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STUDIES ON QUINOLIZINIUM SALTS—V[1]

THE REDUCTION OF QUINOLIZINIUM BROMIDE WITH SODIUM BOROHYDRIDE AND LITHIUM ALUMINUM HYDRIDE[2]

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Abstract—Reduction of quinolizinium bromide (I) with LAH and $NaBH_4$ in THF causes ring-opening reactions leading to pyridine derivatives (V and XIII respectively). The $NaBH_4$ reduction of I in ethanol results in the formation of the quinolizine derivatives (VIII–XI). The hydride reduction in water proceeds similarly with the formation of VIII–XI, accompanied by a small amount of quinolizidine (VII). Carrying out the hydride reduction of I in deuterium oxide or ethanol-d results in incorporation of deuterium into the reduction products. Apparently the reduction involves deuteration of enamine intermediates and subsequent reduction of the resulting iminium ions. It is noteworthy that a possible intermediate, 4*H*-quinolizine (IVa) is reversibly protonated at C-1. Together with the reduction mechanism of I, the chemistry of the parent quinolizine (IVa) is described.

AN EARLIER paper[3] described Grignard reactions of quinolizinium bromide (I) leading to 4-substituted-1-(2-pyridyl)-1,3-butadiene (III). The ring-opening reaction was postulated to proceed by way of 4-substituted-4*H*-quinolizine (II), although this type of quinolizine has not been prepared successfully[4] and only the adducts from pyridines and dimethyl acetylene dicarboxylate are known.[5] On the basis of the Grignard reactions it was concluded that simple quinolizine derivatives undergo facile isomerization to the thermodynamically more stable butadiene (III). In the present paper which deals with metal hydride reductions of I, we discuss the chemistry of the parent quinolizine (IVa) which is as yet unknown.

The LAH reduction of I in tetrahydrofuran resulted in the formation of an unstable oil. The oil showed terminal methylene absorption bands at 912 and 1080 cm^{-1} and a conjugated double bond band at 1635 cm^{-1} in the IR spectrum. The catalytic hydrogenation of the oil over 5% Pd–C in glacial acetic acid afforded 2-n-butylpyridine with an approximately 2 mole-equivalent uptake of hydrogen. These data indicate that the hydride reduction product is 1-(2-pyridyl)-1,3-butadiene (V)* which has been also produced on treatment of 1,2,3,4-tetrahydro-2-hydroxyquinolizinium iodide (VI) with sodium acetate.[4b] The geometry of the 1,2-double bond in V is assumed to be *cis* by analogy with the geometries of the major product of Grignard reactions.[3,6]

The hydride reduction is thought to proceed by a pathway involving a ring-opening reaction of 4*H*-quinolizine (IVa). The parent quinolizine should result predominantly from hydride attack at C-4 (or C-6) of I, although we could not exclude the possibility of the isomerization of 2*H*- or 9a*H*-quinolizine (IVb or c) to IVa.[5,7]

* We wish to thank Prof. V. Boekelheide for kindly supplying us with an authentic sample.

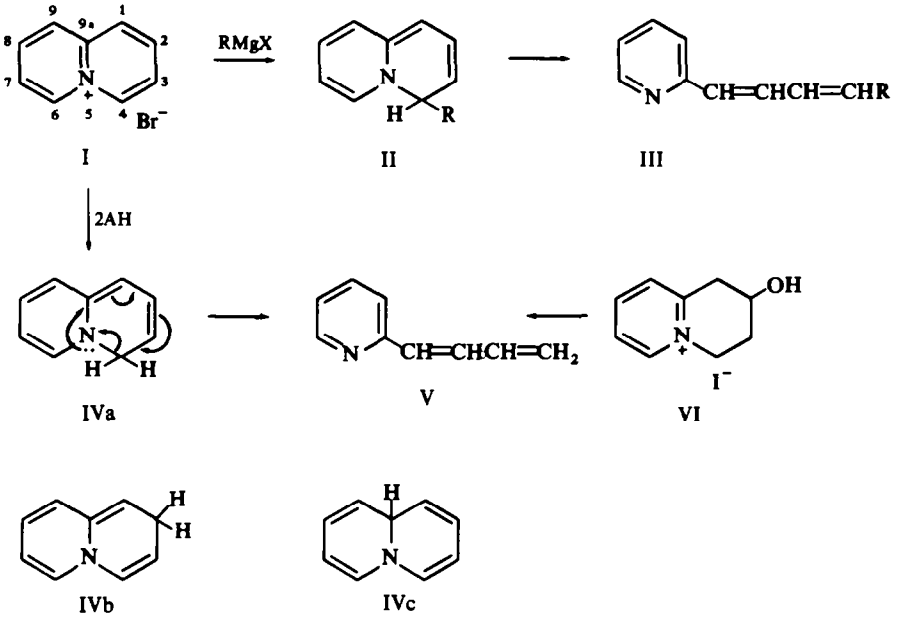


CHART 1

This assumption is based on Grignard reaction studies[3] and MO calculations[7] of quinolizinium ion which indicate that the most preferred nucleophilic reaction takes place at C-4 (or C-6).

On the other hand, the reduction of I with sodium borohydride (1·1 moles) in ethanol afforded a more stable oil with the UV spectrum showing end-absorption. Catalytic hydrogenation of the oil gave a saturated amine (VII) with the consumption of about 1·6 mole-equivalent of hydrogen. The hydrogenated product was assumed to

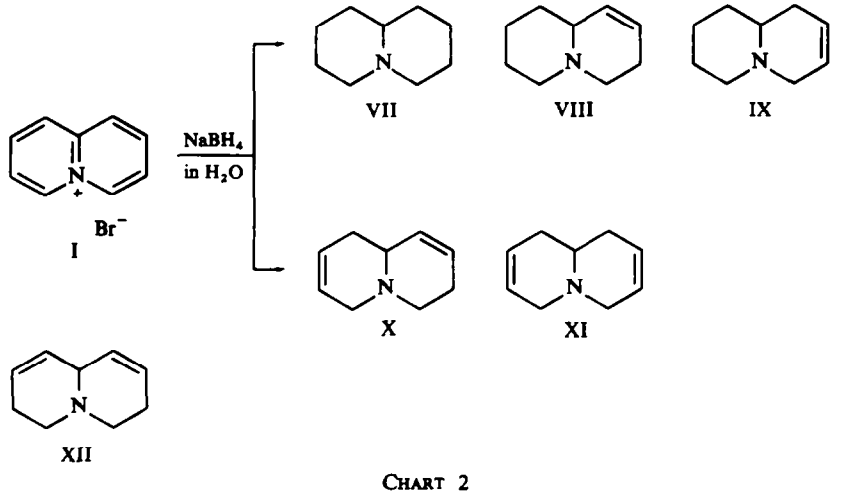


CHART 2

be quinolizidine (VII) by the analytical and spectral data, and identified with an authentic sample. Gas chromatography showed the borohydride reduction product to comprise four components (VIII–XI) in a ratio of 1 :0·92 :2·2 :1·4. These products were most effectively separated by 20% polydiethylene glycol succinate on 30–60 mesh Chromosorb W.[8] Catalytic hydrogenation of each of the separated amines yielded VII on consuming one mole-equivalent of hydrogen in VIII and IX, and two, in X and XI. The results indicate that the borohydride reduction proceeds without ring-opening of the original ring in contrast with the LAH reduction.

The location of the double bonds was determined on the basis of pK'_a values, and IR, UV and NMR spectra. According to Leonard *et al.*[9,10] salt formation of an enamine causes a decided shift (ca. 20–50 cm^{-1}) in the double bond stretching region toward higher frequency corresponding to the structural transformation: $\rangle C{=}\overset{+}{C}{-}N\langle \rightarrow \rangle CH{-}\overset{+}{C}{=}\overset{+}{N}\langle$. The double bond stretching bands of the unsaturated quinolizidine hydriodides showed no appreciable shifts compared with those of the free bases (VIII–XI). The UV spectra of VIII–XI showed no absorption maximum above 220 mμ[11] suggesting absence of enamine structures in the quinolizidine rings. This was further confirmed by the pK'_a values of VIII–XI in water (VIII, 9·62; IX, 9·68; X, 8·77; XI, 9·31)* indicating a lower basicity than that of enamines[12] (e.g. the perchlorate salt of 1,2,3,6,7,8-hexahydro-4*H*-quinolizine has no titratable group below pH 12 in water.[10]). These observations excluded an enamine structure for the reduction products, and thus the monoenes and the dienes must be chosen from five possible structures (VIII–XII).

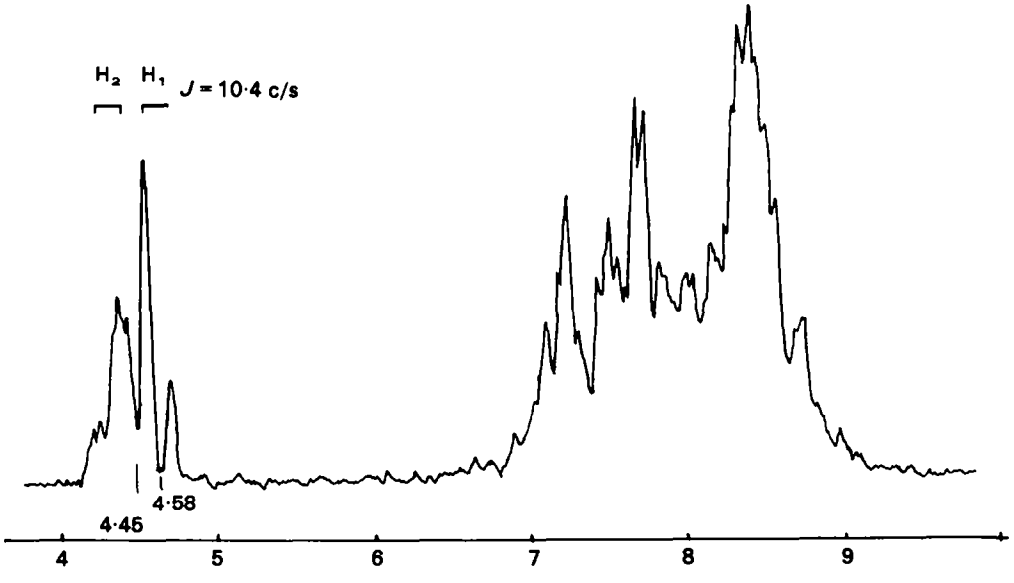


FIG. 1-1 NMR spectrum of VIII in $CDCl_3$.

* In the communication[2] erroneous values were given.

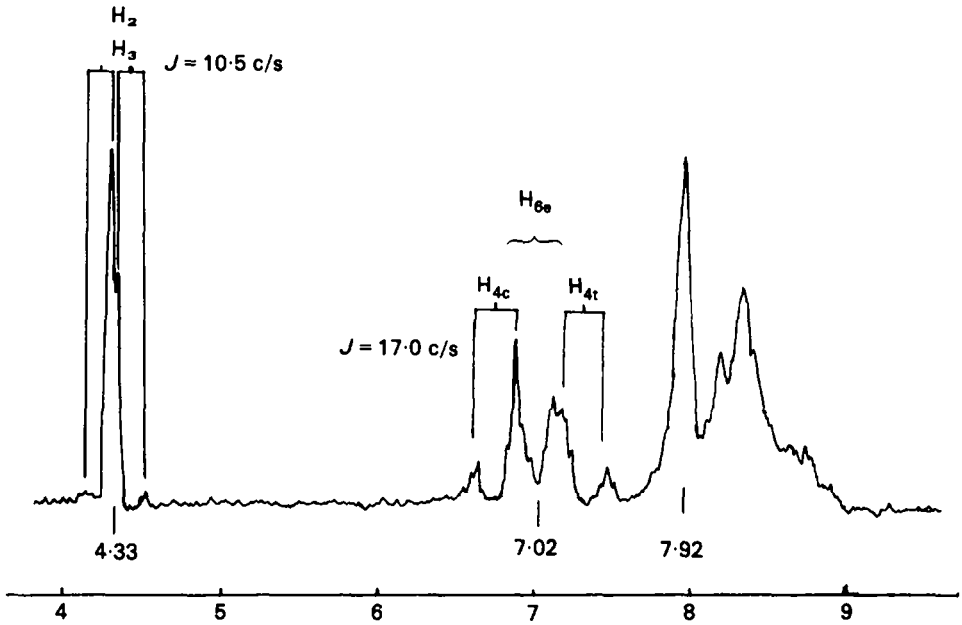


FIG. 1-2 NMR spectrum of IX in $CDCl_3$.

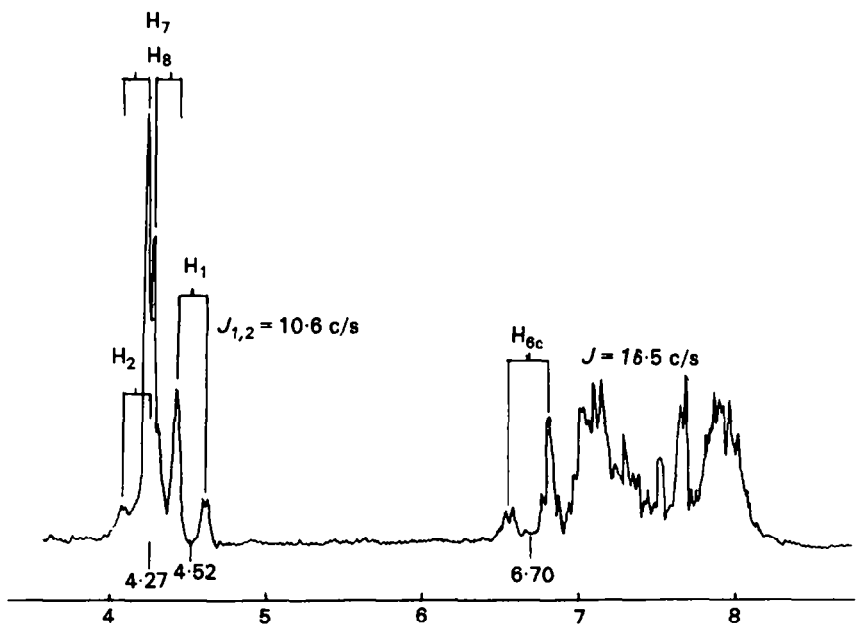


FIG. 1-3 NMR spectrum of X in $CDCl_3$.

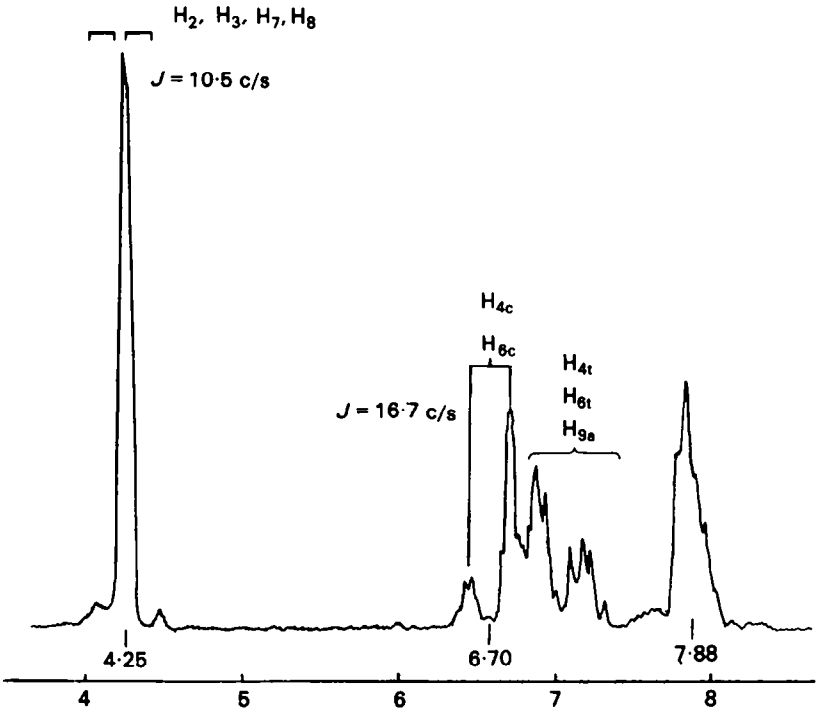


FIG. 1-4 NMR spectrum of XI in $CDCl_3$.

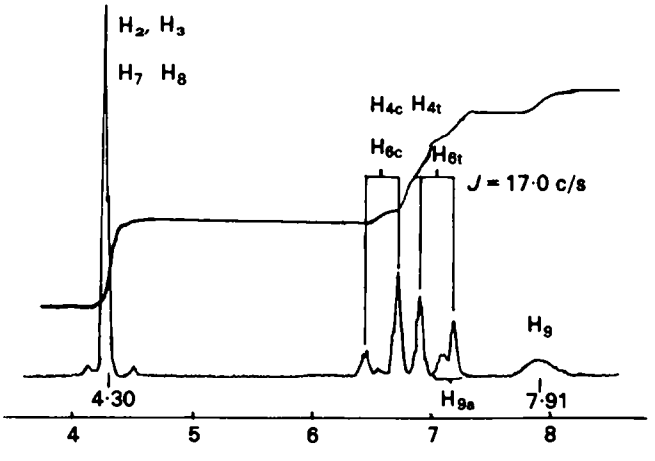


FIG. 1-5 NMR spectrum of deuterated analogues of XI (main component, XVII).

The IR spectrum of 3,6,7,8,9.9a-hexahydro-4*H*-quinolizine (VIII) showed a Bohlmann band[13] at 2743 cm^{-1}* with an intensity comparable to that of VII in which the *trans*-fused conformation predominates.[14] The intensity of the band was reduced to a large extent in the 4,9a-dideuterated analogue prepared from sodium borodeuteride reduction of 1,2,3,4-tetrahydroquinolizinium bromide.[1] The NMR spectrum of VIII shows complicated multiplets at 6·8–9·0 τ except the olefinic proton multiplet centered at 4·45 τ. The broad doublet (J = 10·4 c/s) at 4·58 τ was assigned to the C-1 proton by comparison with the spectrum of 4,9a-dideuterated analogue in which C-2 proton couples with one of the C-3 protons with a coupling constant of 4·4 c/s.

The other monoene must be the remaining possible amine, 1,6,7,8,9,9a-hexahydro-4*H*-quinolizine (IX). Two olefinic protons appeared as a symmetrical broad quartet (J = 10·5 c/s) centered at 4·33 τ strongly resembling 1,2,5,6-tetrahydropyridine.[15] The NMR spectrum of the tetrahydropyridine has been completely analysed by decoupling experiments, and the broadening of the olefinic proton peaks has been ascribed to vicinal and long-range couplings of the olefinic protons with allylic protons. The three-proton multiplet centered at 7·02 τ was assigned to the C-4 protons attached to two deshielding groups, nitrogen and a double bond, and C-6 equatorial proton (H_{6e}). The chemical shift of the C-6 equatorial proton is consistent with the spectral data of VII in which the corresponding protons appear as a broad doublet at 7·2 τ.[16] The two signals with J = 17 c/s centered at 6·77 τ is due to the C-4 proton (H_{4c}) *cis* to the nitrogen lone pair electrons. The remaining proton multiplets at 7·6–9·0 τ could not be analysed because of complete overlapping, except C-1 protons at 7·92 τ. The hexahydroquinolizine (IX) showed relatively lower intensity of a Bohlmann band at 2759 cm^{-1}.

The olefinic protons of 3,6,9,9a-tetrahydro-4*H*-quinolizine (X) appeared as a multiplet comprising two types of peaks characteristic of VIII and IX. The somewhat broad doublet at 4·52 τ shows the presence of olefinic C-1 proton as shown in VIII. The C-2 proton multiplet seems to overlap with other olefinic proton peaks centered at 4·27 τ in close similarity to those of IX. The two signals with J = 16·5 c/s centered at 6·70 τ are assignable to the C-6 proton (H_{6c}) *cis* to the nitrogen lone pair electrons as in IX. The diene (X) also showed a prominent IR absorption band at 2742 cm^{-1} comparable in intensity to that of VII.

The olefinic protons of 1,6,9,9a-tetrahydro-4*H*-quinolizine (XI) appeared as a symmetrical broad quartet (J = 10·5 c/s) at 4·25 τ characteristic of the 2,3-double bond in the quinolizidine ring. On the basis of the above data, the remaining protons were assigned as shown in Fig. 1. The IR spectrum of XI showed a weaker absorption band at 2751 cm^{-1} than that of IX, although it was much stronger than that of the 4,9a-d_2 analogue of IX.[1]

The mass spectral fragmentations[1] were in accord with the structures (VIII–XI) thus assigned. Furthermore, VIII was identified as the picrate by infrared spectral comparison with an authentic sample,† and IX and X were identical with those obtained from the borohydride reduction of 3,4-dihydroquinolizinium bromide.[1]

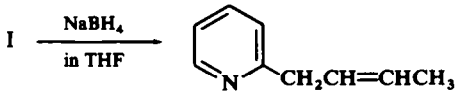
The product ratio differed by changing the mole ratio of I and sodium borohydride,

* Bohlmann bands discussed below were measured with a Perkin-Elmer Model 221 double-beam spectrophotometer provided with NaCl and grating interchange and most prominent band was chosen.

† We express our gratitude to Prof. N. J. Leonard for kindly supplying us with an authentic sample.

although the yield was almost unchanged. With water as solvent, a small amount of quinolizidine (VII) was produced in addition to VIII–XI. Quinolizidine (VII) was similarly separated by preparative gas chromatography and identified by comparison with an authentic sample.

In contrast, the sodium borohydride reduction of I in tetrahydrofuran afforded an oily substance in a rather poor yield. The reduction product contained no quinolizines such as VII–XI, but a pyridine derivative (XIII). This pyridine (XIII) was separated by preparative gas chromatography and purified as picrate, m.p. 119–120°. The free base showed an infrared absorption band at 1655 cm^{-1} due to isolated double bond and UV absorption maxima at 258, 264 and 270 mμ characteristic of 2-alkylpyridine.[17] The hydrogenation of XIII over 5% Pd–C in acetic acid afforded 2-n-butylpyridine. Furthermore, it was proved that XIII was a pyridine derivative substituted with $—CH_2CH=CHCH_3$ by the NMR spectrum (Experimental).



XIII

CHART 3

From the decided difference between the hydride reductions in protic and aprotic solvents it appears that protonations take part in the hydride reduction in the protic solvents. The LAH reduction in the aprotic solvent causes a ring-opening isomerization of the initial product (IVa) to V possibly with a shift of the nitrogen lone pair electrons. On the other hand, IVa with enamine structure may undergo protonation in protic solvents either at C-1,3,7 or 9 other than nitrogen. The protonation on a carbon atom gives an iminium ion subsequently reducible by a hydride ion and prevents the cleavage of the C-4—N bond of IVa. The borohydride reduction of I in ethanol may proceed with most preferred C-4 hydride attack and subsequent C-1 protonation to give 1,4-dihydroquinolizinium ion (XIV). The Hückel MO calculations* suggest that kinetically controlled protonation of IVa should take place

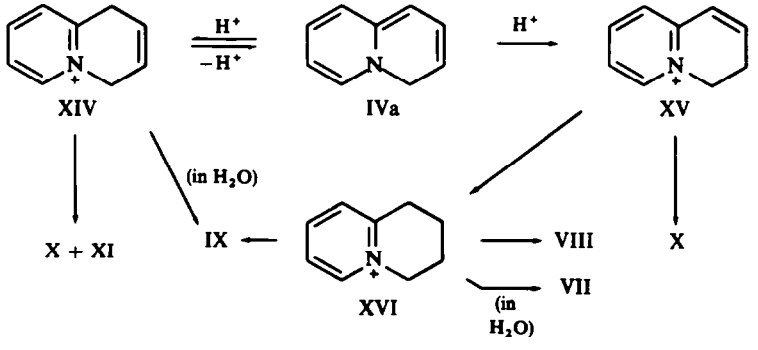


CHART 4

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

preferentially at C-1. 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 atoms adjacent to nitrogen, 0·1; the CN resonance integral (k), 0·8.[7,18] The order of the π-electron densities at C-1

TABLE 1. π-ELECTRON DENSITIES IN 4*H*-QUINOLIZINE (IVa) AT $k = 0{\cdot}8$, $h = 1{\cdot}5$, $h = 0{\cdot}1$.

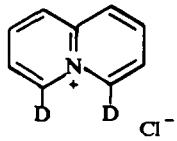
Position (i)	1	2	3	5(N)	6	7	8	9	9a
q_i	1·208	0·991	1·187	1·736	0·910	1·043	0·942	1·022	0·961

and C-3 was insensitive to 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 dihydroquinolizinium ion (XIV) may undergo reduction to give X and XI possibly by a pathway similar to that of the borohydride reduction of 1,2,3,4-tetrahydroquinolizinium ion (XVI).[1]

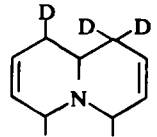
Another possible protonation of IVa could occur at C-3 affording the thermodynamically more stable 3,4-dihydroquinolizinium ion (XV) which can yield VIII–X.[1] This type of protonation has been observed on treatment of 4*H*-quinolizine derivatives, adducts of pyridines and dimethyl acetylene dicarboxylate, with a strong acid.[5] Although isolation or detection of the reduction intermediates (XIV and XV) failed probably because of more rapid reduction of the intermediates, experiments using deuterated solvents support the reduction mechanism postulated above.

First of all, I was treated with deuterium oxide in order to examine hydrogen-deuterium exchange of I in deuterium oxide. Although practically no hydrogen-deuterium exchange of I in deuterium oxide was observed in the NMR spectrum in 24 hr at room temperature, a broad doublet ($J = 7{\cdot}0$ c/s) at 0·74 τ assigned to the C-4 and C-6 protons disappeared in several hours under strongly alkaline conditions. The H–D exchange does not seem to occur significantly at C-4 and C-6 prior to the borohydride reduction of I in deuterium oxide, since the reduction products show an extremely weak, broad band in 2000–2100 cm^{-1} region.[1] However, such exchange was not observed with ethanol-d as solvent. Consequently, the following spectral

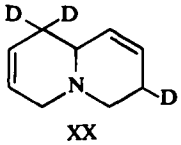
XVII



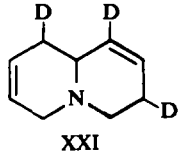
XVIII



XIX



XX



XXI

CHART 5

description concerns the products obtained from the reduction in ethanol-d, although there is no marked difference between the spectral data of both reduction products.

Carrying the sodium borohydride reduction out in deuterium oxide or ethanol-d resulted in the incorporation of D atoms into the quinolizine derivatives which exhibited C–D stretching absorption bands[19] in the IR spectra. These products showed the same retention times as the undeuterated amines (VII–XI) on gas chromatogram and the picrates, no depression in mixed m.ps with those of VII–XI.

The reduction mechanism discussed herein is based on the 2,7-diene product, since number and position of deuterium atoms incorporated are evident from the NMR spectrum.

The IR spectrum of the 2,7-diene product exhibited a C–D stretching band at 2150 cm^{-1}, but no band near 2250 and 2050 cm^{-1} indicating absence of vinyl deuterium or deuterium on carbons adjacent to nitrogen. The deuterated diene showed an intense parent ion peak at *m/e* 138, three higher mass units than that of XI, indicative of predominant formation of a trideuterated analogue (XVII) in the 2,7-diene. The most important fragmentation for XI is cleavage of one ring with formation of the *m/e* 54 fragment, which shifted to *m/e* 56 and 55 in nearly equal abundance in the deuterated analogue. Another prominent fragment at *m/e* 81 in XI also shifted to *m/e* 82 and 83 in the deuterated analogue. The three D atoms were shown to be at C-1 and C-9 by the NMR spectrum showing only one proton broad peak at 7·91 τ (Fig. 1–5).

If all deuterations involved in the reduction of IVa are kinetically controlled and reductions immediately follow deuterations, the diene should contain two deuterium atoms, since deuteration occurs in two steps. It is unlikely that one deuterium atom results from H–D exchange of I prior to the hydride reduction, since I most readily undergoes exchange at C-4 and C-6. For confirmation, I was treated with NaOD-D_2O solution and the resulting dideuterated quinolizinium chloride (XVIII) was reduced with the borohydride in deuterium oxide. The corresponding product was shown to be the pentadeuterated analogue (XIX) by molecular ion peak at *m/e* 140

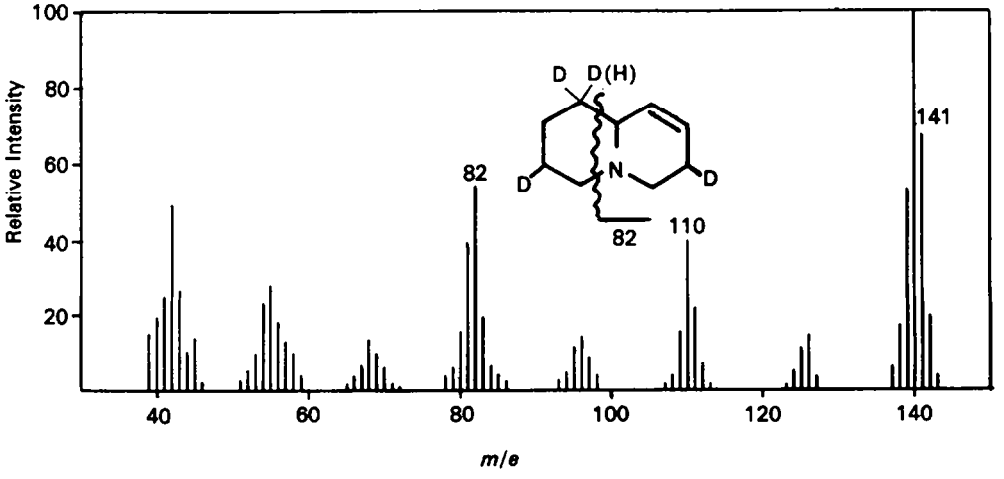
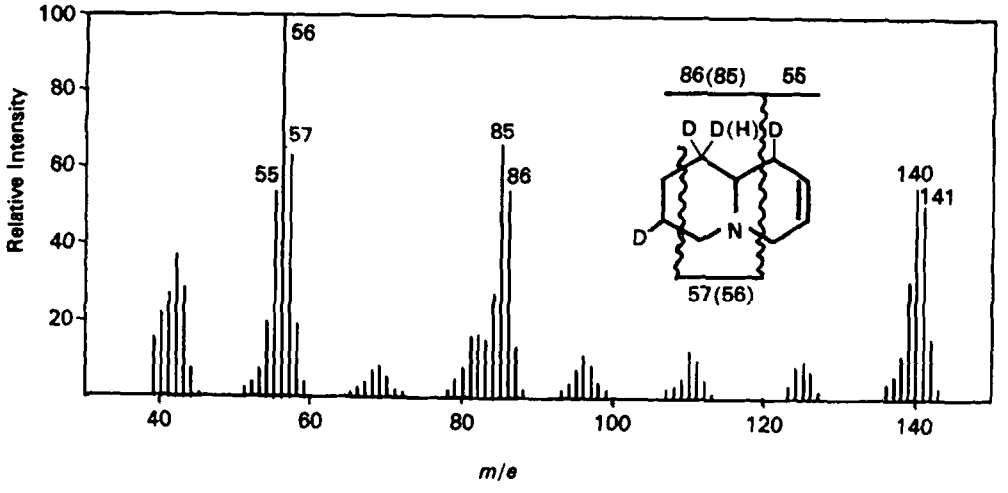


FIG. 2-1


Relative Intensity
100
80
60
40
20
56
57
55
85
86
140
141
86(85) 55
D D(H) D
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57(56)
40
60
80
100
120
140
m/e

FIG. 2-2

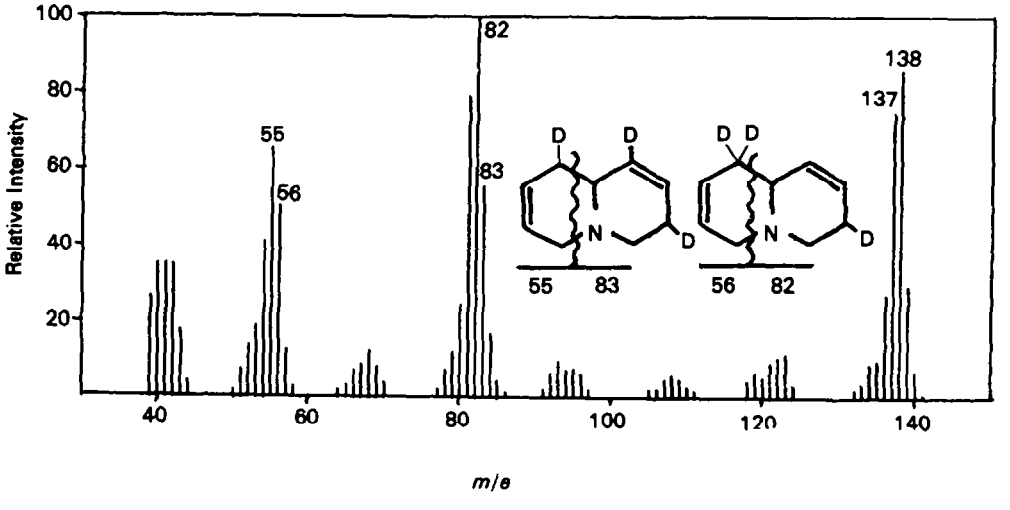
Relative Intensity
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FIG. 2-3

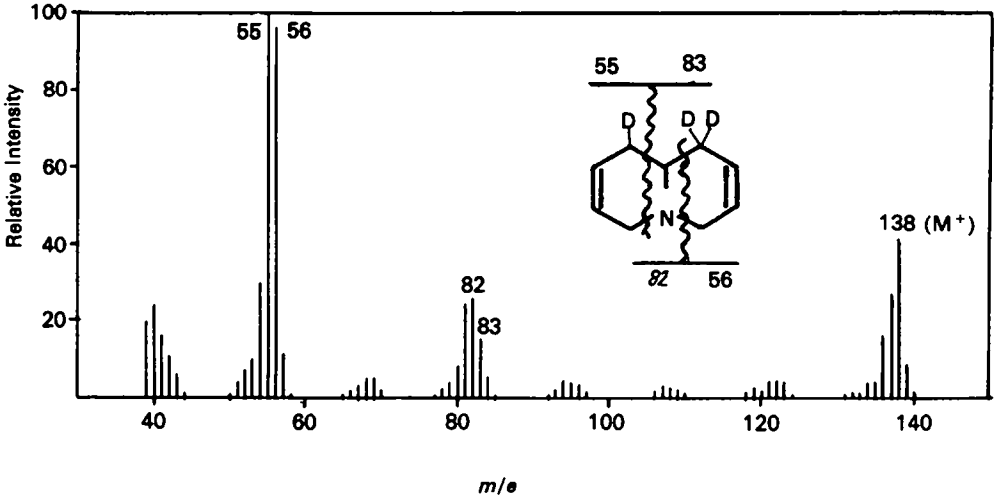

FIG. 2-4

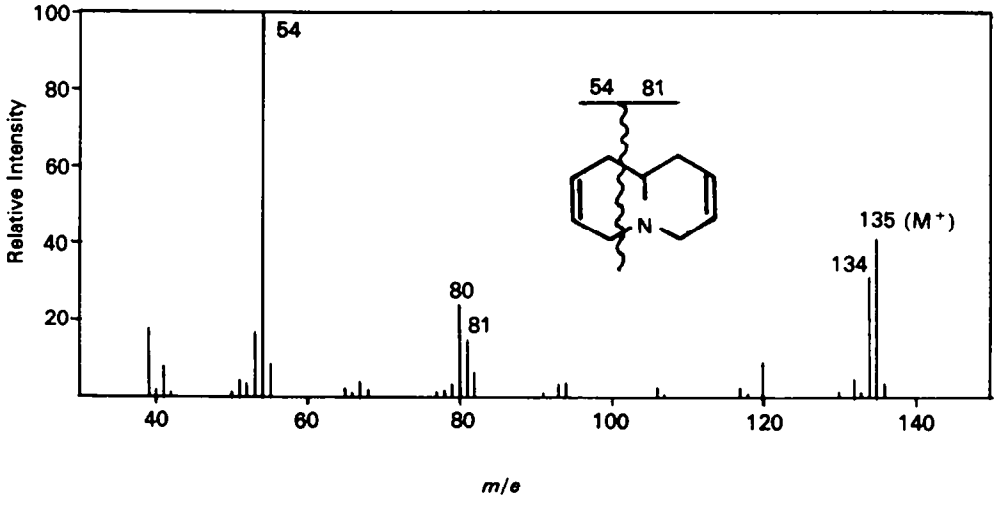

FIG. 2-5

FIG. 2 Mass spectra of XI (5) and deuterated products (1–4) obtained from the sodium borohydride reduction of I in EtOD.

and the NMR spectrum showing four vinyl protons (4·32 τ), one C-1 or C-9 proton (7·88 τ) and three protons (6·55–7·30 τ) on carbons adjacent to nitrogen.

Further, it was found that the reduction products did not undergo isomerization and H–D exchange under the reduction conditions. Thus, only a rapid equilibration in a deuteration step can account for the trideuteration at C-1 and C-9. The equilibration would occur in the first of the two deuteration steps, since the second deuteration should proceed by a mechanism similar to that of the reduction of 1,2,3,4-tetrahydroquinolizinium ion (XVI).[1] The quinolizine intermediate (IVa) can be regarded as an anhydropyridine derivative conjugated with a double bond and thus in the alkaline medium is expected an equilibration between IVa and the non-conjugated quaternary ion (XIV) derived by protonation.[20] The 2,3-double bond of XIV may facilitate the reverse reaction, removal of a proton from C-1. The equilibration can introduce two deuterium atoms at C-1 giving dideuterated ion (XXII). This ion (XXII) undergoes the second reduction at C-6 giving a dienamine (XXIV). Subsequently, XXIV is deuterated at C-9 and the resulting iminium ion (XXV) is finally reduced to afford XVII. Similarly, the quaternary ion (XXII) is reduced at C-9a to give a dienamine (XXVI). The kinetically controlled deuteration of XXVI and subsequent reduction of the resulting iminium ion (XXVII) leads to a trideuterated 1,7-diene (XX).

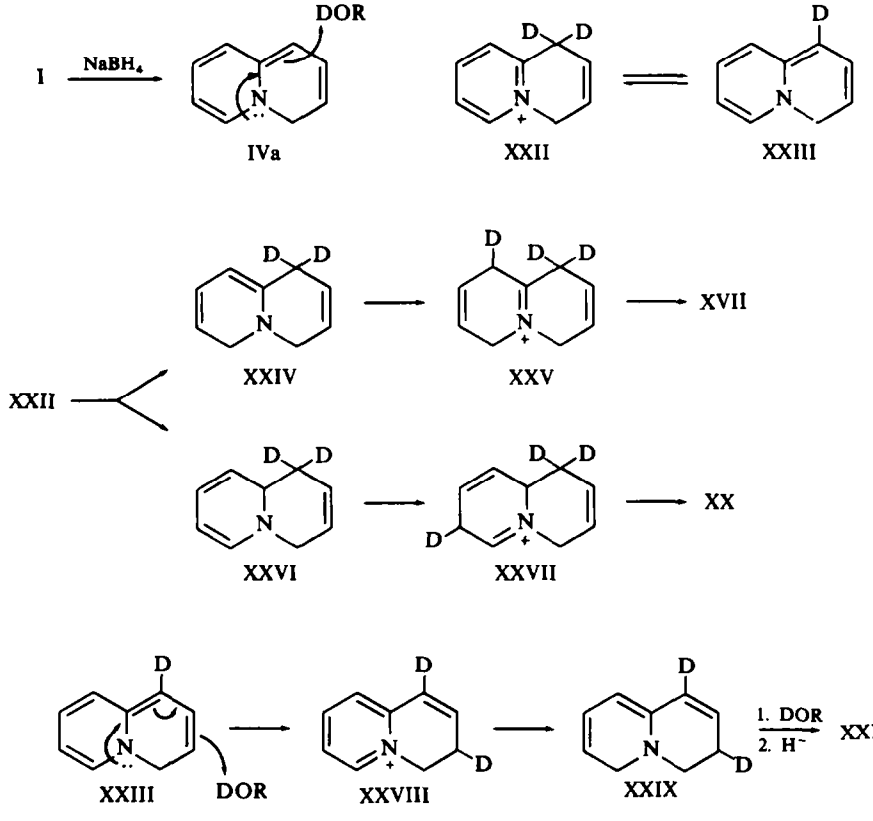

CHART 6

Since a thermodynamically more stable product is formed under equilibrating conditions,[21] the C-3 deuteration of XXIII may increase with the formation of 3,4-dihydro ion (XXVIII), which competes with the hydride reduction of 1,4-dihydro ion (XXII). The reduction of XXVIII leads to 1,7-diene (XXI) via an intermediate (XXIX) by a pathway postulated in the preceding paper.[1] The mechanistic assumption is in accord with the spectral data of the 1,7-diene product showing a very weak band at 2250 cm^{-1} due to vinyl deuterium[19] in the IR spectrum and decrease of the integrated area of the C-1 proton doublet in the NMR spectrum.[1] The amount of deuterium incorporated at C-1 was estimated to be 0·3–0·5 atom of D per molecule on the basis of the NMR spectrum. Furthermore, the mass spectrum indicated partial shift of *m/e* 81 in X to *m/e* 83 in the deuterated 1,7-diene product. Such vinyl deuterium was not detected in the infrared spectra of the other deuterated tetrahydro- and hexahydroquinolizines, and no isomerization of XI to X occurred under the reduction conditions. Thus, X is concluded as being formed by two pathways involving C-1 or C-3 protonation of IVa and subsequent hydride reduction of the resulting ions (XIV and XV).

For the formation of the two monoenes (VIII and IX) two pathways seem to be involved in the hydride reduction. One possibility is the reduction of the 3,4-dihydro-

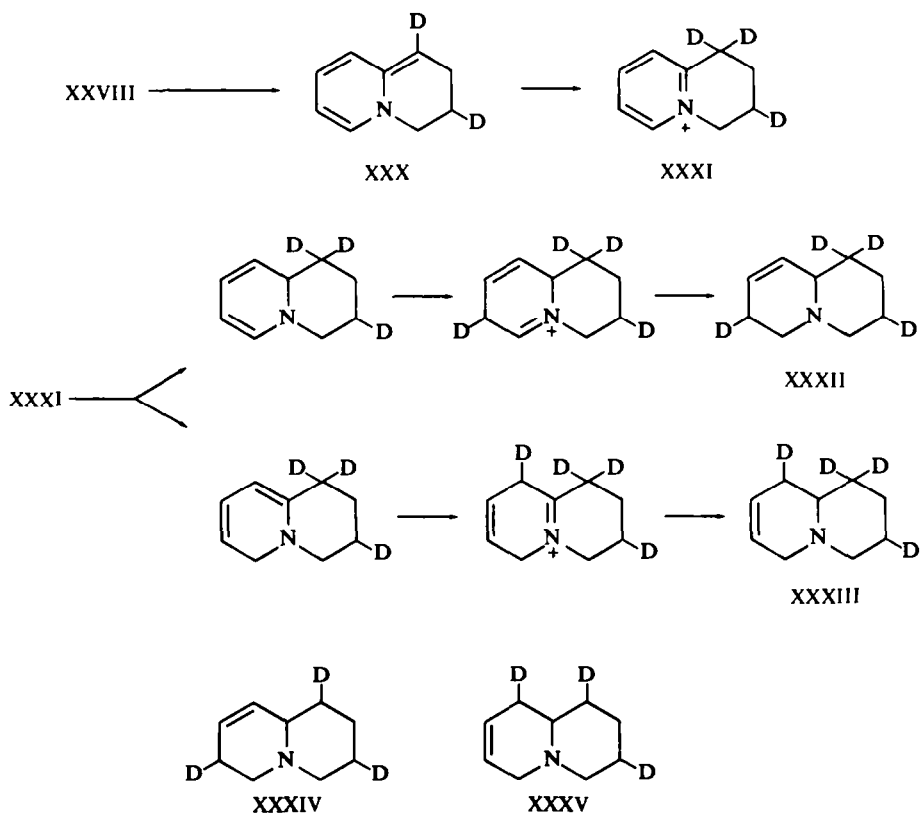

CHART 7

quinolizinium ion intermediate (XV) yielding VIII and IX in addition to X.[1] The reduction of the dideuterated intermediate ion (XXVIII) proceeds by a pathway previously postulated,[1] affording tetradeuterated monoenes (XXXII and XXXIII) as illustrated in Chart 7. A second possible pathway consists of an initial hydride attack at C-2 of I to give 2*H*-quinolizine (IVb). As would be assumed from the above discussion, the reduction of IVb may proceed by repetition of kinetically controlled protonation and reduction of the resulting iminium ion leading to VIII and IX. Such processes lead predominantly to the trideuterated monoenes (XXXIV and XXXV) in the hydride reduction in the deuterated solvents.

2-Monoene (IX) gives rise to prominent peaks at *m/e* 137 (M^+), 136 (M − 1), 83 (base peak) and 55, whereas *m/e* 137 (M^+), 136 (M − 1, base peak), 108, and 81 peaks are prominent in the mass spectrum of VIII.[1] As is evident from mass spectral comparison of the deuterated monoenes with VIII and IX, the tetradeuterated analogues are produced, together with the trideuterated monoenes. However, the formation ratio of tri- and tetradeuterated monoenes could not be determined because of uncertainty of M − 1 (H)/M − 2 (D) ratio. The spectrum of the deuterated 2-monoene shows that the corresponding peaks have shifted partially from *m/e* 83 and 55 to 86 and 57. These shifts suggest that in the saturated ring there are three D atoms, two of which are at C-9. For the deuterated 1-monoene the peak shifted from *m/e* 81 to 82 and there was a partial shift from *m/e* 108 to 110. This observation is quite reasonable, if two deuterium atoms are present at C-9 and the remaining two, at C-3 and C-7, as would be anticipated from mechanistic assumptions. The NMR spectra of the deuterated monoenes confirmed the presence of approximately one D atom at the allylic position as illustrated. The above data can best be rationalized, if the formation of VIII and IX follows the first course where the initially formed 4*H*-quinolizine (IVa) is protonated reversibly and then reduced further with hydride ion.

On the other hand, the formation of the trideuterated monoenes (XXXIV and XXXV) does not necessarily support the second possible reduction mechanism, since the first course may afford XXXIV and XXXV by some C-3 deuteration of IVa and subsequent reduction prior to the H–D exchange at C-1. Moreover contamination with a small amount of hydroxylic solvent leads to the formation of some trideuterated monoenes even by the first reduction pathway. The above descriptions can account for the formation of some dideuterated dienes.

The less abundant peak at *m/e* 142 in the deuterated monoenes and at *m/e* 139 in the deuterated dienes indicate concomitant formation of pentadeuterated monoenes and tetradeuterated dienes as minor deuterated components. Similarly, such minor deuterated analogues were produced in the hydride reductions of 1,2,3,4-tetrahydro- and 3,4-dihydroquinolizinium ions (XVI and XV) in deuterium oxide, although the ratio of the minor/major deuterated analogue was smaller in each deuterated product.[1]

For initial hydride reduction of I there is another possibility of the hydride attack at C-9a. However, this possibility was ruled out by production of no 3,4,6,7-tetrahydro-9a*H*-quinolizine (XII), because the C-9a reduction may involve kinetically controlled protonations of the resulting 9a*H*-quinolizine (IVc) and subsequent reductions leading to the expected product.

Although the deuterated quinolizidine was not examined to elucidate the mechanism for its formation, apparently quinolizidine (VII) is formed via a tetrahydro ion (XVI).[1]

Similarly, in the hydride reduction of I in water it seems probable that the intermediate ion (XIV) is reduced partially to IX involving hydride attack at C-8 of XIV.

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 determined 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).

Reduction of quinolizinium bromide (I) *with lithium aluminum hydride*

To a soln of 0·8 g of LAH in 100 ml dry THF was added 4·2 g of I with stirring at room temp. The mixture was stirred for 3 hr and then the excess hydride was decomposed with wet ether. After filtration and washing with ether, the filtrate was dried over Na_2SO_4, and the solvent was evaporated to give 1·7 g of a dark red oil. Distillation of the crude product gave V as a very unstable orange oil, b.p. 45° (bath temp, 0·3 mm Hg); λ_{max}^{EtOH} mμ (ε): 262 (15,700), 292·5 (12,800); ν_{max}^{liq} cm^{-1}: 1080, 912 (terminal methylene). The oil was purified as the picrate. The picrate of V was prepared and recrystallized from EtOH, m.p. 152–152·5°. (Found: C, 49·90; H, 3·38; N, 15·54. Calc. for $C_{15}H_{12}O_7N_4$: C, 50·00; H, 3·36; N, 15·55%).

Catalytic hydrogenation of 1-(2-*pyridyl*)-1,3-*butadiene* (V)

A soln of 0·7 g of V in 30 ml glacial AcOH was hydrogenated in the presence of 50 mg of 5% Pd–C. After the consumption of H_2 ceased, the catalyst was removed by filtration and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in water and the soln was made basic with K_2CO_3, and extracted with ether. The ether layer was dried over K_2CO_3, and the solvent was removed. Distillation of the residue gave 2-n-butylpyridine which was identical with an authentic sample.

Reduction of quinolizinium bromide (I) *with sodium borohydride in tetrahydrofuran*

To a suspended soln of 0·90 g of $NaBH_4$ in 350 ml THF was added 4·2 g of I and the mixture was stirred for 75 hr at room temp. Insoluble materials were removed by filtration, and the filtrate cooled with ice-salt bath was acidified with glacial AcOH. The soln was concentrated *in vacuo*, and water was added. The mixture was made basic with Na_2CO_3, and the organic material was extracted with ether. The ether extract was dried over Na_2SO_4, the solvent was removed and the residue was distilled to give 360 mg of a liquid, b.p. 130–135° (bath temp, 85 mm Hg). The liquid was shown by gas chromatography to contain several kinds of impurities. Preparative gas chromatography afforded XIII as a colorless liquid which was further purified as the picrate, yellow needles, m.p. 119–120°. (Found: C, 50·01; H, 3·98; N, 15·64. $C_{15}H_{14}O_7N_4$ requires: C, 49·73; H, 3·90; N, 15·47%). The spectral data of XIII are shown below: ν_{max}^{liq} cm^{-1}: 1665 (C=C). λ_{max}^{EtOH} mμ: 258, 264, 270; NMR ($CDCl_3$): τ 8·31 (3H, broad d*, J = 5·0 c/s, Me), 4·48 (2H, m, —CH=CH—), 6·53 (2H, CH_2), 1·65 (1H, two qu's, C-6 H of the pyridine ring), 2·40–3·25 (3H, m, C-3, C-4, C-5 H of the pyridine ring).

Reduction of quinolizinium bromide (I) *with sodium borohydride in ethanol*

To an ice-cold and stirred soln of 4·2 g (0·020 mole) of I in 50 ml EtOH was added dropwise a soln of 0·85 g (0·022 mole) $NaBH_4$ in 50 ml EtOH over a period of a few min. The reaction mixture was stirred for additional 3 hr and then left at room temp for 20 hr. Glacial AcOH was added dropwise to the mixture and the solvent was evaporated *in vacuo*. The residue was dissolved in water and the soln was made strongly basic with excess K_2CO_3 and extracted with ether. After the organic layer was dried over K_2CO_3, the residue obtained on removal of the solvent was distilled to give 1·15 g of a colorless liquid, b.p. 110–140° (bath temp, 50 mm Hg). The liquid was found a 1:0·92:2·2:1·4 mixture of VIII, IX, X and XI. The quinolizine derivatives were separated by preparative gas chromatography and characterized as follows:

3,6,7,8,9,9a-*Hexahydro*-4H-*quinolizine* (VIII). Colorless liquid, b.p. 115–120° (bath temp, 67 mm Hg); $\nu_{max}^{CCl_4}$ cm^{-1}: 1664, 3040 (C=C). (Found: C, 78·49; H, 10·90; N, 9·92. Calc. for $C_9H_{15}N$: C, 78·77; H, 11·02;

*d = doublet; m = multiplet; qu = quartet.

N, 10·21%). pK'_a (in water), 9·62. The picrate was prepared in ether and recrystallized from EtOH, yellow plates, m.p. 182–183°. (Found: C, 49·11; H, 5·01; N, 15·20. Calc. for $C_{15}H_{18}O_7N_4$: C, 49·18; H, 4·95; N, 15·30%). The m.p. of a mixture with an authentic sample* was undepressed. The hydriodide was prepared by adding conc HI to a soln of VIII in EtOH and recrystallized from EtOH, colorless crystals, m.p. 214–215°; ν_{max}^{Nujol} 1665 cm^{-1} (C=C). (Found: C, 40·76; H, 6·06; N, 5·21. Calc. for $C_9H_{16}NI$: C, 40·77; H, 6·08; N, 5·28%).

1,6,7,8,9,9a-*Hexahydro*-4H-*quinolizine* (IX). A colorless liquid, b.p. 115–120° (bath temp, 63 mm Hg); $\nu_{max}^{CCl_4}$ cm^{-1}: 1670, 3040 (C=C); pK'_a (in water), 9·68. (Found: C, 78·53; H, 10·95; N, 9·93. $C_9H_{15}N$ requires: C, 78·77; H, 11·02; N, 10·21%). The picrate was prepared in ether and recrystallized from EtOH, m.p. 197–198°. (Found: C, 49·03; H, 5·03; N, 15·17. $C_{15}H_{18}O_7N_4$ requires: C, 49·18; H, 4·95; N, 15·30%). The hydriodide, colorless plates, m.p. 216–217°; ν_{max}^{Nujol} cm^{-1}: 1669 (C=C). (Found: C, 40·71; H, 6·07; N, 5·43. $C_9H_{16}NI$ requires: C, 40·77; H, 6·08; N, 5·28%).

3,6,9,9a-*Tetrahydro*-4H-*quinolizine* (X). A colorless liquid, b.p. 115–120° (bath temp, 70 mm Hg); $\nu_{max}^{CCl_4}$ cm^{-1}: 1665, 3050 (C=C); pK'_a (in water), 8·77. (Found: C, 79·74; H, 9·55; N, 10·44. $C_9H_{13}N$ requires: C, 79·95; H, 9·69; N, 10·36%). The picrate, yellow needles, m.p. 182–183°. (Found: C, 49·40; H, 4·48; N, 15·35. $C_{15}H_{16}O_7N_4$ requires: C, 49·45; H, 4·43; N, 15·38%). The hydriodide, colorless prisms, m.p. 206–207°; ν_{max}^{Nujol} cm^{-1}: 1664 (C=C). (Found: C, 41·00; H, 5·40; N, 5·48. $C_9H_{14}NI$ requires: C, 41·08; H, 5·36; N, 5·32%).

1,6,9,9a-*Tetrahydro*-4H-*quinolizine* (XI). A colorless liquid, b.p. 120–125° (bath temp, 70 mm Hg). It solidified on standing, m.p. 39–40°; $\nu_{max}^{CCl_4}$ cm^{-1}: 1668, 3040 (C=C); pK'_a (in water), 9·31. (Found: C, 79·69; H, 9·52; N, 10·38. $C_9H_{13}N$ requires: C, 79·95; H, 9·69; N, 10·36%). The picrate, yellow needles, m.p. 193°. (Found: C, 49·47; H, 4·58; N, 15·32. $C_{15}H_{16}O_7N_4$ requires: C, 49·45; H, 4·43; N, 15·38%). The hydriodide, colorless plates, m.p. 183–184°; ν_{max}^{Nujol} cm^{-1}: 1665 (C=C). (Found: C, 40·73; H, 5·23; N, 5·37. $C_9H_{14}NI$ requires: C, 41·08; H, 5·36; N, 5·32%).

Catalytic hydrogenation of sodium borohydride reduction mixture of I *and the separated quinolizine derivatives* (VIII–XI)

The reduction mixture (217 mg) was hydrogenated over 50 mg of PtO_2 in a soln of 50 ml EtOH and 5 ml conc HCl. About 1·6 mol-equiv of H_2 was taken up. The mixture was filtered and the filtrate was concentrated to dryness *in vacuo*. The residue was dissolved in a small amount of water, made strongly basic with excess K_2CO_3, and extracted with ether. The organic layer was dried over K_2CO_3, the solvent was removed, and the residue was distilled to give VII as a colorless liquid. The IR spectrum was identical with that of an authentic sample. The picrate of VII was prepared in ether and recrystallized from EtOH as yellow plates, m.p. 198–198·5°, which did not depress the m.p. of an authentic sample. Catalytic hydrogenations of VIII-XI were carried out in the same manner as above. The two monoenes (VIII and IX) took up one mole of H_2 and the two dienes (X and XI), two moles of H_2 to give VII.

Reduction of quinolizinium bromide (I) *with sodium borohydride in water*

To a cooled and stirred soln of 2·1 g (0·010 mole) of I in 25 ml H_2O was added 1·59 g (0·042 mole) $NaBH_4$. The mixture was stirred for 3 hr with cooling and then 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 extract was dried over K_2CO_3 and distilled, after removal of the solvent, to give 550 mg of a mixture of VII-XI, b.p. 100–140° (bath temp, 40 mm Hg). Gas chromatography showed that the mixture contained VII–XI in a ratio of 0·21 :1 :0·80 :0·56 :0·73. These products were identical with the samples obtained from the reduction in ethanol.

Reduction of quinolizinium bromide (I) *with sodium borohydride in ethanol-d*

Ethanol-d was prepared by the method of Shiner and Smith.[22] A soln of 4·2 g (0·02 mole) of I in 50 ml EtOH-d was added a soln of 1·0 g (0·026 mole) $NaBH_4$ in 50 ml EtOH-d. After the reduction mixture was stirred for 3 hr with cooling and for additional 20 hr at room temp, the usual work-up led to 1·41 g of a mixture of the deuterated analogues of VIII–XI in a ratio of 1 :2·0 :3·2 :16·0. The four deuterated products showed the same retention times as those of the normal amines (VIII–XI). The deuterated analogue of XI solidified. It melted at 39–40° and showed no mixed m.p. depression with XI. All the picrates of the deuterated amines did not depress the m.ps of the picrates of VIII–XI respectively. Main isotopic components of

* See footnote † on page 402

the deuterated analogues of VIII–XI are as follows: 3,6,7,8,9a-hexahydro-4*H*-quinolizine-3,7,9,9-d_4 and $-3,7,9$-d_3 (XXXII and XXXIV), $\nu_{max}^{CCl_4}$ cm^{-1}: 3030, 1650 (C═C), 2100–2200 (C–D); 1,6,7,8,9,9a-hexahydro-4*H*-quinolizine-1,7,9,9-d_4 and $-1,7,9$-d_3 (XXXIII and XXXV), $\nu_{max}^{CCl_4}$ cm^{-1}: 3030, 1667 (C═C), 2100–2200 (C–D); 3,6,9,9a-tetrahydro-4*H*-quinolizine-1,3,9-d_3 and $-3,9,9$-d_3 (XXI and XX), $\nu_{max}^{CCl_4}$ cm^{-1}: 3040, 1658 (C═C), 2250 (vinyl D), 2100–2200 (C–D); 1,6,9,9a-tetrahydro-4*H*-quinolizine-1,1,9-d_3 (XIX), $\nu_{max}^{CCl_4}$ cm^{-1}: 3040, 1668 (C═C), 2100–2200 (C–D).

Reduction of quinolizinium bromide (I) *with sodium borohydride in deuterium oxide*

A soln of 4·2 g of I in 50 ml D_2O was similarly reduced with 3·18 g $NaBH_4$ to give 1·24 g of a colorless oil, b.p. 110–135° (bath temp, 46 mm Hg). Gas chromatography showed that the reduction product was a 0·45 : 1 : 1·8 : 0·61 : 1·2 mixture of the deuterated analogues of VII–XI. The spectral data of these products were almost identical with those of the deuterated quinolizines from the reduction in EtOH-d.

Reduction of 4,6-d_2-*quinolizinium chloride* (XVIII) *with sodium borohydride in deuterium oxide*

To a soln of 3·5 g of I in 60 g D_2O was added 0·7 ml 40% NaOD soln and stirred for 24 hr at room temp. After the mixture was neutralized with ca. 20% DCl soln, the solvent was evaporated to dryness *in vacuo* and the residue was dried at about 100° *in vacuo*. The NMR spectrum of the resulting XVIII contaminated with NaCl and NaBr showed no broad doublet peaks due to the C-4 and C-6 protons of I. The NMR spectrum of I in D_2O showed the C-4 and C-6 proton doublet (J = 7·0 c/s) at 0·74 τ and the remaining 6-proton multiplet at 1·3–2·1 τ (internal standard, $(CH_3)_3SiCH_2CH_2CH_2SO_3Na$). To a cooled and stirred soln of the crude XVIII in 42 g of D_2O was added 2·65 g of $NaBH_4$. Treatment of the reduction mixture as described above gave 1·30 g of a colorless liquid, b.p. 100–140° (bath temp, 58 mm Hg). Preparative gas chromatography of the liquid afforded the deuterated analogues of VII–XI. In this experiment only XIX was characterized in order to confirm the reduction mechanism of I. The deuterated analogue of XI solidified on standing and melted at 39–40°. It showed no depression in mixed m.p. with XI. The mass spectrum showed the intense parent ion peak at *m/e* 140 indicating the predominant formation of XIX; $\nu_{max}^{CCl_4}$ cm^{-1}: 3040, 1665 (C═C), 2100–2200, 2025 (C–D); NMR ($CDCl_3$): τ 4·32 (4H, olefinic protons), 6·55–7·30 (3H, protons on carbons adjacent to nitrogen), 7·88 (1H, C-1 or C-9 H).

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REFERENCES

[1] Part IV: T. Miyadera and Y. Kishida, *Tetrahedron* **25**, 209 (1969).
[2] Part of this work has been reported in a preliminary communication: T. Miyadera and Y. Kishida, *Tetrahedron Letters* 905 (1965).
[3] T. Miyadera, E. Ohki and I. Iwai, *Chem. Pharm. Bull., Tokyo* **12**, 1344 (1964).
[4] [a] V. Boekelheide and J. P. Lodge, *J. Am. Chem. Soc.* **73**, 3681 (1951);
[b] V. Boekelheide and W. G. Gall, *Ibid.* **76**, 1832 (1954);
[c] A. Richards and T. S. Stevens, *J. Chem. Soc.* 3067 (1958);
[d] V. Prelog and K. Balenović, *Chem. Ber.* **74**, 1508 (1941).
[5] R. M. Acheson, *Advances in Heterocyclic Chemistry* (Edited by A. R. Katritzky) Vol. 1; p. 143. Academic Press, New York and London (1963).
[6] T. Miyadera, *Chem. Pharm. Bull., Tokyo* **13**, 503 (1965).
[7] R. M. Acheson and D. M. Goodall, *J. Chem. Soc.* 3225 (1964).
[8] M. Horiguchi, *Chem. Pharm. Bull., Tokyo* **15**. 1169 (1967).
[9] N. J. Leonard and V. W. Gash, *J. Am. Chem. Soc.* **76**, 2781 (1954).
[10] N. J. Leonard, A. S. Hay, R. W. Fulmer and V. W. Gash, *Ibid.* **77**, 439 (1955).
[11] N. J. Leonard and D. M. Locke, *Ibid.* **77**, 437 (1955).
[12] R. Adams and J. E. Mahan, *Ibid.* **64**, 2588 (1942).
[13] F. Bohlmann, *Chem. Ber.* **91**, 2157 (1958).
[14] C. D. Johnson, R. A. Y. Jones, A. R. Katritzky, C. R. Palmer, K. Schofield and R. J. Wells, *J. Chem. Soc.* 6797 (1965).
[15] J. N. Shoolery, *Disc. Faraday Soc.* No. 34, 104 (1962).