Anal. Calcd for $C_{21}H_{36}O_4$ (352): C, 71.55; H, 10.3. Found: C, 71.40; H, 10.35.

Further elution yielded a mixture of alcohols of **30** and **31** (2.13 g) followed by isomer B, **30**[23] (4.84 g). The ir and nmr of this isomer were essentially identical with that of isomer A.

Anal. Calcd for $C_{21}H_{36}O_4$ (352): C, 71.55; H, 10.3. Found: C, 71.39; H, 10.04.

Methyl 5-(3-Hydroxyoctyl)-2-oxocyclopentaneheptanoate (32 and 33).—A solution of keto alcohol **30** (1.06 g) in methanol (25 ml) was hydrogenated with 10% palladium/charcoal (0.360 g). The catalyst was filtered and washed with hot methanol. The crude product was chromatographed to yield alcohol **32** (0.75 g): ν_{max} 3450, 1735 cm^{-1}; nmr δ 3.65 (4 H, s, carbomethoxyl).

Anal. Calcd for $C_{21}H_{38}O_4$ (354): C, 71.14; H, 10.80. Found: C, 71.11; H, 10.85.

In a similar manner as described above, alcohol **31** (2.5 g) was hydrogenated to yield keto alcohol **33** (1.32 g). The infrared and the nmr spectra were essentially identical with those of alcohol **32**.

Anal. Calcd for $C_{21}H_{38}O_4$ (354): C, 71.14; H, 10.80. Found: C, 71.13; H, 10.85.

The two alcohols **32** and **33** were indistinguishable by gc or by tlc in at least two different systems.

Hydrolysis of Alcohols 30, 31, 32, and 33.—Pure samples of the esters **30–33** were hydrolyzed in methanolic sodium hydroxide to yield the corresponding acids. The acids obtained from alcohols **31**, **32**, and **33** were oils, whereas that from alcohol **30** was a solid and crystallized from ether–hexane to yield an analytical sample, mp 85–86°. The ir showed characteristic acid absorption: nmr δ 5.62 (2 H, m, vinylic), 4.3 (1 H, m, carbinolic), 0.92 (3 H, t, terminal methyl).

Anal. Calcd for $C_{20}H_{34}O_4$ (338.47): C, 70.97; H, 10.13. Found: C, 70.72; H, 10.19.

Registry No.—**1**, 34546-57-1; **5a**, 34603-59-3; **5b**, 34603-60-6; **6a**, 34603-61-7; **6b**, 34603-62-8; **7a**, 34603-63-9; **7b**, 34603-64-0; **8**, 22973-15-5; **9**, 34603-66-2; **10**, 34603-67-3; **11**, 34603-68-4; **13**, 28764-52-5; **14**, 22973-16-6; **16**, 34546-58-2; **17**, 34546-59-3; **18**, 34647-02-4; **19**, 34546-60-6; **20**, 28764-72-9; **21**, 28764-73-0; **21** free acid, 16887-10-8; **22**, 28764-56-9; **23**, 22973-17-7; **24**, 28764-75-2; **27**, 34603-78-6; **30**, 34603-79-7; **30** free acid, 34603-80-0; **31**, 34603-81-1; **32**, 20592-62-5; **33**, 34603-77-5; 1-carbomethoxy-2-oxocyclopentaneheptanoic acid Me ester, 34546-61-7; 2-oxocyclopentaneheptanoic acid 2,4-DNP, 34546-62-8; 5-oxo-1-cyclopentene-1-heptanoic acid, 5239-43-0.

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General Methods of Alkaloid Synthesis. X. The Total Synthesis of the Sceletium Alkaloids (±)-Joubertiamine, (±)-*O*-Methyljoubertiamine, and (±)-Dihydrojoubertiamine

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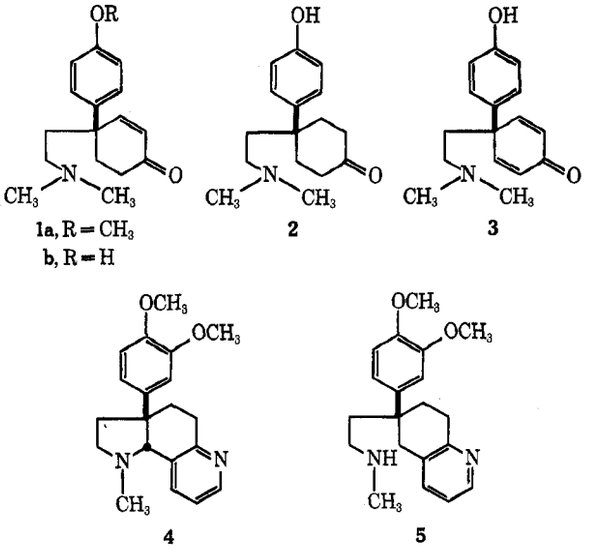
An efficient synthesis of the pharmacologically interesting Sceletium alkaloid (±)-*O*-methyljoubertiamine (**1a**) and its conversion into (±)-joubertiamine (**1b**) and (±)-dihydrojoubertiamine (**2**) is described.

Renewed interest in the mesembrine alkaloids[2,3] has been catalyzed by the recent characterization[4–7] of several new bases found in various Sceletium species which are used by the natives of Southwest Africa in the preparation of a pharmacologically interesting drug known as "Channa" or "Koegoed." These include the seco-mesembrine alkaloids joubertiamine (**1b**),[4] dihydrojoubertiamine (**2**),[4] and dehydrojoubertiamine (**3**)[4] and the fused pyridine bases Alkaloid A_4 (**4**)[6,7] and tortuosamine (**5**).[7]

Inspection of the structural features of these new Sceletium alkaloids coupled with their potential physiological activity prompted the present investigation designed to test further two fundamental principles of alkaloid synthesis which have found application in the synthesis of mesembrine (**6**) itself,[8] the closely related



(1) A. P. Sloan Fellow, 1969–1971.

(2) For a review see A. Popelak and G. Lettenbauer, "The Alkaloids," Vol. IX, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1967, p 467.

(3) In the older literature reference is made to the isolation of many of these alkaloids from the genus *Mesembryanthemum* Dill from which the names of several of these bases were derived. However, recently this classification has been revised to the genus *Sceletium* N. E. Brown (Ficoidaceae or Aizoaceae). Therefore, reference to these bases as mesembrine alkaloids is technically a misnomer.

(4) R. R. Arndt and P. E. J. Kruger, *Tetrahedron Lett.*, 3237 (1970).

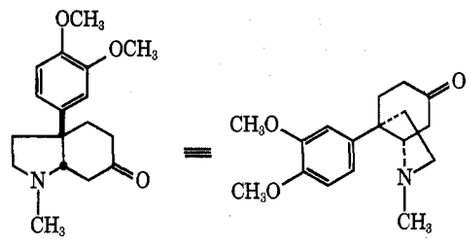
(5) P. W. Jeffs, G. Ahmann, H. F. Campbell, D. S. Farrier, G. Ganguli, and R. L. Hawks, *J. Org. Chem.*, **35**, 3512 (1970).

(6) P. W. Jeffs, P. A. Luhan, A. T. McPhail, and N. H. Martin, *Chem. Commun.*, 1466 (1971).

(7) F. O. Snyckers, F. Strelow, and A. Wiechers, *ibid.*, 1467 (1971).

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

Amaryllidaceae alkaloid elwesine (**7**),[9] and other structurally diverse natural products such as the pyridine alkaloids myosmine and apoferrorosamine,[10] the Aspidosperma base aspidospermine,[11] and the parent skeletons of various Erythrina[12] and hasubanan[13] alkaloids.



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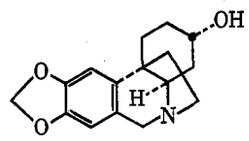

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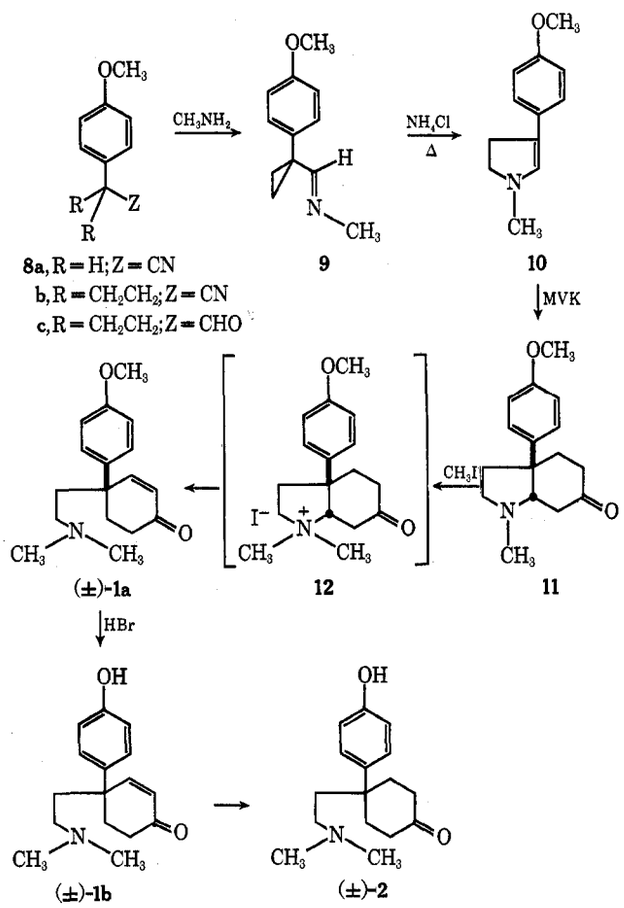
Key steps in each of these syntheses featured either the acid-catalyzed thermally induced rearrangement of a cyclopropyl imine as a general device for obtaining appropriately substituted 1- or 2-pyrrolines[8a,b,9,10,11b,13b] and/or methyl vinyl ketone annelation of these and other endocyclic enamines.[8,9,11a,12,13] We now report the application of both of these increasingly important general methods to the synthesis of the pharmacologically interesting Sceletium alkaloids (±)-*O*-methyljoubertiamine (**1a**), (±)-joubertiamine (**1b**), and (±)-dihydrojoubertiamine (**2**).

The present synthesis begins with *p*-methoxyphenyl acetonitrile (**8a**) whose cyclopropanation was achieved in 75% yield by means of ethylene dibromide and lithium amide base in glyme as solvent. These conditions followed from our previous studies[8a,9] in which the beneficial effect of employing the more covalent lithium salts in generating electronically destabilized carbanions of this type was established. Selective reduction of the resultant nitrile **8b** with diisobutylaluminum hydride in benzene provided an 86% yield of the corresponding aldehyde **8c**. Transformation of the latter intermediate into aldimine **9** was accomplished in 91% yield and simply required stirring a benzene solution of **8c** and excess methylamine for 2 days at room temperature in the presence of suspended magnesium sulfate.

The crucial rearrangement of imine **9** to pyrroline **10** proceeded in virtually quantitative yield at 140° by employing ammonium chloride as the acidic catalyst. Annelation of this endocyclic enamine with methyl vinyl ketone as described previously[8c,9] yielded exclusively the cis octahydroindolone **11** in 93% yield. The gross structural and stereochemical features of this intermediate were readily confirmed by comparison of its pmr spectrum with that of mesembrine (**6**).[8a] These spectra were virtually identical in the highly diagnostic aliphatic region.

Conversion of the octahydroindolone **11** into (±)-*O*-methyljoubertiamine (**1a**)[14] required N-methylation and subsequent β elimination of the resultant quaternary ammonium salt **12**. This was accomplished in one operation by refluxing **11** in neat methyl iodide followed by work-up in aqueous base. The synthesis of racemic joubertiamine (**1b**) was completed by demethylation of **1a** in hot hydrobromic acid. Confirmation of the structural assignment was made by comparison of the infrared, ultraviolet, pmr, and mass spectra with those of the natural base and by catalytic hydrogenation to racemic dihydrojoubertiamine (**2**) and an identical comparison.[15]



8a, R = H; Z = CN
b, R = CH_2CH_2; Z = CN
c, R = CH_2CH_2; Z = CHO

9 **10** **11** **12** (±)-**1a** (±)-**1b** (±)-**2**

Experimental Section[16]

1-(*p*-Methoxyphenyl)cyclopropanecarbonitrile (8b).—*p*-Methoxybenzyl cyanide (1.38 g, 9.4 mmol), freshly prepared $LiNH_2$ (540 mg, 23.5 mmol), and 15 ml of dry glyme was placed in a 100-ml oven-dried jacketed flask equipped with N_2 flushing system, condenser, and magnetic stirrer. Ethylene dibromide (2.0 g, 10.6 mmol) was added over a 10-min period with cooling

(9) R. V. Stevens, L. E. DuPree, Jr., and P. L. Loewenstein, *J. Org. Chem.*, **37**, 977 (1972).

(10) R. V. Stevens, M. C. Ellis, and M. P. Wentland, *J. Amer. Chem. Soc.*, **90**, 5576 (1968).

(11) (a) R. V. Stevens, R. K. Mehre, and R. L. Zimmerman, *Chem. Commun.*, 877 (1968); (b) R. V. Stevens, J. M. Fitzpatrick, M. Kaplan, and R. L. Zimmerman, *ibid.*, 857 (1969).

(12) R. V. Stevens and M. P. Wentland, *ibid.*, 1104 (1968).

(13) (a) D. A. Evans, C. A. Bryan, and G. M. Wahl, *J. Org. Chem.*, **35**, 4122 (1970); (b) S. L. Keely, Jr., A. J. Martinez, and F. C. Tahk, *Tetrahedron*, **26**, 4729 (1970).

(14) Dr. A. Wiechers of the University of Pretoria, South Africa, has recently isolated *O*-methyljoubertiamine and *O*-methyldihydrojoubertiamine from *Sceletium spp.* and assigned the absolute configurations shown: private communications, Sept 10 and Nov 11, 1971.

(15) We are grateful to Professor Arndt and Dr. Kruger[4] for providing us with this data.

(16) Infrared spectra were obtained on a Beckman IR-8 spectrometer. Uv spectra were secured in 95% ethanol solutions recorded on a Bausch and Lomb Spectronic 505 instrument and pmr spectra were obtained on a Varian A-56/60A spectrometer using tetramethylsilane as internal standard. Mass spectra were taken on a Consolidated Electrodynamics Corp. 21-110 high resolution spectrometer. Melting points and boiling points are uncorrected. Microanalyses were performed by the Elek Microanalytical Laboratory, Torrance, Calif.

after which steam was carefully admitted into the jacket. After the evolution of NH_3 had ceased, the dark brown solution was cooled and freed of solvent under reduced pressure, and water was cautiously added to the residue. Extraction with CH_2Cl_2, drying over Na_2SO_4, and distillation yielded 1.27 g (75%) of a colorless oil: bp 92–94° (0.25 mm); ir (neat) 2200 cm^{-1}; pmr δ 7.05 (symmetrical AA'BB' q, 4 H), 3.80 (s, 3 H), 1.46 (symmetrical A_2B_2 m, 4 H).

Anal. Calcd for $C_{11}H_{11}NO$: C, 74.51; H, 6.88; mol wt, 173.21. Found: C, 74.21; H, 6.87; mol wt, 173 (mass spectrum).

1-(*p*-Methoxyphenyl)cyclopropanecarboxaldehyde (8c).—Nitrile **8b** (1.28 g, 7.38 mmol) was dissolved in 13 ml of sodium-dried benzene in a flask equipped with N_2 flushing system, dropping funnel, and magnetic stirrer. Freshly prepared diisobutylaluminum hydride in benzene (0.0368 g/ml, 10.3 mmol) was added dropwise and the mixture was allowed to stir for 2 hr. The solution was then carefully poured into 200 ml of 5% H_2SO_4 and the mixture was stirred for 1 hr. The layers were separated and the aqueous phase was extracted with ether. The combined organic layers were dried over $MgSO_4$ and freed of solvent *in vacuo*, and the residue was distilled, providing 1.1 g (86%) of a colorless oil: bp 75.2–76.5° (0.3 mm); ir (neat) 1720 cm^{-1}; pmr δ 9.46 (s, 1 H), 7.03 (symmetrical AA'BB' q, 4 H), 3.76 (s, 3 H), 1.40 (symmetrical A_2B_2 m, 4 H).

Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; mol wt, 176.21. Found: C, 74.75; mol wt, 176 (mass spectrum).

***N*-Methylaldimine (9).**—Aldehyde **8c** (9.2 g) was dissolved in 350 ml of sodium-dried benzene and 1 g of anhydrous $MgSO_4$ was added. The solution was cooled to 0–5° and saturated with dry methylamine gas. The mixture was stirred at room temperature for 48 hr, whereupon reaction was complete. Filtration and removal of the solvent *in vacuo* provided a light yellow oil which upon distillation gave 8.86 g (91%) of a colorless oil: bp 80–81° (0.3 mm); ir (neat) 1663 cm^{-1}; pmr δ 7.57 (t, 1 H), 7.03 (symmetrical AA'BB' q, 4 H), 3.79 (s, 3 H), 3.23 (d, 3 H), 1.19 (symmetrical A_2B_2 m, 4 H); calcd mol wt, 189.25; found mol wt, 189 (mass spectrum).

***N*-Methyl-3-(*p*-methoxyphenyl)-2-pyrroline (10).**—Aldimine **9** (141 mg) and 20 mg of NH_4Cl was heated under N_2 at 140° for 2 hr. The melt was cooled to 70° and extracted several times with hot hexane. Removal of the solvent provided yellow crystals which were sublimed at 65° (0.3 mm). In this manner 139 mg (98%) of white crystals of the pyrroline were obtained: mp 92–95°; ir ($CHCl_3$) 1680 cm^{-1}; uv (95% EtOH) 208 mμ (ϵ 1500), 222 (1500), 292 (3000); pmr δ 6.82 (symmetrical AA'BB' q, 4 H), 6.12 (t, 1 H), 3.73 (s, 3 H), 2.68–3.30 (m, 4 H), 2.59 (s, 3 H); calcd mol wt, 189.25; found mol wt, 189 (mass spectrum).

***cis*-Octahydroindolone (11).**—Pyrroline **10** (3.2 g) was dissolved in 200 ml of anhydrous ether and saturated with dry HCl. Removal of the ether provided a gummy hydrochloride salt which was dissolved in 20 ml of acetonitrile. Freshly distilled methyl vinyl ketone (2 ml) was added to the solution and the solution was brought to reflux under N_2 for 9 hr. The mixture was cooled and then poured into 350 ml of 5% HCl and extracted with ether to remove neutral materials. The aqueous solution was basified with KOH pellets and extracted with ether. The organic layer was washed with saturated NaCl solution and dried over Na_2SO_4, and the solvent was removed *in vacuo*, yielding 4.09 g (93%) of essentially pure product. Kugelrohr bulb distillation at 110° (0.3 mm) provided analytically pure *cis*-octahydroindolone (**11**): ir (neat) 1715 cm^{-1}; pmr δ 7.10 (symmetrical AA'BB' q, 4 H), 3.81 (s, 3 H), 2.81 (s, 3 H), 1.98–3.10 (m, 11 H); calcd mol wt, 259.34; found mol wt, 259 (mass spectrum).

Anal. Calcd for $C_{15}H_{21}NO_2$: C, 74.10; H, 8.16. Found: C, 73.94; H, 8.30.

(±)-*O*-Methyljoubertiamine (1a).—Octahydroindolone **11** (951 mg) was dissolved in 15 ml of CH_3I and the solution was refluxed under N_2 for 24 hr. Removal of the solvent left a white solid **12**, mp 135–138°, which was dissolved in 20 ml of 0.5 *N* KOH and extracted with ether. After drying over $MgSO_4$ the solvent was removed leaving 590 mg (62%) of essentially pure **1a**. Kugelrohr bulb distillation at 120° (0.25 mm) provided an analytical sample of **1a** as a colorless oil: ir (neat) 1680 cm^{-1}; pmr δ 7.22, 6.85 (dd, J = 7.50 cps, 4 H), 7.15, 6.05 (dd, J = 8.75 cps, 2 H), 3.81 (s, 3 H), 2.00–2.23 (m, 14 H); calcd mol wt, 273.36; found mol wt, 273 (mass spectrum).

(±)-Joubertiamine (1b).—*O*-Methyljoubertiamine (**1a**) was demethylated by heating in hot 48% HBr under N_2 for 3.5 hr. The resultant dark solution was cooled, basified with KOH solution, and extracted with ether to remove any neutral materials. The aqueous layer was then neutralized by addition of powdered NH_4Cl and extracted with ether. The ether extracts were combined, dried over $MgSO_4$, and freed of solvent, leaving yellow needles of **1b** (80%), mp 126–130° dec. The ir, uv, pmr, and mass spectra of this material were identical with those recorded for natural joubertiamine.[4,15]

(±)-Dihydrojoubertiamine (2).—(±)-Joubertiamine (**1b**) was smoothly and quantitatively reduced over a 10% Pd/C catalyst in CH_3OH. The ir, uv, pmr, and mass spectra of this material were identical with those recorded for the natural product.[4,15]

Registry No.—**1a**, 34603-52-6; **1b**, 34603-53-7; **8b**, 16728-00-0; **8c**, 34603-55-9; **9**, 34603-56-0; **10**, 34603-57-1; **11**, 34603-58-2.

Acknowledgments.—We are grateful to the National Science Foundation and The Robert A. Welch Foundation for support of this research. The nmr and mass spectrometers used in this investigation were secured with funds provided, in part, by the National Science Foundation.