SYNTHESIS AND STUDY OF SOME IMIDAZOLE DERIVATIVES

III. Chloroacetic Esters of 4(5)-Hydroxymethylimidazole*

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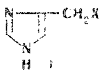
The preparation of esters of 4(5)-hydroxymethylimidazole with mono-, di-, and trichloroacetic acids is described. It has been established that in the reaction of imidazolylmethyl chloroacetate with diethanolamine, the latter is alkylated with the imidazolylmethyl part of the ester, giving rise to bis(2-hydroxyethyl)aminomethylimidazole.

There is little information in the literature on esters of 4(5)-hydroxymethylimidazole [2–4]. Nevertheless, these compounds are of definite interest particularly in respect of the study of their biological activity.

In the present paper we describe the synthesis of imidazolylmethyl esters of monochloroacetic (I), dichloroacetic (II), and trichloroacetic (III) acids by the reaction of the chlorides of these acids with 4(5)-hydroxymethylimidazole. The hydrochlorides of the esters form colorless crystalline substances soluble in water and ethanol and insoluble in other solvents. When an attempt was made to use imidazolylmethyl chloroacetate (Ia) to obtain the imidazolylmethyl ester of bis(2-hydroxyethyl)aminoacetic acid (Ib) by its reaction with diethanolamine, the latter underwent alkylation by the imidazolylmethyl part of the ester with the formation of bis(2-hydroxyethyl)aminomethylimidazole (Ic).


a X=$OCOCH_2Cl$
b X=$OCOCH_2N(CH_2CH_2OH)_2$
c X=$N(CH_2CH_2OH)_2$
d X=$N(CH_2CH_2Cl)_2$

The structure of this compound was confirmed by the results of elementary analysis, the absence from its IR spectra (taken by V. E. Chistyakov under the direction of M. M. Kaganskii) of an absorption maximum corresponding to an ester carbonyl at 1717–1750 cm^{-1}, and its conversion into di(2-chloroethyl)aminomethylimidazole (Id), which we have prepared previously [1].

EXPERIMENTAL

The 4(5)-imidazolylmethyl esters were obtained by heating 4(5)-hydroxymethylimidazole hydrochloride with an excess (2.5- to 5-fold) of the corresponding acid chloride (70°–75° C, 6 hr for I; 30°–40° C, 1 hr for II; and 50°–60° C, 2 hr for III). The precipitates were washed with chloroform, benzene, and acetone.

Hydrochloride of 4(5)-imidazolylmethyl monochloroacetate (I). Yield 97%. Mp 142°–143° C (after treatment with hot acetone). Found, %: C 33.9; H 3.94, Cl 32.81; N 13.42. Calculated for $C_6H_7ClN_2O_2 \cdot HCl$, %: C 34.0; H 3.79; Cl 33.65; N 13.27.

Hydrochloride of 4(5)-imidazolylmethyl dichloroacetate (II). Yield 95%. Mp 132° C (precipitated with ether from ethanolic solution). Found, %: C 29.31; H 2.65; Cl 42.45; N 11.77. Calculated for $C_6H_6Cl_2N_2O_2 \cdot HCl$, %: C 29.32; H 2.81; Cl 43.38; N 11.41.

Hydrochloride of 4(5)-imidazolylmethyl trichloroacetate (III). Yield 73.5%. Mp 113°–114° C. Found, %: C 26.65; H 2.16; N 9.97. Calculated for $C_6H_5Cl_3N_2O_2 \cdot HCl$, %: C 25.71; H 2.14; N 10.00.

Alkylation of diethanolamine with imidazolylmethyl monochloroacetate. With gentle heating, 4.02 g (0.04 mole) of triethylamine and 5.5 g (0.05 mole) of diethanolamine in 20 ml of anhydrous ethanol were added to 4.3 g (0.02 mole) of I in 50 ml of anhydrous ethanol. The mixture was boiled for 7 hr, after which another 2.01 g of triethylamine was added. Then it was stirred without heating for 12 hr, and after this, with cooling, a current of hydrogen chloride was passed through to give a pH of 7–8. The precipitate of triethylamine and diethanolamine hydrochlorides was filtered off. Hydrogen chloride was passed through the filtrate again. At pH 2–1, a resinous product was formed which was converted on trituration into resinous crystals of the dihydrochloride of bis(2-hydroxyethyl)aminomethylimidazole. Mp 153°–155° C (from anhydrous ethanol). Yield 25%. Found, %: C 36.90; H 6.31; Cl 26.79; N 15.92. Calculated for $C_8H_{15}N_3O_2 \cdot 2HCl$, %: C 37.2; H 6.59; Cl 27.51; N 16.28.

Dipicrate—yellow crystals. Mp 178°–180° C. Found, %: C37.15; H 3.27; N 19.63. Calculated for $C_8H_{15}N_3O_2 \cdot 2C_6H_3N_3O_7$, %: C 37.32; H 3.26; N 19.60.

Bis(2-chloroethyl)aminomethylimidazole dihydrochloride. This was obtained by treating the bis(hydroxyethyl) derivative from the preceding synthesis with thionyl chloride [1]. Colorless crystals with mp 167°–168° C (from anhydrous ethanol). Found, %: C 31.84; H 5.24, Cl 47.87; N 14.29. Calculated for $C_8H_{13}Cl_2N_3 \cdot 2HCl$, %: C 32.54; H 5.08; Cl 48.19; N 14.24%. A mixture with the dihydrochloride obtained previously [1] gave no depression of the melting point.

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*For communication II, see [1].