ISSN 1070-4280, Russian Journal of Organic Chemistry, 2016, Vol. 52, No. 7, pp. 1007–1011. © Pleiades Publishing, Ltd., 2016.
Original Russian Text © G.S. Borodkin, A.A. Kolodina, E.A. Gusakov, I.G. Borodkina, P.B. Chepurnoi, S.B. Zaichenko, Yu.A. Sayapin, V.I. Minkin, 2016, published in Zhurnal Organicheskoi Khimii, 2016, Vol. 52, No. 7, pp. 1013–1017.

Two-Dimensional Correlation NMR Study of the Structure of By-product in the Reaction of 2-Methylquinoline with 3,5-Di-*tert*-butyl-1,2-benzoquinone

G. S. Borodkin[a], A. A. Kolodina[a], E. A. Gusakov[a], I. G. Borodkina[a], P. B. Chepurnoi[a], S. B. Zaichenko[a], Yu. A. Sayapin[b],* and V. I. Minkin[a, b]

[a] *Institute of Physical and Organic Chemistry, Southern Federal University, pr. Stachki 194/2, Rostov-on-Don, 344090, Russia*

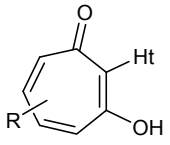
[b] *Southern Scientific Center, Russian Academy of Sciences, ul. Chekhova 41, Rostov-on-Don, 344006 Russia*
**e-mail: sayapin@ipoc.sfedu.ru*

Received May 3, 2016

Abstract—The reaction of 2-methylquinoline with 3,5-di-*tert*-butyl-1,2-benzoquinone afforded a mixture of 5,7-di-*tert*-butyl-3-hydroxy-2-(quinolin-2-yl)cyclohepta-2,4,6-trien-1-one and previously unknown 10-*tert*-butylindolo[1,2-*a*]quinoline-8,11-dione. The structure of the latter was determined by two-dimensional heteronuclear correlation NMR spectroscopy.

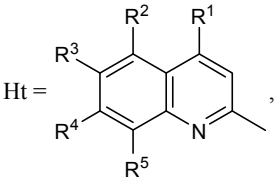
DOI: 10.1134/S1070428016070149

Reactions of 1,2-benzoquinones with 2-methyl-substituted nitrogen heterocycles involve expansion of the *ortho*-quinone ring to produce 2-(quinolin-2-yl)- [1], 2-(quinoxalin-2-yl)- [2], 2-(quinazolin-2-yl)- [3], 2-(4-oxo-1,3-benzoxazin-2-yl)- [4], and 2-(benzazol-2-yl)-1,3-tropolones [5]. The resulting 2-hetaryl-substituted 1,3-tropolones **1** exhibit antibacterial [4] and cytotoxic activity [6] and are promising for use in medicinal chemistry. The yield of **1** in these ring expansion reactions of *ortho*-quinones is sensitive to the nature of the nitrogen heterocycle and substituents therein and reaction conditions; as a rule, the yield is higher in reactions with six-membered heterocycles. When the reactions of 2-methylquinolines with 1,2-benzoquinones were carried out by heating in boiling *o*-xylene in the presence of a catalytic amount

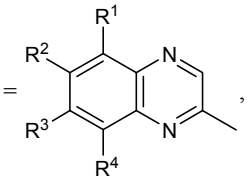


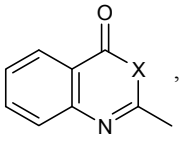
1

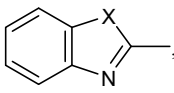
R = H, NO_2, Cl, *t*-Bu.



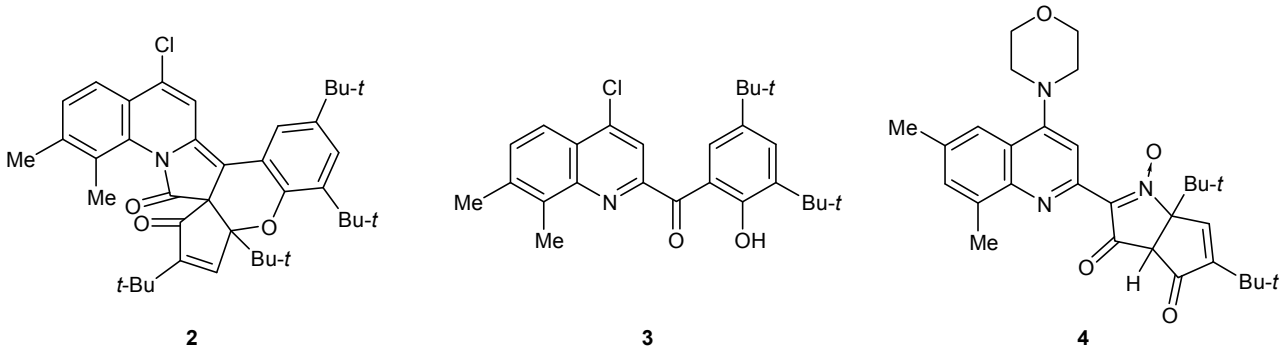
Ht = , R^1 = H, Cl, morpholin-4-yl, piperidin-1-yl, $R^2 = R^3 = R^4 = R^5$ = H, Me, NO_2;



Ht = , R^1 = H, $R^2 = R^3 = R^4$ = H, F; Ht = 

, X = O, NH; Ht = 

, X = O, S.



2 **3** **4**

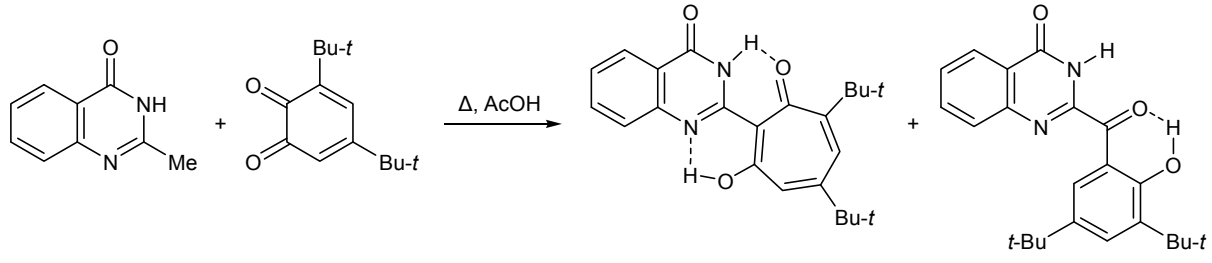
of *p*-toluenesulfonic acid [7], the yield of 2-(quinolin-2-yl)-1,3-tropolones did not exceed 30% [1]. The reactions of 2-methylquinolines with 3,5-di-*tert*-butyl-1,2-benzoquinone in boiling *o*-xylene were accompanied by side processes leading to compounds **2** and **3** whose structure was determined by X-ray analysis [1].

If initial 2-methylquinoline possesses a donor substituent (morpholin-4-yl, piperidin-1-yl, etc.) on C^4, its reaction with 4,6-di-*tert*-butyl-3-nitro-1,2-benzoquinone could give rise to bicyclic systems like **4** [8, 9]. We later [1] proposed a milder procedure for the above reaction, which implied heating the reactants at 60–70°C in acetic acid. This procedure made it possible to avoid formation of by-products **2**–**4**, while the yield of 1,3-tropolones **1** was improved to 50–80%. However, it was not always that the reactions were selective. For instance, the reaction of 2-methylquinazolin-4(3*H*)-one (**5**) with 3,5-di-*tert*-butyl-1,2-benzoquinone (**6**) in acetic acid gave a mixture of 1,3-tropolone **7** and compound **8** which is analogous to **3** (Scheme 1) [3]. Lower yield of the target product and formation of by-products were also observed in the reactions of **6** with 2-methylquinolines having no substituent on C^8 under mild conditions.

The present work was aimed at studying the structure of the minor product formed in the reaction of 2-methylquinoline (**9**) with quinone **6** in acetic acid. This reaction afforded 2-(quinolin-2-yl)-1,3-tropolone **10** and previously unknown 10-*tert*-butylindolo[1,2-*a*]-quinoline-8,11-dione (**11**) (Scheme 2). We succeeded in determining the structure of **11** only after having performed X-ray analysis of 3-*tert*-butyl-10,10-dimethyl-10*H*-indolo[1,2-*a*]indole-1,4-dione (**13**) which was unexpectedly obtained as the major product (yield 89%) in the reaction of 2,3,3-trimethyl-3*H*-indole (**12**) with quinone **6** [10] (Scheme 3). The structure of **11** was assigned on the basis of similarity of its NMR spectra to those of **13** and was also confirmed by IR and mass spectra.

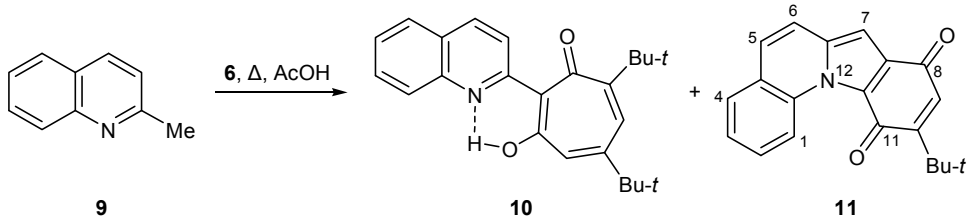
Complete assignment of the ^1H and ^{13}C NMR signals of **11** was made using two-dimensional homo- (^1H–^1H COSY, NOESY) and heteronuclear correlation

Scheme 1.



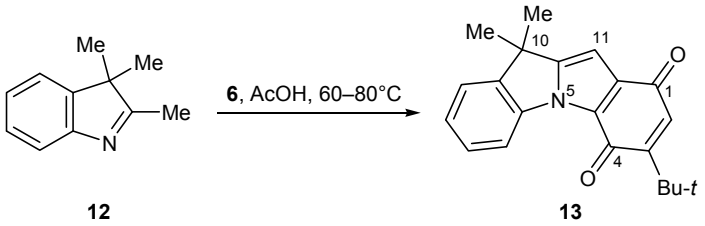
5 **6** **7**, 50% **8**, 18%

Scheme 2.



9 **10** **11**

Scheme 3.



12 **13**

techniques (^{1}H–^{13}C HSQC, HMBC and ^{1}H–^{15}N HMBC). The NOESY spectra of **11** and **13** showed cross-peaks between the *tert*-butyl protons and 9-H (**11**) or 2-H (**13**) (Fig. 1). Compound **11** displayed correlations between the pyrrole 7-H and quinoline 6-H protons, whereas the pyrrole 11-H proton of **13** showed NOE with the methyl protons, and the latter gave a cross-peak with 9-H. The absence of cross-peaks between the quinone proton and protons of the benzene fragment indicated their remoteness from each other in both structures.

The ^{1}H–^{13}C HMQC and HMBC correlations for compounds **11** and **13** are given in table. The key HMBC correlations are also shown in Fig. 2. In the ^{1}H–^{15}N HMBC spectrum of **11** we observed cross-peaks between the quinoline nitrogen atom (δ_N 185.4 ppm) and 7-H, 6-H, and 1-H (δ 6.52, 7.37, and 9.71 ppm, respectively).

Comparison of signal multiplicities in the ^{13}C NMR spectra of **11** and **13** recorded without decoupling from protons indicated strong similarity of their structures (Fig. 3). In the ^{13}C NMR spectrum of **11** (**13**), the C^{7a} (C^{11a}) quaternary carbon atom resonated as a doublet of doublets at δ_C 123.7 (130.2) ppm due to long-range couplings with 7-H (11-H) and 9-H (2-H). The C^{11} (**11**) and C^4 (**13**) carbonyl carbon signals were doublets at δ_C 184.8 and 177.1 ppm with almost similar coupling constants (10.9 and 10.5 Hz, respectively).

Thus, we were the first to isolate 10-*tert*-butylindolo[1,2-*a*]quinoline-8,11-dione and determine its structure by two-dimensional heteronuclear correlation NMR spectroscopy.

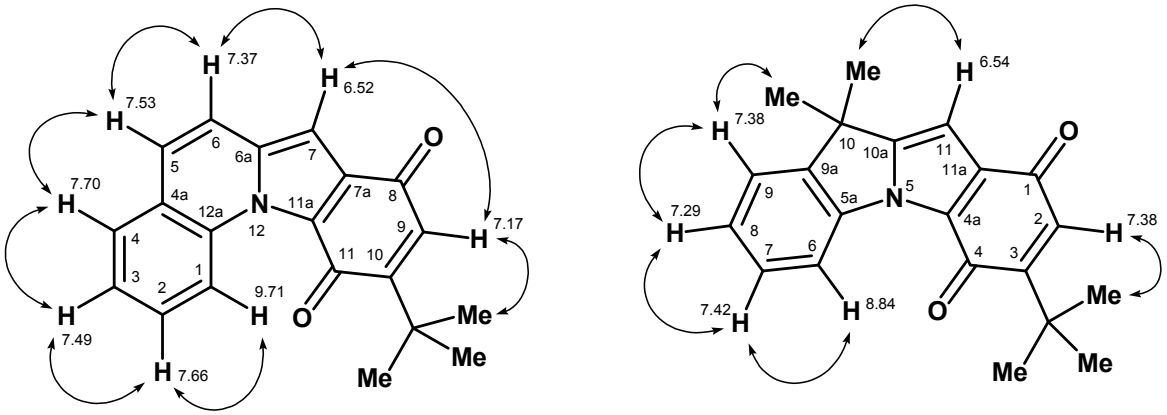


Fig. 1. Correlations in the ^{1}H–^{1}H NOESY spectra of compounds **11** and **13**; proton chemical shifts are given (δ, ppm).

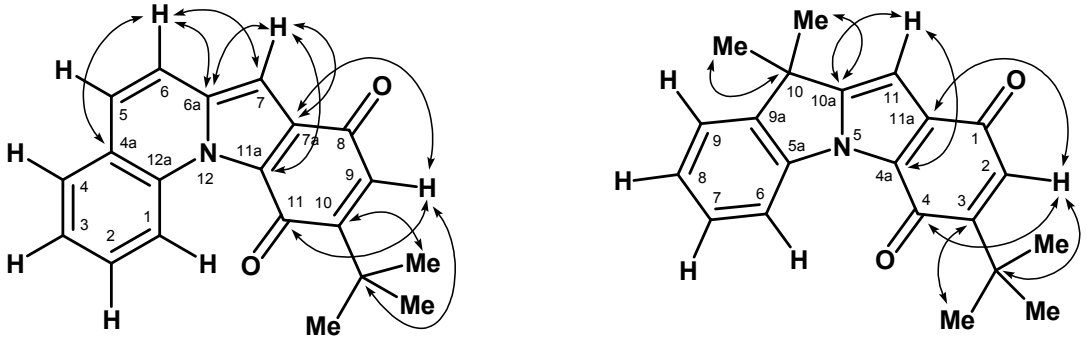


Fig. 2. Key correlations in the ^{1}H–^{13}C HMBC spectra of compounds **11** and **13**.

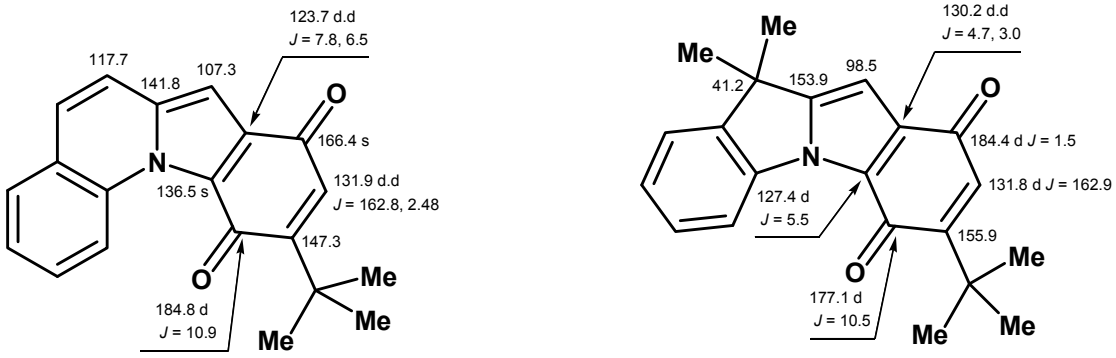


Fig. 3. Signals of some carbon atoms in the ^{13}C NMR spectra of compounds **11** and **13** recorded without decoupling from protons (δ_C, ppm; *J*, Hz).

Correlations in the HMQC and HMBC spectra of compounds **11** and **13** in $CDCl_3$[a]

δ, ppm	δ_C, ppm	
	HMQC	HMBC
Compound **11**		
1.32 (*t*-Bu)	29.4	29.4 [C(**C**H$_3$)$_3$], 34.9 [**C**(CH$_3$)$_3$], 147.1 (C^{10})
9.71 (1-H)	121.2	125.5 (C^{4a}), 126.3 (C^3)
7.66 (2-H)	129.1	128.4 (C^4), 134.8 (C^{12a})
7.49 (3-H)	126.3	121.2 (C^1), 125.5 (C^{4a})
7.70 (4-H)	128.4	129.0 (C^5), 129.1 (C^2), 134.8 (C^{12a})
7.53 (5-H)	129.0	117.7 (C^6), 125.5 (C^{4a}), 128.4 (C^4), 134.8 (C^{12a}), 141.8 (C^{6a})
7.37 (6-H)	117.7	107.3 (C^7), 125.5 (C^{4a}), 141.8 (C^{6a})
6.52 (7-H)	107.3	117.7 (C^6), 123.7 (C^{7a}), 131.9 (C^9), 136.7 (C^{11a}), 141.8 (C^{6a}), 166.4 w (C^8=O)
7.17 (9-H)	131.9	34.9 [**C**(CH$_3$)$_3$], 107.3 (C^7), 123.7 (C^{7a}), 184.8 (C^{11}=O)
Compound **13**		
1.35 (*t*-Bu)	29.9	29.9 [C(**C**H$_3$)$_3$], 155.9 (C^3)
1.51 (Me)	27.4	41.2 (C^{10}), 153.9 (C^{10a})
8.84 (6-H)	116.6	126.3 (C^8), 145.6 (C^{9a})
7.42 (7-H)	128.2	122.8 (C^9), 138.3 (C^{5a})
7.29 (8-H)	126.3	116.6 (C^6), 145.6 (C^{9a})
7.38 (9-H)	122.8	128.2 (C^7), 138.3 (C^{5a})
6.54 (11-H)	98.5	127.4 (C^{4a}), 153.9 (C^{10a})
6.50 (2-H)	131.8	35.7 [**C**(CH$_3$)$_3$], 130.2 (C^{11a}), 177.1 (C^4=O)

[a] Signals were assigned on the basis of the ^1H–^1H COSY, NOESY and ^1H–^{13}C HMQC, HMBC correlations.

EXPERIMENTAL

The ^1H, ^{13}C, and ^{15}N NMR spectra were recorded on a Bruker Avance 600 spectrometer. The ^1H chemical shifts were measured relative to the residual proton signal of the solvent. The IR spectra were recorded on a Varian 3100FT-IR Excalibur Series spectrometer equipped with an ATR accessory. The mass spectra (electron impact, 70 eV) were obtained on a Shimadzu GCMS-QP2010SE instrument with direct sample admission into the ion source. Aluminum oxide of Brockmann activity grade II or III was used for column chromatography. The melting points were determined on a Fischer–Johns melting point apparatus. The IR and NMR spectra were recorded using the facilities of the Molecular Spectroscopy Joint Center of the Southern Federal University.

5,7-Di-*tert*-butyl-3-hydroxy-2-(quinolin-2-yl)-cyclohepta-2,4,6-trien-1-one (10) and 10-*tert*-butylindolo[1,2-*a*]quinoline-8,11-dione (11). A solution of 13.2 g (0.06 mol) of 3,5-di-*tert*-butyl-1,2-benzoquinone (**6**) and 4.3 g (0.03 mol) of 2-methylquinoline (**9**) in 15 mL of acetic acid was stirred for 14 days at 60°C. The mixture was diluted with water and extracted with methylene chloride (3×100 mL). The extract was washed with 10% aqueous sodium carbonate (3×100 mL) and water (3×100 mL), dried over anhydrous Na_2SO_4 for 3–4 h, and passed through a column charged with Al_2O_3. The column was eluted with petroleum ether (bp 40–70°C)–methylene chloride (1:1), and the first yellow (R_f 0.7, **10**) and second red (R_f 0.3, **11**) fractions were collected. The eluates were evaporated, and the products were recrystallized from propan-2-ol.

Compound **10**. Yield 4.6 g (43%), yellow crystals, mp 134–135°C; published data [1]: mp 126–128°C. IR spectrum, ν, cm^{-1}: 1633, 1607, 1593, 1553, 1447,

1367, 1300. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.25 s (9H, 5-*t*-Bu), 1.39 s (9H, 7-*t*-Bu), 6.62 d (1H, 4-H, *J* = 1.5 Hz), 6.69 d (1H, 6-H, *J* = 1.5 Hz), 7.44–8.18 m (6H, quinoline), 19.3 br.s (1H, OH). Mass spectrum, *m*/*z* (I_{rel}, %): 361 (4) $[M]^+$, 333 (62), 318 (100), 290 (29), 57 (23), 40 (80). Found, %: C 79.61; H 7.40; N 3.72. $C_{24}H_{27}NO_2$. Calculated, %: C 79.74; H 7.53; N 3.87. *M* 361.48.

Compound **11**. Yield 0.05 g (0.5%), red–brown crystals, mp 179–180°C. IR spectrum, ν, cm^{-1}: 3092, 2992, 2962, 2908, 2865, 1663, 1611, 1556, 1540, 1455, 1424, 1388, 1354, 1332, 1296, 1253, 1143, 1100, 1051, 909, 866, 802, 761, 737, 701, 681, 641, 591. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.32 s (9H, *t*-Bu), 6.52 s (1H, 7-H), 7.17 s (1H, 9-H), 7.37 d (1H, 6-H, *J* = 9.0 Hz), 7.49 d.d (1H, 3-H, *J* = 8.0 Hz), 7.53 d (1H, 5-H, *J* = 9.0 Hz), 7.66 d.d (1H, 2-H, *J* = 8.7 Hz), 7.70 d (1H, 4-H, *J* = 8.0 Hz), 9.71 d (1H, 1-H, *J* = 8.7 Hz). ^{13}C NMR spectrum (62.90 MHz, $CDCl_3$), δ_C, ppm: 29.4 q.sept [3C, C(**C**H_3)$_3$, *J* = 126.5, 4.6 Hz], 34.9 m [**C**(CH_3)$_3$], 107.3 d (1C, C^7, *J* = 177.1 Hz), 117.7 d (C^6, *J* = 168.6 Hz), 121.2 d.d (C^1, *J* = 166.3, 7.0 Hz), 123.7 d.d (C^{7a}, *J* = 7.8, 6.5 Hz), 125.5 m (C^{4a}), 126.3 d.d (C^3, *J* = 163.3, 8.1 Hz), 128.4 d.d.d (C^4, *J* = 161.7, 7.7, 4.4 Hz), 129.0 d (C^5, *J* = 171.4 Hz), 129.1 d.d (C^2, *J* = 158.7, 3.9 Hz), 131.9 d.d (C^9, *J* = 160.9, 2.5 Hz), 134.8 m (C^{12a}), 136.7 s (C^{11a}), 141.8 d.d (C^{6a}, *J* = 15.6, 9.0 Hz), 147.1 m (C^{10}), 166.4 s (C^8), 184.8 d (C^{11}, *J* = 10.9 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 303 (25) $[M]^+$, 275 (72), 260 (51), 247 (22), 232 (100), 217 (134), 204 (7), 190 (10), 167 (6), 140 (3), 128 (7), 115 (6), 102 (9), 95 (8), 71 (5), 57 (10). Found, %: C 78.96; H 5.52; N 4.46. $C_{20}H_{17}NO_2$. Calculated, %: C 79.19; H 5.65; N 4.62. *M* 303.36.

3-*tert*-Butyl-10,10-dimethyl-1*H*-indolo[1,2-*a*]-indole-1,4(10*H*)-dione (13) was synthesized as described in [10]. Yield 89%, bright orange crystals, mp 211–212°C; published data [10]: mp 208–209°C. IR spectrum, ν, cm^{-1}: 3127, 2957, 2926, 2868, 1638, 1590, 1474, 1419, 1359, 1238, 1195, 1100, 1017, 895, 854, 758, 726, 708, 650. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.35 s (9H, *t*-Bu), 1.51 s (6H, CH_3), 6.50 s (1H, 2-H), 6.54 s (1H, 11-H), 7.26–7.43 m (3H, H_{arom}), 8.84 d (1H, 6-H, *J* = 8.0 Hz). ^{13}C NMR spectrum (62.90 MHz, $CDCl_3$), δ_C, ppm: 27.4 q.q (2C, CH_3, *J* = 129.0, 4.6 Hz), 29.9 q.sept [3C, C(**C**H_3)$_3$, *J* = 126.7, 4.7 Hz], 35.7 m [**C**(CH_3)$_3$], 41.2 m (C^{10}), 98.5 d.d (C^{11}, *J* = 177.5, 1.5 Hz), 116.6 d.d (C^6, *J* = 168.8, 7.7 Hz), 122.8 d.d (C^9, *J* = 159.4, 8.7 Hz), 126.3 d.d (C^8, *J* = 161.9, 7.6 Hz), 127.4 d (C^{4a}, *J* = 5.5 Hz), 128.2 d.d (C^7, *J* = 161.5, 7.4 Hz), 130.9 d.d (C^{11a}, *J* = 3.0, 4.7 Hz), 131.8 d (C^2, *J* = 162.9 Hz), 138.3 d.d (C^{5a}, *J* = 10.2, 8.4 Hz), 145.6 m (C^{9a}), 153.9 m (C^{10a}), 155.9 m (C^3), 177.1 d (C^4, *J* = 10.5 Hz), 184.4 d (C^1, *J* = 1.5 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 319 (56) $[M]^+$, 304 (100), 289 (2), 276 (18), 262 (4), 246 (4), 218 (13), 204 (3), 191 (8), 167 (8), 140 (9), 130 (8), 115 (7), 102 (7), 77 (6), 40 (14). Found, %: C 78.82; H 6.44; N 4.18. $C_{21}H_{21}NO_2$. Calculated, %: C 78.97; H 6.63; N 4.39. *M* 319.40.

This study was performed under financial support by the Ministry of Education and Science of the Russian Federation in the framework of the project part of state assignment in the sphere of research activity (project no. 4.967.2014/K).

REFERENCES

1. Minkin, V.I., Aldoshin, S.M., Komissarov, V.N., Dorogan, I.V., Sayapin, Yu.A., Tkachev, V.V., and Starikov, A.G., *Russ. Chem. Bull., Int. Ed*., 2006, vol. 55, p. 2032.
2. Sayapin, Yu.A., Komissarov, V.N., Duong Nghia Bang, Dorogan, I.V., Minkin, V.I., Tkachev, V.V., Shilov, G.V., Aldoshin, S.M., and Charushin, V.N., *Mendeleev Commun*., 2008, vol. 18, p. 180.
3. Sayapin, Yu.A., Gusakov, E.A., Kolodina, A.A., Komissarov, V.N., Dorogan, I.V., Tkachev, V.V., Shilov, G.V., Nosova, E.V., Aldoshin, S.M., Charushin, V.N., and Minkin, V.I., *Russ. Chem. Bull., Int. Ed*., 2014, vol. 63, p. 1364.
4. Sayapin, Yu.A., Gusakov, E.A., Dorogan, I.V., Tupaeva, I.O., Teimurazov, M.G., Fursova, N.K., Ovchinnikov, K.V., and Minkin, V.I., *Russ. J. Bioorg. Chem*., 2016, vol. 42, p. 224.
5. Sayapin, Yu.A., Tupaeva, I.O., Kolodina, A.A., Gusakov, E.A., Komissarov, V.N., Dorogan, I.V., Makarova, N.I., Metelitsa, A.V., Tkachev, V.V., Aldoshin, S.M., and Minkin, V.I., *Beilstein J. Org. Chem*., 2015, vol. 11, p. 2179.
6. Duong Nghia Bang, Sayapin, Yu.A., Hoang Lam, Nguyen Dang Duc, and Komissarov, V.N., *Chem. Heterocycl. Compd*., 2015, vol. 51, p. 291.
7. Sayapin, Yu.A., Komissarov, V.N., Minkin, V.I., Tkachev, V.V., Aldoshin, S.M., and Shilov, G.V., *Russ. J. Org. Chem*., 2005, vol. 41, p. 1539.
8. Minkin, V.I., Komissarov, V.N., and Sayapin, Yu.A., *Arkivoc*, 2006, part (vii), p. 439.
9. Profatilova, I.A., Sayapin, Yu.A., Bumber, A.A., Askalepova, O.I., Vasilevskii, S.V., and Komissarov, V.N., *Vestn. Yuzhn. Nauch. Tsentra*, 2005, no. 4, p. 21.
10. Sayapin, Yu.A., Tupaeva, I.O., Gusakov, E.A., Shilov, G.V., Tkachev, V.V., Aldoshin, S.M., and Minkin, V.I., *Dokl. Chem*., 2015, vol. 460, p. 33.