[CONTRIBUTION FROM THE RESEARCH DEPARTMENT OF THE ORGANIC CHEMICALS DIVISION, MONSANTO CHEMICAL CO.]

A Study of the Nitric Acid Oxidation of Cyclohexanol to Adipic Acid[1]

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During a study of the nitric acid oxidation of cyclohexanol (I) to adipic acid (V), 6-nitro-6-hydroxyiminohexanoic acid (II) and octahydro-5aH,10aH-4a,9a-epoxydibenzo-*p*-dioxin-5a,10a-diol (VIII) were isolated from reactions which were performed at temperatures from 10 to 20°. The structure proof of compounds II and VIII led to two new substances, 6-amino-6-hydroxyiminohexanoic acid (III) and 6-oxocyclohexen-1-yl benzoate (XI), as well as new routes for preparing the known substances 1,2-cyclohexanedione (X), its phenylosazone IX, and adipamic acid (IV). In view of the results obtained from acid hydrolysis and nitric acid oxidation of compounds II and VIII, a mechanism might be postulated for the nitric acid oxidation of cyclohexanol to adipic acid and the chief side products, glutaric and succinic acid, at temperatures above 35° by assuming the theoretical intermediate formation of compound II, compound VIII and/or compound X. No evidence, however, was found for the presence of the latter three particular compounds when operating at temperatures above 35° which are normally employed in this oxidation reaction.

In this Laboratory, cyclohexanol (I) was oxidized by 67% nitric acid in a 1 to 3 mole ratio, respectively, at 55 to 60° in the presence of a vanadium catalyst to give adipic acid (V) in 90% yield. When no catalyst was used, the yield of adipic acid was 82%.[2] A partition chromatographic procedure based on the work of Bulen, Varner and Burrell[3] was used to analyze the mother liquors and wash liquors for other organic acidic components. Glutaric acid (VI), succinic acid (VII), oxalic acid[4] as well as adipic acid were found along with trace amounts of several unidentified organic acids which will be discussed later. An analysis of the gases produced in these reactions, using a procedure based on the work of Johnson,[5] indicated the presence of a large quantity of N_2O as well as NO, NO_2, CO_2 and an inert gas which was presumably N_2.

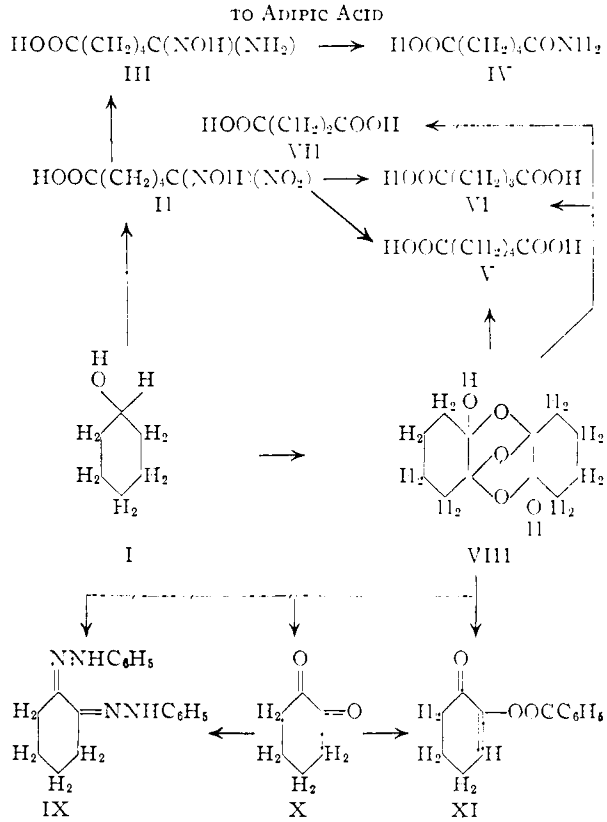
Since the yield of adipic acid was quite high even when the catalyst was omitted, it seemed feasible to suspect that this was a case of directed oxidation and that a study of the reaction might yield the intermediates involved and a key to the mechanism of the reaction. Previous to this paper, no reference could be found in the literature regarding a detailed experimental study of the mechanism of this reaction; however, there have been some fragmentary postulations as to certain possible intermediates.

When cyclohexanol was caused to react with 67% nitric acid in a 1 to 3 mole ratio, respectively, at 20°, 6-nitro-6-hydroxyiminohexanoic acid (II) was isolated. For preparative purposes, it was found that the use of a 6 to 1 mole ratio of nitric acid to cyclohexanol gave a purer product in greater isolable yield.

Hydrogenation of the nitrolic acid II in glacial acetic acid using 5% platinum-on-carbon as catalyst gave 6-amino-6-hydroxyiminohexanoic acid (III). The amidoxime III reacted with nitrous acid at 10° to give adipamic acid (IV), a known compound.[6]

Hydrolysis of the nitrolic acid II with 5% hydrochloric acid gave adipic acid in almost quantitative yield. Also it was noticed that II decomposed on standing at room temperature for 3 or 4 weeks into adipic acid. It is known that nitrolic acids hydrolyze to the corresponding carboxylic acids and N_2O. The former are also known to decompose on heating to carboxylic acids, NO_2 and N_2.[7]

A STUDY OF THE NITRIC ACID OXIDATION OF CYCLOHEXANOL TO ADIPIC ACID



The conversion of the nitrolic acid II through the amidoxime III to adipamic acid along with the

(1) Presented before the Division of Organic Chemistry at the 128th National Meeting of the American Chemical Society, Minneapolis, Minn., September, 1955.

(2) The oxidation of cyclohexanol by nitric acid to give adipic acid has been known for many years, and there have been numerous papers and patents issued regarding this conversion. No attempt will be made here to cite all of the references; however, for a relatively comprehensive list, see "Organic Syntheses," Coll. Vol. I, 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 18.

(3) W. A. Bulen, J. E. Varner and R. C. Burrell, *Anal. Chem.*, **24**, 187 (1952).

(4) Oxalic acid was detected by direct titration with permanganate.

(5) C. L. Johnson, *Anal. Chem.*, **24**, 1572 (1952).

(6) G. H. Jeffery and A. I. Vogel, *J. Chem. Soc.*, 1101 (1934), prepared adipamic acid by treating methyl hydrogen adipate with aqueous ammonia.

(7) V. Meyer and P. Jacobson, Lehrbuch der organischen Chemie, Vol. I, Part 1, Berlin and Leipzig, 1922, p. 409.

hydrolysis of II directly to adipic acid conclusively proved its structure.

When compound II was oxidized with 45% nitric acid[8] at 60°, the total amount of adipic acid which precipitated and that found in the combined mother liquor and wash liquor on chromatographic analysis represented a yield of 93%. Also a yield of 1.8% of glutaric acid was found in the combined liquors. Trace amounts of a number of other materials were eluted from the chromatographic column in a manner similar to the unidentified organic acids found in the combined liquors from the oxidation of cyclohexanol by nitric acid at 55 to 60°. Chromatographic separation and infrared analysis indicated that some of these unidentified acids may be 6,6-dinitrohexanoic acid and also cyanocarboxylic acids.

From the results obtained from the acid hydrolysis of II and the oxidation of II with 45% nitric acid, the formation of adipic acid and some of the glutaric acid in the oxidation of cyclohexanol by nitric acid at temperatures above 35° might be explained by assuming the theoretical intermediate formation of the nitrolic acid II. However, no evidence was found for the presence of the nitrolic acid II when operating at temperatures above 35° which are normally employed for the nitric acid oxidation of cyclohexanol to adipic acid.

In order to determine whether glutaric acid, which was found in the liquors from the oxidation of the nitrolic acid II, could have arisen from the oxidation of adipic acid, the latter was stirred and heated for 24 hours in 20% nitric acid at 65° and in 50% nitric acid at reflux temperature (115°). Only adipic acid could be found on chromatographic analysis of the liquors from both experiments. From these experiments, it must be concluded that the glutaric acid, which was formed in small amounts when II was oxidized with 45% nitric acid, resulted from the direct oxidation of II and not from the oxidation of adipic acid, which was principally formed.

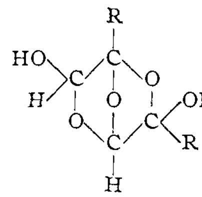
When cyclohexanol and 67% nitric acid were caused to react in a 1 to 3 mole ratio at 10 to 15°, a small amount of material, which is believed to be a hemihydrate form of 1,2-cyclohexanedione (X), octahydro-5aH,10aH-4a,9a-epoxydibenzo-*p*-dioxin-5a,10a-diol (VIII), was isolated along with the nitrolic acid II. For preparative purposes, it was found that the use of 50% nitric acid gave a 40% yield of the compound VIII. Molecular weight determinations by the Menzies ebullioscopic method in dioxane and in acetone as well as an elemental analysis indicated that the empirical formula for VIII was $C_{12}H_{18}O_5$. An infrared analysis (Nujol mull) and functional group tests indicated the presence of the hydroxyl grouping and the cyclic ether linkage.

When compound VIII was caused to react with phenylhydrazine in glacial acetic acid, 1,2-cyclohexanedione phenylosazone (IX) was formed. The structure of the phenylosazone IX was confirmed by preparing a known sample of the phenylosazone IX from 1,2-cyclohexanedione (X).[9] The infrared spectra (Nujol mulls) of the two materials were identical.

Compound VIII reacted with benzoyl chloride in pyridine to give 6-oxocyclohexen-1-yl benzoate (XI). The benzoate XI also was prepared from X in the same manner. The infrared spectra of the two materials were identical as were their melting points, thus confirming the structure of XI.

When VIII was treated with dilute acid or base, the diketone X was formed as determined by infrared analysis. The acid treatment gave the purest product.

On the basis of the evidence gathered from infrared analysis, functional group tests and molecular weight determinations on VIII as well as the conversion of the latter to the phenylosazone IX, the benzoate XI and the diketone X, the structure for compound VIII was assigned. Recently Kuhn and Trischmann[10] have designated the following structure for a white crystalline material which was



R = $(CH_3)_2C{=}CH$—

formed when 4-methyl-2-oxo-3-pentenal was exposed to air.

When VIII was oxidized with 35% nitric acid[8] and the resulting solution analyzed chromatographically, the chief products were succinic acid, glutaric acid and adipic acid in a 10:3:1 weight ratio, respectively. In order to determine whether succinic acid could have arisen from the oxidation of glutaric acid, which was also formed, the latter was stirred and heated with 50% nitric acid at 85° for 24 hours. Only glutaric acid could be found on chromatographic analysis of the reaction solution. It must, therefore, be concluded that succinic acid, which was formed when VIII was oxidized, resulted from the direct oxidation of VIII or the diketone X and not from the oxidation of glutaric acid, which also was formed. Since it also was shown that adipic acid could not be oxidized under similar conditions, glutaric acid could not have arisen from adipic acid, which also was formed.

From the results obtained from the oxidation of VIII with 35% nitric acid and the acid hydrolysis of VIII, the formation of some of the glutaric acid, all of the succinic acid, and a small amount of the adipic acid in the oxidation of cyclohexanol by nitric acid at temperatures above 35° might be explained by assuming the theoretical intermediate formation of compound VIII or, more probably, the diketone X. However, no evidence was found for the presence of compound VIII or the diketone X when operating at temperatures above 35° which

(8) Since the nitric acid concentration drops from 67% to about 25% during the oxidation when carried out at 60°, an intermediate concentration of nitric acid was employed in the oxidation of II as well as in the oxidation of compound VIII which will be discussed later.

(9) Compound X was prepared by oxidizing cyclohexanone with selenium dioxide in the manner described by E. G. Rauh and G. F. Smith, *J. Org. Chem.*, **10**, 199 (1945). Infrared analysis of X showed that the compound exists to a considerable extent in its monoenolic form. See O. Wallach, *Ann.*, **437**, 173 (1924), and G. Schwarzenbach and C. Wittwer, *Helv. Chim. Acta*, **30**, 663 (1947).

(10) R. Kuhn and H. Trischmann, *Ann.*, **573**, 55 (1951).

are normally employed for the nitric acid oxidation of cyclohexanol to adipic acid.

Cyclohexyl nitrite has been isolated in small amounts from the entrained liquid from the gaseous effluent in the oxidation of cyclohexanol with 67% nitric acid at 95°. The cyclohexyl nitrite was identified by boiling point (31° (10 mm.)) and by comparison of its infrared spectrum with that of a pure sample of the nitrite which was prepared according to the method outlined by Hunter and Marriott.[11] The typical nitrite band appeared at 6.15 μ. The significance of the nitrite, if any, in the oxidation reaction has not yet been determined. Also other phases of the oxidation reaction are still under investigation.

Experimental

Nitric Acid Oxidation of Cyclohexanol (I) (55–60°).—Cyclohexanol (50.0 g., 0.5 mole) was added with stirring to 141 g. (1.5 moles) of 67% nitric acid, which contained 0.14 g. of ammonium vanadate as catalyst, over a period of one hour while the temperature was maintained at 55 to 60°. After all of the cyclohexanol was added, the temperature of the reaction mixture was held at 55 to 60° until heat was required to maintain this temperature. The reaction mixture was heated to 95° and then cooled slowly to 0°. The adipic acid was filtered, washed two times with 50 ml. of ice-water and dried; yield 64.2 g. (87.9%), m.p. 151–152°.

The combined mother liquor and wash liquor was analyzed chromatographically.[3] Oxalic acid (0.2 g.),[4] succinic acid (0.5 g.), glutaric acid (4.7 g.) and adipic acid (1.4 g.) were present along with trace amounts of unidentified organic acids. The total amount of adipic acid which was formed was 65.6 g. which represents a yield of 90%.

An analysis of a sample of the off-gases from this reaction[5] indicated the presence of N_2O, NO, NO_2, an inert gas (presumably N_2) and CO_2 in an approximate 11:5:2:1:1 volume ratio, respectively.

6-Nitro-6-hydroxyiminohexanoic Acid (II).—Cyclohexanol (50 g., 0.5 mole) was added dropwise over a period of 30 to 45 minutes to 282 g. (3.0 moles) of 67% nitric acid with stirring while the temperature of the reaction mixture was maintained at 20°. The reaction mixture was stirred an additional 15 minutes at 20° and then was cooled to 0°. The reaction mixture was quenched by adding 150 ml. of ice-water over a period of 10 minutes. The yellow solid was filtered, washed thoroughly with 200 ml. of ice-water and dried; yield 50–60 g. (53–63%), m.p. 74–75° dec.

In order to obtain analytically pure material, crude II may be recrystallized by dissolving the material in about 100 ml. of methanol and adding 300 ml. of ice-water slowly while keeping the temperature at 10°. The solution is then evaporated under an air jet to one-fourth its original volume, and the solid is collected, m.p. 77–78° dec.

Anal. Calcd. for $C_6H_{10}N_2O_5$: C, 37.89; H, 5.30; N, 14.73. Found: C, 37.89; H, 5.45; N, 14.67.

Compound II forms a blood-red solution when dissolved in dilute sodium hydroxide solution, which is characteristic of the nitrolic acid grouping. A molecular weight determination in dioxane by the cryoscopic method gave 192 ± 10 (theory 190.2). Infrared analysis (Nujol mull) fully agreed with the postulated structure. The carbonyl band of the carboxylic acid function appeared at 5.88 μ. The hydroxyl groups of the oxime and carboxylic acid functions showed up as a strong associated hydroxyl band at 3.24 μ. Also a band at 5.98 μ indicated the presence of the oxime group. The nitro band appeared at 6.41 μ.

6-Amino-6-hydroxyiminohexanoic Acid (III).—Crude II (8.6 g., 0.045 mole) was hydrogenated at 25° and a pressure of one atmosphere in 65 ml. of glacial acetic acid using 2.4 g. of 5% platinum-on-carbon as catalyst. Eighty-five per cent. of the calculated amount of hydrogen for the formation of the amidoxime was absorbed. The acetic acid was distilled under reduced pressure at 50°. The resulting oil was then triturated with acetone, whereupon solidification occurred. The product was filtered and dried; yield 6.0 g. (83%). After recrystallization from methanol, the m.p. was 156–157° dec.

Anal. Calcd. for $C_6H_{12}N_2O_3$: C, 44.99; H, 7.55; N, 17.49. Found: C, 44.93; H, 7.32; N, 17.29.

Infrared analysis (Nujol mull) gave an unusual spectrum in which the absorption was intense, indicating an extremely polar substance. The carbonyl band of the carboxylic acid function appeared at 5.88 μ. The hydroxyl groups of the oxime and carboxylic acid functions showed up as a broad associated hydroxyl band in the 3.5 μ region. Two sharp NH bands at 2.99 and 3.15 μ indicated the presence of the amino group.

Adipamic Acid (IV).—Compound III (0.8 g., 0.005 mole) was dissolved in a solution of 0.6 g. of concentrated hydrochloric acid in 10 ml. of water. The resulting solution was cooled to 10° and a solution of 0.41 g. (0.006 mole) of sodium nitrite in 5 ml. of water was added with stirring over a period of 15 minutes. The reaction solution was allowed to stir for 6 hours at 10° during which time a precipitate formed. The reaction mixture was allowed to stand overnight at room temperature and then was cooled to 0° and filtered. The product was recrystallized from methyl ethyl ketone; yield 0.36 g. (50%), m.p. 161–162°.[12]

Anal. Calcd. for $C_6H_{11}NO_3$: N, 9.65; neut. equiv., 145.2. Found: N, 9.49; neut. equiv., 145.8.

Infrared analysis (Nujol mull) indicated the presence of the primary amide function by the two NH bands at 2.99 and 3.14 μ and the amide bands at 6.03 and 6.32 μ. The carbonyl and hydroxyl bands of the carboxylic acid function appeared at 5.88 and 3.24 μ, respectively.

Adipic Acid (V) from 6-Nitro-6-hydroxyiminohexanoic Acid (II).—Compound II (1.2 g., 0.0063 mole) and 20 ml. of 5% hydrochloric acid were stirred while heating at 60° for 2 hours. The resulting solution was cooled to 0° and filtered, whereupon 0.7 g. of adipic acid was obtained. Evaporation of the filtrate gave an additional 0.2 g. of adipic acid; yield 0.9 g. (98%), m.p. 151–152°.

Nitric Acid Oxidation of 6-Nitro-6-hydroxyiminohexanoic Acid (II).—The nitrolic acid II (7.8 g., 0.041 mole) was added to 20.5 g. of 45% nitric acid with stirring at 60° over a period of one-half hour. The reaction was exothermic and brown fumes of NO_2 were evolved. After all of II had been added, the reaction mixture was heated for an additional one-half hour at 60°, cooled to 0°, and filtered. The resulting adipic acid was washed with 10 ml. of ice-water and dried; yield 5.1 g.

The combined mother liquor (13 ml.) and wash liquor (10 ml.) was analyzed chromatographically.[3] The amount of adipic acid present in the combined liquors was 0.45 g. Therefore the total amount of adipic acid which was formed was 5.55 g. (92.7%). Glutaric acid (0.1 g., 1.8%) was also found in the combined liquors. Likewise, trace amounts of a number of other materials were eluted from the chromatographic column in a manner similar to the unidentified organic acids found in the combined liquors from the oxidation of cyclohexanol with 67% nitric acid at 55 to 60°. Chromatographic separation and infrared analysis indicated that 6,6-dinitrohexanoic acid and cyanocarboxylic acids may be some of these trace materials.

Octahydro-5aH,10aH-4a,9a-epoxydibenzo-*p*-dioxin-5a,-10a-diol (VIII).—Cyclohexanol (150 g., 1.5 moles) was added to 567 g. (4.5 moles) of 50% nitric acid at 10 to 15° over a period of 2.5 hours with stirring. The mixture was then cooled to 0° and stirred for 3 hours at this temperature while air was blown over the surface of the mixture. The precipitate was filtered and slurried with a large quantity of ether in order to dissolve compound II, which was also formed. The product was filtered and dried; yield 72.7 g. (40%), m.p. 144° dec.

Anal. Calcd. for $C_{12}H_{18}O_5$: C, 59.47; H, 7.49. Found: C, 59.39; H, 7.46.

Molecular weight determinations by the Menzies ebullioscopic method in dioxane and in acetone gave values of 238 and 246, respectively (theory 242). By infrared analysis (Nujol mull) a spectrum was obtained which exhibited a strong sharp hydroxyl band at 2.92 μ. A series of strong sharp bands in the 8 to 12 μ region (strongest bands: 8.26, 9.28, a doublet (9.87 and 9.94), and 11.33 μ) were considered indications for cyclic ether linkages. There was no evidence in the spectrum for any type of unsaturation. Functional group tests indicated no hydration, epoxide or peroxide. Assuming the empirical formula to be $C_{12}H_{18}O_5$,

(11) L. Hunter and J. A. Marriott, *J. Chem. Soc.*, 285 (1936).

(12) Reference 6, m.p. 161°.

a determination for percentage hydroxyl indicated two hydroxyl groups in the molecule.

1,2-Cyclohexanedione Phenylosazone (IX).—Compound VIII (1.0 g.) was suspended in a solution of 3 g. of glacial acetic acid in 20 ml. of water and 5.0 g. of phenylhydrazine was added slowly with stirring. An exothermic reaction took place with the formation of a yellow solid. The reaction mixture was then heated gently on a steam-bath for 10 minutes, cooled and filtered. The product was recrystallized from ethanol; yield 2.2 g. (92%), m.p. 151–152° dec.

Anal. Calcd. for $C_{18}H_{20}N_4$: C, 73.94; H, 6.91; N, 19.16. Found: C, 73.61; H, 6.91; N, 19.24.

Treatment of 1,2-cyclohexanedione (X)[9] with phenylhydrazine in acetic acid in the same manner as VIII was treated also gave the phenylosazone IX[13] (m.p. 152–153° dec.). The infrared spectra of the two samples of the phenylosazone IX, which were prepared from VIII and the diketone X, were identical when run as Nujol mulls. The strong bands in these spectra appeared at 6.27, 6.42, 6.67, 8.05 and 13.35 μ.

6-Oxocyclohexen-1-yl Benzoate (XI).—Compound VIII (2.0 g.) was suspended in 12 ml. of dry pyridine and 3.0 ml. of benzoyl chloride was added dropwise with stirring. An exothermic reaction occurred with the formation of a white precipitate. The mixture was then heated on a steam-bath for 5 minutes, cooled to room temperature, and poured into 25 ml. of ice-water with stirring. A yellow oily mass precipitated. The supernatant liquid was decanted, and the yellow mass was treated twice with 20 ml. of 5% sodium carbonate solution. The residue was then dissolved in 10 ml. of pyridine and poured on ice. The precipitate was filtered and recrystallized from isopropyl alcohol; yield 2.5 g. (70%), m.p. 89–90°.

Anal. Calcd. for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59; mol. wt., 216. Found: C, 71.87; H, 5.76; mol wt., 221 (in acetone by the Menzies ebullioscopic method).

When the diketone X[9] was caused to react with benzoyl chloride in pyridine in the same manner as compound VIII was treated, the resulting product melted at the same temperature as the benzoate XI which was prepared from VIII (89–90°). A mixed melting point of the two substances gave no depression. Also, the infrared spectra of the two materials ($CHCl_3$ solution) were identical and fully agreed with the postulated structure. The monoconjugated ketone functional band appeared at 5.93 μ. A band at 5.78 μ indicated an aryl ester. Bands at 6.26 and 6.68 μ indicated the phenyl ring.

1,2-Cyclohexanedione (X) from VIII.—Compound VIII (1.0 g.) was stirred and heated at 60° in 15 ml. of 10% hydrochloric acid for 3 hours. The resulting yellow-green solution was cooled, saturated with sodium chloride, and extracted with ether. After drying the ether extract over sodium sulfate and evaporating the ether, there remained 0.6 g. of a yellow-green oil which contained about 80% of the diketone X based on infrared analysis (2% $CHCl_3$ solution) as compared with the spectrum of a pure sample of the diketone X.[9] This represents a yield of about 53%.

The infrared spectrum of X in chloroform solution shows that the compound exists to a considerable extent in its monoenolic form. Strong sharp monoconjugated ketone and hydroxyl bands appear at 5.99 and 2.89 μ, respectively.

Nitric Acid Oxidation of VIII.—Fifteen ml. of 35% nitric acid was heated to 80° with stirring. A small quantity of VIII was added, whereupon the reaction mixture turned yellow-green and then dark red-brown. The exothermic reaction, which liberated NO_2 fumes, caused the temperature to rise to 100°. This temperature was maintained while a total of 2.0 g. of compound VIII was slowly added. After all of VIII was introduced, the reaction solution was heated at 100° for 15 minutes. The solution was then submitted for chromatographic analysis[3] in order to determine the acidic components which were formed. The analysis revealed that 0.81 g. of succinic acid, 0.25 g. of glutaric acid and 0.08 g. of adipic acid were formed.

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(13) No reference could be found of the preparation of IX directly from the diketone X; however, H. Sen and S. K. Ghosh, *Quart. J Indian Chem. Soc.*, **4**, 477 (1927), reported the melting point of IX to be 153–154° when prepared from 1,2-cyclohexanedione monophenylhydrazone. Other references to IX give melting points which range from 150 to 154°.

[CONTRIBUTION FROM THE PHARMACEUTICAL INSTITUTE, MEDICAL FACULTY, UNIVERSITY OF KYUSHU]

Preparation and Stereochemistry of *dl*-2-Aminocyclohexane Thiols[1]

BY TANEZO TAGUCHI AND MASAHARU KOJIMA

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dl-trans-2-Aminocyclohexanethiol was obtained from either *dl-trans*- or *dl-cis*-2-benzoylaminocyclohexyl tosylate with, respectively, retention or inversion of configuration by treatment with thiourea in absolute ethanol, and alkaline hydrolysis of the resulting *dl-trans*-2-benzoylaminocyclohexylisothiuronium tosylate. The mechanisms and assignment of configurations are discussed. The mechanism is supported by the fact that *meso-cis*-cyclohexenimine upon treatment with thiobenzoic acid gives the N-benzoyl derivative of the same *dl*-2-aminocyclohexanethiol. *dl-cis*-2-Aminocyclohexanethiol was obtained by fusion of *dl-trans*-2-thiobenzoylaminocyclohexanol with phosphorus pentoxide, followed by hydrolysis. Fusion of *dl-cis*-2-phenyl-4,5-cyclohexanoöxazoline with phosphorus pentasulfide gave a racemic 2-phenyl-4,5-cyclohexanothiazoline which was converted to *dl-trans*-2-aminocyclohexyl thiobenzoate hydrochloride by treatment with hydrochloric acid and thus designated as *trans*. Fusion of *dl-trans*- or *dl-cis*-2-benzoylaminocyclohexanol with phosphorus pentasulfide resulted in mixtures of *dl-trans*- and *dl-cis*-2-phenyl-4,5-cyclohexanothiazolines. The *cis*-thiazoline was much more stable to mineral acid than the *trans* isomer.

It seemed valuable to seek information on the stereochemistry of aminothiols, particularly in comparison with diastereoisomeric aminoalcohols. For this reason an investigation of the 2-aminocyclonexanethiols was undertaken.

Treatment of either the *trans*-I, or *cis*-II form of *dl*-2-benzoylaminocyclohexyl tosylate with thiourea in absolute ethanol gave a *dl*-2-benzoylaminocyclohexylisothiuronium tosylate, which upon alkaline hydrolysis yielded a *dl*-2-benzoylaminocyclohexanethiol of m.p. 161–162° (V). This suggests that the reaction proceeds by different mechanisms for the *cis* and the *trans* starting material.

It is well known that substitution reactions of the *trans* isomer I proceed with a neighboring group effect of the acyl group through the intermediate *dl-cis*-2-phenyl-4,5-cyclohexanoöxazoline (IIIa), while

(1) Studies in Stereochemistry, VII.