1.0 g. of sodium bicarbonate. The oil which separated was collected with chloroform, and the separated chloroform extract washed successively with 0.1 *N* hydrochloric acid, sodium bicarbonate solution, and water, and dried. Evaporation gave an oil, which was taken up in 15 ml. of absolute ethanol. Two milliliters of petroleum ether (b.p. 30–80°) was added. After 4 days at 0–5°, the crystals which had separated were collected, giving 224 mg. (16%) of colorless product, m.p. 125–127°. A sample recrystallized again, for analysis, melted at 133–134°.

Anal. Calcd. for $C_{28}H_{28}O_8S$: C, 64.10; H, 5.34. Found: C, 64.22; H, 5.36.

On hydrolysis with 50% acetic acid, this product gave 4-O-*p*-toluenesulfonylpinitol, m.p. 191° dec. (reported m.p.[16c] 193° dec.).

allo-Inositol Configurational Series

DL(1234/56) Diastereomer of 6-Bromoquercitol, M.p. 160°. 6-Bromo-6-deoxy-*allo*-inositol, IX.—A mixture of 3.2 g. of the pentaacetate[3] (m.p. 153°), derived from *epi*-inositol by reaction with acetyl bromide, with 64 ml. of *M* hydrochloric acid in 50% ethanol was boiled under reflux for 5 hr. On evaporation a light brown sirup was obtained. Volatile impurities were removed by repeated addition and evaporation of absolute ethanol. The resulting sirup was taken up in 15 ml. of 2-methyl-2-propanol (treated with charcoal). After the solution had stood 24 hr. at room temperature, the *hygroscopic* crystals which had separated were collected on a sintered glass funnel *from which moist air was excluded*, and dried over phosphorus pentoxide *in vacuo*. The colorless crystals obtained weighed 0.95 g., m.p. 159–160° dec. Including a second crop, m.p. 158–160°, and a third crop, m.p. 158–160° dec., the yield was 1.40 g. (82%). A sample recrystallized again, for analysis, showed no change in melting point.

Anal. Calcd. for $C_6H_{11}BrO_5$: C, 29.65; H, 4.56; Br, 32.86. Found: C, 29.80; H, 4.73; Br, 32.27.

On hydrogenolysis, this product gave DL-*allo*-quercitol[4a] (see following text).

Conversion of the Bromoquercitol, M.p. 160°, to DL-*allo*-Quercitol, XXXI.—A 950-mg. sample of the bromoquercitol (m.p. 160°) was hydrogenated with Raney nickel and Amberlite IR-45 resin[12] in the same manner described for the m.p. 236° chloroquercitol isomer. The crude hydrogenation product was taken up in 15 ml. of absolute ethanol, and the solution kept at room temperature for 24 hr. The crystals which had separated were collected, giving 300 mg. of colorless product, m.p. 260–261° dec. The product was shown by mixture melting point and infrared spectrum to be identical with DL-*allo*-quercitol.[4a]

A sample of the quercitol was acetylated, giving DL-*allo*-quercitol pentaacetate, m.p. 92–94°, identical by mixture melting point and infrared spectrum with an authentic sample.[4a]

Nuclear Magnetic Resonance Spectra of the DL-(12346/5) Diastereomers of 6-Chloro-, 6-Bromo-, and 6-Iodoquercitol (XXVIII-XXX).—The spectra were taken in deuterium oxide, using tetramethylsilane external reference. A strong HDO peak appeared in each spectrum at about δ 5.2 p.p.m. The chloroquercitol[4a] (m.p. 192°) showed a 1-proton multiplet (about 8 peaks) centered at δ 4.1; another 1-proton multiplet (about 5 peaks) centered at 4.3; and a 4-proton multiplet (about 7 peaks) centered at δ 4.6. The 4-proton multiplet was almost split at its center into two 2-proton multiplets (δ 4.5, 4.7).

The spectra of the bromoquercitol[4a] (m.p. 203°) and iodoquercitol[4a] (m.p. 214°) were similar to that of the chloro analog, but showed no tendency for separation of the 4-proton multiplet at δ 4.6 into two smaller multiplets.

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Synthesis of Δ⁵-Pregnene-3α,16α,20α-triol[1]

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The partial syntheses of Δ⁵-pregnene-3α,16α,20α-triol and its 20β-epimer are described.

Recently[3] we reported the isolation and characterization of Δ⁵-pregnene-3α,16α,20α-triol (Ha) from the urine of a patient with adrenocortical carcinoma, which was the first description of the natural occurrence of a 3α-hydroxy-Δ⁵ steroid. The partial synthesis of this unsaturated triol by an unambiguous route is described in the present report. In addition, all four Δ⁵-pregnene-3,16α,20-triols isomeric at positions 3 and 20 have been prepared by another route.

The starting material in both instances was 3β-acetoxy-Δ⁵,¹⁶-pregnadien-20-one (A). The 16α-hydroxyl group was introduced by the method of Julian and coworkers.[4] Selective oxidation of the Δ¹⁶ bond of A with alkaline hydrogen peroxide followed by reacetylation gave 3β-acetoxy-16α,17-oxido-Δ⁵-pregnen-20-one (B).[4] Reduction of the oxide B with chromous acetate[5] yielded 3β-acetoxy-16α-hydroxy-Δ⁵-pregnen-20-one (C). Impure C was generally carried directly to the next stage. Lithium aluminum hydride reduction of C gave a mixture of Δ⁵-pregnene-3β,16α,20α- and 20β-triols (D and Ea) which were separated readily by partition chromatography on silica gel. These epimers had been prepared and the configuration at C-20 assigned by Hirschmann and co-workers.[6] The triol Ea has been isolated from natural sources.[3,7,8]

The inversion of the 3β-hydroxy group of the 20α-triol E, while preserving the configurations at 16 and 20, was accomplished by a procedure based on studies of

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(2) Pennsalt Chemicals Corporation, Philadelphia, Pa.

(3) D. K. Fukushima, M. Smulowitz, and K. I. H. Williams, *J. Biol. Chem.*, **236**, 3147 (1961).

(4) P. L. Julian, E. W. Meyer, W. J. Karpel, and I. R. Waller, *J. Am. Chem. Soc.*, **72**, 5145 (1950).

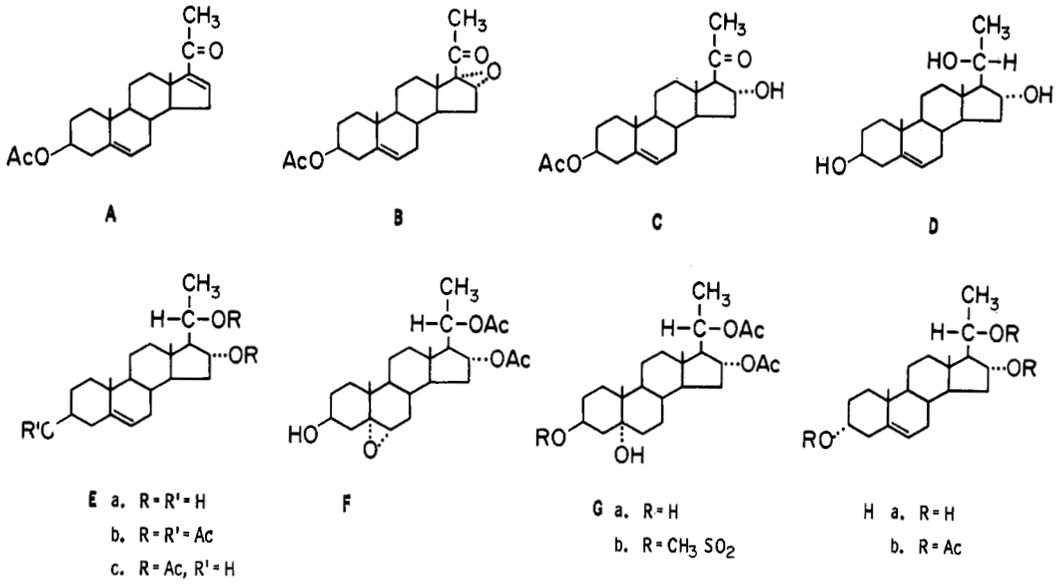
(5) W. Cole and P. L. Julian, *J. Org. Chem.*, **19**, 131 (1954). Chromous acetate was prepared by the method described in H. F. Walton, "Inorganic Preparations," Prentice-Hall, Inc., New York, N. Y., 1948, p. 161.

(6) H. Hirschmann, F. B. Hirschmann, and M. A. Daus, *J. Am. Chem. Soc.*, **74**, 539 (1952).

(7) K. Fotherby, *Biochem. J.*, **71**, 209 (1959).

(8) H. Hirschmann and F. B. Hirschmann, *J. Biol. Chem.*, **184**, 259 (1950).

CHART 1



Plattner and co-workers[9] on the rearrangement of cholesterol to epicholesterol (Δ^5-cholesten-3α-ol) *via* 3β-methanesulfonoxycholestan-5α-ol with diethylaniline and acetyl chloride. Δ^5-Pregnene-3β,16α,20α-triol (Ea) was converted to triacetate Eb which was then selectively saponified to diacetate Ec with one equivalent of sodium hydroxide in cold aqueous alcohol.[8] Epoxidation with monoperphthalic acid gave the 5α,6α-oxide F which was separated from the reaction mixture by crystallization from acetone; additional material was obtained by partition chromatography of the mother liquors.

Catalytic hydrogenation of 5,6α-oxido-5α-pregnane-3β,16α,20α-triol 16,20-diacetate (F) with Adams' catalyst in acetic acid resulted in a mixture from which 5α-pregnane-3β,5,16α,20α-tetrol 16,20-diacetate (Ga) was isolated. Treatment of Ga with methanesulfonyl chloride in pyridine gave the expected 3β-mesylate Gb in good yield. With acetyl chloride and diethylaniline in chloroform, followed by hydrolysis, Gb was converted to Δ^5-pregnene-3α,16α,20α-triol (Ha) identical with the natural product.

In the alternate synthesis of triol Ha the addition of benzyl alcohol to the Δ^{16}-20-ketone A and acetylation yielded 3β-acetoxy-16α-benzyloxy-Δ^5-pregnen-20-one (I) as described by Hirschmann.[6] Reduction with lithium aluminum hydride removed the acetyl group and yielded a mixture of 20-hydroxy epimers (J); fractional crystallization of a portion of the mixture yielded 16α-benzyloxy-Δ^5-pregnene-3β,20β-diol, characterized by conversion to Δ^5-pregnene-3β,16α,20β-triol (D).

In order to utilize the method by Ruzicka and Goldberg[10] described for the preparation of a 3α-hydroxy-Δ^5 steroid by Raney nickel hydrogenation of a 3-keto-Δ^5 compound, mixture J was oxidized with chromic acid in acetone.[11] A product with carbonyl absorptions at 1709 cm.$^{-1}$ and 1718 cm.$^{-1}$ and with a very weak hydroxyl absorption was obtained. These indicated that both the 3- and 20- hydroxyl groups had been oxidized to give 16α-benzyloxy-Δ^5-pregnene-3,20-dione (K). Without purification K was hydrogenated in 95% ethanol with W-2 Raney nickel catalyst. Although Hirschmann[12] earlier noted that Raney nickel hydrogenation cleaved a 16α-benzyl ether and simultaneously reduced a 20-ketone, the present reduction product retained the 20-ketone as judged by infrared spectrometry. The compound was formulated, therefore, as 3,16α-dihydroxy-Δ^5-pregnen-20-one (L). No attempts to separate the C-3 hydroxy epimers were made at this stage since the 3,16α,20-triols isomeric at C-3 and C-20 could be readily separated. Therefore, L was reduced with lithium aluminum hydride to give a mixture of the four triols. Digitonin precipitation separated the 3α-hydroxy triols Ha and M from the 3β-hydroxy triols D and Ea. Partition chromatography of the "α-fraction" gave Δ^5-pregnene-3α,16α,20α-triol (Ha), identical with the natural material as well as Ha prepared by the first route; this was followed by Δ^5-pregnene-3α,16α,20β-triol (M) in roughly a 1:3 ratio. A small amount of Δ^5-pregnene-3β,16α,20β-triol (D) also was isolated; this 3β-isomer has been reported previously[6] to appear in the soluble "α-fraction."

Partition chromatography of the "β-fraction" gave the previously described Δ^5-pregnene-3β,16α,20α-triol (Ea) and 3β,16α,20β-triol (D) in roughly a 1:3 ratio.

Experimental[13]

3β-Acetoxy-16α-hydroxy-Δ^5-pregnen-20-one (C).—Moist chromous acetate prepared from the reduction of 50 g. of potassium dichromate was added to a solution of 17 g. of 3β-acetoxy-16α,17-oxido-Δ^5-pregnen-20-one (B) in 450 ml. of acetic acid and 100 ml. of water.[5] The mixture was stirred at room temperature under nitrogen for 16 hr. and then filtered. The filtrate was poured into 1200 ml. of water and extracted with methylene chloride. The organic extract was washed with water, sodium bicarbonate solution, and water, dried, and the solvent evaporated. Re-

(9) Pl. A. Plattner, A. Fürst, F. Koller, and W. Lang, *Helv. Chim. Acta*, **31**, 1455 (1948).

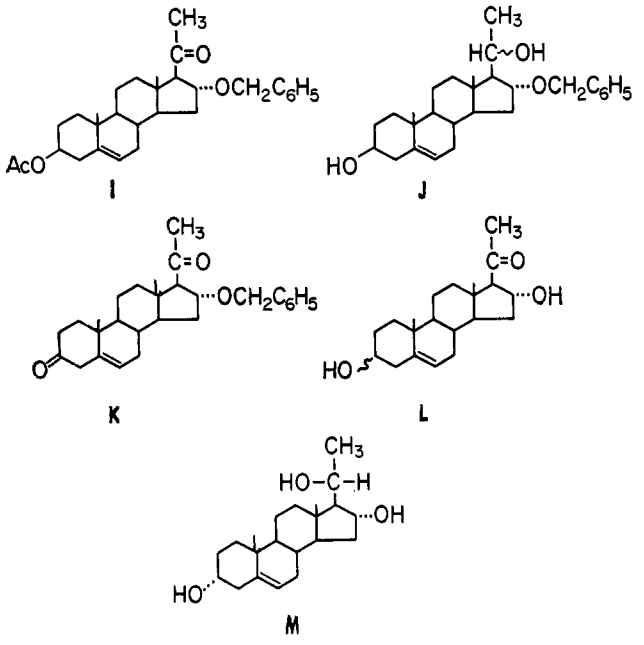
(10) L. Ruzicka and M. W. Goldberg, *ibid.*, **19**, 1407 (1936).

(11) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(12) H. Hirschmann, F. B. Hirschmann, and J. W. Corcoran, *ibid.*, **20**, 572 (1955).

(13) Melting points were taken on a micro hot stage and are corrected. Optical rotations were determined in chloroform unless otherwise stated. Infrared spectra were determined in a Perkin-Elmer Model 21 spectrophotometer; calcium fluoride prism 4000–2750 cm.$^{-1}$, 1800–1600 cm.$^{-1}$, 1500–1280 cm.$^{-1}$; sodium chloride prism 1300–650 cm.$^{-1}$; sh = shoulder; * = not present in carbon tetrachloride solution.

CHART 2



crystallization of the residue from benzene gave 3.2 g. of 3β-acetoxy-16α-hydroxy-Δ^5-pregnen-20-one (C), m.p. 165–168°. The mother liquor which was principally the desired product was used in the next step. The analytical sample of C melted at 169–171° and the 3,16-diacetate prepared from it melted at 172–174°. The infrared spectra of both compounds were identical with that of authentic samples.

Δ^5-Pregnene-3β,16α,20α- and 20β-triols (D and Ea).—A solution containing 13.5 g. of crude 3β-acetoxy-16α-hydroxy-Δ^5-pregnen-20-one (C) in 250 ml. of ether and 150 ml. of freshly distilled tetrahydrofuran was added to a solution of 5 g. of lithium aluminum hydride in 1000 ml. of anhydrous ether. The mixture was stirred for 4 hr. and excess reagent was destroyed with ethyl alcohol followed by 10% sulfuric acid. The product obtained was chromatographed on 1100 g. of silica gel containing 40% ethanol. Elution with 5% ethanol in methylene chloride yielded 3 g. of Δ^5-pregnene-3β,16α,20α-triol (Ea) which on recrystallization from methanol melted at 247–248° (reported[6] m.p. 245–247°); $[\alpha]^{27}D$ −72.9° (ethanol). Acetylation with pyridine and acetic anhydride afforded the triacetate (Eb), m.p. 177–178° (reported[6] m.p. 178.5–180°).

Elution with 8% ethanol in methylene chloride gave 4 g. of Δ^5-pregnene-3β,16α,20β-triol (D), m.p. 269,274–282° (reported[6] m.p. 294–298°). The triol was homogeneous as judged by chromatograpny on a thin layer of silica gel G with ethyl acetate. The triacetate prepared from it melted at 168–170°; $[\alpha]^{26}D$ −104° (reported[6] m.p. 167.5–168.5°; $[\alpha]D$ −93°).

Δ^5-Pregnene-3β,16α,20α-triol 16,20-Diacetate (Ec).—T a solution of 1.57 g. (3.4 mmoles) of Δ^5-pregnene-3β,16α,20α-triol triacetate (Eb) in 300 ml. of ethanol and 100 ml. of water was added 28.3 ml. (3.7 mmoles) of 0.12 *M* sodium hydroxide in methanol. The mixture was stored at 5° for 18 hr. and a drop of acetic acid added. The solvent was removed *in vacuo*. The residue was extracted with ethyl acetate, washed with water, dried, and the solvent evaporated. Chromatography on 100 g. of acid-washed alumina and elution with 10% ethyl acetate in benzene yielded 945 mg. of the 16,20-diacetate (Ec), m.p. 188–190° (reported[8] m.p. 185.5–187.5°). The completely saponified Δ^5-pregnene-3β,16α,20α-triol (Ea), 157 mg., was eluted with 20% ethanol in ethyl acetate.

5,6α-Oxido-5α-pregnane-3β,16α,20α-triol 16,20-Diacetate (F).—A solution of 1.18 g. of Δ^5-pregnene-3β,16α,20α-triol 16,20-diacetate (Ec), in 40 ml. of chloroform was mixed with 100 ml. of 0.16 *M* monoperphthalic acid in ether. The mixture was stored at 5° for 16 hr. and then diluted with ethyl acetate. The solution was washed with sodium bicarbonate solution and water, dried, and the solvent evaporated. The crystalline residue was washed with acetone yielding 517 mg. of 5,6α-oxido-5α-pregnane-3β,16α,20α-triol 16,20-diacetate (F), m.p. 211–218°. The analytical sample of F from acetone melted at 214–219°, $[\alpha]^{27}D$ −121°; ν_{max}^{KBr} 3480, 1737, 1707*, 1267, 1246, 1151, 1066, 1046, 1035, 1020 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 68.64; H, 8.71.

An additional 400 mg. of the diacetate F was obtained upon chromatography of the acetone washes, 552 mg.

5α-Pregnane-3β,5,16α,20α-tetrol 16,20-Diacetate (Ga).—A solution of 820 mg. of the oxide diacetate F (see preceding section) in 35 ml. of acetic acid was hydrogenated for 21 hr. in the presence of 600 mg. of prereduced Adams' catalyst. The reduction mixture was extracted with methylene chloride, washed with dilute base and water, and the solvent removed. The residue was chromatographed on 100 g. of silica gel containing 40 ml. of ethanol. Elution with 2% ethanol in methylene chloride afforded 400 mg. of 5α-pregnane-3β,5,16α,20α-tetrol 16,20-diacetate (Ga). Recrystallization from benzene yielded 242 mg. of the tetrol diacetate (Ga), m.p. 196–199°; $[\alpha]^{27}D$ −56.9°; ν_{max}^{KBr} 3465 (sh), 3435, 1743, 1714*, 1272, 1255 (sh), 1245, 1166, 1036, 1028 (sh), 958 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{40}O_6$: C, 68.78; H, 9.24. Found: C, 68.22; H, 9.37.

5α-Pregnane-3β,5,16α,20α-tetrol 3-Mesylate 16,20-Diacetate (Gb).—A mixture of 156 mg. of 5α-pregnanetetrol 16,20-diacetate (Ga), 0.5 mg. of methanesulfonyl chloride, and 5 ml. of pyridine was stored at room temperature for 2 hr. It was then poured into water and extracted with methylene chloride. The organic extract was washed successively with dilute acid and base and water and the solvent removed to give 210 mg. of product. Trituration with ether and filtration afforded 5α-pregnane-3β,5,16α,20α-tetrol 3-mesylate 16,20-diacetate (Gb), m.p. 157–158°; $[\alpha]^{25}D$ −49.7°; ν_{max}^{KBr} 3600, 3535, 1738 (sh), 1729, 1712*, 1264, 1252, 1175, 1040, 926, 868, 821 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{42}O_8S$: C, 60.67; H, 8.23. Found: C, 60.27; H, 8.32.

Δ^5-Pregnene-3α,16α,20α-triol (Ha).—A solution of crude mesylate Gb prepared from 40 mg. of tetrol diacetate Ga, 5 ml. of diethylaniline, 5 ml. of acetyl chloride, and 5 ml. of chloroform was refluxed for 5 hr. The solution was then concentrated *in vacuo* and diluted with ether. The ether solution was washed with dilute acid, dilute base, and water, dried, and the solvent evaporated to give an oily product. Chromatography on acid-washed alumina and elution with 3% ethyl acetate in benzene gave 20 mg. of oil. The infrared spectrum of the oil was identical with that of Δ^5-pregnene-3α,16α,20α-triol triacetate (Hb) previously prepared from natural product. Saponification of the triacetate Hb with methanolic potassium hydroxide yielded 12 mg. of Δ^5-pregnene-3α,16α,20α-triol (Ha), m.p. 230–232°; $[\alpha]^{27}D$ −84.9° (dioxane). The infrared spectrum in potassium bromide dispersion was identical with that of the natural product and the melting point of Ha was not depressed, 230–230.5°, on admixture with the natural triol, m.p. 230–231°.

16α-Benzyloxy-Δ^5-pregnene-3β,20-diol (J).—A solution of 5 g. of 3β-acetoxy-16α-benzyloxy-Δ^5-pregnen-20-one (I)[7] in 750 ml. of ether was added during 1 hr. to an ether solution containing a large excess of lithium aluminum hydride and the reaction mixture was heated at reflux for another hour. The excess reducing agent was destroyed and the reaction product was extracted thoroughly with ethyl acetate. The organic phase was washed successively with 10% sulfuric acid, water, 5% sodium bicarbonate, and finally with water to neutrality. The solution was dried and the solvent removed under reduced pressure. The crystalline residue weighed 5 g. after triturations with small volumes of carbon tetrachloride. Fractional crystallizations of a portion of the residue from acetone gave 16α-benzyloxy-Δ^5-pregnene-3β,20β-diol (J), m.p. 162–166°; ν_{max}^{KBr} 3340, 1667, 1094, 1048, 970, 875, 740, 696 cm.$^{-1}$.

Anal. Calcd. for $C_{28}H_{40}O_3 \cdot {}^1/_2H_2O$: C, 77.56; H, 9.72. Found: C, 77.77; H, 9.57.

Acetylation of 16α-benzyloxy-Δ^5-pregnene-3β,20β-diol with acetic anhydride in pyridine in the usual manner gave the diacetate, m.p. 112.5–114°; $\nu_{max}^{CS_2,\ CCl_4}$ 1734, 1667, 1243, 1071, 1028, 968, 732, 696 cm.$^{-1}$.

Anal. Calcd. for $C_{32}H_{44}O_5$: C, 75.55; H, 8.79. Found: C, 75.37; H, 8.53.

Hydrogenolysis of 16α-benzyloxy-Δ^5-pregnene-3β,20β-diol with Raney nickel in ethanol gave Δ^5-pregnenetriol-3β,16α,20β (D), the infrared spectrum of which was identical with an authentic sample.

Δ^5-Pregnene-3,16α,20-triols.—To an ice-cold solution of 3.96 g. of 16α-benzyloxy-Δ^5-pregnene-3β,20δ-diol (J) in 500 ml. of

acetone (freshly distilled from potassium permanganate) under a nitrogen atmosphere was added 5.7 ml. of chromic acid solution[11] (26.72 g. of chromium trioxide in 23 ml. of concentrated sulfuric acid diluted to 100 ml. with water) over 1 min. with stirring. After an additional 3 min. of stirring, the mixture was poured into 10 l. of ice–water and filtered. The solid product was dried in a vacuum desiccator overnight, dissolved in methylene chloride, filtered, and evaporated to dryness in the cold to yield 3.18 g. of white solid. The infrared spectrum of this material in carbon disulfide solution showed carbonyl absorption at 1709 cm.$^{-1}$ (20-ketone) and 1718 cm.$^{-1}$ (sh) (3-ketone) as well as absorption bands consistent with the presence of a benzyl ether grouping and weak hydroxyl absorption. The carbonyl absorptions of another sample in a potassium bromide pellet were at 1711 and 1693 cm.$^{-1}$. The remainder of the product was carried to the next step without additional purification by solution in 500 ml. of redistilled 95% ethanol and shaking with hydrogen in the presence of several grams of W-2 Raney nickel at room temperature and atmospheric pressure. The reaction mixture was filtered and solvent removed. The product was triturated with a small volume of ether. The ether-insoluble material (1.54 g.) had a strong carbonyl absorption band at 1706 cm.$^{-1}$ in carbon disulfide solution and was presumably a mixture of 3α + β,16α-dihydroxy-Δ^5-pregnen-20-one (L). Since the desired isomeric Δ^5-pregnene-3,16α,20-triols could be separated readily, no attempts at fractionation of the 3α- and 3β-hydroxy epimers of L were made.

Crude L (1.5 g.) was dissolved in a minimum amount of freshly distilled tetrahydrofuran and added to an excess of lithium aluminum hydride in ether. The reaction mixture was allowed to stand at room temperature for 40 hr. and then worked up in the usual fashion. The solid product was triturated with a small volume of ether and the residual solid (1.37 g.) was treated with 6 g. of digitonin in 100 ml. of 90% ethanol. This was allowed to stand at room temperature overnight and extracted with ethyl acetate. The solvent was removed and 872 mg. of crude "α-fraction" was obtained. The insoluble digitonide was dissolved in 35 ml. of pyridine, diluted with 2 l. of ethyl acetate, and filtered. The filtrate was washed with 10% hydrochloric acid, water, sodium bicarbonate solution, and finally with water, dried over anhydrous sodium sulfate, and distilled to give 500 mg. of crude "β-fraction."

The "β-fraction" was chromatographed on 175 g. of silica gel containing 70 ml. of ethanol on the stationary phase. Elution with 6% ethanol in methylene chloride yielded 110 mg. of Δ^5-pregnene-3β,16α,20α-triol (Ea) which melted at 243.5–245.5° after recrystallization from methanol. Further elution with 6% and 8% ethanol in methylene chloride gave 270 mg. of Δ^5-pregnene-3β,16α,20β-triol (D), m.p. 268, 280–287°; the infrared spectrum in potassium bromide dispersion was identical with that of D obtained in the previous synthesis. The sample was free of impurity as judged by thin layer chromatography on silica gel G with ethyl acetate.

The "α-fraction" was chromatographed on 150 g. of silica gel and 60 ml. of ethanol. Elution with 4% ethanol in methylene chloride gave 83 mg. of **Δ^5-pregnene-3α,16α,20α-triol (Ha)** which melted at 229.5–230° after recrystallization from ethanol. The infrared spectrum in a potassium bromide dispersion was identical in all respects with that of the triol from natural sources. Acetylation with acetic anhydride and pyridine yielded the triacetate Hb, m.p. 136–137°, after recrystallization from methanol. The triacetate prepared from the urinary triol had m.p. 133–135°; m.m.p. was 137–139°. The infrared spectra of the two samples were identical in all respects in carbon disulfide solution.

Elution with 5% ethanol in methylene chloride gave 355 mg. of fractions containing Δ^5-pregnene-3α,16α,20β-triol (M), m.p. 224–225°, after recrystallization from methanol; $[\alpha]^{27}D$ −94.3° (ethanol); ν_{max}^{KBr} 3530 (sh), 3460, 3390, 1663, 1086, 1064, 1049, 1020, 881, 867, 804 cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.23; H, 10.15.

The **triacetate** was prepared by the action of acetic anhydride in pyridine and melted at 137.5–140° after several recrystallizations from methanol; $[\alpha]^{26}D$ −81.6°; $\nu_{max}^{CS_2, CCl_4}$ 1738, 1667, 1239, 1158–1151 (sh), 1046, 1035, 1020 cm.$^{-1}$. Further elution with 5% ethanol in methylene chloride gave small amounts of Δ^5-pregnene-3β,16α,20β-triol (D) identical with that isolated from the β-fraction.

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. We also thank Dr. A. Bowers of Syntex Company, Mexico City, for the gift of a generous supply of starting material.

Secondary Hydrogen Isotope Effects on Deoxymercuration[1]

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Secondary isotope effects on the rate of acid-induced deoxymercuration of 2-phenyl-2-methoxyethylmercuric iodide have been studied. Deuterium substitution at the 2-carbon gives k_H/k_D, 1.12. Deuterium substitution at the 1-carbon gives k_H/k_D, 0.91. The latter is one of a small number of inverse isotope effects that have been observed. From these and results previously presented it is concluded that the deoxymercuration transition state has a partial positive charge on the carbon from which oxygen is leaving and also has some olefin–mercuric iodide complex character.

In a previous paper[2] the acid-induced deoxymercuration rate for $CH_3OCD_2CD_2HgI$ (II) was compared with that for $CH_3OCH_2CH_2HgI$ (I). They were very similar (k_H/k_D = 1.06), and from this it was concluded that the transition state must resemble the protonated starting state, IX. More recent studies of relative reactivities[3] indicate that this view was oversimplified. It was shown that either the carbonium ion, VII, or the olefin mercuric iodide complex, VIII, or both, must contribute to the transition state electronic structure. The present paper describes further work on secondary hydrogen isotope effects, involving isotopic substitution in $C_6H_5CH(OCH_3)CH_2HgI$ (III) designed to shed more light on the electronic structure of the transition state and to explain the apparent discrepancy between the results obtained from the secondary isotope effect and those obtained from the effect of substitution.

Results

Well established synthetic methods were used to prepare III, $C_6H_5CD(OCH_3)CH_2HgI$ (IV), $C_6H_5CH(OCH_3)CD_2HgI$ (V), and $C_6H_5CD(OCH_3)CD_2HgI$ (VI). Acid-induced deoxymercuration rates were

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(2) M. M. Kreevoy and L. T. Ditsch, *J. Am. Chem. Soc.*, **82**, 6127 (1960).

(3) L. L. Schaleger, M. A. Turner, T. C. Chamberlin, and M. M. Kreevoy, *J. Org. Chem.*, **27**, 3421 (1962).