Russian Journal of Organic Chemistry, Vol. 40, No. 7, 2004, pp. 1041–1046. Translated from Zhurnal Organicheskoi Khimii, Vol. 40, No. 7, 2004, pp. 1082–1087.

Fused Polycyclic Nitrogen-Containing Heterocycles: IX.* Oxidative Fusion of Imidazole Ring to 3-Benzoylquinoxalin-2-ones

V. A. Mamedov,[1] A. A. Kalinin,[1] E. A. Gorbunova,[1] I. Bauer[2], and W. D. Habicher[2]

[1] *Arbuzov Institute of Organic and Physical Chemistry, Kazan Research Center, Russian Academy of Sciences, ul. Arbuzova 8, Kazan, 420088 Tatarstan, Russia*
e-mail: mamedov@iopc.kcn.ru

[2] *Drezden University of Technology, Institute of Organic Chemistry, Drezden, D-01062 Germany*

Received July 24, 2003

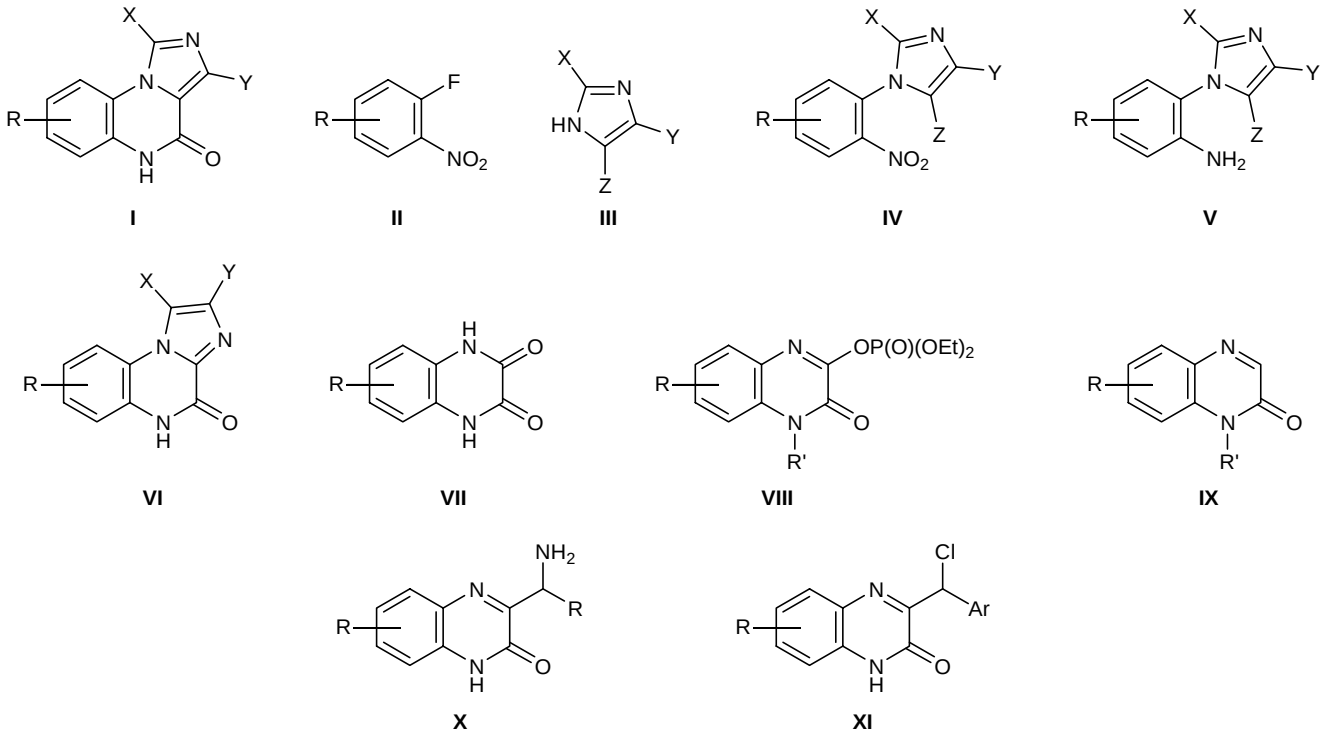
Abstract—3-α-Chlorobenzyl- and 3-benzoylquinoxalin-2-ones react with benzylamine in DMSO to give intermediate 3-(α-benzyliminobenzylidene)quinoxalin-2-one which is capable of existing in several tautomeric forms. The subsequent oxidative cyclocondensation leads to imidazo[1,5-*a*]quinoxalin-4-one. This new procedure for building up imidazo[1,5-*a*]quinoxalin-4-one system has been applied to the synthesis of various bis(imidazo[1,5-*a*]quinoxalin-4-ones).

Quinoxaline and imidazo[1,5-*a*]quinoxalin-4-one ring systems constitute structural fragments of various biologically active substances and medicines; therefore, new functionalized derivatives of quinoxalines and azoloquinoxalines are often used as key compounds in the synthesis of biologically active substances. For example, they have been used as template reagents in the synthesis of GABA/diazepine receptor agonists and antagonists [2], cAMP and cGMP phosphodiesterase inhibitors [3], A_1- and A_{2a}-adenosine receptor agonists [4], and key materials in the preparation of numerous pharmacologically active compounds [5–8]. Prior to our studies, several procedures for the synthesis of imidazo[1,5-*a*]quinoxalin-4-ones **I** have been reported. One of these includes a three-step process. In the first step, nucleophilic substitution of the fluorine atom in 2-fluoronitrobenzenes **II** by imidazoles **III**, (X ≠ H, Z = H) gives 1-(2-nitrophenyl)imidazoles **IV** (X ≠ H, Z = H) [3–5, 9]. Compounds **IV** are then reduced to imidazolylanilines **V** (X ≠ H, Z = H) which react with carbonyldiimidazole to afford imidazo[1,5-*a*]quinoxalin-4-ones. Although this proce-dure has been developed in sufficient detail and is very convenient for the synthesis of 1-substituted imidazo-[1,5-*a*]quinoxalin-4-ones **I** (X ≠ H) [3–5], it cannot be applied to the preparation of imidazo[1,5-*a*]quinoxalin-4-ones **I** having no substituent in position *1* (X = H): The reaction with the corresponding imidazoles **III** (X = H) yields exclusively isomeric imidazo[1,2-*a*]-quinoxalin-6-ones **VI** [3–5, 9].

The second procedure is based on reactions of diethyl imidazole-4,5-dicarboxylates **III** (Y = Z = CO_2Et) with 2-fluoronitrobenzene, which result in formation of 1-(2-nitrophenyl)imidazole-4,5-dicarboxylates **IV** (Y = Z = CO_2Et) [8]. Reduction of the latter gives the corresponding anilines **V** (Y = Z = CO_2Et) which undergo cyclization to ethyl 4-oxoimidazo[1,5-*a*]quinoxaline-3-carboxylates **I** (Y = CO_2Et) [8]. According to the third method, 2,3-dioxoquinoxalines **VII** are converted into phosphates **VIII** which react with aryl isocyanides to afford 3-arylimidazo-[1,5-*a*]quinoxalin-4-ones **I** [2, 6, 7]. Finally, the fourth procedure includes reaction of *p*-tolylsulfonylmethyl isocyanide with various quinoxalin-2-ones **IX** having no substituent at C^3. This method provides the possibility for preparing imidazo[1,5-*a*]quinoxalin-4-ones **I** with free positions *1* and *3* (X = Y = H) [10].

We previously developed new procedures for the synthesis of imidazo[1,5-*a*]quinoxalin-4-ones on the basis of retrosynthetic analysis of the target structures. The key steps in these procedures include reactions of 3-α-amino- and 3-α-chlorobenzylquinoxalin-2-ones **X** and **XI** with synthetic equivalents of one- and two-atom building blocks, respectively. The proposed

* For communication VIII, see [1].



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

VI **VII** **VIII** **IX**

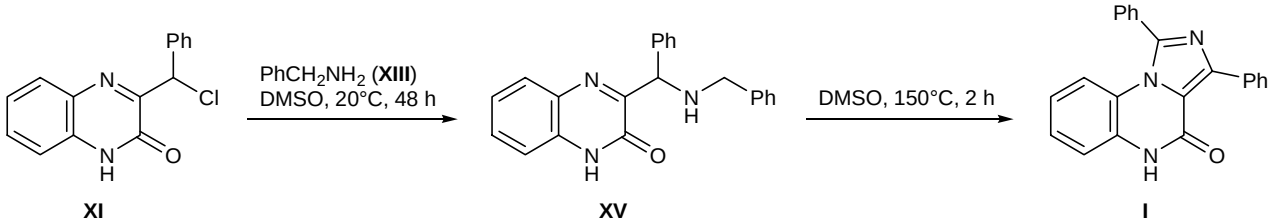
X **XI**

procedures ensured formation of both substituted and 1-unsubstituted imidazo[1,5-*a*]quinoxalin-4-ones **I** (X = H, SH, OH, SAlk, Me, Ar; Y = Ar) in high yields [11–14]. It should be noted that in the first case we were able to use almost all kinds of synthetic equivalents of the RC^{2+} unit, while in the second case only potassium thiocyanate (KSCN) and sodium cyanate (NaOCN) were used as equivalents of the $C^{+}{=}N^{-}$ synthon. In continuation of these studies, in the present work we examined reactions of 3-α-chlorobenzylquinoxalin-2-one (**XI**) and 3-benzoylquinoxalin-2-one (**XII)** with benzylamine (**XIII**) and *m*-bis(aminomethyl)benzene (**XIV**) with a view to obtain imidazo[1,5-*a*]quinoxalin-4-ones **I**.

We have found that 3-(α-chlorobenzyl)quinoxalin-2-one (**XI**) reacts with benzylamine (**XIII**) in DMSO at room temperature to give 3-(α-benzylaminobenzyl)-quinoxalin-2-one (**XV**) which undergoes intramolecular ring closure to imidazoquinoxaline **I** (X = Y = Ph, R=H) on heating in DMSO for 2 h or under conditions of thermolysis at 225±3°C (10 min) (Scheme 1). Obviously, imidazole ring fusion in compound **XV** involves oxidation to Schiff base **XVIa** which can give rise to tautomers **XVIb** and **XVIc**. Nucleophilic attack by the N^4 atom on the C=N carbon atom in **XVIc** leads to closure of imidazole ring and formation of imidazoquinoxaline ring system **XVId**; the subsequent oxidation of **XVId** with atmospheric oxygen or DMSO [15] leads to tricyclic structure **I** (X = Y = Ph, R = H; Scheme 2).

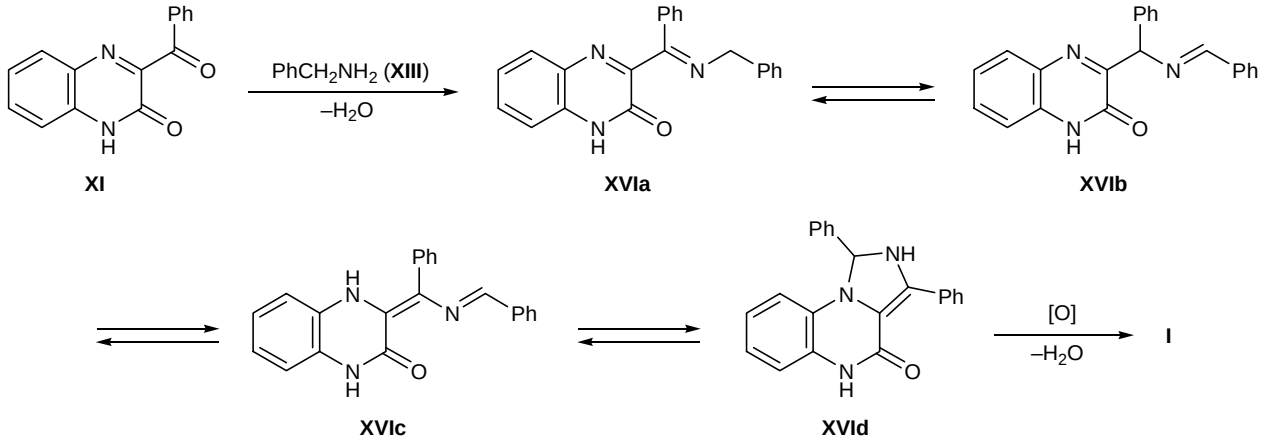
In order to elucidate the way of formation of compound **I** (X = Y = Ph, R = H), we examined the reaction of 3-benzoylquinoxalin-2-one (**XII**) [11, 16] with benzylamine (**XIII**). It was presumed that the reaction could also give initially Schiff base **XVIa** and that oxidative intramolecular cyclization of the latter will lead to product **I**. In fact, heterocyclic ketone **XII** reacted with benzylamine (**XIII**) in DMSO at about

Scheme 1.



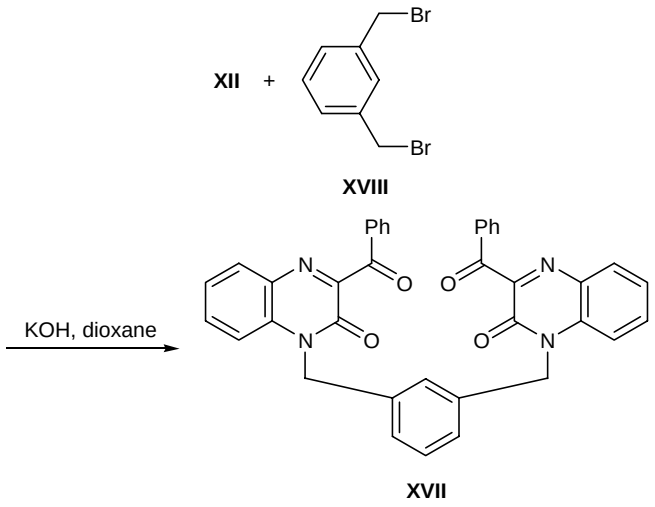
XI **XV** **I**

Scheme 2.

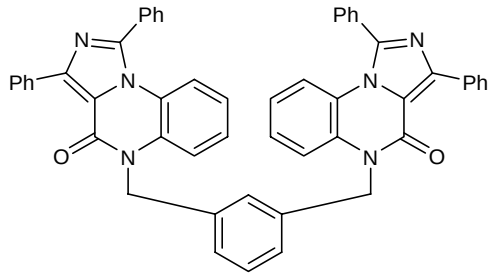


150°C (2 h), and the corresponding imidazoquinoxaline **I** was formed in quantitative yield. An analogous reaction was successful with compounds containing two 3-benzoylquinoxalin-2-one fragments, e.g., with 1,3-bis(3-benzoyl-2-oxoquinoxalin-1-ylmethyl)benzene (**XVII**) which is readily available via alkylation of **XII** with 1,3-bis(dibromomethyl)benzene (**XVIII**) in boiling dioxane in the presence of KOH (Scheme 3).

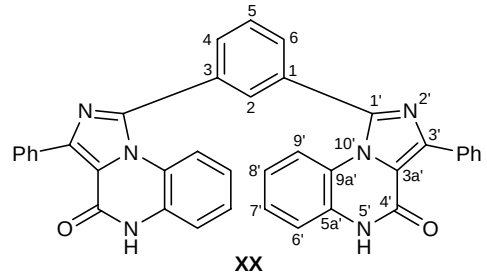
Scheme 3.



The reaction of **XVII** with benzylamine occurred under the conditions given above for the reaction of **XII** and was complete in 4 h; the product was 1,3-bis-(1,3-diphenyl-4-oxoimidazo[1,5-*a*]quinoxalin-5-ylmethyl)benzene (**XIX**). The IR spectrum of **XIX** contained no ketone carbonyl absorption bands, and signals from 32 aromatic protons (four phenyl groups and three *o*-phenylene fragments) were present in the ^{1}H NMR spectrum. The structure of **XIX** was also proved by independent synthesis, by reaction of compound **I** (X = Y = Ph, R = H) with 1,3-bis(bromomethyl)benzene (**XVIII**). Samples of **XIX** obtained by the two methods had identical IR and ^{1}H NMR spectra and melting points (no depression of the melting point was observed on mixing).



By reaction of 3-benzoylquinoxalin-2-one (**XII**) with 1,3-bis(aminomethyl)benzene (**XIV**) instead of dibromo derivative **XVIII**, we obtained chelate-like compound **XX** of a different type. This product is promising not only as ligand but also as building block for macroheterocyclic compounds due to the presence of lactam moieties in the two fixed imidazoquinoxaline fragments. The yield of **XX** attained 97% when the reaction was carried out in DMSO for 72 h at 150±2°C under argon.



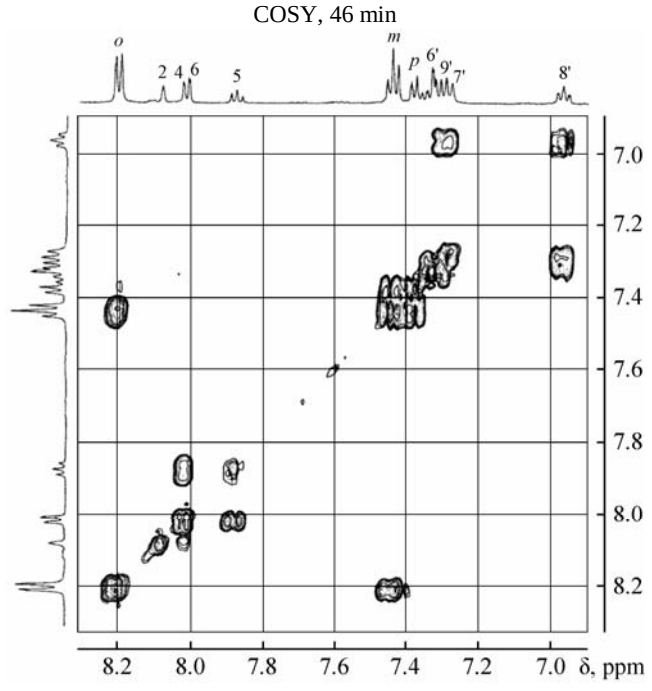


Fig. 1. Two-dimensional homonuclear ^{1}H NMR spectrum (COSY) of compound **XX** in the region δ 6.9-8.3 ppm.

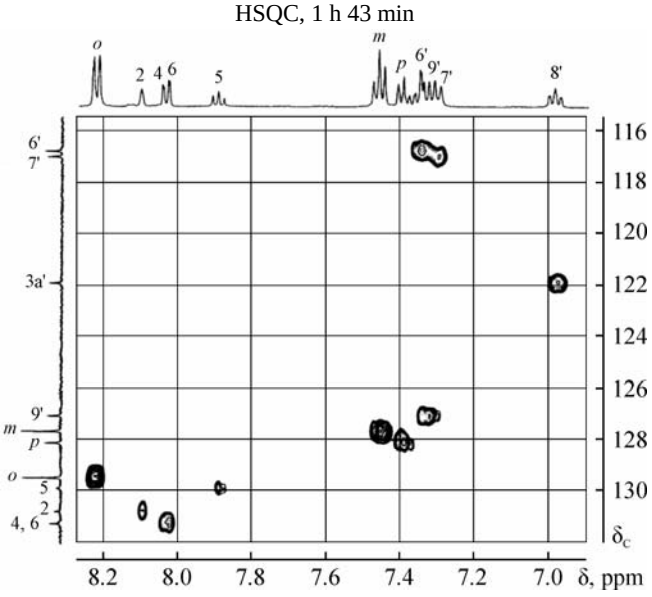


Fig. 2. Two-dimensional heteronuclear ^{13}C–^{1}H NMR spectrum (HSQC) of compound **XX** in DMSO.

The structure of compound **XX** was established on the basis of its elemental composition and IR and ^{1}H and ^{13}C NMR spectra (including two-dimensional NMR techniques). The ^{1}H and ^{13}C NMR spectra of **XX** were interpreted using a combination of double homonuclear (COSY) and heteronuclear resonance (HSQC and HMBC) [17, 18]. Molecule **XX** consists of four proton-containing fragments: 1,3-phenylene, two *ortho*-fused benzene rings, two phenyl groups, and two NH groups. The COSY spectrum shown in (Fig. 1) clearly indicates correlations between three protons of the *m*-phenylene fragment (δ 7.87, 8.02, and 8.08 ppm), three protons of the phenyl groups (δ 7.37, 7.44, and 8.21 ppm), and four protons of the fused benzene rings (δ 6.97, 7.29, 7.31, and 7.34 ppm), separately from each other. These signals were unambiguously assigned on the basis of their multiplicity, position, and intensity in the ^{1}H NMR spectrum. Taking into account these data and cross peaks in the HSQC spectrum (Fig. 2), we identified signals in the ^{13}C NMR spectrum, which belong to carbon atoms attached to protons. Signals from carbon atoms with no protons attached thereto were assigned using the HMBC technique (Fig. 3) which is based on correlation of long-range proton–carbon constants ($^{2}J_{CH}$). The HMBC spectrum also allowed us to distinguish signals from protons in positions *6*/*9* and *7*/*8*, which have similar multiplicities. Protons in positions *6* and *8* give cross peaks with C^{9a}, while those at C^{7} and C^{9}, with C^{5a}.

EXPERIMENTAL

The melting points were determined on a Boetius device. The IR spectra were recorded on a UR-20 spectrometer from samples dispersed in mineral oil. The ^{1}H NMR spectra were measured on a Bruker MCL-250 spectrometer at 250.13 MHz. The two-dimensional NMR spectra of compound **XX** were obtained on a Bruker DRX-500 instrument (500.13 MHz for ^{1}H and 125.75 MHz for ^{13}C).

1,3-Diphenylimidazo[1,5-*a*]quinoxalin-4(5*H*)-one (I, X = Y = Ph, R = H). *a.* Quinoxaline **XV**, 0.20 g (0.6 mmol), was placed in a test tube and was heated for 10 min at 225±3°C on an oil bath. After cooling, 10 ml of acetone was added, and the mixture was heated for 5 min under reflux and cooled, and the precipitate was filtered off. Yield 0.11 g (56%) (cf. [13]).

b. A solution of 0.30 g (0.9 mmol) of quinoxaline **XV** in 7 ml of DMSO was heated for 2 h at 150°C. It was then cooled and poured into water, and the precipitate was filtered off and washed with water. Yield 0.27 g (91%).

c. Benzylamine, 0.80 g (7.5 mmol), was added to a solution of 1.20 g (4.8 mmol) of quinoxaline **XII** in 10 ml of DMSO. The mixture was heated for 2 h at 150°C, cooled, and poured into water, and the precipitate was filtered off and washed with water. Yield 1.10 g (98%).

3-(α-Benzylaminobenzyl)quinoxalin-2(1*H*)-one (XV). Benzylamine, 0.80 g (7.5 mmol), was added to a solution of 1.00 g (3.7 mmol) of quinoxaline **XI** in 15 ml of DMSO, and the mixture was stirred for 3 h and was left to stand for 2 days. The solution was poured into water, and the precipitate was filtered off and washed with water. Yield 97%, mp >180°C (decomp.; from *i*-PrOH). IR spectrum, ν, cm^{-1}: 700, 755 , 777, 960, 1095, 1220, 1415, 1480, 1670, 2500–3300. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.72 d (1H, C**H**$_A$H$_B$Ph, J = 13.72 Hz), 3.75 d (1H, CH$_A$**H**$_B$Ph, J = 13.72 Hz), 5.29 s (1H, C**H**Ph), 7.20–7.55 m (13H, 2C$_6$H$_5$, 6-H, 7-H, 8-H), 7.84 d.d (1H, 5-H, J = 8.36, 1.52 Hz). Found, %: C 77.60; H 5.47; N 12.46. $C_{22}H_{19}N_3O$. Calculated, %: C 77.40; H 5.61; N 12.31.

1,3-Bis(3-benzoyl-2-oxo-1,2-dihydroquinoxalin-1-ylmethyl)benzene (XVII). A mixture of 0.80 g (3.2 mmol) of quinoxaline **XII**, 0.30 g (5.4 mmol) of KOH, and 30 ml of dioxane was heated for 1 min under reflux, 0.45 g (1.7 mmol) of 1,3-bis(bromomethyl)benzene was added, and the mixture was heated for 3 h under reflux. The solvent was distilled off, water was added to the residue, and the precipitate was filtered off and washed with a solution of KOH and water. Yield 78%, mp 118–120°C (from acetone–methanol, 1:1). IR spectrum, ν, cm^{-1}: 615, 693, 725, 1119, 1169, 1254, 1324, 1344, 1400, 1560, 1602, 1651, 1683. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 5.50 s (2H, CH$_2$), 7.19 d (2H, 4-H, 6-H, J = 7.58 Hz), 7.22–7.31 m (4H, 8'-H, 2-H, 5-H), 7.35 d.d.d (2H, 6'-H or 7'-H, J = 7.45, 7.45, 0.6 Hz), 7.40–7.55 m (6H, *p*-H, *m*-H), 7.63 d.d (2H, 7'-H or 6'-H, J = 7.58, 7.15 Hz), 7.92 d.d (2H, 5'-H, J = 8.00, 1.68 Hz), 8.01 d.d (4H, *o*-H, J = 7.70, 1.25 Hz). Found, %: C 75.80; H 4.47; N 9.01. $C_{38}H_{26}N_4O_4$. Calculated, %: C 75.73; H 4.35; N 9.30.

1,3-Bis(1,3-diphenyl-2-oxoimidazo[1,5-*a*]quinoxalin-5-ylmethyl)benzene (XIX). *a*. Benzylamine, 0.10 g (0.93 mmol), was added to a solution of 0.20 g (0.33 mmol) of quinoxaline **XVII** in 7 ml of DMSO. The mixture was heated for 4 h at 150°C, cooled, and poured into water, and the precipitate was filtered off and washed with water. Yield 57%, mp 296–298°C (from DMSO). IR spectrum, ν, cm^{-1}: 696, 714, 745, 873, 1176, 1223, 1259, 1301, 1378, 1604, 1651. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 5.40 s (4H, CH$_2$), 6.77 d.d (2H, 7'-H or 8'-H, J = 8.00, 7.58 Hz), 6.90–7.70 m (26H, 8'-H or 7'-H, 9'-H, 6'-H, 2-H, 4-H, 5-H, 6-H, 1-C$_6$H$_5$, *m*-H and *p*-H in 3-Ph), 7.92–8.02 m (4H, *o*-H in 3-Ph). Found, %: C 79.87; H 4.52; N 11.04. $C_{50}H_{36}N_6O_2$. Calculated, %: C 79.77; H 4.82; N 11.16.

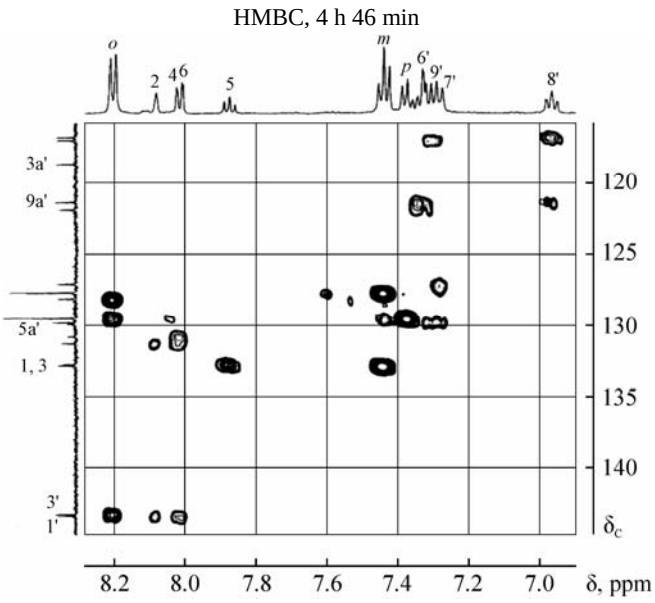


Fig. 3. Two-dimensional heteronuclear ^{13}C–^{1}H NMR spectrum (HMBC) of compound **XX** in DMSO.

b. *m*-Bis(bromomethyl)benzene, 0.12 g (0.45 mmol), was added to a mixture of 0.30 g (0.89 mmol) of compound **I** (X = Y = Ph, R = H), 0.10 g (1.8 mmol) of KOH, and 10 ml of DMSO. The mixture was stirred for 3 h and was left overnight. It was then poured into water, and the precipitate was filtered off and washed with water. Yield 75%.

1,3-Bis(3-phenyl-4(5*H*)-oxoimidazo[1,5-*a*]quinoxalin-1-ylmethyl]benzene (XX). 1,3-Bis(aminomethyl)benzene, 0.35 g (2.6 mmol), was added to a solution of 1.00 g (4.8 mmol) of quinoxaline **XII** in 10 ml of DMSO, and the mixture was heated for 72 h at 150°C. It was then cooled, and the precipitate was filtered off and washed with isopropyl alcohol. IR spectrum, ν, cm^{-1}: 704, 759, 910, 1104, 1342, 1486, 1562, 1608, 1660, 2500–3220. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 6.97 d.d.d (2H, 8'-H, J = 7.67, 7.67, 1.54 Hz), 7.29 d.d (2H, 7'-H, J = 8.21, 7.49 Hz), 7.31 d (2H, 9'-H, J = 7.49 Hz), 7.34 d.d (2H, 6'-H, J = 8.04, 1.54 Hz), 7.37 d.d (2H, *p*-H, J = 7.24, 7.24 Hz), 7.44 d.d (4H, *m*-H, J = 7.70, 7.25 Hz), 7.87 d.d (1H, 5-H, J = 7.81, 7.81 Hz), 8.02 d.d (2H, 4-H, 6-H, J = 7.81, 1.52 Hz), 8.08 s (1H, 2-H), 8.21 d.d (4H, *o*-H, J = 7.82, 1.22 Hz), 11.47 s (2H, NH). ^{13}C NMR spectrum, δ$_C$, ppm: 116.76 (C$^{6'}$), 116.97 (C$^{7'}$), 118.68 (C$^{3a'}$), 121.37 (C$^{9a'}$), 121.91 (C$^{8'}$), 127.10 (C$^{9'}$), 127.70 (C^{m}), 128.15 (C^{p}), 129.52 (C^{o}), 129.82 (C$^{5a'}$), 129.92

(C^5), 130.82 (C^2), 131.30 (C^4, C^6), 132.79 (C^1, C^3), 132.87 (C^i), 143.35 ($C^{3'}$), 143.47 ($C^{1'}$), 155.22 ($C^{4'}$).

This study was performed under financial support by the Russian Foundation for Basic Research (project no. 03-03-32865), by the joint program of CRDF and Ministry of Education of the Russian Federation "Basic Research and Higher Education" (project no. REC-007), and (in part) by the Charitable Foundation for Promotion of Domestic Science.

REFERENCES

1. Mamedov, V.A., Gubaidullin, A.T., Nurkhametova, I.Z., Litvinov, I.A., and Levin, Ya.A., *Russ. J. Org. Chem*., 2004, vol. 40, p. 534.
2. Jacobsen, E.J., Stelzer, L.S., Belonga, K.L., Karter, D.B., Im, W.B., Tang, V.H., Von Voigtlander, P.F., and Petke, J.D., *J. Med. Chem*., 1996, vol. 39, p. 3820.
3. Davey, D.D., Erhardt, P.W., Cantor, E.H., Greenberg, S.S., Ingebretsen, W.R., and Wiggins, J., *J. Med. Chem*., 1991, vol. 34, p. 2671.
4. Colltta, V., Cecchi, L., Catarzi, D., Filacchioni, G., Martini, C., Tacchi, P., and Lucacchini, A., *Eur. J. Med. Chem*., 1995, vol. 30, p. 133.
5. Ohmori, J., Shimizu-Sasamata, M., Okada, M., and Sakamoto, S., *J. Med. Chem*., 1997, vol. 40, p. 2053.
6. TenBrink, R.E., Jacobsen, E.J., and Gammill, R.B., US Patent no. 5541324, 1996; *Chem. Abstr*., 1996, vol. 125, no. 195687.
7. Hansen, H.C. and Watjen, F., EP Patent no. 344943 A1, 1989; *Chem. Abstr*., 1990, vol. 112, no. 216962.
8. Lee, T.D. and Brown, R.E., US Patent no. 4440929, 1984; *Chem. Abstr*., 1984, vol. 101, no. 7202.
9. Campiani, G., Morelli, E., Gemma, S., Nacci, V., Butini, S., Hamon, M., Novellino, E., Greco, G., Cagnotto, A., Goegan, M., Cervo, L., Valle, F.D., Fracasso, C., Caccia, S., and Mennini, T., *J. Med. Chem*., 1999, vol. 42, p. 4362.
10. Chen, P., Barrish, J.C., Iwanovich, E., Lin, J., Bednarz, M.S., and Chen, B-Ch., *Tetrahedron Lett*., 2001, vol. 42, p. 4293.
11. Kalinin, A.A., Mamedov, V.A., and Levin, Ya.A., Abstracts of Papers, *Peterburgskie vstrechi-98. Khimiya i primenenie fosfor-, sera- i kremniiorganicheskikh soedinenii* (St. Petersburg Meetings-98. Chemistry and Application of Organophosphorus, Organosulfur, and Organosilicon Compounds), St. Petersburg, 1998, p. 102.
12. Mamedov, V.A., Kalinin, A.A., Rizvanov, I.Kh., Azancheev, N.M., Efremov, Yu.Ya., and Levin, Ya.A., *Khim. Geterotsikl. Soedin*., 2002, p. 1279.
13. Mamedov, V.A., Kalinin, A.A., Azancheev, N.M., and Levin, Ya.A., *Russ. J. Org. Chem*., 2003, vol. 39, p. 125.
14. Kalinin, A.A., Mamedov, V.A., and Levin, Ya.A., Abstracts of Papers, *Peterburgskie vstrechi. 13 Mezhdunarodnaya konferentsiya po khimii soedinenii fosfora, 4 Mezhdunarodnyi simpozium po khimii i primeneniyu fosfor-, sera- i kremniiorganicheskikh soedinenii* (St. Petersburg Meetings. 13th Int. Conf. on the Chemistry of Phosphorus Compounds, 4th Int. Symp. on the Chemistry and Application of Organophosphorus, Organosulfur, and Organosilicon Compounds), St. Petersburg, 2002, p. 158.
15. Mamedov, V.A., Krokhina, L.V., and Il'yasov, A.V., *Khim. Geterotsikl. Soedin*., 1994, p. 1105.
16. Mamedov, V.A., Kalinin, A.A., Gubaidullin, A.T., Litvinov, I.A., and Levin, Ya.A., *Khim. Geterotsikl. Soedin*., 2003, p. 101.
17. Friebolin, H., *Basic One- and Two-Dimensional NMR Spectroscopy*, Weinheim: VCH, 1993, p. 368.
18. Braun, S., Kalinowski, H.-O., and Berger, S., *100 and More Basic NMR Experiments: A Practical Course*, Weinheim: VCH, 1996.