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CONSTITUENTS OF THE ROOT OF *DICTAMNUS ALBUS* L.

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Abstract—In addition to several known constituents and their artefacts, the root of *Dictamnus albus L.* has yielded the new natural products, isomaculosidine (9) and preskimmianine (15, R = Me).[1]*

In connection with our interest[2] in the biogenetic origin of fraxinellone (1), we have made a thorough examination of the root of the plant in the hope of finding intermediates in the conversion of limonin (2) to fraxinellone (1), since both of these compounds are constituents of this plant.

Dictamnus albus L., a member of the Rutaceae, occurs widely and, because of ignition of the gas given off by the plant, it has been known[3] as the 'gas plant' or the 'burning bush.' Considerable claims have been made for the powdered root as a folk remedy[3] and the plant has a photosensitising action on the skin. Previous chemical studies have shown the plant to contain the limonoids limonin (2),[3-6] fraxinellone (1)[2,3,7] and obacunone (3)[8] as well as a lactone dictamnolide,[8] $C_{28}H_{30-32}O_9$ of unknown structure. The furanoquinoline alkaloids dictamnine (4, R = Me)[3,9,10] skimmianine (5, R = Me)[10-12] and γ-fagarine (6, R = Me)[13,14] have been isolated from the plant and various amines,[15] anthocyanins,[16] monoterpenes[16] and flavonol glycosides[16,17] have also been found. Further constituents are the furocoumarin bergapten (7)[18] and the coumarin auraptene (8).[19]

We have extracted the powdered root of *Dictamnus albus L.*,[20] by the method of Pailer *et al.*[7] The root was extracted with ethanol in a soxhlet and the extracts were treated with base to saponify any lactones present. The non base-soluble material was separated into acid-soluble and neutral fractions.

Chromatography of the acid-soluble fractions on silica gel yielded four compounds, three of which were quickly identified from UV and NMR spectroscopy as O-ethylnordictamnine (4, R = Et), O-ethylnor-γ-fagarine (6, R = Et) and O-ethylnorskimmianine (5, R = Et). These were readily converted into the known[21] natural products dictamnine (4, R = Me), γ-fagarine (6, R = Me) and skimmianine (5, R = Me) respectively on treatment with acidic methanol. The O-ethyl compounds can be assumed to be artefacts of the isolation procedure, since treatment of dictamnine (4, R = Me),[22] skimmianine (5, R = Me)[23] and γ-fagarine (6, R = Me)[23] with ethanolic potassium hydroxide is known to result in exchange of this type and other furanoquinoline alkaloids[24] behave in similar fashion.

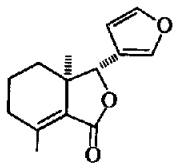
The fourth neutral compound, $C_{14}H_{13}NO_4$, m.p. 170–172° had an NMR spectrum characteristic of a linear furanoquinoline in the iso-series[25] with α- and β-furan protons ($J = 2$ Hz) at 2·76 and 3·01 τ, *meta* coupled aromatic protons at 2·42 and 3·28 τ, and OMe and N-Me singlets at 5·90, 6·08 and 6·10 τ. Isomaculosidine (9) m.p. = 167–168°, a known degradation product of the alkaloid maculosidine (10),[26,27] has a reported NMR spectrum[25] which corresponds well with these data but the UV spectrum has not been reported. That we have found isomaculosidine for the first time as a natural product was proved by hydrogenolysis to the hydroxyquinolone (11, R = H) which had a characteristic[28] blue shift in base in the UV spectrum. The hydroxyquinolone (11, R = H) was methylated by diazomethane to 11 (R = Me) the structure of which was proven by the following synthesis.

Reaction of 2,4-dimethoxyaniline with diethylethylmalonate yielded the quinolone (12, R = H).[26] Attempts to methylate this quinolone with methyl iodide and sodium hydride in benzene resulted mainly in alkylation of the ambident anion at position 3, the major product (13) having both ketonic and amide CO bands in the IR spectrum and C-Me and N-Me singlets at 8·60 τ and 6·51 τ respectively in the NMR spectrum. There was a smaller amount of 11 (R = Me) present, identical in its spectra to the degradation product of isomaculosidine. This compound, the product of N,O-dialkylation was the sole product when the reaction was carried out with dimethylsulphate and potassium hydroxide in dimethylformamide.

Isofuranoquinoline alkaloids are very rare in nature but there is no reason to suppose that our extraction procedure could have produced isomaculosidine as an artefact, and so the compound must be a natural product.

The neutral fraction of the non-base soluble portion of the extract of the root of *D. albus* was chromatographed to yield fraxinellone, $C_{14}H_{16}O_3$,

*The implications of the structure of preskimmianine in the biosynthesis of skimmianine are discussed in reference 1, and later work is reported in reference 41.



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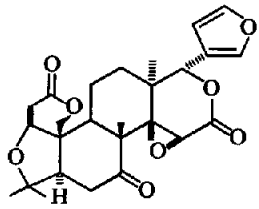

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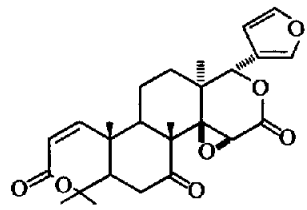

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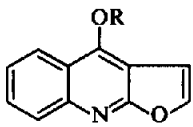

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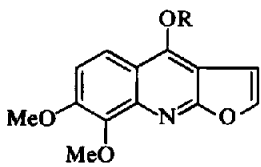

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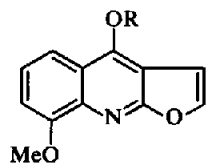

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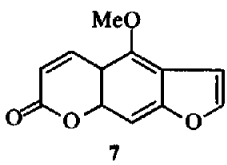

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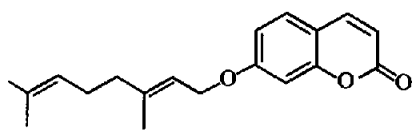

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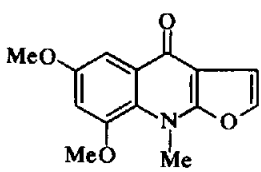

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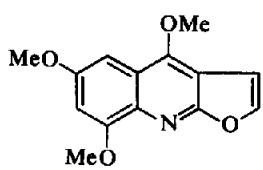

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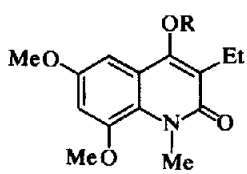

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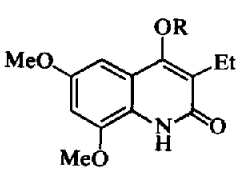

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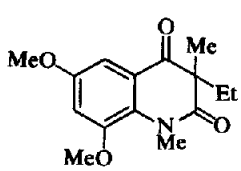

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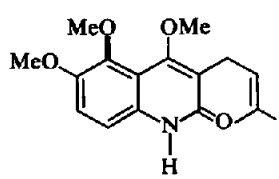

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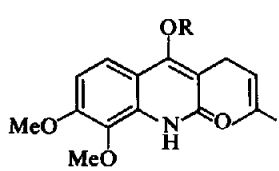

15

m.p. 117° $[\alpha]_D$ −45·6°, and a solid $C_{29}H_{50}O$, m.p. 143–144°, $[\alpha]_D$ −35·3°, which formed an acetate, m.p. 137–138°, $[\alpha]_D$ −40·1°, on treatment with acetic anhydride and pyridine. This latter compound was concluded to be the sitosterol (m.p. 142–143°, $[\alpha]_D$ −34·6°; acetate m.p. 137–138°, $[\alpha]_D$ −40·1°) which was isolated by Kuwada from the root of *Dictamnus albus*.[29] A further solid material, m.p. 69–71°, was a mixture of fatty acids with the highest molecular weight acid having molecular weight 424. Esterification with diazomethane followed by GLC analysis showed the solid to be a mixture of seventeen esters in two homologous series.[30]

The final product of this neutral fraction proved to be a new alkaloid, $C_{17}H_{21}NO_4$, m.p. 151–152°, with NH and amide absorption in the IR spectrum and an UV spectrum typical of a 2-quinolone.[31,32] The NMR spectrum was very informative with an exchangeable (N—H) proton at 0·85 τ, two *ortho* coupled aromatic protons at $\tau = 2{\cdot}52$ and 3·15 (J 9 Hz), methoxyl singlets at $\tau = 6{\cdot}03$(6H) and 6·06(3H), vinylic Me singlets at $\tau = 8{\cdot}20$ and 8·31 and a one-proton triplet at 4·69 τ ($J = 6{\cdot}5$ Hz) coupled to a two-proton doublet at $\tau = 6{\cdot}63$. From these data only two structures **14** or **15** (R = Me) are possible for the alkaloid.

Structure **15** (R = Me) has the same OMe substitution pattern as skimmianine (**5**, R = Me) and skimmianine is a constituent of *Dictamnus albus L.* Furanoquinoline alkaloids have long been assumed[33–35] to be derived from isopentenyl precursors, an assumption which has recently been proven by the radioactive feeding work of Grundon[36,37] and so we assumed that **15** (R = Me) was the more likely of the two possible structures and commenced upon the following synthesis of the compound.

1-Chloro-3-methylbut-2-ene can be made from 3-methylbut-2-enol by the method of Grundon[38] but we find that it can be synthesised much more conveniently by addition of hydrochloric acid to isoprene.[39] The chloride was reacted with sodium diethylmalonate to yield diethyl-2-(3-methylbut-2-enyl)-malonate[38] 2,3-Dimethoxyaniline was prepared by Hofmann rearrangement of 2,3-dimethoxybenzamide using a modification of the method of Mauthner.[40]

Condensation of 2,3-dimethoxyaniline with diethyl-2-(3-methylbut-2-enyl)-malonate in refluxing diphenyl ether yielded the 4-hydroxycarbostyril (**15** R = H) as prisms, m.p. 214–216° which had the expected spectral data. Treatment of **15** (R = H) with diazomethane afforded 3-(3-methylbut-2-enyl)-4,7,8-trimethoxy-2-quinolone (**15**, R = Me) which was identical in all respects to the alkaloid from *Dictamnus albus L.* Because of its probable implication in the biosynthesis of skimmianine* we have named this alkaloid preskimmianine.

The base-soluble portion of the saponification of the *Dictamnus albus L.* extract yielded limonin (**2**) and fraxinellone (**1**) as the only characterisable products.

EXPERIMENTAL

M.ps were determined on a Kofler block, and are uncorrected. IR spectra were determined on a Perkin-Elmer 237 instrument and UV spectra were recorded on a Unicam SP800 spectrophotometer for MeOH solns (unless otherwise stated). NMR spectra were recorded on Varian A60, T60 or HA 100 instruments for $CDCl_3$ solns (unless otherwise stated), mass spectra were recorded on Hitachi RMU6 or AEI MS9 instruments, and optical rotations were determined on a Perkin-Elmer 141 polarimeter. Microanalyses were performed by Mr. and Mrs. A G. Olney.

Extraction of the root of Dictamnus Albus L. Dried powdered root of *Dictamnus albus L*[20] (7·5 Kg) was continuously extracted in a soxhlet apparatus for 72 hr with hot EtOH (95%; 15 l.). The volume was reduced to 4 l. and the soln was made alkaline by addition of solid KOH (500 g). The alkaline soln was left overnight at room temp and refluxed for 30 min to complete saponification of any lactones present. Water (2 l.) was added and the alcohol was removed *in vacuo*. The soln was filtered and extracted with ether (5 × 500 ml) The extracts were washed with 2N HCl (3 × 250 ml) and water, and dried (Na_2SO_4). The solvent was removed *in vacuo* to yield the *non-saponifiable neutral fraction* (50·1 g).

The acidic wash above was neutralised with sat $NaHCO_3$ aq soln and extracted with ether. The extracts were dried (Na_2SO_4) and the solvent removed *in vacuo* to yield the *non-saponifiable acid-soluble fraction* (6·1 g).

The original KOH soln was acidified to pH 2 with conc. HCl at ice-bath temp and the soln was extracted with chloroform (5 × 250 ml). The chloroform extracts were washed first with sat $NaHCO_3$ aq, then with 2N NaOH and finally with water. The chloroform extracts were then dried (Na_2SO_4) and the solvent was removed *in vacuo* to yield the *saponifiable neutral fraction* (1·4 g).

The $NaHCO_3$ wash from the saponifiable neutral fraction was neutralised with dil HCl and exhaustively extracted with chloroform. The chloroform extracts were washed with water and dried (Na_2SO_4). The solvent was removed *in vacuo* to yield the *carboxylic acid fraction* (3·2 g).

The NaOH wash from the saponifiable neutral fraction was neutralised and worked up in the same way as the $NaHCO_3$ wash to yield the '*phenolic*' *fraction* as a brown semi-solid (2·2 g).

(1) *The non-saponifiable acid-soluble fraction* was carefully chromatographed on silica gel. Elution with light petroleum (60–80°)–benzene (1:2) yielded *O-ethyl-nordictamine* (**4**, R = Et) as a white solid which was recrystallised from EtOH as needles (380 mg), m.p. 95–96° (lit.[22] 95°) (Found: C, 73·12; H, 5·49; N, 6·95; $C_{13}H_{11}NO_2$ requires: C, 73·22; H, 5·20; N, 6·57%), λ_{max} = 236 (4·73), 242 (4·70), 300 (sh, 3·87) 308 (3·92), 316 (3·91), 326 (sh, 3·79) and 330 nm. (log ϵ 3·88) shifting to λ_{max} = 241 (4·82), 299 (sh, 3·79), 311 (3·91), 328 (3·90), and 341 nm (sh, log ϵ 3·70) in acid. The NMR spectrum showed absorption at τ 1·70–2·74 (4H, m, aromatics), 2·43 (1H, d, 3 Hz, α-furan), 3·06 (1H, d, J = 3 Hz, β-furan), 5·34 (2H, q, J = 7·5 Hz, OCH_2CH_3) and 8·45 (3H, t, J = 7·5 Hz, Et).

Elution with benzene yielded *O-ethyl-nor-γ-fagarine* (**6**, R = Et) as a solid (200 mg) which was crystallised

from EtOH as needles, m.p. 142–143° (lit.[23] m.p. 143°), (Found: C, 69·50; H, 5·69; N, 5·74; $C_{14}H_{13}NO_3$ requires: C, 69·12; H, 5·39; N, 5·76%) λ_{max} = 243 (4·64), 260 (3·70), 270 (3·44), 298 (3·55), 311 (3·64), 325 (3·61) and 338 nm (log ϵ 3·58) shifting to λ_{max} = 249 (4·64), 270 (sh, 3·44) 280 (sh, 3·34) 300 (3·34) 315 (3·47) and 342 nm (log ϵ 3·60) in acid. The NMR spectrum showed absorption at τ 2·12 (1H, d × d, J_1 = 8, J_2 = 2 Hz, aromatic), 2·66 (1H, t, J = 8 Hz, aromatic), 2·99 (1H, d × d, J_1 = 8, J_2 = 2 Hz aromatic), 2·42 (1H, d, J = 3 Hz, α-furan) 3·07 (1H, J = 3 Hz, β-furan), 5·35 (2H, q, J = 7·5 Hz, —OCH_2CH_3), 5·96 (3H, s, OCH_3), and 8·47 (3H, t, J = 7·5 Hz, —OCH_2CH_3).

Elution with benzene:ether (95:5) yielded *O-ethylnorskimmianine* (**5**, R = Et)(126 mg) which was recrystallised from EtOH as needles m.p. 135–136° (lit.[23] m.p. = 138°) (Found: C, 66·03; H, 5·52, N, 5·10; $C_{15}H_{15}NO_4$ requires: C, 65·92; H, 5·53; N, 5·13%) λ_{max} = 240 (sh, 4·77), 248 (4·96), 268 (3·45), 306 (sh, 3·77), 319 (3·91), 331 (3·91), and 344 (sh, log ϵ 3·77), shifting in acid to λ_{max} = 252 (4·92), 279 (sh, 3·71) 308 (sh 3·68) 321 (3·90) and 348 nm (log ϵ 3·93). The NMR spectrum showed absorption at τ 1·96 (1H, d, J = 9 Hz, aromatic), 2·81 (1H, d, J = 9 Hz, aromatic), 2·44 (1H, d, J = 3 Hz, α-furan), 3·08 (1H, d, J = 3 Hz, β-furan), 5·88 (3H, s, OCH_3), 5·98 (3H, s, OCH_3), 5·33 (2H, q, J = 7 Hz, OCH_2CH_3) and 8·45 (3H, t, J = 7 Hz, OCH_2CH_3).

Elution with benzene:ether (4:1) afforded *isomaculosidine* (**9**) (45 mg) which was crystallised from EtOH as needles, m.p. 170–172° (lit.[26,27] m.p. 167–168°) (Found: C, 64·81; H, 5·12; N, 5·63; $C_{14}H_{13}NO_4$ requires: C, 64·86; H, 5·05; N, 5·40%), λ_{max} = 249 (4·29) 262 (sh, 4·07), 290 (3·36) 330 (sh, 3·50), 345 (3·69) 360 nm (3·69), shifting in acid to λ_{max} = 256 (4·37) 306 (sh, 3·42) 317 (3·52), 347 (sh, 3·46) and 360 nm (log ϵ 3·42). The NMR spectrum exhibited absorption at τ = 2·76 (1H, d, J = 2 Hz, aromatic) 3·01 (1H, d, J = 2 Hz, aromatic), 2·42 (1H, d, J = 3 Hz, α-furan), 3·28 (1H, d, J = 3 Hz, β-furan), 5·90 (3H, s, OCH_3) 6·08 (3H, s, OCH_3) and 6·10 (3H, s, NCH_3).

(2) *The non-saponifiable neutral fraction* was chromatographed on neutral grade III alumina. Elution with benzene yielded **1** (10·2 gm) which was recrystallised from EtOH as needles m.p. 117°, $[\alpha]_D^{EtOH}$ −45·6° (lit.[7] m.p. 116°, $[\alpha]_D$ −44° (Found: C, 72·18; H, 7·08; $C_{14}H_{16}O_3$ requires: C, 72·39; H, 6·94%), ν_{max}^{NUJOL} = 1745 cm^{-1} (unsaturated γ-lactone), λ_{max} = 215 and 315 nm. The NMR and mass spectra were as expected from the lit.[7]

The remaining fractions from the column were gums but on rechromatography on grade II alumina, elution with light petroleum (60–80°) afforded fraxinellone (0·1 g) and elution with light petroleum:benzene (1:1) afforded a white crystalline solid (850 mg) which was recrystallised from EtOH as needles, m.p. 143–144° $[\alpha]_D^{CDCl_3}$ = −35·3° (Found: C, 83·69; H, 11·88; $C_{28}H_{50}O$ requires: C, 83·99; H, 12·15%); ν_{max}^{NUJOL} = 3350 cm^{-1} (OH). Treatment of this compound with Ac_2O in dry pyridine overnight at room temp afforded the acetate, ν_{max}^{NUJOL} = 1735 cm^{-1}, which was recrystallised from aqueous EtOH as plates, m.p. = 137–138° $[\alpha]_D^{CHCl_3}$ = −40·1°. The sitosterol previously isolated from *D. albus*[29] had m.p. 142–143° $[\alpha]_D$ = −34·6°; acetate, m.p. 137–138° $[\alpha]_D$ = −40·1°.

Further elution with light petroleum (60–80°):benzene (1:1) gave a waxy solid (5·3 g) which was 'recrystallised' from benzene with m.p. 69–71°. The NMR spectrum showed but a sharp singlet at τ 8·74 and ν_{max} = 3000 (H-bonded OH), and 1700 cm^{-1} (CO_2H). The highest ion in the mass spectrum was *m/e* = 424. This fatty acid material was esterified by treatment with ethereal diazomethane at room temp and the mixture of esters was subjected to GLC on a 5 ft column of 5% carbowax 20 M on 100–120 mesh chromosorb G at 225° with a flow rate of 50 ml/min N_2, using a model 64 Pye 104 chromatograph. There were 17 major components in the mixture and the plot of log (Rt) with number of carbons (arbitrarily chosen) showed two parallel straight lines. This indicated that these compounds formed two homologous series of fatty esters.[30]

Elution with benzene:ether [95:5] yielded a colourless solid (33 mg) which crystallised from MeOH as plates m.p. 151–152° (Found: C, 67·59; H, 6·99; N, 4·72; $C_{17}H_{21}NO_4$ requires: C, 67·31; H, 6·98; N, 4·62%); *m/e* = 303 [parent], 288 [P—Me], 272 [P—OMe] 260 [P—NHCO], 248 [P—CH=C=Me_2]; ν_{max}^{NUJOL} = 3100 (NH), 1635 (2-quinolone) and 1600 cm^{-1} (aromatic C=C), λ_{max} = 218 (4·67), 232 (sh, 4·43), 249 (4·22), 257 (4·23), 287 (3·91), 297 (3·95), 309 (4·00) 321 (4·09) and 334 nm (log ϵ 3·99) unchanged on addition of acid or base. The NMR spectrum is reported in the discussion and we have named the compound *preskimmianine* (**15**, R = Me).

(3) *The carboxylic acid fraction* yielded no isolable pure compounds on chromatography.

(4) *The 'phenolic'* fraction was chromatographed on silica gel to yield limonin (0·79 g), m.p. 290–292° $[\alpha]_D^{acetone}$ −122° (lit.[5] m.p. −298°, $[\alpha]_D$ = −125°).

(5) *The saponifiable neutral fraction* on chromatography on silica gel yielded further amounts of limonin (28 mg) and fraxinellone (210 mg) but no other compounds.

Treatment of the alkaloids (**4**, **5** *and* **6**, R = Et) *with acidic methanol.* In a typical experiment, the alkaloid (50 mg) was dissolved in MeOH (30 ml) containing 5N HCl (0·3 ml) and heated under reflux for 5 days. The alcohol was removed *in vacuo*, water was added and the aqueous soln was extracted with chloroform. The extracts were dried [Na_2SO_4] and the solvent removed *in vacuo* give a 70 to 90% yield of the product.

Alkaloid **4** (R = Et) yielded dictamnine which was recrystallised from aqueous EtOH as needles, m.p. 130–132°, undepressed on admixture with a sample of natural dictamnine.[21]

Alkaloid **5** (R = Et) yielded skimmianine which was recrystallised from MeOH as needles m.p. 174–176°, undepressed on admixture with a sample of the natural product.[21]

Alkaloid **6** (R = Et) yielded γ-fagarine which was recrystallised from EtOAc/ether as prisms, m.p. 139–140° (lit.[42] m.p. 140–141°).

Hydrogenolysis of isomaculosidine (**9**). Isomaculosidine (7 mg) was dissolved in abs EtOH (10 ml) and reduced with H_2 in the presence of prereduced Adams PtO_2. When uptake of H_2 had ceased, the soln was filtered through celite and the solvent was removed *in vacuo*, to yield **11** (R = H) as a crystalline solid (5·4 mg), m.p. 212–216°, ν_{max}^{NUJOL} = 1615 cm^{-1} (amide), λ_{max} = 233, 253, 271 (sh), 282, 292, 324, 338, 351 (sh) nm which shifted to λ_{max} = 233 (sh), 240 (sh) 252 (sh), 309, 326 (sh) 343 (sh) nm in alkali. The NMR spectrum (DMSO-d_6) showed absorption at τ = 2·87 (1H, d, J = 2·5 Hz, aromatic), 3·17 (1H, d, J = 2·5 Hz, aromatic), 6·08 (3H, s), 6·14 (3H, s) and 6·23 (3H, s) (N—CH_3 and OCH_3), 7·34 (2H, q, J = 7 Hz, O—CH_2CH_3) and 8·96 (3H, t, J = 7 Hz, —OCH_2-CH_3).

Methylation of **11** (R = H). The product from the above reaction (5·4 mg) was dissolved in MeOH (15 ml) and treated with an excess of an ethereal soln of diazo-

methane at room temp for 12 hr. The solvent was removed *in vacuo* to yield a semi-solid with spectral data identical to an authentic sample of **11** (R = Me) prepared as in the following experiments.

3-Ethyl-4-hydroxy-6,8-dimethoxy-2-quinolone (**12**, R = H) was prepared from diethyl ethylmalonate and 2,4-dimethoxyaniline by the method of Prager *et al* [26]

Methylation of 3-ethyl-4-hydroxy-6,8-dimethoxy-2-quinolone (**12**, R = H)

(1) *Methyl iodide, sodium hydride in benzene/dimethylformamide.* Compound **12** (R = H; 250 mg) and NaH (50 mg) were suspended in dry benzene (40 ml), refluxed for 4 hr under N_2 and allowed to cool to room temp. Dimethylformamide (4 ml) and MeI (2 ml) were added and the mixture was refluxed for 12 hr under N_2. The mixture was cooled, poured onto a mixture of ice and water and extracted with chloroform. The extracts were dried (Na_2SO_4) and the solvent removed *in vacuo* to yield a yellow oil (200 mg) shown by NMR and TLC to consist of two components only. Repeated fractional recrystallisation from light petroleum (b.p. 60–80°) afforded pure samples of the two components.

The major component (**13**) crystallised as bright yellow prisms, m p. 97–99° (Found: C, 65·08; H, 6·76; N, 4·96; $C_{15}H_{19}NO_4$ requires: C, 64·96; H, 6·91; N, 5·05%); *m/e* = 277; $\nu_{max}^{CHCl_3}$ = 1693 (ketone), 1658 cm^{-1} (amide); λ_{max} = 244 (4·39), 288 (3·25), 374 nm (log ε 3·40) with no change on addition of acid or base. The NMR spectrum had absorption at τ 3·01 (1H, d, J = 3 Hz, 1H, aromatic), 3·24 (1H, d, J = 3 Hz, aromatic) 6·13 (3H, s), 6·19 (3H, s) and 6·51 (3H, s) (N-Me and OMe), 8·13 (2H, q, J = 7·5 Hz, C—CH_2CH_3), 8·60 (3H, s, C—Me) and 9·18 (3H, t, J = 7·5 Hz, CH_2CH_3).

The minor component **11** (R = Me) crystallised as pale yellow prisms, m.p. 119–121°, (Found: C, 65·09; H, 6·88; N, 4·85; $C_{15}H_{19}NO_4$ requires: C, 64·96; H, 6·91; N, 5·05%); *m/e* = 277; $\nu_{max}^{(HCl_3}$ = 1640 cm^{-1} (amide), λ_{max} = 218 (4·33), 236 (4·34), 257 (4·24), 282 (3·74), 292 (3·69), 331 (sh, 3·32) 349 (3·49) and 363 nm (3·40) with no change on addition of acid or base. The NMR spectrum had absorption at τ = 3·14 (1H, d, J = 3 Hz, aromatic), 3·34 (1H, d, J = 3 Hz, 1H, aromatic), 6·11 (3H, s) 6·13 (3H, s) and 6·15 (6H, s) (N-Me and OMe), 7·30 (2H, q, J = 7·5 Hz; —CH_2CH_3) and 8·82 (3H, t, J = 7·5 Hz, CH_2CH_3).

(2) *Dimethyl sulphate, potassium hydroxide in dimethylformamide.* Compound **12** (R = H; 2·0 g) was dissolved in DMF (25 ml) and powdered KOH (4·8 g) was added. Me_2SO_4 (10 g) was added at such a rate that the temp of the mixture did not exceed 40–45°, and the mixture was heated to 50–55° for 10 hr. The resultant soln was poured into water and the aqueous soln was extracted with chloroform. The extracts were dried (Na_2SO_4) and the solvent removed *in vacuo* to yield **11** (R = Me) as a dark green gum which crystallised on standing (2·15 g, 97%). This was recrystallised from light petroleum (b.p. 60–80°) as prisms m.p. 119–120°, identical in all respects with the minor component of the methylation carried out with MeI and NaH in benzene and DMF, and with the compound **11**, (R = Me) obtained from hydrogenation and methylation of isomaculosidine

1-Chloro-3-methylbut-2-ene.[39] Conc HCl (425 ml) was added slowly with vigorous stirring to isoprene (500 ml) so that the temp was never in excess of 30°. The mixture was stirred vigorously at room temp for 2 days and the organic layer was separated off and dried ($NaHCO_3$). The product was distilled at atm pressure, fractions boiling at 30–80° consisting mainly of isoprene. The fractions (141 g) boiling at 106–121° all had the same NMR spectrum of τ = 4·85 (1H, t, J = 8 Hz, olefinic), 6·25 (2H, d, J = 8 Hz, C=C—CH_2Cl) and 8·57 (6H, broad s, CH_3—C=C) and were identical with a sample of 1-chloro-3-methylbut-2-ene prepared by Grundon's procedure.[38] A further fraction, b.p. 141°, had absorption in the NMR spectrum at τ = 6·42 (2H, t, J = 8 Hz, 1H, CH_2Cl), 7·82 (2H, t, J = 8 Hz, C—CH_2—C) and 8·45 [6H, s, CH_3—C] and was evidently 1,3-dichloro-3-methyl-butane.

2,3-Dimethoxybenzamide was prepared by the method of Mauthner.[40]

2,3-Dimethoxyaniline. An alkaline soln of sodium hypochlorite was made by passing Cl_2 (16 g) into a cold soln of 56·7 g NaOH in 360 ml water and 215 g cracked ice. 2,3-Dimethoxybenzamide (39 g) was added in one portion and the mixture was warmed on the water bath to 70–80° and kept at this temp for 2 hr, a further 85 g NaOH in 85 ml water being added after 1 hr. The mixture was cooled and extracted with ether. The extracts were dried (Na_2SO_4) and the solvent removed to give an oil which was distilled at 100–101° and 1·5 mm Hg (lit.[38] b.p. 136–138° and 15 mm Hg); ν_{max}^{liquid} = 3460, 3370 cm^{-1} (NH). The NMR spectrum had absorption at τ = 3·16 (1H, d × d, J_1 = 8, J_2 = 8·5 Hz, aromatic), 3·58–3·77 (2H, m, aromatic) and 6·20 (8H, s, OCH_3 and NH_2).

3-(3-Methylbut-2-enyl)-4-hydroxy-7,8-dimethoxy-2-quinolone (**15**, R = H). Diethyl 2-(3-methylbut-2-enyl) malonate[38] (8·1 g) and 2,3-dimethoxyaniline (5·45 g) were dissolved in redistilled diphenyl ether (70 ml) and heated at reflux under N_2 for 2·5 hr. The soln was cooled and the pale yellow solid which separated out was filtered off and washed with diethyl ether to yield a cream solid (3·113 g) m.p. = 214–216°, *m/e* = 289·12956 ($C_{16}H_{19}NO_4$ requires: 289·13140), ν_{max}^{NUJOL} = 3340 (OH, NH), 1635 cm^{-1} (amide), λ_{max} = 225, 245 (sh), 254 (sh), 300 (sh), 313·5, 325 (sh) nm shifting to 225, 244 (sh), 254 (sh), 297 (sh), 309, 321 (sh) nm in base. The NMR spectrum (DMSO-d_6) had absorption at τ = −0·33 (1H, broad singlet, exchangeable in D_2O, NH), 2·39 (1H, d, J = 9 Hz, aromatic) 3·06 (1H, d, J = 9 Hz, aromatic), 4·85 (1H, t, J = 7 Hz, olefinic), 6·08 (3H, s, OCH_3), 6·18 (3H, s, OCH_3) 6·76 (2H, d, J = 7 Hz, CH_2CH=C), 8·25 (3H, s, CH_3—C=C) and 8·37 (3H, s, CH_3—C=C). The compound exhibited a purple colouration in alcoholic ferric chloride soln.

3-(3-Methylbut-2-enyl)-4,7,8-trimethoxy-2-quinolone (**15**, R = Me). 3-(3-Methylbut-2-enyl)-4-hydroxy-7,8-dimethoxy-2-quinolone (2·997 g) was partially dissolved in MeOH (400 ml) and treated with excess ethereal diazomethane at room temp for 12 hr. The solvent was removed *in vacuo* to yield a green-yellow gum (2·95 g) which was chromatographed on silica gel. Elution with benzene : ether (9 : 1) afforded a solid which recrystallised from MeOH as plates (0·670 g) m.p. = 151–152°, undepressed on mixing with the alkaloid preskimmianine. The spectral data were identical to those of preskimmianine

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