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# 7α-Carboalkoxy Steroidal Spirolactones as Aldosterone Antagonists

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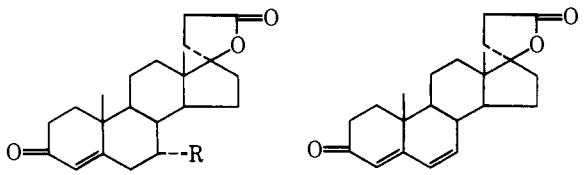
A variety of esters of 17-hydroxy-3-oxo-17α-pregn-4-ene-7α,21-dicarboxylic acid γ-lactone (**7a**) was synthesized in a sequence using the corresponding 3-oxo-4,6-diene (**2**) as starting material. The methyl (**5**), ethyl (**7c**), and isopropyl (**7e**) esters as well as the C-1 unsaturated methyl ester (**8a**) showed good oral and subcutaneous activity (MED ≤ 0.71 mg) as DCA antagonists in the adrenalectomized rat. The corresponding potassium salts of the opened lactone **10a,b,d** and **11a** appeared to have slightly increased oral potency under these test conditions (MED ≤ 0.41 mg). Some general observations on structure–activity relationships are made.

Aldosterone, synthesized in the adrenal cortex, is a potent mineralocorticoid which plays an important role in regulating the electrolyte composition of the body fluid by promoting the excretion of potassium and retention of sodium ions. An excess of this hormone is observed in such edematous states as congestive heart failure, nephrosis, and cirrhosis of the liver, as well as in primary aldosteronism.[1]

It is well known that many steroids which possess a spirolactone side chain at C-17 are aldosterone antagonists.[2,3] Principal examples of this class of steroid are spironolactone (1a, Aldactone) and canrenone (**2**). It is in the treatment of the above-mentioned disorders that spirolactones have their therapeutic value. In addition, spironolactone (1a) is receiving increased attention as a hypotensive drug in the treatment of essential hypertension[4] even though excess aldosterone is not directly observed.




1a, R = SAc
b, R = H

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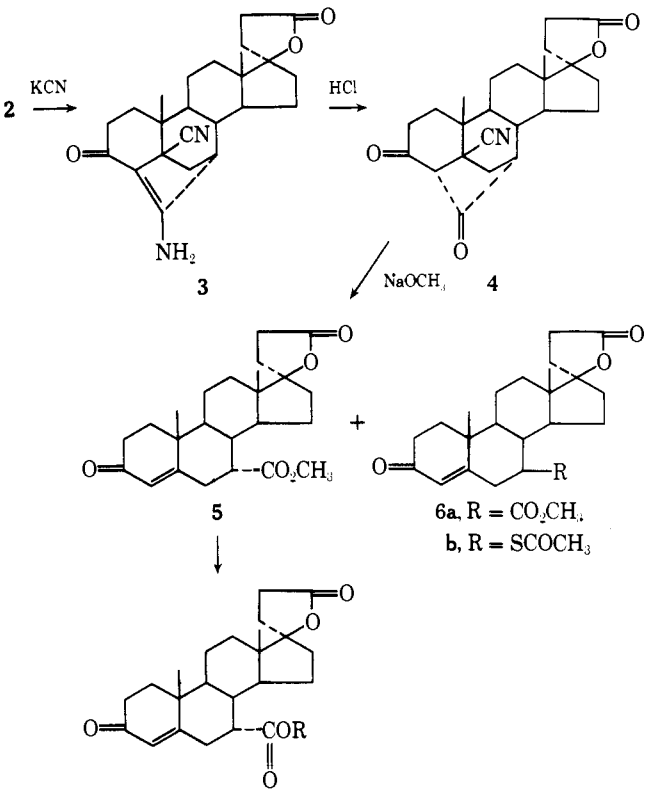
In the search for more potent analogs of spironolactone (1a), it has been found that introduction of a carboalkoxy function in the 7α position imparts to the steroidal spirolactone good antimineralocorticoid activity and provides a new series of antagonists. This paper describes the synthesis and diuretic activities of these compounds.

**Chemistry.** The synthetic sequence utilized canrenone (**2**)[3a] as the starting material. It was converted to the methyl ester **5** according to the sequence used earlier by Christiansen and Johnson[5] on $\Delta^6$-testosterone. Treatment of **2** with excess KCN in refluxing aqueous methanol buffered with ethyl acetate gave the steroidal aminomethylidyne compound **3** in yields up to 41%. Although the yield of **3** is modest, and despite the fact that there are several other products in the reaction mixture, the basic nature of **3** allows it to be easily isolated by extraction of the crude reaction product with dilute HCl. Treatment of **3** with dilute HCl on the steam bath under heterogeneous reaction conditions gave the diketone **4**, generally in yields greater than 90%. The diketone **4** was cleaved with sodium methoxide in refluxing methanol to give two compounds. The first and major compound was isolated by direct crystallization and was assigned the structure of the 7α isomer **5**. The second product was isolated in only small yield after chromatogra-




**7a**, R = H
b, R = $CO_2$-*i*-$C_4H_9$
c, R = $C_2H_5$
d, R = *n*-$C_3H_7$
e, R = *i*-$C_3H_7$
f, R = *n*-$C_4H_9$
**7g**, R = *i*-$C_4H_9$
h, R = c-$C_5H_9$
i, R = $CH_2CH{=}CH_2$
j, R = *i*-$C_6H_{13}$
k, OR = $SC_2H_5$

Table I.[a] ORD and CD Data on 5 and 6a

| | ORD[b] | | CD | |
|---|---|---|---|---|
| | $a$, deg | $\lambda$, mμ | $\theta$, deg | $\lambda$, mμ |
| 5 | −30 | 350 | −1902 | 332 |
| 1b | −63 | 352 | −4110 | 331 |
| 6a | −72 | 352 | −5307 | 332 |

[a] The solvent was dioxane. [b] These are multiple negative Cotton effect curves; $\lambda$ and $a$ are those of the most negative extremum for each compound.

phy of the mother liquors from the reaction. It was isomeric with 5 and was assigned the structure of the 7β compound 6a. Spectral comparison of 5 and 6a, including their ORD, CD, and NMR spectra, allowed confirmation of these structural assignments.

The ORD and CD data are displayed in Table I. As shown, both the molecular amplitude ($a$) and the molecular ellipticity ($\theta$) for 5 are more positive than those for either 6a or the parent unsubstituted steroid 1b, with isomer 6a having the lowest values. These data compare favorably with that observed for 7α,17α-dimethyl-, 7β,17α-dimethyl-, and 17α-methyltestosterone[6] and are completely consistent with theoretical considerations.[7]

The NMR spectrum of 5 showed the equatorial proton signal on C-7 as a broad peak centered at 2.83 ppm. The total bandwidth of this signal is ca. 17 Hz (bandwidth at half-maximum amplitude is 3.8 Hz) and this is consistent with the summation of two axial–equatorial coupling constants ($J_{6\,ax,7\,eq}$ and $J_{7\,eq,6\,ax}$) and one equatorial–equatorial coupling constant ($J_{6\,eq,7\,eq}$). Were this proton on C-7 in an axial position as in 6a, a total bandwidth in excess of 20 Hz ($J_{6\,ax,7\,ax} + J_{7\,ax,8\,ax} + J_{6\,eq,7\,ax}$) would have been expected.

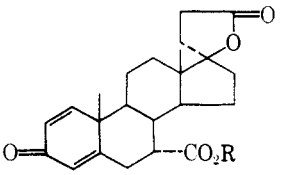
In addition, the signal for the proton on C-7 of 6a is not observed and is apparently at higher field than that for the C-7 proton of 5, buried under the broad signal for the steroid hydrocarbon protons. That the chemical shifts of axial protons generally occur at higher field than equatorial protons is well documented.[8,9]

Treatment of diketone 4 with sodium ethoxide in refluxing ethanol yielded a crude product containing several spots on TLC. Although a small yield of the ethyl ester could be obtained after chromatography, this approach was unsuitable for the synthesis of esters other than methyl.

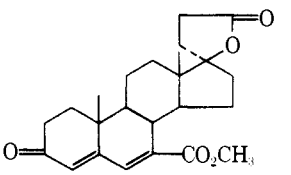
Consequently, the methyl ester 5 was saponified to the carboxylic acid 7a using excess aqueous KOH in refluxing MeOH. This reaction was slow, presumably because of steric hindrance, but it did proceed cleanly.

When treated with thionyl chloride or oxalyl chloride, 7a yielded only tarry, decomposed materials. However, 7a could be converted to the stable, mixed anhydride 7b by treatment with isobutyl chloroformate in the presence of *N*-methylmorpholine in THF at −10°. Reaction of 7b with the appropriate alcohol at reflux then gave the desired ester. The reaction times and the physical properties of these compounds are described in Table II. The thioethyl ester 7k was prepared by treatment of the mixed anhydride of 7a and ethyl chloroformate with ethanethiol.

The 3-oxo-$\Delta^{1,4}$-unsaturated compounds 8a and 8b were prepared by treating 5 and 7e, respectively, with dichlorodicyanobenzoquinone (DDQ) in refluxing benzene or dioxane under neutral conditions. The 3-oxo-$\Delta^{4,6}$-unsaturated ester 9 was prepared by treatment of 6a with DDQ in dioxane at room temperature in the presence of dry HCl. Treatment of 5 with DDQ under these conditions resulted only in the introduction of a double bond at C-1. Similarly, only 6a, and not 5, reacts with chloranil to give the C-6 unsaturated 9. These results are consistent with earlier observations that steroids bearing 7α substituents do not undergo quinone dehydrogenation reactions to yield C-6 unsaturated products but that 7β-substituted steroids will.[6,10]



8a, R = $CH_3$
b. R = $i$-$C_4H_9$



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In addition, the potassium salts 10 and 11 of the opened lactones of several of these compounds were prepared. Selective saponification of the spirolactone function was easily achieved by treatment of the steroid with 1 equiv of aqueous KOH in methanol. The reaction ordinarily was stirred at room temperature overnight and warmed briefly before work-up. Nearly quantitative yields of analytically pure material could be obtained when analytically pure lactone was employed. These compounds and certain of their physical properties are listed in Table III.

**Biological Data.** The compounds were assayed in a 4-hr test in groups of four adrenalectomized male rats, each animal being treated subcutaneously with 12 μg of deoxycorticosterone acetate (DCA) and 2.5 ml of isotonic saline solution prior to administration of the test compound.[11] The median effective dose (MED) for anti-DCA activity was established by determining the dosage (mg/rat) necessary for 50% inhibition of urinary electrolyte effects (i.e., increase in Na:K ratio) of administered DCA. Test results for both the spirolactones and the potassium salts are shown in Table IV.

Table II.[a] Physical Constants and Reaction Times for 7c–j

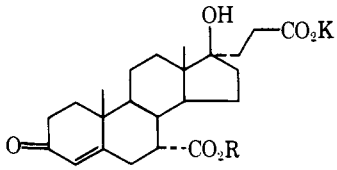
| Compd | R | Heating time, hr | Mp, °C | $[\alpha]_D$, deg ($c$) | $\lambda$, mμ ($\epsilon$) | Formula (analyses) |
|---|---|---|---|---|---|---|
| 7c | $C_2H_5$ | 46 | 146–147 | +25 (0.992) | 242 (16,700) | $C_{25}H_{34}O_5$ (C,H) |
| 7d | $n$-$C_3H_7$ | 72 | 150–152 | +23 (0.052) | 242 (18,400) | $C_{26}H_{36}O_5$ (C,H) |
| 7e | $i$-$C_3H_7$ | 48 | 183–185 | +16 (0.837) | 242 (16,900) | $C_{26}H_{36}O_5$ (C,H) |
| 7f | $n$-$C_4H_9$ | 65 | 152–154 | +23 (1.046) | 242 (16,500) | $C_{27}H_{38}O_5$ (C,H) |
| 7g | $i$-$C_4H_9$ | 8[b] | 200–202 | +17 (1.092) | 243 (17,500) | $C_{27}H_{36}O_5$ (C,H) |
| 7h | $c$-$C_5H_9$ | 63 | 207–209 | +17 (0.514) | 243 (16,100) | $C_{28}H_{38}O_5$ (C,H) |
| 7i | $-CH_2CH{=}CH_2$ | 64 | 191.5–194 | +30 (1.015) | 242 (17,200) | $C_{25}H_{34}O_5$ (C,H) |
| 7j | $i$-$C_5H_{11}$ | 3[b] | 118–120 | +21 (1.077) | | $C_{29}H_{42}O_5$ (C,H) |

[a] Reaction procedure and spectral solvents are described in the Experimental Section. [b] Reaction was run on the steam bath.

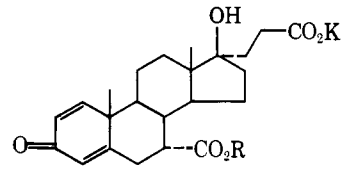
**Table III.** Physical Properties of the Potassium Salts

| Compd | $[\alpha]_D$, (c)[a] | $\lambda_{max}$, mμ (ε)[b] | Formula (analyses) |
|---|---|---|---|
| 10a | +8 (0.089) | 242 (16,200) | $C_{24}H_{33}O_6K$ (K) |
| 10b | +5 (1.023) | 244 (15,100) | $C_{25}H_{35}O_6K \cdot H_2O$ (K) |
| 10c | +10 (0.996) | 243 (16,400) | $C_{26}H_{37}O_6K$ (K) |
| 10d | | 244 (15,400) | $C_{26}H_{37}O_6K$ (K) |
| 10e | +20 (1.000) | 243 (15,300) | $C_{27}H_{39}O_6K$ (K) |
| 10f | +18 (0.092) | 243 (16,200) | $C_{28}H_{39}O_6K$ (K) |
| 10g | +17 (1.000) | 244 (13,800) | $C_{25}H_{35}O_6K$ (K) |
| 11a | −18 (0.999) | 244 (15,500) | $C_{24}H_{31}O_6K$ (K) |
| 11b | −11 (0.093) | 243 (14,800) | $C_{26}H_{35}O_6K$ (K) |

[a] Rotations determined in $H_2O$. [b] Uv spectra determined in MeOH.



10a, R = $CH_3$
b, R = $C_2H_5$
c, R = $n$-$C_3H_7$
d, R = $i$-$C_3H_7$
e, R = $n$-$C_4H_9$
f, R = c-$C_5H_9$
g, R = $CH_2CH{=}CH_2$



11a, R = $CH_3$
b, R = $i$-$C_3H_7$

Examination of the subcutaneous test data for the spirolactones (Table IV) allows several general observations on structure–activity relationships to be made. First, it is obvious that the size of the alkyl group of the ester greatly influences potency. The compounds of greatest potency are the methyl, ethyl, *n*-propyl, and isopropyl esters **5** and **7c–e**, respectively. If the chain is lengthened further (**7f,j**), made branched (**7g**), cyclic (**7h**), or unsaturated (**7i**), the antimineralocorticoid potency is diminished. The thioethyl ester **7k** also has low potency.

The requirements for oral activity are more limiting. All spirolactones showing activity on subcutaneous administration showed decreased potency on oral administration. Only the methyl (**5**), ethyl (**7c**), and isopropyl (**7e**) esters show strong oral potency. The conversion of the lactone to the opened potassium salt tends to increase the oral potency of the structure under these test conditions. Indeed, in the cases of methyl esters **5** and **10a** and the C-1 unsaturated methyl esters **8a** and **11a**, the MED's were reduced nearly to the values observed on subcutaneous administration.

Second, insertion of a double bond at C-1, which usually causes an increase in oral potency over the corresponding C-1 saturated compound,[3a] met with mixed results in this series. The methyl ester **8a** appeared to have somewhat greater oral potency than its C-1 saturated counterpart **5**, while the reverse was true for the isopropyl esters **7e** and **8b**. Again, conversion of the spirolactones to the opened potassium salts (**11a,b**) resulted in improvement in the potency of both these C-1 unsaturated compounds.

**Table IV.** DCA Blocking Potencies

| Spirolactones | MED[a] sc[b] | MED[a] ig[c] | Salts | MED, ig[c,d] |
|---|---|---|---|---|
| 1a[e] | 0.33 | 0.48 | | |
| 5 | 0.33 | 0.71 | 10a | 0.30 |
| 7c | 0.12 | 0.22 | 10b | 0.18 |
| 7d | 0.35 | >2.4 | 10c | 0.92 |
| 7e | 0.09 | 0.54 | 10d | 0.41 |
| 7f | 1.16 | 2.0 | 10e | 1.83 |
| 7g | >2.4 | >2.4 | | |
| 7h | >2.4 | >2.4 | 10f | >2.4 |
| 7i | 0.75 | >2.4 | 10g | >2.4 |
| 7j | >2.4 | | | |
| 8a | 0.27 | 0.43 | 11a | 0.23 |
| 8b | 0.07 | 0.92 | 11b | 0.39 |
| 6a | >2.4 | >2.4 | | |
| 9 | >2.4 | | | |
| 7k | 0.83 | >2.4 | | |

[a] Minimal effective dose (mg/rat) necessary for 50% inhibition of urinary electrolyte effects induced by administered DCA. Rats weighed 150–200 g. See text. [b] Subcutaneous administration. [c] Intragastric administration. [d] Administered in saline solution. [e] Potency values for **1a** are taken from R. C. Tweit and C. M. Kagawa, *J. Med. Chem.*, 7, 524 (1964), ref 8.

Finally, the low potency of both the 7β-carbomethoxy compound **6a** and the C-6 unsaturated ester **9** strongly indicates that, for appreciable mineralocorticoid antagonist activity to be present, the substituent must be on the α face of the steroid. This observation is consistent with the earlier report that **6b**, the 7β epimer of spironolactone, had a very low potency (MED > 2.4 mg).[8]

## Experimental Section

All melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra were taken in $CDCl_3$ on a Varian A-60A or a Varian T-60 spectrometer using tetramethylsilane as an internal standard. Ultraviolet spectra were obtained in MeOH on a Beckman DK-2A. Infrared spectra were obtained in $CHCl_3$ on a Beckman IR-12. Optical rotations are specific rotations taken in $CHCl_3$ on a Perkin-Elmer Model 141 polarimeter. ORD–CD curves were obtained in dioxane on a Durrum-Jasco J-20 ORD/CD spectropolarimeter. Potassium analyses were obtained by atomic absorption spectrophotometry on a Perkin-Elmer instrument, Model 403. Other elemental analyses were also obtained on a Perkin-Elmer instrument, Model 240.

**7α,4-(Aminomethylidyne)-5-cyano-17-hydroxy-3-oxo-5β,17α-pregnane-21-carboxylic Acid γ-Lactone (3).** The procedure of Christiansen and Johnson[5] was employed. A solution of canrenone (**2**, 50.5 g, 0.15 mol) and KCN (49.9 g, 0.77 mol) in MeOH (575 ml), EtOAc (80 ml), and $H_2O$ (160 ml) was refluxed with stirring for 4.5 hr.

After standing at room temperature overnight, the solvent was removed in vacuo. The residual brown oil was dissolved in $H_2O$ and neutralized to pH 7 with dilute HCl. (Note: this operation was carried out in a well-ventilated hood. Liberated HCN was swept with nitrogen into excess NaOH solution and ultimately destroyed with NaOCl solution.) The resulting precipitate was filtered, washed with distilled water, and air-dried. This material was suspended in $CH_2Cl_2$ (1 l.) and extracted three times with 6 *N* HCl (200-ml portions). The acid extracts were combined and brought to pH 7 by the addition of sodium hydroxide pellets while cooling with an ice bath. The resulting tan precipitate was filtered, washed with distilled water by decantation, and dried in a vacuum oven to give 24.9 g (41.5%) of crude **3**, mp 272–278°. Recrystallization of this material from acetone gave analytically pure material: mp 278–283°; $[\alpha]_D$ −104° (*c* 1.025); $\lambda_{max}$ 301 mμ (ε 17,100); ν 3440,

2230, 1780, 1650, 1622 $cm^{-1}$; NMR 0.95 (C-18), 1.17 ppm (C-19). Anal. ($C_{24}H_{30}N_2O_3$) C, H, N.

**4α,7α-Carbonyl-5-cyano-17-hydroxy-3-oxo-5β,17α-pregnane-21-carboxylic Acid γ-Lactone** (4). A slurry of amine **3** (25 g, 0.063 mol) in 1 *N* HCl (400 ml) was heated on the steam bath for 5 hr with vigorous mechanical stirring. The reaction mixture was chilled, filtered, and dried to give 24.7 g (98%) of crude 4, mp 287–291°. An analytical sample was prepared by recrystallization of the material from *i*-PrOH or MeOH: mp 287–291°; $[\alpha]D$ +51° (*c* 1.036); $\lambda_{max}$ 304 mμ (ε <1000); ν 1765, 1775, 2240, 1710 $cm^{-1}$; NMR 0.97 (C-18), 1.37 (C-19), 3.32 ppm (C-4, exchangeable). Anal. ($C_{24}H_{29}NO_4$) C, H, N.

**17-Hydroxy-3-oxo-17α-pregn-4-ene-7α,21-dicarboxylic Acid Methyl Ester γ-Lactone** (5). Sodium methoxide was prepared by the addition of sodium metal (1.3 g, 0.057 g-atom) to anhydrous methanol (150 ml). Compound 4 (2.10 g, 0.005 mol) was added and the solution was refluxed with stirring for 25 hr.

The reaction mixture was allowed to cool to room temperature, concentrated in vacuo to 50 ml, and poured onto 3 *N* HCl (300 ml). The resulting slurry was stirred at room temperature for 1 hr, chilled in the refrigerator, and filtered to give 1.90 g of **5** as a white powder. This material was dried and recrystallized from methanol to give 1.36 g in two crops, mp 193–195°. An analytical sample was prepared by a second recrystallization from methanol: mp 193–195°; $[\alpha]D$ +32° (*c* 1.032); $\lambda_{max}$ 242 mμ (ε 15,200); ν (KBr) 1785, 1730, 1676 $cm^{-1}$; NMR 2.83 (C-7), 3.63 ($-OCH_3$), 0.98 (C-18), 1.23 ppm (C-19). Anal. ($C_{24}H_{32}O_5$) C, H.

**17-Hydroxy-3-oxo-17α-pregn-4-ene-7β,21-dicarboxylic Acid Methyl Ester γ-Lactone (6a).** Chromatography of the recrystallization mother liquors of **5** led to the isolation of **6a**. A typical procedure is described herein. Mother liquors (4.8 g) were chromatographed on Mallinckrodt SilicAR CC-7 (400 g) using varying mixtures of benzene and ethyl acetate as eluents. Early cuts of the 15% EtOAc–$C_6H_6$ fraction gave compound **6a** (1.2 g) as a white crystalline product. This material was recrystallized from acetone to give analytically pure material: mp 238–240°; $[\alpha]D$ +33° (*c* 1.066); $\lambda_{max}$ 239 mμ (ε 16,900); ν 1768, 1734, 1670, 1625 $cm^{-1}$; NMR 3.64 ($-OCH_3$), 5.74 (C-4), 0.98 (C-18), 1.24 ppm (C-19). Anal. ($C_{24}H_{32}O_5$) C, H.

Succeeding cuts of the 15% EtOAc–$C_6H_6$ fraction yielded a mixture of **5** and **6a** (1.4 g) as an oil. Finally, crystalline **5** (0.61 g) was obtained on further elution with this solvent mixture.

**17-Hydroxy-3-oxo-17α-pregn-4-ene-7α,21-dicarboxylic Acid γ-Lactone (7a).** Analytically pure methyl ester **5** (10.0 g, 0.025 mol) was dissolved in a solution of methanol (260 ml) and 5% aqueous KOH solution (140 ml). The reaction mixture was refluxed for 20 hr, cooled, and concentrated in vacuo to 100 ml. This residual aqueous solution was filtered and acidified to pH 2 using dilute HCl with vigorous sitrring. After stirring for 3 hr, the granular precipitate was filtered, air-dried briefly, and dissolved in $CH_2Cl_2$ (350 ml).

The organic layer was washed once with saturated aqueous NaCl solution and four times with aqueous 5% $KHCO_3$ solution. The basic extracts were acidified as above and the white precipitate was filtered to give 5.0 g of **7a** as a fine white powder after drying at 50° under vacuum: mp 255–260° dec; $[\alpha]^{22}D$ −24° (*c* 0.997); ν 1668, 1711, 1740 as shoulder on 1770, 3440–2420, 3520, 3700 $cm^{-1}$; $\lambda_{max}$ 244 mμ (ε 14,700); NMR 5.74 (C-4), 2.87 (C-7), 1.23 (C-18), 0.97 (C-19), 7.76 ppm (1 H exchangeable). Anal. ($C_{23}H_{30}O_5$) C, H.

From the $CH_2Cl_2$ layer, after drying ($Na_2SO_4$, $MgSO_4$) was obtained 3.8 g of neutral material, composed mostly of methyl ester **5**. This, when treated with 5% aqueous KOH (50 ml) in MeOH (100 ml) at reflux for 4 hr and worked up as above, yielded an additional 2.0 g of **7a** for a total yield of 72.5%.

**17-Hydroxy-3-oxo-17α-pregn-4-ene-7α,21-dicarboxylic Acid γ-Lactone Anhydride with Isobutyl Hydrogen Carbonate (7b).** To a stirred, cold (−10°) solution of acid **7a** (2.21 g, 5.7 mmol) and *N*-methylmorpholine (0.55 ml) in THF (25 ml) was added isobutyl chloroformate (0.62 ml, 0.64 g, 4.68 mmol). An immediate white precipitate of *N*-methylmorpholine hydrochloride appeared.

After 10 min, the precipitate was filtered and the filtrate concentrated in vacuo to give 2.16 g (79%) of a light yellow oil that crystallized on standing in the refrigerator. This crude material was suitable for use in subsequent esterification reactions.

Recrystallization of a portion of this material from Skellysolve B furnished an analytical sample: mp 144–146°; $\lambda_{max}$ 240 mμ (ε 16,500); ν 1820, 1675, 1775 $cm^{-1}$; NMR 5.80 (C-4), 4.07 ppm (d, *J* = 5 Hz, $-OCH_2CHMe_2$). Anal. ($C_{28}H_{38}O_7$) C, H.

**General Procedure for Preparation of Esters from Anhydride 7b.** Anhydride **7b** was dissolved in the appropriate alcohol (*c* range 1.3–10 g of steroid per 100 ml of alcohol) and the solution heated at reflux (or on the steam bath where otherwise noted) for an extended period of time (see Table II). At the end of the reaction period, the alcohol was stripped in vacuo and the residual crude ester dissolved in ethyl acetate. This solution was extracted three times with 5% aqueous $KHCO_3$ solution and once with saturated aqueous NaCl solution and dried ($Na_2SO_4$, $MgSO_4$).

In the case of **7g**, the crude ester so isolated was purified by direct recrystallization from MeOH. All other esters were first chromatographed. Compounds **7c** and **7e** were subjected to column chromatography on Mallinckrodt SilicAR CC-7 (adsorbent:substrate weight ratio 30:1); the former was eluted with a 15% EtOAc–$C_6H_6$ mixture and the latter with a 10% EtOAc–$C_6H_6$ mixture. Esters **7d,f,h,i** were chromatographed on E. Merck $SiO_2$ (weight ratio 100:1) and all were eluted with either 10 or 15% EtOAc–$C_6H_6$ mixture.

Compound **7j** was subjected to dry column chromatography on Mallinckrodt SilicAR CC-7 (weight ratio 200:1). Analytical samples were obtained by recrystallization from MeOH and, in the case of **7j**, from ethyl ether.

The uv spectral data for these compounds are listed in Table II. The infrared spectra of all of these compounds in $CHCl_3$ possessed bands at approximately 1775 (lactone), 1730 (ester), 1670 (conjugated ketone), and 1625 $cm^{-1}$ (C=C). The NMR spectra ($CDCl_3$) of all these esters showed signals in the vicinity of 5.77 (C-4) and 2.83 ppm (equatorial H on C-7) as well as signals for the protons of the particular ester function.

**17-Hydroxy-3-oxo-7-thio-17α-pregn-4-ene-7α,21-dicarboxylic Acid *S*-Ethyl Ester γ-Lactone (7k).** The mixed anhydride was prepared from acid **7a** (1.5 g, 3.89 mmol) and ethyl chloroformate (1.71 g, 15.18 mmol) at 0° with stirring in a solution of triethylamine (5 ml) and $CH_2Cl_2$ (4 ml). The reaction was allowed to come to room temperature and stirred overnight. Excess ethanethiol (2 ml) was added and the reaction stirred for 24 hr at room temperature.

The reaction mixture was concentrated in vacuo. The residue was dissolved in $CH_2Cl_2$ (50 ml) and washed successively with 1 *N* HCl, $H_2O$, 5% $NaHCO_3$, and $H_2O$. After drying ($Na_2SO_4$, $MgSO_4$), 1.47 g of a brown foam was obtained. This material was subjected to dry column chromatography on Mallinckrodt SilicAR CC-7 (200 g after equilibration overnight with 16 ml of water) using 12% EtOAc–$C_6H_6$ as the eluent. Two fractions of good purity were obtained: 0.31 g, mp 202–204°; 0.10 g, mp 200–202°. An analytical sample was obtained by simple digestion of the former sample with ethyl ether: mp 202–204°; $[\alpha]D$ −64° (*c* 0.664); $\lambda_{max}$ 244 mμ (ε 18,300); ν 1770, 1682, 1624 $cm^{-1}$. Anal. ($C_{25}H_{34}O_4S$) C, H, S.

**17-Hydroxy-3-oxo-17α-pregna-1,4-diene-7α,21-dicarboxylic Acid Methyl Ester γ-Lactone (8a).** A solution of methyl ester **5** (3.19 g, 0.080 mol) and dichlorodicyanobenzoquinone (2.73 g, 0.012 mmol) in dioxane (150 ml) was refluxed with stirring for 24 hr. The reaction mixture was cooled and stripped in vacuo to give a tan solid. This material was digested with $CH_2Cl_2$ (200 ml) and the insoluble material was filtered. The filtrate was extracted successively with 2% aqueous $Na_2SO_3$, saturated NaCl, 5% NaOH, and saturated NaCl. After drying and evaporation of solvent, there was obtained 2.0 g of a brown foam.

This material was subjected to column chromatography on E. Merck $SiO_2$ (adsorbent:substrate weight ratio 200:1). Elution with 15% EtOAc–$C_6H_6$ gave 0.45 g of the desired product **8a**. Recrystallization from methanol gave 0.36 g of analytical material: mp 234–237°; $[\alpha]D$ +9° (*c* 0.942); $\lambda_{max}$ 240 mμ (ε 19,680); ν 1774, 1740, 1670, 1630, 1610 $cm^{-1}$; NMR 7.40 (d, *J* = 10 Hz, C-1), 6.02 (C-4), 6.23 (d of d, *J* = 10 and 2 Hz, C-2), 3.62 ($OCH_3$), 1.25 (C-19), 1.00 ppm (C-18). Anal. ($C_{24}H_{30}O_5$) C, H.

**17-Hydroxy-3-oxo-17α-pregna-1,4-diene-7α,21-dicarboxylic Acid Isopropyl Ester γ-Lactone (8b).** A solution of ester **7e** (1.30 g, 3.0 mmol) and DDQ (0.81 g, 3.5 mmol) in dioxane (125 ml) was refluxed vigorously with stirring for 16 hr. The reaction was worked up in the same manner as for compound **8a** to give 1.0 g of a crude brown oil. This material was chromatographed on Mallinckrodt SilicAR CC-7 (adsorbent:steroid ratio 50:1). Elution with 10 and 15% EtOAc–$C_6H_6$ yielded 0.200 g of **8b**, homogeneous on TLC. An analytical sample was obtained by recrystallization from ethyl ether: mp 233–235°; $[\alpha]D$ −10° (*c* 0.692); ν 1771, 1728, 1665 $cm^{-1}$; $\lambda_{max}$ 244 mμ (ε 16,120). Anal. ($C_{26}H_{34}O_5$) C, H.

**17-Hydroxy-3-oxo-17α-pregna-4,6-diene-7,21-dicarboxylic Acid Methyl Ester γ-Lactone (9).** The procedure of Turner and Ringold[10] was employed. Anhydrous HCl gas was bubbled at a moderate rate for 2 min through a stirred solution of **6a** (0.51 g,

1.27 mmol) in dry dioxane (50 ml). A cold water bath was used to protect against any undue heating. Dichlorodicyanobenzoquinone (DDQ) (0.30 g, 1.32 mmol) was then added and after a few minutes, a tan precipitate appeared. The reaction was stirred for 1.75 hr at room temperature during which time an increasing amount of precipitate was observed.

The reaction mixture was filtered to give 0.28 g of reduced DDQ. The filtrate was stripped in vacuo. The yellow gummy residue was dissolved in $CH_2Cl_2$ and filtered to remove a faint turbidity. This filtrate was extracted twice with 2% $Na_2SO_3$ solution, once with saturated NaCl solution, twice with 5% KOH solution, and twice with saturated NaCl solution. The $CH_2Cl_2$ solution was dried ($Na_2SO_4$, $MgSO_4$) and stripped in vacuo to give 0.39 g of a yellow gum. This material was chromatographed on Mallinckrodt SilicAR CC-7 (40 g) using mixtures of benzene and ethyl acetate as eluents. The product was eluted with 5% EtOAc–$C_6H_6$ and recrystallized from MeOH to give 128 mg of analytically pure **9**: mp 207–210°; $[\alpha]D$ +241° (*c* 0.115); $\lambda_{max}$ 283–285 mμ (ε 27,800); ν 1770, 1725, 1669 $cm^{-1}$; NMR 5.84 (C-4), 6.60 (d, $J = 2.5$ Hz), 3.80 ($OCH_3$), 1.12 ppm (C-18, 19). Anal. ($C_{24}H_{30}O_5$) C, H.

**General Procedure for the Preparation of Potassium Salts 10 and 11.** All potassium salts listed in Table III were prepared in exactly the same way. The steroid was slurried in methanol (0.07–0.09 g/ml) and treated with 0.95–0.99 equiv of aqueous standardized KOH solution. The resulting heterogeneous mixture was stirred at room temperature overnight and warmed at 60–65° for 20 min. This yielded a light yellow solution that was concentrated in vacuo and dried by azeotroping with ethanol. The residual material, either a white solid or a yellow oil, was treated with EtOAc to give a white flocculent solid. This was filtered, washed several times with EtOAc, and dried on the filter to give the potassium salt of the opened lactone. An analytical sample was obtained by further drying at 80° in vacuo. These materials were characterized by obtaining potassium analyses and their ir, uv, and NMR spectra. The uv spectral data are included in Table III. The infrared spectra of these compounds in KBr possessed bands at approximately 1735 (ester), 1680 (conjugated ketone), 1625 (C=C), and 1570 $cm^{-1}$ ($CO_2^-$). The NMR spectra in $D_2O$ showed signals in the vicinity of 6.15 (C-4) and 3.08 ppm (equatorial H on C-7) as well as the expected signals for the C-18 and C-19 methyl groups and the particular ester function.

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