BENZO[1,2-d:3,4-d']DIIMIDAZOLE DERIVATIVES

I. SYNTHESIS OF 3-ALKYL- AND 3,6-DIALKYL DERIVATIVES

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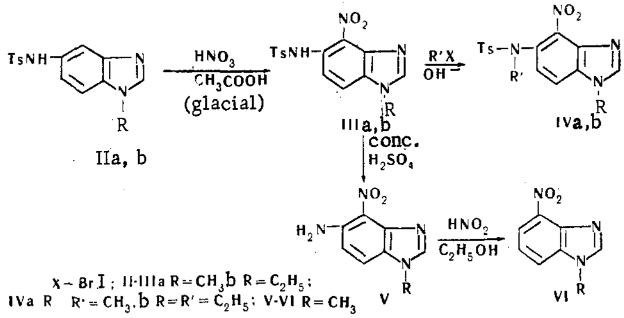
A new path for the synthesis of 3-monoalkyl- and 3,6-dialkyl-substituted benzo[1,2-d:3,4-d']-diimidazole is described: 5-tosylamino-1-alkylbenzimidazole is converted to the 4-nitro derivative by nitration in glacial acetic acid, and the imidazole ring is closed after alkylation and cleavage of the tosyl group.

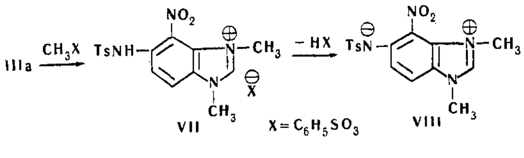
Compounds of the benzo[1,2-d:3,4-d']diimidazole series (angular diimidazolobenzene, I) have been investigated to only a small extent. Only 2-methyl-, 2,7-dimethyl-, and 2,7-bis(p-azidophenyl) derivatives are known [1-3]. The transformations of this condensed system have not been investigated.

We have developed a comparatively simple path for the synthesis of 3-monoalkyl- and 3,6-dialkyl-substituted benzo[1,2-d:3,4-d']diimidazole. It is based on the observation that in the nitration of 5-tosylamino-1-methylbenzimidazole (IIa) with nitric acid in glacial acetic acid at 90-100° the nitro group enters the 4 position rather than the 5 position, as occurs in the nitration of 5-acetamino-2-methylbenzimidazole [4]. The position of the nitro group was established by elimination of the amino group (after removal of the tosyl radical with concentrated H_2SO_4) by means of the diazo reaction; the mononitro compound (VI) obtained had mp 168-169° and was identical to 1-methyl-4-nitrobenzimidazole obtained by countersynthesis via the method described in [5].



X – Br, I; II-IIIa R = CH_3, b R = C_2H_5;
IVa R = R' = CH_3, b R = R' = C_2H_5; V-VI R = CH_3

Alkylation of nitrotosylamino derivative III with alkyl halides in an alcoholic alkaline medium proceeds at the NH group rather than at the N heteroatom (see [6]); in fact, the methylation product (IVa) differs markedly from the isomeric betaine VIII which is formed from benzenesulfonate VII by reaction with ammonia.



The aminonitro derivatives (IX, Table 1) obtained by hydrolytic cleavage of the tosyl radical, are converted into derivatives of angular diimidazolobenzene (XI, Table 2) by reduction to diamines with subsequent cyclization by reaction with 85% formic acid.

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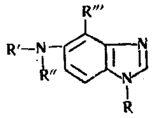
TABLE 1. 5-Amino-1-alkylbenzimidazole Derivatives



Comp.	R	R'	R''	R'''	mp	Empirical formula	Found, %				Calc., %				Yield, %
							C	H	N	S	C	H	N	S	
IIa	CH_3	H	Ts	H	274	$C_{15}H_{15}N_3O_2S$	60,10	5,34	13,90	10,40	59,78	5,02	13,94	10,64	86
IIb	C_2H_5	H	Ts	H	250—251	$C_{16}H_{17}N_3O_2S$	60,90	5,57	—	10,08	60,93	5,43	—	10,17	85
IIIa	CH_3	H	Ts	NO_2	200—201	$C_{15}H_{14}N_4O_4S$	52,20	4,17	16,07	9,14	52,02	4,07	16,18	9,26	70
IIIb	C_2H_5	H	Ts	NO_2	191—192	$C_{16}H_{16}N_4O_4S$	53,25	4,70	—	8,91	53,32	4,48	—	8,90	60
IVa	CH_3	CH_3	Ts	NO_2	215—216	$C_{16}H_{16}N_4O_4S$	53,20	4,68	15,55	8,69	53,32	4,48	15,55	8,90	82
IVb	C_2H_5	C_2H_5	Ts	NO_2	203—204	$C_{18}H_{20}N_4O_4S$	55,87	5,33	—	8,52	55,66	5,19	—	8,25	62
IXa	CH_3	CH_3	H	NO_2	136—137	$C_9H_{10}N_4O_2$	52,66	5,21	27,09	—	52,42	4,89	27,17	—	94
IXb	CH_3	H	H	NO_2	242—243	$C_8H_8N_4O_2$	50,27	4,28	29,30	—	50,00	4,20	29,17	—	92
IXc	C_2H_5	C_2H_5	H	NO_2	134—135	$C_{11}H_{14}N_4O_2$	56,17	6,23	23,69	—	56,40	6,02	23,92	—	98
IXd	C_2H_5	H	H	NO_2	182—183	$C_9H_{10}N_4O_2$	52,30	4,63	27,06	—	52,42	4,89	27,17	—	93

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*Compounds IIa, IIb, IVa, and IVb are colorless crystals; IIIa is lemon-yellow plates; IIIb is pale-yellow prisms; IXa and IXc are red prisms; IXb and IXd are orange crystals; IIa and IIb were purified by precipitation; IXb was purified by crystallization from water and the remaining substances were crystallized from alcohol.

TABLE 2. N-Alkyl Substituted Benzo[1,2-d:3,4-d']diimidazoles (XIa-d)

Comp.	R	R′	mp*	λ_{max}, nm ($\lg \varepsilon$)**	Empirical formula	Found, %			Calc., %			Yield, %
						C	H	N	C	H	N	
XIa	CH_3	CH_3	237—238 (benzene)	265 (4,12); 273 (4,26); 284 (4,21); 294 (3,80)	$C_{10}H_{10}N_4$	64,50	5,64	30,15	64,50	5,41	30,09	80
XIb	CH_3	H	318—319 (water)	265 (4,00); 279 (3,93); 289 (3,74)	$C_9H_8N_4$	62,93	4,73	32,34	62,78	4,68	32,54	89
XIc	C_2H_5	C_2H_5	192—193 (benzene)	265 (4,01); 273 (4,18); 284 (4,09); 295 (3,69)	$C_{12}H_{14}N_4$	67,26	6,79	26,21	67,26	6,59	26,15	71
XId	C_2H_5	H	323—324 (water)	265 (3,94); 279 (3,86); 289 (3,68)	$C_{10}H_{10}N_4$	64,30	5,76	—	64,50	5,41	—	90

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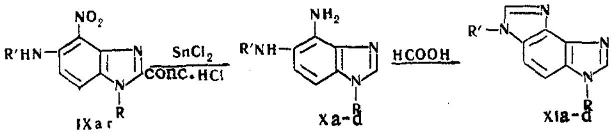
*Compounds XIa-d are colorless crystalline substances.

†The UV spectra were obtained in alcohol with an SF-4 spectrophotometer.



IX-XIa $R = R' = CH_3$; b $R = CH_3$, $R' = H$; c $R = R' = C_2H_5$; d $R = C_2H_5$, $R' = H$

The IR spectra of XI are in agreement with their angular structure. It is well known that the IR spectra of tetrasubstituted benzenes which have two hydrogen atoms in the ortho position with respect to each other are characterized by a strong absorption band from 860-800 cm^{-1}, while the absorption band is located at 900-860 cm^{-1} in the presence of isolated hydrogen atoms [7]. The IR spectra of XIa-d have strong absorption bands at 791, 802, 793, and 800 cm^{-1}, respectively, while no strong bands are observed from 900-860 cm^{-1}. We also obtained the UV spectra of XIa-d (Table 2). They indicate a significant difference from the spectra of linear diimidazolobenzene and its 1,7-dimethyl derivative [8].

EXPERIMENTAL

1-Methyl-5-tosylaminobenzimidazole (IIa). An alcohol solution of equimolecular amounts of 5-amino-1-methylbenzimidazole, tosyl chloride, and sodium acetate was refluxed for 1.5 h. The reaction product was purified by dissolving in 10% alkali, boiling with activated charcoal, and neutralizing with hydrochloric acid to pH 8; IIa precipitates in the form of snow-white prisms (Table 1).

1-Methyl-4-nitro-5-tosylaminobenzimidazole (IIIa). Compound IIa [30.1 g (0.1 mole)] was dissolved in 90 ml of glacial acetic acid, the solution was cooled to 10-20°, and 13.2 ml (0.2 mole) of nitric acid (sp. gr. 1.40) in 25 ml of glacial acetic acid was added in 30 min. The solution was then gradually heated to 90-100° and held at this temperature for 1.5 h. The solution was then cooled, the precipitated IIIa was filtered, and 24 g of IIIa was isolated by heating for 30 min with a saturated aqueous solution of sodium acetate.

Ethyl Derivatives IIb and IIIb. These were obtained in the same way as IIa and IIIa (Table 1).

1-Methyl-4-nitro-5-(N-methyltosylamino)benzimidazole (IVa). Compound IIIa [10.35 g (0.03 mole)] and 1.62 g of sodium hydroxide were dissolved in 170 ml of alcohol and 12 ml of water. The solution was cooled, and a solution of 5.4 ml (0.09 mole) of methyl iodide in 12.5 ml of alcohol was added with stirring in the course of 1 h. The mixture was stirred for 30 min at 15-20° and for 2 h while heating on a water bath. The precipitate that formed on cooling was filtered and weighed 7.4 g. Another 1.3 g of IVa was isolated from the filtrate with water.

4-Nitro-1-ethyl-5-(N-ethyltosylamino)benzimidazole (IVb). This compound was obtained by ethylation of IIIb with ethyl bromide under conditions similar to those used to obtain IVa.

1-Methyl-5-methylamino-4-nitrobenzimidazole (IXa). Compound IVa [3.6 g (0.01 mole)] was dissolved with stirring and cooling in 12 ml of concentrated H_2SO_4. The solution was stirred for 2 h at 10-20° and then heated to 50° for 1 h. The solution was cooled, poured over ice, and neutralized with 22% ammonium hydroxide. The bright-red precipitate was filtered and weighed 1.95 g.

Compounds IXb, c, and d were similarly obtained (Table 1).

Reduction of Nitroamines (IXa-d) to Diamines (Xa-d). Stannous chloride (0.3 mole) was added in portions to a solution of 0.1 mole of IX in 130 ml of hydrochloric acid (sp. gr. 1.19). The mixture was heated on a water bath for 1.5 h, cooled, and 40% sodium hydroxide was added until the mixture gave a strongly alkaline reaction. The mixture was extracted with chloroform to give 65-80% of product. The diamines are readily oxidized and are therefore cyclized without purification.

3,6-Dimethylbenzo[1,2-d:3,4-d']diimidazole (IXa). A solution of 1.24 g of Xa in 5 ml of 85% formic acid was refluxed for 3 h, after which 5 ml of water was added, and the solution was neutralized with concentrated ammonium hydroxide. The cyclization product was extracted with chloroform to give 1.04 g of product. The compound was soluble in alcohol, water, acetone, insoluble in ether and heptane, and slightly soluble in benzene (Table 2).

3-Methylbenzo[1,2-d:3,4-d']diimidazole (XIb). This compound was obtained in the same way as XIa. The compound precipitated in the form of a snow-white precipitate which was soluble in alkali on treatment of the reaction mixture with ammonia.

Ethyl derivatives XIc and d were similarly obtained (Table 2).

1-Methyl-4-nitrobenzimidazole (V). Compound IXb [2.88 g (0.015 mole)] and 2.1 ml of concentrated H_2SO_4 were added to 8.6 ml (0.15 mole) of ethanol. The mixture was cooled to 0° and 1.05 g (0.015 mole) of sodium nitrite in 2.5 ml of water was added gradually at 5-10°. The resulting solution of diazonium salt was heated on a water bath with a reflux condenser until nitrogen evolution ceased (1 h). The ethanol and acetaldehyde were removed by distillation, 5 ml of water was added, and the mixture was neutralized with concentrated ammonium hydroxide and extracted with chloroform to give 1.02 g (38%) of pale-yellow needles with mp 168-169° (from benzene). Found %: C 54.27; H 3.93; N 23.90. $C_8H_7N_3O_2$. Calculated %: C 54.23; H 3.98; N 23.71. The compound obtained was identical to that obtained by countersynthesis via the method in [5] according to chromatography and a mixed melting point test.

1,3-Dimethyl-4-nitro-5-tosylaminobenzimidazolium Benzosulfate (VII). Equimolecular amounts of IIIa and methyl benzenesulfonate were melted at 120-130° for 2 h to give 83% of colorless cubic crystals with mp 228-229° (alcohol). Found %: C 51.19; H 4.28; N 11.03; S 12.30. $C_{22}H_{22}N_4O_7S_2$. Calculated %: C 50.95; H 4.28; N 10.80; S 12.36.

1,3-Dimethyl-4-nitro-5-tosylaminobenzimidazolium Betaine (VIII). Compound VII was treated for 20 min with concentrated ammonium hydroxide and the precipitate was filtered to give 95% of orange prisms with mp 303-304° (decomp.). Found %: C 53.22; H 4.47; S 9.16. $C_{16}H_{16}N_4O_4S$. Calculated %: C 53.32; H 4.48; S 8.90.

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