quickly dissolved on treatment at 0° with ethereal diazomethane, and excess reagent was immediately removed by nitrogen purging. Following washing with water and removal of solvent, the solid crystallized from methanol as tiny plates (0.68 g) melting at 137–140° to an opaque liquid which cleared at 150°. For analysis the sample was recrystallized from 95% ethyl alcohol to give plates: mp 139–140° to an opaque liquid clearing sharply at 152–153°; $[\alpha]^{23}D$ +150.4° (*c* 1.2); ν_{max} 3200 (hydroxyl), 1735 (methyl ester), and 1700 cm^{-1} (ketone).

Anal. Calcd for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81. Found: C, 73.21; H, 9.37.

Methyl 3β-Tetrahydropyranyloxy-20-oxo-21-nor-5α-cholanate (7i).—To a solution of methyl 3β-hydroxy-20-oxo-21-nor-5α-cholanate (**7h**, 0.87 g) in benzene (15 ml) was added dihydropyran (5 ml) and toluene-*p*-sulfonic acid monohydrate (40 mg). The mixture was stirred for 45 min at room temperature and then washed with saturated aqueous sodium bicarbonate and water (five times). Concentration gave a viscous oil (1.33 g) which crystallized from methanol as blades: (0.85 g) mp 93–95° (recrystallization from the same solvent did not change the melting point); $[\alpha]D$ +77.30° (*c* 0.41); $\nu_{max}^{CCl_4}$ 1739 (methyl ester), 1702 (ketone), and 1025 cm^{-1} (tetrahydropyranyl ether); pmr (CCl_4) δ 0.56 (s, 3 H, CH_3-18), 0.8 (s, 3 H, CH_3-19), 2.43 (s, with broad base, 4 H, $-COCH_2CH_2CO_2-$), 3.5 (s, 3 H, methyl ester), and 4.5 (diffuse signal, 1 H, acetal).

Anal. Calcd for $C_{29}H_{46}O_5$: C, 73.38; H, 9.77; O, 16.85. Found: C, 73.10; H, 9.53; O, 17.47.

3β-Tetrahydropyranyloxy-20-oxo-21-nor-5α-cholanic Acid (7j).—Methyl 3β-tetrahydropyranyloxy-20-oxo-21-nor-5α-cholanate (**7i**, 0.70 g) in methanol (30 ml) was diluted with potassium carbonate (0.75 g) in water (7.5 ml) and the solution was heated at reflux for 4 hr. Methanol was removed *in vacuo* and the solution was cooled to 0° and cautiously acidified with hydrochloric acid (1 *N*). The mixture was immediately extracted with diethyl ether (three times) and the ethereal solution was washed with water (three times). Removing solvent provided a crystalline product (0.70 g) melting at 118–120° to a clear liquid which resolidified by 165° and remelted at 250–252° dec. The analytical specimen recrystallized from isopropyl ether as prisms: mp 125° (resolidifies at 165°) and 253–255°; $[\alpha]D$ +90.23° (*c* 0.13); $\nu_{max}^{CHCl_3}$ 2400–2800 (w, b, carboxylic acid), 1700 (20 ketone and carboxyl), and 1010 cm^{-1} (tetrahydropyranyl ether).

Anal. Calcd for $C_{28}H_{44}O_5$: C, 73.00; H, 9.63; O, 17.37. Found: C, 72.66; H, 9.76; O, 17.63.

Registry No.—Methoxymethylenetriphenylphosphorane, 23411-16-7; **2a**, 23439-92-1; **2b**, 23406-62-4; **2c**, 23406-63-5; **3a**, 23406-64-6; **3b**, 23406-65-7; **4**, 23439-93-2; **5b**, 23439-94-3; **7b**, 23439-95-4; **7c**, 23406-66-8; **7d**, 23439-96-5; **7e**, 23439-97-6; **7f**, 23439-98-7; **7g**, 23406-67-9; **7h**, 23439-99-8; **7i**, 23406-68-0; **7j**, 23440-00-8.

Bufadienolides. 5. Synthesis of Cardenolides[1,2]

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Boron trifluoride catalyzed lead tetraacetate oxidation of 3β-acetoxy-20-oxo-5α-pregnane and of pregnenolone acetate was employed to obtain the corresponding 21-acetoxy derivatives. Reaction of 3β,21-diacetoxy-20-oxo-5α-pregnane (**1**) with the anion prepared from diethyl cyanomethylphosphonate and subsequent treatment with hydrochloric acid afforded the corresponding nitrile (**2**) and derived imino lactone hydrochloride (**3a**). Acid hydrolysis of the imino lactone gave 3β-acetoxy-5α-cardenolide (**4b**). Analogous transformation of ketone **6** provided 3β-acetoxy-Δ⁵-cardenolide (**10b**). The two-step reaction sequence from readily available α-hydroxy ketones provides a potentially useful route to imino lactones and butenolides.

Among the naturally occurring cardenolides, several are well known medically for their specific effect upon heart muscle. Recently, unsaturated lactones of the cardenolide type have been found to inhibit cell growth.[2,3] Increasing availability of steroid butenolides related to the natural cardenolides for biological evaluation was considered an important objective of the overall bufadienolide investigation. Accordingly, when one series of experiments directed at the bufadienolide ring system began to seem impractical, they were diverted to provide the following new synthesis of cardenolides.[4]

Initially, 3β-acetoxy-20-oxo-5α-pregnane was oxidized using lead tetraacetate to 3β,21-diacetate **1**.[5a] Later the boron trifluoride catalyzed lead tetraacetate oxidation procedure[5b] was found superior for this purpose. Next, the carbanion derived from diethyl cyanomethylphosphonate was allowed to condense with 20 ketone **1**. Following removal of solvent the residue was treated with 2 *N* hydrochloric acid–diethyl ether. A crystalline product (24–65% yield) separated which was shown to be imino lactone hydrochloride **3a**.[6] The ether extract contained nitrile **2** in yields up to 72%. If instead the crude reaction product was treated first with water–diethyl ether, only nitrile **2** was obtained. The imino lactone formulation was supported by spectral evidence and confirmed by hydrolytic (methanol–hydrochloric acid) cleavage to cardenolide **4**. Under milder conditions, acid treatment was used to obtain

(1) (a) Part 4: G. R. Pettit, B. Green, G. L. Dunn, and P. Sunder-Plassmann, *J. Org. Chem.*, **35**, 1385 (1970). (b) 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.

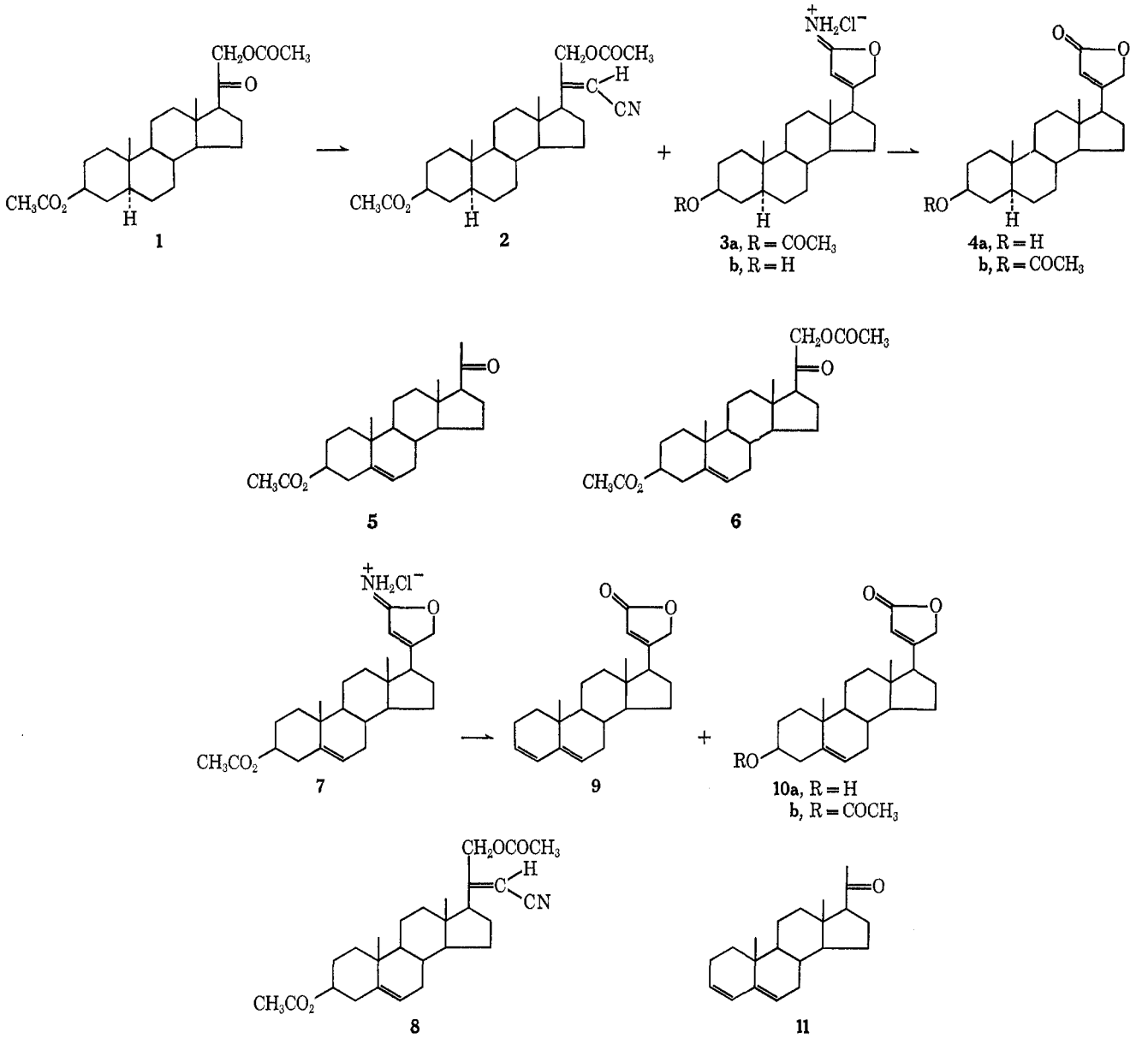
(2) The present study was based in part on the doctoral dissertation of C. L. Herald, submitted to the Graduate School, Arizona State University, Aug 1968. A preliminary account was given: G. R. Pettit and J. P. Yardley, *Chem. Ind.* (London), 553 (1966).

(3) G. R. Pettit, B. Green, and G. Dunn, *J. Org. Chem.*, **35**, 1367 (1970), footnotes 15 and 16.

(4) See P. E. Sonnet, *ibid.*, **33**, 3662 (1968), and for a summary of recent methods used to obtain cardenolides consult S. Sarel, Y. Yanuka, and Y. Shalon, *Israel J. Chem.* (Proceedings), **5**, 48p (1967); J. M. Ferland, Y. Lefebvre, and R. Deghenghi, *Tetrahedron Lett.*, 3617 (1966); W. Fritsch, U. Stache, and H. Ruschig, *Justus Liebigs. Ann. Chem.*, **699**, 195 (1966); N. Danieli, Y. Mazur, and F. Sondheimer, *Tetrahedron*, **22**, 3189 (1966). Leading references prior to 1966 may be found in ref 2.

(5) (a) T. Reichstein and C. Montigel, *Helv. Chim. Acta*, **22**, 1212 (1939); (b) J. D. Cocker, H. B. Henbest, G. H. Phillipps, G. P. Slater, and D. A. Thomas, *J. Chem. Soc.*, 6 (1965).

(6) Preparation of imino lactone **3a** constitutes the first example of such cardenolide derivatives. In general imino lactones are rarely encountered; for a survey see B. A. Cunningham and G. L. Schmir, *J. Org. Chem.*, **31**, 3751 (1966); B. Kamenar, C. K. Prout, and J. D. Wright, *J. Chem. Soc.*, 661 (1966); H. E. Zaugg, R. J. Michaels, A. D. Schaefer, A. M. Wenthe, and W. H. Washburn, *Tetrahedron*, **22**, 1257 (1966); H. Nohira, Y. Nishikawa, Y. Furuya, and T. Mukaiyama, *Bull. Chem. Soc. Jap.*, **38**, 897 (1965); H. Peter, M. Brugger, J. Schreiber, and A. Eschenmoser, *Helv. Chim. Acta*, **46**, 577 (1963); D. H. R. Barton, J. M. Beaton, L. E. Geller, and M. M. Pechet, *J. Amer. Chem. Soc.*, **83**, 4076 (1961).



alcohol **3b**. Both cardenolide **4a** and the corresponding acetyl derivative **4b** had earlier been obtained by Ruzicka and colleagues,[7] and the specimens obtained here displayed corresponding physical constants and were further characterized by results of ultraviolet, infrared, and proton magnetic resonance spectral studies.

The geometry assigned olefin **2** is based on repeated attempts to convert this isomer into imino lactone **3a**. Thus the nitrile and 21-acetoxy methylene groups are assumed to manifest the *trans* relationship indicated.[8]

To make a preliminary appraisal of the new imino lactone and cardenolide syntheses scope, pregnenolone acetate (**5**) was oxidized to 21 acetate **6** and the latter was condensed with diethyl cyanomethylphosphonate as outlined above. If the reaction mixture was first diluted with water, only negligible amounts of imino lactone **7** could be detected. On the other hand, initial reaction with cold 2 *N* hydrochloric acid–diethyl ether provided 10–47% yields of imino lactone **7** accompanied by varying (18–55%) quantities of nitrile **8**. Subjecting imino lactone hydrochloride **7** to acid hydrolysis as used effectively with analogous lactone **3a** led to a mixture of products, among which was detected diene **9**. Under milder conditions using 0.6 *N* hydrochloric acid in methanol and a 7-hr reaction period, cardenolide **10a** was obtained in 90% yield accompanied by 9% diene **9**. Structures assigned cardenolides **9** and **10** were supported by results of elemental and spectral analyses. Further, pregnenolone acetate (**5**) was al-

(7) L. Ruzicka, P. A. Plattner, and J. Pataki, *Helv. Chim. Acta*, **25**, 79 (1942).

(8) The general reaction between diethyl cyanomethylphosphonate anion and 20-oxo steroids has been described: A. K. Bose and R. T. Dahil, Jr., *J. Org. Chem.*, **30**, 505 (1965). See also A. K. Bose and R. M. Ramer, *Steroids*, **11**, 27 (1968).

Reaction of ketone **1** with diethyl ethoxycarbonylmethylphosphonate in a Wittig sequence should lead directly to cardenolide **4a**, but at the time this reagent was assumed unreactive toward 20-oxo steroids (see Bose and colleagues). More recently, reaction between the anion of diethyl methoxycarbonylmethylphosphonate and 20-oxo-21-hydroxy-pregnanes has been shown, in fact, to be exothermic and to yield the corresponding cardenolide (see Fritsch and colleagues, ref 4). The 21-hydroxy group apparently has a strong orienting effect on the approaching phosphonate, and combined with thermodynamically favorable ring formation leads to a very efficient (95% yield) reaction. Presumably, the reactions described herein leading to, *e.g.*, imino lactone **3a**, might proceed in higher yield employing 20-oxo-21-hydroxypregnane precursors. The present study was already complete when this prospect came into view.

lowed to react with hydrochloric acid in methanol under conditions similar to those initially applied to imino lactone **3a**. Following chromatographic separation of the product on activated alumina and crystallization of a fraction eluted by 20:1 hexane–ethyl acetate from hexane, a 24% yield of diene **11** was obtained. Previously, diene **11** was prepared[9] by Raney nickel desulfurization of the 3-benzylthio ether of 20-oxopregna-3,5-diene.

The ready availability of various methyl ketones suggests that the α-hydroxy ketone → imino lactone → butenolide route illustrated for obtaining cardenolides **4** and **10** provides a potentially useful method for obtaining such lactones. Presently, acid sensitivity and structural effects of the ketone upon stereochemical course of the modified Wittig step would seem to be two important considerations in evaluating overall yields.

Experimental Section

Tetrahydrofuran (from sodium), all other solvents, and diethyl cyanomethylphosphonate [bp 87–89° (0.15 mm), Aldrich Chemical Co.] were redistilled. A dispersion (*ca.* 54%) of sodium hydride in mineral oil was employed as supplied by the Metal Hydrides Division, Ventron Corp. The phosphonate modification of the Wittig reaction was conducted in a nitrogen atmosphere. Acetylation was effected using 5:1 acetic anhydride–pyridine at room temperature overnight. All solvent extracts of aqueous mixtures were dried over anhydrous magnesium sulfate. Basic alumina ("Suitable for Chromatography," Merck, Rahway, N. J.) and silica gel (0.2–0.5 mm, E. Merck, Darmstadt) were used for column chromatography. Chromatography columns were prepared using a slurry of silica gel in a solvent of lesser polarity than that anticipated for initial elution. The mixture to be chromatographed was dissolved in chloroform and a slurry of silica gel in chloroform was added to the solution. Removal of solvent *in vacuo* gave a silica gel powder coated with the mixture. Addition of the powder to the silica gel column gave a uniform band of adsorbed material. Thin layer chromatograms were prepared on microscope slides using silica gel HF_{254} (E. Merck) and developed either with iodine or concentrated sulfuric acid. Preparative thin layer chromatograms were performed with 1 mm of silica gel HF_{254}.

Each analytical sample appeared as a single spot on a thin layer chromatogram and was colorless unless stated otherwise. Melting points were recorded using a Fisher-Johns melting point apparatus and were uncorrected. The ultraviolet (Cary spectrophotometer), optical rotatory dispersion (at 25°, JASCO ORD/UV-5), infrared (in potassium bromide), and nuclear magnetic resonance (deuteriochloroform solution, tetramethylsilane as internal standard Varian A-60) measurements were recorded by Miss K. Reimer. Mass spectra (Atlas CH-4B) were recorded by Dr. P. Brown. Specific rotations (chloroform solution) at the sodium D line were obtained with a Rudolph polarimeter or were provided by Dr. P. Demoen, Janssen Pharmaceutica, Beerse, Belgium. Elemental microanalyses were determined in the laboratory of Dr. A. Bernhardt, Max Planck Institut, Mülheim, Germany.

3β,21-Diacetoxy-20-oxopregn-5-ene (6).—The 3β,21 diacetates were prepared by the method of Cocker and colleagues.[5b] To a solution of pregnenolone acetate (**5**, 10 g) and lead tetraacetate (17 g) in benzene (380 ml) was added a solution of methanol (18 ml) plus boron trifluoride etherate (56 ml). The solution was stirred at room temperature for 4 hr and then poured into water. The organic layer was separated and washed four times with water. Removal of solvent gave a yellow solid which crystallized from ethyl acetate–hexane to give shiny plates (8 g, 69% yield): mp 163–166° (lit.[10] mp 165–167°); pmr δ 0.70 and 1.04 (C-18 and -19 methyls), 2.06 and 2.19 (C-3 and -21 acetates), 4.75 and 4.55 (AB quartet, J = 17 cps, C-21 methylene) and 5.40 (multiplet, 6 H).

3β,21-Diacetoxy-20-oxo-5α-pregnane (1).—The method of preparation was the same as that for **6** described in the previous experiment. Here 10 g of 3β-acetoxy-20-oxo-5α-pregnane gave 9.7 g of product. By chromatography of a benzene solution of the crude product on neutral alumina, all color was removed. Crystallization from benzene–hexane gave a pure sample of the title compound (8.4 g, 71%), mp 150–152° (lit.[5a] mp 152–153°).

Reaction of 3β,21-Diacetoxy-20-oxo-5α-pregnane (1) with Diethyl Cyanomethylphosphonate.—To a cold suspension in an ice bath of sodium hydride oil dispersion (1.9 g) in tetrahydrofuran (130 ml) was added diethyl cyanomethylphosphonate (8.5 ml) in tetrahydrofuran (30 ml) dropwise and with stirring. Next, 3β,21-diacetoxy-20-oxo-5α-pregnane (**1**, 6 g) in tetrahydrofuran (150 ml) was added rapidly to the colorless solution. The solution was stirred at room temperature for 47 hr. Removal of solvent gave an orange oil which was treated with cold 2 N hydrochloric acid (200 ml) and diethyl ether. A fine crystalline solid appeared which was collected, washed with water and ether, and dried in a vacuum oven at 70° (25 mm) for 2 hr to give crude 3β-acetoxy-5α-iminocard-20(22)-enolide hydrochloride **3a** (1.52 g, 24%), mp 205–224° dec. Recrystallization from methanol–ether gave an analytical sample: mp 210–225° dec; ν_{max}^{Nujol} 1740, 1670, 1600, 1240, and 1030 cm^{-1}; pmr δ 0.63 and 0.83 (C-18 and -19 methyls), 2.01 (acetate), 4.63 (3α proton), 5.44 (multiplet, C-21 methylene), and 6.75 (multiplet, H-22).

Anal. Calcd for $C_{25}H_{38}O_3NCl$: C, 68.87; H, 8.78; N, 3.21; Cl, 8.13. Found: C, 68.60; H, 8.80; N, 3.05; Cl, 8.22.

The ether layer was separated and washed successively with water, 2 N sodium hydroxide, and three portions of water. Aqueous and basic extracts were reextracted with diethyl ether. The combined ethereal extract was washed twice with water and evaporated to dryness, giving a light tan oil. Tlc with 2:1 hexane–ethyl acetate mobile phase showed the product to contain mostly one component plus mineral oil. Crystallization of product from ethyl acetate–hexane gave slightly yellow needles (4.6 g, 72%). Three recrystallizations from the same solvents provided a colorless, analytical sample of 3β,21-diacetoxy-20-cyanomethyl-5α-pregn-20(22)ene (**2**): mp 108–109°; λ_{max}^{EtOH} 222 mμ (ε 13,800); ν_{max} 2850–2950, 2220, 1750, 1725, 1625, 1260, 1230, and 1035 cm^{-1}; $[\alpha]^{25}D$ +34° (*c* 1.21, chloroform); pmr δ 0.60 and 0.85 (C-18 and -19 methyls), 2.02 (C-3β acetate), 2.17 (C-21 acetate), 4.75 and 4.88 (AB quartet, J = 14 cps, C-21 methylene), and 5.41 (slightly broadened singlet, H-22 vinyl).

Anal. Calcd for $C_{27}H_{39}O_4N$: C, 73.43; H, 8.90; N, 3.17. Found: C, 73.40; H, 9.05; N, 3.34.

Reaction of 3β,21-Diacetoxy-20-oxopregn-5-ene (6) with Diethyl Cyanomethylphosphonate.—With sodium hydride oil dispersion (2.65 g), diethyl cyanomethylphosphonate (11.5 ml), and tetrahydrofuran (200 ml), 3β,21-diacetoxy-20-oxo-pregn-5-ene (**6**) was converted into 3β-acetoxy-Δ⁵-iminocard-20(22)-enolide hydrochloride (**7**, 1.51 g, 47%) and 3β,21-diacetoxy-20-cyanomethylpregna-5,20(22)-diene (**8**, 0.75 g, 18%).

Removal of solvent from the reaction mixture after 48 hr left a light-colored oil which was treated with cold 2 N hydrochloric acid (200 ml) and diethyl ether (100 ml). A colorless, crystalline solid appeared in the aqueous phase. The solid was collected, washed with water and diethyl ether, and dried in a vacuum oven at 70° (25 mm) for 2 hr to give hydrochloride **7**, mp 224–230° dec. Recrystallization from ethanol–diethyl ether gave an analytical sample: mp 222–230° dec; λ_{max}^{EtOH} 235 mμ (ε 13,000); ν_{max} 2800–3000, 1750, 1660, 1610, 1240, and 1025 cm^{-1}; $[\alpha]^{25}D$ −48° (*c* 1.27, chloroform); pmr δ 0.68 and 1.04 (C-18 and -19 methyls), 2.05 (acetate), 4.62 (multiplet, H-3), 5.46 (broad multiplet, C-21 methylene, H-6), and 6.72 (slightly broadened singlet, H-22).

Anal. Calcd for $C_{25}H_{36}O_3NCl$: C, 69.18; H, 8.36; N, 3.23; Cl, 8.17. Found: C, 69.39; H, 8.33; N, 3.09; Cl, 8.02.

The ether layer was separated and washed successively with 2 N sodium hydroxide and water. Removal of solvent gave a pale yellow solid which was chromatographed on silica gel (40 g). Elution with 4:1 hexane–ethyl acetate gave colorless, crystalline 3β,21-diacetoxy-20-cyanomethyl-pregna-5,20(22)-diene (**8**, 0.75 g). Three recrystallizations from ethyl acetate–hexane gave an analytical sample: mp 182–183°; λ_{max}^{EtOH} 222 mμ (ε 14,600); ν_{max} 3000, 2250, 1750, 1740, 1625, 1230–1260, and 1040 cm^{-1}; $[\alpha]^{25}D$ −19° (*c* 2.85, chloroform); pmr δ 0.65 and 1.05 (C-18 and -19 methyls), 2.05 (C-3β acetate), 2.17 (C-21 acetate), 4.77

(9) J. Romo, M. Romero, C. Djerassi, and G. Rosenkranz, *J. Amer. Chem. Soc.*, **73**, 1528 (1951).

(10) L. Ruzicka, T. Reichstein, and A. Furst, *Helv. Chim. Acta*, **24**, 76 (1941).

and 4.90 (AB quartet, J = 14 cps, C-21 methylene), 5.41 (multiplet, H-6), and 5.44 (slightly broadened singlet, overlapped H-6 signal, H-22).

Anal. Calcd for $C_{27}H_{37}O_4N$: C, 73.77; H, 8.48; N, 3.19. Found: C, 73.91; H, 8.63; N, 3.08.

3β-Hydroxy-5α-card-20(22)-enolide (4a).—To a solution of imino lactone hydrochloride **3a** (6.5 g) in methanol (50 ml) was added water (150 ml) and concentrated hydrochloric acid (60 ml). The suspension was stirred at reflux for 15 hr. Next, solid from the cooled mixture was collected and dried to give 5.2 g of crude 3β-hydroxy-5α-card-20(22)-enolide (**4a**, 96%). Recrystallization from chloroform–methanol gave colorless crystals (2.71 g): mp 244–245° (lit.[7] mp 248–250°); λ_{max}^{MeOH} 217 mμ (ε 13,600); ν_{max} 3600, 3000, 1810, 1750, 1630, and 1040 cm^{-1}; pmr δ 0.63 and 0.82 (C-18 and -19 methyls), 4.73 (triplet, J = 1.5 cps, C-21 methylene), and 5.84 (multiplet, J = 1.5 cps, H-22).

Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 76.87; H, 9.64.

Acetylation of 3β-hydroxy-5α-card-20(22)-enolide (**4a**) in 5:1 acetic anhydride–pyridine gave crude acetate. Chromatography on neutral alumina provided crystalline 3β-acetoxy-5α-card-20(22)-enolide, mp 193–194° (lit.[7] mp 193–194°).

When 3β-acetoxy-5α-iminocard-20(22)-enolide hydrochloride (**3a**, 94 mg) was treated with methanol (4 ml)–concentrated hydrochloric acid (1 ml) and heated at reflux for 25 min, partial hydrolysis of the 3β acetate to 3β-hydroxy-5α-iminocard-20(22)-enolide occurred. A crystalline solid (47 mg) was obtained: mp 254–267° dec; ν_{max}^{Nujol} 1670 and 1600 cm^{-1} with absence of absorption at 1790, 1740, and 1240 cm^{-1}.

3β-Hydroxy-Δ^5-card-20(22)-enolide (10a).—To a solution of imino lactone **7** (1.1 g) in methanol (48 ml) was added water (240 ml) and concentrated hydrochloric acid (12 ml). The mixture was stirred at reflux for 7 hr, cooled, and filtered. The crude product was dried in a vacuum oven at 75° (25 mm) for 1 hr. Chromatography on silica gel (30 g) and elution with 4:1 hexane–ethyl acetate gave 0.079 g (9%) of colorless, crystalline Δ^{3,5}-diene **9**, which recrystallized from ethyl acetate–hexane as needles, mp 204–207°. Two recrystallizations from the same solvent gave an analytical sample: mp 202–207°; λ_{max}^{EtOH} 234 mμ (ε 24,100); ν_{max} 2950, 1770, 1740, 1605, and 885 cm^{-1}; $[\alpha]^{25}D$ −104° (*c* 1.11, chloroform); pmr δ 0.68 and 0.98 (C-18 and -19 methyls), 4.78 (triplet, J = 1.5 cps, C-21 methylene), 5.43 (multiplet, H-6), 5.71 (multiplet, H-3), 6.07 (multiplet, overlapped with H-22 signal, H-4), and 5.89 (multiplet, J = 1.5 cps, H-22).

Anal. Calcd for $C_{23}H_{30}O_2$: C, 81.61; H, 8.93. Found: C, 81.46; H, 8.72.

Continued elution with 1:1 ethyl acetate–methanol gave a pale yellow solid (0.86 g, 90%): mp 240–245° (lit.[10] mp 260–262°); ν_{max} 3300–3600, 3000, 1790, 1760, 1740, and 1625 cm^{-1}; pmr δ 0.67 and 1.04 (C-18 and -19 methyls), 4.78 (broad singlet with fine splitting, C-21 methylene), 5.88 (broad singlet with fine splitting, H-22), and 5.39 (multiplet, H-6). The sterol was acetylated with 5:1 acetic anhydride–pyridine and the crude acetate was chromatographed on silica gel (30 g). Elution with 4:1 hexane–ethyl acetate gave 0.60 g of crystalline 3β-acetoxy-Δ^5-card-20(22)-enolide (**10b**). Recrystallization from acetone–hexane gave colorless crystals, mp 170–172° (lit.[10] mp 173–174°); a second recrystallization from ethyl acetate–hexane gave crystals, mp 153–154° and 173–174°. After thorough drying for 2 days at 80° (0.25 mm), an analytical sample was obtained: mp 156–158°; λ_{max}^{EtOH} 215 mμ (ε 16,300); ν_{max} 3000, 1800, 1770, 1735, 1630, 1240, and 1040 cm^{-1}; pmr δ 0.67 and 1.04 (C-18 and -19 methyls), 2.05 (acetate), 4.78 (broad singlet, C-21 methylene), 5.42 (multiplet, H-6), and 5.87 (multiplet, H-22); mass spectrum *m/e* 398 (parent ion, 3%), 338 (M − 60, base ion, 100%), and 323 (M − 75, 34%).

Anal. Calcd for $C_{25}H_{34}O_4$: C, 75.34; H, 8.60. Found: C, 75.46; H, 8.63.

Acid Hydrolysis of 3β-Acetoxy-20-oxopregn-5-ene (5).—To 3β-acetoxy-20-oxopregn-5-ene (**5**, 0.2 g) in methanol (15 ml) was added 3 *N* hydrochloric acid (55 ml). The suspension was stirred, heated at reflux for 20 hr, and cooled. An oil separated and was extracted with diethyl ether. The ethereal solution was washed three times with water. Removal of solvent *in vacuo* gave a light yellow oil. Tlc with 4:1 hexane–ethyl acetate mobile phase showed the oil to contain largely one component with traces of seven others, one of which corresponded to starting material. Chromatography on basic alumina (6 g, 3% water) and elution with 20:1 hexane–ethyl acetate gave a colorless oil (0.15 g). Crystallization from hexane gave 20-oxo-pregna-3,5-diene **11** (0.04 g, 24%), mp 116–121° (lit.[9] mp 139–142°). Although diene **11** appeared as a single spot by tlc with 4:1 hexane–ethyl acetate mobile phase and uv and pmr spectra gave no evidence of an impurity, the melting point was less reassuring. The uv spectrum follows: λ_{max}^{EtOH} 234 mμ (ε 20,900) and 225 (19,400) [lit.[9] λ_{max}^{EtOH} 234 mμ (ε 20,000) and 228 (18,700)]. A pmr spectrum showed signals at δ 0.69 and 0.99 (C-18 and -19 methyls), 2.15 (C-21 methyl), and 5.45–6.10 [5.45 (multiplet, H-6, three vinyl protons), 5.72 (multiplet, H-3), and 6.10 (doublet, J = 9 cps, H-4)].

Registry No.—**2**, 23330-57-6; **3a**, 23330-58-7; **4a**, 23330-59-8; **6**, 1693-63-6; **7** hydrochloride, 23367-46-6; **8**, 23367-47-7; **9**, 23330-79-2; **10a**, 19637-05-9; **10b**, 23330-61-2; **11**, 1093-87-4; 3β-hydroxy-5α-iminocard-20(22)-enolide, 23330-62-3.