Structural studies of conformers of 3-(*N*-acetyl-*N*-arylamino)tropones by heteronuclear, two-dimensional, and dynamic NMR spectroscopy and X-ray diffraction analysis*

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Acylation of 5,7-di(*tert*-butyl)-2-(5,8-dimethyl-4-piperidinoquinolin-2-yl)-3-(3,5-dimethylphenylamino)tropone leads to the corresponding 3-(*N*-acetyl-*N*-arylamino)tropone. Heteronuclear, two-dimensional, and dynamic NMR spectroscopy were used to determine structures of conformers of *N*-acetyl-3-arylaminotropone. The structure of 3-[*N*-acetyl-*N*-(3,5-dimethylphenyl)amino]-5,7-di(*tert*-butyl)-2-(5,8-dimethyl-4-piperidinoquinolin-2-yl)-tropone was established by X-ray diffraction studies.

Key words: quinolines; 1,3-tropolones; intramolecular hydrogen bond; heteronuclear, two-dimensional, dynamic NMR spectroscopy; X-ray diffraction studies.

The interest to tropolone derivatives is caused by their antitumor activity,[1] ability to inhibit plant growth.[2] They serve as efficient bioisosteric analogs of benzoic acids in some retinoid structures.[3]

Earlier, we have found that the reaction of 3,5-di(*tert*-butyl)-1,2-benzoquinone with 2-methylquinoline derivatives led to 2-(quinolin-2-yl)-1,3-tropolone derivatives **1** (see Refs 4 and 5) (Scheme 1). Functionalization of a tropone ring with arylamines[6] is based on the introduction of a chlorine atom at position 3 of the tropone ring of **1** with subsequent nucleophilic substitution with primary amines. The structure of 2-(quinolin-2-yl)-substituted 3-aminotropones **2** is distinguished by the presence of an intramolecular hydrogen bond.[4,5]

Results and Discussion

In solution 3-aminotropone **2** exists in the dynamic tautomeric equilibrium N...H...N. The signal for the proton of the NH group of compound 2 in the ^{1}H NMR spectrum resonates in the low field (δ 14—15) as a broad singlet,[6] which is shifted up-field relative to the similar signal of 1,3-tropolone **1** by 4—5 ppm.[4] The presence in 2-(quinolin-2-yl)-1,3-tropolone (**1**) of a stronger intramolecular bond O—H...N, as compared to arylaminotropones **2**, made it impossible to carry out reactions typical of the OH group.

In the present work, we found that arylaminotropone **2** can be easily acylated with acetic anhydride with the formation of *N*-acetyl derivative **3** in 74% yield (see Scheme 1).

The structure of compound **3** was confirmed by ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy, and mass spectrometry. Analysis of the dynamic ^{15}N NMR spectrum showed the absence of the acylotropic transformations **3 (Ac)** to **3′ (Ac)**. Studies of molecule **3** by single crystal X-ray diffraction showed that the independent part of the unit cell contains two molecules, one of which has a disordered piperidine fragment (Fig. 1, *a*). In this case, the shaded and nonshaded groups in the single crystal are in the ratio 0.63 to 0.37. Figure 1, *b* shows the second molecule, which has no disordering.

The C=O bond distances in the molecules are as follows: O(1)—C(1) = 1.216(3), O(2)—C(40) = 1.224(3), O(51)—C(51) = 1.228(3), O(52)—C(90) = 1.219(3) Å.

* Dedicated to Academician of the Russian Academy of Sciences V. I. Minkin on the occasion of his 80th birthday.

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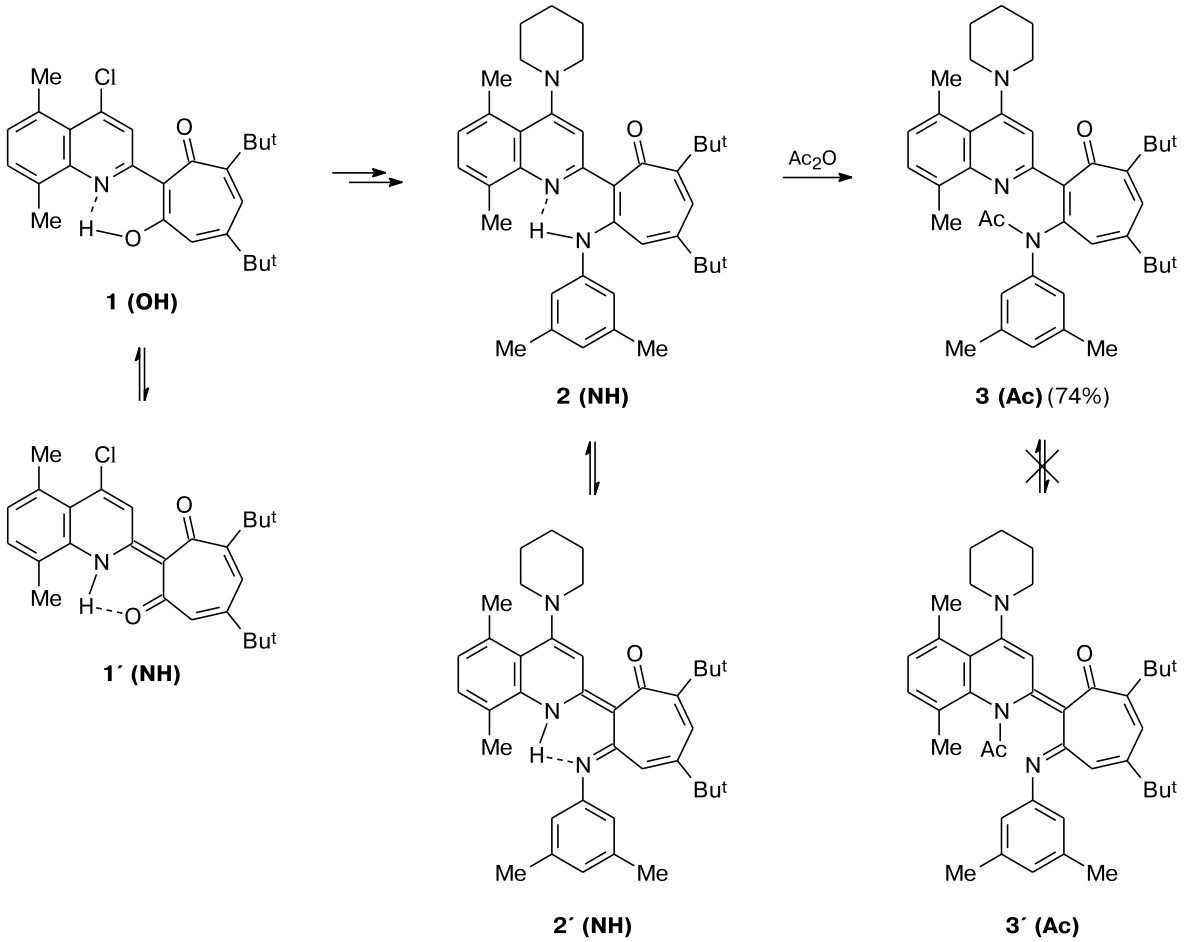
Scheme 1



The absence of the intramolecular hydrogen bond, found earlier[6] in similar compounds and stabilizing the arrangement of the quinoline and the tropolone fragments in one plane, leads to the turn of these groups around the C(2)—C(8) bond, with the torsional angle N(1)—C(8)—C(2)—C(1) being 127.6°; a similar turn around the

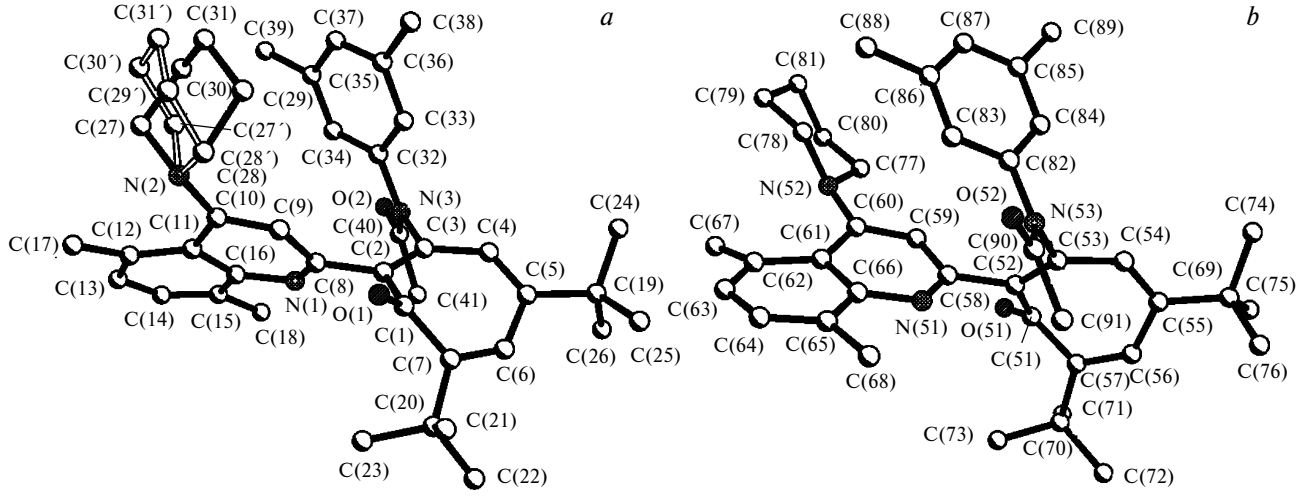


Fig. 1. Molecular structure of 3-[*N*-acetyl-*N*-(3,5-dimethylphenyl)amino]-5,7-di(*tert*-butyl)-2-(5,8-dimethyl-4-piperidinoquinolin-2-yl)tropone (**3**) (two independent molecules, hydrogen atoms are omitted).

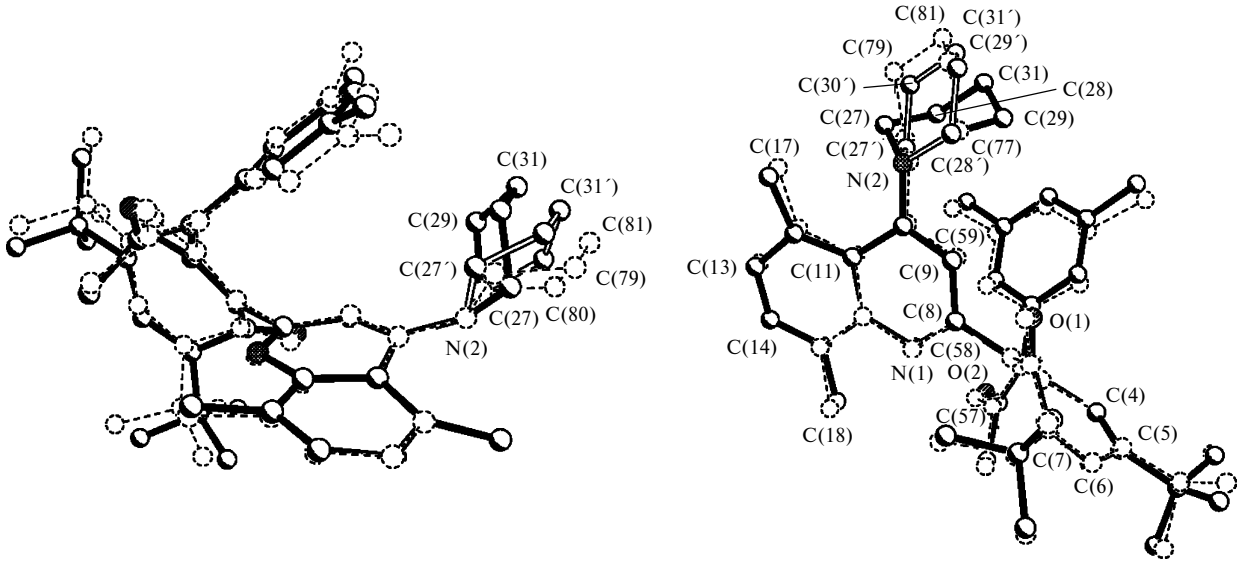


Fig. 2. Superimposition of molecules **3** at the atoms of the quinoline and the tropolone fragments.

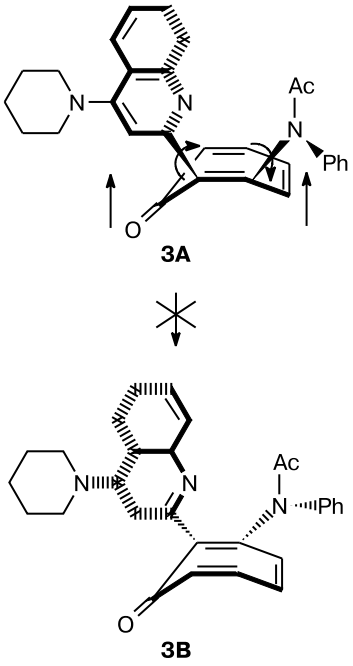
C(52)—C(58) bond is equal to 119.2°. The tropolone ring has the *boat* conformation.

The superimposition of the molecules by the atoms of the quinoline and the tropolone fragments (Fig. 2) reveals the character of positional differences of the piperidine groups relative to the main parts of the molecules, which superimpose well enough. Thus, three conformers of one molecule coexist in the single crystal in the ratio 3 : 2 : 1 (shown in Fig. 2 in the dashed, shaded, and nonshaded lines, respectively).

The molecule of compound **3** exists as two optically active atropisomers **3A** and **3B** (Scheme 2), the formation of which can be explained by the attack of the electrophile (the acyl group) at the NH group of aminotropone **2** according to the bimolecular electrophilic substitution mechanism with subsequent inversion to isomer **3A** or **3B**. Theoretically, the racemization can be achieved through the inversion of the seven-membered ring with a simultaneous turn of both aromatic substituents by 180° around the C(2)—C(8) and C(3)—N(3) bonds, which bond them to the tropolone ring (see Scheme 2). However, the rotation of sterically overloaded quinoline and *N*-acylphenyl fragments around the C(2)—C(8) and C(3)—N(3) bonds in isomers **3A** or **3B** is hindered, that stabilizes these atropisomeric configurations. The modeling of the reaction of rotation of the tropolone fragment around the C(2)—C(8) bond showed that in the course of this process, the distance between the hydrogen atoms of the methyl groups at atom C(18) of the quinoline ring and at atom C(38) of the *N*-phenyl fragment become considerably smaller than the sum of their van der Waals radii, that makes this process hardly possible.

The change in the conformation of a part of enantiomeric molecules disturbs the identity of their geometric

Scheme 2



configuration and transforms the racemate to a mixture of diastereomers. Thus, in the crystal unit cell we observe two pairs of enantiomers, differing in the position of the piperidine ring.

In the ^{1}H NMR spectrum of compound **3** in solution in $CDCl_3$, broadening of signals is observed at room temperature, while cooling of the solution leads to the appearance of signals for the protons of two isomeric forms in the ratio 7 : 3 (Fig. 3). The signals collapsed when the temper-

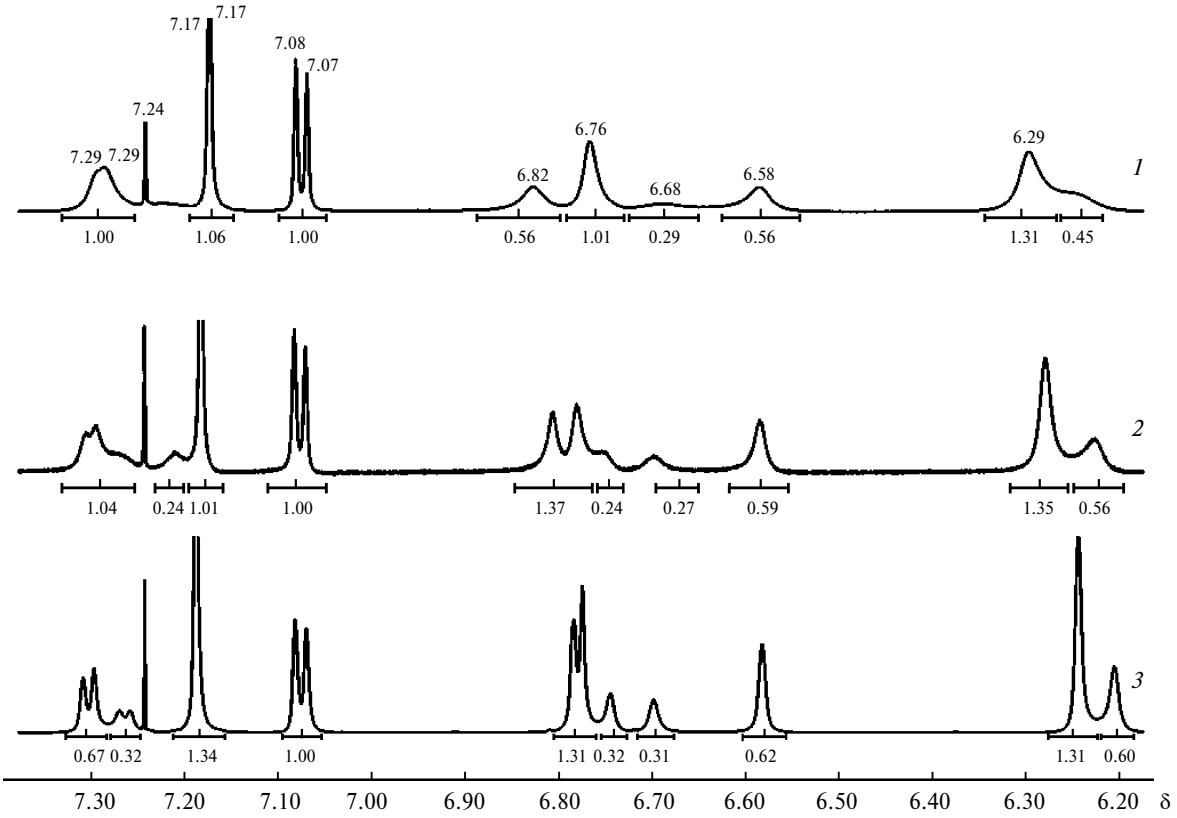


Fig. 3. Doubling of signals in the ^{1}H NMR spectra of compound **3** upon decrease in temperature: 30 (*1*), 20 (*2*), and 9 °C (*3*), solvent $CDCl_3$.

ature of the solution of compound **3** in DMSO was increased to 80 °C (Fig. 4).

In order to identify the conformers of compound **3** existing in solution, a full assignment of signals in the ^{1}H NMR spectrum was made based on the characteristic chemical shift values and analysis of the cross-peaks in the 2D ^{1}H—^{1}H correlation spectra COSY and NOESY, as well as on the HSQC data obtained upon reduction of

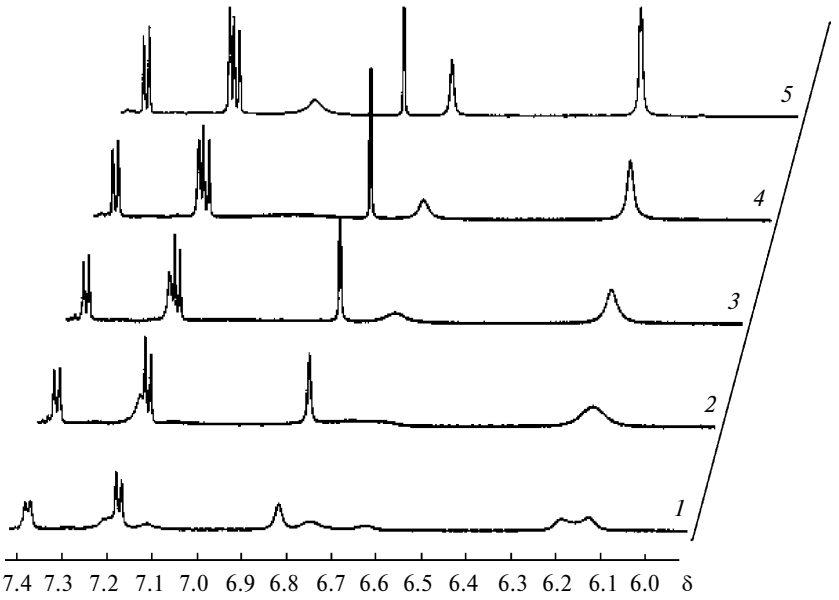


Fig. 4. Collapse of signals in the ^{1}H NMR spectra of compound **3** upon increase in temperature: 30 (*1*), 40 (*2*), 50 (*3*), 60 (*4*), 80 °C (*5*), solvent DMSO-d_6.

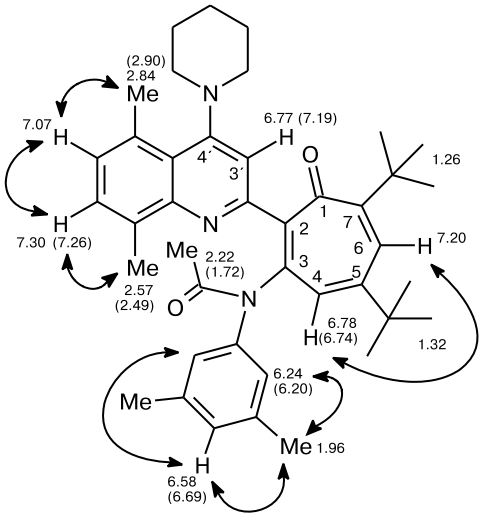


Fig. 5. Scheme of principal COSY correlations (10 °C) and assignment of signals in compound **3** (here and further, chemical shifts for the protons changing their values upon conversion to the less occupied conformation are given in parentheses).

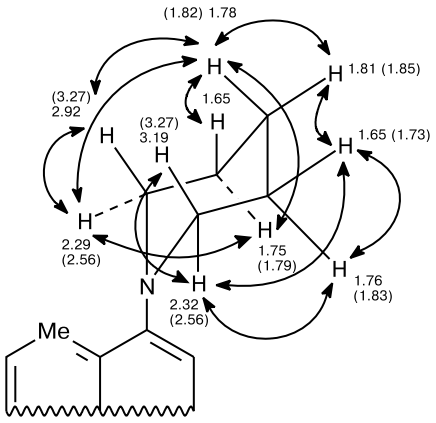


Fig. 6. Scheme of principal COSY correlations (10 °C) and assignment of signals in the piperidine ring of compound **3**.

temperatures to 10 °C. Figures 5 and 6 show chemical shifts for the predominant and the minor conformations, as well as the correlations of the spectrum COSY observed in both forms.

In the NOESY spectra of compound **3**, apart from the through-space interactions, the exchange correlations are observed between the signals of equivalent atoms and groups of atoms of two forms of molecule **3** (Fig. 7). This indicates a high enough rate of isomerization interconversions ($10^2 < k_{ex} < 10^{-2}$ s^{-1}).

The through-space correlations NOESY for both forms are given in Table 1 and schematically shown in Fig. 8. Analysis of these data did not show any considerable differences in the mutual arrangement of the fragments of two isomeric forms of molecule **3**.

Analyzing the 2D low-temperature spectra, we paid special attention to the structure of the piperidine ring, since in the crystal lattice the disordering of its conformation results in the existence of two pairs of enantiomeric molecules in the unit cell. However, the correlations confirming a long enough existence in solution of the conformer, which is shaded in Figs 1, *a* and 2, are absent in the spectra under consideration. The key through-space correlations NOESY for the protons of the piperidine ring are schematically shown in Fig. 9. It should be noted that

Table 1. Coordinates of cross-peaks (δ) in the NOESY and HSQC spectra of compound **3** (10 °C)

^{1}H NMR	NOESY, ^{1}H	HSQC, ^{13}C
7.30 (7.26) (H(7´))	7.09, 2.57 (7.07, 2.49)	128.2 (127.8)
7.20 (H(6))	1.32, 1.26	127.7 (125.9)
7.07 (H(6´))	7.30, 2.85 (7.26)	128.2 (127.9)
6.78 (6.74) (H(4))	6.24, 2.22, 1.32, 1.26 (6.20, 1.72, 1.32, 1.26)	126.1 (126.3)
6.77 (7.19) (H(3´))	3.28, 3.20, 2.93, 2.57, 2.30, 2.28 (3.28, 3.20, 2.93, 2.57, 2.30, 2.28)	112.0 (112.3)
6.58 (6.69) (*p*-Ph)	6.24, 1.96 (6.20, 1.96)	126.8 (128.6)
6.24 (6.20) (*o*-Ph)	6.78, 6.58, 2.57, 2.22, 1.96, 1.32, 1.26 (6.74, 6.69, 1.96, 1.32, 1.26)	122.6 (125.1)
3.19 (3.27) (α-CH_2)	7.19, 6.77, 2.84, 2.32, 2.29, 1.81, 1.78, 1.75, 1.65 (2.56, 1.83—1.75, 1.65)	54.2 (54.4)
2.92 (3.27) (α-CH_2)	7.19, 6.77, 2.32, 2.29, 1.81, 1.78, 1.76, 1.65 (2.56, 1.83—1.75, 1.66)	54.0 (54.4)
2.84 (2.90) C(5´)CH_3	7.07, 3.19, 2.92, 1.96, 1.85—1.73 (7.07, 1.96, 1.85—1.75)	22.1 (22.2)
2.57 (2.49) C(8´)CH_3	7.30, 6.24, 2.22, 1.96 (7.26, 1.72, 1.96)	19.1 (19.0)
2.32 (2.56) (α-CH_2)	7.19, 6.77, 3.19, 2.92, 1.75, 1.65, 1.26 (7.19, 1.79, 3.27)	54.2 (54.4)
2.29 (2.56) (α-CH_2)	7.19, 6.77, 3.19, 2.92, 1.76, 1.65, 1.26 (7.19, 1.83, 3.27)	54.0 (54.4)
2.22 (1.72) (C(O)CH_3)	6.78, 6.24, 2.57, 1.32 (6.74, 2.49, 1.32)	24.7 (22.8)
1.96 ($C_6H_3(C\underline{H}_3)_2$)	6.58, 6.24, 2.84, 2.57 (6.69, 6.20, 2.90, 2.49)	21.1 (20.8)
1.65 (1.73) (β-CH_2)	3.19, 2.84, 2.32, 2.29, 1.85—1.75 (3.27, 2.56, 1.84—1.78)	25.6 (25.6)
1.76, 1.75 (1.83, 1.79) (β-CH_2)	3.19, 2.92, 2.84, 1.65 (3.27, 2.90, 1.73)	25.6 (25.6)
1.78, 1.81 (1.82, 1.85) (γ-CH_2)	3.19, 2.92, 1.65, 1.32, 1.26	24.2 (24.2)
1.32 (Bu^t(5))	7.20, 6.78, 6.24, 2.84, 2.57	30.5 (30.9)
1.26 (Bu^t(7))	7.20, 6.78, 6.24, 2.57	30.9 (30.5)

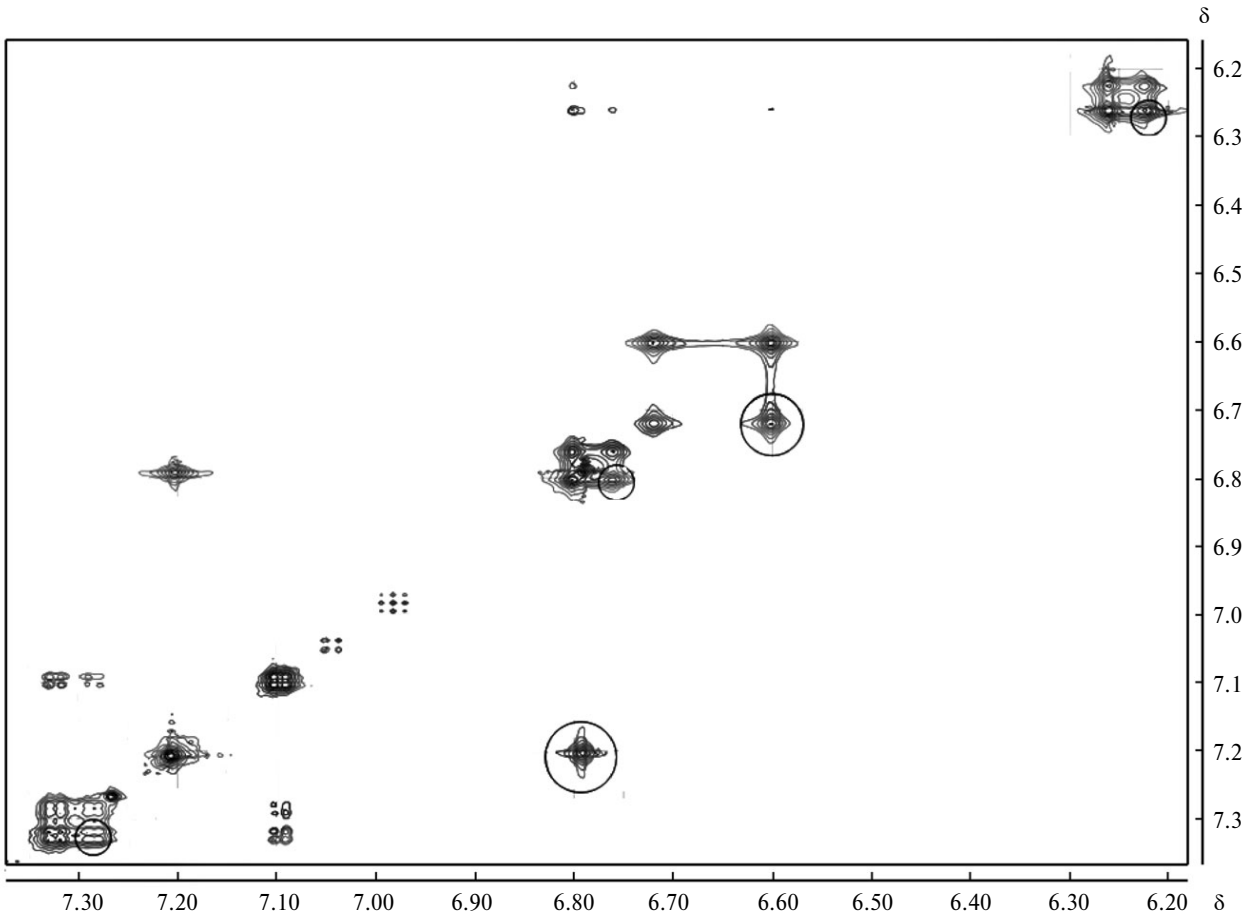


Fig. 7. A fragment of the NOESY spectrum of compound **3** with the marked exchange interactions (10 °C).

in the predominant form, the quinoline proton H(3′) interacts with four α-protons of the piperidine ring, but does not interact with the protons of β- and γ-units. The methyl group (δ_H 2.84) at *peri* position to the piperidine ring gives a cross-peak only with one of α-protons at δ_H 3.19. The spectrum NOESY also exhibits cross-peaks of this methyl group with protons of β- and γ-units at δ_H 1.74—1.83, but shows no correlation with β-protons at δ_H 1.65. Similar correlations were observed for the minor form of molecule **3**. Such spatial interactions indicate that molecules of compound **3** exist in solution in the conformations close to that given in Fig. 1, *a* or shown in dashed line in Fig. 2.

The temperature dependence of the NMR spectra and the presence of the exchange interactions in the spectra NOESY indicate that the dynamic processes of isomerization of molecular structure are rapid enough. Possible mechanisms of such reactions can be determined by the rotation of substituents in the system, as well as by the inversion of the tropolone and the piperidine fragments.

Since the rotation of the quinoline and the *N*-acyl substituents at positions 2 and 3 of the tropone ring is sterically hindered and the analysis of the low-temperature spatial interactions in the molecule did not reveal the inter-

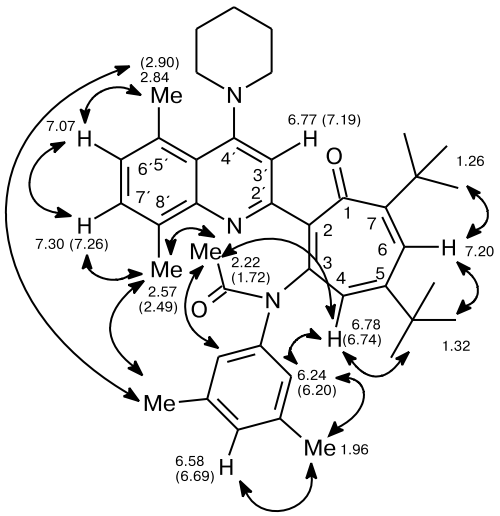


Fig. 8. Scheme of principal NOESY correlations in compound **3** (10 °C).

conversion of the piperidine ring, the most probable reasons for the observed dynamics of the NMR spectra can be both the inversion of the tropolone fragment and the rota-

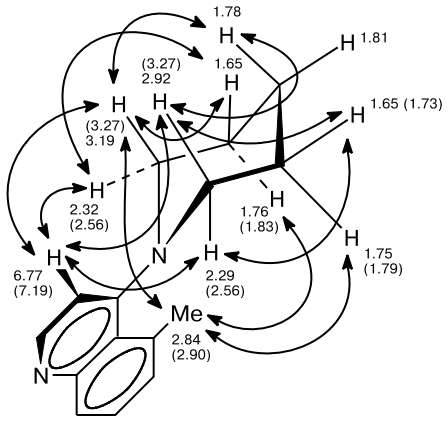


Fig. 9. Scheme of principal NOESY correlations (10 °C) in the piperidine ring of compound **3**.

tion of the acyl group around the C—N bond. The temperature dependence of the NMR signals of compound **3** in the region δ 6.1—6.2 (see Fig. 4) indicates the proceeding of the dynamic process in solution in DMSO with the activation barrier calculated using the Eyring equation and found to be equal to 15.7 kcal mol^{-1}. Close values of these parameters are characteristic of the rotation around the C—N bond in amides.[7] At the same time, the inversion of the tropolone ring will possibly have a lower barrier, since a similar process in the cycloheptatriene system, a structurally close seven-membered molecule, is accompanied by the passing an energy barrier of ~6 kcal mol^{-1} (see Ref. 8). These processes agree with the observed differences in the correlations NOESY and the change in the chemical shifts of the NMR signals on going from the major to the minor stereoisomer. The signal of proton H(3′) undergoes the largest downfield shift (δ_H 6.77 → 7.19), since upon inversion this proton comes out of the shielding region due to the magnetic anisotropy of the tropone C=O group. The signal of the acyl methyl shifts upfield (δ_H 2.22 → 1.72), its spatial interactions with the *ortho*-phenyl protons disappear, as do the interactions of the *ortho*-phenyl protons with the methyl group at position 8 of the quinoline ring.

In conclusion, the structure of the conformers of *N*-acetyl-3-arylaminotropones was studied by NMR spectroscopy and X-ray diffraction analysis, using representative **3** as an example. Based on the data of heteronuclear, two-dimensional, and dynamic spectroscopy, it was found that there exist rapid enough dynamic processes related to the isomerization of the molecular structure. According to the preliminary evaluation of a possibility of different reaction channels for isomerization, the most likely cause for the observed dynamics of the NMR spectra can be the rotation of the acyl group around the C—N bond. Besides, the inversion of the tropolone fragment can have a certain influence on the change in the spectral pattern.

Experimental

^{1}H, ^{13}C, ^{15}N NMR spectra were recorded on a Bruker AVANCE 600 spectrometer. The ^{1}H and ^{13}C signals were assigned relative to the signals of the corresponding deuterated solvents, whereas the ^{15}N NMR signals relative to the signals of CH_3NO_2. In the recording of NOESY spectra, the mixing time was 0.1 s. IR spectra were obtained on a Varian 3100FT-IR Excalibur Series spectrometer, using the frustrated total internal reflection technique (FTIR). Mass spectra were recorded on a Finnigan MAT INCOS 50 mass spectrometer. Chromatography was carried out on a column with Al_2O_3 of Brockmann II—III activity. Melting points were measured in glass capillaries on a PTP apparatus and were not corrected. 5,7-Di(*tert*-butyl)-3-(3,5-dimethylphenylamino)-2-(5,8-dimethyl-4-piperidinoquinolin-2-yl)tropone (**2**) was obtained as described.[6] IR and NMR spectra were recorded using facilities of the Molecular Spectroscopy Multi-user Center of the Southern Federal University.

3-[*N*-Acetyl-*N*-(3,5-dimethylphenyl)amino]-5,7-di(*tert*-butyl)-2-(5,8-dimethyl-4-piperidinoquinolin-2-yl)tropone (3). A solution of compound **2** (1 mmol) in acetic anhydride (7 mL) was refluxed for 7 h. A cooled solution was diluted with cold water and extracted with chloroform (50 mL). The extract was dried with anhydrous Na_2SO_4, concentrated, and subjected to chromatography on a column with Al_2O_3 (eluent chloroform—hexane, 1 : 1), collecting a colorless fraction with R_f 0.8. The solvent was evaporated, the residue was recrystallized from 2-propanol. The yield was 74%, colorless crystals with m.p. 202—203 °C (2-propanol). IR, ν/cm^{-1}: 1680, 1654, 1608, 1583, 1560, 1518, 1496, 1465, 1371, 1360, 1320, 1291, 1263, 1243, 1211, 1197, 1172, 1152, 1132, 1105, 1067, 1034, 1007, 974, 951, 930, 898, 860, 841, 818. ^{1}H NMR ($CDCl_3$, 10 °C), δ: 1.26 (s, 9 H, Bu^t(7)); 1.32 (s, 9 H, Bu^t(5)); 1.63—1.85 (m, 7 H, H_{piper}, C(O)Me); 1.96 (s, 6 H, $C_6H_3(\underline{C}H_3)_2$); 2.22 (s, 2 H, C(O)Me); 2.22—2.34 (m, 1.4 H, H_{piper}); 2.49 (s, 1 H, C(8′)Me); 2.57 (m, 2.7 H, C(8′)Me, H_{piper}); 2.84 (s, 2 H, C(5′)Me); 2.90—2.93 (m, 1.5 H, C(5′)Me, H_{piper}); 3.19 (m, 0.7 H, H_{piper}); 3.27 (m, 0.6 H, H_{piper}); 6.20 (s, 0.6 H, $H_{o\text{-}Ph}$); 6.24 (s, 1.4 H, $H_{o\text{-}Ph}$); 6.58 (s, 0.7 H, $H_{p\text{-}Ph}$); 6.69 (s, 0.3 H, $H_{p\text{-}Ph}$); 6.74 (s, 0.3 H, $H(4)_{trop}$); 6.77 (s, 0.7 H, $H(3')_{quinoline}$); 6.78 (s, 0.7 H, $H(4)_{trop}$); 7.07 (d, 1 H, $H(6')_{quinoline}$, J = 3.5 Hz); 7.20 (m, 1.3 H, $H(6)_{trop}$, $H(3')_{quinoline}$); 7.26 (d, 0.3 H, $H(7')_{quinoline}$, J = 3.5 Hz); 7.30 (d, 0.7 H, $H(7')_{quinoline}$, J = 3.5 Hz). ^{13}C NMR ($CDCl_3$, 10 °C), δ: 19.0 (C(8′)$\underline{C}H_3$); 19.1 (C(8′)$\underline{C}H_3$); 20.8 ($C_6H_3(\underline{C}H_3)_2$); 21.1 ($C_6H_3(\underline{C}H_3)_2$); 22.1 (C(5′)$\underline{C}H_3$); 22.2 (C(5′)$\underline{C}H_3$); 22.8 (C(O)$\underline{C}H_3$); 24.2 (γ-$C_{piper}$); 24.7 (C(O)$\underline{C}H_3$); 25.3, 25.4 25.5, 25.6 (β-C_{piper}); 30.5 (C(5)C($\underline{C}H_3)_3$); 30.9 (C(7)C($\underline{C}H_3)_3$); 37.3, 37.4, 37.6, 37.9, 54.0 (α-C_{piper}); 54.2 (α-C_{piper}); 54.4 (α-C_{piper}); 112.0 (C(3′)); 112.3 (C(3′)); 122.6 $(C(2)_{Ph})$; 122.7, 122.8, 125.1 $(C(2)_{Ph})$; 125.9 (C(6)); 126.1 (C(4)); 126.3 (C(4)); 126.8 $(C(4)_{Ph})$; 127.7 (C(6)); 127.8 (C(7′)); 127.9 (C(6′)); 128.2 (C(6′); C(7′)); 128.6 $(C(4)_{Ph})$; 132.1, 132.2, 135.3, 137.3, 138.3, 138.8, 141.2, 141.7, 141.9, 142.9, 143.3, 149.2, 149.3, 151.3, 152.1, 153.2, 154.8, 156.1, 158.8, 159.4, 170.2, 171.1, 192.3, 193.4. ^{15}N NMR ($CDCl_3$, 10 °C), δ: 69.2 (N_{piper}), 148.1 (NAc) (150.3 minor), 293.0 (N_{quinol}). Found (%): C, 79.48; H, 8.26; N, 6.56. $C_{41}H_{51}N_3O_2$. Calculated (%): C, 79.70; H, 8.32; N, 6.80; O, 5.18.

X-ray diffraction analysis. The crystal unit cell parameters and a three-dimensional set of intensities were obtained on a KUMA-DIFFRACTION KM-4 automated diffractometer (Mo-Kα radiation, graphite monochromator) from a low-quali-

ty sample. Compound $C_{41}H_{51}N_3O_2$ crystallizes in a triclinic crystal system with the following parameters: a = 12.346(3), b = 15.979(3), c = 20.864(4) Å, α = 106.68(3), β = 101.50(3), γ = 102.43(3)°, V = 3697.4(13) Å^3, Z = 4, d_{calc} = 1.110 g cm^{-3}, μ(Mo-Kα) = 0.068 mm^{-1}, the space group $P\bar{1}$. Intensities of 15284 reflections were measured for a 0.20×0.17×0.15-mm single crystal within the angle range ($2\theta \le 52.02°$) using the $\omega/2\theta$-scan technique. After averaging intensities of equivalent reflections, the operating array of measured F^2_{hkl} and $\sigma(F^2)$ consisted of 14568 reflections, of which only 5367 reflections were with $F^2 > 4\sigma(F^2)$. The structure was solved by direct method and refined by full-matrix least squares method in anisotropic approximation for nonhydrogen atoms. In the crystal structure, all the H atoms were localized in the Fourier synthesis of difference electron density. Further, the coordinates and isotropic thermal parameters for all the atoms were refined using a riding model. The final parameters of refinement are as follows: R_1 = 0.0561, on the observed reflections with $I \ge 2\sigma(I)$; R_1 = 0.23 on all the measured reflections, GOOF = 0.882. After the refinement was complete, the maximum and the minimum values of the difference electron density were 0.222 and −0.298 e Å^{-3}. All the calculations were performed using the SHELXTL[9] software package.

Computer modeling. The evaluation of possible isomerization pathways of *N*-acetyl-3-arylaminotropones was carried out using the GAUSSIAN 03[10] software package within the density functional theory. The calculations used the PBE0[11,12] hybrid functional and the 6-31G** basis. A polarizing continuum model (CPCM)[13] with parameters corresponding to DMSO (ε = 46.7) was used to make allowance for the solvent effect.

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