Bufadienolides. 3. A Synthetic Route to Isocardenolides[1]

GEORGE R. PETTIT,[2a] BRIAN GREEN, ARUN K. DAS GUPTA,[2b]
PHILIP A. WHITEHOUSE, AND JOHN P. YARDLEY

Department of Chemistry, University of Maine, Orono, Maine 04473, and Department of Chemistry, Arizona State University, Tempe, Arizona 85281

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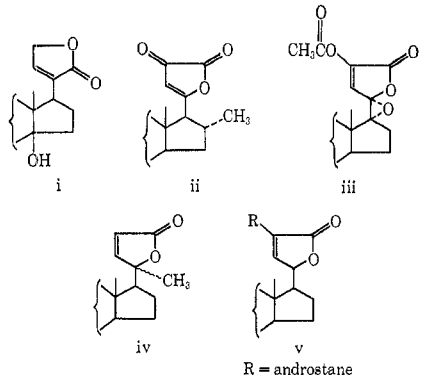
A Bestmann reaction employing 3β-acetoxy-20-oxo-21-iodo-5-pregnene (**2**) and carbomethoxymethylenetriphenylphosphorane was used to complete a synthesis of methyl 3β-acetoxy-2-oxo-21-nor-5-*trans*-22-choladienate (**1**), which upon irradiation in sunlight gave *cis* isomer **5**. Similarly, 3β-acetoxy-20-oxo-21-iodo-5,16-pregnadiene (**6**) was converted into *trans* side-chain olefin **7** and *cis* side-chain olefin **8**. Palladium-catalyzed hydrogenation of triene **8** resulted in methyl 3β-acetoxy-20-oxo-21-nor-5α-cholanate (**9a**) accompanied by small amounts of the corresponding 3-deoxy derivative **9b** and 3β-acetoxy-20-hydroxy-21-nor-5α-cholanic acid γ-lactone (24 → 20). Subjecting triene **8** to sodium borohydride reduction in ethanol yielded isocardanolide **10**. The principal objective, synthesis of isocardenolide **11**, was realized by selective reduction of ketone **5** with sodium borohydride in dimethylformamide.

Although a variety of synthetic approaches[3] to cardenolides[4] have been described, only one example each of the two possible isocardenolides bearing an unsubstituted lactone ring have been recorded.[5] Synthesis of γ-keto acrylate **1** was considered the key stage in a systematic approach to bufadienolide[6] and isocardenolide systems. Condensation of pregnenolone with glyoxylic acid followed by methylation and acetylation steps was initially employed to obtain ketone **1**, but increasing demand for this compound led us to develop a more efficient synthesis.[7] The first steps comprised conversion of pregnenolone acetate into the 20-enol acetate followed by treatment with N-iodosuccinimide to provide 21-iodo-20 ketone **2**.[8a] Treatment of this compound with carbomethoxymethylenetriphenylphosphorane[9] in toluene provided *trans* olefin **1** in 43% yield.[10]

Some related experiments aimed at further simplifying conversion of a 20-oxopregnane into a γ-keto acrylate derivative were also explored, including the treatment of 3β-acetoxy-20-oxo-5α-pregnane with dioxane dibromide[11] to yield 21-bromo ketone **3**.[12,13] It is interesting to note here that direct halogenation of a 20-oxopregnane bearing a proton at C_{17} yields the 17α-halo derivative; however, bromination of a 20 ketal has been used for substitution at C_{21}.[14] To confirm the structural assignment **3**, diazo ketone **4a** was allowed to react with hydrogen bromide to give the 21 bromide, which was identical with the dioxane dibromide product. Conversion of 21 bromide **3** into the corresponding 21 iodide employing sodium iodide proved unsatisfactory, but application of the Bestmann reaction to the bromide afforded, in low yield, *trans* olefin **4b**.

Both the glyoxylic acid and iodo ketone synthetic routes to olefin **1** yielded the yellow *trans* geometrical isomer, whose pmr spectrum showed the 22- and 23-olefin proton signals as a pair of doublets at δ 6.28, 6.54, 6.82, and 7.04 with a coupling constant of 15 cps, characteristic of a *trans* configuration.[15] A minor constituent of the Bestmann reaction product was the colorless *cis* isomer **5**, showing a pair of doublets in the pmr spectrum at δ 5.81, 5.90, 6.17, and 6.36 with J = 11 cps, assignable to 22,23-*cis* protons. An infrared spectral comparison of the *cis* and *trans* isomers also supported these assignments. The conjugated double-bond absorption of the *trans* isomer appears at 1628 cm^{-1} and for the *cis* isomer at 1620 cm^{-1}



(1) (a) Part 2: G. R. Pettit, B. Green, and G. L. Dunn, *J. Org. Chem.*, **34**, 1377 (1969). (b) This investigation was supported by Public Health Service Research Grants CY-4074 (C3) to CA-04074-07 and CA-10115-01 from the National Cancer Institute. (c) A preliminary report of the present study was summarized in part by G. R. Pettit, B. Green, A. K. Das Gupta, and G. L. Dunn, *Experientia*, **20**, 248 (1964).

(2) (a) To whom correspondence should be addressed at Arizona State University; (b) Research Division, East India Pharmaceutical Works, Calcutta, India.

(3) For leading references, consult G. R. Pettit, C. L. Herald, and J. P. Yardley, *J. Org. Chem.*, **35**, 1389 (1970); J. M. Ferland, Y. Lefebvre, and R. Deghenghi, *Tetrahedron Lett.*, 3617 (1966). The chemistry of butenolides has been reviewed: Y. S. Rao, *Chem. Rev.*, **64**, 353 (1964). For more recent advances, see W. W. Epstein and A. C. Sonntag, *J. Org. Chem.*, **32**, 3390 (1967); P. E. Sonnet, *Chem. Ind.* (London), 1296 (1967).

(4) T. Reichstein, *Naturwissenschaften*, **54**, 53 (1967).

(5) The designation isocardenolide has been suggested (**1a**) as a means of designating cardenolide-type steroids where the butenolide ring has been substituted at positions 21 or 22 instead of 20. An example (**11**) of the parent 21 isomer was described in a prelimary report[1c] of the present study, and the 22 counterpart (i) has recently been reported (see Ferland, ref 3). Beginning in 1959, several lactone-substituted isocardenolides (ii–v) were synthesized; see, respectively, K. Heusler, J. Kebrle, C. Meystre, H. Ueberwasser, P. Wieland, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **42**, 2043 (1959); R. D. Hoffsommer, H. L. Slates, D. Taub, and N. L. Wendler, *J. Org. Chem.*, **27**, 353 (1962); B. Camerino and U. Valcavi, U. S. Patent 3,068,229 (1962); *Chem. Abstr.*, **58**, 9183 (1963); J. E. Baldwin, *Tetrahedron*, **20**, 2933 (1964).

(6) G. R. Pettit, B. Green, and G. L. Dunn, *J. Org. Chem.*, **35**, 1367 (1970).

(7) The phosphorane step we wish to designate as the Bestmann reaction; see ref 6, footnote 34, and ref 10.

(8) (a) C. Djerassi and C. T. Lenk, *J. Amer. Chem. Soc.*, **75**, 3493 (1953).

(9) O. Isler, H. Gutmann, N. Montavon, R. Rüegg, G. Ryser, and P. Zeller, *Helv. Chim. Acta*, **40**, 1242 (1957).

(10) H. J. Bestmann, *Angew. Chem. Int. Ed. Engl.*, **4**, 583 (1965).

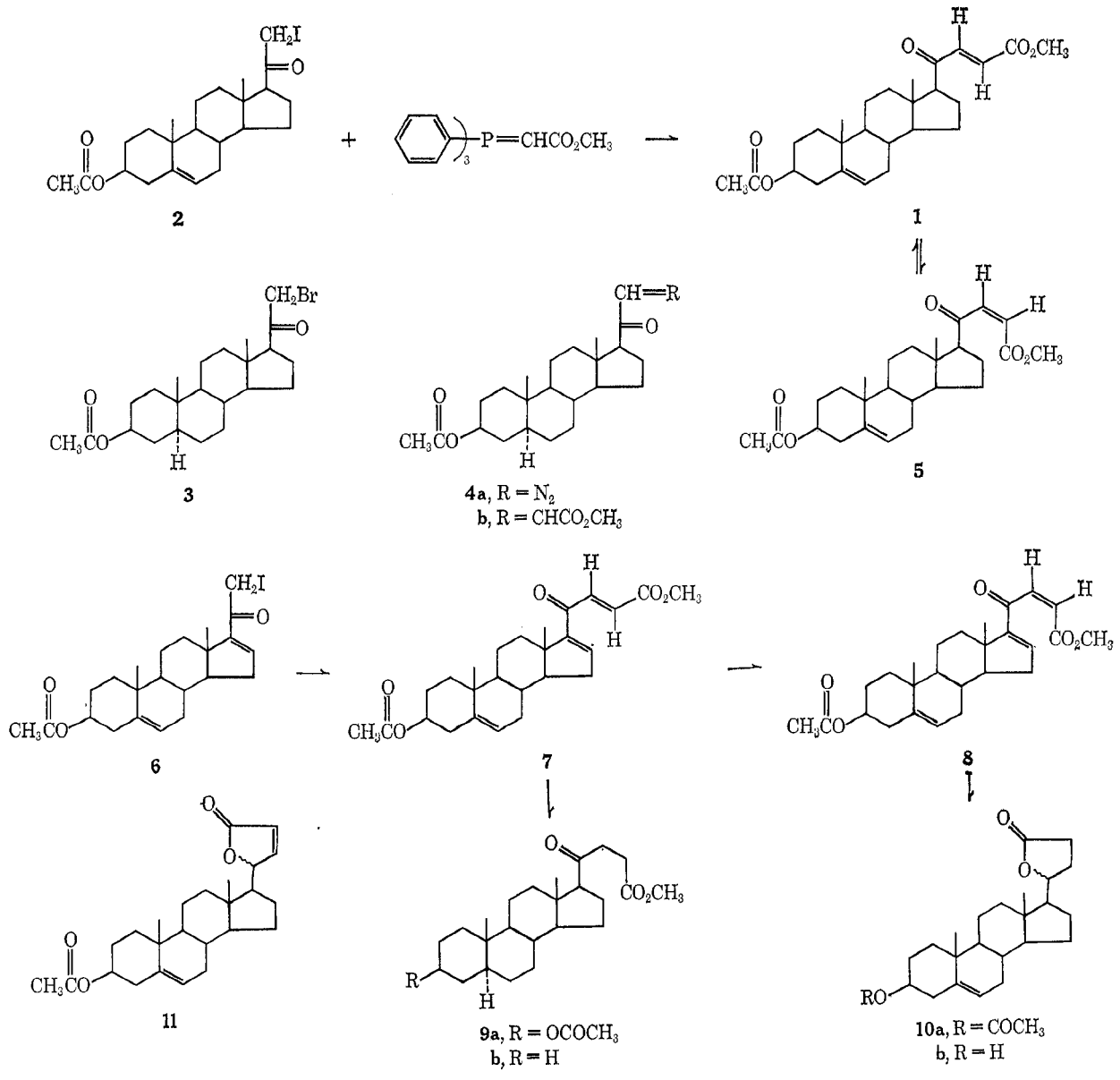
(11) N. N. Suvorov, L. V. Sokolava, Z. A. Yaroslavtseva, Z. D. Ovchimnikov, V. S. Murasheva, and F. Y. Leibel'man, *J. Gen. Chem. USSR*, **31**, 3469 (1961).

(12) We thank Dr. S. K. Sengupta for a rotatory dispersion curve of this compound.

(13) C. Djerassi, I. Fornaguera, and O. Mancera, *J. Amer. Chem. Soc.*, **81**, 2383 (1959).

(14) A. Marquet and J. Jacques, *Bull. Soc. Chim. Fr.*, **90** (1962).

(15) K. L. Rinehart, C. E. Coverdale, and P. K. Martin, *J. Amer. Chem. Soc.*, **88**, 3150 (1966).



with increased intensity. To provide further material, *trans* olefin **1** in benzene was irradiated with a sun lamp to give, after 5 days, a high yield of the *cis* isomer, which could be reconverted into the *trans* form by mild acid treatment.

An indication of the general utility of the transformation **2** → **5** was obtained by converting 3β-acetoxy-20-oxo-5,16-pregnadiene into 21-iodo ketone[16a] **6** and thence to yellow *trans* olefin **7** and colorless *cis* olefin **8**. The pmr data for both isomers supported the assignments, and both *cis* and *trans* isomers displayed double-bond absorption at 1580 cm^{-1}; in this case absorption was more intense for the *trans* isomer. Palladium-catalyzed hydrogenation of *trans* olefin **7** led to saturated ester **9a**, previously obtained[1a] by hydrogenation of *trans* olefin **1**, together with small amounts of the corresponding 3-deoxy derivative **9b** and 3β-acetoxy-20-hydroxy-21-nor-5α-cholanic acid γ-lactone (24 → 20) as observed earlier.[1a] A more selective reduction was achieved when an equilibrium mixture (1:6 *trans–cis*) was allowed to react with sodium borohydride in cold ethanol. Following a 4-hr period the previously obtained lactone **10a** was formed in reasonable yield. For purposes of evaluating the ease of reduction of the 16 double bond under these conditions, 3β-acetoxy-20-oxo-5,16-pregnadiene was treated in the same way to give as the major product, after reoxidation of the 20 alcohol with Jones reagent, pregnenolone acetate.[16b]

The route to isocardenolide **11** was satisfactorily completed by selective reduction of *cis* isomer **5** using sodium borohydride in dimethylformamide at room temperature. The pmr spectrum of lactone **11**, particularly the doublet centered at δ 7.25 (J = 5 cps) attributable to the C-23 olefinic proton, and the double doublet centered at δ 5.86 of the C-22 proton, confirmed the structural formulation. The C_{18} methyl signal was split, indicating, as with other borohydride reductions of the 20-keto group,[1a] that the product was a mixture of C-20 epimers. The reduction reaction was quite sensitive to experimental conditions and could be diverted, as already mentioned, with γ-keto acrylate **8** to yield lactone **10a**.

(16) (a) C. Djerassi and C. T. Lenk, *J. Amer. Chem. Soc.*, **76**, 1722 (1954). (b) *Cf.* D. Kupfer, *Tetrahedron*, **15**, 193 (1962).

Isocardenolide 11 was studied by Dr. K. Repke using an ATPase test system and found completely inactive up to concentrations as high as 0.1 m*M*; it therefore appeared devoid of any cardiac activity.[17]

General endocrinological evaluation of the steroids reported herein is being carried out under auspices of the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

Experimental Section[18]

Methyl 3β-Acetoxy-20-oxo-21-nor-5-*trans*-22-choladienate (1).—To a refluxing solution of carbomethoxymethylenetriphenylphosphorane[9] (18.1 g, 54 mmol) in toluene (120 ml) was added in one portion under nitrogen, 3β-acetoxy-20-oxo-21-iodo-5-pregnene[8a] (12.5 g, 25.9 mmol) in toluene (60 ml). The solution quickly became straw colored and solid material began to separate after 5 min. After the solution had been heated at reflux for 4 hr and cooled, the solid phase (8.6 g) was collected and washed with toluene. The filtrate and washings were treated with methyl bromoacetate (3.8 ml), and heated at reflux for 2 hr to give a thick precipitate which was separated upon cooling (4.3 g). After standing at room temperature for 20 hr, the filtrate was concentrated to a dark brown residue (16 g) which was chromatographed on acid-washed alumina. Elution with benzene gave a yellow solid (6.02 g), which recrystallized from benzene–hexane as yellow needles (4.75 g, 43%): mp 156–158° (three recrystallizations from methanol did not change the melting point); $[\alpha]^{22}D$ +43.5° (*c* 0.8); ν_{max} 1730, 1250 (acetate), 1735 (methyl ester), 1690 (conjugated ketone), and 1628 cm^{-1} (conjugated double bond); pmr δ 1.97 (singlet, 3 protons, 3 acetate), 3.68 (singlet, 3 protons, methyl ester), 5.20 (multiplet, 1 proton, C-6 olefin H), and 6.28, 6.54, 6.82 and 7.04 (quartet, 2 protons, J = 15 cps, 22,23-*trans* protons).

Anal. Calcd for $C_{26}H_{36}O_5$: C, 72.86; H, 8.47; O, 18.67. Found: C, 73.00; H, 8.39; O, 18.81.

3β-Acetoxy-20-oxo-21-bromo-5α-pregnane (3). Method A.—To purified dioxane (7 ml)–heptane (7 ml) at 0° was added, with occasional shaking, a cooled solution of bromine (14 g) in heptane (14 ml). The yellow precipitate which separated from the deep brown solution was collected, washed with heptane, and dried *in vacuo*. The dioxane dibromide slowly decomposed on storage. To a stirred solution of 3β-acetoxy-20-oxo-5α-pregnane (5.0 g, 14 mmol) in methanol (85 ml)–chloroform (15 ml) was added dioxane dibromide (3.5 g, 14.1 mmol) in methanol (15 ml) at 20°. Decolorization occurred after 90 min with simultaneous separation of a white solid. Stirring was continued for an additional 15 min and the mixture was diluted with chloroform (400 ml) and washed successively with 4% aqueous sodium hydroxide solution and water, followed by evaporation of the chloroform solution to yield a solid. Recrystallization from methanol–diethyl ether afforded crystals, mp 140–143° (3.8 g), mmp 115–129° with starting material. The analytical specimen[19] was obtained by two recrystallizations from methanol, mp 148–149.5°, $[\alpha]^{23}D$ +90.8° (*c* 0.091).

Anal. Calcd for $C_{23}H_{35}O_3Br$: C, 62.84; H, 8.03; Br, 18.19. Found: C, 63.04; H, 8.00; Br, 18.01.

Method B.[20]—Hydrogen bromide gas was bubbled slowly through the yellow solution of diazo ketone **4** (0.30 g, see part 7) in dry diethyl ether (50 ml) at room temperature. After 20 min the color disappeared, and evaporation of solvent gave a crystalline residue (0.35 g), mp 136–140°. One recrystallization from benzene–hexane yielded crystals, mp 143–146°, identical[21] with a specimen prepared by method A.

Methyl 3β-Acetoxy-20-oxo-21-nor-5α-chol-*trans*-22-enate (4b).—Bromo ketone **3** (4.4 g) was condensed with carbomethoxymethylenetriphenylphosphorane (6.8 g) in toluene (40 ml) as summarized for synthesis of olefin **1** (see above). Isolation and recrystallization from 95% ethanol gave 1.2 g of *trans* olefin **4b** as pale yellow prisms: mp 129–130°; ν_{max} 1730, 1680, 1658, and 1240 cm^{-1}.

Anal. Calcd for $C_{26}H_{38}O_5$: C, 72.52; H, 8.90; O, 18.58. Found: C, 72.67; H, 9.00; O, 18.21.

Methyl 3β-Acetoxy-20-oxo-21-nor-5-*cis*-22-choladienate (5). Procedure A.—During the preparation of methyl 3β-acetoxy-20-oxo-21-nor-5-*trans*-22-choladienate (**1**), a 2.7-g fraction obtained by elution with benzene was crystallized from methanol to give yellow *trans* isomer **1** (1.8 g). Upon concentration, the mother liquors gave a sticky, colorless product (0.9 g). Three recrystallizations from methanol led to colorless plates (0.12 g), mp 172–176°. Two more recrystallizations from the same solvent gave an analytical specimen of *cis* isomer **5**: mp 177–179°; $[\alpha]D$ +33.7° (*c* 0.697); ν_{max} 1730 (acetate and methyl ester), 1690 (conjugated ketone), and 1620 cm^{-1} (conjugated double bond); pmr δ 1.97 (singlet, 3 protons, 3 acetate), 3.64 (singlet, 3 protons, methyl ester), 5.20 (multiplet, 1 proton, H-6), and 5.81, 5.90, 6.17, and 6.36 (2 doublets, 2 protons, J = 11 cps, 22,23-*cis* protons).

Anal. Calcd for $C_{26}H_{36}O_5$: C, 72.86; H, 8.47. Found: C, 72.92; H, 8.61.

Procedure B.—A sample (0.10 g) of methyl 3β-acetoxy-20-oxo-21-nor-5-*trans*-22-choladienate (**1**) in benzene was irradiated with a General Electric sun light for 5 days, during which time the yellow color gradually faded.

Progress of the reaction was followed by thin layer chromatography, the *cis* isomer having a lower R_f value than the *trans* isomer. Removal of solvent afforded a crystalline residue. Three recrystallizations from methanol gave a pure sample as colorless plates (0.075 g), mp 176–178°, identical[21] in all respects with material obtained by method A.

Conversion of Methyl 3β-Acetoxy-20-oxo-21-nor-5-*cis*-22-choladienate to the *trans* Isomer (5 → 1).—Methyl 3β-acetoxy-20-oxo-21-nor-5-*cis*-22-choladienate (**5**, 50 mg) in methanol (3 ml)–diethyl ether (3 ml) was treated with 1 drop of 2 *N* hydrochloric acid at room temperature. After 20 hr the solution which had gradually developed a yellow color was diluted with diethyl ether and washed twice with water. Drying and evaporation furnished a pale yellow oil. The crude product crystallized and a thin layer chromatogram indicated largely *trans* isomer **1**, a trace of *cis* isomer **5**, and a smaller amount of more polar material, a hydrolysis product.

Methyl 3β-Acetoxy-20-oxo-21-nor-5,16-*trans*-22-cholatrienate (7).—A solution of 3β-acetoxy-20-oxo-21-iodo-5,16-pregnadiene[16a] (**6**, 6.5 g, 13.5 mmol) in dry toluene (30 ml) was added to a refluxing solution of carbomethoxymethylenetriphenylphosphorane (9.4 g, 28.07 mmol) in toluene (60 ml). The reaction was performed exactly as described above with 21-iodo pregnene **2** to yield a sticky solid (9.6 g). Chromatography on acid-washed alumina and elution with 2:1 benzene–hexane furnished a yellow solid (2.8 g), which recrystallized from acetone–methanol as silky, yellow needles, mp 153–154°. Further attempts to purify caused a drop in melting point and were not pursued: ν_{max} 1728 (methyl ester and acetate), 1661 (ketone), 1620 (conjugated double bond), and 1580 cm^{-1} (16 double bond); pmr δ 1.97 (singlet, 3 protons, 3 acetate), 3.68 (singlet, 3 protons, methyl ester), 5.20 (multiplet, C-6 olefin proton), 6.70 (multiplet, C-16 olefin proton), and 6.33, 6.60, 7.22, and 7.46 (2 doublets, 2 protons, J = 15 cps, 22,23-*trans* protons).

Anal. Calcd for $C_{26}H_{34}O_5$: C, 73.21; H, 8.04; O, 18.70. Found: C, 73,13; H, 8.07; O, 18.87.

Methyl 3β-Acetoxy-20-oxo-21-nor-5,16-*cis*-22-cholatrienate (8).—A solution of methyl 3β-acetoxy-20-oxo-21-nor-5,12-*trans*-22-cholatrienate (**7**, 0.27 g) in benzene (10 ml) was irradiated during 4 days[22] with a General Electric sun lamp at a distance of 4 ft. Removal of solvent *in vacuo* gave a very pale yellow oil which crystallized upon trituration with hexane. Recrystallization from hexane afforded nearly colorless crystals (0.22 g), mp 110–115°; a second crop (0.04 g) melted at 108–112°. Recrystalliza-

(17) We are grateful to Dr. K. Repke, Institute für Biochemie, Berlin, for this valuable information.

(18) Unless otherwise described, the infrared spectra were determined using potassium bromide pellets and optical rotation values were observed at 20° in chloroform solution. Proton magnetic resonance measurements (by Dr. R. A. Hill) were made in deuteriochloroform solution with tetramethylsilane as internal standard. Melting points were observed using a Kofler melting point apparatus. Other general experimental techniques, reagents, and chromatographic absorbents are summarized in the experimental introduction of part 2.[1a]

(19) Reference 12 reports a melting point of 142–143°; R. E. Marker and H. M. Crooks [U. S. Patent 2,369,065 (1945); *Chem. Abstr.*, **39**, 4197 (1945)] quote a melting point of 145–147°.

(20) We wish to thank David S. Blonda for assistance with this experiment.

(21) Mixture melting point determination and infrared spectral comparison supported this observation.

(22) The *cis/trans* ratio appeared by tlc to have reached an equilibrium value. A pmr spectrum of the equilibrium mixture indicated the *cis/trans* ratio to be 17:3.

tion of the first crop from hexane gave colorless prism clusters (0.18 g), mp 112–115°. A final recrystallization from hexane–isopropyl ether gave the analytical specimen as plate clusters: mp 113–115°; $[\alpha]_D$ −34.3° (*c* 0.58); ν_{max} 1728 (methyl ester and acetate), 1655 (ketone), 1638 (sh, conjugated double bond), and 1580 cm^{-1} (w, 16 double bond); pmr δ 1.97 (singlet, 3 protons, 3 acetate), 3.56 (singlet, 3 protons, methyl ester), *ca.* 5.2 (multiplet, C-6 olefin proton), *ca.* 6.2–6.3 (multiplet, C-16 olefin proton), 5.68, 5.87, and 6.24 (obscured), and 6.42 (2 doublets, J = 11 cps, 22,23-*cis* protons).

Anal. Calcd for $C_{26}H_{34}O_5$: C, 73.21; H, 8.04; O, 18.76. Found: C, 72.92; H, 8.01; O, 19.20.

Hydrogenation of Methyl 3β-Acetoxy-20-oxo-21-nor-5,16-*trans*-22-cholatrienate (7).—A solution of methyl 3β-acetoxy-20-oxo-21-nor-5,16-*trans*-22-cholatrienate (**7**, 0.45 g) in ethyl acetate (25 ml) was shaken under slightly positive pressure of hydrogen with palladium on charcoal catalyst (0.2 g, 10%) for 3 hr at room temperature. Filtration and evaporation of solvent gave a colorless solid whose thin layer chromatogram indicated **methyl 3β-acetoxy-20-oxo-21-nor-5α-cholanate** (**9a**) as major product, accompanied by small amounts of **methyl 20-oxo-21-nor-5α-cholanate** (**9b**) and **3β-acetoxy-20-hydroxy-21-nor-5α-cholanic acid γ-lactone (24 → 20)**.[1a,21] Recrystallization from methanol gave blades (0.25 g), mp 119–122°. Two more recrystallizations from methanol raised the melting point to 123–125°, but a thin layer chromatogram still suggested presence of a small amount of 3-deoxy derivative **9b**. Thus a sample (0.14 g) was chromatographed on acid-washed alumina (6 g) to give, on elution with benzene, methyl ester **9a**[21] (0.11 g), pure by tlc. Recrystallization from ethanol afforded blades, mp 126–128°, $[\alpha]_D$ +63° (*c* 0.78).

Sodium Borohydride Reduction of Methyl 3β-Acetoxy-20-oxo-21-nor-5,16,22-cholatrienate (8).—An equilibrium mixture (1.3 g) comprising *ca.* 85% *cis* olefin **8** and 15% *trans* olefin **7** in ethanol (40 ml) was cooled in an ice bath and treated dropwise with sodium borohydride (0.63 g) in ethyl alcohol (10 ml). The course of the reaction was monitored by thin layer chromatography, and after 4 hr essentially no starting material remained. The mixture was poured with stirring into ice–dilute hydrochloric acid and extracted with chloroform. The combined extract was washed with water and concentrated to dryness to give a residue which was chromatographed on acid-washed alumina (10 g). Elution with diethyl ether gave an oily solid fraction weighing 0.72 g, which was purified by preparative layer chromatography using six plates and 2:1 benzene–ethyl acetate as the mobile phase. The specimen of lactone **10a** obtained was crystallized from acetone–hexane to yield 0.46 g. A pure specimen recrystallized from methanol as plates, mp 226–229°.

In another experiment, 0.45 g of the *cis–trans* mixture in ethanol (40 ml) was reduced as described above with sodium borohydride (0.41 g) in ethanol (10 ml). Upon preparative layer chromatography, the less polar product (R_f 0.5–0.6) led to 0.26 g of lactone **10a**, and a more polar (R_f 0.3) fraction was found to be the 3β-hydroxy derivative **10b** (51 mg). Two recrystallizations of alcohol **10b** from acetone afforded 18 mg, mp 246–249°. Both specimens (**10a** and **10b**) were identical[21] with authentic samples.[1a]

Sodium Borohydride Reduction of 3β-Acetoxy-20-oxo-5,16-pregnadiene.—Reduction of 3β-acetoxy-20-oxo-5,16-pregnadiene (1.0 g) in ethanol (40 ml) using sodium borohydride (0.70 g) in ethanol (20 ml) was conducted as summarized for ketone **8** (see above). In this case, reduction appeared by tlc to be complete in 3 hr and 20 min at room temperature. A sample (0.28 g) of the crude product (1.0 g) in acetone (10 ml) was treated with an 8 *N* chromium trioxide reagent[23] until oxidant was present in slight excess (*ca.* 0.2 ml). After 2 min, isopropyl alcohol (0.2 ml) was added and the solution was diluted to 100 ml with water. Extraction with diethyl ether and purification by preparative layer chromatography (three plates using 2:1 benzene–ethyl acetate as mobile phase) and collection of the band with R_f 0.65–0.72 led to 0.16 g of pregnenolone acetate[21] estimated by pmr and ir measurements to be more than 90% pure. The minor contaminant appeared to be starting material.

3β-Acetoxy-20-hydroxy-21-nor-5,22-choladienic Acid γ-Lactone (24 → 20) (11).—To a solution of methyl 3β-acetoxy-20-oxo-21-nor-5-*cis*-22-choladienate (**5**, 0.30 g, 0.7 mmol) in dimethylformamide (21 ml) at room temperature was added sodium borohydride (0.14 g, 3.65 mmol) in water (2 ml) with magnetic stirring. After 7 hr the mixture was poured into water and acidified with 2 *N* hydrochloric acid to give a gelatinous precipitate which was collected by filtration and washed with water. A solution of the colorless solid (0.27 g) in 2:1 benzene–hexane was chromatographed on silica gel (10 g) to yield in 3:1 → 73:27 benzene–chloroform a solid (0.23 g). Recrystallization from diethyl ether or isopropyl ether gave crystals, mp 223–227°. The analytical specimen separated from isopropyl ether as blades: mp 225–227°; ν_{max} 1745 (unsaturated γ lactone) and 1720 cm^{-1} (acetate); $[\alpha]_D$ −51.8° (*c* −0.62); pmr 0.75, 0.83 (doublet, 3 protons, CH_3-18), 1.01 (singlet, 3 protons, CH_3-19), 1.97 (singlet, 3 protons, 3 acetate), 5.2 (multiplet, C-6 olefin proton), 5.86 (double doublet, J = 5 cps, C-22 olefin proton), and 7.2 and 7.3 (doublet, J = 5 cps, C-23 olefin proton).

Anal. Calcd for $C_{25}H_{34}O_4$: C, 75.34; H, 8.60. Found: C, 74.82; H, 8.71.

Registry No.—**1**, 2330-45-2; **4b**, 23330-46-3; **5**, 23367-42-2; **7**, 23330-47-4; **8**, 23367-43-3; **9a**, 23330-48-5; **11**, 23330-49-6.

(23) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).