[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HOWARD UNIVERSITY]

THE TAUTOMERISM OF OXIMES

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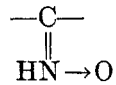
The oximes are tautomeric substances in that they furnish both oximino (I) and nitronic (II) derivatives. In addition, when certain special structural requirements in the remainder of the molecule are satisfied, they may furnish cyclic derivatives corresponding to structures I and II.

I



II

The examples of individual oximes which furnish both oximino and nitronic derivatives are far too numerous even for listing,[1] but, by contrast, the cases in which the tautomeric possibilities of oximes have been explored in detail and where derivatives of tautomeric modifications of pairs of stereoisomeric oximes have been obtained and studied are limited to the following four.

Semper and Lichtenstadt[2] isolated and characterized the methyl ethers and *N*-methyl derivatives of both oximes of phenyl *p*-tolyl ketone, while Plowman and Whitely[3] secured comparable derivatives from the oximes of mesoxmono-*p*-tolylamide (III). Brady and Mehta[4] described the methyl ethers and *N*-methyl derivatives of both oximes of *p*-nitrobenzophenone, and Griffiths and Ingold[5] obtained from *o*-phthalaldehyde derivatives of the open-chain oxime, and isolated cyclic oximino and nitronic modifications. This last work we shall discuss in some detail later. To this brief list we have now to add another example of oxime-nitrone tautomerism which involves also ring-chain tautomerism. The case in point is furnished by the monoximes of *cis*-phenyldibenzoylethylene (IV).

III

IV

[1] *Cf.* FREUDENBERG, "Stereochemie," Franz Deuticke, Vienna, **1933**, pp. 992-6 and 1035-6.

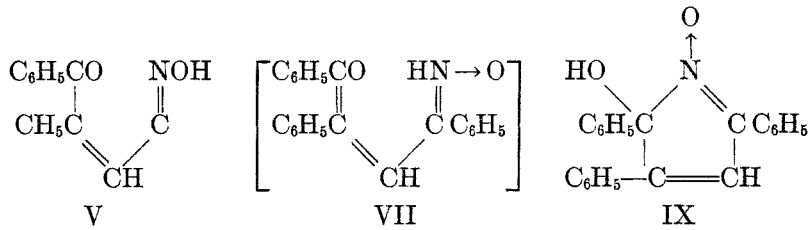
[2] SEMPER AND LICHTENSTADT, *Ber.*, **51**, 928 (1918).

[3] PLOWMAN AND WHITELY, *J. Chem. Soc.*, **125**, 587 (1924).

[4] BRADY AND MEHTA, *ibid.*, **125**, 2297 (1924).

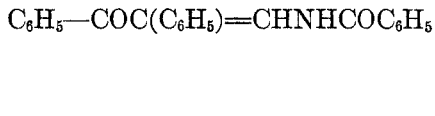
[5] GRIFFITHS AND INGOLD, *ibid.*, **1925**, 1698.

When *cis*-phenyldibenzoylethylene (IV) is treated with hydroxylamine in acidic or basic solution only the relatively unhindered carbonyl group reacts with the reagent. From the two monoximes, (V) and (VI), two nitronic tautomers, (VII) and (VIII), and two cyclic modifications, (IX) and (X), are possible. Of these six tautomers we have isolated, as such or in the form of derivatives, the four corresponding to the unbracketed formulas below. The two modifications which could not be isolated are, as will be pointed out in more detail later, precisely those from which ring closure to the cyclic tautomers would be expected to take place, and their non-existence constitutes to the best of our information the first chemical evidence as to the configuration of oxime derivatives of the nitronic type.

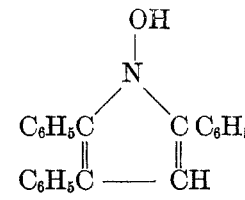


In earlier work it was shown[6] that when *cis*-phenyldibenzoylethylene and hydroxylamine hydrochloride react the product is the hydroxypyrrolenine nitrone (IX) which can be converted to and obtained from the open chain oxime (V). The cyclic nitrone is stable in acid media while the oxime is stable in alkaline media. Presumably, in the reaction between the diketone and hydroxylamine hydrochloride, the oxime is first formed and is then converted to the nitrone in the acid solution. The structure and configuration of the oxime (V) were established by a Beckmann rearrangement to the amide (XI) and by the hydrolysis of this amide to benzoic acid, formic acid, desoxybenzoin, and ammonia. The structure of the cyclic nitrone (IX) was shown by its reduction, *via* the hydroxypyrrole (XII), to triphenylpyrrole (XIII).

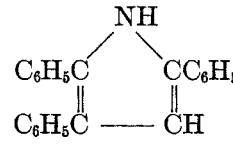
[6] BLATT, *J. Am. Chem. Soc.*, **56**, 2774 (1934); **58**, 590 (1936).



XI



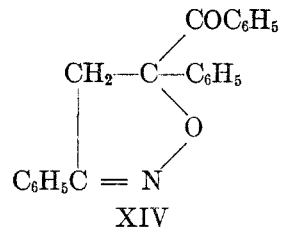
XII



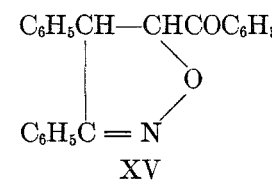
XIII

In none of the reactions of the oxime (V) or the nitrone (IX) was there obtained any evidence for the existence of the open-chain nitrone (VII).

In the experimental portion of this article are found the details of the reaction between *cis*-phenyldibenzoylethylene and hydroxylamine. This reaction was first studied by Olivera-Mandalà and Calderaro[7] who obtained a product melting at 140–141°, which had the composition of a monoxime of the diketone, was inert toward all the reagents which they tried, and which they considered to be an isoxazoline—either (XIV) or (XV). We have never succeeded in isolating this material but this failure is none too surprising, for the reaction between phenyldibenzoylethylene and hydroxylamine, like that between benzalacetophenone and the same reagent,[8] is unusually complex, and in order to secure reproducible results must be carried out under rather carefully specified conditions. Operating as we did the principal product of the reaction was found to be the hydroxyorthoxazine (X).



XIV



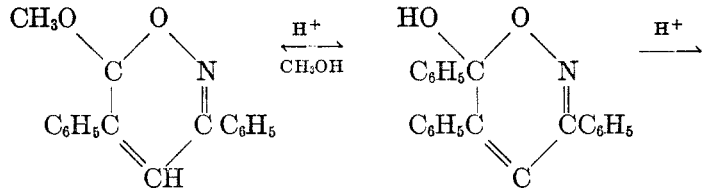
XV

The most striking feature of the chemical behavior of the orthoxazine (X) is its sensitivity to acids. With methyl alcohol and hydrochloric acid

[7] Olivera-Mandalà and Calderaro, *Gazz. chim. ital.*, **44**, II, 85 (1914).

[8] Fleck, Dissertation, Leipzig, **1903**; Auwers and Müller, *J. prakt. Chem.*, **137**, 57 (1933).

it furnishes in a rapid reaction the methyl ether (XVI). In all probability this etherification, like that of so many tertiary alcohols and glycosides, is readily reversible for if contact with the alcoholic acid is at all prolonged a characteristic cleavage to benzonitrile and the dimethyl acetal of phenylbenzoylacetaldehyde (XVII) occurs. The acetal is obviously a secondary product, for acetic acid alone brings about direct cleavage of the hydroxyorthoxazine to benzonitrile and oxymethylene desoxybenzoin, and oxymethylene desoxybenzoin, as has recently been shown,[9] furnishes with hydrochloric acid and methyl alcohol the acetal (XVII). The acid cleavage establishes the carbon chain present in the orthoxazine as well as the location of the nitrogen atom, while the ease of etherification indicates the presence of a tertiary, glycosidic hydroxyl group.



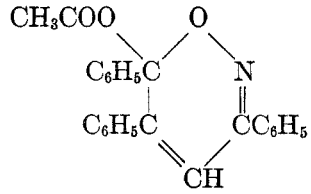
XVI X

$$C_6H_5—CN + C_6H_5—COC(C_6H_5)=CHOH$$
$$+$$
$$C_6H_5—COCH(C_6H_5)CH(OCH_3)_2$$

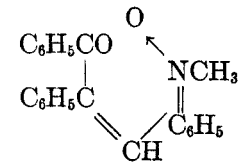
XVII

From the orthoxazine (X) it was not possible to secure either reactions of or derivatives of the open chain oxime (VI) but derivatives of the open-chain nitrone (VIII) could be secured. With acetic anhydride, the orthoxazine furnishes the acetate (XVIII) which is easily converted to the ether (XVI). With benzenesulfonyl chloride there is no reaction, and with phosphorus pentachloride the principal process is cleavage. The orthoxazine, which is insoluble in aqueous alkali, dissolves readily in alcoholates, and these solutions on treatment with methyl iodide yield, together with small amounts of the methoxyorthoxazine (XVI), principally the methyl derivative (XIX) of the open-chain nitrone. The structure of this methylation product follows from its ready hydrolysis by hydrochloric acid to *cis*-phenyldibenzoylethylene and β-methylhydroxylamine hydrochloride.

[9] BLATT, *J. Am. Chem. Soc.*, **60**, 1164 (1938).



XVIII



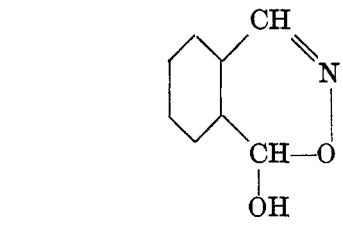
XIX

The information obtained from the study of the monoximes of *cis*-phenyldibenzoylethylene and presented in the preceding paragraphs constitutes, it is believed, the most complete description available up to this time of oxime tautomerism in all its forms. The most interesting result of the study is that it makes possible the assignment of configurations to the nitronic tautomers of oximes and to their derivatives. The basis for assigning these configurations is the following. The configuration of the oxime (V) follows from its behavior on a Beckmann rearrangement assuming a *trans* shift to have taken place. The nitronic tautomer of this oxime could be either (VII) or (VIII). But (VII) is precisely the tautomer which on structural and steric grounds would be expected to be the precursor of the cyclic nitrone (IX) and consequently the configuration (VII) is the one to be assigned to the non-existent open-chain nitronic tautomer of (V). In converse fashion the stereoisomeric oxime (VI) is, on structural and steric grounds, the precursor of the hydroxyorthoxazine (X) and the non-existence of the oxime (VI) is understandable on this basis. The open-chain nitronic tautomer of this oxime has, by exclusion, the configuration (VIII) and such a configuration is consistent with the existence of derivatives of this tautomer. The configurations thus arrived at are, it will be noticed, those which correspond to the respective oximes with which the nitrones are tautomeric and no shifts in the relative positions of the oxygen and nitrogen atoms are involved in the tautomerism. This is only reasonable and to be expected but it is nevertheless satisfying to have substantiating evidence from ring closure. Especially is this true since in the past it has been generally assumed that the alkyl derivatives of the nitronic tautomers of the oximes corresponded in configuration to the oximes from which they were prepared and this correspondence has been used as the basis of one method of assigning configurations to the oximes themselves.[10]

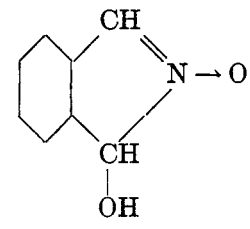
If the conclusions arrived at in the last paragraph with respect to the configurational relationship between an oxime and the tautomeric nitrone are generally valid, then it follows that Griffiths and Ingold[5] in their study of the cyclic tautomers of *o*-phthalaldehyde monoxime, mentioned at the

[10] SUTTON AND TAYLOR, *J. Chem. Soc.*, **1931**, 2190.

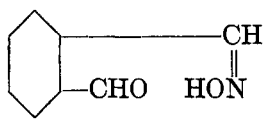
beginning of this article, were dealing with a more complex situation than was realized at the time. For they obtained from *o*-phthalaldehyde and hydroxylamine the two products (XX) and (XXI) which are the cyclic modifications corresponding to the oxime (XXII) and the nitrone (XXIII). These results indicate that both stereoisomeric oximes, (XXII) and (XXIV), are formed in the reaction between the aldehyde and hydroxylamine, and that they undergo cyclicization, the former in the oximino form and the latter in the nitronic form.



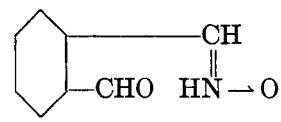
XX



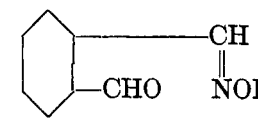
XXI



XXII



XXIII



XXIV

EXPERIMENTAL

The course of the reaction between *cis*-phenyldibenzoylethylene and hydroxylamine varies so widely with the concentrations of the reactants and the operating conditions that, in order to obtain the hydroxyorthoxazine (X), it is essential to adhere closely to the following directions. A solution of 5.6 g. (0.08 mole) of hydroxylamine hydrochloride in 10 cc. of water is chilled and added to a cold solution of 3.2 g. (0.08 mole) of sodium hydroxide in 10 cc. of water. The resulting alkaline solution is added to 12.5 g. (0.04 mole) of *cis*-phenyldibenzoylethylene dissolved in 200 cc. of boiling alcohol. The orange colored reaction mixture is kept gently boiling for an hour during which time an odor of benzonitrile develops and a small precipitate of sodium chloride forms. It is then diluted with 140 cc. of hot water, which dissolves the salt, and allowed to cool slowly.

The precipitate of hydroxyorthoxazine (X) which forms on cooling is filtered and dried.* The crude product, which is obtained in the form of glistening plates, discolored yellow, weighs between 5.3 and 5.8 g. It is crystallized by solution in 50 cc. of hot alcohol, filtration and addition of 15 cc. of hot water to the filtrate.

* The filtrate on standing turns dark and occasionally deposits a colorless solid which is sparingly soluble in alcohol and which, when purified by crystallization from that solvent, melts at 191–192°. This material furnishes on analysis the following figures: C, 80.3; H, 6.0. This composition corresponds roughly to the substance, $C_6H_5COCH(C_6H_5)CH(NH_2)COC_6H_5$ (calc'd for $C_{22}H_{19}NO_2$: C, 80.24; H, 5.8), and the material gives a positive isonitrile test. It was not examined further, however, since it was not regularly obtained.

This furnishes from 5.0 to 5.5 g. of product which melts at 159-160°. Material of this degree of purity is satisfactory for all the reactions of the orthoxazine but it retains a very slight yellow color which can only be removed by repeated crystallization. Removal of the color in this way does not change the melting point.

Anal. Calc'd for $C_{22}H_{17}NO_{12}$: C, 80.7; H, 5.2.
Found: C, 80.8; H, 5.35.

3,5,6-Triphenyl-6-hydroxyorthoxazine (*X*) is moderately soluble in hot alcohol and sufficiently soluble in the cold to make it advisable to add water to its alcoholic solutions on crystallization. It is only sparingly soluble in carbon tetrachloride, ether and petroleum ether and is moderately soluble in methyl alcohol, acetone, benzene and chloroform. It is destroyed by prolonged heating with alcoholic alkali. Benzenesulfonyl chloride in pyridine, cold, is without effect on the orthoxazine but phosphorus pentachloride in ether causes cleavage to benzonitrile. In the pentachloride reaction there is occasionally obtained a small amount of a high-melting solid; the yield is so small, however, and the reaction so erratic that the material was not examined in any detail.

Action of acids on the orthoxazine (*X*).—When 0.3 g. of the hydroxyorthoxazine was dissolved by warming in 1.9 cc. of methyl alcohol and 0.1 cc. of concentrated hydrochloric acid, the solution became milky after two to three minutes and solidified when rubbed with a glass rod. Filtration furnished 0.25 g. of the methyl ether (XVI), which melted at 105-107°, and crystallization from methyl alcohol yielded the pure ether melting at 108°.

Anal. Calc'd for $C_{23}H_{19}NO_2$: C, 80.9; H, 5.6; OCH_3, 9.1.
Found: C, 81.4; H, 5.4; OCH_3, 9.1.

Throughout the etherification of the orthoxazine as described in the last paragraph there is a persistent odor of benzonitrile. This has its origin in the simultaneous cleavage of the orthoxazine which is brought about by acids and which can be carried out either with the orthoxazine or its methyl ether and in the presence or absence of alcohol. The following experiments are typical.

When 0.3 g. of the hydroxyorthoxazine (X) was dissolved by warming in 2.5 cc. of methyl alcohol and 0.1 cc. of concentrated hydrochloric acid and the solution was left overnight, it deposited on chilling 0.2 g. of the dimethylacetal of phenylbenzoylacetaldehyde (XVII) which was identified by comparison with a synthetic sample of the acetal.[9] Similarly, when 3.25 g. of the methoxyorthoxazine (XVI) suspended in 25 cc. of methyl alcohol and 1 cc. of concentrated hydrochloric acid was warmed for a half hour then left overnight, the pale yellow solution on chilling deposited 1.6 g. of the acetal (XVII) which was identified by a mixture melting point determination. The filtrate, after the separation of the acetal, was shaken out with ether and water, then with 10% sodium hydroxide. The ether extract on evaporation left an oil which smelled of benzonitrile and which furnished 1.0 g. of benzamide on hydrolysis with hydrogen peroxide and alkali.[11] Cleavage in the absence of alcohol is illustrated by the following experiments. When the orthoxazine (X) was dissolved by warming in glacial acetic acid, the acid removed by evaporation over potassium hydroxide at room temperature in a desiccator and the residue distilled in vacuum, benzonitrile was identified in the distillate by hydrolysis to benzamide. In a parallel experiment starting with the methoxyorthoxazine (XVI), oxymethylene desoxybenzoin was identified in the distillate by the formation of its copper derivative with copper acetate, by the melting point of a mixture of this copper derivative with a synthetic sample, and by the characteristic wine-red coloration

[11] McMaster and Langreck, *J. Am. Chem. Soc.*, **39**, 114 (1917).

shown by the alcoholic solution of the copper derivative on the addition of ferric chloride.[12]

Acetylation of the orthoxazine (*X*).—When 0.5 g. of the hydroxyorthoxazine was dissolved by warming in 2 cc. of acetic anhydride and the solution, after cooling, was poured into water the acetoxyorthoxazine (XVIII) was formed in quantitative yield. For analysis the product was crystallized from alcohol.

Anal. Calc'd for $C_{24}H_{19}NO_3$: C, 78.0; H, 5.1.
Found: C, 77.9; H, 5.25.

3,5,6-Triphenyl-6-acetoxyorthoxazine (*XVIII*) is sparingly soluble in alcohol and crystallizes splendidly from that solvent in colorless, transparent cubes which melt at 117–118°. The close relationship of this acetate to the hydroxyorthoxazine (X) is shown by its behavior toward alcoholic acid and alkali. When 0.5 g. of the acetate was dissolved by warming for two minutes with 1.9 cc. of methyl alcohol and 0.1 cc. of concentrated hydrochloric acid, the odor of methyl acetate was very noticeable. On scratching the warm solution with a glass rod, 0.4 g. of the methoxyorthoxazine (XVI), identified by a mixture melting point determination, precipitated. Similarly when 0.5 cc. of normal sodium hydroxide was added to a solution of 0.18 g. of the acetate in 3 cc. of hot ethyl alcohol, the reaction mixture turned yellow and the odor of ethyl acetate was apparent. After five minutes, dilution with 2.5 cc. of water and chilling furnished 0.1 g. of the hydroxyorthoxazine (X).

Methylation of the orthoxazine (*X*).—When 3.3 g. of the orthoxazine was dissolved in 20 cc. of sodium methylate solution containing 0.46 g. of sodium, a clear yellow solution resulted. Four grams of methyl iodide was added and the reaction mixture was left at room temperature for twenty hours. Cautious addition of a small volume of water precipitated 0.8 g. of the methoxyorthoxazine (XVI). The filtrate, after removal of this precipitate, was taken up in ether and shaken out with water. The ether extract furnished 2.0 g. of the nitrone (XIX)—part of which precipitated in the separatory funnel—and an additional 0.15 g. of the methoxyorthoxazine. The nitrone was crystallized from methyl alcohol and melted at 167°.

Anal. Calc'd for $C_{23}H_{19}NO_2$: C, 80.9; H, 5.6.
Found: C, 80.97; H, 5.7.

The structure of the nitrone (XIX), which showed no methoxyl groups in a Zeisel analysis, was determined by hydrolysis. A solution of 1.1 g. of the nitrone in 5 cc. of methyl alcohol and 0.5 cc. of hydrochloric acid was heated on the steam bath for thirty minutes. Addition of 5 cc. of water precipitated 1 g. of *cis*-phenyldibenzoylethylene, identified by a mixture melting point, and evaporation of the filtrate after removal of this precipitate left a crystalline residue of β-methylhydroxylamine hydrochloride which melted at 82–85° and reduced Fehling's solution in the cold.[13]

SUMMARY

When *cis*-phenyldibenzoylethylene reacts with hydroxylamine in acidic or basic solution only the relatively unhindered carbonyl group is involved. From the two stereoisomeric monoximes thus formed, two nitronic tautomers and two cyclic tautomers are theoretically possible. Four of these six tautomers have been described, and it has been shown that each nitrone has the same configuration as the oxime with which it is tautomeric.

[12] WISLICENUS AND RUTHING, *Ann.*, **379**, 242 (1911).
[13] KIRPAL, *Ber.*, **25**, 1715 (1892).