954. *Studies in the Steroid Group. Part LVII.* Side-chain Degradation of 3β-Acetoxy-5α : 8α-epidioxyergosta-9 : 22-diene.*

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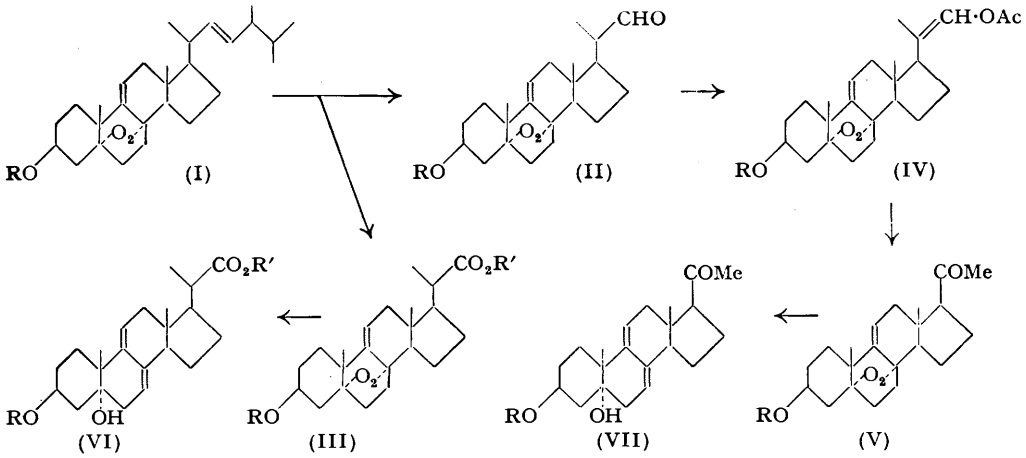
Controlled ozonolysis of 3β-acetoxy-5α : 8α-epidioxyergosta-9 : 22-diene (I; R = Ac) afforded a mixture of the bisnorcholenaldehyde (II; R = Ac) and the bisnorcholenic acid (III; R = Ac; R′ = H). The aldehyde has been degraded *via* its enol acetate to the ketone (V; R = Ac), which with zinc and acetic acid gave the 7 : 9-diene (VII; R = Ac).

From the experiments described in the present series of papers, there are indications that the order of reactivity of the ethylenic bonds in dehydroergosterol epidioxide and its esters

* Part LVI, preceding paper.

is 6 : 7 > 22 : 23 > 9 : 11. Thus, as shown in the preceding paper, under mild conditions of hydrogenation dehydroergosteryl acetate epidioxide first gives the $\Delta^{9(11):22}$-steroid (I; R = Ac) (" dihydro-acetate "), in which it seemed possible that the double bond in the side chain could be oxidised selectively.

The first experiments were carried out on the dihydro-acetate (I; R = Ac) and dihydrobenzoate (I; R = Bz) by adding a solution of ozone in ethyl acetate (a saturated solution at − 70°, the strength of which could be assessed independently) to a similar solution of the steroid. The blue colour of the ozone solution was very rapidly discharged during the addition, but after one equiv. of ozone had been consumed, further addition of ozone solution gave a pale blue reaction mixture, the colour persisting for at least a minute. These



titration experiments with solutions of ozone, together with the isolation of the bisnorcholenaldehyde (II), indicated the superior reactivity of the 22 : 23-ethylenic bond in compounds of formulæ (I), and also afforded a very convenient method of carrying out controlled ozonolyses on small quantities of materials. In large-scale experiments, ozonized oxygen was passed into the steroid solution at −70° until a moderately permanent blue colour appeared.

The ozonides were decomposed in various ways (see Experimental), the yields of aldehyde being of the order of 35—50%. The corresponding bisnorcholenic acid (III; R′ = H) could be isolated in each case in yields of about 10%. These acids were further characterized as their methyl esters, which were converted in good yield into 5α-hydroxy-7 : 9-dienes (VI) by the zinc–acetic acid reduction procedure described in the previous paper.

Conditions for the conversion of the acetate-aldehyde (II; R = Ac) into its enol acetate (IV; R = Ac) were somewhat critical. Owing to the relative instability of the peroxide bridge the conditions employed by Bergmann and Stevens (*J. Org. Chem.*, 1948, **13**, 10) and by Heyl and Herr (*J. Amer. Chem. Soc.*, 1950, **72**, 2617) for similar conversions, were found to be too drastic. However, by working at 120—125°, by using potassium acetate as catalyst, and by limiting the quantity of acetic anhydride, the enol acetate (IV; R = Ac) was obtained in 60% yield.

Ozonolysis of the enol acetate afforded the $C_{(20)}$-keto-compound (V; R = Ac) in 30% yield. This ketone was readily converted into the diene (VII; R = Ac) by zinc and acetic acid. Further transformations of the above compounds containing degraded side-chains, in particular, experiments involving the introduction of oxygen at $C_{(11)}$, will be described later.

Experimental

General experimental directions are given in the preceding paper.

3β-Acetoxy-5α : 8α-epidioxybisnorchol-9-en-22-al (II; R = Ac) *and the Corresponding Acid* (III; R = Ac, R′ = H).—A solution of 3β-acetoxy-5α : 8α-epidioxyergosta-9 : 22-diene (3 g.)

in ethyl acetate was cooled to −70° and treated with a saturated (at −70°) solution of ozone in ethyl acetate until a faint blue colour persisted. Raney nickel (4 c.c. of thick sludge in ethyl acetate) was added and the mixture was heated under reflux until the solution no longer gave a blue colour with starch–potassium iodide paper (20—30 minutes). The solution, after filtration, was washed several times with 2% aqueous potassium hydroxide, then dried (Na_2SO_4) and evaporated. The residue was chromatographed in benzene–light petroleum (1 : 3) on deactivated alumina (100 g.). Elution with the same solvent mixture gave some material that was rejected (negative 2 : 4-dinitrophenylhydrazine test). Elution with benzene (2 l.) gave material (1·4 g.), which on recrystallization from *iso*propyl ether gave the aldehyde (700 mg.), m. p. 180—185°; a second crop (200 mg.) had m. p. 173—177°. The pure *aldehyde* crystallized from *iso*propyl ether as plates, m. p. 190—195° (decomp.), $[\alpha]_D$ −13° (*c*, 0·76) (Found: C, 71·35; H, 8·6. $C_{24}H_{34}O_5$ requires C, 71·6; H, 8·5%). It readily formed a yellow 2 : 4-dinitrophenylhydrazone.

The ozonide could also be decomposed (*a*) by heating it under reflux with water and a trace of Adams platinum oxide (to decompose hydrogen peroxide formed), (*b*) by shaking it with hydrogen (or bubbling hydrogen through) in the presence of reduced Adams catalyst, (*c*) by shaking it with aqueous ferrous sulphate solution, or (*d*) by shaking it with an aqueous solution containing potassium iodide and sodium thiosulphate (this solution is slightly alkaline and dissolves some of the bisnorcholenic acid which is thereby rendered difficult to recover). By none of these processes was the yield of the aldehyde substantially improved.

Acidification of the alkaline washings precipitated crude 3β-acetoxy-5α : 8α-bisnorchol-9-enic acid (200 mg.), which after recrystallization from aqueous acetone formed laths, m. p. 201—205° (decomp.), $[\alpha]_D$ −18° (*c*, 1·44). Ethereal diazomethane afforded *methyl* 3β-*acetoxy*-5α : 8α-*epidioxybisnorchol*-9-*enate*, needles (from methanol), m. p. 171—175°, $[\alpha]_D$ −13° (*c*, 1·11) (Found: C, 69·5; H, 8·45. $C_{25}H_{36}O_6$ requires C, 69·4; H, 8·4%). Hydrolysis of the ester with warm 5% methanolic potassium hydroxide gave, after acidification, the parent hydroxy-acid, sparingly soluble in organic solvents. A suspension of the hydroxy-acid in dry ether was treated with diazomethane, affording *methyl* 5α : 8α-*epidioxy*-3β-*hydroxybisnorchol*-9-*enate* (III; R = H, R′ = Me), needles (from methanol), m. p. 176—178°, $[\alpha]_D$ −26° (*c*, 0·91) (Found: C, 70·9; H, 9·0. $C_{23}H_{34}O_5$ requires C, 70·75; H, 8·8%).

Methyl 3β-*Acetoxy*-5α-*hydroxybisnorchola*-7 : 9-*dienate* (VI; R = Ac, R′ = Me).—Zinc dust (4 g.) was added in small portions to a hot solution of methyl 3β-acetoxy-5α : 8α-epidioxybisnorchol-9-enate (3 g.) in acetic acid (25 c.c.), the mixture then being heated under reflux for 10 minutes. The steroid was isolated with ether; recrystallization from methanol afforded the *diene* (2·0 g.) as needles, m. p. 191—193°, $[\alpha]_D$ +69° (*c*, 1·16) (Found: C, 72·35; H, 8·9. $C_{25}H_{36}O_5$ requires C, 72·1; H, 8·7%). Light absorption: Max. 2430 Å; ε = 15,300. The same compound was obtained, but in poorer yield, by hydrogenation of (III; R = Ac, R′ = Me) in ethyl acetate in the presence of Raney nickel.

5α : 8α-*Epidioxy*-3β-*hydroxybisnorchol*-9-*ene*-22-*al* (II; R = H).—A solution of 3β-hydroxy-5α : 8α-epidioxyergosta-9 : 22-diene [prepared by hydrolysis of the acetate (1 g.)] in ethyl acetate (20 c.c.) was treated with ozone (1 mol.) at −70°. The solution was then added to a suspension of reduced hydrated platinic oxide (50 mg.) in ethyl acetate (25 c.c.) also at −70°, and a stream of hydrogen was passed through this mixture while it was allowed to warm to 20° and then until a test with starch–potassium iodide indicated complete decomposition of the ozonide. The solution was extracted with 2% aqueous alkali; drying (Na_2SO_4) and evaporation of the ethyl acetate solution afforded a neutral fraction (665 mg.), which was introduced in benzene (20 c.c.) and chloroform (5 c.c.) on to a column of alumina (30 g.; deactivated with 5% of water). Elution with benzene–ether (4 : 1) gave a fraction (290 mg.), which when recrystallized from *iso*propyl ether gave the *hydroxy-aldehyde* as blunt needles, m. p. 155—160°, $[\alpha]_D$ −37·5° (*c*, 1·17) (Found: C, 73·0; H, 8·9. $C_{22}H_{32}O_4$ requires C, 73·3; H, 8·95%).

Acetylation of this steroid with acetic anhydride–pyridine at 20° overnight gave the 3-acetate as blades (from *iso*propyl ether), m. p. 183—189° (undepressed on admixture with the material described above), $[\alpha]$ −12° (*c*, 0·56).

3β-*Benzoyloxy*-5α : 8α-*epidioxybisnorchol*-9-*en*-22-*al* (II; R = Bz) *and the Corresponding Acid* (III; R = Bz, R′ = H).—A solution of 3β-benzoyloxy-5α : 8α-epidioxyergost-9 : 22-ene (600 mg.) in chloroform (25 c.c.) was cooled to −60°. A solution of ozone (1·1 mols.) (at −70°) was then added. The rate at which the blue colour disappeared decreased as the addition proceeded; at the end the colour persisted for more than 2 minutes. The solution was warmed to 20°, Adams catalyst (70 mg.) then being added and the mixture shaken with hydrogen until 1 mol. (33 c.c.) had been taken up. After filtration, the solvent was removed under reduced

pressure, and the residue (560 mg.) was chromatographed on deactivated alumina (60 g.). Elution with light petroleum–benzene (3 : 2) gave 3β-benzoyloxy-5α : 8α-epidioxyergost-9(11)-ene (85 mg.) as needles, m. p. and mixed m. p. with an authentic sample, 191—192°, $[\alpha]_D$ −10° (*c*, 1·24), after crystallization from methanol. Elution with light petroleum–benzene (1 : 3) afforded the *aldehyde*, which crystallized from ethyl methyl ketone–light petroleum (b. p. 80—100°) (1 : 1) as platelets (210 mg.), m. p. 191—200°, $[\alpha]_D$ −12° (*c*, 1·62) (Found : C, 75·0; H, 7·75. $C_{29}H_{36}O_5$ requires C, 74·95; H, 7·8%). Recrystallization of this aldehyde from methanol–ethyl methyl ketone containing a trace of mineral acid gave the *dimethyl acetal* as needles, m. p. 208—218°, $[\alpha]_D$ −6° (*c*, 0·70) (Found : C, 72·6; H, 8·25; OMe, 11·6. $C_{31}H_{42}O_6$ requires C, 72·9; H, 8·3; OMe, 12·1%).

In another experiment, an ethereal solution of the material obtained by reduction of the ozonide was extracted with 2% aqueous potassium hydroxide. This extract was acidified and the organic acid isolated with ether. Recrystallization of the solid obtained by evaporation of the ether from dioxan–*iso*propyl ether (1 : 3) yielded 3β-*benzoyloxy*-5α : 8α-*epidioxybisnorchol*-9(11)-*enic acid* as needles, m. p. 215—230°, $[\alpha]_D$ −11·5° (*c*, 1·32) (Found : C, 71·85; H, 7·55. $C_{29}H_{36}O_6$ requires C, 72·45; H, 7·55%). Ethereal diazomethane gave the *methyl* ester, needles [from methanol–ethyl methyl ketone (1 : 1)], m. p. 232—237°, $[\alpha]_D$ −8° (*c*, 0·87) (Found : C, 72·9; H, 7·95. $C_{30}H_{38}O_6$ requires C, 72·85; H, 7·75%).

Methyl 3β-*Benzoyloxy*-5α-*hydroxybisnorchola*-7 : 9-*dienate* (VI; R = Bz, R′ = Me).—Zinc dust (750 mg.) was added in small portions to a solution of the foregoing ester (650 mg.) in acetic acid (15 c.c.) at 95°. The mixture was then heated under reflux for 15 minutes, and poured into water and the steroid isolated with ether. Recrystallization from acetone–methanol (1 : 1) afforded the *diene benzoate* as needles, m. p. 213·5—217°, $[\alpha]_D$ +55·5° (*c*, 0·83) (Found : C, 75·1; H, 8·3. $C_{30}H_{38}O_5$ requires C, 75·3; H, 8·0%). Light absorption : Max., 2340, 2730, and 2800 Å; ε = 26,500, 900, and 750 respectively.

3β : 22-*Diacetoxy*-5α : 8α-*epidioxybisnorchola*-9 : 20(22)-*diene* (IV; R = Ac).—3β-Acetoxy-5α : 8α-epidioxybisnorchol-9-en-22-al (8 g.), fused potassium acetate (2 g.), and redistilled acetic anhydride (40 c.c.) were heated at 120—125° (oil-bath temp.) for 6 hours. The reaction mixture was diluted with benzene and filtered. The solvent was removed by evaporation under reduced pressure, and the light brown residue was introduced in benzene (100 c.c.) and light petroleum (100 c.c.) on to a column of deactivated alumina (100 g.). Elution with benzene–light petroleum (1 : 1) and crystallization from methanol afforded crude enol acetate (4·7 g.), m. p. 162—165°. Further recrystallization from methanol yielded the pure enol *acetate* as platelets, m. p. 171—175°, $[\alpha]_D$ −18° (*c*, 1·57) (Found : C, 70·15; H, 8·2. $C_{26}H_{36}O_6$ requires C, 70·25; H, 8·15%).

3β-*Hydroxy- and* 3β-*Acetoxy*-5α : 8α-*epidioxy*allo*pregn*-9-*en*-20-*one* (V; R = H; and R = Ac).—A solution of the enol acetate (7·5 g.) in ethyl acetate (200 c.c.), cooled to −70°, was treated with a solution of ozone in ethyl acetate until a faint blue colour persisted. The solution was warmed to room temperature, and water (20 c.c.) and Adams catalyst (50 mg.) were added. The mixture was heated under reflux until it failed to give a blue colour with starch–potassium iodide. The cooled solution was extracted once with 2% aqueous potassium hydroxide; acidification of the alkaline washings gave no precipitate. The neutral fraction obtained by evaporation of the dried ethyl acetate solution was chromatographed in benzene on alumina (200 g.). The first benzene eluate (700 c.c.) afforded a gum (1·29 g.) which was saponified with potassium hydroxide (500 g.) in methanol (20 c.c.) at room temperature overnight. Dilution with water and isolation with ether gave solid (1·2 g.), which on crystallisation from methanol gave 5α : 8α-*epidioxy*-3β-*hydroxy*allo*pregn*-9-*en*-20-*one* (520 mg.), m. p. 225° which after further crystallisation from methanol formed needles, m. p. 217—227° (decomp.), $[\alpha]_D$ +24° (*c*, 0·38) (Found : C, 73·05; H, 8·55. $C_{21}H_{30}O_4$ requires C, 72·8; H, 8·75%). The second benzene eluate (3000 c.c.) gave a solid residue (1·9 g.) on evaporation, which afforded 3β-*acetoxy*-5α : 8α-*epidioxy*allo*pregn*-9-*en*-20-*one* (1·3 g.), m. p. 175—179°, on recrystallisation from methanol. The pure material formed plates, m. p. 175—177°, $[\alpha]_D$ +43° (*c*, 0·57) (Found : C, 70·9; H, 8·45. $C_{23}H_{32}O_5$ requires C, 71·1; H, 8·3%). The infra-red spectrum in CS_2 showed peaks at 1708 cm.$^{-1}$ ($C_{(20)}$ ketone), and at 1737 cm. (acetate group) (cf. Jones *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 2024).

3β : 5α-*Dihydroxy*allo*pregna*-7 : 9-*dien*-20-*one* (VII; R = H).—Zinc dust (1 g.) was added in small portions to 5α : 8α-epidioxy-3β-hydroxy*allo*pregn-9-en-20-one (520 mg.) in acetic acid (15 c.c.) at the b.p. After 10 minutes' refluxing, the zinc was filtered off, water added, and the steroid isolated with ether. Recrystallisation of the solid product from methanol–*iso*propyl ether gave 3β : 5α-*dihydroxy*allo*pregna*-7 : 9-*dien*-20-*one* as needles, m. p. 169—172°, $[\alpha]_D$

+59·7° (*c*, 1·04) (Found: C, 76·35; H, 9·15. $C_{21}H_{30}O_3$ requires C, 76·3; H, 9·15%). Light absorption: Max., 2430 Å, $\varepsilon = 18,600$; inflexion, 2370—2380 Å, $\varepsilon = 16,500$. The above compound with acetic anhydride and pyridine at room temperature gave the 3-*acetate*, m. p. 182·5—183·5°, $[\alpha]_D$ +95° (*c*, 0·68) (Found: C, 74·1; H, 8·8. $C_{23}H_{32}O_4$ requires C, 74·15; H, 8·65%). Light absorption: Max., 2420 Å, $\varepsilon = 17,000$; inflexion 2350 Å, $\varepsilon = 15,600$.

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