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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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]

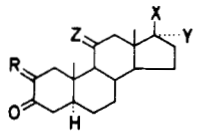
(1) Steroids. CCLXII: A. D. Cross, *J. Am. Chem. Soc.*, submitted for publication.

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

(3) J. C. Orr, O. Halpern, P. G. Holton, F. Alvarez, I. Delfin, A. de La Roz, A. M. Ruiz, and A. Bowers, *J. Med. Chem.*, **6**, 166 (1963).

(4) (a) F. L. Weisenborn, D. C. Remy, and T. L. Jacobs, *J. Am. Chem. Soc.*, **76**, 1552 (1954); (b) H. J. Ringold, E. Batres, O. Halpern, and E. Necoechea, *ibid.*, **81**, 427 (1959).

(5) J. Edwards and H. J. Ringold, *ibid.*, **81**, 5262 (1959).



Ia, X = OH; Y = H; Z = H_2; R = CHOH

b, X = OCC_2H_5 (=O); Y = H; Z = H_2; R = $CHOCC_2H_5$ (=O)

c, X = OCC_2H_5 (=O); Y = H; Z = H_2; R = CHOH

d, X = OH; Y = CH_3; Z = H_2; R = CHOH; with Δ^4 double bond

e, X =  ; Y = H; Z = R = H_2

f, X =  ; Y = H; Z = H_2; R = CHOH

g, X = ; Y = H; Z = H_2; R = CHOH; with Δ^4 double bond

h, X = $C(CH_3)$=O; Y = H; Z = H_2; R = CHOH; with Δ^4 double bond

i, X =  ; Y = OH; Z = R = H_2; with Δ^4 double bond

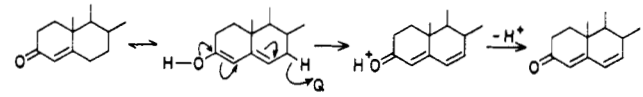
j, X =  ; Y = OH; Z = H_2; R = CHOH; with Δ^4 double bond

readily absorbed 1 molar equiv. of bromine and an amorphous 2ξ-bromo compound was obtained in good yield. However, attempts to dehydrobrominate this substance to the desired 2-formyl Δ^1-3-ketone (IIa) with either collidine[6a] or calcium carbonate in dimethylacetamide[6b] proved to be abortive and this particular approach was abandoned.

We next focused our attention on the chemical dehydrogenation of 2-hydroxymethylene-3-keto steroids with tetrasubstituted *p*-benzoquinone reagents.[7] The first extensive studies devoted to the dehydrogenation of steroidal ketones with *p*-benzoquinones are due to Agnello and Laubach.[8,9] This work was particularly significant since it demonstrated that the one-step conversion of a Δ^4-3-ketone to the corresponding $\Delta^{4,6}$-dienone could be carried out conveniently with chloranil in a variety of solvents. The development of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) by the British Drug Houses group[10] followed several years later, and now this highly efficient and versatile quinone has replaced chloranil as the reagent of choice for dehydrogenating Δ^4-3-keto steroids. The former effects Δ^1-introduction, except in the presence of acid, the latter effects Δ^6-introduction.

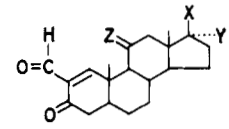
Experimental evidence provided by both Agnello, *et al.*,[8] and Mandell[11] indicated that the species attacked by the quinone reagent was not the Δ^4-3-keto steroid *per se* but rather its corresponding enol (see Scheme I). The correctness of this mechanism was confirmed, after the completion of our work, by Ringold and Turner in a

SCHEME I



detailed study of the dehydrogenation of Δ^4-3-keto steroids with DDQ in acidic and neutral media.[12]

The early mechanistic evidence[8,11] suggested to us that α-hydroxymethylene ketones might be susceptible to dehydrogenation by a high-potential quinone such as DDQ since these substances exist mainly in the enolic form. Accordingly, dioxane solutions of 17β-hydroxy-2-hydroxymethylene-5α-androstan-3-one (Ia) and DDQ (1.1 molar equiv.) were mixed together at room temperature and a precipitate of 2,3-dichloro-5,6-dicyanohydroquinone began to form almost immediately (1–2 min.), indicating that an oxidation reaction had taken place.



IIa, X = OH; Y = H; Z = H_2

b, X = OCC_2H_5 (=O); Y = H; Z = H_2

c, X = $C(CH_3)$=O; Y = H; Z = H_2

d, X = OH; Y = CH_3; Z = H_2; with Δ^4 double bond

e, X = $C(CH_3)$=O; Y = H; Z = H_2; with Δ^4 double bond

f, X =  ; Y = OH; Z = H_2; with Δ^4 double bond

g, X = $C(CH_3)$=O; Y = OH; Z = H_2; with Δ^4 double bond

h, X,Y = bismethylenedioxy; Z =  ; with Δ^4 double bond

i, X = $C(CH_2OAc)$=O; Y = OH; Z =  ; with Δ^4 double bond

j, X,Y = bismethylenedioxy; Z = O; with Δ^4 double bond

k, X = $C(CH_2OH)$=O; Y = OH; Z = O; with Δ^4 double bond

The reaction was then quenched by adding methylene chloride and by passing the resulting solution through a column of alumina. Evaporation of the combined eluates afforded the nicely crystalline 2-formyl-17β-hydroxy-5α-androst-1-en-3-one (IIa) in 50% yield. This substance exhibited maximal absorption in the ultraviolet at 242 mμ (ethanol); a 5-mμ hyposochromic shift of the absorption maximum occurred upon the addition of acid. The addition of alkali produced a characteristic bathochromic shift with the absorption maximum appearing at 310 mμ. The infrared spectrum (chloroform) of the 2-formyl Δ^1-3-ketone (IIa) showed strong carbonyl bands at 5.88 and 5.95 μ as well as a band of medium intensity at 6.23 μ due to the carbon–carbon stretching vibration of the Δ^1-double bond. The most conclusive evidence for the presence of the 2-formyl-Δ^1-3-keto system in the quinone dehydrogenation product was provided by its nuclear mag-

(6) *Inter alia*, see (a) C. Djerassi and C. R. Scholz, *J. Am. Chem. Soc.*, **69**, 2404 (1947); (b) G. F. H. Green and A. G. Long, *J. Chem. Soc.*, 2532 (1961).

(7) For an extensive review on quinone dehydrogenations, see L. M. Jackman in "Advances in Organic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1960, p. 329.

(8) E. J. Agnello and J. D. Laubach, *J. Am. Chem. Soc.*, **79**, 1257 (1957); **82**, 4293 (1960).

(9) For an earlier example, see A. Wettstein, *Helv. Chim. Acta*, **23**, 388 (1940).

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

(11) L. Mandell, *J. Am. Chem. Soc.*, **78**, 3199 (1956).

(12) H. J. Ringold and A. Turner, *Chem. Ind.* (London), 211 (1962).

netic resonance (n.m.r.) spectrum[13] which showed two one-proton singlets at 473.2 and 601 c.p.s., which were attributed to the C-1 olefinic and aldehydic protons, respectively.

A smooth dehydrogenation also occurred when 17β-hydroxy-2-hydroxymethylene-17α-methylandrost-4-en-3-one (Id)[4b] was exposed to DDQ in dioxane solution. Thus, treatment of this substance according to the experimental conditions of the preceding reaction gave the desired 2-formyl-17β-hydroxy-17α-methylandrosta-1,4-dien-3-one (IId) in 78% yield. The ultraviolet spectrum of this substance was characterized by maxima at 222 and 245 mμ (ethanol), with well-defined changes occurring upon the addition of either acid or alkali. A more detailed account of the ultraviolet spectra of IId and related compounds will be deferred until later in the discussion. The infrared spectrum of the dienone IId exhibited a strong band at 5.84 μ for the aldehyde substituent and three additional bands at 6.05, 6.15, and 6.25 μ for the $\Delta^{1,4}$-3-keto group.[14] In the n.m.r. spectrum of IId three one-proton singlets appeared at 370.2, 470.6, and 615.8 c.p.s. for the C-4 and C-1 olefinic protons and the aldehydic proton, respectively.

From the preceding experiments it was concluded that 2-formyl Δ^1- and $\Delta^{1,4}$-3-ketones could be obtained by the dehydrogenation of the appropriate 2-hydroxymethylene derivatives with DDQ. However, prior to extending this reaction to a wider variety of starting materials, a more detailed study of the first dehydrogenation was undertaken in order to define more clearly the scope and limitations of this reaction.

Dioxane at room temperature was the preferred solvent for the dehydrogenation and was used for all reactions. Dehydrogenations were run in a variety of solvents (*e.g.*, acetone, methylene chloride, tetrahydrofuran, acetonitrile), but these experiments were less satisfactory because of the reduced solubility of either the DDQ or the starting material. Consistent yields of the 2-formyl-Δ^1-3-keto compound IIa were obtained with 1.1–1.5 molar equiv. of the quinone reagent. A two–three-fold excess of DDQ had little effect on the over-all yield of IIa.

The most critical factor encountered in the dehydrogenation of the hydroxymethylene compound Ia was the time permitted for this reaction. Substantially lower yields of the aldehyde IIa were obtained when the reaction was left for a 10-min. period or longer. A short reaction time (1–2 min.) at room temperature was always used. Separation of the steroid from the hydroquinone was effected by standard procedures, namely chromatography on alumina or by extraction with dilute aqueous alkali, and comparable yields of IIa were obtained with either procedure. However, later experience showed that this was not always the case with other compounds (see Table I).

The generality of this new dehydrogenation reaction was substantiated by treating a representative number of 2-hydroxymethylene-3-ketoandrostane and -pregnane derivatives with DDQ, and these results are recorded in Table I. The respective 2-formyl Δ^1- and $\Delta^{1,4}$-3-

TABLE I

2-FORMYL Δ^1- AND $\Delta^{1,4}$-3-KETONES

Dehydrogenation product[a]	Yield,[b] % Method A	Method B	M.p., °C.	[α]D, deg.	λ_{max}^{KBr}, μ	Formula	Calcd., % C	H	O	Found, % C	H	O
2-Formyl-17β-hydroxy-5α-androst-1-en-3-one (IIa)[c]	50	50	215–217[d]	+23	5.88, 5.95, 6.23[e]	$C_{20}H_{28}O_3$	75.91	8.92	15.17	75.78	8.96	15.29
2-Formyl-17β-hydroxy-5α-androst-1-en-3-one 17-propionate (IIb)	35[f]	...	110–113[g]	+33	5.75, 5.90, 6.21	$C_{23}H_{32}O_4$	74.16	8.66		73.96	8.67	
2-Formyl-5α-pregn-1-en-3-one (IIc)	14[h]	...	194–196	+109	5.86, 5.96, 6.22	$C_{22}H_{30}O_3$	77.15	8.83	14.02	76.70	8.79	14.36
2-Formyl-17β-hydroxy-17α-methylandrosta-1,4-dien-3-one (IId)[i]	78	...	107–110[j]	−67	5.85, 6.05, 6.18, 6.25	$C_{21}H_{28}O_3 \cdot C_3H_6O$	74.57	8.87		74.08	8.55	
2-Formylpregna-1,4-diene-3,20-dione (IIe)	63	...	164–166[k]	+57	5.86, 6.01, 6.03, 6.21	$C_{22}H_{28}O_3$	77.61	8.29	14.10	77.91	7.94	14.11
20-Cycloethylenedioxy-2-formyl-17α-hydroxypregna-1,4-dien-3-one (IIf)	71[l]	80	220–223[m]	−57	5.85, 6.00, 6.15, 6.21	$C_{24}H_{32}O_5$	71.97	8.05		72.15	8.08	
2-Formylprednisolone (IIh)[n]	50	65	269–271[j]	−61	5.85, 6.00, 6.15, 6.21	$C_{24}H_{30}O_7$	66.96	7.02	26.02	66.27	7.42	26.02
2-Formylprednisone (IIj)[o]	30	48	256–260[j]	±0	5.86, 6.00, 6.15, 6.22	$C_{24}H_{28}O_7$	67.27	6.59	26.14	67.52	6.65	26.06

[a] All reactions were run in dioxane solution at room temperature with 1.1 molar equiv. of DDQ for 1 min. unless otherwise stated. [b] Reported yields refer to highest obtained from several reactions. Each product was crystallized once after the initial purification by methods A or B. [c] See ref. 5 for the preparation of the starting 2-hydroxymethylene compound. [d] Crystallized from ethyl acetate. [e] Spectrum determined in chloroform. [f] This product was purified by chromatography on silica gel. [g] Crystallized from ether–hexane. [h] The purification of this product is described in detail in the Experimental section. [i] See ref. 4b for the preparation of the starting 2-hydroxymethylene compound. [j] Crystallized from acetone–hexane. [k] Crystallized from acetone. [l] Dehydrogenation left for 5 min. [m] Crystallized from acetone–hexane containing a trace of pyridine. [n] For the preparation of the starting 2-hydroxymethylene compound, see J. A. Edwards, M. C. Calzada, and A. Bowers, *J. Med. Chem.*, **7**, 528 (1964). [o] See ref. 23 for the preparation of the starting 2-hydroxymethylene compound.

(13) The n.m.r. spectra were taken in deuteriochloroform solution with a tetramethylsilane internal reference. Chemical shifts, Δ, are quoted as cycles per second from the reference. A Varian A-60 spectrometer was used, in turn calibrated against a Varian HR 60 instrument suitably equipped for calibration by the standard side-band technique.

(14) R. N. Jones, P. Humphries, E. Packard, and K. Dobriner, *J. Am. Chem. Soc.*, **72**, 89 (1950).

TABLE II

ULTRAVIOLET ABSORPTION SPECTRA OF 2-FORMYL Δ^1-3-KETONES

Steroid	λ_{max}, mμ (log ε) EtOH	EtOH + HCl[a]	EtOH + NaOH[b]	Dioxane
2-Formyl-17β-hydroxy-5α-androst-1-en-3-one (IIa)	241 (3.90)	236 (3.92)	305 (4.22)	245 (3.98)
2-Formyl-17β-hydroxy-5α-androst-1-en-3-one 17-propionate (IIb)	240 (3.84)	236 (3.87)	305 (4.16)	245 (3.89)
2-Formyl-5α-pregn-1-en-3-one (IIc)	241 (3.89)	236 (3.95)	304 (4.23)	245 (3.98)

[a] Solutions were acidified with 1 drop of concentrated hydrochloric acid and the spectra were determined 10 min. later. [b] Solutions were treated with 1 drop of aqueous 10% hydroxide and the spectra were determined 10 min. later.

TABLE III

ULTRAVIOLET ABSORPTION SPECTRA OF 2-FORMYL $\Delta^{1,4}$-3-KETONES[a]

Steroid	λ_{max}, mμ (log ε) EtOH	EtOH + HCl[b]	EtOH + NaOH[c]
2-Formyl-17β-hydroxy-17α-methylandrosta-1,4-dien-3-one (IId)	222 (4.17)	248 (4.14)	242 (4.17)
	247 (4.07)		348 (4.00)
2-Formylpregna-1,4-diene-3,20-dione (IIe)	221 (4.08)	247 (4.02)	242 (4.15)
	247 (4.14)		348 (3.99)
20-Cycloethylenedioxy-2-formyl-17β-hydroxypregna-1,4-dien-3-one (IIf)	223 (4.06)	248 (4.17)	243 (4.12)
	248 (4.13)		347 (3.96)
2-Formyl-17β-hydroxypregna-1,4-diene-3,20-dione (IIg)	220 (4.05)	247 (4.12)	242 (4.09)
	247 (4.12)		348 (3.93)
2-Formylprednisolone-BMD (IIh)	221 (4.16)	246 (4.14)	243 (4.16)
	245 (4.07)		348 (4.01)
2-Formylprednisolone 21-acetate (IIi)	220 (4.18)	247 (4.14)	244 (4.14)
	244 (4.08)		347 (4.01)
2-Formylprednisone-BMD (IIj)	219 (4.09)	241 (4.18)	241 (4.18)
			351 (3.99)
2-Formylprednisone (IIk)	215 (4.18)	242 (4.15)	241 (4.18)
			349 (3.99)

[a] Spectra of compounds IId–k measured in dioxane solution exhibited only strong end absorption. [b] Solutions were acidified with 1 drop of concentrated hydrochloric acid and the spectra were determined 10 min. later. [c] Solutions were treated with 1 drop of aqueous 10% sodium hydroxide and the spectra were determined 10 min. later.

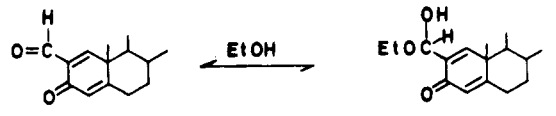
ketones were identified by their elementary analyses and by ultraviolet, infrared, and n.m.r. spectroscopy.

The 2-hydroxymethylene derivatives which served as the precursors for the 2-formyl compounds IIb, c, e, and f have not been previously described. The syntheses of these intermediates are not exceptional and require no comment (see Experimental section).

Three of the 2-formyl-$\Delta^{1,4}$-dienones listed in Table I were subjected to further reactions in order to obtain the 2-formyl derivatives of the parent steroid hormones. Thus treatment of the 2-formyl-11β-hydroxy-BMD (IIh) under controlled conditions with boiling 60% formic acid[15] gave 2-formylprednisolone which was characterized as its 21-acetate derivative IIi. 2-Formylprednisone (IIk) was also prepared from its bismethylenedioxy derivative IIj in a similar manner. 2-Formyl-17α-hydroxypregna-1,4-diene-3,20-dione (IIg) was obtained in good yield from the corresponding 20-ketal IIf by mild acid hydrolysis.

Ultraviolet Spectra.—In Table II the ultraviolet spectra of the 2-formyl-$\Delta^{1,4}$-dienones are recorded for neutral, acidic, and alkaline ethanol solutions. It is apparent from the samples run in pure ethanol that two different chromophores are contributing to the observed ultraviolet spectra (maxima at *ca.* 220 and 245 mμ). Presumably, the 2-formyl $\Delta^{1,4}$-3-ketones exist in equilibrium with the hemiacetal form (Scheme II) and these two species give rise to dissimilar spectra.

SCHEME II



To substantiate this point, the spectra of compounds IId–k were next determined in ethanol containing hydrochloric acid (conditions which facilitate hemiacetal formation). The changes observed were quite striking particularly with the 11-keto compounds (IIj and k). The lower wave-length absorption band disappeared completely and all compounds exhibited a single maximum between 242 and 248 mμ. Therefore, the longer wave-length maximum refers to the hemiacetal chromophore[16] which is as expected the predominant species in acidic medium. The unusual spectra of 2-formylprednisone-BMD and its formic acid hydrolysis product (single maxima at 215 and 219 mμ, respectively) show that these compounds exist essentially in the free aldehyde form. Thus the 2-formyl-$\Delta^{1,4}$-3-keto chromophore is characterized by an absorption maximum at or near 220 mμ.

In nonhydroxylic solvents the equilibrium shifted completely to the side of the aldehyde form. This was demonstrated by measuring the spectra of compounds IId–k in dioxane which resulted in the disappearance of the longer wave-length absorption band. The maximum near 220 mμ was not observed because of the strong solvent absorption in this region.

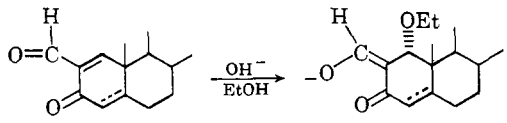
The spectra of the 2-formyl Δ^1-3-ketones IIa–c were also measured in the same manner in an attempt to establish the aldehyde–hemiacetal equilibrium with this series of compounds. These results are given in

(15) R. E. Beyler, F. Hoffman, R. M. Moriarty, and L. H. Sarett, *J. Org. Chem.*, **26**, 2421 (1961).

(16) The values observed for this chromophore are in good agreement with the 247-mμ absorption maximum reported for the 2-methyl-$\Delta^{1,4}$-3-keto chromophore by A. Bernstein, M. Heller, R. Littell, S. M. Stolar, R. H. Lenhard, W. S. Allen, and I. Ringler, *J. Am. Chem. Soc.*, **81**, 1696 (1959).

Table II. Although the existence of an equilibrium is inferred by this data, the evidence is less convincing for the following reasons. The wave-length shifts occurring in acid medium and in dioxane are much less pronounced in this series. The agreement between the spectra measured in ethanolic hydrochloric acid (λ_{max} 236 mμ) and that of the 2-methyl-Δ^1-3-keto chromophore (λ_{max} 241 mμ)[17] is not good. Finally, the magnitude of the solvent effect between ethanol and dioxane is not known for the 2-formyl Δ^1-3-ketones. Clearly these facts preclude a satisfactory interpretation of the data set forth in Table II. In alkaline medium the ultraviolet spectra of the 2-formyl Δ^1- and $\Delta^{1,4}$-3-ketones also exhibited a series of well-defined changes which were quite unexpected for these structures[18] (see Tables II and III). In fact, these spectra are very similar to the alkaline spectra of 2-hydroxymethylene-3-keto and Δ^4-3-keto steroids.[19,20] This suggests that the alkali shifts are due to the addition of alkoxide at C-1 and that the species responsible for the observed spectra is the sodio salt of the 1-ethoxy-2-hydroxymethylene 3-ketone (see Scheme III).

SCHEME III



Experimental[21]

17β-Hydroxy-2-propionoxymethylene-5α-androstan-3-one 17-Propionate (Ib).—A solution of 5 g. of 17β-hydroxy-2-hydroxymethylene-5α-androstan-3-one (Ia)[5] in 75 ml. of propionic anhydride–pyridine mixture (1:2) was left standing for 20 hr. at room temperature and then poured into 750 ml. of ice–water. The precipitate was collected, washed with water, and dried to yield 5.8 g. of bispropionate Ib of satisfactory purity for the next reaction. A small sample was purified by crystallization from acetone–hexane and exhibited m.p. 169–171°; $[\alpha]_D$ +22°; λ_{max} 256 mμ (log ϵ 4.08); λ_{max}^{KBr} 5.62, 5.79, 5.93, and 6.22 μ.

Anal. Calcd. for $C_{26}H_{38}O_5$: C, 72.52; H, 8.90; O, 18.58. Found: C, 72.71; H, 8.92; O, 18.59.

17β-Hydroxy-2-hydroxymethylene-5α-androstan-3-one 17-Propionate (Ic).—A solution of 3 g. of the bispropionate derivative Ib in 600 ml. of ethyl acetate was added to 300 ml. of aqueous 2 *N* hydrochloric acid and the resulting mixture was shaken vigorously for 20 min. After separation of the aqueous phase, the ethyl acetate solution was washed with water to neutrality, dried (Na_2SO_4), and evaporated to yield 1.9 g. of the 2-hydroxymethylene compound Ic. Three crystallizations of a small sample from acetone–hexane afforded an analytical specimen with m.p. 180–182°; $[\alpha]_D$ +31°; λ_{max} 283 mμ (log ϵ 3.97); λ_{max}^{KBr} 3.30–3.55, 5.75, and 6.35–6.45 μ.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.46; H, 9.04.

20-Cycloethylenedioxy-5α-pregnan-3β-ol.—A solution of 143 g. of 3β-hydroxy-5α-pregnan-20-one in 3 l. of benzene and 230 ml. of ethyleneglycol was added to a 5-l. flask equipped with a water separator. After the addition of 8.7 g. of *p*-toluenesulfonic acid monohydrate, the mixture was heated under reflux with stirring until water no longer distilled from the reaction (*ca.* 72 hr.). Ethyl acetate (2 l.) was added to the hot solution which was then washed with dilute aqueous sodium carbonate and water, dried (Na_2SO_4), and concentrated. Crystallization of the crude product from methylene chloride–methanol containing 1 drop of pyridine furnished 53 g. of the ketal, m.p. 174–175°, and a second crop of 41.7 g. with m.p. 171–173°. Several crystallizations of a small sample from the same solvent combination gave an analytical sample, m.p. 174–176°, $[\alpha]_D$ +93°.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76; O, 10.05. Found: C, 78.97; H, 10.74; O, 10.12.

20-Cycloethylenedioxy-5α-pregnan-3-one (Ie).—A slurry of chromium trioxide–pyridine complex, prepared by the cautious addition of 20 g. of chromium trioxide to 120 ml. of cold pyridine, was added to a cold solution of 20 g. of the foregoing ketal in 120 ml. of pyridine. The reaction mixture was left in the cold (*ca.* 5°) for 18 hr. and then diluted with 2.5 l. of ether. The insoluble precipitate was separated by filtration and the filtrate, after saturation with sulfur dioxide, was washed with water, dilute aqueous tartaric acid solution, and water. Concentration of the sodium sulfate dried ether solution followed by crystallization from methylene chloride–methanol containing 1 drop of pyridine furnished 16.9 g. of 20-cycloethylenedioxy-5α-pregnan-3-one (Ie), m.p. 184–186°. A pure sample of Ie prepared from the same solvent pair exhibited m.p. 186–188°, $[\alpha]_D$ +33°, λ_{max}^{KBr} 5.80 μ.

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07; O, 13.31. Found: C, 76.36; H, 9.96; O, 13.25.

20-Cycloethylenedioxy-2-hydroxymethylene-5α-pregnan-3-one (If).—A solution of 10 g. of 20-cycloethylenedioxy-5α-pregnan-3-one (Ie) in benzene (300 ml.) was boiled until 50 ml. of solvent had been removed by distillation. Sodium methoxide (6 g.) and ethyl formate (10 ml.) were added to the cooled solution which was stirred at room temperature in a nitrogen atmosphere for 12 hr. and left standing for an additional 24 hr. Sufficient water was added to dissolve the precipitated sodium salt, and the aqueous phase was separated. This was acidified with a slight excess of 5% aqueous tartaric acid solution and the liberated hydroxymethylene compound was extracted with ethyl acetate. Evaporation of the solvent provided 10.5 g. of If which was obtained as a yellow powder with m.p. 176–178°, $[\alpha]_D$ +68°, λ_{max} 282 mμ (log ϵ 3.91), λ_{max}^{KBr} 6.45 μ.

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34; O, 16.47. Found: C, 73.94; H, 9.36; O, 16.63.

2-Hydroxymethylenepregn-4-ene-3,20-dione (Ih).—A solution of 20-cycloethylenedioxy-2-hydroxymethylenepregn-4-en-3-one (Ig,[22] 0.5 g.) in acetone (50 ml.) containing concentrated hydrochloric acid (0.3 ml.) was left standing at room temperature for 30 min. This solution was diluted with 300 ml. of water, and the product was extracted by shaking with three 150-ml. portions of ethyl acetate. The combined extracts were washed with water to neutrality, dried (Na_2SO_4), and concentrated to dryness. Crystallization of the solid residue from acetone–water yielded 0.3 g. of the 2-hydroxymethylene compound (Ih): m.p. 158–160°, three additional crystallizations from the same solvent pair raised the melting point to 164–166°; $[\alpha]_D$ +141°; λ_{max} 253 and 307 mμ (log ϵ 4.08 and 3.80); λ_{max}^{KBr} 5.87, 6.10, and 6.38 μ.

Anal. Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.92; O, 14.08. Found: C, 77.39; H, 8.92; O, 14.08.

20-Cycloethylenedioxy-17α-hydroxy-2-hydroxymethylenepregn-4-en-3-one (Ij).—A mixture of 16 g. of 20-cycloethylenedioxy-17α-hydroxypregn-4-en-3-one (Ii),[23] 10 g. of sodium methoxide, 16.7 ml. of ethyl formate, and 450 ml. of dry benzene was stirred for 18 hr. at room temperature in a nitrogen atmosphere. The precipitate was collected and dried, and the benzene filtrate was extracted once with 500 ml. of water. The dried solid was added to the aqueous extract and the resulting suspension was stirred for several minutes with 200 ml. of 5% aqueous tartaric acid solution. The precipitate which remained was collected, washed with water, and dried. There was obtained 12 g. of crude 2-hydroxymethylene compound Ij which exhibited m.p. 210–215°, λ_{max} 253 and 307 mμ (log ϵ 4.06 and 3.77). Since this

(17) For example see R. Mauli, H. J. Ringold, and C. Djerassi, *J. Am. Chem. Soc.*, **82**, 5494 (1960).

(18) Since the aldehyde is incapable of enolization and the ketone should not be stable in the enolic form, then the addition of alkali should produce little change in the ultraviolet spectra of these compounds.

(19) In basic medium 2-hydroxymethylene-3-keto steroids of the pregnane series show maximal absorption at 314.5 mμ in the ultraviolet. The corresponding 2-hydroxymethylene-Δ^4-3 ketones are characterized by two maxima at 242 and 357 mμ: see R. Hirschmann, P. Buchschacher, N. G. Steinberg, J. H. Fried, R. Ellis, G. J. Kent, and M. Tishler, *J. Am. Chem. Soc.*, **86**, 1520 (1964).

(20) We are indebted to the referee for drawing our attention to this point.

(21) All rotations are for chloroform solutions at 16–22° and ultraviolet spectra for ethanol solutions, except where stated otherwise. Microanalyses were by Midwest Micro Laboratories, Indianapolis 20, Ind., or by Dr. A. Bernhardt, Mülheim (Ruhr), Germany.

(22) H. M. Kissman, A. S. Hoffman, and M. J. Weiss, *J. Org. Chem.*, **26**, 2610 (1961).

(23) P. L. Julian, E. W. Meyer, and I. Ryden, *J. Am. Chem. Soc.*, **72**, 367 (1950).

product failed to crystallize from a number of solvents, it was dehydrogenated without further purification.

General Procedure for the Dehydrogenation of 2-Hydroxymethylene-3-keto Steroids.—All reactions were carried out at room temperature. The dioxane was purified by distillation from sodium hydroxide pellets and redistillation from sodium.

A solution of the steroid (0.5 g.) in 12.5–25 ml. of dioxane was treated with 1.1–1.5 molar equiv. of DDQ in an equal volume of the same solvent. After standing for 1–5 min. the reaction mixture was diluted with 150–500 ml. of methylene chloride, and the product was isolated by employing either of the following procedures.

Method A.—The above methylene chloride solution was washed with several portions of 2% aqueous sodium hydroxide solution and then with water until neutral. The sodium sulfate dried extract was treated with decolorizing carbon, filtered through Celite, and concentrated to dryness *in vacuo*.

Method B.—The above methylene chloride solution was filtered through a column of neutral alumina (40 times the weight of starting material). The column was washed with an additional quantity of methylene chloride, then with ethyl acetate, if necessary, and the combined eluates were evaporated.

Usually the crude dehydrogenation products so obtained were nicely crystalline solids and could be purified further by direct crystallization. Compounds which could not be purified in this manner were chromatographed on alumina or silica gel.

2-Formyl-5α-pregn-1-ene-3,20-dione (IIc).—A solution of 1.2 g. of DDQ in 20 ml. of dioxan was added to a solution of 2 g. of 20-cycloethylenedioxy-2-hydroxymethylene-5α-pregnan-3-one (If) in 100 ml. of dioxane. After 1.5 min. methylene chloride (200 ml.) was added, and the resulting solution was filtered through a column of 120 g. of alumina. One liter of solvent was passed through the column and then the combined eluates were evaporated to dryness. An acetone solution (100 ml.) of the oily product containing 15 drops of concentrated hydrochloric acid was left standing at room temperature for 1 hr. and then diluted with ethyl acetate. This solution was washed with water, dried (Na_2SO_4), and evaporated. A benzene solution of the oily residue was adsorbed on a column of 50 g. of silica gel and the 2-formyl-5α-pregn-1-ene-3,20-dione (IIc) was eluted with benzene–ethyl acetate (9:1). Several crystallizations from acetone–hexane gave 0.25 g. of IIc, m.p. 194–196°. Additional constants are reported in Table I.

2-Formyl-11β,17α,21-trihydroxypregna-1,4-diene-3,20-dione 21-Acetate (2-Formylprednisolone 21-Acetate, IIi).—A solution of 60% formic acid (18 ml.) was heated to boiling and then cooled briefly. After the addition of 0.5 g. of 17α,20:20,21-bismethylenedioxy-2-formyl-11β-hydroxypregna-1,4-dien-3-one (IIh), the hot solution was heated quickly to the boiling point, in a nitrogen atmosphere, maintained at this temperature for 3.5 min. and then cooled rapidly in an ice bath. The cold reaction mixture was poured into 200 ml. of saturated brine, and the product was extracted with methylene chloride. The combined methylene chloride extracts were washed with dilute sodium carbonate solution and water, dried (Na_2SO_4), and concentrated.

A second 0.5-g. portion of IIh was processed in the same manner, and the product was added to the residue of the first hydrolysis with 50 ml. of methanol. The resulting solution was cooled to 0° and treated with an equal volume of 1% methanolic sodium hydroxide. After standing for 30 min. at 0° in a nitrogen atmosphere, the reaction mixture was neutralized with acetic acid and poured into 250 ml. of saturated brine. Isolation with methylene chloride afforded 0.7 g. of oil which was acetylated in the usual manner with 20 ml. of acetic anhydride–pyridine mixture (1:2) at room temperature for 5 hr. The semicrystalline acetate (0.5 g.) was dissolved in methylene chloride and chromatographed on 20 g. of silica gel. Elution with methylene chloride–ethyl acetate mixtures (1:4 and 1:1) provided 0.2 g. of 2-formylprednisolone 21-acetate, m.p. 240–245°. A pure sample of this substance, prepared by crystallization from acetone–hexane, exhibited m.p. 253–255°; $[\alpha]_D$ +76°; λ_{max} 220 and 244 mμ (log ε 4.18 and 4.08); λ_{max}^{KBr} 5.75, 5.90, 6.03, 6.17, and 6.25 μ.

Anal. Calcd. for $C_{21}H_{30}O_7$: C, 66.96; H, 7.02; O, 26.02. Found: C, 67.24; H, 7.17; O, 25.62.

17α,21-Dihydroxy-2-formylpregna-1,4-diene-3,11,20-trione (2-Formylprednisone, IIk).—A solution of 0.35 g. of 2-formylprednisone-BMD (IIj) in 20 ml. of 60% formic acid was heated under reflux for 15 min., and the product was isolated as described in the preceding experiment. Treatment of the crude residue (0.33 g.) in methanol (16 ml.) with a solution of 0.12 g. of sodium hydroxide in an equal volume of methanol according to the hydrolysis conditions for the preceding experiment gave 0.3 g. of crude 2-formylprednisone (IIk). Purification on a column of silica gel (12 g.) followed by crystallization (acetone–hexane) of the fractions eluted with methylene chloride–acetone (6:1) furnished 0.1 g. of IIk: m.p. 246–248°; $[\alpha]_D$ +96°; λ_{max} 215 mμ (log ε 4.18); λ_{max}^{KBr} 5.80–5.90, 6.00, 6.15, and 6.25 μ.

Anal. Calcd. for $C_{22}H_{26}O_6$: C, 68.38; H, 6.78; O, 24.84. Found: C, 68.14; H, 6.75; O, 25.05.

Synthesis and Chemistry of 16-Methylene and Δ^{15}-16-Methyl Cortical Steroids

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The synthesis of 16-methylene cortical steroids by two routes is described. The first route consists of the four-step conversion of 3α,17α-dihydroxy-16-methylenepregnane-11,20-dione (Ia) into 16-methyleneprednisone 21-acetate (IV). The second process, involving formation and acid-catalyzed opening of 16β-methyl 16α,17α-oxides, is illustrated by the conversion of 9α-fluoroprednisolone 21-acetate (XIV) into 16-methylene-9α-fluoroprednisolone 21-acetate (XXVII) and its endocyclic isomer, Δ^{15}-16-methyl-9α-fluoroprednisolone 21-acetate (XXVIII). During the course of this work, the reaction of 16-methylene and Δ^{15}-16-methyl-17-hydroxypregnenes with bromonium ion to yield bromo oxides and the Kägi–Miescher rearrangement of certain 17α-hydroxy-20-ketopregnane-20-semicarbazones were studied.

In this paper we present the details of our studies on the isomeric 16-methylene and Δ^{15}-16-methyl cortical steroids.[1,2]

Our first objective was 16-methyleneprednisone 21-acetate (IV) which we hoped to prepare by suitable modification of 3α,17α-dihydroxy-16-methylenepregnane-11,20-dione (Ia)[3,4] utilizing procedures compatible with the reactivity of the 16-*exo* double bond. Reaction of Ia with 1.2 molar equiv. of bromine led to the 21-bromide IIa in 80% yield.[5] The 21-acetate IIb

(1) For preliminary accounts of portions of this work, see (a) D. Taub, R. D. Hoffsommer, and N. L. Wendler, *J. Org. Chem.*, **25**, 2258 (1960); (b) R. D. Hoffsommer, D. Taub, and N. L. Wendler, *Chem. Ind.* (London), 251 (1961).

(2) Aspects of this field have been investigated by other groups: *inter alia* (a) H. J. Mannhardt, F. v. Werder, K. H. Bork, H. Metz, and K. Brückner, *Tetrahedron Letters*, **No. 16**, 21 (1960); (b) E. Batres, T. Cardenas, J. A. Edwards, G. Monroy, O. Mancera, C. Djerassi, and H. Ringold, *J. Org. Chem.*, **26**, 871 (1961).

(3) D. Taub, R. D. Hoffsommer, H. L. Slates, C. H. Kuo, and N. L. Wendler, *J. Am. Chem. Soc.*, **80**, 4435 (1958); **82**, 4012 (1960).

(4) G. Nominé, D. Bertin, and A. Pierdet, *Tetrahedron*, **8**, 217 (1960).