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Preparation, Separation and Identification of Some *para*-Substituted *ONN* and *NNO trans*-Azoxybenzenes

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A series of *para*-substituted azoxybenzenes was obtained as model compounds for the investigation on the mechanism of Wallach rearrangement. Oxidation of azobenzenes with hydrogen peroxide in acetic acid solution, provided mixtures of α and β isomers. Some couples of the products were separated, using chromatography and crystallization techniques, and identified on the basis of their carbon NMR and mass spectra. The SCSD algorithm can be applied to the interpretation of the ^{13}C-NMR spectra. Recognition of the *ipso* and *para* carbons suffice to the identification of an isomer, hence there are no strong interactions between the azoxy group and another substituent across the aromatic ring. Fragmentation of azoxybenzenes under electron impact occurs preferentially on the oxidized side of the azoxy bridge. Relative intensities of daughter ions differentiate the *ONN* = α and *NNO* = β isomers in most cases.

Key words: azoxybenzenes, isomerism, NMR, mass spectrometry

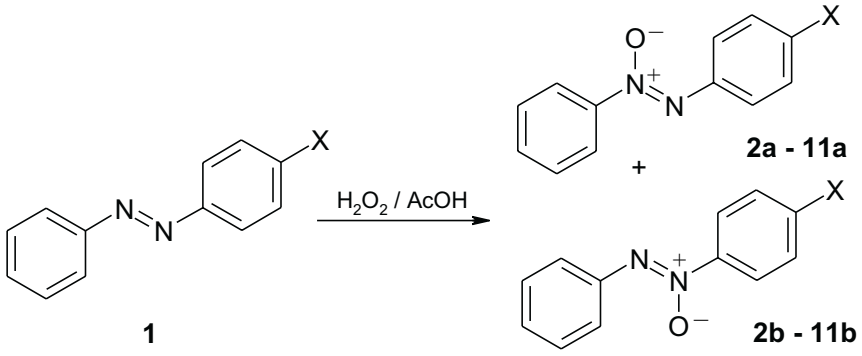
Isomerization of azoxybenzene to 4-hydroxyazobenzene, under influence of sulphuric acid of moderate concentration, used to be called Wallach rearrangement from the name of its discoverer [1]. Formally, the oxygen atom migrates from nitrogen to the aromatic ring, in fact, the transformation is intermolecular. It may be considered as the aromatic nucleophilic substitution with the remote leaving group [2]. Rearrangement of [^{15}N]-azoxybenzene indicated that either of the *para*-carbons might be a migration terminus, hence a symmetrical transition state was postulated [3]. Its structure remains controversial being formulated either as the dication [4] or *N,N′*-diphenyloxadiaziridine [5]. Another possibility is that both para positions, in the protonated substrate molecule, are equally susceptible to the nucleophilic attack of water molecule [6].

Unsymmetrical azoxyarenes, *i.e.* the compounds containing different aromatic systems bound with the azoxy bridge, proved to be useful models in investigation of the mechanism. Different susceptibilities of the isomers to the action of an acidic catalyst and positional selectivity of the migration provide some information on the nature of an intermediate or intermediates [7, 8]. Mono-substituted azoxybenzenes may be also employed for that purpose, provided that their structure is firmly established. Oxidation of azobenzenes with peroxides is the most frequently used preparative method. However it provides a mixture of isomers *ONN* (α) and *NNO* (β). Their separation and identification is not an easy task. 4-(*N,N*-Dimethylamino)-azoxybenzene with m.p. 122°C was described for the first time as the β isomer [9], later it was

claimed that the compound belonged to the α series [10]. The controversy was resolved finally by the X-ray diffraction method; the compound appeared to be *NNO* isomer [11]. Several other discrepancies can be found in the literature. The aim of this work is to find out a simple and infallible method of determining the structures of isomers and estimating the composition of their mixtures.

RESULTS AND DISCUSSION

The title compounds were prepared using three commonly known methods [12]. Condensation of 4-substituted anilines with freshly prepared nitrosobenzene provided corresponding azobenzenes (**1**), which were subsequently oxidized, yielding mixtures of azoxybenzenes in various ratios (method A). The amino group ($X = NH_2$) was protected by acetylation. Butter Yellow (C.I. 11020, CAS [60–11–7]) gave very complex mixture because the *N,N*-dimethylamino group is also a nucleophilic centre which reacts with the peroxide. Corresponding azoxybenzenes (**5a** and **5b**) were obtained on another path.



The isomers were separated by column chromatography with the careful control by HPLC, GCMS and capillary electrophoresis methods. Only in some cases (X = OH, NH_2 or SO_2Me) both isomers were obtained in a pure state. Most frequently (X = COOH, NO_2, OMe, Br) combination of chromatography and fractional crystallization provided only one compound pure and a mixture of both. All attempts to separate isomeric *trans*-4-methyl- and 4-fluoroazoxybenzenes were unsuccessful. Preparative separation of the isomers is possible only if azoxybenzene contains a strongly polar substituent. Bromination of azoxybenzene gave its 4-bromo-*ONN* derivative (**11a**) in good yield; nitration also occurred at the same site (method B). The third route was applied to the pure isomers and involved transformation of the substituent (X = OH, NH_2) into another one (method C). Methylation of amines **3a** and **3b**, with dimethyl sulphate in an alkaline aqueous solution, proceeded with some difficulties yielding mixtures of the products **4** and **5**, which had to be separated from the unchanged substrate by the chromatographic techniques. The results are collected in Table 1, some typical examples are given in the experimental part.

Table 1. *para*-Substituted *ONN* and *NNO*-azoxybenzenes.

No	Substituent	*ONN*-Azoxybenzenes (α)			*NNO*-Azoxybenzenes (β)		
		Method	Yield %	Melting point °C	Method	Yield %	Melting point °C
2	COOH	A	5[a]	243–245	C	14	265–266
3	NH_2	A	40	138–139	A	21	137–138
4	NHMe	C[b]	33	91–92	C[b]	19	61–62
5	NMe_2	C[b]	18	127–129	C[b]	9	121–122
6	NO_2	A[c]	33	156–158	–	–	–
7	OH	A	35	160–161	A	7	111–112
8	OMe	A	36	71–73	A	16	39–40
9	SO_2Me	A	57	142–143	A	15	138–139
10	F	C	49	62–63	C	34	60–61
11	Br	B	85	73–74	A	12	94–95

a) Most of *trans*-azoxybenzene-4-carboxylic acid was isolated (71% yield) as the mixture containing equal amounts of α and β isomers; well shaped crystals had high and sharp melting point 246–247°C; b) Mono and dimethyl derivatives were obtained from the same batch and separated by chromatography, adjusted yield was *ca.* 83% in both cases since significant amounts of the substrates were recovered unchanged; c) The same compound was obtained (14% yield) by nitration of azoxybenzene.

The structures of **3a**, **3b** and **7a** were determined by the X-ray diffraction method [13, 14], so they may be considered as unambiguous. It may be assumed that the products derived from these compounds (method C) have analogous structures as **4a** and **4b** (X = NHMe) or **5a** and **5b** (X = NMe_2). We have registered spectra of both series (α and β) looking for the method of their differentiation. The carbon NMR spectroscopy appeared to be useful for that purpose in spite of that the spectra consisted of eight signals in the narrow range of 110–160 ppm. In the case of *para*-fluoroazoxybenzenes, the peaks derived from the substituted ring can be recognized directly, due to the characteristic $^{13}C–^{19}F$ coupling. Interpretation of the spectra of **8a** and **8b** was based on the analogy with the spectra of 4,4′-azoanisole and 4,4′-azoxyanisole. We have assumed that the influence of a substituent on the chemical shifts of carbons in the unsubstituted ring is negligible. Consequently, we could assign some signals, appearing at the same site of the ppm scale to the primed (C-1′– C-4′) carbons and calculate the substituent-induced chemical shift differences (SCSD) of the azoxy group. They are collected in Table 2 (in brackets); it can be seen that the azoxy bridge is not magnetically symmetrical. The SCSD's for the *ortho* and *para* positions in the rings on the oxidized and unoxidized side of the bridge differ for 7.7 ppm and the differences have the opposite signs. These increments, together with the SCSD's for other substituents [15], were used for calculation of the chemical shift values in 1,4-disubstituted rings. The agreement between predicted and observed values were qualitative only, but sufficient to unequivocal assignment of resonances to particular

carbon atoms. This is well known, that limited accuracy is the main disadvantage of the methods based upon the additivity rule [16,17]. Our interpretation of the spectra of some *para*-substituted azoxybenzenes is presented in Tables 3 and 4.

Table 2. Chemical shifts of unsubstituted rings in 4-substituted azoxybenzenes.

Position	α (SCSD)	β (SCSD)
Ipso	147.7 ± 0.3 (+ 19.2)	143.7 ± 0.5 (+ 15.2)
Ortho	132.5 ± 1.0 (+ 4.0)	124.8 ± 0.4 (– 3.7)
Meta	129.2 ± 0.2 (+ 0.7)	128.8 ± 0.1 (+ 0.3)
Para	121.7 ± 0.5 (– 6.8)	129.3 ± 0.7 (+ 0.8)

Table 3. Carbon NMR spectra of *para*-substituted azoxybenzenes in DMSO-d_6 solutions (the *ONN* or α series).

Position	NH_2	NHMe	NMe_2	OH	OMe	F	Br	NO_2
C-1	130.6	130.6	130.8	136.1	137.1	140.1	142.5	148.4
C-2, 6	128.3	128.2	127.8	127.9	127.6	127.7	127.0	125.6
C-3, 5	112.9	110.8	111.0	115.4	114.1	115.9	131.9	124.4
C-4	151.4	151.6	151.1	159.3	160.3	161.8	122.3	140.4
C-1′	147.7	147.7	147.7	147.8	147.7	147.6	147.6	147.4
C-2′, 6′	133.3	133.2	133.2	131.4	131.6	132.2	132.4	133.0
C-3′, 5′	129.0	129.0	129.0	129.2	129.1	129.3	129.3	129.4
C-4′	121.3	121.3	121.4	121.7	121.8	122.1	122.0	122.3
Me	–	29.2	[a]	–	55.5	–	–	–

a) Overlapped with the solvent, in proton NMR spectrum, the *N*-methyl group gives a strong line at 6.76 ppm.

Application of the increments, derived from monosubstituted compounds, to the prediction of chemical shift values in disubstituted derivatives of benzene, usually gives some discrepancies (Δδ) between the calculated and estimated chemical shifts, because the interactions between the substituents are not taken into account. The differences (Δδ) were tabulated for comparison and confirmation of the assignments but the results were rather confusing and difficult to interpretation. Within the α series, the calculated values for C-1 (Δδ = +4.4 ppm) and C-2 (Δδ = +6.2 ppm) exceeded the estimated ones, while those predicted for C-4 were for 5.3 ppm lower. Moreover, they were independent of the electron withdrawing or releasing properties of a substituent in *para*-position. The analogous effect in the β series was limited to the *ipso* (C-1) carbon (Δδ = –4.5 ppm). This is well known, that steric interactions between neighbouring substituents may disturb the additivity rule [16,17], but the case of azoxybenzenes indicates that some other interaction, neither steric nor mesomeric, can also influence the accuracy of the empirical additivity models. We cannot explain the origin of the Δδ values, but their constancy confirms our interpretation of the spectra.

Table 4. Carbon NMR spectra of *para*-substituted azoxybenzenes in DMSO-d_6 solutions (the *NNO* or β series).

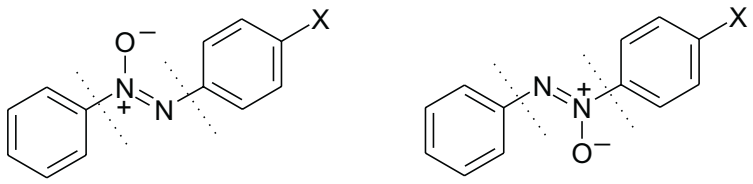
Position	Me	COOH	NH_2	NMe_2	OH	OMe	F	Br
C-1	145.5	150.7	136.1	136.1	139.6	140.8	144.1	146.8
C-2, 6	121.9	133.0	123.7	123.4	124.0	123.8	124.5	124.1
C-3, 5	129.6	130.8	112.5	110.7	115.4	114.1	116.1	132.4
C-4	142.4	122.9	152.8	152.5	161.0	162.2	164.0	125.7
C-1′	143.6	143.8	144.2	144.1	143.8	143.7	143.4	143.3
C-2′, 6′	125.2	125.6	124.5	124.6	124.7	124.8	125.0	125.0
C-3′, 5′	128.9	129.4	128.7	128.7	128.8	128.9	128.9	128.9
C-4′	129.4	130.8	128.7[a]	128.6	129.1	129.3	129.8	130.0
Me	20.8	[b]	–	39.7	–	55.8	–	–

a) Isochronic with C-3′; b) The resonance of the carboxyl group appears at 166.6 ppm and differs slightly (167.0 ppm) from that of the α isomer.

The separation and purification of the isomers were controlled by the GCMS method. Under proper conditions, two well-separated peaks were observed. The great advantage of the GCMS method is that it can be applied to the mixtures, providing some information of their composition. Obviously, the differences in the mass spectra of closely related isomers cannot be spectacular, but due to the similar fragmentation routes, the total ion current should be similar for both isomers. Consequently, the intensities of the peaks on chromatograms are the good measure of the isomer proportions in a mixture, confirmed by the HPLC method. Mass spectra of the pure samples revealed some relevant differences in fragmentation of α and β isomers, distinctive for both series.

In the mass spectra of *para*-substituted azoxybenzenes, the molecular ion forms one of the most abundant peaks in the spectrum (Table 5). Their intensities are usually higher in the α series except compounds **6** and **9**, containing electron-withdrawing substituents. The observation has no diagnostic value, but indicates that the character of a substituent influences fragmentation modes as well as its position in relation to the azoxy bridge. The cleavage of the Ar–N bond is the main route of fragmentation. The bond breaking within the substituents is of secondary importance. Expulsion of the *N*-oxygen atom also does not interfere, giving rise to weak peaks (1–3%) at m/z = $[M - 16]^+$. Either of the bonds, shown on the scheme below, can be cleaved and the positive charge can appear on either of both fragments. The behaviour of the isomers, under electron impact, is different and it suffice to recognize a particular compound as the member of the α or β series. It has been found that the peak m/z = 77 is more intense within the α series, *i.e.* when the cleavage occurs on the oxidized side of the azoxy group and the positive charge is retained on the aromatic ring. It is consistent with the earlier data [18,19] but two compounds do not obey this rule, probably due to a different site of ionization. It should be mentioned there, that the same $[Ph]^+$ fragment may emerge from the expulsion of the substituted ring, leading to the $[PhN_2O]^+$

ion (m/z = 121) and further fragmentation involving elimination of the N_2O molecule. However, the daughter ions at m/z = 121 are observed only in few spectra as the peaks of low intensity (1–3%).



α β

Table 5. Electron impact (70 eV) mass spectra of some *para*-substituted azoxybenzenes. The intensities of the relevant peaks are given in percents, in respect to the base peak.

Substituent X	Intensities of some diagnostic signals (%)							
	mol. Ion $[M]^+$		m/z = 77		$[M - 121]^+$		$[M - 77]^+$	
	α	β	α	β	α	β	α	β
COOH	34	85	100	35	6	78	1	1
NH_2	63	38	34	14	7	100	2	0
NHMe	93	74	47	56	10	100	0	0
NMe_2	93	90	36	48	11	90[a]	0	0
NO_2	34	81	100	61	3	88	1	2
OH	100	53	95	32	11	100	4	4
OMe	100	100	79	48	11	46	3	2
SO_2Me	25	76	100	86	3	98[b]	0	0
F	72	37	100	15	16	100	3	1
Br	50	39	100	30	24	100	2	0

a) M/z = 134 is the base peak; b) M/z = 65 is the base peak, in both cases fragmentation of the aromatic ring is observed.

Moreover, elimination of phenyl radical gives rise to the peaks of low or extremely low intensities in most spectra (two last columns in Table 5) hence, the peaks at m/z = 77 must be formed in the first step of fragmentation. From the structural point of view, the most significant fragmentation route is the expulsion of the PhN_2O radical; within the β series, the fission of the Ar–N bond gives rise to the peaks of low-to-medium intensity. On the contrary, the cleavage of the azoxy bridge on its oxidized side produces very intensive fragmentation ions, forming base peaks in some spectra. The differences in the fragmentation paths of *NNO* and *ONN* isomers are sufficient for identification purposes in most cases. The method fails in the case of *para*-methylazoxybenzene; its spectrum is dominated with peak at m/z = 91 due to the unusual stability of tropylium cation. The position of the methyl group in relation to the azoxy bridge has no influence on the fragmentation routes.

The problem of fragmentation – structure relationship was discussed in the recent monograph [20] with the final conclusion that "the position of the *N*-oxide in the azoxy moiety could not be determined directly using mass spectrometry". In fact, various rearrangements, accompanying cleavages of the bonds, complicate the mass spectra and diminish their diagnostic value. However, within the series of closely related derivatives of azoxybenzene, combination of carbon NMR and mass spectrometry resolves the problem of the α – β isomerism. An example of azoxybenzene-4-carboxylic acid is illustrative. It has been claimed that oxidation of *para*-azobenzenecarboxylic acid provides the *NNO*-isomer as the main product [21,22]. We have found that both isomers are formed in the comparable amounts with a small preponderance the *ONN*-isomer, which can be isolated in a pure state. The rest of the product was obtained as the mixture containing equal amounts of **2a** and **2b** forming well-shaped crystals with high and sharp (246–248°C) melting point. Carboxylic acid is not an exception, there are some other couples (X = NH_2, NMe_2, SO_2Me, F) with similar melting points, which form corresponding *NON*-azoxybenzenes melting at nearly the same temperature. Resolution of the problem whether these are solid solutions or molecular complexes requires further investigations.

EXPERIMENTAL

Proton and carbon NMR spectra were recorded on a Tesla BS 567A spectrometer (2.3 T). The chromatographic analyses were performed using Hewlett-Packard GC system HP 6890 with Mass Selective Detector 5973, equipped with the on-column inlet and the capillary HP-1 methyl siloxane column. For the registration of mass spectra, the SIS direct insertion probe system was employed. HPLC analyses were carried out on Beckman chromatograph, System Gold, equipped with the detector D1, type 168 and a column Alltech Alltima C-18 (150 × 4.6 mm). The mixture (3:7 v/v) of 0.1% aqueous TFA and acetonitrile was used as the eluent.

4-Methoxy-*NNO*- and 4-methoxy-*ONN*-azoxybenzene (method A): To the stirred solution of 4-methoxyazobenzene (2.12 g, 0.01 mol) in acetic acid (20 ml), hydrogen peroxide (10 ml of 30% H_2O_2) was added. The mixture was maintained at 50°C for 3 h and poured on ice water (200 ml). A yellow precipitate was collected by filtration, washed with cold water and dried. The crude product (2.00 g, m.p. 43–52°C) contained nearly equal amounts of both isomers, according to HPLC analyses. It was adsorbed on silicagel from benzene solution and chromatographed using the *flesh* technique. The first fraction, eluted with the benzene – n-heptane 1:1 mixture, was evaporated and the residue crystallized twice from isooctane. 4-Methoxy-*NNO*-azoxybenzene (0.36 g, 16%) was obtained as light yellow needles, m.p. 39–40°C. MS, m/z (int.): 228 (M^+, 100), 212 (1), 200 (6), 185 (9), 135 (13), 121 (50), 107 (46), 92 (20), 77 (49). IR (KBr): 1478 (asymmetric NNO stretch); 1328 (symmetric NNO stretching vibrations). ^{1}H-NMR (DMSO-d_6): 8.19–8.33, m, 2H (H-2, H-6); 8.04, m, 1H (H-4′); 7.48–7. 67, m, 4H (remaining aromatic protons); 3.88, s, 3H (methoxy group). The next homogeneous fraction, eluted with benzene, provided 4-methoxy-*ONN*-azoxybenzene (0.42 g, 36%) after analogous treatment. It forms yellow needles, m.p. 71–73°C. MS, m/z (int.): 228 (M^+, 100), 151 (3), 121 (62), 107 (11), 106 (26), 95 (22), 77 (79). IR (KBr): 1479 (asymmetric NNO stretch); 1324 (symmetric NNO stretching vibrations). ^{1}H-NMR (DMSO-d_6): 8.21–8.35, m, 3H (H-2′, H-4′, H-6′); 7.63, m, 4H (protons *ortho* to the azoxy bridge); 7.11, d ^3J = 9.0 Hz, 2H (H-3, H-5).

4-Bromo-*ONN*-azoxybenzene (method B): Azoxybenzene (4.95 g, 25 mmol) was dissolved in acetic acid (120 ml), bromine (1.41 ml, 27.5 mmol) was added and the mixture was stirred for 4 h on the water bath maintained at 50°C. A solution was left for the night at room temperature. Long transparent needles were collected by filtration, washed with cold acetic acid and crystallised from methanol (100 ml) yielding 4-bromo-*ONN*-azoxybenzene (5.89 g, 85%), m.p. 73–74°C. MS, m/z (int.): 278 (49), 276 (M^+, 50),

249 (6), 247 (6), 199 (2), 169 (38), 157 (23), 155 (24), 145 (8), 143 (8), 141 (10), 115 (7), 105 (19), 91 (22), 90 (29), 77 (100). IR (KBr): 1480, 1324 (NNO stretching vibrations). ^{1}H-NMR (DMSO-d_6): 8.21– 8.31, m, 2H (H-2′, H-6′);8.06, d ^3J = 8.9 Hz, 2H (H-3, H-5); 7.61–7.78, m, 5H (remaining aromatic protons).

4-Fluoro-*ONN*-azoxybenzene (method C): 4-Amino-*ONN*-azoxybenzene (2.13 g, 0.01 mol) was dissolved in the mixture of acetic (30 ml) and hydrochloric acid. To the cooled (0 – 5°C) solution, sodium nitrite (0.80 g, 15 mmol) dissolved in water (1.5 ml) was added dropwise during 0.5 h. Tetrafluoroboric acid (15 ml of 40% HBF_4) was added and a precipitate of diazonium tetrafluoroborate was collected by filtration. It was washed with the cold HBF_4, methanol, diethyl ether and dried. The salt was mixed with the three-fold amount of silicagel and heated slowly on an oil bath until a reaction began (at *ca.* 150°C). The mixture was kept at this temperature for 0.7 h, cooled and extracted with ether in Soxhlet apparatus. The extract was chromatographed on silicagel, using n-heptane and benzene – n-heptane 1:1 mixture as the eluents. From the second fraction, after repeated crystallization from the eluent, 4-fluoro-*ONN*-azoxybenzene (1.06 g, 49%) was obtained, m.p. 62–63°C. MS, m/z (int.): 216 (M^+, 72), 187 (22), 159 (9), 139 (3), 95 (16), 91 (22), 83 (17), 77 (100). IR (KBr): 1492, 1328 (NNO stretching vibrations). ^{1}H-NMR (DMSO-d_6): 8.16–8.31, 5H (aromatic protons); 7.65, dd ^3J = 6.9 Hz, ^4J = 1.9 Hz, 2H (H-2′, H-6′); 7.39, dd $^3J = {}^3J_{FH}$ = 9.0 Hz, 2H (H-3, H-5).

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