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THE ALKALOIDS OF *CROTON SPARSIFLORUS**

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Abstract—Three proaporphine bases provisionally designated crotsparine (I), m.p. 193–194°, *N*-methylcrotsparine (III), m.p. 223–225°, and *N,O*-dimethylcrotsparine (IV), m.p. 125–127°; two dihydroproaporphines, crotsparinine (II), m.p. 184–185°, and *N*-methylcrotsparinine (V), m.p. 160–161°, and the known aporphine alkaloid, sparsiflorine (X), m.p. 229–231°, have been isolated from *Croton sparsiflorus* Morong and their structures and stereochemistry assigned. *N*-Methylcrotsparine is of biological interest as a hypotensive agent.

INTRODUCTION

RECENT investigations on *Croton* species have yielded interesting dienone-alkaloids.[1] The biogenetic role of these bases in the formation of aporphine[2] and morphine alkaloids[3] has been confirmed by tracer experiments.

Croton sparsiflorus Morong (Syn *C. bonplandium* Bail) is a weed of common occurrence on the plains of India. Earlier investigations had led to the isolation of an aporphine base, sparsiflorine (X), from this plant.[4] A programme for screening Indian plants for a wide range of biological activity[5] led to the isolation of a new proaporphine base, *N*-methylcrotsparine,[6] that showed marked hypotensive activity[7] and prompted a detailed study of the alkaloidal constituents of this plant. Brief notes on the structures of the proaporphine base, crotsparine (I),[6] and a dihydroproaporphine base, crotsparinine (II),[8] have been communicated earlier. A fuller account of the work leading to these structures and information regarding other alkaloidal constituents of the plant is now presented.

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[1] L. J. HAYNES, K. L. STUART, D. H. R. BARTON and G. W. KIRBY, *J. Chem. Soc.* (C) 1676 (1966); C. CHAMBERS, L. J. HAYNES and K. L. STUART, *Chem. Commun.* 449 (1966); L. J. HAYNES, G. E. M. HUSBANDS and K. L. STUART, *Chem. Commun.* 15 (1967); C. CHAMBERS and K. L. STUART, *Chem. Commun.* 328 (1968); L. J. HAYNES, G. E. M. HUSBANDS and K. L. STUART, *J. Chem. Soc.* (C) 951 (1968); K. L. STUART and M. P. CAVA, *Chem. Rev.* **68**, 321 (1968).

[2] D. H. R. BARTON, D. S. BHAKUNI, G. M. CHAPMAN and G. W. KIRBY, *J. Chem. Soc.* (C) 2134 (1967); A. R. BATTERSBY and T. H. BROWN, *Chem. Commun.* 170 (1966); A. R. BATTERSBY, R. T. BROWN, J. H. CLEMENTS and G. IVERACH, *Chem. Commun.* 230 (1965); A. R. BATTERSBY, T. H. BROWN and J. H. CLEMENTS, *J. Chem. Soc.* 4550 (1965).

[3] D. H. R. BARTON, G. W. KIRBY, W. STEGLICH, G. M. THOMAS, A. R. BATTERSBY, T. A. DOBSON and H. RAMUZ, *J. Chem. Soc.* 2423 (1965); see also K. HEYDENEREICH and S. PFEITER BROWN, *Chem. Commun.* 130 (1960).

[4] A. CHATTERJEE, P. L. MAJUMDAR, R. MUKERJEE, S. K. SAHA and S. K. TALAPATRA, *Tetrahedron Letters* 1539 (1965).

[5] D. S. BHAKUNI, M. L. DHAR, M. M. DHAR, B. N. DHAWAN and B. N. MEHROTRA, *Indian J. Exptl. Biol.* 7, 250 (1969).

[6] D. S. BHAKUNI and M. M. DHAR, *Experientia* **24**, 1026 (1968).

[7] M. P. DUBE, R. C. SRIMAL and B. N. DHAWAN, *Indian J. Pharmacol* (in press).

[8] D. S. BHAKUNI and M. M. DHAR, *Experientia* **25**, 354 (1969).

RESULTS AND DISCUSSION

Three proaporphine bases provisionally designated crotsparine (I), m.p. 193–195°, *N*-methylcrotsparine (III), m.p. 223–225°, and *N,O*-dimethylcrotsparine (IV), m.p. 125–127°, two dihydroproaporphines, crotsparinine (II), m.p. 184–185°, and *N*-methylcrotsparinine (V), m.p. 160–161°, and an already known aporphine alkaloid, sparsiflorine (X), m.p. 229–231°, have been isolated from ethanol extracts of *Croton sparsiflorus* Morong. The relative concentration of the bases isolated from this plant were found to vary seasonally.

The presence of a cross-conjugated dienone system[1] in the proaporphine bases crotsparine ($C_{17}H_{17}NO_3$), *N*-methylcrotsparine ($C_{18}H_{19}NO_3$) and *N,O*-dimethylcrotsparine ($C_{19}H_{21}NO_3$)

TABLE 1. NMR (τ) DATA OF ISOLATED ALKALOIDS AND THEIR DERIVATIVES

Proaporphines	N–R′	C(1)	C(2)	C(3)				
Crotsparine (I)	—	—	6·21	3·40	2·9	3·60		
N-Methylcrotsparine (III)	7·63	—	6·20	3·40	3·04	3·67		
N,O-Diacetylcrotsparine (VII)	7·80	7·97	6·26	3·32	3·06	3·70		
N-Methyl-*O*-acetylcrotsparine (VIII)	7·63	7·98	6·27	3·30	3·06	3·70		
N,O-Dimethylcrotsparine (IV)	7·64	6·42	6·22	3·37	3·03	3·68		
N-Acetylcrotsparine (I; R′ = OAc)	7·81	—	6·17	3·34	3·10	3·67		
Crotsparinine (II)	—	—	6·21	3·50	3·06	3·88		
N-Methylcrotsparinine (V)	7·65	—	6·24	3·48	3·14	4·09		
N-Methyl-*O*-acetylcrotsparinine (Va)	7·64	7·80	6·21	3·32	3·10	4·06		
N-Methyltetrahydrocrotsparine (IX)	7·70	—	6·22	3·65	—	—		
N-Methylcrotsparininol (XVII)	7·67	7·78	6·20	3·37	—	—		
Aporphines	**N–R′**	**C(1)**	**C(2)**	**C(3)**	**C(8)**	**C(9)**	**C(10)**	**C(11)**
Sparsiflorine (X)	—	—	6·10	3·27	2·60	2·60	2·60	2·20
N-Methyl-*O,O*-diacetylsparsiflorine (XII)	7·47	7·72	6·18	3·26	2·68(d)	3·01(q)	7·70	2·30(d)
N-Methyl-*O,O*-diethylsparsiflorine (XIII)	7·52	8·57(t) 5·92(q)	6·15	3·44	2·92	3·30	8·74(d) 5·92(q)	2·02
N-Acetylnornuciferine (XIV R = Me; R′ = Ac)	7·80	6·29	6·08	3·25	2·65	2·65	2·65	1·53

$\beta\beta'$ protons 8 lines; J::i = 2·5, J:: = J:i:i = 10 c/sec. $\alpha\alpha'$ protons 8 lines; J::i = 1·5 c/sec; d = doublet; q = quartet; t = triplet.

and of an enone system in the dihydroproaporphines crotsparinine ($C_{17}H_{19}NO_3$) and *N*-methylcrotsparinine ($C_{18}H_{21}NO_3$) is indicated by the i.r. and u.v. spectra of these compounds and confirmed by their NMR spectra. Two overlapping AB quartets of the α and β protons of an unsymmetrical 4,4-disubstituted cyclohexa-2,5-dienone are present in the NMR spectra of the proaporphine bases and an AB quartet is seen in the spectra of the dihydroproaporphine bases. The NMR spectra also indicate the presence of one OMe function in crotsparine and crotsparinine, two OMe groups in *N,O*-dimethylcrotsparine and the presence of one N-Me and one OMe group in *N*-methylcrotsparine and *N*-methylcrotsparinine (Table 1). The signal for the single aromatic proton present in all these bases appears as a singlet at τ 3·42–3·50. The presence of an OH and an NH function in the crotsparine and crotsparinine

molecules is indicated by i.r. spectra and confirmed by the formation of *N,O*-diacetylcrotsparine[9] (VII) and *N,O*-diacetylcrotsparinine[10] respectively, when these bases are acetylated.

N-Methylcrotsparine and *N*-methyl crotsparinine, the two *N*-methyl bases isolated from this plant, can be readily prepared from crotsparine and crotsparinine, respectively, by treatment with HCHO–HCOOH.[11] Acetylation of the *N*-methyl bases with acetic anhydride–pyridine gives *O*-acetyl-*N*-methylcrotsparine (VIII) and *O*-acetyl-*N*-methylcrotsparinine respectively.

Both crotsparine and *N*-methylcrotsparine on treatment with methyl iodide in the presence of anhydrous potassium carbonate yield *N,O*-dimethylcrotsparine methiodide. This compound appears to be identical with *N,O*-dimethylcrotonosine methiodide[12] in all respects excepting for its optical rotation.

The fact that *N*-methylcrotsparinine is a dihydro derivative of *N*-methylcrotsparine is shown by catalytic hydrogenation. *N*-Methylcrotsparine when hydrogenated in the presence of PtO_2 takes up 2 mol of hydrogen whereas in the case of *N*-methylcrotsparinine the uptake of hydrogen is 1 mol. The compounds obtained in both cases were identical in all respects and on methylation yielded *N,O*-dimethyltetrahydrocrotsparine methiodide. This compound resembled *N,O*-dimethyltetrahydrocrotonosine methiodide[13] in all respects except rotation.

The location of the OMe group in crotsparine and in *N*-methylcrotsparine at position 2 and of the OH function at position 1 is suggested by the chemical shifts of the OMe signals in the NMR spectra of these bases. The OMe signals in the spectra of crotsparine (I) and *N*-methylcrotsparine (III) are at τ 6·21 and 6·20 respectively. This signal is at τ 6·15 in the NMR spectrum of glaziovine[13] but at τ 6·48 in the spectrum of L-(–)*N*-methylcrotonosine[1] and at τ 6·30 in the spectrum of linearisine.[1] Confirmation of this suggestion was obtained by isomerization of these dienones to the corresponding aporphines, which have established structures. Thus crotsparine and *N*-methylcrotsparine on treatment with HCl gave apocrotsparine (X) and *N*-methylapocrotsparine (XI) respectively. The former compound is identical in all respect with sparisflorine[4] whereas the latter is enantiomeric with 3,5-dihydroxy-6-methoxyaporphine (XI) isolated from *Ocotea glaziovii*.[13] Apocrotsparine is converted into *N*-methylapocrotsparine by *N*-methylation with HCHO–HCOOH. *N*-Methylapocrotsparine forms *O,O*-diacetyl-*N*-methylapocrotsparine (XII) and *O,O*-diethyl-*N*-methylapocrotsparine (XIII) when treated with pyridine–acetic anhydride and diazoethane respectively. Both apocrotsparine and *N*-methylapocrotsparine on methylation give the same *N,O,O*-trimethylapocrotsparine methiodide identical with *N,O,O*-trimethylsparsiflorine methiodide.[4]

The fact that the proaporphine bases could give rise to aporphine bases lacking oxygen functions in ring D[14] was confirmed as follows: crotsparine and *N*-methylcrotsaprine were reduced to the corresponding epimeric alcohols. The mixture of alcohols from crotsparine on treatment with cold dil.–HCl furnished the aporphine (XIV). The aporphine (XV) was obtained on similar treatment of the mixture of alcohols from *N*-methylcrotsparine. Methylation of these aporphines with diazomethane gave the known *N*-nornuciferine[11] and nuciferine[15] respectively.

[9] A. CHATTERJEE and P. L. MAJUMDAR, *J. Indian Chem. Soc.* **45**, 1087 (1968).
[10] K. L. STUART, L. J. HAYNES, M. BARRETT and G. E. M. HUSBANDS, *Tetrahedron Letters* 4473 (1968).
[11] S. M. KUPCHAN, B. DASGUPTA, E. FUJITA and M. L. KING, *Tetrahedron* **19**, 227 (1963).
[12] L. J. HAYNES and K. L. STUART, *J. Chem. Soc.* 1784, 1789 (1963).
[13] B. GILBERT, M. E. A. GILBERT, M. M. DEOLIVEIRA, O. RIBERIO, E. WENKERT, B. WICKBERG, U. HOLLSTEIN and H. RAPOPORT, *J. Am. Chem. Soc.* **86**, 694 (1964).
[14] D. H. R. BARTON and T. COHEN, *Festschrift A. Stoll*, p. 117, Birkhauser, Basle (1957).
[15] H. R. ARTHUR and H. J. CHEUNG, *J. Chem. Soc.* 2306 (1959).

N-Methylcrotsparinine also yields epimeric alcohols when reduced with $NaBH_4$ but the mixture does not dehydrate to give an aporphine. The mixture of epimeric alcohols when carefully chromatographed furnishes *N*-methylcrotsparininol-*l*. *N*-Methylcrotsparinol-*l* (XVI) was obtained by the same procedure from the $NaBH_4$ reduction products of *N*-Methylcrotsparine. Both these alcohols form diacetates.

The characteristic features in the mass spectra of crotsparine, crotsparinine, *N*-methylcrotsparine, *N*-methylcrotsparinine and *N,O*-dimethylcrotsparine are that the base peaks are due to the molecular ions and that these ions decompose to ions (*c*) by a retro-Diels-Alder reaction, a common process on electron impact of proaporphine and aporphine bases.[16] Other common ions in the mass spectra of these bases are the M-1 ions (*a*) and M-29 ions (*b*).

The configuration of crotsparine, *N*-methylcrotsparine, crotsparinine and *N*-methylcrotsparinine has been determined as follows: *N*-methylcrotsparine when treated with an ethereal solution of diazomethane gives a mixture, from which *N,O*-dimethylcrotsparine can be isolated by chromatography. Pronuciferine[17] is enantiomeric with *N,O*-dimethylcrotsparine and has been shown by chemical[18] and circular dichroism[19] studies to have the D-configuration. As catalytic reduction of *N*-methylcrotsparine and *N*-methylcrotsparinine yield the same compound, crotsparine and crotsparinine must, therefore, have the L-configuration. The same conclusion is reached by a comparison of the optical rotations of the proaporphines and the isomeric aporphines.[6]

Crotoflorine[9] and jacularine,[10] which have been recently isolated as their acetates from *Croton sparsiflorus* and *C. linearis* respectively, are most probably identical with crotsparine and with crotsparinine respectively.

EXPERIMENTAL

I.r. spectra were determined in KBr, u.v. spectra in EtOH, 60 Mc/s NMR spectra in $CDCl_3$ with TMS as internal standard and optical rotations unless otherwise indicated in $CHCl_3$. TLC was done on silica gel with C_6H_6–EtoAc–Et_2NH (7:2:1) as the solvent and Grade III alumina was used for column chromatography. Uncorrected capillary m.p.s are reported. Pet-ether refers to petroleum-ether fraction, b.p. 60–80°. Solutions of alkaloids were dried with anhydrous Na_2SO_4.

Extraction. Croton sparsiflorus Morong (whole plant) was collected around Lucknow in the month of December. The air-dried material (10 kg) was extracted with 95% EtOH (4 × 25l), solvent removed below 60° and the dark-green viscous residue obtained extracted with 10% tartaric acid (5 × 300 ml). The acidic solution was defatted with pet-ether (5 × 300 ml) and $CHCl_3$ (3 × 300 ml) and its pH adjusted to 6 by adding a solution of $NaHCO_3$. This solution was then extracted with $CHCl_3$ (4 × 300 ml), the $CHCl_3$ extract washed with water, dried and solvent removed to give the crude alkaloidal mixture (A) (20 g).

The aqueous solution left after $CHCl_3$ extraction was made distinctly basic (pH 10) with Na_2CO_3, extracted with $CHCl_3$ (4 × 300 ml) and the $CHCl_3$ extract worked up similarly to yield a second batch of the crude alkaloidal mixture (B) (35 g).

Isolation. Crude alkaloidal mixture (A) (20 g) was chromatographed on alumina (800 g). The column was successively eluted with C_6H_6, C_6H_6–$CHCl_3$ (4:1), (3:2), (2:3) then with $CHCl_3$, $CHCl_3$–MeOH (98:2), (96:4) and finally with (90:10). Fractions of 100 ml were collected and elution was followed by examining alternate fractions by TLC.

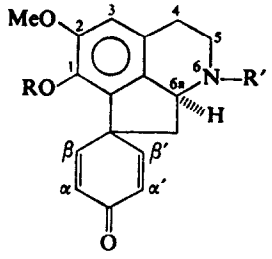
N,O-*Dimethylcrotsparine* (*IV*). The C_6H_6 eluates giving a single spot on TLC were pooled and solvent removed. The residue crystallized from EtOAc in needles (80 mg), m.p. 125–127°. (Found: C, 73·0; H, 7·2. $C_{19}H_{21}NO_3$ required: C, 73·3; H, 6·8%.) M^+, 311; ν_{max} 1652, 1612, 1602, 1282 cm^{-1}. The compound was found identical with base A from *C. linearis*[11] i.r., u.v. and TLC).

[16] M. TOMITA, A. KATO, T. IBUKA and H. FURUKUWA, *Tetrahedron Letters*, 2825 (1965); M. BALDWIN, A. G. LONDON, A. MACCOLL, L. J. HAYNES and K. L. STUART, *J. Chem. Soc.* (C) 154 (1967).

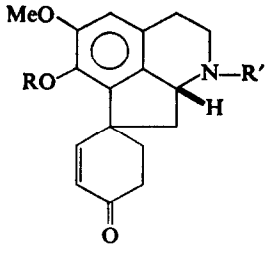
[17] K. BERNAUER, *Helv. Chim. Acta* **46** 1783 (1963); **47**, 2119, 2122 (1964).

[18] M. P. CAVA, K. NOMURA, R. H. SCHLESSINGER, K. T. BUCK, D. DOUGLAS, R. F. RAFFAUF and J. WEISBACH, *Chem. & Ind.* 282 (1964).

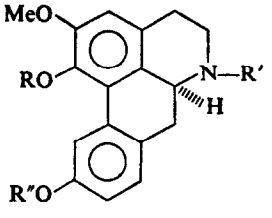
[19] G. SNATZKE and G. WOLLENBERG, *J. Chem. Soc.* (C) 1681 (1966).



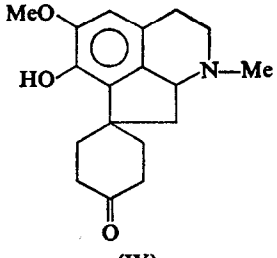
(I) R = R′ = H
(III) R = H, R′ = Me
(IV) R = R′ = Me
(VII) R = R′ = AcO
(VIII) R = AcO, R′ = Me



(II) R = R′ = H
(V) R = H, R′ = Me
(VA) R = Ac, R′ = Me



(X) R = R′ = R″ = H
(XI) R = R″ = H, R′ = Me
(XII) R′ = Me, R = R″ = AcO
(XIII) R′ = Me, R = R″ = Et



(IX)

N-*Methylcrotsparinine* (*V*). (*a*) $CHCl_3$ eluates gave a mixture of *N*-methylcrotsparine and *N*-methylcrotsparinine. The mixture was rechromatographed on alumina. The fractions giving single spot on TLC and running faster than the other were mixed and solvent removed. The product crystallized from EtOAc, m.p. 160–161°; $[\alpha]_D$ + 244° (C, 0·92). (Found: C, 72·0; H, 7·3. $C_{18}H_{21}NO_3$ required: C, 72·2; H, 7·0%.) M^+, 299; ν_{max} 1662, 1610, 1130, 850 cm^{-1}. The compound was not identical (TLC) with linearisine from *C. linearis*.[14] (*b*) Crotsparinine (80 gm), HCHO (2 ml) and HCOOH (2 ml) were heated on a steam bath for 30 min. The excess of HCHO and HCOOH were removed *in vacuo* and the residue dissolved in water, basified (Na_2CO_3) and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with water, dried, solvent removed and the *N*-methylcrotsparinine crystallized from EtOAc.

N-*Methylcrotsparine* (*III*). (*a*) The second base that very closely followed *N*-methylcrotsparinine on $CHCl_3$ elution (TLC control) of the alumina column was *N*-methylcrotsparine. It crystallized from EtOAc, m.p. 223–225°. (Found: C, 72·3; H, 6·5. $C_{18}H_{19}NO_3$ required: C, 72·7; H, 6·4%.) M^+, 297; ν_{max} 1655 and 1618 cm^{-1}. Picrate m.p. 200–203°. (*b*) Crotsparine (100 mg) on methylation[11] with HCHO (2 ml) and HCOOH (2 ml) at pH 4·5 (pH adjusted with Na_2CO_3) as in the case of crotsparinine gave *N*-methylcrotsparine.

Crotsparinine (*II*). Elution of the alumina column with $CHCl_3$–MeOH (98:2) yielded a mixture of two very closely associated compounds. The mixture of the bases was rechromatographed on alumina to afford crotsparinine which crystallized from EtOAc, m.p. 184–185°; $[\alpha]_D$ + 215° (C, 2·37). (Found: C, 71·5; H, 6·3. $C_{17}H_{19}NO_3$ required: C, 71·6; H, 6·6%.) M^+, 285; ν_{max} 3485, 2890, 1665, 1604 and 1600 cm^{-1}; λ_{max} 228 and 285 nm (log ε 4·28 and 3·10).

Crotsparine (*I*). The compound that followed crotsparinine very closely on elution of the column with $CHCl_3$–MeOH (98:2) (TLC control) was crotsparine. It crystallized from $CHCl_3$–EtOAc, m.p. 193–195°; $(\alpha)_D$ − 30°. (Found: C, 71·7; H, 6·3. $C_{17}H_{17}NO_3$ required: C, 72·1; H, 6·0%.) M^+, 283; ν_{max} 3490, 2896, 1664, 1624 cm^{-1}; λ_{max} 235 nm. Base HCl, m.p. 278°.

Sparsiflorine (*XI*). (*a*) Subsequent elution of the alumina column with $CHCl_3$–MeOH (96:4) yielded sparsiflorine (single spot on TLC), which crystallized from MeOH as needles, m.p. 227–229°. (Found: C, 71·5; H, 6·5. $C_{17}H_{17}NO_3$ required: C, 72·1; H, 6·0%.) (M^+ 283). Base HCl $(\alpha)_D$ + 38° (H_2O); ν_{max} 3200, 2950, 1600 and 1590 cm^{-1}; λ_{max} 266, 276, 308 nm. (*b*) Crotsparine (150 mg) in 6 N HCl (10 ml) was heated at 100° for 1 hr to give apocrotsparine, which crystallized by adding of a few drops of conc. HCl. Apocrotsparine was found identical with sparisflorine[4] (mixed m.p., i.r., u.v., TLC).

Methylation of crude bases. The alkaloidal mixture (B) (10 g), HCHO (50 ml) and HCOOH (50 ml) were heated on a steam bath for 1 hr after adjusting the pH of the solution to 4–5 with Na_2CO_3. Removal of volatile

reactants gave a mixture of methylated bases that was purified by dissolving in acid and precipitating with base twice.

Isolation of N-*methylated bases.* The purified mixture of methylated bases (5 g) was subjected to countercurrent distribution over 100 tubes, using $CHCl_3$ as the stationary phase and 0·2 N acetate buffer (pH 5·57) as the mobile phase. Tubes 4–30 gave 3·2 g of a mixture of two closely associated compounds (TLC). Careful chromatography of this material on alumina yielded *N*-methylcrotsparinine (V) (300 mg) and *N*-methylcrotsparine (*III*) (800 mg).

N-*Methylsparsiflorine* (*XI*). (*a*) Tubes 50–74 (single spot TLC) yielded *N*-methylsparsiflorine which crystallized from MeOH in needles, m.p. 148–151° (dec.); $(\alpha)_D$ + 30° (C, 0·2). (Found: C, 72·3; H, 6·6; N, 5·1. $C_{19}H_{19}NO_3$ required: C, 72·7; H, 6·4; N, 4·7%.) M^+, 297; λ_{max} 217, 267, 275 and 307 nm; (log ϵ 3·8, 1·02, 1·34, 0·94). Picrate, m.p. 199–202°; Methiodide, m.p. 250–253°. (*b*) *N*-Methylcrotsparine (50 mg) was isomerized[13] with 3 N HCl to *N*-methylapocrotsparine. The aporphine was found identical with (–)3,5-dihydroxy-6-methoxyaporphine (*XI*)[13] (*i.r., u.v. and TLC*). (*c*) *Apocrotsparine (60 mg) was methylated* with HCHO–HCOOH to give *N*-methylsparsiflorine.

N,O-*Diacetylcrotsparine* (*VII*). Crotsparine (150 mg) in pyridine (2 ml) and Ac_2O (5 ml) was kept at room temp. for 20 hr. The diacetate (100 mg) after purification on alumina in benzene crystallized from MeOH in needles, m.p. 165–166°. (Found: C, 68·5; H, 5·9; N, 3·6. $C_{21}H_{21}NO_5$ required: C, 68·7; H, 5·7; N, 3·5%.) ν_{max} 1772, 1670, 1642, 1260 cm^{-1}.

N-*Acetylcrotsparine*. *N,O*-Diacetylcrotsparine (50 mg) in $CHCl_3$ was heated in the presence of NH_4OH (1 ml) on a steam bath for 10 min to give *N*-acetylcrotsparine, m.p. 255–257°. (Found: C, 69·8; H, 6·1. $C_{19}H_{19}NO_4$ required: C, 70·1; H, 5·8%.) ν_{max} 1670, 1640 cm^{-1}.

N,O-*Diacetylcrotsparinine*. Crotsparinine (80 mg) was acetylated with pyridine (2 ml) and Ac_2O (3 ml) in the usual way to give *N,O*-diacetylcrotsparinine. λ_{max} 205, sh. 230, 280 nm; NMR: τ 7·83, 7·80; 6·18; ν_{max} 1770, 1665, 1637 cm^{-1}. (Found: C, 68·0; H, 6·3. $C_{23}H_{23}NO_5$ required: C, 68·3; H, 6·2%.) The compound appears identical with *N,O*-diacetyljacularine.[14]

O-*Acetyl*-N-*methylcrotsparine* (*VIII*). *N*-Methylcrotsparine (60 mg) was acetylated with Ac_2O (3 ml) and pyridine (2 ml). The acetylated product crystallized from EtOAc, m.p. 169–170°. (Found: C, 70·6; H, 6·4; N, 4·2. $C_{20}H_{21}NO_4$ required: C, 70·8; H, 6·2; N, 4·1%.) ν_{max} 1772, 1670, 1642, 1260 cm^{-1}.

O-*Acetyl*-N-*methylcrotsparinine* (*VB*). *N*-Methylcrotsparinine (40 mg) was treated with Ac_2O (2 ml) in pyridine (2 ml) to give the acetyl derivative, m.p. 159–160°. (Found: C, 70·3; H, 6·9; N, 4·3. $C_{20}H_{23}NO_4$ required: C, 70·4; H, 6·7; N, 4·1%.) ν_{max} 1765, 1662, 1610, 1280, 1110 cm^{-1}.

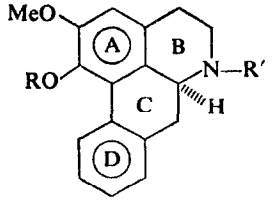
N,O-*Dimethylcrotsparine methiodide*. Crotsparine (200 mg) in MeOH (20 ml) was refluxed in the presence of K_2CO_3 (1 g) and MeI (3 ml) for 1 hr. The methiodide was extracted with $CHCl_3$ and crystallized from EtOH (110 mg), m.p. 174–176°. (Found: C, 52·7; H, 5·4. $C_{20}H_{24}INO_3$ required: C, 53·0; H, 5·3%. ν_{max} 1670, 1610 and 1125 cm^{-1}.)

N-*Methyltetrahydrocrotsparine* (*IX*). (*a*) *N*-Methylcrotsparine (60 mg) was hydrogenated in AcOH in the presence of PtO_2. The product crystallized from C_6H_6 to give the tetrahydro derivative, m.p. 332–335°; $(\alpha)_D$ – 40 (MeOH). (Found: C, 71·5; H, 7·9; N, 4·9. $C_{18}H_{23}NO_3$ required: C, 71·7; H, 7·6; N, 4·6%.) ν_{max} 3540, 1700 cm^{-1}. (*b*) *N*-Methylcrotsparinine (50 mg) was hydrogenated in the presence of PtO_2 to give the N-methyltetrahydrocrotsparinine. This compound was found identical to N-methyltetrahydrocrotsparine.

N,O-*Dimethyltetrahydrocrotsparine methiodide*. *N*-Methyltetrahydrocrotsparine (50 mg) in MeOH (25 ml) was treated[12] with MeI (3 ml) and K_2CO_3 (250 mg). The methiodide crystallized from Me_2CO–MeOH, m.p. 260° (dec). (Found: C, 52·2; H, 6·4. $C_{20}H_{28}INO_3$ required: C, 52·5; H, 6·2%.) The methiodide appeared identical with N,O-dimethyltetrahydrocrotsonosine methiodide.[14]

O,O-*Diethyl*-N-*methylapocrotsparine* (*XIII*). *N*-Methylapocrotsparine (55 mg) in MeOH was treated with diazoethane to give the diethyl derivative, which crystallized from C_6H_6, m.p. 247–248°. (Found: C, 74·2; H, 7·9. $C_{22}H_{27}NO_3$ required: C, 74·7; H, 7·6%.)

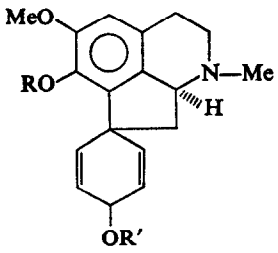
O,O-*Diacetyl*-N-*methylapocrotsparine* (*XII*). *N*-Methylapocrotsparine (50 mg) was treated with Ac_2O (3 ml) and pyridine (2 ml) to give the acetyl derivative, m.p. 232–234°. (Found: C, 69·6; H, 6·3. $C_{22}H_{23}NO_5$ required: C, 69·3; H, 6·0%.)



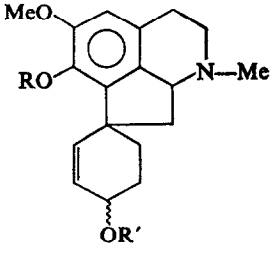
(XIV) R = R' = H
(XV) R = H, R' = Me

1-*Hydroxy*-2-*methoxyaporphine* (*XIV*). Crotsparine (150 mg) in MeOH (20 ml) was reduced with $NaBH_4$ (200 mg). It was then treated with dil. HCl to effect dehydration[12] and give the aporphine hydrochloride (90 mg), m.p. 220° (dec). ν_{max} 1612, 1570, 1490 and 780 cm^{-1}. (Found: C, 66·6; H, 6·4. $C_{18}H_{20}ClNO_2.\frac{1}{2}H_2O$ required: C, 66·2; H, 6·2%.) The free base (50 mg) liberated from the base HCl was methylated with CH_2N_2 to give a product, m.p. 125–129°; $(\alpha)_D$ + 145° (EtOH) identical with (–)-nornuciferine[11] (TLC) excepting for their optical rotations.

1-*Hydroxy*-2-*methoxy*-N-*methylaporphine* (*XV*). *N*-Methylcrotsparine (120 mg) was treated with $NaBH_4$ and the mixture of epimeric alcohols dehydrated[13] with HCl to give the aporphine. B.HCl, m.p. 225° (dec); $(\alpha)_D$ + 145° (dioxane); ν_{max} 1612, 1570, 1490, 780 cm^{-1}. (Found: C, 66·6; H, 6·5. $C_{18}H_{20}ClNO_2.\frac{1}{2}H_2O$ required: C, 66·2; H, 6·2%.) The free base, m.p. 166–168°, was methylated with CH_2N_2 to give a product, m.p. 163°, identical with nuciferine[16] (TLC).

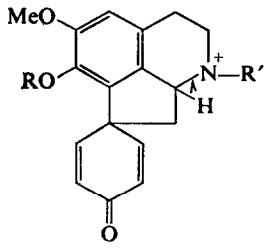


(XVI) R = R' = H

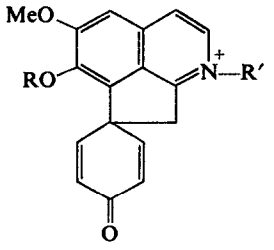


(XVII) R = R' = H

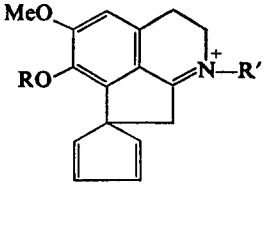
N-*Methylcrotsparinol* (*XVI*). *N*-Methylcrotsparine (200 mg) in MeOH was stirred with $NaBH_4$ (400 mg) at room temp. for 1 hr. The crude product was chromatographed on alumina and the $CHCl_3$ eluate (TLC one spot) gave the alcohol which crystallized from EtOAc, m.p. 107–109°. (Found: C, 72·0; H, 7·3. $C_{18}H_{21}NO_3$ required: C, 72·2; H, 7·0%.) The alcohol (80 mg) was treated with Ac_2O–pyridine to give the diacetate, m.p. 162–163°.



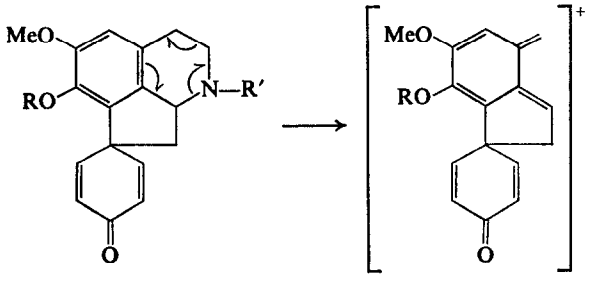
(I) M^+



(*a*) M^+-1



(*b*) M^+-29



(*c*) M^+-29, M^+-43

N-*Methylcrotsparininol* (*XVII*). *N*-Methylcrotsparinine (150 mg) was reduced with $NaBH_4$ and the mixture of epimeric alcohols chromatographed to give an alcohol, m.p. 103–104°. (Found: C, 71·5; H,

7·7. $C_{18}H_{23}NO_3$ required: C, 71·7; H, 7·6%.) The alcohol (60 mg) was acetylated with Ac_2O–pyridine to give the diacetate, m.p. 162–163°.

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