Biomimetic Polyene Cyclizations.[1-3] Participation of the Methylacetylenic Terminator and Nitroalkanes. A Synthesis of Testosterone

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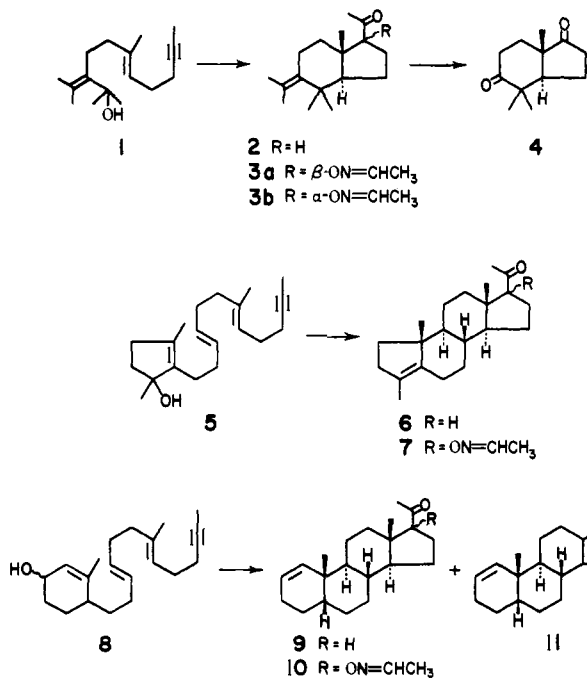
Abstract: The aim of this study was to examine nitroalkanes as trapping agents for the presumed intermediary vinyl cation formed in the acid-catalyzed cyclization of allylic alcohols **1, 5,** and **8**. Treatment of a solution of the allylic alcohols **1, 5,** and **8** with excess trifluoroacetic acid in nitroethane resulted in the formation of the isomeric oxime ethers **3, 7,** and **10**. Confirmation of the trans-fused hydrindan skeleton of **3** was established by oxidative degradation to the known dione **4**. The use of nitroethane as the cyclization solvent allows for the formation of syn and anti forms of the oxime ethers, thereby increasing the complexity of the products formed. This problem was eliminated by using 2-nitropropane as the cyclization solvent. Cyclization of **8** in 2-nitropropane with trichloroacetic acid yielded the oxime ether **12** which was readily converted to diol **13** with lithium aluminum hydride in refluxing THF. The stereoisomeric mixture of diols was converted, by two different synthetic pathways (see Schemes I and V), into the 17-hydroxypregnan-20-ones **15** and **16** and *dl*-testosterone benzoate (**34**). Catalytic reduction of the Δ^1 olefinic bond in diol **13**, followed by oxidation of the secondary hydroxyl group with *N*-bromosuccinimide, afforded *dl*-17α-hydroxy-5β,17β-pregnan-20-one (**15**) and *dl*-17β-hydroxy-5β,17α-pregnan-20-one (**16**). Alternatively, treatment of the diol **13** with periodic acid gave ketone **28** which upon reduction with sodium borohydride and esterification of the resulting hydroxyl group with benzoyl chloride afforded the benzoate **30**. Oxidation of **30** with *tert*-butyl chromate, followed by reduction of the Δ^1 olefinic bond, gave ketone **32**. Enol acetylation of ketone **32**, followed first by bromination, then dehydrobromination, and cleavage of the resulting semicarbazone, resulted in the completion of a facile synthesis of *dl*-testosterone benzoate (**34**) in 18% overall yield from trienynol **8**.

Discussion

It was shown in previous studies[4,5] that the acid-catalyzed cyclization of dienynol **1** and trienynols **5** and **8**, all possessing methylacetylenic terminators, leads to ketones **2, 6,** and **9**, respectively, when the postulated intermediary polycyclic vinyl cation is trapped by certain nucleophiles such as ethylene carbonate. In the course of studying a variety of nucleophilic trapping agents, it was discovered that nitroalkanes perform this function in an interesting manner, reacting with the vinyl cation to give oximino ethers (e.g., **3, 7,** and **10**). While our work was in progress, Semenovskii et al.[6] disclosed the results of their studies showing that nitroalkanes act as nucleophilic trapping agents for vinyl cations to give oximino ethers. In our systems these substances provide entries into the 17-hydroxypregnan-20-one as well as the 17-oxygenated steroid systems, and the present paper constitutes a detailed account of this study which has culminated in a synthesis of *dl*-testosterone benzoate (**34**).

When a solution of the known[4] dienynol **1**, contaminated with 12% of the homoallylic alcohol, in nitroethane was stirred with an excess of trifluoroacetic acid for 15 min at −78 °C, an oily product was isolated and shown by VPC to contain ca. 80% of a 55:45 mixture of two compounds. This mixture was tentatively formulated as the isomeric oxime ethers **3a** and **3b** based on the following spectral and chemical evidence. The IR spectrum displayed carbonyl absorption at 5.83 μ and imine absorption at 6.12 μ. The ^{1}H NMR spectrum of a chromatography fraction enriched in **3a** included singlets at δ 1.07 and 1.20 ppm for the three methyl groups attached to quaternary carbon atoms and at 1.66 and 1.80 ppm for the isopropylidene methyl groups. In addition, a singlet appeared at δ 2.07 ppm for the acetyl methyl group, a doublet at 1.90 ppm for the ethylidene methyl group, and a quartet at 6.83 ppm for the vinyl proton. The ^{1}H NMR spectrum of another chromatography fraction enriched in **3b** included singlets at δ 0.70, 1.15, 1.23, 1.70, and 1.82 ppm (see above) in addition to a singlet at 2.03 ppm for the acetyl methyl group, a doublet at 1.90 ppm for the ethylidene methyl group, and quartet at 6.90 ppm for the vinyl proton. The assignment of **3a** and **3b** as the α-acetyl and β-acetyl isomers, respectively, is based on the positions of the C-8 methyl group in the ^{1}H NMR spectra at 1.07 and 0.70 ppm, respectively, which is analogous to the positions of the corresponding C-18 methyl group in authentic samples of 17β-hydroxy-5β,17α-pregnan-20-one (**16**) at 0.92 ppm and 17α-hydroxy-5β,17β-pregnan-20-one (**15**) at 0.70 ppm, described below.



Irradiation at δ 6.90 ppm of the specimen enriched in **3b** produced a collapse of the doublet at 1.90 ppm to a singlet. Furthermore, when benzene-d_6 was used as the solvent, the sample enriched in **3b** showed upfield shifts of ca. 0.46 ppm for the doublet at 1.90 ppm and the quartet at 6.90 ppm. Confir-

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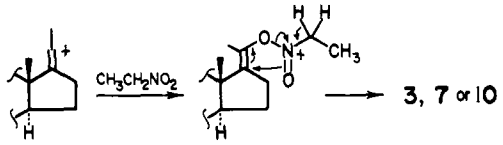
mation of the structure was obtained by degradation of the cyclization product to the known[7] *trans*-hydrindandione **4** upon oxidation with excess ruthenium tetroxide in carbon tetrachloride.[8]

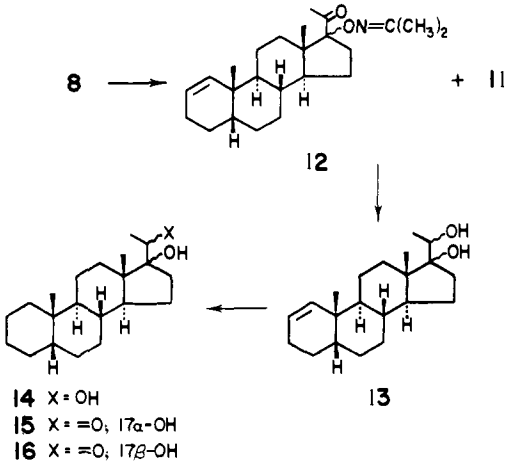
Initial efforts to extend this reaction to the tetracyclic series involved similar cyclization of the known[4] allylic alcohol **5**, which gave a ca. 1:1 mixture of the C-17 epimeric oxime ethers **7** by comparison of the C-18 methyl group peak heights in the ^{1}H NMR spectrum. The IR and ^{1}H NMR spectra were similar to those for **3** and were in complete accord with structure **7**. A rationalization of the formation of these oxime ethers is suggested by the following equation.



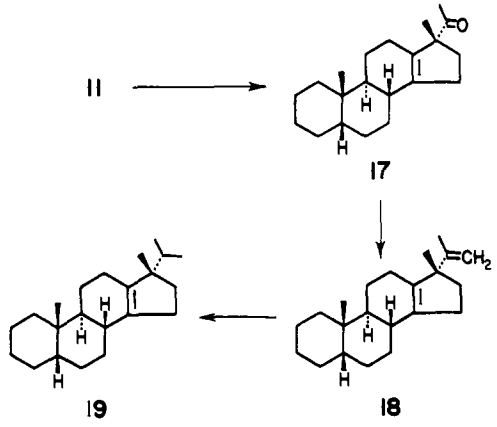
Attention was next turned to a more detailed study of the cyclization of the known[5] trienynol **8**. By analogy to this work described below, we feel that the structural assignments **3** and **7** in the preliminary studies are now secure. Cyclization of trienynol **8** with ca. 1% trifluoroacetic acid in nitroethane at −30 °C for 3 h afforded a 71% yield of the epimeric oxime ethers **10** as well as 13% of a new, nitrogen-free ketone which appeared to be the product **11** resulting from backbone rearrangement (see below). The structural assignment of the epimeric oxime ethers **10** was based on IR and ^{1}H NMR data which were similar to those described above for **3**; however, these products were isomerically complex. Attention was, therefore, turned to the use of 2-nitropropane in place of nitroethane with the expectation that the elimination of the possibility of syn and anti forms would simplify the isomer problems. Thus, treatment of a solution of the trienynol **8** with trichloroacetic acid in 2-nitropropane at 0 °C for 4 h gave an oily mixture consisting of 79% of the oxime ether **12** and 14% of the rearranged ketone **11** as shown by VPC (see Scheme I). Preparative TLC afforded a 45% yield of the oxime ether which was shown by comparison of the C-18 methyl group peak heights in the ^{1}H NMR spectrum to be a ca. 1:1 mixture of the 17α- and 17β-acetyl isomers. The IR spectrum showed carbonyl absorption at 5.86 μ and imine absorption at 6.11 μ. The ^{1}H NMR spectrum included singlets at δ 0.64 and 0.97 ppm for the C-18 methyl group of the α-acetyl and β-acetyl isomers, respectively, at 1.00 ppm for the C-19 methyl group of both isomers, and at 1.83, 1.87, 1.90, 1.99, 2.03, and 2.06 ppm for the methyl groups adjacent to the carbonyl and oxime groups. In addition, there were two singlets at δ 5.54 and 5.60 ppm for the olefinic protons in ring A.

Cyclization of the trienynol **8** in 2-nitropropane in the presence of stannic chloride at ca. −20 °C for 1 h provided a

Scheme I



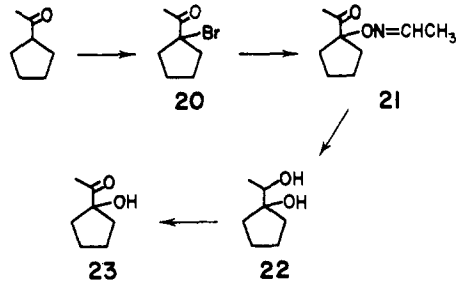
Scheme II



mixture consisting of 81% of the rearranged ketone **11** and 9% of the isomeric oxime ethers **12** as shown by VPC. Purification of the product by LC followed by evaporative distillation and recrystallization afforded pure rearranged ketone **11**, mp 65.5–67.0 °C. The IR spectrum showed carbonyl absorption at 5.91 μ while the ^{1}H NMR spectrum included singlets at δ 0.98 ppm for the C-19 methyl group, at 1.12 ppm for the C-17 methyl group, and at 2.03 ppm for the acetyl methyl group. In addition, absorption was present at δ 5.60 ppm for the olefinic protons at C-1 and C-2. Cyclization of the trienynol **8** with trifluoroacetic acid in nitrobenzene at 0 °C for 2 h also provided a 37% yield of the rearranged ketone **11** (ca. 86% pure by VPC) as well as nonvolatile impurities. The rearranged ketone was assigned the structure shown in formula **11** based on the aforementioned spectral data as well as the chemical transformations described below (see Scheme II). Hydrogenation of **11** over 10% palladium on carbon at room temperature and atmospheric pressure resulted in reduction of the Δ^1 olefinic bond to give ketone **17**, mp 82–83 °C, which, when treated with methylenetriphenylphosphorane, formed the normal Wittig product **18**. The carbonyl absorption found in the IR spectrum of ketone **17** was absent and absorption at 6.09 and 11.20 μ due to an exocyclic methylene group was present. The ^{1}H NMR spectrum was also consistent with the assigned structure **18**, showing singlets at δ 0.90 ppm for the C-19 methyl group, 1.13 ppm for the C-17 methyl group, 1.67 ppm for the isopropenyl methyl group, and 4.70 ppm for the olefinic protons. The crude product was hydrogenated over palladium on carbon at room temperature and atmospheric pressure to give 17β-methyl-17α-isopropyl-18-nor-Δ^{13}-5β-androstene (**19**), which was identical by IR, ^{1}H NMR, and VPC coinjection with an authentic specimen[9] prepared previously from 5β-pregnan-20-one.

Although spectral data strongly suggested that the oxime ether structure **12** was correct, it seemed desirable to convert it to a known steroid. The transformations involving the conversion of the oxime ether moiety to a hydroxyl group were first carried out on a model compound (see Scheme III). The known[10] bromo ketone **20** was treated with the sodium salt of acetaldoxime to afford the oxime ether **21**. Attempts to effect

Scheme III

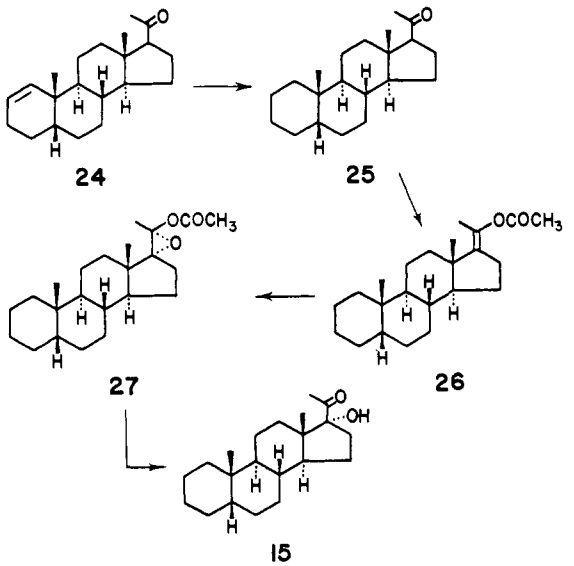


reductive cleavage of the N-O bond to give the known[11] α-hydroxy ketone **23** in one step were not successful. Catalytic hydrogenolysis under a variety of conditions as well as reduction with chromous acetate[12] gave either complex mixtures of products or unreacted starting material. However, it was observed that lithium aluminum hydride in refluxing THF readily effected hydrogenolysis of the N-O bond in addition to reducing the carbonyl group to give the known[13] diol **22**. Several methods were investigated for the conversion of the secondary hydroxyl group to a keto group without effecting concomitant cleavage of the vicinal diol to carbonyl fragments. Jones reagent (with or without added manganese salts),[14] Collins reagent,[15] and silver carbonate on Celite[16] all gave predominantly cyclopentanone. However, aqueous *N*-bromosuccinimide[17] readily effected the conversion of diol **22** to the known[11] α-hydroxy ketone **23**.

Similarly, treatment of the unpurified mixture of oxime ethers **12** (see Scheme I) with excess lithium aluminum hydride in refluxing THF afforded an isomeric mixture of diols **13** in 54% yield after preparative TLC. Since **13** can exist in four possible stereoisomeric forms it was not fully characterized; however, its ^{1}H NMR and IR spectra were entirely consistent with the assigned structure. Hydrogenation of the diol mixture **13** was effected with palladium on carbon at room temperature and atmospheric pressure to give diol **14** as a mixture of stereoisomers in 98% yield. The ^{1}H NMR spectrum indicated the absence of olefinic protons. Oxidation of **14** with *N*-bromosuccinimide followed by preparative TLC effected separation of the hydroxy ketones **15** and **16** which were thus obtained in ca. 69% combined yield from **13** correcting for about 11% of recovered diol. Recrystallization of **15** from hexane gave colorless needles, mp 148-149 °C, identical by ^{1}H NMR, IR, TLC, and mixture melting point with an authentic sample of *dl*-17α-hydroxy-5β,17β-pregnan-20-one, synthesized as described below from *dl*-Δ^1-5β-pregnen-20-one.[5b] Recrystallization of **16** from hexane gave colorless needles, mp 159-164 °C, identical by ^{1}H NMR, IR, TLC, and VPC coinjection with an authentic sample of *d*-17β-hydroxy-5β,17α-pregnan-20-one.[18]

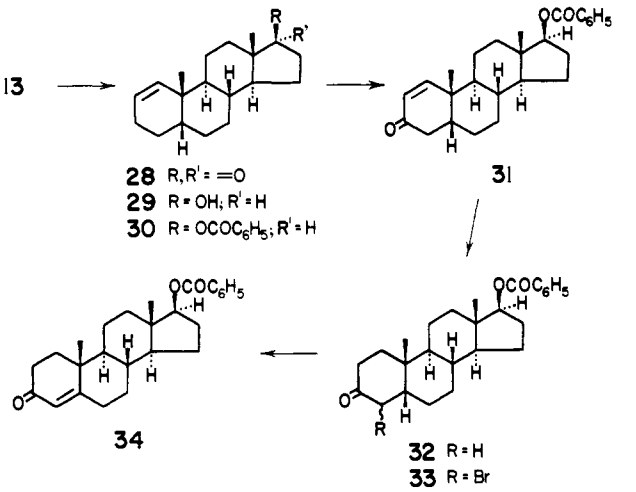
An authentic specimen of *dl*-17α-hydroxy-5β,17β-pregnan-20-one (**15**) was synthesized from *dl*-Δ^1-5β-pregnen-20-one (**24**)[5b] in the following manner (see Scheme IV).

Scheme IV



Reduction of the Δ^1 olefinic bond with 10% palladium on carbon at room temperature and atmospheric pressure afforded the known[19] 5β-pregnan-20-one (**25**) as a 32:68 mixture of the 17α- and 17β-acetyl epimers as shown by VPC. The crude ketone **25** was treated with acetic anhydride in the presence of *p*-toluenesulfonic acid monohydrate[20] to give the $\Delta^{17,20}$-enol acetate **26**. Selective α-epoxidation with peracetic acid[21] followed by rearrangement of the epoxy acetate **27** in aqueous sodium hydroxide solution afforded *dl*-17α-hydroxy-5β,17β-pregnan-20-one (**15**) as colorless needles, mp 148-149 °C, in 48% yield from **25**.

Scheme V



The formation of a mixture of C-17 epimers **12** in the cyclization of **8** detracts from the usefulness of this route for the total synthesis of 17α-hydroxyprogesterone. However, additional studies, e.g., with hindered nitroalkanes, hopefully may reveal a method of realizing stereoselectivity.

The isomeric mixture of diols **13** which proved to be so useful in the conversion of oxime ether **12** to hydroxy ketones **15** and **16** also promised to be degradable to a 17-oxy steroid. This possibility was indeed realized and has culminated in a stereospecific synthesis of *dl*-testosterone benzoate (**34**). This approach is all the more attractive because trienynol **8** has been obtained in its optically active forms which have been shown to undergo cyclization without racemization to give the enantiomeric tetracyclic products.[5] Therefore it follows that the *d* form of **8** will lead to the enantiomer **9** of natural configuration, which in turn will give *d*-testosterone benzoate. The details of the synthesis of racemic material are described below (see Scheme V).

Oxidation of the crude diol mixture **13** with aqueous periodic acid[22] at room temperature, followed by purification of the crude product with Girard reagent T,[23] afforded ketone **28** in 51% yield. Reduction of the C-17 ketone with sodium borohydride in ethanol at room temperature, followed by esterification of the resulting hydroxyl group with benzoyl chloride in pyridine, gave benzoate **30** in 93% yield from **28**. Oxidation of the crude benzoate **30** with *tert*-butyl chromate reagent[24] in tetrachloroethylene containing glacial acetic acid and acetic anhydride at 85 °C for 45 min gave the enone **31**, which was used in the next step without purification. Catalytic reduction with palladium on carbon at room temperature and atmospheric pressure afforded ketone **32**, which, after two recrystallizations, afforded colorless plates, mp 112.5-114.0 °C, identical by ^{1}H NMR, IR, and TLC with authentic 17β-hydroxy-5β-androstan-3-one benzoate (**32**).[25]

The conversion of **32** into **34** was accomplished in four steps without isolation of intermediates. Thus, reaction of ketone **32** with acetic anhydride in the presence of perchloric acid[26] gave a mixture consisting of predominantly the desired Δ^3-enol acetate, contaminated with lesser amounts of the Δ^2 isomer. Treatment with bromine in carbon tetrachloride in the presence of epichlorohydrin to act as an acid scavenger[27] afforded a mixture containing predominantly the 4-bromo ketone **33**. Reaction of **33** with semicarbazide, followed by hydrolysis with aqueous pyruvic acid of the intermediary α,β-unsaturated

semicarbazone[28] and purification by preparative TLC, gave *dl*-testosterone benzoate (**34**), mp 178–182 °C, in 45% yield overall from **28** (18% yield overall from trienynol **8**). Three recrystallizations from absolute ethanol afforded **34** as colorless plates, mp 184.0–185.5 °C, identical by ^{1}H NMR, IR, and TLC with an authentic, naturally derived specimen of testosterone benzoate.

Experimental Section[29]

General Considerations. The prefix *dl* has been omitted from the names of all racemic compounds described in this section. Microanalyses were performed by E. H. Meier and J. Consul, Department of Chemistry, Stanford University. Melting points were determined on a Kofler hot-stage microscope calibrated against totally immersed Anschutz thermometers. NMR spectra were recorded under the supervision of Dr. L. J. Durham on Varian Associates A-60, T-60, and XL-100 spectrometers. Deuteriochloroform was used as the solvent unless indicated otherwise and chemical shifts are reported as δ values in parts per million relative to tetramethylsilane = 0. Mass spectra were determined on either an Associated Electrical Industries MS-9 or an Atlas CH-4 spectrometer under the supervision of Dr. A. M. Duffield. Infrared (IR) spectra were recorded on Perkin-Elmer Models 137 and 421 spectrometers. Vapor-phase chromatographic (VPC) analyses were performed on either a Perkin-Elmer 810 (aluminum column) or a Hewlett-Packard HP 402 chromatograph (glass column) using the following $\frac{1}{8}$ in. columns: 6 ft 3% OV-17 on Gas-Chrom Q (glass), 3% XE-60 on Gas-Chrom Q (glass), 4 ft 5% SE-30 on Gas-Chrom Q (glass), and 5% Carbowax 20M on Chromosorb W (aluminum). Nitrogen was used as the carrier gas on the Perkin-Elmer chromatograph and helium was used as the carrier gas on the Hewlett-Packard chromatograph. Disk chart integrations are uncorrected for detector response. Analytical and preparative thin layer chromatography (TLC) was performed using silica gel HF_{254} (E. Merck AG) as the adsorbent at 0.25 and 1.0 mm thicknesses, respectively. Analytical plates were visualized by spraying with a solution of 2% ceric sulfate in 2 N sulfuric acid; then heating the plate at 180 °C for 5–10 min. High-pressure liquid chromatography (LC) was performed on a Waters ALC-201 chromatograph using a refractive index detector. "Evaporative distillation" refers to bulb-to-bulb short-path distillation in which the bulb was heated in a hot-air oven (Büchi Kugelrohrofen). The cited temperatures for these distillations refer to the maximum temperature attained by the oven during the distillation and are thus not true boiling points.

Cyclization of Alcohol 1. *O*-(1-Acetyl-5-isopropylidene-4,4,8β-trimethyl-9α-hydrindan-1-yl)acetaldoxime (3). A solution of 246 mg (1.0 mmol) of the known[4] alcohol **1** (contaminated with 12% of the homoallylic alcohol as shown by VPC) in 125 mL of dry nitroethane was stirred under nitrogen at −78 °C while 4 mL (6.2 g, 54 mmol) of trifluoroacetic acid was added via syringe over a period of 30 s. The deep-orange reaction mixture, which changed to a purple color after a few minutes, was stirred at −78 °C for 15 min, then poured into excess saturated aqueous sodium bicarbonate solution. Ether extraction[29] afforded 304 mg of orange oil, which was shown by VPC (5% SE-30, 160 °C) to consist of two major peaks (80% of the total peak area) in a ratio of 55:45.

Chromatography on Florisil (19:1 to 9:1 hexane–ether) afforded 166 mg of pale yellow oil. The first fraction containing the isomeric oxime ethers was 95% two peaks by VPC and was enriched (10:1) in the α-acetyl epimer **3a**, while the last fraction was 95% two peaks by VPC and was enriched (5:95) in the β-acetyl epimer **3b**. The 10:1 mixture of **3a** and **3b** exhibited the following properties: IR (film) 5.85 (C=O), 6.12 (C=N), 7.42, 10.23, 11.17, 13.60 μ; ^{1}H NMR 1.07 (s, 3, C-8 CH_3), 1.20 (s, 6, C-4 CH_3's), 1.66 (br s, 3, isopropylidene CH_3), 1.80 (br s, 3, isopropylidene CH_3), 1.4–2.0 (m, methylene envelope), 1.90 (d, J = 6 Hz, 3, N=CHCH_3), 2.07 (s, 3, acetyl CH_3), 2.30 (m, 2, C-6 protons), 6.83 ppm (q, J = 6 Hz, 1, N=CHCH$_3$); TLC R_f 0.64 (5:1 hexane–ethyl acetate).

The 5:95 mixture of **3a** and **3b** exhibited the following properties: IR (film) 5.83 (C=O), 6.12 (C=N), 7.44, 10.66, 11.14 μ; ^{1}H NMR 0.70 (s, 3, C-8 CH_3), 1.15 (s, 3, C-4 CH_3), 1.23 (s, 3, C-4 CH_3), 1.70 (br s, 3, isopropylidene CH_3), 1.82 (br s, 3, isopropylidene CH_3), 1.5–2.0 (m, methylene envelope), 1.90 (d, J = 5.5 Hz, 3, N=CHCH_3), 2.03 (s, 3, acetyl CH_3), 2.40 (m, 2, C-6 protons), 6.90 ppm (q, J = 5.5 Hz, 1, N=CHCH$_3$); TLC R_f 0.64 (5:1 hexane–ethyl acetate). A chromatography fraction consisting of a 1:1 mixture of **3a:3b** by VPC exhibited the following mass spectrum (70 eV): *m/e* 305 (M^+), 262 (M − 43), 203 (M − 102), 43 (base peak, M − 262).

A sample was purified by preparative TLC followed by evaporative distillation at 160 °C (0.01 mm) to afford a specimen which was 95% one peak by VPC.

Anal. ($C_{19}H_{31}NO_2$) H, N; C: calcd, 74.71; found, 72.02.

A 100-MHz ^{1}H NMR spectrum of the specimen enriched in **3b** showed collapse of the doublet at 1.90 ppm to a singlet when the quartet at 6.90 ppm was irradiated.

^{1}H NMR (benzene-d_6) of the sample enriched in **3b** showed upfield shifts of 0.46–0.47 ppm for the doublet at 1.90 ppm and the quartet at 6.90 ppm.

Oxidative Degradation of the Epimeric Oxime Ethers 3. To a solution of 20 mg of the chromatographed epimeric oxime ethers **3** (in a ratio of 55:45 by VPC) in 3 mL of carbon tetrachloride ("spectro" quality) was added 4 mL of a solution of ruthenium tetroxide in carbon tetrachloride (prepared according to a published procedure[8]), resulting in an instantaneous precipitation of black ruthenium dioxide. The mixture was stirred for 1 h and the excess oxidant was destroyed by titration with isopropyl alcohol; then the mixture was diluted with chloroform and washed with 5% aqueous sodium hydroxide[29] to give 4 mg of colorless oil, which was shown by IR, TLC, and VPC coinjection (4 ft 5% SE-30, 140 °C) to be identical with the known[7] dione **4**.

A mixture from a similar run[30] was shown by IR and TLC to contain the dione **4**.

Cyclization of Trienynol 5. *O*-(20-Oxo-3-methyl-*A*-nor-3-pregnen-17-yl)acetaldoxime (7). A solution of 175 mg (0.55 mmol) of allylic alcohol **5**[4] (>95% one peak by VPC) in 175 mL of dry nitroethane was cooled (−23 °C), and then 2.6 mL (1.57 g, 26.5 mmol) of trimethylamine was added via precooled syringe, followed by 5 mL (7.65 g, 66 mmol) of trifluoroacetic acid. After stirring for 1 h at −23 °C under nitrogen no marked color change was noted and VPC (3% XE-60, 190 °C) indicated only starting material. An additional 5 mL (7.65 g, 66 mmol) of trifluoroacetic acid was added and the resulting deep-purple solution was stirred under nitrogen at −23 °C for 2 h, then poured into excess saturated aqueous sodium bicarbonate solution. Ether extraction[29] afforded 227 mg of yellow oil, which was shown by VPC (3% XE-60, 190 °C) to consist of a major broad peak (69% of the total peak area) with a retention time of 7.1 min.

The aforementioned sample was combined with 87 mg (60% one peak on VPC) from another run and the total 314 mg was chromatographed on ca. 7 g of Florisil (19:1 pentane–ether) to give 52 mg of a pale yellow oil which was 85% one peak by VPC and showed one spot on TLC (R_f 0.64, 6:4 pentane–ethyl acetate). Evaporative distillation at 130 °C (0.01 mm) removed the volatile impurities, and then the residue was purified by evaporative distillation at 190 °C (0.01 mm) to give a specimen of **7** as a colorless oil which showed one peak on VPC (3% XE-60, 190 °C): IR (film) 5.85 (C=O), 6.11 (C=N), 7.43 μ; ^{1}H NMR 0.66 (s, 3, C-18 CH_3, β-acetyl isomer), 0.89 (s, 6, C-19 CH_3), 1.00 (s, 3, C-18 CH_3, α-acetyl isomer), 1.57 (s, 6, C-4 vinyl CH_3), 1.88 (d, 6, J = 6 Hz, C-23 vinyl CH_3), 2.03 (s, 3, α-acetyl CH_3), 2.06 (s, 3, β-acetyl CH_3), 0.7–2.6 (methylene envelope), 6.81 (q, 1, J = 6 Hz, C-22 vinyl proton, α-acetyl isomer), 6.86 ppm (q, 1, J = 6 Hz, C-22 vinyl proton, β-acetyl isomer); mass spectrum (70 eV) *m/e* 357 (M^+), 314 (M − 43), 255 (M − 102, base peak).

Anal. ($C_{23}H_{35}NO_2$) C, H, N.

Cyclization of Trienynol 8 with Trifluoroacetic Acid in Nitroethane. *O*-(Δ^1-20-Oxo-5β-pregnen-17-yl)acetaldoxime (10). A solution of 25.7 mg (0.086 mmol) of the known[5] allylic alcohol **8** in 6 mL of dry nitroethane was stirred under nitrogen at −30 °C while 0.063 mL (93 mg, 0.82 mmol) of trifluoroacetic acid was added via syringe. The mixture was stirred at −30 °C for 3 h, after which time 10 mL of saturated aqueous sodium bicarbonate was added; then the mixture was stirred for an additional 1.5 h at room temperature. Ether extraction using a base wash[29] gave 30 mg of pale yellow oil which was purified by preparative TLC (1% ethyl acetate in pentane, five elutions, R_f 0.14) to afford 10.8 mg (35% yield) of epimeric oxime ethers **10** as a colorless oil which showed one peak on VPC (3% XE-60, 186 °C): IR (film) 5.84 (C=O), 6.08 μ (C=N); ^{1}H NMR (CCl_4) 0.60 (s, 3, C-18 CH_3, β-acetyl isomer), 0.93 (s, 3, C-18 CH_3, α-acetyl isomer), 0.98 (s, 6, C-19 CH_3), 1.77–2.13 (m, 12, N=CHCH_3, acetyl CH_3), 0.5–2.8 (methylene envelope), 5.40, 5.45 (2 s, 4, C-1 and C-2 vinyl protons), 6.68 ppm (br m, 2, N=CHCH$_3$).

A sample was purified by evaporative distillation; however, a satisfactory combustion analysis could not be obtained.

A crude mixture from a similar run was shown by VPC coinjection experiments (3% XE-60, 200 °C) to contain 71% of the epimeric oxime ethers **10** and 13% of the rearranged ketone **11**, the structure proof of which is described below.

Cyclization of Trienynol 8 with Trichloroacetic Acid in 2-Nitropropane. *O*-(Δ^1-20-Oxo-5β-pregnen-17-yl)acetone Oxime (12). A solution of 49.2 mg (0.16 mmol) of the known[5] allylic alcohol **8** (>95% one peak by VPC) in 10 mL of dry 2-nitropropane was stirred under nitrogen at 0 °C while 0.48 mL (0.83 mmol) of a 1.72 M solution of trichloroacetic acid in 2-nitropropane was added in a dropwise manner via syringe. The resulting mixture was stirred at 0 °C for 2 h; then an additional 0.48 mL of the trichloroacetic acid solution described above was added and stirring was continued for 2 h at 0 °C. The mixture was diluted with 10 mL of a saturated aqueous sodium bicarbonate solution, then extracted with ether using a base wash[29] to give 61.8 mg of pale yellow oil, consisting of 79% of the oxime ether **12** and 14% of the ketone **11** as shown by VPC (3% XE-60, 189 °C). Purification by preparative TLC (R_f 0.38 and 0.33, 19:1 hexane–ethyl acetate, two elutions) afforded 27.7 mg (45% yield) of the oxime ether **12** as a colorless oil which was shown by VPC (3% XE-60, 190 °C) to be >95% one peak.

An analytical specimen was obtained by preparative TLC (19:1 hexane–ethyl acetate, seven elutions) followed by evaporative distillation at 190 °C (0.01 mm): IR ($CHCl_3$) 5.86 (C=O), 6.11 μ (C=N); ^{1}H NMR 0.64 (s, 3, C-18 CH_3, β-acetyl isomer), 0.97 (s, 3, C-18 CH_3, α-acetyl isomer), 1.00 (s, 6, C-19 CH_3), 1.83, 1.87, 1.90, 1.99, 2.03, 2.06 (6 s, 18, N=C(CH_3)$_2$, acetyl CH_3), 0.5–3.0 (br m, methylene envelope), 5.54, 5.60 ppm (2 s, 4, C-1 and C-2 vinyl protons).

Anal. ($C_{24}H_{37}NO_2$) C, H, N.

Cyclization of Trienynol 8 with Stannic Chloride in 2-Nitropropane. 17β-Methyl-18-nor-5β-pregna-1,13-dien-20-one (11). A solution of 146.2 mg (0.49 mmol) of the known[5] allylic alcohol **8** in 14 mL of 2-nitropropane was stirred under nitrogen at −40 °C while 0.57 mL (4.87 mmol) of anhydrous, fuming stannic chloride was added in a dropwise manner via syringe. The mixture was stirred between −30 and −20 °C for 1 h, after which time saturated aqueous sodium bicarbonate was added. Ether extraction using a base wash[29] afforded 84.4 mg of clear, yellow oil, which was purified by preparative TLC (R_f ca. 0.67, 4:1 hexane–ethyl acetate) to give 61.5 mg of a clear, colorless oil consisting of 81% of the rearranged ketone **11** and 9% of the isomeric oxime ethers **12** as shown by VPC (3% OV-17, 219 °C).

An analytical sample of ketone **11** was obtained by LC (4 ft × 1/8 in. Corasil II, 0.5% ethyl acetate in hexane) followed by evaporative distillation at 170 °C (0.025 mm).

Recrystallization from methanol–water afforded **11** as colorless plates, mp 65.5–67.0 °C: IR ($CHCl_3$) 5.91 μ (C=O); ^{1}H NMR 0.98 (s, 3, C-19 CH_3), 1.12 (s, 3, C-17 CH_3), 2.03 (s, 3, acetyl CH_3), 0.8–2.6 (br m, methylene envelope), 5.60 ppm (s, 2, C-1 and C-2 vinyl protons).

Anal. ($C_{21}H_{30}O$) C, H.

Cyclization of Trienynol 8 with Trifluoroacetic Acid in Nitrobenzene. 17β-Methyl-18-nor-5β-pregna-1,13-dien-20-one (11). A solution of 155.4 mg (0.52 mmol) of the known[5] allylic alcohol **8** in 15 mL of nitrobenzene was stirred under nitrogen at 0 °C while 0.43 mL (636 mg, 5.6 mmol) of trifluoroacetic acid was added in a dropwise manner via syringe. The mixture was stirred at 0 °C for 2 h, after which time 5 mL of a saturated aqueous sodium bicarbonate solution was added. Ether extraction using a base wash[29] gave 148.7 mg of a dark red-orange oil consisting of ketone **11** as well as nonvolatile impurities as shown by VPC (3% OV-17, 210 °C). Chromatography on silica gel (3–9% ethyl acetate in hexane) afforded 72.4 mg of a yellow oil which was decolorized and then filtered through Woelm neutral alumina, activity grade I, with 7:3 hexane–ethyl acetate to give 64.6 mg (37% yield) of colorless oil which was shown by VPC coinjection (3% OV-17, 210 °C) to contain 86% of ketone **11**. The IR and ^{1}H NMR spectra were superimposable on those of an authentic specimen described above.

17β-Methyl-18-nor-Δ^{13}-5β-pregnen-20-one (17). A mixture of 182 mg (0.61 mmol) of ketone **11** (>90% one peak by VPC) which had been desulfurized with Raney nickel in ethanol, 10 mL of ethyl acetate, and 180 mg of 10% palladium on carbon was hydrogenated at room temperature and atmospheric pressure for 2 h. The catalyst was removed by filtration through Celite; then the filtrate was concentrated at reduced pressure to afford 167 mg of a colorless oil which crystallized on standing at 0 °C.

An analytical sample of ketone **17** as colorless needles was prepared by four recrystallizations from methanol–water: mp 82–83 °C; IR ($CHCl_3$) 5.90 μ (C=O); ^{1}H NMR 0.90 (s, 3, C-19 CH_3), 1.13 (s, 3, C-17 CH_3), 2.07 (s, 3, acetyl CH_3), 0.5–2.6 ppm (br m, methylene envelope); mass spectrum (70 eV) *m/e* 300 (M^+), 258 (M − 42), 257 (M − 43, base peak), 161 (M − 139), 147 (M − 153).

Anal. ($C_{21}H_{32}O$) C, H.

17β-Methyl-17α-isopropyl-18-nor-Δ^{13}-5β-androstene (19). A dispersion of 202 mg (0.57 mmol) of methyltriphenylphosphonium bromide, mp 231–232 °C, in 15 mL of dry 1,2-dimethoxyethane was stirred under nitrogen while a 2.0 M solution of *n*-butyllithium in hexane was added slowly until a permanent yellow color persisted. A 0.21-mL sample (0.42 mmol) of a 2.0 M solution of *n*-butyllithium in hexane was added in one portion, and the mixture was stirred at room temperature for 45 min. A solution of 85 mg (0.27 mmol) of ketone **17**, 95% one peak by VPC, in 3 mL of 1,2-dimethoxyethane was added to the yellow solution of ylide; then the mixture was stirred overnight at room temperature, then at 70–75 °C for 1 h. The resulting mixture was concentrated, and hexane was added to precipitate the triphenylphosphine oxide. The supernatant was filtered through Florisil with hexane to give 77 mg of colorless oil. Preparative TLC (R_f 0.74, pentane) afforded 52 mg (57% yield of diene **18**, which was 93% one peak by VPC (3% OV-17, 180 °C): IR (film) 6.09 (C=C), 11.20 μ (C=CH_2); ^{1}H NMR 0.90 (s, 3, C-19 CH_3), 1.13 (s, 3, C-17 CH_3), 1.67 (s, 3, isopropenyl CH_3), 0.5–2.8 (br m, methylene envelope), 4.70 ppm (s, 2, C=CH_2).

A mixture of 16.6 mg (0.052 mmol) of diene **18** (93% one peak by VPC), 10 mL of ethyl acetate, and 20 mg of 10% palladium on carbon was hydrogenated at room temperature and atmospheric pressure for 1 h. The mixture was filtered through Celite, and then the solvent was removed at reduced pressure to give 16 mg (96% yield) of 18-norandrostene **19** as a colorless oil which was ca. 90% one peak by VPC (3% OV-17, 166 °C): ^{1}H NMR (CCl_4) 0.75 (d, J = 6 Hz, 3, isopropyl CH_3), 0.85 (d, J = 6 Hz, 3, isopropyl CH_3), 0.89 (s, 3, C-19 CH_3), 0.94 (s, 3, C-17 CH_3), 0.5–2.6 ppm (br m, methylene envelope). The above sample was identical with an authentic specimen of the known,[9] naturally derived 17β-methyl-17α-isopropyl-18-nor-Δ^{13}-5β-androstene (**19**) by IR, ^{1}H NMR, and VPC coinjection (3% OV-17, 166 °C).

***O*-(1-Acetylcyclopentyl)acetaldoxime (21).** A 388-mg sample (9.16 mmol, 57% dispersion in mineral oil) of sodium hydride was added to 30 mL of dry dimethyl sulfoxide. After evolution of hydrogen had ceased, a solution of 735 mg (12.9 mmol) of acetaldoxime (Aldrich Chemical Co., 99% pure) in 5 mL of dry dimethyl sulfoxide was added in one portion. The resulting solution was stirred under nitrogen at room temperature for 30 min, and then a solution of 1.54 g (8.1 mmol) of 1-bromo-1-acetylcyclopentane (**20**)[10] in 2 mL of dry ether was added and the stirring was continued for 1 h. The reaction was quenched by the addition of 10 mL of water, and then the mixture extracted with pentane using a base wash[29] to afford 866 mg of oxime ether **21** as a colorless oil. Chromatography on silica gel (0–7% ether in pentane) gave 509 mg (37% yield) of **21** as a colorless oil.

An analytical specimen, prepared by evaporative distillation at 50 °C (0.50 mm) of a comparable sample, showed one peak on VPC (5% Carbowax 20M, 93 °C): IR (film) 5.82 (C=O), 6.08 μ (C=N); ^{1}H NMR (CCl_4) 1.86 (d, J = 6 Hz, 3, N=CHCH_3), 2.04 (s, 3, acetyl CH_3), 1.47–2.40 (m, 8, methylene envelope), 6.76 ppm (q, J = 6 Hz, 1, N=CHCH$_3$).

Anal. ($C_9H_{15}NO_2$) C, H, N.

1-(1-Hydroxyethyl)cyclopentanol (22). A solution of 98.4 mg (0.58 mmol) of the aforementioned chromatographed oxime ether **21** in 5 mL of dry THF was added to a suspension of 52 mg (1.37 mmol) of lithium aluminum hydride in 15 mL of dry THF. The resulting mixture was stirred at reflux under nitrogen for 2 h and then allowed to cool to room temperature. The excess hydride was quenched by the dropwise addition of water, and then the mixture was extracted with ether using a base wash[29] to give 37.2 mg (50% yield) of diol **22** as a clear oil: IR (film) 2.90 μ (OH); ^{1}H NMR (CCl_4) 1.13 (d, J = 6.5 Hz, 3, CH_3), 1.62 (br m, 8, methylene envelope), 3.24 (br s, 2, OH), 3.58 (q, J = 6.5 Hz, 1, CH_3CHOH). The IR and ^{1}H NMR spectra were identical with the spectra of the known[13] diol **22**.

1-Acetylcyclopentanol (23). A published procedure[17] was utilized. A mixture of 59.1 mg (0.45 mmol) of crude diol **22**, 97 mg (0.54

mmol) of *N*-bromosuccinimide, 1.0 mL of dioxane, and 0.1 mL of water was stirred at room temperature for 2 h. Ether extraction[29] afforded 92.3 mg of a clear oil, which was shown by TLC (R_f 0.28, 4:1 hexane–ethyl acetate) and IR to be essentially pure ketol **23** by comparison with authentic material.[11] The sample, which was contaminated with traces of dioxane, was not subjected to further purification: IR (film) 2.84 (OH), 5.84 μ (C=O).

17-Hydroxy-Δ^1-5β-pregnen-20-ol (13). A solution of 272 mg (0.73 mmol) of the crude oxime ether mixture **12** in 3 mL of dry THF was added to a suspension of 200 mg (5.26 mmol) of lithium aluminum hydride in 20 mL of dry THF. The resulting mixture was stirred at reflux under nitrogen for 3 h, and then allowed to cool to room temperature. The excess hydride was quenched by adding a 10% aqueous sodium hydroxide solution in a dropwise manner until a granular precipitate was formed. The supernatant was decanted and the salts were washed three times with ether. The combined ethereal solutions were washed[29] to give 225 mg of colorless oil. Purification by preparative TLC (R_f ca. 0.4, 7:3 hexane–ethyl acetate) afforded 126 mg (a yield of ca. 54%) of diol **13** as a mixture of isomers: IR (film) 2.86 (OH), 13.95, 14.12 μ (*cis*-RCH=CHR); ^{1}H NMR (CCl_4) 0.76, 0.83, 0.98 (3 s, 6, C-18 and C-19 CH_3's), 1.05 (d, J = 6 Hz, 3, C-21 CH_3), 2.03 (br s, 2, OH), 0.5–2.7 (br m, methylene envelope), 3.85 (m, 1, *H*COH), 5.46 ppm (s, 2, C-1 and C-2 vinyl protons). Since **13** can exist in four stereoisomeric forms, no further purification was attempted.

17-Hydroxy-5β-pregnan-20-ol (14). A solution of 126 mg (0.40 mmol) of the aforementioned chromatographed diol **13** in 7 mL of ethyl acetate was stirred with two spatula tips of Raney nickel at room temperature for 45 min. The mixture was filtered through Celite, dried, and then concentrated at reduced pressure to give 132 mg of pale yellow oil. The desulfurized diol **13** was dissolved in a minimal volume of ethyl acetate and then added to 10 mL of ethyl acetate containing 90.5 mg of 10% palladium on carbon. The mixture was hydrogenated at atmospheric pressure and room temperature for ca. 1 h, and then the catalyst was removed by filtration through Celite and the solvent removed at reduced pressure to give 124 mg (98% yield) of diol **14** as a white semisolid: IR (film) 2.90 μ (OH); ^{1}H NMR 0.78, 0.86, 0.92 (3 s, 6, C-18 and C-19 CH_3's), 0.5–2.7 (br m, methylene envelope), 3.97 ppm (m, 1, *H*COH). Since diol **14** can exist in four stereoisomeric forms, no further purification was attempted.

17α-Hydroxy-5β,17β-pregnan-20-one (15) and 17β-Hydroxy-5β,17α-pregnan-20-one (16). A published procedure[17] was used. A 53.1-mg sample (0.30 mmol) of *N*-bromosuccinimide, recrystallized from water (mp 176–177 °C), was added to a solution of 70.4 mg (0.22 mmol) of the aforementioned crude diol **14** in 1.5 mL of dioxane and 0.15 mL of water. The mixture was stirred at room temperature in subdued light for 5 h, then was diluted with water and extracted with ether using a wash with a 5% aqueous sodium thiosulfate solution[29] to give 73.4 mg of colorless oil. Preparative TLC (19:1 hexane–ethyl acetate, continuous elution for 18 h) gave 7.8 mg (11% recovery) of unreacted diol **14** as a colorless oil, 16.4 mg (24% yield) of 17β-hydroxy-5β,17α-pregnan-20-one (**16**) and 26.5 mg (38% yield) of 17α-hydroxy,5β,17β-pregnan-20-one (**15**) as colorless solids.

Three recrystallizations of **16** from hexane afforded colorless needles, mp 159–164 °C, identical by ^{1}H NMR, IR, and VPC coinjection (3% XE-60, 181 °C) with an authentic sample of *l*-17β-hydroxy-5β,17α-pregnan-20-one.[18] The above specimen exhibited the following properties: IR ($CHCl_3$) 2.76, 2.78, 2.89 (OH), 5.87 μ (C=O); ^{1}H NMR 0.92 (s, 6, C-18 and C-19 CH_3), 2.27 (s, 3, acetyl CH_3), 0.6–2.6 (br m, methylene envelope), 2.50 ppm (s, 1, OH); TLC R_f 0.45 (7:3 hexane–ethyl acetate).

Recrystallization of **15** from hexane gave colorless needles, mp 148–149 °C. On admixture with an authentic specimen of 17α-hydroxy-5β,17β-pregnan-20-one (**15**), described below, mp 148–149 °C, the mp was 148–149 °C. This specimen exhibited the following spectral properties: IR ($CHCl_3$) 2.76, 2.78, 2.85 (OH), 5.86 μ (C=O); ^{1}H NMR 0.70 (s, 3, C-18 CH_3), 0.92 (s, 3, C-19 CH_3), 2.26 (s, 3, acetyl CH_3), 0.6–2.5 (br m, methylene envelope), 2.70 ppm (s, 1, OH); TLC R_f 0.50 (7:3 hexane–ethyl acetate).

The IR and ^{1}H NMR spectra of **15**, described above, were identical with the spectra of an authentic sample of *dl*-17α-hydroxy-5β,17β-pregnan-20-one (**15**) synthesized as described below from *dl*-Δ^1-5β-pregnen-20-one.[5b]

5β-Pregnan-20-one (25). A mixture of 93.7 mg (0.31 mmol) of Δ^1-5β-pregnen-20-one (**24**)[5b] (>95% one peak by VPC) which had been desulfurized with Raney nickel in ethyl acetate, 15 mL of ethyl acetate, and 59 mg of 10% palladium on carbon was hydrogenated at room temperature and atmospheric pressure for ca. 45 min. The catalyst was removed by filtration through Celite; then the filtrate was concentrated at reduced pressure to give 93.9 mg (99% yield) of 5β-pregnan-20-one (**25**) as a pale tan oil, which consisted of a 32:68 mixture of the 17α-acetyl:17β-acetyl epimers by VPC (3% OV-17, 210 °C) as shown by coinjection with an authentic sample of naturally derived 5β-pregnan-20-one (**25**).[5b,19]

17α-Hydroxy-5β-pregnan-20-one (15). A published procedure[20] was utilized. A solution of 93.9 mg (0.31 mmol) of the aforementioned crude ketone **25**, 12 mL of acetic anhydride, and 60.5 mg of *p*-toluenesulfonic acid monohydrate was heated at reflux; then ca. 8 mL of the acetic acid–acetic anhydride mixture was removed by slow distillation over a period of 4 h. The pot residue was allowed to cool to room temperature and then extracted with ether using a base wash[29] to give 80.8 mg of red-brown oil. The oil was filtered through Woelm neutral alumina, activity grade I, with petroleum ether (bp 60–68 °C) to afford 81 mg of the crude enol acetate **26** as a colorless oil, contaminated with traces of starting ketone **25**: IR (film) 5.69 μ (C=O).

A published procedure[21] was used. A solution of 81 mg of the aforementioned crude enol acetate **26** in 2.5 mL of chloroform was treated with 6 mg of sodium acetate and 0.5 mL of 40% peracetic acid. The resulting mixture was stirred at room temperature for 2.5 h, then extracted with chloroform using a wash with 5% aqueous sodium hydroxide to yield 84.1 mg of a colorless oil which was shown by IR to contain starting material. This mixture was resubmitted to the epoxidation conditions described above for an additional 12 h to give 83.5 mg of epoxy acetate **27** as a colorless oil: IR (film) 5.65, 5.73 μ (C=O).

A solution of 83.5 mg of the aforementioned crude epoxy acetate **27** in 5 mL of methanol and 2 mL of a 0.71 N aqueous sodium hydroxide solution was stirred at room temperature for 1 h. Extraction with methylene chloride[29] gave 13.5 mg of colorless oil. The aqueous extract was acidified to ca. pH 4 with 3.6% aqueous hydrochloric acid and then extracted with ether[29] to give an additional 50.3 mg of colorless oil. The crude oils were combined and purified by preparative TLC (7:3 hexane–ethyl acetate) to afford 47.5 mg (48% overall yield from **25**) of 17α-hydroxy-5β-pregnan-20-one (**15**) as a colorless oil which crystallized on standing.

Two recrystallizations from hexane yielded an analytical specimen of **15** as colorless needles, mp 148–149 °C: IR ($CHCl_3$) 2.76, 2.78, 2.85 (OH), 5.88 μ (C=O); ^{1}H NMR 0.70 (s, 3, C-18 CH_3), 0.91 (s, 3, C-19 CH_3), 2.24 (s, 3, acetyl CH_3), 0.5–2.5 (br m, methylene envelope), 2.68 ppm (s, 1, OH).

Anal. ($C_{21}H_{34}O_2$) C, H.

Δ^1-5β-Androsten-17-one (28). A published procedure[22] was used. A solution of 403 mg (1.27 mmol) of the crude diol **13** in 40 mL of methanol was stirred while a solution of 336 mg (1.47 mmol) of periodic acid in 6.9 ml of water was added. The resulting solution was stirred overnight at room temperature, and then the methanol was removed at the rotary evaporator and the residue was diluted with water. Ether extraction using a base wash[29] gave 421 mg of pale tan oil, which was purified by treatment with Girard reagent T[23] to afford 175 mg (51% yield) of ketone **28** as a clear oil which crystallized on standing at room temperature, mp 86–92 °C, and was >98% one peak on VPC (3% XE-60, 172 °C).

Two recrystallizations of a comparable sample from petroleum ether (bp 60–68 °C) gave an analytical specimen of **28** as colorless needles, mp 98.5–100.5 °C: IR ($CHCl_3$) 5.76 μ (C=O); ^{1}H NMR 0.86 (s, 3, C-18 CH_3), 1.02 (s, 3, C-19 CH_3), 0.5–2.8 (br m, methylene envelope), 5.56 ppm (s, 2, C-1 and C-2 vinyl protons).

Anal. ($C_{19}H_{28}O$) C, H.

Δ^1-5β-Androsten-17β-ol (29). A solution of 66.3 mg (0.24 mmol) of ketone **28**, mp 92–97 °C, in 5 mL of ethanol was added in a dropwise manner with stirring to a solution of 20 mg (0.53 mmol) of sodium borohydride in 10 mL of ethanol. The resulting solution was stirred at room temperature for 1 h; then 3 mL of water was added. The ethanol was removed at the rotary evaporator, and the residue was extracted with ether using a base wash[29] to give 69 mg (100% yield) of androstenol **29** as a white foam which was >99% one peak on VPC (3% XE-60, 165 °C).

Two recrystallizations of a comparable sample from hexane afforded an analytical specimen of **29** as colorless needles, mp 137–138 °C: IR ($CHCl_3$) 2.76 (OH), 9.16, 9.34, 9.53, 9.66 μ (C-O); ^{1}H NMR 0.74 (s, 3, C-18 CH_3), 1.02 (s, 3, C-19 CH_3), 0.6–2.5 (br m, methylene

envelope and OH), 3.63 (t, J = 7 Hz, 1, C-17 proton), 5.59 ppm (s, 2, C-1 and C-2 vinyl protons).

Anal. ($C_{19}H_{30}O$) C, H.

Δ^1-5β-Androsten-17β-ol Benzoate (30). A solution of 69 mg (0.25 mmol) of alcohol **29** (>99% one peak on VPC) in 2 mL of pyridine containing 0.5 mL of benzoyl chloride was heated on a steam bath with frequent agitation for 30 min. The resulting mixture was cooled to 0 °C, and then 0.5 mL of 85% lactic acid was added. After standing at room temperature for 20 min, the mixture was diluted with water and then extracted with ether using a wash with saturated aqueous cupric sulfate followed by a base wash[29] to give 88.2 mg (93% yield) of benzoate **30** as a colorless oil which crystallized on standing.

An analytical specimen as colorless plates was prepared by three recrystallizations of a comparable sample from absolute ethanol, mp 131–134 °C: IR ($CHCl_3$) 5.84 (ester C=O), 7.81, 8.93 μ; ^{1}H NMR 0.93 (s, 3, C-18 CH_3), 1.02 (s, 3, C-19 CH_3), 0.6–2.7 (br m, methylene envelope), 4.81 (t, J = 7 Hz, 1, C-17 proton), 5.56 (s, 2, C-1 and C-2 vinyl protons), 7.2–8.2 ppm (2 m, 5, aromatic protons).

Anal. ($C_{26}H_{34}O_2$) C, H.

Δ^1-5β-Androsten-3-oxo-17β-ol Benzoate (31). A modification of a published procedure[24] was employed. A solution of 88.2 mg (0.23 mmol) of crude benzoate **30** in 0.5 mL of glacial acetic acid, 0.1 mL of acetic anhydride, and 1.5 mL of tetrachloroethylene was stirred at 85 °C under nitrogen while a freshly prepared solution of 0.625 mL (1.56 mmol) of 2.5 M *tert*-butyl chromate reagent[24] in tetrachloroethylene containing 0.5 mL of glacial acetic acid and 0.1 mL of acetic anhydride was added. The resulting dark mixture was heated with stirring at 86–88 °C under nitrogen for 45 min, then cooled to room temperature and treated with 4 mL of saturated aqueous oxalic acid. After stirring for 10 min, the mixture was diluted with water and then extracted with ether[29] to give 91.1 mg of crude ketone **31** as a pale yellow, crystalline solid.

An analytical specimen was obtained by preparative TLC (R_f 0.5, 7:3 hexane–ethyl acetate) of a comparable sample, followed by recrystallization from hexane–acetone to give ketone **31** as colorless needles, mp 190–191 °C: IR ($CHCl_3$) 5.84 (ester C=O), 5.97 (enone C=O), 7.72, 7.80, 8.91 μ; ^{1}H NMR 0.96 (s, 3, C-18 CH_3), 1.21 (s, 3, C-19 CH_3), 0.7–2.9 (br m, methylene envelope), 4.85 (t, J = 7 Hz, 1, C-17 proton), 6.36 (AB q, J = 10 Hz, $\Delta\nu$ AB = 54 Hz, 2, C-1 and C-2 vinyl protons), 7.22–8.20 ppm (2 m, 5, aromatic protons).

Anal. ($C_{26}H_{32}O_3$) C, H.

17β-Hydroxy-5β-androstan-3-one Benzoate (32). A 91.1-mg sample (0.23 mmol) of the crude enone **31** was dissolved in a minimal volume of ethyl acetate and then added to 20 mL of ethyl acetate containing 90 mg of 10% palladium on carbon. The mixture was hydrogenated at room temperature and atmospheric pressure for ca. 45 min; then the catalyst was removed by filtration through Celite and the solvent removed at reduced pressure to give 98.8 mg of colorless oil. Preparative TLC (9:1 hexane–ethyl acetate, continuous elution for 2 h) afforded 59.1 mg (65% yield from benzoate **30**) of ketone **32** as a colorless oil which crystallized after seeding with authentic material, TLC (R_f 0.45, 7:3 hexane–ethyl acetate).

An analytical specimen was prepared by two recrystallizations of a comparable sample from absolute ethanol to afford 17β-hydroxy-5β-androstan-3-one benzoate (**32**) as colorless plates, mp 112.5–114.0 °C: IR ($CHCl_3$) 5.85 (C=O), 7.80, 8.90 μ; ^{1}H NMR 0.94 (s, 3, C-18 CH_3), 1.02 (s, 3, C-19 CH_3), 0.6–3.1 (br m, methylene envelope), 4.89 (t, J = 7 Hz, 1, C-17 proton), 7.27–8.20 ppm (2 m, 5, aromatic protons).

This sample was identical by IR, ^{1}H NMR, and TLC (R_f 0.45, 7:3 hexane–ethyl acetate) with authentic 17β-hydroxy-5β-androstan-3-one benzoate.[25]

Anal. ($C_{26}H_{34}O_3$) C, H.

Testosterone Benzoate (34). A published procedure[26] was utilized. A solution of 59.1 mg (0.15 mmol) of ketone **32**, purified by preparative TLC, in 6 mL of enol acetylation Reagent B[26] (10^{-2} M perchloric acid and 10^{-1} M acetic anhydride in ethyl acetate) was stirred at room temperature under nitrogen for 15 min. Ethyl acetate extraction using a base wash[29] gave 64.8 mg (99% yield) of crude enol acetate: IR (film) 5.70 (acetate C=O), 5.82 μ (benzoate C=O). No effort was made to determine the ratio of Δ^2 to Δ^3 isomers as was done previously.[31]

A published procedure[27] was employed. A solution of 0.027 mL (0.14 mg-atom) of a 5.1 M solution of bromine in carbon tetrachloride was added in a dropwise manner with stirring under nitrogen to a cold (0 °C) solution of 64.8 mg (0.15 mmol) of the crude enol acetate mixture described above in 2 mL of carbon tetrachloride containing 0.06 mL of epichlorohydrin. The resulting mixture was stirred at 0 °C for 10 min, and then the solvent was removed at reduced pressure to give 77.1 mg (107% yield) of crude bromo ketone **33** as a pale yellow oil which crystallized on standing: IR (film) 5.78 (C=O), 5.82 μ (ester C=O).

A published procedure[28] was used. A solution of 36.4 mg (0.33 mmol) of semicarbazide hydrochloride and 26.6 mg (0.33 mmol) of sodium acetate in 0.41 mL of water was added to a solution of 77.1 mg (0.16 mmol) of the aforementioned crude bromo ketone mixture **33** in 3.3 mL of dioxane. After stirring at room temperature under nitrogen for 2 h, a solution of 0.1 mL of pyruvic acid in 0.9 mL of water was added to the mixture, and then the stirring was continued overnight. Methylene chloride extraction using a wash with cold, 1 N aqueous sodium hydroxide[29] afforded 60 mg of a clear oil which crystallized on standing. Preparative TLC (9:1 hexane–ethyl acetate, continuous elution for 4 h) gave 41.7 mg (71% yield from **32**) of testosterone benzoate (**34**) as a colorless, crystalline solid, mp 178–182 °C, which appeared to be homogeneous by TLC (R_f 0.32, 7:3 hexane–ethyl acetate).

An analytical sample was prepared by three recrystallizations of a comparable sample from absolute ethanol to give **34** as colorless plates, mp 184.0–185.5 °C: IR ($CHCl_3$) 5.84 (ester C=O), 6.00 (enone C=O), 7.80, 8.90 μ; ^{1}H NMR 0.98 (s, 3, C-18 CH_3), 1.20 (s, 3, C-19 CH_3), 0.7–2.7 (br m, methylene envelope), 4.87 (t, J = 7 Hz, 1, C-17 proton), 5.75 (s, 1, C-4 vinyl proton), 7.25–8.25 (2 m, 5, aromatic protons).

Anal. ($C_{26}H_{32}O_3$) C, H.

This sample of racemic material was identical by ^{1}H NMR, IR, and TLC with an authentic, naturally derived specimen of testosterone benzoate (obtained from Steraloids, Inc., Pawling, N.Y., mp 188–192 °C).

Acknowledgments. We thank the National Institutes of Health and the National Science Foundation for support of this research.

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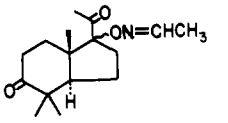
(29) In cases where products were isolated by solvent extraction, the procedure generally followed was to extract the aqueous layer with several portions of the indicated solvent; then the organic layers were combined and washed with water followed by saturated brine. The organic layer was dried over anhydrous sodium sulfate or magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure (water aspirator) using a rotary evaporator. The use of the term "wash" indicates washing the combined organic layers with saturated aqueous sodium bicarbonate solution ("base wash"), with dilute aqueous hydrochloric acid ("acid wash"), or with the indicated solution prior to the aforementioned washing with water.
(30) In an experiment performed by R. J. Parry, oxidation of **3** with the ruthenium tetroxide solution for only 3 min afforded a product which was identified by IR, VPC, and mass spectrometry as i. Further treatment of i with ruthenium tetroxide for 3 h afforded a mixture of i and the dione **4**.



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Elucidation of the Course of the Electron Impact Induced Fragmentation of α,β-Unsaturated 3-Keto Steroids[1,2]

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Abstract: A series of deuterium-labeled Δ^4- and $\Delta^{1,4}$-3-keto steroids has been synthesized in order to investigate the diagnostic, electron impact-induced fragmentations, notably ring B cleavages, characteristic of these compounds. Such information is important in the structure elucidation of new steroids and is especially relevant in view of the recent isolation of Δ^4- and $\Delta^{1,4}$-3-keto steroids from marine organisms, in addition to the almost ubiquitous presence of these functionalities in adrenal and sex hormones. The introduction of a ketone functionality into various positions of the steroid nucleus permitted the labeling of carbon atoms 6, 7, 8, 9, 11, 12, 15, 16, and 17. In agreement with earlier studies, the 8β-hydrogen atom was shown to play a key role in the hydrogen migrations accompanying the ring B scissions. Hydrogen atoms from C-11, -14, and -15 were also implicated. Mechanisms are presented to explain the fragmentations. The differences between the mass spectra of the two types of α,β-unsaturated ketones, as well as among substituted analogues, are analyzed in terms of these mechanisms.

Recently there has been a significant resurgence in the search for new steroids from natural sources, most notably the marine environment.[4] Because of the extremely small quantities involved, the structure elucidation of these new compounds often relies solely upon gas chromatography–mass spectral measurements. Accurate interpretation of these data demands an adequate knowledge of the mechanisms of the principal fragmentation processes arising from a particular structural feature. The recent isolation of $\Delta^{1,4}$-3-keto steroids from marine organisms[5] and human urine[6] prompted us to examine the electron impact induced fragmentations of such dienones since very little attention has been given to their mass spectrometric behavior,[7] even though the $\Delta^{1,4}$-3-ketone moiety is also an important feature of many medicinally important corticosteroids. Deuterium labeling was required to establish the course of the diagnostic cleavages of the $\Delta^{1,4}$-3-keto steroids and, since these compounds are generally prepared from Δ^4-3-keto precursors, the key fragmentations of the latter steroids[8] were reinvestigated. The behavior of the Δ^4-3-keto steroids under electron impact has commanded considerable interest[7] because of the frequent occurrence of this functionality in the progestational and androgenic sex hormones as well as in the corticosteroids. More recently such steroids have been obtained from marine sources.[9] In contrast to their saturated counterparts, these α,β-unsaturated 3-keto steroids exhibit characteristic mass spectral fragmentations of a general type (i.e., consistent from one class of steroids to another) which are usually independent of ring substituents. These compounds are thus ideal candidates for mechanistic investigations.

The mass spectra of some representative Δ^4- and $\Delta^{1,4}$-3-keto steroids are presented in Figures 1 and 2. As demonstrated previously,[8] the prominent peaks in the high-mass region of the 4-androsten-3-one (**1**) spectrum are *m/z* 230 (M − 42; loss of ketene from ring A), *m/z* 215 (M − 57; loss of ketene plus a methyl radical), *m/z* 187 (M − 85; loss of C-1, 2, 3, 10, and 19), *m/z* 149 (M − 123) and *m/z* 124. The latter two ions result from fission of the 6–7 and 9–10 bonds of ring B with the charge remaining on either the hydrocarbon or oxygen-containing fragment, respectively. These characteristic peaks also prevail in the mass spectra of 4-pregnen-3-one (**2**) and 4-cholesten-3-one (**3**), with the additional appearance of ions resulting from loss of the respective C-17 side chains.

The most striking difference in the spectra of the $\Delta^{1,4}$-3-ketones is the very high percentage of the total ion current that is carried by the *m/z* 122 ion (ring B cleavage). The spectra do not display the M − 42 (loss of ketene) or M − 85 ions which are characteristic of the Δ^4 analogues. Small peaks are present in the spectrum of 1,4-androstadien-3-one (**4**) at *m/z* 229 (M − 41; loss of C_3H_5), *m/z* 149 (M − 121; fission of the 6–7 and 9–10 bonds of ring B), and *m/z* 135 (M − 135; rupture of the 7–8 and 9–10 bonds of ring B). These diagnostic ions are also seen in the spectra of the heretofore unknown 1,4-pregnadien-3-one (**5**) and of 1,4-cholestadien-3-one (**6**). The origins and identities of these ions were corroborated by metastable defocusing experiments (Table I) and high-resolution mass measurements.

Hydrogen migrations play an important role in the ring B cleavages of both the Δ^4- and $\Delta^{1,4}$-3-keto steroids as well as

0002-7863/80/1502-0807$01.00/0