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STUDIES ON QUINOLIZINIUM SALTS—IV[1]

THE REDUCTIONS OF 3,4-DIHYDRO- AND 1,2,3,4-TETRAHYDROQUINOLIZINIUM BROMIDE WITH SODIUM BOROHYDRIDE[2]

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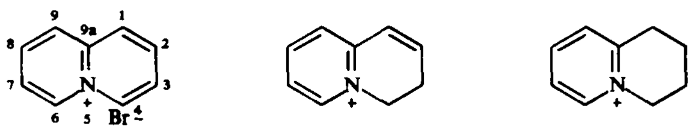
Abstract—This investigation was undertaken in order to clarify the sodium borohydride reduction mechanism of 3,4-dihydro- and 1,2,3,4-tetrahydroquinolizinium ions (II and III) which are possible intermediates in the reduction of quinolizinium bromide (I). The hydride reduction of the tetrahydroquinolizinium bromide (IV) or water yields hexahydroquinolizines (VII and VIII), together with a small amount of quinolizidine (VI). Similar reduction of 3,4-dihydroquinolizinium bromide (V) affords a tetrahydroquinolizine (IX) in addition to VI–VIII. The two bromides were also reduced with sodium borohydride in deuterium oxide and with sodium borodeuteride in water to give the deuterated quinolizine derivatives. On the basis of the isotopic experiments and mass spectral studies, it was concluded that these reductions may proceed by kinetically controlled protonations of enamine intermediates and subsequent hydride reduction of the resulting iminium ions. The reduction mechanisms of IV and V in the protic solvents are discussed.

AS PART of an investigation of the nucleophilic reactions of quinolizinium bromide (I) we examined the reduction of I with sodium borohydride and LAH.[2] During studies on sodium borohydride reduction of I in protic solvents, 3,4-dihydroquinolizinium ion (II) was assumed to be an intermediate in the formation of quinolizidine and unsaturated quinolizidines (VI–IX). This assumption led us to investigate the borohydride reduction of II in protic solvents, and further that of 1,2,3,4-tetrahydroquinolizinium ion (III), a possible intermediate derived from II. The present paper is concerned with the borohydride and borodeuteride reduction of the bromides (IV and V) and mass spectral studies on unsaturated quinolizidines (VII–IX) and their deuterated analogues. The structural determination of VII–IX and the reduction mechanism of I will be described in the following paper[3] on the basis of this investigation.



I II III

CHART 1

The reduction of 1,2,3,4-tetrahydroquinolizinium bromide (IV) with sodium borohydride in water afforded 3,6,7,8,9,9a- and 1,6,7,8,9,9a-hexahydro-4*H*-quinolizine (VII and VIII), accompanied by a small amount of VI. The products were separated by preparative gas chromatography using 20% polydiethylene glycol succinate on

Chromosorb-W and identified by the IR spectral comparison with samples obtained from the borohydride reduction of I. With ethanol as solvent, the borohydride reduction of IV afforded VII and VIII, but VI could not be detected even by gas chromatography of the reduction mixture.

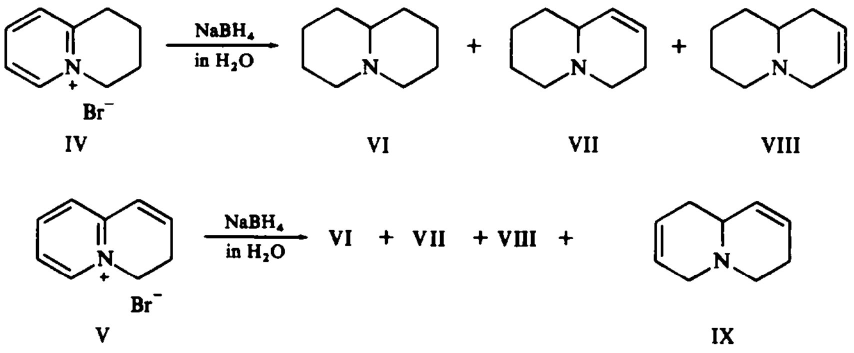


Chart 2

3,4-Dihydroquinolizinium bromide (V) was also reduced with sodium borohydride in water yielding 3,6,9,9a-tetrahydro-4*H*-quinolizine (IX) in addition to VI–VIII. All the products separated by preparative gas chromatography were identical with the hydride reduction products of I. Similar reduction of V in ethanol afforded VII–IX and gas chromatography detectable amounts of VI.

The most characteristic features in the mass spectrum of VII are the pronounced M − 1 (*m*/*e* 136), M − 29 (*m*/*e* 108), *m*/*e* 81 and *m*/*e* 80 peaks, whereas VIII shows prominent peaks at *m*/*e* 136, 83 and 55. The diene (IX) shows a prominent M − 1

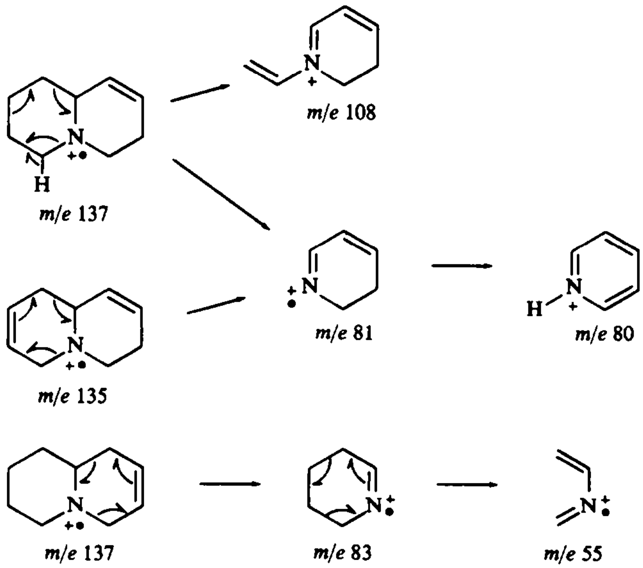


Chart 3

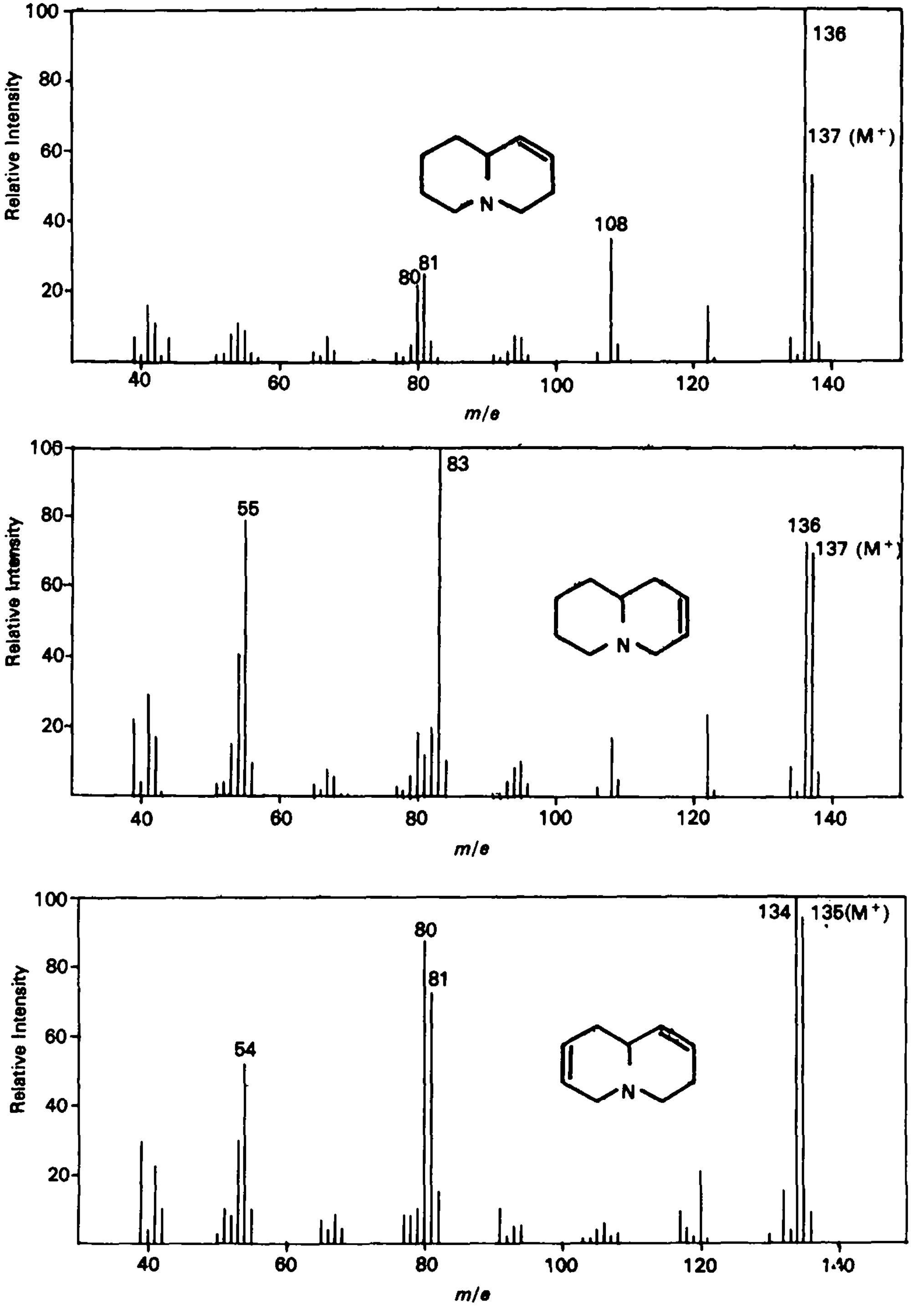


FIG. 1-1 Mass spectra of undeuterated quinolizine derivatives: (a) VII; (b) VIII; (c) IX.

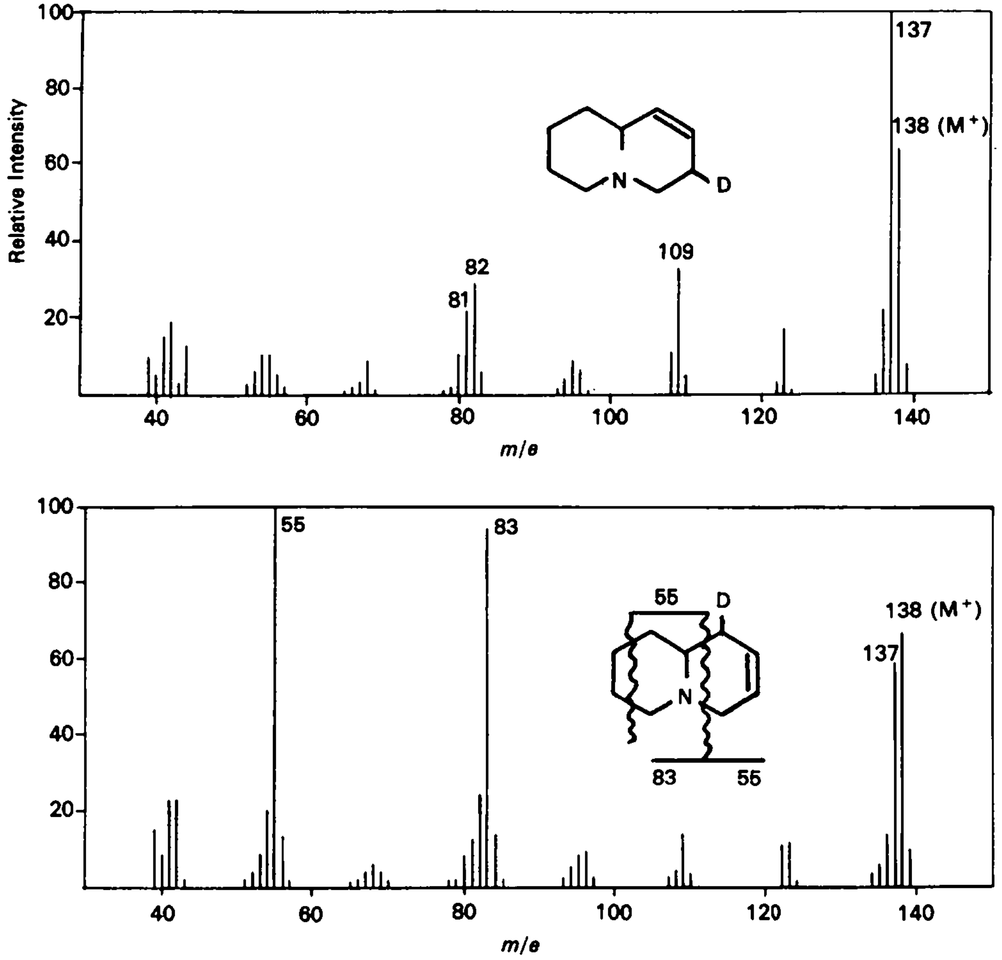


FIG. 1-2 Mass spectra of deuterated products obtained from the sodium borohydride reduction of IV in D_2O:

(a) deuterated analogues of VII (main, X);
(b) deuterated analogues of VIII (main, XI).

(*m/e* 134) peak and fragment peaks at *m/e* 81 and 80 characteristic of VII. The fragmentation schemes which produce these prominent ions are postulated as shown in Chart 3.

The borohydride reduction of IV in deuterium oxide resulted in the formation of deuterated monoenes (X and XI) and quinolizidine. The deuterated products were separated by preparative gas chromatography, converted to picrates and identified by admixture with undeuterated amine picrates. The monoene products showed C–D stretching absorption bands[4] near 2150 cm^{-1}, but no olefinic C–D stretching band[4] in the IR spectra. The mass spectra showed prominent molecular ion peak at *m/e* 138, suggesting predominant incorporation of one D atom during the hydride reduction. It is apparent that dideuteration does not occur significantly as shown

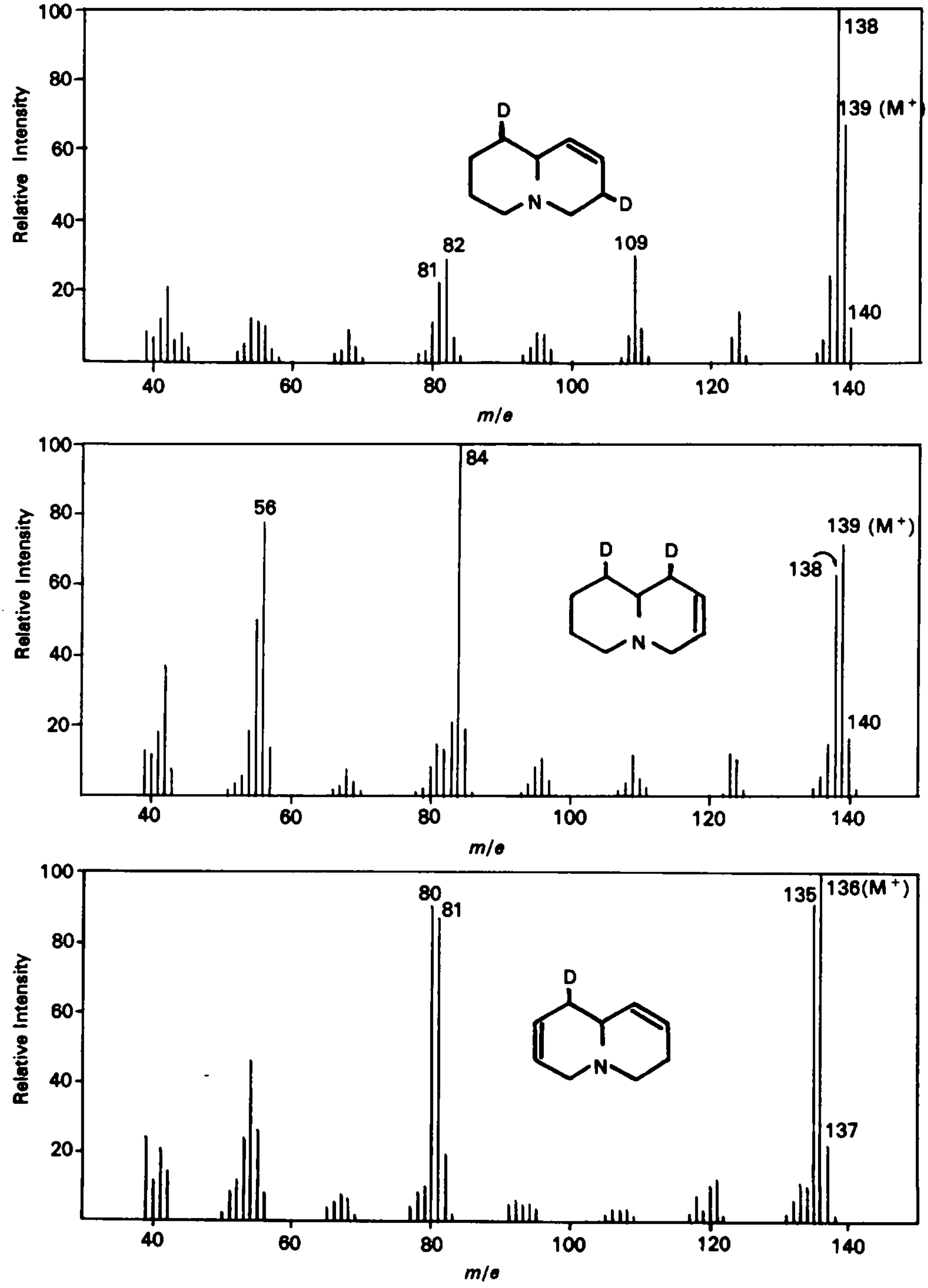


FIG 1-3 Mass spectra of deuterated products obtained from the sodium borohydride reduction of V in D_2O:

(a) deuterated analogues of VII (main, XIV);
(b) deuterated analogues of VIII (main, XV);
(c) deuterated analogues of IX (main, XVI).

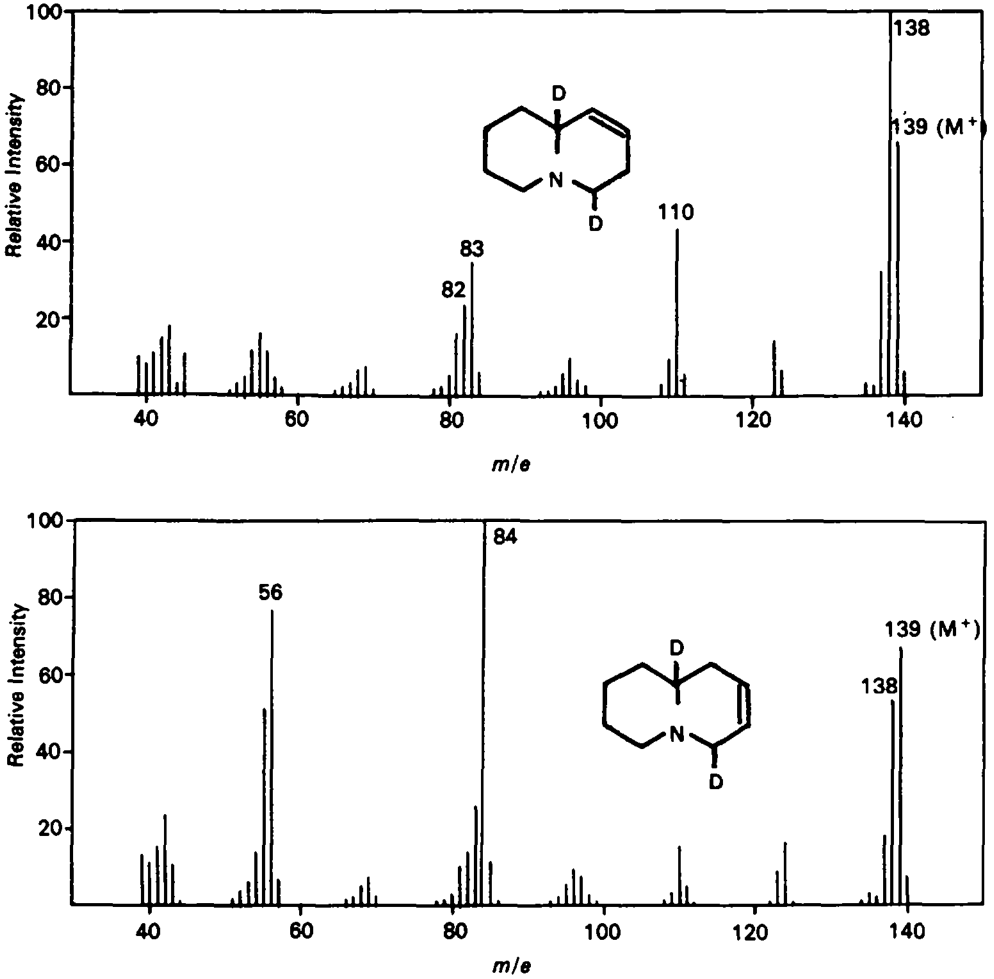


FIG. 1-4 Mass spectra of deuterated products obtained from sodium borodeuteride reduction of IV in H_2O:

(a) XII; (b) XIII.

by comparison of m/e 139 peak with m/e 138 peak in VII and VIII. The deuterium atom incorporated was shown to be in the unsaturated rings by mass spectral fragmentations and further at C-3 and C-1 of VII and VIII respectively by the NMR spectra. Although the NMR spectra of VII and VIII in deuterochloroform showed complicated overlapping multiplets, measurements in trifluoroacetic acid resulted in resolution of the allylic proton peaks.

The reduction of IV with sodium borodeuteride in water afforded deuterated hexahydroquinolizines (XII and XIII), together with a small amount of deuterated quinolizidine. The molecular ion peak at m/e 139 in the mass spectra of XII and XIII corresponds to the incorporation of two D atoms into the monoenes. The two D

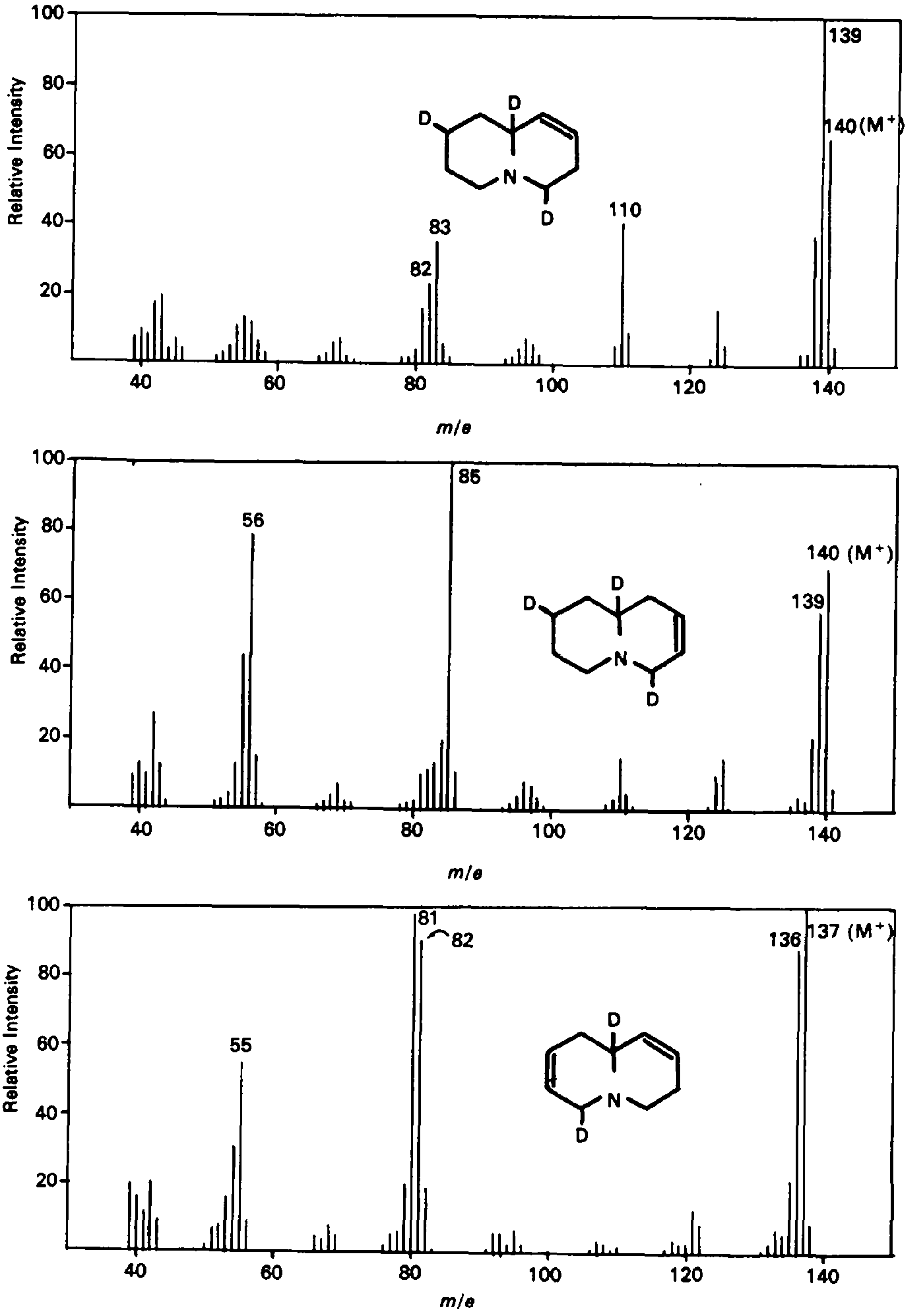


FIG. 1-5 Mass spectra of deuterated products obtained from sodium borodeuteride reduction of V in H_2O:

(a) XVII; (b) XVIII; (c) XIX.

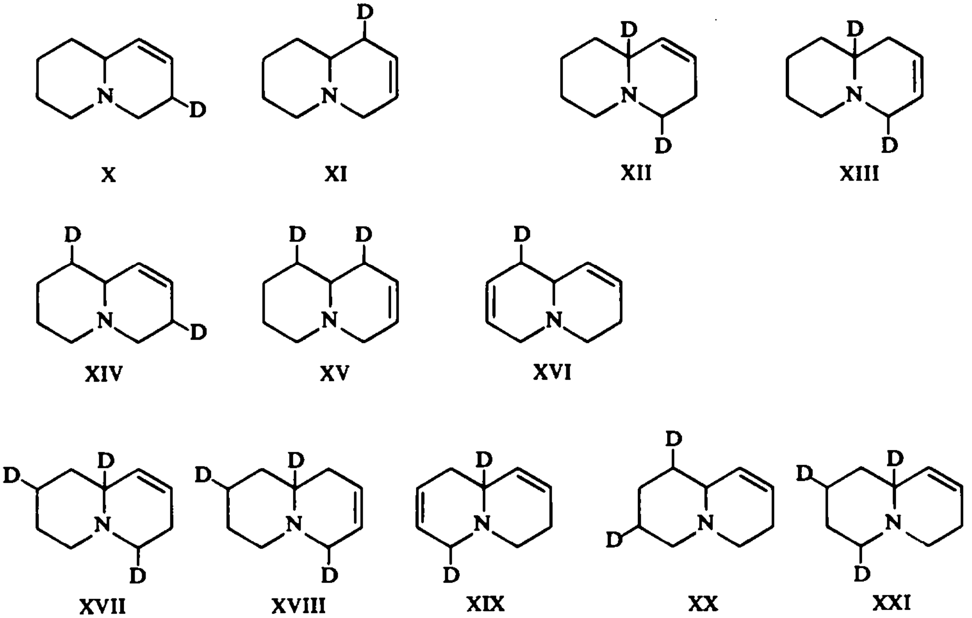


Chart 4

atoms are retained in the *m/e* 83 fragment from XII, while the *m/e* 84 fragment from XIII has only one D atom. The position of the D atoms was established by the NMR spectra in trifluoroacetic acid which showed the disappearance of two hydrogens on carbons adjacent to nitrogen. The dideuterated monoenes (XII and XIII) showed C–D stretching bands near 2050 cm^{-1} in addition to normal C–D stretching bands near 2150 cm^{-1}. The former bands are ascribable to C-4 and C-9a D atoms *trans* to nitrogen lone pair electrons. The corresponding axial D atoms in quinolizidine ring appear near 2000 cm^{-1}.[5]

The reduction of V with sodium borohydride in deuterium oxide also afforded deuterated quinolizidine, hexahydro- and tetrahydroquinolizines showing C–D stretching bands at 2100–2200 cm^{-1}. Absent in the spectrum were vinyl deuterium and deuterium on carbons adjacent to nitrogen. The mass spectra of the monoenes show an intense molecular ion peak at *m/e* 139 indicating predominant formation of dideuterated hexahydroquinolizines (XIV and XV). As compared with the mass spectra of VII and VIII, slightly enhanced peaks at *m/e* 140 suggest that the reduction involves some trideuteration in deuteration steps. Evidently one D atom is present in the saturated ring of XIV and XV, since one D atom is retained in the *m/e* 82 and 84 fragments from XIV and XV respectively. The position of the D atom can be rationalized by the shift of *m/e* 55 peak in VIII to *m/e* 56 in XV. The other allylic D atom of XIV and XV was established by the NMR spectra (in CF_3COOH) in which a C-3 and a C-1 proton appeared as a broad peak centered at 7·37 and 7·50 τ respectively.

On the other hand the mass spectrum of the deuterated diene showed that XVI is produced predominantly as the diene product, accompanied by a small amount of a dideuterated diene. It appears that the deuteration occurs with a little larger di-/monodeuteration ratio than that in the formation of X and XI. The D atom incorporated into XVI was shown to exist in the left ring by the presence of both *m/e* 80 and 81 without shift in the spectrum of XVI. The incorporation of one D atom was also indicated by the NMR spectrum showing the disappearance of one proton from the allylic position non-adjacent to nitrogen.

The dihydro bromide (V) was reduced with sodium borodeuteride in water to give 4,8,9a-trideuterated hexahydroquinolizines (XVII and XVIII) and 6,9a-dideuterated tetrahydroquinolizine (XIX), together with a small amount of deuterated quinolizidine. The distribution of D atoms incorporated was ascertained precisely as being two in the diene and three in the monoenes by the mass spectra showing molecular ion peaks at *m/e* 139 and 140 respectively. The NMR spectra in trifluoroacetic acid showed that XVII–XIX have two D atoms on carbons adjacent to nitrogen, while XVII and XVIII carry additional D atom in the saturated ring. The appearance of *m/e* 56 and 110 fragments in the mass spectra of XVII and XVIII respectively indicate that the deuteride reduction of V involves attack of a deuteride ion at C-2.

Since the tetrahydroquinolizinium bromide (IV) can be regarded as a quaternary pyridinium derivative, the sodium borohydride reduction of IV is expected to proceed by a pathway similar to the reduction of quaternary pyridinium salts. This experiment is consistent with the mechanism postulated for the hydride reduction of the pyridinium salts[6] in protic solvents or deuterium oxide. Initial hydride attack at C-6 or C-9a of IV leads to dienamine intermediates (XXII and XXIII). Subsequently, kinetically controlled protonation occurs at the center of the dienamine systems and the resulting non-conjugated iminium ions are further reduced to VII and VIII. This reduction mechanism is reasonable, since the borohydride reduction of IV in deuterium oxide led to the predominant formation of the monodeuterated monoenes (X and XI). The initial hydride reduction of IV in ethanol seems to occur exclusively at C-6 or C-9a. If IV undergoes hydride reduction at C-8, quinolizidine (VI) should be formed by protonations and subsequent reductions of the resulting dienamine (XXIV). It is noteworthy that in the reduction of IV, quinolizidine (VI) was formed using water as solvent, but not with ethanol.

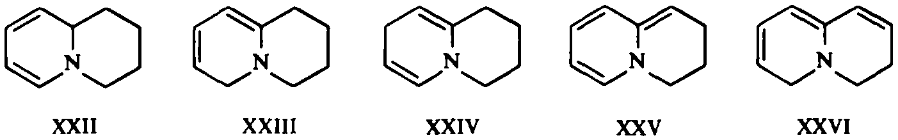


CHART 5

Apparently the reduction of V to the quinolizine derivatives proceeds by an initial reduction at C-2 and C-6, followed by protonations and subsequent hydride reductions of the resulting iminium ions. When the initial reduction occurs at C-2, an enamine (XXV) of an anhydropyridine type is formed which is then converted to the tetrahydroquinolizinium ion (III) by kinetically controlled protonation. By such a process the hydride reduction of V in deuterium oxide leads to 1-deuterated tetrahydroquinolizinium ion (XXVII). As in the reduction of IV, the reduction of XXVII may proceed by two pathways involving the hydride reduction at C-6 and C-9a. The resulting dienamines (XXVIII and XXX) undergo kinetically controlled deuteration to form dideuterated iminium ions (XXIX and XXXI) which can be reduced to XIV and XV respectively. In the formation of VII there is a possibility that initial reduction might occur at C-8 of V. If the initial reduction had occurred at C-8, isotopic isomers (XX and XXI) should have been produced, together with XIV and XVII respectively. However, this possibility was excluded by the observations that *m*/*e* 81/80 ratio in VII was almost identical with the ratio of the corresponding fragments in the deuterated analogue (XVII), and XIV showed only one C-3 proton peak at the corresponding field in the NMR spectrum in trifluoroacetic acid.

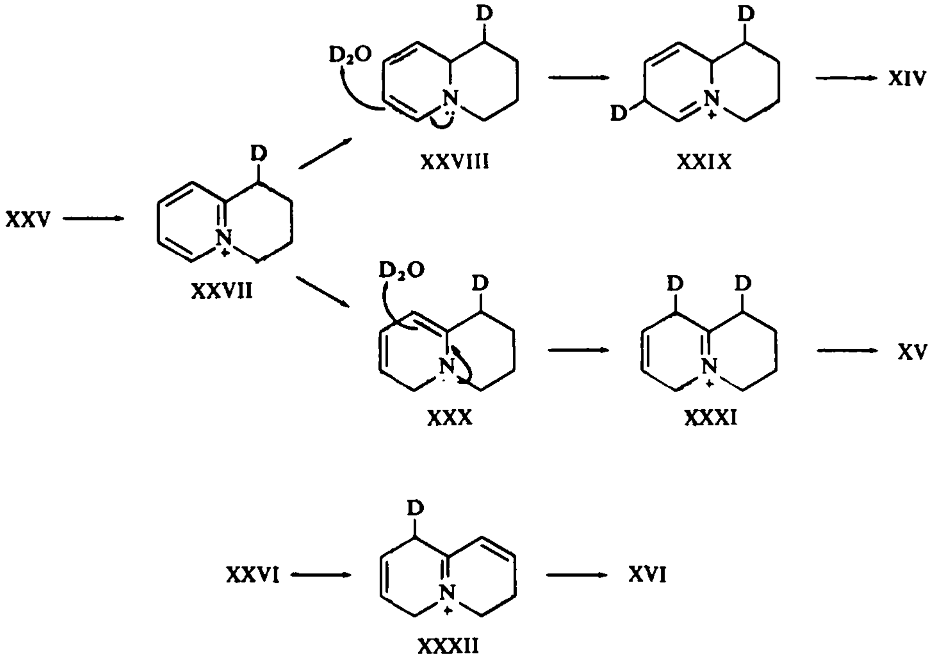


Chart 6

The initial step in the formation of IX is thought to be a hydride attack at C-6 of V to form a trienamine intermediate (XXVI). The formation of IX from XXVI can be explained by the preferred protonation at C-9 and subsequent C-9a reduction of the resulting iminium ion. This assumption is consistent with HMO calculations*

Table 1. π-Electron densities in 3,6-dihydro-4H-quinolizine (XXVI) at k = 0·8, h = 1·5, h = 0·1

Position (i)	1	2	5(N)	7	8	9	9a
q_i	1·007	0·982	1·902	1·064	0·994	1·078	0·973

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* The calculations were carried out by Drs. K. Okamoto and C. Tamura of the Laboratories.

of XXVI indicating that kinetically controlled protonation should take place preferentially at C-9. The total π-electron densities given in Table 1 were obtained with the following parameters: the Coulomb parameter (h) for nitrogen, 1·5; the auxiliary inductive Coulomb parameter (h') for the carbon atom adjacent to nitrogen, 0·1; the CN resonance integral (k), 0·8.[7] The π-electron density at C-9 was the highest with variation of the parameters in the range of $h = 1{\cdot}0$–$1{\cdot}5$, $h' = 0$–$0{\cdot}2$, $k = 0{\cdot}5$–$1{\cdot}0$. The deuteration of XXVI proceeds with predominant formation of a monodeuterated iminium ion (XXXII) to be subsequently reduced to XVI. As described above, the ratio of di-/monodeuteration in this deuteration step is a little higher than in the formation of the deuterated monoenes (X and XI). The higher ratio may be ascribed to more facile interconversion between the trienamine (XXVI) and the iminium ion (XXXII) conjugated with a double bond. The resulting ion (XXXII) can be reduced at C-9a to give XVI, although there is a possibility that XXXII might undergo partial reduction at C-2, followed by kinetically controlled deuteration and subsequent reduction leading to XV.

Another possibility for the reduction of V involves attack of a hydride ion at C-9a. The C-9a reduction of V would lead to 3,4,6,7-tetrahydro-9a*H*-quinolizine (XXXIV) via an enamine (XXXIII). In fact, the tetrahydroquinolizine (XXXIV) was not produced and thus the possibility was ruled out, suggesting that V is not susceptible to the C-9a hydride reduction.

XXXIII XXXIV

CHART 7

Although the deuterated quinolizidines were not studied using NMR or mass spectra, it is very likely that quinolizidine (VI) is produced via the tetrahydro ion (III) derived from V.

EXPERIMENTAL

All m.ps were uncorrected. The NMR spectra were determined on a Varian A-60 spectrometer. Chemical shifts were given in τ values with TMS as the internal standard. The IR spectra were obtained on a Perkin–Elmer Model 221 double-beam spectrophotometer. All mass spectra were obtained using a Hitachi Model RMU 6D mass spectrometer operating at 70 eV. Samples were introduced through an inlet system at room temp. Preparative gas chromatography was performed isothermally at 150–160° with He gas as the carrier gas on a Yanagimoto GCG-3 Chromatograph equipped with a thermal conductivity detector. Column used was 20% polydiethylene glycol succinate on 30–60 mesh Chromosorb W (3-m × 0·5-cm.).

1,2,3,4-*Tetrahydroquinolizinium bromide* (IV). The bromide IV was prepared according to the procedure of Moynehan *et al.*[8] with the modification that γ-phenoxypropyl bromide was used in place of γ-ethoxypropyl bromide. Picolyllithium was prepared from 4·72 g of Li, 53·3 g of bromobenzene and 31·5 g 2-picoline in 250 ml dry ether. To the stirred and cooled soln was added dropwise a soln of 73·0 g γ-phenoxypropyl bromide in 50 ml ether. After addition the mixture was stirred for additional 3 hr at room temp. The usual work-up gave 39·5 g of 2-(4-phenoxybutyl)pyridine as almost colorless oil, b.p. 160–165° (2 mm Hg). Found: C, 78·92; H, 7·77; N, 6·19. $C_{15}H_{17}ON$ requires: C, 79·26; H, 7·54; N, 6·16%. The pyridine derivative (19·5 g) was dissolved in 150 ml 48% HBr. The mixture was gently refluxed until distillation of phenol was complete. The usual work-up afforded 11·4 g of IV as colorless needles, m.p. 228–229° (recrystallized from EtOH–AcOEt). Found: C, 50·58; H, 5·65; N, 6·43. Calc. for $C_9H_{12}NBr$: C, 50·48; H, 5·65; N, 6·54%.

Reduction of 1,2,3,4-*tetrahydroquinolizinium bromide* (IV) *with sodium borohydride*

A *With ethanol as solvent.* To an ice-cold and stirred soln of 4·2 g of IV in 50 ml EtOH was added dropwise a soln of 0·82 g $NaBH_4$ in 30 ml EtOH over a period of 5 min. The mixture was stirred for 3 hr, after addition was complete, and left at room temp for 20 hr. To the mixture 8 ml of glacial AcOH was added dropwise, and the solvent was removed *in vacuo*. The residue was dissolved in a small volume of water and the soln was made basic with excess K_2CO_3, and the organic material was extracted with ether. The ether extract was dried over K_2CO_3, ether was removed and the residue was distilled to give 1·94 g (72·2%) of a colorless liquid, b.p. 90–100° (bath temp, 30 mm Hg). Gas chromatography showed that the product was a 1:0·90 mixture of VII and VIII. The monoenes (VII and VIII) were separated by preparative gas chromatography and identical in all respects, including IR absorption, with the samples obtained from I. VII, NMR (CF_3COOH): τ 3·75–4·55 (2H, multiplet, vinyl protons), 5·70–7·05 (5H, m*, protons on carbons adjacent to nitrogen), 7·05–7·65 (2H, m, C-3 H_2), 7·65–8·70 (6H, m, C-7, C-8, C-9 protons). VIII, NMR (CF_3COOH): τ 3·75–4·50 (2H, m, vinyl protons), 5·65–7·35 (5H, m, protons on carbons adjacent to nitrogen), 7·35–7·78 (2H, m, C-1 H_2), 7·78–8·70 (6H, m, C-7, C-8, C-9 protons).

B *With water as solvent.* To a cooled and stirred soln of 1·05 g of IV in 10 ml water was added a cooled soln of 0·44 g $NaBH_4$ in 5 ml water. The mixture was stirred for 3 hr with cooling and for additional 4·5 hr at room temp. Excess K_2CO_3 was added to the reaction mixture and the organic material was extracted with ether. The ether layer was dried over K_2CO_3 and the residue obtained by removal of the solvent was distilled to give 450 mg of a colorless liquid, b.p. 115–120° (bath temp, 73 mm Hg). Gas chromatography indicated that the distilled liquid was a 0·08:1:0·56 mixture of VI, VII and VIII. These products were separated by preparative gas chromatography and identified with authentic samples.

C *With deuterium oxide as solvent.* To a cooled and stirred soln of 0·877 g $NaBH_4$ in 30 ml D_2O was added 2·14 g of IV. After the mixture was stirred for 3 hr with cooling and then for 4·5 hr at room temp, it was worked up as described above to give 1·10 g of a colorless liquid, b.p. 115–120° (bath temp, 72 mm Hg). Gas chromatography showed the liquid to be a 0·15:1:0·64 mixture of the deuterated analogues of VI, VII and VIII. The NMR and mass spectra show that the deuterated 3,6,7,8,9,9a- and 1,6,7,8,9,9a-hexahydro-4*H*-quinolizine contain 3-d and 1-d analogue (X and XI) respectively as the main isotopic component. The NMR spectra showed disappearance of approximately one allylic proton non-adjacent to nitrogen and the IR spectra showed C–D stretching bands at 2100–2200 cm^{-1}. The picrates showed no mixed m.p. depression with the picrates of the undeuterated amines (VI–VIII).

Reduction of 1,2,3,4-*tetrahydroquinolizinium bromide* (IV) *with sodium borodeuteride in water*

To a cooled and stirred soln of 2·1 g of IV in 20 ml H_2O was added dropwise a soln of 0·86 g of $NaBD_4$ in 10 ml H_2O during a short time. The mixture was similarly treated to give 0·92 g of a colorless liquid, b.p. 120° (bath temp, 64 mm Hg). Gas chromatography showed that the distilled liquid contained deuterated quinolizidine, XII and XIII in a ratio of 0·07:1:0·40. The number and position of the D atoms in XII and XIII were established by NMR (in CF_3COOH) and mass spectra. The IR spectra of XII and XIII showed C–D stretching bands at 2100–2200 and 2000–2100 cm^{-1} (C–D stretching bands at 2100–2200 cm^{-1} are very weak compared with those at 2000–2100 cm^{-1}). The picrates of these products showed no mixed m.p. depression with those of VI–VIII.

Reduction of 3,4-*dihydroquinolizinium bromide* (V)† *with sodium borohydride*

A *With ethanol as solvent.* To a cooled and stirred soln of 3·4 g of V in 30 ml EtOH was added dropwise a soln of 0·69 g $NaBH_4$ in 20 ml EtOH. The mixture was stirred for 3 hr with cooling and then left at room temp for 20 hr. The reduction mixture was worked up as described for the reduction of IV in EtOH to afford 1·35 g of a liquid of b.p. 110–130° (bath temp, 60 mm Hg). The liquid was shown by gas chromatography to be a 0·02:1:0·82:2·7 mixture of VI–IX. The unsaturated products (VII–IX) were separated by preparative gas chromatography and identified by IR spectral comparisons with the samples obtained from the reduction of I with $NaBH_4$. IX, NMR (CF_3COOH): τ 3·65–4·46 (4H, vinyl protons), 5·58–7·00 (5H, m, protons on carbons adjacent to nitrogen), 7·10–7·80 (4H, m, C-1 H_2, C-9 H_2).

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* m = multiplet.

† The bromide V was prepared according to the procedure of Boekelheide and Ross.[9]

B *With water as solvent.* To a cooled and stirred soln of 1·05 g of V in 15 ml water was added a cooled soln of 0·85 g $NaBH_4$ in 10 ml H_2O. The mixture was stirred with cooling for 3 hr and for additional 4·5 hr at room temp. The mixture was worked up as described for the reduction of IV in water to give a 0·09 : 1 :0·42 :0·48 mixture of VI–IX, which were separated by preparative gas chromatography.

C *With deuterium oxide as solvent.* To a cooled and stirred soln of 0·82 g $NaBH_4$ in 18 ml D_2O was added 1·5 g of V. The mixture was stirred and worked up as described above to give 0·565 g of a 0·08 :1 :0·55 :0·94 mixture of the deuterated analogues of VI–IX. These were separated by preparative gas chromatography. The NMR and mass spectra showed that the deuterated 3,6,7,8,9,9a-hexahydro-, 1,6,7,8,9,9a-hexahydro- and 3,6,9,9a-tetrahydro-4*H*-quinolizine contained the 3,9-d_2, 1,9-d_2 and 9-d analogues XIV, XV and XVI respectively as the main isotopic component. The IR spectra of the deuterated quinolizines showed C–D stretching bands at 2100–2200 cm^{-1}. The picrates showed no depression in mixed m.p. with those of VI–VIII.

Reduction of 3,4-*dihydroquinolizinium bromide* (V) *with sodium borodeuteride in water*

To a cooled and stirred soln of 3·15 g of V in 45 ml H_2O was added dropwise 2·82 g $NaBD_4$ in 30 ml H_2O. The mixture was stirred and worked up as described above to give 1·40 g of a 0·04 :1 :0·42 :0·84 mixture of deuterated quinolizidines, XVII, XVIII and XIX. The IR spectra of the separated quinolizines showed C–D stretching bands at 2000–2100 and 2100–2200 cm^{-1}.

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