proton. The fact that no more such stabilization seems to be occurring in $Cl_3CCH(OH)O^-$ or $F_3CCH(OH)O^-$ than in $HOCH_2O^-$ suggests that in none of the three cases does the internal hydroxy group compete significantly with hydrogen bonding by the more acidic protons of water. The more acidic proton in $HOC(CF_3)_2O^-$ can compete, however, and the result is a ~0.54 larger increase in pK produced on replacing α hydrogen by α-hydroxy. If this interpretation is correct, the negative charge in $HOC(CF_3)_2O^-$ is increasing the pK by 6.17 − 0.54 or 5.63 units. Thus, we would estimate that phenylglyoxal hydrate, for example, whose pK_1 is 11.19,[18] has a pK_2 of 17.42.

Experimental Section

Hexafluoroacetone hydrate (PCR) was used without further purification. The strengths of its aqueous solutions were determined by titration with standard base. Potentiometric titrations were carried out using a Radiometer automatic titrator (ABU 1, PHM 26, and SBR 2c with a type B electrode) with a 2.5-mL buret in the manual mode. The total elapsed time for a titration was less than 15 min and the temperature of the solution was 25.0 ± 0.2 °C.

Registry No.—Hexafluoroacetone hydrate, 677-71-4.

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Chemistry of Trifluoroacetic Anhydride–Haloacetic Acid Reactions with Medroxyprogesterone

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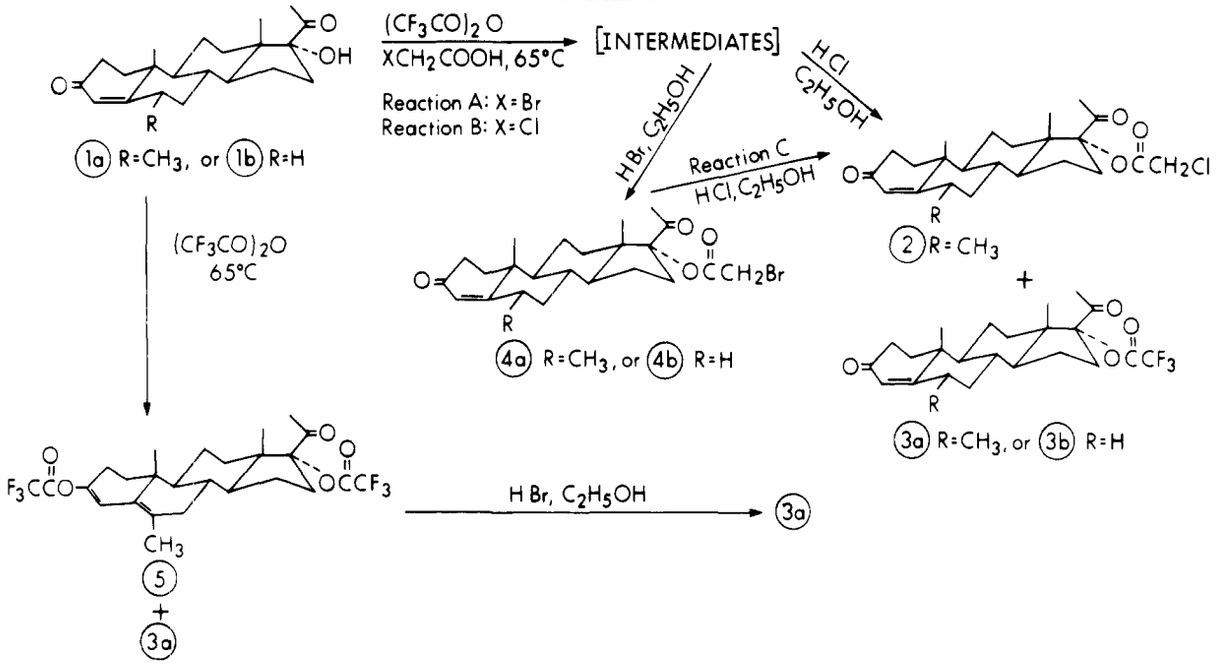
Reaction of medroxyprogesterone with bromoacetic acid–trifluoroacetic anhydride at 25 °C for 1 h gives, after workup, complete recovery of starting material. The same reaction conducted at 65 °C for 1 h produces an inseparable mixture of products. Treatment of the mixture with dilute ethanolic HCl permits isolation of medroxyprogesterone 17-trifluoroacetate and the transhalogenated product medroxyprogesterone 17-chloroacetate, in approximately equal amounts. Substituting ethanolic HBr during the second reaction step provides medroxyprogesterone 17-bromoacetate in 25–30% overall yield. Similar results were obtained with 17α-hydroxy-4-pregnene-3,20-dione. When phenylacetic acid is substituted for bromoacetic acid in the reaction sequence analogous results are obtained. Reaction of medroxyprogesterone at 65 °C in trifluoroacetic anhydride alone gives two products shown to be medroxyprogesterone 17-trifluoroacetate and 3,17α-dihydroxy-6α-methyl-3,5-pregnadien-20-one bis(trifluoroacetate). Electron-withdrawing substitutents on acetic acid appear to direct the mixed anhydride reaction, and this effect is discussed. Both medroxyprogesterone 17-bromoacetate and 17α-bromoacetoxyprogesterone inactivate the enzyme 20β-hydroxy steroid dehydrogenase (E.C.1.1.1.53) from *Streptomyces hydrogenans* in a time-dependent and irreversible manner while the corresponding chloroacetoxy and trifluoroacetoxy esters do not.

A series of bromoacetoxyprogesterone isomers was previously synthesized in this laboratory to serve as active site directed irreversible inhibitors to study the active site topography of 20β-hydroxy steroid dehydrogenase (E.C.1.1.1.53) from *Streptomyces hydrogenans*.[1] Among these alkylating agents, 16α-bromoacetoxy-4-pregnene-3,20-dione, 11α-bromoacetoxy-4-pregnene-3,20-dione, and 17β-bromoacetoxy-4-estren-3-one terminate pregnancy in rats.[2,3] Continuation of these enzymological and reproductive biological investigations required the synthesis of 17α-bromoacetoxyprogesterone (17α-bromoacetoxy-4-pregnene-3,20-dione) and medroxyprogesterone bromoacetate (17α-bromoacetoxy-6α-methyl-4-pregnene-3,20-dione). The latter compound is a steroid alkylating agent structurally analogous to medroxyprogesterone acetate, a powerful progestin.[4] The present report describes the result obtained when the tertiary hydroxyl steroid precursors were treated with haloacetic acid–trifluoroacetic anhydride mixtures under a variety of conditions.

Treatment of medroxyprogesterone (**1a**, Scheme I) with a bromoacetic acid–trifluoroacetic anhydride mixture at 25 °C for 1 h gave, after workup, recovery of starting material. Under similar reaction conditions a variety of aliphatic carboxylic acids are reported to give good yields of the corresponding medroxyprogesterone 17-esters.[4] Therefore, the earlier described reaction conditions had to be modified in order to obtain the desired 17-halo acetates.

When we conducted the mixed anhydride reaction at 65 °C, TLC analysis of the crude product revealed that at least four new compounds had been formed, and 30–40% of the starting material remained unreacted. This mixture could not be separated by either TLC or column chromatography. Since it was likely that some of the products contained a 3-enol ester function[7] we attempted to simplify the mixture by selectively

Scheme I



removing the C-3 ester groups[16] with dilute ethanolic hydrochloric acid (Scheme I). This reaction succeeded in reducing the mixture to three components which could be separated by short column silica gel chromatography[8] into starting material (ca. 40% recovered), medroxyprogesterone 17-trifluoroacetate (**3a**, Scheme I), and medroxyprogesterone 17-chloroacetate (**2**, Scheme I). Isolation of the chloroacetate is interesting in view of the fact that the first esterification step contained bromoacetic acid. The transhalogenation reaction is discussed below. Elemental analysis, NMR, IR, and UV spectral data supported the structural assignments, represented in Scheme I.

When the above reaction sequence was conducted with chloroacetic acid then compound **2** was obtained. Accordingly, when bromoacetic acid was used during the esterification step and ethanolic HBr was used in the second step then medroxyprogesterone 17-bromoacetate (**4a**, Scheme I) was obtained. Treatment of the bromoacetate **4a** with ethanolic HCl resulted in transhalogenation to give the corresponding chloroacetate **2** accompanied by some ester cleavage which produced starting material **1a**.

That ethanolic HCl treatment of the intermediates obtained from the reaction of **1a** with trifluoroacetic anhydride–bromoacetic acid gave chloroacetate **2** was suprising. No bromoacetate **4a** could be detected. Although we had previously encountered similar transhalogenation when a hydroxy steroid was treated with a mixture of bromoacetic acid–thionyl chloride in *N,N*-dimethylformamide (DMF),[1a] the earlier results could be rationalized in terms of a previously established, solvent-dependent nucleophilic hierarchy, i.e., $Cl^- > Br^-$ in DMF.[9] However, our present observation is not consistent with the general view that protic solvents produce the nucleophilic order $Br^- > Cl^-$.[10] To further examine this point **4a** was treated with ethanolic HCl, which expectedly produced **2**. Admittedly, our transhalogenation could result from a mass effect since the calculated molar ratio of Cl to Br in the reaction **1a**-intermediate + HCl → **2** is approximately 9:1. This would imply that the protic nature of the solvent is not very significant in establishing the order of nucleophilicity under our reaction conditions. It is clear, however, that to obtain **4a** from the intermediates derived from trifluoroacetic anhydride–bromoacetic acid and **1a**, ethanolic HBr rather than HCl must be used during selective deacetylation of the 3-enol esters.

Although earlier reports of the mixed anhydride method did not mention the production of steroid trifluoroacetates,[4-6] under our reaction conditions these were among the major products obtained. When medroxyprogesterone was treated with trifluoroacetic anhydride alone at 65 °C, TLC showed that two new components were formed in approximately equal amounts. One of the components was identified as the 17-trifluoroacetate **3a**. The second component (**5**), which possesses greater mobility than **3a** on TLC, was isolated by column chromatography. The IR spectrum of compound **5** contains bands at 1790 and 1725 cm^{-1}, due respectively to the trifluoroacetate and C-20 keto groups. There were no significant absorptions observed in the 1500 to 1700 cm^{-1} region, which suggested the absence of a conjugated C-3 keto group. This was further confirmed by comparing the NMR spectrum of **5** with that of **3a**. The 3,17-bis(trifluoroacetate) **5** exhibited resonance signals at τ 3.75 and 8.33, assigned to H-4 and the C-6 allylic methyl group, respectively. Moreover, the signal due to the C-19 protons of **3a** observed as a singlet at τ 8.80, is shifted upfield by 0.2 ppm to τ 9.02 in the spectrum of **5**. These results coincide with estimated changes in location of shielding and deshielding regions[11,12] associated with a shift in the π-electron system over C-3, C-4, and C-5.

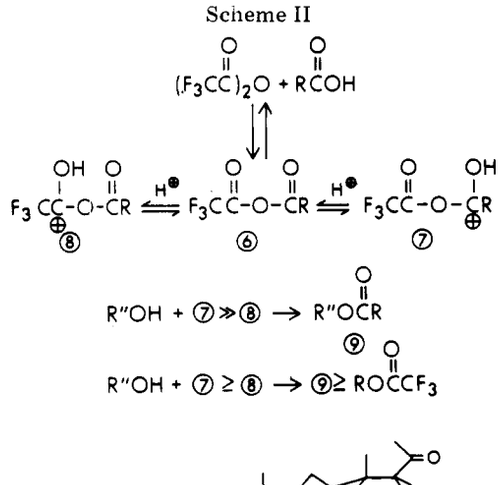
In order to estimate the relative amounts of **3a** and **5** produced in the reaction of **1a** with trifluoroacetic anhydride at 65 °C (Scheme I), just prior to the workup the reaction mixture was chromatographed in varying amounts on TLC plates. The appropriate zones were carefully removed, quantitatively extracted with methanol, and quantitated spectrophotometrically by obtaining the absorbance of the solutions at 235–240 nm. Approximately 20% of **1a** remained unreacted and the products **3a** and **5** comprised 35 and 45%, respectively, of the mixture at this point in the reaction sequence. Apparently during the $NaHCO_3$ workup procedure some of **5** is hydrolyzed to **3a** and **1a**, and a small amount of **3a** is converted to **1a**. This would account for the 40% recovery of starting material and final yields of approximately 30% for each of **3a** and **5** obtained after complete workup. When the reaction mixture is treated with ethanolic HCl and then worked up, about 50–60% of **1a** is recovered along with 40–50% of **3a**.

These results show that during the synthesis of either **2** or **4** a substantial amount of trifluoroacetylation competes against haloacetylation at the 17 position. Moreover, enol esterification at the 3 position can produce several mixed

diesters. Four possible 3,17-diester derivatives and four possible 3- or 17-monoester derivatives are potentially obtainable by reaction of 1 with bromoacetic acid–trifluoroacetic anhydride. Thus, when haloacetic acids are used in the mixed anhydride reaction with 17α-hydroxyprogesterone derivatives it is necessary to selectively convert the 3-enol esters to the corresponding Δ^4 3-ketone with an acid so that the desired 17-monoester derivative can be isolated.

The mixed anhydride reaction, in which trifluoroacetic anhydride is present in large excess while the tertiary hydroxy compound and aliphatic carboxylic acid are in equimolar quantities, generally produces good yields (e.g., 60–90%) of the corresponding tertiary ester, under mild conditions (e.g., 1 h at 25 °C).[13] Therefore, the necessity of using more vigorous conditions to effect only a 30–40% coversion of the tertiary hydroxy steroid to the desired haloacetate in the present synthesis raises questions concerning the limiting factor in the mechanism of this reaction. Most likely the selectivity in condensation of an aliphatic carboxylic acid in the presence of a large excess of trifluoroacetic anhydride with an alcohol to give the corresponding ester is due to the relative ease with which the aliphatic carbonyl group is protonated (7) compared to the trifluoromethylcarbonyl group (8) in the intermediate mixed anhydride (6, Scheme II). Formation of the intermediates 7 and 8 no doubt precedes intervention of the alcohol in the reaction mechanism.[14] Thus the nature of the R group in the anhydride 6 directs this reaction. The presence of a bromine or chlorine atom on the carbon adjacent to the carbonyl group, when a haloacetic acid is used, is expected to have a significant electron-withdrawing effect which destabilizes the corresponding intermediate 7 (R = XCH_2; X = Br or Cl). Thus the amount of intermediate 8 formed relative to 7 when R contains an α-halogen atom is probably sufficient to produce serious competition against the desired esterification process. That electronic effects direct the mixed anhydride reaction is further evidenced by the fact that under the same conditions which produce more than 80% esterification when an aliphatic carboxylic acid is used,[13] phenylacetic acid produces only 15% of the corresponding ester.[15]

Scheme II



The new steroid bromoacetates react with amino acids and form steroid–amino acid conjugates, analogous to those obtained for 11α-bromoacetoxyprogesterone, and under the conditions which we described in elaborate detail elsewhere.[17] Also, incubations of 20β-hydroxy steroid dehydrogenase (4.2×10^{-7} M) with 17-bromoacetoxyprogesterone (5×10^{-5} M) or with medroxyprogesterone bromoacetate in 0.05 M phosphate buffer containing 15% glycerol at pH 7.0 and at 25 °C caused a time-dependent ($t_{1/2}$ = 15 h) and irreversible inactivation, similar to that observed by us with other affinity labeling steroid bromoacetates.[1] By contrast, the corresponding steroid 17-chloroacetates did not inactivate this enzyme. This is consistent with our earlier findings that the more reactive bromoacetoxy group provides a steroid derivative which can be an active *affinity labeling* compound while a chloroacetoxy group does not.[1b]

We are currently conducting experiments with the above affinity labeling steroids to determine the nature of their biological activity in the pregnant rat. Thus far we know that these compounds do not interfere with pregnancy under the same conditions which cause termination of pregnancy when 16α-bromoacetoxyprogesterone is used.[2,3] Therefore the new compounds are being tested for possible long-acting progestational activity, and also for antiovulatory activity.

Experimental Section

All melting points were determined in a Mel-Temp apparatus and are reported uncorrected. Steroids were purchased from Steraloids, Inc., Wilton, N.H., and reagents and solvents were from Fisher Scientific Co. Ultraviolet spectra were determined in methanol with a Beckman Model 25 spectrophotometer. Infrared spectra were determined in KBr, unless otherwise stated, with a Beckman Acculab 4 spectrometer. Nuclear magnetic resonance spectra were determined in deuteriochloroform with tetramethylsilane as internal standard in a Varian T-60 spectrometer, and chemical shifts are reported as τ values. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. All the reactions were monitored by thin layer chromatography with Eastman silica gel sheets (no. 6060) containing a fluorescent indicator. Benzene–ethyl acetate (96:4) was used to develop the chromatograms. Iodine and/or ultraviolet light were used for visualization. Silica gel G (Merck AG-Darmstadt) was the adsorbant for short column chromatography. Optical rotations were determined in chloroform using 2% solutions in a 1-dm semimicro (2.5 mL) tube with a Dr. Steeg and Reuter Model SR-5 polarimeter. Removal of solvents was carried out under reduced pressure in a Buchler flash evaporator.

17α-Hydroxy-6α-methyl-4-pregnene-3,20-dione Trifluoroacetate (3a) and 17α-Hydroxy-6α-methyl-4-pregnene-3,20-dione Chloroacetate (2). Reaction A. To a mixture of 300 mg of bromoacetic acid and 1.0 mL of trifluoroacetic anhydride kept at room temperature for 0.5 h was added 700 mg of medroxyprogesterone (**1a**). After stirring the reaction mixture for 1 h at 65 °C, it was cooled, neutralized with 5% $NaHCO_3$, and extracted with ether. The ethereal extract was washed with 5% $NaHCO_3$ and then with water, dried ($MgSO_4$), and filtered. TLC analysis of the filtrate on silica gel G (benzene–ethyl acetate, 96:4) showed it to contain at least four components in addition to starting material. Attempts to separate this mixture by preparative TLC or column chromatography were unsuccessful.

The above ethereal filtrate was concentrated under reduced pressure and the residue was heated under reflux in 25 mL of ethanol containing 0.5% of concentrated HCl for 35 min. The reaction mixture was cooled, neutralized with 5% $NaHCO_3$, and concentrated under reduced pressure. The residue was extracted with ether and the extract was washed successively with 5% $NaHCO_3$ and water, dried ($MgSO_4$), and then filtered. The filtrate, which contained three major components, was concentrated to a solid residue and then chromatographed on a short silica gel column eluted with benzene–ethyl acetate (96:4). Pooled fractions gave compounds **3a, 2,** and starting material **1a.** Recrystallization of **3a** from cyclohexane (trace of acetone) gave 90 mg of crystals: mp 163–165 °C; $[\alpha]^{25}_D$ +117°; λ_{max} 239 nm (ε 16 500). Anal. Calcd for $C_{24}H_{31}F_3O_4$: C, 65.44; H, 7.09; F, 12.94. Found: C, 65.39; H, 7.27; F, 13.32. Strong IR absorptions at 1780 (trifluoroacetate), 1720 (C-20, C=O), 1677 (C-3, C=O), and 1620 cm^{-1} (Δ^4) support structure **3a.** The structural assignment was further confirmed by NMR: τ 9.25 (s, 3, 18-CH_3), 8.92 (d, 3, J = 3.5 Hz, 6α-CH_3), 8.80 (s, 3, 19-CH_3), 7.90 (s, 3, 21-CH_3), 4.22 (narrow m, 1, 4-CH=).

Compound **2** was recrystallized from petroleum ether–trace of acetone to give 75 mg of colorless needles: mp 200–202 °C; $[\alpha]^{25}_D$ +93°; λ_{max} 239 nm (ε 15 300). Anal. Calcd for $C_{24}H_{33}ClO_4$: C, 68.48; H, 7.90; Cl, 8.42. Found: C, 68.40; H, 8.05; Cl, 8.36. ν_{max} 1730 (ester), 1709 (C-20, C=O), 1669 (C-3, C=O), 1612 cm^{-1} (Δ^4); NMR τ 9.29 (s, 3, 18-CH_3), 8.92 (d, 3, J = 3.5 Hz, 6α-CH_3), 8.80 (s, 3, 19-CH_3), 7.90 (s, 3, 21-CH_3), 5.93 (s, 2, $ClCH_2CO$), 4.15 (narrow m, 1, 4-CH=).

Reaction B. To a solution of 204 mg of chloroacetic acid in 1.0 mL of trifluoroacetic anhydride kept at room temperature for 25 min was

added 700 mg of **1a**. After working up the mixture as described for reaction A, 50 mg of **3a** and 65 mg of **2** were obtained. These products were identical in all respects (TLC, UV and IR spectra, mixture melting point) with those obtained by reaction A.

Reaction C. Medroxyprogesterone 17-bromoacetate (**4a**, 250 mg) was heated under reflux in 25 mL of ethanol containing 0.5% of concentrated HCl for 35 min. The solution was then worked up as in reaction A. Chromatography was not required since the crude product could be readily crystallized from acetone–petroleum ether to give 190 mg of **2**.

Medroxyprogesterone 17-Bromoacetate (17α-Bromoacetoxy-6α-methyl-4-pregnene-3,20-dione, 4a). Compound **4a** was prepared from **1a** by a procedure similar to that described above for the preparation of compound **2** by reaction A, except that ethanolic HBr was used instead of ethanolic HCl for selective hydrolysis of the intermediates. Chromatography gave compound **4a** which was recrystallized from petroleum ether (trace of acetone) to give 120 mg of colorless needles: mp 172–174 °C; $[\alpha]^{25}_D$ +63°; λ_{max} 239 nm (ε 15 750). Anal. Calcd for $C_{24}H_{33}BrO_4$: C, 61.93; H, 7.15; Br, 17.17. Found: C, 62.10; H, 7.12; Br, 16.95. ν_{max} 1730 (ester), 1720 (C-20, C=O), 1670 (C-3, C=O), 1614 cm^{-1} (Δ^4); NMR τ 9.30 (s, 3, 18-CH_3), 8.92 (d, 3, J = 3.5 Hz, 6α-CH_3), 8.80 (s, 3, 19-CH_3), 7.93 (s, 3, 21-CH_3), 6.16 (s, 2, $BrCH_2CO$), 4.23 (narrow m, 1, 4-CH=).

17α-Trifluoroacetoxyprogesterone (17α-Hydroxy-4-pregnene-3,20-dione 17-Trifluoroacetate, 3b) and 17α-Bromoacetoxyprogesterone (17α-Bromoacetoxy-4-pregnene-3,20-dione, 4b). Compounds **3b** and **4b** were prepared from **1b** (680 mg) by a procedure similar to that described above for the preparation of compound **4a**. Compound **3b** was recrystallized from acetone–petroleum ether to give 90 mg (10% overall yield) of white crystals: mp 190–192 °C (lit.[5] mp 191–193 °C); $[\alpha]^{25}_D$ +71°; λ_{max} 240 nm (ε 18 000). Similarity of its TLC and IR with that of compound **3a** support the structural assignment which was further confirmed by NMR: τ 9.27 (s, 3, 18-CH_3), 7.90 (s, 3, 21-CH_3), 4.28 (narrow m, 1,4-CH=). Compound **4b** was recrystallized from acetone–petroleum ether to give 110 mg (12% overall yield) of white, crystalline material: mp 165–167 °C; $[\alpha]^{25}_D$ +66°; λ_{max} 239 nm (ε 16 500). Anal. Calcd for $C_{23}H_{31}BrO_4$: C, 61.20; H, 6.92; Br, 17.70. Found: C, 61.40; H, 7.08; Br, 17.60. IR absorption max 1736 (ester), 1717 (C-20, C=O), 1670 (C-3, C=O), 1619 cm^{-1} (Δ^4); NMR τ 9.29 (s, 3, 18-CH_3), 8.92 (d, 3, J = 3.5 Hz, 6α-CH_3), 7.92 (s, 3, 21-CH_3), 6.15 (s, 2, $BrCH_2CO$), 4.29 (8, narrow m, 4-CH=).

3,17α-Dihydroxy-6-methyl-3,5-pregnadien-20-one Bis(trifluoroacetate) (5). A mixture of 1.4 g of medroxyprogesterone **1a** and 3 mL of trifluoroacetic anhydride was heated under reflux for 1 h at 65 °C under anhydrous conditions. It was then cooled and concentrated to about half of the original volume, stirred for 35 min at room temperature with 350 mL of 5% $NaHCO_3$, extracted with ether, dried, and filtered. TLC analysis of the filtrate showed it to contain three steroidal components in addition to starting material. The filtrate was concentrated to a solid residue and chromatographed on a short silica gel column eluted with benzene–ethyl acetate (96:4). Of the two products isolated from pooled fractions, one was found to be identical in all respects (TLC, mixture melting point, spectroscopic data) with **3a** described above, and the second was further purified by recrystallization from petroleum ether to give 500 mg of **5**: mp 78–81 °C; $[\alpha]^{25}_D$ −100°; λ_{max} 243 nm (ε 7200). Anal. Calcd. for $C_{26}H_{30}F_6O_5$: C, 58.21; H, 5.64; F, 21.25. Found: C, 58.75; H, 6.35; F, 17.1 (the instability of the 3-enol trifluoroacetate group results in the unsatisfactory elemental analysis obtained). ν_{max} 1790 (trifluoroacetate), 1725 cm^{-1} (C-20, C=O); NMR τ 9.27 (s, 3, 18-CH_3), 9.02 (s, 3, 19-CH_3), 8.33 (s, 3, 6α-CH_3), 7.90 (s, 3, 21-CH_3), 3.75 (narrow m, 1, 4-CH=).

Conversion of 5 into 3a. Compound **5** (50 mg) was heated under reflux in 4 mL of 0.5% ethanolic HBr for 30 min. The reaction mixture was cooled, neutralized with 5% $NaHCO_3$, and concentrated under reduced pressure. The residue was extracted with ether and the extract was washed successively with 5% $NaHCO_3$ and water, dried ($MgSO_4$), and then filtered. The filtrate was concentrated to a solid residue which was crystallized from cyclohexane (trace of acetone) to give 35 mg of colorless needles, identical (TLC, mixture melting point, spectroscopic data) with **3a**, described above.

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Registry No.—**1a**, 520-85-4; **1b**, 68-96-2; **2**, 61886-08-6; **3a**, 61886-09-7; **3b**, 560-10-1; **4a**, 61886-10-0; **4b**, 61886-11-1; **5**, 61886-12-2; trifluoroacetic anhydride, 407-25-0; bromoacetic acid, 79-08-3; chloroacetic acid, 79-11-8.

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(14) Reference 10, p 320.
(15) We prepared medroxyprogesterone 17-phenylacetate, previously reported by Babcock et al.,[4] under the same conditions used for synthesis of **2**, described in the Experimental Section. Our yields were 10–15% with 80% recovery of starting material, **1a**. The product exhibited the same physical and spectral properties as reported earlier.[4]
(16) British Patent 876 902; *Chem. Abstr.*, **56**, 8806*d* (1962). The patent describes treatment of 17α-hydroxy-19-norprogesterone with an acid anhydride or acid chloride in presence of *p*-toluenesulfonic acid or perchloric acid to form the corresponding enol diester. The diester could be selectively hydrolyzed with aqueous methanolic KOH to regenerate the Δ^4-3-keto grouping.
(17) F. Sweet and J. C. Warren, *Biochem. Biophys. Acta*, **260**, 759 (1972).