g. (0.39 mole) of 2-aminoethylethanolamine.[13] Stirring and heating were continued for 2 hours, the mixture was cooled, and poured slowly into a solution of 90 ml. of concentrated hydrochloric acid in 2 l. of acetone. The product was collected by filtration and recrystallized from ethanol to give 126 g. (80%) of yellow crystals, m.p. 280–283° dec.

The free base was prepared by neutralizing a solution of 77 g. of the dihydrochloride monohydrate in 4 l. of warm water with excess ammonium hydroxide. A gum separated, which crystallized upon scratching. The bright yellow crystals were collected by filtration, washed with water and air-dried; yield 62 g. (98%), m.p. 183°. Recrystallization from a methanol–ethyl acetate mixture yielded yellow crystals, m.p. 182–184°.

Anal. Calcd. for $C_{18}H_{20}ClN_3O_2$: C, 62.51; H, 5.83; N, 12.15. Found: C, 62.61; H, 5.63; N, 12.12.

2,2-Dichloro-N-[2-(6-chloro-2-methoxy-9-acridinylamino)-ethyl]-N-(2-hydroxyethyl)-acetamide (VII).—A suspension of 61 g. (0.18 mole) of 2-[2-(6-chloro-2-methoxy-9-acridinylamino)-ethylamino]-ethanol in a solution of 52 g. (0.36 mole) of methyl dichloroacetate and 250 ml. of absolute ethanol was boiled under reflux for 24 hours. The mixture was cooled in an ice-bath, and the golden yellow rods were collected by filtration and air-dried; yield 49.2 g. (58%), m.p. 169° dec.

Anal. Calcd. for $C_{20}H_{20}Cl_3N_3O_3 \cdot 1^1/_2H_2O$: C, 49.65; H, 4.71; N, 8.68. Found: C, 49.47, 49.77; H, 4.71, 4.79; N, 8.27.

The infrared spectrum showed a characteristic amide carbonyl absorption[22] at 6.04 μ; no ester absorption was observed.

2-[2-(7-Benz[c]acridinylamino)-ethylamino]-ethanol.—A mixture of 50 g. (0.19 mole) of 7-chlorobenz[c]acridine, 19.8 g. (0.19 mole) of 2-aminoethylethanolamine[13] and 200 g. of phenol was stirred and heated on a steam-bath for two hours. The cooled reaction mixture was poured into a solution of 50 ml. of concentrated hydrochloric acid in 1 l. of acetone, the resulting mixture chilled, and the precipitated solid collected by filtration, washed with acetone, and dried. A solution of the crude hydrochloride in 500 ml. of water was made alkaline by the addition of a solution of 20 g. (0.5 mole) of sodium hydroxide in 25 ml. of water, and the solid base collected by filtration and dried. Extraction of the aqueous filtrates with ether and benzene afforded additional free base. Recrystallization of the combined crude base fractions from ethyl acetate (Darco) yielded 45.4 g. (72%) of yellow-green crystals, m.p. 99–100°.

Anal. Calcd. for $C_{21}H_{21}N_3O$: C, 76.10; H, 6.39; N, 12.68. Found: C, 76.16; H, 6.52; N, 12.70.

N-[2-(7-Benz[c]acridinylamino)-ethyl]-2,2-dichloro-N-(2-hydroxyethyl)-acetamide (VIIIa).—A solution of 40 g. (0.12 mole) of 2-[2-(7-benz[c]acridinylamino)-ethylamino]-ethanol and 25 ml. (0.24 mole) of methyl dichloroacetate in 100 ml. of absolute ethanol was boiled under reflux for 15 hours. The mixture was cooled, diluted with petroleum ether (b.p. 30–60°) to a volume of 1 l., and the taffy-like material which separated was solidified by grinding under anhydrous ether. The solid was collected by filtration and dried *in vacuo;* yield 46.2 g. (83%) of hygroscopic yellow solid, m.p. indefinite. Attempts to recrystallize the compound from several organic solvents failed.

Anal. Calcd. for $C_{23}H_{21}Cl_2N_3O_2 \cdot H_2O$: C, 60.00; H, 5.04; N, 9.13. Found: C, 59.68; H, 5.15; N, 9.33.

The infrared spectrum showed a characteristic amide carbonyl absorption[22] at 6.04 μ, and was free of ester absorption.

2-[3-(7-Benz[c]acridinylamino)-propylamino]-ethanol, Dihydrochloride.—A mixture of 50 g. (0.19 mole) of 7-chlorobenz[c]acridine, 23.6 g. (0.20 mole) of 3-aminopropylethanolamine[13] and 200 g. of phenol was stirred and heated on the steam-bath for two hours. The cooled reaction mixture was poured into a solution of 33 ml. of concentrated hydrochloric acid in 1 l. of acetone, the resulting mixture was chilled, and the solid which separated was collected by filtration, washed with acetone and dried; crude yield 82.1 g. (99%). A portion of the crude product precipitated from a methanol–ethyl acetate mixture yielded a hygroscopic yellow solid, m.p. 215–220° (softens 135° with apparent loss of water).

Anal. Calcd. for $C_{22}H_{23}N_3O \cdot 2HCl \cdot H_2O$: C, 60.55; H, 6.24; N, 9.63. Found: C, 60.91, 61.08; H, 6.08, 6.22; N, 10.02, 9.86.

N-[3-(7-Benz[c]acridinylamino)-propyl]-2,2-dichloro-N-(2-hydroxyethyl)-acetamide (VIIIb).—A filtered solution of 48.2 g. (0.110 mole) of the crude 2-[3-(7-benz[c]acridinylamino)-propylamino]-ethanol, dihydrochloride, monohydrate in 300 ml. of hot water was made alkaline by the addition of a solution of 12 g. (0.3 mole) of sodium hydroxide in 20 ml. of water. The mixture was extracted with benzene and butanol, the combined extracts were dried over anhydrous potassium carbonate, and the solvents removed *in vacuo* to give 36 g. (0.104 mole) of the crude amine. A solution of the crude amine in 200 ml. of absolute ethanol was boiled under reflux with 16 ml. (0.15 mole) of methyl dichloroacetate for 6 hours. When the cooled solution was diluted with petroleum ether (b.p. 30–60°) to a volume of 2 l., a viscous sirup separated, which was triturated thoroughly with petroleum ether (b.p. 30–60°) and ether. After one week, the sirup solidified and was pulverized and dried to give 35.9 g. (74.3%) of a yellow powder of indefinite melting point.

Anal. Calcd. for $C_{24}H_{23}Cl_2N_3O_2 \cdot ^1/_2H_2O$: C, 61.94; H, 5.20; N, 9.03. Found: C, 61.67, 61.76; H, 5.40, 5.29; N, 9.04.

The infrared spectrum showed a characteristic amide carbonyl absorption[22] at 6.03 μ, and was free of ester absorption.

DETROIT, MICHIGAN

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[22] Pressed KBr disc.

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Unsaturated Amines. VII. Introduction of α,β-Unsaturation by Means of Mercuric Acetate: Methylquinolizidines

BY NELSON J. LEONARD, RICHARD W. FULMER[1] AND ALLAN S. HAY[2]

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The mercuric acetate dehydrogenation of 1-, 2-, 3- and 4-methylquinolizidine (I) results in the introduction of a double bond at the bridgehead carbon (C-10). The enamines thus obtained form salts (perchlorates were used for characterization) having 5(10)-unsaturation which are of the ternary iminium type. Hydroxylation accompanies the dehydrogenation of 1-methylquinolizidine to some extent, with the coformation of 1-hydroxy-1-methyl-Δ⁹-dehydroquinolizidine. Accurate characterization of the two racemates of 2-methylquinolizidine has been effected along with the dehydrogenation study.

Following the investigation of the mercuric acetate dehydrogenation of quinolizidine[3] and other bicyclic tertiary amines,[4] it was of interest to study the dehydrogenation of the isomeric methyl-substituted quinolizidines (I), in part to answer the fol-

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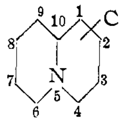
[1] National Science Foundation Fellow, 1954–1955.

[2] Monsanto Chemical Company Fellow, 1953–1954.

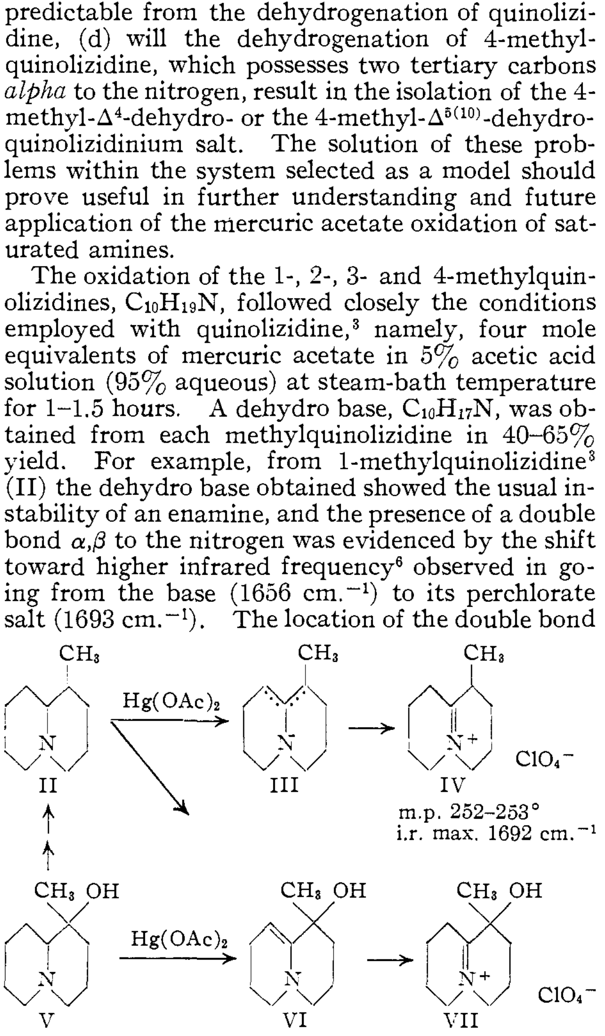
[3] N. J. Leonard, A. S. Hay, R. W. Fulmer and V. W. Gash, THIS JOURNAL, **77**, 439 (1955).

[4] N. J. Leonard, W. J. Middleton, P. D. Thomas and D. Choudhury, *J. Org. Chem.*, **21**, 344 (1956).

lowing questions: (a) will the mercuric acetate treatment of 1-methylquinolizidine result in hydroxylation as well as dehydrogenation, as in the case of 1-methyldecahydroquinoline,[5] which also possesses two tertiary carbons *alpha* and *beta* to the nitrogen, (b) will the unsaturated amine derivable from 1-methylquinolizidine exist primarily as the $\Delta^{1(10)}$-dehydro isomer or as a mixture of $\Delta^{1(10)}$- and Δ^{9}-dehydro bases, (c) will the 2-methyl- and 3-methylquinolizidines behave in the general manner predictable from the dehydrogenation of quinolizidine, (d) will the dehydrogenation of 4-methylquinolizidine, which possesses two tertiary carbons *alpha* to the nitrogen, result in the isolation of the 4-methyl-Δ^{4}-dehydro- or the 4-methyl-$\Delta^{5(10)}$-dehydroquinolizidinium salt. The solution of these problems within the system selected as a model should prove useful in further understanding and future application of the mercuric acetate oxidation of saturated amines.



I



The oxidation of the 1-, 2-, 3- and 4-methylquinolizidines, $C_{10}H_{19}N$, followed closely the conditions employed with quinolizidine,[3] namely, four mole equivalents of mercuric acetate in 5% acetic acid solution (95% aqueous) at steam-bath temperature for 1–1.5 hours. A dehydro base, $C_{10}H_{17}N$, was obtained from each methylquinolizidine in 40–65% yield. For example, from 1-methylquinolizidine[3] (II) the dehydro base obtained showed the usual instability of an enamine, and the presence of a double bond α,β to the nitrogen was evidenced by the shift toward higher infrared frequency[6] observed in going from the base (1656 cm.$^{-1}$) to its perchlorate salt (1693 cm.$^{-1}$). The location of the double bond in the cation of the salt at the bridgehead (IV) was suggested by the physical properties of the perchlorate (high melting point, high frequency and intensity of the infrared maximum in the 6 μ region) and analogy with $\Delta^{5(10)}$-dehydroquinolizidinium perchlorate obtained from quinolizidine. The structure IV was confirmed by independent synthesis. 1-Hydroxy-1-methylquinolizidine, prepared by Grignard addition to 1-ketoquinolizidine, was dehydrated and, from the mixture of dehydro amines, the most basic was isolated as 1-methyl-$\Delta^{5(10)}$-dehydroquinolizidinium perchlorate (IV), identical with the compound obtained *via* mercuric acetate dehydrogenation of 1-methylquinolizidine. Catalytic reduction of either the mixture of dehydro amines or the perchlorate IV resulted in 1-methylquinolizidine, thus establishing the preservation of the ring system in both oxidation and dehydration procedures. In order to determine whether the base, $C_{10}H_{17}N$, derivable from the perchlorate IV (or the corresponding acetate) by alkalization, arises by abstraction of a proton from C-1 alone or from either C-1 or C-9, the infrared and the nuclear magnetic resonance spectra were examined for ethylenic hydrogen absorption. It was concluded that the unsaturated base could be depicted most accurately as a mixture (III) of 1-methyl-$\Delta^{1(10)}$- and 1-methyl-Δ^{9}-dehydroquinolizidine.

Along with the 1-methyl-$\Delta^{5(10)}$-dehydroquinolizidinium perchlorate (IV) isolated from the action of mercuric acetate on 1-methylquinolizidine there was obtained, in about one-tenth the amount of IV, a perchlorate, $C_{10}H_{17}NO \cdot HClO_4$, m.p. 219–220°, which showed infrared absorption characteristic of hydroxyl as well as the ternary iminium grouping ($>C=\overset{+}{N}<$). The structure which suggested itself was that of 1-hydroxy-1-methyl-$\Delta^{5(10)}$-dehydroquinolizidinium perchlorate (VII), since this would be analogous to the major product of mercuric acetate oxidation of 1-methyldecahydroquinoline.[5] The common structural feature of 1-methylquinolizidine and 1-methyldecahydroquinoline is the presence of two tertiary carbons *alpha* and *beta* to the nitrogen. The structure VII was established as correct by synthesis of the same compound *via* mercuric acetate dehydrogenation of 1-hydroxy-1-methylquinolizidine (V). The base corresponding to VII, which exhibited infrared maxima at 3460 (O–H) and 1648 cm.$^{-1}$ ($>C=C<$) and the instability associated with an enamine, is therefore 1-hydroxy-1-methyl-Δ^{9}-dehydroquinolizidine (VI), and a probable intermediate in its formation by mercuric acetate oxidation of II is 1-methyl-$\Delta^{1(10)}$-dehydroquinolizidine.[5] The extent of hydroxylation following dehydrogenation of a tertiary amine having tertiary carbons *alpha* and *beta* to the nitrogen appears to be a function of more than degree of substitution and will be the subject of further consideration.

A mixture of the two racemates of 1-methylquinolizidine (II) was used in the mercuric acetate oxidation reaction since it was recognized that both racemates would lead to product (either IV or VII) in only one racemic form, and this approach was also applicable to the mercuric acetate dehydrogenation of 2-methylquinolizidine. However, it has become important to identify carefully the two racemates of 2-methylquinolizidine because of conflicting data on these compounds reported from two other laboratories. The most recent report, by Winterfeld and Schneider,[7] describes the picrates of the two forms of 2-methylquinolizidine as having melting points 141° and 125–126° and omits reference to the

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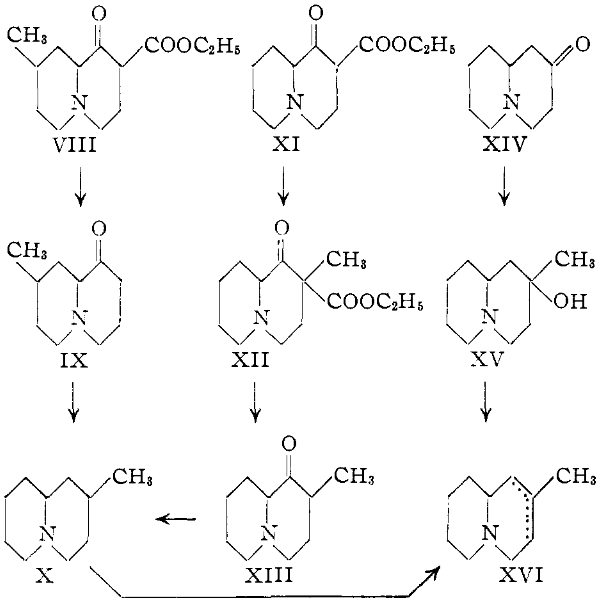
(5) Following article: N. J. Leonard, L. A. Miller and P. D. Thomas, THIS JOURNAL, **78**, 3463 (1956).

(6) N. J. Leonard and V. W. Gash, *ibid.*, **76**, 2781 (1954).

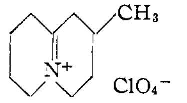
(7) K. Winterfeld and E. Schneider, *Ann.*, **581**, 66 (1953); *Naturwissenschaften*, **40**, 109 (1953).

earlier description of the 2-methylquinolizidines by Clemo and his co-workers.[8–10] While the two racemates of 2-methylquinolizidine were obtained in Clemo's laboratory not *via* the same synthetic sequence and subsequent separation, but by two independent syntheses each of which resulted in the preponderance of one racemate, both routes appear to lead unequivocally to 2-methylquinolizidine (X).



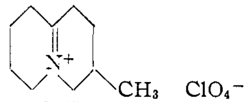
Isomer A (arbitrary designation) of 2-methylquinolizidine was obtained by Clemo, Cook and Raper[9] by the Wolff–Kishner reduction of 1-keto-8-methylquinolizidine (IX), which in turn was obtained by hydrolysis of the Dieckmann product, 2-carbethoxy-1-keto-8-methylquinolizidine (VIII). The derivatives of XA were described as: picrate, yellow prisms, m.p. 150°; picrolonate, yellow prisms, m.p. 197°. The Clemo and Metcalfe route[8] to racemate B of X included the methylation of the Dieckmann product, 2-carbethoxy-1-ketoquinolizidine (XI), hydrolysis of 2-carbethoxy-1-keto-2-methylquinolizidine (XII) to 1-keto-2-methylquinolizidine (XIII), and Wolff–Kishner reduction of XIII. The derivatives of XB were given as: picrate, yellow needles, m.p. 158°; picrolonate, yellow plates, m.p. 219°. The synthetic route XI → X (predominantly B) has been checked in this Laoratory. Moreover, we have succeeded in obtaining both isomers of X pure *via* a single synthetic route followed by isomer separation. 2-Hydroxy-2-methylquinolizidine (XV), made by the action of methyllithium on 2-ketoquinolizidine (XIV), was dehydrated to a mixture of 2-methyldehydroquinolizidines (XVI). This mixture was hydrogenated at 25° and 3 atmospheres in the presence of Raney nickel, and the product was separated into the two racemic forms of X (77% A, 23% B) by fractional distillation using a spinning band column. The pure racemates can now be characterized accurately by the properties of their derivatives: A picrate, short yellow prisms (from ethanol), m.p. 150°; A picrolonate, yellow prisms, m.p. 194–195° dec.; B picrate, yellow needles, m.p. 161–162°; B picrolonate, small yellow plates, m.p. 226.5–228° dec. These results indicate that the picrates and picrolonate (m.p. 175–179°) of "2-methylquinolizidine" described by Winterfeld and Schneider,[7] if analytically pure, either consisted of a mixture of the racemates of X or represented the derivatives of a $C_{10}H_{19}N$ compound with different structure. In the latter case, the synthetic route of Winterfeld and Schneider leading to the supposed "2-methylquinolizidine" would have to be re-examined to determine at which point the procedure was in error.

Authentic 2-methylquinolizidine was subjected to mercuric acetate dehydrogenation, and the product was isolated as the perchlorate. The structure of the salt was deduced as 2-methyl-$\Delta^{5(10)}$-dehydroquinolizidinium perchlorate (XVII) on the basis of its physical properties and analogy with the conversion of both quinolizidine[3] and 1-methylquinolizidine (II) to ternary iminium salts having 5(10)-unsaturation. The hydrogenation of XVII over platinum oxide yielded 2-methylquinolizidine, isomer A predominating. The product from the mercuric acetate dehydrogenation of 3-methylquinolizidine[3] was isolated as the perchlorate, which was similarly assigned the structure 3-methyl-$\Delta^{5(10)}$-dehydroquinolizidinium perchlorate (XVIII). The bases corresponding to XVII and XVIII would logically be expected to be mixtures of the $\Delta^{1(10)}$- and Δ^{9}-dehydro amines.



XVII

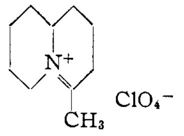
m.p. 205–206°
i.r. max. 1696 cm.$^{-1}$



XVIII

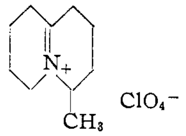
m.p. 211–212°
i.r. max. 1693 cm.$^{-1}$

4-Methylquinolizidine,[11] which has two tertiary carbons *alpha* to the nitrogen, offers the possibility of mercuric acetate dehydrogenation with the introduction of a double bond at either the 4- or the 10-position and resultant isolation of either 4-methyl-Δ^{4}-dehydroquinolizidinium (XIX) or 4-methyl-$\Delta^{5(10)}$-dehydroquinolizidinium perchlorate (XX) (or a mixture). 4-Methyl-Δ^{4}-dehydroquinolizidinium perchlorate (XIX) was synthesized for reference by the addition of methylmagnesium iodide to 4-ketoquinolizidine, which furnished 4-methyl-Δ^{3}-dehydroquinolizidine, convertible to the salt XIX. The infrared maximum in the double bond stretching region shifted from 1651 to 1668 cm.$^{-1}$ in comparing 4-methyl-Δ^{3}-dehydroquinolizidine with the perchlorate salt, indicative of the ternary iminium



XIX

m.p. 176–177°
i.r. max. 1668 cm.$^{-1}$



XX

m.p. 241–242°
i.r. max. 1680 cm.$^{-1}$

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(8) G. R. Clemo and T. P. Metcalfe, *J. Chem. Soc.*, 1518 (1937).

(9) G. R. Clemo, J. G. Cook and R. Raper, *ibid.*, 1183 (1938).

(10) N. J. Leonard and W. C. Wildman, THIS JOURNAL, **71**, 3089 (1949), footnote 9.

(11) N. J. Leonard and E. D. Nicolaides, *ibid.*, **73**, 5210 (1951), and references contained therein.

grouping in XIX. The presence of the $>\mathrm{C}=\overset{+}{\mathrm{N}}<$ moiety in the structure was substantiated by the high-yield reaction of XIX with potassium cyanide[12,13] to give 4-cyano-4-methylquinolizidine. The mercuric acetate dehydrogenation of 4-methylquinolizidine resulted in the isolation of a perchlorate salt (65% yield) isomeric but not identical with XIX. With the presence of the ternary iminium grouping in the salt indicated by the characteristic infrared maximum and the reaction with potassium cyanide, the structure could be assigned as 4-methyl-$\Delta^{5(10)}$-dehydroquinolizidinium perchlorate (XX). There was no evidence of isomerization of one salt to the other (XIX, XX) under the conditions of formation and recrystallization of the perchlorate. Basification of either salt followed by reacidification with perchloric acid returned the original perchlorate.

Experimental[14]

Preparation of 2-Methylquinolizidine. 2-Ketoquinolizidine.—The procedure of Clemo, Metcalfe and Raper[15] was modified. A solution of 57 g. (0.21 mole) of diethyl piperidyl-2-acetate-1-β-propionate, made according to directions similar to those of Sternbach and Kaiser,[16] in 200 ml. of anhydrous xylene was added during 3 hours to 13 g. (0.53 mole) of sodium hydride and 1 ml. of ethanol in 1 l. of refluxing xylene. Stirring at the reflux temperature was continued for 2 hours. The mixture was cooled in ice and 36 g. of glacial acetic acid was added. Water (100 ml.) was added to dissolve the sodium acetate formed, and the xylene layer was extracted three times with 150-ml. portions of 6 *N* hydrochloric acid. The combined acid extracts were heated under reflux for 8 hours. After cooling, the solution was neutralized and saturated with solid potassium carbonate, and the excess solids were collected and washed on the filter with ether. The ether washings were then used to extract the organic material from the aqueous solution. The combined ether fractions were dried, the ether was removed and the residue was distilled, b.p. 64–66° (0.5 mm.) (reported[15] 70–77°, (1.0 mm.)), $n^{20}\mathrm{D}$ 1.4916, yield 24.2 g. (75%). **The picrate** crystallized from ethanol as yellow prisms, m.p. 209–210° (reported[15] 211°).

2-Hydroxy-2-methylquinolizidine.—To a solution of methyllithium formed[17] from 42.6 g. (0.3 mole) of methyl iodide in 100 ml. of anhydrous ether was added during 30 minutes 40 g. (0.26 mole) of 2-ketoquinolizidine in 100 ml. of ether, and the solution was stirred under reflux for 3 hours. The reaction mixture was decomposed by the addition of 10% aqueous sodium hydroxide, and the ether layer was separated. The aqueous alkaline layer was extracted with three 100-ml. portions of ether. The combined ether extracts were dried, the ether was removed, and the residue was distilled through a modified Holzman column, b.p. 73–75° (0.2 mm.), yield 12.8 g. (28%). The compound solidified on standing, m.p. 55.5–56.5°.

Anal. Calcd. for $C_{10}H_{19}NO$: C, 70.94; H, 11.31; N, 8.28. Found: C, 71.12; H, 11.30; N, 8.39.

Dehydration of 2-Hydroxy-2-methylquinolizidine.—To a solution of 25 g. of phosphorus pentoxide in 50 g. of phosphoric acid was added 12.0 g. (0.71 mole) of 2-hydroxy-2-methylquinolizidine. After the evolution of heat had ceased, the flask was heated gradually to 120°, and maintained there for 30 minutes. The semi-solid mass that formed on mixing gradually disappeared, and the temperature was raised to 150° for one hour. The solution was cooled, the acid was neutralized with aqueous potassium carbonate, and solid potassium carbonate was added. The oily layer was extracted with four 50-ml. portions of ether, and the dried ether extracts furnished a residue which was distilled under nitrogen through a modified Holzman column, b.p. 64° (3.5 mm.), $n^{20}\mathrm{D}$ 1.4950, yield 7.45 g. (70%).

Anal. Calcd. for $C_{10}H_{17}N$: C, 79.40; H, 11.34. Found: C, 78.77; H, 11.43.

The picrate of this product, a mixture having 2-methyl-Δ^1-dehydroquinolizidine and 2-methyl-Δ^2-dehydroquinolizidine as probable components, was recrystallized three times from ethanol as yellow needles, m.p. 148–149.3°. No attempt was made at further fractional crystallization.

Anal. Calcd. for $C_{16}H_{20}N_4O_7$: C, 50.52; H, 5.30; N, 14.73. Found: C, 50.80; H, 5.60; N, 14.78.

2-Methylquinolizidine.—A solution of 6.5 g. (0.043 mole) of 2-methyldehydroquinolizidine in 35 ml. of absolute ethanol was hydrogenated at 25° and 3 atm. in the presence of 0.5 g. of Raney nickel catalyst. The catalyst was removed by filtration, the ethanol was distilled at reduced pressure, and the residue was distilled through a micro spinning-band column. Cuts of distillate were taken arbitrarily. There was an over-all distillation range of only two degrees (79–81° (12–12.6 mm.)), $n^{21}\mathrm{D}$ 1.4753 to 1.4780: A racemate, b.p. 80° (12–12.2 mm.) (77% of distillate); B racemate, b.p. 80.5–80.7° (12.3–12.6 mm.), $n^{21}\mathrm{D}$ 1.4778 (23%). Redistillation of the third of five fractions of constant refractive index was performed for the analysis of racemate A. An analytical sample of racemate B was obtained by forming the picrate, recrystallizing the picrate to constant melting point, and regenerating the free base.

Anal. Calcd. for $C_{10}H_{19}N$: C, 78.36; H, 12.50; N, 9.14. Found for A: C, 78.29; H, 12.28; N, 9.26. Found for B: C, 78.55; H, 12.35; N, 9.24.

Picrates made from the separate fractions were recrystallized from ethanol: A picrate, short yellow prisms, m.p. 150°; B picrate, yellow needles, m.p. 161–162°.

Anal. Calcd. for $C_{16}H_{22}N_4O_7$: C, 50.25; H, 5.80; N, 14.66. Found for A: C, 50.25; H, 5.96; N, 14.72. Found for B: C, 50.31; H, 6.05; N, 14.61.

Picrolonates were made in acetone and recrystallized from ethanol: A picrolonate, yellow prisms, m.p. 194–195° dec.; B picrolonate, small yellow plates, m.p. 226.5–228° dec.

Anal. Calcd. for $C_{20}H_{27}N_5O_5$: C, 57.54; H, 6.52; N, 16.78. Found for A: C, 57.46; H, 6.54; N, 17.02. Found for B: C, 57.69; H, 6.46; N, 16.73.

Although definite proof of the stereochemistry of the isomers of X is lacking, our present working assumption is that form A has *cis*-hydrogens at C-2 and C-10.

2-Carbethoxy-1-ketoquinolizidine.—The Dieckmann ring closure of diethyl piperidyl-1-γ-butyrate-2-carboxylate[8] was effected with sodium hydride as described above for 2-ketoquinolizidine. The extraction with 2.2 *N* hydrochloric acid was carried out ice-cold. The cold aqueous acid solution was basified and solid potassium carbonate was added. Ether extraction furnished the keto ester, b.p. 115° (0.1 mm.) (reported[8] 131–134° (0.1 mm.)), 70% yield.

1-Keto-2-methylquinolizidine.—The methylation of 2-carbethoxy-1-ketoquinolizidine and subsequent hydrolysis and isolation followed the directions of Clemo and Metcalfe,[8] b.p. 70–75° (0.2 mm.) (reported 80° (1.0 mm.)), yield of crude product 55%. **2-Methylquinolizidine.**—The Huang-Minlon modification of the Wolff–Kishner reduction was used. A solution of 50 g. (0.3 mole) of 1-keto-2-methylquinolizidine and 35 g. of 85% hydrazine hydrate (0.6 mole) in 450 ml. of triethylene glycol was heated under reflux for 5 hours. Distillate was then collected (28 ml.) while the pot temperature was raised to 230°. The solution was cooled, 100 g. (1.8 moles) of potassium hydroxide was added slowly with stirring, the temperature was raised and then maintained at 220° until nitrogen evolution ceased (about 2 hours). The reaction mixture was poured into 200 ml. of water and the whole was extracted with ether. The residue from the ether extracts was distilled through a spinning-band column. An appreciable quantity of quinolizidine was recovered from the first fractions, indicating

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[12] N. J. Leonard, P. D. Thomas and V. W. Gash, THIS JOURNAL, **77**, 1552 (1955).

[13] N. J. Leonard and A. S. Hay, *ibid.*, **78**, 1984 (1956).

[14] All melting points are corrected. We are indebted to Mrs. Esther Fett, Mrs. Lucy Chang, Mrs. R. Maria Benassi, Mr. Joseph Nemeth and Mr. R. J. Nesset for microanalyses, and to Miss Helen Milkas, Mrs. Louse Griffing and Mr. James Brader for determination of the infrared absorption spectra, using a Perkin–Elmer automatic recording infrared spectrometer, model 21.

[15] G. R. Clemo, T. P. Metcalfe and R. Raper, *J. Chem. Soc.*, 1429 (1936).

[16] L. H. Sternbach and S. Kaiser, THIS JOURNAL, **74**, 2215 (1952).

[17] T. D. Perrine and H. Rapoport, *Anal. Chem.*, **20**, 635 (1948).

the incompleteness of the methylation reaction, and subsequent fractions yielded only one of the isomers (B) of 2-methylquinolizidine, n^{23}_{D} 1.4776; **picrate**, yellow prisms, m.p. 160–161°.

Anal. Calcd. for $C_{16}H_{22}N_4O_7$: C, 50.25; H, 5.80; N, 14.66. Found: C, 50.43; H, 5.83; N, 14.64.

This picrate gave no depression in melting point when mixed with the picrate B described above.

1-Hydroxy-1-methylquinolizidine.—To the Grignard reagent, prepared from 21.2 g. (0.88 gram atom) of magnesium and 123.5 g. (0.87 mole) of methyl iodide in 1.2 l. of anhydrous ether, was added during 30 minutes a solution of 65 g. (0.43 mole) of 1-ketoquinolizidine[18,19] in 300 ml. of ether. The reaction mixture was stirred for 12 hours at 25°. Aqueous sodium carbonate was added, and the ether solution was separated. The aqueous alkaline layer was stirred under reflux with ether, and the ether layer was again separated. The residue obtained from the dried ether extracts was fractionated, b.p. 70–72° (1.0 mm.), yield 52.6 g. (73%). The distillate solidified and was purified by sublimation as colorless needles, m.p. 96–97°.

Anal. Calcd. for $C_{10}H_{19}NO$: C, 70.94; H, 11.31; N, 8.28. Found: C, 70.76; H, 11.51; N, 8.28.

The picrate was made in ether and recrystallized from ether containing a small amount of ethanol as yellow crystals, m.p. 122–123°. No attempt was made to separate the possible racemic forms.

Anal. Calcd. for $C_{16}H_{22}N_4O_8$: C, 48.24; H, 5.57; N, 14.07. Found: C, 48.11; H, 5.44; N, 14.34.

Dehydration of 1-Hydroxy-1-methylquinolizidine.—The procedure was similar to that employed by Clemo and Metcalfe[8] for the dehydration of 1-hydroxy-1-methyloctahydropyrrocoline. To 35 g. (0.21 mole) of 1-hydroxy-1-methylquinolizidine was added cautiously 56 g. (0.27 mole) of phosphorus pentachloride. The immediate exothermic reaction was moderated by cooling the mixture in an ice-bath. To make the reaction mixture more homogeneous, 150 ml. of redistilled carbon disulfide was added and the lumps were broken up with a glass rod. The mixture was then stirred for 2 hours at 25°, and the solvent was removed under reduced pressure. To the residue was added 250 ml. of glacial acetic acid, and the mixture was heated under reflux for 2 hours. Subsequent addition of 25 ml. of concentrated hydrochloric acid was followed by evaporation *in vacuo*. The residue was cooled in ice, made strongly basic with concentrated aqueous sodium hydroxide, and the amine material was extracted with four 40-ml. portions of ether. The ether extracts were concentrated, and 30 ml. of ethanol was added to the residual oil. The resulting solution was treated with a solution of equal parts by volume of 68% aqueous perchloric acid and ethanol until acid to congo red. Fine, light pink needles separated on addition of the first portion of the perchloric acid (22 ml. of acid in all was required). The solid was collected by filtration and recrystallized from ethanol as colorless needles, m.p. 253° with slight decomposition. The salt, that of the most basic amine present, was **1-methyl-$\Delta^{5(10)}$-dehydroquinolizidinium perchlorate** (see below), infrared maximum (mull) 1693 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{18}ClNO_4$: C, 47.71; H, 7.21; N, 5.56. Found: C, 47.60; H, 7.15; N, 5.58.

Most of the solvent was removed *in vacuo* from the perchloric acid–ethanol filtrate. The residue was made basic with sodium hydroxide solution and the unsaturated amine bases were extracted with four 50-ml. portions of ether. The ether extracts were dried, the solvent was removed, and the residue was distilled through a modified Holzman column, weight 13 g., b.p. 78–79° (16–17 mm.), n^{20}_{D} 1.4956, total yield 64%, including 6.9 g. of free base represented in the 11.3 g. of perchlorate salt. The product is a mixture of 1-methyldehydroquinolizidines.

Reduction of the Mixture of 1-Methyldehydroquinolizidines.—A solution of 13.0 g. (0.086 mole) of the mixture of the 1-methyldehydroquinolizidines, 50 ml. of ethanol and 12 ml. of concentrated hydrochloric acid was hydrogenated at 25° and 3 atmospheres using 0.2 g. of platinum oxide. The theoretical uptake of hydrogen was realized in 2 hours. The solution was filtered, and the solvent was removed at reduced pressure. The residue was basified with aqueous sodium hydroxide solution and extracted with four 50-ml. portions of ether. After drying the ether extracts, the solvent was removed and the residue was distilled through a modified Holzman column, b.p. 94–98° (21–23 mm.), yield 10.4 g. (80%).

The picrate was made in ethanol and recrystallized from ethanol–ether. No attempt was made to fractionate the racemates.[3] After two recrystallizations, the mixed 1-methylquinolizidine picrates melted at 171.5–172.5°.

Anal. Calcd. for $C_{16}H_{22}N_4O_7$: C, 50.25; H, 5.80; N, 14.66. Found: C, 50.20; H, 5.91; N, 14.79.

Mercuric Acetate Dehydrogenation of 1-Methylquinolizidine.—The procedure was similar to that employed with quinolizidine.[3] A solution of 86.4 g. (0.27 mole) of mercuric acetate and 10.4 g. (0.068 mole) of 1-methylquinolizidine in 800 ml. of 5% aqueous acetic acid was heated on the steam-bath with stirring. Mercurous acetate began to precipitate within 15 minutes, and after one hour 49.3 g. (140% of theory for abstraction of two hydrogen atoms) of mercurous acetate was collected from the cooled solution by filtration. The filtrate was saturated with hydrogen sulfide to remove excess mercuric ions as black mercuric sulfide. After filtration, 10 ml. of concentrated hydrochloric acid was added and the volume of the solution was reduced *in vacuo* to about 50 ml. The residue was made strongly basic with 40% aqueous sodium hydroxide and extracted with ether. The ether extracts were dried and then treated with perchloric acid in aqueous ethanol until the mixture was acid to congo red. The mushy precipitate was recrystallized once from ether–ethanol to yield 7.4 g. (*ca.* 41%) of a perchlorate salt, softening point about 210°, m.p. 213–216.5°. This material was fractionally crystallized to give two different perchlorate salts, which were identified as **1-methyl-$\Delta^{5(10)}$-dehydroquinolizidinium perchlorate** (m.p. 252–253°, colorless needles, which showed no depression when mixed with a sample prepared, as described above, by the dehydration of 1-hydroxy-1-methylquinolizidine) and **1-hydroxy-1-methyl-$\Delta^{5(10)}$-dehydroquinolizidinium perchlorate** (m.p. 219–220°, colorless needles, which showed no depression on admixture with the mercuric acetate dehydrogenation product from 1-hydroxy-1-methylquinolizidine, described below). The 1-methyl-$\Delta^{5(10)}$-dehydroquinolizidinium perchlorate made up approximately 90% of the crude mixture.

The infrared spectrum (Nujol mull) of 1-hydroxy-1-methyl-$\Delta^{5(10)}$-dehydroquinolizidinium perchlorate had maxima at 1683 ($>C{=}\overset{+}{N}<$) and 3456 cm.$^{-1}$ (O–H).

Anal. Calcd. for $C_{10}H_{18}ClNO_5$: C, 44.86; H, 6.78. Found: C, 44.74; H, 6.53.

1-Methyl-$\Delta^{1(10)}$- and 1-Methyl-Δ^{9}-dehydroquinolizidine.—To a suspension of 5.0 g. of 1-methyl-$\Delta^{5(10)}$-dehydroquinolizidinium perchlorate, m.p. 252–253°, in 20 ml. of water was added 10 ml. of 40% aqueous sodium hydroxide solution. Ether extraction followed by drying and evaporation furnished the free base, which was distilled under nitrogen through a modified Holzman column as a colorless oil, b.p. 64° (4.5 mm.), n^{23}_{D} 1.5186, yield 2.1 g. (67%). It darkened rapidly on exposure to air.

Anal. Calcd. for $C_{10}H_{17}N$: C, 79.40; H, 11.34. Found: C, 79.43; H, 11.30.

The infrared spectrum of the liquid showed a maximum at 1656 cm.$^{-1}$ ($>C{=}C<$) and slight absorption near 3020 cm.$^{-1}$ ($\geqslant C{-}H$). The NMR spectrum[20] showed some ethylenic hydrogen absorption, but in a lower ratio (integrated absorption area) to methylenic hydrogen absorption than exhibited by $\Delta^{1(10)}$-dehydroquinolizidine, consistent with the formulation of the amine liberated from the perchlorate salt as a mixture of the $\Delta^{1(10)}$- and Δ^{9}-dehydro isomers.[20]

Catalytic Reduction of 1-Methyl-$\Delta^{5(10)}$-dehydroquinolizidinium Perchlorate.—A solution of 1.8 g. (6 mmoles) of the perchlorate salt in 30 ml. of distilled water was hydrogenated at 25° and 3 atm. using 0.1 g. of platinum oxide catalyst. The catalyst was removed by filtration, and the product was obtained from the basified filtrate by ether extraction. The picrate was made directly from the ether solution and was recrystallized twice from ethanol as small yellow platelets,

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[18] G. R. Clemo and G. R. Ramage, *Anal. Chem.*, 437 (1931).

[19] N. J. Leonard, S. Swann, Jr., and J. Figueras, Jr., THIS JOURNAL, **74**, 4620 (1952).

[20] We would like to acknowledge the assistance of Dr. Charles Holm and thank him for determining the nuclear magnetic resonance curves and Dr. H. S. Gutowsky for aid in their interpretation.

m.p. 189–191°, essentially identical with the high-melting picrate of 1-methylquinolizidine.[3]

Mercuric Acetate Dehydrogenation of 1-Hydroxy-1-methylquinolizidine.—A solution of 32.0 g. (0.1 mole) of mercuric acetate and 4.2 g. (0.025 mole) of 1-hydroxy-1-methylquinolizidine in 500 ml. of 5% aqueous acetic acid was heated on the steam-bath with stirring for 2 hours. After cooling, 9.1 g. of mercurous acetate (70% of theoretical for reaction of amine with 2 moles of mercuric acetate) was collected by filtration. The perchlorate salt of the product, isolated as from 1-methylquinolizidine, was recrystallized from ethanol as colorless needles, m.p. 220–221°, yield 1.3 g. (20%), identical with the hydroxy ternary iminium salt described above in melting point and infrared absorption spectrum.

Anal. Calcd. for $C_{10}H_{18}ClNO_5$: C, 44.86; H, 6.78; N, 5.23. Found: C, 44.96; H, 6.70, N, 5.12.

Mercuric Acetate Dehydrogenation of 2-Methylquinolizidine.—The dehydrogenation of 2-methylquinolizidine was effected as described for the 1-isomer. The **2-methyl-$\Delta^{5(10)}$-dehydroquinolizidinium perchlorate** formed was recrystallized from ethanol as colorless needles, m.p. 205–206°, yield 42%, infrared maximum (mull) 1696 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{18}ClNO_4$: C, 47.71; H, 7.21; N, 5.56. Found: C, 47.55; H, 7.24; N, 5.53.

Hydrogenation of the perchlorate salt in aqueous solution using platinum oxide furnished the saturated amine, which was found to consist mainly of the 2-methylquinolizidine isomer (A) that formed the low-melting picrate, yellow needles, m.p. 151–152°.

Mercuric Acetate Dehydrogenation of 3-Methylquinolizidine.—The same general method applied to 3-methylquinolizidine[3] furnished **3-methyl-$\Delta^{5(10)}$-dehydroquinolizidinium perchlorate** as long colorless needles, m.p. 211–212° dec., yield 37%, infrared maximum (mull) 1693 cm.$^{-1}$.

Anal. Found: C, 47.97; H, 7.25; N, 5.40.

Catalytic reduction of the perchlorate furnished the saturated amine, which was characterized as 3-methylquinolizidine by means of the picrate and picrolonate derivatives. The picrate was recrystallized to constant melting point, 182–183°, yellow elongated prisms from ethanol, identical with the low-melting picrate (of isomer B) previously described.[3] The picrolonate, yellow prisms, m.p. 224–225°, had the correct analysis for 3-methylquinolizidine picrolonate and was a mixture of isomeric salts A and B.[3]

3-Methyl-$\Delta^{1(10)}$- and 3-Methyl-Δ^9-dehydroquinolizidine.—3-Methyl-$\Delta^{5(10)}$-dehydroquinolizidinium perchlorate was converted to the free base in the usual manner as a colorless oil, b.p. 67° (5 mm.), n^{20}D 1.4910, yield 74%, infrared maxima (liquid film) 1653 and 3015 cm.$^{-1}$. The enamine, logically a mixture of 3-methyl-$\Delta^{1(10)}$- and 3-methyl-Δ^9-dehydroquinolizidine, darkened rapidly on exposure to air and was reconverted to the initial perchlorate salt.

Preparation of 4-Methyl-Δ^3-dehydroquinolizidine.—To the Grignard reagent prepared from 28.4 g. (0.2 mole) of methyl iodide and 4.86 g. (0.2 gram atom) of magnesium in 200 ml. of ether was added slowly 15.3 g. of 4-ketoquinolizidine.[21] The mixture was stirred under reflux for one hour, then allowed to stand at 25° overnight. The ether was removed and the solid residue was heated on the steam-bath for one hour. After addition of a saturated aqueous solution of ammonium chloride, the product was isolated by the procedure previously applied to 10-methylquinolizidine.[3] The colorless oil, b.p. 101° (22 mm.), decomposed rapidly in contact with air; infrared maximum (liquid film) 1651 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{17}N$: C, 79.40; H, 11.34. Found: C, 78.86; H, 11.40.

Hydrogenation of 4-methyl-Δ^3-dehydroquinolizidine in ethanol using platinum oxide furnished the saturated amine which was characterized as 4-methylquinolizidine by conversion to the picrate, m.p. 190–191°, yield nearly 100%, undepressed in melting point on admixture with an authentic sample of 4-methylquinolizidine (high-melting) picrate.[11]

4-Methyl-Δ^4-dehydroquinolizidinium Perchlorate.—A portion of the enamine described above was converted to the perchlorate salt in the usual way as colorless needles, m.p. 176–177°, infrared maximum (mull) 1668 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{18}ClNO_4$: C, 47.71; H, 7.21; N, 5.56. Found: C, 48.00; H, 6.97; N, 5.43.

4-Methyl-Δ^4-dehydroquinolizidinium Picrate.—The picrate of 4-methyl-Δ^3-dehydroquinolizidine crystallized from ethanol as yellow needles, m.p. 135–136°.

Anal. Calcd. for $C_{16}H_{20}N_4O_7$: C, 50.52; H, 5.30, N, 14.73. Found: C, 50.62; H, 5.27; N, 14.86.

4-Cyano-4-methylquinolizidine.—A solution of 2.08 g. (8.3 mmoles) of 4-methyl-Δ^4-dehydroquinolizidinium perchlorate in water was treated with an excess of potassium cyanide. The resulting mixture was extracted with ether, and the residual oil from the combined and dried ether extracts was distilled at 130° (18 mm.), n^{25} 1.4878, yield 1.17 g. (80%).

Anal. Calcd. for $C_{11}H_{18}N_2$: C, 74.11; H, 10.18. Found: C, 74.52; H, 10.02.

Mercuric Acetate Dehydrogenation of 4-Methylquinolizidine.—The method described for the other methylquinolizidine isomers was applied to 4-methylquinolizidine. The perchlorate salt of the enamine crystallized from ethanol as colorless needles, m.p. 241–242° dec., infrared maximum (mull) 1680 cm.$^{-1}$, yield 65%. The salt was very different in properties from 4-methyl-Δ^4-dehydroquinolizidinium perchlorate and could therefore be assigned the structure **4-methyl-$\Delta^{5(10)}$-dehydroquinolizidinium perchlorate**.

Anal. Calcd. for $C_{10}H_{18}ClNO_4$: C, 47.71; H, 7.21; N, 5.57. Found: C, 47.99; H, 7.50; N, 5.55.

10-Cyano-4-methylquinolizidine.—Prepared from 4-methyl-$\Delta^{5(10)}$-dehydroquinolizidinium perchlorate and potassium cyanide, the aminonitrile was a colorless oil, b.p. 121° (20 mm.), n^{25} 1.4882, yield 72%.

Anal. Calcd. for $C_{11}H_{18}N_2$: C, 74.11; H, 10.18. Found: C, 74.14; H, 9.79.

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[21] V. Boekelheide and S. Rothchild, THIS JOURNAL, **71**, 879 (1949).