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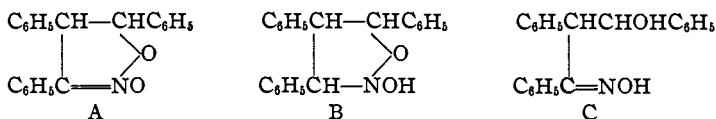
## ISOXAZOLINE OXIDES. X. REDUCTION

BY E. P. KOHLER AND A. R. DAVIS

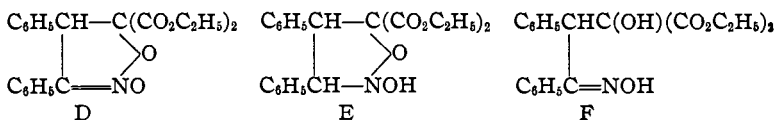
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In order to complete the work on isoxazoline oxides it was desirable to make a more careful study of their behavior toward reducing agents. Two of these oxides have been reduced, heretofore, both of them with zinc and acetic acid. Kohler and Barrett<sup>1</sup> added two atoms of hydrogen to triphenyl isoxazoline oxide (A) and interpreted the product as an hydroxy isoxazolidine (B); but it was found later<sup>2</sup> that the substance is, in reality, an hydroxy oxime (C).



Kohler and Barrett<sup>3</sup> also reduced the ethyl ester of an isoxazoline oxide dicarboxylic acid (D). Here again the reaction stopped with the addition of two atoms of hydrogen, and the product was likewise regarded as an hydroxy isoxazolidine (E). The evidence on which this formula was based is, however, no longer conclusive, and it now seems at least as probable that the substance is the hydroxy oxime (F).



We selected for reduction the ketonic isoxazoline oxide III, and decided to reduce it in steps, in order to note the result of a competition for hydrogen by the three reducible components, the carbonyl group, the unsaturated system  $\text{C}=\text{NO}$ , and the oxide group. Since bases very rapidly transform these ketonic oxides into other reducible substances, reduction in alkaline media was not attempted. These oxides are fairly stable in the presence of dilute acids but all attempts at reducing our substance with metal and acid ended in insoluble polymerization products too complex to unravel; reduction in acid media therefore did not prove feasible.

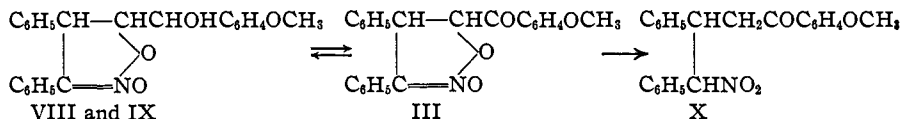
In view of the circumstances which have been described it became necessary to resort to catalytic hydrogenation in neutral solution. Preliminary experiments both with Willstätter's platinum black and with Adams' platinum oxide showed that while the hydrogenation occurs in stages which proceed at different rates, the stages overlap and that there is

<sup>1</sup> Kohler and Barrett, *THIS JOURNAL*, **46**, 2105 (1924).

<sup>2</sup> Kohler and Richtmyer, *ibid.*, **52**, 2038 (1930).

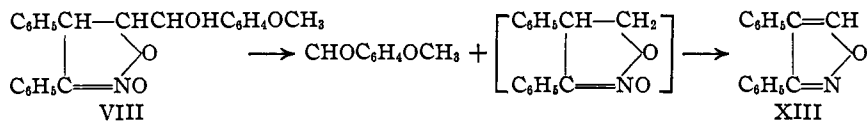
<sup>3</sup> Kohler and Barrett, *ibid.*, **48**, 1770 (1926).

no sharp break in the curve representing the speed of hydrogen absorption. Later operations were therefore carried out in an apparatus with which it was possible to measure the absorbed hydrogen with great accuracy and the process was interrupted as soon as one mole of hydrogen had been consumed. Under these circumstances the product was composed almost entirely of the three substances VIII, IX and X.

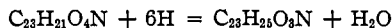


The relative amounts of the stereoisomeric carbinols VIII and IX varied slightly with the conditions, but, to our surprise, these two substances constituted by far the largest part of the primary reduction products. Thus in a typical experiment we obtained 55% of the higher-melting isomer VIII, 20% of the lower-melting isomer IX, 5% of X, and 20% of an oil which doubtless was composed largely of secondary products.

No less surprising is the generation of a nitro group by hydrogenation, but the proof of the structure of these primary reduction products is explicit. The nitro compound X is identical with the product obtained by adding phenyl nitro methane to benzal acetyl anisole. The other two reduction products, VIII and IX, liberate iodine from potassium iodide and chlorine from phosphorus pentachloride; they are, therefore, still oxides. Moreover, chromic acid removes the two hydrogen atoms that have been added and oxidizes the reduction products to the oxide from which they came, while potassium hydroxide cleaves them to anisic aldehyde and 3,4-diphenyl isoxazole.

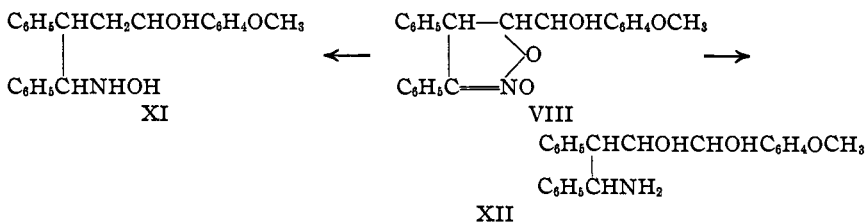


These new oxides, on further hydrogenation, absorb hydrogen more slowly but with great regularity until six additional atoms have been consumed. The solution then deposits a sparingly soluble compound which is formed in accordance with the equation



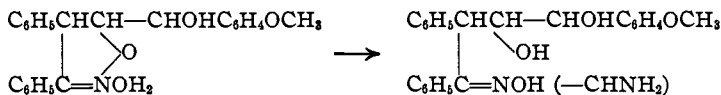
It is not possible to isolate any intermediate between the oxide and this final reduction product. If the operation is stopped short of this final stage, a corresponding quantity of oxide is recovered. For this final reduction product only two formulas have any probability. The formation of a substance with this composition manifestly involves the opening of the isoxazole ring. If this occurred between the oxygen and the carbon atom in the 5-position, as it does in the formation of X, the product would be the

hydroxylamine derivative XI. But it is at least equally probable that the ring is opened in the same manner as it is in triphenyl isoxazole, and this would lead to the formula of the amine XII. Since the reduction product is not only a strong base but also is not oxidized by Fehling's solution it evidently is not the hydroxylamine derivative



These results show quite conclusively that the hydrogen combines far more rapidly with the carbonyl group than it does with any part of the system  $\text{C}=\text{NO}$ . Combined with what had been learned heretofore by the reduction of isoxazoline oxides with metal and acid, they show also that the first step in the reduction is not removal of oxygen, as is the case with amine oxides,<sup>4</sup> azoxy compounds<sup>5</sup> and open-chained nitrones.<sup>6</sup> Nor is it 1,3-addition of hydrogen to the unsaturated system in the manner of the reaction between isoxazoline oxides and Grignard reagents.<sup>7</sup>

It seems not unlikely that the first step in the reduction of all types of oxido compounds is the same. These substances in reality contain an unsaturated oxygen atom. The primary stage in the reduction may well be the addition of hydrogen to this unsaturated oxygen atom; what happens subsequently depends upon the rest of the molecule. In the amine oxides and related substances, loss of water is inevitable because every possible rearrangement product would be unstable; in the isoxazoline oxides the primary product can undergo rearrangement to a stable oxime which may subsequently be reduced to an amine.



## Experimental Part

### Preparation and Proof of Structure

The starting point in the preparation of the oxide was an addition product previously obtained from benzal acetyl anisole and phenyl nitromethane.<sup>8</sup>

<sup>4</sup> Bamberger, *Ber.*, **32**, 342 (1899); Dunstan and Goulding, *J. Chem. Soc.*, **75**, 792 (1899).

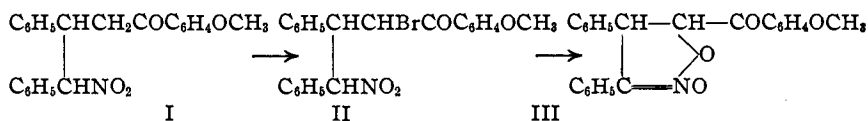
<sup>5</sup> Werigo, *Ann.*, **165**, 202 (1873).

<sup>6</sup> Angeli, *Atti Accad. Lincei*, **20**, I, 546 (1911).

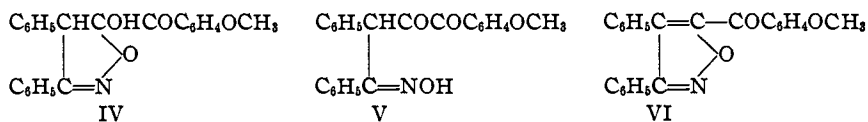
<sup>7</sup> Kohler and Richtmyer, *THIS JOURNAL*, **52**, 2038 (1930).

<sup>8</sup> Kohler and Allen, *ibid.*, **50**, 884 (1928).

This substance, on bromination, gave a mixture of  $\alpha$ -bromo compounds from which hydrogen bromide was eliminated with pyridine,



In proof that the compound thus obtained is an isoxazoline oxide, it was established that potassium acetate isomerizes it to an hydroxy isoxazoline (IV), and that bases convert it both into an open-chained triketone oxime (V) and also into an isoxazole derivative (VI). These are characteristic reactions of isoxazoline oxides.



**Bromination:**  $\alpha$ -Anisoyl- $\alpha$ -bromo- $\beta,\gamma$ -diphenyl- $\gamma$ -nitro Propane (II).—A solution of 100 g. of pure dry addition product in hot chloroform was brominated with 45 g. of bromine. At first only a few drops of bromine were added, the solution was boiled until the color disappeared, then the remainder was dropped into it as fast as it decolorized without further heating. When the solution is boiled during the bromination, and excess of bromine is allowed to accumulate in it, more than one equivalent of bromine is consumed and the product contains a polybromide which interferes with subsequent operations. After recrystallization from chloroform-methyl alcohol, the bromo compound melts at 165°. The crude product melting at 163° is sufficiently pure for nearly all purposes.

*Anal.* Calcd. for  $\text{C}_{23}\text{H}_{20}\text{O}_4\text{NBr}$ : C, 60.8; H, 4.4. Found: C, 60.5; H, 4.6.

**3,4-Diphenyl-5-anisoyl Isoxazoline Oxide (III).**—A suspension of 100 g. of the finely ground  $\alpha$ -bromo compound in 500 cc. of 95% alcohol and 70 g. of pyridine was heated to boiling. Solution was complete in fifteen minutes but the boiling was continued for another ten minutes. On cooling, the isoxazoline oxide separated from the pale purple solution. The crystalline material was collected on a filter, washed with 95% alcohol, then with dilute hydrochloric acid until free from pyridine, and finally with water until free from chloride. The first filtrate and the alcohol washings, on concentration and acidification, yielded 11 g. of crude product which gave 8 g. of recrystallized oxide, making the total yield 79 g. or 92%.

Absolute alcohol gave the same yield as 95% alcohol, but absolute methyl alcohol was found to be unsatisfactory because the reaction was very much slower at the lower boiling point. By recrystallization from chloroform-methyl alcohol the oxide was obtained in colorless needles melting at 158°. It is readily soluble in chloroform, sparingly soluble in methyl alcohol. It can be recrystallized without change from glacial acetic acid, does not reduce permanganate in acetone and is not affected by boiling with sodium dichromate in glacial acetic acid. It liberated iodine from potassium iodide in glacial acetic acid, and it liberated a mixture of chlorine and nitrosyl chloride when heated with phosphorus pentachloride.

*Anal.* Calcd. for  $\text{C}_{23}\text{H}_{19}\text{O}_4\text{N}$ : C, 74.0; H, 5.1. Found: C, 73.7; H, 5.2.

**Rearrangement: 3,4-Diphenyl-5-hydroxy-5-anisoyl Isoxazoline (IV).**—A solution containing 2 g. of the oxide, 1 g. of potassium acetate and a few drops of glacial acetic

acid in 20 cc. of dry methyl alcohol was boiled for an hour. It deposited the crystalline rearrangement product when cooled. The hydroxyl compound is, however, most conveniently prepared directly from the  $\alpha$ -bromo compound. For this purpose 15 g. of finely powdered bromo compound was suspended in a mixture of 325 cc. of methyl alcohol, 500 cc. of water, 20 g. of sodium hydroxide, and 200 cc. of ether. The mixture was shaken until all the bromo compound was in solution—about thirty minutes—then acidified with acetic acid and allowed to stand at room temperature for half an hour. It deposited 10 g. of the hydroxyl compound. This was pale yellow in color but on re-crystallization from chloroform–methyl alcohol, it became colorless and melted at 177°.

*Anal.* Calcd. for  $C_{23}H_{19}O_4N$ : C, 74.0; H, 5.1. Found: C, 74.1; H, 5.1.

The hydroxyl compound was readily soluble in chloroform, sparingly soluble in methyl alcohol. It crystallized from alcohol in colorless prisms, and from ether–petroleum ether in hexagonal plates. It crystallized unchanged from glacial acetic acid. Sodium peroxide oxidized it to anisic acid and diphenyl isoxazolone.

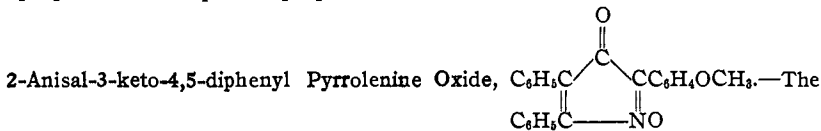
The Benzoate.—Like the hydroxy isoxazolines described in earlier papers in this series, our substance resisted all attempts to methylate it, but it was readily turned into a benzoate. To a solution of 1 g. of the substance in 5 cc. of dry pyridine, 1 cc. of benzoyl chloride was added. The pink solution was kept at room temperature for two hours, during which a solid separated. The mixture was diluted with water, acidified with hydrochloric acid and extracted with ether. The washed and dried solution, on evaporation, deposited the benzoate in silky needles which melted at 173°.

*Anal.* Calcd. for  $C_{30}H_{23}O_5N$ : C, 75.5; H, 4.8. Found: C, 75.3; H, 4.6.

$\alpha$ -Anisyl- $\gamma,\delta$ -diphenyl-butane-trione Oxime (V).—The yellow oxime is formed by the action of alkalis on both the oxide and the hydroxy isoxazoline, but it is most readily prepared directly from the  $\alpha$ -bromo compound. To this end the bromo compound is treated exactly as in the preparation of the hydroxy isoxazoline, but the yellow solution is acidified rapidly with iced hydrochloric acid instead of acetic acid. The yield is 74%.

*Anal.* Calcd. for  $C_{23}H_{19}O_4N(C_2H_5)_2O$ : C, 72.5; H, 6.5. Found: C, 72.3; H, 6.6.

Like all other substances of this type that are known, the oxime crystallizes in yellow prisms containing one molecule of ether. It melts with decomposition at 110°. When a methyl alcoholic solution of the oxime is boiled with a little potassium acetate and acetic acid, it is transformed almost quantitatively into the hydroxy isoxazoline, and when a drop of hydrochloric acid is added to a solution of the oxime in chloroform, it turns purple and soon deposits a purple nitrone.



purple nitrone crystallizes from the chloroform solution in fluffy needles melting at 182° with decomposition.

*Anal.* Calcd. for  $C_{23}H_{17}O_5N$ : C, 77.8; H, 4.8. Found: C, 77.7; H, 5.1.

3,4-Diphenyl-5-anisoyl Isoxazole (VI).—The isoxazole is formed by the action of bases on the  $\alpha$ -bromo compound, the polybromides, the isoxazoline oxide, the hydroxy isoxazoline and the triketone oxime; it represents the final degradation product of all of these substances by weak bases or dilute alkalis. In quantity, it is most conveniently obtained by suspending the  $\alpha$ -bromo compound in methyl alcohol, adding an equal weight of potassium acetate and boiling the mixture. The bromo compound soon dissolves and isoxazole begins to separate in compact crystals along with potassium

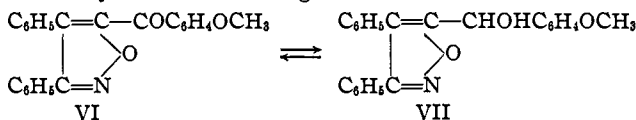
bromide. Since these solids cause serious bumping, it is necessary to filter from time to time and repeat the boiling, but in the end the yield of isoxazole is 94%.

*Anal.* Calcd. for  $C_{22}H_{17}O_3N$ : C, 77.7; H, 4.7. Found: C, 77.3; H, 4.9.

The isoxazole crystallizes in needles which melt at  $156^\circ$ . When pure it is quite colorless, but it usually has a pale yellow color which cannot be removed by recrystallization.

## II. Reduction

We examined the behavior toward reducing agents of the isoxazoline oxide, the hydroxy isoxazoline and the isoxazole. With zinc and acid all these substances except the isoxazole gave very sparingly soluble substances which were evidently condensation as well as reduction products. The isoxazole, however, readily combined with two atoms of hydrogen, being reduced to a substance which liberated a mole of gas from methyl magnesium iodide and which chromic acid reoxidized to the isoxazole—therefore evidently the carbinol ring is intact.



Hydrogenation in the presence of platinum likewise gave only complex products with the hydroxy isoxazoline and the yellow oxime, but with the isoxazoline oxide it gave mainly monomolecular products.

**Reduction of the Isoxazole.**—To a solution of 10 g. of the isoxazole in glacial acetic acid, which was heated on a steam-bath, zinc dust was added in small quantities over a period of two hours. The mixture was filtered, and the filtrate diluted with water, then extracted with ether. The extract, freed from acetic acid, dried and evaporated, deposited a small quantity of solid amid considerable oil which was presumably an acetate. The oil was boiled with methyl alcoholic potassium hydroxide for a short time, the solution diluted with water and extracted with ether. The ether now deposited the solid carbinol; yield, 6.8 g. By recrystallization from carbon tetrachloride-petroleum ether, the substance was obtained in colorless prisms which melted at  $146^\circ$ .

*Anal.* Calcd. for  $C_{22}H_{19}O_3N$ : C, 77.3; H, 5.3. Found: C, 76.6; H, 5.5.

**Oxidation.**—To 0.5 g. of the carbinol in 10 cc. of glacial acetic acid, sodium bichromate was added gradually until there was no further evidence of reduction. The mixture was diluted with water and extracted with chloroform. The extract was washed, dried and concentrated, then diluted with methyl alcohol. It deposited 0.35 g. of pure isoxazole.

**Reduction of the Oxide.**—For the purpose of reduction the oxide was repeatedly recrystallized from the same "reagent methyl alcohol" that was used as solvent in the reductions. The reductions were carried out under atmospheric pressure with a specially constructed apparatus with which it was possible to determine the absorbed hydrogen with great accuracy. The catalyst was Adams' platinum oxide.

In a typical experiment a suspension of 2 g. of the finely ground oxide and 0.2 g. of the catalyst in 100 cc. of methyl alcohol was shaken with hydrogen, using the calibrated apparatus. The oxide was completely in solution after ten minutes. By that time the solution had absorbed 124.9 cc. of hydrogen instead of 120 cc. calculated for two atoms and the operation was stopped immediately.

The yellow solution was decanted from most of the catalyst, filtered and boiled down to about a fourth of its volume. In order to remove a small quantity of colloidal platinum which made trouble unless it was removed at this point, a small quantity of active charcoal was added a few minutes before the boiling was discontinued. The solution was then filtered again and set aside. It deposited a solid which proved to be composed almost entirely of the high-melting reduction product VIII. It was purified by recrystallization from methyl alcohol; yield, 1.1 g.

The filtrate was allowed to evaporate to dryness. It deposited a mixture of large transparent prisms and long silky needles which were separated by hand and purified separately. The prisms (0.4 g.) were found to be a stereoisomer (IX) of the high-melting reduction product and the needles (0.1 g.) were identified as the nitro compound (I).

**3,4-Diphenyl-5-( $\alpha$ -hydroxy-4-methoxy-benzyl) Isoxazoline Oxide, VIII.**—The higher-melting reduction product crystallized from methyl alcohol in flat needles that melted without decomposition at 170°.

*Anal.* Calcd. for  $C_{23}H_{21}O_4N$ : C, 73.6; H, 5.6. Found: C, 73.6; H, 6.0.

The substance liberated iodine from potassium iodide and chlorine from phosphorus pentachloride as readily as did the original oxide.

**Oxidation.**—To a solution of 0.5 g. of the reduction product in boiling glacial acetic acid, sodium bichromate was added in small quantities until the red color of the bichromate appeared in the solution. The mixture was poured into water, which precipitated a solid product. After recrystallization from methyl alcohol, the solid melted at 156°, and the melting point was not changed when mixed with the original oxide; yield, 0.4 g.

**Cleavage.**—A suspension of 3 g. of the reduction product and 1 g. of solid potassium hydroxide in 20 cc. of methyl alcohol was boiled for thirty minutes. The yellow solution was diluted with water and extracted with ether. The washed and dried ethereal layer, when evaporated, left an oil. This was divided into two portions. To the first were added phenylhydrazine and a few drops of acetic acid. It deposited a solid which after purification melted at 122° and which was identified as the phenylhydrazone of anisic aldehyde by comparison with a sample made from the aldehyde.

The second half of the oil was dissolved in ether and freed from the aldehyde by means of saturated sodium bisulfite. The ethereal solution was washed with bicarbonate, dried and evaporated. It left an oil, but a solution of this oil in petroleum ether deposited a solid, which melted at 91° and was identified as diphenyl isoxazole. This will be described later.

**The Stereoisomeric Reduction Product, IX.**—The lower-melting reduction product behaved exactly like the substance which has just been described, liberating iodine from potassium iodide with the same ease and giving the same oxidation and cleavage products. It crystallized from methyl alcohol in six-sided prisms and melted at 160°.

*Anal.* Calcd. for  $C_{23}H_{21}O_4N$ : C, 73.6; H, 5.6. Found: C, 73.7; H, 5.7.

**Reduction of the New Oxide VIII:  $\alpha,\beta$ -Diphenyl- $\gamma,\delta$ -dihydroxy- $\delta$ -anisyl Butyl Amine, XII.**—Quantitative experiments showed that the new oxides are reduced much more slowly than the ketonic compound and that there is no break in the curve representing the rate at which hydrogen is absorbed until six atoms have disappeared. Moreover, an examination of the result of interrupting the process before six atoms of hydrogen had been used showed that all intermediates between the oxide and the final product are more rapidly reduced than the oxide.

Thus 2 g. of the oxide VIII in 100 cc. of methyl alcohol was shaken with hydrogen in the presence of 0.2 g. of platinum until 120 cc. had been absorbed. This required about two hours. The solution, manipulated in the usual manner, yielded 1.2 g. of the starting material and 0.5 g. of reduction product. Allowing for loss during crys-

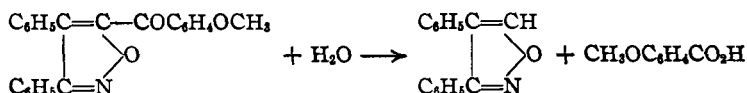
tallization, this quantity of reduction product corresponds to the absorption of six atoms of hydrogen.

In another experiment, 2 g. of the same oxide was reduced completely in seven hours and six atoms of hydrogen were used in the process. The product, isolated in the usual manner, crystallized in needles melting at 208°.

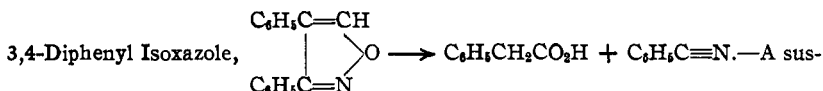
*Anal.* Calcd. for  $C_{22}H_{22}O_2N$ : C, 76.0; H, 6.9; mol. wt., 363. Found: C, 76.1; H, 6.8; mol. wt., 349.

### III. Diphenyl Isoxazole

Inasmuch as the reduction product of anisoyl diphenyl isoxazoline oxide is easily cleaved by alkalis, it seemed worth while to study the behavior of the isoxazole itself because a similar cleavage of this substance would result in a type of disubstituted isoxazole, for which no methods of preparation are known.



It was found that while this cleavage does not take place very readily it can be accomplished and that the yield may be brought to 88%. The structure of the isoxazole was established by ozonization, which led to a product that was hydrolyzed to  $\beta$ -benzil monoxime. Like all other isoxazoles which are not completely substituted, 3,4-diphenyl isoxazole can be further cleaved with alkalis. The mode of cleavage is similar to that of those mono-substituted isoxazoles which have no substituent in the 5-position.



pension of 10 g. of diphenyl anisoyl isoxazole in 50 cc. of 5% ethyl alcoholic potassium hydroxide was boiled for half an hour, then filtered. The operation was repeated with the unchanged isoxazole which had been collected on the filter until none of it was left. The alcoholic filtrates on dilution deposited the new isoxazole as a flocculent precipitate. It was dried and recrystallized from low-boiling petroleum ether; yield 5.5 g. or 88%.

*Anal.* Calcd. for  $C_{18}H_{11}ON$ : C, 81.4; H, 5.0. Found: C, 81.9; H, 5.1.

The isoxazole is readily soluble in all organic solvents. It crystallizes from low-boiling petroleum ether in colorless needles which melt at 91°.

**Ozonization.**—A current of ozonized oxygen containing about 6% of ozone was passed through a solution of 0.5 g. of the isoxazole in ethyl bromide for one and one-half hours. Addition of water and removal of solvent left a cream-colored oil, which was dissolved in 10% aqueous sodium hydroxide. The alkaline solution was extracted with ether, then gradually neutralized with carbon dioxide. It deposited a crystalline solid which was identified as the  $\beta$ -monoxime of benzil by comparison with a sample on hand.

**Alkaline Cleavage.**—A solution of 2 g. of the isoxazole in 20 cc. of 5% methyl alcoholic potassium hydroxide was boiled for two hours, then diluted with water and extracted with ether. The ethereal solution was dried over sodium sulfate and cautiously evaporated. It left an oil which had the odor of benzonitrile and which when boiled with 10% aqueous sodium hydroxide gave benzoic acid. The alkaline solution,



from which the benzonitrile had been removed. was acidified and again extracted with ether. The dried extract left an oil when evaporated, but a solution of this oil in petroleum ether deposited a solid melting at 75°. This was identified as phenylacetic acid by comparison with a sample.

### Summary

1. When a ketonic isoxazoline oxide 
$$\begin{array}{c} \text{R}-\text{CHCH}-\text{COR} \\ | \quad \diagup \text{O} \\ \text{R}-\text{C}=\text{NO} \end{array}$$
 is hydrogenated

it first takes up two atoms of hydrogen at the carbonyl group and forms a new oxide.

2. The reduction of isoxazoline oxides in which there is no carbonyl group doubtless always gives an open-chained hydroxy oxime as the first product; but in catalytic hydrogenations these oximes are reduced to amines.

3. 3,4-Disubstituted isoxazoles, heretofore unknown, can be prepared by cleaving ketonic isoxazoles with bases. When these 3,4-disubstituted isoxazoles undergo further cleavage, they behave like those mono-substituted isoxazoles which have no substituent in the 5-position.

CONVERSE MEMORIAL LABORATORY  
CAMBRIDGE, MASSACHUSETTS

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

## STEREOCHEMISTRY OF PHENYLPYRIDINE COMPOUNDS; THE PREPARATION AND INVESTIGATION OF 2-(2-CARBOXY- 6-CHLOROPHENYL)-PYRIDINE-3-CARBOXYLIC ACID AND 3-(2-CARBOXYPHENYL)-6-PHENYLPYRIDINE-2,4- DICARBOXYLIC ACID. X.<sup>1</sup>

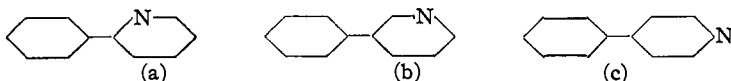
BY CATHERINE CASSELS STEELE<sup>2</sup> AND ROGER ADAMS

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A natural corollary to the development of the study of the optical isomerism exhibited by certain types of substituted diphenyl compounds is an investigation of binuclear compounds similar to diphenyl, and of these the dipyridines and the phenylpyridines resemble diphenyl most closely.

In the case of the phenylpyridines, only one ring—the pyridine nucleus—is different, and they may be divided into three classes; (a) where the N is "ortho," (b) where it is "meta" and (c) where it is "para" to the carbon atom linked to the phenyl nucleus.



Type (a) differs from (b) and (c) in the fact that there cannot be four

<sup>1</sup> For the last two papers in this series, see (a) Stanley and Adams, *THIS JOURNAL*, **52**, 4471 (1930); (b) Browning and Adams, *ibid.*, **52**, 4098 (1930).

<sup>2</sup> Commonwealth Fund Fellow.