Celacinnine, a Novel Macrocyclic Spermidine Alkaloid Prototype

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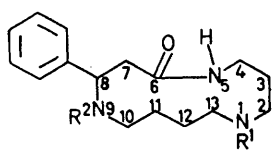
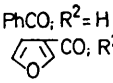
Summary The isolation and structural elucidation of the novel alkaloids celacinnine (**1**), celallocinnine (**4**), celabenzine (**5**), and celafurine (**6**), characterized by the presence of a 13-membered ring reflecting spermidine and cinnamoyl precursorial units, are reported.

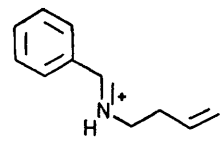
We report the structure of a new alkaloid, celacinnine, isolated from *Maytenus arbutifolia* (Hochst., ex A. Rich) R. Wilczek[1] and *Tripterygium wilfordii* Hook,[2] which is the prototype of a novel series of alkaloids present in members of the Celastraceae family. The alkaloids are characterized by the presence of a 13-membered ring reflecting spermidine and cinnamoyl precursorial units,[3] and represent novel variants of the few known macrocyclic lactam alkaloids derived from spermidine.[4]

Celacinnine (**1**) was first isolated from an aqueous ethanol extract of the twigs of *M. arbutifolia*† as colourless needles:‡ $C_{25}H_{31}N_3O_2$; m.p. 203—204°; $[\alpha]_D^{25}$ − 19° ($CHCl_3$). The i.r. [6·25 μm (unsaturated amide carbonyl)], n.m.r. [τ 2·23 (d, 1H, J 15·5 Hz), 3·12 (d, 1H, J 15·5 Hz), 2·5—2·8 (m, 10H)], m.s. [*m/e* 274 (M^+ − C_9H_7O, 100%), 131 (C_9H_7O, 90%), 103 (C_8H_7, 45%)] and u.v. spectra [u.v. max 223 (infl), 277 nm (ϵ 16,000, 23,000)] all indicated the presence of a *trans*-cinnamide chromophore.[5,6] In addition, the presence of a second monosubstituted benzene ring (n.m.r. signals) and saturated amide carbonyl (6·06 μm) were readily apparent.

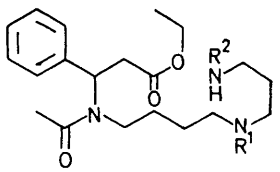
Hydrogenation of (**1**) over 10% Pd–C yielded dihydrocelacinnine (**2**): $C_{25}H_{33}N_3O_2$; m.p. 172–173°; u.v. max 253, 260, 265, 269 nm (ϵ 520, 600, 520, 380); i.r. 6·03, 6·14 μm; n.m.r. τ 2·7—2·8 (m, 10H), no other signals lower than τ 6·0. The single additional unsaturation reflected by the empirical formula of (**1**) was thus attributable to the presence of a ring. Vigorous acid hydrolysis (2N HCl, 150°, 18 h) of (**1**) followed by acetylation of the reaction mixture yielded triacetylspermidine. The empirical formula of (**1**) less the cinnamoyl and spermidine units corresponded to a phenyl propionyl residue. In fact, signals in the n.m.r. of (**1**) [τ 6·00 (t, 1H, J 7 Hz), 7·50 (d, 2H, J 7 Hz)] compared



(1) R^1 = *t*-PhCH=CHCO; R^2=H
(2) R^1 = $PhCH_2CH_2CO$; R^2=H
(3) R^1 = *t*-PhCH=CHCO; R^2=Ac
(4) R^1 = *c*-PhCH=CHCO; R^2=H
(5) R^1 = PhCO; R^2=H
(6) R^1 =  CO; R^2=H



(7)



(8) R^1,R^2= Ac; *t*-PhCH=^{t}CHCO

† The twigs of *M. arbutifolia* were collected in Ethiopia in Jan. 1968. The roots of *T. wilfordii* were collected in Taiwan in Aug. 1971. We thank Dr. Robert E. Perdue, jun., U.S. Department of Agriculture, Beltsville, Md., for supplying the plant material.

‡ Molecular formulae were determined by a combination of elemental analysis and high-resolution m.s. Fragment ions for which empirical formulas are quoted have been verified by high-resolution m.s. N.m.r. spectra were determined on solutions in $CDCl_3$.

favourably with those of *N*-methyl-β-phenyl-β-alanine methyl ester (τ 6·03 and 7·50) but not with the β-phenyl-α-alanine isomer (τ 6·46 and 7·04). Treatment of (**1**) with acetic anhydride in pyridine yielded *N*-acetylcelacinnine (**3**), $C_{27}H_{33}N_3O_3$, in which the n.m.r. signals attributed to the phenyl alanine residue had shifted downfield (τ 4·38 and 7·02). Once again these compared well with the corresponding signals for *N*-acetyl-β-phenyl-β-alanine methyl ester (τ 4·52 and 7·14) but not those for the corresponding α-isomer (τ 5·12 and 6·91). The comparisons served to confirm the β-relationship and also established that the β-phenyl-β-alanine nitrogen atom did not carry the cinnamoyl unit.

The m.s. of (**1**) exhibited a peak at *m/e* 160 ($C_{11}H_{14}N$, 21%) which could reasonably be formed by initial cleavage of the labile C-7–C-8 bond followed by fission of the N-1–C-13 bond and hydrogen transfer to yield an ion of type (**7**). Further support for the attachment of the four carbon end of the spermidine chain to the β-amino group was obtained as follows. Mild acid hydrolysis (6N HCl, 100°, 2 h) of (**1**), followed by esterification and acetylation of the reaction products, led to isolation of the degradation product (**8**), $C_{31}H_{41}N_3O_5$, in which only the saturated amide group had been hydrolyzed. The m.s. of acyclic triacylspermidine derivatives have been extensively studied.[7] Accordingly, the appearance of ions in the m.s. of (**8**) at *m/e* 345 (35%), 333 (10%), and 319 (5%), are attributable to the characteristic spermidine –N–$[CH_2]_3$–N– fragmentation.

The m.s. of celacinnine and its dihydro-derivative exhibited peaks at $M^+ - C_3H_6NO$ [*m/e* 333 (2%) for (**1**), 335 (10%) for (**2**)], attributable to initial cleavage of the C-7–C-8 bond followed by C-3–C-4 fission and hydrogen transfer. Additionally, (**1**) and (**2**) exhibited a peak at *m/e* 146 (C_9H_8NO, 29%) [there was no peak at *m/e* 148 ($C_9H_{10}NO$) for (**2**)] which evidently arises by elimination of the β-amino-amide to yield a di-cinnamoyl spermidine, followed by cleavage of the C-4–N-5 bond.

An isomeric companion alkaloid, celallocinnine (**4**) was also isolated from *M. arbutifolia*. The properties of celallocinnine [m.p. 172—173°; $[\alpha]_D^{25}$ – 24° ($CHCl_3$)] favoured assignment of the *cis*-cinnamide structure (**4**). Hydrogenation over 10% Pd–C yielded dihydrocelacinnine (**2**) and confirmed structure (**4**).

In a later study, (**1**) was isolated from *Tripterygium wilfordii* Hook, along with two structurally related companions. One of these, celabenzine (**5**) [$C_{23}H_{29}N_3O_2$; m.p. 156—158°; $[\alpha]_D^{25}$ 0° ($CHCl_3$)] was shown to be the benzamide analogue of (**1**), on the basis of its spectral data. The other, celafurine (**6**) [$C_{21}N_{27}N_3O_3$; m.p. 154—155°; $[\alpha]_D^{25}$ – 11° ($CHCl_3$)] was similarly shown to be the β-furamide analogue.

Celacinnine (**1**) appears to be the first fully characterized member of a new series of novel macrocyclic spermidine alkaloids.

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