was washed with H₂O. The product was extracted into saturated NaHCO₃ solution which was then acidified with HCl and extracted with Et₂O. Evaporation of the dried (Na₂SO₄) Et₂O gave 0.65 g of the 17β-hydroxy-1,4-seco-5α-androstane-1,4-dioic acid acetate which was esterified with CH₂N₂ to give 8. Recrystallization from MeOH gave 0.50 g of 8. Several recrystallizations from MeOH furnished the analytical sample: mp 116-118°; $[\alpha]^{20}D - 26^{\circ}$ (c 1, CHCl₃); nmr 3.62 and 3.7 ppm (6 H, 2-OCH₃). Anal. (C₂₁H₂₂O₆) C, H.

1,4-Seco-2,3-bisnor- 5α -androstane-1,4,17 β -triol 17-(2'-Tetrahydropyranyl) Ether (9).—Compound 7 was treated with CH₂N₂ in Et₂O to give the corresponding dimethyl ester, as indicated by the nmr spectrum: 0.72 (s, 18-H), 1.12 (s, 19-H), 3.62 and 3.73 ppm (s, s, 3, 3, OCH₃). A solution of 0.5 g of the dimethyl ester in 50 ml of dry dihydropyran and a drop of POCl₃ was stirred at room temperature for 1 hr and evaporated under reduced pressure. The residue was dissolved in ether, washed (NaHCO₂ solution, H₂O), dried (Na₃SO₄), and evaporated to give the crude tetrahydropyranyl ether, as indicated by the nmr spectrum: 0.78 (s, 3, 18-H), 1.12 (s, 3, 19-H), 3.62 and 3.70 ppm (s, s, 3, 3, OCH₂).

This tetrahydropyranyl ether (0.25 g) was dissolved in 50 ml of dry Et₂O and added to 0.5 g of LAH in 100 ml of dry Et₂O. It was refluxed and stirred for 3 hr after which no starting material remained, as shown by tlc. A saturated solution of sodium potassium tartrate was carefully added, and the mixture was filtered. The precipitate was washed with Et₂O, and the combined Et₂O solution was washed (dilute HCl, H₂O), dried (Na₂-SO₄), and evaporated. The residue was crystallized several times from Me₂CO giving colorless crystals, mp 158-160°. Anal. (C₂₂H₃₈O₄) C, H.

1,4-Seco-5 α -androstane-1,4,17 β -triol 1,4-Dimethanesulfonate 17-(2'-Tetrahydropyranyl) Ether (10).—To a cold solution of 0.16 g of 9 in 3 ml of pyridine was added dropwise with stirring, a cold solution of 0.15 g of MeSO₂Cl in 0.5 ml of pyridine. After the addition was complete, the reaction mixture was stirred at 25° for 3 hr. The mixture was diluted with ice-H₂O (100 ml) and the precipitate was filtered and washed (H₂O). It was recrystallized from Et₂O-petroleum ether (bp 30-60°) to give 0.17 g of 10. Several recrystallizations from the same solvent gave the analytical sample: mp 114-116°; nmr, 0.77 (s, 3, 18-H), 0.84 (s, 3, 19-H), 3.4 and 3.5 ppm (2 s, 6, SO₂CH₃). Anal. (C₂₄H₄₂O₈S₂) C, H, S.

1,4-Dibromo-1,4-seco-2,3-bisnor- 5α -androstan-17 β -ol Acetate (11).—To 1.9 g of 2 in 100 ml of stirred, refluxing CCl₄, there was added 1.62 g of red HgO. The reaction mixture was shielded

from light, and Br₂ (1.6 g) was added dropwise. After 1.5 hr, the reaction mixture was allowed to cool, the dark mixture was filtered, and the filtrate was concentrated under vacuum. The residue was chromatographed on Al₂O₃ to give 1.1 g of pure 11 which was recrystallized from MeOH; mp 155–158°, $[\alpha]^{20}D - 2^{\circ} (c 1, CHCl_3)$. Anal. (C₁₉H₃₀Br₂O₂) C, H, Br. 2-Thia-A-nor-5 α -androstan-17 β -ol (12). Procedure A.—A

2-Thia-A-nor- 5α -androstan-17 β -ol (12). Procedure A.—A solution of NaHS was prepared by bubbling H₂S into a suspension of 9 g of NaOMe in 70 ml of HOCH₂CH₂OEt until the exothermic reaction ceased. The resulting mixture was filtered and to 30 ml there was added 0.10 g of 10. The mixture was heated at reflux for 20 min, cooled, and diluted with H₂O. The precipitated product was collected and dried. The protecting ether group was hydrolyzed in 10 ml of EtOH, 3 drops of HCl, and 1 ml of H₂O at 60° for 5 min. The mixture was cooled, evaporated, and extracted with Et₂O to afford a solid (0.050 g). Several recrystallizations from Et₂O-hexane gave the analytical sample, mp 141–143°, $[\alpha]^{20}D + 58^{\circ}$, m⁺ = 280. Anal. (C₁₇H₂₈OS) C, H, S.

Procedure B.—A solution of 0.10 g of **10**, 100 ml of 80% EtOH, and 300 mg of NaS was heated at reflux for 6 hr. After cooling, it was worked up as in procedure A to afford **12**, mp 141-143°.

Procedure C.—To a refluxing solution of 0.70 g of 11 in 100 ml of refluxing EtOH there was added a tenfold excess of NaSH dissolved in the minimum amount of H_2O . Heating was continued for 24 hr when the indicated complete conversion of the dibromide to the product. The solvent was removed under vacuum and the residue was taken up in Et₂O, washed (H₂O), dried (Na₂SO₄), and evaporated to give 0.50 g of 12 as a white solid.

2-Thia-A-nor-5 α -androstan-17 β -ol Acetate (13).—A solution of 0.05 g of 12 in 2 ml of pyridine and 1 ml of Ac₂O was kept overnight at 25°, poured into 20 ml of ice-H₂O, acidified to pH 3, and extracted with Et₂O. The Et₂O was washed several times with H₂O, dried (Na₂O₄), and evaporated to give an oil which was purified by preparative tlc on silica gel to give 13 as an oil soluble in all organic solvents. On drying under vacuum, it crystallized giving a solid which was crystallized from petroleum ether at -70° giving crystals, mp 88-89°, [α]²⁰D +50° (c 1, CHCl₃), m⁺ = 322. Anal. (C₁₉H₅₀O₂S) C, H, S.

2-Thia-A-nor-5 α -androstan-17 β -ol Propionate (14).—A solution of 0.05 g of 12 in 2 ml of pyridine was treated with 1 ml of (EtCO)₂O. It was worked up as in the case of 13, giving a solid, mp 88–90°, $[\alpha]^{20}$ D 64° (c 1, CHCl₃), m⁺ = 336. Anal. (C₂₀H₃₂-O₂S) C, H, S.

The Synthesis and Progestational Activity of Some 1,2α-Cyclomethylene-16-methylene Progesterone Derivatives

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The progestational activities and syntheses of the $1,2\alpha$ -cyclomethylene-16-methylene compounds 4, 15, and 25 and of the precursor 1,4,6-trienes 26, 16, and 23 are reported. In all cases the trienes exhibited higher progestational activity than the corresponding $1,2\alpha$ -cyclomethylene derivatives when tested intramuscularly in the rabbit.

The progestational potentiating effect of the 16methylene moiety has been described.² Recently, progesterone analogs have been reported which have a $1,2\alpha$ -cyclomethylene moiety.^{3,4} We felt it to be of biological interest to combine these two structural features in the same molecule and now report some of our findings with compounds of this type. Specifically, we have synthesized 1,2 α -cyclomethylene-16-methyl-ene-17 α -hydroxy-4,6-pregnadiene-3,20-dione 17-acetate (4), 1,2 α -cyclomethylene-6-methyl-16-methylene-17 α -hydroxy-4,6-pregnadiene-3,20-dione 17-acetate (15), and 1,2 α -cyclomethylene-16-methylene-6-chloro-17 α -hydroxy-4,6-pregnadiene-3,20-dione 17-acetate (25).

The synthesis of the $1,2\alpha$ -cyclomethylene 4 (Scheme

⁽¹⁾ From the Physiology and Biochemistry Department.

^{(2) (}a) E. Shapiro, T. Legatt, L. Weber, M. Steinberg, A. Watnick, M. Eisler, M. G. Hennessey, C. T. Coniglio, W. Charney, and E. P. Oliveto, J. Med. Pharm. Chem., 5, 975 (1962); (b) K. Syhora and R. Mazac, Collect. Czech. Chem. Commun., 31, 2768 (1966).

⁽³⁾ R. Wiechert and E. Kaspar, Chem. Ber., 93, 1710 (1960).

⁽⁴⁾ G. W. Krakower and H. A. Van Dine, J. Org. Chem., 31, 3467 (1966).

1) proceeded from the 4,6-diene $1.^{2b}$ – Dehydrogenation with dichlorodicyanobenzoquinone $(DDQ)^{\scriptscriptstyle 5}$ gave the



1,4,6-triene **2**.⁶ Introduction of the 1,2 α -cyclomethylene moiety into the 1,4,6-trien-3-one system has been accomplished by two methods. One method utilizes CH₂N₂ to give the 1 α ,2 α -pyrazoline which either by pyrolysis³ or on treatment with strong acid⁴ is converted to the desired cyclomethylene compound. The other method utilizes dimethylsulfoxonium methylide⁷ to effect the formation of the 1,2 α -cyclomethylene moiety.^{4,8}

Our experience has been, as may be noted for the preparation of 25, that the yields of cyclomethylene compounds by the first method are low. We therefore chose the second method using the Corey reagent described in ref 8. In order to avoid the base-catalyzed cyclizations of 17α -acetoxy-20-ketopregnanes to β -hydroxylactones and butenolides,⁹ the 17α -hydroxy 2 was used as the substrate and the $1,2\alpha$ -cyclomethylene 3 was obtained in 71% yield after crystallization. Acetylation of 3 using AcOH, trifluoroacetic anhydride (TFAA), and *p*-toluenesulfonic acid monohydrate (*p*-TSA·H₂O),¹⁰ afforded the 17-acetate 4 with the cyclomethylene substituent intact.

The procedure utilized for the preparation of 15^{11} is outlined in Scheme II. Oxidative bromination-de-

(6) D. N. Kirk and V. Petrow, British Patent 899,804 (June 27, 1962).

Note differences of physical constants for 2 in the Experimental Section. (7) E. J. Corey and M. Chaykovsky, J. Amer. Chem. Soc., 87, 1353 (1965).

hydrobromination of 5^{12} with Br_2 in DMF in the presence of LiBr, Li₂CO₃, and CaCO₃ at 80°13 afforded as the major component the 4,6-dienone 6 with the 16β methyl-16,17a-oxido moiety intact. However, some rearrangement of this oxido function did occur and the Δ^{15} -17 α -hydroxy 7 was also isolated in about 8% yield. Alternatively, 6 was obtained by chloranil dehydrogenation of 8.¹¹ When commercial, unrecrystallized chloranil was used, some transformation of the 16β -methyl-16,17 α -oxido function occurred, and in addition to 6, both 7 and the 16-methylene-17 α -hydroxy 9 were also obtained. Dehydrogenation of **6** with DDQ gave the triene 10 which on treatment with sulfuric acid in dioxane, followed by esterification with AcOH, TFAA, and p-TSA afforded the 16-methylene-17 α -acetoxy 16.⁶ Consistent with the results reported for 6-unsubstituted $\Delta^{1,4,6}$ -3-keto steroids,^{4,8} reaction of **10** with the Corey "ylide" reagent gave the $1,2\alpha$ -cyclomethylene 12 in 86% yield. The use of the 16 β -methyl-16,17 α -oxido moiety thus prevented the occurrence of butenolide formation referred to previously.9 A second product was also obtained which did not display, by ir spectroscopy, the nonconjugated 20-ketone, and by nmr (see Experimental Section) showed an additional methylene $(-CH_{2})$ with a chemical shift of 2.94 ppm. We have assigned the $16,17\alpha;20,22$ -bisoxide structure 13, with the stereochemistry at C-20 undetermined. Oxirane formation from saturated ketones with dimethylsulfoxonium methylide has been described previously.⁷ Ring opening of 12 proceeded with H_2SO_4 in dioxane to afford the 16-methylene- 17α -hydroxy 14 in 59% yield. Using HCl in aqueous acetone, 12 was converted to both 14 and the Δ^{15} -16-methyl 11, with the latter being obtained as the major component in 34% yield. The structure of 11 was supported by analytical and nmr data, as well as by comparison of rotations between 14 and 11. A positive rotational difference of 12° is observed for 14 as compared to 11, which is consistent with reported molecular rotations for 16-methylene- 17α -hydroxy compounds being $2-20^{\circ}$ more dextrorotatory than the Δ^{15} -16-methyl-17 α -hydroxy isomers.¹⁴ Acetylation of 14 with AcOH, TFAA, and p-TSA¹⁰ gave the desired $1, 2\alpha$ -cyclomethylene 17-acetate 15 in 67%vield.

The synthesis of the 6-chloro **25** is outlined in Scheme III.¹⁵ Chlorination of 16-methylene- 3β ,17 α dihydroxy-5-pregnen-20-one 3,17-diacetate (**17**)¹⁶ gave selectively the 5α ,6 β -dichloro **18**. Selective hydrolysis of the 3-acetate in **18** with HClO₄ in MeOH–CHCl₃ gave **19**. Oxidation of the 3-hydroxyl function in **19** with CrO₃ in pyridine¹⁷ followed by *in situ* dehydrohalogenation of **20** afforded directly the 3-keto- Δ^4 -6 β -chloro **21**^{2b} in approximately 32% yield. Transformation of **21** to the enol ether **22**^{2b} proceeded smoothly in dioxane with

(16) D. N. Kirk, V. Petrow, M. Stansfield, and D. M. Williamson, J. Chem. Soc., 2385 (1960).

(17) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, J. Amer. Chem. Soc., 75, 422 (1953).

⁽⁵⁾ D. Burn, D. N. Kirk, and V. Petrow, Proc. Chem. Soc., 14 (1960).

⁽⁸⁾ Schering A.G., Eire Patent 965/65 (Oct 14, 1965).

^{(9) (}a) H. G. Lehmann, Angew. Chem. Intern. Ed. Engl., 4, 783 (1965);
(b) G. W. Moersch, D. E. Evans, and G. S. Lewis, J. Med. Chem., 10, 254 (1967);
(c) private communication from these laboratories by Dr. A. Afonso.

⁽¹⁰⁾ E. Shapiro, L. Finckenor, H. Pluchet, L. Weber, C. H. Robinson, E. P. Oliveto, H. L. Herzog, I. I. A. Tabachnick, and E. Collins, *Steroids*, 9, 143 (1967).

⁽¹¹⁾ While this work was in progress, the preparation of **15** by a different route was described by British Drug Houses, Ltd., Belgan Patent 689,273 (April 14, 1967). We thank one of the referees for supplying information pertaining to this patent.

⁽¹²⁾ D. N. Kirk, V. Petrow, and D. M. Williamson, J. Chem. Soc., 2821 (1961).

⁽¹³⁾ The procedure used was essentially described by H. L. Dryden and M. J. Kalm, U. S. Patent 3.270,008 (Aug 30, 1966).

^{(14) (}a) Huang-Minlon, C.-H. Wu, J.-W. Chin, and Y.-C. Cheu. Sci. Sinica (Peking), 11, 1659 (1962); Chem. Abstr., 59, 2985c (1963); (b) F. v. Werder, K. Bruckner, K. H. Bork, H. Metz, B. Hampel, and H. J. Mannhardt, Ber., 95, 2110 (1962); (c) G. H. Phillips, W. Graham, G. I. Gregory, and J. Elks, U. S. Patent 3,040,069 (June 19, 1962).

⁽¹⁵⁾ See ref 2b for the reactions and processes which were employed to prepare some of the intermediates also prepared via Scheme III.



ethyl orthoformate, EtOH, and H₂SO₄. Dehydrogenation of **22** with DDQ in benzene¹⁸ to give the 1,4,6trienone was incomplete and appeared to consist of 4 parts of the 1,4,6-triene **23** to 1 part of the 4,6-diene. The reaction product was treated again with DDQ, this time in dioxane, thereby affording **23**.^{2b} Reaction of **23** with CH₂N₂ gave impure $1\alpha, 2\alpha$ -pyrazoline **24** which was exposed to HClO₄ to give the desired $1, 2\alpha$ -cyclomethylene **25** in approximately 19% yield from the impure pyrazoline.

Biological Activity.—Table I lists the intramuscular

activities of the three 1,2-cyclomethylene-16-methylene compounds we have described as well as the corresponding 1,4,6-trienes. Included also are the oral progestational activities, except for compounds 4 and 26. For comparison, the activities of the related 16-unsubstituted 6-chloro compounds 27 and 28 are also listed. The potentiating effect of the 16-methylene group is revealed in the intramuscular activities found for 23 and 25 as compared to 27 and 28, respectively. Whereas in the 16-methylene series introduction of the $1,2\alpha$ cyclomethylene moiety decreases the intramuscular progestational activity compared to the corresponding

 ^{(18) (}a) H. J. Ringold and A. Turner, Chem. Ind. (London), 211 (1962);
 (b) S. K. Pradhan and H. J. Ringold, J. Org. Chem., 29, 601 (1964).



1,4,6-trienes, the opposite effect can be observed for the 16-unsubstituted **27** and **28**.



Experimental Section¹⁹

16-Methylene-17 α -hydroxy-1,4,6-pregnatriene-3,20-dione (2). —A mixture of 9.00 g (0.0264 mole) of 16-methylene-17 α hydroxy-4,6-pregnadiene-3,20-dione (1) and 18.05 g (0.0795 mole) of DDQ in 450 ml of dioxane was refluxed with stirring for 3.5 hr. Evaporation *in vacuo* afforded a residue to which 500 ml of

TABLE I

PROGESTATIONAL ACTIVITY^a

Compd	Route of admin ^b	
	Im	Oral
29°		2.8
26^d	25.5	
4	6	
16	54.4	29.7
15	15.9	45.6
23	145	76
25	120	15.6
27^{e}	6.4	1.9
28'	75	15.6

^a Progesterone = 1. ^b Progestational activity was determmed in immature rabbits by the method of M. K. McPhail, J. Physiol. (London), 83, 145 (1934). The compounds were dissolved in sesame oil for intramuscular administration or suspended in an aqueous suspending medium (0.9% NaCl, 0.5% carboxymethylcellulose, 0.4% polysorbate 80, and 0.9% Ph-CH₂OĤ) for oral administration. Progesterone in sesame oil was always given intramuscularly. The statistical analysis for the progestational assays utilized the randomized Bloch analysis of variance with Dunnett's and Duncan's multiple comparison procedure (see G. Miller, Jr., "Simultaneous Statistical Inference," McGraw-Hill Book Co., Inc., New York, N. Y., 1967). ^e 17 α -Ethinyl-19-nortestosterone. ^d 16-Methylene-17 α -hydroxy-1,4,6-pregnatriene-3,20-dione 17-acetate, prepared from 2 by acetylation with AcOH, TFAA, and p-TSA H₂O as in ref 10 [mp 203-205-206°; $[\alpha]_D - 192°$; $\lambda_{max} 222 \text{ m}\mu$ ($\epsilon 12,400$), 256 (9950), 299(13,500); $\nu_{max} 1754, 1727, 1664, 1610, \text{ and } 1585 \text{ cm}^{-1}$]. ^e 6-Chloro-17α-hydroxy-1,4,6-pregnatriene-3,20-dione 17-acetate; cf. H. J. Ringold, A. Batres, A. Bowers, J. Edwards, and J. Zderic, J. Amer. Chem. Soc., 81, 3485 (1959). / 1,2a-Cyclomethylene-6-chloro-17 α -hydroxy-4,6-pregnadiene-3,20-dione 17acetate. We thank Berlin Laboratories, Inc., an affiliate of Schering A.G., Berlin, Germany, for a sample of this compound.

⁽¹⁹⁾ All melting points were determined on a Kofier hot stage microscope and are uncorrected. Rotations are in dioxane at 25° at about 1% concentration, uv spectra are of MeOH solutions, and ir spectra are in Nujoi unless otherwise stated. The nmr spectra were measured on a Varian A-60-A spectrometer in CDCls (MesS). Mass spectra were determined on a CEC 21-103 spectrometer using a heated-inlet system at a temperature of 200-230°. Analyses were determined by the Physical Organic Chemistry Department of Schering Corp. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within $\pm 0.4\%$ of the theoretical values.

 C_6H_6 was added, and the supernatant was separated by filtration. Evaporation of the filtrate afforded a residue which was dissolved in 2 l. of EtOAc-Et₂O (1:1). After washing with 5% NaOH, then H₂O, and drying (MgSO₄), the organic phase was evaporated to a residue *in vacuo*. Crystallization from EtOAc yielded 3.50 g (38.9%) of **2**: mp 220-224-225°; [a]D -99°, [a]D -124° (CHCl₃); λ_{max} 221 mµ (ϵ 12,590), 256 (9650), 299 (13,100) [lit.⁶ mp 212-214°, [a]²⁵D - 174° (CHCl₃)]. Anal. (C₂₂H₂₆O₃) C, H.

1,2 α -Cyclomethylene-16-methylene-17 α -hydroxy-4,6-pregnadiene-3,20-dione (3).—To a stirred slurry of 7.68 g of trimethylsulfoxonium iodide in 56 ml of DMSO was added 960 mg of a mixture of NaH-mineral oil (1:1). The reaction mixture was stirred at 25° for 1 hr, and then 2.70 g (0.00798 mole) of 2 was added as a solid. After 3 hr at 25°, the reaction mixture was added to 600 ml of H₂O. Collection of the resulting solid by filtration yielded 2.81 g of crude product. Crystallization from EtOAc gave 2 g (71.4%) of 3, mp 214-216-218°, [α]D +121°, $\lambda_{max} 282 m\mu$ ($\epsilon 20,400$). Anal. (C₂₃H₂₈O₃) C, H.

 $1,2\alpha$ -Cyclomethylene-16-methylene-4,6-pregnadiene-3,20dione 17-Acetate (4).-TFAA (7.0 ml) was slowly added within 5 min to a slurry of 1.75 g of 3, 175 mg of p-TSA · H₂O, and 17.5 ml of HOAc, while maintaining the temperature at approximately 18°. When all the TFAA had been added, the reaction mixture was removed from the ice bath and maintained at room temperature for an additional 15 min. It was then added to 200 ml of H₂O and extracted with CH₂Cl₂, and the extracts were washed (3% NaOH, H₂O until neutral), dried (MgSO₄), and evaporated to a residue in vacuo. This residue was chromatographed on 180 g of silica gel (100-200 mesh). Elution with $Et_2O-C_6H_{14}$ (3:1) afforded 4. Crystallization from EtOAc yielded 1.10 g (56.1%); mp 205-206-207°; $[\alpha]D + 13^\circ$; $\lambda_{max} 282 \ m\mu \ (\epsilon \ 20,600); \ \nu_{max}$ 1754, 1739, 1724, 1666, 1636, and 1600 cm⁻¹; nmr, δ 0.80 (13-CH₃), 1.22 (10-CH₃), 2.07 (17-OCOCH₃), 2.18 (20-CH₃), 5.48 and 5.61 (16--CH₂), 5.51 (4-H), 5.98 and 6.09 (6-H, 7-H) ppm. Anal. (C25H30O4) C, H.

6,16 β -Dimethyl-16,17 α -oxido-4,6-pregnadiene-3,20-dione (6). A. By Chloranil Dehydrogenation.—A solution of 8 (57 g, 0.16 mole) in t-BuOH (2.5 l.) was heated at reflux with chloranil (118 g, 0.48 mole, recrystallized from CH₂Cl₂) for 17 hr. The solids were removed by filtration, and the filtrate was concentrated to dryness. The dark residue was taken up in a mixture of Et₂O-EtOAc (1:1), and the solution was washed (1% NaOH, saturated NaCl solution), dried (Na₂SO₄), and evaporated. The residue was chromatographed over alumina (Merck, activity I, 45 × 6.3 cm). Elution with C₆H₈-Et₂O (1:1) yielded after crystallization from CH₂Cl₂-Et₂O 32 g (57%) of 6, mp 143–144°, [α]p +114° (CHCl₃), λ_{max} 289 m μ (ϵ 24,420). Anal. (C₂₃H₃₀O₃) C, H.

When unrecrystallized commercial chloranil was used in the reaction, **7** and **9** were also formed in addition to **6**. Purification by repeated crystallizations from EtOAc gave **9**: mp 213-218°; $[\alpha]_D - 30^\circ$ (CHCl₃); $\lambda_{max} 289 \text{ m}\mu$ ($\epsilon 24,800$); nmr, $\delta 5.08$ and 5.28 (16--CH₂) ppm. Anal. (C₂₃H₃₀O₃) C, H.

B. By Oxidation-Bromination Sequence.—LiBr (59 g), Li₂CO₃ (70.5 g), and CaCO₃ (70.5 g) were suspended in DMF (650 ml), and after 5 min, 5 (35 g, 0.098 mole) was added. The slurry was heated to 75°, and Br₂ (31.4 g, 0.196 mole) in dioxane (400 ml) was added over a period of 1 hr. After stirring for an additional hr at 75°, the reaction mixture was cooled and filtered, and the filtrate was added to ice-water (121.). The resulting precipitate was filtered, washed with H₂O, and dried. The above reaction was repeated, and the crude products were combined. Crystallization from Me₂CO-C₆H₁₄ yielded 4.8 g (7.7%) of 7: mp 203-206°; $[\alpha]D - 44^\circ$; $\lambda_{max} 287 m\mu (\epsilon 24,800)$; nmr, δ 1.81 and 1.87 (16-CH₃, 6-CH₃), and 6.11 (15-H) ppm. Anal. (C₂₃-H₃₀O₃) C, H.

The major portion of the material, which was contained in the mother liquor, was chromatographed over neutral alumina (Woelm, activity III, 70 \times 5.7 cm). Elution with C₆H₁₄-C₆H₆ (1:1) gave 27.85 g (40%, based upon recovered starting material) of **6** identical with the product obtained by dehydrogenation of **8** with chloranil. Elution with C₆H₆ gave 6.3 g of unreacted starting material.

6,16 β -Dimethyl-16,17 α -oxido-1,4,6-pregnatriene-3,20-dione (10).—A mixture of 6 (3.45 g, 0.00975 mole) and DDQ (11.05 g, 0.0488 mole) and C₆H₆ (250 ml) was heated at reflux for 20 hr. After cooling, the supernatant was separated by filtration and evaporated to dryness *in vacuo*, and the residue was chromatographed over alumina (Merck, activity I, 21 × 4.2 cm). Elution with Et₂O, followed by crystallization from *i*-Pr₂O, yielded 1.10 g (33%) of **10**: mp 140–142°; $[\alpha]_{D}$ + 113° (CHCl₃); λ_{\max} 227 m μ (ϵ 14,800), 255 (9200), 304 (12,250). Anal. (C₂₃H₂₈O₃) C, H.

6-Methyl-16-methylene-17 α -hydroxy-1,4,6-pregnatriene-3,20dione 17-Acetate (16).—A solution of 10 (560 mg, 0.00159 mole) in dioxane (6 ml) was stirred with concentrated H₂SO₄ (0.18 ml) under N₂ for 3 hr. The reaction mixture was added to ice-water, and the resulting precipitate was collected and dried, affording 490 mg of crude solid. Esterification with TFAA (2 ml), AcOH (5 ml), and p-TSA·H₂O (49 mg) gave a product which was chromatographed over Florisil (18 × 1.5 cm). Elution with Et₂O-C₆H₁₄ (1:1) and crystallization from Et₂O-C₆H₁₄ gave 265 mg (42.5%) of 16: mp 225-230°; $[\alpha]_D - 190^\circ$; $\lambda_{max} 227$ m μ (ϵ 14,500), 252-254 (9500), 303 (12,420) [lit.⁶ mp 228-230°: $[\alpha]_D - 188^\circ$ (CHCl₃); $\lambda_{max}^{EtOH} 228$ m μ (ϵ 13,530), 251 (9192), 302 (12,190)]. Anal. (C₂₅H₃₀O₄) C, H.

1,2α-Cyclomethylene-6,16β-dimethyl-16,17α-oxido-4,6-pregnadiene-3,20-dione (12).—NaH (0.0075 mole, 360 mg of a 50% mineral oil suspension) was added to a solution of trimethylsulfoxonium iodide (3 g, 0.0136 mole) in DMSO (22 ml) under N₂. After 2 hr a solution of 10 (1.132 g, 0.00323 mole) in DMSO (12 ml) was added, and the solution was stirred at room temperature for 5 hr. After addition to H₂O, the precipitate was collected by filtration, dried, and crystallized from *i*-Pr₂O-C₆H₁₄ to yield 1.01 g (86%) of 12, mp 184–186°, [α]D +144° (CHCl₃), λ_{max} 287 mμ (ϵ 18,800). Anal. (C₂₄H₃₀O₃) C, H.

From the mother liquor a small amount of **13** was isolated, crystallized from EtOAc; mp 167–170°; $[\alpha]_D + 182^\circ$; $\lambda_{max} 287 m\mu$ (ϵ 18,400); $\nu_{max} 1658$, 1631, and 1587 cm⁻¹; nmr, δ 0.68 and 0.86 (cyclopropyl), 1.06 (13-CH₃), 1.18 (10-CH₃), 1.51 and 1.54 (16-CH₃, 20-CH₃), 1.80 (6-CH₃, m), 2.57 and 2.94 (22-H₂, q, J = 5.5 Hz), 5.69 (4-H), and 5.80 (7-H) ppm. Anal. (C₂₅H₃₂O₃) C, H.

1,2α-Cyclomethylene-6-methyl-16-methylene-17α-hydroxy-4,6-pregnadiene-3,20-dione (14).—A solution of 12 (6.9 g) in dioxane (60 ml) was stirred with concentrated H₂SO₄ (1.5 ml) under N₂ for 3.5 hr. The reaction mixture was added to icewater, and the precipitate was collected by filtration and dried. Crystallization from CH₂Cl₂-*i*-Pr₂O yielded 4.103 g (59%) of 14: mp 210-216°; $[\alpha] p + 124°$; $\lambda_{max} 287 m\mu$ (ϵ 19,000); nmr, δ 5.12 and 5.31 (16-—CH₂) ppm. Anal. (C₂₄H₃₀O₃) C, H.

1,2α-Cyclomethylene-6-methyl-16-methylene-17α-hydroxy-4,6-pregnadiene-3,20-dione 17-Acetate (15).—TFAA (0.64 ml) was added dropwise to a solution of 14 (160 mg) and p-TSA H₂O (16 mg) in AcOH (1.6 ml). After 30 min, the solution was poured into H₂O, and the precipitate was collected, and dried. Crystal-lization from CH₂Cl₂-*i*-Pr₂O gave 119 mg (67%) of 15: mp 231-233°; [α] D +16.5°; λ_{max} 287 mµ (ϵ 19,600) [lit.¹¹ mp 235-237°, λ_{max} 285 mµ (ϵ 18,800), [α] D +10° (CHCl₃)]; ν_{max} 1757, 1724, 1669, 1639, and 1594 cm⁻¹; nmr δ 0.80 (13-CH₃), 1.20 (10-CH₃), 1.87 (6-CH₃, m), 2.07 (17-OCOCH₃), 2.17 (20-CH₃), 5.51 and 5.63 (16-=CH₂), 5.74 (4-H), and 5.87 (7-H) ppm. Anal. (C₂₈H₃₂O₄) C, H.

1,2 α -Cyclomethylene-6,16-dimethyl-17 α -hydroxy-4,6,15pregnatriene-3,20-dione (11).—A solution of 12 (431 mg) in Me₂CO (10 ml) and H₂O (2.5 ml) was stirred with concentrated HCl (2 ml) for 30 min. The solution was added to H₂O and the precipitate was collected, and dried. After several crystallizations from Me₂CO-*i*-Pr₂O, 147 mg (34%) of 11 was obtained; mp 248-260° dec; [α]p +112°; λ_{max} 287 m μ (ϵ 18,850); nmr, δ 1.82 (6-CH₃, 16-CH₃), and 6.00 (7-H, 15-H) ppm. Anal. (C₂₄H₃₀O₃) C, H.

5α,6β-Dichloro-16-methylene-3β,17α-dihydroxypregnan-20one 3,17-Diacetate (18).—To a solution of 17 (11.02 g, 0.0257 mole) in 551 ml of CH₂Cl₂ and 2.38 ml (0.0283 mole) of pyridine, which was stirred at 5°, was added a solution of Cl₂ (0.0283 mole) in CCl₄ (77 mg, Cl₂/ml). The reaction was negative to moist KI-starch paper in less than 2 min. The solution was then washed with H₂O until neutral, dried (MgSO₄), and evaporated to a residue *in vacuo* to yield 12.44 g of crude product. Crystallization from MeOH yielded 9.24 g (72%) of 18: mp 195° dec; $[\alpha]p - 129°$; mmr, δ 5.47 and 5.60 (16-—CH₂) ppm. Anal. (C₂₈H₃₈O₅Cl₂) C, H, Cl.

5α,6β-Dichloro-16-methylene-3β,17α-dihydroxypregnan-20one 17-Acetate (19).—A solution of 18 (13.70 g, 0.0274 mole) in 760 ml of MeOH, 41 ml of CHCl₃, and 27.4 ml of 70% HClO₄ was kept at 5° for 18 hr. Then, 1 l. of H₂O was added, 1 l. of solvent was evaporated *in vacuo*, and insolubles were chilled and collected by filtration to yield 11.4 g of crude product. Crystallization from MeOH yielded 8.71 g (69.5%) of 19: mp 232° dec; [α]D $-132\,^\circ;\ \nu_{\rm max}$ 3355, 3290, 1751, 1730 (sh), and 1718 cm $^{-1}.$ Anal. (C24H34O4Cl2) C, H, Cl.

6β-Chloro-16-methylene-17α-hydroxy-4-pregnene-3,20-dione 17-Acetate (21).—To a slurry of 7.8 g of CrO₃ in 78 ml of pyridine at 15° was added **19** (7.8 g, 0.0171 mole) in 78 ml of pyridine. After 42 hr at room temperature, the reaction mixture was added to 1.6 l. of ice-water and 160 ml of concentrated HCl. The crude product obtained by CH₂Cl₂ extraction was chromatographed on 700 g of silica gel (100-200 mesh). Elution with Et₂O-C₆H₁₄ (3:7) afforded 3.38 g of **21**. Crystallization from Et₂O yielded 2.25 g (31.5%); mp 145° dec: $[\alpha]D - 110°; \lambda_{max}$ 240 mµ (ϵ 15,000) [lit.^{2b} mp 151-153°, $[\alpha]^{20}D - 113°$ (c 1.0, CHCl₃) λ_{max} 240 mµ (log ϵ 4.18)]; mmr, δ 4.74 (6-H, t, J_{HeH7ax} = J_{H₆H₇eq = 2 Hz), and 5.88 (4-H) ppm. Anal. (C₂₄H₃₁O₄Cl) C, H, Cl.}

3-Ethoxy-6-chloro-16-methylene-17 α -hydroxy-3,5-pregnadien-20-one 17-Acetate (22).—To a solution of 21 (5.76 g, 0.0137 mole) in 115 ml of dioxane was added 1.72 ml of EtOH, 17.2 ml of triethyl orthoformate, and 17.2 ml of a solution of H_2SO_4 -dioxane (1:19). After 15 min at 25°, 35 ml of pyridine was added, and the solution was concentrated to a thick paste *in vacuo*. Addition of 10 ml of MeOH and cooling at 5° gave crystalline 22, 4.32 g (70.2%), mp 173° dec, $[\alpha]D - 234°$, $\lambda_{max} 252 \text{ m}\mu$ ($\epsilon 21,650$) [lit.²⁶ mp 177–178°, $[\alpha]^{26}D - 238°$ (c 1.0, CHCl₅), $\lambda_{max} 251 \text{ m}\mu$ (log $\epsilon 4.55$)]. Anal. (C₂₆H₃₅O₄Cl) C, H, Cl.

6-Chloro-16-methylene-17α-hydroxy-1,4,6-pregnatriene-3,20dione 17-Acetate (23).---A solution of 22 (11.34 g, 0.0254 mole) in 1.14 l. of C_6H_6 was added to 17.30 g (0.0762 mole) of DDQ in 1.14 l. of C_6H_6 and stirred at 25° for 6 hr. The reaction mixture was filtered, and the filtrate was evaporated to a residue in vacuo. The residue was dissolved in 31. of $EtOAc-Et_2O(1:1)$, which was washed with 1% NaOH, then with H₂O, dried (MgSO₄), and evaporated to a residue. Since the product appeared by the [silica gel, CHCl₃-EtOAc (9:1)] to be a mixture of approximately 4 parts of $\Delta^{1,4,6}$ -triene to 1 part of $\Delta^{4,6}$ -diene, dehydrogenation was carried out again, as follows. The product (10.56 g) was refluxed in 525 ml of dioxane with 5.72 g of DDQ for 4 hr. Evaporation in vacuo gave a residue to which was added 500 ml of C_6H_6 . The C_6H_6 solution was separated from insolubles and evaporated in vacuo to a residue which was taken up in EtOAe- $\mathrm{Et}_2\mathrm{O}$ and washed as previously described. Evaporation of the solvent gave a crude product, 10.5 g, and two crystallizations from MeOH yielded 23: 5.39 g (51%); mp 220° dec; [a]D -173° ; λ_{max} 228 m μ (ϵ 10,830), infl at 235, 258 (10,450), 297

(11,080) [lit.^{2b} mp 228–230°; $[\alpha]^{29}D = -217^{\circ}$ (c 1.0, CHCl₃); $\lambda_{max} 229 \ m\mu \ (\log \ \epsilon 4.01), 258 \ (4.00), 297 \ (4.03)].$ Anal. (C₂₄H₂₇-O₄Cl) C, H, Cl.

 $1\alpha,2\alpha-(4,3,1-\text{Pyrazolino})$ -6-chloro-16-methylene-17 α -hydroxy-4,6-pregnadiene-3,20-dione 17-Acetate (24),---Into a solution of 6.0 g of 23, in 60 ml of CH₂Cl₂, maintained at approximately 5°, was distilled 600 ml of an Et₂O solution of CH₂N₂ [prepared from bis(N-methyl-N-nitroso)terephthalamide by adding to 96 g of EXR-101²⁰ suspended in 1.2 l. of Et₂O and 192 ml of H₂O, a solution of 48 g of KOH, 192 ml of EtOH, and 96 ml of H₂O). The closed reaction flask was then allowed to remain at 25° for 48 hr. Excess CH₂N₂ was removed by air entrainment. An additional 6 g of 23 was similarly allowed to react with CH₂N₂, and the combined reaction products were chromatographed on silica gel (1200, 964, and 487 g, successive portions, 100–200 mesh) three times, eduting with Me₂CO-C₆H₁₄ (1:3) to obtain 2.80 g of impure 24: $|\alpha|_D + 152^\circ$; $\lambda_{max} 227$ m μ (ϵ 5560) and 287 m μ (ϵ 13,900): ν_{max} 1754, 1739, 1672, 1615, and 1562 cm⁻¹. A satisfactory analysis was not obtained for this substance.

1,2α-Cyclomethylene-6-chloro-16-methylene-17α-hydroxy-**4**,6-pregnadiene-3,20-dione 17-Acetate (25).- A solution of impure 24 (2.6 g) in 515 ml of Me₂CO and 5.2 ml of 70⁺₆ HClO₄ was allowed to react at 25° for 20 min. An equal volume of H₂O was then added, and the pH was adjusted to about 7 with NaHCO₈. Me₂CO was removed *in racuo*, and after extraction with CH₂Cl₂, the crude product of 2.51 g was chromatographed on 250 g of silica gel (100-200 mesh). Elution with Me₂CO-C₆H₄ (3:17) gave 760 mg, principally 25. Crystallization from Et₂O yielded 452 mg (19.3⁺₆); mp 250° dec: $[\alpha]_{\rm D} + 12^{\circ}$; $\lambda_{\rm max}$ 282 mµ (ϵ 17,000); $\nu_{\rm max}$ 1754, 1724, 1666, 1612, and 1589 (vw) cm⁻⁴; nmr δ 0.80 (13-CH₃), 1.23 (10-CH₃), 2.07 (17-OCOCH₃), 2.17 (20-CH₃), 5.50 and 5.63 (16-=CH₂), and 6.20 (4-H, 7-H) ppm. The recovered rotation sample was used for microanalysis and for mass spectroscopic determination. *Anal.* (C₂₅H₂₉O₄Cl+0.5dioxane) C, H, *m* + (428).

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(20) A mixture of the amide with 30% mineral oil, E. I. du Pont de Nemours and Co., Inc., Explosives Department, Wilmington, Del.

Tricyclic Analogs of Melatonin

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The angular tricyclic analog of melatonin, 8-methoxy-6-oxo-3,4,6,7-tetrahydro-1H,5H-azocin[4,5,6-cd]indole (IV) as well as the linear "dehydromelatonin," viz., 5-methoxy-1-acetyl-2,3-dihydropyrrolo[2,3-b]indole (VI) had retained only tiny fractions of the activity of melatonin. The lactam IV and the corresponding amine V showed no major CNS effects in mice and cats.

Melatonin, N-acetyl-5-methoxytryptamine (I),² has been isolated from extracts of pineal glands and identified in peripheral nerves of mammals and man. It is conveniently assayed by its lightening effect on frog melanocytes.³ Its biological properties are different from those of other known lightening agents.⁴

We have now applied the photocyclization of N-

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chloroacetyltryptophan (yielding the lactam II⁵) to the synthesis of the tricyclic dehydromelatonin IV and its reduction product V (Scheme I). On irradiation with a low-pressure mercury lamp in aqueous THF buffered with NaOAc, N-chloroacetyl-5-methoxytryptamine (III) afforded a 46% yield of the cyclized product IV. Reduction of the eight-membered lactam IV with diborane at room temperature gave 8-methoxy-3,4,6,7-tetrahydro-1H,5H-azocin[4,5,6-cd]indole (V), after decomposition of an intermediary, stable borane complex by refluxing in ethanolic KOH.

Tryptamine and tryptophan derivatives are con-

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