Sceletium Alkaloids.[1] Structures of Five New Bases from *Sceletium namaquense*

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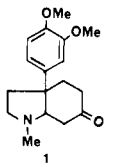
The structures of five new alkaloids are reported. These include *N*-acetyltortuosamine (**6**), the dihydropyridone base (**5**) related to *Sceletium* alkaloid A_4 (**3**), and three new alkaloids with the joubertiamine (**2**) skeleton represented by 4-(3,4-dimethoxyphenyl)-4-[2-(acetylmethylamino)ethyl]cyclohexanone (**20**), 4-(3-methoxy-4-hydroxyphenyl)-4-[2-(acetylmethylamino)ethyl]cyclohexadienone (**24**), and (−)-3′-methoxy-4′-*O*-methyljoubertiaminol (**13**). The stereochemistry of joubertinamine (**18**) is suggested by ^{1}H NMR spectral data.

Introduction

Although the number of *Sceletium* species of the family *Aizoaceae* examined for alkaloids has been restricted by their inaccessibility, the efforts of investigators have been rewarded with increasing examples of interesting alkaloids. To date, alkaloids elaborated from four-ring systems have been reported: the 3a-aryl-*cis*-octahydroindole class exemplified by mesembrine (**1**),[2] the ring C-seco mesembrine alkaloids represented by joubertiamine (**2**),[9] a tetracyclic pyridine alkaloid class with only two reported members, the first being *Sceletium* alkaloid A_4 (**3**),[3,4] and finally a ring C-seco *Sceletium* alkaloid A_4 group illustrated by the structure of tortuosamine (**4**).[4]



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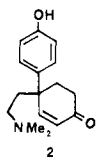

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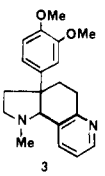

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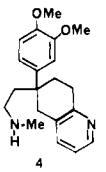

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In addition to the diverse and interesting types afforded by *Sceletium* species, the study of their biosynthetic origins has received some considerable effort.[5] In spite of this, the biosynthesis of these alkaloids remains far from being completely solved. We have continued to investigate the characterization of new compounds from species such as *Sceletium namaquense* as a means of seeking the revelation of unknown biogenetic relationships among alkaloids of this family.[6] The five new members presented in this paper are found to fall into three of the four structural classes adumbrated above.

Dihydropyridone Base[7]

Prior to our reexamination of the nonphenolic alkaloids of *S. namaquense*, Stevens and co-workers[8] predicted that an alkaloid with the structure **5** might be a natural product in keeping with an assumed biogenetic relationship to *Sceletium* alkaloid A_4. Indeed, the polar column residue from the alumina chromatography of the nonphenolic alkaloids of *S. namaquense* was shown to contain several new components by GLC. Column chromatography of the residue over alumina yielded the major component as an oil, which was purified by preparative layer chromatography.

This compound was an optically active base that was shown to have the molecular formula $C_{20}H_{26}N_2O_3$ from an accurate mass measurement of the molecular ion in the mass spectrum. The proton NMR spectrum at 100 MHz and the IR spectrum were important in identifying the new compound as a secondary amide; a strong carbonyl absorption at 1675 cm^{-1} and a band at 3420 cm^{-1} are diagnostic for this functionality and the appearance of a singlet at δ 7.50 that exchanged deuterium upon addition of D_2O in the NMR spectrum provided the key support for this conclusion. Other assignable signals in the NMR spectrum included two isochronous *O*-methyl signals at δ 3.92, an *N*-methyl signal at δ 2.50, and a three-proton multiplet centered at δ 6.80, which in conjunction with the presence of the low-field *O*-methyl signals was indicative of a veratryl group. Additional support for the presence of a secondary amide came from the mass spectral fragmentation pattern that featured ions derived from loss of several HNCO(R) fragments, giving abundant ions at *m/e* 299 (M − HCNO), 285 (M − HNC_2H_2O), and 283 (M − HNC_2H_4O) with complementary ions at *m/e* 57 (HNC_2H_2O) and 59 (HNC_2H_4O) at low mass.

The fact that this alkaloid contained two nitrogen atoms with one of them probably being in a secondary amide led us to suspect the identity of this compound with the dihydropyridone alkaloid synthesized by Stevens and coworkers.[8] A sample of the synthetic 2-dihydropyridone was obtained from Professor Stevens and its chromatographic and spectral identity with the naturally occurring base was established.

The elucidation of the structure of this alkaloid as **5** thus provides the second member of the tetracyclic class of *Sceletium* alkaloids. Its isolation may represent a postmesembrine intermediate along the biosynthetic pathway

(1) This paper is part 10 in the series "*Sceletium* Alkaloids". For part 9 of this series, see ref 5a.

(2) A. Popelak and G. Lettenbauer, "The Alkaloids", R. H. F. Manske, Ed., Academic Press, New York, 1967, Vol. 9, pp 467-482.

(3) P. W. Jeffs, P. A. Luhan, A. T. McPhail, and N. H. Martin, *Chem. Commun.*, 1466 (1967).

(4) F. O. Synckers, F. Strelow, and A. Wiechers, *Chem. Commun.*, 1467 (1971).

(5) (a) P. W. Jeffs, J. M. Karle, and N. H. Martin, *Phytochemistry*, *17*, 719 (1978); (b) P. W. Jeffs, H. F. Campbell, D. S. Farrier, G. Ganguli, N. H. Martin, and G. Molina, *ibid.*, **13**, 933 (1974).

(6) P. W. Jeffs, T. M. Capps, D. B. Johnson, J. M. Karle, N. H. Martin, and B. Rauckman, *J. Org. Chem.*, **39**, 2703 (1974).

(7) Some of the discussion concerning the dihydropyridone base has been reported in preliminary form: P. W. Jeffs and T. M. Capps, *Tetrahedron Lett.*, 131 (1979).

(8) R. V. Stevens, P. M. Lesko, and R. Lapalone, *J. Org. Chem.* **40**, 3495 (1975).

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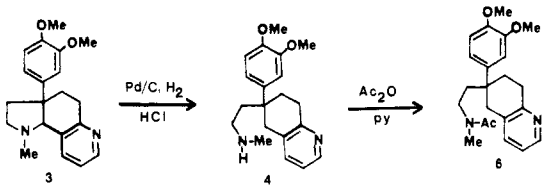
Scheme I



to *Sceletium* A_4 and tortuosamine.[6]

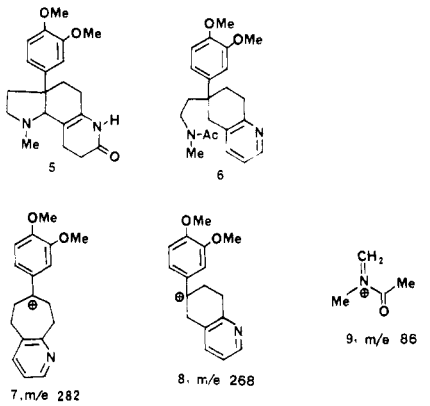
N-Acetyltortuosamine

The isolation of tortuosamine from *Sceletium tortuosum* by Wiechers and co-workers[4] in 1971 introduced the ring C-seco *Sceletium* A_4 structural class and with our concurrent studies on the structure of *Sceletium* alkaloid A_4 led to the extension of the number of known ring systems from two to four.

In our earlier studies, *N*-formyltortuosamine and an unidentified alkaloid were initially separated on the basis of their differing solubilities in ether. After separation of the crude alkaloidal extract via the base hydrochlorides, the nonphenolic alkaloids were refluxed in ether. In the event, *N*-formyltortuosamine and tortuosamine were insoluble and were isolated by column chromatography over alumina. The ether-soluble fraction contained mesembrine, mesembrenone, mesembrane,[10] and two other alkaloids, which, as described below, proved to be *N*-acetyltortuosamine (**6**) and 3′-methoxy-4′-*O*-methyljoubertiaminol (**13**).

After removal of mesembrine and mesembrenone from the ether-soluble fraction, repetitive column and layer chromatography led to the isolation of mesembrane and the two unidentified alkaloids. The formula of one of these as $C_{22}H_{28}N_2O_3$ was obtained by an accurate mass measurement of the molecular ion in its mass spectrum and its ^1H NMR spectrum at 100 MHz clearly indicated a 2,3-disubstituted pyridine system, exhibiting a well-defined AMX pattern at δ 8.39 (J = 5.0 and 2.0 Hz), 7.50 (J = 8.0 and 2.0 Hz) and 7.13 (J = 8.0 and 5.0 Hz).[11] Also, the NMR spectrum provided confirmation of a veratryl group from the observation of a three-proton pattern in the aromatic region in conjunction with signals associated with two methoxyl resonances. A strong carbonyl absorption at 1664 cm^{-1} in the IR spectrum was indicative of an amide carbonyl and this was supported by doubling of the signals characteristic of both an *N*-methyl (δ 2.78 and 2.80) and two aromatic methoxyl groups (δ 3.78, 3.79, 3.81, and 3.82). The temperature dependence of the spectrum showed not only the expected coalescence of each of these pairs of signals at 87 °C but also resulted in the collapse of a three-proton doublet centered at δ 1.98. The chemical shift and temperature dependence of the latter signal indicated that the amide was present as an *N*-acetyl group, a conclusion that was aided by our experience with *N*-formyltortuosamine.[6]

The foregoing spectral results suggested that the alkaloid could be formulated as *N*-acetyltortuosamine (**6**). This conclusion was supported further by its mass spectral fragmentation pattern and confirmed by its synthesis from *Sceletium* A_4. The most important features of the mass spectrum were the observation of ions derived from the sequential loss of fragments of an *N*-acetylethanamine side chain, giving rise to abundant ions at m/e 282 and 268 (ions **7** and **8**, respectively), and a complementary ion **9** (m/e 86) at low mass.

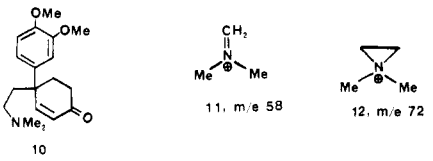


A partial synthesis of **6** from *Sceletium* A_4 was readily effected (Scheme I): *Sceletium* A_4 (**3**) was hydrogenolyzed under acidic conditions to tortuosamine (**4**), which was then *N*-acetylated with acetic anhydride to give a product that was identical in its spectral and chromatographic properties with the naturally occurring alkaloid.

This natural product constitutes the third member of the tortuosamine class of *Secletium* alkaloids to be identified.

3′-Methoxy-4′-*O*′-methyljoubertiaminol

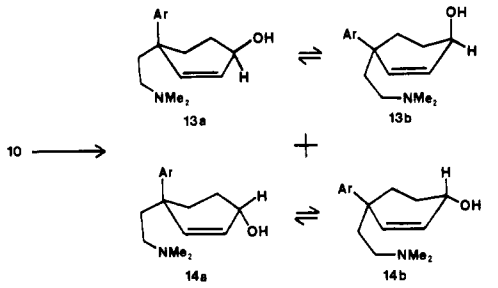
Besides *N*-acetyltortuosamine, another previously unidentified alkaloid was isolated and characterized from the ether-soluble, nonphenolic alkaloid fraction as mentioned above. Preparative layer chromatography yielded the compound as a crystalline solid, mp 100.5 °C. The alkaloid exhibited a molecular ion with a mass corresponding to the formula $C_{18}H_{27}NO_3$ in its high-resolution mass spectrum. Its 100-MHz proton NMR spectrum revealed the presence of a veratryl group and a two-proton singlet at δ 5.90 in the olefinic region. A strong hydroxyl absorption band at 3410 cm^{-1} in the IR spectrum coupled with a one-proton multiplet centered at δ 4.25 with a broad half-band width (18.5 Hz) indicated the presence of an equatorial alcohol in a cyclohexenyl ring. Two three-proton singlets at δ 3.84 and 3.83 for methoxyl signals were consistent with the aromatic three-proton veratryl pattern common in the *cis*-octahydroindole mesembrine alkaloids, but the presence of a six-proton singlet at δ 2.19 characteristic of a dimethylamine group suggested that this alkaloid belonged to the joubertiamine class. This conclusion was supported by its mass spectral fragmentation pattern, which showed many features in common with the spectrum of the known compound 3′-methoxy-4′-*O*-methyljoubertiamine (**10**), including a base peak at m/e 58 and an abundant peak at m/e 72 (ions **11** and **12**, respectively), which appear in the mass spectra of both compounds. These ions originate from cleavage of a (dimethylamino)ethyl side chain and are characteristic of alkaloids in the joubertiamine class.[12]



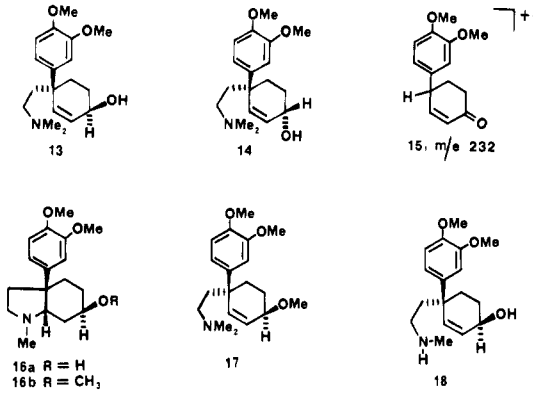
Consideration of all spectral data led to the conclusion that the structure of the alkaloid was the allylic alcohol

(9) R. R. Arndt and P. E. J. Kruger, *Tetrahedron Lett.*, 3237 (1970).
(10) T. M. Capps, K. D. Hargrave, P. W. Jeffs, and A. T. McPhail, *J. Chem. Soc., Perkin Trans. 2*, 1098 (1977).
(11) F. W. McDonald, A. W. Decera, and G. L. Cook, *Appl. Spectrosc.*, **22**, 325 (1968).
(12) N. H. Martin, D. Rosenthal, and P. W. Jeffs, *Org. Mass Spectrom.*, 11, 1 (1976).

Scheme II



13 or its epimer 14. Strong evidence in support of this proposed structure can be found again in the mass spectrum of the alkaloid. The mass spectrum of 10 exhibits an ion at m/e 232 (structure 15) arising from β cleavage of the (dimethylamino)ethyl side chain accompanied by hydrogen transfer with retention of charge on the nonnitrogen fragment.[12] One would expect a corresponding ion at m/e 234 for 13 or 14, which is, in fact, obtained and is of even greater abundance than ion 12.



For confirmation of the structure for the alkaloid, including its stereochemistry at the 6-position, (−)-3′-methoxy-4′-*O*-methyljoubertiamine was reduced with sodium borohydride (Scheme II). The major product proved to be identical in its chromatographic and spectral properties with the naturally occurring base. Although this justified the assignment of the allylic alcohol structure to the natural product, the not inconsequential problem of distinguishing between 13 and 14 remained. While the hydride reduction of most unhindered cyclohexanones yields the equatorial alcohol,[13] the extension of these data to conjugated cyclohexenone systems is not entirely justified[14] and in this particular situation is further compounded by a paucity of knowledge with respect to the conformational bias of 4,4-disubstituted cyclohexenols.

It appeared that the configuration of the hydroxyl group could be established by a Hofmann degradation of (−)-mesembranol (16a), which has the relative and absolute stereochemistry shown.[15,16] Unfortunately, however, the reaction was not amenable to a clear interpretation in that the Hofmann elimination of (−)-mesembranol methiodide yielded not only a major product (96%) identical with the naturally occurring allylic alcohol but also another product (4%) that was recognized as the epimer (13 or 14) from its identity with the minor product from the borohydride reduction of 10. The production of the two allylic alcohols 13 and 14 from the Hofmann degredation of (−)-mesembranol presented a serious ambiguity in interpreting the results. It is important to note that the 96:4 ratio is of no significance in establishing the stereochemical correlation between (−)-mesembranol and the Hofmann products; the major isomer could have the opposite configuration at C-6 to that of (−)-mesembranol by virtue of being formed via a solvolytic pathway under the conditions of the reaction, which involve hot aqueous base.

In an unsuccessful attempt to obviate this problem, a modified Hofmann procedure[17] was attempted in which the methiodide of 16a in Me_2SO was reacted with potassium *tert*-butoxide. Unfortunately, the reaction under these conditions failed to provide any trace of either of the two alcohols 13 or 14. To resolve this issue, (−)-6-*O*-methylmesembranol[19] (16b) was converted to its methiodide and subjected to the classical Ag_2O–H_2O Hofmann procedure, which had been successful for mesembranol. The product from the reaction showed both a three-proton singlet at δ 3.34 and a two-proton singlet at δ 5.92 at 80 MHz in accord with the assignment of its structure as the allylic methyl ether 17. The retention of the 6-*O*-methyl group assured the integrity of the C-6–O bond during the Hofmann elimination and it only remained to interrelate 17 with the naturally occurring allylic alcohol. This was accomplished by selective O-methylation of the major product from the Hofmann elimination of (−)-mesembranol; the allylic alcohol was converted to its potassium salt with KH in THF and alkylated with methyl iodide. The sole product from the reaction proved identical in every respect with the Hofmann product 17, demonstrating that the relative and absolute stereochemistry of the alkaloid is correctly represented by structure 13.

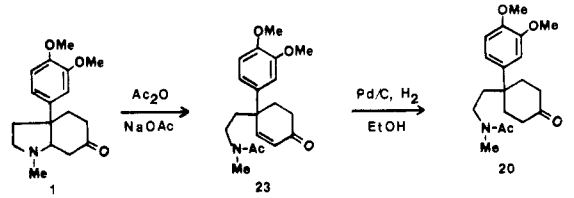
In the course of characterizing the epimeric alcohols 13 and 14 it was noted that the olefinic NMR signals exhibited by α-allylic alcohol 14 differed greatly from the singlet shown by its epimer at 80 MHz. A well-separated ($\Delta\nu$ = 44 Hz) AB quartet is obtained in the spectrum of 14 at 80 MHz. Since joubertinamine, an alkaloid reported by Wiechers et al.[21] with a previously undesignated stereochemistry, also exhibits a singlet for the olefinic protons at 100 MHz in its ^{1}H NMR spectrum, this suggests that the stereochemistry of the 6-allylic hydroxyl can be assigned the β configuration as shown in 18.

4-(3,4-Dimethoxyphenyl)-4-[2-(acetylmethylamino)ethyl]cyclohexanone

The ether-insoluble fraction of crude alkaloids of *S. namaquense* contains *N*-formyltortuosamine and Δ^7-mesembrenone[6] as the most abundant components. GLC examination of the partially purified fraction also showed the presence of yet another alkaloid that was isolated as an oil after alumina column chromatography followed by successive preparative layer chromatography. The new base, $C_{19}H_{27}NO_4$, exhibited signals in its 100-MHz ^{1}H-NMR spectrum associated with a veratryl group: a three-proton aromatic pattern centered at δ 6.91 and a six-proton signlet at δ 3.94. A doubling of the signals

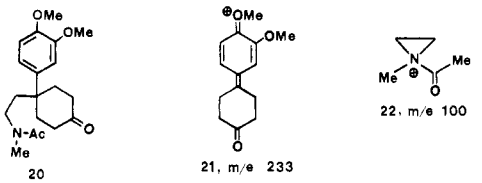
(13) P. A. Plattner, H. Heusser, and A. B. Kulkarni, *Helv. Chim. Acta*, **32**, 265 (1949).
(14) O. R. Vail and D. M. S. Wheeler, *J. Org. Chem.*, **27**, 3803 (1962).
(15) P. W. Jeffs, R. L. Hawks, and D. S. Farrier, *J. Am. Chem. Soc.*, **91**, 3831 (1969).
(16) P. Coggon, D. S. Farrier, P. W. Jeffs, and A. T. McPhail, *J. Chem. Soc. B*, 1267 (1970).
(17) E. W. Warnhoff, P. Reynolds-Warnhoff, and S. Valverde-Lopez, *Ann. Chim. (Rome)*, **68**, 797 (1972).
(18) W. Döpke, H. Flentije, and P. W. Jeffs, *Tetrahedron*, **24**, 2297 (1968).
(19) R. L. Hawks and P. W. Jeffs, unpublished observations.
(20) C. A. Brown, *J. Am. Chem. Soc.*, **95**, 982 (1973); *J. Org. Chem.*, **39**, 3913 (1974).
(21) K. Psotta, F. Strelow, and A. Wiechers, *J. Chem. Soc., Perkin Trans. 1*, 1063 (1979).
(22) R. L. Hawks, Ph.D. Dissertation, Duke University, Durham, NC, 1970.

Scheme III



observed at chemical shifts associated with an *N*-methyl group (δ 2.86 and 2.90) and the methyl group of an *N*-acetyl function (δ 1.90 and 1.95) and the expected temperature dependence in which each pair collapsed into singlets at 80 °C was consistent with the presence of an *N*-acetyl group, which was in accord with a 1658-cm^{-1} band in the IR spectrum of the alkaloid.

A second carbonyl absorption at 1710 cm^{-1} in the IR spectrum suggested the presence of a cyclohexanone moiety and, more importantly, the mass spectral fragmentation pattern provided further support for this contention. The primary diagnostic features of the latter were ions derived from loss of a *N*-acetylethanamine side chain, giving rise to the base ion at *m/e* 233 and the complementary ion at *m/e* 100 at low mass. These data suggested structure **20** for the new alkaloid since the ions at *m/e* 233 and 100 could then be represented as **21** and **22**, respectively.[12] Ion **22** is also found in the mass spectrum of *N*-acetyltortuosamine albeit of much lower abundance.



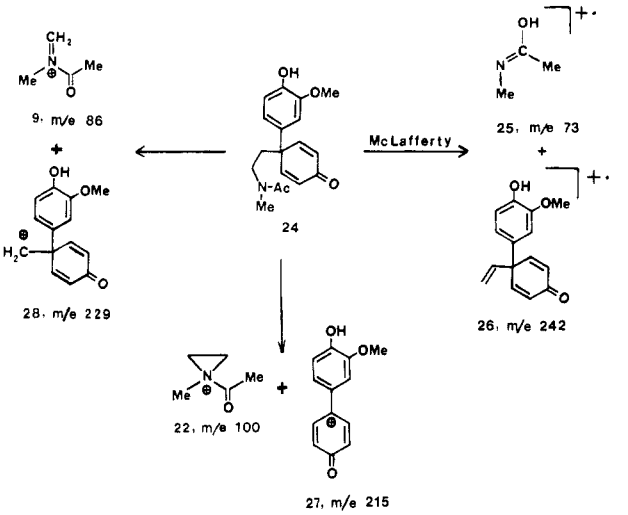
Confirmation of structure **20** for the new base was accomplished by its derivation from mesembrine (Scheme III). N-Acetylation of mesembrine in acetic anhydride with added sodium acetate combined with basic workup yielded compound **23**, which was catalytically reduced to give a product that proved to be identical with the natural base by chromatographic and spectral comparisons.

4-(3-Methoxy-4-hydroxyphenyl)-4-[2-(acetylmethylamino)ethyl]cyclohexadienone

The course of the typical alkaloid extraction procedure involves acidic conditions that might obscure the detection and isolation of acid-labile alkaloids. The rationale for considering such an eventuality as a possibility was based on the premise that the biosynthetic route to this family of alkaloids has been shown to involve dienone intermediates.[5] Such intermediates if they were present in the plant in any significant concentrations would certainly not survive the conditions of the typical isolation procedure. Since isolation of dienone intermediates could provide valuable information relating to unsolved biosynthetic questions, an extraction process was devised that avoided acid treatment in isolating the phenolic alkaloid fraction from *S. namaquense*. The crude plant extract was dissolved in chloroform, which was then extracted with aqueous sodium carbonate to remove acidic compounds. The chloroform solution was then washed with aqueous sodium hydroxide to remove phenolic materials; the aqueous extract was adjusted to pH 9 by addition of CO_2, and the phenolic alkaloids were removed by extraction with chloroform.

Repetitive alumina column chromatography of the mixture of alkaloids so obtained yielded a fraction with

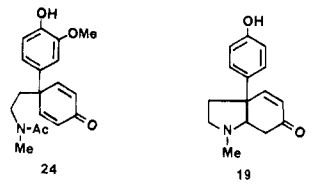
Scheme IV



several new compounds when analyzed by GLC. The major component in the mixture was labile to chromatography on silica gel so it was separated from all other compounds in the fraction by preparative layer chromatography over alumina to give the new base as a crystalline solid, mp 107.5 °C.

The 100-MHz proton NMR spectrum of the new compound ($C_{18}H_{21}NO_4$) indicated the presence of a *N*-acetylethanamine group based on experience with the preceding alkaloid in this account and also *N*-acetyltortuosamine. Thus, three three-proton doublets, centered at δ 3.84, 2.99, and 2.15 all collapsed to three-proton singlets at 50°C. In contrast to the cyclohexanone alkaloid **20**, this compound exhibited a strong dienone carbonyl band at 1665 cm^{-1}. Further evidence for this could be found in the appearance of the olefinic region of the proton NMR spectrum: Two two-proton doublets with the same apparent coupling constant were observed, centered at δ 6.98 and 6.35 (J_{app} = 14 Hz).

The evidence suggests that structure **24** should be given to the new alkaloid. This proposal was bolstered by mass

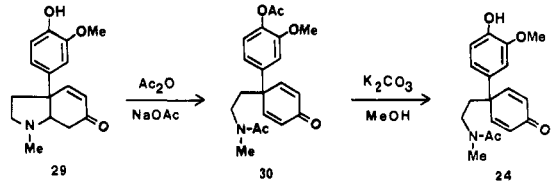


spectral data. An interesting McLafferty rearrangement, unobserved in **20**, can be invoked to account for the derivation of the base peak at *m/e* 73 (ion **25**) and its complementary ion at *m/e* 242 (ion **26**). As with compound **20** fragmentation of the *N*-acetylethanamine side chain gives rise to abundant ions at *m/e* 100 and 86 and complementary ions at *m/e* 215 (**27**) and 229 (**28**), respectively.[12] These data are summarized in Scheme IV.

The placement of the phenol function at the 4′-position was clearly arbitrary but was confirmed by the following synthesis of **24** (Scheme V). The known alkaloid 4′-*O*-demethylmesembrenone[6] (**29**) was smoothly converted to the dienone intermediate **30** whose *O*-acetyl group was cleaved with methanolic base to give compound **24**, the synthetic material identical in all respects with the naturally occurring alkaloid.

The isolation of alkaloids of the joubertiamine class having dioxygenated aryl groups (cf. **13**, **18**, **20**, **24**) is of biosynthetic significance since they provide a link between the joubertiamine systems and the tricyclic mesembrine

Scheme V



alkaloids, most of which have dioxygenated aryl groups. Biogenetic unification in the opposite sense has been provided by the isolation of the monooxygenated-aryl mesembrine alkaloid sceletenone (**19**).[6]

Experimental Section

General Methods. All melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were obtained for solutions in $CHCl_3$ on Perkin-Elmer Model 137, 237, 621, and 297 spectrophotometers. Proton nuclear magnetic resonance (NMR) spectra were recorded at 60 MHz on a Varian T-60, a Varian EM-360, and a Jeol FX-60 spectrometer, at 80 MHz on an IBM NR-80 spectrometer, at 90 MHz on a Bruker HFX-90 spectrometer, at 100 MHz on a Jeol MH-100 spectrometer, at 220 MHz on a Varian HR-220 spectrometer, and at 250 MHz on a spectrometer constructed at Carnegie-Mellon Institute and on a Bruker WM-250 spectrometer. Carbon-13 spectra were recorded at 22.63 MHz on a Bruker HFX-90 spectrometer and at 15.96 MHz on a Jeol FX-60 spectrometer. All chemical shifts are reported in δ units relative to tetramethylsilane and all samples were run in deuteriochloroform unless otherwise stated. Low-resolution mass spectra were determined on Du Pont 21-490 and 21-491 mass spectrometers and on a Hewlett-Packard 5992 gas chromatograh–mass spectrometer. High-resolution mass spectra were recorded on an AEI MS-902 mass spectrometer utilizing a direct inlet system. CD and ORD spectra were obtained on a JASCO ORD/CD spectropolarimeter. A Perkin-Elmer Model 241 polarimeter was used for obtaining optical rotations. Gas–liquid chromatography (GLC) was carried out on a Hewlett Packard 402 instryument with 8 ft by 0.125 in. glass columns and a Varian Aerograph 1200 with 6 ft by 0.0625 in. metal columns. The column packings were 3% OV-17, 3% SE-30, 3% QF-1, or 3% XE-60 on Gas-Chrom Q (100–200 mesh). Chromatographic materials were obtained from E. Merck (AG), Darmstadt, Germany.

Extraction of Alkaloids from *Sceletium namaquense*. Several methods were utilized in the extraction of the alkaloids from this plant; the procedure described represents one of the more satisfactory methods.

Dried plant material of *S. namaquense* (3.5 kg) was placed in a Soxhlet extractor and extracted with 15 L of 95% ethanol for 17 h. The extracted material was transferred in portions to a blender and macerated further with 10 L of ethanol. The combined ethanol extracts were concentrated to ca. 2.5 L and acidified with 5% tartaric acid. The aqueous acidic solution was extracted with ether (5 × 500 mL) and the ether extract was discarded. After basification of the aqueous phase with Na_2CO_3, the solution was extracted successively with $CHCl_3$ (10 × 500 mL) and $CHCl_3$/MeOH, 4:1 (1 × 300 mL). The $CHCl_3$ extracts were combined, the solvent was concentrated to ca. 1.5 L, and the solution was filtered to remove small quantities of insoluble components. The $CHCl_3$ filtrate was extracted with 1 N NaOH (3 × 200 mL) and washed thoroughly with water. Evaporation of the $CHCl_3$ solution yielded 120 g of nonphenolic alkaloids. The phenolic alkaloids (20 g) were recovered from the NaOH by adjusting to pH 9 (with CO_2) and extracting with $CHCl_3$ (5 × 100 mL).

Isolation of Ether-Insoluble Nonphenolic Alkaloids. The nonphenolic alkaloid fraction (120 g) was extracted with refluxing ether (3 × 500 mL) to remove 60 g of ether-soluble alkaloids containing largely mesembrine and mesembrenone. The ether-insoluble residue (60 g) was dissolved in 1200 mL of $CHCl_3$/MeOH (3:1) and passed through a column (4 ft by 3 in.) containing 1400 g of silica gel (170–200 mesh). Evaporation of the total eluate gave 50 g of alkaloidal material. A portion of this fraction (20 g) was dissolved in $CHCl_3$ (100 mL) and chromatographed over neutral alumina (1400 g, activity IV) contained in a 4 ft by 3 in column. The column was eluted with 3 L of solvent, using a linear solvent gradient of $CHCl_3$–$CHCl_3$/MeOH (4:1), and 15 mL fractions were collected: 1–120, nonalkaloidal material (3.70 g); 121–143 mesembrine (1.63 g); 144–175, mesembrenone (1.5 g), 176–205 mesembrenone, *Sceletium* A_4, (–)-3′-methoxy-4′-*O*-methyljoubertiamine, and other alkaloids (2.5 g); 206–215, 4-(3,4-dimethoxyphenyl)-4-[2-(acetylmethylamino)ethyl]cyclohexanone and unidentified alkaloids (1.45 g); 216–225, *N*-formyltortuosamine and unidentified alkaloids (3.11 g); 226–235, Δ^7-mesembrenone and tortuosamine (1.11 g); and 236–330, the dihydropyridone base (**5**) and unidentified components (5.85 g).

4-(3,4-Dimethoxyphenyl)-4-[2-(acetylmethylamino)-ethyl]cyclohexanone (20). Fractions 206–215 (1.45 g) were subjected to successive preparative TLC on silica gel (containing 5% K_2CO_3) in $CHCl_3$/MeOH (4:1), alumina in $CHCl_3$/EtOAc (4:1), alumina in $CHCl_3$/MeOH (9:1), and finally silica gel in $CHCl_3$/EtOAc (4:1) to give 4-(3,4-dimethoxyphenyl)-4-[2-(acetylmethylamino)ethyl]cyclohexanone (**20**), homogeneous by GLC and TLC as an oil: IR 1658 cm^{-1} (amide C=O); 100-MHz ^1H NMR δ 1.97 and 2.05 (2 s, 3 H), 2.85 and 2.90 (2 s, 3 H), 3.94 (s, 6 H), 6.91 (m, 3 H); 100-MHz ^1H NMR (100 °C) δ 2.01 (s, 3 H), 2.91 (s, 3 H), 3.97 (s, 6 H), 6.94 (m, 3 H); mass spectrum, *m/e* (relative intensity) 333 (100, M^+), 233 (85), 100 (40), 86 (35); molecular ion at 333.1943 (calcd for $C_{19}H_{27}NO_4$: 333.1943).

4-(3,4-Dimethoxyphenyl)-4-[2-(acetylmethylamino)-ethyl]cyclohexenone (23). Mesembrine (200 mg) was stirred in acetic anhydride (3 mL) containing sodium acetate (20 mg) for 2 h. The mixture was poured into water, basified with K_2CO_3, and extracted with $CHCl_3$ to yield 190 mg of **23** as an oil. Molecular ion at *m/e* 331.1780 (calcd for $C_{19}H_{25}NO_4$: 331.1783).

4-(3,4-Dimethoxyphenyl)-4-[2-(acetylmethylamino)-ethyl]cyclohexanone (20). The enone **23** (150 mg) was taken up in 95% EtOH and hydrogenated at atmospheric pressure over Pd/C (15 mg) for 2 h. Filtration of the catalyst followed by removal of the solvent yielded 130 mg of **20** as an oil. The chromatographic properties and spectral data of this product were identical with those of the natural base.

Isolation of *N*-Acetyltortuosamine (6). Column fractions 227–309 (5.3 g) were applied to a silica gel column (300 g) using a linear solvent gradient of $CHCl_3$ and EtOAc. Two hundred 15-mL fractions were collected and analyzed by GLC. TLC and GLC showed fractions 175–190 to contain a new alkaloid.

The mixture (1.85 g) was subjected to preparative TLC on alumina in $CHCl_3$/MeOH (7:3), alumina in $CHCl_3$ (2×), silica gel in $CHCl_3$/MeOH (9:1), and finally alumina in $CHCl_3$ (3×) to yield *N*-acetyltortuosamine (**6**), as an oil, pure by GLC and TLC: IR 1664 (amide C=O) cm^{-1}; CD (95% EtOH) $[\theta]_{280}$ +10 000° $[\theta]_{260}$ –4300°; 250-MHz ^1H NMR δ 1.96 and 2.02 (2 s, 3 H), 2.78 and 2.80 (2 s, 3 H), 7.13 (dd, 1 H, J = 8.0, 5.0 Hz), 7.5 (dd, 1 H, J = 8.0, 2.0 Hz), 8.39 (dd, 1 H, J = 5.0, 2.0 Hz); mass spectrum, *m/e* (relative intensity) 368 (40, M^+), 282 (60), 268 (100), 100 (10), 86 (20); molecular ion at 368.2096 (calcd for $C_{22}H_{28}N_2O_3$: 368.2009).

Hydrogenolysis of *Sceletium* A_4.[11] *Sceletium* A_4 (**3**; 94 mg) was dissolved in water (3 mL) containing 50 μL of 12 N HCl and 10% palladium catalyst (2 mg) was added. The mixture was stirred at 55 °C under hydrogen for 42 h until hydrogenolysis was complete. Chromatography on silica gel plates (made up in 5% K_2CO_3 solution), using $CHCl_3$/MeOH (3:2) as the solvent, yielded tortuosamine (**4**) as a colorless oil. The chromatographic (GLC and TLC) and spectral data (IR, CD, NMR, and mass spectrum) of this product were identical with those of naturally occurring tortuosamine.

N-Acetylation of Tortuosamine (4). Tortuosamine (70 mg) was stirred at room temperature with 5 mL of acetic anhydride for 10 h. Basification of the reaction with saturated Na_2CO_3 solution followed by extraction with $CHCl_3$ afforded *N*-acetyltortuosamine (**6**; 50 mg). The chromatographic (GLC and TLC) and spectral data (NMR, CD, mass spectrum, and IR) for this synthetic material were identical with those of the natural base.

Isolation of Dihydropyridone Base (5). Fractions 236–330 (5.85 g) were applied to an alumina column (activity IV, 250 g). A linear solvent gradient of $CHCl_3$/MeOH (1:1) and MeOH was used and 225 ten-milliliter mL fractions were collected. Fractions 200–225 (520 mg) contained a new alkaloid relatively pure by GLC and TLC. This fraction was applied to alumina (preparative tlc)

and developed in $CHCl_3$/MeOH (1:1). A band with R_f 0.60 was removed and shown to contain the new component in 60% purity by GLC. This fraction (105 mg) was subjected to chromatography over silica gel (containing 5% K_2CO_3), using $CHCl_3$/MeOH (3:2, 2×) as the solvent. A band of R_f 0.65 (65 mg) was applied to alumina and developed in $CHCl_3$/MeOH (6:5, 2×). A band of R_f 0.45 contained the dihydropyridone (**5**) as an oil, pure by GLC and TLC: IR 3420 (NH), 1695 (NC=C), 1675 (NC=O) cm^{-1}; 100-MHz NMR δ 2.5 (s, 3 H), 3.92 (s, 6 H), 6.80 (s, 3 H), 7.52 (s, 1 H, disappeared upon addition of D_2O); CD (95% EtOH), $[\theta]_{241}$ −10 500°; mass spectrum, m/e (relative intensity) 342 (60, M^+), 327 (20), 314 (18), 299 (23), 285 (30), 283 (35), 59 (100), 57 (75); molecular ion at 342.1947 (calcd for $C_{20}H_{26}N_2O_3$: 342.1943).

3′-Methoxy-4′-*O*-methyljoubertiaminol (13a or 14b). Fractions 101–226 (6.75 g) were applied to a silica gel column (350 g), and the column was eluted with a linear solvent gradient of $CHCl_3$ and MeOH. One hundred and fifty 25-mL fractions were collected, and GLC examination showed that fractions 65–80 (2.2 g) contained a new base. This mixture was subjected to successive preparative TLC on alumina in $CHCl_3$/MeOH (9:1), alumina in $CHCl_3$/EtOAc (9:1), silica gel in $CHCl_3$/EtOAc (4:1), and finally silica gel (made up in 5% K_2CO_3 solution) in $CHCl_3$/MeOH (9:1) to yield 3′-methoxy-4′-*O*-methyljoubertiaminol (**13a** or **14b**) as a solid pure by TLC and GLC: I R 3410 (OH) cm^{-1}; 100-MHz NMR δ 2.3 (s, 6 H), 3.86 and 3.87 (2 s, 6 H), 4.3 (M, 1 H, half-bandwidth 18.5 Hz), 5.90 (s, 2 H), 6.9 (m, 3 H); $[\alpha]^{25}_D$ −12.4° (*c* 2.6, MeOH); mass spectrum m/e (relative intensity) 305 (2.0, M^+), 234 (7.8), 72 (3.7), 58 (100); mp 100.5 °C (ether/hexane); molecular ion at 305.1994 (calcd for $C_{18}H_{27}NO_3$: 305.1990).

Reduction of (−)-3′-Methoxy-4′-*O*-methyljoubertiamine (10). 3′-Methoxy-4′-*O*-methyljoubertiamine (100 mg) was dissolved in EtOH (5 mL) and 180 mg of sodium borohydride was added. The reaction mixture was refluxed for 2 h and then quenched with 1 N HCl. Basification with K_2CO_3 followed by extraction with $CHCl_3$ yielded 105 mg of a two-component mixture. The mixture was chromatographed over silica gel in $CHCl_3$/MeOH (9:1). A band of R_f 0.60 contained the axial alcohol (**13b** or **14a**) and another band of R_f 0.25 contained (−)-3′-methoxy-4′-*O*-methyljoubertiaminol (**13a** or **14b**). The chromatographic (GLC and TLC) and spectral data (NMR, IR, and mass spectrum) of the equatorial alcohol were identical with those of the natural base; mp 100 °C (ether/hexane).

The axial alcohol (20 mg) was isolated from the reaction mixture and was shown to be pure by GLC and TLC: IR 3415 (OH) cm^{-1}; $[\alpha]^{26}_D$ −48° (*c* 0.21, MeOH); 100-MHz NMR δ 2.63 (s, 6 H), 2.7 (s, 1 H, disappeared upon addition of D_2O), 3.85 and 3.90 (2 s, 6 H), 4.02 (m, 1 H, half-bandwidth 8 Hz), 5.91 (d of d, 2 H), 6.78 (m, 3 H); mp 92.5 °C (EtOAc); molecular ion at 305.1988 (calcd for $C_{18}H_{27}NO_3$: 305.1990).

Hofmann Degradation of (−)-Mesembranol (16a). To a solution of 110 mg (0.378 mmol) of (−) mesembranol in 40 mL of acetone was added 2.5 mL (5.7g, 40 mmol) of freshly distilled methyl iodide (MeI) under N_2 at room temperature. After the mixture was stirred for 5 h, the solvent was evaporated to give the methiodide as a light-yellow foam, which was immediately dissolved in 35 mL of MeOH/H_2O (1:1), 250 mg (1.05 mmol) of Ag_2O was added in one portion under N_2 at room temperature, and the mixture allowed to stir overnight. Excess Ag_2O and slightly pink AgI were filtered away on a Celite pad, and the ammonium hydroxide salt of *N*-methyl **16a** was isolated as an oil after evaporation of solvent (121 mg, 99%). Pyrolysis was effected by dissolving this yellow oil in H_2O and removing the solvent on a rotary evaporator to dryness and then heating the residue at 105 °C for 30 min. This was followed by washing the slightly darkened residue with CH_2Cl_2/ether (1:3) to remove the product as a mixture of the free amines **13** and **14**. Several repetitions of this procedure resulted in 108 mg (94%) of the product mixture as a colorless oil. The naturally occurring **13** was separated from **14** by its dissolution in EtOAc, the unnatural epimer being precipitated. This afforded pure 13 as an oil, which easily crystallized to yield 102.6 mg (89%) of alkaloid whose chromatographic, spectral, and melting point data were identical with an authentic sample of **13**. Crystalline **14** was given by the treatment with EtOAc, yielding 5.5 mg (4.6%) of pure alkaloid identical in all respects with the minor product of borohydride reduction of **10**.

Hofmann Degradation of (−)-Mesembranol (16a). Alternate Procedure. The procedure of Warnhoff was followed:[17] 30 mg (0.103 mmol) of **16a** was converted to its methiodide as before and dissolved in 3 mL of anhydrous Me_2SO. To this solution was added 18 mg (0.161 mmol) of sublimed potassium *tert*-butoxide in two portions under N_2 at room temperature. The reaction mixture was allowed to stir at room temperature for 48 h at which time it was quenched by dilution with 30 mL of H_2O and washed three times with CH_2Cl_2 (75 mL total). The combined extract was washed with brine and dried, and the solvent was evaporated. The resulting reddish-yellow oil (2.3 mg) displayed no volatile components by GC/MS and proved to be a complex mixture of decomposition products by NMR, with no trace of olefin product.

Hofmann Degradation of *O*-Methylmesembranol (16b). *O*-Methylmesembranol was prepared from (−)-mesembranol by the procedure of Hawks.[22] To a solution of 45 mg (0.147 mmol) of **16b** in 20 mL of acetone was added excess MeI under N_2 at room temperature and after 5 h of stirring all solvent was removed to yield the methiodide as a white solid. This was immediately dissolved in 25 mL of MeOH/H_2O (1:1) and stirred overnight with 175 mg (0.735 mmol) of Ag_2O. This mixture was pyrolyzed in a manner identical with the pyrolysis step in the Hofmann degradation of **16a** to yield 30 mg (64%) of pure **17** after two repetitions of the procedure. The product was a colorless oil: 80-MHz NMR δ 2.23 (s, 6 H), 3.34 (s, 3 H), 3.85 and 3.86 (2 s, 6 H), 3.80 (br m, 1 H), 5.92 (s, 2 H), 6.82 (m, 3 H); $[\alpha]^{25}_D$ −9.1° (*c* 0.49, MeOH); mass spectrum, m/e (relative intensity) 319 (1.8, M^+), 248 (4.1), 72 (3.5), 58 (100); molecular ion at m/e 319.2149 (calcd for $C_{19}H_{29}NO_3$: 319.2147).

Methylation of 3′-Methoxy-4′-*O*-methyljoubertiaminol (13). Potassium hydride (24.5 mg, 0.61 mmol) was washed several times with anhydrous THF under N_2 flush in a two-necked flask. A solution of 30 mg (0.098 mmol) of **13** in 30 mL of dry THF was added dropwise to the magnetically stirred THF–KH slurry. After stirring for 30 min at room temperature, 60 μL of a 0.228 g/mL solution of MeI in THF was added in one portion via syringe. After 1–2 min the reaction mixture deposited a white precipitate. The reaction mixture was allowed to stir for 1 h (GC control) and then was quenched by dilution with 25 mL of MeOH and then pouring of the mixture into brine. This was extracted three times with CH_2Cl_2 (60 mL total); the combined extract was then washed with brine and dried, and the solvent was evaporated to give 31 mg of a yellow oil. This material was subjected to preparative TLC (silica gel; 5% MeOH in $CHCl_3$) to give 27 mg (86%) of **17**, identical in every respect with the product from Hofmann degradation of *O*-methylmesembranol.

Isolation of the Ether-Soluble Nonphenolic Alkaloids. The ether-soluble alkaloids (60 g) from *S. namaquense* were passed through a silica gel precolumn (2000 g), using $CHCl_3$/MeOH (1:1). Removal of the solvent yielded 46 g of alkaloids. A fraction of these ether-soluble alkaloids (20 g), composed primarily of mesembrine and mesembrenone, was placed on an alumina column (activity IV, 1000 g). A linear solvent gradient of benzene/$CHCl_3$ and $CHCl_3$ was utilized and 375 fifteen-milliliter fractions were collected. Fractions 1–100 contained neutral material, mesembrine, and (−)-mesembrane (2.05 g); 101–226 contained mesembrine, mesembrenone, and 3′-methoxy-4′-*O*-methyljoubertiaminol (6.75 g); 227–309 contained mesembrenone, *Sceletium* A_4, *N*-acetyltortuosamine, and unidentified components (5.30 g); and 310–375 contained unidentified components (4.1 g).

Isolation of 4-(3-methoxy-4-hydroxyphenyl)-4-[2-(acetylmethylamino)ethyl]cyclohexadienone (24). Dried plant material from *S. namaquense* (500 g) was macerated in a blender with 95% EtOH (4 L). The mixture was filtered and the filter cake was placed in a Soxhlet extractor and further extracted with 95% EtOH (5 L). The combined EtOH extracts were taken to dryness in vacuo, and the residue was taken up in $CHCl_3$ (2 L). The $CHCl_3$ was extracted with 10% K_2CO_3 (2 L) and the aqueous layer discarded. The $CHCl_3$ was then extracted with 10% NaOH (1 L) to remove the phenolic components. The phenolic fraction (5 g) was recovered by adjusting the NaOH solution to pH 9 (with CO_2) and extracting into $CHCl_3$ (5 × 100 mL). The phenolic components were applied to an alumina column (activity IV, 200 g), utilizing a linear solvent gradient of $CHCl_3$ and $CHCl_3$/EtOAc (1:1). One hundred 40-mL fractions were collected and analyzed by GLC and TLC. Fractions 40–55 contained a new alkaloid in

20% purity by GLC. This fraction (1.05 g) was subjected to preparative layer chromatography over alumina in $CHCl_3$, alumina in $CHCl_3/Et_2O$ (4:1, 2×), alumina in $CHCl_3$/EtOAc (97:3), and finally alumina in $CHCl_3$ to yield 4-(3-methoxy-4-hydroxyphenyl)-4-[2-(acetylmethylamino)ethyl]cyclohexadienone (**24**) as a solid: mp 107.5 °C; IR 3540 (phenolic OH), 1637 (amide C=O), 1665 (dienone C=O) cm^{-1}; 100-MHz NMR δ 2.97 and 3.01 (2 s, 3 H), 3.82 and 3.86 (2 s, 3 H), 6.35 (d, 2 H, J = 14 Hz), 6.98 (d, 2 H, J = 14 Hz), 6.85–6.93 (m, 3 H); mass spectrum m/e (relative intensity) 315 (20, M^+), 273 (15), 242 (45), 229 (20), 215 (40), 100 (45), 86 (40), 73 (100); molecular ion at 315.1472 (calcd for $C_{18}H_{21}NO_4$, 314.1470).

Acetylation of 4′-*O*-Demethylmesembrenone (29). A mixture of 100 mg of **32**, 3 mL of acetic anhydride, and 10 mg of anhydrous sodium acetate was stirred at room temperature for 4 h. The mixture was diluted with water (100 mL), basified with solid K_2CO_3, and extracted with $CHCl_3$ (2 × 50 mL). The $CHCl_3$ was washed with water and dried over magnesium sulfate. The solvent was removed in vacuo to yield 4-(3-methoxy-4-acetoxyphenyl)-4-[2-(acetylmethylamino)ethyl]cyclohexadienone (**30**) as an oil, pure by GLC and TLC: molecular ion at m/e 357.1573 (calcd for $C_{20}H_{23}NO_5$: 357.1576).

O-Deacetylation of 4-(3-Methoxy-4-acetoxyphenyl)-4-[2-(acetylmethylamino)ethyl]cyclohexadienone (30). A 50-mg sample of **30** was stirred with 3 mL of absolute methanol and anhydrous K_2CO_3 (10 mg) for 6 h at room temperature. The mixture was diluted with 50 mL of water and extracted with $CHCl_3$ (2 × 50 mL). The $CHCl_3$ was washed with water and dried over sodium sulfate. The solvent was removed to give a product exhibiting chromatographic and spectral data identical with those of the natural base **24**.

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Registry No. **1**, 24880-43-1; **3**, 35135-35-4; (-)-**4**, 35722-04-4; **5**, 82545-08-2; (+)-**6**, 82545-10-6; (-)-**10**, 59096-18-3; **13**, 59096-21-8; (-)-**16a**, 23544-42-5; (-)-**16b**, 82545-11-7; (-)-**17**, 82545-14-0; **20**, 82545-07-1; **23**, 82545-09-3; **24**, 82545-13-9; **29**, 82597-44-2; **30**, 82545-12-8; mesembrenone, 25516-12-5; *N*-formyltortuosamine, 59096-17-2; Δ^7-mesembrenone, 59122-98-4.

Synthesis and Absolute Configuration of (*R*)-(+)- and (*S*)-(-)-5-(1,3-Dimethylbutyl)-5-ethylbarbituric Acid

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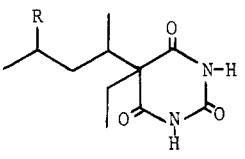
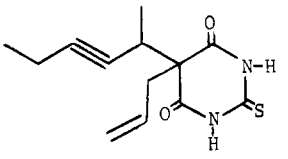
(*R*)-(+)- and (*S*)-(-)-5-(1,3-dimethylbutyl)-5-ethylbarbituric acids, which show excitatory–convulsant and sedative–hypnotic effects in mice, respectively, were synthesized by a sequence of reactions that permitted assignment of the absolute configuration of these enantiomers. Racemic 3,5-dimethylhexanoic acid was prepared in three steps from 4-methyl-2-pentanone by Wittig–Horner reaction with triethyl phosphonoacetate, hydrogenation of the resulting α,β- and β,γ-unsaturated ester mixture, and alkaline hydrolysis of the ethyl ester obtained. An optical resolution of this acid afforded relatively large quantities of the (*R*)-(+) and (*S*)-(-) enantiomers of previously established absolute configuration. Optical purity of >99% was determined for these enantiomers by HPLC analysis of the amides formed with optically pure (*R*)-(+)- or (*S*)-(-)-1-phenylethylamine. Transformation of (*R*)-(+)- and (*S*)-(-)-3,5-dimethylhexanoic acids to the title compounds by a route shown earlier not to involve racemization thus afforded the enantiomeric barbiturates of >99% optical purity and of established absolute configuration.

Racemic 5-(1,3-dimethylbutyl)-5-ethylbarbituric acid [(±)-DMBB, (±)-**1**] was first synthesized[1] and characterized[1,2] as a convulsant many years ago. Subsequent studies[3,4] using partially resolved material revealed that the convulsant action resided in the (+) isomer while the (-) isomer showed the classical sedative–hypnotic actions common to many barbiturates such as pentobarbital [(±)-**2**]. The relationship between mechanism of action of barbiturates and benzodiazepines has recently come under close scrutiny since the discovery that (±)-pentobarbital [(±)-**2**] potentiates the γ-aminobutryic acid (GABA)[5] enhancement of benzodiazepine binding to membrane-bound receptors[6,7] and also enhances benzodiazepine receptor affinity in the absence of GABA as do (±)-**1**, the enantiomers of **2**, and other barbiturates.[7,8] The different pharmacological profiles of (±)-DMBB [(±)-**1**][1-3] and pentobarbital [(±)-**2**][3,9] in vivo and the close structural similarity of these compounds (which differ only by one methyl group at the 3-position in the butyl side chain) suggested that the optically pure enantiomers of **1** could



(±)-**1**: R = CH_3

(±)-**2**: R = H



(±)-**3**

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