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The Synthesis of C-21 Substituted Corticosteroids*

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By the reaction of prednisolone and dexamethasone with 2,2-dimethoxypropane, the synthesis of the 17α,21-acetonides of these corticosteroids was examined. The utility of the 17α,21-acetonide function as a protecting group for the labile cortical dihydroxyacetone function is demonstrated. It is particularly valuable for the direct introduction into intact corticoids of C-21 substituents. The synthesis of 21α-methyl and 21-trifluoroacetyl analogs of prednisolone and dexamethasone are described. Condensation of the 17α,21-acetonides with formaldehyde yields the 21-methylene derivatives **13** and **14**, which serve as intermediates for the synthesis of the 21β-nitroethyl derivative **17** and the γ-lactone **19**.

Corticosteroid dihydroxyacetone side chains react with 2,2-dimethoxypropane in an acid catalyzed exchange reaction to form 17α,21-acetonides.[2] Acetals and ketals as well as *ortho* esters can be employed in this reaction to form the corresponding cyclic condensation products.[3] The 17α,21-acetonide function is a useful protecting group for the labile dihydroxyacetone side chain for many synthetic operations on corticosteroids. The stability of this blocking group towards chlorination, mesylation and base-catalyzed elimination have been established.[4] The ability to directly introduce substituents at C_{21} *via* the base-catalyzed reactions of the $\Delta^{20,21}$ enolate ion of these 17α,21-acetonides is a useful synthetic feature of particular interest with this blocking group. Comparable reactivity at C_{21} is absent in the other commonly employed blocking groups for the dihydroxyacetone side chain such as the 17α: 20: 20: 21 bismethylenedioxy function[5] and the C_{20}-ethylene ketal,[6] since these protecting groups directly mask the C_{20}-ketone function.

We report on the use of the 17α,21-acetonide blocking group for the synthesis of C-21 modified corticosteroids. Reaction of prednisolone **1** with 2,2-dimethoxypropane in dimethylformamide as solvent in a *p*-toluenesulfonic acid catalyzed reaction gives the 17α,21-isopropylidenedioxy derivative **2** in good yield. Treatment of this acetonide derivative with potassium *t*-butoxide and methyl iodide in *t*-butanol yielded the C-21 monomethylated derivative **3**.

Hydrolytic reversal of acetonide **3** with regeneration of the intact cortical side chain proceeded readily with 60% acetic acid to yield 21-methylprednisolone **4**, which was characterized as the 21-acetate **5**. This direct alkylation method for the introduction of a C-21 methyl group on the intact corticosteroid side chain offers distinct synthetic advantage over the multistep synthetic routes previously described.[5]

The physical properties of **5** as noted in the experimental section are in excellent agreement with 21-methylprednisolone-21-acetate assigned as the 21α-hydroxy configuration by the

* Dedicated to the memory of Prof. Eiji Ochiai.

1) Location: *333 Ravenswood Avenue, Menlo Park, California 94025, USA.*

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

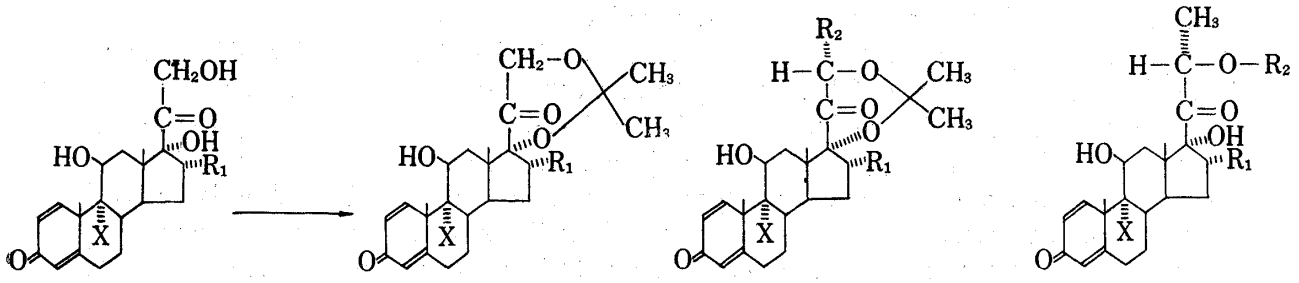
3) *a*) R. Gardi, R. Vitali, and A. Ercoli, *J. Org. Chem.*, **27**, 668 (1962); *b*) R. Gardi, R. Vitali, and A. Ercoli, *Tetrahedron Letters*, **1961**, 448; *c*) R. Gardi, R. Vitali, and A. Ercoli, *Gazz. Chim. Ital.*, **93**, 413 (1963).

4) *a*) C.H. Robinson, L.E. Finkenor, R. Tiberi, and E.P. Oliveto, *J. Org. Chem.*, **26**, 2863 (1961); *b*) A.L. Nussbaum, E. Yuan, D. Dincer, and E.P. Oliveto, *ibid*, **26**, 3925 (1961).

5) R. Beyler, F. Hoffman, R.M. Moriarty, and L.H. Sarett, *J. Org. Chem.*, **26**, 2421 (1961).

6) W.S. Allen, S. Bernstein, and R. Littell, *J. Am. Chem. Soc.*, **76**, 6116 (1954).

Fischer convention.[7] This C-21α-configuration assignment was securely established by oxidative cleavage of the C-17—C-20 bond of a C-21 methylated cortical side chain derivative with subsequent conversion of the non-steroidal fragment to L(+)-lactic acid methyl ester acetate.[7] Since the C-21 methylated compound **5** is configurationally related it is also assigned the C-21α-hydroxy stereochemistry.



1 : X=H, R_1=H
6 : X=F, R_1=CH_3

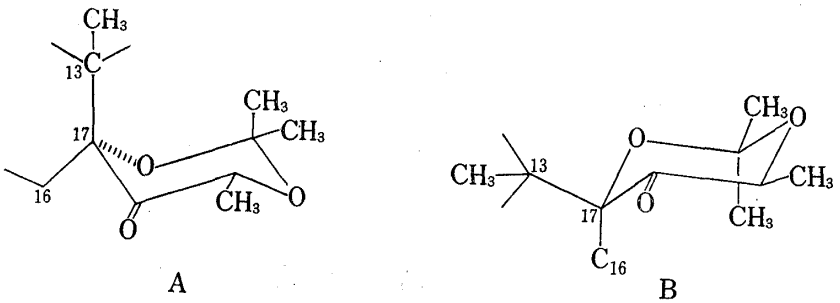
2 : X=H, R_1=H
7 : X=F, R_1=CH_3

3 : X=H, R_1=H, R_2=CH_3
8 : X=F, R_1=CH_3, R_2=CH_3
17 : X=H, R_1=H, R_2=$-CH_2-CH_2-NO_2$
18 : X=H, R_1=H, R_2=$-CH_2CH(CO_2C_2H_5)_2$

4 : X=H, R_1=H, R_2=H
5 : X=H, R_1=H, R_2=$-C(=O)-CH_3$
9 : X=F, R_1=CH_3, R_2=H
10 : X=F, R_1=CH_3, R_2=$-C(=O)-CH_3$

Chart 1

Several interesting features about the C-21 methylation process of the 17α,21-acetonide can be noted. The virtual absence of C-21-dimethylated product is attributed to steric effects. Since stereoelectronic considerations in the methylation of the $\Delta^{20,21}$ enolate ion favors approach of methyl iodide in a direction perpendicular to the plane of the enolate ion[8] both possible conformers of the C-21 mono-methylated derivative A or B present serious 1,3-nonbonded interactions to the approaching electrophilic methyl iodide and effectively prevent dimethylation even in the presence of excess potassium *t*-butoxide and methyl iodide. The absence of concomittant ring A methylated products indicates that the ring A $\Delta^{1,4}$ dienone system remains unenolized with potassium *t*-butoxide in *t*-butanol. Conversion of the $\Delta^{1,4}$ dien-3-one to the $\Delta^{1,(3),(5)}$ trienolate ion however has been effected with potassium *t*-butoxide in dimethylsulfoxide[9] or with sodium bistrimethylsilylamide.



A B

Chart 2

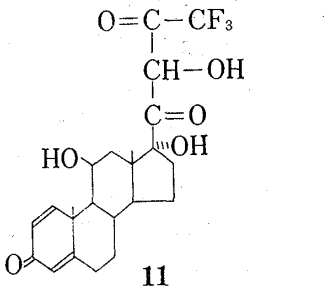
7) *a*) E.J. Agnello, R. Pinson, Jr., S.K. Figdor, G.M.K. Hughes, H.W. Ordway, B.M. Bloom, and G.D. Laubach, *Exper.*, **16**, 357 (1960); *b*) E.J. Agnello, S.K. Figdor, G.M.K. Hughes, H.W. Ordway, R. Pinson, B.M. Bloom, and G.D. Laubach, *J. Org. Chem.*, **28**, 1531 (1963).
8) H. House in "Modern Synthetic Reactions," W.A. Benjamin, Menlo Park, CA, 1972, p. 587.
9) E.L. Shapiro, T. Legatt, L. Weber, E.P. Oliveto, M. Tanabe, and D.F. Crowe, *Steroids*, **3**, 183 (1964).

Since 21-methylprednisolone is reported to retain systemic antiinflammatory activity with a significant reduction in the sodium retaining properties[7,11] the synthesis of 21-methyl-9α-fluoroprednisolone derivatives from an intact corticosteroid was studied. Elimination of the powerful sodium retaining properties in the potent antiinflammatory 9α-fluoroprednisolone derivatives is a particularly desirable and useful objective. The generality of the C-21 methylation process was therefore examined and extended with 9α-fluoro-16α-methylprednisolone-17α,21-acetonide **7** (dexamethasone 17α,21-acetonide).

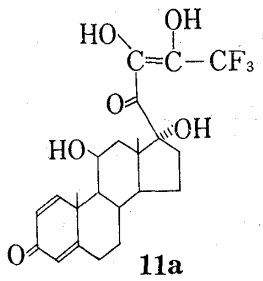
The base catalyzed methylation of this 17α,21-acetonide **7**, followed by 50% formic acid catalyzed acetonide reversal of **8** led directly to 21-methyldexamethasone **9**. Unlike an earlier report,[12] concomittant base catalyzed reversion of the 9α-fluoro-11β-ol grouping to the 9β,11β-oxide was not observed in this methylation process using potassium *t*-butoxide.

The significant retention and accompanying modification of biological activity by C-21 methylation of the cortical side chain encouraged us to examine further extensions of base catalyzed reactions for the introduction of other C-21 substituents on cortical 17α,21-acetonides. Base catalyzed condensation of **2** with ethyl trifluoroacetate followed by aqueous acetic acid deacetonation yielded the fluorinated derivative **11**. The absence of saturated carbonyl absorptions for the C-20 ketone and the trifluoroacetyl function in the infrared (IR) spectrum of **11** indicates that it exists in an enolized form **11a**. The ultraviolet (UV) spectral data, λ_{max}^{EtOH} 245 and 310 nm, are in agreement with this formulation. Sodium ethoxide catalyzed condensation of the acetonide **2** with benzaldehyde gave the 21-benzylidene derivative **12**.

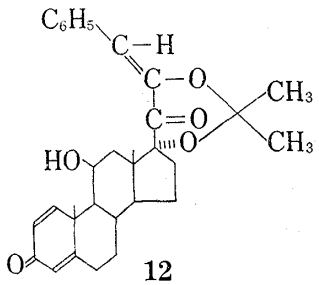
Reaction of the acetonides **2** and **7** with aqueous formaldehyde in ethanol solution in the presence of sodium bicarbonate afforded the 21-methylene-17α,21-acetonides **13** and **14**. Aqueous acetic acid hydrolysis of these acetonides gave the respective C-20—C-21 diones **15** and **16** in the prednisolone and dexamethasone series respectively. The dione **15** in the prednisolone



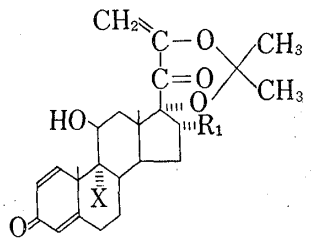
11



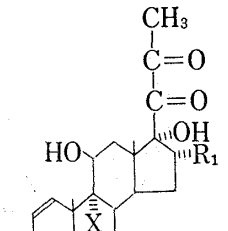
11a



12



13 : X=H, R_1=H
14 : X=F, R_1=CH_3



15 : X=H, R_1=H
16 : X=F, R_1=CH_3

Chart 3

10) M. Tanabe and D.F. Crowe, Chem. Comm. 1498 (1969).
11) *a*) J.G. Llaurado and J.A. Schneider, *Fed. Proc.*, **19**, 159 (1960); *b*) J.G. Llaurado, *Endocrinol.*, **58**, 390 (1956).
12) W.A. Allen, C.C. Pidacks, R.D. Schaub, and M.J. Weiss, *J. Org. Chem.*, **26**, 5046 (1961).

series is reported to possess significant antiinflammatory activity which is on the order of prednisolone itself.[13]

Two alternative procedures for the preparation of these C-20—C-21 diones have been reported. The direct C-21 condensation of prednisolone acetate with aqueous formaldehyde[14] followed by alumina catalyzed elimination of acetic acid and C-21 to C-17 transacetylation yields the 17-acetate of the dione **15**. In the other reported procedure[7b] dehydrochlorination of 21-chloromethylprednisolone gives the dione **15**. These C-20—C-21 diones are reported to be useful intermediates for the preparation of C-21 methylated corticoids,[7] since regioselective C-21 microbiological reduction stereospecifically yields the C-21α-ols, whereas regioselective C-21 sodium borohydride reduction affords the epimeric 21β-ols.

In our studies the 21-methylene-17α,21-acetonide **13** proved to be a valuable intermediate for the introduction of other more complex C-21 substituents by serving as a reasonably reactive acceptor in Michael-type additions. Thus reaction of **13** with nitromethane in methanol with sodium methoxide as base readily yielded the 21(β-nitroethyl)-acetonide **17**. In a similar fashion addition of diethylmalonate to the 21-methylene derivative **13** also proceeded readily to yield an oily diester Michael adduct **18**. Without attempting further characterization of intermediates, the diester was hydrolyzed with alcoholic potassium hydroxide to a diacid. At this stage hydrolytic removal of the acetonide function with 50% acetic acid liberated the free corticosteroid as an oil. The oily diacid was then thermally decarboxylated at 160° to give the desired C-21 substituted γ-lactone **19** in the prednisolone series as a crystalline solid, which had a characteristic band in the infrared for a γ-lactone at 5.65 μ.

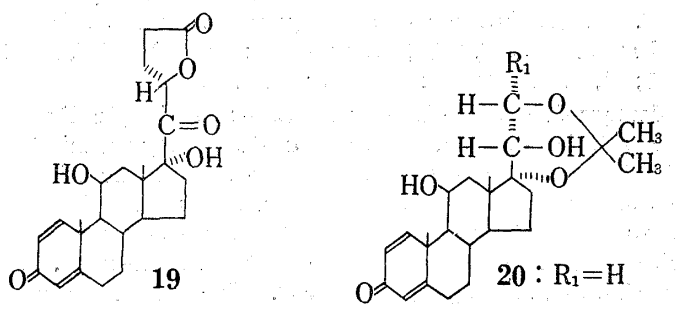


Chart 4

No attempt was made to establish rigorously the C-21 stereochemistry of the γ-lactone **19**. However, since it is also synthesized from a 17α,21-acetonide with eventual base-catalyzed equilibration at C-21 analogous to the preparation of 21-methylprednisolone, the γ-lactone **19** is also assigned the C-21α-hydroxy configuration.

In agreement with Gardi,[15] we have also noted that selective reduction of the C-20 ketone function in prednisolone-17α,21-acetonide **2** can be achieved with sodium borohydride in aqueous dimethylformamide according to the method of Taub[16] to yield exclusively the C-20α-ol **20**.

Experimental[17]

11β,17α,21-Trihydroxypregna-1,4-diene-3,20-dione-17α,21-acetonide (Prednisolone-17α,21-Acetonide) (2)——A solution of 2.0 g of prednisolone in 4 ml of dimethylformamide and 15 ml of 2,2-dimethoxypropane and a crystal of *p*-toluenesulfonic acid was refluxed for 6 hr. The solvents were then removed at reduced pressure and the residue dissolved in benzene and absorbed on 40 g of acid-washed alumina (Merck). Elution with benzene and chloroform–benzene 1 : 2 yielded 970 mg of crystalline material, mp 215—285°. The analy-

13) S. Noguchi, H. Otsuka, M. Obayashi, M. Imanishi, and T. Takahashi, *Steroids*, **12**, 9 (1968).
14) *a*) S. Noguchi and K. Morita, *Chem. Pharm. Bull.* (Tokyo), **11**, 1235 (1963); *b*) S. Noguchi, F. Nakayama and K. Morita, *ibid.*, **12**, 1180 (1964).
15) R. Gardi, R. Vitali, A. Ercoli, and W. Klyne, *Tetrahedron*, **21**, 179 (1965).
16) D. Taub, R.D. Hoffsommer, and N.L. Wendler, *J. Am. Chem. Soc.*, **81**, 3291 (1959).
17) Melting points were determined on a Fischer-Johns block and are uncorrected. All optical rotations are reported in chloroform solution unless otherwise noted at a concentration of 1%. All compounds had IR bands at 1670 cm^{-1} and 3330 cm^{-1} for the 3-keto-$\Delta^{1,4}$-diene system and 11β-ol respectively. Only additional relevant IR bands are reported for each compound.

tical sample was prepared by crystallization from acetone, mp 243—247°, $[\alpha]_D^{23}+106°$. *Anal.* Calcd. for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 72.10; H, 7.87. UV λ_{max}^{EtOH} nm ε: 244 (15350).

11β,17α,21α-Trihydroxy-21-methylpregna-1,4-diene-3,20-dione-17α,21-acetonide (21-Methylprednisolone-17α,21-acetonide) (3)——To a solution of potassium *t*-butoxide prepared from 700 mg of potassium in 50 ml of *t*-butanol was added 10 g of prednisolone 17α,21-acetonide. After solution of the acetonide had occurred, 15 ml of methyl iodide was added and the mixture was refluxed with stirring under a nitrogen atmosphere for 2 hr. The mixture was poured into water and extracted with chloroform. The chloroform solution was dried over sodium sulfate and concentrated at reduced pressure. The residue was crystallized from acetone and afforded 620 mg of 21-methylprednisolone-17α,21-acetonide in three consecutive crops, mp 223—238°. Some of these fractions in later methylation reactions contained varying amounts of methoxyl groups (1.8 to 2.7%) by an analytical Zeissel determination. This result indicates that O-methylation of the 21-methylated $\Delta^{20(21)}$-enolate ion occurs in preference to C-21 dimethylation on carbon. The analytical sample was prepared by further crystallization from acetone, mp 245°, $[\alpha]_D^{23}+93°$. *Anal.* Calcd. for $C_{25}H_{34}O_5$: C, 72.44; H, 8.27. Found: C, 72.40; H, 8.50.

11β,17α,21α-Trihydroxy-21-methylpregna-1,4-diene-3,20-dione (21-Methylprednisolone) (4)——A solution of 612 mg of 21-methylprednisolone-17α,21-acetonide dissolved in 10 ml of acetic acid and 10 ml of water was heated on a steam bath under a nitrogen atmosphere for 1.5 hr. The solution was concentrated at reduced pressure and the residue crystallized from acetic acid and ether to yield 177 mg, mp 120—124°. Two successive crops afforded a further 200 mg, mp 115—118°. The analytical sample was prepared by crystallization from acetic acid, mp 129—133°, $[\alpha]_D^{23}+56°$. Reported mp 117—120°; $[\alpha]_D+111°$ (diox)[7]; mp 117—120°, $[\alpha]_D+111°$ (pyr).[13] *Anal.* Calcd. for $C_{23}H_{30}O_5\cdot H_2O$: C, 67.32; H, 8.22. Found: C, 67.19; H, 8.42. UV λ_{max}^{EtOH} nm ε: 243 (14000).

11β,17α,21α-Trihydroxy-21-methylpregna-1,4-diene-3,20-dione-21-acetate (21-Methylprednisolone-21-acetate) (5)——A solution of 100 mg of 21-methylprednisolone-17α,21-acetonide in 4 ml of acetic acid and 4 ml of water was heated on a steam bath for 1.5 hr under a nitrogen atmosphere. The residue obtained after concentration at reduced pressure was dissolved in 1 ml of pyridine and 1 ml of acetic anhydride and allowed to stand overnight. The solvents were removed at reduced pressure and the residue crystallized from acetone–hexane to yield 24 mg, mp 215—219°. The analytical sample was prepared by crystallization from acetone, mp 218—224°, $[\alpha]_D^{24}+97°$. Reported mp 221—222°, $[\alpha]_D+122°$ (diox)[7]; mp 220—221°, $[\alpha]_D+110°$ (pyr).[13] *Anal.* Calcd. for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74. Found: C, 68.42; H, 7.65.

9α-Fluoro-11β,17α,21α-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione-17,21-acetonide (9α-Fluoro-16α-Methylprednisolone-17α,21-acetonide) (7)——A solution of 500 mg of 9α-fluoro-16α-methylprednisolone in 2 ml of dimethylformamide and 3 ml of 2,2-dimethoxypropane with 25 mg of *p*-toluenesulfonic acid was refluxed for 12 hr. The solution was concentrated to dryness at reduced pressure and the residue dissolved in benzene. The insoluble material was filtered to afford 150 mg of recovered 9α-fluoro-16α-methylprednisolone, mp 244—247°. The filtrate was absorbed on 10 g of Florisil. Elution with benzene–ether, 1:1, yielded crystalline material from ether–methylene chloride, 211 mg, mp 248—253°. The analytical sample was prepared by repeated crystallizations from methylene chloride–ether, mp 263—264°, $[\alpha]_D^{23}+83°$. *Anal.* Calcd. for $C_{25}H_{33}O_5F$: C, 69.42; H, 7.69. Found: C, 69.28; H, 7.56.

9α-Fluoro-11β,17α,21α-trihydroxy-16α,21-dimethylpregna-1,4-diene-3,20-dione-17,21-acetonide (9α-Fluoro-16α,21α-dimethylprednisolone-17α,21-acetonide) (8)——To a solution of 290 mg of potassium in 100 ml of dry *t*-butanol was added 802 mg of 9α-fluoro-16α-methylprednisolone-17α,21-acetonide. After the steroid had completely dissolved at room temperature, 20 ml of methyl iodide was added and the mixture stirred at room temperature for 15 min under a nitrogen atmosphere and poured into water. The mixture was extracted with chloroform and the chloroform extracts dried over sodium sulfate and concentrated to dryness at reduced pressure. The residue was crystallized from methylene chloride–ether, 512 mg, mp 233—237°. The analytical sample was crystallized from acetone, mp 252—258°, $[\alpha]_D^{31}+72°$. *Anal.* Calcd. for $C_{26}H_{35}O_5F$: C, 69.93; H, 7.90; F, 4.25. Found: C, 69.65; H, 7.98; F, 4.14.

9α-Fluoro-11β,17α,21α-trihydroxy-16α,21-dimethylpregna-1,4-diene-3,20-dione (9α-Fluoro-16α,21-dimethylprednisolone) (9)——A solution of 90 mg of 9α-fluoro-16α,21-dimethylprednisolone-17α,21-acetonide in 7 ml of 50% formic acid was heated for 2 hr on a steam bath under a nitrogen atmosphere. Water was added and the solution concentrated to dryness at reduced pressure. The residue was crystallized from methylene chloride, 41 mg, mp 241—245°. The analytical sample was crystallized from methylene chloride and dried in high vacuum at 140°, mp 243—246°, $[\alpha]_D^{24}+79°$. *Anal.* Calcd. for $C_{23}H_{31}O_5F$: C, 67.96; H, 7.67. Found: C, 67.63; H, 7.59.

9α-Fluoro-11β,17α,21α-trihydroxy-16α,21-dimethylpregna-1,4-diene-3,20-dione-17-acetate (9α-Fluoro-16α,21-dimethylprednisolone-21-acetate) (10)——A solution of 350 mg of 9α-fluoro-16α,21-dimethylprednisolone-17α,21-acetonide in 25 ml of 50% formic acid was heated on a steam bath for 2 hr under a nitrogen atmosphere. The solution was concentrated to dryness at reduced pressure and the residue dissolved in 2 ml of pyridine and 2 ml of acetic anhydride and allowed to stand overnight. The solvents were removed at reduced pressure and the residue crystallized from methanol, 150 mg, mp 234—240°. *Anal.* Calcd. for $C_{25}H_{33}O_6F$: C, 66.95; H, 7.41. Found: C, 66.55; H, 7.22.

11β,17α,21-Trihydroxy-21-trifluoroacetylpregna-1,4-diene-3,20-dione (21-Trifluoroacetyl-prednisolone) (11)——To a solution of potassium *t*-butoxide prepared from 500 mg of potassium in 50 ml dry *t*-butanol was added 1.0 g of prednisolone-17α,21-acetonide followed by 1.78 g of ethyltrifluoroacetate distilled from phosphorus pentoxide. The solution was stirred with refluxing for 4 hr under a nitrogen atmosphere and then allowed to stand at room temperature overnight. The dark brown solution was concentrated to dryness at reduced pressure to a solid residue. To effect deacetonation, the residue was heated with 50 ml of 50% acetic acid for 20 min on a steam bath followed by an additional 25 ml of acetic acid and heating continued for an additional 0.5 hr. The mixture was diluted with water, cooled and filtered to afford 955 mg of 21-trifluoroacetylprednisolone, mp 269—270°. The analytical sample was crystallized from chloroform–absolute ethanol, mp 270—271°. *Anal.* Calcd. for $C_{23}H_{27}O_6F_3$: C, 60.60; H, 5.98. Found: C, 60.85; H, 6.10. UV $\lambda\lambda_{max}^{CH_3CN}$ nm (ε): 245, 310 (9900, 4400).

11β,17α,21-Trihydroxy-21-benzylidenepregna-1,4-diene-3,20-dione-17α,21-acetonide (21-Benzyli denprednisolone-17α,21-acetonide) (12)——To a solution of 2 g of prednisolone-17α,21-acetonide in 100 ml of boiling methanol was added 1 g sodium methoxide and 5 ml of benzaldehyde. The solution was stirred overnight at a bath temperature of 50° with the gradual precipitation of the benzal derivative. To the cooled mixture 125 ml of water was added and the solid collected by filtration. After drying, the material was crystallized from acetone–methanol to yield 1.62 g, mp 289—292°. Further concentration of the mother liquor afforded an additional .42 g, mp 288—291°. *Anal.* Calcd. for $C_{31}H_{38}O_5$: C, 75.89; H, 7.81. Found: C, 75.93; H, 7.57. IR ν_{max}^{KBr} cm^{-1}: 3330, 1670. UV λ_{max}^{EtOH} nm (ε): 234,326 (16600, 13900).

11β,17α,21-Trihydroxy-21-methylenepregna-1,4-diene-3,20-dione-17α,21-acetonide (21-Methyleneprednisolone-17α,21-acetonide) (13)——To a solution of 3.0 g of prednisolone-17α,21-acetonide in 120 ml of ethanol was added 750 mg of sodium bicarbonate and 30 ml of 37% formaldehyde solution. The mixture was stirred and heated at 65—70° for 16 hr. Water was added and the ethanol removed at reduced pressure. The solid was filtered and washed with water to yield 2.89 g, mp 192—198°. Recrystallization from acetone yielded a total of 1.46 g, mp 213-215°, $[\alpha]_D^{24}$+28°. *Anal.* Calcd. for $C_{25}H_{32}O_5$: C, 72.79; H, 7.82. Found: C, 72.69; H, 7.77. IR ν_{max}^{KBr} cm^{-1}: 3330, 1670.

9α-Fluoro-11β,17α,21α-trihydroxy-16α-methyl-21-methylenepregna-1,4-diene-3,20-dione-17α,21-acetonide (21-Methylene-9α-fluoro-16α-methylprednisolone-17α,21-acetonide) (14)——To a solution of 250 mg of 9αfluoro-16α-methylprednisolone in 15 ml of ethanol and 4 ml of 37% formaldehyde solution was added 80 mg of sodium bicarbonate. The mixture was stirred at 70° for 16 hr. Water was added and the ethanol removed at reduced pressure. The solid was filtered, dried and crystallized from acetone, 142 mg, mp 228—235°, $[\alpha]_D^{31}$+244°. *Anal.* Calcd. for $C_{26}H_{33}O_5F$: C, 70.25; H, 7.48. Found: C, 69.84; H, 7.68.

11β,17α-Dihydroxy-21-methylpregna-1,4-diene-3,20,21-trione (15)——A solution of 400 mg of 21-methylene-prednisolone-17α,21-acetonide in 25 ml of 50% acetic acid was heated on a steam bath under a nitrogen atmosphere for 2 hr. The solution was concentrated to dryness at reduced pressure and the residue crystallized from acetone to yield 110 mg, mp 189—198°. The analytical sample was prepared by repeated crystallizations from acetone, mp 205—209°, $[\alpha]_D^{23}$+128°, reported[7] mp 206—208°, $[\alpha]_D$+91° (diox). *Anal.* Calcd. for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 70.01; H, 7.22.

9α-Fluoro-11β,17α-dihydroxy-16α,21-dimethylpregna-1,4-diene-3,20,21-trione (16)——A solution of 118 mg of 21-methylene-9α-fluoro-16α-methylprednisolone-17α,21-acetonide in 9 ml of 50% formic acid was heated on a steam bath under a nitrogen atmosphere for 2.5 hr. The solution was concentrated to dryness at reduced pressure and the residue crystallized from methylene chloride, 42 mg, mp 214—219°. *Anal.* Calcd. for $C_{23}H_{29}O_5F$: C, 68.30; H, 7.23. Found: C, 67.50; H, 7.14.

11β,17α,21-Trihydroxy-21-(2′-nitroethyl)pregna-1,4-diene-3,20-dione-17α,21-acetonide (21-(β-Nitroethyl)-prednisolone-17α,21-acetonide) (17)——To a solution of 50 mg of sodium in 20 ml of methanol was added 412 mg of prednisolone-17α,21-acetonide. After heating to bring the steroid into solution, 0.1 ml of nitromethane in 0.15 ml of methanol was added dropwise. The solution was refluxed for 15 min, cooled and acidified with dilute acetic acid. Further dilution with water precipitated a solid which was filtered and dried. The solid was dissolved in benzene and absorbed on 6 g of Florisil. The benzene–ether, 1: 1, fractions afforded 134 mg of crystalline material from ether, mp 225—228.° *Anal.* Calcd. for $C_{26}H_{35}O_7N$: C, 65.94; H, 7.45. Found: C, 66.12; H, 7.58. IR ν_{max}^{KBr} cm^{-1}: 3450, 1725, 1670, 1560.

11β,17α,21-Trihydroxy-21-(2′-carboxyethyl)pregna-1,4-diene-3,20-dione → 21-lactone (21-(β-Carboxyethyl)-prednisolone-lactone) (19)——To a solution of 470 mg of sodium in 200 ml of absolute ethanol was added 655 mg of 21-methyleneprednisolone-17α,21-acetonide and 4.6 ml of diethyl malonate. The yellow solution was refluxed for 2 hr under a nitrogen atmosphere, cooled and neutralized with dilute acetic acid, and extracted with chloroform. The chloroform extracts were washed with water and dried over sodium sulfate. Removal of the chloroform at reduced pressure yielded a yellow oily diester as indicated by the infrared spectrum. For saponification of the ester functions, the material was dissolved in 50 ml of ethanol containing 4 g potassium hydroxide and 5 ml water and the solution refluxed under a nitrogen atmosphere for 1 hr. The solution was cooled, diluted with water and acidified with cold dilute hydrochloric acid to pH 3 and extracted with a total of 500 ml of chloroform. The chloroform extracts were washed with water, dried over sodium sulfate and concentrated to dryness at reduced pressure to a solid residue. For deacetona-

tion, the reisude was dissolved in 50 ml of 50% acetic acid and heated on a steam bath under a nitrogen atmosphere. After 2 hr, the solution was diluted with water and concentrated to dryness at reduced pressure to an oily residue. To effect decarboxylation and lactonization, the oily residue was heated for 7 min at a bath temperature of 160° in a flask evacuated to 0.5 mm of mercury. After cooling, crystallization of the residue from acetone afforded a total of 175 mg of lactone in two crops, mp 253—255°, $[\alpha]_D^{26}+220°$ (tetrahydrofuran). *Anal.* Calcd. for $C_{24}H_{30}O_6$: C, 69.55; H, 7.30. Found: C, 69.34; H, 7.31. IR ν cm^{-1}: 3450, 1780, 1735, 1670.

11β,17α,20α,21-Tetrahydroxypregna-1,4-diene-3-one-17α,21-acetonide (20)——To a solution of 400 mg of prednisolone-17α,21-acetonide in 40 ml of dimethylformamide was added a solution of 115 mg of sodium borohydride in 5 ml of water. The solution was allowed to stand overnight at room temperature, cooled and the excess sodium borohydride decomposed with acetic acid. The solution was diluted with water and the precipitated solid was filtered and dried, 220 mg, mp 275—276°, $[\alpha]_D+20°$ (chloroform). Reported[15] mp 275—276°, $[\alpha]_D+25°$ (diox). *Anal.* Calcd. for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.66; H, 8.47.

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