interpretation of the catalytic oxidation of the furan ring.

Summary

1. An improved technique has been developed for the catalytic oxidation of organic substances especially of substances of low volatility.

2. The catalytic oxidation of furfural has been investigated under various conditions of temperature, molal ratio and time of contact using vanadium pentoxide as the catalyst. Bismuth vanadate, and a mixed catalyst, 10% molybdenum oxide–90% vanadium pentoxide, were also used as catalysts.

3. The catalytic oxidation of furan, furfuryl alcohol and furoic acid has also been investigated.

4. In all cases maleic acid was the chief solid product formed in yields ranging from 65% from furan to 22.5% from furfuryl alcohol.

5. A mechanism of the oxidation has been proposed.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE DEPARTMENT OF SURGERY, COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY]

A Synthesis of Conjugated Bile Acids. I. Glycocholic Acid

BY FRANK CORTESE AND LOUIS BAUMAN

We were interested in a practical method for the preparation of sizable quantities of the naturally occurring conjugated bile acids in a reasonable state of purity. Their isolation from the bile by available methods is an uncertain procedure; the yields are poor and the products of doubtful homogeneity.

The only synthetic method to be found in the literature is that of Bondi and Mueller,[1] who coupled the azide of cholic acid with glycine and taurine. This method did not appear to be particularly practical for our purposes. Moreover, we noted that Bondi and Mueller apparently did not obtain taurocholic acid in a crystalline state. Wieland[2] used the same method for the preparation of glycodeoxycholic and taurodeoxycholic acids, but he doubted their identity with the naturally occurring substances.

By protecting the hydroxyl groups of cholic acid with formyl groups, we were able to make the acid chloride, and this was coupled with glycine in alkaline solution. The new synthesis is cheap and gives a good over-all yield, 25–35 g. of glycocholic acid being obtained from 50 g. of crystalline cholic acid.

Experimental Part

Triformylcholic Acid.—A mixture of 50 g. of cholic acid, m. p. 202–203° (corr.) and 100 cc. of redistilled formic acid (sp. g. 1.20) was warmed at 50–55° for five hours and then evaporated to dryness under reduced pressure at the same temperature. To a boiling solution of the residue in 500 cc. of 95% alcohol, 600 cc. of water was added at such a rate that no precipitation occurred. The solution was allowed to cool with stirring until crystals appeared; after twenty-four hours at room temperature the product was filtered off, washed with an ice-cold mixture of 50 cc. of water and 60 cc. of 95% alcohol, and dried at 100°. The yield was 35–43 g. (60–75%). It was recrystallized, with little loss, from a mixture of 500 cc. of 95% alcohol and 600 cc. of water, from which it separated in rosets of needles melting at 206–207° (corr.). Further recrystallization from benzene and petroleum ether failed to change the melting point.

Anal. Calcd. for $C_{27}H_{40}O_8$: C, 65.85; H, 8.13. Found: C, 66.03; H, 8.01.

The acid cannot be titrated accurately with dilute alkali owing to the susceptibility of the formyl groups to hydrolysis. 0.5599 g. on boiling for one hour with 25 cc. of alcohol and excess of 0.1 *N* sodium hydroxide consumed 44.76 cc. of the alkali (calcd. 45.51 cc.).

The use of stronger formic acid than that indicated did not improve the yield.

Triformylcholyl Chloride.—A solution of 50 g. of pure triformylcholic acid (dried at 110° for five hours) in 50 cc. of freshly redistilled thionyl chloride was spontaneously evaporated in the hood under a strong draft after standing for one to three hours. The gummy residue was worked up with petroleum ether (30–60°) to a white powdery mass. After one more evaporation to dryness, it was washed with petroleum ether and air dried for about fifteen minutes. The yield was 49–51 g., or 95–98%.

The fresh material starts to discolor at about 125° and decomposes at about 147° (corr.) with weak foaming. After two days' exposure to the air, a sample was recrystallized from benzene and petroleum ether and was found to have been completely hydrolyzed to triformylcholic acid, as shown by a mixed melting point.

0.3658 g. of fresh material hydrolyzed as indicated above for triformylcholic acid consumed 35.15 cc. of alkali (calcd. 35.79 cc.).

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[1] Bondi and Mueller, *Z. physiol. Chem.*, **47**, 499 (1906).

[2] Wieland, *ibid.*, **106**, 181 (1919).

Triformylcholyl Amide.—Two grams of fresh triformylcholyl chloride was stirred with concentrated ammonia for fifteen minutes. The product was filtered, washed with water and air dried. The yield was 1.9 g. It was insoluble in water and dilute sodium hydroxide. Recrystallized from a mixture of benzene, acetone and petroleum ether, it consisted of tiny needles in clusters and melted at 187° (corr.).

Anal. Calcd. for $C_{27}H_{41}O_7N$: N, 2.85. Found: N, 2.93.

Cholyl Amide.—Triformylcholyl amide, 1.4 g., was treated in 15 cc. of boiling 95% alcohol, made alkaline to phenolphthalein with sodium hydroxide, for fifteen minutes. After diluting to 100 cc. with distilled water and a little ether, the cholyl amide crystallized out in the icebox, in rosets of needles. Recrystallized from 15% alcohol and air dried, it softened at about 107° and decomposed at about 115° (corr.) with foaming. This behavior will be discussed in a future report in connection with the para acids.

Anal. Calcd. for $C_{24}H_{41}O_4N \cdot 3H_2O$: N, 3.04. Found: N, 2.98.

An air-dried sample, dried at room temperature over phosphorus pentoxide under a moderate vacuum to constant weight for seven days, lost 11.41% H_2O (calcd. 11.71%).

Re-exposure to air to constant weight caused a gain in weight in three days of 4.57% (calcd. increase for 1 H_2O: 4.42%).

Glycocholic Acid.—We found that a relatively large excess of both glycine and alkali was necessary. Much less glycine than the amount we adopted may be used, but the resulting product is more difficult to get crystalline.

A mixture of 80 g. of glycine, 1650 cc. of normal sodium hydroxide (or 120 g. of glycine hydrochloride in 1650 cc. of 1.75 *N* sodium hydroxide) and 49 g. of fresh triformylcholyl chloride was stirred for about three hours to a perfectly clear solution. After twenty-four hours it was stirred at 60–65° for one hour, gradually cooled to 0° and made acid to Congo Red with ice-cold 18% hydrochloric acid. After standing for twenty-four hours in the icebox, the precipitate was filtered by suction and washed well with water. The filtrate was saved for the recovery of the unused glycine. The gummy cake was dissolved in 400 cc. of hot 95% alcohol, 3300 cc. of cold distilled water stirred in and the milky solution put away in the icebox for twenty-four hours. The tiny, slender needles of glycocholic acid were filtered by gentle suction, washed well with ice water and air dried. The yield was 36–41 g., or 76–87%.

Most of the melting points recorded in the literature for glycocholic acid are too high. This is obviously due to mixture of this acid with the isomeric paraglycocholic acid. As Letsche[3] pointed out, the melting point depends upon the rate of heating. We have adopted the method of immersing the sample in a bath preheated to the desired temperature and noting whether the specimen sinters and foams completely within thirty seconds. The melting point of our crude material was 121° (uncorr.) and recrystallization from alcohol and water did not materially raise it. However, it was purified for analysis as follows. Four grams was suspended in 400 cc. of distilled water at room temperature, the water brought to boiling slowly, with stirring, filtered hot and the filtrate allowed to cool to room temperature. The precipitated acid was filtered, washed well with water and air dried, to give 2.4 g. (The undissolved para acid may be recovered as glycocholic acid by solution in a little hot alcohol and adding excess water.) Two grams of this material was recrystallized from 5% alcohol, washed well with water and air dried. The melting point of the 1.7 g. of pure acid obtained was about 130° (uncorr.) by our method. A sample of natural glycocholic acid purified in the same manner had the same melting point.

Anal. Calcd. for $C_{26}H_{43}O_6N \cdot 1.5H_2O$: C, 63.36; H, 9.41; N, 2.85. Found: C, 63.15; H, 9.23; N, 2.57.

An air-dried sample dried at room temperature over phosphorus pentoxide under a moderate vacuum to constant weight for forty-eight hours lost 5.75% H_2O (calcd. 5.49%).

0.5375 g. titrated in 25 cc. of neutral 95% alcohol consumed 10.97 cc. of 0.1 *N* sodium hydroxide (calcd. 10.93 cc.). $[\alpha]^{28}\text{D}$ +30.8° (*c*, 7.5; 95% C_2H_5OH). This corresponds to +32.5° for the anhydrous acid (Letsche,[3] $[\alpha]^{18}\text{D}$ +32.3°).

Paraglycocholic Acid.—Letsche's[3] method of heating on the water-bath was found to be uncertain. We covered glycocholic acid with a little water and refluxed until the gummy material hardened. Then an excess of water was added and refluxing continued for five hours. It was filtered at once, washed by suction with boiling water and air dried. It had the same microscopic appearance as Letsche's[3] product but it did not appear to be very pure. It started to sinter at about 170°, softened progressively from 180° on and melted at 192–195° (corr.) with weak foaming. Letsche's[3] m. p. for a probably purer material was 193–195° (uncorr.). Our glycocholic acid therefore behaves in the same manner as the naturally occurring product.

Recovery of the Glycine.—The filtrate containing the excess of glycine was evaporated to dryness under diminished pressure. The pulverized residue was covered with concentrated hydrochloric acid, warmed a bit and stirred well. After cooling, it was filtered through glass wool, washing with concentrated acid. The filtrate was evaporated to dryness again under diminished pressure. It was finally taken up in 500 cc. of distilled water, charcoaled, filtered and evaporated under diminished pressure. The residue was dried in a vacuum desiccator over anhydrous calcium chloride and sodium hydroxide pellets for several hours. When dry it was pulverized and the drying continued until every trace of acid fumes had vanished. The recovery amounted to 100 g., indicating a loss of only 6 g. of glycine.

The over-all yield of glycocholic acid in the preceding process, based on crystalline cholic acid, is 40–60%. Glycodeoxycholic, taurocholic and taurodeoxycholic acids have also been made by this process and will be reported on in the future. These products are being compared with reference to their effect on the solubility of cholesterol, singly, in mixtures and also in the presence of lecithin, soaps and other bile constituents. We plan to use this method for coupling cholic and deoxycholic acids with other compounds containing reactive hydrogen atoms.

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(3) Letsche, *Z. physiol. Chem.*, **60**, 462 (1909).

We wish to thank Dr. and Mrs. Reginald Auchincloss for helping to make this work possible and to express our appreciation to Professors H. T. Clarke and O. Wintersteiner for permitting the use of apparatus. Thanks are likewise due to Mr. W. Saschek for performing the microanalyses.

Summary

1. A new synthesis yielding 40–60% of glycocholic acid is reported.

2. The following new compounds are described: triformylcholic acid, triformylcholyl chloride and triformylcholyl amide.

NEW YORK, N. Y. RECEIVED MAY 22, 1935

[CONTRIBUTION FROM THE PITTSBURGH EXPERIMENT STATION, U. S. BUREAU OF MINES]

Activity and Activation Energy in Heterogeneous Catalysis of Gas Reactions[1]

BY H. H. STORCH[2]

In a number of heterogeneous catalytic reactions[3,4,5] the use of the rate equation $k = Ae^{-E/RT}$ has led to an apparent relationship of the type $A = C_0e^{cE}$ where C_0 and c are constants, E is the activation energy, and A the activity constant. Unfortunately the energetics of the particular reactions chosen to illustrate this relationship are not simple. Thus, all but a few of the dehydrogenation reactions cited by Balandin[3] are apparently of first order,[6] and the contributions of the heats of adsorption to the E values are not known. Cremer's[4] comparison of the rates of decomposition of ethyl alcohol at atmospheric pressure by aluminum oxide, reduced indium oxide, and scandium oxide is of doubtful value because of the very marked retardation by water vapor and the lack of measurements on the order of the reaction, thus making impossible any precise statement concerning the significance of the E values. The same objections may be made to the use of similar data of Adkins and Perkins[7] on the decomposition of various alcohols by aluminum oxide and of Adkins and Nissen[8] on the decomposition of formic acid by various aluminum oxide catalysts.

The data of Eckell[5] on the oxidation of carbon monoxide by $Al_2O_3 + Fe_2O_3$ catalysts indicate a first order reaction with respect to the partial pressure of carbon monoxide; hence there is some uncertainty concerning the effect of possible variations in the heats of adsorption on the E values for the various catalysts. There is also a definite uncertainty as to the influence of adsorbed water vapor, for the water-gas reaction, $CO + H_2O = CO_2 + H_2$, may well be the rate-controlling step.

The problem of the relationship between activity and activation energy has also been discussed in connection with the activated adsorption of gases, particularly of hydrogen by similar catalysts.[9] In the experiments on activated adsorption the order of the reaction has not in any case been definitely determined, and the temperature coefficients are very variable depending upon the amount of gas adsorbed. The activation energies calculated from such measurements cannot therefore be conclusively designated as an invariant characteristic of a given surface reaction.

For the purpose of this discussion it seemed desirable to use data for zero order decompositions of a single reactant in which there is no retardation by reaction products and for which the rate measurements were made with a known degree of precision. These restrictions limit the discussion to the data of Palmer and Constable[10] on the dehydrogenation of various alcohols by copper catalysts, of Dohse[11] on the dehydration of various alcohols by bauxite, the dehydrogenation of methanol by zinc oxide,[12] and of Schwab and Schultes[13] and of Hüttig *et al.*[14]

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[1] Published by permission of the Director, U. S. Bureau of Mines. (Not subject to copyright.)

[2] Principal Physical Chemist, U. S. Bureau of Mines, Pittsburgh Experiment Station, Pittsburgh, Pa.

[3] Balandin, *Z. physik. Chem.*, **B19**, 451 (1932).

[4] Cremer, *ibid.*, **A144**, 231 (1929).

[5] Eckell, *Z. Elektrochemie*, **39**, 807, 855 (1933).

[6] That the assumption made by Balandin of zero order for all the reactions is erroneous can readily be seen from an inspection of the data of Zelinsky and Balandin [*Z. physik. Chem.*, **A126**, 267 (1927)].

[7] Adkins and Perkins, THIS JOURNAL, **47**, 1163 (1925).

[8] Adkins and Nissen, *ibid.*, **45**, 809 (1923).

[9] Howard and Taylor, *ibid.*, **56**, 2263 (1934).

[10] Palmer and Constable, *Proc. Roy. Soc.* (London), (a) **A107**, 255 (1925); (b) **A108**, 355 (1925); (c) **A113**, 254 (1927).

[11] (a) Dohse and Kälberer, *Z. physik. Chem.*, **B5**, 131 (1929); (b) Dohse, *ibid.*, **B6**, 343 (1930).

[12] Dohse, *ibid.*, **B8**, 159 (1930).

[13] Schwab and Schultes, *ibid.*, **B9**, 265 (1930).

[14] Hüttig, Schreiber and Kittel, *ibid.*, **A171**, 83 (1934).