Synthesis of 18-Substituted Steroids. Part I. 18,21-Dihydroxypregn-4-ene-3,20-dione (18-Hydroxydeoxycorticosterone)

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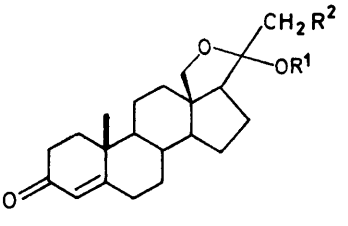
The reaction between an 18-hydroxypregnan-20-one [in the hemiacetal form (1b)] and lead tetra-acetate gives the 21-acetoxy-derivative in high yield, opening the way to a new and efficient synthesis of 18-hydroxydeoxycorticosterone. The preparation of the 1,2-didehydro-derivative of 18-hydroxydeoxycorticosterone is also described.

THE title compound (18-hydroxy-DOC), which exists in the hemiacetal form (1a), was first identified and isolated as a naturally occurring steroidal metabolite from rat adrenals in 1961.[1] It is thought to be a hypertensive agent [2] but biological studies have been hampered by limited supplies and by the lack of a convenient synthesis. It was first prepared in a low yield by aerobic incubation of 21-hydroxypregn-4-ene-3,20-dione with beef adrenals.[3] The first chemical synthesis, starting from the naturally occurring steroidal alkaloid conessine and involving fifteen steps, was reported in 1959.[4] Dehydration of 18-hydroxyprogesterone [as the hemiacetal (1b)] to the vinyl ether (2a) followed by a selective hydroxylation of the exocyclic double bond *in situ* has been claimed to proceed in 20% overall yield,[5] but was unsuccessful in our hands.

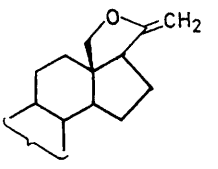
Attempts to use several known procedures [6] for 21-acetoxylation were unsuccessful or gave unacceptable yields when applied to 18-acetoxypregnan-20-ones. These experiments are merely summarised below. 21-Acetoxylation leading to a satisfactory synthesis of 18-hydroxy-DOC (1a) was ultimately achieved by direct reaction of 18 ⟶ 20-hemiacetals with lead tetra-acetate.

Exploratory Experiments.—The 3,3-ethylenedioxy-18,-20-hemiacetal (3a) was first prepared by the hypoiodite-photolysis route.[7] Photolysis of 3,3-ethylenedioxy-pregn-5-en-20β-ol [8] (4) with lead tetra-acetate and iodine, followed by oxidation, gave 3,3-ethylenedioxy-18-iodopregn-5-en-20-one (5), which was converted into the 18,20-hemiacetal (3a) by silver-ion-promoted hydrolysis in aqueous dioxan. Forced acetylation of the hemiacetal (3a) gave the 18-acetoxy-20-ketone (6). An attempted Claisen condensation with diethyl oxalate in the presence of sodium hydride caused quantitative reversion to the hemiacetal (3a), ruling out the possibility of 21-acetoxylation *via* a 21-oxalyl intermediate.[9] The Keana–Schumaker [10] sequence of reactions, useful for selective halogenation of the methyl group of methyl ketones, was also not fruitful. The initial step involving acid-catalysed condensation of the 18-acetoxy-20-ketone (6) with 2-aminoethanol could not be achieved, the starting material being unchanged.



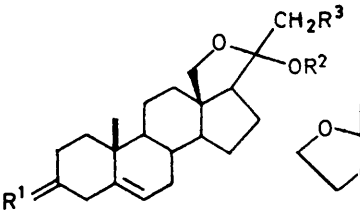
(1)

a; $R^1 = H, R^2 = OH$
b; $R^1 = R^2 = H$
c; $R^1 = H, R^2 = OAc$
d; $R^1 = H, R^2 = Br$

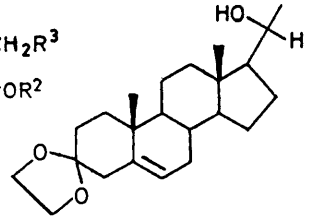


(2)

a; Δ^4-3-oxo
b; 3β-acetoxy-5α
c; 3β-acetoxy-Δ^5

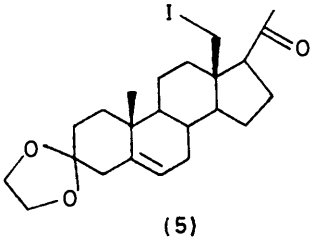


(3)



(4)

a; $R^1 = \square$, $R^2 = R^3 = H$
b; R^1 = β-OAc, α-H, $R^2 = R^3 = H$
c; R^1 = β-OH, α-H, $R^2 = R^3 = H$
d; R^1 = β-OAc, α-H, $R^2 = H$, R^3 = OAc
e; R^1 = β-OH, α-H, $R^2 = H$, R^3 = OAc
f; R^1 = β-OH, α-H, $R^2 = H$, R^3 = Br



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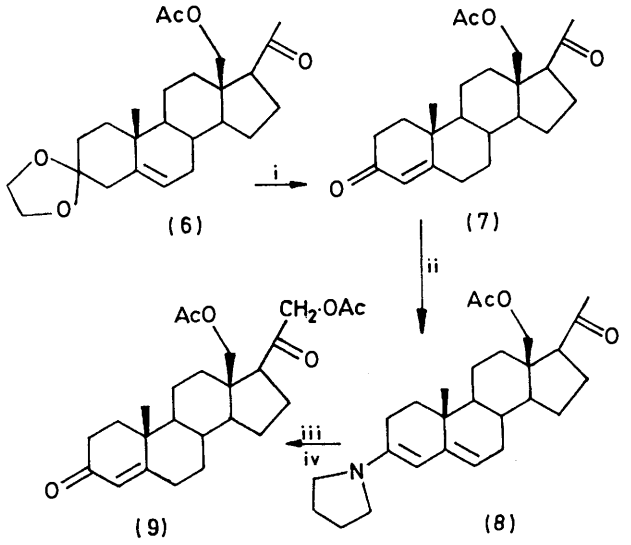
[1] M. K. Birmingham and P. J. Ward, *J. Biol. Chem.*, 1961, **236**, 1661; F. G. Peron, *Endocrinology*, 1961, **69**, 39.
[2] J. C. Melby, S. L. Dale, R. J. Grekin, R. Gaunt, and T. E. Wilson, *Rec. Progr. Hormone Res.*, 1972, **28**, 287.
[3] F. W. Kahnt, R. Neher, and A. Wettstein, *Helv. Chim. Acta*, 1955, **38**, 1237.
[4] R. Pappo, *J. Amer. Chem. Soc.*, 1959, **81**, 1010.
[5] M. P. Li, C. P. Lantos, H. Traikov, M. K. Birmingham, and T. H. Chan, *J. Steroid Biochem.*, 1970, **1**, 259.
[6] C. Djerassi, 'Steroid Reactions,' Holden-Day, San Francisco, 1963, pp. 537—592.
[7] Ch. Meystre, K. Heusler, J. Kalvoda, P. Wieland, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, 1962, **45**, 1317.
[8] F. Sondheimer, M. Velasco, and G. Rosenkranz, *J. Amer. Chem. Soc.*, 1955, **77**, 192.
[9] A. Ercoli and P. de Ruggieri, *Gazzetta*, 1954, **84**, 312.
[10] J. F. W. Keana and R. R. Schumaker, *Tetrahedron*, 1970, **26**, 5191.

An attempted direct acetoxylation of the 18-acetoxypregnan-20-one (6) with lead tetra-acetate, using the improved procedure by Henbest *et al.*,[11] cleaved the 3,3-ethylenedioxy-group. To overcome this complication, the ethylenedioxy-group in compound (6) was

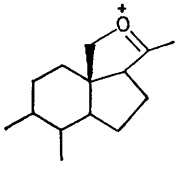


Reagents: i, HCl–aq. MeOH; ii, pyrrolidine–MeOH; iii, $Pb(OAc)_4$–BF_3,OEt_2, C_6H_6–MeOH (19 : 1); iv, $NaHCO_3$–aq. EtOH

hydrolysed with acid to give 18-acetoxyprogesterone (7), and the Δ^4-3-oxo-system was then protected by conversion to the 3-pyrrolidin-1-yl-3,5-diene (8). Acetoxylation, followed by removal of the protective group[12] with aqueous sodium hydrogen carbonate, led to a highly complex mixture from which 18,21-diacetoxypregn-4-ene-3,20-dione (9) was isolated in very poor yield. Despite apparent homogeneity (t.l.c.), the product failed to crystallise. The structure was clear from its n.m.r. spectrum (see Experimental section). Although alkaline hydrolysis of the diacetate (9) furnished 18-hydroxy-DOC (1a), the poor yield in the acetoxylation step made it necessary to devise a more satisfactory synthesis.

Enol acetylation of 3β,18-diacetoxypregn-5-en-20-one[13] with isopropenyl acetate afforded the corresponding $\Delta^{17(20)}$- rather than the expected[14] $\Delta^{20(21)}$-enol acetate, precluding the usual epoxidation route to 21-hydroxy-steroids. Details of these and other experiments, which showed that the 18-acetoxy-group has a profound effect on the chemistry of the pregnan-20-one side-chain, will be published separately.

Direct C-21 *Acetoxylation of* 18,20-*Hemiacetals*.—Choay *et al.*[15] found that hydrogenolysis of 3β-acetoxy-20-methoxy-18,20-epoxy-5α-pregnane in the presence of Adams catalyst in acetic acid gave (20*S*)-3β-acetoxy-18,20-epoxy-5α-pregnane free from the (20*R*)-isomer. The stereospecificity could result from reduction of either the oxonium ion (10) or the vinyl ether (2b),



(10)

which could exist in equilibrium with the oxonium ion in the acidic medium; adsorption of either reactive intermediate on to the surface of the catalyst by the completely unhindered rear face of the molecule, would lead exclusively to the (20*S*)-18,20-ether.

Prompted by these considerations to look for evidence that such an equilibrium exists, we found[16] that the hemiacetal (3b),[17] when dissolved in anhydrous chloroform containing acetic [^{2}H]acid, suffered replacement of the C-21 hydrogen atoms, as seen by the disappearance of the C-21 methyl signal in the n.m.r. spectrum. The reversibility of the reaction was demonstrated by the reappearance of the C-21 methyl signal when the labelled material was treated under identical conditions with unlabelled acetic acid.

Mass spectra (*m/e*) of the hemiacetal (3b) and its 21-deuterio-derivatives

Relative abundances of ions in parentheses: *m/e* 296 or 298 ≡ 100%

Compound		M^+	(a) $M^+ - H_2O$ (or HDO)	(b) $M^+ -$ HOAc	(c) $M^+ - [H_2O(HDO) +$ HOAc]	(d) $M^+ - [H_2O(HDO) +$ HOAc + Me]
Unlabelled hemiacetal		374(0)	356 (<1%)	314 (10%)	296 (100%)	281 (21%)
Labelled hemiacetal	21-D_2	376(0)	357 (−HDO) (<1%), 358 (−H_2O) (<1%)	316 (3%)	297 (96%)	282 (23%)
	21-D_3	377(0)	358 (−HDO) (<1%)	317 (5%)	298 (100%)	283 (22%)

The most significant fragment ions seen in the mass spectra of the hemiacetal (3b) and the labelled material are given in the Table. The peaks listed indicate that the molecular ion loses: (a) a molecule of water (HDO from the labelled species); (b) a molecule of acetic acid;

[11] H. B. Henbest, D. N. Jones, and G. P. Slater, *J. Chem. Soc.*, 1961, 4472; J. D. Cocker, H. B. Henbest, G. H. Phillips, G. P. Slater, and D. A. Thomas, *ibid.*, 1965, 6.

[12] B. Gadsby and M. R. G. Leeming, *Chem. Comm.*, 1968, 596; B.P. 1,225,760/1971; Ger. Offen., 1,801,410/1969 (*Chem. Abs.*, 1969, **71**, 81,648h).

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

[14] H. van der Haege, E. R. Katzenellenbogen, K. Dobriner, and T. F. Gallagher, *J. Amer. Chem. Soc.*, 1952, **74**, 2810; R. B. Moffett and D. I. Weisblat, *ibid.*, p. 2183.

[15] P. Choay, C. Monneret, and Qui Khuong-Huu, *Bull. Soc. chim. France*, 1973, 1456.

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

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

(c) both water and acetic acid; (d) water, acetic acid, and the C-19 methyl group. Fragment ions from the labelled material had *m/e* values indicative of the presence of both the 21-D_3 and the 21-HD_2 species in comparable amounts; slight loss of deuterium may have occurred during work-up after the reaction with deuterioacetic acid. There was no evidence for labelling at C-17, and the reason can be seen from attempts to construct a Dreiding model of the necessary $\Delta^{17(20)}$-vinyl ether intermediate, which is inordinately strained.

Although the transient $\Delta^{20(21)}$-vinyl ether (2c) could be neither isolated nor detected in solution, the feasibility of electrophilic reactions at C-21 using 18-hydroxypregnan-20-one hemiacetals or their 20-alkoxy-derivatives was apparent. We found accordingly that the hemiacetals (1b), (3b), and (3c) reacted smoothly with lead tetra-acetate in acetic acid affording the 21-acetoxy-compounds (1c), (3d), and (3e), respectively, in high yield. The n.m.r. spectra of these 21-acetates exhibited a pair of singlets each for the C-21 methylene and C-21 acetoxy-protons, and unresolved broadened resonances for the C-18 methylene protons, suggesting that each product was a mixture of C-20 epimers. The unequal intensities of these signals indicated the predominance of one of the isomers.

18-Hydroxy-DOC (1a) was obtained either by alkaline hydrolysis of the 21-acetate (1c), or alternatively by Jones oxidation of the 3β-hydroxy-group, in the 21-monoacetate (3e), followed by alkaline hydrolysis.

Routes via *Halogenohydrins*.—Routes involving the introduction of a halogen atom at C-21 before functionalisation at C-18 were not productive. For instance, when 3β-benzoyloxy-21-chloropregn-5-en-20β-ol was subjected to the hypoiodite sequence of reactions, 3β-benzoyloxy-21-chloropregn-5-en-20-one was obtained in about 75% yield, with no evidence for any attack upon C-18.[18] It was, on the other hand, possible [16] to brominate at C-21 after functionalising C-18, thereby providing an alternative route to 18,21-dihydroxypregnan-20-one hemiacetals. The hemiacetals (1b) and (3c), when treated with an equimolar amount of trimethyl(phenyl)-ammonium perbromide [19] in dry tetrahydrofuran, gave the bromohydrins (1d) and (3f), respectively, characterised only by the disappearance of the C-21 methyl resonance in the n.m.r. spectra of the crude products. 18-Hydroxy-DOC (1a) could then be obtained by alkaline hydrolysis of the bromohydrin (1d) in aqueous dioxan, or by Jones oxidation of the bromohydrin (3f) in acetone, followed by alkaline hydrolysis in aqueous dioxan. The relatively lower overall yields in these reactions, however, demonstrate the superiority of the method involving direct C-21 acetoxylation, described above.

While recrystallising 18-hydroxy-DOC (1a) in glassware washed with chromic acid, we have occasionally noticed the formation of a crystalline and chromatographically less polar material, the chemical structure of which is at present under investigation.* Stringent measures are, therefore, necessary to exclude acid during work-up of 18-hydroxy-DOC (1a), and the use of traces of a base such as pyridine or triethylamine as a stabiliser is strongly recommended.

1,2-*Didehydro*-18-*hydroxy-DOC*.—This compound was synthesised as the key intermediate required for selective tritiation of the olefinic 1,2-bond to prepare tritium-labelled 18-hydroxy-DOC. Attempts to dehydrogenate 18-hydroxyprogesterone hemiacetal (1b) with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in benzene [20] failed to give a recognisable product. 18-Acetoxyprogesterone (7), however, underwent the required dehydrogenation with an equimolar quantity of DDQ in benzene, affording 18-acetoxypregna-1,4-diene-3,20-dione in 60% yield. Alkaline hydrolysis to 1,2-didehydro-18-hydroxyprogesterone hemiacetal followed by acetoxylation at C-21 with lead tetra-acetate, and alkaline hydrolysis, gave the 1,2-didehydro-derivative of 18-hydroxy-DOC (1a).

EXPERIMENTAL

M.p.s were determined with a Reichert microscope. I.r. spectra were determined for KBr discs unless stated otherwise. U.v. spectra are for ethanolic solutions. N.m.r. spectra were determined at 100 MHz for solutions in deuteriochloroform with tetramethylsilane as internal standard. Deactivated alumina refers to Spence type H treated with 5% of aqueous 10% acetic acid. T.l.c. was performed with Merck silica gel HF 254. Cyclohexane was distilled over calcium hydride. Dioxan was heated under reflux with lithium aluminium hydride for 30 min and distilled before use. Tetrahydrofuran (THF) was purified by successively heating under reflux for 30 min with sodium hydroxide pellets, and sodium wire, and distilled over lithium aluminium hydride before use. All solvents for chromatography were redistilled. Petroleum refers to the fraction of boiling range 60—80°. Unless specified otherwise, yields of products isolated by chromatography refer to material obtained after crystallisation from a suitable solvent, quoted in parentheses.

3,3-*Ethylenedioxy*-18-*hydroxypregn*-5-*en*-20-*one* 18,20-*Hemiacetal* (3a).—3,3-Ethylenedioxypregn-5-en-20β-ol [8] (4) (8 g) was irradiated [7] in boiling cyclohexane (1.2 l) containing lead tetra-acetate (24 g), iodine (3.1 g), and calcium carbonate (8 g). The crude product was isolated and oxidised with Jones reagent (5 ml) in acetone (100 ml) at 0 °C according to the published procedure.[7] The resulting gum containing 3,3-ethylenedioxy-18-iodopregn-5-en-20-one (5) was dissolved in aqueous 90% dioxan (700 ml), and silver acetate (8 g) was added. The mixture was heated rapidly with stirring to 60—65 °C and held at this temperature for 4 h, then cooled, filtered, and evaporated under reduced pressure. The residue was dissolved in ether, and the solution was filtered to remove traces of inorganic residues, and evaporated under reduced pressure. The yellow semi-solid product, in benzene–petroleum (1 : 1; 200—225 ml),

* The preparation and acetoxylation of vinyl ethers of type (2) has been described since the submission of the manuscript (M. Biollaz, J. Kalvoda, and J. Schmidlin, *Helv. Chim. Acta*, 1975, **58**, 1425). From our spectroscopic evidence, the ' less polar material' formed when 18-hydroxy-DOC is crystallized in the presence of traces of acid seems likely to be the ' non-hydroxylic dimer ' of unspecified structure described by R. Pappo (U.S.P. 2 911 404/1959).

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

[19] L. F. Fieser and M. Fieser, ' Reagents for Organic Synthesis,' Wiley, New York, 1967, p. 1720.

[20] A. B. Turner and H. J. Ringold, *J. Chem. Soc.*, 1967, 1720.

was chromatographed on deactivated alumina (900 g) previously washed with the solvent mixture (2 l). 3,3-Ethylenedioxy-17α-iodoandrost-5-ene (0.61 g) was eluted with benzene–petroleum (1 : 1); m.p. 160—163° (acetone) (lit.,[21] 159—165°). Elution with benzene containing 20—30% petroleum afforded 3,3-ethylenedioxypregn-5-en-20-one (1.45 g), m.p. 178—180° (acetone) (lit.,[8] 180—181°), $\nu_{max.}$ 1 705 and 1 100 cm^{-1}; τ 9.38 (s, 13β-Me), 8.96 (s, 10β-Me), 7.90 (s, 21-H_3), 6.1 (s, O·CH_2·CH_2·O), and *ca.* 4.6 (m, 6-H). Further elution with the same solvent mixture gave 3,3-*ethylenedioxy*-17β,18-*cyclo*-17α-*pregn*-5-*en*-20-*one* (0.64 g), m.p. 220—223° (methanol), $\nu_{max.}$ 3 060, 1 675, 1 105, and 1 095 cm^{-1}; τ 9.00 (s, 10β-Me), 8.78 and 9.08 (ABq, *J* 4 Hz, 18-H_2), 7.90 (s, 21-H_3), 6.1 (s, O·CH_2·CH_2·O), and *ca.* 4.6 (m, 6-H) (Found: C, 77.5; H, 8.9. $C_{23}H_{32}O_5$ requires C, 77.5; H, 9.0%). Elution with benzene gave a small amount of 3,3-ethylenedioxypregn-5-eno-20,18-lactone, $\nu_{max.}$ 1 760 cm^{-1}. Careful gradient elution with benzene containing up to 7% ether, and then with benzene containing up to 5% ethyl acetate, gave a mixture of unidentified products (0.8 g) which did not crystallise.

Elution with benzene containing 7—10% ethyl acetate afforded the *hemiacetal* (3a) (1.2 g), m.p. 146—147° (acetone); $\nu_{max.}$ 3 460, 1 110, and 1 090 cm^{-1}; τ 9.05 (s, 10β-Me), 8.52 (s, 21-H_3), 6.29 (s, 18-H_2), 6.07 (s, O·CH_2·CH_2·O), and *ca.* 4.6 (m, 6-H) (Found: C, 73.7; H, 9.1. $C_{23}H_{34}O_4$ requires C, 73.8; H, 9.1%). Finally, elution with benzene containing 11—14% ethyl acetate afforded 18-hydroxyprogesterone 18,20-hemiacetal (1b) (0.11 g), m.p. 153—156° (acetone) (lit.,[22] 159—160°); $\lambda_{max.}$ 240 nm (ε *ca.* 15 000); $\nu_{max.}$ 3 420, 1 665, and 1 615 cm^{-1}; τ 8.89 (s, 10β-Me), 8.53 (s, 21-H_3), 6.28 (s, 18-H_2), and 4.25 (m, 4-H).

18-*Acetoxy*-3,3-*ethylenedioxypregn*-5-*en*-20-*one* (6).—The hemiacetal (3a) (1.3 g) was acetylated in pyridine–acetic anhydride (3 : 1; 50 ml) at 100 °C for 24 h under nitrogen. The gum obtained after conventional work-up was chromatographed on deactivated alumina (150 g) which had been washed previously with petroleum–benzene (1 : 1; 500 ml). Elution initially with petroleum–benzene (1 : 1) followed by petroleum containing increasing amounts of benzene (up to 80%) afforded the 18-*acetoxy*-20-*ketone* (6) (0.71 g), m.p. 170—172° (petroleum); $\nu_{max.}$ 1 735, 1 702, 1 250, 1 105, and 1 100 cm^{-1}; τ 8.97 (s, 10β-Me), 7.99 (s, 18-AcO), 7.77 (s, 21-H_3), 5.95 (O·CH_2·CH_2·O, s superimposed on the 18-H_2 ABq), and *ca.* 4.6 (m, 6-H) (Found; C, 72.3; H, 8.7. $C_{25}H_{36}O_5$ requires C, 72.1; H, 8.65%). Elution with benzene containing up to 10% ether gave crude starting material (3a) (0.15 g).

18-*Acetoxyprogesterone* (7).—Hydrochloric acid (4N; 0.2 ml) was added to the 18-acetoxy-20-ketone (6) (0.64 g) in methanol (60 ml) and the mixture was left at room temperature overnight. Saturated aqueous sodium hydrogen carbonate (0.1 ml) was then added and the mixture was concentrated to a small volume. Ether (200 ml) was added and the ethereal solution was washed with water, dried (K_2CO_3), and evaporated to furnish the 18-acetoxy-20-ketone (7) (0.45 g), m.p. 136—137° (petroleum) (lit.,[7] 136.5—137.5°); $\lambda_{max.}$ 240 nm (ε *ca.* 16 000); $\nu_{max.}$ 1 735, 1 700, 1 665, and 1 605 cm^{-1}; τ 8.82 (s, 10β-Me), 8.03 (s, 18-AcO), 7.85 (s, 21-H_3) 6.17 and 5.85 (ABq, J_{AB} 11.5 Hz, 18–H_2), and *ca.* 4.32 (m, 4-H).

Conversion of 18-*Acetoxyprogesterone* (7) *into* 18-*Hydroxy-DOC* (1a).—Compound (7) (0.15 g) in anhydrous methanol (0.5 ml) was treated with pyrrolidine (0.06 ml). The yellow solution was warmed momentarily and left at room temperature for a short while. The enamine (8) which crystallised out was filtered off, washed with a few drops of ice-cold methanol, and dried (yield 0.15 g); $\nu_{max.}$ 1 735, 1 700, 1 640, and 1 250 cm^{-1}. The crude enamine (8) was dissolved in anhydrous ethanol-free chloroform and the solution was saturated with dry hydrogen chloride. The solvent was then evaporated off under reduced pressure at 25 °C, and the residual gum was dissolved in anhydrous benzene–methanol (19 : 1; 10 ml) and cooled in an ice-bath. Freshly distilled boron trifluoride–ether complex (0.6 ml) and lead tetra-acetate (0.2 g) were added and the mixture was then stirred under nitrogen for 4.5 h at 20—22 °C, poured into ice–water, and extracted with dichloromethane. The organic phase was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure. The residue in aqueous 95% ethanol (30 ml) was stirred with saturated sodium hydrogen carbonate solution (0.5 ml) for 2 h at room temperature. The mixture was then neutralised with dilute acetic acid and evaporated to a small volume under reduced pressure and extracted with ether (200 ml). The extract was washed with water, dried ($MgSO_4$), and evaporated and the residual gum was chromatographed on eight 20 cm^2 t.l.c. plates. After six developments in benzene–ether, the broadest band visible under u.v. radiation was extracted with chloroform to furnish a gum (35 mg) containing 18,21-diacetoxyprogesterone (9), which did not crystallise; $\nu_{max.}$ (film) 1 735—1 740, 1 665, 1 607, and 1 230—1 240 cm^{-1}; τ 8.85 (s, 10β-Me), 8.07 (s, 18-AcO), 7.88 (s, 21-AcO), 6.18 and 5.90 (ABq, J_{AB} 11.5 Hz, 18-H_2), 4.66 (s, 21-H_2), and 4.33 (m, 6-H). The crude diacetate (9) in aqueous 90% methanolic potassium hydroxide (0.1N; 10 ml) was heated under reflux for 30 min. Extraction with dichloromethane gave crude 18-hydroxy-DOC (1a), which was purified by t.l.c. The product (6 mg), m.p. 159—161° (acetone containing 0.1% triethylamine), was identical with an authentic specimen of 18-hydroxy-DOC, provided by Searle Scientific Services.

Treatment of the Hemiacetal (3b) *with Acetic* [^{2}H]*Acid*.—Acetic [^{2}H]acid (0.2 ml) was added to the hemiacetal (3b) [17] (30 mg) in anhydrous ethanol-free chloroform (0.6 ml). After 24 h, ether was added and the solution was washed successively with sodium hydrogen carbonate and water, dried, and evaporated. A small portion of the residue was dissolved directly in deuteriochloroform for n.m.r. study. The remainder was crystallised from anhydrous ether for mass spectral analysis (see Table). The 21-proton signal which appeared at τ 8.52 in the spectrum of the hemiacetal (3b) was absent in that of the deuteriated material, but was restored when the deuteriated material was treated as above with unlabelled acetic acid.

18-*Hydroxy-DOC* (1a) *from the Hemiacetal* (1b) via *the* 21-*Monoacetate* (1c).—Lead tetra-acetate (0.65 g) was added to 18-hydroxyprogesterone (0.45 g) in anhydrous acetic acid (10 ml). After stirring for 15 min at room temperature, the mixture was poured into water and the crude 21-monoacetate (1c) (0.52 g) was isolated by extraction with ether. A sample (50 mg) crystallised from ether to provide material (1c) of m.p. 154—156° (lit.,[4] 158—159°); $\lambda_{max.}$ 240 nm (ε *ca.* 17 000); $\nu_{max.}$ 3 480, 1 735, 1 665, 1 602, and 1 230—1 250 cm^{-1}; τ 8.80 (s, 10β-Me), 7.90 (s, AcO), 6.20 (s, 21-H_2), 5.6—6.0 (m, 18-H_2), and 4.26 (m, 4-H). The product was a mixture of C-20 isomers (*ca.* 2 : 1) as was

[21] M. Biollaz and J. Kalvoda, *Helv. Chim. Acta*, 1972, **55**, 366.
[22] F. Buzzetti, W. Wicki, J. Kalvoda, and O. Jeger, *Helv. Chim. Acta*, 1959, **42**, 388.

apparent from the relatively less intense singlets at τ 7.88 (18-AcO) and 6.32 (21-H_2), ascribed to the minor component (Found: C, 71.3; H, 8.2. Calc. for $C_{23}H_{32}O_5$: C, 71.15; H, 8.25%). The crude 21-monoacetate (0.47 g) was heated under reflux for 30 min with aqueous 90% methanolic potassium hydroxide (1N; 30 ml). After concentration under reduced pressure to *ca.* 10 ml, the compound (1a) (0.35 g) was precipitated by addition of water; m.p. 158—161° (acetone containing 0.1% triethylamine); $\lambda_{max.}$ 240 nm (ε *ca.* 16 000), $\nu_{max.}$ 3 340—3 460, 1 660—1 670, 1 610, and 1 060 cm^{-1}; τ ($CDCl_3$ containing 1% C_5D_5N), 8.88 (s, 10β-Me), 6.0—6.6 (m, 18-H_2 and 21-H_2), and 4.27 (m, 4-H) (Found: C, 72.8; H, 8.7. Calc. for $C_{21}H_{30}O_4$: C, 72.9; H, 8.8%).

18-*Hydroxy-DOC* (1a) *from the Hemiacetal* (3b) via *the* 21-*Monoacetate* (4f).—The hemiacetal (3b) (0.5 g) was heated with methanolic potassium hydroxide (0.1N; 30 ml) for 0.5 h, and the hemiacetal (3c) was isolated by evaporation of most of the solvent and addition of water. The crude product was acetoxylated in anhydrous acetic acid (10 ml) with lead tetra-acetate (0.75 g) to give the 21-monoacetate (3e) as described above for the conversion of the hemiacetal (1b) into the 21-acetate (1c). The crude product in acetone (30 ml) was then stirred at 0 °C for 5 min with Jones reagent (0.5 ml). The excess of oxidant was destroyed with aqueous 5% sodium disulphite and the product was isolated by extraction with ether. The residue was hydrolysed by boiling under reflux with aqueous 90% methanolic potassium hydroxide (0.1N; 40 ml) and the crude gum (1a), isolated by extraction with dichloromethane, was chromatographed on deactivated alumina (30 g). Elution with benzene containing *ca.* 2% ethyl acetate furnished 18-hydroxy-DOC (1a) (0.2 g), m.p. 159—163°.

3β,21-*Diacetoxy*-18-*hydroxypregn*-5-*en*-20-*one* 18,20-*Hemiacetal* (3d).—The hemiacetal (3b) (0.1 g) in dry acetic acid (1.5 ml) was stirred at room temperature for 15 min with lead tetra-acetate (0.14 g), and the diacetate (3d) (83 mg) was precipitated by addition of water; m.p. 172—176° (acetone), $\nu_{max.}$ 3 450, 1 740, 1 720, and 1 250 cm^{-1}; τ 9.05 (s, 10β-Me), 7.99 (s, AcO), 7.89 (s, 21-AcO), 6.20 (s, 21-H_2), 5.65—6.00 (m, 18-H_2), *ca.* 5.40 (m, 3-H), and *ca.* 4.60 (m, 6-H). The product was a mixture of C-20 isomers (*ca.* 2 : 1) as was apparent from the relatively weaker singlets at τ 7.84 (21-OAc) and 6.32 (21-H_2) attributed to the minor component (Found: C, 69.5; H, 8.3. Calc for $C_{25}H_{36}O_6$: C, 69.45; H, 8.3%).

18-*Hydroxy-DOC* (1a) *from the Hemiacetal* (3c) via *the Bromohydrin* (3f).—Trimethyl(phenyl)ammonium perbromide [19] (93.2% available bromine; 0.65 g) was added to a solution of the hemiacetal (3c) (0.5 g) in dry THF (20 ml). After stirring for 5 min the mixture was diluted with ether and washed successively with 5% sodium hydrogen carbonate and water. Drying (K_2CO_3) followed by evaporation afforded the crude bromohydrin (4h) (0.55 g), which was oxidised in acetone (10 ml) at 0 °C with Jones reagent and isolated with ether. The gum left on evaporation was redissolved in aqueous 70% dioxan (30 ml) and aqueous potassium hydroxide (6%; 3 ml) was added. The yellow solution was then left at 65—70 °C for 20 min, and 18-hydroxy-DOC (1a) (0.11 g) was isolated by extraction with dichloromethane followed by chromatography on deactivated alumina; m.p. 158—160°.

18-*Hydroxy-DOC* (1a) *from the Hemiacetal* (1b) via *the* 21-*Bromide* (1d).—The hemiacetal (1b) (0.1 g) in dry THF was treated with trimethyl(phenyl)ammonium perbromide (93.2% available bromine; 0.12 g) as described above for the bromination of the hemiacetal (3c). The crude product containing the bromo-hemiacetal (1d) in aqueous 70% dioxan (5 ml) was treated for 20 min at 65—70 °C with aqueous potassium hydroxide (6%; 0.75 ml). Extraction with dichloromethane gave a yellow semisolid residue from which 18-hydroxy-DOC (1a) (10 mg) was isolated by t.l.c.; m.p. 156—159°.

1,2-*Didehydro*-18-*hydroxy-DOC*.—A solution of DDQ (0.15 g) and 18-acetoxyprogesterone (7) (0.2 g) in dry benzene (10 ml) was heated under reflux for 17 h. The precipitated hydroquinone was filtered off, and the filtrate after dilution with ether was washed twice with aqueous 1% sodium hydroxide and finally with water. The residue from the dried ethereal solution was chromatographed on eight 20 cm^2 t.l.c. plates. After three developments in benzene–ether (3 : 1), the broadest visible band (u.v.) was extracted with ethyl acetate to furnish crude 18-acetoxypregna-1,4-diene-3,20-dione (0.12 g); $\nu_{max.}$ 1 745, 1 705, 1 650—1 670, 1 625, 1 600, 1 230, 1 040, and 890 cm^{-1}; τ 8.78 (s, 10β-Me), 8.02 (s, AcO), 7.82 (s, 21-H_3), 6.14 and 5.80 (ABq, J_{AB} 12 Hz, 18-H_2), 3.92br (s, 4-H, $W_{\frac{1}{2}}$ 5 Hz), 3.78 (dd, $J_{1.2}$ 10, $J_{2.4}$ 2 Hz, 2-H), and 2.98 (d, $J_{1.2}$ 10 Hz, 1-H). The crude material was heated for 30 min with methanolic potassium hydroxide (1N; 6 ml) and the product was isolated by extraction with ether to furnish crude 1,2-didehydro-18-hydroxyprogesterone (0.1 g), $\nu_{max.}$ 3 410—3 420, 1 655, 1 620, and 1 600 cm^{-1}; τ 8.96 (s, 10β-Me), 8.54 (s, 21-Me), 6.28 (s, 18-H_2), 3.96br (s, $W_{\frac{1}{2}}$ 4 Hz, 4-H), 3.80 (dd, $J_{1.2}$ 10, $J_{2.4}$ 2 Hz, 2-H), and 3.00 (d, $J_{1.2}$ 10 Hz, 1-H). The crude product was stirred with lead tetra-acetate (0.14 g) in anhydrous acetic acid (0.5 ml) for 15 min at room temperature. The crude acetoxylated material, isolated with ether, was heated for 30 min in aqueous 90% methanolic potassium hydroxide (0.1N; 5 ml).

1,2-*Didehydro*-18-*hydroxy-DOC* (0.07 g), isolated with ether, crystallised from acetone containing 0.1% pyridine; m.p. 172—174°, $\lambda_{max.}$ 239 nm (ε *ca.* 15 000); $\nu_{max.}$ 3 320—3 360, 1 665, 1 620, and 1 600 cm^{-1}; τ 8.84 (s, 10β-Me), 6.00—6.50 (m, 18-H_2 and 21-H_2), 3.92 (m, $W_{\frac{1}{2}}$ 5 Hz, 4-H), 3.80 (dd, $J_{1.2}$ 10, $J_{2.4}$ 2 Hz, 2-H), and 3.00 (d, $J_{1.2}$ 10 Hz, 1-H) (Found: C, 73.1; H, 8.2. $C_{21}H_{28}O_4$ requires C, 73.3; H, 8.1%.)

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