RESEARCH IN THE IMIDAZOLE SERIES.
93.* SYNTHESIS OF DERIVATIVES OF BENZIMIDAZOLYL-1-ACETIC ACID

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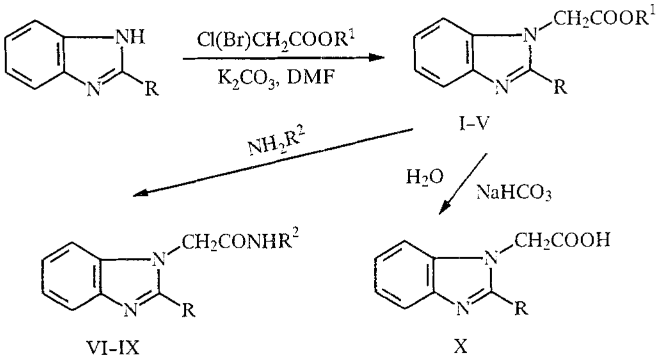
A simple method has been developed for obtaining esters of benzimidazolyl-1-acetic acid and its 2-alkyl (or aralkyl) derivatives, by reaction of benzimidazoles with esters of chloroacetic or bromoacetic acid in DMF in the presence of anhydrous potassium carbonate. The method of synthesis of amides of these acids has been simplified.

Derivatives of benzimidazolyl-1-acetic acid and its 2-substituted derivatives have received very little attention. Information has been reported on a few esters [2-4], amides [4], and hydrazides [2] of these acids. The esters were obtained by interaction of silver [2, 3] or sodium [4] salts of benzimidazoles with esters of chloroacetic or bromoacetic acid; the amides were obtained by heating the esters with ammonia or amines in a sealed tube at 125°C [4].

These methods of synthesis of the esters and amides of benzimidazolyl-1-acetic acid suffer from certain complications in carrying out the reactions; also, the yields are low (21-45%).

Since we are proposing to use the esters of benzimidazolyl-1-acetic acids as starting substances in the synthesis of biologically active compounds, we have developed a simpler method for obtaining the esters, as reported briefly in [5]. The method consists essentially of reacting benzimidazole or its 2-alkyl or 2-aralkyl derivatives with esters of chloroacetic or bromoacetic acid in anhydrous DMF in the presence of anhydrous potassium carbonate. The yields of the esters I-V (Table 1) are 70-97%.



In studying the reactions of the esters, for example III, with ammonia and amines, we found that this process goes forward smoothly upon heating in water or ethanol. The yields of the amides VI-VIII are 53-99%. By the interaction of compound III with hydrazine hydrate, we obtained the corresponding hydrazide IX; and by saponification of the ester V in an aqueous solution of sodium bicarbonate, we obtained 2-benzylbenzimidazolyl-1-acetic acid (X) as a simple derivative of the preparation Dibasol (2-benzylbenzimidazole).

In the IR spectra of compounds I-X, there are absorption bands representing the CO and NH groups of the ester and amide moieties, in the 1680-1735 and 3200-3500 cm^{-1} regions, respectively.

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*For Communication 92, see [1].

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TABLE 1. Characteristics of Synthesized Compounds

Compound	R	R^1	R^2	Empirical formula	mp, °C (and solvent for (crystallization)	Yield, %
I	H	Me	—	$C_{10}H_{10}N_2O_2$	85...86 (CCl_4)	84
II	Me	Me	—	$C_{11}H_{12}N_2O_2$	118...119* (CCl_4)	76
III	Me	Et	—	$C_{12}H_{14}N_2O_2$	158...160 (CCl_4)	85
IV	Et	Et	—	$C_{13}H_{16}N_2O_2$	78...79 (CCl_4)	70
V	CH_2Ph	Et	—	$C_{18}H_{18}N_2O_2$	115...116** (CCl_4)	97
VI	Me	—	H	$C_{10}H_{11}N_3O$	236...237 (MeOH)	53
VII	Me	—	Bu	$C_{14}H_{19}N_3O$	165...166 (H_2O)	53
VIII	Me	—	Cyclobutyl	$C_{14}H_{17}N_3O$	158...160 (acetone)	99
IX	Me	—	NH_2	$C_{10}H_{12}N_4O$	239...240 (MeOH)	96
X	CH_2Ph	—	—	$C_{16}H_{14}N_2O_2$	214...215 (MeOH)	53

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*According to [3], mp 117-119°C.

**According to [2], mp 115-116°C.

EXPERIMENTAL

The characteristics of the synthesized compounds I-X are listed in Table 1. The IR spectra of the compounds were taken in an UR-10 instrument in the form of suspensions in white mineral oil.

The results of elemental analyses for C, H, and N were in agreement with the calculated values.

Methyl Ester of Benzimidazolyl-1-acetic Acid (I). To a solution of 11.8 g (0.1 mole) of benzimidazole in 70 ml of anhydrous DMF, 11.9 g (0.11 mole) of methyl chloroacetate and 13.8 g (0.1 mole) of anhydrous K_2CO_3 were added. The mixture was stirred for 20-24 h at 80-90°C, the precipitate was filtered off, the filtrate was evaporated under vacuum, the residue was dissolved in chloroform, the solution was washed with water and dried with Mg_2SO_4, and the solvent was driven off. Yield 16.2 g. The esters II-V were obtained analogously. In the synthesis of compound II we used methyl bromoacetate.

Amide of 2-Methylbenzimidazolyl-1-acetic Acid (VI). A solution of 4.36 g (0.017 mole) of compound III in 25 ml of 25% aqueous ammonia was refluxed for 4 h and then cooled; the precipitate was filtered off, washed with water, and dried. Yield 2.0 g.

Amides of 2-Methylbenzimidazolyl-1-acetic Acid (VII, VIII). A solution of 8.72 g (0.04 mole) of compound III and 10-15 g (0.14-0.21 mole) of n-butylamine or cyclobutylamine in 50 ml of anhydrous ethanol was refluxed for 18-20 h; the solvent and the excess amine were taken off under vacuum, and the residue was filtered and washed with ether. Yield of VII 5.2 g, VIII 9.8 g.

Hydrazide of 2-Methylbenzimidazolyl-1-acetic Acid (IX). A solution of 10.9 g (0.05 mole) of compound III and 6.4 g (0.2 mole) of hydrazine hydrate in 30 ml of methanol was left for 10-12 h at 18-20°C; the precipitate was filtered off, washed with methanol, and dried. Yield 9.8 g.

2-Benzylbenzimidazolyl-1-acetic Acid (X). A mixture of 2.94 g (0.01 mole) of compound V and 1.75 g (0.022 mole) of $NaHCO_3$ in 20 ml of water was refluxed 4 h; the undissolved residue was filtered off, the filtrate was acidified with formic acid to pH 6, and the precipitate was filtered off, washed with water, and dried. Yield 1.36 g.

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