We are indebted to Dr. J. W. E. Glattfeld of the University of Chicago for a sample of pure *d*-erythronic lactone and to Dr. W. T. Haskins of this Institute for carrying out some of the analyses.

Summary

The hydrolysis of the products of the periodic acid oxidation of cornstarch and cotton cellulose by 0.1 *N* aqueous hydrochloric acid at 98–99° has been shown to produce glyoxal and *d*-erythrose. These results prove that periodic acid breaks the carbon chain of the $C_6H_{10}O_5$ units of starch and cellulose between carbon atoms 2 and 3, and confirm the generally accepted structure of the predominating units in these polysaccharides. The possible presence of other types of units in minor quantities is not excluded by these results.

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CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE COLLEGE OF LIBERAL ARTS AND SCIENCES OF TEMPLE UNIVERSITY]

The Preparation of 3,7,12-Trioxy-23-aminonorcholane from Cholic Acid

BY WILLIAM T. CALDWELL

The remarkable role played by numerous derivatives of cyclopentanoperhydrophenanthrene in the initiation or maintenance of normal or abnormal growth imparts to them a peculiarly absorbing interest. However diverse the origins of sterols, bile acids, vitamin D, sex hormones, cardiac glycosides, toad poisons and carcinogenic hydrocarbons may be, their structural formulas suggest the possibility that various organisms may elaborate them from some common source or, at least, may be able to convert some of them into others. A comparison of the structures of such pairs of substances as pregnanediol and lithocholic acid, bufotalin and cholic acid or digitoxigenin and desoxycholic acid, makes clear the effect of changes involving, for the most part, the group attached to C-17; in the case of the last pair, it does not seem unreasonable to ascribe the marked difference in physiological action to the presence of the unsaturated lactone ring rather than to the change in position occupied by an hydroxyl group.

It seemed worth while, therefore, to attempt the preparation of various compounds by modifying the nature of the group attached to C-17. A consideration of the physiological activity of such substances as tyramine and histamine suggested that the introduction of an amino group into the radical attached to C-17 might result in the development of interesting pharmacological action; furthermore, if this could be done by a method such as the classic one due to Curtius, it would have the added value of an independent method of degradation made applicable to bile acids. This is no new thought as is quite clear from the statements made by Wieland, Schlichting and Jacobi[1] in the article in which they describe their very valuable method of degradation. After pointing out that attempts to degrade cholanic acid by way of the azide or amide had failed, they add, "So bestätigten zahlreiche Versuche—ein wenig erfreuliches und dem Aufwand an Arbeit nicht entsprechendes Ergebnis—nur wieder die mehrfach gemachte Erfahrung, dass an dem grossen Komplex des Gallensäure Moleküls die typischen Gruppenreaktionen häufig schwierig und regelwidrig ablaufen."[1a]

The application to cholic acid of Lindemann's modification of the Curtius reaction,[2] however, leads quite normally, as will be described below, to the formation of 3,7,12-trihydroxy-23-aminonorcholane.

A search of the literature disclosed the fact that Curtius himself had been interested in applying his method for the preparation of this same compound, reporting its preparation by E. Müller in the year 1906,[3] and giving to it the name "cholamine." However, many years later Borsche and Schwarz[4] called attention to the fact that the formation of this substance by Müller's method, involving, as it did, the

(1) Wieland, Schlichting and Jacobi, *Z. physiol. Chem.*, **161**, 80 (1926).

(1a) "Thus numerous experiments confirmed repeatedly the experience that, in the great complex of the bile acid molecule, the usual group reactions frequently proceed abnormally and with difficulty—a result giving little satisfaction and involving an incommensurate outlay of work."

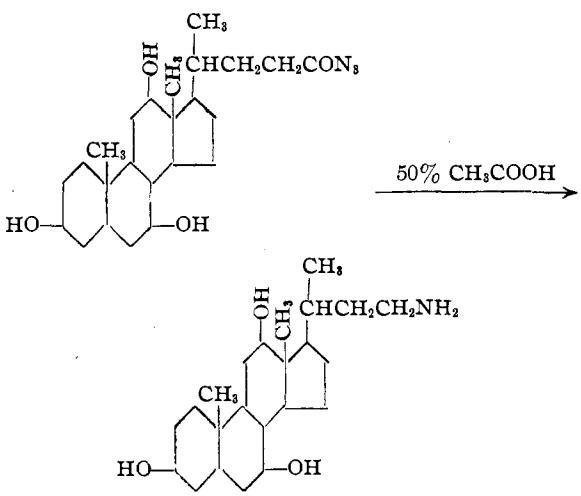
(2) Lindemann, *Helv. Chim. Acta*, **11**, 1028 (1928).

(3) Curtius, *Ber.*, **39**, 1389 (1906).

(4) Borsche and Schwarz, *ibid.*, **60**, 1843 (1927).

distillation of the urethan derived from cholylazide with caustic potash, was difficult to reconcile with subsequent observations of Wieland and Weil[5] to the effect that cholic acid, upon distillation *in vacuo*, even without the addition of dehydrating agents, loses water and forms cholatrienic acid. They pointed out, too, that "cholamine" had been incompletely characterized analytically in that no C or H determinations had been reported. Finally, their various attempts to repeat the preparation of "cholamine" failed in every case.

The preparation of 3,7,12-trihydroxy-23-aminonorcholane (cholamine) described below, by employing Lindemann's treatment of the azide with acetic acid, avoids the drastic hydrolysis of the urethan and leads, without difficulty and with good yield, directly to the desired product, in accordance with the equation



Comparison of the physical properties of Curtius' "cholamine" with those of this compound shows that the two are not identical. Although no record appears concerning the melting point of the free base, the hydrochloride is described as turning brown around 80°, melting at 120° and decomposing 20° higher with evolution of gas; the chloroplatinate turned brown in the neighborhood of 180° and melted at 193° forming a dark brown liquid. This compound, on the other hand, melting at 185–187°, forms a hydrochloride that showed no signs of change by 250°, but, when placed in a bath preheated to 260°, could be heated above 300° before showing any noticeable change in appearance, melting at 306–307° to a viscous honey-colored oil. The chloroplatinate melted at 230–232° with decomposition to a black tar. The compounds show a number of marked differences in solubility; they differ, too, in color, for "cholamine" crystallized from ethyl acetate as bright yellow needles, while this substance is snow-white.

(5) Wieland and Weil, *Z. physiol. Chem.*, **80**, 287 (1912).

Experimental Part

Hydrated methyl cholate,[6] m. p. 110–115° was converted into the azide[7] in the usual way. After filtering with suction, the wet cake, consisting of approximately 10 g. of azide and 90 g. of water, was broken into pieces, placed in 120 cc. of glacial acetic acid, and immediately warmed on the steam-bath under a reflux condenser. A lively evolution of the approximately theoretical volume of carbon dioxide and nitrogen (measured by displacement of water) took place, chiefly between 70 and 80°. After warming on the steam-bath until all evolution of gas had stopped (fifteen to twenty minutes), the clear solution was cooled thoroughly and then treated with the amount of concentrated potassium hydroxide required to neutralize the acetic acid used. The calculated amount of alkali required to liberate all organic base formed was added after the acid solution had just turned alkaline. The white solid that separated was filtered off with suction and, being only very slightly soluble in water, was washed thoroughly until free of inorganic base. For further purification, the compound was dissolved in ethanol in which it is very soluble, then water was added until the solution became opalescent and finally the mixture was concentrated on the steam-bath. In this way the product is obtained easily in the form of fine white crystals of the dihydrate, melting at 185–187°; yield, 70%, based on hydrazide used. It is very slightly soluble in benzene, ethyl acetate or ether; easily soluble in acetone, ethyl alcohol, chloroform and pyridine; insoluble in petroleum ether. Although very slightly soluble in water, it imparts a strong basic reaction to red litmus.

The dihydrate, on warming for two hours at 120°, becomes anhydrous. In this form it is more soluble in benzene, from which it separates in hair-like, fluffy, white needles, which, however, do not have a sharp melting point, softening after drying over sulfuric acid *in vacuo*, between 128 and 150°. They may be reconverted into the dihydrate by dissolving in alcohol and then adding water.

The hydrochloride, precipitated by hydrogen chloride gas from chloroform solution, melts at 306–307°; soluble in water, only slightly so in alcohol.

The chloroplatinate darkens somewhat at 226° and melts with decomposition at 230–232°.

Anal. Calcd. for $C_{23}H_{41}O_3N$: C, 72.76; H, 10.88; N, 3.69. Found: C, 72.71, 72.14; H, 10.52; N, 3.54.

Anal. Calcd. for $C_{23}H_{41}O_3N \cdot 2H_2O$: C, 66.50; H, 10.86; N, 3.37; H_2O, 8.67. Found: C, 66.91, 67.17; H, 10.85, 10.90; N, 3.83, 3.10; H_2O, 8.32.

Summary

The Lindemann modification of the Curtius

(6) Morsman, Steiger and Reichstein, *Helv. Chim. Acta*, **20**, 5 (1937).

(7) Bondi and Müller, *Z. physiol. Chem.*, **47**, 501 (1906).

reaction has been shown to be applicable to a bile acid as a method of degradation by the conversion of cholic acid into 3,7,12-trioxy-23-aminonorcholane.

The product is different from that obtained by E. Müller in Curtius' laboratory by hydrolysis of the appropriate urethan.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF HOFFMANN-LA ROCHE, INC., NUTLEY, NEW JERSEY]

2-Alkylthio-5-alkyl- and 2-Alkylthio-5,5-dialkylbarbituric Acids

BY JOHN LEE

Renewed interest of late in the 5,5-dialkyl-2-thiobarbituric acids has led to the preparation of some substances of therapeutic value by the condensation of dialkyl malonic esters with thiourea.[1-3] Tabern and Volwiler[2] report that the alkylation of 5,5-dialkylthiobarbituric acids does not give crystalline products but have as yet given no report of their proposed attempt to produce these substances from alkylated thioureas. A recent patent[4] discloses such a condensation, but, as is shown later, this patent must be viewed with some reserve. The present paper reports the preparation of 2-alkylthio-5,5-dialkylbarbituric acids through the 2-alkylthio-5-alkylbarbituric acids, both types of compound being previously unknown.

In an attempt to prepare 5,5-dialkyl-2-thiobarbituric acids by the alkylation of 5-monoalkyl-2-thiobarbituric acids, it was noted that the materials so obtained were not identical with those obtained by the condensation of the corresponding 5,5-dialkylmalonic esters with thiourea. When 5-isopropyl-2-thiobarbituric acid (I) was alkylated with allyl bromide, a material melting at 224–225° was obtained, whereas 5,5-allylisopropyl-2-thiobarbituric acid, since reported in the literature,[3] has a m. p. of 176.5°. Oxidation of the new acid (V) with hydrogen peroxide gave 5-isopropylbarbituric acid (IV) identical with that produced by the condensation of urea with isopropyl diethylmalonate, showing that the allyl group was introduced into the 2-position, the product being 5-isopropyl-2-allylthiobarbituric acid (V). This reaction course seems to be general since the oxidation of the methylation product of 5-isopropyl-2-thiobarbituric acid (II) also gives 5-isopropylbarbituric acid. Alkylation with methyl sulfate therefore also introduced the methyl group on the sulfur. With ethyl sulfate under the same conditions the reaction did not proceed. With other reagents containing reactive halogen, as, for example, 2-chlorocyclohexanone, the reaction occurs and presumably takes the same course.

The 5-alkyl-2-alkylthiobarbituric acids are comparatively stable, well-crystallized materials. On long standing in air they evolve thiol-like odors. Alcoholic solutions of the acids with aqueous ferric chloride give, in the case of the methylthio compound, a violet coloration. With the higher alkylthio compounds no color reaction is obtained.

Further alkylation of the 5-alkyl-2-alkylthiobarbituric acids results in the smooth formation of trialkyl compounds. With halides the reaction is best conducted in absolute alcoholic solution, but with methyl sulfate it also proceeds in the usual manner in aqueous solution. The point of attachment of the newly introduced alkyl group is not immediately apparent. In the case of allylation of 5-isopropyl-2-methylthiobarbituric acid the structures III or IIIb might arise. Oxidation experiments on this reaction product with permanganate and with hydrogen peroxide resulted in no identifiable compounds, nor did hydrolysis with acid or alkaline solution produce any. Similar degradation experiments were attempted with the product obtained by ethylation of 5-isopropyl-2-methylthiobarbituric acid since this does not contain the easily degraded allyl group. It was expected, analogously to the production of 5-isopropyl barbituric acid from 5-isopropyl-2-methylthiobarbituric acid, that the relatively stable 5,5-ethylisopropylbarbituric acid would have been obtained if the ethyl group was attached to the 5 carbon atom. Such an acid could not be isolated. The suspicion that the newly introduced alkyl group might be attached

(1) Miller, Munch and Crossley, *Science*, **81**, 615 (1935).
(2) Tabern and Volwiler, THIS JOURNAL, **57**, 1961 (1935).
(3) Miller, Munch, Crossley and Hartung, *ibid.*, **58**, 1090 (1936).
(4) I. G. Farbenindustrie, British Patent 468,683.