

SYNTHESIS AND REACTIONS OF IMIDAZO[1,2-*a*]BENZIMIDAZOLE DERIVATIVES. I.

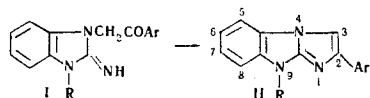
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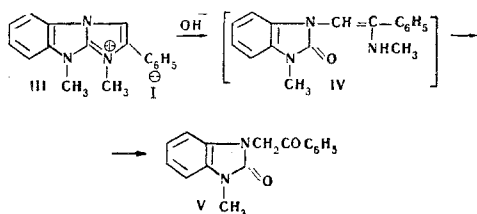
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Some reactions of imidazo[1,2-*a*]benzimidazole derivatives have been studied: the cleavage of their quaternization products, bromination, and the replacement of the bromine in position 3.

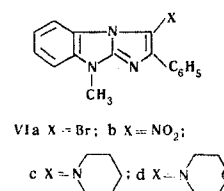
Recently, derivatives of the barely studied imidazo[1,2-*a*]benzimidazole system (II) have been obtained by the cyclization of 1-alkyl-2-imino-3-phenacylbenzimidazolines (I) [1-3]. We have effected the synthesis of new representatives of the series (table) and have considered some of their reactions.



The action of methylating agents on IIa ($R = \text{CH}_3$, $\text{Ar} = \text{C}_6\text{H}_5$) leads to the formation of the quaternary salt III. When this is heated with dilute alkali, the hydroxyl ion attacks the "guanidine" carbon atom, the $\text{C}=\text{N}$ [1] bond ruptures, and the benzimidazolone derivative (V) is produced. The reaction can be used to determine the position of the substituents in the nucleus.



The reaction of IIa with bromine in chloroform forms a monobromo derivative, the methyl benzene-sulfonate derivative of which is decomposed by alkali to give 1-methylbenzimidazolone. On this basis, it may be concluded that the bromine atom is present in position 3 or in the aryl radical. Since the properties of the monobromo derivative differ from those of 2-*p*-bromophenyl-9-methylimidazo[1,2-*a*]benzimidazole (IIb) obtained by independent synthesis, in which the bromine is nonlabile, the product of the bromination of IIa must be attributed to the structure of the 3-bromo-substituted compound VIa. Thus, IIa reacts with bromine in a similar manner to imidazo[2,1-*b*]thiazole derivatives [4, 5].



The halogen atom in compound VIa possesses a fairly high mobility. Consequently, by heating it with sodium nitrite in dimethylformamide, it is possible to convert it into nitro derivative VIb [6]. Reaction under the same conditions with piperidine or morpholine leads, respectively, to the N-piperidino derivative (VIc) and the N-morpholino derivative (VIId).

1-Alkyl- and 1-Aralkyl-2-imino-3-phenacylbenzimidazolines (Ia-c) and the Products of Their Cyclization (IIa-c)

Compound	R	Ar	Mp, °C (solvent for crystallization)	Empirical formula	Found, %			Calculated, %			Yield, %
					C	H	N	C	H	N	
Ia	CH ₃	C ₆ H ₅	146° (aqueous ethanol)	C ₁₆ H ₁₅ N ₃ O · H ₂ O	67.75	6.06	15.08	67.82	6.05	14.84	99.0
Ib	CH ₃	<i>p</i> -BrC ₆ H ₄	161° (decomp., methanol)	C ₁₆ H ₁₄ BrN ₃ O · 1/2H ₂ O ^{3*}	54.13	4.50	11.96	54.41	4.28	11.90	98.0
Ib · HBr	CH ₃	The same	284-285° (decomp., ethanol)	C ₁₆ H ₁₄ BrN ₃ O · HBr	45.30	3.64	10.04	45.21	3.56	9.88	73.0
Ic	CH ₂ C ₆ H ₅	C ₆ H ₅	170-171° (aqueous ethanol)	C ₂₁ H ₁₉ N ₃ O	77.52	5.75	12.43	77.39	5.61	12.30	98.0
Ic · HBr	CH ₂ C ₆ H ₅	The same	267-268° (decomp., ethanol-ether)	C ₂₁ H ₁₉ N ₃ O · HBr	62.63	4.75	—	62.57	4.77	—	73.0
IIa	CH ₃	C ₆ H ₅	120° (aqueous ethanol)	C ₁₆ H ₁₃ N ₃	77.67	5.31	17.09	77.71	5.30	16.99	91.5
IIb ^{1*}	CH ₃	<i>p</i> -BrC ₆ H ₄	153° (methanol)	C ₁₆ H ₁₂ BrN ₃ ^{3*}	58.97	3.77	12.95	58.91	3.71	12.88	66.0
IIc ^{2*}	CH ₂ C ₆ H ₅	C ₆ H ₅	147° (methanol)	C ₂₁ H ₁₇ N ₃	81.51	5.26	12.99	81.70	5.31	12.99	93.3

^{1*}The base was obtained by triturating the hydrochloride with an excess of 40% alkali.

^{2*}The hydrochloride of IIb was moistened with water and triturated with 40% alkali, and the base was extracted with acetone.

^{3*}Ib. Found, %; Br 22.55. Calculated, %; Br 22.62. IIb. Found, %; Br 24.54. Calculated, %; Br 24.50.

EXPERIMENTAL

The 2-iminobenzimidazoline derivatives (I) were obtained by the reaction of 2-amino-1-methyl- or 2-amino-1-benzylbenzimidazole with phenacyl bromide or its p-bromo derivative (table).

2-Imino-1-methyl-3-phenacylbenzimidazoline (Ia). The base was isolated in the form of the hydrate from a hot aqueous solution of the hydrobromide [3] by the action of a saturated solution of Na_2CO_3 . At 100–120° C it lost two molecules of water, being converted into **IIa**.

9-Methyl-2-phenylimidazo[1,2-a]benzimidazole (IIa). Compound **Ia** was boiled with an excess of phosphorus oxychloride or conc. HCl for 4 hr [2]. The resulting hydrochloride was dissolved in ethanol with a small excess of ammonia, and the base was precipitated with ice water. Storage at 25–30° C led to the resinification of the substance.

9-Methyl-2-phenylimidazo[1,2-a]benzimidazole methiodide (III). An ethanolic solution of 1 mM of **IIa** and 2 mM of methyl iodide was boiled for 2 hr 30 min. After cooling, the precipitate was filtered off and washed with ethanol. Yield 72%. Snow-white needles (from ethanol) with mp 234° C (decomp.). Found, %: N 11.00; I 32.50. Calculated for $\text{C}_{17}\text{H}_{16}\text{IN}_3$, %: N 10.80; I 32.60.

Cleavage of III. A solution of 1 g of **III** and 0.25 g of KOH in 10 ml of 50% ethanol was boiled for 1 hr. The oil that deposited was separated off and triturated with ether. Yield 0.48 g (70%). Colorless needles (from ethanol) with mp 167–168° C. The compound was identical with 1-methyl-3-phenacylbenzimidazolone obtained by independent synthesis.

1-Methyl-3-phenacylbenzimidazolone (V). An ethanolic solution of equivalent amounts of 1-methylbenzimidazolone [7] and phenacyl bromide was boiled for 10 min, KOH (1 equivalent) was added, the mixture was shaken until the alkali had dissolved, and the precipitate of potassium bromide was filtered off. After cooling, **IV** separated out, and it was purified by chromatography on alumina. Yield 64%, mp 168° C. Found, %: C 70.80; H 5.37. Calculated for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_2$, %: C 70.87; H 5.55.

The oxime of compound V, mp 210° C (from aqueous ethanol). Found, %: N 15.54. Calculated for $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_2$, %: N 15.56. Picrate, bright orange needles (from ethanol) with mp 182° C (decomp.). Found, %: N 14.47. Calculated for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_2 \cdot \text{C}_6\text{H}_3\text{N}_3\text{O}_7$, %: N 14.49.

3-Bromo-9-methyl-2-phenylimidazo[1,2-a]benzimidazole (VIa). With vigorous stirring, a solution of 5 mM of bromine in chloroform was added over 30 min at 20° C to a solution of 1.24 g (5 mM) of **IIa** in dry chloroform. After 30 min, the hydrobromide that had deposited was filtered off and washed with chloroform. Yield 2.0 g (98%), mp 245° C (decomp.). When the hydrobromide was treated with 5% alkali, an oily product separated out which crystallized on trituration with ether. Yield 1.33 g (98%). Snow-white needles with mp 148° C (from ethanol). Found, %: C 58.77; H 3.83; Br 24.31; N 12.93. Calculated for $\text{C}_{16}\text{H}_{12}\text{BrN}_3$, %: C 58.92; H 3.71; Br 24.50; N 12.88.

Methyl benzenesulfonate derivative of 3-bromo-9-methyl-2-phenylimidazo[1,2-a]benzimidazole. A mixture of 0.65 g (2 mM) of **VIa** and 0.55 ml (4 mM) of methyl benzenesulfonate was heated at 80° C for 30 min. After cooling, the mixture was triturated with ether and the precipitate was filtered off. Yield 0.96 g (96%). Snow-white

needles with mp 227° C (from ethanol–ether). Found, %: N 8.51; 8.47. Calculated for $\text{C}_{23}\text{H}_{20}\text{BrN}_3\text{O}_3\text{S}$, %: N 8.43.

Decomposition of the methyl benzenesulfonate derivative. The salt (1.45 g) was boiled with 5 ml of 10% caustic potash for 30 min. The oily deposit was separated off, and the solution was neutralized to pH 7 and repeatedly extracted with ether. Evaporation of the ether yielded 0.21 g (48.8%) of 1-methylbenzimidazolone in the form of snow-white needles with mp 190–191° C. A mixture with authentic 1-methylbenzimidazolone [7] gave no depression of the melting point.

9-Methyl-3-nitro-2-phenylimidazo[1,2-a]benzimidazole (VIb). A mixture of 0.33 g (1 mM of **VIa** and 0.08 g of sodium nitrite in 3 ml of dimethylformamide was boiled for 1 hr, and the hot solution was filtered from the sodium bromide. After cooling, small lemon-yellow needles deposited. Yield 0.23 g (80%), mp 205° C (from ethanol–acetone). Found, %: N 19.05, 19.28. Calculated for $\text{C}_{16}\text{H}_{12}\text{N}_4\text{O}_2$, %: N 19.17. The compound did not change on being boiled with water and dilute alkali.

9-Methyl-2-phenyl-3-piperidinoimidazo[1,2-a]benzimidazole (VIc). A solution of 0.5 g (1.5 mM) of **VIa** and 0.7 g (8 mM) of piperidine in 5 ml of dimethylformamide was boiled for 2 hr. The solvent was distilled off under reduced pressure. The residue was treated with water and extracted with ether. From the ethereal extracts 0.47 g of dirty-yellow crystals was obtained. Colorless needles with mp 134–135° C (from petroleum ether). Found, %: C 76.74; H 6.89; N 16.68%. $\text{C}_{21}\text{H}_{22}\text{N}_4$, %: C 76.33; H 6.71; N 16.96.

9-Methyl-3-morpholino-2-phenylimidazo[1,2-a]benzimidazole (VI d) was obtained in a similar manner to **VIc** with a yield of 90%. Colorless needles yellowing slightly on storage with mp 212–213° C (from petroleum ether). Found, %: C 72.19; H 6.06; N 16.99. Calculated for $\text{C}_{20}\text{H}_{20}\text{N}_4\text{O}$, %: C 72.28; H 6.06; N 16.86.

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