no evidence of any alkali-insoluble material. After acidification with concentrated hydrochloric acid and cooling, the solution was extracted with two portions of diethyl ether. The ether extract was then dried over anhydrous sodium sulfate, filtered, and the ether removed by distillation. The resulting residue, on distillation, yielded 14.7 g. of an acid (corresponding to II) boiling at 145–153° (2–3 mm.), $n^{20}\text{D}$ 1.4385.

Anal. Calcd. for $C_{12}H_{20}O_2$: neut. equiv., 196. Found: neut. equiv., 205.3.

This acid was found to be soluble in aqueous sodium bicarbonate, giving a solution which reduced potassium permanganate. It rapidly absorbed bromine with the evolution of hydrogen bromide and the formation of an oily derivative.

The ethyl ester prepared from this unsaturated 12-carbon acid had the properties: b. p. 131° (5 mm.); $n^{25}\text{D}$ 1.4642; d^{25}_4 0.9365.

Anal. Calcd. for $C_{14}H_{24}O_2$: C, 74.96; H, 10.78; sap. equiv., 224.3; M_R, 65.87 (from atomic refractivity constants given in Lange, "Handbook of Chemistry," 3rd Edition, 1939, p. 855). Found: C, 75.22, 75.59; H, 10.52, 10.97; sap. equiv., 223.9; M_R, 66.12 (R. Lorentz and H. Lorenz formula).

Hydrogenation of the acid in the presence of Raney nickel catalyst at 125° and 120 atm. hydrogen pressure for three hours yielded cyclohexanecaproic acid, from which was obtained a solid *p*-bromophenacyl ester identical with the *p*-bromophenacyl ester of an authentic sample of cyclohexanecaproic acid.[5]

Action of Potassium Hydroxide on Cyclohexanone (300°—eighteen hours).—A stainless steel bomb was charged with 125 g. of cyclohexanone and 250 g. of potassium hydroxide, the air was flushed out with nitrogen, and the mixture heated with agitation at 300° for eighteen hours. At the end of this time, the mixture was cooled and the grayish solid which separated was removed and discarded. The remaining oily product was extracted with water and the aqueous extract acidified with hydrochloric acid to yield an oily, water-insoluble acid. This acid on distillation gave a fraction amounting to 25 g. boiling at 160–180° (10 mm.). Redistillation of this product yielded cyclohexanebutyric acid boiling at 136–139° (4 mm.), m. p. 26.5–28.5°.

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.65; neut. equiv., 170.2. Found: C, 70.52; H, 10.34; neut. equiv., 178.5.

The *p*-bromophenacyl ester of this acid was found to melt at 76–77° and showed no depression in melting point when mixed with a sample of the *p*-bromophenacyl ester of an authentic sample of cyclohexanebutyric acid.

2-Allylcyclohexanone.—This was prepared by the method of Cornubert[6] using allyl chloride instead of allyl iodide, b. p. 80–87° (13–15 mm.), $n^{25}\text{D}$ 1.4662 to 1.4669.[6,7]

Action of Potassium Hydroxide on 2-Allylcyclohexanone.—In an atmosphere of nitrogen 20 g. of 2-allylcyclohexanone was added with stirring to 75 g. of potassium hydroxide at 240–250°. After twenty minutes the mixture was cooled, and the upper layer of yellowish solid was separated mechanically from the lower layer of potassium hydroxide and dissolved in water. Neutral products were removed from the aqueous layer by extraction with ether, and the aqueous layer was then acidified with the formation of a yellow oil. After separation and drying of the oil, it yielded, upon distillation, two fractions, the first (2 g.), boiling at 33–34° (5 mm.), and the second (4 g.) boiling at 157–170° (5 mm.).

The first fraction was demonstrated to be propionic acid: neut. equiv. Calcd. for $C_3H_6O_2$: 74.1. Found: 75.5, 75.6.

The *p*-bromophenacyl ester, m. p. 57.5–59°, showed no depression in melting point when mixed with the ester of an authentic specimen of propionic acid. The *p*-bromophenacyl ester of acrylic acid melted at 67.5–68° and mixtures of this ester with that of the ester in question melted at 53.5–56.5°.

The second, high-boiling fraction was shown to yield cyclohexanecaproic acid when hydrogenated.

Summary

1. Treatment of cyclohexanone with molten potassium hydroxide at 250–280° yields a 12-carbon unsaturated acid, and at 300° cyclohexanebutyric acid.

2. 2-Allylcyclohexanone is converted by molten potassium hydroxide at 250° to the same 12-carbon unsaturated acid; the allyl side chain appears as propionic acid.

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(5) Supplied through the courtesy of the Dow Chemical Company. See also Hiers and Adams, THIS JOURNAL, **48**, 2385 (1926).

(6) Cornubert and Maurel, *Bull. soc. chim.*, **49**, 1498 (1931).

(7) Cope, Hoyle and Heyl, THIS JOURNAL, **63**, 1843 (1941).

WILMINGTON, DELAWARE RECEIVED DECEMBER 19, 1947

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

p-Toluenesulfonates of 20-Hydroxypregnanes

BY LEWIS HASTINGS SARETT

The conversion of pregnane-3(α),20-diol 3-acetate 20-tosylate to Δ^{17}-pregnene-3(α)-ol by treatment with pyridine has been described.[1] The present work reports some additional applications of this useful procedure for the preparation of substituted ethylenes from secondary alcohols.[2]

Pregnane-3(α),12(α),20-triol 3,12-diacetate[3] (I), was prepared by catalytic reduction of pregnane-3(α),12(α)-diol-20-one diacetate.[4] With *p*-toluenesulfonyl chloride I yielded a diacetate tosylate, which on refluxing with collidine gave a crystalline mixture of Δ^{17}- and Δ^{20}-pregnene-3(α),12(α)-diol diacetate (IIa and IIb). From the mixture obtained by hydroxylation of II, a readily crystalline 3(α),12(α),17,20-tetrol (III) could be separated. Periodate cleavage then yielded *etio*-cholane-3(α),12(α)-diol-17-one, isolated as the diacetate (IV).[5] Oxidation of the amorphous glycol mixture which remained gave some *etio*-desoxycholic acid (V).

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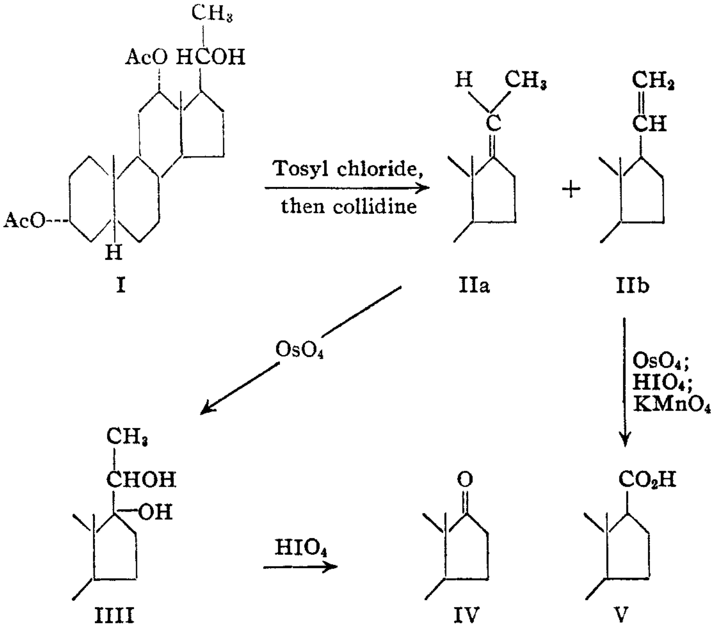
(1) Hirschmann, *J. Biol. Chem.*, **140**, 797 (1941).

(2) See, for example, *inter alia*, Ferns and Lapworth, *J. Chem. Soc.*, **101**, 273 (1912); Barnett and Reichstein, *Helv. Chim. Acta*, **21**, 426 (1938); v. Euw and Reichstein, *Helv. Chim. Acta*, **29**, 654 (1946).

(3) The configuration of the C-12 hydroxyl group in desoxycholic acid is taken as α, in accordance with the proofs of Gallagher and Long, *J. Biol. Chem.*, **162**, 495 (1946), and of Sorkin and Reichstein, *Helv. Chim. Acta*, **29**, 1218 (1946).

(4) Hoehn and Mason, THIS JOURNAL, **60**, 1493 (1938).

(5) We are indebted to Dr. L. F. Fieser of Harvard University for an authentic sample of this compound for comparison.

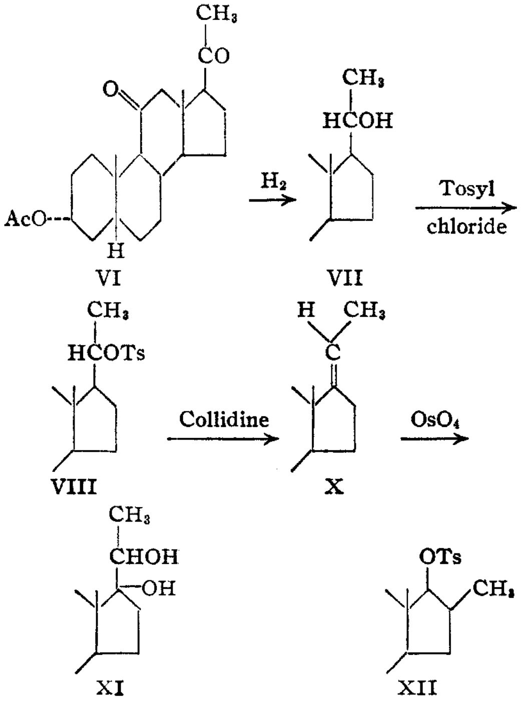


I IIa IIb IIII IV V

A more thorough investigation of the 11-keto series was facilitated by the ready crystallizability of the intermediates; in addition the reactions appeared to proceed more smoothly. The reduction of pregnane-3(α)-ol-11,20-dione acetate (VI) afforded one of the possible pregnane-3(α),20-diol-11-one 3-acetate epimers (VII) in an 85% yield. The other was present only to the extent of a few per cent. With *p*-toluenesulfonyl chloride VII gave the acetate tosylate VIII, which occurred in several crystalline modifications.

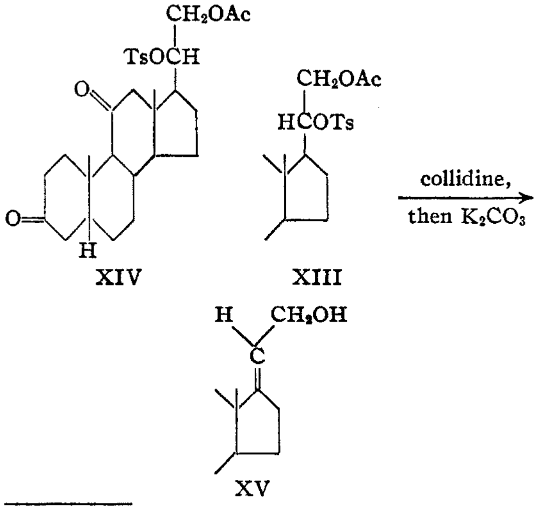
After treatment of the tosylate with collidine, a crystalline mixture of the Δ^{17} and Δ^{20} derivatives was obtained in which the Δ^{17} isomer (or isomers) preponderated. Ozonolysis of this mixture of acetates gave *etio*-cholane-3(α)-ol-11,17-dione acetate together with some 3(α)-acetoxy-11-keto-*etio*-cholanic acid. A pure Δ^{17}-pregnene-3(α)-ol-11-one (X) could be isolated by saponification of the mixture of acetates and repeated recrystallization of the product. Hydroxylation of X gave a triolone (XI), which with chromic acid was oxidized to *etio*-cholane-3,11,17-trione.

An additional product of the reaction of pregnane-3(α),20-diol-11-one 3-acetate 20-tosylate (VIII) with collidine was an isomeric acetate tosylate. Reductive hydrolysis of this material with sodium amalgam gave a ketodihydroxy derivative isomeric with pregnanediolones. Evidently a fundamental rearrangement occurred, probably to a D-homo derivative such as XII.



VI VII VIII X XI XII

The applicability of the tosylate-collidine method for introducing the 17,20 double bond was tested also in the 21-acetoxy series. Partial acetylation of pregnane-20(β),21-diol-3,11-dione[6] and the epimeric glycol[6] gave the respective 21-monoacetates from which the corresponding acetate tosylates (XIII and XIV) were prepared. Only one of these mixed esters—that derived from the arbitrarily designated 20(β) series—reacted readily with collidine at the boiling point. It gave a non-crystalline acetate which was very easily hydrolyzed to a derivative of the empirical formula $C_{21}H_{30}O_3$; m. p. 128°; $[\alpha]^{25}D$ +63°. This substance upon hydroxylation with osmium tetroxide, followed by acetylation of the resulting triol, gave the same pregnane-17(α),20,21-triol-3,11-dione diacetate previously obtained by hydroxylation of a Δ^{17}-pregnene-21-ol-3,11-dione.



XIV XIII XV

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[6] Sarett, THIS JOURNAL, 68, 2478 (1946).

This latter compound melted erratically at about 150° and had [α]D +56° but was not obtained analytically pure. Both the 128° and the 150° pregnenes gave amorphous acetates. An attempt to repeat the preparation of the higher melting pregnene gave only the lower melting product. Although, unfortunately, none of the former has been available for direct comparison, the data suggest that the two Δ^{17}-pregnene-21-ol-3,11-dione compounds are merely crystal modifications.

Experimental[7]

Δ^{17}- and Δ^{20}-Pregnene-3(α),12(α)-diol Diacetate (IIa and IIb).—A solution of 1.02 g. of pregnane-3(α),12(α)-diol-20-one diacetate in 50 cc. of acetic acid was shaken with 0.5 g. of platinum oxide under hydrogen until the theoretical quantity of hydrogen was taken up. The solution was then filtered, concentrated *in vacuo* and dissolved in ether. The ethereal solution was washed with aqueous carbonate, then with water, and concentrated to dryness. A sample of the crude pregnane-3(α),12(α),20-triol 3,12-diacetate was chromatographed but could not be obtained crystalline. The diacetate (1.02 g.) was then dissolved in 2 cc. of pyridine and treated with 850 mg. of *p*-toluenesulfonyl chloride. After standing at room temperature for sixteen hours, the solution was diluted with water and extracted with ether. The ethereal solution was washed with aqueous carbonate, dilute hydrochloric acid and with water and concentrated to dryness. The amorphous diacetate tosylate weighed 1.262 g. It was next refluxed with 20 cc. of collidine for twenty-five minutes, the solution cooled, diluted with ether, washed with dilute sulfuric acid and with water. The ethereal solution was concentrated to dryness and the residue was crystallized twice from methanol. The product (580 mg.) consisted of a mixture of Δ^{17}- and Δ^{20}-pregnene-3(α),12(α)-diol diacetate, m. p. 155–159°.

Anal. Calcd. for $C_{25}H_{38}O_4$: C, 74.59; H, 9.52. Found: C, 74.74; H, 9.78.

Hydroxylation of Δ^{17}- and Δ^{20}-Pregnene-3(α),12(α)-diol Diacetate.—A solution of 560 mg. of pregnene mixture (m. p. 155–159°) in 10 cc. of absolute ether was treated with 500 mg. of osmium tetroxide and 350 mg. of dry pyridine. After ten minutes the ether was removed *in vacuo*, the residue dissolved in 30 cc. of alcohol and the solution treated with 1.0 g. of sodium sulfite dissolved in 20 cc. of water. The mixture was refluxed for three hours and then filtered. To the filtrate was added 10 cc. of 1 *N* aqueous potassium hydroxide and the whole refluxed an additional half hour. The alcohol was removed *in vacuo* and the residual suspension extracted with chloroform. Concentration of the washed chloroform solution, followed by crystallization of the residue from acetone gave 80 mg. of a crude pregnane-3(α),12(α),17,20-tetrol (III), m. p. 253–259°. This material was not purified further but was suspended in 5 cc. of methanol to which was added 1.11 cc. of water containing 55 mg. of periodic acid. The suspension was swirled from time to time and after forty-five minutes the tetrol had dissolved. The solution was permitted to stand for an additional half hour and then concentrated to a small volume *in vacuo*. The aqueous suspension was extracted with ethyl acetate. Concentration of the ethyl acetate to a small volume gave a crystalline precipitate consisting of starting material. This was removed and the material in the mother liquors (67 mg.) heated in the steam-bath with a small volume of pyridine and acetic anhydride for thirty minutes. The acetylation mixture was then diluted with water and worked up in the usual manner. Crystallization of the product from ether–petroleum ether gave 45 mg. of *etio*-cholane-3(α),12(α)-diol-17-one diacetate, m. p. and mixed m. p. 157–158°.

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.73; H, 8.78. Found: C, 70.76; H, 8.89.

The mother liquors of the tetrol III were concentrated to dryness *in vacuo* and weighed 320 mg. They were similarly oxidized with periodic acid and then acetylated with pyridine–acetic anhydride as before. The crude diacetoxy-*etio*-cholanic aldehyde was then dissolved in 7 cc. of acetone and treated with 2.5 cc. of 5% aqueous potassium permanganate. After standing at room temperature for forty-five minutes, the mixture was concentrated to a small volume in a stream of air at 15°, then acidified with dilute sulfurous acid and extracted with ether. The ethereal solution was extracted with 1 *N* aqueous potassium hydroxide solution and the latter was then heated on the steam-bath for one hour. The alkaline solution was cooled, acidified with dilute hydrochloric acid and the precipitate washed and dried. Crystallization of the amorphous powder (60 mg.) from acetone gave 46 mg. of *etio*-desoxycholic acid, m. p. and mixed melting point, 290–294°.

Pregnane-3(α),20-diol-11-one 3-Acetate (VII).—A solution of 6.15 g. of pregnane-3(α)-ol-11,20-dione acetate in 125 cc. of acetic acid was shaken under hydrogen with 1.0 g. of platinum oxide. After six hours the theoretical amount of hydrogen had been taken up and the reaction had stopped. The solution was filtered and a large volume of water was added to the filtrate. The crystalline precipitate was washed with water and dried. It weighed 6.10 g. and melted at 182–199°. After recrystallization from benzene–petroleum ether and from dilute acetone, the product melted at 205–206°: $[\alpha]^{25}D$ +66°; yield, 83%.

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.65. Found: C, 73.07; H, 9.98.

A sample of the combined mother liquors of the monoacetate was heated with pyridine–acetic anhydride and then chromatographed over alumina. The crystalline fractions melting above 200° were combined and after several recrystallizations from alcohol and from ether pure pregnane-3(α),20(*epi*)-diol-11-one diacetate, m. p. 234–235°, was obtained. The yield was 1.5% based on the 20-ketone (VI).

Anal. Calcd. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.95; H, 9.24.

Pregnane-3(α),20-diol-11-one Diacetate.—A sample of pregnane-3(α),20-diol-11-one 3-acetate (m. p. 205–206°) was heated with acetic anhydride-pyridine on the steam-bath for fifteen minutes. The addition of water gave the crystalline diacetate, m. p. 160.5–161.0°; $[\alpha]^{25}D$ +81°.

Anal. Calcd. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.88; H, 9.18.

Pregnane-3(α),20-diol-one-11.—A sample of pregnane-3(α),20-diol-11-one 3-acetate (m. p. 205–206°) was refluxed for fifteen minutes with 1 *N* methanolic potassium hydroxide. The crystalline diol was precipitated with water and recrystallized from acetone. It melted at 236–238°.

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.47; H, 10.20.

Pregnane-3(α),20(*epi*)-diol-11-one.—A sample of pregnane-3(α),20(*epi*)-diol-11-one diacetate (m. p. 234–235°) was saponified similarly. The diol melted at 219°.

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.29; H, 10.29.

Pregnane-3(α),20-diol-11-one 3-Acetate 20-Tosylate (VIII).—To a solution of 4.75 g. of pregnane-3(α),20-diol-11-one 3-acetate in 9 cc. of pyridine was added 4.0 g. of recrystallized *p*-toluenesulfonyl chloride. The solution was permitted to stand at room temperature overnight and was then treated with sufficient water to destroy the excess acid chloride. After further dilution with water, extraction with chloroform, and successive washings with dilute hydrochloric acid, dilute sodium carbonate and water, the solution was concentrated to

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[7] All rotations were taken in acetone; c∼1.0. All melting points are corrected.

dryness *in vacuo*. Crystallization from ether-petroleum ether gave 6.80 g. of solvated product, melting at 100°, resolidifying and melting again at 141–143°. Recrystallization from dilute methanol gave a non-solvated product, m. p. 144–145°; $[\alpha]^{25}D$ +57.5°.

Anal. Calcd. for $C_{30}H_{42}O_6S$: C, 67.89; H 7.97. Found: C, 67.92; H, 7.86.

After standing at room temperature for a month, the sample melted at 173°. In subsequent preparations only this higher melting form was obtained.

Δ^{17}-Pregnene-3(α)-ol-11-one (X).—A solution of 6.50 g. of pregnane-3(α),20-diol-11-one 3-acetate 20-tosylate in 50 cc. of redistilled collidine was refluxed for twenty-five minutes. The solution was cooled, diluted with petroleum ether, washed with dilute hydrochloric acid and with water and concentrated to a small volume. Crystals (200 mg.) of the isomeric acetate tosylate XII (?) separated and were filtered and set aside. The mother liquors were concentrated to dryness and the residue crystallized from methanol at 0°. The crude pregnenes weighed 3.61 g. and melted at 60–82°. The mixture was refluxed for thirty minutes with 30 cc. of 1.1 *N* methanolic potassium hydroxide, then diluted with water and permitted to crystallize. After a number of recrystallizations from methanol 1.4 g. of pure Δ^{17}-pregnene-3(α)-ol-11-one was obtained. It melted at 191–192° and had $[\alpha]^{25}D$ +55°. Refluxing the tosylate with 2 *N* methanolic potassium hydroxide gave smaller yields of this unsaturated compound.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.68; H, 10.12. Found: C, 79.57; H, 10.10.

A sample was converted to the acetate (IX) with pyridine–acetic anhydride. After recrystallization from methanol it melted at 125°.

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.07; H, 9.56. Found: C, 77.03; H, 9.54.

Isomeric Tosylate (XII) (?).—The 200 mg. of crystals which separated from the collidine reaction product described above was recrystallized from methanol and melted at 197–200°, $[\alpha]^{25}D$ +46.5°. It was almost entirely stable to further treatment with collidine.

Anal. Calcd. for $C_{30}H_{42}O_6S$: C, 68.81; H, 8.24. Found: C, 68.70; H, 8.36.

Isomeric Diol from XII (?).—A suspension of 300 mg. of the tosylate XII (?) m. p. 197–200°, in 12 cc. of methanol and 3 cc. of water was stirred with 25 g. of 4% sodium amalgam overnight. The suspension was decanted from mercury and filtered. Recrystallization from a large volume of methanol gave a product which melted at 294–297°, and was isomeric with pregnanediolone.

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.70; H, 10.25.

Similar reduction of a sample of VIII (m. p. 173°) gave pregnane-3(α),20-diol-11-one, m. p. and mixed m. p. 236–238°.

Diacetate of Isomeric Diol.—A sample of isomeric diol (m. p. 294–297°) was heated with pyridine–acetic anhydride on the steam-bath for one hour. The addition of water gave crystals, m. p. 183°.

Anal. Calcd. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.99; H, 9.02.

Ozonolysis of Crude Δ^{17}-Pregnene-3(α)-ol-11-one Acetate (IX).—Twenty-five grams of crude pregnene-17-ol-3(α)-one-11 acetate (an amorphous product direct from the detosylation with collidine was used) was ozonized and the product treated according to a previously described procedure.[8] A total of 8.43 g. of acidic material was obtained which was saponified and gave upon crystallization from ethyl acetate 2.13 g. of 3(α)-hydroxy-11-keto-*etio*-cholanic acid, m. p. and mixed m. p. 296–298°. The neutral fraction (16.5 g.) gave 10.2 g. of ketones from which 7.2 g. of pure *etio*-cholanol-3(α)-11,17-dione was obtained.

Pregnane-3(α),17,20-triol-11-one (XI).—A sample (100 mg.) of Δ^{17}-pregnene-3(α)-ol-11-one (X) in 20 cc. of absolute ether was treated with 100 mg. of osmium tetroxide and two drops of pyridine. After one hour the mixture was concentrated to dryness *in vacuo*, dissolved in 5 cc. of alcohol and treated with a solution of 300 mg. of sodium sulfite in 5 cc. of water. The mixture was refluxed for two hours, filtered, concentrated to a small volume, diluted with water and extracted with chloroform. The chloroform extract was concentrated to dryness and the residue crystallized from ether. The triol melted at 189–191°. A second crystalline form, m. p. 210–212°, was obtained by crystallization from benzene. The compound showed a strong tendency to separate as a gel from non-polar solvents and could not be obtained free of solvents. Prolonged heating appeared merely to lead to decomposition.

The diacetate was prepared with pyridine–acetic anhydride in the usual manner. It melted at 227–228°, $[\alpha]^{25}D$ +24°.

Anal. Calcd. for $C_{25}H_{38}O_6$: C, 69.10; H, 8.82. Found: C, 69.06; H, 8.65.

***etio*-Cholane-3,11,17-trione from XI.**—A solution of 450 mg. of pregnane-3(α),17,20-triol-11-one (XI) (purified through the diacetate) in 5.5 cc. of 90% acetic acid was treated with 10 cc. of 90% acetic acid containing 500 mg. of chromic acid. After fifty minutes at room temperature, the solution was diluted with water and extracted twice with chloroform. The washed chloroform solution was concentrated to dryness and the residue was chromatographed over 10 g. of acid washed alumina. The fractions from 9:1 ether–chloroform to 1:9 ether–chloroform contained the *etio*-cholanetrione, m. p. and mixed m. p. 134–135°. Subsequent fractions gave a product, m. p. 177–182°, the amount of which was too small to permit complete purification.

Pregnane-20(α),21-diol-3,11-dione 21-Acetate 20-Tosylate (XIV).—To a solution of 378 mg. of pregnane-20(α),21-diol-3,11-dione (m. p. 182–183°) in 1.05 cc. of absolute dioxane was added 576 mg. of a dioxane solution containing 161 mg. of acetic anhydride and 138 mg. of pyridine. After standing at room temperature for sixty hours, the solution was evaporated *in vacuo* and the residue chromatographed. Ether–chloroform mixtures eluted crystals of 21-monoacetate which after several recrystallizations from ether melted at 166–170° and weighed 97 mg. A total of 186 mg. of this partially purified monoacetate was treated with 125 mg. of tosyl chloride in 0.2 cc. of pyridine. After standing at room temperature overnight, the solution was diluted with water and taken up in ether. The washed ethereal solution was concentrated to dryness. The amorphous tosylate (254 mg.) was sparingly soluble in dry ether.

Pregnane-20(β),21-diol-3,11-dione 21-Acetate 20-Tosylate (XIII).—A sample (362 mg.) of pregnanediol-20(α),21-dione-3,11 (m. p. 168°) was similarly converted to the monoacetate. The crude product was chromatographed and gave 227 mg. of crude monoacetate together with some diacetate and starting material. The amorphous monoacetate with tosyl chloride gave 212 mg. of tosylate, m. p. 176–180°. After two recrystallizations from acetone a sample melted at 193–194°.

Anal. Calcd. for $C_{30}H_{40}O_7S$: C, 66.15; H, 7.40. Found: C, 66.26; H, 7.23.

A sample (250 mg.) of the 20(α)-tosylate (XIV) was refluxed for twenty-five minutes with collidine. Only 20% of the theoretical amount of collidine *p*-toluenesulfonate was formed. Chromatography of the product gave a small amount of oily reaction product, the remainder consisting of starting material or a rearrangement product thereof. Saponification of the detosylated material gave a non-crystalline product.

Δ^{17}-Pregnene-21-ol-3,11-dione (XV).—A solution of 166 mg. of crystalline 20(β)-tosylate (XIII) in 4 cc. of collidine was refluxed for twenty-five minutes. The solution was cooled and diluted with petroleum ether; 86 mg. (82%) of collidine *p*-toluenesulfonate separated. The solution was then diluted with ether, washed with dilute hydrochloric acid and concentrated to dryness, The residue (130 mg.) was chromatographed over 3.5 g. of alumina. The eluates obtained with 10-cc. portions of 3:7, 2:8 and 1:9 petroleum ether–ether, with 10 cc. of ether and with 10 cc. of 9:1 ether–chloroform were combined and gave 69 mg. of amorphous Δ^{17}-pregnene-21-ol-3,11-dione acetate. This was dissolved in 3.5 cc. of methanol and treated with a solution of 2 cc. of water containing 60 mg. of potassium carbonate and 60 mg. of potassium bicarbonate. After two hours at room temperature, the solution was acidified with 2 drops of acetic acid and concentrated to a small volume *in vacuo*. The oily precipitate was dissolved in chloroform, washed and the solution concentrated to dryness. The residue (54 mg.) was chromatographed over 2 g. of alumina. The fraction eluted with 1:1 ether–chloroform and mixtures with an increasing proportion of chloroform could be crystallized from a small volume of ether. The combined crystals weighed 30 mg. and melted at 127.5–128°. Recrystallization from ether raised the melting point to 128–128.5°.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.33; H, 9.15. Found: C, 76.63; H, 9.38.

A 5-mg. sample was permitted to stand at room temperature with acetic anhydride-pyridine for two hours. The product was an oil, from which the original alcohol could be obtained by saponification.

Δ^{17}-Pregnene-21-ol-3,11-dione from Δ^{17}-Pregnene-3(α),21-diol-11-one 21-Hemisuccinate.—A sample of 159 mg. of the 21-hemisuccinate of Δ^{17}-pregnene-3(α),21-diol-11-one was oxidized and then saponified as previously described[8]. Crystallization of the product gave 70 mg. of Δ^{17}-pregnene-21-ol-3,11-dione, m. p. 128°. It did not depress the melting point of XV.

Pregnene-17(α),20,21-triol-3,11-dione Diacetate from XV.—A sample (82 mg.) of Δ^{17}-pregnene-21-ol-3,11-dione, (XV), m. p. 128°, was treated with osmium tetroxide, hydrolyzed and acetylated as previously described.[8] The crystalline diacetate weighed 72 mg., melted at 212–213°, and had $[\alpha]^{25}D$ +95°. A mixed melting point with the original sample showed no depression.

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Summary

The application of the *p*-toluenesulfonate-tertiary amine reaction to certain 20-hydroxypregnenes is described. In the case of pregnane-20(β),21-diol-3,11-dione 21-acetate 20-tosylate, Δ^{17}-pregnene-21-ol-3,11-dione was obtained.

(8) Sarett, *J. Biol. Chem.*, **162**, 601 (1946).

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[Contribution from the Noyes Chemical Laboratory, University of Illinois]

The Preparation of 2-Alkylbutadienes[1]

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The observation[4] that emulsion copolymers of isoprene with styrene contain more diene units joined in the 1,4-manner than do the corresponding butadiene–styrene copolymers suggested the importance of investigating other 2-alkylbutadienes. The literature on the synthesis of this class of dienes is very limited. 2-Ethyl-1,3-butadiene has been reported as a product of dehydrohalogenation of 3-methyl-3,4-dibromopentane,[5] but no evidence of structure was presented. 2-Isopropyl-1,3-butadiene has been prepared by von Braun and Keller[6] by the Hofmann degradation of 2-isopropyl-1,4-diaminobutane. While this method gave a well-characterized product, the starting materials needed for the synthesis are not readily available. This communication describes the synthesis of 2-isopropyl-1,3-butadiene[7] by various routes, one of which appears to be a good general method for making 2-alkylbutadienes.

2-Isopropylbutadiene was first obtained by dehydration of 2-isopropyl-1,4-butanediol through acetylation and pyrolysis. The diol was synthesized by the method of Adkins and Wojcik.[8] The final yield of diene based on diethyl isopropylidenesuccinate was about 4%. An attempt to find an improved preparation of diethyl isopropylsuccinate through the addition of isopropyl-metal halides to diethyl maleate or fumarate did give the ester in 30% yields but the over-all reaction was still not a satisfactory one for preparative work.

A second series of reactions was then investigated. The starting material was isovaleraldehyde (I). It was converted either to isopropylacrolein (III) or to 2-isopropyl-3-hydroxypropionaldehyde (II) and then by the Grignard reaction and subsequent dehydration to the desired diene. Different sequences of reactions were tried and these are indicated in the chart.

The final choice of steps is that indicated by the heavy arrows. The Mannich intermediate[9] (VI) was not isolated but was converted directly to isopropylacrolein (VII). The unsaturated carbinol

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[2] Present address: General Electric Company, Schenectady, New York.

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[4] I. M. Kolthoff, T. S. Lee and Mary Anne Mairs, *J. Polymer Sci.*, **2**, 220 (1947).

[5] Pariselle and Simon, *Compt. rend.*, **173**, 86 (1921).

[6] von Braun and Keller, *Ber.*, **64**, 2617 (1931).

[7] The desirability of synthesizing this diene was first brought to our attention by Drs. W. E. Messer and V. C. Neklutin of the United States Rubber Company.

[8] Adkins and Wojcik, This Journal, **55**, 4939 (1933); **56**, 2424 (1934).

[9] Mannich, Lesser and Silten, *Ber.*, **65**, 378 (1932).