Action of Some Steroids on the Central Nervous System of the Mouse. I. Synthetic Methods

J. D. Cocker, J. Elks, P. J. May, F. A. Nice, G. H. Phillipps, and W. F. Wall

Glaxo Research Ltd., Greenford, Middlesex, England

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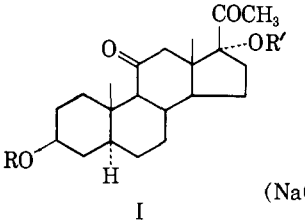
The preparation is described of a number of previously unreported steroids, required for tests of their hypnotic activity. The compounds, which are prepared by conventional methods, are chiefly 5α- or 5β-pregnan-20-ones, substituted at C-3 by hydroxy or oxo groups; other substituents include hydroxy groups at positions 11, 16, and 21, an oxo group at position 11, methyl groups at positions 3, 6, and 16, 9,11- and 11,12-epoxy groups, and halogen atoms at position 21. Also described is the preparation of some androstane and D-homoandrostane derivatives, oxygenated at positions 3, 11, and 17 or 17a. Most of these compounds, as well as a number of known substances of similar type, are esterified with polybasic acids, thus allowing formation of water-soluble salts. Hemisuccinates and monoesters of some other dicarboxylic acids are prepared from the steroid alcohol and the appropriate acid anhydride. Phosphates of several 3-hydroxy steroids are prepared from the alcohol and dibenzyl phosphorochloridate with subsequent removal of the protecting groups by hydrogenolysis. The pyrophosphate of 21-hydroxy-5β-pregnane-3,20-dione is prepared from the corresponding 21-monobenzyl phosphate, by treatment with dicyclohexylcarbodiimide and subsequent removal of the benzyl groups with sodium iodide. Some basic esters of 3α-hydroxy-5β-pregnane-11,20-dione are prepared from the alcohol *via* the chloroacetate and iodoacetate.

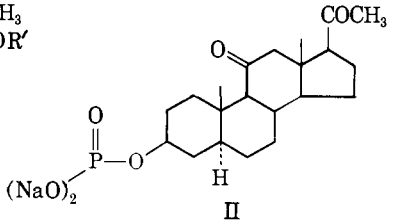
In connection with the program of biological tests described in the accompanying paper[1] it was necessary to prepare a number of steroids bearing water-solubilizing groups. Since the initial results suggested that the desired hypnotic activity on intravenous administration occurred only with the pregnane derivatives, we concentrated on the variation of substituents in this nucleus.

For the most part, we used the well-known method of converting steroid alcohols into their hemisuccinates, whose sodium salts usually are sufficiently water soluble. The preparative methods, which are conventional, and the products obtained are described in the Experimental section.

The 17-acetate 3-hemisuccinate [I, R = $CO(CH_2)_2CO_2H$; R′ = Ac] of 3β,17-dihydroxy-5α-pregnane-11,20-dione was prepared from the 3-hemisuccinate by acetylation with acetic anhydride in presence of perchloric acid; there was no apparent transesterification at C-3. An attempt to introduce the ester groupings in the alternative order was unsuccessful, because the 3,17-diacetate (I, R = R′ = Ac) could not be selectively hydrolyzed to the 17-monoacetate (I, R = H; R′ = Ac).



I



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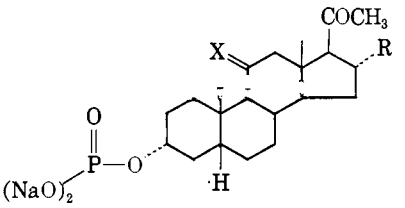
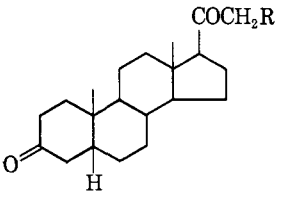


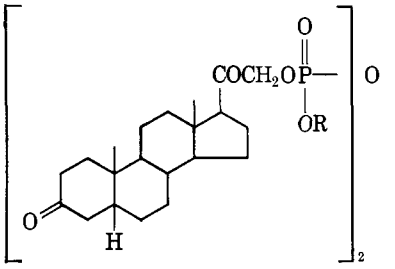
III

The instability of the salts of the hemisuccinates (particularly those of the 21-hydroxy compounds) in aqueous solution was something of a disadvantage, and several of the more promising alcohols were converted into their phosphates.

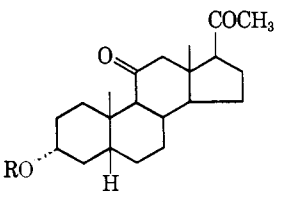
Thus, 3β-hydroxy-5α-pregnane-11,20-dione, 3α-hydroxy-5β-pregnan-20-one, 3α-hydroxy-5β-pregnane-11,20-dione, and 3α-hydroxy-16α-methyl-5β-pregnane-11,20-dione were all treated with dibenzyl phosphorochloridate, and the resulting crude 3-dibenzyl phosphates were hydrogenolyzed to give the corresponding free phosphates, isolated as their disodium salts II and III (X = H_2, R = H; X = O, R = H; and X = O, R = Me), respectively.



IV



V



VI

(1) R. M. Atkinson, B. Davis, M. A. Pratt, H. M. Sharpe, and E. G. Tomich, *J. Med. Chem.*, **8**, 426 (1965).

For the preparation of the pyrophosphate derivative of 21-hydroxy-5β-pregnane-3,20-dione (IV, R = OH), this alcohol was converted, *via* its methanesulfonate (IV, R = OSO_2Me), into the 21-iodo compound (IV, R = I). Reaction of this last compound with silver dibenzyl phosphate, best in acetonitrile, gave the 21-dibenzyl phosphate [IV, R = $OPO(OCH_2C_6H_5)_2$], which was monodebenzylated by sodium iodide to give the 21-monobenzyl phosphate [IV, R = $OPO(OH)(OCH_2C_6H_5)$]. This was condensed, by means of dicyclohexylcarbodiimide, to the corresponding pyrophosphate (V, R = $CH_2C_6H_5$) which was further debenzylated by sodium iodide to the required P^1P^2-bis(3,20-dioxo-5β-pregnan-21-yl) P^1P^2-disodium pyrophosphate (V, R = Na).

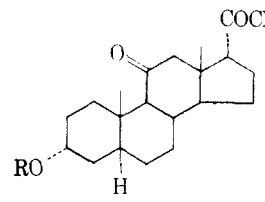
Since the hemisuccinate and the phosphate of 3α-hydroxy-5β-pregnane-11,20-dione (VI, R = H) showed particularly favorable properties in the biological tests, this alcohol was chosen as the parent for an investigation of the effect of various other water-solubilizing groups. The sulfate (VI, R = SO_3H), hemimaleate (VI, R = $COCH{=}CHCO_2H$), hemiglutarate [VI, R = $CO(CH_2)_3CO_2H$], hemidiglycolate (VI, R = $COCH_2O$-CH_2CO_2H), and hemiphthalate (VI, R = COC_6H_4-CO_2H-*o*) were all prepared from the steroid alcohol and the appropriate acid anhydride in pyridine. Reaction of 3α-hydroxy-5β-pregnane-11,20-dione (VI, R = H) with N-acetyl-L-glutamic anhydride gave a compound whose analysis was that expected for the steroid hemi-N-acetylglutamate, but we have no evidence as to whether it was the α- or γ-monoester or, indeed, a mixture of both.

In another series of derivatives of compound VI (R = H), water solubility was conferred by esterification with amino acids. Thus, treatment with chloroacetic anhydride in pyridine gave the chloroacetate (VI, R = $COCH_2Cl$), which was converted by sodium iodide into the corresponding iodoacetate (VI, R = $COCH_2I$). This compound reacted with ammonia and with diethylamine to give the aminoacetate (VI, R = $COCH_2NH_2$) and the diethylaminoacetate (VI, R = $COCH_2NEt_2$), respectively; the latter reacted with ethyl iodide to yield the quaternary salt (VI, R = $COCH_2N^+Et_3 \cdot I^-$). Finally, the iodoacetate, on treatment with N-methylmorpholine, gave the morpholinoacetate methiodide (VI, R = $COCH_2 \cdot MeN^+C_4H_8O \cdot I^-$).

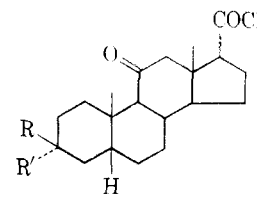
Many of the steroid alcohols from which these water-soluble derivatives were prepared are already adequately described in the literature, and the same is true of a number of other steroids whose activity, on intravenous administration as suspensions, is discussed in the following paper. Several, however, are new, and their preparation is summarized here; many of the syntheses used follow conventional lines that require no comment beyond the preparative method given in the Experimental section.

3β-Hydroxy-5α-androstan-11-one was prepared by Wolff–Kishner reduction of 3β-hydroxy-5α-androstane-11,17-dione, advantage being taken of the unreactivity of the 11-oxo group under usual reaction conditions.

3α,21-Dihydroxy-5β-pregnane-11,20-dione diacetate (VII, R = Ac; R′ = OAc) underwent selective hydrolysis of the primary acetoxy group on treatment with *ca.* 1 equiv. of potassium bicarbonate. The resulting 3-monoacetate (VII, R = Ac; R′ = OH), was



VII

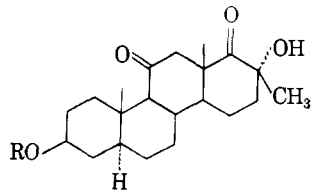


VIII

converted into its 21-methanesulfonate (VII, R = Ac; R′ = OSO_2Me) [which was accompanied, in one experiment, by the 21-chloro compound (VII, R = Ac; R′ = Cl)] and thence into 3α-hydroxy-21-iodo-5β-pregnane-11,20-dione acetate (VII, R = Ac; R′ = I). Attempts to hydrolyze the 3-acetate 21-methanesulfonate to the corresponding 3-alcohol with alkali were unsuccessful, but treatment with methanolic perchloric acid yielded the desired compound (VII, R = H; R′ = OSO_2Me). This, in turn, was converted into the corresponding 21-fluoro (VII, R = H; R′ = F) and 21-iodo compounds (VII, R = H; R′ = I) by reaction with potassium hydrogen fluoride in dimethylformamide and with sodium iodide in acetone, respectively. Finally, 3α-hydroxy-21-iodo-5β-pregnane-11,20-dione (VII, R = H; R′ = I) was treated with triethylammonium *t*-butylacetate and with potassium thioacetate to give the 21-*t*-butylacetoxy (VII, R = H; R′ = $OCOCMe_3$) and the 21-acetylthio compound (VII, R = H; R′ = SCOMe), respectively.

For the preparation of 6α-methyl-5β-pregnane-3,20-dione, the commercially available 6α-methylpregna-4,16-diene-3,20-dione was reduced catalytically. The isomeric 6α-methyl-5α-pregnane-3,20-dione (a known compound) was produced simultaneously, but fractional crystallization served to separate the two compounds.

The epimeric 3-methyl-3-hydroxy-5β-pregnane-11,20-diones (VIII, R = Me; R′ = OH) and (VIII, R = OH; R′ = Me) were synthesized from 5β-pregnane-3,11,20-trione 20-ethylene ketal by treatment with methylmagnesium iodide and subsequent deketalization, the epimers being separated chromatographically. Configurations at C-3 were assigned to the isomers on the basis of the ease of their elution from the column, the less strongly adsorbed compound being regarded as the axial 3β-ol; their infrared spectra were in agreement with these assignments.



IX

The D-homoandrostane (IX) was prepared from 3β,17-dihydroxy-5α-pregnane-11,20-dione (I, R = R′ = H). Reaction of this compound with boron trifluoride was very slow, but the 3-monoformate (I, R = CHO; R′ = H) was readily rearranged by the same reagent to a compound that we formulate as 3β,17α-dihydroxy-17β-methyl-D-homo-5α-androstane-11,17a-dione 3-formate (IX, R = CHO), by analogy with the same rearrangement in the 3α-hydroxy 5β-

series.[2] In accordance with this, the diol (IX, R = H), obtained by hydrolysis of the formate, showed evidence, in its infrared spectrum, of hydrogen bonding between the hydroxy and ketone groups in ring D.

Of the remaining compounds referred to in the following paper or used as intermediates, 16β-methyl- and 16,16-dimethyl-3α-hydroxy-5β-pregnane-11,20-dione, and 3α-hydroxy-16-methyl-5β-pregn-16-ene-11,20-dione were kindly supplied by the Schering Corp. A few other new compounds (numbered in Tables I and II of the following paper as **18**, **25**, **28**, **84**, **118**, **140**, **149**, **150**, and **161–168** inclusive) will be described in papers that we hope to publish shortly.

Experimental

The bold-faced numbers that follow the subtitled names of certain compounds are the numbers identifying these compounds in the following paper. Unless otherwise stated, melting points were determined on the Kofler block, and rotations were determined in $CHCl_3$ solution (*c* 1).

3β-Hydroxy-5α-androstan-11-one.—A mixture of 3β-hydroxy-5α-androstane-11,17-dione acetate[3] (4.0 g.), NaOH pellets (4.0 g.), 95% hydrazine hydrate (4.0 ml.), and triethylene glycol (40 ml.) was kept at 180° for 2 hr. Dilution of the cooled solution with water precipitated a product which was then acetylated by treatment for 36 hr. at room temperature with pyridine (25 ml.) and acetic anhydride (25 ml.). The product was isolated by extraction with ether and chromatographed on alumina; benzene–hexane and benzene eluted **3β-hydroxy-5α-androstan-11-one acetate,** which was crystallized from methanol to give 1.37 g. of material with m.p. 87–90°; $[\alpha]D$ +56°; ν_{max} (in CS_2) 1732 and 1242 (acetate) and 1708 cm.$^{-1}$ (ketone).

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.9; H, 9.7. Found: C, 76.2; H, 9.5.

The free alcohol, obtained by hydrolysis with boiling 4% methanolic NaOH and sublimation at 120° (0.0005 mm.), had m.p. 159–160°; $[\alpha]D$ +62°; ν_{max} (in CS_2) 3600 and 1038 (equatorial OH) and 1708 cm.$^{-1}$ (ketone).

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.6; H, 10.4. Found: C, 78.9; H, 10.4.

3α,21-Dihydroxy-5β-pregnan-20-one (**75**).—3α,21-Dihydroxy-5β-pregnan-20-one 21-acetate[4] (0.7 g.) in methanol (70 ml., oxygen-free) was treated with $KHCO_3$ (0.7 g.) in water (7 ml., oxygen-free), and stirred at room temperature under nitrogen for 1 hr. Dilution with water, extraction with chloroform, and crystallization from ethyl acetate–petroleum ether (b.p. 60–80°) gave the product: m.p. 151–153°; $[\alpha]D$ +99°; ν_{max} (in $CHBr_3$) 3600–3500 (OH) and 1702 cm.$^{-1}$ (ketone).

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.4; H, 10.2. Found: C, 75.5; H, 10.2.

17,21-Dihydroxy-5α-pregnane-3,20-dione was prepared from its 21-acetate,[5] a solution of which in CH_2Cl_2 was treated, under nitrogen, with 1 equiv. of 0.1 *N* methanolic NaOH. After 15 min. at room temperature the solution was acidified to phenolphthalein with acetic acid, concentrated *in vacuo*, and diluted with water. The precipitated diol, after crystallization from acetone, had m.p. 219–220°; $[\alpha]D$ +47°; ν_{max} (in $CHBr_3$) 3600 and 3500 (OH) and 1702 cm.$^{-1}$ (ketone).

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.4; H, 9.3. Found: C, 72.5; H, 9.4.

6α-Methyl-5β-pregnane-3,20-dione (**79**) **and 6α-Methyl-5α-pregnane-3,20-dione** (**22**).—6α-Methylpregna-4,16-diene-3,20-dione[6] (700 mg.) in ethyl acetate (40 ml.) was hydrogenated at room temperature and pressure in the presence of 5% Pd–C (150 mg.); absorption of hydrogen was complete (2 moles) in 55 min. The catalyst was filtered off, the filtrate was evaporated to dryness, and the residue was crystallized from ethyl acetate–hexane to give material (253 mg.), m.p. 151–153°. Recrystallization gave **22** (195 mg.) as plates, m.p. 153–154° (lit.[7] m.p. 152–153°).

Evaporation of the mother liquors from the first crystallization, and recrystallization of the residue from hexane gave a mixture (303 mg.) of the 5α- and 5β-isomers, predominantly the latter. The mother liquors from this crop were evaporated and the residue was crystallized from a little hexane, to give **79** (123 mg.): m.p. 99–102°; $[\alpha]D$ + 90°; ν_{max} (in CS_2) 1715 (ketone) and 1358 cm.$^{-1}$ ($COCH_3$).

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.9; H, 10.4. Found: C, 80.0; H, 10.2.

3α-Hydroxy-16α-methyl-5β-pregnan-20-one (**72**).—Methylmagnesium bromide, prepared from magnesium turnings (5 g.) and methyl bromide (20 ml.) in ether (100 ml.), was treated with cuprous bromide (40 mg.) followed by 3α-hydroxy-5β-pregn-16-en-20-one acetate (2 g.) in ether (200 ml.). The mixture was boiled under reflux for 4 hr., cooled, and treated with saturated aqueous NH_4Cl (100 ml.). The product was isolated by extraction with ether, crystallization from ethyl acetate, and chromatography on alumina (60 g.). Elution with benzene–ether (1:1) gave a solid (0.9 g.), m.p. 140–142°. Further crystallization did not raise the melting point; ν_{max} (in CS_2) 3620 and 1038 (equatorial OH), 1710 (ketone), and 1354 cm.$^{-1}$ ($COCH_3$).

Anal. Calcd. for $C_{22}H_{36}O_2$: C, 79.5; H, 10.9. Found: C, 79.2; H, 10.9.

5α-Pregn-1-ene-3,11,20-trione (**52**).—2α-Bromo-5α-pregnane-3,11,20-trione[8] (1.85 g.) in freshly distilled collidine (15 ml.) was boiled under reflux for 1 hr. The suspension was cooled, diluted with an equal volume of dioxane, and filtered. The filtrate was washed with 2 *N* H_2SO_4 and water, dried, and evaporated. The residue was triturated with a little aqueous methanol, and the solid was filtered off and chromatographed on alumina. The eluate was evaporated, and the residue was crystallized from aqueous methanol to give colorless needles: m.p. 208–213°; $[\alpha]D$ 150°; λ_{max}^{EtOH} 229 mμ (log ε 4.09); ν_{max} (in CS_2) 1712 (ketones), 1686 and 780 (Δ^1-3-ketone), and 1355 cm.$^{-1}$ ($COCH_3$).

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.8; H, 8.6. Found: C, 76.8; H, 8.4.

3α,21-Dihydroxy-5β-pregnane-11,20-dione 3-Acetate (**115**).—3α,21-Dihydroxy-5β-pregnane-11,20-dione diacetate[4] (3.33 g., 7.7 mmoles) in methanol (333 ml., oxygen-free) was treated with a solution of $KHCO_3$ (0.827 g., 8.27 mmoles) in water (8.27 ml.). The reaction mixture was shaken under nitrogen for 1 hr. at room temperature and poured into water. Brine was added, and the product was isolated with $CHCl_3$; solution in benzene (30 ml.) and seeding precipitated 3α,21-dihydroxy-5β-pregnane-11,20-dione (0.12 g.), which was removed by filtration. The filtrate was evaporated to dryness and the residue was crystallized from ether to give the monoacetate (2.225 g.), m.p. 133–136.5°; this still contained a little diol. Crystallization from wet ether gave material with m.p. 134–136° (lit.[9] m.p. 137–138°).

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.7; H, 8.8. Found: C, 70.3; H, 8.9.

3α,21-Dihydroxy-5β-pregnane-11,20-dione 3-Acetate 21-Methanesulfonate (**122**).—3α,21-Dihydroxy-5β-pregnane-11,20-dione 3-acetate (11.05 g.) in dry pyridine (104 ml.) was cooled to −20° and treated with methanesulfonyl chloride (10.53 ml.). After 40 min. at 0°, the mixture was poured into ice–water, and the precipitate was crystallized from dry methanol; yield 10.02 g., m.p. 154–157°. Further crystallization from methanol gave material with m.p. 162–164° (lit.[10] m.p. 164.5–166°); $[\alpha]D$ +110°; ν_{max} (in $CHBr_3$) 1728 and 1255 (acetate) and 1710 cm.$^{-1}$ (ketone).

Anal. Calcd. for $C_{24}H_{36}O_7S$: C, 61.5; H, 7.7. Found: C, 61.9; H, 7.8.

3α-Hydroxy-21-chloro-5β-pregnane-11,20-dione Acetate (**127**).—3α,21-Dihydroxy-5β-pregnane-11,20-dione 3-acetate (2.89 g.) was treated with methanesulfonyl chloride in pyridine at 0° for 70 min. and the 21-methanesulfonate (2.2 g.) was isolated as above; the mother liquors yielded another crop of crystals (0.31 g.), m.p. 130–141°, which, on further crystallization from meth-

(2) N. L. Wendler, D. Taub, S. Dobriner, and D. K. Fukushima, *J. Am. Chem. Soc.*, **78**, 5027 (1956).

(3) J. von Euw and T. Reichstein, *Helv. Chim. Acta*, **25**, 988 (1942).

(4) J. D. Cocker, H. B. Henbest, G. H. Phillipps, G. P. Slater, and D. A. Thomas, *J. Chem. Soc.*, 6 (1965).

(5) G. Rosenkranz, J. Pataki, St. Kaufmann, J. Berlin, and C. Djerassi, *J. Am. Chem. Soc.*, **72**, 4081 (1950).

(6) Purchased from Koch-Light Laboratories Ltd.

(7) A. L. Nussbaum, T. L. Popper, E. P. Oliveto, S. Friedman, and I. Wender, *J. Am. Chem. Soc.*, **81**, 1228 (1959); P. F. Beal, M. A. Rebenstorf, and J. E. Pike, *ibid.*, **81**, 1231 (1959).

(8) B. J. Magerlein, *J. Org. Chem.*, **24**, 1564 (1959).

(9) L. H. Sarett, *J. Am. Chem. Soc.*, **71**, 1165 (1949).

(10) N. L. Wendler, R. P. Graber, and G. G. Hazen, *Tetrahedron*, **3**, 144 (1958).

anol, gave a small quantity of **127**: m.p. 163.5–165°; $[\alpha]_D$ +134°; ν_{max} (in CS_2) 1758 and 1242 (acetate) and 1712 cm.$^{-1}$ (ketone).

Anal. Calcd. for $C_{23}H_{33}ClO_4$: C, 67.5; H, 8.1; Cl, 8.7. Found: C, 67.5; H, 8.0; Cl, 8.7.

3α-Hydroxy-21-iodo-5β-pregnane-11,20-dione Acetate (128).—3α,21-Dihydroxy-5β-pregnane-11,20-dione 3-acetate 21-methanesulfonate (1.407 g.) in dry acetone (35 ml.) was treated with dry NaI (1.385 g.) in dry acetone (28 ml.), and the mixture was boiled under reflux for 15 min., during which time a white solid separated. Water (7 ml.) was added, and the solution was concentrated *in vacuo* and cooled. The deposited crystals (1.34 g.) had m.p. 144.5–146°, unchanged by crystallization from aqueous acetone; $[\alpha]_D$ +137.5°; ν_{max} (in CS_2) 1734 and 1238 (acetate) and 1710 cm.$^{-1}$ (ketone).

Anal. Calcd. for $C_{23}H_{33}IO_4$: C, 55.2; H, 6.7; I, 25.4. Found: C, 55.0; H, 6.6; I, 25.2.

3α,21-Dihydroxy-5β-pregnane-11,20-dione 21-Methanesulfonate (120).—A solution of 3α,21-dihydroxy-5β-pregnane-11,20-dione 3-acetate 21-methanesulfonate (8.05 g.) in dry methanol (280 ml.) at −20° was treated with 60% aqueous perchloric acid (16 ml.) and stirred for 16 hr. at room temperature. The mixture was then poured into water (1 l.) and the product was isolated with chloroform and crystallized from ethyl acetate; 4.52 g., m.p. 170–172°. A recrystallized sample had m.p. 175–177°; ν_{max} (in Nujol) 3370 (bonded OH), 1705 (ketone), and 1686 cm.$^{-1}$ (bonded ketone).

Anal. Calcd. for $C_{22}H_{34}O_6S$: C, 61.9; H, 8.0. Found: C, 62.3; H, 8.1.

21-Fluoro-3α-hydroxy-5β-pregnane-11,20-dione (126).—To a stirred solution of the foregoing 21-methanesulfonate (**120**) (1.0 g.) in dimethylformamide (30 ml.) was added dry potassium hydrogen fluoride (1.0 g.), and the mixture was stirred on the steam bath under nitrogen for 17 hr. The mixture was cooled and ice-water (70 ml.) was added gradually; after being left at 5° for 24 hr. the solid (459 mg.) was filtered off and washed with water. The filtrate was diluted to *ca.* 500 ml. and extracted with ethyl acetate to give a further 346 mg. of solid. The combined solids were chromatographed on Florisil; elution with 10% ethyl acetate in benzene gave 272 mg. of material which, after further crystallization from ethyl acetate–petroleum ether, gave the product (116 mg.), m.p. 198–202°, $[\alpha]_D$ +135°. The analytical sample had m.p. 201–203°.

Anal. Calcd. for $C_{21}H_{31}FO_3$: C, 72.0; H, 8.9. Found: C, 72.3; H, 8.9.

3α-Hydroxy-21-iodo-5β-pregnane-11,20-dione.—The 21-methanesulfonate (1.25 g.) in acetone (28 ml.) was treated with NaI (1.25 g.) in acetone (16 ml.), and the mixture was boiled under reflux for 15 min. A little water was added to dissolve the precipitate, most of the acetone was distilled, the residue was diluted with water, and the resulting oil was extracted with ether. Evaporation of the washed and dried extract gave a froth (1.3 g.) that could not be induced to crystallize.

3α,21-Dihydroxy-5β-pregnane-11,20-dione 21-*t*-Butylacetate (119).—Crude 3α-hydroxy-21-iodo-5β-pregnane-11,20-dione (1.1 g.), prepared as above, was dissolved in acetone (10 ml.) and added to a solution of *t*-butylacetic acid (2.5 ml.) and triethylamine (1.5 ml.) in acetone (5 ml.). The mixture was boiled under reflux for 2.5 hr., cooled, and added slowly to ice–water (250 ml.). The aqueous layer was decanted, the residual gum was dissolved in ethanol, and the solvent was evaporated to leave a froth (1.15 g.) which was chromatographed on Florisil (50 g.). Elution with 5% ethyl acetate in benzene gave 779 mg. of material with m.p. 99–107°. An analytical sample, crystallized from ethyl acetate–petroleum ether (b.p. 60–80°), had m.p. 102–106°; $[\alpha]_D$ +98°; ν_{max} (in CS_2) 3600 (OH), 1744 and 1225 (21-ester), 1728 (20-ketone), and 1712 cm.$^{-1}$ (ketone).

Anal. Calcd. for $C_{27}H_{42}O_5$: C, 72.6; H, 9.5. Found: C, 72.4; H, 9.5.

21-Acetylthio-3α-hydroxy-5β-pregnane-11,20-dione (124).—3α-Hydroxy-21-iodo-5β-pregnane-11,20-dione (1.07 g.), prepared as above, was dissolved in acetone (50 ml.) and added to a suspension of potassium thioacetate (0.714 g.) in acetone (50 ml.). The mixture was heated under reflux in a stream of nitrogen for 2 hr., cooled, and most of the acetone was removed under reduced pressure. The product was isolated by extraction with ethyl acetate and chromatography on Florisil (50 g.). The material 0.77 g.) which was eluted with 5 and 10% ethyl acetate in benzene and was crystallized from ethyl acetate–petroleum ether (b.p. 60–80°) had m.p. 128–130°; $[\alpha]_D$ +130°; ν_{max} (in CS_2) 3620 (OH) and 1715 and 1705 cm.$^{-1}$ (ketone).

Anal. Calcd. for $C_{23}H_{34}O_4S$: C, 67.9; H, 8.4. Found: C, 68.0; H, 8.5.

3β-Hydroxy-17-(2-tetrahydropyranyloxy)-5α-pregnane-11,20-dione (47).—3β,17-Dihydroxy-5α-pregnane-11,20-dione 3-acetate[11] (0.508 g.) in redistilled dihydropyran (4 ml.) was treated with redistilled phosphoryl chloride (1 drop). An exothermic reaction resulted, and the solution was cooled and kept at room temperature for 23 hr. Isolation of the product with ether gave a yellow oil which was treated with petroleum ether (b.p. 40–60°) to give a crystalline solid (0.255 g.), m.p. 189–197°. Crystallization from ethyl acetate gave 3β-hydroxy-17-(2-tetrahydropyranyloxy)-5α-pregnane-11,20-dione acetate: m.p. 205–211°; $[\alpha]_D$ +37°; ν_{max} (in CS_2) 1734 and 1242 (acetate), 1712 (ketone), and 1130, 1075, and 1035 cm.$^{-1}$ (ether).

Anal. Calcd. for $C_{32}H_{50}O_6$: C, 70.8; H, 8.9. Found: C, 70.8; H, 9.0.

Treatment of the acetate (1.0 g.) in a boiling mixture of methanol (12 ml.) and benzene (4 ml.) with 20% aqueous $KHCO_3$ (3.5 ml.) for 4 hr., gave the corresponding 3-alcohol, which, after crystallization from ethyl acetate–petroleum ether (b.p. 60–80°), weighed 0.445 g. and had m.p. 213–217°; $[\alpha]_D$ +46°; ν_{max} (in Nujol) 3550 (OH), 1702 (ketone), and 1130, 1075, and 1035 cm.$^{-1}$ (ether).

Anal. Calcd. for $C_{30}H_{48}O_5$: C, 72.2; H, 9.3. Found: C, 71.9; H, 9.3.

3β,16α-Dihydroxy-5α-pregnane-11,20-dione (36).—16α,17α-Epoxy-3β-hydroxy-5α-pregnane-11,20-dione[12] (8.0 g.) in acetic acid (576 ml.) and water (192 ml.) was treated under nitrogen with chromous acetate (18 g.), and the mixture was stirred for 18 hr. The solution was extracted repeatedly with chloroform, and the mixture was washed with aqueous $NaHCO_3$ and water. The combined extracts were dried ($MgSO_4$) and evaporated to dryness. After trituration of the residue with chloroform and crystallization from methanol, the solid (3.5 g.) had m.p. 229–234° (sublimation); $[\alpha]_D$ +69° (*c* 1.0, 1:1 $CHCl_3$–MeOH); ν_{max} (in Nujol) 3300 (OH) and 1700 cm.$^{-1}$ (ketone).

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 72.4; H, 9.3. Found: C, 72.2; H, 9.5.

3β-Hydroxy-16β-methyl-5α,17α-pregnane-11,20-dione.—3β-Hydroxy-16β-methyl-5α-pregnane-11,20-dione[13] (0.743 g.) was dissolved in 1% ethanolic KOH (70 ml.). After 105 min. at room temperature the rotation had fallen to $[\alpha]_D$ −3.8°, and boiling the solution under reflux for 30 min. caused no further change. Water was added to the point of precipitation, and the bulk of the solvent was removed *in vacuo*. After addition of more water and neutralization with CO_2, the product was filtered off and dried, giving 0.711 g. of material, m.p. 195–206°. Crystallization from methanol gave material with m.p. 208.5–209.5° (previous change of crystalline form); $[\alpha]_D$ −8.9°; ν_{max} (in $CHBr_3$) 3620 (OH), 1698 (ketone), and 1360 cm.$^{-1}$ ($COCH_3$).

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.3; H, 9.9. Found: C, 76.6; H, 9.4.

3β-Hydroxy-16α-methyl-5α-pregnane-11,20-dione.—To a Grignard reagent prepared from magnesium (4.32 g.) and methyl iodide (24 ml.) in ether (85 ml.), cuprous chloride (0.04 g.) was added, followed by 3β-hydroxy-5α-pregn-16-ene-11,20-dione acetate[14] (2.06 g.) in tetrahydrofuran (230 ml.). During the addition, ether (50 ml.) had to be added to prevent the mixture from solidifying. After the addition (35 min.), the reaction mixture was refluxed for 4 hr., cooled, and treated with saturated NH_4Cl (100 ml.). The product, isolated by extraction with methylene chloride and crystallization from ethyl acetate, had m.p. 184.5–186°; $[\alpha]_D$ +99°; ν_{max} (in CS_2) 3620 and 1044 (equatorial OH) and 1710 cm.$^{-1}$ (ketone).

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.3; H, 9.9. Found: C, 76.1; H, 9.8.

3α-Hydroxy-3β-methyl- (102) and 3β-Hydroxy-3α-methyl-5β-pregnane-11,20-dione (103).—A solution of 5β-pregnane-3,11,20-trione 20-ethylene ketal[15] (3.0 g.) in tetrahydrofuran (30 ml.) was added slowly to a stirred solution of methylmagnesium iodide

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[from magnesium (1.0 g.) and methyl iodide (4.81 g.)] in ether (10 ml.), and the solution was boiled under reflux with stirring under nitrogen for 2 hr. Saturated NH_4Cl solution was added to the cooled reaction mixture, and the product was isolated with $CHCl_3$. The resulting froth was heated at 100° for 1 hr. in acetic acid (40 ml.) with water (30 ml.) in order to remove the ketal group, and the product was again isolated with $CHCl_3$, and chromatographed on alumina (120 g.). The first fractions (844 mg.), eluted with benzene containing up to 15% of ether, were mixtures, as judged from their infrared spectra. Benzene containing 25% ether eluted 547 mg. of crystalline material, which crystallized from ethyl acetate to give **103**, m.p. 192–195.5°, $[\alpha]_D$ +114.5°. The infrared spectrum in $CHBr_3$ showed bands at 3620 and 870 (axial OH) and 1700 cm.$^{-1}$ (ketone).

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.3; H, 9.9. Found: C, 76.0; H, 9.8.

After elution of mixtures (130 mg.) with ether, 20% methanol in ether eluted **102** (326 mg.), which crystallized from ethyl acetate–hexane to give the analytical sample (196 mg.), m.p. 168–170°, $[\alpha]_D$ +112°. The infrared spectrum in $CHBr_3$ showed bands at 3600 and 915 (equatorial OH) and 1700 cm.$^{-1}$ (ketone).

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.3; H, 9.9. Found: C, 76.0; H, 10.0.

11β-Hydroxy-5α-pregnane-3,20-dione 3,20-Bisethylene Ketal.—5α-Pregnane-3,11,20-trione 3,20-bisethylene ketal[16] (3.44 g.) and $NaBH_4$ (1.7 g.) in ethanol (118 ml.) and water (12 ml.) were refluxed for 2 hr. Water was added, most of the ethanol was distilled, the residue was diluted with water, and the precipitate was crystallized from aqueous ethanol containing pyridine. The 11β-hydroxy compound had m.p. 163–164°; $[\alpha]_D$ +33°; ν_{max} (in Nujol) 3620–3520 (OH), and 1100, 1080, and 1052 cm.$^{-1}$ (ketal).

Anal. Calcd. for $C_{25}H_{40}O_5$: C, 71.4; H, 9.6. Found: C, 71.2; H, 9.6.

11β-Hydroxy-5α-pregnane-3,20-dione (60).—The foregoing bisketal (2.84 g.) in acetic acid (80 ml.) and water (80 ml.) was heated at 100° for 2 hr. Most of the solvent was removed *in vacuo*, water was added, and the precipitated product (2.08 g., m.p. 224–228°) was crystallized from acetone–hexane and from ethanol to give material: m.p. 230–231°; $[\alpha]_D$ +117°; ν_{max} (in $CHBr_3$) 3600 (OH), 1700 (ketone), and 1354 cm.$^{-1}$ ($COCH_3$).

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.9; H, 9.7. Found: C, 75.9; H, 9.7.

9α,11α-Epoxy-3β-hydroxy-5α-pregnan-20-one (61).—9α,11α-Epoxy-3β-hydroxy-5α-pregnan-20-one acetate[17] (2.0 g.) was boiled under reflux for 4 hr. with $KHCO_3$ (1.4 g.) in methanol (24 ml.) and water (7.0 ml.). Water (10 ml.) was added, most of the methanol was removed *in vacuo*, then more water (*ca.* 100 ml.) was added. The crystalline precipitate (1.71 g.) was recrystallized to give a solid (1.175 g.): m.p. 180–183.5°; $[\alpha]_D$ +45°; ν_{max} (in $CHBr_3$) 3620 (OH), 1700 (ketone), 1358 ($COCH_3$), and 910 cm.$^{-1}$ (epoxide).

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.9; H, 9.7. Found: C, 75.9; H, 9.6.

9β,11β-Epoxy-3β-hydroxy-5α-pregnan-20-one (63).—3β-Hydroxy-5α-pregn-9-en-20-one acetate[17] (2.0 g.) in dioxane (100 ml.) was treated with 0.46 *N* aqueous perchloric acid (10 ml.) followed by N-bromoacetamide (808 mg.), added in one lot to the stirred solution, light being excluded. After 35 min., aqueous sodium metabisulfite was added until the yellow color was discharged, followed by 2 *N* NaOH (11 ml.) to bring the pH above 10, and sufficient water (30 ml.) to give a homogeneous solution. After 30 min., glacial acetic acid (10 ml.) was added to bring the pH to 6. The dioxane was removed *in vacuo* and water was added to precipitate a gummy solid (1.83 g.).

This crude product was reacetylated by heating at 100° for 45 min. in acetic anhydride (10 ml.) and pyridine (20 ml.). The mixture was evaporated *in vacuo*, finally with methanol, and the crystalline residue (1.9 g.) was taken up in ethyl acetate (5 ml.) and hexane (50 ml.) and charcoaled. The filtered solution was evaporated to dryness and the residue was crystallized from aqueous methanol and then from hexane to give 9β,11β-epoxy-3β-hydroxy-5α-pregnan-20-one acetate (879 mg.): m.p. 115–118.5°; $[\alpha]_D$ +84°; ν_{max} (in CS_2) 1738 and 1245 (acetate), 1710 (ketone), and 912 cm.$^{-1}$ (epoxide).

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.8; H, 9.1. Found: C, 74.0; H, 9.2.

Hydrolysis by the method used for the corresponding 9α,11α-epoxide gave the 3β-alcohol: m.p. 190–193°; $[\alpha]_D$ +101°; ν_{max} (in $CHBr_3$) 3620 (OH), 1700 (ketone), 1358 ($COCH_3$), and 905 cm.$^{-1}$ (epoxide).

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.9; H, 9.7. Found: C, 76.0; H, 9.7.

11α,12α-Epoxy-5β-pregnane-3,20-dione (139).—5β-Pregn-11-ene-3,20-dione[18] (2.0 g.) in $CHCl_3$ (40 ml.) was treated with 3 *N* monoperphthalic acid in ether (10 ml.) and after 16 hr. the mixture was washed with aqueous $NaHCO_3$ and water. After removal of the solvent *in vacuo*, the product was crystallized from ethyl acetate–hexane and from methanol; yield 1.03 g., m.p. 180–183°, $[\alpha]_D$ +83°.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.3; H, 9.1. Found: C, 76.2; H, 9.0.

3β-Hydroxy-D-homo-5α-androstane-11,17a-dione (147) was prepared from the corresponding 3-acetate[19] (2.1 g.), which was boiled under reflux for 4 hr. with methanol (24 ml.) and 20% aqueous $KHCO_3$ (7 ml.). Dilution with water and crystallization from acetone–hexane gave the 3-alcohol (1.13 g.): m.p. 171–172°; $[\alpha]_D$ −21.8° (*c* 2.4); ν_{max} (in CS_2) 3620 (OH) and 1715 cm.$^{-1}$ (ketone).

Anal. Calcd. for $C_{20}H_{30}O_3$: C, 75.4; H, 9.5. Found: C, 75.3; H, 9.5.

3β,17-Dihydroxy-5α-pregnane-11,20-dione 3-Formate.—A suspension of 3β,17-dihydroxy-5α-pregnane-11,20-dione[20] (5.0 g.) in benzene (250 ml.) was treated with 98% formic acid (50 ml.) and the mixture was slowly distilled, 150 ml. of distillate being collected in 2 hr. Benzene (200 ml.) was added and the distillation was continued until formic acid no longer passed over. The mixture was evaporated to dryness *in vacuo*, and the residue was crystallized from benzene; 4.3 g.; m.p. 207–211°; $[\alpha]_D$ +15° (*c* 2.5); ν_{max} (in CS_2) 1725 and 1180 (formate) and 1700 cm.$^{-1}$ (ketone).

Anal. Calcd. for $C_{22}H_{32}O_5$: C, 70.2; H, 8.6. Found: C, 70.5; H, 8.4.

3β,17α-Dihydroxy-17β-methyl-D-homo-5α-androstane-11,17a-dione (148).—The foregoing formate (4.2 g.) in dioxane (100 ml.) was treated with boron trifluoride etherate (3 ml.) at room temperature for 23 hr. The mixture was diluted with water and filtered, and the product was crystallized from methanol to give **3β,17α-dihydroxy-17β-methyl-D-homo-5α-androstane-11,17a-dione 3-formate** (1.01 g.); m.p. 172–174°; $[\alpha]_D$ +39.0° (*c* 2.02, dioxane); ν_{max} (in CS_2) 1724 and 1180 (formate) and 1710 cm.$^{-1}$ (ketone).

Anal. Calcd. for $C_{22}H_{32}O_5$: C, 70.2; H, 8.6. Found: C, 69.8; H, 8.7.

Hydrolysis of this ester (360 mg.) by heating on the steam bath for 1 hr. in 50% aqueous acetic acid (10 ml.) gave the 3,17-diol which, after crystallization from acetone–petroleum ether, formed needles (169 mg.), m.p. 209–210°, $[\alpha]_D$ +56° (*c* 1.86, dioxane). The infrared spectrum in $CHBr_3$ showed bands at 3600 and 3500 (OH) and 1715 and 1705 cm.$^{-1}$ (ketone).

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.4; H, 9.3. Found: C, 72.3; H, 9.3.

Preparation of Hemisuccinates. Method A.—The alcohol and an equal weight of succinic anhydride in about 10 vol. of pyridine were kept at room temperature for about 24 hr. The solution was poured onto 10 vol. of ice and water and acidified with HCl. The hemisuccinate was collected by filtration (or, rarely, by extraction), dried, and crystallized.

Method B was identical with method A, except that the reaction was carried out at 100° for *ca.* 4 hr.

Method C was identical with the foregoing, but the reaction was carried out at the boiling point for 4 hr.

The compounds prepared in these ways are listed in Table I; any significant departures from these methods are noted in footnotes to the table.

3β,17-Dihydroxy-5α-pregnane-11,20-dione 17-Acetate 3-Hemisuccinate (46).—3β,17-Dihydroxy-5α-pregnane-11,20-dione 3-hemisuccinate (Table I) (0.4 g.) in a mixture of acetic acid (20 ml.) and acetic anhydride (4 ml.) was treated with toluene-*p*-

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TABLE I

PREPARATION AND PROPERTIES OF HEMISUCCINATES

Nucleus	Parent alcohol: Substituents: Oxo	Hydroxy	Acetoxy	Methyl	Others	Method of prepn.	Crystn. solvent[a]	Product: No.[b]	Position of hemi-succinate	M.p., °C.	[α]D,[c] deg.	Formula	Calcd., %: C	H	Found, %: C	H
5α-Androstane		3β				C	AN	143	3	175–176	−6.1	$C_{29}H_{36}O_4$	73.4	9.6	73.8	9.6
	11	3β				C	EA–PE	144	3	195–196.5	+32	$C_{23}H_{34}O_5$	70.7	8.8	70.7	8.6
	11,17	3β				C	MC–IPE	145	3	247–250	+92	$C_{23}H_{32}O_6$	68.3	8.0	68.6	7.9
D-Homo-5β-androstane	11,17	3α,17aβ		17aα		B	AC–PE	154	3	213–215	+40.9[d]	$C_{25}H_{36}O_5 \cdot 0.5H_2O$	65.6	8.1	65.7	7.9
5α-Pregnane		3β				C	AN	2	3	144–145	+9.0	$C_{25}H_{40}O_4$	74.2	10.0	73.8	9.8
		3β,11β,20β				C	AC	59	3	199–200	+11	$C_{25}H_{40}O_6$	68.8	9.2	68.5	9.1
	20	3β				C	EA	4	3	200–202[e]	+65	$C_{25}H_{38}O_5$	71.7	9.2	72.0	9.0
	20	3β	21			C	AN	13	3	183–185	+70.5	$C_{27}H_{40}O_7$	68.0	8.5	68.0	8.3
	20	3β		16α		B[f]	EA–PE	11	3	178–179.5	+55.6	$C_{26}H_{40}O_5$	72.2	9.3	72.5	9.5
	20	3β			9α,11α-Epoxy	B	EA–PE	62	3	190–193	+36.5	$C_{25}H_{36}O_6$	69.4	8.4	69.7	8.4
	20	3β,11β				C	AN	57	3	226–228	+77	$C_{25}H_{38}O_6$	69.1	8.8	69.4	8.8
	20	3β,16α				C[g]	EA–PE	10	3,16	195–198[h]	+17	$C_{29}H_{42}O_9$	65.1	7.9	64.9	7.9
	20	3β,11β,17α				C	AN	58	3	211.5–212	+4	$C_{25}H_{38}O_7$	66.6	8.5	66.4	8.3
	3,20	21				A	AC	24	21	238–240	+102	$C_{25}H_{36}O_6$	69.4	8.4	69.0	8.2
	3,20	17α,21				A	EA	23	21	215–217	+61.9[d]	$C_{28}H_{36}O_7$	66.9	8.1	66.8	8.0
	11,20	3β				C	EA	33	3	211–214	+76	$C_{25}H_{36}O_6$	69.4	8.4	69.2	8.3
	11,20	3α				C	EA–PE	31	3	179–181	+96	$C_{25}H_{36}O_6$	69.4	8.4	69.8	8.6
	11,20	3β	21			C	EA	48	3	174–176	+77	$C_{27}H_{38}O_8$	66.1	7.8	65.8	7.6
	11,20	3β		16α		B	EA–PE	39	3	189–190.5	+71.4	$C_{26}H_{38}O_6$	69.9	8.6	69.9	8.6
	11,20	3β		16β		B	EA	41	3	179–184.5	+47.7	$C_{26}H_{38}O_6$	69.9	8.6	70.1	8.6
	11,20	3β			16α,17α-Epoxy	C	EA–PE	38	3	189–192	+69	$C_{25}H_{36}O_7$	67.2	7.7	66.9	7.4
	11,20	21				A	EA–PE	29	21	146–151	+84.4	$C_{25}H_{36}O_6$	69.4	8.4	69.0	8.9
	11,20	3β,16α				C[g]	EA–PE	37	3,16	188–190	+38	$C_{29}H_{40}O_{10}$	63.5	7.4	63.4	7.7
	11,20	3β,17α				C	EA	45	3	215–216	+10.9[i]	$C_{25}H_{36}O_7 \cdot 0.5C_4H_8O_2$	65.8	8.2	66.0	8.0
	11,20	3β,17α	21			C	CH–B	49	3	181–182	+62	$C_{27}H_{38}O_9$	64.0	7.6	63.6	7.2
	11,20	3β,17α,21				C	AN	50	3,21	185–186	+53.5	$C_{29}H_{40}O_{10}$	61.7	7.1	61.7	7.3
	12,20	3β				B	MA	6	3	196–198	+124	$C_{25}H_{38}O_5$	69.4	8.4	69.7	8.2
	3,11,20	21				A	AC	54	21	217–220	+100	$C_{25}H_{34}O_7$	67.2	7.7	67.6	7.9
	3,11,20	17α,21				A	AN	53	21	212–213	+109.5	$C_{25}H_{34}O_8$	64.9	7.4	65.2	7.7
5α,17α-Pregnane	11,20	3β		16β		B	EA–PE	42	3	186.5–187.5	−14.7	$C_{26}H_{38}O_6$	69.9	8.6	69.9	8.5
5α-Pregn-9-ene	20	3β				B	EA–PE	15	3	156.5–162	+69	$C_{25}H_{36}O_5$	72.1	8.7	72.2	8.8
	20	3β,17α				C	AC	19	3	228–229	+22.1[d]	$C_{25}H_{36}O_6$	69.4	8.4	69.5	8.3
	20	3β,17α	21			C	EA	20	3	193.5–195	+35.5	$C_{27}H_{38}O_8$	66.1	7.8	66.0	7.9
5α-Pregn-16-ene	20	3β				C	EA–PE	5	3	163–164	+33	$C_{25}H_{36}O_5$	72.1	8.7	72.2	8.6
	11,20	3β				C	AN	35	3	194–195.5[j]	+58	$C_{25}H_{34}O_6$	69.7	8.0	69.8	8.0
	11,20	3β		16		B	EA	43	3	216–223[k]	+27	$C_{26}H_{36}O_6$	70.2	8.2	70.5	8.0
	12,20	3β				B	EA	7	3	231–236	+115	$C_{25}H_{34}O_8$	69.7	8.0	69.9	8.2

5β-Pregnane	11	3α	20,20-Ethylenedioxy	B	EA–PE	129	3	171.5–172.5	+68.9	$C_{23}H_{40}O_7$	68.0	8.5	68.0	8.9	
	20	3α		B	EA	66	3	164–166[l]	+109	$C_{25}H_{38}O_5$	71.7	9.2	72.1	9.2	
	20	3α	16α	B[f]	...	73	3	104–107	+88.8	$C_{26}H_{40}O_5 \cdot H_2O$	69.3	9.4	69.0	9.3	
	20	3β		C	MA	69	3	214–218[m]	+77.2	$C_{25}H_{38}O_5$	71.7	9.2	71.8	9.2	
	20	3α,11β		B	EA–PE	138	3	150–153	+106.3	$C_{25}H_{38}O_6$	69.1	8.8	69.3	8.8	
	3,20	17α,21		A	EA–PE	80	21	184–185	+61.9	$C_{25}H_{36}O_7$	66.9	8.1	66.9	8.4	
	11,20	3α		B	EA	90	3	174–175[n]	+114.5[n]	$C_{25}H_{36}O_6$	69.4	8.4	69.6	8.5	
	11,20	3α	21	B	EA	123	3	174–175	+113.5	$C_{27}H_{38}O_8$	66.1	7.8	66.0	7.8	
	11,20	3α		B	EA	125	3	...[o]	+93	$C_{22}H_{40}O_6$	73.8	7.7	73.6	7.6	
	11,20	3α	21-Benzylidene	B	EA–PE	105	3	152–153	+105	$C_{26}H_{38}O_6$	69.9	8.6	69.9	8.5	
	11,20	3α	16α	B	EA–PE	108	3	165–166	+78.9	$C_{26}H_{38}O_5$	69.9	8.6	69.7	8.6	
	11,20	3α	16β	B	EA–PE	111	3	119–124	+67.3	$C_{27}H_{40}O_6$	70.4	8.7	70.1	8.7	
	11,20	3α	16α,16β	B[f]	...	117	21	95–96.5	+88	$C_{25}H_{36}O_7$	66.9	8.1	66.6	8.1	
	11,20	3α,21		A	AN	134	21	161–164	+90	$C_{25}H_{34}O_7$	67.2	7.7	67.2	7.6	
	3,11,20	21		A	EA–PE	131	21	215–217	+80	$C_{25}H_{34}O_8$	64.9	7.4	64.9	7.4	
	3,11,20	17α,21		A	AN	77	3	149–151	+109.5	$C_{25}H_{36}O_5$	72.1	8.7	72.1	8.8	
5β-Pregn-9-ene	20	3α		B	EA	142	3	145–146	+30	$C_{27}H_{38}O_7$	68.3	8.1	68.6	7.9	
Pregn-5-ene	20	3β	21	C	EA										

[a] AC = acetone, AN = acetonitrile, B = benzene, CH = chloroform, EA = ethyl acetate, IPE = isopropyl ether, MA = methanol, MC = methylene chloride, PE = petroleum ether. [b] See following paper. [c] In $CHCl_3$ unless otherwise stated. [d] In dioxane solution. [e] R. A. Lucas, D. F. Dickel, R. L. Dziemian, M. J. Ceglowski, B. L. Hensle, and H. B. MacPhillamy, *J. Am. Chem. Soc.*, **82**, 5668 (1960). [f] Crude product purified by solution in aqueous or aqueous alcoholic $NaHCO_3$, removal of nonacidic material by filtration or extraction with ether, acidification of the aqueous phase, and, where possible, recrystallization of the precipitated hemisuccinate. [g] 2.5 g. of succinic anhydride to 1 g. of steroid. [h] A. Wettstein, R. Neher, and P. A. Desaulles [German Patent 1,135,902 (1962)] give m.p. 195–196°. [i] $[\alpha]_D$ +39.5° in dioxane. [j] λ_{max}^{EtOH} 234.5 mμ (log ε 3.97). [k] λ_{max}^{EtOH} 247 mμ (log ε 3.98). [l] Chas. Pfizer & Co., Inc. [British Patent 804,521 (1958)] gives m.p. 160–161.2°. [m] Chas. Pfizer & Co., Inc. [British Patent 804,521 (1958)] gives m.p. 203.4–208°. [n] S. A. Szpilfogel and G. A. Overbeek [Dutch Patent 87,804 (1958)] give m.p. 172–173°, $[\alpha]_D$ +119° (dioxane). [o] λ_{max}^{EtOH} 221.5 mμ (log ε 4.02), 227 (4.00), and 291 (4.34).

sulfonic acid hydrate (0.4 g.). After being left for 2 hr. at room temperature, the reaction mixture was poured into ice–water, and the precipitate was filtered off, dried, and dissolved in cold ethyl alcohol (25 ml.). The filtered solution was treated with $NaHCO_3$ (0.25 g.) in water (4 ml.), diluted with water (200 ml.), and filtered through kieselguhr. Acidification of the filtrate with 2 *N* HCl and crystallization of the precipitate from ethyl acetate–petroleum ether (b.p. 40–60°) gave the product (0.22 g.): m.p. 197–199° (slight previous sintering); $[\alpha]_D$ +11.4°; ν_{max} (in Nujol) 1732 and 1250 (acetate), 1732 and 1175 (hemisuccinate), and 1708 cm.$^{-1}$ (ketone and CO_2H).

Anal. Calcd. for $C_{27}H_{38}O_8$: C, 66.1; H, 7.8. Found: C, 66.0; H, 7.7.

3β-Hydroxy-5α-pregnane-11,20-dione 3-Disodium Phosphate (34).—3β-Hydroxy-5α-pregnane-11,20-dione[14] (5.48 g., 0.0165 mole) in dry $CHCl_3$ (160 ml.) and dry pyridine (18 ml.) was treated with a solution of dibenzyl phosphorochloridate (0.048 mole) in CCl_4 (120 ml.). After 2 days at room temperature, $CHCl_3$ was added to give a homogeneous solution, which was washed with 2 *N* HCl and saturated aqueous $NaHCO_3$ and dried (Na_2SO_4). Removal of the solvent *in vacuo* gave a gum, which was extracted with boiling ether. Removal of the ether gave crude 3β-hydroxy-5α-pregnane-11,20-dione 3-dibenzyl phosphate (9.43 g.), which was dissolved in ethanol (100 ml.) containing 0.5 *N* H_2SO_4 (0.4 ml.) and hydrogenated at room temperature and pressure in presence of 10% Pd–C (0.997 g.) (approx. 2 hr.). The catalyst was filtered off and the filtrate was concentrated to small volume *in vacuo*. The residue was taken up in methanol (40 ml.) and water (8 ml.) and titrated to pH 9.4 with 2 *N* NaOH solution. The volume was adjusted to 250 ml. by the addition of methanol and the solution was left at 0° overnight. After filtration through kieselguhr to remove inorganic phosphate, evaporation to dryness under reduced pressure gave the crude steroid disodium phosphate. This was shaken for 4 hr. at room temperature with methanol (150 ml.) and the resultant cloudy solution was filtered through kieselguhr to remove traces of inorganic phosphate. Evaporation of the filtrate *in vacuo* gave the product as a white solid (5.76 g.). Crystallization was effected by dissolving the product in a hot mixture of ethyl acetate (80 ml.), methanol (35 ml.), and water (15 ml.). The resultant hot, clear solution was treated with ethyl acetate (50 ml.), and the solution was cleared by the addition of a few drops of water. Cooling this solution afforded 2.72 g. of glistening plates: m.p. 220–228° (cap.); $[\alpha]_D$ +81° (*c* 0.802, water); ν_{max} (in Nujol) 1703 (ketone), 1140–1090 and 980 cm.$^{-1}$ (phosphate).

Anal. Calcd. for $C_{21}H_{31}Na_2O_6P \cdot 3H_2O$: C, 49.4; H, 7.3; P, 6.1. Found: C, 49.9; H, 7.1; P, 5.3.

3α-Hydroxy-5β-pregnan-20-one 3-Disodium Phosphate (67).—3α-Hydroxy-5β-pregnan-20-one (2.42 g.) was phosphorylated as described above for 3β-hydroxy-5α-pregnane-11,20-dione. The product [2.092 g.; dried at 105° (0.1 mm.) for 8 hr.] crystallized as plates, m.p. 270–285°, $[\alpha]_D$ +88.5° (*c* 1.49, water).

Anal. Calcd. for $C_{21}H_{33}Na_2O_5P \cdot 3H_2O$: C, 50.8; H, 7.9; P, 6.2. Found: C, 50.3; H, 8.1; P, 6.5.

3α-Hydroxy-5β-pregnane-11,20-dione 3-Disodium Phosphate (91).—3α-Hydroxy-5β-pregnane-11,20-dione (2.35 g., 7.08 mmoles) in dry ether (25 ml.) and dry pyridine (18 ml.) was cooled to −70° and treated with dibenzyl phosphorochloridate (20 mmoles) in CCl_4 (15 ml.). The mixture was kept at −70° for 20 min. with occasional shaking and then for 16 hr. at *ca.* −43°. Benzyl alcohol (2 ml.) was added, and the mixture was left for a further 2 hr. at −23°. Ether (200 ml.) was added and the organic phase was washed with HCl and $NaHCO_3$ and then dried. Removal of the solvent left a pale yellow oil (9.17 g.) which was dissolved in ethyl acetate (100 ml.) containing 2 *N* H_2SO_4 (0.1 ml.) and hydrogenated at room temperature and pressure in presence of 10% Pd–C (0.85 g.). Hydrogenation was complete (1190 ml., at NTP) in 2.5 hr. After removal of the catalyst by filtration, the filtrate was evaporated *in vacuo* to a white froth (4.5 g.), which was dissolved in methanol (35 ml.) and water (10 ml.) and titrated to pH 9.9 with 2 *N* NaOH. Methanol (100 ml.) was added and after 1 hr. at 5° inorganic phosphate was filtered off. The filtrate was evaporated to dryness *in vacuo* and the treatment with methanol was repeated. The solid obtained by evaporation was extracted with two 40-ml. portions of boiling benzene, and the residue was thoroughly dried (P_2O_5) and crystallized from a mixture of ethyl acetate–methanol–water (59:32:9 by vol.). The product separated as crystals (63.5% yield): $[\alpha]_D$ +107° (*c* 1.05, water); ν_{max} (in Nujol) 1705 (ketones) and 1100–990 cm.$^{-1}$ (phosphate).

Anal. Calcd. for $C_{21}H_{31}Na_2O_6P \cdot 4H_2O$: C, 47.7; H, 7.4; P, 5.9. Found: C, 47.2; H, 7.1; P, 6.5.

3α-Hydroxy-16α-methyl-5β-pregnane-11,20-dione 3-Sodium Phosphate (106).—3α-Hydroxy-16α-methyl-5β-pregnane-11,20-dione[21] (1.21 g.) was treated with dibenzyl phosphorochloridate and then with benzyl alcohol to destroy excess reagent as described in the paragraph above. The crude dibenzyl steroid phosphate (4.935 g.) was taken up in absolute ethanol (50 ml.), treated with 10% Pd-C (0.406 g.), and hydrogenated at room temperature and pressure (55 min.). The disodium salt was prepared and separated from inorganic phosphate as above and then crystallized from a mixture of ethyl acetate (43 ml.), methanol (23 ml.), and water (7.9 ml.); 0.567 g.: $[\alpha]_D$ +100° (*c* 0.932, water); ν_{max} (in Nujol) 1705 (ketones) and 1068 and 995 cm.$^{-1}$ (phosphate).

Anal. Calcd. for $C_{22}H_{33}Na_2O_6P \cdot 0.5H_2O$: C, 55.1; H, 7.1; P, 6.5. Found: C, 55.2; H, 7.4; P, 6.9.

21-Hydroxy-5β-pregnane-3,20-dione Methanesulfonate.—21-Hydroxy-5β-pregnane-3,20-dione[22] (15.4 g.) in anhydrous pyridine (150 ml.) was treated with methanesulfonyl chloride (15.5 ml.), and the mixture was kept at 0–5° for 30 min. and poured, with rapid stirring, into ice-water (2 l.). The product was isolated with $CHCl_3$ (250 ml.) and crystallized from aqueous acetone to give material (12.85 g.) with m.p. 144–150°. Further crystallization gave the analytical sample: m.p. 148–152°; $[\alpha]_D$ +96.0°; ν_{max} (in Nujol) 1706 (ketone) and 1355 and 1176 cm.$^{-1}$ (sulfonate).

Anal. Calcd. for $C_{22}H_{34}O_5S$: C, 64.3; H, 8.3; S, 7.8. Found: C, 64.8; H, 8.1; S, 7.7.

21-Iodo-5β-pregnane-3,20-dione.—The foregoing 21-methanesulfonate (5.0 g.) in acetone (150 ml.) was boiled under reflux with NaI (5.0 g.) for 15 min. The solvent was removed *in vacuo*, and the residue was triturated with water containing a little sodium thiosulfate, and was then crystallized from aqueous acetone to give the product: m.p. 120–123°; ν_{max} (in CS_2) 1714 and 1704 cm.$^{-1}$ (ketones).

Anal. Calcd. for $C_{21}H_{31}IO_2$: C, 57.0; H, 7.1; I, 28.7. Found: C, 57.2; H, 6.8; I, 28.6.

21-Hydroxy-5β-pregnane-3,20-dione 21-Benzyl Sodium Phosphate (86).—Silver dibenzyl phosphate (4.95 g.) in acetonitrile (300 ml.) was treated with 21-iodo-5β-pregnane-3,20-dione (5.06 g.) in acetonitrile (50 ml.), and the mixture was boiled under reflux for 1 hr. The solvent was removed under reduced pressure, $CHCl_3$ was added, and the AgI filtered off. The filtrate was washed with aqueous $NaHCO_3$ and water, dried, and evaporated to give **21-hydroxy-5β-pregnane-3,20-dione 21-dibenzyl phosphate** as a gum (6.97 g.) that could not be crystallized.

A solution of this material in acetone (300 ml.) was boiled under reflux for 5.5 hr. with NaI (4.16 g.). Removal of the solvent *in vacuo* gave a yellow froth which was treated with water and extracted with ether. The aqueous layer was adjusted to pH 1.5 with 2 *N* HCl and extracted with chloroform. The extract was washed with water and dilute aqueous sodium thiosulfate, dried (Na_2SO_4), and evaporated *in vacuo*. The residual gum (4.68 g.) in methanol (80 ml.) and water (20 ml.) was titrated with 2 *N* NaOH, and the solution was brought back to pH 7.5 by addition of Zeo-Karb 225 in the acid form. Filtration, removal of the solvent, and crystallization of the residue from acetone gave the product (3.83 g.) as a hygroscopic white powder: m.p. 143–147°; $[\alpha]_D$ +64.5° (*c* 0.97, water); ν_{max} (in Nujol) 1710 (ketones), 1237 and 1075 (phosphate), and 755 and 695 cm.$^{-1}$ (Ph).

Anal. Calcd. for $C_{28}H_{38}NaO_6P \cdot 2H_2O$: C, 60.0; H, 7.5; P, 5.5. Found: C, 59.7; H, 7.9; P, 5.8.

P^1,P^2-Bis(3,20-dioxo-5β-pregnan-21-yl) P^1,P^2-Disodium Pyrophosphate (85).—The foregoing steroid benzyl phosphate (2.513 g.) in 5% aqueous methanol (20 ml.) was passed through a short column of Zeo-Karb 225 (acid form). The column was washed with the same solvent until no longer acidic. The eluate was evaporated *in vacuo*, and the residual free acid (2.38 g.) was dissolved in dioxane (30 ml.) and treated with dicyclohexylcarbodiimide (0.893 g.) in dioxane (20 ml.). After 30 min. at room temperature glacial acetic acid (1 ml.) was added and after a further 30 min. the precipitate of dicyclohexylurea was filtered off, and the filtrate was evaporated *in vacuo* to a gum. This was taken up in acetone (50 ml.), and the solution was filtered and evaporated to give a gum (2.515 g.) which would not crystallize. This material (2.51 g.) in acetone (100 ml.) was treated with anhydrous NaI (2.19 g.) in acetone (20 ml.), and the mixture was boiled under reflux for 4 hr. After being cooled, the precipitated material (1.72 g.) was obtained as a pale yellow hygroscopic solid, m.p. 190–194°, $[\alpha]_D$ +67° (*c* 0.9, water). The analytical sample was prepared by dissolving this material in acetone–benzene (3:1) by dropwise addition of alcohol, filtering, and concentrating. The material so obtained had m.p. 194–200°; ν_{max} (in Nujol) 1716 (ketones), 1250, 1120, 1078, and 946 cm.$^{-1}$ (pyrophosphate).

Anal. Calcd. for $C_{42}H_{62}Na_2O_{11}P_2 \cdot 2H_2O$: C, 56.9; H, 7.5; P, 7.0. Found: C, 56.8; H, 7.5; P, 7.1.

Miscellaneous Esters of 3α-Hydroxy-5β-pregnane-11,20-dione Sulfate (95).—The pyridine–SO_3 reagent was prepared by adding chlorosulfonic acid (4 vol.) dropwise, with good stirring, to a solution of pyridine (10 ml.) in chloroform (15 ml.) at 0°. The mixture was stirred for 5 min. after the addition was complete and was then filtered, and the solid was washed quickly with pyridine to remove the $CHCl_3$. The reagent was stored in a desiccator until required and was used without drying.

3α-Hydroxy-5β-pregnane-11,20-dione (3 g.) in dry chloroform (75 ml.) was treated with the pyridine–SO_3 reagent (7.5 g.), and the mixture was stirred at room temperature for 6.5 hr. and then filtered. The residue was washed with $CHCl_3$ (10 ml.), and petroleum ether (about 400 ml.) was added to the filtrate. After being left at 4° overnight, the supernatant liquid was decanted, and the solid residue (6.69 g.) of crude 3α-hydroxy-5β-pregnane-11,20-dione hydrogen sulfate was dried *in vacuo* at room temperature.

To a solution of this material (3.08 g.) in water (50 ml.) was added a saturated solution of NaCl in water (60 ml.) with good stirring. The precipitated crude sodium salt (1.94 g.) was filtered off, washed with a little NaCl solution, and dried *in vacuo* (P_2O_5). The crude product was warmed to about 35° for 1 min. with absolute methanol (20 ml.), the solution was filtered, and the filtrate was evaporated to leave a solid (968 mg.). A portion (300 mg.) of this residue was dissolved in ethyl acetate–methanol–water (4.5:2.3:0.7), the solution was filtered and evaporated *in vacuo* at room temperature to small bulk, more ethyl acetate was added, and a small amount of white oil was removed by filtration. Addition of excess ethyl acetate then gave the crystalline **sodium salt** (116 mg.): m.p. 160–162°; $[\alpha]_D$ +107.5° (*c* 0.78, water); ν_{max} (in Nujol) 1710 (ketone) and 1230 and 1215 cm.$^{-1}$ (sulfate).

Anal. Calcd. for $C_{21}H_{30}NaO_5S \cdot 3H_2O$: C, 51.6; H, 7.6. Found: C, 50.7; H, 6.9.

Hemimaleate (94).—3α-Hydroxy-5β-pregnane-11,20-dione (1 g.) and maleic anhydride (2 g.) were heated at 65–75° for 2 hr. The cooled mixture was dissolved in the minimum of acetone and poured into water with vigorous stirring. The resulting oil was washed several times by decantation with water, dissolved in dilute $NaHCO_3$, and reprecipitated by pouring into cold dilute HCl. Further purification in the same way gave an amorphous solid: 887 mg.; m.p. 65–68°; $[\alpha]_D$ +114.5° (*c* 1.05, dioxane); ν_{max} (in $CHBr_3$) 1732 and 1250 (ester) and 1706 cm.$^{-1}$ (ketone and CO_2H).

Anal. Calcd. for $C_{29}H_{38}O_6 \cdot 0.5H_2O$: C, 68.3; H, 8.0. Found: C, 68.5; H, 8.0.

Hemiglutarate (92).—3α-Hydroxy-5β-pregnane-11,20-dione (2.13 g.), glutaric anhydride (1.93 g.), and pyridine (10 ml.) were heated for 1 hr. on the steam bath and then kept at room temperature for 3 days. The dark solution was poured with stirring onto iced dilute HCl (150 ml.), and the gum which separated was washed with water by decantation and dissolved in dilute $NaHCO_3$ solution. Acidification gave amorphous 3α-hydroxy-5β-pregnane-11,20-dione hemiglutarate (1.1 g.), m.p. 59–64°, $[\alpha]_D$ +108° (*c* 1.07, dioxane).

A portion of the hemiester (350 mg.) was dissolved in aqueous methanol and charcoaled, and $NaHCO_3$ (66 mg., 1.0 equiv.) in a little water was added. Evaporation of the solution gave a glass which was dissolved in water, filtered through kieselguhr, and again evaporated *in vacuo* at room temperature. The crude sodium salt was dissolved in wet ethyl acetate containing a drop of methanol and the solution was quickly boiled down to small volume. Addition of hexane gave the sodium salt, a white, amorphous, hygroscopic powder (218 mg.), m.p. >236° dec. (cap.), $[\alpha]_D$ +83.5° (*c* 1.82, water).

Anal. Calcd. for $C_{29}H_{37}NaO_6 \cdot H_2O$: C, 64.2; H, 8.0. Found: C, 64.5; H, 8.0.

Hemidiglycolate (93).—3α-Hydroxy-5β-pregnane-11,20-dione (2 g.), diglycolic anhydride (2 g.), and pyridine (10 ml.) were

(21) G. E. Arth, D. B. R. Johnston, J. Fried, W. W. Spooncer, D. R. Hoff, and L. H. Sarett, *J. Am. Chem. Soc.*, **80**, 3160 (1958).

(22) C. D. Laubach, U. S. Patent 2,708,651 (1955).

heated for 30 min. on the steam bath and then left for 3 days at room temperature. After being poured into iced *N* HCl (150 ml.), the solid material was filtered off, dried, and recrystallized once from wet toluene and once by dropwise addition of water to an ice-cold solution of the derivative in aqueous acetone (1:1). The crystalline product (1.1 g.) had m.p. 65–68°; $[\alpha]_D$ +118° (*c* 1.19, dioxane); ν_{max} (in Nujol) 1735 and 1220 (ester), and 1720 and 1708 cm.$^{-1}$ (ketone).

Anal. Calcd. for $C_{25}H_{36}O_7 \cdot 0.5H_2O$: C, 65.6; H, 8.1. Found: C, 65.1; H, 8.3.

Hemiphthalate (96).—3α-Hydroxy-5β-pregnane-11,20-dione (2 g.) and phthalic anhydride (935 mg.) were dissolved in pyridine (15 ml.), left at room temperature for 20 hr., and then heated on the steam bath for 1.5 hr. The solution was poured on to iced dilute HCl and the solid material was filtered off. Purification was achieved by dissolving the crude hemiester in dilute $NaHCO_3$ solution, acidifying with dilute HCl, and recrystallizing the product twice from ethyl acetate-petroleum ether (b.p. 40–60°) to give the hemiphthalate (1.19 g.); m.p. 220–221° (cap.); $[\alpha]_D$ +104° (dioxane); ν_{max} (in Nujol) 1728 and 1290 (benzoate), 1705 (ketone), and 1688 cm.$^{-1}$ (CO_2H).

Anal. Calcd. for $C_{29}H_{36}O_6$: C, 72.5; H, 7.5. Found: C, 72.5; H, 7.7.

Hemi-N-acetyl-L-glutamate (101).—N-Acetyl-L-glutamic anhydride (1.99 g.) and 3α-hydroxy-5β-pregnane-11,20-dione (4.05 g.) in pyridine (10 ml.) were heated on the steam bath for 1 hr. and left for a further 2.5 hr. at room temperature. The mixture was poured into iced water which was then just neutralized by the addition of dilute HCl. The flocculent amorphous precipitate was removed by filtration and partitioned between dilute $NaHCO_3$ and ether. The combined aqueous extracts were washed with ether and then poured onto iced dilute HCl. The amorphous precipitate was filtered off, dissolved in methanol, and charcoaled. Evaporation *in vacuo* gave an oil which was again dissolved in dilute $NaHCO_3$ and reprecipitated with dilute HCl to give a solid: m.p. 105–115°; $[\alpha]_D$ +95.5° (*c* 1.9, dioxane); ν_{max} (in $CHBr_3$) 3400 (NH), 1720 (ester), 1705 and 2600 (CO_2H), 1705 (ketone), 1675 and 1516 cm.$^{-1}$ (CONH).

Anal. Calcd. for $C_{28}H_{41}NO_7 \cdot 0.5H_2O$: C, 65.6; H, 8.2. Found: C, 65.3; H, 8.1.

Chloroacetate.—To a solution of 3α-hydroxy-5β-pregnane-11,-20-dione (5 g.) in dry alcohol-free $CHCl_3$ (50 ml.) was added a solution of chloroacetic anhydride (2.5 g.) in pyridine (2.5 ml.), and the mixture was left at room temperature for 16 hr. The solution was then washed with dilute HCl, dilute $NaHCO_3$ solution, and water. The dried solution was evaporated *in vacuo*, and the residue was recrystallized from ether-petroleum ether (b.p. 60–80°), ether, and finally dry methanol to give the analytical sample: m.p. 98–101°; $[\alpha]_D$ +129° (*c* 1.23, dioxane); ν_{max} (in CS_2) 1758 and 1182 (chloroacetate), 1710 (ketone), and 1358 cm.$^{-1}$ ($COCH_3$).

Anal. Calcd. for $C_{23}H_{33}ClO_4$: C, 67.5; H, 8.1; Cl, 8.7. Found: C, 67.2; H, 8.1; Cl, 8.5.

Iodoacetate.—The foregoing chloroacetate (3 g.), NaI (3 g.), and acetone (75 ml.) were refluxed for 1.5 hr. After removal of most of the solvent *in vacuo*, water (50 ml.) was added, and the product was isolated with ether and crystallized from ether–petroleum ether (b.p. 60–80°) and then ether; m.p. 115–117°; $[\alpha]_D$ +95.5° (*c* 1.04, acetone); ν_{max} (in CS_2) 1730 and 1270 (iodoacetate), 1710 (ketone), and 1358 cm.$^{-1}$ ($COCH_3$).

Anal. Calcd. for $C_{23}H_{33}IO_4$: C, 55.2; H, 6.7; I, 25.4. Found: C, 55.5; H, 6.7; I, 25.0.

Aminoacetate (97).—The iodoacetate (2 g.) in acetone (25 ml.) was added slowly to liquid NH_3 (about 1 ml.), and the mixture allowed to stand for 15 min. After evaporation of the solvent, the residue was partitioned between ethyl acetate and dilute HCl. The aqueous phase was poured into dilute $NaHCO_3$ and extracted with ethyl acetate. The residue (259 mg.), after evaporation of the ethyl acetate, was again dissolved in dilute HCl, charcoaled, and basified with $NaHCO_3$ to give the aminoacetate (123 mg.) as an amorphous solid: m.p. 73–77°; $[\alpha]_D$ +115° (*c* 1.45, dioxane); ν_{max} (in $CHBr_3$) 3410 (NH), 1735 and 1218 (ester), and 1712 cm.$^{-1}$ (ketone).

Anal. Calcd. for $C_{23}H_{35}NO_4 \cdot 0.5H_2O$: C, 69.3; H, 9.1. Found: C, 69.2; H, 9.0.

Diethylaminoacetate (98).—The iodoacetate (1.5 g.) in acetone (60 ml.) containing diethylamine (0.75 ml.) was refluxed for 1.5 hr. Evaporation of the solvent gave a mixture of crystals and oil which was crystallized from ether to give the crude diethylaminoacetate, m.p. 87–89°. It was dissolved in dilute HCl and the solution was charcoaled and basified with $NaHCO_3$. Extraction with ether and recrystallization gave the analytical sample with m.p. 89–91°; $[\alpha]_D$ +119° (*c* 1.16, dioxane); ν_{max} (in CS_2) 1730 and 1190 (ester), 1710 (ketone), and 1358 cm.$^{-1}$ ($COCH_3$).

Anal. Calcd. for $C_{27}H_{43}NO_4$: C, 72.8; H, 9.7; N, 3.1. Found: C, 72.8; H, 9.9; N, 2.8.

Diethylaminoacetate Ethiodide (99).—The iodoacetate (512 mg.) in acetone (20 ml.) was treated with triethylamine (0.25 ml.), and the solution was refluxed for 2.5 hr. After removal of solvent the residue was found to be insoluble in water and so was again refluxed in acetone (20 ml.) with triethylamine (1 ml.) for another 2 hr. The residue, after evaporation of solvent, was soluble in hot water. Crystallization from acetone–hexane gave the ethiodide (248 mg.), m.p. 197–200°; a second crop (125 mg.) had m.p. 192–194°. Recrystallization from acetone–hexane gave the analytical sample with m.p. 203–205°; $[\alpha]_D$ +97.5° (*c* 1.34, aqueous dioxane); ν_{max} (in $CHBr_3$) 1735 and 1226 (ester), 1700 (ketone), and 1360 cm.$^{-1}$ ($COCH_3$).

Anal. Calcd. for $C_{29}H_{48}INO_4$: C, 57.9; H, 8.0; I, 21.1; N, 2.3. Found: C, 57.6; H, 8.0; I, 20.6; N, 2.1.

Morpholinoacetate Methiodide (100).—The iodoacetate (750 mg.) in acetone (30 ml.) containing N-methylmorpholine (1 ml.) was refluxed for 30 min. The mixture was cooled and filtered to give the methiodide (550 mg.): m.p. 228–229°, unchanged by crystallization from methanol; $[\alpha]_D$ +87.5° (*c* 1.08); ν_{max} (in $CHBr_3$) 1735 and 1228 (ester), 1700 (ketone), and 1360 cm.$^{-1}$ ($COCH_3$).

Anal. Calcd. for $C_{28}H_{44}INO_5$: C, 55.9; H, 7.4; I, 21.1 Found: C, 55.6; H, 7.4; I, 20.7.