A New Route to 2-Styrylbenzimidazoles

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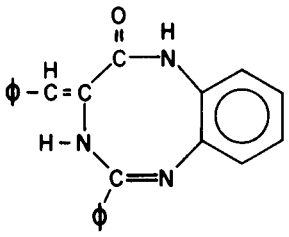
An attempt was made to prepare 2-benzylquinoxalin-3-one by hydrolyzing the azlactone, 2-phenyl-4-benzylidene-5-oxazolone to β-phenylpyruvic acid and then treating this *in situ* with *o*-phenylenediamine (OPDA). The initial hydrolysis apparantly proceeded only as far as opening the azlactone ring forming 2-benzamidocinnamic acid which condensed with OPDA to form a substituted styrylbenzimidazole.

Quinoxalinones can be formed readily by treating α-ketoacids with *o*-phenylenediamine (OPDA) (2a,b). Since β-phenylpyruvic acid is unstable, it was decided to circumvent its isolation by hydrolyzing 2-phenyl-4-benzylidene-5-oxazolone, the azlactone precursor in an acid medium and treat the product with OPDA *in situ*. Since the hydrolysis of an azlactone and the condensation of ketoacids with OPDA are both acid catalyzed, the reaction was expected to proceed.

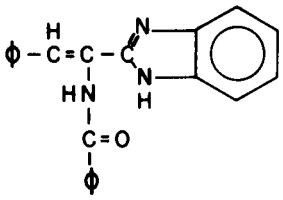
The first attempts to carry out the reaction in aqueous acid (hydrochloric acid or 50% acetic acid) proved futile; the azlactone did not dissolve and was quantitatively recovered unchanged. Upon the addition of dioxane, all reactants dissolved and the reaction proceeded smoothly. A white crystalline homogenous (by TLC) product was isolated.

The desired 2-benzylquinoxalin-3-one was not obtained, but on purification a white crystalline unknown with a m.p. of 250° was isolated in 44% yield. In contrast, the expected quinoxalin-3-one, m.p. 198°, was formed when pure β-phenylpyruvic acid was prepared and then treated with OPDA following the procedure of Morrison (2a). Since the ir, uv and nmr was insufficient for positive identification of the unknown, a structural determination was required. The analytical data was a determining factor in concluding that a styrylbenzimidazole was the product isolated.

The ir spectrum was compatible with what was first believed to be the desired quinoxalin-3-one and although a definite hydroxyl band was not present, the amide band from the expected tautomeric form was, (6). However, the elemental analysis did not agree with the calculated value. The condensation proceeded with the loss of two moles of water. After an examination of the nmr spectrum it was concluded that the compound lacked a methylene group which is an integral portion of a benzyl group. The authentic quinoxalinone made from β-phenylpyruvic acid did show the expected nmr spectrum. It was then concluded that the desired quinoxalinol or quinoxalinone was not the product of the reaction. No other useful data were obtained from the nmr since no known group was present which could be used as a reference. The methoxy derivative was made and its nmr spectrum studied. The integration revealed 19 protons, indicating that the original product contained 17 protons which verified a condensation with the loss of two moles of water.



1



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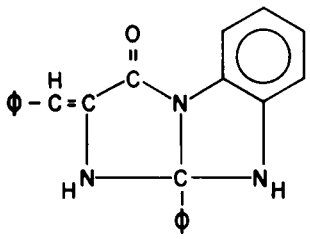

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The unknown product could be one of three possible structures which satisfied both the analytical and spectral data. These are given as **1**, **2**, and **3**. A reasonable mecha-

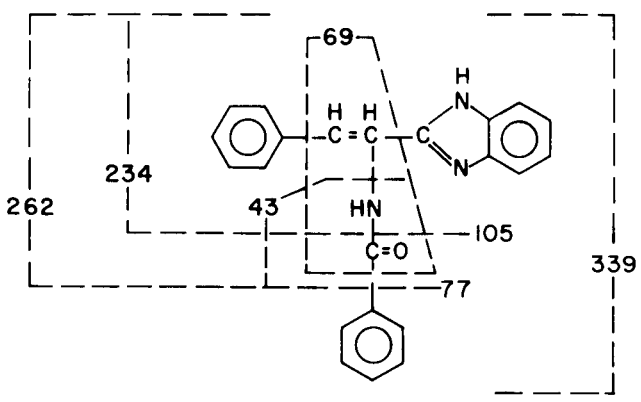


Figure 1. Prospective diagram for mass spectra.

nism could be suggested for the formation of structures **1** and **2** from the reactants. Structure **3** would not likely be formed, although Metlesics *et al.*, (7) did postulate a compound such as this from a similar reaction. Of the three possible formulae, structure **2** was sterically favored and had greater conjugation.

A prospective diagram was made of **2** to see what could be expected from an interpretation of the mass spectrum (Figure 1). After analysis the anticipated peak at 105 was found indicating the presence of a benzoyl group. This can be inferred from structure **2**, but not from **1** or **3**. The molecular weight was 339. Other strong peaks were 43, 69, 71, 77, 234, and 262, all of which can reasonably be shown as fragments of structure **2**.

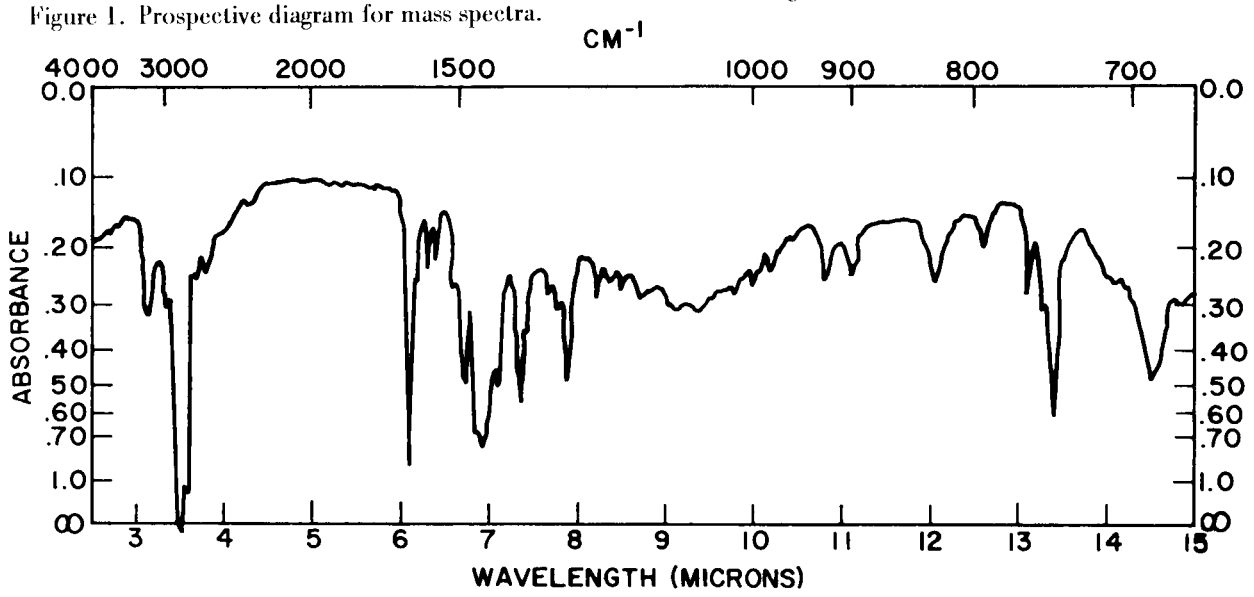


Figure 2. Infrared spectrum of 2-(α-Benzamidostyryl)benzimidazole.

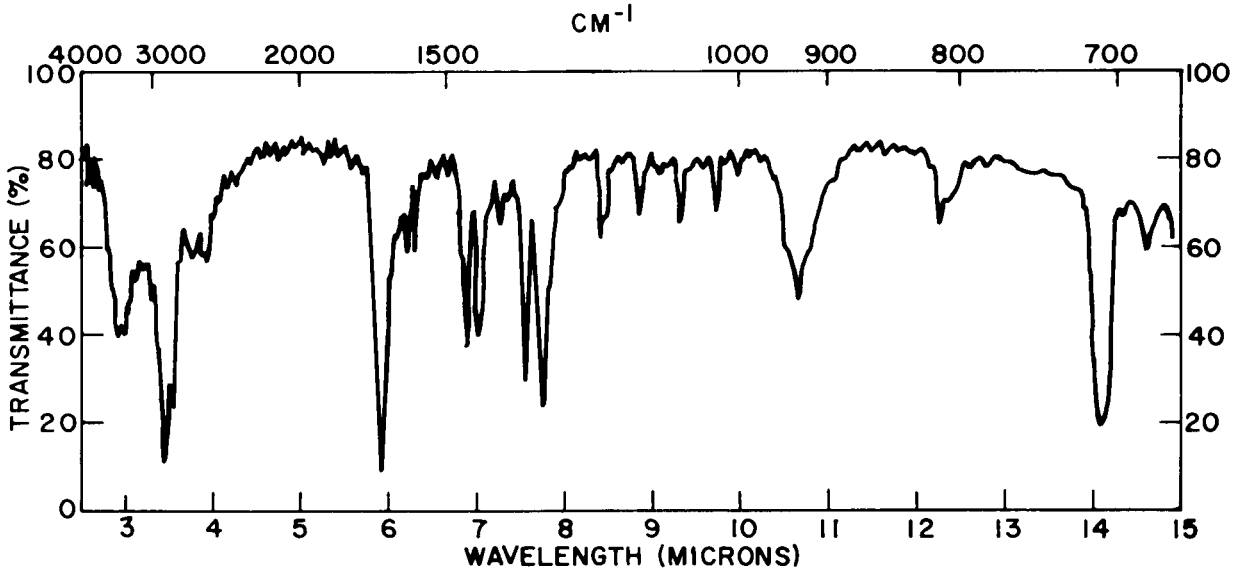
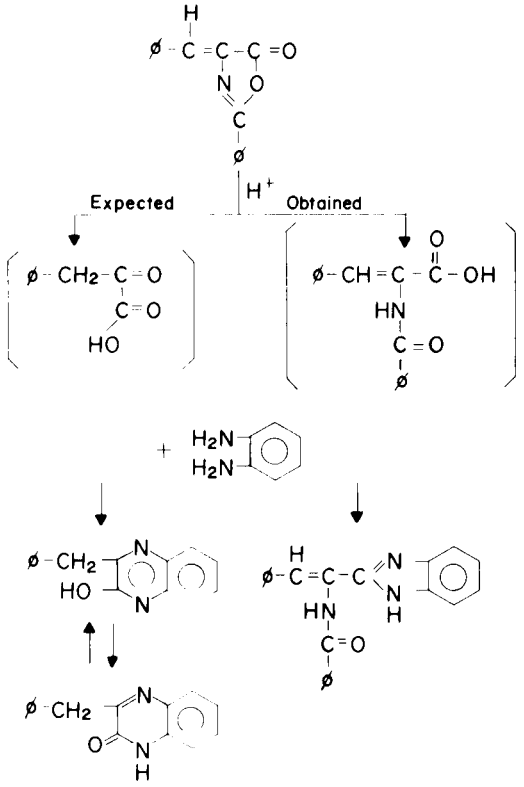


Figure 3. Infrared spectrum of oxidation product of II. Benzimidazole-2-carboxylic acid.

Scheme I



This benzimidazole on oxidation with permanganate should yield benzimidazole-2-carboxylic acid, as should 2-methylbenzimidazole. Oxidation of 2-methylbenzimidazole gave a small yield of the acid. The initial attempts to oxidize the unknown resulted only in the isolation of benzoic acid. Benzimidazole-2-carboxylic acid was later obtained in very low yield when extremely mild conditions were used. The products of both reactions were identical by elemental analysis, mp, ir, and mass spectra and agreed with calculated and literature values for elemental analysis and melting point.

Since the yields of the oxidation of the unknown were so low, an attempt was made to locate the loss products. Although generally nothing was found, during an attempt which involved making the filtrate basic, ammonia evolved, and a small amount of material precipitated out which proved to be benzimidazole-2-formamide. By the formation of the acid and subsequently the amide of the acid, the unknown was shown conclusively to be **2**, as given in Scheme I.

EXPERIMENTAL

The melting points were determined on a Fisher-Johns hot stage apparatus. Infrared spectra were taken on a Perkin Elmer Model Number 137 using nujol mulls. The nuclear magnetic resonance spectra were obtained with a Varian A-60A spectrometer using deuterated DMSO.

2-(α-Benzamidostytyl)benzimidazole (**2**).

To 1.237 mg. (4.92 mmoles) of 2-phenyl-4-benzilidine-5-oxazolone (4.94 mmoles) of OPDA was added 20 ml. of 50% acetic acid, and then 30 ml. of dioxane until the solids were dissolved. The solution was refluxed at 135° for 20 hours with stirring. The reaction mixture was cooled and evaporated to near dryness. The brownish material obtained was redissolved in methanol, Norite A was added, the mixture was boiled for 20 minutes, cooled, and the solid which was separated by filtration was then recrystallized from water; white crystals were then obtained, yield 44%, m.p. 250-251°.

Anal. Calcd. for $C_{22}H_{17}N_3O$: C, 77.80; H, 5.00; N, 12.41. Found: C, 77.78; H, 5.07; N, 12.43.

2-(α-Benzamindo-*p*-methoxystyryl)benzimidazole.

The *p*-methoxy derivative was synthesized in the same way as described above for 2 using *p*-methoxyphenylazlactone, yield, 21% m.p., 262-265°.

Anal. Calcd. for $C_{23}H_{19}N_3O_2 \cdot 1/3\ H_2O$: C, 73.62; H, 5.33; N, 11.21. Found: C, 73.51; H, 5.31; N, 11.02.

Benzimidazole-2-carboxylic Acid.

Potassium permanganate (310 mg., 1.96 mmoles) was dissolved in 40 ml. of water and added to 98.5 mg. (0.74 mmole) of 2-methylbenzimidazole. The mixture was refluxed for two hours. More potassium permanganate (290 mg., 1.83 moles) was added in 40 ml. of water and the mixture refluxed for 2 more hours. The hot solution was filtered and acidified with concentrated hydrochloric acid to *p*H 1. The volume was reduced by evaporation and the crystals which were obtained recrystallized out of water/ethanol. The long white needle crystals were filtered and dried to give 10.2 mg. of product, yield, 2.7% m.p. 166° uncorrected.

Anal. Calcd. for $C_8H_6N_2O_2 \cdot 1\ 1/2H_2O$: C, 50.78; H, 4.80; N, 14.82. Found: C, 51.21; H, 4.77; N, 14.66.

Oxidation Product of **2**.

Compound **2** (340 mg., 1 mmole) was suspended in water and 1 g. of sodium hydroxide and 180 mg. (1.1 mmoles) of potassium permanganate added to it. The reaction mixture was heated for 1 1/2 hours at 95°. The hot solution was filtered, cooled and extracted with ether. On standing, crystals which were homogeneous by TLC (silica hydrogen fluoride, methanol/acetone 1/1) dropped out of the aqueous fraction. The crystals were recrystallized from hot water and yielded 11 mg. of prisms, yield, 6.7% m.p. 169° dec.) (lit. 169-172° with dec.).

Anal. Calcd. for $C_8H_6N_2O_2 \cdot H_2O$: C, 53.33; H, 4.48; N, 15.55. Found: C, 53.42; H, 4.30; N, 15.70.

Benzimidazole-2-formamide.

The mother liquors from the oxidation of **2** were basified with sodium hydroxide. Strong fumes of ammonia were emitted and a precipitate formed. The precipitate was filtered and recrystallized from ethanol to give 5 mg. of material, m.p. >285° with sublimation (lit. <300°).

Anal. Calcd. for $C_8H_7N_3O$: C, 59.60; H, 4.38; N, 26.07. Found: C, 59.31; H, 4.58; N, 26.07.

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