Preparation and Properties of Steroidal 17,20- and 20,21-Acetonides Epimeric at C-20. II. Derivatives of Cortisol and Cortisone[1]

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In a continuation of the previous study,[3] the 17,20- and 20,21-acetonides derived from the C-20 reduction products of cortisol and cortisone were prepared. Oxidation of the 17,20-acetonido-21-ols **7a** and **7b** with chromic anhydride–pyridine gave the respective 21-aldehydes **15a** and **15b** and the 21-oic acids **12a** and **12b**. Esterification of the latter with diazomethane provided products (**13a** and **13b**) which were identical with the acetonation products of the previously prepared methyl esters **14a** and **14b**. Several examples were encountered which illustrate the difference in reactivity of substituents at C-21 in 17,20α- *vs.* 17,20β-acetonides. These included, for the 21-aldehydes, relative rates of hemiacetal formation and, for the methyl esters, relative rates of saponification. The steric factors which account for the greater reactivity at C-21 in 17,20β-acetonides are believed also to account for the epimerization at C-20 of the 20α-methyl ester acetonide **13a** in methanolic sodium hydroxide. The rearrangement without inversion at C-20 of 17,20- to 20,21-acetonides in acetone–sulfuric acid was also observed. Evidence is submitted suggesting that this rearrangement is of the intramolecular type. An unexpected finding was the apparently light-catalyzed spontaneous oxidation in the crystalline state of the 17,20-acetonido-21-acetates **2a** and **2b** to the corresponding 11 ketones.

The C-20-epimeric 20,21-acetonides derived from 11-deoxycortisol have been prepared by Reichstein and his associates,[2] but we are unaware of any prior synthesis of either the 17,20- or 20,21-acetonides of their 11-oxygenated analogs. As an extension of the work described in the previous paper,[3] we have prepared the 17,20- and 20,21-isopropylidene derivatives of the C-20 reduction products of cortisol and cortisone and have interrelated them through a number of transformations. This paper also includes several reactions which are unique for 17,20-acetonides with various substituents at C-21.

Treatment of the readily available pregnenetetrolone 21-acetate **1** (Scheme I) with acetone–perchloric acid for 20 min at room temperature gave the 17,20α-acetonide **2a** in a yield of 76%. The epimeric 17,20β-acetonide **2b** was prepared in an over-all yield of 45% by reaction of cortisol acetate (**3**) with sodium borohydride in dimethylformamide[4] followed by treatment of the crude reduction product with acetone–perchloric acid. Saponification of the acetonide acetates **2a** and **2b** afforded the corresponding 21-ols **4a** and **4b** in excellent yields. Oxidation of the 11β-hydroxy-21-acetates **2a** and **2b** with chromic anhydride in pyridine[5] gave the corresponding 11 ketones **5a** and **5b** in respective yields of 97 and 93%. The 20β epimer **5b** was also prepared independently (62% yield) from cortisone acetate (**6**) in a manner analogous to the preparation of **2b** from **3**. Saponification of the 11-keto-21-acetates **5a** and **5b** furnished the corresponding 21-ols **7a** and **7b**.

The 20,21-acetonides **9a** and **9b** were prepared in yields of 7.5 and 30%, respectively, by reduction of free cortisol (**8**) with sodium borohydride in dimethylformamide followed by treatment of the crude glycerol mixture with acetone–*p*-toluenesulfonic acid. A more satisfactory synthesis of the 20α,21-acetonide **9a** was achieved by saponification of **1** followed by acetonation of the resulting glycerol. Oxidation of the 11β-hydroxy-20,21-acetonides **9a** and **9b** with chromic anhydride in pyridine provided the 11 ketones **10a** and **10b** in yields exceeding 90%. An independent synthesis of these two compounds from cortisone (**11**) was carried out in a manner analogous to the preparation of **9a** and **9b** from **8**. Treatment of **10a** and **10b** with aqueous acetic acid[3] effected cleavage of the dioxolane ring yielding, respectively, Reichstein's substances epi-U and U.[6]

Additional evidence supporting the structures assigned to the 17,20-acetonido-21-ols **7a** and **7b** was sought (Scheme II) by relating them to the acetonation products of the previously described epimeric glycolic esters **14a** and **14b** from cortisone 21-aldehyde.[7] Initial attempts to effect oxidation of **7a** and **7b** at C-21 with chromic anhydride or potassium permanganate in the presence of mineral acid did not yield the desired acidic products. However, following prolonged reaction with chromic anhydride in pyridine, each epimer was converted in part into an acid in which the dioxolane ring remained intact. These acids, which are designated **12a** and **12b**, were converted with diazomethane into the corresponding methyl esters **13a** and **13b** which proved to be identical with the products obtained from the dihydroxy methyl esters **14a** and **14b** following treatment with acetone–perchloric acid. Investigation of the neutral reaction mixture from the chromic anhydride–pyridine oxidation of **7a** and **7b** showed that it contained, in addition to starting material, two products in each case. Each mixture yielded the same mobile component; this substance has the empirical formula $C_{23}H_{30}O_5$ and will be described further in a subsequent publication. The more polar (less mobile) components were shown to be the corresponding 21-aldehydes **15a** and **15b** since, in addition to other evidence, oxidation with potassium chromate in acetic acid followed by esterification with diazomethane afforded the methyl esters **13a** and **13b**. It is of interest that the combined yield of acid and aldehyde from **7b** (39%) is nearly twice that obtained from **7a** (22%). This difference may be understood in stereochemical terms, in that the C-21 hydroxyl group of the 20β epimer **7b** is fixed in a

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(2) (a) H. Reich, C. Montigel, and T. Reichstein, *Helv. Chim. Acta*, **24**, 977, 983 (1941); (b) B. A. Koechlin and T. Reichstein, *ibid.*, **26**, 1328, 1332 (1943).

(3) M. L. Lewbart and J. J. Schneider, *J. Org. Chem.*, **34**, 3505 (1969).

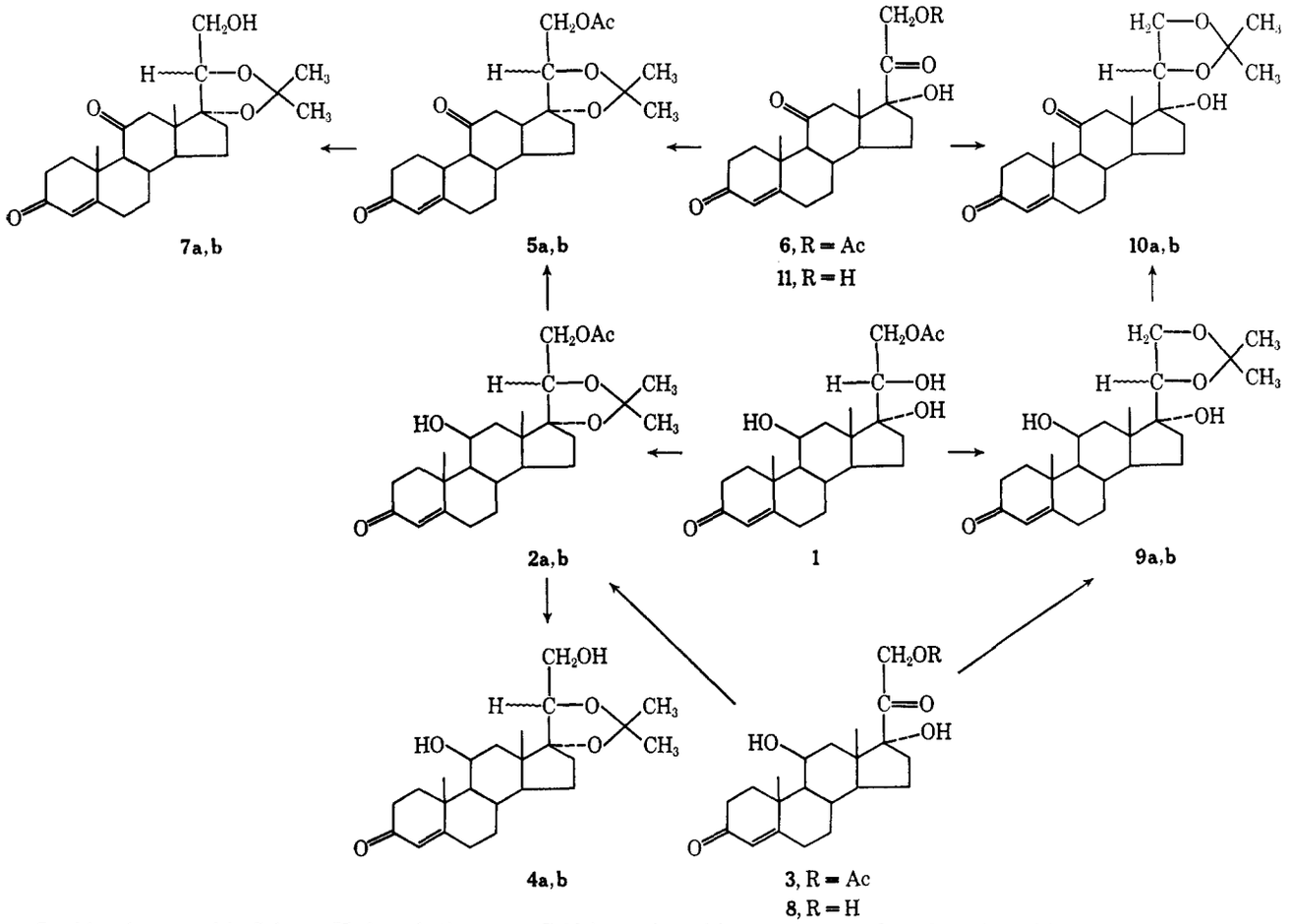
(4) M. L. Lewbart, *ibid.*, **33**, 1695 (1968).

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

(6) (a) R. Neher and A. Wettstein, *Helv. Chim. Acta*, **39**, 2062 (1956); (b) T. Reichstein and J. von Euw, *ibid.*, **24**, 247E (1941).

(7) M. L. Lewbart and V. R. Mattox, *J. Org. Chem.*, **28**, 1773 (1963).

SCHEME I[a]



[a] In this scheme and in Scheme II the substituent at C-20 is α oriented in "a" compounds and β oriented in "b" compounds.

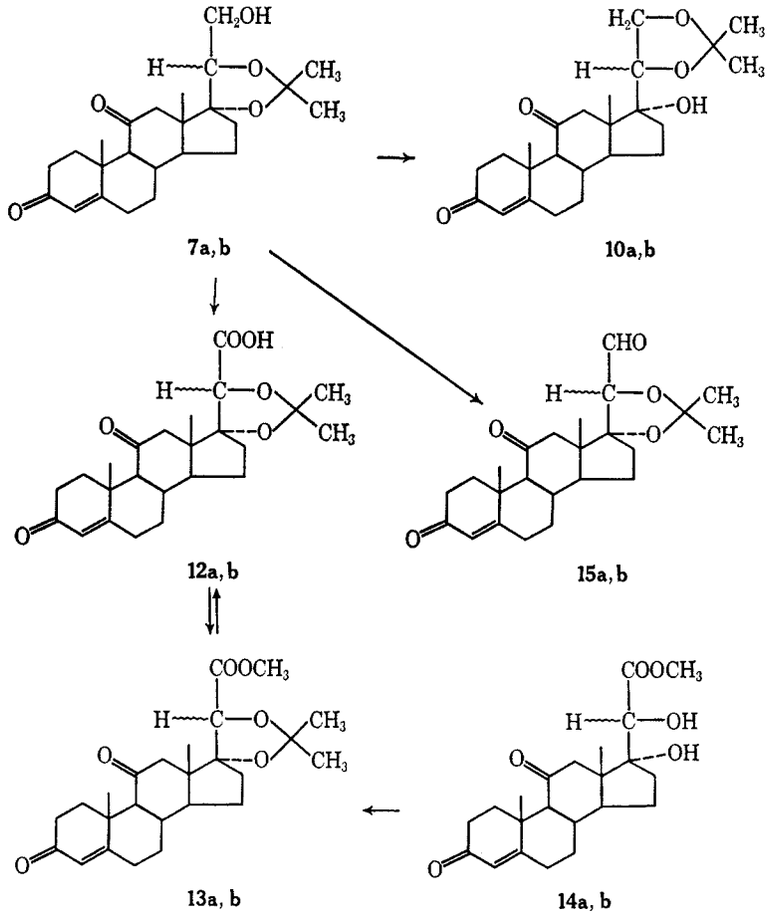
more exposed position (see discussion in previous paper[3]).

Two additional examples which illustrate the greater reactivity of substituents at C-21 in 17,20β-acetonides have been encountered. In the course of determining the optical rotations of the 21-aldehydes **15a** and **15b** in methanol solution, it was observed that the 20α epimer underwent a slow positive shift in α. Since this mutarotation did not occur in chloroform solution, it was concluded that the rotatory shift in **15a** was due to the addition, at a rate slow enough to be observed, of methanol at C-21, and that similar addition of methanol to **15b** occurred too rapidly to be detected. This conclusion was substantiated by determining the infrared spectra of both aldehydes after brief solution in methanol. The spectrum of the 20α epimer was virtually identical with that of the original material, but the 20β epimer existed chiefly as the hemiacetal as evidenced by the generation of a hydroxyl band and a considerable diminution of the aldehyde C–H stretch and carbonyl bands.

The second example was encountered in the course of saponifying the methyl ester acetonides **13a** and **13b**. When treated under identical conditions with 2 equiv of alkali, the 20β epimer was converted into the acid **12b** in 87% yield, whereas the 20α epimer gave an acidic fraction in only 18% yield. However, complete conversion of **13a** into acidic material was achieved by refluxing with excess alkali for 1 hr. Examination of this fraction by thin layer chromatography showed that it consisted of two components in a roughly 3:1 ratio. These were identified as the 17,20α-acetonido acid **12a** (25%) and the 17,20β-acetonido acid **12b** (70%). A possible mechanism for this novel epimerization at C-20 is presented in Scheme III. Attack by hydroxide ion at C-21, which readily occurs in the case of the 20β epimer **13b**, is largely prevented by the steric factors previously mentioned. Instead, a proton is abstracted at C-20 in a, yielding the carbanion b. The asymmetry at C-20 is abolished through formation of its resonance hybrid c. Addition of a proton to b follows, affording the sterically favored 20β-acetonido methyl ester d which rapidly undergoes hydrolysis at C-21 in the normal fashion. As would be predicted by the above mechanism, alkali-catalyzed epimerization of the 17,-20α-acetonido acid does not occur because the carbomethoxyl group is required for the formation of the ionized intermediates b and c.

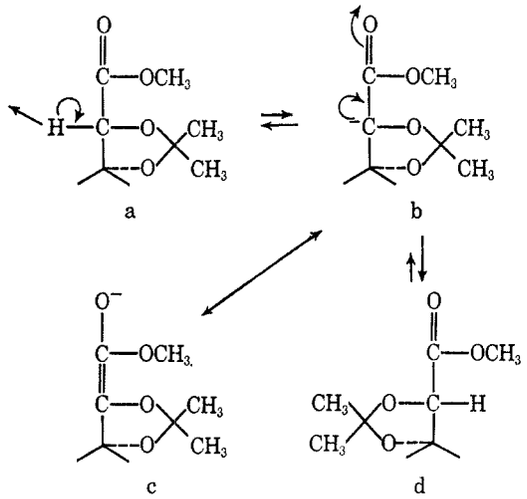
In the course of the unsuccessful oxidation experiments previously alluded to, it was noted that, in systems including acetone and mineral acid, 17,20-acetonides have a tendency to undergo rearrangement without inversion at C-20 to the isomeric 20,21-acetonides (Scheme II). A more detailed comparison of the reactivity of the 17,20-acetonides **7a** and **7b** in acetone–sulfuric acid showed that, under identical conditions, the 20α epimer **7a** was converted into the 20α,21-acetonide **10a** in a yield of 93%, but that only 22% of

SCHEME II[a]



[a] See footnote *a*, Scheme I.

SCHEME III



the 20β epimer was transformed to the isomeric acetonide **10b**. These results are consistent with our previous observations on the greater stability of 17,20β-acetonides. Since treatment of the 17,20α-acetonide **7a** with tetrahydrofuran–sulfuric acid gave, in addition to several other products, the 20α,21-acetonide **10a** in 25% yield, it is likely that the rearrangement proceeds intramolecularly rather than *via* complete cleavage of the isopropylidene group followed by re-acetonation.

Special mention has been made[1] of a remarkable property of the 11β-hydroxy-17,20-acetonido-21-acetates **2a** and **2b**, namely their spontaneous oxidation to the corresponding 11 ketones. It was noted that, on standing in pure crystalline form at room temperature, both compounds deteriorate slowly as judged by a progressive decrease in their melting points. Examination of the crystals at intervals by infrared spectroscopy and thin layer chromatography showed the gradual formation in each case of a single, slightly more mobile product which possessed a new carbonyl group. In subsequent preparative experiments these products were recovered in pure form as the 21-ols. They possessed the same melting point, optical rotation, chromatographic mobility, and infrared spectra as the corresponding 11 ketones **7a** and **7b**. The 11β-ols **2a** and **2b** appeared to be stable when stored at $-15°$, but their deterioration is not appreciably hastened by heating in air at 100° for as long as 3 weeks. In addition, **2a** and **2b** are no more sensitive in solution than other 11β-ols to the action of mild oxidizing agents such as oxygen–platinum, cupric acetate, silver oxide, or lead tetraacetate. That light is an important factor in this oxidation was shown by the following simple experiment. Glass vials containing fresh specimens of **2a** and **2b** were stored at room temperature both in the presence and absence of ambient (fluorescent) light. After 1 month, the melting points of the samples stored in the light fell approximately 20°, whereas the melting points of the covered samples remained unchanged.

This finding constitutes the first published example, as far as we are aware, of the spontaneous oxidation, in the crystalline state, of an 11β-hydroxyl group to the 11 ketone. The 21-acetoxyl group is essential for this

oxidation since the corresponding 21-ols **4a** and **4b** are perfectly stable. Examination of Dreiding models shows no conformational peculiarities of these molecules which would account for their behavior, a conclusion which is reenforced by the fact that both epimers undergo deterioration, and to the same extent.

With minor exceptions, the infrared spectral characteristics of the eighteen 17,20- and four 20,21-acetonides prepared in this study are similar to and supplement those detailed in Tables II and III of the previous paper.[3] Since the glycerols themselves absorb rather strongly in the 1250–1210-cm^{-1} region, the characteristic acetonide bands which occur here are less prominent, and therefore less useful. As noted in the previous paper, both types exhibit a band within the range of 1160–1150 cm^{-1} which is moderate to strong in the 20,21-acetonides and strong to very strong in 17,20-acetonides. Those bands which serve to differentiate between the two types in the series derived from 5β-pregnan-3α-ol are also present in acetonides derived from cortisol and cortisone. Thus all four 20,21-acetonides display a very strong band within the range of 860–850 cm^{-1}, while all 17,20-acetonides have a characteristically strong band in the region 1000–990 cm^{-1}.

Experimental Section

Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Optical rations were determined at 365 and 589 mμ (D line of sodium) in a Zeiss 0.005° photoelectric polarimeter. Measurements were made in methanol solution (unless otherwise stated) in a 0.5-dm tube at a concentration of about 1% and at a temperature of 26 ± 1°. Infrared spectra were determined as KBr pellets with a Beckman IR-8 instrument. Ultraviolet spectra were obtained in methanol solution with a Zeiss RPQ 20A recording spectrophotometer. Descriptions of the column, paper, and thin layer (tlc) chromatographic techniques appear in papers cited previously.[4] Elemental analyses were by August Peisker-Ritter, Brugg, Switzerland.

Reaction mixtures from chromic anhydride–pyridine oxidations were processed by concentration *in vacuo* nearly to dryness, repeated leaching of the residue with ethyl acetate, and successive washing of the combined organic extracts with dilute hydrochloric acid, dilute sodium hydroxide, and neutral brine.

17,20α-Isopropylidenedioxy-21-acetoxy-11β-hydroxypregn-4-en-3-one (2a) from 1.—To a solution of 21-acetoxy-11β,17,20α-trihydroxypregn-4-en-3-one[8] (1 g) in acetone (1 l.) was added 70% perchloric acid (2.5 ml). After 20 min the product was recovered by the general procedure[3] and chromatographed on a 38 × 750 mm silica gel column in ethyl acetate–isooctane (2:1). Fractions (9 ml) were collected at 10-min intervals. Crystallization of the residue from **fractions 121–170** gave prisms (713 mg, mp 206.5–207.5°; 120 mg, mp 204–206°) in a yield of 75.8%: $[\alpha]_{365}$ −48.4°, $[\alpha]_D$ 42.0°; λ_{max} 242 mμ (ϵ 15,600); ν_{max} 1737 and 1228 (acetoxyl) and 1148 and 995 cm^{-1} (17,20-acetonide).

Anal. Calcd for $C_{26}H_{38}O_6$: C, 69.93; H, 8.58; CH_3CO, 9.64. Found: C, 69.98; H, 8.49; CH_3CO, 10.34.

17,20α-Isopropylidenedioxy-11β,21-dihydroxypregn-4-en-3-one (4a) from 2a.—Saponification of 17,20α-isopropylidenedioxy-21-acetoxy-11β-hydroxypregn-4-en-3-one (134 mg) in methanol (2.4 ml) with 1 *N* sodium hydroxide (0.6 ml) for 15 min and recovery of the product with methylene chloride gave 103 mg (85%) of prisms from methanol: mp 258–260°; $[\alpha]_{365}$ −8.39°, $[\alpha]_D$ 49.1°; λ_{max} 242 mμ (ϵ 15,500); ν_{max} 1148 and 990 cm^{-1} (17,20-acetonide).

Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.13; H, 8.90.

17,20α-Isopropylidenedioxy-21-acetoxypregn-4-ene-3,11-dione (5a) from 2a.—To a solution of 17,20α-isopropylidenedioxy-21-acetoxy-11β-hydroxypregn-4-en-3-one (900 mg) in pyridine (15 ml) was added chromic anhydride (900 mg) in pyridine (110 ml). After 22 hr at room temperature, the product was recovered and crystallized from acetone–*n*-hexane as plates (770 mg, mp 211–212°; 100 mg, mp 209–210°) in a yield of 97%: $[\alpha]_{365}$ 407°, $[\alpha]_D$ 83.6°; λ_{max} 238 mμ (ϵ 15,350); ν_{max} 1150 and 991 cm^{-1} (17,20-acetonide).

Anal. Calcd for $C_{26}H_{36}O_6$: C, 70.24; H, 8.16; CH_3CO, 9.68. Found: C, 70.38; H, 8.21; CH_3CO, 9.12.

17,20α-Isopropylidenedioxy-21-hydroxypregn-4-ene-3,11-dione (7a) from 5a.—Saponification of 17,20α-isopropylidenedioxy-21-acetoxypregn-4-ene-3,11-dione (888 mg) with methanolic sodium hydroxide as in the preparation of **4a** from **2a** gave 776 mg (96.6%) of hexagonal plates from methanol: mp 244–246°; $[\alpha]_{365}$ 454°, $[\alpha]_D$ 92.4°; λ_{max} 238 mμ (ϵ 15,200); ν_{max} 1149 and 990 cm^{-1} (17,20-acetonide).

Anal. Calcd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.43; H, 8.54.

17,20β-Isopropylidenedioxy-21-acetoxy-11β-hydroxypregn-4-en-3-one (2b) from 3.—To a solution of cortisol acetate (1 g) in dimethylformamide (25 ml) was added sodium borohydride (75 mg) and sodium bicarbonate (150 mg), each in 1.25 ml of water. After 4 hr at room temperature, excess acetic acid was added, and the solution was saturated with salt and extracted repeatedly with ethyl acetate. The combined organic extracts were washed with brine and concentrated to dryness. To the residue in acetone (500 ml) was added perchloric acid (1.25 ml) and, after 100 min at room temperature, the crude acetonide acetate was recovered and chromatographed on a 34 × 750 mm silica gel column. The system was ethyl acetate–isooctane (1:1), and 9-ml fractions were collected at 10-min intervals. **Fractions 195–350** afforded plates (500 mg, 45.3%) from acetone–*n*-hexane, mp 195–196.5°. Recrystallization from methanol gave the analytical sample: mp 196–197°; $[\alpha]_{365}$ 137°, $[\alpha]_D$ 105°; λ_{max} 242 mμ (ϵ 15,400); ν_{max} 1147 and 1000 cm^{-1} (17,20-acetonide).

Anal. Calcd for $C_{26}H_{38}O_6$: C, 69.93; H, 8.58; CH_3CO, 9.64. Found: C, 69.78; H, 8.60; CH_3CO, 9.81.

17,20β-Isopropylidenedioxy-11β,21-dihydroxypregn-4-en-3-one (4b) from 2b.—Saponification of 17,20β-isopropylidenedioxy-21-acetoxy-11β-hydroxypregn-4-en-3-one (134 mg), as in the preparation of **4a** from **2a**, provided plates from acetone (75 mg, mp 257.5–259.5°; 29 mg, mp 256–257.5°) in a yield of 86%: $[\alpha]_{365}$ 45.4°, $[\alpha]_D$ 83.7°; λ_{max} 242 mμ (ϵ 15,400); ν_{max} 1150 and 1000 cm^{-1} (17,20-acetonide).

Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.10; H, 8.90.

17,20β-Isopropylidenedioxy-21-acetoxypregn-4-ene-3,11-dione (5b) from 2b.—Oxidation of 17,20β-isopropylidenedioxy-21-acetoxy-11β-hydroxypregn-4-en-3-one (100 mg) with chromic anhydride (100 mg) in pyridine (14 ml) was carried out for 18 hr. The product crystallized from ether–*n*-hexane as needles (85 mg, mp 156–157°; 8 mg, mp 153–154°) in a yield of 93%: $[\alpha]_{365}$ 387°, $[\alpha]_D$ 123°; λ_{max} 239 mμ (ϵ 15,850); ν_{max} 1735 and 1225 (acetoxyl) and 1150 and 1000 cm^{-1} (17,20-acetonide).

Anal. Calcd for $C_{26}H_{36}O_6$: C, 70.24; H, 8.16; CH_3CO, 9.68. Found: C, 70.19; H, 8.13; CH_3CO, 9.51.

17,20β-Isopropylidenedioxy-21-acetoxypregn-4-ene-3,11-dione (5b) from 6.—A solution of cortisone acetate (2 g) in dimethylformamide (100 ml) was treated with sodium borohydride (150 mg) and sodium bicarbonate (300 mg), each in 2.5 ml of water. After 3 hr the product was recovered as in the preparation of **2b** from **3**, and treated with perchloric acid in acetone (2.5 ml in 1 l.) for 20 min. The product was chromatographed on a 50 × 900 mm column of silica gel with the system ethyl acetate–isooctane (1:1); 10-ml fractions were collected at a rate of six per hour. Crystallization of the contents of **fractions 332–530** from ether gave 1366 mg (61.8%) of prisms, mp 156–156.5°, which had an infrared spectrum identical with that of the chromic anhydride–pyridine oxidation product of **2b**.

17,20β-Isopropylidenedioxy-21-hydroxypregn-4-ene-3,11-dione (7b) from 5b.—Saponification of 17,20β-isopropylidenedioxy-21-acetoxypregn-4-ene-3,11-dione (1332 mg) with methanolic sodium hydroxide furnished plates (1156 mg) from acetone, mp 258–259°, in a yield of 96%. Data for the analytical sample follow: mp 262–263°; $[\alpha]_{365}$ 536°, $[\alpha]_D$ 125°; λ_{max} 238 mμ (ϵ 15,400); ν_{max} 1150 and 995 cm^{-1} (17,20-acetonide).

Anal. Calcd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.38; H, 8.60.

Spontaneous Oxidation at C-11 of 2a and 2b.—A freshly prepared sample of 17,20α-isopropylidenedioxy-21-acetoxy-11β-hydroxypregn-4-en-3-one, mp 206–207°, was stored at room temperature. The crystals showed a progressive decrease in

(8) J. A. Hogg, F. H. Lincoln, A. H. Nathan, A. R. Hanze, W. P. Schneider, P. F. Beal, and J. Korman, *J. Amer. Chem. Soc.*, **77**, 4438 (1955).

melting point and the gradual appearance in their infrared spectra of a new carbonyl band at 1700 cm^{-1} together with a diminution in hydroxyl absorption. An 11-month-old sample (40 mg, mp 130–140°) was saponified in methanol (1 ml) with 1 *N* sodium hydroxide (0.25 ml) for 15 min at room temperature. Analysis of the reaction mixture by tlc in ethyl acetate–isooctane (3:1) showed an approximately 3:2 mixture of components with mobilities identical with those of the 11β,21-diol **4a** (R_f 0.12) and the 11-keto-21-ol **7a** (R_f 0.21), respectively. The mixture was chromatographed on a 15 × 415 mm Celite column in toluene (90), isooctane (110), methanol (160), and water (40 ml) at a rate of 2 ml/12 min. The residue from **fractions 42–65** weighed 12.4 mg and crystallized from methanol as plates: mp 242–244°; $[\alpha]_{365}$ 453°, $[\alpha]_D$ 93.3°. It did not depress the melting point of **17,20α-isopropylidenedioxy-21-hydroxypregn-4-ene-3,11-dione** prepared by saponification of **5a**, and their ir spectra were identical. The material from **fractions 101–150** (18.8 mg, mp 254–256°) was identical with **17,20α-isopropylidenedioxy-11β,21-dihydroxypregn-4-en-3-one** prepared by saponification of **2a**.

In a similar manner, a freshly prepared sample of 17,20β-isopropylidenedioxy-21-acetoxy-11β-hydroxypregn-4-en-3-one (mp 195–196°), which was stored as above, underwent the same progressive changes in melting point and ir absorption. A 9-month-old sample (40 mg, mp 149–160°) was saponified, and the deacetylated material was chromatographed of a 15 × 275 mm Celite column under the same conditions used for the 20α epimer. From **fractions 27–56** was obtained 12.2 mg of needles: mp 259–260°; $[\alpha]_{365}$ 538°, $[\alpha]_D$ 127°. It did not depress the melting point of **17,20β-isopropylidenedioxy-21-hydroxypregn-4-ene-3,11-dione**, and their ir spectra were superimposable. From **fractions 86–150** was obtained **17,20β-isopropylidenedioxy-11β,21-dihydroxypregn-4-en-3-one** (19.7 mg, mp 254–256°), the saponification product of **2b**.

Reaction of 17,20α-Isopropylidenedioxy-21-hydroxypregn-4-ene-3,11-dione (7a) with Chromic Anhydride–Pyridine.—A solution of the 17,20α-acetonido-21-ol (500 mg) in pyridine (55 ml) was treated with chromic anhydride (500 mg) for 66 hr at room temperature. The crude product was separated into acidic and neutral fractions by partitioning between ethyl acetate and dilute sodium hydroxide solution. The **acidic fraction** (63 mg) was treated with ethereal diazomethane and, after purification of the esterified material on a small silica gel column, 39.8 mg (7.4%) of **methyl 17,20α-isopropylidenedioxy-3,11-dioxopregn-4-en-21-oate (13a)** was obtained: mp 180.5–181.5°; $[\alpha]_{365}$ 431°, $[\alpha]_D$ 92.6°; λ_{max} 238 mμ (ε 15,750); ν_{max} 1758 and 1735 (sh) (carbomethoxyl) and 1152 and 990 cm^{-1} (17,20-acetonide).

Anal. Calcd for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96; CH_3O, 7.21. Found: C, 69.70; H, 7.91; CH_3O, 7.33.

The **netural fraction** (450 mg) was chromatographed on a 41.5 × 650 mm Celite column in toluene (50), isooctane (150), methanol (170), and water (30 ml). Fractions (8 ml) were collected at 10-min intervals. From **fractions 121–190** was obtained 54 mg of rosettes ($C_{23}H_{30}O_5$), mp 245.5–246.5°, from methanol; the nature of this substance will be described in a forthcoming paper.

17,20α-Isopropylidenedioxy-3,11-dioxopregn-4-en-21-al (15a). Fractions 351–500.—Crystallization from acetone–ether afforded 71 mg (14.2%) of needles: mp 186.5–187°; $[\alpha]_{365}$ 507°, $[\alpha]_D$ 127° ($CHCl_3$); λ_{max} 238 mμ (ε 15,700); ν_{max} 2740 and 1734 (aldehyde) and 1152 and 992 cm^{-1} (17,20-acetonide).

Anal. Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 72.07; H, 8.08.

From **fractions 591–840** was recovered 134 mg (26.8%) of starting material (**7a**), mp 240–241°.

Reaction of 17,20β-Isopropylidenedioxy-21-hydroxypregn-4-ene-3,11-dione (7b) with Chromic Anhydride–Pyridine.—The 17,20β-acetonido-21-ol (500 mg) was treated for 66 hr as above, and the reaction mixture was fractionated into acidic and neutral components. The **acidic fraction** (146 mg) was esterified and purified in the manner described for the preparation of **13a**. Crystallization from acetone–*n*-hexane furnished **methyl 17,20β-isopropylidenedioxy-3,11-dioxopregn-4-en-21-oate (13b)** as needles (83 mg, mp 171.5–172.5°; 6.5 mg, mp 169–171°) in a yield of 16.7%: $[\alpha]_{365}$ 549°, $[\alpha]_D$ 129°; λ_{max} 238 mμ (ε 14,300); ν_{max} 1757 and 1730 (carbomethoxyl) and 1153 and 997 cm^{-1} (17,20-acetonide).

Anal. Calcd for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96; CH_3O, 7.21. Found: C, 69.70; H, 7.89; CH_3O, 7.19.

The **neutral fraction** (390 mg) was chromatographed on a 38 × 760 mm Celite column in toluene (70), isooctane (130), methanol (170), and water (30 ml). Fractions (10 ml) were collected every 10 min. Rechromatography of the residue from **fractions 72–120** in an isooctane–methanol–water system gave 22.6 mg of rosettes, mp 244–245°, whose ir spectrum was identical with that of the most mobile neutral product obtained from **7a**.

17,20β-Isopropylidenedioxy-3,11-dioxopregn-4-en-21-al (15b). Fractions 168–261.—Crystallization from ether afforded 109 mg (21.9%) of needles: mp 154–155°; $[\alpha]_{365}$ 537°, $[\alpha]_D$ 121° ($CHCl_3$); λ_{max} 238 mμ (ε 15,400); ν_{max} 2730 and 1730 (aldehyde) and 1153 and 993 cm^{-1} (17,20-acetonide).

Anal. Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 71.84; H, 8.16.

From **fractions 341–450** was recovered 101 mg (20.2%) of starting material (**7b**), mp 257.5–259°.

Methyl 17,20α-Isopropylidenedioxy-3,11-dioxopregn-4-en-21-oate (13a) from 14a.—To a solution of methyl 17,20α-dihydroxy-3,11-dioxopregn-4-en-21-oate[7] (100 mg) in acetone (100 ml) was added perchloric acid (0.25 ml). After 7.5 hr the crude product was recovered and purified on a 20 × 750 mm silica gel column in ethyl acetate–isooctane (1:1). Crystallization from ether gave needles (74 mg, mp 181–182.5°; 10 mg, mp 179–180.5°) in a yield of 76.2%. The ir spectrum was identical with that of the esterified acidic oxidation product from the 21-ol **7a**.

Methyl 17,20β-Isopropylidenedioxy-3,11-dioxopregn-4-en-21-oate (13b) from 14b.—Methyl 17,20β-dihydroxy-3,11-dioxopregn-4-en-21-oate[7] (100 mg) was treated with acetone–perchloric acid and purified on a silica gel column by the same procedure used for its 20α epimer. Crystallization from acetone–*n*-hexane gave fine needles (71.5 mg, mp 171–173°; 5.5 mg, mp 168–170°) in a yield of 69.8%. The ir spectrum was the same as that of the esterified acidic product from the oxidation of **7b**.

Methyl 17,20α-Isopropylidenedioxy-3,11-dioxopregn-4-en-21-oate (13a) from 15a.—A solution of 17,20α-isopropylidenedioxy-3,11-dioxopregn-4-en-21-al (20 mg) and potassium chromate (30 mg) in acetic acid (2 ml) stood for 49 hr at room temperature. Methanol was added and the solvents were removed with a nitrogen stream. The residue was partitioned between methylene chloride and dilute sodium hydroxide to afford acidic (6.1 mg) and neutral (19.5 mg) fractions. The neutral fraction, which consisted largely of starting material, was retreated with potassium chromate in acetic acid for an additional 72 hr, and a second acidic fraction (2.4 mg) was obtained. The combined acidic fractions were esterified with diazomethane, and the neutral product was purified on a silica gel column in ethyl acetate–isooctane (3:2). Crystallization from ether gave 5.9 mg of prisms, mp 180.5–181.5°, whose ir spectrum was identical with that of the acetonation product of **14a**.

Methyl 17,20β-Isopropylidenedioxy-3,11-dioxopregn-4-en-21-oate (13b) from 15b.—Oxidation of 17,20β-isopropylidenedioxy-3,11-dioxopregn-4-en-21-al (20 mg) was carried out for 49 hr as above, affording acidic (4.6 mg) and neutral (13.1 mg) fractions. Re-treatment of the neutral fraction gave an additional 4.9 mg of acidic material. Esterification with diazomethane of the combined acidic fractions and chromatography on silica gel provided 8.8 mg of prismatic needles from acetone–*n*-hexane, mp 171–172.5°. The ir spectrum was identical with that of the acetonation product of **14b**.

Saponification of Methyl 17,20α- and -20β-Isopropylidenedioxy-3,11-dioxopregn-4-en-21-oates (13a and 13b).—To 43 mg (0.1 mmol) each of the methyl ester acetonides in methanol (1 ml) was added 0.2 ml of 1 *N* sodium hydroxide (0.2 mmol). Analysis by tlc in ethyl acetate–isooctane (1:1) after 30 min at room temperature showed approximately 50% conversion of **13b** into acidic material; the 20α epimer was virtually unaffected. After 6 hr, acetic acid (0.05 ml) was added to each solution and the solvents were removed with a current of nitrogen. The **acid fractions** from **13a** and **13b** weighed 7.7 mg and 37.5 mg, respectively; the corresponding **neutral fractions** weighed 34.4 mg and 3.6 mg.

17,20β-Isopropylidenedioxy-3,11-dioxopregn-4-en-21-oic Acid (12b) from 13b.—In another experiment, 86 mg (0.2 mmol) of methyl 17,20β-isopropylidenedioxy-3,11-dioxopregn-4-en-21-oate in methanol (4 ml) was treated with 1 *N* sodium hydroxide (1 ml) for 4 hr. The acidic fraction crystallized as needles from aqueous methanol (76.5 mg, mp 136–138°) in a yield of 92%. Recrystallization from ethyl acetate gave rosettes: mp 214.5–216.5°; $[\alpha]_{365}$ 550°, $[\alpha]_D$ 129°; λ_{max} 238 mμ (ε 15,300); ν_{max} 1158 and 997 cm^{-1} (17,20-acetonide).

Anal. Calcd for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74. Found: C, 69.09; H, 7.93.

17,20α- and -20β-Isopropylidenedioxy-3,11-dioxopregn-4-en-21-oic Acids (12a and 12b) from 13a.—A solution of methyl 17,20α-isopropylidenedioxy-3,11-dioxopregn-4-en-21-oate (156 mg) in a mixture of methanol (10 ml) and 0.2 *N* aqueous sodium hydroxide (5 ml) was refluxed for 1 hr. The acid fraction (160 mg) was chromatographed on a 25 × 720 mm Celite column in toluene (70), isooctane (130), methanol (30), acetic acid (30), and water (140 ml). Fractions (6 ml) were collected every 10 min.

17,20β-Isopropylidenedioxy-3,11-dioxopregn-4-en-21-oic Acid. Fractions 81–120.—Crystallization of the residue (105 mg, 69.6%) from ether gave 96 mg of needles, mp 213.5–216°. The ir spectrum was identical with that of the saponification product of **13b**. Esterification with diazomethane furnished a product with the same ir spectrum as that of the 17,20β-acetonide methyl ester **12b**.

17,20α-Isopropylidenedioxy-3,11-dioxopregn-4-en-21-oic Acid. Fractions 151–200.—This fraction weighed 38 mg (25.2%) and crystallized from ethyl acetate as needles: mp 224.5–226°; $[\alpha]_{365}$ 477°, $[\alpha]_D$ 102°; λ_{max} 238 mμ (ε 14,800); ν_{max} 1155 and 992 cm^{-1} (17,20-acetonide).

Anal. Calcd for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74. Found: C, 69.12; H, 7.57.

On esterification with diazomethane the acid was converted into a product which did not depress the melting point of starting material (**13a**), and their ir spectra were identical.

20α,21-Isopropylidenedioxy-11β,17-dihydroxypregn-4-en-3-one (9a) from 1.—Saponification of 21-acetoxy-11β,17,20α-trihydroxypregn-4-en-3-one furnished Reichstein's substance epi-E (11β,17,20α,21-tetrahydroxypregn-4-en-3-one), mp 247–248°. To a solution of the free glycerol (800 mg) in a mixture of methanol (10 ml) and acetone (200 ml) was added *p*-toluenesulfonic acid (200 mg). After 30 min the product was recovered and crystallized from acetone as platelets (653 mg, mp 243–245°; 155 mg, mp 242–244°) in a yield of 91%: $[\alpha]_{365}$ 1.98°, $[\alpha]_D$ 61.4°; λ_{max} 242 mμ (ε 15,500); ν_{max} 1158 and 860 cm^{-1} (20,21 acetonide).

Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.29; H, 8.92.

20α,21-Isopropylidenedioxy-17-hydroxypregn-4-ene-3,11-dione (10a) from 9a.—Oxidation of 20α,21-isopropylidenedioxy-11β,17-dihydroxypregn-4-en-3-one (155 mg) with chromic anhydride (155 mg) in pyridine (23 ml) was carried out for 22 hr. The product was crystallized from acetone as prisms (99 mg, mp 199–200°; 54 mg, mp 198–199°) in a yield of 99%: $[\alpha]_{365}$ 553°, $[\alpha]_D$ 121°; λ_{max} 238 mμ (ε 15,400); ν_{max} 1161 and 860 cm^{-1} (20,21-acetonide).

Anal. Calcd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.58; H, 8.55.

Hydrolysis of **10a** (40 mg) in 60% acetic acid (5 ml) for 5.5 hr at room temperature gave 35 mg of **17,20α,21-trihydroxypregn-4-ene-3,11-dione** as platelets from acetone: mp 241–242°.

20α- and 20β,21-Isopropylidenedioxy-11β,17-dihydroxypregn-4-en-3-ones (9a and 9b) from 8.—To a solution of cortisol (2 g) in dimethylformamide (50 ml) was added sodium borohydride (150 mg) and sodium bicarbonate (300 mg), each in 2.5 ml of water. After 4 hr excess acetic acid was added and the solution was concentrated *in vacuo*. The resulting oil was partitioned between ethyl acetate and brine. The organic extract in acetone (500 ml) was treated with *p*-toluenesulfonic acid (500 mg) for 1 hr, and the reaction mixture was chromatographed on a 50 × 900 mm silica gel column in ethyl acetate–isooctane (2:1); 10-ml fractions were collected every 10 min.

20β,21-Isopropylidenedioxy-11β,17-dihydroxypregn-4-en-3-one. Fractions 331–481.—Crystallization from acetone–*n*-hexane gave 661 mg of needles, mp 205–207.5°, in a yield of 29.7%: $[\alpha]_{365}$ 117°, $[\alpha]_D$ 99.4°; λ_{max} 242 mμ (ε 15,200); ν_{max} 1157 and 852 cm^{-1} (20,21-acetonide).

Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.11; H, 8.90.

20α,21-Isopropylidenedioxy-11β,17-dihydroxypregn-4-en-3-one. Fractions 501–681.—Platelets (166 mg, 7.5%) were obtained from acetone, mp 243–244°, whose ir spectrum was identical with that of the acetonation product of Reichstein's substance epi-E.

20β,21-Isopropylidenedioxy-17-hydroxypregn-4-ene-3,11-dione (10b) from 9b.—Oxidation of 20β,21-isopropylidenedioxy-11β,17-dihydroxypregn-4-en-3-one (155 mg) with chromic anhydride in pyridine was carried out as in the preparation of **10a** from **9a**, affording 141 mg (91.5%) of platelets from acetone–*n*-hexane: mp 214–215.5°; $[\alpha]_{365}$ 598°, $[\alpha]_D$ 141°; λ_{max} 238 mμ (ε 15,450); ν_{max} 1151 and 850 cm^{-1} (20,21-acetonide).

Anal. Calcd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.70; H, 8.48.

Hydrolysis of **10b** (40 mg) with 60% acetic acid afforded 29.5 mg of needles from acetone, mp 206–207°, which did not depress the melting point of an authentic sample of Reichstein's substance U (11β,17,20β-trihydroxypregn-4-ene-3,11-dione), and their ir spectra were identical.

20α- and 20β,21-Isopropylidenedioxy-17-hydroxypregn-4-ene-3,11-diones (10a and 10b) from 11.—Cortisone (2 g) was treated with sodium borohydride in dimethylformamide for 3 hr as in the reduction of **8**, and the crude, epimeric glycerols were converted into the 20,21-acetonides in an identical manner. The mixture was chromatographed on a 50 × 900 mm silica gel column in ethyl acetate–isooctane (3:7). Fractions (10 ml) were collected at 10-min intervals.

20α,21-Isopropylidenedioxy-17-hydroxypregn-4-ene-3,11-dione. Fractions 296–356.—Crystallization from acetone gave 109 mg (4.9%) of prisms, mp 198.5–199.5°, whose ir spectrum was superimposable with that of the chromic anhydride–pyridine oxidation product of **9a**.

20β,21-Isopropylidenedioxy-17-hydroxypregn-4-ene-3,11-dione. Fractions 371–525.—From the residue was obtained 577 mg (25.8%) of feathery needles from acetone: mp 208–210°. The ir spectrum was identical with that of the chromic anhydride–pyridine oxidation product of **9b**.

Reaction of 17,20α- and -20β-Isopropylidenedioxy-21-hydroxypregn-4-ene-3,11-diones with Acetone–Sulfuric Acid.—To 100 mg each of **7a** and **7b** in acetone (36 ml) was added 4 ml of acetone containing 0.02 ml of concentrated sulfuric acid. After 4 hr at room temperature, 5% sodium bicarbonate (1.5 ml) was added to each solution, and the products were recovered. Each reaction mixture was chromatographed on a 20 × 710 mm Celite column in toluene (70), isooctane (130), methanol (160), and water (40 ml) (2.5-ml fractions every 12 min).

From 7a.—The residue from **fractions 105–155** (92.8 mg, mp 198–199°) was identical with **20α,21-isopropylidenedioxy-17-hydroxypregn-4-ene-3,11-dione** by mixture melting point and ir comparisons. From **fractions 266–340** was recovered 6.6 mg of starting material, mp 237.5–240°.

From 7b.—The residue from **fractions 95–118** weighed 21.6 mg, mp 203–205°, and its ir spectrum was identical with that of **20β,21-isopropylidenedioxy-17-hydroxypregn-4-ene-3,11-dione.** From **fractions 266–380** was recovered 74.7 mg of starting material, mp 257–259°.

Reaction of 17,20α- and -20β-Isopropylidenedioxy-21-hydroxypregn-4-ene-3,11-diones with Tetrahydrofuran–Sulfuric Acid.—To 100 mg each of **7a** and **7b** in tetrahydrofuran (40 ml) was added concentrated sulfuric acid (0.2 ml). After 72 hr at room temperature, the solutions were added to excess aqueous sodium hydroxide solution and the products were recovered by extraction with ethyl acetate.

From 7a.—The reaction mixture was chromatographed on a 20 × 740 mm silica gel column in ethyl acetate–isooctane (3:2); 3-ml fractions were collected every 20 min. After the emergence of fraction 631 the system was changed to ethyl acetate–ethanol (9:1). From **fractions 171–245** was obtained 25.1 mg, mp 197.5–199°, of **20α,21-isopropylidenedioxy-17-hydroxypregn-4-ene-3,11-dione. Fractions 375–560** furnished 18.7 mg, mp 241.5–243.5°, of starting material. An amorphous unknown compound was recovered from **fractions 702–735**. A pool, taken from fraction 751 until material ceased to come off the column, weighed 20.3 mg, mp 241–242.5°. A mixture melting point with **17,20α,21-trihydroxypregn-4-ene-3,11-dione** was 241.5–242.5° and their ir spectra were identical.

From 7b.—Direct crystallization from acetone afforded 48.5 mg of starting material, mp 258–260°. Silica gel chromatography of the mother liquor gave an additional 32.7 mg, raising the recovery of starting material to 81.2%.

Registry No.—**2a**, 21321-66-4; **2b**, 21321-67-5; **4a**, 21321-68-6; **4b**, 21321-68-6; **5a**, 21321-70-0; **5b**, 21321-71-1; **7a**, 21321-72-2; **7b**, 21321-73-3; **9a**, 18072-48-5; **10a**, 18072-50-9; **10b**, 20302-17-4; **12b**, 21339-86-6; **13a**, 21321-77-7; **13b**, 21321-78-8; **15a**, 21321-79-9; **15b**, 21321-80-2; 17,20α-isopropylidene-

dioxy-3,11-dioxopregn-4-en-21-oic acid, 21321-81-3; 20β,21-isopropylidenedioxy-11β,1-dihydroxypregn-4-en-3-one, 18072-49-6.

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A Synthesis of Methyl 2,3,6-Trideoxy-α-D-*erythro*-hexopyranoside (Methyl α-Amicetoside)[1,2]

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The title glycoside **7**, the parent sugar of which is a constituent of the antibiotic amicetin, was synthesized in a sequence of high-yielding steps from methyl 4,6-*O*-benzylidene-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside (**1**), and was characterized as the crystalline 4-(3,5-dinitrobenzoate) (**10**). Hydrogenation of the 2,3 double bond in **1**, followed by treatment of the resultant saturated glycoside (**2**) with *N*-bromosuccinimide, gave methyl 4-*O*-benzoyl-6-bromo-2,3,6-trideoxy-α-D-*erythro*-hexopyranoside (**3**). Treatment of **3** with potassium iodide in *N*,*N*-dimethylformamide gave the crystalline 6-iodo analog **5**, which, after saponification to the 4-hydroxy derivative **6** and subsequent hydrogenation, gave the glycoside **7**. The structures of all products and intermediates were supported by 100-MHz nmr spectral data.

The antibiotic amicetin, isolated from *Streptomyces plicatus* and *Streptomyces vinaceus-drappus*, was shown[5] to contain a 2,3,6-trideoxyhexose component that was named amicetose. In a synthesis[6] that established the stereochemistry of amicetose, ethyl 2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside[7] was reduced to the saturated glycoside, and the latter was converted, by way of the 6-*O*-*p*-tolylsulfonyl and 6-deoxy-6-iodo derivatives, into ethyl 2,3,6-trideoxy-α-D-*erythro*-hexopyranoside, hydrolysis of which gave 2,3,6-trideoxy-α-D-*erythro*-hexose, identical with amicetose. The synthetic sugar and the one isolated from amicetin gave the same 2,4-dinitrophenylhydrazone derivative.

Although the steps in the foregoing sequence of conversions[6] proceed in yields from 47 to 89%, preparation of the starting alkene[7] requires five steps from D-glucose and results in a net yield of only about 10% alkene, corresponding to an over-all yield of about 2% trideoxy sugar. The present communication describes an alternative synthetic route to amicetose by way of methyl 4,6-*O*-benzylidene-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside[8] (**1**), an alkene readily obtained in about 30% yield from the commercially available methyl α-D-glucopyranoside. The synthesis leads from the latter glycoside and proceeds to the methyl α-glycoside (**7**) of amicetose in about 16% over-all yield, with few isolated intermediates. The synthesis makes **7** (methyl 2,3,6-trideoxy-α-D-*erythro*-hexopyranoside) conveniently available for further synthetic transformations into other deoxy sugars,[9] and also amino sugars,[10] that are present in antibiotic substances.

Compound **1**, obtained[8] from methyl α-D-glucopyranoside by the sequence benzylidenation, *p*-toluenesulfonation, and treatment with sodium iodide–zinc dust in *N*,*N*-dimethylformamide (or with potassium ethylxanthate in butyl alcohol), was hydrogenated over palladium on charcoal to give a 95% yield of the saturated glycoside **2**, identical with the crystalline product obtained by Bolliger and Prins,[11] who effected the reduction of **1** to **2** over platinum. Hydrogenation could be terminated readily at the point of saturation of the double bond, with no detectable hydrogenolysis of the *O*-benzylidene group. Treatment of the saturated acetal **2** with *N*-bromosuccinimide in refluxing carbon tetrachloride[12,13] gave methyl 4-*O*-benzoyl-6-bromo-2,3,6-trideoxy-α-D-*erythro*-hexopyranoside (**3**) in 86% yield as an analytically pure syrup. The ir and nmr spectra of **3** confirmed that a benzoate group was present, and the fact that the conversion of **2** into the bromo benzoate had involved a substantial downfield shift of the H-4 signal confirmed that the benzoyloxy group was indeed attached at C-4; the structure **3** was also established independently as the result of further transformations. Full details of all nmr spectra, with assignments that were verified by spin decoupling, are recorded in the Experimental Section.

Attempts to hydrogenate the bromo benzoate **3** in alkaline solution, to remove the *O*-benzoyl group and cleave the bromo substituent to give the 6-deoxy sugar, led mainly to the debenzoylated 6-bromo glycoside **4** and did not appear to provide a convenient route to the desired glycoside (**7**). The syrupy bromo benzoate **3** was converted into the crystalline 6-iodo analog (**5**) in 82% yield by treatment with potassium iodide in *N*,*N*-dimethylformamide at 50°. Conversion of **2** into **5** proceeded in 72–81% yield if careful purification of the intermediate bromide **3** was not performed. The nmr

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