REACTION OF 3,4-DIAMINOFURAZAN WITH β-KETO ESTERS

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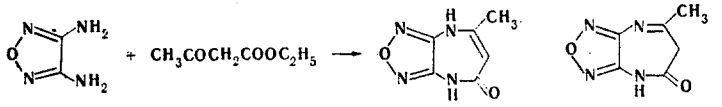
The reaction of some linear and cyclic β-keto esters with 3,4-diaminofurazan was investigated. Products of condensation at the keto group and the corresponding furazanodiazepinones were isolated and characterized. The structures of the compounds obtained are discussed.

In connection with the study of the chemical properties of 3,4-diaminofurazan (I) we investigated its behavior in reactions with β-keto esters. It was found that furazan I reacts under considerably more severe conditions than, for example, o-phenylenediamine [1].

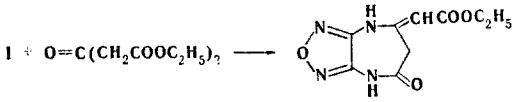
As a result of the reaction of furazan I with acetoacetic ester we obtained 7-methyl-5,8-dihydro-4H-furazano[3,4-b][1,4]diazepin-5-one (II). It is known [1] that diazepinones can exist in two forms — II and III — of which the III form is usually more stable.



I II III

However, analysis of the PMR spectrum of the product provides evidence that the furazanodiazepinone has structure II. The spectrum contains a singlet of CH_3 protons and a singlet of a CH proton (δ 1.82 and 5.11 ppm). Two signals of NH protons (10.07 and 10.44 ppm) are observed in the weak-field region. There are no signals in the region characteristic for the resonance of CH_2 protons (3.62 and 3.93 ppm) [2] of the diazepinone ring (structure III).

The reaction of furazan I with diethyl acetonedicarboxylate leads to a diazepinone for which one can propose enamine structure IV in addition to structures of the II and III type. It has been shown that furazanopyrazinone V has a similar structure [3].



IV

In addition to signals of the protons of an ethyl group (1.16 and 4.11 ppm), singlets of a CH_2 group (3.62 ppm) and a CH group (5.18 ppm) are observed in the PMR spectrum of the furazanodiazepinone; this excludes a structure of the III type, for which signals of two methylene groups should be expected. Signals of NH protons (11.04 and 11.89 ppm) are present in the weak-field region. However, the PMR-spectral data do not make it possible to choose between structures II and IV. The band of the stretching vibrations of the C=O group is found at 1700 cm^{-1} in the IR spectrum of the diazepinone. Such a pronounced shift to the low-frequency region cannot be explained on the basis of a structure of the II type. The decrease in the frequency of the vibrations of the C=O group may occur due to conjugation with the double bond. In the spectrum of V the band of the C=O group is observed at 1711 cm^{-1}. On the basis of this, furazanodiazepinone structure IV seems preferable to a structure of the II type.

The enamino ketone structure of IV and V admits the possibility of the formation of a chelate complex with a hydrogen bond between the ester carbonyl group and the NH proton as in the case of aminocrotonates — structural analogs of IV and V [4]. However, the high frequencies of the vibrations of the C=O group in the IR spectra of IV and V constitute evi-

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TABLE 1. IR and PMR Spectra of 3,4-Diaminofurazan Derivatives

Compound	IR spectrum, ν, cm^{-1}			PMR spectrum, δ, ppm			
	NH_2	NH	C=O	NH_2	NH	CH_3	CH_2
VIIa	3342, 3427	3272	1663	6,02	10,43	1,18	4,11
VIIb	3350, 3410	3285	1653	6,18	9,04	1,13	4,07
VIIc	3350, 3430	3270	1655	6,21	9,15	1,12	4,02
VIII	3345, 3430	3280	1662	6,06	9,09	1,17	4,07

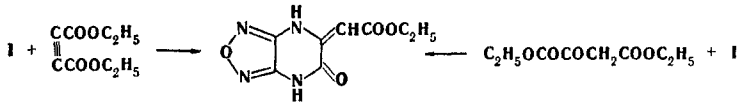
TABLE 2. 3,4-Diaminofurazan Derivatives

Compound	mp, °C*	Found, %			Empirical formula	Calc., %			Yield, %
		C	H	N		C	H	N	
II	231—232	43,7	3,6	33,5	$C_6H_6N_4O_2$	43,4	3,6	33,7	38
IV	145—146	45,1	4,3	22,9	$C_9H_{10}N_4O_4$	45,4	4,2	23,5	77
V	230—232	42,8	3,5	24,8	$C_8H_8N_4O_2$	42,9	3,6	25,0	85
VI	271—273	51,9	4,8	27,4	$C_9H_{10}N_4O_2$	52,4	4,9	27,2	33
VIIa	260—262	49,8	5,2	16,7	$C_{14}H_{18}N_6O_6$	49,7	5,3	16,6	42
VIIb	162—163	50,9	5,8	19,7	$C_{12}H_{16}N_4O_4$	51,4	5,7	20,0	58
VIIc	105—107	53,4	5,9	19,2	$C_{13}H_{18}N_4O_4$	53,1	6,1	19,0	42
VIII	150—151	50,5	5,7	23,3	$C_{10}H_{16}N_4O_3$	50,4	5,9	23,5	76
X	275—277	50,3	4,1	29,0	$C_8H_8N_4O_2$	50,0	4,2	29,2	62

*Compounds II and IV were recrystallized from water; V, VI, VIIa, VIIc, VIII, and X were recrystallized from alcohol; and VIIb was recrystallized from aqueous alcohol.

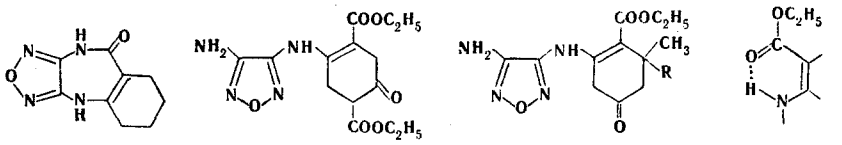
dence that the carbonyl group is free. The inclusion of a nitrogen atom in the ring evidently creates unfavorable steric conditions for the formation of a planar chelate ring [4].

If the starting keto ester contains α- and β-carbethoxy groups, the α-keto ester group undergoes reaction with furazan I to give a furazanopyrazinone. Dihydrofurazanopyrazinone V is formed in the reaction with oxaloacetic ester. Compound V was previously obtained by reaction of furazan I with diethyl acetylenedicarboxylate [3].

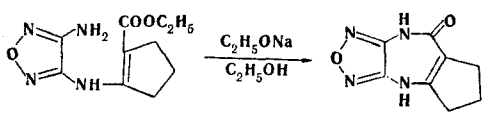


V

We also investigated the reaction of furazan I with some cyclic β-keto esters. The corresponding furazanodiazepinone (VI) was obtained in the reaction with 2-carbethoxycyclohexanone. In addition to signals of protons of methylene groups, signals of two NH protons at 9.37 and 10.61 ppm are observed in the PMR spectrum of VI; this constitutes evidence for the enamine structure of VI. In contrast to this, products of condensation at the carbonyl group were obtained by reaction with substituted carbethoxycyclohexanones and 2-carbethoxycyclopentanone. The IR and PMR spectra of VII and VIII are presented in Table 1.



VI VII a VII b, c IX



VIII X

VII b R = H; c R = CH_3

Compounds VII and VIII exist in the form of a chelate enamino ketone ring (IX) with a hydrogen bond between the NH proton and the ester carbonyl group. In particular, this is indicated by the shift to the weak-field region of the signals of the NH protons in the PMR spectra and the decrease in the stretching vibrations of the C=O group in the IR spectra.

Furazanodiazepinone X was obtained when enamine VII was refluxed in an alcohol solution of sodium ethoxide.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in d_6-DMSO were recorded with a Brucker WH-90 spectrometer (90 MHz) with tetramethylsilane as the internal standard. The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. The compositions of the reaction mixtures and the purity of the products were monitored by thin-layer chromatography (TLC) on Silufol plates.

The characteristics of all of the compounds obtained are presented in Table 2.

7-Methyl-5,8-dihydro-4H-furazano[3,4-b][1,4]diazepinone (II). A solution of 1.0 g (10 mmole) of furazan I and 2.3 g (20 mmole) of acetoacetic ester in 3 ml of acetic acid was refluxed for 8 h, after which it was cooled, and the resulting precipitate was removed by filtration. IR spectrum: 1664 (C=O); 3040, 3170, and 3231 cm^{-1} (NH). According to the TLC data (ether), the mother liquor contains II, starting furazan I, and 3-acetamido-4-aminofurazan.

7-Carbethoxymethylene-5,6,7,8-tetrahydro-4H-furazano[3,4-b][1,4]diazepin-5-one (IV). A solution of 1.0 g (10 mmole) of furazan I and 2.22 g (11 mmole) of diethyl acetonedicarboxylate in 5 ml of acetic acid was refluxed for 6 h, after which the solvent was evaporated. IR spectrum: 1669 (amide C=O); 1700 (ester C=O); 3175 and 3230 cm^{-1} (NH).

Hydrolysis of Diazepinone IV. A solution of 0.48 g (2 mmole) of diazepinone IV in 10 ml of 5% hydrochloric acid was refluxed for 20 min, after which the acid was neutralized with potassium carbonate, and the solution was evaporated. Alcohol (20 ml) was added, and the mixture was heated to the boiling point. The hot solution was filtered, and the alcohol was evaporated from the filtrate. The residue was recrystallized from water to give 0.15 g (75%) of 3,4-diaminofurazan (I).

6-Carbethoxymethylene-4,5,6,7-dihydrofurazano[3,4-b]pyrazin-5-one (V). This compound was obtained by refluxing an acetic acid solution of equimolar amounts of furazan I and oxaloacetic ester and was identified by comparison with a sample obtained by the method in [3].

5,10-Dihydro-4H-cyclohexeno[e]furazano[3,4-b][1,4]diazepin-5-one (VI). This compound was obtained by the procedure used to prepare IV. IR spectrum: 1650 (C=O); 3050, 3149, and 3260 cm^{-1} (NH).

3-(2,5-Dicarbethoxy-4-oxo-1-cyclohexenylamino)-4-aminofurazan (VIIa). A solution of 1.0 g (10 mmole) of furazan I and 2.56 g (10 mmole) of succinylsuccinic ester in 6 ml of acetic acid was refluxed for 3 h, during which a precipitate formed. The precipitate was removed by filtration from the hot reaction mixture.

3-(2-Carbethoxy-3-methyl-5-oxo-1-cyclohexenylamino)-4-aminofurazan (VIIb) and 3-(2-Carbethoxy-3,3-dimethyl-5-oxo-1-cyclohexenylamino)-4-aminofurazan (VIIc). This compound was obtained by the procedure used to prepare VIIa. The product was precipitated from the reaction mixture by the addition of ether.

3-(2-Carbethoxy-1-cyclohexenylamino)-4-aminofurazan (VIII). This compound was synthesized by the method used to prepare VIIa.

5,9-Dihydro-4H-cyclopenteno[e]furazano[3,4-b][1,4]diazepin-5-one (X). A 0.48-g (2 mmole) sample of VIII was refluxed in a solution of sodium ethoxide, obtained from 70 mg of sodium and 3 ml of alcohol, for 20 min, after which 15 ml of water was added, and the solution was neutralized with acetic acid. The precipitate was removed by filtration. IR spectrum: 1645 (C=O); 3130 and 3220 cm^{-1} (NH).

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RESEARCH IN THE CHEMISTRY OF PHENOXAZINES.

XI.* REACTION OF 2-SUBSTITUTED 3-PHENOXAZINONES WITH AMINES

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The 2 position of the quinoid ring undergoes nucleophilic substitution in the reaction of 2-acetoxy- and 2-ethoxy-3-phenoxazinones with amines. In the case of 2- and 7-substituted derivatives of 3-phenoxazinone, replacement of a hydrogen atom or groups in the electrophilic center of the quinoid ring proceeds more readily than attack by the nucleophile on the 7 position in the benzo ring.

It is known [2] that nucleophilic substitution in benzo[a]-9-phenoxazinone takes place in the para position relative to the nitrogen atom in the naphthalene fragment. At the same time, our research has shown that 3-phenoxazinone has two electrophilic centers — the para position relative to the nitrogen atom in the benzenoid portion and the 2 position in the quinoneimine portion of the molecule [3].

Nucleophilic substitution of hydrogen (subsequently designated as S_NH [4]) primarily occurs in the 2 position of the quinoid ring in the reaction of nucleophiles with 3-phenoxazinone derivatives with substituents in the electrophilic center of the benzene ring (the 7 position). Strongly nucleophilic amines are capable of displacing a substituent in the 7 position [5]. This indicates that the S_NH reaction takes place more readily in the 2 position than substitution in the 7 position.

In order to draw some conclusion as to which positions are more reactive with respect to nucleophiles in both S_NH and S_N reactions, in the present research we investigated nucleophilic substitution reactions in the case of 3-phenoxazinone derivatives with substituents in the electrophilic center of the quinoid ring.

2-Hydroxy-3-phenoxazinone (I) [6], which displays weak acidic properties (its pK_a is 6.48 [7]), behaves specifically with amines. It was demonstrated by spectroscopy that I gives only unstable complexes on reaction with amines. An absorption maximum at 505 nm, which corresponds to the 2-hydroxy-3-phenoxazinone anion, obtained by dissolving the sodium salt of I, appears in the electronic absorption spectrum of an alcohol solution of a mixture of I with morpholine. This indicates the saltlike character of complexes of 2-hydroxy-3-phenoxazinone with amines. The formation of an anion naturally hinders S_N reaction of I with amines.

The reaction of 2-acetoxy- (II) [8] and 2-ethoxy-3-phenoxazinones (III) with amines proceeds in a different manner. The result of the reaction of 2-acetoxy-3-phenoxazinone with amines depends markedly on the nucleophilicity of the latter. Replacement of the acetoxy group to give 2-arylamino-3-phenoxazinones (IV-V) occurs in the reaction of II with arylamines. The rate of the competitive deacetylation of 2-acetoxy-3-phenoxazinone, which leads to hydroxy compound I, increases as the nucleophilicity of the arylamine increases, and the yield of the substitution product decreases (Table 1). Thus only 2-hydroxy-3-phenoxazinone is formed in the reaction of II with p-toluidine (pK_a 5.12). Similarly, hydroxy compound I is also formed in the reaction of 2-acetoxy-3-phenoxazinone with N-methylaniline and cycloalkylimines.

*See [1] for communication X.

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