Table I. Relative Binding Affinities

compd	relative binding affinity[a]
17β-estradiol	100
17α-[(phenylseleno)methyl]-17β-estradiol (8)	11.8
16β-(methylseleno)-17α-estradiol 3-methyl ether (1)	<0.1
16α-(phenylseleno)estrone 3-methyl ether (2)	<0.1
3-(selenocyanato)estrone (9)	<0.1

[a] Calculated at $B/B_0 = 50\%$.[15]

to give 150 mg (21%) of **9**: mp 164–165 °C; NMR δ 0.91 (s, 3 H, $C_{18}H_3$), 7.25–7.37 (m, 3 H, Ar H); mass spectrum, *m/e* 360 (M^+). Anal. Calcd for $C_{19}H_{21}NOSe$: C, 63.67; H, 5.91. Found: C, 63.65; H, 6.00.

Binding Studies. The binding of the selenosteroids was analyzed by the [17β-^{3}H]estradiol exchange assay as described by Anderson.[5] Immature (21–25 day) female Sprague–Dawley rats were injected subcutaneously with 5 mg of 17β-estradiol in 0.5 mL of 0.9% NaCl. The animals were killed 45 min to 1 h after injection and the uterine nuclear fraction in TE buffer (0.01 M Tris-HCl, pH 7.4, containing 1.5 mM EDTA) was incubated at 37 °C for 30 min with 2×10^{-8} M [17β-^{3}H]estradiol. Following incubation, the nuclear fractions were washed with TE buffer followed by centrifugation at 800*g* for 10 min. The washed pellet was extracted with ethanol. The extract was added to 10 mL of scintillation fluid [99.5% toluene, 0.45% 2,5-diphenyloxazole, 0.05% 1,4-bis(5-phenyloxazol-2-yl)benzene]. The amount of [17β-^{3}H]estradiol bound was determined with an internal sample liquid scintillation counting system. For competitive-inhibition experiments, various concentrations (10^{-10}–10^{-5} M) of nonradioactive 17β-estradiol or of selenosteroid were added to the reaction mixture together with [17β-^{3}H]estradiol and incubated as described. The results are summarized in Table I.

Registry No. **1a**, 77862-28-3; **2a**, 77942-76-8; **2b**, 77862-29-4; **2c**, 77862-30-7; **3a**, 28336-31-4; **5a**, 1624-62-0; **5a** toluenesulfonylhydrazone, 32164-54-8; **5b**, 7103-48-2; **6b**, 77862-31-8; **6d**, 68687-35-4; **7**, 18119-98-7; **8b**, 77862-32-9; **8c**, 77862-33-0; **8d**, 77882-19-0; **9**, 77862-34-1; 17β-estradiol, 50-28-2; **3a** α-epoxide, 28336-32-5; **3a** β-epoxide, 28344-30-1.

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Facile, High-Yield Synthesis of Spiro C-17 Steroidal Oxetan-3′-ones

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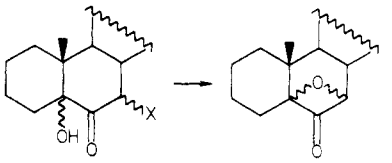
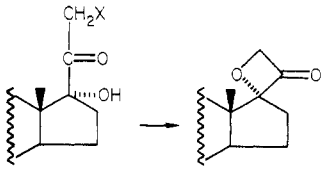
Received March 2, 1981

The facile, high-yield conversion of C-17 α-keto mesylates of glucocorticoids to spiro C-17 oxetan-3′-ones is described. This reaction, involving treatment with strong base (KOH, NaOMe, or KO-*t*-Bu) in EtOH or THF, represents a major improvement for the preparation of these steroid derivatives.

Oxetan-3-ones are four-membered-ring compounds of which only a few examples are known.[1,2] For some reason, steroidal oxetan-3′-ones are readily isolated.[3-9] While there are several methods of preparing oxetan-3-ones (by oxidation,[10-13] by acid-catalyzed decomposition of diazo ketones,[2,14] by photochemical [$_\pi$2 + $_\pi$2] cycloaddition,[15] by epoxidation of allenes,[16] and by intramolecular displacement reactions[3-9]), only intramolecular displacements have been used to prepare steroidal oxetan-3′-ones. These displacements work well for the selective preparation of the α or β 5,7-oxetan-3′-ones (**1** → **2**).[7-9] In contrast, the synthesis of C-17 oxetan-3′-ones (**3** → **4**) requires much more forcing reaction conditions (16 h/80 °C to 24 h/110 °C vs. 7 min/room temperature to 2 h/100 °C for **1** → **2**) and proceeds in poor yields.[3-6] Previous attempts to increase the rate of reaction of **3** → **4** have been unsuccessful.[6] Here we report apparently general conditions which overcome these problems and rapidly provide the C-17 oxetan-3′-ones (**4**) in high yield.



1 **2**



3 **4**

Results and Discussion

During our recent investigation of α-keto mesylates such as **3** (X = OSO_2CH_3),[17] we noted that no reaction of the

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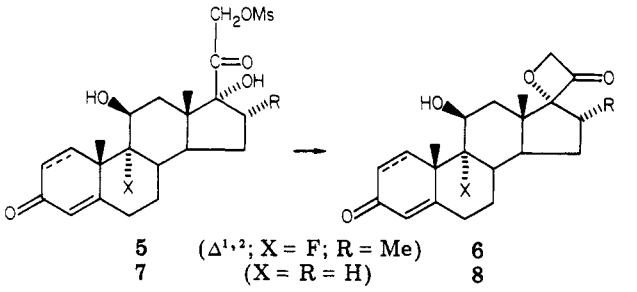
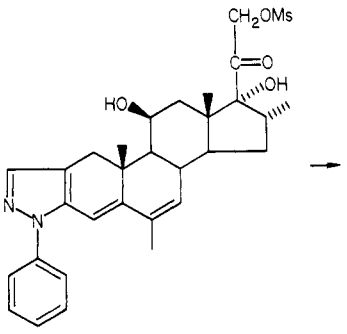
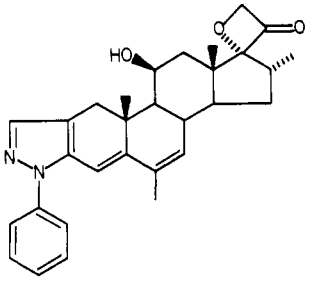
mesylate **3** occurs in EtOH containing 7 equiv of triethylamine, even after 30 h at room temperature. Stronger bases such as KOH are destructive to steroidal C-17 dihydroxyacetone side chains (**3**, X = OH), which are readily cleaved to give 17-keto steroids and other products.[18] However, the α-keto mesylate derivatives (**3**, X = OSO_2CH_3) follow a different course and rapidly react in the presence of KOH, NaOMe, or KO-*t*-Bu to give predominantly the oxetan-3′-ones **4**. Most of our studies have been with dexamethasone 21-mesylate (**5**), but identical results have been obtained with the C-21 mesylates of cortisol (**7**) and deacylcortivazol[19] (**9**).



5 ($\Delta^{1,2}$; X = F; R = Me) **6**
7 (X = R = H) **8**



9

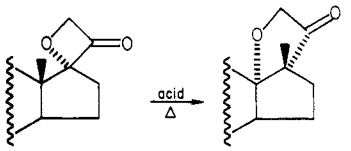


10

Reactions of α-keto mesylates with alkali fluorides in DMF or Me_2SO have previously been described for the preparation of C-17 steroidal oxetan-3′-ones but the yields were low (or not reported).[3-6] In contrast, the reaction of **5** in EtOH with 0.02–0.1 M NaOMe is completed in ≤10 min at room temperature and affords essentially two products—the oxetan-3′-one **6** and the expected substitution product dexamethasone 21-ethyl ether (**3**, where X = OCH_2CH_3) in a ratio of about 3:1, as determined by TLC. The formation of oxetanone **6** is slower at 0 °C and in MeOH as solvent. Increased temperatures appear to accelerate the production of oxetanone **6** in EtOH and to decrease the amount of side reactions. Substitution of potassium *tert*-butoxide as the base gave an even cleaner reaction. Thus treatment of the mesylates **5**, **7**, and **9** with ~1.5 equiv of potassium *tert*-butoxide in boiling EtOH for ≤4 min afforded the respective oxetanones **6**, **8**, and **10** in 75–83% yield after purification by preparative TLC.[20]

In order to avoid the production of 21-ethyl ether substitution products[9] (which appear to have R_f's slightly less than those of the oxetan-3′-ones), we examined the reaction in an aprotic solvent. Treatment of the mesylates **5**, **7**, and **9** in THF at room temperature with 1.5 equiv of potassium *tert*-butoxide for ≤4 min was found to give oxetanones **6**, **8**, and **10** in 76–86% yield after preparative TLC.

Our workup conditions are similar to those which cause deconjugation of α,β-unsaturated ketones.[21] However the UV spectra confirmed the conjugated structures of **8** and **10**. The presence of the 1,4-dien-3-one structure in **6** was supported by the characteristic three-proton pattern at 7.28–6.00 ppm in the NMR spectrum of oxetanone **6**. Acid has been reported to cause a rearrangement of oxetanones to the fused [3.3.0] system (e.g., **11**, eq 1).[3,4,22] This possibility was excluded in the present case on the basis of the characteristic IR bands of oxetan-3-ones[3,4,23] at ~1810 cm^{-1} that were observed for **6**, **8**, and **10**. Furthermore the deshielding of the C-21 methylene protons of **6** by 0.7 ppm is indicative of a four-membered, rather than a five-membered, ring.[24] Final proof came from an X-ray crystallographic structure determination of **6**.[25]



11 (1)

The above-described conditions thus permit, for the first time, a facile, high-yield synthesis of spiro C-17 steroidal oxetan-3′-ones (**4**). When combined with the ready accessibility of C-21 steroidal mesylates,[17,26] our method provides a high yield conversion of the C-17 dihydroxyacetone group of glucocorticoid steroids into oxetan-3′-ones. Thus we have converted dexamethasone, via the mesylate **5**, to TLC pure oxetanone **6** in an overall yield of 82%. Furthermore, our method of choice (potassium *tert*-butoxide/THF/room temperature/≤4 min) is relatively mild and should be compatible with a large variety of functional groups.

Not much is known about the chemistry of oxetan-3-ones. However, in view of the strain incurred by incorporating an sp^2 carbonyl carbon in a four-membered ring and the increased reactivity due to an electronegative oxygen at the α and α′ positions, we expected that addition reactions to the ketone would be facilitated. The possible addition of thiols to give hemithioketals was of particular interest since we previously had observed the intramolecular addition of thiols such as **12** to give the cyclic product **13**.[27] Furthermore, several lines of evidence suggest that such a hemithioketal might be involved in the binding of glucocorticoid steroids to their specific recep-

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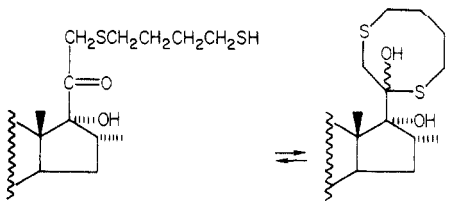

12 13

tors.[27-30] Unfortunately, no appreciable hemithioketal was formed in a $CHCl_3$ solution of oxetanone **6** and ethanethiol with or without triethylamine, as detected by an absence of significant change in the intensity of the 1815-cm^{-1} oxetan-3-one band in the IR spectrum of **6**.

There is very little biological data on steroidal oxetan-3′-ones.[4,6,31] Considering the antimineralocorticoid activities of the C-17 butyrolactone spiroannulated steroids spironolactone and canrenone,[32] we examined the oxetanones **6**, **8**, and **10** derived from glucocorticoid steroids[19] for antiglucocorticoid activity. We have found that **6** and **10** are both biologically active. Furthermore, dexamethasone–oxetanone (**6**) appears to be at least as potent as, and possibly more potent than, any known reversible antiglucocorticoid in whole cell systems.[28,33-35] These results are described in detail elsewhere.[36]

Until now, it has been difficult to readily obtain spiro C-17 steroidal oxetan-3′-ones. Our synthetic procedure has removed this barrier and should facilitate further investigations of this interesting modification of steroid hormones.

Experimental Section

Instrumentation. Melting points were determined on a Fisher-Jones hot-stage melting-point apparatus and are corrected. Beckman 4230 grating infrared and Cary 14 spectrophotometers were used to record IR and UV spectra, respectively. Low-resolution mass spectra were obtained on a Finnigan 1015D (chemical-ionization (CI) mode) spectrometer by Mr. Noel Whittaker of the Laboratory of Chemistry, NIAMDD. Nuclear magnetic resonance (220 mHZ) spectra were acquired by Dr. Herman Ziffer of the Laboratory of Chemical Physics, NIAMDD. Analyses were performed by the Microanalytical Section of the Laboratory of Chemistry, NIAMDD, Bethesda, MD.

Chemicals. Potassium *tert*-butoxide and THF (99.9% pure) were purchased from Aldrich. Silica gel TLC plates were obtained from Analtech. Our syntheses of dexamethasone 21-mesylate (**5**),[17] cortisol 21-mesylate (**7**),[26] and deacylcortivazol 21-mesylate (**9**)[37] are described elsewhere.

General Preparation of Steroidal Oxetan-3′-ones with THF as Solvent at Room Temperature. The mesylate was dissolved in THF (13 mL per mmol of mesylate) at room temperature. The solution was briefly flushed with argon and then treated with 1.5 equiv of potassium *tert*-butoxide in THF to give immediately a yellow to dark orange solution usually accompanied by a precipitate (mesylate concentration 50 mM). After 4 min, 1.5 equiv of hydrochloric acid was added to give a clear, two-phase solution. Additon of H_2O (40 mL per mmol of mesylate) followed by removal of THF from the mixture under reduced pressure and extraction of the precipitated product with CH_2Cl_2 gave, after drying over $MgSO_4$ and removing the solvent under reduced pressure, the crude solid product. TLC-pure material was obtained by dissolution of the solid in $CHCl_3$ and preparative thin-layer chromatography on silica gel.

Dexamethasone–oxetanone **6** was obtained in 84% yield after chromatography with 6% MeOH in $CHCl_3$ (mp 255–260 °C with evolution of gas at 259–260 °C). The same chromatographic system gave a 76% yield of cortisol–oxetanone **8** (mp 235–239 °C). Chromatography with 4% MeOH in $CHCl_3$ afforded an 86% yield of deacylcortivazol-oxetanone **10** (dec 271–277 °C).

General Preparation of Steroidal Oxetan-3′-ones in Boiling Absolute Ethanol. The mesylate was heated to boiling in absolute ethanol and treated with 1.5 equiv of potassium *tert*-butoxide in absolute ethanol (mesylate concentration is 35–50 mM). The hot solution was neutralized with 1.5 equiv of hydrochloric acid and the solvent was removed under reduced pressure (for the preparation of dexamethasone–oxetanone **6**, the resulting precipitate was first removed by filtration). The residue was washed with H_2O and then purified by chromatography on silica gel.

Dexamethasone–oxetanone **6** was purified by column chromatography (three-step gradient of $CHCl_3$ to 5% acetone in $CHCl_3$) to give TLC-pure material in 80% yield (mp 252–259 °C). Preparative thin-layer chromatography afforded cortisol–oxetanone **8** (10% MeOH in $CHCl_3$; mp 236–238 °C) in 75% yield and deacylcortivazol–oxetanone **10** (7% MeOH in $CHCl_3$; dec 274–275 °C) in 83% yield.

Dexamethasone–oxetanone 6: mp 252–254 °C (recrystallization from MeOH–Et_2O gave needles that melted with decomposition at 265 °C); IR (KBr) 3360 (br), 1813, 1660, 1615, 1605, 958, 888 cm^{-1}; chemical-ionization mass spectrum (with CH_4), m/e (relative intensity), 375 (MH^+, 100%); UV (absolute EtOH) λ_{max} 236 nm (ϵ 1.56 × 10^4); ^1H NMR (220 MHz, Me_2SO-d_6 ± D_2O) 7.28 (H_1, 1 H, d, J = 10 Hz), 6.21 (H_2, 1 H, br d, J = 10 Hz), 6.00 (H_4, 1 H, s), 5.45 (C_{11}–OH, 1 H, d, $J \simeq$ 4 Hz), 4.98 (H_{21}, 2 H, s), ~4.18 (H_{11}, 1 H, br d in Me_2SO-d_6/D_2O with J = 10 Hz), 1.49 (C_{10}–CH_3, s), 1.12 (C_{13}–CH_3, s), and 1.01 ppm (C_{16}–CH_3, s). Anal. Calcd for $C_{22}H_{27}O_4F$ (mol wt 374.44): C, 70.56; H, 7.27. Found: C, 70.34; H, 7.39.

Cortisol-oxetanone 8: mp 236–240 °C (lit. mp 237–243 °C dec[4] and 242–244 °C[3]); IR (KBr) 3415, 1807, 1650, 1618, 1233, 1185, 944 cm^{-1}; chemical-ionization mass spectrum (with CH_4), m/e (relative intensity) 345 (MH^+, 100%); UV (absolute EtOH) λ_{max} 242 nm (ϵ 1.47 × 10^4).

Deacylcortivazol-oxetanone 10: mp 275–277 °C dec (recrystallized from $CHCl_3$/petroleum ether); IR (KBr) 3440, 1816, 1601, 1505, 965 cm^{-1}; chemical-ionization mass spectrum (with CH_4), m/e (relative intensity) 471 (MH^+, 100%); UV (absolute EtOH) λ_{max} 315 nm (ϵ 1.89 × 10^4), 285 (shoulder, ϵ 1.58 × 10^4), 225 (shoulder, 1.14 × 10^4). Anal. Calcd for $C_{30}H_{34}N_2O_3$ (mol wt 470.59): C, 76.56; H, 7.28; N, 5.95. Found: C, 76.83; H, 7.03; N, 5.67.

Dexamethasone 21-Ethyl Ether. Dexamethasone 21-mesylate **5** (20 mg, 53 μmol) in 2 mL of absolute EtOH at room temperature was treated with 10 mg of sodium methoxide (185 μmol) for 1 h. The reaction solution was poured into H_2O, neutralized, and extracted with CH_2Cl_2. After the organic layer was dried over $MgSO_4$, preparative thin-layer chromatography (35:10 $CHCl_3$–acetone on silica gel) was used to isolate a minor product with an R_f slightly less than that of the major product, dexamethasone–oxetanone **6**. The minor product (mp 240–243 °C) was assigned the structure of the 21-ethyl ether on the basis of IR (KBr) (3500, 3440, 1719, 1663 cm^{-1}) and chemical-ionization mass spectra [(with NH_3) m/e (relative intensity) 421 (MH^+, 49%), 401 (MH^+–HF, 100%); (with NO) m/e 420 (M^+, 74%), 450 (M^+ + NO, 22%), 400 (M^+–HF, 100%)].

Registry No. **5**, 2265-22-7; **6**, 4089-36-5; **7**, 6677-96-9; **8**, 77826-00-7; **9**, 50630-90-5; **10**, 14000-45-4; dexamethasone 21-ethyl ether, 77826-01-8.

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