Russian Journal of Organic Chemistry, Vol. 39, No. 1, 2003, pp. 125–130. Translated from Zhurnal Organicheskoi Khimii, Vol. 39, No. 1, 2003, pp. 135–140.

Fused Nitrogen-Containing Heterocycles: III.* 4-Oxo-1-phenyl-4,5-dihydroimidazo[1,5-*a*]quinoxalines. A Retrosynthetic Approach

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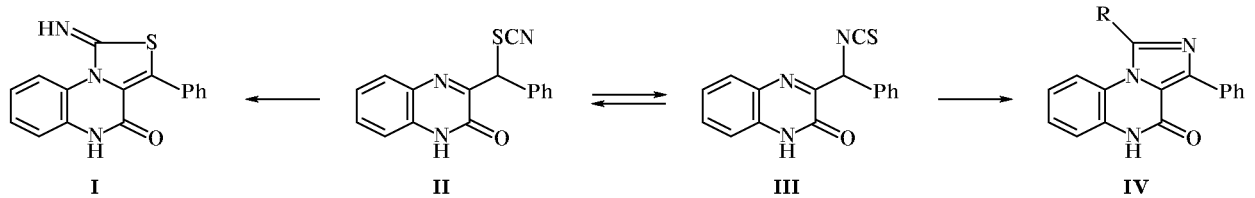
Received June 27, 2001

Abstract—Retrosynthetic analysis of the structure of imidazo[1,5-*a*]quinoxalines made it possible to develop new convenient procedures for preparation of these compounds by reaction of 3-(α-chlorobenzyl)-1,2-dihydroquinoxalin-2-one with potassium thiocyanate or isocyanate as synthetic equivalent of the two-membered $N^{-}=C^{+}$ building blocks and by reaction of 3-(α-aminobenzyl)-1,2-dihydroquinoxalin-2-one with carbon disulfide, triethoxymethane, aromatic aldehydes, or acetic anhydride as synthetic equivalent of the one-membered RC^{3+} synthon.

A wide spectrum of biological activity recently revealed in the series of imidazo[1,5-*a*]quinoxaline derivatives [2–4] and related azoloquinoxalines [5] makes it promising to develop convenient methods for preparation of these fused heterocylic compounds. We previously showed that a relatively short route to 3-phenyl derivatives **IV** is based on the use of readily accessible 3-(α-thiocyanatobenzyl)-1,2-dihydroquinoxalin-2-one (**II**), which is capable of undergoing intramolecular ring closure with formation of not only thiazolo[3,4-*a*]quinoxalin-4-one **I** [6] but also (due to thiocyanate–isothiocyanate rearrangement) compound **III**. The latter is then converted into the target imidazo[1,5-*a*]quinoxaline system **IV** (Scheme 1). This process corresponds to path *1* (through synthon **A**, R = SH) in the retrosynthetic scheme shown below (Scheme 2). As follows from Scheme 2, another synthetic equivalent of **A** may be oxygen-containing analog of **III**, 3-(α-isocyanatobenzyl)-1,2-dihydroquinoxalin-2-one (**V**). Its formation can be represented as a result of nucleophilic substitution of the chlorine atom in 3-(α-chlorobenzyl)-1,2-dihydroquinoxalin-2-one (**VI**) by cyanate ion through its nitrogen atom which is more nucleophilic than oxygen. However, we failed to obtain isocyanate **V** or isomeric cyanate **VII** from **VI** and KOCN in DMSO at room temperature, i.e., under conditions ensuring almost quantitative formation of thiocyanate **II** by analogous reaction with KSCN [6]. A probable reason is too high and versatile reactivity of the expected isocyanate **V** and/or cyanate **VII**. On the other hand, there is no need of isolating compound **V** or **VII** as intermediate products, for the reaction of chloride **VI** with KOCN in boiling dimethylformamide directly gives imidazoquinoxaline **IVa** in a good yield (Scheme 3). The above route to imidazo[1,5-*a*]quinoxalines starting

Scheme 1.



I **II** **III** **IV**

* For communication II, see [1].

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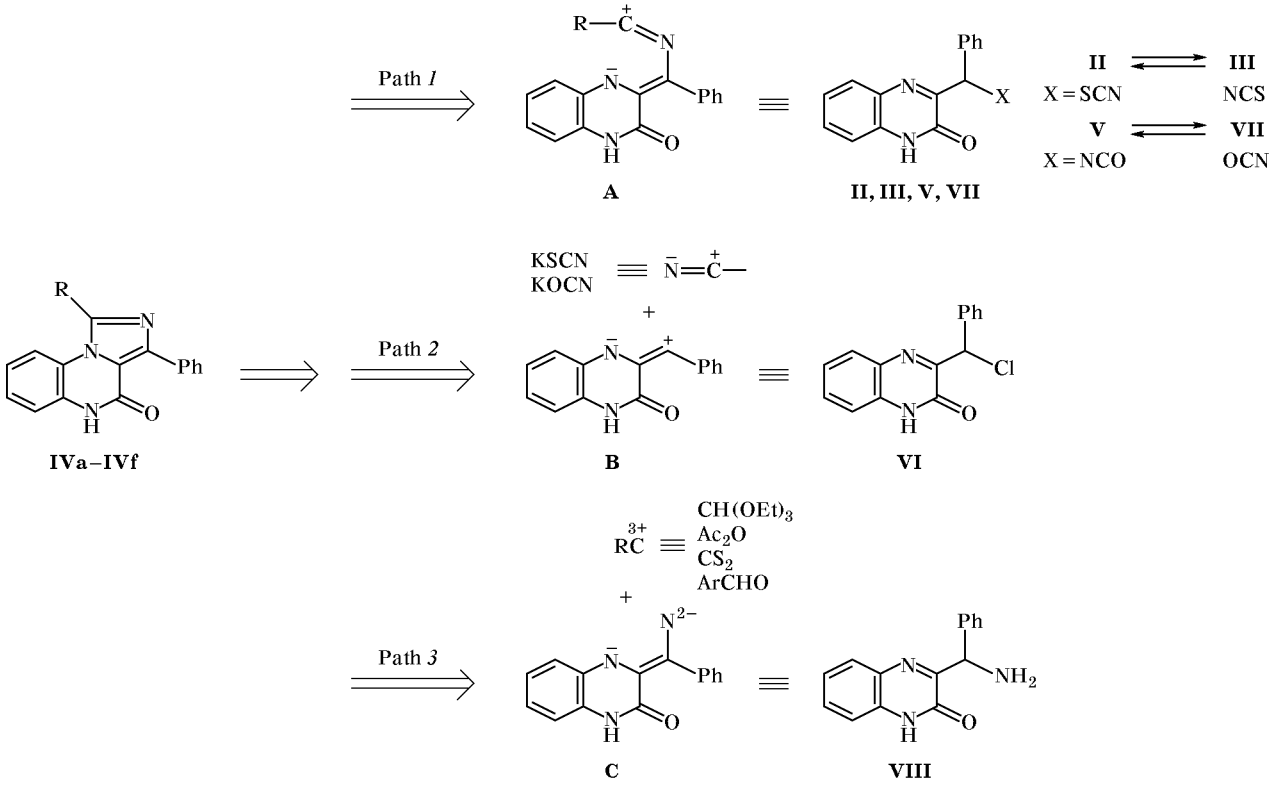
Scheme 2.



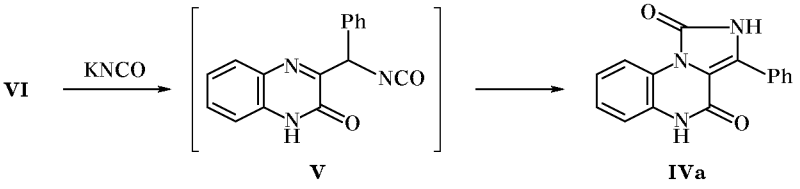
IV, R = OH (**a**), SH (**b**), H (**c**), Ph (**d**), 4-$MeOC_6H_4$ (**e**), Me (**f**).

from accessible chloride **VI** is shorter than the known procedure for building up isocyanate intermediates (as synthetic equivalents of **A**) through the corresponding carboxylic acid hydrazide and azide (according to Curtius) [7].

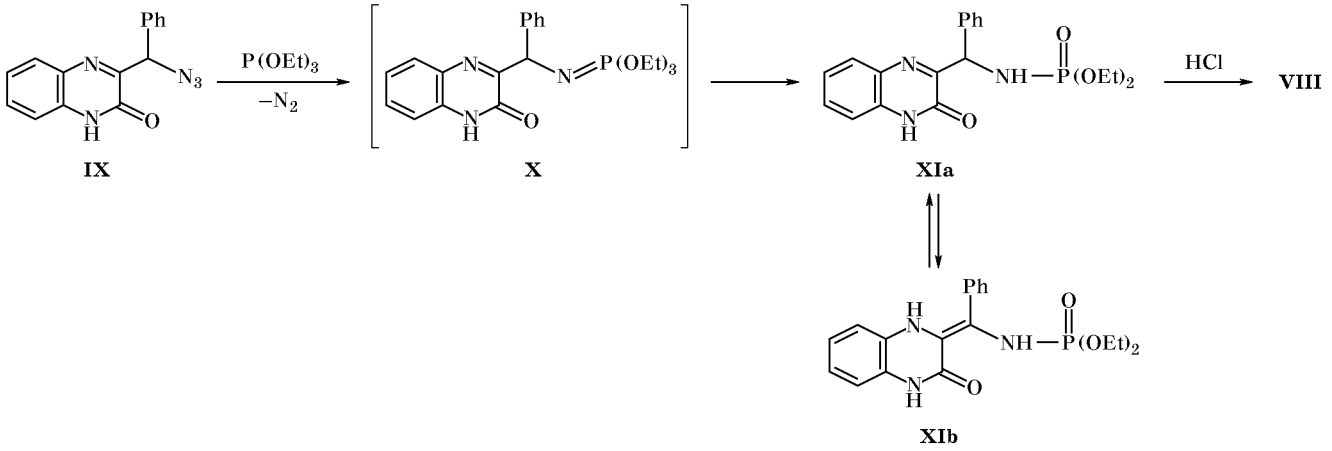
From the retrosynthetic viewpoint, the formation of imidazo[1,5-*a*]quinoxalines **IVa** and **IVb** can also be represented by division of the target structure into synthons **B** and $R\overset{+}{C}{=}N^{-}$; synthetic equivalents of the latter may be potassium cyanate and thiocyanate (path *2* in Scheme 2). Paths *1* and *2* are similar in the preparative respect.

The most attractive is to build up the imidazo-[1,5-*a*]quinoxaline system from synthons **C** and RC^{3+} (path *3* in Scheme 2). Synthetic equivalents of the latter are numerous compounds, e.g., carbon disulfide, ortho esters, acylating agents, etc. However, this approach requires development of procedures for preparation of amine **VIII** as synthetic equivalent of **C**. Our attempt to obtain amine **VIII** from chloride **VI** and ammonia resulted in formation of a mixture of products. The reduction of azide **IX** with $LiAlH_4$ was also unsuccessful [8]. We succeeded in converting the azide moiety into amine by the Staudinger reaction [9]. Azide **IX** smoothly reacted with triethyl phosphite to give unstable phosphorane **X** which underwent hydrolysis by the action of atmospheric moisture during isolation. As a result, 3-(α-diethoxyphosphinoylaminobenzyl)-1,2-dihydroquinoxalin-2-one (**XI**) was obtained (Scheme 4).

Scheme 3.



Scheme 4.



All 3-(α-X-benzyl)-1,2-dihydroquinoxalin-2-ones reported previously [6, 8, 10] (X = Cl, SCN, N_3, NHPh) exist exclusively or almost exclusively in the imino form (the nitrogen atom in position *4* of the quinoxaline ring is pyridine-like). This follows from the presence in the ^{1}H NMR spectra of one signal from proton at sp^3-hybridized carbon atom, δ 6.0–6.5 ppm. According to the ^{1}H NMR data, amidophosphate **XI** also has structure **XIa**. Its IR spectrum contains an absorption band at 1610 cm^{-1} (ν C=N) in addition to strong bands corresponding to stretching vibrations of the carbonyl group and N–H bond of the amidophosphate moiety (1665 and 3190 cm^{-1}, respectively). The aminobenzyl (**XIa**) rather than aminobenzylidene (**XIb**) structure is also confirmed by signals in the upfield region of the ^{1}H NMR spectrum. Signals from the methyl protons of the ethoxy groups appear as two doublets of doublets (rather than triplets) with coupling constants ^3J of 7.32 and 6.72 Hz, while the corresponding methylene protons (δ 3.75–4.00 ppm) give rise to two groups of unresolved multiplets (rather than doublets of quartets); the signal intensity ratio is 3:1. These data indicate the presence of two spin systems ABM_3X and $A'B'M_3X$, which is possible if the molecule contains an asymmetric carbon atom. In order to determine the coupling constants $^2J_{AB}$ and $^3J_{POCH}$, the ^{1}H NMR spectra were recorded with successive irradiation of samples at the resonance frequences corresponding to all nuclei constituting the ABM_3X system. The resulting values, $^2J_{AB}$ = 14.5 Hz and $^3J_{POCH}$ = 10.5 Hz were refined by simulation of the spectrum with the use of WIN

Table 1. Yields, melting points, and elemental analyses of imidazo[1,5-*a*]quinoxalin-4-ones **IVa** and **IVd**–**IVf** and quinoxalin-2-ones **VIII**, **XI**, and **XII**[a]

Comp. no.	Yield, %	mp, °C (solvent)	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
IVa	60	>360 (DMSO)	68.93	4.10	17.57	$C_{16}H_{11}N_3O_2$	69.31	4.00	17.31
IVd	58	313–315 (DMF–*i*-PrOH, 1:2)	78.70	4.27	12.46	$C_{22}H_{15}N_3O$	78.32	4.48	12.46
IVe	93	330–332 (DMF–*i*-PrOH, 1:2)	75.11	5.11	11.21	$C_{23}H_{17}N_3O_2$	75.19	4.66	11.44
IVf	53	266–268 (AcOH–H_2O, 1:1)	73.92	4.37	15.05	$C_{17}H_{13}N_3O$	74.17	4.76	15.26
VIII	81	224–226 (H_2O)	61.05	5.15	14.34	$C_{15}H_{13}N_3O \cdot 1.25HCl$[b]	60.69	4.84	14.15
XI	75	170–173 (*i*-PrOH)	59.32	5.72	11.08	$C_{21}H_{26}N_3PO_4$[c]	58.91	5.97	10.84
XII	56	259–261 (AcOH–H_2O, 1:1)	69.56	4.58	14.45	$C_{17}H_{15}N_3O_2$	69.61	5.15	14.33

[a] The data for compounds **IVb** and **IVc** and methods of their purification were identical to those reported in [1].

[b] Found Cl, %: 14.39. Calculated Cl, %: 14.93.

[c] Found P, %: 7.95. Calculated P, %: 7.99.

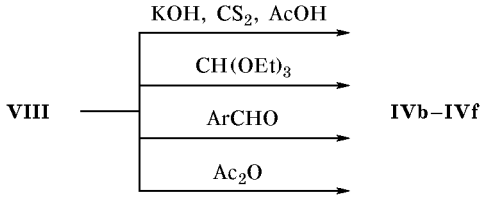
Table 2. IR and ^{1}H NMR spectra of imidazo[1,5-*a*]quinoxalin-4-ones **IVa** and **IVd**–**IVf** and quinoxalin-2-ones **VIII**, **XI**, and **XII**

Comp. no.	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum (DMSO-d_6), δ, ppm
IVa	1670 (C=O), 1700 (C=O), 2400–3220 (NH)	7.09–7.48 m (6H, 6-H, 7-H, 8-H, *m*-H, *p*-H), 7.90 d (2H, *o*-H, *J* = 6.9 Hz), 8.75 d (1H, 9-H, *J* = 7.9 Hz), 10.87 br.s (1H, NH), 11.87 br.s (1H, NH)
IVd	1615 (C=N), 1660 (C=O), 2570–3220 (NH)	6.84–7.02 m (2H, quinoxaline), 7.23–7.67 m (10H, quinoxaline; *m*-H, *p*-H), 8.17 d (2H, *o*-H, *J* = 7.34 Hz), 11.44 br.s (1H, NH)
IVe	1610 (C=N), 1660 (C=O), 2570–3220 (NH)	3.90 s (3H, CH_3), 6.82–7.02 m (1H, *p*-H), 7.15 d (1H, 9-H, *J* = 8.9 Hz), 7.18 d (2H, *m*-H in $MeOC_6H_4$, *J* = 8.5 Hz), 7.26–7.56 m (5H, 6-H, 7-H, 8-H; *m*-H in Ph), 7.65 d (2H, *o*-H in $MeOC_6H_4$, *J* = 8.5 Hz), 8.12–8.28 m (2H, *o*-H in Ph), 11.50 br.s (1H, NH)
IVf	1605 (C=N), 1660 (C=O), 2480–3220 (NH)	2.95 s (3H, CH_3), 7.18–7.22 m (1H, *p*-H), 7.24–7.42 m (5H, 6-H, 7-H, 8-H, *m*-H, *p*-H), 8.05 d (1H, 9-H, *J* = 8.3 Hz), 8.14 d (2H, *o*-H, *J* = 8.3 Hz), 11.30 br.s (1H, NH)
VIII	1662 (C=O), 2370–3520 (NH)	5.80 s (1H, PhC**H**, 7.36–7.62 m (8H, C_6H_5, 6-H, 7-H, 8-H), 7.88 d (1H, 5-H, *J* = 6.83 Hz), 9.12 br.s (2H, NH_2); 11.80 br.s (1H, NH)
XI	1610 (C=N), 1662 (C=O), 2490–3330 (NH)	1.12 d.d (3H, C**H**$_3$CH$_2$, *J* = 7.32, 6.72 Hz), 1.17 d.d (3H, C**H**$_3$CH$_2$, *J* = 7.32, 6.72 Hz), 3.29–3.96 m (4H, 2CH$_3$C**H**$_2$), 5.81 d (1H, PhC**H**, *J* = 8.64 Hz), 7.23–7.53 m (8H, C_6H_5, 6-H, 7-H, 8-H), 7.91 d (1H, 5-H, *J* = 6.91 Hz)
XII	1610 (C=N), 1660 (C=O), 2580–3220 (NH), 3395 (NH)	1.94 s (3H, CH_3), 6.43 d (1H, PhC**H**, *J* = 8.2 Hz), 7.19–7.46 m (8H, C_6H_5, quinoxaline), 7.79 d (1H, 5-H, *J* = 7.3 Hz), 8.42 br.s (1H, NHAc), 12.43 br.s (1H, N^{1}H)

DAISY program (correlation coefficient R = 0.995). A fairly large difference in the chemical shifts of the methyl protons ($\Delta\delta$ 0.12 ppm) should be noted, as well as an upfield shift (by 0.15 ppm) of a part of the methylene proton multiplet, whose intensity corresponds to one proton. Presumably, this is the result of not only restricted rotation about the partially double N–P bond but also anisochronous effect of the benzene and/or quinoxaline system on three methyl protons and one methylene proton of the ethoxy group.

The desired amine **VIII** was obtain in high yield (as hydrochloride) by treatment of amidophosphate **XI** with dry hydrogen chloride. Reactions of **VIII**·HCl with one-carbon synthons smoothly yields imidazo-[1,5-*a*]quinoxalines **IVb**–**IVf** (Scheme 5). We thus accomplished the synthesis of compounds **IV** according to path *3* (through synthon **C**).

Scheme 5.



Here, aldehydes were only arbitrarily (for the sake of brevity) assigned to synthetic equivalents of RC^{3+}. In fact, they are equivalents of RCH^{2+} whose reaction with **VIII** leads to dihydro derivatives of **IVd** and **IVe**. Products **IVd** and **IVe** are likely to be formed by oxidation of the initially obtained dihydro derivatives with atmospheric oxygen. As a result, aldehydes give rise to the same compounds as those obtained from the corresponding carboxylic acid derivatives, so that the above assumption may be regarded as justified.

By carrying out the reaction of amine **VIII** hydrochloride with acetic anhydride in a stepwise mode, we succeeded in isolating and characterizing intermediate 3-(α-acetylaminobenzyl)quinoxalin-2-one (**XII**) which is a synthetic equivalent of **A**. Intramolecular condensation of **XII** in acetic acid gives imidazo[1,5-*a*]quinoxaline **IVf** (Scheme 6). This reaction may be regarded as one more version of path *1*.

Scheme 6.

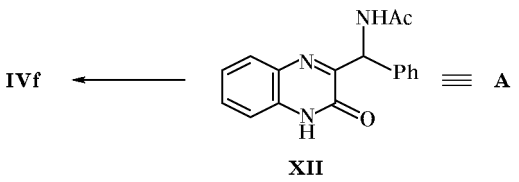
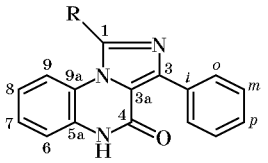


Table 3. ^{13}C NMR spectra of imidazo[1,5-*a*]quinoxalines **IVd**–**IVf** in DMSO–acetone-d_6 (10 : 1), δ_C, ppm (*J*, Hz)



Atom	**IVd**	**IVe**	**IVf**
CH_3	–	55.01 q (*J* = 144.58)	15.58 q (*J* = 129.95)
C^7, C^8	116.21 d.m (*J* = 165.7), 116.42 d.m (*J* = 160.6)	116.16 d.br.d (*J* = 165.5, 9.5) 116.41 d.d.d (*J* = 162.6, 7.4, 2.6)	118.16 d.m (*J* = 162.8) 123.79 d.m (*J* = 163.5)
C^{3a}	118.19 br.s	118.02 br.s	119.42 br.s
C^3	121.07 m	121.20 m	123.39 m
C^6, C^9	121.10 d.d (*J* = 162.74, 7.8), 126.30 d.d (*J* = 63.8, 7.8)	121.11 d.d.d (*J* = 161.8, 8.0, 1.3), 126.20 d.d (*J* = 162.9, 8.6)	127.89 d.d (*J* = 163.9, 8.2), 117.58 d.d.d (*J* = 163.0, 7.9, 1.4)
C^{5a}, C^{9a}	143.06 d.d.d (*J* = 5.7, 4.9, 1.7), 144.07 d.d.d (*J* = 4.2, 4.2, 4.6)	142.90 d.d (*J* = 4.3, 4.2), 144.95 d.d (*J* = 4.2, 4.0)	134.55 d.d (*J* = 8.2, 7.5), 143.69 m
C=O	154.72 s	154.75 s	156.22 s
C=N	160.07 br.s	160.39 br.s	144.73 q (*J* = 7.3)
C^p	127.41 d.t (*J* = 161.8, 7.3), 129.56 d.t (*J* = 161.8, 7.5)	127.35 d.t (*J* = 161.4, 7.8), 129.41 t (*J* = 4.6 Hz)[a]	129.07 d.d.d (*J* = 161.1, 7.8, 7.7)
C^o	129.03 d.d.d (*J* = 167.3, 7.2, 7.1), 129.02 d.d.d (*J* = 166.3, 7.3, 7.1)	129.99 d.m (*J* = 162.1), 130.48 d.d (*J* = 162.1, 7.1)[a]	130.75 d.d.d (*J* = 161.1, 7.7, 7.6)
C^m	128.38 d.d.d (*J* = 162.6, 6.4, 1.9), 126.98 d.d.d (*J* = 159.7, 8.1, 1.0)	126.93 d.d.d (*J* = 159.6, 7.5, 0.8), 114.11 d.d (*J* = 161.5, 4.5)[a]	128.79 d.d (*J* = 159.5, 7.7)
C^i	132.71 t (*J* = 7.4), 131.69 t (*J* = 7.5)	132.70 t (*J* = 8.2), 123.67 t (*J* = 8.2)[a]	130.83 d.d.d (*J* = 1.1, 6.9, 6.8)

[a] Signals of the 4-methoxyphenyl group.

The structure of imidazo[1,5-*a*]quinoxalin-2-ones **IVa**–**IVf** was proved by elemental analyses (Table 1) and IR and ^1H and ^{13}C NMR data (Tables 2, 3).

EXPERIMENTAL

The melting points were determined on a Boetius device. The IR spectra were taken on a UR-20 spectrometer from samples dispersed in mineral oil. The ^1H NMR spectra were recorded on a Bruker MCL-250 instrument at 250.13 MHz. The ^{13}C and ^{31}P NMR spectra were obtained on a Bruker WV-400 spectrometer at 100.60 and 161.98 MHz, respectively.

3-Phenylimidazo[1,5-*a*]quinoxaline-1,4(2*H*,5*H*)-dione (IVa). To a mixture of 0.50 g (1.9 mmol) of 3-(α-chlorobenzyl)-1,2-dihydroquinoxalin-2-one [10] and 6 ml of dry DMF we added a twofold amount of KNCO. The mixture was refluxed for 6 h, cooled, and poured into water. The crystals were filtered off and washed with water and isopropyl alcohol.

1-Mercapto-3-phenylimidazo[1,5-*a*]quinoxalin-4(5*H*)-one (IVb). To a mixture of 0.70 g (2.4 mmol) of aminoquinoxaline **VIII** hydrochloride (see below) and 50 ml of methanol we added 0.6 g (10.7 mmol) of potassium hydroxide. The mixture was refluxed for a few minutes and cooled, 1 ml of carbon disulfide was added, and the mixture was refluxed for 3 h. The mixture was cooled, an additional 1 ml of CS_2 was added, and the mixture was refluxed for 3 h again. After cooling, the crystals were filtered off and washed with water and a mixture of acetic acid with isopropyl alcohol. Yield 0.63 g (90%). The properties of compound **IVb** were identical to those of the product described in [1].

3-Phenylimidazo[1,5-*a*]quinoxalin-4(5*H*)-one (IVc). A mixture of 0.30 g (1 mmol) of aminoquinoxaline **VIII** hydrochloride and 10 ml of triethyl orthoformate was refluxed for 6 h. It was then cooled, and the crystals were filtered off and washed with an aqueous solution of sodium carbonate, water, and

isopropyl alcohol. Yield 0.22 g (84%). The properties of compound **IVc** coincided with those of the product described in [1].

1,3-Diphenylimidazo[1,5-*a*]quinoxalin-4(5*H*)-one (IVd). A mixture of 0.38 g (1.3 mmol) of aminoquinoxaline **VIII** hydrochloride, 10 ml of dioxane, and excess (0.7 ml) benzaldehyde was refluxed for 9 h. The resulting solution was cooled and poured into water, and an aqueous solution of sodium carbonate was added. The crystals were filtered off and washed with water and isopropyl alcohol.

1-(4-Methoxyphenyl)-3-phenylimidazo[1,5-*a*]quinoxalin-4(5*H*)-one (IVe). A mixture of 0.50 g (1.7 mmol) of aminoquinoxaline **VIII** hydrochloride, 10 ml of dioxane, and excess (0.7 ml) *p*-methoxybenzaldehyde was refluxed for 15 h. The product was isolated as described above for compound **IVd**.

1-Methyl-3-phenylimidazo[1,5-*a*]quinoxalin-4(5*H*)-one (IVf). A solution of 0.20 g (0.67 mmol) of aminoquinoxaline **VIII** hydrochloride in 3 ml of acetic anhydride was refluxed for 4 h. The mixture was left overnight, and the crystals were filtered off and washed with an aqueous solution of sodium carbonate, water, and isopropyl alcohol.

3-(α-Aminobenzyl)quinoxalin-2(1*H*)-one hydrochloride (VIII). Dry hydrogen chloride was bubbled over a period of 2 h under stirring through a suspension of 3.0 g (7.2 mmol) of quinoxaline **XI** (see below) in 20 ml of dioxane. Initial quinoxaline **XI** dissolved, and crystals of the product separated from the solution. The mixture was left overnight, and the crystals were filtered off and washed with dioxane. The filtrate was partially evaporated to isolate an additional amount of the product which was filtered off and washed with dioxane.

Diethyl α-[3-oxo-3,4-dihydroquinoxalin-2(1*H*)-ylidene]benzylamidophosphate (XI). Azidoquinoxaline **VI** [8], 8 g (2.88 mmol), and triethyl phosphite, 5 ml, were dissolved in 50 ml of anhydrous dioxane on stirring at 40°C. The solution was stirred for 48 h at room temperature; evolution of nitrogen was observed during the process, and crystals began to separate on the second day. The crystals were filtered off and washed with dioxane. ^{31}P NMR spectrum: δ_P 6.89 (DMSO), 7.10 ppm (AcOH).

***N*-α-(3-Oxo-3,4-dihydroquinoxalin-2-yl)benzylacetamide (XII).** A solution of 0.20 g (0.67 mmol) of aminoquinoxaline **VIII** hydrochloride in 3 ml of acetic anhydride was refluxed for 5 min. The mixture was left overnight, and the crystals were filtered off and washed with a solution of sodium carbonate, water, and isopropyl alcohol.

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