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Stereoisomerism in Biergostatrienol

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IT was recently suggested[1] that biergostatrienol (I), the photodimer of ergosterol, should exist in two isomeric forms due to hindrance to rotation about the 7,7′ bond; separation of (I) into two stereoisomeric constituents, presumed to be rotamers of (I), was cited in support of this hypothesis. However, there is no precedent for the isolation of stereoisomers which owe their separate identities to hindered rotation about a single bond joining two tetra-co-ordinated carbon atoms, (*i.e.* to stereoisomerism of the ethane type), and the above claim thus becomes unique. We offer evidence for the alternative that (I) is a mixture of three stereoisomers, differing in configuration at C-7 and C-7′ (Figure), and show that it is not necessary to suggest hindered rotation in order to account for the isomer number.

Irradiation of ergosterol as previously described[2] afforded (I), m.p. 199—202° decomp., $[\alpha]_D$ − 170° ($CHCl_3$) (lit.[2] m.p. 201—203° decomp., $[\alpha]_D$ − 172°). The diacetate[3] of (I) was fractionally crystallized from chloroform–acetone and the diacetate of the major isomer (A) was thus obtained in almost pure form. The separation was completed by mild alkaline hydrolysis (3% KOH in MeOH) of the mother liquors, followed by preparative t.l.c. of the hydrolysate as previously described.[1] In order of decreasing mobility the three components of (I) were (B) (R_F on silica gel G, 2% MeOH in $CHCl_3$ = 0·410), (A) (R_F = 0·275), and (C) (R_F = 0·245). The three isomers have i.r. and u.v. spectra consistent with the assigned structures and elemental analyses in satisfactory agreement with the molecular formula $C_{56}H_{86}O_2,2H_2O$.† They have the following properties: isomer (A), (34%) from ergosterol, m.p. 189—190°, $[\alpha]_D$ − 215° (pyridine), n.m.r. δ 0·72, 0·82, 0·84, 0·89, 0·97, 1·02, 1·09, 1·19, 3·05, 3·4, and 5·2 p.p.m.; isomer (B), (4·4%) m.p. 177—179°, $[\alpha]_D$ *ca.* − 400 ± 100° (pyridine), δ 0·85, 0·92, 0·99, 1·04, 1·12, 1·18, 1·32, 3·2, 3·7, and 5·3 p.p.m.; isomer (C), (14·5%), m.p. 193—194°, $[\alpha]_D$ − 165° (pyridine), δ 0·70, 0·79, 0·80, 0·855, 0·87, 0·94, 1·0, 1·07, 1·18, and 3·5 p.p.m.

The stereochemistry of (A), (B), and (C) may be tentatively assigned as follows. Statistically, and neglecting other factors, dimerization of ergosterol should lead to the 7α,7′β-isomer in 50% yield, since two out of four combinations lead to this product; on these grounds alone, isomer (A), which is formed in the highest yield, may be assigned the 7α,7′β-configuration. With the help of Dreiding molecular models further insight is provided by a conformational analysis of each isomer, assuming that ring A is in the chair form, ring B is planar or in a flattened boat form, that torsional strain is minimized by staggering the substituents on C-7 and C-7′, and that a further

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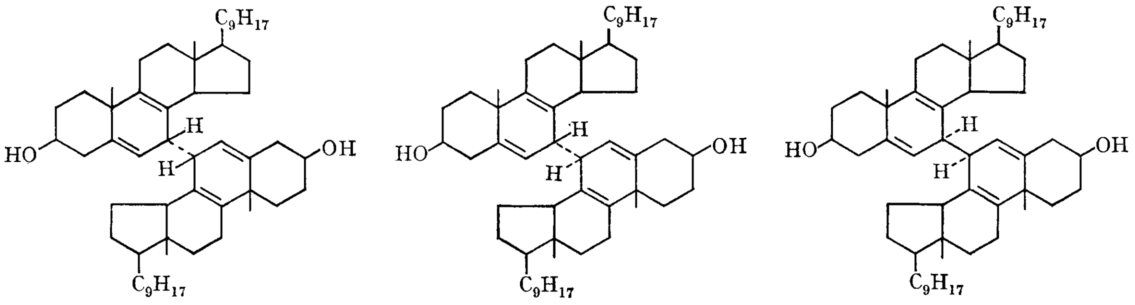
† Bisteroids are known to crystallize with solvents; see: P. Crabbé and J. A. Zderic, *Bull. Soc. chim. belges*, 1961, **70**, 403; P. Crabbé and E. Cisneros, *Rev. Soc. quim. Mexico*, 1965, **9**, 185.



7α, 7′α-Biergostatrienol 7α, 7′β (or 7β, 7′α)-Biergostatrienol 7β, 7′β-Biergostatrienol

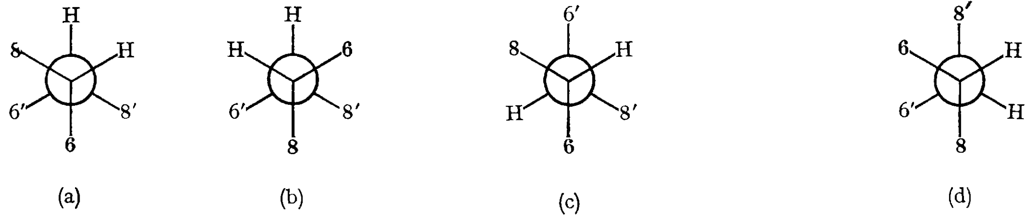


FIGURE. *Structural formulae of the stereoisomeric biergostatrienols. The Newman projection below each formula indicates a conformation discussed in the text; the view is along the* 7,7′ *bond axis and the numbers refer to the carbon atoms attached to* C-7 *and* C-7′.

distinction is afforded between the three torsional isomers on the basis of a qualitative consideration of nonbonded interaction effects. According to this approach, the 7α,7′α-isomer has two favourable conformations [(a) and (b) in the Figure] in which the two steroid nuclei occupy roughly perpendicular planes; (a) may be somewhat more favoured than (b), since ring A of one steroid moiety approaches ring D of the other more closely in (b) than in (a). The 7α,7′β-isomer may adopt at least one favourable conformation [(c) in the Figure]. However, even the most favourable conformation of the 7β,7′β-isomer [(d) in the Figure] is somewhat crowded. We tentatively assign this configuration to isomer (B), which is formed in lowest yield, as dimerization to form this bis-steroid would presumably be hindered by steric factors. By difference, isomer (C) is assigned the 7α,7′α-configuration.

We suggest that there is no basis for believing that torsional barriers exist in any of the three isomers of the magnitude (*i.e.* greater than 20 kcal. mole^{-1}) required to give rise to conformationally stable rotamers.

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[1] P. J. Flanagan and J. B. Thomson, *Tetrahedron Letters*, 1965, 1671.
[2] E. Mosettig and I. Scheer, *J. Org. Chem.*, 1952, **17**, 764.
[3] T. Ando, *Bull. Chem. Soc. Japan*, 1938, **13**, 371.