INVESTIGATIONS IN THE FIELD OF BENZIMIDAZOLE DERIVATIVES

XXI. Bromination of N-Alkyl-Substituted 2-Aminobenzimidazoles and 2-Iminobenzimidazolines*

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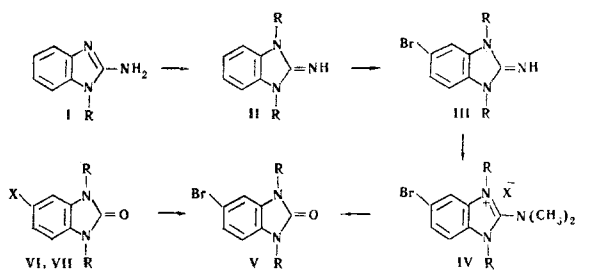
The bromination of 1,3-dialkyl-2-iminobenzimidazolines by the action of potassium bromate and hydrobromic acid leads via the perbromides formed intermediately to 5(6)-monobromo derivatives and, further, to 5,6-dibromoimines. Under these conditions, 1-alkyl-2-aminobenzimidazoles form mixtures of 5- and 6-monobromo-substituted derivatives which, on further bromination, are converted into 5,6-dibromo and, under more severed conditions, into 4,5,6-tribromo derivatives.

Continuing our study of electrophilic substitution reactions in the 2-aminobenzimidazoles [2], we have subjected their 1-alkyl derivatives (I) [3] and the products of the alkylation of the latter—1,3-dialkyl-2-iminobenzimidazolines (II) [4, 5] to bromination by the action of potassium bromate on a solution of the amine (imine) salt in hydrobromic acid. In this process products of the addition of bromine, perbromides (cf. [6, 7]), are first formed, and these change slowly at room temperature and rapidly on being heated in water or dilute acids into the 5-bromo derivatives.

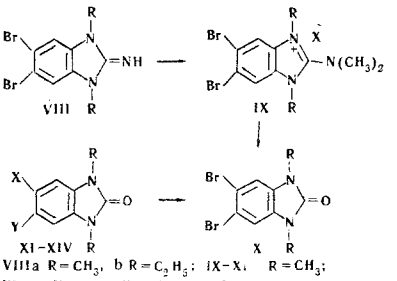
In the bromination of IIa and IIb the first bromine atom enters position 5, as is shown by the conversion of III into Va and Vb, which we have obtained from VI and VII. Since the hydrolysis of Br-substituted imines, especially the 1,3-diethyl derivatives, takes place with very great difficulty, the transition to the benzimidazolones was effected via the stage of the exhaustive methylation of the imino group.



I–V a R = CH_3; b R = C_2H_5

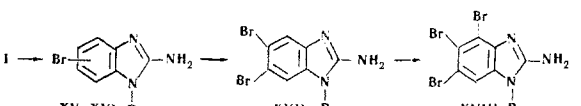
VI X = NO_2, R = C_2H_5; VII X = NH_2 hydrochloride R = C_2H_5

The introduction of a second bromine atom into IIIa and IIIb also takes place via the stage of the formation of perbromides which, however, are converted into the 5,6-dibromo derivatives (VIII) only on heating. The position of the second bromine atom was determined by converting one of these compounds (VIIIa) by hydrolysis (the NH group having been previously alkylated) into a benzimidazolone derivative; it proved to be identical with the dibromobenzimidazolone (X) obtained from 1,3-dimethyl-5,6-dinitrobenzimidazolone (XI) (via XII–XIV) by the successive reduction of the nitro group and replacement of the amino groups formed by bromine using the Sandmeyer reaction (Tables 1 and 2).



VIIIa R = CH_3, b R = C_2H_5; IX–X, R = CH_3;
XI X = Y = NO_2; XII X = NO_2, Y = NH_2;
XIII X = NO_2, Y = Br; XIV X = NH_2, Y = Br

The monobromination of Ia forms a perbromide which changes into XVa and XVIa even at room temperature. The alkylation of this mixture leads to IIIa and, consequently, it contains only the 5- and 6- isomers. The individual compounds were isolated from the mixture by crystallization, and their structure was established by comparison with the substances obtained by means of the Sandmeyer reaction from 2,5- and 2,6-diamino-1-methylbenzimidazoles [10]. The bromination of Ib takes place similarly. The monobromo derivatives so obtained were ascribed to the 5- and 6-substituted series on the basis of spectral data. As reported previously [11], the monochlorination of 2-aminobenzimidazole under the action of H_2O_2 and HCl leads similarly to 2-amino-5(6)-chlorobenzimidazole.



XV, XVI R XVII R XVIII R

XV 5-bromo derivative, XVI 6-bromo derivative

XV–XVIII a R = CH_3; b R = C_2H_5

By means of the method described above two bromine atoms can be introduced into the molecule of Ia or Ib. Under these conditions, 5,6-dibromo derivatives are formed, as has been established by their conversion on alkylation into VIII. Thus, on halogenation, as in other electrophilic substitution reactions in the 2-aminobenzimidazole series, position 5 and 6 are the most reactive [1, 2] (Table 3).

Under more severe conditions (excess of potassium bromate, prolonged heating), tribrominated amines (XVIIIa and XVIIIb) are formed; it was impossible to effect this transformation for the 1,2-dialkylimines.

*For part XX, see [1].

Table 1

Bromo Derivatives of 1,3-Dialkyl-substituted 2-Iminobenzimidazolones

Compound	Mp, °C	Solvent for crystallization	Empirical formula	Found, %				Calculated, %				Yield, %
				C	H	Br	N	C	H	Br	N	
IIIa	122*	Aqueous ethanol (2 : 1)	$C_9H_{10}BrN_3$	45.25	4.31	33.46	17.55	45.02	4.20	33.28	17.50	78
IIIb**	116,5—117	Petroleum ether	$C_{11}H_{14}BrN_3$	49.41	5.21	30.23	15.67	49.27	5.26	29.80	15.67	80
VIIIa	207—208	Benzene-petroleum ether (1 : 1)	$C_9H_9Br_2N_3$	34.03	2.95	50.28	13.22	33.89	2.84	50.10	13.17	85
VIIIb	127—128*	Aqueous ethanol (1 : 1)	$C_{11}H_{13}Br_2N_3$	37.87	3.72	45.87	12.39	38.07	3.77	46.05	12.11	79

* After prolonged drying of the substance at 60-70° C or in vacuum over P_2O_5.

** The compound was obtained with the assistance of V. I. Stupishina.

Table 2

Derivatives of 1,3-Dialkylbenzimidazolones

Compound	Method of preparation	Mp, °C	Solvent for crystallization	Empirical formula	N, %		Yield %
					found	calculated	
VI	a	136	Aqueous ethanol	$C_{11}H_{13}N_3O_3$	17.87	17.87	56
VII	b	286—288	Alcohols	$C_{11}H_{15}N_3O \cdot HCl$	14.27	14.67	86
Vb	c	133—134	Aqueous ethanol	$C_{11}H_{13}BrN_2O$	10.48	10.41	75
XII	d	321—322	Acetic acid	$C_9H_{10}N_4O_3$	25.23	25.22	80
XIII	c	262—262	Ethanol	$C_9H_8BrN_3O_3$	14.76	14.69	84
XIV	b	209—210	Carbon tetrachloride	$C_9H_{10}BrN_3O$	16.63	16.41	71
X	c	248	Benzene-petroleum ether	$C_9H_8Br_2N_2O$	8.77	8.75	83

[a] Alkylation of 5-nitrobenzimidazolone with ethyl iodide in an ethanolic solution of alkali. [b] Reduction of the nitro compound with tin and conc HCl; the hydrochloride of VII was isolated after the precipitation of the tin with hydrogen sulfide, while the amine XIV was extracted with ethanol after the decomposition of the complex salt with alkali. [c] Diazotization of the amine in dil HCl at 0° C and addition of the diazonium solution to a mixture of 3 moles of cuprous bromide and conc HCl heated to 70° C. The diazotization of the amine XII was carried out in conc HCl using an excess of sodium nitrite. [d] Partial reduction with sodium disulfide in aqueous ethanolic solution.

Table 3

Bromine Derivatives of 1-Alkyl-2-Aminobenzimidazoles

Compound	Mp, °C	Solvent for crystallization	Empirical formula	Found, %				Calculated, %				Yield, %	λ_{max}, nm (log ε)
				C	H	Br	N	C	H	Br	N		
XVa	244	Water	$C_8H_8BrN_3$	42.73	3.64	35.32	18.16	42.50	3.57	35.34	18.59	93	293 (4.02)
XVIa	270	Aqueous ethanol (3:2)	$C_8H_8BrN_3$	42.63	3.76	34.75	18.64	42.50	3.57	35.34	18.59		257 (3.95); 294—6 (4.01)
XVb	196	Water	$C_9H_{10}BrN_3$	44.73	4.31	32.96	17.55	45.02	4.20	33.28	19.50	81	293 (3.98)
XVIb	224—225	Aqueous ethanol (2:1)	$C_9H_{10}BrN_3$	44.66	4.30	33.56	17.70	45.02	4.20	33.28	17.50		257 (3.92); 295—6 (3.97)
XVII	247—247.5	Aqueous ethanol (1:1)*	$C_8H_7Br_2N_3$	31.49	2.25	52.38	13.99	31.51	2.31	52.40	13.78	77**	
XVIIb	215—216	Aqueous ethanol (1:1)*	$C_9H_9Br_2N_3$	34.33	2.70	50.14	12.95	33.89	2.84	50.10	13.17	74**	
XVIIIa	337—338	Aqueous pyridine (1:1)	$C_8H_6Br_3N_3$	25.42	1.85	62.00	11.06	25.03	1.57	62.45	10.95	61**	
XVIIIb	298—299	Aqueous pyridine (1:1)	$C_9H_8Br_3N_3$	27.35	2.22	59.81	10.82	27.16	2.03	60.25	10.56	57**	

*The amine isolated from the reaction mixture was first purified by washing out the impurities boiling water.
**The yield obtained in the bromination of the amine I is shown.

Since in an acid medium the amines and imines are present in the form of cations of similar structure, this difference in properties must, apparently, be explained by the screening of positions 4 and 7 of the imines by the alkyl groups on the N-atoms. On this basis it may be assumed that in the bromination of XVII the third atom enters position 4, since attack in position 7 is sterically hindered.

The N-ethyl-substituted amines (imines) brominate with somewhat greater difficulty than their methyl analogs. For the N-ethyl-substituted amines, the conversion of the perbromides into the bromo derivative requires prolonged heating. The bromination of IIa at 20° C leads to the formation not only of the monosubstituted derivative but also of some amount of the dibromo derivative, which is not the case for IIb.

We also obtained IIIa and IIIb, and X by the reaction of bromine on II in chloroform*. This reaction takes place with low yields.

EXPERIMENTAL

Synthesis of the monobrominated amines and imines. A solution of 10 mM of the amine (imine) in 10–15 ml of conc HBr (d 1.4), prepared with heating, was cooled to 20–23° C (in the case of **IIa**, to 3–5° C) and, with stirring, a solution of 0.56 g (3.3 mM) of potassium bromide in the minimum amount of water was slowly added. Then the mixture was slowly heated** in the water bath, the water in the bath being brought to the boil, and was kept there until it had undergone decoloration. Then it was cooled, and the precipitate was filtered off and dissolved in hot water, and the base was precipitated with ammonia (amines) or conc NaOH (imines).

Isolation of the isomeric XV and XVI. A) Three grams of a mixture of **XVa** and **XVIa** was treated with 300 ml of boiling water, the hot solution was filtered, and the insoluble residue was recrystallized from aqueous ethanol (3:2). The substance (0.9 g) consisted of **XVIa**, since it was identical with the substance obtained from 2,6-diamino-1-methylbenzimidazole by the Sandmeyer reaction*.

The aqueous mother solution was evaporated and the residue was crystallized from toluene, giving another 0.3–0.4 g of impure **XVIa**. The toluene was distilled from the mother solution to half bulk, and from this residue petroleum ether precipitated **XVa**, which was recrystallized from water. Yield 0.5 g. The compound was identical with that obtained from 2,5-diamino-1-methylbenzimidazole by the Sandmeyer reaction.

B) A mixture of isomeric **XVb** and **XVIb** (3.8 g) was recrystallized from 50 ml of aqueous ethanol (2:1). On recrystallization from aqueous ethanol, 1.2 g of **XVIb** deposited. The aqueous ethanolic mother solution was evaporated and the residue was treated as described in (A); after repeated crystallization from water, 0.6–0.7 g of **XVb** was obtained.

The individuality of the compounds obtained was checked by chromatographing them on plates coated with a thin layer of alumina in the solvent system chloroform–acetone–ethanol (1 : 2 : 0.2)**.

The 5,6-dibromo derivatives of the amines (XVIIa, b) and of the imines (VIIIa, b) were obtained in a similar manner to the monobromo derivatives using 0.66 mole of $KBrO_3$. The reaction was carried out in dil HBr (2:1).

Passage from 2-iminobenzimidazolines to benzimidazolones. The methylation and hydrolysis of **IIIa, IIIb,** and **VIII** were carried out in two stages, since under the action of even a large excess of methylbenzenesulfonate (MBS) the N-monomethyl derivative is formed predominantly. Compounds **IIIa, IIIb,** and **VIIIa** were heated with 2 moles of MBS at 80–100° C for 1 hr. The melt was triturated with ether, heated with 20% NaOH solution in the water bath for 10–15 min until the smell of methylamine had disappeared and the mixture was extracted with hot benzene. The extracts were shaken with dil (1:1) HBr, and from the acid extract concentrated alkali precipitated the bases. After drying, the substances were again fused with MBS at 100–120° C, the melt was treated as described above, the benzene extracts were combined, the benzene was distilled off, and the residue was crystallized from aqueous ethanol. Yield 53–56%. The **Va, Vb,** and **X** formed

*These experiments were carried out with the participation of V. I. Stupishina.

In the bromination of **Ia, the reaction mixture was not heated but was left overnight at room temperature.

*When 3 moles of cuprous bromide was used, the yield amounted to 70–80%.

**This system of solvents was used for the chromatography of all the other brominated amines and imines.

were identical with the compounds obtained by independent synthesis (Table 2).

1-Alkyl-2-amino-4,5,6-tribromobenzimidazoles (XVIIIa, b). A mixture of 10 mM of I and 200 ml of dil (2:1) HBr was heated to 35-40° C, and 50 mM of finely ground potassium bromate was added over 2-3 hr. Then the mixture was heated very slowly (6-7 hr) to 90-95° C and was kept there until the yellow color had disappeared. The salt was filtered off, washed with hot water, and triturated with ammonia, and the base was treated with 30-40 ml of boiling ethanol. The insoluble residue, the tribromo derivative, was recrystallized from aqueous pyridine.

The alkylation of the bromo derivatives with alkyl iodides was carried out as described previously [4, 5]. The yields were about 90%. The tribromosubstituted amines do not alkylate under these conditions.

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