[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

DIPHENYL ISOXAZOLONE
A STUDY OF THE TAUTOMERISM OF ISOXAZOLONES

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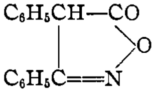
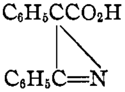
RECEIVED OCTOBER 13, 1927 PUBLISHED FEBRUARY 4, 1928

Diphenyl isoxazolone was first described by Beckmann and Paul,[1] who in 1891 obtained it incidentally while studying the action of sodium on desoxybenzoin. Realizing that the substance must be an anhydride of the oxime of phenyl benzoyl acetic acid, they considered the two formulas

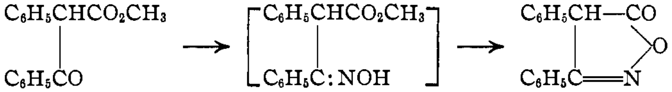




When they found that it could be titrated with a standard base of which it neutralized exactly one equivalent, they decided in favor of the second formula and named it "anhydro oximido benzoyl acetic acid."

Six years later Walther and Schickler[2] came across the substance again while examining the action of hydroxylamine on the amide of phenyl benzoyl acetic acid. They were unaware of the earlier work, made a faulty analysis of their product and, impressed by its acidity, formulated it as the oxime of phenyl benzoyl acetic acid.

Quite recently the same substance turned up again, this time as a product of the oxidation of 3,4-diphenyl-5-hydroxy-5-benzoyl isoxazoline with sodium peroxide.[3] It was then made synthetically by the most general reaction available for the preparation of isoxazolones:



The isoxazolone was described as a substance capable of existing in two modifications—the ordinary form first mentioned by Beckmann and Paul, and an unstable, lower-melting, more acidic form which immediately yielded a copper derivative when its ethereal solution was shaken with aqueous copper acetate. This conclusion led to the present investigation. If correct, it would mean that diphenyl isoxazolone is the only isoxazolone derivative—perhaps the only heterocyclic compound—of which desmotropic modifications can be isolated, and it would also mean that diphenyl isoxazolone would be the best material for the study of the structure of solid isoxazolones, and of their tautomerism in solution.

This conclusion now appears to us to be doubtful because we have been unable to prepare a sample of isoxazolone that does not immediately yield

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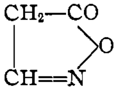
[1] Beckmann and Paul, *Ann.*, **266**, 20 (1891).

[2] Walther and Schickler, *J. prakt. Chem.*, [2] **55**, 316 (1897).

[3] Kohler, THIS JOURNAL, **46**, 1741 (1924).

a copper derivative. The analytical sample (0.5 g.) left from the earlier work gave an ethereal solution which, when shaken with aqueous copper acetate, at first produced only a faint opalescence. Then, very gradually, apparently as a consequence of rearrangement, it deposited the deep blue copper derivative, complete deposition requiring several hours. Numerous attempts to prepare another sample showing this behavior were all unsuccessful; we are therefore unable to exclude the possibility that lower-melting preparations contain a small quantity of an impurity which does not materially change the composition.

But even though we failed to isolate desmotropic modifications we nevertheless secured reliable evidence on the structure of the isoxazolone, both as solid and in solutions. The various methods by which alkyl and aryl isoxazolones have been prepared leave no doubt as to the nature of the carbon chain or the position of the hydrocarbon residues; the only uncertainty is the location of one hydrogen atom. This is created by the fact that various isoxazolone derivatives correspond to three tautomeric forms of the parent substance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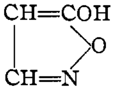
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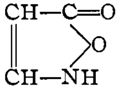
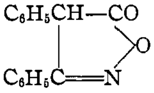

III

Most authors represent alkyl and aryl isoxazolones as derivatives of form I—largely, doubtless, because this form is most closely related to the substances from which these isoxazolones are usually obtained. Uhlenhuth,[4] who made the most extensive investigation of mono- and di-alkyl isoxazolones, adopted Formula III because he found that phenyl isoxazolone, when methylated by way of the silver salt, gave an N-methyl derivative—evidence that would not now be regarded as weighty. Formula III was also preferred by Moureu and Lazennec[5] because in their opinion it agrees best with all methods of preparation.

The corresponding formulas for the possible modifications of diphenyl isoxazolone are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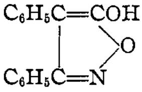
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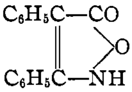
VI

In order to get a basis on which to distinguish between these formulas we have titrated solutions of the substance with bromine by the Kurt Meyer method, examined the behavior of the substance itself as well as that of its acyl and alkyl derivatives towards ozone, and determined both the

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[4] Uhlenhuth, *Ann.*, **296**, 36 (1897).

[5] Moureu and Lazennec, *Bull. soc. chim.*, [4] **1**, 1092 (1907).

quantity of gas evolved and the amount of reagent consumed when the substance reacts with methyl magnesium iodide.

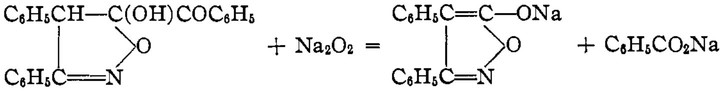
The bromine titrations show quite conclusively that solutions of diphenyl isoxazolone contain at least two forms. Unless prepared in a special manner, alcoholic solutions give bromine values which indicate 90% of "enolic" modifications. Since these solutions are strongly acidic, give color reaction with ferric chloride and copper derivatives with copper salts, this "enolic" modification must be the hydroxy isoxazol represented by V. In addition to this hydroxylic form the solution must contain 10% of one or both of the other modifications. In order to distinguish between these forms we subjected solutions of the isoxazolone to the action of ozone.

The forms represented by IV and V would not be expected to yield ozonides and neither of these forms would be likely to give definite products when oxidized with concentrated ozone, because the former contains no ethylenic linkage and the second is essentially aromatic. The modification represented by VI, on the other hand, would be expected to form an ozonide like every other phenylated ethylene derivative. Experiments showed that the isoxazolone is very slowly attacked by 6% ozone but neither forms an ozonide nor yields any of the normal decomposition products of ozonides. It can safely be concluded, therefore, that solutions of diphenyl isoxazolone contain a mixture of the "ketonic" modification IV and the "enolic" modification V; there is no evidence of the presence of form VI.

The bromine titrations also supply conclusive evidence that the solid isoxazolone is not the enolic modification. When these titrations were made as speedily as possible, with the purest materials that could be prepared, in apparatus that had been carefully steamed, they always gave values far below the usual 90% and in one case even below 50% of enol. The freshest solutions therefore contain the least enol, and since there is no evidence whatsoever of the presence of the imino form, even in the most concentrated solutions, it seems necessary to conclude that the solid substance is the "ketonic" modification V. The "keto-enol" system differs from most others only with respect to the rapidity with which it attains equilibrium.

II. Preparation

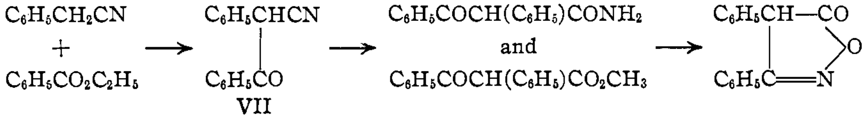
Of the various methods of formation enumerated in the introduction, two merit consideration as methods of preparation: the oxidation of hydroxy benzoyl diphenyl isoxazoline and the action of hydroxylamine on phenyl benzoyl acetic ester. The first is represented by the equation



This method gives an excellent yield but the hydroxy isoxazoline can be obtained only by a long series of reactions[6] starting with phenyl nitro methane. The preparation of this is in itself an arduous task. Our procedure for the oxidation was as follows.

To a solution of 70 g. of sodium peroxide in 800 g. of ice and 700 cc. of water is added, gradually, 35 g. of the hydroxy isoxazoline. This mixture is stirred for eight hours, then left overnight. The next day the sodium salt is collected on a filter and washed with dilute sodium carbonate, filtrate and washings being discarded. The sodium salt is dissolved in 600–800 cc. of water, the solution filtered, the clear filtrate acidified and left to itself until the precipitation is complete. The precipitate is thoroughly washed with water, dried and boiled with ether. This removes benzoic acid and small quantities of other impurities and leaves a crude product that melts at 150–155°; yield, 90%.

The successive steps in the second method of preparation are as follows:



$$C_6H_5CH_2CN + C_6H_5CO_2C_2H_5 \longrightarrow C_6H_5CH(CN)COC_6H_5 \longrightarrow C_6H_5COCH(C_6H_5)CONH_2 \text{ and } C_6H_5COCH(C_6H_5)CO_2CH_3 \longrightarrow$$

VII

Here the principal difficulty lies in the first step. By a modification of the procedure of Bodroux it was found possible to effect this condensation on a large scale and since, contrary to the observations of Walther and Schickler, the isoxazolone can be made from the amide as well as from the ester, this method of preparation proved to be the more convenient.

Phenyl Benzoyl Aceto Nitrile (VII).—After preliminary trials with the various agents that have been used for condensing ethyl benzoate with benzyl cyanide[7] we decided in favor of Bodroux's method but, possibly owing to the quality of our sodamide, our yield was only 35%. By changing the procedure and also the proportions of reactants this was increased to 60% which is still much lower than the 85% reported by Bodroux. Our procedure was as follows.

In a one-liter flask fitted with a dropping funnel, reflux condenser and motor stirrer, 40 g. of finely powdered sodamide is placed under 500 cc. of absolute ether. To this is added in the course of half an hour, during which the mixture is stirred constantly, 60 g. of benzyl cyanide. The mixture, which during the addition acquires a dark red color, is boiled for half an hour, then cooled in an ice-bath while 75 g. of ethyl benzoate is added. This requires about half an hour and is accompanied by the separation of a yellow solid. The mixture is then kept at room temperature for several hours.

The products from two or three such operations are combined and slowly poured into cold 50% alcohol. The resulting solution is diluted with water until it separates into two layers. The aqueous layer is thoroughly extracted with ether, then acidified with a mixture of ice and concentrated hydrochloric acid. This precipitates the nitrile as an oil which slowly solidifies. After washing with chilled methyl alcohol and drying,

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[6] Ref. 3, p. 1738.

[7] (a) Walther and Schickler, ref. 2, p. 308; (b) Ghosh, *J. Chem. Soc.*, **109**, 116 (1916); (c) Bodroux, *Bull. soc. chim.*, [4] **9**, 651 (1911); (d) *ibid.*, p. 726. After we had prepared our material, Wislicenus, Eichert and Marquart, *Ann.*, **436**, 92 (1925), described a preparation in which they used metallic potassium as a condensing agent. This gave a yield of 80%.

the yield of crude solid is 120–130 g. from 120 g. of benzyl cyanide, or 55–60%. The crude nitrile—m. p. 90–92°—is readily purified by crystallization from dry methyl alcohol, but this is unnecessary if it is to be used for making the isoxazolone.

For the purpose of converting the nitrile into diphenyl isoxazolone it was first esterified with methyl alcohol and hydrochloric acid, essentially as described in earlier papers. The result was a mixture of ester and amide in proportions that depended on the conditions. Each of these was turned into the isoxazolone. To this end a methyl alcoholic solution of the substance and 20% excess of hydroxylamine hydrochloride was boiled—for two hours in the case of the ester, four hours in the case of the amide. Most of the isoxazolone crystallized on cooling; the balance was precipitated by diluting the solution with water. Both ester and amide gave practically quantitative yields of a crude washed and dried product which melted and decomposed at 150°. For most purposes this was simply boiled with dry ether which removed small quantities of impurities and thereby raised the melting point to 155–157°. The purest product was obtained by careful recrystallization from benzene. This melted and decomposed sharply at 159°.

3,4-Diphenyl isoxazolone is readily soluble in methyl and ethyl alcohols, sparingly soluble in chloroform, carbon tetrachloride and benzene, almost insoluble in ether. Its resistance to hydrolytic agents is impressive; neither prolonged boiling with saturated methyl alcoholic potassium hydroxide nor protracted heating to 110–115° with concentrated hydrochloric acid produced any effect at all, and more than 85% of it was recovered after long boiling with a 60% solution of sulfuric acid in methyl alcohol. It likewise resists the action of hydroxylamine and phenyl hydrazine and a sample which had been boiled for five hours with zinc dust and glacial acetic acid was recovered almost quantitatively by diluting the solution with water.

III. Salt Formation

Inasmuch as diphenyl isoxazolone is strongly acidic, there is no difficulty in preparing its salts. Beckmann and Paul[8] analyzed the silver salt and found that its composition corresponds to that of a metallic derivative. Walther and Schickler,[9] unaware of the earlier work, repeated the analysis and reported values corresponding to a salt of the open chained oximido acid. Since then so many salts of other disubstituted isoxazolones have been found to be metallic derivatives that there now can be scarcely any question that the salts of these isoxazolones are formed by replacement of hydrogen by a metal. We analyzed a sample of the silver salt which had been dried at 120° and confirmed the values obtained by Beckmann and Paul, but we also found that the salt tenaciously retains considerable amounts of water. Thus a salt which had been dried to constant weight in a vacuum desiccator gave low values for silver and lost water when heated to 120°. The loss, however, was less than half of that required for a salt of the open chained acid.

In addition to the silver and sodium salts we found the copper acetate and magnesium bromide salts useful, the former as a means of detection and identification and the latter for operations in ethereal solution. For our purpose the sodium salt was made by dissolving 5 g. of the isoxazolone

[8] Ref. 1, p. 20.

[9] Ref. 2, p. 316.

in 50 cc. of saturated sodium carbonate diluted with an equal volume of water. This solution when chilled deposited a hydrated form that melted at 50° and resolidified at 120°. The thoroughly dried salt is very hygroscopic.

The Copper Salt, $C_{15}H_{10}ONOCuOCOCH_3$.—The mixed copper salt was made by shaking an ethereal solution of the isoxazolone with aqueous copper acetate and also by adding the acetate to an aqueous solution of the sodium salt. The products are identical. The salt separates as a deep blue or purple crystalline precipitate. As it is insoluble alike in water and in organic solvents it serves well as a means of detecting small quantities of the isoxazolone. For the purpose of analysis it was washed with water and acetone and dried to constant weight.

Anal. Calcd. for $C_{17}H_{13}O_4NCu$: Cu, 17.75. Found: 17.47.

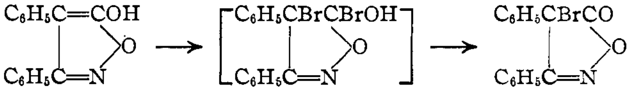
The analysis indicates a mixed salt and the presence of the acetic acid residue was confirmed by warming the salt with alcohol and concentrated sulfuric acid.

The Magnesium Bromide Salt.—An ethereal solution of this mixed salt was made by adding the isoxazolone to an excess of ethyl magnesium bromide and warming the mixture until the evolution of gas ceased. Owing to the insolubility of the isoxazolone in ether the reaction is slow but a quantitative experiment with methyl magnesium iodide in *iso*-amyl ether showed that even after prolonged heating only one molecule of reagent had been consumed and that one molecule of methane was liberated. The ethereal solutions are generally yellow and sometimes they develop a brown color but direct experiment showed that the isoxazolone is recovered quantitatively when the solutions are acidified. The color is doubtless due to a small quantity of iron compounds in the reagent; it disappears on addition of water. No attempt was made to isolate the mixed salt; it was used only in ethereal solution immediately after it had been prepared.

IV. Halogenation and Oxidation

Halogenation and oxidation are grouped together here because diphenyl isoxazolone is so easily oxidized that, unless special precautions are taken, operations intended to give halogen compounds give, instead, large quantities of the oxidation product. For this reason it is best to prepare the chlorine compound by the action of phosphorus pentachloride. The bromine compound can be made by adding bromine to solutions of the ketone but both the bromine and the solvent must be thoroughly dry.

Since the halogen compounds behave neither like hypo halides nor like imine halides they must be derived from the carbonyl form of the isoxazolone. Brominations which are carried out in solutions in which the substance is largely enolic doubtless start with the usual addition reaction



V VIII

4-Bromo-3,4-diphenyl Isoxazolone (VIII).—The finely powdered solid isoxazolone was suspended in dry carbon tetrachloride and treated with a slight excess of bromine which had been distilled from phosphorus pentoxide. The solid dissolved with evolution of hydrogen bromide. The solution, on evaporation under diminished pressure, left an oil that solidified when rubbed with methyl alcohol. After recrystallization from methyl alcohol the solid melted at 72°; yield, 90%. The same bromine compound was formed when dry bromine was added to a chilled ethereal solution of the magnesium derivative. It is not attacked by ozone and it is insoluble in alkalies, but prolonged heating with methyl alcoholic potassium hydroxide destroys it.

Anal. Calcd. for $C_{15}H_{10}O_2NBr$: C, 56.96; H, 3.2. Found: C, 56.66; H, 3.25.

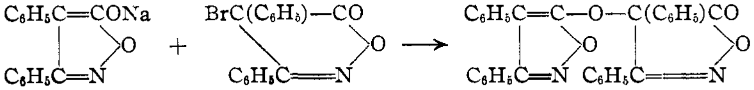
4-Chloro-3,4-diphenyl Isoxazolone.—Three g. of phosphorus pentachloride was added to 3 g. of the isoxazolone suspended in 40 cc. of chloroform. After the vigorous initial reaction had subsided, the mixture was boiled for forty-five minutes, then filtered and evaporated under diminished pressure. It left an oil which was dissolved in ether. The ethereal solution deposited the solid which after purification melted at 77–78°; yield, 50%.

Anal. Calcd. for $C_{15}H_{10}O_2NCl$: C, 66.3; H, 3.7. Found: C, 65.9; H, 3.85.

One of the conspicuous properties of diphenyl isoxazolone is the ease with which it is oxidized. The solid form is stable in the air but its solutions develop color and gradually deposit a sparingly soluble, colorless oxidation product. This is formed rapidly when solutions in suitable solvents are treated with ferric chloride, bromine that has not been carefully dried, nitrous and nitric acids. It is formed also from the sodium salt by such oxidizing agents as bromine, potassium permanganate and potassium ferricyanide. Its composition and molecular weight indicate that its formation involves the removal of two atoms of hydrogen from two molecules of the isoxazolone. In agreement with this it was found that in the oxidation with permanganate only one atom of oxygen is required to oxidize two molecules of the salt and that the product is insoluble in alkalies.

A similar dimolecular oxidation product was obtained by Volhard[10] from 3-benzyl-4-phenyl isoxazolone. From the composition of this substance and its insolubility in alkalies, Volhard concluded that it is formed from two molecules of the "ketonic modification" by removing two atoms of hydrogen and adding one atom of oxygen. The resulting formula seemed to us *a priori* rather improbable. Carbon and hydrogen determinations do not with certainty establish the presence or absence of an additional oxygen atom, but the quantity of permanganate required to form the substance from the sodium salt shows conclusively that the oxygen consumption corresponds to one atom for two molecules of isoxazolone.

Since an ether formed by removing one atom of hydrogen from the carbonyl, the other from the enolic modification would likewise be insoluble in alkalies, we undertook the synthesis of such a compound. We found that the oxidation product can be obtained by the interaction of the bromo compound and the dry sodium salt in absolute ether



IX

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[10] Volhard, *Ann.*, **296**, 9 (1897).

While we do not regard this evidence as conclusive, we deem it likely that the oxidation products which are so readily formed from the disubstituted isoxazolones are ethers of the type represented by IX. The process of oxidation thus appears to be quite similar to that of phenols; in alkaline solutions these likewise are readily oxidized to dimolecular products in which one half of the molecule is aromatic, the other half alicyclic.[11]

Preparation.—From the isoxazolone the oxidation product is very easily obtained with nitrous acid. Thus 15 g. of sodium nitrite was added little by little to a solution of 5 g. of the isoxazolone in acetic acid. After the addition the solution was left to itself for forty-five minutes, then made alkaline with sodium carbonate and extracted with ether. The ethereal solution gave 3.6 g. of crude product melting at 148°—a yield of 70%. By the same procedure, nitric acid which had been freed from nitrous acid gave a yield of 60%; as there were no nitro compounds the substance is evidently more easily oxidized than nitrated.

The best method of preparation is by oxidation of the sodium salt. A solution of the isoxazolone in the minimum quantity of half saturated sodium carbonate is treated with finely powdered permanganate until the color persists. The excess of permanganate and the oxides of manganese are removed with bisulfite and acid, leaving the product as a finely divided solid which is easily purified by recrystallization from a mixture of acetone and methyl alcohol; yield, 90%.

The only method of preparation that gave any clue as to the structure of the oxidation product was carried out as follows. Equivalent quantities of the thoroughly dried sodium salt and the bromine substitution product were suspended in dry ether. Reaction is slow and incomplete. The mixture was boiled for ten hours, then filtered. The solid was washed with methyl alcohol to remove unchanged bromo compound and with water to free it from bromide. The crude product melted with decomposition at 152–155° and a mixture of this and the pure substance at 154–156°.

Anal. Calcd. for $C_{30}H_{20}O_4N_2$: C, 76.2; H, 4.3. Found: C, 76.3; H, 4.4.

In boiling acetone the molecular weights found were 467 and 473 instead of 473 calculated for the dimolecular compound.

The oxidation product is sparingly soluble in ether and in methyl alcohol, readily soluble in acetone. It is insoluble in alkalies. On prolonged boiling with methyl alcoholic potassium hydroxide it is altered but does not yield isoxazolone. Towards constant boiling hydriodic acid it shows the normal behavior of an oxygen ether. Thus when 1.18 g. was boiled for two hours with the calculated quantity of acid, it gave 0.4 g. of isoxazolone and an oil that was insoluble in alkalies but readily soluble in organic solvents.

V. Titration with Bromine

The first titrations were made by the procedure which is commonly used for determining by the Kurt Meyer method the quantity of enolic modification in a keto-enol mixture. The isoxazolone was dissolved in about 50 cc. of absolute alcohol, bromine in excess was added to the solution, then β-naphthol and finally potassium iodide. After two to three minutes the liberated iodine was titrated with standard thiosulfate, using the disappearance of the iodine color as end-point. The values are shown in the following table.

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[11] Pummerer, Puttfarcken and Schopflocher, *Ber.*, 58, 1808 (1925).

TABLE I

TITRATION VALUES WITH BROMINE

	Substance, g.	Thiosulfate, (0.1026 N) cc.	Iodine, g. per mole	Enol, %
1	0.2303	17.20	230.5	90.8
2	.2810	20.50	225.3	88.7
3	.1634	11.82	223.3	87.9
4	.1634	12.30	232.3	91.5
5	.1634	11.80	223.3	87.8

The first two values were obtained in determinations which were parallel except that the first was made at 24°, the second with chilled reagents at −5°. The remaining three values were obtained with an alcoholic solution which had been kept in the dark for fifteen days. Of these three values the last two represent parallel determinations made after adding a drop of dilute hydrobromic acid and allowing the solutions to stand for several minutes. These values indicate that solutions of diphenyl isoxazolone contain about 90% of "enolic" modification and that they reach equilibrium with great rapidity, but before this interpretation could be accepted it was necessary to establish that the missing material could not be accounted for by oxidation or the formation of a bromine compound that is not readily reduced by hydrogen iodide.

For the purpose of determining whether an appreciable amount of oxidation occurs during the titrations we repeated the operation with a larger quantity of material and in the absence of β-naphthol which interferes with the detection of the oxidation product. To a solution of 1.084 g. of the isoxazolone was added first a slight excess of bromine, then potassium iodide in excess. After three minutes the liberated iodine was removed with the dilute thiosulfate, the solution diluted and extracted with ether. The ethereal solution was washed in succession with calcium chloride, half saturated sodium carbonate and water, and then evaporated. It left a small wet residue which was dissolved in 2–3 cc. of methyl alcohol. This solution was inoculated with oxidation product, but beyond a slight cloudiness no solid appeared. Since this procedure should detect at least 0.04 g. of the oxidation product, the titration values are not vitiated by oxidation.

In order to test the rapidity and completeness with which the bromo isoxazolone is reduced by potassium iodide in acid solution, a drop of dilute hydrobromic acid was added to a solution of 0.4471 g. of the bromo isoxazolone. Potassium iodide was then added in excess and after two minutes the liberated iodine was titrated. It required 27.10 cc. of the standard thiosulfate solution, equivalent to 98.25% of the bromo compound.

In view of the rapidity with which the equilibrium is established it seemed improbable that the nature of the solid substance could be established by the Kurt Meyer method but, since no other could be used with a substance having so high a melting point, it was tried. To this end the titrations were repeated with materials purified with great care in apparatus that had been thoroughly steamed immediately before use. The values now were:

Table II

Substance, g.	Thiosulfate, (0.1021 N) cc.	Iodine, g. per g. m.	Enol, %
0.1109	6.70	185.6	73.1
.1402	5.49	120.2	47.3
.1903	10.50	185.6	66.7

The variations in the values obtained in such shifting systems are, inevitably, large but the consistently low results show that the solid cannot be the enolic modification.

VI. Alkylation and Acylation

The most interesting reactions of diphenyl isoxazolone are alkylation and acylation. For the study of the former we selected methylation and benzylation. Methylation can be accomplished in a great variety of ways, all of which lead to the same methyl derivative. This was formed when methyl iodide was added to a solution of the isoxazolone in methyl alcoholic sodium methylate, when methyl iodide was allowed to react with the dry sodium salt suspended in benzene or the dry silver salt suspended in ether, by the action of dimethyl sulfate on the sodium salt in water or on the magnesium bromide salt in ether, and by boiling a pyridine solution of the isoxazolone with methyl iodide.

Little is known about the course of alkylation of isoxazolones. Uhlenhuth[12] made the methyl and ethyl derivatives of phenyl isoxazolone from the silver salt. By boiling the methyl compound with alcoholic potash he obtained a small quantity of a volatile base which he caught in hydrochloric acid and turned into a chloroplatinate. The analysis of the chloroplatinate gave a value for platinum from which he concluded that the base was methyl amine and, therefore, that the methylation product was an N-methyl derivative. The evidence seems inconclusive because the value for platinum lies almost exactly midway between that of an ammonium and a methyl ammonium chloroplatinate.

We degraded our methyl derivative in accordance with Uhlenhuth's procedure but obtained only traces of a volatile base—far too little for identification. The principal degradation product was desoxybenzoin but we also obtained a small quantity of benzoic acid. These substances could not arise from a C-methyl but they might be formed equally well from an O-methyl or an N-methyl derivative. A Zeisel methoxyl determination which gave a negative result eliminated the oxygen ether and ozonization finally supplied positive evidence that the substance is an N-methyl ester. The degradation with bases doubtless is represented by the

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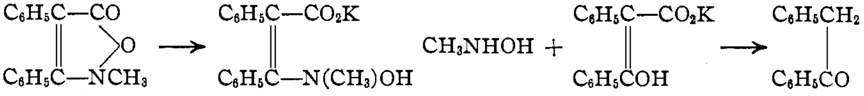
[12] Uhlenhuth, ref. 4, p. 46.

following scheme which shows that methyl amine, if formed at all, would be a secondary product.



X

N-Methyl-3,4-diphenyl Isoxazolone (X).—For preparing the ether in quantity we prefer the following method. The isoxazolone (47.4 g.) was dissolved in 120 cc. of methyl alcoholic sodium methylate containing 7 g. of sodium. To this solution was added 56.8 g. of methyl iodide. The mixture was boiled until neutral, then made strongly alkaline with sodium methylate and while still hot diluted with much water. On cooling it deposited 27 g. of the methyl derivative, and ether extracted 4 g. more. The alkaline solution contained 16 g. of unchanged isoxazolone which was recovered by acidification; yield, 91%. The ether was purified by recrystallization from ether and petroleum ether, or methyl alcohol and water. It crystallizes in needles and melts at 92°.

Anal. Calcd. for $C_{16}H_{13}O_2N$: C, 76.5; H, 5.2. Found: C, 76.4; H, 5.3.

The methyl ether was not affected by heating for twelve hours at 110–115° with concentrated hydrochloric acid, and heating with hydriodic acid in the Zeisel apparatus gave no methyl iodide. It was insoluble in aqueous alkali but when boiled with strong methyl alcoholic potassium hydroxide for two hours, 1.8 g. left an oil from which 0.5 g. of pure recrystallized desoxybenzoin and 0.1 g. of benzoic acid were extracted.

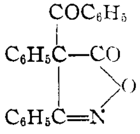
Ozonization.—Ozonized oxygen containing about 6% of ozone was passed for 3 hours through a solution of 2.6 g. of the methyl ether in 35 cc. of carbon tetrachloride. The solvent was removed under diminished pressure and the ozonide first treated with water, then warmed with dilute sodium hydroxide and finally distilled with steam in order to remove nitrogenous products. From the residue ether extracted a small quantity of unchanged substance. The alkaline layer was acidified and treated with phenyl hydrazine. It deposited the phenyl hydrazone of benzoyl formic acid, which was identified by comparison with a sample on hand.

The N-benzyl Ether.—The benzyl derivative was made in the hope that it might be more suitable for studying the action of bases on the N-alkyl derivatives. This proved not to be the case. It melts at 123° and its behavior towards alkalies and ozone is exactly like that of the methyl derivative.

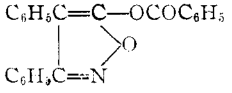
Anal. Calcd. for $C_{22}H_{17}O_2N$: C, 80.7; H, 5.2. Found: C, 80.4; H, 5.3.

Acylation was first studied with benzoyl chloride and then, since ozonization of the benzoate did not clearly exclude the possibility that the acyl group might go to carbon atom 4, it was repeated with chloro formic ester, which almost invariably forms O-acyl derivatives. Benzoylation in pyridine, in water by the Schotten-Baumann reaction, and in ether by the action of benzoyl chloride on the magnesium bromide derivative gave the same benzoate.

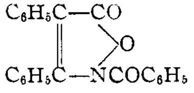
It is difficult to secure absolutely explicit evidence as to the structure of the acyl derivatives. The three possible formulas of the benzoate are



XI



XII



XIII

The third of these formulas is definitely excluded by the results of ozonization. A substance with this structure should, like the ethers, form an ozonide which on decomposition with water would give phenyl glyoxylic acid as one of the products. The benzoate does not form an ozonide. It is slowly attacked by concentrated ozone, but no treatment of the resultant oil yields even a trace of phenyl glyoxylic acid which can be detected with the very delicate color reaction of this substance.

A substance with the structure represented by XII would be expected to behave towards ozone essentially like triphenyl isoxazol which, as has been shown by Meisenheimer,[13] can be oxidized to a derivative of benzilmonoxime. Despite many attempts we were never able to isolate benzil, its monoxime or any other definite oxidation product. The experiments with ozone, therefore, do not serve to distinguish between formulas XI and XII. There remains only the behavior towards hydrolytic agents. Both acids and bases regenerate the isoxazolone much more easily than they would be expected to hydrolyze a substance like that represented by XI. Indeed, one would be inclined to predict that the primary action of strong bases on such a substance would be ring-opening, and that the final product would be triphenyl isoxazol. In the absence of more explicit evidence, however, the detailed structure of the acylation products of isoxazolones must be regarded as unknown.

The Benzoate.—The crude benzoate obtained in pyridine or by the Schotten-Baumann reaction melted at 126–127°, while that from the magnesium bromide derivative melted at 135°. It was at first suspected that the lower-melting preparation might contain isomeric benzoates, but careful fractional crystallization failed to disclose such isomerism. The benzoate crystallizes well both from ether and from alcohol in needles melting at 138–139°.

Anal. Calcd. for $C_{22}H_{15}O_3N$: C, 77.4; H, 4.4. Found: C, 77.5; H, 4.4.

The Ethyl Carbonate.—Twice the calculated quantity of chloro carbonic ester was added to 5 g. of the dry sodium salt suspended in absolute ether. The mixture was boiled for an hour, then poured into water. The ethereal layer, washed with sodium carbonate and water, dried and evaporated, gave 4.3 g. of ester—a yield of 85%.

Anal. Calcd. for $C_{18}H_{15}O_4N$: C, 69.9; H, 4.9. Found: C, 69.8; H, 4.9.

The ester crystallized well but always softened at 103° before it melted at 109–110°. The ester was rapidly hydrolyzed by bases, yielding 90% of isoxazolone after it had been heated for fifteen minutes with methyl alcoholic potassium hydroxide. Its behavior towards ozone was precisely like that of the benzoate.

Summary

The paper contains a method for preparing 3,4-diphenyl isoxazolone in quantity and an account of the experiments made for the purpose of establishing the structure of the solid form, the equilibrium in solution and the structure of the bromination, acylation and alkylation products.

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[13] Meisenheimer, *Ber.*, **54**, 3211 (1921).