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Tautomeric Structure of 1-Oxy-2-phenylbenzimidazole (I)

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The synthesis of 3-methyl-2-phenylbenzimidazole-1-oxide (VIII) has been accomplished. Consequently, it has been possible to establish the tautomeric structure of I as 1-hydroxy-2-phenylbenzimidazole (Ia). Contrary to recent observations on the parent 1-oxybenzimidazole (IV), I shows no tendency to exist as an *N*-oxide (Ib) in aqueous solution.

We have previously reported the formation of 1-hydroxy-2-phenylbenzimidazole (Ia) by the reaction of benzaldehyde with *o*-nitroaniline and the more convenient synthesis of this same compound by the heterocyclization of *N*-benzyl-*o*-nitroaniline (II) (5).

A tautomeric relationship involving *N*-hydroxy (Ia) and *N*-oxide (Ib) forms is possible for this system (6). Indeed, in the case of the parent substance, 1-oxybenzimidazole (IVa, b) such tautomerism has been observed in that the reaction with diazomethane leads to the products (V, VI) (7).

By virtue of the n.m.r. spectrum of I in trifluoracetic acid and also its photosensitivity, we had earlier drawn the tentative conclusion that I is best represented by the *N*-hydroxy form Ia (5a). This was in variance with the view of Kew and Nelson for the parent heterocycle IV where their preference was the *N*-oxide tautomer (IVb) (8). However, Takahashi and Kano studied the ultraviolet absorption spectra of IV-VI and found that the tautomeric structure was dependent on the solvent (9). The spectrum of IV in ethanol closely resembled that of V while aqueous IV compared with the *N*-oxide (VI).

We had, in fact, been following an identical line of attack on the problem of obtaining more definitive evidence for the structure of our 2-phenyl derivative I. Like Takahashi and Kano (9), we had been hopeful of synthesizing the key *N*-oxide (VIII) by the ammonium sulfide reductive ring closure of Niementowski (10). However, unlike the above authors we were unsuccessful in obtaining VIII by this approach.

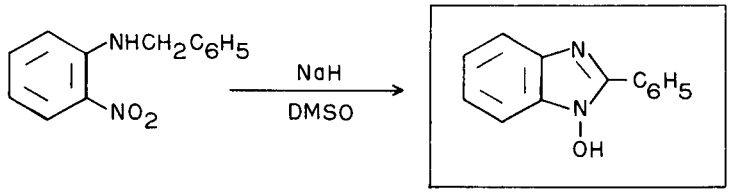
Other approaches were considered. *N*-Oxidation was of some interest in its own right as several authors have previously commented on the disinclination of benzimidazoles to form *N*-oxides by direct oxidation (5, 8, 9). Pursuant to our interest in obtaining VIII, we studied the possible *N*-oxidation of 1-methylbenzimidazole, and as with other benzimidazoles, the desired *N*-oxide was not obtained. However, a product was isolated in micro yield, and by its strong carbonyl and nitrogen-hydrogen infrared absorption peaks, it appeared to be 1-methylbenzimidazolinone-2 (11). Thus, the *N*-oxide might have been initially formed, for Kew and Nelson have observed the rearrangement of *N*-oxybenzimidazole to an imidazolinone (8), while more recently, Sawlewicz has reported the similar acetylative oxidation of both benzimidazole and the corresponding 5-nitro derivative (12).

Since the heterocyclization of *N*-benzyl-*o*-nitroaniline had proven to be an excellent method of synthesis of I (5a), it was hoped that the parallel reaction of *N*-benzyl-*N*-methyl-*o*-nitroaniline (VII) to form the *N*-oxide (VIII) would occur as readily. However, under a variety of conditions investigated, it did not.

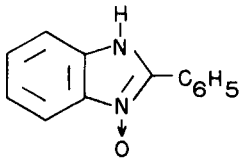
This frustrating synthetic problem was finally resolved by the timely publication of the synthesis of the isomeric 2-methyl-3-phenylbenzimidazole-1-oxide (X) by Schulenberg and Archer (13); their excellent method proved to be equally successful for our desired VIII. It had been observed that merely a catalytic amount of hydrogen chloride in the reaction mixture resulted in only reduction of the nitro intermediate (13). In our series, we noted the same pattern. With a catalytic amount of hydrogen chloride, the intermediate IX underwent selective reduction of the nitro group to give the *o*'-aminobenzanilide (XI). On the other hand, when an excess of hydrogen chloride was employed, heterocyclization occurred to yield the desired *N*-oxide (VIII) (hydrochloride). The free base (VIII) itself was then also isolated with some difficulty.

The other derivative for comparison of ultraviolet spectra and elucidation of tautomeric structures was, of course, 1-methoxy-2-phenylbenzimidazole (III). This was best prepared by an improved method involving reaction of I with dimethyl sulfate under alkaline conditions. The earlier described procedure using diazomethane (5a) was capricious and often led to impure products. The observation of Hyashi *et al.*, (7) would suggest that the product was a mixture (similar to V + VI) resulting from tautomerism.

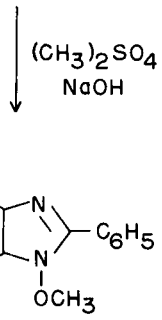
The hydrochloride of III was also readily prepared. The shift in the methyl peaks in the n.m.r. spectra of δ 3.77 p.p.m. for *N*-CH_3 *versus* δ 3.92 for *O*-CH_3 was in the expected direction (14) and was confirmatory for the structure of these substances.



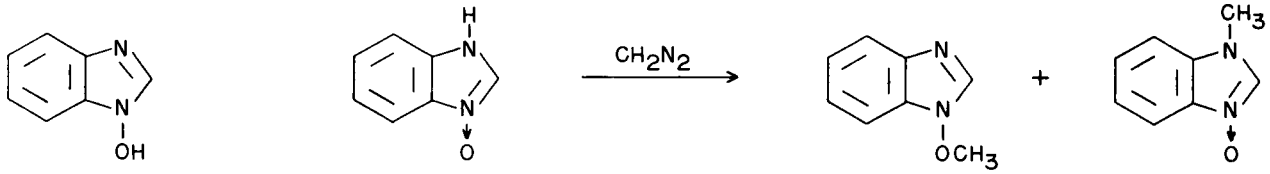
II Ia



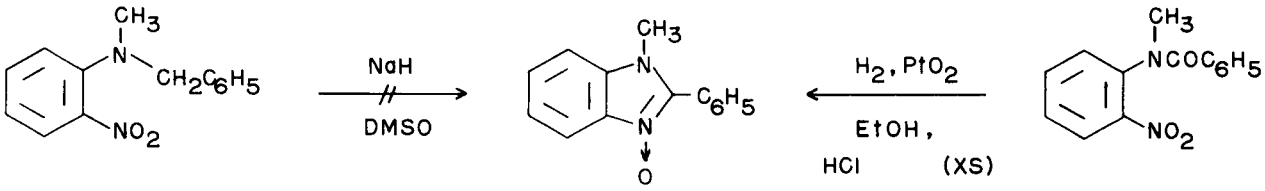
Ib



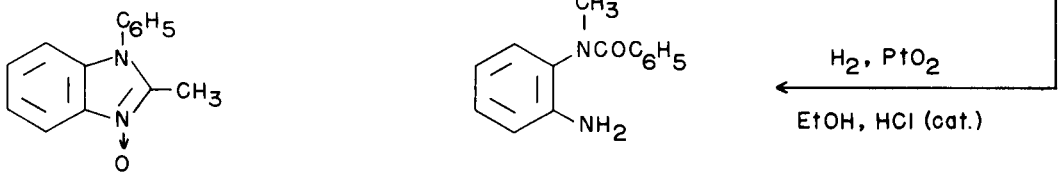
III



IVa IVb V VI



VII VIII IX



X XI

The ultraviolet spectrum of I showed λ max (H_2O), 296 (ε, 18,800) and was quite similar to that of 1-methoxy-2-phenylbenzimidazole, λ max (H_2O), 296 (ε, 21,800). Whereas the spectrum of I diverged from that of the *N*-oxide (VIII), λ max (H_2O), 287 (ε, 13,400) and from that of the isomer X, λ max, 283 (ε, 8,000) (13). Unlike the findings of Takahashi and Kano for the parent 1-oxybenzimidazole (IV), the spectra were similar for both aqueous and ethanolic solutions of I.

In conclusion, it can be stated that the tautomeric structure of the *N*-oxybenzimidazole series is dependent on both the solvent and the over-all nature of the molecule. But thus far, the *N*-hydroxy form has been more apparent than the *N*-oxide tautomer. Specifically, in the current 2-phenyl series, no definitive evidence for the *N*-oxide form has been observed chemically or physically even in aqueous solutions.

EXPERIMENTAL

All melting points are corrected. The microanalytical work was performed by the Galbraith Laboratories, Knoxville, Tenn., and the Analytical Section of 3M. The infrared spectra were determined by Beckman IR-5 and IR-8 spectrophotometers, the ultraviolet spectra on a Carey Model-14 spectrometer, and the n.m.r. spectra on a Varian A-60 spectrometer with tetramethylsilane as an internal standard. All chemical shifts are reported in δ units relative to tetramethylsilane taken as zero; the splitting pattern follows: m, multiplet; s, singlet; and then the number of protons by integration.

1-Methylbenzimidazole and Attempted *N*-Oxidation.

Since 1-methylbenzimidazole has been obtained in only 11% yield in a previous preparation (15), details for the following high-yield procedure are given herewith. To a solution of 26.8 g. (0.23 mole) of benzimidazole (16) suspended in 450 ml. of 2.5 *N* sodium hydroxide solution (ice bath) was added dropwise with stirring 28.6 g. (0.23 mole) of dimethyl sulfate. Stirring of the reaction mixture was continued for 2 hours at room temperature. The oil which had separated during this period was extracted with ether-benzene (1.5:1, 4 x 300 ml.). The combined extracts were washed with saturated sodium chloride solution (300 ml.). After removal of the solvent, the residue was distilled under reduced pressure to yield a yellow oil, b.p. 89-94° (0.1 mm.), which crystallized in the receiver. Recrystallization from petroleum ether (b.p. 30-60°) gave 24.3 g. (80%), m.p. 63-65°, lit. (15) m.p. 61-62°.

To 2.64 g. (0.02 mole) of 1-methylbenzimidazole in 6 ml. of glacial acetic acid was added 3.5 ml. of 30% hydrogen peroxide, and the mixture was heated at 65° for 1 day. A second portion of 3 ml. of 30% hydrogen peroxide was added, and heating was continued for an additional day. After work-up, 1.93 g. of a tan residue was obtained. Although this could not be purified by crystallization, sublimation gave a micro quantity of what appeared to be 1-methylbenzimidazolinone-2, m.p. 175-180° [lit. (11) m.p. 190-192°]; ν max (KBr), (cm^{-1}) N-H 3450 (s), C=O 1712 (s).

1-Hydroxy-2-phenylbenzimidazole (Ia).

To a stirred suspension of 1.06 g. (0.044 mole) of sodium hydride in 20 ml. of anhydrous dimethyl sulfoxide was added dropwise a solution of 4.56 g. (0.02 mole) of *N*-benzyl-*o*-nitroaniline (II) (5a) in 10 ml. of dimethyl sulfoxide (17). After the resulting mixture had been heated at 90° for 12 hours, the solvent was removed *in vacuo*. The residue was washed thoroughly with water and filtered yielding 3.15 g. (75%) of Ia: m.p. 225-226° dec. (18) [lit. (5a) m.p. 220 dec.]; ν max (KBr), (cm^{-1}) O-H 3450 (w); λ max (EtOH), 298 (ε, 21,500), 239 mμ (ε, 19,500); λ max (H_2O), 296 (ε, 18,800), 239 mμ (ε, 20,400).

N-Benzyl-*N*-methyl-*o*-nitroaniline (VII).

A mixture of 9.45 g. (0.06 mole) of *o*-chloronitrobenzene and 20.7 g. (0.18 mole) of benzylmethylamine (18) was heated at 90° for 5 hours (nitrogen). After the mixture had cooled, ether was added, and the hydrochloride was removed by filtration. The ether solution was then washed with water and dried over anhydrous sodium sulfate. The ether was removed, and the residue was distilled *in vacuo* to yield 9.2 g. (63%) of an orange oil, b.p. 115-120° (0.05 mm.); a sample for analysis was redistilled, b.p. 118-119° (0.05 mm.).

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.82; N, 11.57. Found: C, 69.38; H, 5.89; N, 11.81.

Attempted Heterocyclization of VII to VIII.

Either by the procedure described for the heterocyclization of II to I or under numerous other conditions investigated, it was impossible to obtain VIII from VII. Other experiments included such variations as sodium hydroxide-methanol, sodium ethoxide-ethanol, and sodium hydroxide-dioxane-water. Further, some of these reaction media were subjected to the pressure resulting from a sealed tube heated at 150-200°.

1-Methoxy-2-phenylbenzimidazole (III).

In an improved procedure, a stirred solution of 210 mg. (1.0 mmole) of I in 1.5 ml. of 10% sodium hydroxide solution was added 130 mg. (1.0 mmole) of dimethyl sulfate, and the resulting mixture was stirred for 20 minutes. The mixture was filtered, and the product was washed thoroughly with water to yield 220 mg. (98%), m.p. 106-108°. Recrystallization from isopropyl ether gave 200 mg. (89%), m.p. 107-108°, lit. (5a) m.p. 102-104°; n.m.r. ($CDCl_3$) 3.92 (s,3), 7.20-8.40 (m,9); λ max (EtOH), 297 (ε, 21,800), 238 mμ (ε, 18,800); λ max (H_2O), 296 (ε, 21,800), 239 mμ (ε, 17,200).

1-Methoxy-2-phenylbenzimidazole (III) Hydrochloride.

Anhydrous hydrogen chloride was passed into an ether solution of III to give a hydrochloride, m.p. 134-137° dec; λ max (EtOH), 310 (ε, 25,000), 240 mμ (ε, 19,000); λ max (H_2O), 295 (ε, 21,600), 239 mμ (ε, 16,900).

Anal. Calcd. for $C_{14}H_{13}ClN_2O$: C, 64.49; H, 5.02; Cl, 13.60. Found: C, 64.5; H, 5.0; Cl, 13.4.

N-Methyl-2-nitrobenzanilide (IX).

Although IX has been prepared previously in 58% yield by treatment of 2-nitrobenzanilide with potassium hydroxide-dimethyl sulfate (19), the following alternate procedure gives a superior yield. To 15.2 g. (0.1 mole) of recrystallized *N*-2-nitroaniline (20) heated at 65° was added with stirring 15.0 g. (0.1 mole) of benzoyl chloride dropwise; heating was then continued for 2 hours. Recrystallization of the resulting crystalline precipitate from benzene-petroleum ether (b.p. 40-60°) yielded 24.0 g. (94%) of pale yellow plates, m.p. 79-81°, lit. (19) m.p. 80-81°.

Reduction of IX. A. Catalytic Hydrochloric Acid. 2-Amino-*N*-methylbenzanilide (XI).

Contrasting conditions involving different quantities of hydrochloric acid lead to different products in the two procedures following. A mixture of 7.70 g. (0.03 mole) of IX, 0.50 g. of platinum oxide and 1 ml. of concentrated hydrochloric acid in 200 ml. of absolute ethanol was hydrogenated in a 300-ml. Paar bomb at 500 p.s.i. at room temperature for 1 hour. The catalyst was filtered off, and the solvent was removed to give 6.0 g. (89%) of XI, m.p. 125-126°; recrystallization from benzene gave 5.8 g. (86%), m.p. 126-127°, lit. (19) m.p. 126-127°.

B. Excess Ethanolic Hydrogen Chloride. 3-Methyl-2-phenylbenzimidazole-1-oxide (VIII) Hydrochloride (21).

A mixture of 7.70 g. (0.03 mole) of IX, 0.50 g. of platinum oxide, and approximately 200 ml. of ethanolic hydrogen chloride (2.4-3.3 g. of dry hydrogen chloride in 200 ml. of absolute ethanol) was placed in a 300-ml. Paar bomb. The hydrogenator was charged to 500 p.s.i. with hydrogen and shaken at room temperature for 30 minutes. The warmed mixture was filtered to remove the catalyst and then cooled yielding the crude hydrochloride 5.5-6.6 g. (73-87%). Recrystallization of 5.5 g. of crude material from ethanol yielded 4.5 g. (60%) of a colorless solid, m.p. 217-230° dec.; n.m.r. (D_2O) 4.08 (s,3), 7.75-8.16 (m,9), λ max (EtOH), 286 (ε, 16,500), 239 mμ (ε, 29,500); λ max (H_2O), 287 (ε, 16,200), 239 mμ (ε, 27,400).

Anal. Calcd. for $C_{14}H_{13}ClN_2O$: C, 64.49; H, 5.02; Cl, 13.60; N, 10.75. Found: C, 64.6; H, 5.1; Cl, 13.3; N, 10.7.

3-Methyl-2-phenylbenzimidazole-1-oxide (VIII).

A suspension of 1.3 g. (0.05 mole) of the hydrochloride of VIII in 30 ml. of 20% potassium carbonate was stirred for 1 hour and then extracted with chloroform (3 x 50 ml.). The combined chloroform extracts were dried over anhydrous magnesium sulfate, and the solvent was removed. The crude oil solidified and was crystallized from ethyl acetate yielding 1.0 g. (84%), m.p. 166-171° dec.; n.m.r. ($CDCl_3$) 3.77 (s,3), 7.78-8.55 (m,9); λ max (EtOH), 291 (ε, 15,300),

237 mμ (ε, 30,400); λ max (H_2O), 287 (ε, 15,400), 237 mμ (ε, 31,000).

Anal. Calcd. for $C_{14}H_{12}N_2O$: C, 74.99; H, 5.38; N, 12.49. Found: C, 74.9; H, 5.6; N, 12.4.

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(3) N.S.F. Summer Fellow, 1963, N.S.F. Cooperative Fellow, 1963-64; present address, Minnesota Mining and Manufacturing Company, St. Paul, Minnesota.

(4) N.S.F. Cooperative Fellow, 1960-62.

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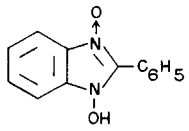

XIV

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