Absolute Configuration and Biosynthesis of Tiliacorine and Tiliacorinine

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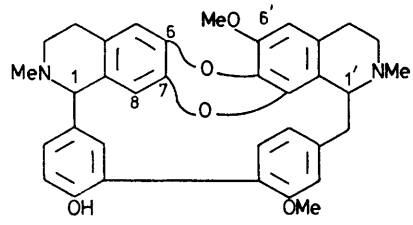
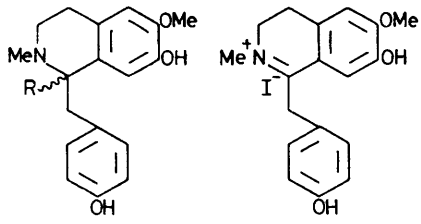
Summary Biosynthetic experiments with (*R*)- and (S)-*N* methylcoclaurines in *Tiliacora racemosa* Colebr. established that tiliacorine has the (*S*) and (*R*) configuration at the asymmetric centres C(1) and C(1′), respectively, and tiliacorinine has the (*SS*) configuration at both asymmetric centres.

THE diastereomeric bisbenzylisoquinoline alkaloids tiliacorine[1] and tiliacorinine[1] have been assigned the structure[2] (**1**). The absolute configuration at the asymmetric centres C(1) and C(1′) in both the bases cannot be determined by the usual sodium–ammonia cleavage method[3] because the two lower rings of these bases are linked through a direct carbon-to-carbon bond, rather than through the much more common diaryl ether bridge.[4]



(1)



(2a) R = H, (+)-(S)
(2b) R = H, (−)-(R)

(3)

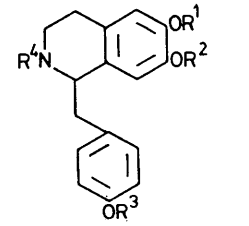
According to established biogenetic theory[5,6] both tiliacorine and tiliacorinine can be formed in nature by inter- and intra-molecular oxidative coupling of the two *N*-methylcoclaurine units. The 1,4-dioxan bridge present in (**1**) can be generated by loss of one MeO^+ group from one of the *N*-methylcoclaurine (**6**) units.[4,7]

TABLE. Tracer experiment on *T. racemosa* Colebr.

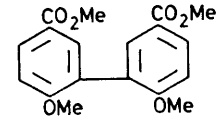
Precursor fed	% Incorporation into Tiliacorine	% Incorporation into Tiliacorinine
(±)-[U^{14}C] Tyrosine ..	0·09	0·06
(±)-[1-^{3}H] (**4**) ..	0·10	0·09
(±)-[3′,5′,8-$^3H_3$] (**5**) ..	0·14	0·12
(±)-[3′,5′,8-$^3H_3$] (**6**) ..	0·18	0·15
(±)-[3′,5′,8-$^3H_3$] (**7**) ..	0·0004	0·00045
[N-$^{14}CH_3$] (**3**)	0·12	0·10
(±)-[1-^{3}H, N-$^{14}CH_3$] (**6**) ..	0·15	0·12
(±)-[1-^{3}H, 6-O-$^{14}CH_3$] (**6**) ..	0·19	0·16
(−)-(*R*)-[3′,5′,8-$^3H_3$] (**2b**) ..	0·16	0·004
(+)-(*S*)-[3′,5′,8-$^3H_3$] (**2a**) ..	0·15	0·28

Feeding of (±)-tyrosine (Table), (±)-norcoclaurine (**4**) (±)-coclaurine (**5**), (±)-^{1}*N*-methylcoclaurine (**6**), (±)-*NOO* trimethylcoclaurine (**7**), and didehydro-*N*-methylcoclaurinium iodide (**3**) established that (**4**), (**5**), and (**6**) are efficient precursors of tiliacorine and tiliacorinine in *Tiliacora racemosa* Colebr. (Menispermaceae). The efficient incorporation of (**3**) is probably due to prior reduction *in vivo* to (**6**). As expected (**7**) was not incorporated into tiliacorine and tiliacorinine.

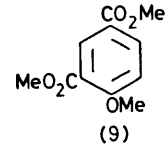
Labelled tiliacorine and tiliacorinine derived from (±)-[3′,5′,8-$^3H_3$]-*N*-methylcoclaurine (**6**)‡ feedings were separately converted into *O*-methyltiliacorine dimethiodide[1] and *O*-methyltiliacorinine dimethiodide[1] by treatment with methyl iodide–sodium methoxide. Alkaline permanganate oxidation of the dimethiodides,[1] followed by methylation with diazomethane of the acids so formed yielded, in each case, (**8**) and (**10**). Oxidation of labelled *O*-methyltiliacorine dimethiodide[1] (molar activity 2·63 × 10^5 dis. min^{-1} $mmol^{-1}$) gave (**8**) (molar activity 1·78 × 10^5 dis. min^{-1} $mmol^{-1}$) and (**10**) (molar activity 8·36 × 10^4 dis. min^{-1} $mmol^{-1}$) having essentially 2/3 and 1/3 radioactivity, respectively, of the parent base.§ Similar results were obtained for the degradation of *O*-methyltiliacorinine.



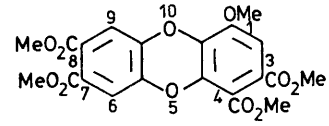
(4) $R^1 = R^2 = R^3 = R^4 = H$
(5) $R^2 = R^3 = R^4 = H, R^1 = Me$
(6) $R^1 = R^4 = Me, R^3 = R^2 = H$
(7) $R^1 = R^2 = R^3 = R^4 = Me$



(8)



(9)



(10)

Feeding of (±)-[1-^{3}H,N-$^{14}CH_3$] (**6**) gave tiliacorine and tiliacorinine labelled both with ^{14}C and ^{3}H. The ratios of these radioatoms in the precursor and biosynthetic bases

† The precursors (**3**)—(**6**) were prepared by standard methods [D. H. R. Barton, D. S. Bhakuni, G. M. Chapman, and G. W. Kirby, *J. Chem. Soc.* (C), 1967, 2134]; (**7**) was obtained by treatment of (**6**) with diazomethane. Details of the counting method employed are given by D. S. Bhakuni, S. Tewari, and R. S. Kapil, *J.C.S. Perkin I*, 1977, 706. The precursors were fed by the wick feeding method.

‡ Tritium was introduced specifically into positions *ortho* to the phenolic hydroxy groups in the precursors by base catalysed exchange (G. W. Kirby and L. Ogunkoya, *J. Chem. Soc.*, 1965, 6914). Uniformity of the labelling in the *ortho* positions was established by degradation of the labelled precursor (**6**).

§ Taking into account the loss of tritium in oxidative coupling, the distribution of the radioactivity in (**8**) and (**10**) formed by oxidative degradation of the biosynthetic bases derived from specifically and uniformly labelled (**6**) demonstrated that (±)-(**6**) is incorporated into both units of the dimers.

were practically unchanged.¶ Feeding of (±)-[1-^{3}H, 6-*O*-$^{14}CH_3$]-(**6**) also yielded tiliacorine and tiliacorinine labelled with ^{14}C and ^{3}H, but the ^{14}C and ^{3}H ratios in the precursor was 1:30 and in the biosynthetic tiliacorine and tiliacorinine was 1:61 and 1:59·5, respectively.**

Parallel feeding experiments with (−)-(*R*)-*N*-methylcoclaurine (**2b**) and (+)-(*S*)-*N*-methylcoclaurine (**2a**) gave, in each case, radioactive tiliacorine. Labelled tiliacorine derived from the (+)-(*S*)-form (**2a**) was converted into tiliacorine dimethiodide[1] by treatment with methyl iodide with practically no loss of radioactivity. Alkaline permanganate oxidation which destroys the phenolic ring of the tiliacorine dimethiodide[1] (molar activity $10{\cdot}65 \times 10^5$ dis. min^{-1} mmol^{-1}) gave (**9**)[1] (inactive) and (**10**) (molar activity $5{\cdot}19 \times 10^5$ dis. min^{-1} mmol^{-1}). Tiliacorine derived from the (−)-(*R*)-form (**2b**) was converted into tiliacorine dimethiodide[1] (molar activity $1{\cdot}75 \times 10^5$ dis. min^{-1} mmol^{-1}) and was similarly degraded to (**9**) (molar activity $1{\cdot}5 \times 10^5$ dis. min^{-1} mmol^{-1}) and (**10**) (radioinactive). These results thus established the (*S*)- and (*R*)-configuration at the asymmetric centres C(1) and C(1′), respectively, in tiliacorine.

Parallel feeding of the (+)-(*S*) and (−)-(*R*) isomers (**2a**) and (**2b**) demonstrated that the former was incorporated into tiliacorinine 70 times more efficiently than the latter. Labelled tiliacorinine derived from the (+)-(*S*)-form (**2a**) was converted into *O*-methyltiliacorinine dimethiodide[1] by treatment with methyl iodide–sodium methoxide. Alkaline permanganate oxidation of the *O*-methyltiliacorinine dimethiodide (molar activity $1{\cdot}8 \times 10^5$ dis. min^{-1} mmol^{-1}) followed by methylation with diazomethane of the acids so formed gave (**8**) (molar activity $1{\cdot}22 \times 10^5$ dis. min^{-1} mmol^{-1}) and (**10**) (molar activity $5{\cdot}72 \times 10^4$ dis. min^{-1} mmol^{-1}) having essentially 2/3 and 1/3 radioactivity, respectively. The results thus established the (*SS*) configuration at the two asymmetric centres C(1) and C(1′), respectively, in tiliacorinine.

Trapping experiments by feeding (±)-tyrosine to *T. racemosa* Colebr plants showed fairly high incorporation (0·50%) into (**6**). Thus (**6**) is a true precursor of (**1**).

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¶ Since there is no loss of hydrogen from C(1) in the precursor in the biotransformation and stereospecificity is maintained in the biosynthesis of the bisbenzylisoquinoline alkaloid from the 1-benzyltetrahydroisoquinoline precursor [D. H. R. Barton, G. W. Kirby, and A. Wiechers, *J. Chem. Soc.* (*C*), 1966, 266], this demonstrates that the stereochemistry of these asymmetric centres remain unchanged during biosynthesis.

** The loss of the MeO$^+$ group from one of the *N*-methylcoclaurine units in the formation of the 1,4-dioxan bridge in cocsulin has been confirmed (D. S. Bhakuni, V. M. Labroo, A. N. Singh, and R. S. Kapil, *J.C.S. Perkin I*, 1977, in the press).

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