SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF ARYL-(1-ALKYLBENZIMIDAZOLYL-2)-CARBINOLS

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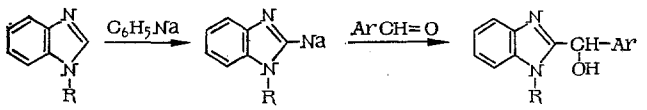
2-Benzylbenzimidazole, whose hydrochloride is known in pharmacology by the name "diabazol," possesses a rather broad range of physiological activity [1, 2]. In connection with this, it became of interest to synthesize and test the physiological activity of aryl-(1-alkylbenzimidazolyl-2)-carbinols (I-VI; see Table 1), which are similar in structure to 2-benzylbenzimidazole. The synthesis of these compounds was accomplished in accordance with the following scheme:



I-VI

The reaction between 2-sodium-1-alkylbenzimidazoles and aromatic aldehydes proceeds quite easily and provides good yields of the final products. This route differs from the previously described method of preparing arylbenzimidazolyl carbinols, which was based on the condensation of o-phenylenediamines with mandelic acid derivatives [3], by the ready availability of the starting compounds.

The hypotensive properties of I-VI were investigated in tests on rabbits. When the hydrochlorides of III, IV, and V were injected in a dose of 5 mg/kg, the blood pressure was lowered by 20.5 ± 1.3 mm, 19 ± 0.4 mm, and 21.3 ± 1.3 mm. An increase in the dose of the hydrochlorides of III and IV to 10 mg/kg is not noticeably reflected in the hypotensive effect. The hydrochlorides of II, V, and VI in doses of 10 mg/kg lower the pressure by 26.5 ± 3.8 mm, 33.5 ± 4.1 mm, and 15 ± 2 mm. When diabazol is injected in doses of 5-10 mg/kg, the magnitude of (the duration of) the hypotensive effect of the hydrochlorides of II-VI and diabazol is 5-10 min.

The hydrochlorides of I-VI can cause weak terminal anesthesia. The index of anesthesia in units [4] for these compounds is equal to 274, 425, 112, 121, 280, and 293, respectively. Two-percent aqueous solutions of the preparations were used.

The ability to prevent arrhythmia caused by the intravenous injection of barium chloride in experiments on rabbits was detected for the hydrochloride of V. When it was intravenously injected in a dose of 20 mg/kg within 15 min prior to the injection of barium chloride, no extrasystoles were detected in the majority of cases. Extrasystoles, which continued for about an hour or more, appeared in the control rabbits within 1-2 min after the injection of barium chloride.

The LD_{50} of the hydrochlorides of I-VI came to 626, 751, 183, 675, 676, and 614 mg/kg, respectively. Their toxicity was determined on white mice; the preparations were injected subcutaneously.

EXPERIMENTAL

1-Methyl- and 1-Propylbenzimidazoles. These were prepared by the methods described in [5].

Aryl-(1-alkylbenzimidazolyl-2)-carbinols (I-VI). A suspension of 2.2 g (0.096 g-atom) of powdered sodium in 40 ml of toluene was activated with isoamyl alcohol and added at 30-35°C with agitation in a

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TABLE 1. Aryl-(1-alkylbenzimidazolyl-2)-carbinols and Their Hydrochlorides

Compound	R	Ar	Yield (in %)	Melting point (°C)	Found (in %)				Empirical formula	Calculated (in %)			
					C	H	Cl	N		C	H	Cl	N
I	n = C_3H_7	4 = $(CH_3)_2NC_6H_4$	64	153 — 4	73,52	7,36	—	13,91	$C_{19}H_{23}N_3O$	73,75	7,49	—	13,58
I·HCl				199 — 200	—	—	10,57	12,61	$C_{19}H_{23}N_3O \cdot HCl$	—	—	10,25	12,14
II	n = C_3H_7	4 = $(C_2H_5)_2NC_6H_4$	57	135 — 6	74,37	7,97	—	12,78	$C_{21}H_{27}N_3O$	74,73	8,06	—	12,46
II·HCl				155 — 6	—	—	9,63	10,97	$C_{21}H_{27}N_3O \cdot HCl$	—	—	9,48	11,24
III	n = C_3H_7	3,4 = $(CH_3O)_2C_6H_3$	69	150 — 1	69,85	6,94	—	8,75	$C_{19}H_{22}N_2O_3$	69,91	6,79	—	8,58
III·HCl				205 — 6	—	—	10,04	8,12	$C_{19}H_{22}N_2O_3 \cdot HCl$	—	—	9,77	7,72
IV	n = C_3H_7	4 = $CH_3OC_6H_4$	50	110 — 1	72,51	6,47	—	9,14	$C_{18}H_{20}N_2O_2$	72,95	6,80	—	9,45
IV. HCl				178 — 9	—	—	10,72	8,02	$C_{18}H_{20}N_2O_2 \cdot HCl$	—	—	10,66	8,42
V	CH_3	4 = $(C_2H_5)_2NC_6H_4$	70	173 — 4	73,97	7,02	—	13,93	$C_{19}H_{23}N_3O$	73,75	7,49	—	13,58
V. HCl				210 — 2	—	—	10,32	12,18	$C_{19}H_{23}N_3O \cdot HCl$	—	—	10,25	12,14
VI	CH_3	4 = $(CH_3)_2NC_6H_4$	57	154 — 5	72,99	6,4	—	15,07	$C_{17}H_{19}N_3O$	72,57	6,80	—	14,95
VI·HCl				174 — 7	—	—	11,53	22,98	$C_{17}H_{19}N_3O \cdot HCl$	—	—	11,16	13,22

nitrogen atmosphere to 5.2 g (0.046 mole) of chlorobenzene in 5 ml of toluene over a 30 min period. Within 1 h, a solution of 0.03 mole of 1-alkylbenzimidazole in 20 ml of toluene was added at −15°C to the phenylsodium obtained. 1-Methylbenzimidazole was metallized for 1 h and 1-propylbenzimidazole for 2 h. A total of 0.04 mole of an aromatic aldehyde was introduced into the suspension of 2-sodium-1-alkylbenzimidazole formed and the mixture was stirred for 1 h. At the end of the reaction, the remaining sodium was combined with 10 ml of 80% alcohol, then the mixture was treated with 2·40 ml of 10% hydrochloric acid. The hydrochloride extract was made alkaline with a 40% sodium hydroxide solution while cooling; the precipitated carbinol was filtered off and recrystallized from a petroleum ether-benzene mixture.

Hydrochlorides of Aryl-(1-alkylbenzimidazolyl-2)-carbinols. Dry hydrogen chloride was passed into a solution of 5 g of the carbinol in 100 ml of benzene until the precipitate ceased to form. The hydrochloride was filtered off, dissolved in a minimum quantity of absolute alcohol, and it was precipitated with ether, after which it was dried in a vacuum desiccator.

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