and the mixture was refluxed for 4.5 hr. Sodium chloride was removed by filtration, and the solvent was removed. The residue was triturated with 1500 ml of ether, filtered, and concentrated to a volume of 120 ml. The solution was cooled and 9.76 g of carbinol was obtained. The solution was concentrated and an additional 1.38 g of alcohol crystallized. The total yield was 74% of material having $[\alpha]^{23}D$ +17.4° (*c* 0.98, chloroform), mp 178–179.5°. This procedure was applied to (±)-phenylbiphenylyl-α-naphthylmethoxyacetamide and triphenylmethoxyacetamide with similar results.

Anal. Calcd for $C_{29}H_{22}O$: C, 90.12; H, 5.74. Found: C, 89.84; H, 5.74.

(−)-Phenylbiphenylyl-α-naphthylcarbinol was prepared according to the procedure in the preceding paragraph, mp 175–177°, $[\alpha]^{23}D$ +3.17° (*c* 1.42, benzene); $[\alpha]^{23}D$ 16.5° (*c* 1.2. chloroform).

Resolution of Carbinol by the Method of Wallis and Adams.[8] (±)-Phenylbiphenylyl-α-naphthylmethylthioglycolic acid–toluene was prepared as described by Wallis. The acid (56 g) was dissolved in 100 ml of warm acetone and added while still warm to an acetone suspension of brucine (42 g). The solution was warmed until clear. The solution did not deposit crystals. The solvent was removed *in vacuo*, and the glassy residue was dissolved in hot ethyl acetate. The cooled solution deposited crystals. In subsequent resolutions of the thioacid, acetone proved satisfactory. The first crop of crystals weighed 44 g and had $[\alpha]^{23}D$ −15.6° (*c* 2.68, chloroform). The salt was recrystallized by dissolving it in a minimum amount of boiling chloroform and adding petroleum ether (bp 60–70°) until cloudiness persisted at the boiling point. The solution was set aside overnight. The solid was filtered and dried (33 g) and its rotation was determined, $[\alpha]^{23}D$ −16.8° (*c* 2.85, chloroform). Wallis found −16.93°.

The acid was liberated from the brucine salt as described by Wallis, $[\alpha]^{23}D$ −13.2° (chloroform).

One gram of (−)-acid was dissolved in acetone and treated with aqueous silver nitrate. The resulting precipitate of silver salt was removed by filtration and washed with acetone. The aqueous acetone filtrate was diluted with water and stirred for 1 hr until the precipitated alcohol coagulated. The precipitate was filtered and dried (300 mg), $[\alpha]^{23}D$ +10.5° (*c* 0.96, chloroform); $[\alpha]^{24}D$ +4.4° (*c* 0.08, carbon tetrachloride). The rotation in chloroform corresponds to alcohol of 58% optical purity, the remainder being racemic material.

The alcohol samples were recovered from the solutions used to determine the rotations, and the combined material was dissolved in a minimum quantity of boiling ether. The cooled solution was seeded with a tiny crystal of (+)-carbinol and set aside overnight. The majority of material was in the form of clusters of heavy short needles, together with a few well-formed cubes. The latter were removed mechanically and the ether supernatant was decanted. The ether was combined with the cubes and the whole taken to dryness. The residue (80 mg) showed a rotation of $[\alpha]^{23}D$ 1.5° (*c* 0.79, chloroform). The needles showed a rotation of $[\alpha]^{23}D$ +16 ±1° (*c* 0.57, chloroform).

Acknowledgment. This work was aided by the gift of a sample of pure brucine by the Mallinckrodt Chemical Works. The authors are indebted to C. Elliger, L. DeBow, J. Robbins, and N. Werstiuk for conducting several pilot experiments.

Structure of the Mesembranols and the Absolute Configuration of Mesembrine and Related Alkaloids[1,2]

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Contribution from the Department of Chemistry, Duke University, Durham, North Carolina 27706. *Received January 27, 1969*

Abstract: The relative configurations of the epimeric alcohols, (−)-mesembranol (**2**) and (−)-6-epimesembranol (**3**), have been established by spectral studies of the alcohols and their O-acetyl derivatives **4** and **5**. Supporting evidence for the configurational assignments is presented from the saponification rates of **4** and **5** and rates of acetylation of the alcohols. In the latter reaction an unusually facile acetylation of 6-epimesembranol is consistent with neighboring group participation by the nitrogen to account for the rate enhancement. Analysis of the nmr spectrum of the alkaloid mesembrine indicates that it also exists predominantly with ring B in the chair conformation **1A** in which the aryl substituent is quasi-axial. Interpretation of the CD spectrum of mesembrine on the basis of this conformation for ring B leads to a reassignment of the absolute configuration of mesembrine as indicated by structure **1**. A discussion of the conformational features of mesembrine is presented.

Interest in the constituents of certain *Sceletium* species of the family *Aizoaceae*, which are indigenous to Southwest Africa, has stemmed from the time of recognition of their use for the preparation of the drug *Channa*.[4]

Alkaloidal substances were first detected in the *Channa* drug in 1896.[7] In 1914, Hartwich and Zwicky[8] isolated an amorphous base which they termed "mesembrin." In view of more recent studies, this material most likely consisted of a mixture of alkaloids. In a subsequent study Rimington and Roets[9] assigned to mesembrine the empirical formula $C_{17}H_{23}NO_3$ deduced from analyses of the crystalline picrate and chloroplatinate. Later Bodendorf and Krieger[10]

(1) This work was supported by the National Science Foundation (Grant GB 4361) and a Biomedical Sciences support grant to Duke University (PHS Grant 5-S05-FR07070), and constituted part of the material submitted by D. S. Farrier in partial fulfillment of the requirement of the Ph.D. degree of Duke University, Oct 1968.

(2) The subject of this paper constituted part of a symposium lecture given by P. W. J. at the Southeastern Regional Meeting of the American Chemical Society, Tallahassee, Fla., Dec 5, 1968.

(3) National Aeronautics and Space Administration Fellow, 1965–1968.

(4) This is the name given to the drug in the earliest reference available to us[5] in which its use by the Hottentots and Bushman, tribes endemic to the region at that time, was reported. Later references[6] refer to this under both the name *Channa* and *Kougoed*; the latter term probably has its origins in the language of the early Dutch settlers.

(5) P. Kolben "The Present State of the Cape of Good Hope," Vol. I, 2nd ed, G. Medley, trans., W. Innys and R. Manby, London, 1738, p 212.

(6) E. M. Holmes, *Pharm. J. Trans.*, **9**, 810 (1874); C. F. Juritz, *Rep. Jt. Meet. Brit. Assn. S. Afr. Assn. Advan. Sci.*, **1**, 216 (1905).

(7) I. Meiring, *Trans. S. Afr. Phil. Soc.*, **9**, 48 (1898).

(8) G. Hartwich and E. Zwicky, *Deut. Apotheker-Z.*, 949 (1914).

(9) C. Rimington and G. C. S. Roets, *Onderstepoort J. Vet. Sci. Anim. Ind.*, **9**, 187 (1937).

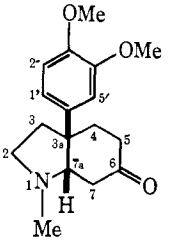
described a crystalline hydrochloride of mesembrine along with two new alkaloids, mesembrenone[11] and channanine, which were isolated from *Channa*. The structure of mesembrine as N-methyl-3a-(3′,4′-dimethoxyphenyl)-6-oxo-*cis*-octahydroindole (**1**) was finally elucidated in 1960 through degradative and synthetic studies by Popelak and coworkers.[14] Isolation and structural studies of mesembrine and related alkaloids have been summarized in a recent review.[12]

The first total synthesis of (±)-mesembrine by Shamma and Rodriguez[15] and subsequent elegant, and more expeditious, syntheses[16] of (±)-**1** have amply confirmed the structural and stereochemical features deduced by Popelak and coworkers for this alkaloid.

In the course of investigating the chemistry and biosynthesis of mesembrine and related alkaloids,[17] it became important to establish the stereochemistry of the C-6 hydroxyl in (−)-mesembranol (**2**), which was first reported by Bodendorf and Krieger[10] as the only product obtained from catalytic hydrogenation of (−)-mesembrine. Later Shamma and coworkers[13] found that **2** occurs in *S. strictum*, but no attempts to elucidate the configuration of the C-6 hydroxyl in the alkaloid were reported.

Preparation of the Epimeric C-6 Mesembranols. Catalytic hydrogenation of mesembrine over platinum was repeated under the conditions previously reported.[10] Gas chromatographic examination of the product on completion of the hydrogenation showed that the reaction led exclusively to the crystalline alcohol **2** in quantitative yield. In contrast, reduction of mesembrine with sodium borohydride in methanol afforded mesembranol as the minor constituent of a two-component mixture. Separation of the major product—presumably 6-epimesembranol (**3**)—from the accompanying mesembranol could be effected by analytical gas and thin layer chromatography but separation by preparative chromatographic techniques was extremely difficult; only "dry-column" chromatography[18] with continuous solvent gradient (see Experimental Section) was found to be really effective. The analytical and spectral data, which are discussed in detail in the sequel, were in complete accord with the expected assignment of the major product as (−)-6-epimesembranol (**3**). Corroboration of the epimeric relationship between (−)-**2** and (−)-**3** was established by their conversion to (−)-mesembrine on oxidation with chromic acid.

Acetylation of the alcohols **2** and **3** could be accomplished readily to afford the corresponding O-acetates (−)-**4** and (−)-**5**, respectively. Reduction of **4** and **5** with lithium aluminum hydride afforded the parent alcohols in high yield.



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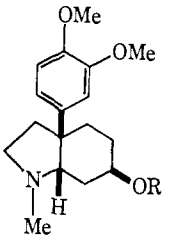
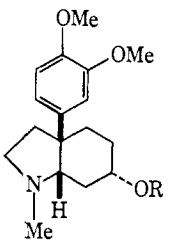


2, R = H
4, R = Ac



3, R = H
5, R = Ac

Spectral Studies. The nmr spectra of mesembranol and 6-epimesembranol and their corresponding O-acetyl derivatives were examined. The C-6 hydrogen resonance signal, which was of paramount interest for configurational assignments, was obscured by the methoxyl resonances in the deuteriochloroform spectra of the alcohols but was clearly resolved when benzene was employed as a solvent (Figure 1). Assignment of the C-6 hydrogen signal in the alcohols was evident from its chemical shift and the characteristic downfield shift of this signal in the spectra of the derived acetates (Figure 2). Recorded in Table I are the chemical shift and half-height width ($W_{1/2}$)[19] of this signal as found in the two alcohols and their acetates.

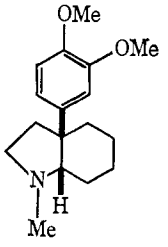
Table I. C-6 and C-7a Hydrogen Resonance Signals

Compound	C-6 hydrogen δ	C-6 hydrogen $W_{1/2}$, Hz	C-7a hydrogen δ	C-7a hydrogen J_{app}, Hz
Mesembranol[a]	4.08	24.0	2.83	2.5
O-Acetylmesembranol[b]	5.10	23.5	2.83	3.0
6-Epimesembranol[a]	4.00	9.0	2.79	2.5
O-Acetyl-6-epimesembranol[b]	4.88	11.0	2.85	6.0
Mesembrine[a,b]			2.94	3.0

[a] Measured in benzene at 100 MHz. [b] Measured in $CDCl_3$ at 100 MHz.

(10) K. Bodendorf and W. Krieger, *Arch. Pharm.* (Weinheim), **290**, 441 (1957).

(11) Some confusion exists on the naming of this compound; two spellings have appeared, mesembrinine[10] and mesembrenine.[12] Neither of these trivial names is appropriate in view of the subsequent demonstration of its structure as an α,β-unsaturated ketone. A similar situation exists in the related alcohol nomenclature, to which the trivial name mesembrinol has been applied.[13] Adaptation of the name mesembrane (i), which has been synthesized and so named,[14] as the parent name for this ring system and subsequent designation of the related alkaloids according to current convention would alleviate much of the confusion. It is particularly important to correct this somewhat ambiguous nomenclature while the alkaloids of known structure in this series in the literature are restricted to three examples—mesembrine, mesembrenine, and mesembrinol—since investigations in this laboratory pending publication will more than triple this number. Therefore all names used subsequently in this paper will be based on the proposed convention, with the exception of mesembrine. Adoption of the more systematic name mesembranone in this case would only create confusion due to the frequent appearance of the name mesembrine in the current literature.



i

(12) A. Popelak and Lettenbauer, "The Alkaloids," Vol. IX, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1968.

(13) E. Smith, N. Hosansky, M. Shamma, and J. B. Moss, *Chem. Ind.* (London), 402 (1961).

(14) (a) A. Popelak, E. Haack, G. Lettenbauer, and H. Spingler, *Naturwissenschaften*, **47**, 156 (1960); (b) *ibid.*, **47**, 231 (1960).

(15) M. Shamma and H. R. Rodriguez, *Tetrahedron Lett.*, 4347 (1965).

(16) R. V. Stevens and M. P. Wentland, *J. Amer. Chem. Soc.*, **90**, 5580 (1968); S. L. Keely, Jr., and F. C. Tahk, *ibid.*, **90**, 5584 (1968); T. J. Curphey and H. L. Kim, *Tetrahedron Lett.*, 1441 (1968).

(17) P. W. Jeffs, W. C. Archie, and D. S. Farrier, *J. Amer. Chem. Soc.*, **89**, 2509 (1967); P. W. Jeffs, D. S. Farrier, and G. Ganguli, Abstracts, Vth Natural Product Congress of the International Union of Pure and Applied Chemistry, London, July 1968, p C10.

(18) B. Loev and M. Goodman, *Chem. Ind.* (London), 2026 (1967).

(19) (a) A. Hassner and C. Heathcock, *J. Org. Chem.*, **29**, 1350 (1964), and references cited therein; (b) S. G. Levine, N. Eudy, and C. F. Leffler, *ibid.*, **31**, 3995 (1966).

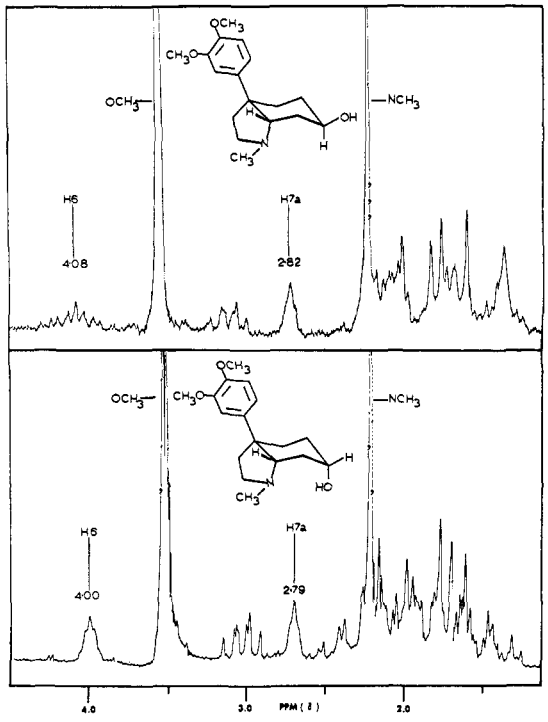


Figure 1. Partial 100-MHz nmr spectra of mesembranol (**2**) and 6-epimesembranol (**3**) in benzene.

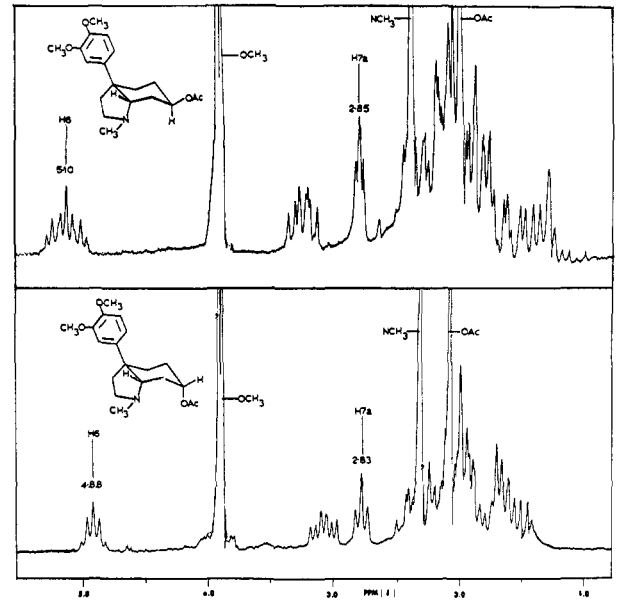


Figure 2. Partial 100-MHz nmr spectra of O-acetylmesembranol (**4**) and O-acetyl-6-epimesembranol (**5**) in $CDCl_3$.

The distinction of axial and equatorial alcohols in an epimeric pair can usually be made on the basis of the relative chemical shift criteria and/or the half-band width characteristics of the methine hydrogen signal. Inspection of the spectra of mesembranol and its O-acetyl derivative shows very broad signals for the C-6 resonance whose half-band width values are in excellent agreement with the values reported[19a] for axial hydrogens in AX_2Y_2 systems. In comparison, the C-6 hydrogen signal in 6-epimesembranol and its O-acetate has a much narrower half-band width, which is only consistent with this proton being equatorial in character.

On the basis of characterization of mesembranol as an equatorial alcohol and 6-epimesembranol as an axial alcohol from the half-band width criteria, the chemical shift of the C-6 methine hydrogen signals in the spectra of these compounds and their O-acetyl derivatives does not follow the usual trend, *i.e.*, the axial hydrogen in **2** appears at slightly lower field than in its equatorial counterpart **3** (Table I). This reversal of the normal course of relative chemical shifts occurs because the C-6 hydrogen signals in mesembranol and its O-acetate appear at anomalously low field for axial hydrogens. It is well known that long-range deshielding effects by π systems and polar groups may in some cases be sufficient to cause a reversal[20] and the results in no way vitiate the assignments made from the more reliable half-band width data. A rational explanation of the relative chemical shifts of the C-6 hydrogen could be provided once full details of both configuration and conformation were established (*vide infra*).

The infrared spectrum of mesembranol shows a free OH stretching absorption at 3628 cm^{-1} in dilute solutions of carbon tetrachloride. In contrast, 6-epimesembranol shows the complete absence of any free OH band; instead a broad OH absorption (band width *ca.* 575 cm^{-1}) occurs at 3380 cm^{-1} in CCl_4 solution which persists over the concentration range 1.5×10^{-3} *M* to 6.4×10^{-4} *M*. The position of this absorption maximum, and its concentration independence, are indicative of an intramolecular hydrogen bond[23] of the type OH–N. Assignment of the bands at 3628 cm^{-1} and 3380 cm^{-1} in **2** and **3** to hydroxyl stretching frequencies was confirmed by their disappearance on exposure of the alcohols to deuterium oxide.[24]

Consideration of the nmr and ir results leads to some striking conclusions regarding the configurational and conformational picture in these two alcohols and their acetates. If discussion of the conformation of ring **B** in these compounds is restricted to structures involving only chair forms, the C-6 epimeric alcohols may be represented by the four structures shown in Chart I.

Conformations **2B** and **3B** of the C-6 epimeric alcohols have the bulky 3,4-dimethoxyphenyl substituent equatorial, and preliminary considerations would suggest that they are more stable than **2A** and **3A**, respectively, in which this group is axial. However, the demonstration of the presence of a strong intramolecular OH–N hydrogen bond, coupled with the nmr evidence for the equatorial nature of the C-6 hydrogen in 6-epimesembrinol, is only consistent with the axial phenyl conformation, **3A** for this compound. Arguments in favor of the contribution of the strong hydrogen bond for the stabilization of this conformation are immediately suggested, but the fact that the nmr spectra of the epimeric alcohol **2** and its acetate **4** clearly estab-

(20) *Cf.* relative chemical shifts of axial and equatorial hydrogens α to the carbonyl in cyclohexanones[21] and the deshielding of axial hydrogens by various electronegative groups situated in a 1,3-diaxial relation.[22]

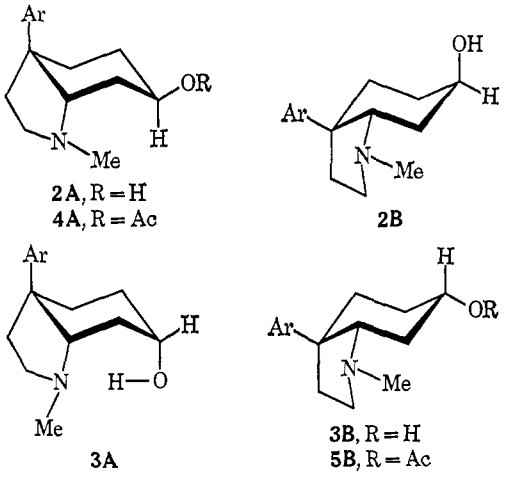
(21) G. J. Karabatsos, G. C. Sonnichsen, H. Hsi, and D. J. Fenoglio, *J. Amer. Chem. Soc.*, **89**, 5067 (1967).

(22) N. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., New York, N. Y., 1964, p 184.

(23) M. Tichy, *Advan. Org. Chem.*, **5**, 115 (1965).

(24) H. M. Fales and Q. V. Robertson, *Tetrahedron Lett.*, 111 (1962), and references cited therein.

Chart I. Chair Conformations of C-6α and C-6β Mesembranols and Their O-Acetyl Derivatives, Ar ≡ 3,4-Dimethoxyphenyl



2A, R = H
4A, R = Ac

2B

3A

3B, R = H
5B, R = Ac

lish the equatorial disposition of the oxygen function in same compounds implies that they too must possess the same ring **B** conformation as 6-epimesembranol.

Furthermore, although the C-6 hydrogen signal in the spectrum of the O-acetate **5** is somewhat broader than in its parent alcohol **3** it is clearly not in accord with an axial hydrogen signal. This precludes the representation of this acetate in conformation **5B** and is in best accord with its existing predominantly[25] in the same conformation as the alcohols **2** and **3**.

Thus, the preliminary nmr and ir spectral results point clearly to a ground-state conformation in which the *3,4-dimethoxyphenyl substituent occupies an axial position in both epimeric mesembranols and their O-acetyl derivatives.*

In view of this totally unexpected result, further detailed analysis of the nmr spectra of these and related compounds was pursued in an attempt to corroborate these findings.

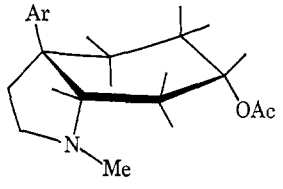
The C-7a hydrogen is situated at a strategic position for providing conformational information on ring **B** in this series, and location and analysis of its resonance were therefore of prime importance.

Two one-proton signals, a triplet and multiplet, appear in the spectra of mesembrine, the mesembranols, and their O-acetyl derivatives in the region between δ 2.7 and 2.95 in which the C-7a hydrogen resonance is expected to occur. It was possible to assign the triplet to the C-7a hydrogen resonance from the observation that it collapsed to a singlet in the spectrum of 5,5,7,7-d_4-mesembrine as a result of the removal of its spin coupling by replacement of the hydrogens on C-7 with deuterium. The triplet nature of the signal and the small splitting observed, which are recorded in Table I as apparent coupling constants, are only consistent with an equatorial C-7a hydrogen which is approximately equally coupled to the adjacent C-7 methylene hydrogens. Inasmuch as the small splittings reflect couplings, the values are in accord with equatorial–axial and equatorial–equatorial couplings expected if the C-7a hydrogen bisects the angle between the adjacent C-7 hydrogens.[27]

The equatorial nature of the C-7a hydrogen indicated by the foregoing results affords strong support for the axial aryl conformations **2A** and **3A** as the preferred conformations of mesembranol and 6-epimesembranol, respectively.

A further indication supporting the proposed stereochemical assignments of the mesembranols is obtained from a comparison of the chemical shift of the N-methyl hydrogens in this series. Mesembrine, mesembranol, and its O-acetyl derivative show N-methyl signals over the range δ 2.32–2.36, in excellent agreement with the value of δ 2.36 for the analogous signal of the simple model, N-methylpyrrolidine. In contrast, 6-epimesembranol and its O-acetate reflect the proximity of the *cis* relation of the C-6 oxygen function by the perturbation of the N-methyl signals in these compounds, which appear at δ 2.46 and 2.26, respectively.

The anomalously low-field position of the C-6 hydrogen signal in mesembranol and its O-acetyl derivative may now be accounted for satisfactorily in terms of the proposed structures **2A** and **4A**, respectively, since it is in this conformation that deshielding of the hydrogen in question would be predicted from its *cis* 1,3 diaxial relationship to the nitrogen atom.[22] Distortion of the axial aryl conformation of ring **B** in O-acetyl-6-epimesembranol, alluded to earlier in discussing half-band width data of the C-6 hydrogen signal, is vindicated by the observation of a comparable increase in the spin coupling of the C-7a hydrogen (see Table I). Such an effect might be anticipated to occur in order to release the 1,3 interactions of the N-methyl and C-6 acetoxyl groups. The relative increases in coupling are small enough to preclude inversion to the other chair form corresponding to **2B**, and the most satisfactory representation is the distorted half-chair **5A**.[28]



5A

The stereochemical assignments of mesembranol (**2**) and 6-epimesembranol (**3**) are therefore supported by infrared spectral studies and from an analysis of nmr spectral results which provide interlocking evidence for the alcohols **2** and **3** existing in the preferred conformations **2A** and **3A**, respectively, in which the bulky aryl substituent is axial. Only in the case of O-acetyl-6-epimesembranol is there any evidence for a ring **B** conformation other than the axial aryl chair conformation of the mesembranols, and even in this case the distorted chair form **5A** is preferred over **5B**.

(25) The *cis* B:C ring juncture in the mesembranols and their relatives permits, in principle, conformational inversion of the cyclohexane ring to occur. Evidence that O-acetylmesembranol is conformationally homogeneous with respect to ring B was suggested by the absence of any significant changes in its nmr spectrum over the temperature range −40 to 80°. The extension of these conclusions to **2** and **3** is reasonable, and is supported by the C-6 hydrogen half-band width data for these compounds.[26]

(26) N. C. Franklin and H. Feltkamp, *Angew. Chem. Int. Ed. Engl.*, 4, 774 (1965).

(27) Reference 22, p 80.

(28) A similar, but much more pronounced, distortion of ring B evidently occurs in 6-epimesembranol methiodide as inferred from the characteristics of both C-6 and C-7a proton signals. Details of the structure of this compound are under investigation by X-ray analysis in collaboration with Professor A. T. McPhail.

Table II. Rates of Hydrolysis of the O-Acetylmesembranols **4** and **5** and Rates of Acetylation of Mesembranol and 6-Epimesembranol

Compound	Reaction	Temp, °C	$t_{1/2}$, sec	k_1, sec^{-1}
O-Acetyl-mesembranol (**4**)	Saponification	25	21.0×10^2	3.3×10^{-4}
O-Acetyl-6-epi-mesembranol (**5**)	Saponification	25	45.0×10^2	1.54×10^{-4}
Mesembranol (**2**)	Acetylation	0	11.9×10^3	5.83×10^{-5}
6-Epimesembranol (**3**)	Acetylation	0	28.8×10^2	2.41×10^{-4}

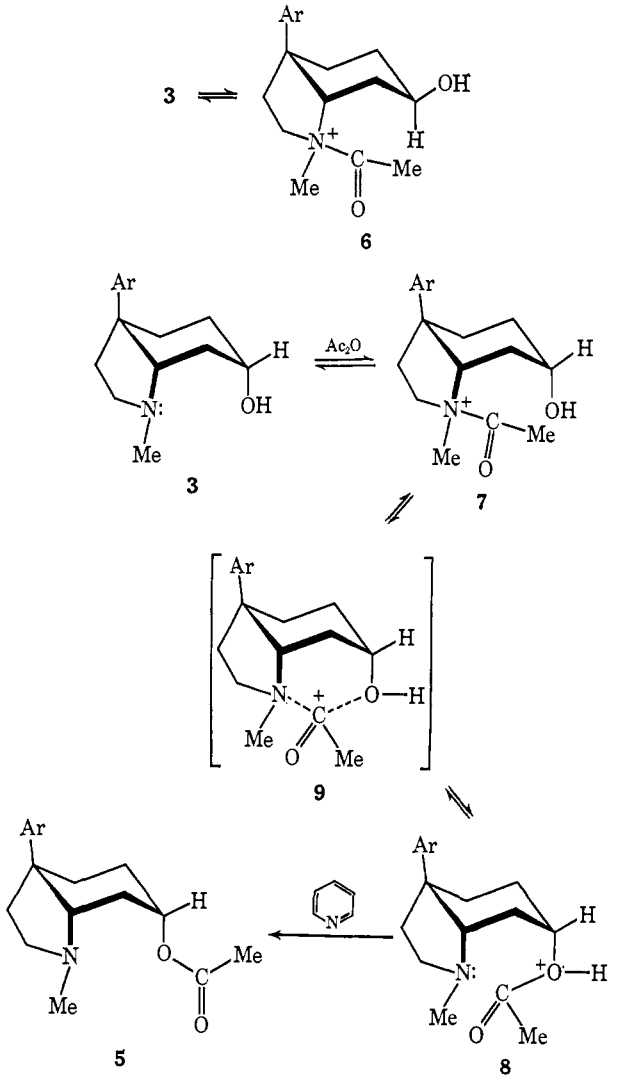
Kinetic Studies. The conformational characteristics of the mesembranols derived from the spectral studies were rather surprising and we sought further evidence on the problem through kinetic studies.

The rates of saponification of esters of cyclohexanol derivatives reflect the steric environment of the oxygen substituent[29] and as a consequence of the greater steric demands of the intermediate in this reaction, equatorial acetates are hydrolyzed 2–3 times more rapidly than their axial epimers.

Hydrolysis of (−)-O-acetylmesembranol (**4**) and (−)-O-acetyl-6-epimesembranol (**5**) in 0.5 *N* K_2CO_3 in methanol–water (1:1) was carried out at 25° under conditions designed to give pseudo-first-order kinetics. The results shown in Table II indicate that in consonance with the assignment of O-acetylmesembranol as an equatorial acetate, it hydrolyzed approximately twice as fast as the epimeric acetate **5**.

Application of the kinetic method to the acetylation of cyclohexanols[30] provides a complementary approach to the saponification reaction and normally one observes corresponding relative rates for the epimeric pair in each reaction. It was therefore interesting to find that the relative rates of acetylation of the alcohols **2** and **3** with acetic anhydride and pyridine appeared to be in the reverse order to the relative rates of saponification, *i.e.*, the axial alcohol, 6-epimesembranol, was acetylated more rapidly than its epimer. Moreover, not only were the relative rates the inverse of those expected for axial and equatorial alcohols but a comparison of $t_{1/2}$ values indicated that acetylation of the axial alcohol **3** is four times as rapid as its equatorial counterpart. This rate enhancement is readily understood if one considers that the alcohols **2** and **3** undergo reversible formation of the acetyl ammonium salts **6** and **7** in acetic anhydride, which in the case of the latter salt is followed by N → O intramolecular acyl transfer[31] to afford the O-protonated acetate **8** *via* the cyclic transition state **9**. Obviously the opportunity for intramolecular O-acylation is not available in the case of the salt **6** which therefore is converted to the O-acetate **4** by the usual intermolecular processes.

The kinetic results are therefore in full accord with the configurational and conformational assignments made on the basis of the spectral studies.



Absolute Configuration of Mesembrine

Shamma and coworkers made the reasonable assumption that of the two chair forms **1A** and **1B** the latter represented the preferred conformation of mesembrine and on the basis of its ORD spectrum they represented the absolute stereochemistry of the alkaloid as corresponding to the enantiomer of **1B**. However, the nmr spectrum of mesembrine is not consistent with its representation as **1B** or its enantiomer since the disposition of the C-7a hydrogen is clearly equatorial from the triplet nature of its resonance signal (Table I). Therefore the evidence for the absolute configuration of this alkaloid needs to be reexamined.

Although the absence of *trans*-diaxial coupling in the C-7a hydrogen signal excludes the conformational representation of mesembrine as **1B** or its enantiomer,

(29) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 222.

(30) E. L. Eliel and F. J. Biros, *J. Amer. Chem. Soc.*, **88**, 3334 (1966).

(31) A. Nickon and L. F. Fieser, *ibid.*, **74**, 5566 (1952); H. O. House, H. C. Muller, C. G. Pitt, and P. P. Wickham, *J. Org. Chem.*, **28**, 2407 (1963); G. Fodor and K. Nador, *J. Chem. Soc.*, 721 (1953). An alternative explanation of the observed rate of enhancement is to consider that the acetylation of **3** proceeds with intramolecular general base catalysis with the nitrogen functioning as the internal base. (T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. 1, W. A. Benjamin, Inc., New York, N. Y., 1966, p. 125.) Such an alternative proposal in no way affects the stereochemical conclusions derived from the above arguments.

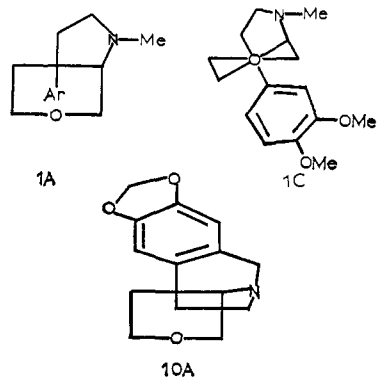
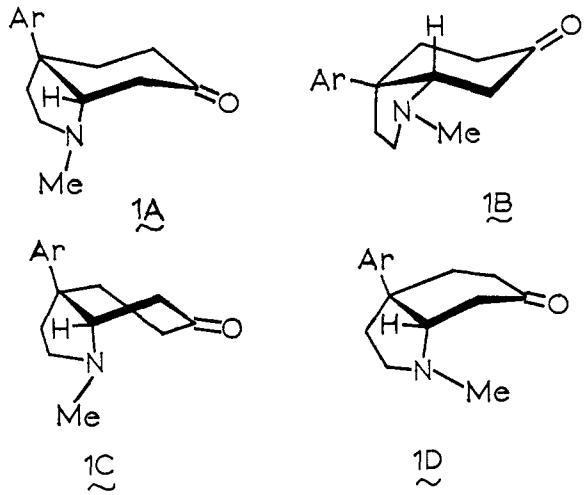


Figure 3. Octant projections of mesembrine (**1A** and **1C**) and dihydrooxocrinine (**10A**).

the twist form **1C** and the boat form **1D** show the same dihedral angle relationship between the C-7a hydrogen and neighboring methylene hydrogens as in the chair form **1A**. The energy differences between chair conformers and flexible forms in substituted cyclohexanones is often quite small in comparison to the corresponding



cyclohexanols, and situations exist where nonchair forms contribute significantly to the conformer population. Examination of Dreiding models of the three conformers **1A**, **1C**, and **1D** reveals that the boat form **1D** possesses nonbonded "flagpole" interactions of the C-4β and C-7β hydrogens which, in the absence of other compensating factors, suggests it should be the least stable of the three. An estimate of the relative stabilities of the chair and twist forms on a similar basis could not be made with any confidence. Fortunately the representation of mesembrine as the chair form **1A** or twist form **1C**, or an equilibrium mixture of **1A** and **1C**, is of no consequence to assigning its absolute configuration since the negative Cotton effect previously observed in the ORD spectrum of the alkaloid[13] is predicted by both of these conformations in this antipodal series from their octant projections (see Figure 3). Thus (−)-mesembrine possesses the absolute configuration represented by structure **1**. Consequently, this assignment leads to the absolute stereochemistry of (−)-mesembranol (**2**) and permits a correlation to be made for other alkaloids of this series.

Although the octant projections of **1A** and **1C** both predict a negative Cotton effect, previous studies[32]

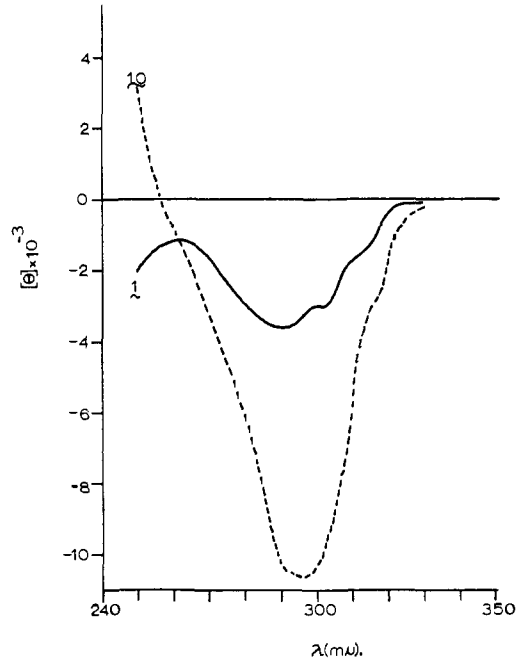
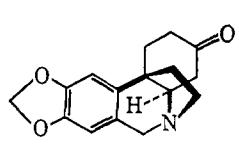


Figure 4. Circular dichroism curves of mesembrine (**2**) and dihydrooxocrinine (**10**) recorded in dioxane.

have shown that twist forms of cyclohexanones exhibit abnormally large Cotton effect amplitudes. Therefore, despite the fact that both upper right and lower right octants of **1C** contain substituent groups which would largely counterbalance each other's rotatory contribution, the chirality of the skewed cyclohexanone ring places both C-7a and C-4 in negative octants and leads to the prediction of a strong Cotton effect for this conformer. Consequently, conformation **1A** would be expected to afford a weaker Cotton effect than **1C** from a comparison of their octant projections.

In the absence of even semiquantitative data on the rotatory contribution of the highly polarizable nitrogen substituent and the two-carbon bridge in mesembrine, it is necessary to seek some suitable system for a comparison of its rotational strength.

(−)-Dihydrooxocrinine (**10**),[33] which is derived from the *Amaryllidaceae* alkaloid, (−)-crinine, constitutes an excellent model, since not only is its absolute configuration known,[34] but more importantly, the tetracyclic nature of the ring system places certain restrictions on the conformation of the cyclohexanone ring, which must surely exist as indicated in **10A**.



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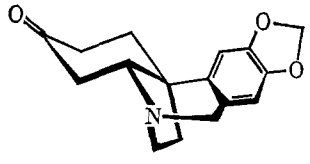


10A

The circular dichroism spectra of the two ketones **1** and **10** (Figure 4) show that while both display negative maxima for the n → π* band, the rotational strength

(32) D. Djerassi and W. Klyne, *Proc. Nat. Acad. Sci. U. S.*, **48**, 1093 (1402).
(33) W. C. Wildman, *J. Amer. Chem. Soc.*, 80, 2567 (1958).
(34) For the absolute configuration of (−)-crinine, see P. W. Jeffs, F. L. Warren, and W. G. Wright, *J. Chem. Soc.*, 1090 (1960); R. J. Highet and P. F. Highet, *J. Org. Chem.*, 33, 3105 (1968).

of the absorption band is much weaker for (−)-mesembrine.

This result is consistent with (−)-mesembrine existing predominantly in the chair form **1A** which would be anticipated to show a weaker Cotton effect than **10A** from a comparison of their octant projections shown in Figure 3. Consequently, if the twist form **1C** exists in equilibrium with **1A** it presumably makes only a small contribution at room temperature.

Analysis of the Conformational Features of Mesembrine. The foregoing results provide firm evidence for representing the preferred ground-state conformations of mesembrine and the related alcohols **2** and **3** as the axial aryl conformations **1A, 2A,** and **3A,** respectively. Although no satisfactory explanation can be advanced at present to account for this interesting, if unexpected, result, some comment on the analysis of the conformational features of the mesembrine series is desirable. In the absence of dipolar interactions, which cannot be important in view of the similar conformations adopted by both epimeric mesembranols and also mesembrine, the conformational energies of the two chair forms will be determined principally by nonbonded interactions, by torsional effects, and to a lesser extent by angle strain.

Inspection of a Dreiding model of mesembrine shows that the cyclohexanone ring is a distorted chair in both **1A** and **1B** as the result of its annulation by the *cis*-fused five-membered nitrogen-containing ring. This distortion is more apparent in **1A** and results in a favorable relief of the 1,3 diaxial interactions in this conformer by virtue of the C-3a aryl substituent, and the C-7a nitrogen bond becoming quasi-axial. Although the distortion of ring **B** in conformer **1B** occurs, it is minimal in comparison to **1A**, but does provide some small relief of the nonbonded 1,3 interaction of the axial hydrogens at C-5 and C-7 with the quasi-axial-like C-3a–C-3 bond.

The distortion of ring **B** in **1A** helps in understanding why the energy difference between it and the alternative **1B** might not be very great but is hardly sufficient to account for the greater stability of the former; obviously other factors are involved.

One of the most important of these may be associated with torsional effects in the five-membered ring. In this connection, Dreiding models indicate that the ring C conformation in **1A** is a half-chair[35] rather than the envelope conformation, which exists for the five-membered ring in **1B**.

Another factor which would appear to favor **1A** over **1B** is the steric effects associated with the N-methyl group.[36] In contrast to **1A**, where the N-methyl (and the nitrogen lone pair) are relatively free from any serious van der Waals repulsions, conformer **1B** experiences steric repulsion from both C-7 methylene hydrogens, which are situated equidistant at *ca.* 1.6 Å. This effect is not significantly relieved in any of the possible rotamers of the N-methyl group.

Lastly, rotation about the C-3a aryl band in Dreiding models of **1A** and **1B** shows that the aryl hydrogens in both of these conformations are involved in strong nonbonded interactions. The minimum internuclear H–H distances between the various nonaromatic hydrogens and the closest point on an arc described by the C-1 and C-5′ aryl hydrogens as the aromatic ring is rotated about the C-3a–aryl bond are shown in Figure 5. An estimation of the van der Waals nonbonded interaction incurred by this rotation process suggests that there are only two rotamer conformations (see Figure 5) of the aryl group in either **1A** or **1B** in which these interactions are minimized [aryl C-1′ (or C-5′) hydrogen–hydrogen distance >1.8 Å]. Unfortunately, too many uncertainties exist, such as the "size" of the nitrogen lone pair and the energy parameter which measures its interaction with an aryl hydrogen, to make any confident estimate of the relative stabilities of these conformers.

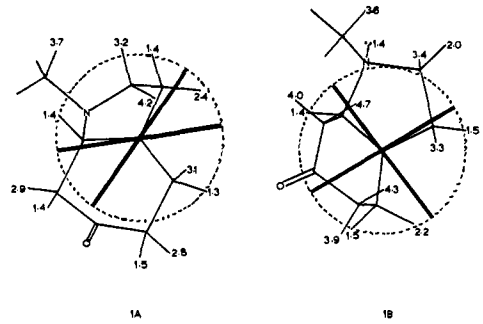


Figure 5. Projections of conformers **1A** and **1B** viewed along the aryl–C-3a bond showing minimum internuclear H–H distances between the C-1′ and C-5′ aryl hydrogens and the other nonaromatic hydrogens as the aryl ring is rotated through 360°.

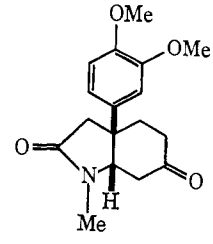
In summary, although distortion of ring **B** in conformation **1A** overcomes many of the unfavorable 1,3 diaxial interactions associated with the axial aryl group and the N-methyl–C-7 methylene *peri* interaction[37] may destabilize **1B**, no obvious factors emerge from an analysis of the two conformations **1A** and **1B** which lead unequivocally to the prediction that the former should be preferred.

The same subtle factors which are responsible for the conformational preference in mesembrine are also obviously responsible for the mesembranols existing in the axial aryl conformations. These observations predicate the need for a study of the conformational

(35) F. V. Brutcher and W. Bauer, *J. Amer. Chem. Soc.*, **84**, 2230 (1962).

(36) The effects of the N-methyl interactions are only considered for one of the two possible orientations of this group in each ring conformer; the alternative configuration leads to increased nonbonded interactions and therefore may be disregarded.

(37) After this manuscript was complete a preliminary communication appeared by T. Oh-ishi and H. Kugita [*Tetrahedron Lett.*, 5445 (1968)] on the synthesis of (±)-mesembrine in which the authors drew attention to the small couplings of the C-7a proton signal in the nmr spectrum of (±)-mesembran-2,6-dione (ii). The axial aryl conformation of ring B rather than the alternative form was suggested as being more consistent with this observation. The interaction of the N-methyl with the C-7 methylene is removed by virtue of the amide character of the nitrogen and indicates that the preference for the axial aryl conformation in this series is essentially independent of this interaction.



ii

characteristics of simple models based on the *cis*-octahydroindole system.[37a]

Experimental Section

Melting points were taken on a Thomas-Hoover capillary apparatus and are corrected. Routine infrared spectra were measured with Perkin-Elmer Models 137 and 237 Infracord recording spectrophotometers. Ir studies of the mesembranols were performed in spectrograde CCl_4 previously dried over molecular sieves (4 Å). The spectra were obtained with both a Perkin-Elmer Model 421 and a Beckman IR-7 spectrophotometer. High dilution samples (5×10^{-3} *M*) were run in 3-mm matched cells with NaCl windows or a 1-cm "infrasil" cell when D_2O was added.

The nmr spectra reported were recorded[38] in benzene or $CDCl_3$ at 100 MHz on a Varian HA-100 high-resolution nmr spectrometer. Chemical shifts are estimated to be ±2 Hz. Glpc analyses were carried out on an F & M Model 402 high-efficiency gas chromatograph with dual flame ionization detectors using a 8 ft × 0.125 in. glass column packed with 4% Carbowax 20M on Aeropak 30 and maintained at 250° (column A). Alternately employed was an 8 ft × 0.125 in. glass column packed with 4% SE 30 on Aeropak 30 maintained at 220° (column B). Mass spectra[39] were obtained with a MS-902 mass spectrometer using a direct inlet system and operated with an ionization energy of 70 eV. CD curves were obtained with a Cary 60 spectropolarimeter.

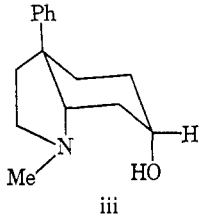
Chromatographic materials were obtained from E. Merck (AG), Darmstadt, Germany. All reagents and solvents used were of reagent quality, and all solvents were redistilled. The removal of solvents was accomplished under reduced pressure on a Büchi rotary evaporator at steam bath temperatures.

Catalytic Hydrogenation of Mesembrine (1). A solution containing 235 mg of **1** in10 ml of isopropyl alcohol was added rapidly to *ca.* 200 mg of prereduced platinum catalyst in 10 ml of isopropyl alcohol. The mixture was stirred under 1 atm of hydrogen and the progress of the reaction followed by periodic sampling and glpc analysis of the mixture. The reaction, which was complete in 120 min, gave mesembranol (**2**) as the exclusive product. Crystallization of the hydrogenation product from acetone gave 173 mg of pure (−)-mesembranol, mp 145–146°, which was identical in every respect with an authentic sample.[40]

Reduction of Mesembrine with $NaBH_4$. (−)-Mesembrine (200 mg) in 10 ml of MeOH was added to a solution containing 200 mg of $NaBH_4$ in 2 ml of MeOH and the mixture refluxed for 30 min. The mixture was cooled and 5 ml of 10% NaOH solution was added. Concentration of the resulting solution to 10 ml and ether extraction of the aqueous concentrate gave 194 mg of an oily residue which contained 40% mesembranol (**2**) and 60% 6-epimesembranol by glpc analysis on column A. The alcohol **2** crystallized from the mixture on standing in ethyl acetate; several crystallizations of this material gave pure (−)-mesembranol, mp 143–145°, $[\alpha]^{30}D$ −32° ($CHCl_3$) [lit.[13] mp 143–146°; $[\alpha]D$ −30° (EtOH)], mass spectrum, *m/e* (relative intensity) 291 (91), 290 (100), 274 (29), 219 (25), 204 (11). The ir spectrum in CCl_4 at high dilution (1.6×10^{-3} *M*) showed only free OH stretching at 3625 cm^{-1} which disappeared on addition of D_2O and was replaced by a new band at 2680 cm^{-1}.

Anal. Calcd for $C_{17}H_{25}NO_3$: *m/e* 291.1835. Found: *m/e* 291.1820.

(37a) NOTE ADDED IN PROOF. H. Taguchi, T. Oh-ishi, and H. Kugita [*Tetrahedron Lett.*, 5763 (1968)] have shown that the alcohols iii and iv exist in the chair form in which the phenyl group is axial.



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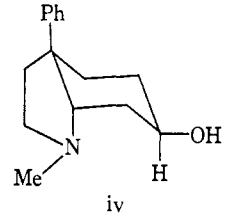

iv

(38) Obtained through the courtesy of Professor Charles A. Moreland, North Carolina State University.

(39) Recorded through the cooperation of the Research Triangle Mass Spectrometry Center which is sponsored by a Special Facilities Grant No. FR-0330-01, National Institutes of Health.

(40) The identity of these two compounds and all such similar comparisons of any two compounds was determined by a comparison of melting points, mixture melting points, thin layer and gas chromatographic data, and infrared and mass spectra.

The mother liquors from the crystallization of mesembranol were taken to dryness and the residue was applied in 2 ml of benzene to a dry-packed column[18] of neutral alumina (17 g; activity 2). Elution of the column was effected with a linear solvent gradient of benzene through benzene–ethyl acetate (3:1). Combination of fractions 1–75 (825 ml) contained the alcohol **3** (monitored by glpc) and fractions 76–100 contained mixtures of **2** and **3** in which the former predominated. Removal of the solvent from the combined fraction 1–75 gave 115 mg of a colorless oil which was distilled to give pure (−)-6-epimesembranol (**3**); bp 172–174° (0.10 mm); $[\alpha]D$ −5° ($CHCl_3$) [lit.[12] bp 168° (0.10 mm); $[\alpha]D$ −3.8° (MeOH)]; mass spectrum 291 (92), 290 (96), 274 (39), 219 (100), 204 (43). The ir spectrum in CCl_4 solution showed a broad adsorption band (*ca.* 575 cm^{-1}) at 3380 cm^{-1} over the concentration range 1.5×10^{-3} *M* to 6.4×10^{-4} *M*. Addition of D_2O to the cell resulted in the slow disappearance of this band.

Anal. Calcd for $C_{17}H_{25}NO_3$: *m/e* 291.1835. Found: *m/e* 291.1832.

6-Epimesembranol Methiodide. A mixture of 44 mg of **3** and 5 ml of methyl iodide in 5 ml of acetone was heated at reflux for 2.5 hr. The mixture was cooled and evaporated to dryness. Crystallization of the residue from methanol–ether afforded 46.5 mg of white solid, which was recrystallized to give the pure methiodide, mp 220.5–221.5°.

Anal. Calcd for $C_{18}H_{28}NO_3I$: C, 49.89; H, 6.51. Found: C, 49.72; H, 6.46.

Oxidation of the Alcohols (a) 2 and (b) 3. a. Chromic acid reagent[41] was added at the rate of one drop/min for 6 min to a stirred, ice-cold solution of 19 mg of mesembranol (**2**) in acetone (5 ml). After a further 3 min the reaction was quenched by the addition of 3 ml of water. The solution was concentrated in a stream of nitrogen to remove acetone and then basified with 3 ml of saturated Na_2CO_3. Extraction of the basic solution with ether and the usual work-up afforded mesembrine (13 mg) identified from a comparison with an authentic sample and by preparation of its hydrochloride, mp 203–205.5° (undepressed on admixture with mesembrine hydrochloride).

b. 6-Epimesembranol (**3**), 10 mg in acetone (5 ml), was treated as in procedure a above except that the reaction mixture was allowed to stand for 8 min at 0° after addition of chromic acid reagent to effect complete oxidation. The product, 7 mg, was identified as mesembrine by comparison of its spectral and chromatographic properties with those of authentic material.

O-Acetylmesembranol (4). A mixture consisting of 40 mg of mesembranol, 2 ml of Ac_2O, and *ca.* 0.1 ml of pyridine was allowed to stand at room temperature for 18 hr. The resulting purple solution was then poured into a separatory funnel containing water and ether (5 ml each) and basified by intermittent shaking with portions of saturated Na_2CO_3. The purple color was retained in the aqueous phase. The ether layer was separated, washed once with water, and dried over K_2CO_3. The filtered solution was evaporated and then evacuated at 0.1 mm to afford a quantitative yield of **4** as a light yellow oil, homogeneous by glpc (column A); ir (neat): 1738 cm^{-1} (C=O); mass spectrum 333 (37), 274 (100), 219 (41).

Anal. Calcd for $C_{19}H_{27}NO_4$: *m/e* 333.1940. Found: *m/e* 333.1971.

O-Acetyl-6-epimesembranol. A mixture of 39 mg of the alcohol **3** and one drop of pyridine in 1 ml of Ac_2O was allowed to stand at room temperature for 7 min, after which time it was poured into ether and the ether solution washed with saturated carbonate (2 ml) and then with water (2 ml). The ether layer was separated, dried (K_2CO_3), filtered, and evaporated to afford **5** as a lightly colored oil (37 mg) which was homogeneous by glpc (column A); ir (neat): 1735 cm^{-1} (C=O); mass spectrum 333 (15), 274 (100), 219 (10).

Anal. Calcd for $C_{19}H_{27}NO_4$: *m/e* 333.1940. Found: *m/e* 333.1949.

$LiAlH_4$ Reduction of the Acetates (a) 4 and (b) 5. a. Acetate **4**, 35 mg, in 2 ml of dry ether was added to a refluxing solution of *ca.* 50 mg of $LiAlH_4$ in 20 ml of ether. After 30 min the reaction mixture was cooled and first treated cautiously with 3 ml of water and then with 20 ml of 10% KOH solution. Extraction of the aqueous solution with ether (four 5-ml portions) afforded an oil (24 mg) on removal of the solvent from the combined ether extract. Crystallization of the oil gave mesembranol, large prisms, mp 144–144.5°, identified by chromatographic and spectral comparisons with an authentic sample.

(41) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

b. A solution of 43 mg of the acetate **5** in 2 ml of dry ether was reduced in the same manner as described in a to give 39.2 mg of 6-epimesembranol, oil, ir (CCl_4) 3380 cm^{-1} (OH), identified by the usual chromatographic comparisons with those of an authentic specimen.

CD Spectra of Mesembrine (1) and Dihydrooxocrinine (10). Mesembrine (*c* 0.0196, dioxane at 25°), $[\theta]_{340}$ 0°; $[\theta]^{sh}_{312}$ −1480°; $[\theta]^{sh}_{301}$ −2989°; $[\theta]_{295}$ −3610°; $[\theta]_{260}$ −1243°. Dihydrooxocrinine (*c* 0.0055, dioxane at 25°), $[\theta]_{340}$ 0°; $[\theta]$ −10.610°; $[\theta]_{287}$ 0°.

Kinetics. The saponification rates of the acetates **4** and **5** were carried out at 25 ± 0.1° in aqueous methanol with a large excess of K_2CO_3 to ensure that the reaction would follow pseudo-first-order kinetics. Acetylation reactions of the alcohols **2** and **3** were performed at 0 ± 0.1° in pyridine using a large molar excess of acetic anhydride in order to simplify the kinetic treatment of the results.

Saponification of Acetates 4 and 5. A sample (3.8 mg) of each of the acetates **4** and **5** was weighed accurately and dissolved separately in 1.0 ml of MeOH. After allowing each of these solutions to reach 25°, 0.5 ml of aqueous 0.5 *N* K_2CO_3 solution was added, and the mixtures were stirred. Aliquots were removed periodically and analyzed (in triplicate) by glpc using column B. Each aliquot was first treated with 10% HCl, followed by basification with Na_2CO_3, then extracted with ethyl acetate prior to analysis. Very satisfactory first-order kinetics plots were obtained.

Acetylation of 2 and 3. A solution of mesembranol (35 mg) in 4.5 ml of pyridine was cooled to 0°. The solution was stirred and 0.5 ml of acetic anhydride introduced. Aliquots were removed periodically and transferred to stoppered tubes containing 0.5 ml of saturated Na_2CO_3 solution and *ca.* 0.1 ml of ethyl acetate. The contents of the tubes were shaken vigorously for about 1 min, and a portion of the ethyl acetate layer was removed for analysis (in triplicate) by glpc on column B. Acetylation of 6-epimesembranol (37 mg) was carried out in an identical manner. Excellent first-order kinetic plots were obtained for each of these runs.

Acknowledgment. We are very grateful to Dr. R. J. Highet, National Institutes of Health, for recording the CD spectra and for some preliminary high-resolution ir spectral measurements. We also wish to thank Professor W. C. Wildman, Iowa State University, and Dr. A. Popelak, C. F. Boehringer and Soehne, Manneheim, Germany, for providing generons gifts of mesembrine.

The Conformational Analysis of Saturated Heterocycles. XX.[1] The Stereochemistry of Base-Catalyzed Hydrogen–Deuterium Exchange of Methylene Protons α to a Sulfinyl Group

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Abstract: The base-catalyzed hydrogen–deuterium exchange of the α-sulfinyl protons in the conformationally rigid *cis*- and *trans*-4-phenyltetrahydrothiopyran 1-oxides is stereoselective in water and methanol-1-*d* and nonstereoselective in *t*-butyl alcohol-1-*d* and dimethyl sulfoxide–methanol. The kinetics in methanol-1-*d* are interpreted in terms of two competing pseudo-first-order reactions, one for the α-axial proton and one for the α-equatorial proton. The order of proton acidity adjacent to a sulfinyl group is concluded to be (a) *trans* to S=O and *gauche* to sulfur lone pair, (b) *gauche* to S=O and to sulfur lone pair, (c) *gauche* to S=O and *trans* to sulfur lone pair.

The sulfoxide group activates adjacent C–H atoms toward base-catalyzed hydrogen–deuterium exchange. The methylene hydrogens in benzyl methyl sulfoxide undergo exchange at unequal rates,[4] and Wolfe and Rauk[5] attempted to deduce the stereochemistry of the preferential exchange from nmr considerations. However, it later[6] became clear that the assumptions made regarding the shielding effect of the S=O (↔ $S^+—O^-$) group might not be valid. Although calculations[7] appear to support the original assignment, it was clearly desirable to obtain direct evidence for the stereochemistry of exchange α to sulfinyl centers. We felt that such evidence could be obtained by the use of conformationally rigid compounds; although such compounds have apparently not been used previously to determine the effect of a functional group on the relative acidities of adjacent methylene protons, this would seem to be a general method. We now describe the results of work on the sulfoxides I and II. 4-Phenyltetrahydrothiopyran was converted into the *cis*-sulfoxide (II) by *t*-butyl hypochlorite oxidation, the method used previously[8] for the 4-*p*-chlorophenyl analog. The conversion of the *cis*- to the *trans*-sulfoxide (I) was accomplished *via* the ethoxysulfonium salt, for which the same analogy exists.[9] The conformation of the *cis*-sulfoxide from 4-*p*-chlorophenyltetrahydrothiopyran has been confirmed by X-ray methods;[10] our conformations were assigned by analogy in preparation and by direct comparison of infrared spectra with the corresponding 4-*p*-chlorophenyl derivatives. Marked similarities were found

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