N-Tosyl-D-3,4-dimethoxy-α-methylphenethylamine[14] (V). (a) From X.—The gummy ditosylate (1.64 g.) in 58 ml. of dry purified[30] tetrahydrofuran was added dropwise during 15 minutes with magnetic stirring to a suspension of 0.82 g. of lithium aluminum hydride in 33 ml. of tetrahydrofuran. The mixture was stirred at room temperature for 0.5 hr., refluxed for 3 hr., chilled, treated with water and 4 *N* hydrochloric acid and extracted with chloroform. The extract was washed with sodium chloride and potassium carbonate solutions, dried with potassium carbonate, concentrated, chromatographed on neutral alumina and the product eluted with chloroform. Evaporation and crystallization from ether–pentane yielded 0.93 g. (84%) of colorless elongated prisms arranged in rosettes, m.p. 74.5–76.0°. Recrystallization from ether–pentane provided material, m.p. 75.6–76.6°, $[\alpha]^{20}D$ −29.3° (*c* 2.00, ethanol), $[\alpha]^{20}D$ −10.0° (*c* 2.00, chloroform).

(b) From D-(−)-3,4-Dimethoxy-α-methylphenethylamine[7] (IV).—A solution of 1.00 g. of IV and 3 g. of tosyl chloride in 15 ml. of dry pyridine was kept at room temperature for 1 hr. and poured into a slurry of ice, water and 20 ml. of concd. hydrochloric acid. The oil, which crystallized on standing in the refrigerator, was washed with water, then chromatographed and recrystallized as above; yield 1.20 g. (67%), m.p. 75.6–76.6° (no depression with a sample prepared under (a)), $[\alpha]^{20}D$ −28.9° (*c* 2.26, ethanol), $[\alpha]^{21}D$ −9.8° (*c* 2.00, chloroform). Samples prepared under (a) and (b) had identical infrared spectra.

Anal. Calcd. for $C_{18}H_{23}NO_4S$: C, 61.87; H, 6.63; N, 4.01; S, 9.18. Found: C, 61.86; H, 6.42; N, 4.12; S, 8.96.

N-Tosyl-L-3,4-dimethoxy-α-methylphenethylamine, prepared from L-(+)-3,4-dimethoxy-α-methylphenethylamine[7] in 59% yield, formed rosettes of colorless elongated prisms, m.p. 76.2–77.2°, $[\alpha]^{20}D$ +29.4° (*c* 2.00, ethanol), $[\alpha]^{20}D$ +10.6° (*c* 2.01, chloroform).

N-Tosyl-DL-3,4-dimethoxy-α-methylphenethylamine was obtained by mixing the enantiomers or (in 68% yield) by reduction of ditosyl-DL-3,4-dimethoxyphenylalaninol. It was crystallized with difficulty by slow evaporation of its ether solution at 3° and melted at 63–67°. Its infrared spectrum in chloroform was identical with that of the D-isomer.

Acknowledgments.—The authors are greatly indebted to Dr. W. Klyne of the Postgraduate Medical School of London for very valuable advice and to Dr. Frederick E. King of British Celanese Ltd., London, for suggesting an improved method for the isolation of guaiaretic acid. Miss Mary M. Trail carried out a large portion of the experimental procedures, including determination of the melting point diagram and of the optical rotations. Microanalyses were performed by Dr. W. C. Alford and his staff.

BETHESDA 14, MARYLAND

[CONTRIBUTION FROM THE CHEMICAL RESEARCH AND DEVELOPMENT DIVISION OF THE SCHERING CORPORATION]

Reaction of Steroids with Diazomethane[1]

BY ALEXANDER L. NUSSBAUM AND FLORENCE EMILIE CARLON

RECEIVED FEBRUARY 18, 1957

The action of diazomethane in ether–methanol upon certain steroids has been investigated. This reagent not only saponifies acetate groups at C-21 but also causes homologation of the side chain. Evidence is presented that the new compounds are homologous 20,22-epoxides. A model compound possessing this structure was prepared and correlated with a known compound.

The recent report on the use of diazomethane as a catalyst in transesterification[2] led us to investigate that method in the hydrolysis of the 21-acetates of a number of physiologically active steroids, since the usual methods of saponification cause concomitant side reactions.[3]

When 17α,21-dihydroxy-$\Delta^{1,4}$-pregnadiene-3,11,-20-trione 21-acetate[4] (Ia) was exposed to the action of an excess of diazomethane in ether–methanol solution, the ester group was lost, but the resulting product was not identical with the predicted hydrolysate Ib. Although its melting point was similar to that of 17α,21-dihydroxy-$\Delta^{1,4}$-pregnadiene-3,11,20-trione[4] (Ib) and no depression of this melting point was observed upon admixture with the new material, the two compounds were definitely not identical, as shown by their infrared spectra, optical rotations and migration rates in paper chromatography. The same material could also be obtained directly from non-acetylated 17α,21-dihydroxy-$\Delta^{1,4}$-pregnadiene-3,11,20-trione (Ib). Elemental analysis indicated that the new substance was a homolog of its alcohol precursor. It could be monoacetylated and resaponified.

The new material possessed a high intensity maximum at 239 mμ in the ultraviolet. This could arise from either the original dienone or a newly formed enone chromophore. However, survival of the dienone system was indicated by the characteristic absorption doublet in the infrared at 6.16 and 6.22 μ[4] and by polarographic data.[5] Failure of diazomethane to attack the ring system was not entirely unexpected, since the work of Wettstein[6] and that of Djerassi and Scholz[7] has shown that the double bond of a steroidal Δ^4-3-ketone is resistant to that reagent.[8]

(1) Part of the results reported in this paper were published in a communication to the editor of *Chemistry & Industry*, 1313 (1956); other parts were presented before the Miami Meeting of the American Chemical Society, April 7–12, 1957.

(2) H. Bredereck, R. Sieber and L. Kamphenkel, *Chem. Ber.*, **89**, 1169 (1956).

(3) See, for instance, N. L. Wendler and R. P. Graber, *Chemistry & Industry*, 549 (1956).

(4) H. L. Herzog, A. Nobile, S. Tolksdorf, W. Charney, E. B. Hershberg, P. L. Perlman and M. M. Pechet, *Science*, **121**, 176 (1955).

(5) Peter Kabasakalian and James McGlotten, THIS JOURNAL, **78**, 5032 (1956). We are indebted to Mr. T. Coniglio of these laboratories for his kind assistance in the measurement of the polarographic reductions.

(6) A. Wettstein, *Helv. Chim. Acta*, **27**, 1803 (1944).

(7) Carl Djerassi and C. R. Scholz, *J. Org. Chem.*, **14**, 661 (1949).

(8) Addition of diazomethane to α,β-unsaturated ketones was first described by E. Azzarello, *Gazz. chim. ital.*, II, **36**, 50 (1906). The validity of the statement[7] that the addition of diazomethane to steroidal α,β-unsaturated ketosteroids is characteristic of the Δ^{16}-20-one-moiety has received further support from the failure of 3,17-diketo-Δ^1-androstene to add diazomethane: Carl Djerassi and Alexander L. Nussbaum, unpublished experiment performed at Wayne State University.

Oxidative degradation of the new substance with chromic acid[9] gave 3,11,17-triketo-$\Delta^{1,4}$-androstadiene(III).[10] It could be concluded, therefore, that the methylene group had entered into the side chain. This was supported by the observation that the original dihydroxyacetone grouping had not survived the reaction. The new substance failed to give a purple color with 2,3,5-triphenyltetrazolium chloride,[11] and the carbonyl band in the infrared spectrum of the starting material attributable to the interaction of the C_{21}-acetate with the C_{20}-ketone at 5.80 μ gave way to a simple acetate band at 5.74 μ[12] in the acetate of the new substance. The C_{20}-carbonyl seemed to be involved in the new transformation. In order to facilitate interpretation of the infrared spectrum, the reaction was carried out on prednisolone where there was no ketone function at C-11 which would complicate absorption in the carbonyl region. When 11β,-17α,21-trihydroxy-$\Delta^{1,4}$-pregnadiene-3,20-dione 21-acetate (Ic) was exposed to the action of diazomethane in ether–methanol, there was again obtained a new homolog, which did not exhibit any infrared absorption typical of saturated ketones. Furthermore, sodium bismuthate[13] treatment of the new compounds failed to cleave the side chain, indicating the absence of a dihydroxyacetone group.

All these facts were in agreement with the view that a methylene group had added to the side chain carbonyl with the formation of an epoxide, a reaction often observed in diazomethane chemistry.[14] Thus, the reaction products of Ia (or b) and Ic were formulated as IIa and IIc, respectively. This formulation was supported by the fact that the free alcohols of these reaction products (see following) showed a new band in the infrared near 8.05 μ which can be attributed to the epoxide grouping.[15]

Their migration rates in a paper chromatographic system[16] were slightly greater than those of the parent substances, indicating a slight decrease in polarity expected from the proposed transformation. An analogous reaction has been observed by Prins and Reichstein[17] who obtained a 20,21-epoxide from the reaction of 17α-formyltestosterone.

An investigation of the scope of this reaction showed that, under the conditions used, only those steroids possessing the complete dihydroxyacetone side chain undergo the transformation described to any appreciable extent. In addition to Ia (or b) and Ic, the following compounds were submitted to the reaction: cortisone acetate (Id), Δ^6-cortisone (Ie)[18] and Compound S (If). The corresponding bisnorcholane-epoxides are formulated in Chart I. Desoxycorticosterone (IV), lacking a hydroxyl group at C-17, failed to react as smoothly as the preceding steroids of the cortisone type: only small amounts of the homolog V could be isolated after careful chromatography.

Also submitted to the reaction were 17-hydroxyprogesterone, 21-hydroxypregnenolone and allopregnanolone acetate. None of these compounds underwent the reaction here discussed; in each case starting material was recovered in high yield. A slight degree of acetate hydrolysis was observed in the case of allopregnanolone acetate (4%).

The new substances show uniform negative molecular rotation differences (see Table I). Their physical (especially spectral) properties are in agreement with the arguments here outlined.

TABLE I

MOLECULAR ROTATION DIFFERENCES

Starting material (1)	M_D of (1) (2)	M_D of product (alcohol) (3)	ΔM_D (3) − (2) (4)
Prednisone acetate (Ia)	617	402	−215
Prednisolone acetate (Ic)	364	82	−282
Cortisone acetate (Id)	754	519	−235
Δ^6-Cortisone (Ie)	932	723	−209
Compound S (If)	423	195	−228
Desoxycorticosterone acetate (IV)	589	328	−261
3β,17α,21-Trihydroxy-Δ^5-pregnen-20-one 3,21-diacetate	−106	−213	−107

In order to confirm the course of the proposed reaction, it was carried out on 3β,17α,21-trihydroxy-Δ^5-pregnen-20-one 3,21-diacetate (VIa)[19] (Chart II). The expected 3β,17α,21-trihydroxy-Δ^4-bisnorcholene-20 ξ,22-epoxide 3-acetate (VIIa) was obtained. Reduction of the diacetate VIIb with lithium aluminum hydride gave a mixture of tetrols (VIIIa), from which, upon acetylation, a homogeneous 3,21-diacetate (VIIIb) could be isolated in moderate yield. The same mixture of tetrols had been prepared previously[19] by a Grignard reaction on VIa, and upon repetition of this work, followed by acetylation, we were able to isolate the same diacetate (VIIIb) as had been obtained from the model compound. While this method of synthesis does not give any knowledge concerning the stereochemistry at C-20, it does establish the structure of the carbon skeleton.

Preliminary biological studies indicate compounds IIa, IIc and IId to be essentially devoid of eosinopenic, anti-inflammatory and glycogen-depositing activity. The homolog of desoxycorticosterone (V) appeared to have lost all of its sodium-retaining characteristics. We are indebted to Drs. S. Tolksdorf and P. Perlman of our laboratories for these data.

(9) A. S. Meyer, *J. Biol. Chem.*, **203**, 469 (1953).

(10) H. L. Herzog, C. C. Payne, M. A. Jevnik, D. Gould, E. L. Shapiro, E. P. Oliveto and E. B. Hershberg, THIS JOURNAL, **77**, 4781 (1955).

(11) R. B. Burton, A. Zaffaroni and E. H. Keutmann, *J. Biol. Chem.*, **188**, 763 (1951).

(12) R. Norman Jones, P. Humphries, F. Herling and Konrad Dobriner, THIS JOURNAL, **74**, 2820 (1952).

(13) C. J. W. Brooks and J. K. Norymberski, *Biochem. J.*, **55**, 371 (1953).

(14) C. D. Gutsche, "The Reactions of Diazomethane and its Derivatives," in R. Adams, ed., "Organic Reactions," Vol. VIII, John Wiley and Sons, Inc., New York, N. Y., 1954, pp. 364 *et seq.* We are indebted to Dr. D. Gould of these laboratories for first suggesting the epoxide as a possibility.

(15) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954.

(16) U. S. Patent 2,658,023.

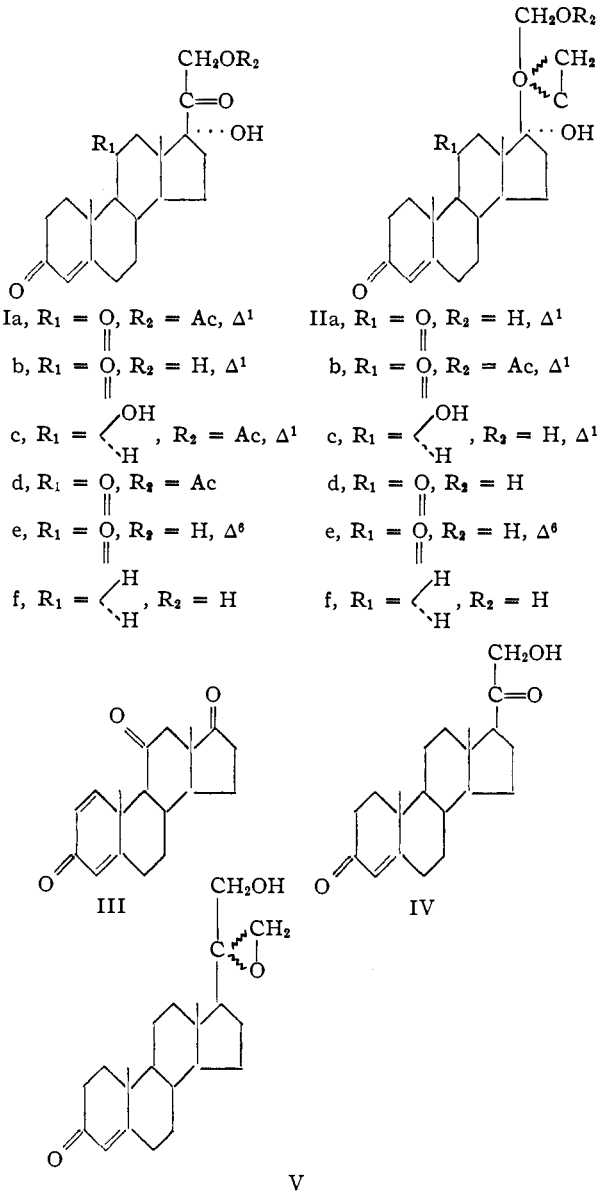
(17) D. A. Prins and T. Reichstein, *Helv. chim. Acta*, **24**, 945 (1941).

(18) V. R. Mattox, E. L. Worosh, G. A. Fleischer and E. C. Kendall, *J. Biol. Chem.*, **197**, 261 (1952). The additional double bond in ring B again failed to add diazomethane.[8]

(19) H. G. Fuchs and T. Reichstein, *Helv. Chim. Acta*, **24**, 804 (1941).

Acknowledgment.—Credit is due to Drs. E. P. Oliveto, D. H. Gould, H. L. Herzog and J. Meinwald for their kind interest in helpful discussions, and especially to Dr. E. B. Hershberg, who helped in the preparation of the manuscript.

CHART I



Experimental[20]

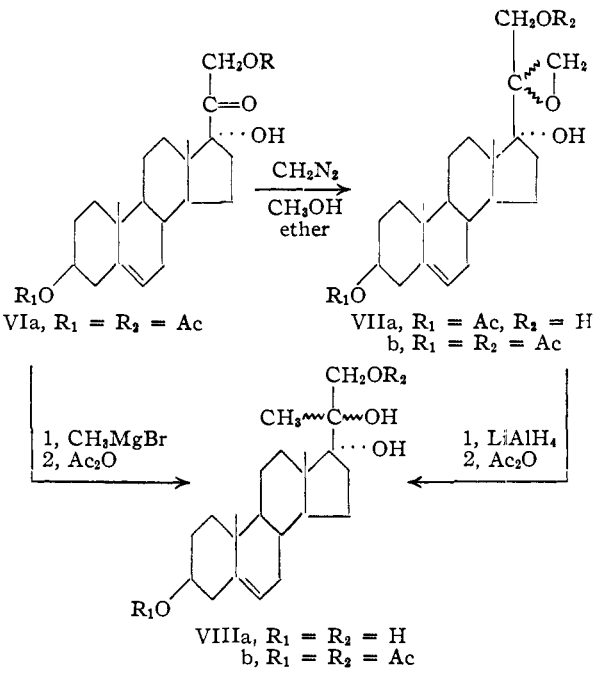
17α,21-Dihydroxy-$\Delta^{1,4}$-bisnorcholadiene-3,11-dione-20ξ,22-epoxide (IIa).—The following procedure is typical of all subsequent preparations of the homologs: 17α,21-Dihydroxy-$\Delta^{1,4}$-pregnadiene-3,20-dione 21-acetate (Ia) (600 mg.) was dissolved in 20 ml. of methanol, and into this solution was filtered another solution of *ca.* 1.2 g. of diazomethane in 60 ml. of ether,[21] and the mixture was allowed to stand for a period of five days at room temperature.[22]

(20) All melting points were taken on a Kofler block. Rotations were carried out in a 1-dm. tube at a concentration of *ca.* 1% in dioxane, unless otherwise specified. Analyses and spectral data were obtained by the Microanalytical and Physical Chemistry Departments of these laboratories.

(21) *Cf.* Th. J. de Boer *et al.*, *Org. Syntheses*, **34**, 2496 (1954).

(22) A subsequent study by paper chromatographic methods showed an optimum reaction time of 50 hr.

CHART II



The small amount of "polymethylene" which had appeared was then filtered off, the solution was concentrated to dryness under vacuum, and the crystalline residue was dissolved in methanol, treated with charcoal and recrystallized from the same solvent. A first crop of 420 mg., m.p. 226–231°, was obtained. Fourfold recrystallization from methanol gave the analytical sample, m.p. 239–241°, $[\alpha]^{25}D$ +108.2°, λ_{max}^{MeOH} at 239 mμ (ε 15,600); λ_{max}^{Nujol} at 3.03, 5.85, 5.99, 6.16, 6.22 and 8.03 μ.

Anal. Calcd. for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 70.90; H, 7.79.

17α,21-Dihydroxy-$\Delta^{1,4}$-bisnorcholadiene-3,11-dione-20ξ,22-epoxide 21-Acetate (IIb).—A sample of relatively crude free alcohol IIa (200 mg.) was dissolved in 1 ml. of pyridine, 1 ml. of acetic anhydride was added and the resulting solution allowed to stand overnight. It was then poured into ice, filtered and air-dried to give 185 mg. of a product melting 195–198°. Recrystallization from methylene chloride-ether gave 145 mg., m.p. 210–212°. A further wasteful recrystallization from acetone gave the analytical sample, m.p. 213–215°, $[\alpha]^{25}D$ +113.2; λ_{max}^{Nujol} at 2.97 5.74(sh), 5.85, 6.03, 6.16, 6.23 and 8.12 μ.

Anal. Calcd. for $C_{24}H_{30}O_6$: C, 69.52; H, 7.30. Found: C, 69.50; H, 7.00.

Saponification[23] of IIb.—The foregoing acetate (60 mg.) was suspended in 3 ml. of methanol and placed in an atmosphere of nitrogen. To this solution 0.2 ml. of a stock solution of 0.67 g. of sodium methylate in 15 ml. of methanol was added and the reaction was allowed to proceed at room temperature for 18 minutes. All of the material was observed to dissolve after 5 minutes, but some solid reappeared after 10 minutes. Aqueous methanol (0.06 ml. of a solution containing 3 ml. of methanol and 0.2 ml. of water) was then added and the reaction time extended another 6 minutes. Finally, 2 ml. of ice-water was added, and the mixture was concentrated under vacuum at 35°. A few pieces of ice were added, and the resulting suspension filtered with suction. The solid was washed well with water and air-dried to give 49.5 mg., m.p. 220–235°. One recrystallization from methanol gave paper chromatographically pure free alcohol IIa, m.p. 235–239°, identified by its infrared spectrum.

3,11,17-Triketo-$\Delta^{1,4}$-androstadiene (III).—17α,21-Dihydroxy - $\Delta^{1,4}$ - bisnorcholadiene - 3,11 - dione - 20ξ,22-epoxide (117.5 mg.) was dissolved in 6.6 ml. of glacial acetic acid previously distilled over chromium trioxide.

(23) U. S. Patent 2,634,277 in *C. A.*, **48**, 1448c (1954), and **49**, 14044 (1955).

An oxidizing solution consisting of 300 mg. of chromium trioxide, 0.36 ml. of water and 3.6 ml. of acetic acid was prepared and 0.91 ml. of the latter was added to the steroid solution. The resulting suspension was allowed to react overnight at room temperature and then poured into ice. Sodium thiosulfate (100 mg.) was added and then enough sodium hydroxide to produce a definite alkaline reaction. The neutral products were then extracted with methylene chloride and the extract washed with dilute acid and water. After drying over sodium sulfate and vacuum concentrating, a yellow oil (51.6 mg.) was obtained, which crystallized from petroleum ether to give 26.5 mg., m.p. 158–187°. One recrystallization from methylene chloride–hexane gave III, m.p. 187–193°, having an infrared spectrum identical with that of a genuine sample of 3,11,17-triketo-$\Delta^{1,4}$-androstadiene.

11β,17α,21-Trihydroxy-$\Delta^{1,4}$-bisnorcholadiene-3-one-20ξ,22-epoxide (IIc).—11β,17α-21-Trihydroxy-$\Delta^{1,4}$-pregnadiene-3,-20-dione 21-acetate (Ic) (3 g.) was treated with 6 g. of diazomethane as above. It did not crystallize from any of the common solvents but did so from its own oil and remained crystalline upon trituration with a little ice-cold methanol. Filtration gave 880 mg. of material, m.p. 135–150°.

Chromatography of the mother liquors on Florisil gave 110 mg. of a material eluted with benzene–5% acetone. Upon recrystallization from acetone, this material had a melting point of 192–220°; λ_{max}^{Nujol} at 2.86, 5.86, 6.04, 6.19 and 6.24 μ (not identical with 11β,17α,21-trihydroxy-$\Delta^{1,4}$-pregnadiene-3,20-dione). It was not further examined at this time. With 30% acetone-benzene, 1.62 g. of a more polar eluate was obtained. This material had properties similar to those of the substance which originally crystallized from the crude reaction mixture. Like the latter, it was impossible to recrystallize from the common solvents, but eventually it was found to form a crystalline solvate with methylene chloride. One recrystallization from methanol–methylene chloride gave 960 mg., transition point with partial melting 135–150°, definite m.p. 213–222°. Two more recrystallizations from the same solvent gave the analytical sample, transition range 136–152°, definite m.p. 215–219°; λ_{max}^{MeOH} at 244 mμ (ϵ 15,000), $[\alpha]^{25}D$ +17.3°; λ_{max}^{Nujol} at 2.98, 6.04, 6.21, 6.26 and 8.05 μ.

Anal. Calcd. for $C_{22}H_{30}O_5 \cdot CH_2Cl_2$: C, 60.13; H, 7.02. Found: C, 60.25; H, 7.33.

An acetate was prepared in the usual manner and was found to have the following properties: m.p. 240–243°, λ_{max}^{MeOH} at 243 mμ (ϵ 15,000); λ_{max}^{Nujol} at 2.85(sh), 2.94, 5.74, 6.03 and 6.19 μ.

Anal. Calcd. for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74. Found: C, 69.55; H, 7.98.

17α,21-Dihydroxy-Δ^4-bisnorcholene-3,11-dione-20ξ,22-epoxide (IId).—17α,21-Dihydroxy-Δ^4-pregnene-3,11,20-trione 21-acetate (Id) (1.5 g.) was treated with 3 g. of diazomethane as described. Chromatography on Florisil gave 510 mg. of product, m.p. 210–232°. Several recrystallizations from methanol failed to improve the sharpness of the melting point, and eventually the following properties were measured from a sample that had been recrystallized four times: m.p. 225–245°,[24] $[\alpha]^{25}D$ +138.1°, λ_{max}^{MeOH} at 238 (ϵ 15,400); λ_{max}^{Nujol} at 2.92, 5.89, 6.12 and 8.05 μ.

Anal. Calcd. for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08. Found: C, 70.54; H, 8.08.

17α,21-Dihydroxy-$\Delta^{4,6}$-bisnorcholadiene-3,11-dione-20ξ,22-epoxide (IIe).—17α,21-Dihydroxy-$\Delta^{4,6}$-pregnadiene-3,11,-20-trione 21-acetate (Ie) (1 g.) was treated with the usual excess of diazomethane in the manner described. Crystallization from methanol gave 354 mg. of a product with m.p. 230–270°. Two recrystallizations from methanol gave the analytical sample, transition range 220–230°, m.p. 280–286, $[\alpha]^{25}D$ +194.2°, λ_{max}^{MeOH} at 280.5 (ϵ 24,700); λ_{max}^{Nujol} at 2.98, 5.84, 6.10, 6.19, 6.31 and 8.14 μ.

Anal. Calcd. for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 70.87; H, 7.33.

17α,21-Dihydroxy-Δ^4-bisnorcholen-3-one-20ξ,22-epoxide (IIf).—17α,21-Dihydroxy-Δ^4-pregnene-3,20-dione (If) (1.5 g.) was converted as usual. Crystallization from methanol gave 830 mg., m.p. 223–236°. Two recrystallizations from methanol gave the analytical sample, (vacuum capillary) m.p. 245–246°, $[\alpha]^{25}D$ +54.0°, λ_{max}^{MeOH} at 242 mμ (ϵ 16,800); λ_{max}^{Nujol} at 2.97, 5.99, 6.21(w) and 8.05 μ.

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.16; H, 8.95.

Preparation of an **acetate** in the usual manner gave a product with m.p. 217–220°, $[\alpha]^{25}D$ +78.5°, λ_{max}^{MeOH} at 242 (ϵ 15,800); $\lambda_{max}^{CHBr_3}$ at 5.74, 6.01, 6.19 and 8.13 μ.

Anal. Calcd. for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.60; H, 8.69.

21-Hydroxy-Δ^4-bisnorcholen-3-one-20ξ,22-epoxide (V).—21-Hydroxy-Δ^4-pregnen-3,20-dione (IV) (1.5 g.) was subjected to the action of diazomethane, as described above. The oily residue was chromatographed over Florisil, and from the ether eluates, 181 mg. of V, m.p. 166–172°, was obtained. Two recrystallizations from ethyl acetate gave the analytical sample, m.p. 164–168°, followed by phase transition to needles melting at 172–173°, $[\alpha]^{25}D$ +95.1°, λ_{max}^{MeOH} at 242 mμ (ϵ 17,000); λ_{max}^{Nujol} at 2.97, 6.09, 6.19, 8.02 and 12.22 μ.

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.96; H, 9.26.

3β,17α,21-Trihydroxy-Δ^5-bisnorcholene-20ξ,22-epoxide 3-Acetate (VIIa).—3β,17α,21-Trihydroxy-Δ^5-pregnen-20-one 3,21-diacetate (VIa) (7.5 g.) was treated with diazomethane in the usual manner. The dry residue was crystallized from methanol–ethyl acetate to yield a first crop of 3.51 g., m.p. 205–211°, and a second crop, 0.51 g., m.p. 180–195°. Attempts to purify this material by chromatography were unsuccessful, and the first crop was used as such for subsequent reactions. An analytical sample was prepared from the crude material by fourfold recrystallization from acetone, ethyl acetate and methanol. No significant changes in melting points were observed, and the final sample possessed the following properties: m.p. 207–213°, $[\alpha]^{25}D$ −52.9°; $\lambda_{max}^{CHBr_3}$ at 2.87, 5.81, 6.03(sh), 8.02, 12.31 and 12.48 μ.

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 71.25; H, 8.97. Found: C, 71.09; H, 8.92.

3β,17α,21-Trihydroxy-Δ^5-bisnorcholene-20ξ,22-epoxide 3,21-Diacetate (VIIb).—The foregoing monoacetate (2.43 g.) was dissolved in 10 ml. of pyridine and an equal volume of acetic anhydride was added. After overnight standing, the reaction mixture was poured into ice-water. The resulting solid was filtered off and crystallized from methanol to give 2.21 g., m.p. 164–182°. This crude material was used as such in the subsequent reduction. An analytical sample was obtained by fourfold recrystallization from methanol: m.p. 190–196°, $[\alpha]^{24}D$ −13.1° ($CHCl_3$); $\lambda_{max}^{CHBr_3}$ at 2.76, 2.86, 3.00, 5.73(sh), 5.81, 5.94(sh), 12.28 and 12.50 μ.

Anal. Calcd. for $C_{26}H_{36}O_6$: C, 69.93; H, 8.58. Found: C, 69.88; H, 8.45.

3β,17α,20ξ,21-Tetrahydroxy-Δ^5-bisnorcholene 3,21-Diacetate. A. From Xb *via* Reduction with Lithium Aluminum Hydride.—Lithium aluminum hydride (2.00 g.) was dissolved in 100 ml. of dry tetrahydrofuran, and to it was added 2.03 g. of the diacetate VII dissolved in 75 ml. of tetrahydrofuran. The reaction mixture was allowed to reflux overnight and then the excess reagent was destroyed with ethyl acetate. Dilute sulfuric acid (200 ml., 5% aqueous) was added and the reaction products partitioned between water and ethyl acetate. The organic phase was washed with sodium bicarbonate and water and eventually dried and concentrated. Crystallization of the residue from ethyl acetate gave 500 mg. of a product, m.p. 185–215°, which did not show absorption in the carbonyl region of the infrared spectrum. The material was dissolved in 5 ml. of pyridine, and an equal volume of acetic anhydride was added. The solution was allowed to stand overnight and was then poured into ice-water. The resulting crude (m.p. 145–170°) was crystallized from ethyl acetate to give 267 mg. of VIIIb, m.p. 217–230°. After three recrystallizations from methanol, there remained 127.2 mg. of an analytical sample, m.p. 228–235°, $[\alpha]^{24}D$ −70.1°; λ_{max}^{Nujol} at 2.84, 5.76, 5.82, 5.98(sh) and 8.02 μ.

Anal. Calcd. for $C_{26}H_{40}O_6$: C, 69.61; H, 8.99. Found: C, 69.57; H, 8.85.

B. From VIa *via* Grignard Reaction.—Methylmagnesium bromide was prepared in the usual manner by allowing 15 ml. of methyl bromide to react with 5.7 g. of magnesium

(24) A capillary melting point, however, was 217–223°, as previously reported.

turnings in 350 ml. of anhydrous ether. A solution of 5 g. of 3β,17α,21-trihydroxy-Δ⁵-pregnen-20-one 3,21-diacetate (VIa) was then added dropwise and the resulting reaction mixture was allowed to reflux overnight. The suspension was cooled, and 500 ml. of 5% sulfuric acid was added. After 2 hr. of agitation, the two phases were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic fractions were washed with sodium bicarbonate and water to neutrality and dried over sodium sulfate. Vacuum concentration gave a crude product which was acetylated immediately. (In another experiment, methylation of 2.18 g. of VIa gave a crude which was crystallized from ethyl acetate to give 790 mg. with m.p. 214–248°. This material, in spite of the great discrepancy of the melting point, possessed an infrared spectrum very like that of the lithium aluminum hydride reduction product of VIIa. However, like the latter, it could not be purified by conventional techniques.) The entire residue was dissolved in 50 ml. of pyridine, and 50 ml. of acetic anhydride was added. The solution was allowed to stand at room temperature overnight and then poured into ice-water. The resulting solid was filtered and recrystallized from methanol to give 1.12 g., m.p. 185–202°. Three recrystallizations from ethyl acetate followed by two from methanol gave an analytical sample, 250 mg., m.p. 225–232°, no depression upon admixture of the diacetate from the lithium aluminum hydride reduction of VIIa, infrared spectrum identical with that of the latter, $[\alpha]^{25}_{D}$ −64.9°.

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The Synthesis of Some 14-Iso-11-ketosteroids. Stereochemical Course of Chemical and Catalytic Reduction of a 14β-Δ⁸-11-Ketosteroid[1,2]

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RECEIVED JANUARY 17, 1957

The lithium–ammonia reduction product of Δ⁸-22a,25a,5α,14β-spirosten-3β-ol-11-one (IVa) was shown to be 22a,25a,5α,-14β-spirostan-3β-ol-11-one (VIa) by converting the latter to the known 14β,17α-allopregnan-3β-ol-20-one acetate (XIb). With a reference compound (VI) of known stereochemistry now being available, application of conformational analysis leads to the assignment of the 8α,9α-orientation (V) to the *catalytic hydrogenation* product of IV. The elucidation of the stereochemistry of the *chemical reduction* product (VI) has a bearing on the evaluation of conformational factors involved in the metal–ammonia reduction of unsaturated ketones.

Recently, there has been undertaken in these laboratories a program aimed at the synthesis of steroid hormones with an abnormal configuration at C-8[4] and/or C-14 in order to evaluate the consequences of such a minor stereochemical change upon biological activity. The starting material for all the projected syntheses was Δ⁸-22a,25a,5α-spirosten-3β-ol-11-one (I)[5] since it is readily available[6] from diosgenin and can be transformed into the various C-8 and C-14 isomers.

Treatment of the unsaturated ketone I with base effects isomerization at C-14[6] and the resulting 14β-Δ⁸-11-ketone (IV) yields two different saturated 14-iso(β)-11-ketones depending upon whether chemical or catalytic reduction methods are employed. It already has been pointed out[6] that in the absence of a reference compound (as is the case with II in the 14α-series), a stereochemical assignment in the 14β-series is difficult since of the four possible isomers (V–VIII), all but one (VIII) can exist in an all-chair conformation.[7] Since precise information about the stereochemistry of these reduction products was necessary in order that the subsequent transformation to steroid hormone isomers be of stereochemical value, correlation of one of the reduction products of IV with a steroid of known configuration was attempted. The results of this work and its bearing upon certain aspects of carbanion reduction processes[8] form the subject of this paper.

The lithium–ammonia reduction product of Δ⁸-22a,25a,5α,14β-spirosten-3β-ol-11-one (IVa), now shown to be 22a,25a,5α,14β-spirostan-3β-ol-11-one (VIa), was transformed by a modified Wolff–Kishner reduction[9] and subsequent acetylation to 22a,-25a,5α,14β-spirostan-3β-ol acetate (IXb).[10] Con-

(1) We are indebted to the American Cancer Society through the Committee on Growth of the National Research Council for a research grant.

(2) A portion of this material has been described in a preliminary communication (C. Djerassi and G. H. Thomas, *Chemistry & Industry*, 1228 (1954).

(3) Postdoctorate research fellow, 1953–1955.

(4) *Cf.* C. Djerassi, A. J. Manson and A. Segaloff, *J. Org. Chem.*, **21**, 490 (1956); C. Djerassi, H. Bendas and A. Segaloff, *ibid.*, **21**, 1056 (1956); C. Djerassi, A. J. Manson and H. Bendas, *Tetrahedron*, **1**, 22 (1957).

(5) For nomenclature see C. Djerassi, T. T. Grossnickle and L. B. High, THIS JOURNAL, **78**, 3166, ref. 10 (1956).

(6) C. Djerassi, W. Frick, G. Rosenkranz and F. Sondheimer, *ibid.*, **76**, 3496 (1953).

(7) See Table I in ref. 6.

(8) *Cf.* D. H. R. Barton and C. H. Robinson, *J. Chem. Soc.*, 3045 (1954), and references cited.

(9) D. H. R. Barton, A. A. J. Ives and B. R. Thomas, *ibid.*, 2056 (1955). We are indebted to Prof. Barton for providing us with the experimental details prior to publication.

(10) The argument might be raised that even though the saturated 11-ketone was found to be stable to base, it could still have been represented by the 8β,9β-11-ketone VII and that IX (8β,9α) is produced in the Wolff–Kishner reduction by a "kinetic inversion" *via* the 8β,9α-ketone VI similar to the observed (ref. 5) reduction of the alkali-stable 14-iso(β)-digitogenone to gitogenin (14α). Such a kinetic inversion would require a considerable difference in the reactivity of the carbonyl groups in VI and VII which cannot be determined experimentally since only one isomer is known. However, two arguments can be offered against such an assumption: (a) the good yield in the Wolff–Kishner reduction (VI → IX) in contrast to the poor one observed in the digitogenin series (ref. 5); (b) conformational analysis which would suggest that VI should be more stable than VII in spite of the fact that both can exist in all-chair conformations. Not only is the 9–11 bond axial in VII, but there exists also a 1,3-diaxial interaction between the 7–8 and 13–17 bonds which is not found in VI. In any event, none of the other stereochemical assignments made in this paper are affected by this question since the 8β-orientation has been proved rigorously by conversion to XI.

It should be noted that in the 14α-series the 8β,9β-isomer can be isomerized with base to the natural 8β,9α-derivative (P. Bladon, H. B. Henbest, E. R. H. Jones, B. J. Lovell, G. W. Wood, J. Elks, R. M. Evans, E. E. Hathway, J. F. Oughton and G. H. Thomas, *J. Chem. Soc.*, 2921 (1953)), but on the other hand the conformational difference between the two isomers is a much more striking one (see Table I in ref. 6 and A. Crawshaw, H. B. Henbest, E. R. H. Jones and A. A. Wagland, *ibid.*, 3420 (1955)) as compared to the 14β-series.