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# Chemistry and Stereochemistry of 16-Substituted 17,20;20,21-Bismethylenedioxy Steroids[1]

BY W. T. MORELAND, D. P. CAMERON, R. G. BERG AND C. E. MAXWELL, III

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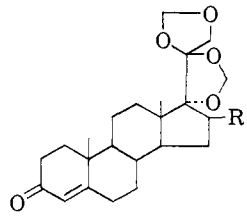
The preparation of isomeric 17,20;20,21-bismethylenedioxy (BMD) derivatives from 16β-bromo-17α,21-dihydroxypregn-4-ene-3,20-dione is reported. Evidence indicating that these represent 20R- and 20S-forms of the BMD group is presented and tentative assignment of the 20R-configuration to the familiar levorotatory BMD species is made. Displacements of 16β-bromine from the 20R-isomer are described which provide a means for introducing new 16β-substituents.

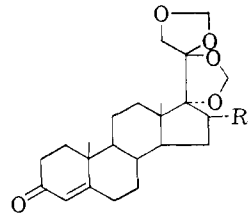
In the course of a study of corticosteroid structure-activity relationships,[2] it became desirable to find new means for introducing substituents in position 16.[3] A survey of possible methods suggested that protection of the side-chain as the 17,20;20,21-bismethylenedioxy (BMD) derivative[4] in a steroid having bromine at C-16 might provide a useful intermediate for this purpose. It appeared that if displacements of halogen could be accomplished at this stage, a series of new derivatives might become available which could be converted to potentially active corticoids[5] in relatively few steps. Accordingly, investigation of the preparation and properties of 16β-bromo-17,20;20,21-bis-methylenedioxypregn-4-ene-3-one (I)[8] was undertaken.

Treatment of 16β-bromo-17α,21-dihydroxypregn-4-ene-3,20-dione with aqueous formaldehyde and hydrochloric acid in chloroform or methylene chloride as originally described[4] did not give promising results, but when the organic phase was changed to a mixture of benzene and hexane, a product crystallized directly from the reaction mixture in 50% yield. This material had the high melting point, papergram mobility and negative rotation expected[4] for the desired 16β-bromo-BMD (I). Careful examination of the mother liquors revealed a second product which was isolated in fair yield under slightly modified conditions. This proved to be an isomeric, *dextrorotatory* product (II) believed to be an example of the hitherto undetected 20-epimeric BMD's.

Hydrolysis of either I or II in aqueous acetic acid in the presence of a small amount of perchloric acid furnished the starting 16β-bromodiol which was converted without isolation to the known 16α,17α-epoxy-21-hydroxypregn-4-ene-3,20-dione acetate.[9]



| 3-Ketones | R | 3-Ketals |
|---|---|---|
| I | -Br | Ia |
| III | -H | IIIa |
| V | $-OCH_3$ | |
| VI | -OH | VIa |
| VII | $-OCOCH_3$ | VIIa |
| VIII | -F | |
| IX | $-OCH(CH_3)_2$ | |
| X | (=O) | Xa |



| 3-Ketones | R | 3-Ketals |
|---|---|---|
| II | -Br | IIa |
| | -H | IVa |

The levorotatory isomer I could be related to previously encountered BMD's by hydrogenolytic removal of bromine from its 3-ethylene ketal Ia and selective hydrolysis of the resulting halogen-free ketal IIIa with aqueous methanolic sulfuric acid. The product of this hydrolysis (III) was identical with the BMD prepared directly from 17α,21-dihydroxypregn-4-ene-3,20-dione.[4,10] In a similar sequence, the dextrorotatory isomer II was converted to the ketal IIa and then to a bromine-free ketal IVa. In this series, however, selective hydrolysis of the ketal was not realized, and IVa was completely hydrolyzed to 17α,21-dihydroxypregn-4-ene-3,20-dione under conditions which smoothly transformed IIIa into III. A comparison of molecular rotations for the two series of isomers is shown in Table I.

Halogen-free displacement products were readily obtained from the levorotatory isomer I provided electrophilic assistance from silver ions was furnished. Although brief warming of I in methanolic silver nitrate was sufficient to precipitate silver bromide, examination of the steroidal product suggested a mixture of nitrate ester and methoxy compound which proved impractical to separate. Substitution of silver perchlorate, however, avoided

(1) Portions of this work have been reported in earlier communications: W. T. Moreland, R. G. Berg and D. P. Cameron, *J. Am. Chem. Soc.*, **82**, 504 (1960); W. T. Moreland, R. G. Berg, D. P. Cameron, C. E. Maxwell, III, J. S. Buckley and G. D. Laubach, *Chemistry & Industry*, 1084 (1960).

(2) (a) Background literature is discussed in L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp. 682–701. (b) More recent summaries of corticoid structure–activity include W. E. Dulin, F. L. Schmidt and S. C. Lyster, *Proc. Soc. Exptl. Biol. Med.*, **104**, 345 (1960); I. Ringler, S. Mauer and E. Heyder, *ibid.*, **107**, 451 (1961).

(3) Since completion of this work there have been additional reports of: (a) 16β-fluorine, D. E. Ayer and W. P. Schneider, *J. Am. Chem. Soc.*, **82**, 1249 (1960); (b) 16α-fluorine, B. J. Magerlein, R. D. Birkenmeyer and F. Kagan, *ibid.*, **82**, 1252 (1960); (c) 16α-methoxy, S. Bernstein, M. Heller and S. M. Stolar, *Chemistry & Industry*, 516 (1961).

(4) R. E. Beyler, R. M. Moriarty, F. Hoffman and L. H. Sarett, *J. Am. Chem. Soc.*, **80**, 1517 (1958); *J. Org. Chem.*, **26**, 2421 (1961).

(5) In spite of the essentially equivalent activities of 16α- and 16β-methyl derivatives,[2] it was apparent from the deleterious effects of 16β-chlorine[6] and 16β-acetoxyl[7] that configuration of the new substituents might be of considerable importance and that it would be most desirable to obtain members in the 16α-series.

(6) R. E. Beyler and F. Hoffman, *J. Org. Chem.*, **21**, 572 (1956).

(7) S. Bernstein, M. Heller and S. M. Stolar, *J. Am. Chem. Soc.*, **81**, 1256 (1959).

(8) Nomenclature where possible conforms with the "IUPAC Definitive Rules for Nomenclature of Steroids," *ibid.*, **82**, 5577 (1960).

(9) P. L. Julian, E. W. Meyer, W. J. Karpel and I. R. Waller, *ibid.*, **72**, 5145 (1950).

(10) R. E. Beyler and L. H. Sarett, U. S. Patent 2,888,457 (May 26, 1959).

such mixtures and this salt in refluxing methanol or aqueous acetone smoothly converted I to, respectively, the 16β-methoxy-BMD V or the 16β-hydroxy analog VI. Similarly, silver acetate in refluxing acetic acid gave the 16β-acetoxy compound VII and silver fluoride in 2-propanol furnished the 16β-fluoro-BMD VIII accompanied by a small amount of the isopropoxy derivative IX. By contrast, the dextrorotatory isomer II was completely unreactive under similar conditions. When treatment sufficiently vigorous to remove bromine was used, there was disruption of the molecule to unrecognizable products.

TABLE I

ISOMERIC BMD DERIVATIVES

| Substituents 3- | 16- | Levorotatory series Compound | $M_D$ | Dextrorotatory series Compound | $M_D$ |
|---|---|---|---|---|---|
| Ketone | Br | I | −210 | II | +464 |
| Ketal | Br | Ia | −471 | IIa | +313 |
| Ketone | H | III | − 74 | .. | ... |
| Ketal | H | IIIa | −512 | IVa | + 38 |

The products V, VI and VII were shown to have identical stereochemistry by interconversion; *i.e.*, acetylation of the alcohol VI furnished the acetate VII, while methylation[11] converted VI to the methoxy compound V. The fluoro and isopropoxy analogs VIII and IX were assumed to have the same configuration.[12] Evidence for the orientation at C-16 was first sought by lithium aluminum hydride reduction of the protected 16-ketone Xa (prepared by oxidation of the alcohol VI and selective ketal formation at the 3-ketone) which would be expected to give the more hindered 16β-alcohol.[13] Acetylation of the product from this reduction gave material identical with the 3-ketal VIIa prepared from the silver acetate product VII. The 16β-configuration was therefore indicated for the substituents introduced in the displacement reaction. Subsequent conversion of the acetate VII to the known 16β,17α,21-trihydroxypregn-4-ene-3,20-dione 16,21-diacetate[14] confirmed this assignment.

Removal of the BMD protection with 60% formic acid[4] and subsequent treatment with methanolic sulfuric acid to cleave formates furnished 16β-methoxy- and 16β-fluoro-17,21-dihydroxypregn-4-ene-3,20-dione, respectively, from V and VIII.

The $\Delta^{9(11)}$-analog of I was prepared similarly from 16β-bromo-17α,21-dihydroxypregna-4,9(11)-diene-3,20-dione and is also indicated to be in the levorotatory series. Treatment of this product with silver perchlorate in methanol furnished the expected $\Delta^{9(11)}$-16β-methoxy-BMD which could be converted as above to 16β-methoxy-17α-21-dihydroxypregna-4,9(11)-diene-3,20-dione.

## Discussion

Formation of BMD derivatives from 17α,21-dihydroxy-20-keto steroids introduces a new asymmetric center at C-20[4] and should lead to the epimeric 20R- and 20S-forms.[15] Models show that the environment of the ring which incorporates C-17 and C-20 should be little changed in passing from one isomer to the other. The terminal ring bridging C-20 and C-21 determines isomerism and is so located that its plane is roughly parallel with the axial 13(18)-bond. Rotation at C-20 therefore brings 20-oxygen in the 20R-isomer or the C-21 methylene group in the 20S-form in close proximity to C-18. The interactions occurring between 18- and 21-hydrogens in the latter case appear to be exceptionally severe. Contrasting relationships with the smaller 16β-hydrogen on the other side appear less important.

In the previously reported examples of BMD formation only one isomer has been encountered and these have all been characterized by a large negative shift in molecular rotation relative to the original steroid.[4] The major product (I) of BMD formation in the presence of 16β-bromine was shown by direct chemical means to belong to the familiar levorotatory series, but in addition it was possible to isolate a second, *dextrorotatory* isomer II. Comparison of the latter material and the products derived from it with counterparts in the isomeric series (see Table I) shows the substantial difference in optical rotation which is the most obvious distinguishing feature. Other physical properties such as high melting points, solubility characteristics, and infrared absorption[16] which have been previously described[4] for BMD's are grossly similar. These relationships and the fact that chemical evidence limits isomerism to the side-chain make it clear that the bromo compounds II and IIa and the halogen-free product IVa are members of a new series of dextrorotatory BMD derivatives inverted at C-20 with respect to the familiar levorotatory products. The striking differences in molecular rotation are comparable to rotational changes ascribed to an analogous spiroketal inversion at C-22 in sapogenins.[18]

Evidence for the absolute configuration at C-20 in the BMD's is provided by the following observation. Infrared absorption of the 16β-hydroxy-BMD VI in 0.0026 *M* carbon tetrachloride solution shows the single sharp band at 3620 cm.$^{-1}$ typical for an *unbonded* secondary alcohol.[19] Measurements from models of VI in the 20S-form indicate a

(11) M. Neeman, M. C. Caserio, J. D. Roberts and W. S. Johnson, *Tetrahedron*, **6**, 36 (1959).

(12) This was subsequently verified for the fluoro compound VIII by the similarity of properties and activities of derived products[1] to 16β-fluoro derivatives prepared in another way.[3a]

(13) Reference 2a, p. 268; *cf.* S. Bernstein, M. Heller and S. M. Stolar, *J. Am. Chem. Soc.*, **77**, 5327 (1955).

(14) K. Heusler and A. Wettstein, *Chem. Ber.*, **87**, 1301 (1954).

(15) The system of R and S nomenclature [R. S. Cahn, C. K. Ingold and V. Prelog, *Experientia*, **12**, 81 (1956)] is preferred over the more cumbersome $\alpha_F$ and $\beta_F$ usage which can be applied as follows. Bridging to 17α-oxygen fixes one of the 20-oxygens in the α-configuration in either isomer. The remaining oxygen at C-20 can then be unambiguously designated from Fischer projections referred to terminal-ring-opened forms as proposed in "Tentative Recommendations of the Steroid Nomenclature Sub-Committee," *IUPAC Information Bulletin No. 11*, Munich, 1959, p. 50. In this system, the 20R- and 20S-forms become, respectively, 17α,20α;20$\alpha_F$,21- and 17α,20α;20$\beta_F$,21-bismethylenedioxy.

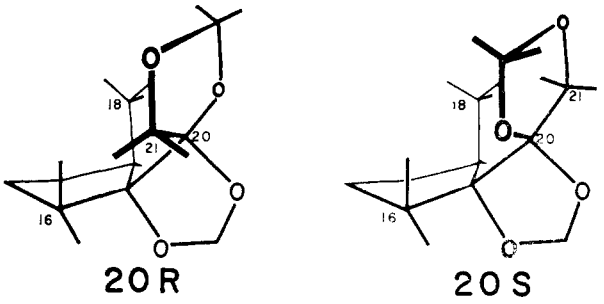
(16) The infrared spectra in both series are characterized by a number of strong bands in the C–O stretching region between 9.0 and 11.5 μ. It is of interest that the sapogenins, which similarly contain a spiroketal function, also show distinctive absorption in this region.[17]

(17) C. R. Eddy, M. E. Wall and M. K. Scott, *Anal. Chem.*, **25**, 266 (1953); R. N. Jones, E. Katzenellenbogen and K. Dobriner, *J. Am. Chem. Soc.*, **75**, 158 (1953).

(18) M. E. Wall, *Experientia*, **11**, 340 (1955); ref. 2a, pp. 826 ff.

(19) S. A. Barker, J. S. Brimacombe, A. B. Foster, D. H. Whiffen and G. Zweifel, *Tetrahedron*, **7**, 10 (1959).

minimum distance of approximately 1 Å. between hydrogen of the 16β-hydroxyl and 20-oxygen in the terminal ring. As these groups appear ideally




situated for intramolecular hydrogen bonding,[20] VI would be expected to show strongly bonded hydroxyl absorption were it in the 20S-series. Consideration of VI in its 20R-form shows the oxygen nearest 16β-hydroxyl to be that attached at C-21. Although the corresponding distance for bonding in this isomer appears to be less than 2 Å., the model suggests effective shielding between the ether oxygen and the 16-alcohol by C-21 methylene. The observed absence of intramolecular hydrogen bonding in VI therefore seems to be accommodated only in the 20R-form; accordingly, VI must be 16β-hydroxy,17α,20;20,21-bismethylenedioxy-(20R)-pregn-4-ene-3-one. It follows from the interconversions represented by the products in Table I that levorotatory BMD's in general must have the 20R-configuration and, by difference, that the dextrorotatory isomers are 20S.

It had been anticipated that displacement products realized from the 16β-bromo-(20R)-BMD I would result from approach of the entering group to the relatively unhindered α-face and would have the inverted (16α) configuration.[21] The results show, however, that the displacement proceeded exclusively with net retention of configuration and without rearrangement. This stereochemical course implies participation by one of the ether oxygens, presumably that attached at C-17 because it is the nearest even though it does not appear to be very favorably situated. The unreactive nature of 16β-bromine in the 20S-isomer II suggests that this participation occurs as shielding on the α-side which determines the configuration of the products but does not materially assist in the removal of bromine.[22] The greater reactivity of bromine in the 20R-isomer I may be the result of steric acceleration[22] due to extraordinary crowding by the nearby C-21 methylene group. The inert character of bromine in the 20S-form II must then be a consequence of exchanging this methylene group for oxygen. The now-proximal 20-ether oxygen, because of smaller size and/or altered electronic character, apparently cannot aid in halogen removal from this neopentyl-like position.

The conditions for the BMD-forming reaction are such that the ratio of isomers might be expected to be the net result of relative rates of formation and hydrolysis mediated to an unknown degree by solubility effects in the two-phase system. The familiar levorotatory (20R)-BMD's have been characterized by remarkable stability to hydrolysis by mineral acids[4] whereas, if the single 16-unsubstituted dextrorotatory example (IVa) is representative of the series, the 20S-isomers are readily susceptible to attack by acids.[23] Thus, the usual predominance of levorotatory isomer in BMD formation could be the result of greater stability under the strongly acidic conditions of preparation. This difference in ease of hydrolysis is compatible with the assignment of 20R-configuration (having less severe strain near C-18) to the more resistant form. In an extension of this, it is reasonable that bromine at C-16 should impose more strain in the 20R-isomer in which it is near C-21 than it would in the 20S-isomer where it is near 20-oxygen. The additional stress introduced by the halogen might therefore act to reduce the net difference between isomers and permit isolation of both under the altered conditions found to be favorable in this series. The present data, however, do not distinguish between possible effects of the organic-phase solvent and factors concerned with the ease of acid-catalyzed formation or cleavage so that precise evaluation of reasons for the isolation of one or both isomers is not possible at this time.

**Acknowledgments.**—We are indebted to Dr. M. W. Miller for assistance with certain of the reactions, to Mr. W. H. McMullen for the hydrogen bonding spectrum, and to Drs. J. S. Buckley and G. D. Laubach for their advice and encouragement.

## Experimental[24]

**16β-Bromo-17α,21-dihydroxypregn-4-ene-3,20-dione.**—A solution of 58.0 g. (dry basis) of 16β-bromo-17α,21-dihydroxypregn-4-ene-3,20-dione 21-acetate[9] in 552 ml. of chloroform and 2.00 l. of methanol was stirred at room temperature with a solution of 145 ml. of concentrated (37%) hydrochloric acid and 224 ml. of water for 24 hours. The organic solvents were removed under reduced pressure at an internal temperature below 30° with concurrent portionwise addition of 880 ml. of water. The resulting precipitate was filtered and washed with water to yield (dry basis) 42.9 g. (81%) of the bromoalcohol. Attempts to recrystallize this compound invariably resulted in decomposition and loss of bromine. A carefully dried sample of the material was prepared as described; m.p. 128° dec., $[\alpha]^{27}D$ +108° (*c* 2); $\lambda_{max}^{CH_2Cl_2}$ 2.81, 2.88, 5.72 μ.

*Anal.* Calcd. for $C_{21}H_{29}O_4Br$: C, 59.29; H, 6.87; Br, 18.79. Found: C, 59.33; H, 6.74; Br, 18.99.

**16β-Bromo-17α,20;20,21-bismethylenedioxypregn-4-ene-3-one. Levorotatory (20R)-Isomer (I).**—A slurry of 10.0 g. (dry weight) of moist bromohydrin from the previous step in 96 ml. of benzene, 96 ml. of 37% aqueous formaldehyde, 96 ml. of concentrated hydrochloric acid and 27 ml. of water was stirred at 37° for 3 hours. Hexane (500 ml.) was added dropwise over the next 3 hours and the resulting mixture stirred 18 hours at 37°. The crude product, isolated from the chilled mixture by filtration, was washed thoroughly with water and recrystallized from aqueous dimethylformamide to give 5.43 g. (50%) of the 16β-bromo-(20R)-BMD (I), m.p. 205° dec. Recrystallization from methanol

(20) *Cf.* L. P. Kuhn, *J. Am. Chem. Soc.*, **74**, 2492 (1952).

(21) Ref. 2a, p. 14; *cf.* G. S. Hammond, M. F. Hawthorne, J. H. Waters and B. M. Graybill, *J. Am. Chem. Soc.*, **82**, 704 (1960), and references therein for discussions of silver-ion-assisted displacements.

(22) A. Streitwieser, Jr., *Chem. Revs.*, **56**, 571 (1956).

(23) Compare the complete hydrolysis of IVa after a 90 min. reflux in *ca.* 0.2 *N* methanolic sulfuric acid with the stability reported[4] for the levorotatory isomers in *ca.* 1 *N* acid after 11 hours.

(24) Unless otherwise specified, rotations are in dioxane, ultraviolet absorptions in methanol, and infrared spectra in potassium bromide pellets. The infrared data reported in microns were obtained in a Perkin–Elmer model 21 infrared spectrophotometer; that reported in reciprocal centimeters was determined in a Beckman model IR-7 in a 1-cm. cell.

gave an analytical sample, m.p. 208° dec.; $\lambda_{max}$ 240 mμ, ε 16,700; $\lambda_{max}$ 9.24, 10.09, 10.60, 11.54, 13.00, 13.82 μ; $[\alpha]^{27}D$ − 45.2° (*c* 2).

*Anal.* Calcd. for $C_{23}H_{31}O_5Br$: C, 59.10; H, 6.69; Br, 17.10. Found: C, 59.20; H, 6.78; Br, 17.59.

**Dextrorotatory (20S)-Isomer (II).**—In a similar run, unchanged except that the proportion of benzene was increased 5-fold and the hexane (270 ml.) was added after 24 hours, the mixture was stirred an additional 48 hours at room temperature and the organic layer separated, washed with water and concentrated to dryness *in vacuo*. Crystallization of the residue from 120 ml. of methanol gave a first crop of 2.67 g. (24.4%) of I, m.p. 210° dec. Concentration to 45 ml. provided a second crop of 2.28 g. (20.8%), m.p. 182–184°. Recrystallization of the latter from dimethylformamide containing 3% water gave a first crop (0.80 g.), m.p. 176–196°, $[\alpha]^{26}D$ +43°. Further dilution with water furnished 1.08 g. of a lower melting, *dextrorotatory* isomer II, m.p. 182° dec., $[\alpha]^{26}D$ + 100°. Recrystallization from acetonitrile gave a sample for analysis, m.p. 185° dec., $[\alpha]^{26}D$ +100° (*c* 3.7); $\lambda_{max}$ 240 mμ, ε 17,100; $\lambda_{max}$ 9.23, 10.14, 10.57, 11.57, 13.09, 13.88 μ.

*Anal.* Calcd. for $C_{23}H_{31}O_5Br$: C, 59.10; H, 6.69; Br, 17.10. Found: C, 59.16; H, 6.88; Br, 17.22.

**Conversion of II to I.**—A solution of 2.0 g. of the dextrorotatory isomer II, $[\alpha]^{25}D$ +100°, in 9 ml. of methylene chloride was treated with 7.7 ml. each of concentrated hydrochloric acid and 37% aqueous formaldehyde and then 60 ml. of hexane was added over 1 hour. After 48 hours at room temperature, filtration gave 0.75 g. of material, m.p. 202° dec., $[\alpha]^{27}D$ −19°, indistinguishable from pure **I**. An additional 1.2 g. of mixed isomers, m.p. 185–186° dec., $[\alpha]^{27}D$ +2.7°, was obtained from the organic layers after evaporation and recrystallization of the residue from acetonitrile.

**Conversion of I and II to 16α,17α-Epoxy-21-hydroxypregn-4-ene-3,20-dione Acetate.**—Parallel reactions using 1.4 g. of I and II (plus a separate control with 1.27 g. of the original bromohydrin) *in* 15 ml. of glacial acetic acid, 5 ml. of water and 2 ml. of ethylene glycol with 0.1 ml. of 70% aqueous perchloric acid gave, after 3 hours at 95° and dilution with 200 ml. of water, crude products which were further treated for 18 hours at room temperature with equal volumes (10 ml. per g.) of acetic anhydride and pyridine. Water was added to destroy excess anhydride and the resulting mixtures were dissolved in 2.5 volumes of acetone and refluxed briefly with excess potassium acetate. In each case, dilution with water gave products having infrared absorption and papergram mobility identical with that of authentic 16α,17α-epoxy-21-hydroxypregn-4-ene-3,20-dione acetate.[9] The yields were: from I, 67% (m.p. 129–135°); from II, 68% (m.p. 126–132°); from the control, 50% (m.p. 141–148°).

**16β-Bromo-17α,20;20,21-bismethylenedioxy-3,3-ethylenedioxypregn-5-ene. Levorotatory (20R)-Isomer (Ia).**—Twenty grams of the levorotatory isomer I, m.p. 208–209°, was converted to the 3-ethylene ketal using the procedure described below for Xa. After 5 hours at 40–45°, the more volatile solvents were removed under reduced pressure at 25° and the resulting slurry was stirred overnight at room temperature. Filtration and recrystallization from 2-propanol–methylene chloride gave 11.6 g. (53%) of the ketal Ia, m.p. 200–205°, having no ultraviolet absorption at 240 mμ. An additional 4.0 g. (20%) of starting material was recovered from the recrystallization mother liquors on further concentration.

Two recrystallizations from cyclohexane gave the sample for analysis, m.p. 204–210°, $[\alpha]^{27}D$ −95° (*c* 0.98); $\lambda_{max}$ 9.17, 10.03, 10.62, 11.45 μ.

*Anal.* Calcd. for $C_{25}H_{35}O_6Br$: C, 58.71; H, 6.90; Br, 15.63. Found: C, 58.52; H, 6.92; Br, 15.40.

**Dextrorotatory (20S)-Isomer (IIa).**—In a similar fashion, 5 g. of the dextrorotatory isomer of 16β-bromocortexolone BMD (II, m.p. 184°) was converted to its 3-ethylene ketal. The product crystallized from the reaction mixture after 4 hours at 40–45°. This was filtered after stirring overnight at room temperature to give 2.7 g. (50%) of the bromoketal IIa, m.p. 239–246°, having no ultraviolet absorption at 240 mμ. Two recrystallizations from 2-propanol–methylene chloride gave the analytical sample, m.p. 245–247°, $[\alpha]^{28}D$ +61° (*c* 1.0); $\lambda_{max}$ 9.18, 10.15, 10.52, 11.54 μ.

*Anal.* Calcd. for $C_{25}H_{35}O_6Br$: C, 58.71; H, 6.90; Br, 15.63. Found: C, 58.52; H, 6.89; Br, 15.80.

**17α,20;20,21-Bismethylenedioxy-3,3-ethylenedioxypregn-5-ene. Levorotatory (20R)-Isomer (IIIa).**—A mixture of 2.5 g. of the bromo ketal Ia (m.p. 200–205°), 0.5 g. of 10% palladium-on-charcoal and 1.0 g. of potassium hydroxide in 175 ml. of ethanol and 50 ml. of benzene was shaken in an atmosphere of hydrogen (2 atm.) until one equivalent had been absorbed (2.5 hours). After filtration of the catalyst the solvents were removed under reduced pressure, the residue dissolved in methylene chloride and washed with water until neutral. The solvent was evaporated and the residue recrystallized from 2-propanol–methylene chloride to give 1.9 g. (90%) of halogen-free product, m.p. 205–206°. The sample for analysis was recrystallized sequentially from acetonitrile and cyclohexane; m.p. 206–209°, $[\alpha]^{26}D$ −118° (*c* 1.0); $\lambda_{max}$ 9.08, 10.00, 10.60, 11.51 μ.

*Anal.* Calcd. for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.44; H, 8.43.

**Dextrorotatory (20S)-Isomer (IVa).**—Using the same procedure, 2.5 g. of the bromo ketal IIa (m.p. 245–247°) absorbed 1 equivalent of hydrogen in 3 hours. The catalyst was filtered and washed with a total of 200 ml. of benzene and the combined filtrate and washings were washed to neutrality and concentrated to dryness under reduced pressure. The crystalline residue was triturated with hexane to give 1.45 g. (68.5%) of halogen-free product, m.p. 224–230°. Recrystallization from 2-propanol–methylene chloride and then cyclohexane gave the sample for analysis, m.p. 234–236°, $[\alpha]^{26}D$ +9° (*c* 1.0); $\lambda_{max}$ 9.14, 10.15, 10.65, 11.55 μ.

*Anal.* Calcd. for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.22; H, 8.30.

**17α,20;20,21-Bismethylenedioxypregn-4-ene-3-one. Levorotatory (20R)-Isomer (III).**—Treatment of the halogen-free ketal IIIa (1 g.) with 1 ml. of 8% (v./v.) aqueous sulfuric acid in 10 ml. of methanol[25] for 90 min. on a steam-bath gave, after dilution with water, 0.8 g. (89%) of product, m.p. 249–251°. Recrystallization from methylene chloride–2-propanol gave a 63% recovery of the 3-ketone III, m.p. 254–257°, $[\alpha]^{26}D$ −17.6° (*c* 1); $\lambda_{max}$ 241 mμ, ε 16,300.

This sample was identical with the BMD derivative prepared directly from 17α,21-dihydroxypregn-4-ene-3,20-dione.[4,10]

Similar treatment of the isomeric 20S-ketal IVa failed to give the corresponding ketone IV, but instead gave an 87.5% yield of the parent 17α,21-dihydroxypregn-4-ene-3,20-dione, m.p. 198–201°, identified by comparison with authentic material.

**16β-Methoxy-17α,20;20,21-bismethylenedioxy-(20R)-pregn-4-ene-3-one (V).**—A solution of 5 g. of silver perchlorate in 50 ml. of toluene was dried by distillation (to about 50% of original volume) and then added to a mixture of 1 g. of the (20R)-bromo-BMD I and 2.0 g. of silver oxide in 250 ml. of anhydrous methanol. The resulting slurry was refluxed with stirring for 2 hours (silver mirror deposited). The residue obtained after filtration and concentration under reduced pressure was extracted with methylene chloride and the resulting solution was washed thoroughly with water and evaporated to dryness. Crystallization from aqueous methanol gave 0.71 g. (79%) of the methoxy-BMD V, m.p. 179–180° (Br, 0.76%).

The analytical sample from aqueous dioxane showed a double melting point, 173–175° and 185–187.6°, $[\alpha]^{25.5}D$ +6.5° (*c* 3.6); $\lambda_{max}$ 240 mμ, ε 16,300; $\lambda_{max}$ 9.05, 9.15, 9.99, 10.58, 11.35 μ.

*Anal.* Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19; methoxyl, 7.24. Found: C, 68.65; H, 8.43; methoxyl, 7.50.

**16β-Hydroxy-17α,20;20,21-bismethylenedioxy-(20R)-pregn-4-ene-3-one (VI).**—A mixture of 2 g. of the (20R)-bromo-BMD I, 2 g. of silver perchlorate in 35 ml. of water and 150 ml. of acetone was heated under reflux with stirring for 12 hours. The reaction mixture was filtered from insoluble silver salts and concentrated *in vacuo*. The residue was dissolved in methylene chloride (75 ml.), filtered, and the filtrate washed with water until the aqueous washes gave a negative test for silver ion. Upon concentration there was obtained 1.62 g. of crude 16-hydroxy compound VI which was crystallized from aqueous methanol to give 1.32 g. (77%), m.p. 224–226° (Br, <0.2%). Recrystal-

(25) W. S. Allen, S. Bernstein and R. Littell, *J. Am. Chem. Soc.*, **76**, 6116 (1954).

lization from isopropyl ether gave the analytical sample, m.p. 231–233.6°, $[\alpha]^{28}D$ −12.5° (*c* 3.8); $\lambda_{max}$ 241 mμ, ε 16,750; $\lambda_{max}$ 2.88, 9.20, 9.95, 10.60, 11.46 μ; $\nu_{max}^{CCl_4}$ 3620 cm.$^{-1}$.

*Anal.* Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.04; H, 8.04.

**The acetate VII**, m.p. 196–198.2°, prepared by treatment of VI with acetic anhydride in pyridine at room temperature for 48 hours, was identical in all respects with that prepared from the bromo-BMD I with silver acetate (see below).

A mixture of VI (530 mg.) and fluoboric acid (50 mg.) with sufficient ethereal diazomethane[13] to give a stable yellow coloration furnished after 4 days at room temperature, 473 mg. of a crude methoxy compound. A single recrystallization from aqueous methanol gave material having a double melting point, 172–174° and 184.6–185.4°, $[\alpha]^{26}D$ +6.2° (*c* 2.5), which was indistinguishable from the 16β-methoxy-BMD V prepared directly from I with methanolic silver perchlorate (see above).

**16β-Acetoxy-17α,20;20,21-bismethylenedioxy-(20R)-pregn-4-ene-3-one (VII).**—A solution of 5 g. of the bromo-BMD I prepared by warming in 125 ml. of glacial acetic acid and 6 ml. of acetic anhydride was added rapidly to a warmed solution of 3 g. of silver acetate and 2.5 g. of sodium acetate trihydrate in 500 ml. of acetic acid containing 9 ml. of acetic anhydride. The resulting mixture, which precipitated silver bromide almost immediately, was stirred at 95° for 90 min. and filtered hot. The filtrate was concentrated to 50 ml. under reduced pressure and filtered again to remove additional silver salts. Dropwise addition of 150 ml. of water gave on filtration, 4.07 g. (85%) of the acetoxy-BMD VII, m.p. 194–198°, suitable for further use.

Recrystallization from acetonitrile gave the analytical sample, m.p. 197–198°, $[\alpha]^{27}D$ +4.5° (*c* 3.6); $\lambda_{max}$ 241 mμ, ε 16,400; $\lambda_{max}$ 5.76, 8.14, 9.17, 10.01, 10.54, 11.40 μ.

*Anal.* Calcd. for $C_{25}H_{34}O_7$: C, 67.24; H, 7.68. Found: C, 67.48; H, 7.56.

Saponification of VII with methanolic sodium hydroxide at room temperature (1 hour) gave a 90% yield of hydroxy-BMD, m.p. 231–237°, $[\alpha]^{25}D$ − 12.1° (*c* 3.7), identical with the product VI prepared above from I with silver perchlorate in aqueous acetone.

**The 3-ketal VIIa**, m.p. 220–245°, prepared in 73% yield from 0.5 g. of VII in the procedure described below for Xa, was recrystallized for analysis from isopropyl ether; m.p. 228–229°, $[\alpha]^{27}D$ −81° (*c* 2.8, chloroform); $\lambda_{max}^{CH_2Cl_2}$ 5.71, 8.09 μ.

*Anal.* Calcd. for $C_{27}H_{38}O_8$: C, 66.10; H, 7.81. Found: C, 65.84; H, 7.80.

**16β-Fluoro-(VIII) and 16β-Isopropoxy-17α,20; 21-bismethylenedioxy-(20R)-pregn-4-ene-3-one (IX).**—A solution of 58.0 g. of the bromo-BMD I in 2.89 l. of dry 2-propanol and 290 ml. of toluene was heated to boiling with vigorous stirring. Five 32-g. portions of anhydrous silver fluoride were then added at 40-min. intervals and heating was continued an additional 75 min., slow distillation being maintained throughout. The cooled reaction mixture was then filtered and concentrated to dryness *in vacuo*. In order to remove remaining silver salts, the residue was dissolved in methylene chloride, washed thoroughly with water and again concentrated to dryness. The product was crystallized from isopropyl ether to yield 37.6 g. (74.6%) of VIII, m.p. 225–227° dec. Recrystallization from dimethylformamide containing a small amount of water gave the analytical sample, m.p. 228–229° dec., $[\alpha]^{26}D$ +5.9° (*c* 1.0); $\lambda_{max}$ 240.5 mμ, ε 16,700; $\lambda_{max}^{CH_2Cl_2}$ 9.18, 10.65 μ.

*Anal.* Calcd. for $C_{23}H_{31}O_5F$: C, 67.96; H, 7.69; F, 4.67. Found: C, 67.95; H, 7.65; F, 4.69.

From the original filtrate there was obtained 2.2 g. (4%) of the isopropoxy compound IX, m.p. 139–150°. Recrystallization from aqueous methanol and then methylene chloride–isopropyl ether gave the sample for analysis, m.p. 149–152°, $[\alpha]^{26}D$ +5.9° (*c* 1.0); $\lambda_{max}$ 241 mμ, ε 16,850; $\lambda_{max}$ 9.25 μ.

*Anal.* Calcd. or $C_{26}H_{38}O_6$: C, 69.93; H, 8.58. Found: C, 69.67; H, 8.70.

**17α,20;20,21-Bismethylenedioxy-(20R)-pregn-4-ene-3,16-dione (X).**—To 7.5 g. of the 16β-hydroxy-BMD VI in 75 ml. of 90% aqueous acetic acid maintained at 10–15° was added a solution of 3.4 g. of chromium trioxide in 13.5 ml. of the same solvent mixture. After 90 min. at 10–15°, the reaction was quenched by the addition of 10 ml. of methanol. Dropwise addition of 225 ml. of water, filtration and thorough washing with water gave 6.1 g. (82%) of the 16-ketone X, m.p. 199–205°. Recrystallization from 2-propanol gave the analytical sample, m.p. 207–210°, $[\alpha]^{25}D$ −155° (*c* 1.6); $\lambda_{max}$ 240 mμ, ε 16,900; $\lambda_{max}^{CH_2Cl_2}$ 5.72 μ.

*Anal.* Calcd. for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51. Found: C, 68.40; H, 7.47.

**17α,20;20,21-Bismethylenedioxy-3,3-ethylenedioxy-(20R)-pregn-5-ene-16-one (Xa).**—A mixture of 0.5 g. of the 16-keto-BMD X in 10 ml. of ethylene glycol, 5 ml. of methylene chloride and 1.5 ml. of triethyl orthoformate with 5 mg. of *p*-toluenesulfonic acid monohydrate was stirred 4 hours at 45–50°. Crystalline product had precipitated after 1 hour. The reaction mixture was allowed to cool to room temperature, filtered and the product recrystallized from 2-propanol–methylene chloride to give 0.31 g. (56%) of Xa, m.p. 221–227°, $[\alpha]^{27}D$ −240° (*c* 1.0); no absorption at 240 mμ, $\lambda_{max}^{CH_2Cl_2}$ 5.72 μ.

*Anal.* Calcd. for $C_{25}H_{34}O_7$: C, 67.24; H, 7.68. Found: C, 67.07; H, 7.81.

**The 16-oxime** was prepared in refluxing aqueous pyridine and recrystallized from cyclohexane; m.p. 231–239°, $[\alpha]^{27}D$ −186° (*c* 0.99); $\lambda_{max}^{CH_2Cl_2}$ 2.81, no absorption between 5.0 and 6.5 μ.

*Anal.* Calcd. for $C_{25}H_{35}O_7N$: C, 65.05; H, 7.64; N, 3.04. Found: C, 65.07; H, 7.61; N, 3.11.

**Lithium Aluminum Hydride Reduction of the 16-Ketone.**—A solution of 0.5 g. of the monoketone Xa in 200 ml. of anhydrous ethyl ether was added to a stirred suspension of lithium aluminum hydride (1.05 g.) in 100 ml. of ether and the reaction mixture was heated under reflux in 1.5 hours. The excess hydride was destroyed by cautious addition of water (2.8 ml.) and a solution of 9.6 g. of sodium potassium tartrate in 8 ml. of water was added. The resulting mixture was filtered, the insoluble material extracted with ether, and the combined organic layers washed with water and dried. The product, which separated during concentration, weighed 0.47 g., m.p. 202–215°. Recrystallization from isopropyl ether gave **16β-hydroxy-17α,20;20,21-bismethylenedioxy-3,3-ethylenedioxy-(20R)-pregn-5-ene (VIa)**, m.p. 233–236°, $[\alpha]^{27}D$ −118.5° (*c* 2.7, chloroform); $\lambda_{max}^{CH_2Cl_2}$ 2.74, 9.12, 10.00, 10.56, 11.55 μ.

*Anal.* Calcd. for $C_{26}H_{36}O_7$: C, 66.94; H, 8.09. Found: C, 66.75; H, 8.13.

Acetylation of the reduction product (183 mg.) for 24 hours at room temperature in 0.8 ml. each of pyridine and acetic anhydride furnished 152 mg. of an acetate, m.p. 221–225°. Recrystallization from isopropyl ether gave material, m.p. 222–224°, which was identical with the **ketal acetate VIIa** prepared above from the silver acetate product VII.

**16β,17α,21-Trihydroxypregn-4-ene-3,20-dione 16,21-Diacetate.**—To a mixture of 12 ml. of ethylene glycol and 235 ml. of 60% formic acid preheated to 96° was added 4.20 g. of the acetoxy-BMD VII (silver acetate product). After stirring 30 min. at this temperature, the hot solution was poured onto 1.6 kg. of crushed ice. The product was extracted into methylene chloride, washed thoroughly with water and concentrated under reduced pressure to an oil. A solution of 3.4 ml. of 10% sulfuric acid in 100 ml. of methanol was added and, after 1 hour at 26°, 400 ml. of water was added and most of the methanol removed under reduced pressure. The product was again extracted into methylene chloride, washed with water and the solvent removed *in vacuo*. The resulting glass (2.31 g.) after 12 hours in a mixture of 10 ml. of acetonitrile, 7 ml. of pyridine and 7 ml. of acetic anhydride was poured into ice-water. After partial concentration under reduced pressure, the mixture was taken up in methylene chloride, washed with dilute hydrochloric acid and then with water to neutrality. The residue from this solution (3.5 g.) was crystallized from ethyl acetate to give, in three crops, 1.5 g. of the title compound, m.p. 163–165°. Recrystallization from ethyl acetate–cyclohexane gave a product (m.p. 166.8–167.6°, $[\alpha]^{27}D$ + 102.4° (*c* 2.6, chloroform); $\lambda_{max}$ 240 mμ, ε 17,900; $\lambda_{max}$ 2.98, 5.73, 5.80 μ) which was identical by mixed melting point and paper chromatographic and infrared comparisons with an authentic sample.[14,26]

(26) We are indebted to Dr. Seymour Bernstein for providing comparison samples of this compound and its 16α-epimer.

**16β-Methoxy-17α,21-dihydroxypregn-4-ene-3,20-dione.**—To 80 ml. of 60% formic acid at 90° was added 2.70 g. of the methoxy-BMD V. The resulting solution was stirred for 19 min. at this temperature and then quenched in 320 ml. of ice-water. Filtration gave 1.58 g. of crude product directly and an additional 0.78 g. was obtained by extraction of the filtrate with methylene chloride. The fractions were combined and treated with 58 ml. of methanol and 2.0 ml. of 10% sulfuric acid for 2 hours at room temperature to remove residual formates. After addition of 120 ml. of water, most of the methanol was removed under reduced pressure and the product extracted with methylene chloride. Thorough washing with water and evaporation gave 1.96 g. of a glassy residue which crystallized from benzene to provide 1.06 g. (42.5%) of 16β-methoxycortexolone, m.p. 148–149°. Recrystallization from benzene gave the sample for analysis, m.p. 149.4–150°, $[\alpha]^{26}D$ +111.5° (*c* 3.1); $\lambda_{max}$ 241 mμ, ε 15,750; $\lambda_{max}$ 2.98, 5.82, 8.95 μ.

*Anal.* Calcd. for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57; methoxyl, 8.24. Found: C, 70.14; H, 8.46; methoxyl, 8.00.

**The 21-Acetate** had m.p. 148–150° (from methanol), $[\alpha]^{26}D$ +86° (*c* 0.99, chloroform); $\lambda_{max}$ 241 mμ, ε 16,800; $\lambda_{max}$ 2.93, 5.73, 5.87, 8.06, 8.94.

*Anal.* Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19; methoxyl, 7.42. Found: C, 69.10; H, 8.04; methoxyl, 7.01.

**16β-Fluoro-17α,21-dihydroxypregn-4-ene,3,20-dione.**—To a refluxing mixture of 280 ml. of 90% technical formic acid, 135 ml. of water and 22.5 ml. of ethylene glycol was added 7.50 g. of the fluoro-BMD VIII in one portion. After heating an additional 25 minutes the solution was cooled by adding 400 ml. of ice-water. The mixture was concentrated under reduced pressure to 50 ml. at a maximum internal temperature of 45°. The residue was treated with water and methylene chloride, and the organic layer washed with water, dried and concentrated. Small amounts of 21-formate in the resulting crude product were cleaved by treating the residue at 25° for 1 hr. with 60 ml. of methanol containing 0.186 g. of concentrated sulfuric acid. After adding 150 ml. of water, most of the methanol was removed under reduced pressure and the product extracted into methylene chloride and washed with water. The methylene chloride was displaced with benzene yielding 4.71 g. (70%) of crystalline product, m.p. 175–177° dec. Recrystallization from benzene gave the analytical sample, m.p. 178–179° dec., $[\alpha]^{27}D$ +89° (*c* 1.0); $\lambda_{max}$ 240.5 mμ, ε 16,900; $\lambda_{max}^{CH_2Cl_2}$ 2.86, 5.82 μ.

*Anal.* Calcd. for $C_{21}H_{29}O_4F$: C, 69.20; H, 8.02; F, 5.21. Found: C, 69.05; H, 8.06; F, 5.02.

Acetylation at 0° for 16 hours with acetic anhydride in pyridine gave the **21-acetate**, m.p. 178–180° (from aqueous acetone), $[\alpha]^{27}D$ +76.7° (*c* 1.0); $\lambda_{max}$ 241 mμ, ε 16,700; $\lambda_{max}^{CH_2Cl_2}$ 2.88, 5.70, 5.83, 8.17 μ.

*Anal.* Calcd. for $C_{23}H_{31}O_5F$: C, 67.96; H, 7.69; F, 4.67. Found: C, 67.96; H, 7.65; F, 4.75.

**16β-Bromo-17α,21-dihydroxypregna-4,9(11)-diene-3,20-dione.**—16β - Bromo - 17α,21 - dihydroxypregna - 4,9(11)-diene-3,20-dione 21-acetate[27] (2.50 g.) in a mixture of methylene chloride (24 cc.), methanol (83 cc.), water (9.4 cc.) and 37% hydrochloric acid (5.7 cc.) was stirred 17 hours at 30–31°. Water (42 cc.) was added slowly while the organic solvents were simultaneously evaporated under reduced pressure at less than 32°. Crystallization was encouraged by scratching when the product first started separating from solution. The resulting thick slurry was filtered and the cake washed with water and dried to give 2.03 g. (89%) of the bromodiol, m.p. 129° dec.; $\lambda_{max}$ 2.97, 5.80 μ.

*Anal.* Calcd. for $C_{21}H_{27}O_4Br$: C, 59.58; H, 6.43; Br, 18.88. Found: C, 59.25; H, 6.59; Br, 19.12.

**16β-Bromo-17α,20:20,21-bismethylenedioxy-(20R)-pregna-4,9(11)-diene-3-one.**—A suspension of the bromohydrin from the previous step (1.49 g.) in a mixture of benzene (23 cc.), 37% formalin (15 cc.) and 37% hydrochloric acid (15 cc.) was stirred vigorously at 25°. After complete solution of the steroid (about 1 hour), hexane (75 cc.) was added in ten portions during 3 hours. After an additional reaction period of 16 hours, the solids were dissolved with methylene chloride and the organic layer separated, washed with water and concentrated. Crystallization of the residue from dimethylformamide–water gave 1.07 g. (65%) of the $\Delta^{9,(11)}$-bromo-BMD, m.p. 203° dec. Recrystallization from the same solvent pair gave the sample for analysis, m.p. 205° dec., $[\alpha]^{27.5}D$ −39.1 (*c* 1.0, chloroform); $\lambda_{max}$ 239 mμ, ε 17,300; $\lambda_{max}$ 9.15, 10.05, 10.65 μ.

*Anal.* Calcd. for $C_{23}H_{29}O_5Br$: C, 59.36; H, 6.28; Br, 17.17. Found: C, 59.62; H, 6.49; Br, 17.29.

**16β-Methoxy-17α,20:20,21-bismethylenedioxy-(20R)-pregna-4,9(11)-diene-3-one.**—To a solution of 5 g. of $\Delta^{9(11)}$-bromo-BMD from the previous step in 35 ml. of toluene (concentrated from 50 ml. to remove last traces of water) was added 750 ml. of absolute methanol. The mixture was then heated to reflux temperature, and 10 g. of silver oxide (predried *in vacuo* at 100°) and a solution of 25 g. of silver perchlorate (dried at 25° *in vacuo*) in 60 ml. of dry toluene were added. After 3-hour reflux with stirring under nitrogen, the mixture was filtered to remove insoluble silver salts, concentrated under reduced pressure to about 45 ml. and filtered again. Addition of 250 ml. of water gave 4.2 g. (94%) of 16β-methoxy-$\Delta^{9(11)}$-BMD, m.p. 196–198° (Br, 0.2%), which was recrystallized from methylene chloride–methanol to give 3.6 g. (80%), m.p. 205–207°. Recrystallization from isopropyl ether furnished the analytical sample, m.p. (original) 204–207°, (after drying) 198–199°; $[\alpha]^{27}D$ +10.5° (*c* 2.5); $\lambda_{max}$ 239 mμ, ε 16,850; $\lambda_{max}$ 9.20, 10.01, 10.51, 11.47 μ.

*Anal.* Calcd. for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74; methoxyl, 7.46. Found: C, 69.32; 8.04; methoxyl, 7.45.

**16β-Methoxy-17α,21-dihydroxypregna-4,9(11)-diene-3,20-dione.**—To a refluxing mixture of 240 ml. of 60% formic acid and 15 ml. of ethylene glycol was added 5 g. of the 16β-methoxy-$\Delta^{9(11)}$-BMD. After 10 min. additional heating at reflux temperature, the reaction was quenched by addition to 2 kg. of ice. Partial concentration under reduced pressure gave a slurry which was filtered to collect crystallized product and the filtrate was extracted with 200 ml. of methylene chloride (in 3 portions). The extract was washed with water and concentrated to dryness under reduced pressure and the residue, combined with the crystalline material isolated earlier, was stirred 1 hour at room temperature with a mixture of 125 ml. of methanol and 4.2 ml. of 10% (v./v.) sulfuric acid. Dilution with 150 ml. of water and removal of most of the methanol under reduced pressure gave 3.65 g. of the title 16β-methoxydiol, m.p. 181–182°. Recrystallization from benzene gave the sample for analysis, m.p. 187–189°, $[\alpha]^{26}D$ +113° (*c* 1); $\lambda_{max}$ 239 mμ, ε 16,150; $\lambda_{max}$ 5.82, 8.94 μ.

*Anal.* Calcd. for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08; methoxyl, 8.29. Found: C, 70.43; H, 8.11; methoxyl, 8.46.

The **21-acetate**, prepared by 24-hour acetylation with acetic anhydride in pyridine, was recrystallized from ethanol and dried at 100° (0.05 mm.) for 48 hours, m.p. 140–142°, $[\alpha]^{27}D$ +72° (*c* 1.0), $\lambda_{max}$ 239 mμ, ε 16,650; $\lambda_{max}$ 5.71, 5.81, 8.13, 8.91 μ.

*Anal.* Calcd. for $C_{24}H_{32}O_6$: 69.21; H, 7.74; methoxyl, 7.46. Found: C, 69.38; H, 7.86; methoxyl, 7.56.

(27) L. B. Barkley, M. W. Farrar, W. S. Knowles and H. Raffelson, *J. Am. Chem. Soc.*, **76**, 5017 (1954); W. S. Allen, S. Bernstein, L. I. Feldman and M. J. Weiss, *ibid.*, **82**, 3696 (1960).