RESEARCH ON BENZIMIDAZOLE DERIVATIVES. XXXVII.*

2-BENZAZOLONITRILE OXIDES

E. B. Tsupak, N. K. Chub, A. M. Simonov,
and V. A. Kruchinin

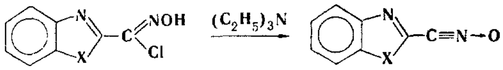
UDC 547.785.5'787.3'789.
6:543.422.4

It was shown by IR spectroscopy that 2-benzazolonitrile oxides, which are formed by the action of triethylamine on 2-benzazolylmethylhydroxamoyl chlorides, are extremely labile; the presence and nature of a substituent near the fulmide group and the basicity of the heterocyclic fragment of the molecule have a great effect on their stabilities.

We have previously expressed the assumption that the reaction of 2-benzimidazolylmethylnitrolic acids and 2-benzimidazolylmethylhydroxamoyl chlorides with 1,3-dicarbonyl compounds in the presence of bases proceeds through a step involving the formation of nitrile oxides. Although attempts to isolate them preparatively proved to be unsuccessful [2], we were able to confirm our assumption spectroscopically.

The vibrational spectra of nitrile oxides [3] contain characteristic bands at 2300 ($C \equiv N$) and 1350 cm^{-1} ($N \rightarrow O$). Inasmuch as it is difficult to observe the long-wave bands in the spectra of the compounds under investigation because of the superimposition of the skeletal vibrations of the heteroring, we used the band of nitrile absorption to identify the nitrile oxides.

The starting compounds for the preparation of the nitrile oxides were benzoxazolyl- (Ig), benzothiazolyl- (If), and benzimidazolyl-2-methylhydroxamoyl (Ic) chlorides as well as 1-methyl- (Ib), 1,5-dimethyl- (Id), 1-isopropyl- (Ia), and 1-methyl-5-nitrobenzimidazolyl-2-methylhydroxamoyl (Ic) chlorides. It was found that the spectra of solutions obtained by the action of triethylamine on suspensions of the hydroxamoyl chlorides in methylene chloride contain an intense absorption maximum at 2310 cm^{-1}, and this constitutes evidence for the formation of nitrile oxides (IIa-g).



I a-g II a-g

X = NR, S, O

It should be noted that, in addition to the maximum, absorption of triethylamine hydrochloride dissolved in the methylene chloride, which is observed as a broad band, the start of which is superimposed on the region of nitrile vibration, also appears in the investigated portion of the spectrum. Because of this, the desired maximum can be observed only over a narrow range of intensities that does not exceed 22-24%.

Inasmuch as the spectrum cannot be recorded earlier than 1-2 min after mixing of the reagents and some of the nitrile oxides undergo considerable changes in this time interval,

---

*See [1] for communication XXXVI.

Rostov State University, Rostov-on-Don. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 526-529, April, 1975. Original article submitted May 27, 1974; revision submitted September 31, 1974 [sic].

TABLE 1. Results of an IR-Spectroscopic Investigation of 2-Benzazolonitrile Oxides (RC ≡ N→O)

Compound	Benzazolyl R	δ, %	pK_a for R—H	Note
IIa	1-Isopropyl-2-benzimidazolyl	0		
IIb	1-Methyl-2-benzimidazolyl	9	5,57[4]	
IIc	2-Benzimidazolyl	24	5,53[5]	In ether δ = 20%
IId	1,5-Dimethyl-2-benzimidazolyl	9	5,22[6]	
IIe	1-Methyl-5-nitro-2-benzimidazolyl	16	3,40[7]	
IIf	2-Benzothiazolyl	24	1,41[8]	After 5 min δ = 16%
IIg	2-Benzoxazolyl	22	0,50[8]	After 5 min δ = 20%.

it was impossible to establish the true magnitude of the intial intensity of the nitrile absorption. We calculated it using as the standard the spectrum of the most stable 1-isopropyl-2-benzimidazolonitrile oxide (Ia), in which the desired maximum exceeds the intensity of the triethylammonium chloride peak (2400 cm^{-1}) by 10%.

The spectra in each experiment were recorded two to three times with recording of the time elapsed from the moment the reagents were mixed. The relative stability of the nitrile oxide can be judged from the decrease in the intensity of the absorption maximum in the elapsed time interval, which characterizes the decrease in the concentrations of the nitrile oxides.

The results of the investigation and the pK_a values of the corresponding heterocycles are presented in Table 1; the symbol "δ" designates the decrease in the intensity of the nitrile absorption 10 min after the beginning of the experiment.

The results make it possible to uncover two factors that affect the stabilities of the 2-benzazolonitrile oxides.

A large role is played by the presence and nature of a substituent near the fulmide group. Thus 1-isopropyl-substituted benzimidazole IIa, the presence of which in the reaction solution was detected even after 15 h, although the intensity of the nitrile absorption decreased by 18%, proved to be the longest-lived nitrile oxide. The lifetime of IIb, which contains a methyl group attached to the nitrogen atom, is limited to minutes; unsubstituted nitrile oxides are more labile. This is apparently explained by the steric effect of the substituents: the 1 position in IIa-e is similar to the ortho position in a six-membered ring, the introduction of alkyl substituents into which made it possible to obtain unrestrictedly long-lived nitrile oxides [9-11].

In addition, the stabilities of the investigated compounds are associated with the basicity of the azole fragment of the molecule. This is seen distinctly in the case of 1-methyl- (IIb), 1,5-dimethyl- (IId), and 1-methyl-5-nitro-2-benzimidazolonitrile (IIe) oxides, in which the steric effect of the ortho substituents is constant. The concentration of IIb and IId, the pK_a values of which are 5.57 and 5.22, respectively, decrease approximately identically (δ = 9%), whereas the slightly basic 5-nitro-substituted IIe (pK_a 3.40) undergoes changes much more rapidly (δ = 16%). A similar relationship is also observed in benzothiazolonitrile oxide IIf and benzoxazolonitrile oxide IIg.

The literature does not contain data on this sort of effect of the basicity on the stabilities of nitrile oxides, probably because of the small amount of study devoted to nitrile oxides containing basic functional groups. The indications that electron-donor para substituents in the aromatic series increase the activity of nitrile oxides [12] are valid only for dimerization to furoxans. It should be noted that 2-benzimidazolonitrile oxides display peculiar properties. Thus attempts to isolate such characteristic nitrile oxide self-condensation products as furoxans [13] in this case were unsuccessful, although this transformation does occur in the pyridine series [14].

It is interesting that 2-benzimidazolonitrile oxide IIc displays anomalously low stability. The ionization constant of benzimidazole is 5.53, and it therefore should have been expected that the δ value for IIc would be close to the values of IIb and IId. However, the band of nitrile absorption in methylene chloride solution could not be observed 1 min after mixing of the reagent, although it is known that nitrile oxide IIc is formed under the reaction conditions [2]. The low stability of nitrile oxide IIc can be explained by the peculiarities of the structure of the benzimidazole ring: the pyrrole nitrogen atom in it readily loses a proton on reaction with bases, and the resulting anion reacts readily with the fulmide groups of neighboring molecules.

EXPERIMENTAL METHOD

The IR spectra were recorded with a UR-20 spectrometer at 2200-2400 cm^{-1}. The investigated solutions were obtained by the action of triethylamine on suspensions of the 2-benzazolylmethylhydroxamoyl chlorides (Ia-g) in 10 ml of methylene chloride. Weighed samples of the hydroxamoyl chlorides were selected in such a way that the nitrile oxide concentration in solution was ∿ 0.13 mole/liter, which corresponds to an intensity of 75-90% in the absorption maximum of the $C\equiv N$ bond; the spectra were recorded at room temperature. The measurements were first made 1-2 min after the addition of triethylamine, and the second measurements were made 10 min after the addition of triethylamine [after 5 min and after 10 min for benzothiazolo- (IIf) and benzoxazolonitrile (IIg) oxides].

2-Benzimidazolylmethylhydroxamoyl chloride and its 1-methyl-, 1,5-dimethyl-, and 1-methyl-5-nitro-substituted derivatives were described in [2].

1-Isopropyl-2-benzimizolylmethylhydroxamoyl Chloride (Hydrochloride) (Ia). This compound was obtained in 92% yield by chlorination of 1-isopropyl-2-formylbenzimidazole oxime in glacial acetic acid [2]. The colorless prisms (from glacial acetic acid) had mp 191° (dec.). Found %: C 48.3; H 5.2; Cl 25.8; N 15.6. $C_{11}H_{13}ClN_3O\cdot HCl$. Calculated %: C 48.3; H 4.8; Cl 26.0; N 15.4.

1-Isopropyl-2-formylbenzimidazole Oxime. This compound was obtained in 60% yield as colorless needles with mp 230° (dec., from alcohol) by reaction of 1-isopropyl-2-formylbenzimidazole with hydroxylamine as described in [15]. Found %: N 20.8. $C_{11}H_{13}N_3O$. Calculated %: N 20.6.

2-Benzothiazolylmethylhydroxamoyl Chloride (If). This compound, with mp 178° (dec.), was obtained in 83% yield by bubbling chlorine through a solution of 2-formylbenzothiazole oxime [16] in dioxane. Found %: C 44.7; H 2.5; Cl 16.2; S 14.5. $C_8H_5ClN_3OS$. Calculated %: C 45.5; H 2.4; Cl 16.7; S 15.1.

2-Benzoxazolylmethylhydroxamoyl Chloride (Ig). This compound, with mp 184° (dec.), was obtained in 83% yield by chlorination of 2-benzoxaldoxime [16] in glacial acetic acid–dioxane (3:1). Found %: C 49.2; H 2.6; Cl 17.6. $C_8H_5ClN_2O$. Calculated %: C 48.8; H 2.5; Cl 18.1.

LITERATURE CITED

1. I. I. Popov, P. V. Tkachenko, and A. M. Simonov, Khim. Geterotsikl. Soedin., 523 (1975).
2. E. B. Tsupak, N. K. Chub, A. M. Simonov, and N. M. Miroshnichenko, Khim. Geterotsikl. Soedin., 812 (1972).
3. A. Quilico, Experientia, 26, 1169 (1970).
4. R. Schwarzenbach and K. Lutz, Helv. Chim. Acta, 23, 1162 (1940).
5. A. Albert, R. Goldacre, and J. Phillips, J. Chem. Soc., 2240 (1948).
6. M. T. Davis, P. Mamalis, V. Petrov, and B. Sturgeon, J. Pharmacol., 3, 420 (1951).
7. J. H. Ridd and B. U. Smith, J. Chem. Soc., 1363 (1960).
8. Yu. L. Kaminskii, Isotopic Exchange of Hydrogen in Five-Membered Aromatic Heterocycles, Author's Abstract of Master's Dissertation [in Russian], GIPKh, Leningrad (1970), p. 12.
9. C. Grundmann and I. M. Dean, J. Org. Chem., 30, 2809 (1965).
10. C. Grundmann and R. Richter, J. Org. Chem., 32, 2308 (1967).
11. C. Grundmann and R. Richter, J. Org. Chem., 33, 476 (1968).
12. G. Babaro, A. Battaglia, and A. Dondoni, J. Chem. Soc., B, 588 (1970).
13. C. Grundmann, Fortschr. chem. Forsch., 7, 86 (1966).
14. R. H. Wiley and B. J. Wakefield, J. Org. Chem., 25, 546 (1960).
15. M. T. Le Bris and H. Wahl, Bull. Soc. Chim. France, 343 (1959).
16. S. E. Forman, J. Org. Chem., 29, 3323 (1964).