Structures of the Toxisterols$_2$.† *X*-Ray Crystal Structure of Toxisterol$_2$-A 3,5-Dinitrobenzoate

By ANTHONY G. M. BARRETT, DEREK H. R. BARTON,* MARTYN H. PENDLEBURY, LAWRENCE PHILLIPS, RICHARD A. RUSSELL, and DAVID A. WIDDOWSON

(*Chemistry Department, Imperial College, London* SW7 2AY)

and CHARLES H. CARLISLE and PETER F. LINDLEY*

(*Crystallography Department, Birkbeck College, Malet Street, London* WC1E 7HX)

Summary The structures of toxisterol$_2$-A, -B, and -C have been determined by spectroscopic and chemical evidence supplemented by an *X*-ray crystallographic study of toxisterol$_2$-A 3,5-dinitrobenzoate.

TOXISTEROLS are substances of undetermined structure and of reputed biological activity originally described about 50 years ago.[1] Only one toxisterol (toxisterol$_2$-A) has been properly characterised before.[1] All toxisterols have a u.v. maximum near 250 nm. We report the isolation, characterisation (Table) and structure determination of three such compounds, toxisterols$_2$-A, -B, and -C.

0·4% citric acid at room temperature for 22—25 h gave a resin. Repeated chromatography over alumina (Grade II) gave (from 40 g of resin) toxisterol$_2$-A [as 3,5-dinitrobenzoate (190 mg)], -B (50 mg) and -C [as benzoate (410 mg)]. We have not yet located the fourth possible stereoisomer.

^{1}H N.m.r., u.v., and i.r. data, which need not be detailed here, showed that all three toxisterols$_2$ had the 22(23)-*trans*-double bond intact and contained a cyclic heteroannular diene system of the type –CH=CH–C=C–(Me)–. Since the C_{-18} methyl group was also present in all compounds the vinylic methyl was presumed to be the original C_{-19} methyl.

TABLE

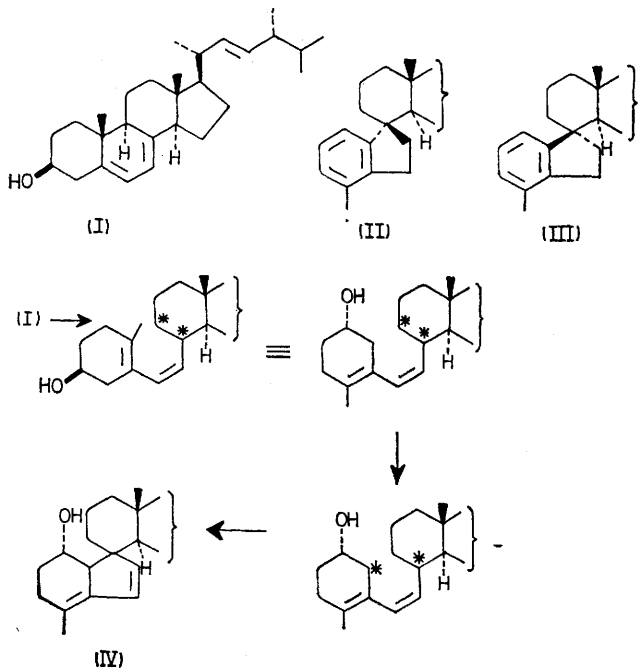
Toxisterols$_2$	M.p.	$[\alpha]_D$ ($CHCl_3$)	λ_{max}/nm (ϵ)	Other derivatives
A(V)	Oil	−157°	250(21,000)[a]	*p*-Phenylazobenzoate[b] m.p. 124—126°
Acetate	103—105°		250(20,000)[c]	Benzoate m.p. 106—108°
3,5-Dinitrobenzoate[d]	173—174°	−1	232(28,000)[a]	*p*-Nitrobenzoate m.p. 102—104°
B (VI)	107—109°	+169	253(22,000)[c]	
C (VII)	Oil	+17	250(17,000)[a]	
Benzoate	Oil	+133	228(25,000)[a] 235(22,000) 250(17,000)	

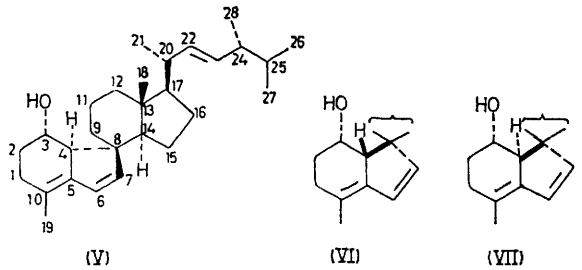
[a] In cyclohexane. [b] Lit.,[1] m.p. 125—126°. [c] EtOH. [d] Lit.,[1] m.p. 171—172°.

Irradiation (Phillips HPK 125 W type 57203 B/00) of ergosterol (I) in degassed ethanol containing 5% water and

The ^{13}C n.m.r. spectra were especially helpful and showed that an 'extra' quaternary carbon was present.

† The subscript 2 indicates that the compounds are derived from ergosterol rather than cholesterol (subscript 3).





that these compounds were 1,2,3-trisubstituted benzenes with one of the substituents being methyl.

Accepting the data at their simplest level of interpretation and using the plausible hydrogen atom transfer depicted in the Scheme, then structure (IV) seems reasonable for the toxisterols$_2$. This permits four stereoisomers about C-4 and C-8. The relationship of the configuration at C-3 (unchanged) and that at C-4 was established by ^{1}H n.m.r. spectroscopy. The configuration at the C-8 spiran centre was determined by the Nuclear Overhauser effect in the proton n.m.r. spectrum between the C-18 methyl group and the C-7 vinyl hydrogen (observed for the A isomer, but not for the B and C isomers).

Toxisterols$_2$-A, -B and -C can therefore be represented by formulae (V), (VI), and (VII) respectively. The complete structure of toxisterol$_2$-A was also determined independently by an *X*-ray crystallographic study of the derived 3,5-dinitrobenzoate.

Crystal data: $C_{35}H_{46}O_6N_2$, monoclinic, $a = 6{\cdot}358(1)$, $b = 21{\cdot}808(3)$, $c = 12{\cdot}259(2)$ Å, $\beta = 102{\cdot}81(1)°$, space group $P2_1$ (C_2^2, No. 4), $D_c = 1{\cdot}18$ cm^{-3}, $Z = 2$. μ(Cu – K_α = 6·6 cm^{-1}).

X-Ray intensity data were collected using Ni-filtered Cu radiation on a Hilger-Watts Y290 automated four-circle diffractometer. 1856 Independent reflections for which $I \geqslant 3\sigma(I)$ were measured over the range $0 \leqslant \theta \leqslant 70°$, and were corrected for Lorentz and polarisation effects; no correction was made for absorption. Several attempts to determine the structure using direct methods of phase determination were unsuccessful. The structure was eventually solved with extreme difficulty using a vector verification technique[2] to locate the 3,5-dinitrobenzoate unit, followed by iterative Fourier syntheses to find the remaining atoms. The structure has been refined using a partial full-matrix method to give a conventional *R* value of 0·056 with all non-hydrogen atoms treated anisotropically.

The figure is a stereo-drawing of the sterol portion of the molecule viewed along the crystallographic *y* axis, and

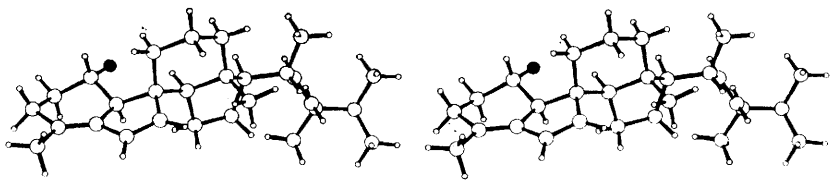


FIGURE. A stereo-drawing of toxisterol$_2$-A, showing the configuration at the spiro carbon atom C-8. The shaded atom at C-3 is the oxygen atom of the 3,5-dinitrobenzoate group which has been omitted for clarity.

Treatment of toxisterol$_2$-A with $CHCl_3$–HCl afforded smoothly a benzene derivative (II), m.p. 88—89·5°, $[\alpha]_D$ –55° (all $[\alpha]_D$ in $CHCl_3$). Treatment of toxisterol[2]-B and -C in the same way gave a different benzene (III), m.p. 69—71°, $[\alpha]_D$ + 6·0°. The n.m.r. and i.r. data showed clearly shows the spiro-configuration at C-8. The methyl hydrogen atoms have been placed in calculated positions but the remainder were located from a difference Fourier synthesis.

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[1] P. Westerhof and J. A. Keverling Buisman, *Rec. Trav. chim.*, 1956, **75**, 1245; and references there cited.
[2] P. B. Braun, J. Hornstra, and J. I. Leenhouts, *Philips Res. Repts.*, 1969, **24**, 85.