[CONTRIBUTION FROM THE LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

STEROIDAL CYCLIC KETALS. III.[1,2] HYDROCORTISONE AND RELATED CORTICOIDS

ROSE ANTONUCCI, SEYMOUR BERNSTEIN, MILTON HELLER, ROBERT LENHARD, RUDDY LITTELL, AND JAMES H. WILLIAMS

Received August 13, 1952

The purpose of this paper is to describe the preparation of hydrocortisone[3] (XIV), 11-epi-hydrocortisone (XV), and Reichstein's Substance E diacetate (V) from cortisone[4] (VII), or its acetate (III), by an essentially new and facile method which entails the protection of carbonyl groups as ethylene ketals.[5]

In this connection, Wendler, Huang-Minlon, and Tishler (1) have selectively protected the C-3, and -20 carbonyl groups of cortisone (VII) by semicarbazone formation. Moreover, these investigators demonstrated that cortisone acetate (III) formed only a 3-mono-semicarbazone. This revealed that the C-21 acetate group hindered the condensation reaction at the neighboring C-20 position. This steric effect has been noted previously by Mancera (2). Lithium borohydride reduction of cortisone-3,20-di-semicarbazone, followed by acetylation, and hydrolysis of the semicarbazone groupings (exchange reaction with pyruvic acid) afforded hydrocortisone acetate (XVI).

Reichstein's Substance S acetate (I) (Flowsheet I) on treatment with excess ethylene glycol (benzene, *p*-toluenesulfonic acid) afforded a mono-ethylene ketal to which the structure II has been assigned. The product exhibited no selective absorption in the ultraviolet region of the spectrum. The coincident rearrangement of the double bond from the C-4 to the -5 position during the formation of ethylene ketals of Δ^4-3-ketosteroids has been discussed previously (3). It is to be noted that here also the C-21 acetate group hindered the condensation of the C-20 carbonyl group with ethylene glycol. Similarly, only a 3-mono-ethylene ketal (IV) was obtained from cortisone acetate (III) (64% yield). However,

[1] Paper II, Antonucci, Bernstein, Lenhard, Sax, and Williams, *J. Org. Chem.*, **17**, 1369 (1952).

[2] Presented in part before the Organic Group at the Fourth Annual Meeting of the New York Section, American Chemical Society, New York, N. Y., February 8, 1952.

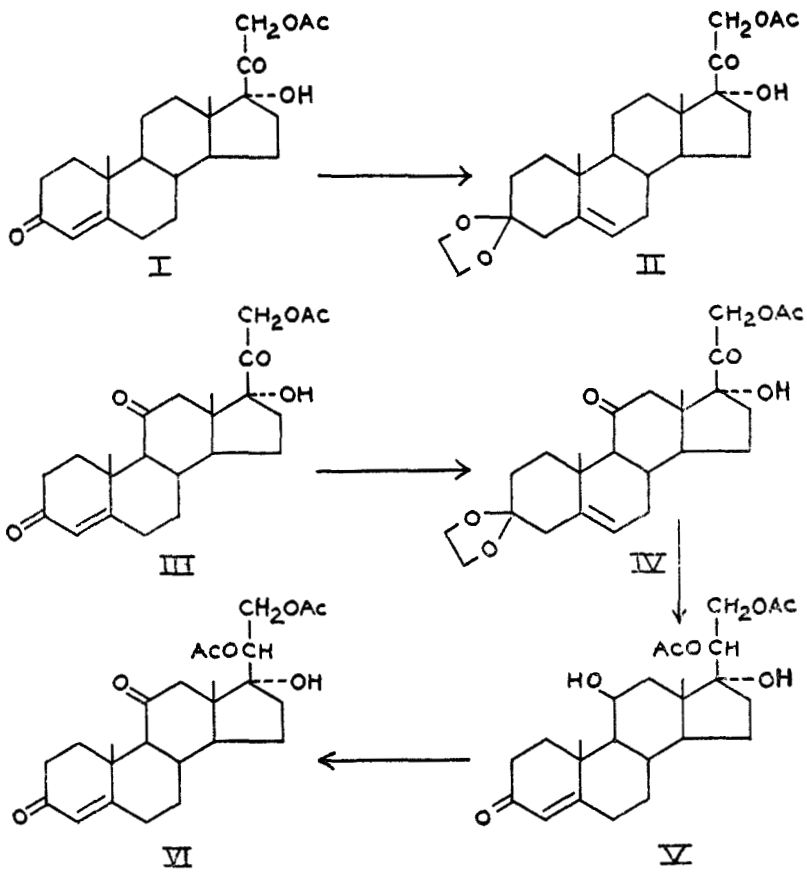
[3] Hydrocortisone = Kendall's Compound F = Reichstein's Substance M. The expression "hydrocortisone" was first used by E. C. Kendall in a paper before the American Academy of Orthopaedic Surgeons, Chicago, Illinois, January, 1951.

[4] Cortisone = Kendall's Compound E = Reichstein's Substance Fa = Wintersteiner's Compound F. For the expression "cortisone," see Hench, Kendall, Slocumb, and Polley, *Trans. Assoc. Am. Physicians*, **62**, 64 (1949).

[5] Other investigators have employed such a protective grouping in the steroid field; see, Fernholz and Stavely, Abstracts of the 102nd meeting of the American Chemical Society, Atlantic City, N. J., September 8–12, 1941, p. M39; Fernholz, U. S. Patents 2,356,154 (August 22, 1944) and 2,378,918 (June 26, 1945); Julian, Meyer, and Ryden, *J. Am. Chem. Soc.*, **72**, 367 (1950); **71**, 756 (1949); Julian, *Recent Progress in Hormone Research, The Proceedings of the Laurentian Hormone Conference*, Vol. VI, p. 195, Academic Press Inc., Publishers, New York, N. Y., 1951; and Rosenkranz, Pataki, and Djerassi (7b). (This last publication appeared after completion of our work.)

application of the reaction to cortisone (VII) (Flowsheet II) afforded the 3,20-di-ethylene ketal (VIII) (44% yield). (A further study of the preparation of this key intermediate is now in progress). The di-ketal (VIII) showed no selective absorption in the ultraviolet region of the spectrum. In addition, it was further characterized by conversion to the corresponding C-21 acetate (IX).

FLOWSHEET I

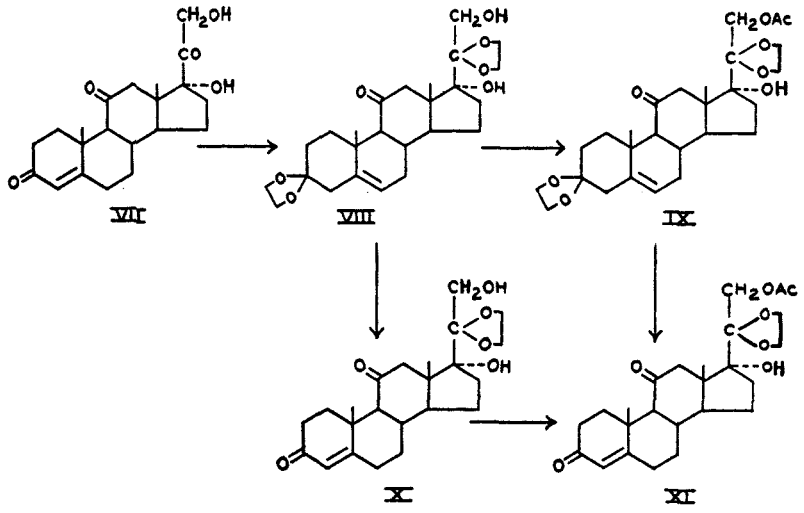


In previous papers of this series (3) it was shown that aqueous acetic acid rather than dilute sulfuric acid may be used in the hydrolysis of steroid ethylene ketals. Application of this hydrolytic procedure to the di-ethylene ketal of cortisone (VIII) led to a very interesting result. Treatment of VIII with 90% aqueous acetic acid removed selectively the C-3 ketal, and afforded the C-20 mono-ethylene ketal (X) of cortisone. The structure of X was indicated by elemental analysis, ultraviolet absorption spectrum, λ_{max} 238 mμ (characteristic of 11-keto-Δ^4-3-ketosteroids, *vide infra*), and a negative color test for the α-ketol group with 2,3,5-triphenyltetrazolium chloride reagent (4). Acetylation gave XI, identical in all respects with the product obtained by selective hydrolysis of the di-ethylene

ketal (IX) of cortisone acetate with 50% aqueous acetic acid. Compound XI (negative test) gave a positive test for the α-ketol group after treatment with dilute sulfuric acid. This was indicative of complete hydrolysis to cortisone (VII), which gives a decidedly positive test. These transformations establish a unique method for the selective protection of the C-20 carbonyl group in compounds of the "cortisone" type. No information is available on the application of this hydrolytic procedure to compounds of the "desoxycorticosterone" type (*i.e.*, C-17-$COCH_2OH$) in which the 17α-hydroxyl group is not present.

The mono-ethylene ketal (IV) (Flowsheet I) of cortisone acetate in tetrahydrofuran was treated with lithium aluminum hydride in ether; the reduction product was hydrolyzed with dilute sulfuric acid, and was reacetylated. In this manner, Reichstein's Substance E diacetate (V) (1, 5) was obtained. The product (V) gave a negative α-ketol color test, possessed an ultraviolet absorption maximum at 242 mμ (11-hydroxy-Δ^4-3-ketosteroid), and on oxidation with chromic acid was converted into Reichstein's Substance U diacetate (VI) (5b). Compound VI gave a negative α-ketol color test, possessed an ultraviolet absorption maximum at 237 mμ (11-keto-Δ^4-3-ketosteroid), and in concentrated sulfuric acid exhibited a maximum at 283 mμ and a minimum at 230 mμ (6). The *generally* stereospecific reduction of the C-11 and -20 carbonyl groups to afford hydroxy-compounds in the β-configuration at both centers has already been demonstrated (1, 5c, d, 7).

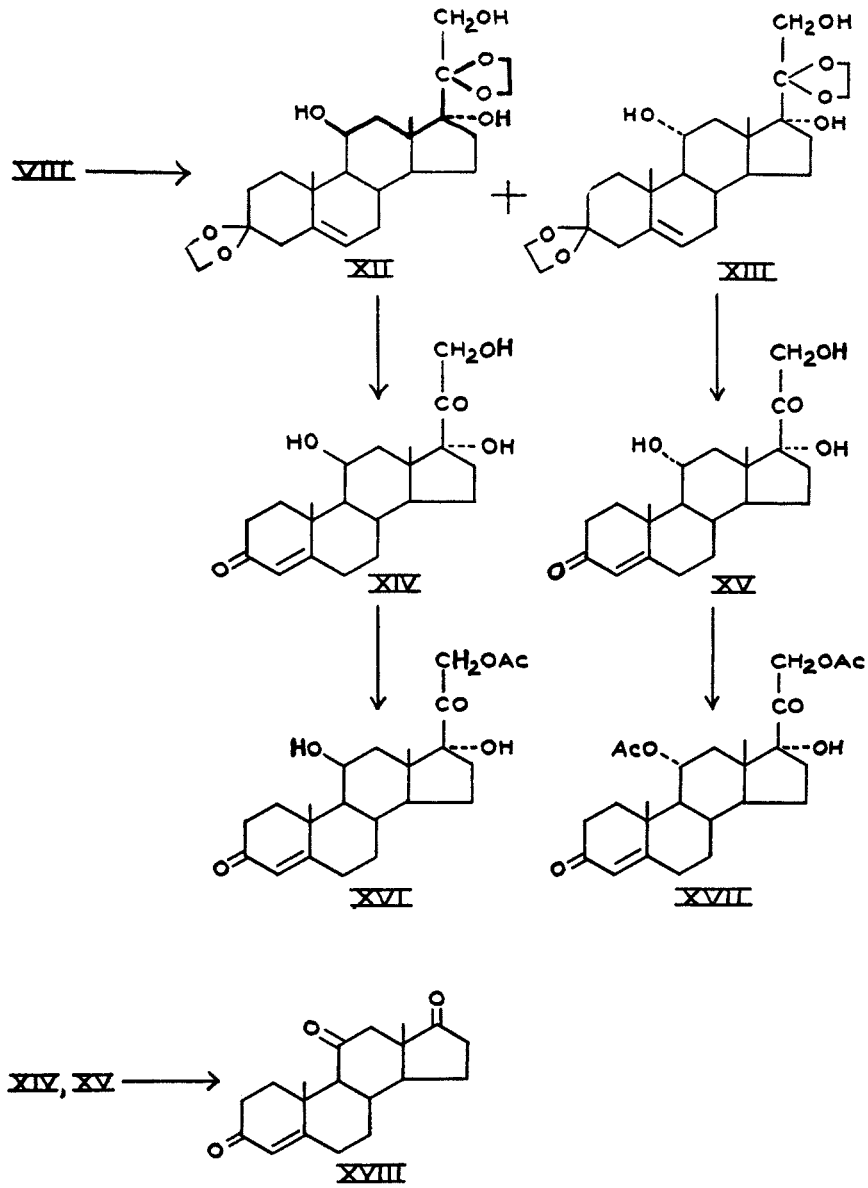
FLOWSHEET II



In the above described procedure for the preparation of Reichstein's E diacetate (V) we were primarily interested in the establishment of the synthetic route; conditions for optimal yields were not explored.

The synthesis of Reichstein's Substance E diacetate (V) from cortisone acetate (III) has been reported by others, who employed a similar procedure except for different protective groups at C-3, *i.e.*, enol-ether (5c, d), and semicarbazone (1).

FLOWSHEET III



When the di-ethylene ketal (VIII) of cortisone (Flowsheet III) in tetrahydrofuran was reduced with lithium aluminum hydride in ether, there was obtained two C-11 diastereomers which were readily separated and purified by recrystallization from suitable solvents; 11β-hydroxycompound (XII), m.p. 184–186°, $[\alpha]_D$ − 53° (pyridine), and 11α-hydroxycompound (XIII), m.p. 299–301°, $[\alpha]_D$

−31° (pyridine). The respective yields of XII and XIII were 58% (pure) and 8% (crude). The infrared spectra (not shown here) were different, and confirmed the non-identity of the two compounds. To our knowledge, this is the first time the 11α-isomer has been isolated and characterized in a lithium aluminum hydride reduction of a C-11 carbonyl group.

FIGURE I

INFRARED SPECTRA OF HYDROCORTISONE AND 11-EPI-HYDROCORTISONE

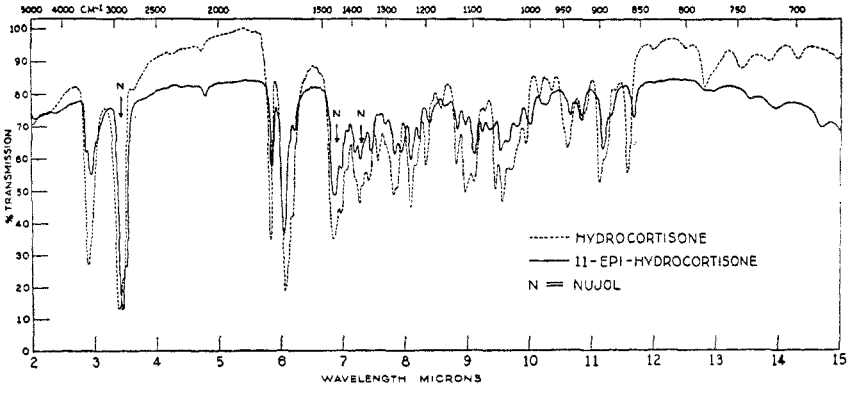
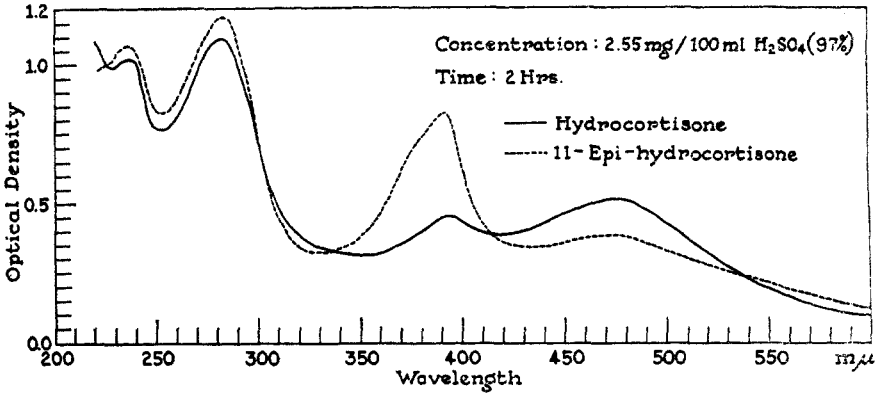


Figure II

SULFURIC ACID CHROMOGEN SPECTRA



Dilute sulfuric acid hydrolysis of the 11β-hydroxy-di-ketal (diethylene ketal of hydrocortisone) (XII) afforded in 70% yield pure hydrocortisone (XIV), whose properties were in excellent agreement with those reported in the literature (1, 5a, 6a, 8). Moreover, the infrared absorption spectrum of hydrocortisone (XIV) was identical with that of an authentic sample (Figure I) and the sulfuric acid chromogen spectrum was practically identical with that indicated by Zaffaroni (6c), and others (9) (Figure II). The monoacetate (XVI) was obtained on acetylation.

Dilute sulfuric acid hydrolysis of the 11α-hydroxy-di-ketal (di-ethylene ketal

of 11-epi-hydrocortisone) (XIII) afforded in 40% yield pure 11-epi-hydrocortisone (XV). The structure of the latter was indicated by the following evidence.

Elemental analysis, and an "active" hydrogen determination with lithium aluminum hydride showed the presence of three hydroxyl groups.

The compound on acetylation afforded a diacetate as indicated by analysis.[6]

The ultraviolet absorption spectrum of XV, λ_{max} 242 mμ, was characteristic of an 11-hydroxy-Δ^4-3-ketosteroid.

The sulfuric acid chromogen spectrum, showed about the same maxima and minima as for hydrocortisone (XIV), but the shape of the curves were decidedly

TABLE I

OPTICAL ROTATIONS OF 11-OXYGENATED STEROIDS

11-KETOCOMPOUND $[\alpha]_D$	11β-HYDROXYCOMPOUND $[\alpha]_D$	11α-HYDROXYCOMPOUND $[\alpha]_D$
11-Ketoprogesterone +239° (Ac)[a] (12)	11β-Hydroxyprogesterone +223° (Ac) (12) +217° (Ac) (7b)	11α-Hydroxyprogesterone +179° (C) (13)
22-Isoallospirostane-3β-ol-11-one −30°(C)[b]	22-Isoallospirostane-3β,11β-diol −49° (C)[b]	22-Isoallospirostane-3β,11α-diol −69° (C)[b]
Cortisone +201° (AA)[c]	Hydrocortisone +163° (AA)[c]	11-Epi-hydrocortisone +117° (AA)[c]
Reichstein's Substance U diacetate +177° (Ac)[c]	Reichstein's Substance E diacetate +164° (Ac)[c]	—
Di-ethylene ketal of cortisone ±0° (P)[c]	Di-ethylene ketal of hydrocortisone −52.9° (P)[c]	Di-ethylene ketal of 11-Epi-hydrocortisone −31° (P)[c]

[a] Ac = Acetone; C = Chloroform; AA = Absolute alcohol; P = Pyridine. [b] C. Djerassi, *et al.*, see footnote 6. [c] This work.

different (Figure II). Both spectra were conducted in a quantitative manner at identical concentrations and times of standing in sulfuric acid. It is significant that these two diastereomers may be differentiated in this manner. This enhances the possible utility of this type of spectral analysis for structural work.

The optical rotations of XIV and XV conform with the generalization of Borgstrom and Gallagher (10) that 11β-hydroxycompounds have a higher "positive" rotation than the corresponding 11α-isomer. In Table I are listed several C-11 epimeric pairs of compounds. These are additional to those listed by Borgstrom and Gallagher. Also in Table I are listed a number of the corresponding 11-keto-

[6] An 11α-hydroxyl group (in contrast to the 11β-isomer) is capable of acetylation, as shown by Long and Gallagher, *J. Biol. Chem.*, **162**, 511 (1946), and Gallagher and Long, *J. Biol. Chem.*, **162**, 521 (1946); see also, Djerassi, Batres, Velasco, and Rosenkranz, *J. Am. Chem. Soc.*, **74**, 1712 (1952).

TABLE II

ULTRAVIOLET ABSORPTION MAXIMA—11-KETOSTEROIDS

COMPOUND	λ_{max} mμ	SOLVENT[a]	REF.
Adrenosterone	237	AA	[b]
	239	A(?)	14
Dehydrocorticosterone acetate	237.5	A	15
12α-Bromodehydrocorticosterone acetate	238	M	16
Reichstein's Substance U diacetate	237	AA	[b]
	237.5	A	15
	238.5	A	14
Cortisone	238	AA	[b]
	238	A	16
Cortisone acetate	238	AA	[b]
	238	A	14
	238	A	17
Δ^4-Pregnene-17α, 21-diol-3, 11, 20-trione-21-acetate-20-ethylene ketal	237	AA	[b]

[a] AA = Absolute alcohol; A = Alcohol; M = Methanol. [b] This work.

TABLE III

ULTRAVIOLET ABSORPTION MAXIMA—11-HYDROXYSTEROIDS

COMPOUND	λ_{max} mμ	SOLVENT[a]	REF.
11β-Hydroxyprogesterone	242	A	7b
11α-Hydroxyprogesterone	242	A	13
Corticosterone	240	A	5a
Reichstein's Substance E diacetate	241	AA	[b]
	241	M	5d
Hydrocortisone	242	AA	[b]
	241	A	5a
	242	M	8b
Hydrocortisone acetate	242	AA	[b]
	242	M	8b
	242.5	A	1
11-Epi-hydrocortisone	242	AA	[b]
11-Epi-hydrocortisone diacetate	240	AA	[b, c]

[a] A = Alcohol; AA = Absolute alcohol; M = Methanol. [b] This work. [c] It should be noted that acetylation of the 11α-hydroxyl group produced a hypsochromic effect of 2 mμ. This *may* be generally true.

compounds. An examination of Table I shows that the Borgstrom and Gallagher generalization may be extended to include these 11-ketocompounds, *i.e.* in order of decreasing positive rotation: 11-keto > 11β-hydroxy > 11α-hydroxy. It is to be noted that ketals do not conform to this generalization.[7]

The infrared spectra of hydrocortisone (XIV) and 11-epi-hydrocortisone (XV) are given in Figure I. The curves are very similar, but sufficiently different to confirm non-identity.

11-Epi-hydrocortisone (XV) on oxidation with chromic acid gave adrenosterone (XVIII), identical in all respects with a sample obtained in a similar manner from hydrocortisone (XIV).

Summarily, the evidence strongly supported the structure of XV as indicated.

During the course of this investigation there emerged evidence which suggested that on the basis of ultraviolet spectral analysis one may distinguish between 11-keto- and 11-hydroxy-Δ^4-3-ketosteroids (*e.g.*, cortisone and hydrocortisone). In Tables II and III are listed a number of such 11-keto- and 11-hydroxy-compounds. The 11-ketocompounds generally exhibit a maximum at about 238 mμ (range, 237–238 mμ), whereas the 11-hydroxycompounds (α- or β-configuration) exhibit one at about 242 mμ (range, 240–242.5 mμ). Thus, if a Δ^4-3-ketosteroid contains an oxygen function at C-11, one may decide, *a priori*, on the basis of the absorption maximum, whether the C-11 substituent is a ketone or hydroxyl group. Dorfman (11) has made this observation independently. This generalization, it is understood, may or may not pertain to compounds containing additional nuclear substituents.

EXPERIMENTAL

Absorption spectra. The spectra were determined in absolute alcohol with a Beckman quartz spectrophotometer (Model DU). The sulfuric acid chromogen spectra were determined with a Cary recording spectrophotometer (Model 11S).

Melting points. All m.p.'s are uncorrected, and were determined with uncalibrated Anschütz thermometers.

Optical rotations. The sample was dissolved in the stated solvent to make a 2-ml. solution, and the rotation was determined in a 1-dm. semi-micro tube at wavelength 5893 Å (D), and, in some cases, also at 5461 Å (Hg).

Petroleum ether. The fraction used had b.p. 64–66°, and was purified with concentrated sulfuric acid and potassium permanganate.

Δ^5-Pregnene-17α,21-diol-3,20-dione-3-ethylene ketal-21-acetate (ethylene ketal of Reichstein's Substance S acetate) (II). A mixture of 1 g. of Reichstein's Substance S acetate (I), 8 ml. of ethylene glycol, 50 ml. of benzene, and 30 mg. of *p*-toluenesulfonic acid monohydrate was reacted in the same manner as described in a previous publication (3) (reflux 5½ hours). During the course of the reaction, crystals separated, and they were collected and washed with water after allowing the mixture to stand at room temperature overnight, wt. 0.77 g., m.p. 247–253°; λ_{max} none. Recrystallization from pyridine-water afforded 0.60 g. of pure II, m.p. 266–270° (deep red melt), $[\alpha]_D^{29}$ −9.8° (14.3 mg., pyridine, α_D −0.07°); $[M]_D$ −42°.

Anal. Calc'd for $C_{25}H_{36}O_6$ (432.54): C, 69.42; H, 8.39.
Found: C, 69.72; H, 8.72.

[7] That ketals show abnormal behavior in steroid rotation analysis has been indicated by work which will be discussed in a future publication.

Δ^5-Pregnene-17α,21-diol-3,11,20-trione-3-ethylene ketal-21-acetate (ethylene ketal of cortisone acetate) (IV). *A.* A mixture of 2 g. of cortisone acetate (III), 16 ml. of ethylene glycol, 70 ml. of benzene, and 60 mg. of *p*-toluenesulfonic acid monohydrate was reacted in the manner described (reflux 4 hours, then allowed to stand at room temperature overnight). Initially, the cortisone acetate was not in solution; however, as the reaction proceeded it dissolved and shortly thereafter the product separated. The latter was collected and was washed successively with benzene, methanol, dilute methanol, sodium bicarbonate solution, water, and methanol; wt. 1.65 g., m.p. 264–269°, λ_{max} none. Recrystallization from dilute pyridine, and dilute dimethylformamide afforded 1.31 g. of IV, m.p. 260–264°. Recrystallization of an aliquot (100 mg.) from dilute pyridine to constant rotation gave 78 mg., m.p. 267–268.5°, $[\alpha]_D^{29}$ +46.2°, $[\alpha]_{Hg}^{29}$ +63.4° (15.15 mg., pyridine, α_D +0.35°, α_{Hg} +0.48°) α_{Hg}/α_D 1.37; $[M]_D$ +206°; 58% yield.

Anal. Calc'd for $C_{25}H_{34}O_7$ (446.52): C, 67.24; H, 7.68.
Found: C, 67.36; H, 7.85.

B. In another run with 5.0 g. of cortisone acetate (III), 40 ml. of ethylene glycol, 175 ml. of benzene, and 150 mg. of *p*-toluenesulfonic acid monohydrate, there was obtained 3.98 g. of IV (recrystallized from dilute pyridine), m.p. 265–267°, 64% yield.

Δ^4-Pregnene-11β,17α,20β,21-tetrol-3-one-20,21-diacetate (Reichstein's Substance E diacetate) (V). A solution of 1.2 g. of the 3-ethylene ketal of cortisone acetate (IV) in 135 ml. of tetrahydrofuran was treated with 19 ml. of a saturated ethereal solution of lithium aluminum hydride and the mixture was refluxed for 2½ hours. The excess hydride was cautiously decomposed with water, and the resulting mixture was filtered. The product was extracted from the filtrate with ether and ethyl acetate. The combined extracts were washed, dried, and evaporated *in vacuo*. This afforded a glass which was treated with 13 ml. of 8½% (v/v) sulfuric acid in 100 ml. of methanol, and was refluxed for 40 minutes. Solid sodium bicarbonate was added to the cooled mixture, which was then filtered, and evaporated *in vacuo*. Benzene was added to the residue, and evaporated *in vacuo* for removal of traces of water. The benzene treatment was repeated. The residue was acetylated at room temperature for 15 hours with 5 ml. of acetic anhydride and 5 ml. of pyridine. Water was added, and the product was extracted with ethyl acetate. The extract was washed with water, dried, and evaporated. The residue was triangularly recrystallized from ether, ethyl acetate, and ethyl acetate-ether. This afforded 160 mg. of pure V[8] m.p. 231–232°; 58 mg., m.p. 228–230°, and 75 mg., m.p. 217–221°.

The main fraction exhibited the following properties: λ_{max} 241 mμ, ε 15,300; sulfuric acid chromogen: λ_{max} 242–248 (infl.), 252 (infl.), 281, 326–336 (plateau) and 464 mμ, λ_{min} 225 and 368–374 mμ; negative α-ketol test with 2,3,5-triphenyltetrazolium chloride, $[\alpha]_D^{25}$ +164°, $[\alpha]_{Hg}^{25}$ +205° (12.8 mg., acetone, α_D +1.05°, α_{Hg} +1.31°) α_{Hg}/α_D 1.25, $[M]_D$ +735°.

Δ^4-Pregnene-17α,20β,21-triol-3,11-dione-20,21-diacetate (Reichstein's Substance U diacetate) (VI). Reichstein's Substance E diacetate (V) (110 mg.) was oxidized in same manner as described by Reichstein and von Euw (5b), and afforded 70 mg. of VI[9] (from ethyl acetate), m.p. 257–259°, λ_{max} 237 mμ, ε 16,500; sulfuric acid chromogen: λ_{max} 282–283 mμ, λ_{min} 230 mμ; negative 2,3,5-triphenyltetrazolium chloride test for α-ketol; $[\alpha]_D^{27}$ +177°, $[\alpha]_{Hg}^{27}$ +217° (6 mg., acetone, α_D +0.53°, α_{Hg} +0.65°) α_{Hg}/α_D 1.23 $[M]_D$ +789°.

Δ^5-Pregnene-17α,21-diol-3,11,20-trione-3,20-di-ethylene ketal (di-ethylene ketal of cortisone) (VIII). *A.* A mixture of 0.5 g. of cortisone (VII), m.p. 218–220°, $[\alpha]_D^{26}$ +201°, λ_{max} 238 mμ, ε 15,600; 4 ml. of ethylene glycol, 18 ml. of benzene, and 15 mg. of *p*-toluenesulfonic acid monohydrate was reacted in the manner described (reflux 5 hours). Three recrystalli-

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[8] Reichstein and von Euw (5b): m.p. 228–230°, $[\alpha]_D^{22}$ +162.7° (acetone); Sarett, Feurer, and Folkers (5c): m.p. 229–231°, $[\alpha]_D^{24}$ +161.3 (acetone); Julian, Meyer, Karpel, and Cole (5d): m.p. 230–231° (in vac.), $[\alpha]_D^{23}$ +163° (acetone), $\lambda_{max}^{methanol}$ 241 mμ, log ε 4.3; Wendler. Huang-Minlon, and Tishler (1): m.p. 229–231°.

[9] Reichstein and von Euw (6): m.p. 252–253°, $[\alpha]_D^{21}$ +178.5° (acetone); Sarett (14): m.p. 252–253.5°, $[\alpha]_D$ +179° (acetone).

zations of the crude product from acetone-petroleum ether gave 22 mg., m.p. 234–238.5°; λ_{max} none. From the mother liquors an additional 46 mg. was obtained, m.p. 232–238.5°, $[\alpha]_D^{26}$ −7.5°, $[\alpha]_{Hg}^{26}$ −12.4° (16.1 mg., chloroform, α_D −0.06°, α_{Hg} −0.10°) α_{Hg}/α_D 1.67, $[M]_D$ −34°, $[\alpha]_D^{30}$ ±0° (23.6 mg., pyridine, α_D −0.01°).

Anal. Calc'd for $C_{25}H_{36}O_7$ (448.54): C, 66.94; H, 8.09.
Found: C, 67.02; H, 8.40.

B. In another run with 1.0 g. of cortisone (VII), 35 ml. of benzene, 8 ml. of ethylene glycol, and 30 mg. of *p*-toluenesulfonic acid monohydrate, there was obtained 450 mg., m.p. 234–240°. From the acetone-petroleum ether mother liquor an additional 100 mg. was obtained, m.p. 234–239°, 44% yield.

Δ^5-Pregnene-17α,21-diol-3,11,20-trione-3,20-di-ethylene ketal-21-acetate (di-ethylene ketal of cortisone acetate) (IX). The di-ethylene ketal (VIII) of cortisone (90 mg.) was acetylated at room-temperature for 30 hours with 2 ml. of acetic anhydride and 4 ml. of pyridine. The residue obtained on evaporation *in vacuo* of the mixture was treated with ether, and filtered, wt. 80 mg., m.p. 223–226°. Two recrystallizations from acetone-ether afforded 25 mg. of IX, m.p. 226.5–228°. An additional 15 mg., m.p. 227–228°, was obtained from the mother liquors. $[\alpha]_D^{31}$ ±0° (10.4 mg., chloroform, α_D −0.02°). Infrared analysis (Nujol): acetate carbonyl present. Admixture m.p. determination with VIII showed non-identity, m.p. 202–235°.

Anal. Calc'd for $C_{27}H_{38}O_8$ (490.57): C, 66.10; H, 7.81.
Found: C, 66.10; H, 7.87.

Δ^4-Pregnene-17α,21-diol-3,11,20-trione-20-ethylene ketal (X). A solution of 200 mg. of the diketal (VIII) in 4 ml. of 90% acetic acid was heated on the steam-bath for 20 minutes. It was poured cautiously into 50 ml. of cold saturated sodium bicarbonate solution, and the product was extracted with chloroform. The extract was washed with water, dried, and evaporated *in vacuo*. Recrystallization of the residue from dilute methanol afforded 55 mg. of X, m.p. 233–236°, λ_{max} 238 mμ, ε 15,200 (another run, ε 16,500); $[\alpha]_D^{27}$ +154° (20.6 mg., chloroform, α_D +1.59°). Negative α-ketol test.

Anal. Calc'd for $C_{23}H_{32}O_6$ (404.49): C, 68.29; H, 7.97.
Found: C, 68.26; H, 8.02.

Δ^4-Pregnene-17α,21-diol-3,11,20-trione-20-ethylene ketal-21-acetate (XI). *A.* Compound X (100 mg.) on acetylation with acetic anhydride and pyridine afforded 80 mg. of XI, m.p. 212–214° (recrystallized from dilute methanol), λ_{max} 237–238 mμ, ε 16,700; $[\alpha]_D^{29}$ +153° (10.6 mg., chloroform, α_D +0.81°), $[M]_D$ +682°.

B. The 3,20-diketal-21-acetate (IX) (140 mg.) was dissolved in 10 ml. of 50% acetic acid, and the solution was heated on the steam-bath for ½ hour. Evaporation and recrystallization of the residue from dilute methanol afforded 29 mg., of XI, m.p. 212–215°, λ_{max} 237 mμ, ε 16,400. Admixture m.p. determination with sample of XI prepared above (*A*) gave no depression; negative α-ketol test.

Anal. Calc'd for $C_{25}H_{34}O_7$ (446.52): C, 67.24; H, 7.67.
Found: C, 67.33; H, 7.76.

A few milligrams of XI was heated for 10 minutes with 2 ml. of 8½% (v/v) sulfuric acid. The mixture was made alkaline with sodium hydroxide, and gave a positive α-ketol test with 2,3,5-triphenyltetrazolium chloride.

Δ^5-Pregnene-11β,17α,21-triol-3,20-dione-3,20-di-ethylene ketal (XII). *A.* A saturated solution of lithium aluminum hydride in ether (9 ml.) was added to a solution of 985 mg. of the di-ethylene ketal (VIII) of cortisone in 60 ml. of tetrahydrofuran, and the mixture was refluxed for 2 ¾ hours. The excess hydride was destroyed by the cautious addition of water. Ether was added, and the mixture was filtered. The filtrate was transferred to a separatory-funnel, and the ether layer was separated. The water layer was extracted several times more with ether. The combined ether extracts were washed with water, dried with magnesium sulfate, and evaporated *in vacuo*. Crystallization of the residue with acetone gave 18 mg. of XIII (C_{11}-α), m.p. 281–287° d. Concentration of the mother liquor with simultaneous addition of petroleum ether gave 80 mg., m.p. 252–272° (primarily XIII).

Further concentration of the mother liquor gave 650 mg. of impure XII, m.p. 184.5–200°. Two recrystallizations of the third fraction from acetone-petroleum ether gave 0.49 g. of pure XII, m.p. 184–186°; $[\alpha]_D^{21}$ −34.5°, $[\alpha]_{Hg}^{21}$ −44.3° (20.3 mg., chloroform, α_D −0.35°, α_{Hg} −0.45°) α_{Hg}/α_D 1.29; $[M]_D$ −155° (chloroform), $[\alpha]_D^{21}$ −52.9°, $[\alpha]_{Hg}^{21}$ −64.5° (12.1 mg., pyridine, α_D −0.32°, α_{Hg} −0.39°) α_{Hg}/α_D 1.22; $[M]_D$ −238° (pyridine).

Anal. Calc'd for $C_{25}H_{38}O_7$ (450.55): C, 66.64; H, 8.50; No. "active" H, 3.00.
Found: C, 66.81; H, 8.75; No. "active" H, 3.28.

B. In another run with 1.75 g. of VIII, 110 ml. of tetrahydrofuran, and 17 ml. of a saturated ethereal solution of lithium aluminum hydride, there was obtained 1.01 g. of XII, m.p. 181–182.5° (58% yield), and 134 mg. of impure XIII, m.p. 259–274° (7.6% crude yield).

Δ⁵-Pregnene-11α,17α,21-triol-3,20-dione-3,20-di-ethylene ketal (XIII). Compound XIII (18 mg., m.p. 281–287°; 80 mg., m.p. 252–272°) described above in preparation of XII was recrystallized from ethanol and methanol-acetone, m.p. 299–301°, $[\alpha]_D^{25}$ −31°, $[\alpha]_{Hg}^{25}$ −35° (9.7 mg., pyridine, α_D −0.15°, α_{Hg} −0.17°) α_{Hg}/α_D 1.13; $[M]_D$ −139°.

Anal. Calc'd for $C_{25}H_{38}O_7$ (450.55): C, 66.64; H, 8.50; No. "active" H, 3.00.
Found: C, 67.02; H, 8.51; No. "active" H, 3.1.

Δ⁴-Pregnene-11β,17α,21-triol-3,20-dione (XIV). *A.* A solution of the di-ethylene ketal of cortisone (VIII) (850 mg.) in 50 ml. of tetrahydrofuran was treated with 8 ml. of a saturated ethereal solution of lithium aluminum hydride in the manner described above. Addition of acetone to the crude reaction product gave 150 mg. of impure Δ⁵-pregnene-11α,17α,21-triol,3,20-dione-3,20-di-ethylene ketal (XIII), m.p. 250–285°. Evaporation of the mother liquor gave approximately 700 mg., m.p. 165–205°, which was dissolved in 90 ml. of methanol, and treated with 9 ml. of 8½% (v/v) sulfuric acid. The mixture was refluxed for 40 minutes, neutralized with sodium bicarbonate solution, filtered, and the filtrate was evaporated to dryness *in vacuo*. Water was added, and the product was extracted with ethyl acetate. The extract was washed with water, dried, and evaporated *in vacuo*. Crystallization of the residue from acetone-petroleum ether, followed by a recrystallization from acetone-ether gave 210 mg. of XIV,[10] m.p. 218–221°. From the mother liquor an additional 100 mg. was obtained, m.p. 215–217°; λ_{max} 242 mμ, ε 15,600; sulfuric acid chromogen: λ_{max} 237, 282, 393 and 474 mμ; λ_{min} 229, 252, 350 and 417 mμ; $[\alpha]_D^{28}$ +163°, $[\alpha]_{Hg}^{28}$ +196° (15 mg., absolute alcohol, α_D +1.22°, α_{Hg} +1.47°) α_{Hg}/α_D 1.20; $[M]_D$ +590°. Infrared absorption spectrum was identical in all respects with that of an authentic sample (Upjohn).

Anal. Calc'd for $C_{21}H_{30}O_5$ (362.45): No. "active" H, 3.00. Found: No. "active" H, 2.74.

B. One gram of pure Δ⁵-pregnene-11β,17α,21-triol-3,20-dione-3,20-di-ethylene ketal (XII) in 100 ml. of methanol was hydrolyzed with 10 ml. of 8½% (v/v) sulfuric acid in the above manner. Addition of acetone to the crude product gave 324 mg. of XIV, m.p. 217–219°, λ_{max} 242 mμ, ε 15,500. From the mother liquor an additional 197 mg., m.p. 215.5–218.5°, and 63 mg., m.p. 210–213° were obtained; 70% yield (based on first two fractions).

Δ⁴-Pregnene-11α,17α,21-triol-3,20-dione (XV). The diketal (XIII) (160 mg.) in 50 ml. of alcohol was treated with 5 ml. of 8% (v/v) sulfuric acid, and the mixture was refluxed for 40 minutes on the steam-bath. Solid sodium bicarbonate was added, and the mixture was filtered. The filtrate was evaporated *in vacuo* to near dryness, and the product was extracted thoroughly with ethyl acetate. The extract was washed with water, and evaporated. The residue was crystallized from acetone-petroleum ether, wt. 80 mg., m.p. 203.5–206° (bubbles in melt), λ_{max} 242 mμ, ε 16,000. Recrystallization from acetone-petroleum ether gave 50 mg. (40% yield) of XV,[11] m.p. 212.5–213.5° (bubbles in slightly yellow melt with

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[10] Wintersteiner and Pfiffner (6a): m.p. 217°, $[\alpha]_D^{25}$ +209° (alc.); Reichstein (5a): m.p. 207–210° d., $[\alpha]_D^{22}$ +167.2° (alc.); Mason, Hoehn, and Kendall (8a): m.p. 217–220°, $[\alpha]_{Hg}^{25}$ +178° (alc.?); Wendler, Graber, Jones, and Tishler (8b): m.p. 215.5–221° d. (with slight previous softening), $[\alpha]_D^{24}$ +163° (methanol), $\lambda_{max}^{methanol}$ 242 mμ, $E_{1cm}^{1\%}$ 443; Kahnt and Wettstein (8c): m.p. 214–219°, $[\alpha]_D$ +168° (alc.).

[11] Murray and Peterson, U. S. Patent 2,602,769 (July 8, 1952): m.p. 209–212°, 217–219° (m.p. dependent on crystal form), $[\alpha]_D^{24}$ +113° (methanol) (This patent issued after completion of our work.)

previous softening at 210°, m.p. dependent upon rate of heating and temperature of bath when sample inserted). Admixture melting point determination with XIV (11β-isomer) (m.p. 217–219°) showed non-identity, m.p. about 200–208°. Positive 2,3,5-triphenyltetrazolium chloride test for α-ketol grouping; λ_{max} 242 mμ, ϵ 15,800; $[\alpha]_D^{29}$ +117° (17.3 mg., absolute alcohol, α_D +1.01°, $[M]_D$ +424°; sulfuric acid chromogen: λ_{max} 237, 282, 393 and 474 mμ, λ_{min} 252, 329 and 432 mμ.

Anal. Calc'd for $C_{21}H_{30}O_5$ (362.45): C, 69.58; H, 8.34; No. "active" H, 3.00.
Found: C, 69.68; H, 8.63; No. "active" H, 3.42.

Δ^4-Pregnene-11β,17α,21-triol-3,20-dione-21-acetate (XVI). Δ^4-Pregnene-11β,17α,21-triol-3,20-dione (XIV) (100 mg.) was acetylated at room temperature for 16 hours with 4.0 ml. of pyridine and 2.0 ml. of acetic anhydride. Evaporation *in vacuo*, and addition of ether to the residue gave 100 mg., m.p. 207–209°. Three recrystallizations from acetone-ether gave 42 mg. of XVI,[12] m.p. 221–223°. Concentration of the mother liquors afforded an additional 25 mg., m.p. 219–221.5°. λ_{max} 242 mμ, ϵ 16,100; $[\alpha]_D^{28}$ +138°, $[\alpha]_{Hg}^{28}$ +166° (5.8 mg., acetone, α_D +0.40°, α_{Hg} +0.48°) α_{Hg}/α_D 1.20; $[M]_D$ + 557°. Admixture melting point determination with an authentic sample of XVI (m.p. 218–219°, Merck) indicated identity, m.p. 219–220.5°. Admixture melting point determination with a sample of XIV showed non-identity, m.p. 199–201°.

Δ^4-Pregnene-11α,17α,21-triol-3,20-dione-11,21-diacetate (XVII). Compound XV (50 mg.) was acetylated at room temperature for 17 hours with 2 ml. of pyridine, and 1 ml. of acetic anhydride. Evaporation *in vacuo* of the reaction mixture gave an oil which was crystallized from acetone-petroleum ether; wt. 47 mg., m.p. 197.5–200°. Recrystallization from acetone-petroleum ether afforded 37 mg. of pure XVII,[13] m.p. 205–207°, λ_{max} 239–240 mμ, ϵ 15,500. $[\alpha]_D^{30}$ +114° (5.1 mg., acetone, α_D +0.29°), $[M]_D$ +508°.

Anal. Calc'd for $C_{23}H_{32}O_6$ (404.49) (Monoacetate): C, 68.29; H, 7.97.
Calc'd for $C_{25}H_{34}O_7$ (446.52) (Diacetate): C, 67.24; H, 7.68.
Found: C, 67.57, 67.18; H, 7.90, 7.79.

In another run the diacetate melted at 208.5–209.5° (recrystallized from dilute acetone), λ_{max} 240 mμ, ϵ 15,500. Admixture melting point determination with the starting material (XV) showed non-identity, m.p. about 186–190°.

Δ^4-Androstene-3,11,17-trione (adrenosterone) (XVIII). *A. From Δ^4-pregnene-11β,17α,21-triol-3,20-dione* (XIV) according to Reichstein (5a). M.p. 224–225°,[14] λ_{max} 237 mμ, ϵ 14,900; $[\alpha]_D^{30}$ +277° (4.99 mg., absolute alcohol, α_D +0.69°), $[M]_D$ +831°.

B. From Δ^4-pregnene-11α,17α,21-triol-3,20-dione (XV). Compound XV (50 mg.) in 4 ml. of glacial acetic acid was treated with a solution of 60 mg. of chromic anhydride in 2 drops of water and 6 ml. of glacial acetic acid. The mixture was allowed to stand at room temperature for 22 hours and was then evaporated *in vacuo* with very moderate warming. Water was added to the residue, and the product was extracted with ether. The extract was washed successively with 4% (v/v) sulfuric acid, 5% sodium hydroxide solution, and water. The dried extract was concentrated until crystals separated when petroleum-ether was added. This afforded 18 mg. of XVIII, m.p. 224–225°, λ_{max} 237 mμ, ϵ 15,200. Admixture melting point determination with sample prepared above (*A*) indicated identity, m.p. 224–225°. The infrared spectra (Nujol) of preparations *A* and *B* were identical in all respects.

Acknowledgment. We wish to thank Dr. R. C. Gore (Stamford Research Laboratories, American Cyanamid Co.) and Mr. William Fulmor for the infrared

[12] Reichstein (18): m.p. 223–225°; Wendler, Graber, Jones, and Tishler (8b): m.p. 218.5–220.5°, 218–221.5°, $[\alpha]_D^{25}$ +150.7° (acetone), +157.5° (dioxane), $\lambda_{max}^{methanol}$ 242 mμ, $E_{1cm}^{1\%}$ 371, 380.

[13] Murray and Peterson, U. S. Patent 2,602,769 (July 8, 1952), m.p. 198–202°, $[\alpha]_D^{22}$ +115° (chloroform).

[14] Reichstein (5a, 19): m.p. 220–223°; $[\alpha]_D^{20}$ +262° (abs. alc.); Sarett (14): m.p. 222–224°; $[\alpha]_D^{25}$ +281° (acetone); $\lambda_{max}^{alc.}$ 239 mμ, ϵ 13,800.

spectra, Mr. Walter Muller for the sulfuric acid chromogen spectra, Mr. Walter Hearn for the composition of the flowsheets and figures, and Messrs. Louis M. Brancone, Samual S. Modes, and William S. Allen for the microanalytical data.

SUMMARY

1. Reaction of cortisone acetate with ethylene glycol gave the 3-ethylene ketal, whereas cortisone gave the 3,20-di-ethylene ketal.

2. Treatment of the di-ethylene ketal of cortisone or its acetate with aqueous acetic acid selectively hydrolyzed the 3-ketal.

3. Reichstein's Substance E diacetate has been synthesized by lithium aluminum hydride reduction of the 3-ethylene ketal of cortisone acetate, followed by hydrolysis and reacetylation.

4. Lithium aluminum hydride reduction of the di-ethylene ketal of cortisone afforded principally the 11β-hydroxy-diketal, with a small quantity of the 11α-diastereomer. Acid hydrolysis of the diastereomeric ketals afforded hydrocortisone and 11-epi-hydrocortisone. Evidence for the structure of both compounds is presented.

5. Certain generalizations regarding optical rotatory power, and absorption spectra of 11-oxygenated steroids are discussed.

PEARL RIVER, NEW YORK

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