Summary

1. Simple as well as mixed aryl thioketones were prepared in good yields by the action of hydrogen sulfide–hydrogen chloride on the corresponding oxo ketone.

2. The above method is not applicable to the preparation of nitro thioketones.

3. The substitution of a biphenyl or α-naphthyl group for a phenyl group in thiobenzophenone greatly enhances the stability of the carbon–sulfur linkage.

4. The new thioketones show the typical reactions of the thiocarbonyl group. They show absorption bands around 5900 Å.

CHAPEL HILL, N. C. RECEIVED MAY 25, 1935

[CONTRIBUTION FROM THE KENT AND GEORGE HERBERT JONES CHEMICAL LABORATORIES, UNIVERSITY OF CHICAGO]

The Trihydroxybutyric Acids[1]

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For a number of years, studies have been in progress in these Laboratories on the preparation and identification of the possible products of the saccharinic acid transformation of the tetroses. In the course of this work, ten of the eleven theoretically possible C_4-saccharinic (dihydroxybutyric and isobutyric) acids have been prepared and to some extent characterized.[2] Equally important in the program are the trihydroxybutyric (*d*- and *l*-erythronic and *d*- and *l*-threonic) acids which offer possible source material for the preparation of the tetroses whose transformations it is proposed eventually to study.

Both the optically active and the racemic forms of erythronic lactone have long been known.[3] Braun[4] has recently prepared crystalline *dl*-threonic acid (m. p. 98°). The active forms of the acid are as yet unknown. *d*-Threonic lactone[5] has been discovered among the alkaline oxidation products of *l*-arabinose; *l*-threonic lactone[6] similarly among the oxidation or degradation products of *d*-galactose and *d*-glucose. The latter has also been obtained by Wohl and Momber[7] from glyceral acetal.

Perusal of the literature cited shows that while *dl*-erythronic lactone may be prepared in large quantities rather easily, all of the forms of threonic acid still remain practically unknown in amounts larger than a few grams. The object of the work reported below was to prepare enough *dl*-threonic acid or lactone to allow a thorough study of this substance. This object was only partially achieved.

Cohen[8] working in these Laboratories, prepared a mixture of *dl*-erythronic and *dl*-threonic acids by the oxidation of vinylglycolic ester with potassium chlorate and osmic acid. It was proposed to extend the work of Cohen in the hope that it would prove possible to set up a definite procedure for the isolation of the acid sought. This object has been accomplished.

Vinylglycolic acid, $CH_2{=}CHCHOHCOOH$, was found to be a better starting material than its ethyl ester, and silver chlorate a more satisfactory oxidizing agent than potassium chlorate. A mixture of the two acids was obtained in over 90% yield. From this mixture there was obtained (a) by a process involving differential neutralization of the two acids with barium hydroxide, 20% crystalline erythronic lactone and 7.2% threonic phenylhydrazide; and (b) by direct treatment with phenylhydrazine 4% of erythronic phenylhydrazide and 2% threonic phenylhydrazide with approximately one-half more recovered by reworking the filtrates and washings. Of the two processes, (a) is to be recommended as the better one. Because of the difficulty of the procedure and because the yield of threonic acid is so poor, other sources for its preparation are being sought.

Experimental Part

Cohen showed the presence of the threonic and erythronic acids by oxidation of the product with dilute nitric

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(1) This article is abstracted from a dissertation presented by R. E. Hoen in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Chicago.

(2) The last paper in this field is by Glattfeld and Chittum, THIS JOURNAL, **55**, 3663 (1933).

(3) For a list of the literature references on the various forms of this acid, see Glattfeld and Forbrich, *ibid.*, **56**, 1209 (1934).

(4) Braun, *ibid.*, **52**, 3176 (1930).

(5) Nef, Hedenburg and Glattfeld, *ibid.*, **39**, 1638 (1917).

(6) Anderson, *Am. Chem. J.*, **42**, 423 (1909); Glattfeld, *ibid.*, **50**, 150 (1913).

(7) Wohl and Momber, *Ber.*, **50**, 458 (1917). See also Micheel and Kraft, *Z. physiol. Chem.*, **216**, 233 (1933).

(8) Abstracts of Theses, University of Chicago Science Series, VI, 125 (1927–28).

acid. The nitric acid oxidation yielded racemic and mesotartaric acids. He also isolated small quantities of the phenylhydrazides of *dl*-erythronic and *dl*-threonic acids from the reaction mixture and reported the melting point of the former as 144–146° and of the latter as 172–173°. The pure phenylhydrazides prepared in the present work were shown to have melting points as follows: *dl*-erythronic phenylhydrazide, 147.5°; *dl*-threonic phenylhydrazide, 167.5°. The final procedures developed in this work are given below.

Preparation of Acrolein Cyanhydrin.—A modification of the method of Lobry de Bruyn[9] and van der Sleen[10] was employed. Alcohol-washed potassium cyanide as previously specified was found to be quite unnecessary. Sodium cyanide, dried by subjection to a temperature of 160–180° for two hours, was pulverized finely in a large mortar while still hot. In a two-liter round-bottomed flask equipped with two dropping funnels and a mechanical stirrer, were placed 125 g. of the sodium cyanide and 800 cc. of alcohol-free dry ether. The cyanide was kept in partial suspension by vigorous stirring while 150 cc. of glacial acetic acid and 100 cc. (1.5 moles) of freshly distilled acrolein were added dropwise and simultaneously. To minimize polymerization, about 15 cc. of the acid was introduced before any acrolein was allowed to enter the flask. The entire amounts of reagents were added within one and one-half hours, and, by means of a water-bath, the temperature of the mixture was maintained at 20–22°. If the ether was very dry, the reaction was promoted by the addition of 2–5 cc. of water. After two hours, the stirrer was stopped, and the mixture was allowed to stand until the odor of acrolein ceased to be appreciably noticeable (three hours). The solution was filtered with slight suction, and the salts washed twice with fresh ether (150-cc. portions). The combined ether solution was concentrated as much as possible, finally at 120 mm. and 65°. The residue of light straw-colored crude acrolein cyanhydrin weighed 120 g. It was not purified further.

Zinc Vinylglycolate and Vinylglycolic Acid.—To 120 g. of crude acrolein cyanhydrin was added with constant stirring and cooling when necessary 175 cc. of concentrated hydrochloric acid in the course of one hour. It was necessary to add the acid very cautiously, at first in 5–10 cc. portions. Temperatures above 75° were avoided. When spontaneous rise of temperature ceased, the mixture was kept at 70–75° by means of a water-bath for two hours. Sufficient water was added to dissolve the ammonium salts, and the yellowish liquid was subjected to extraction with 15 portions (1000 cc. in all) of ether. The extract was concentrated under diminished pressure to remove the ether. The residue was added to 40 g. of zinc oxide and 100 cc. of water and warmed to 90° for one hour. After the mixture had been cooled, the zinc salts set to a nearly solid mass, which was stirred with an equal volume of ethanol. The solid was freed of liquid by filtration, and finally washed with ethanol and with ether. The product when recrystallized three times from water (during which process any unchanged zinc oxide was removed by filtration), washed as before, and dried at 110°, weighed 74 g. (37% on the basis of the acrolein used). At 85°, 100 cc. of water dissolves 65 g. of the salt, and at 30° only 17 g.

Anal. Calcd. for $C_8H_{10}O_6Zn$: Zn, 24.44. Found: Zn, 24.31.

Vinylglycolic acid was obtained from zinc vinylglycolate by solution of 100 g. of the salt in twice the calculated quantity of dilute sulfuric acid (40 cc. of concentrated acid in 250 cc. of water), 10 to 15-fold extraction with alcohol-free ether (a total of 850–1000 cc.), and concentration of the ethereal extract under diminished pressure. Fractional distillation of the nearly colorless residue gave a fraction between 113 and 120° at 5.0–5.5 mm. which weighed 55 g., and which solidified nearly completely in the receiver. The crystalline product melted at 42–44°, and was very hygroscopic.[11] Titration of a sample of the substance indicated that it consisted largely of the lactone form of the acid. Further characterization of the product was not undertaken since van der Sleen had reported so fully his investigation of it.

Oxidation of Vinylglycolic Acid.—In a glass-stoppered bottle protected from sunlight there were placed 40 g. of crystalline vinylglycolic acid, 750 cc. of water, and 25 cc. of 0.3% solution of osmium tetroxide. The darkened solution rapidly became nearly colorless when there was added to it a solution of 5 g. of silver chlorate in a minimum volume of cold water. As soon as the dark color due to the lower oxides of osmium returned, additional portions of silver chlorate were introduced until a total of 35 g. had been added in the course of five days. When oxidation appeared to be practically complete (little unsaturation indicated by test with bromine water), the reaction mixture was extracted three times with benzene, treated with gaseous sulfur dioxide to destroy unreduced chlorates, filtered from precipitated silver chloride, carefully balanced with barium hydroxide, and filtered again. After concentration of the filtrate to 150 cc., and three-fold extraction of low molecular weight acids from it with ether, a final adjustment of barium and sulfate ions was made to ensure no excess of barium ion. Complete concentration of the filtrate under reduced pressure at 60° left 50 g. of a slightly colored viscous acidic gum which consisted largely of a mixture of trihydroxybutyric acids and their lactones.

Isolation of *dl*-Erythrolactone from Oxidized Vinylglycolic Acid.—Fifty grams of the crude oxidized acid gums prepared as above was neutralized with barium hydroxide in the cold to the first transient pink of phenolphthalein. This required 30 g. of barium hydroxide in 275 cc. of water (approximately one-half of the total calculated amount). The solution of lactones and barium salts was immediately poured into four liters of absolute ethanol, and the filtrate was separated as rapidly as possible from the precipitate with the aid of a suction filter precoated with acid-washed norit. Concentration of the filtrate under diminished pressure yielded a colorless viscous residue, which was freed of organically bound chlorine by addition of 2 g. of silver acetate and 50 cc. of water, and heating to 90° for two hours. Silver and bar-

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[9] Lobry de Bruyn, *Rec. trav. chim.*, **4**, 221 (1885).

[10] Van der Sleen, *ibid.*, **21**, 209 (1902).

[11] Lobry de Bruyn reported an analysis of this acid, and indicated that it melted at about 40°. Van der Sleen showed that the successive fractions of distillate under conditions comparable to those here reported consisted of increasingly higher concentrations of the lactone form. He reported that it melted at 33°.

ium were removed, and the solution was evaporated to dryness at 60–65° under diminished pressure. When cooled and seeded with *dl*-erythronic lactone, the viscous residue set to a nearly solid mass of crystals from which 10 g. (20%) of *dl*-erythrolactone (m. p. 88°) was isolated by addition of ethyl acetate, filtration and recrystallization from ethyl acetate.

***dl*-Threonic Phenylhydrazide from Oxidized Vinylglycolic Acid.**—The precipitated barium salts were freed of barium in the usual manner. The final viscous residue obtained by concentration of the filtrate from the barium sulfate at reduced pressure did not crystallize. To one-half (10 g.) of the non-crystalline residue was added an equal weight of phenylhydrazine and 20 cc. of absolute methanol. After twelve hours, 10 cc. of ethyl acetate was added to the partly solid mass, and the crystalline material was freed of mother liquor by filtration and washed with cold ethyl acetate. Three recrystallizations of the product from methanol gave 3 g. of threonic phenylhydrazide (7.2%) which melted at 167.5°. The melting point (167°) of the phenylhydrazide prepared from a sample of Braun's[4] crystalline threonic acid in our possession was not depressed by admixture with the product described above.

Anal. Calcd. for $C_{10}H_{14}N_2O_4$: N, 12.39. Found: N, 12.08.

Isolation of *dl*-Threonic Acid from its Phenylhydrazide.—Five grams of the phenylhydrazide of m. p. 167.5° prepared as above was treated with an equal weight of barium hydroxide and 10 cc. of water, covered with a layer of toluene and heated under a reflux condenser for five hours. The liberated organic bases were removed by five-fold extraction with toluene and one extraction with ether. The aqueous solution was again covered with toluene, refluxed for five hours, and the extraction repeated.[12] The solution was freed of barium in the usual manner, clarified by filtration through acid-washed norit, and concentrated to dryness under diminished pressure at not over 60°. The residue was extracted with anhydrous ether to remove traces of phenylhydrazine decomposition products, and was allowed to remain in a desiccator for a week. A small amount (30 mg.) of crystalline product appeared about the edges and was separated by filtration from the viscous liquid. After recrystallization from acetone, this material melted at 95°, and when mixed with authentic *dl*-threonic acid (m. p. 98° for this sample), the melting point was 96°. A mixture of the product with *dl*-erythrolactone melted at 85°.

The non-crystalline viscous product was subjected to distillation at 3 mm. The colorless viscous distillate (156–161°) failed to crystallize even when seeded with *dl*-threonic acid. Titration of the substance at room temperature and at 100° with dilute alkali indicated over 85% lactone content. Treatment of the distillate with phenylhydrazine yielded a product of m. p. 167° identical with the original *dl*-threonic phenylhydrazide. It would therefore appear that the conditions imposed in this preparation favored the lactonization of threonic acid, and thus possibly account for the limited crystallization of the free acid.

Separation of *dl*-Erythronic and *dl*-Threonic Phenylhydrazides by Fractional Crystallization.—Thirty grams of the acid gums from oxidation of vinylglycolic acid was treated with 25 g. of phenylhydrazine and 50 cc. of absolute methanol. After twelve hours the precipitated phenylhydrazides were freed of mother liquor, washed with ethyl acetate, and recrystallized from 125 cc. of methanol. The white crystalline product weighed 7 g. and melted at 133–137°. This melting point range was found in separate experiments to indicate 60–80% *dl*-erythronic phenylhydrazide and 40–20% *dl*-threonic phenylhydrazide. A careful reworking of the mother liquors frequently gave a product of higher *dl*-threonic phenylhydrazide content.

Seven grams of the mixed phenylhydrazides, m. p. 133–137°, was dissolved in 70 cc. of hot absolute methanol. The solution was cooled by immersion of the container in tap water for about twenty minutes and was stirred occasionally. Shorter times give little precipitate, and much longer times yield the same mixture as before. The white precipitate was promptly collected on a filter and washed with ethyl acetate. The product weighed 3.5 g. and melted at 138–143°. Recrystallization of the substance three or four times from absolute methanol and twice from absolute ethanol gave finally 2 g. of pure white crystals which melted at 147.5° (4% yield), and which did not depress the melting point of authentic *dl*-erythronic phenylhydrazide.

The filtrate and washings from the 3.5 g. of crystals above were concentrated to about 15 cc. and allowed to stand for twenty-four hours, the crystals collected on a filter and washed with ethyl acetate. This product (3 g., m. p. 140–148°) was dissolved in 40 cc. of hot absolute methanol and the solution filtered and allowed to cool slowly. The precipitate was recrystallized five times from ethyl acetate. The product weighed 1.0 g., melted at 167.5° (2% yield), and did not depress the melting point of authentic *dl*-threonic phenylhydrazide.

Summary

1. Improved procedures for the preparation of acrolein cyanhydrin and vinylglycolic acid are described. The melting point, 42–44°, of vinylglycolic acid (lactone?) is higher than previously reported.

2. A mixture of trihydroxybutyric acids has been prepared by oxidation of vinylglycolic acid with osmic acid activated silver chlorate. From this oxidation product, the components *dl*-erythrolactone and *dl*-threonic acid have been isolated and identified. In uncrystallized form, *dl*-threolactone was also shown to be present.

3. The melting points of *dl*-erythronic and *dl*-threonic phenylhydrazides were found to be 147.5 and 167.5°, respectively.

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(12) Much difficulty was encountered in the quantitative removal of phenylhydrazine with barium hydroxide, or by means of the recently published procedure of oxidation with cupric sulfate; see Hann and Hudson, THIS JOURNAL, **56**, 957 (1934).