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(21) Nicotinamide is used as the proton acceptor in the first step in order to minimize the solubility of the base hydrochloride in the acetonitrile solvent. The latter is used in place of ether to maximize the solubility of choline chloride (5).

Formation of 14α-Cardenolides from 21-Acetoxy-20-keto Steroids

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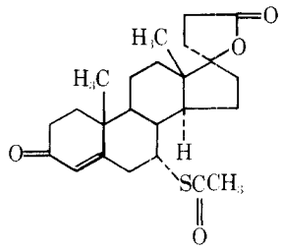
The Emmons–Horner condensation of diethyl cyanomethylenephosphonate with 21-acetoxy-20-keto steroids has been studied. The reaction with 21-acetoxypregnenolone gives a 20-cyanomethylene steroid as a single isomer. The 3-enol ethers of deoxycorticosterone acetate, 11-dehydrocorticosterone acetate, and corticosterone diacetate react similarly. Δ^1-Corticosterone acetate reacts directly with the ylide only at C-20 to form the corresponding 20-cyanomethylene derivative. These modified corticoids undergo ready dehydrogenation to form 1,4-, 4,6-, and 1,4,6-unsaturated ketones. When these cyanomethylene derivatives react with 1 equiv of *p*-toluenesulfonic acid in refluxing aqueous ethanol, transesterification of the 21-acetate and hydrolysis of the nitrile occurs to form a cardenolide ring in high yield. These mild conditions are compatible with a wide variety of other functional groups in the steroid. The corresponding cardanolides have been prepared by ketalization of the 3-ketone and subsequent hydrogenation and deketalization.

We were interested in preparing cardenolides and cardanolides related to the known anti-aldosterone steroid, Spironolactone **1**. If the usual hormonal steroid stereochemistry is introduced into the cardenolides (i.e., C/D-trans) and, additionally, when the requisite 3-keto-4-ene grouping is present, the structural similarity between **2** and **1** becomes apparent.[1]



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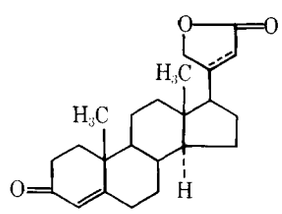
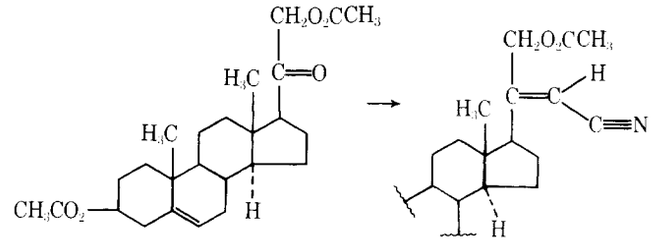


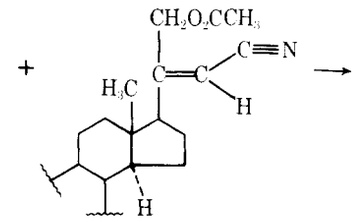
2 ($\Delta^{20,22}$)

31

An apparently simpler reaction, proceeding in very high yield, for the formation of the steroid cardenolide ring was described by Fritsch.[2] This involved the reaction of a 21-hydroxy-20-ketone moiety with the anion of trimethyl phosphonoacetate in a modified Horner–Emmons reaction to yield directly the cardenolide ring in yields of greater than 95%.[3] When this reaction was attempted using deoxycorticosterone, we were never able to achieve yields of more than 25%, and this particular reaction appeared to be limited in its applicability. Similar observations were reported by Yoshii and Ozaki on the same condensation with 21-hydroxypregnenolone.[4] During the time that these studies were in progress, Pettit reported on the formation of cardenolides from 21-acetoxy-20-ketones and diethyl cyanomethylenephosphonate.[5] The reaction between 21-acetoxypregnenolone acetate **3** and the Horner–Emmons ylide formed a mixture of 20-cyanomethylene isomers **4** and **6** which were not separated, but the crude reaction mixture was directly reacted with hydrochloric acid to form the iminocardenolide hydrochloride **5** and the pure (*E*)-cyanomethylene isomer **6**. Compound **5** could then be hydrolyzed in refluxing hydrochloric acid to give the cardenolide **7**. The assignment of stereochemistry for **6** was based on repeated



3 **6**



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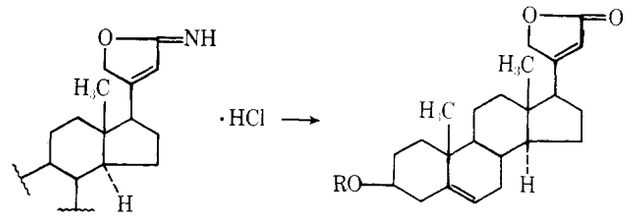

5

7. R = $OCCH_3$
8. R = H

unsuccessful attempts to convert it into the cardenolide **7**.[5]

The enol ether **9** of deoxycorticosterone was prepared using standard methods and condensed with the anion of diethyl cyanomethylenephosphonate to give the enol ether **10** which could be hydrolyzed in aqueous acetic acid to the enone **11** in an overall yield of 58%. When basic hydrolysis of the 21-acetate in **11** was attempted only extensive degradation occurred and this approach to the 21-hydroxy compounds was abandoned. As a consequence, acid-catalyzed transesterification

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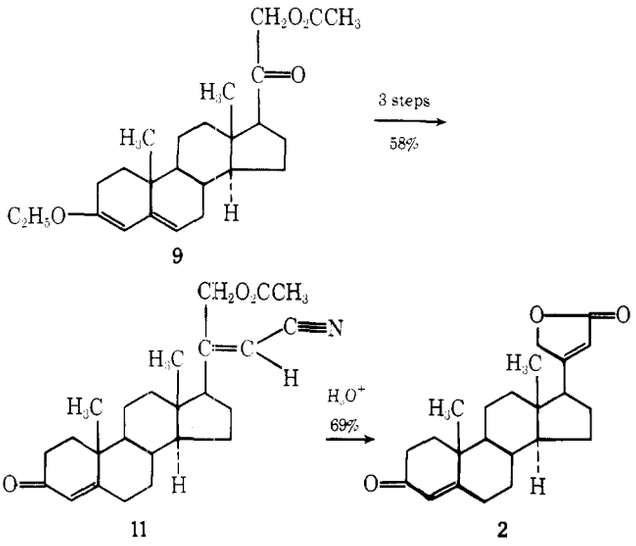


was attempted using *p*-toluenesulfonic acid in absolute methanol. Only a small amount of a new product was formed and the yield was a function of the amount of catalyst present. The product was isolated and identified as the known cardenolide **2**.[2] The probable mechanism involved transesterification of **11** to the 21-hydroxy compound which adds to the nitrile to form the imino lactone and which, in turn, is hydrolyzed to the cardenolide **2** and ammonia by the water of hydration of the tosyl acid. The liberated ammonia neutralizes the acid, thereby stopping both the hydrolysis and the transesterification. When 1.1 equiv of acid was used in aqueous ethanol, **11** was smoothly converted into **2** in 69% yield without detectable intermediates.

Because of this facile conversion of the cyanomethylene steroid into a cardenolide, we reinvestigated the reaction with 21-acetoxypregnenolone acetate **3**.[5] Condensation with the ylide gave, again, only a single isomer in 75% yield which was identical with that reported by Pettit for the *E* isomer **6**. Acid-catalyzed transesterification and hydrolysis gave the known 3β-hydroxycardenolide **8** in 95% yield, which was also acetylated to the known **7**.[5] Since we did not detect any isomerization of the cyanomethylene compound during the hydrolysis and no evidence was obtained for any intermediate, the cyanomethylene compound possesses the *Z* configuration (**4**) and Pettit's results were apparently due to incomplete hydrolysis of the cyanomethylene compound **4** into the imino lactone **5**. We were unable to find any of the *E* isomer **6**.

The 11β-acetate and 11-keto derivatives of deoxycorticosterone were also converted into their enol ethers and subsequently into their 20-cyanomethylene derivatives. The data are presented in Scheme I and the yields given are for the overall conversion of 20-keto enones into the 20-cyanomethylene enones. As the formation of the enol ether of corticosterone acetate was very difficult, the 1,4-dienone **12** was prepared on the assumption that the 3-ketone would be sufficiently deactivated to allow exclusive reaction with the ylide at the 20-ketone. In practice this was observed and the 11β-hydroxy-20-cyanomethylene derivative **13** was obtained in 78% yield. Conversion to the 11β-hydroxydienone cardenolide **14** was readily accomplished with aqueous tosyl acid in 65% yield without any evidence for the dienone–phenol rearrangement.[6]

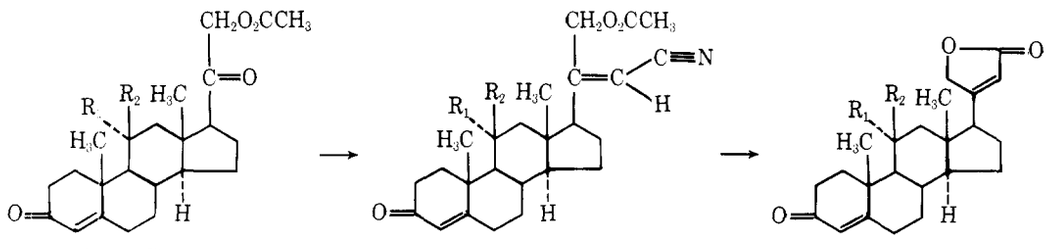
An advantage to isolating the 20-cyanomethylene derivatives as their 3-enol ethers is their facile conversion to the 4,6-dienone or the 1,4,6-trienone by dichlorodicyanobenzoquinone (DDQ) oxidation in aqueous acetone and benzene, respectively.[7] For example, the enol ether of compound **11** was oxidized to the 4,6-dienone **15** and the 1,4,6-trienone **16** in 75 and 43% yields, respectively. The 1,4-dienone **14** was obtained in 43% yield from the enone **11** via DDQ oxidation in refluxing benzene. Similarly, the cardenolide **2** was oxidized to its 1,4-dienone **18** and its 3-enol ether was converted to the 1,4,6-trienone **19**. This time, however, the 4,6-dienone cardenolide **20** was synthesized from the corresponding 4,6-dienone-20-cyanomethylene compound **15** by tosyl acid hydrolysis, indicating the stability of the linear dienone system to these reaction conditions.

The tosyl acid hydrolysis of the 21-acetoxy-20-cyanomethylene grouping into a cardenolide has thus been shown to proceed under very mild conditions and alcohol, acetate, ketone, enone, and 1,4- and 4,6-dienone functions are stable to the reaction conditions effecting this conversion.

The reduction of the cardenolide **2** to the 3β-hydroxy-4-ene **21**, without affecting the cardenolide double bond, was accomplished using lithium aluminum tri-*tert*-butoxide hydride. This reaction was also reported by Ruschig using sodium borohydride.[8] Reaction of **21** with methylene iodide under Simmons–Smith conditions furnished the 4β,5β-cyclopropane **22**.[9] Oxidation of the cyclopropylcarbinol to the 4β,5β-cyclopropyl ketone **24** was readily accomplished using silver carbonate on Celite.[10]

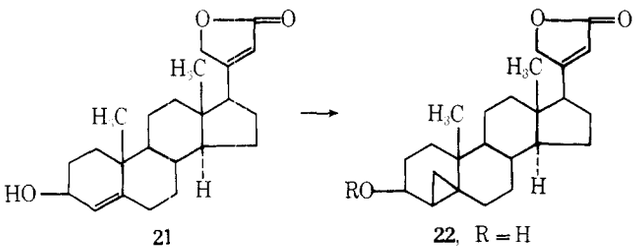
To protect the enone function of **2** during catalytic reduction of the cardenolide double bond, the ketal **29** was formed using the ethylene glycol vacuum distillation technique.[11] Hydrogenation of compound **29** over palladium on carbon gave the cardanolide ketal **30**. Hydrolysis of the ketal was effected by 2.8 M perchloric acid in aqueous tetrahydrofuran,[12] but TLC indicated that the product **31** was contaminated with a small amount of starting material **2** and chromatography was necessary to isolate pure **31** in 85% overall yield from the ketal **2**. A similar series of reactions on the 11-ketocardenolide **26** gave the corresponding cardanolide **32**. While the hydroge-

Scheme I

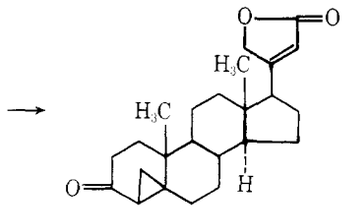


R_1	R_2		
H	H	**11** (58%)	**2** (69%)
O		**25** (76%)	**26** (56%)
H	O_2CCH_3	**27** (31%)	**28** (65%)
H	OH[a]	**13** (78%)[a]	**14** (65%)[a]

[a] $\Delta^{1,4}$-Dienone as starting material and reaction products.

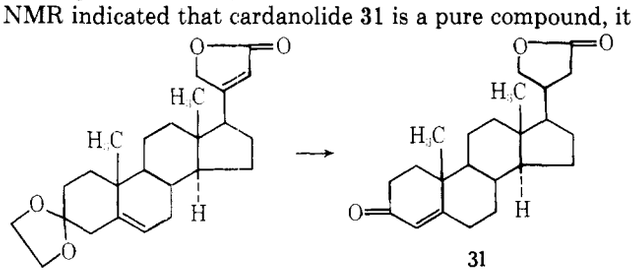


21 22, R = H 23, R = $OCCH_3$



24

nation of 20(22)-noncholenic acid esters was reported to be nonstereospecific,[13] the similar hydrogenation of 14α-cardenolides is either stereospecific or highly stereoselective in forming the (20*R*)-20β-cardanolide.[14] Since both TLC and NMR indicated that cardanolide **31** is a pure compound, it



29 31

probably possesses the 20*R* configuration, but in the absence of additional information this assignment and that of the other 14α-cardanolides prepared in this work has to be considered tentative.

Dehydrogenation of the cardanolide enone **31** and its enol ether with DDQ, analogous to the dehydrogenation of the cardenolide **2**, gave the cross conjugated 1,4-dienone **33**, the linear 4,6-dienone **34**, and the 1,4,6-trienone **35**.

Experimental Section

General. Melting points were run on a Thomas-Hoover Unimelt Capillary Apparatus and are uncorrected. IR spectra were run in potassium bromide, unless otherwise stated, on a Beckman IR-12.Ultraviolet spectra were run in methanol on a Beckman DK-2a spectrometer, and optical rotations were run in chloroform on a Perkin-Elmer Model 141 polarimeter. NMR spectra were recorded on a Varian A-60 spectrometer and were run in deuteriochloroform using tetramethylsilane as an internal standard. The NMR spectra are reported in chemical shift (δ) followed by a first order analysis of the signal shape: s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet. The multiplicity is followed by the coupling constant in hertz, where appropriate, and then the integrated signal intensity. Microanalyses were determined by the Searle Laboratories Microanalytical Service under the direction of Mr. E. Zielinski; chromatographies were performed under the supervision of Mr. R. Nicholson and hydrogenations were conducted under the supervision of Mr. M. Scaros.

The Reaction of 3β,21-Dihydroxy-5-pregnen-20-one Diacetate (3) with Diethyl Cyanomethylphosphonate. To a suspension of 0.83 g of sodium hydride (50% dispersion in mineral oil) in 25 mL of 1,2-dimethoxyethane was added 5.8 g of diethyl cyanomethylphosphonate (Aldrich) in 10 mL of solvent. After reaction had ceased, 10.0 g (24 mmol) of 21-acetoxypregnenolone acetate **3**, Searle Chemicals, in 50 mL of the same solvent was added via an addition funnel. After stirring at room temperature for 1 h, the solution was heated to ca. 80 °C and allowed to cool. This heating was subsequently found to be unnecessary. The reaction mixture was poured into water and then stirred magnetically. After crystallization was complete, the material was filtered and dissolved in methylene chloride. The methylene chloride solution was dried with sodium sulfate and evaporated and the residue was crystallized from ethyl acetate–ether to yield 7.9 g (18 mmol, 75%) of **4** [3β,21-dihydroxy-24-norchola-5,20(22)-diene-23-nitrile diacetate], mp 175–177 °C (lit.[5] mp 182–185 °C), whose spectral characteristics agreed with Pettit's published values.

The Conversion of 4 into the Cardenolide 8. Compound **4** (1.00 g, 2.27 mmol) was suspended in 50 mL of 95% ethanol (containing 5% methanol) and an additional 5 mL of distilled water was added. The mixture was stirred and after the addition of 0.5 g of *p*-toluenesulfonic acid monohydrate brought to reflux. Due to the slower, but still significant, hydrolysis of the 3β-acetate it was necessary to reflux the mixture for 39 h to complete both hydrolyses. The conversion to the cardenolide ring, however, was complete after 16 h. Upon cooling the reaction mixture, a substantial precipitate was evident in the flask and after the addition of 50 mL of distilled water the precipitate was filtered and dried to yield 750 mg (2.11 mmol, 93%) of the cardenolide **8**, 3β,21-dihydroxy-5,20(22)-norcholadieno-23,21-lactone, mp 239–249 °C (lit. mp 240–245 °C), $[\alpha]_{589}^{25}$ −63°, $[\alpha]_{365}^{25}$ −208° (*c* 1.00, chloroform), whose spectral properties were identical with the published values.

A portion of **8** was acetylated in quantitative yield with acetic anhydride–pyridine (1:4:5 w/v/v equivalents), using 4-*N*,*N*-dimethylaminopyridine as a catalyst.[15] Dilution of the acetylation mixture with distilled water gave the 3β-acetate **7**: mp 162–163 °C (lit. mp 170–172,[5] 153–154 °C[16]), $[\alpha]_{589}^{25}$ −57°, $[\alpha]_{365}^{25}$ −197° (*c* 1.00, chloroform). The spectral values of **7** were identical with Pettit's published values.[5]

The Enol Ether of Deoxycorticosterone Acetate 9. Deoxycorticosterone acetate (60 g, 161 mmol, Searle Chemicals) was dissolved in a solution of 180 mL of dioxane, 120 mL of ethanol, and 75 mL of triethyl orthoformate at 0 °C, 3.6 g (18.9 mmol) of *p*-toluenesulfonic acid monohydrate was added, and the solution was stirred at 0 °C for 15 min. The suspension (solids present) was then poured into 3 L of a 2% pyridine–water solution at 0 °C. The precipitate was filtered and washed with 300 mL of 2% pyridine/water to give 48.6 g (121 mmol, 75%) of the enol ether: mp 124–129 °C; UV 239 nm (ϵ) 18 300); IR 1735 (C-20 ketone), 1755 cm^{-1} (acetoxy carbonyl); NMR δ 5.20 (m, 2 H, C-4, 6 H), 4.81 (d, *J* = 17.0 Hz, 1 H, C-21 H), 4.47 (d, *J* = 17.0 Hz, 1 H, C-21 H), 2.15 (s, 3 H, acetoxy methyl H), 0.99 (s, 3 H, C-19), 0.70 (s, 3 H, C-18). Anal. Calcd for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 74.81; H, 9.36.

The Emmons–Horner Condensation of the Enol Ether of Deoxycorticosterone Acetate. Diethyl cyanomethylphosphonate (8.8 g; 50 mmol) was dissolved in 50 mL of tetrahydrofuran and added, under N_2, to a slurry of 2.5 g of NaH (50% in mineral oil) in 50 mL of tetrahydrofuran at 10–15 °C. To the clear yellow-orange solution was added 20 g (50 mmol) of the enol ether of deoxycorticosterone acetate dissolved in 50 mL of tetrahydrofuran. The solution was stirred at room temperature for 24 h and then added to 1 L of 0.25 M HCl and warmed (30–35 °C) for 2 h, filtered, and washed with water and 2% pyridine/methanol. The crude product was then digested in boiling 2% pyridine/methanol, cooled, and filtered to give 14.8 g (35 mmol, 70%) of the cyanomethylene derivative **10**: mp 132–136 °C; UV 232.5 nm (ϵ 27 000); IR 2230 (C≡N), 1755 cm^{-1} (acetoxy carbonyl); NMR δ 5.50 (s, 1 H, cyanomethylene H), 5.12 (m, 2 H, C-4,6), 4.81 (d, *J* = 8.0 Hz, 1 H, C-21 H), 4.22 (d, *J* = 8.0 Hz, 1 H, C-21 H), 2.17 (s, 3 H, acetoxy methyl H), 0.99 (s, 3 H, C-19), 0.65 (s, 3 H, C-18). Anal. Calcd for $C_{27}H_{37}NO_3$: C, 76.56; H, 8.81; N, 3.31. Found: C, 76.58; H, 8.90; N, 2.95.

The Formation of the Cyanomethylene Enone 11. **10** (6.0 g; 14.2 mmol) was dissolved in 40 mL of 60% acetic acid by heating on a steam bath for 30 min. The solution was cooled, diluted with water, and filtered. The crude product was dissolved in hot methanol, cooled, diluted with water, and filtered to give 4.62 g (11.7 mmol, 82.6%) of the enone **11**, [21-(acetyloxy)-3-oxo-24-norchola-4,20(22)-diene-23-nitrile]: mp 167–169 °C; UV 232.5 nm (ϵ 26 000); IR 2220 (C≡N), 1755 (acetoxy carbonyl), 1675 cm^{-1} (C-3 ketone); NMR δ 5.72 (s, 1 H, C-4 H), 5.38 (s, 1 H, cyanomethylene H), 4.92 (d, *J* = 14.0 Hz, 1 H, C-21 H), 4.63 (d, *J* = 14.0 Hz, 1 H, C-21 H), 1.98 (s, 3 H, acetoxymethyl H), 1.18 (s, 3 H, C-19), 0.67 (s, 3 H, C-18). Anal. Calcd for $C_{25}H_{33}NO_3$: C, 75.91; H, 8.41; N, 3.54. Found: C, 75.54; H, 8.63; N, 3.42.

DDQ Dehydrogenation of the Cyanomethylene Enone 11. **11** (1.0 g; 2.53 mmol) was dissolved in 25 mL of dry benzene with stirring under nitrogen. To this solution was added, at room temperature, 0.72 g (3.1 mmol, 1.25 equiv) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in 25 mL of dry benzene. The solution was heated at reflux for 20 h and then cooled, concentrated, and filtered. The remaining solution was then reduced to dryness and the residue was chromatographed over 40 g of Woelm neutral aluminum oxide (activity grade

III). Elution with ethyl acetate–benzene gave 0.48 g (1.22 mmol, 48.2%) of the 3-keto-1,4-dienone **17** [21-(acetyloxy)-3-oxo-24-norchola-1,4,20(22)-triene-23-nitrile]: mp 144.5–146.5 °C; UV 220 nm (ε 23 000); IR 2220 (C≡N), 1755 (acetoxy carbonyl), 1670 cm^{-1} (C-3 ketone); NMR δ 7.03 (d, J = 10.0 Hz, 1 H, C-2 H), 6.22 (d, J = 10.0 Hz, 1 H, C-1 H), 6.08 (s, 1 H, C-4 H), 5.39 (s, 1 H, cyanomethylene H), 4.92 (d, J = 14.0 Hz, 1 H, C-21 H), 4.64 (d, J = 14.0 Hz, 1 H, C-21 H), 2.12 (s, 3 H, acetoxymethyl H), 1.22 (s, 3 H, C-19), 0.68 (s, 3 H, C-18). Anal. Calcd for $C_{25}H_{31}NO_3$: C, 76.30; H, 7.94; N, 3.56. Found: C, 76.40; H, 8.08; N, 3.64.

DDQ Dehydrogenation of the Enol Ether 10. 10 (3.0 g; 7.08 mmol) was dissolved in 150 mL of 95% aqueous acetone. DDQ (1.71 g; 7.44 mmol) was dissolved in 30 mL of 95% aqueous acetone and added dropwise with stirring. The reaction mixture was stirred for 10 min and then reduced to dryness at 25 °C under vacuum. The residue was slurried in 30 mL of benzene and filtered; the filter cake was washed with an additional 15 mL of benzene. The clear yellow solution was chromatographed over 150 g of Woelm neutral aluminum oxide (activity grade III). Elution with ethyl acetate–benzene (50:50) gave, after crystallization from ethyl acetate–diethyl ether, 2.10 g (5.34 mmol, 75.4%) of the 3-keto-4,6-dienone **15** [21-(acetyloxy)-3-oxo-24-norchola-4,6,20(22)-triene-23-nitrile]: mp 167–169 °C; UV 282.5 nm (ε 26 500); IR 2220 (C≡N), 1755 (acetoxy carbonyl), 1665 cm^{-1} (C-3 ketone); NMR δ 6.17 (s, 2 H, C-6, 7 H), 5.70 (s, 1 H, C-4 H), 5.46 (s, 1 H, cyanomethylene H), 4.97 (d, J = 14.0 Hz, 1 H, C-21 H), 4.68 (d, J = 14.0 Hz, 1 H, C-21 H), 2.17 (s, 3 H, acetoxy methyl H), 1.13 (s, 3 H, C-19), 0.70 (s, 3 H, C-18). Anal. Calcd for $C_{25}H_{31}NO_3$: C, 76.30; H, 7.94; N, 3.56. Found: C, 76.36; H, 7.99; N, 3.55.

DDQ Dehydrogenation of the Enol Ether 10 in Aprotic Solvents. 10 (1.0 g; 2.36 mmol) was dissolved in 25 mL of dry benzene and added rapidly, under nitrogen, to 1.14 g (4.96 mmol) of DDQ in 40 mL of dry benzene. The reaction mixture was stirred vigorously at room temperature for 20 min, diluted with 20 mL of dichloromethane, and filtered. The organic solution was evaporated to dryness and chromatographed over 40 g of Woelm neutral aluminum oxide (activity grade III). Elution with ethyl acetate–benzene (50:50) gave, after crystallization from ethyl acetate–hexane, 400 mg of trienone **16** [21-(acetyloxy)-3-oxo-24-norchola-1,4,6,20(22)-tetraene-23-nitrile] (1.01 mmol, 42.6%): mp 155–158 °C; UV 299 nm (ε 12 800); IR 2220 (C≡N), 1755 (acetoxy carbonyl), 1660 cm^{-1} (C-3 ketone); NMR δ 7.08 (d, J = 10.0 Hz, 1 H, C-2 H), 6.29 (d, J = 10.0, 1 H, C-1 H), 6.09 (m, 3 H, C-4, 6,7 H), 5.45 (s, 1 H, cyanomethylene H), 5.98 (d, J = 14.0 Hz, 1 H, C-21), 4.68 (d, J = 14.0 Hz, 1 H, C-21 H), 2.16 (s, 3 H, acetoxymethyl H), 1.22 (s, 3 H, C-19), 0.75 (s, 3 H, C-18). Anal. Calcd for $C_{25}H_{29}NO_3$: C, 76.69; H, 7.43; N, 3.56. Found: C, 76.68; H, 7.38; N, 3.48.

Acid-Catalyzed Conversion of the 21-(Acetyloxy)-20-cyanomethylene Grouping in 11 into the Cardenolide Ring. 11 (3.0 g; 7.58 mmol) was dissolved in 150 mL of ethanol and 7.5 mL of water, and then 1.65 g (8.3 mmol) of p-toluenesulfonic acid monohydrate was added. The solution was heated at reflux for 24 h, cooled to room temperature, and concentrated under vacuum to approximately 35 mL. The solution was diluted with water, chilled, filtered and washed with cold ethanol to give 1.86 g (5.25 mmol, 69.1%) of the cardenolide **2** [21-hydroxy-3-oxo-24-norchola-4,20(22)-dieno-23,21-lactone]: mp 226–227.5 °C; UV 224 nm (ε 22 000); IR 1760 (C-22 carbonyl), 1670 cm^{-1} (C-3 ketone); NMR δ 5.87 (d, 1 H, C-21 H), 5.75 (s, 1 H, C-4 H), 4.78 (s, 2 H, C-23), 1.22 (s, 3 H, C-19), 0.70 (s, 3 H, C-18). Anal. Calcd for $C_{23}H_{30}O_3$: C, 77.93; H, 8.53. Found: C, 78.12; H, 8.63.

DDQ Dehydrogenation of the Cardenolide 2. Compound **2,** 1.90 g (5.36 mmol), was dissolved in 50 mL of dry benzene with stirring under nitrogen. DDQ, 1.56 g (6.75 mmol), was dissolved in 50 mL of dry benzene and added dropwise. The solution was refluxed 24 h, cooled, concentrated, and filtered. The filtrate was reduced to dryness and the residue was chromatographed over 60 g of Woelm neutral aluminum oxide (activity grade III) to give 400 mg of the 1,4-dienone **18** [21-hydroxy-3-oxo-24-norchola-1,4,20(22)-trieno-23,21-lactone] (1.13 mmol, 21.2%): mp 287–290 °C; UV 218 nm (ε 25 000); IR 1755 (C-22 carbonyl), 1665 cm^{-1} (C-3 ketone); NMR δ 7.06 (d, J = 11.0 Hz, 1 H, C-1 H), 6.20 (J = 11.0 Hz, 1 H, C-2 H), 6.08 (s, 1 H, C-4), 5.84 (d, 1 H, C-21), 4.74 (s, 2 H, C-23), 1.25 (s, 3 H, C-19), 0.73 (s, 3 H, C-18). Anal. Calcd for $C_{23}H_{28}O_3$: C, 78.37; H, 8.01. Found: C, 78.41; H, 7.90.

The Enol Ether of the Cardenolide 2. Compound **2,** 2.00 g (5.64 mmol), was dissolved in a solution of 6.0 mL of dioxane, 4.0 mL of ethanol, and 2.5 mL of triethyl orthoformate at 0 °C. p-Toluenesulfonic acid monohydrate (120 mg) was added and the solution was stirred at 0 °C for 15 min. The solution was poured into 100 mL of a 2% pyridine–water solution at 0 °C. The precipitate was filtered, slurried in 20 mL of hot 2% pyridine–methanol, cooled, and filtered to give 1.54 g (4.03 mmol, 71.5%) of the enol ether: mp 173.5–182.5 °C; UV 224.5 (ε 24 300); NMR δ 5.86 (d, 2 H, C-21), 5.20 (m, 2 H, C-4 H + C-6 H), 4.79 (s, 2 H, C-21 H), 1.00 (s, 3 H, C-19), 0.68 (s, 3 H, C-18). Anal. Calcd for $C_{25}H_{34}O_3$: C, 78.49; H, 8.96. Found: C, 77.58; H, 8.97.

Dehydrogenation of the Cardenolide 3-Enol Ether. The enol ether of compound **2,** 1.33 g (3.48 mmol), was dissolved in 35 mL of dry benzene and added rapidly through a dropping funnel to 1.75 g (7.71 mmol) of DDQ in 60 mL of dry benzene. The solution was stirred under nitrogen at room temperature for 15 min and then diluted with 30 mL of dichloromethane. The solution was filtered and the green gummy residue extracted with dichloromethane. The organic was evaporated to dryness and chromatographed over 50 g of Woelm neutral aluminum oxide (activity grade III). Elution with ethyl acetate–benzene (50:50) gave, after crystallization from ethyl acetate, 310 mg (0.885 mmol, 25.4%) of the trienone **19** [21-hydroxy-3-oxo-24-norchola-1,4,6,20(22)-tetraeno-23,21-lactone]: mp 207.5–211.5 °C; UV 298.5 nm (ε 13 000); IR 1740 (C-22 carbonyl), 1650 cm^{-1} (C-3 ketone); NMR δ 7.12 (d, J = 10.5 Hz, 1 H, C-1 H), 6.29 (d, J = 10.5 Hz, 1 H, C-2 H), 5.92 (s, 1 H, C-21), 4.82 (s, 2 H, C-23), 1.22 (s, 3 H, C-19), 0.77 (s, 3 H, C-18). Anal. Calcd for $C_{23}H_{26}O_3$: C, 78.82; H, 7.48. Found: C, 78.42; H, 7.51.

The Preparation of the Cardenolide Linear 4,6-Dienone 20 from 15. Compound **15,** 500 mg (1.27 mmol), was dissolved in 100 mL of methyl alcohol with stirring and then 500 mg (2.63 mmol) of p-toluenesulfonic acid monohydrate was added. The solution was stirred at reflux for 24 h, cooled, concentrated, diluted with water, and filtered. The crude product was recrystallized from methyl alcohol to give 260 mg (0.739 mmol, 58.2%) of dienone **20** [21-hydroxy-3-oxo-24-norchola-4,6,20(22)-trieno-23,21-lactone]: mp 287–290 °C; UV 283 nm (ε 26 500); IR 1760 (C-22 carbonyl), 1670 cm^{-1} (C-3 ketone); NMR δ 6.16 (s, 2 H, C-6, 7 H), 5.88 (s, 1 H, C-21 H), 5.70 (s, 1 H, C-4 H), 4.79 (s, 2 H, C-23), 1.04 (s, 3 H, C-19), 0.72 (s, 3 H, C-18). Anal. Calcd for $C_{23}H_{28}O_3$: C, 78.37; H, 8.01. Found: C, 77.97; H, 8.00.

The Formation of 4β,5β-Methylene Cardenolides. A solution of 5 g of cardenolide **2** in 150 mL of dry tetrahydrofuran was cooled in an ice bath and reacted with 6 g of lithium tri-*tert*-butoxyaluminum hydride until TLC indicated disappearance of the enone. The reaction mixture was poured into water and the mixture was acidified with concentrated hydrochloric acid. The suspension was extracted with chloroform, dried with the sodium sulfate, and evaporated. The residue was triturated with ether to yield 4.1 g of the allylic alcohol **21** which was not characterized except to note the presence of the cardenolide ring (1785, 1760 cm^{-1}) and a hydroxyl group (3500 cm^{-1}) and the absence of an enone in the IR spectrum.[8]

A mixture of 4.0 g (11.2 mmol) of the allylic alcohol **21,** 7.0 g of zinc–lead couple, and 5 mL of methylene iodide was stirred magnetically. Since the reaction was not self-initiating, a few crystals of iodine were added and the temperature held between 40 and 45 °C by intermittent cooling. After the reaction had subsided, stirring was continued overnight. The reaction mixture was then partitioned between chloroform and dilute hydrochloric acid. The aqueous layer was extracted with chloroform and the combined organic solutions were dried with sodium sulfate. The residue, after removal of solvent, was chromatographed over 400 g of silica. Elution with ethyl acetate–benzene (1:4) returned 75 mg of starting material which was followed by 1.42 g (3.84 mmol, 34%) of **22** [3′,4α-dihydro-3β-hydroxycyclopropa(4,5)-5β-24-norchola-4,20(22)-dieno-23,21-lactone]: mp 177–179 °C (ethyl acetate–petroleum ether); IR 1790, 1760, 1750, 1730 cm^{-1}; UV 220 nm (end, ε 16 000); NMR δ 5.85 (m, 1 H), 4.75 (m, 2 H), 4.40 (m, 1 H), 0.98 (s, 3 H), 0.82 (s, 3 H), 0.3 to −0.15 (m, cyclopropyl). Anal. Calcd for $C_{24}H_{34}O_3$: C, 77.80; H, 9.25. Found: C, 77.64; H, 9.36.

A portion (367 mg) of **22** was acetylated using 3.5 mL of acetic anhydride in 5 mL of pyridine and 20 mL of methylene chloride. After standing overnight, the methylene chloride was removed and the residue was poured into water and extracted with chloroform. The organic solution was washed with water and dilute hydrochloric acid, dried with sodium sulfate, and evaporated. The residue was crystallized from ether–petroleum ether to yield 347 mg of the 3β-acetate **23:** mp 124–125 °C; IR 1785, 1755, 1735, 1635 cm^{-1}; UV 220 nm (end, ε 17 000); NMR δ 5.87 (m, 1 H), 5.32 (m, 1 H), 4.80 (m, 2 H), 2.03 (s, 3 H), 0.98 (s, 3 H), 0.63 (s, 3 H), 0.13 (m, cyclopropyl H). Anal. Calcd for $C_{26}H_{36}O_4$: C, 75.69; H, 8.79. Found: C, 75.62; H, 8.84.

The Oxidation of the Cyclopropylcarbinol 22 to the Cyclopropyl Ketone 24. A solution of 502 mg (1.36 mmol) of compound **22** in 125 mL of refluxing toluene was oxidized with 25 g of silver carbonate on Celite[10] until TLC indicated conversion to the cyclopropylenone **24** (16 h). The mixture was filtered and the residue was washed with hot ethyl acetate. The combined organic solutions were

evaporated and the noncrystalline residue was chromatographed on a short silica gel column. Elution with ethyl acetate–benzene (1:3 and 1:1) yielded 375 mg (1.02 mmol, 75%) of the cyclopropylenone **24** [3′,4α-dihydro-3-oxocyclopropa(4,5)-5β-24-norchola-4,20(22)-dieno-23,21-lactone]: mp 188–190 °C (ethyl acetate–petroleum ether); IR 1785, 1750, 1680, 1625 cm^{-1}; UV 220 nm (end, ε 17 500); NMR δ 5.88 (m, 1 H), 4.78 (m, 2 H), 1.10 (s, 3 H), 0.83 (s, 3 H). Anal. Calcd for $C_{24}H_{32}O_3$: C, 78.22; H, 8.75. Found: C, 78.42; H, 8.96.

Ketalization of the Cardenolide 2. Compound **2**, 2.0 g (5.64 mmol), was suspended in 200 mL of ethylene glycol and 100 mg of *p*-toluenesulfonic acid monohydrate was added with stirring. Ethylene glycol (140 mL) was distilled under reduced pressure (0.6 mm at 65–70 °C). The pot residue was cooled to 20 °C and 0.3 mL of pyridine was added, followed by 100 mL of water. The solution was cooled to 10 °C and filtered to give 2.1 g (5.27 mmol, 93.4%) of the ketal **29**: mp 163.5–173.5 °C; IR 1765 cm^{-1} (C-22 carbonyl); NMR δ 5.85 (s, 1 H, C-21 H), 5.37 (m, 1 H, C-6 H), 4.76 (s, 2 H, C-23), 3.97 (s, 4 H, 3-ketal), 1.05 (s, 3 H, C-19), 0.67 (s, 3 H, C-18). Anal. Calcd for $C_{25}H_{34}O_4$: C, 75.34; H, 8.60. Found: C, 75.28; H, 8.68.

The Hydrogenation of the Cardenolide Ring in the Ketal 29. A solution of 6.60 g (16.6 mmol) of **29** in 300 mL of dioxane was hydrogenated over 0.7 g of 5% palladium on carbon at 2 psi. After 98 h, 15.4 mmol of H_2 had been consumed and the uptake stopped. The catalyst was removed and the solution was reduced to dryness to give 7.1 g (17.7 mmol, 107%) of ketal **30**: mp 208–231 °C; IR 1785 cm^{-1} (C-22 ketone); NMR δ 5.35 (m, 1 H, C-6 H), 4.51 (d, J = 6.0 Hz, 1 H, C-23 H), 4.31 (d, J = 6.0 Hz, 1 H, C-23 H), 3.94 (s, 4 H, 3-ketal), 1.04 (s, 3 H, C-19), 0.71 (s, 3 H, C-18). Anal. Calcd for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 72.68; H, 8.80.

The Deketalization of the Ketal 30 to the Cardanolide 31. Ketal **30**, 3.0 g (7.5 mmol), was dissolved in 45 mL of tetrahydrofuran at room temperature and 112.5 mL of 2.66 M (300 mmol) perchloric acid was added. The reaction mixture was then stirred for 10 min and 225 mL of water was added over a 10-min period. Another 75 mL of water was added and the solution was extracted with 2 × 150 mL of benzene–ether (2:1). The organic layer was washed with 0.5 N sodium bicarbonate and water, dried over sodium sulfate, filtered, and reduced to dryness. The crude material was crystallized from methyl alcohol–water to give 2.42 g (6.79 mmol, 90.6%) of **31** with a trace of **2**. The mixture (1.5 g) was chromatographed over Woelm neutral aluminum oxide (activity grade III). Elution with ethyl acetate–benzene (5:95) gave 1.1 g (65%) of pure **31**: mp 154–159 °C; UV 243 nm (ε 16 000); IR 1785 (C-22 carbonyl), 1680 cm^{-1} (C-3 ketone); NMR δ 5.75 (s, 1 H, C-4 H), 4.42 (m, 1 H, C-23 H), 3.86 (m, 1 H, C-23 H), 1.20 (s, 3 H, C-19), 0.75 (s, 3 H, C-18). Anal. Calcd for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.36; H, 8.98.

The 3-Enol Ether of the Cardanolide 31. Ketone **31**, 2.0 g (5.61 mmol), was partially dissolved in a solution of 6 mL of dioxane, 4 mL of ethanol, and 2.5 mL of triethyl orthoformate at 0 °C. To this stirred suspension was added 0.12 g of *p*-toluenesulfonic acid monohydrate and the solution was stirred for 15 min at 0 °C. The solution was poured into 100 mL of a 2% pyridine–water mixture of 0 °C. The product precipitated as a paste and was extracted with chloroform. The chloroform was dried over sodium sulfate, filtered, and reduced to dryness. The residue was crystallized from 1% pyridine–methanol to give 1.82 g (4.73 mmol, 84.3%) of the enol ether. The compound was not further characterized.

DDQ Dehydrogenation of the Cardanolide Enol Ether. The enol ether of compound **31**, 0.58 g (1.5 mmol), was dissolved in 30 mL of 95% aqueous acetone. DDQ (0.36 g, 1.58 mmol) was dissolved in 6 mL of 95% aqueous acetone and added dropwise with stirring to the above solution. After the addition, the solution was stirred for 10 min and then reduced to dryness under vacuum at 25 °C. Residual water was removed by azeotroping with benzene, then 10 mL of benzene was added and the solution was cooled and filtered. The organic filtrate was reduced to dryness and the residue was chromatographed over Woelm netural aluminum oxide (activity grade III). Elution with ethyl acetate–benzene (5:95) gave 328 mg (0.925 mmol, 61.7%) of a 3-keto-4,6-dienone **34** [21-hydroxy-3-oxo-4,6-norcholadieno-23,21-lactone]: mp 186–193 °C; UV 283 nm (ε 26 500); IR 1785 (C-22 ketone), 1670 cm^{-1} (C-3 ketone); NMR δ 6.12 (s, 2 H, C-6, 7 H), 5.67 (s, 1 H, C-4 H), 4.42 (m, 1 H, C-23 H), 3.89 (m, 1 H, C-23 H), 1.13 (s, 3 H, C-19), 0.80 (s, 3 H, C-18). Anal. Calcd for $C_{23}H_{30}O_3$: C, 77.93; H, 8.53. Found: C, 78.23; H, 8.52.

The Cardanolide 1,4,6-Trienone 35. The enol ether of **31**, 0.77 g (2.00 mmol), was dissolved in 20 mL of dry benzene and added rapidly, through a dropping funnel, to 0.93 g (4.1 mmol) of DDQ in 40 mL of dry benzene. The solution was stirred under nitrogen at room temperature for 15 min and then diluted with dichloromethane. The solution was filtered and the filter cake was washed until it became a dry green powder. The organic was evaporated to dryness and chromatographed over Woelm neutral aluminum oxide (activity grade III). Elution with ethyl acetate–benzene (20:80) gave 142 mg (0.403 mmol, 20.1%) of the trienone **35** [21-hydroxy-3-oxo-1,4,6-norcholatrieno-23,21-lactone]: mp 199–203 °C; UV 299 nm (ε 13 100); IR 1785 (C-22 carbonyl), 1665 cm^{-1} (C-3 ketone); NMR δ 7.08 (d, J = 10.0 Hz, 2 H, C-1 H), 6.27 (d, J = 10.0 Hz, 1 H, C-2 H), 6.10 (s, 1 H, C-4 H), 6.02 (m, 2 H, C-6, 7 H), 4.43 (m, 1 H, C-23 H), 3.96 (m, 1 H, C-23 H), 1.22 (s, 3 H, C-19), 0.83 (s, 3 H, C-18). Anal. Calcd for $C_{23}H_{28}O_3$: C, 78.37; H, 8.01. Found: C, 78.69; H, 8.13.

Dehydrogenation of the Cardanolide Enone 31. Cardanolide **31**, 1.00 g (2.81 mmol), was dissolved in 25 mL of dry benzene with stirring under nitrogen. To this solution was added dropwise, at room temperature, 0.79 g of DDQ (3.5 mmol, 1.25 equiv) in 25 mL of dry benzene. The solution was refluxed 24 h, cooled, concentrated, and filtered. The solution was reduced to dryness and the residue was chromatographed over 60 g of E. Merck neutral alumina. Elution with ethyl acetate–benzene (5:95) gave, after crystallization from ethyl acetate–hexane, 410 mg (1.16 mmol, 41.3%) of 3-keto-1,4-dienone **33** [21-hydroxy-3-oxo-1,4-norcholadieno-23,21-lactone]: mp 185–188 °C; UV 243 nm (ε 16 000); IR 1780 (C-22 carbonyl), 1665 cm^{-1} (C-3 ketone); NMR δ 7.08 (d, J = 10.0 Hz, 1 H, C-1 H), 6.24 (d, J = 10.0 Hz, 1 H, C-2 H), 6.09 (s, 1 H, C-4 H), 4.42 (m, 1 H, C-23 H), 3.87 (m, 1 H, C-23 H), 1.28 (s, 3 H, C-19), 0.79 (s, 3 H, C-18). Anal. Calcd for $C_{23}H_{30}O_3$: C, 77.93; H, 8.53. Found: C, 77.84; H, 8.78.

The 20-Cyanomethylene Derivative 25 of 11-Dehydrocorticosterone. Corticosterone acetate was oxidized to the 11-ketone (21-hydroxypregn-4-ene-3,11,20-trione acetate) using Jones reagnet; this product was converted into its 3-enol ether as described for deoxycorticosterone acetate. Reaction with diethyl cyanomethylphosphate followed by acid hydrolysis gave **25** in 75.7% yield from the enol ether: mp 160–163 °C; UV 231 nm (ε 27 500); IR 1755 (acetoxycarbonyl), 1720 (C-11 ketone), 1680 cm^{-1} (C-3 ketone); NMR δ 5.73 (s, 1 H, C-4 H), 5.39 (s, 1 H, cyanomethylene-H), 4.90 (d, J = 16.0 Hz, 1 H, C-21 H), 4.63 (d, J = 16.0 Hz, 1 H, C-21 H), 2.13 (s, 3 H, acetoxymethyl-H), 1.42 (s, 3 H, C-19), 0.64 (s, 1 H, C-18). Anal. Calcd for $C_{25}H_{31}NO_4$: C, 73.32; H, 7.95; N, 3.42. Found: C, 73.21; H, 7.95; N, 3.37.

Hydrolysis and Lactonization of the Cyanomethylene Derivative 25 of 11-Dehydrocorticosterone. Compound **25** was converted, in 56% yield, into the cardenolide **26**, as described for compound **11**: mp 264–267 °C; UV 223 nm (ε 23 600); IR 1755 (acetoxy ketone), 1715 (C-11 ketone), 1675 cm^{-1} (C-3 ketone); NMR δ 5.91 (s, 1 H, C-21 H), 5.77 (s, 1 H, C-4 H), 4.78 (s, 2 H, C-23), 1.44 (s, 3 H, C-19), 0.68 (s, 3 H, C-18). Anal. Calcd for $C_{23}H_{28}O_4$: C, 74.97; H, 7.66. Found: C, 74.64; H, 7.61.

Hydrogenation of 26. Compound **26** was converted into its ketal in a manner analogous to the one employed for compound **2** and hydrogenated in the same manner as **29**. Hydrolysis of the ketal with perchloric acid gave the 11-oxo derivative of **31** in 33.2% yield from **26**: mp 263–266 °C; UV 237 nm (ε 14 600). Anal. Calcd for $C_{23}H_{30}O_4$: C, 74.58; H, 8.16. Found: C, 74.19; H, 8.10.

11β-Acetoxy-21-hydroxy-3-oxo-4,20(22)-norcholadieno-23,21-lactone 28. The 11β-acetate of corticosterone acetate was prepared by acetylation of corticosterone using acetic anhydride and a catalytic amount of *p*-toluenesulfonic acid. The acetoxy ketone was converted into its enol ether which was subjected to the action of the anion of diethyl cyanomethylphosphonate; this gave the 20-cyanomethylene 3-enol ether derivative **31**, which upon hydrolysis afforded compound **27** in 31% yield. The compound was converted directly to the cardenolide with only NMR data used for structure confirmation: NMR δ 5.70 (s, 1 H, C-4 H), 5.40 (s, 2 H, C-11 H + cyanomethylene H), 4.88 (d, J = 14 Hz, 1 H, C-21 H), 4.62 (d, J = 14 Hz, 1 H, C-21 H), 2.12 (s, 3 H, C-21 acetoxymethyl H), 2.04 (s, 3 H, C-11 acetoxymethyl H), 1.17 (s, 3 H, C-19), 0.80 (s, 3 H, C-18).

Compound **27** was converted into the cardenolide **28** (in 65% yield) in the same manner as compound **11**: mp 213–217 °C; UV 227 nm (ε 21 500); IR 1755 (11-acetoxy ketone), 1740 (C-22 carbonyl), 1675 cm^{-1} (C-3 ketone); NMR δ 5.85 (s, 1 H, C-21 H), 5.71 (s, 1 H, C-4 H), 5.43 (m, 1 H, C-11 H), 4.71 (s, 2 H, C-23), 2.06 (s, 3 H, C-11 acetate), 1.30 (s, 3 H, C-19), 0.82 (s, 3 H, C-18). Anal. Calcd for $C_{25}H_{32}O_5$: C, 72.79; H, 7.82. Found: C, 72.84; H, 7.94.

The Condensation of the Cyanomethylenephosphonate with Δ^1-Corticosterone Acetate. In a flamed three-necked flask equipped with a magnetic stirring bar, nitrogen inlet, rubber septum inlet, and an addition funnel was placed 255 mg of a 50% sodium hydride dispersion in mineral oil. After adding 5 mL of dry tetrahydrofuran (benzophenone ketyl), stirring was started and 0.97 mL (5.87 mmol) of diethyl cyanomethylenephosphonate was injected with a syringe. After gas evolution ceased, 1.00 g (2.59 mmol) of Δ^1-corticosterone

acetate [11β,21-dihydroxypregna-1,4-dien-3,20-dione 21-acetate] in 10 mL of dry tetrahydrofuran was added via the addition funnel, and the funnel was washed with an additional 10 mL of solvent. TLC indicated the reaction was complete after 2 h and the solution was poured into water and adjusted to a pH of ca. 4 with acetic acid. From this aqueous suspension, 821 mg (2.01 mmol, 78%) of **13** slowly crystallized: mp 187–194 °C (ethyl acetate–cyclohexane); IR 3400, 2220, 1750, 1665, 1615, 1605 cm^{-1}; UV 218 nm (ε 25 000); NMR δ 7.35 (d, J = 10 Hz, 1 H), 6.28 (dd, J = 10, 2 Hz, 1 H), 6.04 (s, 1 H), 5.43 (s, 1 H), 4.95 (d, J = 14.5 Hz, 1 H), 4.67 (d, J = 14.5 Hz, 1 H), 4.45 (m, 1 H), 2.13 (s, 3 H), 1.48 (s, 3 H), 0.95 (s, 3 H). Anal. Calcd for $C_{25}H_{31}NO_4$: C, 73.32; H, 7.63; N, 3.42. Found: C, 73.07; H, 7.89; N, 3.37.

The Formation of the Cardenolide 14 from the 1,4-Dien-3-one 13. To a solution of **13** (350 mg, 0.86 mmol) in 50 mL of ethanol was added 2.5 mL of distilled water and 0.5 g of p-toluenesulfonic acid monohydrate. The reaction mixture was refluxed for 16 h, cooled, and diluted with 150 mL of distilled water. The precipitate was filtered, dried, and crystallized from methylene chloridine–ethyl acetate–petroleum ether to yield 205 mg (0.57 mmol, 65%) of cardenolide **14** as the monohydrate: mp 256–269 °C; IR 3450, 1780, 1750, 1660, 1625, 1660 cm^{-1}; UV 220 nm (ε 21 000), 244 (sh, 15 500); NMR (Me_2SO-d_6) δ 7.37 (d, J = 10 Hz, 1 H), 6.17 (dd, J = 10, 2 Hz, 1 H), 5.95 (m, 2 H), 4.83 (d, 2 H), 4.57 (d, exchanges with D_2O), 4.23 (m, 1 H), 1.40 (s, 3 H), 0.86 (s, 3 H). Anal. Calcd for $C_{23}H_{28}O_4 \cdot H_2O$: C, 71.48; H, 7.82. Found: C, 71.63; H, 7.64.

Registry No.—**2,** 14030-39-8; **2** enol ether, 53287-13-1; **3,** 1693-63-6; **4,** 66007-63-4; **7,** 23330-61-2; **8,** 19637-05-9; **9,** 2739-50-6; **10,** 65970-05-0; **11,** 65970-06-1; **12,** 58652-04-3; **13,** 65970-17-4; **14,** 65970-18-5; **15,** 65970-08-3; **16,** 65970-09-4; **17,** 65970-07-2; **18,** 6747-92-8; **19,** 66007-62-3; **20,** 53287-14-2; **21,** 24366-43-6; **22,** 65970-10-7; **23,** 65970-11-8; **24,** 65970-12-9; **25,** 65970-13-0; **26,** 65970-14-1; **27,** 65970-15-2; **28,** 65970-16-3; **29,** 65969-98-4; **30,** 65969-99-5; **31,** 65970-00-5; **31** 3-enol ether, 65970-01-6; **31** 11-oxo derivative, 65970-04-9; **33,** 66007-61-2; **34,** 65970-02-7; **35,** 65970-03-8; diethyl cyanomethylphosphonate, 2537-48-6; deoxycorticosterone acetate, 56-47-3.

References and Notes

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New Zearalenone Related Macrolides and Isocoumarins from an Unidentified Fungus

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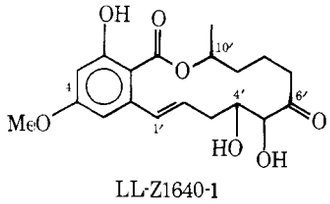
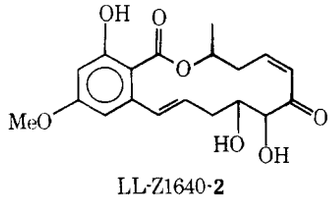
The isolation and characterization of four new zearalenone-like macrolides and three isocoumarins from an unidentified fungus, Lederle Culture Z1640, are reported. By altering the fermentation conditions this organism could be forced to produce curvularin macrolides. X-ray studies on a di-p-chlorobenzoyl derivative of LL-Z1640-1 showed this metabolite to be (4′S,5′S)-4′,5′-dihydroxyzearalenone 4-methyl ether.

Lederle culture Z1640 was selected for study on the basis that crude extracts of shaker-flask fermentations inhibited the growth and motility of the ciliated protozoan *Tetrahymena pyriformis*. Stirred fermentations of this unidentified fungus yielded three zearalenone[1] related metabolites LL-Z1640-**1**, -**2**, and -**4**. Surface fermentation yielded LL-Z1640-**4** and -**3** as the predominant products. In an attempt to obtain the corresponding diphenolic compounds still cultures were incubated in the presence of D,L-ethionine.[2] Under these conditions the mycelium was blanched from the normal very dark color and workup yielded curvularin and dihydrocurvularin[3] and none of the larger macrolides.



LL-Z1640-**1**



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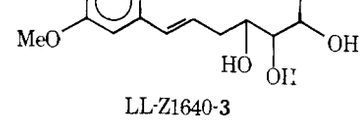
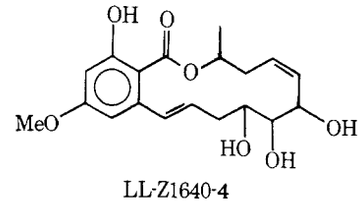


LL-Z1640-**3**



LL-Z1640-**4**

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