STRUCTURE OF REACTION PRODUCTS OF SOME SUBSTITUTED QUINOXALINE *N*-OXIDES WITH CARBANIONS*

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1,2,3-Triazolo[1,5-*a*]- (*II*) and 1,2,4-triazolo[4,3-*a*]quinoxaline 5-oxide (*III*) react with the carbanions of β-diketones and β-keto esters to give enaminones in the same way as their tetrazolo analogue. The difference in mechanism of reactions of these *N*-oxides with carbanions of 3-alkylpentane-2,4-dione and ethyl methyl acetoacetate giving aziridinopolyazoloquinoxalines and ethyl 2-(polyazoloquinoxalin-4-yl)propanoates, respectively, is discussed. It was shown that the reaction with carbanion including the aziridine ring closure proceeds with 3,4-dihydro-3-oxoquinoxaline-1-oxide as well.

The products of a novel reaction of tetrazolo[1,5-*a*]quinoxaline 5-oxide (*I*) with pentane-2,4-dione and ethyl acetoacetate in presence of piperidine were described in the previous paper[1]. These reactions were shown to proceed via 1,3-cycloaddition of a carbanion[1,2] to the carbon atom in position 4 and *N*-oxide oxygen via isoxazolidine intermediate, which after deacylation gives enaminones. Reactions with 3-alkylpentane-2,4-dione under similar conditions result in formation of aziridinotetrazoloquinoxalines. In this paper, products of reactions of 1,2,3-triazolo[1,5-*a*]- (*II*) (ref.[3]) and 1,2,4-triazolo[4,3-*a*]quinoxaline 5-oxide (*III*) (ref.[3]) with carbanions of the above mentioned *C*-acids and ethyl methyl acetoacetate are described.

We presumed that *N*-oxides *II* and *III* would react with carbanions in a similar way. The reaction of *N*-oxide *II* with pentane-2,4-dione in ethanol solution in the presence of piperidine gave 4-acetylmethylene-4,5-dihydrotriazolo[1,5-*a*]quinoxaline (*IV*), with ethyl acetoacetate 4-ethoxycarbonylmethylene-4,5-dihydrotriazolo[1,5-*a*]quinoxaline (*V*) whose enamine structure was verified by means of IR and NMR spectroscopy

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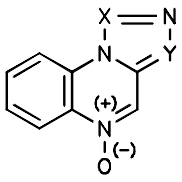
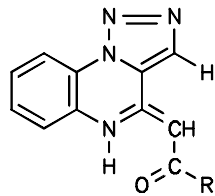
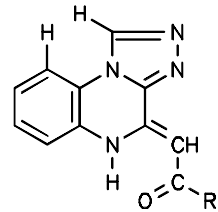
(presence of NH group and values of carbonyl frequency). Under similar conditions the *N*-oxide *III* gave triazolo analogues, namely 4-acetylmethylene- (*VI*) and 4-ethoxycarbonylmethylene-4,5-dihydrotriazolo[4,3-*a*]quinoxaline (*VII*) in lower yields than the *N*-oxide *II*. The use of ethyl benzoylacetate did not change the yield of enamino ester *VII* significantly. The yields of enamino esters *V* and *VII* were higher than those of enamino ketones *IV* and *VI* as a result of higher basicity of the conjugate base ethyl aceto- (or benzoyl)acetate compared with pentane-2,4-dione.







I, X = Y = N
II, X = N, Y = CH
III, X = CH, Y = N

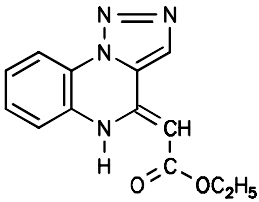
IV, R = CH_3
V, R = OC_2H_5

VI, R = CH_3
VII, R = OC_2H_5

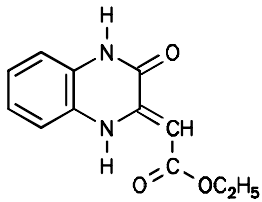
Whilst the compounds *IV* and *VI* show only enamino ketone tautomeric form, according to ^{1}H NMR spectra in $(CD_3)_2SO$ the stabilities of enamino esters *V* and *VII* are not equal and differ from tetrazolo analogue *VIII* (ref.[1]) and 2-ethoxycarbonylmethylene-3-oxo-1,2,3,4-tetrahydroquinoxaline (*IX*) (ref.[4]).

The lowering portion of enamino ester tautomer in the order *VIII* (ref.[1]; 96%) > *VII* (77%) > *IX* (ref.[4]; 63%) > *V* (50%) does not correspond to the lowering number of nitrogen heteroatoms and resonance energy as was found for 1-acylazoles[5]. Therefore, the enaminones *IV* – *VII* cannot be considered to be vinylogues of 1-acylazoles. The lower stability of the enamino ester *V* can be probably explained as a result of repulsive forces of hydrogen atom in position 3 and that on the α-carbon atom of enamino ester group lowering its complanarity with heteroaromatic rings. This interpretation agrees with higher value of carbonyl frequency (Table I). Interaction of hydrogen atoms in positions 1 and 9 of the triazolo derivative *VII* acts in a lesser extent.

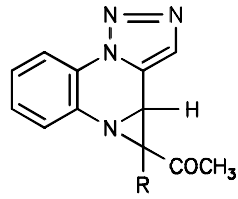
The reactivities of *N*-oxides *II* and *III* were verified by experiments where they reacted with 3-alkylpentane-2,4-dione in the presence of a base in boiling ethanol. *N*-oxide *II* gave 4-acetyl-4-methyl- (*X*) and 4-acetyl-4-ethyl-3*b*,4-dihydroazirino[1,2-*a*]-triazolo[5,1-*c*]quinoxaline (*XI*) by reactions with 3-methyl- and 3-ethylpentane-2,4-dione. We prepared 4-acetyl-4-methyl- (*XII*), 4-acetyl-4-ethyl- (*XIII*) and 4-acetyl-4-propyl-3*b*,4-dihydroazirino[1,2-*a*]triazolo[3,4-*c*]quinoxaline (*XIV*) from *N*-oxide *III* by the reactions with 3-methyl-, 3-ethyl- or 3-propylpentane-2,4-dione, respectively. Using triethylamine as a base in order to synthesize tetracyclic triazolo derivatives, the



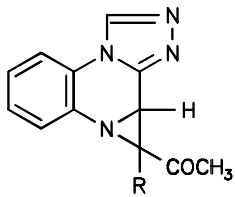
VIII



IX



X, R = CH_3
XI, R = C_2H_5



XII, R = CH_3
XIII, R = C_2H_5
XIV, R = C_3H_7

TABLE I
IR (ν_{CO}, cm^{-1}), NMR (δ, ppm) and UV spectra of enamino ketones and enamino esters *IV* – *VII*

Compound	IR[a]	^{1}H NMR[b]						UV	
		NH	CH	CHCO	CH_2CO	OCH_2	CH_3	λ_{max}	log ε
IV	1 640	12.51	8.52	6.03	–	–	2.12	390	4.65
V	1 665	11.25	8.61	5.30	–	4.57	1.25	361	4.35
		[c]	8.51		4.01	4.25	1.05		
VI	1 641	13.15	9.85	6.36	–	–	2.27	395	4.64
VII[d]	1 655	11.16	10.10	5.75	–	4.22	1.32	356	4.25
		[c]	10.25		4.36	4.20	1.24		

[a] Measured in chloroform; strong band. [b] Measured in $(CD_3)_2SO$. [c] Imine tautomer. [d] ^{13}C NMR spectrum: 196.6 (CO); 147.2, 138.8, 127.6, 120.4 (4 × C_q); 138.9, 128.2, 123.7, 119.8, 116.7, 91.2 (6 × CH); 29.3 (CH_3).

satisfactory yields were reached but, nevertheless, they were lower than those for triazolo derivative *X* and tetrazolo analogues[1]. The difference is obvious from the higher yield of derivative *XI* using piperidine as a stronger base (see Table II).

In our experiments we attempted to prepared tetrazolo analogues[1] of tetracycles *X* and *XII* carrying ethoxycarbonyl group instead of acetyl one. However, by reaction of *N*-oxide *I* with ethyl methylacetoacetate in the presence of a base we obtained the product whose ^{1}H NMR spectrum in $(CD_3)_2SO$ showed at δ 12.38 ppm a signal of NH group which eliminates an isomer with aziridine ring. Abundance of enamine tautomer is only ca 15%, the prevailing imine is ethyl 2-(tetrazolo[1,5-*a*]quinoxalin-4-yl)propanoate (*XV*).

XV, X = Y = N
XVI, X = N, Y = CH
XVII, X = CH, Y = N

Ethyl 2-(1,2,3-triazolo[1,5-*a*]quinoxalin-4-yl)- (*XVI*) and ethyl 2-(1,2,4-triazolo[4,3-*a*]-quinoxalin-4-yl)propanoate (*XVII*) were prepared in a similar way from *N*-oxides *II* and *III*, respectively. IR spectrum of the ester *XVII* exhibits carbonyl band at 1 715 cm^{-1} and an diffuse band of NH group with the maximum at 3 260 cm^{-1} that gives an evidence of enamino ester form. High value of wavenumber of ν(C=O) band eliminates (*Z*)-*s*-*cis* conformer of the coplanar enamino ester group with intramolecular hydrogen bond similar to that of enamino esters *V* and *VII* (1 668, 1 657 cm^{-1}). An intensive band with wavenumber 1 612 cm^{-1} can be assigned to the mode υ(C=O) + δ(NH) according to the analogy with other enamino esters[6]. According to ^{1}H and ^{13}C NMR spectra (see Experimental) the derivatives *XVI* and *XVII* exist in enamino ester form, too. However, the spectrum of *XVII* in hexadeuteriodimethyl sulfoxide shows the imine tautomeric form, which is obviously more stable because of the steric hindrance of coplanarity of the enamino ester group due to the presence of the alkyl group at the α-carbon atom.

Spectral data for tetracycles *X* – *XIV* are given in the Table III. The band assignment to C–H valence and out of plane deformation vibrations was verified by means of comparison of IR spectra of some model compounds (*N*-oxide *III*, 3-chloroquinoxaline-1-oxide) with spectra of their deoxygenated derivatives. Presence of an oxygen atom in position 5 (*N*-oxides *II*, *III*) has a little influence on C–H valence vibration (ca +10 cm^{-1}), but it acts more strongly on the deformation mode (ca –20 cm^{-1}), expecially in

TABLE II

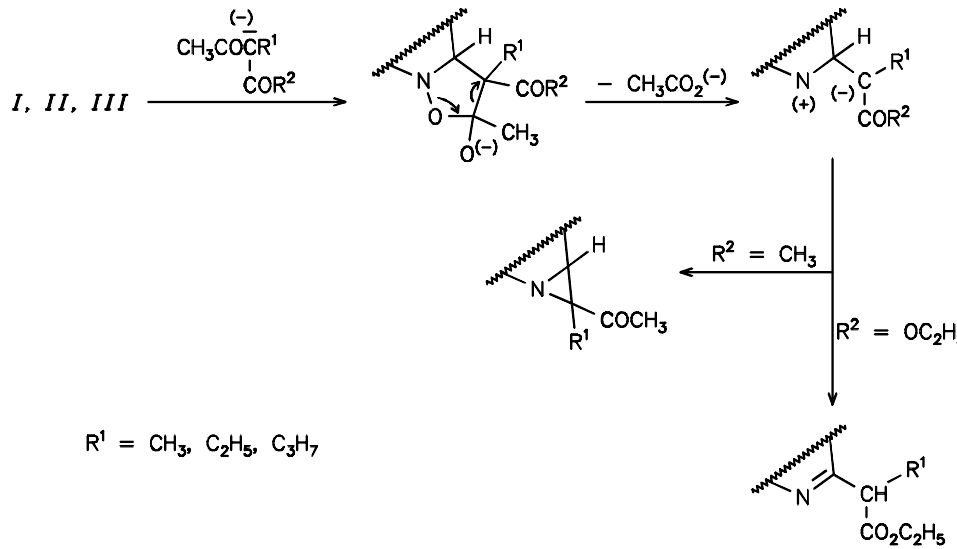
Yields, melting points and analytical data of enamino ketones and enamino esters *IV – VII*, aziridinoquinoxalines *X – XIV* and *XX*, and esters *XV – XVII*

Compound	Yield %	M.p. °C	Formula M.w.	Calculated/Found		
				% C	% H	% N
IV	20	181 – 183	$C_{12}H_{10}N_4O$	63.70	4.46	24.77
			226.2	63.92	4.62	24.67
V	79	158 – 159	$C_{13}H_{12}N_4O_2$	60.95	4.72	21.87
			256.3	60.86	4.74	21.95
VI	13	268 – 269	$C_{12}H_{10}N_4O$	63.70	4.46	24.77
			226.2	63.81	4.64	24.95
VII	41	178 – 180	$C_{13}H_{12}N_4O_2$	60.95	4.72	21.87
			256.3	61.10	5.01	22.02
X	81	144 – 145	$C_{13}H_{12}N_4O$	64.98	5.03	23.32
			240.3	64.80	5.13	23.28
XI	18	122 – 123	$C_{14}H_{14}N_4O$	66.12	5.55	22.04
	8[a]		254.3	66.28	5.75	21.90
XII	13[a]	195 – 197	$C_{13}H_{12}N_4O$	64.98	5.03	23.32
			240.3	64.91	5.31	23.16
XIII	22	193 – 195	$C_{14}H_{14}N_4O$	66.12	5.55	22.04
	0.3[a]		254.3	66.33	5.79	22.30
XIV	17[a]	174 – 176	$C_{15}H_{16}N_4O$	67.14	6.01	20.88
			268.5	66.97	6.12	20.74
XV	11	137 – 138	$C_{13}H_{13}N_5O_2$	57.56	4.83	25.82
			271.3	57.31	5.01	25.61
XVI	18	145 – 146	$C_{14}H_{14}N_4O_2$	62.21	5.22	20.73
			270.3	62.01	5.41	21.01
XVII	7	156 – 158	$C_{14}H_{14}N_4O_2$	62.21	5.22	20.73
			270.3	62.41	5.10	20.60
XX	21	141 – 142	$C_{13}H_{14}N_2O_2$	67.81	6.13	12.17
			230.3	67.69	6.31	12.21

[a] Triethylamine as the base was used.

the α-position (+30 cm^{-1}, 3-chloroquinoxaline-1-oxide). Therefore, *N*-oxide group acts as an electron donor for the α-position, and as a week electron acceptor for the other C–H groups in the compounds under study.

While the carbanions of 3-alkylpentane-2,4-dione give with *N*-oxides *I – III* aziridinopolyazoloquinoxalines *X – XIV* and their tetrazolo analogues[1], the intermediates of the reaction with carbanion of ethyl methyl acetatoacetate do not cyclize with formation of aziridino derivative even if both carbanions differ only in methyl and ethoxy group bonded to the carbonyl carbon atom (Scheme 1). The oxygen atom of the ethoxy group probably weakenes the C(4)–H bond and supports the proton abstraction to form the imino tautomers *XV – XVII*.

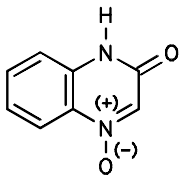


SCHEME 1

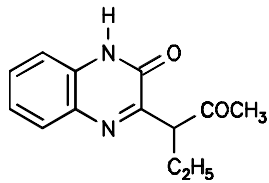
The studies on the formation of aziridinoquinoxaline analogues *X – XIV* were extended to simpler 3,4-dihydro-3-oxoquinoxaline-1-oxide (*XVIII*, refs[2,7]). Its reactivity was verified by the reaction with carbanion of 3-ethylpentane-2,4-dione. One pure compound corresponding either to 3-(3,4-dihydro-3-oxiquinoxalin-2-yl)pentan-2-one (*XIX*) or to 2-acetyl-2-ethyl-3-oxo-1,2*b*,3,4-tetrahydroaziridine[1,2-*a*]quinoxaline (*XX*) was isolated.

Decisive information was obtained from the ^1H NMR spectrum. Instead of three multiplets and one singlet characteristic for the $CH(C_2H_5)COCH_3$ group the spectrum contained two singlets at δ 2.2 ($COCH_3$) and 3.29 ppm (C–H in position 2*b*) with the relative intensity 3 : 1, triplet at δ 0.31 ppm (CH_3) and a multiplet at δ 1.39 – 1.92 ppm (protons of prochiral methylene group bonded to the quaternary chiral carbon atom 2 of

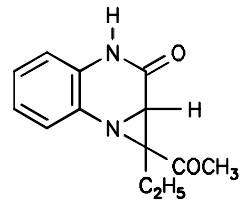
the aziridine ring). The multiplet of the aromatic protons (δ 6.70 – 7.33 ppm) and the broad singlet (δ 9.38 ppm of the NH group associated through hydrogen bonding are in accord with the structure *XX*.



XVIII



XIX



XX

EXPERIMENTAL

Melting points were determined on a Kofler apparatus and are uncorrected. The course of reactions and the purity of products were monitored by TLC on Silufol plates in the following systems: S1, benzene–ethyl acetate (1 : 1), S2, chloroform–ethyl acetate (2 : 1). IR spectra were recorded in chloroform solution and as Nujol mulls, on an IR 75 spectrophotometer (Zeiss); the wavenumber scale was calibrated with polystyrene. Electronic spectra were recorded on a Specord UV-VIS apparatus (Zeiss) in ca 10^{-3} M methanolic solutions. ^{1}H NMR and ^{13}C NMR spectra were measured with a JNM-FX 100 (JEOL) apparatus at 300 K at 99.602 and 25.047 MHz, respectively, or with a Bruker apparatus AM

TABLE III
IR and NMR spectra (in $CDCl_3$) of aziridinotriazoloquinoxalines *X* – *XIV*

Compound	ν_{CH} [a]	ν_{CO} [b]	γ_{CH} [c]		δ, ppm					
			pos.3(1)	pos.6 – 9	pos.3(1)	arom.	CH	CH_2CO	CH_2	CH_3
X	3 160	1 705	830	758	7.85	8.15 – 7.30	4.10	2.35	–	0.92
XI [d]	3 136	1 706	835	755	7.81	8.19 – 7.31	3.94	2.31	1.51 – 1.13	0.88
XII	3 146	1 707	848	766	8.81	7.78 – 7.10	4.14	2.37	–	0.65
XIII	3 144	1 706	858	751	8.62	7.55 – 7.20	4.14	2.36	1.18 – 1.48	0.70
XIV [e]	3 145	1 708	850	748	8.75	7.49 –7.27	4.12	2.29	1.44 – 1.08	0.55

[a] Measured in chloroform solutions; weak band. [b] Strong band. [c] Measured in Nujol; for position 3(1) medium intenzity, for positions 6 – 9 strong intensity. [d] ^{13}C NMR spectrum: 205.5 (CO); 132.3, 127.9, 125.1, (3 × C_q); 132.8, 128.6, 128.0, 11.4 (4 × CH); 50.3 (C_q-4); 38.3 (CH-3*b*); 25.0 ($COCH_3$); 17.1 (CH_2); 9.0 (CH_3). [e] ^{13}C NMR spectrum: 204.5 (CO); 143.3, 132.6, 126.5 (3 × C_q); 136.6, 128.9, 127.9, 126.9, 115.5 (5 × CH); 49.9 (C_q-4); 38.7 (CH-3*b*); 24.4 ($CO\mathbf{C}H_3$); 25.9, 18.2 (2 × CH_2); 14.3 (CH_3).

400.13 and 100.61 MHz, respectively, at the room temperature in deuteriochloroform and hexadeuteriodimethyl sulfoxide. Both the ^1H and ^{13}C chemical shifts (δ, ppm) are related to internal tetramethylsilane.

Synthesis of Enamino Ketones *IV*, *VI*, Esters *V*, *VII*, *XV* – *XVII* and Aziridinoquinoxalines *X* – *XIV*, *XX*. General Procedure

Solution of *N*-oxide *II*, *III* or *XVIII* (3 – 10 mmol), an equivalent amount of the corresponding β-dicarboxylic compound, and piperidine or triethylamine (2 – 5 ml, see Table II) in ethanol (30 – 50 ml) was refluxed for 0.5 – 5 h. After storage for 5 – 24 h at −10 °C the precipitated product was isolated and crystallized from ethanol (charcoal). Derivatives *VI*, *VII* and *XX* were purified on the silica gel column and eluted by the mixture of ethyl acetate–acetone (6 : 1) before crystallization. The yields and analytical data are given in Table II, the NMR, IR and UV spectra are given in Tables I and III.

Ethyl 2-(Tetrazolo[1,5-*a*]quinoxalin-4-yl)propanoate (*XV*)

^1H NMR spectrum ($(CD_3)_2SO$): 8.56 – 7.80 m, 4 H (arom.); 4.73 (CH; 4.21 (OCH_2); 1.81 (α-CH_3); 1.19 (CH_3) (imine tautomer); 12.30 (NH) (enamine tautomer; ≈15%).

Ethyl 2-(1,2,3-Triazolo[1,5-*a*]quinoxalin-4-yl)propanoate (*XVI*)

^1H NMR spectrum ($CDCl_3$): 12.38 (NH); 8.26 (=CH_2); 7.50 – 7.10 (arom.); 4.26 (OCH_2); 2.20 (α-CH_3); 1.36 (CH_3) (enamine tautomer). ^{13}C NMR spectrum ($CDCl_3$): 170.9 (COO); 138.9, 127.3, 121.3, 91.9 (4 × C_q); 134.1, 129.3, 122.3, 116.3, 115.7 (5 × CH); 60.5 (OCH_2); 14.4 (=CCH_3); 13.6 (CH_3) (enamine tautomer).

Ethyl 2-(1,2,4-Triazolo[4,3-*a*]quinoxalin-4-yl)propanoate (*XVII*)

^1H NMR spectrum ($(CD_3)_2SO$): 10.15 (=CH); 8.47 – 7.73 (arom.); 4.69 (CH); 4.16 (OCH_2); 1.72 (α-CH_3); 1.15 (CH_3) (imine tautomer). ^{13}C NMR spectrum ($(CD_3)_2SO$): 171.4 (COO); 152.5, 142.2, 134.9, 124.5 (4 × C_q); 137.9, 129.8, 129.7, 128.0, 116.7 (5 × CH); 60.8 (OCH_2); 14.8 ($CHCH_3$); 14.0 (CH_3) (imine tautomer). ^1H NMR spectrum ($CDCl_3$): 12.29 (NH); 8.92 (=CH); 7.49 – 7.03 (arom.); 4.26 (OCH_2); 2.58 (α-CH_3); 1.37 (CH_3) (enamine tautomer). ^{13}C NMR spectrum ($CDCl_3$): 171.7 (COO); 145.0, 135.5, 129.6, 119.0 (4 × C_q); 136.2, 95.7 (2 × CH); 60.5 (OCH_2); 14.3 (=CCH_3); 13.7 (CH_3) (enamine tautomer).

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