HETEROCYCLIC DIAZO-COMPOUNDS.

3.* STRUCTURE AND UNUSUAL PROPERTIES OF PRIMARY 2-NITROSOAMINOBENZIMIDAZOLES

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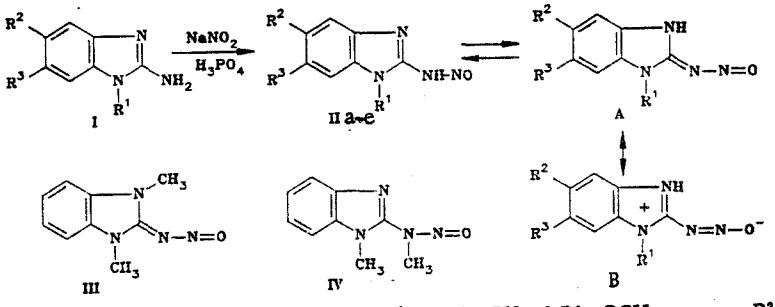
Primary nitrosamines of the benzimidazole series are highly stable, as a result of the existence of the polarized nitrosoimino-form. They have been used to obtain some benzimidazole derivatives.

The usual methods and techniques of diazochemistry are not applicable to 2-diazobenzimidazoles as a result of their uniqueness. For example, benzimidazol-2-diazonium salts are more reactive in the azocoupling reaction than any other diazonium salts [2]. Primary nitrosamines of this series (the predominant form in diazo-equilibria over a wide range of acidities) are anomalously stable in the dry state, and under normal storage conditions they do not undergo appreciable decomposition over periods of nearly ten years. For this reason, in order to arrive at an understanding of the diazotization of 2-amino-1-alkylbenzimidazoles (I) and to determine the optimum conditions for the reaction it is necessary to examine the structures and properties of the corresponding primary nitrosamines.

The primary 2-nitrosoaminobenzimidazoles (IIa-e) are usually readily obtainable by nitrosating the amines (I) with sodium nitrite in 50% phosphoric acid. However, nitrosation of amines containing a methyl or methoxy group in the 6-position is complicated by the formation of self-coupling products [3], apparently as a result of the presence in solution of small equilibrium concentrations of diazonium cations, which are highly reactive. Complications also arise in the nitrosation of N-arylamines, owing to the ability of the corresponding nitrosamines to undergo intramolecular cyclization [4]. In order to obtain N-aryl nitrosamines and nitrosamines (IIc) and (IId), therefore, the method of preparation via the diazotates [5] continues to be of value.



I, II a-e, A, III, IV, B

II a-d $R^1=CH_3$, e $R^1=CH_2C_6H_5$; a,e $R^2=H$, b,c $R^2=CH_3$, d $R^2=OCH_3$; a, c-e $R^3=H$, b $R^3=CH_3$

It is assumed that the higher stability of primary nitrosamines in the azole series as compared with their carbocyclic analogs is due to the existence of the former in the tautomeric nitrosoimino-form A, but this assumption has not hitherto been checked by physicochemical examination of these compounds [6]. Primary 2-nitrosoaminobenzimidazoles form an exception, as became clear during our investigation.

Even a cursory inspection of the UV and IR spectra of (IIa-e) in comparison with those of the model imino (III) and amino-structures (IV) shows that the structures of (IIa-e) differ considerably from that of the secondary nitrosamine (IV), but are very similar to that

*For Communication 2, see [1].

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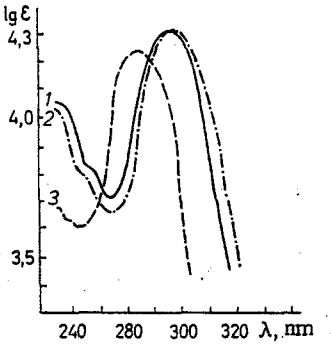


Fig. 1

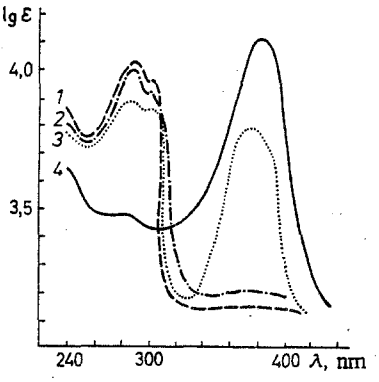


Fig. 2

Fig. 1. UV spectra of 2-nitrosoamino(imino)benzimidazoles in methanol: 1) (IIa), 2) (III), 3) (IV).

Fig. 2. UV spectra of 2-nitrosoaminobenzimidazole (IIa) in phosphoric acid of various concentrations: 1) 50, 2) 60, 3) 85, 4) 95%.

of the imine (III) (Table 1 and Fig. 1). A closer examination of the spectral data and other properties led to the conclusion that the nitrosimine structure possesses considerable intramolecular polarization, corresponding to a considerable contribution by the dipolar structure B to the basic state of the molecule. This conclusion was supported by the presence of very strong long-wave absorption in the UV spectra of the nitroso-compounds (II) and (III) (Table 1), their poor solubility in organic solvents, and the nature of the absorption in the IR spectra. For example, the strong absorption at 1360-1350 and 1405-1380 cm^{-1} in the spectra of solid samples of (II) and (III), which are absent in the secondary nitrosamine (IV) and the original amines (I), is shifted to 1340 and 1415 cm^{-1} respectively in chloroform, in agreement with the assignment of these bands to vibrations involving the fragments $\rangle C{=}N{-}N{=}O \leftrightarrow + \rangle C{-}N{=}N{-}O^-$. In the region of absorption of the $\rangle N{-}N{=}O$ group in secondary aliphatic and aromatic nitrosamines at 1480-1420 cm^{-1} [7], compounds (II) and (III) show no clearly apparent absorption. Secondary nitrosamines, on the other hand, show the strongest absorption in this region. The lower frequency of the absorption of the nitrosoamino-group in (IV) as compared with the analogous absorption in triazoles, tetrazoles, and thiadiazoles [8] is readily explicable by the more electronegative character of these azoles (cf. [9]). Considerable differences exist between (II) and (III), on the one hand, and the nitrosamine (IV) on the other, in the 1600-1500 cm^{-1} region. In the latter, several weak bands are present, whereas in nitrosamines (II) and (III) this region shows strong absorption at 1570-1550 cm^{-1}, which is characteristic of the charged benzimidazole ring [10].

The belief that the nitrosamines (II) are intramolecularly polarized is in accordance with the absorption at high frequencies. On changing from the solid phase to a solution, the absorption at 3260-3210 cm^{-1} is shifted to 3440-3385 cm^{-1}, confirming the existence of intermolecular association in the crystal. It is noteworthy that primary nitrosamines of di-, tri-, and tetrazoles absorb in the solid state at 3460-3450 cm^{-1} [6, 8].

Evidence supporting the polar nitrosimine structure of (II) is provided by their behavior toward acids. For instance, in sulfuric acid solution (acid concentration 0.01 M) neither the nitrosamine (IIa), nor (III) undergo any appreciable changes in the course of two hours, whereas a compound with the fixed amino-structure (IV) undergoes complete denitrosation under these conditions immediately on mixing with the acid. The ease of hydrolysis of (IV) may be due to the formation on protonation of the extremely unstable cation (V), while the diazohydrate structure of (VI), which is in accordance with the most likely site of the polarized nitrosamine B, agrees well with the hydrolytic stability of (II).

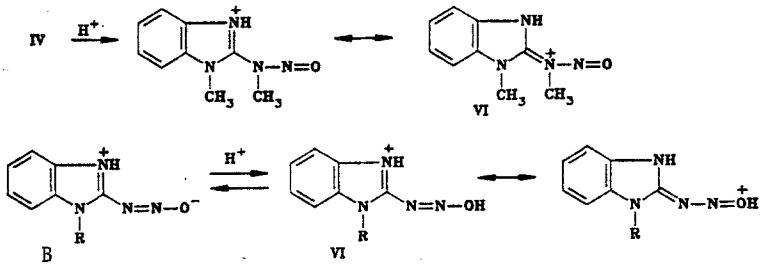
In addition, the protonated diazohydrate structure explains the difficulty of the transformation of the products of the initial diazotization of the amines (I) into diazonium salts, this taking place to a significant extent only in solution in concentrated acids. As

TABLE 1. Spectral Characteristics of 2-Nitrosoamino(imino)-benzimidazoles (II-IV)

Compound	UV spectrum (in methanol), λmax, nm (log ε)	IR spectrum, cm^{-1} (Vaseline oil*)
IIa	250 (3,77), 320 (4,30)	3250, 1616 (av), 1568, 1515 (av), 1485, 1380, 1352, 1238, 1220, 1150
IIb	252 (3,75), 321 (4,41)	3235, 1615 (av), 1570, 1510 (av), 1492, 1384, 1350, 1228, 1154
IIc	250 (3,82), 321 (4,43)	3258, 1620 (av), 1570, 1500 (av), 1380, 1360, 1224, 1152
IId	256 (3,72), 321 (4,45)	3255, 1640 (av), 1570, 1500 (av), 1382, 1350, 1258, 1232, 1165
IIe	251 (3,62), 320 (4,26)	3224, 1620, 1572, 1485, 1405, 1355, 1252, 1180, 1126, 1105
III	250 (3,68), 315 (4,30)	1550, 1510 (av), 1485, 1380, 1356, 1270, 1250, 1176, 1145
IV	—, 291 (4,24)	1620 (av), 1566 (av), 1522 (av), 1500, 1464, 1445, 1415, 1200, 1105

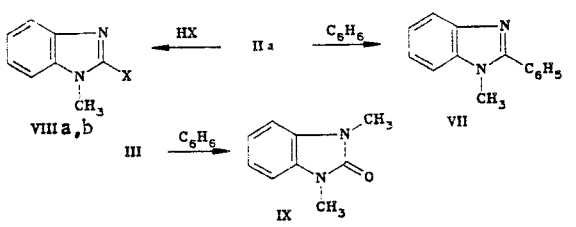
*The regions 3600-3000 and 1500-1200 cm^{-1} were also recorded for suspensions in fluorinated hydrocarbon grease.

Fig. 2 shows, the diazonium absorption at 369 nm observed in the spectra of authentic benzimidazole-2-diazonium tetrafluoroborate [2] in 95% phosphoric acid becomes quite strong in the spectra of the nitrosamine (IIa) in H_3PO_4 solutions only when the concentration of the latter is increased to 85%. In more dilute solutions, a weakly colored reaction product predominates which appears to be (VI), and which can be isolated in the free state and converted into the nitrosamine by careful treatment with dilute ammonia. Since, according to the current view [11], the rate of diazotization in strongly acid media is determined by the final step, the difficulty of carrying out this reaction with (VI) becomes understandable, since the protonated imidazole ring, being an electron acceptor, prevents cleavage of the hydroxyl.



The special nature of the products of the first stage in the diazotization of 2-aminobenzimidazoles is also apparent in the decrease in their stability when electronegative substituents are introduced into the ring, although in the primary nitrosamines of other azoles the reverse is the case [6].

The accessibility and stability of primary nitrosamines in the benzimidazole series presents the problem of finding conditions for carrying out the diazotization of this diazostructure which avoid the difficult step of conversion into the diazonium salts. We have demonstrated this in the case of 2-phenyl- and 2-halo-1-methylbenzimidazoles (VII) and (VIII) respectively.



VIII a X=Cl; b X=Br

In aqueous solutions of hydrohalic acids, replacement by halogen was found to be satisfactory as a result of hydrolysis of the nitrosamines at elevated temperatures, apparently facilitated by nucleophilic attack of the halogen [8]. Replacement by chlorine and bromine was carried out successfully in dry acetonitrile in the presence of copper powder.

Replacement of the nitrosoamino group by aryl was affected by prolonged heating of (IIa) in boiling benzene. It is noteworthy that the nitrosimine (III), which is similar in structure to (IIa), gives high yields of the benzimidazolone (IX) on brief heating in benzene. A similar reaction has been reported with benzothiazoles [12]. The ease with which this reaction takes place in benzimidazoles appears to be due to the polar nature of (III).

Thus, the particular difficulty of diazotization of 2-aminobenzimidazoles* which has for long remained without a satisfactory explanation, is due to the unique structure of the products of the first stage of this reaction, these being the first primary nitrosamines so far examined in which stabilization is effected by transition to the imino-form, which is highly polarized.

EXPERIMENTAL

IR spectra were obtained on a UR-20 apparatus in vaseline oil, chloroform, and in fluorinated hydrocarbon grease. UV spectra were obtained on a Specord M-40 spectrophotometer, in methanol and phosphoric acid of various concentrations. The progress of the reactions and the purity of the products were followed by TLC on grade II alumina in chloroform.

General Method of Preparation of 1-Alkyl-2-nitrosoaminobenzimidazoles (II). The amine (I) (20 mmole) was dissolved with heating in 30 ml of 50% phosphoric acid, the solution cooled to −7°C, and a saturated solution of 3 g (45 mmole) of sodium nitrate in water added dropwise with vigorous stirring at such a rate that the temperature did not exceed −5°C. When the addition was complete, the mixture was stirred for 30 min while the temperature was raised gradually to 0-3°C. It was then diluted with two volumes of water, and 20-23 ml of concentrated ammonia added, care being taken that the temperature did not exceed 5°C. The yellow solid which separated was filtered off, washed with water, and dried first in air, then in a drying cupboard at 50°C. The yield of (IIa) was 83%, (IIb) 77%, (IIc) 70%, (IId) 80%, and (IIe) 62%. The nitrosamine was mixed with 20 ml of water, and 2 ml of concentrated ammonia added). The solution was filtered from insoluble impurities, and neutralized carefully with dilute (1:1) acetic acid to pH 5-6. The solid was filtered off, washed with water, and dried as described above. The constants of the compounds have been reported [5, 13].

1-Methyl-2-chlorobenzimidazole. A stream of dry HCl was passed into a suspension of 1.8 g (10 mmole) of 1-methyl-2-nitrosoaminobenzimidazole and 0.64 g (10 mmole) of freshly-prepared copper powder in 50 ml of dry acetonitrile for 2 h. The copper was removed, and the acetonitrile solution treated with 10 ml of 5% ammonia. The acetonitrile was distilled off, and the solid filtered off and washed with water. Purification on a column of alumina (20 × 2.5 cm) in chloroform gave 1.2 g (71%) of 1-methyl-2-chlorobenzimidazole, mp 111°C (from heptane) [14].

2-Bromo-1-methylbenzimidazole was obtained similarly, yield 63%, mp 104°C (from heptane) [15].

2-Phenyl-1-methylbenzimidazole. A suspension of 1.8 g (10 mmole) of 1-methyl-2-nitrosoaminobenzimidazole in 50 ml of dry benzene was boiled until the solid had dissolved (5 h). The benzene was then removed, then the residue purified on a column of alumina (20 × 2.5 cm) in chloroform. Yield 1.8 g (86%), mp 162°C [16].

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*The first reports of the successful diazotization of 2-amino-1-alkylbenzimidazoles appeared only some 20 years ago.

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PROTON EXCHANGE IN 1-VINYL-1,2,4-TRIAZOLE AND ITS DERIVATIVES

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Proton exchange at $C_{(5)}$ of the triazole ring has been studied in 1-vinyl-1,2,4-triazole, 1-ethyl-1,2,4-triazole, poly-1-vinyl-1,2,4-triazole, and their quaternary salts. The rate of exchange is catalyzed by bases and inhibited by acids.

Proton exchange in 1,2,4-triazoles has received little attention [1, 2]. Rapid hydrogen exchange between a protic solvent and the macromolecule has been reported [1] in studies of the PMR spectra of quaternary salts of poly-1-vinyl-1,2,4-triazole. We have now examined proton exchange in 1-vinyl-1,2,4-triazole (I), its saturated analog 1-ethyl-1,2,4-triazole (II), poly-1-vinyl-1,2,4-triazole (III), and their quaternary salts (IV-VI). The results obtained are shown in Table 1.

PMR spectroscopy showed that on heating (I) and (II) in D_2O, exchange took place involving the proton at $C_{(5)}$ of the triazole ring (Figs. 1 and 2). From the kinetic data for proton exchange in unsubstituted 1,2,4-triazole [2], the following reaction sequence is proposed:

TABLE 1. Half-Exchange Times $\tau_{1/2}$ for 1-Vinyl-1,2,4-triazole and Its Derivatives

Compound	T_{react}	Solvent	$\tau_{1/2}$, min	Compound	T_{react}	Solvent	$\tau_{1/2}$, min
I	60	D_2O	70	IV	53	D_2O+DCl	30
II	60	D_2O	90	V	53	D_2O+DCl	5
III	90	D_2O	360	VI	53	D_2O+DCl	600

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