TWO INDOLOSESQUITERPENES FROM *UVARIA PANDENSIS*

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Abstract—Two new indolosesquiterpenes, (6',7',-dihydro-8',9'-dihydroxy)-3-farnesylindole and (8',9'-dihydroxy)-3-farnesylindole have been isolated from the roots of *Uvaria pandensis*.

INTRODUCTION

Plants of the genus *Uvaria* continue to be a rich source of new natural products of varied structures, some of which have shown interesting antibacterial, antifungal, antitumour and antimalarial activity [1–4]. We recently reported on the isolation of new cyclohexene epoxides [4] and 3-farnesylindole (1) [5] from *U. pandensis* [6], polybenzylated dihydrochalcones from *U. leptocladon* [7] and terpene chalcones and other compounds from *U. scheffleri* [8]. In continuation of our studies of *Uvaria* species found in Tanzania, we have now isolated the two indolosesquiterpenes, (6',7'-dihydro-8,9'-dihydroxy)-3-farnesylindole (2) and (8',9'-dihydroxy)-3-farnesylindole (3) from the dichloromethene extract of the root bark of *U. pandensis*, in addition to (+)-β-senepoxide (4), (+)-pandoxide (5) and (−)-pipoxide (6) [4].

RESULTS AND DISCUSSION

Elution of the dichloromethane extract of air-dried root bark of *U. pandensis* over silica gel with a mixture of ethyl acetate and *n*-hexane (3:7), gave fractions containing a complex mixture of less polar components (as shown by GC), the cyclohexene epoxides 4–6 and the new indolosesquiterpenes 2 and 3, respectively. The two new compounds were separated by prep. TLC using Me$_2$CO–hexane (1:4).

(6',7'-dihydro-8',9'-dihydroxy)-3-Farnesylindole (2), which eluted first, is a viscous oil with formula C$_{23}$H$_{33}$NO$_2$, [M]$^+$ at *m/z* 355, [α]$_D^{20}$ = +12.1° (MeOH; *c* 0.34), IR, 3300–3550 (*br*), 3100, 1665, 1620 and 735 cm^{-1}. The ^{1}H NMR and mass spectra of 2 and 3 resemble those of 1 [5]. However, these spectra in addition show signals due to two secondary hydroxyl groups in both new compounds. Thus, the ^{1}H NMR spectrum of 2 shows one carbinol proton resonance at δ3.40 (obscured by the C-1' methylene signal which has the same chemical shift) and one at δ4.30 (*dd*, *J* =9.5 Hz). The spectrum also shows two olefinic proton signals at δ5.24 (H-2', *t*, *J* =7 Hz and H-10', *d*, *J* =9 Hz). Decoupling experiments indicated that one of these protons is vicinal to the C-1' methylene group (δ 3.40, *J* =7 Hz) while the other one (*J* =9 Hz) is adjacent to the carbinol proton at δ4.30 (H-9', *dd*, *J* =9, 5 Hz). Furthermore, the coupling constants of the signals at δ4.30 (H-9', *dd*, *J* =9,

5 Hz) and δ3.40 (H-8', *br d*, *J* = 5 Hz) suggest that the two signals are due to adjacent protons, indicating the relative positions of H-8' and H-9'. Coupling between H-8' and H-7' is apparently very small, resulting in a broad doublet for H-8', instead of an expected doublet of doublets. Other NMR signals include a singlet at δ1.9 due to three allylic methyl groups at C-3' and at C-11', a doublet at δ0.95 (C-7'-Me, *J* =7 Hz) and multiplets at δ1.85–2.25 and δ1.1–1.7 due to the other aliphatic protons. The
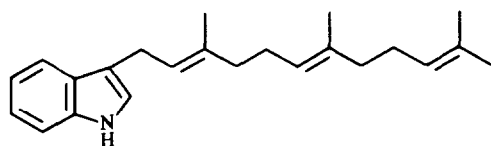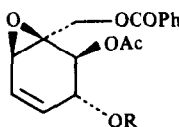

1
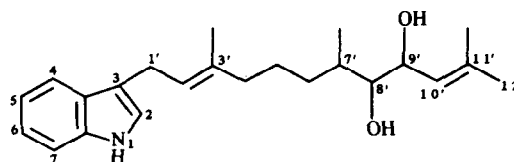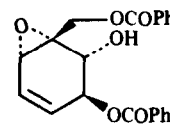

2
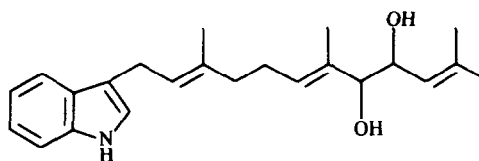
3

4   R = Ac
5   R = Me

6

aromatic region of the ^{1}H NMR spectrum is typical of that expected for an indole which is substituted at C-3 [5, 9–12]. Thus, the aromatic region consists of a poorly resolved signal at $\delta 6.89$ ($J = 1.5$ Hz) which can be assigned to H-2, a broad N-H signal at $\delta 8.02$, a three proton multiplet due to H-5, H-6 and H-7 appears at $\delta 7.08$–7.24 and a multiplet at $\delta 7.53$ which can be assigned to H-4. The mass spectrum of 2 is characteristic of an indole which is substituted with a dioxygenated farnesyl group [5]. Consequently the spectrum shows the loss of a molecule of water from the [M]$^+$ to give a fragment ion at m/z 337, which subsequently cleaves an oxygenated diprenyl group to give a fragment ion at m/z 184. Alternatively the [M]$^+$ may lose an oxygenated prenyl unit to give a peak at m/z 270. Loss of a second such group forms the most stable ion at m/z 130. This fragmentation pattern indicates that the two OH groups in 2 are substituted on the last two prenyl groups of the farnesyl chain. Therefore, the two hydroxyl groups in 2 are at C-8′ and C-9′.

(8′,9′-dihydroxy)-3-Farnesylindole (3), also a viscous oil, has formula $C_{23}H_{31}NO_2$; [M]$^+$ at m/z 353, $[\alpha]_D^{20}$ +23.5 (MeOH; c 0.17); IR, 3300–3450 (br), 3100, 3060, 1665 and 735 cm^{-1}. Its spectral features are comparable with those of 1 and 2. Again the presence of two secondary OH groups is evident from the ^{1}H NMR spectrum, in which the two adjacent carbinol methine signals appear at $\delta 3.76$ (d, $J = 8$ Hz) and $\delta 4.23$ (dd, $J = 8$, 8 Hz). Decoupling experiments showed that the proton at $\delta 4.23$ couples with the other methine carbinol proton at $\delta 3.76$ and also with the olefinic proton which resonates at $\delta 5.07$ ($br\ d$, $J = 8$ Hz). Two more olefinic proton signals appear at $\delta 5.37$ while a broad peak due to four allylic methylene protons occurs at $\delta 2.05$ (H-4′ and H-9′). The allylic methyl resonances appear at $\delta 1.59$ (s, 3H), 1.68 (s, 6H) and 1.75 (s, 3H). Signals between $\delta 6.9$ and 8.05 and at $\delta 3.45$ are comparable to those in 1 and 2, indicating the presence of an indole moiety in 3. These NMR features are in agreement with the present of a farnesyl group in 3 [5, 13], having two adjacent hydroxyl groups at either C-4′ and C-5′ or C-8′ and C-9′, attached to C-3 of an indole moiety. The mass spectrum of 3 was similar to that of 2. Thus, as for 2, the mass spectral fragmentation pattern enabled us to locate the positions of the two hydroxyl groups in 3, at C-8′ and C-9′.

EXPERIMENTAL

Pulverized air-dried root bark (410 g) was extracted × 3 with CH_2Cl_2 for 48 hr. Elution of the crude extract (16.8 g) on silica gel (400 mesh ASTM) with EtOAc–hexane (3:7) gave three fractions containing consecutively a complex mixt. (GC) of less polar unidentified components, a mixt. of three cyclohexene epoxides [(+)-β-senepoxide, (+)-pandoxide and (−)-pipoxide] and the new compounds 2 and 3. The two new compounds were sepd by prep. TLC (silica gel, F254, 1 mm thickness, Me_2CO–hexane, 1:4); compound 2 eluted faster than 3.

(6′,7′-dihydro-8′,9′-dihydroxy)-3-Farnesylindole (2). Viscous, light brownish oil (88 mg, 0.02%), $[\alpha]_D^{20}$ = +12.1 (MeOH; c 0.34), UV (hexane): 280 and 290 nm; (IR ν^{neat}: 3300–3450 (br), 3100, 1455 and 735 cm^{-1}; ^{1}H NMR (90 MHz, CDCl$_3$): $\delta 0.95$ (d, J = 7 Hz, 3H, 7′-Me), 1.24–1.84 (m, H-5′ and H-6′), 1.66 (s, 6H) and 1.73 (s, 3H): 3 × Me, 2.00 (m, 3H, H-4′ and H-7′), 2.20 ($br\ s$, 2H, 2 × OH), 3.40 ($br\ d$, J = 7 Hz, 3H, H-1′ and H-8′), 4.30 (dd, J = 9, 5 Hz, H-9′), 5.24 (m, 2H, H-2′ and H-10′), 6.99 ($dist\ d$, J = 1.5 Hz, H-2), 7.08–7.24 (m, 3H, H-5, H-6 and H-7), 7.53 (m, 1H, H-4) and 8.02 ($br\ s$, 1H, N-H) and MS, m/z (% rel. int.): 355 ([M]$^+$, 18.8), 337 (21.6, [M − H$_2$O]$^+$), 270 (39, [M − C$_5$H$_9$O]$^+$), 184 (13, [270–C$_5$H$_9$O]$^+$ or [M − C$_{10}$H$_{19}$O$_2$]$^+$) and 130 (100, [M − C$_{14}$H$_{24}$O$_2$]$^+$).

(8′,9′-dihydroxy)-3-Farnesylindole (3). Viscous, light brown oil (54 mg, 0.013%), $[\alpha]_D^{20}$ = +23.5 (MeOH; c 0.17), UV (hexane): 280 and 290 nm; IR ν^{neat}, 3300–3450 (br), 3100, 3060, 1455 and 735 cm^{-1}; ^{1}H NMR (90 MHz, CDCl$_3$): $\delta 1.59$ (s, 3H), 1.68 (s, 6H) and 1.75 (s, 3H): 6 × Me groups, 2.05 (m, 4H, H-4′ and H-5′), 2.72 ($br\ s$, 2H, 2 × OH), 3.45 (d, J = 7 Hz, 2H, H-1′), 3.76 (d, J = 7.5 Hz, 1H, H-8′), 4.23 ($dist\ t$, J = 8 Hz, H-9′), 5.07 ($dist\ d$, J = 8 Hz, H-10′), 5.37 (m, 2H, H-2′ and H-6′), 6.93 ($br\ s$, 1H, H-2), 7.07–7.40 (m, 3H, H-5, H-6 and H-7), 7.53 (m, H-4) and 8.05 ($br\ s$, 1H, N-H) and MS, m/z (% rel. int.): 353 (9, [M]$^+$), 335 (13.5, [M − H$_2$O]$^+$), 268 (27.5, [M − C$_5$H$_9$O]$^+$), 184 (26, [268 − C$_5$H$_8$O]$^+$ or [M − C$_{10}$H$_{17}$O$_2$]$^+$) and 130 (100, [M − C$_{14}$H$_{23}$O$_2$]$^+$).

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