SYNTHESIS AND STUDY OF SOME BENZIMIDAZOLE DERIVATIVES

IV. ALKYL AND ARALKYL DERIVATIVES OF 1-(2-AMINOETHYL)-BENZIMIDAZOLE

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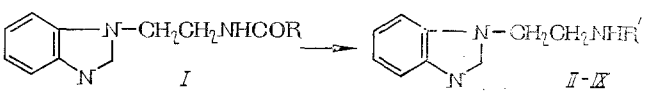
A large number of dialkyl derivatives of 1-(2-aminoethyl)-benzimidazole possessing versatile biological activity is known [1-5].

The synthesis of a series of acyl derivatives of 1-(2-aminoethyl)-benzimidazole displaying definite sedative and antiserotonin activity was previously accomplished by us [6]. Reducing them seemed to be a valuable way to prepare the corresponding alkyl and aralkyl derivatives of 1-(2-aminoethyl)-benzimidazole (I-IX), which have not heretofore been described in the literature, so as to study their biological activity. Lithium aluminum hydride was chosen as the reducing agent.

Reduction of the alkyl derivatives of I was accomplished with lithium aluminum hydride in ether or tetrahydrofuran. It proceeded fairly smoothly and finished in 4-5 h.



All the synthesized compounds (see Table 1) were identified as the oxalates, which are easily formed by treatment of the base with an alcoholic solution of oxalic acid.

All the alkyl and aralkyl derivatives tested (II-IX) showed moderate toxicity – their LD_{50} for mice by intraperitoneal application was 150 to 500 mg/kg (daily observation). The compounds investigated had a slight depressive effect on the central nervous system of the mice; the mobility of the animals was reduced, the rectal temperature was lowered by 2-3°C, there was no change or only a slight increase in the pain-sensitivity threshold during electric shock, and there was no effect on the duration of sleep induced by chloral hydrate. A central muscle-relaxing effect was observed after introduction into the mice of compounds III, IV, and VIII; all compounds, with the exception of VI and IX, exhibited antiserotonin activity according to tests of cramps [7] and diarrhea [8] induced by the precursor of serotonin – 5-hydroxytryptophan. The most pronounced central serotonin-negative properties were observed with compounds II, III, and VIII – their ED according to testing of 5-hydroxytryptophan-induced cramps were less than 1/3 LD.

Comparison of the alkyl and aralkyl derivatives (II-IX) with the acyl ones (I) [6] revealed no significant differences in pharmacological activity.

EXPERIMENTAL

Alkyl and Aralkyl Derivatives of 1-(2-Aminoethyl)-benzimidazole (II-IX). A solution of the acyl derivative of 1-(2-aminoethyl)-benzimidazole (1) (0.01 mole) in absolute ether (or benzene) was added gradually, while stirring and cooling with icewater, to a suspension of lithium aluminum hydride (0.07 mole) in

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TABLE 1. Alkyl and Aralkyl Derivatives of 1-(2-Aminoethyl)-benzimidazole

Compound	R′	Yield (in %)	mp (in °C)	Solvent for crystallization	Found (in %)			Empirical formula	Calculated (in %)		
					C	H	N		C	H	N
II, Dioxalate*	C_2H_5	88	189—90	Alcohol	48,21	5,11	11,48	$C_{11}H_{15}N_3 \cdot 2C_2H_2O_4$	48,78	5,15	11,38
III, Dioxalate†	C_3H_7	80	203—4	80% Alcohol	50,21	5,30	10,74	$C_{12}H_{17}N_3 \cdot 2C_2H_2O_4$	50,10	5,40	10,96
IV, Oxalate	C_5H_{11}	43	199—200	Alcohol	55,42	6,52	11,44	$C_{14}H_{21}N_3 \cdot {}^3/_2C_2H_2O_4$	55,73	6,55	11,47
V, Oxalate	iso-C_5H_{11}	95	202—3	Dimethylformamide + dioxane	55,11	6,56	11,38	$C_{14}H_{21}N_3 \cdot {}^3/_2C_2H_2O_4$	55,73	6,55	11,47
VI, Dioxalate	$C_6H_5—CH_2$	96	192—3	Alcohol	55,54	5,19	9,14	$C_{16}H_{17}N_3 \cdot 2C_2H_2O_4$	55,68	5,00	9,74
VII, Dioxalate	p-$CH_3C_6H_4CH_2$	95	207—8	80% Alcohol	55,60	5,21	9,46	$C_{17}H_{19}N_3 \cdot 2C_2H_2O_4$	56,63	5,16	9,44
VIII, Dioxalate	p-$CH_3OC_6H_4CH_2$	95	194—5	Methyl ethyl ketone + dimethylformamide	61,38	6,31	11,32	$C_{17}H_{19}N_3O \cdot 2C_2H_2O_4$	61,45	5,66	11,30
IX, Dioxalate	3,4,5-$(CH_3O)_3$ $C_6H_2CH_2$	59,7	184—6	Alcohol	52,20	4,83	7,89	$C_{19}H_{23}N_3O_3 \cdot 2C_2H_2O_4$	52,97	5,18	8,06

*Base II, bp 160—162°C (2mm)
†Base III, bp 180—182°C (2mm)

absolute ether (or tetrahydrofuran). The mixture was boiled for 4-5 h on a water bath. After cooling, the excess lithium aluminum hydride and the intermediate complex formed were decomposed by careful addition of a mixture of alcohol and ether and then of 10% sodium hydroxide solution, and the organic layer was decanted and evaporated in vacuo. The base, isolated as an oil, was converted into the oxalate by the usual method.

The bases of the alkyl and aralkyl derivatives (II-IX) were yellow oils which darkened quickly in air and were soluble in alcohol, benzene, and ether. Bases II and III were distilled in vacuo.

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