Combined application of 2D NMR correlation methods and *ab initio* chemical shift calculations to the structure determination of new heterocyclic compounds*

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The combined use of 2D NMR correlation methods and *ab initio* chemical shift calculations is efficient and, in some cases, virtually the only way to determine the structures of new organic compounds. This approach enabled us to establish the structure of the major unusual product of the three-component reaction of imidazo[1,5-*a*]quinoxalin-4-one, bis(2-chloroethyl)amine hydrochloride, and potassium carbonate in DMF.

Key words: 2D NMR correlation spectroscopy, *ab initio* (GIAO DFT) chemical shift calculations, structure, imidazo[1,5-*a*]quinoxalin-4-one, oxazolidin-2-one, alkylation, three-component condensation.

The structure determination of organic compounds is an important step in the development of procedures for the synthesis of new compounds having valuable properties, including pharmaceuticals. However, this may be a difficult and time-consuming problem if the synthesis involves competitive processes giving rise to compounds with isomeric structures, which cannot form suitable single crystals. In such cases, NMR spectroscopy is the most appropriate and reliable method for the structure determination of unknown compounds.

Until recently, the structure determination by NMR spectroscopy has been based on a comparison of the chemical shifts of the compound under consideration with the experimental chemical shifts for models of the fragments of the desired molecule taking into account empirical data on the effects of the adjacent groups (the so-called α, β, γ, and δ effects). Based on the presence of resonances in the characteristic spectral regions, conclusions were drawn about the structures of fragments and the molecule as a whole. However, the chemical shifts are difficult or even impossible to empirically predict in the absence of appropriate models (for new classes of compounds).

The development of methods of NMR correlation spectroscopy aimed at finding spin-spin coupling connectivities between different nuclei (H—H, H—C, and H—N) has been a revolutionary breakthrough in the solution of these problems.[1—3] The HMBC correlations (connectivities), particularly, through long-range proton-carbon (nitrogen) coupling constants, opened the "non-empirical" way for the determination of chemical structures. Nowadays, the structural analysis by NMR spectroscopy involves the initial analysis of spin-spin coupling constants followed by the analysis of chemical shifts. It became possible to consider molecules successively from nucleus to nucleus, distinguish a particular fragment, and, in some cases, determine the structure of the molecule as a whole.

However, if the molecular skeleton contains two or more successive proton-unbound nonmagnetic atoms (*i.e.*, atoms, whose main isotopes have a spin not equal to 1/2; for example, ^{12}C, ^{14}N, or ^{16}O), the use of 2D HMBC correlations (connectivities) becomes impossible because four-bond coupling constants are usually small and, correspondingly, the cross-peaks either have low intensity or are absent. In this case, only fragments to these nuclei can be determined.

Therefore, there is a need for rules for the correct binding of the already known fragments to form the whole molecule. In the case of simple fragments and groups, which are linked, for example, by one bond and for which tabulated empirical data on their influence on the chemical shifts of the adjacent nuclei in the α, β, and γ positions are available, the effects of the assembly of fragments into a molecule on their chemical shifts can be predicted and the validity of the hypothesis can be estimated by comparing with experimental data.[4,5]

* Dedicated to Professor A. V. Il´yasov on the occasion of his 70th birthday.

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However, correct empirical data are either inadequate or not available for new compounds consisting of several heterocyclic fused systems, which are linked to each other through common carbon—carbon and carbon—heteroatom bonds, and nonfused fragments linked to each other by different bridging groups.

Hence, the use of *ab initio* methods for the estimation of chemical shifts holds promise. Probably, this is an ideal way of combining the experimentally determined fragments into a whole molecule.

An analysis of the published data shows that a considerable progress has been achieved in the application of calculation methods to the structure determination of small systems.[6—10] Several attempts to apply these methods to rather large molecules were documented.[11—15] In some cases, the calculations rather reliably reproduced the experimental chemical shifts for such systems.

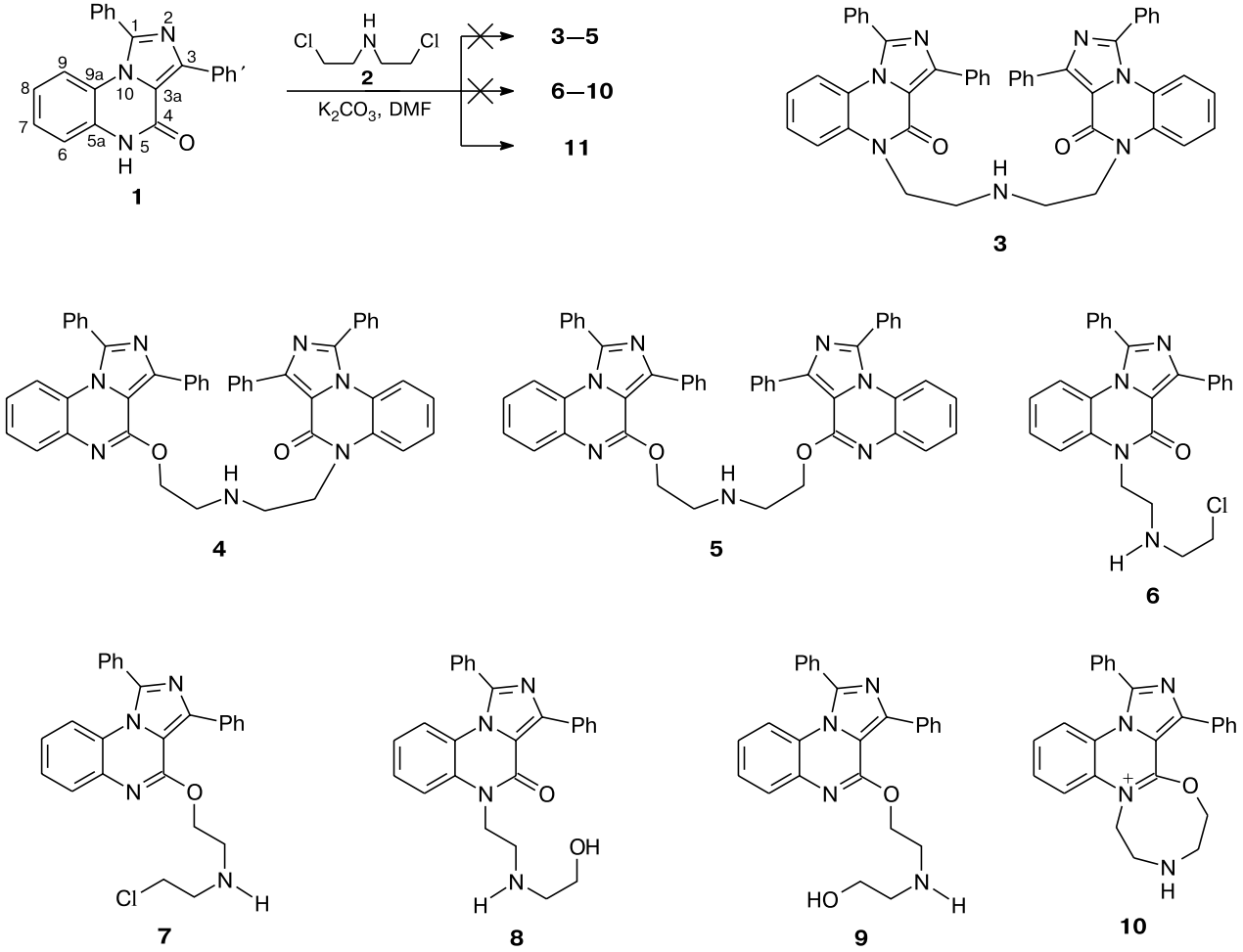
Moreover, the progress in computer technologies and efficient program products enables the application of calculations to rather large molecular systems with relatively low technical demands.

In the present study, we consider the use of this approach for the structure determination of quinoxaline derivatives, which have a broad spectrum of biological activities and, consequently, hold promise as drugs.[16—20] However, the conventional approaches are of limited use for such complex heterocycles.

Results and Discussion

The aim of the present study was to establish the structure of the major product of the reaction proceeding in the three-component imidazo[1,5-*a*]quinoxalin-4-one (**1**)—bis(2-chloroethyl)amine hydrochloride (**2**)—potassium carbonate system in DMF (Scheme 1). The reaction afforded a new compound rather than the expected products of *N*,*N*-, *N*,*O*-, and *O*,*O*-dialkylation of two tricyclic molecules **1** with one bis-chloroethylamine molecule **2** (compounds **3—5**). In the ^{1}H NMR spectrum of the new compound, the ratio of the total integrated intensities of the signals for the aromatic protons and the methylene groups is 14 : 8. The structures of compounds **6**

Scheme 1



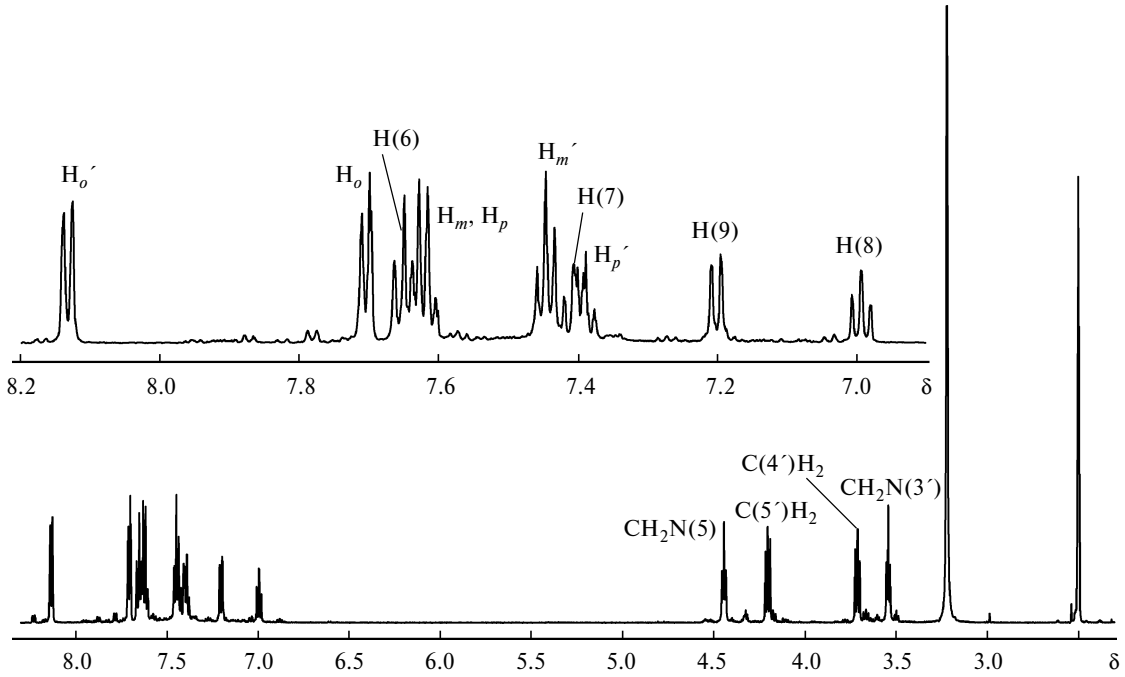


Fig. 1. The ^{1}H NMR spectrum of compound **11** in DMSO at 323 K.

or **7**, which are generated respectively by *N*- or *O*-monoalkylation of quinoxaline **1** with one bis-chloroethylamine molecule **2**, the products of their hydrolysis, **8** or **9**, or product **10** of *N*- and *O*-alkylation of quinoxaline **1** with one molecule **2** could be assigned to this new product. The ^{1}H NMR spectrum is not contradictory to these structures; however, they are inconsistent with the ^{13}C NMR spectroscopic data. Thus, the ^{13}C NMR spectrum shows 23 rather than the expected 22 signals, two signals being observed at low field (δ 158—154). It is difficult to assign one of the latter signals to any one C atom in structures **6—10**.

Therefore, it is impossible or rather difficult to directly determine the structure of the reaction product, *viz.*, compound **11**, with the use of the conventional approach based on a search for characteristic signals in ^{1}H and ^{13}C NMR spectra. Hence, we used a complex approach involving several 2D NMR correlation methods (COSY, HSQC, and HMBC). Apparently, this approach would enable the determination of the structure of the compound or the main fragments, which can be then correctly linked to each other based on the results of *ab initio* (GIAO DFT) chemical shift calculations.

The ^{1}H NMR spectrum of compound **11** (Fig. 1)* shows several multiplets at low field (δ 8.2—6.9) and four signals at δ 4.5—3.5 belonging to the protons of the methylene groups. Based on the 2D COSY data, the spin systems belonging to the following five functional groups were distinguished: the benzene fragment of quinoxaline, two phenyl groups, and two —CH_2—CH_2— fragments. Moreover, the signals for the proton-bound C atoms of these fragments were unambiguously identified taking into account the results of the 2D HSQC experiment.

The structures of the fragments were conclusively established based on ^{1}H—^{13}C HMBC and ^{1}H—^{15}N HMBC correlations.[21] The ^{1}H—^{13}C 2D HMBC spectrum (Fig. 2, *a*) has cross-peaks between the signals of the H(7) and H(9) protons (δ 7.41 and 7.20) of the benzo fragment and the C(5a) atom (δ 129.71) and between the H(6) and H(8) protons (δ 7.66 and 6.99) and C(9a) (δ 122.16). In addition, the ^{1}H—^{15}N 2D HMBC spectrum (Fig. 2, *b*) shows cross-peaks between H(9) and N(10) (δ 168.82) and between H(6) and N(5) (δ 130.20). In this manner, the structure of the benzo fragment up to the N(5) and N(10) atoms inclusive (Fig. 3), *i.e.*, the quinoxaline fragment, was established.

The 2D HMBC spectrum also shows correlations between the *meta* protons and the C_{ipso} atom (δ 131.61) and between the *ortho* protons and the quaternary C atom (δ 144.01) for the first phenyl group (Ph); between the *meta* protons and the C_{ipso} atom (δ 132.72) and between the *ortho* protons and the quaternary C atom (δ 143.70) for the second phenyl group (Ph´) (see Fig. 2, *a*). Hencee, two phenyl fragments up to the quaternary C atoms through which these fragments are bound to the molecular skeleton were identified.

In addition, the ^{1}H—^{13}C 2D HMBC spectrum has an intense cross-peak between the signal for the CH_2 pro-

* In the assignments in the NMR spectra, we used the atomic numbering scheme for the structure of **11** established more recently.

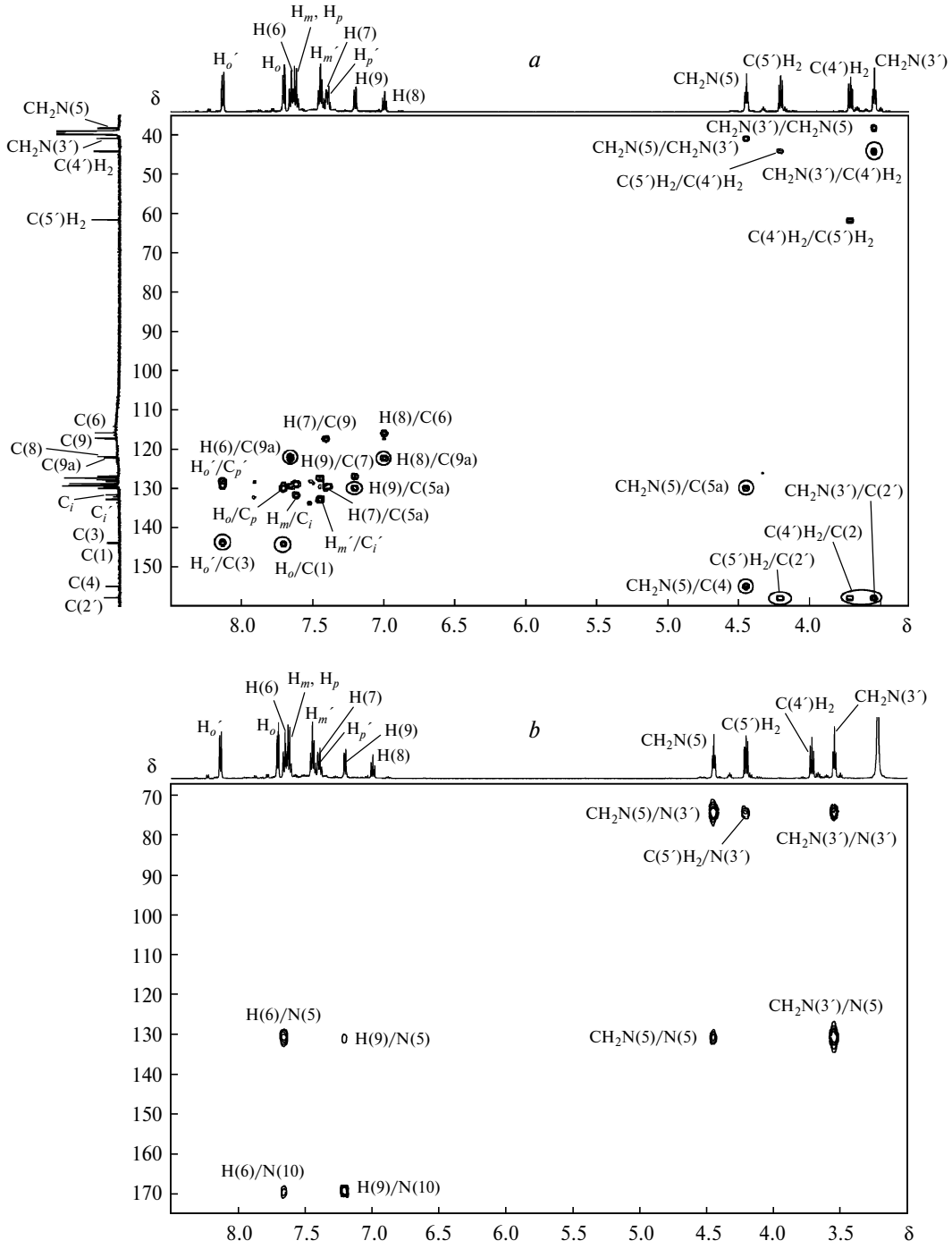


Fig. 2. The 2D HMBC spectrum of compound **11** in DMSO at 323 K: $^{1}H—^{13}C$ (*a*) and $^{1}H—^{15}N$ (*b*).

tons of one aliphatic chain (δ 3.54) and the resonance of the C atom of the CH_2 group (δ 44.18) of another chain, which is indicative of the presence of a covalent bond between these two $CH_2—CH_2$ fragments (see Fig. 2, *a*). The 2D HMBC spectrum also shows cross-peaks between the CH_2 protons (δ 4.44) of one of the $CH_2—CH_2$ groups and the C(5a) (δ 129.71) and C(4) (δ 154.90) atoms of the quinoxaline fragment (see Fig. 2, *a*), which is indicative of the presence of a covalent bond between these protons and the benzo fragment. This fact is additionally confirmed by the $^{1}H—^{15}N$ 2D HMBC spectroscopic data (see Fig. 2, *b*). This spectrum has cross-peaks between the $CH_2—CH_2$ fragments (δ 4.44 and 3.54) and the N(5) atom (δ 130.20). There is also a connectivity between the $CH_2—CH_2$ (δ 4.44 and 3.54) and CH_2 (δ 4.20) fragments and the N(3′) atom (δ 73.60). The above data provide

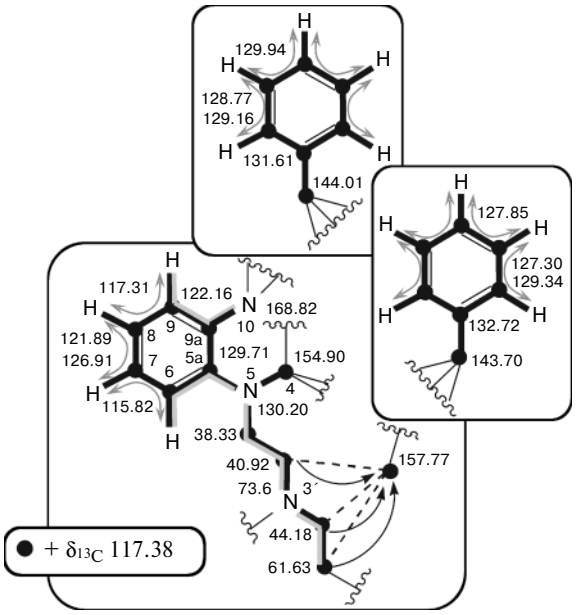


Fig. 3. Principal homonuclear (gray arrows) and heteronuclear correlations (from protons to C atoms, solid lines and arrows; to N atoms, gray lines; dashed lines indicate versions of covalent bonds between nuclei through two or three bonds) and the ^{13}C and ^{15}N chemical shifts for compound **11**.

unambiguous evidence for the presence of a bond between two CH_2—CH_2 fragments through the N(3′) atom.

It should be noted that the ^1H—^{13}C 2D HMBC spectrum shows (see Fig. 2, *a*) cross-peaks between the signals for the protons of three CH_2 groups (δ 4.20, 3.71, and 3.54) and the quaternary C atom (δ 157.77).

However, the ^{13}C NMR spectrum of compound **11** shows yet another signal for the quaternary C atom at δ 117.38, which has no correlations in the 2D HMBC spectrum.

Hence, two phenyl fragments and one structural block consisting of the benzo fragment up to the N(5) and N(10) atoms and the N(5)—CH_2—CH_2—N(3′)—CH_2—CH_2 chain bound to the latter fragment were identified in compound **11** based on the homonuclear (^1H—^1H) and heteronuclear correlation experiments (^1H—^{13}C and ^1H—^{15}N) (see Fig. 3). The structure of the molecular skeleton that links these fragments and contains two quaternary C atoms, one N atom, and one or two O atoms remained unestablished.

The aim of the next step was to correctly link the already found structural blocks to form the whole molecule. As has been demonstrated earlier,[6–15,22–25] *ab initio* quantum chemical calculations of chemical shifts could be an efficient tool for obtaining spectrum-structure correlations. Therefore, a comparison of the experimental ^{13}C and ^{15}N chemical shifts with those calculated for a series of hypothetical structures will enable the correct choice of the real structure.[26]

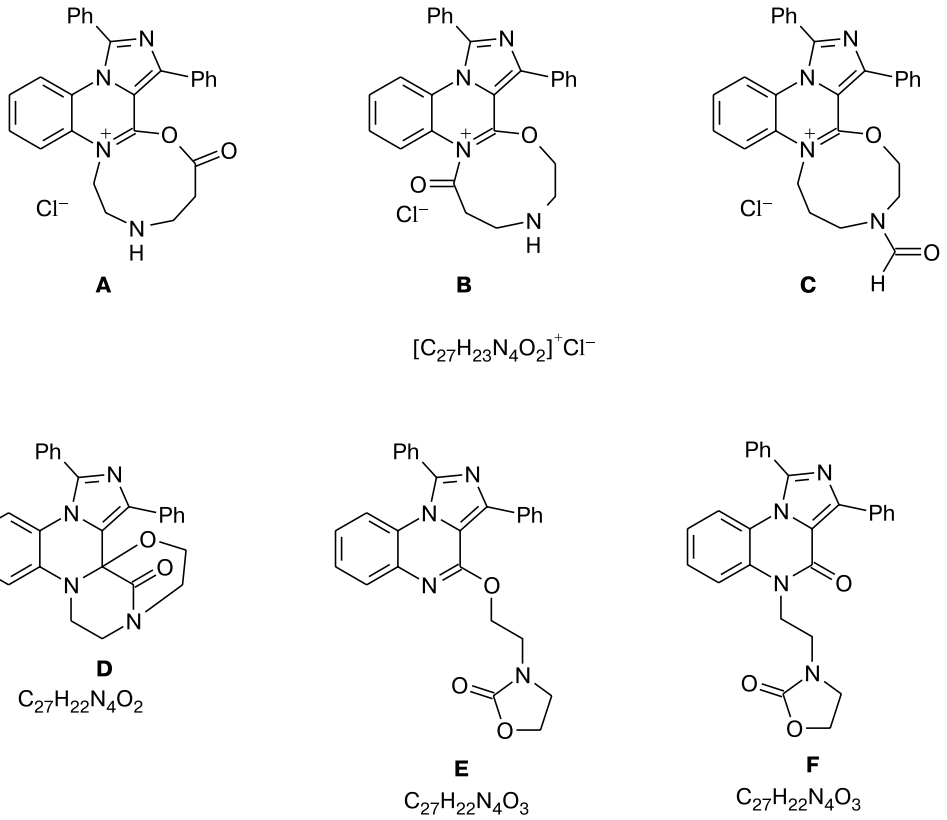
Based on the experimentally established three fragments of the molecule and the additionally found quaternary C atom covalently bound to three methylene groups through two or three bonds (from the 2D HMBC spectrum) and the resonance of the quaternary C atom at δ 117.38, six possible structures (**A—F**) of compound **11** were initially proposed. For these structures, we calculated (GIAO B3LYP/6-31G(d)//HF/6-31G) the ^{13}C and ^{15}N chemical shifts. Taking into account that tricyclic system **1** remains intact upon alkylation (see Scheme 1) involving the N and O atoms of the reactive carbamoyl group and based on the experimentally found fragments, we varied only the structure of the C(4)—N(5)—CH_2—CH_2—N(3′)—CH_2—CH_2 chain with the attached quaternary C atom (δ 157.77) for the possible structural isomers of **11**, the structure of the skeleton of the starting compound **1** being kept unchanged.

Of the six possible structures, four structures (**A—D**) do not correspond to the elemental analysis data. Hence, the decision should be made between the structures **E** and **F**. However, since the present publication has a methodological character, it was desirable to examine the possibilities and find the limitation of the approach based on the combined application of 2D NMR experiments and quantum chemical calculations to the structure determination of organic compounds. Hence, all the above-mentioned six structures are discussed below.

The ^{13}C chemical shifts were analyzed only for the C atoms of the variable fragment (C(4)—N(5)—CH_2—CH_2—N(3′)—CH_2—CH_2 and the C atom at δ 157.77). An analysis of the chemical shifts of the other C atoms of compound **11** (this analysis is not reported in the present paper) demonstrated that the chemical shifts of the above-mentioned C atoms for all possible structures of **11** are virtually identical. In addition, a good correlation between the experimental and calculated data for these C atoms is observed for all isomers of **11**.

The choice of the correct hypothesis was based on the analysis of the statistical errors and the correlation coefficients (Table 1), which serve as the criterion of agreement between the calculations and experiment.* It was demonstrated that the calculated and experimental ^{13}C chemical shifts are best consistent with the structure **F**, although rather high correlation coefficients are observed for most of the possible structures, which is associated with a broad range of the chemical shifts under consideration. The correlation between the experimental and theoretical values is quantitatively described by the rms and the mean absolute deviation (MAD). These parameters are evidence

* The GIAO method at the level of theory used in the present study systematically underestimates the chemical shifts. However, this is not principal for the solution of the problem at hand, and we analyzed only the correlation coefficients and the root-mean square (rms) errors.



in favor of the structure **F**: rms for **F** is 5.3, whereas the minimal rms for the other structures is 10.93 (**B**); MAD is 4.34 for **F**; for the other structures, MAD is no lower than 8.43 (**E**).

Table 1. Correlation coefficients between the experimental and theoretical (GIAO B3LYP/6-31G(d)//HF/6-31G) ^{13}C chemical shifts (R), the root-mean-squares (rms) errors, the slopes (a), the standard deviations (sd), and the mean absolute deviations (MAD = $\Sigma[\,|\delta_{exp} - \delta_{calc}|]/n$) for the structures **A—F**

Structure	R^2	rms	a	sd	MAD
A	0.9484[a]	7.72	0.96	7.89	6.87
	0.9441[b]	12.53	0.91	13.72	10.44
B	0.9373	8.65	0.89	8.84	6.98
	0.9566	10.93	0.95	11.98	10.89
C	0.9527	8.07	0.86	8.25	6.48
	0.9663	10.98	0.87	12.03	9.57
D	0.7825	15.84	0.80	16.19	8.46
	0.6600	30.65	0.70	33.58	20.21
E	0.9755	6.87	0.85	6.93	6.80
	0.9748	11.02	0.84	12.07	8.43
F	0.9962	3.69	0.91	3.78	5.65
	0.9988	5.30	0.90	5.80	4.34

[a] All ^{13}C chemical shifts.

[b] The chemical shifts of the C(4), C(2′), $CH_2N(5)$, $C(3')H_2$, $C(4')H_2$, and $C(5')_2H$ atoms.

As for the ^{15}N chemical shifts, we failed to obtain the experimental chemical shift for the N(2) atom, because the coupling constant $^4J_{H,N}$ in these systems is small and, hence, the intensity of the cross-peak in the 2D HMBC spectrum ($^1H—^{15}N$) between the N(2) atom and the nearest proton is lower than the sensitivity threshold of the method. In this connection, the chemical shifts were analyzed only for three nitrogen atoms (N(5), N(10), and N(3′)). Earlier,[25] it has been found that calculations of the ^{15}N chemical shifts at the B3LYP 6-31G(d) level of theory overestimate the chemical shifts at low field by 15 ppm. Hence, the calculated ^{15}N chemical shifts for the structures **A—F** were calibrated taking into account this correction.

The experimental chemical shifts for three N atoms also provide evidence in favor of the structure **F**. As can be seen from Fig. 4, which shows the deviations of the calculated chemical shifts from the experimental data only for the structure **F**, these deviations are small for all three N atoms simultaneously, whereas the deviations in all other cases are large.

The proposed chemical structure of **11** was confirmed by the results of IR spectroscopy and mass spectrometry.

Our data on the NOE (we used the procedure described earlier[27]) supported the conclusion about the three-dimensional structure of compound **11** (Figs 5 and 6). The strong effects between the *ortho* protons of

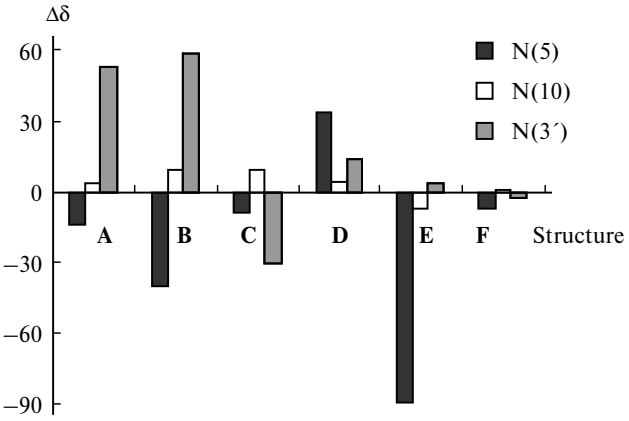


Fig. 4. Differences between the experimental and calculated ^{15}N chemical shifts for the possible structures **A—F** of compound **11**.

one phenyl group (δ 7.70) and the H(9) atom (δ 7.20) of the benzo fragment of quinoxaline are indicative of the spatial proximity of these fragments (see Fig. 5, *e*, *f*); NOE between H(6) (δ 7.66) and $CH_2N(5)$ (δ 4.44) and NOE between $CH_2N(3')$ (δ 3.54) and $CH_2(4')$ (δ 3.71) are indicative of the spatial proximity of the protons of the oxazolidinone and quinoxaline fragments (see Fig. 5, *a—d*). In addition, the effects between $CH_2(5')$ (δ 4.20) and the *ortho* protons of the second phenyl group (δ 8.13) (see Fig. 5, *g*, *h*) confirm the spatial proximity of the oxazolidinone ring and this phenyl group.

Therefore, the structural fragments were unambiguously determined with the use of 2D NMR correlation experiments and the complete structure of oxazolidinylquinoxaline was established by comparing the experimental and calculated ^{13}C and ^{15}N chemical shifts for the possible structures. The conclusion about the structure was confirmed by the results of investigation by other physical methods (IR spectroscopy and mass spectrometry) and NOE measurements.

In conclusion it should be noted that the conventional approach to the structure determination based on a comparison of empirical data for model fragments can give incorrect results for new heterocyclic systems. For example, we analyzed the chemical shifts for the structures **A—F**, which were evaluated with the use of the additive scheme incorporated into the ChemOffice program package.[29] It appeared that information on the chemical shifts for the carbon atom of the $N^+{=}C{-}O$ fragment are lacking in the database, *i.e.*, even the confidence chemical shift for the C(4) atom is absent. Hence, if these structures were formed in the course of the reaction, they could not be established in terms of this empirical approach. Therefore, the combined use of modern 2D NMR experiments and *ab initio* chemical shift calculations is efficient and, in some cases (when other physical methods are unavailable), is virtually the only way to determine the chemical structures of new organic compounds.

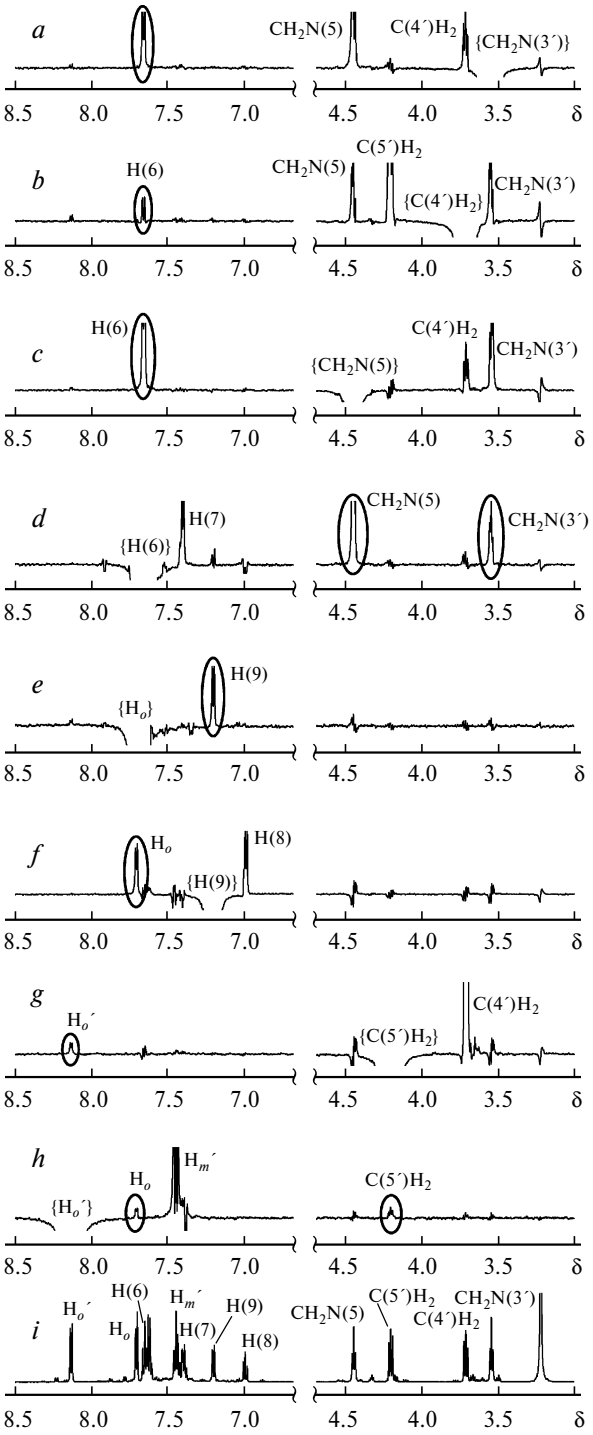


Fig. 5. The ^1H NMR spectra and NOE for compound **11** in DMSO at 323 K.

Experimental

The 1D and 2D NMR experiments (DEPT, NOESY, COSY, HSQC, HMBC, and HMBC $^1H{-}^{15}N$) for compound **11** were

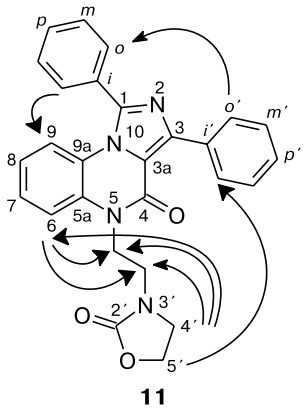


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Fig. 6. Principal NOE and their correlation with the structure of **11**.

carried out on a Bruker Avance-600 spectrometer (600 MHz for ^{1}H, 150.926 MHz for ^{13}C, and 60.796 MHz for ^{15}N) in DMSO-d_6 at 50 °C. The residual signals of DMSO (δ_H 2.50 and δ_C 39.43) were used as the internal standard. The EI mass spectra were recorded on a TRACE MS instrument (Funnigan MAT); the ionizing electron energy was 70 eV; the ion source temperature was 200 °C. The tube evaporator of the direct inlet system was heated in the programming mode from 35 to 250 °C with a step of 35 °C min^{-1}. The mass spectroscopic data were processed with the use of the XCALIBUR program. The matrix-assisted laser desorption/ionization (MALDI) mass spectrum was obtained on a DYNAMO MALDI TOF time-of-flight mass spectrometer (Thermo Bioanalysis Finnigan, USA).

The geometric parameters of the structures were optimized by the RHF method with the 6-31G basis set. The ^{13}C and ^{15}N chemical shifts were calculated by the B3LYP method at the GIAO DFT level of theory with the 6-31G(d) basis set. All calculations were carried out with the use of the GAUSSIAN-98 program package.[28] Tetramethylsilane (^{13}C) and NH_3 (^{15}N) were used as the standards.

5-(2-Oxooxazolidin-3-yl)ethyl-1,3-diphenylimidazo[1,5-*a*]-quinoxalin-4(5*H*)-one (11). Dry K_2CO_3 (0.65 g, 4.7 mmol) was added to a solution of 1,3-diphenylimidazo[1,5-*a*]quinoxalin-4(5*H*)-one (0.2 g, 0.6 mmol) in DMF (20 mL), and the reaction mixture was stirred for 5—10 min. Then bis(2-chloroethyl)amine hydrochloride (0.1 g, 0.6 mmol) was added to the suspension. The reaction mixture was stirred, the temperature of the mixture being maintained at 60 °C. The course of the reaction was monitored by TLC ($CHCl_3$—EtOAc, 3 : 1, as the eluent; Silufol (Kavalier, Czechoslovakia)). The total reaction time was 30 h. The solvent was evaporated *in vacuo* using a water-jet pump, and the residue was treated with a 10% aqueous $NaHCO_3$ solution. The crystals that precipitated were filtered off, washed with water, and dried in air. A mixture of products was obtained in a yield of 0.26 g (96%). Column chromatography afforded product **11** in a yield of 0.16 g, R_f = 0.10 ($CHCl_3$—EtOAc, 6 : 1, as the eluent; silica gel L 100/160 for chromatography, Chemapol), m.p. 249—251 °C. Found (%): C, 71.67; H, 5.18; N, 12.50. $C_{27}H_{22}N_4O_3$. Calculated (%): C, 71.99; H, 4.92; N, 12.44. IR, ν/cm^{-1}: 1734, 1658, 1614, 1541, 1485, 1427, 1390, 1370, 1444, 1327, 1302, 1268, 1227, 1160, 1128, 1113, 1043, 1016, 985, 969, 909, 769, 752, 733, 694, 666, 616, 595, 570. ^{1}H NMR, δ: 3.54 (dd, 2 H, CH_2N(3′), J = 6.6 Hz, J = 5.9 Hz); 3.71 (dd, 2 H, C(4′)H_2, J = 8.1 Hz, J = 7.3 Hz); 4.20 (dd, 2 H, C(5′)H_2, J = 8.1 Hz); 4.44 (dd, 2 H, CH_2N(5), J = 6.6 Hz, J = 5.9 Hz); 6.99 (dd, 1 H, H(8), J = 8.1 Hz, J = 8.0 Hz); 7.2 (d, 1 H, H(9), J = 8.1 Hz); 7.39 (dd, 1 H, $H_{p'}$, J = 7.3 Hz, J = 1.5 Hz); 7.41 (dd, 1 H, H(7), J = 8.1 Hz, J = 1.5 Hz); 7.45 (dd, 2 H, $H_{m'}$, J = 7.3 Hz, J = 1.5 Hz); 7.63 (m, 3 H, H_m, H_p); 7.66 (d, 1 H, H(6), J = 8.8 Hz); 7.70 (dd, 2 H, H_o, J = 6.6 Hz, J = 1.5 Hz); 8.13 (d, 2 H, $H_{o'}$, J = 7.3 Hz). ^{13}C NMR, δ: 38.33 (CH_2N(5)); 40.92 (CH_2N(3′)); 44.18 (C(4′)); 61.63 (C(5′)); 115.82 (C(6)); 117.31 (C(9)); 117.38 (C(3a)); 121.89 (C(8)); 122.16 (C(9a)); 126.91 (C(7)); 127.30 ($C_{m'}$); 127.85 ($C_{p'}$); 128.77 (C_m); 129.16 (C_o); 129.34 ($C_{o'}$); 129.71 (C(5a)); 129.94 (C_p); 131.61 (C_o); 132.72 ($C_{o'}$); 143.70 (C(3)); 144.01 (C(1)); 154.90 (C(4)); 157.77 (C(2′)). MS, m/z (I_{rel} (%)): 450 (100), 397 (8), 363 (37), 350 (87), 337 (67), 219 (22), 89 (13), 56 (13). MALDI-TOF MS (nitroaniline), m/z: 451 [MH].

Compound **11** was studied in the NMR Department of the Multiple-Access Center, the Spectroanalytical Center (SC SAC) for Physicochemical Investigations of Structure, Properties and Composition of Substances and Materials, and the Federal Center for Collective Use of Physicochemical Investigations of Substances and Materials (FCCU PI) (State Contracts of the Ministry of Education and Science of the Russian Federation, Nos 02.451.11.7036 and 02.451.11.7019).

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