readings may not be as accurate as this, especially since the slit opens to its maximum (*i.e.*, 3.0 mm.) at 213–215 mμ.

The values reported in Table I are all observed with diethyl ether as the solvent. In addition, diethylamine and triethylamine, whose spectra have been determined previously in the vacuum ultraviolet,[5] were run in solution under the same conditions used for the cyclic amines. Neither showed a maximum at or above 215 mμ; their extinction coefficients at 215 mμ were, respectively, 350 and 1600.

Absorption spectra were determined for several compounds in cyclohexane as well as in ether. The cyclohexane was purified by shaking with concentrated sulfuric acid, then with water, followed by drying over magnesium sulfate and distilling. With this solvent, the slit width was a maximum at 208 mμ. At 228 mμ, solvent seemed to have little effect on the maxima, since 1-butenylpiperidine (VII) exhibited $\epsilon_{max.}$ 7800 at 228 mμ in cyclohexane.[6,7] The (apparent) maximum for Δ^3 (or Δ^{13})-dehydrosparteine (XIV), however, was shifted in cyclohexane to 208 mμ and $\epsilon_{max.}$ 6900, and quinolizidine failed to show any maximum in cyclohexane at or above 208 mμ (ϵ 4600 at 208 mμ).

Purification of Compounds.—All compounds were of analytical purity.

Diethylamine: redistilled, b.p. 55–55.5°, $n^{20}D$ 1.3869.

Triethylamine: redistilled, b.p. 86.5–87°, $n^{20}D$ 1.4003.

1-Methyl-2-*n*-butylpyrrolidine (I)[20]: redistilled, b.p. 40–41° (28 mm.).[21]

1-*n*-Butyl-2-methyl-Δ^2-pyrroline (II)[20]: redistilled under nitrogen, b.p. 65–66° (17 mm.).

1-Ethyl-2,5-dimethyl-Δ^3-pyrroline (III)[20]: redistilled under nitrogen, b.p. 64.5–66° (85 mm.), $n^{20}D$ 1.4440.

1-Methylpiperidine (IV)[22]: redistilled, b.p. *ca.* 25° at 20 mm.

1-Ethyl-2-methyl-Δ^2-tetrahydropyridine (V)[20]: redistilled under nitrogen, b.p. 57–57.5° (16 mm.).

1-Ethyl-Δ^3-tetrahydropyridine (VI)[1]: redistilled under nitrogen, b.p. 35–36° (28 mm.).

1-Butenylpiperidine (VII)[23]: redistilled under nitrogen, b.p. 84–85° (20 mm.), $n^{20}D$ 1.4810.

1-Allylpiperidine (VIII)[20]: redistilled, b.p. 44–45° (18 mm.), $n^{20}D$ 1.4584.

Quinolizidine (IX)[24]: redistilled, b.p. 75–75.5° (18 mm.), $n^{20}D$ 1.4793.

$\Delta^{1(10)}$-Dehydroquinolizidine (X)[25]: purified through the perchlorate salt, m.p. 232–233° dec.; distilled under nitrogen, b.p. 80° (18 mm.), $n^{28}D$ 1.5116.

Δ^1-Dehydroquinolizidine (XI)[25]: redistilled under nitrogen, b.p. 75–76° (20 mm.), $n^{28}D$ 1.4917.

***l*-Sparteine (XII)**: purified through the sulfate salt; distilled, b.p. 102–103° (0.3 mm.).

Δ^5-Dehydrosparteine (XIII)[26,27]: purified through the perchlorate salt, d.p. 243°; distilled under nitrogen, b.p. 83–84° (0.2 mm.).

Δ^3(or Δ^{13})-Dehydrosparteine (XIV)[27,28]: recrystallized from chloroform–acetone, m.p. 168–169°.

***l*-α-Isosparteine (XV)**[26,29–31]: resublimed at 75–85° (0.1 mm.), m.p. 107–115° (softens at 95°), partially hydrated.

$\Delta^{5,11}$-Didehydrosparteine (XVI)[26,27]: resublimed at 110–115° (0.1 mm.), m.p. 104–106°.

(20) R. Adams and J. E. Mahan, THIS JOURNAL, **64**, 2588 (1942).

(21) The liquid samples were distilled through a modified Holzman column, and the boiling points recorded when very small amounts were distilled may be lower than the literature values.

(22) N. J. Leonard, S. Swann, Jr., and H. L. Dryden, Jr., THIS JOURNAL, **74**, 2871 (1952).

(23) C. Mannich and H. Davidsen, *Ber.*, **69**, 2106 (1936).

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

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

(26) K. Winterfeld and C. Rauch, *Arch. Pharm.*, **272**, 273 (1934).

(27) N. J. Leonard, P. D. Thomas and V. W. Gash, THIS JOURNAL, in press.

(28) Structure is uncertain. P. D. Thomas, Ph.D. Thesis, University of Illinois, 1954.

(29) N. J. Leonard and R. E. Beyler, THIS JOURNAL, **72**, 1316 (1950).

(30) L. Marion and N. J. Leonard, *Can. J. Chem.*, **29**, 355 (1951).

(31) Maria Przybylska and W. H. Barnes, *Acta Cryst.*, **6**, 377 (1953).

URBANA, ILLINOIS

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

Unsaturated Amines. III. Introduction of α,β-Unsaturation by Means of Mercuric Acetate: $\Delta^{1(10)}$-Dehydroquinolizidine[1,2]

BY NELSON J. LEONARD, ALLAN S. HAY, RICHARD W. FULMER AND VIRGIL W. GASH

RECEIVED AUGUST 12, 1954

The mild dehydrogenation of the representative saturated bicyclic tertiary amine, quinolizidine (I), by means of mercuric acetate results in $\Delta^{1(10)}$-dehydroquinolizidine (II), which forms salts of the $\Delta^{5(10)}$-dehydroquinolizidinium type (III). The establishment of the structures is based upon data accumulated from infrared spectra, ultraviolet spectra, pK'_a measurements, Zerewitinoff active hydrogen determinations, reduction with lithium aluminum hydride, and Grignard reaction with the α,β-unsaturated (enamine) salt. The action of methylmagnesium iodide on $\Delta^{1(10)}$-dehydroquinolizidinium perchlorate results in the introduction of a bridgehead methyl group and the formation of 10-methylquinolizidine. The structure of this compound was proved by comparison with the isomeric methylquinolizidines, all of which have now been characterized.

Now that satisfactory diagnostic methods[2–4] exist for differentiating between an α,β-unsaturated tertiary amine and one in which the double bond is further removed from the nitrogen, we are able to proceed more effectively with an examination of various means of introducing a double bond into a saturated amine. Mercuric acetate was selected as the first reagent to be studied because fundamental knowledge concerning its dehydrogenating action was lacking, despite its occasional employment in the modification of alkaloid structures.[5] The saturated bicyclic tertiary amine, quinolizidine

(1) Presented at the 5th Summer Seminar in the Chemistry of Natural Products at the University of New Brunswick, Fredericton, N. B., Canada, August 19, 1953.

(2) Paper II in this series, N. J. Leonard and D. M. Locke, THIS JOURNAL, **77**, 437 (1955).

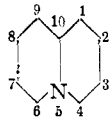
(3) R. Adams and J. E. Mahan, *ibid.*, **64**, 2588 (1942).

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

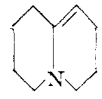
(5) *E.g.*, (a) J. Tafel, *Ber.*, **25**, 1619 (1892); (b) A. Reissert, *ibid.*, **27**, 2244 (1894); (c) J. Gadamer, *Arch. Pharm.*, **253**, 274 (1915); (d) N. V. Subba Rao and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **11A**, 23 (1940); (e) H. Legerlotz, *Arch. Pharm.*, **256**, 123 (1918); (f) J. Gadamer and H. Kollmar, *ibid.*, **261**, 153 (1923); (g) H. Dieterle and P. Dickens, *ibid.*, **264**, 257 (1926); (h) K. Winterfeld, *ibid.*, **266**, 299 (1928); (i) K. Winterfeld and C. Rauch, *ibid.*, **272**, 273 (1934); (j) L. Marion and N. J. Leonard, *Can. J. Chem.*, **29**, 355 (1951); (k) A. R. Battersby and H. T. Openshaw, *J. Chem. Soc.*, S67 (1949); (l) A. R. Battersby, H. T. Openshaw and H. C. S. Wood, *Experientia*, **5**, 114 (1949); (m) P. Karrer and O. Rüttner, *Helv. Chim. Acta*, **33**, 291 (1950); (n) R. N. Hazlett and W. E. McEwen, THIS JOURNAL, **73**, 2578 (1951); (o) H. T. Openshaw and H. C. S. Wood, *J. Chem. Soc.*, 391 (1952); (p) R. F. Tietz and W. E. McEwen, THIS JOURNAL, **75**, 4945 (1953).

(I), possessing a ring structure common to the lupin alkaloids,[6] was selected as a model substrate since the unsaturation introduced into this molecule should be readily amenable to location. Moreover, the knowledge gained with this model should be directly applicable to other tertiary amine and alkaloid systems.

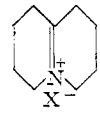
The dehydrogenation of quinolizidine, $C_9H_{17}N$, with mercuric acetate in 5% aqueous acetic acid solution proceeded smoothly at steam-bath temperature. After 1.5 hours, 92% of the mercurous acetate theoretically required for the removal of two hydrogen atoms had precipitated from the solution. A dehydroquinolizidine, $C_9H_{15}N$, was obtained in about 60% yield and was further characterized by the formation of a number of salts. The first step in determining the structure of the new $C_9H_{15}N$ compound was to ascertain that there had been no rearrangement of the bicyclic ring system during the dehydrogenation process. This was accomplished by the hydrogenation of the dehydroquinolizidine perchlorate using platinum, which gave quinolizidine in quantitative yield. The second step in the structure determination implied a decision as to whether the double bond had entered the quinolizidine molecule α,β or β,γ to the nitrogen.



I

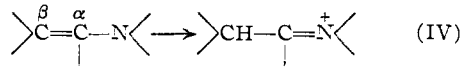


II

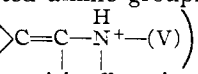
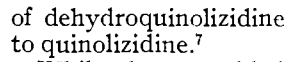


IIIa, ClO_4^-
b, I^-
c, $OC_6H_2N_3O_6^-$

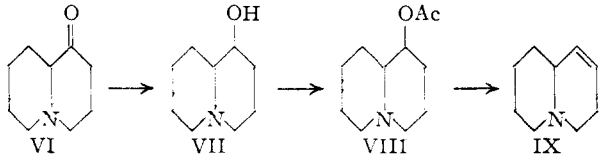
The decision was reached on the basis of data accumulated from infrared spectra, ultraviolet spectra, pK'_a and Zerewitinoff determinations. The infrared spectrum of the pure $C_9H_{15}N$ compound showed absorption at 1652 cm.$^{-1}$, while the perchlorate salt (in the mull) absorbed intensely and sharply at 1696 cm.$^{-1}$ and the hydriodide salt at 1688 cm.$^{-1}$. The shift toward higher infrared frequency in going from an unsaturated amine to its salt has been shown to be an identifying property of α,β-unsaturated amines (enamines),[4] corresponding to the structural transformation



(IV)

Supporting this conclusion was the observation that the dehydroquinolizidine is a strong base, as are α,β-unsaturated tertiary amines in general.[3] The perchlorate salt had no titratable group below pH 12 in water, and the pK'_a determined in 66% dimethylformamide was 11.1. Proof that the salt structures were those (IV) resulting from the addition of a proton to the β-carbon of the α,β-unsaturated amine grouping rather than to the nitrogen  was also obtained by a Zerewitinoff active hydrogen determination. The hydriodide salt of dehydroquinolizidine showed the absence of active hydrogen, while quinolizidine (I) hydriodide, which served as a standard, showed one active hydrogen. Further proof resulted from reduction studies with lithium aluminum hydride. This reagent had no effect upon dehydroquinolizidine (>C=C<) but reduced the perchlorate salt of dehydroquinolizidine () to quinolizidine.[7]

While the assembled evidence was overwhelmingly in favor of α,β-unsaturation in the dehydroquinolizidine produced by mercuric acetate dehydrogenation, it was considered important to prepare a β,γ-unsaturated quinolizidine for the purpose of comparison. Accordingly a synthesis of Δ^1-dehydroquinolizidine (IX) was devised, which proceeded initially by the reduction of 1-ketoquinolizidine (VI) with lithium aluminum hydride to 1-hydroxyquinolizidine (VII), followed by acetylation



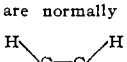
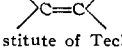
VI VII VIII IX

and pyrolysis of the 1-acetoxyquinolizidine (VIII). The Δ^1-dehydroquinolizidine hydriodide showed a weak infrared absorption band at 1660 cm.$^{-1}$, a contrast in both frequency and intensity with the infrared absorption band observed for the hydriodide of the $C_9H_{15}N$ product of mercuric acetate dehydrogenation. Moreover, the new β,γ-unsaturated amine (IX) and quinolizidine had ultraviolet absorption maxima which were identical within experimental error in both wave length and intensity, while the maximum for the mercuric acetate dehydrogenation product was displaced toward longer wave length and higher intensity.[2]

The final step in the structure determination of the $C_9H_{15}N$ compound involved a choice between the two possible α,β-unsaturated quinolizidines, $\Delta^{1(10)}$-dehydroquinolizidine and Δ^3-dehydroquinolizidine. Although a number of methods directed toward this end may be considered feasible,[8] we selected a chemical method which, in addition, provided a further illustration of nucleophilic attack on an enamine salt and served to increase our knowledge of the properties of substituted quinolizidines. The perchlorate salt of the dehydroquinolizidine was treated with methylmagnesium iodide in ether suspension, and the product which resulted from this heterogeneous Grignard reaction was a methylquinolizidine, isolated in 72% yield. Of incidental interest is the method we employed for working up the Grignard reaction mixture, since it is capable of

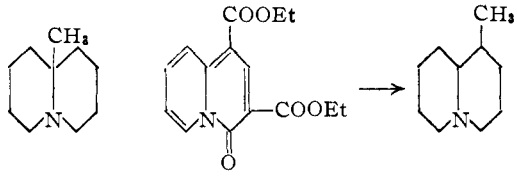
(6) N. J. Leonard, Lupin Alkaloids, Chap. 19 in R. H. F. Manske and H. L. Holmes, "The Alkaloids," Vol. III, Academic Press, Inc., New York, N. Y., 1953.

(7) The successful reduction is but one example of the nucleophilic reactions at carbon, similar to those at the carbon of a carbonyl group, which enamine salts can be expected to undergo.[4]

(8) Infrared absorption bands in the 700–850 cm.$^{-1}$ region, which are normally useful for distinguishing between  and  groupings (Dr. Arthur C. Cope, Massachusetts Institute of Technology, very kindly provided us with infrared curves for the closely related octalin isomers), do not give an unequivocal answer since the parent saturated molecule, quinolizidine, possesses three absorption bands in this region of the spectrum.

general application—at least when small quantities are employed—with other Grignard products containing a basic function. Our method made use of the insolubility of magnesium fluoride, as follows: the excess Grignard reagent was decomposed with saturated ammonium chloride solution, the aqueous layer was treated with sodium fluoride, and the precipitated magnesium fluoride was separated by centrifugation, followed by ether extraction of the basified aqueous solution.

The methylquinolizidine obtained as the Grignard product was identified as 10-methylquinolizidine (X) by a process of elimination. The properties of its derivatives were compared with those of the corresponding derivatives of each of the eight isomeric methylquinolizidines, some of which were known and some of which had to be synthesized, and the racemates separated, for direct comparison. Two picrates, m.p. 187 and 163°, corresponding to the two racemates of 1-methylquinolizidine (XII) have been reported,[9,10] but since a picrate of optically active 1-methylquinolizidine and another of "racemic" 1-methylquinolizidine containing a slight excess of the *levo* enantiomorph have been reported to melt at 185°,[11] there was some interest in checking the properties of the higher melting picrate. The lower melting picrate (163°) also has been described by Winterfeld and Holschneider.[12] Our method of synthesis of 1-methylquinolizidine was to subject 1,3-dicarbethoxy-4-quinolizone (XI) to hydrogenation at high temperature and pressure over copper chromite catalyst, taking advantage, in this process, of the preferential loss of the 3-carbethoxyl group[13] and the hydrogenolysis[14-16] of the C–O bond in the probable intermediate methylol grouping attached to the 1-position. 1-Methylquinolizidine, obtained in 68% yield, was separated into the two racemic forms by fractional distillation using a spinning band column and the picrates were formed, m.p. 192.5–193.5° and 161–162°.



X XI XII

The two racemates of 2-methylquinolizidine have not been obtained by a separation process, but independent syntheses have apparently resulted in the isolation of derivatives of each, judging not only from the melting points described for the picrates, but also from their crystal forms and from the different melting points and crystal forms of the corresponding picrolonates.[17-19] The two racemates of 4-methylquinolizidine have been separated and characterized in this Laboratory[20] and elsewhere.[21] The melting points of the picrates of these methylquinolizidine isomers are listed in Table I. To complete our information, it was necessary to obtain and characterize for the first time the two racemates of 3-methylquinolizidine (XIV). A synthesis of XIV from ethyl α-methyl-γ-(2-pyridyl)-butyrate (XIII), based upon the method which Boekelheide and Rothchild[22] used for the 3-ethyl homolog, led to the isolation of only one racemate. However, the hydrogenation–hydrogenolysis of 2-hydroxymethyl-4-(2′-pyridyl)-1-butanol (XV) in dioxane over copper chromite catalyst at high temperature and pressure produced, in addition to some 3-hydroxymethylquinolizidine,[23] a mixture of both racemates of 3-methylquinolizidine. Their separation by fractional distillation through a spinning band column completed the project of identification of each of the racemates of 1-, 2-, 3- and 4-methylquinolizidine. From the melting points of the picrates alone[24] (Table I), it can be seen that the methylquinolizidine obtained from the enamine perchlorate (above) must be the 10-isomer, with the bridgehead methyl group.

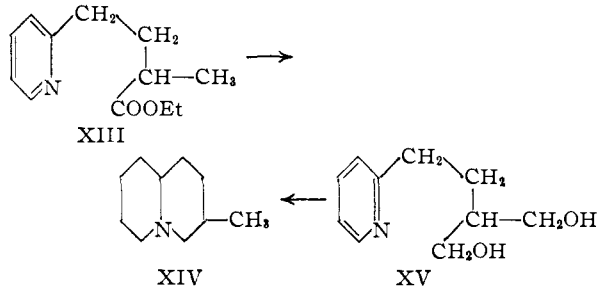


TABLE I

Methylquinolizidine	Picrate, m.p., °C.	
1-	192.5–193.5	161–162
2-	158[18]	150[19]
3-	194.5–195.5	183–184
4-	191–193[20]	182–184[20]
10-	(195)[21]	(187)[21]
	259.5–261.5	

With the point of nucleophilic attack by the Grignard anion established as the 10-position, the structure of the $C_9H_{15}N$ base obtained by the action of mercuric acetate on quinolizidine is proved to be $\Delta^{1(10)}$-dehydroquinolizidine (II), and its salts, including the perchlorate, hydriodide and picrate, must be represented by III. It should be men-

(9) Reference 6, pp. 134, 135.

(10) C. Schöpf, O. Thomä, E. Schmidt and W. Braun, *Ann.*, **465**, 97 (1928).

(11) P. Karrer and A. Vogt, *Helv. Chim. Acta*, **13**, 1073 (1930).

(12) K. Winterfeld and F. W. Holschneider, *Ber.*, **64**, 137 (1931); **66**, 1751 (1933); *Arch. Pharm.*, **273**, 315 (1935).

(13) V. Boekelheide and J. P. Lodge, Jr., THIS JOURNAL, **73**, 3681 (1951).

(14) H. Adkins, "Reaction of Hydrogen," University of Wisconsin Press, Madison, Wis., 1937, p. 88.

(15) N. J. Leonard and E. H. Burk, Jr., THIS JOURNAL, **72**, 2543 (1950).

(16) N. J. Leonard and D. L. Felley, *ibid.*, **72**, 2537 (1950).

(17) N. J. Leonard and W. C. Wildman, *ibid.*, **71**, 3089 (1949), footnote 9.

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

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

(20) N. J. Leonard and E. D. Nicolaides, THIS JOURNAL, **73**, 5210 (1951).

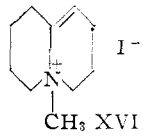
(21) R. Lukeš and F. Šorm, *Collection Czechoslov. Chem. Communs.*, **12**, 356 (1947).

(22) V. Boekelheide and S. Rothchild, THIS JOURNAL, **71**, 879 (1949).

(23) K. Winterfeld and C. Heinen, *Ann.*, **578**, 171 (1952).

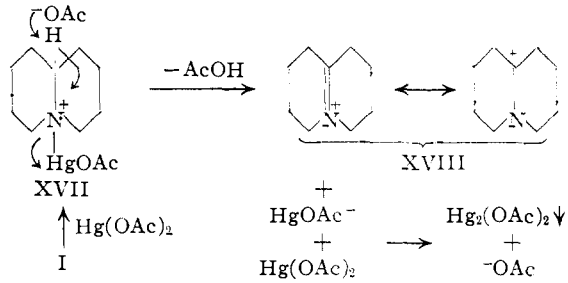
(24) Additional evidence is available from values of the refractive indices, the melting points of the picrolonates, and the infrared absorption spectra.

tioned that the salts III were reconvertible to the base II, which again yielded the same salts. In consideration of the ease of acceptance of a proton at the 1-carbon of $\Delta^{1(10)}$-dehydroquinolizidine (II), it was of interest to learn whether the methyl group of methyl iodide would become attached to the carbon, as in the known alkylations at the β-carbon of other enamines.[25] In the case of II, however, the methylation occurred on the nitrogen,[25b,f] as indicated by the fact that the product did not absorb infrared radiation appreciably in the 6 μ region, in contrast with the behavior of compounds of general type III. The product obtained by treatment of II with methyl iodide is therefore correctly designated as 5-methyl-$\Delta^{1(10)}$-dehydroquinolizidinium iodide (XVI).



XVI

The mechanism of the mercuric acetate dehydrogenation of quinolizidine (I) may be postulated as involving the initial formation of a mercurated complex through the π-electrons on the nitrogen (XVII), in analogy with the initial complex formation through the π-electrons of an olefinic linkage[26] when the reagent is used for dehydrogenation in the steroid series.[27,28] Abstraction of the proton



from the tertiary carbon could be a concerted process (XVII) with cleavage of the nitrogen–mercury bond, which process effectuates the oxidation of the amine moiety. The $HgOAc^-$ (effectively Hg) moiety in the process of separation would be expected to react simultaneously or at least very rapidly[29] with mercuric acetate to give insoluble mercurous acetate. The amine salt would remain in solution in ionized form as $\Delta^{5(10)}$-dehydroquinolizidinium acetate (XVIII), and upon ultimate basification, the abstraction of a proton from the 1-position would permit the isolation of $\Delta^{1(10)}$-dehydroquinolizidine (II).

The method of mild dehydrogenation of a tertiary amine promises to be useful generally in the introduction of α,β-unsaturation, for structure elucidation or for the modification of properties, and in the provision of interesting enamines for a study of their reactions and those of their salts.

Experimental[30]

Quinolizidine Perchlorate.—Prepared from quinolizidine[31] and perchloric acid in methanol, the salt was recrystallized from ethyl acetate–ether, as colorless flakes, m.p. 149–150°.

Anal. Calcd. for $C_9H_{18}ClNO_4$: C, 45.48; H, 6.78; N, 5.89. Found: C, 45.65; H, 7.01; N, 5.85.

In Nujol mull, the salt showed a weak absorption band at 2040 cm.$^{-1}$, a broad absorption band at about 3040 cm.$^{-1}$, and the bands typical of the perchlorate anion.[32]

Quinolizidine Hydriodide.—Prepared in the usual manner, the salt was recrystallized from ethanol, as colorless plates, m.p. 241.5–242°.

Anal. Calcd. for $C_9H_{18}IN$: C, 40.46; H, 6.79; N, 5.24; active H, 0.377. Found: C, 40.56; H, 6.85; N, 5.29; active H, 0.34.[33]

$\Delta^{5(10)}$-Dehydroquinolizidinium Perchlorate (IIIa).—To 20.0 g. (0.0628 mole) of mercuric acetate in 100 ml. of 5% aqueous acetic acid solution was added 2.18 g. (0.0157 mole) of quinolizidine, and the mixture was heated on a steam-bath for 1.5 hours. Mercurous acetate (7.48 g., or 92% of theoretical for the removal of two hydrogen atoms) was removed by filtration, and the filtrate was saturated with hydrogen sulfide to remove excess mercuric ions as black mercuric sulfide. Centrifugation gave a pale yellow supernatant which was made basic by the addition of 40% aqueous sodium hydroxide solution and extracted with ether. The combined ether extracts were dried and treated with a solution of equal parts by volume of 68% perchloric acid and ethanol until acid to congo red paper. The precipitate was recrystallized once from ethanol to give 2.20 g. (59%) of colorless plates, m.p. 227–228° dec.; further recrystallization raised the melting point to 234–235° dec.

Anal. Calcd. for $C_9H_{16}ClNO_4$: C, 45.48; H, 6.79; N, 5.89. Found: C, 45.61; H, 6.70; N, 6.17.

The compound showed no titratable group between *p*H 2 and 12 in water. In 66% dimethylformamide, the pK'_a was 11.1.[34]

In Nujol mull, the compound absorbed intensely and sharply at 1696 cm.$^{-1}$ ($>C{=}\overset{+}{N}<$) and also exhibited a band at 2025 cm.$^{-1}$. The monodispersed spectrum, obtained using a potassium bromide window, had a peak at 1685 cm.$^{-1}$. In one case, where the salt was dissolved in an aqueous solution of potassium bromide, the solution rapidly frozen and freeze dried, and the dry residue pressed into a window, absorption peaks were observed at both 1695 and 1685 cm.$^{-1}$, indicative of the superposition of crystalline and monodispersed spectra.[35]

$\Delta^{1(10)}$-Dehydroquinolizidine (II).—To a suspension of 5 g. of $\Delta^{5(10)}$-dehydroquinolizidinium perchlorate in 20 ml. of water was added 40% aqueous sodium hydroxide solution until the mixture was strongly basic. The mixture was extracted three times with ether, the combined ether ex-

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(29) N. V. Sidgwick, "The Chemical Elements and Their Compounds," Vol. I, Oxford University Press, London, England, 1950, pp. 289–291.

(30) All melting points are corrected. We are indebted to Miss Emily Davis, Mrs. Katherine Pih, Mrs. Esther Fett and Mr. Joseph Nemeth for microanalyses, and to Miss Helen Miklas and Mr. James Brader for determination of the infrared absorption spectra, using a Perkin-Elmer automatic recording infrared spectrometer, model 21.

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

(32) H. Cohn, *J. Chem. Soc.*, 4282 (1952).

(33) Zerewitinoff active hydrogen determinations by the Clark Microanalytical Laboratory, Urbana, Ill.

(34) We are indebted to Mrs. Helen Arndt and Dr. Harold E. Boaz, both of Eli Lilly and Co., Indianapolis, Ind., for the electrometric titrations and for aid in their interpretation.

(35) We are indebted to Dr. R. U. Lemieux, of the Prairie Regional Laboratory, National Research Laboratories, Saskatoon, Sask., Canada, for providing the spectra obtained by the pressed disk technique.

tracts were dried, the ether was removed and the residue was distilled under nitrogen as a colorless oil, b.p. 80° (18 mm.), which darkened rapidly on exposure to air, $n^{28}D$ 1.5116, yield 1.96 g. (68%).

Anal. Calcd. for $C_9H_{15}N$: C, 78.77; H, 11.02. Found: C, 78.59; H, 11.18.

The infrared spectrum of the pure liquid (0.0125 mm.) showed absorption at 1652 (C=C) and 3020 cm.$^{-1}$ (>C–H). Both these bands are absent from the spectrum of the saturated molecule, quinolizidine.

$\Delta^{5(10)}$-Dehydroquinolizidinium Iodide (IIIb).—To 2.24 g. of the perchlorate salt in warm ethanol was added 1.66 g. of potassium iodide dissolved in warm ethanol, and the mixture was maintained at 10° for one hour. The potassium perchlorate (1.39 g.) was removed by filtration. Evaporation of the filtrate gave fine colorless needles in quantitative yield, m.p. 273–275° after recrystallization from ethanol.

Anal. Calcd. for $C_9H_{16}IN$: C, 40.68; H, 6.07; N, 5.27. Found: C, 40.85; H, 6.15; N, 5.12.

The iodide was also prepared directly from $\Delta^{1(10)}$-dehydroquinolizidine in 90% ether–10% ethanol solution by addition of 47% hydriodic acid. In Nujol mull, the salt had an absorption band at 1688 cm.$^{-1}$. A Zerewitinoff determination at 25° and 100° showed the absence of active hydrogen.

$\Delta^{5(10)}$-Dehydroquinolizidinum Picrate (IIIc).—The picrate of $\Delta^{1(10)}$-dehydroquinolizidine, probably in the isomeric form indicated, was prepared from the base in ethanol and recrystallized from ethanol, orange-yellow needles, m.p. 108–109°.

Anal. Calcd. for $C_{15}H_{18}N_4O_7$: C, 49.18; H, 4.95; N, 15.30. Found: C, 49.28; H, 4.82; N, 15.25.

$\Delta^{1(10)}$-Dehydroquinolizidine Methiodide (XVI).—The methiodide of $\Delta^{1(10)}$-dehydroquinolizidine, prepared by treatment of the base with excess methyl iodide, separated as colorless crystals from ethanol–toluene, m.p. *ca.* 278° with decomposition.

Anal. Calcd. for $C_{10}H_{18}IN$: C, 43.04; H, 6.50; N, 5.02. Found: C, 42.74; H, 6.78; N, 4.78.

The infrared spectrum of the methiodide in Nujol mull was essentially devoid of absorption in the 6 μ region.

Reduction of $\Delta^{5(10)}$-Dehydroquinolizidinium Perchlorate. (a) **Catalytic.**—A solution of 0.60 g. of the perchlorate in 20 ml. of ethanol was hydrogenated at atmospheric pressure in the presence of Adams platinum oxide catalyst. After the catalyst was removed by filtration, concentration of the filtrate gave quinolizidine perchlorate, m.p. 149–150°, in quantitative yield, identified by direct comparison with an authentic sample (see above).

(b) **With Lithium Aluminum Hydride.**—To a slurry of 1.0 g. (0.0263 mole) of lithium aluminum hydride in 100 ml. of anhydrous ether was added 3.5 g. (0.0147 mole) of $\Delta^{5(10)}$-dehydroquinolizidinium perchlorate, and the mixture was stirred at reflux for 3 hours. The excess lithium aluminum hydride was destroyed with 40% aqueous sodium hydroxide solution, and the resulting mixture was extracted three times with ether. The ether extracts were dried and evaporated to small volume, and a saturated ethanolic solution of picric acid was added. The yellow plates obtained, m.p. 197–198°, did not depress the melting point of an authentic sample of quinolizidine picrate.[36] $\Delta^{1(10)}$-Dehydroquinolizidine was inactive toward attempted reduction with lithium aluminum hydride, and was recovered to the extent of about 70%, which is normal recovery of this compound following a basification and extraction procedure.

10-Methylquinolizidine (X).—To the Grignard reagent prepared from 6.0 g. (0.042 mole) of methyl iodide and 1.03 g. (0.042 gram atom) of magnesium in 100 ml. of anhydrous ether was added 5.0 g. (0.021 mole) of $\Delta^{5(10)}$-dehydroquinolizidinium perchlorate, and the mixture was stirred under reflux for 2 hours. After decomposition of the excess Grignard reagent with saturated ammonium chloride solution, 50 ml. of a saturated aqueous solution of sodium fluoride was added to the separated aqueous layer, and the precipitated magnesium fluoride was removed by centrifugation. The supernatant was made strongly basic with 40% aqueous sodium hydroxide solution and the basic mixture was extracted three times with ether. The ether solutions were combined and dried, the ether was removed, and the residue was distilled at 95–96° (20 mm.), $n^{28}D$ 1.4859, yield 2.30 g. (72%).

Anal. Calcd. for $C_{10}H_{19}N$: C, 78.36; H, 12.50. Found: C, 78.12; H, 12.71.

The picrate, prepared in ethanol, crystallized as yellow prisms, m.p. 259.5–261.5° dec.

Anal. Calcd. for $C_{16}H_{22}N_4O_7$: C, 50.26; H, 5.80; N, 14.65. Found: C, 50.39; H, 5.78; N, 14.92.

The picrolonate, prepared in ethanol, crystallized as yellow prisms, m.p. 244.5–245.5° dec.

Anal. Calcd. for $C_{20}H_{27}N_5O_5$: C, 57.54; H, 6.52; N, 16.78. Found: C, 57.40; H, 6.38; N, 16.52.

The hydriodide, prepared in ethanol–ether, crystallized as colorless prisms, m.p. 215–217°.

Anal. Calcd. for $C_{10}H_{20}IN$: C, 42.71; H, 7.12; N, 4.98. Found: C, 42.62; H, 7.05; N, 5.06.

1-Hydroxyquinolizidine (VII).—Reduction of 1-ketoquinolizidine (VI)[37] with lithium aluminum hydride in the usual manner gave 1-hydroxyquinolizidine,[37] b.p. 127–130° (18 mm.), in 82% yield, which solidified to colorless crystals, m.p. *ca.* 60° (reported[37] 65–68°).

The picrate crystallized from ethanol as yellow needles, m.p. 174–175°.

Anal. Calcd. for $C_{15}H_{20}N_4O_8$: C, 46.88; H, 5.25; N, 14.58. Found: C, 46.46; H, 5.37; N, 14.53.

1-Acetoxyquinolizidine (VIII).—A solution containing 12 ml. (0.127 mole) of acetic anhydride and 12 g. (0.077 mole) of 1-hydroxyquinolizidine in 100 ml. of anhydrous benzene was heated under reflux for one hour, then poured over crushed ice. Sodium carbonate was added in excess, and the product was isolated by ether extraction. The solvents were removed, and the residue was distilled at 78–79° (0.1 mm.), $n^{29}D$ 1.4790, yield 11.3 g. (75%).

Anal. Calcd. for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71. Found: C, 67.22; H, 9.92.

The picrate, formed in ethanol, was crystallized from the same solvent as yellow plates, m.p. 172–174°.

Anal. Calcd. for $C_{17}H_{22}N_4O_9$: C, 47.88; H, 5.20; N, 13.14. Found: C, 47.90; H, 5.38; N, 13.03.

The hydriodide, prepared in ethanol, separated from this solvent as colorless needles, m.p. 223–225°.

Anal. Calcd. for $C_{11}H_{20}NO_2I$: C, 40.62; H, 6.20; N, 4.31. Found: C, 40.72; H, 6.19; N, 4.06.

Pyrolysis of 1-Acetoxyquinolizidine. Δ^1-Dehydroquinolizidine (IX).—The pyrolysis was carried out at about 535° but otherwise as described for 1-ethyl-4-acetoxypiperidine,[4] and the isolation procedure was similar. The product boiled at 75–76° (20 mm.), $n^{28}D$ 1.4917, conversion 31%.

The picrate of Δ^1-dehydroquinolizidine crystallized from ethanol as yellow needles, m.p. 178–179°.

Anal. Calcd. for $C_{15}H_{18}N_4O_7$: C, 49.18; H, 4.95; N, 15.30. Found: C, 49.42; H, 4.95; N, 15.01.

The hydriodide crystallized from ethanol–ether as colorless elongated prisms, m.p. 209–210°.

Anal. Calcd. for $C_9H_{16}IN$: C, 40.68; H, 6.07; N, 5.27. Found: C, 40.50; H, 6.17; N, 5.28.

In the mull, the salt showed a weak infrared absorption band at 1660 cm.$^{-1}$ (C=C).

3-Hydroxyquinolizidine.—Reduction of 3-ketoquinolizidine[38] with lithium aluminum hydride in ether gave 3-hydroxyquinolizidine, b.p. 128° (14 mm.), as a colorless liquid in 89% yield.

Anal. Calcd. for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.35; H, 10.99; N, 8.85.

The picrate crystallized from ethanol as yellow prisms, m.p. 161.5–162.5°.

Anal. Calcd. for $C_{15}H_{20}N_4O_8$: C, 46.88; H, 5.25; N, 14.58. Found: C, 46.92; H, 5.50; N, 14.51.

The hydriodide crystallized from ethanol as colorless plates, m.p. 214–215°.

Anal. Calcd. for $C_9H_{18}INO$: C, 38.17; H, 6.40; N, 4.95. Found: C, 38.39; H, 6.58; N, 5.04.

3-Methylquinolizidine (XIV).—2-Hydroxymethyl-4-(2′-pyridyl)-1-butanol (XV) was obtained in 67% yield by the

(36) N. J. Leonard and W. C. Wildman, THIS JOURNAL, **71**, 3100 (1949).

(37) G. R. Clemo and G. R. Ramage, *J. Chem. Soc.*, 437 (1931).

(38) N. J. Leonard and S. H. Pines, THIS JOURNAL, **72**, 4931 (1950).

Winterfeld and Heinen[23] modification of the lithium aluminum hydride reduction[22] of diethyl β-(2-pyridyl)-ethylmalonate.[31,39] A solution of 92 g. (0.51 mole) of the aminodialcohol in 250 ml. of purified dioxane was hydrogenated over 30 g. of copper chromite catalyst at 260° and 300 atm. during 6 hours. The solution was filtered and the filtrate was distilled slowly through a packed column at water-pump pressure. Two fractions were collected after solvent removal: b.p. 80–100° (22 mm.) and 135–155° (12–16 mm.). Refractionation gave 13.4 g. (0.087 mole) of 3-methylquinolizidine, b.p. 75–80° (14 mm.). The higher boiling fraction, b.p. 90–95° (2 mm.), proved to be 3-hydroxymethylquinolizidine,[23] 38.8 g. (0.238 mole).

Separation of the Racemates of 3-Methylquinolizidine.—Thirteen grams of 3-methylquinolizidine was distilled slowly through a spinning band column of 26 theoretical plates, fitted with a total condensation, variable take-off distillation head. The pressure was maintained at 14 mm. by means of a manostat, and a reflux ratio of about 10:1 was employed. Cuts of distillate were taken regularly throughout the distillation. The over-all distillation range was 6° (74.5–80.5° (14 mm.)), $n^{20}D$ 1.4776 to 1.4731: A racemate, b.p. 77.5° (14 mm.), $n^{20}D$ 1.4757 (15%); B racemate, b.p. 80.5–81° (14 mm.), $n^{20}D$ 1.4738 (85%).

Anal. Calcd. for $C_{10}H_{19}N$: C, 78.36; H, 12.50; N, 9.14. Found for A: C, 77.96; H, 12.22; N, 9.50; for B: C, 78.41; H, 12.25; N, 9.36.

Picrates were made from the two fractions and recrystallized from ethanol: A picrate, yellow plates, m.p. 194.5–195.5°; B picrate, yellow elongated prisms, m.p. 183–184°.

Anal. Calcd. for $C_{16}H_{22}N_4O_7$: C, 50.25; H, 5.80; N, 14.61. Found for A: C, 50.42; H, 5.69; N, 14.43; for B: C, 50.37; H, 5.71; N, 14.39.

Picrolonates of the two fractions were prepared in and recrystallized from ethanol: A picrolonate, yellow prisms, m.p. 248–250° dec.; B picrolonate, yellow elongated prisms, m.p. 208–209° dec.

Anal. Calcd. for $C_{20}H_{27}N_5O_5$: C, 57.54; H, 6.52; N, 16.78. Found for A: C, 57.48; H, 6.63; N, 16.53; for B: C, 57.59; H, 6.85; N, 16.69.

(39) W. E. Doering and Ruth A. N. Weil, THIS JOURNAL, **69**, 2461 (1947)

Ethyl α-Methyl-γ-(2-pyridyl)-butyrate (XIII).—The addition of diethyl methylmalonate to 2-vinylpyridine in the presence of sodium ethoxide and ethanol, led, as in the case of the ethyl homolog,[22] to a decarbethoxylated product. A 77% yield of ethyl α-methyl-γ-(2-pyridyl)-butyrate was realized, b.p. 111° (2 mm.), $n^{20}D$ 1.4868.

Anal. Calcd. for $C_{12}H_{17}NO_2$: C, 69.53; H, 8.27; N, 6.76. Found: C, 69.78; H, 8.38; N, 7.00.

3-Methylquinolizidine.—A solution of 150 g. (0.75 mole) of ethyl α-methyl-γ-(2-pyridyl)-butyrate in 270 ml. of purified dioxane was hydrogenated over 22 g. of copper chromite catalyst at 260° and 300 atm. The solution was filtered, the solvent removed and the residue fractionated yielding 66.5 g. (58%) of 3-methylquinolizidine, b.p. 82° (15.5 mm.). The entire product was distilled through a spinning band column, and there was no appreciable change in the refractive index, $n^{20}D$ 1.4738, through the 23 fractions taken. (The 1-ml. forerun and the pot residue had slightly higher indices.) **The picrate** was prepared in and recrystallized from ethanol as yellow elongated prisms, m.p. 182–183°, no depression in melting point on mixture with B picrate (above).

1-Methylquinolizidine (XII).—A solution of 85 g. (0.29 mole) of 1,3-dicarbethoxy-4-quinolizone (XI)[13] in 400 ml. of purified dioxane was hydrogenated at 260° and 340 atm. over 22 g. of copper chromite catalyst. The product was isolated by distillation, b.p. 75–77° (11 mm.), yield 68%.

Separation of the Racemates of 1-Methylquinolizidine.—Sixteen grams of 1-methylquinolizidine was distilled slowly through a spinning band column, as for the separation of the 3-isomers. The over-all distillation range was 10° (79–89° (13 mm.)); $n^{20}D$ 1.4728–1.4758.

Picrate A was made from the fraction boiling at 79–81.5° (13 mm.), $n^{20}D$ 1.4740, and was recrystallized from ethanol as small yellow platelets, m.p. 192.5–193.5°. **Picrate B** was made from the fraction boiling at 85–87° (13 mm.), $n^{20}D$ 1.4757, and recrystallized from ethanol as small 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, 50.52; H, 5.72; N, 14.50; for B: C, 50.27; H, 6.12; N, 14.47.

The racemate with the higher refractive index made up about 75% of the total 1-methylquinolizidine.

URBANA, ILLINOIS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTHERN CALIFORNIA]

Studies on Dihydropyridines. I. The Preparation of Unsymmetrical 4-Aryl-1,4-dihydropyridines by the Hantzsch–Beyer Synthesis[1]

BY JEROME A. BERSON AND EARLENE BROWN

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The preparation of some 2'-substituted 4-aryl-1,4-dihydropyridines is described. A consideration of spectra and chemical properties leads to the conclusion that the products of the Hantzsch synthesis arise from "normal" condensation.

In connection with other studies,[2] we have had occasion to prepare a number of dihydropyridines of the types I, II, III and IV.

The classical Hantzsch synthesis[3] of dihydropyridines, involving the condensation of an aldehyde, ammonia and acetoacetic ester or other 1,3-dicarbonyl compound, was modified by Beyer[4] and later by Knoevenagel[5] to allow the preparation of unsymmetrical 1,4-dihydropyridines by condensation of an alkylidene or arylidene 1,3-dicarbonyl compound with a β-amino-α,β-unsaturated carbonyl compound, *e.g.*,[5] ethyl β-aminocrotonate heated with benzylidene acetylacetone gave ethyl 2,6-dimethyl-4-phenyl-5-acetyl-1,4-dihydropyridine-3-carboxylate (IIIa). The present study is concerned with the preparation of some unsymmetrical 4-aryl-1,4-dihydropyridines (in which the 4-aryl group bears an ortho substituent) by these methods and with a consideration of the structures of the products formed.

The Structure of the Products of the Hantzsch–Beyer Synthesis.—In the simplest case, condensation of formaldehyde, ammonia and ethyl acetoacetate leads to 2,6-dimethyl-3,5-dicarbethoxy-1,4-

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(2) J. A. Berson and E. Brown, THIS JOURNAL, **77**, 447, 450 (1955).

(3) A. Hantzsch, *Ber.*, **17**, 1515 (1884); **18**, 1774, 2579 (1885).

(4) C. Beyer, *ibid.*, **24**, 1662 (1891).

(5) E. Knoevenagel and W. Ruschhaupt, *ibid.*, **31**, 1025 (1898).