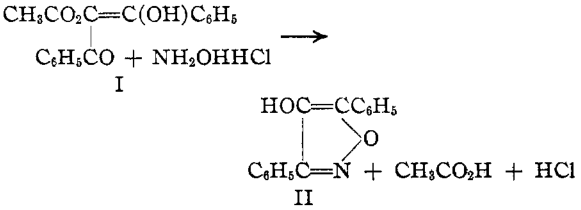
[Contribution from the Chemical Laboratory of Howard University]

3,5-Diphenyl-4-hydroxyisoxazole

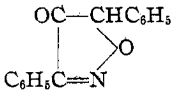
By A. H. Blatt and W. Lincoln Hawkins

Although isoxazolones having a carbonyl group in the 5-position (or their tautomers, the isoxazoles, having a hydroxyl group in the 5-position), are readily available and have been carefully investigated, the isoxazolones having a carbonyl group in the 4-position (or their tautomers, the 4-hydroxyisoxazoles), are practically inaccessible. We have recently found that the acetate of dibenzoylcarbinol (I) on treatment with hydroxylamine hydrochloride undergoes both hydrolysis and cyclicization to furnish a 4-hydroxyisoxazole —3,5-diphenyl-4-hydroxyisoxazole (II)—and in this paper we report a study of the behavior of this material.



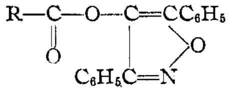
I

II

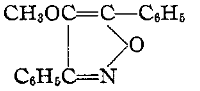


III

We have assigned the hydroxyisoxazole structure (II) rather than the tautomeric isoxazolone structure (III) to our heterocyclic material because it shows in the main the behavior of a phenol. Thus, it is soluble in dilute sodium hydroxide and is, in addition, sufficiently acidic to dissolve in alkali carbonates. Acyl derivatives (IV, R = CH_3 or C_6H_5) are formed when the isoxazole itself is treated with acetic anhydride and when its alkaline solution is treated with benzoyl chloride. With alkali and methyl iodide or sulfate the methyl ether (V) is formed. On oxidation with any one of a variety of oxidizing agents, the isoxazole forms a dimolecular oxidation product.

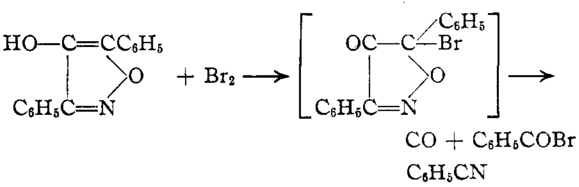


IV

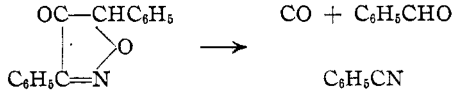


V

The remaining reactions of the isoxazole, bromination and pyrolysis, however, are novel. On bromination the material undergoes cleavage and, after the addition of water, benzonitrile and benzoic acid can be isolated. This cleavage is so rapid that in a Kurt Meyer titration, although the absorption of bromine is instantaneous, no bromo ketone can be detected. The process involved is best represented by the following equation



A similar cleavage takes place when the isoxazole itself is heated. In this case the reaction probably proceeds through the ketonic modification (III) for smooth pyrolysis to furnish benzonitrile, benzaldehyde and carbon monoxide takes place.



This pyrolysis, it may be remarked, is excellent evidence of the structural skeleton present in the substance.

Finally, mention should be made of a peculiar isomerism shown by the isoxazole. When heated in acetic acid with a crystal of iodine, the isoxazole (m. p. 123°) is converted into an isomer which melts at 151°. The behavior of this high melting isomer (pyrolysis, bromination, alkylation, acylation) is identical with that of the original isoxazole. Both isomers are sufficiently stable to permit recrystallization and both isomers can be dissolved in dilute alkali and recovered on acidification. The only method which we have found for returning from the high melting isomer to the low is *via* acetylation and hydrolysis of the acetate. At present we are unable to offer an adequate accounting for this isomerism, but work on this phase of the problem is still in progress and we hope to be able to report on it later.

Experimental

Preparation of 3,5-Diphenyl-4-hydroxyisoxazole (II).— A solution of 4.1 g. of hydroxylamine hydrochloride in 20 cc. of hot water was added to a solution of 11.3 g. of dibenzoylcarbinol acetate[1] in 80 cc. of alcohol and the whole was boiled for two hours, then diluted with 20 cc. of hot water. The hydroxyisoxazole (7.0 g.) which crystallized on cooling was filtered, dried, dissolved in 5% sodium hydroxide and filtered from a small amount of insoluble material The alkaline solution was acidified and the isoxazole was crystallized from ether and petroleum ether.

Anal. Calcd. for $C_{15}H_{11}O_2N$: C, 75.9; H, 4.6. Found: C, 75.7; H, 4.7.

3,5-Diphenyl-4-hydroxyisoxazole is quite soluble in ether and chloroform, moderately soluble in methyl and ethyl alcohols, and sparingly soluble in carbon tetrachloride and petroleum ether. The pure material melts with decomposition at 122–123°. It gives no copper derivative with copper acetate. On standing, especially when exposed to direct sunlight, the isoxazole turns pink and an odor of benzonitrile develops.

Acylation of the Isoxazole (II).—When the isoxazole is heated with an excess of acetic anhydride and the reaction mixture is poured into water, the acetate (IV, R = CH_3) is obtained. The acetate melts at 103°. It crystallizes well from ethyl alcohol and on treatment with alkali is hydrolyzed to regenerate the isoxazole.

Anal. (Acetate) Calcd. for $C_{17}H_{13}O_3N$: C, 73.1; H, 4.66. Found: C, 72.8; H, 4.47.

When the isoxazole dissolved in 5% sodium hydroxide is treated with benzoyl chloride, the benzoate (IV, R = C_6H_5) precipitates at once. The material is crystallized from ether and petroleum ether and melts at 157–158°. With acids it is hydrolyzed to benzoic acid and the isoxazole.

Anal. (Benzoate) Calcd. for $C_{22}H_{15}O_3N$: C, 77.4; H, 4.4. Found: C, 77.4; H, 4.2.

Methylation of the Isoxazole (II).—When the isoxazole in 5% sodium hydroxide was treated with an excess of methyl sulfate, the methyl ether precipitated at once. It was crystallized from ethyl alcohol.

Anal. Calcd. for $C_{16}H_{13}O_2N$: C, 76.5; H, 5.2; OCH_3, 12.35. Found: C, 76.4; H, 5.3; OCH_3, 12.75.

The methyl ether (V) melts at 69–70°. It dissolves readily in ether and benzene, sparingly in ethyl alcohol. The ether is insoluble in alkali and is much more stable to light than the parent isoxazole. A Zeisel determination shows the presence of a methoxyl group.

Oxidation of the Isoxazole (II).—The isoxazole can be oxidized by means of nitrous or nitric acid, potassium permanganate or dichromate, and ferric chloride. Potassium permanganate is the most convenient. Thus, when 1.6 g. of the isoxazole was treated with an excess of alkaline permanganate and the reaction was worked up in the usual manner, 1.3 g. of the oxidation product was obtained. The material was purified by crystallization from alcohol and water and melted at 110–112°.

Anal. Calcd. for $C_{30}H_{20}O_6N_2$: C, 73.7; H, 4.1. Found: C, 73.5; H, 3.9.

Action of Bromine on the Isoxazole (II).—A solution of 1.18 g. of the isoxazole in chloroform chilled to 0° was mixed with a solution of the calculated amount of bromine in 25 cc. of cold chloroform. The bromine was immediately taken up and hydrogen bromide was evolved. Evaporation of the chloroform at a low temperature left an oil, with the odor of benzonitrile, and a small amount of solid material. The oil on treatment with alkaline hydrogen peroxide[2] was converted to benzamide (mixed m. p.); the solid was dissolved in alkali and when precipitated with acid was shown to be benzoic acid.

Pyrolysis of the Isoxazole (II).—Two and four-tenths grams of the isoxazole was heated at 135° until it had melted completely. It was then distilled at reduced pressure. The clear distillate was dissolved in ether and shaken with bisulfite solution. The ether layer was evaporated and benzonitrile was identified by hydrolysis to benzamide.[2] The bisulfite layer and precipitate were treated with sodium carbonate solution and the benzaldehyde thus liberated was identified by conversion to the phenylhydrazone.

When a small amount of isoxazole was heated in a tube connected to a gas buret, a considerable amount of gas was collected. The presence of carbon monoxide in this gas was shown by the reduction of palladous chloride to palladium.[3]

Conversion of the Isoxazole (II) to the High Melting Isomer.—A crystal of iodine was added to 1.0 g. of the isoxazole dissolved in 20 cc. of glacial acetic acid and the reaction mixture was boiled for one hour, then cooled and poured onto ice and water. The iodine was removed with thiosulfate solution and the solid material, after filtering and drying, was crystallized from methyl alcohol.

Anal. Calcd. for $C_{15}H_{11}O_2N$: C, 75.9; H, 4.6. Found: C, 75.7, 75.6; H, 4.6, 4.6.

The pure material melts at 151° with decomposition. Its chemical behavior is the same as that of the isoxazole itself.

Summary

A description is given of the preparation and behavior of 3,5-diphenyl-4-hydroxyisoxazole.

WASHINGTON, D. C. RECEIVED JULY 31, 1934

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[1] Neufville and Pechmann, *Ber.*, **23**, 3375 (1890).

[2] McMaster and Langreck, THIS JOURNAL, **39**, 104 (1917).

[3] Christian and Randall, *J. Biol. Chem.*, **102**, 595 (1933).