THE SYNTHESIS OF 1,2-CYCLOHEXANEDIONEDIOXIME (NIOXIME)

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The extraordinary specificity of dimethylglyoxime for the ions of nickel and palladium and the consequent widespread use of dimethylglyoxime in the analytical chemistry of these metals (1) is marred by the low solubility of the reagent in water. The reagent is used as a solution in alcohol and, on addition to an aqueous solution, dimethylglyoxime may be precipitated and contaminate the nickel or palladium precipitate. 1,2-Cyclohexanedionedioxime has been reported by Wallach (2) to be soluble in water and to be somewhat more sensitive than dimethylglyoxime as a qualitative test for nickel. The object of the present work is to review the methods of preparation of 1,2-cyclohexanedionedioxime with the object of making this reagent available to the analyst. We propose for 1,2-cyclohexanedionedioxime the name *Nioxime.*

1,2-Cyclohexanedionedioxime was first prepared by Wallach (2) in the following way. Cyclohexanone was brominated in glacial acetic acid at 0° yielding 1,3-dibromocyclohexanone-2 which on treatment with aqueous potassium hydroxide yielded 1,3-dihydroxycyclohexanone-2. This loses water spontaneously giving 1-keto-2-hydroxycyclohexene-2, tautomeric with 1,2-cyclohexanedione, which was oximated in aqueous potassium hydroxide solution. Unfortunately the bromination is not easily controlled; higher bromination products result which lower the yield considerably; and the treatment of 1,6-dibromocyclohexanone with alkali also results in the formation of cyclopentane-α-hydroxycarboxylic acid. The over-all yield is exceptionally poor; indeed, numerous experiments by us and by others indicate that the procedure is useless for the preparation of 1,2-cyclohexanedionedioxime in appreciable quantities.

Treibs and Dinelli (3), more or less incidentally, prepared 1,2-cyclohexanedionedioxime for the identification of isonitrosocyclohexanone which they obtained by the action of nitrous acid on cyclohexanonecarboxylic acid.

Jaeger and van Dijk (4) have also reported the synthesis of 1,2-cyclohexanedionedioxime, utilizing as the first step the Claisen condensation of cyclohexanone with diethyl oxalate which gives cyclohexanoneoxalylic ester (ethyl 2-ketocyclohexylglyoxylate), $C_6H_9(=O)(C=O)CO_2C_2H_5$. This ester was then pyrolyzed to cyclohexanonecarboxylic ester (ethyl 2-ketohexahydrobenzoate), $C_6H_9(=O)\text{-}CO_2C_2H_5$, by heating at 210–220°. Jaeger and Bijkerk (5) report a yield of 42 to 52 % of the theoretical for the cyclohexanonecarboxylic ester. The cyclohexanonecarboxylic ester was then converted to 2-isonitrosocyclohexanone-1 by long shaking with an excess of 6% potassium hydroxide and the theoretical amount of sodium nitrite. The reaction mixture was then decomposed with cold 30% sulfuric acid, yielding 2-isonitrosocyclohexanone-1 in 86% yield. The conversion to the dioxime was carried out in methyl alcohol with hydroxylamine hydrochloride and sodium methoxide.

Our own work was first directed to the synthesis of 1,2-cyclohexanedionedioxime through 1,2-cyclohexanedione a substance first prepared by Riley (6) by the oxidation of cyclohexanone with selenium dioxide. We succeeded in this synthesis with an over-all yield of about 25%. Owing to the instability of 1,2-cyclohexanedione it must be isolated at low temperature and thus requires several ether evaporations at 0°, a somewhat inconvenient operation. To minimize the cost, the selenium dioxide must be recovered. Investigations showed that the best results in the oximation step were obtained by the addition of aqueous potassium hydroxide to a mixture of the dione and hydroxylamine hydrochloride at 0° followed by a period of warming. This method of making Nioxime compares favorably with a second method discussed below in cost and convenience.

We next studied the method of Jaegar and van Dijk whose synthesis was outlined above. Jaeger and van Dijk give detailed directions for the synthesis using 1-methyl-2-cyclohexanone and state that the method is general. They themselves applied it to cyclohexanone, 1-methyl-3-cyclohexanone, and 1-methyl-4-cyclohexanone. The first two steps of the synthesis, the formation of ethyl 2-ketocyclohexylglyoxylate and its pyrolysis to ethyl 2-ketohexahydrobenzoate have been worked out in detail in another connection (7). We were unable to repeat the conversion of ethyl 2-ketohexahydrobenzoate to 2-isonitroso-1-cyclohexanone which involves long shaking of the ester with sodium nitrite in a dilute potassium hydroxide solution. On acidification, the isonitroso compound was reported to separate as a non-crystallizable oil. Numerous repetitions of this reaction, following the directions of Jaeger and van Dijk and with modifications, failed to yield the isonitroso compound and the method was finally abandoned.

Our attention was next directed to the more direct synthesis of 2-isonitrosocyclohexanone-1 by the action of an alkyl nitrite on cyclohexanone, a synthesis already carried out by Pezold and Shriner (9) using *dl*-2-octylnitrite. We attempted to carry out the reaction using amyl nitrite but failed to obtain the isonitroso compound. The reaction proceeded in 80% yield using octyl nitrite, although we employed 2-ethyl-*n*-hexyl nitrite, since 2-ethyl-*n*-hexyl alcohol is available commercially. The formation of nitrite from this alcohol is simple and almost quantitative. The reaction of the nitrite and cyclohexanone was carried out with sodium ethoxide in an alcohol-ether solution from which the isonitroso compound was obtained as a red-brown solid containing some sodium ethoxide. The oximation of the isonitroso compound was attempted under different conditions, the best results being obtained in a methyl alcohol solution of the isonitroso compound with an excess of unneutralized hydroxylamine hydrochloride. The over-all yield was about 30% based on the cyclohexanone used.

EXPERIMENTAL

A. SELENIUM DIOXIDE OXIDATION METHOD

1,2-Cyclohexanedione. In a 1-liter 3-necked flask equipped with a thermometer, reflux condenser, and dropping-funnel was placed 250 g. (2.5 moles) of cyclohexanone. The liquid was heated to 70–80° and a solution of 280 g. (2.5 moles) of selenium dioxide in 1500 ml. of 95% ethyl alcohol was added from the dropping-funnel over a period of two hours, keeping the temperature at 70–80°. The material was then refluxed for two more hours. As much of the liquid as possible was then distilled off and the liquid residue decanted from the elemental selenium. The latter was washed several times with ether and the ether extracts combined with the main portion. The ether was removed by distillation and the residual liquid distilled under reduced pressure, 25 mm. About 200 g. of an oil consisting of cyclohexanone, 1,2-cyclohexanedione, and water was thus obtained. A solution of the oil in 1 liter of ether was extracted three times with ice-cold 10% potassium hydroxide solution, the total amount being equivalent to 1.5 times that necessary to react with the oil assumed to be the pure dione in the mono-enol form. The alkaline extract was shaken once with ether to remove unchanged cyclohexanone, acidified with ice-cold hydrochloric acid, and then saturated with salt. The hydrochloric acid solution was then extracted with ether and the ether extract dried over anhydrous magnesium sulfate. The ether was then removed by distillation and the residual oil distilled under vacuum; yield 55 g. (35% based on the selenium dioxide used) of pale green liquid, b.p. 96–97°/25 mm. Somewhat better yields were obtained in later preparations using this method.

It was observed that the entire synthesis should be carried out in the shortest possible time and at a temperature of 0° in order to minimize the loss caused by the side reaction whereby the 1,2-cyclohexanedione is converted by alkali to cyclopentane-α-hydroxycarboxylic acid (Wallach rearrangement). The product was immediately converted to the dioxime since it was noticed that upon standing the dione decomposes slightly.

1,2-Cyclohexanedionedioxime (Nioxime). The conversion of 1,2-cyclohexanone to the dioxime was carried out a number of times with various modifications. In all cases 11.2 g. (0.1 mole) of the dione, 45 g. of potassium hydroxide, and 34 g. (0.5 mole) of hydroxylamine hydrochloride were used. No dioxime was obtained if the reactants were brought together hot. The yield was greatest if the reactants were brought together at 0°, the potassium hydroxide being added rather slowly, but within 15 minutes, to a mixture of the dione and hydroxylamine hydrochloride. Constant stirring was necessary. After bringing the reactants together, a period of heating on a steam-bath of up to two hours materially increased the yield. Owing to the solubility of the dioxime in water the solution was saturated with salt while warm and before the dioxime began to crystallize. The best procedure found was the following.

The 55 g. of 1,2-cyclohexanedione obtained as above was dissolved in 500 ml. of water. The solution was cooled to 0° and 170 g. of hydroxylamine hydrochloride was dissolved in it. A solution of 225 g. of potassium hydroxide in 1000 ml. of water at 0° was added dropwise over a period of 15 minutes with constant stirring. The mixture was then heated for two hours on a steam-bath, cooled to 0°, neutralized with dry ice, saturated with salt, and filtered. The product on the filter was washed once with a small portion of ice-cold water and recrystallized from water; yield 38 g., 70%, of white, needle-like crystals; m.p. 187–188° with decomposition.

B. METHOD OF JAEGER AND VAN DIJK

Ethyl 2-ketocyclohexylglyoxylate and ethyl 2-ketohexahydrobenzoate. These compounds were prepared by the method of Snyder, Brooks, and Shapiro (7). The 2-ketohexahydrobenzoate obtained boiled at 128–130° and had the refractive index 1.4748, agreeing well with the reported values, so that there is no reason to doubt the identity or purity of the material used in the preparation of the isonitroso compound.

2-Isonitrosocyclohexanone. To 70 g. of ethyl 2-ketohexahydrobenzoate was added 28.4 g. of sodium nitrite. No apparent reaction took place. Eight hundred milliliters of 6% potassium hydroxide was added. A white, curdy precipitate formed which dissolved after shaking for a few hours. The solution darkened somewhat as the white precipitate dissolved. The mixture was shaken mechanically for 48 hours. The vessel was opened and transferred to a 2-l. beaker immersed in an ice-salt mixture. To it was slowly added 27 ml. of concentrated sulfuric acid previously cooled to −5° to −6°. No apparent reaction took place during the addition of the first half of the sulfuric acid, potassium carbonate present probably reacting to form potassium bicarbonate. During the addition of the second half of the sulfuric acid, a gas was given off which, at least in part, was carbon dioxide as shown by the clouding of a drop of lime water on a stirring rod. After the addition of the calculated excess of sulfuric acid the solution was tested and found to be acid to litmus but not so to Congo red. No oil separated as was expected from the work of Jaeger and van Dijk.

Since the temperature was 0°, or below, the conditions existing were very nearly the same as those under which Wilson and Read (8) report that isonitrosocyclohexanone nitrite is formed. They report this compound to be unstable, pale yellow needles which decompose at 190° and are soluble in water. If this was formed from the monoxime, the yield would be cut down considerably. Every mole of sodium nitrite that did not react would yield a mole of nitrous acid which would tie up a mole of the monoxime that had been formed.

Working on this assumption, a second preparation starting with 70 g. of the carboxylic ester was carried out. After the period of shaking, the mixture was neutralized with sulfamic acid to decompose any nitrous acid present and thereby prevent the formation of the water-soluble isonitrosocyclohexanone nitrite. The solution was cooled to 0° and the sulfamic acid was added as a solid in small portions with stirring until the reaction mixture was acid. The temperature was kept at 0°. Only a few drops of oil appeared on the surface of the neutralized reaction mixture. This mixture was extracted several times with benzene and the extracts combined. The benzene was distilled off at 35° under the vacuum produced by an aspirator. A small amount of dark red-brown, viscous material was left. This, along with more of the same material obtained from several runs carried out according to Jaeger's procedure, was oximated in methyl alcohol solution with hydroxylamine hydrochloride following the procedure of Jaeger and van Dijk. A small amount of purple product was obtained which in solution gave a red precipitate with nickel chloride; it was obviously highly impure but did contain some dioxime.

The reasons for our failure to duplicate the work of Jaeger and van Dijk still elude us.

C. ISONITROSOCYCLOHEXANONE METHOD

2-Ethyl-n-hexylnitrite-1. 2-Ethyl-*n*-hexanol-1, obtained from the Carbide and Carbon Chemicals Corporation, was converted to the nitrite by the method of Forman, Carr, and Krantz (10); yield 91%; b.p. 63–64°/19 mm.

2-Isonitrosocyclohexanone. The procedure of Pezold and Shriner (9) was followed except that 2-ethyl-*n*-hexylnitrite-1 was used rather than *dl*-2-octylnitrite. After several preliminary preparations a larger quantity of the material was prepared by the following method.

A 5-l. 3-necked flask equipped with a mechanical stirrer and a reflux condenser carrying a calcium chloride tube was suspended in a suitable container that could later be used as an ice-salt bath. A solution of sodium ethoxide was prepared by the cautious addition of 46 g. (2 moles) of clean metallic sodium to 1 liter of absolute ethyl alcohol in the 5-l. 3-necked flask. Cold water was placed in the container around the flask in order to control the rate of the reaction. When solution of the metallic sodium was complete the flask was surrounded by an ice-salt mixture and the contents cooled to below room temperature. There was then added 700 ml. of anhydrous diethyl ether and the cooling was continued until the temperature reached −10° to −15°. Two hundred grams (2.04 moles) of cyclohexanone and 350 g. (2.2 moles) of 2-ethyl-*n*-hexylnitrite-1 were dissolved in 2500 ml. of anhydrous diethyl ether. Vigorous stirring was applied to the cold sodium ethoxide-ether solution, and the cyclohexanone-octylnitrite-ether solution was added dropwise from a dropping-funnel, which replaced the reflux condenser, at such a rate that the temperature did not exceed 5°. About 40 minutes were required for the addition after which the light tan product was stirred for three hours. The product was filtered by suction and washed with anhydrous diethyl ether until the washings were clear. The sodium salt tended to go through the filter, and a second filtration was necessary to remove all the product from the ether solution. More product precipitated when the ether solution was left standing for some time; yield 248 g., 81.6% based on the cyclohexanone used. Found: 17.8, 17.6% sodium by evaporation with sulfuric acid; calculated: 15.24% sodium.

On the basis that the impurity was sodium ethoxide, which contains 33.82% sodium, the product obtained was about 80.4% sodium-2-isonitrosocyclohexanone-1.

1,2-Cyclohexanedionedioxime. To determine the proper conditions for oximating the sodium salt, oximation was tried in (a) an aqueous potassium hydroxide solution; (b) a methyl alcohol solution of potassium hydroxide; (c) a methyl alcohol solution of sodium methoxide; (d) a methyl alcohol solution of unneutralized hydroxylamine hydrochloride; (e) a hot aqueous solution of unneutralized hydroxylamine hydrochloride; and (f) a cold aqueous solution of unneutralized hydroxylamine hydrochloride.

Method (a) failed to yield the dioxime, methods (b), (c), and (f) gave only insignificant amounts of the dioxime, and method (e) yielded only tar. Method (d) was found most promising and was studied in detail. The most satisfactory procedure devised is given here.

To 149 g. (1 mole) of sodium 2-isonitrosocyclohexanone-1 dissolved in 1 liter of methyl alcohol (a dark brown solution) was added 104 g. (1.5 moles) of hydroxylamine hydrochloride dissolved in 2 l. of methyl alcohol. The flask was fitted with a reflux condenser and the mixture was refluxed for twenty-four hours. After it had cooled to room temperature, sodium chloride was filtered off, and the methyl alcohol solution transferred to a 12-inch evaporating dish. The methyl alcohol was allowed to evaporate at room temperature until the volume had been reduced to about 200 ml. White to tan crystals separated, which were filtered, washed with cold water and recrystallized from water; yield 51 g., 41% based on the isonitroso compound having a purity of 80%. Recrystallization of the 1,2-cyclohexanedionedioxime from dioxane yielded a pure white product melting with decomposition at 189–190°.

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SUMMARY

Two methods have been devised for the preparation of 1,2-cyclohexanedionedioxime, a water-soluble dioxime which has considerable promise as an analytical reagent for nickel. One method involves the oxidation of cyclohexanone to 1,2-cyclohexanedione which is then oximated. The second method involves the conversion of cyclohexanone to isonitrosocyclohexanone by treatment with sodium ethoxide and octyl nitrite; the isonitroso compound is then oximated to the dioxime. The over-all yield in both methods is about 30%.

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REFERENCES

(1) DIEHL, "The Application of the Dioximes to Analytical Chemistry," G. Frederick Smith Chemical Company, Columbus, 1940.
(2) WALLACH, *Ann.*, **437**, 172 (1924).
(3) TREIBS AND DINELLI, *Ann.*, **517**, 160 (1935).
(4) JAEGER AND VAN DIJK, *Proc. Acad. Sci. Amsterdam*, **39**, 384 (1936).
(5) JAEGER AND BIJKERK, *Proc. Acad. Sci. Amsterdam*, **40**, 12 (1937).
(6) RILEY, MORLEY, AND FRIEND, *J. Chem. Soc.*, 1875 (1932).
(7) SNYDER, BROOKS, AND SHAPIRO, *Org. Syntheses*, **2**, 531 (1943).
(8) WILSON AND READ, *J. Chem. Soc.*, 1273 (1935).
(9) PEZOLD AND SHRINER, *J. Am. Chem. Soc.*, **54**, 4707 (1932).
(10) FORMAN, CARR, AND KRANTZ, JR., *J. Am. Pharm. Assoc.*, **30**, 133 (1941).