Russian Journal of General Chemistry, Vol. 71, No. 6, 2001, pp. 950–955. Translated from Zhurnal Obshchei Khimii, Vol. 71, No. 6, 2001, pp. 1012–1017.

Tautomerism and Stereodynamics of Indophenols, Amidines, Their Derivatives, and Analogs: XIV.[1] New Methods of Synthesis of Spiro-Fused Quinoxalines

S. V. Kurbatov, N. I. Vikrishchuk, V. I. Simakov, D. N. Kuznetsov, Yu. A. Zhdanov, and L. P. Olekhnovich

Rostov State University, Rostov-on-Don, 344104 Russia

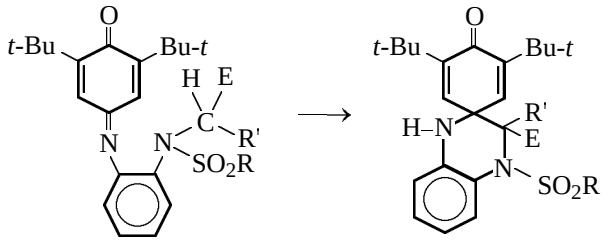
Received September 27, 1999

Abstract — A new procedure was proposed for synthesis of quinoxaline derivatives by *N*-alkylation of 2,6-di-*tert*-butyl-4-(*o*-R-sulfonylaminophenylimino)-2,5-cyclohexadienones and subsequent intramolecular spirocyclization. A necessary condition for the reaction to occur is a high mobility of hydrogen in the *N*-methylene group, which is activated by electron-acceptor aroyl or two ethoxycarbonyl groups.

In the previous communication of this series [1] we described a new intramolecular rearrangement of *O*-methylene derivatives of 2,6-di-*tert*-butyl-4-(*o*-hydroxyphenylimino)-2,5-cyclohexadienones as a preparative route to spirocyclic benzoxazines. Presumably, an analogous transformation can lead to formation of other heterocyclic systems, primarily of quinoxalines which exhibit a broas-spectrum antibacterial and cardioprotecting activity [2]. It is also known that heterocycles containing a spirocyclohexadiene moiety are structural fragments of a number of biologically active natural compounds [3] which are available through a limited set of fairly rare reactions [4].

The goal of the present work was to examine the possibility for synthesizing difficultly accessible spiroquinoxalines like **IV** by intramolecular cyclization of quinonimines **III** (Scheme 1). Quinoxalines **IV** can be obtained by alkylation of 4-(*o*-benzylsulfonylaminophenylimino)-2,6-di-*tert*-butyl-2,5-cyclohexadienone (**I**) with phenacyl bromides in acetone in the presence of anhydrous potassium carbonate or of its thallium salt **II** in acetonitrile (pathways *a* and *b* in Scheme 2). Both these methods gave similar results. We have found no advantages of method *b* from the synthetic viewpoint (such as readiness of the reaction and purity of the products); therefore, most quinoxalines were synthesized according to pathway *a*.

Scheme 1.



III **IV**

R = CH_2Ph, 4-$NO_2C_6H_4$, 4-$CH_3C_6H_4$; R' = COOEt, H; E = C(O)Ar, Ar, $HC{=}CH_2$, COOEt.

The reaction of compound **I** with *p*-nitrophenacyl bromide resulted in formation of product **IV** containing a stereogenic carbon atom. Additional information about possible enantiomerization of spiroquinoxalines like **IV**, e.g., via enolization (Scheme 3), can be derived from the ^1H NMR spectra. The figure shows the ^1H NMR spectra of quinoxaline **IV** and primary product **XVII** formed by reaction of **I** with *p*-nitrobenzyl bromide. The following evidence of spirocyclization can be noted: (1) signals from both *tert*-butyl groups, as well as from protons in positions *2* and *6* of the cyclohexadiene ring become isochronous (δ ~1.3 and ~6.9 ppm, respectively); (2) the two-proton signal at δ ~4.6 ppm from the CH_2CO group is transformed into two one proton signals, NH (δ ~6.1 ppm) and CH (δ ~6.6 ppm); and (3) the singlet from the CH_2SO_2 group is converted into an AB quartet (δ ~4.8 ppm), indicating that molecule **IV** is chiral and that no fast enantiomerization occurs.

By alkylation of *o*-sulfonylamino derivatives **VI** and **VII** with phenacyl bromides and diethyl bromomalonate we obtained spirocyclic compounds **VIII**–**XIV** (Scheme 4). As in the alkylation of 2,6-di-*tert*-

[1] For communication XIII, see [1].

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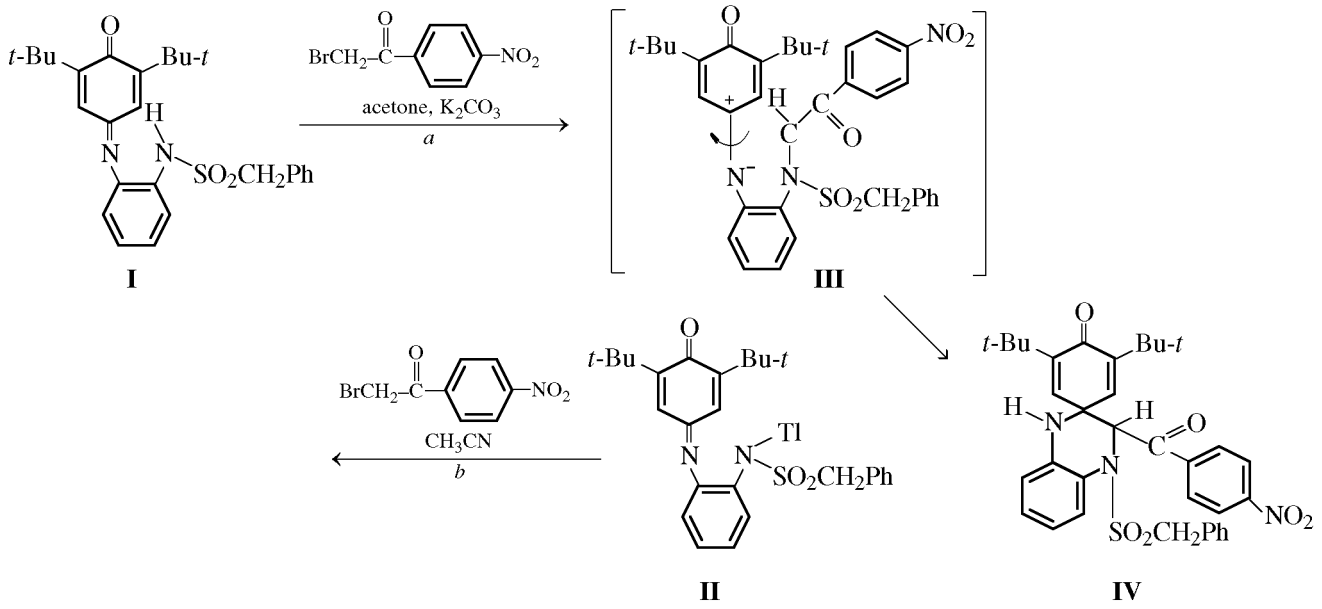
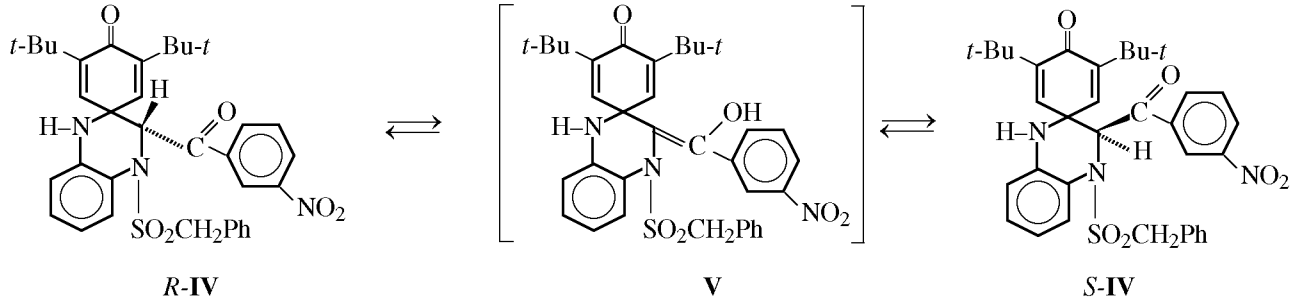
Scheme 2.



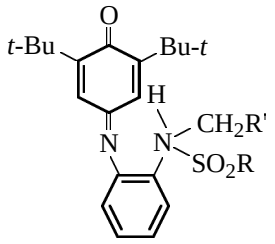
Scheme 3.



butyl-4-(*o*-hydroxyphenylimino)-2,5-cyclohexadienones [1], we failed to isolate even traces of primary alkylation products **III** (Scheme 1): In all cases final spiroquinoxalines **VIII**–**XIV** were obtained.

Unlike spirobenzoxazines [1], in the synthesis of spiroquinoxalines more rigorous requirements are imposed on the electronic nature of the substituent at the *N*-methylene group. We failed to effect cyclization of *N*-allyl and *N*-*p*-nitrobenzyl derivatives **XV**–**XVII** into the corresponding quinoxalines even by prolonged heating in boiling chloropentafluorobenzene or *o*-dichlorobenzene.

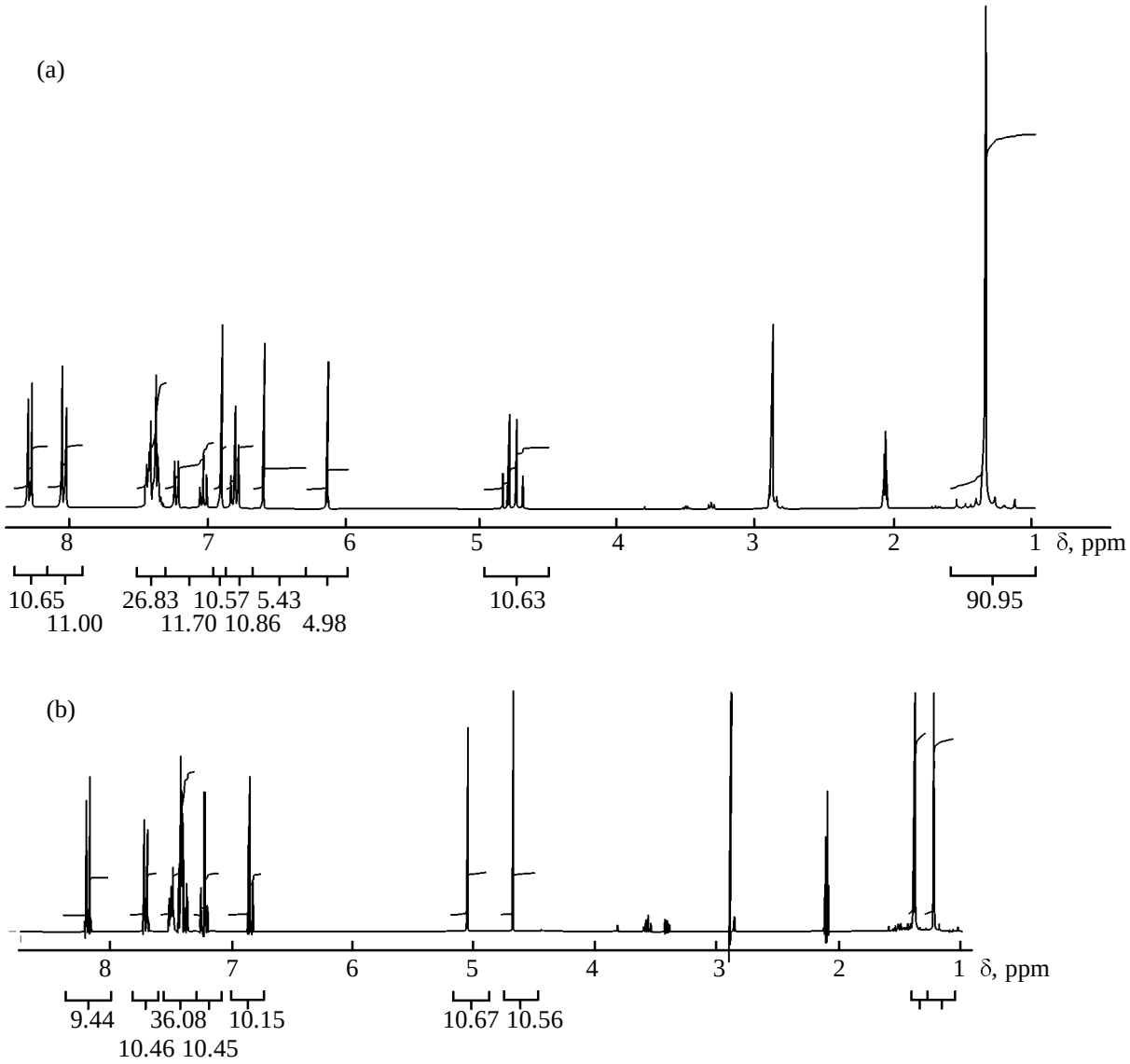
Our attempts to increase the mobility of methylene protons by replacement of vinyl or *p*-nitrophenyl group by the electron-acceptor oxadiazole fragment were unsuccessful: Compounds **XX** and **XXI** did not



XV–**XVII**

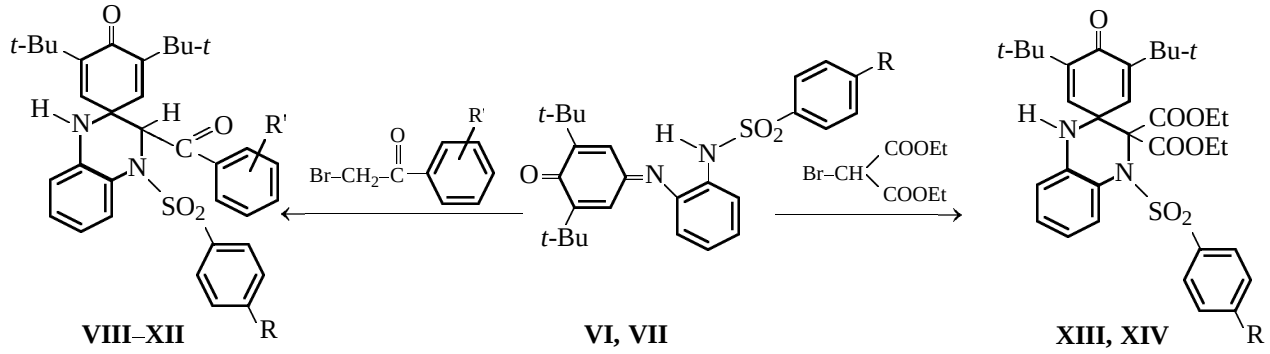
XV, **XVI**, R = 4-$NO_2C_6H_4$; **XVII**, R = CH_2Ph; **XV**, R' = $CH{=}CH_2$; **XVI**, **XVII**, R = 4-$NO_2C_6H_4$.

undergo cyclization into the corresponding spiroquinoxalines (Scheme 5).



^{1}H NMR spectra of (a) 3,5-di-*tert*-butyl-3'-(*p*-nitrobenzoyl)-4'-benzylsulfonylspiro[2,5-cyclohexadiene-1,2'-1',2',3',4'-tetrahydroquinoxalin]-4-one (**IV**) and (b) *N*-[*o*-(3,5-di-*tert*-butyl-4-oxo-2,5-cyclohexadienylideneamino)phenyl]-*N*-(*p*-nitrobenzyl)-phenylmethanesulfonamide (**XVII**) in acetone-d_6 (Varian Unity-300, 300 MHz).

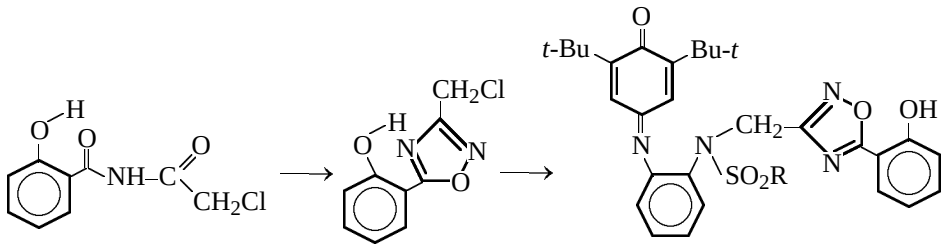
Scheme 4.



VIII–**XII** **VI, VII** **XIII, XIV**

VI, **VIII**–**XI**, **XIII**, R = CH_3; **VII**, **XII**, **XIV**, R = NO_2; **VIII**, R' = H; **IX**, **XII**, R' = 4-Br; **X**, R' = 3-NO_2; **XI**, R' = 3,4-Cl_2.

Scheme 5.

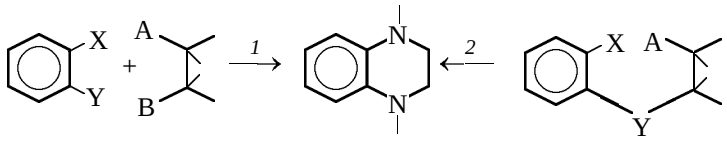


XVIII **XIX** **XX, XXI**

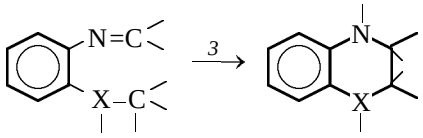
XX, R = 4-$CH_3C_6H_4$; **XXI**, R = 4-$NO_2C_6H_4$.

Thus we have revealed a synthetic potential of the new route to quinoxaline derivatives via noncatalytic intramolecular rearrangement of *N*-alkyl-4-(*o*-R-sulfonylaminophenylimino)-2,6-di-*tert*-butyl-2,5-cyclohexadienones. The previously described syntheses of structurally related heterocycles are limited to two main methods illustrated by Scheme 6 (pathways *1* and *2*). According to these methods, the heterocyclization occurs in the final stage through formation of carbon–heteroelement bonds [5]. The procedure proposed in the present work may be illustrated by pathway *3* according to which the heterocycle is formed by carbon–carbon bond closure.

Scheme 6.



A, B, X, Y = N, O, Hlg.



X = O, N, S(?).

A, B, X, Y = N, O, Hlg.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on Bruker DPX-250 (250 MHz) and Varian Unity-300 spectrometers (300 MHz) at 25°C. The elemental compositions of the newly synthesized compounds were consistent with the calculated values.

***o*-(Benzylsulfonylamino)aniline.** To a solution of 3.2 g of *o*-phenylenediamine in 20 ml of THF we added a solution of 5.7 g of phenylmethanesulfonyl chloride and 2.4 ml (2.37 g) of pyridine in 10 ml of THF. The mixture was stirred for 1 h at room temperature, 150 ml of water was added, and the mixture was heated to the boiling point. It was then cooled, and the light gray precipitate was filtered off and recrystallized from methanol. Colorless crystals, mp 166°C. Yield 5.11 g (65%).

***o*-(*p*-Nitrophenylsulfonylamino)aniline,** mp 160°C, yield 50%, and ***o*-(*p*-tolylsulfonylamino)-aniline,** mp 134°C, yield 65%, were synthesized in a similar way.

4-(2-(Benzylsulfonylaminophenylimino)-2,6-di-*tert*-butyl-2,5-cyclohexadienone (I). A mixture of 3 g of *o*-(benzylsulfonylamino)aniline and 2.52 g of 2,6-di-*tert*-butyl-1,4-benzoquinone [6] in 50 ml of 2-propanol was refluxed for 8 h and left overnight.

The precipitate was filtered off and passed through a column of Al_2O_3 using ethyl acetate as eluent. The eluate was evaporated to dryness, and the residue was recrystallized from isopentyl alcohol. Red crystals. Yield 3.3 g (62%). mp 173°C. ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 1.27 s (9H), 1.33 s (9H), 4.50 s (2H), 6.94 d.d (1H), 7.02 d (1H), 7.12 d (1H), 7.22 d.d (1H), 7.27–7.38 m (5H), 7.67 d.d (1H), 7.74 s (1H).

Compounds **VI** and **VII** were synthesized in a similar way.

2,6-Di-*tert*-butyl-4-[2-(*p*-tolylsulfonylamino)-phenylimino]-2,5-cyclohexadienone (VI). Orange crystals (from 2-propanol). Yield 50%. mp 190°C [7].

2,6-Di-*tert*-butyl-4-[2-(*p*-nitrophenylsulfonyl-amino)phenylimino]-2,5-cyclohexadienone (VII). Yield 40%. Red crystals. mp 234°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.16 s (9H), 1.34 s (9H), 6.63 d.d (1H), 6.70 d (1H), 6.85 d (1H), 7.08 d.d (1H), 7.21 d.d (1H), 7.40 s (1H), 7.61 d (1H), 7.98 d (2H), 8.19 d (2H).

4′-Benzylsulfonyl-3,5-di-*tert*-butyl-3′-(*p*-nitro-benzoyl)spiro[2,5-cyclohexadiene-1,2′-1′,2′,3′,4′-tetrahydroquinoxalin]-4-one (IV). *a*. To a solution of 2.32 g of compound **I** in 20 ml of acetone we added 2 g of freshly calcined potassium carbonate and 1.22 g of *p*-nitrophenacyl bromide. The mixture was refluxed for 1 h, cooled, and filtered, the filtrate was evaporated to dryness, and the residue was recrystallized from isobutyl alcohol. Red crystals. Yield 1.76 g (56%). mp 172°C. The ^{1}H NMR spectrum of **IV** is given in the figure.

b. A mixture of 0.2 g of 4-[*o*-(benzylsulfonyl-amino)phenylimino]-2,6-di-*tert*-butyl-2,5-cyclohexadienone thallium salt and 0.07 g of *p*-nitrophenacyl bromide in 10 ml of acetonitrile was refluxed for 40 min. The precipitate of thallium chloride was filtered off, and the filtrate was evaporated and then treated as described above in *a*.

Compounds **VIII**–**XVII** were synthesized in a similar way (method *a*) from the corresponding 2,6-di-*tert*-butyl-4-(*o*-sulfonylaminophenylimino)-2,5-cyclohexadienones and alkyl halides.

3′-Benzoyl-3,5-di-*tert*-butyl-4′-(*p*-tolylsulfonyl)-spiro[2,5-cyclohexadiene-1,2′-1′,2′,3′,4′-tetrahydro-quinoxalin]-4-one (VIII). Yield 65%. mp 188°C. ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 1.30 s (18H), 2.39 s (3H), 6.04 s (1H), 6.91 s (1H), 6.62 m (3H), 6.84 d.d (1H), 7.04 d.d (1H), 7.30 d (2H), 7.60 m (6H), 8.22 d (2H).

3′-(*p*-Bromobenzoyl)-3,5-di-*tert*-butyl-4′-(*p*-tolyl-sulfonyl)spiro[2,5-cyclohexadiene-1,2′-1′,2′,3′,4′-tetrahydroquinoxalin]-4-one (IX). Yield 50%. mp 155°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.29 s (18H), 2.35 s (3H), 4.10 s (1H), 6.37 s (1H), 6.48 s (2H), 6.55 d (1H), 6.78 d.d (1H), 6.98 d.d (1H), 7.14 d (2H), 7.50 m (3H), 7.62 d (2H).

3,5-Di-*tert*-butyl-3′-(*m*-nitrobenzoyl)-4′-(*p*-tolyl-sulfonyl)spiro[2,5-cyclohexadiene-1,2′-1′,2′,3′,4′-tetrahydroquinoxalin]-4-one (X). Yield 40%. mp 164°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.28 s (18H), 2.35 s (3H), 5.06 s (1H), 6.39 s (1H), 6.53 m (3H), 6.89 d.d (1H), 6.98 d.d (1H), 7.18 d (2H), 7.52 m (3H), 7.66 d.d (1H), 8.40 d (1H), 8.49 d (1H), 8.92 s (1H).

3,5-Di-*tert*-butyl-3′-(*m*,*p*-dichlorobenzoyl)-4′-(*p*-tolylsulfonyl)spiro[2,5-cyclohexadiene-1,2′-1′,2′,3′,4′-tetrahydroquinoxalin]-4-one (XI). Yield 40%. mp 171°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.28 s (18H), 2.34 s (3H), 5.06 s (1H), 6.35 s (1H), 6.49 s (2H), 6.59 d (1H), 6.79 d.d (1H), 6.99 d.d (1H), 7.16 d (2H), 7.51 m (4H), 8.01 d (1H), 8.11 s (1H).

3′-(*p*-Bromobenzoyl)-3,5-di-*tert*-butyl-4′-(*p*-nitro-phenylsulfonyl)spiro[2,5-cyclohexadiene-1,2′-1′,2′,-3′,4′-tetrahydroquinoxalin]-4-one (XII). Yield 70%. mp 165°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.26 s (18H), 5.04 s (1H), 6.48 s (1H), 6.43 s (2H), 6.62 d (1H), 6.88 d.d (1H), 7.05 d.d (1H), 7.51 d (1H), 7.62 d (2H), 7.74 d (1H), 8.02 d (2H), 8.16 d (2H).

Diethyl 3,5-di-*tert*-butyl-4-oxo-4′-(*p*-tolylsul-fonyl)spiro[2,5-cyclohexadiene-1,2′-1′,2′,3′,4′-tetra-hydroquinoxaline]-3′,3′-dicarboxylate (XIII). Yield 30%. mp 160°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.22 t (6H), 1.42 s (18H), 2.44 s (3H), 4.22 m (4H), 5.22 s (1H), 6.57 d (1H), 6.69 d.d (1H), 6.85 d.d (1H), 6.99 d (1H), 7.24 s (2H), 7.32 d (2H), 8.04 d (2H).

Diethyl 3,5-di-*tert*-butyl-4′-(*p*-nitrophenylsul-fonyl)-4-oxospiro[2,5-cyclohexadiene-1,2′-1′,2′,3′,4′-tetrahydroquinoxaline]-3′,3′-dicarboxylate (XIV). Yield 30%. mp 135°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.18 t (6H), 1.49 s (18H), 4.19 m (4H), 5.21 s (1H), 6.52 d (1H), 6.69 d.d (1H), 6.86 d.d (1H), 7.04 d (1H), 7.18 s (2H), 8.32 s (4H).

***N*-Allyl-*N*-[*o*-(3,5-di-*tert*-butyl-4-oxo-2,5-cyclo-hexadienylideneamino)phenyl]-*p*-nitrobenzenesul-fonamide (XV).** Yield 50%. mp 120°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.18 s (9H), 1.24 s (9H), 4.78 s (2H), 5.05 s (2H), 5.77 m (1H), 6.45 d (1H), 6.50 d (1H), 6.58 d (1H), 7.25 m (3H), 7.87 d (2H), 8.18 d (2H).

***N*-[*o*-(3,5-Di-*tert*-butyl-4-oxo-2,5-cyclohexadi-enylideneamino)phenyl]-*N*-(*p*-nitrobenzyl)-*p*-nitro-

benzenesulfonamide (XVI). Yield 80%. mp 178°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.21 s (9H), 1.29 s (9H), 5.06 s (2H), 6.42 d (1H), 6.51 d (1H), 6.52 d (1H), 7.13 m (2H), 7.24 m (1H), 7.49 d (2H), 7.87 d (2H), 8.09 d (2H), 8.19 d (2H).

***N*-[*o*-(3,5-Di-*tert*-butyl-4-oxo-2,5-cyclohexadienylideneamino)phenyl]-*N*-(*p*-nitrobenzyl)phenylmethanesulfonamide (XVII).** Yield 56%. mp 177°C. The ^{1}H NMR spectrum of **XVII** is shon in figure.

***N*-(Chloroacetyl)salicylamide (XVIII).** To a solution of 3.4 g of salicylamide in 80 ml of freshly distilled ethyl acetate we added dropwise while stirring 2 ml of chloroacetyl chloride. The mixture was refluxed for 4 h and cooled, and the precipitate was filtered off and washed with chloroform. Yield 3.8 g (72%). Colorless crystals. mp 173°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 4.67 s (2H), 6.23–6.60 m (4H), 11.20 s (1H).

3-Chloromethyl-5-(*o*-hydroxyphenyl)-1,2,4-oxadiazole (XIX). A suspension of 0.85 g of sodium acetate and 0.72 g of hydroxylamine hydrochloride in 6 ml of glacial acetic acid was refluxed for 10 min. The mixture was cooled, 2.14 g of *N*-(chloroacetyl)-salicylamide was added, and the mixture was refluxed for 1 h, cooled, and diluted with 30 ml of water. The crystals were filtered off. Yield 1.15 g (55%). Colorless crystals. mp 78°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 4.62 s (2H), 5.88 m (2H), 6.27 m (1H), 6.60 d (1H), 10.63 s (1H).

***N*-[*o*-(3,5-Di-*tert*-butyl-4-oxo-2,5-cyclohexadienylideneamino)phenyl]-*N*-[5-(*o*-hydroxyphenyl)-1,2,4-oxadiazol-3-ylmethyl]-*p*-toluenesulfonamide (XX).** A suspension of 6.21 g of oxadiazole **XIX** and 0.15 g of NaI in 5 ml of acetone was refluxed for 1 h. The mixture was cooled, 0.42 g of freshly distilled potassium carbonate and 0.46 g of compound **IV** were added, and the mixture was refluxed for 1 h. The precipitate was filtered off, the filtrate was evaporated, and the residue was recrystallized from 2-propanol. Orange crystals. Yield 58%. mp 179°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.10 s (9H), 1.19 s (3H), 1.30 s (9H), 5.20 s (2H), 6.45 s (1H), 6.55 s (1H), 6.88 d (1H), 7.05 m (2H), 7.40 m (8H). 7.70 d (1H), 10.50 s (1H).

***N*-[*o*-(3,5-Di-*tert*-butyl-4-oxo-2,5-cyclohexadienylideneamino)phenyl]-*N*-[5-(*o*-hydroxyphenyl)-1,2,4-oxadiazol-3-ylmethyl]-*p*-nitrobenzenesulfonamide (XXI)** was synthesized in a similar way by reaction of oxadiazole **XIX** with compound **VII**. Yield 67%. mp 176°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.17 s (18H), 5.27 s (2H), 6.43 s (2H), 6.72 d (1H), 7.01 d.d (1H), 7.10 d (1H), 7.40 m (4H), 7.85 d (1H), 8.11 d (2H), 8.24 d (2H), 10.60 s (1H).

ACKNOWLEDGMENTS

This study was financially supported by the Russian Foundation for Basic Research (project no. 98-03-32 903a) and by the Program "Universities of Russia–Fundamental Research" (project no. 5.3.1387).

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