α-(2-FURYL)QUINOXALINES AND -QUINOXAL-2-ONES WITH A SUBSTITUENT IN THE BENZENE RING

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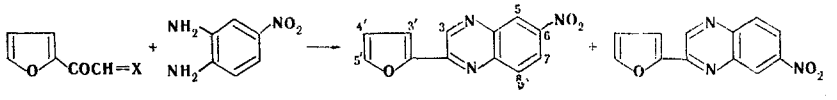
Isomeric 2-(2-furyl)quinoxalines or 3-(2-furyl)quinoxal-2-ones with a substituent in various positions in the benzene ring are formed in the reaction of 2-furylglyoxal or 2-furylglyoxylic acid with 6-hydroxy- or 4-nitro-1,2-diaminobenzene. The structures of the synthesized isomers were confirmed by PMR spectroscopy and their dipole moments.

We have previously shown [1] that a mixture of isomeric 5-hydroxy- and 8-hydroxy-2-(2-furyl)quinoxalines is formed as a result of the condensation of 2-furylglyoxal with 6-hydroxy-1,2-diaminobenzene.

In the present research we studied the condensation of 2-furylglyoxal and 2-furylglyoxylic acid and their derivatives with 6-hydroxy- and 4-nitro-1,2-diaminobenzene. In this case isomeric furylquinoxalines with a substituent in various positions of the benzene ring are formed in both neutral and acidic media.



I, II III IV V

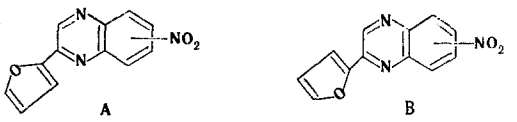
I X=O; II X=NOH

On the basis of the PMR spectra we established that a mixture of 6-nitro-2-(2-furyl)quinoxaline (IV) and 7-nitro-2-(2-furyl)quinoxaline (V) is formed as a result of the reaction of 2-furylglyoxal (I) with 4-nitro-1,2-diaminobenzene (III).

Small differences in the chemical shifts of the 5-H and 8-H protons are observed in the PMR spectra of the isomers (Table 1). Thus the 5-H proton of 6-nitroquinoxaline IV resonates at stronger field than the 8-H proton of the second isomer. On the other hand, the signal of the 8-H proton of nitroquinoxaline IV is found at weaker field than the corresponding signal of the 5-H proton of 7-nitroquinoxaline V; this is probably due to the anisotropic effect of the furyl group. Similar differences in the chemical shifts of the 5-H and 8-H protons of 6-nitro- and 7-nitro-2-(4-bromophenyl)-3-methylquinoxalines [2] are explained by the inductive effects of the methyl and phenyl groups.

Measurement of the integral intensities of the 5-H and 8-H protons of quinoxalines IV and V enabled us to establish the ratio of the isomers in the "crude" reaction products. 6-Nitro isomer IV (95%) is primarily formed when dioxane is used as the solvent, whereas primarily the 7-nitro isomer V (85%) is formed in 3 N hydrochloric acid. The use of 2-furylglyoxal aldoxime (II) as the α-dicarbonyl component leads to the formation of a mixture of isomers IV and V in a ratio of 45 : 55.

The position of the nitro group is also confirmed by a comparison of the experimentally obtained dipole moments of isomers IV and V (4.34 and 5.40 D, respectively) with the moments calculated via a vectorial scheme for rotamers A and B of 6-nitro- (A 4.40 D, B 4.40 D) and 7-nitro-2-(2-furyl)quinoxaline (A 3.70 D, B 4.85 D).



A B

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TABLE 1. PMR Spectra of 6-Nitro- and 7-Nitro-2-(2-furyl)quinoxalines

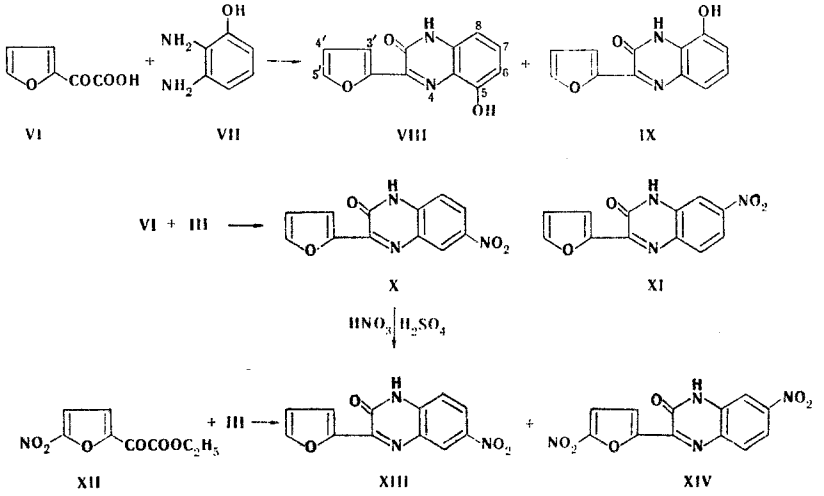
Compound	Chemical shifts, δ, ppm								SSCC, J, Hz				
	3-H	5-H	6-H	7-H	8-H	3′-H	4′-H	5′-H	5—6 or 7—8	5—7 or 6—8	3′—4′	4′—5′	3′—5′
IV	9,48s	8,77d	—	8,45 dd	8,25d	7,68 dd	6,80 dd	8,10 dd	8,7	2,2	3,0	1,2	0,6
V	9,48s	8,20d	8,50 dd	—	8,80d	7,73 dd	6,83 dd	8,10 dd	8,7	2,2	3,0	1,2	0,6

TABLE 2. PMR Spectra of 3-(2-Furyl)quinoxal-2-ones

Compound	Chemical shifts, δ, ppm							SSCC, J, Hz					
	5-H	6-H	7-H	8-H	3′-H	4′-H	5′-H	5—6	5—7	6—7	7—8	3′—4′	4′—5′	3′—5′
*	7,90 dd	7,40 m			7,88 dd	6,77 dd	8,05 dd	7,4	2,9	—	—	3,3	1,7	0,7
VIII	—	6,75 dd	7,31 dd	6,75 dd	7,77 dd	6,71 dd	7,97 dd	—	—	—	7,0	3,0	1,4	0,5
IX	7,33 dd	7,23 dd	7,14 dd	—	7,90dd	6,80 dd	8,06 dd	8,6	2,0	8,6	—	3,3	1,4	0,7
X	8,52 d	—	8,40 dd	7,49 dd	7,89 dd	6,82 dd	8,07 dd	—	2,1	—	8,4	3,0	1,4	0,5
XI				7,90 m										
XIII	8,59 d	—	8,39 dd	7,49d	7,98 d	7,82 d	—	—	2,3	—	8,7	3,5	—	—
XIV		7,97 m			7,89d	7,75 d	—					3,5		

*3-(2-Furyl)quinoxal-2-one.

Stereospecificity of the reaction is also observed in the case of condensations in which 2-furylglyoxylic acid (VI) is used as the α-dicarbonyl component. Reaction of VI with 6-hydroxy-1,2-diaminobenzene (VII) gives a mixture of 5-hydroxy-3-(2-furyl)quinoxal-2-one (VIII) and 8-hydroxy-3-(2-furyl)quinoxal-2-one (IX); primarily 5-hydroxyquinoxalone VIII (87%) is formed in neutral media, and 8-hydroxyquinoxalone IX is the primary product (75%) in acidic media. These quinoxalones have different chromatographic mobilities in a thin layer. One of them, namely, 5-hydroxy isomer VIII, in contrast to the 8-hydroxy isomer, reacts with divalent copper salts to give a complex containing two molecules of the hydroxyquinoxalone and one copper ion. We used the complexing properties of 5-hydroxyquinoxalone VIII for the separation and establishment of the structures of the isomers.



Mixtures of isomeric quinoxalones X and XI and, respectively, XII and XIV, which have a nitro group in the benzene ring, were obtained by reaction of 2-furylglyoxylic acid (VI) or ethyl 5-nitro-2-furylglyoxylate (XII) with 4-nitro-1,2-diaminobenzene (III). Primarily 7-nitroquinoxalone XI (90%) is formed in the reaction of keto acid VI with 4-nitro-1,2-diaminobenzene in neutral media, whereas primarily the 6-nitro isomer X (70%) is formed in acidic media. In connection with the low solubility of quinoxalones XII and XIV, we were unable to establish the precise ratio of the isomers in the mixture by means of the PMR spectra. The isolated 6-nitro-3-(5-nitro-2-furyl)quinoxal-2-one was identical to the dinitroquinoxalone obtained both by nitration of 3-(2-furyl)quinoxal-2-one with a nitrating mixture [3] and by nitration of an authentic sample of 6-nitro-3-(2-furyl)quinoxal-2-one.

TABLE 3. Characteristics of the Synthesized Compounds

Compound	mp, °C	Found, %			Empirical formula	Calc., %			UV spectra		Yield, %[a]	
		C	H	N		C	H	N	λ_{max}, nm	lg ε	A	B
IV	196—197[b]	59,7	2,8	17,2	$C_{12}H_7N_3O_3$	60,0	2,9	17,5	316; 390	4,11; 3,90	99	91
V	234—235[c]	59,8	2,7	17,3	$C_{12}H_7N_3O_3$	60,0	2,9	17,5	385	4,51		
VIII	308—310[b]	62,9	3,7	12,0	$C_{12}H_8N_2O_3$	63,2	3,5	12,3	271; 375; 390 sh	4,13; 4,43; 4,27	90	90
IX	289—291[d]	62,8	3,3	11,9	$C_{12}H_8N_2O_3$	63,2	3,5	12,3	271; 366	4,35; 3,56		
X	333—334[e]	56,2	2,9	16,0	$C_{12}H_7N_3O_4$	56,0	2,7	16,3	312; 380; 400; 410	3,88; 4,02; 4,07; 3,92	85	93
XI	317—318[e]	56,3	2,8	16,1	$C_{12}H_7N_3O_4$	56,0	2,7	16,3	380; 400; 410	3,93; 4,00; 3,92		
XIII	323—325[e]	47,6	1,7	18,2	$C_{12}H_6N_4O_6$	47,7	2,0	18,5	275; 330; 382	4,29; 4,21; 4,29		
XIV	307—308[e]	47,5	1,8	18,4	$C_{12}H_6N_4O_6$	47,7	2,0	18,5	287; 352; 370; 404; 415 sh	4,04; 4,34; 4,34; 4,43; 4,32	92	90

[a]Total yields of the isomers: A) when the condensation was carried out in dioxane; B) when the condensation was carried out in 3 N hydrochloric acid. [b]From dioxane. [c]From dimethyl sulfoxide. [d]From water. [e]From glacial acetic acid.

Thus the character of the substituent in the o-phenylenediamine, the nature of the α-dicarbonyl compound, and the pH of the medium affect the direction of the condensation reaction.

EXPERIMENTAL

The UV spectra of the compounds in a mixture of solvents consisting of 98 vol. % ethanol and 2% dimethylformamide (DMF) were recorded with a Specord UV-vis spectrophotometer. The PMR spectra of 5% solutions of the compounds in dimethylsulfoxide (DMSO) were recorded at 37°C with a Perkin–Elmer R-12A spectrometer (60 MHz) with hexamethyldisiloxane as the internal standard. The dipole moments in dioxane solutions were recorded at 25°C with a Dipol apparatus by the method in [4]. Our experimentally determined dipole moment of 6-nitroquinoxaline (4.08 D) was used for the calculations of the dipole moments by a vectorial scheme; the group moment of the furan ring was assumed to be 0.71 D [5].

6-Nitro-2-(2-furyl)quinoxaline (IV) and 7-Nitro-2-(2-furyl)quinoxaline (V). A 1.24-g (0.01 mole) sample of 2-furylglyoxal [6] was added to a solution of 1.53 g (0.01 mole) of 4-nitro-1,2-diaminobenzene in 20 ml of dioxane or 20 ml of 3 N hydrochloric acid. After 1 h, the precipitated mixture of isomers IV and V was removed by filtration.

Similarly, quinoxalones VIII-XIV were obtained from 2-furylglyoxylic acid [7] or ethyl ester of 5-nitro-2-furylglyoxylic acid [8] and o-phenylenes III and IV (Table 3).

Separation of Isomers VIII and IX. A solution of 1.0 g of copper acetate in 20 ml of alcohol was added to a solution of 1.14 g of the mixtures of isomers obtained in dioxane in 20 ml of DMF, and the precipitated copper complex of 5-hydroxy isomer VIII was removed by filtration. The yield was 0.92 g. Found: C 55.3; H 2.7; N 10.4%. $C_{24}H_{14}CuN_4O_6$. Calculated: C 55.7; H 2.7; N 10.8%. The filtrate was diluted with 50 ml of water, and precipitated isomer IX was removed by filtration. The yield was 0.1 g. A 0.5-g sample of the copper complex was decomposed with 10 ml of concentrated hydrochloric acid, the solution was diluted with water, and the precipitated 5-hydroxyquinoxalone VIII was removed by filtration. The yield was 0.35 g.

6-Nitro-3-(5-nitro-2-furyl)quinoxal-2-one (XIII). This compound was obtained in 38% yield by nitration of 6-nitro-3-(2-furyl)quinoxal-2-one in sulfuric acid by the method in [3].

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EFFECT OF STRUCTURAL FACTORS ON THE REVERSIBLE 1,5-DIKETONE – HYDROXYDIHYDROPYRAN CONVERSION*

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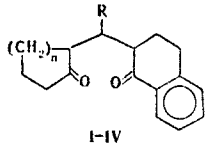
It is shown that δ-bicyclanones with five-membered rings have less of a tendency to undergo conversion to cyclohemiacetals than the analogous compounds with six-membered rings.

The reversible conversion of a 1,5-diketone (A) to a hydroxydihydropyran (B) has been previously established in the case of arylidenedicyclohexanones [2].

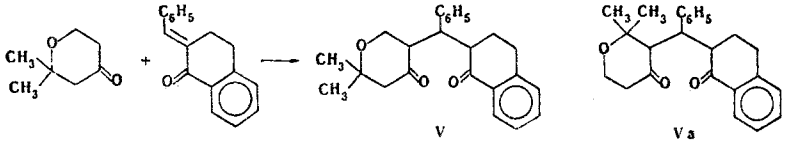
A B

In order to further investigate this conversion we synthesized 1,5-diketones I-VII and examined the forms in which they exist in the solid phase and in solutions and also carried out some reactions with them.

Diketones I and II were synthesized by condensation, respectively, of cyclopentanone and cyclohexanone with 2-dimethylaminomethyl-1-tetralone, and diketones III-V were synthesized by the addition of cyclopentanone, cyclohexanone, and 2,2-dimethyltetrahydro-4-pyrone to benzylidenetetralone.



I-IV



V Va

I R=H, n=1; II R=H, n=2; III R=C_6H_5, n=1; IV R=C_6H_5, n=2

For the synthesis of diketones VI and VII we used the addition of cyclopentanone and cyclohexanone to 2,5-dibenzylidenecyclopentanone. Diketone VI was also obtained by dimerization of 2-benzylidenecyclopentanone under the influence of alkali. Diketone VII was previously described by one of us and Kharchenko [3], and we modified the method for its synthesis only somewhat. The structures of the diketones follow from the method by which they were synthesized and are in agreement with the analytical data. We consider structure Va for the product of addition of dimethyltetrahydropyrone to benzylidenetetralone unlikely, since participation of a sterically hindered methylene group in the Michael reaction is required for its formation.

*Communication XXVIII from the series "Reactions of 1,5-Diketones." See [1] for communication XXVII.

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