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POLYOXYGENATED CYCLOHEXANE EPOXIDE DERIVATIVES FROM THE STEM BARK OF *MONANTHOTAXIS BUCHANANII**

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Key Word Index—*Monanthotaxis buchananii*; Annonaceae; cyclohexane diepoxides; cyclohexene epoxides; polyoxygenated cyclohexenes.

Abstract—From the stem bark of *Monanthotaxis buchananii* five oxygenated cyclohexane epoxide derivatives have been isolated, four of which are novel. One was identified as the 2-methyl ether of (+)-pipoxide and a second as 1α-benzoyloxymethyl-3α-benzoyloxycyclohex-5-en-1β,2β,4β-triol, probably derived from opening of the epoxide ring of a pipoxide precursor. The remaining three compounds are all diepoxides. Two, monanthadiepoxide methyl ether and boesenboxide have diequatorial substituents at C-2 and C-3 with stereochemistry comparable to crotepoxide while the third, epimonanthadiepoxide, has diaxial substituents at C-2 and C-3.

INTRODUCTION

Monanthotaxis buchananii (Engl.) Verdc. (Annonaceae) is a small tree or climber found throughout eastern and central Africa from southern Sudan to Mozambique [2]. A previous examination of the stems and seeds of *M. cauliflora* Chipp. [3–5] yielded several simple flavonoids and 1-benzylisoquinoline alkaloids that are typical of the family. In this paper we report on an investigation of the stem bark of *M. buchananii* and the isolation of a number of benzoyloxy cyclohexane epoxide derivatives.

RESULTS AND DISCUSSION

The ground stem bark was extracted with petrol (bp 60–80°) and then chloroform. Each extract was separately subjected to column chromatography over silica gel eluting with petrol containing increasing amounts of ethyl acetate. The petrol extract yielded a single compound (A) and the chloroform extract four compounds B–E (in order of elution from the column).

Accurate mass measurement (EIMS) for A indicated an empirical formula $C_{22}H_{20}O_6$ with a base peak *m/z* 105 $[C_7H_5O]^+$ for a benzoyl fragment and significant ions for $[M-122]^+$ and $[M-244]^+$ for loss of units of benzoic acid. The ^1H NMR spectrum (Table 1) revealed 10 aromatic protons confirming the presence of two benzoyl groups. Other features of the spectrum were a methoxyl singlet, an AB quartet for an isolated oxymethylene group and five methine protons. These data suggested a cyclohexene nucleus with benzoyloxymethyl, benzoyloxy and methoxyl substituents, the additional oxygen being present as an epoxide (δ 3.55, epoxide oxymethine proton). Analysis of chemical shifts placed the methoxyl and benzoyloxy substituents at C-2 and C-3 respectively. This allowed assignment of structure **1** with coupling constants and optical activity indicating that stereochemistry was comparable to that of (+)-pipoxide (**2**) [6]. (+)-Pipoxide has been isolated from *Piper* (Piperaceae) and *Uvaria* species (Annonaceae) [7,8] while (−)-pipoxide has only been recorded from *Uvaria pandensis* [6]. (+)-Pipoxide-2-methyl ether (**1**) appears to be novel.

The EIMS of B gave a highest fragment at *m/z* 289 for $C_{15}H_{13}O_6$ but NCIMS revealed the $[M]^+$ as 396 ($C_{22}H_{20}O_7$). Spectral characteristics were very similar to those of **1**, the ^1H NMR spectrum revealing the same three substituents and five linked oxymethine protons (Table 1). The major distinction from **1** was in chemical shifts and coupling constants for H-3 to H-5 which indicated absence of the olefinic bond and its replacement by a second epoxide. This suggested structure **3** (trivial name monanthadiepoxide methyl ether) which is supported by a comparison of the ^1H NMR spectrum (Table 1) with those of crotepoxide (**4**) from *Croton macrostachys* (Euphorbiaceae) [9] and boesenboxide (**5**) from a *Boesenbergia* species (Zingiberaceae) [10]. As **3** and both **4** and **5** are dextrorotatory they are presumed to have the same absolute stereochemistry. It is possible for B to exist as the C-2/C-3 epimer **6** (e. g. with H-2β and axial and H-3α and axial) but this conformation has been considered unlikely [6] as the C-2 and 1-benzoyloxymethyl substituents are eclipsed. This problem was examined by means of an NOE experiment. Irradiation of the OMe resonance gave the anticipated enhancement of both H-2 (9%) and H-3 (6%) while irradiation of H-4 led to 10% enhancement for H-5 and 4% for H-3, similar to values observed for an NOE study of **5** [10].

The NCIMS of C gave major ions at $[M]^+$ 424 and 396 and the IR revealed a more complex carbonyl region. The ^1H NMR spectrum indicated C to be a mixture (*ca* 1:1) of **3** and a second diepoxide that differed from **3** in replacement of the methoxyl with an acetoxyl moiety. This minor

*Part 27 in the series 'Chemistry of the Annonaceae'. For Part 26 see ref. [1].

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Table 1. ^{1}H NMR spectra for cyclohexane derivatives

Proton	A(1)	2[6]	B(3)	4[9]	5[10]	C(5)	D(7)	E(11)	11†
H-2	4.12 *d*	4.27 *m*	4.19 *d*	5.73 *d*	5.92 *d*	5.95 *d*	4.31 *dd*	3.79 *dd*	4.78 *dd*
H-3	5.86 *dt*	5.64 *dt*	5.27 *dd*	4.98 *dd*	5.18 *dd*	5.17 *dd*	5.44 *dd*	5.43 *dd*	6.57 *dd*
H-4	5.86 *dt*	5.89 *dt*	3.14 *dd*	3.10 *dd*	3.19 *ddd*	3.19 *dd*	3.46 *dd*	4.28 *dt*	5.01 *d*
H-5	6.06 *ddd*	6.06 *ddd*	3.43 *dd*	3.44 *dd*	3.44 *dd*	3.49 *dd*	3.61 *dd*	5.60 *dd*	6.28 *d*
H-6	3.55 *dd*	3.56 *dd*	3.64 *d*	3.68 *d*	3.72 *dd*	3.72 *d*	3.74 *d*	5.63 *dd*	6.28 *d*
J_{2-3}	8.4	8	9	9	9.5	9.5	4.7	11.1	11.2
$_{3-4}$	2.5	<2	1.5	1.5	1.6	1.7	2.4	7.8	7.8
$_{3-5}$	2.5	2							
$_{4-5}$	9.9	10	3.8	4	3.9	3.8	2.9	1.2	
$_{4-6}$	1.6	2			0.5			1.2	
$_{5-6}$	3.6	4	2.7	2.6	2.7	2.7	2.3	11.5	11
2-OH							10.3	5.3	5.5
4-OH								5.9	
CH_2-7	4.40/	4.52/	4.31/	4.25/	4.26/	4.29/	4.49/	4.31 *s*	5.15/
	4.90	5.04	4.80	4.58	4.60	4.63	4.61		5.27
	(12.1)	(12.0)	(12.1)	(12)	(12.0)	(12.1)	(12.3)		(11.0)
H-Ar	8.06–		8.09–,		8.05–	8.09–	8.02–	8.11–	8.49–
	7.43		7.43		7.42	7.40	7.35	7.48	7.23
OMe	3.60 *s*		3.58 *s*						
OAc					2.06 *s*	2.07 *s*			
2-OH							2.82 *d*	5.53 *d*	7.84 *d*
4-OH								5.36 *d*	
1-OH								5.40 *s*	

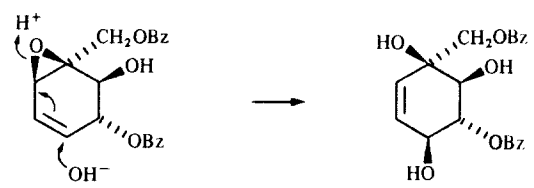
Spectra for A–E run at 250 MHz, in $CDCl_3$ unless otherwise stated.
* Run in DMSO-d_6.
† Run in pyridine-d_5.

component must therefore be boesenboxide (**5**), and this is substantiated by identical ^{1}H NMR data to that previously reported for **5** (Table 1).

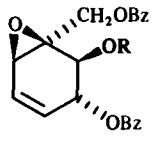
The NCIMS of D indicated $[M]^+$ 382 while the EIMS gave a first significant ion at *m/z* 260 $[C_{14}H_{12}O_5]^+$ for loss of one benzoic acid unit. On this evidence an empirical formula $C_{21}H_{18}O_7$ was assumed. The ^{1}H NMR spectrum confirmed the presence of benzoyloxy and benzoyloxymethyl substituents but neither methoxyl nor acetoxyl. The remaining six signals included an OH proton that coupled to an oxymethine proton which could be placed at C-2 of a monanthadiepoxide-type skeleton. The other major difference from **3** and **5** was the reduction of J_{2-3} to 4.7 Hz and the increase of J_{3-4} to 2.9 Hz. Thus D must differ from **3** to **5** at C-2 and /or C-3, with the most probable conformation being **7** in which both C-2 and C-3 substituents are axial and H-2 does not eclipse the CH_2OBz substituent. This was supported by an NOE study in which irradiation of H-2 led to a 7% enhancement of H-3 and irradiation of H-4 to 7% enhancements of both H-3 and H-5. The similar enhancements in these two experiments suggest H-2, H-3 and H-4 are equidistant from each other and all equatorial or pseudoequatorial, as in **7** (epimonanthadiepoxide). In (−)-senepoxide (**8**) the C-2 and C-3 substituents are also axial but J_{2-3} = 2.5 Hz and optical activity is very strongly laevorotatory (*ca* −200°) [11].

In a further attempt to examine configuration at C-3 D was treated with methanolic HCl with the intention of converting it to the monochlorohydrin derivative **9** in which the 4-hydroxy and 5-chloro substituents are equatorial [9]. Unfortunately this reaction led to the *bis*-chlorohydrin derivative **10** the ^{1}H NMR spectrum of which revealed H-4 with two large (axial–axial) couplings, suggesting that H-3 had epimerized during the reaction. An effort is now being made to obtain further crystalline material of **7** to enable X-ray studies.

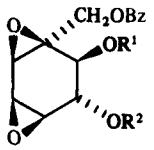
The most polar compound (E) gave $[M]^+$ 384 by NCIMS with the first ion in the EIMS at *m/z* 262 for $[M-122]^+$ indicating an empirical formula $C_{21}H_{20}O_7$. It was insoluble in $CDCl_3$ and an initial ^{1}H NMR spectrum run in DMSO-d_6 revealed the typical benzoyloxymethyl and benzoyloxy groups. Of the remaining eight protons two were *ortho* olefinics and three proved to be hydroxyls, two of which were secondary and one tertiary (Table 1). A second spectrum run in pyridine-d_5 was somewhat simplified and allowed resolution of a CH(OH)–CH(OBz)–CH(OH)–CH=CH system in which the three oxymethine protons were all axial. This must form a cyclohexene system in which the sixth carbon is substituted with the third hydroxyl and the benzoyloxymethyl groups, leading to formulation of E as **11**. The stereochemistry depicted would arise if **11** were formed by the acid-catalysed ring opening of (+)-pipoxide (**2**) (Scheme 1). This appears to be the first report of this type of product. Other epoxide fission products such as the



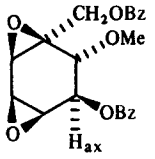
11



1 R = Me
2 R = H



3 R^1 = Me, R^2 = Bz
4 R^1 = R^2 = Ac
5 R^1 = Ac, R^2 = Bz



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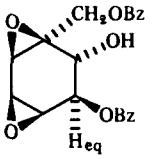
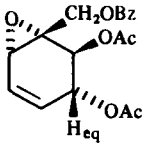


7



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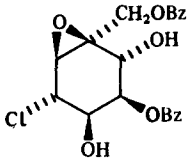

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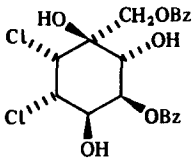

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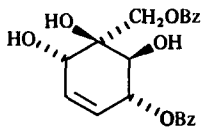

12

Scheme 1.

isomeric zeylenol (**12**) [12], seneol [11] and ferrudiol [13] clearly arise by ring opening of the epoxide with diol formation.

EXPERIMENTAL

Plant material. Stem bark of *Monanthotaxis buchananii* was collected in the Mwanihana Forest Reserve in Tanzania in October 1984 and sun-dried. A voucher, DT 3624, has been deposited at the Herbarium of the Missouri Botanic Gardens.

Extraction and isolation of compounds. The ground stem bark (250 g) was extracted in a Soxhlet apparatus with petrol (bp 40–60°) and then $CHCl_3$. After concn the petrol extract was subjected to CC over silica gel eluting with petrol containing increasing amounts of EtOAc. Elution with 20% EtOAc yielded **1** (150 mg). Similar treatment of the $CHCl_3$ extract gave, with 20% EtOAc, **3** (25 mg) followed by a mixture of **3** and **5** (30 mg). Further elution with 50% EtOAc gave **7** (10 mg) and finally **11** (60 mg).

(+)-*Pipoxide-2-methyl ether* (**1**). Needles from a mixture of petrol and EtOAc, mp 109–111°, $[\alpha]_D$ + 17° ($CHCl_3$; *c* 1.15). Found: $[M]^+$ 380.1223; $C_{22}H_{20}O_6$ requires 380.1269. UV-λ_{max} nm (log ε): 230 (4.44), 275 (3.23), 284 (3.13). IR ν_{max} cm^{-1}: 3060, 2930, 1725, 1710, 1600, 1585, 1450, 1350, 1180, 900, 845. EIMS *m/z* (rel. int.): 380 $[M^+]$ (39), 258 $[M-122]^+$ (37), 217 (30), 215 (51), 154 (58), 136 $[M-244]^+$ (2), 122 $[C_7H_6O_2]^+$ (23), 105 (100).

Monanthadiepoxide methyl ether (**3**). Needles from a mixture of petrol and EtOAc, mp 165–167°, $[\alpha]_D$ + 25° ($CHCl_3$; *c* 0.15). $[M]^+$ 396. UV λ_{max} nm (log ε): 230 (4.47), 275 (3.29), 284 (3.20). IR ν_{max} cm^{-1}: 1745, 1735, 1605, 1455, 1290, 1270, 1115, 925, 715. EIMS *m/z* (rel. int.): 289 (12), 274 $[M-122]^+$ (2), 260 (16), 244 (17), 215 (13), 152 $[M-244]^+$ (28), 122 (27), 105 (100). NCIMS *m/z* (rel. int.): 396 $[M]^+$ (35), 276 (12), 122 (14), 121 (100).

Mixture of **3** *and boesenboxide* (**5**). Amorphous solid. M^+ 424 (NCIMS). IR ν_{max} cm^{-1}: 1750, 1720, 1710.

Epimonanthadiepoxide (**7**). Needles from a mixture of petrol and EtOAc, mp 167–171°, $[\alpha]_D$ −40° ($CHCl_3$; *c* 0.16). M^+ 382 (NCIMS). UV ν_{max} nm (log ε): 229 (4.39), 275 (3.40), 283 (3.38). IR λ_{max} cm^{-1}: 3480, 1740, 1730, 1715, 1550, 1300, 1265, 1130, 1125, 960, 855, 710. EIMS *m/z* (rel. int.): 260 $[M-122]^+$ (1), 138 $[M-244]^+$ (7), 122 (3), 105 (100). NCIMS *m/z* (rel. int.): 382 $[M]^+$ (100), 278 (8), 262 (14), 138 (25), 121 (55). Attempted synthesis of *epimonanthadiepoxide chlorhydrin* (**9**). **7** (5 mg) was dissolved in $CHCl_3$ (1 ml) and mixed with 3 ml of 2 N HCl in MeOH. After 30 min the reaction mixture was evapd to dryness and subjected to CC over silica gel eluting with $CHCl_3$ to give a *bischlorhydrin* product **10** (2 mg). ^1H NMR ($CDCl_3$, 250 MHz): δ5.42 (1H, *t*, *J* = 9.5 Hz, H-4).

1α-*Benzoyloxymethyl-3α-benzoyloxycyclohex-5-en-1β,2β,4β-triol* (**11**). Needles from a mixture of petrol and EtOAc, mp 178–183°, $[\alpha]_D$ −100° (EtOH; *c* 0.24). M^+ 384 (NCIMS). UV-λ_{max} nm (log ε): 228 (4.42), 274 (3.32), 282 (3.28). IR ν_{max} cm^{-1}: 3510, 3310, 3180, 1720, 1695, 1450, 1170, 1130, 720. EIMS *m/z* (rel. int.): 262 $[M-122]^+$ (6), 249 (61), 231 (24), 215 (11), 135 (4), 122 (57), 105 (100). NCIMS *m/z* (rel. int.): 384 (100), 280 (7), 262 (7), 121 (5).

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