Addition of Alkyl Vinyl Ethers to Δ^{16}-20-Keto Steroids. III

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Received June 9, 1964

Reaction of the pentacyclic dihydropyrans, formed by the addition of methyl vinyl ether to Δ^{16}-20-keto steroids, with N-bromosuccinimide and acid has led to 17β-bromo-17-isopregnan-16α-acetaldehyde derivatives. Internal cyclization of these bromoaldehydes with lithium bromide–lithium carbonate–dimethylformamide afforded a dihydrofuran (*e.g.*, **5**). Selective cleavage of the double bond of the dihydrofuran gave the 16α-formyl-17α-hydroxy system, which was converted to the novel 16α-cyano-17α-hydroxy and 16α-hydroxymethyl-17α-hydroxy steroids. Reaction of the primary 16a-alcohol (**11**) with *p*-toluenesulfonyl chloride led to the corresponding tosylate (**12**), which, when treated with base, produced the 16,17-oxetane (**13**).

Two principal methods exist for the elaboration of the 17α,21-dihydroxy 20-ketone system, characteristic of cortical steroids, from the more accessible nonhydroxylated 20-oxopregnanes; these are, first, modifications of the Gallagher approach involving a 17(20)-enol derivative,[1] and the synthesis which employs a Favorskiĭ rearrangement leading to $\Delta^{17(20)}$-pregnen-21-oic analogs.[2] Both methods have been applied to the synthesis of the biologically significant 16α-methyl corticoids.[3] Application of the Favorskiĭ sequence under the usual conditions[2] was notably less efficient in the case of both 16α-methyl[4] and 16α-fluoromethyl[5] steroids; with other 16α-substituted 20-oxopregnanes, such as 16α-cyano derivatives, formed by nucleophilic addition to Δ^{16}-20-ketones, the Favorskiĭ rearrangement did not proceed as in the unsubstituted examples.[6] Also the use of basic conditions for this sequence limits the range of derivatives at C-16 which would be stable. The forcing conditions which are required to prepare 16α-substituted $\Delta^{17(20)}$-enol derivatives also limit the type of compounds to which the Gallagher approach can be applied; for example, with a 16α-chloromethyl derivative[7] the formation of the enol acetate requires refluxing in acetic anhydride; acetyl bromide and the enol acetate is not conveniently formed with acetic anhydride–*p*-toluenesulfonic acid, acetic anhydride–perchloric acid, or acetic anhydride–acetyl chloride.[8] One variation of the Gallagher approach, which avoids this problem, is to make use of the intermediate 17(20)-enol Grignard complex, formed for example in the addition of methylmagnesium bromide to a Δ^{16}-20-ketone[9]; this limits the groups which can be introduced at C-16 to those capable of undergoing a 1,4-Grignard addition. Clearly then, alternative methods would be advisable to avoid these limitations.

The addition of methyl vinyl ether to Δ^{16}-20-keto steroids[10] and some further transformations of the resulting pentacyclic dihydropyrans have been described.[11] Hydroxylation of the 17(20)-double bond in these adducts with osmium tetroxide led to 17α-hydroxy-16α-substituted derivatives; the yields of the conversion products were disappointing, partly because of attack by the hydroxylation reagent on other unsaturated functions in the molecule.[11] Alternative transformations of these enol ethers were therefore investigated. Reaction of the adduct **1**,[10] from 6α-methyl-16-dehydroprogesterone, with N-bromoacetamide (or N-bromosuccinimide) in the presence of perchloric acid or buffered acetic acid, gave a crystalline bromoaldehyde **2** (Scheme I). The positive Cotton effect[12] in the optical rotatory dispersion curve of this compound was surprising since the 17α-bromo 20-ketones prepared from 17(20)-enol acetates have been reported to exhibit a negative Cotton effect curve.[13] Also in the n.m.r. spectrum[14] of **2** the absorption peak of the 18-H of the angular methyl group was at 76 c.p.s.; this large downfield shift from the basic C-18 hydrogen frequency at 39 c.p.s.[10,11] is best explained by a 17β-bromo-17α-acetyl structure; 17α-bromo 20-ketones show a +9-c.p.s. shift of the C-18 methyl, and 17-iso compounds have a +17-c.p.s. effect on the basic absorption frequency.[11] Ths stereochemical assignment is in better accord with the later transformations described below, and suggests that the introduction of a 17-bromo substituent inverts the sign of the Cotton effect curve in both 17α- and 17β-acetyl structures. The formation of these bromoaldehydes by the action of N-bromosuccinimide involves a preferential β-side attack, necessitated by the bulky 16α-substituent.

Oxidation of the aldehyde **2** with the chromium trioxide–pyridine complex[15] gave the corresponding acid which was esterified with diazomethane to methyl ester **3**. Attempted dehydrobromination of **3** with lithium bromide–lithium carbonate–dimethylformamide[16] for 1 hr. at 120° proved to be difficult and gave mainly recovered starting material. The difficulty of

(1) (a) T. H. Kritchevsky and T. F. Gallagher, *J. Am. Chem. Soc.*, **73**, 184 (1951); (b) B. A. Koechlin, T. H. Kritchevsky, and T. F. Gallagher, *ibid.*, **73**, 189 (1951).

(2) J. A. Hogg, P. F. Beal, A. H. Nathan, F. H. Lincoln, W. P. Schneider, B. J. Magerlein, A. R. Hanze, and R. W. Jackson, *ibid.*, **77**, 4436 (1955).

(3) For a recent review of the properties of 16-substituted corticoids, see L. H. Sarett, A. A. Patchett, and S. L. Steelman, "Progress in Drug Research," Vol. 5, E. Jucker, Ed., Birkaeuser Verlag, Basel, 1963, p. 92, *et seq.*

(4) Private communication from F. H. Lincoln of these laboratories.

(5) P. F. Beal and J. E. Pike, *J. Org. Chem.*, **26**, 3887 (1961).

(6) Unpublished observations by the author.

(7) (a) E. Kaspar and R. Wiechert, *Chem. Ber.*, **91**, 2664 (1958); U. Kerb, E. Kaspar, and R. Wiechert, *Naturwissenschaften*, **49**, 232 (1962).

(8) U. Kerb, E. Kaspar, and R. Wiechert (to Schering AG), German Patent 1,117,119 (1961); *Chem. Abstr.*, **56**, 8808 (1962).

(9) K. Heusler, J. Kebrle, C. Meystre, H. Ueberwasser, P. Wieland, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **42**, 2043 (1959).

(10) J. E. Pike, M. A. Rebenstorf, G. Slomp, and F. A. Mackellar, *J. Org. Chem.*, **28**, 2499 (1963).

(11) Paper II of this series: J. E. Pike, G. Slomp, and F. A. MacKellar, *ibid.*, **28**, 2502 (1963).

(12) See C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960.

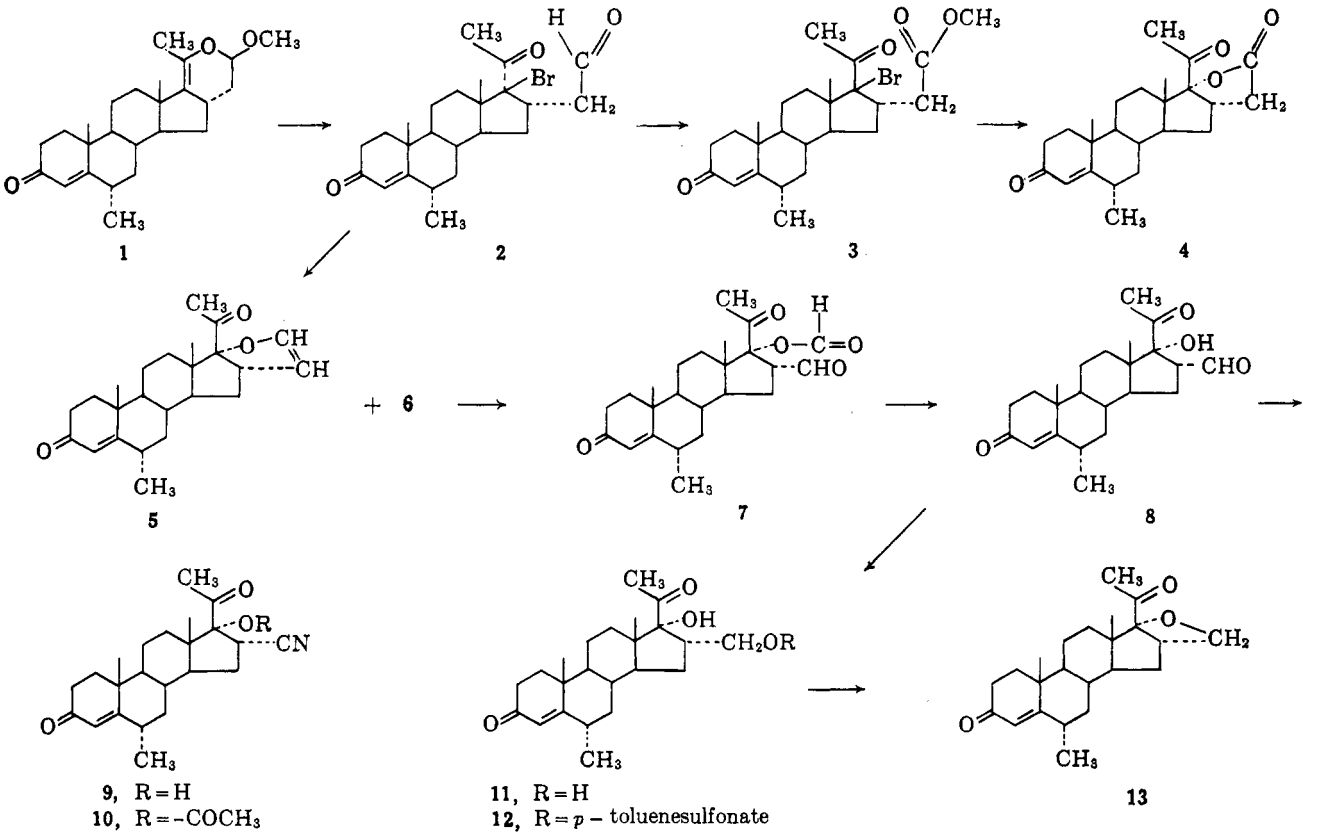
(13) C. Djerassi, I. Fornaguera, and O. Mancera, *J. Am. Chem. Soc.*, **81**, 2383 (1959).

(14) N.m.r. spectra were obtained and analyzed by Dr. G. Slomp and F. A. MacKellar with a Varian DP-60 or A-60 spectrometer operating at 60 Mc. DP-60 spectra were observed on *ca.* 0.15 *M* solutions (generally, unless otherwise indicated in deuteriochloroform) and these spectra were calibrated against internal tetramethylsilane using the audiofrequency sideband technique. Frequencies are reported in cycles per second downfield from tetramethylsilane. The A-60 spectra were run on 0.25 *M* solutions.

(15) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

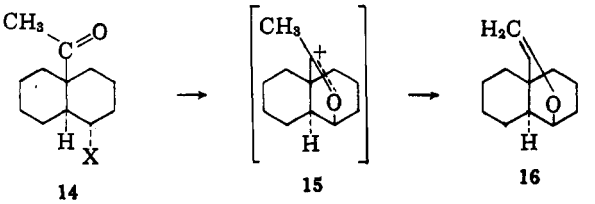
(16) R. Joly, J. Warnant, G. Nomine, and D. Bertin, *Bull. soc. chim. France*, **35**, 366 (1958).

SCHEME I

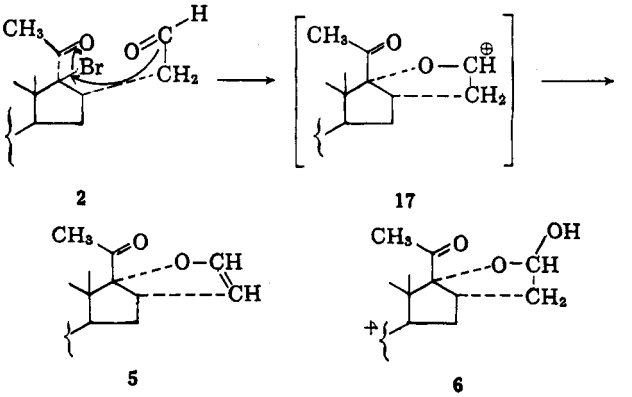


dehydrobromination to give a 16,17-double bond would seem to be due to the *cis* relationship of the 16β-H and the 17β-bromo groups and lends support to the structural assignment to **2**. Analysis of the crude dehydrobromination product by thin layer chromatography showed a very minor, more polar component in addition to the starting material. The infrared spectrum of the crude product showed a minor peak at 1775 cm.$^{-1}$ suggesting the possibility that a lactone was the polar component. Repetition of the transformation for an 18-hr. reaction period then gave as the main product the lactone **4** with the same structure as the type of lactone isolated from the hydroxylation studies.[11] It is worth emphasizing again the value of routine analysis of crude reaction mixtures (as in this case by t.l.c. and infrared spectroscopy), not only to follow a known reaction path, but also to enable the definition of conditions for an unexpected reaction.

These dehydrobromination conditions were then applied to the bromoaldehyde **2**. After chromatography of the total reaction product on Florisil, two main products were obtained. The main, less polar product is formulated as the dihydrofuran **5**. Two features of the n.m.r. spectrum confirmed the other analytical data in supporting this structure. First, the position of the C-18 hydrogen absorption was at 46 c.p.s. suggesting a normal 17β-acetyl configuration,[10,11] and second the presence of the very characteristic n.m.r. absorption peaks associated with the two protons of the dihydrofuran ring.[17] The second, more polar product is the lactol **6** of the type described earlier.[11] This reaction is closely related to the unusual neighboring group effect observed in the case of 10-acetyl-1α-halogeno-*trans*-decalin[18] (**14**), which under solvolysis conditions gives



16. It was suggested[18] that the rate-determining step was the formation of the cation **15** which could take certain reaction courses, one of which was proton abstraction to give the vinyl ether **16**. A similar neigh-



(17) See L. M. Jackman, "Nuclear Magnetic Resonance Spectroscopy," Pergamon Press, London, 1959, p. 62. The 2-H of dihydrofuran is reported to absorb in the n.m.r. spectrum at τ 3.77 and the 3-H at 5.14 in good agreement with the absorption of the two protons of **5** (see Experimental section).

(18) G. Baddeley, E. K. Baylis, B. G. Heaton, and J. W. Rasburn, *Proc. Chem. Soc.*, 451 (1961); see also M. S. Ahmad, G. Baddeley, B. G. Heaton, and J. W. Rasburn, *ibid.*, 395 (1959), and J. R. Holum, D. Jorenby, and P. Mattison, *J. Org. Chem.*, **29**, 769 (1964).

boring group effect would lead *via* the hypothetical intermediate cation **17** both to the dihydrofuran **5** and to the lactol **6**; the formation of the lactone **4** would be similarly explained. If the bromoaldehyde **2** had the alternative 17α-bromo-17β-acetyl configuration, the reaction would be hard to explain in stereochemical terms.

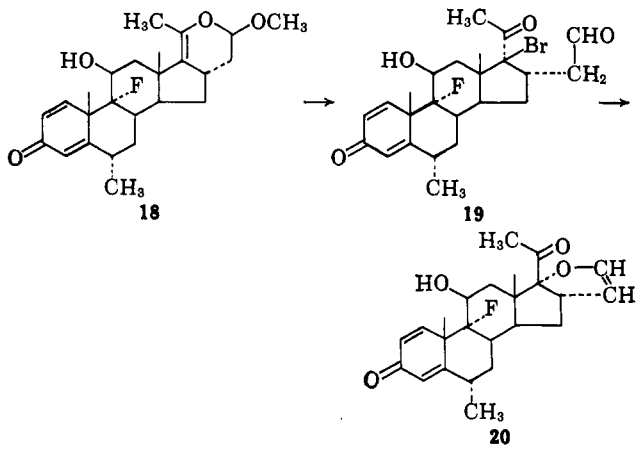
Hydroxylation of the enol ether double bond in **5** with osmium tetroxide gave in high yield a crystalline diol which could be cleaved with lead tetraacetate. Chromatography of the product over Florisil gave the 17α-hydroxy-16α-formyl compound (**8**), hydrolysis of the expected 17α-formate occurring during the chromatography; direct crystallization of the lead tetraacetate cleavage product gave the 17α-hydroxy-16α-formyl-17-formate (**7**). Reaction of the dihydrofuran **5** with a catalytic amount of osmium tetroxide and 2 equiv. of sodium periodate[19] gave the 17α-hydroxy-16α-formyl compound (**8**) directly.

This aldehyde (**8**) proved to be a versatile intermediate for the preparation of many 16α-carbon-substituted derivatives. Reaction of **8** with O,N-bistrifluoroacetylhydroxylamine[20] gave the corresponding 16α-cyano steroid **9** isolated in high yield by direct crystallization from the reaction mixture. This was readily converted to the corresponding 17-acetate (**10**) by the action of acetic anhydride and an acid catalyst followed by mild hydrolysis. Selective reduction of the aldehyde was effected by the action of 1 equiv. of sodium borohydride at 0° for 5 min. to give the 16α-hydroxymethyl intermediate (**11**).

Conversion of this primary alcohol **11** to the corresponding *p*-toluenesulfonate (**12**), followed by treatment with base,[21] gave the oxetane **13**. The n.m.r. spectrum of **13** provided additional confirmation of the four-membered cyclic structure.[22] The 16-H appeared as a broad multiplet centered at 198 c.p.s.; the two 16a-hydrogens appeared one as a triplet centered at 278 c.p.s. and the other as a doublet of doublets centered at 234 c.p.s.

A close analogy for this n.m.r. pattern is the 2-methyl-1-oxobicyclo[2.2.0]hexane studied by Srinivasan[22d] where the peak for the HC—C< was assigned as a broad multiplet at 171 c.p.s., and the —O—C<H/H hydrogen peaks were multiplets at 295 c.p.s. (τ 5.09) and 263 (5.61). A similar steroidal 16,17-oxetane has been described by Kerb and Wiechert, and was prepared by base treatment of a 16α-chloromethyl-17α-hydroxy steroid.[23]

The selectivity of the general procedure was investigated by applying the sequence to a 9α-fluoro-11β-hydroxy-$\Delta^{1,4}$-3-keto steroid. Reaction of the dihydropyran **18** with N-bromosuccinimide–acetic acid gave the bromoaldehyde **19**. Treatment of **19** with lithium bromide–lithium carbonate–dimethylformamide gave as before the dihydrofuran **20**. This method appears therefore to be generally applicable in the presence of a variety of other functional groups.



Experimental[24]

17β-Bromo-6α-methyl-3,20-dioxo-17-isopregn-4-en-16α-acetaldehyde (2).—A solution of N-bromoacetamide (13.2 g.) in 240 ml. of *t*-butyl alcohol was added rapidly with stirring to a solution of 24.0 g. of 16α-ethyl-16b-methoxy-6α-methyl-16b,20-oxidopregna-4,17(20)-dien-3-one in 800 ml. of methylene chloride and 1080 ml. of *t*-butyl alcohol; the temperature was maintained at +2°. Then a solution of 20% perchloric acid (68.0 ml.) and 360 ml. of water was added dropwise over 20 min. keeping the temperature below +5°. After the addition, the mixture was stirred for a further 20 min. and then a solution of 13.2 g. of sodium sulphite in 200 ml. of water was added with stirring. Methylene chloride was added and the reaction mixture was poured into ice–water. The organic material was extracted with methylene chloride, and the extracts were washed with sodium bicarbonate solution and water and dried (sodium sulfate). The solvent was then removed *in vacuo* (bath temperature <50°) and the residue was crystallized from ether to give **2**, 13.78 g., m.p. 135–140° dec.

In a similar run the bromoaldehyde was purified by Florisil[25] chromatography, followed by two recrystallization of the crystalline fractions from acetone–Skellysolve B[26] eluates to give material with m.p. 140–147° dec.; ν_{max}^{Nujol} 2720, 1721, 1698, 1665, and 1605 cm.$^{-1}$; n.m.r. spectrum having a singlet at 72 (C-19 hydrogen), a singlet at 76 (C-18 hydrogen), a singlet at 146 (C-21 hydrogen), a doublet centered at 345.5 (4-H) (J = 2 c.p.s.), a triplet centered at 581.5 (aldehyde C-H) (J = *ca.* 1 c.p.s.), and a doublet at 66 and 60 c.p.s. (6α-methyl); O.R.D. (*c* 0.1, dioxane), $[M]_{317.5}$ 3850°, $[M]_{330}$ 12,900°, $[M]_{380}$ 2050° (positive Cotton effect); λ_{max}^{EtOH} 240 mμ (ϵ 16,850).

Anal. Calcd. for $C_{24}H_{33}BrO_3$: C, 64.15; H, 7.35; Br, 17.82. Found: C, 63.87; H, 7.30; Br, 17.48.

An alternate procedure for adding the hypobromous acid involves N-bromosuccinimide–acetic acid. To a solution of 24 g. of the dihydropyran **1** in 1230 ml. of acetone at 0° was added 13.2 g. of sodium acetate dissolved in 92 ml. of water, followed by 24.4 g. of N-bromosuccinimide, and then 17.6 ml. of acetic acid dissolved in 64 ml. of acetone was added dropwise over 15 min. Isolation was effected by adding aqueous sodium thiosulfate solution, followed by extraction in the cold with ether. The ethereal extracts were washed with water and dried ($MgSO_4$); the residual

(19) R. Pappo, D. S. Allen, R. U. Lemieux, and W. S. Johnson, *J. Org. Chem.*, **21**, 478 (1956).

(20) (a) J. H. Pomeroy and C. A. Craig, *J. Am. Chem. Soc.*, **81**, 6340 (1959); (b) H. M. Kissman, A. S. Hoffman, and M. J. Weiss, *J. Org. Chem.*, **26**, 2610 (1961).

(21) H. B. Henbest and B. B. Millward, *J. Chem. Soc.*, 3575 (1960); see also ref. 22a.

(22) For discussion of the n.m.r. spectra of oxetanes, see (a) A. Rosowsky and D. S. Tarbell, *J. Org. Chem.*, **26**, 2255 (1961); (b) S. Searles, Jr., and H. E. Mortensen, *ibid.*, **27**, 1979 (1962); (c) H. S. Gutowsky, R. L. Rutledge, M. Tamres, and S. Searles, Jr., *J. Am. Chem. Soc.*, **76**, 4242 (1954); (d) R. Srinivasan, *ibid.*, **82**, 775 (1960).

(23) U. Kerb and R. Wiechert, *Chem. Ber.*, **95**, 2956 (1962).

(24) Melting points are corrected. Infrared spectra were recorded on a Perkin-Elmer Model 221 spectrophotometer from Nujol mulls. Ultraviolet spectra were taken on 95% ethanol solutions using a Cary Model 14 spectrophotometer. O.R.D. curves were observed on solutions of the samples (10 mg./10 ml. of dioxane) with a spectrophotometer assembled from a Rudolph Model 80 photoelectric polarimeter equipped with an oscillating polarizer and a Perkin-Elmer universal monochromator.

(25) Florisil is a synthetic magnesia silica gel manufactured by the Floridin Co., Warren, Pa.

(26) A saturated hydrocarbon fraction, b.p. 64–70°.

oil was purified by chromatography as above and recrystallization from acetone–Skellysolve B gave 8.93 g. of bromoaldehyde **2**, m.p. 130–134° dec.

17β-Bromo-6α-methyl-3,20-dioxo-17-isopregn-4-en-16α-acetic Acid, Methyl Ester (3).—A solution of 7.0 g. of the bromoaldehyde **2** in 70 ml. of pyridine was allowed to stand 18 hr. at room temperature with chromium trioxide–pyridine complex (from 7.0 g. of chromium trioxide and 70 ml. of pyridine). Isolation was effected by adding toluene and water to the reaction mixture and removing the insoluble material by filtration (Celite). The organic material was washed with dilute hydrochloric acid and water and dried (sodium sulfate). Removal of the solvent gave an oil which was dissolved in methanol–methylene chloride (1:1, 1 l.) and esterified with excess ethereal diazomethane (3 hr. at room temperature). After decomposition of the excess diazomethane with acetic acid, the solvent was removed *in vacuo*. The residue was dissolved in methylene chloride and chromatographed on Florisil (300 g.). Crystalline material was obtained from the 5–10% acetone–Skellysolve B eluates. These were combined (3.24 g.) and crystallized from methanol to give **3**, 1.73 g., m.p. 125–127°. Further crystallization from methanol gave material with m.p. 130–133°; O.R.D. (*c* 0.1, dioxane), $[M]_{317.5}$ 5760°, $[M]_{330}$ 10100°, $[M]_{380}$ 1070° (positive Cotton effect); λ_{max}^{EtOH} 239 mμ (ε 16,150); ν_{max}^{Nujol} 1735, 1702, 1665, 1603, 1235, 1190, and 1175 cm.$^{-1}$. The n.m.r. spectrum had a singlet at 72 (C-19 hydrogen), a singlet at 76 (C-18 hydrogen), a singlet at 146 (C-21 hydrogen), and a singlet at 220 c.p.s. (ester methoxyl).

Anal. Calcd. for $C_{25}H_{35}BrO_4$: C, 62.63; H, 7.31; Br, 16.7. Found: C, 62.57; H, 7.38; Br, 16.47.

17α-Hydroxy-6α-methyl-3,20-dioxopregn-4-en-16α-acetic Acid, α-Lactone (4).—A mixture of the ester **3** (0.6 g.), lithium bromide (1.0 g.), lithium carbonate (1.0 g.), and dimethylformamide (50 ml.) was heated to reflux under nitrogen for 18 hr. After cooling, the reaction mixture was poured into water and the organic material was isolated by filtration. The solid material was washed with water and dried *in vacuo;* the total material showed essentially one spot on thin layer chromatography (silica gel, 50% ethyl acetate–cyclohexane). This material was dissolved in methylene chloride and chromatographed on 150 g. of Florisil. This gave a main peak eluted with 10% acetone–Skellysolve B (0.23 g.). Crystallization gave **4** from acetone–Skellysolve, 0.185 g., m.p. 190–199°. Further crystallization from acetone–Skellysolve B gave m.p. 198–201°; λ_{max}^{EtOH} 240 mμ (ε 16,050); ν_{max}^{Nujol} 1788, 1712, 1672, 1625, 1241, 1209, 1159, 1080, 1069, and 1007 cm.$^{-1}$; O.R.D. (*c* 0.1, dioxane), $[M]_{460}$ +268°, $[M]_{325}$ +6940°, $[M]_{310}$ +3680°. N.m.r. showed peaks at 46 (C-18 hydrogen), 72 (C-19 hydrogen), a doublet at 61 and 68 (6α-methyl), and a singlet at 137 c.p.s. (C-21 hydrogen).

Anal. Calcd. for $C_{24}H_{32}O_4$: C, 74.97; H, 8.39. Found: C, 74.83; H, 8.78.

17α-Hydroxy-6α-methyl-3,20-dioxopregn-4-en-16α-acetaldehyde, 16b,17-Cyclic Enol Ether (5).—A mixture of the 17β-bromo-compound (**2**) (5.5 g.), lithium bromide (5.5 g.), lithium carbonate (5.5 g.), and dimethylformamide (150 ml., redistilled from phosphorus pentoxide) was heated for 18 hr. in a nitrogen atmosphere at 120–130°, with stirring. Isolation was effected, after cooling, by adding benzene and washing the organic solution three times with water. The benzene layer was dried (sodium sulfate) and the solvent was removed *in vacuo*. After dissolving the residual oil in methylene chloride, the material was chromatographed on Florisil (400 g.). Two main peaks were obtained (1 and 2).

(1) Elution with 5% acetone–Skellysolve B gave fractions which were combined (2.206 g.) and crystallized from ether–Skellysolve B to give **5**, 1.66 g., m.p. 150–153°. Two further crystallizations from acetone–Skellysolve B gave material with m.p. 155–157°; O.R.D. (*c* 0.1, dioxane), $[M]_{315}$ 2990°, $[M]_{327.5}$ 11500°, $[M]_{400}$ 2310° (positive Cotton effect); λ_{max}^{EtOH} 241 mμ (ε 15,850); ν_{max}^{Nujol} 3085, 3040, 1708, 1673, 1612, 1138, 1057, and 1038 cm.$^{-1}$. The n.m.r.p sectrum showed two olefinic protons in addition to the 4-H: a 16b-proton, doublet of doublets centered at 376 c.p.s. (J = 2.5 c.p.s., J = 1.5 c.p.s.), and a 16a-proton, triplet centered at 289 c.p.s. (J = 2.5 c.p.s.). The positions of absorption of these protons are in good agreement with the comparable protons for dihydrofuran.[17] The n.m.r. (see Fig. 1) spectrum had a singlet at 46 (C-18 hydrogen), a singlet at 72 (C-19 hydrogen), a broad multiplet centered at 222 (C-16 hydrogen), a doublet at 60 and 66 c.p.s. (6α-methyl), and a doublet (4-H) 346 c.p.s. (J = *ca.* 2 c.p.s.).

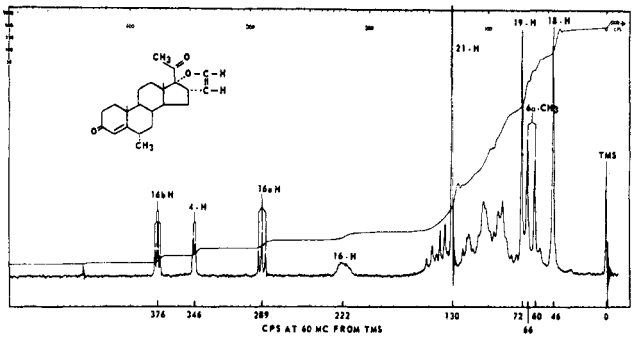


Fig. 1.—Proton magnetic resonance spectrum of dihydrofuran **5**.

Anal. Calcd. for $C_{24}H_{32}O_3$: C, 78.22; H, 8.75. Found: C, 78.05; H, 8.76.

(2) Fractions from 15% acetone–Skellysolve B elution were combined (1.28 g.) and crystallized from ether to give **6**, 0.277 g. Two crystallizations from acetone–Skellysolve B gave material with m.p. 184–188°; λ_{max}^{EtOH} 241 mμ (ε 16,150); ν_{max}^{EtOH} 3340, 1700, 1645, 1595, 1245, 1230, 1210, 1185, 1150, 1078, 1062, 1055, and 1015 cm.$^{-1}$; O.R.D. (*c* 0.1, dioxane), $[M]_{460}$ +334°, $[M]_{325}$ +6480°, $[M]_{310}$ +3480°. N.m.r. showed a singlet at 40 (C-18-hydrogen), a singlet at 71 (C-19-hydrogen), at 132 (C-21-hydrogen), a doublet at 60 and 66 (6α-methyl), and a triplet centered at 337 c.p.s. (J = *ca.* 4.5 c.p.s.) (lactol H).[11]

Anal. Calcd. for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.31; H, 9.49.

17α-Hydroxy-16α-(1,2,2-trihydroxyethyl)-6α-methyl-3,20-dioxopregn-4-ene, 16b,17-Cyclic Ether.—A solution of the dihydrofuran **5**, 0.75 g. in tetrahydrofuran (30 ml.) and ether (30 ml.), was allowed to stand 18 hr. at room temperature with 0.55 g. of osmium tetroxide. Isolation was effected after collecting the solid formed by filtration, by bubbling hydrogen sulfide into the filtrate, and also separately bubbling hydrogen sulfide into a solution of the solid in 200 ml. of methylene chloride–ethanol (1:1). After refiltration, the combined mother liquors gave 0.54 g. of crude diol, which was crystallized from ether to give 0.277 g., crop 1; the redissolved osmate ester gave 0.14 g. of crude diol. Two crystallizations of crop 1 from ethyl acetate–Skellysolve B gave material with m.p. 190–193°; λ_{max}^{EtOH} 241 mμ (ε 15,550); ν_{max}^{Nujol} 3375 (broad), 1705, 1675, 1650, 1603, 1230, 1186, 1130, 1080, 1052, and 1018 cm.$^{-1}$. N.m.r. showed peaks at 40 (C-18-hydrogen), 71 (C-19-hydrogen), 134 (C-21-hydrogen), 260 (16a-hydrogen), and 320 c.p.s. (16b-hydrogen).

Anal. Calcd. for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.72; H, 8.35.

In a similar later run employing 6.1 g. of "dihydrofuran" **5** (combined column fractions) and 4.6 g. of osmium tetroxide, there was obtained 3.18 g. of diol (two crops) after crystallization from ethyl acetate–Skellysolve B.

17-Hydroxy-6α-methyl-3,20-dioxopregn-4-ene-16α-carboxaldehyde (8) and 17-Hydroxy-6α-methyl-3,20-dioxopregn-4-ene-16α-carboxaldehyde, Formate (7).—A solution of the glycol prepared above (0.22 g.) was stirred in 15 ml. benzene for 1 hr. at room temperature with a solution of lead tetraacetate (0.5 g.) in benzene (10 ml.) and toluene (5 ml.). Isolation was effected by pouring the reaction mixture into water and extracting with further benzene. The benzene extracts were washed with sodium thiosulfate solution and water, dried (sodium sulfate), and the solvent was removed *in vacuo*. The resulting oil (0.213 g.) had an infrared spectrum consistent with the 17α-formate 16α-aldehyde structure (**7**). This material was dissolved in methylene chloride and chromatographed on Florisil (25.0 g.). Elution with increasing per cents of acetone in Skellysolve B gave crystalline fractions from the 15% acetone–Skellysolve B eluates. These were combined (0.168 g.) and crystallized from acetone–Skellysolve B to give 0.075 g. Two further crystallizations from acetone–Skellysolve B gave 0.039 g., m.p. 180–185°. This was formulated as **8**: λ_{max}^{EtOH} 240 mμ (ε 16,030); ν_{max}^{Nujol} 3445, 2745, 1700, 1695, 1670, 1605, 1241, 1225, 1196, 1173, and 1110 cm.$^{-1}$. The n.m.r. spectrum showed a singlet at 45 (C-18-hydrogen), a doublet at 60 and 66 c.p.s. (6α-methyl-hydrogen), a singlet at 71 (C-19-hydrogen), a singlet at 138 (C-21-hydrogen), and a singlet at 579 c.p.s. (aldehyde-hydrogen).

Anal. Calcd. for $C_{23}H_{32}O_4$(372.5): C, 74.16; H, 8.66. Found: C, 74.39; H, 8.59.

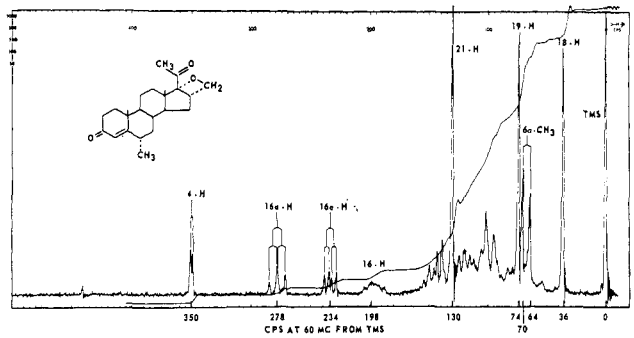


Fig. 2.—Proton magnetic resonance spectrum of the oxetane **13**.

In a similar run the total crude product (1.681 g.) was not chromatographed but was triturated with ether, crystallized once from methylene chloride–Skellysolve B and twice from ethyl acetate–Skellysolve B to give **7**: m.p. 186–189°; λ_{max}^{EtOH} 240.5 mμ (ε 16,250); ν_{max}^{Nujol} 2740, 1725, 1710, 1674, 1610, 1205, 1185, 1155, and 1092 cm.$^{-1}$. N.m.r. spectrum showed peaks at 72 (C-19-hydrogen), 48 (C-18-hydrogen), 126 (C-21-hydrogen), 481 (formate-hydrogen), and a doublet (J = 1.5 c.p.s.) at 578 c.p.s. (aldehyde-hydrogen).

Anal. Calcd. for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 71.74; H, 8.21.

17-Hydroxy-6α-methyl-3,20-dioxopregn-4-ene-16α-carboxaldehyde (8).—A solution of 1.84 g. of the dihydrofuran **5** in 60 ml. of tetrahydrofuran and 30 ml. of water was stirred for 10 min. with 53 mg. of osmium tetroxide. Then 2.5 g. of powdered sodium periodate were added over 30 min. to the stirred solution. After stirring for a further 1.5 hr., isolation was effected by the addition of water and extraction with methylene chloride. The organic extracts were washed with water until the aqueous washings gave a negative starch–iodide test. Removal of the solvent and chromatography of the residue (dissolved in methylene chloride) on 250 g. of Florisil gave crystalline material from the 15% acetone–Skellysolve B eluates. These fractions were combined and crystallized from acetone–Skellysolve B to give **8**, 1.08 g., m.p. 188–191°. The infrared spectrum of this material was the same as that of the sample prepared earlier.

17α-Hydroxy-6α-methyl-3,20-dioxopregn-4-ene-16α-carbonitrile (9).—The 16α-formyl compound **8**, 0.36 g., was dissolved in 15 ml. of benzene, and O,N-bistrifluoroacetylhydroxylamine (0.36 g.) was added, followed by 0.23 ml. of pyridine. After warming the mixture for 5 min. on the steam bath, the reaction was allowed to proceed for 18 hr. at room temperature. The crystalline material which had formed was collected by filtration, washed with ether, and dried to give **9**, 0.208 g., m.p. 265–270°. The mother liquors were washed successively with dilute hydrochloric acid, sodium bicarbonate solution, and water, and dried (sodium sulfate). Chromatography of this residue on Florisil furnished additional nitrile (0.05 g.). Purification of the nitrile by crystallization from methanol gave material: m.p. 267–274°; ν_{max}^{Nujol} 3410, 2240, 1706, 1650, 1595, 1236, 1192, and 1097 cm.$^{-1}$; λ_{max}^{EtOH} 240 mμ (ε 16,000). N.m.r. spectrum showed peaks at 40.5 (C-18-hydrogen), 71 (C-19-hydrogen), and 136 c.p.s. (C-21-hydrogen).

Anal. Calcd. for $C_{23}H_{31}NO_3$: C, 74.76; H, 8.46; N, 3.79. Found: C, 74.36; H, 8.12; N, 3.76.

17α-Hydroxy-6α-methyl-3,20-dioxopregn-4-ene-16α-carbonitrile, Acetate (10).—To a suspension of 0.1 g. of **9** in 10 ml. of carbon tetrachloride and 3 ml. of acetic anhydride was added 60 mg. of 2,4-dinitrobenzenesulfonic acid, and the mixture was stirred at room temperature for 2 hr. The reaction mixture was poured into 100 ml. of saturated sodium bicarbonate solution and the carbon tetrachloride was removed *in vacuo*. The residual suspension was stirred 18 hr. at room temperature with 20 ml. of tetrahydrofuran and 100 ml. of methanol. The crystalline solid had not disappeared after this treatment and an infrared spectrum of a portion of this showed it still to be enol acetate. This solid material was collected by filtration, washed with water, and dried *in vacuo*. This material was then heated in 50 ml. of methanol with 0.5 ml. of concentrated hydrochloric acid for 10 min. on the steam bath. Water (20 ml.) was then added to the cooled solution and the methanol was removed *in vacuo*. The crystalline solid which formed was collected by filtration, washed with water, and dried *in vacuo*. This material was dissolved in methylene chloride and was chromatographed on Florisil, and the crystalline fractions were eluted with 15–20% acetone–Skellysolve and were combined and crystallized from acetone–Skellysolve B to give **10**, 76 mg., m.p. 202–207°. A sample recrystallized from acetone–Skellysolve B had m.p. 204–207°; ν_{max}^{Nujol} 3050, 2240, 1740, 1710, 1660, 1610, 1238, 1180, and 1083 cm.$^{-1}$; λ_{max}^{EtOH} 239.5 mμ (ε 16,650). The n.m.r. spectrum showed a singlet at 39 (C-18-hydrogen), a doublet at 62 and 68 (6α-methyl), a singlet at 71 (C-19-hydrogen), a singlet at 122 (ester methyl), a singlet at 134 (C-21-hydrogen), and a complex multiplet centered at 263 c.p.s. (16β-hydrogen).

Anal. Calcd. for $C_{25}H_{33}NO_4$: C, 72.96; H, 8.08. Found: C, 73.21; H, 8.16.

17α-Hydroxy-16α-(hydroxymethyl)-6α-methylpregn-4-ene-3,20-dione (11).—A solution of 300 mg. of the 16α-formyl compound (**8**) in 20 ml. of tetrahydrofuran and 4 ml. of water was cooled to 0° in an ice–salt bath. Then an ice-cold, freshly prepared solution of sodium borohydride (7.5 mg.) in 3 ml. of water was added to the solution, and the mixture was stirred at 0° for 5 min. Then 10% aqueous acetic acid was added to the solution until the pH was 6 and the tetrahydrofuran was removed *in vacuo*. The crystalline material was collected by filtration, washed with water, and dried *in vacuo*. Extraction of the aqueous layer with methylene chloride gave additional material which was combined with the main crop, and the whole was dissolved in methylene chloride and chromatographed on Florisil (50 g.). Elution with increasing per cents of acetone in Skellysolve B gave crystalline material from the 15% acetone–Skellysolve B eluates (0.272 g.). Crystallization from acetone–Skellysolve B gave **11**: crop 1, 0.145 g., m.p. 184–186°; crop 2 (from ether), 60 mg., m.p. 179–184°. Further crystallization of crop 1 gave material (**11**): m.p. 183–187° (from acetone–Skellysolve B); λ_{max}^{EtOH} 241 mμ (ε 15,950); ν_{max}^{Nujol} 3395, 3300, 1700, 1660, 1607, 1223, and 1196 cm.$^{-1}$. N.m.r. spectrum showed peaks at 46 (C-18-hydrogen), 71.5 (C-19-hydrogen), 136 (21-hydrogen), and a doublet at 61 and 68 c.p.s. (6α-CH_3).

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.75; H, 8.99.

17,16α-(Epoxymethylene)-6α-methylpregn-4-ene-3,20-dione (13).—A solution of the 16α-hydroxymethyl compound (**11**), 300 mg. in pyridine (10 ml.), was allowed to stand 18 hr. at room temperature with 300 mg. of *p*-toluenesulfonyl chloride. Isolation was effected by pouring the reaction mixture into ice–water and extraction with methylene chloride. These extracts were washed with ice-cold dilute hydrochloric acid, sodium bicarbonate solution, and water, and dried (sodium sulfate). Removal of the solvent gave 0.4 g. of an oil which crystallized on contact with ether to give the monotosylate **12**, 0.34 g., m.p. 150–160° dec. Crystallization from methanol gave m.p. 159–161° dec., and a second crystallization from the same solvent raised this to 165–167° dec.; ν_{max}^{Nujol} 3550, 3070, 1733, 1665, 1610, 1599, 1490, 1340, 1165, 1235, 1185, and 807 cm.$^{-1}$; λ_{max}^{EtOH} 227 mμ (ε 21,900), 242 (15,900), and 272 (702). N.m.r. spectrum showed a singlet at 51 (C-18-hydrogen), a doublet at 60 and 66 (6α-methyl), a singlet at 71 (C-19-hydrogen), a singlet at 137 (C-21-hydrogen), a singlet at 147 (aromatic methyl), complex multiplets centered at 441 and 465 (aromatic hydrogens), and a complex multiplet centered at 245 c.p.s. (16a-hydrogens).

Anal. Calcd. for $C_{30}H_{40}O_6S$: C, 68.19; H, 7.58. Found: C, 68.00; H, 7.65.

A solution of potassium *t*-butoxide, 0.6 g. in 25 ml. of *t*-butyl alcohol was added to a solution of 0.839 g. of the monotosylate **12** in 40 ml. of *t*-butyl alcohol and 10 ml. of tetrahydrofuran at 10° in a nitrogen atmosphere. After the addition, additional tetrahydrofuran, 25 ml., was added and the temperature was allowed to rise to 25°. After stirring for 1.5 hr., the reaction was interrupted by the addition of excess dilute hydrochloric acid, and the organic material was extracted with methylene chloride. These extracts were washed with dilute sodium bicarbonate solution and water and dried (sodium sulfate). Removal of the solvent gave 0.751 g. This was dissolved in methylene chloride and chromatographed on Florisil (200 g.), gradient elution (Skellysolve B → acetone). A main fraction was obtained (0.442 g.). This was crystallized from ether and then twice from acetone–Skellysolve B to give the oxetane **13**: m.p. 135–138°; ν_{max}^{Nujol} 1707, 1670, 1608, 1236, 1190, and 1049 cm.$^{-1}$; λ_{max}^{EtOH} 240 mμ (ε 16,250). The n.m.r. spectrum of the oxetane (see Fig. 2) showed a singlet at 36 (C-18-hydrogen), a doublet at 64 and 70 (6α-methyl), a singlet at 74 (C-19-hydrogen), a doublet

centered at 350 (J = *ca.* 2 c.p.s.) (4-hydrogen), a broad multiplet centered at 198 (16β-hydrogen), a doublet of doublets centered at 278, and a doublet of doublets centered at 234 c.p.s. (16a-hydrogens) ($J_{16a,16a'}$ = 6 c.p.s., $J_{16a,16}$ = 7 c.p.s., $J_{16a,16}$ = 4 c.p.s.).

Anal. Calcd. for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.40; H, 9.09.

17β-Bromo-9α-fluoro-11β-hydroxy-6α-methyl-3,20-dioxo-17-isopregna-1,4-diene-16α-acetaldehyde (19).—A solution of the dihydropyran **18**,[27] 4.57 g., was prepared in tetrahydrofuran (40 ml.) and acetone (123 ml.). To this was added a solution of sodium acetate (4.68 g.) in 10 ml. of water. Then with the temperature maintained at 20°, 4.38 g. of N-bromosuccinimide was added with stirring, and the solution was cooled rapidly to 5–10°, when a solution of 3.0 ml. of acetic acid in 6.0 ml. of acetone was added dropwise over 3 min. After the addition, the reaction mixture was maintained at 0–5° for 30 min. and at the end of this time a solution of 2.5 g. of sodium thiosulfate in 35 ml. of water was added, and the reaction mixture was stirred for 5 min. Methylene chloride was added and the organic layer was washed with aqueous saturated sodium bicarbonate solution containing sodium sulfite, and the aqueous washings were re-extracted with methylene chloride. The combined methylene chloride extracts were washed with water and dried (sodium sulfate), and the solvent was removed *in vacuo*. The residue (6.362 g.) was dissolved in methylene chloride (30 ml.) and chromatographed on Florisil (500 g.), gradient elution (Skellysolve B → 50% acetone–Skellysolve B). The main peak obtained was crystallized from acetone–Skellysolve B and gave 3.55 g.: m.p. 210–220° dec., recrystallization of a sample of **19** from acetone–Skellysolve B raised this to 210–215° dec.; λ_{max}^{EtOH} 238 mμ (ϵ 15,590); ν_{max}^{Nujol} 3280, 2720, 1730, 1700, 1660, 1615, 1190, 1120, 1075, and 1020 cm.$^{-1}$. The n.m.r. spectrum showed singlet at 94.5 (C-18-hydrogen), a singlet at 96 (C-19-hydrogen), a singlet at 145 (C-21-hydrogen), and a singlet at 588 c.p.s. (aldehyde C–H).

Anal. Calcd. for $C_{24}H_{30}BrFO_4$: C, 59.88; H, 6.24; Br, 16.63. Found: C, 58.96; H, 6.98; Br, 16.28.

9α-Fluoro-6α-methyl-11β,17α-dihydroxy-1,4-pregnadiene-3,20-dion-16α-acetaldehyde, Cyclic Enol Ether (20).—The bromoaldehyde **19**, 3.76 g., was added to a mixture of dimethylformamide (200 ml., dry), lithium bromide (10 g., dry, freshly fused), and lithium carbonate (6.0 g.). The total reaction mixture was stirred under nitrogen for 18 hr. at 125–130°. After cooling, ethyl acetate was added to the reaction mixture and the insoluble lithium salts were removed by filtration. The ethyl acetate solution was washed with water, dried (magnesium sulfate), and evaporated to dryness *in vacuo*. The residue was dissolved in 200 ml. of methylene chloride and chromatographed on Florisil (500 g.), gradient elution (Skellysolve B → 50% acetone–Skellysolve B). A main peak was obtained and crystallized from acetone–Skellysolve B to give the dihydrofuran **20**: crop 1, 1.37 g., m.p. 273–277°; crop 2, 0.221 g., m.p. 263–265°. Two additional crystallization of a sample of **20** from acetone–Skellysolve B gave material with m.p. 287–289°; λ_{max}^{EtOH} 239 mμ (ϵ 15,600); ν_{max}^{Nujol} 3300, 1715, 1665, 1615, 1250, 1170, 1150, and 1060 cm.$^{-1}$. The n.m.r. spectrum shows a peak at 60 (C-18-hydrogen), 96 (C-19-hydrogen), 130 (C-21-hydrogen), complex multiplet centered at 223 (16-hydrogen), doublet of doublets centered at 292 (16a-hydrogen), and a doublet of doublets centered at 377 c.p.s. (16b-hydrogen) (J = *ca.* 2.5 c.p.s. for all couplings of ABX system).

Anal. Calcd. for $C_{24}H_{29}FO_4$: C, 72.0; H, 7.25; F, 4.75. Found: C, 71.98; H, 7.55; F, 4.58.

Acknowledgment.—The author is indebted to Dr. W. A. Struck and associates for the analyses, O.R.D., and ultraviolet and infrared spectra; to Dr. G. Slomp, F. A. MacKellar, and J. Zieserl for running the n.m.r. spectra and for valuable assistance in the interpretation of the spectra; and to Mr. J. M. Baldwin for valuable technical assistance.

(27) This adduct (**18**) was prepared as described earlier[10] from the corresponding Δ^{16}-20-ketone. An analytical sample of **18** crystallized from methanol had m.p. 220–225°, λ_{max}^{EtOH} 238 mμ (ϵ 16,550). *Anal.* Calcd. for $C_{26}H_{33}O_4F$: C, 72.11; H, 7.93. Found: C, 72.14; H, 8.11.

Steroids. CCLXIII.[1] The Synthesis of 2-Formyl-Δ^1- and- $\Delta^{1,4}$-3-keto Steroids[2]

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Received May 19, 1964

A variety of 2-formyl-Δ^1- and -$\Delta^{1,4}$-3-ketoandrostanes and -pregnanes has been prepared by dehydrogenating the corresponding saturated and unsaturated 2-hydroxymethylene-3-keto steroids with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

In a recent publication from our laboratory, syntheses were reported of a variety of substituted 2-formyl-Δ^2-androstenes.[3] The salient feature of that work was the finding that a substantial myotropic effect could be attributed directly to the 2-formyl Δ^2-moiety. This result prompted us to consider methods for preparing new classes of 2-formyl-substituted steroids. Two systems of potential interest were the 2-formyl Δ^1- and $\Delta^{1,4}$-3-ketones and consequently an efficient procedure was sought for their respective synthesis. A detailed account of this investigation forms the subject of the present communication.[2]

Suitable starting materials for the synthesis of the hitherto undescribed α-formyl-α,β-unsaturated ketone system were the 2-hydroxymethylene-3-keto steroids (*e.g.*, Ia). These highly enolic α-formyl ketones may be readily prepared by base-promoted condensation of 3-ketoandrostanes and -pregnanes with ethyl formate,[4] and, of greater importance to the present work, these substances differ from the title compounds by only two additional hydrogen atoms. The latter property suggested that the conversion of an appropriate hydroxymethylene compound to the required α-formyl-α,β-unsaturated ketone might be effected by suitable elimination or oxidation procedures.

The initial attempts to prepare 2-formyl-17β-hydroxyandrost-1-en-3-one (IIa) were based on the standard bromination–dehydrobromination techniques for producing α,β-unsaturated keto steroids. Thus 17β-hydroxy-2-hydroxymethylene-5α-androstan-3-one (Ia)[5]

(1) Steroids. CCLXII: A. D. Cross, *J. Am. Chem. Soc.*, submitted for publication.

(2) For a preliminary report of this work, see J. A. Edwards, J. C. Orr, and A. Bowers, *J. Org. Chem.*, **27**, 3378 (1962).

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