SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF 2-SUBSTITUTED 1-BENZIMIDAZOLYL-β-PROPIONIC ACIDS

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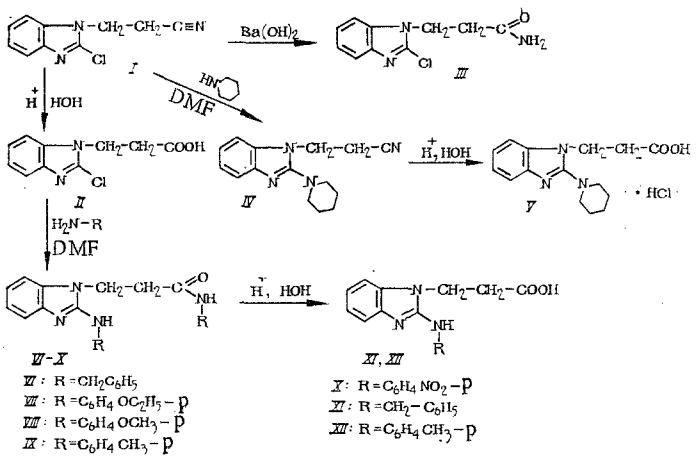
There have been literature reports [1] of 1,2-disubstituted benzimidazoles possessing high cardiovascular activity. We here describe the synthesis of some 1-benzimidazolyl-β-propionic acids and pharmacological studies of some of these compounds.

The starting material used was 1-β-cyanoethyl-2-chlorobenzimidazole (I) [2], which on hydrolysis gives, according to the conditions, either 2-chloro-1 benzimidazolyl-β-propionamide, or the acid (II).

Reaction of (I) with piperidine in DMF results in replacement of the halogen atom by a piperidine residue to give (IV). Acid-catalyzed hydrolysis of (IV) also resulted in hydrolysis of the cyano-group to carboxyl, to give (V). Nucleophilic replacement of the halogen atom in (III) (under very severe conditions) proceeded beyond the formation of 2-substituted 1-benzimidazolyl-β-propionic acids to give the amides (VI-X). In all probability, this reaction proceeds via the formation of quaternary ammonium salts, which decompose to give the amides. Amides (VI) and (IX) are hydrolyzed in acid to the corresponding acids (XI) and (XII). The structures of the compounds obtained were confirmed by their elemental analyses and IR spectra.



The IR spectra of (VI-X) showed absorption at 3330-3250 cm^{-1} (stretching vibrations of the the associated NH group), 1720-1690 cm^{-1} (stretching vibrations of the amide carbonyl group) and 1645-1620 cm^{-1} (the —C—N group).

In the IR spectra of the acids (XI) and (XII), the stretching vibrations of the carbonyl group appeared at higher frequencies (1755-1750 cm^{-1}). Stretching vibrations of the bonded —OH group were seen as a broad band at 3300-3200 cm^{-1} [3].

EXPERIMENTAL CHEMICAL SECTION

IR spectra were obtained on a UR-20 instrument (East Germany), in Vaseline oil and KBr tablets. The analytical results are given in Table 1.

2-Chloro-1-benzimidazolyl-β-propionic Acid (II). A mixture of 20.5 g (10 mmole) of (I) [2] and 10 ml of concentrated hydrochloric acid was boiled for 2 h, cooled, kept for 24 h, and the precipitate diluted with 10 ml of water and filtered. Crystallized from water.

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TABLE 1. 2-Substituted 1-Benzimidazolyl-β-propionic Acids

Compound	mp, °C	Found			Molecular formula	Calculated			Yield, %
		C	H	N		C	H	N	
II	191—2	53,1	4,0	12,21	$C_{10}H_9N_2O_2$	53,46	4,04	12.47	81
III	178—9	54,0	4,1	18,34	$C_{10}H_{10}ClN_3O$	53,69	4,5	18,78	53
IV	280—2	70,5	7,4	22,17	$C_{15}H_{18}N_4$	70,83	7,13	22,03	96
V	200—2	58,01	6,3	13,23	$C_{15}H_{20}ClN_3O_2$	58,15	6,5	13,57	58
VI	220—1	74,97	6,29	14,21	$C_{24}H_{24}N_4O$	74,8	6.03	14,21	63
VII	220—2	64,6	7,0	11,26	$C_{26}H_{28}N_4O_3 \cdot 2H_2O$	64,98	6,71	11,26	68
VIII	222—4	69,4	5,8	13,54	$C_{24}H_{24}N_4O_3$	69,21	5,8	13,45	71
IX	230—1	75,1	5,92	14,22	$C_{24}H_{24}N_4O$	74,97	6,29	14,57	57
X	111—2	59,6	4,1	19,3	$C_{22}H_{17}N_6O_5$	59,2	4,06	18,83	67
XI	>200	68,9	6,0	13,85	$C_{17}H_{17}N_3O_2$	69,08	5,8	14,2	42
XII	>200	69,2	5,6	14,3	$C_{17}H_{17}N_3O_2$	69,08	5,8	14,2	31

Note. Compounds (III-XI) were recrystallized from aqueous methanol, (XII) from aqueous DMF, and (II) from water.

2-Chloro-1-benzimidazolyl-β-propionamide (III). A mixture of 20.5 g (10 mmole) of (I), 3.42 g of barium hydroxide, and 100 ml of water was boiled for 2 h, cooled, neutralized with acetic acid until neutral, and kept for 12 h at 5°C. The solid was filtered off.

1-β-Cyanoethyl-2-N-piperidinobenzimidazole (IV). A mixture of 20.5 g (10 mmole) of (I), 10 ml of piperidine, and 100 ml of DMF was boiled for 4 h, cooled, diluted with an equal volume of water, and the solid which separated filtered off to give (IV).

2-N-Piperidino-2-benzimidazolyl-β-propionic Acid Hydrochloride (V). A mixture of 25.4 g (10 mmole) of (IV) and 100 ml of concentrated hydrochloric acid was boiled for 2-3 h (until all the solid in the flask had dissolved), cooled, the reaction mixture evaporated to dryness in vacuo, and the residue recrystallized from alcohol.

Arylamides and Aralkylamides of 2-N-Arylamino and Aralkylamino-2-benzimidazolyl-β-propionic Acids (VI-X). A mixture of 2.24 g (1 mmole) of (II), 3-4 mmole of the appropriate amine, and 20-30 ml of DMF was boiled for 6 h, cooled, the reaction mixture poured into 250 ml of water, and the solid which separated was filtered off and washed with water to give (VI-X).

2-N-Arylamino- and Aralkylamino-2-benzimidazolyl-β-propionic Acids (XI) and (XII). A mixture of 10 mmole of (VI) or (IX) and 50-100 ml of concentrated hydrochloric acid was boiled for 4-6 h, cooled, the reaction mixture evaporated in vacuo until a small residue remained, diluted with 20-30 ml of water, and filtered to give (XI) and (XII).

EXPERIMENTAL PHARMACOLOGICAL SECTION

Some of the compounds obtained were tested for pharmacological activity. Their acute toxicities were determined, and their diuretic and neurotropic activities examined.

Acute toxicities were determined in intact white mice of both sexes, weighing 18-25 g. The compounds were administered intraperitoneally in physiological saline or as a suspension in Tween-80. Each dose was tested on 5-7 animals. The animals were observed over a period of 10 days. The LD_{50} values were calculated by the method of Kerber [4] (Table 2).

The effects of (IV), (V), and (VI) on the urinary excretory function of the kidneys was studied in experiments on intact white male rats of the Wistar strain weighing 200-360 g by the method of Berkhin [5]. Seventy experiments were carried out in all. The results are shown in Table 2. Diuretic activity was studied in comparison with euphyllin. The results showed that (IV-VI) resulted in a statistically significant increase in diuresis when administered in doses of 10-75 mg/kg, by an average of 8.2-74.89% in comparison with the controls. In a dose of 20 mg/kg, euphyllin increased diuresis by 23.4%. The greatest diuretic activity was displayed by (V), which possesses a β-propionic acid residue in the 1-position.

Neurotropic activity was assessed by the prolongation of the effect of subnarcotic doses of barbiturates [6]. The effects of (IV-VI) on the duration of pentobarbital-sodium sleep were studied in nine groups of male white rats of the Wistar strain (seven animals per group). The duration of narcotic sleep was measured as the time for which the animals were in a lateral position, i.e., from the moment at which the turn-over reflex was lost. As will be

TABLE 2. Effect of the Test Compounds on Diuresis and the Duration of Narcotic Sleep in White Rats (M ± M)

Compound	LD_{50}, mg/kg	Diuresis			Duration of narcotic sleep	
		dose, mg/kg	ml over 6 h	% of control	min	% of control
Control		—	7,49±0.28	100	80.7±0,29	100
IV	175,0±15,9	10	8,29±0,81	110,6	97,2±0,72	120,44
		20	8,11±0,93	108,2	117,5±0,17	145,6
		30	7,34±0,51	98,0	102.1±0,9	126.51
V	257±8,23	10	11,14±1,09	148,73	—	—
		20	12,8±0,81	170,89	113,5±0,31	140,64
		25	11,9±0,92	158,87	—	—
		30	10,92±0,42	145,79	136.8±0.15	169,52
		40	—	—	120.7±0,17	149.56
		50	13,1±0,14	174.89	—	—
		75	11,1±1,06	148,19	—	—
VI	186,0±6,28	10	—	—	119,5±2,72	148,07
		25	11,28±0,53	150,6	—	—
		30	—	—	154,3±2,67	191,1
		50	—	—	145,1±2,44	179,8
Euphyllin		20	9,25±0,45	123,4	—	—
Aminazine		5	—	—	112,14±4,7	138,96

seen from the results (Table 2), (IV-VI) had clearly apparent neuroleptic effects, extending narcotic sleep by 20.4-91.2% in doses of 10-50 mg/kg, in comparison with the controls. The most interesting compound was (VI), which in a dose of 50 mg/kg extended sleep by 91.2% (60 mg/kg).

These studies thus show that the test compounds are of interest in the search for diuretic and neuroleptic drugs in this series of compounds.

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