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ABSOLUTE CONFIGURATION OF CROTSPARINE, CROTSPARININE AND SPARSIFLORINE*

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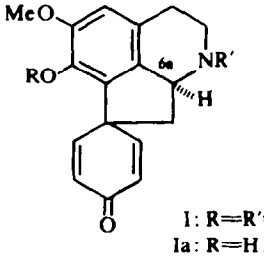
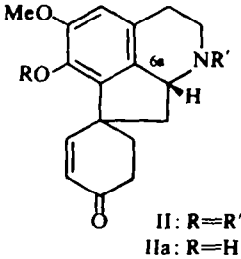
Abstract— Absolute configurations of crotsparine, crotsparinine and sparsiflorine have been determined.

PROAPORPHINES crotsparine (I), N-methylcrotsparine (Ia) and N,O-dimethylcrotsparine (Ia), dihydroproaporphines crotsparine (II), and N-methylcrotsparine (IIa), and the aporphine sparisflorine (III), have been characterized in extracts from *Croton sparsiflorus* Morong.[1] Proaporphines are important biogenetic precursors of aporphines (III, IV), and the latter are obtained chemically from proaporphines by the dienone-phenol or dienol-benzene rearrangements.[3] The absolute configuration of these dienone bases, is, therefore, of importance to biosynthetic and chemical correlation studies.

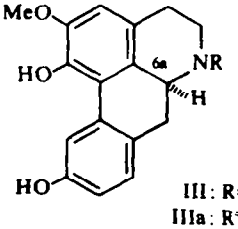
The configuration of proaporphines has been assigned with the aid of CD data,[4] by comparison of the optical rotations of dienone bases and the corresponding aporphines[1] and by degradation procedure.[5] This paper reports assignment of absolute configuration of *Croton sparsiflorus* proaporphines by direct synthesis from 1-benzylisoquinolines.



I: R=R'=H
Ia: R=H; R'=Me
Ib: R=R'=Me

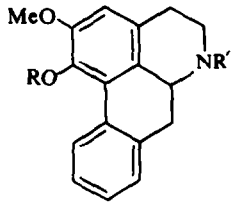


II: R=R'=H
IIa: R=H; R'=Me

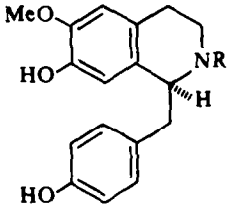


III: R=H
IIIa: R=Me

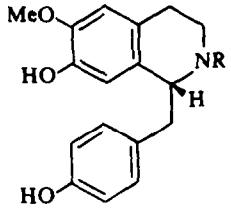
* Communication No. 1721 from the Central Drug Research Institute.



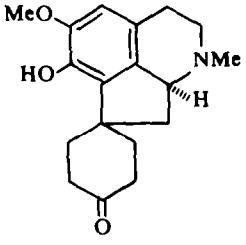
IV



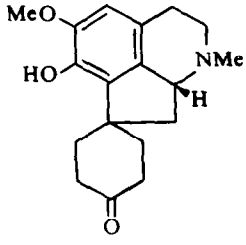
V: R=H
Va: R=Me



VI: R=H
VIb: R=Me



VII



VIII

(±)-O,O'-Dibenzylcoclaurine was prepared by the usual route.[6, 7] Resolution of the racemic mixture with (+)-di-*p*-toluoyl-*l*-tartaric and (−)-di-*p*-toluoyl-*d*-tartaric acids separately furnished (+)- and (−)-O-O'-dibenzylcoclaurine. Acid catalysed hydrogenolysis finally yielded (−)- and (+)-coclaurine (V and VI) respectively of known absolute configuration.[8]

(±)-N-Methylcoclaurine, (±)-coclaurine, (−)-coclaurine and (+)-coclaurine were then separately labelled with tritium *ortho* and *para* to OH groups.[9] Tritium labelled (±)-coclaurine, (+)− and (−)-coclaurines were then separately converted into the corresponding N-Me derivatives and then oxidised with potassium ferricyanide in a two phase system.[10] The radiochemical yields of N-methylcrotsparine, corrected for obligatory loss of tritium, are recorded in Table 1.

TABLE 1

Coclaurine derivative	% Yield of N-methylcrotsparine
(±)-[Aryl-^{3}H]-N-Methylcoclaurine	2·10
(±)-[Aryl-^{3}H]-Coclaurine	2·00
(+)-[Aryl-^{3}H]-Coclaurine	0·006
(−)-[Aryl-^{3}H]-Coclaurine	3·90

N-Methylcrotsparine (Ia) is obtained only from (±)- and (−)-coclaurine, the absolute configuration of the base, is, therefore, identical to that of (−)-coclaurine (V). Acid catalysed isomerisation of N-methylcrotsparine (Ia) yields N-methylsparsiflorine (IIIa) which is also obtained by N-methylation of sparsiflorine (III). Catalytic reduction of N-methylcrotsparinine yields N-methyldihydrocrotsparinine (VIII). N-methyldihydrocrotsparinine and N-methyltetrahydrocrotsparine are enantiomeric. The absolute configuration of crotsparine (I) and sparsiflorine (IIIa) at position 6a is therefore L or (*S*) and that of crotsparinine (II) is D or (*R*).

EXPERIMENTAL

Optical rotations have been determined in MeOH unless indicated. OO′-Dibenzylcoclaurine was prepared by reduction of the corresponding dihydroisoquinoline with $NaBH_4$ in MeOH at 0°. OO′-dibenzylcoclaurine crystallized from EtOH as plates, m.p. 88–89° (lit.[8] 87°).

Resolution of O,O′-*dibenzylcoclaurine*

The salt of (±)-O,O′-dibenzylcoclaurine (1·74 g) and (±)-di-*p*-tolyoyl-*l*-tartaric acid (1·43 g) was fractionally crystallized from EtOH–Et_2O, EtOH and MeOH to give needles (1·4 g) m.p.• 155–157°: $[\alpha]_D$ 85° (*c*, 1·0). This salt was treated with 4N NaOH and the liberated (+)-O,O′-dibenzylcoclaurine purified by chromatography over Al_2O_3. It crystallized from EtOH as plates, m.p. 88–89°, $[\alpha]_D$ 15° (*c*, 0·5): −25° (*c*, 0·5 in $CHCl_3$).

(−)-*Coclaurine hydrochloride.*[8] (+)-O,O′-Dibenzylcoclaurine was treated with 36% HCl in EtOH at 100° for 1½ hr. The resulting (−)-coclaurine HCl crystallized from EtOH as needles, m.p. 165–166°. After drying at 100° *in vacuo* had m.p. 263–264°, $[\alpha]_D$ −13° (*c*, 1·2). The free base had $[\alpha]_D$ −17 (*c*, 1·0).

(−)-O,O′-*Dibenzylcoclaurine.* O,O′-Dibenzylcoclaurine (0·87 g) enriched with the (−)-enantiomer was treated with (−)-di-*p*-toluoyl-*d*-tartaric acid (0·72 g) and was fractionally crystallized from EtOH–Et_2O as plates m.p. 87–88°, $[\alpha]_D$ −15° (*c*, 0·5): −20° (*c*, 0·5 in $CHCl_3$).

(+)-*Coclaurine hydrochloride.*[8] (−)-O,O′-Dibenzylcoclaurine was hydrogenolysed with 35% HCl in the usual way to give (+)-coclaurine HCl, which crystallized from EtOH as needles, m.p. 166–169°. After drying at 100° *in vacuo* had m.p. 261–263°, $[\alpha]_D$ −13° (*c*, 1·2).

(±)-[*Aryl*- ^{3}H]-*N-methylcoclaurine hydrochloride.* A mixture of (±)-N-methylcoclaurine HCl (100 mg), t-BuOK (150 mg) and T_2O (0·35 ml) were sealed in a tube under N_2 and heated at 100° for 110 hr. The mixture was then diluted with H_2O (1·5 ml) and NH_4Cl added. The ppt formed was centrifuged, washed with water and extracted with $CHCl_3$ (3 × 4 ml). After removal of solvent, the residue from the $CHCl_3$ extract was treated with MeOH-HCl to give [3′, 5′, 8- ^{3}H]-N-methylcoclaurine HCl (60 mg), free base m.p. 176°. The base HCl was crystallized from MeOH to a constant activity. The sample of (±)-[Aryl- ^{3}H]-N-methylcoclaurine HCl gave 3·04 × 10^6 dps/mg.

(±)-[*Aryl*- ^{3}H]-*coclaurine hydrochloride.* (±)-coclaurine HCl (110 mg) was heated with t-BuOK (150 mg) in T_2O (0·45 ml) for 100 hr. The resulting mixture was worked up as above to give [3′, 5′, 8- ^{3}H]-coclaourine HCl (65 mg) m.p. 256–258°, which gave 3·7 × 10^6 dps/mg.

(−)-[*Aryl*- ^{3}H]-*coclaurine hydrochloride.* (−)-Coclaurine HCl (80 mg), T_2O (0·4 ml) and t-BuOK (140 mg) were heated for 96 hr. The resulting mixture was worked up to give [3′, 5′, 8- ^{3}H]-coclaurine HCl (55 mg), giving 2·7 × 10^6 dps/mg.

(+)-[*Aryl*- ^{3}H]-*coclaurine hydrochloride.* (+)-Coclaurine HCl (85 mg), T_2O (0·4 ml) and t-BuOK (150 mg) were heated for 100 hr. The resulting mixture on working up afforded [3′, 5′, 8- ^{3}H]-coclaurine hydrochloride (45 mg), which gave 3·9 × 10^6 dps/mg.

Oxidation of (±)-[*aryl*-^{3}H]-*N-methylcoclaurine.* (±)-[Aryl- ^{3}H]-N-methylcoclaurine (5 mg), diluted with inactive (±)-N-methylcoclaurine (47 mg) in 8% NH_4AcO (2·5 ml), was added dropwise to a mixture of $K_3Fe(CN)_6$ (300 mg), 28% NH_4OH (0·5 ml) and $CHCl_3$ (20 ml) at 0° with vigorous stirring under N_2. Stirring was continued for 3 hr. N-methylcrotsparine (40 mg) was then added, the $CHCl_3$ layer collected and the aqueous layer extracted with $CHCl_3$ (3 × 25 ml). The combined $CHCl_3$ extract was washed with sat NaCl aq, dried (K_2CO_3) and solvent removed. The product was chromatographed over Al_2O_3 (grade III). Elution with EtOAc–C_6H_6 (1:9) gave radioactive N-methylcrotsparine (18 mg). The radiochemical yield of N-methylcrotsparine was 2·10%.

Oxidation of (±)-[*aryl*-^{3}H]-*coclaurine.* A mixture of (±)-aryl-^{3}H-coclaurine (15·4 mg) and (±)-N-methylcoclaurine (30 mg) was treated with HCHO/HCOOH to give (±)-[aryl-^{3}H]-N-methylcoclaurine. This compound was then dissolved in 8% NH_4AcO (3 ml) and oxidized with $K_3Fe(CN)_6$ (250 mg) in 28% NH_4OH (0·5 ml) and $CHCl_3$ (20 ml) at 0° under N_2. N-Methylcrotsparine (45 mg) was added and reisolated. The radiochemical yield of N-methylcrotsparine was 2·00%.

Oxidation of (+)-*aryl*-^{3}H-N-*methylcoclaurine.* (−)-Aryl-^{3}H-coclaurine (6·4 mg), diluted with (±)-N-methylcoclaurine (43 mg), was treated with HCHO/HCOOH and the (+)-[aryl-^{3}H]-N-methylcoclaurine thus obtained was oxidized with $K_3Fe(CN)_6$ (300 mg) under identical conditions as above. Inactive N-methylcrotsparine (45 mg) was added at the end of the reaction and labelled N-methylcrotsparine (21 mg) was isolated. Radiochemical yield of N-methylcrotsparine was 3·90%.

Oxidation of (−)-*aryl*-^{3}H-N-*methylcoclaurine.* (+)-aryl-^{3}H-coclaurine (15·7 mg) diluted with (±)-N-methylcoclaurine (45 mg) were treated with HCHO/HCOOH to give (−)-[aryl-^{3}H]-N-methylcoclaurine. This was dissolved in 8% NH_4AcO (0·5 ml) and oxidized with $K_3Fe(CN)_6$ as above. N-methylcrotsparine (33 mg) was added at the end of the reaction and labelled N-methylcrotsparine (20 mg) was isolated. The radiochemical yield of N-methylcrotsparine was only 0·006%.

N-*Methyltetrahydrocrotsparine* (VII). N-Methylcrotsparine (100 mg, $[\alpha]_D$ −115°) in AcOH (10 ml) was hydrogenated over PtO_2 (70 mg). The crude product was chromatographed over Al_2O_3 (grade III) to give N-methyltetrahydrocrotsparine as plates (80 mg) from C_6H_6 m.p. 113–114°, $[\alpha]_D$ −60° (*c*, 0·5): ν_{max}^{KBr} 2930 (OH) and 1720 cm^{-1} (C=O).

N-*Methyldihydrocrotsparinine* (VIII). N-Methylcrotsparinine (100 mg) $[\alpha]_D$ 240° (*c*, 1·0, in $CHCl_3$) was hydrogenated over PtO_2 (60 mg) in AcOH (10 ml) to give N-methyldihydrocrotsparinine (75 mg) m.p. 114–115°, $[\alpha]_D$ +70° (*c*, 0·88). This compound was enantiomeric with N-methyltetrahydrocrotsparine: both compounds had identical m.ps. and IR, UV and NMR spectra.

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