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Detailed Study of Oxidative Esterification and Elimination Reactions Undergone by a Steroidal 17α-Benzoyloxy-20-oxo-21-aldehyde

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Abstract □ The reaction of 17α-benzoyloxy-11β-hydroxy-3,20-dioxo-1,4-pregnadien-21-al as the hemiacetal (**1**) with methanol:acetic acid:potassium cyanide:manganese dioxide followed by acetylation and preparative HPLC of the reaction mixture afforded 11 crystalline products. These products can be conveniently divided into three categories representing side-chain cleavage and oxidative esterification with or without elimination of the benzoyloxy group. Of special interest was the stereospecific formation of the C-17 cyanohydrin acetate **4a** and the *cis* $\Delta^{17(20)}$ enol acetate methyl ester **5**. On the other hand, nonstereospecific addition of HCN to the side chain gave the C-20 epimeric cyanohydrin acetates **7a** and **7b**. The use of activated versus nonactivated MnO_2 plays a major role in determining the quantitative distribution of the products. It was also discovered that even in the absence of MnO_2, the reaction goes to completion. A proposed mechanism which explains the formation of all products is presented.

Following the original detailed description of the preparation and properties of steroidal glycolic acids and their derivatives by one of us,[1,2] the biological importance of this class of compounds was discovered by Monder and Bradlow,[3,4] who showed that they constitute significant metabolites of cortisol in humans. Furthermore, it was later demonstrated that certain 20-oxo and 20-hydroxy acid esters possess both local and topical anti-inflammatory activity without the usual systemic side effects associated with chronic corticosteroid therapy.[5-8] Studies directed toward the development of improved methods of synthesis and a better understanding of the reaction mechanisms involved in their preparation therefore represent a desirable objective for future research.

In 1968 Corey et al.[9] described the preparation of methyl esters from aldehydes using activated manganese dioxide (MnO_2) and methanol (MeOH) in the presence of hydrocyanic acid (HCN). This reaction was applied in the steroid field by Laurent, Gerhards, and Wiechert,[7,8] who prepared alkyl 20-oxo-21-oates by oxidative esterification of the corresponding 21-aldehydes.

A recent paper by Khalil et al.[10] described the reaction of 17α-benzoyloxy-11β-hydroxy-3,20-dioxo-1,4-pregnadien-21-al with potassium cyanide (KCN):acetic acid (ACOH):MeOH:MnO_2. The two products isolated were 11β-hydroxy-1,4-androstadiene-3,17-dione (**2**) and methyl 11β-hydroxy-3,20-dioxo-1,4-pregnadien-21-oate (**15**) in yields of 30 and 44%, respectively. An independent study of the reactions undertaken in this laboratory as a result of former collaboration with Khalil et al. has revealed that a more complex and interesting reaction sequence occurs. Furthermore, we have demonstrated that the two products isolated by the other workers are largely artifactual, arising from the use of silica gel column chromatography.

After carrying out the reaction under identical conditions, we treated the crude product with pyridine:acetic anhydride, trapping as acetates the several labile products which otherwise would have decomposed during subsequent manipulation. The acetylated reaction mixture was subjected to preparative reversed-phase high-performance liquid chromatography (HPLC). Eleven crystalline products (Scheme I) were identified on the basis of UV, IR, MS, NMR, X-ray diffraction, and elemental and functional group analyses. Independent synthesis of several of the products served both to confirm the structural assignments and improve the yields.

Results

Reaction of the glyoxal benzoate hemiacetal **1** (Scheme I) under identical conditions as those employed by Khalil et al.,[10] followed by treatment of the reaction mixture with pyridine:acetic anhydride overnight at room temperature, afforded a complex mixture, as shown by the chromatogram in Figure 1A. (In contrast to the glyoxal hydrate employed by Khalil et al.,[10] we chose to crystallize the glyoxal from methanol, which afforded the hemiacetal.[11] No difference in reactivity under Khalil's conditions was noted.) By use of preparative reversed-phase HPLC in acetonitrile:water and rechromatography of selected fractions in methanol:water, we recovered 11 crystalline compounds in a total isolated

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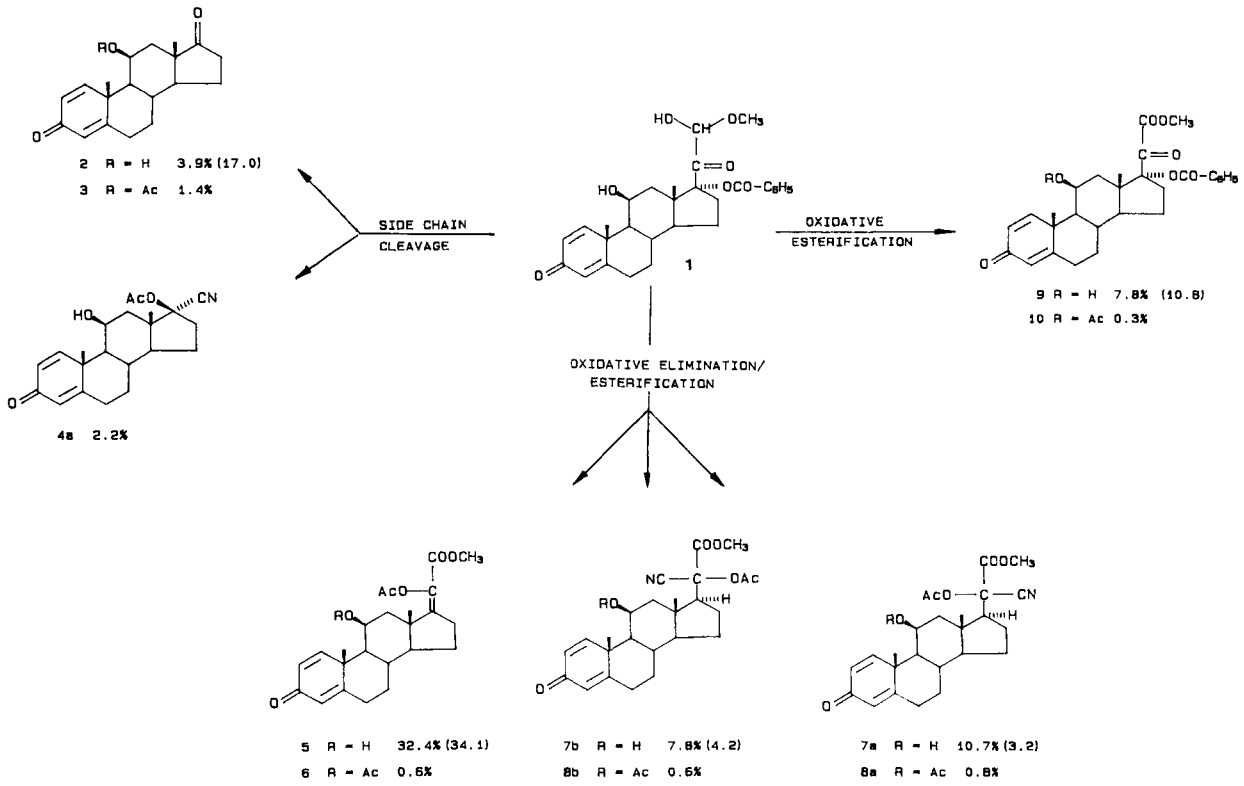


Scheme I

yield of 68.5% (see Scheme I). The reaction products can conveniently be placed in three categories representing side chain cleavage, oxidative esterification with elimination, and oxidative esterification without elimination.

Side-Chain Cleavage Products—The total yield was 7.5%. Compound 2 (3.9%) was identical in all respects with the known 11β-hydroxy-1,4-androstadiene-3,17-dione.[12] Forced acetylation of 2 afforded a product with the same IR spectrum and HPLC retention as 3 (1.4%), thereby establishing its identity as 11β-acetoxy-1,4-androstadiene-3,17-dione.

Based on X-ray diffraction analysis, **4a** was identified as 17α-cyano-17β-acetoxy-11β-hydroxy-1,4-androstadien-3-one. Independent synthesis of **4a** and the C-17 epimeric cyanohydrin acetate **4b** was achieved by reaction of the 17-one 2 with acetone cyanohydrin:triethylamine, followed by acetylation and HPLC (Scheme II). The pure cyanohydrin acetates **4a** and **4b** were each isolated in 6.3% yield. Alternatively, treatment of 2 with MeOH:AcOH:KCN followed by acetylation and HPLC gave **4a** and **4b** in yields of 36.7 and 0.7%, respectively. Significant acetylation at C-11 also occurred during these independent syntheses. Yields and constants for the two 11,17-diacetates **11a** and **11b** are given in the *Experimental Section*.

Oxidative Esterification with Elimination Products—The total yield of the six products in this major category was 52.9%. Compound 5, the main product (32.4%), was identified as methyl 11β-hydroxy-3-oxo-1,4-*cis*-17(20)-pregnatrien-21-oate. The side-chain configuration was established by stereospecific dehydration with thionyl chloride in pyridine of methyl 20β-acetoxy-17-hydroxy-3,11-dioxo-1,4-pregnadien-21-oate (**12**)[6] (Scheme III). The resulting enol acetate[13] **13** was identical with the 11-ketone obtained by oxidation of 5 with chromic anhydride:pyridine. Forced acetylation of 5 gave a product identical with 6 (0.6%).

Compounds **7a** (10.7%) and **7b** (7.8%) were identified as the methyl esters of the C-20 epimeric cyanohydrin acetates. The corresponding 11-acetates **8a** (0.8%) and **8b** (0.6%) were also isolated. Forced acetylation of **7a** and **7b** gave products identical with **8a** and **8b**, respectively. X-ray diffraction analysis of **8a** established the stereochemistry depicted in Scheme I. To our knowledge, this is the first reported successful chromatographic separation of C-17 and C-20 epimeric cyanohydrin acetates.

Oxidative Esterification Products—The combined yield of the two products in this category was 8.1%. Compound **9**, methyl 17α-benzoyloxy-11β-hydroxy-3,20-dioxo-1,4-pregnadien-21-oate (the expected product) was obtained in a yield of 7.8%. Substitution of dichlorodicyanobenzoquinone (DDQ) for MnO_2 resulted in a considerably improved yield (65%) of **9**. Forced acetylation at C-11 afforded a product identical with **10** (0.3%).

Discussion

In comparing our results with those of Khalil et al.[10] it is apparent that marked discrepancies exist. They obtained the 17-one 2 in 30% yield; our recovery was 5.3% for 2 and 3 combined. We obtained in <1% yield the methyl 20-oxo-21-oate **15**, compared with their stated yield of 44%. Since it can be assumed that the crude reaction mixtures in both laboratories were similar, if not identical, the discrepancy must be due to the manner in which the mixtures were subsequently treated. In our preliminary experiments wherein the reaction was carried out without acetylation, both IR analysis and a positive ferric chloride test indicated that enolic material was present, but disappeared in the course of subsequent handling. Stability studies undertaken on the crystalline enol methyl ester **14** (see below) showed

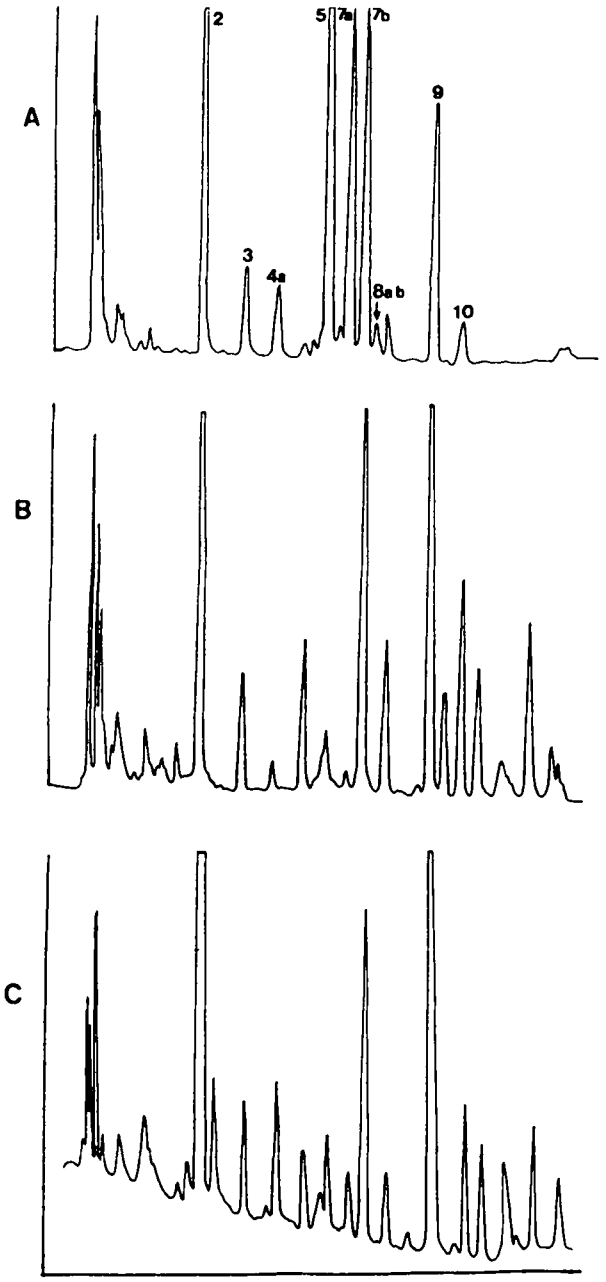
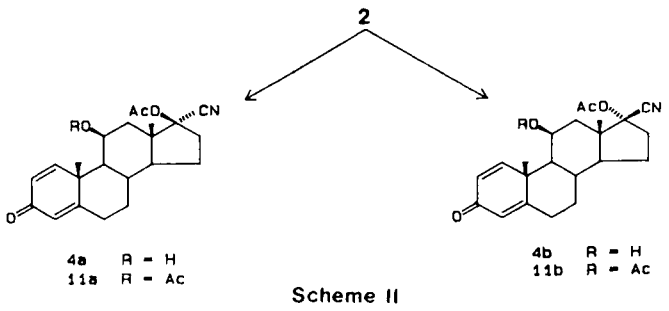


Figure 1—Reversed-phase HPLC of reaction mixture using (**A**) nonactivated MnO_2 (ref 10); (**B**) activated MnO_2 (Aldrich black); and (**C**) activated MnO_2 (Aldrich brown). For identification of the products see Scheme I. The HPLC conditions were as follows: 30–70% ACN/W in 30 min; flow, 8 mL/min; detection, 285 nm; column, Alltech C_{18} (9.4 × 250 mm).

that exposure to either silica gel or heat led to >50% conversion to the 17-ketone 2 and the ketonization product 15, respectively (Scheme IV). It was for this reason that we chose to acetylate the reaction mixture so as to prevent decomposition to the artifacts regarded as products by Khalil et al.[10] We cannot explain, however, their failure to recover the benzoyloxy methyl ester 9, since this product would have survived silica gel chromatography.

A plausible mechanism which explains the formation of all products is shown in Scheme V. Addition of HCN to the aldehyde **a** gives the cyanohydrin **b**. Oxidative abstraction of two hydrogens from **b** forms the oxalyl nitrile **c** which, following attack by methoxide ion, affords the methyl ester benzoate **9**. Alternatively, the cyanohydrin **b** loses the labile C-20 proton with a

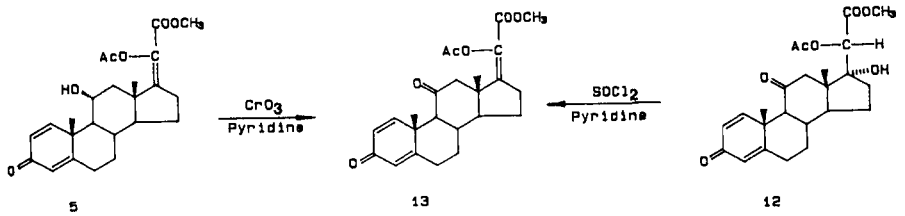


Scheme II

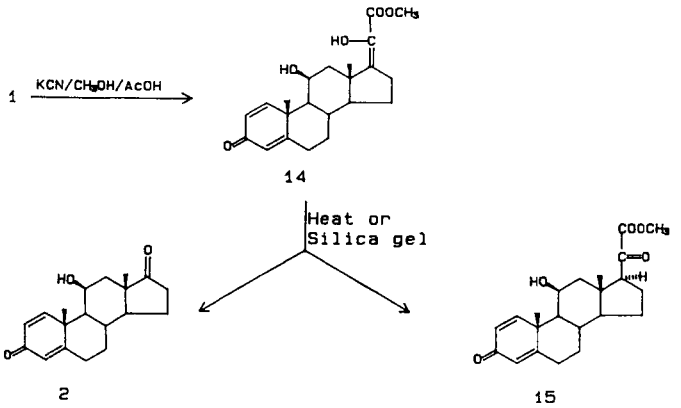
simultaneous shift of two electrons, leading to the enediol **d**. Loss of the C-21 hydroxyl proton followed by a concerted shift of electrons and the elimination of the benzoyloxy group results in formation of the *cis* $\Delta^{17(20)}$ enol **e**. Displacement of the cyano group by methoxide furnishes the enol methyl ester **14**. Side-chain cleavage by a retro aldol pathway leads to the 17-ketone **2**. The apparent stereospecific addition of HCN to **2** gives the cyanohydrin **f**. By contrast, a nonstereospecific addition of HCN across the 17(20) double bond of **14** provides the C-20 cyanohydrins **g** and **h**.

In subsequent studies we found that formation of the enol methyl ester **14** occurs in the absence of MnO_2 in 76.7% yield, contradicting the statement of Khalil et al.[10] that no reaction occurs under these conditions. Presumably, increased reactivity of the C-21 aldehyde group brought about by the adjacent carbonyl group at C-20 and an excellent leaving group at C-17 permits oxidative esterification with elimination merely in the presence of air. We have explored the role of MnO_2 in the reaction described by Khalil et al.[10] Although both Corey et al.[9] and Laurent et al.[7,8] used activated material, Khalil et al. chose to employ nonactivated MnO_2.[14] We carried out preliminary studies wherein the glyoxal benzoate **1** was subjected to Corey conditions using both brown and black activated MnO_2, as well as the nonactivated oxidant. Although a detailed study was not made, it is evident from Figure 1 that following acetylation and preparative HPLC, more side-chain cleavage and oxidative esterification without elimination occurred in the presence of activated MnO_2. On the other hand, the C-20 epimeric cyanohydrin acetates were not recovered under these conditions. A number of unidentified products were also isolated but not further characterized.

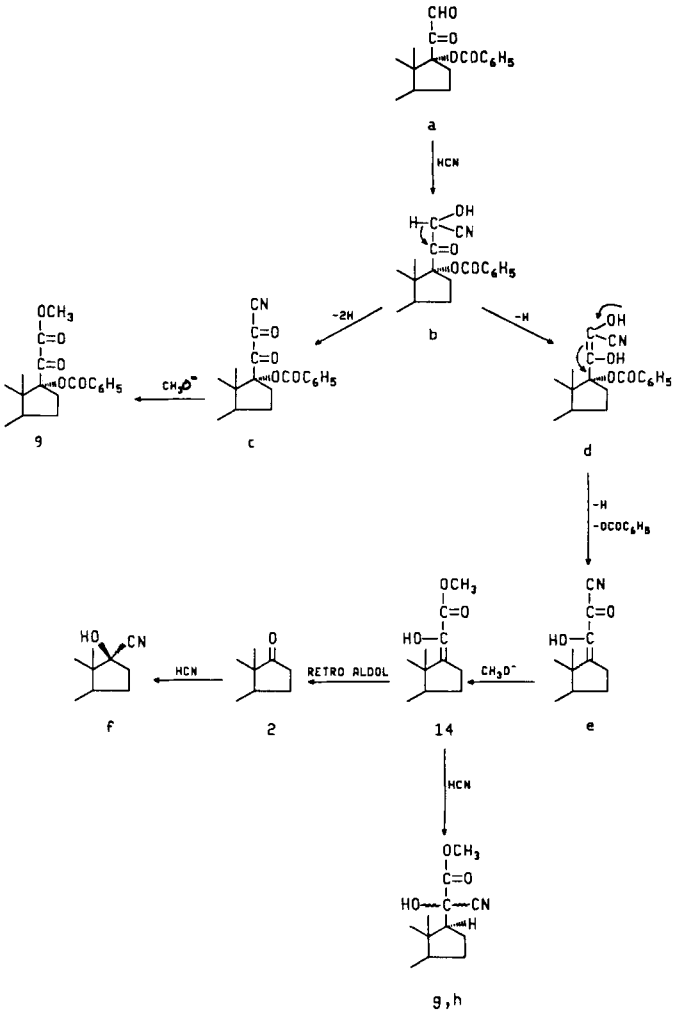
The complexity of the reaction mixture encountered in our study is due in part to the unexpected acetylation of the 11β-hydroxyl group, since five of the isolated products were 11-acetates. This result is surprising since under the mild conditions employed (pyridine:acetic anhydride overnight at room temperature), acetylation at this hindered position should not occur.[15] The possibility exists, therefore, that some component of the reaction mixture promoted this side reaction. Accordingly, pure samples of **2**, **5**, and **9** were treated with pyridine:acetic anhydride under the same conditions as those employed in the original preparation. Based on relative peak heights, HPLC showed in each case conversion to the corresponding 11-acetate in approximately the same proportion as was observed in the crude reaction mixture. Our ability to isolate 11-acetates, therefore, must be ascribed to careful attention to and identification of all HPLC peaks encountered in our study. However, when the Corey reaction was repeated but acetylation carried out for only 1 h, no 11-acetates were recovered. Although the total yield (69.8%) of crystalline products was about the same as with the overnight acetylation, there were significant differences in the quantitative distributions (yields given parenthetically in Scheme I). Especially noteworthy was a considerable reduc-



Scheme III



Scheme IV



Scheme V

tion in yield of the C-17 (none isolated) and C-20 cyanohydrin acetates (3.2 and 4.2% for **7a** and **7b**, respectively) since their moderately hindered hydroxyls react slowly with pyridine:-acetic anhydride. Consequently, the yield of the 17-ketone 2 was significantly higher (17.0%) after the shorter acetylation time. By contrast, the readily acetylable enolic hydroxyl of 14 afforded 5 in a yield (34.1%) comparable to that obtained after overnight acetylation.

Experimental Section

Melting points were obtained with a Fisher-Johns apparatus and are uncorrected. Optical activity was determined in chloroform at 26 ± 1° with a Zeiss 0.005° photoelectric polarimeter at 589 nm (D line of sodium). Ultraviolet (UV) spectra were obtained in methanol (MeOH) using either a Zeiss RPQ20A recording spectrophotometer or a Gilford model 240 instrument.

Infrared (IR) spectra were generated on zinc selenide multiple internal reflectance crystals in a Perkin-Elmer model 681 spectrophotometer. The NMR spectra were obtained on a Varian XL-400 spectrometer. Mass spectra were recorded under positive chemical ionization conditions using a Hewlett-Packard 5985B mass spectrometer. Methane was used as the reagent gas at a pressure of 0.25 torr. Samples were introduced by means of a direct insertion probe. X-ray diffraction analyses were carried out on a Enraf-Nonius CAD4 diffractometer with Cu radiation (k = 1.54178A).

Semipreparative HPLC was carried out in a DuPont model 850 liquid chromatograph coupled with a model 860 absorbance detector using 9.4 mm (i.d.) × 25 cm columns packed with 5 μM octadecyl silane-bonded silica gel (reversed-phase) at a flow rate of 8 mL/min. Preparative HPLC was performed in a Perkin-Elmer Series 3B liquid chromatograph equipped with a LC-75 detector using 22.1 mm (i.d.) × 25 cm columns at a flow rate of 22.5 mL/min. Linear gradients were run at 40 °C using either acetonitrile (ACN):water (W) or MeOH:W. All solvents were purchased as HPLC grade or distilled prior to use in an all-glass apparatus. Thin-layer chromatography (TLC) was performed with 5 × 20 or 10 × 20 cm EM Science $60F_{254}$ silica gel glass plates. The solvent system was toluene:acetone (3:1).

Nonactivated manganese dioxide (MnO_2) was obtained from Mallinckrodt (No. AR 6133, lot no. KPXH). Brown (No. 21, 764-6) and black (No. 22, 432-4) MnO_2 were purchased from Aldrich Chemical Company.

All reactions were carried out at room temperature unless otherwise noted. Reaction mixtures routinely were worked up by dilution with dichloromethane (DCM) and successive washing with dilute acid, alkali, and water. Filtration through anhydrous sodium sulfate was followed by concentration to dryness on a rotary evaporator. All reactions and work-ups involving the generation of hydrocyanic acid were carried out in an efficient hood.

Microanalyses were performed by Galbraith Laboratories, Knoxville, TN.

Reaction of Glyoxal Benzoate Hemiacetal 1 with MnO_2:KCN: AcOH:MeOH—To a solution of **1** (1200 mg, mp 216–220 °C) in MeOH (24 mL) and AcOH (1.2 mL) was added 12.0 g of nonactivated MnO_2

and 1200 mg of KCN. After stirring the mixture in air for 30 min, the insoluble material was filtered off and washed repeatedly with DCM. The combined filtrates were washed with water and concentrated to dryness. The residue was treated with 5 mL each of pyridine and acetic anhydride for 17 h. After addition of MeOH to decompose excess anhydride, the reaction mixture was processed in the usual manner. Preparative HPLC in ACN:W (30 to 70% ACN in 30 min) gave rise to the chromatogram depicted in Figure 1A. Eluates were concentrated to remove most of the organic solvent, then extracted with DCM. Products were recovered, crystallized, characterized, and identified on the basis of decreasing chromatographic mobility.

Compound 2—The crude product (28.6 mg, 3.9%) had an IR spectrum identical with that of reference 11β-hydroxy-1,4-androstadiene-3,17-dione;[12] R_f = 0.23.

Compound 3—The eluate residue weighed 12.0 mg (1.4%). Treatment of **2** (50 mg) in AcOH (0.8 mL) and acetic anhydride (0.2 mL) with *p*-toluenesulfonic acid (25 mg) for 4 h[15] followed by HPLC gave 11β-acetoxy-1,4-androstadiene-3,17-dione as platelets from ethyl acetate (EA):isooctane (ISO), mp 209.5–210 °C; R_f = 0.25. The IR spectrum was identical with that of **3**; $[\alpha]_D$ +152°; UV:λ_{max} 240 nm, • 19 500; IR: 1740 (sh, 17-one), 1728, 1240, 1222 (acetate), 1660, 1620, 1600, and 887 cm^{-1} (1,4-dien-3-one); ^1H NMR: 1.07 (18-CH_3), 1.30 (19-CH_3), 2.12 (11-OAc), 5.55, 6.3 (H-11), 6.05 (H-4), 6.27 (dd, 10.2, H-2), and 6.95 ppm (d, 10, H-1); CIMS: *m/z* (% relative abundance) 343 (41.0) M+H, 283 (100) M-HOCOCH$_3$.

Anal.—Calc. for $C_{21}H_{26}O_4$: C, 73.65; H, 7.65. Found: C, 73.43; H, 7.42.

Compound 4a—Rechromatography of the eluate residue (29.1 mg) in MeOH:W gave 19.9 mg (2.2%) of 17α-cyano-17β-acetoxy-11β-hydroxy-1,4-androstadien-3-one as prisms from EA:ISO, mp 231–233 °C; R_f = 0.24; $[\alpha]_D$ +15.7°; UV: λ_{max} 245 nm, ε 17 900; IR: 3470 (hydroxyl), 2238 (w, cyano), 1755 and 1220 (cyanohydrin acetate), 1660, 1618, 1600 and 887 cm^{-1} (1,4-dien-3-one); ^1H NMR: 1.21 (18-CH_3), 1.46 (19-CH_3), 2.21 (17-OAc), 2.37 (ddd, 13.5, 5.0, 2, H-6eq), 2.57 (tdd, 13.5, 5.5, 2), 2.85 (ddd, 15.0, 10.0, 6.0, H-16), 4.54 (qn, 2, H-11), 6.03 (H-4), 6.28 (dd, H-2), and 7.23 ppm (d, H-1); CIMS: 370 (43.7) M+H, 352 (100) M-H_2O, 310 (13.0) M-$COOCH_3$, 292 (28.1) M-H_2O-$COOCH_3$, 283 (19.2) M-HCN-$COOCH_3$; X-ray: suitable crystals of **4a** ($C_{22}H_{27}NO_4$) for X-ray diffraction studies formed from ethyl acetate:isooctane with space group symmetry of $P4_32_12$ and cell constants of a = 9.056(4) Å and c = 49.591(9) Å for Z = 8 and a calculated density of 1.207 g/cm^3. Of the 1707 reflections measured with an automatic four circle diffractometer equipped with Cu radiation, 1493 were observed (I^3sI). The structure was solved with a direct methods approach, and difference Fourier analysis and refined using full-matrix least-squares techniques.[16] Hydrogens were assigned isotropic temperature factors corresponding to their attached atoms. The function $S1(wF_ow - wF_cw)^2$, with $1 = 1/(sF_o)^2$, was minimized to give an unweighted residual of 0.069. The only short intermolecular contact is a hydrogen bond between O-20 and O-21 with dimensions O20–O21 of 2.87 (tables containing the final fractional coordinates, temperature parameters, bond distances, and bond angles are available as supplementary material).

Anal.—Calc. for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.64; H, 7.23; N, 3.73.

Compounds 4a and 4b from 2—*(a) Triethylamine:Acetone Cyanohydrin Followed by Acetylation*—To a solution of the 17-one (250 mg) in acetone cyanohydrin (2 mL) was added 2 drops of triethylamine. After 15 h, the reaction mixture was partitioned between DCM and W. The crude cyanohydrin mixture was treated with 2 mL each of pyridine and acetic anhydride for 50 h. Analysis by HPLC in ACN:W gave, in addition to **2** and **3**, an unresolved mixture of 11β-hydroxy cyanohydrin acetates (**4a** and **4b**, 82 mg) and a partially separated mixture of 11β-acetoxy cyanohydrin acetates (56 mg). Rechromatography of the **4a**:**4b** mixture in MeOH:W afforded the more mobile 17β-cyano-17α-acetoxy-11β-hydroxy-1,4-androstadien-3-one (**4b**) as prisms (19.5 mg, 6.3%) from EA:ISO, mp 212–213 °C; $[\alpha]_D$ +77.9°; UV: λ_{max} 245 nm, • 17 300; IR: 3470 (hydroxyl), 1755, 1227, 1215 (cyanohydrin acetate), 1660, 1618, 1602, and 890 cm^{-1} (1,4-dien-3-one); ^1H NMR: 1.34 (18-CH_3), 1.48 (19-CH_3), 2.07 (17-OAc), 4.57 (qn, 3, H-11), 6.04 (t.1.5), 6.30 (dd, 10, 2, H-2), and 7.25 ppm (d, 10, H-1); CIMS: 370 (36) M+H, 352 (15.8) M-H_2O, 310 (17.8) M-$COOCH_3$, 292 (100) M-H_2O-$COOCH_3$, 283 (33.1) M-HCN-$COOCH_3$.

Anal.—Calc. for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.57; H, 7.67; N, 3.90.

From the less mobile fraction was obtained 19.5 mg (6.3%) of **4a**, mp 234–235 °C.

Rechromatography of the 11β-acetoxy cyanohydrin acetate mixture in MeOH:W furnished the more mobile 17β-cyano-11β,17α-diacetoxy-1,4-androstadien-3-one (**11b**) as prisms (23 mg, 6.7%) from EA, mp 283–285 °C; $[\alpha_D$ +91°; UV: λ_{max} 239 nm, • 17 100; IR: 1758, 1740, 1235, 1215 (11-acetate and cyanohydrin acetate), 1668, 1629, 1605, 890 cm^{-1} (1,4-dien-3-one); ^1H NMR: 1.21 (18-CH_3), 1.30 (19-CH_3), 2.08 (OAc), 2.14 (OAc), 5.59 (H-11), 6.04 (H-4), 6.29 (H-2), 6.95 (H-1); CIMS: 412 (14.6) M+H, 352 (37.6) M-HOAc, 292 (100) M-(2)HOAc, 265 (58.6) M-HCN-(2)HOAc.

Anal.—Calc. for $C_{24}H_{29}NO_5$: C, 70.05; H, 7.10; N, 3.40. Found: C, 70.03; H, 7.16; N, 3.33.

From the less mobile fraction was obtained 5 mg (1.5%) of **11a** as prisms from EA:ISO, mp 227–228 °C. Forced acetylation of **4a** furnished a product identical in all respects with this less mobile diacetate; $[\alpha]_D$ +43.5°; UV: λ_{max} 239 nm, ε 17 000; IR: 1750, 1735, 1225 (11-acetate and cyanohydrin acetate), 1655, 1622, 1600, and 883 cm^{-1} (1,4-dien-3-one); ^1H NMR: 1.21 (18-CH_3), 1.30 (19-CH_3), 2.08 (OAc), 2.14 (OAc), 5.59 (H-11), 6.04 (H-4), 6.29 (H-2), and 6.95 ppm (H-1); CIMS: 412 (32.5) M+H, 380 (10.6), 353 (100) M-HOAc, 292 (34.9) M-(2)HOAc, 283 (11.5), 265 (15.8) M-HCN-(2)HOAc.

Anal.—Found: C, 69.70; H, 7.08; N, 3.09.

(b) KCN:AcOH:MeOH Followed by Acetylation—A solution of **2** (250 mg) in 2.5 mL of MeOH:AcOH (1:1) was treated with 500 mg of KCN. After 1 h, the product was recovered and acetylated as above in (*a*). Sequential HPLC in ACN:W and MeOH:W furnished 113 mg (36.7%) of **4a**, 2.1 mg (0.7%) of **4b**, 80.5 mg (23.5%) of **11a**, and 4.2 mg (1.2%) of **11b**.

Compound 5—Crystallization from EA followed by rechromatography of the mother liquor in MeOH:W gave 327 mg (32.4%) of prisms, mp 257–260 °C; R_f = 0.26; $[\alpha]_D$ +99.4°; UV: λ_{max} 234 nm, • 27 300; IR: 3420 (hydroxyl), 1760, 1220 (enol acetate), 1725 (carbomethoxyl), 1660, 1620, 1600, and 887 cm^{-1} (1,4-dien-3-one); ^1H NMR 1.19 (18-CH_3), 1.33 (19-CH_3), 2.14 (OAc), 2.19 (OAc), 3.87 (OCH_3), 5.44 (H-11), 6.05 (H-4), 6.39 (dd, H-2), and 6.95 ppm (d, H-1); CIMS: 415 (83.0) M+H, 397 (100) M-H_2O, 383 (95.3) M-CH_3O, 373 (15.1) M-$COCH_2$, 355 (60.8) M-$COOCH_3$.

Anal.—Calc. for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30; OCH_3, 7.49. Found: C, 69.39; H, 7.23; OCH_3, 7.62.

Compound 13 from 5—Treatment of **5** (10 mg) in pyridine (0.5 mL) with excess chromic anhydride for 2.5 h, followed by HPLC in ACN:W gave methyl 20-acetoxy-3,11-dioxo-1,4,*cis*-17(20)-pregnatrien-21-oate **13** as a filterable solid.

Compound 13 from 12—Treatment of methyl 20β-acetoxy-17-hydroxy-3,11-dioxo-1,4-pregnadien-21-oate[6] (**12**) with thionyl chloride in pyridine afforded a product with a new UV chromophore.[13] The IR spectrum was identical with that of **13** obtained by oxidation at C-11 of **5**.

Compound 6—The 11-acetate of **5** was recovered in low yield (7 mg, 0.6%) from the mother liquors of **7b** (see below). Independent synthesis was accomplished by forced acetylation of **5**; for the analytical sample: mp 218–220 °C; R_f = 0.34; $[\alpha]_D$ +129°; UV: λ_{max} 233 nm, • 26 400; IR: 1762, 1205 (enol acetate), 1728 (carbomethoxyl and 11-acetate), 1662, 1630, 1605, and 885 cm^{-1} (1,4-dien-3-one); ^1H NMR: 1.08 (18-CH_3), 1.29 (19-CH_3), 2.13 (OAc), 2.19 (OAc), 5.55 (q, H-11), 6.04 (H-4), 6.27 (ddd, H-2), and 6.91 ppm (d, H-1); CIMS: 457 (39.2) M+H, 425 (25.5) M-OCH_3, 397 (100) M-$COOCH_3$, 355 (76.3) M-$COOCH_3$-$COCH_2$, 337 (20.6) M-$COOCH_3$-$COCH_2$-H_2O.

Anal.—Calc. for $C_{26}H_{32}O_7$: C, 68.40; H, 7.07. Found: C, 68.57, 68.50; H, 7.21, 7.24.

Compound 7a—Direct crystallization followed by rechromatography of the mother liquor in MeOH:W supplied 115 mg (10.7%) of fine needles from methanol, mp 254–256 °C; for the analytical sample: mp 256–257.5 °C; R_f = 0.22; $[\alpha]_D$ +75.3°; UV: λ_{max} 244 nm, ε 17 300; IR: 3400 (broad, hydroxyl), 1758, 1218 (cyanohydrin acetate), 1665, 1616, 1600, and 887 cm^{-1} (1,4-dien-3-one); ^1H NMR: 1.28 (18-CH_3), 1.47 (19-CH_3), 2.22 (OAc), 3.88 (OCH_3), 4.40 (H-11), 6.04 (H-4), 6.29 (H-2), and 7.27 ppm (H-1); CIMS: 442 (82.5) M+H, 424 (69.8) M-H_2O, 373 (22) M-HCN-$COCH_2$, 364 (100) M-H_2O-$COOCH_3$, 355 (63.0) M-$COOCH_3$-HCN.

Anal.—Calc. for $C_{25}H_{31}NO_6$: C, 68.00; H, 7.08; OCH_3, 7.03; N, 3.17. Found: C, 67.94; H, 7.26; OCH_3, 7.31; N, 3.16.

Compound 7b—Processing as with **7a** gave 84 mg (7.8%) of long needles from methanol, mp 284–286 °C; for the analytical sample: mp 286–286.5 °C; R_f = 0.23; $[\alpha]_D$ +42.1°; UV: λ_{max} 244 nm, ε 17 900; IR:

3340 (sharp, hydroxyl), 1755, 1225 (cyanohydrin acetate), 1655, 1610, and 887 cm^{-1} (1,4-dien-3-one); ^1H NMR: 1.25 (18-CH_3), 1.46 (19-CH_3), 2.18 (OAc), 3.85 (OCH_3), 4.38 (H-11), 6.01 (H-4), 6.27 (H-2), and 7.22 ppm; CIMS: 442 (61.9) M+H, 424 (60.9) M-H_2O, 382 (25) M-$COOCH_3$, 364 (100) M-$COOCH_3$-H_2O, 355 (24.0) M-$COOCH_3$-HCN.

Anal.—Found: C, 68.03; H, 7.22; OCH_3, 7.22; N, 3.11.

Compound 8a—The 11-acetate of **7a** was isolated in low yield (10 mg, 0.8%) from the mother liquors as prisms from EA:ISO, mp 197.5–198 °C; R_f = 0.30. Forced acetylation of **7a** afforded a product identical with **8a**; $[\alpha]_D$ +103°; UV: λ_{max} 240 nm, ϵ 16 100; IR: 1758, 1225 (cyanohydrin acetate), 1732 (carbomethoxyl and 11-acetate), 1660, 1628, 1604, and 887 cm^{-1} (1,4-dien-3-one); ^1H NMR: 1.18 (18-CH_3), 1.30 (19-CH_3), 2.14 (OAc), 2.18 (OAC), 3.85 (OCH_3), 5.43 (H-11), 6.03 (H-4), 6.27 (H-2), and 6.29 ppm (H-1); CIMS: 484 (26.0) M+H, 424 (100) M-$COOCH_3$, 364 (78.3) M-$COOCH_3$-H_2O-$COCH_2$, 355 (18.4) M-$COOCH_3$-HCN-$COCH_2$; X-ray: suitable crystals of **8a** ($C_{27}H_{33}NO_7$) for X-ray diffraction studies formed from methanol with a space group symmetry of $P2_1$ and cell constants of a = 10.772(2) Å, b = 8.135(1) Å, c = 30.834(5) Å, and b = 95.03(1)° for Z = 4 and a calculated density of 1.233 g/cm^3. Of the 3933 reflections measured with an automatic four-circle diffractometer equipped with Cu radiation, 3583 were observed (I^3sI). The structure was solved with a direct methods approach and difference Fourier analysis, and was refined using full-matrix least-squares techniques.[16] Hydrogens were assigned isotropic temperature factors corresponding to their attached atoms. A single molecule of methanol was found in the asymmetric unit. The function S1 $(wF_o w - wF_c W)^2$ with $1 = 1/(sF_o)^2$ was minimized to give an unweighted residual of 0.050. No abnormally short intermolecular contacts were noted. Tables containing the final fractional coordinates, temperature parameters, bond distances, and bond angles are available from the authors.

Anal.—Calc. for $C_{27}H_{33}NO_7$: C, 67.06; H, 6.88. Found: C, 66.90; H, 6.65.

Compound 8b—The 11-acetate of **7b** was obtained in low yield (7 mg, mp 213–215 °C) as a companion of **8a**. Forced acetylation of **7b** gave an identical product; R_f = 0.29; $[\alpha]_D$ +87.6°; UV: λ_{max} 240 nm, ϵ 16 800; IR: 1755, 1225 (cyanohydrin acetate), 1735 (carbomethoxyl and 11-acetate), 1665, 1628, 1604, and 888 cm^{-1} (1,4-dien-3-one); ^1H NMR: 1.16 (18-CH_3), 1.30 (19-CH_3), 2.12 (OAc), 2.16 (OAC), 3.85 (OCH_3), 5.36 (H-11), 6.02 (H-4), 6.26 (H-2), 6.90 (H-1); CIMS: 484 (30.2) M+H, 424 (100) M-$COOCH_3$, 364 (63.1) M-$COOCH_3$-$COCH_2$-H_2O.

Anal.—Found: C, 66.60, 66.86; H, 6.79, 6.60.

Compound 9—Direct crystallization from aqueous methanol gave 94 mg (7.8%) of needles, mp 196–198 °C, R_f = 0.27; for the analytical sample: mp 200–202 °C; $[\alpha]_D$ +1.62°; UV: λ_{max} 234 nm, • 26 900; IR: 3440 (hydroxyl), 1740, 1728, 1290, 713 (carbomethoxyl and benzoate), 1700 (sh, 20-one), 1660, 1620, 1602, and 887 cm^{-1} (1,4-dien-3-one); ^1H NMR: 1.06 (18-CH_3), 1.49 (19-CH_3), 3.74 (OCH_3), 3.16 (H-16), 4.60 (H-11), 6.06 (H-4), 6.32 (H-2), 7.31 (H-1), 7.47 (meta), 7.61 (para), 7.95 (ortho); CIMS: 493 (0.9) M+H, 475 (0.7) M-H_2O, 437 (7.7) M-$COOC_6H_5$, 353 (7.6) M-H_2O-$COOC_6H_5$, 123 (100) [$HCOOC_6H_5$+H].

Anal.—Calc. for $C_{29}H_{32}O_7$: C, 70.73; H, 6.55; OCH_3, 6.30. Found: C, 70.50; H, 6.45; OCH_3, 7.19, 7.21.

Compound 9 from 1 Using DDQ—To a stirred solution of glyoxal benzoate hemiacetal (100 mg) in MeOH (2 mL) and AcOH (0.1 mL) was added sequentially 100 mg each of DDQ and KCN. After 30 min, the mixture was diluted with DCM (30 mL). The precipitate was filtered off and washed with DCM. The combined filtrates were washed with water and concentrated to dryness. Analysis by HPLC in ACN:W gave 65 mg (%) of needles from aqueous methanol, mp 198–201 °C. The IR spectrum was identical with that of **9** obtained from **1** in the presence of MnO_2.

Compound 10—Direct crystallization from EA furnished 4 mg (0.3%) of prisms, mp 207–209 °C, R_f = 0.33. Forced acetylation of **9** gave a product identical with **10**; $[\alpha]_D$ +8.55°; UV: λ_{max} 235 nm, ϵ 29 300; IR: 1740, 1725, 1285, 710 (carbomethoxyl and benzoate), 1700 (sh, 20-one), 1728, 1240 (11-acetate), 1660, 1624, 1602, and 885 cm^{-1} (1,4-dien-3-one); ^1H NMR: 0.95 (18-CH_3), 1.31 (19-CH_3), 2.10 (OAc), 3.72 (OCH_3), 3.17 (H-16), 5.67 (H-11), 6.08 (H-4), 6.33 (H-2), 7.02 (H-1), 7.49 (meta), 7.62 (para), 7.95 (ortho); CIMS: 535 (4.0) M+H, 475 (5.7) M-$HOCOCH_3$, 413 (6.0) M-$COOCH_6H_5$, 353 (9.7) M-$COOC_6H_5$-$HOCOCH_3$, 123 (100) [$HCOOC_6H_5$+H]$^+$.

Anal.—Calc. for $C_{31}H_{34}O_8$: C, 69.64; H, 6.41. Found: C, 69.49; H, 6.21.

Compound 14 from 1—To a solution of glyoxal benzoate hemiacetal **1** (500 mg) in MeOH (10 mL) was added AcoH (0.5 mL) and KCN (500 mg). The solution was stirred in air for 15 min, then partitioned between DCM and water. After a second water wash, the solvent was removed. Direct crystallization from DCM:ISO afforded 290 mg (76.7%) of needles, mp 137–140 °C; $[\alpha]_D$ +46.6°; UV: λ_{max} 248 nm, ϵ 26 100; IR: 3480 (hydroxyl), 1665 (conjugated carbomethoxyl), 1665, 1621, 1605, and 890 cm^{-1} (1,4-dien-3-one); ^1H NMR: 1.23 (18-CH_3), 1.48 (19-CH_3), 3.84 (OCH_3), 4.43 (H-11), 5.28 (OH), 5.31 (CH_2Cl_2), 6.02 (H-4), 6.28 (H-2), and 7.30 ppm (H-1); CIMS: 373 (48.3) M+H, 355 (100) M-H_2O, 337 (21.1) M-(2)H_2O, 295 (23.5) M-H_2O-$COOCH_3$.

Anal.—Calc. for $C_{22}H_{28}O_5 \cdot 1/2CH_2Cl_2$: C, 65.62; H, 6.94; O, 19.0. Found: C, 65.44, 66.00; H, 7.26, 7.08; O, 19.70, 19.40.

Effect of Heat on 14—A sample (50 mg) was heated at 100 °C for 15 h in an Abderhalden apparatus attached to a vacuum pump. Analysis by HPLC in MeOH:W gave 0.7 mg (1.7%) of 17-one **2**, 29.4 mg (58.3%) of methyl 11β-hydroxy-3,20-dioxo-1,4-pregnadien-21-oate **15**, and 9.6 mg (19.2%) of starting material.

Effect of Silica Gel Column Chromatography on 14—A sample (50 mg) of enol methyl ester was slowly run through a 15 × 280 mm silica gel bed in 9:1 chloroform:MeOH. The eluate residue (46 mg) was rechromatographed by HPLC in ACN:W. A recovery of 22.5 mg (55.8%) of 17-one **2** and 2.75 mg (5.5%) of the 20-one **15** was achieved.

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