[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF SCHERING CORPORATION]

The Formation of Ketals from Steroid Ketones with Selenium Dioxide and Methanol

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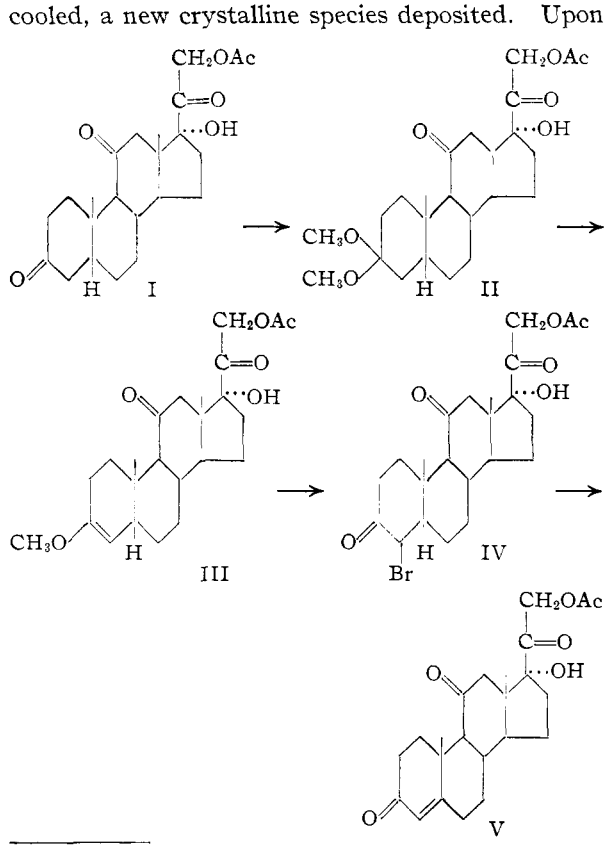
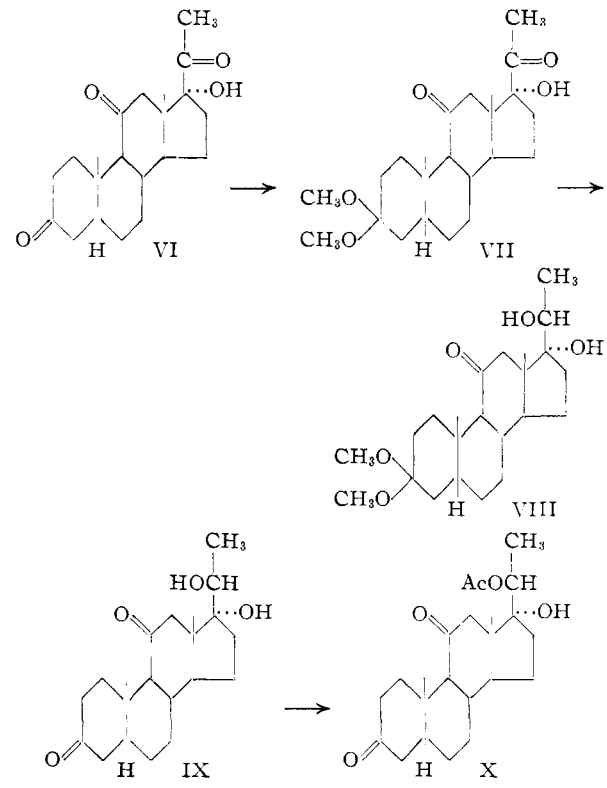
In the presence of selenium dioxide pregnane-17α,21-diol-3,11,20-trione 21-acetate (I) combined with methanol to give the 3,3-dimethoxy ketal (II). Upon pyrolysis, the ketal eliminated methanol to yield 3-methoxy-Δ^3-pregnene-17α,21-diol-11,20-dione 21-acetate (III). The addition of bromine produced the known 4-bromopregnane-17α,21-diol-3,11,20-trione 21-acetate (IV). Pregnane-3,11,20-trione (XI), pregnan-17α-ol-3,11,20-trione (VI) and pregnane-11β,17α-diol-3,20-dione (XVII) all gave the corresponding 3,3-dimethoxy ketals upon reaction with selenium dioxide in methanol. These in turn were converted into the known 3,11-diketo-20β-acetoxy compounds X and XVI. Under the experimental conditions employed, cortisone acetate, Δ^4-androstene-3,17-dione and pregnan-3α-ol-11,20-dione failed to react. Thus the reaction is limited to saturated 3-keto derivatives. Ketone groups at C-11, C-17 and C-20 or at C-3, when conjugated with a Δ^4-double bond, failed to react.

The final steps in the preparation of cortisone acetate (Δ^4-pregnene-17α,21-diol-3,11,20-trione 21-acetate, V) from bile acids comprise the bromination of pregnane-17α,21-diol-3,11,20-trione 21-acetate (I) in the C-4 position,[1] followed by the elimination of hydrogen bromide and the formation of the 4,5-double bond *via* the dinitrophenylhydrazone or semicarbazone[2] either of which may be converted to the 3-ketone by reaction with pyruvic acid,[3a] or with lithium chloride.[3b]

In an attempt to find other routes which might lead to the introduction of the 4,5-double bond, the action of selenium dioxide on I was investigated. When a solution of I and selenium dioxide in methanol was warmed for a short time and then cooled, a new crystalline species deposited. Upon examination of the infrared spectrum, the disappearance of one carbonyl group was disclosed, along with the appearance of a strong, saturated ether bond. Analytical data, plus the fact that this new compound could be easily reconverted to the starting material with aqueous acetic acid (or mineral acids), indicated that the compound was 3,3-dimethoxypregnane-17α,21-diol-11,20-dione 21-acetate (II).

This unexpected reaction of selenium dioxide in methanol probably is the normal formation of a steroid ketal in which the selenium dioxide is functioning simultaneously as the acid catalyst and as the dehydrating agent, removing the water formed and thus driving the reaction to completion.



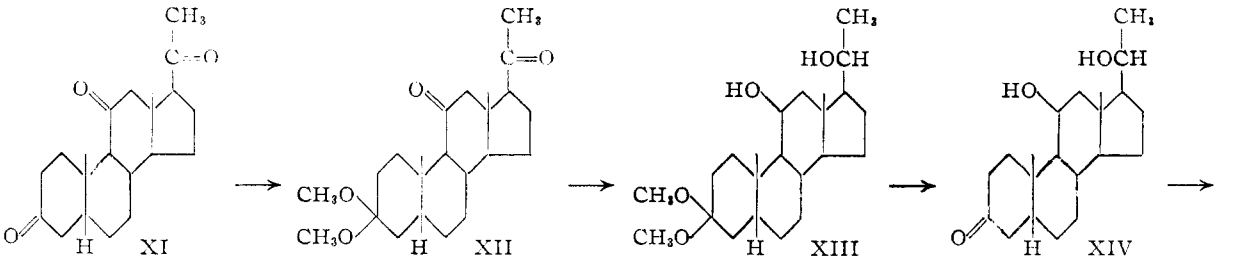


The dimethyl ketal II melted at about 180–190° with vigorous evolution of gas, which was presumed to be the elimination of a molecule of methanol. When a sample was pyrolyzed at 200° for a short length of time, a new compound was obtained, m.p. 208–210°, which was identified as

(1) V. Mattox and E. C. Kendall, *J. Biol. Chem.*, **185**, 593 (1950).

(2) V. Mattox and E. C. Kendall, *ibid.*, **188**, 287 (1951); B. Koechlin, T. Kritchevsky and T. F. Gallagher, *ibid.*, **184**, 393 (1950).

(3) (a) E. B. Hershberg, *J. Org. Chem.*, **13**, 542 (1948); (b) R. P. Holysz, THIS JOURNAL, **75**, 4432 (1953).



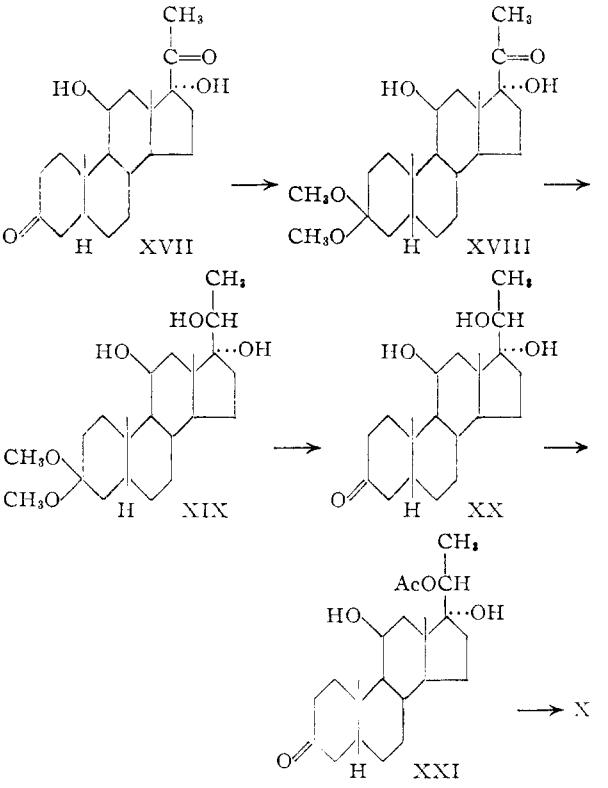
3 - methoxy - Δ^3 - pregnene - 17α,21 - diol - 11,20-dione 21-acetate (III) (methyl enol ether of 4,5-dihydrocortisone acetate) by means of analysis, infrared spectrum, bromination experiments and hydrolysis to pregnane-17α,21-diol-3,11,20-trione 21-acetate. The high degree of stability of the ketol side-chain to this pyrolytic treatment was unexpected.

In a similar type of reaction, Serini and Koster[4] converted cholestanone diethylacetal to its enol ether by refluxing the ketal in xylene.

The enol ether III added bromine readily in either methylene chloride or acetic acid solution to form 4-bromopregnane-17α,21-diol-3,11,20-trione 21-acetate (IV); the latter solvent gave a bromide with a somewhat higher rotation, and presumably a higher purity. Either bromide preparation could be converted to cortisone acetate (V) *via* the semicarbazone procedure.

The reaction of N-bromosuccinimide with coprostanone enol acetate has been reported[5] to give Δ^4-cholesten-3-one directly. The first step was presumed to be allylic bromination at C-5. However, when the same reaction was attempted with the enol ether III, a bromide was obtained which had an infrared spectrum identical with that of the bromide obtained by the addition reaction and which was also converted to cortisone acetate by the standard procedure. Therefore the bromide from III must be 4-bromopregnane-17α,21-diol-3,11,20-trione 21-acetate (IV) and not the 5-bromo compound which would be expected from allylic bromination. The 4-bromide may arise from either the addition of bromine or of N-bromosuccinimide to the double bond, although the former is a more likely possibility especially in light of the recent investigation[6] on the addition of bromine to ethylenic double bonds by using N-bromosuccinimide.[7]

The action of selenium dioxide and methanol on a number of other steroid ketones was investigated, and under the experimental conditions employed, ketal formation was found to be limited to saturated 3-keto derivatives. Ketone groups at C-3 conjugated with a Δ^4-double bond, at C-11, C-17 or at C-20 failed to react. For example, cortisone acetate (V), Δ^4-androstene-3,17-dione and pregnan-3α-ol-11,20-dione did not react, but pregnane-3,11,20-trione (XI), pregnan-17α-ol-3,11,20-trione (VI) and pregnane-11β,17α-diol-11,20-dione (XVII) all gave the corresponding 3,3-dimethoxy ketals.



The structure of these ketals was proved by conversion to the known 3,11-diketo-20β-hydroxy compounds, isolated as the acetates X and XVI. 3,3-Dimethoxypregnane-11,20-dione (XII) and 3,3-dimethoxypregnane-11β,17α-diol-20-one (XVIII) were reduced completely to the 11β,20β-diols XIII and XIX. After splitting the ketals with dilute acid, acetylation of the C-20 hydroxyl group and oxidation of the C-11 hydroxyl group, there were obtained the known pregnane-17α,20β-diol-3,11-dione 20-acetate (X) and pregnan-20β-ol-3,11-dione 20-acetate (XVI).

(4) A. Serini and M. Koster, *Ber.*, **71**, 1766 (1938).

(5) B. Armbrecht and M. Rubin, Abstracts of Papers, 119th Meeting of the American Chemical Society, April, 1951.

(6) E. A. Braude and E. S. Waight, *J. Chem. Soc.*, 1116 (1952); *cf.*, however, R. Paul and S. Tchelitcheff, *Compt. rend.*, **236**, 1968 (1953).

(7) One of the referees has suggested that III may be converted rapidly to I, and that I may be the species being brominated (by either Br_2 or N-bromosuccinimide). However, I in methylene chloride or acetic acid reacts *very slowly* with bromine; also while the reaction of III with N-bromosuccinimide gave the 4-bromide IV, the reaction of I under the same conditions gave the starting material in *ca.* 90% yield.

3,3-Dimethoxypregnan-17α-ol-11,20-dione (VII) can be reduced selectively[8] with sodium borohydride to the 3,3-dimethoxypregnane-17α,20β-diol-11-one (VIII). Hydrolysis of the ketal group, followed by acetylation at C-20, yields pregnane-17α,20β-diol-3,11-dione 20-acetate (X).

Further studies of ketal formation with selenium dioxide and methanol in the androstane and etiocholane series will be reported later.

Experimental[9]

3,3-Dimethoxypregnane-17α,21-diol-11,20-dione 21-Acetate (II).—A solution of 15.00 g. of pregnane-17α,21-diol-3,11,20-trione 21-acetate (dihydrocortisone acetate, I) and 15.0 g. of selenium dioxide in 350 ml. of C.P. methanol was kept at 50–55° for 1 hour. The precipitate obtained upon cooling the solution was collected with suction and after drying weighed 11.85 g., m.p. 179–215°. Recrystallization from methanol gave two crops: 9.72 g., m.p. 193–195° with gas evolution, and 1.45 g., m.p. 184–190° with gas evolution. An analytical sample, recrystallized again from methanol, melted at 181–184° with gas evolution, $[\alpha]^{24}D$ +71.3° (acetone). Infrared absorption studies showed the loss of a carbonyl group, and the appearance of the C–O–C group.

Anal. Calcd. for $C_{25}H_{38}O_7$: C, 66.64; H, 8.50. Found: C, 66.72; H, 8.80.

Hydrolysis of the 3,3-Dimethyl Ketal.—A solution of 0.39 g. of II in 15 ml. of glacial acetic acid was warmed on the steam-bath to about 75°, 15 ml. of water was added and the solution was allowed to stand overnight while cooling slowly to room temperature. The resulting crystals were collected, washed and dried: yield 0.18 g., m.p. 230–234°, $[\alpha]^{21}D$ +81.3° (acetone). Dilution of the filtrate with water gave an additional 0.15 g., m.p. 226–229°, $[\alpha]^{21}D$ +83.3°; total yield 94%. Neither fraction gave a melting point depression when mixed with dihydrocortisone acetate (I), and the infrared spectra were identical with that of dihydrocortisone acetate.

3-Methoxy-Δ^3-pregnene-17α,21-diol-11,20-dione 21-Acetate (III).—A small flask containing 9.72 g. of I was heated gradually and with constant stirring in a Wood's metal-bath to a temperature of 200° over a period of about 30 minutes. Upon cooling, the solidified residue was recrystallized from acetone to yield 4.70 g. (52%) of III, m.p. 208–210°, $[\alpha]^{21}D$ +120.9° (acetone).

Anal. Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 68.91; H, 8.51.

Hydrolysis of 0.50 g. of III as described for the 3,3-dimethoxy compound yielded 0.36 g. (75%), m.p. 231–233°. There was no depression in m.p. on admixture with dihydrocortisone acetate, and the infrared spectra were identical.

4-Bromopregnane-17α,21-diol-3,11,20-trione 21-Acetate (IV).—(a) Bromination in Methylene Chloride.—A solution of 1.00 g. of III in 40 ml. of methylene chloride was cooled in an ice-bath and brominated by the dropwise addition of 0.40 g. of bromine dissolved in 10 ml. of methylene chloride. Decolorization was instantaneous and copious fumes of hydrogen bromide were evolved. The solvent was removed under reduced pressure, leaving a residue which crystallized upon the addition of acetone. Recrystallization of this material from aqueous acetone gave 0.57 g., m.p. 184–185° dec., $[\alpha]^{21}D$ +79.6° (acetone).

(b) Bromination in Acetic Acid.—A solution of 0.50 g. of III in 10 ml. of glacial acetic acid at 25° was brominated by the dropwise addition of 0.20 g. of bromine in 4 ml. of acetic acid. Fumes of hydrogen bromide were again evolved. The solution was poured into water and the solid was collected on a filter and washed with water. Recrystallization from aqueous acetone gave 0.35 g. of IV, m.p. 184–186° dec., $[\alpha]^{21}D$ +91.4° (acetone).

Anal. Calcd. for $C_{23}H_{31}O_6Br$: Br, 16.53. Found: Br, 16.61.

(c) Bromination with N-Bromosuccinimide.—A suspension of 1.00 g. of III in 100 ml. of carbon tetrachloride was heated to reflux. The addition of 0.45 g. of N-bromosuccinimide caused most of the solid to dissolve within 5 minutes and reflux was continued 25 minutes longer. The solution was cooled and the resulting solid collected with suction, washed with water and dried. Recrystallization from aqueous acetone gave 0.46 g., $[\alpha]^{23}D$ +105.1° (acetone).

Cortisone Acetate (V).—The bromides were put through the semicarbazone formation and split as described previously.[2,3]

	Bromide G.	Bromide $[\alpha]D$	Crude V G.	Crude V M.p., °C.	Recrystallized V
(a)	0.38	+79.6°	0.24	200–222	0.13 g., m.p. 227–233° d., ϵ_{237} 14,600, $[\alpha]D$ + 201.5°
(b)	.38	+91.4°	.26	223–232	.21 g., m.p. 228–233° d., ϵ_{237} 14,000, $[\alpha]D$ +197.3°
(c)	.59	+105.1°	.39	210–225	.31 g., m.p. 227–233° d., ϵ_{237} 13,200, $[\alpha]D$ +189.4°

All rotations were in dioxane and the ultraviolet determinations in 95% ethanol. The crude cortisone acetate (V) was crystallized from aqueous acetone. Infrared spectra showed no significant differences between the three samples and a reference sample of cortisone acetate.

3,3-Dimethoxypregnane-11β,17α-diol-20-one (XVIII).—A solution of 5.00 g. of pregnane-11β,17α-diol-3,20-dione and 5.0 g. of selenium dioxide in 100 ml. of C.P. methanol was kept at 50° for 2 hours and at room temperature (30°) for four hours. No crystals formed, whereupon a solution of 5 g. of potassium hydroxide in C.P. methanol was added and the alkaline solution was poured into water. The precipitated solid was collected with suction, washed with water and dried; weight 4.56 g. Recrystallization from ether–hexane gave two crops of XVIII, 3.95 g., m.p. 164–168° with gas evolution and 0.44 g., m.p. 156–159° with gas evolution. A sample recrystallized for analysis melted at 168–171° dec., $[\alpha]D$ +23.5° (chloroform).

Anal. Calcd. for $C_{23}H_{38}O_5$: C, 70.01; H, 9.71. Found: C, 70.06; H, 9.81.

Pregnane-11β,17α,20β-triol-3-one 20-Acetate (XXI).—To a solution of 3.92 g. of 3,3-dimethoxypregnane-11β,17α-diol-20-one (XVIII) in 100 ml. of C.P. methanol containing 0.4 g. of potassium hydroxide was added a solution of 4.00 g. of sodium borohydride in 10 ml. of water. After refluxing for 16 hours, the solution was diluted with water and extracted three times with methylene chloride. The combined extracts were washed twice with water, dried over sodium sulfate and evaporated, leaving a colorless oil. In order to hydrolyze the dimethoxy group, this residue was taken up in 20 ml. of acetic acid, treated with 20 ml. of hot water and heated for 15 minutes on the steam-bath. After cooling, the solution was diluted with water and extracted with methylene chloride. The extracts were washed with dilute sodium bicarbonate solution and water, dried over sodium sulfate, and evaporated. The residue, again an oil, was acetylated by treating with acetic anhydride in pyridine overnight at room temperature. The solution was diluted with water and extracted with methylene chloride. The extracts were washed with water, dilute hydrochloric acid, water, dilute sodium bicarbonate solution and water. After drying over sodium sulfate and evaporating there remained 3.45 g. of crystalline material. Recrystallization from acetone gave two crops: 1.57 g., m.p. 248–250°, and 0.43 g., m.p. 239–241°. A second crystallization of the first crop gave 1.44 g. of product, m.p. 250–252°, $[\alpha]^{28}D$ +63.0° (chloroform).

Anal. Calcd. for $C_{23}H_{36}O_5$: C, 70.37; H, 9.25. Found: C, 70.76; H, 9.53.

3,3-Dimethoxypregnan-17α-ol-11,20-dione (VII).—A solution of 2.00 g. of pregnan-17α-ol-3,11,20-trione (VI) and 2.00 g. of selenium dioxide dissolved in 80 ml. of C.P. methanol was allowed to stand 2 days at room temperature. The solution was made alkaline by the addition of a methanolic solution of 3 g. of potassium hydroxide and poured into water. After filtration and drying, the crude product weighed 1.87 g. The material was recrystallized from ether–hexane (in the presence of a few drops of pyridine), and gave 1.35 g. of VII, m.p. 138–141° with bubbling. Another crystallization raised the m.p. to 148–150° dec., $[\alpha]^{25}D$ +35.0° (chloroform).

(8) E. P. Oliveto and E. B. Hershberg, THIS JOURNAL, **75**, 488 (1953).

(9) All melting points are corrected. All rotations were taken in a one-decimeter tube at a concentration of about 1%. Analyses and optical data were obtained by the Microanalytical and Physical Chemistry Departments of these laboratories.

Anal. Calcd. for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24. Found: C, 70.25; H, 9.41.

Pregnane-17α,20β-diol-3,11-dione 20-Acetate (X). (a).—A solution of 1.20 g. of 3,3-dimethoxypregnane-17α-ol-11,20-dione (VII) in 40 ml. of C.P. methanol was added to a solution of 1.2 g. of sodium borohydride in 4 ml. of water. The mixture was allowed to stand at room temperature (24°) for three hours and then processed as before. Hydrolysis of the dimethoxy group followed by acetylation as described above yielded 1.17 g., m.p. 183–190°. Recrystallization from ethanol gave two crops: 0.61 g., m.p. 215–222°, and 0.06 g., m.p. 251–253°. A mixture m.p. of the second crop with pregnane-11β,17α,20β-triol-3-one 20-acetate showed no depression, and the infrared spectra were identical. A second crystallization of the first crop yielded 0.52 g. of X solvated with ethanol, m.p. 222–224°, $[\alpha]^{25}D$ +59.5° (acetone); reported[10] m.p. 222–224°.

Anal. Calcd. for $C_{23}H_{34}O_5 \cdot C_2H_5OH$: C, 68.77; H, 9.23. Found: C, 68.66; H, 9.61.

(b).—A solution of 0.50 g. of pregnane-11β,17α,20β-triol-3-one 20-acetate in 75 ml. of C.P. acetone and 7.5 ml. of water was cooled to 3° and treated with 0.35 g. of N-bromoacetamide. After 18 hours at 3°, a solution of 1 g. of sodium sulfite in a minimum amount of water was added and the acetone was removed under reduced pressure. The concentrated suspension was diluted with water and the solid collected with suction weighed 0.48 g., m.p. 218–220°. Recrystallization from ethanol gave 0.42 g., m.p. 223–225°, $[\alpha]^{26}D$ +59.6° (acetone). A mixture m.p. with the sample prepared in (a) showed no depression.

3,3-Dimethoxypregnane-11,20-dione (XII).—A solution of 1.00 g. of pregnane-3,11,20-trione (XI) in 40 ml. of C.P. methanol was treated with 1.00 g. of selenium dioxide and allowed to stand 2 days at room temperature. The solution was made alkaline by the addition of 1 g. of potassium hydroxide in methanol, and poured into water. Filtration yielded 0.85 g. of material melting at 136–143°. Recrystallization from hexane gave 0.75 g., m.p. 140–142°, $[\alpha]^{25}D$ +130.4° (chloroform).

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.48; H, 9.85.

Pregnan-20β-ol-3,11-dione 20-Acetate (XVI).—A solution of 1.70 g. of 3,3-dimethoxypregnane-11,20-dione in 80 ml. of C.P. methanol containing 0.2 g. of potassium hydroxide was added to a solution of 3.40 g. of sodium borohydride in 8 ml. of water. After refluxing for 16 hours, the solution was cooled and worked up as previously described. The dimethoxy group was hydrolyzed by treatment with 50% acetic acid and the residue was acetylated, again as described previously in the formation of X. This material was taken up in 100 ml. of C.P. acetone and 20 ml. of water. The solution was cooled to 3° and 1.78 g. of N-bromoacetamide was added. After 3 hours at 3°, the solution was poured into 1 l. of water containing 3 g. of sodium sulfite. Filtration yielded 1.43 g. of solid melting at 150–170°. This material was taken up in C.P. benzene and chromatographed on 17 g. of Florisil (100/200 mesh). Elution with benzene gave 0.96 g. of material, m.p. 165–198°. Two recrystallizations from methanol yielded 0.49 g., m.p. 201–203°, $[\alpha]^{25}D$ +66.6° (acetone); reported[11] m.p. 201–203°.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.56; H, 9.45.

(10) L. H. Sarett, THIS JOURNAL, **71**, 1169 (1949).

(11) L. H. Sarett, *ibid.*, **71**, 1165 (1949).

BLOOMFIELD, NEW JERSEY

[CONTRIBUTION FROM THE CHEMICAL AND BIOLOGICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY]

Steroidal Cyclic Ketals. XI.[1] The Conversion of 11-*epi*-Hydrocortisone into Hydrocortisone

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11-*epi*-Hydrocortisone (I) by use of a modified procedure was converted into its 3,20-bis-ethylene ketal (II) in over 70% yield. The latter was selectively oxidized at the C-11-hydroxyl group by chromium trioxide–pyridine complex to afford in 89% yield the bis-ethylene ketal (IIIa) of cortisone. Reduction of IIIa with sodium borohydride in tetrahydrofuran and aqueous sodium hydroxide, followed by acid hydrolysis gave in 72% yield (from IIIa) hydrocortisone (V). These transformations established a four step process for the conversion of 11-*epi*-hydrocortisone (I) into hydrocortisone (V) in 45–50% yield.

The facile conversion of Reichstein's Substance S into 11-*epi*-hydrocortisone (I) by microbiological hydroxylation is now well established.[2] This remarkable transformation with the subsequent conversion (70%) of I into cortisone acetate[2] constituted one of the most direct syntheses of the latter.

However, the preparation in good yield of hydrocortisone (V) from 11-*epi*-hydrocortisone (I), has presented a more complex problem.[3] An obvious solution would appear in the utilization of cortisone as an intermediate prepared as indicated. Two methods have been described for the conversion of cortisone (from its acetate) into hydrocortisone.[4] Both entailed selective protection of the C-3 and 20-carbonyl groups of cortisone by either semicarbazone[4a] or ethylene ketal[4b] formation. The intermediate was reduced with a metal hydride, and the reduction product in turn was converted into hydrocortisone acetate[4a] or hydrocortisone.[4b] These processes afforded low yields, and were only of academic interest.

Subsequently, Fried and Sabo[5] announced an essentially five-step synthesis of hydrocortisone acetate from 11-*epi*-hydrocortisone (I) *via* 9-dehydro-Reichstein's Substance S acetate ($\Delta^{4,9(11)}$-pregnadiene-17α,21-diol-3,20-dione 21-acetate).[6]

(1) Paper X, S. Bernstein, Milton Heller and Stephen M. Stolar, THIS JOURNAL, **76**, 5674 (1954).

(2) H. C. Murray and D. H. Peterson, U. S. Patent 2,602,769 (July 8, 1952); D. H. Peterson, S. H. Eppstein, P. D. Meister, B. J. Magerlein, H. C. Murray, H. M. Leigh, A. Weintraub and L. M. Reineke, THIS JOURNAL, **75**, 412 (1953); J. Fried, R. W. Thoma, J. R. Gerke, J. E. Herz, M. N. Donin and D. Perlman, *ibid.*, **74**, 3962 (1952); F. W. Kahnt, C. Meystre, R. Neher, E. Vischer and A. Wettstein, *Experientia*, **8**, 422 (1952).

(3) Model substance work recently carried out in this Laboratory [S. Bernstein, R. Lenhard and J. H. Williams, *J. Org. Chem.*, **19**, 41 (1954)] has indicated that any Walden inversion approach for the conversion of 11-*epi*-hydrocortisone (I) into hydrocortisone (V) would be difficult.

(4) (a) N. L. Wendler, Huang-Minlon and M. Tishler, THIS JOURNAL, **73**, 3818 (1951); (b) R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell and J. H. Williams, *J. Org. Chem.*, **18**, 70 (1953).

(5) J. Fried and E. F. Sabo, THIS JOURNAL, **75**, 2273 (1953).

(6) This compound has been prepared in this Laboratory by an independent route from the bis-ethylene ketal IVb of hydrocortisone acetate [S. Bernstein, R. Littell and J. H. Williams, *ibid.*, **75**, 4830 (1953); see also R. P. Graber, A. C. Haven, Jr., and N. L. Wendler, *ibid.*, **75**, 4722 (1953)].