable by the number and kinds of protons identified in their spectra. The additional resonance associated with III and not to be found in VIa occurs at considerably lower field and is characteristic of a much less covalent (more positive hydrogen) bond to carbon than the remaining –C–H bonds. This corresponds very well to the description of the bromomethinyl, *i.e.*, the proton bonded to carbon substituted by the electronegative bro-

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[7] E. J. Corey and R. A. Sneen, THIS JOURNAL, **78**, 6269 (1956).

[8] See for examples S. Winstein and D. S. Trifan, *ibid.*, **71**, 2953 (1949); **74**, 1154 (1952).

mine atom that is evident only in the structure assigned to III. The absence of this resonance in VI and the correspondence of areas and displacements of the observed bonds with the assigned structures complete the identifications.

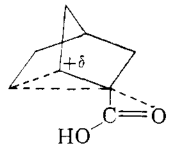
One other observation in the n.m.r. data table merits attention; the bridge and bridgehead hydrogens of the bicyclo[2.2.1]heptane nucleus are very similar to each other and almost indistinguishable at ordinary resolution (at 40 Mc.). Furthermore, they are apparently at lower fields and are somewhat less covalent than the ring methylene hydrogens. This increased ionic character of the bridge and bridgehead hydrogens in bicyclic structures has been observed repeatedly in these laboratories and will be discussed in a future publication.

The assignment of the *exo*-bromo *endo*-carboxy structure IIIa to the bromination product is distinguished from the epimeric arrangement of these groups in structure IIIb. This assignment is based on the now firm conclusion that the hydrogenolysis with the zinc and acetic acid reagent did not proceed with rearrangement and in fact occurred in the normal fashion[7] *via* protolysis of the enolic intermediate, more or less parallel to the steric course of the bromination of the acid chloride leading to formation of VI. Thus the bromine in VI must have the same configuration as the $C_2$-hydrogen in the zinc–acetic acid hydrogenolysis product I.

**The Course of Rearrangement during Bromination.**—Evidently the hydrogenolysis with $LiAlH_4$ of the rearranged bromoacid IIIc involved reversion[9] of the Wagner–Meerwein rearrangement by which IIIc had been formed under HVZ conditions from I or II. It remained to be determined at which step the isomerization had occurred during the bromination. It seemed likely that the acid chloride or anhydride, which have been presumed to form as the enolizable intermediates in the HVZ reaction, had resulted initially in the unrearranged bromoacid chloride VI, which, in turn, had undergone Wagner–Meerwein rearrangement to IIIc in the presence of the electrophilic catalyst used in the HVZ ($PCl_3$ + $Br_2$ or $POCl_3$). However, when I or II was treated with $PCl_3$ + $Br_2$ in an excess of $SOCl_2$ only the unrearranged bromoacid chloride VI was obtained; nor could any isomerization of VI be effected by prolonged heating on the steam-bath with $POCl_3$ or $PCl_3$ + $Br_2$. Evidently the bromoacid chloride VI (or IIIa, OR = Cl) was *not* a precursor of the product of HVZ bromination. This conclusion could also be deduced from the results of experiments involving direct bromination of the acids I or II in the absence of extraneous electrophilic reagents or polar solvents like $PCl_3$ or $SOCl_2$. Normally in the absence of such reagents direct bromination of carboxylic acids takes a random course with substitution occurring at all C–H bonds on a hydrocarbon chain, due to the fact that enolization involving the carboxylic acid group is considerably reduced from the situation in other carbonyl compounds where bromination occurs exclusively alpha. But, when nearly equimolar amounts of bromine and I were heated together on a steam-bath, HBr was rapidly evolved. After seven hours the reaction, worked up in the usual manner, afforded an excellent yield of the rearranged bromoacid IIIc.

All of these observations appear to be understandable on the basis of well established mechanistic concepts if it is assumed that the *exo*-bromo-*endo*carboxylic acid (IIIA, R = H) (or possibly anhydride) is formed first during the bromination. This substance which was reported by Alder, Hartmann and Roth[2] is apparently quite reactive compared to ordinary aliphatic and alicyclic α-bromoacids and undergoes ready isomerization in polar media, analogous to the behavior of camphene hydrochloride.[10] When the acid chloride VI was warmed at 35° in aqueous methanol containing two equivalents of base, the bromine was entirely replaced within a 4-hour period and the ether extracted product was identified as a fairly pure sample of 2-*exo*-hydroxy-2-*endo*-carboxynorbornane.[11] The formation of the rearranged bromoacid IIIc during mild oxidation of the unrearranged bromoaldehyde V at room temperature in peracetic–acetic acid solution is also explained by the high Wagner–Meerwein reactivity of the postulated intermediate bromoacid IIIa (R = H).

Assuming anchimeric assistance[12] for ionization the C–Br bond and intermediate bridged ion formation,[8,12] it would appear that an additional factor must enter which depends on the nature and extent of substitution at the brominated carbon. In IIIa (R = H) the carboxylic acid group affords little retardation of the C–Br bond ionization as compared to the effect of the strongly electron-attracting acid chloride group. Conceivably stabilization of the bridged ion by the carboxylic acid group may be achieved through the equivalent of α-lactone formation as in



Vaughan and Schoenthaler recently considered a similar intermediate in the Wagner–Meerwein rearrangement of bromoacids in a series of dibenzo-[2,2.2]bicyclooöctadienes.[13] An analogous intermediate has much less likelihood of occurring in the acid chloride because of the group dipolar resonance involving the unshared pairs of both the carbonyl oxygen and halogen. Moreover, such α-lactone participation has increased likelihood of occurrence with the anhydride group because of the very

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[9] The term retro-Wagner–Meerwein rearrangement is suggested to denote reversal of the course of Wagner–Meerwein rearrangement as retro-pinacol is used for reversal of the course of pinacol rearrangement.

[10] H. Meerwein and K. Van Emster, *Ber.*, **53**, 1821 (1920); **55**, 2506 (1922); see also P. D. Bartlett, *et al.*, THIS JOURNAL, **60**, 1585 (1938); **63**, 1273 (1941).

[11] The complete identification of this substance by degradative and synthetic methods and by evidence deduced from boric acid conductivity and periodic acid tests on its diol reduction product constitutes the basis of a future report from these laboratories on another subject. These data are published in the Ph.D. thesis of G. Null, University of Delaware, Newark, Del., June, 1958.

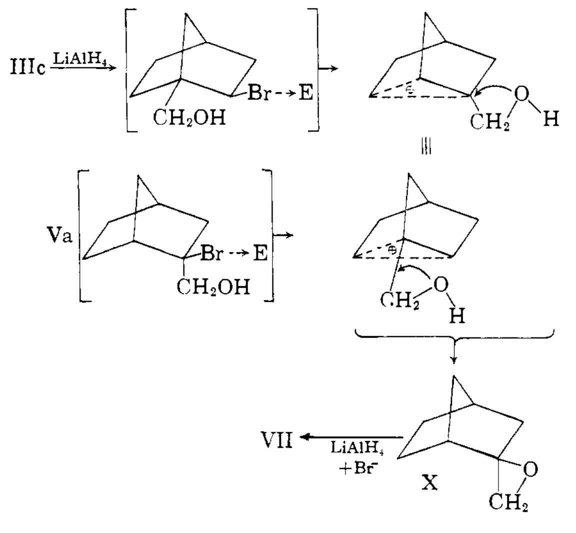
[12] S. Winstein, C. R. Lindegren, H. Marshall and L. L. Ingraham, *ibid.*, **75**, 147 (1953).

[13] W. R. Vaughan and A. C. Schoenthaler, *ibid.*, **80**, 1956 (1958), and preceding articles in this series.

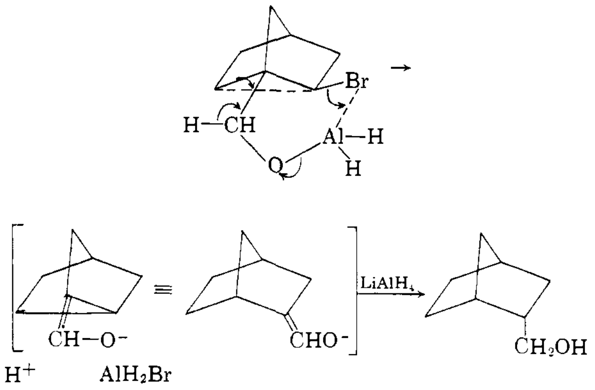
reduced dipolar resonance involving the ether oxygen. A bromoanhydride intermediate in the HVZ reaction would be expected on this basis to undergo Wagner–Meerwein isomerization with greater facility than the bromoacid chloride.

The ability of the carboxamide oxygen to enter into neighboring group participation is well established.[14] The initial formation in the isoimidinium salt during acylation of amides[15] appears to be another example of the inherent nucleophilicity of the carboxamide oxygen atom. The implication of this property is borne out by the observation of Boehme that the carboxamide of IIIa, (OR = $NH_2$), experiences a rearrangement when heated above its melting point or on standing in basic solution.[3] The course of the bromination of the acid derivatives and the occurrence of the Wagner–Meerwein rearrangement thus appears to be correlated with resonance factors and the residual nucleophilic properties characteristic of the carbonyl oxygen.

**The Mechanism of Rearrangement during Hydrogenolysis with $LiAlH_4$.**—It has been shown above that rearrangement occurs during reduction of a $\beta$-bromoacid derivative with $LiAlH_4$ but fails to occur during hydrogenolysis with palladium–charcoal or zinc–acetic acid reagent. The retro-Wagner–Meerwein rearrangement that attends the reduction with $LiAlH_4$ is consistent with either of two alternative reaction mechanisms. On the basis of a carbonium ion mechanism leading from the bromohydrin an intermediate epoxide is predicted which then undergoes further reduction with the $LiAlH_4$, as shown below, where E represents the electrophilic properties of the aluminum. Note that the identical bridged ion is presumed to form either from IX or Va *via* electrophilic assistance to ionization of the *exo*-bromine and this, in turn, results in the *exo*-epoxide X. The stabilization of the bridged ion by participation of the carbinol group is considered to be the driving force for reversal of the Wagner–Meerwein rearrangement that had initially produced the bromoacid derivative IIIc. It has been established by Eliel and Delmonte[16] that the course of $LiAlH_4$ reduction of the epoxide intermediate in the hydrogenolysis of $\alpha$-bromocarbonyl compounds is the reverse of the normal one, in that the least substituted alcohol is produced. The abnormal behavior was attributed to the presence of bromide ions.



Illustrations produced by Curtin and Meislich[17] in which it is proved that the epoxide is often not an intermediate in the specific ion-catalyzed rearrangement of $\alpha$-bromohydrins suggest that the carbonium ion mechanism considered above must be viewed with reservations until further study. Moreover, the retro-Wagner–Meerwein rearrangement may also be visualized as occurring from the bromohydrin *via* a cyclic mechanism formally analogous to routes by which the allylic rearrangement is often reversed.[18]



**The Relative Rates of Bromination of Norbornane-2-carboxylic Acids.**—The observation of stereospecificity in the course of kinetically controlled ketonization in cyclohexane systems[19] initially suggested this inquiry into the factors that regulate the analogous reactions in the bicyclo[2.2.1]heptane system. Bromination of the $\alpha$-carbonyl position is normally understood to involve an enolic intermediate.[20] This system is particularly suited for study of the stereochemical course of addition to the enol because the resulting brominated structure contains no further enolizable hydrogen that might lead to epimerization and the thermodynamically most stable product.

When norbornane-2-*endo*-carboxylic acid (I) was brominated in the presence of a small amount of phosphorus trichloride or oxychloride under familiar Hell–Volhard–Zelinsky conditions[21] a single bromoacid was obtained in good yield. The same product resulted when the *exo* isomer II was sub-

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[14] See for examples, K. Pfister, C. A. Robinson, A. C. Shabica and M. Tishler, THIS JOURNAL, **70**, 2297 (1948), and G. E. McCasland, R. K. Clark and H. E. Carter, *ibid.*, **71**, 637 (1949).

[15] D. Davidson and H. Skovronek, *ibid.*, **80**, 376 (1958).

[16] E. L. Eliel and D. W. Delmonte, *ibid.*, **80**, 1737 (1958).

[17] D. Y. Curtin and E. K. Meislich, *ibid.*, **74**, 5905 (1952).

[18] For examples of this see J. Meisenheimer and J. Link, *Ann.*, **479**, 211 (1930), and J. D. Roberts, W. G. Young and S. Winstein, THIS JOURNAL, **64**, 2157 (1942).

[19] H. E. Zimmerman, *J. Org. Chem.*, **20**, 549 (1955); THIS JOURNAL, **78**, 1168 (1956); H. E. Zimmerman and H. J. Giallombardo, *ibid.*, **78**, 6259 (1956), et seq.

[20] See for a full discussion of this point, L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapt. VIII.

[21] R. Linstead, W. von E. Doering, S. Davis, P. Levine and R. Whetstone, THIS JOURNAL, **64**, 1985 (1942).

jected to identical reaction conditions. The rates of formation of product from I and II were shown to be significantly different, however, the *endo*-acid undergoing bromination approximately five times more rapidly than the *exo*.[22] Clearly, the same product must have formed stereospecifically from a common enolic intermediate arising from both the *endo*- and *exo*-acids. The rate difference corresponds, therefore, to the greater ease of enolization of the *endo* isomer; that is, an *exo* proton is more readily abstracted by base than the heavily shielded (axial) *endo* proton. Corey and Sneen[7] have reported that in enolization–ketonization reactions of certain alicyclic systems stereoelectronic factors favor axial over equatorial attack by a factor of at least 12 when correction is made for steric retardation of axial attack. It would appear that the bicyclic system (which is essentially the boat form of cyclohexane) affords a steric factor in electrophilic reactions of the ring that outweighs the stereoelectronic preference and produces complete favor for equatorial attack.

## Experimental

All melting points given below are uncorrected.

**Norbornane-2-*endo*carboxylic acid** (I) was prepared according to a procedure by Alder and co-workers.[23] The purification steps to separate the *exo* isomer described by Ver Nooy and Rondestvedt[24] were followed in detail. **Norbornane-2-*exo*-carboxylic acid** (II) was obtained from 1 (above) following the method of Alder and Stein.[23,25] **2-Norbornane-*endo*-carboxaldehyde** (IVa) was prepared following the method of Diels and Alder.[26] **Norbornane-2-*endo*-carboxaldehyde** (IV) was obtained by reduction of IVa over platinum catalyst in a Parr hydrogenator at approx. 3 atmospheres. The product, vacuum distilled (b.p. 42–44° at 0.8 mm.), $n^{25}$D 1.4760 (lit.[26] b.p. 75–76° at 25 mm.). gave a negative unsaturation test and yielded an almost quantitative 2,4-dinitrophenylhydrazone derivative, m.p. 143–144° after recrystallization from ethanol.

*Anal.* Calcd. for $C_{14}H_{16}N_4O_4$: C, 55.25; H, 5.30; N, 18.41. Found: C, 54.79; H, 5.25; N, 18.87.

**The Bromination of Norbornane-2-*endo*-aldehyde.**—Using the method of Heilbron, *et al.*,[27] 90 g. (0.72 mole) of aldehyde IV, 265 cc. of freshly distilled chloroform and 50 g. of finely powdered calcium carbonate was cooled to −5 to −15° and treated under stirring with 115.8 g. of bromine in 100 cc. of chloroform, added dropwise during 4 hr. After the addition was completed, the reaction was allowed to warm to room temperature (26°) and stirred overnight. The chloroform solution was freed from the calcium carbonate by filtration, washed several times with sodium bicarbonate solution, twice with sodium thiosulfate solution, several times with water and finally leaving a red-brown liquid residue which was distilled: b.p. 71–72° (1 mm.), 80.4 g., yield 55%. This compound gave positive tests with 2,4-dinitrophenylhydrazone reagent and alcoholic silver nitrate. *Anal.* Calcd. for $C_8H_{11}BrO$: Br, 39.35. Found: Br, 40.06. Note: This bromoaldehyde is quite unstable and rapidly decomposes unless stored under refrigeration.

**The Reaction of 2-*exo*-Bromonorbornane-2-*endo*-aldehyde (V) with Sodium Borohydride.**—To a well-stirred mixture of 2.35 g. (0.062 mole) of sodium borohydride and 60 cc. of absolute ethanol, cooled to 16°, was added dropwise 14 g. (0.07 mole) of the bromoaldehyde V dissolved in 15 cc. of absolute ethanol. After the addition was completed (45 min.), the reaction mixture was stirred at 16° for an additional 45 min., then at room temperature (26°) for 2.5 hr. The reaction mixture was treated with 60 cc. of 6 *N* sulfuric acid, then poured into 200 cc. of water and extracted three times with diethyl ether. The ether extracts were washed with water and dried over magnesium sulfate. Approximately 12.2 g. of the crude bromohydrin was obtained after removal of the solvent. Owing to the ready decomposition of this compound when heated, no distillation was attempted on the whole amount. An aliquot was distilled for analysis: b.p. 55–56° (0.4 mm.). This distillate gave positive test for hydroxyl with ceric nitrate reagent and for bromine with alcoholic silver nitrate. Because of the ready decomposition of the bromohydrin on standing, a good analysis could not be obtained. The crude bromohydrin Va was subjected to hydrogenolysis to yield the corresponding alcohol VII, b.p. 62° (0.5 mm.), $n^{25}$D 1.4870; derivative. *p*-nitrobenzoate, m.p. 87–87.5°. Admixture of this derivative with an authentic sample gave no m.p. depression and the infrared spectra of known and unknown *p*-nitrobenzoates were identical.

*Anal.* Calcd. for $C_{15}H_{17}NO$: C, 65.41; H, 6.22. Found: C, 65.57; H, 6.16.

**The Reduction of V with Aluminum Isopropoxide.**—Following the procedure of Elderfield, *et al.*,[28] 12.9 g. (0.064 mole) of the bromoaldehyde V was added, during 5 min., to a vigorously boiling mixture of 12 g. of aluminum isopropoxide and 40 cc. of 2-propanol. Distillation, at the rate of 2 to 3 drops per sec., was carried out for 45 min.; during this time fresh 2-propanol was added to maintain a constant volume. On completion of the reaction, the 2-propanol was removed in a rotating evaporator. The residue was treated with a mixture of 20 cc. of concentrated hydrochloric acid and 30 g. of cracked ice, then extracted four times with diethyl ether. The ether extracts were washed four times with a saturated magnesium sulfate solution and dried over magnesium sulfate. Evaporation of the solvent yielded 9 g. of a viscous brown liquid which gave positive tests with ceric nitrate reagent and alcoholic silver nitrate.

The crude bromohydrin Va was subjected to hydrogenolysis to yield the corresponding alcohol VII, b.p. 70–71° (1–1.2 mm.), $n^{25}$D 1.4860; derivative, *p*-nitrobenzoate, recrystallized from methanol, m.p. 83–84°. A mixed m.p. and a comparison of infrared spectra proved this *p*-nitrobenzoate to be identical with the known alcohol derivative.

**The HVZ Bromination of the Norbornane-2-carboxylic Acids I and II; The Preparation of III and its Derivatives.**—Initially 49.2 g. (0.35 mole) of the acid I or II, 63.8 g. (0.4 mole) of bromine and 1.5 cc. of phosphorus trichloride were heated on a steam-bath (80–90°) for 7.5 hr. After cooling, the mixture was taken up in diethyl ether, the ether solution washed with sodium bisulfite, then several times with water and finally dried over magnesium sulfate. On removal of the ether, a yellow crystalline solid was obtained which weighed 60.4 g., yield generally 70–80%. The solid on being washed with (30–60°) petr. ether, decolorized with Norite, and recrystallized from benzene or nitroethane gave a m.p. of 151° (uncor.).

*Anal.* Calcd. for $C_8H_{11}BrO_2$: C, 43.83; H, 5.06; Br, 36.48. Found: C, 44.05; H, 5.12; Br, 36.46.

**Derivatives: The Bromoacid Chloride IIIc (OR = Cl).**—A solution of 11.0 g. of the bromoacid product above in 20 cc. of thionyl chloride was refluxed on the steam-bath until HCl evolution had ceased (about 2 hours). The excess thionyl chloride was boiled off under vacuum leaving a light tan solid; recrystallization from pentane yielded a colorless product, m.p. 51–53°.

**The Bromoacid Amide IIIc (OR = $NH_2$).**—A solution of 3.0 g. of the bromoacid chloride (above) in 10 cc. of ether was dropped into an ice-cold (*ca.* −5°) concd. aqueous ammonia under vigorous agitation. After addition the mixture was heated on a steam-bath until all the ether had boiled away. The residual precipitate, after filtration and washing with warm water and recrystallization from benzene–ethyl acetate melted at 174°. *Anal.* Calcd. for

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[22] The relative rates of bromination of *exo*- and *endo*-acids in the present of $PCl_3$ must still be considered an indication of the greater enolizability of the *endo*-acid. The occurrence of rearrangement in the bromoacid does not affect this rate relationship since the reaction was followed directly by a bromimetric titration; see Experimental.

[23] K. Alder, G. Stein, M. Liebamann and E. Rolland, *Ann.*, **514**, 197 (1934).

[24] C. D. Ver Nooy and C. S. Rondestvedt, THIS JOURNAL, **77**, 3583 (1955).

[25] K. Alder, G. Stein, E. Rolland and G. Schulze, *Ann.*, **514**, 211 (1934).

[26] O. Diels and K. Alder, *ibid.*, **460**, 98 (1928).

[27] I. Heilbron, E. Jones, R. Richardson and F. Sondheimer, *J. Chem. Soc.*, 737 (1949).

[28] R. C. Elderfield, C. B. Kremer, S. M. Kupchan, O. Birstein and G. Cortes, THIS JOURNAL, **69**, 1259 (1947).

$C_8H_{12}BrNO$: C, 44.05; H, 5.55. Found: C, 44.13; H, 5.54.

**The Methyl Ester of IIIc (R = Me).**—An excess of freshly prepared diazomethane[29] (dried over potassium hydroxide) was added dropwise with stirring to a solution of 19 g. (0.087 mole) of the bromoacid III in 300 cc. of diethyl ether maintained at 0°. A yellow color, evidence of an excess of diazomethane, persisted after the addition had been carried out for 0.5 hr. The excess diazomethane was evaporated on a steam-bath and the remaining ether solution was dried over magnesium sulfate. Removal of the ether left a slightly yellow liquid which was fractionally distilled: b.p. 108–110° (4.8 mm.), $n^{24}\mathrm{D}$ 1.5056, wt. 16.2 g., yield 80%.

**The Hydrogenolysis of the Methyl Ester of III with Zinc–Acetic Acid.**—A mixture of 14.5 g. (0.062 mole) of the bromo ester, 20.3 g. (0.31 mole) of zinc and 100 ml. of glacial acetic acid was warmed to 40° and stirred for 42 hr. The gray reaction mixture was poured into water, extracted several times with 30–60° petr. ether, and the combined extracts dried over magnesium sulfate. The colorless liquid, which remained on distillation of the ether, was fractionally distilled: b.p. 52–53° (1.8 mm.), $n^{17}\mathrm{D}$ 1.4670, yields 40–50%. The infrared spectrum of this liquid was superimposable on that of a sample of methyl norbornane-1-carboxylate prepared from an authentic sample of the acid by methylation with diazomethane according to the procedure of reference 29, as used above.

**Hydrogenolysis with $LiAlH_4$.**—A suspension of $LiAlH_4$ (0.16 mole) in anhydrous ethyl ether was first prepared and a solution of the bromoacids or their methyl esters, 0.012 mole in ether, was added dropwise during 2 hours to the vigorously stirred suspension. Upon completion of the addition the reaction mixture was refluxed overnight and then allowed to stand at room temperature for about a day. After decomposition of the excess $LiAlH_4$, the mixture was worked up by acidification, extraction and drying of the combined ether extracts over magnesium sulfate. Upon evaporation of the solvent the residual pale yellow oil was still slightly contaminated with bromohydrin as evidenced by positive Beilstein halogen test, silver nitrate test and ceric nitrate test for the hydroxyl function. Since any residual bromohydrin, however slight, always produced decomposition and polymerization in the distillation pot, the precaution was taken to subject the total oil to hydrogenolysis with palladium–charcoal in the manner previously described. Judging from the amount of hydrogen taken up during hydrogenolysis the yellow oil contained less than 5% bromohydrin. Upon working up the hydrogenolyzed mixture a viscous tan colored liquid resulted which was then subjected to fractionation; yield, *ca.* 50% (over-all) of a cut, b.p. 56–57° (0.8 mm.), $n^{20}\mathrm{D}$ 1.4904; *p*-nitrobenzoate, recrystallized from ethanol, m.p. 85–86°. The infrared spectra of this alcohol and its *p*-nitrobenzoate derivative were identical with those of the alcohol and its derivative prepared in these laboratories by reduction of I with $LiAlH_4$, *viz.*, 2-*endo*-methylolnorbornane (VII), $n^{20}\mathrm{D}$ 1.4910.

**The Determination of the Relative Rates of Bromination of Norbornane-2-*endo*-carboxylic Acid (I) and Norbornane-2-*exo*-carboxylic Acid (II).**—Standard solutions: (1) 5 g. of *endo*-acid II diluted to 100 cc. with purified carbon tetrachloride, (2) 5 g. of *exo*-acid V diluted to 100 cc. with purified carbon tetrachloride; (3) 4.5 g. of bromine and 5 cc. of phosphorus oxychloride diluted to 25 cc. with purified carbon tetrachloride.

**Procedure.**—Into a 25-cc. ampoule was pipetted 5 cc. of the standard acid solution and 2 cc. of the standard bromine–phosphorus oxychloride solution. The ampoule was rinsed with 2 cc. of purified carbon tetrachloride, cooled in a Dry Ice–acetone-bath, sealed and immersed in boiling water. At the end of one hour, the ampoule was cooled, opened, emptied into 50 cc. of water and rinsed repeatedly with purified carbon tetrachloride; 10 cc. of concentrated hydrochloric acid was added followed by 3 g. of potassium iodide and after standing for 5 min. the sample was titrated with 0.1016 *N* sodium thiosulfate.

**Rate Results.**—The average of 7 determinations $k_{\mathrm{endo}}/k_{\mathrm{exo}} = 4.71 \pm 0.19$.

**The Bromination of I in Thionyl Chloride Solution; the Preparation of VI and Derivatives.**—When a solution consisting of 54.7 g. of I and 120 cc. of thionyl chloride was made, vigorous bubbling was observed while the flask became cold to the touch. After 2 hours of reflux on the steam-bath, addition of 65 g. of bromine was begun and completed in half an hour. The reaction was completed by allowing it to reflux overnight on the steam-bath. Excess bromine and thionyl chloride were stripped off at the water-pump, the residue flushed with 200-cc. portions of benzene to remove the final traces of volatile contaminant and the residual bromoacid chloride distilled under vacuum; b.p. 90–95° (2 mm.).

**The Methyl Ester of VI (IIIa, R = Me).**—A solution of 6.0 g. of the bromoacid chloride VI (above) in 30 cc. of anhydrous methanol was allowed to remain at room temperature overnight and the reaction completed by refluxing for 1 hour on the steam-bath. The solvent was then removed under vacuum, the residue taken up in ether, washed with dilute bicarbonate solution and dried over magnesium sulfate. The residue after removal of the solvent was distilled under reduced pressure, gave a center cut consisting of nearly 4.0 g. of colorless liquid, b.p. 76° (1 mm.), $n^{24}\mathrm{D}$ 1.5051. Although the refractive index of the corresponding IIIc ester was almost the same, comparison of the infrared spectra and the n.m.r. spectra showed they were entirely different.

**Hydrogenolysis of the Methyl Ester of VI with Zinc and Acetic Acid.**—Repeating the procedure used above for hydrogenolysis of the IIIc ester resulted in a colorless liquid, b.p. 53–55° (2 mm.). The infrared spectrum of this product was completely superposable on that of Ia.

**Hydrolysis of the Bromoacid Chloride VI (IIIa, OR = Cl).**—A mixture consisting of 10 g. of the bromoacid chloride VI, 330 cc. of $H_2O$, 100 cc. of methanol and 5.6 g. of KOH was rapidly agitated while the temperature was raised to 35°. After about 1 hour the turbidity disappeared and a sample of solution cooled in the ice-bath remained homogeneous. Heating at 35–40° was continued for an additional hour, the reaction solution cooled and remained at room temperature overnight before neutralizing to *p*H 2 with dilute $H_2SO_4$. The product was extracted into ether by means of a continuous liquid–liquid extractor, the ether extracts dried over magnesium sulfate and the solvent evaporated. The oily residue was crystallized from ether–hexane solution in the ice-chest, the colorless crystals triturated with cold hexane and recrystallized from nitroethane; m.p. 113–114°. This substance was identical in infrared spectrum with an authentic sample of 2-*exo*-hydroxy-2-*endo*-carboxynorbornane[11]; mixed melting point showed no depression.

**Oxidation of the Bromoaldehyde V to Bromoacid IIIc.**—A solution consisting of 8.5 g. of bromoaldehyde V, 9 cc. of glacial acetic and 12 cc. of peracetic acid (40%, Becco) was made up at 15° and slowly warmed to room temperature. After standing for 24 hours at temperatures between 20–23° the solution was poured into 500 cc. of cold water and extracted with five 50-cc. portions of ether successively. The combined ether extracts were washed with dilute sodium bisulfite until a test for peracetic acid in the ether layer was negative. After drying over magnesium sulfate and evaporating the solvent, the crude residue (7.1 g.), recrystallized twice from ethyl acetate hexane and once from nitroethane, melted fairly sharply at 151°. This product did not depress the melting point of a pure sample of IIIc and had an identical infrared spectrum.

**Nuclear Magnetic Resonance Measurements.**—The data recorded in the accompanying table were obtained by means of a Varian High Resolution nuclear magnetic resonance spectrometer and associated electromagnet at 40 Mc. and field of approximately 10,000 gauss. Spectra were calibrated in terms of displacements in cycles per second from the proton resonance of water at 25°.

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[29] A. H. Blatt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 165.