Further work on the method is in progress but owing to the very limited time available for this work it was thought advisable to publish the progress at this time.

Summary

1. A protective colloid prepared from gum arabic has been utilized in the Nesslerization of ammonia in the presence of alkali sulfates.

2. By this method a higher concentration of ammonia nitrogen can be Nesslerized in an ordinary Kjeldahl digestion solution than by previous methods even in the absence of any extraneous salts.

3. The limit of accuracy for the colorimetric determination of nitrogen by this method appears to be the accuracy of the colorimeter readings.

Champaign, Illinois

[Contribution from the Chemical Laboratory of Harvard University]

ISOXAZOLINE OXIDES. VIII

By E. P. Kohler

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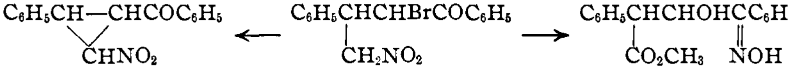
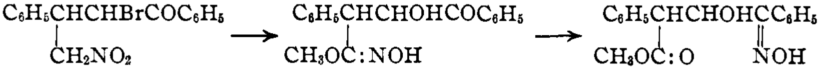
It has been shown that cold methyl alcoholic potassium acetate transforms certain α-bromo-γ-nitro ketones into cyclopropane derivatives and hydroxy oximido esters.[1] The oximido esters were unexpected



II I III

products. Their discovery led to an investigation of the mechanism by which substances so remotely related are formed from the nitro ketones. The mechanism has not been established completely, but a significant intermediate has been isolated, and the facts which have been accumulated provide a basis for a reasonable explanation.

The method of investigation was based on the fact that no compounds corresponding to the hydroxy oximido esters are formed from bromonitro ketones in which the nitro group is attached to a secondary carbon atom. This observation led to the inference that the oximido esters are formed by rearrangement of some hydroxamic acid derivative because the formation of such derivatives is peculiar to primary nitro compounds. A plausible series of steps would be



$$\underset{CH_2NO_2}{\underset{|}{C_6H_5CHCHBrCOC_6H_5}} \longrightarrow \underset{CH_3OC:NOH}{\underset{|}{C_6H_5CHCHOHCOC_6H_5}} \longrightarrow \underset{CH_3OC:O\qquad NOH}{\underset{|\qquad\qquad \|}{C_6H_5CHCHOHCC_6H_5}}$$

I IV III

For the purpose of testing this hypothesis, methyl alcoholic potassium acetate was unsuitable because the solution steadily increases in acidity

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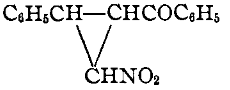
[1] (a) Kohler and Shohan, This Journal, **48**, 2425 (1926); (b) Kohler and Goodwin, *ibid.*, **49**, 219 (1927).

as the reaction progresses. In place of it was used a buffered solution prepared by suspending a large excess of sodium carbonate and sodium bicarbonate in dry methyl alcohol. Towards this solution the two stereomeric bromine compounds represented by I behaved quite differently: the lower-melting isomer gave, mainly, three of the four possible cyclopropane derivatives, while the higher-melting compound yielded, along with cyclopropane derivatives, a substance isomeric with the hydroxy oximido ester. This proved to be the hydroxamic ether represented by IV.

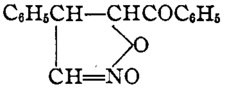
When the hydroxamic ether is shaken or warmed with a methyl alcoholic solution of potassium acetate and acetic acid it passes rapidly and almost quantitatively into the hydroxy oximido ester. It, therefore, doubtless is a real intermediate in the process by which the bromo nitro ketone is converted into the oximido ester. Two problems still remain: to account for the formation of the hydroxamic ether, and to explain the transposition of the oximido group.

With respect to the first problem it is well known that while primary nitro compounds are readily transformed into hydroxamic acids, this occurs only in the presence of acids; bases either form salts of aci-nitro forms or, if too dilute, have no action on the nitro group. Direct experiment showed, moreover, that beyond developing a feeble yellow color, neither potassium acetate nor methyl alcoholic sodium carbonate has any action on the unbrominated nitro ketone. The bromine in the α position, therefore, plays an important part in the process.

In order to provide a proper role for the α bromine atom, and also to account for the fact that the hydroxamic ether is much more readily formed from one of the stereo-isomeric bromine compounds than from the other, one inevitably turns to cyclic intermediates. Two types of cyclic compounds have been obtained by eliminating hydrogen bromide from α-bromo-γ-nitro ketones: nitro cyclopropane derivatives[2] and isoxazoline oxides.[3] In the case under consideration these cyclic products would be represented by II and V.



II



V

Three of the four possible cyclopropane derivatives are in hand. As they are quite insensitive to methyl alcoholic sodium carbonate they cannot be involved in the formation of the hydroxamic ether. All efforts to prepare the oxide V were fruitless, but from the behavior of known oxides and that of analogously constituted furoxanes it is possible to

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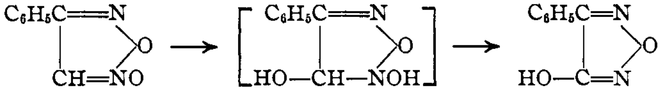
[2] Kohler and Engelbrecht, This Journal, **41,** 1379 (1919).

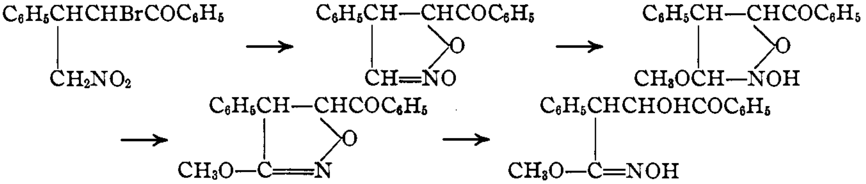
[3] Kohler and Barrett, *ibid.*, **48,** 1770 (1926).

foresee that this oxide would be exceedingly sensitive and that it would be rearranged into more stable substances both by acids and by bases. Its nearest relative, phenylfuroxane VI, in the presence of bases rapidly changes to the hydroxy furazane VII[4]



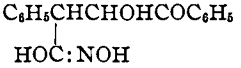
VI VII

In accordance with this behavior methyl alcoholic sodium carbonate would first transform the isoxazoline oxide into a methoxy isoxazolidine, but since isoxazoline rings are readily opened by bases, the final product would be the hydroxamic ether. The most probable mechanism is, therefore

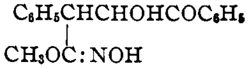


Inasmuch as acids hydrolyze hydroxamic ethers to esters, and hydroxy ketones readily form oximes in acid solution, the transition from the hydroxamic ether to the oximido ester could be adequately explained by successive hydrolysis and oxime formation. But no free hydroxylamine can be detected at any stage of the process and none can be caught by allowing the reaction to take place in the presence of a large quantity of an aldehyde. It seems at least as probable therefore that the transposition of the oximido group occurs by way of cyclic intermediates. There is at present no experimental evidence on this point.

As a result of this and earlier investigations it now appears certain that whenever hydrogen bromide is eliminated from α-bromo-γ-nitro ketones the two possible primary products are nitro cyclopropane derivatives and isoxazoline oxides. Since these nitro cyclopropane derivatives are not attacked either by dilute bases or acids, they can almost invariably be isolated. All isoxazoline oxides are sensitive both to bases and acids; they can consequently be isolated only in favorable cases; usually secondary products appear in place of the isoxazoline oxides. The nature of these secondary products depends on that of the nitro ketone and on the medium in which hydrogen bromide is eliminated. In a basic medium bromo ketones which contain a primary nitro group give either a hydroxamic acid or its ether



$$\begin{array}{l} C_6H_5\underset{\displaystyle \mathrm{HOC{:}NOH}}{\underset{|}{C}}HCHOHCOC_6H_5 \end{array}$$



$$\begin{array}{l} C_6H_5\underset{\displaystyle \mathrm{CH_3OC{:}NOH}}{\underset{|}{C}}HCHOHCOC_6H_5 \end{array}$$

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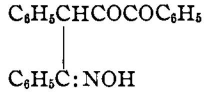
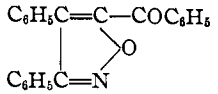
[4] Wieland and Semper, *Ann.*, **358**, 47 (1907).

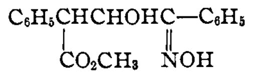
Secondary nitro compounds, under the same conditions, yield either monoximes of triketones or isoxazole derivatives



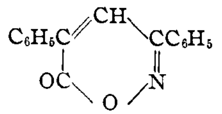
$$\begin{array}{l} C_6H_5CHCOCOC_6H_5 \\ \quad | \\ C_6H_5C:NOH \end{array}$$



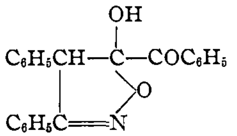
In an acid medium the products from the primary nitro compounds are oximido esters or oxazine derivatives

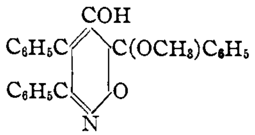


$$\begin{array}{l} C_6H_5\underset{\overset{|}{CO_2CH_3}}{C}HCHOH\underset{\overset{\|}{NOH}}{C}—C_6H_5 \end{array}$$



The corresponding products from secondary nitro compounds are hydroxy isoxazolines or oxyazines of a different type.





Experimental Part

The reagent used in this investigation—a suspension of anhydrous sodium carbonate in dry methyl alcohol—was first tried separately with each of the stereo-isomeric bromonitro ketones. Both reacted rapidly when the mixture was shaken sufficiently vigorously and both gave a number of products, all of which contained nitrogen.

The methyl alcoholic solution obtained from the lower-melting isomer, when concentrated, readily deposited a large quantity of a solid which was identified as the known cyclopropane derivative melting at 95°. The filtrate left an oil which slowly solidified and from which two additional products melting at 88 and 140° were ultimately isolated. These with cold concentrated sodium alcoholate gave the characteristic reaction of nitro cyclopropane ketones[5]

The solution obtained from the higher-melting isomer likewise first deposited the known cyclopropane derivative but the filtrates from this slowly deposited a much higher-melting solid which was exceedingly difficult to handle until it was discovered that from solutions containing acetone it crystallizes fairly well in tables containing acetone of crystallization.

Analyses and a molecular weight determination showed that this new product is isomeric with the oximido ester. A methoxyl determination proved the presence of one such group and a quantitative examination

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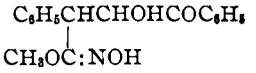
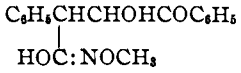
[5] Kohler and Engelbrecht, This Journal, **41**, 1379 (1919).

of its behavior towards methyl magnesium iodide showed that it consumed three moles of reagent and liberated two moles of methane gas. These analytical results show that the substance contains a methoxyl group, two active hydrogen atoms presumably present as hydroxyl and one group capable of combining with methyl magnesium iodide—probably carbonyl. Unlike the oximido ester, it does not form a copper derivative when its ethereal solution is shaken with copper acetate; it, therefore, does not contain the system —C(OH)C(NOH)—. In combination with the known origin of the substance, these facts leave only two possible formulas

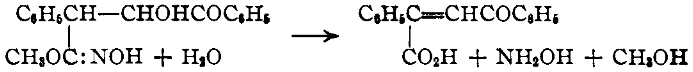


$$\begin{array}{l}C_6H_5CHCHOHCOC_6H_5\\ \qquad\ |\\ CH_3OC{:}NOH\end{array}$$



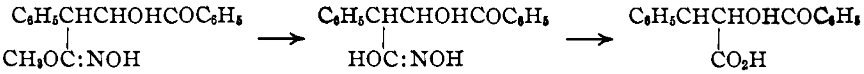
$$\begin{array}{l}C_6H_5CHCHOHCOC_6H_5\\ \qquad\ |\\ HOC{:}NOCH_3\end{array}$$

The first formula is confirmed, the second excluded, by the following transformations. Acetic acid and dilute solutions of mineral acids in methyl alcohol convert the substance into the oximido ester III, while concentrated hydrochloric acid in methyl alcohol both hydrolyzes and eliminates water, leaving *trans*-α-phenyl-β-benzoyl acrylic acid.



$$\begin{array}{l}C_6H_5CH{-}CHOHCOC_6H_5\\ \qquad\ |\\ CH_3OC{:}NOH + H_2O\end{array} \longrightarrow \begin{array}{l}C_6H_5C{=}CHCOC_6H_5\\ \quad\ |\\ CO_2H + NH_2OH + CH_3OH\end{array}$$

The substance, while indifferent to weak and dilute bases, dissolves readily in strong alkaline solutions and is reprecipitated by carbon dioxide and other acids. This typical behavior of oximes excludes the second formula. If the alkaline solutions are allowed to stand for some hours before acidification, the result is an acid which gives the characteristic reactions of hydroxamic acids and which can be further hydrolyzed to an hydroxy acid of known structure



$$\begin{array}{l}C_6H_5CHCHOHCOC_6H_5\\ \qquad\ |\\ CH_3OC{:}NOH\end{array} \longrightarrow \begin{array}{l}C_6H_5CHCHOHCOC_6H_5\\ \qquad\ |\\ \quad HOC{:}NOH\end{array} \longrightarrow \begin{array}{l}C_6H_5CHCHOHCOC_6H_5\\ \qquad\ |\\ \qquad CO_2H\end{array}$$

After a sample of the hydroxamic ether had become available for inoculation it was possible to get the substance by starting with the mixture of stereomeric bromine compounds and, since the separation of this mixture is an exceedingly laborious operation, most of the substance was prepared in this manner. The procedure was as follows.

Fifty grams each of the mixed bromo compounds and anhydrous sodium carbonate were suspended in 300 cc. of dry methyl alcohol. The mixture was vigorously shaken on a mechanical shaker for four hours, then poured into a liter of water. This precipitated a yellow oil which was suspended in a faintly yellow aqueous solution. Four lots were poured together and extracted with ether. The water solution contained only a minute amount of organic material. The ethereal layer was thoroughly washed with water to remove methyl alcohol, then dried over calcium chloride and freed from ether. This left 140–150 g. of bromine-free yellow oil.

The oil was dissolved in 200 cc. of acetone, the solution diluted with 275–300 cc.

of petroleum ether, then inoculated with a sample of the hydroxamic ether which had been recently recrystallized from acetone-petroleum ether and set aside. In the course of twenty-four hours it gradually deposited 24–26 g. of fairly pure ether in well-formed tables, and 3–4 g. more of less pure substance separated in the course of a week. After purification by recrystallization from the same mixture of solvents the total yield was 21 g.

The filtrate from the hydroxamic ether was freed from acetone and petroleum ether, the oil dissolved in 300 cc. of warm methyl alcohol, the solution inoculated with the cyclopropane derivative melting at 95°, then gradually cooled, finally to —20°. It deposited 75–100 g. of almost pure product. The filtrate from this, when allowed to evaporate very slowly in covered beakers, finally turned into a pasty mush. By draining off the liquid at a low temperature with a pump and patiently recrystallizing the solid from ether-petroleum ether this was finally separated. It yielded 3 substances, the known cyclopropane derivative melting at 95°, and two new cyclopropane derivatives melting, respectively, at 88° and 140–142°.

The Cyclopropane Derivatives

The new cyclopropane derivatives crystallize in fine needles. They resemble each other so closely that it is impossible to distinguish them except by melting point and solubility.

Anal. Calcd. for $C_{16}H_{13}O_3N$: C, 71.9; H, 5.0. Found: I (88°): C, 71.9; H, 5.2; II (140°): C, 72.0; H, 4.9.

Each of these substances was dissolved in concentrated sodium methylate as directed in an earlier paper.[6] The lower-melting compound gave 3.5, the higher-melting 3.1 g., of the copper derivative of benzoyl phenacetyl methane—proving that these substances are stereo-isomers of the known benzoyl phenyl nitro cyclopropane.

The Hydroxamic Ether. IV

The ether crystallizes from acetone in transparent tables containing one molecule of acetone which is slowly given off at the ordinary temperature.

Anal. Calcd. for $C_{17}H_{17}O_4NC_3H_6O$: C, 67.6; H, 6.9. Found: C, 67.4; H, 7.1.

When the substance is pure, it can be recrystallized from ether and petroleum ether from which it separates in small, thick plates which are free from solvent.

Anal. Calcd. for $C_{17}H_{17}O_4N$: C, 68.2; H, 5.8; OCH_3, 10.2. Found: C, 68.4; H, 6.0; OCH_3, 10.2.

The ether is extremely soluble in alcohol and in acetone, moderately soluble in ether, insoluble in petroleum ether. It melts with decomposition at about 190°.

Behavior toward Bases.—The hydroxamic ether dissolves readily in excess of cold 20% aqueous sodium hydroxide. If the resulting pale yellow solution is immediately acidified all of the ester is recovered; if it is shaken with acetic anhydride it deposits a mono-acetate of the ester; and if it is kept for some hours and then acidified the product is the corresponding hydroxamic acid.

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[6] Kohler and Engelbrecht, THIS JOURNAL, **41**, 1383 (1919).

The Acetate.—The acetate is most readily made by dissolving the ether in acetic anhydride, warming the solution for a few minutes on a steam-bath and then pouring it into ice water. It crystallizes from ether and from methyl alcohol in stout needles, from ether-petroleum ether in prisms. It melts with effervescence at about 185°.

Anal. Calcd. for $C_{19}H_{19}O_5N$: C, 66.9; H, 5.6; OCH_3, 9.1. Found: C, 66.8; H, 5.7; OCH_3, 8.4.

The Hydroxamic Acid.—A solution of 10 g. of the hydroxamic ether in excess of 10% aqueous sodium hydroxide was kept for five hours at the ordinary temperature, then extracted with ether. This removed 0.4 g. of unchanged hydroxamic ether. The alkaline solution was cooled in ice water, covered with 25 cc. of ether and acidified with iced dilute sulfuric acid. The ethereal layer promptly began to deposit colorless needles melting with decomposition at about 160°. The aqueous layer, even though it had been extracted with ether five times, deposited another gram of the same acid in the course of a week; total yield of crude product, 7.2 g.

The acid is extremely difficult to purify because in solution it gradually changes to a more soluble acid. From a mixture of ether and petroleum ether it occasionally separated in well-formed tables.

Anal. Calcd. for $C_{16}H_{15}O_4N$: C, 67.3; H, 5.3. Found: C, 67.1; H, 5.1.

The acid is readily soluble in alcohol, moderately soluble in ether, sparingly soluble in water. It forms a khaki-colored copper compound both when its ethereal and when its aqueous solution is shaken with copper acetate. Both ethereal and aqueous solutions also give blood-red solutions when they are added to methyl alcoholic ferric chloride. In polar solvents the hydroxamic acid apparently undergoes a spontaneous rearrangement into the isomeric oximido ester. Thus in an attempt at recrystallization a solution of 2 g. of the acid in methyl alcohol was diluted with water until it was definitely turbid. In the course of a few days the turbidity disappeared and the solution then gave a vivid green instead of a khaki-colored copper compound. Upon inoculation it deposited 1.4 g. of the isomeric oximido acid melting at 168°.[1b]

Behavior of the Hydroxamic Ether toward Acids.—The sole action of acids on the hydroxamic ether appears to be its rearrangement to the isomeric oximido ester, for while other products can be obtained by vigorous treatment with mineral acids, all of these are also formed by similar treatment of the oximido ester. The rearrangement can be brought about almost quantitatively with methyl alcoholic potassium acetate and acetic acid. Thus a solution of 2 g. of the ether, 2 g. of the acetate and 5 cc. of acetic acid in 20 cc. of dry methyl alcohol was boiled for half an hour, then cooled and poured into ether and water. The ethereal layer was shaken with sodium carbonate, washed with water, dried and concentrated. It gave 1.72 g. of pure oximido ester and a small quantity of a contaminated product.

Trans-α-phenyl-β-benzoyl Acrylic Acid

The unsaturated ketonic acid is the final product in the degradation of the hydroxamic ether by acids. It is formed when the ether itself, the hydroxamic acid, the oximido ester, the oximido acid or the ketonic acid is heated with methyl alcoholic hydrochloric acid. This was established by heating each of these substances for several hours with a mixture of equal volumes of methyl alcohol and concentrated hydrochloric acid. The best yield (80%) was obtained from the oximido ester. The acid is readily soluble in acetone and alcohol, sparingly in ether. It was purified by crystallization from a mixture of acetone and petroleum ether, from which it separates in small, lustrous tables melting without decomposition at 202°.

Anal. Calcd. for $C_{16}H_{12}O_3$: C, 76.2; H, 4.8. Found: C, 76.5; H, 4.8.

Structure.—An aqueous solution of permanganate was dropped into a cold and rapidly stirred solution of 2 g. of the acid in sodium bicarbonate until the permanganate color persisted for fifteen minutes. The oxide of manganese was dissolved by adding sulfur dioxide, the solution strongly acidified and extracted with ether. The dried ethereal solution, on evaporation, left a residue weighing 2.18 g. With phenylhydrazine this gave 3.05 g. of a phenylhydrazone melting at 161–162°, and identified as the hydrazone of phenyl glyoxylic acid by comparison with a sample on hand. Oxidation with permanganate, therefore, ends in two molecules of phenyl glyoxylic acid.

Synthesis.—Although the result of oxidation left no doubt as to the structure of the unsaturated acid it seemed best to synthesize it because it does not, like the isomer described in an earlier paper,[7] give an oxazine when treated with hydroxylamine. The synthesis by way of α-phenyl-β-benzoyl propionic acid presents no difficulties. When this ketonic acid is brominated it gives two isomeric β-bromo derivatives melting, respectively, at 195 and 208°, both with decomposition. The lower-melting compound crystallizes from ether in large prisms containing ether of crystallization which is lost at the ordinary temperatures.

Anal. Calcd. for $C_{16}H_{13}O_3Br$: C, 57.7; H, 3.9. Found: C, 57.5; H, 4.0.

This bromo compound readily dissolves in an equivalent quantity of normal aqueous sodium carbonate, but it soon becomes cloudy and in the course of a week it deposits a considerable quantity of crystalline material composed of the acid and an indifferent compound which will be described elsewhere. The mixture was easily separated by extraction with sodium carbonate. The acid obtained in this manner was the same as that formed by the hydrolysis of the hydroxamic acid.

Summary

An investigation of the process by which methyl alcoholic potassium acetate transforms certain α-bromo-γ-nitro ketones into β-hydroxy-γ-oximido esters leads to the conclusion that the primary product of the reaction is an isoxazoline oxide. Potassium acetate first transforms this into an hydroxamic ether, which was isolated, and the acetic acid formed in the reaction rearranges the hydroxamic ether to the oximido ester.

CAMBRIDGE 38, MASSACHUSETTS

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[7] Ref. 1 b, p. 226.