hours; while with one more addition of 10 cc., 60 g. of gas was finally taken up in six hours. The total amount of catalyst was thus 44 cc. (50 g.), and the total weight of hydrogen sulfide absorbed was 338 g. (80% of the calculated amount).

On the other hand, with 2 cc. of acetyl bromide, 135 g. of hydrogen sulfide was absorbed by 1500 g. of anhydride at 35–40°; on the further addition of 2 cc. no more gas was taken up during three hours. At this point 10 cc. more of acetyl bromide was added, when 116 g. of gas was absorbed in six hours, whereupon absorption ceased. On addition of another 10 cc. of bromide, absorption was resumed and 234 g. of sulfide was taken up in 19 hours. The total amount of catalyst was thus 24 cc. (40 g.), and the total weight of hydrogen sulfide absorbed was 485 g. (14% more than the calculated amount). This batch was treated with 25 g. of anhydrous sodium acetate and fractionally distilled, when 660 g. (68% of the calculated quantity) of pure thio-acetic acid was obtained.

Summary

1. Thio-acetic acid may be conveniently prepared in approximately 70% yield by passing hydrogen sulfide into acetic anhydride containing about 2% of acetyl chloride, hydrogen chloride, or acetyl bromide.

2. Acetic anhydride alone and acetyl chloride alone do not react with hydrogen sulfide.

3. Acetyl bromide is a more effective catalyst than acetyl chloride.

4. The progress of the reaction shows two stages, the first of which (20–30%) requires only one-tenth of the amount of catalyst necessary for the completion of the reaction.

ROCHESTER, NEW YORK

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

ISOXAZOLINE OXIDES

II. BENZOYL-DIPHENYL-ISOXAZOLINE OXIDE

BY E. P. KOHLER

RECEIVED MAY 21, 1924 PUBLISHED JULY 7, 1924

It has been shown that the removal of hydrogen bromide from certain α-bromo-γ-nitro ketones leads to the formation of a new type of cyclic compound which was called an isoxazoline oxide.[1] The presence of an isoxazole ring in the new substance was established beyond reasonable doubt but details of structure and the mechanism of many of the peculiar reactions were left for later consideration. The present paper deals with some of these problems.

In order to secure less sensitive compounds, to diminish the number of possible reactions, and to get products with more favorable physical properties, it seemed best, if possible, to introduce an additional group in the 3 position of the oxide. It has now been found that oxides with a phenyl group in this position can be made without difficulty by means of a series of reactions similar to those employed in the earlier work. Thus, phenyl-

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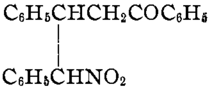
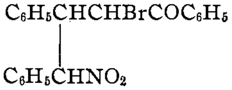
[1] Kohler, THIS JOURNAL, **46**, 503 (1924).

nitromethane combines fairly readily with benzalacetophenone and forms two stereo-isomeric γ-nitro ketones, (I). Each of these, when brominated, gives a pair of monobromo derivatives in which the bromine is in the alpha position (II). These four bromine derivatives differ from the pair used in the earlier paper in that none gives any cyclopropane derivative; all form oxide (III) only and the four between them give two stereo-isomeric oxides.



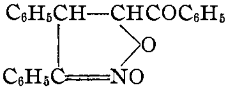
$$\begin{array}{l}\mathrm{C_6H_5CHCH_2COC_6H_5}\\ \quad|\\ \mathrm{C_6H_5CHNO_2}\end{array}$$

I



$$\begin{array}{l}\mathrm{C_6H_5CHCHBrCOC_6H_5}\\ \quad|\\ \mathrm{C_6H_5CHNO_2}\end{array}$$

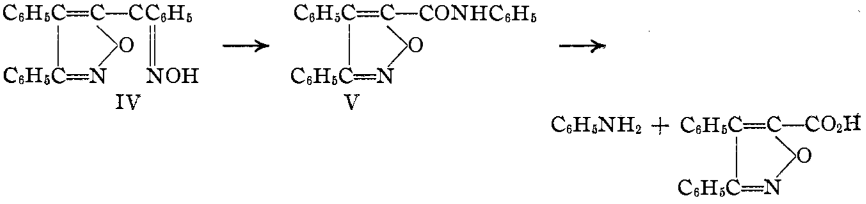
II



III

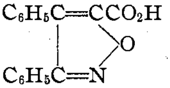
The phenylated oxides have little in common with the simpler representative that was described in the earlier paper. They lack completely the power to form addition products with water, alcohols, ammonia and other substances containing active hydrogen which is the most characteristic property of the unphenylated compound. Strong bases do not rupture the molecule as they do that of the simpler oxide; either they form metallic derivatives or under other conditions induce a series of transformations in which the carbon chain remains intact and which ends with loss of water. Acid chlorides and anhydrides instead of introducing acyl groups merely eliminate water.

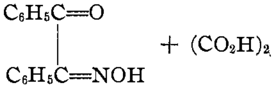
There is adequate evidence to show that despite the great differences in properties which have been noted the phenylated and unphenylated compounds are similarly constituted. The dehydration product that is formed by acid chlorides and by bases must be the ketonic isoxazole (VIII). It behaves like a typical aromatic ketone, forms an oxime, is reducible to a secondary alcohol from which it is regenerated by oxidation, and gives tertiary alcohols when treated with organic magnesium compounds. When its oxime undergoes a Beckmann rearrangement it is isomerized to a substance which can be hydrolyzed to aniline and a monobasic acid.



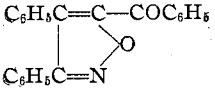
IV V VI

Moreover, the monobasic acid obtained in this way forms an ozonide which when decomposed with water gives benzil mono-oxime and oxalic acid.



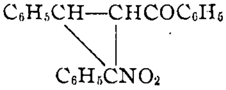


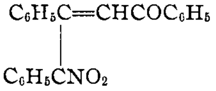
VII

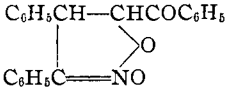


VIII

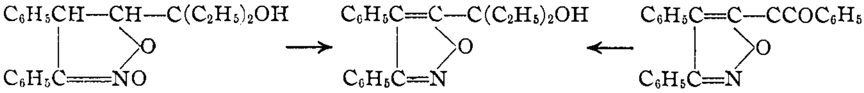
These transformations prove beyond all question that the "stripped" compound is the ketonic isoxazole (VIII); but they leave some doubt as to the nature of the substances from which it is formed. These cannot be the cyclopropane derivatives represented by IX, for the latter were made from the γ-bromo compounds and were found to be quite different in character. It is conceivable, although *a priori* improbable, that the parent substances might be the unsaturated nitro compounds (X) instead of the oxide (III) and that the isoxazole ring is closed in the process of stripping instead of during the elimination of hydrogen bromide.


IX


$$\begin{array}{l} C_6H_5C{=}CHCOC_6H_5 \\ \quad | \\ C_6H_5CNO_2 \end{array}$$
X

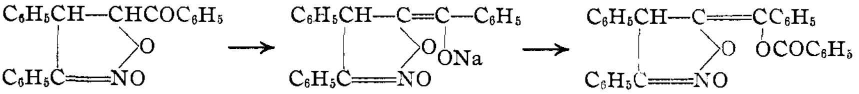

III

The behavior of these substances towards Grignard reagents indicates, however, that these substances cannot be nitro compounds of any sort. All published results show that organic magnesium compounds invariably reduce aromatic and saturated aliphatic nitro compounds, and results shortly to be published from this Laboratory prove that they either form 1,4-addition products with unsaturated nitro compounds or else, when the hindrance to addition is too great, reduce these also. Neither of these reactions takes place with the substances in question; both give the normal reactions of carbonyl compounds and all the rest of the molecule is unaffected. This is proved adequately by the fact that elimination of water from the product results in the formation of the same substance that is obtained by treating the isoxazole with the Grignard reagent.


XI XII VIII

In view of all of these facts there seems to be no room for doubt that these substances are isomeric isoxazoline oxides; the differences between their properties and those of the simpler oxide are not due to difference in structure but to the phenyl group in the γ-position.

Bases attack the phenylated oxide as readily as they do the simpler representative of the class. It was possible to follow the course of the reaction step by step, to isolate the successive products and to prove their structure. When the lower-melting oxide is treated with concd. sodium hydroxide solution it forms a colorless sodium compound which contains one atom of sodium and from which acids regenerate the oxide. Benzoyl chloride converts the sodium compound into a benzoate which is likewise colorless. Since no corresponding compounds are formed from the Grignard product (XI) these substances must be derivatives of an enolic modification of the oxide.

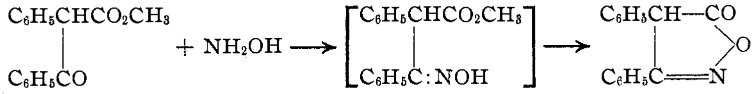


XIII XIV

The sodium compound is insoluble and apparently undergoes little, if any change in the strongly alkaline solution, but when the solution is diluted until the concentration of the hydroxide is under 3% it dissolves freely and the solution immediately begins to turn yellow. A similar yellow solution is obtained when an ethereal solution of either oxide is shaken with dil. sodium hydroxide solution or when the pure sodium compound is dissolved in water. These yellow solutions slowly become darker with time, then a colorless precipitate begins to form, the color gradually fades and the solution finally becomes almost colorless again. The precipitate is practically pure isoxazole (VIII) and the solution contains sodium benzoate, a small quantity of the sodium derivative of a substance which has the composition $C_{15}H_{11}O_2N$, and a correspondingly small quantity of some other colorless substance which has not as yet been obtained in solid form. When a correspondingly dilute solution of sodium peroxide is substituted for that of the hydroxide, the isoxazoline oxide dissolves at once, the solution remains colorless, no isoxazole is formed, and the oxide is oxidized quantitatively to benzoic acid and the substance with the composition $C_{15}H_{11}O_2N$.

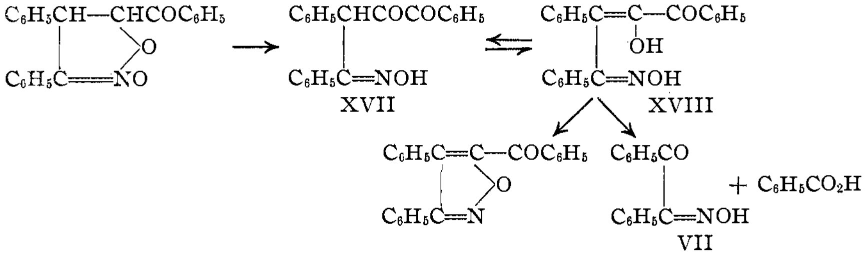
These facts show that in dilute alkaline solution the oxide undergoes two entirely distinct transformations. One of these is an oxidation-reduction reaction which results in benzoic acid and the substance $C_{15}H_{11}O_2N$, the other leads to the isoxazole by way of a yellow or orange sodium compound.

The substance $C_{15}H_{11}O_2N$ is capable of existing in two modifications, an enolic form which gives a deep blue copper compound when shaken with copper acetate, and a more stable form which does not form a copper derivative in this way but is readily soluble in sodium carbonate. It was made synthetically by means of a reaction which proves that it is 3,4-diphenyl-isoxazolone.

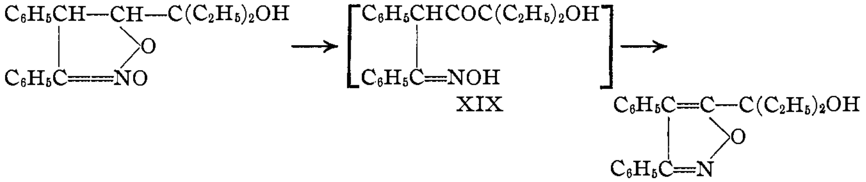


XV XVI

The yellow compound, intermediate between the isoxazoline oxide and the isoxazole was more difficult to manage but was finally isolated as a brilliant yellow solid containing ether of crystallization. It does not form a copper compound with copper acetate but is soluble in sodium carbonate solution. Strong bases convert it quantitatively into isoxazole. Its structure was established by analysis and treatment with sodium peroxide which oxidizes it cleanly to benzil mono-oxime and benzoic acid.



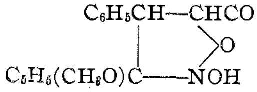
Since, as is evident, the stripping of the isoxazoline oxide by bases involves opening and reclosing the isoxazole ring, it is reasonable to assume that the stripping of the Grignard product proceeds in the same manner.



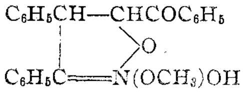
It has not been possible, however, to isolate any intermediate compound in this case. As was to be expected because the hydrogen in the 5 position is not alpha to a carbonyl group, the substance does not lose water nearly so easily as the oxide. Moreover, an intermediate ketone like XIX would be colorless—therefore give no indication of its presence—and the second step is the reaction by which isoxazoles are commonly made from diketones and which is known to take place with great rapidity.

It has also been impossible thus far to establish the mechanism by which dehydrating agents convert the oxides into the isoxazole. Solutions of the oxide in very cold acetyl chloride invariably assume the characteristic greenish-yellow color of diketones, as do also those in the purest alcohols. The color of the alcoholic solutions increases for a time and then apparently becomes constant. The solutions in acetyl chloride gradually deposit the colorless isoxazole. One is tempted, therefore, to assume that in these solvents the oxide is in equilibrium with the diketone (XVI) or with one of its acetyl derivatives, but since this diketone does not give a trace of isoxazole when it is treated with acetyl chloride it seems best to defer the consideration of this problem until more facts are available.

It seems inadvisable also to undertake a discussion of the structure of the unsaturated system C-NO. It may be pointed out, however, that the inability of the phenylated oxides to combine with methyl alcohol and similar substances supports, in a manner, the formula for such addition products that was proposed in the earlier paper. For while a phenyl group in the 3 position would be expected to offer a hindrance to the formation of an addition product like XX, there seems to be no reason why it should in any way affect the formation of one like XXI.



XX



XXI

Experimental Part

Addition of Phenyl-nitromethane to Benzalacetophenone

Phenyl-nitromethane does not combine as readily as nitromethane with unsaturated ketones but the addition can be accomplished without difficulty. The process is reversible but the addition can be made almost complete because the product is very sparingly soluble. The tendency to form trimolecular addition products which is so pronounced in the case of nitromethane is so slight here as to be negligible unless the reaction mixtures are kept for an unnecessary length of time. When the addition is brought about by boiling a methyl alcoholic solution containing equivalent quantities of the addends with a small quantity of sodium methylate, the product is composed almost entirely of a single substance. When the reaction is allowed to proceed more slowly at the ordinary temperature in the presence of one equivalent of the methylate, the result is a mixture of two stereo-isomers in variable proportions.

Thus a solution of 40 g. of the ketone, 28 g. of the nitro compounds and enough sodium methylate to impart distinct alkalinity in 500 cc. of dry methyl alcohol was boiled for two hours, during which it solidified almost completely. The mixture was filtered with suction, the solid washed thoroughly with methyl alcohol containing a small quantity of acetic acid and finally with ether, dried and recrystallized by dissolving it in the minimum quantity of boiling chloroform and adding an equal volume of boiling absolute methyl alcohol. This gave 58.5 g. or 86% of a product which after several more recrystallizations melted at 181–182°. The filtrate slowly deposited a mixture from which 3 g. of a second product was obtained by prolonged fractional crystallization from mixtures of chloroform and methyl alcohol. This separated in small nuggets of fine needles and melted at 131–132°.

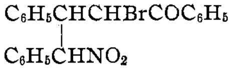
A similar solution was treated with one equivalent of sodium methylate and allowed to stand at the ordinary temperature for several days. The resulting solid, which when crude melted at about 130°, ultimately gave about 80% of the higher-melting and about 20% of the lower-melting compound.

Analysis. Calc. for $C_{22}H_{19}O_3N$: C, 76.2; H, 5.5. Found: (182°) C, 76.2; H, 5.6; (132°) C, 76.4; H, 5.5.

β,γ-Diphenyl-γ-nitro-propiophenone (1).—The higher-melting compound is readily soluble in boiling chloroform, moderately soluble in acetone, very sparingly soluble in ether and in methyl alcohol. It crystallizes in long, thin, transparent needles. The lower-melting isomer is readily soluble in boiling methyl alcohol. Both substances dissolve in methyl alcohol containing slightly more than one equivalent of sodium methylate. The solutions gradually turn yellow, and when these yellow solutions are acidified and shaken with ether, the ether extracts a small quantity of benzal acetophenone, showing that the addition reaction is reversible. When the yellow solutions are allowed to stand for a longer time they slowly deposit a very high-melting solid which contains nitrogen, doubtless the trimolecular addition product.

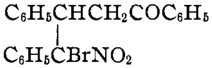
Bromination

Each of the addition products, when brominated directly, gives two isomeric monobromo derivatives. Since nitroparaffins are not attacked by bromine in neutral or acid solutions it is *a priori* probable that these are the four possible inactive stereo-isomeric α-bromo compounds (II).



$$\begin{array}{l} C_6H_5CHCHBrCOC_6H_5 \\ \quad\;\;| \\ C_6H_5CHNO_2 \end{array}$$

II



$$\begin{array}{l} C_6H_5CHCH_2COC_6H_5 \\ \quad\;\;| \\ C_6H_5CBrNO_2 \end{array}$$

XXII

It is conceivable, however, that owing to the presence of the phenyl group bromine might in this case also enter the γ-position (XXII). The higher-melting addition product was, therefore, also brominated in alkaline solution. The two isomeric γ-bromo compounds thus obtained were quite different both in chemical and in physical properties from the substances formed by direct bromination.

Bromination of the Higher-Melting Addition Product.—A suspension of 57 g. of the nitroketone in 150 cc. of chloroform was boiled with a little bromine for 15 minutes without effect. It was then exposed to direct sunlight for several hours but this also failed to start the reaction. A small quantity was, therefore, decanted into a test-tube, decolorized with a few drops of acetone, and returned to the rest of the mixture. The reaction then started briskly and thereafter bromine disappeared as rapidly as it was added until the solution contained 26 g.—slightly more than one equivalent. All the nitroketone had dissolved meanwhile. In order to remove hydrogen bromide and the excess of bromine, the clear yellow solution was boiled in an open flask but it almost immediately began to deposit a solid bromo compound and it solidified to a cake on cooling. This was ground with methyl alcohol, collected on a filter, and thoroughly washed with ether. The solid melted at 180° when crude and at 185° after several recrystallizations from chloroform and methyl alcohol.

Analysis. Calc. for $C_{22}H_{18}O_3NBr$: C, 62.3; H, 4.2. Found: C, 62.4; H, 4.4.

This bromo compound crystallizes in fine, transparent, friable needles. It is readily soluble in boiling chloroform, moderately soluble in methyl alcohol, and it crystallizes well from either solvent or from both. A second bromo compound was obtained by evaporating the filtrates and subjecting the residue to a systematic fractional crystallization. It separated in clusters of white needles and melted at 162°.

Analysis. Calc. for $C_{22}H_{18}O_3NBr$: C, 62.3; H, 4.2. Found: C, 62.0; H, 4.3.

The appearance of this substance which was always obtained in opaque indistinct crystals suggested a mixture rather than a pure substance; but the melting point was sharp and it was lowered nearly 20° by admixture of the higher-melting isomer.

Bromination of the Lower-Melting Addition Product.—The lower-melting nitroketone was brominated in exactly the same way as its isomer. The mixture of bromine compounds was separated without much difficulty by recrystallization from methyl alcohol. One of them crystallizes in large, lustrous needles arranged in clusters and melts at 155°. The other separates in fine needles and melts at 125–127°.

Analyses. Calc. for $C_{22}H_{18}O_3NBr$: C, 62.3; H, 4.2. Found: (155°) C, 62.0; H, 4.2; (127°) C, 62.1; H, 4.4.

β,γ-Diphenyl-γ-bromo-γ-nitro-propiophenone (XXII).—A solution of 25 g. of the higher-melting nitroketone in sodium methylate (3 g. of sodium in 150 cc. of methyl alcohol) was cooled in a freezing mixture and treated with bromine until the color no longer disappeared when the mixture was shaken. The solid which appeared during the reaction was thoroughly washed with water and methyl alcohol and recrystallized from a mixture of chloroform and methyl alcohol. It was thus separated into two substances one of which crystallized in friable needles and melted, with decomposition, at 178–80°, while the other crystallized in very thin, transparent needles and melted at 136–138°.

Analyses. Calc. for $C_{22}H_{18}O_3NBr$: C, 62.3; H, 4.2. Found: (180°) C, 62.3; H, 4.4; (138°) C, 62.0; H, 4.2.

These γ-bromo compounds are quite different from all of the monobromo derivatives obtained by direct bromination; they decompose at a comparatively low temperature, are practically not attacked by potassium acetate at the ordinary temperature and lose hydrogen bromide only very slowly even when boiled with alcoholic solutions of the acetate.

Preparation of the Isoxazoline Oxides

All four of the α-bromo compounds lose hydrogen bromide when they are shaken with methyl alcoholic potassium acetate at the ordinary temperature, but owing to their slight solubility it is difficult to complete the reaction in this manner. At the boiling point of the solvent the reaction proceeds but does not stop with the oxide. The product is always contaminated with variable quantities of the substances that are formed by the action of dilute alkalies on the oxides. All of these, however, except the isoxazole are removed without difficulty. Whatever the procedure, the bromine compounds obtained from the higher-melting addition product give a single oxide which melts at 123°, while each of the pair of bromine compounds from the lower-melting isomer gives a mixture composed of the oxide melting at 123° and an isomer that melts at 151°.

PROCEDURE.—Fifty g. of freshly fused potassium acetate was added to 70 g. of the finely ground bromine compound suspended in 300 cc. of boiling methyl alcohol. A yellow color developed at once, the solid dissolved rapidly, and potassium bromide began to separate. After boiling for 20 minutes all of the solid had disappeared. The mixture was then cooled in a freezing mixture for several hours and filtered. The solid was washed first with chilled methyl alcohol, finally with water until free from bromide and dried. One recrystallization from methyl alcohol gave 40 g. of a pure substance which melted at about 93°. The filtrate was diluted with water. This precipitated a pale yellow solid which contained isoxazole as well as oxide. After a number of recrystallizations this gave 10 g. of pure oxide and 3.5 g. of a less pure product, making the total yield 54 g. When the bromine compound melting at 162° was treated in the same way, it likewise gave only the product melting at 93°; but each of the bromine compounds melting at 155° and 127° gave, in addition to this substance, another product which melted at 151°.

3,4-Diphenyl-isoxazoline Oxide (III).—The product which melts at 93° crystallizes from methyl alcohol in colorless tables, containing one molecule of solvent which it loses very slowly at the ordinary temperature, but rapidly with effervescence at the melting point. The alcohol-free substance can be obtained in crystalline form melting at 123° by recrystallization from a mixture of absolute ether and petroleum ether. From most other solvents it separates with solvent of crystallization. It separates from ethyl, propyl, *iso*propyl and butyl alcohol in needles that melt with effervescence. From benzene and carbon tetrachloride it separates either in large, well-shaped, transparent crystals containing a molecule of solvent, or in white clusters of minute needles that are free from solvent and melt at 123°.

Analyses. Calc. for $C_{22}H_{17}O_3N$: C, 76.9; H. 5.0. Found: C, 76.8; H, 5.1. Calc. for $C_{22}H_{17}O_3N.CH_3OH$: C, 73.6; H, 5.6; CH_3OH, 8.3. Found: C, 73.3; H, 5.4; CH_3OH 8.5. Calc. for $C_{22}H_{17}O_3N.C_6H_6$: C_6H_6, 18.5. Found: C_6H_6, 17.9.

The oxide is fairly readily soluble in all common solvents except petroleum ether. Its solutions in alcohols gradually turn yellow while those in all other solvents remain colorless.

The Isomeric Isoxazoline Oxide.—The isomeric isoxazoline oxide, which is obtained in relatively small quantities from the second pair of bromine compounds, crystallizes in flat needles and melts at 151°. It is moderately soluble in alcohol and ether, readily soluble in alcohol and chloroform. Its solutions in alcohols, like those of the isomer, slowly turn yellow with time or more rapidly when boiled.

Analysis. Calc. for $C_{22}H_{17}O_3N$: C, 76.9; H, 5.0. Found: C, 76.8; H, 5.2.

THE SODIUM DERIVATIVE (XIII).—The sodium derivative is most readily made by shaking an ethereal solution of the oxide with a 3 to 5% solution of sodium hydroxide in concd. sodium carbonate solution until the precipitate, which forms at once, assumes a filterable form. The precipitate is collected on a filter, washed with sodium carbonate, then rapidly with ice water, a mixture of methyl alcohol and ether, and finally with dry ether. It is thus obtained as a mat of colorless needles, readily soluble in methyl alcohol, sparingly soluble in ice water. Its water solution, which gradually assumes a yellow color, gives no copper derivative when shaken with ether and copper acetate.

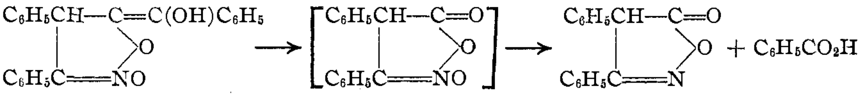
Analysis. Calc. for $C_{22}H_{16}O_3N.Na$: Na, 6.3. Found: 6.1.

THE BENZOATE (XIV).—The dried sodium compound was added in small quantities to an ethereal solution of 1 molecular equivalent of benzoyl chloride stratified on top of concd. aqueous sodium carbonate. The solid turned pink after each addition and became colorless again when vigorously shaken. The mixture was shaken until free from benzoyl chloride, the solid collected on a filter, washed, dried and recrystallized from benzene. It was thus obtained in aggregates of fine white needles, very sparingly soluble in alcohol and ether, moderately in benzene. The benzoate melts at 190°. It is hydrolyzed by 3% sodium hydroxide solution with a rapidity that is surprising in view of its slight solubility.

Analysis. Calc. for $C_{29}H_{21}O_4N$: C, 77.8; H, 4.7. Found: C, 78.2; H, 5.0.

Oxidation of the Oxides and Synthesis of the Isoxazolone

Alkaline solutions of the oxide reduce permanganate, but in these solutions the oxide is in part rearranged into other products which likewise reduce permanganate. This is shown by the fact that the relative amounts of benzoic acid formed vary in different experiments and bear no simple relation to the amounts of the oxide used. Solutions of sodium peroxide, on the other hand, produce exactly one molecular equivalent of benzoic acid. They therefore cleave the carbon chain at only one point. It was hoped that by using this reagent it might be possible to oxidize the substance to an isoxazolone oxide (XXIV); but while there are some indications that such an oxide is formed it has not been possible thus far to isolate it. The product always is the isoxazolone (XVI) which may be due either to reduction of the oxide by the peroxide or to some other oxidation-reduction reaction.



XXIII XXIV XVI

The properties of the oxidation product showed pretty clearly that it must be the isoxazolone but in order to establish the structure beyond all doubt, it was synthesized from the methyl ester of phenylbenzoylacetic acid. This ester has been made by Rattner[2] who described it as a liquid. His preparation must have been extremely impure, however, because the pure ester which is obtained by alcoholysis of the nitrile[3] is a stable, well-crystallized solid that melts at 75°. Hydroxylamine hydrochloride converts the ester rapidly and completely into the isoxazolone.

Oxidation with Sodium Peroxide.—Five g. of the finely powdered lower-melting oxide was added to a clear solution of 10 g. of sodium peroxide in 200 cc. of water. The oxide was rapidly changed to its sodium derivative, a part of which crystallized from the solution. The solid soon disappeared again and a new sodium compound began to appear. The mixture was kept at the ordinary temperature for 24 hours, the solid sodium compound collected on a filter, washed with sodium carbonate, water and methyl alcohol and dried. It weighed 3.1 g. It crystallized in plates, was stable in the air, and dissolved in methyl alcohol and in water without appreciable hydrolysis. The clear solution in water precipitated a deep purple-copper compound when added to aqueous copper acetate.

The sodium compound was decomposed by stirring it into a mixture of ice and hydrochloric acid. This gave rise to a crystalline solid which was washed with ice water and immediately recrystallized by solution in acetone and rapid re-precipitation with petroleum ether. It separated in needles that dissolved readily in ether and when heated rapidly melted at about 113°.

Analysis. Calc. for $C_{15}H_{11}O_2N$: C, 76.0; H, 4.6. Found: C, 76.0; H, 4.3.

This substance must be the enolic modification of diphenyl-isoxazolone because its ethereal solution gives a copper compound when shaken with copper acetate. When its ethereal solution is boiled for a short time, it deposits the ketonic form which is sparingly soluble in ether, crystallizes in hard, lustrous tables and melts with decomposition at about 150°.

Analysis. Calc. for $C_{15}H_{11}O_2N$: C, 76.0; H, 4.6. Found: C, 75.8; H, 5.0.

3,4-Diphenyl-isoxazolone (XVI) does not form a copper derivative when its ethereal solution is shaken with copper acetate solution but it is readily soluble in dil. aqueous sodium carbonate as well as sodium hydroxide. Since the sodium derivative is very sparingly soluble in saturated sodium carbonate solution, it is easily obtained in a perfectly pure condition. By acidifying its concentrated aqueous solution at a low temperature, it is not difficult to get the pure enolic modification.

From the filtrate left after removing the solid sodium derivative of the isoxazolone, acids precipitated a mixture which by treatment with hot water was easily separated into more of the isoxazolone and benzoic acid. The filtrate contained nothing else.

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[2] Rattner, *Ber.*, **21,** 1321 (1888).

[3] Walther and Schickler, *J. prakt. Chem.*, [2] **55,** 308 (1897).

Methyl Phenyl-benzoyl-acetate (XV).—A solution of 25 g. of phenyl-benzoyl-acetonitrile in 75 cc. of dry methyl alcohol was cooled in a freezing mixture and saturated with dry hydrogen chloride. As the solution remained perfectly clear it was evident that the alcoholysis was slow. The container was, therefore, closed with a drying tube and kept in an ice chest for a week, during which a dense white precipitate accumulated in the liquid. The mixture was poured onto cracked ice and the pasty precipitate handled in the usual manner. It gave 1.5 g. of a solid that was sparingly soluble in ether and crystallized in inconspicuous plates which melted at 150–170°—doubtless the amide—20 g. of the methyl ester, and a small quantity of methyl benzoate. The methyl ester was purified by recrystallization from 75% methyl alcohol.

Analysis. Calc. for $C_{16}H_{14}O_3$: C, 75.6; H, 5.6. Found: C, 75.2; H, 5.6.

The methyl ester is readily soluble in all common solvents except petroleum ether. It crystallizes in large, colorless needles and melts at 75°. For the purpose of converting it into the isoxazolone, a methyl alcoholic solution of 1.5 g. of the ester and 0.5 g. of hydroxylamine hydrochloride was boiled for 10 hours. Most of the solvent was then evaporated and the residue poured into water. This precipitated a solid which was found to be identical in every way with the product formed when the oxide was oxidized with sodium peroxide.

Action of Bases on the Oxides

Solutions of the oxides in concentrated alkalies are colorless; they remain colorless for a long time but if they are diluted beyond a certain point they soon become yellow. Solutions in most organic solvents are likewise colorless and they remain so indefinitely but solutions in alcohols always become yellow. Addition of a small quantity of acid to the alcoholic solution appears to accelerate the development of color without producing any other effect, while addition of bases both speeds up the development and intensifies the depth of the color. When the color of these alkaline solutions reaches a certain depth, isoxazole begins to separate; the color then remains constant for a time as the amount of isoxazole increases, but finally fades. Without entering at this time on a consideration of the processes involved it is evident that in order to get any considerable quantity of the yellow substance it is necessary to employ a relatively large quantity of dilute base. The procedure was, therefore, as follows.

A suspension of 5 g. of the oxide in 500 cc. of 2% aqueous sodium hydroxide and 5 cc. of ether was shaken continuously for 24 hours. The ethereal layer, containing isoxazole which was partly in solution and partly suspended in well-formed crystals, was separated and the deep yellow or orange-colored solution shaken with fresh ether to remove the last of the isoxazole. The solution was then cautiously acidified in the presence of a small quantity of ether. The solution became colorless while the ethereal layer became dark yellow or at times green. This layer soon began to deposit a greenish-yellow compound in small, well-formed tables. These were thoroughly washed with ether and recrystallized by solution in a small quantity of acetone and precipitation with absolute ether.

The filtrate from the yellow crystals was shaken with sodium bicarbonate solution which extracted small quantities of diphenyl-isoxazolone and benzoic acid. The aqueous layer when strongly acidified and extracted with ether gave small additional quantities of these same substances. In an average experiment 5 g. of the oxide gave 1.5 g. of isoxazole, 2 g. of the yellow compound, and small, variable quantities of isoxazolone and benzoic acid.

Much the most convenient method of making the yellow substance is to start with the bromine compound. This is so sparingly soluble in dilute alkalies that reaction is extremely slow but it can be accelerated by addition of an alcohol. The procedure was as follows. A mixture composed of 20 g. of the bromine compound, 18 g. of potassium hydroxide, 2000 cc. of water, 500 cc. of methyl alcohol, and 600 cc. of ether was shaken continuously for 40 hours. The products were isolated as in the preceding experiment. The result was 5 g. of unchanged bromine compound, most of which was suspended in the ethereal layer, 3.5 g. of isoxazole, mostly dissolved in the ether, 8.6 g. of the yellow compound and 2.5 g. of an oily mixture containing isoxazolone, benzoic acid and other products.

α,γ,δ-Triphenyl-butanetrione Oxime (XVII).—The yellow compound crystallizes from ether with one molecule of solvent which it holds tenaciously up to the melting point; its presence was established by heating the substance above the melting point and condensing the ether.

Analyses. Calc. for $C_{22}H_{17}O_3N.(C_2H_5)_2O$: C, 74.8; H, 6.5; N, 3.4. Found: C, 74.6; H, 6.5; N, 3.8.

The substance does not give off ether below the temperature at which it decomposes. The ether can, however, be got rid of by dissolving the substance in dry benzene, sweeping out most of the ether with a dry current of air and diluting the benzene solution with petroleum ether. It is thus obtained in nodules of small indistinct needles which melt to give a pink liquid at about 150° and decompose immediately afterwards.

Analysis. Calc. for $C_{22}H_{17}O_3N$: C, 77.0; H, 5.0. Found: C, 76.8; H, 5.1.

The oxime is readily soluble in alcohol and acetone, moderately in benzene, very sparingly in ether. The crude product obtained by the methods which have been described is frequently dark green but after several recrystallizations from acetone and ether, the substance appears in large, lemon-yellow prisms or tables. It dissolves freely in sodium hydroxide, more slowly in sodium carbonate. It is precipitated completely when its alkaline solutions are saturated with carbon dioxide, and no copper derivative is formed when its ethereal solution is shaken with copper acetate. It is, as would be expected, a very reactive substance, but the only reactions that have been studied thus far are those with strong bases and with alkaline oxidizing agents.

Action of Strong Bases.—The oxime dissolves rapidly in concd. sodium hydroxide, the clear orange-colored solution immediately begins to deposit isoxazole and the color changes to a pale yellow. Further change is very slow, but in time the solution becomes completely colorless. It contains then a small quantity of the sodium derivative of the isoxazolone, an amount of sodium benzoate equivalent to the isoxazolone and a small quantity of another product which thus far has not been obtained in a solid form. The principal process is, therefore, dehydration; but there is another which involves reciprocal oxidation and reduction, and cleavage.

Oxidation with Sodium Peroxide.—The finely powdered oxime dissolved rapidly in a 5% aqueous solution of sodium peroxide. The solution has the deep orange color of the corresponding solution in sodium hydroxide but it remains perfectly clear and the orange tone gradually disappears. A solution of 2 g. of the oxime in 200 cc. of the peroxide solution was kept at the ordinary temperature for 24 hours, then acidified with hydrochloric acid. It slowly deposited a colorless solid which after one recrystallization from a mixture of ether and petroleum ether melted sharply at 118°.

Analysis. Calc. for $C_{14}H_{11}O_2N$: C, 74.7; H, 5.0. Found: C, 74.5; H, 5.1.

The substance has the composition of a benzil-mono-oxime but its melting point is 4° higher than that given for the β-oxime and 20° lower than that of the alpha compound. Both oximes were made from benzil in the usual way; the β-oxime melted at 113–114° as usual and the melting point was not much affected by recrystallization, but when the oxime was dissolved in sodium hydroxide and reprecipitated with hydrochloric acid, its melting point became sharp at 118°. A mixture of this preparation and the oxidation produce likewise melted at 118°.

The Isoxazole

One of the most characteristic properties of the isoxazoline oxide is the ease with which it loses water and passes into the isoxazole. As this is sparingly soluble in the common organic solvents, crystallizes with great ease, and is insensitive to acids, bases and oxidizing agents, it is readily detected even when formed only in small quantities. It was obtained as a by-product in the preparation of the oxides and the ketonic oxime; it constitutes the principal product of the reaction between the oxides and acetyl chloride or phosphorus pentachloride, and it is formed whenever either of the oxides is allowed to react with organic or inorganic bases. It is most readily prepared by adding a little concd. aqueous ammonia to a methyl alcoholic solution of the lower-melting oxide.

A solution of 10 g. of the lower-melting oxide in 100 cc. of methyl alcohol was treated with 2 cc. of concd. ammonia and set aside. It became bright yellow at once and began to deposit the isoxazole in well-shaped crystals within an hour. After five days the mixture was filtered and the crystals washed with methyl alcohol. The yield was 6.5 g., or nearly 90%, and while slightly discolored, the crystals melted sharply at 167°. The solid was recrystallized from a mixture of chloroform and methyl alcohol.

Analysis. Calc. for $C_{22}H_{15}O_2N$: C, 81.2; H, 4.9. Found: C, 81.0; H, 4.5.

3,4-Diphenyl-5-benzoyl Isoxazole (VIII).—3,4-Diphenyl-5-benzoyl isoxazole (VIII) is very sparingly soluble in alcohol and in ether, moderately in benzene and in acetone, readily in chloroform. It crystallizes from acetone in small lustrous prisms, from chloroform in large tables and it melts at 167°.

REDUCTION.—Five g. of zinc dust and enough water to start a lively evolution of hydrogen were added to a solution of 2 g. of the isoxazole in glacial acetic acid. The mixture was heated on a steam-bath for three hours, then diluted with much water and shaken with ether. The ethereal solution was freed from acetic acid and evaporated. It left 1.8 g. of a solid that crystallized from benzene in aggregates of fine needles.

Analysis. Calc. for $C_{22}H_{17}NO_2$: C, 80.7; H, 5.2. Found: C, 80.6; H, 5.1.

The analysis shows that the substance contains two more atoms of hydrogen than the isoxazole. It reacts vigorously with ethylmagnesium bromide, ethane is evolved, and a solid magnesium compound separates from the solution. When this is decomposed with acids the reduction product is recovered. The substance is, therefore, a secondary alcohol formed by reduction of the benzoyl group.

3,4-Diphenyl-5-(hydroxybenzyl) Isoxazole.—The reduction product is sparingly soluble in ether, readily in hot methyl alcohol. It crystallizes best from hot benzene in which it is moderately soluble. Potassium permanganate acts on it very slowly but chromic acid in warm glacial acetic acid rapidly oxidizes it back to the ketone.

Reaction with Ethylmagnesium Bromide.—To a solution of the magnesium compound made from 1.2 g. of magnesium in the usual manner 2 g. of the isoxazole was added as a finely powdered solid. The reaction was vigorous but there was no evolution of gas. The mixture was boiled for a few minutes, then decomposed with iced acid. The resulting solid was recrystallized from ether and petroleum ether.

Analysis. Calc. for $C_{24}H_{21}O_2N$: C, 81.2; H, 5.9. Found: C, 81.0; H, 5.8.

The tertiary alcohol (XII) crystallizes in large, colorless needles and melts at 145°. It is readily soluble in all common organic solvents except petroleum ether.

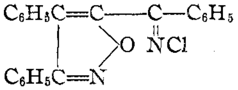
The Oxime (IV).—A mixture of 7 g. of the ketone, 10 g. of potassium hydroxide, and 4 g. of hydroxylamine hydrochloride in 50 cc. of methyl alcohol was boiled for two hours, then poured into water. The clear solution precipitated an oil when it was acidified. This was extracted with ether, the ethereal solution washed and dried in the usual manner and evaporated. The residue was an oil but it solidified when rubbed with methyl alcohol. After one crystallization from methyl alcohol, from which it separated in needles, the oxime melted sharply at 177°. The yield was 7 g.

Analysis. Calc. for $C_{22}H_{16}O_2N_2$: C, 77.6; H, 4.7. Found: C, 77.8; H, 4.6.

Rearrangement to the Anilide (V).—The finely powdered oxime was added gradually to excess of phosphorus pentachloride suspended in dry ether. When the effervescence stopped, the ethereal solution was poured in small quantities into water that was kept near the boiling point and shaken constantly. The resulting yellow paste solidified completely after boiling for 10 minutes. The solid was composed of two substances which were separated by recrystallization from a mixture of acetone and methyl alcohol. The principal product was the anilide which crystallized in small colorless prisms and was very sparingly soluble in alcohol, readily in boiling acetone; yield, 5.2 g.

Analysis. Calc. for $C_{22}H_{16}O_2N_2$: C, 77.6; H, 4.7. Found: C, 77.4; H, 4.4.

The second product formed in the Beckmann rearrangement separated in small lustrous yellow prisms melting at 139°. It contained chlorine and its composition corresponds to that of the imide chloride



Analysis. Calc. for $C_{22}H_{15}ONCl$: C, 73.6; H, 4.2. Found: C, 73.7; H, 4.2.

Hydrolysis of the Anilide to 3,4-Diphenyl-isoxazole Carboxylic Acid (VI).—Four g. of the finely ground anilide was suspended in 100 cc. of alcohol to which 25 cc. of 30% aqueous potassium hydroxide had been added, and the mixture boiled for two hours. From the resulting solution, which remained colorless throughout the operation, the alcohol was removed by distillation. The residue was diluted with water and acidified. As the precipitate was pasty, the liquid was extracted with ether and the ethereal solution shaken with sodium carbonate. This formed a sodium salt which, while readily soluble in water, was very sparingly soluble in dil. sodium carbonate solution and crystallized from it in remarkably long, fine needles. The acid corresponding to this salt crystallized from a mixture of ether and petroleum ether in small thin plates and melted at 170°. The yield was quantitative.

Analysis. Calc. for $C_{16}H_{11}O_3N$: C, 72.4; H, 4.2. Found: C, 72.5; H, 3.9.

Oxidation of the Acid.—The acid does not reduce permanganate but it readily combines with ozone. When the ozonide was warmed with water it gave an acid solution in which small quantities of nitric and benzoic acids were detected in the usual manner and an oil which was extracted from its ethereal solution with sodium hydroxide. The alkaline solution was neutralized with hydrochloric acid which precipitated a solid. After recrystallization from a mixture of ether and petroleum ether this melted at 118° and a sample prepared by mixing it with β-benzil-mono-oxime melted at the same temperature.

Reaction between the Oxide and Ethylmagnesium Bromide.—The oxide was treated with the Grignard reagent for the purpose of determining the relative activity of the C=NO and carbonyl groups. When the operation is carried out at a low temperature only one equivalent of the magnesium compound reacts and the product is a tertiary alcohol in which the isoxazoline oxide system remains intact. When the temperature is allowed to rise, there is a slow evolution of ethane, the solution becomes pale yellow, and in the end the product is the same tertiary alcohol that is formed by the action of ethylmagnesium bromide on the isoxazole.

An ethereal solution containing 8 g. of the low-melting oxide was added drop by drop to a similar solution of ethylmagnesium bromide which had been made from 2.5 g. of magnesium and which was kept in a freezing mixture. As soon as all of the oxide had been added, the mixture was divided into two portions, one of which was poured into iced acid while the other was allowed to warm to the ordinary temperature. The first portion gave a solid which was moderately soluble in ether, crystallized in bunches of needles and melted at 168°.

Analysis. Calc. for $C_{24}H_{23}O_3N$: C, 77.2; H, 6.2. Found: C, 77.4; H, 6.2.

The substance is not attacked by aqueous ammonia or dil. aqueous sodium hydroxide, but alcoholic potassium hydroxide and sodium methylate remove water and transform it quantitatively into the same substance that was obtained by treating the isoxazole with ethylmagnesium bromide. It is, therefore, the tertiary alcohol corresponding to the oxide and the first action of the Grignard reagent is on the carbonyl group.

The portion of the solution which was allowed to warm slowly evolved a gas—doubtless ethane. It was boiled for several hours, then poured into iced acid and handled in the usual manner. It gave a different solid which crystallized in large needles and melted at 145°. It proved to be the same substance that had previously been obtained by the action of ethylmagnesium bromide on the isoxazole, and the action of alcoholic potash on the product from the oxide. Excess of Grignard reagent, therefore, removes water from the primary product.

Summary

1. The paper deals with an isoxazoline oxide which has a phenyl group in place of the hydrogen atom in the 3 position of the isoxazole ring.
2. The phenyl group in the 3 position opposes a hindrance to all addition reactions involving the system, $>C=NO$.
3. Organic magnesium compounds combine more readily with a carbonyl group than with the unsaturated system, $C_6H_5—\overset{|}{C}=\overset{|}{N}O$.
4. Under the influence of bases, isoxazoline oxides undergo a remarkable series of rearrangements, the mechanism of which has in part been established.

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