amine, 1.28 g. (0.04 g. atom) of sulfur, and 0.04 g. of iodine in 20 ml. of *o*-dichlorobenzene was refluxed at 180° for fifteen minutes. The acid is unstable under these conditions for carbon dioxide as well as hydrogen sulfide was evolved. The reaction mixture yielded 2.2 g. of the acid.

In another experiment, 4.82 g. (0.02 mole) of 2-carboethoxydiphenylamine and 1.28 g. of sulfur was heated without solvent in a bath at 285–300°. Hydrogen sulfide was evolved slowly at first, and then the odor of ethyl mercaptan was quite pronounced. Heating was discontinued after two hours, when the evolution of gas had ceased. The products isolated were 1.5 g. of the ester initially used, 0.2 g. of phenothiazine, but no phenothiazine-ester. The phenothiazine is probably formed as a consequence of pyrolysis of the ester, or decarboxylation of the acid (formed by cleavage of the ester) to give diphenylamine which then reacts with sulfur in the usual manner.

[B] **Coupling Reactions with 2,2'-Diaminodiphenyl Disulfide.**—One of these coupling reactions was patterned after the method used by Kehrmann and Nossenko[9] for the preparation of 1-nitrophenothiazine. A solution of 2,2'-diaminodiphenyl disulfide,[10] 2-bromo-3-nitrobenzoic acid,[11] and of sodium acetate in ethanol was refluxed for twenty-four hours. The diamine and acid were recovered.

A second coupling reaction was a modification of a procedure by Ullmann and Hoz.[12] A mixture of 2,2'-diaminodiphenyl disulfide, potassium *o*-chlorobenzoate, sodium acetate, amyl alcohol, and a trace of copper bronze was refluxed for two hours. The diamine and *o*-chlorobenzoic acid were recovered.

Summary

Phenothiazine is metalated by *n*-butyllithium in the 1-position or ortho to the nitrogen. The structure of the 1-carboxyphenothiazine, obtained by carbonation of the metalation product, was established indirectly by cyclization reactions.

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[9] Kehrmann and Nossenko, *Ber.*, **46**, 2809 (1913).

[10] Teppema and Sebrell, THIS JOURNAL, **49**, 1751 (1927).

[11] Culhane, "Organic Syntheses," Coll. Vol. I, 125 (1941).

[12] Ullmann and Hoz, *Ann.*, **355**, 352 (1907).

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY No. 296]

A Large-Scale Preparation of D-Altrose. D-Altrose Oxime and its Rate of Mutarotation[1]

BY ROBERT C. HOCKETT AND LEONARD B. CHANDLER[2]

In 1926, Kunz and Hudson,[3] by the action of aluminum chloride on a chloroform solution of octaäcetyl β-lactose, obtained the "acetochloro" derivative of a new disaccharide which they named neolactose, and which was proved to be a D-galactosyl-D-altrose. Richtmyer and Hudson[4] later improved this preparation by using phosphorus pentachloride along with aluminum chloride, isolated crystalline neolactose and a number of its derivatives, and showed how crystalline D-altrose may be obtained from the disaccharide despite the tendency of this hexose to form an anhydride when it is treated with hydrochloric acid.

When a sample of D-altrose was needed in this Laboratory, we undertook to repeat the preparation described by these authors, both on a much increased scale and with the introduction of short-cuts to eliminate a number of manipulations.

The chief modification was as follows: "α-aceto-chloroneolactose" formed from octaäcetyl lactose but not isolated, was subjected directly to hydrolysis by hydrochloric acid in a water–acetone solution under such conditions as to (1) hydrolyze the chlorine, (2) to remove the acetate groups, and (3) to break the disaccharide link all in a single operation yielding a mixture containing hydrochloric acid, acetic acid, glucose, galactose, altrose and altrosan. Hydrochloric acid was removed with lead carbonate followed by silver carbonate, metallic ions by hydrogen sulfide, acetic acid by distillation, and glucose and galactose by yeast fermentation. Finally, altrose and altrosan were recovered as D-altrose dibenzyl mercaptal as described by Richtmyer and Hudson.[4] From this derivative the crystalline sugar was obtained without seed, as described by Richtmyer and Hudson.[4]

The over-all yield from one kilogram of D-lactose monohydrate was 18 g. of crystalline D-altrose or 3.7% of the theoretical. A more efficient method of preparation of this sugar from α-methyl-D-glucoside was subsequently described by Richtmyer and Hudson.[5]

The oxime of D-altrose and measurements of the rate of mutarotation of this derivative in aqueous solution are described for the first time.

We wish to thank Doctors Hudson and Richtmyer, with whom we made arrangements in connection with this work.

Experimental

D-Altrose Oxime.—Two grams (0.0111 mole) of crystalline altrose was treated with 0.0282 mole of hydroxylamine in methanol at room temperature overnight. After a brief warming on the steam-bath, the solution was concentrated to a colorless sirup (diminished pressure) which was dissolved in a minimum volume of dry methanol. Absolute ethanol was added to turbidity and the solution soon deposited 1.7 g. of fine prisms. Recrystallized by dissolving in 10 cc. of water, filtering, concentrating to a sirup and repeating the process described above, the compound was obtained with a maximum melting point of 143–144° and a

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[1] This paper is taken from a thesis submitted by Leonard B. Chandler to the Graduate School of the Massachusetts Institute of Technology in partial fulfillment of the requirements for the degree of Doctor of Philosophy, in October, 1939.

[2] Present address: Nylon Division, E. I. du Pont de Nemours and Company, Wilmington, Delaware.

[3] Kunz and Hudson, THIS JOURNAL, **48**, 1978, 2435 (1926).

[4] Richtmyer and Hudson, *ibid.*, **57**, 1716 (1935).

[5] Richtmyer and Hudson, *ibid.*, **63**, 1729 (1941).

rotation[6] at equilibrium (103 hr.) of −9.8° (C, 2.408; t, 24.9°; H_2O). The crystals are easily soluble in water, slightly in methanol, and insoluble in ethanol, ether, acetone and chloroform.

Anal. Calcd. for $C_6H_{13}O_6N$: C, 36.9; H, 6.66; N, 7.17. Found: C, 36.9, 37.1, 36.7; H, 6.15, 6.84, 6.86; N, 6.93, 7.04.

Mutarotation of D-Altrose Oxime.—A sample of 0.2422 g. of twice recrystallized material was dissolved into 10.06 cc. of aqueous solution. Twenty-two measurements of the rotations were made in a 2-dm. tube at 25.0 ± 0.5°. The reaction followed an unimolecular course, the calculated velocity constant ($k_1 + k_2$) being 0.0040 with an average variation of ±0.0001. In making this calculation the value obtained for the rotation at t = 748 min. was taken as the rotation at infinite time rather than that at t = 6540 min. since hydrolysis is appreciable after very long contact with water. The pH of the water was 5.8.

By plotting log ($\alpha_t - \alpha_\infty$) against time in minutes, a very nearly straight line was obtained. By extrapolation of this line to zero time, the value of log ($\alpha_0 - \alpha_\infty$) was determined graphically and the initial specific rotation[6] found to be −64.0°.

Summary

A large-scale and abbreviated procedure for the preparation of crystalline D-altrose from D-lactose by the method of Richtmyer and Hudson is described.

The oxime of D-altrose is described and measurements of its rate of mutarotation recorded.

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[6] All rotations referred to in this paper represent specific rotations of the D line of sodium unless specified otherwise. Concentrations are grams of solute in 100.0 cc. of solution.

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Condensation of Cyclohexene Oxide, 1,2-Dichlorocyclohexane, and 3,4-Dichlorohexane with Anisole[1]

BY CHARLES C. PRICE AND GEORGE P. MUELLER[2]

This investigation was undertaken to explore the possibility of synthesizing vicinal *bis*-(p-hydroxyphenyl)-hexanes and cyclohexanes by some modification of the Friedel–Crafts type reaction. Such substances are of particular interest in connection with their ability to simulate the physiological activity of the hormone, estrone.

Kursanoff[3,4] has reported the isolation of a diphenylcyclohexane, m. p. 169–171°, which he believed to be the 1,2-isomer, from the aluminum chloride-catalyzed condensation of 1,2-dichlorocyclohexane with benzene. This material has now been shown to be the 1,4-isomer.[5,6] Nenitzescu and Curcaneanu isolated a greater amount of liquid 1,3-diphenylcyclohexane than the crystalline 1,4-isomer. It is thus obvious that, as so frequently happens with the Friedel–Crafts reaction, rearrangement occurred in the replacement of the chlorine atoms. Other similar rearrangements in vicinal, negatively-substituted halides also have been observed.[7]

It was hoped that, due to the greater reactivity of the aromatic nucleus in anisole or phenol, or by modification of the conditions of the Friedel–Crafts condensation, this tendency toward rearrangement might be modified. This hope was only partially realized. Condensations of anisole with 1,2-dichlorocyclohexane using aluminum chloride as the catalyst or with cyclohexene oxide or 1,2-dihydroxycyclohexane using boron fluoride as the catalyst produced poor yields of mixtures of condensation products from which two diastereoisomeric 1,3-dianisylcyclohexanes (I and II), m-dianisylbenzene (III) and anisylcyclohexane (IV) were isolated and identified. The fact that no 1,4-dianisylcyclohexane or p-dianisylbenzene was isolated is an indication that the tendency to rearrangement was at least somewhat less with anisole than with benzene.

The terphenyl was assigned the meta-orientation on the basis of the non-identity of the free phenol, its dimethyl ether and diacetate with the corresponding ortho and para isomers[8] and zinc dust distillation to yield a small amount of material with the proper melting point for m-terphenyl itself.

The 1,3-dianisylcyclohexane, the free phenol and its diacetate each differs from the known 1,1-isomers.[9]

The production of 1,3-dianisylcyclohexane, as well as m-dianisylbenzene and anisylcyclohexane, may be accounted for by the intermediate formation of 3-anisylcyclohexene (V). The anisyl group in the cycloölefin should direct addition of a second molecule of anisole to form 1,3-dianisylcyclohexane.[10] Disproportionation of hydrogen between the 3-anisylcyclohexene (V) and the 1,3-dianisylcyclohexanes would account for the

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[1] Presented before the Organic Division at the 104th Meeting of the American Chemical Society, Buffalo, New York, September 7, 1942.

[2] Eli Lilly and Company Fellow, 1941–1943.

[3] Kursanoff, *Ann.*, **318**, 309 (1901).

[4] Bodroux, *Ann. chim.*, [10] **11**, 511 (1929).

[5] Nenitzescu and Curcaneanu, *Ber.*, **70B**, 346 (1937).

[6] Corson and Ipatieff, THIS JOURNAL, **60**, 747 (1938).

[7] Nenitzescu and Gavat, *Ann.*, **519**, 260 (1935); *Ber.*, **70B**, 1883 (1937); Nenitzescu and Przemetzki, *ibid.*, **69B**, 2706 (1936); Nenitzescu and Curcaneanu, *Bull. chim. soc. Romania*, [2] **1**, 125 (1939) (*C. A.*, **37**, 3740 (1943)).

[8] Price and Mueller, THIS JOURNAL, **66**, 632 (1944).

[9] Schmidlin and Lang, *Ber.*, **43**, 2819 (1910); von Braun, *Ann.*, **472**, 55 (1929).

[10] See, *e. g.*, Price and Karabinos, THIS JOURNAL, **62**, 1159 (1940).