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3-PRENYLINDOLES FROM *MURRAYA PANICULATA* AND THEIR BIOGENETIC SIGNIFICANCE*

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Key Word Index—*Murraya paniculata*; Rutaceae; 3-prenylindole; 1-methoxyindole; coumarin; chemotaxonomy; biogenesis.

Abstract—Three new 3-prenylindoles named paniculidines A, B and C were isolated from the root bark of *Murraya paniculata* together with the known coumarins murralongin and osthol. Their structures were elucidated as methyl 2-(*R*)-methyl-4-(3-indolyl)-butyrate, 2-(*R*)-methyl-4-(1-methoxy-3-indolyl)-1-butanol and 2-(*R*)-methyl-4-(3-indolyl)-1-butanol, respectively, based on the spectroscopic and chemical evidence. The chemotaxonomic and biogenetic aspects of 3-prenylindole in *Murraya* has been discussed in conjunction with carbazole biogenesis.

INTRODUCTION

Murraya paniculata (Linn.) Jack is a rutaceous shrub occurring throughout tropical and subtropical Asia, its distribution extends in the west to India, in the north to southern China and the Okinawa Islands, and in the south and east to New Guinea, New Caledonia and northern Australia. The leaves and bark of this plant are of wide medicinal value as a folk medicine for the treatment of stomach and toothache or as a stimulant and tonic in southeast Asia. Consequently the aerial part of this plant has long been the subject for extensive chemical investigations, and a number of coumarins [2–13], flavones [4, 11, 12, 14, 15] and essential oils [16] have been isolated. Although the root bark is also used as an anodyne or local anesthesia for the treatment of gout, contusion and bone ache in China and its surroundings, there has been much less information available on constituents of the subterranean part of the plant [17]. We are thus encouraged to investigate the root bark of *Murraya paniculata*. This paper deals with the isolation and structure elucidation of three new 3-prenylindoles, and also refers to the chemotaxonomical importance of these compounds in the genus *Murraya* as well as their biogenetic significance in relation to the carbazole alkaloid.

RESULTS

Fresh root bark collected in Taiwan was extracted with chloroform to give a dark brown extract. The extract was consecutively chromatographed on silica gel to yield compounds **1**–**5**. Compounds **1**–**3** were found to be a new class of indoles, and named paniculidines A–C, respectively. Compounds **4** and **5** were readily identified with the known compounds osthol [18] and murralongin [19], respectively. It should be noted that the structure of murralongin was revised to **5** by our previous investigation [20].

The structures of paniculidines A and B have already been elucidated as **1** and **2**, respectively, based on the spectroscopic data [1]. Further chemical investigation revealed the presence of a minor alkaloid, for which a new name of paniculidine C was proposed. Its structure was readily elucidated as **3** by comparison with the spectral data of **1** and **2**, and identified with the one arising from either reduction of **1** with lithium aluminium hydride or hydrogenation of **2** over 10% Pd-C. The structures of these prenylindoles were finally confirmed by chemical synthesis carried out as follows. The half ester of the phenylhydrazone of 6-methyl-2-ketopimelic acid formed when benzenediazonium salt and 2-carboethoxy-6-methyl-cyclohexane-1-one were applied to the Japp-Klingemann reaction [21]. Indole ring closure of the half ester took place readily when heated in alcohol with sulphuric acid. The dibasic ester thus obtained was subjected to alkaline hydrolysis followed by decarboxylation to afford 2-methyl-4-(3-indolyl)-butyric acid, which was identical in mmp and IR spectrum to the one obtained from alkaline hydrolysis of **1**. Esterification of the acid with diazomethane readily gave *dl*-paniculidine A. Reduction of *dl*-paniculidine A with lithium aluminium hydride afforded *dl*-paniculidine C. Recently, 2-methyl-4-(1-methoxy-3-indolyl)-1-butanol was synthesized in a racemic form [22], which was identified with paniculidine B in the IR, ^{1}H and ^{13}C NMR spectra. Thus, all of the structures of paniculidines A, B and C were established unequivocally.

All of compounds **1**–**3** have a common chiral centre at C-2′. Their absolute configurations were determined empirically from the ^{1}H NMR analysis of the (*R*)-α-methoxy-α-trifluoromethyl-phenylacetate (MTPA) of **3** and its chemical correlation to **1** and **2**. According to Kasai *et al.* [23], in the ^{1}H NMR spectrum of the MTPA

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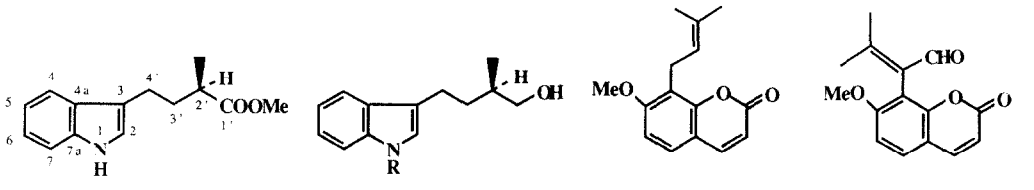


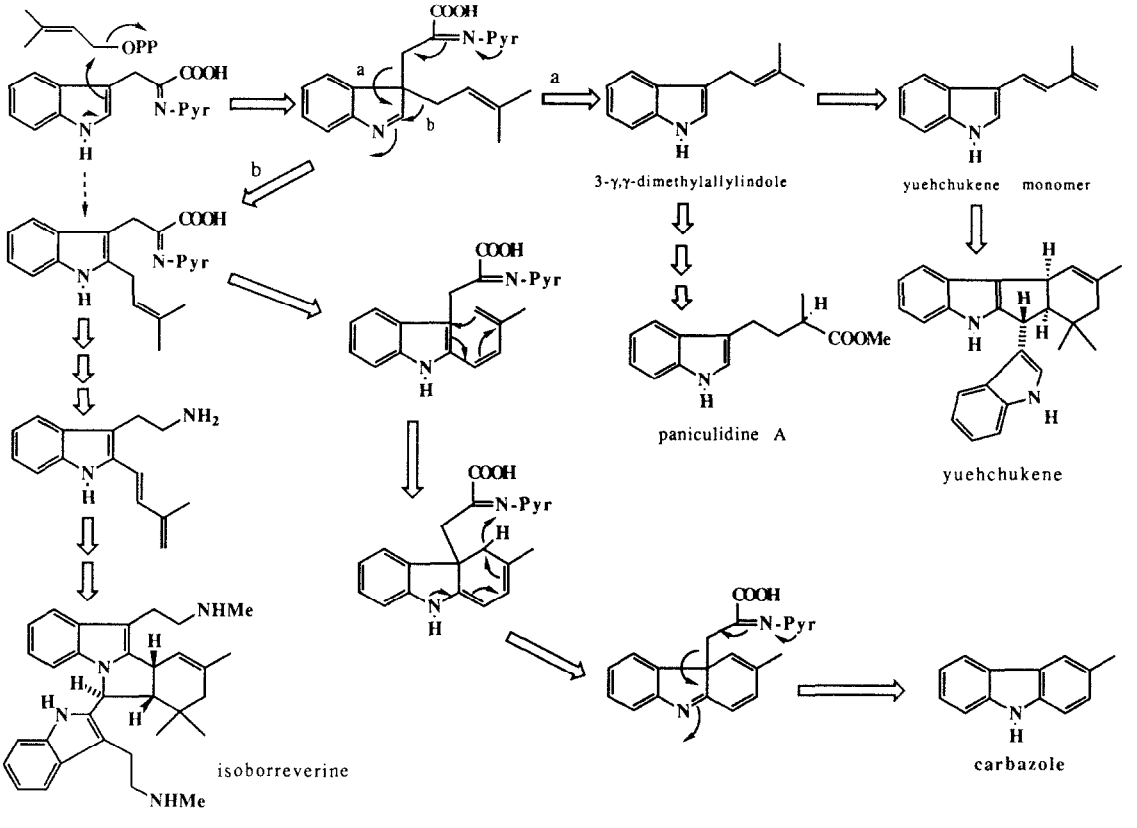
1 2 R=OMe 3 R=H 4 5

ester of primary alcohols with a chiral carbon carrying H, Me and a linear alkyl group, as in compounds **2, 3**, the signals due to the primary carbinol protons appear as an equivalent 2H doublet in the case where the combination of the two chiral centres is either (*R,S*) or (*S,R*), whereas they are observed as non-equivalent double doublet when it is either (*R,R*) or (*S,S*). It was observed that the spectrum of the (*R*)-MTPA ester of **3** exhibited signals of non-equivalent carbinol protons (δ4.14 and 4.32, 1H each, *dd*, $J_1 = 10.5$, 6.2 Hz, $J_2 = 10.5$, 5.2 Hz, $CDCl_3$, 100 MHz) corresponding to the latter case, while that of the racemic ester gave rise to the mixed pattern of both cases. Since all of three 3-prenylindoles have been found to have the same absolute stereochemistry by chemical correlation, the chirality of **1–3** at C-2′ was established as *R*.

DISCUSSION

Although the occurrence of the simple indole has been observed in a number of plants including *Murraya* species [24], only one 3-prenylindole had been reported from *Uvaria elliotiana* (Annonaceae) [25]. Since then a few 3-prenylindoles have been isolated from *Annondium mannii* [26] and *Monodora tenuifolia* [27], both of which belong to the Annonaceae family, but their occurrence in nature remains rare. A dimeric indole alkaloid yuehchukene (shown in Scheme 1) isolated from the root of *Murraya paniculata* [17] appears to be formed via non-enzymatic condensation of the corresponding monomer (shown in Scheme 1), which is thus considered to be related to **1–3**. Though more than one thousand indole alkaloids have been known from natural resources, there have been only a few reports on the isolation of compounds possessing the 1-methoxyindole moiety [28–33]. The isolation of paniculidine B is of significance as the only naturally occurring prenylated 1-methoxyindole.

The indole alkaloid is generally characterized as being of tryptamine origin derived from decarboxylation of tryptophan. By contrast, the 3-prenylindole markedly differs from the ordinary indole alkaloid in that the side chain of tryptophan has been displaced by the prenyl unit rather than undergoing decarboxylation. A possible mechanism for the biogenesis of 3-prenylindole can be



Scheme 1. Possible biogenetic relationships between 3-prenylindole and carbazole.

postulated as shown in Scheme 1. The introduction of the C_5-unit of the mevalonate origin at C-3 of tryptophan, followed by loss of the serine residue, would give rise to 3-γ,γ-dimethylallylindole *via* the intermediacy of the indolenine. Loss of serine from tryptophan would be effected in the form of a coenzyme-bound Schiff's base, which can be viewed as a retro-reaction in the well-established scheme of tryptophan biosynthesis [34]. It is noteworthy that 3-γ,γ-dimethylallylindole, a possible primary product derived from condensation of tryptophan and a C_5-unit, has been isolated from *M. paniculata* of Okinawan origin together with paniculidines A, C and yuehchukene (Prof. H. Furukawa, personal communication), which lends support to the above scheme.

Though it is generally conceived that C-2 is much less reactive than C-3 in the indole nucleus, there has been experimental evidence that substitution at C-2 also occurs through either rearrangement from C-3 or to a lesser extent a direct alkylation when C-3 is substituted [35]. This would be the chemical basis for the biogenesis of 2-prenyltryptamine which has been found in *Borreria* (Rubiaceae) [36] and *Flindersia* (Rutaceae) [37] in the form of dimers. The presence of a 2-prenyltryptamine derivative (isoborreverine; shown in Scheme 1) in the Rutaceae family arouses particular interest in view of its biogenetic relationship to the carbazole, the biogenesis of which has long been disputed [38], since 2-prenyltryptamine would be a proximate precursor that undergoes cyclization followed by loss of side chain to give the carbazole nucleus with a methyl substituent at the required position (Scheme 1). Of interest to note from the chemotaxonomical viewpoint, Kong *et al.* [39] have discussed a dichotomy in *Murraya* between species producing a prenylindole dimer yuehchukene, to which *M. paniculata* is applied, and those producing the carbazole such as *M. koenigii* and its allies. In this context, whether prenylation of tryptophan occurs at C-2 or C-3 may be envisaged as a key biogenetic step in the chemotaxonomic division of *Murraya*. As an alternative route for the carbazole biogenesis, the possible intermediacy of 3-prenyl-4-hydroxyquinoline-2-one was discussed earlier, and it was depicted hypothetically as undergoing decarbonylation followed by cyclization to form the carbazole nucleus [39]. The presence of prenylated 4-hydroxyquinoline-2-ones in a number of rutaceous plants seems to be looked upon as evidence for this hypothesis [40]. Both this, and our newly proposed hypotheses, commonly regard 2-prenylindole as a possible intermediate of carbazole. However, the previous hypothesis [39] overlooked that 2-prenylindoles remain unknown in nature, but only 2-prenyltryptamines, which are apparently of tryptophan origin, occur in some plants. In addition, chemical sequences involving transformation of quinolone into indole has been discussed only as loss of carbonyl in the previous hypothesis, but there has been no chemical basis available that allows it to occur under mild conditions.

EXPERIMENTAL

General procedure. Mps: uncorr; IR: $CHCl_3$ unless otherwise stated; UV: EtOH; $[\alpha]_D$: $CHCl_3$; ^1H NMR (400 or 100 MHz) and ^{13}C NMR (100 or 25 MHz): $CDCl_3$ with TMS as int. standard; CC: silica gel (Wakogel C-200 or Kieselgel 60); TLC: 0.25 mm precoated silica gel ($60F_{254}$, Merck); C_6H_6–Me_2CO, C_6H_6–$CHCl_3$ or *n*-hexane–$CHCl_3$–*iso*-PrOH; Spots were detected by UV light (254 nm) or spraying 10% H_2SO_4 followed by heating.

Table 1. ^{13}C NMR data of paniculidines A, B and C (100 MHz, δppm, TMS as internal standard)

C	A	B	C
2	121.3 *d*	120.3 *d*	121.2 *d*
3	114.9 *s*	112.9 *s*	116.1 *s*
4a	127.3 *s*	123.9 *s*	127.3 *s*
4	118.5 *d*	119.0 *d*	118.6 *d*
5	121.8 *d*	122.2 *d*	121.5 *d*
6	118.7 *d*	119.2 *d*	118.7 *d*
7	111.0 *d*	108.2 *d*	111.1 *d*
7a	136.3 *s*	132.7 *s*	136.2 *s*
1′	177.3 *s*	68.0 *t*	67.9 *t*
2′	38.9 *d*	35.5 *d*	35.2 *d*
3′	33.9 *t*	33.4 *t*	33.3 *t*
4′	22.6 *t*	22.5 *t*	22.3 *t*
5′	16.8 *q*	16.6 *q*	16.4 *q*
OMe	51.3 *q*	65.3 *q*	—

Plant materials. M. paniculata was collected near Heng-Chun in Taiwan, and identified by one of the authors (F.-C. H.). A voucher specimen is on deposit at the Herbarium of the University Museum, University of Tokyo.

Extraction and isolation. The air-dried and ground root bark of *M. paniculata* (13 kg) was extracted with $CHCl_3$ (18 l) at room temp. for 24 hr. The soln was evapd under red. pres. to give the syrupy extract (110 g). The extract (50 g) was chromatographed over silica gel (680 g) with C_6H_6–Me_2CO mixtures as eluant increasing the amount of Me_2CO stepwise. Fractions (13.5 g) eluted with C_6H_6–Me_2CO (24:1) were repeatedly subjected to CC over silica gel on elution with C_6H_6–$CHCl_3$ mixtures of increasing polarity, yielding **1** (760 mg), **2** (150 mg), **3** (10 mg) and **4** (50 mg). Fractions eluted with C_6H_6–Me_2CO (6:1) were repeatedly chromatographed over silica gel with *n*-hexane–$CHCl_3$–*iso*-PrOH (9:1:1) to give **5** (60 mg).

Paniculidine A (**1**). $[\alpha]_D^{24}$ −32° ($CHCl_3$, *c* 0.1); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3480 (NH), 2940, 1728 (COOMe), 1452; UV λ_{max}^{EtOH} nm (log ε): 277sh (3.75), 283 (3.78), 292 (3.71); ^1H NMR (400 MHz, $CDCl_3$): δ1.12 (3H, *d*, *J* = 7 Hz, 5′-Me), 1.72 (1H, *ddt*, *J* = 7, 14, 8 Hz, 3′-H(H)), 2.01 (1H, *ddt*, *J* = 7, 14, 8 Hz, 3′-H(H)), 2.46 (1H, *ddq*, *J* = 7, 7, 7 Hz, 2′-H), 2.66 (2H, *t*, *J* = 8 Hz, 4′-H_2), 3.56 (3H, *s*), 6.80 (1H, *br d*, *J* = 2.5 Hz, 2-H), 7.01 (1H, *ddd*, *J* = 8, 8, 1.5 Hz, 6-H), 7.07 (1H, *ddd*, *J* = 8, 8, 1.5 Hz, 5-H), 7.19 (1H, *dd*, *J* = 8, 1.5 Hz, 4-H), 7.50 (1H, *dd*, *J* = 8, 1.5 Hz), 7.95 (1H, *br s*, exchangeable with D_2O, 1-H); EIMS *m/z* (rel. int.): 231 $[M]^+$ (25), 144 $[M-MeCHCOOMe]^+$ (15), 130 $[M-CH_2CH(Me)COOMe]^+$ (100); HRMS Found: 231.1208. $C_{14}H_{17}NO_2$ requires: 231.1256.

Paniculidine B (**2**). $[\alpha]_D^{20}$ +21° ($CHCl_3$, *c* 0.025); IR ν_{max}^{neat} cm^{-1}: 3350 (OH), 2920, 1450, 1230; UV λ_{max}^{EtOH} nm (log ε): 279 (3.69), 292 (3.71); ^1H NMR (400 MHz, $CDCl_3$): δ0.98 (3H, *d*, *J* = 7.0 Hz, 5′-Me), 1.48 (1H, *dddd*, *J* = 5.5, 8.0, 10.0, 13.5 Hz, 3′-H(H)), 1.69 (1H, *m*, 2′-H), 1.81 (1H, *dddd*, *J* = 5.5, 6.3, 10.0, 13.5 Hz, 3′-H(H)), 2.67 (1H, *dddd*, *J* = 1.0, 6.3, 10.0, 15.0 Hz, 4′-H(H)), 2.78 (1H, *dddd*, *J* = 1.0, 5.5, 10.0, 15.0 Hz, 4′-H(H)), 3.43 (1H, *dd*, *J* = 6.5, 11.0 Hz, 1′-H(H)), 3.50 (1H, *dd*, *J* = 5.5, 11.0 Hz, 1′-H(H)), 3.99 (3H, *s*, OMe), 7.02 (1H, *br d*, *J* = 1.0 Hz, 2-H), 7.08 (1H, *ddd*, *J* = 8.5, 8.5, 1.5 Hz, 6-H), 7.21 (1H, *ddd*, *J* = 8.5, 8.5, 1.5 Hz, 5-H), 7.37 (1H, *ddd*, *J* = 8.5, 1.5, 0.7 Hz, 4-H), 7.56 (1H, *ddd*, *J* = 8.5, 1.5, 0.7 Hz, 7-H); EIMS *m/z* (rel. int.): 233 $[M]^+$ (35), 160 $[M-CH_2CH(Me)CH_2OH]^+$ (100), 130 (62), 129 $[M-CH_2CH(Me)CH_2OH-OMe]^+$ (31); HRMS Found: 233.1419. $C_{14}H_{19}NO_2$ requires: 233.1416.

Paniculidine C (**3**). $[\alpha]_D^{20}$ +45° ($CHCl_3$; *c* 0.035); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3480 (NH), 3400 (OH), 2920, 1453; UV λ_{max}^{EtOH} nm (logε); 278sh (3.68), 284 (3.76), 292 (3.71); ^1H NMR (400 MHz, $CDCl_3$): δ1.03 (3H, *d*, *J* = 7.0 Hz, 5′-Me), 1.55 (1H, *dddd*, *J* = 5.7, 8.1, 9.9, 13.2 Hz, 3′-H(H)), 1.74 (1H, *m*, 2′-H), 1.87 (1H, *dddd*, *J* = 5.7, 6.4, 9.9, 13.2 Hz, 3′-H(H)), 2.75 (1H, *dddd*, *J* = 0.7, 6.4, 9.9, 14.7 Hz, 4′-H(H)), 2.86 (1H, *dddd*, *J* = 0.7, 5.7, 9.9, 14.7 Hz, 4′-H(H)), 3.50 (1H, *dd*, *J* = 6.4, 10.3 Hz, 1′-H(H)), 3.57 (1H, *dd*, *J* = 5.7, 10.3 Hz, 1′-H(H)), 6.98 (1H, *br*, 2-H), 7.11 (1H, *ddd*, *J* = 7.8, 7.0, 1.1 Hz, 6-H), 7.18 (1H, *ddd*, *J* = 8.2, 7.0, 1.1 Hz, 5-H), 7.35 (1H, *ddd*, *J* = 8.2, 1.1, 0.7 Hz, 4-H), 7.61 (1H, *ddd*, *J* = 7.8, 1.1, 0.7 Hz, 7-H) EIMS *m/z* (rel. int.): 203 $[M]^+$ (27), 131 (22), 130 $[M - CH_2CH(Me)CH_2OH]^+$ (100); HRMS Found: 203.1322. $C_{13}H_{17}NO$ requires: 203.1310.

Hydrolysis of compound **1**. Compound **1** (20 mg) was hydrolysed under reflux in 3% methanolic KOH (10 ml) for 1 hr, and the reaction mixture was neutralized and extracted with AcOEt. The organic layer was evaporated, and then recrystallized from *n*-hexane to afford colourless prisms (13 mg), mp 99–101°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3480 (NH), 2940, 1705 (COOH), 1452; EIMS *m/z* (rel. int.): 217 $[M]^+$ (25), 143 (16), 130 $[M - CH_2CH(Me)COOH]^+$ (100). (Found: C, 71.99; H, 6.91; N, 6.37. Calc. for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45%).

Conversion of compound **1** *to* **3**. A soln of **1** (100 mg) in dry THF (10 ml) was added under stirring to an ice-cold THF soln (40 ml) of $LiAlH_4$ (50 mg). The mixture was kept at 0° for 1 hr, and then worked-up in the usual manner to give a colourless oil in a partially racemic form, which was identical to **3**. $[\alpha]_D^{21}$ +18° ($CHCl_3$, *c* 0.2).

Conversion of compound **2** *to* **3**. A mixture of **2** (20 mg), 10% Pd-C (20 mg) and MeOH (12 ml) was shaken in the hydrogen atmosphere for 3 hr. The filtration of the mixture followed by evaporation afforded the oily residue (18 mg), which was identical to **3**. $[\alpha]_D^{21}$ +48° ($CHCl_3$, *c* 0.05).

Preparation of (R)-MTPA ester of paniculidine C. α-Methoxy-α-trifluoromethyl-phenylacetyl chloride was prepared by refluxing a mixture of the corresponding acid (100 mg) and oxalyl chloride (0.5 ml) in dry benzene (10 ml) for 48 hr. A mixture of MTPA chloride and **3** (3 mg) in dry pyridine (5 ml) was stirred at 60° for 24 hr, and the solvent was removed under vacuum. The residue was subjected to prep. TLC (silica gel; C_6H_6) to give a MTPA ester. ^1H NMR (100 MHz, $CDCl_3$): δ1.01, (3H, *d*, *J* = 6.0 Hz), 1.4–2.1 (3H, *m*), 2.77 (2H, *br t*, *J* = 7.5 Hz), 3.52 (3H, *br*), 4.14 (1H, *dd*, *J* = 10.5, 6.2 Hz), 4.32 (1H, *dd*, *J* = 10.5, 5.2 Hz), 6.91 (1H, *br*), 7.0–7.6 (4H, *m*), 7.90 (1H, *br*).

Ethyl 2-methyl-4-(2-carboethoxy-3-indolyl)-butyrate. The ice-cold solns of benzenediazonium chloride, generated from aniline (1.54 g), $NaNO_2$ (1.12 g) and concd HCl (4 ml), and KOH (4 g in 10 ml H_2O) were added alternately to the mixture of 2-carboethoxy-6-methyl-cyclohexane-1-one (2.72 g) and ice (10 g) so that the alkali was always in excess. The reaction mixture was acidified with concd HCl, extracted with AcOEt, and the AcOEt layer was evapd to dryness. The resulting phenylhydrazone half ester of 6-methyl-2-ketopimelic acid (dark reddish gum) was dissolved in 50 ml of EtOH containing 5 ml of concd H_2SO_4. The mixture was refluxed for 2 hr, poured into H_2O, and extracted with AcOEt. The organic layer was concentrated, and the residue was subjected to CC on elution with C_6H_6 to furnish ethyl 2-methyl-4-(2-carboethoxy-3-indolyl)-butyrate (1.28 g), colourless needles from *n*-hexane, mp 49–50°. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3460 (NH), 2980, 1715, 1450, 1379. (Found: C, 68.02; H, 7.37; N, 4.41. Calc. for $C_{18}H_{23}O_4N$: C, 68.12; H, 7..31; N, 4.41%).

dl-*Paniculidine A*. The ester prepared above (1.20 g) was hydrolysed with 3% methanolic KOH to give quantitatively 2-methyl-4-(2-carboxy-3-indolyl)-butyric acid, colourless needles from AcOH, mp 184–185°. The dibasic acid (1.0 g) was decarboxylated by heating at 220° until the evolution of CO_2 ceased, and the resulting residue was dissolved in 3% aq. NaOH. The alkaline soln was washed with Et_2O and acidified with concd HCl to furnish ppt. (0.65 g). The ppt. was collected and repeatedly recrystallized from aq. EtOH to give colourless prisms of mp 99–100°, which was identified with the one obtained from hydrolysis of **1**. The synthetic 2-methyl-4-(3-indolyl)-butyric acid was methylated with CH_2N_2 to give *dl*-paniculidine A in quantitative yield, which was identical to natural paniculidine A in the IR, ^1H and ^{13}C NMR spectra. *dl*-Paniculidine C was also prepared by reduction of *dl*-paniculidine A with $LiAlH_4$ according to the procedure stated above.

Osthol (**4**). Colourless needles, mp 82–83° (*n*-hexane); ^1H NMR (100 MHz, $CDCl_3$): δ1.67 (3H, *s*), 1.84 (3H, *s*), 3.52 (2H, *br d*, *J* = 7.3 Hz), 3.92 (3H, *s*), 5.22 (1H, *br t*, *J* = 7.3 Hz), 6.23 (1H, *d*, *J* = 9.5 Hz), 6.82 (1H, *d*, *J* = 8.5 Hz), 7.29 (1H, *d*, *J* = 8.5 Hz), 7.61 (1H, *d*, *J* = 9.5 Hz); EIMS *m/z* (rel. int.): 244 $[M]^+$ (100), 229 (75), 213 (33), 201 (52), 189 (55), 131 (29).

Murralongin (**5**). Colourless needles, mp 137–138° (Et_2O); IR ν_{max}^{KBr} cm^{-1}: 1725 (CHO), 1655, 1600, 1490; UV λ_{max}^{EtOH} nm: 233, 324; ^1H NMR (100 MHz, $CDCl_3$): δ1.79 (3H, *s*), 2.43 (3H, *s*), 3.84 (3H, *s*), 6.23 (1H, *d*, *J* = 9.5 Hz), 6.90 (1H, *d*, *J* = 8.5 Hz), 7.45 (1H, *d*, *J* = 8.5 Hz), 7.65 (1H, *d*, *J* = 9.5 Hz), 10.22 (1H, *s*); ^{13}C NMR (25 MHz, $CDCl_3$): δ19.8 (*q*), 24.8 (*q*), 56.2 (*q*), 107.6 (*d*), 112.8 (2 × *s* and *d*), 128.5 (*d*), 129.0 (*s*), 143.6 (*d*), 152.8 (*s*), 159.5 (*s*), 159.8 (*s*), 160.9 (*s*), 188.6 (*d*); EIMS *m/z* (rel. int.): 258 $[M]^+$ (100), 229 (21), 215 (94), 214 (24), 201 (27), 199 (40), 187 (57), 171 (32).

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