144. *Steroids and Related Compounds. Part XI. Some Derivatives of Zymosterol.*

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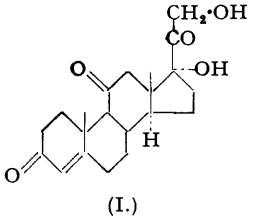
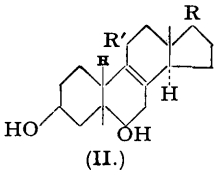
The possibility of introducing an oxygen atom at position 11 of a $\Delta^{8(9)}$-steroid has been examined.

Reaction of zymost-8-enol (III) with selenium dioxide failed to give the 11-hydroxy-compound, the dehydro-compound (IV) being obtained. Chromic acid oxidation of zymosteryl acetate dibromide was likewise unsuccessful, a keto-group being introduced at $C_{(7)}$.

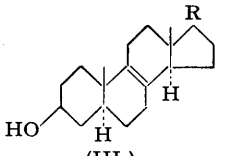
The direct introduction of an oxygen atom at position 11 of a steroid substituted at positions 3 and 17 would form an attractive route to compounds such as Cortisone (I). Such a reaction has indeed been realised biochemically: when 11-deoxycorticosterone is perfused through isolated adrenal glands, corticosterone is recovered from the perfusates (Hechter, Jacobsen, Jeanloz, Levy, Marshall, Pincus, and Schenker, *J. Amer. Chem. Soc.*, 1949, **71**, 3261). Though highly significant from the biogenetic standpoint, this method is not applicable practically,



(I.)

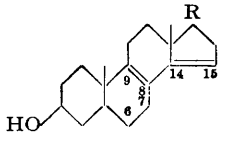


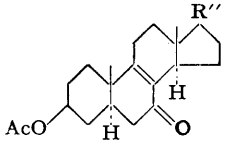
(II.)



(III.)

(IV.)





(V.)

(R = C_8H_{17}; R″ = CHMe·[CH_2]$_2$·CH:CMe_2)

and the markedly selective character of bio-oxygenation processes lends small encouragement to the existence of chemical equivalents. Direct chemical oxidation at $C_{(11)}$ would almost certainly require the presence of a contiguous activating ethylenic grouping at position 8 : 9, a point well illustrated by results obtained in the " Westphalen series " in which 3 : 6-dihydroxy-5-methyl-10-norcholest-8(9)-ene (II; R′ = H) is converted into the 3 : 6 : 11-trihydroxy-derivative (II; R′ = OH) by selenium dioxide (Petrow, *J.*, 1939, 998; Davies and Petrow, *J.*, 1949, 2973). We therefore turned our attention to model experiments employing zymost-8-enol (III), a fairly accessible steroid of the required type.

Reaction of (III) with selenium dioxide occurred readily in boiling ethanol. In contrast to the results with (II; R = H), however, oxidation failed to give an 11-hydroxy-compound, and a dehydrozymostenol, m. p. 119—120°, $[\alpha]_D$ −12·9° (in chloroform), was obtained instead in good yield. The ultra-violet absorption spectrum of this compound showed it to be a hetero-annular conjugated diene. The unsaturated linkages may, therefore, be at 8 : 14, 7 : 9(11), 6 : 8(14) or 7 : 14. Of these, the last is eliminated by the failure of the compound to react with maleic anhydride. The 7 : 9(11) and 6 : 8(14) formulations are likewise rendered improbable by the low negative rotation of the dehydro-stenol (cf. Eck and Hollingsworth, *J. Amer. Chem. Soc.*, 1942, **64**, 140; Barton, *J.*, 1946, 512). The compound may, therefore, be assigned the constitution of cholesta-8 : 14-dien-3β-ol (IV).

The formulation (IV) had previously been assigned by Heath-Brown, Heilbron, and Jones (*J.*, 1940, 1482) to a " dehydro-α-zymostenol," m. p. 98—99°, $[\alpha]_D$ −9·1° (in chloroform), obtained by selenium dioxide oxidation of α-zymostenol [cholest-8(14)-en-3β-ol]. Evidence supporting this structure, however, was limited to spectroscopic study and to analogy with the known behaviour of α-ergostenol under similar experimental conditions (Callow, *J.*, 1936, 462). Employing larger quantities of material, we now find " dehydro-α-zymostenol " to be

identical in melting point, etc., with our dehydrozymostenol, the constitution of which may, therefore, be considered as finally established.

Chromic acid oxidation of the Δ^8-stenol appeared to offer another potential route to 11-oxygenated compounds of the desired type. The possibility of such a reaction had previously been discussed by Stavely and Bollenback (*J. Amer. Chem. Soc.*, 1943, **65**, 1290) who studied the oxidation of " α "-dihydroergosterol, regarded by them as a $\Delta^{8(9)}$-stenol. The formulation assigned to this compound, however, has since proved to be incorrect (cf. Wieland and Benend, *Annalen*, 1943, **554**, 1) so that conclusions based on this evidence must be accepted with caution. Chromic acid oxidation of the Westphalen diacetate (cf. II; R = H) leads readily to the corresponding 11-ketone 8 : 9-oxide (Petrow, *loc. cit.*). Experiments on the oxidation of zymosteryl acetate dibromide proved only partly successful, owing to profound degradation of the molecule. Debromination of the product, followed by chromatography, however, led to the isolation of a new αβ-unsaturated ketone, although in very low yield. Its formulation as 7-ketozymosteryl acetate (V) followed from its conversion into a 2 : 4-dinitrophenylhydrazone, and the observation (Fieser and Fieser, " Products Related to Phenanthrene," Rheinhold Publ. Corpn., 3rd edn., p. 229) that oxidation of compounds with a ditertiary double bond never involves the migration of the double bond from its original position.

Reaction between zymost-8-enol and *N*-bromosuccinimide, mercuric chloride, or lead tetra-acetate failed to give products which could be characterised.

The foregoing results point strongly to the conclusion that effective activation of the $C_{(11)}$-methylenic grouping cannot be achieved by introduction of an unsaturated linkage in the 8(9)-position. The steric hindrance of the angular methyl grouping at $C_{(10)}$ cannot, of course, be excluded from consideration as an inhibiting factor in the desired conversions. Nevertheless, Fieser's recent postulates (*Experientia*, 1950, **6**, 312) on this matter do not support the view that steric effects, *per se*, will prevent the admission of groups at $C_{(11)}$ provided that such entrance occurs from the less-hindered rear side of the molecule.

Experimental.

M. p.s are uncorrected. Optical rotation were measured in chloroform solution in a 2-dm. tube. Ultra-violet absorption spectra were kindly determined by Dr. R. Stuckey and Mr. P. Stross, B.Sc., Analytical Department, The British Drug Houses, Ltd.

Preparation of Zymost-8-enol (III).—Consistently improved yields of zymost-8-enol were obtained by employing the general technique of Wieland, Rath, and Benend (*Annalen*, 1941, **548**, 19) but using platinum oxide catalyst prepared as described by Cook and Linstead (*J.*, 1934, 946).

Reduction of Zymosterol Dibromide.—The following unsuccessful attempts were made to prepare zymost-8-enol by reduction of zymosterol dibromide.

(i) Zymosterol dibromide (2 g.), suspended in benzene (25 ml.), potassium hydroxide solution (0·55 g. in 1 ml. of water), ethanol (100 ml.), and Raney nickel were shaken with hydrogen. Absorption (90 ml.) was complete in *ca.* 1½ hours. Zymosterol, m. p. 108—110° (93%), was recovered from the filtered solution.

(ii) A suspension of zymosterol dibromide (0·17 g.) in dry benzene (40 ml.) was added to a solution of lithium aluminium hydride in ether (25 ml. of 0·7%), and the mixture heated under reflux for 1 hour. The product was treated with water and acidified to Congo-red with 3N-sulphuric acid, and the material recovered in the usual way. Crystallisation from methanol gave zymosterol, m. p. 108—109° (91%), converted into the acetate, m. p. 103—104°, both compounds showing no m. p. depression on admixture with authentic specimens.

Dehydrozymost-8-enol (*Cholesta-8 : 14-dien-3β-ol*) (IV).—Zymost-8-enol (8·0 g.) in boiling ethanol (200 ml.) was treated with selenium dioxide (8·0 g.) in water (25 ml.), and the mixture heated under reflux for 1 hour. Precipitated selenium was removed by filtration, the mixture taken to dryness, and residual selenium removed by passage of a benzene solution through a short alumina column (½ × 1″). Crystallisation from methanol (Kieselguhr) gave dehydrozymost-8-enol (60%), small needles, double m. p. 119—120° and 125—126°, $[\alpha]_D^{24}$ −12·9° (*c*, 0·580), $\lambda_{max.}$ 250 mμ., log ε = 4·3 in alcohol (Found : C, 84·9; H, 11·4. $C_{27}H_{44}O$ requires C, 84·3; H, 11·5%). The *acetate* separated from methanol in plates, m. p. 101—102°, $[\alpha]_D^{23\cdot5}$ −22·9° (*c*, 0·553) (Found : C, 81·9; H, 10·7. $C_{29}H_{46}O_2$ requires C, 81·6; H, 10·9%). The *benzoate*, crystallised from acetone, had m. p. 147—148°, $[\alpha]_D^{23}$ −6·9° (*c*, 0·594) (Found : C, 83·5; H, 9·8. $C_{34}H_{48}O_2$ requires C, 83·6; H, 9·9%).

Dehydro-α-zymostenol.—Prepared from α-zymostenol as described above, the compound formed small needles (40%), m. p. 119—120° and 125—126°, $[\alpha]_D^{26}$ −13·7° (*c*, 0·615), $\lambda_{max.}$ 250 mμ., log ε = 4·3 in alcohol. The acetate formed plates (from methanol), m. p. 101—102°, $[\alpha]_D^{15}$ −23·2° (*c*, 0·494) (Found : C, 82·1 : H, 10·6%). The benzoate had m. p. 147—148°, $[\alpha]_D^{23}$ −6·5° (*c*, 0·388) (Found : C, 83·2; H, 9·7%). The compounds gave no depression on admixture with the corresponding derivatives prepared from zymost-8-enol.

Zymosteryl Acetate Dibromide.—Zymosterol dibromide (2·7 g.) in pyridine solution (50 ml.) was treated with acetic anhydride (14 ml.) for 12 hours at room temperature. Crystallisation of the product from chloroform–ethanol gave zymosteryl acetate dibromide, m. p. 169°, $[\alpha]_D^{17\cdot5}$ +5·9° (*c*, 0·603) (Found :

C, 59·6; H, 7·9; Br, 26·8. Calc. for $C_{29}H_{46}O_2Br_2$: C, 59·4; H, 7·9; Br, 27·2%). Reindel and Weichmann (*Annalen*, 1930, **482**, 120) give m. p. 168—169° (corr.), $[\alpha]_{5461}$ −9·7°.

7-Ketozymosteryl Acetate (V).—(i) A suspension of zymosteryl acetate dibromide (4·4 g.) in acetic acid (100 ml.) and acetic anhydride (5 ml.) at 54° was treated, with stirring, with powdered chromium trioxide (3·1 g.) added during 1 hour. After a further 2 hours at this temperature the mixture was diluted with water and extracted with ether, and the ethereal layer washed successively with water, 5% aqueous ammonia, and water, then dried, and the ether removed. The resulting residue in ethanol (200 ml.) was heated under reflux with activated zinc (13 g.) for 1 hour and the resulting product, in benzene solution, passed through a column (8 × 1″) of activated alumina (B.D.H.). Removal of the benzene, followed by crystallisation from methanol, gave *7-ketozymosteryl acetate*, needles (50 mg.), m. p. 135—136°, $[\alpha]_D^{21}$ −32·2° (*c*, 0·815); $\lambda_{max.}$ 252 mμ., log ε = 4·0 in alcohol (Found: C, 78·8; H, 9·6. $C_{29}H_{44}O_3$ requires C, 79·1; H, 10·0%).

The 2 : 4-*dinitrophenylhydrazone* formed orange needles (from ethanol), m. p. 227° (decomp.) (Found: C, 67·5; H, 7·5; N, 9·4. $C_{35}H_{48}O_6N_4$ requires C, 67·7; H, 7·7; N, 9·0%).

(ii) Zymosteryl acetate dibromide was oxidised as described above and the product isolated with ether. Trituration with boiling acetone gave crude 7-ketozymosteryl acetate dibromide (2·7 g.), m. p. 176—178°, which could not be freed from a persistent impurity. Treatment with 2 : 4-dinitrophenylhydrazine gave *7-ketozymosteryl acetate dibromide* 2 : 4-*dinitrophenylhydrazone*, orange needles (from ethanol), m. p. 196—198° (Found: C, 53·8; H, 6·1; N, 7·3. $C_{35}H_{48}O_6N_4Br_2$ requires C, 53·8; H, 6·1; N, 7·2%). Debromination of the crude 7-ketozymosteryl acetate dibromide led to 7-ketozymosteryl acetate, m. p. 134—135°, not depressed on admixture with a sample prepared as in (i).

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