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DAPHNIPHYLLUM ALKALOIDS—II*

SECODAPHNIPHYLLINE AND METHYL HOMOSECODAPHNIPHYLLATE

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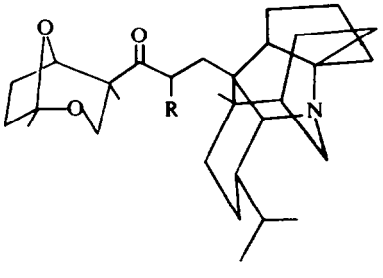
Abstract—Isolation and structures of two new alkaloids, secodaphniphylline (I) and methyl homosecodaphniphyllate (II), are described. The structure of the latter, established by X-ray analysis of its bromoacetyl derivative, is in full agreement with its chemical and spectral data. The structure of the former was deduced by chemical correlation between I and II. The 2-azabicyclo-[3.3.1]non-1-ene system, an unusually stable anti-Bredt's-rule imine, was formed from II.

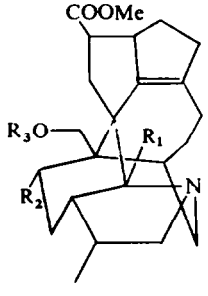
AN ALKALOID of *Daphniphyllum macropodum* Miquel was first isolated in 1909 as a white amorphous powder, m.p. 75–84°, $C_{27}H_{41}O_4N$, and named daphnimacrine. Since then no further studies on the alkaloids of this plant appear to have been made. We have examined the alkaloidal components of the bark and leaves of the same plant and isolated eleven new alkaloids.†

The chemical and spectral properties of the major alkaloids, daphniphylline (III) and yuzurimine (V), indicated that it would be difficult to determine the structures by chemical methods alone.

Finally, X-ray diffraction studies indicated that daphniphylline and yuzurimine had the unusual structures III and V, respectively.[1]



III R = $OCOCH_3$
IV R = H



V R_1 = OH, R_2 = $OCOCH_3$, R_3 = $COCH_3$
VI R_1 = R_2 = R_3 = H

* Part I: see ref. 1

* Alkaloidal components of the fruits of the same plant are now in progress

The structures of codaphniphylline (IV) and yuzurimine-B (VI) have also been established by chemical transformation.[1, 2]

Thus, daphniphyllum alkaloids have novel structures, and their carbon skeletons consist of thirty carbon atoms for III and IV, and twenty two carbon atoms for V and VI.

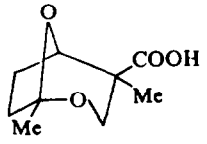
Here the structures of secodaphniphylline (I) and methyl homosecodaphniphyllate (II) are described, a new type of alkaloid different from daphniphylline and yuzurimine.

Firstly the structural relationship between these two alkaloids will be discussed. In a comparison of the NMR spectra between secodaphniphylline (I: $C_{30}H_{47}O_3N$; m.p. 129–130°; ν_{max}^{KBr} 3400 and 1704 cm^{-1}) and methyl homosecodaphniphyllate (II: $C_{23}H_{37}O_2N$; m.p. 102·5–103°; ν_{max}^{KBr} 3360 and 1735 cm^{-1}), the former (I) has each signal corresponding to protons of the ketal-acid (VII), a degradation product of daphniphylline (III).[1] On the other hand, these signals are not found in the latter, but instead a Me signal for the ester group is observed at 3·67 ppm. The remaining signals are nearly identical in both compounds (Table 1).[3]

TABLE 1. NMR SPECTRA OF I, II AND VII

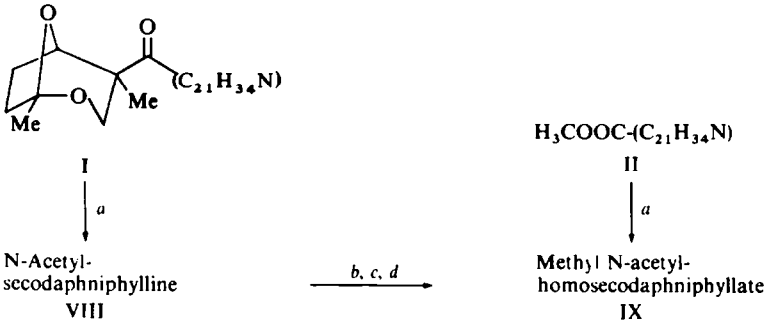
VII	I	II
	0·77 (3H, s)	0·79 (3H, s)
1·03 (3H, s)	0·89 (3H, s)	
	0·89 (3H, d, J = 6 Hz)	0·89 (6H, d, J = 6 Hz)
	0·90 (3H, d, J = 6 Hz)	
1·50 (3H, s)	1·42 (3H, s)	
	2·51 (1H, d, J = 4·2 Hz)	2·53 (1H, d, J = 4·2 Hz)
	2·6–2·9 (2H, m)	2·1–2·5 (2H, m)
	3·01 (1H, br. s)	2·98 (1H, br. s)
3·63 (1H, d, J = 12 Hz)	3·49 (1H, d, J = 12 Hz)	
4·30 (1H, dd, J = 12, 2 Hz)	4·23 (1H, dd, J = 12, 2 Hz)	
4·77 (1H, m)	4·62 (1H, m)	
		3·67 (3H, s)

VII



When considered in the light of this fact, the difference of molecular weight between I and II (110) as well as the appearance of common fragment peaks (*m/e* 344, 328, 316, 286 and 216) in their mass spectra suggests that secodaphniphylline (I) must have the tentative structure (I) which can formally be constructed with methyl homosecodaphniphyllate (II) and ketal-acid VII (Fig. 2). Accordingly, chemical correlation between I and II was carried out, as shown in Fig. 2.[3]

The N-acetyl secodaphniphylline (VIII), an acetylation product of I, was converted into methyl N-acetylhomosecodaphniphyllate (IX: m.p. 106·5°; $C_{25}H_{39}O_3N$; ν_{max}^{KBr} 1750 and 1650 cm^{-1}) by Beckmann rearrangement followed by methanolysis,



[a] Ac_2O-pyridine, at room temperature overnight
[b] $NH_2OH \cdot HCl$-pyridine, at 90° for 24 hr.
[c] MsCl-pyridine, at 80° for 24 hr.
[d] 6N HCl-MeOH, under reflux for 24 hr.

FIG. 2

which was proved to be identical with the N-acetyl derivative of II in m.p., IR and mass spectra.

Finally, treatment of methyl homosecodaphniphyllate (II) with bromoacetyl bromide and K_2CO_3 in dry benzene afforded the corresponding N-bromoacetyl derivative (X: m.p. 117·5–118·5°, $C_{25}H_{38}O_3NBr$), found suitable for X-ray diffraction study which indicated that the structure of methyl N-bromoacetyl-homosecodaphniphyllate was represented by X.[4] Accordingly, the structures of methyl homosecodaphniphyllate and secodaphniphylline should be represented by II and I, respectively.

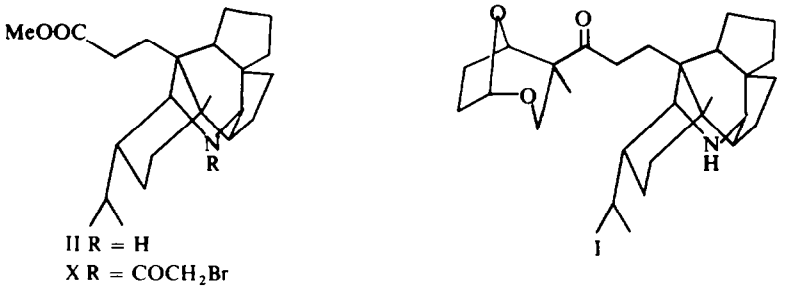


FIG 3

In fact, the structures of the two new alkaloids (I and II) are in good agreement with their chemical and spectral properties, as already described. In particular, the remarkable peak at *m/e* 286 in mass spectra of I and II can be attributable to the fragment ion (A) as shown overleaf.

However, a characteristic peak at *m/e* 272 cannot be found but is observed in the mass spectra of daphniphylline (III) as well as methyl homodaphniphyllate (XV).*

Next, we describe the formation of the 2-azabicyclo[3.3.1]-non-1-ene system, an unusually stable anti-Bredt's-rule imine.[5] When treated with $Pb(OAc)_4$ in dry

* The characteristic peaks at *m/e* 286 and 272 can be explained by the formation of two fragment ions (B and C).[1]

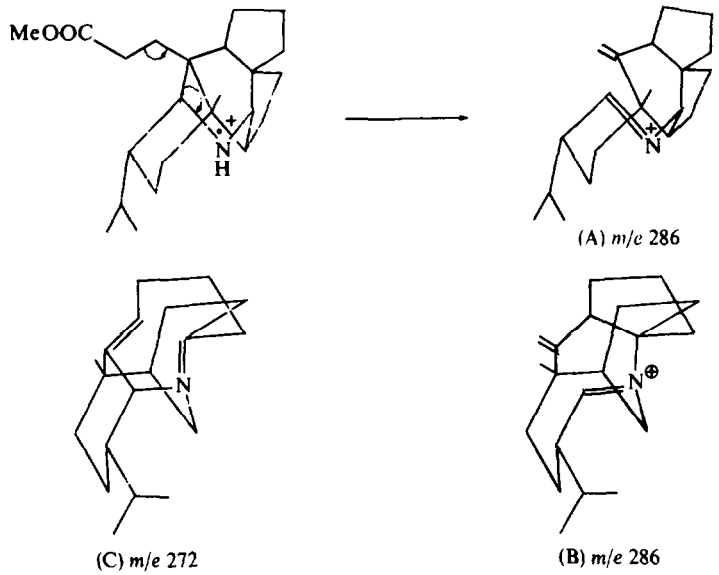


FIG 4

benzene at room temperature for 1 hr, methyl homosecodaphniphyllate (II) afforded an oxidation product (XI: $C_{23}H_{35}O_2N$; m.p. 96–98°; $\nu_{max}^{CHCl_3}$ 1736 and 1600 cm^{-1};* ν_{max}^{KBr} 1739 and 1589 cm^{-1}; *m/e* 357; $\delta_{TMS}^{CDCl_3}$ 0·88 (3H, d, J = 6Hz), 0·92 (3H, d, J = 6Hz), 0·93 (3H, s), 3·73 (3H, s) and 4·24 ppm (1H, d, J = 3·5Hz)). The imine (XI) was recon-

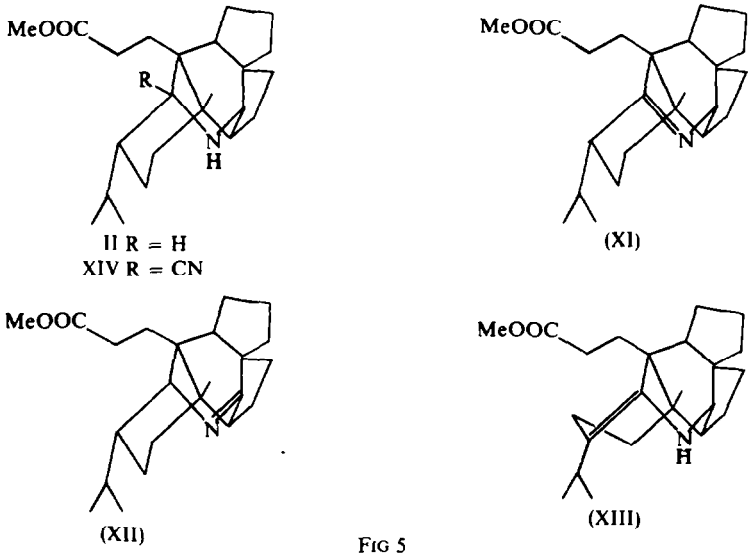


FIG 5

* An IR absorption band at 1600 cm^{-1} can be assigned to C=N absorption usually observed in the region of higher wave-number (1690–1640 cm^{-1})

verted into starting material (II) in quantitative yield on treatment with $NaBH_4$ at room temperature for 1 hr or by catalytic hydrogenation over PtO_2 in MeOH (room temperature, 1 hr), indicating that no rearrangement of the carbon skeleton took place in the course of oxidation of II with $Pb(OAc)_4$. On the basis of the above chemical properties and spectral data, the structure of the oxidation product must be XI, containing the 2-azabicyclo[3.3.1]non-1-ene system (Fig. 5).

Structure XII, which contains the 2-azabicyclo[2.2.2]oct-1-ene system, can be ruled out on steric grounds, and enamine structure XIII can also be ruled out since the oxidation product has no NH absorption band in its IR spectrum, and no signals corresponding to an NH group can be observed in the NMR spectrum.

Furthermore, treatment of the imine (XI) with excess NaCN in DMF (90–100°, 3 hr) afforded a cyano-compound (XIV: *m/e* 384; $\nu_{max}^{CHCl_3}$ 2240 and 1735 cm^{-1}). However, acetylation of XI with Ac_2O pyridine (room temperature, overnight) did not give the corresponding N-acetyl derivative, but the imine (XI).

The facile formation of the imine (XI) may be attributed to the following. (i) The

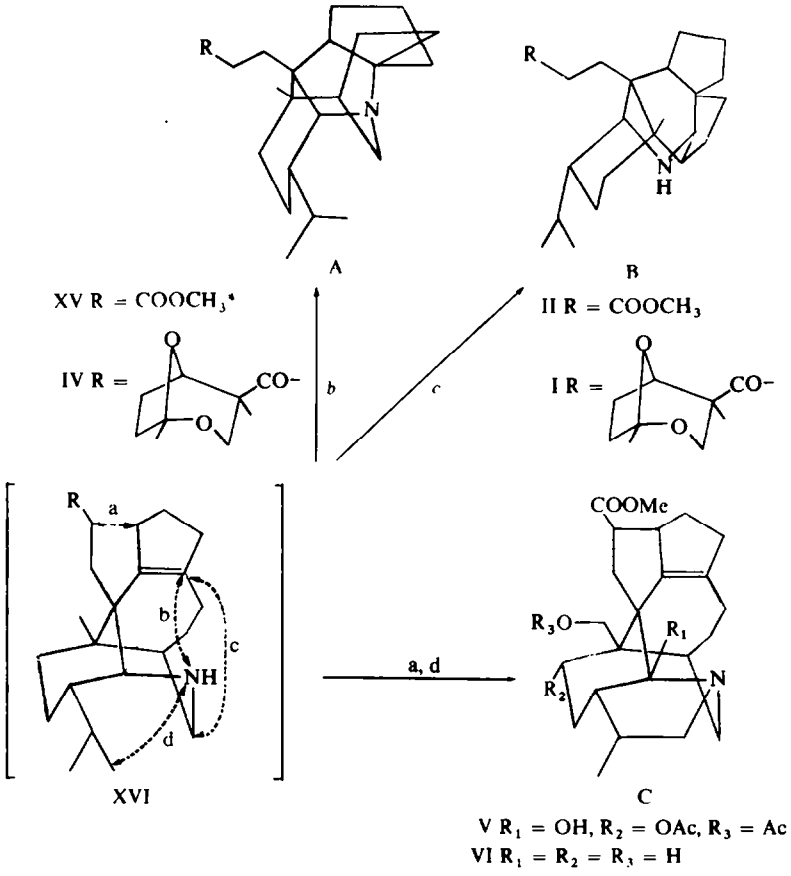


FIG 6. Structural relationships among daphniphyllum alkaloids

* Methyl homodaphniphyllate (XV) has been isolated from the fruits of *Daphniphyllum macropodum* Miquel.[6]

cyano-compound (XIV) has the boat conformation of its 2-azabicyclo[3.3.1]-nonane system fixed by a part of the 2-azabicyclo[2.2.2]octane system. (ii) The strain energy must be increased by the formation of the imine, whereas steric repulsion between the cyano group and the other substitutions in XIV can be relieved. Thus, the imine (XI) has the 2-azabicyclo[3.3.1]non-1-ene system,* an anti-Bredt's-rule imine, which is very stable on account of the fixed boat conformation as discussed above.

These daphniphyllum alkaloids are structurally divided into three groups A, B and C (Fig. 6). From a biogenetic point of view, such a tentative component as XVI is considered as a common intermediate of these alkaloids (Fig. 6). Although our efforts have been focussed on the isolation of biogenetically important XVI from the plant, we have not yet succeeded in the isolation of XVI. Biosynthetic studies on these alkaloids are also in progress.

EXPERIMENTAL

M.ps are uncorrected. IR spectra were recorded on JASCO IR-S. NMR spectra were recorded on a Nihondenshi JNM-C 60H (60 Mc) and a Varian A-60 NMR spectrometer (60 Mc) using $CDCl_3$ as solvent. Chemical shifts are given in ppm relative to internal TMS. Coupling constants are given in Hz (s, singlet; d, doublet; t, triplet, dd, double doublet; m, multiplet). Mass spectra were obtained on a Hitachi RMU-6C mass spectrometer operating with an ionization energy of 70 eV. Column chromatography was carried out on basic alumina (Nakarai Chemical Co., *ca.* 300 mesh) and silicic acid (Mallinckrodt, 100 mesh).

Isolation. Wet leaves and chopped bark of *Daphniphyllum macropodum* Miguel* (1000 Kg) was immersed in MeOH (400 l) at room temperature for 2 weeks, and then filtered off. The methanolic soln was concentrated under reduced press to about 40 l, diluted with equal volume of water, and washed with ether (30 l) to remove chlorophyll and acidic and neutral substances. The aqueous soln was made basic with 4N NaOH gradually (pH 9–13), and then extracted with ether (120 l). The ethereal layer was extracted with 0·1N HCl (30 l) for purification. This aqueous soln was made basic again with 4N NaOH gradually (pH 9–13) and extracted with ether (100 l). The ethereal extracts were washed with water (3 l), dried over Na_2SO_4, and concentrated under reduced press to give an oil (630 g).

The oil was chromatographed on alumina (3 kg) and eluted, in the following order, with *n*-hexane, *n*-hexane-benzene (1 :1), benzene, $CHCl_3$ and $CHCl_3$-MeOH (1 :1) to give 4 fractions.

Elution with *n*-hexane gave an oil (*ca.* 10 g) which was rechromatographed on alumina using *n*-hexane as an eluent to give three pure alkaloids: alkaloid-A_1 (1 g),** alkaloid-A_2 (1·1 g) and methyl homosecodaphniphyllate (1·7 g).

Elution with *n*-hexane-benzene (1 :1) gave an oil (*ca.* 10 g) which was rechromatographed on alumina (100 g) using *n*-hexane and *n*-hexane-benzene (1 :1) as eluents to give two alkaloids: secodaphniphylline (1·13 g) and alkaloid-C (0·18 g).

Elution with benzene gave an oil (150 g) which was rechromatographed on alumina (1·5 Kg) using *n*-hexane and *n*-hexane-benzene (1 :1) as eluents to give two alkaloids: daphniphylline (100 g) and codaphniphylline (0·3 g).

Elution with $CHCl_3$ gave an oil (*ca.* 250 g) which was rechromatographed on silicic acid (1·5 Kg) using $CHCl_3$ and $CHCl_3$-MeOH (1–10%) as eluents to give three alkaloids: yuzurimine-A (1 g), yuzurimine (150 g) and yuzurimine-B (0·5 g).

Finally, elution with $CHCl_3$—MeOH (1 :1) gave an oil (*ca.* 50 g) which was rechromatographed on silicic acid (500 g) using $CHCl_3$—MeOH (10%) as solvent to give an alkaloid, yuzurimine-C (1·4 g).

Acetylation of secodaphniphylline (I). Acetic anhydride (1 ml) was added to a soln of I (100 mg) in pyridine (1 ml). The resulting soln was allowed to stand at room temp overnight, and the solvent and excess Ac_2O removed under reduced press to give an oil, purified by chromatography on alumina (1 g) using *n*-hexane

* Recently, the synthesis and chemistry of the anti-Bredt's-rule olefin bicyclo[3.3.1]non-1-ene have been reported in detail.[7]

† Thd leaves and bark was collected at Gifu-ken in June.

** The physical and spectral data of these alkaloids are summarized in Table 2.

TABLE 2

Alkaloid-A_1: $C_{23}H_{33}O_3N$: m.p. (methiodide) 225–226°: ν_{max}^{KBr} 2765, 1742 and 1676 cm^{-1}; *m/e* 371, 356, 343, 328, 314, 312, 300 and 287; $\delta_{TMS}^{CDCl_3}$ 1·00 (3H, t, J = 7·1Hz), 1·01 (3H, d, J = 6·8 Hz), 2·15 (3H, s), 3·62 (3H, s), 3·94 (1H, d, J = 11·3Hz), 4·31 (1H, d, J = 3·0Hz) and 4·49 (1H, dd, J = 11·3, 1·9Hz) ppm. (Found: C, 56·47; H, 7·17; N, 2·70. $C_{23}H_{33}O_3N \cdot CH_3I$ requires: C, 56·14; H, 7·07; N, 2·72%).

Alkaloid-A_2: $C_{24}H_{37}O_4N$: m.p. (methiodide) 229–230°, ν_{max}^{KBr} 2700 and 1740 cm^{-1}; *m/e* 403, 388, 372, 360 and 344; $\delta_{TMS}^{CDCl_3}$ 0·85 (3H, t, J = 7·4Hz), 2·17 (3H, s), 3·21 (3H, s), 3·64 (3H, s) and 3·93 (2H, s) ppm. (Found: C, 54·51; H, 7·44; N, 2·51. $C_{24}H_{37}O_4N \cdot CH_3I$ requires: C, 55·04; H, 7·39; N, 2·90%).

Methyl homosecodaphniphyllate (II): m.p. 102·5–103° (from *n*-hexane): *m/e* 359, 344, 316, 300, 286, 216 and 206. (Found: C, 76·63; H, 10·46; N, 3·70. $C_{23}H_{37}O_2N$ requires: C, 76·83; H, 10·37; N, 3·90%).

Secodaphniphylline (I): m.p. 129–130° (from *n*-hexane); *m/e* 469, 454, 426, 344, 316, 300, 286 and 216. (Found: C, 76·31; H, 10·31; N, 3·13. $C_{30}H_{47}O_3N$ requires: C, 76·71; H, 10·09; N, 2·98%).

Alkaloid-C: $C_{23}H_{35}O_2N$: m.p. 194·5–195·5° (from *n*-hexane-benzene); ν_{max}^{KBr} 1737 cm^{-1}; *m/e* 357, 342, 314, 298 and 275; $\delta_{TMS}^{CDCl_3}$ 0·91 (3H, d, J = 6Hz), 0·93 (3H, d, J = 6Hz), 1·05 (3H, s) and 3·80 (1H, dd, J = 15, 6Hz) ppm. (Found: C, 77·17; H, 9·73; N, 4·52. $C_{23}H_{35}O_2N$ requires: C, 77·26; H, 9·87; N, 3·92%).

Daphniphylline and codaphniphylline: The physical and spectral data were described in the previous paper.[1]

Yuzurimine, yuzurimines-A and B: The physical and spectral data will be reported elsewhere in detail.

to afford a colourless oil (98 mg): $\nu_{max}^{CCl_4}$ 1709 and 1647 cm^{-1}; *m/e* 511, 496, 468, 441, 429, 341 and 328; $\delta_{TM}^{CDCl_3}$ 0·73 (3H, d, J = 5·4 Hz), 0·78 (3H, s), 0·85 (3H, s), 1·12 (3H, d, J = 5·4 Hz), 1·40 (3H, s), 2·12 (3H, s), 2·7–3·1 (2H, m), 3·49 (1H, d, J = 12 Hz), 3·52 (1H, d, J = 4·2 Hz), 4·24 (1H, dd, J = 12, 2 Hz), 4·35 (1H, s) and 4·67 (1H, m) ppm.*

Formation of methyl N-acetyl homosecodaphniphyllate (IX) from N-acetylsecodaphniphylline (VIII). To a soln of N-acetylsecodaphniphylline (VIII, 25 mg) in pyridine (1 ml) hydroxylamine hydrochloride (25 mg) was added with stirring. The resulting soln was heated at 90–100° for 24 hr. After cooling, the reaction soln was diluted with water (1 ml), and then extracted with a lot of benzene. The extract was dried (Na_2SO_4) and concentrated under reduced press to afford an oil.

To a soln of this oil in pyridine (0·5 ml) MesCl (20 mg) was added with stirring. The resulting soln was warmed at 80° overnight. After cooling, the soln was diluted with water (0·5 ml), and extracted with benzene. The extract was dried over Na_2SO_4 and concentrated under reduced press to afford an unstable oil.

The resulting oil was heated under reflux with 6N HCl—MeOH (1:1 (1 ml))overnight. After cooling, the acidic soln was made basic with Na_2CO_3 to pH 9–10. Extraction with benzene afforded an oil, which was chromatographed on alumina (*ca.* 0·1 g). Elution with *n*-hexane gave an oil, which was crystallized from *n*-hexane to give colourless plates: m.p. 105–106°; ν_{max}^{KBr} 1750 and 1650 cm^{-1}; *m/e* 401, 386, 370, 358, 331, 328 and 319. This compound was completely identical to methyl N-acetyl homosecodaphniphyllate (IX) (m.p. and IR spectrum).

Acetylation of methyl homosecodaphniphyllate (II). According to the same procedure described in acetylation of I, II (100 mg) afforded methyl N-acetyl homosecodaphniphyllate (IX, 90 mg): $C_{25}H_{39}O_3N$; m.p. 105–106° (from *n*-hexane); ν_{max}^{KBr} 1750 and 1650 cm^{-1}; *m/e* 401, 386, 370, 358, 331, 328 and 319; $\delta_{TMS}^{CDCl_3}$ 0·76 (3H, d, J = 5·5Hz), 0·83 (3H, s), 1·11 (3H, d, J = 5·5Hz), 2·13 (3H, s), 3·54 (1H, d, J = 5Hz), 3·68 (3H, s) and 4·30 (1H, br. s) ppm. (Found: C, 74·45; H, 10·03; N, 3·41. $C_{25}H_{39}O_3N$ requires: C, 74·77; H, 9·79; N, 3·49%).

Formation of methyl N-bromoacetyl homosecodaphniphyllate (X). Bromoacetyl bromide (0·1 ml) was added to a soln of II (100 mg) in anhyd benzene (2 ml) containing K_2CO_3. After stirring at room temp overnight, the reaction soln was diluted with water, and extracted with CH_2Cl_2. Evaporation of solvent, after drying (Na_2SO_4), afforded an oil, which was chromatographed on alumina (*ca.* 1 g). Elution with *n*-hexane-Et_2NH (100:0·5) gave a solid (X), which was recrystallized from *n*-hexane–benzene to give colourless plates (X): m.p. 117–118·5°; $C_{25}H_{38}O_3NBr$; ν_{max}^{KBr} 1744 and 1637 cm^{-1}; *m/e* 481, 479, 466, 450, 448, 400 and 330. (Found: C, 62·64; H, 8·10; N, 3·24. $C_{25}H_{38}O_3NBr$ requires: C, 62·49; H, 7·97; N, 2·92%).

Oxidation of methyl homosecodaphniphyllate (II) with $Pb(OAc)_4$. A soln of $Pb(OAc)_4$ (50 mg, dried under reduced press for 1 hr) in anhyd benzene (1·5 ml) was added to a soln of II (25 mg) in anhyd benzene (1·5

* This oil was directly used for the next experiment.

ml) at room temp with stirring. After stirring at room temp for 1 hr, the soln was diluted with water and extracted with benzene. Evaporation of the solvent, after drying (Na_2SO_4), afforded an oil, which was chromatographed on alumina (150 mg). Elution with benzene afforded a solid, which was recrystallized from *n*-hexane to give colourless plates (XI): m.p. 96–98°; $C_{23}H_{35}O_2N$; $\nu_{max}^{CHCl_3}$ 1736 and 1600 cm^{-1} (2600, 1735 and 1630 cm^{-1} for hydrochloride); ν_{max}^{KBr} 1739 and 1600 cm^{-1}; *m/e* 357, 342, 328, 326, 314, 302, 298, 289 and 284; $\delta_{TMS}^{CDCl_3}$ 0·88 (3H, d, J = 6Hz), 0·92 (3H, d, J = 6Hz), 0·93 (3H, s), 3·73 (3H, s) and 4·24 (1H, d, J = 3·5Hz) ppm. (Found: C, 77·43; H, 10·21; N, 4·28. $C_{23}H_{35}O_2N$ requires: C, 77·26; H, 9·87; N, 3·92%).

Sodium borohydride reduction of the imine XI). $NaBH_4$ (5 mg) was added to the soln of the imine (20 mg) in MeOH (0·5 ml) at room temp. After stirring at room temp for 1 hr, the soln was diluted with water (1 ml) and extracted with benzene to afford white crystals (15 mg) of methyl homosecodaphniphyllate (m.p. and IR spectrum).

Catalytic hydrogenation of the imine (XI). Catalytic hydrogenation of the imine (20 mg) in MeOH (3 ml) was carried out over PtO_2 (5 mg) at room temp for 1 hr. After filtration of catalyst, the solvent was evaporated under reduced press to give white crystals (17 mg) of methyl homosecodaphniphyllate (II) (m.p. and IR spectrum).

Reaction of the imine (XI) *with* NaCN. A soln of XI (20 mg) and excess NaCN (20 mg) in anhyd DMF (0·4 ml) was heated at 90–100° for 3 hr. After cooling, the reaction soln was diluted with water and extracted with benzene. Evaporation of solvent, after drying (Na_2SO_4), afforded an oil, which was separated by prep. TLC (Silica Gel GF_{254}: Merck) using *n*-hexane-Et_2O-$HNEt_2$ (20:20:3) as solvent to afford an unstable oil (XIV), the structure of which was supported by spectral data (*m/e* 384 (M^+ for $C_{24}H_{36}O_2N_2$), 357, 353, 341, 314 and 311; $\nu_{max}^{CHCl_3}$ 3440, 2240 and 1735 cm^{-1}).

Attempted acetylation of the cyano-compound (XIV). According to the same procedure described in acetylation of I, XIV (10 mg) afforded an oil, which was crystallized from *n*-hexane to give colourless plates (6 mg). This compound was completely identical with the imine (XI) (m.p. and IR spectrum).

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