Chemistry of Heterocyclic Compounds, Vol.35, No. 1, 1999

INVESTIGATIONS ON IMIDAZOLES

98.* REACTIONS OF NITROHALOIMIDAZOLES WITH AMINO ACIDS

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The reaction of 5-chloro(bromo)-1-methyl(1,2-dimethyl)-4-nitroimidazoles and 4-chloro-1-methyl-5-nitroimidazole with amino acids has been studied. This has enabled a series of N-(4-nitro-5-imidazolyl)- and N-(5-nitro-4-imidazolyl)- substituted amino acids to be synthesized. Esters of some of these acids have been obtained.

Three groups of biologically active amino acids containing the imidazole nucleus within their structure are known. These are the irreplaceable amino acid histidine [2], the biosynthetic precursor of the purine nucleotides 4(5)-amino-5(4)-imidazolecarboxamide and its antagonists [3-7], and 1-carboxyalkylimidazoles [8-11] in which a nitrogen atom is common to both amino acid and imidazole.

N-Substituted amino acids in which one hydrogen atom of the amino group is replaced by imidazole residue have not been described in the literature. With the aim of obtaining this type of compound we have studied the reaction of 5-chloro-1-methyl-4-nitro- (I), 5-bromo-1,2-dimethyl-4-nitro- (II), and 4-chloro-1-methyl-5-nitroimidazoles (III) with a series of aliphatic and aromatic amino acids (glycine, valine, β-alanine, γ-aminobutyric, *p*-aminophenylacetic, and *m*- and *o*-aminobenzoic acids).

The reaction of nitrohaloimidazoles I and II with amino-acids proceeds readily on heating the components in water or in *n*-butanol in the presence of potassium hydroxide and leads to formation of the corresponding N-imidazolyl-substituted amino acids IV - IX (in 65-80% yield).

The reaction of 5-halo-4-nitroimidazoles I and II with anthranilic acid proceeds with significantly more difficulty. It occurs only under the conditions of the Ullman reaction, i.e. on extended boiling in amyl alcohol in the presence of sodium bicarbonate and cuprous chloride catalyst. The more reactive 4-chloro-1-methyl-5-nitroimidazole III reacts with anthranilic acid without a catalyst. Yields of the N-imidazolyl-substituted anthranilic acids X - XII were 61-72%.

The esters of certain N-imidazolylamino acids (especially anthranilic) XIII - XVI are of particular interest.

Acid X is readily esterified in methanol in the presence of hydrogen chloride with formation of methyl ester XIII (in 90% yield). Acid XI, which is similar in structure, under the same conditions forms methyl ester XIV in 20% yield. Ester XIV was obtained in high yield (86%) by the reaction of acid XI with dimethyl sulfate in DMF in the presence of potassium carbonate.

N-(1-Methyl-5-nitro-4-imidazolyl)anthranilic acid XII as its potassium salt was esterified with dimethyl sulfate and alkyl halides (CH_3I, C_2H_5I) in DMF. The methyl XV and ethyl XVI esters were obtained in this way in 61-65% yield. Samples of ester XV obtained by the different methods proved to be identical.

*For Part 97 see [1].

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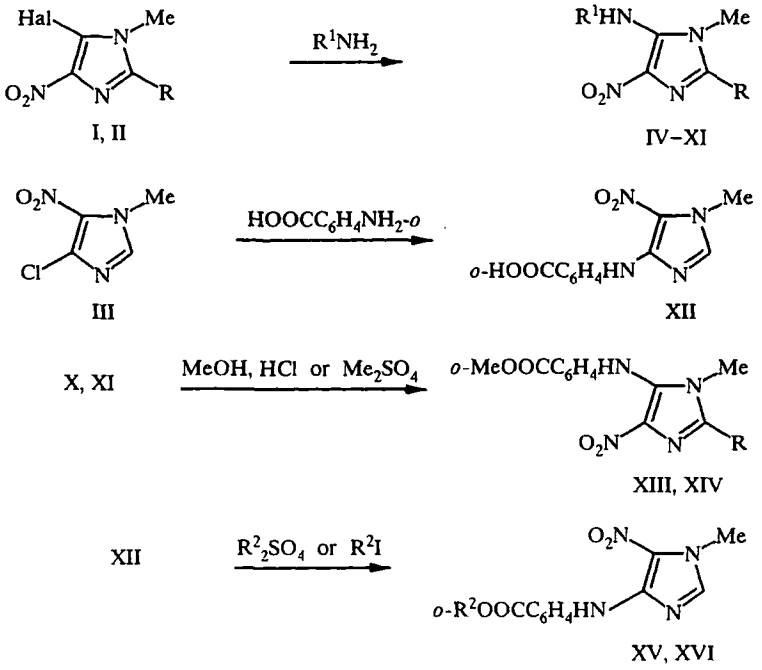
0009-3122/99/3501-0045$22.00©1999 KluwerAcademic/Plenum



I Hal = Cl; II Hal = Br; I, IV, VI – X, XIII R = H; II, V, XI, XIV R = Me; IV, V $R^1 = CH_2COOH$; VI $R^1 = CH_2CH_2COOH$; VII $R^1 = CH_2CH_2CH_2COOH$; VIII $R^1 = p\text{-}C_6H_4CH_2COOH$; IX R^1 = m-C_6H_4COOH; X, XI $R^1 = o\text{-}C_6H_4COOH$; XV R^2 = Me; XVI R^2 = Et

The data obtained indicate that alkylation of N-nitroimidazolylanthranilic acids XI and XII by both dimethyl sulfate and by alkyl halides occurs at the carboxyl group with the formation of esters, the secondary amino group was not affected.

The structures of compounds IV - XVI were confirmed by data of elemental analysis, IR, PMR, and mass spectra.

Peaks for the molecular ions corresponding to the molecular weight of these substances were recorded in the mass spectra of compounds IV, IX, X, XII, and XVI.

In the IR spectra of compounds IV - XVI absorption bands for the NO_2 group at 1350-1410 and 1500-1570, for the NH group at 1590-1640 and 3120-3350, and for the CO group at 1670-1740 cm^{-1} have been observed.

The PMR spectra taken for the set of compounds confirmed their structure as N-imidazolyl-substituted amino acids.

EXPERIMENTAL

The IR spectra of compounds were taken on a UR 20 instrument in KBr disks. Mass spectra were obtained on a Varian MAT 112 spectrometer by direct insertion of samples into the ion source. Temperature of the ionization chamber was 180°C, energy of ionizing electrons 70 eV. The PMR spectra were drawn on a Tesla BS 497 spectrometer with an operating frequency of 100 MHz, internal standard was HMDS. A check on the progress of reactions and the homogeneity of the compounds obtained was carried out by TLC on Silufol UV 254 plates.

5-Chloro-1-methyl-4-nitroimidazole (I) [12], 5-bromo-1,2-dimethyl-4-nitroimidazole II [13], and 4-chloro-1-methyl-5-nitroimidazole III [14] were obtained by known methods.

N-(1-Methyl-4-nitro-5-imidazolyl)glycine (IV). Glycine (1.5 g, 0.02 mole) and compound I (1.61 g, 0.01 mole) were added to a solution of KOH (1.12 g, 0.02 mole) in water (70 ml). The mixture was heated at 70-90°C for 1.5 h, cooled, and acidified to pH 6 with dilute HCl. The precipitated solid was filtered off, washed with water, and dried. Compound IV (1.5 g) was obtained.

Compounds V, VII, VIII, and IX were obtained in much a same way (Table 1).

TABLE 1. Data of Elemental Analysis of Compounds IV - XVI

Compound	Empirical formula	Found, % / Calculated, %			Mp,°C	Yield, %
		C	H	N		
IV	$C_6H_8N_4O_4$	35,97 / 36,00	4,13 / 4,03	27,83 / 27,99	217...218	75
V	$C_7H_{10}N_4O_4$	39,45 / 39,26	4,79 / 4,71	25,91 / 26,16	193,5...194,5	70
VI	$C_7H_{10}N_4O_4$	39,29 / 39,26	4,82 / 4,71	25,77 / 26,16	203,5...204,5	78
VII	$C_8H_{12}N_4O_4 \cdot H_2O$	39,74 / 39,02	5,85 / 5,69	22,41 / 22,76	158...161	65
VIII	$C_{12}H_{12}N_4O_4$	52,60 / 52,17	4,43 / 4,38	20,33 / 20,28	190...192	80
IX	$C_{11}H_{10}N_4O_4$	50,72 / 50,36	4,19 / 3,84	20,97 / 21,37	214...215	61
X	$C_{11}H_{10}N_4O_4$	50,56 / 50,36	4,00 / 3,84	21,32 / 21,37	206...207	72
XI	$C_{12}H_{12}N_4O_4$	51,95 / 52,17	4,51 / 4,38	19,85 / 20,28	228...230	63
XII	$C_{11}H_{10}N_4O_4$	50,73 / 50,36	4,12 / 3,84	21,34 / 21,37	221,5...223	61
XIII	$C_{12}H_{12}N_4O_4$	51,90 / 52,17	4,21 / 4,38	20,15 / 20,28	213...214	90
XIV	$C_{13}H_{15}N_4O_4$	53,86 / 53,60	4,88 / 5,15	19,24 / 19,24	210...211	86
XV	$C_{12}H_{12}N_4O_4$	51,85 / 52,17	4,30 / 4,38	20,47 / 20,28	192...193	61...65
XVI	$C_{13}H_{14}N_4O_4$	53,57 / 53,79	5,19 / 4,82	18,77 / 19,31	138...140	62

N-(1-Methyl-4-nitro-5-imidazolyl)-β-alanine (VI). β-Alanine (1.78 g, 0.02 mole) and compound I (1.61 g, 0.01 mole) were added to a solution of KOH (1.12 g, 0.02 mole) in *n*-butanol (100 ml). The mixture was boiled for 2 h, cooled, the solid mixture of potassium chloride and the potassium salt of acid VI was filtered off, dissolved in water, and treated as for the preparation of compound IV. Yield of compound VI was 1.7 g.

N-(1-Methyl-4-nitro-5-imidazolyl)anthranilic Acid (X). A mixture of anthranilic acid (6.85 g, 0.05 mole), $NaHCO_3$ (8.4 g, 0.1 mole), and *n*-amyl alcohol (50 ml) was heated at 140-145°C for 30-40 min with a Dean and Stark stillhead until distillation of water had ceased. Compound I (8.05 g, 0.05 mole) and cuprous chloride (1.0 g) were added to the suspension of sodium anthranilate. The mixture was boiled for 5-6 h, cooled, the precipitate

TABLE 2. IR Spectral Characteristics and Molecular Ion Peaks (M^+) of Compounds IV - XVI

Compound	M^+	IR spectrum, ν, cm^{-1}		
		NO_2	NH	CO
IV	201	1350, 1550	1640, 3300	1740
V		1350, 1550	1640, 3300	1740
VI		1410, 1550	1610, 3280	1680
VII		1360, 1550	1620, 3340	1710
VIII		1350, 1540	1620, 3350	1730
IX	262			
X	262	1370, 1500	1600, 3120	1700
XI		1370, 1550	1590, 3260	1670
XII	262	1350, 1570	1620, 3120	1680
XIII			1600, 3300	1700
XIV		1370, 1560	1600, 3310	1690
XV		1350, 1540	1610, 3140	1700
XVI	290	1355, 1540	1600, 3140	1700

TABLE 3. PMR Spectral Characteristics of Compounds IV, VI, VII, and IX-XVI

Compound	Chemical shift, δ, ppm*			
	$N—CH_3$ (3H, s)	$C_{(2)}—H$ (1H, s)	benzene ring protons	protons of other groups
IV	3,85	7,52		4,48 (2H, d, J = 6 Hz, NCH_2); 7,74 (1H, t, J = 6 Hz, NH)
VI	3,79	7,38		
VII	3,80	7,32		1,88 (2H, m, β-CH_2); 2,39 (2H, t, J = 8 Hz, CH_2NH); 3,61 (2H, m, CH_2COOH)
IX	3,46	7,71	6,95 (1H, m, 2-H); 7,40 (3H, m, 4,5,6-H)	9,06 (1H, br. s, NH)
X	3,65	8,31	6,40 (1H, d, J = 8 Hz, 3-H); 6,85 (1H, t, J = 8 Hz, 4-H); 7,20 (1H, t, J = 8 Hz, 5-H); 7,80 (1H, d, J = 8 Hz, 6-H)	
XI	3,45		6,60 (1H, m, 4-H); 6,90 (1H, m, 5-H); 7,38 (1H, m, 3-H); 8,00 (1H, m, 6-H)	2,38 (3H, s, $C_{(2)}CH_3$)
XII	3,95		7,02 (1H, t, J = 6 Hz, 4-H); 7,54 (1H, t, J = 8 Hz, 5-H); 7,96 (2H, m, $C_{(2)}$-H, 3-H); 8,90 (1H, d, J = 7 Hz, 6-H)	5,50 (1H, br. s, OH); 12,30 (1H, br. s, NH)
XIII	3,65	8,32	6,40 (1H,d, J = 5 Hz, 3-H); 6,85 (1H, t, J = 6 Hz, 4-H); 7,15 (1H, t, J = 6 Hz, 5-H); 7,76 (1H, d, J = 5 Hz, 6-H)	3,42 (3H, s, OCH_3)
XIV	3,74			2,41 (3H, s, CCH_3); 3.32 (3H, s, OCH_3)
XV	4,10	8,46	7,12 (1H, t, J = 8 Hz, 4-H); 7,65 (1H, t, J = 8 Hz, 5-H); 8,00 (1H, d, J = 6 Hz, 3-H); 8,95 (1H, d, J = 8 Hz, 6-H)	3,99 (3H, s, OCH_3); 11,90 (1H, s, NH)
XVI	4,11	8,45	7,12 (1H, t, J = 6 Hz, 4-H), 7,64 (1H, t, J = 6 Hz, 5-H); 8,00 (1H, d, J = 8 Hz, 6-H); 8,98 (1H, d, J = 8 Hz, 3-H)	1,40 (3H, t, J = 8 Hz, CH_3CH_2); 4,40 (2H, q, J = 6 Hz, CH_2CH_3); 11,91 (1H, br. s, NH)

*Spectra taken in solutions: IV, XV, XVI in HMP-d_{18}; VI, VII, IX, XI, XII in DMF-d_7; X, XIII in CF_3COOD; XIV in D_2SO_4.

was filtered off, dissolved in water, and the solution filtered. The filtrate was acidified with dilute HCl to pH 6, the precipitate filtered off, washed with water, and dried. Compound X (9.2 g) was obtained.

The acids XI and XII were synthesized analogously with the difference that compound XII was obtained without the use of cuprous chloride.

Methyl N-(1-Methyl-4-nitro-5-imidazolyl)-anthranilate (XIII). A moderate stream of HCl was passed for 1.5 h into a suspension of acid X (0.5 g, 3.7 mmole) in methanol (40 ml). The solution was then heated at 50-60°C for 2 h, cooled, and neutralized with aqueous sodium carbonate solution to pH 7, the solvent was distilled off in vacuum, the solid residue washed with water, and dried. Compound XIII (0.47 g) was obtained.

Methyl N-(1,2-Dimethyl-4-nitro-5-imidazolyl)-anthranilate (XIV). A mixture of acid XI (2.76 g, 0.01 mole), dimethyl sulfate (3.5 ml, 0.04 mole), and anhydrous potassium carbonate (1.4 g, 0.01 mole) in DMF (10 ml) was heated at 70-80°C for 5 h. The reaction mixture was cooled, poured into water (100 ml), the precipitate was filtered off, washed with water, and dried. Compound XIV (2.5 g) was obtained.

Methyl N-(1-Methyl-5-nitro-4-imidazolyl)-anthranilate (XV). A. A mixture of acid XII (5.2 g, 0.02 mole), dimethyl sulfate (4.7 ml, 0.05 mole), and anhydrous potassium carbonate (3.5 g, 0.025 mole) in acetone (150 ml) was boiled for 5 h. The solution was filtered hot, the filtrate cooled, the solid which separated was filtered off, washed with acetone, and dried. Compound XV (2.2 g) was obtained. Additional quantity of XV (1.17 g) was obtained by evaporating the mother liquor and washing the residue with water. The total yield of ester XV was 3.37 g (61%).

B. A mixture of acid XII potassium salt (0.5 g, 1.7 mmole), methyl iodide (0.2 ml, 3.4 mmole), and anhydrous potassium carbonate (0.3 g, 2 mmole) in anhydrous DMF (5 ml) was heated at 30-40°C for 30 min, then boiled for 30 min. The reaction mixture was cooled, and poured into water (50 ml). The precipitate was filtered off, washed with water and dried. Ester XV (0.3 g, 65%) was obtained. A mixing test of samples of compound XV obtained by methods A and B gave no depression of melting point.

Ethyl N-(1-Methyl-5-nitro-4-imidazolyl)anthranilate (XVI). A mixture of acid XII potassium salt (1.0 g, 3.3 mmole), anhydrous potassium carbonate (0.6 g, 4 mmole), and ethyl iodide (0.5 ml, 6.6 mmole) in anhydrous DMF (10 ml) was heated at 90°C (in a bath) for 30 min, cooled, and poured into water (100 ml). The precipitate was filtered off, washed with water, and dried. Ester XVI (0.6 g) was obtained.

Compounds IV-XVI were yellow crystalline substances, soluble with difficulty in water in the cold, and in the majority of organic solvents. Substances were purified for analysis by crystallization from water IV-VIII, water-CH_3COOH IX, X, water-DMF XI, XII, methanol XIII, and acetone XIV-XVI.

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