The Preparation and C-20 Configuration of the 5α,17α-Pregnane-3β,20-diols[1]

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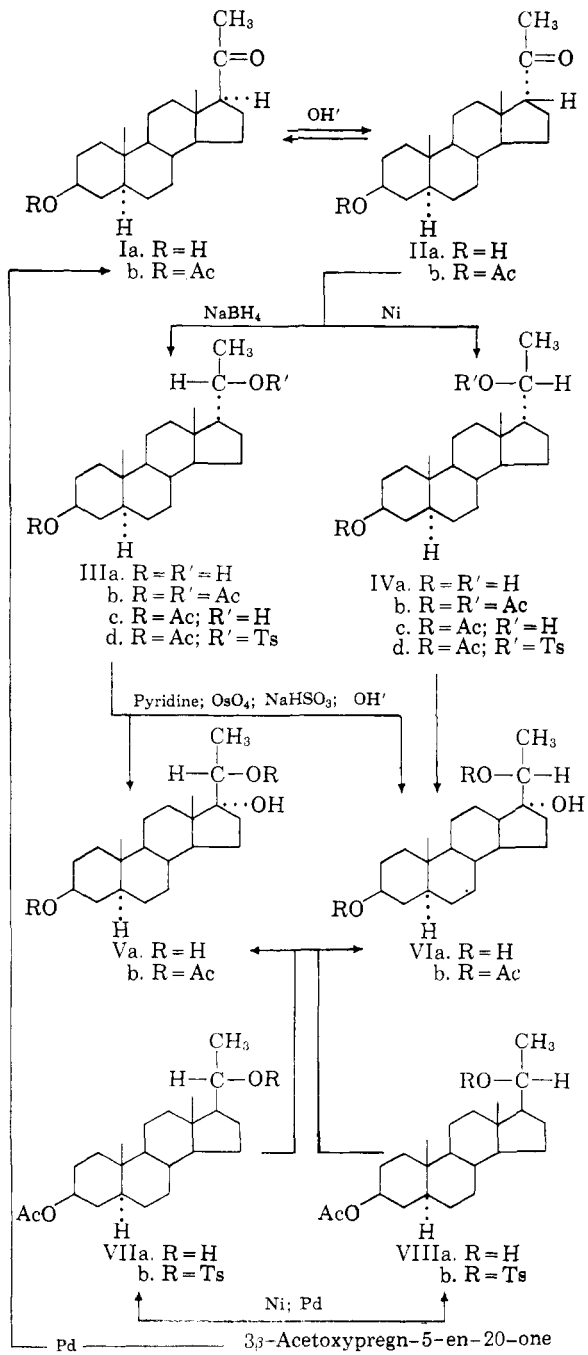
5α,17α-Pregnane-3β,20α-diol and its 20-epimer have been prepared. Configurations are assigned on the basis of the geometry of the Δ^{17}-olefins that result from heating 20-tosylates with pyridine. In both the 17α and 17β series that tosylate which cannot readily assume antiparallel orientations of the departing groups undergoes predominantly *cis* elimination. Evidence has been obtained in the 17β series that this process requires participation of a base.

During the examination of the urine of a patient with adrenal hyperplasia, 3α-hydroxy-5β,17α-pregnan-20-one was isolated under conditions which when tested in control experiments failed to produce it from its 17-epimer.[2] The case for the natural occurrence of 17α-pregnanes would be strengthened materially if 17α-pregnane-3,20-diols could be isolated from natural sources. To facilitate the search for such compounds we have prepared a pair of 20-epimers and investigated their configurations at C-20. The work to be reported was directed towards the synthesis of the two 5α,17α-pregnane-3β,20-diols since starting material and reference compounds were readily available in the 3β-hydroxy-5α series.

3β-Hydroxy-5α-pregnan-20-one (Ia) was epimerized at C-17 as described by Butenandt and Mamoli.[3] The separation of the two 17-epimers, which as has been shown by Shoppee[4] had been accomplished only partially in the earlier work,[3] was facilitated by our finding that the sequence of their elution from alumina columns depends on the characteristics of the adsorbent. With a slightly acidic preparation the 17α-isomer (IIa) emerged first from the column and could be purified with ease. The procedures which were used for the reduction of the C-20 keto group of IIb possessed only moderate stereospecificity. Reduction with sodium borohydride gave more IIIc than IVc, whereas the reverse was found on hydrogenation with nickel. Purification of the reaction products by recrystallization was successful only after chromatography. The molecular rotations of the pure monoacetates, of the free diols (IIIa and IVa) and of the diacetates (IIIb and IVb) are given in Table I and are compared with those observed in the 17β series. In contrast to the latter,[5-7] the shifts in molecular rotations of the new 20-alcohols on acetylation are not characteristic of their configuration. Moreover, the data disprove the postulate[5] that the contribution of a 20-hydroxy and 20-



(1) Most of the data in this report were taken from a thesis submitted by David M. Glick in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Western Reserve University. The investigation was supported by Grant C-1679 of the National Institutes of Health, U.S. Public Health Service, and by a research fellowship to one of us (D.M.G.) under Training Grant 2G-35.

(2) C. de Courcy, unpublished data from this laboratory.

(3) A. Butenandt and L. Mamoli, *Ber.*, **68**, 1847 (1935).

(4) C. W. Shoppee, *J. Chem. Soc.*, 1671 (1949).

(5) L. F. Fieser and M. Fieser, *Experientia*, **4**, 285 (1948).

(6) L. H. Sarett, *J. Am. Chem. Soc.*, **71**, 1175 (1949).

(7) W. Klyne and D. H. R. Barton, *ibid.*, **71**, 1500 (1949).

TABLE I

MOLECULAR ROTATIONS[a] (IN DEGREES) OF 5α-PREGNANE-3β,20-DIOLS AND THEIR ACETATES

Configuration			[M]D for C-20						
								OH(α-β)	
C-17	C-20	Cpd.	Diol	3-Ac	Di-Ac	OA − cOH	OAc(α-β)	Found	Calcd.[e]
α	α	III	−1	−32	−12	+20			
							+77	+83	+50
α	β	IV	−80	−115	−89	+26			
β	α	VII	+72[b]	+21	+ 8[d]	−13			
							−117	+35	+15
β	β	VIII	+12[c]	−14	+125[d]	+139			

[a] All entries are based on measurements in alcohol except those marked [b] and [c] which were taken in chloroform. [b] Klyne and Barton.[7] [c] Mean of two measurements by W. Klyne and E. Miller, *J. Chem. Soc.*, 1972 (1950). [d] H. Hirschmann, and F. B. Hirschmann, *J. Biol. Chem.*, **184**, 259 (1950). [e] Calculations according to Brewster[24] with the following constants: $k(C-H)^2 = 60°$ and $k(C-O)(C-H) = k(C-H)^2 - k(C-H)(O-H) = 60° - 50° = 10°$.[24] The conformations used are stated in the text.

acetoxy group of a given configuration is independent of the configuration at C-17.[8] Clearly, a comparison with 17β compounds cannot establish configurations at C-20. These were assigned on the basis of the products that result from the elimination of toluenesulfonic acid from the 20-*p*-toluenesulfonates IIId and IVd.

The elimination reaction has been carried out in the 17β series with both 20α and 20β compounds[9,10] and was interpreted as a concerted *trans*-elimination by Klyne.[11] The main product of the reaction of 5β-pregnane-3α,20α-diol 3-acetate 20-tosylate with boiling pyridine[9] must have been a *trans*-Δ^{17}-olefin (XII) since *cis*-hydroxylation with osmium tetroxide gave the 17α,20β-glycol as the main product.[9,12] The reaction of 3α-acetoxy-20β-tosyloxy-5β-pregnan-11-one was carried out in boiling collidine[10] and gave a complex mixture of about 9% Δ^{20}-olefin, 3% of an isomeric tosylate, and 36% of the *cis*-Δ^{17}-olefin (XI) which was characterized by its conversion to the 17α,20α-glycol by osmylation.[6,10]

As the two starting compounds for these elimination reactions showed structural differences besides their antipodal configurations at C-20, and since they were allowed to react with bases of different spatial requirements and at rather different temperatures, we studied the eliminations of the tosylates IIId and IVd as well as those of their 17-epimers (VIIb and VIIIb) under standardized conditions. The 17β-compounds were prepared from 3β-acetoxypregn-5-en-20-one by nickel and by palladium hydrogenation and by tosylation of the resulting 20-epimers (VIIa and VIIIa). Eliminations were conducted in boiling pyridine for two hours. Three of the reactions were complete as judged by the absence of tosylate absorption bands[13] in the infrared spectra of the olefins, whereas the product from tosylate VIIIb still showed the presence of about 20% of a tosylate. This component after purification showed absorption bands characteristic of 3β-acetoxy and tosyloxy groups in an infrared spectrum which, however, was distinctly different from that of the starting compound VIIIb. Further elimination of toluenesulfonic acid proceeded at a much slower rate and was not complete even after a sample of VIIIb had been heated with pyridine for twenty-three hours at 130°.

Attempts to purify the olefins were successful only in one instance (IVd). The reaction mixtures, therefore, were analyzed after the acetoxy olefins had been converted to triols. Only two triols could be detected by paper chromatography of the products derived from the four tosylates. These triols could be separated almost completely by quasi-gradient elution from alumina columns[14] by means of a concave gradient as suggested by Lakshmanan and Lieberman.[16] The separation achieved is illustrated in Fig. 1. The triols were identified as 5α-pregnane-3β,17,20α-triol[17] (Va) and 5α-pregnane-

(8) The validity of this method of assigning configurations to the 17β,20-glycols and 17β,20,21-glycerols has been questioned before.[6,7] These compounds have been correlated with each other [I. Salamon and T. Reichstein, *Helv. Chim. Acta*, **30**, 1929 (1947)] but no certain assignment of their C-20 configuration has been possible. One of those made (L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, 1959, pp. 631–632) was based on the assumption that the hydroxylation of the 17–20 double bond with osmium tetroxide had yielded a 17β,20-glycol. Strong evidence against this structure for the glycol in question has been given by I. Salamon [*Helv. Chim. Acta*, **32**, 1306 (1949)]. The data in the present paper also do not support the view that frontal attack occurs to a significant extent in the osmylation of the 17–20 double bond. Finally, F. Ramirez and S. Stafiej [*J. Am. Chem. Soc.*, **78**, 644 (1956)] made an assignment for 17β,20-glycols by comparing the shift in molecular rotation of their 20-acetates on epimerization at C-17 with the corresponding shift of the 17-hydroxy-20β-amine N-acetates. Since the quantitative agreement was not particularly close regardless of the identity of the 17β,20β-glycol, and since no reference data for the corresponding rotational shift for 17-hydroxy-20α-amine N-acetates are available the assignment of Ramirez and Stafiej probably should be regarded as tentative.

(9) H. Hirschmann, *J. Biol. Chem.*, **140**, 797 (1941).

(10) L. H. Sarett, *J. Am. Chem. Soc.*, **70**, 1690 (1948).

(11) W. Klyne, *Chem. Ind.* (London), 426 (1951).

(12) H. Hirschmann, *J. Am. Chem. Soc.*, **74**, 5357 (1952).

(13) In addition to the three strong and sharp bands listed by R. N. Jones and F. Herling [*J. Org. Chem.*, **19**, 1252 (1954)] there are other intense bands which appear to be associated with the tosyloxy group. Some of these had rather constant positions in 3β-[14,15] and 20-tosyloxy compounds (7.32–7.33 μ and 12.28–12.30 μ) whereas the wave lengths of others depended on the point of attachment to the steroid molecule. For example, the 20-tosylates IIId, IVd, VIIb, and VIIIb showed a strong peak at 12.79 ± 0.02 μ, which was absent from the spectra of the 3β-tosyloxy-5α-steroids examined.[14,15]

(14) H. Hirschmann, F. B. Hirschmann, and A. P. Zala, *J. Biol. Chem.*, **236**, 3141 (1961).

(15) J. W. Corcoran and H. Hirschmann, *J. Am. Chem. Soc.*, **78**, 2325 (1956).

(16) T. K. Lakshmanan and S. Lieberman, *Arch. Biochem. Biophys.*, **53**, 258 (1954).

(17) M. Steiger and T. Reichstein, *Helv. Chim Acta*, **21**, 546 (1938).

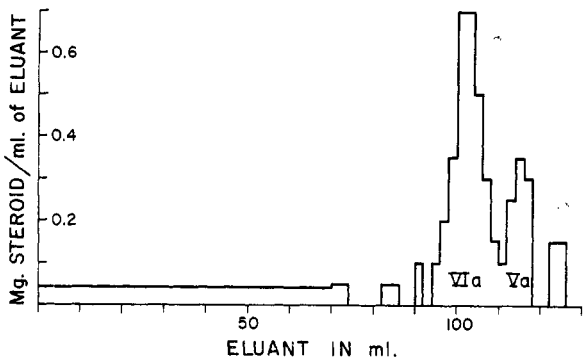


Fig. 1.—Chromatographic separation of the 5α-pregnane-3β,17,20-triols Va and VIa prepared from tosylate IIId. Details of procedure are given in the Experimental.

3β,17,20β-triol[17] (VIa) by their mobilities on paper and after acetylation, by the infrared spectra and melting points of the diacetates. In the case of the products derived from the new compounds, III and IV, additional criteria were used for identification. The reference samples of compounds V and VI were obtained from 3β-acetoxy-17-hydroxypregn-5-en-20-one by reduction with lithium aluminum hydride[18] and hydrogenation in the presence of palladium–calcium carbonate. The proportions of the 20-epimeric triols which were obtained from the various tosylates are given in Table II.

TABLE II

PROPORTION OF 20-EPIMERIC TRIOLS RESULTING FROM ELIMINATION REACTIONS[a]

Tosylate	Configuration C-17	Configuration C-20	5α-Pregnane-3β,17,20-triols as 20α (Va), %	5α-Pregnane-3β,17,20-triols as 20β (VIa), %
IIId	α	α	30	70
IVd	α	β	0	100
VIIb	β	α	8	92
VIIIb	β	β	41[b]	59

[a] Tosylates were heated in boiling pyridine for two hours and the products converted to triols *via* osmates. [b] A pyridine solution of VIIIb kept at 130° for twenty-three hours also yielded 41% of these triols as 5α-pregnane-3β,17,-20α-triol (Va).

Since the ratios of the two triols obtained from the elimination products of VIIIb after it had been heated in pyridine for two and for twenty-three hours were identical, the two olefins appear to be stable under the reaction conditions. The results given in Table II show, therefore, that these reactions could not have proceeded exclusively by *trans*-elimination, since all tosylates gave the 17α,-20β-glycol as the predominant product. If several modes of elimination seem equally feasible, ionic eliminations have shown a preference for *trans*-elimination regardless of the molecularity of the process.[19] One would expect, therefore, that that member of a 20-epimeric pair which furnishes a given olefin in higher yield would be the one that can form it by *trans*-elimination. This expectation is borne out in the 17β-series since the tosylate known to have the α-configuration at C-20 (VIIb) gave the higher proportion of the 17α,20β-glycol. It seemed justified, therefore, to assign the 20β-configuration to that isomer of the 17α-series which gave the 17α,20β-glycol (VIa) as the sole product.

A more detailed consideration of factors which might affect the probability of a molecule assuming the conformation required for *trans*-elimination supports this assignment. To this end, models[20] were constructed of the isomeric structures and measurements taken on each of the three staggered conformations resulting from rotation around the 17–20 bond. The differences of the sums of the van der Waals radii and the measured interatomic distances were taken as an index of instability and are listed in Table III. The data indicate that those conformations which place C-21 *trans* to the hydrogen at C-17 are much less stable than the other staggered conformations. In the 17β series this has been pointed out previously and can be supported by a number of observations.[15] The remaining conformations are compared in Fig. 2. We conclude that the antiparallel orientation of the 17-hydrogen and of the tosyloxy group required for *trans* elimination is the clearly preferred conformation in only one instance (IV, D). The compound assigned this structure has given the *trans* olefin (XII) as the sole product. The situation does not seem quite as favorable for this process in the case of VII since conformations E and F appear to be rather similar in stability. This might explain the formation of a small amount of *cis* olefin from VIIb. Antiparallel orientations of oxygen and of hydrogen at C-17 do not represent favored conformations for III and VIII. It is not surprising, therefore, that these tosylates do not yield as much *cis* olefin (XI) as IV and VII yield *trans* (XII). The process which results in *cis* elimination in ionic reactions and which must be responsible for the rather extensive formation of XII from III and VIII is usually pictured as an E_1 elimination.[21] Another mechanism (E_2) for ionic *cis* eliminations has recently been observed with compounds possessing activated hydrogens.[22] It has been described as a concerted elimination from skewed orientations of the departing groups.[22a] Although the hydrogen at C-17 is not particularly acidic, this mechanism is indicated at least for VIIIb. When this compound was heated in formic acid complete heterolysis was observed. The spectrum of the product showed the presence of a formoxy instead of a tosyloxy group and indicated that there was in addition a partial

(18) H. Hirschmann and F. B. Hirschmann, *J. Biol. Chem.*, **187**, 137 (1950).

(19) D. J. Cram in M. S. Newman, "Steric Effects in Organic Chemistry," John Wiley and Sons, New York, 1956, pp. 314–329.

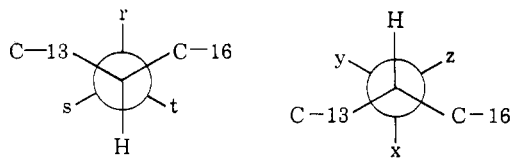
(20) D. H. R. Barton, *Chem. Ind.* (London), 1136 (1956).

(21) See *e.g.* S. Bernstein, R. H. Lenhard, and J. H. Williams, *J. Org. Chem.*, **19**, 41 (1954).

(22) (a) F. G. Bordwell and P. S. Landis, *J. Am. Chem. Soc.*, **79**, 1593 (1957), and references cited therein; (b) J. Weinstock, J. L. Bernardi, and R. G. Pearson, *ibid.*, **80**, 4961 (1958); (c) E. D. Hughes and J. C. Maynard, *J. Chem. Soc.*, 4087 (1960).

TABLE III

COMPRESSIONS[a] IN MOLECULAR MODELS OF C-20 ALCOHOLS



IX X

17β-Compounds (IX)

	C-18	12β-H	16β-H	17α-H
r = H	0.8			
O	1.0			
C	1.6		0.6	
s = H	0.1			
O	.2			
C	.7	0.6		0.4
t = C			.4	.4

17α-Compounds (X)

	12α-H	12β-H	14α-H	16α-H	17β-H
x = H			0.2		
O	0.1		.4		
C	.6		1.3	0.4	
y = H	.1				
O	.4				
C	1.0	0.6			0.4
z = C				.6	.4

[a] The "compressions" listed are the differences in Å. of the sums of the appropriate van der Waals radii (methyl 2.0, oxygen 1.4, and hydrogen 1.2 Å., L. Pauling, "The Nature of the Chemical Bond," 2nd ed., Cornell University Press, Ithaca, N. Y., 1944, p. 189) and the measured atomic distances. No additional interactions were found in toluenesulfonates.

ester exchange at C-3. The structure of the unesterified compound which differs from either 20-epimer of 5α-pregnane-3β,20-diol is being investigated.[23] No *trans*-Δ[17]-olefin could be detected. Since its formation from VIIIb evidently required an effective base like pyridine, the base must have participated in the transition state of the elimination reaction.

Confirmation for the correctness of the conformational analyses and of the configurations on which they are based, can be found in the observed molecular rotations. Expected values were calculated for the contributions of the 20-hydroxyl group by the method of Brewster,[24] on the assumption that A, D, and G are the prevailing conformations of III, IV, and VIII, respectively, and that solutions of VII contained equal amounts of E and F (Fig. 2). As shown in Table I the calculated molecular rotation differences between 20-epimers have the correct sign in the 17α and 17β series and

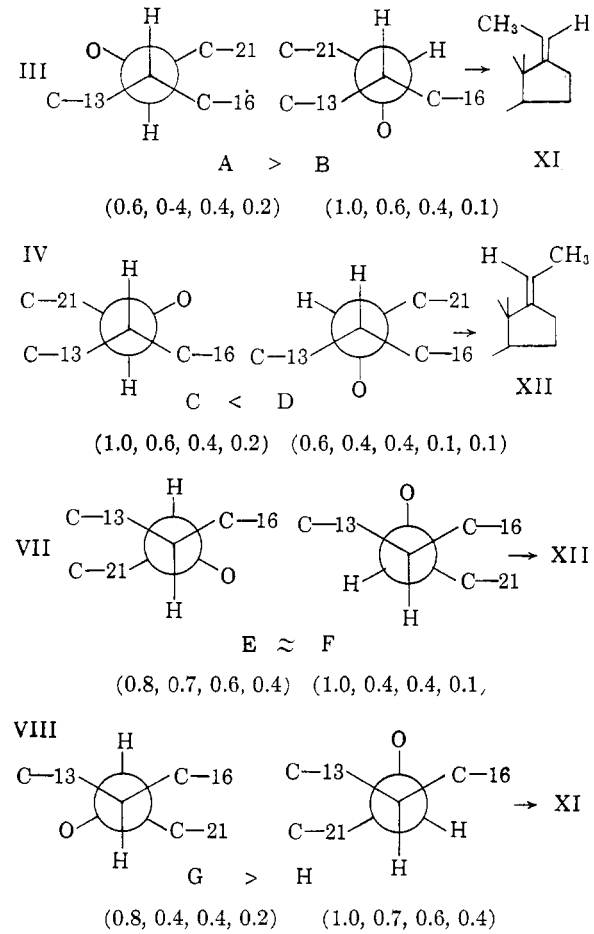


Fig. 2.—Conformations of C-20 alcohols. The numbers in parentheses indicate the "compressions" associated with each conformation and are taken from Table III.

appear to be in reasonable quantitative accord with the experimental values.

The differences between the optical rotations of IIIa and IVa or between their diacetates probably provide the best criteria for extending the configurational assignments to other 20-hydroxy 17α-steroids with different structures in rings A or B. The infrared maxima listed for IIIb and c and for IVb and c in the Experimental also show differences between epimers some of which are likely to occur also in other pairs. Finally the relative mobilities of the 4 diols IIIa, IVa, VIIa, and VIIIa have been measured by simultaneous paper chromatography. The results are given in Table IV.

TABLE IV

R_F OF 5α-PREGNANE-3β,20-DIOLS[a]

Config. at C-17	Config. at C-20	
	α	β
α	0.59	0.64
β	.50	.60

[a] Solvent system: heptane, isoöctane, toluene, methanol, and water; 25:25:50:80:20 volumes.

(23) On mechanistic grounds we regard 17α-methyl-D-homo-5α-androstane-3β,17aβ-diol[uranediol [R. V. Brooks, W. Klyne, E. Miller, and J. Y. F. Patterson, *Biochem. J.*, **51**, 694 (1952)]] as being the most probable structure for this compound. NOTE ADDED IN PROOF. The identity of the rearranged product with uranediol has been established by mixture melting points and comparisons of the infrared spectra of the free diol and of the diacetate with reference samples kindly supplied by Dr. Klyne. The rearrangement to uranediol took place also when 5α-pregnane-3β,20β-diol 20-(hydrogen sulfate) was heated with dilute hydrochloric acid.

(24) J. H. Brewster, *J. Am. Chem. Soc.*, **81**, 5475 (1959).

Experimental

General Procedures.—All melting points reported are corrected. Infrared spectra were measured on solutions in carbon disulfide, except those of triols, diols, and of the rearranged diol monotosylate. The latter were determined on pressings in potassium bromide. All peaks between 7.5 and 11.5 μ except very weak ones are listed for compounds IIIb and c and IVb and c. Their strong peaks are given in italics, shoulders in brackets. Rotations were measured in 95% ethanol on steroids dried at elevated temperatures (55–110°, depending on melting points) *in vacuo*. The tube length was 20 cm.

Hydrolyses were performed by heating acetates under reflux in 5 ml. of 80% ethanol containing 35 mg. of sodium hydroxide for 1–2 hr. Acetylations were done at room temperature in a 2:1 mixture of pyridine and acetic anhydride for 16–20 hr. The excess of anhydride was hydrolyzed by the slow addition of water to the chilled mixture.

Paper chromatography was done by the general method of Bush[25] with the following solvent systems: (1) heptane, isoöctane, toluene, methanol, and water; 25:25:50:80:20 for diols and (2) heptane, isoöctene, toluene, isopropyl ether, methanol, and water; 15:15:60:10:80:20 for triols.[14] Spots were made visible by heating strips which had been dipped into a phosphomolybdic acid solution and dried.[26] This color reaction is not as sensitive for 5α-pregnane-3β,20,-21-triols as it is for 5α-pregnane-3β,17,20-triols. Small amounts of the former, therefore, can escape detection by this method.

3β-Acetoxy-5α-pregnan-20-one (Ib).—3β-Acetoxypregn-5-en-20-one (342 mg.) in 25 ml. of ethanol was shaken with 735 mg. of 1% palladium–calcium carbonate in an atmosphere of hydrogen for 50 min. The product was recrystallized from acetone and yielded 297 mg. of Ib. It had m.p. 147–148°; $[\alpha]^{22}D$ +79° (*c* 1.0). The compound has been prepared by a variety of methods; a representative m.p. is 145–147°[27]; $[\alpha]D$ +79.8°.[28]

3β-Acetoxy-5α,17α-pregnan-20-one (IIb).—The method of Butenandt and Mamoli[3] was used to prepare II from I. Repeated isomerizations and fractional precipitations of 597 mg. of Ib yielded 394 mg. of a mixture of Ia and IIa in which IIa predominated (60%). The mixture was adsorbed on a column (22 × 246 mm.) of 103 g. of alumina and eluted with benzene–ether solutions. The early eluates (143 mg.) were recrystallized from methanol to constant specific rotations. The rotation was not changed by recrystallization from ether–petroleum ether (*cf.* ref. 4). An aliquot (50 μg.) of the product traveled as a single spot in the system isooctene, methanol, and water (10:8:2) with R_F 0.56 under conditions which allowed the detection of 2.5 μg. of Ia (R_F 0.52) either alone or in admixture with IIa. Compound IIa showed m.p. 141.5–142° (reported[4] 139°) and $[\alpha]D$ −70° (*c* 1.4, drying temp. 80°; reported[4] −78°). The acetate (IIb) was recrystallized from dilute methanol and showed m.p. 130.5–131.5° (reported[4] 118–119° and 119–122°) and $[\alpha]D$ −69° (*c* 1.3, drying temp. 80°; reported[4] −73 and −75°).

The alumina used for fractionation was a product of Harshaw Chemical Co. which had been washed with water containing enough acetic acid to lower the pH to 4.3, then copiously with water and dried at 150°. When suspended in water the alumina imparted a pH of 5.1 to the water. When an alumina preparation was used which had been washed with less acetic acid and which gave a final pH of 7.7, the order of elution was reversed. Emergence of a 17β- before a 17α-20-ketone has been reported repeatedly.[29] The preparations of alumina used by these workers[29] apparently had not been washed with acid.

Reduction of 3β-Acetoxy-5α,17α-pregnan-20-one (IIb). A. With Sodium Borohydride.—A solution of 89 mg. of IIb in 10 ml. of isopropyl alcohol was treated with 157 mg. of sodium borohydride and kept at room temperature for 20 hr. The excess hydride was decomposed with dilute hydrochloric acid and the product extracted with ether which was then washed with sodium bicarbonate solution and with water. The rotation of the reaction product (89 mg.) was that of a mixture of 75% IIIc and 25% IVc. These were separated by chromatography as described below.

B. With Raney Nickel.—This catalyst[30] (about 4 g.), 88 mg. of IIa, and 20 ml. of ethanol were shaken in an atmosphere of hydrogen for 45 min. The product was adsorbed on a column 190 × 36 mm. of 90 g. of a 2:1 mixture of silica gel–Celite which had been prewashed.[14] Elution was made from a mixing vessel containing 1800 ml. of 5% ethanol in benzene. With the transfer of each 10-ml. portion of eluant to the column, 1.0 ml.of 50% ethanol in benzene was added to the mixing vessel. The elution peaks of IVc and IIIc were observed when about 350 and 385 ml., respectively, of eluate had been collected. The proportion of IVc was estimated as 70% from the areas under the elution curves. The final products described below were free of their 20-epimers. This was shown by paper chromatography of the hydrolysis products, IIIa and IVa.

5α,17α-Pregnane-3β,20α-diol (III).—The **3-monoacetate (IIIc)** separated by chromatography was recrystallized from 80% ethanol. It showed m.p. 131–132°, $[\alpha]^{29}D$ −9° (*c* 0.7) and the following λ_{max}[31] 7.59, 7.76, *8.06*, 8.34, 8.53, 8.69, 8.83, 9.09, 9.23, 9.56, *9.74*, [9.86], 10.10, 10.31, 10.41, ~ 10.62, ~ 10.82, 11.07, and 11.28 μ.

Anal. Calcd. for $C_{23}H_{38}O_3$: C, 76.19; H, 10.57. Found: C, 76.48; H, 10.57.

Hydrolysis of IIIc gave the free **diol (IIIa)** which was recrystallized from methanol and showed m.p. 180–181°, $[\alpha]^{22}D$ −0.3° (*c*, 0.3).

Acetylation of IIIc gave the **diacetate (IIIb)** which was recrystallized from methanol. It had m.p. 91–93° and $[\alpha]^{21}D$ −3° (*c* 0.4) and λ_{max}[31] *8.06*, [8.31], 8.53, 8.67, 8.83, 8.98, 9.05, 9.25, 9.35, *9.54*, *9.74*, 10.11, ~ 10.32, 10.42, 10.54, 10.85, 11.06, and 11.27 μ.

Anal. Calcd. for $C_{25}H_{40}O_4$: C, 74.21; H, 9.97. Found: C, 74.41; H, 10.13.

5α,17α-Pregnane-3β,20β-diol (IV).—The **3-acetate (IVc)** prepared from IIb was recrystallized from methanol. The final product had m.p. 160–160.5°, $[\alpha]D$ −32° (*c* 0.3, and λ_{max}[31] 7.75, *8.06*, [8.23], 8.52, 8.67, 8.83, 8.95, ~9.05, 9.20, 9.42, [9.62], *9.77*, [9.97], 10.15, 10.30, 10.38, [10.50], 10.67, 10.81, 11.05, 11.25 μ.

Anal. Calcd. for $C_{23}H_{38}O_3$: C, 76.19; H, 10.57. Found: C, 76.11; H, 10.44.

The free **diol (IVa)** obtained by hydrolysis of IVb was recrystallized from methanol. It had m.p. 158–158.5°; $[\alpha]^{22}D$ −25° (*c* 0.2).

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.69; H, 11.32. Found: C, 79.30; H, 11.18.

Acetylation of the monoacetate IVc yielded the **diacetate (IVb)** which was recrystallized from methanol. It showed m.p. 125.5–126°, $[\alpha]^{21}D$ −22° (*c* 0.55) and λ_{max}[31] *8.06*, [8.32], [8.41], 8.52, 8.68, 8.76, *8.84*, 8.97, 9.14, 9.27, 9.43, 9.61, *9.75*, [9.88], 10.16, 10.38, 10.49, 10.55, 10.85, 11.05, and ~ 11.26 μ.

Anal. Calcd. for $C_{25}H_{40}O_4$: C, 74.21; H, 9.97. Found: C, 73.89; H, 9.93.

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(31) Bands common to the spectra of compounds IIIb, IIIc, IVb, and IVc with the exception of the one near 10.83 μ are among those given by Jones and Herling[32] in their listing of bands attributable to 3β-acetoxy-5α-steroids.

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Preparation of the 3β-Acetoxy-5α-pregnan-20-ols (VIIa and VIIIa).—The Raney nickel catalyst used was prepared according to Mozingo,[30] since in other work[26] this type has given a higher proportion of the 20α-epimer than had a more active product. The catalyst (2.1 g.), 406 mg. of 3β-acetoxypregn-5-en-20-one, and 29 ml. of ethanol were shaken with hydrogen for 100 min. The product, after hydrogenation with 812 mg. of palladium–calcium carbonate in 30 ml. of ethanol, was chromatographed on a column (12 × 114 mm.) of 15 g. of acid-washed alumina with benzene (20–100%)–petroleum ether mixtures as eluants. The **20β-isomer (VIIIa)** was eluted first. After recrystallization from acetone and from petroleum ether it had m.p. 173–174° and $[\alpha]^{22}D$ −4° (*c* 1.0); reported[7] m.p. 168–169°, $[\alpha]^{Chl.}D$ −6°. **5α-Pregnane-3β,20α-diol 3-acetate (VIIa)** which was recrystallized from petroleum ether showed m.p. 132–133° and $[\alpha]^{22}D$ +6° (*c* 0.7).

By rechromatographing intermediate fractions a total of 92 mg. of VIIa and of 259 mg. of VIIIa was obtained. Each final product was free of its 20-epimer, as was shown by paper chromatography of the hydrolysis products. Their R_F are given in Table IV.

Tosylations.—5α-Pregnane-3β,20β-diol 3-acetate (VIIIa) (39 mg.) was allowed to stand with 206 mg. of *p*-toluenesulfonyl chloride in 1.5 ml. of pyridine at room temperature for 17 hr. and after the addition of water to the chilled solution, for one additional hour. The mixture was diluted with benzene and washed in the cold with water, dilute hydrochloric acid, dilute sodium bicarbonate, and water. The solvent was removed *in vacuo* and the residue (50 mg.) was recrystallized from acetone. **5α-Pregnane-3β,20β-diol 3-acetate 20-*p*-toluenesulfonate (VIIIb)** had a rather variable m.p. up to 164–166°, with dec., and had λ_{max} 257, 263, 268, and 274 mμ in dioxane.

Anal. Calcd. for $C_{30}H_{44}O_5S$: C, 69.73; H, 8.58. Found: C, 70.07; H, 8.70.

The tosylate VIIb prepared from VIIa in this manner melted at 129–131°, with dec. Since the two tosylates of the 17α-series gave spectrographic evidence of decomposition during attempts towards their purification, fresh preparations were used immediately for elimination reactions.

Elimination Reactions. A. 5α,17α-Pregnane-3β,20α-diol 3-Acetate 20-*p*-Toluenesulfonate (IIId).—This compound prepared from 18.0 mg. of IIIc was heated under a reflux with 4 ml. of pyridine under anhydrous conditions for 2 hr. The mixture was extracted with ether, which was then washed with dilute hydrochloric acid, sodium bicarbonate, and water. The product (14.1 mg.) was allowed to react with 60 mg. of osmium tetroxide in 0.85 ml. of pyridine for 21 hr. A solution of 173 mg. of sodium bisulfite in 2.6 ml. of water and 2.2 ml. of pyridine was added and the mixture was stirred magnetically for 30 min.[33] The product was extracted with methylene chloride and freed of pyridine by washing with hydrochloric acid and with water. The resulting triol 3-acetates (15.3 mg.) gave on alkaline hydrolysis 12.9 mg. of crude triols. An aliquot was chromatographed on paper and showed (outside of the solvent front) only two spots. These had the same mobilities as reference samples of Va and of VIa. The remainder (12.7 mg.) was adsorbed on a column (12 × 180 mm.) of 23 g. of alumina (Woelm, almost neutral, hydrated with 6% of water). Elution was made from a mixing vessel which at the start contained 429 ml. of 0.8% absolute ethanol in benzene. With each transfer of 2 ml. of eluent to the column, 0.2 ml. of ethanol was added to the mixing vessel. The early eluates (Fig. 1) contained 2.7 mg. of a product with absorption maxima characteristic of a hydroxyl group (2.77 and 9.63 μ[34]) and of olefinic hydrogen (3.32 μ). Since the curve differed significantly from the spectrum of the purified hydroxy olefin fraction derived from VIIIb (mixture of *cis* and *trans*), the product is probably a rearrangement product. It was not investigated further. The weights of the later eluates showed two main maxima. The material (5.5 mg.) of the first peak was identified as 5α-pregnane-3β,17,20β-triol (VIa) by paper chromatography and by its infrared spectrum. This fraction was acetylated to yield diacetate VIb which melted after recrystallization from dilute methanol at 159.5–160.5° and at 158.5–160° in admixture with a reference sample (m.p. 158–159.5°). The infrared spectra of both preparations agreed. The material of the second elution peak (2.4 mg.) was identified as 5α-pregnane-3β,17,20α-triol (Va) in the same manner. Its diacetate melted at 242–243° and at 244–245° in admixture with a reference sample melting at 246–247.5°.

B. 5α,17α-Pregnane-3β,20β-diol 3-Acetate 20-*p*-Toluenesulfonate (IVd).—This tosylate derived from 17.2 mg. of IVc gave by analogous procedures 14.1 mg. of crude acetoxy olefin, 15.4 mg. of triol 3-acetate and 13.1 mg. of free triol. Since this material showed only a single spot on paper chromatography, purification by adsorption chromatography was omitted. Recrystallization from dilute methanol yielded 5α-pregnane-3β,17,20β-triol (VIa) with m.p. 208–210.5° which was not depressed by admixture with a reference sample (m.p. 209.5–211.5°). The first mother liquor gave no indication of the presence of a triol other than VIa when examined by paper chromatography and infrared spectroscopy. The crystals were acetylated and the product identified as VIb as described above under A.

In a separate run the intermediate product, ***trans*-Δ[17]-5α-pregnen-3β-ol acetate** was purified by recrystallization from methanol. The final product showed m.p. 125.5–126° (reported[35] m.p. 120–121.5°), $[\alpha]^{21}D$ +19° (*c* 0.3) and λ_{max} 3.30, 12.09, and 12.28 μ. Another *trans*-Δ[17]-olefin was found to have λ_{max} 12.07 and 12.28 μ.[12]

C. 5α-Pregnane-3β,20α-diol 3-Acetate 20-*p*-Toluenesulfonate (VIIb).—Compound VIIb (25.3 mg.) gave 10.6 mg. of triols which on recrystallization gave 10.1 mg. of crystals melting at 204–208°. Since the crude product had shown two spots on paper chromatography, crystals and mother liquors were combined and chromatographed on alumina to give 6.9 mg. of VIa and 0.6 of Va.

D. 5α-Pregnane-3β,20β-diol 3-Acetate 20-*p*-Toluenesulfonate (VIIIb).—This tosylate (48.6 mg.) gave 31.7 mg. of elimination products, 34.9 mg. of crude triol 3-acetates, and 27.9 mg. of crude triols. Chromatography yielded in addition to 9.6 mg. of triol VIa and 6.7 mg. of triol Va, 7.7 mg. of material in the earlier eluates which consisted mainly of a diol monotosylate. To characterize this reaction product prior to alkaline hydrolysis, another portion of 33.8 mg. of the crude triol 3-acetates was partitioned twice between 85% methanol and petroleum ether containing 5% benzene. The upper phases contained 9.4 mg. which on recrystallization from acetone gave two crops with identical infrared spectra of an unidentified toluenesulfonate (5.8 mg.) with m.p. 165–166° with dec. The spectra which were distinctly different from that of VIIIb showed acetate bands[32] at 5.77, 8.06, and 9.74 μ, tosylate bands[13] at 7.34, 8.42, 8.50, 9.09, and 12.32 μ.

In another run 23.5 mg. VIIIb in 4 ml. of pyridine were heated (130°) in a sealed tube for 23 hr. and yielded successively 12.7 mg. of acetoxy olefins, 14.2 mg. of triol 3-acetates, and 11.0 mg. of triols, which on chromatography gave 4.7 mg. of VIa, 3.2 mg. of Va, and 1.4 mg. in the early eluates. The ultraviolet spectrum of the acetoxy olefin fraction indicated a tosylate content of about 3%.

Solvolysis of 5α-Pregnane-3β,20β-diol 3-Acetate 20-*p*-

(33) This procedure by J. S. Baran [*J. Org. Chem.*, **25**, 257 (1960)] gave higher yields than osmylation in ether containing 1% pyridine followed by cleavage with lithium aluminum hydride [D. H. R. Barton, D. A. J. Ives, and B. R. Thomas, *J. Chem. Soc.*, 903 (1954)] but did not alter the proportion of triols V and VI. Only the latter procedure was used with the elimination products of VIIb.

(34) This strong band in the spectrum of a 5α-steroid is characteristic of a 3β-hydroxy group [R. N. Jones and G. Roberts, *J. Am. Chem. Soc.*, **80**, 6121 (1958)].

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Toluenesulfonate (VIIIb).—A solution of tosylate VIIIb (37.6 mg.) in 20 ml. of ~99% formic acid was heated under a reflux for 2 hr. and then concentrated *in vacuo*. The product was extracted with benzene which was washed with sodium bicarbonate solution and with water. The spectra of the dry residue (27.6 mg.), of its first mother liquor and of the crude diacetate described below showed no tosylate bands nor any of the three bands reported above for *trans*-Δ^{17}-5α-pregnen-3β-ol acetate. Recrystallization from methanol–acetone and from acetone gave 3.0 mg. of rods with m.p. 216–219° and λ_{max} 8.06 and 9.74 μ (acetate)[32] and 8.50 μ (formate).[26] The spectrum differed from that of the crude reaction product in having weaker formate and stronger acetate absorption. An aliquot of the crude product was hydrolyzed to yield material of which all but a very small amount traveled as a single spot with the same R_F as 5α-pregnane-3β,20β-diol. Non-identity was shown by comparison of the spectra of the diacetates.

Benzfuroxans. The Crystal and Molecular Structure of 5-Chlorobenzfurazan 1-Oxide and 5-Bromobenzfurazan 1-Oxide[1]

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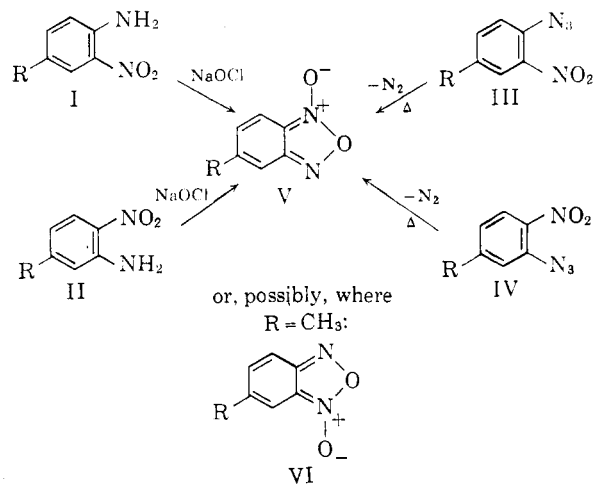
From a complete X-ray crystallographic study, 5-chlorobenzfuroxan is shown to have the 5-chlorobenzfurazan 1-oxide structure (Va), in which the chlorine substituent is *para* to the N-oxide nitrogen atom. The crystal structure of 5-bromobenzfuroxan is isomorphous, and the molecular structure is assumed to be analogous, that is 5-bromobenzfurazan 1-oxide (Vb).

In all cases of unsymmetrically substituted isomeric pairs of *o*-nitroanilines, including the nitrochloroanilines[2] Ia and IIa, the nitrotoluidines[2] Ic and IIc, and the nitronaphthylamines[3] VII and VIII, which have been subjected to alkaline sodium hypochlorite oxidation, only a single benzfuroxan product has been isolated. Similarly, with all the isomeric pairs of *o*-nitrophenylazides, the nitrobromophenylazides[4] IIIb and IVb and the nitrotolylazides[4] IIIc and IVc, and the nitronaphthylazides[5] IX and X, which have been subjected to thermal decomposition, only a single benzfuroxan product has been isolated. If the *o*-nitrogen atoms were to become incorporated in an unsymmetrical benzfuroxan (such as V–VI and XI–XII), analogous to the aliphatic furoxans,[6] as has been proposed,[7] then two isomeric products (V and VI, or XI and XII) might have been anticipated. Formation of a single product was rationalized[7,8] by assuming a relatively rapid interconversion in solution or in the liquid phase of the less stable isomer into the more stable isomer, proceeding through a single *o*-dinitrosobenzene intermediate (such as XIII). An alternative explanation has been advanced in which the product is itself considered to be a symmetrical resonance hybrid *o*-dinitrosobenzene (XIII↔XIV↔XV), a Ψ-*o*-dinitrosobenzene derivative,[9] and ultraviolet spectral evidence was cited in support of this view.[10]



	R
Ia, IIa, Va, VIa	Cl
Ib, IIIb, IVb, Vb, VIb	Br
Ic, IIc, IIIc, IVc, Vc, VIc	CH_3

Since the chemical approach to the structure of the benzfuroxans gives an ambiguous answer, resort to a purely physical approach appeared desirable. While our work was in progress, it was reported from proton resonance data that benzfurazan 1-oxide (V. R = H)[11–13] and 4,7-dibromo-

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