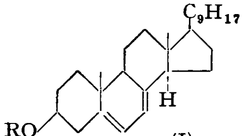
The Isomerisation of Unsaturated Steroids in Liquid Sulphur Dioxide.

By A. W. D. Hudgell, J. H. Turnbull, and Walter Wilson.

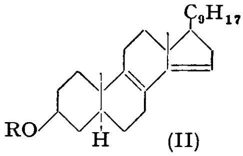
[Reprint Order No. 4790.]

Migration of double bonds in unsaturated steroids often occurs under the influence of liquid sulphur dioxide. Ergosterol and ergosterol D (preferably as acetates) both rearrange to give high yields of pure ergosterol B_1, which thus becomes readily accessible. 5 : 6-Dihydroergosteryl acetate in liquid sulphur dioxide affords 3β-acetoxyergosta-8(14) : 22-diene.

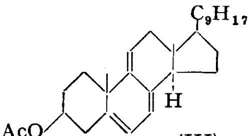
During unsuccessful attempts to prepare an adduct from ergosterol (I; R = H) and (liquid) sulphur dioxide, complete rearrangement to ergosterol B_1 (II; R = H) occurred. The effect of liquid sulphur dioxide on other unsaturated steroids was therefore studied. Whilst these experiments were in progress, De Vries and Backer (*Rec. Trav. chim.*, 1952, **71**, 719) reported experiments on the action of sulphur dioxide in ether or ergosterol; they obtained a mixture of isomers, in which only ergosterol B_3 was characterised. No sulphur dioxide adduct was obtained. In a recent preliminary communication, the isomerisation in liquid sulphur dioxide of 9(11)-dehydroergosterol (III) into the 6 : 8(14) : 9(11) : 22-tetraene (IV) is described (Laubach, Schreiber, Agnello, Lightfoot, and Brunings, *J. Amer. Chem. Soc.*, 1953, **75**, 1514).



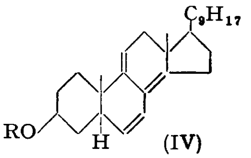
(I)



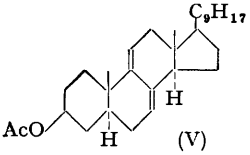
(II)



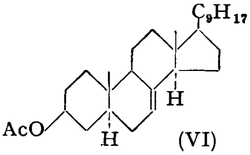
(III)



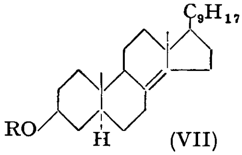
(IV)



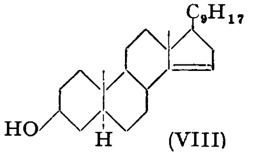
(V)



(VI)



(VII)



(VIII)

In our experiments (Table 1), steroids (usually the acetates) and liquid sulphur dioxide were sealed in Carius tubes, without rigorous exclusion of moisture, and left for several hours at a suitable temperature. Under these conditions, isolated double bonds in the side-chain or at the 5 : 6-position are stable, 7 : 8-double bonds migrate to the 8 : 14-position, and 5 : 7- and 7 : 9(11)-dienes are both isomerised giving the 8(9) : 14-diene system.

Ergosteryl B_1 acetate (II; R = Ac) was obtained in 86% yield from ergosteryl acetate (I; R = Ac), or from ergosteryl D acetate (V). Some specimens of ergosterol B_1 described in the literature are probably impure. The structure of our product has been confirmed independently by Professor D. H. R. Barton (personal communication).

5 : 6-Dihydroergosteryl acetate (VI) was isomerised to 3β-acetoxyergosta-8(14) : 22-diene (VII; R = Ac); molecular-rotation values (Table 2) for the product agree well

with those computed from the data of Barton, Cox, and Holness (*J.*, 1949, 1773). The presence of a tetra-substituted 8(14)-double bond is confirmed by the nature of the absorption near 200 mμ (Bladon, Henbest, and Wood, *J.*, 1952, 2737); trisubstituted double bonds appear to be absent (no characteristic absorption bands in the 3000—3100 cm.$^{-1}$ region). Ergosta-8(14) : 22-dien-3β-ol had not been obtained previously (cf. Barton, Cox, and Holness, *loc. cit.*; Fieser, Rosen, and Fieser, *J. Amer. Chem. Soc.*, 1952, **74**, 5397). Since the completion of our work, Laubach and Brunings (*J. Amer. Chem. Soc.*, 1952, **74**, 705) obtained 3β-acetoxyergosta-8(14) : 22-diene by mild hydrogenation of ergosteryl B_2 acetate, and Nes and Mosettig (*J. Org. Chem.*, 1953, **18**, 276) have isomerised 5 : 6-dihydroergosterol to ergosta-8(14) : 22-dien-3β-ol over copper–chromium oxide.

TABLE 1. *Rearrangement of unsaturated steroids in liquid sulphur dioxide.*

Steroid [1]	Conditions	Product	Yield (%)
5 : 6-Dihydroergosteryl acetate (VI)	100°/18 hr.	3β-Acetoxyergosta-8(14) : 22-diene (VII; R = Ac)	50
Ergosterol (I; R = H)	100°/18 hr.	Ergosta-8(9) : 14 : 22-trien-3β-ol (ergosterol B_1) (II; R = H)	60
Ergosteryl acetate (I; R = Ac)	100°/18 hr.	3β-Acetoxyergosta-8(9) : 14 : 22-triene (II; R = Ac)	86
3β-Acetoxyergosta-7 : 9 : 22-triene (ergosteryl D acetate) (V)	24°/18 hr.	3β-Acetoxyergosta-8(9) : 14 : 22-triene (II; R = Ac)	67
9(11)-Dehydroergosteryl acetate (III)	20°/18 hr.	Sterol (unidentified)	11

[1] Under similar conditions, the following steroids were recovered (80—100%) unchanged: cholesterol, cholesteryl acetate, stigmasteryl acetate, fucosteryl acetate. Gums were obtained from 7-dehydrocholesteryl acetate and benzoate, zymosterol, zymosteryl acetate, and calciferol.

TABLE 2. *Molecular rotations.*

	Sterol	Acetate	Benzoate
Ergosta-8(14) : 22-dien-3β-ol (VII) (calc.) [1]	−59°	− 99°	−103°
Ergosta-14 : 22-dien-3β-ol (VIII) (calc.) [1]	−15	− 45	+ 13
" β "-Dihydroergosterol [2]	−36	− 75	− 40
5 : 6-Dihydroergosterol [3] (VI)	−76	− 88	− 50
Ergosta-8(14) : 22-dien-3β-ol [4] (VII)	−64	−101	− 95

[1] Calc. from figures given by Barton, Cox, and Holness (*loc. cit.*), allowing +103° for the reduction of a 22 : 23-double bond. [2] Barton, Cox, and Holness, *loc. cit.* [3] Barton and Cox, *J.*, 1948, 1354. [4] Present work.

Liquid sulphur dioxide converted several unsaturated steroids into non-crystalline, sulphur-free products. In the case of zymosterol, mixtures of $C_{(8)}$- or $C_{(9)}$-epimers could be formed when the double bond migrates. 9(11)-Dehydroergosteryl acetate gave a syrup; after hydrolysis, this gave a small yield of an unidentified crystalline sterol: this had twin absorption maxima at 271 and 281 mμ, suggesting the possible presence of a 5 : 7-diene system. There was no evidence for the formation, under the conditions used, of the 6 : 8(14) : 9(11) : 22-tetraene (IV) (Laubach *et al.*, *loc. cit.*) or of the remarkable hydroanthracene derivative obtained by Nes and Mosettig (*J. Amer. Chem. Soc.*, 1953, **75**, 2787) from dehydroergosterol and hydrogen chloride.

In the rearrangement of ergosteryl acetate in liquid sulphur dioxide, the results were less satisfactory when moisture was rigorously excluded. It is believed the isomerisations are initiated by protons produced in the H_2O–SO_2 system. The use of liquid sulphur dioxide is often advantageous instead of the customary reagents for isomerising unsaturated steroids (*e.g.*, hydrogen chloride in chloroform or hydrogenation catalysts; see Fieser and Fieser, " Natural Products Related to Phenanthrene," Reinhold Publ. Corpn., New York, 1949, pp. 240, 255). In particular pure ergosterol B_1 and ergosta-8(14) : 22-dien-3β-ol now become readily accessible.

EXPERIMENTAL

$[\alpha]_D$ are in $CHCl_3$.

Isomerisation of Ergosteryl Acetate.—The acetate (5·0 g.), in a dry Carius tube, was cooled to −60°, and commercial liquid sulphur dioxide (25 c.c.) was added; no precautions were taken to prevent access of moisture. The tube was sealed and heated at 100° (water-bath) for 18 hr.

The tube was cooled, the sulphur dioxide evaporated in a stream of nitrogen, and the orange-brown crystalline residue triturated with methanol. The product, m. p. 131—133°, was recrystallised from ethanol, giving ergosteryl B_1 acetate (86%), m. p. 137—138·5°, $[\alpha]_D$ $-50°$, $\lambda_{max.}$ 250 mμ (ε 18,000) (Found: C, 82·05; H, 10·45. Calc. for $C_{30}H_{46}O_2$: C, 82·1; H, 10·6%), giving the sterol, m. p. 134—136·5°, $[\alpha]_D$ $-41°$, both unchanged by chromatography on alumina. Fieser, Rosen, and Fieser (*loc. cit.*) record: ergosterol B_1, m. p. 144—145°, $[\alpha]_D$ $-47°$; acetate, m. p. 143—144°, $[\alpha]_D$ $-60°$, $\lambda_{max.}$ 250 mμ (ε 12,300); this low ε value indicates that their material was not quite pure (Barton and Brooks, *J.*, 1951, 257, give $\lambda_{max.}$ 248 mμ, ε 19,800, for dehydro-" α "-ergostenyl acetate which has the same chromophoric system).

Similar experiments (see Table 1) gave the following products.

3β-Acetoxyergosta-8(14) : 22-diene (isolated by chromatography and recrystallised from ethanol), m. p. 131—132°, $[\alpha]_D$ $-19·6°$, $\lambda_{max.}$ 210 mμ (ε 7400) (Found: C, 82·1; H, 10·9. Calc. for $C_{30}H_{48}O_2$: C, 81·75; H, 11·0%), giving the sterol, m. p. 145—148°, $[\alpha]_D$ $-15°$, and the *benzoate*, m. p. 134—135°, $[\alpha]_D$ $-19°$ (Found: C, 83·6; H, 10·05. $C_{35}H_{50}O_2$ requires C, 83·6; H, 10·3%). Nes and Mosettig (*J. Org. Chem.*, 1953, **18**, 276) give: sterol, m. p. 129—130°, $[\alpha]_D$ $-14°$; acetate, m. p. 120—122°, $[\alpha]_D$ $-24°$. Laubach and Brunings (*loc. cit.*) report for the acetate m. p. 122·6—124°, $[\alpha]_D$ $-26·5°$. These m. p.s are appreciably lower than those observed in the present experiments.

Ergosta-8(9) : 14 : 22-trien-3β-ol (crystallised from ethanol), m. p. 139—140°, $[\alpha]_D$ $-42°$ (Found: C, 81·7; H, 11·2. Calc. for $C_{28}H_{44}O,C_2H_5{\cdot}OH$: C, 81·4; H, 11·4%), giving an acetate, m. p. 135·5—136°, $[\alpha]_D$ $-46°$, $\lambda_{max.}$ 250 mμ (ε 18,000).

3β-Acetoxyergosta-8(9) : 14 : 22-triene (crystallised from ethanol), m. p. 132—133°, $[\alpha]_D$ $-56°$, $\lambda_{max.}$ 249 mμ (ε 18,000), from ergosteryl D acetate.

Unidentified *sterol* (isolated in the last experiment of the Table by alkaline hydrolysis and then chromatography), m. p. 122·5—123°, $[\alpha]_D$ $-23°$, $\lambda_{max.}$ 271 (ε 8800) and 281 mμ (ε 8400) (Found: C, 82·55; H, 10·4. $C_{30}H_{44}O_2$ requires C, 82·5; H, 10·2%); it gives no adduct with maleic anhydride in boiling benzene.

The authors are grateful to Professor M. Stacey, F.R.S., for encouragement and guidance, and thank the Distillers Company Ltd. for support, Glaxo Laboratories Ltd. for a gift of ergosterol, and Professor D. H. R. Barton for details of unpublished experiments.

CHEMISTRY DEPARTMENT, THE UNIVERSITY,
EDGBASTON, BIRMINGHAM, 15.

Received, November 12th, 1953.]