Synthesis of 18-Substituted Steroids. Part III.[1] Reactions of 18-Substituted Pregnan-20-ones

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An 18-acetoxy-substituent inhibits some of the usual reactions of the pregnan-20-one side chain, and causes preferential formation of the $\Delta^{17(20)}$- rather than the usual $\Delta^{20(21)}$-enol acetate with isopropenyl acetate. 20,20'-Anhydro-dimers can arise from an 18-hydroxypregnan-20-one in the 18 ⟶ 20-hemiacetal form. The formation and cleavage of 17β,18-cyclo-17α-pregnan-20-ones is described.

We recently reported [2,3] a convenient route for the synthesis of 18,21-dihydroxypregn-4-ene-3,20-dione (' 18-hydroxy-deoxycorticosterone '; ' 18-hydroxy-DOC '), which exists in the hemiacetal form (1). Some of our exploratory work, while failing to achieve a satisfactory synthesis of 18-hydroxy-DOC, nevertheless yielded new information about the influence of C-18 substitution on the chemistry of the pregnan-20-one side-chain, as well as providing some novel steroidal derivatives. We now describe the more significant results of these exploratory experiments, which were aimed at the introduction of a C-21 hydroxy-group as the final, crucial stage in the elaboration of the 18,21-dihydroxypregnan-20-one system. The 18-hydroxy-function had been introduced [3] into either 3β-acetoxypregn-5-en-20-one or progesterone by application of the ' hypoiodite ' series of reactions.[4]

Reactions of 18-*Acetoxypregnan*-20-*ones*.—18-Acetoxyprogesterone, as its 3,3-ethylenedioxy-derivative (3), was obtained by forced acetylation [4] of the parent hemiacetal (2). As already reported,[3] attempts to introduce a C-21 substituent by the 21-oxalyl route [5] or by the Keana–Schumaker ketimine halogenation procedure [6] were unsuccessful. The acid-catalysed condensation of the 20-ketone with 2-aminoethanol could not be achieved, the acetoxy-ketone (3) being unchanged, although 3,3-ethylenedioxypregn-5-en-20-one, 3,3-ethylenedioxy-17β,18-cyclo-17α-pregn-5-en-20-one (12) (see below), and 3β-acetoxy-17β,18-cyclo-17α-pregn-5-en-20-one (14) [7] condensed with 2-aminoethanol under the usual conditions to furnish the corresponding 20-imines. A 21-acetoxylation was ultimately achieved

[1] Part II, D. N. Kirk and M. S. Rajagopalan, 1976, in the press.

[2] D. N. Kirk and M. S. Rajagopalan, *J.C.S. Chem. Comm.*, 1974, 145.

[3] D. N. Kirk and M. S. Rajagopalan, *J.C.S. Perkin I*, 1975, 1860.

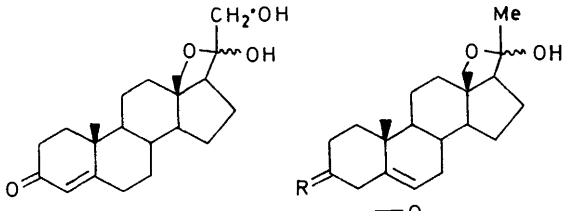
Ch. Meystre, K. Heusler, J. Kalvoda, P. Wieland, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, 1962, **45**, 1317.

[5] H. Ruschig, *Angew. Chem.*, 1948, **60***A*, 247; A. Ercoli and P. de Ruggieri, *Gazzetta*, 1954, **84**, 312; G. I. Poos, R. M. Lukes, G. E. Arth, and L. H. Sarett, *J. Amer. Chem. Soc.*, 1954, **76**, 5031.

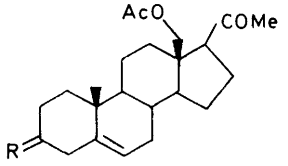
[6] J. F. W. Keana and R. R. Schumaker, *Tetrahedron*, 1970, **26**, 5191.

[7] M. S. Rajagopalan, unpublished results.

by treating the 3-pyrrolidyl-3,5-diene derivative of 18-acetoxyprogesterone with lead tetra-acetate, but in extremely low yield.[3]



(1) (2) R = (4) R = β-AcO,H



(3) R = (5) R = β-AcO,H

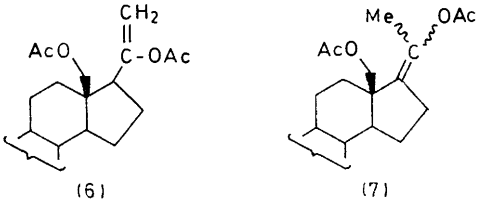
Acid-catalysed enol acetylation of pregnan-20-ones with isopropenyl acetate normally [8,9] leads to $\Delta^{20(21)}$-enol acetates, opening the way to a convenient synthesis of 21-hydroxy-20-ketones by epoxidation and hydrolysis.[9] Use of acetic anhydride gives instead the $\Delta^{17(20)}$-enol acetate. As a suitable intermediate for enol acetylation, 3β,18-diacetoxypregn-5-en-20-one (5) was prepared by the forced acetylation of 3β-acetoxy-18-hydroxypregn-5-en-20-one (' 18-hydroxypregnenolone acetate '), which exists as the hemiacetal (4).

Enol acetylation of the 3,18-diacetoxy-20-ketone (5) with isopropenyl acetate gave a less polar product (t.l.c.) which exhibited the usual i.r. absorption for an enol acetate ($\nu_{max.}$ 1 745—1 750 cm^{-1}) but lacked the expected olefinic absorption in the region 1 640—1 650 cm^{-1}, suggesting that the product was not the required $\Delta^{20(21)}$-enol acetate (6) but was probably a $\Delta^{17(20)}$-enol acetate (7).

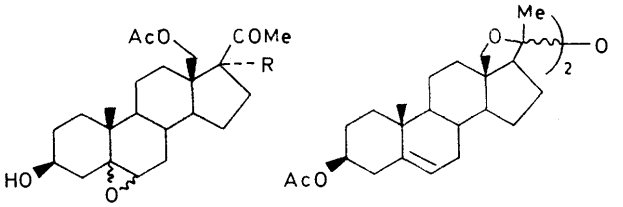
Uncertainties regarding the interpretation of the n.m.r. spectrum necessitated use of a chemical method for confirming the site of side-chain unsaturation. The enol acetate (7) was therefore epoxidised, initially with a molar equivalent of *m*-chloroperbenzoic acid, and the product was hydrolysed with potassium hydrogen carbonate in aqueous methanol, which did not affect the 18-acetoxy-group. The n.m.r. spectrum of the crude product (8) lacked the C-6 olefinic proton resonance, but included a doublet (J 3.5—4 Hz) at τ 7.10 characteristic [10] of the 6β-proton of a 5α,6α-epoxide, indicating a preferential α-epoxidation of the Δ^5-olefinic bond. A sharp singlet for the C-21 methyl protons (τ 7.82) was clearly due to the regeneration of the pregnan-20-one system by hydrolysis of the enol acetate. A similar product was obtained by epoxidation of the Δ^5-olefinic bond in the 3,18-diacetate (5), followed by hydrolysis with potassium hydrogen carbonate in aqueous methanol. When the enol acetate (7) was epoxidised with a large excess of peroxy-acid and the product mixture hydrolysed with potassium hydrogen carbonate in aqueous methanol, as before, the n.m.r. spectrum of the resulting material still had a three-proton singlet (τ 7.78) due to the methyl ketone side chain, as well as the signal characteristic of the 6β-proton of the 5α,6α-epoxy-function. The presence of an additional hydroxy-group, which must be at C-17 (9) in view of the sequence of reactions, was apparent from the higher polarity (t.l.c.) of the new compound (9) as compared with the earlier product (8). These results show that the enol acetate must have been the 17(20)-enol derivative (11) rather than the required $\Delta^{20(21)}$-compound. It was not studied further.

The foregoing experiments indicate that the 18-acetoxy-substituent exerts a profound effect on the chemistry of the pregnan-20-one side-chain. Normal attack is retarded or inhibited both at C-20 and at C-21, suggesting considerable steric interference between the 18-acetoxy-group and the pregnan-20-one side chain.

Formation of 20,20′-*Anhydro-dimers.*—When forced acetylation [4] of the hemiacetal (4), for preparation of the 18-acetoxy-20-ketone, was carried out with acetic



(6) (7)



(8) R = H (9) R = OH (10)

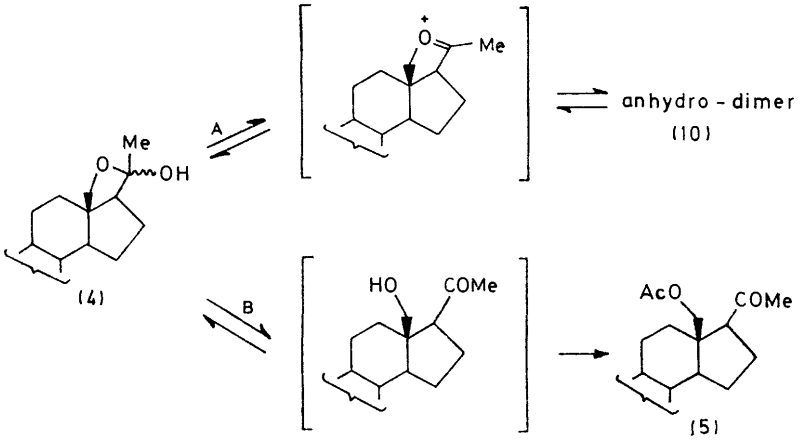
anhydride in pyridine in a relatively dilute solution the reaction mixture contained the 3,18-diacetate (5) and unchanged hemiacetal. On the other hand, when the reaction was carried out in acetic anhydride containing a relatively small amount of pyridine or in a fairly concentrated solution, a substantial quantity of a 20,20′-anhydro-dimer (10) crystallised directly out of the reaction mixture, lowering the yield of the diacetate (5). The anhydro-dimer, conveniently isolable by filtration, was more mobile than the diacetate (5) on t.l.c., had an unusually high melting point (>300 °C), and was practically insoluble in most of the common

[8] R. B. Moffett and D. I. Weisblat, *J. Amer. Chem. Soc.*, 1952, , 2183.

[9] H. van der Haege, E. R. Katzenellenbogen, K. Dobriner, and T. F. Gallagher, *J. Amer. Chem. Soc.*, 1952, **74**, 2810.

[10] A. D. Cross, *J. Amer. Chem. Soc.*, 1962, **84**, 3206.

organic solvents, excluding chloroform and dichloromethane. The only carbonyl absorption was that of the 3β-acetoxy-group (1 735 cm^{-1}), and there was no absorption in the hydroxy-region of the i.r. spectrum. The n.m.r. spectrum showed only one signal each for the

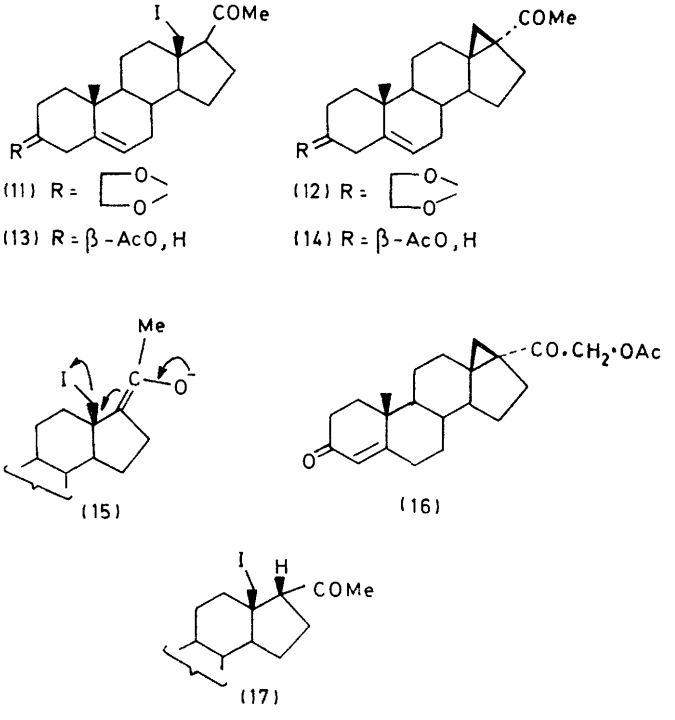


SCHEME Competing formation of anhydro-dimer and 18-acetoxypregnan-20-one

acetoxy-methyl and 10β-methyl groups, and for the C-6 olefinic and C-3 methine protons. Broadening of the signal at τ 6.1—6.5 due to the C-18 methylene protons, and the presence of weaker singlets close to the main 21-methyl proton signal at τ 8.66, indicated that the anhydro-dimer was a mixture of isomers at C-20 of its component steroid units. For comparison, the 20-methoxy-analogue of the hemiacetal (4) also exhibited a singlet at τ 8.66 due to the C-21 protons, and an AB quartet in the region τ 6.2—6.6 (18-CH_2), apparently being a single isomer at C-20.

We envisage formation of the ' dimer ' by dehydration of the hemiacetal (4) *via* the oxonium ion shown in the Scheme. Anhydro-dimers derived from other hemiacetals have been recorded,[11,12] and a similar mechanism has recently been invoked.[12] The formation of the 18-acetate and the anhydro-dimer under different conditions may be explained by the existence of the two types of equilibrium (A and B) represented in the Scheme. Equilibrium A is apparently favoured by a large excess of acetic anhydride, the dimer being formed by a nucleophilic attack of the 20-hydroxy-group of the hemiacetal on the oxonium ion. This reaction will also be favoured in a concentrated solution when the dimer, being sparingly soluble, separates out. Equilibrium B is favoured in the more basic medium containing a large excess of pyridine, or in media in which the dimer is sufficiently soluble to prevent its deposition. Greater solubility probably explains the fact [3] that no anhydro-dimer was isolated from the acetylation of 18-hydroxyprogesterone (hemiacetal) even in a concentrated solution.

17β,18-*Cyclo*-17α-*pregnan*-20-*ones*.—One of several by-products isolated during the silver ion-promoted hydrolysis of the 18-iodo-20-ketone (11), an intermediate in the ' hypoiodite ' reaction sequence,[3] was identified as 3,3-ethylenedioxy-17β,18-cyclo-17α-pregn-5-en-20-one (12). 3β-Acetoxy-17β,18-cyclo-17α-pregn-5-en-20-one (14) was likewise a by-product during the preparation of the hemiacetal (4) from 3β-acetoxypregn-5-en-20β-ol. Supporting evidence for the 17β,18-cyclo-structures came



from an intense i.r. carbonyl absorption at 1 675—1 680 cm^{-1}, characteristic of cyclopropyl ketone conjugation,[13] and a weak but sharp cyclopropyl C–H stretching band [14] at 3 060 cm^{-1}. The cyclopropyl

[11] K. Heusler, J. Kalvoda, P. Wieland, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, 1962, **45**, 2575.
[12] J. T. Edward, M. Kaufman, R. W. Wojtowski, D. M. S. Wheeler, and T. M. Barrett, *Canad. J. Chem.*, 1973, **51**, 1610.
[13] I. Fleming and D. H. Williams, ' Spectroscopic Methods in Organic Chemistry,' McGraw-Hill, London, 1966, p. 62.
[14] S. A. Leibman and B. J. Gudzinowicz, *Analyt. Chem.*, 1961, **33**, 931.

protons at C-18 appeared as an AB quartet in the n.m.r. spectrum (see Experimental section). Apparently the only previous reference to a 17β,18-cyclo-17α-pregnane (' 17,18-cycloprogesterone ') is a footnote to a paper concerned with C-19 substituted compounds.[11]

The yields of cyclopropyl ketones from the reactions of the hypoiodite sequence were found to depend upon the scale of the reaction, and in particular upon how rapidly the desired reaction temperature for the silver-ion-promoted solvolysis of the iodo-ketone was attained. In small batches, where the reaction mixture could be heated rapidly, only traces if any of the cyclopropyl ketone could be detected. In handling large batches, however, a longer time elapsed before the required solvolysis temperature could be attained and significant amounts of the 17,18-cyclo-steroid could be isolated. The cyclopropyl ring closure probably takes place *via* a $\Delta^{17(20)}$-enolate (15),[15] for when the 18-iodo-20-ketones (11) and (13) were heated with methanolic potassium hydroxide (conditions which strongly favour enolisation), the 18-hydroxy-20-oxo-hemiacetals were not formed at all, but there was a corresponding increase in the yields of the cyclopropyl ketones.

In contrast with the low reactivity of an 18-acetoxy-pregnan-20-one, a 21-acetoxy-group was easily introduced into the cyclopropyl ketone (12) *via* bromination at C-21 by the Keana–Schumaker [6] method, to give 21-acetoxy-17β,18-cyclo-17α-pregn-4-ene-3,20-dione (16). We therefore explored the possibility of reopening the cyclopropyl ring to achieve a novel synthesis of 18-hydroxy-DOC (1).

Hydrogen iodide in anhydrous acetic acid [15,16] has been used to open the cyclopropyl ring of other steroidal cyclopropyl ketones. The cyclopropyl ketone (14) was used as a model compound for reaction with hydrogen iodide. The n.m.r. spectrum of the crude product exhibited an AB quartet in the region τ 6.4—6.7 (J_{AB} 8 Hz) due to the expected 18-iodomethyl group, and a singlet at τ 7.85 for the C-21 protons of the methyl ketone. The AB quartet due to the cyclopropyl protons in the starting material had disappeared. The cyclopropyl carbonyl absorption at 1 680 cm^{-1} in the i.r. spectrum was replaced by an intense band at 1 710 cm^{-1}. The formation of an 18-iodo-20-ketone was corroborated further by restoration of the cyclopropyl ketone absorption at 1 680 cm^{-1} when a sample of the crude iodo-ketone was heated in methanolic potassium hydroxide. It seems likely, however, that the pregnane side chain in the ring-opened material was in the 17α-configuration (17), for the new iodo-ketone did not yield any hemiacetal (4) when treated in the usual way with silver acetate in aqueous dioxan. Isomerisation at C-17 to give the pregnan-20-one with the normal (17β) configuration does not appear to be feasible for it would require the $\Delta^{17(20)}$-enolic intermediate, which gives the cyclopropyl ketone rather than undergoing 17α-protonation to give the 17β-side-chain. Other instances of a preference for the 17α-configuration in 18-substituted pregnan-20-ones have been reported.[17] It was concluded from these experiments that 17β,18-cyclopregnan-20-ones are unlikely to be suitable intermediates for preparing 18-hydroxy-DOC (1).

[15] J. F. Kerwin, M. E. Wolff, F. F. Owings, B. B. Lewis, B. Blank, A. Magnani, C. Karasch, and V. Georgian, *J. Org. Chem.*, 1962, **27**, 3628.

[16] M. Akhtar, D. H. R. Barton, and P. G. Sammes, *J. Amer. Chem. Soc.*, 1965, **87**, 4601.

EXPERIMENTAL

For methods and materials, see ref. 3.

Acetylation of the Hemiacetal (4)*: Preparation of* 3β,18-*Diacetoxypregn-5-en-20-one* (5).—Acetic anhydride (2 ml) was added to the hemiacetal (4) [18] (1 g) in dry pyridine (15 ml), and the solution was heated at 100 °C under nitrogen for 48 h. After conventional work-up, the crude product was chromatographed on deactivated alumina (100 g) previously washed with petroleum–benzene (1 : 1; 500 ml). Elution with petroleum–benzene (1 : 1) gave the 3β,18-diacetate (5) (0.45 g), m.p. 122—124° (from petroleum) (lit.,[19] 123—125°); $\nu_{max.}$ 1 740, 1 725, 1 710, and 1 230 cm^{-1}; τ 8.97 (s, 10β-Me), 8.03 (s, 3-OAc), 7.98 (s, 18-AcO), 7.80 (s, 21-H_3), 6.04 and 5.86 (ABq, J_{AB} 11.5 Hz, 18-H_2), *ca.* 5.32 (m, 3-H), and *ca.* 4.6 (m, 6-H).

Isolation of the Anhydro-dimer (10).—The hemiacetal (4) (1 g) in hot pyridine (3 ml) was treated with acetic anhydride (7 ml) and heated at 100 °C under nitrogen for 24 h. During this period a solid separated out. The mixture was cooled to 0 °C, and the solid was collected and washed with pyridine–acetic anhydride (1 : 3) and finally with hexane. Crystallisation from dichloromethane–acetone afforded the 20,20′-*anhydro-dimer* (10) (0.24 g), m.p. 315—317°; $\nu_{max.}$ 1 735 and 1 250 cm^{-1}; τ 9.05 (s, 10β-Me), 8.66 (s, 21-H_3), 8.00 (s, AcO), 6.10—6.50 (m, 18-H_2), *ca.* 5.4 (m, 3-H), and *ca.* 4.6 (m, 6-H) (Found: C, 75.6; H, 9.2. $C_{46}H_{66}O_7$ requires C, 75.6; H, 9.1%). The filtrate was worked up conventionally, to furnish the 3,18-diacetate (5) (0.27 g) and the starting material (0.11 g) after chromatography on alumina.

Enol Acetylation of the 3β,18-*Diacetate* (5).—A solution of the diacetate (5) (0.5 g) in isopropenyl acetate (4 ml) containing toluene-*p*-sulphonic acid (0.06 g) was distilled slowly through a short fractionating column for 10 h, isopropenyl acetate being added occasionally to maintain a volume of 3—4 ml. The mixture was then poured into water and the product was isolated with ether and chromatographed on deactivated alumina (50 g). Elution with petroleum–benzene (9 : 1) afforded the crude enol acetate (7) (0.35 g), which failed to crystallise; $\nu_{max.}$ (film) 1 745—1 750br cm^{-1} (no absorption near 1 710 cm^{-1}).

Experiments to locate the Site of Side-chain Unsaturation in the Enol Acetate (7).—In a series of three experiments (*a*)—(*c*), the 3β,18-diacetate (5) and the enol acetate (7) were epoxidised separately with the amount of *m*-chloroperbenzoic acid indicated, in the minimum volume of benzene, overnight at room temperature: (*a*) 3,18-diacetate (5) (50 mg) and peroxy-acid (25 mg); (*b*) enol acetate (7) (75 mg) and peroxy-acid (25 mg); (*c*) enol acetate (7) (75 mg) and peroxy-acid (65 mg). The crude

[17] J. Schmidlin and A. Wettstein, *Helv. Chim. Acta*, 1962, **45**, 331.

[18] Ch. Meystre, A. Wettstein, O. Jeger, G. Anner, K. Heusler, and P. Wieland, Swiss. P. 410,936/1966 (*Chem. Abs.*, 1967, **66**, 65,745d).

[19] G. D. Searle and Co., B.P. 886,790/1962 (*Chem. Abs.*, 1962, **57**, 919h).

mixtures were hydrolysed with potassium hydrogen carbonate (2%) in aqueous 90% methanol under reflux for 1 h. Extraction with ether gave crude solid products which were examined by t.l.c. and n.m.r. The major components in the products from experiments (*a*) and (*b*) had identical chromatographic mobilities; the major component from experiment (*c*) was more polar. The n.m.r. spectra of the products [(8), mainly 5α,6α-epoxide] from experiments (*a*) and (*b*) were identical: τ 8.05 (s, 18-AcO), 7.82 (s, 21-H_3), 7.10 (d, *J* 3.5 Hz, 6β-H), and 5.8—6.5 (m, 18-H_2 and 3-H). The n.m.r. spectrum of the product from experiment (*c*) differed only in the position of the 21-H_3 signal, which appeared at τ 7.78.

3,3-Ethylenedioxy-17β,18-cyclo-17α-pregn-5-en-20-one (12).—3,3-Ethylenedioxy-20β-hydroxypregn-5-ene (1 g) was converted into the 18-iodo-20-ketone (11) as described previously.[3] The crude gum in methanol (80 ml) was treated with methanolic potassium hydroxide (8 ml; 5%). After heating under reflux for 1 h the solution was evaporated to a small volume and the product was isolated with ether and chromatographed on alumina (110 g). Elution with petroleum–benzene (1 : 1) gave some non-polar material which was not characterised. Elution with benzene–petroleum (7 : 3), afforded first crude 3,3-ethylenedioxypregn-5-en-20-one (0.21 g), followed immediately by the 17β,18-cyclo-steroid (12) (0.16 g), m.p. 220—223°, identical with the sample obtained earlier.[3]

3β-Acetoxy-17β,18-cyclo-17α-pregn-5-en-20-one (14).—3β-Acetoxy-20β-hydroxypregn-5-ene (1 g) was converted into the 18-iodo-20-ketone (13) as described,[18] and the crude product in methanol (80 ml) was hydrolysed as in the foregoing preparation to give crude 3β-hydroxy-17β,18-cyclo-17α-pregn-5-en-20-one, which was acetylated (acetic anhydride–pyridine) and chromatographed on deactivated alumina (100 g). Some non-polar material was eluted with petroleum. Elution with petroleum containing 10—20% benzene afforded pregnenolone acetate (crude yield 0.37 g). Elution with petroleum containing 30—40% benzene gave 3β-*acetoxy-17β,18-cyclopregn-5-en-20-one* (14) (0.19 g), m.p. 126—128° (from petroleum), $\nu_{max.}$ 3 060, 1 735, 1 680, and 1 240 cm^{-1}; τ 9.00 (s, 10β-Me), 7.98 (s, AcO), 7.84 (s, 21-H_3), 8.78 and 9.08 (ABq, *J* 4 Hz, 18-H_2), *ca.* 5.4 (m, 3α-H), and *ca.* 4.6 (m, 6-H) (Found: C, 77.3; H, 9.1. $C_{23}H_{32}O_3$ requires C, 77.5; H, 9.0%).

21-Acetoxy-17β,18-cyclo-17α-pregn-4-ene-3,20-dione (16).—The 17β,18-cyclo-steroid (12) (0.25 g) in toluene (5 ml) was treated with toluene-*p*-sulphonic acid (0.05 g) and 2-aminoethanol (2 ml) with stirring under reflux, and with removal of water by a Dean–Stark separator. After 5 h, more 2-aminoethanol (0.5 ml) was added and the reaction was continued for 1 h. The mixture was then diluted with benzene, which was washed with water until neutral. Drying (K_2CO_3) followed by evaporation under reduced pressure afforded the crude 20-imine ($\nu_{max.}$ 1 650 cm^{-1}), containing only traces of starting material (weak i.r. band at 1 680 cm^{-1}). (The 3,3-ethylenedioxy-group was unaffected by the reaction conditions.) The imine was stirred at room temperature in anhydrous ether containing *N*-bromosuccinimide (freshly crystallised; 0.13 g) until the yellow colour was discharged (2.5 h). Hydrochloric acid (0.1N; 50 ml) was then added and the mixture was stirred overnight at room temperature. The organic phase was washed with water, dried (K_2CO_3), and evaporated. The residue, in methanol (50 ml) containing concentrated hydrochloric acid (0.05 ml) was boiled under reflux for 5 min. (This step was necessary to complete cleavage of the 3,3-ethylenedioxy-group.) After evaporation of most of the methanol, the crude 21-bromo-compound was isolated in ether. This product, in dry acetone (12 ml), was then heated under reflux with sodium iodide (0.1 g) for 15 min. After cooling to room temperature, potassium hydrogen carbonate (0.5 g) and glacial acetic acid (0.4 ml) were added and the mixture was stirred and heated under reflux overnight. The product, extracted with ether, was a gum. Preparative t.l.c. (seven developments) in benzene–ether (4 : 1), and extraction of the broadest visible band (u.v.) with chloroform gave *21-acetoxy-17β,18-cyclo-17α-pregn-4-ene-3,20-dione* (16) (0.13 g), m.p. 161—162° (from petroleum), $\lambda_{max.}$ 240 nm (ε 18 000); $\nu_{max.}$ 3 060, 1 752, 1 702, 1 670, 1 607, and 1 230 cm^{-1}; τ 8.84 (s, 10β-Me), 7.84 (s, AcO), 8.72, 8.98 (ABq, *J* 4 Hz, 18-H_2), 5.16 (s, 21-H_2), and 4.26 (m, 4-H) (Found: C, 74.6; H, 7.9. $C_{23}H_{30}O_4$ requires C, 74.5; H, 8.1%).

Cyclopropyl Ring-opening in Compound (14).—Sodium iodide (18 mg, 0.12 mmol) and an anhydrous solution of perchloric acid in acetic acid (2.1 ml; 0.057M) were added to the 17,18-cyclo-steroid (14) (43 mg, 0.12 mmol) in anhydrous acetic acid (1 ml). After 10 min in the dark, the mixture was poured into ice–water and extracted with ether. The organic phase was washed successively with aqueous 5% sodium thiosulphate, saturated sodium hydrogen carbonate, and water. Drying (K_2CO_3) and evaporation afforded a yellow gum, $\nu_{max.}$ (film) 1 735 and 1 710 cm^{-1} (no absorption at 1 680 cm^{-1}); τ 9.00 (s, 10β-Me), 7.96 (s, AcO), 7.85 (s, 21-H_3), 6.57 and 6.46 (ABq, J_{AB} 8 Hz, 18-CH_2I), *ca.* 5.35 (m, 3-H), and *ca.* 4.6 (m, 4-H). (The AB quartet due to the cyclopropyl protons in the starting material had disappeared.) The crude gum was divided into two equal parts. Part (*a*) was treated with methanolic potassium hydroxide under conditions described above for the conversion of the iodo-ketone (11) into (12). The carbonyl stretching band at 1 680 cm^{-1}, due to the cyclopropyl ketone, reappeared in the i.r. spectrum of the resulting crude product. Part (*b*) was treated with silver acetate in aqueous 90% dioxan under the usual conditions [3,4] for the conversion of the crude iodo-ketone (13) into the hemiacetal (4). T.l.c. of the crude product showed the complete absence of material having the same R_F value as the hemiacetal (4).

Progesterone was kindly provided by Organon Laboratories Ltd., Newhouse, Lanarkshire, and pregnenolone acetate by G. D. Searle and Co. Ltd., High Wycombe, Bucks. N.m.r. spectra were determined by Dr. R. E. Morgan.

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