(R_f 0.51, probably a keto acid). The ketonic impurities were removed by treatment with Girard's reagent and the product was crystallized from petroleum ether to yield tricycloekasantalic acid, m.p. and m.m.p. 76°; infrared bands at 3058, 2667, 1704, 1408, 946, 878, 855, and 821 cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.00; H, 9.50.

The alcohol (XV) also yielded tricycloekasantalic acid (XVII), when oxidized with permanganate as described.

The Prins Reaction on α-Santalene (XIV) under Thermal Conditions.—α-Santalene (22.4 g., 0.11 mole) was refluxed with paraformaldehyde (3.49 g., 0.11 mole) and glacial acetic acid (350 ml.) for 26 hr. Acetic acid was distilled, the residue was diluted and repeatedly extracted with ether, washed with sodium carbonate and water, and dried (Na_2SO_4). Removal of solvent yielded the unsaturated acetate (22.81 g.), which was saponified by refluxing with alcoholic potassium hydroxide (300 ml., 0.5 *N*) for 2 hr. to yield the crude product (20.56 g.). On fractionation using a spinning band column, the earlier fractions (4.17 g.) were found to consist of a β-santalene-type hydrocarbon from physical properties, elemental analysis, and infrared spectrum. The intermediate fractions (10.54 g.) consisted of the alcohol XIX. The last fractions contained mostly diols.

The alcohol XIX is a colorless liquid having a sandalwood odor, b.p. 150–155° (bath) at 1 mm., $[\alpha]^{27}D$ −11.92° (*c* 11.11), $n^{28}D$ 1.5036; infrared bands at 3333, 3050, 1631, 1037, 885, and 877 cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 81.56; H, 11.10.

A sample of the alcohol purified by phthalization had identical properties.

It absorbed 1.93 moles of hydrogen on catalytic hydrogenation in presence of Adams catalyst in glacial acetic acid.

The Prins Reaction on β-Santalene (XVIII) under Thermal Conditions.—β-Santalene (10.7 g., 0.05 mole) was refluxed with paraformaldehyde (1.84 g., 0.06 mole) and glacial acetic acid (100 ml.) for 24 hr., and the product was worked up as in the case of α-santalene to yield the acetate ester (11 g.). This was saponified by alcoholic potassium hydroxide (140 ml., 0.5 *N*), and the product was fractionated using a spinning band column to remove unchanged β-santalene (2.74 g.) and higher boiling diols (1.52 g., b.p. 140–156° at 3 mm.). The alcohol (XIX, 4.07 g.) was further purified by chromatography on neutral alumina (100 g., grade II) when a colorless, viscous liquid having a sandalwood odor was obtained, b.p. 140–150° (bath) at 2 mm., $[\alpha]^{28}D$ −17.58° (*c* 9.98), $n^{30}D$ 1.5045. Its infrared spectrum was identical with that of the alcohol obtained from α-santalene by thermal reaction.

Anal. Calcd. for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 81.62; H, 11.14.

Quantitative hydrogenation showed the presence of two double bonds.

Ozonolysis of Alcohol XIX.—The alcohol (2.70 g.) was ozonized in chloroform (25 ml.) at 0° to completion (6 hr.). After removal of solvent, the ozonide was decomposed with water (35 ml.). The volatile portion gave the dimedone derivative of formaldehyde, m.p. and m.m.p. 189°. The nonvolatile portion (XX, 1.56 g.), after being extracted with sodium bicarbonate, distilled at 170–190° (bath) at 0.4 mm.; infrared bands at 3521, 1724, and 1045 (NaCl prism), and 1732 and 1709 cm.$^{-1}$ (CaF_2 prism).

Anal. Calcd. for $C_{14}H_{22}O_3$: C, 70.55; H, 9.31. Found: C, 72.60; H, 10.34.

A better analysis could not be obtained.

Oxidation of the Keto Alcohol (XX) by Sodium Dichromate–Sulfuric Acid.—The keto alcohol (1 g.) was oxidized with sodium dichromate (1.53 g.) and sulfuric acid (1.11 ml.) in aqueous medium as described before. The reaction mixture was steam distilled; the distillate contained acetic acid (R_f 0.19), identified by paper chromatography. Work-up of the residue yielded an acid mixture which contained mainly camphenilonylacetic acid (R_f 0.51), small proportions of norcampholidylacetic acid (XXII, R_f 0.41), and acetic acid (R_f 0.19). Genuine samples of acids XXI and XXII for comparison were obtained by ozonizing bicycloekasantalic acid in acetic acid.[6]

Oxidation of the Keto Alcohol (XX) by Chromic Acid.—The keto alcohol (1 g.), when oxidized with acetic acid (10 ml.), chromic anhydride (0.98 g.) in water (1 ml.), and glacial acetic acid (10 ml.) according to the procedure described earlier, yielded the acid XXI (0.25 g.) identified by paper chromatography; methyl ester (diazomethane), b.p. 130–140° (bath) at 0.6 mm., infrared bands at 1748 cm.$^{-1}$.

Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.62; H, 9.13.

Acknowledgment.—The authors are grateful to Mr. H. Gopinath for the infrared spectra, Mr. V. S. Pansare and colleagues for the microanalyses, Dr. S. Kanthamani and Dr. G. Lakshmi Kumari for paper chromatography, and Dr. V. G. Naik for the v.p.c. analysis. One of the authors (S. R.) gratefully acknowledges a Junior Research Fellowship awarded to her by the Council of Scientific and Industrial Research, Government of India, during the period of this work.

Azabicyclic Alcohols. I. Stereochemistry of the Hydroxyquinolizidines[1]

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Each of the 1-, 2-, and 3-hydroxyquinolizidine racemates has been synthesized and characterized. Configurational and conformational assignments have been made on the basis of infrared and n.m.r. spectra, gas–liquid chromatographic retention data, and chemical evidence. In all cases a *trans*-quinolizidine ring fusion is shown to exist. In the case of the 1- and 3-hydroxyquinolizidines, intramolecular hydrogen bonding occurs between the bridgehead nitrogen and an axial β-hydroxyl group.

Although the quinolizidine ring system (I) occurs in many natural products,[2] the simple hydroxyquinolizidines are not known to exist in nature. In the 1-, 2-, and 3-hydroxyquinolizidines, two epimeric racemates are possible, depending upon the configuration of the hydroxyl group relative to that of the bridgehead (C-10) hydrogen. For each epimer both a *cis* and a *trans* ring fusion are possible, and interconversion between the two forms can occur by inversion of the electron pair on the bridgehead nitrogen. Previous studies of these compounds have been reviewed.[3,4] Only recently, however, have the two epimers of the 1- and 2-hydroxyquinolizidines been characterized and configurational assignments given.[5,6] Complete

(1) Presented in part at the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963.

(2) N. J. Leonard, "The Alkaloids," Vol. III, R. H. F. Manske and H. L. Holmes, Ed., Academic Press, New York, N. Y., 1953, p. 120.

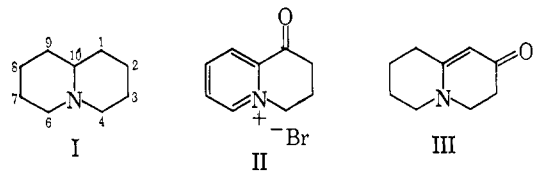
(3) W. L. Mosby, "Heterocyclic Systems With Bridgehead Nitrogen Atoms," Part Two, Interscience Publishers, Inc., New York, N. Y., 1961, p. 1001.

(4) R. E. Counsell and T. O. Soine, *J. Am. Pharm. Assoc.*, **49**, 289 (1960).

(5) G. A. Swan, *J. Chem. Soc.*, 2051 (1958).

(6) F. Bohlmann, E. Winterfeldt, O. Schmidt, and W. Reusche, *Chem. Ber.*, **94**, 1767 (1961).

conformational assignments have been made only in the 2-hydroxy series.[6] In this paper, we discuss configurational and conformational assignments and the correlations which have been made as a result of our studies of the 1-, 2-, and 3-hydroxyquinolizidines. A following paper[7] will discuss reduction studies of the corresponding ketones. Succeeding papers will deal with systematic studies of other azabicyclic alcohol systems.



I II III

Results and Discussion

Reductions of 1-, 2-, and 3-ketoquinolizidine give mixtures of the corresponding amino alcohol racemates.[7] In each system the epimers were readily separated by gas–liquid chromatography (g.l.c.) and designated A and B according to the order in which they were eluted from a Carbowax column. Retention times of these epimers and the corresponding ketones are given in Table I. In the case of the 1- and 3-hydroxyquinolizidines, the A-racemates show retention times which are significantly shorter than that of the corresponding *ketones*. Since the relative retention times of the alcohols presumably are dependent upon hydrogen bonding with the Carbowax substrate, this result suggests that intramolecular hydrogen bonding[8] between the nitrogen atom and hydroxyl group exists in epimer A of the 1- and 3-hydroxyquinolizidines.[9] Stereomodels reveal that this bonding is possible only when the β-hydroxy group is in an axial conformation.

TABLE I

G.L.C. AND pK_a DATA FOR KETO- AND HYDROXYQUINOLIZIDINES

Quinolizidine derivative	M.p., °C.	Retention time,[a] min.	pK_a[b]
1-Keto		5.7	8.06
1-Hydroxy, epimer A (VII)	80–81	4.9	10.20
1-Hydroxy, epimer B (VIII)	71–72	8.5	8.73
2-Keto		6.4	8.08
2-Hydroxy, epimer A (XI)	103–104	8.6	9.53
2-Hydroxy, epimer B (XII)	88–89	9.6	9.20
3-Keto		6.9	8.3[c]
3-Hydroxy, epimer A (IX)	23–25	4.7	9.87
3-Hydroxy, epimer B (X)	65–66	10.2	8.60

[a] Measured from air peak on a 10 ft. × 0.25 in. column of Carbowax 20 M (15%) on Gas-Chrom P support at 210° and 120 ml./min. (He). [b] 0.0050 ionic strength (μ) unless otherwise indicated. [c] 0.04 ionic strength. Estimated to be pK_a = 8.2 at 0.005 μ.

Intramolecular hydrogen bonding is not possible for either of the 2-hydroxyquinolizidine epimers with the piperidinol ring in a chair conformation, and accordingly, no anomaly is observed in the g.l.c. retention times in this system.

Infrared spectral analysis clearly corroborates the conclusions suggested by the g.l.c. results. The pertinent spectral data are summarized in Table II.

TABLE II

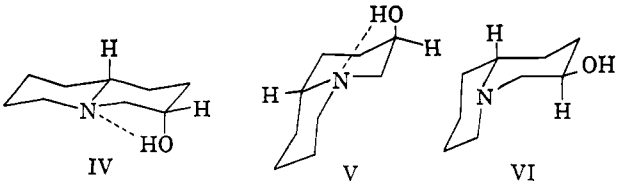
INFRARED SPECTRAL DATA[a] FOR HYDROXYQUINOLIZIDINES

Hydroxyquinolizidine, epimer	Free OH	Bonded OH, Intra	Bonded OH, Inter	Bohlmann bands
1-OH, A		3526		2800, 2777
1-OH, B	3618		3100–3400	2795, 2750
2-OH, A	3625		3100–3400	2802, 2764
2-OH, B	3620		3100–3500	2801, 2762
3-OH, A		3527		2797, 2757
3-OH, B	3609		3100–3500	2800, 2762

[a] Absorption maxima are given in cm.$^{-1}$ for the 1- and 3-hydroxy epimers in dilute carbon disulfide solution, for the 2-hydroxy epimers in dilute carbon tetrachloride solution.

In dilute carbon disulfide solution, the A-epimers of 1- and 3-hydroxyquinolizidine show no detectable absorption in the free OH stretching region ($\tilde{\nu}$ >3600 cm.$^{-1}$). In the bonded OH stretching region, however, each shows a single band whose intensity and position are unaffected by further dilution. This result is typical of intramolecularly N···HO bonded systems.[10] The B-epimers of 1- and 3-hydroxyquinolizidine and both of the 2-hydroxy epimers show the characteristically sharp free OH band above 3600 cm.$^{-1}$ and a broad hydrogen-bonded OH band in the 3100–3500 cm.$^{-1}$ region. Further dilution results in a decrease in the relative intensity of the bonded band, accompanied by a corresponding increase in that of the free OH band. In every case, the broad band was completely eliminated at high dilution. These results are typical of intermolecularly N···HO bonded systems[10]

1- and 3-Hydroxyquinolizidines.—If one assumes only all-chair ring conformations to be important,[11] one *trans* (*e.g.*, IV) and two *cis* ring conformers (*e.g.*, V and VI) need to be considered for these systems. However, *cis* ring conformation VI may be excluded on



IV V VI

the grounds that intramolecular hydrogen bonding would not be possible for either epimer in this conformation. Intramolecularly bonded conformations IV and V, however, are of opposite configuration (*cis*-3,10-H and *trans*-3,10-H, respectively). Therefore, the fact that only one of the two epimers in both the 1-

(7) C. P. Rader, G. E. Wicks, Jr., R. L. Young, Jr., and H. S. Aaron, *J. Org. Chem.*, **29**, 2252 (1964).

(8) G.l.c. has been shown [C. H. DePuy and P. R. Story, *Tetrahedron Letters*, **No. 6**, 20 (1959)] to be useful in the detection of intramolecular hydrogen bonding between a hydroxyl group and a carbon–carbon double bond. The effect of intramolecular hydrogen bonding on relative retention times of the epimeric normuscarines has been noted (C. H. Eugster in "Advances in Organic Chemistry," Vol. II, R. A. Raphael, E. C. Taylor, and H. Wynberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1960, p. 450), though not in comparison to that of their carbonyl analogs.

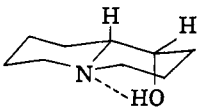
(9) Intramolecular hydrogen bonding has been shown to occur in the structurally related 3-hydroxypiperidine; *cf.* (a) G. Hite, E. E. Smissman, and R. West, *J. Am. Chem. Soc.*, **82**, 1207 (1960); (b) J. Sicher and M. Tichý, *Tetrahedron Letters*, **No. 12**, 6 (1959), and references cited therein.

(10) A. R. H. Cole in "Technique of Organic Chemistry," Vol. XI (Part 1), A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, Chapter 3.

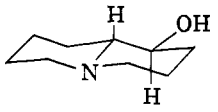
(11) Boat conformations may be excluded on the basis of unfavorable steric interactions; see E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p. 204, *et seq.*

and 3-hydroxy systems shows intramolecular hydrogen bonding, and correspondingly, no free OH absorption, establishes that the stereochemistry of the ring fusion must be the same within the respective epimeric pairs, and that the possible equilibrium between the *cis* and *trans* ring fusions in these systems must lie so far to one side as to be undetectable by infrared methods.

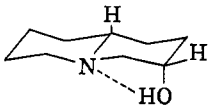
In order to make a configurational assignment for the 1- and 3-hydroxyquinolizidines, therefore, the stereochemistry of the ring fusion must be determined. Here, the empirical correlation of Bohlmann[12] may be applied. Thus, it has been shown that for quinolizidines, one or more prominent infrared bands in the 2700–2800 cm.$^{-1}$ region is indicative of a *trans* ring fusion. As summarized in Table II, all six of the hydroxyquinolizidines show these characteristic absorptions. This correlation was previously used[6] to assign the *trans* ring fusion to the 2-hydroxyquinolizidine epimers. On this basis, therefore, the configurations and prevailing conformations of the epimeric 1- and 3-hydroxyquinolizidines may be assigned as VII, VIII and IX, X, respectively.



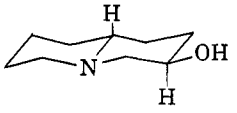
epimer A
VII



epimer B
VIII



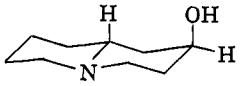
epimer A
IX



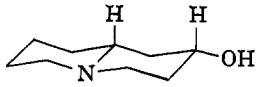
epimer B
X

The configurations of the 1-hydroxyquinolizidines previously have been assigned[5] on the basis that the catalytic reduction of 1-keto-1,2,3,4-tetrahydroquinolizinium bromide (II) gives a single 1-hydroxyquinolizidine, m.p. 80–81°, logically assigned the *cis*-1,10-hydrogen configuration. The epimeric amino alcohol, therefore, was assigned[5] the *trans*-1,10-hydrogen configuration. The fact that we have shown intramolecular hydrogen bonding for the *cis*-1,10-hydrogen epimer and the absence of such bonding for the *trans*-1,10-hydrogen epimer constitutes an independent verification of the Bohlmann correlation for both epimers. Similar chemical verification does not exist for the 3-hydroxy system.

2-Hydroxyquinolizidines.—The conformations of the 2-hydroxy epimers as previously assigned[6] are given by XI and XII. That these epimers possess an axial



epimer A
XI



epimer B
XII

and equatorial hydroxyl group, respectively, has also been established[13] by analysis of the shape of their free O–H stretching bands. This result independently establishes the *trans* ring fusion for this system, therefore, since a *cis* ring fusion should permit each epimer to assume a predominant equatorial conformation for the respective hydroxyl groups. The fact that we find the equatorial alcohol (XII) to have a slightly longer g.l.c. retention time than its epimer on the Carbowax column (Table I) is in accord with this assignment and with the g.l.c. retention times reported for axial *vs.* equatorial hydroxy decalols[14] and steroids.[15] This assignment is also in accord with a correlation by which the position of the free O–H stretching absorption (Table II) of an axial hydroxyl group has been shown[10,16] to occur at a slightly higher frequency (5–10 cm.$^{-1}$) than that of its equatorial epimer. The possibility that a significant population (>2%) of the boat conformation exists in the 2-hydroxy epimers may be dismissed on the grounds that both 2-hydroxyquinolizidines show no infrared spectral evidence of intramolecular hydrogen bonding (Table II).

Independent evidence that epimer B has a *cis*-2,10-hydrogen configuration may be obtained from the catalytic reduction of $\Delta^{1,10}$-2-ketoquinolizidine (III). Reduction of 2-ketoquinolizidine on 5% ruthenium on carbon in ethanol gives a 60:40 B–A ratio, while reduction of III under the same conditions produces an 87:13 B–A ratio.[7] Assuming that the preponderance of hydrogen adds from the same side of the molecule[17] in the $\Delta^{1,10}$-system, one concludes that the increase in the percentage of B represents an increase in that epimer which has the *cis*-2,10-hydrogen configuration.

The conformational assignments of the 1-, 2-, and 3-hydroxyquinolizidines as given above are in agreement with the theory that alkali metal–alcohol reductions of six-membered ring ketones give a preponderance (>80% in these systems[7]) of the more stable equatorial hydroxyl epimer (B) in each case.[18] The effect of intramolecular hydrogen bonding upon this equilibrium as reported[19] in the 2-tropinol system was not studied here. Our results correspond to those reported[20] for the lupinine–epilupinine system.

N.m r. Correlations.—N.m.r. spectra of the hydroxyquinolizidine racemates were examined, and the pertinent data are summarized in Table III. The sharp hydroxyl and broader carbinol proton peaks may be readily identified, since their chemical shifts place them clearly apart from the other protons. In each system, the carbinol proton of the B-epimer absorbs at a higher field and has a greater band width (W_H) than its corresponding A-epimer. Both theory[21] and accumulated n.m.r. evidence[22] have shown that an axial carbinol proton should have a greater degree of spin–spin coupling with vicinal protons and thus give a broader peak than its equatorial counterpart. The band-width data summarized in Table III, there-

(12) (a) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958); (b) E. Wenkert and D. K. Roychaudhuri, *J. Am. Chem. Soc.*, **78**, 6417 (1956).

(13) H. S. Aaron and C. P. Rader, *ibid.*, **85**, 3046 (1963).

(14) W. Hückel, D. Maucher, O. Fechtig, J. Kurz, M. Heinzel, and A. Hubele, *Ann.*, **645**, 115 (1961).

(15) W. J. A. Vandenheuvel and E. C. Horning, *Biochim. Biophys. Acta*, **64**, 416 (1962).

(16) A. R. H. Cole, P. R. Jefferies, and G. T. A. Müller, *J. Chem. Soc.*, 1222 (1959), and preceding papers in this series.

(17) R. L. Burwell, *Chem. Rev.*, **57**, 895 (1957).

(18) In strained or hindered carbonyl ring systems, the less stable epimer may be obtained; *cf.*, ref. 28. The hydroxyquinolizidines, however, clearly do not fall in this category.

(19) M. R. Bell and S. Archer, *J. Am. Chem. Soc.*, **82**, 4642 (1960).

(20) N. J. Leonard, "The Alkaloids," Vol. VII, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1960, p. 264.

(21) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

(22) E. W. Garbisch, Jr., *J. Org. Chem.*, **27**, 4249 (1962), and references cited therein.

TABLE III

N.M.R. SPECTRAL DATA[a] FOR HYDROXYQUINOLIZIDINES

Quinolizidine	—Carbinol proton— τ	—Carbinol proton— W_H[b] (c.p.s.)	—CH_2— protons not —adjacent to N— τ[c]	—CH_2— protons not —adjacent to N— W_H[b] (c.p.s.)
Unsubstituted			8.49	30
1-OH, epimer A	6.62	7.5	8.38	34
1-OH, epimer B	6.87	16	8.40	28
2-OH, epimer A	6.02	7	8.50	23
2-OH, epimer B[d]	6.53	23	8.35	30
3-OH, epimer A	6.26	6.5	8.49	20
3-OH, epimer B	6.38	19	8.41	24
Piperidine			8.53	7.0

[a] Obtained for 10% carbon tetrachloride solutions using tetramethylsilane as internal standard. [b] W_H = band width at one-half of the peak height. [c] Center of broad band due to these protons. [d] 20% solution.

fore, indicate that racemates A and B possess equatorial and axial carbinol hydrogens, respectively, in agreement with the conformational assignments made on the basis of the infrared and g.l.c. data. Moreover, the relative positions of the carbinol hydrogen bands of the two epimers, when compared with correlations[23] of chemical shifts of carbinol protons, also agree with these conformational assignments.

Unfortunately, we are unable to make a ring fusion assignment based upon the analysis of these n.m.r. spectra. The fact that a broad band is observed for the methylene hydrogens not adjacent to nitrogen cannot be used to assign a *trans* ring fusion (by analogy to the results reported[24] for the *cis* and *trans* decalin systems), because infrared data have shown that these *substituted* quinolizidine systems are conformationally stable regardless of the type of ring fusion. Thus, the fact that *unsubstituted* quinolizidine shows a broad band for the hydrogens not adjacent to nitrogen (Table III) is indicative of a conformationally stable *trans* ring junction (previously assigned[12a] from infrared data), since conformationally mobile piperidine shows a narrow band for these hydrogens (Table III). That the band-width criterion was not applicable to the methylquinolizidines[25] is undoubtedly due to the fact that these compounds are conformationally stable, and not to the differences in the chemical shifts of the ring protons not adjacent to nitrogen as has been suggested.[25b]

pK_a Correlations.—Relative pK_a values of the hydroxyquinolizidines are given in Table I. It should be noted that the intramolecularly bonded 1- and 3-hydroxy racemates (A) are markedly more basic than their corresponding (B) epimers (ΔpK_a of 1.5 and 1.3 units, respectively). A similar relationship has been noted in other systems[26] in which only one epimer shows intramolecular hydrogen bonding. The ΔpK_a value (0.3 units) for the nonintramolecularly bonded 2-hydroxy epimers corresponds to that (0.5 units) reported[27] for the conformationally related, non-intramolecularly bonded[28,29] tropine–pseudotropine system. It is our intention to discuss more fully at a later date the relative basicity of these and related epimeric amino alcohols.

Experimental

All melting points are corrected. Picrate and hydrobromide derivatives were customarily prepared in ether (occasionally in ethanol) and recrystallized from the indicated solvent. The pK_a data were obtained from the half-neutralization point of the titration curve using 0.050 *N* acid and a Beckman Model H-2 pH meter which had been standardized near the pK_a point with commercial buffer solutions. The amine sample was dissolved in sufficient water such that the ionic strength (μ) at the pK_a point would be 0.0050.

The solutions for the n.m.r. spectra were prepared from spectral grade carbon tetrachloride taken directly from the bottle. For 1-hydroxyquinolizidine epimer A, however, freshly distilled solvent was used, and here the hydroxyl and carbinol protons were found to split each other (J = 10.5 c.p.s.). Addition of deuterium oxide resulted in a merging of the carbinol proton multiplets and a disappearance of the hydroxyl proton peak. All proton magnetic resonance spectra were obtained with a Varian Model A-60 spectrometer using Varian precision 5-mm. sample tubes.

A Perkin-Elmer Model 421 dual-grating spectrophotometer was used in all infrared studies. A slit program of 1000 × 1 was used with a scan rate of 110 cm.$^{-1}$/min. The positions of all spectral band maxima should be accurate within ±2 cm.$^{-1}$. Reagent grade solvents were used without further purification.

Ketoquinolizidines.—1-Ketoquinolizidine was synthesized[30] by slight modifications of known[4] procedures. Diethyl piperidyl-1-γ-butyrate-2-carboxylate,[31] b.p. 117–119° (0.65 mm.), single peak (10 min.) on 15% Carbowax 20 M g.l.c. column (5 ft.) at 228° (60 ml./min., He), obtained in 72% yield from undistilled ethyl pipecolate, was cyclized using potassium *t*-butoxide in a Dieckmann condensation to give a 76% yield of 1-ketoquinolizidine, b.p. 106° (13 mm.), $n^{20}D$ 1.4935; lit.[31] b.p. 104° (12 mm.), $n^{20}D$ 1.4935.

The 2- and 3-ketoquinolizidines were synthesized by Regis Chemical Co. under a U. S. Army Chemical Research and Development Contract. 2-Ketoquinolizidine had b.p. 64–69° (1 mm.), $n^{26}D$ 1.4920, picrate m.p. 209–210° (aqueous ethanol); lit.[32] b.p. 70° (1 mm.), picrate m.p. 211°, 209–210°.[33] 3-Ketoquinolizidine had b.p. 65° (0.6 mm.), $n^{22}D$ 1.4930, picrate m.p. 179° (acetone); lit.[34] b.p. 62–63° (0.65 mm.), $n^{20}D$ 1.4926, picrate m.p. 180–182°, 181°.[4] The ketoquinolizidines described above all gave single peaks by g.l.c. analysis (Table I).

Hydroxyquinolizidines.—These were obtained by reduction[7] of the corresponding ketoquinolizidines. Small samples of the pure epimers were isolated by g.l.c. (*cf.* Table I). Larger samples of the 2-hydroxy racemates were chromatographed on Woelm alumina (neutral, activity grade IV) as previously described[6] to give epimer A, m.p. 103–104° (petroleum ether, b.p. 30–55°), lit.[6] m.p. 103–104°, picrate m.p. 189–190° (acetone); and epimer B, m.p. 88–89° (petroleum ether), lit.[6] m.p. 88–89°, picrate m.p. 168–169° (acetone).[35]

The 1-hydroxyquinolizidines (*ca.* 2.5 g.) were chromatographed in ether on grade IV Woelm alumina (300 g.). Each was then recrystallized from petroleum ether to give epimer A, 0.25 g., m.p. 80–80.5°, lit.[5] m.p. 80°, picrate m.p. 156–157° (95% ethanol), lit.[5] m.p. 152–153°, hydrobromide m.p. 231–232° (ace

(23) It has been established that an axial carbinol proton will absorb at a higher field than its equatorial counterpart. See (a) E. L. Eliel, M. H. Gianni, T. H. Williams, and J. B. Stothers, *Tetrahedron Letters*, **No. 17**, 741 (1962); (b) J. I. Musher, *J. Chem. Phys.*, **35**, 1159 (1961).

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tone–ethanol), lit.[5] m.p. 232–233°; and epimer B, 1.0 g., m.p. 71–72°, lit.[5] m.p. 72°, picrate[36] m.p. 174–176° (95% ethanol), hydrobromide m.p. 242–244° (acetone), lit.[5] m.p. 243–244°. Unexpectedly, epimer B was the first eluted from the alumina column in this series. A mixed middle fraction was also obtained.

The 3-hydroxyquinolizidines were isolated by distillation. Thus, 8.0 g. of 3-ketoquinolizidine in 25 ml. of absolute ethanol was completely reduced in 1.5 hr. over 2.0 g. of 5% ruthenium on carbon (Engelhard Industries, Inc.) at 70 p.s.i.g. and 28° in a Parr hydrogenation apparatus. The catalyst was filtered off and the solvent was removed under reduced pressure to give a 76:24 A–B ratio (g.l.c. analysis). Distillation gave fraction 1, 4.0 g. (>98% A), b.p. 51° (0.25 mm.), $n^{28}D$ 1.4930; and fraction 2, 2.8 g. (65% A), b.p. 51–72° (0.25 mm.). Fraction 1 solidified in the freezer to give epimer A, m.p. 23–25°.

Anal. Calcd. for $C_9H_{17}NO$: C, 69.63; H, 11.04; O, 10.31; equiv. wt., 155.2. Found: C, 69.8; H, 11.0; O, 10.6; equiv. wt., 156.

The picrate of A was prepared in ether and gave m.p. 115–117°. Attempts to recrystallize this picrate led to material which melted lower and over a wider range. The hydrobromide gave m.p. 206–208° (acetone).

Anal. Calcd. for $C_9H_{18}BrNO$: C, 45.77; H, 7.68. Found: C, 45.7; H, 7.7.

3-Hydroxyquinolizidine, epimer B, was obtained by reduction of 5.0 g. of 3-ketoquinolizidine in 25 ml. of absolute ethanol over 1.0 g. of 10% palladium-on-carbon catalyst (A. D. Mackay and Co.) at 70 p.s.i.g. of hydrogen and 25°. Reduction was completed in 1 hr. The catalyst was filtered off, and the solvent was removed under reduced pressure to give a 3:97 A–B product ratio (g.l.c. analysis). Distillation (78–81°, 0.25 mm.) gave fraction 1, 0.4 g. (94% B); fraction 2, 1.2 g. (97% B); and fraction 3, 2.6 g. (99% B). On standing in the freezer, fraction 3 crystallized to give epimer B, m.p. 59–62°, which upon recrystallization from petroleum ether melted at 65–66°.

Anal. Calcd. for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02; equiv. wt., 155.2. Found: C, 69.6; H, 11.0; N, 9.1; equiv. wt., 153.

The hydrobromide of B gave m.p. 239–240.5° (acetone–methanol, 2:1).

Anal. Calcd. for $C_9H_{18}BrNO$: C, 45.77; H, 7.68. Found: C, 45.5; H, 7.8.

The picrate of B gave m.p. 161.5–162° upon precipitation from ether.[38]

Acknowledgment.—Some of the infrared spectral data were obtained by Mr. R. Piffath; the elemental analyses were carried out by the Microanalytical Laboratory of the Chemical Research Division of these laboratories.

(36) Picrate m.p. 174–175°[37] and 175.5–176.5°[4] have been obtained from products now known[7] to have been about 84:16 B–A.

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(38) A picrate, m.p. 161.5–162.5°, has been obtained[4,37] by recrystallization of the product from a mixture now known[7] to have been about 85:15 B–A.

Azabicyclic Alcohols. II. Chemical and Catalytic Reduction of the Ketoquinolizidines[1]

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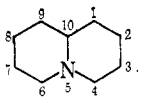
Catalytic hydrogenations of 1-, 2-, and 3-ketoquinolizidine have been studied on platinum oxide, rhodium, ruthenium, and palladium. Epimeric racemates of the corresponding hydroxyquinolizidines have been obtained in proportions which vary with the nature of the catalyst and acidity of the reducing medium. On platinum oxide and rhodium some hydrogenolysis of the carbon–oxygen bond occurs. The unprotonated bridgehead nitrogen atom appears to influence the stereochemistry of the hydrogenations by virtue of its ability to bond with the surface and thus produce an "anchor effect." Alkali metal–ethanol and metal hydride reductions of these ketones give a predominance of the equatorial hydroxyl epimer in all cases.

The addition of hydrogen to a cyclic ketone is capable of providing a convenient method of stereoselective synthesis. It also provides a direct insight into the stereochemistry and mechanism governing the attack of the carbonyl group by various reducing agents. The structural elucidation of the 1-, 2-, and 3-hydroxyquinolizidine racemates (1)[2] has permitted a systematic stereochemical study of the chemical and catalytic reduction of the corresponding ketones.

The general theory of the stereochemistry of catalytic hydrogenation has been summarized by Burwell.[3] In an extended series of investigations,[4] each of the four possible decalone racemates has been reduced catalytically on platinum and by chemical methods. The stereochemical data for the chemical reduction



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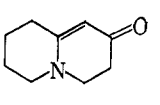

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of various substituted cyclohexanones has recently been reviewed.[5]

The basic purpose of this research was to determine the extent by which the stereoselectivity of the addition of hydrogen to an azabicyclic ketone would vary as a function of substrate, reducing agent, catalyst, conditions, *etc.* In several previous investigations of this general type, appreciable confusion has arisen in the determination of the relative amounts of stereoisomers resulting from the reduction *per se*. The recent development of gas–liquid chromatography (g.l.c.) has provided a most convenient and reliable method for the analysis of reduction mixtures.[6]

(1) Presented in part at the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963.

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