Comparison of the ϵ_{max} values of 3-methylene-A-norcholestane XXII and 3-methyl-$\Delta^{3(5)}$-A-norcholestene XXIII again indicates an effect due to the methyl groups adjacent to the unsaturated center (see the discussion for the Δ^1- and Δ^2-cholestenes).

We conclude that routine examination of ultraviolet absorption spectra below 205 mμ of isolated double bonds and certain carbonyl functions, as well as the effects which substituents and neighboring groups impart, is now possible by means of commercially available purged instruments. The results are comparable to those obtained with vacuum spectrometers, down to about 180 mμ, if suitable solvents are used, and if certain rigid requirements of sufficient energy, low stray light, etc., are met. When considering the shorter wave length region, one must be cognizant of the fact that the apparent maximum often coincides with the cut-off point of the instrument and does not reflect the true variation of λ_{max} and ϵ_{max} with structure.

Acknowledgment. We are indebted to all of those who so generously shared their samples for this study. Particular thanks go to Professor W. G. Dauben and Dr. F. Stitt for their interest and encouragement.

ALBANY 10, CALIF.

[CONTRIBUTION FROM THE MERCK SHARP & DOHME RESEARCH LABORATORIES, MERCK & CO., INC.]

A Novel Cleavage Reaction of Steroid 20,21-Oxalolactones. Synthesis of 16,16-Dimethylprednisone

R. D. HOFFSOMMER, H. L. SLATES, D. TAUB, AND N. L. WENDLER

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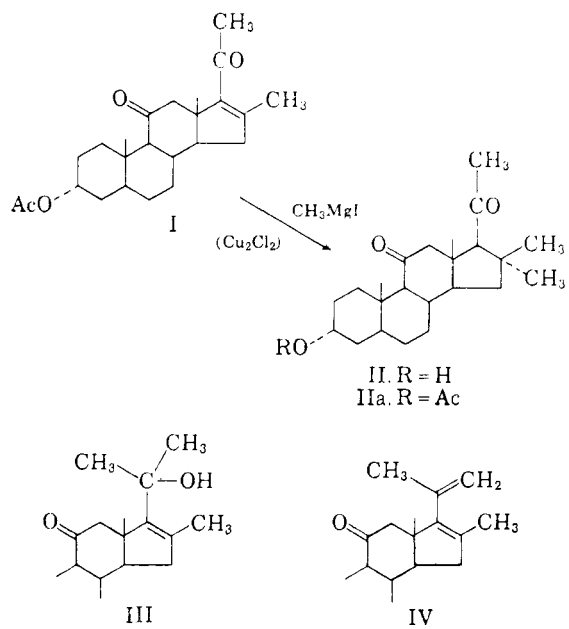
Cleavage of steroid 17α,20-oxidooxalolactones (*e.g.*, VII) with bifunctional amines achieves quantitative release of the corresponding 17α-hydroxy 20-ketone otherwise prone to D-homoannulation under the usual conditions of hydrolysis. This reaction made possible the synthesis of 16,16-dimethylprednisone.

The enhanced anti-inflammatory activity and lack of sodium retention associated with cortical steroid systems possessing a 16α-[1] or 16β-[2]methyl group made it of interest to ascertain the effect of dimethyl substitution at that position. To this end 16,16-dimethylprednisone was synthesized,[3] and the chemistry pertaining to its preparation is the subject of this paper.

The conjugate addition of methylmagnesium iodide to 3α-acetoxy-16-methyl-16-pregnene-11,20-dione (I)[2,4] in the presence of cuprous chloride[5] proceeded in part by 1,4-addition to give 3α-hydroxy-16,16-dimethylpregnane-11,20-dione (II). Although the maximum yield of II realized was 34%, this figure was difficult to achieve and average conversions were in the order of 20–25%. The for-



(1) (a) G. E. Arth, J. Fried, D. B. R. Johnston, D. R. Hoff, L. H. Sarett, R. H. Silber, H. C. Stoerk, and C. A. Winter, *J. Am. Chem. Soc.*, **80**, 3161 (1958); (b) E. P. Oliveto, R. Rausser, L. Weber, A. L. Nussbaum, W. Gebert, C. T. Coniglio, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman, and M. M. Pechet, *J. Am. Chem. Soc.*, **80**, 4431 (1958).

(2) (a) D. Taub, R. D. Hoffsommer, H. L. Slates, and N. L. Wendler, *J. Am. Chem. Soc.*, **80**, 4435 (1958); *J. Am. Chem. Soc.*, **82**, 4012 (1960); (b) E. P. Oliveto, R. Rausser, A. L. Nussbaum, W. Gebert, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman, and M. M. Pechet, *J. Am. Chem. Soc.*, **80**, 6627 (1958).

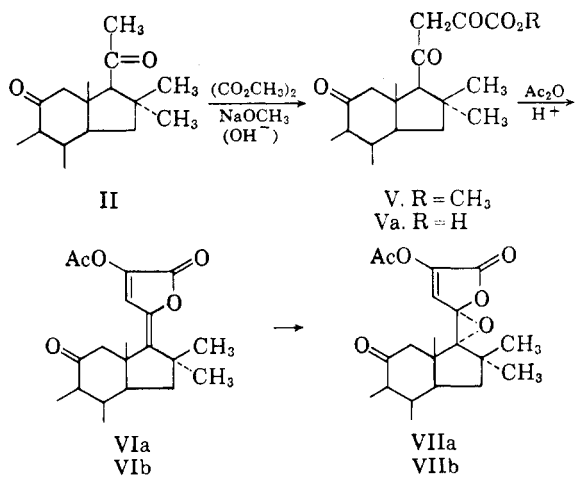
(3) R. D. Hoffsommer, H. L. Slates, D. Taub, and N. L. Wendler, *J. Org. Chem.*, **24**, 1617 (1959).

(4) H. L. Slates and N. L. Wendler, *J. Am. Chem. Soc.*, **81**, 5472 (1959).

(5) Metal chloride-catalyzed 1,4-additions of Grignard reagents to $\Delta^{\alpha,\beta}$-ketones in general was first introduced by M. Kharasch and P. O. Tawney [*J. Am. Chem. Soc.*, **63**, 2308 (1941)]. The conjugate addition of methyl Grignard to Δ^{15}-20-keto steroids, which was first explored by R. E. Marker and H. M. Crooks [*J. Am. Chem. Soc.*, **64**, 1280 (1942)], has been utilized to an increasing extent more recently. In this connection see ref. 1, also R. P. Graber and M. B. Meyers, *Chem. & Ind.*, 1478 (1960); K. Heusler, J. Kebrle, C. Meystre, H. Uberwasser, P. Wieland, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, **42**, 2043 (1959).

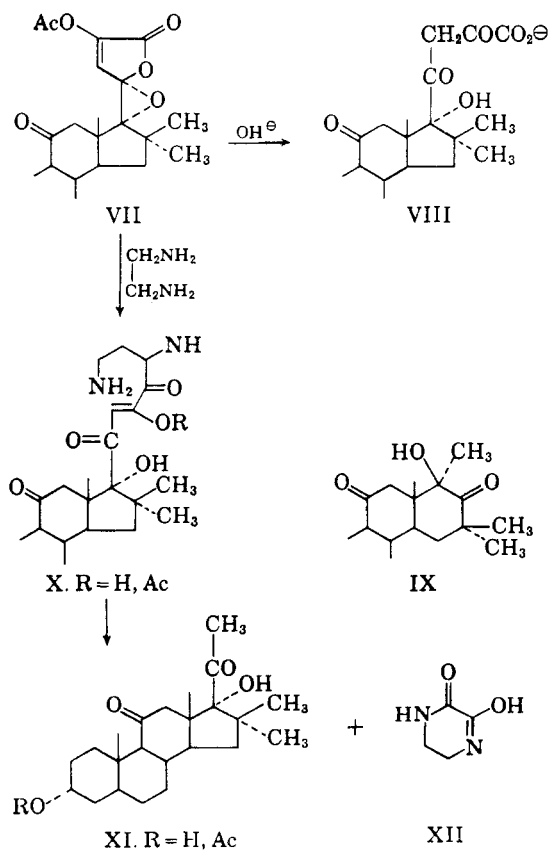
mation of II was erratic and accompanied very possibly by varying amounts of 1,2 (C-20) addition product (III) and its dehydration product (compare IV, see Experimental), as well as unchanged starting material. In order to facilitate the isolation of the 16,16-dimethyl steroid II the total Grignard product after hydrolysis and acetylation was treated with osmium tetroxide; all unsaturated impurities, thereby, were converted to polar hydroxylation products which were easily separated from II on alumina.

The introduction of the 17α-hydroxyl group into II was accomplished by means of the method of Hogg and Nathan,[6] as applied by Sletzinger and Karady to 3α-acetoxy-16α-methylpregnane-11,20-dione.[7] Condensation of 3α-acetoxy-16,16-dimethylpregnane-11,20-dione (IIa) with dimethyl oxalate in the presence of sodium methoxide, followed by base hydrolysis of the intermediate ester V, afforded the 21-glyoxalic acid Va, m.p. 218–221° dec. The latter was converted by acetic anhydride and perchloric acid to the enol lactone VI isolated as a mixture of geometrical isomers: crystalline VIa m.p. 250–260°, $\lambda_{max}^{CH_3OH}$ 296 mμ (22,500) and noncrystalline VIb $\lambda_{max}^{CH_3OH}$ 295 mμ (20,000). Each isomeric enol lactone, in turn, afforded with perbenzoic acid its respective oxide VIIa, m.p. 213–216°, $\lambda_{max}^{CH_3CN}$ 224 mμ (10,500) and VIIb, m.p. 197–203°, $\lambda_{max}^{CH_3CN}$ 226 mμ (11,500). The two isomeric oxidolactones gave a depressed mixed melting point and exhibited different paper-strip mobilities.



In attempts to hydrolyze the oxidolactones VIIa and VIIb by the usual techniques,[6] it became immediately apparent that D-homoannulation intervened (compare IX). The neutral product, m.p. 228–230°, gave a negative Zimmerman test and its NMR spectrum did not possess the normal C-21 methyl band at 7.7 τ.[8]

The ease of D-homoannulation of 16β-methyl-17α-hydroxy-20-keto systems had already been observed.[9] The additional instability, induced ostensibly by the enhanced interaction produced by group congestion in the C-13:C-17:C-16 zone, made it impossible to isolate unrearranged steroid XI from normal hydrolytic procedures designed to produce collapse of the oxidolactone system (see, however, Experimental). Since the initial formation of a 17-hydroxy-21-glyoxalic acid (compare VIII) most probably constitutes the intermediate phase in the alkaline hydrolysis of the oxidolactone VII, its presence as the anion should markedly resist the further attack of hydroxide ion necessary for cleavage to the 17-hydroxy-20-ketopregnane derivative. It was considered, therefore, that by effecting lactone opening with an amine, an intermediate charged species would be avoided; further, if the amine were bifunctional in the proper positional sense a pathway would be available for internal addition with accompanying release of the desired steroid component (compare X). These expectations were fulfilled in a most rewarding way



(6) J. A. Hogg and A. H. Nathan, U. S. Patent **2,740,782**; **2,740,783** (1956).

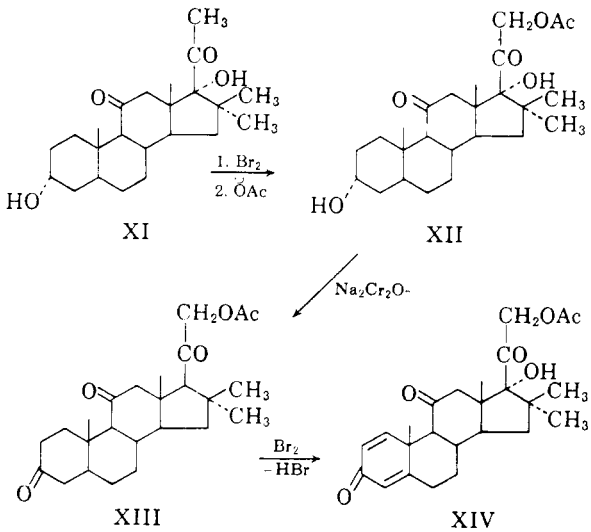
(7) M. Sletzinger and S. Karady, U. S. Patent **2,951,075** (1960); *J. Org. Chem., in press.*

(8) Structure IX is the product to be expected from base-catalyzed D-homoannulation on the basis of prior art. Results of NMR calculation, however, are in better agreement with a 17a-ketone structure [see N. R. Trenner, B. Arison, D. Taub, and N. L. Wendler, *Proc. Chem. Soc.*, 214 (1961)].

(9) D. Taub, R. D. Hoffsommer, H. L. Slates, C. H. Kuo, and N. L. Wendler, *J. Am. Chem. Soc.*, **82**, 4012 (1960).

by ethylene diamine.[10] The latter reagent smoothly and essentially quantitatively converted the oxidolactone VII to 3α-acetoxy-17α-hydroxy-16,16-dimethylpregnane-11,20-dione (XI. R = C_2H_3O) with accompanying formation of the cyclic diamide XII. This facile decomposition was also observed in the 16-monomethyl series. Hydrolysis of the 3-acetate function to give XI (R = H) was accomplished with hydrochloric acid in methanol-chloroform solution.

With the 16,16-dimethyl-17α-hydroxy 20-ketone (XI) in hand, the major barrier to the preparation of the final corticoid derivative XIV was overcome. Bromination of XI (R = H) at C-21 followed by acetoxylation with potassium acetate in acetone led to 21-acetoxy-16,16-dimethylpregnane-3α,17α-diol-11,20-dione (XII). The latter was oxidized by sodium dichromate in aqueous acetic acid to 21-acetoxy-16,16-dimethylpregnane-17α-ol-3,11-20-trione (XIII). Dibromination of XIII at positions 2 and 4 followed by dehydrobromination with dimethylaniline in dimethylformamide gave 16,16-dimethylprednisone 21-acetate (XIV), m.p. 231–235°, $\lambda_{max}^{CH_3OH}$ 238 mμ (14,200).



In the rat systemic granuloma and mouse liver glycogen assays, compound XIV showed respectively no activity and *ca.* one tenth the activity of hydrocortisone.[11]

EXPERIMENTAL[12]

3α-Acetoxy-16,16-dimethylpregnane-11,20-dione (II). To a stirred mixture of 12.5 g. of magnesium turnings in 1250 ml. of dry ether was added dropwise 76.8 g. of methyl iodide in 60 ml. of dry ether, at a rate sufficient to maintain a gentle reflux. The reaction mixture, when addition was complete, was refluxed for 1.5 hr., then cooled to 20° and 0.31 g. of cuprous chloride was added followed by a solution of 23.64 g. of 3α-acetoxy-Δ^{16},16-methylpregnane-11,20-dione in 250 ml. of dry benzene and 1000 ml. of dry ether added at a rapid dropwise rate. The mixture was stirred at reflux for 4 hr., chilled to 0° and treated with 2190 ml. of saturated ammonium chloride solution followed by 200 ml. of water. The aqueous layer was extracted with 500 ml. of benzene. The combined organic phases were washed twice with 400 ml. of water, dried over magnesium sulfate, and the solvent removed *in vacuo*. The residue was treated with 35 ml. of acetic anhydride in 125 ml. of dry pyridine at room temperature overnight. The reaction mixture was pumped to dryness and the residue flushed three times with benzene and once with dioxane. It was then dissolved in 600 ml. of dioxane and treated with 15.55 g. of osmium tetroxide in 100 ml. of dioxane for 48 hr. at room temperature. An additional 250 ml. of dioxane was added, and the mixture was treated with hydrogen sulfide for 2 hr. and filtered through Celite. The solvent was removed from the filtrate *in vacuo* and the residual foam triturated with benzene to yield 2.03 g. of crystalline hydroxylated material. Removal of the solvent from the mother liquor and ether trituration of the residue yielded 7.50 g. (34%) of II; recrystallized from acetone-ether; m.p. 212-217°; λ_{max}^{Nujol} 5.74, 5.84, 5.87 (sh), 8.36, 8.55 μ; $[\alpha]_D^{CHCl_3}$ +76.6°.

Anal. Calcd. for $C_{25}H_{38}O_4$: C, 74.58; H, 9.51. Found: C, 74.80; H, 9.35.

In a previous run the cuprous chloride was added 1 hr. after the 3α-acetoxy-Δ^{16},16-methylpregnane-11,20-dione (200 mg.) had been added to the methylmagnesium iodide. Work-up of the Grignard reaction yielded, as a side product, 29.2 mg. of a crystalline compound, m.p. 140–145° with bubbling and decomposition, $\lambda_{max}^{CHCl_3}$ 2.78, 2.9–3.0, 5.89 μ which quite possibly is the product of 1,2-addition followed in part by dehydration (III and/or IV).

3α-Hydroxy-16,16-dimethyl-11,20-dioxo-21-pregnane-glyoxylic acid (Va). To freshly prepared, dry sodium methoxide from 1.65 g. of sodium was added 7.40 g. of dimethyl oxalate in 35 ml. of benzene. To the stirred mixture was added 5.00 g. of 3α-acetoxy-16,16-dimethylpregnane-11,20-dione (II) in 60 ml. of benzene. The nearly colorless reaction mixture gradually became yellow, and the amorphous sodium enolate of the glyoxylic ester V gradually precipitated. After 16 hr. at 25°, 150 ml. of ice cold 1*N* hydrochloric acid was added and the mixture extracted three times with a total of 200 ml. of ether. The glyoxylic ester V was not isolated but hydrolyzed to the free acid Va by addition of 450 ml. of 1*N* potassium hydroxide to the stirred ether extract. After 3 hr. at 25° and 16 hr. at 5°, the ether washed aqueous layer was cautiously acidified with cold 1*N* hydrochloric acid. The precipitate was filtered, washed with water, and dried in air to give 4.97 g. of glyoxylic acid Va, m.p. 218–221° dec., $\lambda_{max}^{CH_3OH}$ 292 mμ, $E_{cm.}^{1\%}$ 235.

Anal. Calcd.: Neut. equiv. 433. Found: 439.

3α-23-Diacetoxy-16,16-dimethyl-21-normethyl-11-oxo-17(20),22-choladieno-24(20)-lactone (VIa) *and 17(20)-epimer* (VIb). To a stirred suspension of 4.90 g. of glyoxylic acid Va in 50 ml. of carbon tetrachloride kept at 0° was added a cooled mixture (0°) of 50 ml. of acetic anhydride and 0.1 ml. of 70% perchloric acid. The yellow solution was warmed to 25°, and after 45 min., 1 g. of potassium acetate was added. The mixture was concentrated to dryness *in vacuo*, 100 ml. of benzene was added, and the mixture washed with water, 2% sodium carbonate solution, saturated salt solution, and dried over magnesium sulfate. Crystallization of the residue from acetone-ether gave the enol lactone VIa in three crops, 2.73 g. The analytical sample was recrystallized from acetone-ether, m.p. 265–270°; $\lambda_{max}^{CH_3CN}$ 296 mμ (22,500); $\lambda_{max}^{CHCl_3}$ 5.65, 5.77, 5.81, 5.85, 6.17, 8.1 μ.

Anal. Calcd. for $C_{29}H_{38}O_7$: C, 69.85; H, 7.68. Found: C, 70.01; H, 7.39.

(10) N. L. Wendler, U. S. Patent 2,950,297 (1960).

(11) We are indebted to Dr. R. H. Silber of the Merck Institute for Therapeutic Research for the biological assays.

(12) Melting points were taken on a micro hot-stage apparatus and are corrected. We are indebted to R. W. Walker for the infrared spectra, to A. Kalowsky for the ultraviolet spectra, to R. N. Boos and associates for the elemental analyses, and to N. R. Trenner and B. Arison for the NMR spectra.

The noncrystalline mother liquors VIb, $\lambda_{max}^{CH_3CN}$ 295 mμ (20,000), had similar spectral properties, but showed differences in the infrared fingerprint region and was more mobile on paper chromatography in the ligroin-formamide system.

3α,23-Diacetoxy-16,16-dimethyl-21-normethyl-17(20)-oxido-11-oxo-22-choleno-24(20)-lactone VIIa) *and 20-epimer* (VIIb). To 2.70 g. of the crystalline enol lactone VIa was added 16 ml. of 1.305*M* perbenzoic acid in benzene. After 65 hr., 50% benzene-ether was added, and the mixture was washed with cold dilute aqueous sodium bisulfite, dilute potassium carbonate solution, and saturated salt solution, and dried over magnesium sulfate. Crystallization of the residue from ether gave 2.00 g. of enol lactone oxide VIIa, m.p. 209–213°. Recrystallization from acetone-ether gave the analytical sample, m.p. 213–216°, $\lambda_{max}^{CH_3CN}$ 224 mμ (10,500).

Anal. Calcd. for $C_{29}H_{38}O_8$: C, 67.68; H, 7.44. Found: C, 67.62; H, 7.31.

The noncrystalline enol lactone VIb (2.5 g.) was similarly treated with 16 ml. of 1.305*M* perbenzoic acid in benzene to give 1.20 g. of the corresponding enol lactone oxide VIIb, m.p. 197–203°; $\lambda_{max}^{CH_3CN}$ 226 mμ (11,500).

Anal. Calcd. for $C_{29}H_{38}O_8$: C, 67.68; H, 7.44. Found: C, 67.20; H, 7.56.

Base hydrolysis of the enol lactone oxides VIIa + VIIb. (a) *Methanolic aqueous potassium hydroxide.* A solution of 1.00 g. of enol lactone oxide VIIa in 10 ml. of methanol and 30 ml. of 2.5*N* aqueous potassium hydroxide was kept at 25° for 60 hr. Water was added, and the mixture was extracted with 50% ethyl acetate–ether. The organic extract was washed with dilute sodium carbonate solution, saturated salt solution, and dried over magnesium sulfate. Crystallization of the residue (163 mg.) from acetone-ether gave colorless needles, m.p. 228–230° formulated as *3α,17aβ-dihydroxy-16,16-dimethyl-D-homo-5β-androstane-11,17-dione* (IX); negative Zimmerman test; $\lambda_{max}^{CHCl_3}$ 2.73, 2.90, 5.90 μ.; NMR in deuterochloroform, 8.77 (17 or 17a-methyl), 8.83 (19 + 16-methyl), 8.89 (16-methyl), 9.5 τ (18-methyl).

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.40; H, 9.57. Found: C, 72.97; H, 9.14.

Acidification of the original aqueous extract with dilute hydrochloric acid and extraction with ethyl acetate gave 593 mg. of crystalline *3α,17α-dihydroxy-16,16-dimethyl-11,20-dioxo-21-pregnaneglyoxylic acid* (VIII), m.p. 280–283°; $\lambda_{max}^{CH_3OH}$ 285 μ, (8100).

Anal. Calcd.: Neut. equiv. 449. Found: 456.

(b) *2-Phase system-benzene–aqueous sodium hydroxide.* A mixture of 1.00 g. of the enol lactone oxide (either VIIa or VIIb) in 20 ml. of benzene and 40 ml. of 2.5*N* aqueous sodium hydroxide was stirred at 25° for 18 hr. Work-up as in (a) above gave 150 mg. of neutral material and 800 mg. of glyoxylic acid VIII. Crystallization of the neutral fraction from acetone-ether gave 40 mg. of *3α,17α-dihydroxy-16,16-dimethylpregnane-11,20-dione* (XI. R = H), m.p. 178–182°, allotropic form m.p. 172–175°, undepressed with material prepared by the ethylenediamine procedure followed by acid hydrolysis (see below).

Acetylation of XI, R = H (acetic anhydride–pyridine at 25° overnight) gave the 3α-acetate (XI. R = C_2H_3O) identical with material prepared by the ethylenediamine procedure (see below) by mixed melting point and infrared criteria.

3α-Acetoxy-17α-hydroxy-16,16-dimethylpregnane-11,20-dione (XI. R = C_2H_3O) *by the ethylenediamine procedure.* A solution of 500 mg. of enol lactone oxide (VIIa or VIIb) in 10 ml. of tetrahydrofuran was treated with 0.5 ml. of ethylenediamine and allowed to stand at room temperature for 20–24 hr. At the conclusion of this time the reaction mixture was diluted with benzene and the benzene solution washed with dilute hydrochloric acid, sodium bicarbonate solution, and water. The benzene solution was dried and evaporated to give 400 mg. of essentially pure XI [R = C_2H_3O (98.5%)] crystallized from benzene-ether or acetone-ether, m.p. 205–209°; $\lambda_{max}^{CHCl_3}$ 2.92 μ (OH), 5.80 and 8 μ ($C_2H_3O_2$), 5.86, 5.95 sh (11 and 20 C=O).

Anal. Calcd. for $C_{25}H_{38}O_5$: C, 71.71; H, 9.15. Found: C, 71.30; H, 9.29.

3α,17α-Dihydroxy-16,16-dimethylpregnane-11,20-dione (XI. R = H). A solution of 200 mg. of crude 3α-acetoxy,-17α-hydroxy-16,16-dimethylpregnane-11,20-dione, (XI. R = C_2H_3O), in 50 ml. of chloroform was treated with 50 ml. of methanol containing 2.5 ml. of concd. hydrochloric acid. The reaction mixture was allowed to stand overnight (18 hr.). At the end of this period the solvents were evaporated *in vacuo* to a low volume. Water was added and the product extracted with chloroform–ethyl acetate. Last traces of acid were removed by washing with dilute sodium bicarbonate solution. The solvents were removed *in vacuo* and the product crystallized from acetone to give a first crop of 160 mg. of prismatic needles, m.p. 177–182°.

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.40; H, 9.57. Found: C, 73.29; H, 9.42.

Conversion of 3α,23-diacetoxy-16α-methyl-21-normethyl-11-oxo-17(20)-oxido-22-choleno-24(20)-lactone to 3α,17α-dihydroxy-16α-methylpregnane-11,20-dione. A 500-mg. sample of oxidolactone in 10 ml. of tetrahydrofuran was treated with 2 ml. of ethylenediamine and allowed to stand for 20–24 hr. at room temperature. The reaction mixture was worked up as described for the preparation of XI (R = C_2H_3O). The total product was dissolved in 16 ml. of methanol containing 0.8 ml. of concd. hydrochloric acid and stirred for 20 hr. The reaction mixture was worked up as described for the preparation of XI (R = H). The total residue was crystalline and single spot on paper, m.p. 170°, with phase change (needles → prisms), m.p. 188–190°; yield, 350 mg. (90%). The mixed melting point with an authentic sample of 3α,17α-dihydroxy-16α-methylpregnane-11,20-dione[13] was not depressed, and the infrared spectra were the same.

21-Acetoxy-16,16-dimethylpregnane-3α,17α-diol-11,20-dione (XII). To a stirred solution of 1.490 g. of 3α,17α-dihydroxy-16,16-dimethylpregnane-11,20-dione (XI) in 25 ml. of chloroform at 25° was added one drop of 10% hydrogen bromide in acetic acid followed by 0.650 g. of bromine in 15 ml. of chloroform added dropwise (time of addition, 2 hr.). Ether (150 ml.) was added to the nearly colorless solution, and the mixture was extracted with water, dilute potassium bicarbonate solution, and saturated salt solution, and dried over magnesium sulfate. The residue consisted of 1.90 g. of *21-bromo-16,16-dimethylpregnane-3α,17α-diol-11,-20-dione* which crystallized from ether, m.p. 135–142 dec.

To the crude 21-bromo compound (1.85 g.) in 40 ml. of acetone and 0.1 ml. of acetic acid was added 2.00 g. of potassium acetate and 1.60 g. of potassium iodide and the mixture refluxed overnight. The acetone was removed *in vacuo*, water was added and the mixture extracted with ethyl acetate. The latter extract was washed with saturated salt solution and dried over magnesium sulfate. Crystallization of the residue from ether gave massive prisms of the 21-acetoxy compound XII (930 mg.). The analytical sample was recrystallized from acetone-ether; m.p. 206–208°: $\lambda_{max}^{CHCl_3}$ 2.72, 2.90 broad, 5.74, 5.76, 5.85, 8.1 μ.

Anal. Calcd. for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 68.90; H, 8.53.

21-Acetoxy-16,16-dimethylpregnane-17α-ol-3,11,20-trione (XIII). To 500 mg. of the 21-acetoxy-3α,17α-diol (XII) in 15 ml. of acetic acid was added 140 mg. (25% equivalent excess) of sodium dichromate dihydrate in 5 ml. of acetic acid and the mixture kept at 25° for 3 hr. Water was added and the mixture was extracted with chloroform. The latter extract was washed with aqueous potassium bicarbonate, saturated sodium chloride solution and dried over magnesium sulfate. The chloroform was removed *in vacuo* and the residue crystallized from ether to give 360 mg. of prismatic needles of XIII plus additional crystalline material in the

(13) We are grateful to Dr. Tristram of these laboratories for a sample of this substance for comparison purposes.

mother liquors. The analytical sample was recrystallized from acetone-ether, m.p. 203–206°; $[\alpha]_D^{CHCl_3}$ +114°; $\lambda_{max}^{CHCl_3}$ 2.80–2.90, 5.74, 5.79, 5.84, 8.1 μ.

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 69.41; H, 8.39. Found: C, 69.59; H, 8.48.

16,16-Dimethylprednisone 21-acetate (XIV). To a stirred solution of 250 mg. of 21-acetoxy-16,16-dimethylpregnane-17α-ol-3,11,20-trione (XIII) in 5 ml. of chloroform and 0.1 ml. of acetic acid at 0–5° was added 193 mg. of bromine in 5 ml. of chloroform and 1 ml. of acetic acid (time, 25 min.). To the colorless solution was added 120 mg. of sodium acetate in 2 ml. of water, followed by additional water and chloroform. The mixture was extracted with chloroform and the latter extract washed with dilute aqueous potassium bicarbonate and saturated salt solution and dried over magnesium sulfate. The colorless residue (350 mg.) of *2,4-dibromo - 21 - acetoxy - 16,16 - dimethylpregnane - 17α - ol-3,11,20-trione* was dehydrobrominated as follows[14]: It was dissolved in 3 ml. of dimethylformamide, 100 mg. of sodium bromide was added and the mixture stirred at 25° under nitrogen for 1 hr. Dimethylaniline, 0.5 ml., was added and the temperature raised to 135° for 2.5 hr. The purple solution was cooled to 10° and 0.4 ml. of concd. hydrochloric acid in 15 ml. of water was added dropwise. The precipitated crude product was filtered, washed with water, and dried in air. The precipitate was dissolved in ethyl acetate, passed through a column of 1 g. of unground charcoal, which was eluted with ethyl acetate. Crystallization of the residue (225 mg.) of the first 50 ml. eluate from acetone-ether gave 82 mg. of XIV as hexagonal plates, m.p. 224–228°. The analytical sample was recrystallized from acetone-ether, m.p. 231–235°; $[\alpha]_D^{CHCl_3}$ +210°; $\lambda_{max}^{CH_3OH}$ 238 mμ (14,200); $\lambda_{max}^{CHCl_3}$ 2.85, 5.73, 5.76, 5.84, 6.00, 6.14, 6.19 sh., 8.06, 11.20 μ.

Anal. Calcd. for $C_{25}H_{32}O_6$: C, 70.08; H, 7.53. Found: C, 70.02; H, 7.42.

The NMR spectrum of XIV in deuterochloroform was consistent with the normal steroid C-18 methyl (8.90 τ) and side chain structures (21-acetoxymethyl, 5.11 τ) and inconsistent with the isomeric D-homoannulated structures (see ref. 8). Similarly the infrared bands at 5.73 and 5.76 μ are as expected for the normal steroid C-21:C-20-CH_2O-C_2H_3O C=O part structure.

(14) Procedure of J. Day, R. Erickson, and R. Pettebone, U. S. Patent 2,873,284 (1959).

RAHWAY, N. J.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX S. A.]

Steroids. CLXXVI. Claisen Rearrangement of Estrone Allyl Ether[1]

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Rearrangement of estrone allyl ether in refluxing diethylaniline gave a 3:1 mixture of 4-allyl- (III) and 2-allylestrones (II). Each isomer has been reduced to the corresponding C-allyl and C-propylestradiol. Structural assignments have been made on the basis of NMR, infrared and ultraviolet spectra, and on molecular rotation relationships.

The Claisen rearrangement of estrone allyl ether was first carried out by Miescher and Scholz.[2] Their product was noncrystalline but rearrangement was demonstrated to have occurred by the preparation of a crystalline benzoate. Very recently, Patton[3] has shown that both 2-allyl- and 4-allylestrones could be isolated from the rearrangement in crystalline form and he assigned structures to the two isomers on the basis of characteristic C—H deformation bands in the infrared absorption spectra.

While the structural assignments made by Patton are undoubtedly correct, the evidence provided by these absorption bands is not completely unequivocal in the case of the C-allylestrones themselves.

The results now presented are an independent study in which much physical evidence, based on NMR, infrared, and ultraviolet spectra as well as on molecular rotations, has been assembled not only for the C-allylestrones but for certain reduction products.

Rearrangement of estrone allyl ether, under essentially the original reaction conditions,[2,4] gave a product which was only poorly separated by chromatography on silica. However, slow fractional crystallization from ether-hexane resulted in complete separation of the two isomers. The less soluble isomer, to which the 2-allyl structure was assigned, crystallized in colorless plates, m.p. 186–187°, and the more soluble 4-allylestrone separated as rosettes of broad, flat needles, m.p. 136–137°. The ratio of isomers was 1:3 with the latter predominating.

Each isomer was characterized as a crystalline benzoate and a mixture of these in the correct proportions melted at the same temperature as that reported for the benzoate of Miescher and Scholz.[2] Reduction of the C-allylestrones, II and III, by sodium borohydride in aqueous methanol gave the corresponding C-allylestradiols, IV and V, and these were hydrogenated over Adams' catalyst in ethanol to the C-propylestradiols VI and VII.

The distribution of isomers formed in the rearrangement is, at first sight, unusual and would not

(1) Steroids. CLXXV., P. G. Holton and E. Necochea, *J. Pharm. Med. Chem., in press.*

(2) K. Miescher and C. Scholz, *Helv. Chim. Acta*, 20, 1237 (1937).

(3) T. L. Patton, *Chem. & Ind.* (London), 1567 (1960).

(4) The lower boiling point of diethylaniline (176°/570 mm.) necessitated extension of the reaction time to 10 hr. After 5 hr., the original reaction period of Miescher and Scholz,[2] 20% of the ether remained unrearranged.