ARYLAZO- AND ARYLAZOXY-N-NITROFORMAMIDINES

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Phenylhydrazine reacts with S-methylisothionitrourea to give 2-phenylhydrazino-N^2-nitroformamidine, which on oxidation and nitration affords novel arylazo- and arylazoxy-N^2-nitroformamidines. The structures of the products were confirmed by ^1H, ^{13}C, and ^{14}N NMR.

Of the many alkyl, aryl, and heteryl azo and azoxy compounds known, in only a few is the azo or azoxy group attached directly to a functional group (COR, COOR, $CONH_2$, CN, etc.), although some of these show useful physiological activity. Similar compounds containing the N-nitroformamidine group are completely known.

Bearing in mind the similar chemical behavior of the amino group in amides on the one hand, and of nitroguanidine on the other, it was expedient to synthesize arylazo- and arylazoxy-N-nitroformamidines as follows:

$$ArNH{-}NH{-}\underset{\underset{NNO_2}{\|}}{C}{-}NH_2 \longrightarrow ArN{=}N{-}\underset{\underset{NNO_2}{\|}}{C}{-}NH_2 \longrightarrow ArN{=}\overset{\overset{O}{|}}{N}{-}\underset{\underset{NNO_2}{\|}}{C}{-}NH_2$$

We therefore developed a method for the preparation of 2-phenylhydrazino-N^2-nitroformamidine (I) by reacting phenylhydrazine with S-methylisothionitrourea. The yields of (I) obtained after heating the reactants for 3 h at 50-60°C were 70-80%.

As expected, (I) was readily oxidized by Br_2 in an aqueous medium to give near-quantitative yields of the azo-compound (II). Treatment of the latter at 0-5°C with a solution of trifluoroperacetic acid (TFPA) in dichloromethane afforded only one of the two possible isomers of (phenyl-ONN-azoxy)-N^2-nitroformamidine (III) in ~30% yield as a pale yellow crystalline solid which was fully stable (decomp. ~150°C). Considerable resinification occurred during isolation of this compound, indicating that other, unstable compounds were formed on oxidation.

The structures of (II) and (III) were confirmed by elemental analysis, IR and PMR spectroscopy, and in the case of (III), its ^{13}C and ^{14}N NMR spectra (see below).

Literature reports on the oxidation of unsymmetrical arylazo compounds show that the presence of ortho–para-directing groups in the benzene ring facilitate the oxidation of the nitrogen nearest to the ring, whereas meta-directing groups result in the preferred formation of the second isomer [1-4]. We therefore assumed that the oxidation of arylazo-N^2-nitroformamidines bearing electron-acceptor groups such as nitro in the ring would also give the second possible reaction product, namely $ArN{=}N(O)C(=NNO_2)NH_2$.

Our attempts to obtain nitrophenylhydrazo compounds as for (I), by reacting with S-methylisothionitrourea having been unsuccessful, we examined the possibility of synthesizing nitrophenylazo-N^2-nitroformamidines by nitrating (II).

It was found that treatment of (II) with a sulfuric–nitric acid nitrating mixture afforded 65% of the required nitrophenylazo-N^2-nitroformamidines (IV), as a mixture of the meta (IVa) and ortho isomer (IVb) in a ratio (IVa)/(IVb) of ~3/1. The isomers were both isolated in the pure state, and characterized by IR and PMR spectroscopy, and elemental analysis.

The position of the nitro group in the benzene ring in (IVa) and (IVb) was established from the signals for the phenyl protons in the PMR spectra. In the spectrum of (IVa), the

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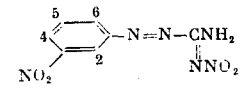
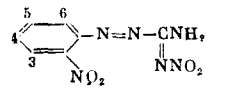
TABLE 1. ^1H Chemical Shifts (diagonal values, ppm) and $^1H-^1H$ Coupling Constants (Hz) for (IVa) and (IVb)

Compound	Atom	H^2	H^4	H^5	H^6
 (IV a)	H^2	8,706	1,90	0,42	2,30
	H^4		8,413	7,98	1,04
	H^5			8,014	8,24
	H^6				8,587
		H^3	H^4	H^5	H^6
 (IVb)	H^3	7,763	8,09	1,33	0,33
	H^4		7,983	7,26	1,30
	H^5			8,009	8,13
	H^6				8,219

signal for H^2 was seen as a triplet with two approximtely equal meta constants, and H^5 as a triplet with two ortho constants; in addition, the signals for H^2 and H^4 were broadened by remote coupling with the nitro group. In the PMR spectrum of (IVb), the signal for H^3 was considerably broadened by spin coupling via the three $^1H-^{14}NO_2$ bonds. This broadening enabled all the signals in the PMR spectrum to be assigned unambiguously. The spectra of both isomers form four-spin ABCD systems, which were analyzed by means of the PANIC iterative program. The accuracy of determination of the coupling constants (J values) and chemical shifts was to within 0.02 Hz. The results are shown in Table 1. The spectrum of (Va) was in full agreement with that for (IVa), indicating that the nitro group is located in the 3-position: $\delta H^2 = 8.96$, $\delta H^4 \approx \delta H^6 = 8.66$, and $\delta H^5 = 8.03$ ppm.

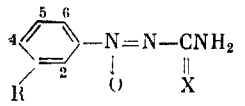
To our surprise, oxidation of the meta isomer (IVa) with TFPA also gave a single azoxynitroformamidine (Va). Also present in the reaction mixture was its hydrolysis product (VIa). The overall yield of azoxy compounds was 30-37%, their proportions varying with the reaction conditions.

The structures of (Va) and (VIa) were established as for (III), by their ^{13}C and ^{14}N NMR spectra (Tables 2 and 3). The ^{14}N spectra of these compounds showed narrow peaks assigned to the NO_2 and N=N groups, confirming the presence of these groups in these compounds. It only remains to point out that the signals for $N-NO_2$ and $C-NO_2$ in the ^{14}N spectrum of (Va) overlap completely to give a single peak with twice the intensity of that for the N=N group. The position of the oxygen in the azoxy group in all three compounds was established by the marked broadening of the C^1 signal in the ^{13}C spectra by coupling through a single bond, $^{13}C-^{14}N=$. This broadening was absent from the ^{13}C $\{^1H, ^{14}N\}$ triple resonance spectra on selective suppression of the ^{14}N signal at the resonance frequency of the nitrogen of the azoxy group. The broadening of the C^3 signal was likewise eliminated at the ^{14}N frequency of the nitro group in (Va) and (VIa).

Triple resonance experiments also permitted the unambiguous assignment of the closely adjacent signals for C^1 and C^3 (Table 2). The additive method [5] was used to assign the remaining signals for the aromatic carbon atoms, but did not make it possible to distinguish between the signals for C^4 and C^6 as a result of the small difference in their chemical shifts.

Additional confirmation for the structure of (Va) was obtained by direct synthesis, by nitration of the azoxy compound (III) with a nitric–sulfuric acid nitrating mixture to give predominantly the meta isomer (Va) in 63% yield. Treatment of pure (Va) with the oxidizing mixture resulted in hydrolysis of the nitro imino group to carbonyl to give (VIa) in 85% yield. It is noteworthy that the azoxy compound (III) is clearly more stable to hydrolysis, since no hydrolysis product was found, although the thermal stabilities of (III) and (Va) are similar.

TABLE 2. ^{13}C NMR Spectral Data for the Azoxy Compounds (δ, ppm from acetone-d_6, δ = 30.0 ppm)



Compound	R	X	C_6H_4R	C=X
(III)	H	NNO_2	*i* 147,4 *o* 123,4 *m* 130,5 *p* 134,9	163,9
(Va)	NO_2	NNO_2	C^1 147,9 C^2 118,9 C^3 149,6 C^4, C^6 129,2; 129,4 C^5 132,4	163,3
(VIa)	NO_2	O	C^1 147,9 C^2 118,5 C^3 149,6 C^4, C^6 128,5; 129,1 C^5 132,1	159,8

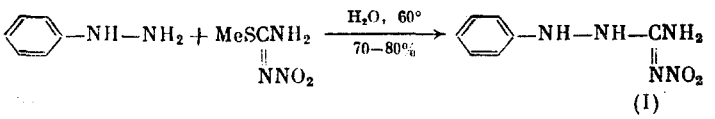
TABLE 3. ^{14}N NMR Shifts (ppm relative to CH_3NO_2) and the Half-Height Widths (in brackets, Hz) of Compounds Obtained

Compound	$C_6H_4NO_2$ * $=N-NO_2$	$-N=$ O	NH_2
(III)	−14,1(33)	−41,0(160)	−281(370)
(Va)	−14,9(50) **	−46,7(160)	−284(310) **
(VIa)	−14,9(50) **	−53,4(90)	−284(310) **

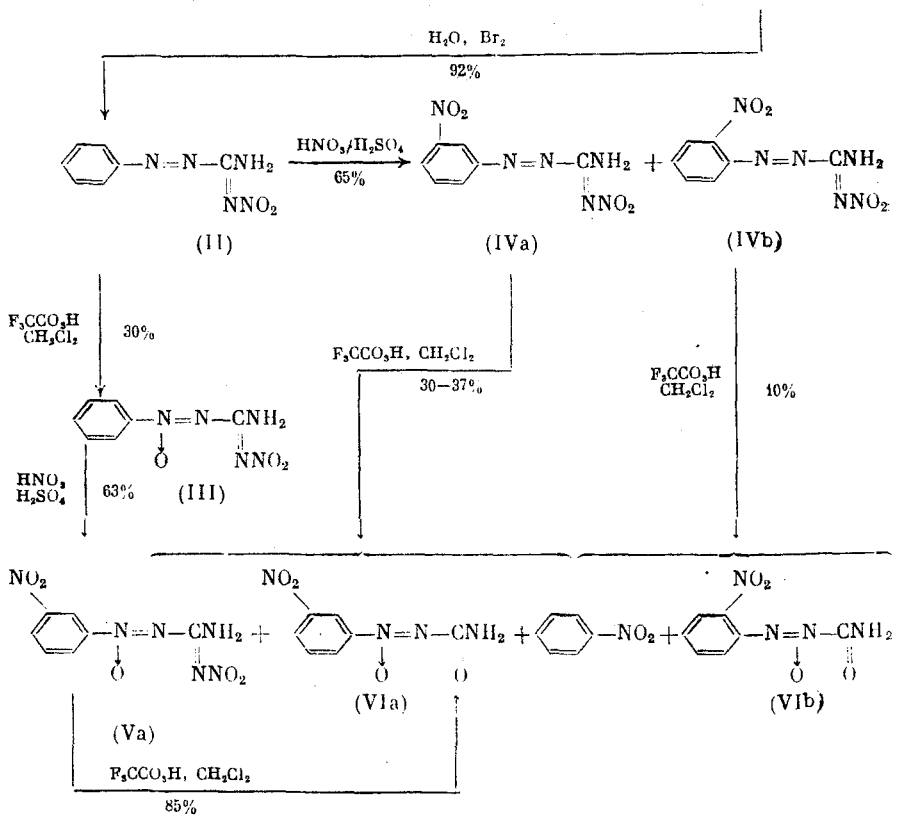
*The signals of all the nitro groups overlapped.
**Mixtures of (Va) and (VIa) in ratios of 1:1 and 3:1 were examined, their signals overlapping completely.

Oxidation of (IVa) with TFPA unexpectedly gives, in addition to the azoxy compounds (Va) and (VIa), nitrobenzene (NB) by an unknown mechanism. Since the latter is not formed on treatment of (Va) with TFPA, or of the azoxy compound (III) with the nitrating mixture, it appears that the NB is not derived from (Va) or (VIa) by oxidation, but perhaps from azoxy compounds in which the N-oxide grouping is in a different position. It is noteworthy that the yield of NB (~50%) is even greater than the sum of the yields of the isolated azoxy compounds. Even higher yields (~70%) of NB are obtained when (IVb) is oxidized with TFPA. In the latter case, some 10% of a compound was also isolated which, from its IR and PMR spectra, was identified as o-nitrophenylazoxyformamide (VIb). The position of the N-oxide oxygen could not be established as a result of the low stability and difficulty of obtaining the compound.

Reactions of Arylazo- and Arylazoxy-N-nitroformamidines



(I)



EXPERIMENTAL

PMR spectra were obtained on Tesla BS-467 (operating freauency 60 MHz) and Bruker WM-250 spectrometers, and ^{13}C and ^{14}N spectra were obtained on a Bruker AM-300 at frequencies of 75.5 MHz and 21.7 MHz, respectively. Chemical shifts were measured relative to acetone: ^{1}H (δ = 2.05 ppm) and ^{13}C (δ = 30.0 ppm), and ^{14}N relative to $MeNO_2$ as external standard (δ = 0.0 ppm) without correction for diamagnetic susceptibility.

IR spectra were obtained on UR-20 and Specord IR instruments, in KBr disks for crystalline solids, and for liquids in the absence of a solvent.

TLC was carried out using Silpearl UV 254, eluent MeOH:C_6H_6:Et_2O = 1:2:7. Melting points were determined on a Boetius hot plate.

S-Methylisothionitrourea was obtained as described in [6].

2-Phenylhydrazino-N^2-nitroformamidine (I). To a solution of 4.38 g (30 mmoles) of phenylhydrazine hydrochloride in 200 ml of water was added 1.68 g (30 mmoles) of KOH, followed by 4.08 g (30 mmoles) of $MeSC(=NNO_2)NH_2$. The mixture was stirred for ~3 h at 50-60°C until evoluton of MeSH had ceased, then kept for 12 h. The colorless precipitate was filtered off, washed repeatedly with water, and air-dried to give 4.2-4.6 g of (I) (72-78% of theoretical), mp 168-169°C (decomp.) (H_2O). IR spectrum (ν, cm^{-1}): 3375 s, 3265 s, 3180 med, 1630 med, 1605 med, 1590 med, 1565 med, 1430 med, 1405 med, 1310 s, 1295 s, 1245 s, 1065 w, 1040 w, 840 w. PMR spectrum (DMSO-d_6, δ, ppm): 6.95 m (C_6H_5), 7.95 s (NH), 8.30 br.s (NH_2), 9.70 s (NH). The compound was identical with that obtained as in [7].

Phenylazo-N^2-nitroformamidine (II). To a suspension of 1.56 g (8 mmoles) of finely ground (I) in 30 ml of water was added portionwise bromine (6 × 0.1 ml) with cooling (0-5°C) and stirring over 30 min. After stirring for 10-15 min at 0-5°C, the orange-brown solid was filtered off, washed repeatedly with ice-water, and air-dried to give 1.4 g (92%) of (II), mp 147-149°C (decomp.) ($CHCl_3$). IR spectrum (ν, cm^{-1}): 3410 med, 3225 s, 3050 w, 1610 v.s, 1525 s, 1775 s, 1435 w, 1315 w, 1240 s, 1195 s, 1140 med, 1060 w, 965 w, 915 med, 850 w. PMR spectrum (DMSO-d_6, acetone-d_6, δ, ppm): 7.75, 7.80 m (C_6H_5); 9.60, 8.90 br.s (NH_2). Found, %: C 43.45, H 3.62, N 35.75. $C_7H_7N_5O_8$. Calculated, %: C 43.53, H 3.65, N 36.26.

General Method of Oxidation of Phenylazo-N^2-nitroformamidines. Dry dichloromethane (10 ml per mole of azo compound) was cooled to 0°C, and concentrated H_2O_2 (0.5 ml/1 mmole)

added, followed by $(F_3CCO)_2O$ (3.5 ml/1 mmole) in a single portion. The temperature rose to 15-20°C. The oxidizing mixture was cooled to 0-5°C, and a solution of the azo compound in dry dichloromethane (8-12 ml/1 mmole) added in several portions. After stirring for 1-2 h in an ice bath, the mixture was kept for 1 day in the refrigerator. During this time, the color of the solution changed from reddish orange to yellow. The mixture was poured onto ice (20-25 g/mmole), and the organic phase separated and washed repeatedly with ice water (until the washings were neutral), dried over $MgSO_4$, and the solvent removed under reduced pressure.

Phenyl-ONN-azoxy-N^2-nitroformamidine (III). Oxidation of 0.4 g (2.08 mmoles) of (II) (see general method) gave 0.26 g of orange-brown crystalline product which darkened rapidly on removal of the solvent. This was extracted with 5-7 ml of benzene, and from the residue there was isolated by TLC 0.1 g of (III) (23%) as a pale yellow, finely crystalline powder, mp 123-126°C ($CHCl_3$). A further 0.03 g (7%) of (III) was isolated following double purification of the benzene extract on silica gel. IR spectrum (ν, cm^{-1}): 3415 med, 3305 med, 1610 med, 1550 med, 1540 med, 1490 med, 1470 med, 1440 w, 1355 med, 1295 s, 1235 s, 1125 med, 1090 w, 1080 w, 1030 w, 950 med, 885 w. PMR spectrum (DMSO-d_6, acetone-d_6, δ, ppm): 7.95, 7.90 m (C_6H_5); 9.60, 9.05 br.s (NH_2). Found, %: C 39.81, H 3.38, N 33.32. $C_7H_7N_5O_3$. Calculated, %: C 40.20, H 3.38, N 33.48.

Nitrophenylazo-N^2-nitroformamidines (IV). To a nitrating mixture, prepared from 10 ml of concentrated nitric acid and 10 ml of concentrated sulfuric acid, was added with vigorous stirring and cooling (0-5°C) in portions over 10-15 min 2 g (10.4 mmoles) of (II). The mixture was stirred for 1 h at 0-5°C, the cooling removed, and the mixture allowed to warm up spontaneously to ~20°C. It was then poured onto 25 g of ice, and the bright orange solid which separated was filtered off and washed repeatedly with ice water. The rapidly deliquescing solid was transferred to a flask, dissolved in acetone, and dried over $MgSO_4$ for 1-2 h. The acetone was removed under reduced pressure, and the solid, dry residue (~2 g) dissolved in boiling benzene and left to crystallize for 1-2 weeks. The large reddish-orange crystals were filtered off, washed with benzene, and air-dried to give 0.7-0.75 g (24-26%) of 3-nitrophenylazo-N^2-nitroformamidine (IVa) crystallizing with half a molecule of benzene, mp 159-161°C (decomp.). IR spectrum (ν, cm^{-1}): 3415 med, 3310 med, 3210 w, 1635 s, 1540 med, 1495 w, 1440 w, 1355 s, 1315 med, 1275 w, 1255 s, 1195 med, 1165 w, 1090 w, 1080 w, 1040 w, 995 w, 945 w, 915 w, 835 w. PMR spectrum (DMSO-d_6, acetone-d_6, δ, ppm): 8.20, 8.36 m (C_6H_4); 9.60, 8.90 br.s (NH_2). Found, %: C 43.27, H 3.20, N 29.90. $C_{10}H_9N_6O_4$. Calculated, %: C 43.32, H 3.27, N 30.31.

The mother liquors, after removal of the meta isomer (IVa), were concentrated to half their volume, and kept for several weeks. The finely crystalline, reddish orange solid was filtered off, washed with benzene, and air-dried to give 0.40-0.42 g (16-17%) of 2-nitrophenylazo-N^2-nitroformamidine (IVb), mp 155-157°C (decomp.) (after further crystallization from benzene). IR spectrum (ν, cm^{-1}): 3415 med, 3310 med, 3095 w, 1645 s, 1578 w, 1525 med, 1485 med, 1450 w, 1345 w, 1320 med, 1260 s, 1207 w, 1170 w, 1090 w, 985 w, 940 w, 870 w, 850 w. PMR spectrum (DMSO-d_6, acetone-d_6, δ, ppm): 7.85, 7.96 m (C_6H_4): 9.55, 8.90 br.s (NH_2). Found, %: C 35.26, H 2.47, N 34.94. $C_7H_6N_6O_4$. Calculated, %: C 35.30, H 2.54, N 35.29.

Using this method, 0.5 g (2.6 mmoles) of (II) was nitrated. The crude product (0.5 g) was subjected to TLC to obtain 0.4 g (65%) of a mixture of (IVa) and (IVb). According to the PMR spectrum, the ratio (IVa)/(IVb) was ≈3/1.

(3-Nitrophenyl-ONN-azoxy)-N^2-nitroformamidine (Va). To a nitrating mixture prepared from 1.5 ml of concentrated nitric acid and 1.5 ml of concentrated sulfuric acid was added portionwise with stirring and cooling (0-5°C) 0.3 g (1.5 mmoles) of (III), and stirring continued for 0.5 h at this temperature. The mixture was then poured onto 30 g of ice. The pale yellow solid, which deliquesced rapidly in air, was filtered off, washed repeatedly with ice water, dissolved in chloroform, and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave 0.3 g of crude product, crystallization of which from chloroform–acetone (~4:1) gave 0.24 g (63%) of (Va), mp 127-129°C. IR spectrum (ν, cm^{-1}): 3430 med, 3320 med, 3110 w, 1625 s, 1540 s, 1505 med, 1495 s, 1375 w, 1355 med, 1260 s, 1160 w, 1120 w, 1030 med, 1010 med, 910 w, 870 w, 825 w. PMR spectrum (DMSO-d_6, acetone-d_6, δ, ppm): 8.35, 8.47 m (C_6H_4); 9.60, 9.05 br.s (NH_2). Found, %: C 32.83, H 2.31, N 32.88. $C_7H_6N_6O_5$. Calculated, %: C 33.08, H 2.38, N 33.08.

Oxidation of 3-Nitrophenylazo-N^2-nitroformamidine (IVa). Oxidized by the general method, 0.52 g (1.86 mmoles) of the meta isomer (IVa) afforded 0.30-0.32 g of a red-brown oil, which was subjected to TLC to give: a) 0.13-0.16 g (30-37%) of a chromatographically inseparable mixture of (3-nitrophenyl-ONN-azoxy)-N^2-nitroformamidine (Va) and (3-nitrophenyl-ONN-azoxy)-formamide (VIa) as a yellowish-brown viscous mass which slowly solidified. IR spectrum (ν, cm^{-1}): 1730 s (C=O), 1625 s (C=NNO_2). PMR spectrum (DMSO-d_6, acetone-d_6, δ, ppm): 7.20, 7.15 br.s (NH_2CO); 8.30, 8.35 m (C_6H_4); 9.60, 9.05 br.s (NHC=NNO_2). b) 0.11-0.12 g (48-52%) of $C_6H_5NO_2$, bp 100°C (20 mm), the IR and PMR spectra of which were identical to those of an authentic sample of nitrobenzene.

Hydrolysis of (3-Nitrophenyl-ONN-azoxy)-N^2-nitroformamidine (Va). Treatment of 0.18 g (0.63 mmole) of (Va) with the oxidizing mixture (see general method of oxidation) gave 0.13 g (65%) of (3-nitrophenyl-ONN-azoxy)formamide (VIa) as a yellowish-brown, viscous mass. IR spectrum (ν, cm^{-1}): 3280 med, 3120 med, 3000 med, 2925 med, 1730 s, 1535 med, 1500 med, 1360 s, 1260 med, 1040 med, 910 w, 855 w, 810 w. PMR spectrum (acetone-d_6, δ, ppm): 8.25 m (C_6H_4); 7.15 br.s (NH_2). Found, %: N 26.40. $C_7H_7N_4O_4$. Calculated, %: N 26.66.

Oxidation of 2-Nitrophenylazo-N^2-nitroformamidine (IVb). Oxidation of 0.45 g (1.88 mmoles) of the ortho isomer (IVb) gave: a) 0.04 g (10%) of (2-nitrophenyl-NON-azoxy)formamide (VIb) as a yellowish-brown, viscous mass, which showed signs of decomposition after a few days at 0°C. IR spectrum (ν, cm^{-1}): 3280 med, 3120 med, 3020 med, 2930 med, 1735 s, 1530 med, 1505 med, 1365 v.s, 1260 med, 1030 med, 910 med, 850 w, 830 w. PMR spectrum (acetone-d_6, δ, ppm): 7.85 m (C_6H_4); 7.15 br.s (NH_2). b) 0.16 g (69%) of nitrobenzene.

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