Synthesis and tautomeric transformations of 2-(*tert*-butyl)-1,2,4-benzotriazine-3(2*H*)-thiones

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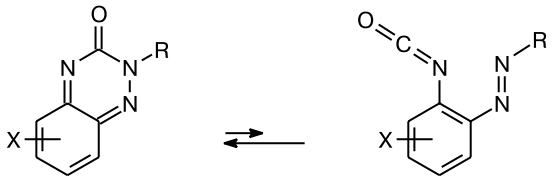
Treatment of 2-(*tert*-butyl)-1,2,3,4-benzotetrazinium tetrafluoroborates with sodium thiocyanate afforded 2-(*tert*-butylazo)phenyl isothiocyanates **3**, which exist in equilibrium with 2-(*tert*-butyl)-1,2,4-benzotriazine-3(2*H*)-thiones **3´**. The equilibrium depends on the substituents R in the benzene ring: the percentage of the open isomer **3** is about 20% for R = H or Me; for R = Cl or Br, the equilibrium is completely shifted to cyclic isomer **3´**. The equilibrium is slow on the time scale of the ^{1}H and ^{13}C NMR experiments. For compounds **3a**/**3´a** (R = H), the spectra at 24 °C show two sets of signals, while those at 0 °C contain only signals for isomer **3´a**.

Key words: diazonium salts, 2-alkylbenzotetrazinium salts, sodium thiocyanate, nitrogen-containing heterocycles, 1,2,4-benzotriazine-3(2*H*)-thiones, aryl isothiocyanates.

2-R-1,2,4-Benzotriazin-3(2*H*)-ones **A** belong to a comparatively well-studied class of compounds. The substituent R can be aryl,[1,2] alkyl,[3] or hydrogen.[4] Formally, the cyclic and open forms could exist in equilibrium (**A** ⇌ **B**); however, in reality, the equilibrium is fully shifted to the cyclic form **A**.

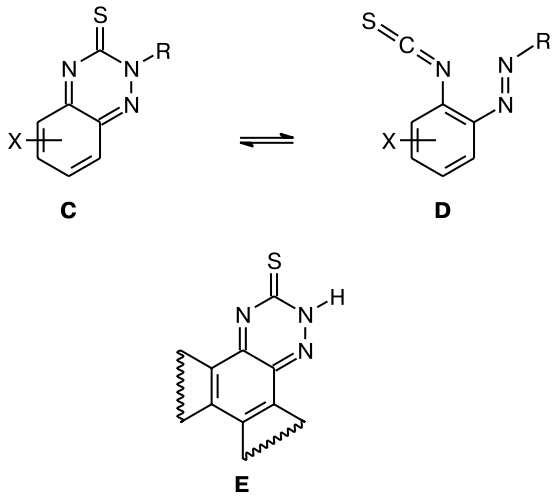


A **B**

2-R-1,2,4-Benzotriazine-3(2*H*)-thiones have been substantially less studied. In the case that R is an aromatic substituent (*e.g.*, 4-Me_2N-C_6H_4), the equilibrium **C** ⇌ **D** is completely shifted to the open form **D** (IR and UV spectroscopic data).[5,6] Annulated structures of the type **E** have also been reported. According to their IR spectra,[7—9] these compounds exist in the cyclic form. Note that some of them exhibit antibacterial activity.[10]

N-Alkyl derivatives of the type **C** or **D** have been unknown to date. Such compounds cannot be obtained by alkylation of compounds of the type **E** because only *S*-alkylation occurs.[7—9]

In the present work, we describe the synthesis of 2-(*tert*-butylazo)phenyl isothiocyanates and discuss their equilibria with 2-(*tert*-butyl)-1,2,4-benzotriazine-3(2*H*)-thiones.



C **D**

E

Results and Discussion

To obtain 2-alkyl-1,2,4-benzotriazine-3(2*H*)-thiones, we employed the earlier discovered reactions of 2-alkylbenzotetrazinium tetrafluoroborates with nucleophiles, which is accompanied by elimination of molecular nitrogen.[11]

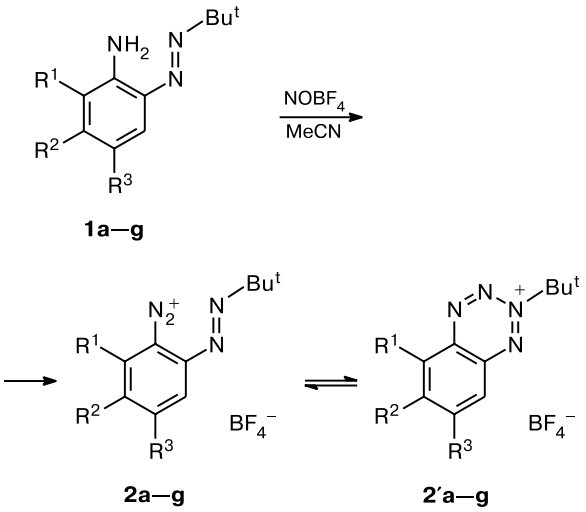
Diazotization of *ortho*-(*tert*-butylazo)anilines **1a—g** with nitrosonium tetrafluoroborate gave the corresponding *ortho*-(*tert*-butylazo)phenyldiazonium tetrafluoroborates **2a—g** (see Ref. 12). As we have found earlier,[12] *ortho*-(alkylazo)phenyldiazonium salts **2** exist in solutions in equilibrium with 2-alkylbenzotetrazinium salts **2´**

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 7, pp. 1192—1195, July, 2006.

1066-5285/06/5507-1239

(Scheme 1), the equilibrium being rapid on the time scale of the NMR experiment.

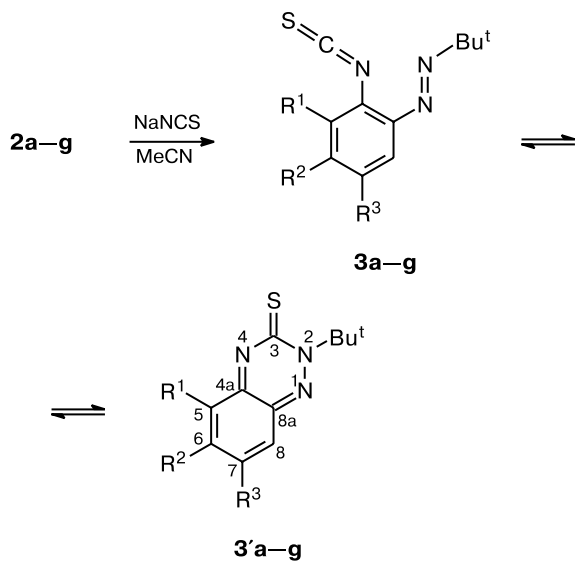
Scheme 1



Compound	R^1	R^2	R^3	Ratio of **2** : **2′**
a	H	H	H	30 : 70
b	H	H	Br	55 : 45
c	H	Br	H	15 : 85
d	H	H	Me	40 : 60
e	H	Me	H	15 : 85
f	Cl	H	Cl	0 : 100
g	Br	H	Br	0 : 100

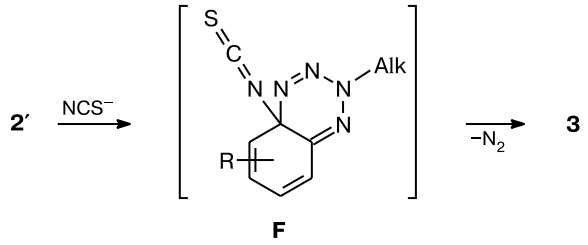
Synthesis of compounds 3/3′. Treatment of solutions of salts **2a—g/2′a—g** in MeCN with an excess of NaNCS (Scheme 2) under mild conditions (20 °C, 5—15 min) gave compounds **3a—g/3′a—g** in 42—72% yields. The ratio of the open form to the cyclic one in salts **2/2′** did not affect the reaction pathway.

Scheme 2



Presumably, the formation of isothiocyanates **3** results from an attack of the thiocyanate anion on the carbon bridgehead of 2-alkylbenzotetrazinium salts **2′**, through the formation of intermediate 1,4-dihydro-1,2,3,4-benzotetrazine **F** followed by elimination of molecular nitrogen (Scheme 3).

Scheme 3



Interestingly, the ambident thiocyanate anion involves exclusively its N atom while attacking 2-(*tert*-butyl)benzotetrazinium salts **2′**. This substantially distinguishes the reaction under study from reactions of thiocyanate anions with diazonium salts. Under the conditions of the Sandmeyer reaction (in the presence of copper or its salts), diazonium salts are attacked by both the N and S atoms of the NCS anion to give mixtures thiocyanates and isothiocyanates, or exclusively by the S atom to form only thiocyanates (see Ref. 13 and references therein).

The synthesis of benzotriazinethiones **3′** is possible as a "one-pot" reaction without isolation of diazonium salts **2**, when starting directly from azoaniline **1**. This was illustrated with a transformation of azoaniline **1a** into compounds **3a/3′a** in total 71% yield.

Note that an attempted preparative synthesis of isothiocyanate **3a** by a reaction of azoaniline **1a** with thiophosgene (common procedure for the preparation of isothiocyanates[14]) failed. This reaction yielded a difficult-to-separate mixture of products.

Equilibrium 3 ⇌ 3′. Spectroscopic studies of 1,2,4-benzotriazine-3(2*H*)-thiones. Compounds **3/3′** were studied by ^{1}H and ^{13}C NMR spectroscopy. Signals were assigned with the use of the selective polarization transfer (SPT) and CH correlation techniques. Compounds **3a/3′a** were examined most thoroughly. The ^{1}H NMR spectra ($CDCl_3$, 24 °C) show two sets of signals corresponding to compounds **3a** and **3′a** in the ratio 15 : 85. Temperature-variable NMR studies showed that cooling of a sample from 24 to 0 °C completely shifts the equilibrium to the cyclic isomer **3′a**. On subsequent warming to 24 °C, the ratio of the isomers returns to the original value; therefore, it is an equilibrium ratio for

these compounds. Compounds **3d,e/3´d,e** behaved analogously.

The cyclic structures of compounds **3´** were confirmed by the downfield shifts of the signals for the *tert*-butyl group (for **3´a—g**, $\delta_{^1H}$ 2.00—2.05; for **3´a,b,f,g**, $\delta_{^{13}C}(\underline{C}Me_3)$ 75.0—75.8) relative to the corresponding signals in isothiocyanates **3** (for **3a,d,e**, $\delta_{^1H}$ 1.21—1.25; for **3a**, $\delta_{^{13}C}(\underline{C}Me_3)$ 57.2), as well as by the upfield shift of the signal of the C atom bound to sulfur (NMR data at 297 K, see Experimental).

The position of the equilibrium **3** ⇌ **3´** depends on the substituents in the benzene ring. The electron-releasing methyl substituents in the *para*- and especially *meta*-positions with respect to the SCN group increase the fraction of the open isomer **3**, while electron-withdrawing substituents (Br and Cl) in both the *ortho,para*- and *meta*-positions with respect to the SCN group completely shift the equilibrium to 1,2,4-benzotriazine-3-thiones **3´** (Table 1). Such effects of the substituents can be explained by the fact that electron-releasing substituents make the C atom of the isothiocyanate group less electrophilic, thus hindering cyclization. In contrast, electron-withdrawing groups increase the electrophilicity of the C atom of the isothiocyanate group, thus favoring the formation of the cyclic isomer.

Experimental

IR spectra were recorded on a Specord M-80 spectrophotometer. Mass spectra were recorded on a Kratos MS-30 instrument (EI, 70 eV). ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (300.13 and 75.5 MHz, respectively). The course of the reactions was monitored by TLC (Silufol UV-254 plates). Chemapol silica gel (L 100/160) was used for column chromatography. Azoanilines **1a—g** and 2-(alkylazo)benzodiazonium tetrafluoroborates **2a—g** were prepared as described earlier.[12]

Synthesis of 2-(*tert*-butyl)-1-(2-isothiocyanatophenyl)diazenes 3a,d,e and 2-(*tert*-butyl)-1,2,4-benzotriazine-3(2*H*)-thiones 3´a—g by reactions of salts 2a—g/2´a—g with sodium thiocyanate (general procedure). Sodium thiocyanate (49 mg, 0.6 mmol) was added in one portion to a stirred solution of salt **2** (0.12 mmol) in anhydrous CH_3CN (5 mL). The reaction mixture was stirred until the starting salt disappeared completely (10—20 min, TLC monitoring). The precipitate of inorganic salts was filtered off and the filtrate was concentrated *in vacuo*. The product was extracted from the residue with hot light petroleum (70—100 °C), concentrated *in vacuo*, and chromatographed with light petroleum–EtOAc (7 : 1) as an eluent.

Table 1. Percentages of the isomers in the equilibrium mixture **3** ⇌ **3´** at 24 °C*

Compound	R^1	R^2	R^3	Isothiocyanate **3** (%)	Triazinethione **3´** (%)
a	H	H	H	15	85
b	H	H	Br	0	100
c	H	Br	H	0	100
d	H	H	Me	20	80
e	H	Me	H	25	75
f	Cl	H	Cl	0	100
g	Br	H	Br	0	100

* According to the ^1H NMR data in $CDCl_3$.

Compounds 3a/3´. The yield of a mixture of **3a/3´a** was 20 mg (72%), violet crystals, m.p. 66—68 °C. Found (%): C, 60.37; H, 5.99; N, 19.03. $C_{11}H_{13}N_3S$. Calculated (%): C, 60.24; H, 5.97; 19.16. IR (KBr), ν/cm^{-1}: 1620 (C=S). MS, *m/z*: 219 $[M]^+$.

2-(*tert*-Butyl)-1-(2-isothiocyanatophenyl)diazene (3a). ^1H NMR ($CDCl_3$, 297 K), δ: 1.24 (s, 9 H, Bu^t); 7.28 (dt, 1 H, J = 8.4 Hz, J = 0.8 Hz); 7.40 (dt, 1 H, J = 8.3 Hz, J = 0.9 Hz); 7.59 (d, 1 H, J = 8.3 Hz); 7.96 (d, 1 H, J = 8.4 Hz). ^{13}C NMR ($CDCl_3$, 297 K), δ: 27.8 (CH_3); 57.2 ($\underline{C}Me_3$); 110.6 (CH); 119.5 (C(3)); 123.8 (CH); 127.4 (C(4)); 133.5; 143.9.

2-(*tert*-Butyl)-1,2,4-benzotriazine-3(2*H*)-thione (3´a). ^1H NMR ($CDCl_3$, 297 K), δ: 2.00 (br.s, 9 H, Bu^t); 7.40 (dt, 1 H, H(7), J = 8.6 Hz, J = 1.2 Hz); 7.50 (d, 1 H, H(5), J = 8.8 Hz); 7.68 (d, 1 H, H(8), J = 8.6 Hz); 7.74 (dt, 1 H, H(6), J = 8.8 Hz, J = 1.3 Hz). ^{13}C NMR ($CDCl_3$, 297 K), δ: 27.8 (CH_3); 75.1 ($\underline{C}Me_3$); 125.8 (C(7) or C(8)); 128.6 (C(8) or C(7)); 129.2 (C(5)); 137.7 (C(8a)); 144.6 (C(4a); 177.7 (C(3)). ^1H NMR ($CDCl_3$, 253 K), δ: 2.02 (s, 9 H, Bu^t); 7.40 (dt, 1 H, H(7), J = 8.6 Hz, J = 1.2 Hz); 7.50 (d, 1 H, H(5), J = 8.8 Hz); 7.68 (d, 1 H, H(8), J = 8.6 Hz); 7.74 (dt, 1 H, H(6), J = 8.8 Hz, J = 1.3 Hz). ^{13}C NMR ($CDCl_3$, 253 K), δ: 27.8 (CH_3); 75.5 ($\underline{C}Me_3$); 126.5 (C(7) or C(8)); 128.9 (C(8) or C(7)); 129.5 (C(5)); 138.1 (C(8a)); 139.9 (C(6)); 145.0 (C(4a)); 178.1 (C(3)).

7-Bromo-2-(*tert*-butyl)-1,2,4-benzotriazine-3(2*H*)-thione (3´b). The yield was 19 mg (52%), blue crystals, m.p. 74—76 °C. Found (%): C, 44.24; H, 4.05; Br, 26.71; N, 14.18. $C_{11}H_{12}BrN_3S$. Calculated (%): C, 44.30; H, 4.06; Br, 26.80; N, 14.09. IR (KBr), ν/cm^{-1}: 1620 (C=S). ^1H NMR (acetone-d_6, 297 K), δ: 2.04 (br.s, 9 H, Bu^t); 7.62 (d, 1 H, H(8), J = 2.2 Hz); 7.69 (dd, 1 H, H(6), J = 8.8 Hz, J = 2.2 Hz); 8.13 (d, 1 H, H(5), J = 8.8 Hz). ^{13}C NMR (acetone-d_6, 297 K), δ: 27.7 (CH_3); 75.0 ($\underline{C}Me_3$); 109.4 (C(7)); 126.7 (C(5)); 128.1 (C(8)); 135.7 (C(8a)); 141.6 (C(6)). MS, *m/z* (integral intensity ratio): 297 : 299 (1 : 1) $[M]^+$.

6-Bromo-2-(*tert*-butyl)-1,2,4-benzotriazine-3(2*H*)-thione (3´c). The yield was 21 mg (57%), blue crystals, m.p. 77—79 °C. Found (%): C, 44.07; H, 4.15; Br, 26.58; N, 14.37. $C_{11}H_{12}BrN_3S$. Calculated (%): C, 44.30; H, 4.06; Br, 26.80; N, 14.09. IR (KBr), ν/cm^{-1}: 1610 (C=S). ^1H NMR (acetone-d_6, 297 K), δ: 2.03 (br.s, 9 H, Bu^t); 7.89 (d, 1 H, H(8), J = 8.7 Hz); 7.71 (dd, 1 H, H(7), J = 8.7 Hz, J = 2.0 Hz); 8.04 (d, 1 H, H(5), J = 2.0 Hz). MS, *m/z* (integral intensity ratio): 297 : 299 (1 : 1) $[M]^+$.

Compounds 3d/3´d. The yield of a mixture of **3d/3´d** was 17 mg (59%), violet crystals, m.p. 71—72 °C. Found (%): C, 62.10; H, 6.65; N, 17.78. $C_{12}H_{15}N_3S$. Calculated (%): C, 61.77; H, 6.48; 18.01. IR (KBr), ν/cm^{-1}: 1620 (C=S). MS, *m/z*: 233 $[M]^+$. The ^1H and ^{13}C NMR spectra (297 K) show two sets of signals corresponding to compounds **3d** and **3´d** (**3d** : **3´d** = 20 : 80).

2-(*tert*-Butyl)-1-(2-isothiocyanato-5-methylphenyl)diazene (3d). ^1H NMR ($CDCl_3$, 297 K), δ: 1.25 (s, 9 H, Bu^t); 2.19 (s,

3 H, CH_3); 7.56 (dd, 1 H, H(4), J = 8.5 Hz, J = 2.1 Hz); 7.82 (d, 1 H, H(6), J = 2.1 Hz); 7.88 (d, 1 H, H(3), J = 8.5 Hz).

2-(*tert*-Butyl)-7-methyl-1,2,4-benzotriazine-3(2*H*)-thione (3´d). ^{1}H NMR ($CDCl_3$, 297 K), δ: 1.93 (s, 3 H, CH_3); 2.03 (br.s, 9 H, Bu^t); 7.31 (d, 1 H, H(5), J = 8.2 Hz); 7.53 (dd, 1 H, H(6), J = 8.2 Hz, J = 1.7 Hz); 7.73 (d, 1 H, H(8), J = 1.7 Hz). ^{1}H NMR ($CDCl_3$, 253 K), δ: 2.02 (s, 9 H, Bu^t); 7.31 (d, 1 H, H(5), J = 8.3 Hz); 7.53 (dd, 1 H, H(6), J = 8.3 Hz, J = 1.7 Hz); 7.73 (d, 1 H, H(8), J = 1.7 Hz).

Compounds 3e/3´e. The yield of a mixture of **3e/3´e** was 12 mg (42%), violet crystals, m.p. 60–62 °C. Found (%): C, 62.02; H, 6.34; N, 17.74. $C_{12}H_{15}N_3S$. Calculated (%): C, 61.77; H, 6.48; 18.01. IR (KBr), ν/cm^{-1}: 1630 (C=S). MS, m/z: 233 $[M]^+$. The ^{1}H and ^{13}C NMR spectra (297 K) show two sets of signals corresponding to compounds **3e** and **3´e** (**3e** : **3´e** = 25 : 75).

2-(*tert*-Butyl)-1-(2-isothiocyanato-4-methylphenyl)diazene (3e). ^{1}H NMR ($CDCl_3$, 297 K), δ: 1.21 (s, 9 H, Bu^t); 2.17 (s, 3 H, CH_3); 7.21 (d, 1 H, H(3), J = 2.2 Hz); 7.56 (d, 1 H, H(6), J = 8.8 Hz); 7.59 (d, 1 H, H(5), J = 8.8 Hz, J = 2.2 Hz).

2-(*tert*-Butyl)-6-methyl-1,2,4-benzotriazine-3(2*H*)-thione (3´e). ^{1}H NMR ($CDCl_3$, 297 K), δ: 1.89 (s, 3 H, CH_3); 2.01 (s, 9 H, Bu^t); 7.48 (d, 1 H, H(8), J = 8.6 Hz); 7.64 (dd, 1 H, H(7), J = 8.6 Hz, J = 2.1 Hz); 8.11 (d, 1 H, H(5), J = 2.1 Hz). ^{1}H NMR ($CDCl_3$, 253 K), δ: 1.90 (s, 3 H, CH_3); 2.01 (s, 9 H, Bu^t); 7.48 (d, 1 H, H(8), J = 8.6 Hz); 7.64 (dd, 1 H, H(7), J = 8.6 Hz, J = 2.1 Hz); 8.10 (d, 1 H, H(5), J = 2.1 Hz).

2-(*tert*-Butyl)-5,7-dichloro-1,2,4-benzotriazine-3(2*H*)-thione (3´f). The yield was 18 mg (52%), violet crystals, m.p. 92–94 °C. Found (%): C, 46.02; H, 3.64; Cl, 24.14; N, 14.72. $C_{11}H_{11}Cl_2N_3S$. Calculated (%): C, 45.84; H, 3.85; Cl, 24.60; N, 14.58. IR (KBr), ν/cm^{-1}: 1650 (C=S). ^{1}H NMR (acetone-d_6, 273 K), δ: 2.05 (s, 9 H, Bu^t); 7.64 (d, 1 H, H(8), J = 1.8 Hz); 8.37 (d, 1 H, H(6), J = 1.8 Hz). ^{13}C NMR (acetone-d_6, 273 K), δ: 28.0 (CH_3); 75.8 ($\underline{C}Me_3$); 118.1 (C(8)); 145.9 (C(6)). MS, m/z (integral intensity ratio): 287 : 289 : 291 (4 : 2 : 1) $[M]^+$.

5,7-Dibromo-2-(*tert*-butyl)-1,2,4-benzotriazine-3(2*H*)-thione (3´g). The yield was 20 mg (45%), violet crystals, m.p. 85–86 °C. Found (%): C, 34.99; H, 2.65; Br, 42.32; N, 11.16. $C_{11}H_{11}Br_2N_3S$. Calculated (%): C, 35.04; H, 2.94; Br, 42.38; N, 11.14. IR (KBr), ν/cm^{-1}: 1640 (C=S). ^{1}H NMR (acetone-d_6, 253 K), δ: 2.00 (s, 9 H, Bu^t); 8.18 (d, 1 H, H(8), J = 1.9 Hz); 8.34 (d, 1 H, H(6), J = 1.9 Hz). ^{13}C NMR (acetone-d_6, 253 K), δ: 27.5 (CH_3); 75.6 ($\underline{C}Me_3$); 131.2 (C(8)); 144.6 (C(6)). MS, m/z (integral intensity ratio): 375 : 377 : 373 (1 : 2 : 1) $[M]^+$.

Synthesis of compounds 3a/3´a from *ortho*-(*tert*-butylazo)aniline 1a. A solution of aniline **1a** (177 mg, 1 mmol) in anhydrous CH_3CN (5 mL) was added at −15 °C to a stirred suspension of $NOBF_4$ (129 mg, 1.1 mmol) in anhydrous CH_3CN (5 mL). Stirring was continued under the same conditions for 20 min. Then NaNCS (405 mg, 5 mmol) was added and the reaction mixture was warmed to room temperature and stirred for 15 min. The precipitate of inorganic salts was filtered off and the filtrate was concentrated *in vacuo*. The product was extracted from the residue with hot light petroleum (70—100 °C), concentrated *in vacuo*, and chromatographed with benzene as an eluent to give a mixture of compounds **3a/3´a** (171 mg, 71%), which were identical with the previously obtained samples.

This work was financially supported by the Russian Foundation for Basic Research (Project No. 04-03-32432).

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Received May 2, 2006;
in revised form June 27, 2006