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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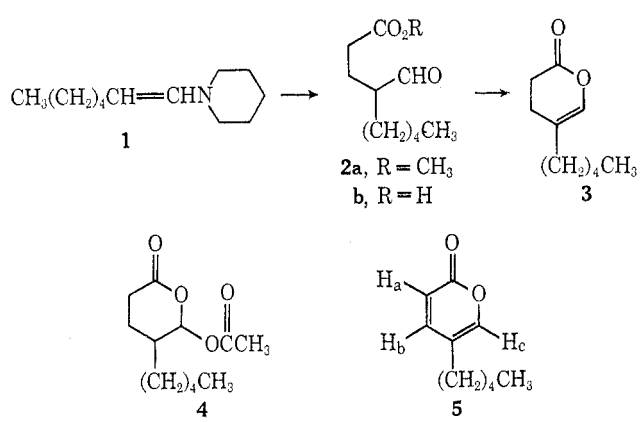
A new synthetic route to 5-substituted 2-pyrones is described. Alkylation of enamine **1** with methyl acrylate, cyclization of carboxylic acid **2b** employing *p*-toluenesulfonic acid in benzene, and dehydrogenation of enol lactone **3** with a palladium catalyst or by a N-bromosuccinimide sequence 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.



(1) Part 6 and Steroids and Related Natural Products. LIV: G. R. Pettit, J. C. Knight, and C. L. Herald, *J. Org. Chem.*, **35**, 1393 (1970). The present investigation was supported by Public Health Service Research Grants CA-04074-05, CA-10115-01, CA-10115-02, and CA-10115-03 from the National Cancer Institute. The mass spectrometers were obtained using National Science Foundation Grants GB-4939 and GP-6979.

(2) Based in part on dissertations submitted by D. C. Fessler and K. D. Paull to the Graduate School, Arizona State University, Oct 1968 and Sept 1969, respectively.

(3) A preliminary report of the present study has been published: G. R. Pettit, D. C. Fessler, K. D. Paull, P. Hofer, and J. C. Knight, *Can. J. Chem.*, **47**, 2511 (1969).

(4) J. Fried and R. C. Elderfield, *J. Org. Chem.*, **6**, 566 (1941).

(5) For these references see G. R. Pettit, B. Green, G. L. Dunn, and P. Sunder-Plassmann, *ibid.*, **35**, 1385 (1970). D. Bertin, L. Nedelec, and J. Mathieu, French Patent 1,369,962 (1962); *Chem. Abstr.*, **62**, 616 (1965). F. Sondheimer, W. McCrae, and W. G. Salmond, *J. Amer. Chem. Soc.*, **91**, 1228 (1969).

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

(7) For a review refer to J. Szmuszkovicz in "Advanced Organic Chemistry: Methods and Results," Vol. 4, R. A. Raphael, E. C. Taylor, and H. Wynberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, pp 1–113.

(8) Condensation of propiolates with enamines of ketones can lead to a variety of products: K. C. Brannock, R. D. Burpitt, V. W. Goodlett, and J. G. Thweatt, *J. Org. Chem.*, **29**, 818 (1964).

(9) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963); H. Fritz and O. Fischer, *Tetrahedron*, **20**, 1737 (1964).

(10) An investigation of the preparation and properties of such enol lactones has recently been summarized: P. Haverkamp Begeman, V. Lambert, and W. T. Weller, *Rec. Trav. Chim. Pays-Bas*, **87**, 1335 (1968). The enol lactones were found sensitive to both oxygen and water and darkened rapidly on exposure to air. See also ref 13b for synthesis of δ-lactones.

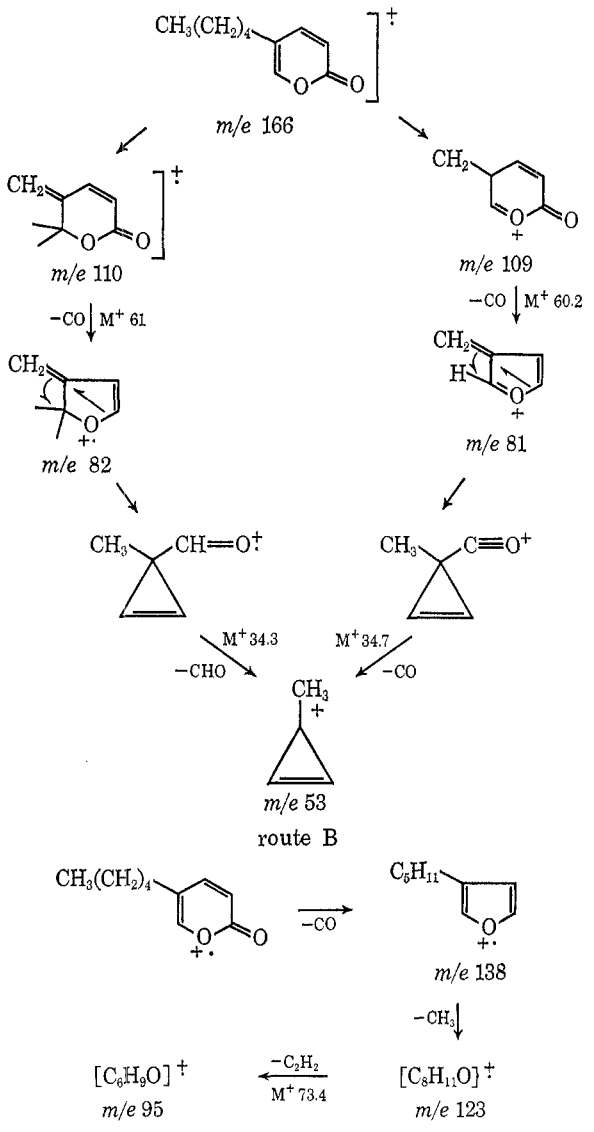
(11) (a) B. E. Edwards and P. N. Rao, *J. Org. Chem.*, **31**, 324 (1966). (b) N. P. Shusherina, E. A. Luk'yanets, T. L. Tsilevich, and R. Ya Levina, *J. Org. Chem. USSR*, **2**, 1194 (1966). (c) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Amer. Chem. Soc.*, **74**, 4223 (1952); T. M. Harris and C. S. Combs, Jr., *J. Org. Chem.*, **33**, 2399 (1968).

Dehydrogenation of enol lactone **3** to pyrone **5** was achieved by means of a palladium catalyst in refluxing *p*-cymene,[12] which provided a 50% yield of pyrone **5**. Pyrone **5** was also obtained in 42% yield somewhat less conveniently by bromination of enol lactone **3** with N-bromosuccinimide followed by dehydrobromination with lithium bromide in dimethylformamide.[13]

The structure of pyrone **5** was amply supported by mass and spectral data. Based on recent studies of the mass spectral fragmentation of 2-pyrones,[14] routes A and B have been suggested for the observed fragmentation of pyrone **5** (Scheme I). A number of the postulated transformations received support from metastable ions (M^+). Cleavage at the benzyl bond appeared to be the primary mode (route A) of molecular ion (*m/e* 166) fragmentation. Formation of the benzylic-type ion (*m/e* 109) is a transformation characteristic of alkylbenzenes,[15] and as with alkylbenzenes containing side chains longer than propyl, the β cleavage was accompanied by rearrangement of one hydrogen atom, giving rise to the ion at *m/e* 110. Loss of carbon monoxide from both the *m/e* 110 and 109 ions could then lead to furan-type ions at *m/e* 81 and 82. The *m/e* 53 ion might then arise from the *m/e* 82 ion by migration of a hydrogen atom and loss of CHO, or from the *m/e* 81 ion by migration of a hydrogen atom and loss of carbon monoxide. Pertinent aspects of the remaining mass spectrum can be interpreted by initial loss of carbon monoxide from the molecular ion as suggested by route B.

SCHEME I

POSSIBLE FRAGMENTATION OF 5-PENTYLPYRAN-2-ONE (5)



Other spectral characteristics of pyrone **5** were in complete accord with an α-pyrone structure. The ultraviolet absorption maximum at 298 mμ (ϵ 5150)[16] and infrared[17a] absorption at 1755, 1730, 1650, and 1550 cm^{-1} were as anticipated. The pmr spectrum[17b] exhibited a doublet at δ 6.15 (J = 11 Hz) for H_a, a pair of doublets at δ 7.2 (J = 3 and 11 Hz) for H_b, and a doublet centered at δ 7.23 (J = 3 Hz) for H_c. With the structure of pyrone **5** thereby firmly established, the new route to 5-substituted 2-pyrones was next extended to two typical steroidal aldehydes, namely, **7e** and **12e**.

Nitrile **6a** was prepared by allowing dehydroepiandrosterone acetate to react with the carbanion derived from diethyl cyanomethylphosphonate[18] in tetrahydrofuran. Saponification of the 3-acetate followed by reaction with dihydropyran provided tetrahydropyranyl ether **6b**. The plan here was to reduce nitrile **6b** using lithium triethoxyaluminohydride[19] to the corresponding aldehyde. However, attempts to reduce nitriles **6a** or **6b** or the partially reduced derivatives **7a** or **7b** proved unsatisfactory. To circumvent this problem, the 17(20) olefin was selectively hydrogenated over 5% palladium on calcium carbonate to yield nitrile **7a**. Similarly, olefin **6b** was easily reduced to **7b**. Saponification of nitrile **7a** led to carboxylic acid **7c**, which was acetylated using acetic anhydride–acetic acid to provide acid **7d**. The acid chloride derived from carboxylic acid **7d** was reduced[20] over a palladium catalyst to give aldehyde **7e**[21] in 83% yield. Condensation of aldehyde **7e** with piperidine gave enamine **7f**. Alkylation of enamine **7f** with methyl acrylate in acetonitrile followed by hydrolysis gave a two-component mixture. Preparative layer chromatography on silica gel led to recovery of aldehyde **7e** and methyl ester **8a** (50% yield). Attempts to improve conversion of aldehyde **7e** into methyl ester **8a** by changing reaction conditions and solvent did not result in any improvement, and

(12) D. Rosenthal, P. Grabowich, E. Sabo, and J. Fried, *J. Amer. Chem. Soc.*, **85**, 3971 (1963).

(13) See, *e.g.*, (a) B. Berkoz, L. Cuellar, R. Grezemkovsky, N. V. Avila, and A. D. Cross, *Proc. Chem. Soc.*, 215 (1964); (b) V. Lambert, W. T. Weller, and J. C. M. Schogt, *Rec. Trav. Chim. Pays-Bas*, **86**, 504 (1967).

(14) Some controversy over the furan-like ion structure has been raised: W. H. Pirkle and M. Dines, *J. Amer. Chem. Soc.*, **90**, 2318 (1968). We wish to thank Professor P. Brown for a very helpful discussion of the mass spectrum of pyrone **5**.

(15) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," 2nd ed, Holden-Day, Inc., San Francisco, Calif., 1967, p 81.

(16) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," The Macmillan Co., New York, N. Y., 1964, p 140.

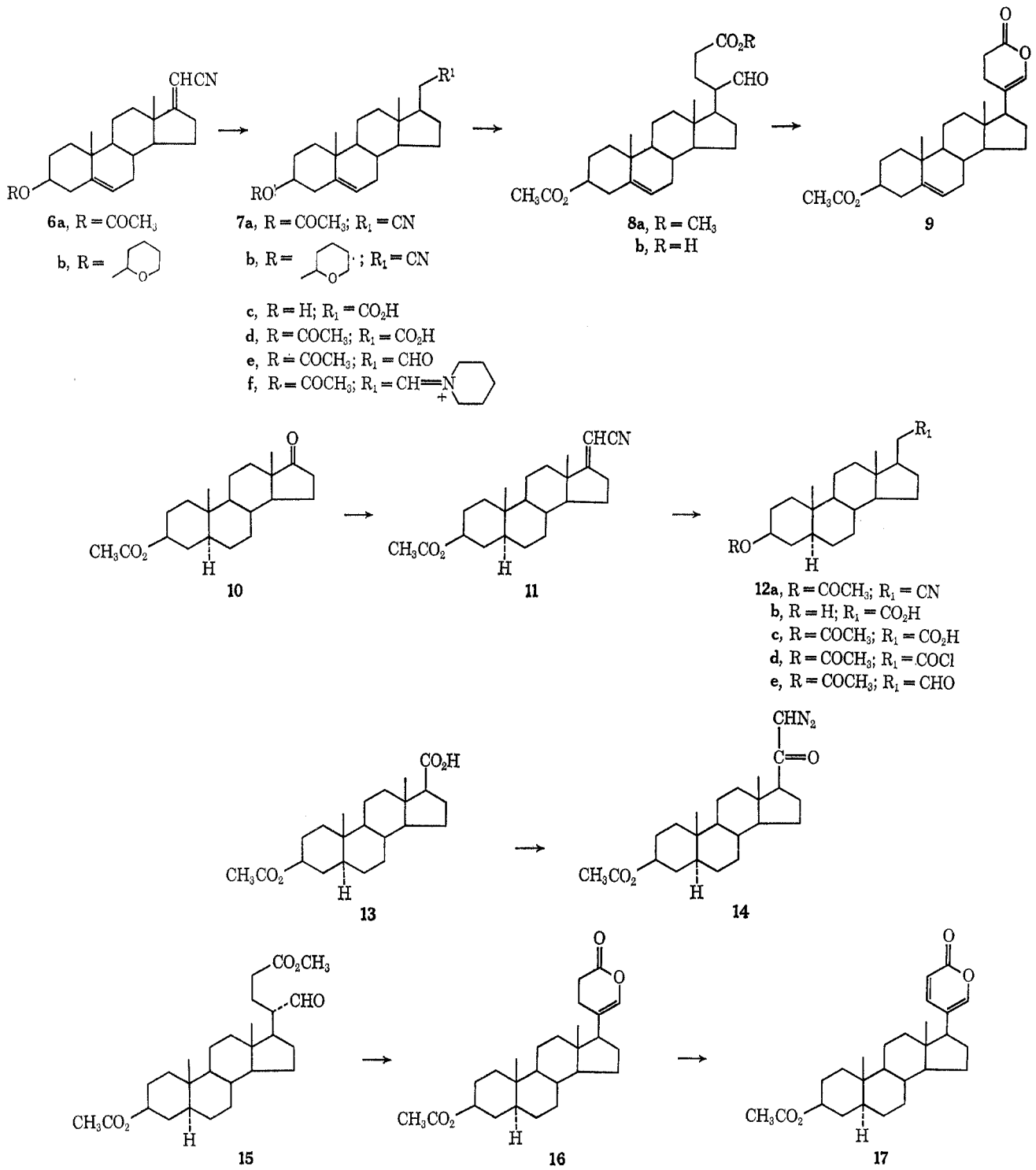
(17) (a) R. H. Wiley and S. C Slaymaker, *J. Amer. Chem. Soc.*, **78**, 2393 (1956); R. N. Jones, C. L. Angell, T. Ito, and R. J. D. Smith, *Can. J. Chem.*, **37**, 2007 (1959). (b) W. H. Pirkle and M. Dines, *J. Heterocycl. Chem.*, **6**, 1 (1969).

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

(19) H. C. Brown and C. P. Garg, *J. Amer. Chem. Soc.*, **86**, 1085 (1964).

(20) See, *e.g.*, Y. Egawa, M. Suzuki, and T. Okuda, *Chem. Pharm. Bull.* (Tokyo), **11**, 589 (1963); a review by E. Mosettig and R. Mozingo, *Org. React.*, **4**, 362 (1948); I. G. Csizmadia, J. Font, and O. P. Strausz, *J. Amer. Chem. Soc.*, **90**, 7360 (1968).

(21) W. R. Benn, *J. Org. Chem.*, **33**, 3113 (1968).



the best yield was realized by recycling recovered aldehyde **7e**. Conversion of methyl ester **8a** into enol lactone **9** (30–40% yield) was conducted as noted above for the conversion of methyl ester **2a** into enol lactone **3**. By an analogous series of reactions, 3β-acetoxy-17-oxo-5α-androstane (**10**) was converted, *via* nitrile **11**, carboxylic acid **12c**, aldehyde **12e**, and methyl ester **15**, into enol lactone **16**. In this case, carboxylic acid **12c** was also prepared by hydrogenation of acid **7d** and by Wolff rearrangement of diazo ketone **14**[5a] prepared from 17-carboxylic acid **13**. Enol lactones **9** and **16** represent the first examples of buf-20(21)-enolides.

Interestingly, a considerable number of experiments directed at dehydrogenating enol lactone **9** or **16** in *p*-cymene using palladium on carbon proved quite ineffectual. More vigorous reaction conditions than those employed for formation of pyrone **5** led to extensive production of side products. Model experiments, primarily with enol lactone **3**, attempting to utilize 2,3-dichloro-5,6-dicyanoquinone in refluxing dioxane (with or without acid catalyst)[22] or trityl perchlorate[23] in refluxing acetic acid, led only to isolation of starting material. Treatment with selenium dioxide[24] in re-

(22) D. Walker and J. D. Hiebert, *Chem. Rev.*, **67**, 153 (1967).

(23) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York., N. Y., 1967, p 1256.

(24) C. R. Engel and S. Rakhit, *Can. J. Chem.*, **40**, 2153 (1962); E. J. Agnello and G. D. Laubach, *J. Amer. Chem. Soc.*, **79**, 1257 (1957).

fluxing *t*-butyl alcohol gave a mixture of products among which, *e.g.*, pyrone **5** was not detected by thin layer chromatography. With the rigid steric requirements of lactones **9** and **16** possibly obviating the palladium on carbon technique, the potentially less versatile N-bromosuccinimide method was evaluated.[25] Application of the N-bromosuccinimide reaction used to obtain pyrone **5** from enol lactone **3** also proved unsatisfactory.[25] Eventually a practical and reliable method for dehydrogenation of buf-20(21)-enolide **16** to bufa-20,22-dienolide **17** was achieved by heating with sulfur[25] for 30 min at 221–227°. Yields of bufadienolide, **17** amounted to 60–70%. Use of the new method with olefins such as **9** required milder conditions and led to an extensive study of steroid–sulfur reactions which will be reported in a further contribution. Once synthesis of bufadienolide **17** was satisfactorily realized, objectives of the present investigation were complete.

The new synthesis of 5-substituted 2 pyrones illustrated by transformation of heptaldehyde to pyrone **5** presents a convenient route to such substances. Also, the reaction sequence offers a particularly useful approach to buf-20(21)-enolides. Synthesis of such steroidal lactones and subsequent sulfur dehydrogenation to the corresponding bufadienolides should more readily allow assessment of structure–activity relationships in this area of steroid chemistry.

Experimental Section

Catalytic hydrogenations were performed at room temperature using a slight positive pressure of hydrogen. Ether refers to diethyl ether and ligroin to fractions boiling at 60–110°. Acetonitrile (from phosphorus pentoxide), tetrahydrofuran (from potassium hydride), heptaldehyde, and diethyl cyanomethylphosphonate (at 1.5 mm) were redistilled prior to use. Dimethylformamide was distilled from calcium oxide and stored over molecular sieve type 4-A. All solvent extracts of aqueous solutions were dried with magnesium sulfate or sodium sulfate.

Neutral alumina (E. Merck, A. G. Darmstadt) and silica gel (E. Merck, 0.05–0.2 mm) were used for column chromatography. Silica gel HF_{254} (E. Merck) spread on microscope slides was employed for thin layer chromatography. The thin layer chromatographic solvents were, unless differently indicated, 4:1 or 7:3 hexane–ethyl acetate, and with acidic compounds 9:1:0.1 hexane–ethyl acetate–acetic acid. Visualization involved iodine vapor or heating with 2% ceric sulfate in 2 *N* sulfuric acid. ChromAR 1000 (Mallinckrodt) or silica gel HF_{254} (1.5 mm layer) were employed for preparative layer separations. Identity of specimens was established by infrared spectral and thin layer chromatographic comparison.

Elemental microanalytical data were provided by Dr. A. Bernhardt, Max-Planck Institut, Mülheim, Germany. Liquid analytical samples were prepared by distillation employing a 1-in. simple column. All samples submitted for analysis were colorless and exhibited a single spot on a thin layer chromatogram. Melting points were determined with a Kofler melting point apparatus. Spectra were recorded by D. C. F. and Miss K. Reimer as follows (unless otherwise noted): infrared, Beckman IR-12 in potassium bromide (solids) or neat (liquids); optical rotatory dispersion, JASCO ORD/UV-5 (dioxane solution); pmr, Varian A-60 (deuteriochloroform solution and tetramethylsilane as internal standard). Low-resolution mass spectra were determined by Mr. E. Bebee by using an Atlas CH-4B, and high-resolution mass spectra by Dr. P. Brown employing an Atlas SM-1B. Both mass spectrometers were equipped with a molecular beam type inlet system.

Methyl 4-Formylnonanoate (2).—A solution of 1-piperidinohept-1-ene (**1**, 36.3 g),[26] methyl acrylate (27.7 g, 25% excess), and acetonitrile (300 ml) was heated at reflux for 40 hr. Acetic acid (10 ml) and water (60 ml) were added and refluxing was continued for 1 hr. The solution was saturated with sodium chloride and the organic layer was washed with saturated sodium chloride solution (100 ml). Evaporation and distillation of the residue at reduced pressure gave a colorless liquid (30.0 g). A pure sample was prepared by redistillation: bp 114° (4 mm); $n^{24}D$ 1.4412; ν_{max} 1745 (broad), 1440, 1255, and 1170 cm^{-1}; pmr δ 3.7 (3 H, methyl ester) and 9.54 (1 H, J = 4 cps, aldehyde).

The 2,4-dinitrophenylhydrazone crystallized from methanol as yellow needles, mp 70.5–72°.

Anal. Calcd for $C_{17}H_{24}N_4O_6$: C, 53.67; H, 6.36; N, 14.73. Found: C, 53.69; H, 6.52; N, 14.74.

5-Pentyl-3,4-dihydropyran-2-one (3).—Enough methanol and tetrahydrofuran were added to a mixture of methyl 4-formylnonanoate (5 g) and aqueous (40 ml) sodium carbonate (2.5 g) to give a homogeneous solution. After 3 hr at room temperature, the solvent was evaporated at reduced pressure until a clear solution resulted. The solution was washed with ether (two 50-ml portions) and acidified with 10% hydrochloric acid. The precipitated oily layer was extracted with ether (two 50-ml portions) and the combined ethereal extract was washed with water (50 ml) and evaporated at reduced pressure to yield crude acid **2b**. The acid (3.7 g) was heated for 24 hr at reflux in benzene (100 ml) containing *p*-toluenesulfonic acid (0.1 g), with continuous separation of water. The benzene solution was washed with saturated sodium bicarbonate solution (two 25-ml portions) and water (25 ml) and concentrated at reduced pressure, and the residue was distilled *in vacuo* to yield enol lactone **3** (2.7 g). An analytical sample was prepared by redistillation: bp 102–103° (1.5 mm); $n^{24}D$ 1.4648; ν_{max} 1770 (carbonyl), 1680 (olefin), 1350, 1150, 1090, and 940 cm^{-1}; pmr δ 6.4 (quintet, 1 proton, J = 1 cps, vinyl proton).

Anal. Calcd for $C_{10}H_6O_{12}$: C, 71.39; H, 9.59. Found: C, 71.24; H, 9.53.

2-Oxo-5-*n*-pentyl-6-acetoxytetrahydropyran (4). Method A.—A solution of acid **2b** (4.2 g) in ethyl acetate (150 ml) was treated for 10 min with the 2 M acetic anhydride and 2 × 10^{-3} M perchloric acid reagent described by Edwards and Rao.[11a] The solution was washed with saturated sodium bicarbonate (150 ml) and concentrated at reduced pressure, and the residue was distilled *in vacuo* to yield lactol acetate **4** (3.4 g) as a colorless liquid. A pure sample was obtained by redistillation: bp 160–161° (4.0 mm); $n^{24}D$ 1.4569; ν_{max} 2920, 1770 (broad), 1225, and 1120 cm^{-1}; pmr δ 2.18 (s, 3 H, acetate methyl), 6.28 (d, J = 4 cps) integrating as one proton, and 6.58 (d, J = 2 cps); mass spectrum m/e (rel intensity) 168 (M − 60, 35), 156 (21), 140 (16), 112 (100), 96 (70), and 84 (72).

Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 62.78; H, 8.68.

Method B.—A mixture of acid **2b** (1.6 g), isopropenyl acetate (3 ml), and 72% perchloric acid (2 drops)[11b] was held for 15 min at reduced pressure on a rotary evaporator to remove acetone. The reaction mixture was diluted with ethyl acetate (30 ml), washed with saturated sodium bicarbonate solution, and concentrated under reduced pressure, and the oily residue was distilled *in vacuo* to provide 1.0 g of lactone **4**.

Method C.—A solution of acid **2b** (1.6 g) and acetic anhydride (10 ml)[11c] was heated at reflux under nitrogen for 2 hr. Sodium acetate (0.03 g) was added and heating at reflux was continued for 2 hr. The acetic anhydride was removed azeotropically using toluene and the resulting oil was distilled *in vacuo* to yield lactone **4** (0.6 g) and a mixture (0.8 g) of lactones **3** and **4**.

5-Pentylpyran-2-one (5). Procedure A. Palladium on Carbon.—A mixture of commercial-grade (Eastman) *p*-cymene (50 ml) and 10% palladium on carbon (1 g) was dried by azeotropic removal of solvent (10 ml). To the mixture was added 5-pentyl-3,4-dihydropyran-2-one (**3**, 3.0 g), and heating at reflux was continued for 6.5 hr. Nitrogen was bubbled through the mixture. Following concentration by distillation to *ca.* 25 ml the solution was chromatographed on silica gel (90 g). Elution with 4:1 hexane–ethyl acetate gave 1.7 g of crude product. A pure specimen of pyrone **5** was obtained by redistillation: bp 101–102°

(25) With lower boiling δ enol lactones, halogenation followed by dehydrohalogenation has been extensively used for obtaining 2-pyrones: N. P. Shusherina, R. Y. Levina, E. A. Luk'yanets, and I. S. Trubnikov, *J. Gen. Chem. USSR*, **32**, 3534 (1962); N. P. Shusherina, R. Y. Levina, Z. S. Sidenko, and M. Y. Lur'e, *Zhur. Obshch. Khim.*, **29**, 403 (1959); N. P. Shusherina, E. A. Luk'yanets, and R. Y. Levina, *J. Gen. Chem. USSR*, **34**, 18 (1964); N. P. Shusherina, E. A. Luk'yanets, and R. Y. Levina, *J. Org. Chem. USSR*, **1**, 2266 (1965). However, application of these methods to buf-20(21)-enolide **16** proved unworkable.

(26) R. Dulou, E. Elkik, and A. Veillard, *Bull. Soc. Chim. Fr.*, 967 (1960).

(0.8 mm); λ_{max} 298 mμ (ε 5150); mass spectrum *m/e* (rel intensity) 166 (M^+, 57), 138 (7), 110 (52), 109 (100), 99 (26), 95 (14), 82 (28), 81 (33), and 53 (45); ν_{max} 1755 and 1730 (pyrone carbonyl doublet), 1650 and 1550 (vinyl), and 1120 and 830 cm^{-1}; pmr δ 2.5 (triplet, 2 H, *J* = 7 cps, benzylic protons), 6.15 d, *J* = 11 cps, H_a), 7.2 (two doublets, *J* = 11 and 3 cps, H_b), and 7.23 (d, *J* = 3 cps, H_c).

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49; mol wt, 166.099373 [mass spectrum *m/e* 166 (M^+)]. Found: C, 72.50; H, 8.68; mol wt, 166.105060. Calcd for $C_6H_5O_2$: mol wt, 109.028952. Found: mol wt, 109.031643 (mass spectrum *m/e* 109).

Procedure B. N-Bromosuccinimide.—A mixture of 5-pentyl-3,4-dihydropyran-2-one (**3**, 0.3 g), N-bromosuccinimide (0.36 g), benzoyl peroxide (0.05 g), and carbon tetrachloride (10 ml) was heated at reflux for 1 hr. The mixture was cooled and washed with water (two 10-ml portions), and solvent was removed under reduced pressure. The oily residue was heated under a nitrogen atmosphere in dimethylformamide (5 ml) containing lithium bromide (0.52 g) at 100° for 2 hr. The solution was partitioned between water and ethyl acetate. The ethyl acetate layer was washed with water (four 20-ml portions) and evaporated at reduced pressure to yield a brown oil (0.35 g), which was chromatographed on silica gel (3 g). Elution with 4:1 hexane–ethyl acetate gave 0.14 g of pyrone **5**.

Upon standing for *ca.* 2 weeks at room temperature in a sealed vial protected from light, pyrone **5** became yellow and a more polar contaminant was detected by thin layer chromatography.

3β-Acetoxy-20-cyano-21-norpregna-5,17(20)-diene (6).—A solution of diethyl cyanomethylphosphonate (71.0 g) in tetrahydrofuran (250 ml) was added dropwise under nitrogen to a stirred suspension of sodium hydride (8.5 g of 51% in oil) in tetrahydrofuran (400 ml) at ice-bath temperature. The clear yellow solution was stirred for 0.5 hr. A solution of 3β-acetoxy-17-oxoandrost-5-ene (20.0 g) in tetrahydrofuran (200 ml) was added and the resulting solution was allowed to stand at room temperature for 16 hr. The mixture was concentrated under reduced pressure to *ca.* 200 ml, poured into water (600 ml), and extracted with ethyl acetate. The ethyl acetate layer was washed with water and evaporated under reduced pressure to a pasty solid contaminated with mineral oil, which crystallized from ethyl acetate–hexane as needles (8.6 g). The filtrate was concentrated under reduced pressure and the residue was extracted with several portions of boiling hexane (500 ml total). Concentration of the hexane, followed by cooling, yielded a colorless solid which crystallized from methanol as needles (7.4 g) and was identical with the product from the first crop. Two recrystallizations from methanol afforded a pure sample as needles: mp 228–231°; $[\alpha]_D$ −84°; ν_{max} 2218 (C≡N), 1735, and 1250 cm^{-1} (acetate); pmr δ 0.85 (3 H, C-18 methyl), 1.08 (3 protons, C-19 methyl), 2.05 (3 protons, acetate), 5.0 (triplet, 1 H, *J* = 3 cps, H-20), and 5.3 (multiplet, 1 H, H-6).

Anal. Calcd for $C_{23}H_{31}NO_2$: C, 78.14; H, 8.84; N, 3.96. Found: C, 78.07; H, 8.67; N, 4.16.

3β-Acetoxy-20-cyano-21-norpregna-5-ene (7a).—A mixture of diene **6** (16.2 g) and 5% palladium on calcium carbonate (2 g) in tetrahydrofuran (400 ml) was hydrogenated for 24 hr. The solution was filtered through Celite and evaporated under reduced pressure to a white solid (16.0 g), mp 188–189.5°. The crystallizations from methanol afforded a pure sample as fluffy needles: mp 195–196°; ν_{max} 2250 (C≡N), 1735, and 1240 cm^{-1} (acetate); RD (24°, *c* 0.505) $[\alpha]_{650}$ −39.6°, $[\alpha]_{589}$ −51.5°, $[\alpha]_{450}$ −106.9°, $[\alpha]_{350}$ −277.7°, $[\alpha]_{300}$ −376.2°, and $[\alpha]_{250}$ −782.2°; pmr δ 0.67 (3 H, C-18 methyl), 1.08 (3 H, C-19 methyl), and 2.05 (3 H, acetate).

Anal. Calcd. for $C_{23}H_{33}NO_2$: C, 77.70; H, 9.36; N, 3.94. Found: C, 77.53; H, 9.52; N, 3.90.

3β-(Tetrahydropyran-2′-yloxy)-20-cyano-21-norpregna-5,17(20)-diene (6b).—A solution prepared from dihydropyran (1.85 g), *p*-toluenesulfonic acid (0.1 g), benzene (250 ml), tetrahydrofuran (50 ml), and 3β-hydroxy-20-cyano-21-norpregna-5,17(20)-diene (6.0 g, obtained from saponification of acetate **6a**) was stirred at room temperature for 24 hr. The solution was concentrated under reduced pressure to *ca.* 150 ml, washed with 10% sodium carbonate solution (400 ml) and water (50 ml), and evaporated at reduced pressure to a colorless solid which crystallized from methanol (yield 6.3 g). Two recrystallizations from 100% ethanol gave an analytical sample: mp 181–188°; ν_{max} 2960, 2220 (C≡N), 1645 (C=C), and 1040 cm^{-1}; pmr δ 0.84 (singlets for C-18 methyl of *cis* and *trans* isomers), 0.95, 1.0 (3 H, C-19 methyls), 4.7 (broad, 1 H), 5.1 (triplet, 1 H, *J* = 2 cps, H-20), and 5.3 (broad, 1 H, H-6).

Anal. Calcd for $C_{26}H_{37}NO_2$: C, 78.92; H, 9.44; N, 3.54. Found: C, 79.1; H, 9.24; N, 3.28.

3β-(Tetrahydropyran-2′-yloxy)-20-cyano-21-norpregna-5-ene (7b).—Nitrile **6b** (1.0 g) was hydrogenated over 5% palladium on calcium carbonate (0.4 g) as described for **6a** to yield **7b** (0.7 g). Crystallization from 100% ethanol followed by two recrystallizations from methanol afforded an analytical sample: mp 158–160°; ν_{max} 2940, 2245 (C≡N), 1450 (doublet), and 1040 cm^{-1}; pmr δ 0.62 (3 H, C-18 methyl), 1.0 (3 H, C-19 methyl), 4.7 (broad, 1 H), and 5.3 (broad, 1 H, H-6).

Anal. Calcd for $C_{26}H_{39}NO_2$: C, 78.54; H, 9.89; N, 3.52. Found: C, 78.37; H, 9.70; N, 3.36.

3β-Acetoxypregna-5-en-21-oic Acid (7d).—A solution of nitrile **7a** (15 g) and potassium hydroxide (10 g) in ethylene glycol (400 ml) was heated at reflux under a nitrogen atmosphere until evolution of ammonia ceased. The warm reaction mixture was poured over ice (1 l.), acidified with 5 *N* sulfuric acid, and filtered. The resulting acid **7c** was dissolved in 2:1 acetic anhydride–acetic acid and allowed to stand for 8 hr. The acetylation mixture was poured into water (300 ml). After 12 hr the crude product (11.0 g) was collected by filtration. Three recrystallizations from acetone–hexane led to a pure sample as needles: mp 187–187.5°; ν_{max} 1735 (acetate), 1710 (acid), 1240, and 1040 cm^{-1}; RD (24°, *c* 0.504) $[\alpha]_{650}$ −39.7°, $[\alpha]_{589}$ −51.6°, $[\alpha]_{450}$ −96.2°, $[\alpha]_{350}$ −176.5°, $[\alpha]_{300}$ −327.4°, and $[\alpha]_{250}$ −719.2°; pmr δ 0.67 (3 H, C-18 methyl) and 1.08 (3 H, C-19 methyl).

Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.74; H, 9.10.

3β-Acetoxypregna-5-en-21-al (7e).—A solution of oxalyl chloride (5 ml) in benzene (15 ml) was added to an ice-cold solution of carboxylic acid **7d** (3.0 g) in benzene (50 ml). The pale yellow solution was allowed to stand for 1.5 hr and solvent was evaporated under reduced pressure to a yellow solid. Traces of oxalyl chloride were removed by addition and evaporation of dry benzene (three 50-ml portions).

The acid chloride was dissolved in dry toluene (50 ml) and heated in an oil bath to 110° with palladium on barium sulfate (0.5 g of 5%). Hydrogen was then bubbled through the mixture for 2 hr. Upon cooling, the solution was filtered through basic alumina. Continued elution with benzene and removal of solvents at reduced pressure led to a colorless solid (2.4 g), mp 141–145°. Two crystallizations from hexane afforded a pure sample: mp 141–142.5° (lit. mp 141–144°); ν_{max} 2880, 1735, 1245, and 1140 cm^{-1}; RD (24°, *c* 0.504) $[\alpha]_{650}$ −44.6°, $[\alpha]_{589}$ −50.6°, $[\alpha]_{300}$ −398.8°, $[\alpha]_{274}$ −259.9°, and $[\alpha]_{250}$ −436.5°; pmr δ 0.60 (3 H, C-18 methyl), 1.08 (3 H, C-19 methyl), and 9.8 (triplet, 1 H, *J* = 2 cps, aldehyde).

Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.09; H, 9.65.

Methyl 3β-Acetoxy-21-oxochol-5-en-24-oate (8a).—A mixture of aldehyde **7e** (1 g), anhydrous potassium carbonate (2 g), piperidine (1 g), and dry toluene (50 ml) was stirred at room temperature for 3 hr. The solution was filtered and evaporated under reduced pressure to dryness. Traces of piperidine were removed by addition and evaporation of dry toluene (two 50-ml portions). To enamine **7f** in acetonitrile (75 ml) was added methyl acrylate (0.5 g) and the solution was heated at reflux for 60 hr. Acetic acid (0.2 ml) and water (4 ml) were added and heating at reflux was continued for 1 hr. The reaction mixture was cooled, washed with saturated sodium chloride solution, and concentrated under reduced pressure to an oil (1 g). The two-component oil (tlc) was separated by preparative layer chromatography with 7:3 hexane–ethyl acetate development. The two zones were scraped from the plate and eluted with ethyl acetate. The top zone led to a solid identical with starting aldehyde (0.3 g) and the lower zone yielded methyl ester **8a** (0.5 g) which crystallized as needles from hexane: mp 109–111°; ν_{max} 1740 (broad), 1255, 1225, and 1050 cm^{-1}; pmr δ 0.70, 0.75, (C-18 methyls of the C-20 epimers), 1.05 (C-19 methyl), 2.05 (3 H, acetate), 3.7 (3 H, methyl ester), 4.6 (broad, 1 H, H-6), and 9.54 (d, 1 H, *J* = 4.5 cps, aldehyde).

Anal. Calcd for $C_{27}H_{40}O_5$: C, 72.94; H, 9.10. Found: C, 73.04; H, 9.09.

3β-Acetoxy-14α-bufa-5,20(21)-dienolide (9).—A solution composed of methyl ester **8a** (0.1 g), 5% aqueous sodium carbonate (1.5 ml), methanol (1 ml), and tetrahydrofuran (2 ml) was stirred at room temperature for 1.5 hr. The organic solvents were removed at reduced pressure and the resulting aqueous mixture was

acidified with 5 *N* sulfuric acid. The mixture was extracted with ethyl acetate, and after removal of solvent a thin layer chromatographic analysis indicated that some hydrolysis of the 3-acetate group had occurred.[27] Thus the crude acid **8b** was reacetylated by treatment with 1:5 acetic anhydride–pyridine for 1 hr followed by addition of 50% acetic acid and evaporation to dryness. Acid **8b** in benzene (25 ml) containing *p*-toluenesulfonic acid (0.04 g) was heated at reflux for 12 hr with continuous separation of water. The benzene solution was washed with water. After evaporation at reduced pressure the resulting yellow solid was purified by preparative layer chromatography with 7:3 hexane–ethyl acetate development. Elution of the major zone with ethyl acetate gave lactone **9** (0.04 g), which crystallized from ethyl acetate–hexane as needles: mp 184–186°; ν_{max} 1780 (enol lactone), 1735 (acetate), 1675 (olefin), 1260, and 1020 cm^{-1}; RD (25°, *c* 0.485) $[\alpha]_{650}$ −41.2°, $[\alpha]_{589}$ −53.2°, $[\alpha]_{450}$ −84.7°, $[\alpha]_{350}$ −123.5°, and $[\alpha]_{300}$ −185.5°; pmr δ 0.60 (C-18 methyl), 1.05 (C-19 methyl), 4.6 (broad, 1 H, H-3), and 6.4 (broad singlet, 1 H, H-21).

Anal. Calcd for $C_{26}H_{36}O_4$: C, 75.69; H, 8.80. Found: C, 75.82; H, 8.62.

3β-Acetoxy-20-cyano-21-nor-5α-pregna-17(20)-ene (11).—The experimental procedure employed for obtaining nitrile **6** was repeated employing sodium hydride (12.9 g, 0.29 mmol of 54% in mineral oil), diethyl cyanomethylphosphonate (61 g, 0.35 mmol), 3β-acetoxy-17-oxo-5α-androstane (48 g, 0.15 mmol), and tetrahydrofuran (750 ml). The ketone was added during a 1-hr period and the resulting yellow solution was stirred at room temperature for 19 hr. At that point no starting material was detected by tlc and the solution was concentrated at reduced pressure to *ca.* 200 ml, diluted with water, and extracted with ethyl acetate. The combined ethyl acetate extract (400 ml) was washed successively with 5% aqueous sodium bicarbonate, water, and saturated aqueous sodium chloride. Following removal of solvent the residue was recrystallized from ethyl acetate–ligroin to yield 36 g of needles, mp 127–188°. Two impurities in trace amounts were present, as evidenced by a thin layer chromatogram. Further purification was accomplished as now summarized for the mother liquor material. The ethyl acetate–ligroin filtrate was concentrated and the viscous, oily residue was chromatographed in pentane on a column of silica gel (200 g). Elution with pentane eliminated the mineral oil and the fraction obtained with benzene was recrystallized from benzene–pentane to yield 9.6 g of nitrile **11**, which exhibited one spot on a tlc plate with 4:1 pentane–ethyl acetate mobile phase. The total yield of comparable product amounted to 89%. Two recrystallizations from ethyl acetate–pentane and another two from methanol afforded an analytical specimen as needles: mp 199–200°; ν_{max} 2210 (C≡N), 1730, 1640, and 1245 cm^{-1}.

Anal. Calcd for $C_{23}H_{33}NO_2$: C, 77.70; H, 9.36; N, 3.94. Found: C, 77.52; H, 9.45; N, 4.05.

3β-Acetoxy-20-cyano-21-nor-5α-pregnane (12a).—A mixture of olefin **11** (20 g), 5% palladium on calcium carbonate (5 g), and tetrahydrofuran (500 ml) was hydrogenated for 48 hr as reported above for preparation of nitrile **7a**. Three recrystallizations from methanol afforded an analytical sample as needles: mp 200–202°; ν_{max} 2240 (C≡N), 1725, and 1250 cm^{-1}.

Anal. Calcd for $C_{23}H_{35}NO_2$: C, 77.27; H, 9.87; N, 3.92. Found: C, 77.52; H, 9.52; N, 4.05.

3β-Acetoxy-5α-pregnan-21-oic Acid (12b). Method A. From 3β-Acetoxy-20-cyano-21-nor-5α-pregnane (12a).—Base hydrolysis of nitrile **12a** (19.5 g) was conducted for 27 hr in refluxing ethylene glycol (400 ml) containing potassium hydroxide (11 g) as described above using nitrile **7a**. The crude product was acetylated with 1:3 acetic anhydride–pyridine at room temperature. The acetylation mixture was diluted with water and extracted with ethyl acetate. Following removal of ethyl acetate the residue was dissolved in hot acetic acid and water was added to the opalescence point. Upon cooling the solid which separated was collected, washed with water, and recrystallized from methanol to yield 17.1 g, mp 190–195° (lit.[28] mp 191–193°), of carboxylic acid **12b**. The acid displayed one spot on a thin layer chromatogram with 4:1:0.5 pentane–ethyl acetate–acetic acid and was used without further purification.

Method B. From 3β-Acetoxy-5α-androstane-17β-carboxylic Acid (13).—A solution of 3β-acetoxy-5α-androstane-17β-carboxylic acid (**13**, 18 g)[29] in thionyl chloride was prepared. After 3 hr at room temperature the thionyl chloride was removed by slow distillation followed by addition and evaporation under reduced pressure of dry benzene. The crude residue was crystallized from ligroin to give the pure acid chloride, and the mother liquor was treated with 1:1 water–acetic acid. By the latter means 2.7 g of acid **13** was recovered. A solution of the recrystallized acid chloride in ether (400 ml) was added dropwise to an ethereal solution of diazomethane and stirred for 14 hr, after which the solvent was distilled. The yellow, oily residue crystallized from ligroin to give three crops of the crude diazo ketone, which were combined and chromatographed in 19:1 pentane–ethyl acetate on a column of silica gel (200 g). Elution with 17:3 pentane–ethyl acetate and recrystallization from pentane afforded 3β-acetoxy-20-oxo-21-diazo-5α-pregnane[5a] (5.6 g), mp 133–137°. Additional diazo ketone was obtained from the ligroin mother liquor to provide a total yield of 8.1 g (49%): ν_{max}^{Nujol} 2100, 1735, and 1610 cm^{-1}.

Anal. Calcd for $C_{23}H_{34}N_2O_3$: C, 71.47; H, 8.87. Found: C, 71.67; H, 8.76.

A solution of the diazo ketone (5.6 g) in dioxane (30 ml) was added dropwise over 20 min to a stirred suspension of freshly prepared silver oxide from 4 g of silver nitrate in dioxane (50 ml) containing 10% aqueous sodium thiosulfate (40 ml). After 45 min at 60°, *ca.* 90% of the calculated volume of nitrogen had been evolved. The mixture was cooled, diluted with 10% potassium carbonate solution (25 ml), and extracted with 1:1 pentane–ether (200 ml). The dark ethereal layer was extracted with 10% potassium carbonate (four 50-ml portions). The combined basic extract was cooled and carefully acidified with 6 *N* nitric acid. The aqueous mixture was extracted with chloroform (three 150-ml portions) and the organic layer was filtered through a layer of Celite. The chloroform solution was extracted with 10% potassium carbonate (four 30-ml portions) and the aqueous extract was cooled and acidified with 6 *N* hydrochloric acid. Again the precipitated acid was extracted with chloroform. Removal of solvent gave a glassy residue which solidified upon trituration with pentane. Reacetylation with 1:1 acetic anhydride–pyridine (at room temperature for 24 hr, followed by hydrolysis with water–acetic acid) and crystallization from water–acetic acid gave acid **12b** (3.0 g, 54%), mp 187–193°.

Method C. From 3β-Acetoxypregna-5-en-21-oic Acid (7d).—A specimen of carboxylic acid **7d** (5.0 g) in tetrahydrofuran (150 ml) was hydrogenated employing 10% palladium on carbon (0.75 g) as catalyst. After 24 hr, catalyst (0.5 g) was added and hydrogenation was resumed until complete as evidenced by pmr. Recrystallization from acetone–hexane gave 2.9 g (with another 2.0 g recovered from the mother liquor) of carboxylic acid **12b**, shown to be homogeneous by tlc. Two recrystallizations from acetone–hexane gave a product melting at 190–191°.

The specimens of carboxylic acid **12b** prepared by methods A, B, and C were shown to be identical, thereby confirming the 17β side-chain orientation.

3β-Acetoxy-21-formyl-5α-pregnane (12e).—The treatment of acid **12b** (2.7 g)[28] with oxalyl chloride followed by hydrogenation over 10% palladium on barium sulfate as described for aldehyde **7e** gave aldehyde **12e** (1.9 g, 72%). Crystallization from hexane afforded an analytical sample: mp 125–128°; ν_{max} 2940, 1740 (broad), 1255, and 1040 cm^{-1}; RD (25°), *c* 0.450) $[\alpha]_{400}$ −16.0°, $[\alpha]_{305}$ −66.7°, and $[\alpha]_{260}$ +11.1°; pmr δ 0.62 (3 H, C-18 methyl), 0.86 (3 H, C-19 methyl), 2.18 (3 H, acetate), and 9.8 (triplet, 1 H, J = 2 cps, aldehyde).

Anal. Calcd for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.81; H, 9.96.

Later the above Rosenmund reduction was somewhat improved by carefully regulating with a water aspirator the hydrogen flow while maintaining a slightly reduced internal pressure. The reaction mixture temperature was maintained (oil bath) at 90–93° for 2 hr. Yields of aldehyde **12e** ranged from 86 to 96%, but in two experiments on a 10-g (acid **12b**) scale the yield dropped to *ca.* 60%.

Methyl 3β-Acetoxy-20-formyl-21-nor-5α-cholanate (15).—The piperidino enamine of aldehyde **12e** (2.7 g) was prepared and alkylated with methyl acrylate as summarized in the experiment leading to ester **8a**. The resulting oil (2.5 g) was dissolved in 19:1 hexane–ethyl acetate and adsorbed on a column of silica gel

(27) Higher concentrations of tetrahydrofuran in the saponification-step suppressed hydrolysis of the 3 acetate and eliminated need for reacetylation.

(28) R. E. Marker, H. Crooks, E. Jones, and A. Shabica, *J. Amer. Chem. Soc.*, **64**, 1276 (1942).

(29) P. Kurath and M. Capezzuto, *ibid.*, **78**, 3527 (1956).

(150 g). Continued elution with the same solvent resulted in some (0.45 g) recovery of aldehyde **12e**. Elution with 9:1 hexane–ethyl acetate afforded methyl ester **15** (1.5 g). An analytical sample was obtained by preparative chromatography on ChromAR 1000 with 17:3 hexane–ethyl acetate development (band eluted with ether) followed by crystallization from ethyl acetate–hexane: mp 123–126°; ν_{max} 2960, 1740 (broad), 1390, and 1260 cm^{-1}; pmr δ 0.62 (singlets, 3 H, C-18 methyl of C_{20} epimers), 0.7, 0.8 (3 H, C-19 methyl), 2.05 (3 H, acetate), 3.65 (3 H, methyl ester), and 9.5 (d, J = 4 cps, aldehyde).

Anal. Calcd for $C_{27}H_{42}O_5$: C, 72.61; H, 9.48. Found: C, 72.91; H, 9.26.

In somewhat larger scale experiments, molecular sieve type 4A (3.5 g/3 g of aldehyde **7e**) was employed in place of anhydrous potassium carbonate with comparable results. The crude product in 2:1 pentane–benzene was chromatographed on a column of silica gel (250 g/3 g of starting aldehyde). Fractions eluted by 9:1 pentane–ethyl acetate contained aldehyde **12e** and those elated with 17:3 pentane–ethyl acetate contained methyl ester **15**. Yields of methyl ester **15** ranged from 45 to 49%.

3β-Acetoxy-5α-14α-buf-20(21)-enolide (16).—To a solution of methyl ester **15** (0.55 g) in tetrahydrofuran (15 ml)–methanol (6 ml) was added 10 ml of 5% aqueous sodium carbonate. The mixture was stirred at room temperature for 3 hr, neutralized with 6 *N* hydrochloric acid and concentrated to *ca.* 10 ml using a rotating evaporator. The aqueous phase was acidified with 6 *N* hydrochloric acid and extracted with ethyl acetate. The combined ethyl acetate extract was extracted with 10% aqueous potassium carbonate. Next, the combined aqueous solution was acidified with 6 *N* hydrochloric acid and extracted with ethyl acetate. The ethyl acetate extract was washed with water and evaporated to yield 0.38 g (72%) of colorless, crystalline carboxylic acid exhibiting one spot on a thin layer chromatogram with 4:1:0.2 pentane–ethyl acetate–acetic acid mobile phase. A specimen (0.53 g) prepared in the same manner was dissolved in dry benzene (50 ml) containing *p*-toluenesulfonic acid (0.06 g). The solution was heated at reflux for 25 hr employing a Dean–Starke trap containing molecular sieve type 4-A. The solution was cooled and added to a column of silica gel (7 g). Elution with benzene (400 ml) gave 0.37 g (73%) of colorless crystals, mp 181–184°. The product **16** appeared as a single spot on a thin layer chromatogram with 4:1 pentane–ethyl acetate mobile phase. Recrystallization from ethyl acetate–hexane afforded an analytical sample as needles: ν_{max} 2940, 1760 (enol lactone carbonyl), 1740 (acetate carbonyl), 1670 (olefin), 1260, and 1140 cm^{-1} (doublet); RD (25°, *c* 0.515) $[\alpha]_{420}$ 0° (slightly negative 420–650°), $[\alpha]_{350}$ +27.2°, $[\alpha]_{320}$ +58.3°, and $[\alpha]_{300}$ +166.9°; pmr δ 0.60 (3 H, C-18 methyl), 0.83 (3 H, C-19 methyl), 2.05 (3 H, acetate), and 6.36 (broad, 1 H, H-21).

Anal. Calcd for $C_{26}H_{38}O_4$: C, 75.32; H, 9.24. Found: C, 75.27; H, 8.99.

3β-Acetoxy-5α-14α-bufa-20,22-dienolide (17).—An intimate mixture of enol lactone **16** (0.10 g) and sulfur (0.20 g) was heated at 221–227° under a nitrogen atmosphere for 0.5 hr. After 1 min in the required temperature range, evolution of hydrogen sulfide was detected using moist lead acetate paper and by odor. After cooling, the mixture was dissolved in carbon disulfide. A thin layer chromatogram with 4:1 pentane–ethyl acetate mobile phase indicated a major component accompanied by a lesser quantity of starting material **16** and a more polar side product. The carbon disulfide solution was chromatographed on a column of silica gel (20 g). The oily fraction (**17**) eluted by 2:1 benzene–ether weighed 0.06 g (60%) and was essentially pure by tlc. The analytical sample was further purified by preparative tlc on ChromAR 1000 with 10:1 pentane–ethyl acetate mobile phase and recrystallized twice from methanol to afford needles: mp 194–195°; λ_{max} 300 mμ (ϵ 5500); ν_{max} 1740, 1640, 1540, 1250, 835, and 800 cm^{-1}; pmr δ 0.53 and 0.83 (C-18 and -19 methyls), 4.7 (diffuse, H-3α), 6.25 (d, J = 10.5 cps, H-23), and 7.20–7.41 (complex, 2-pyrone ring protons).[30]

Anal. Calcd for $C_{26}H_{38}O_4$: C, 75.69; H, 8.80; mol wt, 412. Found: C, 75.75; H, 9.03; mol wt, 412 (mass spectrum).

Registry No.—**2a**, 23079-69-8; 2,4-dinitrophenylhydrazone of **2a**, 23330-09-8; **3**, 23079-70-1; **4**, 23330-10-1; **5**, 23079-71-2; **6a**, 2312-10-9; **6b**, 23330-13-4; **7a**, 23330-14-5; **7b**, 23330-15-6; **7d**, 23330-16-7; **7e**, 16934-54-6; **8a**, 23367-52-4; **9**, 23017-35-8; **11**, 23330-19-0; **12a**, 23017-30-3; **12e**, 23017-32-5; **15**, 23017-33-6; **16**, 23017-34-7; **17**, 23017-36-9; 3β-acetoxy-20-oxo-21-diazo-5α-pregnane, 23330-24-7.

(30) Decoupling experiments showed the doublet at δ 6.18 coupled to the δ 7.20–7.41 signals and further supported the structural assignment.

Bufadienolides. 8. 12(13→14)*abeo* Skeletal Rearrangements[1]

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Several methods were developed for converting isodigitoxigenin (**2a**) into methyl acetals **4b** and **4c**. Of these, methanolysis (followed by acetylation) of isodigitoxigenin in the presence of *p*-toluenesulfonic acid proved most useful. Each isomer reached an equilibrium corresponding to *ca.* 3:1 acetal **4c** to **4b** within 15 min in benzene containing *p*-toluenesulfonic acid. Addition of dihydropyran to the equilibrium mixture resulted in excellent conversion into vinyl ether **5a**. Heating either acetal **4b** or **4c** in benzene containing *p*-toluenesulfonic acid led to a skeletal rearrangement culminating in formation of C-norcardenolide **6**. In addition to results of physical measurements, the structure of spiran **6** was confirmed by degradation to methyl ketone **8**. Similar rearrangement of isodigitoxigenin gave spiran **9** accompanied by C-norcardenolide **6**. Treating lactone **9** with *p*-toluenesulfonic acid in methanol–water provided acetals **10a** and **10b**, which on further contact with *p*-toluenesulfonic acid in refluxing benzene gave lactone **9** and cardenolide **6**. Evidence underlying the stereochemical assignments noted for structures **4**, **9**, and **10** was also discussed.

Selection of digitoxigenin (**1a**) as a starting point for total synthesis of isobufalin and bufalin required a number of accessory experiments. Protection of the 14-oxygen substituent during reconstruction of the digitoxigenin lactone ring seemed best performed by utilizing isodigitoxigenin (**2a**), which could be converted to hemiacetal **4a**. Model experiments could then be undertaken to determine the direction of cleavage reactions which might be anticipated with acetals such as **2b** and **4c**. Accordingly, digitoxin (**1b**)[3a] was con-

(1) (a) Part 7: G. R. Pettit, D. C. Fessler, K. Paull, P. Hofer, and J. C. Knight, *J. Org. Chem.*, **35**, 1398 (1970). 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. Summaries, in part, of the present investigation have been presented: (b) T. R. Kasturi, G. R. Pettit, and J. Occolowitz, *Chem. Commun.*, 334 (1967); (c) G. R. Pettit, J. C. Knight, and T. R. Kasturi, *ibid.*, 688 (1967).

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