12-*Oxygenated Pregnane Derivatives. Part III.* Ketals of* allo*Pregnane*-12 : 20-*diones.*

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17α-Hydroxy*allo*pregnane-12 : 20-diones undergo ethylene ketal formation exclusively at $C_{(12)}$ differing from analogous 11 : 20-diones which undergo this reaction at $C_{(20)}$.

In work leading to the preparation of 21-acetoxy-17α-hydroxy*allo*pregnane-3 : 12 : 20-trione (Part II) * we had occasion to prepare some ethylene ketals of *allo*pregnane-12 : 20-diones. The results obtained form the subject of the present communication.

The conversion of an isolated 20-carbonyl group into the cyclic ketal has previously been recorded. Rosenkranz, Pataki, and Djerassi (*J. Org. Chem.*, 1952, **17**, 290) converted 3α-acetoxypregnane-11 : 20-dione smoothly into the 20-ethylene ketal by heating it with ethylene glycol and toluene-*p*-sulphonic acid in benzene. The introduction of a 16α : 17α-epoxy-residue or of a 17α-hydroxyl group into this system exerts little, if any, effect on ketal formation (cf. Julian, " Recent Progress in Hormone Research," Academic Press Inc., 1951, Vol. VI, p. 202), which is, however, completely suppressed by a 21-acetoxyl residue (Antonucci, Bernstein, Lenhard, Sax, and Williams, *J. Org. Chem.*, 1952, **17**, 1369). Hydrolysis of the last group removes the steric factors inhibiting ketal formation, cortisone, for example, passing readily into a 3 : 20-di(ethylene ketal), which undergoes selective hydrolysis to the 3-ketone on treatment with 90% acetic acid (Antonucci, Bernstein, Heller, Lenhard, Littell, and Williams, *ibid.*, 1953, **18**, 70).

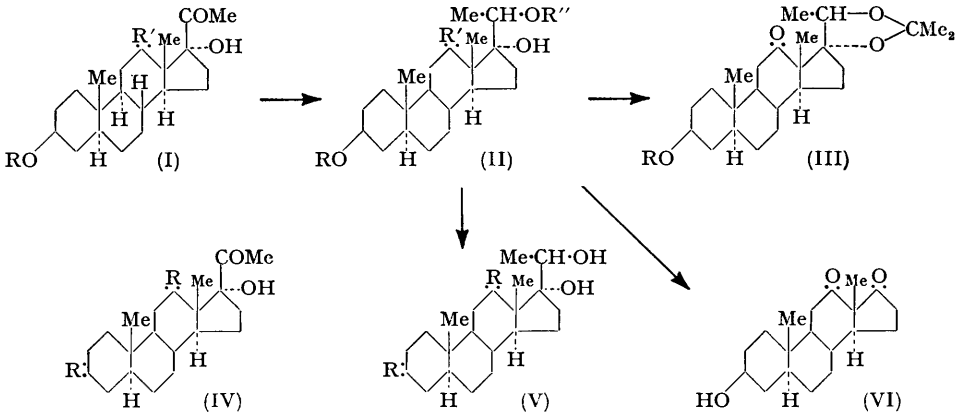
We now find that 3β : 17α-dihydroxy*allo*pregnane-12 : 20-dione (I; R = H, R′ = O) forms only a monoketal on treatment with ethylene glycol and toluene-*p*-sulphonic acid under the usual conditions, or preferably on dissolution in the glycol to which is subsequently added some boron trifluoride–ether complex. The constitution of 12 : 12-ethylenedioxy-3β : 17α-dihydroxy*allo*pregnan-20-one (I; R = H, R′ = ·O·CH_2·CH_2·O·) is assigned to this compound on the basis of the following evidence.

Reduction of the ketal with sodium borohydride leads to the formation of 12 : 12-ethylenedioxy*allo*pregnane-3β : 17α : 20ξ-triol (II; R = R″ = H, R′ = ·O·CH_2·CH_2·O·), hydrolysed by 90% acetic acid to 3β : 17α : 20ξ-trihydroxy*allo*pregnan-12-one (II; R = R″ = H, R′ = O), which was characterised as the 3 : 20-diacetate. Attempts to effect the hydrolysis by the toluene-*p*-sulphonic acid–acetone method of Djerassi, Batres, Romo, and Rosenkranz (*J. Amer. Chem. Soc.*, 1952, **74**, 3634) led to the *iso*propylidene derivative of the foregoing hydrolytic product. The constitution of this hydrolytic product is conse-

* Part II, *J.*, 1954, 2209.

quently that of a 17α : 20ξ-diol, the alternative formulation of a 12β : 17α-diol-20-one being excluded by the stereochemical impossibility of forming an *iso*propylidene link between a 12β- and a 17α-hydroxyl group. The conclusion thus reached was established beyond reasonable doubt by oxidation of (II; R = R″ = H, R′ = O) with sodium bismuthate (Norymberski, *Biochem. J.*, 1953, **55**, 371) to 3β-hydroxyandrostane-12 : 17-dione (VI), which formed a monoacetate and was oxidised by *N*-bromoacetamide in aqueous acetone to androstane-3 : 12 : 17-trione. *Inter alia* we observed that (II; R = R″ = H, R′ = O) with one molar proportion of bromine gives a monobromo-derivative, which regenerates the original ketone on successive treatment with sodium iodide and potassium acetate in acetone.

Reaction of 17α-hydroxy*allo*pregnane-3 : 12 : 20-trione (IV; R = O) with excess of ethylene glycol and boron trifluoride–ether complex led to the formation of the 3 : 12-diethylene ketal (IV; R = ·O·CH_2·CH_2·O·), which reverted to the original diketone on treatment with 90% acetic acid. The constitution assigned to the ketal was confirmed by its reduction with sodium borohydride to 3 : 3-12 : 12-bisethylenedioxy*allo*pregnane-17α : 20ξ-diol (V; R = ·O·CH_2·CH_2·O·), hydrolysed by 90% acetic acid to 17α : 20ξ-dihydroxy*allo*pregnane-3 : 12-dione (V; R = O) which formed a 20-monoacetate and was separately obtained by oxidation of (II; R = R″ = H, R′ = O) with *N*-bromoacetamide.



The foregoing results reveal that in 17α-hydroxy*allo*pregnane-12 : 20-diones ketal formation occurs exclusively on the 12-carbonyl group. In accordance therewith we find that 3β-acetoxy*allo*pregnane-12 : 20-dione (cf. Part II) forms only a monoethylene ketal and monohemithioethylene ketal which are accordingly formulated as 12-derivatives.

Experimental

Optical rotations were measured in chloroform solution in a 1-dm. tube.

12 : 12-*Ethylenedioxy*-3β : 17α-*dihydroxy*allo*pregnan*-20-*one* (I; R = H, R′ = ·O·CH_2·CH_2·O·).—3β : 17α-Dihydroxy*allo*pregnane-12 : 20-dione (8·75 g.) in ethylene glycol (90 ml.) was treated with boron trifluoride–ether complex (14 ml.). After 16 hr. at room temperature the solution was diluted with chloroform and washed neutral with water. After removal of the solvent, the residue was purified from chloroform–ethyl acetate or from methanol. The 12-*ethylene ketal* formed crystals, m. p. 255—259° (softens 252°), $[\alpha]_D^{26}$ +74° (*c*, 0·422) (Found : C, 70·2; H, 9·4. $C_{23}H_{36}O_5$ requires C, 70·4; H, 9·2%). The *acetate* formed prisms, m. p. 209—211°, $[\alpha]_D^{25}$ +68° (*c*, 0·434), from methanol or acetone–hexane (Found : C, 69·3; H, 8·5. $C_{25}H_{38}O_6$ requires C, 69·1; H, 8·8%).

12 : 12-*Ethylenedioxy*allo*pregnane*-3β : 17α : 20ξ-*triol* (II; R = R″ = H, R′ = ·O·CH_2·CH_2·O·).—The foregoing ketal (2 g.) in methanol (240 ml.) was treated portionwise with sodium borohydride (2 g.) in water (20 ml.). Acetic acid (3 ml.) was added after 3 hr., the solvent removed under reduced pressure, and the residue crystallised from acetone–methanol. The *triol* formed prisms, m. p. 223—225°, $[\alpha]_D^{25}$ +22° (*c*, 0·468) (Found : C, 70·3; H, 9·8. $C_{23}H_{38}O_5$ requires C, 70·0; H, 9·7%).

3β : 17α : 20ξ-*Trihydroxy*allo*pregnan*-12-*one* (II; R = R″ = H, R′ = O).—The foregoing compound (400 mg.) was heated with 90% acetic acid (12 ml.) for 45 min. on the steam-bath. The product was isolated with chloroform and purified from acetone. 3β : 17α : 20ξ-*Trihydroxy*-allo*pregnan*-12-*one* formed prisms, m. p. 222—224°, $[\alpha]_D^{25}$ +54° (*c*, 0·480) (Found : C, 71·4; H, 10·0. $C_{21}H_{34}O_4$ requires C, 71·9; H, 9·7%). The 3 : 20-*diacetate* formed needles, m. p. 149—150°, $[\alpha]_D^{27}$ +56° (*c*, 0·460) (Found : C, 69·1; H, 8·4. $C_{25}H_{38}O_6$ requires C, 69·1; H, 8·7%).

3β-*Hydroxy*-17α : 20-iso*propylidenedioxy*allo*pregnane*-12 : 20-*dione* (III; R = H).—3β : 17α : 20ξ-Trihydroxy*allo*pregnane-12 : 20-dione (200 mg.) in acetone (20 ml.) was treated with toluene-*p*-sulphonic acid (50 mg.) for 20 hr. at room temperature. After extraction with ether the *product* was purified from ether–hexane. It had m. p. 161—163°, $[\alpha]_D^{24}$ +31° (*c*, 0·400) (Found : C, 73·8; H, 9·7. $C_{24}H_{38}O_4$ requires C, 73·5; H, 9·8%). The *acetate* formed plates, m. p. 188—190°, $[\alpha]_D^{25}$ +24° (*c*, 0·414) (Found : C, 72·7; H, 9·3. $C_{26}H_{40}O_5$ requires C, 72·2; H, 9·3%).

3β-*Hydroxyandrostane*-12 : 17-*dione* (VI).—3β : 17α : 20ξ-Trihydroxy*allo*pregnan-12-one (1·47 g.) in 50% acetic acid (150 ml.) was shaken with sodium bismuthate (24 g.) for 9 hr., after which the mixture was poured into potassium hydroxide solution (15 g. in 1 l.) and extracted with benzene (200 ml.). The product so obtained proved difficult to purify. Acetylation gave 3β-*acetoxyandrostane*-12 : 17-*dione*, glistening plates, m. p. 165—166°, $[\alpha]_D^{19}$ +164° (*c*, 0·25) (Found : C, 72·9; H, 8·4. $C_{21}H_{30}O_4$ requires C, 72·8; H, 8·7%), after crystallisation from acetone–hexane. Hydrolysis with potassium carbonate in aqueous methanol furnished 3β-*hydroxyandrostane*-12 : 17-*dione*, silky needles, m. p. 127—129°, $[\alpha]_D^{19\cdot5}$ +173° (*c*, 0·25) (Found : C, 75·2; H, 9·8. $C_{19}H_{28}O_3$ requires C, 75·0; H, 9·3%).

Androstane-3 : 12 : 17-*trione*.—The foregoing compound (600 mg.) was treated with *N*-bromoacetamide (600 mg.) in aqueous acetone (150 ml. of 90%) for 8 hr. at room temperature. The mixture was poured into water and the product isolated with chloroform and debrominated with zinc dust in acetic acid (20 ml. at 60° for 30 min.). Crystallisation from acetone–hexane yielded *androstane*-3 : 12 : 17-*trione*, crystals, m. p. 179—181°, $[\alpha]_D^{19\cdot5}$ +227° (*c*, 0·25) (Found : C, 75·2; H, 8·9. $C_{19}H_{26}O_3$ requires C, 75·5; H, 8·7%).

11ξ-*Bromo*-3β : 17α : 20ξ-*trihydroxy*allo*pregnan*-12-*one*.—A stirred solution of 3β : 17α : 20ξ-trihydroxy*allo*pregnan-12-one (1·2 g.) in chloroform (20 ml.) was treated dropwise with bromine (27 ml.; 0·128M in chloroform). The product, after crystallisation from chloroform–ether, yielded the 11ξ-*bromo*-derivative, m. p. 158—159°, $[\alpha]_D^{24}$ −42° (*c*, 0·40) (Found : C, 59·4; H, 7·7; Br, 20·3. $C_{21}H_{33}O_4Br$ requires C, 58·7; H, 7·7; Br, 18·7%).

3 : 3-12 : 12-*Bisethylenedioxy*-17α-*hydroxy*allo*pregnane*-20-*one*.—A solution of (IV; R = O) (2 g.) in benzene (80 ml.) and ethylene glycol (20 ml.) was distilled slowly to remove traces of water. Toluene-*p*-sulphonic acid (75 mg.) was then added and the solution heated under reflux for 6 hr. The product, after crystallisation from ethyl acetate, yielded the *diketal*, m. p. 222—224°, $[\alpha]_D^{25}$ +80° (*c*, 0·450) (Found : C, 69·2; H, 8·7. $C_{25}H_{38}O_6$ requires C, 69·1; H, 8·8%), also prepared by the boron trifluoride route (see above).

3 : 3-12 : 12-*Bisethylenedioxy*allo*pregnane*-17α : 20ξ-*diol*.—This *diketal*, prepared by reduction of the foregoing compound with sodium borohydride in aqueous methanol, formed hexagonal prisms, m. p. 211—213°, $[\alpha]_D^{27}$ +25° (*c*, 0·398) (Found : C, 68·7; H, 9·1. $C_{25}H_{40}O_6$ requires C, 68·8; H, 9·2%).

17α : 20ξ-*Dihydroxy*allo*pregnane*-3 : 12-*dione* (V; R = O).—(i) The foregoing diketal was hydrolysed with 90% acetic acid for 1 hr. at 100° and the product crystallised from aqueous methanol. 17α : 20ξ-*Dihydroxy*allo*pregnane*-3 : 12-*dione* formed glistening leaflets, m. p. 227—229° (decomp.), $[\alpha]_D^{22}$ +75° (*c*, 0·472) (Found : C, 72·4; H, 9·1. $C_{21}H_{32}O_4$ requires C, 72·4; H, 9·2%).

(ii) 3β : 17α : 20ξ-Trihydroxy*allo*pregnan-12-one (250 mg.) in *tert.*-butanol (7 ml.) and water (0·5 ml.) was treated with *N*-bromoacetamide (250 mg.) for 7 hr. at room temperature. The product, after brief debromination with zinc dust in acetic acid, was crystallised from acetone–hexane, to give the product described under (i), m. p. and mixed m. p. 231—233°, $[\alpha]_D^{24}$ +86° (*c*, 0·446).

Acetylation of the compounds from (i) and (ii) gave 20-*acetoxy*-17α-*hydroxy*allo*pregnane*-3 : 12-*dione*, m. p. 205—206°, $[\alpha]_D^{28}$ +79° (*c*, 0·418) (Found : C, 70·8; H, 8·7. $C_{23}H_{34}O_5$ requires C, 70·8; H, 8·8%), after crystallisation from ether–hexane.

3β-*Acetoxy*-12 : 12-*ethylenedioxy*allo*pregnan*-20-*one* had m. p. 155—157°, $[\alpha]_D^{25}$ +99° (*c*, 0·418) (Found : C, 72·5; H, 8·9. $C_{25}H_{38}O_5$ requires C, 71·8; H, 9·1%), after crystallisation from ether–hexane and finally from methanol.

The 3β-*hydroxy*-20-*ketone*, prepared by hydrolysis of the foregoing compound (1·72 g.) in

methanol (150 ml.) with potassium carbonate (1·0 g.) in water (10 ml.) for 1 hr. under reflux, had m. p. 195—197°, $[\alpha]_D^{24}$ +97° (Found: C, 73·0; H, 9·5. $C_{23}H_{36}O_4$ requires C, 73·4; H, 9·6%), after purification from chloroform–ether.

3β-*Acetoxy*allo*pregnane*-12 : 20-*dione* 12-*hemithioethylene ketal*, m. p. 175—177°, $[\alpha]_D^{24}$ +112° (*c*, 0·528) (Found: C, 68·7; H, 8·4; S, 7·5. $C_{25}H_{38}O_4S$ requires C, 69·1; H, 8·8; S, 7·4%), was obtained by treating 3β-acetoxy*allo*pregnane-12 : 20-dione (1 g.) in freshly distilled dioxan (7·5 ml.) with 2-mercaptoethanol (2 ml.), fused zinc chloride (1·5 g.), and anhydrous sodium sulphate (1·5 g.) for 18 hr. at room temperature. The product in benzene–light petroleum (1 : 1) was run through an alumina column (150 g.), eluted with the same solvent mixture (150 ml.), and crystallised from chloroform–ether.

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