

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]
ASYMMETRIC SYNTHESSES. I. THE ACTION OF OPTICALLY ACTIVE NITRITES ON CYCLIC KETONES

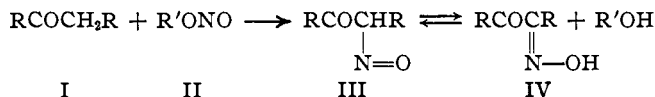
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Most authentic and well recognized chemical asymmetric syntheses involve the creation of a new asymmetric carbon atom in a molecule which has been rendered optically active by combination with an active group. Subsequent removal of the original active group then leaves an active molecule without the use of the usual resolution of a racemic modification.¹ The success of such asymmetric syntheses depends on a difference in the rate of formation of two diastereoisomers. In the present study a new type of asymmetric synthesis was observed in the reaction of an active nitrite with a ketone.

The formation of an α -isonitroso ketone or α -oximino ketone by the action of a nitrite on a ketone is a well-known reaction. It is utilized as the first step in the synthesis of dimethylglyoxime² and in the preparation of 1,2-diketones.³ The mechanism ascribed to the reaction is usually represented as follows



The product actually isolated is undoubtedly an oxime (IV) as shown by its reactions and by the fact that it is light yellow in color whereas nitroso compounds are usually green. The nitroso compound (III) is usually indicated as the intermediate because of other reactions of nitrites and nitrous acid. Chief among these may be mentioned the formation of, (1) nitrosoamines⁴ from secondary amines and nitrous acid; (2) *p*-nitrosodimethylaniline⁵ from dimethylaniline and nitrous acid; (3) *p*-nitrosophenol or quinone monoxime⁶ from phenol and nitrous acid. Wallach⁷ has prepared nitroso pinene and reduced it to pinane-oxime. Ponzio⁸ and

¹ Marckwald, *Ber.*, **37**, 349 (1904); *ibid.*, **37**, 1368 (1904); McKenzie, *J. Chem. Soc.* **85**, 1249 (1904); *ibid.*, **87**, 1373 (1905).

² Behrend and Tryller, *Ann.*, **283**, 244 (1894); Gandarin, *J. prakt. Chem.*, [2] **77**, 414 (1908); Biltz, *Z. anal. Chem.*, **48**, 164 (1909); Adams and Kamm, *THIS JOURNAL*, **40**, 1285 (1918).

³ V. Pechmann, *Ber.*, **20**, 3162 (1887); Russanow, *ibid.*, **24**, 3504 (1891); Fittig, Daimler and Keller, *Ann.*, **249**, 182 (1889); Otte and v. Pechmann, *Ber.*, **22**, 2115 (1889).

⁴ Fischer and Hepp, *ibid.*, **19**, 2991 (1886); **20**, 1247 (1887); **45**, 1098 (1912).

⁵ Baeyer and Caro, *ibid.*, **7**, 810, 963 (1874); Meldola, *J. Chem. Soc.*, **39**, 37 (1881).

⁶ Goldschmidt, *Ber.*, **17**, 213 (1884); Baeyer and Caro, *ibid.*, **7**, 811, 967 (1874).

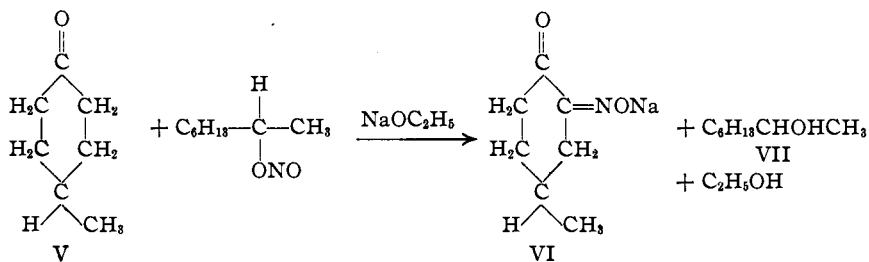
⁷ Wallach, *Ann.*, **245**, 251 (1888); *ibid.*, **389**, 186 (1912).

⁸ Ponzio and co-workers, *Gazz. chim. ital.*, **53**, 305 (1923); **53**, 297 (1923); **56**, 247 (1926).

co-workers still regard the geometric and structural isomers of the oximes as the forms (III) and (IV) above.

It is evident that the nitroso compound (III) contains an asymmetric carbon atom and hence if any indication could be obtained showing its presence proof of the intermediate step would be shown. However, no resolution of form (III) is possible since it is undoubtedly tautomeric with (IV).

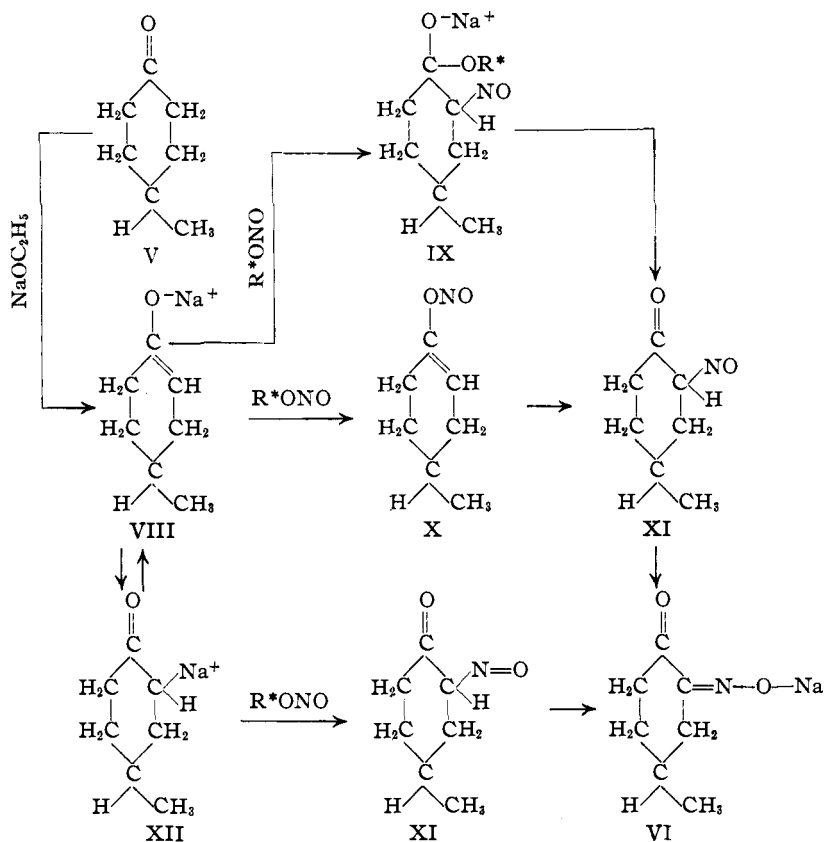
In order to obtain evidence indicating intermediate steps the above reaction was carried out between a cyclic ketone, 4-methylcyclohexanone, and the optically active nitrites, (*d*)- and (*l*)-2-octyl nitrite in an alcohol ether solution. The main reaction was



It will be noted that 4-methylcyclohexanone (V) has no asymmetric carbon atoms and does not exist in isomeric forms whereas in the oxime (VI) the carbon atom (4) carrying the methyl group is now asymmetric. When (*d*)-2-octyl nitrite was used it was actually found that the sodium salt of the oxime (VI) which precipitated from the solution was optically active and *levo*-rotatory. On the other hand, (*l*)-2-octyl nitrite gave a *dextro*-rotatory sodium salt of the oxime. The only other optically active product in the above reaction is octanol-2 (VII) or possibly some sodium 2-octylate. In a separate experiment it was shown that sodium octylate did not precipitate under the conditions used and also that sodium ethylate on (*l*)-2-octyl nitrite produced (*l*)-sodium octylate whereas the oxime obtained with this same nitrite was *dextro* rotatory. Similar condensations with cyclohexanone gave optically inactive products.

The formation of these oximes in an optically active state involves an asymmetric synthesis of a new and unusual type since the active group is split off during the reaction. The optically active oxime must have been produced by a preferential reaction occurring at some intermediate stage. Many mechanisms suggest themselves as possibilities, among which may be mentioned those shown: ($\text{R}^* = (d) \text{ or } (l)\text{-2-octyl radical}$).

According to the first mechanism the active nitrite adds to the double bond of the enol form (VIII) giving (IX), which splits off NaOR^* producing (XI) which in turn rearranges to the oxime (VI). This mechanism shows an actual combination between the active group and the cyclic ketone.



The second mechanism depends for its success on a difference in the rate of reaction of the (*d*) and (*l*) forms of (VIII) with the active nitrite to produce (X), which then rearranges to (XI) and finally to the oxime (VI).

The third possibility likewise involves a preferential rate of reaction between the active nitrite and one of the four optical isomers of (XII). It represents a direct introduction of the nitroso group on the carbon atom. The present experimental evidence does not enable a mechanism to be assigned but does definitely show that asymmetric intermediates are involved.

Experimental

Preparation of 4-Methylcyclohexanone.—A mixture of 94 g. of 4-methylcyclohexanol in 30 cc. of concentrated sulfuric acid (sp. gr. 1.84) and 125 cc. of water was placed in a 2-liter, three-necked flask, fitted with a mercury-sealed stirrer, condenser, thermometer and a dropping funnel. To this mixture a solution of 90 g. of sodium dichromate in 125 cc. of water and 30 cc. of concentrated sulfuric acid was added slowly over a period of forty minutes with stirring. The temperature was allowed to rise to 65° and then external cooling was applied with an ice-salt bath. After one-third of the dichromate solution was added the temperature rise was rapid and had to be watched

carefully. The mixture was allowed to remain on the ice-salt bath for six hours with stirring. The mixture was steam distilled and the ketone separated. The aqueous layer was distilled again, obtaining more ketone. The product was dried over anhydrous calcium chloride and distilled⁹ at 168 to 170°. The yield of 65 g. was 70.4% of the theoretical.

(d) and (l) Octanol-2.—Octanol-2 was resolved by crystallization of the brucine salts of the acid phthalic ester according to the procedure given in "Organic Syntheses,"¹⁰ The (*d*)-octanol-2 distilled at 85–86° at 20 mm.; $\alpha_D^{25} +10.15^\circ$; the (*l*)-octanol-2 at 83–84° at 20 mm.; $\alpha_D^{25} -10.30^\circ$.

(dl)-2-Octyl Nitrite.—In a 3-liter, three-necked flask, 165 g. of sodium nitrite and 130 g. of (*dl*)-octanol-2 were placed. The mixture was cooled to 10° by surrounding the flask with ice and salt. The flask was fitted with a mechanical stirrer and a dropping funnel, one neck remaining open. By means of the dropping funnel 40 cc. of concentrated sulfuric acid was very slowly added. The mixture was stirred vigorously and the temperature kept below 25°. After all the acid had been added, the stirring was continued and water added. The light yellow oil which rose to the surface was poured into a large separatory funnel. More water was added with stirring, the salt mixture allowed to settle, and the oil again poured into the separatory funnel. The extraction was continued until no more oil separated. The nitrite was washed several times with distilled water to remove sulfuric acid and dried over calcium chloride for a few moments. The crude (*dl*)-2-octyl nitrite was obtained which yielded on distillation 110 g. of pure nitrite, b. p. 72–74° at 18 mm., $n_D 1.4272$, $d_{20}^{20} 0.852$.

(d)-2-Octyl Nitrite.¹¹—The (*d*)-2-octyl nitrite was prepared by the procedure given above for the inactive nitrite: b. p. 70–75° at 18 mm., $\alpha_D^{25} +6.90$, $n_D 1.4270$, $d_{20}^{20} 0.852$.

(l)-2-Octyl Nitrite.—The (*l*)-2-octyl nitrite was prepared by the same procedure as that given for (*dl*)-2-octyl nitrite: b. p. 70–75° at 18 mm., $\alpha_D^{25} -7.53$, $n_D 1.4270$, $d_{20}^{20} 0.852$.

Condensation of Cyclohexanone with (*dl*)-2-Octyl Nitrite.—In a 500-cc. three-necked flask fitted with a reflux condenser, stirrer and dropping funnel was placed a mixture containing 2.3 g. of sodium dissolved in 50 cc. of absolute alcohol plus 70 cc. of absolute ether. The contents of the flask were kept at a temperature between -10° and -15° by surrounding the flask with ice and salt mixture. A solution of 10 g. of cyclohexanone and 19.7 g. of (*dl*)-2-octyl nitrite in 250 cc. of absolute ether was added slowly to the sodium ethylate solution. Stirring was continued for three hours. The light tan condensation product was filtered with suction. Since the product was very hygroscopic the air which passed through the precipitate was dried by a U-tube containing anhydrous. The product was washed with absolute ether until the odor of octyl alcohol could no longer be detected. It was then dried in a vacuum desiccator over phosphorus pentoxide; yield 10.5 g. (68.8%).

Anal. Calcd. for $C_8H_{16}O_2NNa$: N, 9.40. Found: N, 9.44, 9.38.

Condensation of Cyclohexanone with (*d*)-2-Octyl Nitrite.—Cyclohexanone condensed with (*d*)-2-octyl nitrite, $\alpha_D = +6.9$, according to the above procedure. The condensation product, identical with that obtained above, was dissolved in absolute alcohol and found to be optically inactive.

Condensation of 4-Methylcyclohexanone with (*l*)-2-Octyl Nitrite.—This condensation was carried out under the same experimental conditions as the condensation of

⁹ Sabatier and Mailhe, *Compt. rend.*, **140**, 352 (1905); Perkin, *J. Chem. Soc.*, **89**, 836 (1906); Wallach, *Ann.*, **346**, 249 (1906).

¹⁰ "Organic Syntheses," J. Wiley and Sons, Inc., New York, 1926, Vol. VI, p. 68.

¹¹ Shriner and Young, *THIS JOURNAL*, **52**, 3332 (1930).

cyclohexanone and octyl-2-nitrite. To 2.3 g. of sodium dissolved in 50 cc. of absolute alcohol was added 70 cc. of absolute ether. This mixture was cooled to -10° and 11.45 g. of methyl-4-cyclohexanone and 10.85 g. of *l*-2-octyl nitrite ($\alpha_D -7.53^{\circ}$) in 250 cc. of absolute ether added slowly with stirring. The condensation product was washed with absolute ether and dried; yield, 2.16 and 2.50 g. In this condensation less than a molar quantity of nitrite was used in order to prevent any possible formation of dioxime. The rotations obtained on two runs of product were $\alpha_D^{25} +16.51$ and $\alpha_D^{25} +17.55^{\circ}$. The product racemized in twelve hours.

Anal. Calcd. for $C_7H_{10}O_2NNa$: N, 8.58. Found: N, 8.25, 8.40.

Condensation of 4-Methylcyclohexanone with (*d*)-2-Octyl Nitrite.—The condensation was carried out in exactly the same manner as the condensation of 4-methylcyclohexanone with *l*-2-octyl nitrite. The rotation of the *d*-2-octyl nitrite condensation product gave $\alpha_D^{25} -12.2^{\circ}$. The rotation dropped to zero in ten hours.

Anal. Calcd. for $C_7H_{10}O_2NNa$: N, 8.58. Found: N, 8.45, 8.33.

Each of the above sodium salts of the oximes was dissolved in alcohol and acidified with dilute hydrochloric acid. Addition of ferric chloride to this solution gave a red color in each case. Another alcohol solution which had been acidified with acetic acid gave a grass-green color with dilute copper acetate solution, which is characteristic of the α -oximes¹² whereas the β -oximes give no color. Since all of the above oximes gave the same grass-green color they probably have the same configuration.

Action of Sodium Ethylate on (*l*)-2-Octyl Nitrite.—A solution of 0.23 g. of sodium in 5 cc. of absolute alcohol and 7 cc. of absolute ether was prepared. This solution was cooled to -10° and 1.1 g. of (*l*)-2-octyl nitrite in 25 cc. of ether was added with stirring. The mixture was kept at -10° and stirred for three hours. There was no precipitate and the ether solution containing sodium octylate showed a negative rotation. The (*l*)-2-octyl nitrite was hence converted to the (*l*)-sodium-2-octylate without any Walden inversion. After standing at room temperature for six hours no precipitate had appeared, which showed that the sodium derivatives of the active oximes were not contaminated with sodium-2-octylate.

Summary

The condensation of 4-methylcyclohexanone with (*d*)-2-octyl nitrite in the presence of sodium ethylate produces a levo sodium derivative of the oxime. The (*l*)-2-octyl nitrite produced the (*d*)-oxime. Cyclohexanone and (*d*) or (*l*)-2-octyl nitrite gave optically inactive products.

Several mechanisms for this new type of asymmetric synthesis are discussed.

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¹² Taylor and Marks, *J. Chem. Soc.*, 2303 (1930); *ibid.*, 2018 (1931).