Bufadienolides. 4. Reaction of 20-Oxo Steroids with Methoxymethylenetriphenylphosphorane[1]

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Reaction of 20-oxo-5-pregnenes **1a–1c** with the ylide prepared from methoxymethyltriphenylphosphonium chloride was studied in detail. Vinyl ether **2a** was also obtained along with a comparable amount of 3β-acetoxy-26,27-bisnor-5,20(22)cholestadiene (**3a**), employing the mixture of phosphoranes from methoxymethyltri-*n*-butylphosphonium chloride. Acid-catalyzed hydrolysis of vinyl ether **2** afforded aldehyde **4**. Attempts to condense methoxymethylenetriphenylphosphorane with *trans* olefinic ketone **5a**, *cis* olefinic ketone **6a**, or saturated ketone **7a** led to extensive side reactions attributable to the methyl ester group. Use of the carboxylic acid (**7j**) or the *t*-butyl ester (**7b**) or amide (**7d**) eliminated side reactions but satisfactory involvement of the 20 ketone was not realized.

A potentially efficient method planned[3a] for transforming a 20-oxopregnane to a bufadienolide involved two key stages comprising (a) the condensation of the ketone with a glyoxylic acid derivative to yield a β-acyl acrylate (**1a** → **6a**) and (b) the condensation of the acrylate with methoxymethylenetriphenylphosphorane to afford an open-chain precursor[3b] (**6b**) of the 2-pyrone. Simultaneously with studies[3a,4] aimed at obtaining the necessary acrylic acids, model experiments needed for the vinyl ether step were also initiated and are summarized herein.

When the generation of a 21-aldehyde substituent *via* the methoxymethylene derivative of a 20 ketone was considered in 1957, Wittig-type reactions employing a methoxymethylenephosphorane had not been described, but condensation of methoxymethylenetriphenylphosphorane with tigogenone, a 3-oxo steroid, was reported in the following year[5] and, subsequently, Wittig[6] described an extensive investigation of this route to vinyl ethers and aldehydes, emphasizing the synthetic utility of such reactions. Consequently, experiments now described were limited to the required 20-oxo steroid model compounds.

Reaction between pregnenolone acetate (**1a**) and methoxymethylenetriphenylphosphorane was selected for detailed examination. The ylide which was prepared from the corresponding phosphonium chloride using either *n*-butyllithium or potassium *t*-butoxide[7] as base gave, after several days with pregnenolone acetate in ether, vinyl ether **2a** in 30% yield. The use of tetrahydrofuran as solvent and pregnenolone (**1b**) increased the yield to 42%, but to improve this still further the use of an aliphatic phosphorane[8] such as methoxymethylenetri(methoxymethyl)phosphorane was considered. In order to obtain the precursor phosphonium salt of this ylide, an organometallic derivative of chloromethyl methyl ether would have been required. At that time no workable procedure was available,[9] and so the more readily available phosphorane mixture derived from methoxymethyltri-*n*-butylphosphonium chloride[10] was employed, leading on reaction with pregnenolone (**1b**) to vinyl ether **2a** in 35% yield (after acetylation) accompanied by a similar quantity of olefin **3a**. Addition of *n*-butyllithium to pregnenolone and acid-catalyzed dehydration (following acetylation) of the resulting tertiary alcohol provided an authentic specimen of the latter. Location of the side-chain double bond was substantiated by appearance of two (C-6 and C-22) olefin proton signals at δ 5.1–5.5 in the pmr spectrum. Before it could be determined whether olefin **3a** arose from excess *n*-butyllithium accompanying the phosphorane reagent or whether preparation of vinyl ether **2a** could be substantially improved using methoxymethylenetri(methoxymethyl)-phosphorane a more convenient route was found and these points were not further pursued.

A survey[11] of the Wittig reaction with various keto steroids indicated that functional groups, *i.e.*, hydroxyl and acetoxy, decreased the yield but that the tetrahydropyranyl ether protecting group did not have this detrimental effect. Condensing pyranyl ether **1c** with methoxymethylenetriphenylphosphorane in tetrahydrofuran afforded vinyl ether **2c** in 47% yield, but replacing tetrahydrofuran by diethylene glycol dimethyl ether and heating the mixture at reflux for 7 hr raised conversion to 83%.[12] Treating vinyl ethers **2b** and **2c** with 70% perchloric acid–diethyl ether[5] resulted in ready hydrolysis to aldehyde **4**, previously obtained[13] by ozonolysis of stigmasterol. With good overall conversion of 20-oxopregnane **1c** into aldehyde **4** established, extension to 20-oxonorcholadienates **5a** and **6a** was next undertaken.

(1) (a) Preceding contribution: G. R. Pettit, B. Green, A. K. Das Gupta, P. A. Whitehouse, and J. P. Yardley, *J. Org. Chem.*, **35**, 1381 (1970). (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.

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(3) (a) G. R. Pettit, B. Green, and G. L. Dunn, *J. Org. Chem.*, **35**, 1367 (1970). (b) Later we learned that analogous intermediates derived from isopropyl and cyclohexyl bromides have been hydrolyzed to the corresponding 5-substituted 2-pyrones: R. Nicoletti, *Ann. Chim.* (Rome), **51**, 1260 (1961).

(4) G. R. Pettit, B. Green, and G. L. Dunn, *J. Org. Chem.*, **35**, 1377 (1970).

(5) S. G. Levine, *J. Amer. Chem. Soc.*, **80**, 6150 (1958). We are indebted to Dr. Levine for providing us with his experimental procedure prior to publication.

(6) (a) G. Wittig and E. Kanuss, *Angew. Chem.*, **71**, 127 (1959); (b) G. Wittig, W. Böll, and K. H. Krück, *Chem. Ber.*, **95**, 2514 (1962).

(7) *Cf.* R. E. Ireland and P. W. Schiess, *J. Org. Chem.*, **28**, 6 (1963).

(8) S. Tripett and D. M. Walker, *Chem. Ind.* (London), 933 (1960); A. W. Johnson and R. B. LaCount, *Tetrahedron*, **9**, 130 (1960).

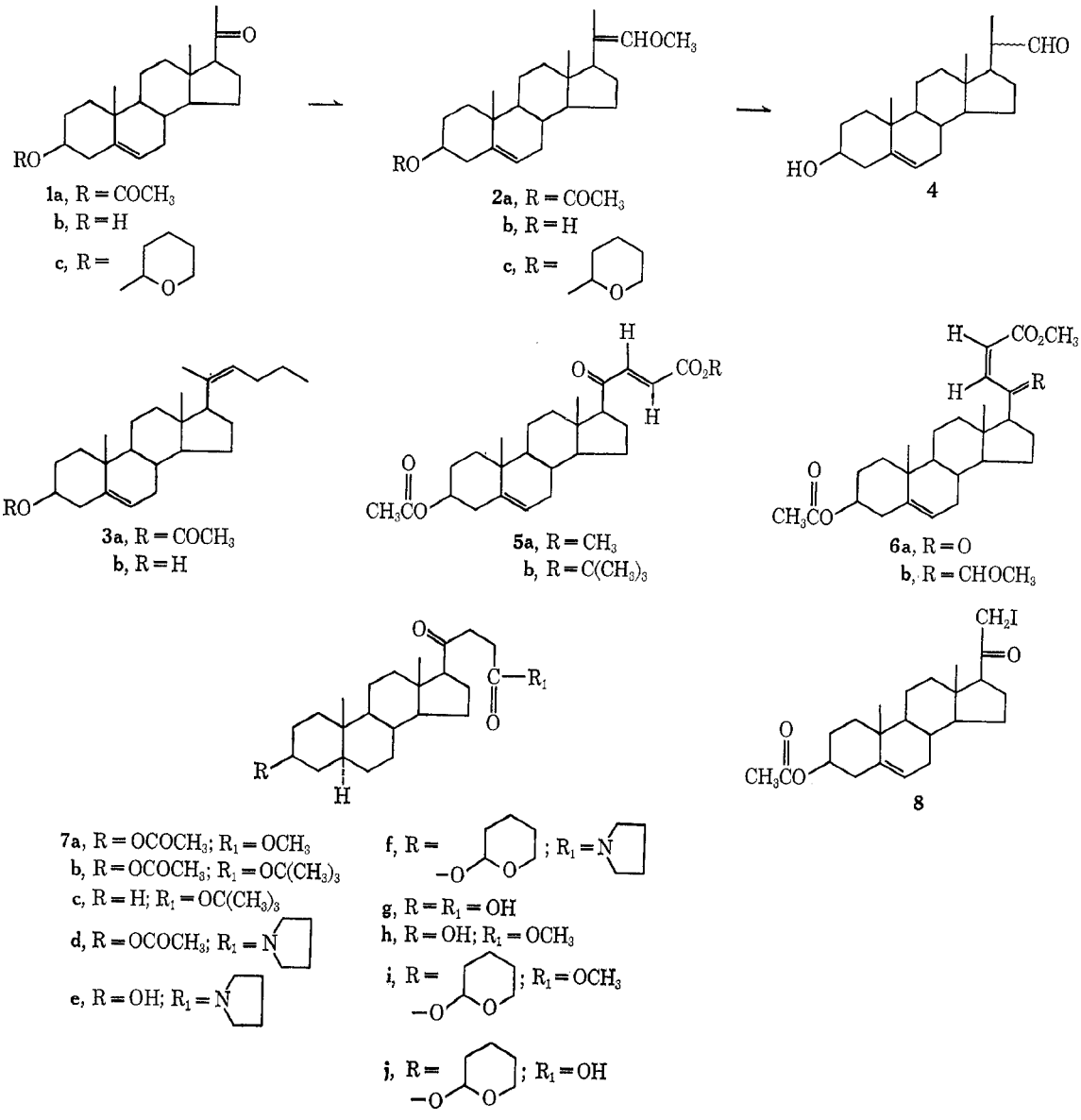
(9) Since then organometallic derivatives of chloromethyl methyl ether have been described: H. Normant and C. Crisan, *Bull. Soc. Chim. Fr.*, 459 (1959); U. Schöllkopf and H. Küppers, *Tetrahedron Lett.*, 1503 (1964).

(10) *Cf.* D. E. Bissing, *J. Org. Chem.*, **30**, 1296 (1965); C. Screttas and A. F. Isbell, *ibid.*, **27**, 2573 (1962).

(11) F. Sondheimer and R. Mechoulam, *J. Amer. Chem. Soc.*, **79**, 5029 (1957).

(12) An infrared spectral study suggested presence of the other geometrical isomer in the mother liquors, indicating higher yields of the vinyl ether; this isomer was not isolated.

(13) M. E. Herr and F. W. Heyl, *J. Amer. Chem. Soc.*, **74**, 3627 (1952).



Efforts to cause the phosphorane to react selectively with these isomers employing various modifications of the procedure developed for synthesis of **2a**, including generation of the reagent in dimethyl sulfoxide,[14] gave only complex reaction mixtures, suggesting involvement of the olefinic[15] and/or ester groups. Similar unencouraging results were obtained using saturated keto ester **7a**, thereby implicating the methyl ester.[16] Protection of the 24-carboxylate function was then undertaken by condensing *t*-butylcarboxymethylenetriphenylphosphorane with 21-iodo ketone **8** to provide *t*-butyl ester **5b**,[4] which was converted by palladium-catalyzed hydrogenation into the saturated analog **7b** and a small amount of the 3-deoxy derivative **7c**. Interestingly, keto ester **7b** was essentially unaffected by treatment with methoxymethylenetriphenylphosphorane in dimethyl sulfoxide.

Limited reactivity at the 20-oxo position of ester **7a** had been initially attributed to increased steric shielding as compared to 20 ketone **1a**, resulting in competitive reaction at the ester carbonyl; in the case of the *t*-butyl ester it is obvious that both carbonyl groups are now too sterically hindered for successful involvement.

Reducing the protecting group size by using pyrrolidine amide **7d** did not improve the situation, and again substantial amounts of starting material were recovered. Alcohol **7e** and tetrahydropyranyl ether **7f** were also prepared during this period but offered no advantage over 3β-acetoxy amide **7d**. Finally, it was decided to protect position 24 as the carboxylate anion and position 3 with a tetrahydropyranyl ether group. Toward this end, ester **7a** was saponified and the resulting carboxylic acid **7g** was remethylated to provide ester **7h**. Following reaction with dihydropyran, **7i** was isolated and converted into acid **7j**. Attempts at condensing the dimethyl sulfoxide soluble lithium salt with methoxymethylenetriphenylphosphorane or the more nucleophilic O,O-diethylcyanomethylphosphonate[17] led to good recovery of starting material **7j** emphasizing the serious steric effect at C-20 of the cholanic acid

(14) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).

(15) Double bonds of α,β-unsaturated ketone systems are known to react with phosphoranes to give cyclopropane derivatives: H. L. Bestmann and F. Seng, *Angew. Chem.*, **74**, 154 (1962).

(16) Selective reaction at the ketone position of keto esters can be accomplished by adding a phosphonate carbanion to excess ester. The carbanion derived from O,O-diethylmethoxymethylphosphonate appeared attractive, but would lack the requisite stability. See A. W. Johnson "Ylid Chemistry," Academic Press Inc., New York, N. Y., 1966, pp 141, 203.

(17) A. K. Bose and R. T. Dahill, Jr., *J. Org. Chem.*, **30**, 505 (1965).

side chain.[18] By this time, an alternate route[19] to the bufadienolide system had proved feasible and one of the next steps of proceeding *via* a 20-oxo-24-nitrile or other small carboxylic acid precursor was not undertaken. The preceding experiments did serve to further define steric requirements for Wittig reactions involving 20-oxo steroids.

Experimental Section

Each Wittig reaction was performed in a nitrogen atmosphere. Hexane solutions of *n*-butyllithium were obtained from Foote Mineral Co., while *n*-butyllithium in diethyl ether solution was prepared[20] and standardized. The diethyl ether, tetrahydrofuran, toluene, and dihydropyran were redistilled from sodium. Benzene and dimethylsulfoxide (heated at 60° for 20 hr with the hydride) were redistilled from calcium hydride. All other solvents, including pyrrolidine (from potassium hydroxide), were also redistilled. Infrared (in potassium bromide, Baird spectrophotometer) and proton magnetic resonance (deuteriochloroform solution unless described otherwise with tetramethylsilane as internal standard, Varian A-60) spectra were recorded by Dr. R. A. Hill, University of Maine. Other general experimental techniques, reagents, and chromatographic absorbents are summarized in the experimental introduction of part 2.[4]

3β-Acetoxy-20-methoxymethylene-5-pregnene (2a). Method A.—To a stirred suspension of methoxymethyltriphenylphosphonium chloride[6b] (1.9 g, 5.54 mmol) in diethyl ether (50 ml) was gradually added a solution of *n*-butyllithium in hexane (3.5 ml, 1.6 *N*, 5.6 mmol). The salt slowly dissolved to give a deep red solution. After 15 min, 3β-acetoxy-20-oxo-5-pregnene (**1a**, 2.0 g, 5.59 mmol) in diethyl ether (80 ml) was added dropwise during 15 min. The mixture became turbid and stirring was continued 24 hr at room temperature, followed by heating at reflux for 6 hr. Another period at room temperature (24 hr) was followed by a 3-hr reflux period. The solid phase was collected and washed with diethyl ether, and the filtrate was washed well with water, dried, and treated during 20 hr with methyl iodide. The supernatant liquid was decanted from precipitated solid and evaporated *in vacuo* to yield a semicrystalline mass (2.8 g) which was triturated with hot hexane (0.06 g, insoluble), and the solution was chromatographed on basic alumina (30 g). A cream-colored, crystalline solid (0.785 g) was eluted by 1:1 hexane–benzene. Recrystallization from chloroform–methanol gave slender needles, mp 142° (0.29 g). Two further recrystallizations from the same solvent gave needles: mp 151–152°; ν_{max} 1730 (acetate), 1670, and 1130 cm^{-1} (vinyl ether); pmr[21,22] δ 0.55 and 1.0 (C-18 and -19 methyls), 1.58 (C-21 methyl), 2.01 (C-3 acetate), 3.55 (methoxy), 5.38 (complex, C-6 olefin proton), and 5.78 (complex, C-22 olefin proton).

Anal. Calcd for $C_{25}H_{38}O_3$: C, 77.67; H, 9.91; O, 12.42. Found: C, 77.71; H, 9.75; O, 12.19.

Further elution of the column with 1:1 and 3:1 benzene–hexane gave 3β-acetoxy-20-oxo-5-pregnene (0.21 g).[22]

Method B.—To a stirred suspension of methoxymethyltriphenylphosphonium chloride[6b] (6.70 g, 19.5 mmol) in tetrahydrofuran (75 ml) was added dropwise an ethereal solution of butyllithium (10 ml, 1.29 *N*, 12.9 mmol). The deep red mixture was stirred at room temperature for 2 hr. Solid 3β-hydroxy-20-oxo-5-pregnene (**1b**, 1.02 g, 3.25-mmol) was added in one portion and the reaction mixture was allowed to stand for 22 hr at room temperature. Following a 24-hr period at reflux, the brown solution was cooled and filtered to remove precipitated solid (2.9 g). The filtrate was diluted with diethyl ether (100 ml) and washed with water (200 ml). The aqueous phase was washed with diethyl ether (two 150-ml portions) and the combined ethereal solution was dried and concentrated *in vacuo* to furnish a dark oil (3.5 g) which was acetylated for 22 hr at room temperature. The resulting oily product (3.7 g) was chromatographed on basic alumina (100 g). The first material eluted by 1:1 benzene–hexane was triphenylphosphine (0.09 g)[22] followed in the same solvent mixture by vinyl ether **2a** as a solid (0.60 g, 42%), mp 110–116°. Two recrystallizations from methanol afforded needles: mp 125–130°; ν_{max} 1730 (acetate), 1670, and 1130 cm^{-1} (vinyl ether).

Method C.[18]—To a suspension of triphenylmethoxymethylenephosphonium chloride (73 mmol) in diethyl ether (300 ml) was added 65 ml of 1.03 *N* potassium *t*-butoxide in *t*-butyl alcohol. The reaction was conducted in a nitrogen atmosphere with stirring and 1 hr later pregnenolone acetate (**1a**, 5.1 g, 15.3 mmol) in tetrahydrofuran (150 ml) was added to the orange-red mixture over a 15-min period. The mixture was stirred at reflux temperature for 20 hr, cooled, diluted with water, and extracted with diethyl ether. The crude product was isolated and reacetylated essentially as summarized in method B to give a solid which was chromatographed on neutral alumina (120 g), and the fractions eluted by 2:1 hexane–benzene were recrystallized from methylene chloride–methanol containing a trace of pyridine to give 2.4 g of colorless crystals melting at 142–148°. Recrystallization from the same solvent mixture afforded a pure sample melting at 152–154°.

Method D.—A solution of butyllithium (10 ml, 1.46 *N*, 14.6 mmol) in pentane–heptane was added dropwise to a stirred solution of methoxymethyltri-*n*-butylphosphonium chloride[23] (6.2 g, 21.9 mmol) in tetrahydrofuran (50 ml). After 2 hr at room temperature, solid 3β-hydroxy-20-oxo-5-pregnene (**1b**, 1.15 g, 3.65 mmol) was added to the yellow solution and stirring was continued for 20 hr at room temperature and for 24 hr at reflux temperature. Following isolation and acetylation as described in method B, the brown solid (1.3 g) was chromatographed on basic alumina (40 g). Elution with 1:1 benzene–hexane gave as the first fraction **3β-acetoxy-26,27-bisnor-5,20(22)-cholestadiene (3a**, 0.55 g),[22] mp 110–112°. Four recrystallizations from aqueous methanol gave an analytical specimen of **3a**: mp 113–113.5°; $[\alpha]_D$ 0°; ν_{max} 1730 cm^{-1} (acetate); pmr[21] δ 0.55, 0.95, 1.08, 1.68 (C-21 methyl), 2.08 (C-3 acetate), and 5.1–5.5 (multiplet, 2 olefin protons).

Anal. Calcd for $C_{27}H_{42}O_2$: C, 81.34; H, 10.63. Found: C, 81.44; H, 10.38.

A second fraction eluted by the same solvent system was **3β-acetoxy-20-methoxymethylene-5-pregnene (2a**, 0.46 g),[22] mp 130–138°. Five recrystallizations from methanol afforded an analytical specimen: mp 152–154°; $[\alpha]_D$ −69.3° (*c* 1.167); ν_{max} 1720 (acetate), 1670, and 1130 cm^{-1} (vinyl ether).

Anal. Calcd for $C_{25}H_{38}O_3$: C, 77.66; H, 9.91. Found: C, 77.92; H, 9.78.

Alternate Synthesis of 3β-Acetoxy-26,27-bisnor-5,20(22)-cholestadiene (3a).—A solution of 3β-hydroxy-20-oxo-5-pregnene (2.0 g, 6.3 mmol) in tetrahydrofuran (30 ml) was treated dropwise for 10 min with an ethereal solution of *n*-butyllithium (15 ml, 0.95 *N*, 14.2 mmol). The temperature rose to 50° and the mixture became turbid. After 15 hr at room temperature, solvent was removed *in vacuo* and the resulting viscous residue was warmed with aqueous hydrochloric acid (17%). The aqueous suspension was extracted with chloroform and the extract was concentrated to a brown oil (2.3 g) which was heated at reflux 24 hr in acetic anhydride (40 ml)–glacial acetic acid (20 ml). Excess reagents were removed *in vacuo* and the residue was treated for 1 hr with saturated aqueous sodium bicarbonate. Extraction with chloroform, drying, and evaporation gave a yellow oil (2.2 g), which was chromatographed on acid-washed alumina (75 g). Elution with 1:1 benzene–hexane led to a colorless oil (1.76 g). Trituration with methanol gave a solid (0.7 g), mp 85–90°. Four recrystallizations from methanol gave colorless plates of olefin **3a**: mp 111.5–112°;[22] ν_{max} 1730 (acetate) and 1250 cm^{-1} (acetate).

3β-Hydroxy-26,27-bisnor-5,20(22)-cholestadiene (3b).—A solution of 3β-acetoxy-26,27-bisnor-5,20(22)-cholestadiene (**3a**, 0.42 g) in 5% methanolic potassium hydroxide solution was allowed to remain at room temperature for 14 hr. The solution was filtered to remove precipitated solid (0.13 g) and the filtrate was added to water (100 ml). Extraction with diethyl ether gave a colorless, viscous residue (0.19 g). The oil and precipitated solid were combined and crystallized from methanol to yield plates (0.30 g), mp 129–130°. Three recrystallizations from methanol gave the analytical specimen: mp 129.5–130°; $[\alpha]_D$ −65.1° (*c* 0.615); ν_{max} 3400 cm^{-1} (hydroxyl).

(18) We wish to thank Dr. J. P. Yardley for performing these experiments.

(19) G. R. Pettit, D. Fessler, K. Paull, P. Hofer, and J. C. Knight, *J. Org. Chem.*, **35**, 1398 (1970).

(20) A. I. Vogel, "Practical Organic Chemistry," 3rd ed, Longmans, Green and Co., New York, N. Y., 1957, p 932.

(21) Recorded by Dr. D. C. Fessler.

(22) Confirmed by mixture melting point and infrared spectral comparison with an authentic specimen.

(23) Prepared in impure form from tri-*n*-butylphosphine and methyl chloromethyl ether.

Anal. Calcd for $C_{25}H_{40}O$: C, 84.21; H, 11.31. Found: C, 83.66; H, 10.97.

3β-Hydroxy-20-methoxymethylene-5-pregnene (2b).—A sample of 3β-acetoxy-20-methoxymethylene-5-pregnene (**2a**, 0.38 g) was saponified and isolated by chloroform extraction as summarized for alcohol **3b**. The yellow, oily product (0.27 g) was triturated with methanol–water at −5° to give a solid (0.25 g, 73%), mp 133–136°. Four recrystallizations from aqueous ethyl alcohol gave shiny plates: mp 143–144°; $[\alpha]_D$ −70.6° (*c* 0.802); ν_{max} 3400 (hydroxyl), 1670, and 1130 cm^{-1} (vinyl ether).

Anal. Calcd for $C_{23}H_{36}O_2$: C, 80.19; H, 10.53. Found: C, 79.97; H, 10.43.

3β-Tetrahydropyranyloxy-20-methoxymethylene-5-pregnene (2c).—A stirred suspension of methoxymethyltriphenylphosphonium chloride (2.16 g, 5.65 mmol) in tetrahydrofuran (20 ml, distilled from lithium aluminum hydride) and diethylene glycol dimethyl ether (20 ml, distilled from lithium aluminum hydride) was treated dropwise with an ethereal solution of butyllithium (5.8 ml, 0.95 *N*, 5.50 mmol). After 3 hr at room temperature, 3β-tetrahydropyranyloxy-20-oxo-5-pregnene (**1b**, 0.90 g, 2.25 mmol)[8a] in tetrahydrofuran (5 ml)–diethylene glycol dimethyl ether (5 ml) was added dropwise to the deep red solution. Stirring was continued for 20 hr at room temperature. The tetrahydrofuran was then removed by distillation and replaced by diethylene glycol dimethyl ether (20 ml) and the temperature was raised to cause refluxing (160°) and maintained there for 7 hr. The turbid brown mixture was concentrated to half volume *in vacuo*, cooled to room temperature, and treated with methyl bromoacetate (3 ml). After 12 hr at 5°, the solution was decanted from precipitated solid and washed with water six times. Evaporation *in vacuo* of solvent gave a dark oil (1.5 g), which was chromatographed on basic alumina (25 g). Elution with 2:1 hexane–benzene provided an oil (0.86 g, 83%), which on crystallization from acetone gave a solid (0.30 g): mp 80–90°; ν_{max} 1670, 1130 (vinyl ether), and 1030 cm^{-1} (tetrahydropyranyl ether). Evaporation of the mother liquor gave an oil (0.55 g) identical spectrally[22] with the solid form of vinyl ether **2c**.

Five recrystallizations of the solid from methanol yielded needles suitable for analysis, mp 116–117°, $[\alpha]_D$ −46.8° (*c* 1.282).

Anal. Calcd for $C_{28}H_{44}O_3$: C, 78.45; H, 10.35. Found: C, 78.49; H, 10.01.

3β-Hydroxy-4-pregnene-20-aldehyde (4).—A solution of 3β-tetrahydropyranyloxy-20-methoxymethylene-5-pregnene (**2c**, 0.70 g) in perchloric acid–diethyl ether (20 ml) was left at room temperature for 14 hr. Dilution with water and extraction with chloroform led to a dark, viscous residue (0.50 g). Chromatography on acid-washed alumina (15 g) and elution with 4:1 benzene–chloroform gave a pale yellow solid (0.37 g, 69%), which recrystallized from benzene–hexane as colorless microneedles: mp 151–156° (lit.[13] mp 150–152°); $[\alpha]_D$ −54.3° (*c* 0.58); $[\alpha]^{25}_D$ −59.3°; ν_{max} 3400 (hydroxyl), 2700 (w), and 1720 cm^{-1} (aldehyde).

Anal. Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 80.39; H, 10.42.

***t*-Butyl 3β-Acetoxy-20-oxo-21-nor-5-*trans*-22-choladienate (5b).**[24]—To a solution of *t*-butylcarboxymethylenetriphenylphosphorane[25] (15 g, 0.04 mol) in refluxing toluene (200 ml) was added in one portion 3β-acetoxy-20-oxo-21-iodo-5-pregnene[26] (**8**, 10.5 g, 0.022 mol). Heating at reflux was maintained for 5 hr and, following addition of *t*-butyl bromoacetate (4.4 ml), continued for 2 hr longer. After cooling, the solution was filtered (16.0 g of salt) and toluene was removed *in vacuo*. The residue was chromatographed on neutral alumina (450 g) and elution with 2:1 benzene–hexane. Benzene provided *trans* olefin **5b** as a yellow solid (4.2 g, 38%), mp 140–146°. Two recrystallizations from isopropyl ether gave an analytical specimen as yellow prisms: mp 149–150°; $[\alpha]_D$ +27.5° (*c* 2.26); ν_{max} 1732 (*t*-butyl ester), 1715 (C-3 acetate), 1688 (C-20 ketone), 1670 and 1628 (C-22,23 olefin), 1368 (*t*-butyl), and 1255 cm^{-1} (acetate); pmr δ 1.49 (s, 9 H, *t*-butyl), 1.97 (3 H, C-3 acetate), and the C-22,23 olefin protons at 6.22 and 6.48 (d, 1 H, J = 15 cps) and 6.74 and 6.99 (d, 1 H, J = 15 cps).

(24) We thank Philip A. Whitehouse for assistance with this experiment.
(25) T. Moriwake, *J. Org. Chem.*, **31**, 983 (1966).
(26) C. Djerassi and C. Lenk, *J. Amer. Chem. Soc.*, **75**, 3493 (1953).

Anal. Calcd for $C_{29}H_{42}O_5$: C, 74.01; H, 9.00; O, 17.00. Found: C, 74.25; H, 8.97; O, 17.25.

Hydrogenation of *t*-Butyl 3β-Acetoxy-20-oxo-21-nor-5-*trans*-22-choladienate (5b).—A solution of olefin **5b** (0.80 g) in ethyl acetate (40 ml) was shaken for 4 hr under hydrogen with 10% palladium on charcoal (0.25 g). The solution was filtered and concentrated to a viscous oil containing four components, and a solution of the mixture in hexane was chromatographed on silica gel (30 g). A fraction (35 mg) eluted by benzene and pure by thin layer chromatography crystallized from methanol to yield ***t*-butyl 20-oxo-21-nor-5α-cholanate (7c)** as needles: mp 103–105°; $[\alpha]_D$ +90° (*c* 0.4); $\nu^{CHCl_3}_{max}$ 1750, 1710, 1370, and 1160 cm^{-1}.

Anal. Calcd for $C_{27}H_{44}O_3$: C, 77.83; H, 10.64; O, 11.52. Found: C, 77.92; H, 10.43; O, 11.71.

A fraction (0.58 g) eluted by 7:3 benzene–chloroform crystallized after a long period from methanol. Recrystallization from methanol gave ***t*-butyl 3β-acetoxy-20-oxo-21-nor-5α-cholanate (7b)** as prisms: mp 81–83°; $[\alpha]_D$ + 68° (*c* 0.82); $\nu^{CCl_4}_{max}$ 1740, 1705, 1360, 1235, and 1140 cm^{-1}; pmr δ 1.38 (s, 9 H, *t*-butyl), 1.88 (s, 3 H, acetate), and 2.38 (m, 4 H, $COCH_2CH_2CO_2$).

Anal. Calcd for $C_{29}H_{46}O_5$: C, 73.38; H, 9.77; O, 16.85. Found: C, 73.31; H, 10.16; O, 16.54.

Pyrrolidine Amide of 3β-Acetoxy-20-oxo-21-nor-5α-cholanic Acid (7d).—A solution of methyl ester **7a** (0.26 g) in pyrrolidine (3 ml) was allowed to remain at room temperature for 7 days. The mixture was diluted with diethyl ether and the solution was washed with water, 2% hydrochloric acid, and water. Solvent was removed and the residue was shown by thin layer chromatography with 1:1 hexane–ethyl acetate mobile phase to contain no starting material. The product was chromatographed on silica gel, and benzene–chloroform fractions removed trace impurities. Elution with chloroform gave 0.25 g of amide **7d**. Three recrystallizations from hexane–diethyl ether provided an analytical sample as needles: mp 124–125°; ν_{max} 1740 (C-3 acetate), 1710 (C-20 ketone), 1650 (amide), and 1230 cm^{-1} (acetate).

Anal. Calcd for $C_{29}H_{45}NO_4$: C, 73.84; H, 9.62; N, 2.97; O, 13.57. Found: C, 73.59; H, 9.76; N, 3.10; O, 13.50.

Pyrrolidine Amide of 3β-Hydroxy-20-oxo-21-nor-5α-cholanic Acid (7e).—The aminolysis reaction described above (see **7d**) was repeated employing 1 g of methyl ester **7a** and 10 ml of pyrrolidine. In this case, reaction was allowed to progress for 10 days and the crude product was chromatographed on 30 g of silica gel. The fractions eluted by chloroform to 99:1 chloroform–methanol afforded 0.65 g of 3β-acetoxy amide **7d**. A fraction eluted by 9:1 chloroform–methanol gave 0.15 g of 3β-hydroxy amide **7e**. Three recrystallizations from methanol–methylene chloride yielded a pure sample as crystals: mp 222–224°; tlc, 19:1 chloroform–methanol; $[\alpha]_D$ +67° (*c* 0.51); ν_{max} 3350, 1705, and 1620 cm^{-1}.

Anal. Calcd for $C_{27}H_{43}NO_3$: C, 75.48; H, 10.09; N, 3.26; O, 11.17. Found: C, 75.64; H, 9.89; N, 3.20; O, 11.30.

Pyrrolidine Amide of 3β-Tetrahydropyranyloxy-20-oxo-21-nor-5α-cholanic Acid (7f).—A solution composed of benzene (2 ml), 3β-hydroxy amide **7e** (0.1 g), dihydropyran (0.7 ml), and *p*-toluenesulfonic acid monohydrate (10 mg) was stirred at room temperature for 30 min. The mixture was poured into ice–aqueous sodium carbonate and extracted with diethyl ether. The ethereal solution was washed well with water and concentrated. A solution of the residue in hexane containing 1% ethyl acetate was chromatographed on silica gel (3 g). The fractions eluted by 2:3 hexane–ethyl acetate to pure ethyl acetate afforded pyranyl ether **7f**. Two recrystallizations from hexane–methylene chloride afforded an analytical specimen (0.08 g): mp 117–119°; tlc, ethyl acetate; $[\alpha]_D$ +65° (*c* 0.62); ν_{max} 1700, 1645, and 1030 cm^{-1} (ether).

Anal. Calcd for $C_{32}H_{51}NO_4$: C, 74.81; H, 10.01; N, 2.73; O, 12.46. Found: C, 74.62; H, 9.66; N, 2.88; O, 12.93.

Methyl 3β-Hydroxy-20-oxo-21-nor-5β-cholanate (7h).—A solution composed of methyl 3β-acetoxy-20-oxo-21-nor-5α-cholanate (**7a**, 1.14 g), methanol (45 ml), water (12 ml), and potassium carbonate (1.2 g) was heated at reflux for 4 hr. Evaporation *in vacuo* to small volume and acidification with hydrochloric acid (2 *N*) gave a white precipitate which was collected and washed with water. Drying furnished a solid (0.90 g) sparingly soluble in a variety of organic solvents. 3β-Hydroxy-20-oxo-21-nor-5α-cholanic acid (**7g**) was obtained: ν^{Nujol}_{max} 3600 (vs, hydroxyl), 2500–2800 (w, b carboxylic acid), and 1720 cm^{-1} (vs, carboxylic acid). It was used without further purification. The acid **7g** (0.89 g) suspended in 1:1 chloroform–methanol

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).