# D-Homoannulation of Pregnane 17,20-Glycols[1]

KENNETH I. H. WILLIAMS, MILDRED SMULOWITZ, AND DAVID K. FUKUSHIMA[2]

*Sloan-Kettering Institute for Cancer Research and Institute for Steroid Research, Montefiore Hospital, New York, New York*

*Received November 20, 1964*

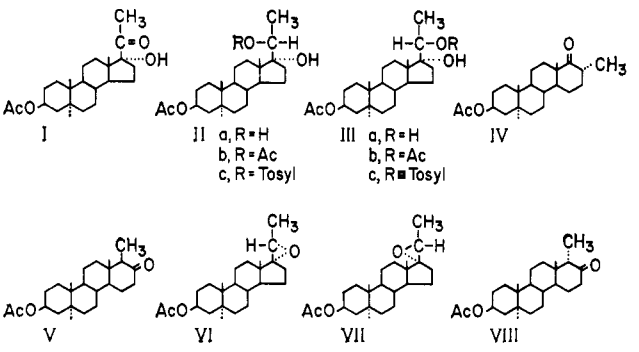
Treatment of 5α-pregnane-3β,17α,20β-triol 3-acetate 20-*p*-toluenesulfonate with (1) potassium acetate and aqueous acetone, (2) heat, and (3) sodium iodide–acetone and silver nitrate afforded 3β-acetoxy-17α-methyl-D-homo-5α-androstan-17a-one. The epimeric 20α-toluenesulfonate yielded 3β-acetoxy-17α-methyl-D-homo-5α-androstan-17-one. Hot acid treatment of 5α-pregnane-3β,17α,20β-triol 20-sulfate gave uranolone (3β-hydroxy-17α-methyl-D-homo-5α-androstan-17a-one). The stereochemistry of D-homoannulation of the 17,20-glycols is discussed.

It has been shown that the pinacol–pinacolone rearrangement of pregnane-17,20-diols with acid leads to the formation of pregnan-20-one as the major product.[3–5] It was postulated that the rearrangement occurred with the intermediate formation of a carbonium ion at C-17 followed by a shift of the proton from C-20.[3] However, if the leaving group in these 17,20-glycols were at C-20, a migration of C-13 or C-16 could occur resulting in the formation of 17α-methyl-D-homo-17-ketone or 17-methyl-D-homo-17a-ketone.[6] D-Homoannulation of analogous steroids, 17-hydroxy-20-amino-$C_{21}$ steroids, by nitrous acid deamination, has been studied by Ramirez and Stafiez.[7] These authors proposed a mechanism whereby the stereochemical course of ring expansion involving a bridge-type transition state with C-17, C-20, and C-16 or with C-17, C-20, and C-13 (Figure 1) could be analyzed, dependent on the steric strain of the transition state. They found in accordance with theory that the nitrous acid deamination of 20α-amino-5α-pregnane-3β,17α-diol and 20β-amino-5α,17α-pregnane-3β,17β-diol led to 3β-hydroxy-17aα-methyl-D-homo-5α-androstan-17-one and 3β-hydroxy-17aβ-methyl-D-homo-5α-androstan-17-one, respectively.[7] However, the other two isomers of the amino alcohols could not be prepared to complete the study. The four isomers of 5α-pregnane-3β,17,20-triols are well known and it was hoped that the 20-tosylates of these triols would lead to D-homo ketones and extend the study of Ramirez and Stafiez.

The 20-epimers, IIa and IIIa, of 5α-pregnane-3β,-17α,20-triol 3-monoacetate were readily prepared by catalytic hydrogenation of 3β-acetoxy-17α-hydroxy-5α-pregnan-20-one (I) (see Chart I). The compounds were characterized by the formation of the diacetates IIb and IIIb. The 20-tosylates (IIc and IIIc) of the respective epimers were prepared in the usual manner with *p*-toluenesulfonyl chloride and pyridine at 5°.

The rearrangement of 20β-tosylate IIc was carried out by three procedures: treatment with (1) potassium acetate–aqueous acetone, (2) heat, and (3) sodium iodide–acetone and silver nitrate. In all cases the principal product was 3β-acetoxy-17α-methyl-D-homo-5α-androstan-17a-one (IV) with no evidence for the formation of other D-homo isomers. A small amount of the 17α,20α-oxide VI was isolated in the reaction of tosylate IIc with potassium acetate in aqueous acetone. The possibility, therefore, existed that the oxide VI was the intermediate in the D-homoannulation of IIc to IV. On treatment with potassium acetate in acetone under the rearrangement conditions of IIc, oxide VI was recovered unchanged. On heating oxide VI with an equivalent amount of *p*-toluenesulfonic acid in toluene, a nonpolar material was obtained. There was no evidence for the formation of D-homo ketone IV or for unchanged oxide. These results appear to eliminate an oxide intermediate in the D-homoannulation.

CHART I




The rearrangement of the 20α-tosylate IIIc with potassium acetate and acetone yielded 3β-acetoxy-17aα-methyl-D-homo-5α-androstan-17-one (VIII), the product resulting from migration of C-13, in 50% yield as the sole ketonic product. A small amount of 17α,20β-oxido-5α-pregnan-3β-ol acetate (VII) was formed. The oxide VII was prepared from the 20α-tosylate IIIc with base and was found not to be transformed to the D-homo ketone VIII under the rearrangement condition. This confirms the above study that the 17,20-oxides are not intermediates in the D-homoannulation. Thermal rearrangement of tosylate IIIc also resulted in the cleavage of the bond between C-13 and C-17. The D-homo 17-ketone formed, however, was the thermodynamically stable epimer, 3β-acetoxy-17aβ-methyl-D-homo-5α-androstan-17-one (V). It is almost certain that the axially oriented 17aα-methyl derivative VIII had been first formed which was then epimerized to the thermodynamically stable 17aβ-methyl-D-homo ketone V.

The steric course of D-homoannulation of the epimeric 17α-hydroxy 20-tosylates proceeded according to the theory postulated for the nitrous acid deamination of 17-hydroxy-20-amino steroids.[7] The rearrangement

(1) This investigation was supported by Public Health Service Research Grant No. CA 07304-01 from the National Cancer Institute and a grant from the American Cancer Society.

(2) To whom inquiries should be addressed.

(3) D. K. Fukushima and T. F. Gallagher, *J. Biol. Chem.*, **226**, 725 (1957).

(4) W. Klyne, *Ciba Found. Colloq. Endocrinol.*, **7**, 127 (1953).

(5) J. Rosselet, J. W. Jailer, and S. Lieberman, *J. Biol. Chem.*, **225**, 977 (1957).

(6) Bisnor-5α-cholane-3β,17α,20-triol (20-methyl-5α-pregnane-3β,17α,20-triol) has been rearranged to 3β-hydroxy-17a,17a-dimethyl-D-homo-5α-androstan-17-one under acidic conditions: M. Uskokovic, M. Gut, and R. I. Dorfman, *J. Am. Chem. Soc.*, **81**, 4561 (1959). This glycol does not have an asymmetric carbon at C-20 and therefore the effect of the orientation of the C-20 hydroxyl group on the course of D-homoannulation could not be examined.

(7) F. Ramirez and S. Stafiez, *ibid.*, **78**, 644 (1956); **77**, 134 (1955).

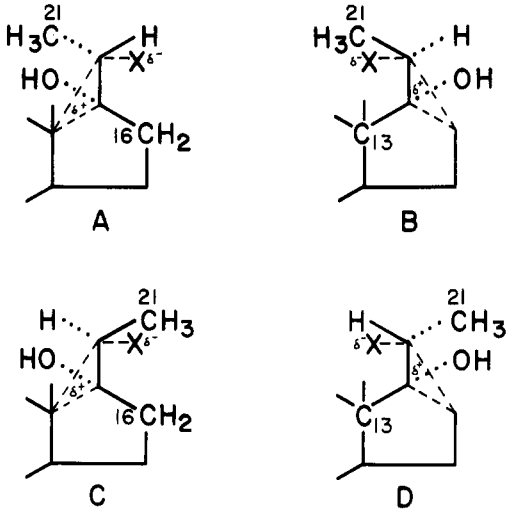


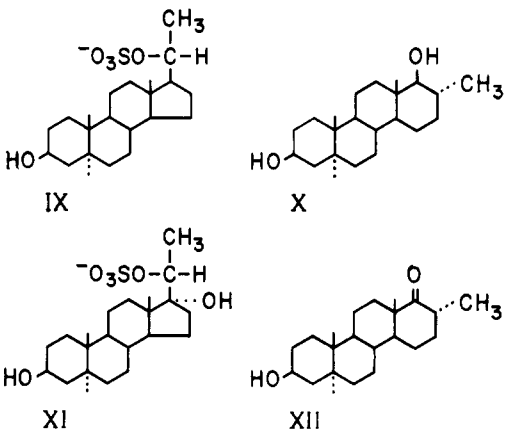

Figure 1.

of 17α-hydroxy-20α-tosylate IIIc would then be depicted to go *via* the transition state A (Figure 1) wherein the groups opposed, 21-$CH_3$–OH, H–16-$CH_2$, are smaller than those, 21-$CH_3$–13-C, H–OH, in the transition state B (Figure 1). The migration of C-13 to C-20 *via* A would then result in the formation of the D-homo 17-ketone with an inversion of the methyl group at C-20 to yield the axial 17aα-methyl derivative VIII under mild conditions. The same D-homo ketone was obtained by the ring expansion of the 20α-amino-5α-pregnane-3β,17α-diol with nitrous acid. The rearrangement of the 17α-hydroxy 20β-tosylate IIc would be predicted to proceed *via* transition state D (Figure 1) in which the opposing groups, 21-$CH_3$–OH, H-13-C, are smaller than those in transition state C (Figure 1) leading to a D-homo 17a-ketone. As expected the product formed was 3β-acetoxy-17α-methyl-D-homoandrostan-17a-one (IV) in which the 17α-methyl group has the stable equatorial conformation.

Attempts were made to study the rearrangement of isomeric 5α,17α-pregnan-17β-ol 20-tosylates. However, treatment of 5α,17α-pregnane-3β,17β,20α-triol 3-monoacetate with *p*-toluenesulfonyl chloride and pyridine did not afford the desired tosylate but gave a variety of unknown products. The 17β,20β derivative yielded a product with the characteristics of the 17,20-oxide. Since no *p*-toluenesulfonate could be obtained, further studies with 17β,20-dihydroxy steroids were abandoned.

A D-homo steroid, uranediol (X, 17α-methyl-D-homo-5α-androstane-3β,17aβ-diol) (see Chart II) has been isolated from pregnant mare's urine.[8] It was shown recently that uranediol is an artifact produced by the acid hydrolysis of the 20-sulfate of 5α-pregnane-3β,20β-diol (IX).[9] Pregnane-3α,17α,20α-triol and Δ⁵-pregnene-3β,17α,20α-triol are normal constituents of human urine and are excreted in large amounts by patients with adrenal carcinoma.[10,11] It is conceivable that in these patients such triols may be excreted as 20-sulfate conjugates. Since it was shown above that the

CHART II




20-tosylates of the 17α,20-glycols could be rearranged to D-homo ketones, a possibility existed that D-homo-annulation of the 20-sulfates of these glycols could also be effected under the conditions of acid hydrolysis of urinary steroid conjugates. In order to test this possibility, the 20-sulfate of 5α-pregnane-3β,17α,20β-triol (XI) was prepared from the triol 3-monoacetate IIa with pyridine sulfate by the method of Levitz[12] followed by saponification of the acetate at room temperature. Saponification of the sulfate at higher temperature resulted in the formation of the 17α,20α-oxide.

On heating the 20-sulfate XI with 1 *N* hydrochloric acid, 5α-pregnane-3β,17α,20β-triol and 3β-hydroxy-17α-methyl-D-homo-5α-androstan-17a-one (XII), also known as uranolone, were obtained. The D-homo ketone XII is the same product obtained from the 20β-tosylate IIc. Therefore in analogy with the steric course of rearrangement of the tosylates, the 20-sulfates of the epimeric, 3,17α,20α-triols should give, on acid treatment, the 17aβ-methyl-D-homo 17-ketones such as V. Solvolysis of the 20-sulfate XI by the method of Burstein and Lieberman[13] with ethyl acetate saturated with 0.1 *N* sulfuric acid afforded 5α-pregnane-3β,17α,-20β-triol with no trace of the D-homo ketone XII.

## Experimental[14]

**5α-Pregnane-3β,17α,20-triol 3-Monoacetate (II and III).**—3β-Acetoxy-17α-hydroxy-5α-pregnan-20-one (I, 16.32 g.) in 300 ml. of ethyl acetate and 300 ml. of acetic acid was hydrogenated in the presence of 3 g. of Adams catalyst at room temperature. The reduction mixture was filtered through a Celite mat and the solvent was removed *in vacuo*. The crystalline residue, 15.77 g., was chromatographed on 1300 g. of silica gel containing 520 ml. of ethanol. Elution with 2% ethanol in methylene chloride at a rate of 1 ml./min. afforded 9.34 g. of 5α-pregnane-3β,17α,-20β-triol 3-monoacetate (IIa). Recrystallization from ethyl acetate and methanol yielded the monoacetate IIa: m.p. 196–200°; $[\alpha]^{28}D$ −14.7°; $\nu_{max}^{CS_2,CCl_4}$ 1734, 1245, 1152, 1133, 1094, 1028, 966, and 902 cm.$^{-1}$. Acetylation yielded 5α-pregnane-3β,17α,20β-triol 3,20-diacetate (IIb) which had an infrared spectrum identical with that of an authentic sample.

Further elution of the chromatographic column with 2% ethanol in methylene chloride yielded 2.08 g. of 5α-pregnane-3β,17α,20α-triol 3-monoacetate (IIIa). Recrystallization from ethyl acetate gave IIIa: m.p. 190–191.5°; $[\alpha]^{28}D$ −28.6°;

(8) R. E. Marker, E. Rohrmann, and E. L. Wittle, *J. Am. Chem. Soc.*, **60**, 1561 (1938); W. Klyne, *Nature*, **166**, 559 (1950).

(9) H. Hirschmann and J. S. Williams, *J. Biol. Chem.*, **238**, 2305 (1963).

(10) D. K. Fukushima, H. L. Bradlow, L. Hellman, and T. F. Gallagher, *J. Clin. Endocrinol. Metab.*, **23**, 266 (1963).

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

(12) M. Levitz, *Steroids*, **1**, 117 (1963).

(13) S. Burstein and S. Lieberman, *J. Biol. Chem.*, **233**, 331 (1958).

(14) Melting points were taken on a micro hot stage and are corrected. Optical rotations were determined in chloroform. Infrared spectra were determined on a Perkin-Elmer Model 21 spectrophotometer; uncorrected band values: calcium fluoride prism 4000–2750 cm.$^{-1}$, 1500–1280 cm.$^{-1}$; sodium chloride prism 1300–650 cm.$^{-1}$; br = broad.

$\nu_{max}^{CS_2,CCl_4}$ 1734, 1244, 1152, 1133, 1079, 1028–1018, 960, 903, and 878 cm.$^{-1}$. Acetylation afforded the known diacetate IIIb.

**5α-Pregnane-3β,17α,20β-triol 3-Acetate 20-*p*-Toluenesulfonate (IIc).**—A solution of 3.78 g. of 5α-pregnane-3β,17α,20β-triol 3-monoacetate (IIa) and 2.28 g. of *p*-toluenesulfonyl chloride in 50 ml. of pyridine was stored at 5° for 48 hr. The mixture was poured into cold water, filtered, and washed with dilute hydrochloric acid and water. The product, 5.22 g., was recrystallized from acetone to give 5α-pregnane-3β,17α,20β-triol 3-acetate 20-*p*-toluenesulfonate (IIc): m.p. 132–134°; $[\alpha]^{22}D$ +0.5°; $\nu_{max}^{KBr}$ 1716, 1270, 1191, 1179, 1100, 1066, 1030, 971, 891, 890, 818, 809, 789, 724, 678, 667, and 659 cm.$^{-1}$.

*Anal.* Calcd. for $C_{30}H_{44}O_6S$: C, 67.64; H, 8.33; S, 6.02. Found: C, 67.86; H, 8.82; S, 6.20.

**5α-Pregnane-3β,17α,20α-triol 3-Acetate 20-*p*-Toluenesulfonate (IIIc).**—Treatment of 1.26 g. of 5α-pregnane-3β,17α,20α,-triol 3-monoacetate (IIIa) with 0.69 g. of *p*-toluenesulfonyl chloride in 30 ml. of pyridine afforded 1.80 g. of crude IIIc. Recrystallization from acetone yielded 5α-pregnane-3β,17α,20α-triol 3-acetate 20-*p*-toluenesulfonate (IIIc): m.p. 118.5–120°; $[\alpha]^{21}D$ −30°; $\nu_{max}^{KBr}$ 1723, 1255, 1174, 1099, 1026, 956, 906, 883 (br), 787, 728, and 673 cm.$^{-1}$.

*Anal.* Calcd. for $C_{30}H_{44}O_6S$: C, 67.64; H, 8.33; S, 6.02. Found: C, 67.98; H, 8.74; S, 5.95.

**Rearrangement of Tosylate IIc. A. Potassium Acetate–Acetone.**—A mixture of 100 mg. of 5α-pregnane-3β,17α,20β-triol 3-acetate 20-*p*-toluenesulfonate (IIc) and 123 mg. of potassium acetate in 4 ml. of water and 15 ml. of acetone was refluxed for 6 hr. and then stored at room temperature overnight. The reaction mixture was poured into water, extracted with ether, and washed with sodium bicarbonate solution and water. The extract was dried over sodium sulfate and the solvent was removed to give 48 mg. of product. Chromatography on alumina and elution with benzene–petroleum ether (1:1) afforded 15 mg. of 3β-acetoxy-17α-methyl-D-homo-5α-androstan-17a-one (IV). Recrystallization yielded IV, m.p. 169–171°, which had an infrared spectrum identical with that of an authentic sample.[15] Further elution of the chromatographic column yielded 2 mg. of 3β-acetoxy-17α,20α-oxido-5α-pregnane (VI). No evidence for the formation of the isomers of D-homo ketone IV was found.

**B. Heat.**—A solution of 50 mg. of 5α-pregnane-3β,17α,20β-triol 3-acetate 20-*p*-toluenesulfonate (IIc) in 50 ml. of dry toluene was refluxed for 1 hr. The product (45 mg.) was chromatographed on a thin layer of silica gel G with cyclohexane–ethyl acetate (7:3). Elution of the band of steroid, $R_f$ 0.52, gave 31 mg. of 3β-acetoxy-17α-methyl-D-homo-5α-androstan-17a-one (IV). Recrystallization from methanol yielded 17 mg. of IV, m.p. 171.5–172°; the infrared spectrum was identical with that of an authentic sample.

**C. Sodium Iodide and Acetone.**—A mixture of 100 mg. of tosylate IIc and 200 mg. of sodium iodide in 25 ml. of acetone was refluxed for 3 hr., stored at room temperature overnight, and then refluxed for 4 hr. The cooled solution was filtered and the solvent was removed *in vacuo*. The residue was dissolved in ethyl acetate and washed with water, sodium thiosulfate solution, and water. The ethyl acetate solution was dried and the solvent was evaporated to give 73 mg. of product. This was dissolved in 3 ml. of ethyl alcohol and treated with 37 mg. of silver nitrate for 24 hr. The reaction mixture was worked up to give 67 mg. of product. Chromatography on alumina gave 30 mg. of the D-homo 17a-ketone IV, m.p. 163–170°. Recrystallization from methanol yielded IV, m.p. 169–171°; the infrared spectrum was identical with that of an authentic sample.

**Treatment of Tosylate IIIc. A. Potassium Acetate–Acetone.**—5α-Pregnane-3β,17α,20α-triol 3-acetate 20-*p*-toluenesulfonate (100 mg., IIIc) was refluxed for 6 hr. with 123 mg. of potassium acetate in 4 ml. of water and 15 ml. of acetone. The reaction mixture was worked up in the same manner as above for IIc to give 70 mg. of product. Chromatography on alumina and elution with benzene–petroleum ether (1:1) yielded 2 mg. of 17α,-20β-oxido-5α-pregnan-3β-ol acetate (VII) as judged by infrared spectrophotometry and mobility ($R_f$ 0.52) on a thin layer of silica gel G with cyclohexane–ethyl acetate (7:3). Further elution afforded 34 mg. of 3β-acetoxy-17aα-methyl-D-homo-5α-androstan-17-one (VIII) contaminated with a trace of the 17aβ-methyl epimer. Recrystallization from acetone–water yielded VIII, m.p. 125–129°; the infrared spectrum and the mobility ($R_f$ 0.39) on a thin layer of silica gel G with cyclohexane–ethyl acetate (7:3) were identical with an authentic sample.[7]

**B. Heat.**—5α-Pregnane-3β,17α,20α-triol 3-acetate 20-*p*-toluenesulfonate (25 mg., IIIc) was heated at 100° for 30 min. Recrystallization from acetone yielded 3β-acetoxy-17aβ-methyl-D-homo-5α-androstan-17-one (V), m.p. 164–166°; the infrared spectrum was identical with an authentic sample.

**17α,20α-Oxido-5α-pregnan-3β-ol Acetate (VI).**—A solution of 500 mg. of 5α-pregnane-3β,17α-20β-triol 3-acetate 20-*p*-toluenesulfonate (IIc) in 25 ml. of acetone and 6 ml. of 1 *N* aqueous potassium hydroxide was stored at 5° overnight. The product was precipitated with water, collected on a filter, and dried. Acetylation in the cold with acetic anhydride and pyridine yielded 320 mg. of the acetate. Chromatography on alumina gave 194 mg. of the oxide VI, m.p. 119–155°. Recrystallization from acetone–water yielded 17α,20α-oxido-5α-pregnan-3β-ol acetate (VI): m.p. 154–163°; $[\alpha]^{21}D$ −3.1°; $\nu_{max}^{KBr}$ 1738, 1249, 1151 (br), 1134, 1031, 966, 956, and 891 cm.$^{-1}$.

*Anal.* Calcd. for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.27; H, 9.82.

**17α,20β-Oxido-5α-pregnan-3β-ol Acetate (VII).**—A solution of 197 mg. of 5α-pregnane-3β,17α,20α-triol 3-acetate 20-*p*-toluenesulfonate (IIIc) in 15 ml. of acetone and 3 ml. of 1 *N* aqueous potassium hydroxide was stored at 5° for 40 hr. and then worked up as above. The product was reacetylated and recrystallized from acetone–water to yield 17α,20β-oxido-5α-pregnan-3β-ol acetate (VII): m.p. 153–170°; $[\alpha]^{21}D$ −4.3°; $\nu_{max}^{KBr}$ 1732, 1255, 1155, 1133, 1029, 971, 950, and 891 cm.$^{-1}$.

*Anal.* Calcd. for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.86; H, 10.31.

**Attempted D-Homoannulation of Oxides VI and VII. A. 17α,20α-Oxido-5α-pregnan-3β-ol 3-Acetate (VI).**—A solution of 50 mg. of oxide VI and 62 mg. of potassium acetate in 2 ml. of water and 7.6 ml. of acetone was refluxed for 5 hr. and stored at room temperature overnight. The reaction mixture was worked up as with IIc. The infrared spectrum and the mobility ($R_f$ 0.71) on a thin layer of silica gel G with cyclohexane–ethyl acetate (1:1) were identical with those of the starting material. Recrystallization gave oxide VI, m.p. 155–166°. There was no indication of the formation of the D-homo 17a-ketone (IV).

A mixture of 2 mg. of oxide VI and 1 mg. of *p*-toluenesulfonic acid in 3 ml. of toluene was refluxed for 1 hr. The reaction product was chromatographed on a thin layer of silica gel G with cyclohexane–ethyl acetate (7:3) and stained with phosphomolybdic acid. There was no indication for the presence of the D-homo ketone IV ($R_f$ 0.52) or the oxide VI ($R_f$ 0.46). A compound with a higher mobility ($R_f$ 0.63) was obtained. The structure was not characterized since the interest in the reaction was the transformation to D-homo ketone IV.

**B. 17α,20β-Oxido-5α-pregnan-3β-ol Acetate (VII).**—A solution of 30 mg. of the oxide VII and 37 mg. of potassium acetate in 1.2 ml. of water and 4.6 ml. of acetone was refluxed for 23 hr. and worked up as above. The product isolated had an infrared spectrum identical with the starting material and there was no indication of the presence of the D-homo-17-one (VIII). Recrystallization from methanol yielded 16 mg. of 17α,20β-oxido-5α-pregnan-3β-ol 3-acetate (VII), m.p. 158–171°; the infrared spectrum and the mobility ($R_f$ 0.51) on thin layer of silica gel G with cyclohexane–ethyl acetate (7:3) were identical with the starting material.

**5α-Pregnane-3β,17α,20β-triol 20-Sulfate (XI).**—A solution of 2.0 g. of 5α-pregnane-3β,17α,20β-triol 3-monoacetate (IIa) in 10 ml. of pyridine was added to a solution of 0.78 ml. of concentrated sulfuric acid, 1.46 ml. of acetic anhydride, 12 ml. of chloroform, and 35 ml. of pyridine.[12] The mixture was stirred at room temperature for 1 hr. and allowed to stand overnight. The solution was made alkaline, pH 11, with 5% sodium hydroxide solution and extracted with benzene. The aqueous portion was allowed to stand for 1 hr. and then extracted with 1-butanol. The solvent was removed to give 1.97 g. of a mixture of the 3-acetoxy and 3-hydroxy steroid 20-sulfate.

A portion (500 mg.) of the above mixture was saponified with 50 ml. of methanol and 2.5 ml. of 2% sodium hydroxide solution at room temperature for 48 hr. The solvent was removed *in vacuo*, the residue was dissolved in 1-butanol and washed with water, and the solvent was removed. The residue was crystallized from methanol–ether to give 360 mg. of sodium 5α-preg-

(15) D. K. Fukushima, S. Dobriner, and R. S. Rosenfeld, *J. Org. Chem.*, **26**, 5025 (1961).

nane-3β,17α,20β-triol 20-sulfate (XI). The analytical sample melted at 133–141°.

*Anal.* Calcd. for $C_{21}H_{35}NaO_6S$: C, 57.51; H, 8.05; S, 7.31. Found: C, 57.29; H, 8.34; S, 7.57.

**Solvolysis of Sulfate XI with Hydrochloric Acid.**—A solution of 10 mg. of 5α-pregnane-3β,17,20β-triol 20-sulfate (XI) in 8 ml. of 1 *N* hydrochloric acid was heated on the steam bath for 1 hr. It was then extracted with ethyl acetate, washed with base and water, and dried over sodium sulfate; the solvent was evaporated to give 6 mg. of product. Preparative thin layer chromatography of the product on silica gel G with cyclohexane–ethyl acetate (1:1) gave materials with $R_f$ of 0.4 and 0.2. Acetylation of substance with $R_f$ 0.4 yielded 3β-acetoxy-17α-methyl-D-homo-5α-androstan-17a-one (IV). Recrystallizations from methanol gave 0.5 mg. of the D-homo ketone IV, m.p. 165.5–167.5°; the infrared spectrum in potassium bromide dispersion was identical with that of the authentic sample.

The substance with $R_f$ 0.2 on acetylation yielded 5α-pregnane-3β,17α,20β-triol 3,20-diacetate verified by its infrared spectrum.

**Solvolysis of Sulfate XI in Moist Acidic Ethyl Acetate.**—A solution of 6.6 mg. of sulfate XI in 10 ml. of 0.1 *N* sulfuric acid solution and 2.5 g. of sodium chloride was extracted with 40 ml. of ethyl acetate. The moist acidic ethyl acetate solution was incubated at 37° for 24 hr. and washed with base and water; the solvent was evaporated to give 3 mg. of 5α-pregnane-3β,-17α,20β-triol, m.p. 185–197°. No trace of the D-homo 17a-ketone could be detected.

**Treatment of Sulfate XI with Base.**—A solution of 8 mg. of sulfate XI in 1 ml. of methanol and 4 ml. of 5% sodium hydroxide solution was refluxed for 2 hr. It was extracted with ethyl acetate, washed with water, and dried over sodium sulfate; the solvent was evaporated to give 3.5 mg. of product. Acetylation with pyridine–acetic anhydride yielded 4 mg. of 17α,20α-oxido-5α-pregnan-3β-ol 3-acetate (VI), $R_f$ 0.67, on a thin layer of silica gel G with ethyl acetate–cyclohexane (1:1). Recrystallization from methanol yielded oxide VI, m.p. 167–169°; the infrared spectrum in potassium bromide dispersion was identical with that of the authentic sample.

**Acknowledgment.**—We wish to acknowledge the interest and support of Dr. T. F. Gallagher throughout this investigation. We are grateful to Mrs. Beatrice S. Gallagher for the determination and interpretation of the infrared spectra.

# Tetranonacontane[1]

RUSSELL R. REINHARD AND JOSEPH A. DIXON[2]

*Whitmore Laboratory, College of Science, The Pennsylvania State University, University Park, Pennsylvania*

*Received November 2, 1964*

A general method of synthesis for high molecular weight *n*-paraffin hydrocarbons has been applied to the synthesis of tetranonacontane. The viscosities and densities at three temperatures of this hydrocarbon are reported.

Very high molecular weight *n*-paraffins are of interest because they provide model systems for studying and relating the properties of linear polymers to their molecular weights.[3,4] In addition, a number[5,6] of empirical and theoretical correlations of physical properties as a function of molecular weight have been proposed for these "simplest" hydrocarbons and it is important to determine whether such correlations are valid, particularly at the higher molecular weights where many configurations are possible in both the liquid and solid state. However, only a few syntheses of *n*-paraffins larger than $C_{50}$ have been reported and physical property data are almost nonexistent.

All of the syntheses in the literature have a Wurtz reaction as a key step. Carothers[7] synthesized *n*-pentacontane ($C_{50}H_{102}$), *n*-hexacontane ($C_{60}H_{122}$), and *n*-heptacontane ($C_{70}H_{142}$) by a bifunctional Wurtz reaction from decamethylene dibromide and finely divided sodium in dry ether. The hydrocarbons $C_{20}H_{42}$, $C_{30}H_{62}$, and $C_{40}H_{82}$ represented 25% of the product and were separated by fractional crystallization. The remainder was separated by molecular distillation into fractions of $C_{50}H_{102}$, $C_{60}H_{122}$, $C_{70}H_{142}$, and a residue thought to consist of higher polymers. No properties but the melting points were reported. Doolittle and Peterson[8] prepared *n*-tetrahexacontane from 1-bromodotriacontane (derived from the $C_{32}$-alcohol of carnauba wax) and sodium sand in dry ether. In addition to the melting point these authors determined the densities and viscosities over a range of temperatures.

The pioneering syntheses of *n*-dooctacontane ($C_{82}H_{166}$) and *n*-hectane ($C_{100}H_{202}$) were accomplished by Ställberg, Ställberg-Stenhagen, and Stenhagen[9] who used the Wurtz reaction to couple, in the case of *n*-hectane, two 1-iodopentacontane ($C_{50}H_{101}I$) molecules. Melting points and certain crystal data were obtained.

This paper reports a relatively large-scale (100 g.) synthesis of *n*-tetranonacontane. The synthetic route used avoids the Wurtz reaction and is applicable to the preparation of other high molecular weight *n*-paraffins. In addition, the densities and viscosities of *n*-$C_{94}$ over a range of temperature are reported and compared with similar data for previously studied straight-chain hydrocarbons.

**Synthesis.**—The synthetic route used in the present work is outlined in Scheme I. The Wurtz coupling reaction was avoided because it has been observed in this laboratory[10] and elsewhere that the formation of branched-chain products frequently accompanies the formation of the desired straight-chain compounds.

$$RCH_2CH_2X + Na \longrightarrow RCHCH_2CH_2R + RCH(CH_3)-CH(CH_3)R + RCH_2CH_2CH_2CH_2R$$

(1) Abstracted from a thesis submitted by R. R. Reinhard in partial fulfillment of the requirements for the Ph.D. degree, 1961.

(2) To whom inquiries should be made.

(3) M. G. Broadhurst, *J. Chem. Phys.*, **36**, 2578 (1962).

(4) M. Kuratee and S. Iside, *ibid.*, **23**, 1126 (1955).

(5) M. G. Broadhurst, *J. Res. Natl. Bur. Std.*, **A66**, 241 (1962), and references therein.

(6) P. J. Flory and A. Vrij, *J. Am. Chem. Soc.*, **88**, 3548 (1963).

(7) W. H. Carothers, J. W. Hill, J. E. Kirby, and R. A. Jacobson, *ibid.*, **52**, 5279 (1930).

(8) A. K. Doolittle and R. H. Peterson, *ibid.*, **73**, 2145 (1951).

(9) G. Ställberg, S. Ställberg-Stenhagen, and E. Stenhagen, *Acta Chem. Scand.*, **6**, 313 (1952).

(10) S. G. Clark, II, and R. W. Schiessler, unpublished results.