thetic bromides do not show up so well: the undecyl may be estimated to contain at least 65% of the primary, the tridecyl, 41, the pentadecyl 60, the heptadecyl 12 and the nonadecyl only 3. The melting points of the bromides put them in the same order as to purity.

Experimental

The procedure of Gilman[4] for the preparation of the Grignard reagents was followed. These reagents were used according to the method of Wilkinson,[5] for making the alkenes, which were separated from the disproportionation by-products of the Grignard reaction, heated with sodium and distilled. The properties of the new alkenes are to be found in Table I. The bromine numbers were determined by the method of Francis[6] as modified by Cortese.[7]

Preparation of Derivatives.—To prepare a derivative, 0.3 to 0.5 cc. of the alkyl halide was measured into a test-tube with 3 cc. of alcohol and about 10% excess of the phenol. As $C_{19}H_{29}Br$ is a solid, it was weighed. This mixture was heated to effect solution and a slight excess of 1 *N* alcoholic potash added. The test-tube was stoppered loosely and placed with others in a beaker of water kept at about 70° for about twelve hours. At the end of the heating any alcohol that had evaporated was replaced and 2 cc. of hot water added. The mixture was boiled for a moment and then cooled quickly with violent shaking. This caused the derivative to separate as a granular solid which was collected on a filter and washed twice with water. The product was crystallized twice or thrice from alcohol. For better comparison the derivatives of the authentic and synthetic bromides were prepared at the same time with the same reagents and the crystallizations were carried on side by side. The final melting points were kindly taken by Mrs. Carrie Gutman Moses with a standardized thermometer.

For preparing derivatives para substituted phenols were used. Experience in another investigation had shown that these give derivatives that are readily purified and melt at convenient temperatures. The monoalkyl hydroquinone ethers will be described later along with other derivatives made from them.

(4) Gilman, Zoellner and Dickey, THIS JOURNAL, **51**, 1579 (1929).
(5) Wilkinson, *J. Chem. Soc.*, **120**, 3057 (1931).
(6) Francis, *Ind. Eng. Chem.*, **18**, 821 (1926).
(7) Cortese, *Rec. trav. chim.*, **48**, 504 (1929).

Summary

1. A method has been devised for transforming an alkyl bromide into another alkyl bromide having a carbon chain longer by three units.

2. A method has been worked out for assaying the mixture of bromides obtained by the addition of hydrobromic acid to unsaturates.

3. By the preparation of known crystalline derivatives the formation of primary bromides by the addition of hydrobromic acid to alpha alkenes in the presence of peroxides has been confirmed.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Sterols. XLIV. Pregnanone-3 and Related Compounds*

BY RUSSELL E. MARKER AND ELMER J. LAWSON

Although all the pregnanediols, pregnanolones, and pregnanediones isomeric about C_3, C_5 and C_{20} have been described,[1] none of the corresponding pregnanols and pregnanones are known. Since we now have indications of the occurrence in urines of pregnane derivatives having only one oxygen atom,[2] we have begun the synthesis of compounds of this type for purposes of comparison and physiological testing. The present paper describes the preparation of pregnanone-3 and the isomeric 3-pregnanols.

Pregnanol-3(α)-one-20 was reduced by the Clemmensen method with amalgamated zinc and a mixture of acetic and concentrated hydrochloric acids. The reaction mixture, carried through the acid succinate separation, yielded only 19 mg. of pregnanol-3(α), but about 250 mg. (m. p. 102°) of what proved to be pregnanol-3 acetate could be crystallized from the non-hydroxylated fraction, and a further crop of pregnanol-3(α) was obtained from the mother liquor after alkaline hydrolysis and acid succinate separation. The non-hydroxylated fraction, amounting to about 20% of the reaction mixture, did not yield any crystalline products.

Since it was thought at first that the crystalline product might be a pregnene, which could be identified by ozonolysis to give 3||4 pregnane-3,4-diacid,[3] or an isomer, this acid was prepared by the Clemmensen reduction of 20-keto-3||4-pregnane-3,4-diacid.[4] The latter forms a 2,4-

(*) Paper XLIII, THIS JOURNAL, **60**, 1904 (1938).
(1) Marker, Kamm, Wittle, Oakwood, Lawson and Laucius, THIS JOURNAL, **59**, 2291 (1937).
(2) Unpublished results from This Laboratory
(3) This nomenclature is suggested by Sobotka, "Chemistry of the Sterids," Williams and Wilkins, Baltimore, Md., 1938, p. 163.
(4) Butenandt, *Ber.*, **63**, 659 (1930); **64**, 2529 (1931).

dinitrophenylhydrazone, but, after the reaction with zinc and hydrochloric acid, the product no longer forms such a derivative. The same 3||4-pregnane-3,4-diacid was formed in small amounts when pregnanol-3(α) was oxidized with chromic acid. The major reaction product, pregnanone-3, was hydrogenated in acid solution to give pregnanol-3(β).

Since most of the pregnanol-3(α) formed in the Clemmensen reduction of pregnanol-3(α)-one-20 was converted by the acetic acid present into its acetate, model experiments were tried with *epi*- and β-cholestanol. When these were refluxed with amalgamated zinc and acetic acid–hydrochloric acid the chief reaction products were unreacted *epi*-cholestanol, and β-cholestyl acetate, respectively. Evidently, when a Clemmensen reaction is run on a hydroxy ketone, the reaction mixture should be subjected to alkaline hydrolysis to isolate the product. In this connection it also should be noted that the Clemmensen reduction of hydroxylated steroids frequently removes the hydroxyl groups. For example, the diacetate of 4-hydroxystigmasterol is reduced to stigmastane[5] and the hydroxyketocholanic acids give some cholanic acid.

Experimental Part

The pregnanol-3(α)-one-2 used in these experiments was isolated from human pregnancy urine[6] and melted at 134°. Apparently it can exist in two polymorphic forms, for sometimes crystals, m. p. 148°, are obtained. It forms a 2,4-dinitrophenylhydrazone which melts at 229° after recrystallization from alcohol.

Anal. Calcd. for $C_{27}H_{38}O_5N_4$: C, 64.9; H, 7.7. Found: C, 64.8; H, 8.0.

Pregnanol-3(α).—A mixture of 40 g. of amalgamated zinc, 100 cc. of concentrated hydrochloric acid, and 1 g. of pregnanol-3(α)-one-20 in 100 cc. of acetic acid was refluxed gently. The initial pink color of the solution was discharged in ten minutes, and after another ten minutes an oil had separated. After two hours of heating the solution was cooled, diluted with water, and extracted with ether. The ethereal extract was washed with sodium carbonate solution and water, and the ether removed. The sirupy residue was treated with Girard's reagent to remove traces of ketonic material, and then separated into hydroxylated and non-hydroxylated fractions in the usual manner.

The non-hydroxylated sirup, consisting almost all of the product, crystallized on standing a week; so it was triturated with 5 cc. of alcohol, collected on a funnel, and washed with small amounts of alcohol to give 370 mg. of crystals, m. p. 87–93°. One recrystallization from methanol gave 190 mg. of plates, m. p. 101–102°. This was recrystallized to a constant m. p., 106°. It was saturated to bromine and catalytic hydrogenation and did not give a Beilstein test for halogens. Analysis showed it to be the acetate of pregnanol-3(α).

Anal. Calcd. for $C_{23}H_{38}O_2$: C, 79.7; H, 11.1. Found: C, 79.3; H, 11.1.

One hundred and ninety milligrams of the acetate was hydrolyzed by heating with 0.2 g. of sodium hydroxide in 5 cc. of alcohol for one-half hour. The product, isolated by extraction of the diluted solution with ether, was recrystallized from slightly diluted alcohol and methanol to give pure pregnanol-3(α), m. p. 148°, as needle-rosets.

Anal. Calcd. for $C_{21}H_{36}O$: C, 83.2; H, 11.4. Found: C, 83.4; H, 11.4.

The total mother liquor from the crystallization of the acetate was hydrolyzed and carried through the acid–succinate separation, to give an additional quantity of pregnanol-3(α). The yield of pregnanol-3(α) from pregnanol-3(α)-one-20 was about 50%, of which only 19 mg. was obtained from the original hydroxylated fraction.

Pregnanone-3.—To a solution of 200 mg. of pregnanol-3(α) in 10 cc. of acetic acid was added 80 mg. of chromic anhydride in 5 cc. of 90% acetic acid. After standing for one and one-half hours at room temperature, a little methanol was added to destroy any excess chromic acid, and the solution was concentrated *in vacuo*. The residue was diluted and extracted with ether, and the ether extract washed free of chromium salts with dilute hydrochloric acid and water. The ether solution was extracted with 5% sodium carbonate and washed with water.

Acidification of the alkaline extract gave a flocculent acid which coagulated on standing. It was collected and washed with water and small amounts of hot alcohol to give 7 mg. of 3||4-pregnane-3,4-diacid, m. p. 297°, as proved by mixed melting point determination with an authentic sample (*vide infra*).

The neutral ethereal extract was evaporated and the residue crystallized several times from diluted alcohol to give 140 mg. of pregnanone-3, as needles, m. p. 115°. It gave a red coloration with alcoholic *m*-dinitrobenzene and aqueous potassium hydroxide, showing the presence of a 3-carbonyl group.

Anal. Calcd. for $C_{21}H_{34}O$: C, 83.4; H, 11.3. Found: C, 83.6; H, 11.3.

Fifteen milligrams of pregnanone-3 was treated in the usual manner with alcoholic semicarbazide acetate solution. The resulting semicarbazone, m. p. 133°, proved to be difficult to purify because of its great solubility in all ordinary solvents except ether. The 2,4-dinitrophenylhydrazone, however, proved to be a satisfactory derivative. After crystallization from alcohol, it melted at 163°.

Anal. Calcd. for $C_{27}H_{38}O_4N_4$: C, 67.0; H, 8.0. Found: C, 66.7; H, 8.2.

Pregnanol-3(β).—A solution of 100 mg. of pregnanone-3 in 20 cc. of acetic acid and five drops of 48% aqueous hydrobromic acid was added to 50 mg. of previously reduced platinum oxide in 20 cc. of acetic acid, and the mixture was shaken in a hydrogen atmosphere at 35 lb. (2.3 atm.) pressure for two hours. The catalyst was removed by filtration, and the acetic acid removed *in vacuo*. The residue was heated for twenty minutes with 0.3 g. of sodium

(5) Marker and Rohrmann, THIS JOURNAL, **60**, 1073 (1938).
(6) Marker and Kamm, *ibid.*, **59**, 1373 (1937).

hydroxide in 8 cc. of alcohol, diluted and extracted with ether. The washed ethereal extract was evaporated, and the crystalline residue dissolved in 10 cc. of hot alcohol. To this solution was added a hot solution of 0.4 g. of digitonin in 20 cc. of alcohol. The next day the digitonide was filtered, dried and decomposed in the usual manner to give the carbinol. After recrystallization from slightly diluted alcohol, the pregnanol-3(β) was obtained as needles, m. p. 144°, which depressed with pregnanol-3(α) to 115–120°.

Anal. Calcd. for $C_{21}H_{36}O$: C, 82.8; H, 11.8. Found: C, 82.9; H, 11.8.

Twenty milligrams of pregnanol-3(β) was converted into its acetate by refluxing for a half hour with 2 cc. of acetic anhydride. After recrystallization from dilute alcohol, it melted at 87°.

Anal. Calcd. for $C_{23}H_{38}O_2$: C, 80.1; H, 11.3. Found: C, 80.4; H, 11.5.

3||4-Pregnane-3,4-diacid.—The 20-keto-3||4-pregnane-3,4-diacid used in these experiments was obtained by D. M. Jones of this Laboratory as a by-product in the preparation of pregnanedione, and it had a melting point of 270°. It formed a 2,4-dinitrophenylhydrazone which was crystallized from alcohol to a constant m. p. 210°.

Anal. Calcd. for $C_{27}H_{36}O_8N_4$: C, 59.6; H, 6.7. Found: C, 59.5; H, 7.0.

A mixture of 40 g. of amalgamated zinc, 1 g. of 20-keto-3||4-pregnane-3,4-diacid, 100 cc. of concentrated hydrochloric acid, and 100 cc. of acetic acid was refluxed for five hours, small portions of acetic acid and hydrochloric acid being added from time to time. The suspended acid was collected and washed with ether to give 0.53 g., m. p. 260–270°. This product was purified by leaching with boiling alcohol, in which, in contrast to 20-keto-3||4-pregnane-3,4-diacid, it is very insoluble. Extraction of the acetic acid–hydrochloric acid filtrate with ether, and concentration of the latter gave an additional quantity of the product, 3||4-pregnane-3,4-diacid, m. p. 297°. This acid is extremely insoluble in all ordinary solvents.

Anal. Calcd. for $C_{21}H_{34}O_4$: C, 71.4; H, 9.7. Found: C, 71.3; H, 9.5.

A solution of 30 mg. of 3||4-pregnane-3,4-diacid in 20 cc. of methanol and 10 drops of concentrated sulfuric acid was concentrated to one-third volume by heating for two hours on a steam-bath. The solution was diluted with water, extracted with ether, and the ethereal extract washed with sodium carbonate solution and water. After evaporation of the ether, the residue was crystallized from methanol to give the dimethyl ester of 3||4-pregnane-3,4-diacid, m. p. 147°.

Anal. Calcd. for $C_{23}H_{38}O_4$: C, 72.5; H, 10.1. Found: C, 72.2; H, 9.9.

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Summary

The preparations of pregnanone-3 and the isomeric 3-pregnanols are described. The Clemmensen reduction, in the presence of acetic acid, of hydroxylated compounds may give rise to acetylated products.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Sterols. XLV. The Neutral Reduction Products of Equilenin*

BY RUSSELL E. MARKER, EWALD ROHRMANN, EUGENE L. WITTLE AND FRANK H. TENDICK

While the phenolic reduction products of equilenin have been studied rather extensively[1-3] no such study has been reported on the neutral reduction products which often accompany the phenolic reduction products. Marker *et al.*[2] carried out the catalytic hydrogenation of equilenin in acidic solution and found that the main product of the reaction was $\Delta^{5,7,9}$-oestratrienol-17. All searches for completely saturated compounds in the reaction were unsuccessful, indicating the extreme stability of the $\Delta^{5,7,9}$-oestratrienol-17 to further reduction.

Marker[3] made an extensive study of the phenolic reduction products of equilenin, α-dihydroequilenin, and β-dihydroequilenin, using sodium and amyl alcohol. In every case it was found that the reaction gave approximately 20% of phenolic reduction products, the remainder consisting largely of neutral reduction products. The phenolic reduction products were shown to be the α- and β-oestradiols. We have now extended these studies to the neutral reduction products of these reactions. The neutral fraction from the reduction of equilenin gave a diol (I) $C_{18}H_{24}O_2$, melting at 172°. This same compound was produced by the analogous reduction of α-dihydroequilenin, thus establishing the configuration of the hydroxyl group at C_{17}. The

(*) Paper XLIV, THIS JOURNAL, **60**, 2438 (1938).

(1) Wintersteiner, Schwenk, Hirschmann and Whitman, THIS JOURNAL, **58**, 2652 (1936).

(2) Marker, Kamm, Oakwood and Tendick, *ibid.*, **59**, 768 (1937).

(3) Marker, *ibid.*, **60**, 1897 (1938).