Bufadienolides. 6. Synthesis of 17β-(6′α-Pyronyl)androstanes[1,2]

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Condensation of aldehyde **2a** with the anion prepared from diethyl cyanomethylphosphonate provided the isomeric *cis,trans*- and *cis,cis*-dienes **3a** and **4**. The geometrical isomers gave Cotton-effect curves with opposite sign. Similarly, aldehyde **5** led to olefins **6a** and **7**. Ozonolysis of the isomeric dienes **6a** and **7** gave, in each case, 17β-carboxylic acid methyl ester **8**, thereby eliminating the possibility of epimerization at position 17. Aldehyde **2a**, on condensation with the anion derived from diethyl carbethoxymethylphosphonate, gave a single product, *cis,trans* olefin **3b**. The ester **3b** was converted into isobufadienolide **10** by hydrolysis with perchloric acid in ether, saponification with 5% potassium hydroxide in methanol, and enol lactonization with ethyl acetate–acetic anhydride–perchloric acid. A related but more efficient synthesis of 2-pyrone **10** was realized using *t*-butyl ester **6b**. An even more convenient new synthesis of 6-substituted 2-pyrones was achieved by condensation of the aldehyde (*e.g.*, **2a**) precursor with malonic acid. The scope of this new reaction was illustrated by preparing isobufadienolides **10**, **12**, and **16** and pyrone **14**.

Development of practical synthetic approaches to isomeric[3] bufadienolides was considered for biological reasons[2,4] an important aspect of our overall effort concerned with bufadienolide chemistry. The isobufadienolides[3] would allow an evaluation of minor structural modifications upon possible antineoplastic, cardiac, and anesthetic responses. Preparation of 6′ isobufadienolides [17β-(6′-α-pyronyl)androstanes] was selected for initial solution. As with cardenolide[1,5] and bufadienolide[6] syntheses, approaches were restricted to a few major reaction steps from readily available steroid precursors. Several useful methods are already known for obtaining 6-substituted 2-pyrones.[7] None of these seemed readily adaptable to a 20-oxopregnane precursor. Consequently, a new synthesis of 6-substituted 2-pyrones was undertaken based on the mild formylation reaction reported by Bernstein and colleagues.[8] Pregnenolone acetate (**1**) was converted with ethyl orthoformate–perchloric acid into aldehyde **2a**. Condensation of aldehyde **2a** with the anion prepared from diethyl cyanomethylphosphonate proceeded well at room temperature and provided a two-component mixture corresponding to *cis,trans*[9] and *cis,cis* olefins **3a** and **4**, which were separated by preparative thin layer chromatography. The proton magnetic resonance spectra of each isomer was consistent with the assigned structure. The optical rotatory dispersion Cotton-effect curves were of opposite sign, suggesting either the beginning of helical asymmetry in the diene system or opposite configurations at position 17. To confirm or eliminate the latter possibility, aldehyde **5** was analogously treated with the anion from diethyl cyanomethylphosphonate. Again, two isomeric nitriles (**6a** and **7**) were obtained and displayed Cotton-effect curves of opposite sign. Each was oxidized with ozone at −60° and intermediary ozonides were reduced. The methyl 17β-carboxylate **8** was the exclusive product from each isomer, thus obviating the possibility of epimerization having occurred at position 17.

Application of an acid-catalyzed cyclization (to imino lactones) reaction to the isomeric nitriles, as already successfully applied to obtaining cardenolides,[1] could now be explored. However, olefins **3a** and **4**, upon treatment with hydrochloric acid in methanol, hydrobromic acid–acetic acid, or boron trifluoride ethereate–acetic acid, led to a variety of products, among which neither the anticipated imino lactone nor the 2-pyrone could be detected. Accordingly, to reduce the possibility of side reactions, the anion derived from diethyl carbethoxymethylphosphonate was condensed with aldehyde **2a** to provide *cis,trans*-butadiene **3b**. Increased steric requirements for the ethoxycarbonyl substituent seemed to have a marked directive influence (*cf.* Bose and colleagues in ref 1) on the Wittig reaction, as presence of the isomeric *cis,cis* olefin was not detected. Similarly, condensation of aldehyde **5** with the anion prepared from diethyl *t*-butoxycarbonylmethylphosphonate afforded *cis,trans*-butadiene **6b** as exclusive product. Assuming[8] a *trans* alkoxy–aldehyde group relationship in olefins **2** and **5**, the geometrical configurations of dienes **3**, **4**, and **6** were further assigned by examining the olefin–proton coupling constants. The proton magnetic resonance spectrum of ester **3b** is illustrative. The doublet signal at δ 5.53 with J_{ab} = 12 cps was assigned to the H_a (C-21) proton of ester **3b**. The adjacent downfield doublet at δ 5.68 with J_{bc} = 15 cps was attributed to the H_c proton and the less shielded quartet at δ 7.66 with J_{ab} = 12 and J_{bc} = 15 cps to H_b. Possible further support for the *trans* relationship of protons H_b and H_c in ester **3b** was obtained by irradiating (infrared lamp) the olefin in benzene. A new isomer was isolated and tentatively formulated as *trans,cis* olefin **9** (or alternatively the *cis,cis* isomer). Vinyl protons H_a, H_b, and H_c of the butadiene resulted in coupling

(1) This investigation was supported by Public Health Service Research Grants CA-04074-07, CA-10115-01, and CA-10115-02 from the National Cancer Institute. Part 5 and Steroids and Related Natural Products. LIII: G. R. Pettit, C. L. Herald, and J. P. Yardley, *J. Org. Chem.*, **35**, 1389 (1970).

(2) Refer to J. C. Knight, G. R. Pettit, and C. L. Herald, *Chem. Commun.*, 445 (1967), for a preliminary report.

(3) For steroids bearing, at the 17β position 3′-, 4′-, or 6′-substituted 2-pyrone rings, the term isobufadienolides is proposed. The first example of a 6′ isobufadienolide was reported in preliminary form,[2] while an example of the 3′ system was described: D. Rosenthal, J. Fried, P. Grabowich, and E. F. Sabo, *J. Amer. Chem. Soc.*, **84**, 877 (1962). No member of the 4′ isobufadienolides appears to be known.

(4) See G. R. Pettit, B. Green, and G. Dunn, *J. Org. Chem.*, **35**, 1367 (1970), for a summary.

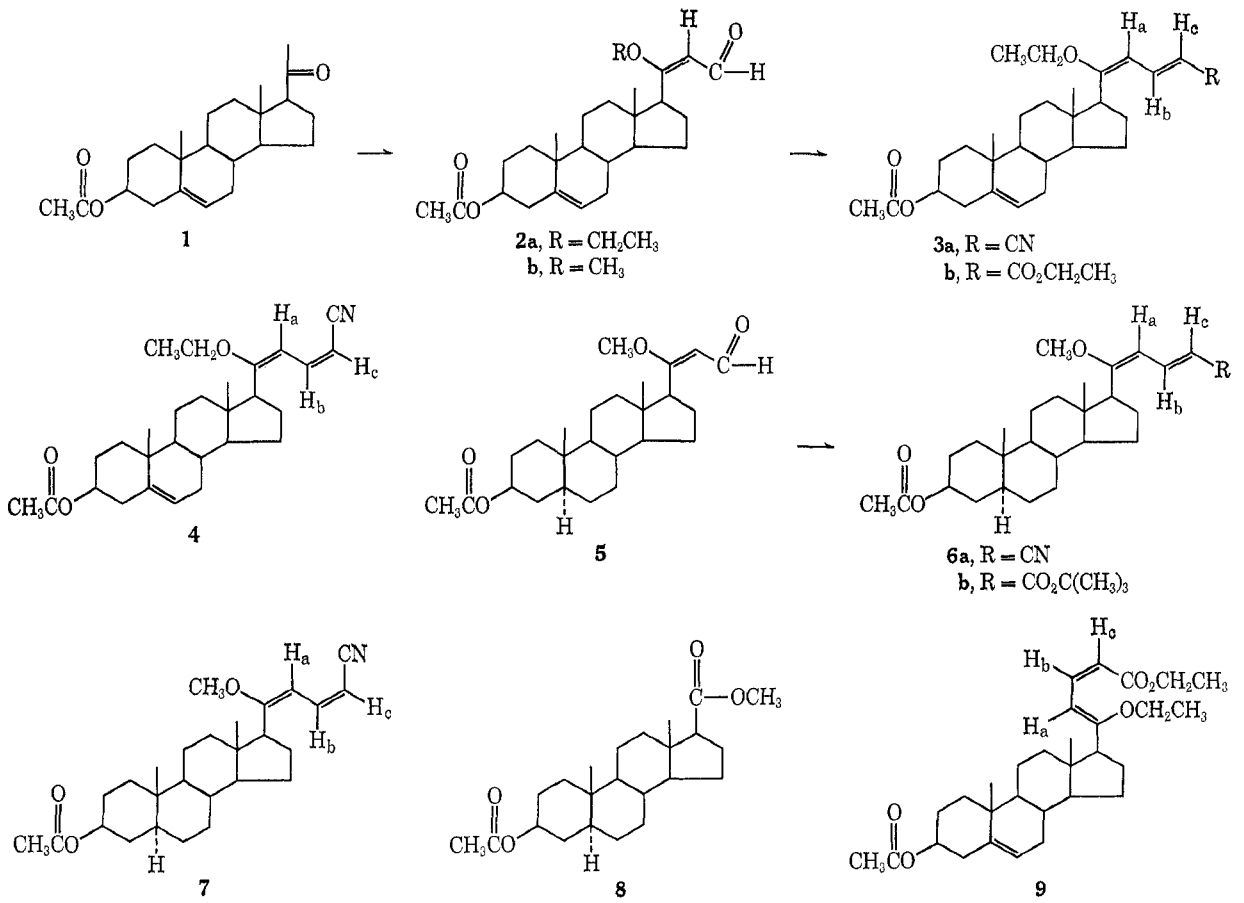
(5) G. R. Pettit and J. P. Yardley, *Chem. Ind.* (London), 553 (1966).

(6) G. R. Pettit, D. Fessler, K. Paull, P. Hofer, and J. C. Knight, *J. Org. Chem.*, **35**, 1389 (1970).

(7) (a) V. Lamberti, W. T. Weller, and J. C. M. Schogt, *Rec. Trav. Chim. Pays-Bas*, **86**, 504 (1967); (b) N. P Shusherina, N. D. Dmitrieva, E. A. Lukyanets, and R. Y. Levina, *Russ. Chem. Rev.*, **36**, 175 (1967).

(8) J. P. Dusza, J. P. Joseph, and S. Bernstein, *J. Amer. Chem. Soc.*, **86**, 3908 (1964). In this preliminary communication the *trans* orientation of alkoxy and formyl groups in aldehydes **2a** and **2b** was favored.

(9) In this paper, the designations *cis* and *trans* are determined by disposition of carbon substituents along the butadiene system.



constants of J = 4 or 6 cps attributed to *cis* relationships.

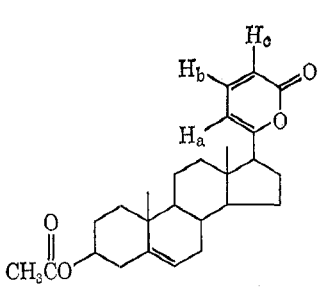
Ester **3b** was transformed into 2-pyrone **10** as follows. Enol ether hydrolysis to ketone **11** was followed by ultraviolet absorption spectra. After 4.5 hr at room temperature, reaction was complete and the ester was saponified with methanolic potassium hydroxide. A 2-min contact at ice-bath temperature with the acetic anhydride–perchloric acid enol lactonization reagent[10] provided 6′-isobufadienolide **10** in 7.4% yield. The low yield was attributed to competitive side reactions such as reverse aldol condensation during the saponification step. However, the yield was considerably improved by eliminating the saponification step and using *t*-butyl ester **6b** and *p*-toluenesulfonic acid in benzene for the cyclization sequence. Concurrently, the following pleasant discovery was made. When aldehyde **2a** was allowed to condense with malonic acid, pyrone **10** was obtained in one step. The extraordinary convenience of this Knoevenagel-[11]type reaction nicely satisfied requirements for a practical 6′-isobufadienolide synthesis, and the alternative butadiene (*cf.* **3b** or **6b**) route was discontinued.

Optimal reaction conditions for the Knoevenagel step were developed using aldehydes **2b** and **5**. A 1:2:2 mole ratio of aldehyde, malonic acid, and piperidine (or morpholine) in excess pyridine at steam-bath temperature for 1 hr proved quite effective. Dilution with water, washing with dilute hydrochloric acid, and finally purification of the pyrone by column chromatography on silica gel provided pyrones **10** and **12** in 54% yields. Substitution of N-methylmorpholine or triethylamine for the secondary amine led only to recovery of starting aldehyde. Elimination of the secondary amine or marked reduction of its concentration also inhibited pyrone formation. The scope of the two-step pyrone synthesis was further ascertained using aldehydes **13a** and **15**. Each aldehyde was obtained from the corresponding 3 or 20 ketone by treatment with trimethyl orthoformate–perchloric acid, and with only preliminary purification was used in the Knoevenagel reaction. By this means, reasonably pure specimens of pyrone **14** and isobufadienolides **16a** and **16b** were obtained in *ca.* 20% conversion. Interestingly, one of the side products accompanying (in 25% yield) pyrone **14** was a nitrogen-containing steroid assigned enamine structure **13b**. Support for the enamine formulation resided with results of element microanalyses, maximum ultraviolet absorption at 344 mμ (ε 15,080), infrared absorption bands at 1740, 1650, and 1605 cm^{-1}, a proton magnetic resonance signal at δ 9.66 attributable to an aldehyde proton, and lack of a signal for methoxyl and broad signals at δ 3.37 and 1.64 (piperidine protons).

The pmr spectrum of pyrone **14** proved valuable for interpreting the isobufadienolide pyrone ring proton signals. The H_c proton of pyrone **14** appeared as a doublet at δ 6.16 with J_{cb} = 9 cps and H_b as a doublet at δ 7.10 with J_{bc} = 9 cps. The doublet at δ 6.04 with J = 7 cps exhibited, for example, by bufadienolide **16a** would then correspond to the H_a proton with the H_c doublet at δ 6.18 (J_{cb} = 10 cps) and the H_b quartet at δ 7.32 (J_{ba} = 7, J_{bc} = 10 cps) completing the inter-

(10) B. E. Edwards and P. N. Rao, *J. Org. Chem.*, **31**, 324 (1966).

(11) A comprehensive review of the Knoevenagel reaction has been prepared: G. Jones, *Org. React.*, **15**, 204 (1967).



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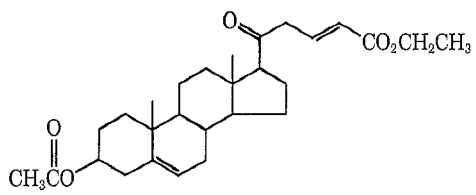

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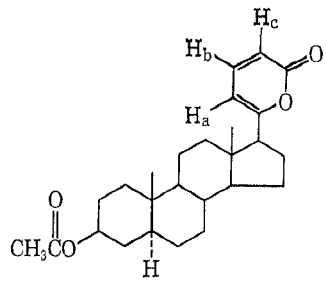

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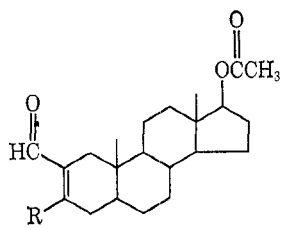
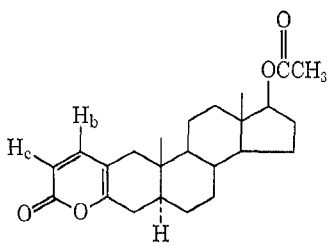


13a, R = OCH_3

b, R = N



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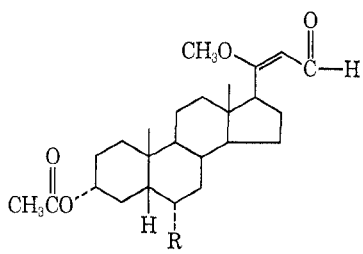
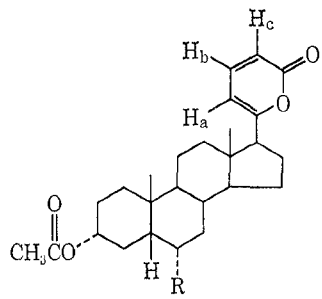


15a, R = H

b, R = $OCOCH_3$



16a, R = H

b, R = $OCOCH_3$

pretation.[12] Isobufadienolides **10**, **12**, and **16** displayed analogous pyrone-ring pmr signals and characteristic[13] maximal ultraviolet absorption near 300 mμ. Results of these physical measurements combined with infrared[7b,14] spectra and elemental analyses adequately confirmed the structure of each 2-pyrone.

The preceding facile two-step conversion of ketones into 6-substituted 2-pyrones offers promise of being generally applicable to obtaining such oxygen heterocyclic compounds. A comprehensive study of the mechanism and side products arising from the malonic acid step may implicate an iminium salt intermediate.[11,15]

Experimental Section

Preparative thin layer chromatograms were performed using 20 × 20 mm glass plates coated with 1 or 2 mm of silica gel HF_{254} (E. Merck). Melting points were recorded using a Kofler or Fisher-Johns melting point apparatus. Other general experimental methods used here are summarized in the experimental section of part 5.[1]

3β-Acetoxy-20-ethoxy-21-formylpregna-5,20-diene (2a).—With the procedure outlined by Bernstein and colleagues,[8] perchloric acid (1.8 ml) was added to a suspension of pregnenolone acetate (1, 3.3 g) in triethyl orthoformate (50 ml). The solution was swirled for 3 min and pyridine (5 ml) was added followed by water (150 ml). The yellow mixture was extracted with diethyl ether and the ethereal extract was washed well with water. Removal of solvent *in vacuo* gave a solid residue which recrystallized from methanol as large, pale yellow blades (2.5 g): mp 176–178° (another recrystallization from methanol raised the melting point to 182–186°); pmr δ 0.68 and 1.03 (C-18 and -19 methyls), a triplet centered at 1.36 (methyl of ethyl group, J = 3 cps), 2.02 (acetate), 2.9–3.3 (H-17α), a quartet centered at 3.84 (methylene of ethyl group, J = 3 cps), 5.32 (H-6 vinyl), 5.40 (doublet, J = 8 cps, H-21 vinyl), and 9.89 (doublet, J = 8 cps, aldehyde proton).

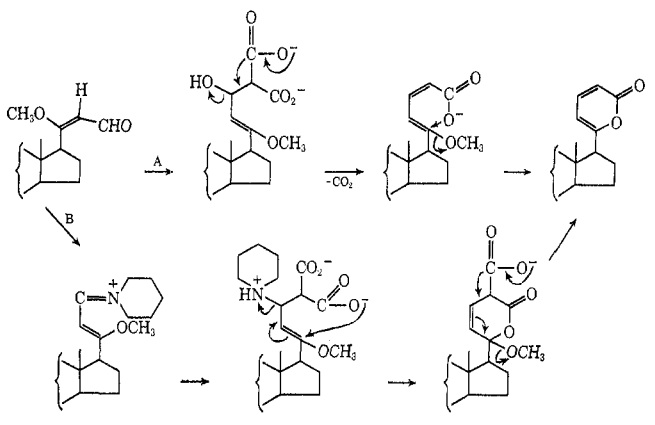
3β-Acetoxy-20-ethoxy-24-cyano-21-norchola-5,20(22),23-triene (3a and 4).—To a cool (ice bath) suspension of sodium hydride oil dispersion (3.4 g) in tetrahydrofuran (60 ml) was added diethyl cyanomethylphosphonate (15 g) in tetrahydrofuran (60 ml), dropwise with stirring. With an elapsed time of *ca.* 10 min, reaction had subsided and aldehyde **2a** (6.2 g) in tetrahydrofuran (150 ml) was added in one portion. Stirring at room temperature was continued for 3 days; optimum reaction time was not determined. Solvent was removed *in vacuo* from the clear orange solution and the residual orange oil was dissolved in diethyl ether. The ethereal solution was washed successively with 2 *N* hydrochloric acid, 2.5 *N* sodium hydroxide, and water. Distillation of the ether gave a yellow solid. Two recrystallizations from methanol provided small rosettes (5.7 g), mp 154–156°. A thin layer chromatogram revealed the product to be a two-component mixture (the *cis,cis* and *cis,trans* isomers). Preparative thin layer chromatography with 1:9 ligroin–ethyl acetate mobile phase, run three times, led to the less polar *cis,cis* isomer **4** and the more polar *cis,trans* isomer **3a**. The *cis,trans* isomer **3a** recrystallized from methanol–chloroform as short, shining needles: mp 195–196°; λ_{max} 295 mμ (ε 30,530); $[\alpha]_D$ −283° (*c* 1.09); RD (*c* 0.05, ethanol) $[\alpha]_{300}$ −4500°, $[\alpha]_{350}$ −2500°, $[\alpha]_{400}$ −1100°, $[\alpha]_{450}$ −700°, $[\alpha]_{500}$ −500°, $[\alpha]_{550}$ −400°, and $[\alpha]_{589}$ −300°; pmr δ 0.68 and 1.06 (C-18 and -19 methyls), a triplet centered at 1.36 (methyl of ethyl group, J = 7 cps), 2.06 (acetate), 2.98 (H-17α), a quartet centered at 3.86 (methylene of ethyl group J = 7 cps), 5.07 (doublet, J = 16 cps, H_c), 5.52 (doublet, J = 12 cps, H_a), 5.47 (H-6), and 7.32 (quartet, J_{ab} = 12 cps, J_{bc} = 16 cps, H_b).

(12) We wish to thank Dr. M. Dines and Dr. W. H. Perkel, Department of Chemistry, University of Illinois, Urbana, Ill., for kindly informing us that they have "consistently found that the splitting constant for the vinyl protons on carbons 3 and 4 of the pyrone ring vary from 9–10 Hz while those for protons on carbons 4 and 5 are in the range 5.5–6.8 Hz."

(13) K. Meyer, *Helv. Chim. Acta*, **46**, 178 (1963).

(14) R. H. Wiley and S. C. Slaymaker, *J. Amer. Chem. Soc.*, **78**, 2393 (1956); R. N. Jones, C. L. Angell, T. Ito, and R. J. D. Smith, *Can. J. Chem.*, **37**, 2007 (1959); R. N. Jones and B. S. Gallagher, *J. Amer. Chem. Soc.*, **81**, 5242 (1959).

(15) Without benefit of additional study, mechanistic pathways such as A or B seem likely with B the more probable.



Anal. Calcd for $C_{28}H_{39}NO_3$: C, 76.85; H, 8.98; N, 3.20. Found: C, 76.99; H, 8.73; N, 3.33.

The *cis,cis* isomer **4** recrystallized from methanol–chloroform as light, fluffy needles: mp 194–195°; λ_{max} 295 mμ (ε 28,270); $[\alpha]_D$ +15° (*c* 0.60); RD (*c* 0.058, ethanol) $[\alpha]_{330}$ +1414°, $[\alpha]_{350}$ +655°, $[\alpha]_{400}$ +207°, $[\alpha]_{450}$ +138°, $[\alpha]_{500}$ +86°, and $[\alpha]_{589}$ 0°; pmr δ 0.66 and 1.04 (C-18 and -19 methyls), 1.36 (triplet, methyl of ethyl group, J = 7 cps), 2.04 (acetate), 2.6–2.9 (H-17α), 3.92 (quartet, methylene of ethyl group, J = 7 cps), 4.78 (H_c, doublet, J_{bc} = 11 cps), 5.40 (H-6), 5.85 (doublet, J_{ab} = 13 cps, H_a), and 7.08 (quartet, J_{ab} = 13 cps, J_{bc} = 11 cps, H_b).

Anal. Found: C, 77.16; H, 9.33; N, 3.52, 3.93.

3β-Acetoxy-20-methoxy-24-cyano-21-nor-5α-chola-20(22),23-diene (6a and 7).—The general procedure used for obtaining dienes **3a** and **4a** was repeated using diethyl cyanomethylphosphonate in tetrahydrofuran (50 ml), 3.4 g of sodium hydride oil dispersion in tetrahydrofuran (50 ml), and 3β-acetoxy-20-methoxy-21-formyl-5α-pregna-20-ene (4.7 g)[8] in tetrahydrofuran (100 ml). In this case, a thin layer chromatogram of the crude product indicated partial acetate hydrolysis and the mixture was acetylated. The *cis,cis*- and *cis,trans*-butadienes were separated by preparative thin layer chromatography with 5:1 hexane–ethyl acetate mobile phase. A 0.67-g aliquot from 3.4 g of crude material gave 0.16 g of *cis,trans* isomer **6a** and 0.14 g of *cis,cis* isomer **7**. Each isomer was subjected to another preparative thin layer chromatogram to yield 0.083 g of *cis,trans*- and 0.13 g of *cis,cis*-diene. The *cis,trans*-diene **6a** recrystallized from methanol–chloroform as plates: mp 185–186°; $\lambda_{max}^{CH_3OH}$ 292 mμ (ε 35,900); ν_{max} 2950, 2210, 1740, 1610, 1280, 1250, 1040, 960, and 860 cm^{-1}; $[\alpha]^{20}D$ −133° (*c* 0.42); RD (*c* 0.05, methanol) $[\alpha]_{240}$ +1680°, $[\alpha]_{254}$ −3080°, $[\alpha]_{328}$ −3080°, $[\alpha]_{400}$ −840°, and $[\alpha]_{589}$ −240°; pmr δ 0.58 and 0.82 (C-18 and -19 methyls), 2.01 (acetate), 3.62 (methoxyl), 5.04 (doublet, J_{bc} = 15 cps, H_c), 5.46 (doublet, J_{ab} = 11 cps, H_a), and 7.23 (quartet, J_{ab} = 11 cps, J_{bc} = 15 cps, H_b).

Anal. Calcd for $C_{27}H_{39}NO_3$: C, 76.19; H, 9.24; N, 3.29. Found: C, 76.06; H, 9.26; N, 3.37.

The *cis,cis* isomer **7** recrystallized from methanol–chloroform as needles: mp 188–189°; $\lambda_{max}^{CH_3OH}$ 292 mμ (ε 25,600); ν_{max} 3000, 2240, 1750, 1240, 1040, 845, and 730 cm^{-1}; $[\alpha]^{20}D$ +130° (*c* 0.62); RD (*c* 0.05, methanol) $[\alpha]_{238}$ −4560°, $[\alpha]_{256}$ +1360°, $[\alpha]_{322}$ +2360°, $[\alpha]_{400}$ +280°, $[\alpha]_{589}$ +40°; pmr δ 0.59 and 0.83 (C-18 and -19 methyls), 2.01 (acetate), 3.68 (methoxyl), 4.77 (doublet, J_{bc} = 9 cps, H_c), 5.84 (doublet, J_{ab} = 11 cps, H_a), and 7.67 (quartet, J_{bc} = 9 cps, J_{ba} = 11 cps, H_b).

Anal. Found: C, 76.33; H, 9.19; N, 3.41.

Ozonolysis of 3β-Acetoxy-20-methoxy-24-cyano-21-nor-5α-chola-20(22),23-diene (6a and 7).—Ozone (Welsbach Ozonator, 60 V, oxygen at 6 psi, flowmeter 0.04) was passed for 15 min through a gas dispersion tube into a solution of *cis,cis*-diene **7** (66 mg) in dry ethyl acetate (20 ml) at −60°. The solution was next flushed with oxygen for 10 min and concentrated to a crystalline residue. Zinc dust (0.2 g) was added to a solution of the solid in glacial acetic acid (5 ml). After 30 min at room temperature, the solution was filtered and diluted with water. The crystals which separated were collected, washed with water, and dried to yield 47 mg (81%) of pure (by thin layer chromatography) methyl 3β-acetoxy-5α-androstane 17β-carboxylate (**8**), mp 149–151°.

Employing the same procedure with *cis,trans* isomer **6a** (51.5 mg) in ethyl acetate (25 ml) gave 44 mg (98%) of pure (by thin layer chromatography) ester **8**, mp 146–148°. Both specimens of ester **8** were identical with an authentic specimen as evidenced by thin layer chromatographic and infrared (ν_{max} 3000, 1750, 1265, and 1045 cm^{-1}) comparison. The pmr spectra were also identical and displayed signals at δ 0.64 and 0.82 (6 methyl protons), 2.01 (acetate), 3.67 (methoxyl), and 4.66 (multiplet, H-3α).

3β-Acetoxy-20-ethoxy-24-ethoxycarbonyl-21-norchola-5-*cis*-20(22)-*trans*-23-triene (3b).—The ylide prepared from diethyl carbethoxymethylphosphonate (6.7 g) in tetrahydrofuran (20 ml) and sodium hydride oil dispersion (1.1 g) in tetrahydrofuran (20 ml) was allowed to react with aldehyde **2** (2.1 g) in tetrahydrofuran (50 ml) as described above for obtaining isomeric olefins **3a** and **4**. In this experiment, the reaction was allowed to proceed for *ca.* 22 hr. The crude product recrystallized from methanol as needles (1.85 g), mp 141–145°. Further purification by preparative thin layer chromatography with 17:3 ligroin–ethyl acetate mobile phase gave an analytical specimen: mp 153–155°; $\lambda_{max}^{CHCl_3}$ 305 mμ (ε 27,500); $[\alpha]_D$ −249° (*c* 4.08); ν_{max} 1730 (acetate), 1700 (ethyl ester), and 1240 cm^{-1}; pmr δ 0.66 and 1.02 (C-18 and -19 methyls), 1.32 and 1.26 (triplets, J = 7 cps, methyls of ethoxys), 2.04 (acetate), 2.90 (H-17α), 3.93 and 4.20 (quartets, J = 7 cps, methylenes of ethoxys), 4.60 (multiplet, H-3α), 5.42 (multiplet, H-6 vinyl), 5.53 (doublet, J_{ab} = 12 cps, H_a), 5.68 (doublet, J_{cb} = 15 cps, H_c), and 7.66 (quartet, J_{ab} = 12 cps, J_{cb} = 15 cps, H_b).

Anal. Calcd for $C_{30}H_{44}O_5$: C, 74.34; H, 9.15. Found: C, 74.41; H, 9.03.

Irradiation of 3β-Acetoxy-20-ethoxy-24-ethoxycarbonyl-21-norchola-5-*trans*-20(22)-*trans*-23-triene (3b).—A specimen of *cis,trans* isomer **3b** (1.0 g) in benzene (100 ml) was irradiated with a Sylvania industrial infrared lamp (250 W) for 73 hr. The reaction mixture was chromatographed on silica gel (200 g) and a fraction eluted by 19:1 ligroin–ethyl acetate afforded an isomer tentatively assigned *trans,cis* structure **9**. Recrystallization from methanol gave 0.05 g of diamond-shaped plates: mp 147–149°; λ_{max} 305 mμ (ε 25,800); ν_{max} 1730, 1700, and 1240 cm^{-1}; $[\alpha]_D$ −6° (*c* 1.26); pmr δ 0.66 and 1.02 (C-18 and -19 methyls), 1.28 (triplet, J = 7 cps, methyl of ethoxy), 1.32 (triplet, J = 7 cps, methyl of ethyl ester), 2.04 (acetate), 3.92 (quartet, J = 7 cps, methylene of ethoxy ether), 4.14 (quartet, J = 7 cps, methylene of ethyl ester), 4.6 (multiplet, H-3α), 5.38 (multiplet, H-6 vinyl), 5.33 (quartet, J_{bc} = 4 cps, J_{ba} = 6 cps, H_b), 6.88 (doublet, J_{ab} = 6 cps, H_a), and 6.96 (doublet, J_{cb} = 4 cps, H_c).

Anal. Calcd for $C_{30}H_{44}O_5$: C, 74.34; H, 9.15. Found: C, 74.31; H, 9.19.

The nmr spectrum of the remaining material showed it to be substantially unchanged olefin **3b**.

3β-Acetoxy-20-methoxy-24-*t*-butoxycarbonyl-21-nor-5α-chola-*cis*-20(22)-*trans*-23-diene (6b).—Synthesis of *t*-butyl ester **6b** (1.4 g) was accomplished using diethyl *t*-butoxycarbonylmethylphosphonate[16] (7.8 g), sodium hydride oil dispersion (1.0 g), aldehyde **5** (2.0 g), and tetrahydrofuran (200 ml total) essentially (16-hr reaction period) as summarized for obtaining ethyl ester **3b**. The product in hexane was chromatographed on silica gel (50 g). Elution with 9:1 hexane–ethyl acetate provided 1.4 g of *cis,trans* olefin **6b**. Recrystallization from hexane afforded an analytical sample: mp 154–156°; $\lambda_{max}^{CHCl_3}$ 301 mμ (ε 10,400); ν_{max} 2950, 1735, 1715, 1625, 1375, 1300, 1260, 1150, 985, and 870 cm^{-1}; $[\alpha]^{25}D$ −150° (*c* 2.33); pmr δ 0.60 and 0.83 (C-18 and -19 methyls), 1.49 (*t*-butyl), 2.02 (acetate), 3.62 (methoxyl), 5.50 (doublet, J_{ab} = 11 cps, H_a), 5.64 (doublet, J_{bc} = 14 cps, H_c), and 7.55 (quartet, J_{ab} = 11 cps, J_{bc} = 14 cps, H_b).

Anal. Calcd for $C_{31}H_{48}O_5$: C, 74.36; H, 9.65. Found: C, 74.20; H, 9.84.

3β-Acetoxy-17β-(6′α-pyronyl)androst-5-ene (10). Method A.—To a diethyl ether (100 ml) solution of *cis,trans* olefin **3b** (1g) was added 72% perchloric acid (1 ml)–water (0.5 ml). Hydrolysis of the enol ether was followed by viewing disappearance of the ultraviolet absorption maxima at 305 mμ and was complete after 4.5 hr at room temperature. The solution was washed well with water and solvent was removed *in vacuo*. A solution of the residue (keto ester **11**) in 5% potassium hydroxide–methanol (100 ml) was heated at reflux for 20 min. Following concentration of solvent, neutral material was removed by extraction with chloroform and the acidic fraction was added to a cold (ice bath) ethyl acetate solution (200 ml) containing 1 *M* acetic anhydride and 10^{-3} *M* perchloric acid.[10] Two minutes later the yellow solution was diluted with diethyl ether and washed with dilute aqueous sodium bicarbonate. Removal of solvent led to a yellow oil which was triturated with boiling ligroin. Removal of solvent from the ligroin extract gave a pale yellow oil (0.75 g) that partially crystallized on standing. The semisolid in 9:1 ligroin–ethyl acetate was chromatographed on silica gel (80 g). Elution with 4:1 ligroin–ethyl acetate provided a fraction which crystallized from diethyl ether as fine needles (0.17 g): mp 213–216°; λ_{max} 305 mμ (ε 6,270); ν_{max} 1730, 1630, and 1550 cm^{-1}; $[\alpha]_D$ −67° (*c* 0.82); pmr[17] δ 0.66 (C-18 methyl), 1.04 (C-19 methyl), 2.04 (C-3 acetate), 4.6 (multiplet, H-3α), 5.4 (multiplet, H-6), 6.01 (quartet, J_{bc} = 6.5 cps, J_{ac} = 0.75 cps, H_a), 6.13 (quartet, J_{ab} = 9 cps, J_{ac} = 0.75 cps, H_c), and 7.27 (quartet, J_{ab} = 9 cps, J_{cb} = 6.5 cps, H_b).

Anal. Calcd for $C_{26}H_{34}O_4$ (mol wt, 410): C, 76.06; H, 8.35. Found: C, 76.30; H, 8.22; mol wt, M^+ − 60 at *m/e* 350 (mass spectrum).[18]

(16) B. J. Magerlein and F. Kagan, *J. Amer. Chem. Soc.*, **82**, 593 (1960).

(17) We are indebted to Dr. J. Kutney for providing the 100-MHz spectra.

Method B.—To a benzene solution (30 ml) containing *t*-butyl ester (**6b**, 0.10 g) was added a few small crystals of *p*-toluenesulfonic acid and 3 drops of water. The solution was heated at reflux and benzene was allowed to slowly distil. After 18 hr, the solution was allowed to cool to room temperature. The benzene solution was washed well with water and dried. Chromatography of crude material on silica gel (6 g) gave two compounds. The less polar compound **17** was eluted with 9:1 hexane–ethyl acetate. Crystallization of the colorless oil (28 mg) from ethanol–water gave colorless crystals: mp 105–107°; ν_{max} 3000, 1740, 1700, 1660, 1630, 1240, 1030, and 970 cm^{-1}; pmr δ 0.60 and 0.84 (C-18 and -19 methyls), 2.03 (acetate), 1.88 (doublet of doublet J = 6.5, 1.5 cps, methyl on double bond), 6.17 (doublet J = 15 cps, with fine splitting, J = 1.5 cps), and 6.83 (complex multiplet, H_b).[19]

Pyrone **12** was eluted with 6:1 hexane–ethyl acetate. Recrystallization of colorless, crystalline solid (37 mg) gave needles, mp 232–234°, identical spectrally with pyrone prepared by method C.

Method C.—The following procedure proved very convenient and was routinely used for obtaining pyrone **10**. To aldehyde **2b** (2.0 g, 4.8 mmol), prepared from ketone **1** and trimethyl orthoformate as summarized for obtaining aldehyde **2a**,[8] in pyridine (40 ml) was added malonic acid (1.0 g, 9.6 mmol) and piperidine (1 ml, 10 mmol). The solution was heated on a steam bath for 1 hr and evolution of carbon dioxide was noted. Upon cooling to room temperature the mixture was poured into cold (ice bath) 2 *N* hydrochloric acid. The yellow solid which separated was extracted with chloroform and the combined extract was washed with 2 *N* hydrochloric acid and water. Following removal of solvent, the residue was chromatographed on silica gel (100 g). Elution with 4:1 hexane–ethyl acetate provided 1.1 g (55%) of pyrone **10**. Recrystallization from chloroform–hexane gave 0.89 g of pale yellow crystals, mp 213–217°. Alternatively, recrystallization from ethyl acetate gave almost colorless crystals with the same melting point. Comparison of pyrone **10** specimens from methods A and B by mixture melting point determination and infrared spectra confirmed their mutual identity.

3β-Acetoxy-17β-(6′α-pyronyl)-5α-androstane (12).—The method B procedure for obtaining pyrone **10** was employed for converting 2.0 g of aldehyde **5** into α-pyrone **12**. Crude product was chromatographed on silica gel (150 g). Elution with 5:1 hexane–ethyl acetate gave 1.1 g (54%) of oily pyrone. Crystallization from chloroform–hexane gave 0.79 g of yellow crystals, mp 234–238°. Two recrystallizations from the same solvent provided a colorless, crystalline, analytical specimen: mp 235–237°; $\lambda_{max}^{CHCl_3}$ 307 mμ (ε 7,930); ν_{max} 2950, 1735, 1630, 1555, 1250, and 820 cm^{-1}; $[\alpha]^{25}D$ +9.8° (*c* 6.86); RD (*c* 0.57, chloroform) $[\alpha]_{348}$ +326°, $[\alpha]_{400}$ +67°, and $[\alpha]_{589}$ +7°; pmr δ 0.64 and 0.85 (C-18 and -19 methyls), 2.02 (acetate), 6.00 (doublet, J_{bc} = 6.5 cps, H_a), 6.14 (doublet, J_{ab} = 9 cps, H_c), and 7.29 (partially masked quartet, J_{bc} = 6.5 cps, J_{ab} = 9 cps, H_b).

Anal. Calcd for $C_{26}H_{36}O_4$: C, 75.69; H, 8.79. Found: C, 75.59; H, 8.62.

2-Formyl-3-methoxy-17β-acetoxy-5α-androst-2-ene (13a).—To 3-oxo-17β-acetoxy-5α-androstane (5.5 g) in trimethyl orthoformate (85 ml) was added dropwise 2.7 ml of 70% perchloric acid with stirring. After 5 min at room temperature, a yellow solid began to separate and the mixture was warmed to 40° for 7 min. Addition of pyridine (10 ml) followed by water precipitated a yellow solid which was extracted with diethyl ether. The ethereal extract was washed with water and concentrated to dryness. The crude aldehyde was chromatographed on silica gel (250 g). A fraction (3.2 g, 51%) eluted by 4:1 hexane–ethyl acetate corresponded to aldehyde **13a**. Crystallization from acetone–hexane provided 2.0 g of needles: mp 191–197° (lit.[20] mp 210–214°); $\lambda_{max}^{CH_3OH}$ 280 mμ (ε 13,500) [lit.[20] $\lambda_{max}^{CH_3CH_2OH}$ 278.5 mμ (ε 13,560)]; ν_{max} 2950, 1750, 1650, 1580, 1240, and 1040 cm^{-1}; pmr δ 0.72 and 0.83 (C-18 and -19 methyls), 2.05 (acetate), 3.75 (methoxyl), 4.58 (multiplet, H-17α), and 10.10 (aldehyde proton).

17β-Acetoxy-5α-androstano[2,3-*e*]-2-pyrone (14).—With aldehyde **13a** (3 g), malonic acid (1.5 g), pyridine (100 ml), and piperidine (1.5 ml), conversion into pyrone **14** was accomplished as summarized above for obtaining pyrone **10** and the crude product was chromatographed on silica gel (120 g). A fraction (1 g) eluted by 4:1 hexane–ethyl acetate was rechromatographed on 40 g of silica gel to provide 0.6 g (20%) of 17β-acetoxy-5α-androstano-[2,3-*e*]-2-pyrone (**14**). Crystallization from acetone–hexane gave a pure specimen of crystals (0.5 g): mp 207–210°; $\lambda_{max}^{CHCl_3}$ 312 mμ (ε 7450); ν_{max} 2950, 1735, 1640, 1550, 1240, 1030, and 820 cm^{-1}; $[\alpha]^{25}D$ +68° (*c* 4.71); RD (*c* 1.95, chloroform) $[\alpha]_{360}$ +471°, $[\alpha]_{400}$ +226°, and $[\alpha]_{589}$ +60°; pmr δ 0.82 (C-18 and -19 methyls), 2.07 (acetate), 4.66 (multiplet, H-17α), 6.16 (doublet, J_{cb} = 9 cps, H_c), and 7.10 (doublet, J_{bc} = 9 cps, H_b); mass spectrum *m/e* 384 (parent ion, 100%), 370 (M − 14, 9%), 356 (M − 28, 49%), 342 (M − 42, 34%), 324 (M − 60, 53%), and 309 (M − 75, 39%).

Anal. Calcd for $C_{24}H_{32}O_4$: C, 74.97; H, 8.39. Found: C, 75.21; H, 8.37.

A fraction (0.86 g) eluted by acetone from the silica gel column chromatogram crystallized from chloroform–hexane as pale yellow crystals, mp 203–205° dec, formulated as **2-formyl-3-(N-piperidino)-17β-acetoxy-5α-androst-2-ene (13b)**. An analytical specimen was obtained: $\lambda_{max}^{CH_3OH}$ 244 mμ (ε 15,080); ν_{max} 3000, 1740, 1650, 1600, 1240, 1200, 1130, and 1040 cm^{-1}; $[\alpha]^{25}D$ +141° (*c* 2.28); pmr δ 0.70 and 0.80 (C-18 and -19 methyls), 1.64 (multiplet, methylene), 2.02 (acetate), 3.37 (multiplet, 4 H, $-CH_2N-$), and 9.66 (aldehyde proton).

Anal. Calcd for $C_{27}H_{41}NO_3$: C, 75.83; H, 9.66; N, 3.28. Found: C, 75.72; H, 9.57; N, 3.31.

3α-Acetoxy-17β-(6′α-pyronyl)-5β-androstane (16a).—A sample of 3α-acetoxy-20-oxo-5β-androstane (5g) was converted into 3α-acetoxy-20-methoxy-21-formyl-5β-pregna-20-ene (**15a**, 2.7 g) using the general procedure summarized for obtaining aldehyde **2b**. A specimen of aldehyde **15a** gave the following data: mp 105–108°; ν_{max} 2950, 1735, 1650, 1600, 1240, and 1020 cm^{-1}; pmr δ 0.64 and 0.96 (6 methyl protons), 2.04 (acetate), 3.15 (multiplet, H-17α), 3.68 (methoxyl), 4.77 (multiplet, H-3β), 5.56 (doublet, J = 8 cps, H-21 vinyl), and 9.90 (doublet, J = 8 cps, aldehyde proton). Aldehyde **15a** (5.5 g) was condensed in pyridine (80 ml)–morpholine (2.5 ml) with malonic acid (2.5 g) as summarized for the synthesis of pyrone **10** (method B). The crude product was chromatographed on silica gel (150 g) and a fraction eluted by 4:1 hexane–ethyl acetate gave 1.6 g of viscous, yellow oil. Crystallization of the oil from benzene–hexane provided 1.2 g (21%) of pyrone **16a**, mp 147–148°. Two recrystallizations from acetone–hexane gave an analytical sample with the same melting point: $\lambda_{max}^{CHCl_3}$ 307 mμ (ε 8,870); ν_{max} 2950, 1750, 1640, 1560, 1260, 1090, 1040, and 795 cm^{-1}; $[\alpha]^{25}D$ +75° (*c* 0.91); RD (*c* 0.096, chloroform) $[\alpha]_{344}$ +1000°, $[\alpha]_{400}$ +167°, and $[\alpha]_{589}$ +42°; pmr δ 0.62 and 0.97 (C-18 and -19 methyls), 2.06 (acetate), 4.70 (multiplet, H-3β), 6.04 (doublet, J_{bc} = 7 cps, H_a), 6.18 (doublet, J_{ab} = 10 cps, H_c), and 7.32 (quartet, J_{bc} = 7 cps, J_{ab} = 10 cps, H_b), mass spectrum *m/e* 412 (parent ion, 10%), 352 (M − 60, base ion, 100%), and 337 (M − 75, 51%).

Anal. Calcd for $C_{26}H_{36}O_4$: C, 75.69; H, 8.79. Found: C, 75.93; H, 8.74.

3α,6α-Diacetoxy-17β-(6-α-pyronyl)-5β-androstane (16b).—A sample (1.5 g) of 3α,6α-diacetoxy-20-methoxy-21-formyl-5β-pregna-20-ene was prepared from 3α,6α-diacetoxy-20-oxo-5β-pregnane (2.0 g): ν_{max} 2950, 1740, 1660, 1600, 1240, and 1020 cm^{-1}; pmr δ 0.63 and 1.00 (C-18 and -19 methyls), 2.05 (acetate), 3.70 (methoxyl), 4.75 (multiplet, H-3β), 5.19 (multiplet, H-6β), 5.53 (doublet, J = 8 cps, H-21), and 9.90 (doublet, J = 8 cps, aldehyde proton). Aldehyde **15b** (1.5 g), pyridine (30 ml), morpholine (0.8 ml), and malonic acid (0.75 g) were combined according to the general procedure summarized for obtaining pyrone **10** (method B). Chromatography with 2:1 hexane–ethyl acetate as eluent of the crude product on silica gel (50 g) gave 0.88 g (57%) of pyrone **16b** containing small amounts of side products. Rechromatography on basic alumina (24 g) and elution with 5:1 hexane–ethyl acetate provided 0.38 g (24%) of colorless oil. The oil crystallized from acetone–hexane as crystals (0.20 g), mp 151–153°. Slow recrystallization led to a pure specimen as needles: mp 152–155°; $\lambda_{max}^{CHCl_3}$ 305 mμ (ε 8,490); ν_{max} 3000, 1750, 1640, 1560, 1240, 1020, and 800 cm^{-1}; $[\alpha]^{25}D$ −9° (*c* 0.44); RD (*c* 0.75, chloroform) $[\alpha]_{352}$ −6°, $[\alpha]_{400}$ −5°, and $[\alpha]_{589}$ −3°; pmr δ 0.62 and 1.00 (C-18 and -19 methyls), 2.04 and 2.06 (6 acetate methyl protons), 4.73 (multiplet, H-3β),

(18) We wish to thank John Occolowitz for providing the mass spectral data.

(19) The pmr spectrum of the less polar compound showed an olefin splitting pattern very similar to that of crotonic acid: "Varian Spectra Catalog," Vol. 1, No. 62, N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, Ed., Varian Associates, 1962.

(20) D. Burn, G. Cooley, J. W. Ducker, B. Ellis, D. N. Kirk, and V. Petrow, *Tetrahedron Lett.*, 733 (1964).

5.20 (multiplet, H-6β), 6.02 (doublet, J_{bc} = 7 cps, H_a), 6.18 (doublet, J_{ab} = 10 cps, H_c), and 7.31 (quartet, J_{ab} = 10 cps, J_{bc} = 7 cps, H_b); mass spectrum *m/e* 470 (parent ion, 56%), 410 (M − 60, 3%), 350 (M − 120, 58%), and 335 (M − 135, 100%, base ion).

Anal. Calcd for $C_{28}H_{38}O_6$ (mol wt, 470): C, 71.46; H, 8.14. Found: C, 71.37; H, 7.94.

Registry No.—**2a**, 23330-29-2; **3a**, 23330-30-5; **3b**, 15019-24-6; **4**, 23330-32-7; **6a**, 23367-40-0; **6b**, 23330-33-8; **7**, 23330-34-9; **8**, 3330-50-5; **9**, 23330-36-1; **10**, 15019-25-7; **12**, 23330-38-3; **13a**, 23367-41-1; **13b**, 23330-39-4; **14**, 23330-40-7; **15a**, 23330-41-8; **16a**, 23330-42-9; **16b**, 23330-43-0.

Bufadienolides. 7. Synthesis of 3β-Acetoxy-5α,14α-bufa-20,22-dienolide[1-3]

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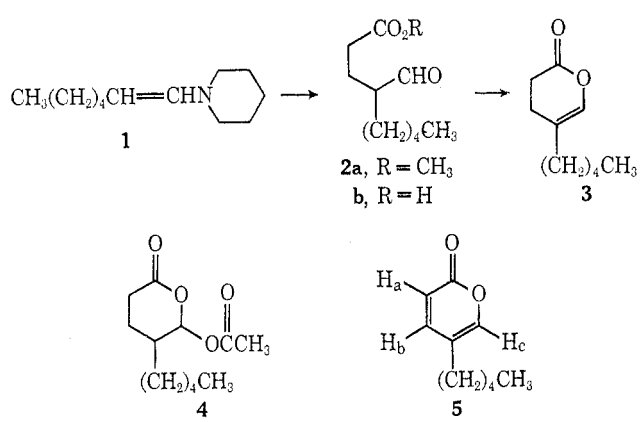
A new synthetic route to 5-substituted 2-pyrones is described. Alkylation of enamine **1** with methyl acrylate, cyclization of carboxylic acid **2b** employing *p*-toluenesulfonic acid in benzene, and dehydrogenation of enol lactone **3** with a palladium catalyst or by a N-bromosuccinimide sequence comprised the key steps to α-pyrone **5**. Other methods (utilizing derivatives of acetic acid) investigated for the enol lactonization reaction gave mainly lactone **4**. Application to bufadienolide chemistry was studied by transformation of dehydroepiandrosterone *via* intermediates **6–8** to 3β-acetoxy-14α-bufa-5,20(21)-dienolide (**9**). Similar conversion of epiandrosterone acetate (**10**) led to bufenolide **16**, which was dehydrogenated to bufadienolide **17** using sulfur. Other dehydrogenation methods, including those quite useful with enol lactone **3**, were unsatisfactory.

Two 5-substituted 2-pyrones were synthesized in 1941.[4] Twenty years elapsed before further syntheses of such 2-pyrones were described.[5] A total of *ca.* six such examples have been reported. For reasons already elaborated[6] we wished to find an effective synthesis of 5-substituted 2-pyrones which could be conveniently adapted to synthesis of bufadienolides. After a number of superficially promising syntheses had been eliminated, the following approach proved satisfactory and was studied in detail. The new method is based on an aliphatic aldehyde precursor, and heptaldehyde was selected for model experiments.

Condensation of heptaldehyde with piperidine provided enamine[7] **1**. Since attempts to condense enamine **1** with ethyl propiolate in dioxane or dimethylformamide solution were unpromising,[8] the use of methyl acrylate was investigated. Alkylation[9] of enamine **1** with methyl acrylate in refluxing acetonitrile gave aldehyde **2a** in 75% yield following hydrolysis. Mild saponification of methyl ester **2a** provided carboxylic acid **2b**. Benzene containing *p*-toluenesulfonic acid proved most effective (64%) for conversion of acid **2b** into enol lactone **3**.[10] When preparation of enol lactone **3** was attempted employing the acetic anhydride–perchloric acid reagent in ethyl acetate[11a] or isopropenyl acetate–perchloric acid,[11b] the exclusive product was tetrahydropyran **4**. With acetic anhydride–sodium acetate[11c] a mixture of both lactones **3** and **4** was obtained. Structure assignments for the oily lactones **3** and **4**, are based on the method of synthesis and supporting spectral data. For example, lactone **3** exhibited carbonyl absorption at 1770 cm^{-1} and olefin stretching at 1680 cm^{-1} characteristic of a δ-enol lactone. In the pmr spectrum the vinyl proton signal appeared as a quintet (J = 1 Hz) at δ 6.4. Lactol acetate **4** exhibited an acetate methyl singlet at δ 2.18, and the proton at position 6 appeared as two doublets centered at δ 6.28 (J = 5 Hz) and 6.58 (J = 2 Hz), indicating a mixture of configurational isomers.



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