Chemistry of the Annonaceae. Structures of Uvarindoles A—D, Four New Benzylated Indole Alkaloids from *Uvaria angolensis*

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Uvaria angolensis stem bark has yielded four novel alkaloids based on indole substituted with between two and four 6-hydroxybenzyl units; uvarindoles A (**1**) and B (**2**) are identified as indole so substituted at the 1,2,3 and 1,2,3,5 positions respectively, uvarindole C (**3**) as a 2,3-substituted indole with as the 2 substituent a hydroxybenzoyl unit, and uvarindole D (**4**) as a dihydroindol-3-one with one hydroxybenzyl unit situated at N(1) and with two units at C(2).

The genus *Uvaria* is well known as a source of flavonoids substituted with 6-hydroxybenzyl units and several of these have been isolated from *U. angolensis.*[1] An investigation of the stem bark of this species collected in Tanzania confirmed the presence of benzylated chalcones and gave in addition a number of novel benzylated indoles which are reported here and benzylated sesquiterpenes which are still under investigation. Four indole derivatives were isolated from a light petroleum (b.p. 40—60 °C) extract by column chromatography and subsequent preparative t.l.c. and were characterised as follows.†

Uvarindole A (**1**), $C_{29}H_{25}NO_3$, crystallizes from ethyl acetate–cyclohexane as needles, m.p. 66—68 °C. The u.v. spectrum showed a typical indole chromophore[2] (λ_{max} 225, 277, and 292 nm) and the mass spectrum gave major ions at *m/z* 130 $[C_9H_8N]^+$ and 117 $[C_8H_7N]^+$ for an indole and at 107 $[C_7H_7O]^+$ for a hydroxybenzyl unit with the fragmentation pattern consisting of recurring loss of *m/z* 107 from the molecular ion suggesting that the compound is indole substituted with three hydroxybenzyl units. This was confirmed by ^{1}H and ^{13}C n.m.r. studies. The former revealed sixteen aromatic protons which could be resolved into four series of ABCD protons for the occurrence of four *ortho* disubstituted moieties. The placement of the hydroxybenzyl groups at N(1), C(2), and C(3) of indole follows from this. The N-substituted benzyl methylene was identified by the deshielded methylene resonance (δ_H 5.22, δ_C 42.1) whereas for the C(2) and C(3) substituents these were observed at δ_H 4.21 and 4.14 and at δ_C 24.8 and 25.9. ^{13}C N.m.r. resonances for C(2) and C(3) of the indole were observed at δ_C 135.4 and 109.8 respectively, in

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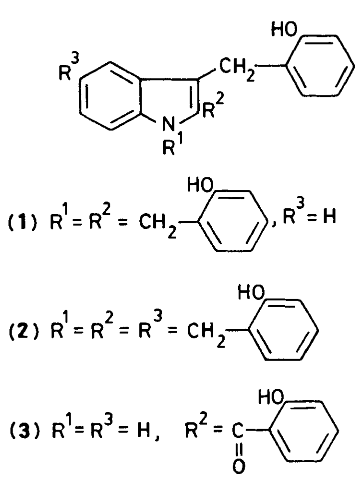
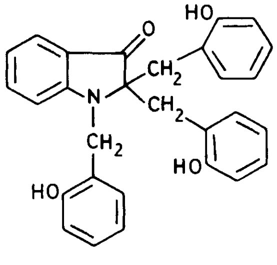
† U.v. spectra were run in methanol and i.r. spectra as KCl discs. Electron impact mass spectra were obtained at 70 eV with the probe temperature at 150 °C. All n.m.r. spectra were run in $CDCl_3$ using tetramethylsilane as internal standard except for uvarindole D where $(CD_3)_2CO$ was used. ^{1}H N.m.r. spectra were run at 360 MHz and ^{13}C n.m.r. spectra at 90.56 MHz. A full report of all spectral data will be made elsewhere.





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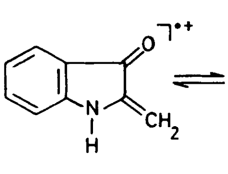
good agreement with published data for alkaloids such as corynantheine.[3]

Uvarindole B (**2**), $C_{36}H_{31}NO_4$, was obtained only as a gummy solid. The empirical formula suggested this was an analogue of (**1**) containing an additional hydroxybenzyl unit. This was confirmed by mass spectral fragmentation which was comparable to that of (**1**). N.m.r. studies revealed the presence of nineteen aromatic protons and of an N-benzyl and three C-benzyl units. Typically the most deshielded aromatic proton in the ^1H n.m.r. spectrum of these compounds is that for H(4). In (**2**) this was observed as a doublet at δ_H 7.29 (*J* 1 Hz) indicating that the adjacent position of the indole is substituted and suggesting structure (**2**). This was sustained by the ^{13}C n.m.r. spectrum which was similar to (**1**) except for the appearance of an additional singlet at δ_C 130.3 for C(5) and the deshielding of the C(4) resonance from δ_C 118.9 [in (**1**)] to δ_C 122.4. These shifts are in close agreement with those noted on conversion of indole into 5-methylindole.[4]

Uvarindole C (**3**), $C_{22}H_{17}NO_3$, crystallizes from chloroform as needles, m.p. 151—153 °C. This compound contains only two hydroxybenzyl units but three oxygens. The location of the additional oxygen as part of a benzoyl unit was indicated by the mass spectrum which, in addition to normal fragments, gave *m/z* 121 $[C_7H_5O_2]^+$ for the benzoyl unit and by δ_C 192.5 in the ^{13}C n.m.r. spectrum for the benzoyl carbonyl group. The ^1H n.m.r. spectrum revealed twelve aromatic protons as three ABCD systems, a single methylene (δ_H 4.33, δ_C 28.0) for a C-benzyl, and an NH proton at δ_H 11.35. Placement of the benzoyl at C(2) and the benzyl at C(3) followed from the ^{13}C n.m.r. spectrum. The indole carbon atom at the point of attachment of the benzoyl unit will be shielded whilst the β-carbon atom will be deshielded. The observed resonances for C(2) and C(3) were δ_C 129.8 and 119.8 compared with 135.2 and 107.4 in corynantheine.[3] Thus C(2) is shielded and C(3) is deshielded requiring placement of the benzoyl group at C(2).



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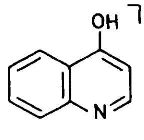

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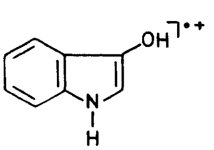

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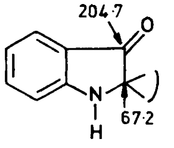

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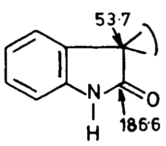

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Uvarindole D (**4**), $C_{29}H_{25}NO_4$, crystallizes as yellow plates from chloroform–methanol, m.p. 170—174 °C. The u.v. spectrum (λ_{max} 233, 272, and 419 nm) was similar to those of indoxyl compounds rather than to those of simple indoles.[5] The presence of a carbonyl group was indicated by i.r. (ν_{max} 1670 cm^{-1}) and ^{13}C n.m.r. (δ_C 204.7) spectra. Both ^1H and ^{13}C n.m.r. spectroscopy revealed an unsubstituted indole aromatic ring and three hydroxybenzyl substituents, one of which is at N(1). The remaining two benzyl methylenes were observed as equivalent AB quartets (δ_H 3.24 and 3.36, *J* 14.2 Hz) requiring the two protons of each methylene to be non-equivalent but the two C-benzyl substituents to be equivalent to each other. This situation can be satisfied by a *geminal* arrangement. Using this argument uvarindole D must be a 2,3-dihydroindolone with the carbonyl at C(2) or C(3) and *gem*-dibenzyl groups on the other carbon atom. This is supported by the appearance of a singlet at δ_C 76.3 in the ^{13}C n.m.r. spectrum and by the absence of ions for the indole nucleus in the mass spectrum and their replacement by *m/z* 145 $[C_9H_7NO]^+$ [(**5**) or (**6**)] and *m/z* 133 $[C_8H_7NO]^+$ (**7**). Assignment of the carbonyl to C(3) follows from the ^{13}C n.m.r. chemical shifts for the carbonyl carbon and *geminal* quaternary carbon atoms which agree with those for ibolutеine (**8**)[6] rather than those for tasmanin (**9**).[7] The proposed structure (**4**) for uvarindole D has subsequently been confirmed by *X*-ray analysis.[8]

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