206. *Steroids and the Walden Inversion. Part IV. Derivatives of 6-Ketositostane and 6 : 17-Diketoandrostane.*

By C. W. Shoppee.

On the basis of the proven (β)-orientation of the hydroxyl group in " β "-sitosterol and dehydro*iso*androsterone (Part III, preceding paper), configuration at C_3 is now assigned to various derivatives of 6-ketositostane and 6 : 17-diketoandrostane.

In Part I (*J.*, 1946, 1138), configurations were assigned to the epimeric 3-chlorositostanes * which undergo bimolecular acetolysis (mechanism S_N2) to give respectively sitostanol and *epi*-sitostanol : the " β "-chloride, m. p. 118°, is 3(α)-chlorositostane, and the " α "-chloride, m. p. 108°, is 3(β)-chlorositostane. In Part II (*J.*, 1946, 1147) it was suggested that preservation of configuration in nucleophilic substitution reactions at C_3 in 5 : 6-unsaturated steroids was due to the intervention of the polarisable electrons of the double bond, which not only facilitate separation of the atom or group replaced at C_3 as the anion so that reaction occurs by mechanism S_N1, but also interact with the resulting positive charge at C_3 to maintain configuration in the intermediate cation. Experimental support for the correctness of this suggestion has recently been given by Winstein and Adams (*J. Amer. Chem. Soc.*, 1948, **70**, 838) who have shown that acetolysis of cholesteryl *p*-toluenesulphonate at 50° occurs by mechanism S_N1.

In Part III (preceding paper) it was proved that the hydroxyl group in " β "-sitosterol (I) and dehydro*iso*androsterone (as I) is (β)-orientated, and on this basis, consideration is now extended to derivatives of these two substances.

" β "-Sitosterol (I) by treatment with phosphorus pentachloride gives sitosteryl chloride (Burian, *Monatsh.*, 1897, **18**, 551; Vanghelovici and Angelescu, *Bul. Soc. Chim. România*, 1935, **17**, 184; Marker and Lawson, *J. Amer. Chem. Soc.*, 1937, **59**, 2711) which is 3(β)-chlorositost-5-ene (II),† since catalytic reduction gives a quantitative yield of 3(β)-chlorositostane (V), m. p. 108° (Marker and Lawson, *loc. cit.*). The same sitosteryl chloride (II) is now found to be obtained by use of thionyl chloride alone or in the presence of pyridine, so that here again the steric course of the replacement of the hydroxyl group by chlorine is independent of the reagent within the range of reagents and conditions examined.

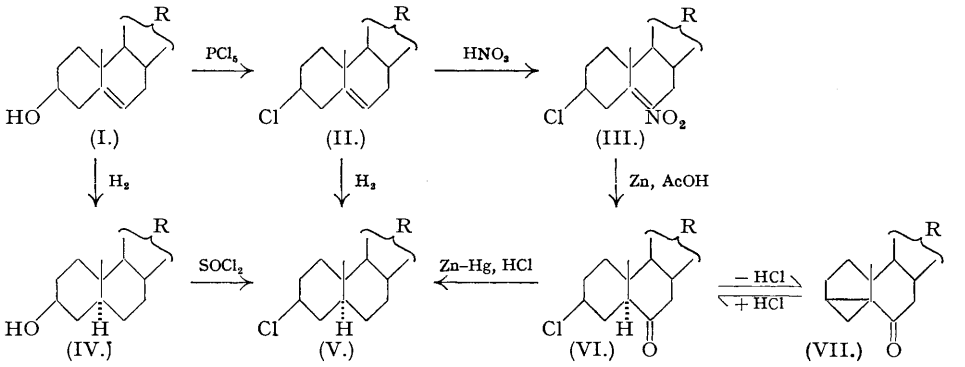
Nitration of sitosteryl chloride (II) in the presence of nitrite yields 3(β)-chloro-6-nitrositost-5-ene (III), which by reduction with zinc and acetic acid gives a chloro-ketone, m. p. 112°, which is 3(β)-chlorositostene-6-one (VI). This structure is consistent with its reduction by the Clemmensen method (Vanghelovici and Angelescu, *loc. cit.*) to the sitostanyl chloride, m. p. 108°, which has been shown to be 3(β)-chlorositostane (V) since it is obtained from sitostanol (IV) by treatment with thionyl chloride (retention of configuration) and from *epi*sitostanol by use of phosphorus pentachloride (inversion of configuration) (Part I, *loc. cit.*). The chloro-acid, m. p. 277°, obtained by Vanghelovici and Angelescu (*loc. cit.*) by oxidation of 3(β)-chloro-sitostan-6-one (V) with nitric acid is clearly 3(β)-chlorositostane-6‖7-dicarboxylic acid.

Whilst *i*-sterols and their derivatives will be dealt with in a future paper it is however

* Also termed 3-chlorostigmastanes.

† The sitosteryl bromide obtained by Vanghelovici and Vasiliu (*Bul. Soc. Chim. România*, 1935, **17**, 251) from " β "-sitosterol by use of phosphorus tribromide is analogously 3(β)-bromositost-5-ene.

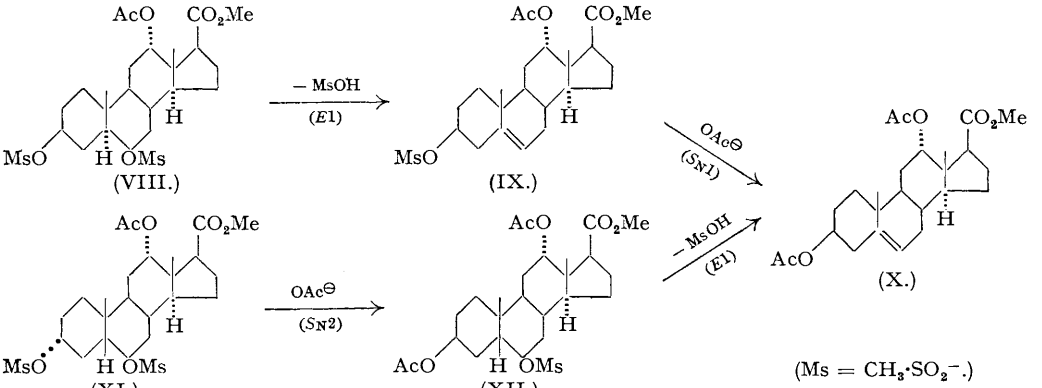
appropriate here to indicate that the substance, m. p. 77°, obtained by Vanghelovici and Angelescu from 3(β)-chlorositostan-6-one (VI) by treatment with sodium amalgam in boiling ethanol and described by them as sitostan-6-one, is actually *i*-sitostan-6-one (VII) since it is readily obtained from the chloro-ketone (VI) by sublimation in a vacuum and is reconverted into (VI) by the action of hydrochloric acid.



In the sitostane series R = $C_{18}H_{34}$; in the androstan-17-one series R = $C_8H_{12}O$.

In the androstane series, compounds analogous to the foregoing have been described to which configuration at C_3 can now be assigned. 3(β)-Hydroxyandrost-5-en-17-one (dehydro*iso*androsterone) (I) by treatment with phosphorus pentachloride (1 mol.), thionyl chloride, or hydrochloric acid gives uniformly 3(β)-chloroandrost-5-en-17-one, m. p. 157° (II), with retention of configuration, since by hydrogenation this yields 3(β)-chloroandrostan-17-one, m. p. 173° (V) (cf. Part II, *loc. cit.*); it follows that the quantities of the chloro-ketone (II) isolated from male urine by Butenandt and Dannenbaum (*Z. physiol. Chem.*, 1934, **229**, 185; with Hanisch and Kudszus, *ibid.*, 1935, **237**, 57) and encountered in pathological urines by other workers, represent equivalent quantities of dehydro*iso*androsterone (I), originally excreted as such or as a conjugate, *e.g.*, with glucuronic acid, and converted into (II) during hydrochloric acid hydrolysis of the urine.

Nitration of the unsaturated chloro-ketone (II) gives 3(β)-chloro-6-nitroandrost-5-en-17-one (III) (Blunschy, Hardegger, and Simon, *Helv. Chim. Acta*, 1946, **29**, 199), reduced by zinc and acetic acid to 3(β)-chloroandrostane-6 : 17-dione (VI). Analogy suggests that the bromodiketone described by Butenandt and Suranyi (*Ber.*, 1942, **75**, 591) is 3(β)-bromoandrostane-6 : 17-dione (as VI); these authors obtained it from *i*-androstane-6 : 17-dione (VII) in quantitative yield by treatment with hydrobromic acid in acetic acid at 20°, and showed that removal of the elements of hydrogen bromide by use of hot collidine or with potassium acetate in acetic acid regenerated *i*-androstane-6 : 17-dione (VII).



Reference may here be made to a remarkable experimental result recently recorded by Lardon (*Helv. Chim. Acta*, 1947, **30**, 597, especially 604). The 3(β) : 6-dimethanesulphonyl ester of the androstane derivative (VIII) by treatment with silver acetate in hot acetic acid yields the

3(β)-acetoxyandrost-5-ene derivative (X) with retention of configuration at C_3 (Jeanloz, Prins, and von Euw, *ibid.*, 1947, **30**, 374); this result clearly indicates that the first stage in the transformation is the elimination by mechanism *E*1 of methanesulphonic acid to give (IX), which, by virtue of the 5 : 6-double bond so introduced, undergoes unimolecular acetolysis of the 3(β)-methanesulphonyl group (mechanism S_N1) with preservation of configuration at C_3 to yield the 3(β)-acetoxyandrost-5-ene compound (X).

The isomeric 3(α) : 6-dimethanesulphonyl ester of the ætiocholane derivative (XI) by treatment with silver acetate in hot acetic acid yields the same 3(β)-acetoxyandrost-5-ene derivative (X) with inversion of configuration at C_3 (Lardon, *loc. cit.*). This result indicates equally clearly that here the primary reaction is a bimolecular acetolysis (mechanism S_N2) of the saturated ester (XI) to give with inversion the saturated 3(β)-acetoxy-6-methanesulphonyl ester (XII), which subsequently eliminates the elements of methanesulphonic acid (mechanism *E*1) to produce the unsaturated 3(β)-acetoxy-compound (X).

If *trans*-elimination, being the rule (cf. Watson, " Modern Theories of Organic Chemistry ", 2nd Ed., 1941, p. 223), is the more facile process, these results suggest that in (VIII) the 6-methanesulphonyl group is (β)-orientated (C_5–H/C_6–OMs : *trans*), whilst in (XI) the 6-methanesulphonyl group is also (β)-orientated (C_5–H/C_6–OMs : *cis*), so that the elimination reaction takes preference over the substitution reaction in the conversion (VIII) ⟶ (X) but that the situation is reversed in the conversion (XI) ⟶ (X).

Experimental.

Commercial sitosterol (1 g.) was added to redistilled thionyl chloride (3 c.c.), and the clear solution left for 10 minutes at room temperature; the resulting pink solution was poured into ice-cold N-sodium carbonate, and the precipitate filtered off and well washed with water. The precipitate was stirred with successive quantities of warm pentane, in which it largely dissolved, and the united pentane extracts filtered through a column of aluminium oxide (Spence, activity I—II, 30 g.) prepared in pentane. The column was eluted twice with pentane (100 c.c.); the original filtrate and these eluates by evaporation gave residues which crystallised spontaneously. The crystallisates all melted at 87—88°, and were united and recrystallised from acetone to give pure 3(*β*)-chlorositost-5-ene (200 mg.) as prisms, m. p. 88—89°. The same compound was obtained by carrying out the reaction in the presence of pyridine (cf. Daughensbaugh and Allison, *J. Amer. Chem. Soc.*, 1929, **51**, 3665), and gave no depression with a specimen prepared using phosphorus pentachloride.

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