m.p. 173–175°; $[\alpha]^{28}D$ +3° (*c* 0.8, $CHCl_3$); λ_{max}^{KBr} 2.90, 10.89, and 11.09 μ.

Anal. Calcd. for $C_{30}H_{42}O_2$: C, 78.89; H, 10.59. Found: C, 78.71; H, 10.59.

Heterocyclic Steroids in the Antiinflammatory Series[1]

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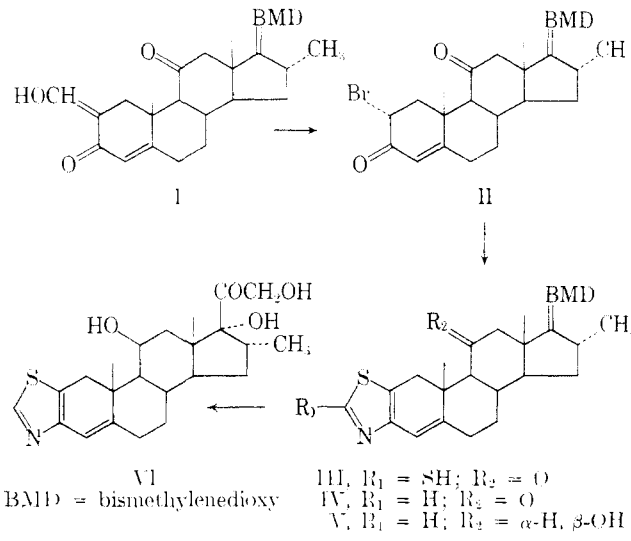
A number of heterocyclic-fused steroids have been prepared as an extension of the lead provided by the steroidal [3,2-*c*]pyrazoles as antiinflammatory agents. The syntheses of steroidal [3,2-*d*]thiazoles, [2,3-*d*]imidazoles, [3,2-*d*]triazoles, and [3,2-*d*]pyrimidines related to cortisone are described. The 3′-phenyl[3,2-*d*]-3′H-1′,2′,3′-triazole function has been found to be a powerful activity-enhancing group.

Pharmacologically active steroids with a pyrazole function fused to positions C-2 and -3 were first reported in the androgen series.[2] More recent reports from these laboratories[3] demonstrated that the [3,2-*c*]-pyrazoles of antiinflammatory steroids were also consistent with activity. Particularly interesting was the finding that the 2′-phenyl[3,2-*c*]pyrazole group[3a] was the most potent activity-enhancing function in the antiinflammatory series yet discovered.

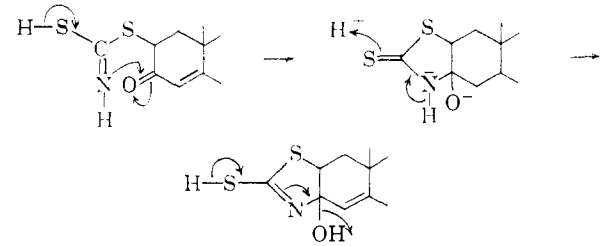
It was a matter of interest to determine if the antiinflammatory activity of the steroidal pyrazoles was unique, or could be maintained by other heterocyclic fusions. To that end a number of representative compounds were synthesized.

Preparation of a thiazolo steroid was undertaken because this structure is known to retain biological activity in the androgen series[4,5] (see Chart I). A convenient starting material was 17α,20;20,21-bismethylenedioxy-2-formyl-16α-methyl-4-pregnene-3,11-dione (I), which was obtained from 17α,20;20,21-bismethylenedioxy-16α-methyl-4-pregnene-3,11-dione[6] by condensation with ethyl formate. Bromination and subsequent deformylation afforded the 2α-bromo ketone II.[7] Reaction of II with a thioamide was expected to yield a thiazole, since 4,5-allodihydro-2-bromo-3-keto steroids readily undergo this reaction.[4,5,8] In the present case it appears that the first step, replacement of the C-2 bromine by the sulfur of thiourea, proceeded normally. However, the subsequent ring closure with the Δ⁴-analogs could not be accomplished even by reflux in dimethylformamide. In contrast, ammonium dithiocarbamate[10] reacted smoothly at room temperature to yield the 2-mercaptothiazole III. The facile ring closure is most probably assisted by the 2′-mercapto group as indicated.

CHART I



Removal of the 2′-mercapto group could be carried out by nitric acid oxidation, or better with alkaline hydrogen peroxide and subsequent acidification of the sulfinic acid sodium salt.[10] Reduction of the C-11 ketone and removal of the BMD protecting group[11]



(1) For a preliminary communication concerning some of these compounds, see J. H. Fried, P. Buchschacher, and H. Mrozik, *Steroids*, **2**, 399 (1963).

(2) R. O. Clinton, *et al.*, *J. Am. Chem. Soc.*, **83**, 1478 (1961).

(3) (a) R. Hirschmann, N. G. Steinberg, P. Buchschacher, J. H. Fried, G. J. Kent, M. Tishler, and S. L. Steelman, *ibid.*, **85**, 120 (1963); (b) J. H. Fried, H. Mrozik, G. E. Arth, T. S. Bry, N. G. Steinberg, M. Tishler, R. Hirschmann, and S. L. Steelman, *ibid.*, **85**, 236 (1963); (c) R. Hirschmann, P. Buchschacher, N. G. Steinberg, J. H. Fried, R. Ellis, G. J. Kent, and M. Tishler, *ibid.*, **86**, 1520 (1964); (d) R. Hirschmann, N. G. Steinberg, E. F. Schoenewaldt, W. J. Paleveda, and M. Tishler, *J. Med. Chem.*, **7**, 352 (1964); (e) R. G. Strachan, N. G. Steinberg, M. Tishler, and R. Hirschmann, *ibid.*, **7**, 355 (1964).

(4) J. A. Zderic, O. Halpern, H. Carpio, A. Ruiz, D. C. Limon, L. Magaña, H. Jiménes, A. Bowers, and H. J. Ringold, *Chem. Ind.* (London), 1625 (1960).

(5) N. J. Doorenbos and C. P. Dorn, Jr., *J. Pharm. Sci.*, **50**, 271 (1961); **51**, 414 (1962).

(6) M. Sletzinger and W. Gaines, to be published.

(7) The assignment of bromine to the α-position is supported by the hypsochromic shift of the carbonyl stretching frequency upon replacement of the C-2 hydrogen by bromine.[8]

(8) G. R. Allen, Jr., and M. J. Weiss, *J. Am. Chem. Soc.*, **82**, 2840 (1960).

(9) H. Antaki and V. Petrow, *J. Chem. Soc.*, 901 (1951).

(10) J. M. Sprague and A. H. Land, "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1957, p. 484.

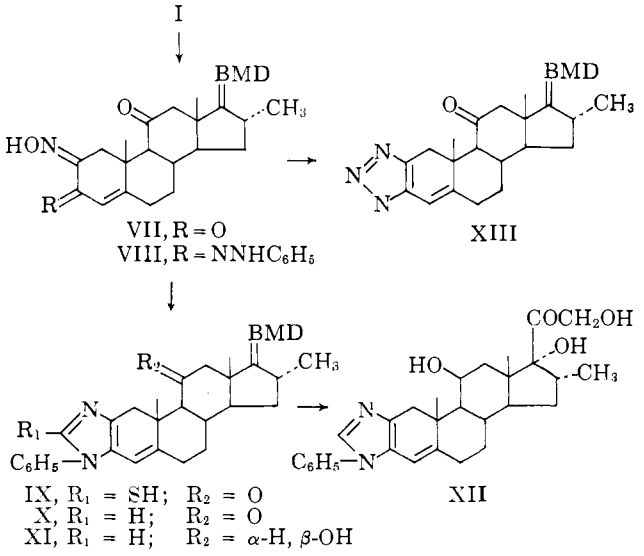
(11) R. E. Beyler, R. M. Moriarty, F. Hoffman, and L. H. Sarett, *J. Am. Chem. Soc.*, **80**, 1517 (1958).

afforded 11β,17α,21-trihydroxy-16α-methyl-20-oxo-4-pregnene[3,2-*d*]thiazole (VI).

In order to determine if basicity is an important consideration for biological activity in the heterocyclic series, the closely related but somewhat more basic analog of the active phenylpyrazole, 11β,17α,21-trihydroxy-16α-methyl-20-oxo-1′-phenyl-4-pregnen[2,3-*d*]imidazole, was synthesized.

Nitrosation[12] of the 2-formyl 3-ketone I afforded the corresponding 2-hydroxyimino 3-ketone VII. It was planned to reduce this compound to the amino ketone with zinc in acetic acid, but isolation of this product could not readily be accomplished. However, reduction of the hydroxyimino ketone with zinc in acetic acid in the presence of phenylisothiocyanate afforded directly a 50% yield of the 1′-phenyl-2′-mercaptoimidazole IX (see Chart II). Oxidative removal of the mercapto

CHART II



group with alkaline hydrogen peroxide and subsequent acidification[10] led to the 1′-phenylimidazole X. Reduction of the C-11 ketone with lithium aluminum hydride furnished the corresponding 11β-ol XI. The structure of XI was consistent with ultraviolet, infrared and nuclear magnetic resonance[13] spectra. The latter showed the C-4 proton at τ 4.05 indicating that the C-4,5 double bond was not attacked during the course of lithium aluminum hydride reduction. Removal of the bismethylenedioxy protecting group[11] afforded 11β,17α,21-trihydroxy-16α-methyl-20-oxo-1′-phenyl-4-pregnen[2,3-*d*]imidazole (XII).

In order to determine the effect of ring size on activity 11β,17α,21-trihydroxy-16α-methyl-20-oxo-2′-phenyl-4-pregnene[3,2-*d*]pyrimidine (XXI) was synthesized. Reaction of 17α,20;20,21-bismethylenedioxy-2-formyl-16α-methyl-4-pregnen-11β-ol (XVII) with benzamidine[14] afforded 17α,20;20,21-bismethylenedioxy-11β-hydroxy-16α-methyl-2′-phenyl-4-pregnene[3,2-*d*]pyrimidine (XIX). Hydrolysis of the bismethylenedioxy protecting group[11] afforded the desired pyrimidine XXI[15] (Chart III).

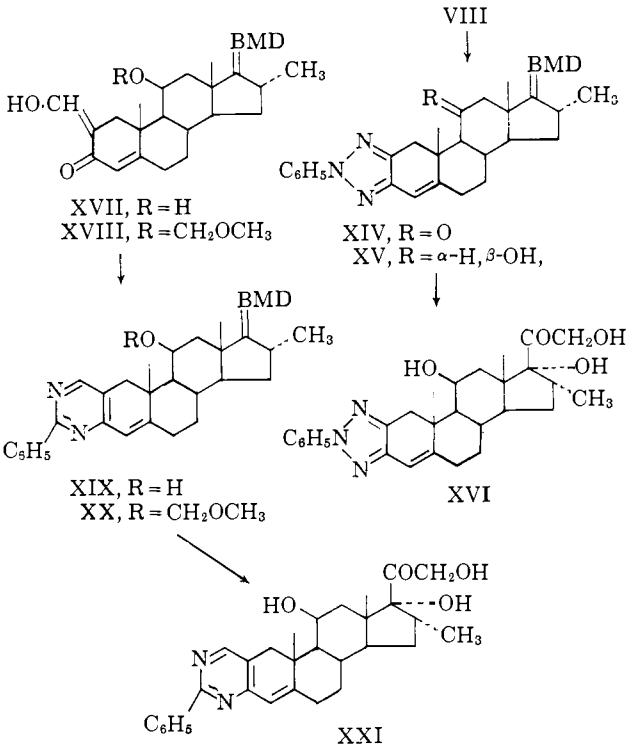
(12) M. Gates, *J. Am. Chem. Soc.*, **72**, 228 (1950).

(13) Nuclear magnetic resonance spectra were run on a Varian 60 Mc. spectrometer at a concentration of *ca.* 20 mg. in 0.3 ml. of deuteriochloroform. $\tau = \nu/60 + 3.5$ where ν is the observed band position in c.p.s. relative to benzene as external standard. *Cf.* G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

(14) A. Pinner, *Ber.*, **26**, 2122 (1893).

Finally, a number of triazole derivatives were synthesized because of the close relation, both sterically and electronically, to the corresponding pyrazoles.[16] Reaction of the hydroxyimino ketone VII with hydrazine and potassium hydroxide[17] gave 17α,20;20,21-

CHART III



bismethylenedioxy-16α-methyl-11-oxo-4-pregnene[3,2-*d*]-1′,2′,3′-triazole (XIII).[18]

The preparation of 11β,17α,21-trihydroxy-16α-methyl-20-oxo-2′-phenyl-4-pregnene[3,2-*d*]-2′H-1′,2′,3′-triazole (XVI) was carried out by conversion of VII to the phenylhydrazone VIII which was cyclized with phosphorus pentachloride in chloroform[19] to 17α,20;20,21-bismethylenedioxy-16α-methyl-11-oxo-2′-phenyl-4-pregnene[3,2-*d*]-2′H-1′,2′,3′-triazole (XIV) (see Chart III). Subsequent reduction at C-11 and hydrolysis of the bismethylenedioxy protecting group afforded XVI.

An attempt to cyclize VIII with copper sulfate produced a compound which had one additional atom of oxygen compared to the triazole XIV. This compound is formulated as the triazole 1′-N-oxide (XVIa).

The 3′-phenyltriazole of 6,16α-dimethyl-4,6-pregnadiene-11β,17α,21-triol-3,20-dione 21-acetate was prepared because of the remarkable potency of the corresponding 2′-phenylpyrazole.[3] Reaction of 17α,20;20,21-bismethylenedioxy-16α-methyl-5α-pregnane-

(15) This synthesis could also be carried out with the corresponding C-11 methoxymethyl derivative XVIII which is a by-product formed in the conversion of 16α-methylhydrocortisone to the bismethylenedioxy derivative. The C-11 methoxymethyl is cleaved during the hydrolysis of the bismethylenedioxy function.

(16) G. Nathansohn, E. Testa, and N. Di Mola [*Experientia*, **18**, 57 (1962)] have reported the synthesis of a number of triazolo androstanes.

(17) H. Rapoport and H. H. Chen, *J. Org. Chem.*, **25**, 313 (1960); H. Rapoport and W. Nilsson, *J. Am. Chem. Soc.*, **83**, 4262 (1961).

(18) Reduction at C-11 and hydrolysis of the BMD protecting group were carried out to yield 11β,17α,21-trihydroxy-16α-methyl-20-oxo-4-pregnene-[3,2-*d*]-1′,2′,3,-triazole (XIIIa); however, this compound could not be obtained crystalline. On the basis of paper strip chromatography, the sample sent for biological assay contained about 70% of XIIIa.

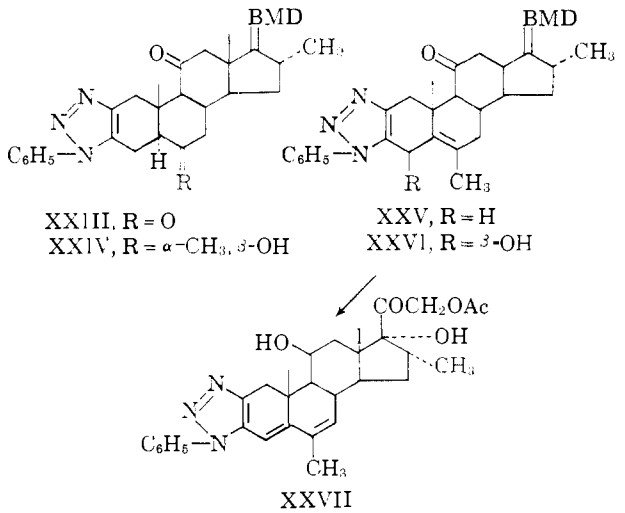
(19) F. R. Benson and W. L. Savell, *Chem. Rev.*, **46**, 1 (1950).

3,6,11-trione (XXII)[20] with excess morpholine afforded the monoenamine[21] which on treatment with phenylazide[22] led to the [3,2-*d*]-3′-phenyltriazole XXIII as the only crystalline derivative having triazole functionality.

Only a 3,2-triazole is consistent with the results of subsequent synthetic steps. The morpholine group in the precursor must then of necessity be located at C-3 and the assignment of the phenyl follows by analogy with other additions of phenylazide to enamines.[16,22]

The 6-ketophenyltriazole XXIII was converted to the 6α-methylcarbinol XXIV with methylmagnesium iodide. Thionyl chloride-pyridine dehydration afforded 17α,20;20,21-bismethylenedioxy-6,16α-dimethyl-11-oxo-3′-phenyl-5-pregneno[3,2-*d*]-3′H-1′,2′,3′-triazole (XXV) (see Chart IV). The position of the double bond

CHART IV



was confirmed by the n.m.r. spectrum which showed the absence of olefinic protons. Selenium dioxide[23] oxidation furnished the carbinol XXVI. The structure was assigned on the basis of n.m.r. which shows the absence of olefinic protons ruling out all reasonable alternatives but a 4- or 7-ol. The 4α- or 7β-ol can be ruled out on the basis of molecular rotation differences.[24] The 4β-structure is preferred over the 7α-ol by analogy with the results of selenium dioxide oxidation of cholesterol.[23] Reduction of XXVI at C-11 with sodium borohydride followed by treatment of the crude product with hot 60% aqueous formic acid resulted in both dehydration of the 4,6-diene system and BMD cleavage. Treatment of the crude product with sodium methoxide to remove formate esters and acetylation yielded 11β,17α-2-trihydroxy-6,16α-dimethyl-20-oxo-3′-phenyl-4,6-pregnadiene[3,2-*d*]-3′H-1′,2′,3′-triazole 21-acetate (XXVII) which was purified by partition chromatography followed by percolation through silica gel.

Of the heterocyclic derivatives prepared, three showed antiinflammatory activity.[25] The thiazole VI was 0.5 times hydrocortisone. The triazole XIIIa was 1.3 times hydrocortisone and the 3′-phenyltriazole XXVII was 190 times hydrocortisone. Only the 3′-phenyltriazole function is an activity-enhancing group. It potentiates the activity of the parent steroid 6,16α-dimethyl-4,6-pregnadiene-11β,17α,21-triol-3,20-dione by a factor of *ca.* 6. The strict structural requirements for antiinflammatory activity are nicely demonstrated by the 1′-phenylinidazolo, 3′-phenyl-triazolo, and 2′-phenylpyrazolo steroids. These compounds are isosteric and isoelectronic; however, the phenylinidazole is totally inactive while the latter compounds are highly potent antiinflammatory agents in animals.

No activity was observed with the 2′-phenyltriazolo as well as for the 1′-phenylpyrazolo steroid again indicating rather remarkable structural specificity for antiinflammatory activity.

Experimental[26]

17α,20;20,21-Bismethylenedioxy-2-formyl-16α-methyl-4-pregnene-3,11-dione (I).—A solution of 13.5 g. of 17α,20;20,21-bismethylenedioxy-16α-methyl-4-pregnene-3,11-dione in 400 ml. of benzene was dried by azeotropic distillation. It was cooled in ice, 20 ml. of ethyl formate and 4 g. of a 53% sodium hydride dispersion in mineral oil were added, followed by 0.25 ml. of a 0.6 *M* solution of sodium methoxide in methanol. The reaction mixture was stirred in an atmosphere of nitrogen overnight at room temperature. Water (30 ml.) was added carefully with cooling, and the crystalline precipitate was aged for 30 min. and filtered. The precipitate was suspended in 500 ml. of chloroform and acidified with saturated sodium NaH_2PO_4 solution with cooling. The chloroform layer was washed with water and saturated NaCl solution, dried over Na_2SO_4, and concentrated to 25 ml. to yield 3.9 g. of I, m.p. 226–240°. Addition of ether to the mother liquor afforded another 2.6 g., m.p. 210–226°. Recrystallization from chloroform and ethyl acetate yielded an analytical sample, m.p. 224–232° dec; $[\alpha]^{25}D$ +10° (*c* 1.00, $CHCl_3$); $\lambda_{max}^{CH_3OH}$ 241 mμ (ε 12,200) and 308 mμ (ε 4900); $\lambda_{max}^{CHCl_3}$ 3.66, 5.78, 5.88, 6.08, 6.34, and 9.15 μ.

Anal. Calcd. for $C_{25}H_{32}O_7$: C, 67.55; H, 7.26. Found: C, 67.46; H, 7.18.

17α,20;20,21-Bismethylenedioxy-2α-bromo-16α-methyl-4-pregnene-3,11-dione (II).—A solution consisting of 500 mg. of I, 38 mg. of sodium acetate, 25 ml. of chloroform, and 25 ml. of methanol was cooled in ice. A solution of 130 mg. of bromine in chloroform was added with stirring, followed by 25 ml. of a 2.5 *N* aqueous NaOH. After 15 min. of vigorous stirring, the product was taken up in chloroform and crystallized from methylene chloride–ether to yield 365 mg. of II. Recrystallization from the same solvents afforded a sample, m.p. 187–191° dec; $[\alpha]^{24}D$ +86° (*c* 0.5, $CHCl_3$); $\lambda_{max}^{CH_3OH}$ 240 mμ (ε 13,400); $\lambda_{max}^{CHCl_3}$ 5.90, 6.14, 9.1–9.2 μ.

Anal. Calcd. for $C_{25}H_{31}BrO_6$: C, 58.17; H, 6.31; Br, 16.13. Found: C, 58.50; H, 6.24; Br, 15.72.

17α,20;20,21-Bismethylenedioxy-2′-mercapto-16α-methyl-11-oxo-4-pregnene[3,2-*d*]thiazole (III).—A stirred solution consisting of 2.18 g. of ammonium dithiocarbamate in 70 ml. of water and 70 ml. of dimethylformamide maintained under nitrogen was cooled in an ice bath and 2.80 g. of II in 140 ml. of dimethylformamide was added over a period of 1 hr. Stirring was continued at room temperature overnight and III was separated by filtration to yield 1.66 g., m.p. 225–240° dec. Two further crystallizations from chloroform–ether and methylene chloride–ether

(20) This compound was first prepared from 16α-methyl-17α,20;20,21-bismethylenedioxy-3-ethylenedioxy-5,6-oxidopregnan-11-one[6] by M. Sletzinger and S. Karady, m.p. 244–252°, $[\alpha]^{25}D$ −33° ($CHCl_3$). Calcd. for $C_{24}H_{32}O_7$: C, 66.69; H, 7.46. Found: C, 66.69; H, 7.45. The synthesis of the corresponding 16-desmethyl derivative and the discussion of the stereochemistry at C-5 has been reported [J. H. Fried, G. E. Arth, and L. H. Sarett, *J. Am. Chem. Soc.*, **81**, 1235 (1959)].

(21) F. W. Heyl and M. E. Herr, *ibid.*, **75**, 1918 (1953).

(22) K. Alder, G. Stein, and W. Friedrichsen, *Ann.*, **501**, 1 (1933); R. Fusco, G. Bianchetti, and D. Pocar, *Gazz. chim. ital.*, **91**, 849 (1961).

(23) O. Rosenheim and W. W. Starling, *J. Chem. Soc.*, 377 (1937).

(24) The molecular rotation difference in going from XXV to XXVI is −165°. The corresponding ΔMD values for cholesterol to the 4α-, 4β-, 7α-, and 7β-carbinols are +54, −88, −208, and +124° (L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 227).

(25) S. L. Steelman, E. R. Morgan, and R. H. Silber, *Steroids*, **1**, 163 (1963). We are indebted to Dr. S. L. Steelman, Merck Institute for Therapeutic Research, for carrying out these determinations.

(26) Melting points were determined on a Kofler micro hot stage and are corrected. We wish to thank R. Boos and his associates for microanalyses, A. Kalowsky for ultraviolet absorption spectra, R. Walker and N. Allen for the infrared spectra, B. Arison and Dr. N. R. Trenner for the n.m.r. spectra and V. Powell and F. Lostbourne for the rotations herein reported.

afforded a sample for analysis, m.p. 248–250° dec; $[\alpha]^{24}D$ +72° (*c* 0.6, $CHCl_3$); $\lambda_{max}^{CH_3OH}$ 248 mμ (ε 11,200), 327 (13,200), 337 (13,600); $\lambda_{max}^{NaOH-CH_3OH}$ 246 mμ (ε 20,000), 293 mμ (ε 10,600); $\lambda_{max}^{CHCl_3}$ 3.0–3.2, 3.7, 5.88, 6.23, 9.05–9.20 μ.

Anal. Calcd. for $C_{25}H_{31}NO_5S_2$: C, 61.33; H, 6.38; N, 2.86; S, 13.10. Found: C, 61.02; H, 6.42; N, 2.32; S, 12.73.

17α,20;20,21-Bismethylenedioxy-16α-methyl-11-oxo-4-pregnene[3,2-*d*]thiazole (IV).—A solution of 200 mg. of III in 40 ml. of tetrahydrofuran was treated with 2 equiv. of sodium methoxide. The precipitated salt was dissolved by addition of 40 ml. of methanol. Two equivalents of 0.1 *N* aqueous hydrogen peroxide was added with stirring over a period of 5 min. and stirring was continued for an additional 90 min., followed by the addition of 20 ml. of 2 *N* sulfuric acid. The product was isolated by extraction with chloroform. Crystallization from chloroform–ether afforded 145 mg. of IV, m.p. 295–305° dec. A sample for analysis after chromatography on acid washed alumina was obtained by elution with benzene–ether (19:1) and crystallization from methylene chloride–ether, m.p. 322–325° dec; $[\alpha]^{24}D$ +121° (*c* 0.5, $CHCl_3$); $\lambda_{max}^{CHCl_3}$ 271 mμ (ε 8400); $\lambda_{max}^{CHCl_3}$ 5.88, 6.1, 6.5, 9.06 μ.

Anal. Calcd. for $C_{25}H_{31}NO_5S$: C, 65.62; H, 6.84; N, 3.06; S, 7.00. Found: C, 64.94; H, 7.08; N, 3.14; S, 6.95.

17α,20;20,21-Bismethylenedioxy-11β-hydroxy-16α-methyl-4-pregnene[3,2-*d*]thiazole (V).—A suspension consisting of 125 mg. of IV, 125 mg. of lithium aluminum hydride, and 25 ml. of tetrahydrofuran was refluxed for 1 hr. under nitrogen, cooled in ice, and excess lithium aluminum hydride decomposed with 1.75 ml. of water. The product was filtered, concentrated to dryness, and chromatographed on acid-washed alumina. Elution with benzene–ether (9:1 and 3:1) and crystallization from ether–petroleum ether (b.p. 30–60°) afforded 65 mg. of V, m.p. 217–219°. Recrystallization from acetone–ether–petroleum ether gave a sample for analysis, m.p. 219–220°; $[\alpha]^{24}D$ +60° (*c* 0.62, $CHCl_3$); $\lambda_{max}^{CH_3OH}$ 263 mμ (ε 9680); $\lambda_{max}^{CHCl_3}$ 2.75, 3.0, 6.1, 6.5, 9.08 μ.

Anal. Calcd. for $C_{25}H_{33}NO_5S$: C, 65.33; H, 7.24; N, 3.05; S, 6.98. Found: C, 65.65; H, 7.06; N, 2.65; S, 6.72.

11β,17α,21-Trihydroxy-16α-methyl-20-oxo-4-pregnene[3,2-*d*]thiazole (VI).—A mixture of 200 mg. of V in 20 ml. of 60% aqueous formic acid was heated for 30 min. at 100° under nitrogen. The solution was cooled with ice, extracted with chloroform, washed with aqueous sodium bicarbonate solution, and taken to dryness. The white foam obtained was dissolved in 20 ml. of dry methanol, and 0.15 equiv. of a solution of sodium methoxide in methanol was added. The solution was stirred for 12 min. at room temperature under nitrogen and treated with 1 drop of acetic acid. Most of the methanol was removed *in vacuo* at a bath temperature of 35°. The residue was taken up in chloroform, washed to neutrality, and taken to dryness. Crystallization from acetone–ether afforded 75 mg. of VI, m.p. 131–135°. Two further recrystallizations from acetone–ether and acetone–petroleum ether gave a sample for analysis, m.p. 131–137°; $[\alpha]^{24}D$ +150° (*c* 0.43, $CHCl_3$); $\lambda_{max}^{CH_3OH}$ 263 mμ (ε 8500); $\lambda_{max}^{CHCl_3}$ 3.0–3.1, 5.86, 6.15, and 6.52 μ.

Anal. Calcd. for $C_{23}H_{31}NO_4S$: C, 66.15; H, 7.49. Found: C, 65.97; H, 7.78.

17α,20;20,21-Bismethylenedioxy-2-hydroxyimino-16α-methyl-4-pregnene-3,11-dione (VII).—A solution of 1.0 g. of I in 6 ml. of methylene chloride, 30 ml. of glacial acetic acid, and 2 ml. of water was cooled in ice. Sodium nitrite (158 mg.) in 7 ml. of water was added with stirring, and stirring was continued for 30 min. at 0° in an atmosphere of nitrogen. At the end of this time, 60 ml. of ice–water was added to the reaction mixture. The product was extracted with methylene chloride and washed with water, saturated $NaHCO_3$, and NaCl solutions. The methylene chloride solution was dried over $MgSO_4$ and concentrated to dryness *in vacuo*. Crystallization from ethyl acetate yielded 540 mg., m.p. 240–247° dec. Several recrystallizations from ethyl acetate afforded an analytical sample of VII, m.p. 255–257° dec; $[\alpha]^{25}D$ +66° (*c* 0.97, $CHCl_3$); $\lambda_{max}^{CH_3OH}$ 260 mμ (ε 13,790); $\lambda_{max}^{CHCl_3}$ 3.04, 5.84, 5.93, 6.14 μ.

Anal. Calcd. for $C_{24}H_{31}NO_7$: C, 64.70; H, 7.01; N, 3.14. Found: C, 64.66; H, 7.20; N, 3.51.

17α,20;20,21-Bismethylenedioxy-2′-mercapto-16α-methyl-11-oxo-1′-phenyl-4-pregnen[2,3-*d*]imidazole (IX).—Zinc dust was added to a solution of 3.25 g. of VII and 3.3 ml. of phenylisothiocyanate in 65 ml. of glacial acetic acid, in *ca.* 100-mg. portions every 5–10 min. during 1 hr. with stirring. Stirring was continued at room temperature for an additional 3 hr. The suspension was filtered, concentrated *in vacuo*, and taken up in ethyl acetate. The ethyl acetate solution was washed with water and saturated NaCl solution, dried over Na_2SO_4, and concentrated *in vacuo* to yield 5 g. of a brown oil. The greater part of the excess phenyl isothiocyanate could be removed at 50° *in vacuo*.

The material was adsorbed from benzene on silica gel. The fractions eluted with benzene containing 25–50% ether were combined to yield 2 g. of a yellow foam. Crystallization from ethyl acetate afforded 1.23 g. of IX, m.p. 240–245°. Two further recrystallizations from methylene chloride–ethyl acetate gave a sample for analysis, m.p. 291–294° (evacuated capillary); $[\alpha]^{25}D$ +76° (*c* 0.71, $CHCl_3$); $\lambda_{max}^{CH_3OH}$ 270 mμ (ε 8750) and 321 mμ (ε 13,900); $\lambda_{max}^{CH_3OH-NaOH}$ 331 mμ (ε 11,800); $\lambda_{max}^{CHCl_3}$ 2.96, 3.15, 3.7, 3.78, 5.90, 6.24, 9.1–9.2 μ.

Anal. Calcd. for $C_{31}H_{36}N_2O_5S$: C, 67.82; H, 6.61; N, 5.11; S, 5.84. Found: C, 67.96; H, 6.64; N, 5.50; S, 6.14.

17α,20;20,21-Bismethylenedioxy-16α-methyl-11-oxo-1′-phenyl-4-pregnen[2,3-*d*]imidazole (X).—A solution consisting of 5.56 mmoles of sodium methoxide in methanol was added with stirring to a solution of 1.53 g. of the thiol IX (2.78 mmoles) in 255 ml. of acetonitrile maintained under an atmosphere of nitrogen. This was followed by the addition of 5.56 mmoles of hydrogen peroxide (0.1 *N* aqueous solution) which was added dropwise over a period of 10 min. The solution was stirred for 45 min. Then 125 ml. of 2 *N* sulfuric acid was added with vigorous stirring. Gas evolution was observed. After 15 min. the product was extracted with ethyl acetate, washed with saturated aqueous $NaHCO_3$ solution, followed by saturated NaCl solution, and dried over $MgSO_4$. Concentration to dryness afforded 1.5 g. of a yellow foam. Chromatography on 50 g. of silica gel and elution with benzene–ether (1:1), ether, and ether–chloroform (19:1) mixtures afforded 798 mg. of crude product. Crystallization from methylene chloride–ether yielded 520 mg. of X as yellow crystals, m.p. 222–242° dec. Further crystallization from methylene chloride–ethyl acetate and methylene chloride–acetone afforded a sample for analysis, m.p. 249–255° dec; $[\alpha]^{25}D$ +113° (*c* 0.50, $CHCl_3$); $\lambda_{max}^{CH_3OH}$ 225 mμ (ε 17,100), 290 (9900), and 295 (10,100); λ_{max}^{KBr} 5.88, 6.21, 6.64, 9.15, and 14.4 μ.

Anal. Calcd. for $C_{31}H_{36}N_2O_5$: C, 72.07; H, 7.02; N, 5.42. Found: C, 71.86; H, 6.77; N, 5.52.

17α,20;20,21-Bismethylenedioxy-11β-hydroxy-16α-methyl-1′-phenyl-4-pregnen[2,3-*d*]imidazole (XI).—A suspension consisting of 320 mg. of the ketone X in 55 ml. of tetrahydrofuran and 320 mg. of lithium aluminum hydride was refluxed in an atmosphere of nitrogen for 3 hr., then cooled in ice, and excess lithium aluminum hydride was destroyed with 4.0 ml. of water. The suspension was filtered, and the filtrate was taken to dryness. A slightly yellow foam was obtained. Crystallization from acetone–ether afforded 216 mg. of XI, m.p. 200–205°. One further recrystallization from the same solvents gave a sample for analysis, m.p. 212–215°; $[\alpha]^{25}D$ +55° (*c* 0.54, $CHCl_3$); $\lambda_{max}^{CH_3OH}$ 227 mμ (ε 16,000), 288 (9400), and 293 (9600); $\lambda_{max}^{CH_3OH-HCl}$ 222 mμ (ε 10,500), 278 (11,000), and 283 (11,300); $\lambda_{max}^{CHCl_3}$ 3.1–3.15, 6.23, 6.65, and 9.1–9.3 μ.

Anal. Calcd. for $C_{31}H_{38}N_2O_5$: C, 71.79; H, 7.39; N, 5.40. Found: C, 71.68; H, 7.52; N, 5.52.

11β,17α,21-Trihydroxy-16α-methyl-20-oxo-1′-phenyl-4-pregnen[2,3-*d*]imidazole (XII).—A suspension consisting of 150 mg. of the BMD XI and 15 ml. of 60% aqueous formic acid was heated for 30 min. at 100° in an atmosphere of nitrogen. The solution was cooled rapidly in ice, ice water was added, and the product was taken up in chloroform. The chloroform layer was washed sequentially with water, saturated $NaHCO_3$ solution, water, and saturated NaCl solution, dried over Na_2SO_4, and evaporated to dryness *in vacuo*. The crude product was dissolved in 100 ml. of dry methanol, 0.15 equiv. of sodium methoxide was added, and the solution was stirred for 15 min. at room temperature in a nitrogen atmosphere. One drop of glacial acetic acid was added and the greater part of the methanol was removed *in vacuo* at room temperature. The residue was taken up in ethyl acetate. The solution was washed with saturated $NaHCO_3$ and NaCl solution, dried over Na_2SO_4, and concentrated to a white glass. Crystallization from acetone afforded 75 mg. of XII, m.p. 159–177°. The mother liquor gave an additional 38 mg. of compound. Recrystallization from methanol–ether, methylene chloride–acetone–ether, and methylene chloride–ether gave a sample for analysis, m.p. 180–184° dec;

$[\alpha]^{25}D$ +132° (*c* 0.50, $CHCl_3$); $\lambda_{max}^{CH_3OH}$ 225 mμ (ε 22,300), 288 (9800), and 293 (10,000); $\lambda_{max}^{CHCl_3}$ 2.85–3.1, 5.85, 6.20, 6.63 μ.

Anal. Calcd. for $C_{29}H_{36}N_2O_4$: C, 73.08; H, 7.61. Found: C, 72.43; H, 7.75.

17α,20;20,21-Bismethylenedioxy-16α-methyl-11-oxo-4-pregnene[3,2-*d*]-1′,2′,3′-triazole (XIII).—A mixture of 2.7 g. of VII, 240 ml. of ethylene glycol, 33 ml. of hydrazine monohydrate, and 24 g. of 85% KOH was refluxed in a nitrogen atmosphere for 4 hr. The reaction mixture was cooled to room temperature, 600 ml. of water was added, and 600 mg. of a brown precipitate was collected by filtration. The filtrate was extracted continuously for 3 days with chloroform, giving 1.8 g. of a brown foam. The latter was combined with the precipitate and chromatographed on 80 g. of silica gel. The eluates with benzene and 10, 25, and 50% ether (520 mg.) afforded 170 mg. of crystalline XIII, m.p. 275–285° dec. from ethyl-acetate. Recrystallization from chloroform gave the analytical sample, m.p. 281–286° dec; $[\alpha]^{25}D$ +49° (*c* 0.25, $CHCl_3$); $\lambda_{max}^{CH_3OH}$ 258 mμ (ε 12,300); λ_{max}^{Kbr} 5.89, 6.01, 6.21, 6.54, 9.05 μ.

Anal. Calcd. for $C_{24}H_{31}N_3O_5$: C, 65.28; H, 7.08; N, 9.52. Found: C, 65.23; H, 6.90; N, 9.75.

17α,20;20,21-Bismethylenedioxy-2-hydroxyimino-16α-methyl-4-pregnene-3,11-dione 3-Phenylhydrazone (VIII).—A solution of 300 mg. of the 2-oxime VII in 9 ml. of ethanol and 120 mg. of phenylhydrazine was kept at room temperature overnight. Water and benzene–ether (~1:1) were added and the organic layer was washed twice with 2 *N* HCl, saturated $NaHCO_3$ solution, and water. A brown amorphous material (353 mg.) was obtained. A portion of 340 mg. was dissolved in 4 ml. of benzene and filtered through 1 g. of acid-washed alumina. Elution with 30 ml. of benzene yielded 302 mg. of tan amorphous VIII, $\lambda_{max}^{CH_3OH}$ 366 mμ (ε 16,100), 249 mμ (ε 14,100).

17α,20;20,21-Bismethylenedioxy-16α-methyl-11-oxo-2′-phenyl-4-pregnene[3,2-*d*]-2′H-1′,2′,3′-triazole (XIV).—To an ice-cooled solution of 100 mg. of the crude hydroxyimino phenylhydrazone VIII in 20 ml. of chloroform and 7 ml. of pyridine was added 300 mg. of phosphorus pentachloride in two portions. After stirring for 15 min., the brown solution was heated to 65° for 10 min. The cooled reaction mixture was diluted with *ca.* 50 ml. of chloroform and washed sequentially with water, 2.5 *N* HCl, and finally with water to neutrality. The crude gummy material was dissolved in 7 ml. of benzene and chromatographed on 6 g. of acid-washed alumina. Benzene (250 ml.) and benzene–ether (50:1, 70 ml.) eluted 73 mg. of pale yellow material which was crystallized twice from methylene chloride–ether to give 46 mg. of fine, colorless needles (XIV), m.p. 277–279°. The crystallization of the combined mother liquors yielded another 12 mg., m.p. 277–279°. For analysis XIV was crystallized twice from methylene chloride–methanol, m.p. 279–279.5°; $[\alpha]^{25}D$ −8° (*c* 1.0, $CHCl_3$); $\lambda_{max}^{CH_3OH}$ 310 mμ (ε 32,000), 304 mμ (ε 32,500).

Anal. Calcd. for $C_{30}H_{35}N_3O_5$: C, 69.61; H, 6.82. Found: C, 69.58; H, 6.70.

17α,20;20,21-Bismethylenedioxy-11β-hydroxy-16α-methyl-2′-phenyl-4-pregnene[3,2-*d*]-2′H-1′,2′,3′-triazole (XV).—A solution of 570 mg. of 11-ketophenyltriazole XIV in 50 ml. of methylene chloride, 150 ml. of a saturated solution of sodium borohydride in 2-propanol, and 15 ml. of water was stirred at room temperature for 30 hr. A probe, worked up as described below, showed that most of the 11-carbonyl was reduced. Triethylamine (1 ml.) was added and the solution was stirred an additional 60 hr. The reaction mixture was cooled in ice and the excess sodium borohydride was destroyed with 2.5 *N* HCl (final pH~6.5). Water (300 ml.) was added and the steroid was extracted with ethyl acetate. The organic layer was washed with water four times, dried, and evaporated. This material (722 mg.) plus 122 mg. of mother liquors of an earlier run were dissolved in 10 ml. of benzene and chromatographed on 18.5 g. of acid-washed alumina. Benzene–ether (50:1, 180 ml.; 25:1, 180 ml.; and 25:2, 130 ml.) eluted a total of 620 mg. of solid, which was crystallized once from methylene chloride–methanol to yield 461 mg. of XV, m.p. 236–237°. For analysis a sample was crystallized twice from methylene chloride–methanol (plus a trace of water) and very fine needles (different in shape from the product with m.p. 236–237°) were obtained, m.p. 212–212.5°[27]; $[\alpha]^{25}D$ −38° (*c* 1.0, $CHCl_3$); $\lambda_{max}^{CH_3OH}$ 310 mμ (ε 32,600), 305 mμ (ε 32,600).

Anal. Calcd. for $C_{30}H_{37}N_3O_5$: C, 69.34; H, 7.18. Found: C, 68.94; H, 6.99.

Further elution of the column with benzene–ether (5:1) and ether yielded an oily product (40 mg.) which was not crystallized. Treatment with pyridine–acetic anhydride (1:1) overnight at room temperature resulted in complete acetylation, indicating that the 11α-hydroxy isomer of XV was present.

11β,17α,21-Trihydroxy-16α-methyl-20-oxo-2′-phenyl-4-pregnene[3,2-*d*]-2′H-1′,2′,3′-triazole (XVI).—A solution of 400 mg. of 11-hydroxyphenyltriazole XV in methylene chloride was evaporated to dryness. The amorphous product was then dissolved in 400 ml. of 60% aqueous formic acid and was heated under nitrogen for 20 min. on the steam bath. The reaction mixture was filtered and the filtrate was concentrated to dryness *in vacuo*. The product (265 mg.) was dissolved in 35 ml. of pure methanol and treated for 10 min. at room temperature under nitrogen with 28 mg. of sodium methoxide. After addition of a few drops of glacial acetic acid (pH of the solution ~6.5), the solution was taken to dryness *in vacuo*. The solid was dissolved in a little methanol and the solution was diluted with ethyl acetate and washed twice with saturated NaCl solution. The resulting semicrystalline material (218 mg.) was crystallized from methanol–ethyl acetate to yield 168 mg. of XVI, m.p. 235–236°; $[\alpha]^{25}_{546}$ −43° (*c* 2.9, $CHCl_3$); $\lambda_{max}^{CH_3OH}$ 310 mμ (ε 32,400), 304 mμ (ε 32,900).

Anal. Calcd. for $C_{28}H_{33}N_3O_4 \cdot 0.5CH_3OH$: C, 69.35; H, 7.55. Found: C, 69.73; H, 7.60.

17α,20;20,21-Bismethylenedioxy-16α-methyl-11-oxo-2′-phenyl-4-pregnene[3,2-*d*]-2′H-1′,2′,3′-triazole N-1′-Oxide (XVIa).—A solution of 500 mg. of VIII in 150 ml. of dioxane, 20 ml. of chloroform, and 70 ml. of water was heated to reflux, and 1.5 g. of chalcanthite was added in three portions. The brown solution was kept at reflux for 1.5 hr. The cooled reaction mixture was diluted with water, filtered, and the filtrate was concentrated to dryness *in vacuo*. The filter cake was suspended in methylene chloride and water, and the organic phase was combined with the concentrated filtrate. The methylene chloride solution was washed twice with water, 2.5 *N* HCl, and 2 *N* KOH. The neutral product (437 mg.) was dissolved in 10 ml. of benzene and added to a column of 21 g. of acid-washed alumina. Elution with benzene–ether mixtures produced 338 mg. of XVIa. Two crystallizations from methylene chloride–ether afforded fine needles, m.p. 269°; $[\alpha]^{25}_{546}$ +15° (*c* 1.0, $CHCl_3$); $\lambda_{max}^{CH_3OH}$ 227, 252, and 297 mμ (ε 15,600, 16,700, and 18,800); λ_{max}^{Nujol} 5.91, 6.14, 6.43, 6.58 μ.

Anal. Calcd. for $C_{30}H_{35}N_3O_6$: C, 67.57; H, 6.61. Found: C, 67.64; H, 6.35.

17α,20;20,21-Bismethylenedioxy-11β-hydroxy-16α-methyl-2′-phenyl-4-pregnene[3,2-*d*]pyrimidine (XIX) and 17α,20;20,21-Bismethylenedioxy-11β-methoxymethyleneoxy-16α-methyl-2′-phenyl-4-pregnene[3,2-*d*]pyrimidine (XX).—A crude mixture (1.0 g.) of 2-formyl-16α-methylhydrocortisone BMD XVII and the corresponding 11β-methoxymethylene ether XVIII, 863 mg. of benzamidine hydrochloride dihydrate, and 244 mg. of sodium methoxide in 50 ml. of dimethylformamide was refluxed under nitrogen for 4 hr. The solvent was distilled under reduced pressure and the residue was shaken with ethyl acetate and water. The organic layer was washed to neutrality with water, dried, concentrated, and the product was purified by chromatography on acid-washed alumina. Elution with benzene–15% ether afforded 171 mg. of XX. A sample for analysis was crystallized from methanol–ether and from ethyl acetate, m.p. 205–208°; $\lambda_{max}^{CH_3OH}$ 258, 307 mμ (ε 40,700, 9600); $\lambda_{max}^{CH_3OH-HCl}$ 276 mμ (ε 29,150).

Anal. Calcd. for $C_{34}H_{42}N_2O_6$: C, 71.05; H, 7.39; N, 4.87. Found: C, 70.84; H, 7.29; N, 4.34.

Elution with benzene–40% ether gave 174 mg. of XIX. A sample for analysis was crystallized from acetone–ether and from ethyl acetate, m.p. 158–161°; $\lambda_{max}^{CH_3OH}$ 258, 307 mμ (ε 38,700, 8550); $\lambda_{max}^{CH_3OH-HCl}$ 276 mμ (ε 25,600).

Anal. Calcd. for $C_{32}H_{38}N_2O_5$: C, 72.43; H, 7.22; N, 5.28. Found: C, 72.32; H, 7.16; N, 4.75.

11β,17α,21-Trihydroxy-16α-methyl-20-oxo-2′-phenyl-4-pregnene[3,2-*d*]pyrimidine (XXI).—Reaction of either XX or XIX with 60% aqueous formic acid for 30 min. on the steam bath followed by sodium methoxide treatment yielded XXI. A sample for analysis was crystallized from ethyl acetate, m.p.

(27) In an earlier run another low-melting polymorph of XV was obtained. The two forms (m.p. 236–237 and 159–161°) could be interconverted by cross seeding. The low-melting form crystallized from ether or ether–petroleum ether.

216–220°; $[\alpha]^{25}D$ +108° (*c* 0.54, acetone); $\lambda_{max}^{CH_3OH}$ 258, 307 mμ (ε 40,500, 9500); $\lambda_{max}^{CH_3OH-HCl}$ 276 mμ (ε 27,400).

Anal. Calcd. for $C_{30}H_{36}N_2O_4$: C, 73.74; H, 7.43. Found: C, 73.63; H, 7.79.

17α,20;20,21-Bismethylenedioxy-16α-methyl-6,11-dioxo-3′-phenyl-5α-pregnane[3,2-*d*]-3′H-1′,2′,3′-triazole (XXIII).—A solution consisting of 2.0 g. of XXII and 2 ml. of morpholine in 20 ml. of benzene was refluxed vigorously for 1 hr. in the presence of Linde molecular sieves contained in a Soxhlet extractor. The cooled enamine was concentrated *in vacuo*, flushed once with benzene (infrared 5.87, 6.07, 6.16 μ), and refluxed overnight with 1.5 ml. of phenyl azide and 30 ml. of benzene. The solution was concentrated *in vacuo* and chromatographed on 100 g. of acid-washed alumina. Elution with chloroform and crystallization from ethyl acetate yielded 530 mg. of XXIII. A sample for analysis was crystallized from chloroform–ethyl acetate, m.p. 350°; $[\alpha]^{25}D$ +5° (*c* 1.0, $CHCl_3$); $\lambda_{max}^{CH_3OH}$ 228 mμ (ε 10,800); λ_{max}^{Nujol} 5.90, 6.28, 6.68 μ.

Anal. Calcd. for $C_{30}H_{35}N_3O_6$: C, 67.52; H, 6.61; N, 7.88. Found: C, 67.45; H, 6.49; N, 7.58.

17α,20;20,21-Bismethylenedioxy-6β-hydroxy-6α,16α-dimethyl-11-oxo-3′-phenyl-5α-pregnane[3,2-*d*]-3′H-1′,2′,3′-triazole (XXIV).—Five milliliters of 1 *N* methylmagnesium iodide in ether was added to an azeotropically dried solution of 0.6 g. of XXIII and 200 ml. of benzene at *ca.* 40°. The suspension was allowed to come to room temperature and ice–water was added after a total reaction time of 45 min. After filtration, the benzene layer was separated, dried, and concentrated *in vacuo*. Crystallization from ethyl acetate–chloroform afforded 410 mg. of XXIV, m.p. 350–360° dec; $[\alpha]^{25}D$ +14° (*c* 1.0, $CHCl_3$); $\lambda_{max}^{CH_3OH}$ 229 mμ (ε 11,200); λ_{max}^{Nujol} 2.9, 5.92, 6.29, 6.67 μ.

Anal. Calcd. for $C_{31}H_{39}N_3O_6$: C, 67.74; H, 7.15; N, 7.65. Found: C, 67.54; H, 7.01; N, 7.51.

17α,20;20,21-Bismethylenedioxy-6,16α-dimethyl-11-oxo-3′-phenyl-5-pregnene[3,2-*d*]-3′H-1′,2′,3′-triazole (XXV).—A solution consisting of 1.2 ml. of thionyl chloride in 7 ml. of ice-cold pyridine was added to 300 mg. of XXIV in 8 ml. of pyridine at 5°. The solution was allowed to come to room temperature and poured into ice–water after a total reaction time of 35 min. The precipitate was filtered and crystallized from ethyl acetate to yield 280 mg. of XXV, m.p. 245–254°; $[\alpha]^{25}D$ +5° (*c* 1.0, $CHCl_3$); $\lambda_{max}^{CH_3OH}$ shoulder at 224 mμ (ε 11,200); λ_{max}^{Nujol} 5.85, 6.28, 6.67 μ.

Anal. Calcd. for $C_{31}H_{37}N_3O_5$: C, 70.03; H, 7.02. Found: C, 69.71; H, 6.80.

17α,20;20,21-Bismethylenedioxy-4β-hydroxy-6,16α-dimethyl-11-oxo-3′-phenyl-5-pregnene[3,2-*d*]-3′H-1′,2′,3′-triazole (XXVI).—A solution of 520 mg. of XXV and 500 mg. of selenium dioxide in 35 ml. of butanone dioxolane was refluxed for 3.5 hr. The cooled solution was filtered, washed with aqueous sodium bicarbonate solution, dried, and concentrated *in vacuo*. Crystallization from ethyl acetate afforded 350 mg. of XXVI. A sample for analysis was recrystallized from ethyl acetate, m.p. 280–300° dec; $[\alpha]^{25}D$ −25° (*c* 1.0, $CHCl_3$); $\lambda_{max}^{CH_3OH}$ 228 mμ (ε 10,600); λ_{max}^{Nujol} 3.07, 5.93, 6.30, 6.70 μ.

Anal. Calcd. for $C_{31}H_{37}N_3O_6$: C, 67.99; H, 6.81. Found: C, 67.01; H, 7.10.

11β,17α,21-Trihydroxy-6,16α-dimethyl-20-oxo-3′-phenyl-4,6-pregnadiene[3,2-*d*]-3′H-1′,2′,3′-triazole 21-Acetate (XXVII).—A solution of 320 mg. of XXVI in 35 ml. of tetrahydrofuran was stirred with 340 mg. of sodium borohydride and 3.5 ml. of water at room temperature for 64 hr. The mixture was poured into aqueous NaH_2PO_4 solution. The product was extracted with chloroform, the extract was dried and concentrated *in vacuo*. The crude 11β-hydroxy steroid (infrared shows the absence of carbonyl absorption) in 30 ml. of 60% aqueous formic acid was heated on the steam cone for 45 min. The cooled solution was diluted with water and extracted with chloroform. The chloroform layer was washed with water and aqueous $NaHCO_3$, dried, and concentrated *in vacuo*. The product dissolved in 10 ml. of methanol was purged with nitrogen and allowed to stand with 0.20 ml. of 0.6 *N* methanolic sodium methoxide for 15 min. at room temperature. After addition of a few drops of acetic acid, the reaction mixture was concentrated *in vacuo*. The residue was taken up in chloroform. The solution was washed with water, dried, concentrated *in vacuo*, and acetylated with 3 ml. of acetic anhydride and 3.5 ml. of pyridine at room temperature overnight. A partition column[28] was packed with 225 g. of Supercel which had been slurried with 2 l. of chloroform–isooctane (1:7) and 225 ml. of formamide, and washed with 3 l. of chloroform–isooctane (1:7) saturated with formamide. The steroid dispersed on 5 g. of Supercel and 5 ml. of formamide saturated with chloroform–isooctane (1:7) was poured onto the column with 50 ml. of chloroform–isooctane (1:7), followed by 15 l. of the same solvent to elute three minor components. The progress of the separation was followed by measuring the absorption density at 315 mμ with a Beckman Model DU spectrophotometer. Elution with 5 l. of chloroform–isooctane (2:6) saturated with formamide followed by percolation of a center cut through silica gel with ether afforded 65 mg. of XXVII, m.p. 204–207°. A sample for analysis was recrystallized from ethyl acetate–ether, m.p. 204–207°; $[\alpha]^{25}D$ +20° (*c* 1.0, $CHCl_3$); $\lambda_{max}^{CH_3OH}$ 263, 318 mμ (ε 10,400, 22,500); $\lambda_{max}^{CHCl_3}$ 2.77, 2.95–3.00, 5.75, 5.80, 6.21, 6.38, 6.59 μ.

Anal. Calcd. for $C_{31}H_{37}N_3O_5$: C, 70.03; H, 7.02. Found: C, 70.16; H, 7.22.

(28) We are indebted to R. Vitali for suggesting this partition system.