with acetone and was recrystallized from propyl alcohol: beautiful needles, m. p. 164°; yield 1.5 g. *Anal.* Calcd. for $C_{17}H_{12}O$: C, 87.9; H, 5.2. Found: C, 88.0; H, 5.4.

9,10-Cyclopentenophenanthrene (X).—The ketone (1.5 g.) was reduced with amalgamated zinc wool (15 g.) and hydrochloric acid and the reaction product again purified by distillation in a high vacuum (0.02 mm.). At 180–190°, a yellowish oil distilled which crystallized spontaneously; from isopropyl alcohol as bent, long needles; m. p. 154°, yield 1.3 g. *Anal.* Calcd. for $C_{17}H_{14}$: C, 93.6; H, 6.4. Found: C, 93.0; H, 6.9. To the constitutional proof given by Bachmann and Kloetzel, nothing has to be added.

Dicyclohexenyl (I, 1.3 g.) and **phenylquinone**[21] (1.3 g.) were heated for four hours at 120–150° in a sealed tube. The product was distilled *in vacuo*, some unchanged dicyclohexenyl distilling over first (b. p. 130–140° at 9 mm.). The reaction product of b. p. 260–280° (1.25 mm.) solidified on standing with light petroleum (b. p. 40–80°) and was recrystallized from ligroin. At the beginning, black clusters of a quinhydrone appeared, then the yellow prisms of the condensation product (VII); after repeated crystallization from xylene, their m. p. was 207–208°. Concd. sulfuric acid gives a dark red solution. *Anal.* Calcd. for $C_{24}H_{26}O_2$: C, 83.2; H, 7.5. Found: C, 82.9, 82.8; H, 7.9, 7.6.

When the same condensation was carried out in nitrobenzene as diluent (6.5 cc.) (four hours of boiling), a dark resin was obtained, which was distilled twice *in vacuo* (b. p. 250–270° at 1.25 mm.), and then triturated with a mixture of methanol and acetone. From isopropyl alcohol it formed clusters, m. p. 140–141°, which gave the same color reaction with concd. sulfuric acid as the above product, but contained two hydrogen atoms less. *Anal.* Calcd. for $C_{24}H_{24}O_2$: C, 83.7; H, 7.0. Found: C, 83.5; H, 7.0.

Dicyclohexenyl (I, 4 cc.) and **2,3-dimethylindone**[22] (3 g.) were heated at 200° in toluene solution (10 cc.) for eight hours. Part of the reactants was recovered unchanged, the condensation product (XI) distilling at 165–175° (0.1 mm.). It formed a yellowish, extremely viscous oil, which could not be induced to crystallize. *Anal.* Calcd. for $C_{23}H_{28}O$: C, 86.3; H, 8.8. Found: C, 85.7, 85.8; H, 9.1, 9.2.

Clemmensen Reduction.—The condensation product (5 g.) was reduced with amalgamated zinc wool (50 g.) and half-concentrated hydrochloric acid. The reaction product was a colorless oil, which had the constant b. p. 240–245° (0.1 mm.); yield 2.3 g. *Anal.* Calcd. for $C_{23}H_{30}$: C, 90.2; H, 9.8. Found: C, 89.7; H, 10.3. The dehydrogenation, carried out at 300° (twenty-four hours) gave traces of a crystalline substance, from bromobenzene prisms, m. p. above 300°, and an oil, which was converted into the picrate in benzene solution; from propyl alcohol brownish-yellow clusters of needles, m. p. 210°. Due to the scarcity of material, the constitution of these two substances was not dealt with.

Summary

The condensation has been studied between dicyclohexenyl and maleic anhydride, cinnamic acid, benzoquinone, naphthoquinone, phenylquinone, 1-cyanocyclopentene-(1), and 2,3-dimethylindone, respectively. Several reactions of the condensation products have been investigated.

REHOVOTH, PALESTINE RECEIVED MARCH 12, 1938

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[21] Kvalnes, THIS JOURNAL, **56**, 2478 (1934).

[22] Burton and Shoppee, *J. Chem. Soc.*, 1156 (1935).

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

Sterols. XXXIII. 3,11-Dihydroxy-12-ketocholanic Acid and Derivatives

BY RUSSELL E. MARKER AND ELMER J. LAWSON

Within the last year the presence of hydroxyl or carbonyl groups at C_{11} has been postulated repeatedly in certain naturally occurring steroids. The arguments for assigning hydroxyl or ketonic groups to this position have been chiefly steric, based on the lack of reactivity of the functional groups. Thus digoxigenin,[1] sarmentogenin,[2] the cortical substances[3] of Reichstein, Kendall, and Wintersteiner and Pfiffner, and uranetriol[4] from mares' pregnancy urine have been supposed to have hydroxyl or ketonic groups at C_{11}. Since the position of the unreactive functional group in these compounds has in every case been established by indirect evidence, it is highly desirable to prepare substances known to have functional groups in the 11-position.

In order to synthesize uranetriol, we have attempted to prepare 3(α),11-dihydroxycholanic acid. While the synthesis of this substance has not been accomplished, we wish to report certain experiments in this direction. We have prepared 3(α),11-dihydroxy-12-ketocholanic acid by bromination and subsequent hydrolysis of 3(α)-hydroxy-12-ketocholanic acid. This synthesis is similar to the synthesis of 11-hydroxy-12-ketocholanic acid from 12-ketocholanic acid by Wieland and Dane.[5]

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[1] Smith, *J. Chem. Soc.*, 1305 (1935).

[2] Tschesche and Bohle, *Ber.*, **69**, 783 (1936).

[3] See Reichstein in Ruzicka and Stepp, "Ergebnisse der vitamin- und Hormonforschung," 1938, p. 334.

[4] Marker, Kamm, Oakwood, Wittle and Lawson, THIS JOURNAL, **60**, 1061 (1938).

[5] Wieland and Dane, *Z. physiol. Chem.*, **216**, 97 (1933).

The preparation of 3(α)-hydroxy-12-ketocholanic acid by methods reported in the literature proved to be tedious and unsatisfactory. Wieland, Dane and Scholz[6] prepared this acid from desoxycholic acid by partial acetylation, oxidation and subsequent hydrolysis. In repeating this work, we found considerable difficulty in obtaining crystalline 3-acetoxy-12-hydroxycholanic acid monoetherate. Kyogoku[7] has reported that the partial hydrogenation of dehydrodesoxycholic acid in acetic acid solution yields a molecular compound of 3-(α)-hydroxy-12-ketocholanic acid and 3(β)-hydroxy-12-ketocholanic acid in the ratio of one part of the former to one of the latter. Our experience with this reaction in general confirms his results, although we doubt that an actual molecular compound is formed, since the product obtained melts over a range 123–129°, and has the properties of a mixture. Kaziro and Shimada[8] have also reported the preparation of 3(α)-hydroxy-12-ketocholanic acid by the partial oxidation of desoxycholic acid.

When desoxycholic acid is half acetylated by refluxing with a slight excess over the theoretical amount of acetic anhydride in acetic acid, the resulting solution oxidized directly with chromic acid, and then the gummy acid mixture hydrolyzed with alkali, the products obtained can be separated readily because of the marked differences in the rates of crystallization of the substances in benzene solution. Desoxycholic acid is almost completely insoluble in cold benzene and separates almost immediately, contaminated with about 10–20% of 3(α)-hydroxy-12-ketocholanic acid. The mother liquor, after standing a few days, deposits a crop of needles of 3(α)-hydroxy-12-ketocholanic acid solvated probably with benzene. The mother liquors from this acid yield no crystalline acids, although considerable amounts of dehydrodesoxycholic acid are probably present.

The ready availability of 3(α)-hydroxy-12-ketocholanic acid now makes possible a simplified preparation of lithocholic acid by a method essentially the same as that employed by Ruzicka and Goldberg.[9] The first crop of desoxycholic acid-3(α)-hydroxy-12-ketocholanic acid may be treated with semicarbazide acetate to yield about 20% of semicarbazone suitable for this preparation.

When 3(α)-hydroxy-12-ketocholanic acid is acetylated, and then treated with 3 moles of bromine for eight hours at 60–80°, under which conditions 12-ketocholanic acid yields 11-bromo-12-ketocholanic acid, a dibrominated product is obtained. By treating the acetylated hydroxyketocholanic acid with bromine under milder conditions, however, monobromination occurs. Since the acetylated bromo acid could not be obtained crystalline, it was hydrolyzed directly to give 3(α),11-dihydroxy-12-ketocholanic acid. By not isolating intermediate products it is thus possible to obtain 3(α),11-dihydroxy-12-ketocholanic acid from desoxycholic acid in an over-all yield of about 15%.

Attempts to remove the carbonyl group at C_{12} in 3(α),11-dihydroxy-12-ketocholanic acid have so far been unsuccessful. The acid yields a semicarbazone which is formed slowly in yields of less than 20% and which does not give satisfactory analyses. When 3(α),11-dihydroxy-12-ketocholanic acid was reduced by the Clemmensen method only oily products were obtained. Apparently the ketonic group at C_{12} is considerably more hindered when a hydroxyl group is present at C_{11}. This fact and the possibility of a facile dehydration of the C_{11}-OH group seem to indicate that some other approach to the synthesis of compounds substituted at C_{11} must be found. Experiments in this direction are now in progress.

We wish to thank Parke, Davis and Co. of Detroit, Mich., for a grant making this work possible.

Experimental Part

3(α)-Hydroxy-12-ketocholanic Acid.—A solution of 50 g. of desoxycholic acid in 150 cc. of acetic acid and 15 cc. of acetic anhydride was refluxed for three hours in an oil-bath at 135°. After cooling, the solution was diluted with 150 cc. of acetic acid, and a solution of 10 g. of chromic acid in 40 cc. of 50% acetic acid was added with stirring over a period of twenty-five minutes. The temperature of the reaction mixture was kept at 20–30° by an ice-water bath. The mixture was stirred for one and one-quarter hours, and then any excess chromic acid was destroyed by adding methanol. The solution was poured into 1200 cc. of water and the gummy solid which precipitated was dissolved in ether. The ether extract was washed with dilute hydrochloric acid and water, and then evaporated, leaving a sirupy residue. This residue was heated for three hours on a steam-bath with a solution of 50 g. of potassium hydroxide in 700 cc. of water. The solution was filtered hot to remove some precipitated chromium hydroxide, the filtrate acidified and the gum extracted with ether. The ethereal solution was washed with water and concentrated. While still hot, 300 cc. of benzene was added to the sirup.

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(6) Wieland, Dane and Scholz, *Z. physiol. Chem.*, **211**, 261 (1932).

(7) Kyogoku, *ibid.*, **246**, 99 (1937).

(8) Kaziro and Shimada, *ibid.*, **249**, 220 (1937).

(9) Ruzicka and Goldberg, *Helv. Chim. Acta*, **18**, 668 (1935).

The solution was concentrated to a volume of about 200 cc. at which point some crystals appeared. After standing for several hours, the crystalline crop was collected and washed with a mixture of 30 cc. of ethyl acetate and about 200 cc. of benzene. This crystal crop, which weighed 15.2 g., m. p. 148–156°, was a mixture of desoxycholic acid and some 3(α)-hydroxy-12-ketocholanic acid. The filtrate from this first crop, on standing a few days, deposited fine needles, which were collected and washed with benzene, to give 21.7 g. of quite pure 3(α)-hydroxy-12-ketocholanic acid containing benzene of crystallization. When heated rapidly, this acid melts at 110°, and on further heating solidifies and melts again at 161–162°; when heated slowly, however, the acid loses benzene without melting, and melts directly at 161–162°.

Anal. Calcd. for $C_{24}H_{38}O_4$: C, 73.8; H, 9.8. Found: C, 73.8; H, 9.8.

The acid did not give a coloration when treated with alcoholic *m*-dinitrobenzene and potassium hydroxide.

Five-tenths gram of the 3(α)-hydroxy-12-ketocholanic acid was heated for two hours at 130° with 1 cc. of acetic anhydride and 3 cc. of acetic acid. The reaction mixture was poured into water and the solid which precipitated was crystallized three times from alcohol to give 3(α)-acetoxy-12-ketocholanic acid, m. p. 195°. The highest melting point reported in the literature is 197–198°.

Anal. Calcd. for $C_{26}H_{40}O_5$: C, 72.3; H, 9.4. Found: C, 72.3; H, 9.4.

Lithocholic Acid.—A mixture of 8 g. of 3(α)-hydroxy-12-ketocholanic acid (prepared as described above), 4 g. of semicarbazide hydrochloride, 5 g. of sodium acetate and 60 cc. of alcohol was refluxed overnight on a steam-bath. The mixture set to a stiff gel after the first hour of heating. The cooled mixture was filtered and the solid washed once with alcohol. After treating the crude semicarbazone with boiling water, it weighed 8 g., m. p. 233–234°. A portion of the semicarbazone was recrystallized several times from alcohol to give a constant melting point of 241°.

Anal. Calcd. for $C_{25}H_{41}O_4N_3$: C, 67.2; H, 9.2. Found: C, 66.6; H, 9.3.

Lithocholic acid was prepared from this semicarbazone by a method similar to that used by Ruzicka and Goldberg.[9] Ten grams of sodium was dissolved in 110 cc. of benzyl alcohol by refluxing for several hours. The flask was heated a few minutes *in vacuo* at 110° to remove toluene, and then 9.5 g. of 3(α)-hydroxy-12-ketocholanic acid semicarbazone was added and the mixture heated for twenty-one hours in an oil-bath at 190°. At the end of this time very little gas was being generated.

The reaction mixture was diluted with water and ether, and the alkaline layer extracted with more ether to remove all the benzyl alcohol. The alkaline solution was acidified and the gummy precipitate crystallized once from diluted alcohol, and then twice from diluted acetic acid to give 2.2 g. of somewhat impure lithocholic acid, m. p. 178°. A portion was crystallized several more times from acetic acid to give a pure product, m. p. 184°.

Anal. Calcd. for $C_{24}H_{40}O_3$: C, 76.6; H, 10.7. Found: C, 76.4; H, 10.8.

3(α),11-Dihydroxy-12-ketocholanic Acid.—Attempts to isolate the 3(α)-acetoxy-11-bromo-12-ketocholanic acid employed as an intermediate in this synthesis gave uncrystallizable gums. Therefore, the bromo acid was not isolated as such, but hydrolyzed directly to the desired product.

Twenty grams of 3(α)-hydroxy-12-ketocholanic acid in 50 cc. of acetic acid and 10 cc. of acetic anhydride was heated in an oil-bath at 135° for one and one-half hours. After cooling the solution, 50 cc. of 1.05 *M* bromine in acetic acid and 0.5 cc. of 48% aqueous hydrobromic acid were added, and the mixture heated for three hours in a water-bath at 70°. After standing overnight the solution was poured into seven volumes of water, and the precipitated gum extracted with ether. The ethereal solution was washed with water and evaporated. The residual sirup was dissolved in 200 cc. of methanol, and a solution of 40 g. of potassium hydroxide in 35 cc. of water added. This caused the solution to become very dark. The solution was heated for two hours on a steam-bath and diluted to one liter with ice and water. The free acid was precipitated as a flocculent solid by adding dilute hydrochloric acid with stirring. The acid was filtered, washed with water and dried, giving about 20 g. of brown, granular solid. This crude acid was dissolved in 350 cc. of boiling benzene and the resulting solution, after decanting from some black tar, set aside to crystallize.

After standing a few weeks, the solution was filtered and the crystals washed with hot benzene and with a very small amount of cold ethyl acetate. The crystalline product, melting at 182–184°, was clarified in alcohol and recrystallized from diluted alcohol to give 7 g. of 3(α),11-dihydroxy-12-ketocholanic acid, m. p. 193°. After several more crystallizations from alcohol, the melting point remained constant at 196°. 3(α),11-Dihydroxy-12-ketocholanic acid is soluble in ethyl acetate and alcohol but only sparingly soluble in benzene.

Anal. Calcd. for $C_{24}H_{38}O_5$: C, 70.9; H, 9.4. Found: C, 71.3, 71.1; H, 9.6, 9.7.

Three hundred milligrams of 3(α),11-dihydroxy-12-ketocholanic acid in 1 cc. of acetic acid and 5 cc. of acetic anhydride was refluxed for two hours. The solvent was removed *in vacuo*, and the residue crystallized from alcohol to give a product, m. p. 268°, which proved to be 3(α)-acetoxy-11-hydroxy-12-ketocholanic acid.

Anal. Calcd. for $C_{26}H_{40}O_6$: C, 70.5; H, 8.8. Found: C, 70.6; H, 8.9.

A mixture of 1 g. of 3(α),11-dihydroxy-12-ketocholanic acid, 0.5 g. of semicarbazide hydrochloride, 0.65 g. of sodium acetate, and 15 cc. of alcohol was refluxed on a steam-bath for fifteen hours. The mixture was diluted with water, filtered and washed with water to give 1 g. of solid, m. p. 170–185°. After two crystallizations from alcohol, 180 mg. of the semicarbazone, m. p. 232°, was obtained. Repeated crystallization of this product from ethyl acetate raised the melting point to 238°.

Summary

Simplified procedures for the preparation of 3(α)-hydroxy-12-ketocholanic acid and lithocholic acid are described. From 3(α)-hydroxy-12-ketocholanic acid, 3(α),11-dihydroxy-12-ketocholanic

acid may be prepared by acetylation, bromination and subsequent hydrolysis. Attempts to prepare 3(α),11-dihydroxycholanic acid from this by the Wolff–Kishner and Clemmensen methods have been unsuccessful.

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[CONTRIBUTION FROM THE WILLIAMS OIL-O-MATIC HEATING CORPORATION]

Hydrogen Bonds Involving the C–H Link. The Solubility of Haloforms in Donor Solvents

BY G. F. ZELLHOEFER, M. J. COPLEY[1] AND C. S. MARVEL[1]

A recent paper[2] by one of the authors reported the solubilities of a number of low boiling halogenated hydrocarbon refrigerants in a variety of organic solvents. Since the publication of this paper, the measurements have been extended to include other types of halogenated hydrocarbons and new solvents. In this paper the earlier results and the new data are discussed in order to give a comprehensive picture of the factors leading to high solubility.

The halogenated hydrocarbons which have been used in this investigation include the types CH_3X, CH_2X_2, CHX_3, CX_4, C_2H_5X and C_2X_6 where X may be either a chlorine or a fluorine atom. The solvents which were tested include ethers, thioethers, esters, ether-esters, ketones, aldehydes, alcohols, alcohol-ethers, primary and tertiary amines, amides, nitro compounds, hydrocarbons and halogenated hydrocarbons. It has been observed that almost invariably solvents which contain donor atoms (oxygen or nitrogen) dissolve the halogenated hydrocarbons, which have at least one hydrogen atom in the molecule, in excess of the amount predicted from Raoult's law. The generality of this effect which is greatest for the CHX_3 type has led us to suggest that the formation of a hydrogen bond ($C{-}H{\leftarrow}O$ or $C{-}H{\leftarrow}N$) is the important factor in producing this high solubility.[3]

It has been known for some time that mixtures of halogenated hydrocarbons of the types CHX_3 and C_2HX_5, where X is a halogen atom, with ethers and ketones show large negative deviations[4,5] from Raoult's law. This behavior has been attributed to compound formation[6,7] between the two components. Further evidence indicating the same conclusion has been obtained from measurements of heats of mixing,[8] of viscosities,[9] of dielectric constants,[10] and of freezing points.[11] The bonding forces responsible for complex formation have been assumed to be either chemical and resulting from the formation of a coördinate link, or physical and due to forces between dipoles.

A suggestion as to the type of coördinate link formed was made by Glasstone[10] in 1936. He determined the total polarization of mixtures of ethers, acetone and quinoline with a number of halogenated hydrocarbons ($CHCl_3$, CH_3CCl_3, $CHBr_3$, CHI_3, CCl_4, CBr_4, C_2HCl_5, C_2Cl_6). His results were interpreted by him as indicating considerable complex formation. It is most pronounced in the case of halogenated hydrocarbons of the type CHX_3, and this led him to suggest the existence of a hydrogen bond between the hydrogen of the CHX_3 and the oxygen of the ether and ketone, or the nitrogen of quinoline. One may picture the bond as formed by the donation of an unshared pair of electrons of the oxygen or nitrogen atoms to the hydrogen.[12,13] The presence of the strongly electron-attracting halogen atoms on the carbon loosens the hydrogen and makes it available for coördination to the donor atom. Hence the amount of complex formation should increase as the X in CHX_3 is varied in the order $I < Br < Cl < F$. The complex may be considered as resonating between the two structures

$$[R_2O\ H{-}CX_3] \quad [R_2\overset{+}{O} \longrightarrow H\ \overset{-}{C}X_3]$$

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[1] Chemistry Department, University of Illinois.

[2] G. F. Zellhoefer, *Ind. Chem. Eng.*. **29**, 584 (1937).

[3] As this manuscript was being prepared the paper by Gordy [THIS JOURNAL, **60**, 605 (1938)] giving infrared absorption data which indicate the formation of hydrogen bonds between chloroform and acetone, ethyl acetate and dioxane was published.

[4] Kohnstamm and Dalfsen, *Proc. Akad. Wet.*, **29**, 156 (1901).

[5] Zawidski, *Z. physik. Chem.*, **35**, 129 (1900).

[6] Dolezalek, *ibid.*, **64**, 727 (1908).

[7] Dolezalek and Schulze, *ibid.*, **83**, 45 (1913).

[8] McLeod and Wilson, *Trans. Faraday Soc.*, **31**, 596 (1935).

[9] McLeod, *ibid.*, **30**, 482 (1934).

[10] Glasstone, *ibid.*, **33**, 200 (1937).

[11] Wyatt, *ibid.*, **25**, 43 (1929).

[12] Latimer and Rodebush, THIS JOURNAL, **42**, 1419 (1920).

[13] M. L. Huggins, *J. Org. Chem.*, **1**, 407 (1936).