Norsteroids. V. The Application of the Benzilic Acid Rearrangement to the Synthesis of A-Norpregnanes[1,2]

HAROLD R. NACE AND DAVID H. NELANDER[3]

Metcalf Chemical Laboratories, Brown University, Providence 12, Rhode Island

Received December 2, 1963

5α-Pregn-1-en-2-ol-3,20-dione (a diosphenol) was prepared by (a) conversion of 2α-bromo-5α-pregnane-3,20-dione to the pyridinium salt, treatment of this with *p*-nitroso-N,N-diethylaniline, and hydrolysis of the resulting nitrone; (b) hydrolysis of the bromo ketone to the ketol, followed by oxidation with cupric acetate or bismuth trioxide; and (c) oxygenation of 20,20-ethylenedioxy-5α-pregnan-3-one, followed by hydrolysis of the ketal group. The diosphenol underwent the benzilic acid rearrangement to give a single product, A-nor-5α-pregnan-2-ol-20-one-2-carboxylic acid, in high yield. This compound was converted to other A-norpregnane derivatives.

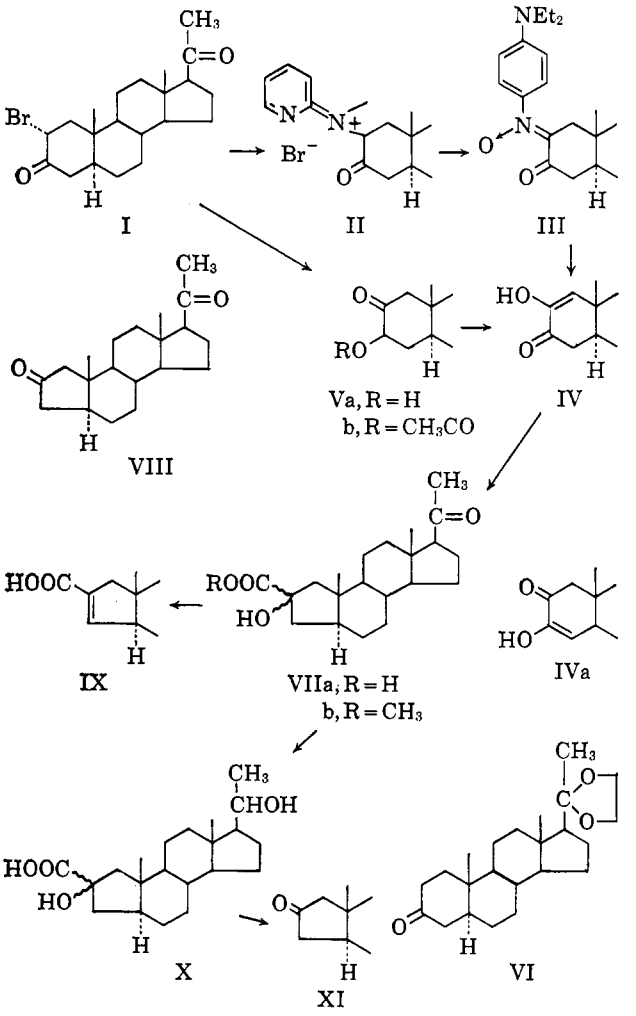
In a previous paper[1] the synthesis of A-norcholestane derivatives by the benzilic acid rearrangement of cholestane-2,3-diosphenols was reported. The yields were practically quantitative and the rearrangement was stereospecific. This method has now been applied to the preparation of A-norpregnane derivatives, interesting compounds because one has recently been shown to possess biological activity.[4]

Since no A-ring 2,3-diketones in the pregnane series could be found in the literature, it was first necessary to find a practical route to such compounds. The classical route to α-diketones (diosphenols) involves the selenium dioxide oxidation of a methylene group adjacent to a carbonyl group. However, in view of the low yields obtained with this method in the cholestane series[5] and the presence of the C-20 carbonyl group, this procedure was not investigated.[6] Because of the ready availability of 2α-bromo-5α-pregnane-3,20-dione (I), several routes using this compound were investigated. The first (and most successful) involved the application to the above bromo ketone of the method developed by Ruzicka, Plattner, and Furrer[7] for the preparation of the diosphenols of cholestane-2,3-dione (see Scheme I). The bromo ketone was treated with pyridine to give 5α-pregnane-3,20-dione-2-pyridinium bromide[8] (II) in 85% yield. The salt was then treated with *p*-nitroso-N,N-diethylaniline to give 5α-pregnane-3,20-dione-2-(*p*-N,N-diethylaminophenyl)nitrone (III) in 78% yield. When the nitrone was hydrolyzed with dilute hydrochloric acid a 93% yield of 5α-pregn-1-en-2-ol-3,20-dione (IV) was obtained. The over-all yield of diosphenol, based on bromo ketone, by this route was 62%, and the method can be used on a relatively large scale.

An alternate path to the diosphenol involves the oxidation of an A-ring ketol. Wendler, Taub, and Graber reported[9] that α-bromo ketones could be hydrolyzed conveniently with aqueous potassium hydroxide to ketols. Using their procedure, the bromo ketone was hydrolyzed to a ketol in 41% yield. An acid fraction, presumably a Favorskiĭ rearrangement product, and an unsaturated ketone were obtained also, but were not investigated further. The crude ketol was purified by chromatography, and its structure tentatively was assigned as 3β-hydroxy-5α-pregnane-2,20-dione (Va) on the following basis. Gallagher and Hollander[10] showed that mild alkaline hydrolysis

SCHEME I

SYNTHESIS OF A-NORPREGNANES



(1) The previous paper in this series: H. R. Nace and M. Inaba, *J. Org. Chem.*, **27**, 4024 (1962).

(2) The major portion of this research was sponsored by the U. S. Public Health Service, National Institutes of Health, Grant AM 05249-02. A preliminary report has been published: H. R. Nace, M. Inaba, and D. H. Nelander, *Trans. N. Y. Acad. Sci.*, **25**, 23 (1962).

(3) Abstracted from the Ph.D. thesis of D. H. Nelander, Brown University, 1963; Jesse Metcalf Fellow, 1960–1961.

(4) (a) F. L. Weisenborn and H. E. Applegate, *J. Am. Chem. Soc.*, **81**, 1960 (1959); L. J. Lerner, A. Bianchi, and A. Borman, *Proc. Soc. Exptl. Biol. Med.*, **103**, 172 (1960). (b) After completion of this work, a report appeared describing the benzilic acid rearrangement of a 3,4-diketopregnane [B. Camerino and U. Valeavi, *Gazz. chim. ital.*, **93**, 735 (1963)].

(5) E. T. Stiller and O. Rosenheim, *J. Chem. Soc.*, 353 (1938).

(6) One attempt was made to oxidize 20,20-ethylenedioxy-5α-pregnan-3-one in 90% ethanol. Only 5α-pregnane-3,20-dione was recovered.

(7) L. Ruzicka, P. A. Plattner, and M. Furrer, *Helv. Chim. Acta*, **27**, 524 (1944).

(8) A. Butenandt, L. Mamoli, H. Dannenberg, L.-W. Mash, and J. Paland, *Ber.*, **72**, 1617 (1939).

(9) N. L. Wendler, D. Taub, and R. P. Graber, *Tetrahedron*, **7**, 173 (1959).

(10) T. F. Gallagher and V. P. Hollander, *J. Biol. Chem.*, **162**, 533 (1946); T. F. Gallagher, *ibid.*, **162**, 539 (1946).

of isomeric α-bromo ketones proceeded with inversion, but that the ketols could then isomerize in the basic medium through the enediol to give a mixture in which the most stable isomer predominated. Since ketols in which the hydroxyl group is equatorial are the most stable, the one in question here must be either 3β-hydroxy-5α-pregnane-2,20-dione (Va) or 2α-hydroxy-5α-pregnane-3,20-dione. This is supported by the infrared spectrum which had a single O–H stretching band at 2.81 μ. An axial hydroxyl group adjacent to a carbonyl group shows two bands at 2.78 and 2.85–2.9 μ.[11]

The choice between the two equatorial isomers was made on the basis of the molecular rotations of the ketol acetate and the parent ketone. Williamson and Johnson[12] showed that acetylation of ketols with acetic anhydride and pyridine proceeds with retention of configuration and no isomerization. As shown in Table I, the 2β-acetoxy and the 3β-acetoxy cholestanone derivatives have large positive molecular rotation differences.

TABLE I

MOLECULAR ROTATIONS OF CHOLESTANE-2,3-KETOL ACETATES

	Ref. 12		ΔMD
	[α]D	MD	(ketol acetate–ketone)
Cholestan-3-one	+41°	+159	
2α-Acetoxy-3-one	+52°	+231	+72
2β-Acetoxy-3-one	+87°	+387	+228
3β-Acetoxy-2-one	+76°	+338	+179
3α-Acetoxy-2-one	+54°	+240	+81

The ketol acetate Vb in question here had [α]D +157°, MD +588, ΔMD +205 (ketol acetate Vb − 5α-pregnane-3,20-dione); thus it is assigned the structure of 3β-hydroxy-5α-pregnane-2,20-dione (Va). The crude ketol was probably a mixture of isomers with ketol Va predominating. Since the hydrolysis was carried out under basic conditions, the formation of some 17-iso compound was expected. However, the acetate prepared from the pure ketol showed only a single peak on v.p.c. analysis, and no attempt was made to isolate isomers from the mother liquors of the pure ketol.

The ketol then was oxidized to the diosphenol by two methods. The first employed cupric acetate in methanol[13] and gave a 25% yield of what appeared to be a mixture of diosphenols, which yielded diosphenol IV on recrystallization. The second method was based on Rigby's[14] qualitative test for ketols which involves the oxidation of them with bismuth trioxide, precipitating bismuth metal. The ketol was oxidized in this manner in acetic acid and the diosphenol was obtained in 40% yield.

Recently a direct method for the conversion of ketones to diosphenols by air or oxygen oxidation in the presence of potassium *t*-butoxide was reported by Bailey, Barton, Elks, and Templeton.[15] They found, however, that in the case of 5α-pregnane-3,20-dione attack also took place at the 17-position to give a mixture of products. This was confirmed in the present work, a gummy intractable mixture being obtained. However, when the 20-carbonyl group was protected by conversion to the ethylene ketal VI the oxidation was successful, and the diosphenol was obtained in 33% yield after hydrolysis of the protective group. This method was only tried on a small scale and with further study it is possible that the yields could be improved.

The diosphenol obtained from the above reactions is assigned the structure of 5α-pregn-1-en-2-ol-3,20-dione (IV) on the basis of its n.m.r. spectrum, which showed a singlet peak at −382 c.p.s. (tetramethylsilane[16b]) owing to a vinyl proton. The vinyl proton at C-1 in this compound has no adjacent protons available for spin–spin coupling and thus should show no splitting. The n.m.r. spectrum of 5α-cholest-3-en-3-ol-2-one[16] had a doublet at −344 c.p.s., J = 12 c.p.s., showing that the C-4 vinyl proton is split by the C-5 proton. When the diosphenol IV was treated under the conditions used by Stiller and Rosenheim[5] to obtain the isomeric diosphenol in the cholestane series, a mixture of the two diosphenols, still rich in IV (*ca.* 75%), was obtained. The n.m.r. spectrum of the mixture still showed a singlet peak at −382 c.p.s. for the C-1 vinyl proton and a doublet peak at −348.5 c.p.s., J = 9 c.p.s., for the vinyl proton at C-4. The two diosphenols could not be separated by t.l.c. and they could not be eluted from a v.p.c. column.

The diosphenol IV was rearranged by treatment with potassium hydroxide in propanol or ethanol to give A-nor-5α-pregnan-2-ol-20-one-2-carboxylic acid (VIIa) in 90% yield. Column chromatography and t.l.c. indicated the presence of only one of the two possible isomers from the rearrangement, showing that the benzilic acid rearrangement again was stereospecific.[1] The hydroxy acid was converted to its methyl ester VIIb, and v.p.c., t.l.c., and column chromatography of this also indicated only a single isomer. In one rearrangement experiment, however, isomers were observed. The hydroxy acid isolated had a lower melting point and a lower optical rotation than the pure acid. Recrystallization of the mixture from acetone–dilute hydrochloric acid converted it to the single hydroxy acid VIIa. The mixture of hydroxy acids was esterified with methanol and v.p.c. analysis of the mixed esters indicated a 3:1 mixture of isomers, one of which had a retention time identical with that of the pure methyl ester VIIb. Presumably the isomerization involves the formation of some 17-iso compound, which is converted back to the 17β compound on treatment with acid (see below for further examples of this behavior). In all but the one experiment this isomerization of the hydroxy acid by the basic reaction medium must have been reversed during the isolation under acidic conditions.

The position of the hydroxyl group and the carboxyl group was established by treating the hydroxy acid with lead tetraacetate in acetic acid, which gave the

(11) N. L. Wendler, D. Taub, S. Dobriner, and D. K. Fukushima, *J. Am. Chem. Soc.*, **78**, 5027 (1956).

(12) K. L. Williamson and W. S. Johnson, *J. Org. Chem.*, **26**, 4563 (1961).

(13) J. C. Sheehan and W. F. Erman, *J. Am. Chem. Soc.*, **79**, 6050 (1957); M. N. Huffman, *J. Biol. Chem.*, **167**, 273 (1947); B. G. Christensen, N. G. Steinberg, and R. Hirshmann, *Chem. Ind.* (London), 1259 (1958).

(14) W. Rigby, *J. Chem. Soc.*, 793 (1951).

(15) E. J. Bailey, D. H. R. Barton, J. Elks, and J. F. Templeton, *ibid.*, 1578 (1962); see also B. Camerino, B. Patelli, and R. Sciaky, *Tetrahedron Letters*, **16**, 554 (1961), and D. H. R. Barton, S. K. Pradhan, S. Sternhell, and J. F. Templeton, *J. Chem. Soc.*, 255 (1961).

(16) (a) We are indebted to Dr. Robert Iacona of this laboratory for this sample. (b) Tetramethylsilane (TMS) was used as an internal reference.

known A-nor-5α-pregnane-2,20-dione[17-19] (VIII) in 90% yield. This material gave only a single peak on v.p.c., but, when a sample was chromatographed on alumina, the benzene eluates showed two peaks on v.p.c. One fraction was shown to contain 35% of an isomer in this manner, and when this fraction was treated with methanolic hydrogen chloride the amount of isomer was reduced to 25%. However, recrystallization of this material from acetone–dilute hydrochloric acid gave complete reconversion to the 17β-A-nor-2,20-dione. This behavior demonstrates that alumina is basic enough to cause isomerization at C-17 and that acetone–dilute hydrochloric acid is superior to methanolic hydrogen chloride for the conversion of 17-isopregnanes to the 17β compounds. Rull and Ourisson[18] prepared the A-nor-2,20-dione by Marker's procedure,[17] which involves only acidic conditions, and obtained a mixture of the 17α and 17β isomers, which must have been formed during purification of the product by alumina chromatography.

The configuration of the substituents at C-2 in the hydroxy acid VIIa is tentatively assigned as 2β-hydroxy-2α-carboxy on the basis of reasoning described previously,[1] but no direct evidence is available to support this assignment.

The hydroxy acid VIIa and its methyl ester proved to be very resistant to dehydration, in agreement with the behavior of the analogous compounds in the cholestane series.[1] The acid was dehydrated by heating at 300° and 0.05 mm. to give A-nor-5α-pregn-2-en-20-one (IX) in 69% yield. The position of the double bond is assigned on the basis of the n.m.r. spectrum, which showed a doublet peak at −432.5 c.p.s., $J = 7$ c.p.s., due to the splitting of the C-3 vinyl proton by the C-5 proton. This splitting is consistent with the calculations made by Dauben, Boswell, and Templeton[20] for the behavior of a 5α-A-nor-2-ene system, and opposite to the result obtained in the cholestane series.[1] There the structure of the olefin obtained by pyrolysis of the hydroxy acid was assigned as the 1-ene on the basis of a single vinyl proton peak at −428 c.p.s. When the n.m.r. spectrum of the same sample was determined with a newer instrument capable of better resolution, it showed a doublet peak at −431 c.p.s., $J = 6$ c.p,s., and accordingly, the unsaturated acid in the cholestane series is also the 2-ene-2-carboxylic acid.

The A-nor-5α-pregnan-2-ol-20-one-2-carboxylic acid was reduced with sodium borohydride to A-nor-5α-pregnane-2,20-β-diol-2-carboxylic acid (X) in 26% yield. The 20β-configuration is assigned on the basis of an analogous reduction of 2,3-seco-5α-pregnan-20-one-2,3-dioic acid by Weisenborn[21] which was shown to give the 20β isomer. The A-nor diol acid X was then cleaved with lead tetraacetate to give A-nor-5α-pregnan-20β-ol-2-one (XI) in 94% yield. This was readily oxidized with Jones' chrominum trioxide reagent[22] to give the known A-nor-5α-pregnane-2,20-dione (VIII) in 80% yield.

Experimental[23]

5α-Pregnane-3,20-dione.—A solution of 1.00 g. (3.16 mmoles) of 5α-pregnane-3β-ol-20-one in 150 ml. of acetone was cooled to 15°, 0.92 ml. of Jones' chromium trioxide reagent[22] was added, and the solution was stirred for 5 min. Then 1 l. of cold water was added; the precipitate was collected, air-dried, and recrystallized from acetone to give 0.94 g. (95%) of 5α-pregnane-3,20-dione, m.p. 198–201°, $[\alpha]^{24}D$ +119° (*c* 1.08, $CHCl_3$), $\lambda_{max}^{CHCl_3}$ 5.85 μ, R_f 1.00 (3:1 benzene–ether or 30:10:1 benzene–ether–acetic acid), T_r 1.16 (225°); lit.[19] m.p. 200–201°, $[\alpha]D$ +121° (*c* 1, $CHCl_3$), $\lambda_{max}^{CCl_4}$ 5.84 μ.

2α-Bromo-5α-pregnane-3,20-dione (I).—This compound was prepared as described previously[24] and had m.p. 200–200.5°, $[\alpha]^{24}D$ +116° (*c* 1, $CHCl_3$), λ_{max}^{KBr} 5.76 and 5.85 μ, R_f 1.29 (3:1 benzene–ether); lit. m.p. 199–202°, $\lambda_{max}^{CCl_4}$ 5.77 and 5.86 μ,[19] $[\alpha]^{24}D$ +104°.[24]

5α-Pregnane-3,20-dione-2-pyridinium Bromide (II).—A solution of 6.3 g. (15.9 mmoles) of 2α-bromo-5α-pregnane-3,20-dione in 40 ml. of dry pyridine was boiled under reflux until a pale yellow precipitate formed. Boiling was continued for 4 hr. and then the solvent was distilled under reduced pressure until a slurry remained. It was cooled to 10°; the precipitate was collected and washed with petroleum ether (b.p. 30–60°) to give 6.4 g. (85%) of the pyridinium bromide II, m.p. 275–276°. T.l.c. (3:1 benzene–ether) indicated that only the immobile salt was present. An analytical sample was prepared by recrystallization from ethanol and had m.p. 276–277°, $[\alpha]^{24}D$ +41° (*c* 1.07, $CHCl_3$), λ_{max}^{KBr} 5.85 and 6.12 μ, lit.[8] m.p. 285°.

Anal. Calcd. for $C_{26}H_{36}BrNO_2$: C, 65.81; H, 7.65. Found: C, 65.25; H, 7.32.

5α-Pregnane-3,20-dione-2-(*p*-N,N-diethylaminophenyl)nitrone (III).—A solution of 5.00 g. (10.2 mmoles) of the pyridinium bromide II in 113 ml. of 1:1 (v./v.) chloroform–ethanol was cooled to 0° and a slurry of 1.87 g. (10.5 mmoles) of *p*-nitroso-N,N-diethylaniline and 11 ml. of 1 *N* sodium hydroxide was added. The mixture was stirred for 4 hr. at room temperature, the organic solvents were evaporated under reduced pressure, and the solid was collected. It was recrystallized from acetone to give 3.34 g. (63%) of the nitrone III, m.p. 183–185°. A second crop of 0.78 g. (15%) had m.p. 177–179°. Further recrystallization from acetone gave an analytical sample, m.p. 184.5–185°; λ_{max}^{KBr} 5.86, 5.96, and 6.24 μ; R_f 0.48 (3:1 benzene–ether) and 0.37 (30:10:1 benzene–ether–acetic acid).

Anal. Calcd. for $C_{31}H_{44}N_2O_3$: C, 75.57; H, 9.00. Found: C, 75.11; H, 8.67.

5α-Pregn-1-en-2-ol-3,20-dione (IV).—To a solution of 7.65 g. (15.6 mmoles) of the nitrone III in 300 ml. of benzene was added 500 ml. of 2 *N* hydrochloric acid, whereupon the deep-red benzene solution immediately turned green. The resulting mixture was stirred for 12 hr. and then the layers were separated. The aqueous layer was extracted with three 300-ml. portions of benzene; the combined benzene layers were washed with 2 *N* hydrochloric acid and with water, and then dried over sodium sulfate; the benzene was evaporated under reduced pressure to give 4.8 g. (93%) of the diosphenol IV. A sample gave a red-brown color with aqueous ferric chloride. Recrystallization from glacial acetic acid gave 4.6 g. (90%), m.p. 225–227°. The analytical sample had m.p. 227–228°; $[\alpha]^{26}D$ +134° (*c* 0.98, $CHCl_3$); λ_{max}^{KBr} 2.90, 5.88, and 6.00 μ; λ_{max}^{EtOH} 270 mμ (ε 7800); R_f 0.34 (3:1 benzene–ether) and 0.98 (30:10:1 benzene–ether–acetic acid).

(17) R. E. Marker, O. Kamm, and D. M. Jones, *J. Am. Chem. Soc.*, **59**, 1595 (1937).

(18) T. Rull and G. Ourisson, *Bull. soc. chim. France*, 1573 (1958).

(19) N. Pappas and H. R. Nace, *J. Am. Chem. Soc.*, **81**, 4556 (1959).

(20) W. G. Dauben, G. A. Boswell, and W. H. Templeton, *ibid.*, **83**, 5006 (1961).

(21) F. L. Weisenborn, U. S. Patent 3,040,091 (1962); *Chem. Abstr.*, **57**, 13,838 (1962).

(22) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(23) Melting points were determined with a Hershberg apparatus and Anschutz thermometers and are corrected. Microanalyses were by Dr. S. M. Nagy and associates, Microchemical Laboratory, Massachusetts Institute of Technology. Analytical samples were recrystallized to constant melting point. Column chromatographic separations were made using silica gel (J. T. Baker and Co., chromatographic grade) or alumina (Merck and Co., Inc., chromatographic grade). For thin layer chromatography (t.l.c.) R_f values are reported relative to the R_f value for 5α-pregnane-3,20-dione, and were determined on glass plates with a 500-μ coating of silica gel. The plates were developed by spraying with a solution of 2,4-dinitrophenylhydrazine and phosphoric acid in 95% ethanol. For vapor phase chromatography (v.p.c.), T_r values refer to relative retention times using a 4-ft. column containing a 1% QF-1 coating on Gas-Chrom Z support. A-Nor-5α-pregnane-2,20-dione was used as the standard.

(24) M. Rubin, H. Wishinsky, and F. Bompard, *J. Am. Chem. Soc.*, **73**, 2338 (1951).

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 75.83; H, 8.94.

The n.m.r. spectrum of the analytical sample showed a single vinyl proton peak at −382 c.p.s. (TMS). Under the conditions used by Stiller and Rosenheim[5] to obtain the base-stable 2,3-diosphenol in the cholestane series, a mixture still rich in the acid-stable form IV (*ca.* 75%) was obtained, m.p. 220–223°. The n.m.r. spectrum of the mixture showed a split vinyl proton at −348.5 c.p.s. (TMS), J = 9 c.p.s., and a hydroxyl proton at −435 c.p.s. for the base-stable form. The single vinyl proton peak for the acid-stable form at −382 c.p.s. was still present, but less intense.

For comparison, the n.m.r. spectrum of 5α-cholest-3-en-3-ol-2-one (diosphenol A)[1,5,16] was determined and it showed a doublet peak at −344 c.p.s., J = 12 c.p.s., assigned to the vinyl proton, and a singlet peak at −435 c.p.s. for the hydroxyl proton.

3β-Hydroxy-5α-pregnane-2,20-dione (Va).—A solution of 4.00 g. (10.1 mmoles) of 2α-bromo-5α-pregnane-3,20-dione (I) in 200 ml. of tetrahydrofuran was added to 4.0 g. of potassium hydroxide in 200 ml. of water and the mixture was boiled under reflux for 30 min. The tetrahydrofuran was distilled under reduced pressure, the residual slurry was cooled, and the white solid was collected and air-dried. (An oily acidic fraction was recovered from the aqueous filtrate by acidification, but was not investigated.)

The white solid was chromatographed on silica gel and the various fractions were examined by t.l.c., using 3:1 benzene–ether. The benzene eluates gave spots of R_f 0.28 and 0.49 (yellow), 0.91 and 1.29 (brown), and 1.48 and 1.70 (pink, unsaturated ketone). The benzene–ether (9:1) eluates gave spots of R_f 0.31 and 0.46 (yellow), and the residues from these eluates were combined to give 1.37 g. (41%) of the ketol Va. (When the reflux time for the hydrolysis was extended to 2 hr., the yield of the ketol was 35%.) Recrystallization from benzene gave material of m.p. 181–185°, $[\alpha]^{24}D$ +120° (*c* 0.99, $CHCl_3$), λ_{max}^{KBr} 2.81 and 5.87 μ, R_f 0.48 (3:1 benzene–ether) and 0.65 (30:10:1 benzene–ether–acetic acid). An analytical sample was obtained by recrystallization from ether–cyclohexane and had m.p. 181–182°, $[\alpha]^{24}D$ +130° (*c* 0.89, $CHCl_3$), λ_{max}^{KBr} 2.81 and 5.87 μ.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 76.01; H, 9.95.

The 3-acetate derivative Vb was prepared by allowing a solution of 100 mg. (0.31 mmole) of pure ketol in 2 ml. of pyridine and 2 ml. of acetic anhydride to stand at room temperature for 2 days. Then 50 ml. of water and 100 ml. of ether were added; the ether layer was removed, washed twice with water, and dried; the ether was evaporated to give 70 mg. (60%) of acetate. T.l.c. showed the absence of any ketol. The product was recrystallized from ether–cyclohexane and then had m.p. 181–182°; $[\alpha]^{24}D$ +157° (*c* 0.77, $CHCl_3$); λ_{max}^{KBr} 5.72, 5.81, 5.89, and 8.10 μ; R_f 0.90 (3:1 benzene–ether); T_r 3.90 (225°).

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.58; H, 9.15.

Oxidation of 3β-Hydroxy-5α-pregnane-2,20-dione (Va). A. By Cupric Acetate.—A mixture of 300 mg. (0.905 mmole) of the ketol Va, 450 mg. of cupric acetate, and 24 ml. of methanol was boiled under reflux for 1 hr. Then 3 ml. of water was added, the solution was boiled for 15 min., and then it was cooled and acidified with dilute hydrochloric acid. The resulting mixture was extracted with ether; the ether extract was washed with water, and cooled to 0°; 50 ml. of 20% aqueous potassium hydroxide was added. The insoluble potassium salt of the diosphenol was collected and then shaken with ether and 2 *N* hydrochloric acid. The ether layer was washed with 5% sodium bicarbonate solution and with water, and then dried; the ether was evaporated to give 75 mg. (25%) of diosphenol IV, m.p. 209–216°. Recrystallization from methanol gave material, m.p. 223–225°, m.m.p. (with authentic material) 221–224°. A sample gave a red-brown color with aqueous ferric chloride solution.

B. Bismuth Trioxide.—To a boiling solution of 100 mg. (0.30 mmole) of the ketol Va in 10 ml. of acetic acid was added 56 mg. of bismuth trioxide. The resulting mixture was boiled under reflux for 2 hr., then cooled, diluted with 50 ml. of water, and extracted with three 100-ml. portions of benzene. The benzene extract was dried over anhydrous sodium sulfate, the benzene was evaporated, and the 110 mg. of crude diosphenol was taken up in ether, converted to the potassium salt, and back to the diosphenol as in A above. Recrystallization from acetic acid and water gave 40 mg. (40%), m.p. 225–226°, m.m.p. (with authentic diosphenol) 225–227°.

20,20-Ethylenedioxy-5α-pregnan-3β-ol.—A solution of 10.0 g. (31.4 mmoles) of 5α-pregnan-3β-ol-20-one, 0.67 g. of *p*-toluenesulfonic acid, and 125 ml. of ethylene glycol in 400 ml. of dry benzene was boiled under reflux with a Dean–Stark water separator. After 40 hr., as no additional amount of water could be detected in the water separator, the solution was cooled, made alkaline with alcoholic potassium hydroxide, washed with water until the washings were neutral, and dried over sodium sulfate. The solvent was removed and the residue was recrystallized from 1:1 acetone–methanol to give 10.24 g. (90%) of the ketal, m.p. 170–171°, $[\alpha]^{26}D$ +16° (*c* 1.32, $CHCl_3$), $\lambda_{max}^{CHCl_3}$ 2.85 μ, R_f 0.50 (3:1 benzene–ether), T_r 0.33 (225°) and 0.28 (210°).

Anal. Calcd. for $C_{23}H_{38}O_3$: C, 76.20; H, 10.56. Found: C, 75.90, H, 10.57.

20,20-Ethylenedioxy-5α-pregnan-3-one (VI).—A slurry of 8.1 g. of chromium trioxide and 80 ml. of dry pyridine was added to a solution of 10.0 g. (27.6 mmoles) of the ketal in 100 ml. of dry pyridine, and the resulting mixture was stirred for 10 hr. Then 180 ml. of water was added, the mixture was filtered, and the precipitate was washed thoroughly with ether. The filtrate and washings were combined; the organic layer was removed, washed with water, dried over sodium sulfate, and evaporated. The residue was recrystallized from methanol to give 6.65 g. of the keto ketal VI, m.p. 187–188°, $[\alpha]^{26}D$ +35° (*c* 1.15 $CHCl_3$), $\lambda_{max}^{CHCl_3}$ 5.87 μ. A second crop of 0.52 g. had m.p. 185–188° (72% total yield).

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.74; H, 10.00.

A 100-mg. sample of the oxo ketol was dissolved in 2.5 ml. of tetrahydrofuran and 1.5 ml. of 3 *N* perchloric acid, and the solution was allowed to stand at room temperature for 8 hr. Then it was diluted with 8 ml. of water and the resulting precipitate was collected. It was recrystallized from acetone and had m.p. 199–201°; lit.[25] m.p. 200.5° for 5α-pregnane-3,20-dione.

Oxygenation of 20,20-Ethylenedioxy-5α-pregnan-3-one (VI).—To a solution of sodium *t*-butoxide in *t*-butyl alcohol (prepared by adding 100 mg. of sodium to 20 ml. of *t*-butyl alcohol) was added a solution of 100 mg. (0.28 mmole) of the keto ketal VI in 10 ml. of *t*-butyl alcohol and the resulting solution was stirred under an atmosphere of oxygen. After 2 hr. the reaction was stopped after an oxygen uptake of 87% of the theoretical value. The mixture was acidified with 4 *N* hydrochloric acid, allowed to stand overnight, and then extracted successively with 200-, 100-, and 50-ml. portions of ether. The ether extract was washed with water, dried over anhydrous sodium sulfate, and evaporated, to give 80 mg. of crude material. This was dissolved in ether and the potassium salt was precipitated by the addition of 50% potassium hydroxide solution. The salt was collected and acidified to give 30 mg. (33%) of the diosphenol, which was recrystallized from an acetic acid–water mixture and then had m.p. 224–226°; λ_{max}^{KBr} 2.90, 5.87, and 5.98 μ; R_f 0.34 (3:1 benzene–ether) and 0.98 (30:10:1 benzene–ether–acetic acid).

A-Nor-5α-pregnan-2-ol-20-one-2-carboxylic Acid (VIIa).—A solution containing 500 mg. (1.51 mmoles) of the diosphenol IV and 4.7 g. of potassium hydroxide in 130 ml. of 1-propanol and 10 ml. of water was boiled under reflux for 14 hr. The solution then was concentrated under reduced pressure to 50 ml., acidified, and extracted with three 100-ml. portions of ether. The ether extract then was washed with water and extracted with three 100-ml. portions of half-saturated sodium bicarbonate solution. The bicarbonate extract was acidified and extracted with three 100-ml. portions of ether. This ether extract was washed with water, dried over sodium sulfate, and evaporated to give 559 mg. of crude acid. Recrystallization from an ether–petroleum ether (b.p. 30–60°) mixture gave 475 mg. (90%) of the A-noracid VIIa, m.p. 240–241°; $[\alpha]^{26}D$ +98° (*c* 1.02, $CHCl_3$); λ_{max}^{KBr} 2.98 (broad), 5.79, and 5.88 μ; R_f 0.10 (3:1 benzene–ether) and 0.49 (30:10:1 benzene–ether–acetic acid). The analytical sample was prepared by recrystallization from an acetone–dilute hydrochloric acid mixture, and had m.p. 239–240°, $[\alpha]^{25}D$ +96° (*c* 0.99, $CHCl_3$).

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.37; H, 9.26. Found: C, 72.12; H, 9.06.

When ethanol was used instead of 1-propanol, essentially the same yields were obtained, but there was less trouble with emulsions during the ether extractions.

Rearrangement of a mixture of the two diosphenols gave the same hydroxy acid VIIa.

(25) A. Butenandt and G. Fleischer, *Ber.*, **68**, 2094 (1935).

From one experiment, hydroxy acid was obtained which had m.p. 236–238°, $[\alpha]^{26}D$ +53° (*c* 1.04, $CHCl_3$). Recrystallization of a sample from a mixture of acetone and dilute hydrochloric acid gave a quantitative recovery of the hydroxy acid with m.p. 240–241°, $[\alpha]^{24}D$ +99° (*c* 0.84, $CHCl_3$).

A sample of the acid (m.p. 236–238°) was esterified with 5% methanolic hydrogen chloride (see below) to give an oil, $[\alpha]^{24}D$ +43° (*c* 1.05, $CHCl_3$), R_f 0.83 (3:1 benzene–ether). The oil was analyzed by v.p.c. and gave two peaks, T_r 0.88 and 1.13 (225°), ratio of the peak areas, 1:3. Assuming the oil to be a 3:1 mixture of the 17β and 17α isomer, the ΔM_D value for 17$\beta \rightarrow$ 17α was determined, using the molecular rotation of the pure ester (M_D +141), and was found to be −283. The agreement with the ΔM_D value of −262 calculated from the molecular rotations of 5α-pregnan-3β-ol-20-one and 17-iso-5α-pregnan-3β-ol-20-one[26] strongly indicates that considerable amounts of the 17α isomer were formed under the basic conditions of the rearrangement.

Methyl A-Nor-5α-pregnan-2-ol-20-one-2-carboxylate (VIIb).—A solution of 50 mg. of the hydroxy acid in 25 ml. of 5% methanolic hydrogen chloride was boiled under reflux for 5 hr. The solvent was removed, the oily residue was taken up in ether, and the ether solution was washed successively with water, 5% sodium bicarbonate solution, and water. After drying the solution, the ether was distilled and the oily residue was recrystallized from ether–petroleum ether to give the methyl ester VIIb, m.p. 126–126.5°; $[\alpha]^{24}D$ +62° (*c* 0.34, $CHCl_3$); λ_{max}^{KBr} 2.82, 5.75, and 5.84 μ; R_f 0.82 (3:1 benzene–ether); T_r 1.15 (225°).

Anal. Calcd. for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.95; H, 9.64.

A-Nor-5α-pregnane-2,20-dione (VIII).—A solution of 100 mg. (0.29 mmole) of the hydroxy acid VIIa and 190 mg. of lead tetraacetate in 10 ml. of glacial acetic acid was stirred at room temperature for 2 days and then heated on a steam bath for 1 hr. Then 25 ml. of water was added, the mixture was extracted with five 50-ml. portions of ether, and the ether extract was washed with water until the washings gave no precipitate or yellow color when 10% potassium iodide solution was added. The ether solution then was washed with 5% sodium bicarbonate solution, dried over sodium sulfate, and the ether was distillled. The residue was recrystallized from ethanol–water to give 78 mg. (90%) of the 2,20-dione VIII, m.p. 177–179°, $[\alpha]^{26}D$ +257° (*c* 1.01, $CHCl_3$), λ_{max}^{KBr} 5.74 and 5.87 μ, R_f 1.04 (3:1 benzene–ether), T_r 1.00 (225°); lit. m.p. 180°,[17] 174–178°, $\lambda_{max}^{CCl_4}$ 5.75 and 5.85 μ, $[\alpha]D$ +134° (*c* 1, $CHCl_3$)[19], $[\alpha]D$ +255°.[18]

The bis-2,4-dinitrophenylhydrazone derivative was prepared by dissolving 27 mg. of the 2,20-dione in 10 ml. of ethanol and adding a filtered solution of 66 mg. of 2,4-dinitrophenylhydrazine in 5 ml. of ethanol containing 16 drops of concentrated hydrochloric acid. The resulting slurry was heated on a steam bath for 5 min. and then allowed to stand at room temperature for 3 days. Then the red precipitate was collected, washed thoroughly with ethanol containing concentrated hydrochloric acid, and recrystallized from chloroform–ethanol to give 31 mg. (55%), m.p. 281–282°, lit.[19] m.p. 261–263°.

A 640-mg. sample of pure 2,20-dione VIII was taken up in benzene and chromatographed on a column of 50 g. of alumina. V.p.c. analysis of each of the fifteen benzene eluates showed that a mixture of two components was present, T_r 0.73 and 1.00 (225°). The content of the minor component (T_r 0.73) increased until it reached a maximum of 35% in the tenth fraction. This fraction was evaporated to dryness, the residue was taken up in methanolic hydrogen chloride, boiled for 2 min., and then the methanol was evaporated. V.p.c. analysis of the residue showed, that the content of the minor component had been reduced to 25%. The 75:25 mixture was then recrystallized from acetone–dilute hydrochloric acid and the pure 17β-2,20-dione was recovered in quantitative yield, only one peak, T_r 1.00, on v.p.c.

A-Nor-5α-pregn-2-en-20-one-2-carboxylic Acid (IX).—A 9-mm. Pyrex test tube, containing 170 mg. (0.488 mmole) of the hydroxy acid VIIa, was evacuated to 0.05 mm., bathed with a yellow flame until the white solid darkened slightly, and then sealed. The tube was then kept in a Wood's metal bath at 300° until the bubbling ceased (15 min.). The crude product had R_f 1.08 with faint spots at 1.24 and 1.35 (30:10:1 benzene–ether–acetic acid). It was taken up in benzene and chromatographed on a column of 150 g. of silica gel. Benzene eluted 22 mg. of an oil; λ_{max}^{film} 3.40, 5.78, and 5.86 μ. Benzene–ether (9:1) eluted 111 mg. (69%) of A-nor-5α-pregn-2-en-20-one-2-carboxylic acid (IX), m.p. 258–260°. Recrystallization from ether–petroleum ether gave 101 mg. (63%), m.p. 259–260°; $[\alpha]D$ +118° (*c* 0.95, $CHCl_3$); λ_{max}^{KBr} 2.95, 5.87, and 6.21 μ; λ_{max}^{EtOH} 226 mμ (ϵ 10,100) at 1.1 $\times 10^{-4}$ mole per liter; R_f 1.00 (30:10:1 benzene–ether–acetic acid). A sample decolorized a basic potassium permanganate solution.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.12; H, 9.09.

The n.m.r. spectrum of the unsaturated acid showed a doublet at −432.5 c.p.s. (TMS), J = 7 c.p.s.

A-Nor-5α-pregnane-2,20β-diol-2-carboxylic Acid (X).—To an aqueous suspension of 500 mg. (1.44 mmoles) of the hydroxy acid in 40 ml. of water containing 60 mg. of sodium hydroxide was added a solution of 110 mg. (2.88 mmoles) of sodium borohydride and 30 mg. of sodium hydroxide in 10 ml. of water. The mixture was heated to 50° and the resulting solution was stirred for 24 hr. The mixture then was cooled in an ice bath, acidified with dilute hydrochloric acid, and extracted with four 300-ml. portions of ether. The ether extract was washed with water and dried over sodium sulfate; and the ether was evaporated to give 410 mg., m.p. 211–215°. This material was powdered and boiled in 100 ml. of chloroform for 5 min.; the undissolved solid was removed. This solid was recrystallized twice from acetone to give 130 mg. (26%) of A-nor-5α-pregnane-2,20β-diol-2-carboxylic acid (X), m.p. 251.5–252.5°; $[\alpha]^{25}D$ +20° (*c* 0.23, $CHCl_3$); λ_{max}^{KBr} 2.85, 2.94, and 5.90 μ; R_f 0.29 (30:10:1 benzene–ether–acetic acid).

Anal. Calcd. for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 72.03; H, 9.68.

A-Nor-5α-pregnan-20β-ol-2-one (XI).—A mixture of 27 mg. (0.077 mmole) of A-nor-5α-pregnane-2,20-β-diol-2-carboxylic acid (X), 60 mg. of lead tetraacetate, and 15 ml. of glacial acetic acid was heated on a steam bath until solution occurred, and then the solution was allowed to stand at room temperature for 2 days. Ether (150 ml.) and water (150 ml.) were added, and the ether layer was removed and washed with water until the washings were colorless on treatment with 10% potassium iodide solution.

Then the ether layer was washed twice with 100-ml. portions of 5% sodium bicarbonate solution and once with 100 ml. of water, and dried over sodium sulfate. The ether was removed to give 22 mg. (94%) of A-nor-5α-pregnan-20β-ol-2-one (XI), m.p. 216–218°, R_f 0.48 (3:1 benzene–ether). Recrystallization from ether–petroleum ether gave 20 mg. (85%), m.p. 217–218°; $[\alpha]^{25}D$ +43° (*c* 0.57, $CHCl_3$); λ_{max}^{KBr} 2.81, 5.74, and 9.04 μ; T_r 0.35 (225°).

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.60. Found: C, 78.84; H, 10.74.

A 10-mg. (0.033 mmole) sample in 5 ml. of acetone was treated with 1 ml. of Jones chromium trioxide reagent.[22] The solution was stirred for 5 min.; 50 ml. of water was added; the white solid was collected and recrystallized from ether–petroleum ether to give 8 mg. (80%) of A-nor-2,20-dione VIII, m.p. 177–180°, m.m.p. (with an authentic sample) 177–180°, λ_{max}^{KBr} 5.75 and 5.88 μ, R_f 1.07 (3:1 benzene–ether), T_r 0.99 (225°).

(26) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Co. New York, N. Y., 1959, p. 566.