Steroids. CCLXXXVIII.[1] The Synthesis of 18-Methylprogesterone and Related Compounds[2]

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Reaction of 3β,20β-dihydroxypregn-5-en-18-oic acid 3-acetate 18,20-lactone (**1a**) with an excess of methyl magnesium chloride afforded 3β,20β-dihydroxy-18-methylpregn-5-en-18-one (**2a**), which was reduced by a modified Wolff–Kishner procedure to 18-methylpregn-5-ene-3β,20β-diol (**3a**). Oxidation of the latter provided 18-methylprogesterone (**7a**) from which a number of 18-methylated androstanes and pregnanes were prepared. The stereochemistry and conformation of the 17β-acetyl side chain in the 18-methylated 20-ketopregnanes were deduced from optical rotatory dispersion and nmr data.

The synthesis of 18-alkylestranes has been achieved by two laboratories utilizing total synthesis procedures.[5,6] However, the extension of this work to 18-alkylandrostanes and 18-alkylpregnanes has been reported only in the patent literature.[7]

We required an efficient route to 18-methylpregnanes and investigated synthesis from 18-oxygenated intermediates. This scheme offered several advantages over a total synthesis[8] since the problems associated with the introduction of the C-19 angular methyl group and the pregnane side chain were avoided. In this paper we describe a convenient synthesis of 18-methylprogesterone (**7a**) starting with 3β,20β-dihydroxypregn-5-en-18-oic acid 3-acetate 18,20-lactone (**1a**)[9] and discuss the conversion of this product into a number of other 18-methylated steroids. (See Chart I.)

The success of this investigation depended upon the development of an efficient method for converting the lactone **1a** to 3β,20β-dihydroxy-18-methylpregn-5-en-18-one (**2a**). In general, γ-lactones react with 2 equiv of Grignard reagent to afford ring-cleaved products although, in certain instances, cyclic monoadducts (lactols) may be obtained under controlled conditions.[10] In the case of the acetoxy lactone **1a** it was anticipated that the rigidly fixed lactone ring would react with methyl Grignard to afford only a monoadduct since the initially formed complex would be sufficiently hindered to resist further attack by the reagent.[11,12]

Treatment of the acetoxy lactone **1a** with a large excess (*ca.* 40 equiv) of methylmagnesium bromide in boiling tetrahydrofuran or at 100° in a sealed tube gave as the only detectable product the corresponding hydroxy lactone **1b**, which resulted from Grignard-induced cleavage of the 3-acetoxy group. More promising results were obtained in pilot experiments using methylmagnesium chloride and conditions were ultimately developed (using 16 molar equiv of 3 *N* methylmagnesium chloride in toluene under reflux for 4 days) whereby the keto diol **2a** was obtained in 83% yield. This product showed strong carbonyl absorption in the infrared spectrum at 1680 cm^{-1} (hydrogen-bonded ketone) and the required three-proton singlet at 139 cps in the nmr spectrum[13] attributable to the 13β-acetyl grouping. The keto diol **2a** afforded a crystalline semicarbazone, **2c**, and was further characterized as the diacetate **2b**. When the Grignard reaction mixture was exposed to dilute mineral acid during work-up, the yield of the keto diol **2a** was substantially reduced and an appreciable quantity of a less-polar product (by tlc) was formed. The nmr spectrum of the crude mixture revealed a pair of doublets at low field, suggesting that the impurity was the cyclized 18-methylene 18,20-oxide **1c**. Although no attempt was made to resolve this mixture, treatment of the keto diol **2a** with *p*-toluenesulfonic acid in boiling benzene accompanied by azeotropic removal of water afforded authentic 18-methylen-18,20β-oxidopregn-5-en-3β-ol (**1c**)[14] which exhibited the expected pair of doublets for the *exo*-methylene protons at 232 and 261 cps, $J = 2$ cps, in the nmr spectrum. This product was identical by tlc with the foregoing impurity in the keto diol **2a**.

When 3β,20β-dihydroxy-18-methylpregn-5-en-18-one (**2a**) was subjected to the Huang-Minlon modification[15] of the Wolff–Kishner reductive procedure, the desired 18-methylpregn-5-ene-3β,20β-diol (**3a**) was obtained in moderate yield (*ca.* 40%), but this result was not reproducible.[16] A more detailed examination of the reaction revealed that hydrazone formation did not occur with hydrazine hydrate in diethylene glycol at 155°. Moreover, the starting ketone **2a** was recovered essentially unchanged after exposure to hydrazine hydrate in diethylene glycol at 200° for 3 hr.[17] Clearly,

(1) Steroids. CCLXXXVII: R. Ginsig and A. D. Cross, *J. Org. Chem.*, in press.

(2) "18-Methyl" is the methyl group of the 13β-ethyl moiety.

(3) Syntex Postdoctoral Fellow, 1964–1965.

(4) To whom inquiries should be addressed.

(5) H. Smith, *et al.*, *J. Chem. Soc.*, 4472 (1964).

(6) L. Velluz, G. Nominé, R. Bucourt, A. Pierdet, and P. Dufay, *Tetrahedron Letters*, 127 (1961).

(7) For examples, see G. Nominé, R. Bucourt, and A. Pierdet, U. S. Patents 3,119,841 (Jan 28, 1964) and 3,179,660 (April 20, 1965).

(8) For a recent review, see L. Velluz, J. Valls, and G. Nominé, *Angew. Chem. Intern. Ed. Engl.*, **4**, 181 (1965).

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

(10) See M. S. Kharasch and O. Reinmuth in "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954, Chapter 8.

(11) For a discussion of the mechanism of addition of Grignard reagents to ester linkages, see ref 10, pp 553, 554.

(12) A pertinent example has been described [Roussel-Uclaf, German Patent 1,157,222 (1964)], in which 3-cycloethylenedioxy-11β,20β-dihydroxypregn-5-en-18-oic acid 11,18-lactone is stated to react with methyl Grignard to afford the 18-methyl-18-keto adduct, isolated as the corresponding lactol.

(13) Unless otherwise stated, nmr spectra were recorded for deuteriochloroform solutions using a Varian A-60 spectrometer and tetramethylsilane as internal reference. Chemical shifts, expressed in cycles per second downfield from the reference signal, are accurate to better than ±1 cps and are quoted to the nearest 0.5 cps.

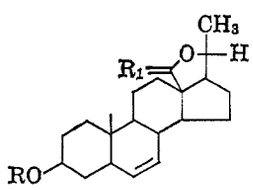
(14) The analogous 18,20-oxidopregn-20-ene system has been described by R. Pappo, *J. Am. Chem. Soc.*, **81**, 1010 (1959).

(15) Huang-Minlon, *ibid.*, **68**, 2487 (1946).

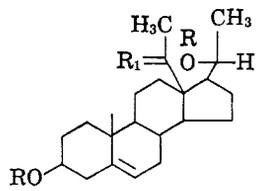
(16) With the exception of our initial success, the Huang-Minlon reduction (at 200–220°) of **2a** led to a multiplicity of products from which the diol **3a** was isolated in low yield.

(17) This finding indicated that a number of competing reactions occurred in the presence of alkali, above 200°, in addition to hydrazone formation and subsequent reduction.

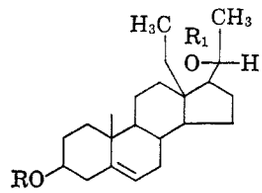
CHART I



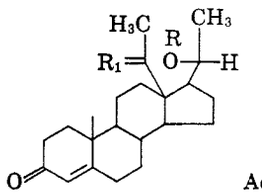
1a, R = $COCH_3$; R_1 = O
b, R = H; R_1 = O
c, R = H; R_1 = CH_2



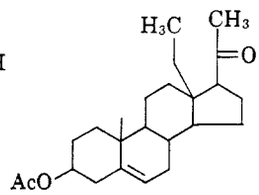
2a, R = H; R_1 = O
b, R = $COCH_3$; R_1 = O
c, R = H; R_1 = N-$NHCONH_2$
d, R = H; R_1 = N-NH_2
e, R = H; R_1 = N-N=$C(CH_3)_2$



3a, R = R_1 = H
b, R = $COCH_3$; R_1 = H
c, R = R_1 = $COCH_3$



4a, R = H; R_1 = H_2
b, R = $COCH_3$; R_1 = H_2
c, R = H; R_1 = O



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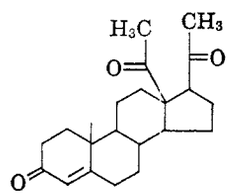
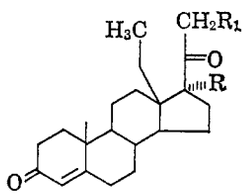
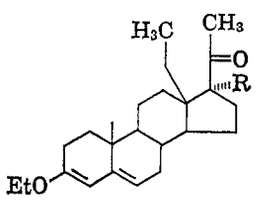


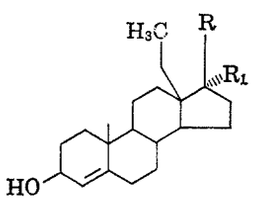
6



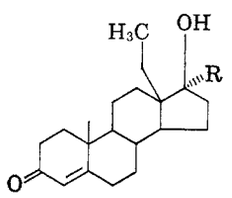
7a, R = R_1 = H
b, R = OH; R_1 = H
c, R = $OCOH_3$; R_1 = H
d, R = H; R_1 = $OCOCH_3$
e, R = OH; R_1 = $OCOCH_3$



8a, R = H
b, R = OOH



9a, R = -CHOHCH$_3$; R_1 = OH
b, R, R_1 = O
c, R = OH; R_1 = H
d, R = OH; R_1 = C≡CH



10a, R = H
b, R = C≡CH

more vigorous conditions were required to induce hydrazone formation and this was achieved by the method of Nagata and Itazaki.[18] Thus, treatment of the keto diol **2a** with hydrazine dihydrochloride–hydrazine hydrate–triethylene glycol at 145° gave a hydrazone which exhibited spectral properties consistent with the formulation **2d**. A crystalline acetone azine **2e** was obtained after attempted crystallization of the hydrazone **2d** from acetone. When the crude hydrazone **2d** in diethylene glycol was added to a solution of potassium hydroxide in hydrazine hydrate–diethylene glycol, maintained under reflux at 225°, smooth reduction took place and the desired 18-methylpregn-5-ene-3β,-20β-diol (**3a**) was obtained in 70% over-all yield from the keto diol **2a**. As expected, this product showed no carbonyl absorption in the infrared, and the nmr spectrum (DMSO-d_6 solvent) showed two doublets centered at 238 and 272 cps (J = 5 cps) confirming the presence of the two secondary hydroxyl groups. The nmr spectrum of the derived diacetate **3c** showed a triplet, centered at 46.5 cps (J = 6 cps) for the methyl protons of the 13β-ethyl group.

18-Methylpregn-5-ene-3β,20β-diol (**3a**) was next oxidized by the Oppenauer procedure to give a mixture separable by chromatography. The two principal components were 18-methylprogesterone (**7a**) and 20β-hydroxy-18-methylpregn-4-ene-3-one (**4a**), obtained in 18 and 65% yields, respectively.[19] The hydroxy ketone **4a** underwent oxidation with chromic acid in acetone solution[20] to complete the synthesis of 18-methylprogesterone (**7a**).

The selective oxidation at C-3 in 18-methylpregn-5-ene-3β,20β-diol (**3a**) was paralleled by the selective acetylation of the 3β-hydroxyl group. Brief exposure of the diol **3a** to acetic anhydride–pyridine afforded a mixture containing principally the 3-monoacetate **3b** (*ca.* 45% by tlc) and the unchanged diol from which the former was separated by chromatography. The constitution of the monoacetate was confirmed by oxidation to 3β-acetoxy-18-methylpregn-5-en-20-one (**5**), the structure of which followed from infrared, nmr, and optical rotatory dispersion data.

The keto diol **2a** was also oxidized selectively at C-3 by the Oppenauer procedure to give 20β-hydroxy-18-methylpregn-4-ene-3,18-dione (**4c**) which, in turn, was oxidized with chromic acid to 18-methylpregn-4-ene-3,18,20-trione (**6**).

The presence of the 18-methyl substituent did not impede the ability of 20-ketopregnanes to undergo reactions leading to 17α- and 21-hydroxylated compounds. Thus, 3-ethoxy-18-methylpregna-3,5-dien-20-one (**8a**) underwent oxygenation[21] in the presence of potassium *t*-butoxide in *t*-butyl alcohol–tetrahydrofuran to give the crystalline 17α-hydroperoxide **8b**, which was converted to 17α-hydroxy-18-methylprogesterone (**7b**) by treatment with zinc dust in acetic acid. Acid-catalyzed acetylation of the latter provided the 17α-acetoxy derivative **7c** *via* the intermediate 3,17α-diacetoxy-18-methylpregna-3,5-dien-20-one.

Both 18-methylprogesterone (**7a**) and its 17α-hydroxy analog **7b** were acetoxylated at C-21 by successive treatment with calcium oxide–iodine and potassium acetate–acetone[22] to afford 21-acetoxy-18-methylpregn-4-ene-3,20-dione (**7d**) and 21-acetoxy-17α-hydroxy-18-methylpregn-4-ene-3,20-dione (**7e**), respectively.

The use of 17α-hydroxy-18-methylprogesterone (**7b**) as a source of 18-methylandrostanes was also investi-

(18) W. Nagata and H. Itazaki, *Chem. Ind.* (London), 1194 (1964).

(19) Under identical conditions, the Oppenauer oxidation of pregn-5-ene-3β,20β-diol afforded a 1:2 mixture of progesterone and 20β-hydroxypregn-4-en-3-one.

(20) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(21) E. J. Bailey, D. H. R. Barton, J. Elks, and J. F. Templeton, *ibid.*, 1578 (1962).

(22) H. J. Ringold and G. Stork, *J. Am. Chem. Soc.*, **80**, 250 (1958).

TABLE I

NMR SPECTRAL DATA FOR 13β-ACETYL AND 13β-ETHYL STEROIDS[a]

Steroid	18-Methyl-H resonance centered at	19-H resonance singlet
18-Methylene-18,20β-oxidopregn-5-en-3β-ol (**1c**)	...	63.5
3β,20β-Dihydroxypregn-5-en-18-oic acid 3-acetate 18,20-lactone (**1a**)	...	67
18-Methylpregn-5-ene-3β,20β-diol 3-acetate (**3b**)	>60	60
18-Methylpregn-5-ene-3β,20β-diol 3,20-diacetate (**3c**)	46.5 (t)[b]	60
3β,20β-Dihydroxy-18-methylpregn-5-en-18-one (**2a**)	139	54
3β,20β-Dihydroxy-18-methylpregn-5-en-18-one diacetate (**2b**)	124.5	54
3β,20β-Dihydroxy-18-methylpregn-5-en-18-one hydrazone (**2d**)	111 (107.5[c])	53.5 (49[c])
3β,20β-Dihydroxy-18-methylpregn-5-en-18-one acetone azine (**2e**)	111 (105[c])	54 (50[c])
18-Methylpregn-5-ene-3β,20β-diol (**3a**)	Not resolved	56[c]
20β-Hydroxy-18-methylpregn-4-en-3-one (**4a**)	Not resolved	70
20β-Hydroxy-18-methylpregn-4-ene-3,18-dione (**4c**)	140.5	65
18-Methylprogesterone (**7a**)	40.5 (t)	70.5
18-Methylpregn-4-ene-3,18,20-trione (**6**)	125 or 130.5	66
3β-Hydroxy-18-methylpregn-5-en-20-one acetate (**5**)	39.5 (t)	60.5
20β-Hydroxy-18-methylpregn-4-en-3-one acetate (**4b**)	48 (t)	70.5

[a] See ref 13. [b] t = triplet. [c] Nmr in DMSO-d_6.

gated. Removal of the 17β-acetyl side chain, accomplished by the procedure of Ward, Orr, and Engel,[23] involved the reduction of **7b**, by lithium tri-*t*-butoxyaluminum hydride, to 18-methylpregn-4-ene-3β,17α,-20ξ-triol (**9a**) followed by cleavage at C-17 by lead tetraacetate. 3β-Hydroxy-18-methylandrost-4-en-17-one (**9b**) was thereby obtained and converted into 18-methyltestosterone (**10a**) by hydride reduction to the corresponding Δ⁴-3β,17β-diol **9c**,[24] followed by selective oxidation of the allylic 3β-alcohol with 2,3-dichloro-5,6-dicyano-1:4-benzoquinone (DDQ).[25]

The carbonyl group of the hydroxy ketone **9b** reacted sluggishly with potassium acetylide in liquid ammonia[26] and afforded a mixture of the 17α-ethynylated product **9d** and the starting material (3:2 by tlc) from which the former was separable by chromatography on alumina and crystallization. Oxidation of the crude ethynylation mixture with DDQ[25] followed by preparative tlc provided 17α-ethynyl-18-methyltestosterone (**10b**).

The presence of the 18-alkyl substituent in 18-methyl-20-ketopregnanes might be expected to alter the stability and conformation of the 17-acetyl side chain. However, rotatory dispersion measurements carried out with several 18-methylated 20-ketones revealed that the side chain is β oriented and also adopts the same conformation as the side chain of parent 20-ketones.[27] These conclusions were substantiated also by nmr spectroscopy (see below). Thus, 3β-hydroxy-18-methylpregn-5-en-20-one acetate (**5**) exhibited an intensely positive Cotton-effect curve virtually superimposable upon the curve of pregnenolone acetate (see Experimental Section). Similarly, 18-methylprogesterone (**7a**) and 17α-hydroxy-18-methylprogesterone (**7b**) displayed Cotton-effect curves identical with those of progesterone[28] and its 17α-hydroxylated counterpart.

The nmr spectra of the compounds variously substituted at C-18 and C-20 revealed significant shifts for the 18-methyl proton[29] and 19-proton resonances which accompanied the modification of functionality at C-18 and C-20 (see Table I). In both 18-methylen-18,20β-oxidopregn-5-en-3β-ol (**1c**) and 3β,20β-dihydroxypregn-5-en-18-oic acid 3-acetate 18,20-lactone (**1a**) the 10β-methyl protons lie close to the plane of the unsaturated function at C-18 and consequently experience deshielding.[30] This leads to downfield shifts of the 19-H resonance in the enol ether **1c** and the lactone **1a** amounting to 3.5 and 7.0 cps, respectively, compared with the resonances observed for 18-methylpregn-5-ene-3β,20β-diol 3-acetate (**3b**) and the corresponding diacetate **3c**.[31]

In the nmr spectrum of 3β,20β-dihydroxy-18-methylpregn-5-en-18-one (**2a**) and the derived diacetate **2b** the 19-H resonance undergoes an upfield shift of 6.0 cps relative to 18-methylpregn-5-ene-3β,20β-diol 3-acetate (**3b**) and the diacetate **3c**. This indicates that the C-19 angular methyl group of the keto diol **2a** lies in the shielding "cone"[30] of the carbonyl group at C-18. Therefore, the preferred conformation of the 13-acetyl group must be that depicted in A or B (see Figure 1) where nonbonded interactions between the 13β-acetyl methyl group and β-protons or substituents on rings C and D and at C-20 are minimized. Upfield shifts for the 19-H resonance were also observed with the hydrazone **2d** (6.5 cps) and the acetone azine **2e** (6.0 cps). When solutions in DMSO-d_6 were used, the position of the 19-H resonance for the hydrazone **2d** and the acetone azine **2e** could be compared with that for 18-methylpregn-5-ene-3β,20β-diol

(23) M. C. Ward, J. C. Orr, and L. L. Engel, *J. Org. Chem.*, **30**, 1421 (1965).

(24) Assignment of the β configuration to the 17-hydroxyl group of the diol **9c** follows from the earlier investigations of Smith and collaborators,[5] who showed by nmr spectroscopy that 18-alkyl 17-ketones are reduced by metal hydrides to the 17β-ols. In this publication it was also demonstrated that carbanion reagents attack these ketones from the α face, giving 17α-substituted 17β-alcohols.

(25) D. Burn, V. Petrow, and G. O. Weston, *Tetrahedron Letters*, **No. 9**, 14 (1960).

(26) This result was not unexpected, since the Wyeth investigators experienced the same difficulty with the addition of lithium acetylide to 18-alkyl 17-ketones in the gona-1,3,5(10)-triene series.[5]

(27) For a detailed account of this topic, see K. M. Wellman and C. Djerassi, *J. Am. Chem. Soc.*, **87**, 60 (1965), and references cited therein.

(28) C. Djerassi, R. Riniker, and B. Riniker, *ibid.*, **78**, 6377 (1956).

(29) See ref 2. Considerable confusion exists in the nmr steroid literature owing to the incorrect use of the term "18-methyl" to describe what is correctly the 18-proton or 13β-methyl resonance.

(30) See L. M. Jackman in "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Ltd., London, 1959, p 122.

(31) It is known that acetylation of a 3β- or a 20β-hydroxyl group in the 5-ene series has little effect on the position of the 19-H resonance.[32]

(32) See N. S. Bhacca and D. H. Williams in "Applications of N.M.R. Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, Chapter 2.

(**3a**) (insoluble in deuteriochloroform), and similar upfield shifts (7.0 and 6.0 cps, respectively) were observed. Nmr spectral comparisons revealed a similar shielding by the 18-keto group in the cases of the Δ^4-3-ketones **4a** and **4c** (upfield shift of 5.0 cps) and **7a** and **6** (upfield shift of 4.5 cps).

The functionality at C-20 greatly influenced the position of the 18-methyl resonance in both the 13β-acetyl and 13β-ethyl steroids. Comparison of the resonance owing to the 18-methyl protons of 3β,20β-dihydroxy-18-methylpregn-5-en-18-one (**2a**, 139 cps) with that of the corresponding diacetate **2b** (124.5 cps)[33] revealed an upfield shift of 14.5 cps associated with acetylation at C-20β. In the nmr spectrum of 18-methylpregn-5-ene-3β,20β-diol 3-acetate (**3b**), where the 18-methyl proton resonance triplet (J = 6–7 cps)[34] was partially obscured by the 19-H singlet and the 21-H doublet, the center of the triplet must be between 60 and 70 cps. In the diacetate **3c** the triplet is centered at 46.5 cps, also indicating therefore a similar strong upfield shift. Acetylation at C-20β in the 13β-methyl steroids causes a smaller diamagnetic shift (7.5 cps)[32] of the 18-proton resonance. Interestingly, the presence of the free 20β-alcohol does not modify the influence of the 13β-acetyl group on the 19-H resonance.

In the pregnane series the position of the 18-H resonance in 20β-acetoxy derivatives is similar to that in the corresponding 20-ketones.[32,35] In contrast, 13β-ethyl steroids show 18-methyl proton resonances which reveal different shieldings owing to the 20β-acetoxy and the C-20 carbonyl groups. The upfield shift (7.0 cps) on passing from the 20β-acetate **3c** ($\nu_{18\text{-}CH_3}$ = 46.5 cps) to the corresponding 20-ketone **5** ($\nu_{18\text{-}CH_3}$ = 39.5 cps) is paralleled in the change from the acetoxy ketone **4b** ($\nu_{18\text{-}CH_3}$ = 48.0 cps) to the related diketone **7a** ($\nu_{18\text{-}CH_3}$ = 40.5 cps).

The above nmr spectral observations require that the 13β-ethyl group and the 17β-acetyl side chain adopt the conformation depicted in C (Figure 1) in which the 18-methyl group is strongly shielded by the 20-ketone. Conformations D and E (Figure 1), which would be expected to produce a similar shielding effect, may be disregarded as high-energy rotomers of C.[27]

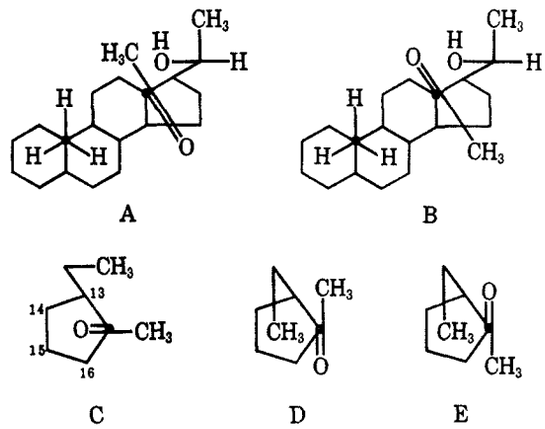


Figure 1.—A and B represent an 18-methyl-18-ketopregnane as viewed from C-18 and C-13. C, D, and E represent partial structures of an 18-methyl-20-ketopregnane (unsubstituted at C-17α and C-21) as viewed from C-20 to C-17.

Experimental Section[36]

3β,20β-Dihydroxy-18-methylpregn-5-en-18-one (2a).—3β,20β-Dihydroxypregn-5-en-18-oic acid 3-acetate 18,20-lactone (**1a**, 28 g) was heated under reflux in toluene (700 ml) with 3 N methylmagnesium chloride in tetrahydrofuran (400 ml) during 4 days. The reaction mixture was cooled, poured onto ice, diluted with water, and extracted by ethyl acetate. The organic layer was washed with water, dried, and evaporated to give a crystalline product (25 g) from which the keto diol **2a** was obtained as prisms, mp 181–188° (21.7 g), after crystallization from acetone–hexane. The analytical sample had mp 187–190°; $[\alpha]_D$ −56°; ν_{max} 3400, 1680, and 1060 cm^{-1}; ORD, $[\phi]_{600}$ −103°, $[\phi]_{500}$ −250°, $[\phi]_{400}$ −440°, $[\phi]_{350}$ −710°, $[\phi]_{311}$ −1260°, $[\phi]_{282}$ −820°, $[\phi]_{239}$ −1410°, $[\phi]_{220}$ ±0°, $[\phi]_{213}$ +705° (c 0.1, dioxane); nmr, 54 (19-H), 70 (J = 6 cps) (21-H), 139 (18-methyl H), 210 (broad multiplet for 3-H and 20-H), and 322 cps (multiplet for 6-H).

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89; O, 13.85. Found: C, 76.48; H, 10.04; O, 13.86.

The keto diol **2a** was acetylated with acetic anhydride–pyridine to give the diacetate **2b** which crystallized from acetone–methanol as plates: mp 140–141°; $[\alpha]_D$ −38°; ν_{max} 1740, 1700, and 1245 cm^{-1}; ORD, $[\phi]_{600}$ −185°, $[\phi]_{350}$ −800°, $[\phi]_{325}$ −1130°, $[\phi]_{278}$ −220°, $[\phi]_{262}$ −280°, $[\phi]_{248}$ ±0°, $[\phi]_{232}$ +1280°, $[\phi]_{229}$ +1360°, $[\phi]_{217}$ +920° (c 0.1, dioxane); nmr, 54 (19-H), 71 (J = 6 cps) (21-H), 121.5 (3-acetoxy H), 124.5 (13-acetyl H and 20-acetoxy H), 275 (broad multiplet for 3-H and 20-H), and 322 cps (multiplet for 6-H).

Anal. Calcd for $C_{26}H_{38}O_5$: C, 72.52; H, 8.90; O, 18.58. Found: C, 72.06; H, 8.72; O, 18.77.

A solution of the keto diol **2a** (100 mg) in ethanol (10 ml) was treated with semicarbazide hydrochloride (170 mg) and sodium acetate (170 mg), and the resulting solution was heated under reflux for 16 hr. Addition of water precipitated the semicarbazone **2c** which was crystallized from ethanol: mp 229–230°; $[\alpha]_D$ −100° (pyridine); ν_{max} 3350, 1640, and 1055 cm^{-1}.

Anal. Calcd for $C_{23}H_{37}N_3O_4 \cdot 0.5H_2O$: C, 66.98; H, 9.27; N, 10.19; O, 13.54. Found: C, 66.73; H, 9.77; N, 9.92; O, 13.13.

18-Methylen-18,20β-oxidopregn-5-en-3β-ol (1c).—The foregoing keto diol **2a** (1.0 g) was dissolved in benzene (120 ml) containing p-toluenesulfonic acid (100 mg). Solvent (20 ml) was removed by distillation and a further 50 ml of benzene was added. After removal of a further 40 ml of distillate, the solution was neutralized by an excess of potassium bicarbonate and evaporated to dryness *in vacuo*. Isolation by extraction with ether gave a crude product which was dissolved in benzene and filtered through alumina (100 g) to give the required enol ether **1c**, which crystallized from acetone–hexane as fine needles: mp 140–148°; $[\alpha]_D$ −30°; ν_{max} 3430, 1660, 1610, 1190, 1040, and 795 cm^{-1}; nmr 63.5 (19-H), 76 (J = 6 cps) (21-H), 210 (broad multiplet for 3-H), 250 (quartet, J = 6 cps) (20-H), 232 and 261 (J = 2 cps) (18-methylene), and 323 cps (multiplet for 6-H).

Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.83; O, 9.74. Found: C, 80.63; H, 9.92; O, 9.67.

Hydrazone Formation from the Keto Diol 2a.—A solution of the keto diol (12.2 g) in triethylene glycol (400 ml) was heated under reflux at 145° with hydrazine hydrate (80%, 80 ml) and hydrazine dihydrochloride (25 g) during 5 hr. The mixture was allowed to cool and was poured into water. The gelatinous hydrazone was extracted with ethyl acetate and the organic layer was washed with water, dried, and evaporated to give

(33) In 3β-acetoxy Δ^5-steroids (possessing no polar groups in rings A or B other than a Δ^5 double bond), the acetoxy protons usually resonate at 120–122 cps: A. D. Cross, unpublished observations. Thus, the six-proton singlet at 124.5 cps in the nmr spectrum of the diacetate **2b** must represent the resonances of both the C-20 acetoxy and the 13-acetyl methyl groups.

(34) The apparent coupling constant for the 18-methyl protons is evident in the spectra of compounds **5** and **7a** where the methyl triplet is clearly separated from the rest of the spectrum.

(35) Spectra determined in these laboratories for pregnenolone acetate and pregn-5-ene-3β,20β-diol diacetate displayed, in each case, 18-proton resonances at 38.5 cps.

(36) Melting points are uncorrected. All rotations are for chloroform solutions at 16–22° and ultraviolet spectra are for methanol solutions. Infrared spectra were determined in potassium bromide disks with a Perkin-Elmer Model 237 spectrometer. Optical rotatory dispersion measurements were made with a Jasco ORD–UV 5 spectropolarimeter. We are indebted to Dr. L. Throop and staff for these measurements. Microanalyses were by Midwest Micro Laboratories, Indianapolis 20, Ind., or by Dr. A. Bernhardt, Mülheim (Ruhr), Germany.

a colorless solid (13 g). A portion was crystallized from ethyl acetate–hexane to give the analytical sample of the hydrazone **2b** as fine needles: mp 178–187°; $[\alpha]_D$ −63°; ultraviolet, log ϵ_{210} 3.81; ν_{max} 3400, 1630, and 1025 cm^{-1}; nmr, 53.5 (19-H), 66.5 (J = 6 cps) (21-H), 111 (CH_3—C=N), 210 (broad multiplet for 3-H and 20-H), and 323 cps (multiplet for 6-H); nmr (in DMSO-d_6), 49 (19-H), 60 (J = 6 cps) (21-H), 108 (CH_3—C=N), 249 (doublet, J = 5 cps) (OH), 268 (doublet, J = 4 cps) (OH), 317 (multiplet for 6-H), and 329 cps (−NH_2).

Anal. Calcd for $C_{22}H_{36}N_2O_2$: C, 73.29; H, 10.07; N, 7.77; O, 8.88. Found: C, 73.55; H, 10.21; N, 7.81; O, 9.02.

Conversion of the Hydrazone 2d to the Acetone Azine 2e.—Crude hydrazone **2d** (400 mg) was heated under reflux in acetone (20 ml) during 1 hr. Addition of hexane followed by removal of solvent by distillation and subsequent cooling gave the acetone azine **2e** as stout prisms (273 mg): mp 165–167°; $[\alpha]_D$ −53°; ν_{max} 3420, 1640, and 1050 cm^{-1}; nmr, 54 (19-H), 67.5 (J = 6 cps) (21-H), 111, 119, 122.5 (three CH_3—C=N), 210 (broad multiplet for 3-H and 20-H), and 323 cps (multiplet for 6-H); nmr (in DMSO-d_6), 50 (19-H), 62 (J = 6 cps) (21-H), 105, 115, 117 (three CH$_3$—C=N), 254 (doublet, J = 5 cps) (OH), 270 (doublet, J = 4 cps) (OH), and 317 cps (multiplet for 6-H).

Anal. Calcd for $C_{25}H_{42}N_2O_2$: C, 74.58; H, 10.52; N, 6.96; O, 7.95. Found: C, 75.21; H, 10.22; N, 6.73; O, 7.93.

18-Methylpregn-5-ene-3β,20β-diol (3a).—A solution of hydrazine hydrate (100%, 20 ml) in diethylene glycol (200 ml) was distilled, under nitrogen, until the internal temperature reached 225°. Potassium hydroxide (10 g) was then added cautiously and distillation was continued, under nitrogen, until the temperature again reached 225°. A solution of the crude hydrazone **2d** (15 g) in diethylene glycol (150 ml) was then added slowly so that the temperature of the reaction mixture was maintained at reflux at 225°. The resulting solution was hetaed under reflux in a nitrogen atmosphere for 5 hr, cooled, and diluted with water, and the precipitate was collected by filtration, washed with water, and dried *in vacuo* to yield 12 g of crude diol **3a**. The product from two such experiments crystallized from methanol to give 18.5 g of 18-methylpregn-5-ene-3β,20β-diol (**3a**), mp 230–240°. Further crystallization from methanol afforded the analytical sample as prisms: mp 244–245°; $[\alpha]_D$ −84°; ν_{max} 3350 and 1040 cm^{-1}; nmr (in DMSO-d_6), 56 (19-H), 61 (J = 6 cps) (21-H), 205 (broad multiplet for 3-H and 20-H), 238 (J = 5 cps) (OH), 272 (J = 5 cps) (OH), and 320 cps (multiplet for 6-H).

Anal. Calcd for $C_{22}H_{36}O_2$: C, 79.46; H, 10.92; O, 9.63. Found: C, 79.59; H, 10.75; O, 9.72.

The foregoing diol (136 mg) was acetylated with pyridine (5 ml) and acetic anhydride (3 ml) in the usual manner to give the diacetate **3c** which crystallized from acetone–hexane as plates (98 mg): mp 129–130°; $[\alpha]_D$ −56°; ν_{max} 1730, 1240, and 1020 cm^{-1}; nmr, 46.5 (J = 6 cps) (18-methyl-H), 60 (19-H), 69 (J = 6 cps) (21-H), 120.5 (3- and 20-acetoxy H), 280 (broad multiplet for 3-H and 20-H), and 322 cps (multiplet for 6-H).

Anal. Calcd for $C_{26}H_{40}O_4$: C, 74.96; H, 9.68. Found: C, 75.01; H, 9.65.

Oppenauer Oxidation of 18-Methylpregn-5-ene-3β,20β-diol (3a).—A solution of the diol **3a** (2.2 g) in toluene (50 ml) and cyclohexanone (8 ml) was boiled until 10 ml of distillate was collected. Cyclohexanone (3 ml) and aluminum isopropoxide (2 g) were then added and the mixture was heated at reflux for 15 min, cooled, and poured into water (150 ml) containing acetic acid (5 ml). The mixture was steam distilled to remove solvents and the resultant emulsion was extracted with three 150-ml portions of ether. The organic layer was washed with water, 2 N hydrochloric acid, and saturated sodium bicarbonate solution, dried (Na_2SO_4), and evaporated to give a semicrystalline gum. This was dissolved in hexane–benzene (2:1) and adsorbed on alumina (200 g). Elution with benzene gave 18-methylprogesterone (**7a**, 390 mg), mp 168–169°, identical in all respects with an authentic sample obtained in the succeeding experiment. Elution with benzene–ether (9:1) gave 20β-hydroxy-18-methylpregn-4-en-3-one (**4a**, 1.40 g), which afforded the analytical sample as prisms from acetone–hexane: mp 155–156°; $[\alpha]_D$ +79°; λ_{max} 242 mμ (log ϵ 4.25); ν_{max} 3520, 1665, and 1610 cm^{-1}; ORD, $[\phi]_{600}$ +330°, $[\phi]_{400}$ +530°, $[\phi]_{362}$ −400°, $[\phi]_{356}$ −330°, $[\phi]_{349}$ −670°, $[\phi]_{325}$ +4900° (c 0.1, dioxane); nmr, 68 (J = 6 cps) (21-H), 70 (19-H), 226 (broad multiplet for 20-H), and 343 cps (multiplet for 4-H).

Anal. Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37; O, 9.68. Found: C, 79.87; H, 10.20; O, 9.92.

Acetylation of 20β-hydroxy-18-methylpregn-4-en-3-one (**4a**) in the usual manner afforded the acetate **4b**, which crystallized from acetone–hexane as prisms: mp 194.5–195.5°; $[\alpha]_D$ +128°; λ_{max} 243 mμ (log ϵ 4.15); ν_{max} 1740, 1680, 1620, and 1260 cm^{-1}; nmr, 48 (J = 7 cps) (18-methyl H), 70.5 (19-H), 70 (J = 6 cps) (21-H), 120 (20-acetoxy H), 283 (broad multiplet for 20-H), and 343 cps (multiplet for 4-H).

Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.37; H, 9.74; O, 12.88. Found: C, 77.40; H, 9.73; O, 13.03.

18-Methylprogesterone (7a).—A solution of the hydroxy ketone **4a** (1.5 g) in acetone (45 ml) containing anhydrous magnesium sulfate (4 g) was oxidized with 8 N chromium trioxide in sulfuric acid (3.0 ml) at 0° during 25 min. The reaction mixture was processed as described below and afforded 18-methylprogesterone (**7a**, 1.3 g): mp 169–171°; $[\alpha]_D$ +204°; λ_{max} 242 mμ (log ϵ 4.20); ν_{max} 1700, 1670, and 1610 cm^{-1}; ORD, $[\phi]_{600}$ +640°, $[\phi]_{400}$ +1900°, $[\phi]_{378}$ +2100°, $[\phi]_{366}$ +1700°, $[\phi]_{356}$ +2300°, $[\phi]_{351}$ +2100°, $[\phi]_{304}$ +13,700°, $[\phi]_{273}$ +2050° (c 0.1, dioxane); nmr, 40.5 (J = 7 cps) (18-methyl H), 70.5 (19-H), 131 (21-H), and 344 cps (multiplet for 4-H).

Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.83; O, 9.74. Found: C, 80.40; H, 9.79; O, 9.94.

18-Methylpregn-5-ene-3β,20β-diol 3-Acetate (3b).—The diol **3a** (300 mg) was acetylated with acetic anhydride (3 ml) in pyridine (7 ml) at 25° during 20 min to give a crude product which was filtered through alumina (30 g) in benzene solution. This yielded 150 mg of the 3-monoacetate **3b** (80% purity by tlc), which was purified by crystallization from acetone–hexane: mp 175–175.5°; $[\alpha]_D$ −78°; ν_{max} 3570, 1730, 1260, and 1030 cm^{-1}; nmr, 60 (19-H), 67 (J = 7 cps) (21-H), 121 (3-acetoxy H), 225 (broad multiplet for 20-H), 275 (broad multiplet for 3-H), and 323 cps (multiplet for 6-H).

Anal. Calcd for $C_{24}H_{38}O_3$: C, 76.96; H, 10.23; O, 12.82. Found: C, 77.20; H, 10.00; O, 12.92.

3β-Hydroxy-18-methylpregn-5-en-20-one Acetate (5).—The diol monoacetate **3b** (246 mg) was dissolved in acetone (15 ml) containing anhydrous magnesium sulfate (1 g), and the mixture was cooled to 0°. Chromium trioxide (8 N) in sulfuric acid (0.7 ml) was added during 10 min after which time the mixture was stirred for 2 min and the excess of oxidant destroyed by 2-propanol. The crude product was isolated by extraction with ether dissolved in benzene and filtered through alumina (30 g). The resultant keto acetate **5** crystallized from methanol as prisms (163 mg): mp 128–130°; $[\alpha]_D$ +20°; ν_{max} 1730, 1705, 1240, and 1025 cm^{-1}; ORD, $[\phi]_{600}$ ±0°, $[\phi]_{400}$ +420°, $[\phi]_{330}$ +4100°, $[\phi]_{316}$ +7300°, $[\phi]_{313}$ +7200°, $[\phi]_{309}$ +7250°, $[\phi]_{296}$ ±0°, $[\phi]_{268}$ −11,800°, $[\phi]_{237}$ −9900°, $[\phi]_{214}$ −12,500° (c 0.1, dioxane); nmr, 39.5 (J = 7 cps) (18-methyl H), 60.5 (19-H), 121 (3-acetoxy H), 132 (21-H), 275 (broad multiplet for 3-H), and 323 cps (multiplet for 6-H).

Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.37; H, 9.74; O, 12.88. Found: C, 77.28; H, 9.75; O, 13.02.

Oppenauer Oxidation of 3β,20β-Dihydroxy-18-methylpregn-5-en-18-one (2a).—A solution of the keto diol **2a** (1.62 g) in toluene (35 ml) containing cyclohexanone (4 ml) was boiled until 10 ml of distillate was collected. Cyclohexanone (2.5 ml) and aluminum isopropoxide (800 mg) were added, and the resulting mixture was heated under reflux for 15 min and processed as described previously to give 20β-hydroxy-18-methylpregn-4-ene-3,18-dione (**4c**) as prisms (980 mg) from acetone–hexane: mp 159–160°; $[\alpha]_D$ +93°; λ_{max} 242 mμ (log ϵ 4.18); ν_{max} 3480, 1700, 1670, and 1615 cm^{-1}; ORD, $[\phi]_{600}$ +270°, $[\phi]_{400}$ +620°, $[\phi]_{365}$ −140°, $[\phi]_{358}$ +100°, $[\phi]_{351}$ −280°, $[\phi]_{340}$ +1700°, $[\phi]_{325}$ +4400° (c 0.1, dioxane); nmr, 65 (19-H), 70 (J = 7 cps) (21-H), 140.5 (18-methyl H), 212 (broad multiplet for 20-H), and 344 cps (multiplet for 4-H).

Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.68; H, 9.57.

18-Methylpregn-4-ene-3,18,20-trione (6).—The hydroxy diketone **4c** (2.2 g) in acetone (50 ml) was oxidized, as before, by 8 N chromium trioxide–sulfuric acid to give a crude product which was dissolved in ethyl acetate–hexane (3:1) and filtered through a column of silica gel (120 g). This afforded the triketone **6** (1.4 g), which formed prisms from acetone–hexane: mp 158–159.5°; $[\alpha]_D$ +189°; λ_{max} 240 mμ (log ϵ 4.14); ν_{max} 1700, 1670, and 1610 cm^{-1}; ORD, $[\phi]_{600}$ +450°, $[\phi]_{500}$ +800°, $[\phi]_{400}$ +1330°, $[\phi]_{386}$ +1400°, $[\phi]_{367}$ +750°, $[\phi]_{359}$ +1110°, $[\phi]_{352}$ +710°, $[\phi]_{341}$ +3540° (c 0.1, dioxane); nmr, 66 (19-H), 125 and 130.5 (18-methyl H and 21-H), and 345 cps (multiplet for 4-H).

Anal. Calcd for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83; O, 14.02. Found: C, 77.29; H, 8.82; O, 14.22.

3-Ethoxy-18-methylpregna-3,5-dien-20-one (8a).—18-Methylprogesterone (**7a**, 1.06 g) in dioxane (10 ml) was stirred with ethyl orthoformate (1.0 ml) and *p*-toluenesulfonic acid (50 mg), in the presence of Drierite, at 25° for 2.5 hr. The mixture was poured into aqueous potassium bicarbonate and extracted with ether. The ether solution was dried over sodium sulfate and evaporated in the presence of a trace of pyridine. The resultant orange gum was dissolved in hexane–benzene (4:1) and filtered through alumina (50 g) to give the enol ether **8a** (910 mg), which crystallized as plates from methanol containing a trace of pyridine: mp 98–101°; $[\alpha]_D$ −42°; λ_{max} 241 mμ (log ε 4.29); ν_{max} 1705, 1655, 1630, and 1180 cm^{-1}; nmr, 40 (J = 7 cps) (18-methyl H), 58 (19-H), 77 (J = 7 cps) (CH_3–CH_2–O), 132 (21-H), 227 (J = 7 cps) (CH_3–CH_2–O), and 310 cps (broad multiplet for 4-H and 6-H).

Anal. Calcd for $C_{24}H_{36}O_2$: C, 80.85; H, 10.18; O, 8.98. Found: C, 81.02; H, 10.08; O, 9.13.

3-Ethoxy-17α-hydroperoxy-18-methylpregn-3,5-dien-20-one (8b).—The enol ether **8a** (500 mg) in tetrahydrofuran (5 ml) was added to 1 *N* potassium *t*-butoxide in *t*-butyl alcohol (15 ml), and the resulting solution was shaken at 0° under an atmosphere of oxygen. The uptake of oxygen ceased at 35 ml after 15 min. The solution was neutralized to pH 7 by 1 *N* acetic acid and extracted with ethyl acetate, and the organic layer was washed with water, dried (Na_2SO_4), and evaporated at 30° to yield a crystalline solid. Crystallization from acetone–water gave the 17α-hydroperoxide **8b** (87 mg): mp 127–129°; $[\alpha]_D$ −79°; λ_{max} 243 mμ (log ε 4.24); ν_{max} 3460, 1715, 1655, 1630, and 1170 cm^{-1}.

Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34; O, 16.47. Found: C, 74.10; H, 9.24; O, 16.44.

17α-Hydroxy-18-methylprogesterone (7b).—The crude hydroperoxide **8b** (3.1 g) in acetic acid (100 ml) was stirred with zinc dust (6 g) at 25° during 12 hr. The mixture was filtered and the residue was washed with ether. The filtrate was diluted with ether, washed with water and saturated sodium bicarbonate solution, dried (Na_2SO_4), and evaporated to leave a colorless crystalline mass (3.0 g) containing *ca.* 60% (by tlc) of the required hydroxy diketone. Purification by means of preparative tlc[37] on HF silica gel with chloroform–methanol (9:1) afforded 17α-hydroxy-18-methylprogesterone **7b** (1.6 g), which crystallized from acetone-hexane as prisms: mp 230–232° $[\alpha]_D$ +85°; λ_{max} 241 mμ (log ε 4.22); ν_{max} 3490, 1705, 1660, and 1615 cm^{-1}; ORD, $[\phi]_{589}$ +410°, $[\phi]_{378}$ +1130°, $[\phi]_{365}$ +650°, $[\phi]_{358}$ +1060°, $[\phi]_{352}$ +960°, $[\phi]_{316}$ +10,600°, $[\phi]_{285}$ +520° (*c* 0.1, dioxane); nmr, 39.5 (J = 7 cps) (18-methyl-H), 70.5 (19-H), 138.5 (21-H), 181.5 (O*H*), and 345 cps (multiplet for 4-H).

Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36; O, 13.93. Found: C, 76.75; H, 9.45; O, 14.02.

17α-Hydroxy-18-methylprogesterone Acetate (7c).—17α-Hydroxy-18-methylprogesterone (**7b**, 950 mg) was treated with *p*-toluenesulfonic acid (50 mg) in acetic anhydride (5 ml) at 100° for 1 hr and subsequently at 25° for 15 hr. The mixture was poured into aqueous potassium bicarbonate and extracted with ether. The organic layer was washed with sodium bicarbonate solution, dried (Na_2SO_4), and evaporated to leave an orange gum. A solution of this crude product in dioxane (20 ml) was treated with 2 *N* hydrochloric acid (5 ml) and heated under reflux for 1 hr. The solution was diluted with water and extracted with ether to give a product which was subjected to preparative tlc on HF silica gel in chloroform–methanol (100:1). The required acetate **7c** (600 mg) was recrystallized from acetone–hexane as plates: mp 218–220°; $[\alpha]_D$ +65°; λ_{max} 240 mμ (log ε 4.20); ν_{max} 1735, 1715, 1675, 1620, and 1255 cm^{-1}; nmr, 40.5 (J = 7 cps) (18-methyl-H), 71.5 (19-H), 126 and 127 (21-H and 17-acetoxy-H), and 345 cps (multiplet for 4-H).

Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87; O, 16.56. Found: C, 74.47; H, 8.71; O, 16.72.

21-Hydroxy-18-methylpregn-4-ene-3,20-dione 21-Acetate (7d).—18-Methylprogesterone (**7a**, 870 mg) in methanol (4 ml) and peroxidic tetrahydrofuran (peroxide content, 0.1 iodine equiv/l.; 7 ml) was stirred with calcium oxide (1.2 g) and iodine (1.2 g) at 25° for 2.5 hr. The mixture was diluted with dichloromethane and filtered. The filtrate was washed with four 50-ml portions of 5% sodium thiosulfate solution and water, dried (Na_2SO_4), and evaporated at 30° to leave an orange gum. This product was heated, under reflux, with anhydrous potassium acetate (1.5 g) in acetone (15 ml) during 20 hr. The mixture was evaporated at 30° and extracted with dichloromethane, the organic layer was washed with water, dried (Na_2SO_4), and evaporated to afford an orange gum which was heated under reflux in methanol (20 ml) with sodium metabisulfite (500 mg) in water (8 ml) for 1 hr. The solvents were removed *in vacuo* and the residue was extracted with dichloromethane. The organic layer was washed with water, dried (Na_2SO_4), and evaporated to give a crude product which was subjected to preparative tlc on GF silica gel in ethyl acetate–hexane (1:1) to afford the required 21-acetate **7d** (316 mg), which crystallized from acetone-hexane as plates: mp 174–175°; $[\alpha]_D$ +187°; λ_{max} 240 mμ (log ε 4.23); ν_{max} 1750, 1720, 1670, 1620, 1235, and 1070 cm^{-1}; nmr, 40.5 (J = 7 cps) (18-methyl H), 71 (19-H), 130 (21-acetoxy H), 285.5 (21-H), and 346 cps (multiplet for 4-H).

Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87; O, 16.56. Found: C, 74.38; H, 8.85; O, 16.72.

17α,21-Dihydroxy-18-methylpregn-4-ene-3,20-dione 21-Acetate (7e).—17α-Hydroxy-18-methylprogesterone (**7b**, 1.0 g) was subjected to the iodination reaction and potassium acetate treatment as described above for 18-methylprogesterone (**7a**). The resultant mixture (1.0 g) was resolved by preparative tlc on HF silica gel in chloroform–methanol (19:1) to give the corresponding 21-acetate **7e** (650 mg), which crystallized from acetone–hexane as stout needles: mp 186–188°; $[\alpha]_D$ +138°; λ_{max} 242 mμ (log ε 4.20); ν_{max} 3360, 1760, 1725, 1650, 1610, and 1230 cm^{-1}; nmr, 38 (J = 7 cps) (18-methyl H), 70.5 (19-H), 129.5 (21-acetoxy H), 193 (O*H*), 278, 296, 316, 334 (21-H), and 345 cps (multiplet for 4-H).

Anal. Calcd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51; O, 19.88. Found: C, 71.54; H, 8.48; O, 20.03.

3β-Hydroxy-18-methylandrost-4-en-17-one (9b).—A solution of 17α-hydroxy-18-methylprogesterone (**7b**, 4.0 g) in dry tetrahydrofuran (200 ml) was stirred with lithium tri-*t*-butoxyaluminum hydride (20 g) at 0° during 7 hr and at 25° for a further 15 hr. Water was added and the mixture was concentrated to a small volume *in vacuo*. The residue was extracted with ethyl acetate, and the organic layer was washed with water and saturated sodium bicarbonate solution, dried (Na_2SO_4), and evaporated to leave a pale yellow gum. This product in acetic acid (200 ml) was allowed to react with lead tetraacetate (12 g) at 25° with stirring during 1.3 hr. Ethylene glycol (20 ml) was then added to destroy the excess of oxidant; the solution was diluted with water and extracted by ethyl acetate. The organic layer was washed with water and saturated sodium bicarbonate solution, dried (Na_2SO_4), and evaporated to afford a semisolid mass (3.7 g) which was dissolved in hexane–benzene (1:1) and adsorbed on alumina (150 g). Elution with the same solvent and with benzene afforded intractable gums. Elution with benzene–ether (19:1) afforded 3β-hydroxy-18-methylandrost-4-en-17-one (**9b**, 2.3 g), which crystallized from acetone–hexane as plates: mp 138–141°; $[\alpha]_D$ +98°; no intense ultraviolet absorption above 230 mμ; ν_{max} 3470 and 1730 cm^{-1}; nmr, 47 (J = 7 cps) (18-methyl-H), 64 (19-H), 123.5 (O*H*), 250 (broad multiplet for 3-H), and 320 cps (multiplet for 4-H).

Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00; O, 10.58. Found: C, 79.53; H, 10.08; O, 10.72.

18-Methylandrost-4-ene-3β,17β-diol (9c).—The hydroxy ketone **9b** (250 mg) in tetrahydrofuran (13 ml) was reduced by lithium tri-*t*-butoxyaluminum hydride (650 mg) with stirring at 25° during 2 hr. Isolation by extraction with ether afforded the required diol **9c**, which crystallized from acetone–hexane as prisms (168 mg): mp 168°; $[\alpha]_D$ +56°; ν_{max} 3400 and 1055 cm^{-1}; nmr (in DMSO-d_6), 18-methyl-H resonance not resolved, 58.5 (19-H), 235 (broad multiplet for 3-H), 263, 268, 275 (overlapping doublets for two O*H* groups), and 312 cps (multiplet for 4-H).

Anal. Calcd for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59; O, 10.51. Found: C, 79.05; H, 10.81; O, 10.35.

18-Methyltestosterone (10a).—The diol **9c** (170 mg) in anhydrous dioxane (5 ml) was oxidized with DDQ (200 mg) at 25° during 2.5 hr and the mixture was kept at 0° for 15 hr. The reaction mixture was diluted with dichloromethane (40 ml) and adsorbed on alumina (50 g). Elution with ether afforded a yellow crystalline solid (118 mg), which was purified by preparative tlc on HF silica gel in chloroform–methanol (30:1). This provided 18-methyltestosterone (110 mg), which crystal-

(37) Preparative tlc was conducted using silica gels GF and HF (from Brinkmann Instruments Inc., New York, N. Y.) at thicknesses of 0.25 and 1.3 mm and steroid loadings of 1 and 6 mg/cm, respectively.

lized from acetone–hexane as needles: double mp 174–175, 182–184°; $[\alpha]D$ +85°; λ_{max} 241 mμ (log ε 4.21); ν_{max} 3370, 1680, 1615, and 1060 cm^{-1}; nmr, 62 (J = 6 cps) (18-methyl H), 71 (19-H), 129.5 (OH), 225 (broad multiplet for 17-H), and 344 cps (multiplet for 4-H).

Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00; O, 10.58. Found: C, 79.50; H, 10.16; O, 10.63.

17α-Ethynyl-18-methylandrost-4-ene-3β,17β-diol (**9d**).—A solution of 3β-hydroxy-18-methylandrost-4-en-17-one (**9b**, 980 mg) in dichloromethane (5 ml) and ether (20 ml) was added to a solution of potassium acetylide (from 390 mg of potassium) in liquid ammonia (100 ml). The mixture was stirred for 6 hr, ammonium chloride (800 mg) was added, and the ammonia was allowed to evaporate overnight. The residue was extracted with dichloromethane and water and the organic layer was washed with water, dried (Na_2SO_4), and evaporated to give a pale yellow solid which contained *ca.* 30% of starting material by tlc. The crude product was adsorbed on alumina (100 g), and elution with benzene–ether (4:1 and 1:1) afforded a mixture of the ethynyldiol **9d** and the unchanged hydroxy ketone **9b** (*ca.* 2.5:1, 900 mg) from which the ethynyldiol **9d** was isolated by crystallization from acetone–hexane as prisms: mp 190–191°; $[\alpha]D$ −4°; ν_{max} 3540, 3460, 3270, and 1055 cm^{-1}; nmr (in pyridine-d_5), 62 (19-H), 197 (ethynyl H), 280 (broad multiplet for 3-H), and 341 cps (multiplet for 4-H).

Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.83; O, 9.74. Found: C, 80.75; H, 9.96; O, 9.65.

17α-Ethynyl-17β-hydroxy-18-methylandrost-4-en-3-one (**10b**).—A mixture (800 mg) containing the crude ethynyldiol **9d** (70%) and the hydroxy ketone **9b** in dioxane (25 ml) was oxidized by DDQ (1.0 g) with stirring at 25° for 5.5 hr. The reaction mixture was worked up through dichloromethane to give a crude product (810 mg), which was subjected to preparative tlc on GF silica gel in chloroform–methanol (100:1). 17α-Ethynyl-17β-hydroxy-18-methylandrost-4-en-3-one (**10b**, 420 mg) was thereby obtained and crystallized from acetone–hexane as prisms: mp 242–244°; $[\alpha]D$ +27°; λ_{max} 243 mμ (log ε 4.20); ν_{max} 3370, 3290, 1655, 1610, and 1065 cm^{-1}; nmr (in DMSO-d_6), 56.5 (J = 6 cps) (18-methyl H), 68 (19-H), 194.5 (ethynyl H), 313 (OH), and 338 cps (multiplet for 4-H).

Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26; O, 9.80. Found: C, 80.84; H, 9.17; O, 9.66.

The ORD of 3β-hydroxypregn-5-en-20-one acetate was $[\phi]_{600}$ ±0°, $[\phi]_{400}$ +350°, $[\phi]_{330}$ +3400°, $[\phi]_{316}$ +6200°, $[\phi]_{311}$ +6100°, $[\phi]_{309}$ +6150°, $[\phi]_{296}$ ±0°, $[\phi]_{269}$ −10,200°, $[\phi]_{237}$ −8400°, and $[\phi]_{215}$ −10,800° (*c* 0.1, dioxane).

The ORD of 17α-hydroxyprogesterone was $[\phi]_{589}$ +440°, $[\phi]_{378}$ +1020°, $[\phi]_{365}$ +530°, $[\phi]_{358}$ +1020°, $[\phi]_{352}$ +960°, $[\phi]_{316}$ +10,800°, and $[\phi]_{285}$ +1420° (*c* 0.1, dioxane).

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Carboxylation of β-Dicarbonyl Compounds through Dicarbanions. Cyclizations to 4-Hydroxy-2-pyrones[1]

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Six β-diketones and 2-acetyl-1-napthol were converted to disodio salts by treatment with excess sodium amide. Suspensions of the disodio salts in ether were treated with carbon dioxide to afford the corresponding terminal carboxylic acids in yields of 31–74%. The acids were cyclized by means of liquid hydrogen fluoride to the corresponding 4-hydroxy-2-pyrones in excellent yields. Carboxylation of ethyl dipotassioacetoacetate afforded acetonedicarboxylic acid monoethyl ester. Diketo acids have previously been postulated to be precursors of certain aromatic natural products; the efficient syntheses of these acids and the related 4-hydroxy-2-pyrones provide a basis for future investigation of the metabolism of these compounds.

Treatment of β-dicarbonyl compounds with 2 equiv of an alkali amide affords the corresponding dicarbanions, which undergo condensations selectively at the γ position. By this method many β-diketones, β-keto esters, and β-ketoaldehydes have been condensed with alkyl halides, aldehydes, ketones, and esters.[2] However, no systematic study has been made of the reaction of dicarbanions of dicarbonyl compounds with carbon dioxide to form the corresponding carboxylic acids; only two examples have been reported.[2a,3] The carboxylation of benzoylacetone (**1a**) is one of these (see Scheme I).

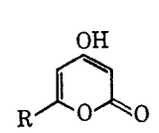
This paper reports more thorough studies that have been made of the carboxylation reaction to form these acids and of the cyclization of the diketo acids **2a–f** to 4-hydroxy-2-pyrones (**3a–f**). Certain of these dicarbonyl acids are of interest in investigations of the biosynthesis of phenolic compounds.

SCHEME I

$$RCOCH_2COCH_3 \xrightarrow[\text{liq } NH_3]{NH_2^-} RCO\bar{C}HCO\bar{C}H_2 \xrightarrow[2.\ H^+]{1.\ CO_2,\ \text{ether}} RCOCH_2COCH_2CO_2H$$

1a, R = C_6H_5	**2a**, R = C_6H_5
b, R = CH_3	**b**, R = CH_3
c, R = $C_6H_5CH_2CH_2$	**c**, R = $C_6H_5CH_2CH_2$
d, R = $(CH_3)_2CHCH_2$	**d**, R = $(CH_3)_2CHCH_2$
e, R = $C_6H_5CH{=}CH$	**e**, R = $C_6H_5CH{=}CH$
f, R = $(C_6H_5)_2C{=}CH$	**f**, R = $(C_6H_5)_2C{=}CH$
g, R = H	**g**, R = H
h, R = C_2H_5O	**h**, R = C_2H_5O

Initially a short search was made with diketone **1a** for preferred conditions to effect the carboxylation reaction (Table I). Sodium amide afforded a significantly better yield of keto acid **2a** than had potassium



3a, R = C_6H_5
b, R = CH_3
c, R = $C_6H_5CH_2CH_2$
d, R = $(CH_3)_2CHCH_3$
e, R = $C_6H_5CH{=}CH$
f, R = $(C_6H_5)_2C{=}CH$
g, R = H

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(2) For examples see (a) C. R. Hauser and T. M. Harris, *J. Am. Chem. Soc.*, **80**, 6360 (1958); (b) J. F. Wolfe, T. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **29**, 3249 (1964); (c) T. M. Harris and C. R. Hauser, *J. Am. Chem. Soc.*, **84**, 1750 (1962).

(3) W. I. O'Sullivan and C. R. Hauser, *J. Org. Chem.*, **25**, 1110 (1960).