SELECTIVE ALKYLATION OF IMIDAZOLE-4(5)-CARBOXAMIDES

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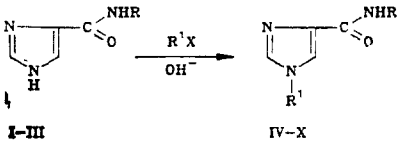
Alkylation of imidazole-4(b)-carboxamides by alkyl halides or dimethylsulfate leads to the selective formation of 1-alkyl-imidazole-4-carboxamides.

The aim of this work was the development of a synthetic method for 1-alkylimidazole-4-carboxamides which are compounds with potential neurotropic activity [1]. The method involves alkylation of the corresponding imidazole-4(5)-carboxamides by alkyl halides or dimethylsulfate in alcoholic media.

Alkylation of asymmetrically substituted imidazoles usually leads to formation of 1,4- and 1,5- derivatives [2-5]. 1-Alkylimidazole-5-carboxylic acids and derivatives are readily obtained by the classical Jones method [6]. Amongst the 1-alkylimidazole-4-carboxylic acids, the 1-methyl derivatives have been synthesized by decarboxylation of 1-methylimidazole-4,5-dicarboxylic acid [7], cyclization of 2-amino-3-methylaminopropopionic acid [8], or by deamination of ethyl 5-amino-3-methylaminopropionic acid [8], or by deamination of ethyl 5-amino-1-methylimidazole-4-carboxylate [9]. However, these methods cannot be used as a general method for obtaining the 1-alkylimidazole-4-carboxylic acids.

We now report the synthesis of the indicated compounds by alkylation of imidazole-4-carboxamides. Alkylation of I-III by alkyl halides was carried out with a 3-5 fold excess of alkylating agent and base in the medium of the corresponding alcohol. The best results were obtained with portionwise addition of the alkylating agent (2-3 times over a day). Alkylation by dimethylsulfate was carried out in aqueous base solution.



I-III IV-X

I R=H, II R=CH_3, III R=C_6H_5, IV R=H, R^1=CH_3, V R=H, R^1=C_2H_5, VI R=H, R^1=C_3H_7, VII R=CH_3, R^1=CH_3, VIII R=CH_3, R^1=C_2H_5, IX R=CH_3, R^1=C_3H_7, X R=C_6H_5, R^1=CH_3

The structures of IV-VIII were proved by PMR spectral data (Table 1). The 1,4- and 1,5- substituted imidazoles differed in their proton spin-spin couplings: For 1,4- isomers they were always greater than 1 Hz but less for the 1,5- isomers [8]. The values of compounds IV-VIII synthesized by us corresponded to the 1,4- isomers. The structure of IV was also confirmed by an independent synthesis via amidation of ethyl 1-methylimidazole-4,5-dicarboxylate, synthesized by method [9].

Compound X, obtained by alkylation of anilide III using dimethylsulfate, was identical to a sample obtained by decarboxylation of 1-methylimidazole-4,5-dicarboxylic acid using method [7].

Thus alkylation of imidazole-4(5)-carboxamides in alkaline medium occurs regioselectively with the formation of 1-alkylimidazole-4-carboxamides.

EXPERIMENTAL

PMR Spectra were taken on a Varian HA-100 (100 MHz) instrument with HMDS as internal standard.

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TABLE 1. Parameters for Compounds IV-IX

Compound	mp, °C (from $CHCl_3$)	Empirical formula	PMR spectrum (in $CDCl_3$), ppm (J = 1.2 Hz)*						Yield, %
			2-H, d	5-H, s	NH_2, s	R, d ($3H$ CH_3)	R'		
							2H, CH_2	3H, CH_3	
IV	209...211	$C_5H_7N_3O$	—	—	—	—	—	—	80
V	138...142	$C_6H_9N_3O$	7,55	7,37	7,02; 7,26	—	3,92, dq	1,40,t	65
VI	191...193	$C_7H_{11}N_3O$	7,51	7,33	6,98, 6,08	—	3,81,t; 1,77, dq	0,82,t	80
VII	144...145	$C_6H_9N_3O$	7,40	7,27	—	2,85	—	3,6 s	80
VIII	54...56**	$C_7H_{11}N_3O$	7,48	7,37	—	2,87	3,92, q	1,37,t	81
IX	118...120	$C_8H_{13}N_3O$	7,46	7,32	—	2,85	3,85,t; 1,75, dq	0,82,t	78

*VII-IX δ 7.13 ppm (NH, br s, J = 1.2 Hz).
**Low melting amide solidified chromatographically pure without crystallization.

Satisfactory elemental analytical data for C, H, and N were obtained for compounds IV-X.

TLC was performed on Silufol UV-254 plates with ethanol-triethylamine (15:1) as eluent and UV visualization. Imidazole-4(5)-carboxamide and methylcarboxamide were obtained by method [11] and imidazole-4(5)-carboxanilide by [12].

1-Methylimidazole-4-carboxymethylamide (VII). A. Alkylation by Methyl Iodide. KOH (0.67 g, 12 mmole) and imidazole-4(5)-carboxymethylamide (II, 0.5 g, 4 mmole) were dissolved in absolute methanol (10 ml) and methyl iodide (1.71 g, 0.75 ml, 12 mmole) added with stirring. After one day further aliquots of KOH (0.45 g, 8 mmole) and methyl iodide (1.14 g, 0.5 ml, 8 mmole) were added. After 2 days the precipitated potassium iodide was filtered off and the solution evaporated to dryness. The precipitate was extracted with boiling chloroform (2 × 20 ml) and the extract evaporated to give the product (0.45 g, 80%) with mp 143-145°C,

B. Alkylation by Dimethylsulfate. Compound II hydrate (1 g) was dissolved in NaOH (20 ml) and dimethylsulfate (1.5 ml) added dropwise with stirring. The reaction mixture was stirred for 2 h, extracted with chloroform (6 × 15 ml) and worked up as described as before to give 0.68 g (70%).

C. Amidation of Ethyl 1-Methylimidazole-4-carboxylate. Aqueous methylamine (20%, 10 ml) was poured into the ethyl ester of the starting acid (0.1 g) [9] and stirred at room temperature. According to TLC (ethyl acetate-ethanol, 2:1), the starting material was absent in the reaction mixture after 1 h. It was then evaporated to dryness and the residue crystallized from chloroform (0.077 g, 85%).

The 1-methyl- (IV), 1-ethyl- (V), 1-propyl- (VI) imidazole-4-carboxamides and 1-ethyl- (VIII) and 1-propyl- (IX) imidazole-1-carboxymethylamides were obtained by alkylation of compounds I and II by the corresponding alkyl halide as for compound VII (method A).

1-Methylimidazole-4-carboxanilide (X). A. 1-Methylimidazole-4,5-dicarboxylic acid (3 g) was refluxed in aniline (30 ml) for 10 h and the aniline steam distilled. Compound X fell out of the aqueous solution on cooling (2.1 g, 66%) with mp 154-156°C (water). According to [3] mp = 143-143.5°C. Imidazole-4(5)-carboxanilide (3 g) was dissolved in NaOH (10%, 30 ml) at 35°C and dimethylsulfate (2.3 g, 1.73 ml, 18 mmole) added. The reaction mixture was stirred at this temperature for 2 h and the precipitated compound X filtered off (1.8 g, 56%).

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NMR SPECTRA OF CYCLIC NITRONES.

5*. ^{13}C NMR SPECTRA OF THE POTENTIAL TAUTOMERIC SYSTEMS OF AMINO-, HYDROXY-, AND MERCAPTONITRONES IN THE SERIES OF 3-IMIDAZOLINE 3-OXIDE

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The position of the tautomeric equilibrium in amino-, hydroxy, and mercaptonitrones was determined by the ^{13}C NMR method for the case of the derivatives of 3-imidazoline-3-oxide. It was shown that the tautomeric equilibrium in the OH and SH derivatives is shifted toward the oxo and thioxo forms (∿95%). The chemical shifts of the carbon atoms of the nitrone group in the α-N-, α-O-, and α-S-substituted nitrones lie in the region of 137-150 ppm.

While continuing a systematic study of the properties of cyclic nitrones, we investigated the ^{13}C NMR spectra of 3-imidazoline-3-oxides, containing N-, O-, and S-substituents at the α-carbon atom, and we also used this method to investigate the possibility of tautomerism of the keto–enol type in hydroxy- and mercaptonitrones. The available published data do not make it possible to reach a conclusion about the realization of such tautomerism [2].

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The question of the preferred existence of the amino derivatives in the form of the aminonitrone (AN) in the 2-aminopyrroline 1-oxide series was resolved on the basis of an analysis of their IR spectra [3]. The most suitable method for investigation of the tautomerism of the amino, hydroxy, and mercapto derivatives of pyridine proved to be the ^{14}N NMR method, whereas the ^{13}C NMR method only made it possible to estimate the position of the tautomeric equilibrium qualitatively as a result of the small differences in the chemical shifts [4, 5]. On the other hand, for these reasons neither method made it possible to determine quantitatively the position of the tautomeric equilibrium in the corresponding derivatives of pyridine N-oxide [6].

*For Communication 4, see [1].

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