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Dedicated to Full Member of the Russian Academy of Sciences O.N. Chupakhin on his 80th anniversary

Synthesis of Acylhydrazones of Sterically Hindered Hydroxybenzaldehydes Based on Phloroglucinol

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Abstract—New acylhydrazones containing sterically hindered phenolic fragments with different degrees of steric shielding were synthesized by reactions of 2,2′,2″-[benzene-1,3,5-triyltris(oxy)]triacetic acid trishydrazide with hydroxybenzaldehydes. According to the NMR data, the products in solution exist as relatively stable conformational *cis*/*trans* isomers with respect to the C(O)–NH bond.

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Symmetric sterically hindered benzenetriol derivatives attract strong interest from the practical viewpoint as efficient, heat-resistant, and nontoxic antioxidants [1]. High antioxidant activity of such compounds as 1,3,5-tris(3,5-di-*tert*-butyl-4-hydroxybenzyl)mesitylene and 1,3,5-tris(3,5-di-*tert*-butyl-4-hydroxybenzyl)resorcinol is determined, among other factors, by their steric structure [2]. Molecules of these compounds adopt a *basket* conformation which favors cooperative effect of phenolic hydroxy groups [3, 4].

A promising class of polyfunctional antioxidants comprises hybrid structures based on sterically hindered phenols and hydrazones. The latter exhibit thermal and light stabilizer properties and are capable of acting as traps for peroxy radicals, forming complexes with transition metals, and promoting hydroperoxide degradation according to the molecular mechanism [5, 6].

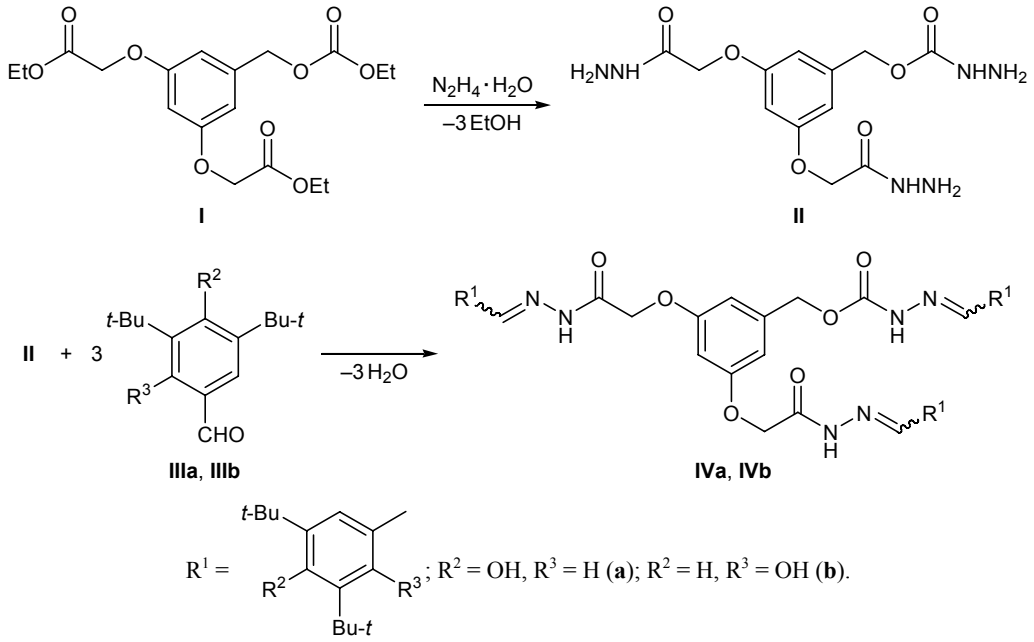
The goal of the present work was to synthesize new efficient polyfunctional antioxidants for polymers and organic media. For this purpose, we examined reactions of phloroglucinol derivatives with sterically hindered hydroxybenzaldehydes characterized by different degrees of steric shielding. New symmetric acylhydrazones **IVa** and **IVb** were obtained according to Scheme 1.

It is known that under normal conditions acylhydrazones can exist as different conformers resulting from *cis*/*trans* isomerism with respect to the amide bond and *E*/*Z* isomerism with respect to the double C=N bond [7]. Moreover, molecules **IVa** and **IVb** contain a number of polar groups which may be involved in hydrogen bonds. Therefore, the ^{1}H NMR spectra of these compounds recorded at room temperature display fairly complicated patterns, and each group of protons gives rise to a number of signals. Elevated temperature facilitates conformational transitions and hydrogen bond rupture, which leads to simpler spectra.

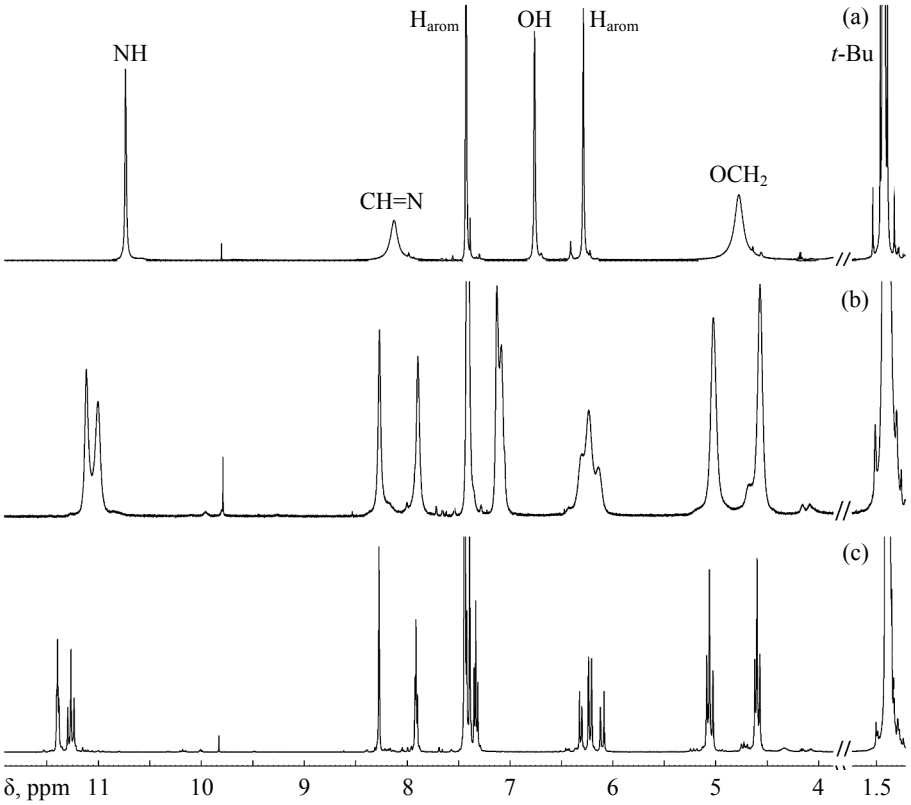
The ^{1}H NMR spectra of **IVa** and **IVb** in DMSO-d_6 at 130°C contained distinct singlets from protons in the *tert*-butyl groups (δ 1.30–1.44 ppm), a broadened singlet from the methylene protons (δ 4.75–4.80 ppm), singlets from aromatic protons (δ 6.43–7.47 ppm), a broadened singlet from the CH=N proton (δ 8.17–8.53 ppm), and a singlet from the NH protons (δ 10.79–11.45 ppm). Nonequivalent aromatic protons in **IVb** appeared as doublets with a coupling constant *J* of 2.3 Hz.

Reduction of the temperature from 130 to 70°C leads to doubling of the NH, CH=N, and OCH_2 proton signals in the spectrum of **IVa** due to restricted rotation about the amide C(O)–NH bond, while further reduction of the temperature to 30°C induced additional

Scheme 1.

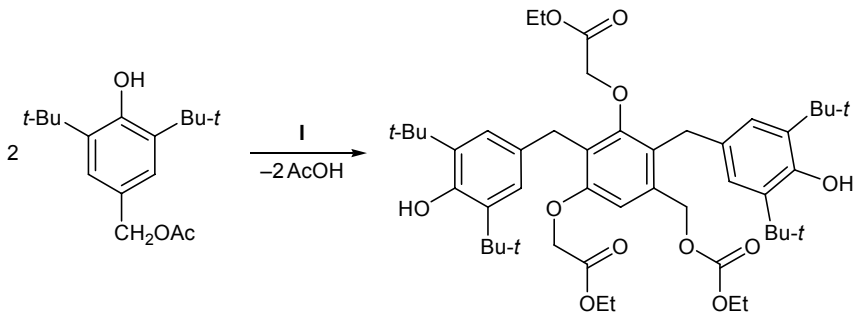


splitting of each of the above signals into three components (see figure). Analogous signal splitting was observed by us previously in the spectrum of calix[4]arene bishydrazone [8]. Presumably, at a temperature close to ambient hydrazone **IVa** in solution is represented by an equilibrium mixture of four conformers with *cis*/*cis*/*cis*, *cis*/*cis*/*trans*, *cis*/*trans*/*trans*, and *trans*/*trans*/*trans* orientations of the hydrazone fragments.



^{1}H NMR spectra of 2,2′,2″-[benzene-1,3,5-triyltris(oxy)]tris[*N*′-(3,5-di-*tert*-butyl-4-hydroxybenzylidene)acetohydrazide] (**IVa**) in DMSO-d_6 recorded at (a) 130, (b) 70, and (c) 30°C.

Scheme 2.



V **VI**

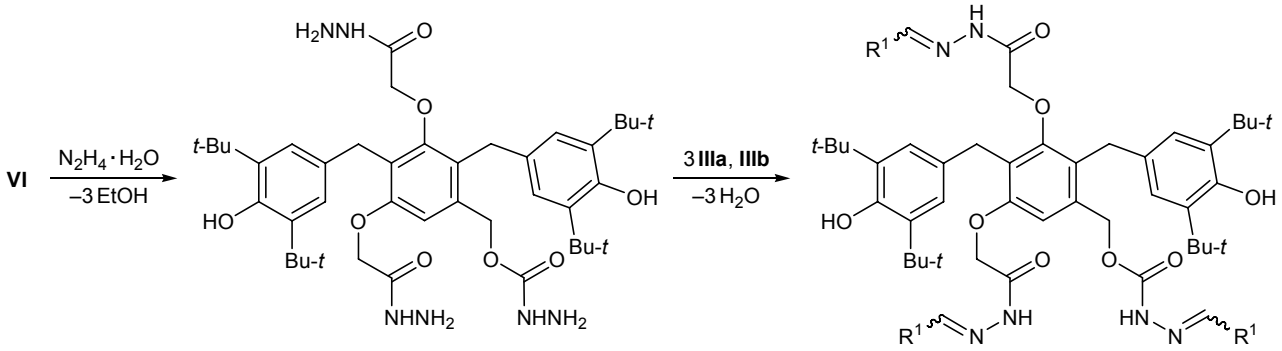
Each *cis*- or *trans*-hydrazone fragment is sensitive to the conformation of the two other hydrazone fragments adopting *cis*/*cis*, *cis*/*trans*, or *trans*/*trans* conformation, which eventually determines the observed ^{1}H NMR pattern.

With a view to obtain new polyphenolic structures tris-ester **I** was subjected to benzylation with acetate **V**. Presumably, steric factors allow introduction of only two sterically hindered hydroxybenzyl fragments into molecule **I** (Scheme 2). The use of excess benzyl acetate **V** and attempts to introduce the third hydroxybenzyl fragment into preliminarily isolated compound **VI** were unsuccessful. The structure of **VI** as pentasubstituted benzene derivative was confirmed by the presence of one aromatic proton signal (δ 6.19 ppm) in the ^{1}H NMR spectrum, as well as of double sets of signals from protons in the $OCH_2C(O)$, OCH_2CH_3, and CH_3 groups with an intensity ratio of 2 : 1. It should be noted that the signal of the $OCH_2C(O)$ group in the *ortho* position with respect to the two hydroxybenzyl substituents appears 0.5 ppm upfield relative to the corresponding signal from the two other $OCH_2C(O)$ fragments. Presumably, protons in the first $OCH_2C(O)$ group appear in the area shielded by π-electrons of aromatic rings in the hydroxybenzyl substituents.

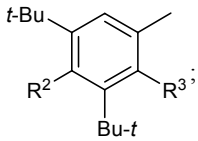
Dibenzyl derivative **VI** was used to synthesize the corresponding acylhydrazones as shown in Scheme 3. Like compounds **IVa** and **IVb**, proton signals of acylhydrazones **VIIIa** and **VIIIb** were readily assigned in the ^{1}H NMR spectra recorded at 130°C. Here, a good correlation with the spectra of **IVa** and **IVb** was observed. In the spectra of **VIIIa** and **VIIIb** the chemical shift of protons in the benzylidenehydrazinocarbonylmethoxy fragment in the *ortho* position with respect to the two 4-hydroxybenzyl fragments differs from the chemical shift of analogous protons in the two other fragments. As noted above for ester **VI**, the first $OCH_2C(O)$ signal is located in a stronger field.

The isolated compounds containing sterically hindered phenolic and hydrazone fragments attract interest from the practical viewpoint as polyfunctional inhibitors of radical chain oxidation processes. On the

Scheme 3.



VII **VIIIa**, **VIIIb**

R^1 = 

; R^2 = OH, R^3 = H (**a**); R^2 = H, R^3 = OH (**b**).

other hand, both sterically hindered phenols and acylhydrazones are known as pharmacophores responsible for various kinds of biological activity [9, 10], which stimulates interest in further versatile studies of such hybrid structures.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker Avance-600 spectrometer at 600.13 MHz; the chemical shifts were measured relative to the residual proton signals of the deuterated solvents. The mass spectra (MALDI-TOF) were obtained on a Bruker Ultraflex III instrument using plastic and metal targets and 2,5-dihydroxybenzoic acid as matrix.

Tris-ester **I** was synthesized according to the procedure described in [11].

2,2′,2″-[Benzene-1,3,5-triyltris(oxy)]tris(acetohydrazide) (II). A mixture of 0.80 g (2.08 mmol) of ester **I**, 1.3 g of hydrazine hydrate, and 8 mL of DMF was heated for 2 h under reflux. The mixture was cooled and poured into water, and the precipitate was filtered off, washed with water, and dried in air. Yield 0.61 g (86%), white powder, mp >300°C (decomp.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 4.43 s (6H, CH_2), 6.20 s (3H, H_{arom}), 9.32 br.s (3H, NH). Mass spectrum, *m*/*z*: 365 $[M + Na]^+$, 381 $[M + K]^+$. Found, %: C 42.48; H 5.65; N 24.16. $C_{12}H_{18}N_6O_6$. Calculated, %: C 42.10; H 5.26; N 24.56. *M* 342.31.

2,2′,2″-[Benzene-1,3,5-triyltris(oxy)]tris[*N*′-(3,5-di-*tert*-butyl-4-hydroxybenzylidene)acetohydrazide] (IVa). A mixture of 0.2 g (0.58 mmol) of hydrazide **II**, 0.45 g (1.93 mmol) of aldehyde **IIIa**, 5 mL of DMF, 5 mL of ethanol, and 0.04 mL of acetic acid was stirred for 26 h at 80°C. The mixture was cooled, and the precipitate was filtered off, washed with hot ethanol, and dried in air. Yield 0.50 g (86%), white powder, mp 225–227°C. ^{1}H NMR spectrum (DMSO-d_6, 130°C), δ, ppm: 1.44 s (54H, *t*-Bu), 4.80 br.s (6H, OCH_2), 6.32 s (3H, OH), 6.79 s (3H, H_{arom}), 7.47 s (6H, H_{arom}), 8.17 br.s (3H, CH=N), 10.79 s (3H, NH). Mass spectrum, *m*/*z*: 992 $[M + H]^+$, 1014 $[M + Na]^+$, 1030 $[M + K]^+$. Found, %: C 69.46; H 8.30, N 14.12. $C_{57}H_{78}N_6O_9$. Calculated, %: C 69.06; H 7.93; N 14.53. *M* 991.28.

2,2′,2″-[Benzene-1,3,5-triyltris(oxy)]tris[*N*′-(3,5-di-*tert*-butyl-2-hydroxybenzilidene)acetohydrazide] (IVb) was synthesized in a similar way from 0.25 g (0.73 mmol) of hydrazide **II** and 0.56 g (2.41 mmol) of aldehyde **IIIb** using 6 mL of DMF, 6 mL of ethanol, and 0.06 mL of acetic acid; reaction time 30 h. Yield 0.60 g (82%), white powder, mp 198–200°C. ^{1}H NMR spectrum (DMSO-d_6, 130°C), δ, ppm: 1.30 s (27H, *t*-Bu), 1.43 s (27H, *t*-Bu), 4.75 s (6H, OCH_2), 6.43 s (3H, H_{arom}), 7.16 d (3H, H_{arom}, $^4J_{HH}$ = 2.4 Hz), 7.36 d (3H, H_{arom}, $^4J_{HH}$ = 2.4 Hz), 8.53 s (3H, CH=N), 11.45 s (3H, NH), 11.55 br.s (3H, OH). Mass spectrum, *m*/*z*: 992 $[M + H]^+$, 1014 $[M + Na]^+$, 1030 $[M + K]^+$. Found, %: C 69.44; H 8.26; N 14.28. $C_{57}H_{78}N_6O_9$. Calculated, %: C 69.06; H 7.93; N 14.53. *M* 991.28.

Triethyl 2,2′,2″-[2,4-bis(3,5-di-*tert*-butyl-4-hydroxybenzyl)benzene-1,3,5-triyltris(oxy)]triacetate (VI). A mixture of 2.28 g (5.94 mmol) of ester **I**, 3.63 g (13.06 mmol) of acetate **V**, 10 mL of acetic acid, and 0.02 mL of perchloric acid was stirred for 3 h at 20°C. The precipitate was filtered off, washed with water, and dried in air. Yield 3.31 g (68%), white powder, mp 166–167°C (from acetonitrile). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.23 t (3H, CH_3, $^3J_{HH}$ = 7.0 Hz), 1.27 t (6H, CH_3, $^3J_{HH}$ = 7.0 Hz), 1.38 s (36H, *t*-Bu), 3.97 s (4H, Ar**C**$\mathbf{H}_2$), 4.04 s (2H, OCH_2C=O), 4.19 q (2H, O**C**$\mathbf{H}_2$$CH_3$, $^3J_{HH}$ = 7.0 Hz), 4.26 q (4H, O**C**$\mathbf{H}_2$$CH_3$, $^3J_{HH}$ = 7.0 Hz), 4.54 s (4H, OCH_2C=O), 4.96 s (2H, OH), 6.19 s (1H, H_{arom}), 7.10 s (4H, H_{arom}). Mass spectrum: *m*/*z* 821 $[M]^+$. Found, %: C 70.57; H 8.61. $C_{48}H_{68}O_{11}$. Calculated, %: C 70.22; H 8.35. *M* 821.06.

2,2′,2″-[2,4-Bis(3,5-di-*tert*-butyl-4-hydroxybenzyl)benzene-1,3,5-triyltris(oxy)]tris(acetohydrazide) (VII). A mixture of 0.66 g (0.80 mmol) of compound **VI**, 0.4 g of hydrazine hydrate, 5 mL of DMF, and 1 mL of water was heated for 2 h under reflux. The precipitate was filtered off, washed with water, and dried in air. Yield 0.51 g (81%), white powder, mp 285–287°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.28 s (36H, *t*-Bu), 3.81 s (2H, OCH_2C=O), 3.84 s (4H, Ar**C**$\mathbf{H}_2$), 4.27 br.s (6H, NH_2), 4.48 s (4H, OCH_2C=O), 6.53 s (1H, H_{arom}), 6.56 s (2H, OH), 6.92 s (4H, H_{arom}), 8.88 s (2H, NH), 9.15 s (1H, NH). Mass spectrum, *m*/*z*: 779 $[M + H]^+$, 801 $[M + Na]^+$, 817 $[M + K]^+$. Found, %: C 65.15; H 7.80; N 10.40. $C_{42}H_{62}N_6O_8$. Calculated, %: C 64.76; H 8.02; N 10.79. *M* 778.99.

2,2′,2″-[2,4-Bis(3,5-di-*tret*-butyl-4-hydroxybenzyl)benzene-1,3,5-triyltris(oxy)]tris[*N*′-(3,5-di-*tert*-butyl-4-hydroxybenzylidene)acetohydrazide] (VIIIa). A mixture of 0.20 g (0.26 mmol) of hydrazide **VII**, 0.19 g (0.80 mmol) of 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde (**IIIa**), 5 mL of DMF, 5 mL of ethanol, and 0.02 mL of acetic acid was stirred for 20 h

at 80°C. The mixture was poured into water, and the precipitate was filtered off and dried in air. Yield 0.32 g (87%), white powder, mp 245–246°C. ^{1}H NMR spectrum (DMSO-d_6, 130°C), δ, ppm: 1.30 s (36H, *t*-Bu), 1.42 s and 1.43 s (54H, *t*-Bu), 4.00 s (4H, ArC**H**$_2$), 4.25 br.s (2H, OCH_2C=O), 4.81 br.s (4H, OCH_2C=O), 5.94 br.s (2H, OH), 6.70 s (1H, H_{arom}), 6.77 s (3H, OH), 7.03 br.s (4H, H_{arom}), 7.42 s and 7.44 br.s (6H, H_{arom}), 8.05 s (2H, CH=N), 8.15 s (1H, CH=N), 10.49 br.s (3H, NH). Mass spectrum, *m*/*z*: 1429 $[M + H]^+$, 1451 $[M + Na]^+$, 1467 $[M + K]^+$. Found, %: C 73.34; H 8.84; N 5.49. $C_{87}H_{122}N_6O_{11}$. Calculated, %: C 73.18; H 8.61; N 5.89. *M* 1427.96.

2,2′,2″-[2,4-Bis(3,5-di-*tert*-butyl-4-hydroxybenzyl)benzene-1,3,5-triyltris(oxy)]tris[*N*′-(3,5-di-*tert*-butyl-2-hydroxybenzylidene)acetohydrazide] (VIIIb) was synthesized in a similar way from 0.30 g (0.39 mmol) of hydrazide **VII** and 0.30 g (1.27 mmol) of aldehyde **IIIb** using 6 mL of DMF and 6 mL of ethanol; reaction time 24 h. Yield 0.43 g (84%), white powder, mp 165–167°C. ^{1}H NMR spectrum (DMSO-d_6, 130°C), δ, ppm: 1.31 s (54H, *t*-Bu), 1.32 s (9H, *t*-Bu), 1.43 s (18H, *t*-Bu), 1.45 s (9H, *t*-Bu), 4.05 s (4H, ArC**H**$_2$), 4.12 s (2H, OCH_2C=O), 4.76 s (4H, OCH_2C=O), 6.02 s (2H, OH), 6.84 s (1H, H_{arom}), 7.00 s (4H, H_{arom}), 7.12 d (1H, H_{arom}, $^4J_{HH}$ = 2.5 Hz), 7.14 d (2H, H_{arom}, $^4J_{HH}$ = 2.5 Hz), 7.36 d (2H, H_{arom}, $^4J_{HH}$ = 2.5 Hz), 7.37 d (1H, H_{arom}, $^4J_{HH}$ = 2.5 Hz), 8.37 s (2H, CH=N), 8.49 s (1H, CH=N), 11.02 s (2H, NH), 11.06 s (1H, NH), 11.50 br.s (3H, OH). Mass spectrum, *m*/*z*: 1429 $[M + H]^+$, 1451 $[M + Na]^+$, 1467 $[M + K]^+$. Found, %: C 73.53; H 8.84; N 5.52. $C_{87}H_{122}N_6O_{11}$. Calculated, %: C 73.18; H 8.61; N 5.89. *M* 1427.96.

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