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RESEARCH ON AFRICAN MEDICINAL PLANTS -XXV[+]- THE (1R,2S) ABSOLUTE CONFIGURATION OF NYASICOSIDE. ITS OCCURRENCE IN CURCULIGO RECURVATA.

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Abstract - The (R) configuration at C-1 of nyasicoside and its derivatives was assigned by comparison of the Cotton effect with those of optically active phenylcarbinols, whereas the (S) configuration at C-2 was assigned by the application of the CD exciton chirality method for the diol bis p-bromobenzoates.

Nyasicoside[1], 1, is a monoglucoside of 1,5-bis(3',4'-dihydroxyphenyl)-1,2-dihydroxy-pentan-4-yne isolated together with hypoxoside[2], nyasoside[3], mono-nyasine A and B[4], and nyaside[5] from the rhizomes of *Hypoxis nyasica*. In the earlier studies the small amount of nyasicoside isolated did not allow for the assignment of the absolute configuration for the diol unit. A reasonable amount of 1 has now been isolated from the rhizomes of another species of Hypoxidaceae, *Curculigo recurvata* Dryand of Eastern Zaire. It is considered an "all-cure" medicament, in particular, the rhizomes are used by the Bashi tribe of the Kivu Province as an oral decoction or for the treatment of snake bites and arthropod stings[6].

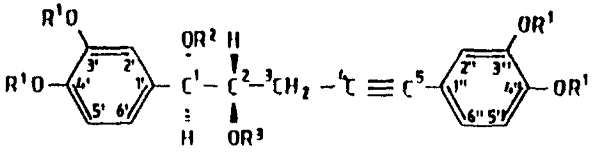
Nyasicoside, 1, as well as its tetramethyl derivative, 2, and the corresponding tetramethylaglucone, 3, showed a strongly positive Cotton effect ($[\theta]_{245}$= +8000, $[\theta]_{245}$= +25000, and $[\theta]_{245}$= +22600, in the corresponding order) due to the phenyl chromophore and the stereogenic benzylic carbon, C-1.

By comparison with the circular dichroism (CD) curves of some phenylcarbinols, (1R)-phenylethandiol, $[\theta]_{255}$ = +300, (1R)-phenylephrine hydrochloride, $[\theta]_{270}$= +1150 and (1R,2S)-ephedrine hydrochloride, $[\theta]_{255}$= +700, the same (1R) configuration was assigned to 1, 2, and 3.

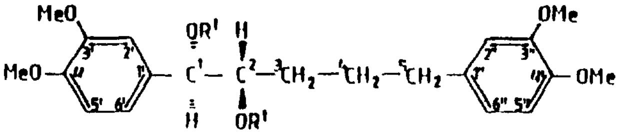
Dedicated to Prof. G.B. Marini-Bettolo on the occasion of his 75th birthday.

[+] Part XXIV: P. Rasoanaivo, C. Galeffi, G. Multari, and M. Nicoletti, submitted to *Planta Med.*.

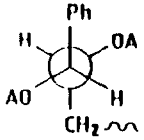
In order to establish the absolute configuration of the stereogenic centre C-2 of 1-3, the CD exciton chirality method, utilized for phenylglycols[7] through the typical exciton split Cotton effects of the corresponding bis p-bromobenzoates, was applied to 3, and its tetrahydro derivative 4.



	R^1	R^2	R^3
1	H	H	β-D-glucose
2	Me	H	β-D-glucose
3	Me	H	H
5	Me	A	A

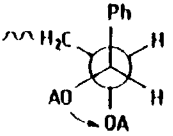


	R^1
4	H
6	A



A

NIL



B

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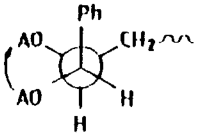

C

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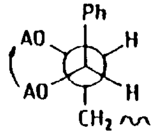
1*R*, 2*S*



D

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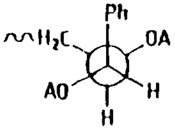
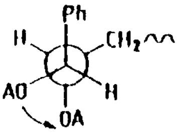


E

NIL



F

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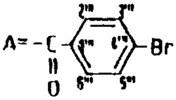
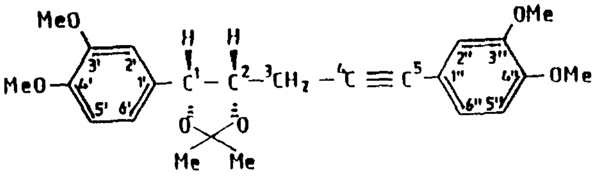
1*R*, 2*R*





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However different results were obtained for the two substances. As a matter of fact, whereas the bis p-bromobenzoate of 3, which corresponds to 5, showed practically nil exciton chirality, its tetrahydro derivative, 6, showed a strongly negative exciton chirality. Among the six possible conformers, A-C for (1R,2S) and D-F for (1R,2R), the value of the coupling constant J_{1-2} (7.5 Hz in 5 and 6) rules out the conformers A and F with trans orientation of H-1 and H-2. The strongly negative exciton chirality of 6 is, therefore, consistent only with the conformer B of the 1R,2S diasteroisomer. The practically nil exciton chirality of 5 is explicable in terms of the presence of two equally populated conformers, B and C. These results are in agreement with the conformational preference for the gauche oxygen functions in the diesters of 1-phenyl-1,2-butandiols [8], as in the corresponding free diols stabilized by intermolecular hydrogen bonding.

Table 1. ^{1}H NMR chemical shift assignments of 4-7.*

	4	5	6	7
1	4.45,d J=7.0	6.31,d J=7.5	6.00,d J=7.5	4.83 J=8.5
2	3.76,q J=7.0	5.71,dt J=7.5,5.0	5.70,dt J=7.5,5.0	3.96,dt J=8.5,5.0
3	1.70,m	2.80,dd J=17.0,5.0	1.5-1.8	2.70,dd J=18.0,5.0
	1.90,m	2.61,dd J=17.0,5.0	1.5-1.8	2.79,dd J=18.0,5.0
4	1.45,m	-	1.5-1.8	-
5	2.58, dt J=14.0,7.0 2.62,ddd J=14.0,7.5,6.0	-	2.4-2.6	-
2'	6.80,d J=2.0	7.02,d J=2.0	6.91,d J=2.0	6.96,d J=2.0
5'	6.88,d J=8.0	6.84,d J=8.0	6.80,d J=8.0	6.83,d J=8.0
6'	6.55,dd J=8.0,2.0	7.10,dd J=8.0,2.0	6.97,dd J=8.0,2.0	6.96,dd J=8.0,2.0
2"	7.05,d J=2.0	6.81,d J=2.0	6.55,d J=2.0	6.81,d J=2.0
5"	6.98,bs	6.74,d J=8.0	6.68,d J=8.0	6.74,d J=8.0
6"	6.98,bs	6.93,dd J=8.0,2.0	6.54,dd J=8.0,2.0	6.89,dd J=8.0,2.0
2"', 6"'	-	7.82,7.88,d J=8.0	7.75,7.80,d J=8.0	-
3"', 5"'	-	7.48,7.51 J=8.0	7.44,7.48,d J=8.0	-
MeO	3.94(2),3.99(2)	3.80,3.81 3.82,3.84	3.75,3.80 3.81,3.83	3.79(2),3.82(2)
MeC	-	-	-	1.55,1.57

*Coupling constant values are in Hz and chemical shifts in δ.
4 in CD_3OD, 5-7 in $CDCl_3$.

The *erythro* configuration (1*R*,2*S*) could thus be assigned unambiguously to compounds 5 and 6 and therefore to 1-4.

A partial confirmation of the *erythro* configuration is the high value of the coupling constant J_{1-2} (8.5 Hz) of the acetonide of the diol 3, 7, more consistent with a *cis* relationship between the two hydrogens.

The different exciton chirality between 5 and 6 shows that it is difficult to establish the preferred conformation(s) for the application of the CD exciton chirality method in the acyclic polyols.

The presence in *Curculigo recurvata* of nyasicoside, 1, norlignan type Ph-C_5-Ph as well as the other isolated from genus *Hypoxis* [1-5], is therefore a taxa common to the two genera *Curculigo* and *Hypoxis*, which were associated in the same family, Hypoxidaceae, because of the morphological similarity [9].

Table 2. ^{13}C NMR chemical shift assignments of 4-7.*

	4	5	6	7
1	78.2	76.7	77.5	82.3
2	76.1	73.6	75.3	80.9
3	35.6	22.2	34.8	22.4
4	28.0	82.1	26.8	82.9
5	32.7	83.5	30.0	83.5
1'	135.9^a	128.6^a	128.3^a	130.3
2'	112.7^b	114.4^b	111.9^b	114.8
3'	149.5^c	149.7^c	149.3^c	149.4^a
4'	149.4^c	149.4^c	149.6^c	149.4^a
5'	112.3^b	111.0^b	111.4^b	111.5^b
6'	121.0^d	120.1	120.3^d	119.6
1"	135.0^a	115.3	134.2	115.8
2"	111.9^b	111.3^b	111.4^b	111.2^b
3"	149.2^c	149.2^c	149.3^c	148.7^a
4"	147.6^c	148.6^c	147.4^c	149.4^a
5"	111.0^b	110.5^b	110.7^b	110.3^b
6"	120.2^d	124.7	120.2^d	124.8
1"'	-	128.3^a,128.4^a	128.9^a,129.6^a	-
2"', 6"'	-	131.1, 131.2	131.0, 131.7	-
3"', 5"'	-	131.8	131.8	-
4"'	-	128.4^a	128.7^a,128.8^a	-
C=O	-	164.8, 165.1	164.8, 165.5	-
MeO	56.2	55.8, 55.9	55.7, 55.8 55.9, 56.0	55.9, 56.0
O-C-O	-	-	-	109.1
MeC	-	-	-	27.2, 27.3

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* Chemical shift values in ppm. 4 in CD_3OD, 5-7 in $CDCl_3$.

[a, b, c, d] These signals may be interchanged in the same column.

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EXPERIMENTAL

Separations were carried out by CCD (counter-current distribution) using a Craig Post apparatus (200 stages, 10·10 ml, upper and lower phase), and by CCC (counter-current chromathography) using an Ito multy layer coil separator. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AM 400 spectrometer (TMS as internal reference). The spectral data of compounds 4-7 are reported in tables 1 and 2, respectively. Circular dichroism (CD) curves (MeOH) were registered with a Jasco J-40 apparatus.

Plant material, extraction and separation. Rhizomes of *C. recurvata* Dryand were collected at Lwiro (Kivu, Zaire) in November 1988, and in January-February 1989. The identification was made by Prof. J. Lejoly (Laboratoire de Botanique Systématique et de Phytosociologie, Université Libre de Bruxelles , Belgique). A voucher specimen is deposited with the Herbarium at Département de Biologie, Centre de Recherche en Sciences Naturelles, Lwiro (Zaire). The dried material (1.6 Kg) was ground, exhaustively extracted with aqueous MeOH (80%) and the eluate was then evaporated. The residue (220 g) was submitted by 9 g portions to CCD between H_2O:EtOAc:*n*-BuOH:Acetone 20:16:4:1. The fraction at K_r= 0.8 (0.5 g), purified with the same solvent system, gave pure nyasicoside (140 mg), identified by comparison with an authentic sample.

For the preparation of tetramethylnyasicoside, 2, and its aglucone, tetramethylnyasicol, 3, see reference 1.

Hydrogenation of 3: 4. Tetramethylnyasicol (120 mg) dissolved in 90% aqueous methanol (10 ml) was hydrogenated in presence of 5% Pt($BaSO_4$) (20 mg). After one night, the catalyst was removed by filtration and the residue of the solution was purified by CCC using H_2O:Acetone:Cyclohexane:EtOAc 5:4:5:3. The compound resisted any attempt of crystallization. EIMS, m/z: 376 (M^+, $C_{21}H_{28}O_6$).

Tetramethylnyasicol-1,2-bis-p-bromobenzoylester, 5. P-Bromobenzoyl chloride (300 mg) was added to a solution of 3 (90 mg) in anhydrous pyridine (3 ml), and kept overnight at 60 °C. The reaction mixture, after quenching with MeOH, was evaporated to dryness and purified by CCD using H_2O:EtOH:Acetone:*n*-hexane 4:6:3:10. Pure 5 was obtained, K_r=1. Crystals from *n*-hexane, m.p. 109-11°C, $[\alpha]_D$= -13.0 (c 0.6, $CHCl_3$). (Found: C, 56.75; H, 4.28. Calc. for $C_{35}H_{30}O_8Br_2$: C, 56.92; H, 4.09 %).

Tetrahydrotetramethylnyasicol-1,2-bis-p-bromobenzoylester, 6. The same procedure utilized for the preparation of 5 was utilized for 6. The compound resisted any attempt of crystallization. $[\alpha]_D$= -20.0 (c 1.5, $CHCl_3$). CD, $[\theta]$ (λ_{max}, nm): -32000 (257). The second Cotton effect is not measurable on account of the predominant absorption.

Tetramethylnyasicol acetonide, 7. Compound 3 (30 mg) and zinc chloride (100 mg) were stirred in anhydrous acetone overnight. The reaction mixture was evaporated, and purified by CCC using H_2O:EtOH:Acetone:Cyclohexane 3:1:6:7 to give pure 7. Crystals from n-hexane, m.p. 76-8°C. EIMS, m/z: 412 (M^+). (Found: C,69.58; H, 6.98. Calc. for $C_{24}H_{28}O_6$: C, 69.88; H, 6.84 %).

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