37.97. Found: C, 39.77; H, 3.43; N, 18.93; F, 37.78.

α-N-Benzoyl-2-trifluoromethylhistamine (3c). A solution of 4.13 g (0.01 mol) of **2c** (mp 198–199 °C)[20] in 80 mL of trifluoroacetic anhydride was stirred and refluxed for 1 h. A second portion of **2c** (4.13 g) was added and refluxing was continued for 5 h. The solvent was distilled and a solution of the residue in 100 mL of methanol was refluxed for 1 h. The solution was stored overnight at room temperature and a colorless, Pauly-negative precipitate (1.46 g) was separated. This material crystallized from ethanol (mp 261 °C dec, *m/e* 492). Evaporation of the methanol filtrate gave a tarry residue which was chromatographed on 200 mL of silica gel 60. Elution with ether gave 3.9 g (68.8%) of **3c** as pale yellow crystals. Recrystallization from benzene–tetrahydrofuran gave colorless plates: mp 179–180 °C; NMR ($CDCl_3$) δ 2.95 (2, t, J = 7 Hz, β-CH_2), 3.67 (2, t, J = 7 Hz, α-CH_2), 7.07 (1, s, H-4 or 5), 7.4–8.0 (5, m, C_6H_5).

Anal. Calcd for $C_{13}H_{12}N_3F_3O$ (283.3): C, 55.13; H, 4.27; N, 14.83; F, 20.12. Found: C, 55.23; H, 4.42; N, 14.50; F, 19.98.

2-Trifluoromethylhistamine Dihydrochloride (3d). A solution of 2.13 g (7.5 mmol) of **3c** in 200 mL of 3 N hydrochloric acid and 15 mL of ethanol was heated on steam for 24 h. The reaction mixture was evaporated to dryness under reduced pressure. The residual material was freed of benzoic acid by trituration, twice with ether and twice with 2-propanol, giving 1.56 g (82.5%) of **3d**·2HCl. Recrystallization from ethanol gave colorless needles: mp 210–212 °C; NMR (D_2O) δ 3.14, 3.26 (4, q, A_2B_2, J = 6.0 Hz, α and β CH_2's), 7.52 (1, s, H-4 or 5).

Anal. Calcd for $C_6H_8N_3F_3$·2HCl (252.1): C, 28.59; H, 4.00; N, 16.67; F, 22.61. Found: C, 28.36; H, 4.35; N, 16.42; F, 22.88.

α-N-Benzoyl-2-trifluoromethyl-L-histidine Methyl Ester (3e). A suspension of 4.71 g (0.01 mol) of **2e**[21] in 80 mL of trifluoroacetic anhydride was stirred and refluxed for 2 h (solution was complete after 0.5 h). An additional 4.71 g of **2e** was added and refluxing was continued for 5 h. The solvent was removed by distillation and a solution of the residual material in 100 mL of methanol was refluxed for 0.5 h. The solvent was evaporated and the residual material was chromatographed on 200 mL of silica gel 60. Elution of the column with ether gave benzoic acid, followed by **3e.** The Pauly-positive fractions were pooled and concentrated to give 4.8 g (70.3%) of light yellow crystals. Recrystallization from benzene gave **3e** as colorless plates: mp 157–159 °C; NMR ($CDCl_3$) δ 3.25 (2, d, J = 5.8 Hz, β-CH_2), 3.70 (3, s, OCH_3), 5.05 (1, t, J = 5.8 Hz, α-CH), 6.95 (1, s, H-4 or 5), 7.4–8.0 (5, m, C_6H_5); $[\alpha]^{20}_D$ −37.7° (*c* 0.5, CH_3OH).

Anal. Calcd for $C_{15}H_{14}F_3N_3O_3$ (341.3): C, 52.79; H, 4.14; N, 12.31; F, 16.70. Found: C, 52.53; H, 4.17; N, 12.04; F, 16.29.

2-Trifluoromethyl-L-histidine Dihydrochloride (3f). A solution of 2.05 g (6 mmol) of **3e** in 200 mL of 3 N hydrochloric acid and 20 mL of ethanol was heated on steam for 24 h. The reaction mixture was concentrated to 100 mL and was extracted with three 50-mL portions of ether to remove benzoic acid. The aqueous layer was evaporated to dryness to give **3f**·2HCl as a colorless powder, mp 237–238 °C. This material was triturated twice with ether and was dried overnight in vacuo at 50 °C. Crystallization of the salt or of the neutral amino acid could not be effected: NMR (D_2O) δ 3.32 (2, d, J = 7.0 Hz, β-CH_2), 4.32 (1, t, J = 7.0 Hz, α-CH), 7.44 (1, s, H-4 or 5); $[\alpha]^{20}_D$ −3.80° (*c* 0.6, H_2O, pH 1.9), −14.06° (*c* 5, H_2O, pH 7.2).

Anal. Calcd for $C_7H_8O_2N_3F_3$·2HCl (296.1): C, 28.40; H, 3.40; N, 14.19; F, 19.25. Found: C, 28.22; H, 3.32; N, 13.79; F, 19.08.

pK Determinations. pK values were obtained by titration in aqueous solution at 25 °C, calculations being based on 7–10 readings. For **3a:** pK_1 = 2.06 ± 0.03; pK_2 = 10.00 ± 0.05. For **3b:** pK_1 = 2.54 ± 0.02; pK_2 = 10.34 ± 0.06.

Registry No.—**2a,** 33511-28-3; **2b,** 66675-19-2; **2c,** 66675-20-5; **2e,** 66675-21-6; **3a,** 66675-22-7; **3b,** 66675-23-8; **3c,** 66675-24-9; **3d**·2HCl, 66675-25-0; **3e,** 66675-26-1; **3f**·2HCl, 66675-27-2.

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Acid-Catalyzed Rearrangements of the Dihydroxyacetone Side Chain in Steroids during Ketal Exchange

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Discussion

The synthesis of steroid derivatives often makes it necessary to protect the hydroxy groups that are present. One method of accomplishing this goal is by converting the substrate into a ketal or an ortho ester. Gardi et al.[2] reported that the reaction of hydrocortisone and prednisolone with 2,2-diethoxypropane gave not only the expected 17α,21-acetonides (**1** and **2,** respectively) but also the 17α,21-acetonide 11β-(1′-ethoxy-1′-methyl)ethyl ethers (**3** and **4,** respectively). Similarly, the reaction of hydrocortisone with triethyl orthoacetate gave 17α,21-(1′-ethoxy)ethylidenedioxy 11β-(1′,1′-diethoxy)ethyl ether (**5**) in addition to the expected 17α,21α-(1′-ethoxy)-ethylidenedioxy derivative (**6**).

The Italian workers[2,3] relied on relatively mild conditions which involved a brief distillation of benzene suspensions of the steroid in the presence of a ketal, acetal, or ortho ester and a trace of an acid catalyst. However, in our hands this procedure generally did not lead to the previously reported protected steroid by-products. Instead, ketal exchange yielded **10** and **11** which are formally the result of a Mattox[4] rearrangement although in one reaction the Mattox rearrangement product itself underwent exchange at the 11β position to yield **17.** Only if the 21 position of the dihydroxyacetone side chain was acylated was an 11β-ether obtained without rearrangement, and this required a much longer reaction time.[2] The Mattox rearrangement of a dihyroxyacetone side chain is commonly encountered whenever steroids come in contact with acidic media; however, this is its first observation during acetonide formation.[5]

The reaction of hydrocortisone with 2,2-dimethoxypropane consistently gave four products: a trace of 11β-hydroxy-3-methoxy-3,5-pregnadien-20-one 17α,21-acetonide (**9**),[6] 40–50% of hydrocortisone 17α,21-acetonide (**1**),[2] 12–15% of **10,** and 2–3% of **11. 10** and **11** had almost identical mass spectra and infrared spectra but their NMR spectra and TLC behavior were decidedly different. The mass spectra of **10** and **11** showed an M^+ at (*m/e*) 416 instead of at (*m/e*) 489 for the

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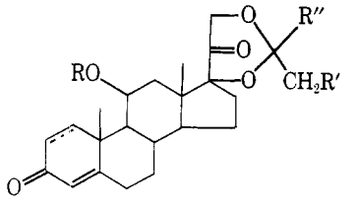
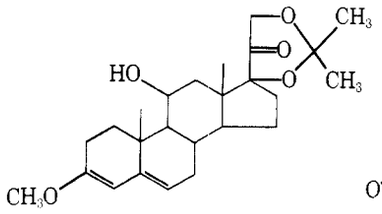
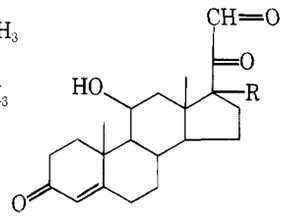
Scheme I



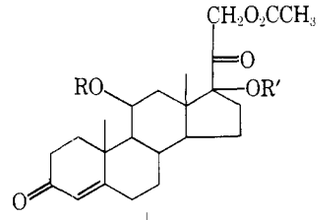
1, R, R′ = H; R″ = CH_3
2, R, R′ = H; R″ = CH_3; Δ^1
3, R = $(CH_3)_2\dot{C}OC_2H_5$; R′ = H; R″ = CH_3
4, R = $(CH_3)_2\dot{C}OC_2H_5$; R′ = H; R″ = CH_3; Δ^1
5, R = $CH_3\dot{C}(OC_2H_5)_2$; R′ = H; R″ = OC_2H_5
6, R, R′ = H; R″ = OC_2H_5
7, R, R′, R″ = H
8, R = $CH_3\dot{C}HOC_2H_5$; R′, R″ = H



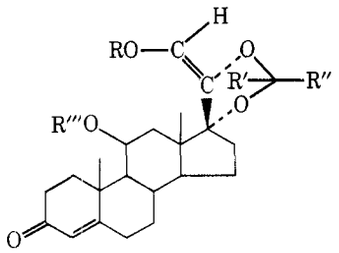
9



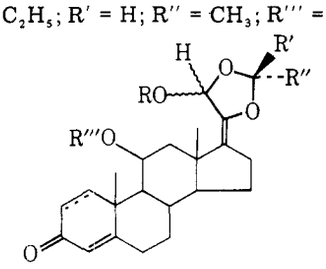
13, R = H
14, R = OH



18, R = $CH_3\dot{C}HOC_2H_5$; R′ = H
19, R, R′ = $CH_3\dot{C}HOC_2H_5$



11, R, R′, R″ = CH_3; R‴ = H
17, R = C_2H_5; R′ = H; R″ = CH_3; R‴ = $CH_3\dot{C}HOC_2H_5$



10, R, R′, R″ = CH_3; R‴ = H
12, R = C_2H_5; R′, R″ = CH_3; R‴ = H
15, R = C_2H_5; R′, R″ = CH_3; R‴ = H; Δ^1
16, R = C_2H_5; R′ = CH_3; R″ = H; R‴ = $CH_3\dot{C}HOC_2H_5$

expected bisacetonide;[2] the infrared spectra exhibited an O–H absorption. The integration of the region from δ 3.0–0.8 in the NMR spectra of **10** and **11** did not show the expected two sets of $(CH_3)_2C(O–)_2$ absorptions;[2] only one set of absorptions was observed. They also showed that the 21-CH_2OH group had been degraded. Instead of a two-proton absorption, an absorption which integrated for only one proton was found downfield in the region from δ 5.6–5.3. The NMR spectra of **10** and **11** also contained absorptions due to CH_3O.

Hydrolysis of **10** and **11** confirmed that they were not the by-products previously isolated.[2] Instead of hydrocortisone, aldehydes were isolated under conditions from which hydrocortisone was obtained from the acetonide **1**.[7] Aldehyde **13** which was obtained by hydrolysis of **10** was identified by comparison with a sample of aldehyde obtained by an independent synthesis.[8] The spectral properties of aldehyde **14** from the hydrolysis of **11**[9] corresponded in all important points to the properties of **13**.

Since reaction of **13** with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid did not afford **10**, it is not likely that **13** is formed first and then undergoes reaction with 2,2-dimethoxypropane although hydrocortisone under the same conditions but in the absence of the 2,2-dimethoxypropane does produce trace amounts of **13**. Also, since further reaction of **1** with 2,2-dimethoxypropane did not produce **9**, **10**, or **11**, acetonide **1** is apparently not involved in the formation of **10** or **11**.

Reaction of hydrocortisone with 2,2-diethoxypropane in the presence of *p*-toluenesulfonic acid gave the same qualitative results as its reaction with 2,2-dimethoxypropane,[10] the structure of **12** being assigned by spectroscopic comparison with **10** and by elemental analysis. Reaction of prednisolone with 2,2-diethoxypropane also failed to give the previously reported bisacetonide,[2] giving instead **15** which is analogous to the products isolated from the reaction of ketals with hydrocortisone.

Only in two cases was it possible to obtain 11β-ethers. Reaction between hydrocortisone and 1,1-diethoxyethane gave a complex mixture which could only partially be separated. Compound **7**, as well as the rearranged 11β-ether **16**, was isolated and fully characterized. Evidence for the presence of **8** and **17** in the remaining mixture was based on the mass spectra M^+ (*m/e*) 460 for **8** and 488 for **17**. Reaction between 1,1-diethoxyethane and hydrocortisone 21-acetate gave not only the 11β- (**18**) but also the bis[11β,17α-(1′-ethoxy)ethoxy] derivative (**19**). It required 2 h to effect complete dissolution of the steroid reactant and resulted in rather poor yields of the desired products.[11]

Reinvestigation of the reaction of hydrocortisone with trialkyl orthoacids gave only the previously reported diastereomers resulting from exchange and no by-products or rearrangement products.

In conclusion, it has been shown that the by-products obtained during ketal exchange with steroids were not bisketals but instead were the result of a Mattox rearrangement of an intermediate in the ketal exchange.

Experimental Section

All melting points were uncorrected. Microanalyses were performed by Midwest Microlab, Ltd., Indianapolis, Ind. TLC were run on Brinkman Polygram sil G/UV_{254}. SilicAR CC-7 was obtained from Mallinckrodt as well as the bulk solvents used for chromatography and reactions. NMR spectra were run on a Varian T-60 spectrometer using $(CH_3)_4Si$ as an internal standard. Infrared spectra were determined on a Beckman Acculab 4 spectrometer and UV were obtained using a Cary 14 instrument. Optical rotations were obtained using a Carl Zeiss instrument. Mass spectra were performed by Mr. Bob Drake at the University of Kansas using a Varian CH-5 mass spectrometer at 70 eV. The steroid starting materials were obtained from Sigma. All other chemicals were obtained from Aldrich unless otherwise specified.

Reaction of 2,2-Dimethoxypropane with Hydrocortisone. All exchange reactions, unless otherwise stated, were run in the following manner. A modification of the procedure of Gardi et al.[2] was used. Hydrocortisone (12.0 g, 0.033 mol) was suspended in 1500 mL of boiling benzene and 100 mL of benzene was distilled. Then 16 mL of dimethoxypropane was added to the benzene suspension and 6 mL

of a hot solution of 0.4% *p*-toluenesulfonic acid in benzene was added immediately afterwards. Benzene was distilled at a rapid rate from the suspension and after 15 min a clear solution was obtained; the distillation was continued for 10 min more. Pyridine (0.5 mL) was added to quench the reaction which then was cooled to room temperature. The benzene was evaporated in vacuo and the resulting residue was chromatographed on SilicAR CC-7 (600 g) using ether–heptane 1:9 to 2:8 to ether–acetone–heptane 2:1:7 as the eluents in the above order to give four fractions.

The first fraction (<50 mg) was obtained as a white solid; an analytically pure sample was not obtained. The NMR spectrum of the crude material suggested its identity as 11β-hydroxy-3-methoxy-3,5-pregnadien-20-one 17α,21-acetonide (**9**): TLC (silica gel, ether) R_f 0.57; NMR ($CDCl_3$) δ 5.10 (broad s, 2, C**H**=C), 4.65–4.35 (s, 1, C**H**O), 4.17 (AB quartet, J = 18 Hz, $\Delta_{\nu AB}$ = 12.5 Hz, 2, O=CC**H**$_2$O), 3.60 (s, 3, C**H**$_3$O), 1.47 and 1.43 (two s, 6, –O(C**H**$_3$)$_2$CO–), 1.21 (s, 3, C**H**$_3$C), 0.91 (s, 3, C**H**$_3$C), and 3.0–0.8 (m, 17, C**H**$_2$ and C**H**, and 1, O**H**).

The second fraction deposited 0.26 g (mp 173–177 °C) of 11β-hydroxy-3-methoxy-4,17(20)-pregnadien-3-one 20,21-acetonide (**10**) as fine white needles when the ether was allowed to evaporate at room temperature: TLC (silica gel, ether) R_f 0.44; IR (KBr) 3440 (s, OH), 1710 and 1605 (w), and 1645 cm^{-1} (s, C=O); NMR ($CDCl_3$) δ 5.66 (s, 1, O=CC**H**=C), 5.33 (s, 1, OC**H**O), 4.5–4.3 (m, 1, C**H**OH), 3.4 (s, 3, OC**H**$_3$), 1.53, 1.50, and 1.47 (three s, 9, C**H**$_3$C and O(C**H**$_3$)$_2$CO), and 1.17 (s, 3, C**H**$_3$C); $[\alpha]^{26}_D$ +150° (*c* 0.59, CH_3OH); mass spectrum (*m/e*) 416 (M^+); UV (CH_3OH) λ_{max} 242 nm (ϵ 15 900).

Anal. Calcd for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 71.93; H, 8.79.

The mother liquor from the second fraction was concentrated and the resulting residue was crystallized from ether–hexane to give 1.88 g (mp 164–168 °C) of **10** as white crystals. This second crop of crystals had the same infrared, UV, and mass spectrum as the first as well as the same TLC and elemental analysis, but the optical rotation ($[\alpha]^{26}_D$ + 123° (*c* 0.55, CH_3OH)) and NMR spectra were different with the methoxy signal at δ 3.4 and the methyl signal at δ 1.17 being split.[12]

The third fraction gave 323 mg (mp 144–146 °C) of 11β-hydroxy-21-methoxy-4,20-pregnadien-3-one 17α,20-acetonide (**11**) as a fibrous white solid from heptane: TLC (silica gel, ether) R_f 0.36; IR (KBr) 3400 (s, OH), 1710 and 1605 (w), and 1645 cm^{-1} (s, C=O); NMR ($CDCl_3$) δ 5.63 (s, 1, O=CC**H**=C), 5.5–5.35 (m, 1, C=C**H**O), 4.5–4.3 (m, 1, C**H**OH), 3.37 (s, 3, OC**H**$_3$), 1.50, 1.43, and 1.40 (three s, 9, C**H**$_3$C and O(C**H**$_3$)$_2$CO), and 1.13 (s, 3, C**H**$_3$C); UV (CH_3OH) λ_{max} 242 nm (ϵ 16 600); $[\alpha]^{26}_D$ +163° (*c* 0.45, CH_3OH); mass spectrum (*m/e*) 416 (M^+).

Anal. Calcd for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 72.19, H, 8.87.

The fourth fraction deposited 3.71 g (mp 184–185 °C (lit.[2] mp 194–195 °C) of 11β-hydroxy-4-pregnene-3,20-dione 17α,21-acetonide (**1**) as fine white needles: TLC (silica gel, ether) R_f 0.28; IR (KBr) 3460 (s, OH), 1700 and 1600 (m), and 1645 cm^{-1} (s, C=O); NMR ($CDCl_3$) δ 5.67 (s, 1, O=CC**H**=C), 4.5–4.3 (m, 1, C**H**OH), 4.3–4.15 (m, 2, OC**H**$_2$C=O), 1.47 (s, 9, O(C**H**$_3$)$_2$CO and C**H**$_3$C), and 0.93 (s, 3, C**H**$_3$C): UV (CH_3OH) λ_{max} 242 nm (ϵ 16 300); $[\alpha]^{27}_D$ +147° (*c* 0.62, CH_3OH), (lit.[2] $[\alpha]_D$ +142° (dioxane)); mass spectrum (*m/e*) 402 (M^+).

Anal. Calcd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.46; H, 8.41.

The mother liquor from the fourth fraction was concentrated to give 0.79 g (mp 181–182 °C), 0.75 g (mp 177–179 °C) and 0.57 g (mp 176–178 °C) of the 17α,21-acetonide as successive crops of crystals which were identical in all other ways with the first crop of crystals.

The following reactions were run in a similar manner:

Reaction of 2,2-Diethoxypropane with Hydrocortisone. This reaction gave 242 mg (mp 156–159 °C, 7% yield from ether–hexane, 20:20) of 11β-hydroxy-21-ethoxy-4,17(20)pregnadien-3-one 20,21-acetonide (**12**) as the first fraction: IR (KBr) 3470 (s, OH), 1710 and 1605 (w), and 1650 cm^{-1} (s, C=O); NMR ($CDCl_3$) δ 5.70 (s, 1, CH=C), 5.40 (s, 1, OC**H**O), 4.5–4.3 (m, 1, C**H**OH), 3.95–3.4 (m, 2, C**H**$_2$O), 2.7–0.7 (m, 33, C**H**$_3$, C**H**$_2$, and C**H**); $[\alpha]^{29}_D$ + 101 ° (*c* 1, CH_3OH); mass spectrum (*m/e*) 430 (M^+); TLC (silica gel, ether) R_f 0.48.

Anal. Calcd for $C_{26}H_{38}O_5$: C, 72.51; H, 8.89. Found: C, 72.25; H, 9.03.

The second fraction (1.04 g, mp 171–173 °C 30% yield) gave **1** which was identical with **1** obtained above.

Reaction of 1,1-Diethoxyethane with Hydrocortisone. This reaction gave 1.54 g (mp 45–55 °C) of 11β-(1′-ethoxy)ethoxy-21-ethoxy-20,21-ethylidenedioxy-4,17(20)-pregnadien-3-one (**16**) as the first fraction: 12% yield; TLC (silica gel, ether) R_f 0.64; IR (KBr) 1660 cm^{-1} (s, C=O); NMR ($CDCl_3$) δ 5.70 (s, 1, O=CC**H**=C), 5.65–5.35 (m, 2, CH_3C**H**(O–)$_2$ and C=CC**H**(O–)$_2$), 4.87 (q, 1, J = 5 Hz, CH_3C**H**(O–)$_2$), 4.45–4.10 (m, 1, C**H**O), 3.9–3.3 (m, 4, C**H**$_2$O); $[\alpha]^{25}_D$ +106° (*c* 0.49, dioxane); mass spectrum (*m/e*) 488 (M^+).

Anal. Calcd for $C_{29}H_{44}O_6$: C, 71.28; H, 9.08. Found: C, 71.01; H, 9.34.

A number of other fractions were obtained at this point which were mixtures. Structures for the components of the mixtures suggested by mass spectra and NMR spectra are presented in the discussion.

The final fraction (1.30 g, mp 191–195 °C, from ether–cyclohexane) was identified as 11β-hydroxy-17α,21-ethylidenedioxy-4-pregnene-3,20-dione (**7**): 13% yield; TLC (silica gel, ether) R_f 0.33; IR (KBr) 3440 (s, OH) and 1695 and 1655 cm^{-1} (s, C=O); NMR ($CDCl_3$) δ 5.70 (s, 1, O=CC**H**=C), 5.0 (q, 1, J = 5 Hz, CH_3C**H**(O–)$_2$), 4.65–4.35 (m, 1, C**H**O), 4.32 (s, 2, O=CC**H**$_2$O), 1.47 (s, 3, C**H**$_3$C), 1.00 (s, 3, C**H**$_3$C), 1.41 (d, J = 5 Hz, 3, CH_3CH(O–)$_2$), and 2.8–0.8 (m, 17, C**H**$_2$, C**H**, 1, O**H**); $[\alpha]^{27}_D$ +148° (*c* 0.5, dioxane); mass spectrum (*m/e*) 388 (M^+).

Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.49; H, 8.47.

Reaction of 1,1-Diethoxyethane with Hydrocortisone 21-Acetate. This reaction gave 0.86 g (an oil) of 11β,17α-bis[(1′-ethoxy)ethoxy]-21-acetyloxy-4-pregnene-3,20-dione (**19**) as the first fraction: 7% yield; TLC (silica gel, ether) R_f 0.43; IR (KBr) 1740, 1720, and 1660 cm^{-1} (s, C=O); NMR ($CDCl_3$) δ 5.70 (s, 1, O=CC**H**=C), 5.07 (AB quartet, J = 16 Hz, $\Delta_{\nu AB}$ = 12 Hz, 2, O=CC**H**$_2$O), 4.95–4.5 (m, 2, CH_3C**H**(O–)$_2$), 4.5–4.2 (m, 1, C**H**O), 3.6–3.05 (m, 4, CH_3C**H**$_2$O–), 2.17 (s, 3, C**H**$_3$C=O), 1.45 (s, 3, C**H**$_3$C), 0.81 (s, 3, C**H**$_3$C), and 2.7–0.7 (m, 29, C**H**, C**H**$_2$, and C**H**$_3$); $[\alpha]^{25}_D$ +127° (*c* 0.5, dioxane); mass spectrum (*m/e*) 548 (M^+).

The second fraction (3.83 g, mp 127–129 °C from petroleum ether bp 30–37 °C) was identified as 11β-(1′-ethoxy)ethoxy-17α-hydroxy-21-acetyloxy-4-pregnene-3,20-dione (**18**): 32% yield; TLC (silica gel, ether) R_f 0.25; IR (KBr) 3500 (s, OH) and 1730, 1715, and 1645 cm^{-1} (s, C=O); NMR ($CDCl_3$) δ 5.7 (s, 1, O=CC**H**=C), 4.97 (s, 2, O=C-C**H**$_2$O), 4.70 (q, J = 5 Hz, 1, CH_3C**H**(O–)$_2$), 4.5–4.35 (m, 1, C**H**O), 3.55 (q, J = 7 Hz, CH_3C**H**$_2$O), 2.18 (s, 3, C**H**$_3$C=O), 1.45 (s, 3, C**H**$_3$C), 0.87 (s, 3, C**H**$_3$C), and 2.8–0.8 (m, 23, C**H**, C**H**$_2$, C**H**$_3$, 1, O**H**); $[\alpha]^{24.5}_D$ +188° (*c* 0.53, dioxane); mass spectrum (*m/e*) 476 (M^+).

Anal. Calcd for $C_{27}H_{40}O_7$: C, 68.04; H, 8.46. Found: C, 68.03; H, 8.41.

Reaction of 2,2-Diethoxypropane with Prednisolone. This reaction gave 0.38 g (mp 167–170 °C) of 11β-hydroxy-21-ethoxy-1,4,17(20)-pregnatrien-3-one 20,21-acetonide (**15**) as white crystals from the first fraction. The filtrate was further concentrated to give 0.21 g (mp 147–151 °C, total yield of 17%) more of **15**. The samples were identical by TLC (silica gel, ether): IR (KBr) 3380–3360 (m, OH), 1710 (w), 1600 and 1580 (m), and 1640 cm^{-1} (s, C=O); NMR ($CDCl_3$) δ 6.7 (AX quartet, 2, J_{AX} = 10 Hz, $\Delta_{\nu AX}$ = 63 Hz, O=CC**H**=-C**H**=C**H**), 5.97 (sharp m, 1, O=CC**H**=C), 5.33 (sharp m, 1, =CC**H**(O–)$_2$), 4.5–4.3 (m, 1, C**H**OH), 3.85–3.35 (m, 2, CH_3C**H**$_2$O), 3.0–0.7 (m, 29, C**H**$_3$, C**H**$_2$, CH, O**H**); $[\alpha]^{25}_D$ + 93.5° (*c* 0.5, C_2H_5OH); mass spectrum (*m/e*) 428 (M^+).

Anal. Calcd for $C_{26}H_{36}O_5$: C, 72.86; H, 8.42. Found: C, 72.41; H, 8.10.

The second fraction (R_f 0.38) was concentrated in vacuo to give 1.47 g (mp 202–210 °C, 44% yield) of prednisolone 17α,21-acetonide (**2**) as a white solid: IR (KBr) 3360 (m, OH), 1705 (m, C=O), 1645 (s, C=O), and 1600 cm^{-1} (m, C=C); NMR ($CDCl_3$) δ 6.7 (AX quartet, 2, J_{AX} = 10 Hz, $\Delta_{\nu AX}$ = 63 Hz, O=CC**H**=CH); 5.97 (sharp m, 1, O=CC**H**=C), 4.6–4.35 (m, 1, C**H**OH), 4.2–4.05 (m, 2, O=CC**H**$_2$OC), 3.0–0.7 (m, 25, C**H**$_3$, C**H**$_2$, C**H**, 1, O**H**); $[\alpha]^{25}_D$ +110° (*c* 1, dioxane) (lit.[2] $[\alpha]_D$ +104° (dioxane)); mass spectrum (*m/e*) 400 (M^+).

Anal. Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 71.85; H, 7.83.

The Hydrolysis of 11β-Hydroxy-21-methoxy-4,17(20)-pregnadien-3-one 20,21-Acetonide (10). The procedure of Robinson et al.[7] was used. The 20,21-acetonide (**10**) (200 mg) was suspended in 1.5 mL of glacial acetic acid and 0.5 mL of water and heated at 95 °C for 1 min. The solution that resulted was evaporated to dryness and the residue was extracted with 100 mL of ether. The ether solution exhibited only one spot upon analysis by TLC (silica gel, ether). It was dried over Na_2SO_4 and concentrated to 20 mL then diluted with 80 mL of heptane to give 143 mg (mp 178–190 °C) of 11β-hydroxy-3,20-dioxo-4-pregnen-21-al (**13**) as a tan solid whose spectral properties (NMR, IR, UV) and TLC were identical with those of the aldehyde prepared by a known route.[8]

The Hydrolysis of 11β-Hydroxy-21-methoxy-4,20(21)-pregnadien-3-one 17α,20-Acetonide (11). The same procedure as above was used except that the residue obtained upon concentration of the reaction mixture was crystallized from CH_2Cl_2–heptane (2:20 mL) to give 55 mg (from 95 mg of **11**, mp 110.5–115 °C foaming) of

11β,17α-dihydroxy-3,20-dioxo-4-pregnen-21-al (**14**) with 0.5 M CH_2Cl_2 as a solvate: TLC (silica gel, ether) R_f 0.23; IR (KBr) 3500 (w), 3400 (m, OH) and 1655 and 1635 cm^{-1} (s, C=O); NMR ($CDCl_3$) δ 9.77 (s, 1, CH=O), 6.1–5.7 (m, 1, OH), 5.73 (s, 1, O=CCH=C), 5.31 (s, 1, CH_2Cl_2), 4.6–4.35 (m, 1, CHO), 1.5 (s, 3, CH_3C), 1.37 (s, 3, CH_3C), and 2.8–0.85 (m, 17, CH, CH_2, and 1, OH); UV (CH_3OH) λ_{max} 242 nm (ε 17 000) and 278.5 nm (ε 13 300); $[\alpha]^{25}_D$ +117.7° (c 0.95, dioxane); mass spectrum (*m/e*) 359 ($M^+ - 1$).

Anal. Calcd for $C_{21}H_{28}O_5 \cdot 0.5CH_2Cl_2$: C, 64.08; H, 7.25. Found: C, 64.30; H, 7.15.

The NMR and mass spectra of the crude product were identical with those of the pure aldehyde as its solvate except for the presence of the singlet at δ 5.31 in the NMR spectrum due to CH_2Cl_2.

Registry No.—**1**, 34332-34-8; **2**, 13542-30-8; **7**, 66777-47-7; **8**, 66777-48-8; **9**, 55388-47-1; **10** isomer 1, 66777-49-9; **10** isomer 2, 66777-50-2; **11**, 66777-51-3; **12**, 66777-52-4; **13**, 20287-97-2; **14**, 14760-49-7; **15**, 66777-53-5; **16**, 66777-54-6; **17**, 66777-55-7; **18**, 66777-56-8; **19**, 66777-57-9; hydrocortisone, 50-23-7; 2,2-dimethoxypropane, 77-76-9; 2,2-diethoxypropane, 126-84-1; 1,1-diethoxyethane, 105-57-7; hydrocortisone 21-acetate, 50-03-3; prednisolone, 50-24-8.

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Acid-Catalyzed Addition of Secondary Phosphines to Vinyl Ethers

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Although certain olefins with electron-withdrawing substituents (e.g., acrylonitrile[1] or alkyl acrylates[2]) add P–H bonds without catalysts, phosphine addition to double bonds normally requires radical initiation,[3,4] or an acidic or basic catalyst.[4] Because of the relatively high basicity of substituted phosphines, the acid-catalyzed reactions require nearly stoichiometric amounts of acid and do not proceed to tertiary phosphines.[5] We have found, however, that vinyl ethers add secondary phosphines in the presence of catalytic amounts of acid to yield the tertiary phosphine (Markownikoff product) in good yields.

Results and Discussion

Heating a mixture of di-*tert*-butylphosphine and methyl vinyl ether without added catalyst to above 130 °C yields after several hours di-*tert*-butyl(1-methoxyethyl)phosphine, a product unexpected from base- or radical-catalyzed reactions.[4] In fact, adding catalytic amounts (<5 mol %) of acid to the mixtures greatly reduces the reaction time. Similarly, diethylphosphine reacts with methyl vinyl ether and acid to yield diethyl(1-methoxyethyl)phosphine (eq 1).

$$(C_2H_5)_2PH + CH_2CHOCH_3 \xrightarrow{H^+} (C_2H_5)_2PCH(CH_3)OCH_3 \quad (1)$$

$$(C_2H_5)_2PH + CH_2CHOCH_3 \xrightarrow{AIBN} (C_2H_5)_2PCH_2CH_2OCH_3 \quad (2)$$

Using the same reagents (diethylphosphine and methyl vinyl ether) and a radical initiator, the reaction is regioselective for the *opposite* addition product, diethyl(2-methoxyethyl)phosphine (eq 2). However, attempts to perform this reaction with di-*tert*-butylphosphine gave no addition, except for slow formation of the Markownikoff product. (The expected product, di-*tert*-butyl(2-methoxyethyl)phosphine, was prepared by another method for characterization. It is a stable compound under workup and distillation conditions, with a VPC retention time different from that of the 1-methoxyethyl isomer, and would have been detected by VPC and NMR had it been present.) Although reasons for the failure of $[(CH_3)_3C]_2PH$ to add to the olefin by a radical process are not clear, steric hindrance may contribute to the unreactivity of the $[(CH_3)_3C]_2P\cdot$ radical ($[(CH_3)_3C]_2CH\cdot$ is a persistent radical[6]).

The ability of vinyl ethers to react by an acid-catalyzed process in the presence of strongly basic secondary and tertiary alkyl phosphines[7] contrasts with the behavior reported for other olefins;[5] this reaction appears to be more closely related to the acid-catalyzed addition of phosphines to aldehydes,[8,9] which proceeds through the tertiary phosphine to a quaternary phosphonium salt, $[(RCHOH)_4P]X$. The character of the oxygen-stabilized carbonium ion intermediate in our proposed mechanism (eq 3) reflects this similarity.

$$BH^+ + CH_2{=}CHOR \rightleftharpoons B + CH_3CH^+OR \xrightarrow{R'_2PH} R'_2PC(CH_3)HOR + BH^+ \quad (3)$$

$$B = R'_2PH, R'_2PC(CH_3)HOR$$

Experimental Section

Di-*tert*-butylphosphine[10,11] and diethylphosphine[12] were prepared by literature methods. These compounds and the products are air sensitive and were handled under an atmosphere of prepurified N_2. ^1H NMR spectra were recorded on a Varian EM-360A instrument. Vapor-phase chromatographic analyses were performed on a Hewlett-Packard 5840 instrument using 20 in. × ⅛ in. UCW-982 on Chromosorb W columns. Carbon–hydrogen analyses were performed in the Union Carbide Analytical Section by Mr. J. T. Hildebrand; satisfactory analyses were obtained on methiodide and $PtCl_2$ derivatives of all of the products. Methiodide derivatives were prepared by adding an acetone solution of methyl iodide to an acetone solution of the phosphine; the product crystallizes after several hours. Platinum(II) derivatives of the formula $PtCl_2(phosphine)_2$ were prepared by stirring the phosphine with Na_2PtCl_4 or $PtCl_2(NCC_6H_5)_2$ in methanol and crystallizing the product from CH_2Cl_2–methanol.

Reactions of Di-*tert*-butylphosphine with Methyl Vinyl Ether, with and without Acid. Two NMR tubes, one containing about 0.02 g of CF_3CO_2H (0.18 mmol), were charged with 0.3 g of di-*tert*-butylphosphine (2.1 mmol) and about 0.4 mL of methyl vinyl ether (9 mmoles) was condensed into each. The contents were frozen and the tubes were flame-sealed under vacuum. NMR spectra were recorded both before and after heating at 130 °C for 30 min. The tube without added acid showed no discernible reaction; the tube with acid exhibited about 70% conversion to di-*tert*-butyl(1-methoxyeth-

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