Tetrahedron Letters No.14, pp. 905-912, 1965. Pergamon Press Ltd.
Printed in Great Britain.

THE MECHANISMS OF THE REDUCTIONS OF QUINOLIZINIUM ION WITH LITHIUM ALUMINIUM HYDRIDE AND SODIUM BOROHYDRIDE*

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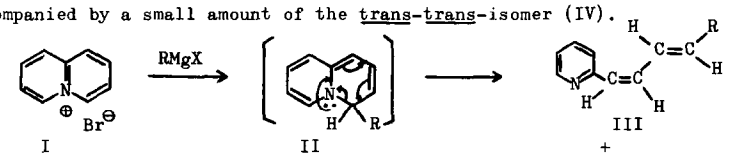
(Received 16 February 1965)

One of the present authors (1) has reported that quinolizinium bromide (I) was considerably reactive toward various Grignard reagents yielding ring opened products, 1-cis-3-trans-4-substituted-1-(2-pyridyl)-1,3-butadiene (III) accompanied by a small amount of the trans-trans-isomer (IV).



I II III + trans-trans isomer IV

R=CH_3, C_6H_5, $C_6H_5CH{=}CH$, $C_6H_5C{\equiv}C$

The probable mechanism for the formation of the butadiene (III) was assumed to involve 4-substituted-4H-quinolizine (II) as an intermediate which rearranges to the thermodynamically more stable aromatic compound as shown above.

The results in this comunication dealing with nucleophilic reductions of I with lithium aluminium hydride and sodium borohydride further support the presence of the reaction intermediate (II) reported earlier (1).

The reduction of I with lithium aluminium hydride in tetrahydrofuran produced 1-(2-pyridyl)-1,3-butadiene (VI) (3) probably of cis configuration,

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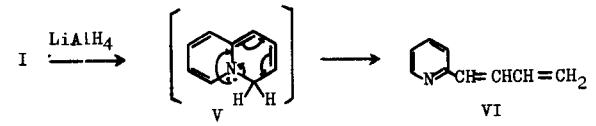
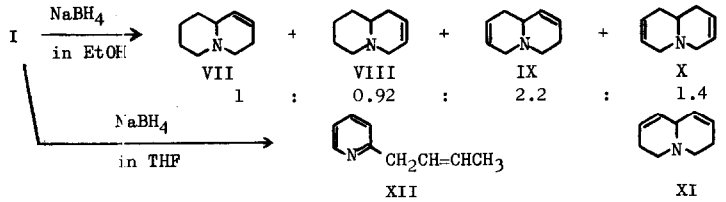
* This paper comprises a portion of the Dissertation submitted by T. Miyadera in partial fulfillment of the requirements for Ph.D. degree at Tohoku University.

picrate,** m.p. 152-152.5°.



The butadiene VI may result from rearrangement of 4H-quinolizine intermediate (V) which has not been synthesized successfully (2,3). In this case, however, the reduction product does not necessarily indicate the preferential attack at position 4 of I by the hydride ion, because there might exist isomerizations among three possible intermediates, 2H-, 4H- and 9aH-quinolizine in the medium (4).

On the other hand, the reduction of I with sodium borohydride in ethanol afforded a mixture of four unsaturated quinolizidines (VII-X) whose complete separation was achieved by gas chromatography using 20% polydiethyleneglycol succinate on Chromosorb-W (30-60 mesh).



On hydrogenation with PtO_2 in dilute hydrochloric acid, all four unsaturated amines gave the same quinolizidine, absorbing the corresponding mole-equivalents of hydrogen. The infrared spectra (5) showing no decided differences between double bond stretching regions of the free bases and the hydriodides, ultraviolet spectra (6) and pK'_a values (7,8) indicate that the unsaturated amines have no enamine double bond (TABLE 1). Consequently, all double bonds must be located either at positions 1, 2, 7 or 8 of the quinolizidine ring. These evidences limited the possibilities for the structures of the four amines isolated to five quinolizidine derivatives (VII-XI).

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

The NMR spectrum of VIII showed a symmetrical quartet (FIG. 1) at 4.33τ (J=10.5 cps) regarded as an intermediate between A_2 and AB type for the olefinic protons, while the olefinic protons of VII appeared as an asymmetrical multiplet (FIG. 2) centered at 4.45 τ ($J_{1,2}$=10.4 cps) showing the presence of non-equivalent olefinic protons. The other proton signals of the latter were complicated exhibiting a composite multiplet between 6.8 and 9.0 τ and the former showed a composite multiplet (FIG. 3) centered at 7.02τ assignable to C_4- protons and an equatorial C_6- proton (9)†. From the spectral evidence the structures of VII and VIII were assigned as 1- and 2-dehydroquinolizidine respectively and VII was identified as the picrate by comparison with an authentic specimen*** (7).

The structure of X was similarly determined from the NMR spectrum which exhibited a symmetrical olefinic proton signal centered at 4.25τ closely similar to VIII, a multiplet (half-band width 13 cps) at 7.88τ due to four allylic protons (C_1=H_2, C_9=H_2) and a multiplet (FIG. 4) centered at 6.70 τ due to five protons on carbons adjacent to the nitrogen.

On the other hand, the olefinic protons of the other diene IX appeared as additive peaks of 1- and 2-dehydroquinolizidine types centered at 4.38 (J=10.6 cps) and 4.27 τ respectively which excluded the remaining possible structure XI. The assignment was further supported by the appearance of a doublet (J=16.4 cps) (FIG. 5) near 6.70τ corresponding to a quasi equatorial C_4-proton of VIII and those at position 4, 6 of X. The other protons showed a complicated multiplet at 7.1 to 8.27τ.

The reduction may furnish 4H-quinolizine as a first intermediate (V), the enamine of which is protonated by protic solvent yielding an iminium ion

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*** The sample for comparison was kindly supplied by Prof. N.J. Leonard.

† The equatorial C_4- and C_6-protons of quinolizidine appear at 0.92 and ca. 0.74 ppm lower field (7.26τ, doublet, J 9.6 cps) than the axial protons at the same positions and C_{9a}-proton respectively.

TABLE 1

	Picrate m.p.(°C)	Hydriodide m.p.(°C)	pK'_a in water	IR (cm^{-1})		
				Free base (in CCl_4) $\nu_{C=C}$	Hydriodide (in Nujol) $\nu_{C=C}$	Free base Bohlmann bands
VII	182-3	214-5	10.55	1664(W)	1665(W)	2750(S) 2800(S)
VIII	197-8	216-7	10.62	1670(W)	1669(W)	2750(S) 2800(S)
IX	182-3	206-7	10.09	1665(W)	1664(W)	2740(S)
X	193	183-4	10.35	1668(W)	1665(W)	2740(S) 2780(S)

FIG. 1

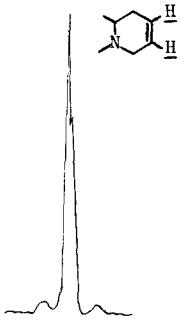


FIG. 2

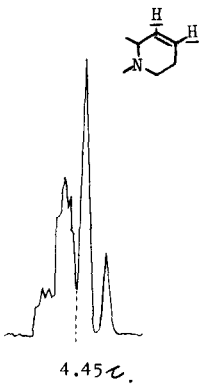


FIG. 3

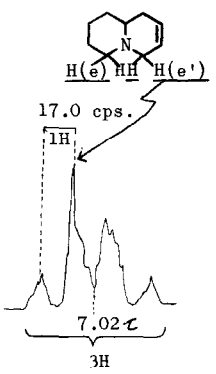


FIG. 4

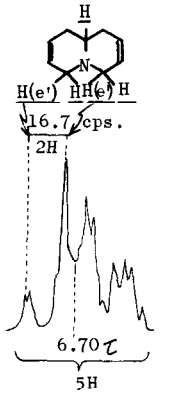
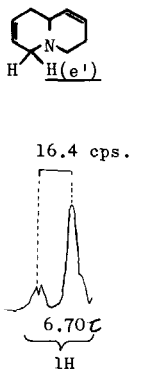
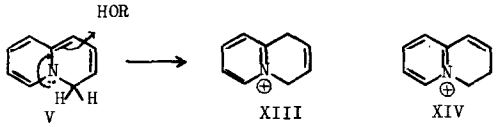


FIG. 5



and subsequently reduced. This mechanistic assumption can account for the fact that the ring opening reaction did not occur yielding instead quinolizidine derivatives in the protic solvent††. The first intermediate V possessing a polyenamine structure might be protonated either at the positions 1, 3, 7 or 9. Among them protonation is most favorable at position 1 or 3 to give aromatic iminium ions (XIII, XIV) (10) considering the facile transformation of an anhydropyridine to the pyridinium ion (11), then the protonated intermediates are further reduced by hydride ion.



V XIII XIV

In a similar reduction of quaternary pyridinium salts using deuterium oxide, Lyle, et al. (12,13) have demonstrated that the dienamine intermediate derived from the initial hydride reduction is deuterated kinetically at the β-position of the dienamine system to non-conjugated iminium ion which is in no equilibrium with the dienamine.

The hydride reduction of bicyclic pyridinium bromide (XXIV) in deuterium oxide gave a similar result yielding monodeutero-1- and 2-dehydroquinolizidine in high yields which were confirmed on the basis of mass spectral analyses. These evidences first predicted the incorporation of two and three deuterium atoms into the dienes (IX, X) and monoenes (VII, VIII) respectively on the reduction of I with sodium borohydride in deuterium oxide.

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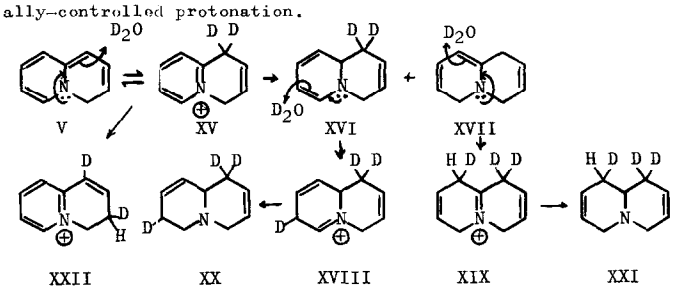
†† By contrast, the reduction of I with sodium borohydride in tetrahydrofuran (THF) afforded a pyridine derivative (XII) in poor yield giving no quinolizidine derivatives. The structure for XII was determined by catalytic hydrogenation of XII to 2-butylpyridine and spectral data exhibiting the presence of an isolated double bond, 2-pyridyl and a methyl group on the double bond (UV λ_{max}^{EtOH} mμ(ε): 258(3660), 264(4250), 270(3100). IR ν_{max}^{liq}: 1655cm^{-1} (C=C). NMR: τ pyridine protons 1.65 (1H), 2.40-3.25(3H), olefinic protons 4.48(2H), methylene protons 6.53 (2H), methyl protons 8.31(3H, doublet J=5.0 cps)). The mechanism for the formation of XII is not clearly demonstrated, but this is not inconsistent with the above assumption for the retention of the original ring on the reduction of I in the protic solvent.

On the contrary, the diene XXI derived from the reduction was proved to contain three deuterium atoms on the basis of mass spectrum indicating the intense parent peak at 138 m/e. The NMR spectrum of the amine showed peaks due to four olefinic protons and five protons on carbons adjacent to nitrogen, but a rather broad peak at 7.91τ due to only one allylic proton on carbon non-adjacent to nitrogen. This observation can be interpreted on the assumption of a rapid equilibration (11) between 4H-quinolizine V of an anhydropyridine type and the protonated iminium ion (XIII). Thus two deuterium atoms are incorporated into V yielding XV, followed by nucleophilic reduction to XVII. The conjugated dienamine XVII must be reduced to XXI after kinetically-controlled protonation.



The formation of another diene XX is similarly possible from XV, but some isotopic isomer of the diene may be produced through another route. According to Ingold's rule, in strong acids or equilibrating conditions protonation would occur at the terminal position 3 of V to give the product of thermodynamic control††† (12). Consequently, at least the terminal protonation might occur to some extent giving conjugated iminium ion (XXII), competing with the hydride reduction of XV. The formation of a small amount of the isotopic isomer of XX (presumably through XXII) is supported by the infrared spectrum of the asymmetrical diene showing a very weak absorption band

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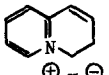
††† Tetramethyl 4H-quinolizine-1,2,3,4-tetracarboxylate is converted into the corresponding thermodynamically stable ion by treatment with perchloric acid (10).

at 2250 cm^{-1} due to olefinic deuterium, as compared with relatively strong and broad band near 2140 cm^{-1} due to saturated C-D stretching (14).

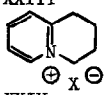
The mechanism for the formation of the monoenes (VII, VIII) from I is not obvious, but a reduction sequence, XXIII→XXIV→VII + VIII ($X=OC_2H_5$) is plausible. That the iminium ion intermediate (XIV) can yield two monoenes (VII, VIII) was demonstrated by the following reduction of XXIII (X=Br).



XXIII

$NaBH_4$ in EtOH → VII + VIII + IX

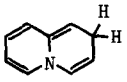
1 : 0.82 : 2.7



XXIV

$NaBH_4$ in EtOH → VII + VIII

1 : 0.90



XXV

Another plausible intermediate for the formation of the monoenes is 2H-quinolizine (XXV), because the borohydride ion possibly reacts at the position 2 of I.

All reductions of I, XXIII and XXIV (X=Br) with sodium borohydride in water yielded a small amount of quinolizidine in contrast with those in ethanol.

The mechanisms for the formations of the quinolizidine, two monoenes and asymmetrical diene (IX) from I will be described in the forthcoming paper on the basis of isotopic and mass spectral studies.

Acknowledgements — The authors wish to acknowledge gratefully helpful discussions of Professors T. Nozoe, Y. Kitahara and K. Nakanishi of Tohoku University, Dr. S. Okuda of the University of Tokyo and Dr. I. Iwai of this laboratory. We are indebted to Naka Factory of Hitachi Ltd. and Dr. M. Funamizu for the mass spectra. Thanks are given to Mr. M. Horiguchi for gas chromatographic studies.

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