Reactions of 5-azido-2-furaldehyde with 2-substituted anilines

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2-Aminothiophenol reduces selectively 5-azido-2-furaldehyde to 5--amino-2-furaldehyde. 2-Aminophenol and 4-nitro-1,2-diaminobenzene both react with 5-azido-2-furaldehyde to form azomethines, which decompose, producing in turn intermediates the cyclization of which leads to the ultimate products, namely bibenzoxazoline, benzoxazine, and quinoxaline derivatives.

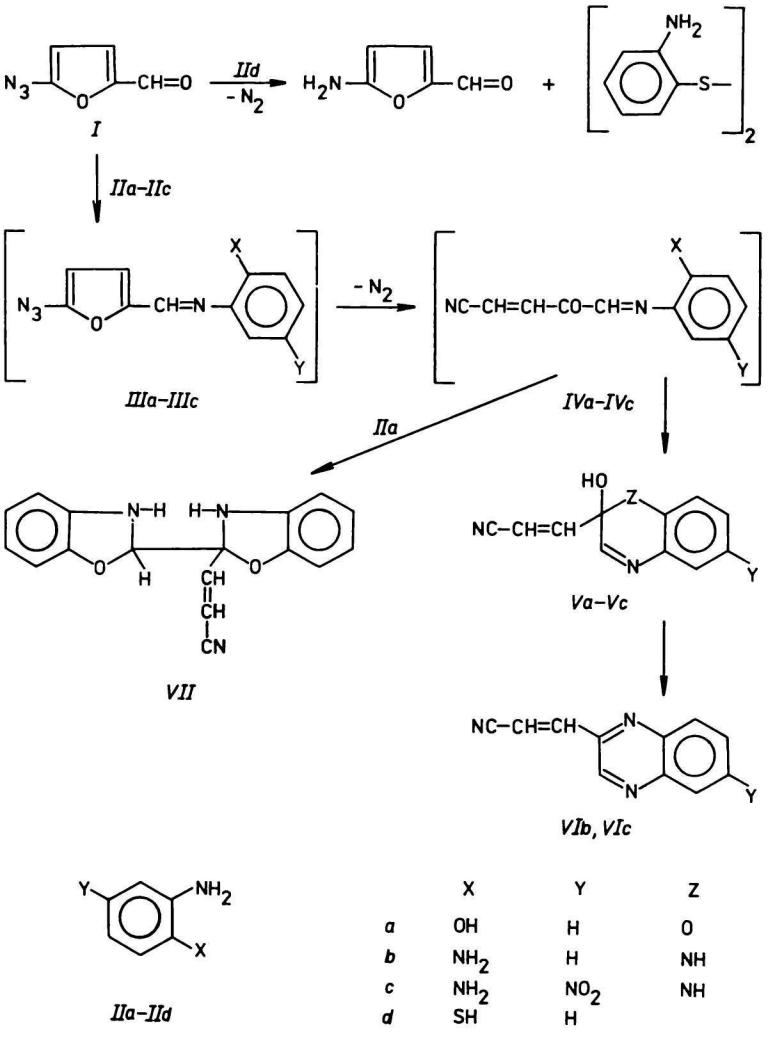
2-Аминотиофенол избирательно восстанавливает 5-азидо-2-фуральдегид в 5-амино-2-фуральдегид. 2-Аминофенол и 4-нитро-1,2-диаминобензол взаимодействуют с 5-азидо-2-фуральдегидом с образованием азометинов, которые затем разлагаются, а возникающие промежуточные соединения циклизуются с образованием дибензоксазолинового, бензоксазинового и хиноксалинового производных.

Reactivity of the azido group in 5-azido-2-furaldehyde (*I*) has so far been studied in the reactions with triphenylphosphine and acetylene [1]. We have already found that compound *I* enters the reaction with compounds possessing an active methylene group *via* the carbonyl group, giving a 5-azido-2-furylidene derivative. This in turn can undergo further reaction with malononitrile or methyl cyanoacetate now engaging the azido group to give a 5-amino-2--furylidene derivative [2]. In the presence of nitrogen-containing bases, such as substituted hydrazines, 1,2-diaminobenzene, condensation takes place, followed by ring-opening-ring closure sequence [3, 4].

Now we present the results of our investigation of the reaction of *I* with substituted anilines *IIa*—*IId* (Scheme 1).

The reaction of *I* with *IId* starts at the azido group, producing 5-amino--2-furaldehyde and 2,2′-diaminodiphenyl disulfide as main products. The former does not react further with *IId*, the latter indicates probable radical cleavage of the addition product, formed from the starting material.

The reaction of *I* with *IIa* proceeds at both reaction centres. Thermolysis of *I* in the presence of *IIa* produced a reaction mixture, from which two compounds have been isolated in the ratio depending on the mole ratio of the



Scheme 1

starting compounds (Scheme 1). Equimolar ratio of *I* and *IIa* gave mainly 2-(2-cyanovinyl)-2-hydroxy-1,4-benzoxazine (*Va*) and a trace amount of 2-(2-cyanovinyl)-2,2′,3,3′-tetrahydro-2,2′-bibenzoxazolyl (*VII*). Working with an excess of *IIa* (mole ratio = 1 : 2) reverses the ratio of products, *VII* being now the principal product [5, 6]. Since in the equimolar version the hydroxy group does not add to the carbon atom of the aldimine bond of the purported intermediate *IVa* (Scheme 1) and consequently there is no benzoxazoline formed, the question arises, where does compound *VII* come from? In principle it

could have arisen either from *Va* or from *IVa*. The reaction of *IIa* and *Va* indeed produced compound *VII*, albeit in only 10 % yield. Despite the low conversion the formation of *VII via Va* remains a plausible route, accounting at the same time for the absence of *Va* in the reaction mixture, formed from *I* and an excess of *IIa*.

4-Nitro-1,2-diaminobenzene (*IIc*) reacted with *I* in dimethyl sulfoxide under formation of a mixture of *E* and *Z* isomers of 3-(6-nitro-2-quinoxalinyl)acrylonitrile (*VIc*) in the mole ratio 2 : 3. Ring-opening reactions of *I* and its derivatives gave so far only *Z* isomers as described in [3, 7]. We assume that even in the above-mentioned example opening of the furan ring proceeds by a concerted mechanism, producing, as in previous cases, a *Z* isomer of compound *VIc* that subsequently isomerizes in dimethyl sulfoxide to some extent to *E* isomer. In order to test this assumption we carried out the reaction of *I* with *IIc* in ethanol (despite low solubility of the amine) and isolated exclusively *Z* isomer of *VIc*. Heating of *Z* isomer of *VIb* to 150 °C for 3 h gave a mixture of *E* and *Z* isomers in the mole ratio 1 : 4 (determined by ^{1}H NMR). When the *Z* isomer of *VIc* was heated to 200 °C within a minute a mixture of *E* and *Z* isomers was obtained in the mole ratio 2 : 1. Isomerization was successful in DMSO as well, 5 min at 100 °C was enough to produce from the pure *Z* isomer of *VIc* a mixture of *E* and *Z* isomers in the mole ratio 1 : 2.

We can thus conclude that 2-aminothiophenol behaves in the reaction with the azide *I* as a monofunctional agent. In contrast to malononitrile or methyl cyanoacetate [2] compound *I* suffered in the reaction with 2-aminothiophenol selective reduction of the azido group, other reactive groups remained untouched.

Other amines on the other hand, *e.g.* 2-aminophenol, 1,2-diaminobenzene, and 4-nitro-1,2-diaminobenzene attacked the carbonyl group of compound *I* in the first place, giving unstable azomethines *IIIa—IIIc*. All attempts to isolate them ended in their explosive decomposition. Controlled decomposition carried out in ethanol or in dimethyl sulfoxide led to compounds *IVa—IVc*. These cyclized intramolecularly to the corresponding quinoxaline *VIb*, *VIc*, benzoxazine *Va* or, if another molecule of 2-aminophenol was available, to bibenzoxazoline derivative *VII*.

Experimental

Infrared spectra were measured with a Zeiss model UR-20 spectrophotometer, ultraviolet spectra with Specord UV VIS, while ^{1}H NMR spectra were recorded with a Tesla 80 MHz model BS 487 C. Melting points were determined in a Kofler hot-stage apparatus. The starting azide *I* was prepared according to [1], the *Z* isomer of 3-(2-quinoxalinyl)acrylonitrile according to [3].

5-Amino-2-furaldehyde

The solution of 2-aminothiophenol (7.5 g; 0.06 mol) in 10 cm^3 of tetrahydrofuran was dropwise added to the stirred solution of 5-azido-2-furaldehyde (4.3 g; 0.03 mol) in 20 cm^3 of tetrahydrofuran, kept at 0 °C. After the 15 min addition of 2-aminothiophenol the reaction was over. The precipitated yellow 5-amino-2-furaldehyde was filtered, washed with cooled ether and dried *in vacuo*, to give 1.2 g (35 %) of 5-amino-2-furaldehyde. The product polymerized on heating.

For $C_5H_5NO_2$ (M_r = 111.1) w_i(calc.): 54.06 % C, 4.53 % H, 12.60 % N; w_i(found): 54.01 % C, 4.48 % H, 12.43 % N. IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$: 3100—3300 (ν(NH_2) bands), 1665 (ν(CH=O)). ^{1}H NMR spectrum (CD_3SOCD_3), δ/ppm: 8.81 (s, 1H, CH=O), 7.13 (s, broad, 2H, NH_2), 7.32 (d, 1H, J = 4.1 Hz, C-3—H furan), 5.23 (d, 1H, J = 4.1 Hz, C-4—H furan).

2-(2-Cyanovinyl)-2-hydroxy-1,4-benzoxazine (Va)

The mixture of 5-azido-2-furaldehyde (4.3 g; 0.03 mol) and 2-aminophenol (3 g; 0.03 mol) in 50 cm^3 of tetrahydrofuran was heated for 2 h in the nitrogen atmosphere on a 50 °C water bath. The resulting dark solution was purified with charcoal and rotoevaporated to dryness. Rubbing with a glass rod of the oily residue in chloroform gave yellow crystals, which after recrystallization from ethanol gave 1.2 g (18 %) of compound *Va*. The yield can be increased to 35 % by column chromatography of the reaction mixture on silica gel, eluant ethyl acetate. M.p. = 193—194 °C. For $C_{11}H_8N_2O_2$ (M_r = 200.2) w_i(calc.): 65.95 % C, 3.94 % H, 14.00 % N; w_i(found): 65.86 % C, 3.90 % H, 14.28 % N. IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$: 3075—3280 (group of bands, associated OH), 2228 (ν(C≡N)), 1615 (ν(C=N)), 1602 (ν(C=C)), 1268, 1034 (ν(C—O—C)). UV spectrum (methanol), λ_{max}/nm (log {ε}): 340 (4.01), 309 (4.17), 250 (4.08), 218 (4.25). ^{1}H NMR spectrum (CD_3COCD_3), δ/ppm: 6.87—7.43 (m, 5H, aromatic H, CH=N), 7.19 (d, 1H, J = 16 Hz, CH=C—CN), 6.40 (d, 1H, J = 16 Hz, C=CH—CN), 6.12 (s, 1H, OH).

2-(2-Cyanovinyl)-2,2',3,3'-tetrahydro-2,2'-bibenzoxazolyl (VII)

Method A

The mixture of 5-azido-2-furaldehyde (4.3 g; 0.03 mol), 2-aminophenol (6 g; 0.06 mol), and dioxan (75 cm^3) was kept for 3 h at 80 °C. After that the reaction mixture was left to stand at room temperature for 12 h. The precipitate filtered and crystallized from ethanol to give 3.5 g (40 %) of compound *VII*. M.p. = 178 °C. For $C_{17}H_{14}N_3O_2$ (M_r = 291) w_i(calc.): 70.10 % C, 4.46 % H, 14.44 % N; w_i(found): 70.05 % C, 4.42 % H, 14.21 % N. IR spectrum (KBr), $\tilde{\nu}/cm^{-1}$: 3350, 3400 (ν(NH)), 2230 (ν(C≡N)). UV spectrum (methanol), λ_{max}/nm (log {ε}): 290 (3.94), 230 (4.21), 217 (5.01). ^{1}H NMR spectrum (CD_3COCD_3), δ/ppm: 6.56—6.87 (m, 1OH, aromatic H, NH), 6.49 (d, 1H, J = 11 Hz, CH=C—CN), 5.66 (d, 1H, J = 11 Hz, C=CH—CN), 5.19 (d, 1H, CH of benzoxazoline skeleton).

Method B

The mixture of 2-(2-cyanovinyl)-2-hydroxy-1,4-benzoxazine (2 g; 0.01 mol), 2-aminophenol (1 g; 0.01 mol) in 20 cm^3 of THF was kept in nitrogen atmosphere and at 50 °C for 2 h. Then it was left to stand for another 12 h at room temperature. The separated solid was filtered and crystallized from ethanol, or worked up on a silica gel column (ethyl acetate) to give 0.4 g (10 %) of compound *VII*.

3-(6-Nitro-2-quinoxalinyl)acrylonitrile (VIc)

Method A

The mixture of 5-azido-2-furaldehyde (4.2 g; 0.03 mol) and 4-nitro-1,2-diaminobenzene (4.6 g; 0.03 mol) in dimethyl sulfoxide (50 cm^3) was heated to 50—60 °C until the evolution of nitrogen ceased. The mixture was then poured into water, the solid part was filtered off and crystallized from ethyl acetate. Yield = 3.7 g (75 %) of a $Z + E$ isomer mixture of compound *VIc*. M.p. = 180—182 °C. ^{1}H NMR spectrum (CD_3SOCD_3), δ/ppm: 9.44 (s, 1H, C-3—H quinoxaline *E*), 9.35 (s, 1H, C-3—H quinoxaline *Z*), 8.91 (d, 1H, J = 2 Hz, C-5—H quinoxaline *E*, *Z*), 8.63 (dd, 1H, J = 10 Hz, J = 2 Hz, C-7—H quinoxaline *E*), 8.6 (dd, 1H, J = 10 Hz, J = 2 Hz, C-7—H quinoxaline *Z*), 8.33 (d, 1H, J = 10 Hz, C-8—H quinoxaline *E*, *Z*), 8.01 (d, 1H, J = 16 Hz, CH=C—CN, *E*), 7.85 (d, 1H, J = 12 Hz, CH=C—CN, *Z*), 7.18 (d, 1H, J = 16 Hz, C=CH—CN, *E*), 6.49 (d, 1H, J = 12 Hz, C=CH—CN, *Z*).

Method B

To 4-nitro-1,2-diaminobenzene (4.6 g; 0.03 mol) dissolved in 200 cm^3 of boiling ethanol, stirred at 50 °C 5-azido-2-furaldehyde (4.2 g; 0.03 mol) was added. The temperature was kept in the 50—60 °C range until no more nitrogen evolved. The solvent was then evaporated *in vacuo* and the raw quinoxaline derivative crystallized from ethyl acetate. Yield = 5.2 g (80 %) of *Z* isomer of *VIc*. M.p. = 200 °C. For $C_{11}H_6N_4O_2$ (M_r = 226.2) w_i(calc.): 58.41 % C, 2.67 % H, 24.77 % N; w_i(found): 58.34 % C, 2.60 % H, 24.50 % N. IR spectrum (KBr), $\tilde{\nu}$/cm^{-1}: 2227 (ν(C≡N)), 1537, 1356 (ν(NO_2)). UV spectrum (methanol), λ_{max}/nm (log {ε}): 332 (4.19), 261 (4.33), 212 (4.28). ^{1}H NMR spectrum (CD_3SOCD_3), δ/ppm: 9.35 (s, 1H, C-3—H quinoxaline), 8.91 (d, 1H, J = = 2 Hz, C-5—H quinoxaline), 8.63 (dd, 1H, J = 10 Hz, J = 2 Hz, C-7—H quinoxaline), 8.33 (d, 1H, J = 10 Hz, C-8—H quinoxaline), 7.85 (d, 1H, J = 12 Hz, CH=C—CN), 6.44 (d, 1H, J = 12 Hz, C=CH—CN).

Isomerization of Z isomers VIb and VIc

Method A

The *Z* isomer of compound *VIb* or *VIc* was thermally isomerized at its melting point from 1 min to 3 h. The melt was dissolved in CD_3SOCD_3 and the *E*/*Z* ratio was determined by ^{1}H NMR spectroscopy.

VIb heated at 150 °C	after 3 h	$E:Z = 1:4$
VIc heated at 200 °C	after 1 min	$E:Z = 2:1$

The isomerization gave an $E + Z$ mixture of *VIb* with m.p. = 106—110 °C (*Z* isomer of *VIb* has m.p. = 115—116 °C). ^{1}H NMR spectrum of the above mixture of *VIb* isomers (CD_3SOCD_3), δ/ppm: 9.20 (s, 1H, C-3—H quinoxaline *E*), 9.13 (s, 1H, C-3—H quinoxaline *Z*), 7.80—8.25 (m, 4H, C-5—8—H quinoxaline *E*, *Z*), 8.01 (d, $J = 16$ Hz, 1H, CH=C—CN, *E*, INDOR), 7.75 (d, $J = 12$ Hz, 1H, CH=C—CN, *Z*), 7.09 (d, $J = 16$ Hz, 1H, C=CH—CN, *E*), 6.40 (d, $J = 12$ Hz, 1H, C=CH—CN, *Z*).

Method B

Compounds *VIb* and *VIc*, respectively, were heated directly in an NMR tube and the isomeric ratio was determined by ^{1}H NMR experiment.

VIb	DMSO-d_6 100 °C	after 3 h	*Z* with traces of *E*
VIc	DMSO-d_6 100 °C	after 5 min	$E:Z = 1:2$

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