Anal. Calcd. for $C_9H_{11}O_2NFCl$ (219.5): N, 6.4. Found: N, 6.5.

All attempts to prepare the diazonium fluoborate from this amine by the usual procedures were unsuccessful.

Methyl 3,5-Diamino-4-methoxybenzoate.—The methyl ester of 3,5-dinitroanisic acid[14] was reduced catalytically in an ethanol solution and a quantitative yield of the diamine, m. p. 157°, was obtained.

On tetrazotizing the diamine according to the method given by Schiemann and Pillarsky,[15] 55% of the theoretical amount of crystalline tetrazonium fluoborate separated very slowly from the reaction mixture. It was found impossible to control the decomposition of this salt so as to give a practical yield of difluoroanisic acid.

2,6-Diamino-4-nitrophenol.[16]—Hydrogen sulfide was passed into a solution of 75 g. of picric acid in 500 ml. of 28% ammonia and 500 ml. of water. Heat was evolved and cooling was necessary to prevent the temperature from rising above 75°. When the solution cleared and when heat was no longer evolved, the passage of hydrogen sulfide was stopped and the mixture evaporated *in vacuo* until the residue was practically free of ammonia. After filtration the solution was acidified, the precipitate extracted with dilute hydrochloric acid and the extract filtered. Careful addition of acid to the filtrate gave, on cooling, 45% of the theoretical amount of 2,6-diamino-4-nitrophenol, m. p. 169° dec.

Anal. Calcd. for $C_6H_7O_3N_3$ (169): N, 24.8. Found: N, 24.6.

Eight grams of the diamine heated on a steam-bath for one hour with 100 ml. of acetic acid and 9.5 g. of acetic anhydride gave a 65% yield of 2,6-diacetoamino-4-nitrophenol, m. p. 235° with decompn.

2,6-Diamino-4-nitroanisole.—Finely powdered 2,6-diacetamino-4-nitrophenol was treated, at 0° for twenty-four hours with an ethereal solution of diazomethane. A 75% yield of 2,6-diacetamino-4-nitroanisole, m. p. 211°, was obtained by recrystallizing the precipitate with ethyl acetate. 2,6-Diamino-4-nitroanisole, m. p. 180–181°, was obtained in an 85% yield from the diacetyl derivative by saponification with 5 *N* sodium hydroxide.

Anal. Calcd. for $C_7H_9O_3N_3$ (183): N, 22.9. Found: N, 23.0.

A 52% yield of the tetrazonium fluoborate was obtained from the above diamine but it was found that the salt decomposed explosively giving a very small amount of oily product.

2,6-Difluoro-4-nitroanisole.—To 2.4 g. of 2-fluoro-4-nitro-6-aminoanisole,[6b] m. p. 108°, in 3.6 ml. of concd. hydrochloric acid was added 0.9 g. of sodium nitrite in 2 ml. of water and the resulting filtered solution treated with 4 ml. of fluoboric acid. The diazonium fluoborate was obtained in a 60% yield. The decomposition of this salt was difficult to control and it was found impossible to obtain more than a 10% yield of 2,6-difluoro-4-nitroanisole, m. p. 35°.

Anal. Calcd. for $C_7H_5O_3NF_2$ (189): N, 7.4. Found: N, 7.5.

Summary

The synthesis of 3,5-difluoro- and 3-fluoro-5-iodo-*dl*-tyrosine from *o*-anisidine has been described.

PASADENA, CALIFORNIA RECEIVED DECEMBER 1, 1939

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[14] F. Ullmann, *Ann.*, **366**, 94 (1909).

[15] G. Schiemann and R. Pillarsky, *Ber.*, **62**, 3039 (1929).

[16] P. Griess, *Ann.*, **154**, 202 (1870).

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

dl-Threonic Acid from 3-Hydroxy-crotonic Acid

BY J. W. E. GLATTFELD AND E. C. LEE[1]

While *dl*-erythronic lactone can be prepared without difficulty and in quantity directly from 3-hydroxy-isocrotonic lactone[2] which itself is easily obtained in good yield as a by-product in the synthesis of *dl*-2,3-dihydroxybutyric acid,[3] the epimeric tetronic acid, *dl*-threonic acid, is still a rare chemical. The only synthesis of the last-named acid that is reported in the literature was accomplished by Braun.[4] Glycerol-1,3-dichlorohydrin is the starting material and this is converted into *dl*-threonic acid by a procedure consisting of six steps. While the yield in each step is good (varying from 25 to 81%) the over-all yield is only about 2% of the theoretical.[5] As none of the intermediates is available commercially, it becomes necessary to start with glyceroldichlorohydrin in each attempt to synthesize *dl*-threonic

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[1] The material in this article is taken from a dissertation submitted by E. C. Lee in August, 1936, to the faculty of the Division of the Physical Sciences in the University of Chicago in partial fulfilment of the requirements for the Ph.D. degree. Dr. Lee died in June, 1939. This article has been prepared by the senior author.

[2] Braun, THIS JOURNAL, **51**, 235 (1929).

[3] Glattfeld, Leavell, Spieth and Hutton, *ibid.*, **53**, 3164 (1931).

[4] Braun, *ibid.*, **52**, 3167 (1930); **54**, 1133 (1932).

[5] Braun also prepared one of the intermediates, 2-hydroxy-3-chloro-butyronitrile from epichlorohydrin and hydrogen cyanide (Lespieau) in 65% yield as against 25% from glycerol-1,3-dichlorohydrin. This would make the over-all yield of *dl*-threonic acid from the former 6.5% as against 2% from the latter. In spite of the lower yield, Braun seems to consider the dichlorohydrin as the starting material in this procedure for he says [*ibid.*, **52**, 3168 (1930)] "Lespieau's method has the great disadvantage that the handling of anhydrous hydrogen cyanide above its boiling point is very inconvenient. The *new procedure* (italics the author's) avoids this; it involves the treatment of dichlorohydrin with sodium cyanide in aqueous suspension."

acid. This acid is a possible source of *dl*-threose, which is necessary for the study of the saccharinic acid rearrangement of the tetroses which has been undertaken in these laboratories. It is for this reason that efforts to simplify Braun's synthesis or to find a new synthesis for this substance are being continued as opportunity offers. Some improvements have been made in Braun's procedure. These will be reported in another paper. In the present article, the transformation of 3-hydroxy-crotonic acid into *dl*-threonic acid is reported.

The starting material in this synthesis is acrolein. This has been transformed into *dl*-threonic acid with an over-all yield of 4.1% of the theoretical in five steps: acrolein $\xrightarrow{(1)}$ vinylglycolic nitrile $\xrightarrow{(2)}$ ethyl vinylglycolate $\xrightarrow{(3)}$ ethyl 3-bromo-crotonate $\xrightarrow{(4)}$ 3-hydroxy-crotonic acid $\xrightarrow{(5)}$ *dl*-threonic acid.

3-Hydroxy-crotonic acid was not recorded in the literature until 1932, when its preparation was reported by Kirrman and Rambaud.[6] The first three steps in their synthesis were the same as the first three listed under the new procedure indicated above. They then transformed the ethyl 3-bromo-crotonate into ethyl 3-acetoxy-crotonate, which in turn was hydrolyzed to 3-hydroxy-crotonic acid. The entire sketchily-described procedure of Kirrman and Rambaud was repeated. From one mole of acrolein, a few grams of the hydroxy-acid was obtained, but when five moles of acrolein was used, none was obtained. The severe treatment of the 3-bromo-ester with sodium acetate in boiling acetic acid was suspected of causing rearrangement, the longer period of heating required with larger quantities affording more opportunity for this to take place. Conversion of the bromo-ester to the acetoxy-ester was therefore eliminated, the former being hydrolyzed directly to 3-hydroxy-crotonic acid in improved yield by means of aqueous potassium carbonate. Incidentally, the preparation of ethyl vinylglycolate was studied and the yield reported in the literature[7] (49% from acrolein) improved by about 10%.

Experimental Part

Preparation of Ethyl Vinylglycolate (Steps 1 and 2).—The procedure was that used by Lobry de Bruyn[8] and by Van der Sleen.[7] Although these authors give detailed descriptions of the procedure a few comments on it should be made.

The addition of hydrogen cyanide to the acrolein proceeds slowly in a perfectly dry medium. Too much water on the other hand, causes polymerization of both the acrolein and the cyanohydrin. Ether of the proper water content was obtained by washing ordinary ether with saturated salt solution, strong permanganate solution, and water consecutively, shaking up the ether with sodium sulfate, and storing it over the sulfate for fifteen hours. Instead of adding glacial acetic acid in portions to the mixture of acrolein, ether and potassium cyanide, it was found advantageous to add the cyanide (pulverized but not dried) in portions to an ether solution of acrolein and glacial acetic acid at 10° (not lower). After all of the cyanide (1.5 moles) had been added, the reaction mixture was allowed to stand for two hours (no longer) with occasional shaking. Water was then added to dissolve the salt and the extraction with ether and subsequent distillation carried out as soon and as rapidly as possible. The last of the ether was removed at reduced pressure, yielding the crude cyanohydrin as a residue. This was transformed into the ethyl ester essentially by the procedure of Van der Sleen, 2 moles of acrolein (112 g.) giving 160 g. of the ester: a 61% yield.

Preparation of Ethyl 3-Bromo-crotonate (Step 3).—To a vigorously stirred mixture of 54 g. of phosphorus tribromide and 5 cc. of pyridine[9] kept at 20°, was added dropwise a solution of 10 g. of pyridine in 65 g. (0.5 mole) of ethyl vinylglycolate over a period of one and one-half hours. The mixture was stirred an additional half-hour, and then subjected to distillation at 13 mm. until considerable fuming occurred and the distillate became orange. The entire product was redistilled twice to free it of colored material and to complete the rearrangement and then fractionated. The second portion, which distilled at 77.5–84.5° at 6 mm., weighed 49 g.; a yield of 51% on the basis of the ethyl vinylglycolate.

Preparation of 3-Hydroxy-crotonic Acid (Step 4).—A mixture of 49 g. (0.25 mole) of the ester and 83 g. (0.5 mole) of hydrated potassium carbonate in 200 cc. of water kept at 80° was vigorously stirred for four hours at the end of which time it was cooled to 10°. Under vigorous stirring, 75 cc. of concentrated hydrochloric acid was added. Troublesome foaming due to escaping carbon dioxide was controlled by the occasional addition of a small amount of ether. The solution after filtration to remove a small amount of dark oil was concentrated under reduced pressure at 60°. The slightly-colored crystalline residue was heated with 57 cc. of acetone, the solution filtered while hot, and the material on the filter paper washed with three 25-cc. portions of acetone. The combined filtrates were filtered once more and then reduced in volume as completely as possible in vacuum at 45°. The warm residue, partly crystalline, was dissolved in 23 cc. of hot ethyl acetate. The solution was allowed to stand in an ice–salt mixture for an hour. The crystals were separated, washed with a minimum of ethyl acetate, and then recrystallized from 11 cc. of ethyl acetate. The product was dried, first in the air on a porous plate, and then in a desic-

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(6) Kirrman and Rambaud, *Compt. rend.*, **194**, 1168 (1932); **196**, 487 (1933).

(7) Van der Sleen, *Rec. trav. chim.*, **21**, 211 (1902).

(8) Lobry de Bruyn, *ibid.*, **4**, 221 (1885).

(9) Bouis, *Ann. chim.*, **9**, 411 (1928).

cator over concentrated sulfuric acid. It weighed 7.1 g.; a yield of 27.8% on the basis of the bromo-ester. The product melted at 108°, the recorded melting point of 3-hydroxy-crotonic acid.

Preparation of *dl*-Threonic Acid (Step 5).—To 10.2 g. (0.1 mole) of 3-hydroxy-crotonic acid in 500 cc. of water and 2.5 cc. of a 1% aqueous solution of osmic acid was added 6.4 g. (0.033 mole) of silver chlorate in two portions separated by an interval of twenty-four hours. After forty-eight hours the silver chloride was removed by filtration, and the filtrate reduced in volume as completely as possible in vacuum at 60° and 15 mm. The sirupy residue was dissolved in 30 cc. of acetone, the solution filtered from a small amount of dark material, and most of the acetone evaporated from a crystallizing dish on the steam-bath. The material was then stored in a vacuum desiccator over concentrated sulfuric acid until bubbling ceased. The partly crystalline mass was then dissolved in 10 cc. of ethyl acetate and the solution chilled in an ice-salt bath. The crystals were separated and washed with a mimimum of ethyl acetate. The product, which melted at 97°, weighed 6.5 g.; a yield of 48% based on the hydroxy acid. A small portion of the product was recrystallized from the same solvent. This material melted at 99°. It showed no depression of the melting point when mixed with a sample of *dl*-threonic acid which had been prepared by Braun.

Summary

The work of Kirrman and Rambaud on the preparation of 3-hydroxy-crotonic acid was successfully repeated. The yield, however, was very low.

Their procedure has been modified so that 3-hydroxy-crotonic acid can now be obtained in four steps from acrolein in 8.6% yield.

3-Hydroxy-crotonic acid has been oxidized to *dl*-threonic acid with silver chlorate and osmic acid in 48% yield. The over-all yield of threonic acid, from acrolein in five steps, (4.1%) compares favorably with that obtained by Braun (2.5%) in six steps from glycerol-1,3-dichlorohydrin.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, NATIONAL CENTRAL UNIVERSITY, CHINA]

Keto-cyclol Tautomerism of 1,6-Diketones. 1,4-Dibromo-1,4-dibenzoylbutane*

BY TSI-YU KAO

In seeking for a direct method for the preparation of 1,2-dibenzoylcyclobutane (IV) the action of molecular silver on 1,4-dibromo-1,4-dibenzoylbutane was tried. Since silver is a monovalent element it appeared altogether unlikely that it would lead to a Reformatsky condensation such as that reported by Fuson and Farlow.[1] These authors treated 1,4-dibromo-1,4-dibenzoylbutane with zinc and obtained besides 1,4-dibenzoylbutane (III) three other compounds: 2-phenyl-3-benzoylcyclopentanone, 1-phenyl-5-benzoyl-1-cyclopentene (IX), and its oxide (VIII).

Molecular silver actually gave a small yield of the desired cyclobutane derivative, but the chief product was 1-phenyl-5-benzoyl-1-cyclopentene oxide (VIII). The formation of this substance is explained adequately by the keto-cyclol tautomerism of 1,6-diketones. This mechanism explains equally well the formation of the cyclopentene derivatives from the dibromo compound (I) by the action of zinc dust.

While the cyclol forms of simple 1,6-diketones have not been isolated, there is considerable evidence that their existence is possible. For example, Baeyer and Liebig[2] obtained 1-cyclopentenealdehyde as well as adipaldehyde by oxidation of α,α'-dihydroxysuberic acid. Marshall and Perkin[3] showed that 1,4-diacetylbutane when distilled or boiled with alcoholic potash gave 1-acetyl-2-methyl-1-cyclopentene. By the action of sodamide on 1,4-dibenzoylbutane Bauer[4] obtained two isomeric cyclopentene derivatives: 2-phenyl-3-benzoyl-1-cyclopentene and 1-phenyl-2-benzoyl-1-cyclopentene. The latter was prepared by Skraup and Guggenheimer[5] by heating 1,4-dibenzoylbutane at 300–310°. Similarly, 2,4,5-triphenyl-1-benzoyl-1-cyclopentene results when 1,4-dibenzoyl-2,3-diphenylbutane is treated with sodium ethylate.[6] All of these transformations can be explained as due to the elimination of water from the cyclol form of the diketone or diacid.

Still more striking evidence for the existence of the cyclol forms has been furnished by Vogel,[7] who showed that 2,2,3,3-tetramethyl-1,4-diacetylbutane exists only in the cyclol form.

(*) Original manuscript received January 16, 1939.

[1] Fuson and Farlow, THIS JOURNAL, **56**, 1593 (1934).

[2] Baeyer and Liebig, *Ber.*, **31**, 2107 (1898).

[3] Marshall and Perkin, *J. Chem. Soc.*, **57**, 241 (1890).

[4] Bauer, *Compt. rend.*, **155**, 288 (1912).

[5] Skraup and Guggenheimer, *Ber.*, **58B**, 2495 (1925).

[6] Conant and Cutter, THIS JOURNAL, **48**, 1026 (1926).

[7] Vogel, *J. Chem. Soc.*, **128**, 594 (1927).