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Nucleophilic Transformations of Heterocyclic Derivatives of 4-Heteryl-2,4-dioxobutanoic Acids*

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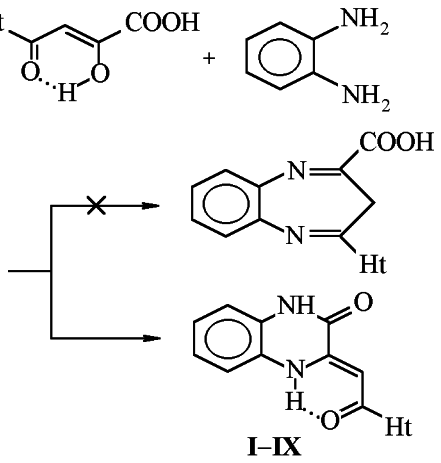
Abstract—Proceeding from 4-heteryl-2,4-dioxobutanoic acids were prepared (*Z*)-3-heteroylmethylene-1,2,3,4-tetrahydro-2-quinoxalones that when treated with oxalyl chloride afforded 3-heteroyl-1,2,4,5-tetrahydropyrrolo[1,2-*a*]quinoxaline-1,2,4-triones. The latter took in reactions with o-aminophenol and *o*-phenylenediamine two different directions.

Heteroylpyruvic acids as well as acylpyruvic acids are convenient models for reactivity studies in β-dicarbonyl compounds, for investigation of their reactions with binucleophilic reagents and for preparation of various heterocyclic polycarbonyl compounds and fused heterocyclic systems.

The target of this study was investigation of reactions between 4-heteryl-2,4-dioxobutanoic acids and *o*-phenylenediamine, synthesis of 3-heteroyl-1,2,4,5-tetrahydropyrrolo[1,2-*a*]quinoxaline-1,2,4-triones, and carrying out reactions of the latter with such nucleophilic reagents as *o*-aminophenol and *o*-phenylenediamine.

(*Z*)-3-Heteroyl-1,2,3,4-tetrahydro-2-quinoxalones (**I**–**IX**) were prepared by heating in DMSO of equimolar quantities of 4-heteryl-2,4-dioxobutanoic acids and o-phenylenediamine. α-Dicarbonyl compounds with *o*-phenylenediamine furnish derivatives of 2(1*H*)-quinoxalones [1, 2] whereas the condensation with *o*-phenylenediamine of β-dicarbonyl compounds yields 3*H*-1,5-benzodiazepines [3, 4, 5]. The presence in the structure of heteroylpyruvic acids of both α- and β-dicarbonyl groups suggests that in reaction with *o*-phenylenediamine both derivatives of quinoxalones and benzodiazepines may be expected. However in reactions with heteroylpyruvic acids same as with aroylpyruvic acids were separated exclusively 2-quinoxalone derivatives [1, 2].

Compounds **I**–**IX** are yellow or orange crystalline substances, sparingly soluble in the common organic solvents. Yields, melting points, and elemental analyses of the compounds synthesized are given in Table 1. Their structure is confirmed by spectral data (Table 2).



I–**IX**

Ht = 2-furyl (**I**), S-Me-2-furyl (**II**), 4-Me-1,3-oxazol-5-yl (**III**), 2,4-Me_2-1,3-oxazol-5-yl (**IV**), 2-thienyl (**V**), 4-Me-5-Ph-2-thienyl (**VI**), 3-Me-5-Ph-2-thienyl (**VII**), 1,3-thiazol-2-yl (**VIII**), 2,4-Me_2-1,3-thiazol-5-yl (**IX**).

In the IR spectra of quinoxalones **I**–**IX** appear the absorption band of the stretching vibrations of keto group in the region 1600–1610 cm^{-1} and amide carbonyl in the region 1670–1680 cm^{-1}. Broad absorption bands in the region 3140–3200 cm^{-1} are due to the NH groups of the quinoxalone ring.

In the ^1H NMR spectra of compounds **I**–**IX** alongside the signals of aromatic protons and protons of the heterocyclic ring (7.07–7.48 ppm) is observed a singlet of the methylene protons (6.26–6.66 ppm),

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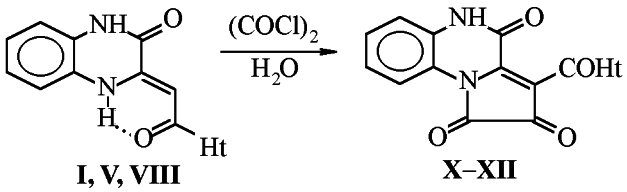
Table 1. Yields, melting points, and elemental analyses of compounds **I**–**XVIII**

Compd. no.	Yield, %	mp, °C	Found, %				Formula	Calculated, %			
			C	H	N	S		C	H	N	S
I	72	294–296	66.45	4.19	10.83		$C_{14}H_{10}N_2O_3$	66.14	3.96	11.02	
II	71	281–282	67.38	4.74	10.65		$C_{15}H_{12}NO_3$	67.16	4.51	10.44	
III	70	313–315	62.37	4.58	15.21		$C_{14}H_{11}N_3O_3$	62.25	4.12	15.61	
IV	78	320–321	63.79	4.82	14.53		$C_{15}H_{13}N_3O_3$	63.60	4.63	14.83	
V	83	275–276	65.15	3.71	10.47	12.00	$C_{14}H_{10}N_2O_2S$	65.10	3.90	10.85	12.41
VI	65	292–294	70.13	4.80	7.43	8.98	$C_{21}H_{16}N_2O_2S$	69.98	4.47	7.77	8.89
VII	69	309–311	69.59	4.65	7.34	8.61	$C_{21}H_{16}N_2O_2S$	69.98	4.47	7.77	8.89
VIII	75	292–293	57.23	3.72	15.65	12.04	$C_{13}H_9N_3O_2S$	57.55	3.34	15.49	11.82
IX	82	300–302	60.44	4.59	14.37	11.01	$C_{15}H_{13}N_3O_2S$	60.19	4.38	14.08	10.71
X	85	226–227 (decomp.)	62.05	2.88	9.37		$C_{16}H_8N_2O_5$	62.34	2.62	9.09	
XI	93	283–285 (decomp.)	59.62	2.55	8.81	9.99	$C_{16}H_8N_2O_4S$	59.26	2.49	8.64	9.87
XII	82	186–187 (decomp.)	55.11	2.50	13.23	10.13	$C_{15}H_7N_3O_4S$	55.38	2.17	12.92	9.86
XIII	74	217–219	65.56	4.10	10.74		$C_{22}H_{15}N_3O_5$	65.83	3.77	10.47	
XIV	81	174–176	63.32	3.85	10.44	7.27	$C_{22}H_{15}N_3O_4S$	63.30	3.62	10.07	7.68
XV	73	205–207	60.51	3.67	13.71	7.78	$C_{21}H_{14}N_4O_4S$	60.28	3.37	13.39	7.66
XVI	70	>320	66.72	3.92	14.51		$C_{22}H_{14}N_4O_4$	66.33	3.54	14.09	
XVII	78	>320	63.48	4.55	13.09	7.53	$C_{22}H_{14}N_4O_3S$	63.76	4.06	13.52	7.74
XVIII	80	312–314	60.47	3.63	16.74	7.98	$C_{21}H_{13}N_5O_3S$	60.72	3.15	16.86	7.72

peak of the amide proton (11.89–12.02 ppm), and the proton of enaminoketone NH group (13.20–13.40 ppm).

The reaction of quinoxalones **I, V, VIII** with oxalyl chloride at boiling in anhydrous chloroform at 60–63°C for 2–2.5 h afforded in virtually quantitative yield 3-heteroyl-1,2,4,5-tetrahydropyrrolo[1,2-*a*]-quinoxaline-1,2,4-triones (**X**–**XII**) similarly to the previously described reaction for 3-aroyl-1,2,3,4-tetrahydro[1,2-a]quinoxaline-1,2,4-triones [6].



I, V, VIII **X–XII**

Ht = 2-furyl (**X**), 2-thienyl (**XI**), 1,3-thiazol-5-yl (**XII**).

Pyrroloquinoxalinetriones **X**–**XII** are dark violet crystal compounds that decompose at melting and are sparingly soluble in the common organic solvents. Yields, melting points, and elemental analyses of compounds **X**–**XII** are listed in Table 1.

In the IR spectra of pyrroloquinoxalinetriones **X**–**XII** are present bands of the stretching vibrations of lactam group $C^1{=}O$ in the region 1740–1770 cm^{-1}, of keto group $C^2{=}O$ in the region 1720–1730 cm^{-1}, of amide group $C^4{=}O$ at 1680–1690 cm^{-1}, of heteroyl carbonyl at 1640–1660 cm^{-1}, and of amide group N^5H in the region 3100–3220 cm^{-1}.

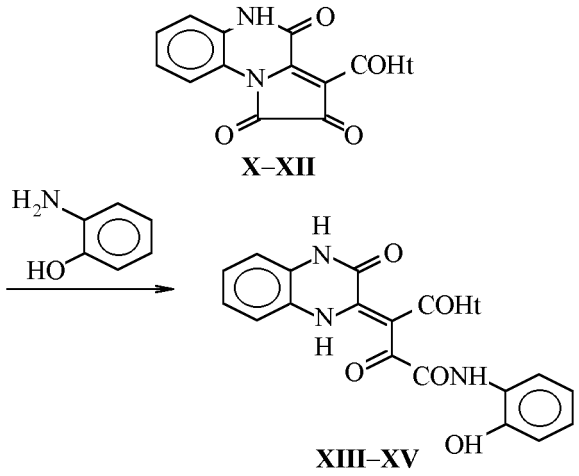
In the ^1H NMR spectra of compounds **X**–**XII** unlike the spectra of the original quinoxalones are lacking the signals of CH proton from vinyl group and NH proton from enaminoketone group. In the spectra appear the signals from aromatic and heteroaromatic protons (7.34–7.57 ppm) and a singlet from N^5H group at 10.74–10.84 ppm. The spectral characteristics observed (Table 2) are consistent with the published data for the known monocyclic 2,3-dihydro-2,3-pyrrolediones [7] and heterocyclic analogs thereof [6, 8].

In the molecules of 4-heteroyl-2,3-dihydro-2,3-pyrrolediones fused with azaheterocycles by the [*a*] side are present several approximately equivalent electron-deficient carbons in positions *2*, *3*, *5* of the

dihydropyrroledione ring providing a possibility of formation in reactions with bifunctional nucleophiles of versatile heterocyclic systems.

Pyrroloquinoxalinetriones **X–XII** react with *o*-aminophenol at short heating to afford *N*-*o*-hydroxyphenylamides of 4-heteryl-2,4-dioxo-(*Z*)-3-(2-oxo-1,2,3,4-tetrahydro-3-quinoxalinylidene)butanoic acids (**XIII–XV**).

Compounds **XIII–XV** are yellow or orange high-melting crystalline substances, sparingly soluble in the common organic solvents. Yields, melting points, and elemental analyses of the compounds synthesized are given in Table 1. Their structure is confirmed by spectral data (Table 2).



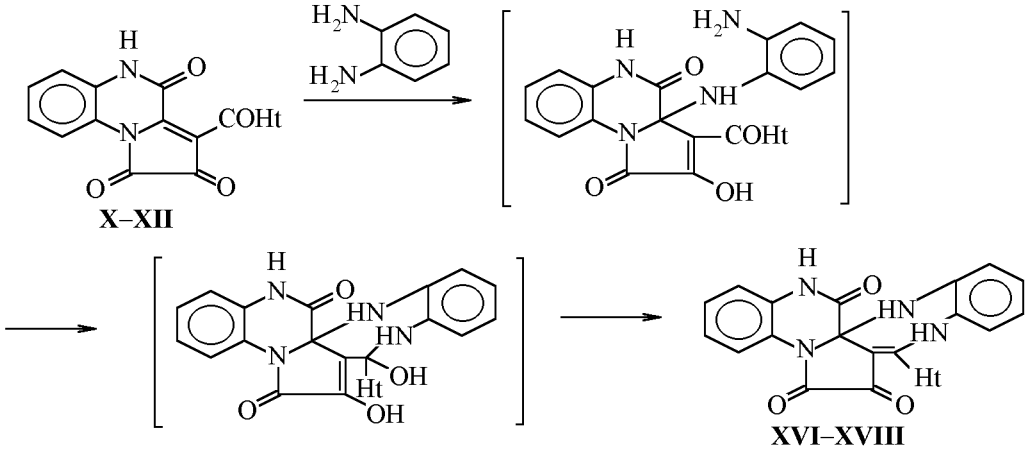
Ht = 2-furyl (**XIII**), 2-thienyl (**XIV**), 1,3-thiazol-5-yl (**XV**).

In the IR spectra of arylamides **XIII–XV** are present absorption bands of stretching vibrations of amide group NH and phenol OH group in the region 3120–3200 cm^{-1}, of group N^4H in heterocycle involved in an intramolecular hydrogen bond of H-chelate type as a broad band in the region 2995–3080 cm^{-1}, and of amide carbonyls in the heterocycle and side chain (1670–1680 cm^{-1}), heteroyl carbonyl (1640 cm^{-1}), of carbonyl group taking part in the intramolecular hydrogen bond of H-chelate type (1580–1610 cm^{-1}).

In the ^1H NMR spectra of compounds **XII–XV** are observed the following signals: a group of peaks belonging to aromatic and heteroaromatic protons in the region 7.14–7.42 ppm, a singlet from the amide proton of the side chain (7.91–9.18 ppm), and singlets from NH groups (7.91–9.18 ppm) and N^4H (12.57–12.64 ppm) of the quinoxalone ring. Compounds **XIII–XV** arise apparently as a result of the initial attack of amino group from o-aminophenol on the carbon in *2*-position of the dihydropyrroledione fragment (on atom C^1 of compounds **XIII–XV**) followed by cycle opening at the C^1–N^{10} bond.

The spectral characteristics of compounds **XIII–XV** are well consistent with the spectra of substituted amides of 3-aminomethylene-4-aryl-2,4-dioxobutanoic acids [9, 10] and of arylamides of (*Z*)-4-aryl-2,4-dioxo-3-(2-oxo-1,2,3,4-tetrahydro-3-quinoxalinylidene)butanoic acids [11]. Therefore compounds **XIII–XV** exist in a form with exo-position of the double bond as is characteristic of 3-acylmethylene-1,2,3,4-tetrahydro-2-quinoxalones [12], and contain an intramolecular hydrogen bond of H-chelate type between NH group of the heterocycle and ketone carbonyl in the side chain, i.e they take form of *Z*-isomers as is also characteristic of the above-mentioned amides and quinoxalones.

3-Heteroylpyrroloquinoxalinetriones **X–XII** react with *o*-phenylenediamine at short boiling in anhydrous dioxane yielding 8-heteryl-6,7,9,14,15,16-



Ht = 2-furyl (**XVI**), 2-thienyl (**XVII**), 1,3-oxazol-5-yl (**XVIII**).

Table 2. Spectral characteristics of compounds **I**–**XVIII**

Compd. no.	IR spectrum, ν, cm^{-1}	^1H NMR spectrum, δ, ppm
I	1600, 1680, 3150, 3200	6.57 s (1H, =CH), 7.48 m (4H arom + 3H thienyl), 11.94 c (1H, NHCO), 13.40 s (1H, N^4H)
II	1610, 1680, 3140, 3160	2.43 s (3H, CH_3), 6.26 d (1H, C^4H furyl), 6.52 s (1H, =CH), 7.07 m (4H arom + 1H, C^3H furyl), 12.02 s (1H, NHCO), 13.15 s (1H, N^4H)
III	1600, 1690, 3140	6.50 c (1H, =CH), 7.18 m (4H arom + 1H furazolyl), 11.94 s(1H, NHCO), 13.21 c (N^4H), 2.43 s (3H, CH_3)
IV	1600, 1670, 3140, 3180	2.48 d (6H, $2CH_3$), 6.52 s (1H, =CH), 7.14 m (4H arom), 11.95 s (1H, NHCO), 13.29 c (1H, N^4H)
V	1610, 1670, 3150	6.66 s (1H, =CH), 7.48 m (4H arom + 3H thienyl), 11.94 s (1H, NHCO), 13.24 s (1H, N^4H)
VI	1610, 1680, 3150, 3200	2.47 s (3H, CH_3), 6.52 s (1H, =CH), 7.45 m (9H arom + 1H thienyl), 12.02 s (1H, NHCO), 13.20 s (1H, N^4H)
VII	1600, 1680, 3150	2.60 s (3H, CH_3), 6.54 s (1H, =CH), 7.41 m (9H arom + 1H thienyl), 11.94 s (1H, NHCO), 13.30 s (1H, N^4H)
VIII	1600, 1680, 3150	6.32 s (1H, =CH), 7.38 m (4H arom + 2H thienyl), 11.92 s (1H, NHCO), 13.25 s (1H, N^4H)
IX	1600, 1680, 3150	2.60 d (6H, $2CH_3$), 6.32 s (1H, =CH), 7.25 m (4H arom), 12.00 s (1H, NHCO), 13.21 s (1H, N^4H)
X	1650, 1680, 1730, 1770, 3150	7.34 m (4H arom + 3H furyl), 10.76 s (1H, NHCO)
XI	1640, 1680, 1710, 1740, 3220	7.57 m (4H arom + 3H thienyl), 10.77 s (1H, NHCO)
XII	1660, 1690, 1720, 1750, 3100	7.53 m (4H arom + 2H thiazolyl), 10.84 s (1H, NHCO)
XIII	1610, 1640, 1680, 1700, 3070, 3200	7.42 m (8H arom + 3H furyl), 9.18 s (1H, NHCO), 12.21 s (1H, NHCO), 12.64 (1H, N^4H)
XIV	1610, 1640, 1680, 1700, 2900, 3120	6.60 t (1H, C^4H thienyl), 7.15 m (8H arom + 2H thienyl), 7.89 s (1H, NHCO), 11.99 c (1H, NHCO), 12.57 s (1H, N^4H)
XV	1610, 1640, 1680, 1700, 3070, 3180	6.62 d (1H, C^5H thiazolyl), 7.14 m (8H arom + 1H, C^3H thiazolyl), 7.91 s (1H, NHCO), 11.92 s (1H, NHCO), 12.60 s (1H, N^4H)
XVI	1670, 1680, 3130, 3300	6.71 t (1H, C^4H furyl), 7.21 m (8H arom + 2H furyl), 7.80 s (1H, $N^{14}H$), 11.88 s (1H, NHCO), 12.64 s (1H, N^9H)
XVII	1660, 1680, 3210, 3350	7.38 m (8H arom + 3H thienyl), 7.74 s (1H, $N^{14}H$), 11.90 s (1H, NHCO), 12.58 s (1H, N^9H)
XVIII	1650, 1670, 3130, 3180	7.48 m (8H arom + 2H thiazolyl), 7.76 s (1H, $N^{14}H$), 11.91 s (1H, NHCO), 12.60 s (1H, N^9H)

hexahydroquinoxalino[1,2-a]pyrrolo[2,3-b][1,5]benzodiazepine-6,7,15-triones (**XVI**–**XVIII**).

Compounds **XVI**–**XVIII** are bright-red high-melting crystalline substances, sparingly soluble in the common organic solvents. They do not show positive reaction on enol hydroxyl with the alcoholic solution of iron(III) chloride (Table 1).

The IR spectra of compounds **XVI**–**XVIII** (Table 2) contain absorption bands of stretching vibrations of NH groups as two broad bands in the region 3130–3400 cm^{-1}, of lactam group $C^6=O$ at 1670–1680 cm^{-1}, of keto and amide carbonyl groups in the region 1650–1670 cm^{-1}.

In the ^1H NMR spectra of compounds **XVI**–**XVIII** (Table 2) appear proton signals from aromatic and heteroaromatic substituent (7.21–7.48 ppm), a singlet from amino group proton $N^{14}H$ (7.74–7.80 ppm), a singlet from amido group proton $N^{16}H$ (11.88–11.91 ppm), and a singlet from enamine group proton N^9H (12.58–12.64 ppm).

Compounds **XVI**–**XVIII** arise presumably as a result of primary attack of o-phenylenediamine on

carbon atom C^{3a} in the pyrroloquinoxalinetrione molecule followed by attack of the second amino group of the reagent on the carbonyl group of the heteroyl moiety and by closure of the benzodiazepine ring.

Compounds **I–IX** were tested for antimicrobial activity on standard strains *E. Coli* M17 and *St.aureus* P-209 and for antiphlogistic activity with negative result. Compounds **X–XII** tested for analgetic activity showed weak effect.

EXPERIMENTAL

IR spectra were recorded on spectrophotometer UR-20 from mulls in mineral oil. ^{1}H NMR spectra were registered on spectrometer Tesla 487 BS (80 MHz), internal reference HMDS. The reaction progress was monitored and the purity of products was checked by TLC on Silufol UV-254 plates, eluent ether–benzene (3 : 2), development in iodine vapor.

(*Z*)-3-Heteroyl-1,2,3,4-tetrahydro-2-quinoxalones (I–IX). To a solution of 5 mmol of 4-heteryl-2,4-dioxobutanoic acid in 20 ml of DMSO was added 5 mmol of *o*-phenylenediamine in 5 ml of DMSO, the mixture was heated for 5–10 min, cooled, the precipitate was filtered off and recrystallized from DMSO.

3-Heteroyl-1,2,4,5-tetrahydropyrrolo[1,2-a]-quinoxaline-1,2,4-triones (X–XII). A solution of 3 mmol of quinoxalone **I, V, VIII** and 3 mmol of oxalyl chloride in 50 ml of anhydrous dichloroethane was boiled for 2–2.5 h, cooled, the precipitate was filtered off.

4-Heteryl-2,4-dioxo-(*Z*)-3-(2-oxo-1,2,3,4-tetrahydro-3-quinoxalinylidene)butanoic acids *N*-*o*-hydroxyphenylamides (XIII–XV). To a solution of 5 mmol of heteroylpyrroloquinoxalinetrione **X–XII** in 30 ml of anhydrous dioxane was added 5 mmol of *o*-aminophenol in 20 ml of anhydrous dioxane. In 10 min the separated precipitate was filtered off and recrystallized from DMSO.

8-Heteryl-6,7,9,14,15,16-hexahydroquinoxalino-[1,2-*a*]pyrrolo[2,3-b][1,5]benzodiazepine-6,7,15-triones (XVI–XVIII). To a solution of 5 mmol of heteroylpyrroloquinoxalinetrione in 30 ml of anhydrous dioxane was added 5 mmol of *o*-phenylenediamine in 20 ml of anhydrous dioxane, and the mixture was boiled for 3–5 min. On cooling the separated precipitate was filtered off and recrystallized from DMSO.

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