Azabicyclic Alcohols. IV. Stereochemistry of the 1- and 2-Hydroxyindolizidine and Hydroxypyrrolizidine Systems[1a]

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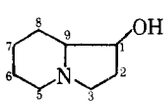
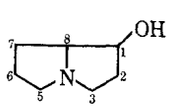
The epimers of the 1- and 2-hydroxyindolizidines and the 1- and 2-hydroxypyrrolizidines have been synthesized and characterized. Stereochemical assignments have been given. The results agree with previous assignments of *trans* and *cis* ring fusions, respectively, for these two systems. A weak intramolecular hydrogen bond is observed in the *cis*-1,9-H-1-hydroxyindolizidine, the *cis*-2,9-H-2-hydroxyindolizidine, and the *trans*-2,8-H-2-hydroxypyrrolizidine isomers.

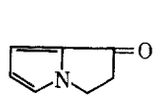
In a continuing study of azabicyclic alcohols,[2] we have investigated the 1- and 2-hydroxyindolizidines (I) and pyrrolizidines (II). None of these alcohols has been found in nature, although the latter are closely related to the well-known necine bases of the pyrrolizidine alkaloids.[3] In each of these four systems, two epimeric racemates are possible, depending upon the configuration of the hydroxyl relative to the bridgehead hydrogen. Prior to this study, only for 1-hydroxyindolizidine were both epimers known and stereochemical assignments given.[4] These assignments, however, were not unequivocal. Of the 2-hydroxyindolizidines, the picrate of one epimer had been reported;[5,6] its configuration was not assigned. A picrate also was reported[5] for the second epimer, but this result is shown below to have been an incorrect characterization. Of the 1-hydroxypyrrolizidines, only one of the epimers was known.[7] Its stereochemistry, however, is shown below to have been incorrectly assigned. Neither of the 2-hydroxypyrrolizidines was known.



I



II



III

Results

Hydroxyindolizidines.—Reductions of the 1- and 2-oxoindolizidines by a variety of catalytic and chemical methods, as summarized in the Experimental Section, gave mixtures of the corresponding epimeric alcohols, designated A and B according to their order of elution from the gas chromatograph. Preparative quantities of the individual isomers were obtained from these mixtures either by fractional distillation or by column chromatography. Infrared and other pertinent physical data for each of these isomers and their corresponding ketones are summarized in Table I. The infrared spectral data were obtained using 0.004–0.005 *M* carbon tetrachloride solutions. At these concentrations, the intermolecular hydrogen bonding was eliminated; the resulting O–H stretching absorptions represent either free or intramolecularly bonded hydroxyl groups.

Hydroxypyrrolizidines.—The synthesis of an epimer of 1-hydroxypyrrolizidine by hydrogenation of 1-oxo-3H-1,2-dihydropyrrolo[1,2-*a*]pyrrole (III) has been described.[7] However, distilled product thus prepared was found (glpc) to consist of a 90–10% mixture of the two epimers (A and B). Enriched (93%) epimer A was obtained as the forerun of a redistillation of this mixture. Epimer B was obtained by oxidative epimerization of epimer A; the equilibrium was shifted exclusively in favor of the B epimer. Catalytic and chemical reductions of 1-oxopyrrolizidine were also carried out, as summarized in the Experimental Section. With the exception of ruthenium on carbon in ethanol, which gave an 85–15% A–B mixture, all of the catalytic hydrogenations produced racemate A, essentially epimerically pure.

The epimers of 2-hydroxypyrrolizidine were obtained from the known 2-oxopyrrolizidine. Interestingly, this study has found that the neat ketone, on standing at room temperature, undergoes a rapid autocatalyzed aldol condensation to form a crystalline dimer, mp 110–112°. Proof of the structure and stereochemistry of this product will be the subject of a future report. Dimer formation was prevented, however, when monomeric ketone was synthesized and handled as its hydrochloride salt. Catalytic reduction of this hydrochloride gave pure 2-hydroxypyrrolizidine epimer B. Oxidative epimerization of epimer B gave a 60–40% A–B mixture, from which epimer A was obtained by fractional distillation. By increasing the reaction time, the equilibrium could be shifted almost exclusively in favor of epimer A. However, undesired side reactions led to a reduction in the total yield of epimer A, when the reaction was allowed to run for more than 5 days. Pertinent physical data for the hydroxypyrrolizidines and their corresponding ketones are summarized in Table II.

Discussion

Stereochemical assignments in these systems may be made on the basis of the above results. In addition, the data serve to define the stereochemical features of pyrrolidinol, when incorporated into a bridgehead nitrogen system by fusion to a six- and a five-membered ring, respectively.

Hydroxyindolizidines.—The preceding paper[2] in this series has shown that the Bohlmann correlation,[8]

(1) (a) Presented in part at the 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965. (b) Monsanto Co., St. Louis, Mo.

(2) Paper III: C. P. Rader, R. L. Young, Jr., and H. S. Aaron, *J. Org. Chem.*, **30**, 1536 (1965).

(3) N. J. Leonard, "The Alkaloids," Vol. VI, R. H. F. Manske, Ed., Academic Press Inc., New York, N. Y., 1960, Chapter 3.

(4) V. Carelli, F. Liberatore, and F. Morlacchi, *Ann. Chim.* (Rome), **51**, 467 (1961).

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

(6) M. J. Martell, Jr., and T. O. Soine, *J. Pharm. Sci.*, **52**, 331 (1963).

(7) R. Adams, S. Miyano, and D. Fles, *J. Am. Chem. Soc.*, **82**, 1466 (1960).

(8) F. Bohlmann, *Chem. Ber.*, **91**, 2157 (1958).

TABLE I

PHYSICAL DATA FOR 1- AND 2-OXO- AND HYDROXYINDOLIZIDINES

Indolizidine compd	Picrate mp, °C[a]	Glpc retention time, min[b]	pK_a[c]	Infrared data,[d] $\tilde{\nu}_{max}$, cm^{-1} OH region	Infrared data,[d] $\tilde{\nu}_{max}$, cm^{-1} Bohlmann region	Nmr data, carbinol proton,[e] τ	Nmr data, carbinol proton,[e] W, cps[f]
1-Oxo	173–174	3.0	6.48		2790, 2732		
1-OH, A (IV)	178–180	3.7	9.69	3623, 3580	2790, 2750, 2725	6.10	11.5
1-OH, B (V)	159–160	5.4	8.58	3632[g]	2795, 2730	6.25	21
2-Oxo	204	3.0	6.24				
2-OH, A (VI)	188–189	4.4	9.15	3624, 3594	2785, 2720	5.90	17
2-OH, B (VII)	177–178	5.8	8.82	3626	2790, 2720	5.75	14

[a] Obtained in this study. [b] Measured from air peak on 5 ft × 0.25 in. column of Carbowax 20 M (15%) on 60–80 Gas-Chrom P at 200° and 60 cc/min (He). [c] Ionic strength at pK_a point, 0.0050. [d] Dilute (0.004–0.005 M) carbon tetrachloride solutions in 1- or 2-cm quartz cells, Perkin-Elmer Model 521 spectrophotometer. [e] Carbon tetrachloride solution, Varian A-60 spectrometer. [f] Band width at one-half peak height. [g] Also has a shoulder at 3609 cm^{-1}.

TABLE II

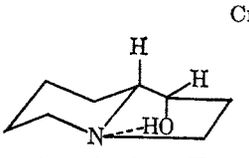
PHYSICAL DATA FOR 1- AND 2-OXO- AND HYDROXYPYRROLIZIDINES

Pyrrolizidine compd	Picrate mp, °C	Glpc retention time, min[a]	Infrared bands[b] in OH region	pK_a[c]
1-Oxo	176.5–179	3.9		
1-OH, A (XI)	243–245	5.9	3630	10.35
1-OH, B (XII)	186–187	7.0	3626[d]	10.25
2-Oxo	185	3.7		8.00
2-OH, A (XIII)	170–71	5.5	3625, 3590[e]	10.42
2-OH, B (XIV)	215–217	6.1	3630	10.25

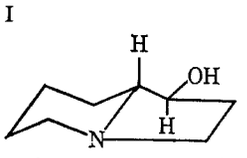
[a] Measured from injection time on a 10 ft × 0.25 in. column of 15% Carbowax 20 M on 60–80 Gas-Chrom P at 120-cc/min He flow rate. Column temperature of 1-substituted system, 212°; 2-substituted system, 219°. [b] Dilute (<0.005 M) carbon tetrachloride solution in 1-cm quartz cell, Perkin-Elmer 221 or 521 (grating) spectrophotometer. [c] Ionic strength at pK_a point, 0.0050. [d] Also has a shoulder at 3610 cm^{-1}. [e] These bands appear as twin peaks of near equal intensity, recorded on a Perkin-Elmer 237B (grating) spectrophotometer.

originally deduced for quinolizidine systems, is also applicable for stereochemical assignment of the ring fusion of indolizidine systems. Thus, from the facts (Table I) that (1) the alcohols all show characteristically strong infrared absorption bands in the Bohlmann region (2700–2800 cm^{-1}), (2) the A epimers show both a free and a weak intramolecular bonded O–H stretching band, and (3) the B epimers show only a free O–H stretching band, we make the structural assignments seen in Chart I.

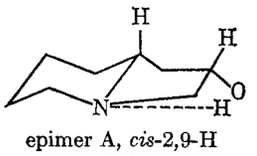
CHART I



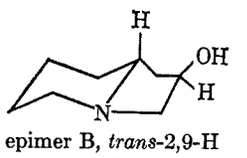
epimer A, *cis*-1,9-H



epimer B, *trans*-1,9-H
V



epimer A, *cis*-2,9-H
VI



epimer B, *trans*-2,9-H
VII

The presence of an appreciable quantity of a *cis*-fused indolizidine in equilibrium with the *trans*-fused conformation would also result in the appearance of both a free and a bonded O–H stretching band. However, the assignment of the *trans* ring fusion is in agreement with the results obtained from the 7- and 8-hydroxyindolizidines,[2] and with calculations based upon a conformational analysis of quinolizidine and indolizidine systems.[9] Thus, in the 8-hydroxyindolizidines, none of the *cis*-fused form could be detected, in spite of the driving force of a relatively strong ($\Delta\tilde{\nu}$ ~105 cm^{-1})[10] intramolecular bonded OH···N system which would be formed. Accordingly, the small free OH absorption at 3623–3624 cm^{-1} in the two A epimers of the 1- and 2-hydroxy systems (IV and VI) is ascribed to rotational conformations of the hydroxyl group, which can arise by the breaking of a relatively weak ($\Delta\tilde{\nu}$ 43 and 30 cm^{-1}, respectively) intramolecular OH···N bond. The absence of intramolecular hydrogen bond formation in the spectra of V and VII agrees with this conclusion. The 3609-cm^{-1} shoulder observed for V is probably due to a rotational conformation[11] of the free O–H group, the $\tilde{\nu}_{max}$ of which is shifted more prominently than usual. The stereochemically related 1-hydroxyquinolizidine epimer B, which is also adjacent to a ring-fused position, has a similar free O–H shoulder (3613 cm^{-1}), as does 1-hydroxypyrrolizidine epimer B (Table II).

The measured intramolecular N···HO distances of 2.7 and 3.0 A for IV and VI, respectively, indicate that these systems are approaching the limit across which hydrogen bonding can occur.[12] These measurements are in agreement with the weak intramolecular bonds observed, and with the slightly stronger bond observed in IV as compared to VI. While not quantitatively determined, the area of the free OH band appears to be slightly larger in VI than in IV, indicating the percentage of free hydroxyl groups is larger in the more weakly bonded compound. In both cases, however, the area of the free OH band is small in comparison to that of the bonded band.

The 1-hydroxyindolizidines were previously obtained from a synthesis in which ethyl β-oxo-β-(2-pyridyl)propionate was reduced to ethyl β-hydroxy-β-(2-piperidyl)propionate (VIII), then thermally cyclized to a 9:1 epimer mixture of 1-hydroxy-3-oxoindolizidine (IX).[4] The latter were separated and reduced to the desired alcohols, the stereochemical

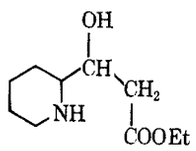
(9) H. S. Aaron, *Chem. Ind.* (London), 1338 (1965).

(10) This value is taken from the intramolecular-bonded epimer, because the geometry of the OH···N system should be very similar when both isomers are in a bonded conformation.

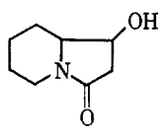
(11) H. S. Aaron and C. P. Rader, *J. Am. Chem. Soc.*, **85**, 3046 (1963).

(12) Drieding stereomodels were used. The formation of the intramolecular hydrogen bond could shorten these distances, somewhat. These values compare with the 2.4 A measured for the strongly intramolecular-bonded 8-hydroxyindolizidine epimer A.

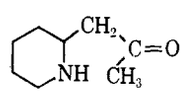
assignments of which were the same as are made from the present study. Apart from some tenuous supporting arguments, however, the earlier assignments were based upon the assumption that the isomer ratio obtained by the cyclization of VIII to IX is subject to thermodynamic control. Actually, this ratio was determined by the isomer ratio already present in VIII, as obtained by hydrogenation of the pyridyl ester. Such systems (VIII) are not known to be subject to thermal equilibration. From the results, a 9:1 ratio of *erythro*:*threo* VIII must have been obtained, a result that is not predictable from current theory.



VIII



IX

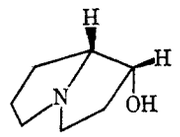


X

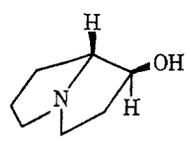
The Clemmensen reduction of 2-oxoindolizidine has been reported to give an epimer of 2-hydroxyindolizidine, characterized as a picrate (mp 133°) and a picrolonate (174°).[5] The melting points of the 2-hydroxyindolizidine picrates (Table I), however, suggest that the above report is in error. Clemmensen reduction of β-ketoamines are now known to produce rearrangement products. As suggested,[6] the most likely product to be expected from this reduction would be isopelletierine (X), which is isomeric with 2-hydroxyindolizidine. We have reexamined this reduction with the aid of glpc and obtained isopelletierine and, surprisingly, 2-hydroxyindolizidine epimer A as the major products. However, the literature procedure,[5] which reports a steam distillation, ether extraction, and vacuum distillation, undoubtedly lost the major portion of the less volatile, water-soluble alcohol, and resulted in the isolation of isopelletierine as an impure picrate, mp 133° (lit.[13] mp 147–148°). The melting point of their picrolonate agrees perfectly with that which we have obtained from isopelletierine. The authentic epimer VI forms a picrolonate, mp 205°.

Hydroxypyrrolizidines.—Here, as with the indolizidines and quinolizidines, an interconversion between *cis*- and *trans*-fused ring conformations can occur. Previous investigators, in consideration of relative bond angle strains, have concluded that the pyrrolizidines exist[14] and react[15] in the *cis*-fused form. Under unusual conditions, however, such as intramolecular lactonization, the system can be forced over into a *trans*-fused configuration.[16] The results of the present study are in agreement with these views. Thus, in the oxopyrrolizidines, the *cis* ring fusion results in a nonplanar system, the adsorption of which upon a catalyst surface should be sterically restricted to the side that is *cis* to the bridgehead (C_8) hydrogen. Catalytic hydrogenation of these ketones should produce the *cis*-1,8-H and *cis*-2,8-H alcohols, respectively. Such is indeed the case, as shown both by the stereospecificity of the hydrogenation reactions and the stereochemistry of each product, as established below.

1-Hydroxypyrrolizidines.—The fact that racemate A can be epimerized into racemate B permits the configurations of these two alcohols to be assigned as XI and XII, respectively. From stereomodels, it may



epimer A, *cis*-1,8-H
XI

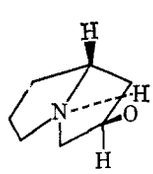


epimer B, *trans*-1,8-H
XII

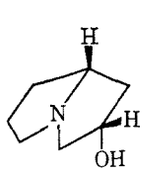
be readily seen that the driving force for the epimerization is the relief of the nonbonded interaction of the hydroxyl group with the C_7 hydrogen in XI. Neither of the 1-hydroxypyrrolizidines shows any firm evidence of intramolecular hydrogen bond formation, although it is possible that the shoulder at 3610 cm^{-1} on the free OH band of epimer B (XII) may be due to an extremely weak intramolecular N···HO interaction. However, this result is more probably due to a rotational conformation[11] of the free OH group, similar to that noted above for V. By comparison, 3-pyrrolidinol shows a single sharp free OH band (3625 cm^{-1}), but with a broadening (down to about 3540 cm^{-1}) on the low-frequency side very near to its base. The assignment of this apparent shoulder is also uncertain. However, comparison to the shape of the shoulder observed for XII suggests that the broadening in the pyrrolidinol case may be due to some weak intramolecular hydrogen bond formation.

The erroneous assignment[7] of the *trans*-1,8-H configuration to epimer A, the product of the catalytic hydrogenation of III, was based upon an assumption that the thermodynamically more stable isomer was obtained from this reaction. As shown above, however, the predominant product is that formed by the *cis* addition of hydrogen to positions 1 and 8 of the unsaturated system.

2-Hydroxypyrrolizidines.—The fact that only the A epimer shows an intramolecular N···HO bond (Table II) permits its configuration and that of its B epimer to be assigned as XIII and XIV, respectively. The



epimer A, *trans*-2,8-H
XIII



epimer B, *cis*-2,8-H
XIV

free OH band (Table II) of XIII is due to the two rotational conformations of the hydroxyl group, which, as in IV and VI, can arise by the breaking of a relatively weak ($\Delta\tilde{\nu}$ 35 cm^{-1}) intramolecular OH···N bond. Unlike the case of the epimeric 1-hydroxypyrrolizidines, examination of the stereomodels reveals no apparent difference in the relative stability of the 2-hydroxy epimers due to nonbonded interactions. Here, however, the weak intramolecular hydrogen bond apparently provided the driving force for the epimerization of XIV to XIII, when the reaction

(13) J. van Noordwijk, J. J. Mellink, B. J. Visser, and J. H. Wisse, *Rec. Trav. Chim.*, **82**, 763 (1963).

(14) *E.g.*, N. J. Leonard and D. L. Felley, *J. Am. Chem. Soc.*, **72**, 2537 (1950); R. Adams and B. L. Van Duuren, *ibid.*, **76**, 6379 (1954).

(15) W. L. Meyer and N. Sapianchiay, *ibid.*, **86**, 3343 (1964).

(16) G. Fodor, F. Uresch, F. Dutka, and T. Széll, *Collection Czech. Chem. Commun.*, **29**, 274 (1964).

was run in dilute solution in a relatively nonpolar medium. The result is analogous to that obtained in the 2-tropinol system,[17] although the conditions used were modified in the present case, because of the very weak character of the XIII intramolecular bond, compared with that of 2β-tropanol.

Other Physical Correlations.—The nmr correlation based upon the position and half-band width of carbinol protons which has been used for conformational assignments of cyclohexanols[18] would not be expected to apply to a five-membered ring system. However, in the 1-hydroxy- (but not the 2-hydroxy-) indolizidines, examination of stereomodels and the data (Table I) suggest that IV and V contain a pseudo-equatorial and pseudo-axial carbinol hydrogen, respectively.

Each intramolecularly bonded alcohol has a shorter glpc retention time (see tables) than its nonbonded epimer. This bond is too weak to reduce the retention time below that of the corresponding ketone, however, as was observed for more strongly bonded alcohols in related systems.[2,19]

The relative basicities of the epimeric alcohols correspond to that expected from the assigned structures.[2,19] A more detailed discussion of basicity correlations of these and related epimers we defer to a future publication.

Experimental Section

Procedures and instrumentation used were the same as previously reported,[19,20] unless otherwise indicated. The petroleum ether was bp 30–60°. The oxoindolizidines and the oxopyrrolizidines all gave single peaks upon glpc analysis. Additional physical data for the compounds reported here are given in Tables I and II.

1-Oxoindolizidine was prepared from ethyl pipecolate, essentially as described.[21] The latter was obtained by hydrogenation of an aqueous solution of ethyl picolinate hydrochloride, mp 145–146.5°, over platinum dioxide in a Parr hydrogenator. The ethyl picolinate hydrochloride was prepared in ether; it was best recrystallized from acetone and a little methanol before reduction. Apparently, its melting point has not been reported previously. 1-Oxoindolizidine has a carbonyl absorption at 1754 cm^{-1} (CCl_4).

2-Oxoindolizidine was synthesized[22] from 2-pyridylacetic acid hydrochloride (Aldrich Chemical Co.) essentially as described.[6] The product had a carbonyl absorption at 1759 cm^{-1} (CCl_4 or neat). Its picrate melted at 204° (lit.[5,6] 187 and 189°) from methanol, unchanged on recrystallization from water.

Anal. Calcd for $C_{14}H_{16}N_4O_8$: C, 45.66; H, 4.38. Found: C, 45.7; H, 4.4.

Oxoindolizidine Reductions.—The ketones were reduced and the products assayed by glpc according to procedures previously described.[20] Thus, catalytic hydrogenations of 1-oxoindolizidine in ethanol and in aqueous hydrochloric acid media, respectively, gave the following percentages of epimer A (IV) in an A–B mixture (where %B = 100 − A): platinum dioxide, 69, 35; 5% rhodium on carbon, 64, 84; 5% ruthenium on carbon, 78, 84; 10% palladium on carbon, 68, 90. Similarly, hydrogenations of 2-oxoindolizidine on these same catalysts gave the following percentages of epimer A (VI): Pt, 79, 80; Rh, 65, 79; Ru, 73, 76; Pd, 60, 59. Chemical reductions of 1- and 2- oxoindolizidine gave A–B mixtures containing the following percentages of the A epimers (IV and VI, respectively): sodium in ethanol–benzene, 18, 64; potassium in ethanol–benzene, 11, 69; sodium borohydride in water, 19, 69; lithium aluminum hydride in ether, 33, 56.

1-Hydroxyindolizidine, Epimer A (IV).—About 14 g of an 85–15% A–B mixture of 1-hydroxyindolizidines was fractionated at 3 mm using an 8-in. spinning-band column (Nester-Faust). The first six fractions (after a small forerun) were combined and simply distilled through a 2-in. Claisen head to give 5 g of epimer A as a colorless oil (>99% epimerically pure), bp 72° (1.8 mm), $n^{25}D$ 1.4996. The compound solidified on standing in the freezer (−20°) and melted at 20–23°. It formed a picrate, mp 178–180° (lit.[4,23] 174–176 and 176–178°).

1-Hydroxyindolizidine, Epimer B (V).—1-Oxoindolizidine (12 g) was reduced with potassium–ethanol in benzene according to a previously reported procedure.[20] The crude product was distilled to give 4.6 g of a 9–91% A–B mixture as a pale yellow oil, bp 67–69° (0.2 mm), $n^{26}D$ 1.4943; picrate, mp 159–160° (lit.[4] 156–157°), from ethanol–petroleum ether.

A 1.5-g sample similarly obtained from another run was chromatographed on 250 g of grade III Woelm neutral alumina and eluted with 1:1 ether–petroleum ether, then ether. The ether fractions were evaporated and the residue was vacuum distilled to give 0.5 g. of V, 94% epimerically pure, which was used for infrared spectral examination. The 6% epimer A impurity was too small to be detected in the dilute solution spectrum, being obscured by the tail of the low-frequency OH shoulder of epimer B.

2-Hydroxyindolizidines.—A mixture of the 2-hydroxyindolizidines (5 g, 60–40% A–B) was dissolved in petroleum ether and chromatographed on 50 g of grade IV neutral Woelm alumina using ether–petroleum ether (1:1) and then ether as the eluents. Fractions of 75–100 ml were collected. Fractions 1–4 were combined and evaporated to yield 1.7 g of epimer A.; fractions 10–18 yielded 0.8 g of epimer B. The 1.7 g of epimer A was combined with 3.0 g obtained from another run and was distilled to give 4.3 g of colorless oil (VI), bp 77° (2 mm), $n^{29}D$ 1.4942, which crystallized in the freezer to a white solid, mp 31–32°, and which formed a picrolonate, mp 204–205° (ethanol).

Anal. Calcd for $C_{18}H_{23}N_5O_6$: C, 53.33; H, 5.72. Found: C, 52.9; H, 5.7.

Epimer A formed a picrate, mp 188–189° (ethanol).

Anal. Calcd for $C_{14}H_{18}N_4O_8$: C, 45.41; H, 4.90. Found: C, 45.8; H, 5.1.

Epimer B, above, was distilled to yield 0.6 g of colorless oil (VII), bp 88° (2 mm), $n^{29}D$ 1.4965, which crystallized in the freezer to a white solid, mp 23–26°. Its picrate melted at 177–178° (lit.[5,6] 175–176°, isolated from mixed A–B products now known to have contained about 65–70% epimer B).

Clemmensen Reduction of 2-Oxoindolizidine.—The procedure of Clemo and Metcalfe[5] was followed, except the product was not steam distilled. Rather, it was taken up in chloroform, concentrated, and examined by glpc on a 10 ft × 0.25 in. column of Carbowax 20 M (15%) on 60–80 Gas-Chrom P at 200° and 120 cc/min. The following components were observed at the indicated retention times (minutes): indolizidine (1.5), probably (see below) one or more dehydroindolizidines (1.7), two very minor unidentified components (3.6 and 4.3), isopelletierine (5.6), 2-hydroxyindolizidine epimer A (7.1), 1-(2-piperidyl)-propan-2-ol (7.5), and 2-hydroxyindolizidine epimer B (9.2). The latter two components were present in very minor amounts. The five compounds cited above were identified by glpc comparison of the reduction mixture admixed with the authentic materials. In addition, samples of the two major components, isopelletierine (X) and 2-hydroxyindolizidine epimer A (VI), were collected from the glpc and identified by infrared spectral comparison with authentic material. The isopelletierine thus collected formed a picrate, mp 143–145° (unrecrystallized) (lit.[13] 147–148°); the 2-hydroxyindolizidine epimer A thus collected formed a picrate, mp 184–185° (unrecrystallized) (*cf.* Table I). The 1.7-min peak was assumed to be a dehydroindolizidine, since it almost completely disappeared when a portion of the total reduction mixture was hydrogenated over platinum dioxide in ethanol. The hydrogenation also resulted in the disappearance of the isopelletierine, accompanied by an increase in the 1-(2-piperidyl)propan-2-ol content. The latter is undoubtedly

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(21) N. J. Leonard, S. Swann, Jr., and J. Figueras, *J. Am. Chem. Soc.*, **74**, 4620 (1952).

(22) Synthesized by Mr. Charles Feit and co-workers, Regis Chemical Co., Chicago, Ill., under a U. S. Army Research and Development Contract.

(23) L. H. Sternbach and S. Kaiser, *J. Am. Chem. Soc.*, **74**, 2215 (1952).

present as a (±)-sedridine–isosedridine mixture.[24] We were not able to separate an authentic mixture of these two isomers on our glpc column. The isopelletierine was prepared by oxidation of 0.5 g of a sedridine–isosedridine mixture in 50 ml of acetone with 2 ml of 8 *N* chromic acid. The product formed a picrolonate, mp 173–174° (ethanol–ether).

1-Oxopyrrolizidine Reductions.—This ketone was synthesized[22] essentially as described.[25] Its carbonyl group absorbs at 1750 cm^{-1} (CCl_4, Perkin-Elmer 237B spectrophotometer). It had $n^{21}D$ 1.4846 (lit.[25] $n^{20}D$ 1.4884) and formed[22] a picrate, mp 176.5–179° (ethanol) (lit.[7,25,26] 175–178, 162–164, and 172.5–173.5°).

Anal. Calcd for $C_{13}H_{14}N_4O_8$: C, 44.07; H, 3.98; N, 15.82. Found: C, 44.29; H, 4.26; N, 15.83.

Catalytic hydrogenations were carried out using platinum dioxide and the supported palladium, rhodium, and ruthenium catalysts indicated above, both in ethanol and in aqueous hydrochloric acid. With the exception of ruthenium on carbon in ethanol, which gave an 85–15% A–B mixture, all produced racemate A, essentially epimerically pure. From chemical reductions, the following percentages of epimer A (in an A–B mixture) were obtained: potassium in ethanol and benzene, 10; sodium in ethanol and benzene, 20; sodium borohydride in water, 60; lithium aluminum hydride, 60. In all of the hydrogenations and reductions, small amounts of lower boiling contaminants were also observed. The alkali metal–ethanol reductions, in addition, also produced small amounts of higher boiling condensation products. None of these contaminants was investigated, and a preparative-scale reduction or hydrogenation of 1-oxopyrrolizidine was not carried out.

1-Hydroxypyrrolizidine, Epimer A (XI).—Products[22,27] obtained by the published procedure[7] were found (glpc) to be approximately 90–10% mixtures of epimers A–B. Redistillation [bp 145° (50 mm)] gave a forerun somewhat enriched (93%) in epimer A, which solidified on standing in the freezer and melted at 25–28°. A picrate, prepared from the original mixture, melted at 243–245° (lit.[7] 244–245).

1-Hydroxypyrrolizidine, Epimer B (XII).—*n*-Pentyl alcohol (200 ml) was added slowly with stirring to 35 g (0.90 g-atom) of potassium in 300 ml of xylene in a 1-l. flask equipped with a magnetic stirrer, reflux condenser, and drying tube. When all of the potassium had reacted, 10 g (0.079 mole) of 1-hydroxypyrrolizidine, epimer A (90% epimerically pure), in 20 ml of xylene, and 2 ml of cyclohexanone were added, and the mixture was refluxed with stirring. After 73 hr at reflux, an additional 2 ml of cyclohexanone was added. The epimerization was followed by the removal of aliquots, which were worked up as described for the total reaction mixture, below, and examined by glpc. After 168 hr, an epimer ratio of 33–67% A–B was obtained, which appeared to be the equilibrium position for these conditions. An additional 200 ml of pentanol was then added, and the mixture was refluxed another 72 hr. At this time, little or no epimer A could be detected. The total mixture was cooled, diluted with 50 ml of water, then acidified to pH 1 with concentrated hydrochloric acid. The organic phase was separated and extracted with three 50-ml portions of 6 *N* acid. These were combined with the original aqueous phase and treated with potassium hydroxide pellets to pH 14, then extracted with six 50-ml portions of chloroform. The latter were combined, dried over sodium carbonate, and concentrated to 6 g of a brown oil. Distillation gave 3.2 g (0.025 mole, 32%) of 1-hydroxypyrrolizidine, epimer B (XII), as a colorless, viscous oil, bp 98–100° (1.25 mm), $n^{25}D$ 1.5001. A picrate, prepared in and recrystallized from ethanol, melted at 186–187°.

Anal. Calcd for $C_{13}H_{16}N_4O_8$: C, 43.82; H, 4.53. Found: C, 43.8; H, 4.7.

2-Oxopyrrolizidine was synthesized essentially as described[28] from 20.0 g (0.082 mole) of diethyl pyrrolidine-1,2-diacetate,[29] except the Dieckmann condensation was run using potassium isopropoxide in toluene. The crude product (8.6 g) was distilled to give 5.4 g (0.043 mole, 53%) of 2-oxopyrrolizidine as a mobile, colorless oil, bp 71° (1.3 mm), $n^{28}D$ 1.4866, mass spectrum mol wt 125 (calcd for $C_7H_{11}NO$, 125.17). The compound was stored under nitrogen in the Dry Ice chest. It darkened rapidly when exposed to the atmosphere. It formed a methiodide, mp 267–268° (methanol–acetone), and picrate, mp 185° (ethanol). The latter, when reexamined as an aged sample, was found to char to a black, carbonaceous residue at 155–165°.

Anal. Calcd for $C_{13}H_{14}N_4O_8$: C, 44.07; H, 3.98. Found: C, 44.0; H, 4.3.

A methiodide sample (previously prepared), mp 273–274°, gave the following analysis.[22]

Anal. Calcd for $C_8H_{14}INO$: C, 35.97; H, 5.28; N, 5.25. Found: C, 36.17; H, 5.25; N, 5.30.

At room temperature, this ketone undergoes a rapid aldol condensation to form a crystalline dimer, from which neither a crystalline picrate nor methiodide has been obtained. Thus, product similarly prepared,[22] but using potassium *t*-butoxide and benzene for the Dieckmann condensation, was obtained as a mobile, colorless liquid, bp 76–79° (3.3 mm), $n^{25}D$ 1.4890, and was shipped to these laboratories in ampoules sealed under nitrogen. Upon arrival, several of the samples had crystallized as the dimer, mp 110–112°, mol wt 250 (mass spectrum). The remaining samples, which were extremely viscous liquids, also crystallized when placed in the freezer (−20°). The aldol dimer was reduced over platinum dioxide in aqueous acid to the so-called diol dimer, mp 156–158°, which was also obtained in varying yields from reductions of freshly distilled monomeric ketone.

Because of this instability, more careful studies of reductions of 2-oxopyrrolizidine were not carried out (as reported for other ketones in this series). In general, however, the ketone was hydrogenated with difficulty, if at all, on supported rhodium, palladium, and ruthenium in ethanol or (for the latter two) in aqueous acid. Hydrogenations with platinum dioxide and rhodium on alumina in aqueous acid were accompanied by varying amounts of hydrogenolysis product (apparently pyrrolizidine, though not isolated and identified as such). In one run, however, the ketone was adjusted to pH 4 and reduced over platinum dioxide in aqueous solution with no detectable hydrogenolysis. From chemical reductions, lithium aluminum hydride in ether produced mainly epimer B (perhaps >95%), while sodium borohydride in water produced a 20–80% A–B mixture.

2-Hydroxypyrrolizidine, Epimer B (XIV).—2-Oxopyrrolizidine (5.9 g, 0.047 mole) in 40 ml of ethanol was reduced over 0.5 g of platinum dioxide in a Parr hydrogenator at an initial 65-psig hydrogen pressure. After 6 hr, hydrogen uptake had ceased. From the less than theoretical uptake of hydrogen, it was calculated that 2.0 g of aldol dimer had been present in the original ketone, or was formed during the reaction and was subsequently reduced to diol dimer. The catalyst was filtered off, and the ethanol was removed under reduced pressure. The residual oil was taken up in 50 ml of ether and placed in the refrigerator overnight. The diol dimer (1.8 g) that precipitated was filtered off, and the filtrate was concentrated and distilled to give 2.7 g (0.021 mole) of 2-hydroxypyrrolizidine epimer B (XIV) as a colorless oil, bp 90° (0.35 mm), shown by glpc to be better than 98% pure and free of any detectable amount of epimer A. It formed a picrate, mp 217–218° (ethanol–ether), and a hydrochloride, mp 191–193° (acetone).

Anal. Calcd for $C_7H_{14}ClNO$: C, 51.38; H, 8.62. Found: C, 50.8; H, 8.9.

Another sample of epimer B crystallized on standing in the freezer and melted at 19–20°. It formed a picrate in ether, mp 215–217°, unchanged on recrystallization from acetone–ether.

Anal. Calcd for $C_{13}H_{16}N_4O_8$: C, 43.82; H, 4.53; O, 35.92. Found: C, 44.1; H, 4.7; O, 35.3.

2-Hydroxypyrrolizidine, Epimer A (XIII).—*n*-Pentyl alcohol (85 ml) was added dropwise with stirring to a suspension of potassium (12 g, 0.31 g-atom) in 200 ml of refluxing xylene in a 2-l. flask equipped with a compensated addition funnel, magnetic stirrer, and reflux condenser with drying tube. After the potassium had completely reacted, 12.6 g (0.10 mole) of 2-hydroxypyrrolizidine, epimer B, in 800 ml of xylene and 60 drops of cyclohexanone were added. The mixture was refluxed with stirring, and the epimerization was followed by removal (at approxi-

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(27) Synthesized by Dr. B. Southers and Mr. R. A. Meara, FMC Corp., Baltimore, Md., under a U. S. Army Research and Development Contract.

(28) G. Clemo and T. Melrose, *J. Chem. Soc.*, 424 (1942).

(29) Synthesized by Dr. D. A. Scola and Mr. P. F. Donovan, Monsanto Research Corp., Boston, Mass., under a U. S. Army Research and Development Contract.

mately 24-hr intervals) of 25-ml aliquots, which were worked up and examined by glpc as described below for the total reaction mixture. After 122 hr, the mixture was cooled and acidified with 100 ml of 6 *N* hydrochloric acid, then shaken in a separatory funnel. The layers were separated, and the xylene layer was extracted with four 100-ml portions of 6 *N* acid. The aqueous layers were combined, warmed, then treated with charcoal, filtered, and concentrated under reduced pressure to about 75 ml. This solution was cooled, treated with excess concentrated sodium hydroxide solution, and extracted with six 50-ml portions of chloroform, which were combined, dried over calcium sulfate, filtered, and concentrated under reduced pressure. The residual oil was distilled at 0.3 mm to give 0.3 g of a forerun (bp 55–83°), plus 5.0 g of 2-hydroxypyrrolizidine (bp 83–87°), obtained as a 60–40% A–B mixture. The forerun was found to be an anomalous $C_{10}H_{19}N$ reaction product that consisted, apparently, of a mixture of two isomers to which we are unable to give unequivocal structure assignments. The alcohol product mixture was twice fractionated through an 8-in. spinning-band column (Nester-Faust) to give 0.6-g and 1.1-g fractions of epimer A as the first two final cuts, 95 and 90% epimerically pure, respectively. These fractions solidified to waxy solids on standing in the refrigerator, and both melted at 36–40°. Epimer A (fraction two) formed a picrate in ether, mp 170–171°, unchanged on recrystallization from acetone–ether.

Anal. Calcd for $C_{13}H_{16}N_4O_8$: C, 43.82; H, 4.53; O, 35.92. Found: C, 43.7; H, 4.7; O, 35.5.

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Monocyclic Terpene Alcohols. II.[1] *p*-Menthan-7-ols, *p*-Menthan-9-ols, and *p*-Menth-3-en-9-ol

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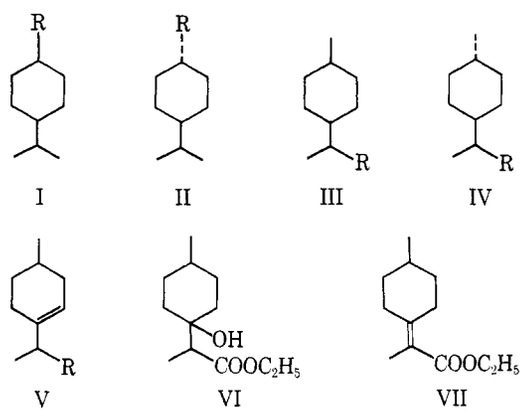
The preparation of several 7- and 9-derivatives of *cis*- and *trans*-*p*-menthane, and *p*-menth-3-ene, is described. Comments are made on the nmr spectra of stereoisomeric pairs.

The present paper gives an account of the work done with the final aim of preparing pure specimens of *cis*- (I, R = CH_2OH) and *trans*-*p*-menthan-7-ol (II, R = CH_2OH) and *cis*- (III, R = CH_2OH) and *trans*-*p*-menthan-9-ol (IV, R = CH_2OH), which were needed in connection with an extensive project on terpene alcohols in progress in this laboratory.[2]

***cis*- and *trans*-*p*-Menthan-7-ol.**—The *p*-menthan-7-ols have been obtained in a state of purity by Verkade, *et al.*,[3] by means of a reaction sequence the key step of which was reduction of cuminic acid and resolution of the resulting stereoisomeric *p*-menthan-7-oic acids by treatment with thiourea. In the present work a modified procedure was used involving catalytic hydrogenation of methyl cuminate followed by preparative vpc of the stereoisomeric mixture of saturated esters. In this way, pure (vpc) samples of the previously undescribed methyl *cis*- (I, R = COOMe) and methyl *trans*-*p*-menthan-7-oate (II, R = COOMe) were obtained, steric assignments being based on the identity of the melting points of the *p*-tosylates and 3,5-dinitrobenzoates of the related alcohols (*vide infra*) with those given in the literature.

Lithium aluminium hydride reduction of the esters afforded the corresponding alcohols, *cis*- (I, R = CH_2OH) and *trans*-*p*-menthan-7-ol (II, R = CH_2OH), which were purified *via* the 3,5-dinitrobenzoates.[4,5]



It is of interest that reduction of the *cis* ester was more difficult than that of the *trans* isomer, and, even after 24 hr of treatment with excess hydride, the resulting alcohol was contaminated by some starting material. As it is known that an axial carbomethoxy group reacts more slowly than an equatorial one,[6] a possible explanation rests on the "partial" axial character of the carbomethoxy group in the *cis* ester.

Pure specimens of *cis*- (I, R = Me) and *trans*-*p*-menthane (II, R = Me) were prepared by lithium aluminum hydride reduction of the *p*-tosylates obtained from stereochemically pure samples of alcohols.[3]

***cis*- and *trans*-*p*-Menthan-9-ol.**—A stereoisomeric mixture of menthan-9-ols was prepared by Frank and Berry[7] by high-pressure hydrogenation of ethyl *p*-menth-3-en-9-oate (V, R = COOEt), and Gollnick

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(2) Research Project sponsored by the U. S. Department of Agriculture, Grant FG-Sp-135.

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(4) Throughout the paper "purification *via* the 3,5-dinitrobenzoate" means preparation of this derivative on a very pure condition by repeated (if necessary) crystallization and subsequent alkaline alumina saponification.[5]

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