

Structure and Acidity of Some Heterocyclic Nitrosazones

Ahmad Sami Shawali

Department of Chemistry, Faculty of Science, University of Kuwait, State of Kuwait

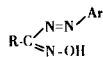
Received October 12, 1976

Several new heterocyclic nitrosazones were prepared and their acid dissociation constants determined in 50 volume percent ethanol-water solution at $25.0 \pm 0.1^\circ$ and μ of 0.10. Infrared, electronic, and pmr spectra of these compounds and some deuterated nitrosazones were also examined and compared with their *O*-methyl derivatives. It is concluded that all compounds have the azo oxime structure and that the stereochemistry around the azo group is *trans*. The data revealed also that the nitrosazones derived from pyridine aldehydes show the existence of equilibria between zwitterionic and neutral molecules. No evidence for the tautomeric nitrosohydrazone form could be obtained.

J. Heterocyclic Chem., **14**, 185 (1977).

Introduction

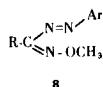
In connection with a study (1) on the acidities of a series of nitrosazones of type 1, traditionally described as arylazobenzaldoximes, we undertook an investigation into the synthesis, spectra, and acid properties of some heterocyclic nitrosazones, namely **3** to **7**, and their *O*-methyl derivatives, **8**. Several nitrosazones of type 1 and 2 have been reported in the earlier literature (2-5), but it appears that no attempt has yet been made to prepare and identify the tautomeric and geometric isomers of any heterocyclic nitrosazone. In an attempt to help remedy this situation, we report in this paper the spectral characteristics of compounds **3** to **8**, and the results of the study of their acid dissociation.



- 1, R = Aryl
2, R = alkyl
3, R = 2-pyridyl

- 4, R = 3-pyridyl
5, R = 4-pyridyl

- 6, R = 2-furyl
7, R = 2-thienyl

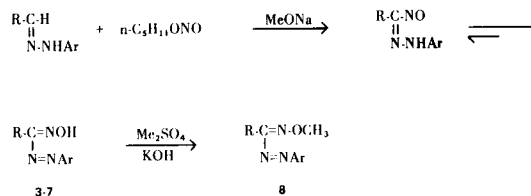


Results and Discussion.

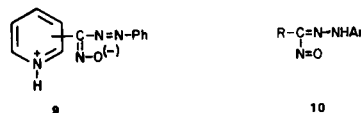
The nitrosazones **3** to **7** were prepared in a rigorously similar manner by treatment of the corresponding heterocyclic aldehyde phenylhydrazone with *n*-amyl nitrite in dry methanol in presence of sodium methoxide. Reaction

of the potassium salts of **3** to **7** with dimethyl sulfate resulted into their *O*-methyl derivatives, **8** (Scheme 1). All compounds were stable both in solid state and in solution. Their spectra indicate that they exist exclusively

Scheme 1



in the assigned azo oxime structure, and that the nitrosazones **3** to **5** appear to have a considerable zwitterion character, **9**. No evidence for the tautomeric nitrosohydrazone structure, **10**, could be obtained.



Thus, the ir spectra of compounds **6** and **7** in the solid state (potassium bromide) and in solution (chloroform or carbon tetrachloride) revealed, in each case, a broad band assignable to an associated OH group in the region 3100-3500 cm^{-1} . The solution phase showed an additional band near 3585 cm^{-1} . The latter band is undoubtedly due to a free OH group of monomeric species. Concentration dependence of the latter band and its absence in

Table I
Nitrosazones and Their *O*-Methyl Derivatives
RC(:NOR')N:NC₆H₄R''

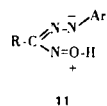
Compound No.	R	R'	R''	M.p., °C	S(a)	Molecular formula	C Found (calcd)	H Found (calcd)	N Found (calcd)	λ max (ethanol) nm (log ε)
3	2-Pyridyl	H	H	169	A	C ₁₂ H ₁₀ N ₄ O	63.92 (63.71)	4.42 (4.46)	24.73 (24.76)	435 (2.52); 308 (4.29)
4	3-Pyridyl	H	H	198	A	C ₁₂ H ₁₀ N ₄ O	63.74 (63.71)	4.57 (4.46)	24.49 (24.76)	436 (2.40); 322 (4.27)
5	4-Pyridyl	H	H	195	A	C ₁₂ H ₁₀ N ₄ O	63.78 (63.71)	4.52 (4.46)	24.82 (24.76)	434 (2.54); 310 (4.31)
6	2-Furyl	H	H	78-79	WM	C ₁₁ H ₉ N ₃ O ₂	60.98 (61.39)	4.85 (4.22)	19.28 (19.52)	450 (2.77); 300 (4.27) (d) 450 (2.74); 300 (4.14)
7	2-Thienyl	H	H	91-92	C	C ₁₁ H ₉ N ₃ OS (b)	57.80 (57.13)	4.19 (3.92)	17.89 (18.17)	450 (2.56); 288 (4.20) (d) 450 (2.59); 290 (4.28)
7a	2-Thienyl	H	CH ₃	130	C	C ₁₂ H ₁₁ N ₃ OS (a)	59.00 (58.75)	4.51 (4.52)	16.72 (17.13)	450 (2.67); 302 (4.23)
8a	3-Pyridyl	CH ₃	H	204	M	C ₁₃ H ₁₂ N ₄ O	65.39 (64.98)	4.97 (5.03)	23.37 (23.32)	470 (1.76); 366 (3.89)
8b	4-Pyridyl	CH ₃	H	132	M	C ₁₃ H ₁₂ N ₄ O	64.84 (64.98)	4.96 (5.03)	23.27 (23.32)	454 (2.92); 364 (3.54)
8c	Phenyl	CH ₃	H	132	M	C ₁₄ H ₁₃ N ₃ O	70.10 (70.27)	5.46 (5.47)	17.70 (17.56)	470 (2.86); 370 (4.43)

(a) Solvent of crystallization: A, acetic acid; M, methanol; WM, water-methanol; C, cyclohexane. (b) *Anal.* Calcd. S: 13.86. Found: 13.82. (c) *Anal.* Calcd. S: 13.07. Found: 12.92. (d) In chloroform.

the spectra of solids support its assignment. Deuteration of the oxime group has pronounced effects on the free and bonded OH bands. For example, phenylazofurfuraldoxime-d and phenylazo-2-thienylalldoxime-d each exhibited in chloroform solution a broad band showing some structure in the region 2100-2530 cm^{-1} and a sharp band near 2650 cm^{-1} . These bands are considered to correspond the associated and free OD stretches respectively. The ratio of $\bar{\nu}_{\text{OH}}/\bar{\nu}_{\text{OD}}$ for the nonbonded groups has a value of ~ 1.35 in both compounds examined. In potassium bromide the deuterated nitrosazones, **6** and **7**, showed only the broad band due to the associated OD group. The spectra of the *O*-methyl derivatives, **8**, did not show any OH bands.

The ir spectra of the nitrosazones **3** to **5** only showed evidence for zwitterion character. Thus each of these compounds exhibited two broad bands around 2500 and 1900 cm^{-1} probably due to proton transfer (6). The absence of these bands in the spectra of the corresponding *O*-methyl derivatives substantiates their assignment.

The N-O stretch in **3** to **7** was observed near 1040 cm^{-1} in the solid state and in solution as well. The band was relatively intense and deuteration has no effect on both its intensity and position. The higher frequency position of the NO band in **3** to **7** than that in simple oximes ($\bar{\nu}_{\text{NO}}$ 930-960 cm^{-1}) might be due to contribution of resonance structure of type **11**, by analogy to the case of quinone monoxime ($\bar{\nu}_{\text{NO}}$ 975-1075 cm^{-1}) (7).

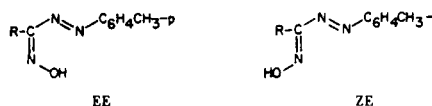


The electronic absorption pattern of **3** to **7** in ethanol or in chloroform is of typical *trans*-azo compounds. For example, in ethanol each compound exhibited a strong π - π^* band ($\log \epsilon > 4$) near 310 nm and a weak n - π^* maximum ($\log \epsilon < 3$) near 430 nm. *trans*-Azobenzene exhibits a similar pattern: λ max (ethanol) nm ($\log \epsilon$) 445 (2.48); 319 (4.29) (8). This identity supports the correctness of the *trans*-azo oxime structure assigned for the nitrosazones **3** to **7**. The absorption pattern of the latter compounds is compared with that of the *O*-methyl derivatives, **8**. Apart from the bathochromic shift induced by *O*-methylation, the spectra of **3** to **7** resemble closely that of **8**. The data are summarized in Table I. Such a resemblance substantiates further the azo oxime structure.

The pmr spectra of the nitrosazones **6** and **7** in deuteriochloroform exhibited an NOH signal in the region 9.4-10.5 ppm; whereas that of **3** appeared near 15.87 ppm. In deuterated dimethylsulfoxide, the nitrosazones **4** and **5**, which were insoluble in deuteriochloroform, showed their NOH signal near 11.50 ppm. In all cases, the NOH signal disappeared upon shaking the solution of the

nitrosazone (deuteriochloroform or DMSO- d_6) with deuterium oxide, and a new peak appeared near 4.63 ppm assignable to deuterium oxide proton resonance. The *O*-methyl derivatives, **8**, in deuteriochloroform showed a singlet for the O-CH₃ protons near 4.43 ppm. These data leave little doubt that the nitrosazones studied have the azo oxime structure.

An interesting feature was observed in the pmr spectrum of **7a** (R = 2-thienyl, Ar = 4-CH₃C₆H₄) in deuteriochloroform. The latter compound exhibited two distinct but almost overlapping methyl proton signals at 2.40 and 2.35 ppm in a ratio of $\sim 1.25:1.00$ respectively. This observation together with the identification of a free OH band in the solution ir spectra suggest the existence of two distinct species in solution. These are probably the EE and ZE isomers of the nitrosazone. This conclusion finds support in the fact that unsymmetrical ketoximes have been reported to exhibit solution equilibria of isomers that can be identified by pmr spectra (9).



pK Values.

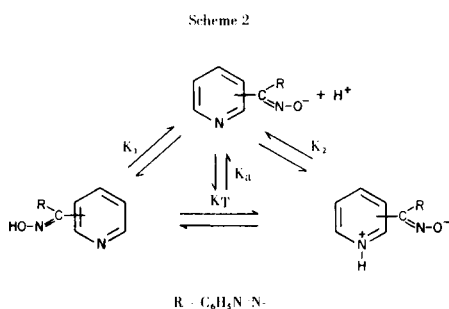
The acid dissociation constants of the nitrosazones **3** to **7** were evaluated spectrophotometrically in 50 volume percent ethanol-water solution at $25.0 \pm 0.1^\circ$ and μ of 0.10. The uv spectra of each nitrosazone vary with pH. Figure 1 shows the collected spectra of the nitrosazone **3**, as typical example, at different pH values. From the pH-absorbance data at λ max of the ambident anion, the pK_a values for the nitrosazones **3** to **7** were calculated. At least two independent runs were conducted for each compound. The pK_a values were reproducible to ± 0.02 pK unit in different experiments. The average values of pK_a determined are listed in Table II.

The data show that the heterocyclic nitrosazones are more acidic than phenylazobenzaldoxime (**1**, R = Ar = C₆H₅) whose pK_a value is 9.89 under similar conditions of solvent composition, temperature and ionic strength (1). The low values of pK_a for compounds **3** to **7** are due to the electronwithdrawing character of the heterocyclic substituent.

For a series of phenylazobenzaldoximes (**1**, R = substituted phenyl, Ar = C₆H₅), the pK_a values determined in 50 volume percent ethanol-water at 25° and μ of 0.1, were correlated by equation [1].

$$[1] \quad \text{pK}_a = 9.90 - 0.737 \sigma_X$$

The equilibrium data of the nitrosazones **6** and **7** appear to be correlated by the same equation. Thus, substitution of the pK_a values determined for **6** and **7** in equation [1] gave the values 0.35 and 0.70 for $\sigma_{2(O)}$ and $\sigma_{2(S)}$ constants respectively. These values compare favourably with the literature values ($\sigma_{2(O)} = 0.29$ and $\sigma_{2(S)} = 0.71$) (10). The pK_a values for the other three nitrosazones **3** to **5** deviate considerably from the Hammett equation [1]. This observation appears to be compatible with the foregoing conclusion that such nitrosazones exhibit equilibria between neutral and zwitterionic molecules. Kabachnik *et al.*, (11) have indicated that a linear Hammett plot would be observed for the effective ionization constant of tautomeric substances when the tautomeric equilibrium being shifted toward one of the possible tautomers. When a second tautomeric form makes its appearance in the equilibrium to a noticeable extent one observes the deviation from linearity. Accordingly, in the ionization reaction of **3** to **5**, the four equilibria shown in Scheme 2 have to be



considered for each nitrosazone. The relations between the equilibrium constants indicated are given by the equations:

$$[2] \quad 1/K_a = 1/K_1 + 1/K_2$$

$$[3] \quad K_T = K_1/K_2$$

Values of the microscopic constants K_1 , K_2 , and K_T are usually not directly accessible, but they can be calculated from the macroscopic constant pK_a determined experimentally, provided one of them is known. According to the method of Jaffe (12), the pK_1 values for the nitrosazones **3** to **5** can be estimated by substituting the appropriate hetero aza substituent constants in equation [1]. In the present work, the σ values 1.1, 1.3, and 1.6 given by Simonetta and Favini (13) for the 2-, 3-, and 4-hetero aza substituents respectively were used to estimate the pK_1 values for the nitrosazones **3** to **5**. The results are given in Table II. From the determined values of pK_a 's and from the estimated pK_1 's, it was possible to calculate the values of pK_2 and in turn K_T constants for the nitrosazones **3** to **5**. The results of such computations are summarized in Table II. The data show that the pre-

Table II
 pK Values for the Nitrosazones,
 $RC(:NOH)N:NC_6H_4R'$

Compound No.	R	R'	pK_a	pK_1	pK_2	K_T
3	2-Pyridyl	H	9.41	9.09	9.12	1.09
4	3-Pyridyl	H	9.44	8.94	9.27	2.16
5	4-Pyridyl	H	9.32	8.72	9.19	2.98
6	2-Furyl	H	9.64			
7	2-Thienyl	H	9.38			
7a	2-Thienyl	4-CH ₃	9.62			

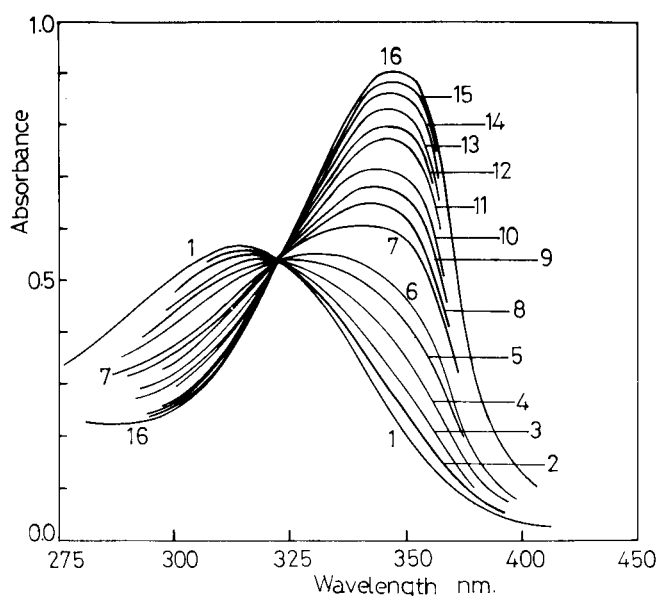
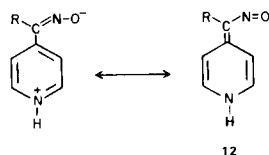


Figure 1. Absorption spectra of nitrosazone **3** at different pH values. $[3] = 2.96 \times 10^{-5} M$ in 50 volume percent ethanol-water at 25° and μ of 0.10. (Run no.) pH: (1) 8.37; (2) 8.57; (3) 8.73; (4) 8.91; (5) 9.03; (6) 9.15; (7) 9.38; (8) 9.45; (9) 9.55; (10) 9.67; (11) 9.84; (12) 9.96; (13) 10.11; (14) 10.32; (15) 10.50; (16) 11.12.

ponderance of zwitterionic to neutral molecules in 50 volume percent ethanol-water solution of the nitrosazones studied is in the order: $5 > 4 > 3$. The variation in K_T may be rationalized in terms of the resonance stabilization of and the degree of charge separation in the zwitterion under consideration. The close proximity of the opposite electrical charges lowers the stability of the zwitterion of **3** and thus the value of K_T for the latter nitrosazone is smaller than that for the isomers **4** and **5**. The possible resonance contribution from structure of type **12** is also expected to increase the stability of the zwitterion of **5** in comparison with **4**, and accordingly the value of K_T for the former is higher than that for the latter nitrosazone.



EXPERIMENTAL

All melting points are uncorrected. Pmr spectra were recorded with a Varian T-60A spectrometer. Uv spectra were measured on a Unicam SP8000 using matched quartz cells (10 mm optical path). Ir spectra were recorded with a Unicam SP1000 spectrophotometer. Elemental analyses were performed by Alfred Bernhardt Microanalytisches Laboratorium, West Germany.

The aldehydes: furfural, thiophene-2-aldehyde, and 2-, 3- and 4-pyridine aldehydes employed were from Fluka Products (Switzerland). The phenylhydrazones of these aldehydes were prepared in a rigorously similar manner by mixing equimolecular amounts of phenylhydrazine and the appropriate aldehyde in ethanol-acetic acid solution. The physical data observed for the hydrazones prepared agreed with literature values. Thiophene-2-aldehyde *p*-tolylhydrazone, not yet reported, was obtained in 87% yield, m.p. 195°; λ max (ethanol) (log ϵ): 360 (4.43); 310 (3.96); 250 (4.20); pmr δ (deuteriochloroform): 2.30 (3H, s, ArCH₃); 7.0-7.5 (7H, Het. H, ArH); 7.88 (1H, s, -CH=N-) ppm; $\bar{\nu}$ (carbon tetrachloride): 3360 (NH); 1620 (C=N) cm⁻¹.

Anal. Calcd. for C₁₂H₁₂N₂S: C, 66.63; H, 5.59; N, 12.95; S, 14.82. Found: C, 66.77; H, 5.56; N, 12.94; S, 14.64.

Preparation of Nitrosazones (3-7). General.

The appropriate phenylhydrazone (0.01 mole) was added to methanolic sodium methoxide solution (0.23 g. of sodium metal and 50 ml. of absolute methanol), followed by the addition of *n*-amyl nitrite (0.012 mole). The mixture was refluxed for 1 hour, cooled then filtered. The filtrate was added with stirring to a cold solution of sodium carbonate (10 g. of sodium carbonate, 150 ml. of water, and 100 g. of ice). The resulting solution was then filtered. Acidification of the alkaline filtrate with dilute sulfuric acid solution precipitated the corresponding nitrosazone, which was collected, dried and then crystallized from the proper solvent (Table I). The compounds prepared together with their physical constants are given in Table I.

Deuteration of the nitrosazones 6 and 7 was carried out by precipitating their solutions in dry dioxane with deuterium oxide.

O-Methylnitrosazones (8a to 8c).

Dimethyl sulfate (0.01 mole) was added dropwise while stirring to an aqueous solution (25 ml.) of the potassium salt of the appropriate nitrosazone (0.01 mole). After the addition was continued for 3 hours, during which the crude *O*-methylnitrosazone (8) precipitated. The latter was collected, washed with cold water and then dried. Recrystallization from acetone or petroleum ether gave 8 in 60 to 70% yield. Table I lists the compounds prepared and their physical properties.

pK_a Determination.

A radiometer pH meter (Model 63) with a combined glass electrode (type GK2301C) was employed in measuring the pH of the solutions. The instrument was accurate to ± 0.01 pH unit. It was calibrated with two standard Beckman buffers of pH 4.01 and 7.00 ± 0.01 . The pH meter readings B recorded in ethanol-water medium were corrected by the use of the relation of van Uitert and Haas (14) namely:

$$pH = B + \log U_H$$

where log U_H is the correction factor at a given composition of the medium at a fixed temperature and ionic strength. In the present work, the value of log U_H in 50 volume percent ethanol-water solution at 25° and μ of 0.10 was determined and turned out to be -0.25.

An aliquot of a stock solution of the appropriate nitrosazone in ethanol was diluted with aqueous sodium chloride solution and ethanol so that the final solution (50 ml.) was 10⁻⁵ M in the sodium chloride and contained 50% by volume of ethanol. The test solution was then transferred to a water-jacketted thermostated cell. The pH was measured and the spectrum was recorded using either the ionic medium or the corresponding aqueous ethanol as a blank. In both cases identical absorbance values in the wavelength range employed were obtained. Then the pH of the test solution was increased by addition of small volumes of concentrated carbonate free sodium hydroxide solution made up from the same solvent. Since the total change in volume did not exceed 1.0%, no correction was made for the concentration variable of the nitrosazone. After each spectral measurement, the pH was checked and in all cases the two values before and after the spectral measurement were found to be the same within the limits of the accuracy of the pH meter. In each run 10 to 15 pH-absorbance readings were taken and the pK_a value was calculated from the data using the equation:

$$pK_a = pH_i + \log(A_b - A_i)/(A_i - A_a)$$

where A_i is the absorbance at the measured pH_i, and A_a and A_b refer to the absorbance values of the neutral and deprotonated species respectively. Each compound was subjected to, at least, two separate pK_a determinations and the average values ± 0.02 are given in Table II.

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