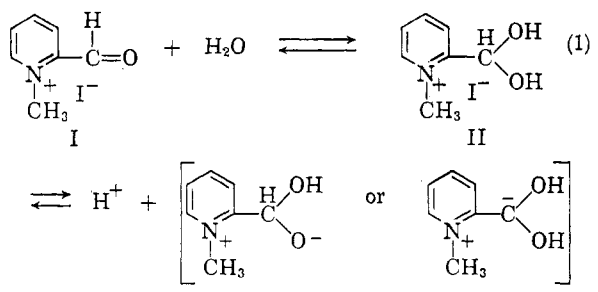
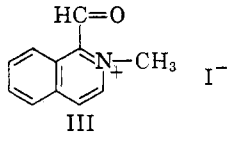
pK_a 9.8–10.0.[1] It was concluded that the titration was due to a neutralization equilibrium (Equation 1) and not a decomposition of the aldehydic function. The ability of I to form a stable *gem*-



(1)

glycol (II) as well as the acid character of II were attributed to the strong electron-withdrawing character of the pyridinium ring. Subsequently, it was found that 1-formyl-2-methylisoquinolinium iodide (III) (in which it would be expected that the



III

π-electron density of the ring at the position of the carbonyl group is markedly lower than in the 2-position of I)[2] was decomposed rapidly during a titration with 0.1*N* alkali at 3–5°. Back titration indicated the presence of a conjugate base of a weak acid of pK_a 4.0. It is reasonable to assume that either the Cannizzaro reaction or cleavage (loss of —CHO as formic acid) occurred. In any case, the discovery that III is attacked by dilute alkali at such a rapid rate is interesting and may stimulate a more thorough investigation.

EXPERIMENTAL

1-Formyl-2-methylisoquinolinium iodide. To 0.97 g. (6.2×10^{-3} mole) of 1-isoquinoline carboxaldehyde (m.p. 53°; reported[3] 55–55.5°) dissolved in acetone and contained in a carbonated beverage bottle was added 8.8 g. (0.062 mole) of methyl iodide. The bottle was capped and heated in an oven at 60° for six days. The reaction mixture was cooled and filtered to give 0.48 g. (26%) of a red crystalline solid (needles) m.p. 203–205° dec. An infrared absorption spectrum was determined in potassium bromide and the curve exhibited a strong absorption band at 5.86 μ in carbonyl stretching region. Ultraviolet absorption maxima in water, 2.5×10^{-5} *M*, mμ (log ϵ): *p*H 6.5, 341(3.65), 282(3.41); *p*H 12.0, 334 (3.65), 272(3.63).

Anal. Calcd. for $C_{11}H_{10}INO$: C, 44.1; H, 3.4; O, 5.3. Found: C, 43.5; H, 3.4; O, 5.6.

Potentiometric titration of 1-formyl-2-methylisoquinolinium iodide (III). Potentiometric titration of III (100 mg. in 10 ml. distilled water) with standard 0.1*N* sodium hydroxide, either at 3–5° or room temperature, gave curves which indicated a pK_a value between 9 and 10 and a neutralization equivalent of 299 ± 5 (calcd. 299). Immediate back titration with 0.1*N* hydrochloric acid indicated a function of pK_a 4.0 and a neutralization equivalent of 600. This neutralization equivalent corresponds to one mole of acid from two moles of carboxaldehyde as would be expected from a Cannizzaro reaction. A Beckmann Model H2 *p*H meter was used in this work.

Acknowledgment. Elemental analyses were performed by the Analytical Research Branch, U. S. Army Chemical Research and Development Laboratories, Army Chemical Center, Md. The author wishes to acknowledge the technical assistance of Arthur Jones and Arthur Melvin and a criticism of the manuscript by Dr. David N. Kramer. The sample of 1-isoquinoline carboxaldehyde was kindly provided by R. M. Poirier of Battelle Memorial Institute.

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(1) G. M. Steinberg, E. J. Poziomek, and B. E. Hackley, Jr., *J. Org. Chem.*, **26**, 368 (1961).

(2) This is based on a qualitative correlation of electron densities of various heterocyclic rings. H. C. Longuet-Higgins and C. A. Coulson, *Trans. Faraday Soc.*, **43**, 87 (1947).

(3) R. S. Barrows and H. G. Lindwall, *J. Am. Chem. Soc.*, **64**, 2430 (1942).

Cortical Steroids as Acetal-Forming Compounds with Aldehydes and Ketones

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The recent communication by Tanabe and Bigley[1] on the 17α,21-isopropylenedioxy steroids has prompted us to report the results of our independent work on the cyclic acetals of steroids with a dihydroxy acetone side chain.

We have prepared several 17α,21-cyclic acetals (Table I) by an acid catalyzed interchange reaction[2] between cortical steroids and lower alkyl acetals of aliphatic, cycloaliphatic, or arylaliphatic aldehydes or ketones.[3] By our procedure (see Experimental) yields were often as high as 90%, particularly in the cases of the cyclopentanone and benzaldehyde derivatives.[4]

When a β-oriented hydroxyl group is present at C-11, this also undergoes the interchange reaction; in this instance, in addition to the expected acetal I,

(1) M. Tanabe and B. Bigley, *J. Am. Chem. Soc.* **83**, 756 (1961).

(2) Nonsteroidal acetals have already been prepared in a similar way. *Cf.* M. Delépine, *Bull. soc. chim. France* (3) **25**, 574 (1901); *Ann. Chim.* (7) **23**, 378 (1901).

(3) Steroids with dihydroxyacetone side chain do not react directly with aldehydes and ketones, or they do so in a quite different manner as in the case of formaldehyde. See R. E. Beyler, R. M. Moriarty, F. Hoffman, and L. H. Sarett, *J. Am. Chem. Soc.* **80**, 1517 (1958).

(4) Benzaldehyde, as well as many other carbonylic compounds, should give two epimeric acetals due to formation of a new asymmetric carbon atom. Up to now, however, we have been able to obtain only one derivative.

TABLE I

17α,21-DERIVATIVE

Derivative of	Reaction with	M.P.	$[\alpha]_D^{20}$	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Cortexolone	Benzaldehyde	162–163	+65	77.39	77.35	7.89	7.69
Cortexolone	Cyclopentanone	178–180	+93	75.69	75.90	8.80	8.83
Cortexolone 3-ethyl enol ether	Cyclopentanone	113–116	−100	76.32	76.45	9.15	9.12
Cortisone	Benzaldehyde	200–203	+100	74.97	75.09	7.19	7.17
Cortisone	Acetone	169–173	+152[a]	71.97	71.88	8.05	8.05
Cortisone	Cyclopentanone	242–243	+155.5	73.21	72.91	8.04	8.00
Cortisone	Cyclohexanone	237–239	+151	73.60	73.42	8.24	8.13
Cortisone 3-ethyl enol ether	Cyclopentanone	127–130	−45	73.98	74.05	8.43	8.41
16α-Bromocortisone	Cyclopentanone	183–184	+183	61.78	62.20	6.58	6.43
Prednisone	Acetaldehyde	196–198	+182	71.85	71.96	7.34	7.36
Prednisone	Butyraldehyde	183–185	+144	72.79	72.39	7.82	7.89
Prednisone	(2-Methyl)butyraldehyde	220–224	+144	73.21	73.18	8.04	8.17
Prednisone	Caproaldehyde	105–108	+140	73.60	73.57	8.24	8.12
Prednisone	Acetone	200–202	+167[b]	72.33	72.32	7.59	7.58
Prednisone	Cyclopentanone	201–203	+146.5	73.56	73.53	7.60	7.51
Prednisone	Cyclohexanone	243–244	+140	73.94	73.59	7.82	7.82
Cortisol	Acetone	194–195	+142	71.61	71.58	8.51	8.37
Cortisol	Cyclopentanone	225–230	+120	72.86	72.64	8.47	8.48
Prednisolone	Acetaldehyde	217–221	+100	71.48	71.30	7.82	8.00
Prednisolone	Acetone	245–246	+104[c]	71.97	71.79	8.05	8.07
Prednisolone	Cyclopentanone	228–230	+90	73.21	73.17	8.04	8.01
9α-Fluoroprednisolone	Acetone	210–212	+99	68.87	68.57	7.46	7.23
	11β,17α,21-BIS DERIVATIVE (II. Y = C_2H_5)						
Cortisol	Acetone	Glass	+108	71.28	71.24	9.08	8.80
Prednisolone	Acetaldehyde	156–160	+140	70.71	70.58	8.35	8.43
Prednisolone	Benzaldehyde	216–218	+110	76.26	76.17	7.27	7.08
Prednisolone	Acetone	Glass	+100	71.57	71.39	8.70	8.45

[a] Reported[1] m.p. 180–185°, $[\alpha]_D$ + 200° (chloroform). [b] Reported[1] m.p. 201–203°, $[\alpha]_D$ + 214° (chloroform). [c] Reported[1] m.p. 243–247°, $[\alpha]_D$ + 106° (chloroform).

a second product II,[5] easily identifiable by infrared spectrum (lack of hydroxyl band)[6] and by paper chromatography,[7] can be isolated.

The ratio of these two derivatives is closely dependent on both the nature and the quantities of the reacting compounds. For example prednisolone reacts with cyclopentanone diethyl acetal, giving primarily the monoderivative I (yield 65%); on the contrary, on reaction with benzaldehyde diethyl acetal, the bisderivative II is obtained in 70% yield. In both instances, however, the minor component is detectable by paper chromatography. With the diethyl acetals of either acetone or acetaldehyde, nearly equal quantities of I and II are obtained; but the ratio can be shifted towards I or II by employing a lesser or greater amount, respectively, of the reagent acetal. Derivatives I and II can be easily separated from the mixture by chromatography on Florisil.

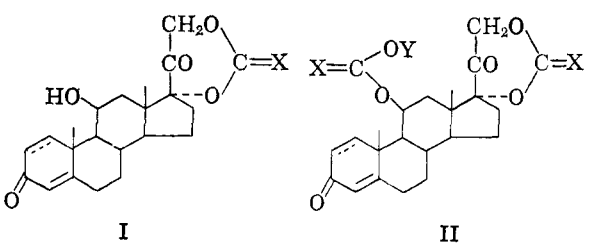
The ability of the 11β-hydroxyl group to give acetals is somewhat decreased by the absence of a free dihydroxyacetone side chain in the starting compound. However, by using the general procedure, we were still able to obtain from prednisolone 21-acetate the corresponding 11-(α-ethoxy)benzyl ether, although not in a fully satisfactory yield. Corticosterone 21-acetate gave the proposed substance in quantities detectable by papergram only.

The parent steroid may be regenerated from all of the above described steroidal acetals, including the bisderivatives II, by acid hydrolysis in a yield higher than 95%; they are stable to base.

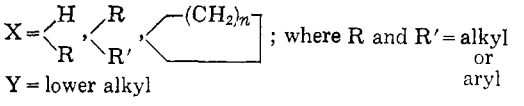
(5) While writing this paper, we have read that D. K. Fukushima and S. Daum, *J. Org. Chem.* 26, 520 (1961), have obtained the 11β-methoxymethyl ether of 17α,20; 20,21-bismethylenedioxyhydrocortisone as a by-product of hydrocortisone BMD preparation.

(6) The infrared spectra of the 17α,21-cyclic acetals in Nujol mull show a characteristic prominent band at 1128–1125 cm.$^{-1}$, as well as a significant shift (10–30 cm.$^{-1}$) of the 20-carbonyl band towards higher frequencies. The compounds with an acetal group at C-11 exhibit a strong and broad absorption between 1130 and 990 cm.$^{-1}$

(7) Using the modified Bush-type system E4 of W. R. Eberlein and A. M. Bongiovanni, *Arch. Biochem. Bioph.* 59, 90 (1958), prednisolone derivatives I exhibit an average R_f corresponding to 0.75, whereas the derivatives II present a R_f value of 0.9.



I II



; where R and R′ = alkyl or aryl

Y = lower alkyl

We have also prepared some 3-enol ethers of 17α,21-acetals,[8] either by enoletherification of the preformed 17α,21-acetal or by acetalization of a 3-enol ether.

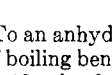
The usefulness of all these compounds as intermediates for several reactions is quite evident; a further advantage is the possibility of obtaining, in 11β,17α,21-trihydroxy steroids, an adequate protection either of the three hydroxy groups or of those of the side chain only, by employing the benzaldehyde and the cyclopentanone acetals, respectively.

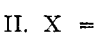
Moreover, some of these acetals are of peculiar biological interest. For instance, prednisolone acetonide (administered orally in oily solution) and prednisolone cyclopentylidenedioxy derivative (applied locally) exhibit an enhanced anti-inflammatory activity in comparison with that of the parent alcohol.[9]

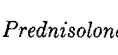
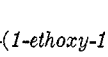
EXPERIMENTAL[10]

The following examples are given to illustrate the methods used to prepare the compounds listed in Table I.

17α,21-Cyclopentylidenedioxy-Δ^4-pregnene-3,11,20-trione. A suspension of 2 g. of cortisone in 800 ml. of benzene containing 5 mg. of *p*-toluenesulfonic acid was rendered anhydrous by brief distillation, at which point 5 ml. of cyclopentanone diethyl acetal was added, the distillation being vigorously continued for 20 min. Neutralization with pyridine, solvent evaporation, and addition of methanol, gave 2.2 g. of the cyclopentylidenedioxy compound, m.p. 232–235°. One crystallization from methanol raised the melting point to 239–240°. Rotation and analytical data are recorded in Table I. Hydrolysis of this acetal (250 mg.) by heating in methanol with a few drops of *N* hydrochloric acid for 15 min. yielded 205 mg. of cortisone, m.p. 217–220°.

17α,21-Cyclopentylidenedioxy-$\Delta^{1,4}$-pregnadiene-11β-ol-3,20-dione (I. X =  , Δ^1). To an anhydrous suspension of 5 g. of prednisolone in 900 ml. of boiling benzene containing 10 mg. of *p*-toluenesulfonic acid, 10 ml. of cyclopentanone diethyl acetal was added, and the mixture was heated with rapid distillation of the solvent. In 15 min. prednisolone was completely dissolved. After 30 min. of distillation a few drops of pyridine was added; the solvent was partially evaporated and the residue chromatographed on 100 g. of Florisil. Elution with petroleum ether–benzene mixtures gave 3.85 g. of the product, m.p. 225–228°, which was recrystallized from methanol.

17α,21-Benzylidenedioxy-$\Delta^{1,4}$-pregnadiene-11β-ol-3,20-dione 11-(α-ethoxy)benzyl ether. (II. X =  , Y = C_2H_5, Δ^1). The reaction of prednisolone (3 g.) with 5 ml. of benzaldehyde diethyl acetal in the presence of 5 mg. of *p*-toluenesulfonic acid, performed according to the general procedure, yielded directly, after solvent evaporation and digestion with methanol, 2.3 g. of product, m.p. 195–210°. The melting point rose to 213–215° after one crystallization from methanol. Hydrolysis of the acetal (300 mg.) with methanolic hydrochloric acid as above described gave 175 mg. of prednisolone, m.p. 234–236°.

Prednisolone 17α,21-acetonide (I. X =  , Δ^1) *and its 11-(1-ethoxy-1-methyl)ethyl ether* (II. X =  , Y = C_2H_5, Δ^1). A. The oily product obtained from the reaction of 3 g. of prednisolone with 15 ml. of acetone diethyl ketal and 9 mg. of *p*-toluenesulfonic acid, carried out in benzene as described above, was chromatographed on 60 g. of Florisil. Elution with petroleum ether–benzene mixtures afforded 1.1 g. of a glass with infrared spectrum and analytical data (recorded in Table I) corresponding to the bisacetal II. Further elution with benzene–ether mixtures yielded 750 mg. of prednisolone acetonide, m.p. 238–241°.

B. The reaction of 5 g. of prednisolone with 8 ml. acetone diethyl ketal performed with the same procedure gave, after solvent evaporation, digestion with petroleum ether and crystallization from methanol, 2.7 g. of acetonide I, m.p. 238–240°. The bisacetal II was detected on papergram only. Hydrolysis of both compounds furnished prednisolone in 95% yield.

17α,21-Cyclopentylidenedioxy-Δ^4-pregnene-3,11,20-trione 3-ethyl enol ether. A suspension of 2 g. of cortisone cyclopentylidenedioxy derivative in 1.9 ml. of ethyl orthoformate, 1.5 ml. of tetrahydrofuran, and 1 ml. of ethanol was treated with 30 mg. of *p*-toluenesulfonic acid and stirred at room temperature for 15 min., at the end of which time the product was completely dissolved. After an additional 30 min., pyridine was added and most of the solvent was removed *in vacuo;* the residue was crystallized by addition of methanol, yielding 1.35 g. of enol ether, m.p. 123–126°. The same compound was also prepared by treating cortisone 3-ethyl enol ether[12] with cyclopentanone diethyl acetal as described above.

Prednisolone 11-(α-ethoxy)benzyl ether 21-acetate. The reaction of prednisolone 21-acetate (2 g.) with benzaldehyde diethyl acetal (5 ml.), carried out according to the general procedure, gave an oily product which was chromatographed on 40 g. of Florisil. Elution with benzene-ether mixtures afforded 300 mg. of the mixed acetal, m.p. 198–200°; $[\alpha]_D^{20}$ + 161°.

Anal. Calcd. for $C_{32}H_{40}O_7$: C, 71.62; H, 7.51. Found: C, 71.46; H, 7.70.

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(8) A. L. Nussbaum, E. Yuan, D. Dincer, and E. P. Oliveto (*in press*, personal communication) have obtained simultaneous formation of 3-methyl enol ether and 17α,21-acetonide by the use of dimethoxypropane. Such enoletherification does not occur when our milder procedure is used.

(9) Biological tests performed by Dr. Giovanni Falconi.

(10) Melting points are uncorrected. Rotations are in dioxane. The authors are indebted to Dr. Sergio Cairoli for the microanalyses and to Dr. Cesare Pedrali for the infrared spectra.

(12) A. Ercoli and R. Gardi, *J. Am. Chem. Soc.* **82**, 746 (1960).

Synthetic Furocoumarins. IV.[1] 2-Methyl-8*H*-furo[3,2-*h*][1]benzopyran-8-one, a Furocoumarin Derived from Catechol

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Several compounds containing the psoralene (I) system of a furan ring fused to the benzene portion of a coumarin have recently attracted much atten-

(1) Part III. K. D. Kaufman and L. R. Worden, *J. Org. Chem., in press.*