INVESTIGATIONS OF IMIDAZO[1,2-a]BENZIMIDAZOLES.
26. 2-HALOMETHYLIMIDAZO[1,2-A]BENZIMIDAZOLES AND THEIR REACTIVE PROPERTIES

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Treatment of 2-aminobenzimidazoles with 1,3-dichloroacetone or radical bromination of 3-alkoxycarbonyl- or 3-acetyl-2-methylimidazo[1,2-a]benzimidazoles leads to the 2-halomethyl derivatives of this heterocycle. The lability of the halogen atom in the synthesized compounds has been demonstrated.

Many imidazo[1,2-a]pyrimidines, including those substituted at position 3, show interesting pharmacological properties. The synthesis and properties of this heterocycle substituted at the 2 position have been little investigated [2-4]. In this study, we have synthesized 2-halomethylimidazo[1,2-a]benzimidazoles which serve as convenient synthons for functionalization at position 2 and so to physiologically active species.

It is known that nitrogen heterocyclic derivatives with an amino or mercapto group alpha to the heteroatom can cyclocondense with 1,3-dichloroacetone to form five membered imidazole or thiazole rings containing a halomethyl group [5-8].

However, 2-amino-1-methylbenzimidazole (Ia) reacts with 1,3-dichloroacetone (II) under the conditions in [5-7] (i.e., refluxing in ethanol) extremely ambiguously and much tarring occurs. Preparative TLC separation of the reaction mixture gave only one compound, in which the chlorine was absent. The PMR spectrum showed a multiplet for the aromatic protons at 7.3-7.12 ppm together with a triplet at 1.2 ppm (3H), a quartet at 3.58 ppm (2H) (ethoxy group), and singlets at 3.64 ppm (3H) and 4.5 ppm (2H) (NCH3 and CH2O groups, respectively). From this data, the elemental analysis, and from an independent synthesis described below, this product can be assigned as 9-methyl-2-ethoxymethylimidazo[1,2-a]benzimidazole (Va). This result suggested that the 2-chloromethyl derivative was highly unstable and prompted a change in the reaction conditions.

Reaction of amine Ia with ketone II in dry acetone at room temperature proceeds quite smoothly but leads to a mixture of 9-methyl-2-chloromethylimidazo[1,2-a]benzimidazole (IIIa) and 2-amino-1-methyl-3-(3-chloroacetyl)benzimidazol chloride (IVa), which is confirmed by further reaction of this mixture. The PMR spectrum of the mixture (in CF3COOH) shows singlets for two N-methyl groups at 3.34 and 3.57 ppm, methylene protons in the acetonyl radical of salt IVa at 4.05 and 4.3 ppm, the CH2Cl group at 5.08 ppm, and a broad amino proton signal for IVa at 6.52 ppm. The IR spectrum showed absorption bands for the quaternary salt IVa "immonium" =N+=C group at 1680 cm−1, a carbonyl group at 1770 cm−1, and an NH2 group at 3170 and 3345 cm−1.

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[Diagram of chemical reactions and structures]

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A similar mixture was obtained when ketone II was treated with 2-amino-1-benzylbenzimidazole (Ib). When the mixture was allowed to stand in CF$_3$COOH for a day, complete cyclization of IV occurred and the PMR spectrum showed in solution only the 2-chloromethyl derivative III.

Due to the high lability of III, the chlorine atom is very reactive, even towards weak nucleophiles and the individual components could not be separated. Thus attempts to crystallize the mixture of III and IV led to 2-hydroxymethylimidazo[1,2-$a$]benzimidazole VI. Treatment of the mixture with ethanol gave the difficultly soluble salts IVa, b virtually pure since III was completely converted to ether V. Heating the mixture of III and IV with secondary amines in an inert solvent gave the 2-aminomethyl products VII.

Bearing in mind the ambiguity of the above reaction we studied the possible preparation of 2-halomethylimidazo[1,2-$a$]benzimidazoles by direct introduction of the halogen atom in 2-methylimidazo[1,2-$a$]benzimidazoles.

It was previously reported [9] that bromination of 2-methylimidazo[1,2-$a$]benzimidazole VIII with bromine in CHCl$_3$ or AcOH gives the 3-bromo derivatives of the heterocycle. The methyl group is not brominated under these conditions. The action of one equivalent of bromosuccinimide on VIII gives a hard to separate, complex mixture containing unreacted VIII together with its mono-, dir-, and tribromo derivatives. Hence we chose 2-methylimidazo[1,2-$a$]benzimidazoles IX as starting materials which had position 3 substituted by the labile alkoxycarbonyl or acetyl groups [10, 11]. Radical bromination of IX using bromosuccinimide gave the 2-bromomethyl derivatives X in high yield. The reaction occurred smoothly without a catalyst upon refluxing the reagents in dry CHCl$_3$ or CC$_4$. As previously reported [12], the acetyl group was not brominated under these conditions. Together with product X there were obtained traces of the dibromo product XI and 1,1'-dialkyl-2-2'-azobenzimidazoles, which had been obtained previously by treatment of imidazo[1,2-$a$]benzimidazoles with various oxidants [13] and by oxidation of 1- substituted 2-aminobenzimidazoles using sodium hypochlorite solution [14]. Compound XI was prepared in high yield by treating the ester or ketone IX with a twofold excess of bromosuccinimide. In the PMR spectra of X, the singlet for the 2-CH$_3$ group at 2.4-2.5 ppm was replaced by a proton signal for CH$_2$Br at 4.7-4.8 ppm. The signal for the CHBr$_2$ proton in XI was even further shifted downfield (7.3-7.5 ppm).

As for III, the obtained bromo derivatives also have a highly labile halogen atom. It is readily substituted by primary, secondary, and tertiary amines by a short reflux of the reagents in benzene. For primary and secondary amines it is necessary