SOME CHEMICAL PROPERTIES AND REACTIONS OF 3-PHENYLIMIDAZO[5, 1-b]BENZOXAZOLE

T. P. Sycheva, I. D. Kiseleva, and M. N. Shchukina

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It has been shown that 3-phenylimidazo[5, 1-b]benzoxazole (I) is stable under conditions of alkaline and acid hydrolysis. When I is oxidized with potassium permanganate, 2-benzoylbenzoxazole is formed. A series of 1-substituted derivatives of I has been obtained by its nitration and bromination and by the Vilsmeier and Mannich reactions. Nitrosation, hydroxymethylation, acetylation, and cyanoethylation reactions of I could not be carried out by the usual methods.

The present work was devoted to a study of the chemical properties of a representative of a new heterocyclic system—3-phenylimidazo[5, 1-b]benzoxazole (I) [1]. Since I is an analog of 3-phenylimidazo[5, 1-b]benzothiazole (XV), which is capable of undergoing electrophilic substitution reactions in position 1 [2], it appeared of interest to compare the reactivities of these two compounds. The presence of an excess of π-electron density in position 1 and 3 of the molecule of imidazo[5, 1-b]benzoxazole was confirmed by calculations using Hückel's molecular orbital method with Pullman's standard parameters [3].

Like XV [2], compound I proved to be extremely stable under conditions of acid and alkaline hydrolysis: it underwent no change on prolonged boiling both with 20% hydrochloric acid. The oxidation of I with potassium permanganate in aqueous potassium carbonate solution at 70° C led to the destruction of the imidazole ring and the formation of 2-benzoylbenzoxazole (II), identical with the compound described previously [4]. A similar cleavage of the imidazole ring was observed in the oxidation of X with chromium trioxide [2].

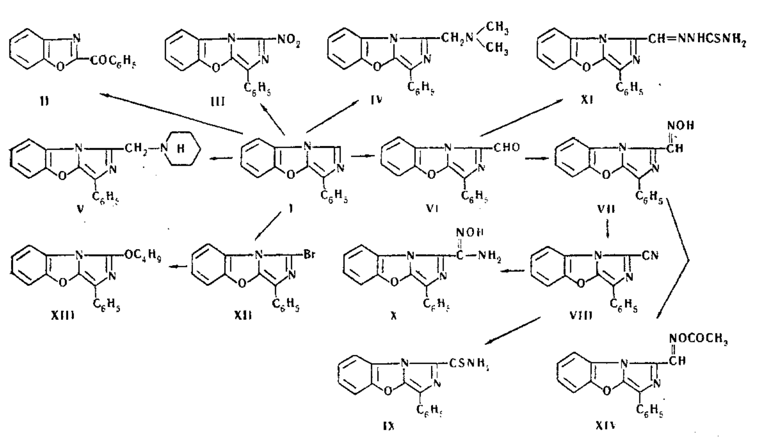
The nitration of I with nitric acid in glacial acetic acid at 50° C gave 1-nitro-3-phenylimidazo[5, 1]benzoxazole (III). However, the yield of this compound was considerably lower than the yield of the corresponding nitro derivative of XV, which is formed at a lower temperature [2]. It was impossible to perform the nitrosation, acetylation, and hydroxymethylation of I by the usual methods; in all cases the starting material was recovered.

Like XV [2], I takes part in the Mannich reaction; under the action of paraformaldehyde and dimethylamine and piperidine hydrochlorides, the bases IV and V were obtained. When piperidine hydrochloride was replaced by free piperidine, the Mannich reaction did not take place and the initial I was recovered. By the action of methyl iodide in benzene, IV was converted into the methiodide. Attempts to replace the dimethylamino group in it by other groups (nitrile, acetyl, etc.) by analogy with the reactions described for quaternary salts of gramine [5] did not lead to satisfactory results.

The formylation of I by the Vilsmeier reaction led to the formation of 3-phenylimidazo[5, 1-b]benzoxazole-1-aldehyde (VI) in good yield. The thiosemicarbazone of VI (XI) was formed only in the presence of acetic acid. From VI the oxime VII was obtained, and on being heated with acetic anhydride in the presence of anhydrous sodium acetate this was converted into the nitrile (VIII). Heating VII in acetic anhydride alone led to the formation only of the acetyl derivatives of the oxime (XIV). 3-Phenylimidazo[5, 1-b]benzoxazole-1-carbothioamide (IX) and the amide oxime (X) were obtained from VIII by the usual methods. (See Scheme on following page.)

The bromination of I with bromine in chloroform or with bromosuccinimide led to 1-bromo-3-phenylimidazo[5, 1-b] benzoxazole (XII) in which it was possible by prolonged heating with butanol in the presence of alkali to replace the halogen by a butoxy group with the formation of XIII. When XII was heated with aqueous alkali, no replacement of the halogen by a hydroxy group took place. In attempts to perform the cyanoethylation of I with acrylonitrile in the presence of the Rodionov catalyst, the starting material was recovered unchanged.

All the derivatives of I synthesized were studied for their antibacterial and, in particular, tuberculostatic activity in the chemotherapy division of VNIKhFI [Ordzhonikidze All-Union Chemical and Pharmaceutical Research Institute] by S. N. Milovanova and T. N. Zykova; these substances possess no appreciable antibacterial activity.



EXPERIMENTAL

The oxidation of I. A suspension of 0.2 g (0.85 mM) of I [1] in a solution of 0.05 g of potassium carbonate in 2 ml of water at 70° C was treated dropwise with a 10% aqueous solution of potassium permanganate until the permanganate ceased to be decolorized. After cooling, the precipitate was filtered off, washed, and treated with ether. The residue from the evaporation of the solvent (0.1 g) was recrystallized from ethanol. Colorless crystals with mp 75–76° C (from ethanol) giving no depression in admixture with a sample of 2-benzoylbenzoxazole (II) obtained by the decomposition of its oxime with anhydrous acetic acid [4]. Found, %: C 75.3; H 4.1. $C_{14}H_9NO_2$. Calculated, %: C 75.3; H 4.1. **Thiosemicarbazone of II**—yellow crystals, mp 194–198° C (from 50% ethanol). Found, %; N 19.0; S 10.6. $C_{15}H_{12}N_4OS$. Calculated, %: N 18.9; S 10.8.

1-Nitro-3-phenylimidazo[5,1-b]benzoxazole (III). A suspension of 0.5 g (2.14 mM) of I in 10 ml of glacial acetic acid was treated dropwise at 16° C with a mixture of 0.21 ml (4.72 mM) of nitric acid (d 1.5) and 1.4 ml of glacial acetic acid. A voluminous white precipitate of the nitrate of I was formed. The mixture was heated at 50° C for 50 min, whereupon the precipitate gradually dissolved and a new bright yellow precipitate separated out. After cooling to room temperature, it was filtered off and was washed with glacial acetic acid and water. Yield 0.15 g; mp 210–213° C (from ethanol). Found, %: C 64.7; H 3.5; N 15.3. $C_{15}H_9N_3O_3$. Calculated, %: C 64.5; H 3.2; N 15.1.

1-Dimethylaminomethyl-3-phenylimidazo[5,1-b]benzoxazole (IV). A mixture of 0.7 g (2.96 mM) of I, 0.18 g (6 mM) of paraformaldehyde, 0.3 g (3.69 mM) of dimethylamine hydrochloride, and 8 ml of isoamyl alcohol was boiled for 1 hr. The precipitate that separated from the hot solution was filtered off after cooling, and was washed with isoamyl alcohol and then with aqueous ammonia and with water. This gave 0.78 g (87.5%) of IV. Colorless crystals with mp 119–120.5° C (from 50% ethanol). Found, %: C 73.9; H 5.8; N 14.0. $C_{18}H_{17}N_3O$. Calculated, %: C 74.2; H 5.9; N 14.4. **Methiodide of IV**—light yellow crystals with decomp. p. 210° C (from water). Found, %: I 29.5. $C_{19}H_{20}N_3OI$. Calculated, %: I 29.3.

1-Piperidinomethyl-3-phenylimidazo[5,1-b]benzoxazole (VI). This was obtained in a similar manner to IV. Yield 75.7%; colorless crystals with mp 123.5–125° C (from ethanol). Found, %: C 76.4; H 6.6; N 12.5. $C_{21}H_{21}N_3O$. Calculated, %: C 76.1; H 6.4; N 12.7.

3-Phenylimidazo[5,1-b]benzoxazole-1-aldehyde (VI). At 0–5° C, 0.5 ml of freshly-distilled phosphorus oxychloride and then a suspension of 0.5 g (2.14 mM) of I in 8 ml of dimethylformamide were added to 3.5 ml of purified dimethylformamide, and the mixture was stirred at 90–95° C for 2 hr. The solid matter rapidly dissolved, and then a precipitate formed. After cooling, the mixture was poured onto ice, and the bright yellow precipitate was filtered off, washed with water and triturated with saturated sodium acetate solution. This gave 0.52 g (92.5%) of VI. Colorless crystals with mp 167–168° C (from ethanol). Found, %: C 73.2; H 3.8; N 10.6. $C_{16}H_{10}N_2O_2$. Calculated, %: C 73.3; H 3.8; N 10.7.

The oxime of VI (VII). A mixture of 1.16 g (4.43 mM) of VI, 0.35 g (5 mM) of hydroxylamine hydrochloride, 11.6 ml of absolute ethanol, and 11.6 ml of anhydrous pyridine was boiled for 4 hr and cooled, and the precipitate was filtered off and was washed with ethanol and water. This gave 1.04 g of VII; faintly yellow crystals, decomp. p. 253–255° C (from butanol). Found, %: C 69.1; H 4.2; N 15.1. $C_{16}H_{11}N_3O_2$. Calculated, %: C 69.3; H 4.0; N 15.1.

Thiosemicarbazone of VI (X)—decomp. p. 313–316° C (from ethanol). Found, %: C 60.9; H 3.9; N 20.4; S 9.1. $C_{17}H_{13}N_5SO$. Calculated, %: C 60.9; H 3.9; N 20.9; S 9.5.

Acetyloxime of VI (XIV). A suspension of 0.2 g of VII in 2 ml of acetic anhydride was boiled for 30 min and cooled, and the precipitate was filtered off and was washed with glacial acetic acid and with water. This gave 0.19 g of XIV, mp 192–194° C (from glacial acetic acid). Found, %: C 68.0; H 4.1; N 13.2. $C_{18}H_{13}N_3O_2$. Calculated, %: C 67.7; H 4.1; N 13.2.

3-Phenylimidazo[5,1-b]benzoxazole-3-carbonitrile (VIII). A mixture of 0.9 g (3.96 mM) of VII, 13.8 ml of acetic anhydride, and 0.46 g of anhydrous sodium acetate was boiled for 3 hr. The hot solution was treated with charcoal and was filtered and cooled, and the precipitate was filtered off, washed with acetic anhydride, acetic acid, and water, and dried. Weight was 0.64 g. After recrystallization from ethanol, 0.4 g of VIII was obtained in the form of colorless needles with mp 179–182° C. Found, %: C 74.2; H 3.4; N 16.0. $C_{16}H_9N_3O$. Calculated, %: C 74.1; H 3.5; N 16.2. The mother liquor from the isolation of the VIII was poured into water, and the precipitate was filtered off, combined with the residue after the evaporation of the alcoholic mother liquors, and treated with ether. After evaporation of the ethereal solution, an additional 0.28 g of VIII was obtained.

3-Phenylimidazo[5,1-b]benzoxazole-1-carbothioamide (IX). A suspension of 0.28 g (1.08 mM) of VIII in 17 ml of absolute ethanol was treated with 0.2 ml of triethylamine, and a current of dry hydrogen sulfide was passed into the mixture at 30° C for 4 hr. After cooling, the precipitate was filtered off and washed with cooled absolute ethanol. This gave 0.3 g of IX in the form of light yellow needles with mp 241–243° C (from glacial acetic acid). Found, %: C 65.8; H 3.9; N 14.5; S 10.5. $C_{16}H_{11}N_3OS$. Calculated, %: C 65.5; H 3.8; N 14.3; S 10.9.

3-Phenylimidazo[5,1-b]benzoxazole-1-carboxamide oxime (XI). A hot solution of 0.28 g (1.08 mM) of VIII in 10 ml of ethanol was treated with a solution of 0.072 g (1.08 mM) of hydroxylamine hydrochloride and 0.054 g (0.51 mM) of sodium acetate in 5 ml of water, the mixture was boiled for 1 hr and cooled, and the precipitate was filtered off and was washed with ethanol and then with water. This gave 0.3 g of XI, mp 220–221° C (from ethanol). Found, %: N 19.0. $C_{16}H_{12}N_4O_2$. Calculated, %: N 19.2.

1-Bromo-3-phenylimidazo[5,1-b]benzoxazole (XII). A) A solution of 1.5 g (6.42 mM) of I in 60 ml of anhydrous chloroform was treated with 0.33 ml (6.5 mM) of bromine in 4 ml of chloroform. The mixture was stirred at 20° C for 3 hr, and the precipitate was filtered off, washed with water, and triturated with a solution of sodium bisulfite. Then the bromide was filtered off again and was washed with water. This gave 2.19 g of XII. Colorless needles, mp 178–180° C (from ethanol). Found, %: C 57.4; H 2.9; N 8.9; Br 25.5. $C_{15}H_9N_2OBr$. Calculated, %: C 57.5; H 2.9; N 8.9; Br 25.5. B) A mixture of 0.2 g (0.85 mM) of I, 0.15 g (0.85 mM) of bromosuccinimide, and 5 ml of freshly-distilled carbon tetrachloride was boiled for 1.5 hr and then the insoluble residue was filtered off from the hot solution. On cooling, the mother liquor deposited 0.27 g of XII with mp 172–175° C, identical with the sample obtained by method (A).

1-Butoxy-3-phenylimidazo[5,1-b]benzoxazole (XIII). A solution of 0.7 g (2.24 mM) of XII and 2.65 g of caustic potash in 62 ml of butanol was boiled for 31 hr. The butanol was evaporated to dryness in vacuum, and the residue was treated with ether. The ethereal solution was washed with water and dried. After the solvent had been driven off, 0.3 g (44%) of XIII was obtained. Colorless crystals with mp 109–111.5° C (from methanol). Found, %: C 74.3; H 5.9. $C_{19}H_{18}N_2O_2$. Calculated, %: C 74.5; H 5.9.

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Ordzhonikidze All-Union Scientific-Research Chemical and Pharmaceutical Institute, Moscow