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Curcapitoside, a Novel Glucosyl-Fused Phenanthropyran Isolated from *Curculigo Capitulata*

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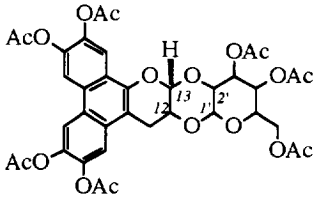
Abstract: Curcapitoside, characterized as the peracetate, is a novel glucosyl-fused phenanthropyran isolated from the rhizome of *Curculigo capitulata*. This novel skeleton was elucidated on the basis of spectral analysis. Copyright © 1996 Elsevier Science Ltd

The herb, *Curculigo capitulata* (Lour.) O. Kuntze (Amaryllidaceae), alias *C. recurvata*, widely distributed in southern and southwestern China, Malaya, India, Australia and Taiwan, is used as tonic, also in the treatment of dysmenorrhea and rheumatism.[1] Past studies on its chemical constituents have resulted in the isolation of several novel acetylenic norlignans with nyasicoside as the major one.[2,3] Being interested in exploring biologically active substances from this folk medicine, we reinvestigated this plant. This study led to the isolation of curcapitoside (**1**), a new compound with a novel glucosyl fused phenanthropyran skeleton, in addition to the reported nyasicoside from the H_2O soluble fraction of EtOH extract of the rhizome. Here the structure elucidation of this compound is described.

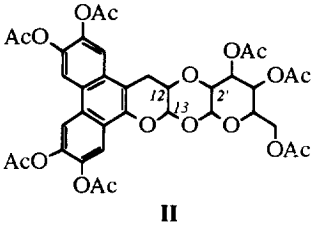
Compound **1**, being unstable during the last step of purification, was characterized as the peracetate derivative **1a**. Compound **1a**,[4] needle crystals, mp. 158-160°C ($CHCl_3$), has a molecular formula $C_{37}H_{36}O_{18}$ deduced from HRFABMS. Its UV spectrum revealed absorptions maxima at 248, 255, 279, 308 and 341 nm, characteristic of a phenanthrene chromophore.[5] The ^{1}H-NMR spectrum of **1a** showed signals of four aromatic protons, seven sugar protons, and four non-sugar aliphatic protons besides seven methyl singlets belonging to the acetyl groups. The four aromatic singlets appearing at δ 7.54, 8.09, 8.20, 8.22 ppm were observed to be long range coupled (δ 7.54 <–> δ 8.20; δ 8.09 <–> δ 8.22) in the COSY-45 spectrum, indicating two pairs of *para* protons. These spectral data and NOE studies, which show mutual enhancements of the singlet at δ 8.20 with the singlet at δ 8.22, would locate H-1 (δ 8.09), H-4 (δ 8.22), H-5 (δ 8.20) and H-8 (δ 7.54). Irradiation at the aromatic singlets also enhanced four different acetyl Me signals, respectively, locating them at δ 2.37 (2-OAc), 2.35 (3-OAc), 2.34 (6-and 7-OAc). Analysis of the signals of seven well resolved sugar protons suggested a β-glucosyl unit with the anomeric proton at δ 5.17 (d, J = 8.7 Hz). Their assignments (Table 1) were further confirmed by the analysis of a COSY-45 spectrum. Among these, chemical shifts of H-3' (δ 5.36), H-4' (δ 5.06) and H-6' (δ 4.08, 4.21) are shifted much more downfield than those in the parent sugar, indicating 3'-OH, 4'-OH and 6'-OH being acetylated. This would leave C-1' and C-2' to be ether linked to other structure moiety. As for the arrangement of the four other aliphatic protons, the proton signal at δ 4.89 (dd) was observed to couple to methylene protons (δ 3.33 and 3.24, each dd) and a methine proton (δ 5.59, s) in the COSY spectrum. The methylene protons were identified as H-11 by an NOE experiment, which enhanced the

signals at δ 3.33 and 3.24 upon irradiation of the H-8 singlet (δ 7.54). Extending this result and the COSY data designated H-12 at δ 4.89 and H-13 at δ 5.59. Furthermore, H-12 and H-13 are *cis* oriented from the NOE studies. Chemical shifts of H-12 and H-13 would suggested C-12 being ether linked and C-13 likely to be an acetal carbon.

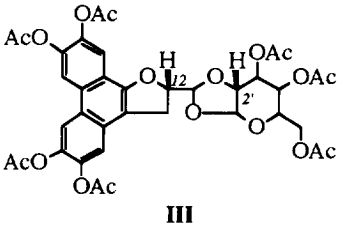
Pooling the above structural information together would propose three possible skeletons for **1a**, i.e. two glucosyl fused phenanthropyrans **I**-**II** and a phenanthrofuran **III**. Skeleton **III** was eliminated from the candidates since a large NOE for H-2' (8.5%) upon irradiation of H-12 was observed. The HMBC data (Table 1) revealed a three-bond coupling of H-13 to C-2' (δ 72.9), assigned from an HMQC spectrum, instead of C-1'. This would further eliminate skeleton **II**, and suggest **I**, whose fused glucosyl moiety is C-1' ether-linked to C-12 and C-2' to C-13, as the only skeleton for **1a**, leaving the stereochemistry to be determined.



I

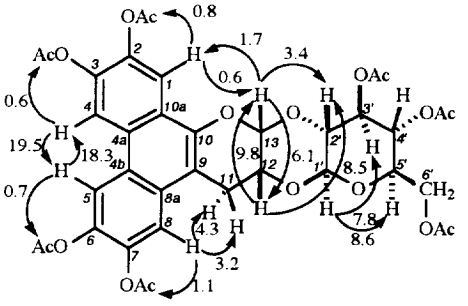


II



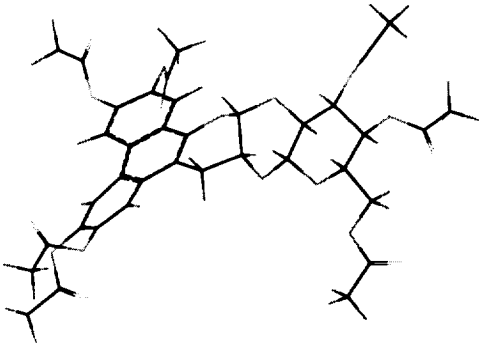
III

NOE studies displayed the enhancement of the H-2' signals (δ 4.02, dd), but not H-1', upon irradiation of the frequency of H-12 or H-13. Incorporating these results with the fixed stereochemistry of the presumed β-D-glucosyl unit, which is the glycone of nyasicoside[6] and related compounds from the same plant origin,[2,3] as guiding post, and also the *cis* relationship of H-12 and H-13 as indicated above determined the 12-*R*, 13-*S* stereochemistry for **1a**. This stereochemistry would arrange the dioxane ring as twisted boat form, for which the larger NOE of H-12 to H-2' than that of H-13 to H-2' is accounted, and this suggestion is supported by the computer assisted modeling study[7] which afforded the energy-minimized conformation as depicted in the figure. This model displays a perpendicular relationship between the planes of phenanthrene and sugar moieties, for which long NOE of H-1 to H-1' accounts.



Other key NOE's H-12 to H-11β (4.1) and H-11α (1.9)
H-1 to H-1' (0.6), H-1' to H-1 (1.0)

NOE's (%, $CDCl_3$) of **1a**



Favored conformation of **1a**

To our knowledge, **1a** represents the first natural occurrence of glucosyl-fused phenanthropyran skeleton.The trivial names, curcapitoside (**1**) and curcapitoside peracetate (**1a**), are made after its plant origin.

This assigned structure was further supported by the mass spectrum in which the fragment ions at *m/z* 380 (**A1**), 338 (**B1**) and 296 (**C1**) were obtained *via* characteristic retro Diels-Alder (RDA) type fragmentation. The major fragment ions at *m/z* 354 (**A2**), 312 (**B2**) and 270 (**C2**, base peak) were formed *via* secondary RDA process.

With ^{1}H-NMR data assigned, the ^{13}C-NMR assignment for **1a** was made by analysis of the 2D NMR spectra, HMQC and HMBC (Table 1).

Table 1. ^{1}H- and ^{13}C-NMR Data (δ/ppm) and 2D NMR data for compound **1a** ($CDCl_3$)

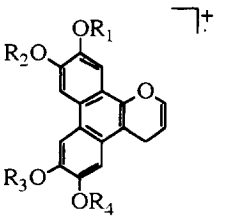
Position	δC (mult.)[a]	δH (mult.)[b,c]	COSY-45 Correlations (H#)	NOESY Correlations (H#)	HMBC (*J*= 8 Hz) Correlations (C#)[d]
1	116.8 d	8.09 s	4	--	3, 4a, 10, 10a
2	141.7 s	--	--	--	--
3	142.0 s	--	--	--	--
4	117.3 d	8.22 s	1	5	2, 4b, 10, 10a
4a	128.4 s	--	--	--	--
4b	130.1 s	--	--	--	--
5	117.6 d	8.20 s	8	4	4a, 6,7, 8a, 9
6	139.7 s	--	--	--	--
7	141.9 s	--	--	--	--
8	116.5 d	7.54 s	5	11α, 11β	6,7,,4b, 9
8a	124.6 s	--	--	--	--
9	106.9 s	--	--	--	--
10	144.6 s	--	--	--	--
10a	123.7 s	--	--	--	--
11	26.7 t	3.24 dd (α)	11β, 12	8, 12	9, 10, 12, 13
		3.33 dd (β)	11α, 12	8, 12	9, 10, 12, 13
12	67.0 d	4.89 dd	11α&β, 13	11α&β, 13, 2'	9
13	94.6 d	5.59 s	12	12, 1', 2'	12, 2'
1'	95.0 d	5.17 d	2'	13, 3', 5'	2', 3'
2'	72.9 d	4.02 dd	1', 3'	12, 13, 4'	1', 3'
3'	72.9 d	5.36 dd	2', 4'	1', 5'	1', 4'
4'	68.8 d	5.06 t	3', 5'	2', 6'a, 6'b	3', 6'
5'	73.1 d	3.80 ddd	4', 6'a, 6'b	1', 3'	4'
6'	61.8 t	4.08 dd (a)	5', 6'b	4', 5', 6'b	4', 5'
		4.21 dd (b)	5', 6'a	4', 5', 6'a	5'

[a] Three acetyl carbons appeared at δ 170.2 (3'), 169.7 (4'), 170.6 (5'); the remaining four acetyl carbons appeared at δ 168.4 (2C), 168.3 (2C), and seven methyl signals of acetyl groups at δ 20.77 (1xC), 20.70 (1xC), 20.66 (4xC) and 20.56 (1xC).

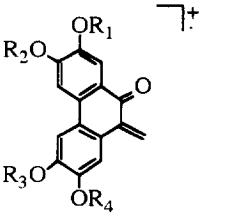
[b] The seven acetyl methyls appeared at δ 2.37 (2), 2.35 (3), 2.34 (6 and 7), 2.11 (3'), 2.03 (4'), 2.04 (5').

[c] Coupling constants (*J*) were as follows: 11α to 11β 18.6 Hz, 11α to 12 4.8 Hz, 11β to 12 3.6 Hz, 1' to 2' 8.7 Hz, 2' to 3' 8.9 Hz, 3' to 4' 9.4 Hz, 4' to 5' 9.4 Hz, 5' to 6'a 1.8 Hz, 5' to 6'b 5.1 Hz, 6'a to 6'b 12.4 Hz.

[d] 3'-Acetyl carbon correlated to H-3' and 3'-OCOMe, 4'-Acetyl carbon correlated to H-4' and 4'-OCOMe, 6'-Acetyl carbon correlated to H-6'b and 6'-OCOMe.



A1: R_1, R_2, R_3, R_4= 2x H, 2x Ac *m/z* 380
B1: R_1, R_2, R_3, R_4= 3x H, 1x Ac *m/z* 338
C1: R_1= R_2= R_3= R_4= H, *m/z* 296



A2: R_1, R_2, R_3, R_4= 2x H, 2x Ac *m/z* 354
B2: R_1, R_2, R_3, R_4= 3x H, 1x Ac *m/z* 312
C2: R_1= R_2= R_3= R_4= H, *m/z* 270

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References and Notes

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4. **1a** was isolated by the following procedure. The EtOH extract (110 g) from the dry powdered rhizome (1.1 kg) was fractionated into $CHCl_3$- (8 g) and H_2O- soluble parts. The aqueous layer was loaded onto an Amberlite XAD-2 column, eluted with H_2O-MeOH (7:3, 1:1, an 0:1). The 30% MeOH fraction (4.96 g) was rechromatographed on a RP-8 lobar column (Merck, B type) eluted with MeOH-H_2O (3:7) to give a **1** containing fraction (400 mg) after the major nyasicoside fraction. Since **1** was unstable during further separation and thus was peracetylated with Ac_2O/py and the product **1a** (24 mg, ca 0.0014% yield as **1**) was obtained *via* purification on a silica gel column eluted with MeOH-$CHCl_3$ (2:98). The physical data of **1a** were obtained from the following instruments: Fisher-Johns melting point apparatus (uncorrected); JASCO DIP-370 digital polarimeter; Perkin Elmer 1760-X infrared FT spectrometer; Hitachi 150-20 UV; JASCO J-710 spectropolarimeter; Finnigan Mat TSQ-700 (EIMS); JEOL JMX-HX110 mass spectrometer (HRFAB); Bruker AMX-400 spectrometer using solvent peak as reference standard, 2D NMR spectra were recorded by using Bruker's standard pulse program. **1a**: needle crystals ($CHCl_3$), mp. 158-160°C; $[\alpha]_D^{22}$= +119.0° ($CHCl_3$, *c*= 1.0); UV(MeOH) λ_{max} (log ε) 248 (sh 4.53), 255 (4.79), 279 (4.43), 308 (3.77), 341 (3.22), 358 (3.18) nm; IR (KBr) ν max 2950, 1760, 1620, 1510, 1460, 1435, 1375, 1240, 1220, 1120, 1060, 905 cm^{-1}; CD (MeOH) $[\theta]_{304}$ +3830°, $[\theta]_{291}$ +3140°, $[\theta]_{269}$ +10250°, $[\theta]_{259}$ +5560°, $[\theta]_{247}$ +20560°, $[\theta]_{235}$ +11040°, $[\theta]_{225}$ +18740°; EIMS (70 eV) *m/z* 768 ($[M]^+$, 0.3), 726 (1), 684 (3.0), 668 (2.8), 642 (5.2), 626 (4.2), 600 (4.0), 396 (8), 380 (**A1**, 9.0), 354 (**A2**, 20), 338 (**B1**, 28), 312 (**B2**, 48.0), 296 (**C1**, 78.0), 270 (**C2**, 100), 258 (24.0), 167 (29.6), 126 (52.0); HRFAB $[M]^+$ *m/z* 768.1895 (calcd for $C_{37}H_{36}O_{18}$, 768.1901).
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7. Molecular modeling was performed by Systematic Search of Sybyl using Tripos Force Fields (TRIPOS, Inc.) to obtain the favored conformation of **1a** with minimum energy.

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