Acetyl chloride—3,5-di(*tert*-butyl)-4-hydroxy-*N,N*-dimethylbenzylamine salt in the benzylation of organic and inorganic sulfur-containing compounds

D. B. Gorbunov, V. N. Voznesenskii, V. V. Ershov, and G. A. Nikiforov*

N. N. Semenov Institute of Chemical Physics, Russian Academy of Sciences, 4 ul. Kosygina, 117977 Moscow, Russian Federation. Fax: +7 (095) 938 2156

The reactions of the quaternary acylammonium salt formed on treatment of 3,5-di-*tert*-butyl-4-hydroxy-*N,N*-dimethylbenzylamine with acetyl chloride, with various organic and inorganic sulfur-containing compounds were studied. The possibility of using this salt for the introduction of a sterically hindered phenol moiety in various sulfur-containing compounds was shown.

Key words: sterically hindered phenols, quaternary ammonium salts, benzylation, thiourea.

Based on the hardness and softness of a series of bases with respect to the benzyl cation, we previously outlined the range of structures capable of benzylation by salts formed in reactions of carboxylic acid halides with 3,5-di(*tert*-butyl)-4-hydroxy-*N,N*-dimethylbenzylamine.[1]

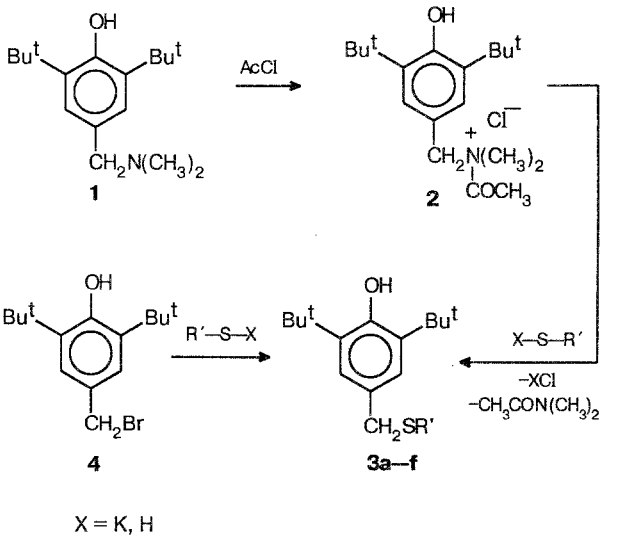
The purpose of the present work is to study the possibility and particular features of benzylation of sulfur-containing compounds with a salt of this type. Acetyl chloride was used in the reaction since in this case the Mannich base (**1**) is transformed to the desired salt (**2**) in 98 % yield. Salt-type systems, namely, KSCN, NH_4SCN, $KSC(S)N(CH_2CH_3)_2$, and $KSC(S)OCH_2CH_3$, as well as 2-mercaptobenzothiazole, thiourea, and *N*-acetylthiourea were used as the sulfur-containing compounds. In the case of 2-mercaptobenzothiazole, thiourea, or *N*-acetylthiourea, an equivalent amount of triethylamine was added to the reaction mixture. The reactions with salt-type systems or 2-mercaptobenzothiazole were carried out in dry acetone. In the case of thiuorea and its acetyl derivative, dry DMF and acetonitrile were used, and solutions of the above compounds were added to a solution of salt **2** in the same solvent. It should be noted that acetonitrile is the best solvent for the reaction of salt **2** with thiourea. In this solvent, the degree of conversion of thiourea is 80 %, while it does not exceed 45 % in DMF. The observed effect is likely due to the "hardness" of the basicity centers of these solvents (for CH_3CN, C_b = 1.34 and E_b = 0.89, whereas for DMF, C_b = 2.48 and E_b = 1.23, where C_b and E_b are the contributions of the hard (electrostatic) and soft (covalent) interactions of a solvent).[2] The solvents stabilize the separation of charges in salt **2** differently, which affects its reactivity.

The reactions of salt **2** with salt-type systems or 2-mercaptobenzothiazole afforded the respective benzyl derivatives (**3a—f**) in satisfactory yields (Scheme 1, Table 1).

The structures of the compounds obtained were confirmed by ^1H NMR data and by an independent synthesis, *i.e.*, the reaction of 3,5-di(*tert*-butyl)-4-hydroxybenzyl bromide (**4**) with the respective sulfur-containing compounds (Table 1).

The structure of 3,5-di(*tert*-butyl)-4-hydroxybenzyl thiocyanate **3d** was also confirmed by its thermal isomerization to the respective isothiocyanate (**5**).

Scheme 1



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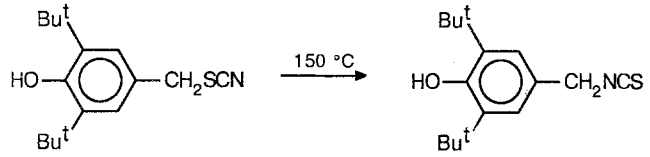
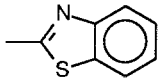
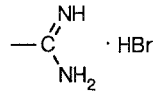
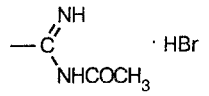


3d **5**

The benzylation of thiourea and its *N*-acetyl derivative should be considered particularly. Bromide **4**, like alkyl halides,[3] reacts with thiourea or *N*-acetylthiourea to give the respective isothiuronium salts, **3e** or **3f** (Table 1).

Table 1. Yields and melting points of compounds **3a—f**

3	R′	M.p./°C	Yield (%)
a	—C(S)OCH$_2$CH$_3$	56—57	83.2 (91)
b	—C(S)N(CH$_2$CH$_3$)$_2$	108—109	84.7 (87)
c		149—150	86.4 (71)
d	—CN	100—101	45.6 (92)
e		225—226	— (93)
f		210—212	— (82)

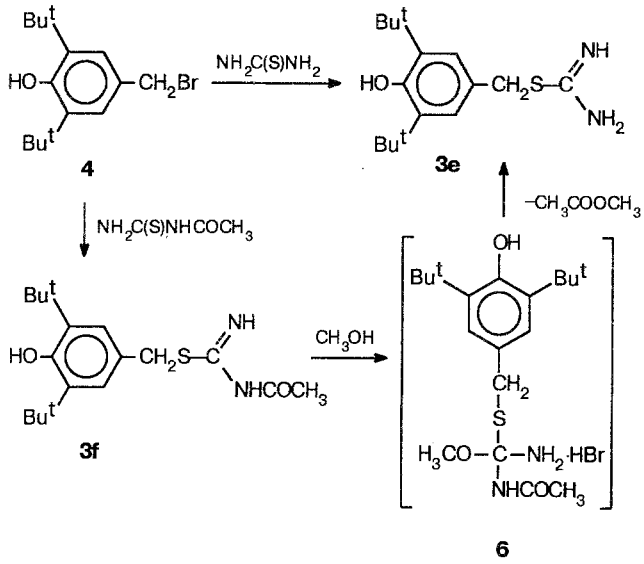
It is remarkable that the structure of the final product derived from *N*-acetylthiourea depends on the solvent used. The reaction in acetone results in product **3f**, whereas that in methanol affords product **3e**. Probably, the facts observed originate from the formation of a labile intermediate **6** when compound **3f** reacts with methanol according to Scheme 2.

It was anticipated that the reaction of compound **2** with thiourea or *N*-acetylthiourea would result in the bases of isothiuronium salts **3e** and **3f** (Scheme 3).

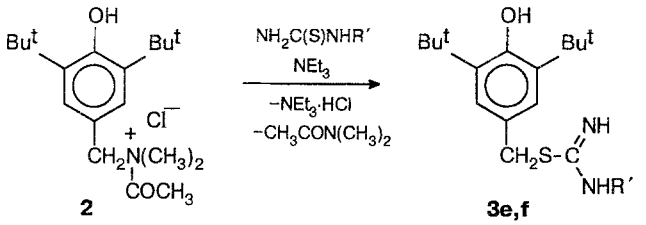
However, the reaction with *N*-acetylthiourea gave rise to a mixture of the original thiourea, quinone **7**, and diarylethylene **8**. Obviously, this is due to the transformation of compound **2** by the action of NEt_3 according to the methylene-quinone mechanism. In fact, the treatment of salt **2** with one equivalent of triethylamine under the same conditions gives compounds **7** and **8** due to dimerization of the intermediate methylenequinone[3] (Scheme 4).

The reaction of salt **2** with thiourea gave a mixture of two substituted thioureas **9** and **10** (Scheme 5).

Scheme 2

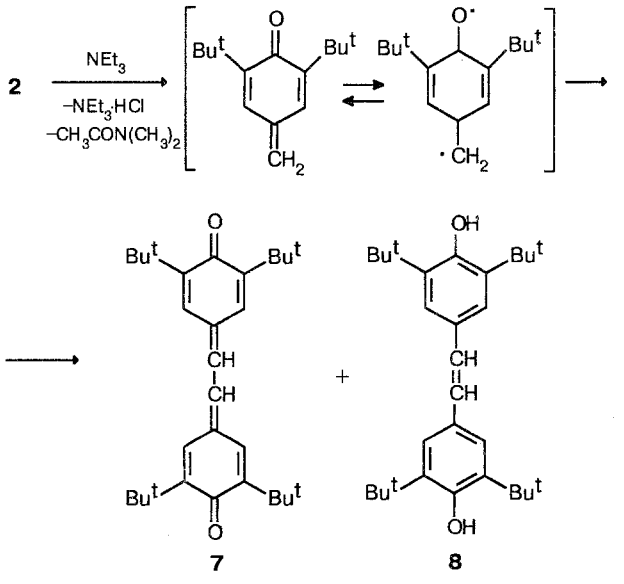


Scheme 3

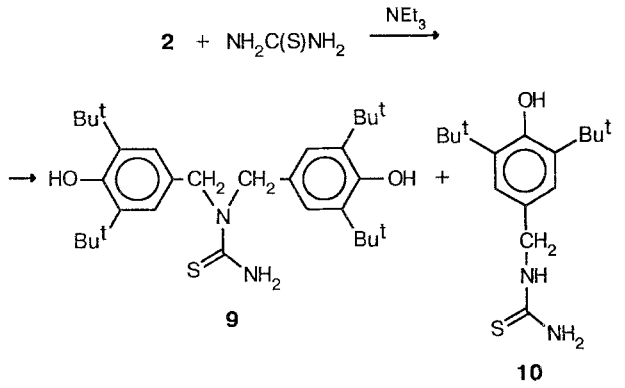


R′ = H, $COCH_3$

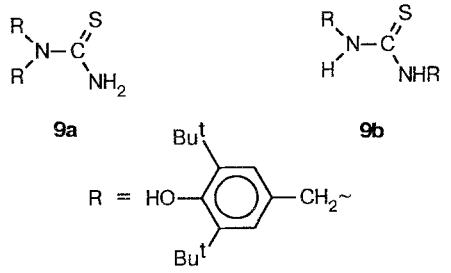
Scheme 4



Scheme 5



The structures of compounds **9** and **10** were confirmed by IR, NMR, and mass spectral data, as well as by chemical transformations of these compounds. The IR and ^{13}C NMR spectral data indicate that the thiocarbonyl group is present in both compounds. The analysis of the mass spectra for compound **9** (molecular ion 512 units, calculated 512 units, initial fragmentation) indicates that molecule **9** contains two sterically hindered phenol moieties. Hence, two alternative structures **9a** and **9b** are possible for compound **9**.



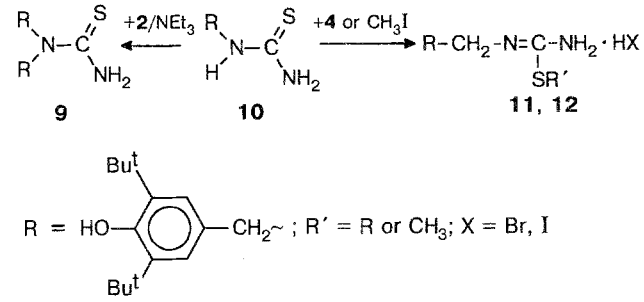
According to the ^{13}C NMR spectral data, thiourea **9** has structure **9a**. Since the molecule is asymmetric and the rotation around the C—N bond is hindered, the carbon atoms of the CH_2 groups are nonequivalent. Their signals at low temperatures are observed as two triplets (or two singlets if the spin-spin interaction with protons is suppressed) which broaden as the temperature is increased. In the limiting case, above 130 °C, they are merged into one triplet (or a singlet if the spin-spin interaction with protons is suppressed). A similar picture is also observed for the ^{13}C signals of *meta* (C-3, C-5) and *para* (C-4) carbon atoms of the aromatic rings. A similar feature is also characteristic for the proton spectra for H_m and CH_2 of compound **9a**.

Table 2 presents the kinetic parameters of hindered rotation in compound **9a** calculated on the basis of the ^{13}C—{H} NMR spectra in DMSO-d_6 by the equations[4]

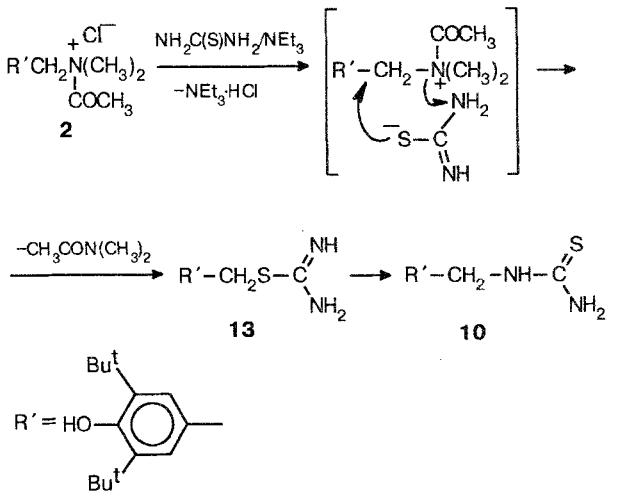
$$K = \frac{\pi\Delta\nu}{\sqrt{2}}$$

and $\Delta G^{\neq} = 4.57 \cdot T_c\,(10.32 + \lg T_c - \lg K)$.

The mass spectral data (molecular ion 294 units, calculated 294 units, initial fragmentation) as well as ^1H and ^{13}C NMR data (the positions of the signals, see Experimental) for compound **10** are in perfect agreement with the structure of *N*-[3,5-di(*tert*-butyl)-4-hydroxy]benzylthiourea. Furthermore, the structure of compound **10** is confirmed by its chemical transformations. For example, heating compound **10** with an equivalent amount of 3,5-di(*tert*-butyl)-4-hydroxybenzyl bromide **4** or with CH_3I in methanol gives the respective isothiuronium salts **11** or **12**. Treatment of compound **10** with an acetone solution of salt **2** in the presence of triethylamine affords product **9**.



To conclude the discussion of the reaction of salt **2** with thiourea, we shall dwell on the possible mechanism involved. Evidently, the initial step of the reaction of salt **2** with the ionized form of thiourea is the synchronous abstraction of *N,N*-dimethylacetamide and addition of the cation formed to the nucleophilic center of thiourea to give unstable 3,5-di(*tert*-butyl)-4-hydroxybenzylisothiourea (**13**) which is transformed to compound **10** under the reaction conditions.



The migration of the benzyl moiety in compound **13** is probably an intermolecular process. The ease of this process is due to the relative stability of the benzyl

Table 2. Kinetic parameters of the hindered rotation in *N,N*-di[3,5-di(*tert*-butyl)-4-hydroxy]benzylthiourea (**9**)

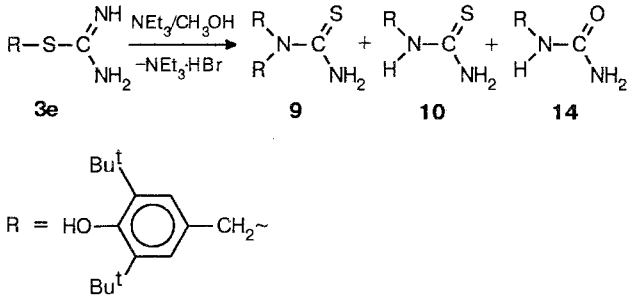
Group observed	T_c/K	Δν/Hz	K/s^{-1}	ΔG$^{\neq}$/kcal mol^{-1}
C-3, C-5	298	100	222.0	14.2
C-4	307	140	310.8	14.5
CH_2	320	360	799.2	14.5

$\Delta G_{avg.}$ = 14.4 kcal mol^{-1}.

cation formed in the reaction. The proposed mechanism is corroborated by the following facts:

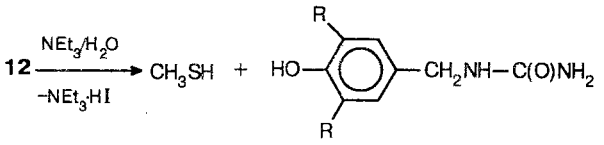
1. It is known[5] that acetylthiourea readily undergoes isomerization into *N*-acetylthiourea during intermolecular processes.
2. The reaction of salt **2** with thiourea results in a mixture of thioureas **9** and **10**.
3. The reaction of compound **3e** with an equivalent amount of NEt_3 in acetone results in a mixture containing products **9** (40 %) and **10** (43 %).
4. The same reaction in methanol results in a decrease in the overall yield of compounds **9** and **10** to 45 %. At the same time, up to 50 % of the product of the reaction of the 3,5-di(*tert*-butyl)-4-hydroxybenzyl cation with methanol, *viz.*, 2,6-di(*tert*-butyl)-4-methoxymethylphenol **14**, is formed (Scheme 6).
5. The treatment of isothiuronium salt **11** with an equivalent amount of NEt_3 in acetone affords only compound **9**, whereas in methanol, a mixture containing products **9** (30 %), **10** (34 %), and **14** (32 %) is formed.

Scheme 6



6. The treatment of isothiuronium salt **12** with excess NEt_3 in aqueous acetone affords methylmercaptane and 3,5-di(*tert*-butyl)-4-hydroxybenzylurea (Scheme 7).

Scheme 7



It should be noted in conclusion that the formation of *N*-substituted thioureas in the reaction of thiourea with salt **2** opens new prospects for easy syntheses of urea derivatives containing a sterically hindered phenol moiety at the nitrogen atom. The procedure for their synthesis may be very promising since *N*-substituted ureas are widely used as additives to fuel oils and in pharmacology.

Experimental

NMR and IR spectra were recorded on Bruker P 80 WY (400 MHz) and Specord M80 (KBr) instruments, respectively. TLC analyses were performed on standard Silufol plates.

The starting 3,5-di(*tert*-butyl)-4-hydroxy-*N,N*-dimethylbenzylamine was crystallized from hexane, m.p. 67—69 °C. Acetyl chloride was purified by distillation. The solvents were purified and dried by standard procedures.[6]

***S*-3,5-Di(*tert*-butyl)-4-hydroxybenzyl-*O*-ethylxanthate. a.** Freshly distilled AcCl (0.76 mL, 0.01 mol) was added to a solution of Mannich base **1** (2.63 g, 0.01 mol) in dry acetone (20 mL). The mixture was kept for 30 min at ~20 °C, and then a solution of potassium *O*-ethylxanthate (1.6 g, 0.01 mol) in dry acetone (25 mL) was added. The mixture was kept for 2 h at 20 °C, then a precipitate of KCl was removed. The mother liquor was concentrated *in vacuo*; the residue was dissolved in hexane (15 mL), filtered, and concentrated *in vacuo* to 1/3 of the original volume. The resulting solution was cooled with dry ice; the crystalline precipitate was separated and dried to give 2.8 g of *S*-3,5-di(*tert*-butyl)-4-hydroxybenzyl-*O*-ethylxanthate, m.p. 56—57 °C, yield 83 %.

Benzyl derivatives **3b—f** were obtained in a similar way. The yields, physicochemical parameters, and spectral data are given in Tables 1 and 3.

b. 3,5-Di(*tert*-butyl)-4-hydroxybenzyl bromide **4** (3.0 g, 0.01 mol) was added to a solution of potassium *O*-ethylxanthate (1.6 g, 0.01 mol) in methanol (20 mL). The mixture was

Table 3. ^{1}H NMR chemical shifts for compounds **3a—f**

3	Solvent	δ							
		$C(CH_3)_3$	CH_2	OH	H_m	CH_2CH_3	CH_2CH_3	H_{Ph}	$COCH_3$
a	C_6D_6	1.31	4.36	4.90	7.23	4.34 к	0.92 т	—	—
b	$CDCl_3$	1.43	4.45	5.10	7.16	3.90 к	1.28 т	—	—
c	$CDCl_3$	1.39	5.58	5.20	7.25	—	—	7.28	—
d	$CDCl_3$	1.45	4.16	5.32	7.15	—	—	—	—
e	$CD_3C(O)CD_3$	1.42	4.57	5.32	7.33	—	—	—	—
f	$CDCl_3$	1.42	4.42	5.35	7.16	—	—	—	2.35

Table 4. ^{13}C NMR chemical shifts for carbon atoms (DMSO-d_6, 130 °C), δ

Atom	9	10	11	12	3f	3e
$C(\underline{C}H_3)_3$	29.88	30.13	30.13	30.17	30.31	30.17
$\underline{C}(CH_3)_3$	33.67	33.95	34.30	34.30	34.45	34.29
C-1	—	—	153.44	—	153.89	153.41
C-1′	152.15	152.43	153.36	153.30	—	—
C-2, C-6	—	—	139.30	—	139.59	139.35
C-2′, C-6′	137.02	138.26	139.07	139.10	—	—
C-3, C-5	—	—	125.08	—	125.65	125.08
C-3′, C-5′	123.23	123.67	125.05	124.07	—	—
C-4	—	—	125.30	—	123.79	125.08
C-4′	126.88	129.00	124.18	125.77	—	—
CH_2—S	—	—	35.93	—	36.21	35.11
CH_2—N	52.75	47.95	47.10	47.11	—	—
C=S	182.87	183.09	—	—	—	—
C—S	—	—	165.37	167.29	170.33	169.62
CO—CH_3	—	—	—	—	171.81	—
CO—CH_3	—	—	—	—	24.41	—
CH_3	—	—	—	13.97	—	—

Note. Carbon atoms of the aromatic ring bonded to the nitrogen atom by a methylene bridge are marked by numerals with an apostrophe.

refluxed for 1 h, cooled, and poured into water (100 mL). The separated resinous mass was extracted with hexane (50 mL); the extract was concentrated *in vacuo* to 3—5 mL and frozen by dry ice. The crystalline precipitate was separated and dried to give 3.1 g (91 %) of compound **3a**, m.p. 56—57 °C. Benzyl derivatives **3b—f** were obtained in a similar way. The yields (in parentheses), physicochemical parameters, and spectral data are given in Tables 1, 3, and 4.

3,5-Di(*tert*-butyl)-4-hydroxybenzyl isothiocyanate (5). Compound **3d** (2.8 g, 0.01 mol) was heated at 150 °C under argon for *ca.* 3 h until it disappeared completely (TLC, Silufol, hexane—benzene, 1 : 1). The resulting black resin was dissolved in a hexane—benzene mixture (1 : 1) and chromatographed on a column with Silpearl 40/100 m. A hexane—benzene mixture (1 : 1) was used as the eluent. The solvent was evaporated *in vacuo*, and the semicrystalline precipitate was recrystallized from hexane to give 2.1 g (75 %) of **5** as white crystals, m.p. 179—180 °C. Found (%): 69.05; H, 8.28; N, 4.91; S, 11.36. $C_{15}H_{21}NOS$. Calculated (%) : C, 69.27; H, 8.36; N, 5.05; S, 11.56. ^1H NMR (C_6H_6), δ: 1.37 ($C(CH_3)_3$), 4.17 (CH_2), 4.90 (OH), 7.32 (H_m).

***N,N*-Di[3,5-di(*tert*-butyl)-4-hydroxy]benzylthiourea (9) and *N*-[3,5-di(*tert*-butyl)-4-hydroxy]benzylthiourea (10).** AcCl (1.45 mL, 0.02 mol) was added to a solution of compound **1** (5.26 g, 0.02 mol) in dry acetonitrile (30 mL). The mixture was kept for 30 min at ~20 °C, and then a solution of thiourea (1.52 g, 0.02 mol) and triethylamine (3.12 mL, 0.02 mol) in dry acetonitrile (30 mL) was added. The resulting reaction mixture was kept for 1 h at ~20 °C and then poured into water (250 mL). The separated semicrystalline mass was extracted with chloroform (2 × 100 mL). The extract was concentrated *in vacuo* to 1/3 of the original volume and chromatographed on a column with Silpearl using chloroform as the eluent. The solvent was distilled off to leave 2.4 g (41 %) of *N,N*-di[3,5-di(*tert*-butyl)-4-hydroxy]benzylthiourea (**9**) (m.p. 204—205 °C. Found (%): C, 72.51; H, 9.27; N, 5.57; S, 6.00. $C_{31}H_{48}N_2O_2S$. Calculated (%): C, 72.61; H, 9.43; N, 5.46; S, 6.25) and 2.65 g (45 %) of *N*-[3,5-di(*tert*-butyl)-4-hydroxy]benzylthiourea (**10**), m.p. 197—198 °C. Found (%): C, 65.42; H, 9.08; N, 9.32; S, 10.58. $C_{16}H_{26}N_2OS$. Calculated (%): C, 65.26; H, 8.90; N, 9.51; S, 10.89. The NMR data are given in Table 4.

***N*-[3,5-Di(*tert*-butyl)-4-hydroxy]benzyl-*S*-methylisothiuronium hydroiodide (12).** CH_3I (0.4 mL, 6 mmol) was added to a solution of compound **10** (1.47 g, 5 mmol) in methanol (30 mL), and the mixture was refluxed for 6 h. Methanol was removed *in vacuo*, and the residue was dissolved in benzene (10 mL). Crystallization was forced by adding hexane. The crystals were separated and dried to give 1.9 g (87.5 %) of compound **12**, m.p. 172—173 °C. Found (%): C, 46.70; H, 6.50; N, 6.13; S, 7.02. $C_{17}H_{29}N_2OSI$. Calculated (%): C, 46.79; H, 6.70; N, 6.42; S, 7.35. The NMR data are given in Table 4.

***N,S*-Di[3,5-di(*tert*-butyl)-4-hydroxy]benzylisothiuronium hydrobromide (11)** was obtained in a similar way in 91 % yield, m.p. 135—136 °C. The ^{13}C NMR data are given in Table 4.

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