SYNTHESIS OF 1-SUBSTITUTED 5-CHLOROIMIDAZOLES*

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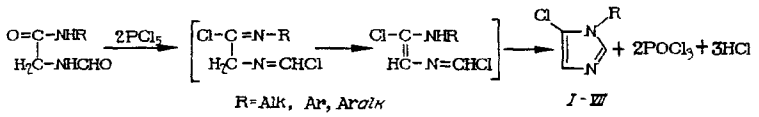
1-Alkyl(aryl, aralkyl)-substituted 5-chloroimidazoles have been only slightly investigated. Only one representative of this series, 1-methyl-5-chlorimidazole (I, see Table 1), has been described which was obtained by the Wallach method from N,N'-dimethyloxamide and PCl_5 [2, 8]. This compound has found application in the synthesis of the immunodepressant agent azathioprine [3, 4] and compounds having antibacterial and antifungal properties [6].

As part of a search for biologically active compounds, it was of interest to carry out the synthesis of new 1-alkyl- and also 1-aryl- and aralkyl-substituted 5-chloroimidazoles. The Wallach method, which is convenient for the synthesis of I, was found to be unsuitable for the synthesis of other 1-alkyl-5-chloroimidazoles. This is due to the fact that during the cyclization of N-methyl-N-alkyl(aralkyl)oxamides by the action of PCl_5, as in the case of other "asymmetric" N,N'dialkyloxamides [7, 9], the formation of two isomers is possible – 1-CH_2R-5-chloro- and 1-CH_3-2-R-5-chloroimidazoles (R = Alk, Ar) – the separation and establishment of the structure of which are very difficult.

We studied the reaction of the previously obtained N-formylglycine alkyl(aralkyl)amides [1] with PCl_5 and developed a new simple synthesis of preparative value of 1-substituted 5-chloroimidazoles (I-VII; see Table 1). As in the case of N,N'-dialkyloxamides [5], the intermediate products in this reaction are probably imide chlorides, which undergo an intramolecular cyclization with splitting off of a HCl molecule and formation of compounds I-VII.

Although the yields of I-VII are not high (30-50%) because of partial resinification, this method is as yet the only one and is acceptable for the preparation of the previously inaccessible II-VII. For the synthesis of I, the method using N,N'-dimethyloxamide [2] still remains the simplest and most economical one [2].



R=Alk, Ar, Arαlk I-VII

The individual state of the purified compounds I-VII was confirmed by TLC, and their structure by the data from the elemental analysis of the bases and their salts, ^{1}H-NMR and mass spectra of I, and also from an alternative synthesis of I according to [2]. There is an intense peak of the molecular ion 116 in the mass spectrum of I (M 116.5), while the ^{1}H NMR spectrum contains signals of the corresponding protons at the 1, 2, and 4-positions of the imidazole ring, which completely agrees with the structure of I as being 1-methyl-5-chloroimidazole. Moreover, samples of base I itself and its salts (picrates and nitrates) obtained by two different methods were found to be identical.

EXPERIMENTAL

For the TLC of the compounds, Silufol-254 plates (produced in CSSR) were used. The ^{1}H NMR spectra were obtained on an XL-200 ("Varian," FRG) spectrometer, using TMS as internal standard. The mass spectra were run on a MAT-112 ("Varian," GFR) mass-spectrometer.

1-Alkyl(aryl, aralkyl)-5-chloroimidazoles (I-VII); see Table 1). A mixture of 0.1 mole of N-formylglycine alkyl(aryl, aralkyl) amide [1], 0.205 mole of PCl_5 and 30-50 ml of $POCl_3$ was cautiously mixed at room temperature. After 3-5 min, the reaction began with spontaneous

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TABLE 1. 1-Alkyl(aryl, aralkyl)-5-chloroimidazoles

Compound	R	Yield, %	bp. °C (pressure, mm Hg)	n_D^{20}	Empirical formula
I	Me	30	84—86 (11)	1,5140	$C_4H_5ClN_2$[a]
II	Et	50	87—89 (12)	1,5030	$C_5H_7ClN_2$
III	*i*-Pr	31	83—84 (4)	1,4951	$C_6H_9ClN_2$
IV	Bu	52	106—108 (8)	1,4912	$C_7H_{11}ClN_2$
V	iso-Bu	30	91—93(6)	—	$C_7H_{11}ClN_2 \cdot C_6H_3N_3O_7$[b]
VI	Ph	41	150—152 (4)	—	$C_9H_8ClN_2 \cdot HCl$ c
VII	CH_2 Ph	49	146—147 (3)	1,5805	$C_{10}H_9ClN_2 \cdot HCl$ d

a) Picrate, mp 167-168°C (from alcohol). Nitrate mp 144-145°C (from alcohol). According to the data in [2], the bp of base I is 53-54°C (0.8 mm), n_D^{20} 1.5110, picrate, mp 167-168°C, nitrate mp 144-145°C.
b) mp 182-183°C (from MeOH).
c) mp 196-197°C (dec., from a 1:4 MeOH-acetone mixture).
d) mp 248-249°C (dec., from acetone).

warming up and foam formation (evolution of gaseous HCl). If necessary, the mixture was cooled on an ice water bath maintaining the temperature below 60°C. After the dissolution of PCl_5, the reaction mixture was stirred for 1-2 h at 20-25°C and 2-3 h at 55-60°C. The $POCl_3$ was then distilled off under vacuum (is reused repeatedly), the residue was cooled, decomposed with crushed ice (40-50 g), the solution was neutralized with aqeous ammonia to pH 8.0-9.0, and extracted with $CHCl_3$, dichloroethane or ethylene chloride (3-4 times with 50-70 ml portions). The extract was washed with water, dried over Na_2SO_4, the solvent was evaporated, and the residue distilled under vacuum to yield compounds I-VII. Mass spectrum of 1: $M^{+\cdot}$ 116. ^1H NMR spectrum of I, $CDCl_3$, δ, ppm: 3.60 (1-CH_3), 7.46 (2-H), 6.94 (4-H). Mixed samples of nitrate and picrate of I with the corresponding salts of I obtained according to [2], did not show depression of the melting points.

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