Tetrahedron. Vol. 28, pp. 1093 to 1095 Pergamon Press 1972 Printed in Great Britain

ABSOLUTE CONFIGURATION OF ISOCOCLAURINE*

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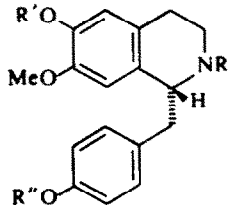
(*Received in the UK 28 September 1971; Accepted for publication 8 November 1971*)

Abstract—Racemic O,O'-dibenzylisococlaurine has been resolved and the absolute configuration of (+) and (−) isococlaurine determined.

(+)-ISOCOCLAURINE (I) WAS FIRST ISOLATED from a commercial sample of *Radix parierae bravae*,[1] which was a sample of *Chondodendron microphyllum* (Eichl.) Moldenke (Menispermaceae). The base has also been obtained by reductive fission of the bisbenzylisoquinoline alkaloids thalmidine,[2] and *o*-methylthalmethine.[3] Both (−) and (+)-N-methylisococlaurine have been similarly obtained from cycleanine[4] and O-methylthalicberine,[5] respectively.

The structure of isococlaurine was assigned by King[1] and subsequently confirmed by synthesis.[6] 1-Benzylisoquinolines have been shown by tracer experiments to be the precursors of a large number of alkaloids.[7] The absolute configuration of these bases is, therefore, of importance to biosynthetic and stereochemical correlation studies. This paper reports the resolution of (±)-O,O'-dibenzylisococlaurine (II) and the determination of the absolute configuration of the enantiomers of isococlaurine.



I: R = R' = R'' = H
II: R' = R'' = Bz, R = H
III: R = R' = R'' = Me

(±)-O,O'-Dibenzylisococlaurine was prepared by the usual Bischler–Napieralski cyclization and borohydride reduction of the dihydroisoquinoline. Racemic II (1 mole) was then treated with (+)-di-*p*-toluoyl-*l*-tartaric acid (1 mole). The resulting salt was successively crystallized from EtOH–ether, EtOH and MeOH to give the (+)-salt with a constant m.p. and rotation. Decomposition of the salt with 4N NaOH afforded (−)-II.(+)-II was obtained by treating the partially resolved free base II with (−)-di-*p*-toluoyl-*d*-tartaric acid. Treatment of the enantiomeric dibenzyl ethers with 36% HCl in EtOH afforded the corresponding (+)- and (−)-isococlaurine hydrochloride. The

* Communication No. 1661 from the Central Drug Research Institute.

chirality of the enantiomers was established by conversion into N,O,O'-trimethylcoclaurines (III) of known absolute configurations.

N-Methylation of (+)-isococlaurine with formaldehyde-formic acid afforded (−)-N-methylisococlaurine and the (+)-enantiomer was similarly obtained from (−)-isococlaurine. A similar change in the sign of rotation has also been observed in the conversion of coclaurine[8] and norlaudanosine[9] to the corresponding N-methyl derivatives. Treatment of the (+) and (−) N-methylisococlaurine separately with diazomethane respectively furnished (+) and (−)-N,O,O'-trimethylisococlaurine identical in all respects with the known (+)- and (−)-O-methylarmepavine (III) respectively.[10]

As (+)-O-methylarmepavine has been related to (+)-laudanosine[10] and the absolute configuration of (+)-laudanosine has been established,[11] the configuration of (−)- and (+)-isococlaurine must be the same as that of (+) and (−)-laudanosine respectively. (+)-isococlaurine can, therefore, be formulated as I.

TABLE 1. $[\alpha]_D$ VALUES FOR ISOCOCLAURINE DERIVATIVES

	(+)-isococlaurine	(−)-isococlaurine
O,O'-Dibenzylisococlaurine (−)-di-*p*-toluoyl-*d*-tartrate	(−)70°	
O,O'-Dibenzylisococlaurine (+)-di-*p*-toluoyl-*l*-tartrate		(+)68°
O,O'-Dibenzylisococlaurine	+19°, −17°*	−20°, +18°*
O,O'-Dibenzylisococlaurine hydrochloride	+26	−25°
Isococlaurine hydrochloride	+16°, +28°†	−18°, −27·5°†
Isococlaurine	+12°	−14°
N-Methylisococlaurine	−78°	+76°
N,O,O,Trimethylisococlaurine	−71°	+82°

* Determined in $CHCl_3$.
† Determined in H_2O.

EXPERIMENTAL

Optical rotations have been determined in MeOH unless indicated.

O,O'-*Dibenzylisococlaurine* was prepared by reduction of the corresponding dihydroisoquinoline[6] with $NaBH_4$ in MeOH at 0°, (+)-O,O'-dibenzylisococlaurine crystallized from MeOH as plates, m.p. 99–101°. (Found: C, 80·38; H, 6·75; N, 2·95. $C_{31}H_{31}NO_3$ requires: C, 80·00; H, 6·7; N, 3·0%).

Resolution of O,O'-*dibenzylisococlaurine*. The salt from (±)-O,O'-dibenzylisococlaurine (1·74 g) and (+)-di-p-toluoyl-*l*-tartaric acid (1·38 g) was fractionally crystallized successively from EtOH–Et_2O, EtOH and MeOH to give needles (1 g) m.p. 142–43°: $[\alpha]_D$ +68° (*c*, 1·0). This salt was treated with 4N NaOH and the liberated (−)-O,O'-dibenzylisococlaurine purified by chromatography over Al_2O_3. It crystallized as plates from EtOH, m.p. 101–102°: $[\alpha]_D$ −20° (*c*, 0·5) and $[\alpha]_D$ +18° (*c*, 0·5 in $CHCl_3$). The corresponding hydrochloride crystallized from EtOH as needles (dried *in vacuo* over P_2O_5) m.p. 165–166°: $[\alpha]_D$ −25° (*c*, 0·5).

(−)-*Isococlaurine hydrochloride*. (−)-O,O'-Dibenzylisococlaurine was treated with 36% HCl in EtOH at 100° for 1½ hr. The resulting (−)-isococlaurine hydrochloride crystallized from MeOH as needles (dried at 100° *in vacuo* over P_2O_5 for 10 hr), m.p. 242–243°: $[\alpha]_D$ −18° (*c*, 0·5); $[\alpha]_D$ −27·5° (*c*, 1·0 in H_2O). (−)-Isocoluarine crystallized from MeOH, m.p. 195–197°: $[\alpha]_D$ −14° (*c*, 0·5).

(+)-N-*Methylisococlaurine*. (−)-Isococlaurine hydrochloride (80 mg) in H_2O (1 ml) was treated successively with 2N NaOH (1 ml), HCOOH 98%, 1·2 ml and aqueous HCHO (37–41%, 1·2) at pH 5. The mixture was heated at 100° for 30 min and excess HCHO removed *in vacuo*. The residue was taken up in H_2O, extracted with ether, basified with $NaHCO_3$ and the liberated base extracted with $CHCl_3$. After

removal of solvent, the residue was chromatographed on Al_2O_3. Elution with $CHCl_3$:EtOH (94:6) gave (+)-*N*-methylisococlaurine (50 mg) m.p. 214-215°; $[\alpha]_D$ +2°. (Lit.[5] $[\alpha]_D$ ±0°). Base hydrochloride crystallized from MeOH-Et_2O as needles (dried at 100° *in vacuo* over P_2O_5), m.p. 244-245°; $[\alpha]_D$ +76° (*c*, 1·0 (Lit.[5] $[\alpha]_D$ +85·8°).

(+)-N,O,O'-*Trimethylisococlaurine*. (+)-N-Methylisococlaurine (45 mg) in MeOH (0·3 ml) was treated with an excess of ethereal CH_2N_2 for 3 days. The resulting base was purified by chromatography on Al_2O_3. Elution with C_6H_6:$CHCl_3$ (9:1) gave (+)-N,O,O'-trimethylisococlaurine (20 mg), m.p. 59–61°; $[\alpha]_D$ +82° (*c*, 0·5 in $CHCl_3$) (Lit.[10] $[\alpha]_D$ +86°).

(+)-*Isococlaurine hydrochloride*. O,O'-Dibenzylisococlaurine (750 mg), enriched with the (+)-enantiomer, was obtained from the resolution experiment described above by extraction with $CHCl_3$ after making alkaline with NaOH. This material was treated with (−)-di-*p*-toluoyl-d-tartaric acid (620 mg) and the resulting salt fractionally crystallized from EtOH-Et_2O, EtOH and MeOH to give (+)-O,O'-dibenzylisococlaurine. Derivatives were subsequently prepared as in the (−)-isococlaurine series. The m.ps of these compounds were found to be close to those of the corresponding enantiomers. Their rotations are given in Table 1.

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