# MANNICH BASES AND METHIODIDES OF 6-(2-FURYL)IMIDAZO[2,1-b]THIAZOLE AND ITS SUBSTITUTED DERIVATIVES

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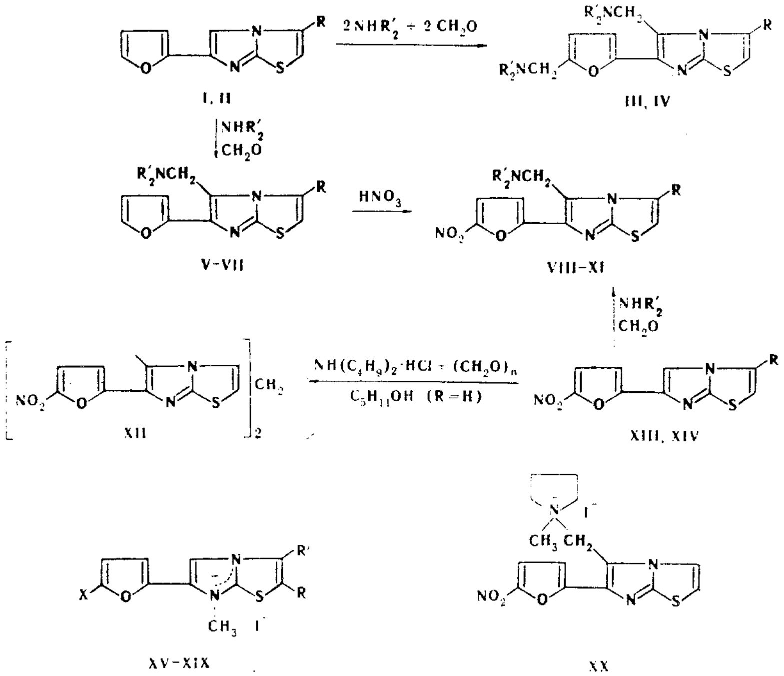
The Mannich reaction in a number of 6-(2-furyl)-substituted imidazo[2,1-b]thiazoles is realized initially in the 5 position of the imidazothiazole system, whereas it is also realized in the 5 position of the furan ring in the presence of excess reagents if the latter position is not substituted. Iodomethylation occurs at the $N_7$ atom of imidazothiazole. The Mannich bases of 6-(5-nitro-2-furyl)imidazo[2,1-b]thiazole are iodomethylated only at the aminomethyl group. The $pK_a$ values of the series of compounds were measured.

In order to study the reactivities of 6-(2-furyl)-substituted imidazo[2,1-b]thiazoles (I, II) we subjected them to aminomethylation and iodomethylation. Secondary amines and a 36% solution of formalin in acetic acid were used to prepare the Mannich bases.



I R=H; II R=$CH_3$; III R=H, $R'_2N$=piperidino; IV R=$CH_3$, $R'_2N$=pyrrolidino; V R=H, $R'_2N$=piperidino; VI R=$CH_3$, $R'_2N$=piperidino; VII R=H, $R'_2N$=morpholino; VIII R=H, $R'_2N$=piperidino; IX R=$CH_3$, $R'_2N$=piperidino; X R=H, $R'_2N$=morpholino; XI R=H, $R'_2N$=pyrrolidino; XIII R=H; XIV R=$CH_3$; XV R=R'=X=H; XVI R=$CH_3$, R'=X=H; XVII R=R'=H, X=$NO_2$; XVIII R=R'=$CH_3$, X=H; XIX R=R'=$CH_3$, X=Br

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TABLE 1. Methiodides XV-XIX

| Compound | R | R′ | X | mp, °C | Empirical formula | Found, % |  |  | Calc., % |  |  | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
|  |  |  |  |  |  | C | H | N | C | H | N |  |
| XV | H | H | H | 218—220 | $C_{10}H_9IN_2OS$ | 36,1 | 2,7 | 8,5 | 36,1 | 2,7 | 8,4 | 45 |
| XVI | H | $CH_3$ | H | 212—213 | $C_{11}H_{11}IN_2OS$ | 38,4 | 3,1 | 8,0 | 38,7 | 3,2 | 8,2 | 60 |
| XVII | H | H | $NO_2$ | 218—219 | $C_{10}H_8IN_3O_3S$ | 31,6 | 2,0 | 10,9 | 31,8 | 2,1 | 11,6 | 7 |
| XVIII | $CH_3$ | $CH_3$ | H | 243—245 | $C_{12}H_{13}IN_2OS$ | 39,7 | 3,6 | 7,4 | 39,9 | 3,9 | 7,8 | 78 |
| XIX | $CH_3$ | $CH_3$ | Br | 255—257 | $C_{12}H_{12}BrIN_2OS$ | 32,4 | 2,6 | 6,5 | 32,8 | 2,7 | 6,5 | 54 |

Like 2-(2-furyl)imidazo[1,2-a]pyridine [1], I and II form bis(aminomethyl) derivatives involving the 5 positions of the imidazothiazole and furan rings when excess aminomethylating agents are present, whereas 6-arylimidazothiazoles [2] react only at the 5 position of the imidazothiazole system.

When equimolecular amounts of the aminomethylating agents are used, substitution occurs primarily in the 5 position of the imidazothiazole system; this was established by subsequent nitration of piperidinomethylation products V and VI, as a result of which we obtained VIII and IX, which were identical to the products of piperidinomethylation of 6-(5-nitro-2-furyl)imidazo[2,1-b]thiazole (XIII) and its 3-methyl-substituted derivative (XIV).

Bis[2-(5-nitro-2-furyl)imidazo[2,1-b]-5-thiazolyl]methane (XII) was obtained instead of a Mannich base in the reaction of XIII with dibutylamine hydrochloride and paraformaldehyde in refluxing amyl alcohol. A similar reaction is observed with 6-chloroimidazo[2,1-b]thiazole in the presence of hydrogen chloride [3].

Furylimidazothiazoles are capable of iodomethylation under the usual conditions (Table 1). It was shown in the case of XIII that when there is a nitro group in the furan ring, iodomethylation is hindered; this is associated with a decrease in the basicity of the compound. The $pK_a$ values for 6-(2′-furyl)imidazo-[2,1-b]thiazole and its 2-methyl-, 3-methyl-, and 5′-nitro-substituted derivatives, respectively, are 2.93, 3.09, 3.17, and 1.90. It was found to be impossible to determine the $pK_a$ value of 2,3-dimethyl-substituted I because of the small difference in the UV spectra in acidic and alkaline media. Iodomethylation of 5-pyrrolidinomethyl-6-(5-nitro-2-furyl)imidazo[2,1-b]thiazole (XI) occurs only at the amino group to give XX. The $pK_a$ value of the pyrrolidino group in Mannich base XI (8.98) is relatively close to the $pK_a$ value of 1-methylpyrrolidine (10.46) [4].

## EXPERIMENTAL

Chromatography was accomplished on Silufol UV-254 in a chloroform–methanol–acetic acid system (15 : 4 : 1). The melting points were determined with a Boetius apparatus and were not corrected. The IR spectra of hexachlorobutadiene (2000-3600 and 1300-1500 $cm^{-1}$) and mineral oil (800-2000 $cm^{-1}$) suspensions of the compounds were obtained with a UR-20 spectrometer.

The UV spectra of $5 \cdot 10^{-5}$ M solutions in alcohol were recorded with a Specord UV-vis spectrometer. The $pK_a$ values were measured with the same apparatus. For this, $5 \cdot 10^{-5}$-$2.5 \cdot 10^{-5}$ M aqueous alcohol solutions of the compounds containing 20% ethanol (by volume) were investigated at 20 ± 1° and various pH values. A borate buffer solution (pH 6.8-10.0) and hydrochloric acid solutions, the acidities of which were determined from the Hammett $H_0$ function [5], and a sodium hydroxide solution (pH 12) were used to create definite acidities of the media. The pH values were measured with an LPU-01 apparatus calibrated with respect to biphthalate (pH 4.00) and borate (pH 9.18) buffer solutions; the accuracy in the determinations was ±0.02. The $pK_a$ values were calculated from the formula

$$pK = pH(H_0) + \lg \frac{[HA]}{[A]}$$

without correction for the ionic strength of the solutions in view of the low concentrations of the buffer mixtures.

<u>5-Piperidinomethyl-6-(5-piperidinomethyl-2-furyl)imidazo[2,1-b]thiazole (III).</u> A solution of 4.16 g (0.05 mole) of formalin and 4.3 g (0.05 mole) of piperidine in 15 ml of acetic acid was added dropwise to a solution of 3.9 g (0.02 mole) of I in 18 ml of acetic acid, after which the mixture was heated and stirred at 60° for 3 h. It was then made alkaline with 20% aqueous sodium hydroxide solution, and the resinous product was separated and triturated with water. It was then dried over sulfuric acid to give a vitreous substance with $R_f$ 0.05 in 67% yield. The product did not crystallize from organic solvents, and it was therefore purified and identified in the form of its salts. The trihydrochloride was obtained as colorless crys-

tals with mp 211-212° (from absolute alcohol—ether) by the action of a solution of hydrogen chloride in absolute alcohol on the base. Found: C 45.7; H 7.1; N 10.6%. $C_{21}H_{28}N_4OS \cdot 3HCl \cdot 3H_2O$. Calculated: C 46.0; H 6.8; N 10.3%. UV spectrum, $\lambda_{max}$, nm (log ε): 275 (4.32).

3-Methyl-5-pyrrolidinomethyl-6-(5-pyrrolidinomethyl-2-furyl)imidazo[2,1-b]thiazole (IV). This compound was similarly obtained. The yield of crude product was 93%. The tripicrate had mp 108-110° (from alcohol). Found: C 45.1; H 3.5; N 17.0%. $C_{20}H_{26}N_4OS \cdot 3C_6H_3N_3O_7$. Calculated: C 45.6; H 3.3; N 17.4%.

5-Piperidinomethyl-6-(2-furyl)imidazo[2,1-b]thiazole (V). This compound was similarly obtained from equimolar amounts of reagents. The yield of product with $R_f$ 0.21 was 79%. The dihydrochloride had mp 194-196° (from absolute alcohol—absolute ether). Found:C 45.4; H 5.5; Cl 18.1%. $C_{15}H_{17}N_3OS \cdot 2HCl \cdot 2H_2O$. Calculated: C 45.7; H 5.8; Cl 17.8%. UV spectrum, $\lambda_{max}$, nm (log ε): 275 (4.22). The di(3,5-dinitrobenzoate) was obtained as a yellow powder with mp 179-181° by the action of 3,5-dinitrobenzoic acid on the base in absolute alcohol after washing with absolute alcohol. Found: C 49.2; H 3.7; N 14.0%. $C_{15}H_{17}N_3OS \cdot 2C_7H_4N_3O_7$. Calculated: C 48.9; H 3.5; N 13.8%.

5-Morpholinomethyl-6-(2-furyl)imidazo[2,1-b]thiazole (VI). This compound, with $R_f$ 0.36, was similarly obtained in 81% yield. The dihydrochloride had mp 190-192° (from absolute alcohol—absolute ether). Found: C 43.7; H 5.0; Cl 19.2%. $C_{14}H_{15}N_3O_2S \cdot 2HCl \cdot 2H_2O$. Calculated: C 44.0; H 5.0; Cl 18.7%. The dipicrate had mp 164-166° (from alcohol). Found: C 42.2; H 3.0; N 16.9%. $C_{14}H_{15}N_3O_2S \cdot 2C_6H_3N_3O_7$. Calculated: C 41.8; H 2.8; N 16.9%. The di(3,5-dinitrobenzoate) had mp 149-151°. Found: C 47.0; H 3.4; N 14.0%. $C_{14}H_{15}N_3O_2S \cdot 2C_7H_4N_2O_6$. Calculated: C 47.1; H 3.2; N 13.8%.

5-Piperidinomethyl-6-(5-nitro-2-furyl)imidazo[2,1-b]thiazole (VIII). A) This compound was similarly obtained in 78% yield as yellow prisms with mp 151-153° (from alcohol) and $R_f$ 0.23. Found: C 53.9; H 4.8; N 16.6%. $C_{15}H_{16}N_4O_3$. Calculated: C 54.2; H 4.8; N 16.8%. UV spectrum, $\lambda_{max}$, nm (log ε): in alcohol 238 (4.28) and 384 (4.19); in 0.1 N HCl 237 (4.30) and 379 (4.19).

B) A solution of crude V in 20 ml of acetic acid was added dropwise with vigorous stirring and ice cooling to a solution of 30 ml of 96% sulfuric acid and 1.25 ml (22 mmole) of 70% nitric acid, after which the mixture was stirred for 1 h and treated with aqueous sodium hydroxide solution until it was weakly alkaline. The resulting precipitate was removed by filtration and washed with water to give 1.66 g (41%) of a product with mp 152-153° (from alcohol). According to the $R_f$ values and UV and IR spectra, the product was identical to a sample prepared by method A. IR spectrum, $cm^{-1}$: 3140 and 3120 (ring $\nu_{CH}$), 2950 and 2870 ($CH_2$ $\nu_{as}$ and $\nu_s$), 1488 (scissors vibrations of the $CH_2$ group), and 1550 and 1340 (nitro group $\nu_{as}$ and $\nu_s$).

3-Methyl-5-piperidinomethyl-6-(5-nitro-2-furyl)imidazo[2,1-b]thiazole (IX). The yield by method A was 82%, and the yield by method B was 32% (based on crude VI). The yellow crystals had mp 158-160° [from aqueous dimethylformamide (DMF)] and $R_f$ 0.28. Found: C 55.1; H 5.0; N 15.9%. $C_{16}H_{18}N_4O_3S$. Calculated: C 55.5; H 5.2; N 16.2%.

5-Morpholinomethyl-6-(5-nitro-2-furyl)imidazo[2,1-b]thiazole (X). The yield by method A was 50%, and the product had $R_f$ 0.55 and mp 149-151° (from alcohol). Found: C 49.9; H 4.3; N 17.1%. $C_{14}H_{14}N_4O_4S$. Calculated: C 50.2; H 4.2; N 16.8%. The dihydrochloride had mp 225-227° (from an alcohol solution of hydrochloric acid). Found: Cl 16.5%. $C_{14}H_{14}N_4O_4S \cdot 2HCl$. Calculated: Cl 16.7%.

5-Pyrrolidinomethyl-6-(5-nitro-2-furyl)imidazo[2,1-b]thiazole (XI). The yield by method A was 84%, and the yellow crystals had mp 142-144° (from alcohol). Found: C 52.7; H 4.3; N 17.2%. $C_{14}H_{14}N_4O_3S$. Calculated: C 52.8; H 4.4; N 17.6%. The dihydrochloride was obtained as yellowish crystals with mp 278-279° (from an alcohol solution of hydrogen chloride). Found: C 42.8; H 4.3; N 14.0%. $C_{14}H_{14}N_4O_3S \cdot 2HCl$. Calculated: C 43.0; H 4.1; N 14.3%.

All of the aminomethylation products (the bases) were quite soluble in DMF, acetic acid, acetone, and hot alcohol, only slightly soluble in ether, and insoluble in petroleum ether and water; in contrast to the starting compounds, they did not sublime in vacuuo. Like the Mannich bases of the 2-(2-furyl)imidazo-[1,2-a]pyridine series [1], III-VII dissolved in concentrated sulfuric acid to give intensely green-colored solutions, in contrast to I and II, which gave carmine-red-colored solutions. The Mannich bases with a nitro group in the furan ring (VIII-XI) dissolved in concentrated sulfuric acid to give yellow-green-colored solutions, whereas starting XIII and XIV formed yellow solutions. Trihydrochloride III and dihydrochlorides V and VI were quite soluble in water. Dihydrochlorides X and XI were more soluble in water than the bases but underwent partial hydrolysis.

Bis[6-(5-nitro-2-furyl)imidazo[2,1-b]-5-thiazolyl]methane (XII). A mixture of 2.35 g (10 mmole) of XIII, 0.6 g (20 mmole) of paraformaldehyde, 1.66 g (10 mmole) of di-n-butylamine hydrochloride, and 50 ml of amyl alcohol was refluxed for 30 min, and the solid material was removed by filtration and washed with dilute ammonium hydroxide to give 0.69 g (29%) of a yellow powder with mp 310-312° (dec., from aqueous DMF). Found: C 47.5; H 2.2; N 17.1%. $C_{19}H_{10}N_6O_6S_2$. Calculated: C 47.3; H 2.1; N 17.4%.

Methiodides (XV-XIX, Table 1). A 10-mmole sample of the appropriate imidazothiazole was refluxed with 25 mmole of methyl iodide in 20 ml of absolute alcohol for 6 h, after which the mixture was diluted with dry ether, and the resulting precipitate was removed by filtration and crystallized from absolute alcohol or absolute alcohol–absolute ether.

In the case of iodomethylation of nitrofurylthiazole, the unchanged starting material was removed by filtration, and the methiodide was isolated by the addition of absolute ether to the filtrate.

The methiodides of the furylimidazothiazoles were colorless crystalline substances that were quite soluble in water, moderately soluble in alcohol, and insoluble in ether. Nitrofurylimidazothiazole methiodide was an orange substance.

5-(N-Methylpyrrolidinomethyl)-6-(5-nitro-2-furyl)imidazo[2,1-b]thiazole Iodide (XX). A mixture of 0.63 g (2 mmole) of XI, 1.4 g (10 mmole) of methyl iodide, and 10 ml of DMF was heated on a water bath for 5 h, after which the methiodide was removed by filtration. An additional amount of the methiodide was precipitated by the addition of ether to the filtrate. The yield of orange crystals with mp 220-221° (after washing with DMF and ether) was 87%, Found: C 38.9; H 3.7; N 11.9%. $C_{15}H_{17}IN_4O_3S$. Calculated: C 39.1; H 3.7; N 12.1%.

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