Unsaturated Amines. XI. The Course of Formic Acid Reduction of Enamines[1]

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The course of the reduction of a model enamine, $\Delta^{1(10)}$-dehydroquinolizidine, with formic acid has been studied by means of deuterium-labeled formic acid (DCOOH, HCOOD, DCOOD). It has been established that the proton of formic acid becomes attached to the β-carbon of the enamine grouping and that this step in the reduction process is reversible. A ternary iminium formate receives favorable consideration as the intermediate. The hydride of the formate ion becomes attached to the α-carbon of the original enamine grouping. The relative rates of mercuric acetate oxidation of quinolizidine and of quinolizidine-10-d indicate the operation of a deuterium isotope effect in this process.
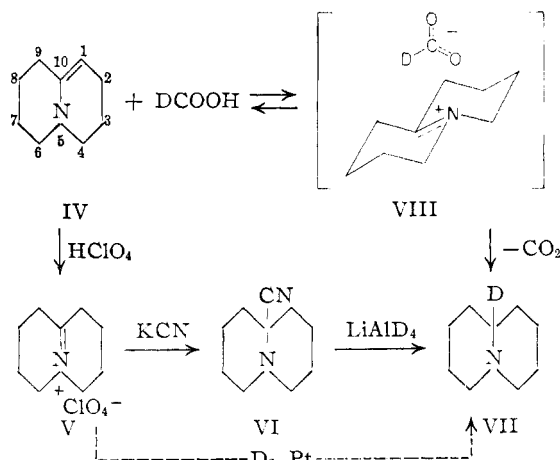
A saturated tertiary amine III is produced by the formic acid reduction of an α,β-unsaturated tertiary amine (enamine) I,[4-6] when C_β-protonation (II) is not sterically prevented.[7]
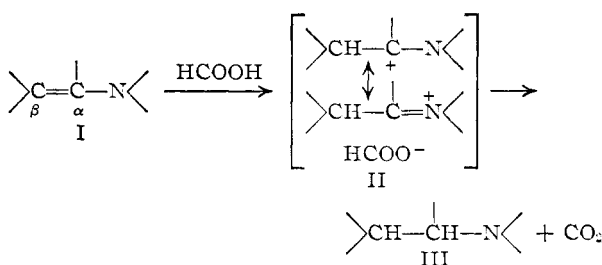
The process is related to the Leuckart reaction[4] and probably constitutes stages in the Leuckart synthesis of saturated tertiary amines.[8-12] The stereochemical course of enamine reduction by formic acid (e.g., (−)-Δ^5-dehydrosparteine → (−)-sparteine; (−)-$\Delta^{6,11}$-didehydrosparteine → (−)-α-isosparteine)[6] and of the Leuckart reaction (e.g. 2-methylcyclohexanone → 2-methylcyclohexylamine (cis > trans))[13] is the same, corresponding to addition of hydrogen from the relatively less hindered side of the ternary iminium grouping (II). One major problem to solve in terms of the mechanism of the formic acid reduction was considered to be the establishment of the origin (with respect to formic acid) of the hydrogen atoms which enter the unsaturated amine. The solution to the problem has been found in the reduction of a model enamine with deuterium-labeled formic acid.

The model enamine, $\Delta^{1(10)}$-dehydroquinolizidine (IV),[14] was reduced with formic-d acid and formic

(1) For previous paper in this series, see N. J. Leonard and F. P. Hauck, Jr., THIS JOURNAL, 79, 5279 (1957).

(2) National Science Foundation Fellow, 1954–1955.

(3) Standard Oil Foundation Inc. (Indiana) Fellow, 1955–1956.

(4) P. L. de Benneville and J. H. Macartney, THIS JOURNAL, 72, 3073 (1950).

(5) P. L. de Benneville, U. S. Patent 2,578,787 (1951).

(6) N. J. Leonard, P. D. Thomas and V. W. Gash, THIS JOURNAL, 77, 1552 (1955).

(7) N. J. Leonard and W. D. Smart, unpublished results.

(8) P. A. S. Smith and A. J. Macdonald, THIS JOURNAL, 72, 1037 (1950).

(9) J. F. Bunnett and J. L. Marks, ibid., 71, 1587 (1949).

(10) W. Speer, German Patent 620,510 (1935) (C. A., 30, 732 (1936)).

(11) W. Speer, German Patent 618,032 (1935) (C. A., 30, 107 (1936)).

(12) I. G. Farbenind. A.-G., French Patent 776,613 (1935) (C. A., 29, 3687 (1935)).

(13) D. S. Noyce and F. W. Bachelor, THIS JOURNAL, 74, 4577 (1952).

(14) N. J. Leonard, A. S. Hay, R. W. Fulmer and V. W. Gash, ibid., 77, 439 (1955).

acid-d, and the individual products were found to be different with respect to the positions occupied by deuterium. The identity of the product obtained in the reduction of $\Delta^{1(10)}$-dehydroquinolizi-

dine with formic-d acid was established as follows. The enamine IV was converted to the salt, $\Delta^{5(10)}$-dehydroquinolizidinium perchlorate (V),[14] from which was obtained, by treatment with potassium cyanide, 10-cyanoquinolizidine (VI). Replacement of the nitrile grouping[1,15] with deuterium was effected with lithium aluminum deuteride. A similar sequence of reactions, terminating with lithium aluminum hydride, had been carried out previously in this Laboratory.[15] The sequence terminating with deuteride can be regarded as an unequivocal synthesis of quinolizidine-10-d (VII). Analysis of this product and its methiodide indicate the presence of one deuterium atom in the molecule. The infrared spectrum of VII showed characteristic maxima in the 5 μ region—specifically, five distinct bands at 2090, 2073, 2013, 1980 and 1948 cm.$^{-1}$, with a shoulder at ca. 1997 cm.$^{-1}$.[16] A check was provided as to the location of the deuterium by its complete removal in the conversion of VII to $\Delta^{1(10)}$-dehydroquinolizidine by mercuric acetate oxidation.[14] The product of deuteration of V in glacial acetic acid-d using platinum oxide had an infrared spectrum very similar to that of the quinolizidine-10-d from VI. However, evidence of exchange elsewhere in the rings during catalytic deuteration was provided by the finding that not all of the deu-

(15) N. J. Leonard and A. S. Hay, ibid., 78, 1984 (1956).

(16) A theoretical treatment of the infrared spectra of quinolizidine-10-d will be published by Dr. Harold Boaz, Eli Lilly and Co., Indianapolis, Ind. Quinolizidine-10-d exhibits these maxima in the 3–4 μ region: 2930, 2850, 2780, 2735, 2660 and 2600 cm.$^{-1}$.

terium was removed (infrared) by mercuric acetate oxidation. The reduction of $\Delta^{1(10)}$-dehydroquin-olizidine (IV) by excess formic-d acid produced a mono-deuterioquinolizidine which was proved to be quinolizidine-10-d by its infrared spectral identity with the authentic sample (from V → VI → VII).

The unique location of a single deuterium in the formic-d acid product (IV → VIII → VII) indicated that the hydrogen atoms of formic acid are not equivalent in this reduction–oxidation process.[17] An intermediate such as IX is thus rendered unlikely since it would be able to acquire either H$^+$ or D$^+$ from the medium.

$$\text{VIII} \longrightarrow \left[\overset{\overset{\displaystyle \backslash \dot{C} /}{|}}{\underset{/ \overset{..}{N} \backslash}{}} \right]^- + \text{D}^+ + \text{CO}_2$$

$$\text{IX}$$
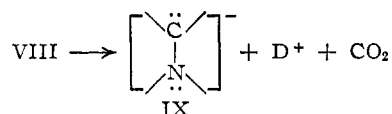
By contrast with the second step in the reduction of IV (VIII → VII), the first step, or protonation (IV → VIII), is reversible. Even at the outset, this was regarded as a logical assumption since it is equivalent to stating that the enamine and formic acid are in equilibrium with the salt. The reversibility of protonation was indicated experimentally by the reduction of $\Delta^{1(10)}$-dehydroquinolizidine with formic acid-d (about two mole equivalents); the deuterioquinolizidine produced contained more than one atom of deuterium per molecule. The infrared spectrum indicated the incorporation of deu-

terium at positions other than C-10 (maxima at 2190, 2162 and 2115 cm.$^{-1}$), and analysis of this deuterioquinolizidine and its methiodide showed that about two deuterium atoms were present per molecule (X). The results were duplicated in other runs and were checked additionally by the reduction of $\Delta^{1(10)}$-dehydroquinolizidine with formic-d acid-d. The product of this reduction was a deuterioquinolizidine (infrared maxima at 2160, 2113, 2065 and 2010 cm.$^{-1}$) containing more than two deuterium atoms per molecule (XI). Reversibility of the salt-formation step would account for the incorporation of the additional deuterium in X and XI by exchange of hydrogen on C-1 and/or C-9 by deuterium.
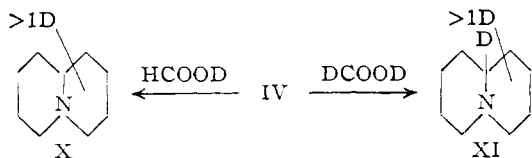
Further confirmation was found in a combination of $\Delta^{1(10)}$-dehydroquinolizidine with formic acid-d kept at 0° for 5 minutes, with no detectable gas evolution. The recovered enamine contained deuterium (about 0.25 D per molecule). Fractionally deuterated enamine also was recovered from a combination of $\Delta^{1(10)}$-dehydroquinolizidine with acetic acid-d kept at 0° for 10 minutes. The possibility of exchange at carbon atoms other than the β-carbon of the enamine system was eliminated by the reduction of 1,3-dimethyl-Δ^2-tetrahydropy-

ridine (XII) with excess formic acid-d. From an examination of the structure of this enamine and its likely formate-salt intermediate XIII, it is obvious that only one atom of deuterium can be introduced at the β-carbon, since this carbon bears no exchangeable proton. The product, a deuterio-1,3-dimethylpiperidine (XIV), did *not* contain more than one atom of deuterium per molecule.
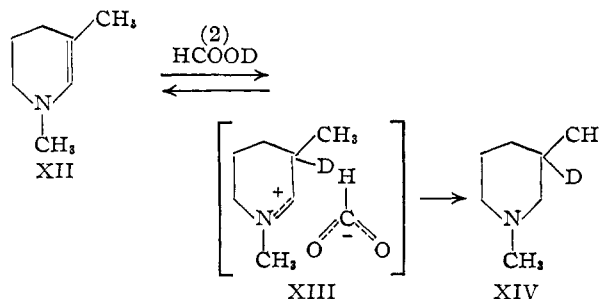
Since it is now safe to assume that hydrogen (deuterium) exchange occurs only at C-1 and C-9 in the bicyclic model, it is possible to calculate the distribution to be expected on the basis of a random exchange in the reaction between $\Delta^{1(10)}$-dehydroquinolizidine and formic acid-d (see experimental quantities). More deuterium actually was found in the saturated amine isolated than one would predict on the basis of a statistical distribution prior to the second step of the reduction. This finding suggests the operation of a deuterium isotope effect (preferential cleavage of C–H over C–D, but negligible difference in the availability of H$^+$ or D$^+$).[18] Due to the relatively rapid rate of the second step in the reduction process, the non-homogeneity of the reduction mixture and product isolation problems, it is possible only to suggest a minimum value, 1.5 for the isotope effect.[19]

If the ternary iminium formate (VIII, H for D), postulated here in the reduction of enamines with formic acid and elsewhere in the Leuckart sequence,[8,13,20,21] is a logical intermediate, it should be possible to reduce the preformed cation with formate anion.[22] Indeed, quinolizidine (VII, H for D) was obtained in 73% yield when a solution of equimolar quantities of $\Delta^{5(10)}$-dehydroquinolizidinium perchlorate (V) and potassium formate in absolute ethanol was stirred for 10 hr. at 25°. The reduction of V was not efficient, however, with formic acid in large excess or with potassium formate in excess formic acid, acetic acid or water, possibly due to the high degree of solvation of the formate ion in these solvents. A large excess of formic acid slows down the rate of reduction of $\Delta^{1(10)}$-dehydroquinolizidine. Whether the incorporation of hydride in the formic acid reduction proceeds by displacement of hydrogen from a formate ion or from formate within an ion pair[13] or through

(17) Cf. the oxidation of formate ion by permanganate (K. B. Wiberg and R. Stewart, THIS JOURNAL, **78**, 1214 (1956)) and the decomposition of a formate ester of chromic acid (H. D. Zeiss and D. A. Pease, Jr., *ibid.*, **78**, 3182 (1956)).

(18) K. Wiberg, *Chem. Revs.*, **55**, 713 (1955).

(19) R. R. Sauers, Ph.D. Thesis, University of Illinois, 1956; also see Experimental section.

(20) J. Hine, "Physical Organic Chemistry," McGraw–Hill Book Co., Inc., New York, N. Y., 1956, p. 265.

(21) E. R. Alexander and R. B. Wildman, THIS JOURNAL, **70**, 1187 (1948).

(22) Cf. R. Lukeš and M. Ferles, *Coll. Czech. Chem. Commun.*, **22**, 121 (1957), and other papers in this series.

a formate ester[8] cannot be decided on the basis of the present information.[22a]

The quinolizidine-10-d made available by this study made it possible to test the proposed mechanism[14] for the mercuric acetate oxidation of tertiary amines. The four-center elimination of HgOAc$^-$ [23] from the N-mercurated complex (e.g., of quinolizidine) with concomitant proton abstraction from C-10 to form the C=N+ double bond (V, OAc$^-$ for ClO$_4$$^-$)[24,25] implies that the C$_{10}$–H bond is being broken in the rate-limiting step. It has now been found that quinolizidine reacts faster than quinolizidine-10-d with mercuric acetate under identical conditions by a factor of approximately 2.3. The figure, which is regarded as a minimum, was arrived at by weighing the mercurous acetate precipitated and by spectral determination of the amount of enamine formed after a given time interval. It is significant that the quinolizidine-10-d recovered after partial oxidation to $\Delta^{1(10)}$-dehydroquinolizidine was of unchanged deuterium content.

Also synthesized in the course of this study were the diastereoisomeric racemates of 1-hydroxyquinolizidine, by separate reductions of 1-ketoquinolizidine with lithium aluminum hydride and with hydrogen and platinum.

Experimental[26]

Preparations of Deuterated Formic Acid. Formic Acid-d.[27]—Commercial 98–100% formic acid was exchanged twice with a 10-fold excess of 99% deuterium oxide. Formic acid-d was isolated from the aqueous phase by saturating with anhydrous copper sulfate and extracting six times with anhydrous ether. The extracts were dried over copper sulfate and distilled, b.p. 37–39° (47 mm.), n^{20}D 1.3646.

Formic-d Acid-d.[27,28]—Anhydrous oxalic acid (10 g., 0.11 mole) was crystallized three times from 9 ml. of deuterium oxide. After each crystallization it was purified by sublimation at ca. 1 mm. Pyrolysis was effected by subliming the acid at ca. 1 mm. into a 10-inch column packed with glass helices and heated to 220°. The formic-d acid-d was collected in a Dry Ice trap. The yield from 8.8 g. (0.096 mole) of oxalic acid-d_2 was 2.2 g. (48%), b.p. 44–44.5° (58 mm.), n^{20}D 1.3692.

Formic-d Acid.[27,28]—Formic-d acid-d was exchanged with distilled water and isolated in the manner indicated for formic acid-d, b.p. 63° (145 mm.), n^{20}D 1.3674.

Reductions of $\Delta^{1(10)}$-Dehydroquinolizidine. With Formic Acid.[4,5]—Rapid addition of 0.80 ml. (0.018 mole) of commercial anhydrous formic acid to 2.3 g. (0.017 mole) of $\Delta^{1(10)}$-dehydroquinolizidine (IV)[14] was accompanied by vigorous evolution of carbon dioxide. The reaction mixture was heated at 60° for 1 hr. Basification followed by ether

extraction and distillation yielded 1.36 g. (58%) of quinolizidine,[29] b.p. 76.5° (20 mm.), n^{20}D 1.4794.

With Formic Acid-d.—To 1.81 g. (0.0132 mole) of cooled $\Delta^{1(10)}$-dehydroquinolizidine was added 1.13 g. (0.0241 mole) of formic acid-d, and the mixture was heated for 2 hr. at 60°. The sequence of cooling, basification, extraction with ether and distillation yielded 1.40 g. (76%) of colorless oil, b.p. 72–73° (17 mm.), n^{20}D 1.4783. The oil was dissolved in 25 ml. of ether containing two drops of ethanol. Portionwise addition of 65% perchloric acid effected separation into two main perchlorate fractions: (1) m.p. 188–196° (0.03 g.), (2) m.p. 149–151° (1.83 g.). Melting points reported for $\Delta^{5(10)}$-dehydroquinolizidinium perchlorate and quinolizidine perchlorate are 234–235° and 149–150°, respectively.[14] Crystallization of fraction 2 from ethyl acetate followed by basification and ether extraction yielded a deuterioquinolizidine, b.p. 71.5° (17 mm.). Characteristic bands were found in the infrared spectrum of a liquid film at 2190(sh), 2162(m) and 2115(w) cm.$^{-1}$.

Anal. Calcd. for C$_9$H$_{16}$DN: atom % D, 5.88; for C$_9$H$_{15}$D$_2$N: atom % D, 11.76. Found: atom % D, 11.90.

The methiodide was prepared in ether and crystallized from acetone, m.p. 322° dec. (immersed at 310°) (reported[30] 329–330° dec.).

Anal. Calcd. for C$_{10}$H$_{19}$DIN: atom % D, 5.00; for C$_{10}$H$_{18}$D$_2$IN: atom % D, 10.00. Found: atom % D, 10.22.

The total number of protons available for exchange from the enamine is 3 × 0.0132 or 0.0396. The number of deuterons available is equal to the number of moles of formic acid-d, i.e., 0.024. The fraction of deuterium in the total amount of exchangeable particles is then 0.024/(0.024 + 0.0396) or 0.38. Since this same fraction also represents the fraction of deuterium in the reduced product, there would be 4 × 0.38 or 1.5 atoms of deuterium per molecule in the reduced product. The deuterium content actually found was about 2.0 atoms per molecule, indicative of an isotope effect (preferential cleavage of C–H over C–D once the deuterium was incorporated).

With Formic-d Acid-d.—To the ice-cold $\Delta^{1(10)}$-dehydroquinolizidine prepared from 4.0 g. (0.0167 mole) of $\Delta^{5(10)}$-dehydroquinolizidinium perchlorate was added rapidly 0.80 ml. (0.017 mole) of formic-d acid-d. The mixture was warmed slowly to room temperature and then heated at 67° for 1.5 hr. The crude colorless oil first isolated weighed 1.52 g. (65%), b.p. 77–78.5° (21 mm.), n^{20}D 1.4857. Fractional crystallization of the perchlorates yielded 1.4 g. of low-melting salt. Basification furnished a deuterioquinolizidine boiling at 74–74.5° (10 mm.). The infrared spectrum showed characteristic maxima at 2160(m), 2113(w), 2065(w) and 2010(m) cm.$^{-1}$. The spectrum also suggested the presence of a trace of enamine.

Anal. Calcd. for C$_9$H$_{15}$D$_2$N: atom % D, 11.76; for C$_9$H$_{14}$D$_3$N: atom % D, 17.64. Found: atom % D, 14.35.

With Formic-d Acid.—Ice-cold $\Delta^{1(10)}$-dehydroquinolizidine prepared from 4.0 g. (0.0167 mole) of the perchlorate salt was treated rapidly with 1.0 g. (0.021 mole) of formic-d acid. The rest of the procedure followed that described above. The crude yield was 1.53 g. (65%), b.p. 73–75.5° (18 mm.), and a pure deuterioquinolizidine was obtained from the low-melting perchlorate fraction, b.p. 75–76° (19 mm.), n^{20}D 1.4801; characteristic infrared maxima at 2090(w), 2073(w), 2013(s), 1997(sh), 1980(w) and 1948(w) cm.$^{-1}$.

Anal. Calcd. for C$_9$H$_{16}$DN: atom % D, 5.88. Found: atom % D, 6.3.

Reduction of 10-Cyanoquinolizidine with Lithium Aluminum Deuteride. Quinolizidine-10-d.—To a slurry of 1.025 g. (0.0244 mole) of lithium aluminum deuteride in 200 ml. of anhydrous ether was added 4.0 g. (0.0244 mole) of 10-cyanoquinolizidine (VI). The mixture was stirred at reflux temperature for 2 days, then decomposed with 120 ml. of 40% sodium hydroxide solution. The ether layer was separated, and the aqueous phase was extracted with five 100-ml. portions of ether. The combined extracts were dried and distilled, yielding 2.9 g. (85%) of quinolizidine-10-d (VII), b.p. 76–77° (21 mm.), n^{20}D 1.4759.

(22a) ADDED IN PROOF.—R. Stewart, *Can. J. Chem.*, **35**, 766 (1957), has reported a kinetic and isotopic study of the related reduction of triphenylmethylcarbinol with formic acid.

(23) Effectively transient Hg⁰. Mercury has been shown to react rapidly with the excess mercuric acetate under these reaction conditions to give insoluble mercurous acetate.

(24) F. L. Weisenborn and P. A. Diassi, THIS JOURNAL, **78**, 2022 (1956).

(25) See also N. J. Leonard, W. J. Middleton, P. D. Thomas and D. Choudhury, *J. Org. Chem.*, **21**, 344 (1956).

(26) All melting points are corrected. Microanalyses were performed by Mr. Jozsef Nemeth and his associates. Special thanks are due Mr. Nemeth for the deuterium analyses, by the falling drop method. We wish to thank Mrs. Louise Griffing and Mr. James Brader for determination of the infrared absorption spectra, using a Perkin–Elmer automatic recording infrared spectrometer, model 21.

(27) D. W. G. Style and J. C. Ward, *J. Chem. Soc.*, 2125 (1952).

(28) R. C. Herman and V. Williams, *J. Chem. Phys.*, **8**, 447 (1940).

(29) V. Boekelheide and S. Rothchild, THIS JOURNAL, **69**, 3149 (1947).

(30) N. J. Leonard and W. C. Wildman, *ibid.*, **71**, 3100 (1949).

Anal. Calcd. for $C_9H_{16}DN$: atom % D, 5.88. Found: atom % D, 5.9.

The infrared spectrum of the pure liquid was identical with the spectrum of the deuterioquinolizidine prepared from reduction of $\Delta^{1(10)}$-dehydroquinolizidine with formic-*d* acid.

The methiodide was made in ether and recrystallized from methanol–ether, m.p. 325° dec. (immersed at 300°).

Anal. Calcd. for $C_{10}H_{19}DIN$: atom % D, 5.00. Found: atom % D, 4.87.

The picrate crystallized as plates from ethanol, m.p. 196–196.5°, in the range reported for quinolizidine picrate.[29,30]

Mercuric Acetate Oxidation of Quinolizidine-10-*d* (Deuteride Product).—Quinolizidine was dehydrogenated with mercuric acetate in the usual manner.[14] The infrared spectrum of the product was identical in every detail with the spectrum of authentic $\Delta^{1(10)}$-dehydroquinolizidine.

Reduction of $\Delta^{5(10)}$-Dehydroquinolizidinium Perchlorate with Deuterium and Platinum Oxide.—$\Delta^{1(10)}$-Dehydroquinolizidinium perchlorate (V) (2.38 g., 0.010 mole) in 12 ml. of glacial acetic acid-*d* was treated with deuterium in the presence of platinum oxide. Addition of 100 ml. of anhydrous ether caused the precipitation of 2.36 g. (98%) of colorless powder, m.p. 150–152°. One recrystallization from ethyl acetate gave material melting at 152–153°. An aqueous solution of the salt was basified, and the amine was isolated by extraction and distillation, b.p. 68–69° (17 mm.), yield 1.0 g. (71%). The infrared spectrum of a liquid film was very similar to that of the quinolizidine-10-*d* obtained from 10-cyanoquinolizidine. However, not all of the deuterium was removed from the catalytic product by mercuric acetate oxidation, as indicated by the weak infrared absorption in the 5 μ region for the product, which otherwise resembled $\Delta^{1(10)}$-dehydroquinolizidine.

Comparative Reactions of $\Delta^{5(10)}$-Dehydroquinolizidinium Perchlorate. With Formic Acid.—A solution of 0.5 g. (2.1 mmoles) of $\Delta^{5(10)}$-dehydroquinolizidinium perchlorate in 4 ml. (100 mmoles) of anhydrous formic acid was heated under nitrogen at reflux for 24 hr. The cooled solution was poured into 100 ml. of anhydrous ether. The precipitate weighed 0.50 g. (100%), m.p. nearly identical with starting material. **With Potassium Formate in Formic Acid.**—A slurry of 2.1 mmoles of $\Delta^{5(10)}$-dehydroquinolizidinium perchlorate, 2.1 mmoles of potassium formate (or sodium formate) and 80 mmoles of formic acid was heated at 68–69° for 2 hr. Basification, ether extraction and perchlorate formation led to the recovery of at least 70% of the starting material. **With Potassium Formate in Ethanol.**—A slurry of 5.0 mmoles of $\Delta^{5(10)}$-dehydroquinolizidinium perchlorate and 5.0 mmoles of potassium formate in 30 ml. of absolute ethanol was stirred for 10 hr. at 25°. Quinolizidine was the major product (73% yield), b.p. 81–81.5° (24 mm.), $n^{20}D$ 1.4807, identified as the perchlorate, m.p. 156–158.5°. **With Potassium Formate in Glacial Acetic Acid or in Water.**—Conditions nearly identical to the above, but with 5 ml. of glacial acetic acid or with 5 ml. of water as the solvent, by contrast, led to recovery of the major amount of the starting material, isolated as $\Delta^{1(10)}$-dehydroquinolizidine, b.p. 91.5–92.5° (22 mm.), $n^{22}D$ 1.5125, and also identified by infrared spectrum and a derivative.

Comparative Reactions of $\Delta^{1(10)}$-Dehydroquinolizidine With Potassium Perchlorate and Formic Acid.—A slurry of 0.855 g. (1.0 mmole) of potassium perchlorate in 8.8 ml. (230 mmoles) of 98–100% formic acid was added slowly to 0.846 g. (6.2 mmoles) of ice-cold $\Delta^{1(10)}$-dehydroquinolizidine and stirred at 0° for 1 hr., then at 67–68° for 2 hr. No gas evolution was observed. Basification with 35 ml. of 30% aqueous sodium hydroxide was followed by ether extraction. The perchlorate salt was made directly, m.p. 226.5–228°, in amount (1.24 g.) corresponding to 85% recovery of starting material. **With a Large Excess of Formic Acid.**—A mixture of $\Delta^{1(10)}$-dehydroquinolizidine and formic acid in 1:10 molar ratio was stirred and maintained at 0° for 1 hr., 30° for 1 hr. and 61° for 18 hr. The colorless oil which was isolated (87% weight yield), b.p. 81–90° (21 mm.), $n^{25}D$ 1.4990, was converted by fractional acidification of the base in ether with a solution of perchloric acid in ether–ethanol to a mixture of quinolizidine perchlorate and $\Delta^{5(10)}$-dehydroquinolizidinium perchlorate, with the latter as major component.

Incorporation of Deuterium in $\Delta^{1(10)}$-Dehydroquinolizidine. With Formic Acid at 0°.—To 0.419 g. (3.1 mmoles) of $\Delta^{1(10)}$-dehydroquinolizidine at 0° was added rapidly 0.286 g. (6.1 mmoles) of ice-cold formic acid-*d*. The mixture was allowed to stand for 5 minutes at 0°. No gas evolution was observed. Rapid basification was followed by ether extraction. The dried extracts were distilled, b.p. 87.5–88° (25 mm.), recovery 0.30 g. (72%).

Anal. Calcd. for $C_9H_{14}DN$: atom % D, 6.67. Found: atom % D, 1.67.

The infrared spectrum of the liquid was similar to that of pure $\Delta^{1(10)}$-dehydroquinolizidine except for several weak bands in the 5 μ region.

With Acetic Acid-*d* at 0°.—Acetic acid-*d* was prepared by mixing 1.05 g. (1.0 mmole) of pure acetic anhydride with 0.20 g. (1.0 mmole) of deuterium oxide. The mixture was allowed to stand overnight, then was frozen in an ice-bath and treated with 1.37 g. (1.0 mmole) of $\Delta^{1(10)}$-dehydroquinolizidine. The mixture was kept at 0° for 10 minutes and then basified and extracted with ether. The recovered base weighed 0.70 g. (51%), b.p. 87.5° (20 mm.). The infrared spectrum indicated the presence of deuterium in the $\Delta^{1(10)}$-dehydroquinolizidine, as in the quenched product from formic acid at 0°.

Complex of Quinolizidine and Formic Acid.—A mixture of 1.172 g. (8.4 mmoles) of quinolizidine and 0.771 g. (17 mmoles) of formic acid was allowed to stand for 6 hr. at 25°. The mixture was distilled, and the portion boiling at 110–111° (19 mm.) was redistilled at 113° (19 mm.) as a colorless oil, $n^{20}D$ 1.4653. The constant-boiling material was analyzed.[4] The infrared spectrum of a liquid film showed broad absorption in the region of 1715 and 1950 cm.$^{-1}$.

Anal. Calcd. for $C_9H_{17}N \cdot 2HCOOH$: C, 57.12; H, 9.15; N, 6.06. Found: C, 53.67; H, 9.06; N, 5.61.

Preparation of 1,3-Dimethyl-Δ^2-tetrahydropyridine (XII). —1,3-Dimethyl-2-piperidone[1] was reduced by the method of Lukeš and Kovář.[31] A refluxing solution of 12.7 g. (0.1 mole) of 1,3-dimethyl-2-piperidone in 125 ml. of reagent butanol was treated rapidly with 11.5 g. (0.5 g. atom) of sodium. After the initial reaction had subsided and the alcoholate had begun to precipitate, 50 ml. of butanol was added. Refluxing was continued for 1.75 hr., corresponding to complete solution of the sodium. The solution was steam distilled. The acidified (HCl) distillate was evaporated to dryness, and the oily hydrochloride salt was basified. Extraction with ether followed by distillation of the dried extracts gave the following fractions: fore-run, 1.2 g.; A, 125–137° (fast temperature rise), $n^{25}D$ 1.4634, 1.10 g. (10%); B, 137–138°, $n^{25}D$ 1.4670, 3.90 g. (35%); C, ca. 138°, $n^{25}D$ 1.4638, 0.88 g. (8%). Fraction B was redistilled at 137–138°, strong infrared maximum (liquid film) at 1673 cm.$^{-1}$.

Anal. Calcd. for $C_7H_{13}N$: C, 75.61; H, 11.79; N, 12.60. Found: C, 75.95; H, 11.70; N, 12.77.

The perchlorate was made in ether and recrystallized from ethanol as colorless needles, m.p. 74–75°. In Nujol, the infrared spectrum of the salt showed strong $>C=\overset{+}{N}<$ absorption at 1690 cm.$^{-1}$ and in addition a peak at 3090 cm.$^{-1}$.

Anal. Calcd. for $C_7H_{14}ClNO_4$: C, 39.73; H, 6.66. Found: C, 39.87; H, 6.62.

The picrate crystallized as orange-yellow needles from ethanol, m.p. 129–132°.

Anal. Calcd. for $C_{13}H_{16}N_4O_7$: C, 45.88; H, 4.74; N, 16.47. Found: C, 45.91; H, 4.67; N, 16.38.

Reduction of 1,3-Dimethyl-Δ^2-tetrahydropyridine. With Formic Acid.—To 0.693 g. (6.1 mmoles) of 1,3-dimethyl-Δ^2-tetrahydropyridine was added 0.565 g. (12.3 mmoles) of 98–100% formic acid. After evolution of carbon dioxide had subsided, the mixture was heated at 63° for 2 hr. The amine was liberated and converted to the picrate, which was recrystallized from ethanol; yield 1.15 g. (55%), m.p. 167.5–168.5° (reported for 1,3-dimethylpiperidine picrate, 165°,[32] 165–168°[33]), undepressed on admixture with an authentic sample.

(31) R. Lukeš and J. Kovář, *Coll. Czech. Chem. Commun.*, **19**, 1215 (1954).

(32) R. Lukeš and J. Pliml, *ibid.*, **15**, 463 (1950).

(33) W. A. Jacobs and L. C. Craig, *J. Biol. Chem.*, **120**, 447 (1937).

With Formic Acid-*d*.—The reduction was carried out on 1.05 g. (9.5 mmoles) of 1,3-dimethyl-Δ^2-tetrahydropyridine using 0.893 g. (19 mmoles) of formic acid-*d*. A colorless liquid, b.p. *ca.* 123°, was obtained, n^{24}D 1.4274, yield 0.393 g. (36%). The infrared spectrum of a liquid film indicated a slight amount of residual unsaturated material (weak absorption maximum at 1672 cm.$^{-1}$) and characteristic peaks at 2150(sh), 2132(m) and 2050(w) cm.$^{-1}$.

The **methiodide** was prepared in ether and recrystallized from ethanol, colorless needles, m.p. 199–200° (reported[32] for 1,3-dimethylpiperidine methiodide 196°).

Anal. Calcd. for $C_8H_{17}DIN$: atom % D, 5.56. Found: atom % D, 4.87.

Diastereoisomeric Racemates of 1-Hydroxyquinolizidine. A. Reduction of 1-Ketoquinolizidine with Lithium Aluminum Hydride.—The reduction of 1-ketoquinolizidine with lithium aluminum hydride[14] was repeated and the product purified by repeated distillation until a maximum melting point, 71–72°, for the solidified distillate was observed, higher than previously reported. The infrared spectrum in Nujol had a broad maximum centered at 3140 cm.$^{-1}$.

Anal. Calcd. for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.90; H, 11.24; N, 8.95.

The **picrate** crystallized as needles from ethanol, m.p. 174–176°.

B. Catalytic Reduction of 1-Ketoquinolizidine.—1-Ketoquinolizidine was hydrogenated at 2 atm. with platinum oxide in glacial acetic acid. The 1-hydroxyquinolizidine obtained initially boiled at 137–139° (24 mm.). It was purified by repeated distillation until a maximum melting point, 74–75°, for the solidified distillate was observed.

Anal. Calcd. for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.70; H, 10.89; N, 9.20.

The infrared spectrum in Nujol had a broad maximum centered at 3160 cm.$^{-1}$ and was different from that of the isomer A (above) in the fingerprint region.

The **picrate** crystallized as needles from ethanol, m.p. 177–178.5°.

Anal. Calcd. for $C_{15}H_{20}N_4O_8$: C, 46.88; H, 5.25; N, 14.58. Found: C, 46.81; H, 5.21; N, 14.57.

The melting point of the picrate B was depressed to 169–175° upon admixture with picrate A (above), which was further indication of the isomeric difference between the 1-hydroxyquinolizidines A and B.[34]

Relative Rates of Quinolizidine and Quinolizidine-10-*d* Oxidation by Mercuric Acetate.—The mercuric acetate oxidation was followed (1) by weighing the mercurous acetate precipitated and (2) by spectral determination of the amount of enamine formed. Quinolizidine, quinolizidine-10-*d* (*Anal.* Calcd. for $C_9H_{16}DN$: atom % D, 5.88. Found: atom % D, 5.78) and 10-methylquinolizidine[14] were employed as substrates. The last-mentioned compound

was used as a blank, to ensure that oxidation at positions other than C-10 was not rapid enough to interfere with the comparison of the oxidation rates of the first two compounds.

(1) Three 300-ml. flasks fitted with condensers were charged with the following materials: 90 ml. of 5% acetic acid, 17.9 g. (0.056 mole) of mercuric acetate and 0.014 mole of one of the three substrates. The flasks were immersed simultaneously in a bath at 82.5 ± 1.5° and were shaken uniformly. The flasks were quenched in an ice-bath after given intervals, and the precipitated mercurous acetate was collected on a filter, dried and weighed, with the following results (representative data):

Time, min.	Total wt. of mercurous acetate collected at each interval			Fraction of theoretical (7.28 g.) for 2e oxidation		
	10-H	10-D	10-CH₃	10-H	10-D	10-CH₃
20	1.8	0.8	0.05	0.25	0.11	..
50	3.2	2.1	.3	.44	.29	0.04
110	4.3	3.3	.6	.59	.45	.12

(2) A 200-ml. flask was charged with 90 ml. of 5% acetic acid and 2.00 g. (0.014 mole) of amine and heated to 80.5 ± 0.5°. Mercuric acetate (18.3 g., 0.574 mole) was added in one portion, and the mixture was stirred vigorously for 20 minutes. Quenching in an ice-bath was followed by the usual amine isolation procedure. For quinolizidine, the isolated bases weighed 1.467 g. (73% recovery), b.p. 79–91° (20 mm.). The optical density difference value for the infrared $>C=C<$ region for a solution of 92 mg. of sample in 1.0 ml. (1.6 g.) of carbon tetrachloride was 0.146. For quinolizidine-10-*d*, the isolated bases weighed 1.505 g. (75% recovery), b.p. 76–86° (20 mm.). For a solution of 135 mg. in 1.0 ml. of carbon tetrachloride, the optical density difference value was 0.095, with the same base line. Assuming Beer's law to hold in this range, the ratio of enamine from quinolizidine to enamine from quinolizidine-10-*d* becomes 2.3.

Recovery of Unexchanged Quinolizidine-10-*d* from Partial Oxidation.—The recovered mixture of bases from the mercuric acetate oxidation of quinolizidine-10-*d* (part 2 just preceding) was dissolved in ether and to it was added in small portions a solution of perchloric acid in ether-ethanol. The high-melting (*ca.* 213°) perchlorate weighed 0.22 g. and the low-melting (152°) perchlorate, 1.32 g. (86%). Basification of the latter, followed by ether extraction and distillation, gave an oil, b.p. 76.5–77.5° (20 mm.), n^{25}D 1.4762, containing 5.78 atom % D.

Reaction of Mercury with Mercuric Acetate.—To a solution of 8.0 g. (0.029 mole) of mercuric acetate in 100 ml. of 5% acetic acid stirred vigorously on the steam-bath was added rapidly 5.0 g. (0.029 g. atom) of mercury. Within 10 minutes mercurous acetate began precipitating; after 1 hr. 11 g. (84%) was collected.

URBANA, ILLINOIS

(34) 1-Ketoquinolizidine was reduced under conditions which are known to give separately the epimeric alcohols a and b from *trans*-1-decalone (H. D. Orloff, *Chem. Revs.*, **54**, 347 (1954)):

If the two 1-hydroxyquinolizidines isolated are discrete epimers, as the data suggest, analogy encourages us to assign their structures tentatively as A (1,10-H's *trans*) and B (1,10-H's *cis*).