972, 935 cm^{-1}; ^1H NMR, see above section; TLC, R_f 0.37 (B, I, slow). Anal. Calcd for the monohydrate $C_{11}H_{24}NO_6P \cdot H_2O$ (mol wt 315): C, 41.90; H, 8.25; N, 4.44; P, 9.84. Found: C, 41.99; H, 8.46; N, 4.17; P, 9.77.

***p*-Nitrophenyl 6-(*O*-Phosphorylcholine)hydroxyhexanoate (8).** The acid 7 was converted to the *p*-nitrophenyl ester 8 as follows: 247 mg (0.79 mmol, as hydrate) of 7 in 5 mL of DMF was treated with 0.40 g (1.70 mmol) of *p*-nitrophenyl trifluoroacetate (Aldrich). After the mixture was stirred for 5 min, during which time 7 slowly dissolved, 0.10 mL (0.86 mmol) of 2,6-lutidine in 1.0 mL of DMF was added over 1 min. A TLC after 1 h showed extensive formation of 8. Another 0.20 g of *p*-nitrophenyl trifluoroacetate was added, followed by another 0.10 mL of lutidine in 1.0 mL of DMF. After the reaction mixture was at held at room temperature for 2 h more, ether was added to precipitate 8. The supernatant was withdrawn, and the oily precipitate (8) was redissolved in acetonitrile and then reprecipitated again with ether. This sequence was repeated once again to give, after removal of the last traces of solvents, 305 mg of 8 as a clear viscous oil (93% yield, assuming mol wt 418). Quantitative yields have sometimes resulted with this procedure: IR (KBr) 3400 (br), 2900, 1750 (s), 1670, 1590 (aromatic), 1560 (aromatic), 1520 (NO_2), 1480, 1340 (NO_2), 1200 (br), 1075 (br), 970, 920, 860, 820 cm^{-1}; ^1H NMR (D_2O) δ 1.2–1.8 (envelope, 6, CH_2), 2.2–2.7 (m, 2, CH_2CO), 3.19 (s, 9, $(CH_3)_3N^+$), 3.4–4.0 (m, 4, CH_2N and $POCH_2$, overlapping), 4.0–4.5 (m, 2, NCH_2CH_2OP), and two two-proton doublets (J = 9 Hz) at δ 7.08 ($H_{2,6}$) and 8.0 ($H_{3,5}$) for the aromatic protons; TLC, R_f 0.58 (B, F, I (slow)), immediate yellow color with NH_3 vapor, only traces of lutidine (0.50) and *p*-nitrophenol ($R_f \sim 1$) detected by fluorescence; UV λ_{max} (CH_3OH) 269 nm (log ϵ 3.81); λ_{max} [0.2 N NaOH–CH_3OH (1:1)] 403 nm (log ϵ 4.13).

Diisopropylethylamine or DBN worked well as nonnucleophilic bases to form 8; however, they could not be completely removed from the preparations and caused the slow decomposition of 8 in roughly a week. Traces of the weaker hindered base 2,6-lutidine are evidently not disadvantageous, as preparations of 8 have been kept for many months in the refrigerator. Traces of *p*-nitrophenol are easily removed by chromatography in CH_3OH on Sephadex LH-20 where it greatly lags behind either 7 or 8.

Acknowledgment. The syntheses of 5 and 8 were undertaken as a direct result of discussions with M. Potter and D. M. Segal, respectively, during which discussions, general structural requirements were posed. The assistance of J. J. Moore in the preparation of 8 is appreciated.

Registry No. 1, 4167-02-6; 2, 5402-55-1; 3, 73839-20-0; 4, 73839-21-1; 5, 73839-22-2; 6, 73839-23-3; 7, 73839-24-4; 8, 73785-43-0; 2-bromoethanol, 540-51-2; 2-(2-thienyl)ethyl 2-bromoethyl phosphate, 73855-19-3; mercuric acetate, 1600-27-7; *tert*-butyl 6-(*O*-(2-bromoethyl)phosphoryl)hydroxyhexanoate, 73839-25-5; $POCl_3$, 10025-87-3.

α-Keto Mesylate: A Reactive, Thiol-Specific Functional Group

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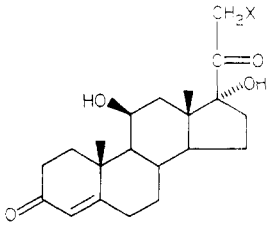
A systematic study of the reactivity of α-keto mesylates with various nucleophiles (i.e., carboxylate, –OH, imidazole, $-NH_2$, thiol acid anion, and –SH) under mildly basic conditions is reported. α-Keto mesylates do not react with imidazole or hydroxyl groups, react extremely slowly (if at all) with carboxylate and primary amines, and react several thousand times faster with thiols and thiol acid anions. The very rapid reaction with thiols occurs only with the dissociated thiolate anion. The addition of a β-hydroxyl group to α-keto mesylates accelerates the reaction with thiolate anions by a factor of 3–12 in acetone but has no effect on reactions run in dimethylformamide. α-Keto mesylates exhibit the same selectivity for thiolate anions, as compared to amines, as do α-keto chlorides. In view of this reactivity and selectivity, the α-keto mesylate appears to be a promising functional group for the electrophilic affinity labeling of biological macromolecules in weakly basic solutions.

α-Keto mesylates are relatively common in synthetic organic chemistry literature.[1-5] Since their main utility has been as a reactive intermediate in the preparation of other products,[1,3-6] we were surprised to find that no systematic study of the reactivity of α-keto mesylates exists.[4] During our preparation of several C_{21}-substituted glucocorticoids,[7-9] we found that α-keto mesylates possess very high, and selective, reactivity for thiols. Herein we describe the results of our studies on α-keto mesylates, including a comparison of the reactivity of α-keto mesylates with the closely related α-keto chlorides and with β-hydroxy-α-keto mesylates, which are even more reactive under some conditions.



1, X = $OSCH_3$ (O)

2, X = $SCCH_3$ (O)

3, X = $SCO\text{-}CH_2\text{-}CH_3$ (S)

Results

Reactivity of β-Hydroxy-α-keto Mesylates. Cortisol-21-mesylate (1) reacts with thiol acid anions such as potassium thiolacetate and potassium *O*-ethyl xanthate in acetone at 0 °C in less than 20 min to give high yields of 2 and 3, respectively.[9] Studies with another β-hydroxy-

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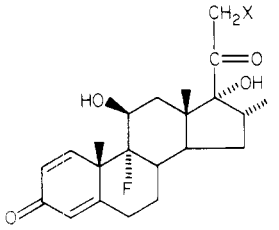
(1) British Patent 899 995 and 899 996, 1962; *Chem. Abstr.* **1962**, *57*, 13 842*f*.

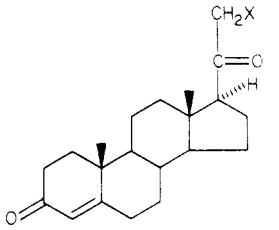
α-keto mesylate, i.e., dexamethasone-21-mesylate (4), revealed that the reaction with thiolate anions also is extremely fast and virtually quantitative. Thus methyl mercaptoacetate (MMA), 1,4-dithiobutane (DTB), β-mercaptoethanol (β-MERC), and 2-(*N*-(*tert*-butyloxy)-carbonyl)aminoethanethiol,[10] each in the presence of equimolar amounts of triethylamine, convert 4 completely to the respective products 5–8 in less than 10–20 min in



4, X = OSO_2CH_3
5, X = SCH_2COOCH_3
6, X = $S(CH_2)_4SH$
7, X = $S(CH_2)_2OH$
8, X = $S(CH_2)_2NHCO_2C(CH_3)_3$
9, X = SCH_2CH_3
10, X = $NHCH_2CH_2CH_3$
11, X = $OC(O)CH_3$
12, X = $S(CH_2)_3NH_2$
13, X = $S(CH_2)_5NH_2$

acetone at 0°C. The reaction of the mesylate 4 with ethanethiol (ET) under similar conditions takes longer (~1 h to give the thioether 9). While the reaction of 4 with MMA in the presence of triethylamine is over in ≤30 s at 0 °C, no reaction occurs with MMA during 90 min at 0 °C in the absence of triethylamine. Imidazole and ethanol (with added triethylamine) exhibited no reaction with 4 in acetone at 0 °C after 96 h. A mixture of 4 and *n*-propylamine gave some reaction of 4 but none of the expected amine 10 after 48 h at room temperature in acetone, during which time a parallel solution of *n*-propylamine in acetone gave virtually no products, as determined by TLC. The desired product 10 could be formed in fair yield, however, under the much more forcing conditions of *n*-propylamine in dimethylformamide at 64 °C for 2 h. Acetate anion in acetone at 0 °C with excess triethylamine reacted very slowly, but cleanly, with 4 to give the acetate 11—after 93 h, the reaction was about 30% complete. In direct competition experiments, β-mercaptoethanol (in acetone at 0 °C) and the α,ω-amino thiols of propane and pentane (in dimethylformamide[11] at room temperature) react with 4 exclusively via attack by sulfur to give 7, 12, and 13, respectively,[11] in 5–20 min.

Effect of β-OH on Reactivity of α-Keto Mesylates. The above studies with 1 and 4 involved mesylates of the relatively uncommon dihydroxyacetone structure. In order to assess the general applicability of simple α-keto mesylates, we selected 14 for further studies. As expected, 14



14, X = OSO_2CH_3
15, X = SCH_2COOCH_3
16, X = $S(CH_2)_4SH$
17, X = $S(CH_2)_2OH$
18, X = SCH_2CH_3
19, X = $S(CH_2)_3NH_2$
20, X = $S(CH_2)_5NH_2$
21, X = $NHCH_2CH_2CH_3$
22, X = Cl

rapidly reacted with thiolate anions (but not with free thiols), gave an extremely slow reaction with amines, and exhibited the same complete preference for reaction with $-S^-$ instead of $-NH_2$ when mixed with amino thiols. Thus, by use of the same conditions as for 4, MMA, DTB, and β-MERC each rapidly converted all of the mesylate 14 to the respective products 15–17; the reaction with ethanethiol to give 18 was, as with the mesylate 4, much slower. The reaction with MMA is extremely fast (complete in <30 s), while the other thiols required 1–2 h at 0 °C to consume all of the mesylate 14. Such a particularly rapid reaction with MMA was also observed with the β-hydroxy-α-keto mesylate 4 and may be related to the fact that the pK_a of the thiol of methyl mercaptoacetate is about two orders of magnitude lower than that of thiols such as DTB and β-MERC.[14] Because the reactions of MMA with the mesylates 4 and 14 were so fast, it was impossible to determine the relative rates of reaction. However, with the thiols DTB, β-MERC, and ET, the reaction of the simple α-keto mesylate 14 was 3–12 times slower than that of the β-hydroxy-α-keto mesylate 4. The choice of solvent also affects the relative reaction rates of α-keto vs. β-hydroxy-α-keto mesylates. Thus the reaction of 14 with α,ω-amino thiols in dimethylformamide is still completely specific for the thiol[11] to give 19 and 20 but, as with 4, is completed in 5–30 min. Displacement of methanesulfonate from 14 by amines is several orders of magnitude slower, as determined for *n*-propylamine. Thus the production of 21 from 14 proceeds in low yield after about 2 h in dimethylformamide at 65 °C and is just perceptable after 48 h at room temperature in acetone. In both cases, many other reaction products are also formed.

α-Keto Mesylates vs. α-Keto Chlorides. α-Keto chlorides, and other halides, are used extensively in organic synthesis and are often prepared via the unisolated α-keto mesylates.[3,5,6,15] We were particularly interested to see if there were any differences in the reactivity of these two similar reactive groups. The α-keto mesylate 14 and α-keto chloride 22 both reacted with the thiolate anions of MMA, DTB, and β-MERC with identical kinetics in acetone at 0 °C to give excellent yields of 15–17, respectively. Likewise, the rates of reaction of 14 and 22 with *n*-propylamine, as determined by TLC analysis, were the same in acetone at 25 °C and in dimethylformamide at 25 or 65 °C. Both 14 and 22 react rapidly and selectively with the thiol of the appropriate amino thiol to give 19 and 20.

(2) U.S. Patent 3 105 083, 1964; *Chem. Abstr.* **1964**, *60*, 3062g.
(3) Counsel, R. E.; Hong, B. H.; Willette, R. E.; Ranade, V. V. *Steroids* **1968**, *11*, 817–826.
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(10) For some reason, perhaps intramolecular hydrogen bonding with the amide N–H, this reaction with the butane-, pentane-, and hexanethiol homologues is very slow.
(11) TLC analysis of the reaction mixture never revealed any UV-absorbing material that also gave a positive Ellman's spray test for free SH groups.[13]
(12) These reactions were run in dimethylformamide at room temperature due to the limited solubility of the amino thiols in nonaqueous solvents.
(13) Glaser, C. B.; Maeda, H.; Meienhofer, J. *J. Chromatog.* **1970**, *50*, 151–154.
(14) Crampton, M. R. In "The Chemistry of the Thiol Group", Part 1; Patai, S., Ed.; Wiley: New York, 1979; p 398.
(15) The preparation of 4 also yielded a trace amount of higher R_f impurity which was determined to be the α-chloro ketone (4, X = Cl): dec 235.5–242 °C; IR (Nujol) 1727 cm^{-1}; chemical-ionization (NH_3) mass spectrum, *m/e* (% abundance) 411 (MH^+, 100), 413 (MH^+ + 2, 35.4).

Discussion

The present results clearly indicate that α-keto mesylates are useful reactive intermediates. Under mildly basic conditions, the reactions of α-keto mesylates are quite specific for thiols and thiol acids. Their virtually complete preference for thiol over amino groups in the presence of amine base has already been used for the preparation of **12**.[8] Likewise, the virtual unreactivity of imidazole, OH, and COOH groups should allow the use of α-keto mesylates in other selective synthetic schemes. The reaction of **4** in acetone with thiolate anions is several thousand times faster than with acetate anion. Due to the very slow reaction with *n*-propylamine in acetone, which also gives other products, it is difficult to determine the relative reaction rates of $-S^-$ vs. $-NH_2$; but, it is likely that thiolate anions are at least several thousand times more reactive than amines with α-keto mesylates under similar conditions. This relative reactivity is even greater for β-hydroxy-α-keto mesylates. These mesylates are essentially unreactive with hydroxyl groups (**4** is stable for at least 20 months at 4 °C in 95% EtOH) and give no products of alkoxide attack in reactions with ethanol or β-MERC[11] and triethylamine in acetone at 0 °C.

On the basis of the "hard acid–soft base" theory,[16] we expected that the α-keto mesylate **14** would display a greater selectivity for thiolate anion vs. primary amine than does the corresponding α-keto chloride **22**. The thiolate anion is a softer base than $-NH_2$ and thus the preferred nucleophile for attack on the soft acid carbon, which should be more reactive in the mesylate than in the chloride due to increased hard–soft dissymetry. Under the conditions we have examined, the α-keto mesylate **14** appears just as reactive and selective as does the α-keto chloride **22**. Since α-keto chlorides have found numerous applications as electrophilic affinity labels[8] (EAL) for proteins,[17-19] α-keto mesylates should also prove to be a useful EAL functional group.

The presence of a β-hydroxyl group accelerates the rate of reaction of α-keto mesylates (i.e., **4** vs. **14**) with thiolate anions in some solvents. X-ray data for a number of steroids indicate that the C_{20}=O and the C_{21}–X (X = OH, OAc, OBz, Br) groups are syn periplannar but anti periplannar to the C_{17}–OH.[20,21] If these X-ray structures accurately reflect the situation in solution, the observed anti-periplaner conformation rules out hydrogen bonding by the β-hydroxyl group as a cause of the increased reactivity of the α-keto mesylate. Alternatively, the higher IR frequency of the C_{20} carbonyl band of cortisol-21-mesylate (**1**; 1728 cm^{-1})[9] and dexamethasone-21-mesylate (**4**; 1733 cm^{-1}) vs. deoxycorticosterone-21-mesylate (**14**; 1715 cm^{-1}) suggests that the increased reactivity of β-hydroxy-α-keto mesylates may be due to electronic effects. A determination of whether steric and/or inductive effects of the β-hydroxyl group are operative requires further studies with appropriately modified β-hydroxy-α-keto mesylates, which could in turn help elucidate their presently unknown mechanism of reaction.[22]

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(19) Powers, J. C. *Methods Enzymol.* **1977**, *46*, 197–208.
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(21) Daux, W. L.; Weeks, C. M.; Rohrer, D. C. *Stereochemistry* **1976**, *9*, 271–383.
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Experimental Section

Instrumentation. Melting points were determined on a Fisher-Johns hot stage or a Thomas-Hoover capillary 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 Hitachi Perkin-Elmer RMU-6E (electron-impact (EI) mode) or Finnigan 1015D (chemical-ionization (CI) mode) spectrometer by Mr. Bill Landis or Noel Whittaker of the Laboratory of Chemistry, NIAMDD. High-pressure liquid chromatographs (high-pressure LC) were run with Waters Associates high-pressure LC equipment on a C_{18} μBondapak column. Analyses were performed by the Microanalytical Section of the Laboratory of Chemistry, NIAMDD, Bethesda, MD.

Dexamethasone-21-mesylate (4).[23] To 105 mg of dexamethasone (0.268 mmol) in 2 mL of anhydrous pyridine at 0 °C under N_2 was added 25 μL of methanesulfonyl chloride (0.322 mmol, 1.2 equiv) with stirring. After 1 h at 0 °C, another 0.8 equiv of methanesulfonyl chloride was added. After a total reaction time of 5 h at 0 °C, the solution was added to 40 mL of ice–water. Filtration, washing with a total of 40 mL of 0 °C water, drying in a desiccator, and finally drying under high vacuum afforded a 91% yield of the crude mesylate (mp 230–231 °C dec), contaminated only by the 21-chloride, as determined by TLC (1:2 benzene–EtOAc on silica gel GF). Two recrystallizations from tetrahydrofuran (THF) gave the analytically pure solid as a solvate, i.e., dexamethasone-21-mesylate–THF (mp 231.0–232.0 °C dec): IR (Nujol) 3367, 1733, 1662, 1364, 1172 cm^{-1}; UV (95% EtOH) λ 239 nm (ε 1.67 × 10^4). Low-temperature EI mass spectrum gave a large peak for tetrahydrofuran at *m/e* 72. Anal. Calcd for $C_{23}H_{31}SFO_7$–THF (mol wt 542.65): C, 59.76; H, 7.24; F, 3.50. Found: C, 59.53; H, 7.52; F, 3.78.

Deoxycorticosterone-21-mesylate (14). To 0.936 mmol of deoxycorticosterone (309 mg) and 1.50 mmol of triethylamine (210 μL) in 10 mL of tetrahydrofuran at 0 °C was added 1.48 mmol of methanesulfonyl chloride in 1.2 mL of tetrahydrofuran over about 5 min. After 25 min, the reaction was warmed at room temperature for 1 h and then filtered. The filtrate was concentrated to 1 mL and added to 20 mL of cold water. The precipitated steroid was filtered, washed with water, and dissolved in 20 mL of methylene chloride to give, after drying over $MgSO_4$ and removing the solvent under reduced pressure, 379 mg (99%) of product. Recrystallization from acetone afforded 62% of the analytical pure product (mp 159.5–161.5 °C); IR (KBr) 1715, 1660, 1615, 1350, 1170 cm^{-1}. Mass spectral peaks were observed in the CI mode with ammonia at *m/e* 409 (MH^+, 100%), 426 (M + 18, 23%), 315 (15%). Anal. Calcd for $C_{22}H_{32}O_5S$: C, 64.67; H, 7.90. Found: C, 65.00; H, 7.91.

Deoxycorticosterone-21-chloride (22) was synthetized as described by Counsel et al.[3]

Synthesis of Dexamethasone- and Deoxycorticosterone-21-thioether Derivatives of Ethanethiol, 1,4-Butanedithiol, β-Mercaptoethanol, and Methyl Mercaptoacetate. Dexamethasone-21-mesylate (**4**), deoxycorticosterone-21-chloride (**22**), or mesylate **14** in dry acetone at 0 °C (final concentration equal to 0.04 to 0.08 M) was added to a 0 °C solution of dry acetone under argon containing 10–15 equiv each of thiol and triethylamine. The reaction, followed by analytical TLC, was stopped by addition to 20 volumes of 0 °C water containing HCl for neutralization (final pH ~3). The precipitated steroids were filtered, washed with cold water, and dissolved in methylene chloride. The crude material, obtained after drying the methylene chloride solutions over $MgSO_4$ and removing the solvent under reduced pressure, was purified on preparative silica gel TLC plates from Analtech.

Dexamethasone-21-SCH_2COOMe (5). The reaction of 10:1 methyl mercaptoacetate–dexamethasone-21-mesylate was complete in less than 30 s. After TLC purification (35:10 $CHCl_3$–acetone), a TLC pure product was obtained in 80% yield (mp 150.5–152 °C); IR (KBr) 3480, 1730, 1705 (br), 1660, 1615, 1290, 890 cm^{-1}. Mass spectral peaks were observed in the CI mode with ammonia at *m/e* 481 (MH^+, 100%), 461 (3%), 377 (28%). Anal.

(23) This procedure was adapted from that of Daniel V. Santi (personal communication).

Calcd for $C_{25}H_{33}O_6SF$: C, 62.48; H, 6.92. Found: C, 62.46; H, 6.74.

Dexamethasone-21-S(CH$_2$)$_4$SH (6). The synthesis has been described by Simons et al.[8]

Dexamethasone-21β-thioethanol (7). The reaction of 10:1 β-mercaptoethanol–dexamethasone mesylate was complete after 15 min. A TLC and high-pressure LC (>99%) pure material was obtained without TLC purification (mp 223–226 °C). Mass spectral peaks were observed in the CI mode with ammonia at m/e 453 (MH^+, 100%), 470 (M + 18, 3%), 377 (5%); IR (KBr) 3480, 3370, 1700, 1655, 1610, 890 cm^{-1}.

Synthesis of 2-*t*-BOC-amino-1-ethanethiol. To cysteamine hydrochloride salt (50 mg, 0.45 mmole) in 250 μL of dioxane–water (80:20) was added a solution of 2-((*tert*-butoxycarbonyl)oxyimino)-2-phenylacetonitrile (125 mg, 0.51 mmol, Aldrich) in 300 μL of dioxane and triethylamine (200 μL, 1.4 mmol)., The reaction was complete after a few seconds (as shown by TLC). The byproduct was precipitated by the addition of ethyl acetate (1 mL). After filtration, the solution was washed with water (7 mL) containing HCl for neutralization of triethylamine, dried over $MgSO_4$, and reduced in volume under argon. Purification by preparative TLC (silica gel; 1% MeOH in $CHCl_3$) afforded 61 mg of a TLC pure, light yellow oil. Mass spectral peaks were observed in the CI mode with ammonia at m/e 178 (MH^+, 100%), 195 (M + 18, 22%), 139 (10%), 122 (23%).

Dexamethasone-21-S(CH$_2$)$_2$NH-*t*-BOC (8). The reaction of 3.3 equiv of 2-*t*-BOC-amino-1-ethanethiol, triethylamine (2.5 mmol) and dexamethasone-21-mesylate (0.335 mmol) in dry acetone (5 mL) at 0 °C was complete (as determined by TLC) after 10 min. After 1 h, the reaction solution was added to 150 mL of 0 °C water and the pH lowered to ~3 with HCl. The precipitated steroid was filtered and dissolved in methylene chloride, which was dried over $MgSO_4$ and evaporated under reduced pressure, giving a light yellow oil which precipitated with petroleum ether to afford the crude product (207 mg). The oil obtained from preparative TLC was crystallized from ethyl acetate to give analytically pure **8** in 71% overall yield (mp 167.5–168.5 °C). Mass spectral peaks were observed in the CI mode with ammonia at m/e 552 (MH^+, 65%), 434 (100%), 377 (83%), 357 (13%); IR (KBr) 3400, 1690 (br), 1665, 1520 cm^{-1}. Anal. Calcd for $C_{29}H_{42}O_6FNS$: C, 63.13; H, 7.67; N, 2.54. Found: C, 62.93; H, 7.83; N, 2.22.

Dexamethasone-21-thioethane (9). The reaction performed with 12:1 ethanethiol–dexamethasone-21-mesylate was complete after ~1 h. TLC purification in acetone–chloroform (10:35) gave a 78% yield of product. Recrystallization from acetone gave a high-pressure LC pure product (mp 187.5–189.5 °C). A mass spectral peak in the CI mode with ammonia was observed at m/e 437 (MH^+, 100%); IR (KBr) 3430, 1700, 1657, 1616, 887 cm^{-1}.

Dexamethasone-21-aminopropane (10). A mixture of 1 equiv of dexamethasone-21-mesylate (0.055 mmole) in 800 μL of DMF and 13 equiv of *n*-propylamine was stirred at 64 °C until all starting material disappeared (2 h). The reaction solution was added to 20 mL of cold saturated aqueous NaCl. The crude product, obtained by extraction with methylene chloride (3 × 10 mL) followed by drying over $MgSO_4$ and removal of solvent by evaporation under argon, was purified by preparative TLC (90:10 chloroform–methanol on silica gel). The purified amine was obtained in 46% yield as the hydrochloride salt after dissolution in methanol containing gaseous hydrochloric acid (1 M) and evaporation. The purity of this product was higher than 95% as shown by high-pressure LC, dec 189–194 °C. The mass spectral peaks were observed in the CI mode with ammonia at m/e 434 (MH^+, 100%), 416 (10%), 333 (12%); IR (KBr) 3400, ~3100 (shoulder), 1720, 1662, 1618, 886 cm^{-1}.

The reaction of dexamethasone-21-mesylate with 13 equiv of *n*-propylamine in dry acetone for 48 h at room temperature gave numerous other more polar products (but not **10**) as shown by analtyical TLC.

Reaction of Imidazole or Ethanol with 4. By use of the general reaction procedure of thiols with dexamethasone-21-mesylate **4**, a 0 °C solution of 4 plus 12 equiv each of imidazole (or ethanol) and triethylamine was followed by analytical TLC. No reaction products were observed after 96 h at 0 °C.

Dexamethasone-21-acetate (11). To a solution of **4** (11.4 mg, 21 μmol) and 12 equiv of triethylamine in 300 μL of dry acetone at 0 °C was added 14 μL of acetic acid (11.6 equiv). After 1 h, no reaction could be detected by analytical TLC using 6% MeOH in $CHCl_3$ on silica gel which can resolve **4** (R_f 0.45) from authentic **11** (from Sigma, R_f 0.51). An additional 8.5 equiv of triethylamine was then added; after another 93 h at 0 °C, the reaction was about 30% complete.

Dexamethasone-21-S(CH$_2$)$_3$NH$_2$ (12). Synthesis of this product has been described by Simons et al.[8]

Dexamethasone-21-S(CH$_2$)$_5$NH$_2$ (13). The synthesis of this product is described elsewhere.[24]

Deoxycorticosterone-21-SCH$_2$COOMe (15). The reaction of 10:1 methyl mercaptoacetate–deoxycorticosterone-21-mesylate was complete in less than 30 s. Analytically pure product (77%; mp 94.0–94.5 °C) was obtained after TLC purification (acetone–chloroform 10:35). Mass spectral peaks were obtained in the CI mode with ammonia at m/e 419 (MH^+, 100%), 436 (M + 18, 22%), 315 (22%); IR (KBr) 1745, 1695, 1660, 1618, 1308, 1195, 1165 cm^{-1}. Anal. Calcd for $C_{24}H_{34}O_4S$: C, 68.86; H, 8.19. Found: C, 69.11; H, 8.00.

The same pure product was obtained by reaction of 10:1 methyl mercaptoacetate–deoxycorticosterone-21-chloride. The reaction was complete in less than 30 s.

Deoxycorticosterone-21-S(CH$_2$)$_4$SH (16). The reaction performed with 10:1 1,4-butanedithiol–deoxycorticosterone-21-mesylate was complete after 2 h. Purification by preparative TLC in benzene–ethyl acetate (4:1) gave the TLC pure (77% yield) product as a light yellow oil. Mass spectral peaks were obtained in the CI mode with ammonia at m/e 435 (MH^+, 100%) and 315 (50%); IR (KBr) 1695, 1670, 1615 cm^{-1}.

This product was also obtained from deoxycorticosterone-21-chloride with 10 equiv of 1,4-butanedithiol. The reaction was complete after 2 h. Purification was the same as above.

Deoxycorticosterone-21-thioethanol (17). The reaction of 10:1 β-mercaptoethanol–deoxycorticosterone-21-mesylate was complete after 1 h. A TLC and high-pressure LC (>98%) pure product was obtained without TLC purification (mp 103–105 °C). Mass spectral peaks were observed in the CI mode with ammonia at m/e 391 (MH^+, 100%), 408 (M + 18, 22%), 373 (20%); IR (KBr) 3410, 1695, 1657, 1610 cm^{-1}.

The reaction of 10:1 β-mercaptoethanol–deoxycorticosterone-21-chloride was complete after 1 h, giving the same TLC and high-pressure LC (>99%) pure product as above. Mass spectral peaks were observed in the CI mode with ammonia at m/e 391 (MH^+, 100%) and 408 (M + 18, 19%).

Deoxycorticosterone-21-thioethane (18). The reaction performed with 12:1 ethanethiol–deoxycorticosterone-21-mesylate required more than 2 h for completion. Purification by TLC in benzene–ethyl acetate (8:1) afforded the product in 85% yield. Recrystallization from ethyl acetate gave analytically pure product (mp 86.5–87 °C). Mass spectral peaks were observed in the CI mode with ammonia at m/e 375 (MH^+, 100%) and 315 (5%); IR (KBr) 1700, 1670, 1620, 1450, 1235 cm^{-1}. Anal. Calcd for $C_{23}H_{34}O_2S$: C, 73,75; H, 9.15; S, 8.56. Found: C, 73.30; H, 9.15; S, 8.56.

Deoxycorticosterone-21-S(CH$_2$)$_3$NH$_2$ (19) and Deoxycorticosterone-21-S(CH$_2$)$_3$NH-*t*-BOC (23). To 0.054 mmol of deoxycorticosterone-21-mesylate in 800 μL of DMF at room temperature was added 0.110 mmol of 3-aminopropanethiol, prepared from the HCl salt according to Simons et al.[8] The reaction was complete after 5 min, as determined by TLC. The product appeared as an equilibrium mixture of free amine and suspected cyclic hemiaminoketal. Addition of 55 μL of di-*tert*-butyl dicarbonate (0.270 mmol) and triethylamine (50 μL, 0.350 mmol) afforded, at room temperature, the amino *t*-BOC derivative (**23**), which was isolated as an oil (76% overall yield) after preparative TLC (benzene–ethyl acetate, 2:1). Mass spectral peaks were observed in the CI mode with ammonia at m/e 504 (MH^+, 100%), 521 (M + 18, 47%), 465 (45%), 315 (72%); IR (KBr) ~3370 (br), ~1690 cm^{-1} (br).

The same product **23** was obtained in the same yield from deoxycorticosterone-21-chloride (0.026 mmol) and 3-aminopropanethiol (0.052 mmole) in DMF (0.4 mL) after 5 min at room

(24) Simons, S. S., Jr.; Pons, M.; Thompson, E. B.; Johnson, D. F., manuscript in preparation.

temperature. Treatment by di-*tert*-butyl dicarbonate gave the amino BOC derivative **23** as shown by TLC.

Hydrolysis of the *t*-BOC derivative **23** (0.020 mmol) in 50 μL of 1 M HCl in acetic acid was complete in less than 1 min. The product was precipitated with ethyl ether (2 mL), centrifuged, washed with ethyl ether, and dried in vacuo to give TLC pure amine **19** as a salt (dec >177 °C). Mass spectral peaks were observed in the CI mode with ammonia at *m/e* 404 (MH^+ 40%), 386 (100%), 315 (35%); IR (KBr) 3430, 3200–3000 (shoulder), 1690, 1665, 1610 cm^{-1}.

Deoxycorticosterone-21-S$(CH_2)_5NH_2$ (20) and Deoxycorticosterone-21-S$(CH_2)_5$NH-*t*-BOC (24). The reaction of 0.082 mmol of deoxycorticosterone-21-mesylate and 0.160 mmol of 5-amino-1-pentanethiol in 2.1 mL of DMF was complete in less than 30 min at room temperature. Di-*tert*-butyl dicarbonate (150 μL, 0.750 mmol) was added with triethylamine (120 μL, 0.840 mmol) to the reaction solution, which was added to 5 mL of ethyl acetate after 2 min and washed with water containing HCl (700 μmol). The organic phase was extracted with dilute HCl, dried over $MgSO_4$, and concentrated under vacuum. The crude product was purified by preparative TLC with benzene–ethyl acetate (4:1) to give the TLC pure amino *t*-BOC derivative **23** in 77% yield as an oil. Mass spectral peaks were obtained in the CI mode with ammonia at *m/e* 532 (MH^+, 40%), 476 (100%), 432 (65%), 315 (22%); IR (KBr) 3380, ~1690 cm^{-1} (br).

The same product (**24**) was obtained from deoxycorticosterone-21-chloride (0.020 mmol) with 5-amino-1-pentanethiol (0.040 mmol) in 500 μL of DMF at room temperature in less than 30 min. Treatment with di-*tert*-butyl dicarbonate (30 μL) and triethylamine (20 μL) gave the same amino *t*-BOC derivative **24** as shown by TLC.

Hydrolysis of **24** and purification of the amine **20** as a salt were accomplished as for **19** to give a TLC pure oil. Mass spectral peaks were obtained in the CI mode with ammonia at *m/e* 432 (MH^+, 100%), 391 (20%), 315 (26%), 237 (24%), 120 (19%); IR (KBr) 3430, ~3100 (shoulder), 1690, 1660, 1610 cm^{-1}.

Deoxycorticosterone-21-aminopropane (21). The reaction of deoxycorticosterone-21-chloride (0.066 mmol) and 16 equiv of *n*-propylamine in 1 mL of DMF at 62 °C was complete after 25 min, as determined by TLC. The reaction solution was added to 10 mL of cold aqueous saturated NaCl. Extraction with ethyl acetate (3 × 10 mL) followed by drying over $MgSO_4$ and removal of solvent under reduced pressure gave the crude amine. Preparative TLC (90:10 $CHCl_3$–MeOH on silica gel) gave >85% pure product (by high-pressure LC) in 67% yield, mp 197–201 °C. A mass spectral peak was observed in the CI mode with ammonia at *m/e* 372 (MH^+, 100%); IR (KBr) ~3420, ~3050 (shoulder), 1720, 1670, 1610, 1450, 1230 cm^{-1}.

The reaction of deoxycorticosterone-21-mesylate (0.070 mmol) with 16 equiv of *n*-propylamine in 1 mL of DMF at 65 °C was over in 30 min but also gave several byproducts. After purification, deoxycorticosterone-21-aminopropane was obtained in 15% yield (mp 196–199 °C). A mass spectral peak was observed in the CI mode with ammonia at *m/e* 372 (MH^+, 100%).

The same reaction in acetone at room temperature with deoxycorticosterone-21-mesylate and -chloride gave many byproducts and less than 10% of deoxycorticosterone-21-aminopropane after 66 h.

Registry No. **4**, 2265-22-7; **5**, 73816-20-3; **7**, 73816-21-4; **8**, 73816-22-5; **9**, 73816-23-6; **10**, 73816-24-7; **11**, 1177-87-3; **12**, 73816-25-8; **13**, 73816-26-9; **14**, 20576-45-8; **15**, 73816-27-0; **16**, 73816-28-1; **17**, 58958-14-8; **18**, 73816-29-2; **19**, 73816-30-5; **20**, 73816-31-6; **21**, 73816-32-7; **22**, 26987-64-4; **23**, 73816-33-8; **24**, 73816-34-9; dexamethasone, 50-02-2; deoxycorticosterone, 64-85-7; methyl mercaptoacetate, 2365-48-2; β-mercaptoethanol, 60-24-2; cysteamine hydrochloride, 52-89-1; 2-*t*-Boc-amino-1-ethanethiol, 67385-09-5; 1,4-butanedithiol; ethanethiol, 75-08-1; 3-aminopropanethiol, 462-47-5; 5-amino-1-pentanethiol, 58657-85-5.

Conformation of Epi-α-cyperone and Related Enones

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The conformations of epi-α-cyperone (10-epieudesma-4,11-dien-3-one, **2**) and its dihydro and 14-nor analogues (**4** and **15**, respectively) have been investigated by a combination of lanthanide induced shift reagent ^1H NMR, ^{13}C NMR, and high-field ^1H NMR techniques. Comparison of these spectral data with those of the normal eudesmane derivatives, α-cyperone (**1**), dihydro-α-cyperone (**3**), and 14-noreudesm-4-en-3-one (**14**) clearly shows that the conformations of all six enones are similar with a half-chair conformation for ring A and a chair conformation for ring B. 11-Methyl-10-epieudesm-4-en-3-one (**5**) was prepared either from 5α-hydroxy-10-epieudesm-11-en-3-one (**6**) or by the Robinson annulation of 2-methyl-5-*tert*-butylcyclohexanone with ethyl vinyl ketone. 14-Nor-11-methyl-10-epieudesm-4-en-3-one (**15**) was prepared by the annulation of 2-methyl-5-*tert*-butylcyclohexanone with methyl vinyl ketone. The ^{13}C lanthanide induced shift and high-field ^1H NMR spectra of enones **5** and **13** indicate that these molecules are not conformationally homogeneous. An X-ray structure determination of the oxime of enone **5** showed that in the solid state ring A exists in a envelope conformation and ring B in a twist conformation with a ψ-equatorial *tert*-butyl group. Crystals of the oxime of **5** belong to the triclinic system, space group $P\bar{1}$, with a = 6.290 (3) Å, b = 12.010 (5) Å, c = 10.341 (5) Å, α = 85.20 (2)°, β = 95.56 (2)°, γ = 101.09 (2)°, and Z = 2. Atomic positional and thermal parameters were refined by least-squares calculations to R = 0.068 over 1609 observed reflections measured by a diffractometer.

Experiments directed toward the elucidation of the structure and stereochemistry of the eudesmanoid sesquiterpene α-cyperone (eudesma-4,11-dien-3-one, **1**) have shown that the Robinson annulation of dihydrocarvone with ethyl vinyl ketone or the equivalent afforded not the expected product (**1**) but a stereoisomer, epi-α-cyperone (7-epieudesma-4,11-dien-3-one, **2**).[2] A coincident investigation of the ORD properties of unsaturated ketones, including α-cyperone (**1**), epi-α-cyperone (**2**), and dihydroepi-α-cyperone (**4**), led Djerassi et al. to conclude that α-cyperone (**1**) had the expected conformation in which ring B was a chair with an equatorial isopropenyl sub-

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(2) (a) McQuillin, F. J. *J. Chem. Soc.* **1955**, 528. (b) Howe, R.; McQuillen, F. J. *J. Chem. Soc.* **1955**, 2423. These workers carried out this annulation using (−)-dihydrocarvone to afford the enantiomer of enone **2**.

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