STUDIES IN THE IMIDAZOLE SERIES

LVI.* SOME NUCLEOPHILIC SUBSTITUTION REACTIONS OF 4(5)-NITRO-5(4)-CHLORO(BROMO)IMIDAZOLES

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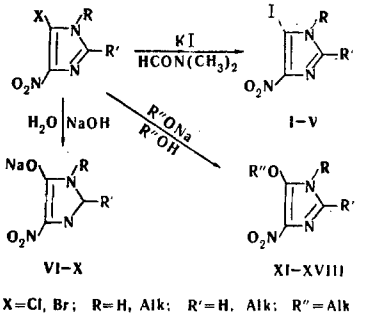
Reaction of the appropriate 4(5)-nitro-5(4)-chloro(bromo)imidazole with potassium iodide, sodium hydroxide, sodium alcoholates, and secondary amines yielded 1-alkyl- and 1,2-dialkyl-4-nitro-5-iodo-, 2-alkyl-4(5)-nitro-5(4)-iodo-, 1-alkyl- and 1,2-dialkyl-4-nitro-5-hydroxy-, 2-alkyl-4(5)-nitro-5(4)-hydroxy-, 1-alkyl- and 1,2-dialkyl-4-nitro-5-alkoxy-, 2-alkyl-4(5)-nitro-5(4)-alkoxy-, 1-alkyl-4-dialkylamino-5-nitro-, and 1-alkyl-4,5-bis(dialkylamino)imidazoles.

In a continuation of our research [2-5], we have studied the reactions of 1-alkyl- and 1,2-dialkyl-4-nitro-5-chloroimidazoles [6], 2-alkyl-4(5)-nitro-5(4)-bromo- and 1,2-dialkyl-4-nitro-5-bromoimidazoles [7] with potassium iodide, sodium hydroxide, and sodium alkoxides; the corresponding 4-nitro-5-iodoimidazoles (I-V) (Table 1), 4-nitro-5-hydroxyimidazoles (stable only in the form of their sodium salts, VI-X), and 4-nitro-5-alkoxyimidazoles (XI-XVIII) were obtained.



X=Cl, Br; R=H, Alk; R'=H, Alk; R''=Alk

In the synthesis of 1,2-dimethyl-4-nitro-5-iodoimidazole (III) it was demonstrated that 1,2-dialkyl-4-nitro-5-iodoimidazoles can also be obtained by the alkylation of 2-alkyl-4(5)-nitro-5(4)-iodoimidazoles (for example, II) with alkyl halides or dialkyl sulfates in alkaline media.

The above methods for the synthesis of 4-nitro-5-iodoimidazoles [8] and 4-nitro-5-hydroxyimidazoles which were already briefly reported in [9], are simpler than known methods for the preparation of 4(5)-nitro-5(4)-iodoimidazoles [10] by treatment of 4,5-diiodoimidazoles with a mixture of nitric and sulfuric acids and of 4-nitro-5-hydroxyimidazoles [11] by heating 1-alkyl-4-nitro-5-chloroimidazoles with potassium arsenite in ethanol.

Prior to our brief publications [9, 12], 4(5)-nitro-5(4)-alkoxyimidazoles were unknown. Two compounds of this series, obtained by the reaction of 1,2-dimethyl-4-bromo-5-nitroimidazole with sodium methoxide and ethoxide, were described only recently [13].

*See [1] for communication LV.

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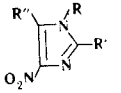
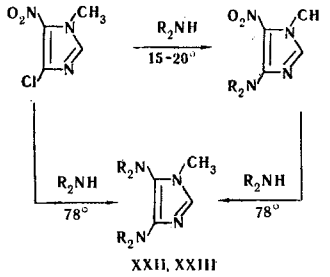
TABLE 1. 4-Nitro-5-iodo(hydroxy, alkoxy, N-heteryl)imidazoles



Comp.	R	R′	R″	mp (decomp)	Empirical formula	Found, %				Calculated, %				Yield, %
						C	H	N	I	C	H	N	I	
I	CH_3	H	I	236—237	$C_4H_4IN_3O_2$	19,3	1,7	16,4	49,6	19,0	1,6	16,6	50,2	63
II	H	CH_3	I	244—245	$C_4H_4IN_3O_2$	19,3	1,5	16,3	50,0	19,0	1,6	16,6	50,2	67
III	CH_3	CH_3	I	199—200	$C_5H_6IN_3O_2$	22,7	2,1	15,2	47,5	22,5	2,3	15,8	47,5	38—83
IV	C_2H_5	CH_3	I	196—197	$C_6H_8IN_3O_2$	25,9	3,0	14,9	45,2	25,6	2,9	15,0	45,2	50
V	CH_2CH_2OH	CH_3	I	163—164	$C_6H_8IN_3O_3$	24,4	2,6	14,2	41,9	24,3	2,7	14,1	42,7	90
VI	CH_3	H	ONa	293—295	$C_4H_4N_3O_3Na$	29,0	2,2	25,0	—	29,1	2,4	25,0	—	74
VII	Na	CH_3	ONa	210—220	$C_4H_3N_3O_3Na_2 \cdot 2H_2O$	21,5	3,2	18,8	—	21,9	3,2	18,2	—	55
VIII	CH_3	CH_3	ONa	245—246	$C_5H_6N_3O_3Na \cdot 2H_2O$	28,2	4,7	19,8	—	27,9	4,9	19,5	—	86
IX	C_2H_5	CH_3	ONa	138—150	$C_4H_8N_3O_3Na \cdot 0{,}5H_2O$	35,8	4,4	20,7	—	35,6	4,5	20,8	—	90
X	C_4H_9	C_3H_7	ONa	93—94	$C_{10}H_{16}N_3O_3Na \cdot H_2O$	45,0	6,6	16,1	—	45,0	6,8	15,7	—	90
XI	CH_3	H	OCH_3	134—135	$C_5H_7N_3O_3$	38,1	4,5	26,3	—	38,2	4,5	26,7	—	77—95
XII	CH_3	H	OC_2H_5	64—65	$C_6H_9N_3O_3$	42,0	5,2	24,3	—	42,1	5,3	24,5	—	90
XIII	CH_3	H	OC_3H_7-*i*	65—66	$C_7H_{11}N_3O_3$	45,1	5,7	22,4	—	45,4	6,0	22,7	—	73
XIV	H	CH_3	OCH_3	186—187	$C_5H_7N_3O_3$	38,6	4,5	26,3	—	38,2	4,5	26,7	—	87
XV	H	CH_3	OC_2H_5	169—170	$C_6H_9N_3O_3$	42,1	5,3	24,3	—	42,1	5,3	24,5	—	79
XVI	CH_3	CH_3	OCH_3	180—181	$C_6H_9N_3O_3$	42,4	5,0	—	—	42,1	5,3	—	—	50
XVII	C_2H_5	CH_3	OC_2H_5	55—56	$C_8H_{13}N_3O_3$	48,1	6,5	20,8	—	48,2	6,6	21,1	—	55
XVIII	CH_2CH_2OH	CH_3	OC_2H_5	103—104	$C_8H_{13}N_3O_4$	44,4	5,9	19,5	—	44,6	6,1	19,5	—	43
XIX	CH_3	H	C_4H_8N[a]	106—107	$C_8H_{12}N_4O_2$	49,2	6,3	28,9	—	49,0	6,2	28,6	—	85
XX	CH_3	H	$C_5H_{10}N$[b]	70—71	$C_9H_{14}N_4O_2$	51,3	6,5	26,8	—	51,4	6,7	26,6	—	78
XXI	CH_3	H	OC_4H_8N[c]	123—124	$C_8H_{12}N_4O_3$	45,5	5,8	26,3	—	45,3	5,7	26,4	—	78

[a]Pyrrolidino.
[b]1-Piperidino.
[c]4-Morpholino.

The reaction of 1-methyl-4-chloro-5-nitroimidazole [6] with secondary amines (pyrrolidine, piperidine, and morpholine), in contrast to the reaction of this compound [2] and 1,2-dialkyl-4-chloro(bromo)-5-nitroimidazoles [2, 13] with ammonia and primary amines, proceeds extremely energetically. When the reaction is carried out in ethanol with cooling (18-20°), 1-methyl-4-N-heteryl-5-nitroimidazoles (XIX-XXI, Table 1) are obtained. Under more severe conditions (70-80°), the nitro group and the chlorine atom are replaced by amine residues to give the corresponding 1-methyl-4,5-di(N-heteryl)imidazoles (XXII and XXIII). These compounds can also be obtained by the reaction of 1-methyl-4-N-heteryl-5-nitroimidazoles by heating with secondary amines. Thus, XXIII was synthesized from XXI.



XXII, XXIII

R_2NH = pyrrolidine, piperidine, morpholine

EXPERIMENTAL

Nitroimidazoles (I-V, Table 1). A. A mixture of 0.02 mole of nitrochloro(bromo)imidazole and 0.06 mole of KI in 50 ml of dimethylformamide was refluxed for 3-5 h, the solvent was removed by vacuum distillation, and the residue was washed with water and crystallized from acetone (I and IV) or water (II, III, and V).

B. A mixture of 1.26 g (0.005 mole) of II, 1.6 g (0.009 mole) of methyl iodide, 6 ml of 1 N NaOH, and 20 ml of methanol was refluxed for 6 h, the solvent was removed by distillation, and the residue was washed with water to give 1.1 g (83%) of III with mp 199-200° (from water).

C. A mixture of 1.26 g (0.005 mole) of II, 0.7 g (0.006 mole) of dimethyl sulfate, 11 ml of 1 N NaOH, and 9 ml of water was heated and worked up as described in B to give 0.5 g (38%) of III with mp 199-200° (from water).

Sodium Salts of Nitrohydroxyimidazoles (VI-X). A solution of 0.02 mole of nitrochloro(bromo)imidazole and 0.04 mole of NaOH in 50-100 ml of 50% methanol was refluxed for 3-5 h, the solvent was removed by vacuum distillation, and the residue was washed with a small amount of water and crystallized from water. In view of its very high solubility in water, IX was separated from NaCl by refluxing in ethanol, filtration from the undissolved NaCl, and vacuum evaporation of the solution. In the preparation of VII, 0.06 mole of NaOH was used per 0.02 mole of 2-methyl-4(5)-nitro-5-(4)-bromoimidazole. The yellow or orange crystalline substances, which were soluble in water and lower alcohols and insoluble in acetone, darkened immediately on acidification of the aqueous solutions.

Nitroalkoxyimidazoles (XI-XVIII). The nitrochloro(bromo)imidazole (0.05 mole) was added to a solution of the sodium alkoxide, prepared from 0.05 g-atom of sodium and 100 ml of the anhydrous alcohol, and the solution was refluxed for 5 h and filtered. The solvent was removed by vacuum distillation, and the residue was washed with water and crystallized from methanol (XI), 50% ethanol (XIII), acetone (XV), ether (XVII), or from water (XII, XIV, and XVIII). In the preparation of XI-XIII, 0.1 mole of sodium alkoxide was used per 0.05 mole of 2-methyl-4(5)-nitro-5(4)-bromoimidazole and, after completion of the reaction and removal of the solvent by distillation, the sodium salts of XI-XIII were dissolved in water and acidified with acetic acid to pH 4-5.

1-Methyl-4-pyrrolidino(piperidino, morpholino)-5-nitroimidazoles (XIX-XXI). A total of 0.18 mole of pyrrolidine, piperidine, or morpholine was added with cooling and stirring to a solution of 0.06 mole of 1-methyl-4-chloro-5-nitroimidazole in 150 ml of absolute ethanol. The solution was stirred at 18-20° for 4 h, allowed to stand overnight, and the solvent was removed by vacuum distillation at no higher than 20°. The resulting orange crystals were washed with water and crystallized from ethanol (XIX and XX) or water (XXI).

1-Methyl-4,5-dipiperidinoimidazole (XXII). Piperidine [13.8 g (0.16 mole)] was added with cooling to a solution of 6.45 g (0.04 mole) of 1-methyl-4-chloro-5-nitroimidazole in 25 ml of absolute ethanol. The reaction mass was refluxed for 5.5 h, cooled to 0°, and filtered away from the precipitate of piperidine hydrochloride. The solvent and excess piperidine were removed from the filtrate by vacuum distillation, and the dark-brown residue was dissolved in chloroform. The solution was washed with water and dried over sodium sulfate, and the solvent was removed by vacuum distillation to give 8.7 g (87%) of impure XXII. The product was a viscous liquid with bp 84° (4 mm) which was soluble in water and organic solvents. The picrate had mp 173-174° (decomp., from ethanol). Found %: C 50.7; H 5.9; N 20.5. $C_{14}H_{24}N_4 \cdot C_6H_3N_3O_7$. Calculated %: C 50.3; H 5.7; N 20.5.

1-Methyl-4,5-dimorpholinoimidazole (XXIII). A. Morpholine [15.6 g (0.18 mole)] was added with cooling to a solution of 9.66 g (0.06 mole) of 1-methyl-4-chloro-5-nitroimidazole and 30 ml of anhydrous ethanol. The mixture was refluxed and worked up as described for the preparation of XXII. The dark-brown liquid remaining after removal of the chloroform by distillation was cooled, and the resulting precipitate was filtered, washed with ether, ethyl acetate, and ether to give 4.2 g (32%) of the hydrate of base XXIII with mp 72-73° (from ether). Found %: C 53.3; H 7.8; N 20.6. $C_{12}H_{20}N_4O_2 \cdot H_2O$. Calculated %: C 53.3; H 8.2; N 20.7. Anhydrous base XXIII with mp 116-117° was obtained by drying the hydrate in a vacuum desiccator over sulfuric acid. Found %: C 57.0; H 8.0; N 22.5. $C_{12}H_{20}N_4O_2$. Calculated %: C 57.1; H 8.0; N 22.2. The hydrochloride had mp 212-213° (decomp., purified by reprecipitation from absolute ethanol with ether). Found %: Cl 12.5. $C_{12}H_{20}N_4O_2 \cdot HCl$. Calculated %: Cl 12.3. The picrate had mp 177-178° (from water). Found %: N 20.0. $C_{12}H_{20}N_4O_2 \cdot C_6H_3N_3O_7$. Calculated %: N 20.4.

B. A mixture of 2.1 g (0.01 mole) of XXI and 2.8 g (0.032 mole) of morpholine in 15 ml of anhydrous ethanol was refluxed for 2.5 h and worked up as in experiment A to give 2.1 g (60%) of base XXIII with mp 72-73° (from ether).

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