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THE STEREOCHEMISTRY OF BICYCLO[3.2.1]OCTANE—XVI[1]

ALLYLIC REACTIVITY OF BICYCLO[3.2.1]OCTENE-2; REDUCTION WITH METAL HYDRIDES[2]

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Abstract—The reductive debromination of *exo*-1-methyl-3,4-dibromobicyclo[3.2.1]octene-2 and its allylic isomer with LAH and LAD was shown to take place by an S_N2' mechanism. Moreover, it was established that the entering deuteride and leaving bromide ions were *cis* to each other.

INTRODUCTION

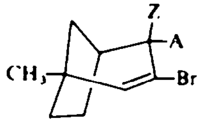
SINCE 1950 bimolecular displacements on allylic halides which proceed with rearrangement have received considerable attention.[4] Nevertheless, very little has been recorded of the reductive dehalogenation of allylic halides with metal hydrides. The earliest cases are those of Hatch. He found that primary acyclic halides were reduced without allylic rearrangement,[5] whereas secondary allylic halides underwent reduction with allylic rearrangement to the *trans*-2-olefins.[6] Hatch suggested that in the latter cases S_N2 attack by metal hydride was sterically prohibited and therefore S_N2' processes supervened.

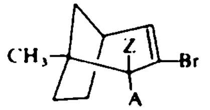
Later, Stork discovered that reduction of α- and β-halocodides with LAH produced only Δ^6- and Δ^7-desoxycodeines, respectively.[7] Here too, it was postulated that suppression of the S_N2 process by steric hindrance gave rise to the observed allylic rearrangement. However, the stereochemistry of the process remained unknown. Therefore, further study, preferably of a simpler system, was desirable.

Accordingly, the study of the stereochemistry of the allylic reactivity of a model secondary cycloalkenyl halide towards metal hydrides was undertaken. The present paper deals with *exo*-1-methyl-3,4-dibromobicyclo[3.2.1]octene-2 (I) and its allylic isomer II which contain a conformationally constrained cyclohexenyl system in which allylic rearrangement and the introduction of deuterium can be easily discerned by nuclear magnetic resonance spectroscopy.

RESULTS AND DISCUSSION

exo-1-Methyl-3,4-dibromobicyclo[3.2.1]octene-2 (I) and its allylic isomer II were prepared in an 80:20 ratio by the addition of dibromocarbene to 1-methylnorbornene.[8] Unfortunately, it proved impossible to obtain I in a pure state. Both bromides (I and II) underwent ready decomposition on heating.[8] Furthermore, allylic interconversion was difficult to prevent. Although chromatographic separation of the *exo*-bromo alcohols (III and IV) presented no difficulty (see below), their subsequent conversion to the allylic chlorides (V and VI) by most careful treatment with thionyl chloride under S_Ni' conditions led to mixtures.[9] However, heating the 80:20 mixture of I and II in boiling *o*-dichlorobenzene altered the ratio to 90:10. Accordingly, metal hydride reduction was carried out on these two mixtures in boiling ethyl ether as solvent over 15 hr. Despite anticipated difficulties, the resultant mixtures of products could be analysed and interpreted quite successfully.





I : Z = Br
III : Z = OH
V : Z = Cl A = H
VII : Z = H
IX : Z = Deut
XI : A = Deut, Z = H

II : Z = Br
IV : Z = OH
VI : Z = Cl A = H
VIII : Z = H
X : Z = Deut
XII : A = Deut, Z = H

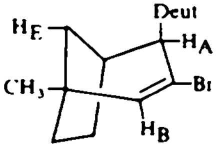
When LAH was used, 1-methyl-3-bromobicyclo[3.2.1]octene-3 (VIII) and 1-methyl-3-bromotricyclo[3.2.1]octene-2 (VII) were habitually formed in a ratio of 84:16 in yields of ca. 90% from both the 80:20 and the 90:10 mixtures.

It appears that the major product owes its origin mainly to the major reactant. However, the minor product could come from the minor or major reactant. Evidently the major course of reduction is allylic rearrangement in which attack by hydride occurs on the *exo* or *endo* side of the appropriate terminus of the allylic system. There is the additional possibility that a minor course involved an S_N2 displacement of bromide by hydride or arose by annihilation of the allylic cation by hydride in a S_N1' process.

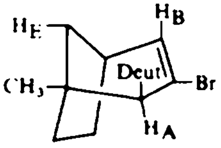
In order to resolve these questions, both the 90:10 and 80:20 mixtures of I and II were reductively dehalogenated with LAD. Oils were obtained in yields of 50–67%. Elemental and mass spectral analysis revealed that the oil had an empirical formula of $C_9H_{12}DBr$. The NMR spectrum showed no signals due to deshielded allylic protons, but revealed clearly the presence of two different kinds of vinyl proton in intensities of 84:16. It is significant that the two different compositions of reactants on reduction with the different metal hydrides give precisely the same amount of allylic rearrangement.

The introduction of deuterium in the reduction process could lead to four products. The major product could be a mixture of *exo*-1-methyl-2-deuterio-3-bromobicyclo-[3.2.1]octene-3 (X) and its *endo* epimer (XII), or be just one of them. Similarly, the minor product could be a mixture of *exo*-1-methyl-3-bromo-4-deuteriobicyclo-[3.2.1]octene-2 (IX) and/or its *endo* epimer (XI).

The two allylic octenes were separated by vapor phase chromatography and then analysed by their NMR spectra. The general spectral features of the bicyclo[3.2.1]-octene-2 skeleton are described fully in the accompanying paper.[10] However, for the present discussion it is sufficient to state that the configuration of an allylic substituent at C_2 or C_4 can be confidently assigned from a consideration of the magnitudes of the long range couplings exhibited by the C_2 and C_4 protons.



IXa



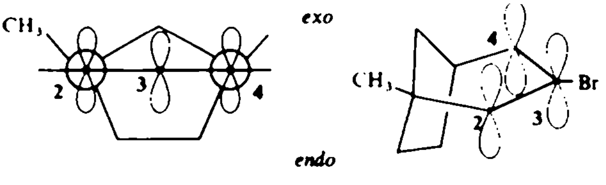
Xa

For the major product, the values of the vinyl-allylic ($J_{BA} = 1{\cdot}2$ Hz) and the W-plan coupling constants[11] ($J_{AE} = 0{\cdot}6$ Hz) indicated that the deuterium substituent has the *exo* configuration at C_2 (Xa and X).

The NMR spectrum of the minor product was similarly examined. The value observed for the vinyl-allylic ($J_{BA} = 1{\cdot}2$ Hz) is only compatible with an *exo* disposition at C_4 for the deuterio substituent (IXa and IX).[*]

If both *exo* and *endo* deuterio-octenes were present together in the major and minor product fractions, then it is unlikely that just one of them would be separated from the other by preparative VPC. Thus it can be concluded that no *endo* substitution by deuterium occurred on reduction (no XII or XI).

In contrast to the steric course of the hydride reduction, reactions of I and II which proceed through cationic intermediates lead to roughly 50% allylic rearrangement. Treatment of the 90:10 mixture or the 80:20 mixture of I and II with aqueous silver nitrate or moist alumina gave the allylic *exo*-hydroxy compounds (III and IV) in equal amounts.[8] Clearly, the reaction involves the intermediacy of the 1-methylbicyclo[3.2.1]oct-2-ene-4-yl ion (XIII) which subsequently is annihilated by attack of water at C_2 or C_4 on the *exo* side. Although steric[13] or torsional[14] effects could be qualitatively responsible for the direction of the stereochemical outcome, the high stereospecificity of the reaction is adequately accommodated by the preferential formation of a *quasi*-axial bond.[15] Similar considerations have been brought forward to account for the stereochemical fate of bicyclo[3.2.1]oct-2-ene-4-yl radicals.[16] Both the *exo* C_2 and C_4 positions appear to be equally comfortable for occupancy by the OH group despite the presence of the bridgehead Me substituent. Thus it would seem that the attractive and repulsive dispersion forces between the Me group and the *gauche* disposed O atom just cancel each other out.[†]



XIII

Therefore it appears at first sight that reduction proceeds predominantly by attack of deuteride ion, on the *exo* face of *exo*-1-methyl-3,4-dibromobicyclo[3.2.1]octene-2 (I), to give solely allylic rearrangement (I → X). In other words, the main course is an S_N2' mechanism. There is also the possibility that a minor course could proceed *via* an S_N1' mechanism in which the allylic cation (XIII) is initially generated and then randomly attacked on the *exo* face by deuteride ion to give both unrearranged and rearranged products. However, this possibility can be safely ruled out by the fact that both deuteride and hydride reduction give the same amount of allylic rearrangement. If there were two competing mechanisms, S_N1' and S_N2', operating in the

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[*] The value of the vinyl-allylic coupling constant is a sufficient index of allylic stereochemistry. The correlation is not only valid for derivatives of bicyclo[3.2.1]octene-2, but also applies to bicyclo[3.2.1]octa-2,6-diene derivatives.[12]

[†] It is unlikely that the position of the double bond will affect the isomer ratio.

reductions then a primary isotope effect would affect the second and not the first with a resulting difference in product composition.

In summary, these reduction results are best explained by prior equilibration of the reactants I and II to an 84:16 mixture followed by attack of deuteride ion and by extension hydride ion, on the *exo* face of the molecule in an S_N2' mechanism. Undoubtedly during reduction metal hydride coordinates with the allylic bromine. However, it is difficult to say unequivocally whether reduction is accomplished by delivery of hydride internally from the coordinated metal hydride or externally. Whichever happens, it is certain that the rupture of the bond to allylic bromine does not precede hydride attack.

The results are significant in that the present S_N2' mechanism does not appear to be compelled for steric reasons. Indeed, external attack by hydride *endo* at C_2 or C_4, and *exo* at C_2 appears sterically hindered to about the same extent. *Exo* approach to C_2 entails a *quasi*-1,3-diaxial interaction, whereas *endo* approach to C_2 or C_4 may suffer the hindrance supposedly characteristic of bridge bicyclic molecules.[13] Thus, stereoelectronic reasons alone can account for the mechanism. Not only are *quasi*-axial bonds made and broken in the transition state,[15] but the *cis* relation of entering deuteride to leaving bromide is compatible with the geometry favored on quantum mechanical grounds for the S_N2' process.[17]

By way of epilogue some comment on the stereochemistry of codeine and its derivatives appears pertinent. For some time there has been evidence to indicate that the C-ring of codeine derivatives exists in the boat conformation.[19] Although no change of existing assignments of stereochemistry appears to be necessary, previous postulates and arguments apparently based on the non-boat conformation need some revision.[7,18,20] Thus, the driving force for the ready rearrangement of α- to β-halocodides (XIV → XV) undoubtedly springs from the conversion of a boat to a chair conformation. Moreover, the prime factor, which decides whether an S_N2 or S_N2' process will take place in codeine and isocodeine derivatives is not steric, but rather depends on the stereoelectronic disposition of the allylic leaving group. It follows from the geometry required for S_N2' processes[17] and from the stereoelectronic disposition of the allylic substituent of the codides that attack by hydride *should* occur *quasi*-axially at C_6 but *quasi*-equatorially at C_8 in β- and α-halocodides, respectively.[7] The formation of Δ^7- and Δ^6-desoxycodeine from XV and XIV on reduction with LAH provides an unambiguous illustration of a bimolecular allylic rearrangement, since the generation of the allylic ion would lead chiefly to the Δ^6 product for the reasons mentioned above.

The results of the present paper substantiate the findings of Stork[7] and further establish that deuteride (and by extension hydride) and allylic halide enter and leave *cis* to each other in the S_N2' process.

EXPERIMENTAL

IR spectra were determined either on a Perkin-Elmer Model 137-B (NaCl prism) or a Beckman Model IR 9 (KBr prism and grating) spectrometer.

NMR spectra were determined at 60 MHz on a Varian Associates Model A-60 or A-60A spectrometer at ca. 37° in 10–20% solns of CCl_4. Chemical shifts were expressed with reference to co-dissolved TMS and are regarded as being accurate to ±1·0 Hz. An account of the double NMR experiments is described elsewhere.[10]

Mass spectral determinations were performed on a Consolidated Electrodynamics Corp. model 21-103-C instrument.

VPC separations were performed analytically on the F and M Model 700 and preparatively on the Nester Faust Prepchromatic Model chromatographs. Reactions were monitored by TLC on microscope slides coated with silica gel (Brinkmann Co.). Preparative TLC was performed on glass plates (10 × 10 in) coated with silica gel (G 12 g and HF 20 g according to Stahl, E. Merck AG., Darmstadt, Germany). Chromatograms were made readable by spraying with 50% H_2SO_4 aq followed by heating or by illumination with UV light. All m.ps and b.ps are uncorrected. Elemental analyses were carried out by Dr. G. Robertson, Florham Park, N.J.

exo-1-Methyl-3,4-dibromobicyclo[3.2.1]octene-2 (I) and *exo*-1-methyl-2,3-dibromobicyclo[3.2.1]octene-3 (II) were prepared as an 80:20 mixture by the addition of dibromocarbene to 1-methylnorbornene.[8] Several attempts at separation were made. Decomposition occurred on VPC. Column chromatography over silica gel, magnesium-silicate ("Florisil"), or alumina and preparative TLC on silica gel using various eluants were equally unsuccessful. A 90:10 mixture of I and II was obtained by thermal equilibration in boiling *o*-dichlorobenzene. Several reduction experiments of both the 80:20 and the 90:10 mixtures were carried out. Typical experiments on the two mixtures are described.

Reduction with lithium aluminum hydride

A soln of the mixture of I and II (10·0 g, 0·036M) in anhyd ether (50 ml) was added dropwise to a suspension of powdered LAH (2·5 g, 0·9M) in ether (100 ml). The resultant mixture was heated under reflux for 15 hr. Afterwards a saturated soln of Na_2SO_4 (5 ml) was added dropwise to decompose excess metal hydride. The ethereal soln was removed from precipitated solids and evaporated. An oil remained which was distilled; the portion which was collected (5·6 g, 82% yield) at b.p. 45°/2 mm consisted of VII and VIII. (Found: C, 53·65; H, 6·50; Br, 39·48. Calc. for $C_9H_{13}Br$: C, 53·75; H, 6·51; Br, 39·74%).

In two other experiments yields of 84 and 90% were obtained. The balance of material was found to be starting material.

The conversion of VII and VIII to 1-methylbicyclo[3.2.1]octanone-3 confirmed that no skeletal rearrangement had occured.[8] The amounts of VII and VIII present in the mixture were estimated from the integrated intensities of the respective signals due to the vinyl protons. The vinyl resonance of VII showed as a closely spaced doublet at 5·91 ppm (J = 1·3 Hz) and that of VIII appeared as a wide doublet at 6·16 ppm (^3J = 7·0 Hz). In different experiments the ratio of VII to VIII was found to be consistently 16:84.

Reduction with lithium aluminum deuteride

A mixture of I and II (4·8 g, 0·02M) was reduced with LAD (1·5 g, 0·2M) in ether according to the above procedure. After work-up an oil was distilled and collected at b.p. 63°/2 mm (2·0 g, 50% yield). The IR absorption spectrum of the neat oil showed maxima at 2101 (weak), 2132 (strong), 2168 (weak) and 2182 (weak) cm^{-1} which are characteristic of C–D frequencies. In the NMR spectra, the vinyl resonances of X and IX were clearly discerned as a wide doublet (^3J = 7·0 Hz) at 6·18 ppm and a finely split triplet at 5·93 ppm.[10] Their integrated intensities were in the ratio 84:16 and were unfailingly constant in several different experiments.

In two subsequent reductions yields of 58 and 66·5% were obtained; however, the remainder of unreacted material was found to be I and II. Consequently, it is reasonably certain that the entire product has been isolated.

Analysis of IX *and* X. (Found: C, 53·43; H, D, 6·56; Br, 39·52. Calc. for $C_9H_{12}DBr$: C, 53·48; H, D, 6·82; Br, 39·54%).

Compounds IX and X were separated by preparative VPC on a column ¼ in diam × 10 ft long packed with 20% N,N-bis-(dicyanoethyl) formamide supported on calcined diatomaceous earth (Chromosorb P, 60–80 mesh) at a column temp of 105–110° and a He flow rate of 100 ml/min. In their IR spectra, IX showed maxima at 2169 and 2184 cm^{-1}, and X showed maxima at 2101 and 2132 cm^{-1}. Both isomers on mass spectral analysis gave parent peaks at m/e = 201 and 203, thereby indicating the incorporation of one D atom per molecule. The double NMR spectra of IX and X indicated that the deuterium substituents were *exo* in both cases.

exo-1-*Methyl-3-bromo-4-hydroxybicyclo*[3.2.1]*octene*-2 (III) *and* exo-1-*methyl-2-hydroxy-3-bromobicyclo*[3.2.1]*octene*-3 (IV)

A mixture of I and II (10·0 g, 0·036M) was dissolved in acetone (50 ml) and a soln of $AgNO_3$ (10·0 g) in water (50 ml) was added. The mixture was heated under reflux for 15 hr. On cooling precipitated AgBr was removed by filtration and the filtrate was extracted with ether. Evaporation of the ether gave a yellow solid which on sublimation gave III and IV as a mixture (6·0 g, 78% yield). III, m.p. 60°, and IV, m.p.

74–75°, were separated by chromatography over silica gel using pentane–ether as eluant. III showed a finely split doublet at 6·18 ppm (^4J = 1·3 Hz) and a doublet at 3·86 ppm (^3J = 3·0 Hz), whereas IV exhibited a doubled doublet at 6·43 ppm (^3J = 7·0 Hz, ^4J = 1·0 Hz) and a broadened singlet at 3·62 ppm for the vinyl and allylic protons. (Found for III: C, 49·48; H, 6·08; Br, 36·60. Found for IV: C, 49·25; H, 5·98; Br, 36·65. Calc. for $C_9H_{13}OBr$: C, 49·78; H, 6·04; Br, 36·81%).

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