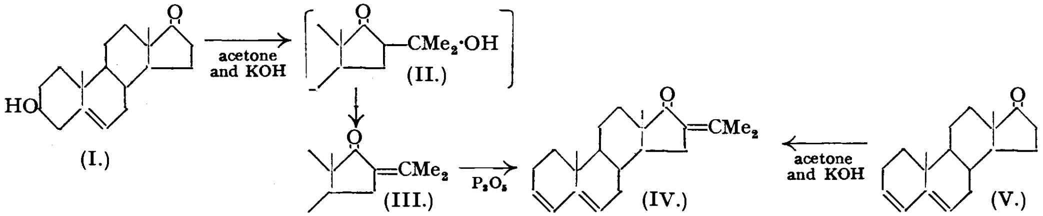
9. 16-iso*Propylideneandrostene Derivatives.*

By Walter C. J. Ross.

An improved method for the preparation of 16-*iso*propylidene-Δ^5-androsten-3-ol-17-one (III) is described. Dehydration of (III) affords 16-iso*propylidene*-$\Delta^{3:5}$-*androstadien*-17-*one* (IV), which on reduction by the Kishner–Wolff procedure yields 16-iso*propylidene*-$\Delta^{3:5}$-*androstadiene.*

trans-Dehydroandrosterone (I) condenses with acetone in the presence of sodium and dry ether to give the *iso*propylidene compound (III), though in poor yield; the higher homologue of (III), from *trans*-dehydroandrosterone and methyl ethyl ketone, is more easily obtained, but here also the yield is only 30% (Butenandt, Schmidt-Thomé, and Weiss, *Ber.*, **1939**, **72**, 417).



During the hydrolysis of some *trans*-dehydroandrosterone acetate residues, it was observed that a sparingly soluble, crystalline product was formed; this was resolved by chromatographic adsorption into a less adsorbed fraction (A) and a more adsorbable, resinous fraction (B). The latter was acetylated, the acetate of (III), m. p. 186—189°, being obtained. The unknown *benzoate*, m. p. 210—212°, was also easily prepared; both these esters on hydrolysis gave the parent keto-alcohol, m. p. 223° (Butenandt *et al.*, *loc. cit.*). The formation of these compounds was traced to the presence of acetone in the methyl alcohol used as a solvent in the hydrolysis, thus suggesting that the condensation of acetone with *trans*-dehydroandrosterone should proceed easily under the right conditions. This was confirmed by heating pure *trans*-dehydroandrosterone acetate with acetone in the presence of methyl-alcoholic potassium hydroxide, whereby an 80% yield of the *iso*propylidene compound (III) was obtained. On one occasion an unstable substance, m. p. 180° with evolution of gas, was formed, but when this was filtered off and warmed with methanol it was readily converted into (III). The intermediate compound is probably the keto-diol (II); owing to its instability, it was not possible to prepare a specimen for analysis.

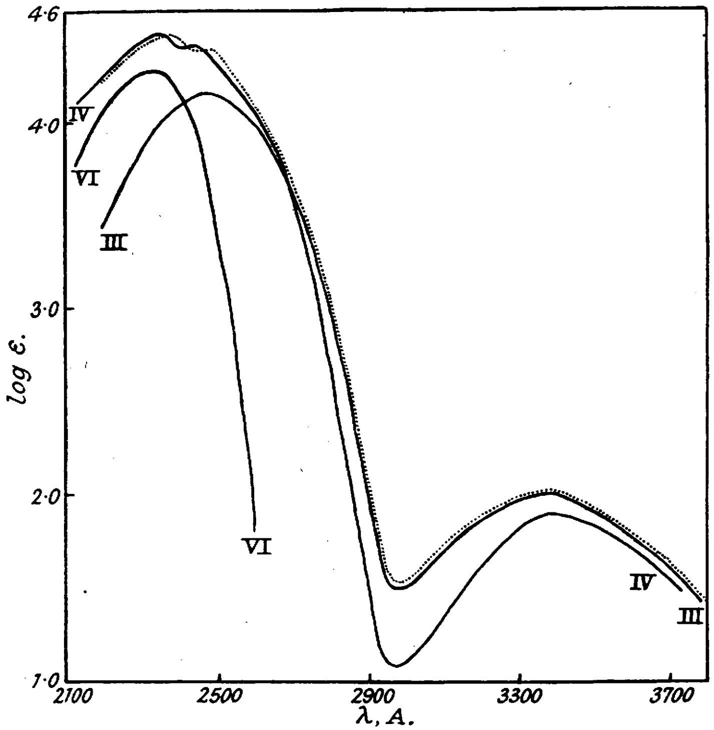
The less adsorbable compound (A) has the composition $C_{22}H_{30}O$ and is evidently produced from (III) by the loss of the elements of water; it could, in fact, be obtained from (III) by heating in benzene with phosphoric oxide. It is therefore 16-iso*propylidene*-$\Delta^{3:5}$-*androstadien*-17-*one* (IV). Similar dehydration of *trans*-dehydroandrosterone (I) yielded $\Delta^{3:5}$-androstadien-17-one (V) (compare Burrows, Cook, Roe, and Warren, *Biochem. J.*, **1937**, **31**, 950), and this condenses with acetone in the presence of methyl-alcoholic potassium hydroxide to give an excellent yield of the *iso*propylidene compound (IV).

The carbonyl group in the *iso*propylidene compounds is in a relatively protected position, for no semicarbazones could be prepared by the usual methods. Nevertheless, 16-*iso*propylidene-$\Delta^{3:5}$-androstadienone (IV) can be reduced by the Kishner–Wolff procedure to give 16-iso*propylidene*-$\Delta^{3:5}$-*androstadiene*, m. p. 140—144°. An attempted reduction of 16-*iso*propylidene-Δ^5-androsten-3-ol-17-one (III) gave an unidentified *product*, m. p. 190—192°, apparently having the composition $C_{20}H_{34}O_3$.

Confirmation of the structures assigned to compounds (III) and (IV) and to 16-*iso*propylidene-$\Delta^{3:5}$-androstadiene is afforded by the examination of their ultra-violet absorption spectra (Figure); (III) shows selective absorption of light with a primary maximum at 2500 A., log $\varepsilon_{max.}$ = 4·17, and a secondary maximum at 3380 A., log $\varepsilon_{max.}$ = 2·0. This type of absorption is characteristic of αβ-unsaturated carbonyl compounds (Evans and Gillam, J., 1941, 815). The absorption curve for the diene shows a maximum at 2350 A., log $\varepsilon_{max.}$ = 4·28, similar to that for $\Delta^{3:5}$-androstadien-17-one (log $\varepsilon_{max.}$ = 4·26 at 2345 A.) and $\Delta^{3:5}$-cholestadiene (log $\varepsilon_{max.}$ = 4·30 at 2350 A.) (Burrows *et al.*, *loc. cit.*). The summation of the absorption curves for (III) and the diene is shown in the figure by the dotted line : the resemblance of this to the curve for (IV) is good evidence for the presence of both chromophores in the last compound.

The *iso*propylidene compounds form needles or prisms according to the conditions of crystallisation. They clearly exist in two forms, for if the temperature is raised quickly the m. p. is lower than when it is raised slowly. This is almost certainly due to the transformation of the low-melting into the high-melting variety at the point of fusion of the former. This behaviour has also been observed in the pregnene series of compounds, particularly with Δ^5-pregnenolone, $\Delta^{5:16}$-pregnadienolone, and progesterone. The last, as prepared in our laboratories, melts at 121° in a rapidly heated but at 128° in a slowly heated bath. If the specimen is first fused at 121° and allowed to resolidify, it will then invariably melt at 128°. A similar behaviour has been observed in the case of Δ^4-cholestenone (Jones and Barton, J., 1943, 602).

The ease of condensation with acetone is a characteristic of the 16-methylene group and is not shared by the 2-methylene group in Δ^4-cholestenone, since the latter is unchanged on treatment with acetone and methyl-alcoholic potassium hydroxide.



III, 16-*iso*Propylidene-Δ^5-androsten-3-ol-17-one. IV, 16-*iso*Propylidene-$\Delta^{3:5}$-androstadien-17-one. VI, 16-*iso*Propylidene-Δ-$^{3:5}$-androstadiene.

EXPERIMENTAL.

(All m. p.'s, which are uncorrected, were taken in a slowly heated bath.)

Hydrolysis of trans-*Dehydroandrosterone Acetate Residues.*—90 G. of resinous material (obtained by the oxidation of cholesteryl acetate dibromide) were refluxed for 2 hours with 90 g. of potassium hydroxide in 400 c.c. of commercial methyl alcohol. The solution, from which solid had begun to separate, was then allowed to cool overnight. The heavy crop of prismatic needles was filtered off and well washed with methyl alcohol, giving 13 g. of solid, m. p. 170—180°. A benzene solution of the product was percolated through a column of activated alumina. From this column benzene eluted 6 g. of solid (A), m. p. 193—195° after recrystallisation from alcohol (Found : C, 84·9; H, 9·8. $C_{22}H_{30}O$ requires C, 85·1; H, 9·8%). This *substance* (IV) formed long needles if the solution was cooled slowly, or prisms if the cooling was more rapid. The more strongly adsorbed material was removed from the column by washing with ether, and the resinous fraction (B) thus obtained was divided into two parts. One part was acetylated by refluxing with acetic anhydride for ½ hour, giving an *acetyl* derivative, m. p. 186—189°, after several recrystallisations from acetone–methyl alcohol (Found : C, 77·4; H, 9·5. $C_{24}H_{34}O_3$ requires C, 77·8; H, 9·3%). The other part, on treatment with benzoyl chloride in pyridine, yielded the *benzoate*, m. p. 210—212°, which formed flattened needles from acetone (Found : C, 79·4; H, 8·9. $C_{27}H_{36}O_3$ requires C, 79·4; H, 8·9%).

16-iso*Propylidene-*Δ^5*-androsten-*3*-ol-*17*-one.*—2 G. of *trans*-dehydroandrosterone acetate were dissolved in a mixture of 10 c.c. each of acetone and methyl alcohol, and after the addition of 2 g. of potassium hydroxide the mixture was refluxed for 1 hour. The cooled mixture was diluted with water and extracted with ether. The residue obtained by evaporating the dried extract formed felted needles from methyl alcohol, m. p. 223° (Found : C, 80·2; H, 10·0. $C_{22}H_{32}O_2$ requires C, 80·4; H, 9·8%). The yield of recrystallised material was 1·6 g. This *ketone* was also obtained by the hydrolysis of the acetate and the benzoate described above.

On one occasion, cooling of the condensation mixture yielded a product, m. p. 180° with evolution of gas, which readily dissolved in methyl alcohol, but when the solution was warmed the less soluble *iso*propylidene compound, m. p. 223°, was deposited.

Δ^4-Cholestenone was recovered unchanged when heated with acetone–methyl alcohol in the presence of potassium hydroxide as described above.

Dehydration of 16-iso*Propylidene-*Δ^5*-androsten-*3*-ol-*17*-one.*—500 Mg. of the *iso*propylidene compound in 5 c.c. of benzene were boiled for ½ hour with 1 g. of phosphoric oxide, which became purple. The benzene solution was percolated through a column of activated alumina and evaporated, and the residue crystallised twice from methyl alcohol, giving, on slow cooling, long needles of 16-*iso*propylidene-$\Delta^{3:5}$-androstadien-17-one, m. p. 192—194°, not depressed by admixture with substance (A) (Found : C, 84·7; H, 9·8%).

$\Delta^{3:5}$*-Androstadien-*17*-one.*—1 G. of *trans*-dehydroandrosterone was dehydrated as described above; the product formed plates, m. p. 85°, from aqueous methyl alcohol. The semicarbazone, formed by heating 200 mg. of the ketone under reflux with 200 mg. of semicarbazide acetate in 5 c.c. of methyl alcohol, melted at 290° (decomp.). $\Delta^{3:5}$-Androstadien-17-one condensed with acetone under the conditions described above to give compound (A), m. p. and mixed m. p. 192—194°. Compound (A) did not form a semicarbazone when refluxed with a solution of semicarbazide acetate.

Reduction of 16-iso*Propylidene-*$\Delta^{3:5}$*-androstadien-*17*-one.*—1 G. of ketone, 2·6 c.c. of 98% hydrazine hydrate, and

0·5 g. of sodium in 10 c.c. of alcohol were heated in a sealed tube for 16 hours at 210°. The product obtained by dilution with water and extraction with ether was not homogeneous; it was therefore dissolved in light petroleum (b. p. 40—60°) and percolated through a column of alumina. The percolate contained a solid, m. p. 139—143°, which was further purified by sublimation at 120°/0·001 mm. The 16-iso*propylidene*-$\Delta^{3:5}$-*androstadiene* now formed plates from methyl alcohol, m. p. 140—144° (Found: C, 88·5; H, 10·8. $C_{22}H_{32}$ requires C, 89·1; H, 10·9%).

Attempted Reduction of 16-iso*Propylidene*-Δ^5-*androsten*-3-*ol*-17-*one*.—The substance was treated with hydrazine hydrate and sodium ethoxide as described above. The *product* crystallised from ether–light petroleum (b. p. 60—80°) in magnificent flattened needles, m. p. 190—192° with evolution of gas (Found: C, 74·4; H, 10·9. $C_{20}H_{34}O_3$ requires C, 74·5; H, 10·6%).

The absorption spectra were measured by Mr. E. A. Braude. The author's thanks are due to Professor G. A. R. Kon for his interest in this work and to Organon Laboratories Ltd. for permission to publish the results.

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