

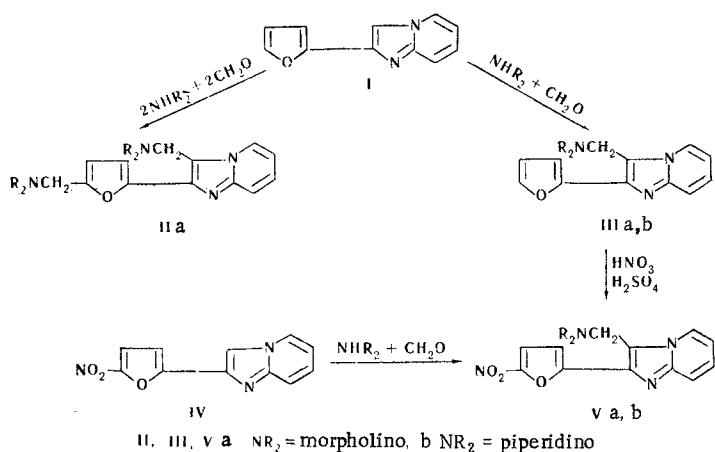
A MINOMETHYLATION OF 2-(2-FURYL)IMIDAZO-
[1,2-*a*]PYRIDINE

N. O. Saldabol, L. L. Zeligman, and
S. A. Giller

UDC 547.721'781'821

The aminomethylation (morpholino- and piperidinomethylation) of 2-(2-furyl)imidazo[1,2-*a*]pyridine proceeds primarily at the 3 position of the imidazopyridine system at equimolecular ratios of the reagents, but also proceeds at the 5 position of the furan ring when there is a slight excess of formaldehyde and amine. The structure of the product of monomorpholinomethylation was proved by nitration to give a mononitro derivative that was identical to the 3-morpholinomethyl-2-(5-nitro-2-furyl)imidazo[1,2-*a*]pyridine prepared by the morpholinomethylation of 2-(5-nitro-2-furyl)imidazo[1,2-*a*]pyridine. Thin-layer chromatography and IR and UV spectroscopy were used to prove the structures.

It is known that imidazo[1,2-*a*]pyridine [1,2] and its 2-aryl derivatives [3] form N,N-disubstituted 3-aminomethyl derivatives with formaldehyde and secondary amines. In addition, furans with electron-donating substituents in the α position undergo the Mannich reaction [4-8]. It could therefore be expected that, in the case of 2-(2-furyl)imidazo[1,2-*a*]pyridine (I), the Mannich reaction might be accomplished both at the 3 position of the imidazopyridine system and at the 5 position of the furan ring.



In fact, a dimorpholinomethylation product is obtained from the reaction of the furylimidazopyridine with excess formalin and morpholine in glacial acetic acid at 60° with subsequent treatment of the reaction mixture with alkali. In view of the fact that the base could not be obtained in pure form because of its hygroscopicity, it was identified as its salts with hydrochloric and 3,5-dinitrobenzoic acids [trihydrochloride trihydrates and tri-(3,5-dinitrobenzoates)].

Since the compound obtained was not nitrated by a mixture of 70% nitric and concentrated sulfuric acids, one can conclude, in agreement with [9], that the 3 position in the imidazopyridine system and the 5 position in the furan ring are occupied, i.e., it has the 3-morpholinomethyl-2-(5-morpholinomethyl-2-furyl)-imidazo[1,2-*a*]pyridine (IIa) structure.

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga. Translated from *Khimiya Geterotsiklichesikh Soedinenii*, No. 6, pp. 818-821, June, 1971. Original article submitted October 30, 1970.

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When the reaction is run with equimolecular amounts of the reagents under the same conditions, one obtains 3-morpholinomethyl-2-(2-furyl)imidazo[1,2-*a*]pyridine (IIIa), the structure of which was established by subsequent nitration with a mixture of 70% nitric acid and concentrated sulfuric acid, in analogy with the nitration of 2-phenylimidazo[1,2-*a*]pyridine [10], as a result of which mononitro derivative Va is obtained. Derivative Va is identical to the product of the morpholinomethylation of 2-(5-nitro-2-furyl)imidazo[1,2-*a*]pyridine (IV), as confirmed by a comparison of the results of elementary analysis, melting points, and UV spectra of the bases and dihydrochlorides of both samples. The IIIa structure of the monomorpholinomethylation product is additionally confirmed by the fact that it does not undergo nitrosation, i.e., the 3 position in the imidazopyridine system is occupied.

Morpholinomethylation of nitrofurylimidazopyridine IV by refluxing with morpholine hydrochloride and paraformaldehyde in n-butanol or amyl alcohol made it possible to obtain 3-morpholinomethyl-2-(5-nitro-2-furyl)imidazo[1,2-*a*]pyridine (Va) in 83% yield, while the method mentioned earlier (in acetic acid) gave a 55% yield. 3-Piperidinomethyl derivatives of 2-(2-furyl)imidazo[1,2-*a*]pyridine (IIIb) and 2-(5-nitro-2-furyl)imidazo[1,2-*a*]pyridine (Vb) were prepared in the same way as morpholinomethyl derivative IIIa.

The products of the aminomethylation of 2-(2-furyl)imidazo[1,2-*a*]pyridine in the base form are viscous but not always crystallizable substances. They were therefore isolated and identified primarily as their salts. The hydrochlorides form hygroscopic crystal hydrates, while the picrates and 3,5-dinitrobenzoates proved to be thermally unstable.

In contrast to the products of the aminomethylation of I, the products of the aminomethylation of nitrofurylimidazo[1,2-*a*]pyridine V are isolated from the reaction mixtures as stable, finely crystalline, light-yellow substances. The dihydrochlorides of Va and Vb are hydrolyzed by water to the free bases. In contrast to the starting furylimidazopyridine, which gives a carmine red color with sulfuric acid, the aminomethylation products dissolve in sulfuric acid to give green solutions. The aminomethylation products, in contrast to the starting furyl- and nitrofurylimidazopyridines, do not sublime in *vacuo*. They are readily soluble in alcohol, acetic acid, and dimethylformamide but are insoluble in water and ether.

As expected, the mono- and diaminomethylation products have UV spectra of the same character as that of the starting I. A difference is observed only in the intensity of the absorption, and the diaminomethyl derivative (II) has the strongest absorption. As compared with the IR spectra of the starting imidazopyridines, the IR spectra of the Mannich reaction products contain absorption bands at ~ 2950 and 2870 cm^{-1} , which correspond to ν_{as} and ν_{s} of the CH_2 group, and at 1480 – 1490 cm^{-1} , which correspond to the scissors vibrations of the CH_2 group in the morpholinomethyl and piperidinomethyl groupings.

EXPERIMENTAL

The UV spectra of $5 \cdot 10^{-5}\text{ M}$ solutions were obtained at a layer thickness of 1 cm with an SF-4a spectrophotometer. The IR spectra of hexachlorobutadiene (2000 – 3600 cm^{-1} and 1300 – 1500 cm^{-1}) and Nujol (800 – 2000 cm^{-1}) suspensions were obtained with a UR-20 spectrometer.

Chromatography was accomplished in an ethyl acetate–isopropyl alcohol–25% ammonium hydroxide (45:35:20) system on plates of the "Silufol" UV₂₅₄ type.

The salts of the Mannich bases were obtained by the addition of absolute alcohol solutions of hydrogen chloride, picric acid, or 3,5-dinitrobenzoic acid to charcoal-purified solutions of the bases in the same solvent. The hydrochlorides were precipitated by the addition of absolute ether.

3-Morpholinomethyl-2-(5-morpholinomethyl-2-furyl)imidazo[1,2-*a*]pyridine (IIa). A 3.68-g (0.02 mole) sample of 2-(2-furyl)imidazo[1,2-*a*]pyridine [11] (I) was dissolved in 18 ml of acetic acid, and a solution of 4.16 g (0.05 mole) of 36% formalin and 4.35 g (0.05 mole) of morpholine in 15 ml of acetic acid was added dropwise. The solution was heated at 60° with constant stirring for 3 h. Neutralization of the mixture with NaOH solution gave a resinous mass that, after drying in a desiccator over H_2SO_4 , was converted to 4.21 g (74.5%) of a glass-like product.

Trihydrochloride of IIa. This was obtained as colorless crystals with mp 185–186°. Found %: C 46.12; H 6.78; Cl 19.73. $\text{C}_{21}\text{H}_{26}\text{N}_4\text{O}_3 \cdot 3\text{HCl} \cdot 3\text{H}_2\text{O}$. Calculated %: C 46.20; H 6.46; Cl 19.41. UV spectrum in 0.1 N HCl: λ_{max} 254, 310 nm; $\log \epsilon$ 4.34, 4.25.

Tri-(3,5-dinitrobenzoate) of IIa. This had mp 103°. Found %: C 49.87; H 3.99; N 13.65. $\text{C}_{21}\text{H}_{26}\text{N}_4\text{O}_3 \cdot 3\text{C}_7\text{H}_4\text{N}_2\text{O}_6$. Calculated %: C 49.51; H 3.75; N 13.74.

3-Morpholinomethyl-2-(2-furyl)imidazo[1,2-*a*]pyridine (IIIa). Like IIa, this was obtained from equimolecular (0.03 mole) amounts of the reagents. The reaction mixture was extracted with 150 ml of ethyl acetate after neutralization. The solvent was removed by distillation to give 67% of a viscous, syrupy mass. Reprecipitation from benzene by petroleum ether gave light crystals with mp 70-72° that darkened in light. Found %: C 67.97; H 6.18; N 14.67. $C_{16}H_{17}N_3O_2$. Calculated %: C 67.81; H 6.04; N 14.83. UV spectrum in alcohol: λ_{max} 255, 330 nm; $\log \epsilon$ 4.45, 4.02. R_f 0.87.

Dihydrochloride of IIIa. This was obtained as colorless hygroscopic crystals that darkened in light and had mp 193-195°. Found %: C 49.45; H 5.39; Cl 18.30. $C_{16}H_{17}N_3O_2 \cdot 2HCl \cdot 2H_2O$. Calculated %: C 49.10; H 5.91; Cl 18.11. UV spectrum in 0.1 N HCl: λ_{max} 255, 310 nm; $\log \epsilon$ 4.16, 4.07.

Dipicrate of IIIa. This had mp 161-163°. Found %: C 45.49; H 3.25; N 17.11. $C_{16}H_{17}N_3O_2 \cdot 2C_6H_3N_3O_7$. Calculated %: C 45.35; H 3.12; N 17.00.

Di-(3,5-dinitrobenzoate) of IIIa. This had mp 159-161°. Found %: C 51.11; H 3.82; N 13.95. $C_{16}H_{17}N_3O_2 \cdot 2C_7H_4N_2O_6$. Calculated %: C 50.92; H 3.56; N 13.85.

3-Piperidinomethyl-2-(2-furyl)imidazo[1,2-*a*]pyridine (IIIb). In analogy to IIIa, this was obtained in 81% yield from I.

Di-(3,5-dinitrobenzoate) of IIIb. This had mp 178-179°. Found %: C 52.46; H 3.71; N 14.04. $C_{17}H_{19}N_3O \cdot 2C_7H_4N_2O_6$. Calculated %: C 52.76; H 3.85; N 13.89.

3-Morpholinomethyl-2-(5-nitro-2-furyl)imidazo[1,2-*a*]pyridine (Va). A. A 2.29-g (0.01 mole) sample of 2-(5-nitro-2-furyl)imidazo[1,2-*a*]pyridine (IV) was dissolved in 12 ml of acetic acid, and a solution of 0.98 g (0.01 mole) of 36% formalin and 1.03 g (0.01 mole) of morpholine in 10 ml of acetic acid was added to it dropwise. The mixture was heated for 2 h on a boiling-water bath with constant stirring. After cooling, the acetic acid was removed by distillation, and an aqueous solution of sodium bicarbonate was added until the mixture gave a neutral reaction. The precipitate was filtered to give 1.81 g (55%) of a product with mp 197-199° (after reprecipitation from dimethylformamide by the addition of water). Found %: N 16.84. $C_{16}H_{16}N_4O_4$. Calculated %: N 17.06.

Dihydrochloride of Va. This was obtained as colorless, hygroscopic crystals that darkened on storage in light and melted at 218-220°. Found %: C 46.20; H 5.00; Cl 16.85. $C_{16}H_{16}N_4O_4 \cdot 2HCl \cdot H_2O$. Calculated %: C 45.83; H 4.80; Cl 16.91. UV spectrum in 0.1 N HCl: λ_{max} 229, 265, 348 nm; $\log \epsilon$ 4.43, 4.06, 4.19.

B. A 4.9-g (0.017 mole) sample of IIIa was dissolved in 15 ml of acetic acid. The solution was cooled with ice and added dropwise with constant stirring to a solution of 1.7 ml (0.026 mole) of 70% nitric acid in 41 ml of concentrated sulfuric acid. The precipitate that formed after stirring for 1 h and the addition of 20% NaOH until the mixture gave a weakly alkaline reaction was filtered and washed with water to give 0.84 g of product. Extraction of the mother liquor with ethyl acetate gave an additional 1.02 g of Va. The overall yield of Va with mp 197-199° (from aqueous dimethylformamide) was 33%. The compound and its dihydrochloride were identical to the samples obtained by method A.

C. A mixture of 2.29 g (0.01 mole) of IV, 0.6 g (0.02 mole) of paraformaldehyde, 1.23 g (0.01 mole) of morpholine hydrochloride, and 25 ml of amyl alcohol was refluxed for 30 min and cooled. The resulting precipitate was filtered and washed with dilute ammonium hydroxide and water to give 2.8 g (83%) of Va as light-yellow crystals with mp 197-199°. This compound and its dihydrochloride were identical to the samples described above.

3-Piperidinomethyl-2-(5-nitro-2-furyl)imidazo[1,2-*a*]pyridine (Vb). Like Va, this was obtained in 74.5% yield from IV by method A and had mp 190-191° (from aqueous methanol). Found %: C 62.39; H 5.28; N 17.44. $C_{17}H_{18}N_4O_3$. Calculated %: C 62.56; H 5.55; N 17.16.

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