The Saturated Pyrrolizidinediols. I. Spectral Studies and the Conversion of an Ester of Dihydroxyheliotridane into the (+) Enantiomer of Hastanecine

A. J. AASEN, C. C. J. CULVENOR, AND L. W. SMITH

Division of Applied Chemistry, C.S.I.R.O., Melbourne, Australia

Received May 14, 1969

The mass and nuclear magnetic resonance spectra of the saturated pyrrolizidinediols and their parent alkaloids show that hastanecine and the amino alcohol from retusine are 7-hydroxy-1-hydroxymethyl derivatives and macronecine is a 2-hydroxy-1-hydroxymethyl derivative, probably 2β-hydroxy-1β-hydroxymethyl-8β-pyrrolizidine. The relative and absolute stereochemistry of hastanecine is established as 7β-hydroxy-1β-hydroxymethyl-8β-pyrrolizidine by the preparation of its enantiomer from an ester of dihydroxyheliotridane by changing the configuration at C-1. The amino alcohol from retusine is identical with turneforcidine.

For a number of years, the saturated pyrrolizidinediols have presented an intriguing problem in stereochemistry. The structures of the readily available platynecine (**1**) and dihydroxyheliotridane (**2**) are well established,[1,2] but the four other diols obtained by hydrolysis of alkaloids, hastanecine from the alkaloid hastacine,[3] turneforcidine from turneforcine,[4] macronecine from macrophylline,[5] and an unnamed amino-alcohol from retusine,[6] have been too inaccessible for detailed study or even for adequate characterization. In 1965, Untch and Martin[7] reported briefly that they had prepared the 8β enantiomers of the unknown diastereomers **3** and **4** by oxidation of platynecine to a 7-keto compound, epimerization at C-8, and reduction back to the 7-hydroxy compounds. Their products were believed to be hastanecine and turneforcidine, although the similarity in physical properties of these two diols and the lack of authentic reference samples made the identifications questionable. Being aware of the difficulties in completing this approach to the problem,[8] we obtained, through the kindness of Dr. L. M. Utkin, samples of hastacine and macrophylline which enabled us to make a comparative study of the mass and nuclear magnetic resonance spectra of hastanecine, macronecine, the amino alcohol from retusine, and their parent (ester) alkaloids. The spectra immediately verified that the amino alcohol from retusine was different from hastanecine, a point not previously clear.

We describe here spectral features which fix the location of the hydroxyl functions in these diols and lead, in addition, to the full stereochemistry of macronecine. We also report an independent determination of the relative and absolute configuration of hastanecine, undertaken when it was found that preliminary conclusions from spectral data regarding the relative stereochemistry of hastanecine and the amino alcohol from retusine[9,10] were contrary to the views of Dr. Untch (personal communication).

(1) N. J. Leonard, "The Alkaloids," Vol. VI, R. H. F. Manske and H. L. Holmes, Ed., Academic Press, New York, N. Y., 1960, p 35.

(2) F. L. Warren, *Progr. Chem. Org. Nat. Prod.*, **12**, 198 (1955); **24**, 329 (1966).

(3) V. S. Konovalov and G. P. Men'shikov, *Zh. Obshch. Khim.*, **15**, 328 (1945).

(4) G. P. Men'shikov, S. O. Denisova, and P. S. Massagetov, *ibid.*, **22**, 1465 (1952).

(5) A. Danilova, L. Utkin, and P. S. Massagetov, *ibid.*, **25**, 831 (1955); **30**, 345 (1960).

(6) C. C. J. Culvenor and L. W. Smith, *Aust. J. Chem.*, **10**, 464 (1957).

(7) K. G. Untch and D. J. Martin, *52nd Ann. Rept. Mellon Inst.*, 11 (1965).

(8) We thank Dr. K. G. Untch for keeping us informed of the progress of his work.

(9) L. B. Bull, C. C. J. Culvenor, and A. T. Dick, "The Pyrrolizidine Alkaloids," North Holland Publishing Co., Amsterdam, 1968, p 87.

Results and Discussion

Mass Spectra.—With diastereoisomers available for comparison, the mass spectra of the diols were immediately useful in defining the location of the hydroxyl groups. The spectra of platynecine, dihydroxyheliotridane, hastanecine, and the amino alcohol from retusine are closely similar and show a base peak, *m/e* 82, and only one other major ion, *m/e* 113. The spectra of macronecine and the 2-hydroxy-1-hydroxymethylpyrrolizidine of undefined stereochemistry prepared by Adams, *et al.*,[11] are similar but differ from the first group in having a base peak, *m/e* 83, and other major ions, *m/e* 98 and 55. A consideration of fission pathways confirms the implication that hastanecine and the amino alcohol from retusine are 7-hydroxy-1-hydroxymethylpyrrolizidines and that macronecine is a 2-hydroxy-1-hydroxymethylpyrrolizidine. The initial bond fissions in saturated pyrrolizidine derivatives are of those bonds which are in a β position to the nitrogen atom, and there is a strong tendency for two such bonds in one ring to break together. In platynecine and the other 7,9 diols, the C-7–C-8 bond is the most labile and the major ions produced are *m/e* 113 (**7**) and 82 (**8**) (*cf.* Neuner-Jehle, *et al.*[12]). Thus, the main features of the spectrum are determined by the 7-hydroxyl group. Retronecanol (**5**) shows a similar effect: $M\cdot^+ \rightarrow [M-44]\cdot^+$ (rel intensity 95) → *m/e* 82 (rel intensity 100). A 6-hydroxyl group, as occurs in crotanecine,[13] should produce a similar result by weakening the C-5–C-6 bond. When the ring A is unsubstituted, as in laburnine and trachelanthamidine (**9**), the dominant break is at the C-8–C-1 bond and leads to the ion **10**, *m/e* 83, which constitutes the base peak. Further loss of a hydrogen radical gives the ion **8**, *m/e* 82, with an intensity 40% of that of **10**. Thus, a base peak of *m/e* 83 is indicative of an unsubstituted ring A. Macronecine does not show the properties of a carbinolamine, and its second hydroxyl group must be at C-1 or C-2 if ring A is unsubstituted. Its mass spectrum closely resembles that of the 2-hydroxy-1-hydroxymethyl isomer and only to a lesser extent the spectrum of 1β-hydroxy-1α-hydroxymethyl-8α-pyrrolizidine (**11**) prepared by catalytic reduction of 1α-hydroxymethyl-1β,2β-epoxy-8α-pyrrolizidine. In particular, the spec-

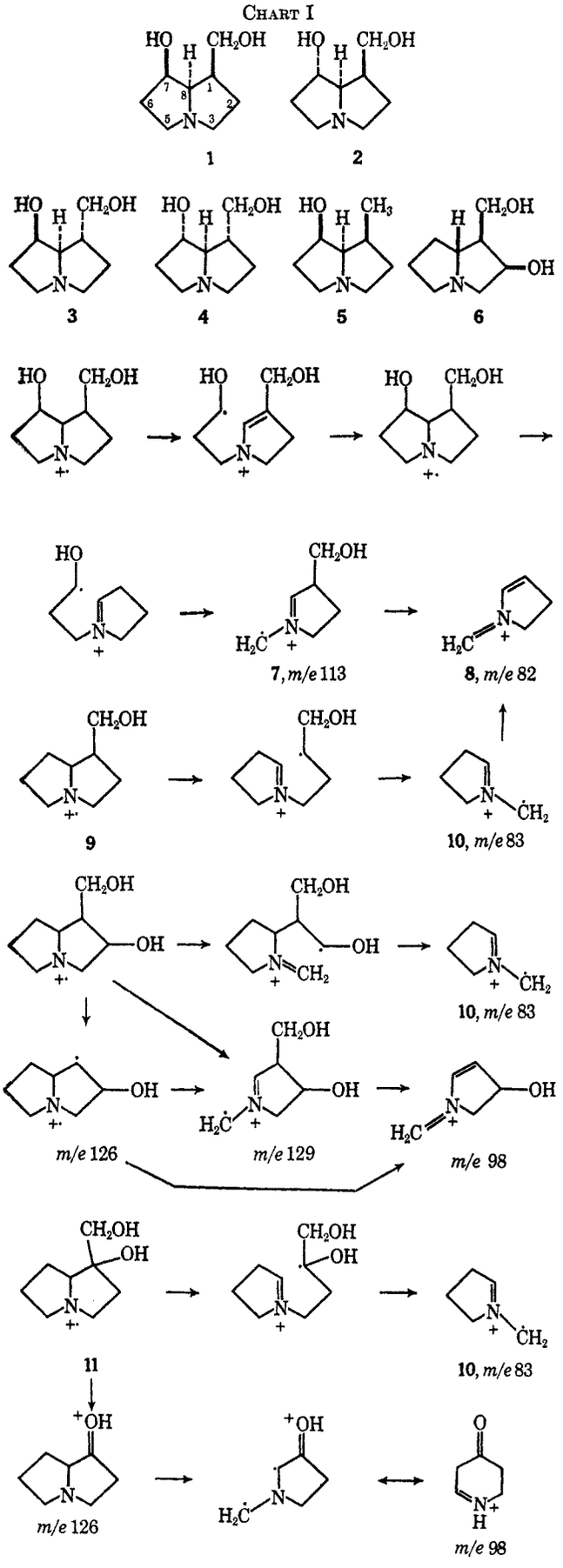
(10) C. C. J. Culvenor, N. I. Koretskaya, L. W. Smith, and L. M. Utkin, *Aust. J. Chem.*, **21**, 1671 (1968).

(11) R. Adams, S. Miyano, and M. D. Nair, *J. Amer. Chem. Soc.*, **83**, 3323 (1961).

(12) N. Neuner-Jehle, H. Nesvadba, and G. Spiteller, *Monatsh. Chem.*, **96**, 321 (1965).

(13) C. K. Atal, K. K. Kapur, C. C. J. Culvenor, and L. W. Smith, *Tetrahedron Lett.*, 537 (1966).

CHART I



trum of the 1-hydroxy compound exhibits a much weaker ion, *m/e* 98, and a stronger ion, *m/e* 126, in accord with the expected preferred fragmentations for these compounds (Chart I).

The mass spectra of the parent alkaloids provide additional support for these conclusions. In the region *m/e* 140–82, which is due largely to fragments of the pyrrolizidine ring, the spectra of platyphylline, hastacine, and retusine are strikingly similar, while that of macrophylline differs. The base peaks for the first group and for macrophylline are at *m/e* 82 and 83, respectively, as for the amino alcohols.

Nuclear Magnetic Resonance Spectra.—The main features of the nuclear magnetic resonance spectra of pyrrolizidine derivatives have been reported previously.[14,15] Measurements on the saturated diols were made in deuteriochloroform and in deuterium oxide; the spectrum of each diol most useful for characterization is shown in Figure 1. In at least one instance, the amino alcohol from retusine, some of the observed coupling constants as well as chemical shifts differed in the two solvents, reflecting an influence of solvation on relative proportions of conformations undergoing averaging.[16] The chemical shifts and coupling constants relating to the pyrrolizidine nucleus in the amino alcohols and in the parent alkaloids are collected in Tables I and II. These data do not assist in arriving at the relative stereochemistry at C-7 of hastanecine and the amino alcohol from retusine. The coupling constants pertaining to H-7 differ only slightly in the two compounds, despite the substantial differences between the values for these constants in the other pair of diastereomers, platynecine and dihydroxyheliotridane. Both hastanecine and the amino alcohol from retusine have the H-9 protons nonequivalent in chemical shift in deuteriochloroform solution but equivalent in deuterium oxide. A possible explanation is the occurrence in deuteriochloroform of intramolecular hydrogen-bonded forms, whereas intermolecular bonded forms would be favored in deuterium oxide.

The spectrum of macronecine (Figure 1d) has a multiplet, δ 4.20, appropriate to a CHOH grouping, thus fixing the location of the second hydroxyl group of this amino alcohol as C-2. The CHOH multiplet is approximately 12 cps wide and has the form of a triplet, suggesting two couplings of *ca.* 5–6 cps and one of *ca.* 1 cps. Since macronecine is a 1β-hydroxymethyl-8β-pyrrolizidine, the couplings are in best agreement with the secondary hydroxyl being 2β in an *exo*-buckled ring, as in diagram **12** (Chart II). This configuration is supported by a consideration of the synthetic 2,9 diol of Adams, *et al.*,[11] for which the mode of origin suggests the configuration 2β-hydroxy-1β-hydroxymethyl-8α-pyrrolizidine (**14**) (now confirmed[17]). The spectrum of this diol contains a similar triplet, δ 4.36, 10.7 cps in width and is so well resolved that all vicinal couplings for ring B can be deduced. The couplings found are: $J_{1,8}$ = 8.2 cps; $J_{1,2}$ = 5.0 cps; $J_{2,3\alpha}$ = 4.2 cps; $J_{2,3\beta}$ = 1.5 cps (this discussion relates to the 8α enantiomer and assumes H-3α is H-3*d* and H-3β is H-3*u* as concluded by Culvenor, *et al.*)[18] These couplings strongly support the 2β,1β,8α configuration and are reasonably consistent only with a molecule *endo*-buckled at C-2 so that H-2α

(14) C. C. J. Culvenor, M. L. Heffernan, and W. G. Woods, *ibid.*, *Tetrahedron Lett.*, **18**, 1605 (1965).

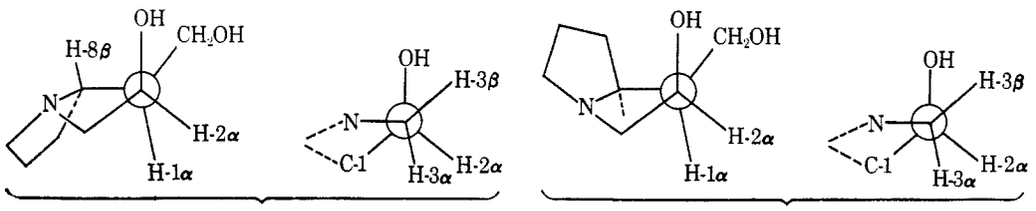
(15) C. C. J. Culvenor and W. G. Woods, *ibid.*, **18**, 1625 (1965).

(16) This effect has been noted in 1,2-disubstituted ethanes: R. C. Hirst and D. M. Grant, *J. Chem. Phys.*, **40**, 1918 (1964).

(17) A. J. Aasen and C. C. J. Culvenor, *J. Org. Chem.*, **34**, 4143 (1969).

(18) C. C. J. Culvenor, G. M. O'Donovan, and L. W. Smith, *Aust. J. Chem.*, **20**, 757 (1967).

CHART II



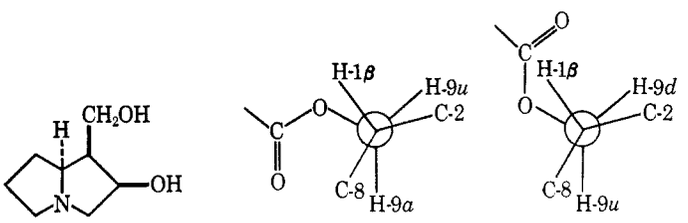


TABLE I

CHEMICAL SHIFTS OF THE DIOLS AND THEIR PARENT ALKALOIDS

Base	Shifts in $CDCl_3$,[a] δ, ppm H-7	H-8	H-9[c]	ΔH-9	Shifts in D_2O,[b] δ, ppm H-7	H-8	H-9[c]	ΔH-9
Platynecine	4.27		3.92	0.0	4.27	3.23	3.93	0.0
Dihydroxyheliotridane	~4.1	3.30	~3.74		4.17	3.20	3.65, 3.84	0.19
Hastanecine	4.08		3.53, 3.74	0.21	4.26		3.63	0.0
Amino alcohol from retusine	4.28		3.44, 3.69	0.25	4.23		3.56	0.0
Macronecine	4.38[d]	~3.36	3.69, 3.74	0.05				
Platyphylline	5.34	3.43	3.95, 4.60	0.65				
Neoplatyphylline	5.49	3.44	3.90, 4.45	0.55				
Hastacine	4.46	3.32	3.84, 4.79	0.95				
Retusine	5.21	3.33	3.71, 4.60	0.89				
Macrophylline			(Assignments uncertain)					

[a] Relative to internal TMS. [b] Relative to internal sodium 3-trimethylsilylpropyl-1-sulfonate. [c] Two values indicate nonequivalence of the geminal pair. [d] Shift of H-2.

TABLE II

COUPLING CONSTANTS OF THE DIOLS AND THEIR PARENT ALKALOIDS[a] IN CYCLES PER SECOND

Base	$^1/_2(J_{6\alpha,7} + J_{6\beta,7})$	$J_{7,8}$	ΣJ_7	$J_{8,1}$	$J_{1,9u}$	$J_{1,9d}$	$J_{9u,9d}$
Platynecine[b]	2.7	3.0	8.4	8.2	($^1/_2$ sum = 5.5)		
Dihydroxyheliotridane	6.6	7.1	20.3	7.4	7.1	7.6	10.8
Hastanecine	3.0, 3.2, 5.8[c]		12.0		6.5	4.6	11.0
Amino alcohol from retusine	4.7	4.7	14.1				
Amino alcohol from retusine[b]	3.4, 3.8, 4.0[c]		11.2		8.3	5.0	9.9
Macronecine					5.0	7.3	11.0
Platyphylline	4.7	4.8	14.1	7.0	2.1	9.0	11.6
Neoplatyphylline	5.8	5.8	17.4	6.5	2.3	9.7	11.1
Hastacine	9.1, 6.0[c]	9.1	24.2		1.6	10.8	10.8
Retusine	7.3	9.3	23.9	7.8	10.7	3.2	10.7

[a] Measured in $CDCl_3$ unless otherwise stated. [b] Measured in D_2O. [c] Splittings in H-7 multiplet.

is situated as in **13**. (Coupling constants of similar magnitude for H-8α and H-1α in a *cis* relationship are observed in platynecine and dihydroxyheliotridane; Table II). A comparison of diagrams **12** and **13** (Chart II) shows that the CHOH proton in **14** forms dihedral angles with adjacent protons closely similar to those proposed for H-2 in macronecine. Final proof that macronecine is 2β-hydroxy-1β-hydroxymethyl-8β-pyrrolizidine (**6**) is provided in the following paper.[17]

Initially, it seemed that the configuration of hastanecine and the amino alcohol from retusine could be derived from the spectra of the parent alkaloids. As macrocyclic diesters, the chemical shifts of the H-7 and H-9 protons in hastacine and retusine are profoundly influenced by the conformations of the CH–O–CO–C groupings. In senecionine and other macrocyclic diesters of retronecine,[19] H-7 occupies a position normal for a secondary ester in the plane of, and *cis* to, the secondary ester carbonyl; it has a chemical shift in the range δ 5.0–5.2. The H-9 protons, on the other hand, are unlike those in most primary esters in that strong magnetic nonequivalence is induced by one proton being held in or close to the plane of the primary ester carbonyl while the other is away from the plane. The maximum degree of nonequivalence from this cause is probably about 1 ppm so that the alkaloids listed in Table I are showing a medium to strong effect of this type. The H-7 shifts are in the normal region except

(19) C. C. J. Culvenor, *Tetrahedron Lett.*, 1091 (1966).

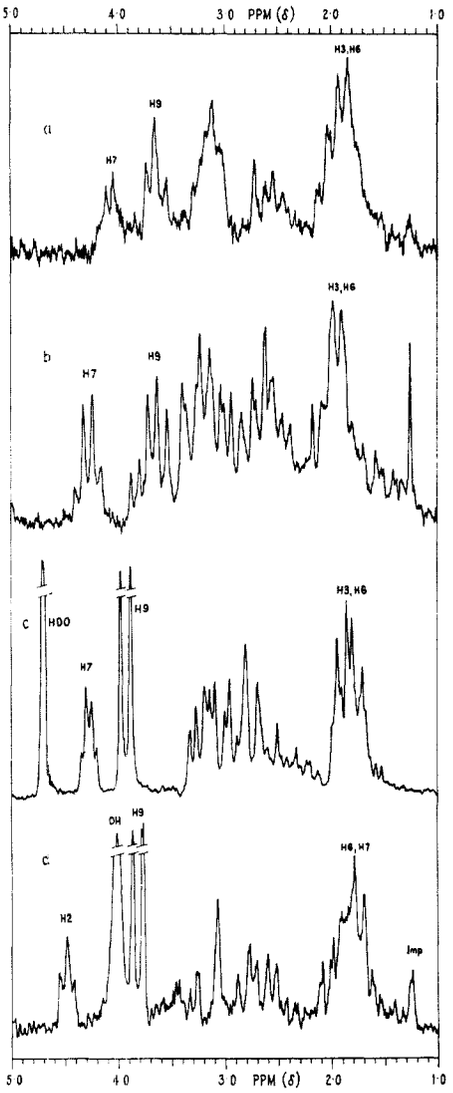


Figure 1.—Nuclear magnetic resonance spectra of the naturally occurring amino alcohols, measured at 60 Mcps: (a) hastanecine in $CDCl_3$; (b) the amino alcohol from retusine (turneforcidine) in $CDCl_3$; (c) platynecine in D_2O; (d) macronecine in $CDCl_3$.

for hastacine, in which the H-7 signals are at unusually high field, δ 4.46. In hastacine, the secondary ester grouping must be prevented from assuming the normal, preferred conformation by strain within the macrocyclic system.

Hastacine also has $J_{1,9d}$ = 10.8 cps and $J_{1,9u}$ = 1.6 cps (Table II; H-9*d* is the more deshielded proton in the plane of the carbonyl group and H-9*u* is the proton at higher field), indicating that H-9*d* and H-1β form a dihedral angle of 150–180° and that the carbonyl group is oriented downward as in **15**. (This discussion refers to 8α enantiomers as drawn in **3** and **4**.) In a Dreiding model incorporating this arrangement, the secondary ester carbonyl cannot simultaneously be planar with the C-7–H-7 bond and *trans*-coplanar with the conjugated ethylidene group in the esterifying acid (integerrinecic acid[10]), whether the ester function is 7α or 7β. The model does not clearly indicate which configuration at C-7 is in best accord with the data. In retusine, however, $J_{1,9d}$ is small (3.2 cps) and $J_{1,9u}$ is relatively large (10.7 cps), the reverse of the situation in hastacine. Thus, this portion of the retusine molecule must be represented as in **16**, with the carbonyl group oriented upwards. Given this condition, a more satisfactory model with a near-planar H-7–C-7–O–CO–C system in the macrocyclic ring can be built with 7β substitution than with 7α substitution. In the platynecine esters, platyphylline and neoplatyphylline, the $J_{1,9u}$ and $J_{1,9d}$ values are similar to those in hastacine, but since the CH_2OCOR grouping is a 1β substituent in these alkaloids, the orientation of the carbonyl group relative to the ring more closely resembles that found in retusine.

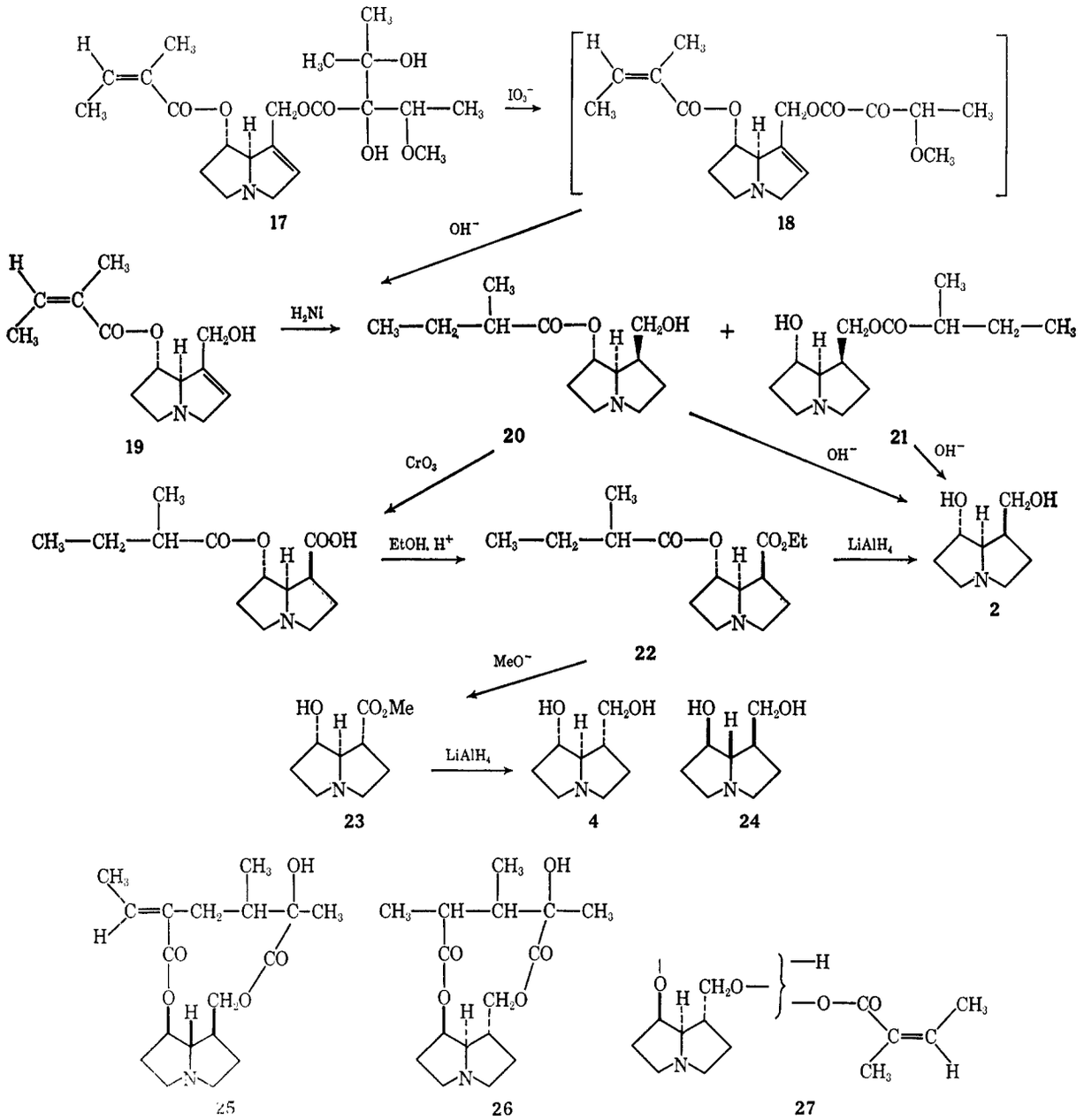
Both hastacine and retusine are unusual in having a very broad H-7 multiplet, ΣJ_7 being 24.2 and 23.9 cps, respectively. Until the closing stages of this investigation, the only spectrum of hastacine available was one measured at 60 Mcps, in which the H-7 and H-9*d* multiplets were overlapping and poorly defined and the value of ΣJ_7 appeared to be 14.5 cps. When measured at 100 Mcps, the multiplets do not overlap and the true value of ΣJ_7 is obvious. The $J_{7,8}$ couplings, 9.1 and 9.3 cps have now been verified by decoupling experiments. When preliminary conclusions were drawn from the early spectra,[9,10] only retusine appeared to be abnormal, and the large value of $J_{7,8}$, 9.3 cps, was taken to indicate a *trans* relationship between the two protons in this alkaloid. This cannot apply to both hastacine and retusine, in one of which H-7 and H-8 must be *cis*. A report of *cis* couplings in five-ring lactones up to 9.3 cps has since come to our attention.[20] We have to conclude that the relative configuration of hastacine and retusine (and of their amino alcohols) at C-7 cannot be determined from their nmr spectra.

The Conversion of a Dihydroxyheliotridane Derivative into the Enantiomer of Hastanecine.—In seeking an independent proof of the stereochemistry of hastanecine and the amino alcohol from retusine, we elected to alter the configuration at C-1 in a suitable derivative of either platynecine or dihydroxyheliotridane. Since these two diols have the thermodynamically less stable β configuration at C-1, inversion should be achieved readily through a 1β-carbethoxy derivative. In order to effect oxidation of the primary alcohol grouping, protection of the C-7 hydroxyl was necessary, and the actual starting point was determined by the availability of 7-angelylheliotridine (**19**). Previously obtained by partial hydrolysis of lasiocarpine (**17**),[21] **19** is formed in better yield by subjecting lasiocarpine to periodate oxidation. The initial product, probably **18**, undergoes alkaline hydrolysis during work-up (Chart III).

Catalytic hydrogenation of 7-angelylheliotridine give 1β - hydroxymethyl - 7α - (2′ - methylbutyroxy) - 8α-pyrrolizidine (**20**), in which the optical state of the 2′-methylbutyryl grouping is probably mixed but for which an essentially pure 1β configuration was established by the formation of dihydroxyheliotridane (**2**) on hydrolysis. Oxidation of **20** with Jones reagent gave the corresponding 1-carboxylic acid, which was esterified with absolute ethanol in the presence of hydrogen chloride. The nmr spectrum of the product and reduction with lithium aluminum hydride to give dihydroxyheliotridane together confirm that it is 1β - carbethoxy - 7α - (2′ - methylbutyroxy) - 8α-pyrrolizidine (**22**). The desired epimerization was conveniently effected by treatment of **24** with sodium

(20) D. Savostianoff and M. Peau, *Bull. Soc. Chim. Fr.*, 4162 (1967).
(21) H. C. Crowley and C. C. J. Culvenor, *Aust. J. Chem.*, **12**, 694 (1959).

CHART III



methoxide. Methanolysis occurred simultaneously, the product being 1α-carbomethoxy-7α-hydroxy-8α-pyrrolizidine (**23**). Reduction of **23** with lithium aluminum hydride gave 7α-hydroxy-1α-hydroxymethyl-8α-pyrrolizidine (**4**), identical with natural (−)-hastanecine in all respects except that it was dextrorotatory. Thus, natural hastanecine must belong to the less common 8β-pyrrolizidine series and is 7β-hydroxy-1β-hydroxymethyl-8β-pyrrolizidine (**24**).

From the hydrogenation of **19**, a by-product was obtained in considerable amount in one run, although only in trace amounts in other runs. It gives dihydroxyheliotridane on hydrolysis and has been shown to be 1β-(2′-methylbutyroxy)methyl-7α-hydroxy-8α-pyrrolizidine (**21**), presumably formed from **20** by internal transesterification. The mass spectrum shows a parent ion, *m/e* 241, and fragment peaks, especially *m/e* 223, 197, 169, 156, 140, and 126, interpretable on the basis of structure **21**. The nmr spectrum has no signal near δ 5.0 appropriate to a CHOCOR proton at C-7, but has multiplets representing three protons in the δ 3.9–4.4 region which are ascribed to CHOH at C-7 (triplet, δ 4.0) and CH_2OCOR (four lines, probably the strong lines of an AB pattern due to the CH_2 protons being slightly nonequivalent, δ *ca.* 4.3). Appropriate signals for the methyl groups are present near δ 1.0.

Since hastanecine is 7β-hydroxy-1β-hydroxymethyl-8β-pyrrolizidine (**24**), the amino alcohol from retusine must have the relative configuration 7β-hydroxy-1α-hydroxymethyl-8α-pyrrolizidine (**3**). A sample of the (dextrorotatory) 8β enantiomer of **3**, kindly supplied by Dr. Untch, was found to be enantiomeric with the amino alcohol from retusine. The two compounds were identical in infrared and nmr spectra and a mixture of the two bases melted 20° below the melting point of the pure compounds. Other examples of racemates melting lower than the optically pure forms are known in the pyrrolizidine series, *e.g.*, 7α-hydroxy-1-methylene-8α-

pyrrolizidine picrate[22] and macronecine.[17] Thus, **3** also represents the absolute configuration of the amino alcohol from retusine.

Further characterization data obtained for the amino alcohol from retusine (mp 118.5–120°, $[\alpha]_D$ −18° in methanol, −3.5° in ethanol; lit.[6] hydrochloride mp 116°) made the identity of this base with turneforcidine (lit.[4] mp 118.5–120°, $[\alpha]_D$ −10.5° in methanol, hydrochloride mp 116°) very probable. However, in the absence of a sample of turneforcidine, an element of doubt remained because of the discrepancy in their specific rotation in methanol. We have very recently removed this doubt by a preparation of the 8α enantiomer (**3**) from 1α-carbomethoxy-7α-hydroxy-8α-pyrrolizidine;[23] the material so obtained has specific rotations of −12.5° in methanol and −4.3° in ethanol, which indicate that the value obtained for the amino alcohol from retusine in methanol is high. The identification of turneforcidine also as **3** is now established.

Thus, the preliminary conclusions drawn from the spectral data in regard to the relative configuration of hastanecine and the amino alcohol from retusine[9,10] were incorrect. The structures of the alkaloids hastacine, retusine, and turneforcine should now be written as **25**, **26**, and **27**, respectively.

Experimental Section

Analyses were made by the Australian Microanalytical Service, Melbourne. R_f values refer to thin layer chromatograms run on plates prepared from a slurry of silica gel (Merck, Silica Gel G, 30 g) and sodium hydroxide (0.1 *N*, 60 ml), kept for at least 1 day before use and developed with methanol.

Mass Spectra.—Mass spectra were recorded on a Hitachi Perkin-Elmer RMU 6D instrument, using a 70-eV ionization potential and direct entry of samples into the ion chamber. The spectra of hastacine, platyphylline, hastanecine, and platynecine have been recorded previously.[10] The main peaks in the spectra of retusine, macrophylline, and their amino alcohols are as follows [*m/e* (rel intensity)]: retusine, 311 (40), 211 (11), 210 (12), 156 (8), 154 (51), 141 (6), 140 (45), 139 (7), 138 (20), 124 (7), 123 (38), 122 (41), 121 (15), 120 (9), 108 (10), 96 (17) 95 (11), 83 (11), and 82 (100); macrophylline, 239 (24), 141 (13), 140 (99), 139 (17), 138 (8), 122 (17), 111 (15), 110 (9), 108 (44), 98 (7), 96 (6), 84 (19), 83 (100), 82 (12), 81 (9) 80 (9) 70 (20), and 55 (70); amino alcohol from retusine, 157 (23), 113 (39), 83 (9), 82 (100), and 55 (6); macronecine, 157 (32), 140 (14), 111 (13), 108 (7), 98 (26), 84 (9), 83 (100), 82 (6), 70 (7), and 55 (22).

The Amino Alcohol from Retusine.—Retusine (131 mg) was refluxed for 16 hr with 15% hydrochloric acid. After cooling, the solution was diluted with water and extracted with ether to give crystalline α-dihydroanhydromonocrotalic acid[6] (64 mg), mp 129–130°. The aqueous mother liquor was evaporated to dryness to give a gum (45 mg) which crystallized on standing in a desiccator overnight. Free base was obtained by passing an aqueous solution of the crude hydrochloride through a column of Deacidite FF resin and eluting with water. The amino alcohol crystallized from acetone as colorless needles: mp 118.5–120°; $[\alpha]^{20}_D$ −3.5° (*c* 1.66, ethanol), $[\alpha]^{20}_D$ −18.1° (*c* 0.54, methanol). The amino alcohol had nmr and mass spectra identical with those of a sample of 7α-hydroxy-1β-hydroxymethyl-8β-pyrrolizidine supplied by Dr. Untch. The latter compound had mp 118–119°, and a mixture with the amino alcohol from retusine melted at 99–101°.

7-Angelylheliotridine (19).—Periodic acid (20 ml) was added to a solution of lasiocarpine (10 g) dissolved in 0.5 *N* sulfuric acid (50 ml). The reaction mixture, which darkened and deposited some black material, was stirred for 3 hr. The solution was washed with chloroform, made alkaline with sodium hydroxide, and extracted immediately with chloroform. The solvent was removed, leaving 7-angelylheliotridine as a gum which crystallized in large prisms from acetone: yield 3.28 g (55%); mp 116–118°, not depressed on admixture with authentic 7-angelylheliotridine.[21] Their nmr spectra were identical.

1β-Hydroxymethyl-7α-(2′-methylbutyroxy)-8α-pyrrolizidine (20).—A solution of **19** (2.8 g) in ethanol (25 ml) was hydrogenated at room temperature and atmospheric pressure using Raney nickel as catalyst. The theoretical amount of hydrogen was consumed in 20 min. The catalyst was removed and the filtrate was concentrated to leave a gum which did not crystallize. The product **20** (2.68 g, 94%) has an appropriate nmr spectrum and was chromatographically homogeneous (R_f 0.31). A picrolonate was obtained as short needles from ethanol; mp 140°.

Anal. Calcd for $C_{23}H_{31}N_5O_8$: C, 54.6; H, 6.2; N, 13.9. Found: C, 54.6; H, 6.0; N, 14.0.

In the initial run, a second product, R_f 0.11 (**20** has R_f = 0.31), was formed. The combined products (564 mg from 575 mg of **21**) were chromatographed on alumina (Woelm, Activity III). Chloroform eluted **20** (337 mg) and chloroform–4% methanol gave the second product as a gum (50 mg). Mass and nmr spectra of the second compound were consistent with the structure 1β-(2′-methylbutyroxy)methyl-7α-hydroxy-8α-pyrrolizidine (**21**) (see Results and Discussion). Only traces of **21** were formed in subsequent runs carried out under seemingly the same conditions. Hydrolysis of **21** (40 mg) was effected by heating with barium hydroxide (150 mg) in water (2 ml) at 100° for 1 hr. Working up as described for the hydrolysis of **20** (below) gave a colorless gum (18 mg, 69%), the nmr spectrum of which was identical with that of dihydroxyheliotridane.

Hydrolysis of 20.—A solution of **20** (70 mg) and barium hydroxide (170 mg) in water (2 ml) was heated at 100° for 1 hr. Carbon dioxide was then bubbled through the solution, the precipitate was filtered, and the filtrate was acidified with sulfuric acid, filtered again, and extracted with ether. The aqueous phase was passed through an anion-exchange resin (Amberlite Resin IRA-400) and concentrated to dryness under reduced pressure to give dihydroxyheliotridane as a colorless gum (42 mg, 92%). The nmr spectrum of the product was superimposable on that of authentic dihydroxyheliotridane.

1β-Carbethoxy-7α-(2′-methylbutyroxy)-8α-pyrrolizidine (22).—Jones reagent, a solution of chromic anhydride (2.1 g) in water (15 ml) and concentrated sulfuric acid (1.8 ml), was added to a solution of **20** (2.53 g) in acetone (75 ml), Some heat was evolved, the reaction mixture rapidly darkened, and a green precipitate formed. After 2 hr of stirring at room temperature (reaction followed by tlc), the mixture was filtered and the green solid was washed several times with acetone. Removal of acetone under diminished pressure from the combined filtrate and washings left the product dissolved in a small volume of aqueous sulfuric acid. The solution was made alkaline with barium hydroxide, filtered, treated with ammonia (5 ml), and extracted with chloroform. The extract contained mainly unchanged **20** (212 mg). The aqueous solution was neutralized with hydrochloric acid and adsorbed on cation-exchange resin [3 × 40 cm column, Amberlite Resin IR-120 (H)]. The product was washed until neutral and eluted with 5% ammonia. The eluent was removed under reduced pressure, leaving a white solid (*ca.* 1.8 g) which was redissolved in ethanol (75 ml) containing hydrogen chloride. After 2 days at room temperature, the ethanol was removed under vacuum and the remaining oil was basified with ammonia and extracted with chloroform. Removal of the solvent left 1β-carbethoxy-7α-(2′-methylbutyroxy)-8α-pyrrolizidine (**22**) as a chromatographically homogeneous (tlc) gum (1.24 g, 42%) with an appropriate nmr spectrum. The picrolonate formed short needles from ethanol; mp 132°.

Anal. Calcd for $C_{25}H_{33}N_5O_9$: C, 54.8; H, 6.1; N, 12.8; O, 26.3. Found: C, 54.3; H, 6.0; N, 13.0; O, 26.9.

To a suspension of lithium aluminium hydride (100 mg) in dry tetrahydrofuran (THF) (20 ml) was added a solution of **22** (57 mg) in THF (20 ml). The mixture was refluxed for 90 min, wet THF was added, and the mixture was filtered through Celite. The solvent was removed, leaving a gum (17 mg, 54%) whose nmr spectrum was superimposable on that of dihydroxyheliotridane.

(−)-1α-Carbomethoxy-7α-hydroxy-8α-pyrrolizidine (23).—The ester **22** (1.06 g) was dissolved in a solution of sodium (350 mg) in dry methanol (4 ml). The mixture, which immediately evolved a pleasant odor of methyl 2-methylbutyrate, was refluxed for 2 min and kept at room temperature for 5 min. Sulfuric acid (0.5 *N*, 50 ml) was added and the solution was

(22) C. C. J. Culvenor and L. W. Smith, *Aust. J. Chem.*, **14**, 284 (1961).
(23) A. J. Aasen and C. C. J. Culvenor, paper in preparation.

washed with chloroform. The washings, after removal of solvent at atmospheric pressure through a 10-cm Vigreux column, yielded a slightly colored oil (173 mg, 40%), $[\alpha]^{18}D$ −1.1° (c 2.3, methanol) [lit.[24] for optically pure ester, $[\alpha]^{27}D$ +21.1° (methanol)] whose nmr spectrum was consistent with methyl 2-methylbutyrate. The aqueous phase was made alkaline with ammonia and extracted 6–8 times with chloroform. Removal of the solvent left 1α-carbomethoxy-7α-hydroxy-8α-pyrrolizidine (**23**) as a colorless oil (493 mg, 71%) which did not crystallize. The nmr spectrum was indicative of one product only, there being one sharp singlet representing the methoxyl group. The hydrochloride formed needles from ethanol–ether: mp 134–135.5°; $[\alpha]^{20}D$ −18.5° (c 2.1, ethanol).

Anal. Calcd for $C_9H_{16}NO_3Cl$: C, 48.8; H, 7.2; N, 6.3. Found: C, 48.6; H, 7.3; N, 6.1.

(+)-**Hastanecine** (4).—A solution of **23** (352 mg) in THF (50 ml) was added to a suspension of lithium aluminium hydride (400 mg) in THF (30 ml). The reaction mixture was refluxed for 45 min and worked up as described above. (+)-Hastanecine crystallized as prisms from acetone: yield 246 mg (82%); mp 113–114°; $[\alpha]^{18}D$ +8.5° (c 2.2, ethanol), $[\alpha]^{18}D$ +8.2° (c 1.4, methanol) [lit. for (−)-hastanecine, mp 113–114°,[5] $[\alpha]^{20}D$ −10° (c 0.43, ethanol),[10] $[\alpha]D$ −9.1° (methanol)[3]]. A mixture melting point of (+)-hastanecine with (−)-hastanecine derived from hastacine was substantially depressed (to approximately 90°). The ir, nmr, and mass spectra were identical with those of (−)-hastanecine.

Anal. Calcd for $C_8H_{15}NO_2$: C, 61.1; H, 9.6; N, 8.9; O, 20.4. Found: C, 61.4; H, 9.6; N, 8.9; O, 20.8.

The hydrochloride formed needles from ethanol–ether; it had mp 132–134°, and did not appear to be hygroscopic as reported by Konovalov and Men'shikov.[3] Excess hydrochloric acid was carefully removed under vacuum in the present work.

Anal. Calcd for $C_8H_{16}NO_2Cl$: C, 49.6; H, 8.3; N, 7.2. Found: C, 49.8; H, 8.5; N, 7.1.

Registry No.—**1**, 520-62-7; **2**, 21824-59-9; **3**, 21850-67-9; **4**, 21824-60-2; **6**, 21824-61-3; **19**, 6029-83-0; **20** (picrolonate), 21824-63-5; **22** (picrolonate), 21824-64-6; **23** (HCl), 21824-65-7; **24**, 21824-66-8; **24** (HCl), 21824-67-9; **25**, 20361-77-7; **26**, 480-86-4; platyphylline, 480-78-4; neoplatyphylline, 20361-76-6.

(24) A. S. Dreiding and J. A. Hartman, *J. Amer. Chem. Soc.*, **75**, 939 (1953); V. M. Micovic and M. Lj. Mihailovic, *Bull. Soc. Chim. Belgrade*, **19**, 329 (1954).

The Saturated Pyrrolizidinediols. II. The Total Synthesis and Stereochemistry of Macronecine

A. J. AASEN and C. C. J. CULVENOR

Division of Applied Chemistry, C.S.I.R.O., Melbourne, Australia

Received May 14, 1969

Macronecine has been synthesised by a two-step reduction of 1-carbethoxy-2,3-dioxopyrrolizidine. The preparation and stereochemical definition of the other three diastereoisomers show that macronecine is 2β-hydroxy-1β-hydroxymethyl-8β-pyrrolizidine.

Macronecine is a dihydroxy amino alcohol obtained by hydrolysis of macrophylline, an alkaloid of the Caucasian species *Senecio macrophyllus*.[1] The degradation of macrophylline to laburnine (1β-hydroxymethyl-8β-pyrrolizidine)[2] established all structural features of macronecine other than the location of the second hydroxyl group. The relationship of macronecine to other saturated pyrrolizidinediols is discussed in the preceding communication,[3] in which it is shown from spectral evidence that macronecine is a 2-hydroxy compound, probably 2β-hydroxy-1β-hydroxymethyl-8β-pyrrolizidine (**1**). A synthesis[4] of **1** was undertaken to confirm this structure (Chart I).

The readily available (±)-1-carbethoxy-2,3-dioxopyrrolizidine (**2**)[5] was chosen as the starting point. This substance appears to exist almost entirely in the enol form (**2b**) rather than the keto form (**2a**). It is not extractable from alkaline solution and it is readily methylated with diazomethane.[5] Apart from the methyl signals, its nmr spectrum measured in deuteriochloroform has multiplets corresponding to only four protons at higher field than δ 3.0, leaving no signals attributable to a proton on C-1. Instead, there is a rounded multiplet at δ 8.9, exchangeable on shaking with deuterium oxide, due to the enolic OH. The spectrum is unaltered by the addition of trifluoroacetic acid. Adams, *et al.*,[5] reduced **2** catalytically in the presence of rhodium and then further with lithium aluminium hydride to obtain a 2-hydroxy-1-hydroxymethylpyrrolizidine of undefined stereochemistry, differing from macronecine. Assuming addition of hydrogen to the unhindered side of the enol double bond, the initial reduction product should be (±)-1β-carbethoxy-2β-hydroxy-3-oxo-8α-pyrrolizidine (**5**) and the final product should be (±)-2β-hydroxy-1β-hydroxymethyl-8α-pyrrolizidine (**9**). This stereochemistry is supported by an analysis of the nmr spectrum of the diol[3] and has now been confirmed by conversion of the substance into (±)-heliotridane by reaction with thionyl chloride followed by removal of the chlorine atoms by hydrogenolysis. The β configuration of the 2-hydroxyl group was confirmed when the 2α-hydroxy-1β-hydroxymethyl diastereomer (**10**), prepared by catalytic reduction of 1β-hydroxymethyl-1α,2α-epoxy-8α-pyrrolizidine (**6**),[6] proved to be different from **9**.

The hydrogenation of **2** in the presence of platinum and ruthenium catalysts also led to **5**, but in the presence of Raney nickel at elevated temperature and pressure this product was accompanied by approximately 15% of another isomer. Although the mixed product was difficult to resolve, nmr spectra revealed signals additional to those of **5** and later found to correspond with those of the 1α-carbethoxy-2α-hydroxy isomer (**3**). Evidently, some *cis* addition of hydrogen had occurred to the more hindered side of the double bond. On treat-

(1) A. Danilova, L. Utkin, and P. S. Massagetov, *Zh. Obshch. Khim.*, **25**, 831 (1955).

(2) A. V. Danilova and L. M. Utkin, *ibid.*, **30**, 345 (1960).

(3) A. J. Aasen, C. C. J. Culvenor, and L. W. Smith, *J. Org. Chem.*, **34**, 4137 (1969).

(4) A preliminary announcement has been made: A. J. Aasen and C. C. J. Culvenor, *Chem. Commun.*, 34 (1969).

(5) R. Adams, S. Miyano, and M. D. Nair, *J. Amer. Chem. Soc.*, **83**, 3323 (1961).

(6) We thank Mr. R. S. Sawhney for the initial preparation of **10** in this way.