Synthesis of a New Anti-inflammatory Steroidal Acid Ester: Methyl 11β-hydroxy-3,20-dioxo-1,4-pregnadien-21-oate

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Abstract □ The synthesis and anti-inflammatory activity of a new steroidal acid ester, methyl 11β-hydroxy-3,20-1,4-pregnadien-21-oate (**5**), are described. This compound has been prepared via three different synthetic routes. The first involves oxidation of the benzoate **3** to the aldehyde **4** followed by a Mattox-type rearrangement of the side chain in conjunction with elimination of the benzoyloxy group. The second method, prolonged reaction of 1-dehydrocorticosterone (**8**) with methanolic cupric acetate, affords methyl ester **5** in low yield. The third approach consists of selective oxidation at C-20 of the methyl 11β,20α and 20β-dihydroxy-3-oxo-1,4-pregnadien-21-oates (**7a** and **7b**) with sulfur trioxide–pyridine complex. The local anti-inflammatory activities of the new ester **5** and intermediates **3**, **4**, **7a**, and **7b** were determined by the cotton-pellet granuloma assay in rats. The anti-inflammatory activity of the title compound is equal to that of the parent steroid, prednisolone. However, unlike the latter compound, the ester does not cause reduction of adrenal and thymus weights or a lowering of plasma corticosterone levels.

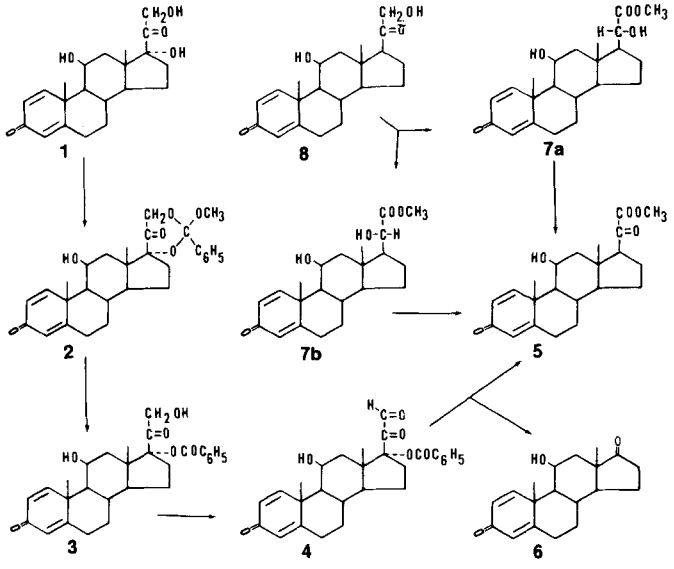
Long-term clinical use of corticosteroids as anti-inflammatory agents is limited because of their many adverse systemic side effects.[1] Topical application of potent corticosteroids has the potential of eliciting diverse systemic toxicities, especially when the steroids are applied under occlusion or on extensive areas.[2-4] Because of this situation the development of anti-inflammatory steroids which are devoid of systemic side effects becomes a most desirable objective.

We have recently shown[5,6] that methyl 11β,17-dihydroxy-3,20-dioxo-1,4-pregnadien-21-oate (methyl prednisolonate) and a C-20-epimeric mixture of methyl 11β,17,20ξ-trihydroxy-3-oxo-1,4-pregnadien-21-oate (methyl 20-dihydroprednisolonate) possess such properties. Moreover, we have isolated the 20α- and 20β-epimers and found that the activity of the epimeric mixture appears to be due mainly to the 20β-epimer.[7,8] Our rationale for synthesizing these steroidal acid esters was based on the expectation that their anti-inflammatory activity would be local only because of their rapid hydrolysis to the inactive steroid 21-oic acids upon entry into the systemic circulation.

The work presented in the present investigation, namely the synthesis of methyl 11β-hydroxy-3,20-dioxo-1,4-pregnadien-21-oate, stemmed from our attempt to improve the preparation of methyl prednisolonate. The anti-inflammatory activities of the title compound and its intermediates are also documented. Steroidal 17-deoxy-20-oxo-21-oates with or without additional substituents at C-6 and/or C-16 have been shown to possess high topical anti-inflammatory activity without systemic side effects by Laurent et al.[9,10]

Results and Discussion

Chemistry—As shown in Scheme I, the benzoate **3** was prepared by the procedure of Ercoli et al.[11] Treatment of prednisolone (**1**) with trimethyl orthobenzoate and pyridinium *p*-toluenesulfonate gave the 17,21-methyl-orthobenzoate **2**. Following acid hydrolysis to the 17-benzoate **3**, oxidation with methanolic cupric acetate gave the corresponding 21-aldehyde **4** which was obtained in high yield as the hydrate. Treatment



Scheme I—Substituent at C-20 is "α" oriented in "a" compound and "β" oriented in "b" compound.

of **4** with potassium cyanide, manganese dioxide, and methanolic acetic acid[12] gave methyl 11β-hydroxy-3,20-dioxo-1,4-pregnadien-21-oate (**5**) and 11β-hydroxy-1,4-androstadiene-3,17-dione (**6**), which were separated by silica gel column chromatography.

Confirmation of the structural assignment for **5** was obtained by its independent synthesis via selective oxidation at C-20 of both methyl 11β,20α and 20β-dihydroxy-3-oxo-1,4-pregnadien-21-oates (**7a** and **7b**) with a sulfur trioxide–pyridine complex in dimethyl sulfoxide–triethylamine.[13] The product obtained by this method was identical in all respects with **5** prepared from **4**.

Preparation of intermediates **7a** and **7b** was accomplished by prolonged reaction of 1-dehydrocorticosterone (**8**) with methanolic cupric acetate.[14] Complete separation of methyl esters **7a** and **7b** was achieved by silica gel column chromatography followed by HPLC. Also recovered in low yields were **5** and the 17-ketone **6**. The structures of all new compounds described herein were confirmed by elemental analysis, IR, ^{1}H NMR, and MS. Thus, the structure of **5** was confirmed as methyl 11β-hydroxy-3,20-dioxo-1,4-pregnadien-21-oate rather than methyl 11,20-dihydroxy-3-oxo-1,4,16-pregnatrien-21-oate.[15]

The loss of the C-17 oxygen function in the reaction sequence from **1** to **5** was not anticipated. As shown in Scheme II, a plausible mechanism for the conversion of **4** to **5** involves, initially, formation of cyanohydrin **b**; the presence of two negative groups (—CN and —OH) at C-21 facilitates removal of the C-21 proton with subsequent enolization between C-20 and C-21, affording **c**. Abstraction of the enolic C-21 proton with a shift of the double bond to C-17/C-20 results in elimi-

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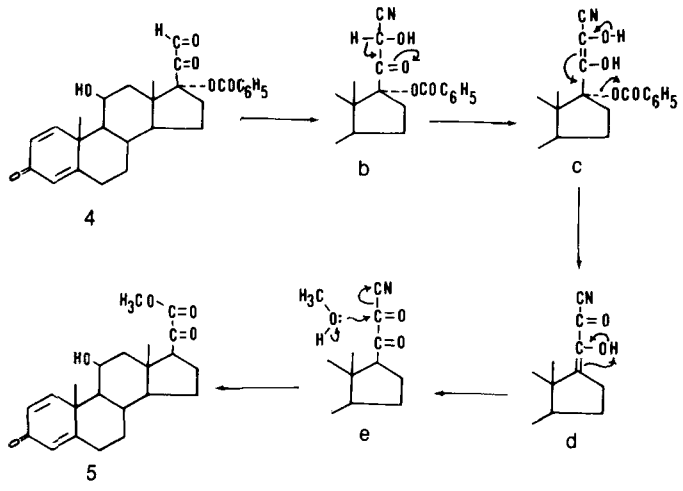

Scheme II

Table I—Effects of Prednisolone and Its Derivatives on Granuloma Formation and Relative Thymus and Adrenal Weight[a]

Test Compound	Dose, mg/Cotton Pellet	Granuloma Inhibition, %	Thymus[b]	Adrenal[b]
Control	0	—	217.8 ± 12.4	14.4 ± 0.4
Prednisolone	2.5	65.7 ± 0.5[d]	91.1 ± 7.9[d]	11.9 ± 0.6[c]
3	2.5	66.9 ± 0.3[d]	30.5 ± 4.3[d]	10.8 ± 0.5[c]
4	2.5	64.1 ± 0.7[d]	101.0 ± 6.2[d]	12.5 ± 0.7[c]
5	2.5	60.9 ± 0.8[d]	241.0 ± 12.0	12.4 ± 0.4
7a	2.5	3.0 ± 3.0	216.5 ± 14.9	13.2 ± 0.9
7b	2.5	3.3 ± 3.4	215.4 ± 2.3	13.8 ± 0.7

[a] Each value represents the mean ± SEM relative weights of six rats in the experimental group. [b] Measured as mg/100 g of body weight. [c] Significantly different from control ($p < 0.05$). [d] Significantly different from control ($p < 0.01$).

nation of the benzoyloxy group, giving the $\Delta^{17,20}$-20-hydroxyoxalonitrile **d** which, after ketone formation and S_N2 displacement of the —CN group by —OCH_3, provides the final product **5**.

This postulated mechanism represents a novel type of Mattox rearrangement which classically involves conversion of a dihydroxyacetone grouping to a 17-deoxy-20-oxo-21-aldehyde in the presence of alcoholic mineral acid.[16] Others subsequently have shown that the rearrangement can occur in refluxing acetic acid in the absence[17] or presence[18] of zinc acetate. We have observed in the present study that conversion of **4** to **5** does not occur in the absence of manganese dioxide, and that substitution of zinc acetate for manganese dioxide brings about the reaction. It therefore appears likely that the metallic compounds function as Lewis acids which are essential in the Mattox-type rearrangement. Finally, a biological equivalent of the Mattox rearrangement has been proposed by Weiss, Monder, and Bradlow[19] to explain the in vivo 17-deoxygenation of cortisol to the 20α- and 20β-hydroxy-21-oic acids. The mechanism proposed also involves formation of several enolic intermediates prior to elimination of the C-17 hydroxyl and internal Cannizzaro reaction of the resulting glyoxal, affording the glycolic acid metabolites.

Anti-inflammatory Activity—The local anti-inflammatory activity of prednisolone and its derivatives was evaluated in the cotton-pellet granuloma bioassay in rats.[20] The systemic activity of locally applied steroids on the hypothalamic-pituitary-adrenal axis (HPA axis) is reflected by such indices as plasma corticosterone levels and adrenal and thymus weights. The results depicted in Table I indicate that **5** significantly inhibits granuloma formation at a dose of 2.5 mg/cotton pellet. The percent granuloma inhibition produced by **5** is comparable to that of prednisolone. In addition, **5** did not suppress adrenal or thymus weights. This finding is in contrast to the thymus and adrenal weight reduction which accompanied the anti-inflammatory activity of prednisolone (**1**), the benzoate **3**, and the 17-benzoyloxy-21-aldehyde **4**. On the other hand, compounds **7a** and **7b**, which differ from **5** only in containing a 20α- or 20β-hydroxyl group, were devoid of anti-inflammatory activity. This finding is especially noteworthy since the 17α-hydroxy analogues of **7a** and **7b** exhibit appreciable anti-inflammatory activity.[7,8]

In Fig. 1 the anti-inflammatory activities of the test compounds were compared with their effect on corticosterone levels. Unlike prednisolone and **3** and **4**, **5** does not decrease plasma corticosterone levels. In Fig. 2 a linear response of **5** on the inhibition of granuloma formation at doses of 1.0, 1.5, 2.0, and 2.5 mg/cotton pellet is shown. The dose of **5** required to inhibit the granuloma formation by 50% (ID_{50}) is 2.1 mg/pellet (95% confidence limits ± 0.25 mg/pellet). The regression line has a slope (b) of −16.0 and a high correlation coefficient (r) value of −0.99 ($p < 0.01$).

These findings indicate that the new steroidal acid ester, **5**, exhibits local anti-inflammatory activity equivalent to that of prednisolone but is devoid of systemic side effects.

Experimental Section

Materials and Methods—Melting points were determined on a Thomas capillary or Fisher-Johns melting point apparatus

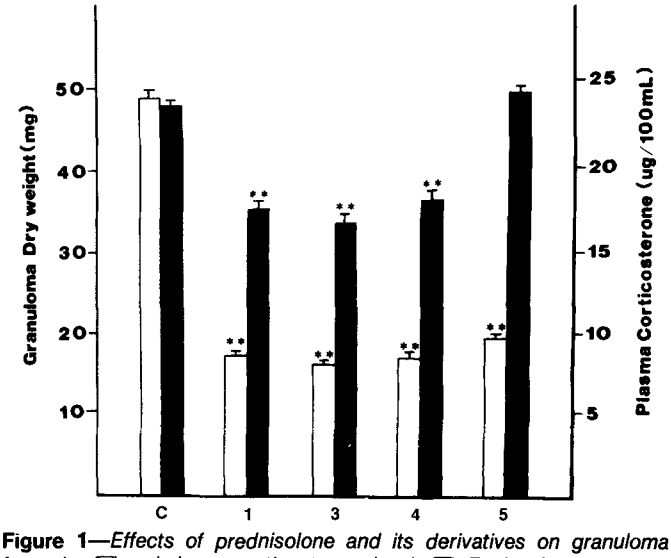

Figure 1—*Effects of prednisolone and its derivatives on granuloma formation (□) and plasma corticosterone levels (■). Each value represents the mean ±SEM of six rats in an experimental group. Key: (**) significantly different from control ($p < 0.01$); (C) control.*

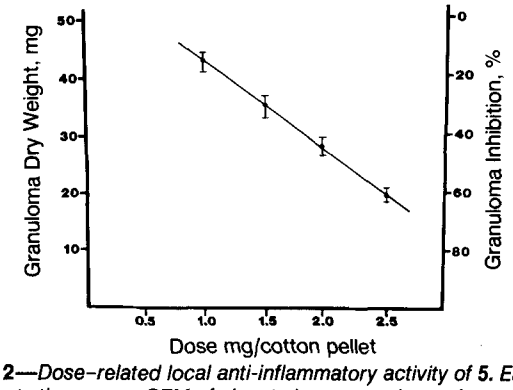

Figure 2—*Dose-related local anti-inflammatory activity of 5. Each value represents the mean ±SEM of six rats in an experimental group.*

and are uncorrected. IR spectra were determined on KRS-5 crystals with a Perkin-Elmer Model 681 spectrophotometer. Optical rotations were determined at 365 and 589 nm (D line of sodium) in a Zeiss 0.005° photoelectric polarimeter. Measurements were made in methanol solution in a 0.5 dm tube at a concentration of ~1% and at a temperature of 26 ± 1°C. UV spectra were obtained in methanol solution with a Gilford Model 240 spectrophotometer. ^{1}H NMR spectra were obtained with a Bruker HX-270, instrument and the chemical shifts are reported in parts per million (δ) down field from tetramethylsilane as an internal standard. MS were recorded on a Finnigan 4510 GCMS using a 70 eV source. The homogeneity of intermediates and products were determined by TLC on Merck silica gel 60F-254 plates with visualization at 254 nm.

17α-Benzoyloxo-11β,21-dihydroxy-1,4-pregnadiene-30,20-dione (3)—The method of Ercoli et al. was employed.[11] To a solution of prednisolone (**1**) (4.0 g, 11 mmol) in dioxane (200 mL) and benzene (320 mL) was added trimethyl orthobenzoate (10 mL) and pyridinium *p*-toluenesulfonate (1 g). The mixture was heated under reflux for 10 h, concentrated under reduced pressure, and extracted with ethyl acetate. The organic phase was washed with water, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure to give an oil.[11] To this residue was added a mixture of glacial acetic acid (80 mL) and water (2 mL), and the mixture was stirred for 1 h at room temperature. The solution was diluted with water and the product extracted with ethyl acetate. The organic phase was washed successively with 2% $NaHCO_3$ and water and then dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to give solid material which was purified by column chromatography (silica gel, chloroform:methanol, 9:1). Recrystallization from acetone–hexane gave **3** as white prisms (3.6 g, 70%); mp 256–258°C (lit.[21] mp 242–246°C); $[\alpha]_{365}$ −97.9°, $[\alpha]_D$ −4.89°; λ_{max}: 233 nm (ϵ 28,600); IR: 3450 (OH), 1720 (20-C=O and benzoate C=O), 1655, 1610, and 890 ($\Delta^{1,4}$-3-C=O), and 1280 and 720 cm^{-1} (benzoate).

Anal.—Calc. for $C_{28}H_{32}O_6$: C, 72.39; H, 6.94. Found: C, 72.20; H, 6.70.

17α-Benzoyloxy-11β-21,21-trihydroxy-1,4-pregnadien-3-one (Hydrate of 4)—To a solution of 17α-benzoyloxy-11β,21-dihydroxy-1,4-pregnadien-3,20-dione (**3**) (1.5 g, 3.3 mmol) in methanol (125 mL) was added a solution of cupric acetate (0.38 g, 2 mmol) in methanol (125 mL) as described by Lewbart and Mattox.[14] Air was bubbled through the mixture for 30 min. A solution of 1% $NaHCO_3$ (100 mL) containing the disodium salt of EDTA (1 g) was added and the methanol was evaporated under reduced pressure at 40°C. The aqueous residue was extracted with ethyl acetate. After being washed with 2% sodium bicarbonate and water, the organic phase was dried over anhydrous sodium sulfate and evaporated to dryness. Recrystallization from acetone–hexane gave compound **4** hydrated as white needles (1.28 g, 80%); mp 121–123°C; $[\alpha]_{365}$ + 17.60°, $[\alpha]_D$ + 22.8°; λ_{max}: 233 nm (ϵ 26,100); IR: 3490 and 3440 (OH), 1720 (20-C=O and benzoate C=O), 1658, 1610, and 890 ($\Delta^{1,4}$-3-C=O), and 1280 and 720 cm^{-1} (benzoate); ^{1}H NMR ($CDCl_3$): δ 0.88 (s, 3, 13-CH_3), 1.4 (s, 3, 10-CH_3), 4.44 (s, 1, 11α-H), 6.04 (m, 1, 4-H), 6.30 (dd, 1, J = 10 and 2 Hz, 2-H), 7.25 (d, 1, J = 10 Hz, 1-H), and 7.5 ppm (m, 5, ArH). Mass spectrum showed M$^+$ at 462 and the base peak at 122.

Anal.—Calc. for $C_{28}H_{30}O_6 \cdot H_2O$: C, 69.98; H, 6.71. Found: C, 70.32; H, 7.00.

Methyl 11β-Hydroxy-3,20-dioxo-1,4-pregnadien-21-oate (5)— To a stirred solution of **4** (1.0 g, 2 mmol) in methanol (20 mL) was added potassium cyanide (1.0 g), manganese dioxide (10 g), and glacial acetic acid (1.0 mL), according to the method of Laurent, Gerhards, and Wiechert.[9] The mixture was mixed at room temperature for 30 min, filtered, and the filtrate diluted with methylene chloride. The organic phase was washed with water, dried over anhydrous sodium sulfate, and the solvent was evaporated to dryness under reduced pressure. The residue was chromatographed on silica gel [chloroform:methanol (9:1)]. Early fractions furnished 350 mg (44%) of **5**. Recrystallization of **5** from acetone–petroleum ether (bp 40–60°C) gave white platelets, mp 178–180°C; $[\alpha]_{365}$ + 960°; $[\alpha]_D$ +188°; λ_{max}: 243 nm (ϵ 16,700); IR: 3490 (OH), 1740 ($COOCH_3$), 1720 (20-C=O), 1660, 1620, and 890 ($\Delta^{1,4}$-3-C=O), and 1270 cm^{-1} (ester C—O stretch); ^{1}H NMR ($CDCl_3$): δ 0.97 (s, 3, 13-CH_3), 1.45 (s, 1, 10-CH_3), 3.68 (s, 3, 21-OCH_3), 4.41 (s, 1, 11α-H), 6.02 (s, 1, 4-H), 6.25 (dd, 1, J = 10 and 2 Hz, 2-H), and 7.25 ppm (d, 1, J = 10 Hz, 1-H); MS m/z (%): M$^+$ at 374 (3.35) and 122 (100).

Anal.—Calc. for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 70.70; H, 7.70. Later fractions afforded 200 mg (30%) of 11β-hydroxy-1,4-androstadiene-3,17-dione (**6**), mp 180–182°C (lit.[22] mp 181–182°C).

Compounds 5, 6, 7a, and 7b from 8—The method of Laurent, Gerhards, and Wiechert[9] was used. To a solution of 11β,21-dihydroxy-1,4-pregnadiene-3,20-dione (**8**)[23] (688 mg, 2 mmol) in methanol (50 mL) was added 200 mg (1 mmol) of cupric acetate monohydrate in an equal volume of methanol. Air was bubbled periodically through the mixture until the blue color persisted. After 140 h at room temperature, EDTA (744 mg, 2 mmol) in water (25 mL) was added and the solution was diluted with brine and extracted with ethyl acetate. The organic layer was washed successively with dilute $NaHCO_3$ solution and NaCl solution, filtered through anhydrous sodium sulfate, and evaporated to dryness. Two recrystallizations from methanol gave 57 mg of methyl 11β,20α-dihydroxy-3-oxo-1,4-pregnadien-21-oate (**7a**) as platelets, mp 232–235°C. The analytical specimen gave the following data: mp 235–237°C, $[\alpha]_{365}$ + 132°, $[\alpha]_D$ + 70.4°; λ_{max}: 244 nm (ϵ 16,500); IR: 3435 and 3360 (OH), 1745 ($COOCH_3$), 1640, 1590, and 1575 cm^{-1} ($\Delta^{1,4}$-3-C=O); ^{1}H NMR ($CDCl_3$): δ 1.07 (s, 3, 13-CH_3), 1.45 (s, 3, 10-CH_3), 3.78 (s, 3, 21-OCH_3), 4.16 (m, 1, 20β-H), 4.37 (m, 1, 11α-H), 5.92 (s, 1, 4-H), 6.25 (dd, 1, J = 10 and 2 Hz, 2-H), and 7.25 ppm (d, 1, J = 10 Hz, 1-H); MS m/z (%): M$^+$ at 374 (3.4) and 122 (100).

Anal.—Calc. for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08. Found: C, 70.38; H, 8.12.

The mother liquor was chromatographed on a 30 × 850 mm silica gel [toluene:acetone (85:15)], collecting 11-mL fractions every 20 min.

Fractions 64–77—Recrystallization from ethyl acetate afforded 53 mg (7%) of methyl 11β-hydroxy-3,20-dioxo-1,4-pregnadien-21-oate (**5**) as needles, mp 179–182°C. The IR, NMR, and MS were almost identical with **5** prepared from **4**.

Fractions 78–84—Obtained as long needles from aqueous methanol (mp 183–186°C) in a yield of 4% (23 mg). The IR spectrum was identical with the above 11β-hydroxy-1,4-androstadiene-3,17-dione (**6**).

Fractions 106–143—Recrystallization from methanol furnished an additional 104 mg of **7a**, for a combined yield of 161 mg (22%).

Fractions 150–225: Methyl 11β,20β-Dihydroxy-3-oxo-1,4-pregnadien-21-oate (7b)—Recrystallization from ethyl acetate afforded **7b** as prismatic needles (206 mg, mp 202–204°C; 39 mg, mp 200–203°C) in a yield of 33%. For the analytical sample: mp 204–206°C; $[\alpha]_{365}$ −169.2°, $[\alpha]_D$ + 119.9°; λ_{max}: 244 nm (ϵ 15,500); IR: 3460 (OH), 1730 ($COOCH_3$), 1655, 1610, 1590, and 887 cm^{-1} ($\Delta^{1,4}$-3-C=O); ^{1}H NMR ($CDCl_3$): δ 1.07 (s, 3, 13-CH_3), 1.45 (s, 1, 10-CH_3), 3.73 (s, 3, 21-OCH_3), 4.04 (m, 1, 20α-H), 4.30 (m, 1, 11α-H), 5.98 (s, 1, 4-H), 6.22 (dd, 1, J = 10 and 2 Hz, 2-H), and 7.25 ppm (d, 1, J = 10 Hz, 1-H); MS m/z (%): M$^+$ at 374 (4.1) and 122 (100).

Anal.—Calc. for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08. Found: C, 70.69; H, 8.19.

Compound 5 from 7a—To a solution of methyl 11β,20α-dihydroxy-3-oxo-1,4-pregnadien-21-oate (**7a**) (748 mg, 2 mmol)

in dimethyl sulfoxide (5 mL) and triethylamine (5 mL), with vigorous stirring at 20–25°C, was added, in a dropwise manner over a 20-min period, sulfur trioxide–pyridine complex (1.0 g) in dimethyl sulfoxide (5 mL) as described by Parikh and Doering.[13] After an additional 30 min of stirring at room temperature, cold, dilute hydrochloric acid was added to pH 4. The mixture was diluted with ice and water and extracted with methylene chloride. The crude product, a binary mixture by TLC, was subjected to preparative liquid chromatography on an ODS column in aqueous acetonitrile. The more mobile component was recrystallized from methanol to give platelets (197 mg, mp 241–243°C) identified as starting material (26% recovery). The less mobile component was recrystallized from ethyl acetate to give prismatic needles (334 mg, mp 179–182°C) in a yield of 45% the NMR and MS spectra were identical with the spectra of **5** prepared from **4**.

Compound 5 from 4b—Treatment of methyl 11β,20β-dihydroxy-3-oxo-1,4-pregnadien-21-oate (**5b**) (75 mg, 0.2 mmol) in dimethyl sulfoxide (1 mL) and triethylamine (1 mL) with sulfur trioxide–pyridine complex (200 mg) in dimethyl sulfoxide (1 mL), as in the preparation of **5** from **4a**, was followed by liquid chromatography in aqueous acetonitrile. From the more mobile fraction 38 mg (51%) of starting material was recovered. The less mobile fraction gave 18 mg (24%) of plates from ethyl acetate–isooctane, mp 177–180°C. The IR spectrum was identical with that of **5** prepared from **4** and **4a**.

Measurements of Anti-inflammatory Activity—Adult male Sprague–Dawley rats weighing 120–140 g were maintained on standard laboratory chow with water ad libitum and kept under controlled conditions for 1 week prior to their use. Cotton pellets weighing 35 ± 1 mg cut from dental rolls were impregnated with steroid solution in acetone (0.2 or 0.4 mL) and the solvent removed by evaporation. The cotton pellets were subsequently injected with 0.2 mL aqueous solution of antibiotics (1 mg penicillin G and 1.3 mg dihydrostreptomycin/mL). Two cotton pellets were implanted subcutaneously, one in each axilla of the rat under light ether anesthesia. Cotton pellets containing only the antibiotic solution were similarly implanted in the control rats. Seven days later, the animals were sacrificed and the two pellets, with their adhering granulomas, were removed, dried for 48 h in an oven at 60°C, and weighed. The increment in dry weight (the difference between the initial and final pellet weight) is taken as a measure of granuloma formation. The adrenal, thymus, and final body weight were also recorded. The adrenal and thymus weight were expressed as relative weights (mg tissue/100 g body weight).

For measuring plasma corticosterone, blood samples were collected through cardiac puncture in heparinized tubes which were immediately centrifuged for 10 min. The plasma was removed and stored at −20°C. Plasma corticosterone levels were assayed by the fluorometric method.[24] Statistical analysis of the data was performed by a *t* test.

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23. This compound (mp 223.5–225.0°C [lit. mp 216–220°C (Schindler, O.; Reichtin, T. *Helv. Chim. Acta.* **1955**, *38*, 874)] was prepared in an overall yield of 68% from corticosterone acetate by reaction with dichlorodicyanoquinone in refluxing benzene followed by deacetylation of the resulting 1-dehydrocorticosterone acetate in methanolic sodium hydroxide.
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