THE LABILITY OF THE HALOGEN IN 5(6)-BROMO SUBSTITUTED BENZIMIDAZOLES

Yu. P. Andreichikov and A. M. Simonov

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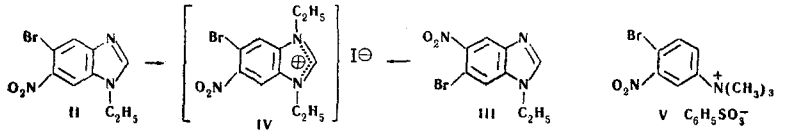
The bromine atom is not labile either in 5-bromo-1-ethylbenzimidazole, its 6-nitro derivative, the isomeric 6-bromo-5-nitro compound, nor in the benzimidazolium salts derived therefrom. The similarly constituted 4-bromo-3-nitrotrimethylphenylammonium salt fairly readily exchanges its bromine atom for an arylamino group.

We have shown experimentally that the halogen atom in 5-bromo-1-ethylbenzimidazole (I) is not replaced by alkyl(aryl)amino groups, even under severe conditions. As a result of the stability of the bromine, heterylation of benzimidazole with I was unsuccessful (see [1]). Reaction of I with butyllithium and with metallic potassium [2] failed to replace the bromine. Thus alkylation of the NH of the imidazole ring of I, like the dimethylamino group in the p-position of the benzene ring [3, 4], greatly reduces the lability of the bromine atom.

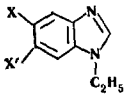
The reactivity of the bromine in I was not increased by introducing a nitro group into the 6-position (II). Its lability in 6-bromo-5-nitro-1-ethylbenzimidazole (III) is also low. This is apparently due to the interruption of the conjugation of the 5–6 bond of the benzimidazole nucleus [5, 6].

Nor is the lability of the halogen atom in the benzene ring of benzimidazole increased by quaternizing the imidazole ring. Although the trimethylammonium group in the p-position of V considerably increases the



II IV III V $C_6H_5SO_3^-$

TABLE 1



Compound	X	X_1	mp, °C	Color and crystalline form *	Molecular formula	Found, % C	Found, % H	Found, % N	Calculated, % C	Calculated, % H	Calculated, % N	Yield, %
VI	NO_2	NO_2	182	Colorless prisms	$C_9H_8N_4O_4$	45.93	3.41	23.90	45.77	3.41	23.72	90
VII	NO_2	NH_2	206—207	Orange prisms	$C_9H_{10}N_4O_2$	52.33	5.13	26.71	52.42	4.89	27.12	57
VIII	NH_2	NO_2	185—186	The same	$C_9H_{10}N_4O_2$	52.69	4.93	27 41	52.42	4.89	27.12	28
II	NO_2	Br	170—171	Colorless needles	$C_9H_8BrN_3O_2$	39.96	2.98	15.69	40.02	2.99	15.56	91
III	Br	NO_2	127	Colorless needles	$C_9H_8BrN_3O_2$	40.27	2.77	16.01	40.02	2.99	15.56	70

*Recrystallization solvent, ethanol.

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mobility of the halogen (we have found that exchange of bromine for the phenylamino group in the quaternary salt V takes place even in boiling alcoholic solution), the benzimidazolium salt IV does not react with aniline even at 180° C (the bromine atom in the starting 3-nitro-4-bromodimethylaniline [7] is stable, and is not replaced by the phenylamino group on boiling in aniline).

EXPERIMENTAL

5-Bromo-1-ethylbenzimidazole (I). This was synthesized by the Sandmeyer reaction from 5-amino-1-ethylbenzimidazole, the copper complex which separated at first being decomposed with sodium sulfide, then further treatment was carried out as in [8]. The compound failed to react with aniline, dimethylamine, or other amines in the presence of copper salts at 190°C.

5-Amino-6-nitro- (VII) and 5-Nitro-6-amino-1-ethylbenzimidazole (VIII). Crystalline sodium sulfide 15.5 g (78 mmole) and 2.5 g (78 mmole) of sulfur were dissolved with heating in 50 ml of water, and a solution of 10.6 g (45 mmole) of 5,6-dinitro-1-ethylbenzimidazole (VI) in 70 ml of ethanol (obtained by reacting 5,6-dinitrobenzimidazole [9] with ethyl iodide and alkali) was added. The mixture was boiled for 2 hr, then cooled, and the orange crystals which separated were filtered off and recrystallized twice from ethanol to give 5.8 g (74%), mp 183-202° C.

A 2.5-g mixture of the isomers was dissolved in chloroform, and separated by chromatography on an alumina column to give 1.42 g of VIII, mp 206-207° C, and 0.64 g of VII, mp 185-186° C. The structure of VIII was established by elimination of the amino group by diazotization, which gave a compound, mp 131-132° C [10], which was identical with 5-nitro-1-ethylbenzimidazole. Therefore the compound with mp 206-207° C was VIII, and that with mp 185-186° C must be assigned structure VII.

5-Bromo-6-nitro- (II) and 5-Nitro-6-bromo-1-ethylbenzimidazole (III). These were obtained by diazotizing VII and VIII, respectively, in HBr, followed by heating with cuprous bromide. The double salts of II and III with cuprous bromide were decomposed with excess ammonia or sodium sulfide. The bromine atom is these compounds did not undergo replacement on prolonged heating (10-20 hr) with aniline, benzylamine or piperidine in dimethylformamide in the presence of copper salts.

5-Bromo-6-nitro-1,3-dimethylbenzimidazolium Iodide (IV). A mixture of II and III, obtained by the Sandmeyer reaction on partialy reduced VI, was fused with ethyl p-toluenesulfonate at 140° C. The melt was triturated with ether, and the salt was filtered off, mp 227° C (from water). The salt was dissolved in a small volume of hot water, and an excess of a concentrated solution of potassium iodide was added, giving 74% of yellow needles, mp 255° C (from water). Found, %: C 31.00; H 3.01; N 10.06. Calculated for $C_{11}H_{13}BrIN_3O_2$, %: C 31.01; H 3.08; N 9.86.

3-Nitro-4-bromophenyltrimethylammonium Benzenesulfonate (IX). A mixture of 4-bromo-3-nitro-N,N-dimethylaniline [11] and methyl benzenesulfonate (10% excess) was fused on an oil bath at 130-140° C for 2 hr. After cooling, the mixture was triturated and washed with hot benzene to give 70% of colorless crystals, mp 218-219° C (decomp, from methanol with ether). Found, %: N 6.66. Calculated for $C_{15}H_{17}BrN_2O_5S$, %: N 6.71.

3-Nitro-4-anilinophenyltrimethylammonium Benzenesulfonate (V). A solution of 2.15 g (5 mmole) of IX, 0.93 g (10 mmole) of aniline, and 0.7 g (5 mmole) of sodium acetate in 15 ml of ethanol was boiled for 8 hr. After distilling off most of the alcohol, 10 ml of water was added, and the aniline was distilled off in a current of steam. Yellow plates separated on cooling, mp 233° C (decomp, from alcohol with ether). Yield 1.15 g (52%). Found, %: N 9.88. Calculated for $C_{21}H_{23}N_3O_5S$, %: N 9.78.

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