275. *Naturally Occurring Oxygen Heterocyclics. Part XI.* Veraguensin.*

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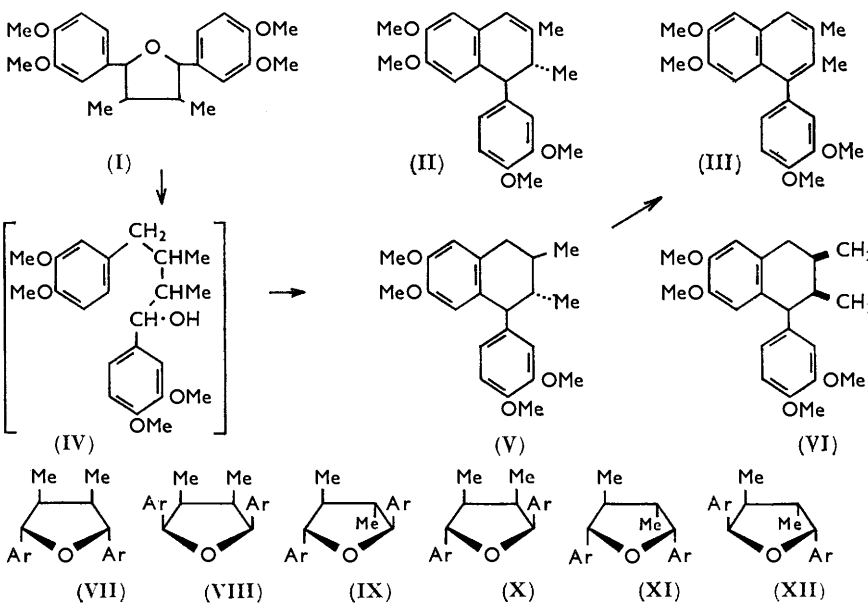
A new optically active lignan, isolated from *Ocotea veraguensis* Mez., has been named veraguensin and its structure (XI) determined by a combination of chemical degradations and nuclear magnetic resonance measurements.

From the hexane extract of the Mexican tree *Ocotea veraguensis* Mez. (fam. Lauraceae) there was isolated a colourless neutral substance which we have now named "veraguensin." Analytical values and the mass-spectrometrically determined molecular weight were consistent with the formula $C_{18}H_{16}O(OMe)_4$, suggesting a compound of the lignan type, isomeric with galgravin [1] and galbelgin.[2] The ultraviolet absorption maxima for these three compounds were identical (231 and 278 mμ), and the infrared spectrum of galgravin was very similar to that of veraguensin.

Birch *et al.*[2] proposed formula (VII) for optically inactive galgravin and (IX) for optically active galbelgin. Another isomer was obtained by Blears and Haworth [3] who assigned to it the all-*cis*-structure (VIII), since its synthesis involved hydrogenation of the corresponding furan; they also found that compound (VIII) was isomerised to galgravin (VII) by acid. Veraguensin was optically active and might, therefore, have structure (X), (XI), or (XII) or an antipode of one of these. It was expected that under the same conditions as converted compound (VIII) into galgravin (VII), a compound (X) would give galgravin (VII), whereas (XI) would give galbelgin (IX).



When veraguensin was treated with perchloric acid in acetic acid for 30 min. at room temperature, a crystalline, optically active compound $C_{22}H_{26}O_4$ (mass spectrometric molecular weight 354) was obtained, with constants very similar to cyclogalbelgin (II)

* Part X, Finnegan, Morris, and Djerassi, *J. Org. Chem.*, 1961, **26**, 1180.

[1] Hughes and Ritchie, *Austral. J. Chem.*, 1954, **7**, 104.
[2] Birch, Milligan, Smith, and Speake, *J.*, 1958, 4471.
[3] Blears and Haworth, *J.*, 1958, 1985.

which was obtained by treating galbelgin (IX) with acid.[2] Blears and Haworth [3] found that galgravin (VII) required six days under similar conditions to form cyclogalgravin, an optically inactive isomer of (II) and, measuring the rates of reaction, Birch *et al.*[2] report that galbelgin (IX) reacted at one-sixth of the rate of galgravin (VII).

The cyclised product (II) from veraguensin was dehydrogenated by palladium–charcoal to dehydroguaiaretic acid dimethyl ether [4] (III), identical with a sample prepared by the dehydrogenation of (—)-galbulin (V).[1]

On reduction with sodium in liquid ammonia [2] veraguensin yielded a dihydro-derivative (IV) (not isolated), which cyclised during chromatography on silica gel to (—)-galbulin (V). Under these conditions galbelgin (IX) is reported to afford (—)-galbulin, while galgravin (VII) gave (±)-isogalbulin (VI; R = H).[2] The latter was correlated with β-conidendryl alcohol dimethyl ether (VI; R = OH) by Schrecker and Hartwell,[5] thus leading to a *cis*-relationship for the methyl groups in (±)-isogalbulin (VI; R = H) and in galgravin (VII), whereas the methyl groups in (—)-galbulin (V), (—)-galbelgin (IX), and veraguensin are *trans*-oriented. This establishes the structure of veraguensin as (XI) or (XII) or an antipode.

Of the three isomeric lignans available to us galgravin (VII) has the simplest nuclear magnetic resonance spectrum.* The peak [6] for aromatic methoxyl appears at τ 6·13, and the aromatic protons form a multiplet between τ 3·10 and 2·90. The protons on the carbon atoms which carry the *cis*-methyl groups also form an ill-defined multiplet centred at τ 7·60. The doublet at τ 9·01 and 8·90 is attributed to the protons of the methyl groups, and the benzylic protons also form a doublet at τ 5·52 and 5·42.

The spectrum of galbelgin (IX) is slightly different. There are two peaks due to the methoxyl groups (τ 6·11 and 6·15), and the multiplet due to the aromatic protons is slightly upfield at τ 3·20—3·00. The position of the doublet assigned to the methyl groups is unchanged but the centre of the multiplet from the methyl-hydrogen atoms is shifted upfield from τ 7·60 to 8·25. The benzylic protons form a doublet shifted downfield to τ 5·42 and 5·39.

The spectrum of veraguensin is rather more complex. The aromatic methoxyl groups yield signals resulting in a barely resolved triplet between τ 6·15 and 6·10. The aromatic protons form a broad multiplet τ 3·20—2·85, and the protons on the methyl-bearing carbon atoms also form a broad multiplet (τ 8·20—7·70). As would be expected from the proposed structure (XI) in which the methyl groups are dissimilar, there is a doublet for each methyl group, one at τ 9·00 and 8·90 and the other upfield at τ 9·41 and 9·30. The benzylic protons also give rise to two doublets, one at τ 5·65 and 5·51 and the other at τ 4·94 and 4·81.

The spectrum of galgravin is entirely consistent with the proposed structure (VII). A model shows considerable interaction between the dimethoxyphenyl groups and thus they will take up preferred conformations away from each other. This has the effect of bringing one or both of the rings with their π-electrons close to the protons on the methyl-carbon atom, with a corresponding shift downfield from the more usual position around τ 8·25 as in galbelgin (IX).

The spectrum of galbelgin (IX), therefore, is also consistent with the proposed structure. The separation of the methoxyl peak is evidently due to slightly different chemical shifts of the *meta*- and the *para*-methoxyl groups.

Because of the asymmetry of the molecule the three peaks for the methoxyl group protons in veraguensin are understandable. The protons on one of the methyl groups

* Nuclear magnetic resonance spectra were measured in deuterochloroform solution with tetramethylsilane as internal standard, on a Varian A–60 spectrometer.

[4] Schroeter, Lichtenstadt, and Irineu, *Ber.*, 1918, **51**, 1587.

[5] Schrecker and Hartwell, *J. Amer. Chem. Soc.*, 1955, **77**, 432.

[6] See Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959.

absorb upfield and these are, therefore, on the methyl which is shielded by a *cis*-dimethoxyphenyl group. Finally, one of the benzylic protons absorbs upfield compared with those of galgravin, the other downfield. This might also be explained by the fact that the aromatic rings, being *cis*-oriented, take up preferred conformations away from each other. The model shows that in this case these planes would probably be at right angles and that benzylic proton which is *trans* to the adjacent methyl group will lie in the plane of the benzene ring to which it is adjacent. It will, therefore, experience increased shielding and absorb upfield. The other benzylic proton absorbs downfield because it lies outside the plane of the adjacent ring leading to decreased shielding.

The chemical evidence presented does not exclude the structure (XII) for veraguensin. The nuclear magnetic resonance spectrum, however, is inconsistent with this structure since the two methyl groups in this structure are in identical situations, as are also the two benzylic protons. Because of this symmetry factor, the signals associated with these protons would not be expected to show the well-defined separations noted above. It follows that veraguensin is represented correctly by formula (XI).

Experimental

Optical rotations refer to chloroform solutions. Ultraviolet spectra were measured for ethanol solutions. M. p.s were determined on the Kofler block.

Extraction of Ocotea veraguensis.—Wood shavings (1·2 kg.) of *Ocotea veraguensis* Mez., collected by Dr. D. K. Cox of the Botanical Department of Syntex, S. A., Mexico City, were exhaustively extracted with hexane (2·5 l.) (Soxhlet). The extract was evaporated to 500 c.c., cooled, and filtered. The filtrate was evaporated to 200 c.c., cooled, and filtered; 275 mg. of crystals were obtained, having m. p. 125—126°. The filtrate was evaporated to dryness and crystallised from a little ether to give 338 mg. of material of m. p. 119—123°. The combined crystals (613 mg.) crystallised from ether, affording 495 mg. of material of m. p. 126—129°. Further crystallisation from ether gave veraguensin (XI), m. p. 128—129°, $[\alpha]_D^{25}$ +34·2° (*c* 1·10) [Found: C, 71·3; H, 7·7; OMe, 32·8%; *M* (mass spectrum), 372. $C_{22}H_{28}O_5$ requires C, 70·9; H, 7·6; OMe, 33·4%; *M*, 372], $\lambda_{max.}$ 231 (ε 14,350) and 278 mμ (ε 4640), $\nu_{max.}$ (in CS_2) 1260, 1231, 1162, 1127, 1033, and 806 cm.$^{-1}$.

Acid Treatment.—Veraguensin (175 mg.) was dissolved in acetic acid (3 c.c.) and a solution (3 c.c.) of 60% perchloric acid (1 c.c.) in acetic acid (5 c.c.) was added. After 30 min. the solution was poured into a 4% solution (250 c.c.) of sodium hydroxide. The mixture was extracted with methylene chloride (5 × 50 c.c.), the extracts were washed once with water, and the solvent was evaporated to an oil (177 mg.) which was filtered through neutral alumina in methylene chloride. An oil (166 mg.) was eluted which crystallised from ether, to give material (105 mg.), m. p. 98—100°, $[\alpha]_D^{28}$ +128° (*c* 2·79). Further crystallisation from ether furnished cycloveraguensin [2] (II), m. p. 100—101°, $[\alpha]_D^{27}$ +135·5° (*c* 0·28), identical with cyclogalbelgin [2] (II) prepared in this laboratory (m. p. 99—100°, $[\alpha]_D^{28}$ +132°) from (−)-galbelgin (IX) [Found: C, 74·4; H, 7·2; OMe, 34·85%; *M* (mass spectrum), 354. Calc. for $C_{22}H_{26}O_4$: C, 74·55; H, 7·4; OMe, 35·1%; *M*, 354], $\lambda_{max.}$ 222 (ε 32,700) and 280 mμ (ε 12,680), $\nu_{max.}$ (in $CHCl_3$) 1585, 1325, 1127, 1112, 1021, and 870 cm.$^{-1}$ (lit.,[2] m. p. 97—98°, $[\alpha]_D$ +125°).

Dehydrogenation of Cycloveraguensin (II).—The evaporated mother-liquors (58 mg.) from the acid-catalysed cyclisation were heated with 10% palladium–charcoal (100 mg.) at 200° for 4 min. The catalyst was washed with methylene chloride; evaporation gave a gum (32·6 mg.) which was crystallised three times from ether to give a pure compound (11 mg.), m. p. 178—179°. This was identical (mixture m. p., infrared spectrum) with dehydroguaiaretic acid dimethyl ether (III) prepared by dehydrogenation of (−)-galbulin [1] (V).

Reduction of Veraguensin with Sodium in Liquid Ammonia.—Veraguensin (150 mg.) was dissolved in ethylene glycol dimethyl ether (10 c.c.), liquid ammonia (25 c.c.) was added, and the mixture was stirred during addition of sodium (50 mg.). After 7 min. the blue colour was removed with methanol, water (1 c.c.) was added, and the ammonia was allowed to evaporate. More water was added. The product, isolated by extraction with methylene chloride, was a gum (141 mg.), $\nu_{max.}$ (in $CHCl_3$) 3700 and 3450 cm.$^{-1}$. This was separated in two portions by preparative thin-layer chromatography on two glass plates (20 × 20 cm.) covered with silicic acid and eluted with methylene chloride–methanol (50 : 1). A small strip was developed with

acidic ceric sulphate solution and showed three bands. The band with the lowest R_F value was extracted with methylene chloride. Evaporation of the solvent gave material (78 mg.), m. p. 128—129°, which was filtered through neutral alumina in methylene chloride. Recovery and recrystallisation from methanol gave (−)-galbulin (V), m. p. and mixed m. p. 131—132°, $[\alpha]_D^{24\cdot5}$ −8·8° (*c* 0·795).

We express our appreciation to Dr. E. Ritchie (University of Sydney) and Professor A. J. Birch (University of Manchester) for supplying us with several lignans, to Dr. D. K. Cox (Syntex, S. A., Mexico City) for the botanical collection, to Dr. H. Budzikiewicz for the mass spectra, to Dr. Lois Durham for the nuclear magnetic resonance spectra, to Mr. E. Meier for the microanalyses, and to the National Heart Institute of the U.S. Public Health Service for financial assistance.

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Stanford, California, U.S.A. [*Received, November 30th,* 1961.]