40°), and cooled with ice and salt. The crystals which precipitated melted at 62–63°.

Basic Esters.—A mixture of 0.015 mole of the acetic acid, 0.015 mole of the basic alkyl chloride[27] and 40 cc. of dry isopropyl alcohol[28] was refluxed for forty hours, the alcohol removed on a steam-bath in a current of air, and the residue washed repeatedly with absolute ether.

In order to obtain the β-morpholinoethyl esters, 0.02 mole of the acetic acid and 7 cc. of pure thionyl chloride were refluxed for two hours. The excess thionyl chloride was removed on a steam-bath under reduced pressure. In order to remove traces of thionyl chloride, 10 cc. of dry benzene was added, and then removed under diminished pressure; this process was repeated three times. The acetyl chloride was cooled with ice, and 2.98 g. (0.0275 mole) of β-morpholinoethyl alcohol, dissolved in 20 cc. of dry benzene added slowly while the mixture cooled in ice and was shaken. The latter was refluxed for two hours on a steam-bath, and the benzene removed under reduced pressure. The crystalline residue was triturated with 50 cc. of water which contained a few drops of hydrochloric acid. The mixture was extracted with ether, the aqueous layer separated, and made alkaline with sodium carbonate solution. The precipitated ester was extracted with ether, and the extract shaken with water to remove any traces of the alcohol. The extract was dried with magnesium sulfate, filtered and hydrogen chloride passed into it. The ester precipitated in crystalline form in about 60% yield.

Summary

Basic esters of α-naphthylacetic, α-naphthylmethyl-, α-naphthylethyl- and α-naphthylphenylacetic acid have been prepared. All of the esters have been found to be antispasmodics, and some of them exhibit high activity.

ANN ARBOR, MICHIGAN RECEIVED FEBRUARY 7, 1944

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[27] The melting point for β-piperidinoethyl chloride hydrochloride was reported to be 208° by Marckwald and Frobenius (*Ber.*, **34**, 3557 (1901)), as well as by Knorr, Hörlein and Roth (*ibid.*, **38**, 3138 (1905)). Dunlop (*J. Chem. Soc.*, **101**, 2202 (1912)) stated that the salt melts at 231°. Prepared by Dunlop's method, we found that the hydrochloride melts at 229–230° and that β-piperidinoethyl chloride boils at 69° (12 mm.).

[28] Method of Horenstein and Pählicke (*Ber.*, **71**, 1654 (1938)).

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

The Synthesis of DL-Threose. Preparation of DL-Tribenzoyl-erythrose

BY W. W. LAKE[1] WITH J. W. E. GLATTFELD

For a number of years these Laboratories have been engaged in the synthesis and characterization of the eleven C_4-saccharinic acids which are the theoretically possible products of the saccharinic acid rearrangement of the aldotetroses as defined in the third paper cited below.[2]

More recently, attempts have been made to synthesize the aldotetroses themselves. Some success has been achieved in the preparation of DL-erythrose[3] by the reduction of DL-erythronic lactone. The present paper reports the development of a method for the synthesis of DL-threose which is needed as the initial material in a proposed study of the saccharinic acid rearrangement of the tetroses.

DL-Threose.—DL-Threonic acid, synthesized by Braun[4] from glycerol dichlorohydrin and recently by Glattfeld and Rietz[5] from allyl alcohol, offered a starting material of the right configuration, which, if successfully reduced, would yield the desired DL-threose. It was thought that the reduction might be accomplished by the complete benzoylation of DL-threonic acid, conversion to the corresponding acid chloride, and reduction of the benzoyl acid chloride by a method similar to that employed by Glattfeld and Kribben[3] in the reduction of DL-triacetyl-erythronic acid. However, benzoylation of DL-threonic acid yielded DL-dibenzoyl-threonic lactone instead of the desired DL-tribenzoyl-threonic acid and indirect methods of obtaining the completely benzoylated acid were thus shown to be necessary.

During the progress of this work, Hurd and Sowden[6] published a satisfactory method for the preparation of fully acetylated aldonic acids by the action of nitrous anhydride in glacial acetic acid on the amides of fully acetylated aldonic acids. About the same time, Robbins and Upson[7] showed that the amides of fully acetylated aldonic acids could be prepared in good yield by direct acetylation of aldonic amides. Glattfeld and Macmillan[8] have shown that the amides of aldonic acids may be conveniently prepared in good yield by the action of liquid ammonia on the corresponding acid lactones. A combination of procedures similar to these seemed, therefore, to offer a promising method for the preparation of fully benzoylated DL-threonic acid from DL-threonic lactone.

It was found that DL-threonic lactone could be readily obtained in good yield by thermal decomposition, at reduced pressure, of the potassium salt of DL-*threo*-2,3-dihydroxy-4-chloro-butanoic acid which is an intermediate in the synthesis of DL-threonic acid by the methods of both Braun[4] and Glattfeld and Rietz.[5] The solid potassium salt of DL-*threo*-2,3-dihydroxy-4-chlorobutanoic acid was prepared in practically quanti-

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[1] This article is condensed from a dissertation presented by W. W. Lake in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the University of Chicago, 1941. Much of the experimental work was carried out in the laboratories of the Texas College of Mines and Metallurgy.

[2] Glattfeld and co-workers, THIS JOURNAL, **42**, 2314 (1920); **43**, 2675 (1921); **47**, 1742 (1925); **49**, 2309 (1927); **53**, 3164 (1931); **55**, 1114 (1933); **55**, 3663 (1933); **60**, 415 (1938).

[3] Glattfeld and Kribben, *ibid.*, **61**, 1720 (1939).

[4] Braun, *ibid.*, **52**, 3167 (1930); **52**, 3176 (1930).

[5] Glattfeld and Rietz, *ibid.*, **62**, 974 (1940).

[6] Hurd and Sowden, *ibid.*, **60**, 235 (1938).

[7] Robbins and Upson, *ibid.*, **60**, 1788 (1938).

[8] Glattfeld and Macmillan, *ibid.*, **56**, 2481 (1934).

tative yield by neutralizing a solution of the acid in absolute alcohol with an absolute alcohol solution of potassium hydroxide. Decomposition of the salt at pressures of 0.1 to 0.5 mm. and temperatures of 180–190° gave a practically pure lactone in about 80% yield based on the salt.

This discovery of a short method for the preparation of DL-threonic lactone should simplify the difficult task of preparing DL-threonic acid. The last step of Braun's[4] original method for the preparation of DL-threonic acid involves the hydrolysis of the barium salt of DL-*threo*-2,3-dihydroxy-4-chlorobutanoic acid with silver oxide, a tedious procedure requiring some thirty-five to forty hours. Braun[9] later developed a method of hydrolysis of the bromo acid, which took less time and gave larger yields, by substituting silver acetate for silver oxide. In the case of DL-*threo*-2,3-dihydroxy-4-chlorobutanoic acid, however, the time required for hydrolysis when silver acetate is used is extended to as much as one hundred sixty hours. Glattfeld and Rietz[5] have used the silver acetate procedure in their improved method for preparing DL-threonic acid. Since DL-threonic lactone can be prepared quickly by thermal decomposition of the potassium salt of DL-*threo*-2,3-dihydroxy-4-chlorobutanoic acid and easily converted into DL-threonic acid by hydrolysis with aqueous barium hydroxide and subsequent removal of the barium with sulfuric acid, this procedure should greatly decrease the time involved in the preparation of DL-threonic acid.

DL-Threonic lactone was converted into DL-threonamide by the method of Glattfeld and Macmillan,[8] the amide benzoylated by dissolving it in pyridine and adding a slight excess of benzoyl chloride, and the DL-tribenzoylthreonamide converted into DL-tribenzoylthreonic acid by treatment with nitrous anhydride in glacial acetic acid according to the method of Hurd and Sowden.[6] The benzoylated acid was smoothly converted into the corresponding acid chloride by the use of carefully purified thionyl chloride and the acid chloride reduced with hydrogen in the presence of palladinized barium sulfate to DL-tribenzoylthreose according to the method developed by Rosenmund.[10] DL-Tribenzoylthreose was hydrolyzed at 0° in an atmosphere of nitrogen by means of an aqueous solution of barium hydroxide. The barium and benzoic acid were quantitatively removed and the solution evaporated to a thick sirup. The sirup was dissolved in absolute methyl alcohol, the solution filtered, and the filtrate concentrated to a thick sirup.

Hydrolysis of the DL-tribenzoylthreose was also accomplished at −15° by Hockett's[11] method, using a 2% solution of sodium methylate in absolute methyl alcohol.

Both methods of hydrolysis yielded a thick sirup which readily reduced Fehling's solution in the cold and formed an osazone which melted at 168° (cor.) when introduced into a bath held at this temperature. When introduced into a bath at 165°, the temperature of which was rising at the rate of 3° per minute, the osazone melted with decomposition at 167–168° (cor.). Ruff[12] gives the m. p. of DL-erythrosazone, which is identical with DL-threosazone, as 164° (cor.); Fischer and Tafel,[13] as 166–167° (uncor.); and Fenton and Jackson,[14] as 167°. Analysis of the freshly prepared osazone gave results in agreement with the theoretical values.

The sirup obtained by hydrolysis of DL-tribenzoylthreose was oxidized with bromine in the barium benzoate by the method of Hudson and Isbell.[15] The product of oxidation when dissolved in pyridine and treated with benzoyl chloride yielded DL-dibenzoylthreonic lactone identical with that previously obtained by benzoylation of DL-threonic acid.

DL-Tribenzoylerythrose.—DL-Erythronic lactone, prepared by the oxidation[16] of the lactone of γ-hydroxy-isocrotonic acid,[17] was carried through the same series of reactions as DL-threonic lactone, yielding a DL-tribenzoyl-erythrose which, however, has not yet been obtained in crystalline form. Work on the crystallization and hydrolysis of this compound to DL-erythrose is being continued.

Experimental Part

I. DL-Threose

Preparation of DL-Threonic Acid.—The improved method of Glattfeld and Rietz[5] not being available at the time this work was carried out, the method of Braun[1] was used with the exception that, in the final stages, removal of water was carried out at room temperature and to the point where the residue remained a *thin* sirup instead of a thick sirup as prescribed by Braun. In our experience crystals of DL-threonic acid will separate only from a thin sirup.

Preparation of DL-Dibenzoyl-threonic Lactone by Benzoylation of DL-Threonic Acid.—One-half gram of crystalline DL-threonic acid was dissolved in 5 g. of pure pyridine and 1.7 g. of freshly distilled benzoyl chloride added dropwise, with shaking and cooling. After standing at room temperature for one hour, the mixture was poured into 200 cc. of cold water. An oil separated, which solidified when the mixture was stirred for one-half hour. The solid was ground to a powder, separated by filtration, and washed well with water. The dried product weighed 1.37 g. Crystallization from absolute alcohol gave 0.68 g. of pure, white crystalline compound which melted at 142.5°.[18]

Anal. Calcd. for DL-dibenzoyl-threonic lactone, $C_{18}H_{14}O_6$: C, 66.34; H, 4.31. Found: C, 66.03; H, 4.36.

Preparation of the Potassium Salt of DL-*threo*-2,3-Dihydroxy-4-chlorobutanoic Acid.—Sixty grams of DL-*threo*-

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[9] Braun, THIS JOURNAL, **54**, 1137 (1932).

[10] Rosenmund, *Ber.*, **51**, 585 (1918).

[11] Hockett, THIS JOURNAL, **57**, 2260 (1935).

[12] Ruff, *Ber.*, **34**, 1367 (1901).

[13] Fischer and Tafel, *ibid.*, **20**, 1090 (1887).

[14] Fenton and Jackson, *J. Chem. Soc.*, **75**, 7 (1899).

[15] Hudson and Isbell, THIS JOURNAL, **51**, 2226 (1929).

[16] (a) Hilmeyer Cohen, Ph.D. dissertation, University of Chicago, 1928; (b) Braun, THIS JOURNAL, **51**, 235 (1929).

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

[18] All melting points were taken with Anschütz thermometers calibrated against a thermometer certified by the U. S. Bureau of Standards, the mercury column being completely immersed in a mechanically stirred bath.

2,3-dihydroxy-4-chloro-butanoic acid was dissolved in 180 cc. of absolute alcohol and slowly neutralized with approximately normal potassium hydroxide in absolute alcohol, using phenolphthalein as indicator. The salt precipitated as a white crystalline powder. The mixture was cooled to room temperature and, after having stood for one hour, the solution was filtered and the solid washed with absolute alcohol. The yield was 73.3 g. or 98% of the theoretical. The salt decomposes in the course of several months at room temperature into DL-threonic lactone and potassium chloride.

Anal. Calcd. for the potassium salt of DL-*threo*-2,3-dihydroxy-4-chlorobutanoic acid, $C_4H_6O_4ClK$: Cl, 18.41. Found: Cl, 18.34.

Preparation of DL-Threonic Lactone.—Ten grams of the potassium salt of DL-*threo*-2,3-dihydroxy-4-chlorobutanoic acid was decomposed in an all-glass apparatus consisting of a 25-cc. round-bottom flask with a short neck, sealed to a small alembic as shown in Fig. 1. The flask was immersed in an oil-bath heated to 180-190° and the pressure maintained at 0.1 to 0.5 mm. The lactone distilled over as a slightly colored, oily liquid. The yield was 5.1 g. or 83% of the theoretical. Distillation at reduced pressure of 25 g. of the crude lactone from a distilling flask with a low side arm, the bulb of which was filled with glass wool to prevent bumping, gave 21 g. of pure, colorless, viscous lactone boiling at 151-151.5° at 0.5 mm. All efforts to obtain the lactone in crystalline form failed.

Anal. Calcd. for DL-threonic lactone: sapon. equiv., 118.1. Found: 117.8.

Saponification of DL-Threonic Lactone.—Two grams of DL-threonic lactone was dissolved in 100 cc. of water. The solution was heated to 70-80°, and neutralized to phenolphthalein with approximately 0.1 *N* barium hydroxide. The neutral solution was treated with the equivalent amount of sulfuric acid, the barium sulfate centrifuged off, and the clear liquid evaporated under reduced pressure at a temperature not exceeding 30° to a *thin* sirup. On standing overnight the sirup crystallized. The crystals were loosened from the flask with acetone, separated by filtration and washed with acetone. After recrystallization from a mixture of 75% acetone and 25% alcohol, the compound melted at 98°. A mixture with a sample of DL-threonic acid prepared by Braun's[4] method melted at 98°.

Preparation of DL-Dibenzoyl-threonic Lactone by Benzoylation of DL-Threonic Lactone.—Four-tenths gram of DL-threonic lactone was dissolved in about 4 cc. of pyridine and treated with a slight excess of freshly-distilled benzoyl chloride. After standing at room temperature for one-half hour, the mixture was poured into 100 cc. of water and the oil which separated was stirred until it solidified. Two crystallizations from alcohol gave a product which melted at 142.5°. The m. p. was not depressed when a sample was mixed with the DL-dibenzoyl-threonic lactone obtained by benzoylating DL-threonic acid.

Preparation of DL-Threonamide.—The procedure of Glattfeld and Macmillan[8] was used. Both the crude lactone (obtained by thermal decomposition of the potassium salt) and the pure redistilled lactone gave the amide, the latter in almost quantitative yield. Seeds were obtained by rubbing a small portion of the residue from the evaporation of the ammonia in a test-tube with a glass rod. The crude product was recrystallized twice from absolute alcohol and yielded hard white crystals of m. p. 116°.

Anal. Calcd. for DL-threonamide, $C_4H_9O_4N$: C, 35.55; H, 6.71; N, 10.37. Found: C, 35.70; H, 6.69; N, 10.31.

Preparation of DL-Tribenzoyl-threonamide.—Twenty grams of finely powdered DL-threonamide was dissolved (partly suspended) in 200 cc. of pure pyridine. Sixty-seven and three-tenths grams (2% excess) of freshly-distilled benzoyl chloride was added in 5-g. portions, with vigorous shaking, and cooling between additions. After the addition of 30 g. of benzoyl chloride, all the amide had gone into solution and after the addition of 50 g., pyridine hydrochloride began to precipitate. After standing at room temperature for two hours, the reaction mixture was poured with vigorous stirring, into 5 liters of water. Without decanting the water from the thick gum which separated, the mixture was seeded[19] and stirred for one hour. At the end of this time the gum had completely solidified. The solid mass was separated and pulverized in a mortar, thrown on a filter, washed with water, and dried. The yield of pale yellow product was 62.2 g. or 94% of the theoretical. The finely powdered crude product was washed with 100 cc. of cold absolute alcohol, which removed most of the colored impurity. The residue, weighing 53.7 g., was recrystallized from 590 cc. of absolute alcohol, using a small amount of norite to remove the final tarces of color. The yield was 46.4 g. of pure white compound melting at 155°.

Anal. Calcd. for DL-tribenzoyl-threonamide, $C_{25}H_{21}O_7N$: C, 67.11; H, 4.73; N, 3.13. Found: C, 67.17; H, 4.72; N, 3.10.

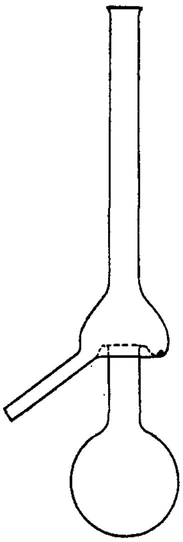

Fig. 1.

Preparation of DL-Tribenzoyl-threonic Acid.—Twenty grams of finely powdered DL-tribenzoyl-threonamide was dissolved (partly suspended) in 80 cc. of glacial acetic acid and cooled to about 15°. Liquid nitrous anhydride[20] was added until the liquid assumed a bluish-green color. Evolution of nitrogen soon started and the tribenzoylamide gradually went into solution. The temperature was not permitted to rise above 20°. After all of the product had gone into solution and the evolution of nitrogen had stopped, the reaction mixture was poured slowly, with vigorous mechanical stirring, into 2 liters of water containing finely crushed ice. DL-Tribenzoyl-threonic acid separated as a brittle, flocculent gum which was separated by filtration together with the excess ice, and washed with ice-water. The filter cake was quickly transferred to a beaker, enough hot water added to melt the ice and soften the gum, and the water decanted. The gum was "worked" with a stirring rod to remove most of the water, partially dissolved by warming with 5 cc. of benzene, seeded[21] and allowed to stand overnight. The solid product thus obtained was finely pulverized in a mortar and dried in a vacuum desiccator over sodium hydroxide and paraffin. The 19.6 g. of crude product was dissolved in 85 cc. of xylene, the hot solution filtered, and the crystals deposited on cooling washed, first with cold xylene and then with petroleum ether. The yield was 15.1 g. of white crystalline powder which melted between 95 and 98°. Recrystallization from xylene yielded 14.2 g. of pure product which melted at 121°.

DL-Tribenzoyl-threonic acid exists in two crystalline modifications, one melting at 95-98°, the other at 121°. The compound has a great tendency to form supersaturated solutions and, when crystallized from a warm solution, the high melting form is obtained. When crystallization takes place from a cold supersaturated solution, the low melting form results. The compound may also be crystallized by dissolving in cold benzene, adding ligroin to faint cloudiness, seeding, and setting aside for twenty-four hours. If the low melting form is recrystallized from a warm solution, it is recovered as the high melting form, and if the

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(19) Seed crystals were obtained by treating a 1-g. sample of the amide in the same manner, decanting the water, dissolving the gum in alcohol and stirring with a glass rod until crystallization started.

(20) Gattermann and Wieland, "Laboratory Methods of Organic Chemistry," 22nd edition, The Macmillan Co., New York, N. Y., 1932, p. 352.

(21) Seed crystals were obtained by following the same procedure with a 1-g. sample of the amide, dissolving the gum obtained in xylene, and rubbing in a test-tube with a stirring rod until crystallization started.

high melting form is recrystallized from a cold supersaturated solution, it separates as the low melting form. One of these forms may be the racemic compound, and the other, a racemic mixture.

Anal. Calcd. for DL-tribenzoyl-threonic acid, $C_{25}H_{20}O_8$: neut. equiv., 448.4; C, 66.96; H, 4.50. Found for the acid of m. p. 95–98°: neut. equiv., 450; C, 66.96; H, 4.50. For the acid of m. p. 121°: C, 66.98; H, 4.54.

Preparation of DL-Tribenzoyl-threonyl Chloride.—Thirty-two grams of DL-tribenzoyl-threonic acid of m. p. 121° was dissolved in 32 cc. of purified thionyl chloride[22] in an all-glass apparatus consisting of a round-bottom flask sealed to a long condenser protected with a drying tube. When the solution was heated in a boiling water-bath, a slow evolution of hydrogen chloride started and the reaction continued smoothly. The reaction mixture was allowed to stand overnight and the following day it was heated for five hours in a boiling water-bath. About half of the excess thionyl chloride was then removed from the apparatus at reduced pressure at the temperature of boiling water, the suction line being connected directly to the drying tube. The mixture was then seeded[23] and the rest of the thionyl chloride removed from the apparatus at reduced pressure. The crystalline mass which remained was dissolved in 200 cc. of hot ligroin (b. p. 80–100°, dried over sodium), seeded and allowed to crystallize. The yield of crude product obtained was 30.9 g. or 93% of the theoretical. The crude product was recrystallized by dissolving it in 35 cc. of warm benzene (dried over sodium); adding 200 cc. of cold, dry, ligroin (b. p. 80–100°); seeding and setting aside for four hours. The crystals were washed, first with dry benzene–ligroin mixture, then with low boiling petroleum ether, and dried in a vacuum desiccator over paraffin and phosphorus pentoxide. The yield of pure, white, well-formed crystals was 25.6 g.; m. p. 113.5°.

Anal. Calcd. for DL-tribenzoyl-threonyl chloride, $C_{25}H_{19}O_7Cl$: sapon. equiv., 93.4; C, 64.31; H, 4.10; Cl, 7.60. Found: sapon. equiv., 93.8; C, 64.37; H, 4.12; Cl, 7.42.

Preparation of DL-Tribenzoyl-threose.—Ten grams of the acid chloride, 20 cc. of xylene (dried over sodium) and 2 g. of palladinized barium sulfate[24] were placed in an all-glass apparatus consisting of a round-bottom flask sealed to a condenser and provided with a side arm reaching to the bottom of the flask. The flask was immersed in a boiling water-bath and hydrogen from a tank was bubbled through the mixture at a sufficient rate to keep the catalyst in suspension. The hydrogen was previously passed through a three-foot drying tube containing calcium chloride, with a three inch section of phosphorus pentoxide in the center. The progress of the reaction was followed by allowing the effluent gases to bubble through a standard solution of sodium hydroxide containing phenolphthalein, changing the solution when the phenolphthalein became colorless. At the end of four hours the reduction was 95–98% complete, on the basis of the hydrogen chloride evolved. The solution was then filtered from the catalyst, about one-third of the xylene was removed at reduced pressure, the solution seeded,[25] and set aside overnight to crystallize. The crystals were separated by filtration and washed, first with cold xylene, and then with low-boiling petroleum ether. The yield, in two crops, was 7.5 g. or 81% of the theoretical. Twenty grams of the product was recrystallized from 60 cc. of xylene, yielding 17.9 g., in two crops, each of which melted at 99–99.5°.

Anal. Calcd. for DL-tribenzoyl-threose, $C_{25}H_{20}O_7$: C, 69.44; H, 4.66. Found: C, 69.39; H, 4.65.

Preparation of DL-Tribenzoyl-threose-2,4-dinitrophenylhydrazone.—One-tenth gram of DL-tribenzoyl-threose was dissolved in 10 cc. of absolute alcohol, 10 cc. of a saturated alcoholic solution of 2,4-dinitrophenylhydrazine added, and the mixture heated to boiling. Several drops of concentrated hydrochloric acid were then added, the mixture boiled for two minutes, cooled, and water added to cloudiness. On standing overnight a crop of crystals was obtained, which was recrystallized from a 50-50 mixture of absolute alcohol and chloroform. The dinitrophenylhydrazone is a yellow, crystalline compound melting at 182°.

Anal. Calcd. for DL-tribenzoyl-threose-2,4-dinitrophenylhydrazone, $C_{31}H_{24}O_{10}N_4$: C, 60.78; H, 3.95; N, 9.15. Found: C, 61.09; H, 4.00; N, 9.25.

Preparation of DL-Threose by Saponification of DL-Tribenzoyl-threose with Sodium Methylate.—Five grams of DL-tribenzoyl-threose was dissolved in 20 cc. of warm anhydrous methyl alcohol. The solution was cooled in a bath of dry-ice and acetone and 29 cc. of approximately 2% sodium methylate in anhydrous methyl alcohol added. The mixture was transferred to an ice–salt-bath and kept at −15° for five hours. An equivalent amount of approximately 0.3 *N* sulfuric acid was then added and the methyl alcohol and water removed under reduced pressure at room temperature. After dissolving the residue in 50 cc. of water, a trace of gum remained. The solution was extracted five times with 50-cc. portions of petroleum ether to remove methyl benzoate and the aqueous solution concentrated under reduced pressure, at room temperature, to about half its volume. After standing overnight, the solution was filtered from a trace of solid and the water removed under reduced pressure at room temperature. The residue was extracted with anhydrous methyl alcohol and the solution filtered from the sodium sulfate. The filtrate was concentrated under reduced pressure, at room temperature, to a thick sirup, which was dried to constant weight at a pressure of 0.1 mm. The yield of slightly colored sirup was 1.17 g. The sirup quickly reduced Fehling solution in the cold.

Preparation of DL-Threose by Saponification of DL-Tribenzoyl-threose with Barium Hydroxide.—The saponification was accomplished by suspending 5 g. of tribenzoyl-threose in 250 cc. of 0.3 *N* barium hydroxide from which solution the air had been previously removed at 0° by ten-minute passage of nitrogen. The glass-stoppered bottle containing the reaction mixture was mechanically shaken in a bath of ice water for six hours and the solution then filtered. The barium was quantitatively removed from the ice-cold filtrate in the usual manner with sulfuric acid, the precipitate removed by use of a centrifuge, and the clear colorless solution concentrated under reduced pressure at room temperature to 50 cc. The precipitated benzoic acid was removed by filtration and extraction with chloroform and the solution concentrated to a thick sirup under reduced pressure and at room temperature. The sirup was dissolved in methyl alcohol, the solution treated with Celite 521 and the filtrate concentrated as completely as possible at 0.1 mm. and at room temperature. The yield was 1.03 g. of a very slightly-colored thick sirup. The sirup quickly reduced cold Fehling solution.

Preparation of DL-Threosazone.—The sugar obtained by the hydrolysis of 2 g. of DL-tribenzoyl-threose was dissolved in 10 cc. of water. One cubic centimeter of acetic acid and 1 cc. of phenylhydrazine were added and the mixture held at 50° for one hour. Reaction started at once and a small amount of clear, red oil separated. On standing overnight the oil partly solidified and a yellow precipitate formed. The oily portion was removed with a stirring rod, dissolved in about 150 cc. of boiling water containing a little acetic acid, the solution filtered and allowed to cool. It yielded an additional amount of yellow precipitate. The combined precipitates were recrystallized twice from about 400 cc. of

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[22] Fieser, "Laboratory Manual of Organic Chemistry," D. C. Heath and Co., New York, N. Y., 1935, p. 339.

[23] Seed crystals were obtained by following the same procedure with a 1-g. sample, dissolving the gum obtained after removal of all the thionyl chloride in benzene, adding ligroin to faint cloudiness and setting aside in the refrigerator for ten days.

[24] Gattermann and Wieland, "Laboratory Methods of Organic Chemistry," 22 edition, The Macmillan Co., New York, N. Y., 1932, pp. 369–370.

[25] Seed crystals were obtained by following the same procedure with a 1-g. sample, removing the xylene at reduced pressure, dissolving the gum obtained in benzene, and letting the solution stand overnight.

water and once from a small amount of benzene. After drying *in vacuo* at 55°, the compound melted at 168° to a lemon-yellow liquid when introduced into a bath held at this temperature. When introduced into a bath at 165° the temperature of which was rising at the rate of 3° per minute, the osazone melted at 167–168° to an orange liquid which immediately began to darken.

Anal.[26] Calcd. for DL-threosazone, $C_{16}H_{18}O_2N_4$: C, 64.41; H, 6.08; N, 18.78. Found: C, 64.42; H, 6.09; N, 18.78.

Oxidation of DL-Threose.—The oxidation procedure of Hudson and Isbell[15] was followed with the sugar obtained by the hydrolysis of 5 g. of DL-tribenzoyl-threose. The bromide ion was removed with silver carbonate and the silver ion quantitatively with hydrochloric acid. The chloroform-extracted solution was concentrated under reduced pressure and at room temperature to a slightly-colored sirup. The sirup was dissolved in about 5 cc. of pyridine and an excess of benzoyl chloride added slowly, cooling between additions. On pouring the mixture into 100 cc. of water, an oil appeared which, when separated from the aqueous layer and rubbed with a little alcohol, solidified. After two crystallizations from alcohol the compound melted at 142.5°, the m. p. previously found for DL-dibenzoyl-threonic lactone. The m. p. was not depressed when a small amount of this substance was mixed with a known sample of DL-dibenzoyl-threonic lactone.

II. DL-Tribenzoyl-erythrose

Preparation of DL-Erythronamide.[8]-DL-Erythronamide was prepared by the same procedure as that used in the preparation of DL-threonamide, but the compound was not obtained in crystalline form. However, the crude product serves for the preparation of the benzoyl-amide.

Preparation of DL-Tribenzoyl-erythronamide.—The crude erythronamide (10 g.) obtained by the procedure of Glattfeld and Macmillan[8] was benzoylated as described above under Preparation of DL-Tribenzoyl-threonamide. Toward the end of the benzoylation reaction, a transient pink color developed which became permanent when benzoylation was complete. The gum which separated when the reaction mixture was poured into water completely solidified after two hours of stirring. The wet, bright pink solid product was pulverized in a mortar and thoroughly washed on a suction funnel with water. The wet cake was refluxed for a few minutes with 200 cc. of alcohol, the mixture cooled, the solution filtered, and the solid washed with cold absolute alcohol. This procedure resulted in the removal of all the colored material and most of the contaminating benzamide and benzoic acid with very little loss of the desired product. The yield was 33.4 g. of crude tribenzoyl-amide or 88% on the basis of the lactone used. The crude product was recrystallized from 600 cc. of a mixture of 35 parts of commercial dioxane and 65 parts of absolute alcohol, yielding 27.8 g. of crystals. A second crystallization from 600 cc. of dioxane–alcohol mixture yielded 22.6 g. of pure product melting at 208°.

Anal.[26] Calcd. for DL-tribenzoyl-erythronamide, $C_{25}H_{21}O_7N$: C, 67.11; H, 4.73; N, 3.13. Found: C, 66.82, H, 4.71; N, 3.41.

Preparation of DL-Tribenzoyl-erythronic Acid.—Twenty grams of DL-tribenzoyl-erythronamide recrystallized from an alcohol–dioxane mixture was carried through the procedure described above under Preparation of DL-tribenzoyl-threonic acid. Dioxane was used as the solvent instead of acetic acid. The gum obtained when the reaction mixture was poured into 3 liters of water completely solidified after two hours of stirring. The wet, solid product was pulverized in a mortar, separated by filtration and washed well with water. The yield was practically quantitative; 20.1 g. of crude product was obtained. The crude product was recrystallized from 150 cc. of benzene and yielded 15.6 g. of the tribenzoyl-acid melting at 151.5–152°.

Anal.[26] Calcd. for DL-tribenzoyl-erythronic acid, $C_{25}H_{20}O_8$: C, 66.96; H, 4.50. Found: C, 67.52; H, 4.70.

Preparation of DL-Tribenzoyl-erythronyl Chloride.—This compound was prepared by the method used in the preparation of the corresponding threonyl chloride. Ten grams of DL-tribenzoyl-erythronic acid yielded 9.4 g. of crystalline acid chloride crystallized from 60 cc. of ligroin (b. p. 80–100°, dried over sodium). Recrystallization from 60 cc. of ligroin gave 8.0 g. of pure tribenzoyl-acid chloride, melting at 103.5°.

Anal.[26] Calcd. for DL-tribenzoyl-erythronyl chloride; $C_{25}H_{19}O_7Cl$: C, 64.31; H, 4.10; Cl, 7.60. Found: C, 64.02; H, 4.28; Cl, 7.48.

Reduction of DL-Tribenzoyl-erythronyl Chloride.—Reduction of this compound was carried out by the same method as that used for the corresponding threonyl chloride. The resulting aldehyde was not, however, obtained in crystalline form. Work on the crystallization and hydrolysis of this compound to DL-erythrose is being continued.

Summary

1. DL-Threonic lactone was prepared by thermal decomposition of the potassium salt of DL-*threo*-2,3-dihydroxy-4-chlorobutanoic acid.

2. DL-Threonic lactone was converted into DL-threonamide, the amide benzoylated, converted into DL-tribenzoyl-threonic acid, and the acid converted into the corresponding acid chloride. The acid chloride was reduced by hydrogen in the presence of palladinized barium sulfate, and the resulting DL-tribenzoyl-threose hydrolyzed to DL-threose.

3. DL-Tribenzoyl-erythrose was prepared from DL-erythronic lactone by a similar series of reactions.

CHICAGO 37, ILLINOIS RECEIVED FEBRUARY 28, 1944

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(26) Analysis by Dr. T. S. Ma.