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NEOISOSTEGANE, A NEW BISBENZOCYCLOOCTADIENOLACTONIC LIGNAN FROM *Steganotaenia araliacea*, HOCHST. (1).

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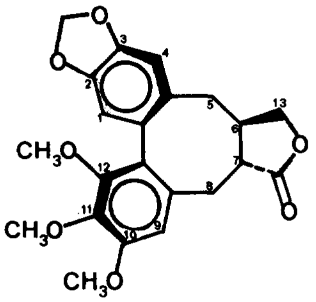
Abstract : The structure of neoisostegane, the first naturally-occurring stegane analogue to be described, was determined by analysis of spectral data, particularly by the application of ^1H - ^1H long range selective proton decoupling experiments at 400 MHz.

As part of a current antitumor screening program on higher plants (2), we are carrying out chemical investigations of the west-african variety of *Steganotaenia araliacea* (3). Besides the four lignans discovered by Kupchan (4) in a sample of east-african origin, we have found a number of new lignans. We describe here the isolation of a new lactonic lignan closely related to isostegane **1a** (5).

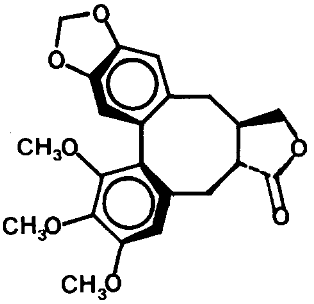
Neoisostegane, **2**, was detected in the CCl_4 fraction using the standard fractionation tree of the National Cancer Institute Screening Program for confirmed active extracts (6). Careful preparative layer chromatography (Silicagel Merck, Si 60 ; Hexane - AcOEt) yielded a new crystalline solid ; mp 71 - 74°C (ether) ; $[\alpha]^{20°}D$ + 65°±5 (C 0.35, $CHCl_3$) ; IR 1776 cm^{-1} (lactone C=O) ; $M^{+\cdot}$ calcd for $C_{23}H_{26}O_7$ 414,1679, found 414,1671 ; NMR (7) (δ, $CDCl_3$) 6.72 (s, 1H) 6.69 (s, 1H) ; 6.52 (s, 1H) ; 3.96 (s, 3H) 3.94 (s, 6H) ; 3.89 (s, 3H) 3.86 (s, 3H). See Table for aliphatic protons.

These preliminary data demonstrated that neoisostegane **2** was a bisbenzocyclooctadienolactonic lignan. Dreiding Models examination and comparison of ^3J aliphatic coupling constants in the four diastereoisomers of stegane **1b** (5) proved that the stereochemistry of **2** is the same as that of isostegane **1a** (8).

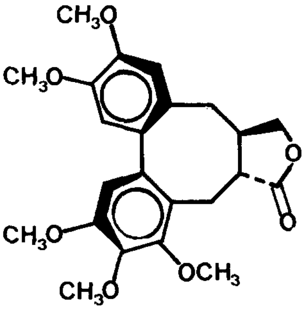
Neoisostegane 2 has a trans lactone with $J_{6,7}$ = 13.2 Hz *versus* 8 Hz in the cis series. A.S. Kende (9) and ourselves (1,5) have previously pointed out that when the iso biaryl junction is present in conjunction with a trans lactone, the 5α - 6 and the 8β - 7 coupling constants are both 0 Hz, as opposed to 8 Hz in the trans-normal (= P*-6R*) series (10). Comparison of the vicinal coupling constants (see table) of 1a and 2 clearly indicated that the two stereochemistries were identical.



1a



1b



2

assignment	δ($CDCl_3$)		assignment	J. Values Hz	
	1a (7)	2 (7)		1a	2
H-5α	2.64 d	2.68 d	5α-5β	12.9	13.2
H-5β	2.44 dd	2.42 dd	5α-6	0	0
H-6	2.15 m	2.23 m	5β-6	9.0	10.0
H-7		2.04 m	6 -13α	6.5	7.2
H-8α	2.30 dd	1.93 dd	6 -13β	10.6	11.4
H-8β	3.12 d	3.69 d	6 -7	13.2	13.2
H-13α	4.40 dd	4.37 dd	7 -8α	9.2	9.2
H-13β	3.78 dd	3.78 dd	7 -8β	0	0
OMe-12	3.57 s	-	8α-8β	13.3	13.4
Other OMe	> 3.8 s	> 3.8 s	13α-13β	8.4	8.4

However 2 differed from 1a in several aspects :

- absence of methylenedioxy group ;
- présence of five methoxyl groups, none of which exhibits a

high-field-methyl in PMR ;

- much larger low-field shift for H-8β.

At this point, analysis of the aromatic region (3H, s) in the ^{1}H NMR spectrum allowed an unambiguous determination of the position of the first four OMe at C-2, C-3, C-9 and C-10 on the isostegane skeleton ; the fifth OCH_3 was located at C-1, C-4, C-9 or C-12 . Irradiation at δ 2.68 (H-5α) lead to a clear enhancement and sharpening of the singlet at 6.69 ppm ($^4J_{4,5\alpha}$= 0,3 Hz) which eliminated the possibility of methoxyl at C-4. Lack of a high-field-methoxyl signal (*versus* isostegane itself) was a good argument (11) for eliminating the methoxyl location at C-1 and C-12. On the other hand, irradiation at 3.69 (H-8β) induced no variation in the aromatic region, which indirectly substantiated this assertion.

Finally, examination of H-8β in **1** and **2** using Dreiding models, clearly explained the particularly low-field shift in PMR of the latter ; in the two cases, H-8β was sterically compressed between lactonic carbonyl and H-9. Concerning **2**, the greater low-field H-8β at δ 3.69 implied that there was a more bulky methoxyl at C-9.

According to these results, **2** is (M*, 6R*, 7R*)-(+)-neoisostegane (5,12)

REFERENCES

(1) First paper : *Tetrahedron Lett.*, *24*, 197, (1983).

(2) We are grateful to Dr. Matthew SUFFNESS (NCI-NIH Bethesda, Md, U.S.A.) for helpful discussion.

(3) Collected in Guinea (Timbo, Fouta-Djallon) during April, 1980. We are grateful to the late. K. KOUROUMA, Institut Polytechnique de Conakry, for his help in botanic collection.

(4) S.M. KUPCHAN, R.W. BRITTON, M.F. ZIEGLER, C.J. GILMORE, R.J. RESTIVO and R.F. BRYAN, *J. Am. Chem. Soc.*, *95*, 1335 (1973).

(5) For an explanation of nomenclature see : J.P. ROBIN, O. GRINGORE and E. BROWN, *Tetrahedron Lett.*, *21*, 2709 (1980). Hitherto steganes have been described exclusively as synthetic compounds. For recent reviews see : M. MERVIC, Y. BEN DAVID and E. GHERA, *Tetrahedron Lett.*, *22*, 5091 (1981)

and R.S. WARD, Chemical Society Reviews, 75, (1982).

(6) NSC B 847 587. M. SUFFNESS and J. DOUROS, Methods in Cancer Research, Vol. XVI, 73 (1979).

(7) ^{1}H Chemical shift assigments and homonuclear decoupling experiments were established at 250 MHz for 1, and at 400 MHz for 2.

(8) Of synthetic origin : E. BROWN and J.P. ROBIN, Tetrahedron Lett., 38, 3613 (1978).

(9) A.S. KENDE and L.S. LIEBESKIND, J. Amer. Chem. Soc., 98, 267 (1976).

(10) This is in agreement with dihedral angles of 90° in 1 and 2.

(11) High-field-OMe is usualy attributed to the anisotropic shielding of hydrogen situated above the plane of the other phenyl ring. A. BROSSI, J.C. BRIEN and S. TEITEL, Helv. Chim. Acta, 52, 678 (1969).

(12) Albert T. SNEDEN and Rickey P. HICKS of Virginia Commonwealth University, (Richmond, Virginia 23284, U.S.A.) have found independently through chemical transformations of naturally-occuring steganacin that the structure 2 is indeed the only possibility (next paper).

Note added in proof :

The ^{1}H-NMR spectra of samples of neoisostegane coming from both sources were superimposable. The Rf's in 4 different solvent systems were also identical.

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