

and was only about 70% pure. Qualitatively, toxicologically and trypanocidally, this material was similar to that obtained in the first case.

It would undoubtedly be possible by further experimentation to secure good yields of the disodium salt but the trouble involved in the preparation of 3,3'-dinitro-4,4'-dihydroxy-azobenzene and the apparent lack of therapeutic value of the product indicate that the results would hardly be worth the time necessary to carry out the experiments.

Summary

By reduction of 3,3'-dinitro-4,4'-dihydroxy-azobenzene to the corresponding diamino-dihydroxy-azobenzene, and by subsequent condensation with formaldehyde and sodium bisulfite, N,N'-dimethylenesulfurous acid-3,3'-diamino-4,4'-dihydroxy-azobenzene has been prepared. Owing to extreme susceptibility of the intermediate diamino compound to oxidation, it is impracticable to attempt to isolate it, and the entire process is carried out in an inert atmosphere.

The product, which is the nitrogen analog of sulfarsphenamine, has a very low toxicity, is excreted very rapidly when injected intravenously and is apparently devoid of trypanocidal power.

BOSTON 17, MASSACHUSETTS

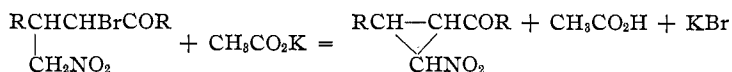
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

A NEW TYPE OF CYCLIC COMPOUNDS

By E. P. KOHLER

RECEIVED NOVEMBER 23, 1923

The following investigation was undertaken for the purpose of ascertaining the reason for the extremely variable yields that are obtained in the preparation of cyclopropane derivatives which have a nitro group attached to one of the carbon atoms of the ring. The reaction by which substances of this type¹ are prepared is represented by the equation

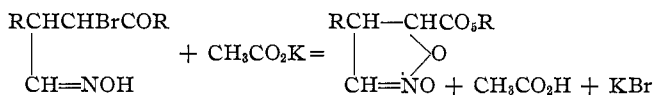


When primary nitro compounds are used, the yields range from 25 to 75%. Secondary nitro compounds give even lower yields and in many cases no cyclopropane at all. The by-products usually appear as uncrystallizable and undistillable oils.

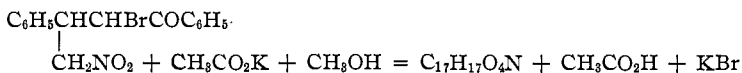
It has not been possible, thus far, to identify all the products of this reaction, but it has now been found that a number of other solid products can be obtained by operating under very specific conditions. These are all due to a second reaction in which hydrogen bromide is eliminated from

¹ THIS JOURNAL, **41**, 1379, 1644, 1698 (1919); **44**, 624 (1922).

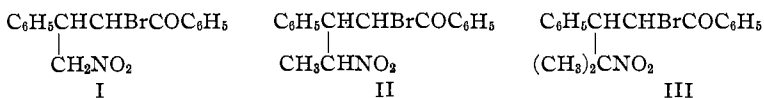
the *aci* form of the nitro compound, and which results in the formation of a new type of cyclic nitrogen compounds



The evidence on which this interpretation is based is as follows. When α -bromo- β -phenyl- γ -nitropropiophenone reacts with potassium acetate in methyl alcohol at low temperatures it gives, in addition to the cyclopropane derivative, a crystalline solid which has the composition $\text{C}_{17}\text{H}_{17}\text{O}_4\text{N}$ and which is formed in accordance with the equation



Since this reaction takes place at a low temperature it is not likely that it involves any transposition of the groups in the nitro ketone. The product is, therefore, probably formed either by direct replacement of bromine by methoxyl, or by elimination of hydrogen bromide followed by addition of methyl alcohol. The first of these alternatives is, *a priori*, improbable because the bromine in α -bromo ketones is ordinarily not so readily replaced. It was considered, nevertheless, because it was not possible to estimate the effect of the nitro group in the γ position upon the activity of this bromine atom. The necessary information on this point was gained by a comparison of the behavior of the following bromo compounds.

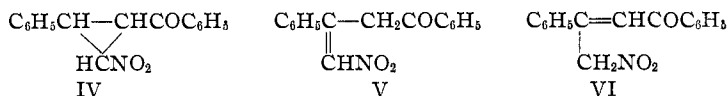


The first of these three closely related substances gives both cyclopropane and the new type of compound, the second gives the new type more readily than the first, and the third does not react at all with methyl alcoholic potassium acetate. Any influence of the nitro group on the replaceability of the bromine in these substances is, therefore, negligible.

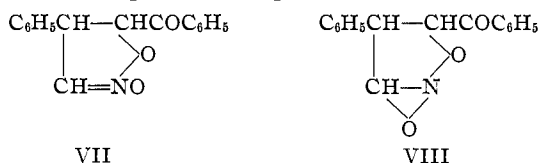
It seems fairly certain from the facts cited, not only that the compound $\text{C}_{17}\text{H}_{17}\text{O}_4\text{N}$ is not due to replacement of bromine by methoxyl but also that its formation involves the elimination of hydrogen bromide and that the hydrogen comes from the γ position. More direct evidence of this mechanism was obtained by allowing the bromo compound to react with potassium acetate in *isopropyl* alcohol. The reaction between these substances never gives good results in solvents that do not participate; in most of them it yields only unmanageable oils, but from the products formed in *isopropyl* alcohol it is possible to isolate another solid product whose composition and molecular weight are represented by the formula $\text{C}_{16}\text{H}_{13}\text{O}_3\text{N}$. In the presence of a little acetic acid this isomer of the cyclo-

propane derivative combines with methyl alcohol and forms the substance $C_{17}H_{17}O_4N$. It is, therefore, doubtless the primary product of the reaction.

Assuming that the reaction between potassium acetate and the bromo ketone does not involve any transposition of groups, there are only three compounds of known type that could be formed by the elimination of hydrogen bromide from the bromo ketone. These are IV, V and VI.



The properties of the substance $C_{16}H_{13}O_3N$ cannot be reconciled with the formulas of any of these compounds. Formula IV represents four possible stereo-isomeric cyclopropane derivatives of which only one is known. The substance in question, however, exhibits none of the characteristic properties of nitrocyclopropane derivatives; it is not reducible to the open-chained saturated nitro compound, alkalis do not transform it into a β -diketone and sodium malonic ester does not convert it into a pyrone derivative. The known cyclopropane derivatives, on the other hand, do not combine with alcohols. The formulas representing ethylenic compounds are equally inconsistent with the behavior of the substance. It is unsaturated, but the type of unsaturation is peculiar; it does not combine with bromine and it is indifferent to permanganate, but it forms stable addition products with water, primary alcohols, ammonia and primary amines. This peculiar unsaturation, the method of preparation, and the properties of the addition products all point to Formula VII or VIII.

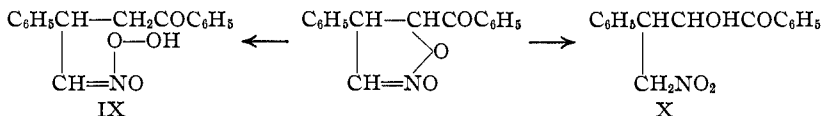


Between these two formulas, which are modeled after those of *iso* nitro compounds, there is at present little to choose, but since the character of the unsaturation resembles that of the amine oxides Formula VII will be used. As substances of this type are related to isoxazolines in the same way that amine oxides are related to amines they will be treated as isoxazoline oxides.

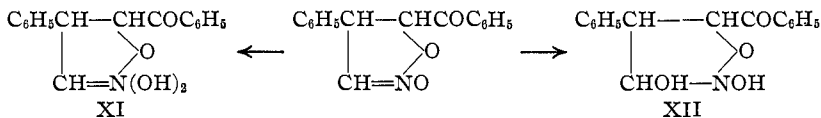
Given a formula to represent the primary product there still remains the problem of the structure of the addition products. The facts are as follows. The oxide forms stable addition products with water, ammonia, alcohols, amines and acetic acid. All these addition products except that with acetic acid belong to the same general type; they resemble one another closely in physical properties, they are mutually convertible, and the most characteristic property of all of them is their ability to form very sparingly

soluble copper derivatives from which they are regenerated by strong acids. They can be benzoylated by means of the Baumann-Schotten reaction; the alcohol addition products thus give monobenzoates, while the water and ammonia addition products give dibenzoyl derivatives. The copper derivatives of all of them are constituted alike, only one of the hydroxyl groups in the water addition product being involved in the formation of the copper derivative.

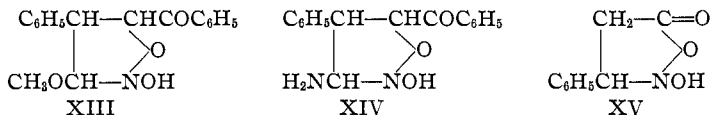
In the presence of a trace of acid, which is essential in the case of alcohols, the addition takes place very rapidly at the ordinary temperature. There is little likelihood, therefore, that it involves the opening of the five-membered ring. Moreover, no open-chained compound likely to be formed would have the properties of these addition products. Thus in the addition of water the ring would doubtless open on either side of the oxygen atom. This would lead to such compounds as are represented by Formulas IX and X.



Substances like these would not form either dibenzoates or copper derivatives. There remains, therefore, only the possibility of addition to the unsaturated system $-\text{CH}=\text{NO}$ which would result in such compounds as XI or XII.

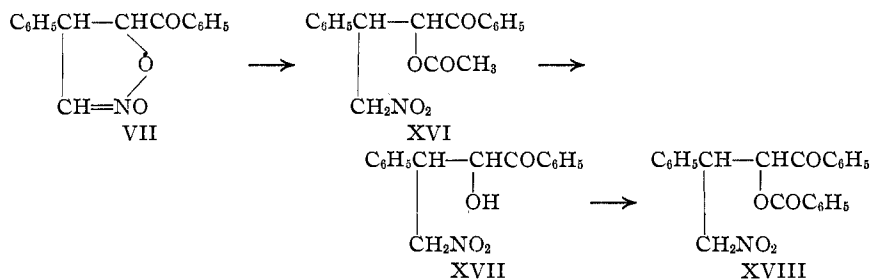


The extraordinary ease with which these addition products are converted into each other inclines one to favor a formula like XI. The methyl alcohol addition product, for example, is changed into the ammonia compound when its ethereal solution is shaken with dil. aqueous ammonia, and the process is reversed completely when methyl alcoholic solutions of the ammonia compound are boiled. Such mobility as this would be expected in compounds of the type represented by XI, but compounds of this type would also be expected to behave essentially like the hydrates and the alcohol addition products of amine oxides and certainly no substance constituted like this would form a dibenzoate. The addition products must, therefore, be the isoxazolidine derivatives, XII-XIV.

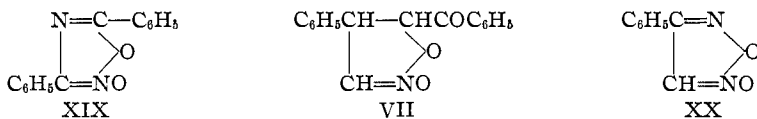


The number of active hydrogen atoms represented in these formulas agrees with that found by benzoylating the substances; the ease with which the various addition products are transformed into one another is accounted for by the fact that they are partially dissociated when dissolved in polar solvents, and the only other substance of this type that is known (XV)—an hydroxy isoxazolidone made by Posner²—likewise forms copper derivatives.

The addition product with acetic acid is of an entirely different type. It is formed in a very slow reaction that requires weeks for completion. It contains no hydroxyl group and is incapable of forming a copper derivative. On hydrolysis it forms a compound which is isomeric with the water addition product but which contains but one hydroxyl group and does not form a copper derivative. All these facts indicate that we are here dealing with a series of open chained compounds VII, XVI, XVII, XVIII.



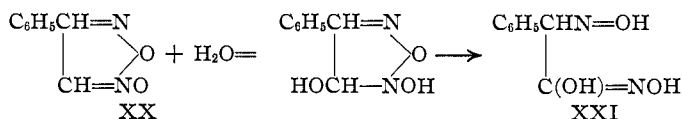
The known substances that are most nearly related to the isoxazoline oxide VII are the oxazoximes XIX and certain furoxans XX.



Little is known of the properties of the oxazoximes but the furoxans have been studied with care, especially by Wieland and his collaborators who established the formula that is now generally accepted. The isoxazoline oxide appears to have little in common with the furoxan XX, which is most nearly like it in composition and structure. The furoxan seems to lack altogether the power to form stable addition products with water, alcohol, and similar substances, which is one of the most characteristic properties of the isoxazoline oxide. The difference, in this respect, may possibly be not so great as it appears to be. The ring in the furoxan is doubtless, much more easily opened than that in the oxide. It is conceivable, therefore, that furoxan addition products analogous to the isoxazolidines very rapidly undergo rearrangement to the isomeric open-chained

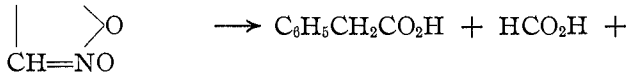
² Posner, *Ber.*, **39**, 3515 (1906).

compounds, which were obtained by Wieland and Semper³ (XXI).

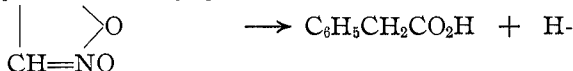


A direct comparison of the furoxan XX with the isoxazoline oxide showed, however, that the former does not react at all with methyl alcohol under conditions under which the latter combines with great rapidity.

To bases the isoxazoline oxide is less sensitive than the furoxan. Thus aqueous sodium carbonate, which at the ordinary temperature rapidly transforms the latter, first into an isomeric hydroxy furane, and then into the hydroxamic acid XXI, produces no effect on the former beyond an extremely slow addition of water. Caustic alkalis, however, attack the oxide briskly, breaking it down rapidly and smoothly in accordance with the equation, $\text{C}_6\text{H}_5\text{CH}-\text{CHCOC}_6\text{H}_5$



$\text{C}_6\text{H}_5\text{CN}$. There are at least three steps in the process; but as it has not been possible as yet to establish the nature of the intermediate products, the only thing that is certain at present is that the benzonitrile is formed from the benzoyl group. This follows from the behavior of the corresponding chloro compound: $\text{C}_6\text{H}_5\text{CH}-\text{CHCOC}_6\text{H}_4\text{Cl}$



$\text{CO}_2\text{H} + \text{ClC}_6\text{H}_4\text{CN}$.

A discussion of the most interesting problem connected with all substances of this type, the structure of the unsaturated system C—NO, will have to be deferred to a later paper; but the reason for the variable yields of cyclopropane derivatives that are obtained when bromonitro ketones react with potassium acetate can be given now. γ -Nitro ketones on bromination generally give a mixture of stereo-isomeric α -bromo derivatives. The relative amounts of the two stereo-isomers obtained from any given nitro ketone are fairly constant and independent of the way in which the bromination is accomplished; but they differ much with different ketones. In the case of all the bromonitro ketones that have been obtained up to this time one of the stereoisomers gives mainly a cyclopropane derivative when it is treated with potassium acetate, while the other bromine compound gives exclusively an isoxazoline oxide or some secondary product formed from such an oxide. The yield of cyclopropane derivative obtained from a mixture of stereo-isomeric bromine compounds, therefore, varies with the relative amounts of the components.

³ Wieland and Semper, *Ann.*, **358**, 56 (1908).

Experimental Part

Preparation of Materials

Addition of Nitromethane to Benzalacetophenone.—The method described in an earlier paper⁴ is not satisfactory for the preparation of large quantities of the nitro ketone. The following procedure gives a better yield and a product that is more easily purified.

Sodium nitromethane is made by adding slowly and with constant stirring 30 g. of nitromethane to a cooled solution of 10 g. of sodium in the minimum amount of dry methyl alcohol. The paste thus formed is very stiff even when a much larger quantity of methyl alcohol is used, but it becomes thin enough to pour freely when a few cubic centimeters of the alcohol are stirred into it. It is immediately poured into a solution of 70 g. of benzalacetophenone in 150 cc. of methyl alcohol which has been warmed to about 50°. When the mixture is *vigorously* shaken the temperature should rise to the boiling point and the sodium nitromethane should dissolve in a few minutes to form a clear amber-yellow solution. Any solid left after this time is likely to be a trimolecular product, while a darker color indicates decomposition of the sodium nitromethane. The yield is better in methyl than in ethyl alcohol; water in the alcohol favors the formation of the trimolecular product which greatly interferes with purification.

The yellow solution is left to itself for 10 minutes, during which it slowly darkens, then cooled in ice water and very cautiously acidified with 30 g. of glacial acetic acid. The best yields are obtained when the liquid is stirred mechanically during the addition of the acid. Too rapid addition of acid at the outset leads to the precipitation of an oil which even though it later solidifies, nevertheless gives a very poor yield. The precipitate is immediately pressed on a suction filter, washed with iced methyl alcohol until pure white in color and then thoroughly with water. It is not advisable to work with much larger quantities, but the washed cakes from a number of such condensations are advantageously combined for purification. For this purpose the washed material is dissolved in chloroform, the solution dried after removal of most of the supernatant water, and concentrated to small volume. The first crop of solid is almost pure nitroketone, while later crystallizations may contain considerable quantities of the trimolecular product. These are recrystallized from alcohol. In an average operation, 280 g. of benzalacetophenone will give 265–270 g. of pure nitroketone, a yield of about 75%.

Bromination and Separation of the Bromine Compounds.—The nitroketone on direct bromination always yields two stereomeric α -bromo compounds that melt at 109° and 129°, and it usually also gives an α,α -dibromo compound that melts at 106°. As the separation of these bromo compounds is exceedingly troublesome, and as the one that is formed in largest amount is the least useful for making isoxazoline oxides, many attempts were made to direct the bromination so as either to get a single product, or to vary the relative amounts of the stereomers. To this end brominations were carried out in nearly all available solvents and at temperatures ranging between -20° and the boiling point of nitrobenzene. In all cases the relative amounts of low- and high-melting isomers were practically the same—about 4 times as much of the former as of the latter, and this ratio was maintained even when the solid ketone was exposed to

⁴ THIS JOURNAL, 38, 889 (1916).

the action of bromine vapor. It was found, however, in the course of these experiments, that when the condensations are successful it is unnecessary to isolate the pure ketone before bromination. The procedure is as follows.

The dried and concentrated chloroform solution, obtained as described under the condensation, is treated with a little bromine, then warmed or exposed to direct sunlight. After the reaction has started, more bromine is added drop by drop until the color shows a definite excess which does not disappear in 10 minutes. This usually requires 40–45 g. of bromine for the product obtained from 70 g. of benzalacetophenone; incomplete bromination results in a mixture that it is almost impossible to separate. Most of the chloroform is now distilled and the hot residue poured into an equal volume of methyl alcohol. The solution, which is usually red or green, rapidly becomes yellow and the product crystallizes promptly. The crystals are thoroughly washed with chilled methyl alcohol until colorless. The yield of washed and dried bromides from 210 g. of benzalacetophenone is about 200 g., and 50 g. of less pure product can be recovered from the filtrates.

Owing to the tendency of the bromo compounds to crystallize in mixed crystals it is uncommonly difficult to separate the mixture obtained in the bromination; but this may be accomplished by persistent fractional crystallization either from methyl alcohol or from a mixture of chloroform and petroleum ether. A mixture of 500 g. ultimately yielded 350 g. of the lower-melting bromine compound, which crystallizes in flat needles and melts at 108° (I), 90 g. of the isomer⁵ which crystallizes in tables or prisms and melts at 129° (II), 16 g. of the α,α -dibromo compound which crystallizes in tables that closely resemble those of the higher-melting monobromo compound, but are much more readily soluble and melt at 106°, and a small quantity of mixed solids.

Analyses. Calc. for $C_{18}H_{14}O_3NBr$: C, 55.2; H, 4.0. Found: (109°) C, 55.0; H, 4.2; (129°) C, 54.9; H, 4.2.

Calc. for $C_{18}H_{13}O_3NBr_2$: C, 45.0; H, 3.0. Found: (106°) C, 45.2; H, 3.2.

Isomerization of the Bromo Compounds.—Since it was not possible to alter the relative amounts of the two monobromo derivatives by brominating under widely different conditions, various attempts were made to change the lower-melting compound into the more desirable isomer. The best results were obtained as follows. Fifty-g. lots of the bromo compound were suspended in 50 cc. of chloroform, the mixture was saturated with hydrogen bromide and heated in sealed tubes at 125° for 24, 48 and 72 hours. The first contained 8 g., the second 10 g. and the third 11 g. of the higher-melting compound. While it is possible in this way to transform some of the lower-melting compound into its isomer, the operation is not remunerative; there are secondary reactions and the separations are more difficult even than those of the original bromination product.

The Iodine Compound.—It was stated in an earlier paper⁴ that potassium iodide in acetone converts the two isomeric bromo compounds into the same iodo compound. This operation has been repeated with the pure bromine compounds with the same result. The resulting iodine compound

⁵ The descriptions of the isomers given by Kohler and Engelbrecht, *THIS JOURNAL*, 41, 1381 (1919) are erroneous. The substances there described are mixtures of the two isomers.

gives mainly cyclopropane derivative, and hence corresponds in configuration to the lower-melting isomer. In this simple replacement reaction, which involves such a mild reagent as potassium iodide and which takes place rapidly at the ordinary temperature, each of the two active components that compose the higher-melting bromo compound, therefore, undergoes a Walden inversion, while those of the lower-melting compound are transformed without change in configuration.

Elimination of Hydrogen Bromide

Hydrogen bromide can be eliminated from the bromo compounds with a number of reagents and under a variety of conditions. The primary products are always a cyclopropane derivative, and an isoxazoline oxide derivative. Unless the sole purpose is the preparation of the cyclopropane derivative the only serviceable combination is potassium acetate, acting at a low temperature, in methyl alcohol. The compounds that have been isolated from the mixture obtained by this combination are the cyclopropane derivative (IV), the methyl alcohol addition product of the isoxazoline oxide (XIII), the water addition product (XII), the open-chained hydroxyl compound (XIV), and a substance that is presumably an isoxazole, but whose structure has not as yet been established. The mixture contains a considerable quantity of other substances. As these are capable of forming copper compounds they may be stereo-isomers of the methyl alcohol and water addition products; but up to this time it has not been possible to isolate any of them in solid form.

The cyclopropane derivative is a relatively inactive substance that crystallizes well from all solvents. The isoxazoline oxide is exceedingly sensitive, and crystallizes only when comparatively free from other substances. Only cyclopropane and oily products are obtained, therefore, when the reaction is carried out in solvents that, like acetone for example, are incapable of combining with the oxide. Dry methyl alcohol is the best solvent because the addition products of the isoxazoline oxide with water and with other alcohols have little crystallizing power. The amount of solvent must be as small as possible, for while the methyl alcohol addition product of the isoxazoline oxide can be precipitated very completely as copper derivative, other copper forming substances are precipitated with it and the product obtained by the action of acids on this mixture of copper compounds generally fails to crystallize. The procedure is, therefore, as follows.

The bromine compound is introduced in 10g. lots into 120g. salt-mouth bottles each of which contains 10 g. of fused potassium acetate in 60 cc. of dry methyl alcohol. The bottles are shaken under the tap as long as the temperature tends to rise, then shaken mechanically for 3 hours. Further 10g. lots of acetate and bromo compound are then added, and this operation is repeated at 3-hour intervals until each bottle contains 50 g. of the bromine compound. In order to complete the reaction, the shaking must be

continued for at least 24 hours after the last addition. The bottles are then allowed to stand in an ice chest for 12 hours to ensure complete separation of the solid products. The contents are filtered with the aid of suction, the solid is washed, first with a little iced methyl alcohol until colorless, then very thoroughly with water until free from bromide and acetate and dried in the air.

The solid now consists of cyclopropane derivative, the methyl alcohol addition product of the isoxazoline oxide, and usually a small quantity of a trimolecular addition product. The cyclopropane derivative is removed by shaking the dry powder with chloroform (150 cc. per 100 g.), filtering and washing with small quantities of boiling chloroform. The residue is recrystallized from methyl alcohol. By this procedure 50 g. of the lower-melting bromo compound gave 34 g. of solid product which yielded 28 g. of cyclopropane derivative and 5 g. of pure methyl alcohol addition product; 50 g. of the higher-melting bromo compound gave 32 g. of solid composed entirely of the isoxazoline oxide addition product; and 500 g. of the washed and dried mixed bromides gave 310 g. of solid product, composed of 209 g. of cyclopropane, 95 g. of isoxazoline oxide addition product, and 4 g. of trimolecular compound. The α -iodo compound gave a little more isoxazoline oxide addition product than the lower-melting bromo compound—8 g. from 56 g. of iodo compound.

The methyl alcoholic filtrates gradually deposit small quantities of the crystalline compound which is presumably an isoxazole. They contain large quantities of substances that are capable of forming copper derivatives. These can be precipitated by pouring them into water, extracting with ether, freeing the ethereal solution from acetic acid and then shaking it with aqueous copper acetate. When the copper derivatives are precipitated fractionally the first fraction generally yields some of the methyl alcohol addition product, but all others have thus far given only oily products.

The Isoxazoline Oxide

It is possible, as stated in the introduction, to isolate a small quantity of the oxide directly from the mixture obtained by allowing potassium acetate to react with the higher-melting bromo compound in *isopropyl* alcohol, but this is not a feasible method of preparation. The oxide is also formed when its methyl alcohol addition product is heated either by itself or in solution in indifferent, high-boiling solvents but the yields here also are very small. The oxide can, however, be liberated very easily from this addition product with the help of one of a number of substances that are capable of reacting with methyl alcohol—concd. sulfuric acid, acetic acid, acetyl chloride, chlorides of phosphorus and acetic anhydride. Most of these also bring about other reactions, but acetic anhydride gives almost a quantitative yield of the oxide. The procedure is as follows.

The finely powdered addition product is suspended in twice its weight of acetic anhydride in a glass-stoppered bottle and the mixture shaken for at least 12 hours. The liquid is then pumped off, the solid washed, first with chilled, alcohol-free ether, and then very thoroughly with water, and dried on a steam-bath. One recrystallization from a mixture of absolute ether and petroleum ether gives a pure product melting at 126°.

Analyses. Calc. for $C_{16}H_{13}O_3N$: C, 71.9; H, 5.0; N, 5.2; mol. wt., 267. Found: C, 71.8; H, 5.2; N, 5.2; mol. wt. (in acetone), 260.

4-Phenyl-5-benzoyl Isoxazoline Oxide (VII).—4-Phenyl-5-benzoyl isoxazoline oxide (VII) crystallizes in large transparent tables. It is readily soluble in acetone, in

chloroform, and in methyl alcohol, moderately soluble in ether, very sparingly soluble in petroleum ether. It is not attacked by permanganate in acetone but is very slowly oxidized to benzoic acid by aqueous permanganate, presumably because it combines with water and thus forms an addition product that is more easily oxidized. It is easily oxidized by chromic acid, but here also the sole organic product is benzoic acid. A solution of the oxide in absolute ether does not immediately produce a precipitate when it is shaken with aqueous copper acetate. This fact can be utilized to detect any of its addition products in the oxide, but the ether used as solvent must be absolutely free from alcohols and amines. When the two solutions are allowed to remain in contact, the khaki-colored copper compound of the water addition product is gradually formed.

Addition Reactions of the Oxide.—In the absence of acids and bases, the oxide behaves like a saturated compound; it does not combine with bromine, is not affected by permanganate and can be boiled with or recrystallized from alcohols without undergoing any change. In the presence of acids and bases it becomes active and combines more or less rapidly with many substances that contain active hydrogen. Few of these substances crystallize well, but as all of them are capable of forming copper derivatives it is not difficult to establish the fact of addition, and to give at least a rough estimate as to the rate of addition. The lower alcohols combine more rapidly than water, and methyl alcohol combines more rapidly than any other substance except possibly ammonia and methyl amine. Higher alcohols and amines do not combine any more rapidly than water, and secondary alcohols do not combine with the oxide at all.

2-Hydroxy-3-methoxy-4-phenyl-5-benzoyl Isoxazolidine (IX).—The crude product of the reaction between methyl alcoholic potassium acetate on the higher-melting bromo compound is easily purified by recrystallization from dry methyl alcohol or from acetone.

Analyses. Calc. for $C_{17}H_{17}O_4N$: C, 68.2; H, 5.7. Found: C, 68.5, 68.2; H, 5.8, 5.8.

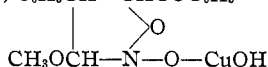
The substance is moderately soluble in boiling methyl alcohol, acetone and ether, very sparingly soluble in water, almost insoluble in chloroform and in carbon tetrachloride. It crystallizes in hard, lustrous prisms. When heated rapidly it melts sharply at 162° ; the colorless melt soon begins to effervesce and in a short time the substance is completely decomposed into methyl alcohol, water, benzonitrile and an insoluble, infusible solid which contains nitrogen and resembles polymeric nitrostyrene. A solution of the substance in acetone slowly reduces permanganate; the oxidation product contains 2 molecular equivalents of benzoic acid. Aqueous permanganate acts more rapidly and forms the same products if the solutions are not allowed to become alkaline. The isoxazolidine derivative dissolves readily in concd. sulfuric acid. The solution is colorless at first but gradually turns to a deep purple color. When the colorless solution is poured onto cracked ice it forms a milky liquid from which ether extracts, mainly, the unchanged substance; but a part of it is transformed into the dihydroxyl compound in the process. The purple solution obtained by allowing the colorless solution to stand for a week and then isolating the product in the same way gave the isoxazoline oxide (75%) and a colorless oil.

Owing to its sensitiveness to alkalis the hydroxy isoxazolidine cannot be benzoylated in the ordinary way. An excellent yield of the benzoate was, however, obtained as follows. An ethereal solution containing 3 g. of the hydroxy compound and 10 g. of benzoyl chloride was shaken for 10 hours with an excess of saturated aqueous sodium carbonate. The ethereal layer was separated, dried and allowed to evaporate. It left a small quantity of high-melting solid imbedded in a colorless oil. A solution of the oil in absolute ether on dilution with an equal volume of petroleum ether deposited the benzoate in large, colorless plates that melted at 114° .

Analyses. Calc. for $C_{24}H_{21}O_6N$: C, 71.4; H, 5.2. Found: C, 71.4; H, 5.3.

THE BENZOATE.—The benzoate is readily soluble in all organic solvents except petroleum ether. Methyl alcoholic hydrogen chloride transformed it into hydroxy-isoxazolidine and methyl benzoate, while hot, aqueous, hydrochloric acid changed it largely into the dihydroxy compound, benzoic acid and methyl alcohol which was identified as formaldehyde. The high-melting solid was the dibenzoate of the dihydroxy-isoxazolidine. When the sodium carbonate solution is too dilute this constitutes the main product.

THE COPPER DERIVATIVE, $C_6H_5CH-CHCOC_6H_5$



.—When an ethereal solution

of the hydroxyl compound is shaken with aqueous copper acetate it immediately forms an olive-green copper derivative. The composition of the copper compound varies with the mode of preparation; but in view of the fact that it is insoluble and is precipitated in such a finely divided condition that washing is both difficult and uncertain, the variations are surprisingly small. The copper content of six preparations—four from the acetate and one each from the chloride and sulfate—ranged between 16.5% and 17.0%, in place of 16.8% calculated from the formula.

The copper compound dissolves in glacial acetic acid, but is probably partially changed to acetate in the process, because absolute ether precipitates compounds of very variable composition from which it is not possible to remove all of the acetic acid by prolonged washing. It is rapidly disintegrated by acetic anhydride which forms a blue solution that soon becomes colorless. When this is poured into water it gives a clear solution that on neutralization with sodium carbonate and extraction with ether yields very nearly the equivalent quantity of isoxazoline oxide. The hydroxyl compound can be recovered from the copper compound by shaking it with cold dil. mineral acid and a small quantity of ether; the cycle, hydroxyl compound to copper derivative and back to hydroxyl compound, involves a loss of only about 5%.

2,3-Dihydroxy-4-phenyl-5-benzoyl Isoxazolidine (XII).—The water addition product is a constant product of the reaction between the bromo compound and alcoholic potassium acetate. It is also formed when an ethereal solution of the methyl alcohol addition product is shaken for a long time with dil. aqueous sodium carbonate or potassium acetate, but it is most easily obtained by dissolving the oxide in glacial acetic acid and gradually diluting the resulting solution with water. It has very slight crystallizing power but may be purified by cautious recrystallization from dil. acetic acid.

Analyses. Calc. for $C_{16}H_{15}O_4N$: C, 67.4; H, 5.3. Found: C, 66.9, 67.1; H, 5.6, 5.4.

The dihydroxyl compound crystallizes in small, hard prisms, melts at 153° and rapidly decomposes immediately afterwards. It is readily soluble in alcohol and acetone, moderately in dil. acetic acid, sparingly in water and ether, and is insoluble in chloroform and carbon tetrachloride. Its aqueous solution reduces permanganate. Its khaki-colored copper compound—precipitated when an ethereal solution is shaken with aqueous copper acetate—was found to contain 17.4% and 17.5% of copper instead of 17.2% calculated for a substance constituted like the copper derivative of the methoxy compound.

THE DIBENZOATE.—A suspension of 2 g. of the finely powdered dihydroxyl compound in 20 cc. of absolute ether was shaken with 5 g. of benzoyl chloride and a large excess of saturated aqueous sodium carbonate until the odor of the chloride disappeared. The ethereal layer, on evaporation, deposited 2.1 g. of a solid which was recrystallized from acetone. It separated in small, lustrous tables which melted at 158–160°.

Analyses. Calc. for $C_{30}H_{23}O_6N$: C, 73.0; H, 4.7. Found: C, 73.4; H, 5.0.

2-Hydroxy-3-ethoxy-4-phenyl-5-benzoyl Isoxazolidine.—The ethyl alcohol addition product was first obtained by removing hydrogen bromide from the bromo compounds in absolute ethyl alcohol. The yield was small and it was extremely difficult to get a solid product. The substance is most easily obtained by dissolving the ammonia addition product in absolute alcohol, adding a trace of acetic acid and evaporating to dryness on a steam-bath. After three or four repetitions of this operation the residue solidifies completely when inoculated with a little of the solid. It was recrystallized from absolute alcohol.

Analyses. Calc. for $C_{13}H_{19}O_4N$: C, 69.0; H, 6.1. Found: C, 69.0; H, 6.3.

The substance melts with decomposition at 168° . It closely resembles the corresponding methoxyl compound in appearance and solubility, and the color of its copper derivative is the same as that of the methoxyl compound. To prove that it is really an ethyl alcohol addition product it was removed with dil. aqueous potassium hydroxide and the presence of ethyl alcohol established by the iodoform reaction.

2-Hydroxy-3-amino-4-phenyl-5-benzoyl Isoxazolidine (XIV).—The ammonia addition product can be made from the oxide but the yield is small because much of the oxide is decomposed by ammonia in the same way that it is decomposed by potassium hydroxide. It is better, therefore, to prepare it from the methyl alcohol addition product. A suspension of 7 g. of the finely powdered substance in 25 cc. of ether was shaken with 100 cc. of 0.05 *N* aqueous ammonia for 12 hours. The clear ethereal layer on evaporation deposited 6.1 g. of a crystalline solid which was recrystallized from acetone.

Analyses. Calc. for $C_{16}H_{16}O_3N$: C, 67.6; H, 5.5; N, 9.9. Found: C, 67.1; H, 5.5; N, 10.0.

The amino compound crystallizes in fluffy needles and melts with decomposition at about 162° . It is readily soluble in acetone and in methyl alcohol, very sparingly soluble in ether and in water. The water solution—prepared at the ordinary temperature—is neutral but on warming becomes alkaline as ammonia is replaced by water, and finally acid as it passes into an open-chained compound. The bluish-green copper derivative behaves like that of the methoxyl compound; it was found to contain 17.0–17.4% of copper instead of 17.5% calculated for a substance of this type.

The Open-Chained Addition Products

When the finely powdered isoxazoline oxide is shaken with acetic anhydride containing acetic acid it passes practically quantitatively into an addition product composed of one molecular equivalent of acid to one of oxide. The process is a very slow one, taking weeks for completion. It may be hastened by warming, but the yield is much smaller and the oily by-products interfere with the isolation of the low-melting acetyl derivative. The substance is also formed when the oxide is heated with glacial acetic acid alone, but some of the water addition product is formed at the same time and it is, therefore, not possible to use the copper acetate test to determine when all of the oxide has disappeared. Since the oxide is obtained by treating the methyl alcohol addition product with acetic anhydride, the most convenient procedure is as follows.

A suspension of the finely ground methoxyl compound in twice its weight of acetic anhydride is allowed to stand or, better, is shaken at the ordinary temperature until solution is complete. The solvents are then distilled as completely as possible under diminished pressure, the temperature of the bath being kept below 110° . The residue

is set aside until it has solidified completely. The solid is ground with a little ether, which removes a small quantity of a colored product, and then crystallized from a mixture of ether and petroleum ether. Thirty g. of methoxy compound, shaken for 17 days, gave 29.5 g. of pure product.

Analyses. Calc. for $C_{18}H_{17}O_5N$: C, 66.1; H, 5.3; N, 4.3. Found: C, 66.0; H, 5.2; N, 4.4.

THE ACETATE (XVI).—The acetate is readily soluble in all common organic solvents except petroleum ether, and separates in large lustrous tables. It melts at 98° and, unlike the addition products described heretofore, it does not decompose until heated to a high temperature—about 200° . It does not form a copper derivative and as it cannot be benzoylated it probably contains no hydroxyl group. It is not attacked by bromine and it does not reduce permanganate either in acetone or in water. Both aqueous alkali and sodium methylate attack it freely and convert it into the same substances that are obtained by the action of these reagents on the isoxazoline oxide. It can, however, be hydrolyzed with ammonia.

Thus, a solution of 5 g. of the substance in 50 cc. of ether was shaken for 24 hours with 50 cc. of *N* aqueous ammonia. The ether layer was separated, washed, dried, concentrated to one-third its volume and diluted with an equal volume of petroleum ether. It deposited 4.2 g. of solid in large, lustrous plates.

Analyses. Calc. for $C_{18}H_{16}O_4N$: C, 67.3; H, 5.3; N, 4.9. Found: C, 66.9; H, 5.6; N, 5.1.

α -Benzoyl- α -hydroxy- β -phenyl- γ -nitro- α -propane (XVII).— α -Benzoyl- α -hydroxy- β -phenyl- γ -nitro propane melts without decomposition at 142° . It is isomeric with the dihydroxy isoxazolidine derivative but cannot be a stereo-isomer because it neither reduces permanganate nor forms a copper derivative, and as it forms only a monobenzoate it contains only one hydroxyl group. However, it gives the same products as the dihydroxy compound when it is treated with strong bases, and it can be converted into the methyl alcohol addition product of the isoxazoline oxide. Thus, a solution of 2 g. of the substance in 10 cc. of dry methyl alcohol was saturated with hydrogen chloride and set aside. The presence of a small quantity of some substance capable of forming a copper compound was detected an hour later. After two days the solution was poured into iced sodium carbonate, the resulting milky liquid extracted with ether, and the copper derivative precipitated in the usual way. This, on acidification, gave 1.6 g. of pure methyl alcohol addition product.

THE BENZOATE (XVIII).—The benzoate was readily obtained by shaking an ethereal solution of the substance with an excess of benzoyl chloride and saturated aqueous sodium carbonate solution. The washed and dried ethereal layer deposited it in needles that, after recrystallization from a mixture of ether and petroleum ether, melted at 106 – 107° .

Analyses. Calc. for $C_{23}H_{19}O_5N$: C, 70.9; H, 4.9. Found: C, 70.7; H, 5.1.

Action of Alkali on the Isoxazoline Oxide and its Addition Products

The isoxazoline oxide is but little affected by sodium carbonate. After an ethereal solution of the oxide had been shaken with a saturated solution of the carbonate for 48 hours the only change that could be detected was a partial transformation into its water addition product—96% of oxide was recovered unchanged. When dil. sodium hydroxide or barium hydroxide was substituted for the carbonate, the aqueous layer quickly turned yellow, but the color soon faded and in a few minutes both layers were colorless.

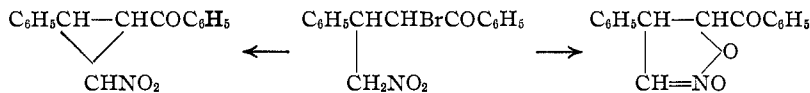
By using an excess of a standard solution and determining the excess it was found that 2 equivalents of base disappear in the process.

The two layers were separated. The ethereal layer was dried and distilled. It contained only phenyl cyanide, which was identified by its odor, its boiling point, an analysis, and hydrolysis to benzoic acid. The aqueous layer was shaken with ether until free from odor, acidified, and extracted with ether. The dried ethereal solution, on evaporation, left a residue that had an extremely pungent odor and partially solidified. By distillation this was separated into a very volatile portion which proved to be formic acid and phenyl acetic acid which was identified by comparison with a specimen on hand. No other products are formed.

By operating in a different manner it has been possible to isolate some of the intermediate product which forms yellow salts with bases, but as the structure of the substance has not been established it seems useless at present to speculate on the mechanism of this reaction.

Summary

1. Elimination of hydrogen bromide from α -bromo- γ -nitro ketones that have hydrogen in the position alpha to the nitro group may result in the formation of two different types of cyclic compounds—a nitrocyclopropane or an isoxazoline oxide.



2. In the case of primary nitro compounds the configuration of the bromine compound determines which of these cyclic compounds is formed.

3. Isoxazoline oxides combine with water, alcohols, ammonia and amines. The resulting isoxazolidine derivatives form characteristic copper compounds when they are shaken with solutions of copper salts.

4. The ring in isoxazoline oxides is not readily opened by acids, but it may be opened with acetic anhydride, which forms the acetate of the corresponding α -hydroxy ketone, or with bases which rapidly transform these oxides into simpler substances.

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NEW BOOKS

Materie, Elektrizität, Energie: die Entwicklung der Atomistik in den letzten Zehn Jahren (Matter, Electricity and Energy: the Development of Atomistics during the past Ten Years). By DR. WALTHER GERLACH, A. O. Professor der Physik an der Universität Frankfurt A. M. Theodor Steinkopff, Dresden und Leipzig, 1923. iv + 195 pp. 68 figs. 22 × 15 cm.

The knowledge of the nature of the electron both in the free and in the combined condition has taken gigantic strides during the past ten