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CYCLOHEXENE EPOXIDES, (+)-PANDOXIDE, (+)-β-SENEPOXIDE AND (−)-PIPOXIDE, FROM *UVARIA PANDENSIS*

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Key Word Index—*Uvaria pandensis*; Annonaceae; cyclohexene epoxides; (+)-pandoxide; (+)-β-senepoxide; (−)-pipoxide.

Abstract—The new cyclohexene epoxide (+)-pandoxide along with (+)-β-senepoxide and (−)-pipoxide were isolated from the stembark, roots and leaves of the new *Uvaria* species *U. pandensis*. Their structures and stereochemical configurations were determined by spectroscopic methods. The pipoxide has an absolute configuration opposite to the one previously isolated from *Uvaria* species. The absolute stereochemical configuration of (+)-β-senepoxide was assigned unambiguously by an X-ray diffraction analysis.

INTRODUCTION

Recent phytochemical investigations on *Uvaria ferruginea* [1-3] have led to the isolation of three cyclohexene epoxides, (−)-senepoxide (**4**), (+)-β-senepoxide (**2**) and (−)-tingtanoxide (**5**). These compounds, together with (+)-pipoxide (**6**) which was isolated from *U. purpurea* [4] and *Piper hockeri* Linn. [5], belong to a new class of natural products [6], some of which exhibit tumour inhibitory, antileukemic or antibiotic activity. *Uvaria pandensis* Verdc† was found near Dar es Salaam, where it is used for the treatment of fever and stomach disorders. In the course of our investigations on the chemical composition of the stembark of *Uvaria pandensis*, we have isolated a new cyclohexene epoxide, (+)-pandoxide (**1**), in addition to (+)-β-senepoxide (**2**), and (−)-pipoxide (**3**). When compounds **1-3** were tested [7] for anti-malarial activity, (−)-pipoxide (**3**) was found to be mildly active (IC 50 12.5 μg/ml), while **1** and **2** showed no significant activity against *Plasmodium falciparum* parasites (D. H. Bray, personal communication).

RESULTS AND DISCUSSION

Extraction of air dried stembark of *Uvaria pandensis* with petrol at room temperature, followed by silica gel chromatography of the crude extract and elution with a mixture of ethyl acetate and petrol (1:4), led to the isolation of the cyclohexene epoxides **1-3**, which eluted in the order **1**, **2** and **3**, respectively. The three compounds were further purified by preparative thin-layer chromatography (silica gel) using acetone-petrol (1:4) as the eluent. The least polar compound, (+)-pandoxide (**1**), was an optically active oil, with $[\alpha]_D^{28} = +35.5°$ ($c = 1.13$, $CHCl_3$) and UV absorption maxima at λ 274 and 280 nm. The IR spectrum showed carbonyl absorptions at 1730 and 1755 cm^{-1}, a strong ether absorption at 1260 cm^{-1} and an absorption at 710 cm^{-1} attributed to a monosubstituted benzene ring. This suggested the resemblance of **1** with the epoxides **2**, **4**, **5** and **6**. The CI mass spectrum of **1** showed prominent peaks at m/z 319 ($[M+1]^+$ 57%), 259 (23%), 137 (base peak), 105 (73.5%) and 123 (36.5%). The mass of the $[M+1]^+$ peak is in agreement with the molecular formula $C_{17}H_{18}O_6$ for **1**. The most conclusive evidence for the structure of **1** was derived from its ^1H NMR spectrum, which had similar features as that of (+)-β-senepoxide (**2**). The spectrum exhibited one methoxy absorption at δ3.38 (*s*), an acetoxy methyl absorption at 2.19 (*s*) and a five proton multiplet at δ7.3-8.1 belonging to the phenyl protons of a benzyloxy group. The appearance of the resonances for both protons H-4 and H-5 with the same chemical shift (δ6.03) as a doublet ($J = 2.5$ Hz) suggested that the methoxy group in **1** is on C-3. Hence, the double bond is almost symmetrically substituted with two ether linkages at the allylic positions C-3 and C-6 (the methoxy and epoxide groups, respectively), resulting in the observed chemical shift equivalence of H-4 and H-5.

Assignment of the stereochemical structure of **1** was based mainly on the resonances of the cyclohexene ring protons at C-2 and C-3. The relative stereochemistry of the two oxygenated substituents at C-2 and C-3 has to be *trans*-diequatorial, considering the vicinal coupling constant $J_{2,3}$ of 8.5 Hz, which is in agreement with a *trans*-diaxial conformation for the protons at C-2 and C-3 (dihedral angle of ~ 180°). This can be achieved either when the C-2 substituent is *cis*(equatorial) or when it is *trans*(equatorial) to the epoxide oxygen. Molecular models suggest that the former conformation is the more favourable one for **1**, since in the latter conformation the benzyloxymethylene group at C-1 and the C-2 substituent are eclipsed. However, another favourable conformation, different from **1**, is one in which the C-2 and C-3

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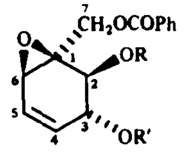
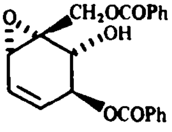
†The name *Uvaria pandensis* Verdc has been proposed by Dr B. Verdcourt of the Royal Botanic Gardens in England. A reference specimen of the plant is kept at the Herbarium, department of Botany, University of Dar es Salaam (L. Mwasumbi no. 12761). The description of the plant has been submitted for publication in Kew Bulletin.



1 R = COMe, R' = Me
2 R = R' = COMe
6 R = H, R' = COPh



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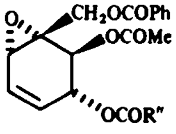

4 R" = Me
5 R" = Ph

oxygenated substituents are *trans*-diaxial, leading to a $J_{2,3}$ value of approximately 2 Hz, as in (−)-β-senepoxide (**4**) and (−)-tingtanoxide (**5**) [3]. Based on the $J_{2,3}$ value of 8.5 Hz we therefore conclude that (+)-pandoxide has a stereochemical configuration as in (+)-β-senepoxide (**2**) [1, 8] (see below).

(+)-β-Senepoxide (**2**), mp 64–66°, $[\alpha]_D^{28} = +100°$ (c = 1.2, $CHCl_3$) showed the same UV and IR absorptions as pandoxide **1**. The mp and $[\alpha]_D$ values are comparable with those of synthetic (+)-β-senepoxide ($[\alpha]_D = +94°$ (c = 1.1, $CHCl_3$) and mp 68–69° [9]. The CI mass spectrum of **2** showed an ion of highest mass at m/z 347.2 $[M+1]^+$ (100%). The other major fragments at m/z 281.1 (17.5%), 183.0 (9%), 165.0 (17%), 123.0 (42%) and 105 (46.5%) are consistent with the molecular structure **2** [1, 2]. The structure of **2** was further confirmed by comparison of its ^1H NMR spectrum (Table 1) with that reported in the literature [1]. The absolute stereochemical configuration of (+)-β-senepoxide was established unambiguously by X-ray diffraction analysis [8]. It was found that this configuration is the same as deduced by Kodpinid *et al.* [1, 2] using chemical correlations. Compound **3** displayed UV, IR, ^1H NMR and CI mass spectra which were identical to those reported for (+)-pipoxide [4, 5, 10]. However, $[\alpha]_D^{28}$ for **3** was −36.5° (c = 0.17, $CHCl_3$), indicating that **3** is the enantiomer of (+)-pipoxide ($[\alpha]_D = +37.9°$, c = 0.16, $CHCl_3$) [10] isolated previously from *Uvaria* species [6].

We have subsequently isolated the three compounds **1**, **2** and **3** from the roots and leaves as well, albeit in smaller quantities.

EXPERIMENTAL

Extraction. The air dried ground stembark (1.4 kg) was extracted × 3 with cold petrol (bp 40–60°) for 36 hr. The crude extract (15.0 g) was fractionated by silica gel chromatography using a mixture of petrol–EtOAc (4:1). A fraction containing a mixture of the three compounds **1**, **2** and **3** was collected. The compounds were separated by preparative TLC (silica gel 60) eluting with a mixture of petrol–Me_2CO (4:1). The compounds eluted in the order **1**, **2** and **3**, respectively (increasing polarity). Compound **1** was further purified by preparative TLC, while **2** and **3** were recrystallized from a mixture of Et_2O and *n*-hexane (1:9).

(+)-*Pandoxide* [(+)-(1R,2S,3R,6R)-*2-acetoxy-1-benzoyloxymethylene-1,6-epoxy-3-methoxycyclohex-4-ene*] (**1**). Oil (120 mg, 0.01%), $[\alpha]_D^{28} = +35.5°$ (c = 1.13, $CHCl_3$); UV λ_{max} 272 and 280 nm; IR ν_{max} cm^{-1}: 3040 (C=C), 1755 (CH–CO–O), 1730 (Ph–CO–O), 1600 (aromatic ring, C–H), 1260 (ether), 1275 (O–CO) and 710 (monosubstituted benzene); ^1H NMR as listed in Table 1; CIMS (CH_4): m/z (rel. int.): 319.1 $[M+H]^+$ (57) calculated $[M+1]^+$ for $C_{17}H_{18}O_6$: 319.32, 259.1 $[M-CH_3COO]^+$ (23), 197.1 $[M-C_6H_5COO]^+$ (18.5), 137 $[M-C_6H_5CO_2-CH_3CO_2-H]^+$, (100), and 105.0 $[C_6H_5CO]^+$ (73.5).

(+)-*β-Senepoxide* [(+)-(1R,2S,3R,6R)-*2,3-diacetoxy-1-benzoyloxymethylene-1,6-epoxycyclohex-4-ene*] (**2**). White crystals (300 mg, 0.02%), mp 64–66° (lit. m.p. natural **2**: 72–73° [1], synthetic **2**: 68–69° [10]) and $[\alpha]_D^{28} = +100°$ (c = 1.2, $CHCl_3$), (lit. $[\alpha]_D$ for natural **2** = +62° (c = 0.55, $CHCl_3$) [1], and for synthetic **2** = +94° (c = 0.55, $CHCl_3$) [10]). The compound showed UV, IR, MS and ^1H NMR data which are identical to the literature values for **2** [1, 2, 9].

(−)-*Pipoxide* [(−)-(1S,2R,3S,6S)-*3-benzoyloxy-1-benzoyloxymethylene-1,6-epoxy-2-hydroxycyclohex-4-ene*] (**3**). White crystals (40 mg, 0.003%), mp 148–150° and $[\alpha]_D^{28} = -36.5°$ (c = 0.17, $CHCl_3$) (literature values for (+)-pipoxide: mp 152°C [4], $[\alpha]_D$ for natural **3** = +36.3° (c = 0.67, $CHCl_3$) [10], and synthetic **3** = +37.9° (c = 0.16, $CHCl_3$) [10]. The compound showed UV, IR, MS and ^1H NMR data which are identical to those of (+)-pipoxide (Table 1).

Table 1. ^1H NMR spectral data for (+)-pandoxide (**1**), (+)-β-senepoxide (**2**) and (−)-pipoxide (**3**)*

Compound	H-2	$J_{2,3}$	H-3	$J_{3,4}$	H-4	$J_{4,5}$	H-5	$J_{5,6}$	H-6	$J_{4,6}$	$J_{3,5}$	AB quartet for H-7
1	5.59 *d*	8.5	4.08 *brd*	~0	6.03 *d*	0	6.03 *d*	2.5	3.54 *t*	2.5	< 2	4.34 and 4.62 $J_{AB} = 12.3$
2	5.65 *d*	8.5	5.56 *dt*	~2	5.79 *td*	10	5.89 *ddd*	4	3.53 *dd*	2	2	4.26 and 4.76 $J_{AB} = 12.3$
3	4.27 *m*	8	5.64 *dt*	< 2	5.89 *dt*	10	6.06 *ddd*	4	3.56 *dd*	2	2	4.48 and 5.02 $J_{AB} = 12.0$

*Spectra were determined in $CDCl_3$ as solvent on a Bruker WH-90, FT NMR instrument operating at 90 MHz. Chemical shifts are reported in δ values from internal standard TMS (δ = 0). J values are given in Hz. Spectral values for other protons in **1**, **2** and **3** are given in the text.

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