the group as a whole; also, for thinking that the amine-oxide retains the structure $(\mathrm{CH_3})_3\mathrm{N}::\overset{\bullet\bullet}{\underset{\bullet\bullet}{\mathrm{O}}}$ in solution, the nitrogen having its usual valence of five (one being polar) and oxygen its valence of two.

The hypothesis of Stewart and Maeser that the amine-oxide has the structure $\mathrm{R}:\mathrm{N}:\overset{\bullet\bullet}{\underset{\bullet\bullet}{\mathrm{O}}}:\mathrm{H}:\overset{\bullet\bullet}{\underset{\bullet\bullet}{\mathrm{O}}}:\mathrm{H}$ in solution is questioned.

Reasons are given for believing that the polar valence of ammonium compounds is properly considered as a "primary valence" and that the differences between "polar" and "non-polar" valences are differences of degree rather than of kind.

URBANA, ILLINOIS

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

ISOXAZOLINE OXIDES

IV. BENZOYL-DIPHENYL-ISOXAZOLINE OXIDE

Second Paper

BY E. P. KOHLER

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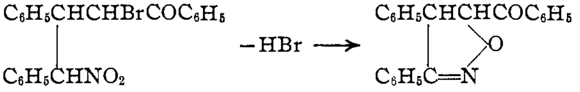
In the first paper[1] I described the products obtained by the action of potassium acetate on the various stereomeric forms of a highly phenylated α-bromo-γ-nitroketone (I). This reaction always gave almost exclusively a substance melting at 123°, but in one case it was possible to isolate an isomer melting at 151° in an amount barely sufficient to show that it was enough like the main product to justify the conclusion that the two compounds were stereoisomers. These substances were assumed to be the two possible forms of diphenyl-benzoyl-isoxazoline oxide.



I II

The properties of the main product (123°) were in fairly good agreement with this interpretation, but two facts provoked some doubt: the substance had no oxidizing power, and it gave the normal reaction of ketones with Grignard reagents. These facts were not completely irreconcilable with the proposed formula but the discovery that triphenyl-isoxazoline oxide,[2] whose structure could be established with more precision, liberates chlorine from phosphorus pentachloride and is reduced by Grignard reagents, necessitated a reëxamination of the problem. As a result, it is now clear that the substance melting at 123° is not an isoxazoline oxide. This conclusion has been reached in the following manner.

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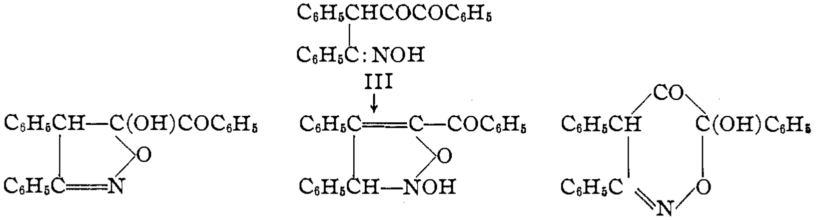
[1] Kohler, THIS JOURNAL, **46**, 1733 (1924).

[2] Kohler and Barrett, *ibid.*, **46**, 2105 (1924).

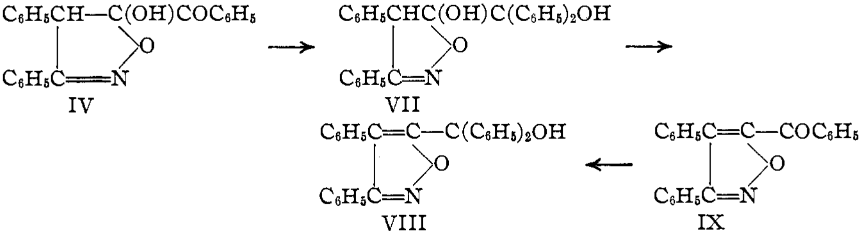
When any one of the 4 stereoisomeric bromine compounds represented by I is boiled with pyridine in methyl alcohol it rapidly loses hydrogen bromide and forms almost quantitatively two isomeric compounds. One of these is the substance melting at 151° which had been obtained in very small quantities by eliminating hydrogen bromide with potassium acetate, the other is a new substance that melts at 183°. By using both pyridine and potassium acetate for eliminating hydrogen bromide from the bromoketone it is possible, therefore, to get 3 isomers melting, respectively, at 183°, 151° and 123°. Two of these very readily change into the third; hence, all three behave alike towards nearly all reagents, but the two primary products—183° and 151°—which are obtained by means of pyridine liberate chlorine from phosphorus pentachloride and do not give the normal reactions of ketones with Grignard reagents. These are, doubtless, the true isoxazoline oxides; they will be described in detail in a later communication. The isomer melting at 123° differs from the true oxides not only in its lack of oxidizing power but also in its ability to form a sodium compound and, consequently, to undergo benzoylation. In the previous paper this was attributed to enolization, but since it is now known that the oxides do not form metallic derivatives thus easily, this explanation is no longer tenable; the substance must be an hydroxyl compound. It can be obtained from the oxides in a variety of ways but the method of preparation that is most significant is based on the observation that while the oxides are colorless, their solutions in nearly all solvents are yellow. It seemed likely, therefore, that the sensitive yellow triketone oxime (III) described in the earlier paper served as an intermediate between the oxides and the hydroxyl compound. Direct experiment showed that, in alcoholic solution, this yellow compound does, in fact, change spontaneously and almost completely into the isomer melting at 123°. This discovery greatly reduces the number of probable formulas of the latter because the only rearrangement that the yellow oxime would be expected to undergo with such ease is cyclicization to the substances represented by IV, V and VI.



IV V VI

None of the substances represented by these formulas would have any oxidizing power, each would have an acidic hydroxyl group and each also would probably give the normal reaction of ketones with organic magnesium compounds, but in the case of the oxazine (VI) the entering group would not assume the position that it actually occupies in the Grignard products. This formula can, therefore, be discarded.

The products of the action of an organic magnesium compound on the two isomeric hydroxy-isoxazolines would, doubtless, be very similar but they would differ completely in acidity. The acidity of an hydroxy-isoxazoline of the type represented by IV is due to the proximity of carbonyl to hydroxyl; it would, therefore, disappear with the carbonyl group. Formula V, on the other hand, represents an hydroxyl compound of which the acidity is independent of the groups attached to the ring; it would, therefore, survive the disappearance of the carbonyl group. The product obtained from the reaction between phenylmagnesium bromide and the substance under consideration has two hydroxyl groups but it does not form a sodium compound, it cannot be benzoylated and it shows no acidity whatsoever. Since the relation between this substance and the product obtained with the isoxazole (IX) shows that the magnesium compound in both cases attacks the carbonyl group, the proof is complete that the isomer melting at 123° is the hydroxy-isoxazoline represented by IV. The following formulas show the relations on which the proof is based.



The new formula accounts admirably for all the properties of the isomer melting at 123°; its lack of oxidizing power, its acidity which is like that of an open-chained α-ketole, and the instabiltiy in solution by virtue of which it is always in equilibrium with the open-chained, yellow oxime and ultimately passes completely into the isoxazole.

Experimental Part

The nitroketone, the various α-bromo compounds and the hydroxy-isoxazoline which constitutes the principal subject of this paper were prepared according to the directions previously given. The preparation of the triketone oxime has been greatly improved, and it is now easier to get the pure hydroxy compound by way of this yellow oxime than directly from the bromoketone.

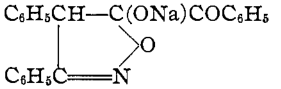
Preparation of α,γ,δ-Triphenyl-butanetrione Oxime (III).—A mixture composed of 20 g. of crude, washed and dried bromo compound, 400 cc. of 5% aqueous sodium hydroxide, 400 cc. of methyl alcohol and 100 cc. of ether is shaken mechanically until both the ethereal and aqueous layers are free from suspended solid. The ether layer is discarded; it contains any impurities in the crude bromine compound and a small quantity of isoxazole. About 75 cc. of ether and 750 g. of cracked ice are added to the aqueous layer, this mixture is shaken vigorously both to cool it and to saturate the aqueous solution with ether. It is then acidified with iced hydrochloric acid, which is prepared by shaking the concentrated acid with finely cracked ice and is added rapidly and in large excess. The acidified solution, when vigorously shaken deposits nearly all of the oxime in the form of small yellow prisms that contain ether of crystallization, the aqueous layer becoming almost colorless. The solid is collected on a filter, very thoroughly washed with water and finally with chilled ether and dried. Small additional quantities of the oxime can be obtained by extracting the filtrate with ether, but this operation is not remunerative; in a successful preparation the ether extract contains small quantities of the oxime, the hydroxy-isoxazoline, diphenisoxazolone and benzoic acid.

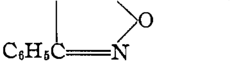
While few substances are more easily prepared than this sensitive oxime, good yields can be obtained only by fairly careful operation. More concentrated alkali, and more prolonged action of dilute alkali convert the oxime slowly but completely into the isoxazole, the isoxazolone and benzoic acid. If the alkaline solution is not saturated with ether before acidification, or if acidified too slowly, or at too high a temperature, the oxime is rapidly changed into the hydroxy-isoxazoline or into a purple anhydro compound that is still under investigation. The crude, dried product is readily purified by solution in a small quantity of warm acetone and reprecipitation with alcohol-free ether. The average yield of pure oxime from pure bromine compound is about 90% and from crude bromine compound about 85%.

The Relation between the Oxime and the Hydroxy-isoxazoline (IV).—The oxime is stable only in solid form; it is peculiarly sensitive to both acids and bases and in solution it is always in equilibrium with other substances. Thus, in chloroform minute traces of acid rapidly transform it into the purple anhydride. It dissolves freely in alcohol, the deep yellow solution soon begins to fade and the hydroxy-isoxazoline separates in long, fine needles containing alcohol of crystallization. This property can be utilized for preparing pure isoxazoline.

For this purpose a few drops of sodium methylate solution are added to a solution of the oxime in five times its weight of methyl alcohol. The solution is boiled until it has become almost colorless, then cooled in a freezing mixture. The hydroxyl compound separates in cubical crystals containing methyl alcohol of crystallization, the yield is almost quantitative and the product, after being washed and dried, is pure.

The most conspicuous properties of this substance were accurately described in the earlier paper, but the names and formulas of a few of its derivatives need revision in accordance with the new formula. Thus, the sodium derivative and the benzoate (which is more easily obtained by means of pyridine than by the Schotten-Baumann reaction) should be represented as follows.

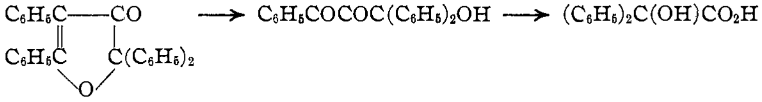




The change in formulas also affects the interpretation of some of the reactions. Thus the isoxazole (IX) is formed with equal ease from the oxides (II), the yellow oxime (III) and from the hydroxy-isoxazoline

(IV). This is not surprising because solutions made by dissolving the oxides contain all three of these substances. In the earlier paper it was assumed that the water is eliminated from an enolic modification of the oxime; it now seems much more probable that the process takes place in the reverse direction and that it is really the hydroxyl compound which is stripped.

Reaction with Phenylmagnesium Bromide.—Inasmuch as the hydroxyl compound crystallizes best from methyl alcohol, from which it separates with alcohol of crystallization, and the removal of this alcohol is a tedious process owing to the low melting point of the substance, it is best to use adequate excess of the magnesium compound and operate with the crystalline form. The primary product of this reaction is the dihydroxyl compound discussed in the introduction. This is obtained quantitatively if the magnesium compound is decomposed immediately. More prolonged action leads to the formation, in variable amounts, of two other substances. One of these is the colorless, tertiary alcohol (VIII) formed by loss of water, the other a pale yellow, nitrogen-free compound that has the composition $C_{28}H_{20}O_2$. By ozonization or, better, very cautious oxidation with chromic acid this yellow compound is degraded to benzoic acid and a deeper yellow product which has the composition $C_{21}H_{16}O_3$, and which on further oxidation gives equivalent amounts of benzoic and benzilic acids. The pale yellow Grignard product is, therefore, a tetraphenylfurone, the successive steps in its degradation to known substances being as follows.



X XI XII

3,4-Diphenyl-5-hydroxy-5-diphenyl Carbinyl Isoxazoline (VII).—To a solution of phenylmagnesium bromide which had been made from 12 g. of magnesium and was contained in a flask provided with a mechanical stirrer, 37.5 g. of the finely-powdered, crystalline hydroxyl compound was added in the course of half an hour. The mixture was stirred for two hours. It remained colorless throughout the operation but deposited a pasty magnesium derivative that gradually solidified. The usual treatment with iced acid gave a crystalline solid. This was thoroughly washed with water, methyl alcohol and ether, and then purified by dissolving it in benzene and diluting this solution with petroleum ether. It separated in small, colorless tables or prisms; m. p., 170–171°. The yield of pure substance was 48 g. or about 90%; no other products were found.

Anal. Calcd. for $C_{28}H_{23}O_3N$: C, 79.8; H, 5.5. Found: C, 79.8; H, 5.9.

An hydroxyl determination by the Zerewitinoff method gave 2.2 equivalents of ethane.

The dihydroxyl compound is readily soluble in alcohol, moderately soluble in benzene, sparingly soluble in ether. It loses water far less easily than the parent substance. Thus it can be crystallized without loss from glacial acetic acid, acetyl chloride and even acetic anhydride which more or less rapidly convert the monohydroxyl compound into isoxazole or other anhydrides. Prolonged boiling with acetic anhydride results in elimination of water, and even very small quantities of acetyl chloride in methyl alcohol rapidly convert it into the methyl ether of the tertiary alcohol (VIII) that is formed by the action of phenylmagnesium bromide on the isoxazole.

The dihydroxyl compound is also comparatively insensitive to bases, and all attempts to make a sodium compound or to open the isoxazoline ring were unsuccessful. Concentrated aqueous sodium hydroxide has no effect. Alcoholic sodium hydroxide, even the dilute water-methyl alcohol-ether mixture used for preparing the yellow oxime from the parent substance, merely eliminates water and forms the isoxazole derivative. These observations show that the dihydroxyl compound behaves quite like the few[3] hydroxy-isoxazoline derivatives that have been described, and that the peculiar sensitiveness of the parent substance need be expected only when hydroxyl, carbonyl and the oxygen of the ring all meet at the same carbon atom.

3,4-Diphenyl-5-diphenylcarbinyl Isoxazole (VIII).—The carbinol is the only product of the reaction between the isoxazole and an *equivalent* quantity of phenylmagnesium bromide. It is moderately soluble in ether and in boiling methyl alcohol, crystallizes from ether in friable needles and from methyl alcohol in lustrous plates; m. p., 157–158°.

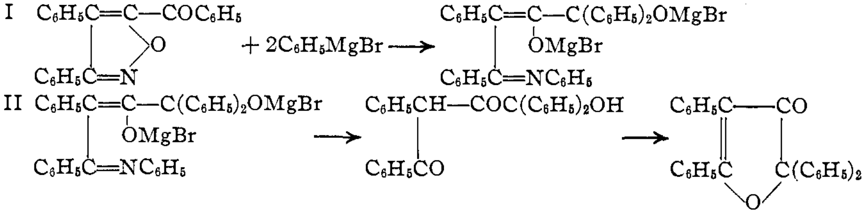
Anal. Calcd. for $C_{28}H_{21}O_2N$: C, 83.4; H, 5.2. Found: C, 83.0; H, 5.3.

Like triphenylcarbinol, which it resembles in many ways, this substance cannot be benzoylated either by the Schotten-Baumann reaction or by using pyridine as a condensing agent, but it forms ethers with the greatest ease. Its solution in sulfuric acid is deep orange-red.

The Methyl Ether.—The methyl ether, made by adding a few drops of acetyl chloride to a solution of the carbinol in methyl alcohol and boiling the mixture for a short time, crystallizes in stout, transparent prisms. It is very sparingly soluble in methyl alcohol, moderately soluble in acetone and melts at 182–183°.

Anal. Calcd. for $C_{29}H_{23}O_2N$: C, 83.4; H, 5.5. Found: C, 83.3; H, 4.4.

2,2,4,5-Tetraphenylfurone-3.—The furone, as has been stated, was, under certain conditions, obtained as a by-product of the reaction between the hydroxy-isoxazoline and phenylmagnesium bromide. It is always formed when excess of this magnesium compound reacts with the isoxazole. In these cases addition of bromine to the mother liquors that were left after the decomposition of the magnesium derivative and the removal of main products, always precipitated a mixture of tribromophenol and tribromo-aniline. Since the amount of phenol was apparently not in excess of that formed whenever phenylmagnesium bromide is made and used in contact with air, it is probable that the successive steps in the formation of the furone may be represented as follows.



The furone is most readily prepared in quantity by heating the dihydroxyl compound. This substance melts without decomposition but begins to effervesce and turn yellow a few degrees above the melting point. One lot of 20 g., that was heated for two hours at 180° under diminished pressure, gave a distillate composed of water, a little oil containing benzoic acid and benzonitrile, and a residue weighing 16.2 g. By crystal-

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[3] Widman, *Ber.*, **49**, 2778 (1916). Jörlander, *Ber.*, **49**, 2783 (1916).

lization from a mixture of acetone and methyl alcohol, this was separated into pure furone (10.2 g.) and diphenylcarbinyl-diphenyl isoxazole (5.1 g.).

Anal. Calcd. for $C_{28}H_{20}O_2$: C, 86.6; H, 5.2. Found: C, 86.8; H, 5.4.

The furone is very sparingly soluble in ether and methyl alcohol and moderately soluble in acetone. It crystallizes in very pale yellow plates; m. p., 178°. Like the highly phenylated unsaturated ketones it resists the action of all ordinary ketone reagents and even that of organic magnesium compounds.

Oxidation.—A saturated solution of the furone in chloroform slowly absorbed ozone. This produced white and orange precipitates which, when decomposed with water, gave a mixture of solid and oily substances that were evidently secondary products. By decomposing a similar mixture with a concd. bisulfite solution it was possible to isolate a small quantity of a dark yellow solid; m. p., 150°. The same solid was obtained in much larger amounts by cautious oxidation with chromic acid. For this purpose 8 g. of finely powdered furone was stirred into a solution of 6 g. of chromic acid in 500 g. of glacial acetic acid that was kept at 90°. All the solid disappeared within 15 minutes. The solution was warmed for another ten minutes and then poured into 5 liters of water. The resulting precipitate was washed with water and methyl alcohol and recrystallized from a mixture of acetone and methyl alcohol; yield, 6.1 g.

Anal. Calcd. for $C_{21}H_{16}O_3$: C, 79.4; H, 5.1. Found: C, 79.4; H, 5.1.

The substance is sparingly soluble in methyl alcohol and in ether and readily soluble in acetone. It crystallizes in stout, yellow needles or plates; m. p., 150°. It is not sensitive to acids, shows none of the peculiarities of triphenylcarbinol and does not form ethers as readily even as diphenylcarbinol. It is rapidly destroyed by bases but the result is not the usual cleavage between carbonyl groups. Thus, dil. sodium hydroxide in methyl alcohol very rapidly converts it into benzophenone and phenylglyoxal.

Oxidation.—A solution of 1.5 g. of chromic acid in glacial acetic acid was added slowly to a hot solution of 2 g. of the diketone in the same solvent. The mixture was immediately diluted with water and distilled with steam. This removed some benzophenone, benzoic acid and most of the acetic acid. From the residue ether removed a mixture of acids. This was partially separated by extraction with petroleum ether, which removed benzoic acid, and by recrystallization from water, which gave pure benzilic acid—identified by comparison with a specimen in hand.

Summary

1. A substance described in an earlier paper as an isoxazoline oxide is in reality an hydroxy-isoxazoline.

2. The peculiar sensitiveness of this substance is not a common property of hydroxy-isoxazolines; it need be expected only in those cases in which carbonyl, hydroxyl and the oxygen atom of the ring meet at the same carbon atom.

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