DIAZO COMPOUNDS OF THE HETEROCYCLIC SERIES

I. 2-(N-NITROSAMINO)BENZIMIDAZOLES

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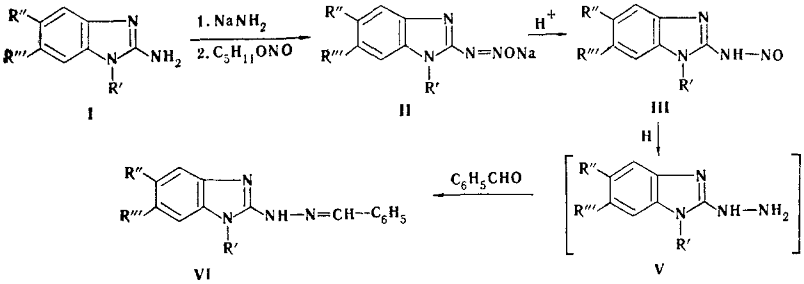
Stable primary N-nitrosamines of the benzimidazole series were obtained by the action of sodium amide and isoamyl nitrite on 1-substituted 2-aminobenzimidazoles and subsequent acidification of the resulting benzimidazole-2-diazotates. The effect of the acidity of the solution on the activity of the benzimidazole-2-diazonium salts formed from the nitrosamines was traced.

Although primary N-nitrosamines of azoles have been known for a long time (see [1] for the literature data), the study of the structure and properties of diazo compounds of azoles with three or more heteroatoms in the ring was begun only recently [2-7]; they were unknown in the imidazole series.

Considering the ease of conversion of the various forms of diazo compounds of azoles to nitrosamines [8], we synthesized their nitroso derivatives (III) from 2-amino-1-substituted benzimidazoles (I) through the intermediate diazotates (II).* We were able to synthesize diazotates II by the Bamberger method [9] by the reaction of excess isoamyl nitrite with the Na derivatives of amines I. In contrast to the diazotates of the benzene series, which are converted to diazo anhydrides at pH 5.5-7.5 [10], benzimidazolediazotates II under these conditions give N-nitrosamines III, which are yellow crystalline substances that are only slightly soluble in organic solvents and burst into flames on heating (see Table 1). Nitrosamines III are amphoteric and readily soluble in dilute acids and alkalis, ammonium hydroxide, and alcohol solutions of alkoxides. When they are added to concentrated sulfuric acid they cause an intense blue coloration; this may be used as a qualitative reaction.

The structure of III† was confirmed by reduction of some of them to substituted hydrazines V, which were identified as the benzylidene derivatives (VI).



a $R'=CH_3$, $R''=R'''=H$; b $R'=R''=CH_3$, $R'''=H$; c $R'=R''=R'''=CH_3$; d $R'=CH_3$, $R''=OCH_3$, $R'''=H$; e $R'=CH_3$, $R''=OC_2H_5$, $R'''=H$; f $R'=C_6H_5$, $R''=R'''=H$; g $R'=CH_2C_6H_5$, $R''=R'''=H$

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*Direct nitrosation, which was successful for the preparation of 2-(N-methyl-N-nitrosamino)-1-methylbenzimidazole IV, did not give positive results in the remaining cases.

†Most of these compounds were analyzed for their nitrogen content only, inasmuch as they explode during attempts to determine C and H.

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TABLE 1. 2-(N-Nitrosamino)benzimidazoles III and Their Benzylidene Derivatives (VI)

Compound	mp, dec., °C (solvent)	Empirical formula	Found, %			Calc., %			Yield, %	ν_{NH}, cm^{-1}	Compound	mp, °C	Empirical formula	Found, %			Calc., %		
			C	H	N	C	H	N						C	H	N	C	H	N
III a	162 (methanol)	$C_8H_8N_4O$	—	—	32,2	—	—	31,8	74	3260	VI a	161—163	$C_{15}H_{14}N_4$	71,7	5,9	22.1	71,9	5,7	22,4
III b	158 (methanol)	$C_9H_{10}N_4O$	—	—	29,0	—	—	29,5	59	3260	VI b	216—217	$C_{16}H_{16}N_4$	72,6	6,3	21.4	72,7	6,1	21,2
III c	148 (acetone)	$C_{10}H_{12}N_4O$	—	—	27,8	—	—	27,4	69	3230	VI c	193—194	$C_{17}H_{18}N_4$	73,2	6,2	20,6	73,3	6,5	20,1
III d	139 (ethanol)	$C_9H_{10}N_4O_2$	—	—	27,1	—	—	27,2	80	3255	VI d	158—160	$C_{16}H_{16}N_4O$	68,9	5,8	19,8	68,5	5,8	20,0
III e	138 (ethanol)	$C_{10}H_{12}N_4O_2$	54,3	5,7	25,5	54,5	5,5	25,4	69	3250	—	—	—	—	—	—	—	—	—
III f	167 (ethanol)	$C_{13}H_{10}N_4O$	65,0	4,3	23,8	65,5	4,2	23,5	75	3220—3230	—	—	—	—	—	—	—	—	—
III g	185 (ethanol)	$C_{14}H_{12}N_4O$	66,8	4,3	22,4	66,6	4,8	22,2	60	3260—3160	—	—	—	—	—	—	—	—	—

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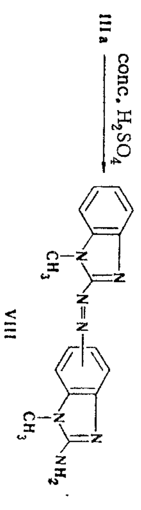
*From benzene-petroleum ether (2 : 1).

The use of IR spectroscopy to prove the structure of III proved to be difficult because of the absence of information on the absorption of primary nitrosamines and because of their poor solubility in organic solvents. Only the intense band at 3250 cm^{-1}, which is absent in the spectra of amines I and nitrosamine IV, can be considered to be sufficiently characteristic for nitrosamines III. In analogy with the corresponding band of secondary amides [11], it can be assigned to the absorption of a bonded NH group, although this band may also be due to the vibration of the NH group of the imidazoline ring of the tautomeric imino form [12]. The second assumption is also confirmed by the similarity between the UV spectra of III and 2-N-nitrosimino-1,3-dimethylbenzimidazoline (VII) [13], which is a compound with a fixed imino structure.

The stability of primary nitrosamines III proved to be quite high; they are stable on prolonged storage in the dark at 20°C (see [1]). Bases of the diethylamine type do not induce denitrosation of these compounds; the addition of amines I even promotes stabilization of III. Rapid denitrosation is observed during the action of concentrated hydrochloric acid. In addition to amine I, small amounts of the 2-chloro derivative and the corresponding benzimidazolone are formed in this case.

Concentrated sulfuric acid has a different effect on III. Partial denitrosation is apparently also observed in this case; the resulting amine I then undergoes diazo coupling with the simultaneously generated diazonium salt, and a mixture of isomeric 5- and 6-azobenzimidazoles (of the VIII type) is obtained. The latter also give the above-mentioned blue coloration in concentrated sulfuric acid.



VIII

Azo compounds VIII were isolated from nitrosamine IIIa in 73% yield and proved to be identical to the products of "self-coupling" of amine Ia previously obtained in [15]. The yields of azo compounds VIII fall when the sulfuric acid is diluted (50 and 42% for 75 and 50% acid, respectively, and only traces of products in 25% acid solution). Products VIII are apparently formed only at acid concentrations adequate for the generation of the active benzimidazole-2-diazonium salt, which contains a protonated imidazole ring [16]. The nitrosamines are not converted to azo compounds VIII in acetic acid, but diazo coupling with active azo components is possible. Thus IIIa and IIIc react with β-naphthol to give the corresponding benzimidazoleazonaphthols (IXa, b), while the formation of azo compounds with mesitylene can be detected only by chromatography. In the absence of acids, nitrosamines IV do not undergo diazo coupling. Compounds IV are apparently converted to diazonium salts with an unprotonated imidazole ring in acids with a low protonating capacity. The activity of these salts should not be anomalously high, as also in the case of thiazole-2-diazonium salts [17].

EXPERIMENTAL

The IR spectra were measured with a UR-20 spectrometer. The samples were prepared as: 1) mineral oil pastes (3700-3800 cm^{-1}); 2) hexafluorobutadiene pastes (1400-1500 cm^{-1} and 2000-3600 cm^{-1}) for III; 3) chloroform solutions (complete spectrum) for IV.

2-Benzimidazolenitrosamines (III). A mixture of 10 mmole of amine I [18] and 12 mmole (0.47 g) of ground sodium amide in 30 ml of absolute diethyl ether was refluxed and stirred vigorously for 1 h, after which 80 mmole (12.4 ml) of freshly distilled isoamyl nitrite in 10 ml of absolute ether was added, and the mixture was refluxed for 2-3 h. The precipitated sodium diazotate (II) was removed by filtration, washed with ether, dried in vacuo, and dissolved with cooling in the minimum amount of water. The solution was acidified to pH 6-7 with dilute acetic acid, and the precipitated nitrosamine (III) was removed by filtration, washed with ice water, dried, and crystallized from acetone or alcohol (see Table 1).

Reduction of Nitrosamines. A 10-ml sample of 15% acetic acid was added to a mixture of 10 mmole of nitrosamine III and 20 mmole (1.3 g) of zinc powder at room temperature. After 30 min, 13 mmole (1.4 g) of benzaldehyde was added, and the mixture was shaken at 30-35° for another 30 min. It was then filtered, and the filtrate was made alkaline with ammonia until it was weakly alkaline. The yellow-green crystals of hydrazone VI were removed by filtration, washed with water, and recrystallized (see Table 1).

Behavior of Nitrosamine III with Respect to Sulfuric Acid Solutions. A 0.18-g sample of nitrosamine IIIa was added in portions, respectively, to 12.5, 25, 50, and 98% sulfuric acid solutions, cooled to 0°. After the mixtures had been allowed to stand at room temperature for 24 h, they were diluted with a small amount of water and treated with sodium carbonate until they were weakly alkaline. They were then treated with three 10-15-ml portions of chloroform, and the chloroform extracts were evaporated. The residue was separated with a column filled with Al_2O_3. A bright-yellow fraction was eluted with chloroform, after which azo compound VIII and amine Ia were extracted by refluxing the Al_2O_3 in alcohol. The alcohol was removed by distillation, and the residue was treated with two 5-ml portions of hot H_2O, from which amine Ia crystallized out on cooling. The residue contained a mixture of isomeric azo compounds VIII. The yields of the azo compounds are presented in the theoretical part of this paper.

2-(N-Methylnitrosamino)benzimidazole (IV). A 0.35-g (5 mmole) sample of $NaNO_2$ was added with stirring at 40-50° in the course of 30-40 min to a solution of 0.2 g (1 mmole) of 2-N-methylaminobenzimidazole hydrochloride in 10 ml of water acidified with two drops of acetic acid. After 10 min, the temperature was raised to 60° and then cooled immediately. The product was extracted with ether. Nitrosamine IV was obtained as light-yellow crystals with mp 88-89° (from petroleum ether). The yield was 0.17 g (89%). Found %: C 56.5; H 5.3; N 29.4. $C_9H_{10}N_4O$. Calculated %: C 56.8; H 5.3; N 29.5.

2-(2'-Hydroxynaphthylazo)-1-methylbenzimidazole (IXa). A 1.7-g (10 mmole) sample of nitrosamine IVa was added to a cooled (to 10°) solution of 1.4 g (10 mmole) of β-naphthol in 10 ml of glacial CH_3COOH. After 24 h, the mixture was diluted to twice its volume with water, made alkaline with ammonia, and filtered to remove azo compound Xa. The product was purified by chromatography with a column filled with Al_2O_3 and subsequent extraction from the Al_2O_3 with alcohol. The yield of product with mp 197-198° (from butanol) was 2.5 g (79%). Found %: C 71.3; H 4.9; N 18.3. $C_{18}H_{14}N_4O$. Calculated %: C 71.5; H 4.7; N 18.5.

2-(2'-Hydroxynaphthylazo)-1,5,6-trimethylbenzimidazole (IXb). This compound, with mp 201-203° (from butanol), was obtained in 76% yield by the method used to prepare IXa. Found %: C 72.7; H 5.5; N 17.1. $C_{20}H_{18}N_4O$. Calculated %: C 72.7; H 5.5; N 17.0.

LITERATURE CITED

1. I. Goerdeler and K. Deselaers, Chem. Ber., 91, 1025 (1958).
2. H. Gehler and I. Gost, Ann., 665, 144 (1963).
3. I. Goerdeler, K. Deselaers, and H. Ginsberg, Chem. Ber., 93, 963 (1960).
4. I. Goerdeler and M. Roegler, Chem. Ber., 103, 112 (1970).
5. I. C. Tobin, R. N. Butler, and F. Z. Scott, Chem. Commun., 112 (1970).
6. R. N. Butler, M. Lambe, and F. Scott, Chem. Ind., No. 1, 628 (1970).
7. M. Lambe, I. C. Tobin, and F. Z. Scott, Chem. Commun., 411 (1970).
8. Houben-Weyl, Methoden der Organischen Chemie, 10/3, Stuttgart (1965), p. 56.
9. A. E. Chichibabin and M. D. Ryazantsev, Zh. Russk. Fiz.-Khim. Obshchestva, 47, 1571 (1915).
10. T. Kauffman, H. O. Friestad, and H. Henkler, Ann., 634, 64 (1960).
11. L. Bellamy, Infrared Spectra of Complex Molecules, Methuen (1958).

12. Yu. N. Sheinker, A. M. Simonov, Yu. M. Yutilov, V. N. Sheinker, and I. I. Perel'shtein, Zh. Organ. Khim., 2, 917 (1965).
13. V. G. Sayapin and A. M. Simonov, Khim. Geterotsikl. Soedin., 1120 (1967).
14. R. N. Williams, R. I. Pace, and G. I. Iacocke, Spectrochim. Acta, 20, 225 (1964).
15. S. N. Kolodyazhnaya and A. M. Simonov, Khim. Geterotsikl. Soedin., 186 (1967).
16. A. M. Simonov and S. N. Kolodyazhnaya, Zh. Organ. Khim., 3, 1146 (1967).
17. I. Goerdeler and H. Haubrich, Chem. Ber., 93, 397 (1960).
18. A. F. Pozharskii and A. M. Simonov, Chichibabin Amination of Heterocycles [in Russian], Rostov-on-Don (1971).