these buret readings after complete absorption in maleic anhydride: 76.2, 77.2, 71.8. The buret readings after absorption in 85% sulfuric acid were 75.0, 75.9, 70.2. These results pointed to the presence of 5.2, 5.5, 5.4% of *cis*-1,3-pentadiene in the sample which otherwise was *trans*.

(4-Chlorocrotyl)-trimethylammonium Chloride.—To 50 g. of 1,4-dichloro-2-butene, b. p. 157–159°, in 200 g. of dry dioxane was added 51 g. of liquid trimethylamine. Solid appeared at once. After two days it was collected and desiccated over sulfuric acid; yield, 67 g. Two crystallizations from absolute ethanol yielded 31 g. of pure white crystals, m. p. 174–176°.

Anal. Calcd. for $C_7H_{15}Cl_2N$: Cl, 38.6. Found: Cl, 37.2.

2-Butene-1,4-bis-(trimethylammonium Chloride).—Forty grams of trimethylamine was added to a solution of 35 g. of 1,4-dichloro-2-butene in 200 ml. of methanol. The solution turned dark red but no precipitate appeared. After three days the solvents were distilled off. Recrystallization of the desiccated solid from absolute alcohol was difficult, but a pure, white product (20 g.), m. p. 261° (dec.), was secured after four crystallizations.

Anal. Calcd. for $C_{10}H_{24}Cl_2N_2$: Cl, 29.2. Found: Cl, 28.9.

The same salt was formed if no solvent was employed, but trouble was encountered by caking. Also, the material was more difficult to decolorize and purify.

High Dilution Condensation of Crotonaldehyde.—The apparatus used was built according to the description of Adams and Kornblum.[13] Four grams of sodium was dissolved in 1500 ml. of methanol in the reaction flask. Fourteen grams of crotonaldehyde, dissolved in 500 ml. of methanol, was let into the flask through the dilution system during thirty-six hours (not continuous). The solvent was removed through an efficient column and the residue was made slightly acidic with acetic acid. Water was added, then ether. From the dried ($CaCl_2$) ether extract was obtained 0.5 g. of a sublimable solid. After recrystallization from benzene, it melted at 68.5–71.5°. Its odor, at first rather sweet, became rancid like that of butyric acid. Its water solution was acidic. It was soluble also in alcohol, ether, benzene. These properties fit those listed[9] for 2,6-dimethyl-5,6-dihydro-3-pyrancarboxylic acid.

Summary

Thermal degradation of (1-methylcrotyl)-trimethylammonium hydroxide gives rise to 1,3-pentadiene, chiefly the *trans* isomer. If 2,3-pentadiene was formed, it was in amounts too small to detect. This formation of conjugated double bonds is in contrast to the formation of both conjugated and cumulative double bonds in the degradation of 2,3-butanebis-(trimethylammonium hydroxide) and is in keeping with the results obtained by Willstätter in the synthesis of cycloöctatetraene.

Reactions of 1,4-dichloro-2-butene and trimethylamine are described. Experiments were performed on the condensation of crotonaldehyde and sodium methoxide at very high dilution in methanol.

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[13] Adams and Kornblum, THIS JOURNAL, **63**, 188 (1941).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY, LAFAYETTE, INDIANA]

Studies on the Synthesis of Lysine[1]

BY ED. F. DEGERING AND LESLIE G. BOATRIGHT

Lysine has been synthesized by a variety of methods. Several new methods have been published recently.[2,3,4] This report describes a new synthesis for lysine, preparation of some possible intermediates, and a reinvestigation of a portion of an earlier reported synthesis.[4]

$HO\cdot(CH_2)_6\cdot OH$ (I) + HBr $\rightarrow$ $Br\cdot(CH_2)_6\cdot OH$ (II), then + HNO_3 $\rightarrow$ $Br\cdot(CH_2)_5\cdot CO_2H$ (III), then + Br_2 $\rightarrow$ $Br\cdot(CH_2)_4\cdot CHBr\cdot CO_2H$ (III), then + NH_3 $\rightarrow$ $H_2N\cdot(CH_2)_4\cdot CHNH_2\cdot CO_2H$ (V), then + HCl $\rightarrow$ $(H_3N\ (CH_2)_4\cdot CHNH_3\cdot CO_2H)^{++}\ 2Cl^-$ (VI)

Compound II was prepared in yields of approximately 80% by use of an efficient liquid–liquid extractor to extract it from the reaction mixture as rapidly as it was formed. Petroleum ether was used as the extracting solvent and only small amounts of 1,6-hexanedibromide were obtained.

Oxidation of II was achieved by use of concentrated nitric acid as the oxidizing agent. Yields of 80% of III were obtained. Bromination of IV was accomplished according to the method of Merchant, *et al.*[5] Ammonolysis of IV with a large excess of aqueous ammonia followed by treatment with hydrochloric acid yielded DL-lysine dihydrochloride in 60% yield. A large excess of ammonia was necessary in order to prevent the formation of 2-piperidinecarboxylic acid by cyclization of IV. The over-all yield of DL-lysine dihydrochloride, based on the glycol I, was 38%.

Attempts were made to prepare open chain compounds from which lysine might be readily prepared, by cleavage of the ether linkage in certain furan derivatives. Ethyl 2-furylglycolate and 2-furylglycolic acid were prepared and subjected to high pressure hydrogenation in the presence of a copper chromite catalyst; however, no open chain compounds were isolated: C_4H_4O-CHO (furaldehyde, VII) + HCN$\rightarrow$$C_4H_4OCHOH$-

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[1] Abstracted from a thesis by Leslie G. Boatright, submitted to the Faculty of the Graduate School of Purdue University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, August, 1949. This work was sponsored by the National Institute of Health, through a fellowship grant to Mr. Boatright. Current addresses: Ed. F. Degering, Miner Laboratories, 9 S. Clinton, Chicago 6, Illinois, and Leslie G. Boatright, American Cyanamid Company, Stamford, Connecticut.

[2] Gaudry, *Can. J. Research*, **B26**, 387 (1948).

[3] Rogers, *et al.*, THIS JOURNAL, **71**, 1837 (1949); Warner and Moe, *ibid.*, **70**, 3918 (1948).

[4] Sayles and Degering, *ibid.*, **73**, 3161 (1949).

[5] Merchant, Wickert and Marvel, *ibid.*, **49**, 1828 (1927).

CN (VIII), then + EtOH/HCl→C_4H_4OCHOH-CO_2ET (IX), then + H^+, water→C_4H_4OCHOH-CO_2H (X).

The cyanohydrin VIII was obtained by treatment of VII with hydrogen cyanide at 0°. When the cyanohydrin was prepared from the bisulfite addition compound of VII and potassium cyanide, it was obtained in an impure state and attempts to effect hydrolysis were unsuccessful. All attempted hydrolyses of VII to the free hydroxy acid X were unsuccessful; however, hydrolysis to IX was effected with an ethanol solution of hydrogen chloride containing one mole of water for each mole of the cyanohydrin. Yields of 45% of IX were obtained.

Hydrogenation of either IX or X with hydrogen and copper chromite at high temperatures and pressures produced no open chain compounds. Hydrogenation of IX with a palladium catalyst yielded only ethyl 2-tetrahydrofurylglycolate.

Earlier investigators[3] reported the condensation of 4-chlorobutyronitrile and acetamidomalonic ester to give 4-acetamido-4,4-dicarbethoxypentanonitrile in low yields. Physical properties reported for this compound differ considerably from those reported by investigators in this laboratory and our experimental procedure is therefore included. DL-Lysine dihydrochloride was prepared in 14% over-all yield from 4-chlorobutyronitrile.

Experimental

6-Bromo-1-hexanol (II).—In a glass tube 25 mm. in diameter, in which a gas dispersion disc was sealed at the lower end, and which was wrapped with electrical resistance wire to control the temperature, is placed 118 g. (1.0 mole) of 1,6-hexadienol[6] and 200 g. (1.2 moles) of aqueous 48% hydrobromic acid. Petroleum ether (b. p. 90–100°) is continuously passed through the contents of the extraction tube for eighteen hours. During the extraction, the contents of the tube are maintained at 80°. The petroleum ether extracts are dried with calcium sulfate and distilled. After removal of the petroleum ether, distillation of the residue at reduced pressure yields 129 g. of 6-bromo-1-hexanol (b. p. 105–106° (5 mm.), $n^{24}\text{D}$ 1.4845, d^{24}_4 1.3838). Distillation of the extracted water–hydrobromic acid–1,6-hexanediol solution yields 5 g. of 1,6-hexane dibromide (b. p. 95° (6 mm.)) and an additional 15 g. of 6-bromo-1-hexanol. Thus a total of 144 g. of 6-bromo-1-hexanol is obtained (yield, 81%).

6-Bromohexanoic Acid (III).—In a three-necked flask fitted with a dropping funnel, an efficient stirrer, and a thermometer is placed 160 ml. (2.58 moles) of concentrated nitric acid (sp. gr. 1.42). While maintaining the contents at 25–30°, 78 g. (0.43 mole) of 6-bromo-1-hexanol is added dropwise to the stirred nitric acid. The addition requires about one hour. Stirring is continued for an additional four hours, after which time the flask is heated on the steam-bath for forty-five minutes. The reaction mixture is diluted with 200 ml. of water and extracted with four 50-ml. portions of ether. These extracts are combined, dried with calcium sulfate, and distilled. Some 6-bromo-1-hexanol (18 g.) is recovered and 54 g. (yield, 91%) of 6-bromohexanoic acid is obtained (b. p. 129–130° (5 mm.)).

2,6-Dibromohexanoic Acid (IV).—Bromination of III was carried out in accordance with the directions of Merchant, *et al.*,[5] to give a 94% yield of 2,6-dibromohexanoic acid (b. p. 175° (6 mm.)).

DL-Lysine Dihydrochloride (VI).—To 600 g. (9.88 moles) of aqueous 28% ammonia solution, 41 g. (0.15 mole) of 2,6-dibromohexanoic acid is added. The resulting solution is placed in a securely stoppered bottle and maintained at 55–60° for four days. At the end of this time, the solution is evaporated at reduced pressure to a thick sirup. A sizable portion of ammonium bromide precipitates. Fifty milliliters of concentrated hydrochloric acid (sp. gr. 1.19) is added and the resulting solution is evaporated to dryness at reduced pressure. The residue of lysine dihydrochloride, 2-piperidinecarboxylic acid, and ammonium bromide is mixed with 200 ml. of hot absolute ethanol. The insoluble ammonium bromide is removed by filtration and the filtrate is cooled to 20°. Addition of a few ml. of ether precipitates the remainder of the ammonium bromide which is removed by filtration. Addition of a few more ml. of ether precipitates about 1 g. of 2-piperidinecarboxylic acid (m. p. 258°). Addition of 400 ml. more of ether precipitates 21 g. of crude lysine (yield, 62%; m. p. 170–175°). Reprecipitating this crude lysine from ethanol with ether again results in the formation of nearly pure lysine dihydrochloride (m. p. 187–188°).

Furfural Cyanohydrin (VIII).—One hundred and ninety-two grams (2.0 moles) of freshly distilled furfural is placed in a three-necked flask fitted with a gas inlet tube, an efficient stirrer, and a reflux condenser through which ice water is circulated. The system is protected from atmospheric water with a drying tube. A few milligrams of potassium carbonate is added to the furfural and the mixture is cooled to 0°. About 60 g. (2.2 moles) of dry hydrogen cyanide[7] is passed into the stirred contents of the flask. Stirring is continued for an additional hour. The resulting cyanohydrin is a yellow oil.

Ethyl 2-Furylglycolate (IX).—To 246 g. (2.0 moles) of vigorously stirred furfural cyanohydrin, a solution of 350 g. (7.60 moles) of absolute ethanol, 80 g. (2.22 moles) of hydrogen chloride, and 36 g. of water, is added over a period of three hours. The resulting solution is stirred and maintained at 0° for fifteen hours. Gaseous ammonia is used to neutralize the excess hydrogen chloride, and the ammonium chloride formed is removed by filtration. The excess ethanol is removed by distillation and the residue is distilled at reduced pressure yielding 145 g. (yield, 45%) of ethyl 2-furylglycolate (b.p. 103° (3 mm.)). This material solidifies when cooled (m. p. 39°) and may be further purified by recrystallization from ethanol. *Anal.* Calcd. for $C_8H_{10}O_4$: C, 56.5; H, 5.88. Found: C, 56.0, 55.9; H, 6.0, 5.9.

2-Furylglycolic Acid.—To a solution of 138 g. (3.45 moles) of sodium hydroxide in 350 ml. of water is added 196 g. (1.15 moles) of ethyl 2-furylglycolate. The resulting solution is maintained at reflux temperature for five hours, made just slightly acidic with 6 *N* hydrochloric acid, and evaporated to near dryness. The residue is stirred with absolute ethanol and filtered. The residue of sodium chloride is washed with ethanol and the washings are combined and boiled with activated carbon. Filtration and evaporation of the filtrate yields 160 g. of crude 2-furylglycolic acid (yield, 97%). This crude acid is purified by recrystallization from absolute ethanol (m. p. 115°).

Ethyl 2-Tetrahydrofuryl Glycolate.—Five grams of 5% palladium on an activated carbon[8] catalyst is added to a solution of 100 g. (0.59 mole) of ethyl 2-furylglycolate and 100 ml. of absolute ethanol. Reduction is begun at 100° at a pressure of three atmospheres. Sufficient hydrogen is absorbed to saturate the double bonds in the furan nucleus in about three hours. Addition of fresh portions of catalyst fails to promote further reduction. Filtration and distillation of the reduction mixture at reduced pressure yields 86 g. (yield, 82%) of ethyl 2-tetrahydrofurylglycolate (b. p. 105° (2 mm.); $n^{15}\text{D}$ 1.4571). *Anal.* Calcd. for

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[6] Kindly supplied by E. I. du Pont de Nemours and Co., Electrochemicals Department, Wilmington 98, Delaware.

[7] Ziegler, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 307.

[8] Mozingo, "Organic Syntheses," **26**, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 78.

$C_8H_{14}O_4$: C, 55.2; H, 8.04. Found: C, 54.8, 54.6; H, 8.05, 8.08.

4-Acetamido-4,4-dicarbethoxypentanonitrile.—Ethyl oximinomalonate is prepared in accordance with the directions of Snyder and Smith.[9] Acetamidomalonic ester is prepared by reduction of ethyl oximinomalonate by a procedure analogous to that used by Albertson[10] for the reduction of ethyl oximinoacetoacetate. A 500-ml. flask is fitted with a reflux condenser, mechanical stirrer, and an addition funnel. The entire apparatus is carefully dried and protected from atmospheric water with a drying tube. Absolute ethanol (200 ml.), which has been dried and distilled from calcium hydride, and 5.7 g. (0.25 mole) of sodium is added to the flask. After the sodium has reacted with the ethanol, 56.7 g. (0.25 mole) of ethyl acetamidomalonate and 30.0 g. (0.32 mole) of 4-chlorobutyronitrile[11] is added. The reaction mixture is maintained at reflux temperature and stirred for eighteen hours, cooled, and filtered from the precipitate of sodium chloride. Distillation of the filtrate yields 12 g. of recovered 4-chlorobutyronitrile and 12 g. of 4-acetamido-4,4-dicarbethoxypentanonitrile (yield, 21.8%; b. p. 132° (5 mm.), n^{20}_D 1.4468, d^{20}_{20} 1.1083, M_D calcd. 69.23, M_D 68.94). *Anal.* Calcd. for $C_{13}H_{20}O_5N_2$: N, 9.85. Found: N, 9.50.

DL-Lysine Dihydrochloride.—In 100 ml. of freshly distilled acetic anhydride, 15 g. (0.053 mole) of 4-acetamido-4,4-dicarbethoxypentanonitrile is dissolved. Platinic oxide catalyst (0.5 g.) is added and reduction begun at a hydrogen pressure of three atmospheres. Three hours is required to complete the reduction. The catalyst is removed by filtration and the acetic anhydride carefully hydrolyzed with 25 ml. of water. The N,N-diacetyllysine is hydrolyzed by boiling the acetic acid solution with 100 ml. of hydrochloric acid (sp. gr. 1.19) for eighteen hours. Evaporation of this solution yields 9.0 g. of lysine dihydrochloride (yield, 77%; m. p. 175–180°). This crude lysine is reprecipitated from absolute ethanol with ether yielding pure lysine dihydrochloride (m. p. 187–188°).

Summary

Two syntheses for lysine and preparation of several possible intermediates has been described.

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[9] Snyder and Smith, THIS JOURNAL, **66**, 350 (1944).

[10] Albertson, *et al.*, *ibid.*, **70**, 1150 (1948).

[11] Allen, "Organic Syntheses," Coll. Vol. I, p. 157, John Wiley and Sons, Inc., New York, N. Y., 1941.

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, LABORATORIES OF THE MOUNT SINAI HOSPITAL]

Neo-fatty Acids[1]

BY HARRY SOBOTKA AND FREDERIC E. STYNLER

The occurrence of branched fatty acids in nature is confined to a few exceptional cases. For example, the fat of the tubercle bacillus contains a fatty acid carrying a methyl group side-chain about the middle of the chain; the normal fatty acids in wool fat or "degras" are accompanied by small amounts of representatives of three other series, namely, α-hydroxy acids and two kinds of branched fatty acids.[2] The members of one series terminate in an isopropyl group $(CH_3)_2CH$- and have been designated iso acids, the others terminate in a *s*-butyl group $(CH_3)(C_2H_5)$-CH- and have been named anteiso acids. Some iso acids[3a,b] and anteiso acids[4a,b] have been synthesized and also acids with a methyl group nearer the middle of the chain,[4a,c] finally acids with a tertiary or a quaternary carbon atom carrying longer side chains.[5a,b,c]

Modification of the terminal portion in long chain aliphatic compounds by side-chains or cyclic groups causes changes in their physico-chemical properties which may become significant for their biochemical behavior and for their technical applications. For reasons, detailed in another publication, which will treat of the surface and colloidal properties of these compounds, we wished to compare fatty acids with two and with three terminal methyl groups.

In the following we describe the synthesis and some of the properties of the neo isomers of the fatty acids with 16, 18, 20, 22 and 24 carbon atoms. In the course of this work we extended the chain of neohexyl chloride by means of ethylene oxide to neoöctyl alcohol.

Preliminary experiments have shown us that in the case of neohexyl chloride the reaction of its Grignard compound with an aldehyde proceeds more smoothly and with better yields than the condensation of the cadmium compound with an acyl chloride. Hence, we prepared the monoethyl ester-aldehydes corresponding to sebacic acid, dodecanedioic acid, and thapsic acid. Their condensation with neohexyl and neoöctyl magnesium chloride leads to products with 16 to 24 carbon atoms including a terminal *t*-butyl group. Because of spontaneous dehydration upon decomposition of the Grignard condensation product, mixtures were usually obtained of a 10- or 12- or 16-hydroxy acid with a pair of satellite mono-unsaturated acids. For their eventual conversion to the saturated acids, we followed in several features the procedures used by Velick and English[4b] for the synthesis of 14-methylpalmitic acid.

Table I summarizes the melting points of the new acids and the refractive indices and boiling points of their methyl esters (concerning the

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[1] We wish to acknowledge support for this work by the Office of Naval Research (NR 057-101).

[2] Weitkamp, THIS JOURNAL, **67**, 447 (1945).

[3] (a) Fordyce and Johnson, *ibid.*, **55**, 3368 (1933); (b) Cason, *ibid.*, **64**, 1106 (1942).

[4] (a) Cason and Prout, *ibid.*, **66**, 46 (1942); Cason, Pippen, Taylor and Wynans, *J. Org. Chem.*, **15**, 135, 139, 148 (1950); (b) Velick and English, *J. Biol. Chem.*, **160**, 473 (1945); (c) Ställberg-Stenhagen, *Arkiv Kemi*, **A22**, no. 19 (1946); **A26**, no. 12 (1948).

[5] (a) Stanley, Jay and Adams, THIS JOURNAL, **51**, 1261 (1929); (b) Polgar and Robinson, *J. Chem. Soc.*, 615 (1943); (c) Cason, *J. Org. Chem.*, **13**, 227 (1948).