was washed with H_2O. The product was extracted into saturated $NaHCO_3$ solution which was then acidified with HCl and extracted with Et_2O. Evaporation of the dried (Na_2SO_4) Et_2O gave 0.65 g of the 17β-hydroxy-1,4-seco-5α-androstane-1,4-dioic acid acetate which was esterified with CH_2N_2 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° (*c* 1, $CHCl_3$); nmr 3.62 and 3.7 ppm (6 H, 2-OCH_3). *Anal.* ($C_{21}H_{32}O_6$) C, H.

1,4-Seco-2,3-bisnor-5α-androstane-1,4,17β-triol 17-(2′-Tetrahydropyranyl) Ether (9).—Compound **7** was treated with CH_2N_2 in Et_2O 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, OCH_3). A solution of 0.5 g of the dimethyl ester in 50 ml of dry dihydropyran and a drop of $POCl_3$ was stirred at room temperature for 1 hr and evaporated under reduced pressure. The residue was dissolved in ether, washed ($NaHCO_3$ solution, H_2O), dried (Na_2SO_4), 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, OCH_3).

This tetrahydropyranyl ether (0.25 g) was dissolved in 50 ml of dry Et_2O and added to 0.5 g of LAH in 100 ml of dry Et_2O. 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 Et_2O, and the combined Et_2O solution was washed (dilute HCl, H_2O), dried (Na_2SO_4), and evaporated. The residue was crystallized several times from Me_2CO giving colorless crystals, mp 158–160°. *Anal.* ($C_{22}H_{38}O_4$) C, H.

1,4-Seco-5α-androstane-1,4,17β-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 $MeSO_2Cl$ 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–H_2O (100 ml) and the precipitate was filtered and washed (H_2O). It was recrystallized from Et_2O–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, SO_2CH_3). *Anal.* ($C_{24}H_{42}O_8S_2$) C, H, S.

1,4-Dibromo-1,4-seco-2,3-bisnor-5α-androstan-17β-ol Acetate (11).—To 1.9 g of **2** in 100 ml of stirred, refluxing CCl_4, there was added 1.62 g of red HgO. The reaction mixture was shielded from light, and Br_2 (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 Al_2O_3 to give 1.1 g of pure **11** which was recrystallized from MeOH; mp 155–158°, $[\alpha]^{20}D$ −2° (*c* 1, $CHCl_3$). *Anal.* ($C_{19}H_{30}Br_2O_2$) C, H, Br.

2-Thia-A-nor-5α-androstan-17β-ol (12). Procedure A.—A solution of NaHS was prepared by bubbling H_2S into a suspension of 9 g of NaOMe in 70 ml of $HOCH_2CH_2OEt$ 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 H_2O. 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 H_2O at 60° for 5 min. The mixture was cooled, evaporated, and extracted with Et_2O to afford a solid (0.050 g). Several recrystallizations from Et_2O–hexane gave the analytical sample, mp 141–143°, $[\alpha]^{20}D$ +58°, m^+ = 280. *Anal.* ($C_{17}H_{28}OS$) 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 tlc indicated complete conversion of the dibromide to the product. The solvent was removed under vacuum and the residue was taken up in Et_2O, washed (H_2O), dried (Na_2SO_4), and evaporated to give 0.50 g of **12** as a white solid.

2-Thia-A-nor-5α-androstan-17β-ol Acetate (13).—A solution of 0.05 g of **12** in 2 ml of pyridine and 1 ml of Ac_2O was kept overnight at 25°, poured into 20 ml of ice–H_2O, acidified to pH 3, and extracted with Et_2O. The Et_2O was washed several times with H_2O, dried (Na_2O_4), 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°, $[\alpha]^{20}D$ +50° (*c* 1, $CHCl_3$), m^+ = 322. *Anal.* ($C_{19}H_{30}O_2S$) C, H, S.

2-Thia-A-nor-5α-androstan-17β-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, $CHCl_3$), m^+ = 336. *Anal.* ($C_{20}H_{32}O_2S$) C, H, S.

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

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Received November 21, 1968

The progestational activities and syntheses of the 1,2α-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 1,2α-cyclomethylene derivatives when tested intramuscularly in the rabbit.

The progestational potentiating effect of the 16-methylene moiety has been described.[2] Recently, progesterone analogs have been reported which have a 1,2α-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 1,2α-cyclomethylene-16-methylene-17α-hydroxy-4,6-pregnadiene-3,20-dione 17-acetate (**4**), 1,2α-cyclomethylene-6-methyl-16-methylene-17α-hydroxy-4,6-pregnadiene-3,20-dione 17-acetate (**15**), and 1,2α-cyclomethylene-16-methylene-6-chloro-17α-hydroxy-4,6-pregnadiene-3,20-dione 17-acetate (**25**).

The synthesis of the 1,2α-cyclomethylene **4** (Scheme

(1) From the Physiology and Biochemistry Department.

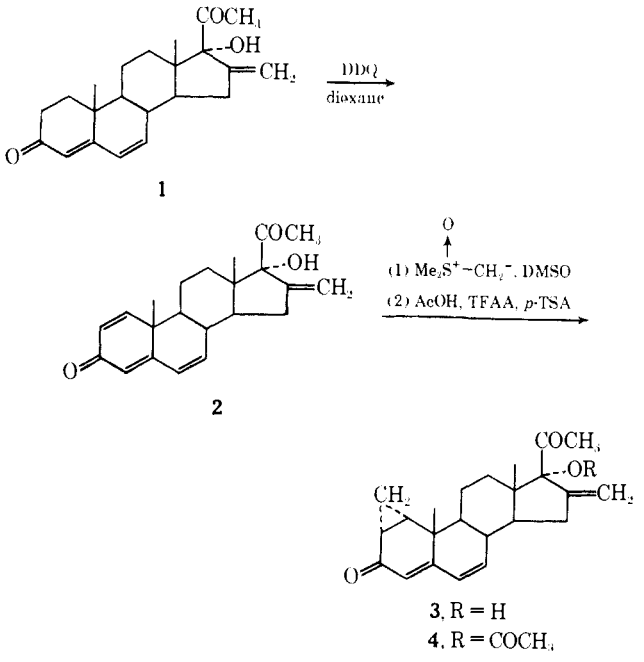
(2) (a) E. Shapiro, T. Legatt, L. Weber, M. Steinberg, A. Watnick, M. Eisler, M. G. Hennessey, C. T. Coniglio, W. Charney, and E. P. Oliveto, *J. Med. Pharm. Chem.*, **5**, 975 (1962); (b) K. Syhora and R. Mazac, *Collect. Czech. Chem. Commun.*, **31**, 2768 (1966).

(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)[5] gave the

SCHEME I



1,4,6-triene **2**.[6] Introduction of the 1,2α-cyclomethylene moiety into the 1,4,6-trien-3-one system has been accomplished by two methods. One method utilizes CH_2N_2 to give the 1α,2α-pyrazoline which either by pyrolysis[3] or on treatment with strong acid[4] is converted to the desired cyclomethylene compound. The other method utilizes dimethylsulfoxonium methylide[7] to effect the formation of the 1,2α-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 1,2α-cyclomethylene **3** was obtained in 71% yield after crystallization. Acetylation of **3** using AcOH, trifluoroacetic anhydride (TFAA), and *p*-toluenesulfonic acid monohydrate (*p*-TSA·H_2O),[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-dehydrobromination of **5**[12] with Br_2 in DMF in the presence of LiBr, Li_2CO_3, and $CaCO_3$ at 80°[13] afforded as the major component the 4,6-dienone **6** with the 16β-methyl-16,17α-oxido moiety intact. However, some rearrangement of this oxido function did occur and the Δ^{15}-17α-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-16,17α-oxido function occurred, and in addition to **6**, both **7** and the 16-methylene-17α-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-17α-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 1,2α-cyclomethylene **12** in 86% yield. The use of the 16β-methyl-16,17α-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 16,17α;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° more dextrorotatory than the Δ^{15}-16-methyl-17α-hydroxy isomers.[14] Acetylation of **14** with AcOH, TFAA, and *p*-TSA[10] gave the desired 1,2α-cyclomethylene 17-acetate **15** in 67% yield.

The synthesis of the 6-chloro **25** is outlined in Scheme III.[15] Chlorination of 16-methylene-3β,17α-dihydroxy-5-pregnen-20-one 3,17-diacetate (**17**)[16] gave selectively the 5α,6β-dichloro **18**. Selective hydrolysis of the 3-acetate in **18** with $HClO_4$ in MeOH-$CHCl_3$ gave **19**. Oxidation of the 3-hydroxyl function in **19** with CrO_3 in pyridine[17] followed by *in situ* dehydrohalogenation of **20** afforded directly the 3-keto-Δ^4-6β-chloro **21**[2b] in approximately 32% yield. Transformation of **21** to the enol ether **22**[2b] proceeded smoothly in dioxane with

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

(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).

(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).

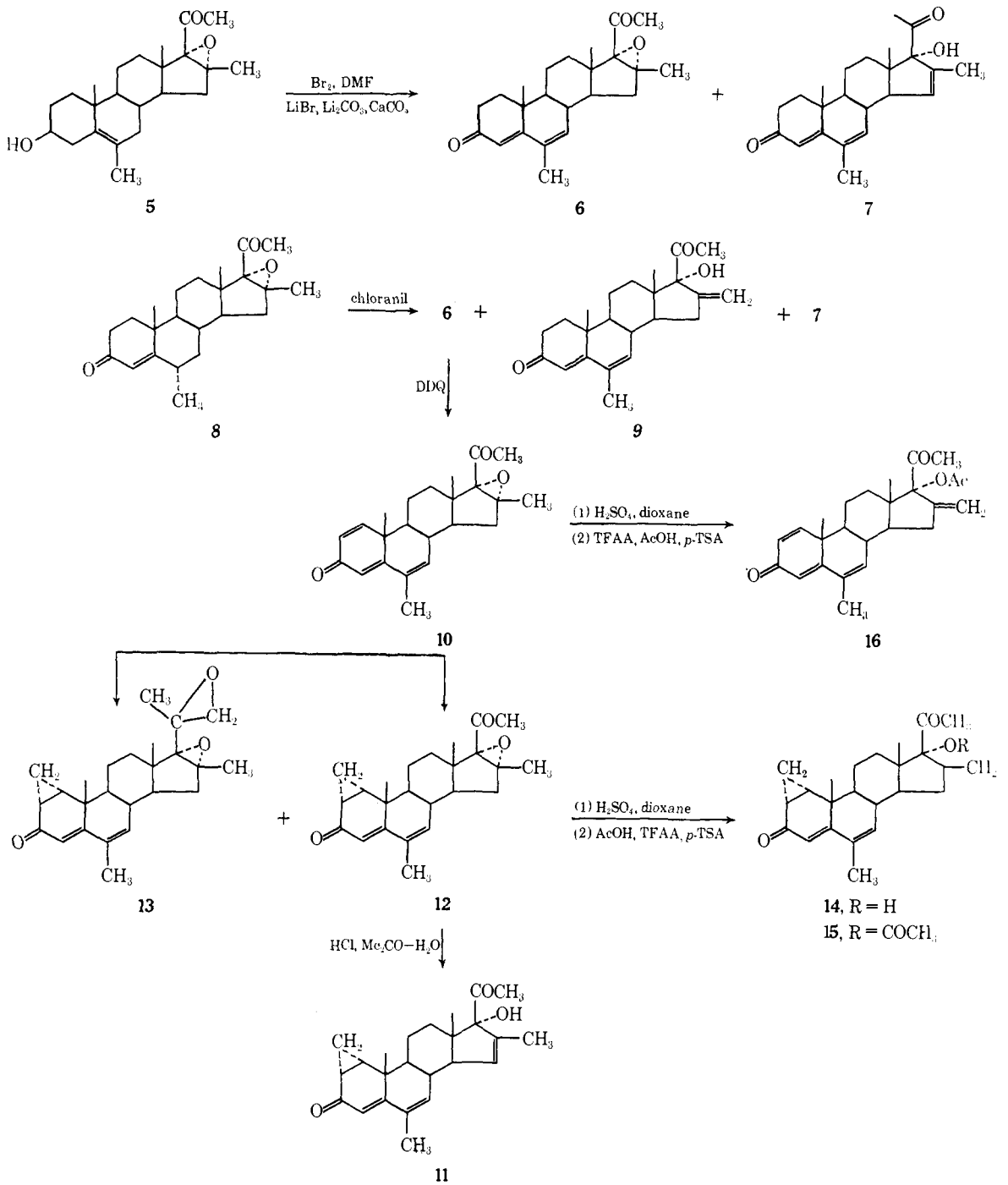
(14) (a) Huang-Minlon, C.-H. Wu, J.-W. Chin, and Y.-C. Cheu, *Sci. Sinica* (Peking), **11**, 1659 (1962); *Chem. Abstr.*, **59**, 2985c (1963); (b) F. v. Werder, K. Bruckner, K. H. Bork, H. Metz, B. Hampel, and H. J. Mannhardt, *Ber.*, **95**, 2110 (1962); (c) G. H. Phillips, W. Graham, G. I. Gregory, 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.

(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).

Scheme II

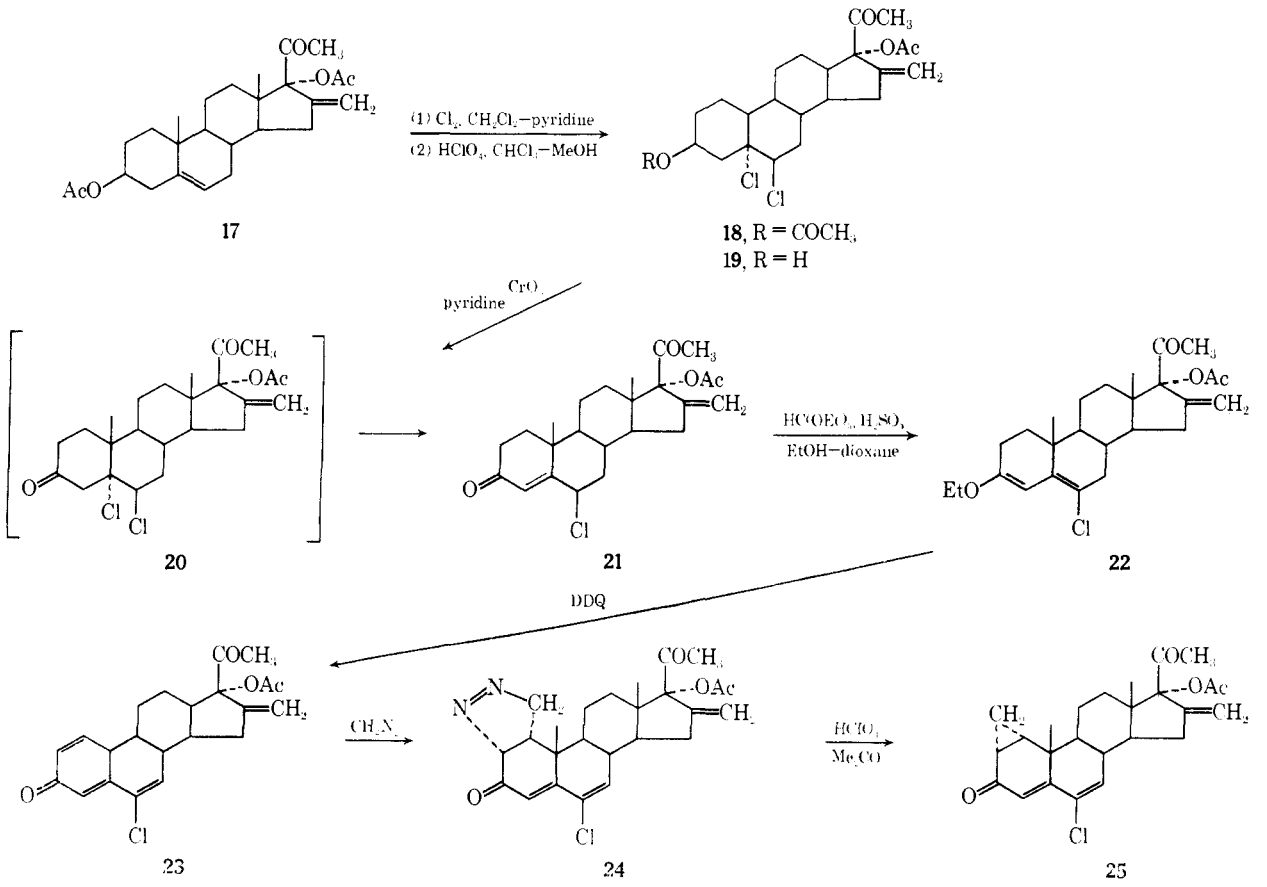


ethyl orthoformate, EtOH, and H_2SO_4. Dehydrogenation of **22** with DDQ in benzene[18] to give the 1,4,6-trienone was incomplete and appeared to consist of 4 parts of the 1,4,6-triene **23** to 1 part of the 4,6-diene. The reaction product was treated again with DDQ, this time in dioxane, thereby affording **23**.[2b] Reaction of **23** with CH_2N_2 gave impure 1α,2α-pyrazoline **24** which was exposed to $HClO_4$ to give the desired 1,2α-cyclomethylene **25** in approximately 19% yield from the impure pyrazoline.

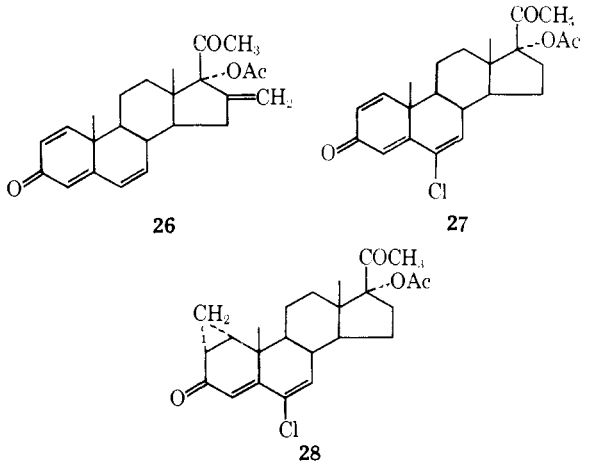
Biological Activity.—Table I lists the intramuscular activities of the three 1,2-cyclomethylene-16-methylene compounds we have described as well as the corresponding 1,4,6-trienes. Included also are the oral progestational activities, except for compounds **4** and **26.** For comparison, the activities 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 1,2α-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).

SCHEME III



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



Experimental Section[19]

16-Methylene-17α-hydroxy-1,4,6-pregnatriene-3,20-dione (2).—A mixture of 9.00 g (0.0264 mole) of 16-methylene-17α-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

(19) All melting points were determined on a Kofler 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 Nujol unless otherwise stated. The nmr spectra were measured on a Varian A-60-A spectrometer in $CDCl_3$ (Me_4Si). 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 ±0.4% of the theoretical values.

TABLE I

PROGESTATIONAL ACTIVITY[a]

Compd	Route of admin[b] Im	Oral
29[c]		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[f]	75	15.6

[a] Progesterone = 1. [b] Progestational activity was determined 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% $PhCH_2OH$) 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). [c] 17α-Ethinyl-19-nortestosterone. [d] 16-Methylene-17α-hydroxy-1,4,6-pregnatriene-3,20-dione 17-acetate, prepared from **2** by acetylation with AcOH, TFAA, and *p*-TSA·H_2O as in ref 16 [mp 203–205–206°; $[\alpha]_D$ −192°; λ_{max} 222 mμ (ε 12,400), 256 (9950), 299(13,500); ν_{max} 1754, 1727, 1664, 1610, and 1585 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). [f] 1,2α-Cyclomethylene-6-chloro-17α-hydroxy-4,6-pregnadiene-3,20-dione 17-acetate. We thank Berlin Laboratories, Inc., an affiliate of Schering A.G., Berlin, Germany, for a sample of this compound.

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–Et_2O (1:1). After washing with 5% NaOH, then H_2O, and drying ($MgSO_4$), 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°; $[\alpha]D$ −99°, $[\alpha]D$ −124° ($CHCl_3$); λ_{max} 221 mμ (ε 12,590), 256 (9650), 299 (13,100) [lit.[6] mp 212–214°, $[\alpha]^{25}D$ −174° ($CHCl_3$)]. *Anal.* ($C_{22}H_{26}O_3$) C, H.

1,2α-Cyclomethylene-16-methylene-17α-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 H_2O. 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°, $[\alpha]D$ +121°, λ_{max} 282 mμ (ε 20,400). *Anal.* ($C_{23}H_{28}O_3$) C, H.

1,2α-Cyclomethylene-16-methylene-4,6-pregnadiene-3,20-dione 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·H_2O, 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 H_2O and extracted with CH_2Cl_2, and the extracts were washed (3% NaOH, H_2O until neutral), dried ($MgSO_4$), 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°; λ_{max} 282 mμ (ε 20,600); ν_{max} 1754, 1739, 1724, 1666, 1636, and 1600 cm^{-1}; nmr, δ 0.80 (13-CH_3), 1.22 (10-CH_3), 2.07 (17-OCOCH_3), 2.18 (20-CH_3), 5.48 and 5.61 (16-=CH_2), 5.51 (4-H), 5.98 and 6.09 (6-H, 7-H) ppm. *Anal.* ($C_{25}H_{30}O_4$) C, H.

6,16β-Dimethyl-16,17α-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 CH_2Cl_2) 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 Et_2O–EtOAc (1:1), and the solution was washed (1% NaOH, saturated NaCl solution), dried (Na_2SO_4), and evaporated. The residue was chromatographed over alumina (Merck, activity I, 45 × 6.3 cm). Elution with C_6H_6–Et_2O (1:1) yielded after crystallization from CH_2Cl_2–Et_2O 32 g (57%) of **6**, mp 143–144°, $[\alpha]D$ +114° ($CHCl_3$), λ_{max} 289 mμ (ε 24,420). *Anal.* ($C_{23}H_{30}O_3$) 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° ($CHCl_3$); λ_{max} 289 mμ (ε 24,800); nmr, δ 5.08 and 5.28 (16-=CH_2) ppm. *Anal.* ($C_{23}H_{30}O_3$) C, H.

B. By Oxidation–Bromination Sequence.—LiBr (59 g), Li_2CO_3 (70.5 g), and $CaCO_3$ (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 Br_2 (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 (12 l.). The resulting precipitate was filtered, washed with H_2O, and dried. The above reaction was repeated, and the crude products were combined. Crystallization from Me_2CO–C_6H_{14} yielded 4.8 g (7.7%) of **7**: mp 203–206°; $[\alpha]D$ −44°; λ_{max} 287 mμ (ε 24,800); nmr, δ 1.81 and 1.87 (16-CH_3, 6-CH_3), and 6.11 (15-H) ppm. *Anal.* ($C_{23}H_{30}O_3$) C, H.

The major portion of the material, which was contained in the mother liquor, was chromatographed over neutral alumina (Woelm, activity III, 70 × 5.7 cm). Elution with C_6H_{14}–C_6H_6 (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 C_6H_6 gave 6.3 g of unreacted starting material.

6,16β-Dimethyl-16,17α-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 C_6H_6 (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 Et_2O, followed by crystallization from *i*-Pr_2O, yielded 1.10 g (33%) of **10**: mp 140–142°; $[\alpha]D$ + 113° ($CHCl_3$); λ_{max} 227 mμ (ε 14,800), 255 (9200), 304 (12,250). *Anal.* ($C_{23}H_{28}O_3$) C, H.

6-Methyl-16-methylene-17α-hydroxy-1,4,6-pregnatriene-3,20-dione 17-Acetate (16).—A solution of **10** (560 mg, 0.00159 mole) in dioxane (6 ml) was stirred with concentrated H_2SO_4 (0.18 ml) under N_2 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·H_2O (49 mg) gave a product which was chromatographed over Florisil (18 × 1.5 cm). Elution with Et_2O–C_6H_{14} (1:1) and crystallization from Et_2O–C_6H_{14} gave 265 mg (42.5%) of **16**: mp 225–230°; $[\alpha]D$ −190°; λ_{max} 227 mμ (ε 14,500), 252–254 (9500), 303 (12,420) [lit.[6] mp 228–230°; $[\alpha]D$ −188° ($CHCl_3$); λ_{max}^{EtOH} 228 mμ (ε 13,530), 251 (9192), 302 (12,190)]. *Anal.* ($C_{25}H_{30}O_4$) 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 N_2. 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 H_2O, the precipitate was collected by filtration, dried, and crystallized from *i*-Pr_2O–C_6H_{14} to yield 1.01 g (86%) of **12**, mp 184–186°, $[\alpha]D$ +144° ($CHCl_3$), λ_{max} 287 mμ (ε 18,800). *Anal.* ($C_{24}H_{30}O_3$) C, H.

From the mother liquor a small amount of **13** was isolated, crystallized from EtOAc; mp 167–170°; $[\alpha]D$ +182°; λ_{max} 287 mμ (ε 18,400); ν_{max} 1658, 1631, and 1587 cm^{-1}; nmr, δ 0.68 and 0.86 (cyclopropyl), 1.06 (13-CH_3), 1.18 (10-CH_3), 1.51 and 1.54 (16-CH_3, 20-CH_3), 1.80 (6-CH_3, m), 2.57 and 2.94 (22-H_2, q, J = 5.5 Hz), 5.69 (4-H), and 5.80 (7-H) ppm. *Anal.* ($C_{25}H_{32}O_3$) 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 H_2SO_4 (1.5 ml) under N_2 for 3.5 hr. The reaction mixture was added to ice–water, and the precipitate was collected by filtration and dried. Crystallization from CH_2Cl_2–*i*-Pr_2O yielded 4.103 g (59%) of **14**: mp 210–216°; $[\alpha]D$ +124°; λ_{max} 287 mμ (ε 19,000); nmr, δ 5.12 and 5.31 (16-=CH_2) ppm. *Anal.* ($C_{24}H_{30}O_3$) 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·H_2O (16 mg) in AcOH (1.6 ml). After 30 min, the solution was poured into H_2O, and the precipitate was collected, and dried. Crystallization from CH_2Cl_2–*i*-Pr_2O gave 119 mg (67%) of **15**: mp 231–233°; $[\alpha]D$ +16.5°; λ_{max} 287 mμ (ε 19,600) [lit.[11] mp 235–237°, λ_{max} 285 mμ (ε 18,800), $[\alpha]D$ +10° ($CHCl_3$)]; ν_{max} 1757, 1724, 1669, 1639, and 1594 cm^{-1}; nmr, δ 0.80 (13-CH_3), 1.20 (10-CH_3), 1.87 (6-CH_3, m), 2.07 (17-OCOCH_3), 2.17 (20-CH_3), 5.51 and 5.63 (16-=CH_2), 5.74 (4-H), and 5.87 (7-H) ppm. *Anal.* ($C_{26}H_{32}O_4$) C, H.

1,2α-Cyclomethylene-6,16-dimethyl-17α-hydroxy-4,6,15-pregnatriene-3,20-dione (11).—A solution of **12** (431 mg) in Me_2CO (10 ml) and H_2O (2.5 ml) was stirred with concentrated HCl (2 ml) for 30 min. The solution was added to H_2O and the precipitate was collected, and dried. After several crystallizations from Me_2CO–*i*-Pr_2O, 147 mg (34%) of **11** was obtained; mp 248–260° dec; $[\alpha]D$ +112°; λ_{max} 287 mμ (ε 18,850); nmr, δ 1.82 (6-CH_3, 16-CH_3), and 6.00 (7-H, 15-H) ppm. *Anal.* ($C_{24}H_{30}O_3$) C, H.

5α,6β-Dichloro-16-methylene-3β,17α-dihydroxypregnan-20-one 3,17-Diacetate (18).—To a solution of **17** (11.02 g, 0.0257 mole) in 551 ml of CH_2Cl_2 and 2.38 ml (0.0283 mole) of pyridine, which was stirred at 5°, was added a solution of Cl_2 (0.0283 mole) in CCl_4 (77 mg, Cl_2/ml). The reaction was negative to moist KI–starch paper in less than 2 min. The solution was then washed with H_2O until neutral, dried ($MgSO_4$), 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; $[\alpha]D$ −129°; nmr, δ 5.47 and 5.60 (16-=CH_2) ppm. *Anal.* ($C_{26}H_{36}O_5Cl_2$) C, H, Cl.

5α,6β-Dichloro-16-methylene-3β,17α-dihydroxypregnan-20-one 17-Acetate (19).—A solution of **18** (13.70 g, 0.0274 mole) in 760 ml of MeOH, 41 ml of $CHCl_3$, and 27.4 ml of 70% $HClO_4$ was kept at 5° for 18 hr. Then, 1 l. of H_2O 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; $[\alpha]D$

$-132°$; ν_{max} 3355, 3290, 1751, 1730 (sh), and 1718 cm^{-1}. *Anal.* ($C_{24}H_{34}O_4Cl_2$) 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 CrO_3 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 CH_2Cl_2 extraction was chromatographed on 700 g of silica gel (100–200 mesh). Elution with Et_2O–C_6H_{14} (3:7) afforded 3.38 g of **21**. Crystallization from Et_2O yielded 2.25 g (31.5%); mp 145° dec; $[\alpha]D$ −110°; λ_{max} 240 mμ (ε 15,000) [lit.[2b] mp 151–153°, $[\alpha]^{20}D$ −113° (*c* 1.0, $CHCl_3$), λ_{max} 240 mμ (log ε 4.18)]; nmr, δ 4.74 (6-H, t, $J_{H_6H_{7ax}} = J_{H_6H_{7eq}}$ = 2 Hz), and 5.88 (4-H) ppm. *Anal.* ($C_{24}H_{31}O_4Cl$) C, H, Cl.

3-Ethoxy-6-chloro-16-methylene-17α-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°, λ_{max} 252 mμ (ε 21,650) [lit.[2b] mp 177–178°, $[\alpha]^{20}D$ −238° (*c* 1.0, $CHCl_3$), λ_{max} 251 mμ (log ε 4.35)]. *Anal.* ($C_{26}H_{33}O_4Cl$) C, H, Cl.

6-Chloro-16-methylene-17α-hydroxy-1,4,6-pregnatriene-3,20-dione 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 3 l. of EtOAc–Et_2O (1:1), which was washed with 1% NaOH, then with H_2O, dried ($MgSO_4$), and evaporated to a residue. Since the product appeared by tlc [silica gel, $CHCl_3$–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 EtOAc–Et_2O 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; $[\alpha]D$ −173°; λ_{max} 228 mμ (ε 10,830), infl at 235, 258 (10,450), 297 (11,080) [lit.[2b] mp 228–230°; $[\alpha]^{20}D$ −217° (*c* 1.0, $CHCl_3$); λ_{max} 229 mμ (log ε 4.01), 258 (4.00), 297 (4.03)]. *Anal.* ($C_{24}H_{27}O_4Cl$) C, H, Cl.

1α,2α-(4,3,1-Pyrazolino)-6-chloro-16-methylene-17α-hydroxy-4,6-pregnadiene-3,20-dione 17-Acetate (24).—Into a solution of 6.0 g of **23**, in 60 ml of CH_2Cl_2, maintained at approximately 5°, was distilled 600 ml of an Et_2O solution of CH_2N_2 [prepared from bis(N-methyl-N-nitroso)terephthalamide by adding to 96 g of EXR-101[20] suspended in 1.2 l. of Et_2O and 192 ml of H_2O, a solution of 48 g of KOH, 192 ml of EtOH, and 96 ml of H_2O]. The closed reaction flask was then allowed to remain at 25° for 48 hr. Excess CH_2N_2 was removed by air entrainment. An additional 6 g of **23** was similarly allowed to react with CH_2N_2, and the combined reaction products were chromatographed on silica gel (1200, 964, and 487 g, successive portions, 100–200 mesh) three times, eluting with Me_2CO–C_6H_{14} (1:3) to obtain 2.80 g of impure **24**: $[\alpha]D$ −152°; λ_{max} 227 mμ (ε 5560) and 287 mμ (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 Me_2CO and 5.2 ml of 70% $HClO_4$ was allowed to react at 25° for 20 min. An equal volume of H_2O was then added, and the pH was adjusted to about 7 with $NaHCO_3$. Me_2CO was removed *in vacuo*, and after extraction with CH_2Cl_2, the crude product of 2.51 g was chromatographed on 250 g of silica gel (100–200 mesh). Elution with Me_2CO–C_6H_{14} (3:17) gave 760 mg, principally **25**. Crystallization from Et_2O yielded 452 mg (19.3%): mp 250° dec; $[\alpha]D$ +12°; λ_{max} 282 mμ (ε 17,000); ν_{max} 1754, 1724, 1666, 1612, and 1589 (vw) cm^{-1}; nmr, δ 0.80 (13-CH_3), 1.23 (10-CH_3), 2.07 (17-OCOCH_3), 2.07 (20-CH_3), 5.50 and 5.63 (16-=CH_2), and 6.20 (4-H, 7-H) ppm. The recovered rotation sample was used for microanalysis and for mass spectroscopic determination. *Anal.* ($C_{25}H_{29}O_4Cl \cdot 0.5$-dioxane) C, H, *m/e* (428).

Acknowledgments.—We are indebted to Mrs. H. M. Marigliano and Mr. M. D. Yudis for interpretation of the nmr spectra, Mrs. F. E. Carlon for technical assistance, and Dr. T. Traubel for the mass spectra.

(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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Received March 24, 1969

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-chloroacetyltryptophan (yielding the lactam II[5]) 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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