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Synthesis of *S*-Alkylisothiuronium Halides by Reaction of Thiourea with ω-(4-Hydroxyaryl)alkyl Halides

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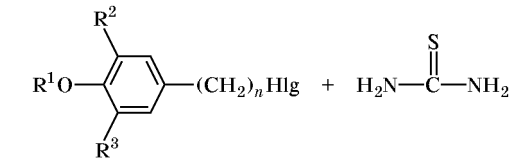
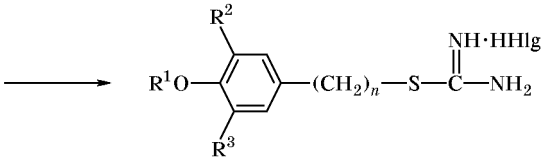
Abstract—A number of new *S*-alkylisothiuronium salts were synthesized by reaction of ω-[4-hydroxy-(methoxy)aryl]alkyl halides with thiourea. The resulting isothiuronium salts in aqueous solution react with sodium (potassium) halides to form halogen exchange products.

As a rule, functional derivatives of sterically hindered phenols exhibit a high biological activity; in particular, they show radioprotective and antitumor properties. The mechanism of their biological action is based on the antioxidating activity [1]. On the other hand, radioprotective and anticarcinogenic activity was reported for various compounds containing an isothiuronium fragment [2, 3]. Therefore, isothiuronium derivatives of sterically hindered phenols can be regarded as promising water-soluble bioantioxidants. The inhibitory activity of 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)- and 3-(3-*tert*-butyl-4-hydroxyphenyl)-propylisothiuronium chlorides in the oxidation of ethyl oleate in aqueous dispersion was demonstrated by us previously [4]; it is assumed that this reaction simulates oxidation of lipids in biological systems [5]. Synthesis of a series of structural analogs of the above compounds will make it possible to compare antioxidant properties of *S*-alkylisothiuronium halides with regard to their structure.

Scheme 1.



I–X



XI–XX

I–**V**, **XI**–**XV**, R^1 = H, R^2 = R^3 = *t*-Bu; **I**, **XI**, Hlg = Cl, *n* = 3; **II**, **XII**, Hlg = Br, *n* = 3; **III**, **XIII**, Hlg = I, *n* = 3; **IV**, **XIV**, Hlg = Cl, *n* = 2; **V**, **XV**, Hlg = Cl, *n* = 4; **VI**, **XVI**, R^1 = R^2 = H, R^3 = *t*-Bu, Hlg = Cl, *n* = 3; **VII**, **XVII**, R^1 = R^2 = R^3 = H, Hlg = Cl, *n* = 3; **VIII**, **XVIII**, R^1 = R^2 = R^3 = H, Hlg = Br, *n* = 3; **IX**, **XIX**, R^1 = Me, R^2 = R^3 = H, Hlg = Cl, *n* = 3; **X**, **XX**, R^1 = Me, R^2 = R^3 = H, Hlg = Br, *n* = 3.

In the present work we have synthesized a number of isothiuronium salts by the known method, i.e., by reaction of thiourea with alkyl halides [6] (Scheme 1). The synthesis of initial compounds **I**–**X** from the corresponding ω-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-alkanols was described by us previously [7].

The reactions of alkyl halides **I** and **II** with an equimolar amount of thiourea were carried out by analogy with the procedures reported in [2, 8]: the reactants were heated in lower alkanols (methanol, ethanol, 2-propanol, and 1-butanol) under reflux. The rate of the process increased as the temperature rose: in 1-butanol the conversion of the initial alkyl halides attained 90–95% in 3–5 h. The yield of the target product did not increase on further increasing the reaction time. Isothiuronium salts **XI** and **XII** can readily be purified from residual initial alkyl halides, for the former are almost insoluble in saturated hydrocarbons. On the other hand, removal of unreacted thiourea by repeated recrystallizations was accompanied by appreciable loss of the target products. The optimal thiourea–alkyl halide ratio was found to be about 1 : 1.2. In this case almost complete conversion of thiourea is attained, which considerably simplifies the procedures for isolation and purification

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Synthesis of *S*-[4-hydroxy(methoxy)aryl]alkylisothiuronium halides

Initial comp. no.	Reagent	Reaction time, h	Product no.	Yield, %	mp, °C
I	$SC(NH_2)_2$[a]	5	**XI**	92	165
II	$SC(NH_2)_2$[a]	4	**XII**	95	211
III	$SC(NH_2)_2$[a]	5	**XIII**	93	220
VII	$SC(NH_2)_2$[a]	3	**XVII**	79	235
VIII	$SC(NH_2)_2$[a]	4	**XVIII**	77	205–206
IX	$SC(NH_2)_2$[a]	3	**XIX**	86	141–142
X	$SC(NH_2)_2$[a]	3	**XX**	87	113
I	$SC(NH_2)_2$[b]	4	**XI**	88	165
I	$SC(NH_2)_2$[b]	5	**XI**	91	165
I	$SC(NH_2)_2$[b]	7	**XI**	94	165
IV	$SC(NH_2)_2$[b]	7	**XIV**	84	193
V	$SC(NH_2)_2$[b]	7	**XV**	89	151
VI	$SC(NH_2)_2$[b]	7	**XVI**	80	206
XI	NBr		**XII**	93	211
XI	NaI		**XIII**	96	220
XII	NaCl		**XI**	92	165
XII	NaI		**XIII**	93	220
XIII	NaCl		**XI**	93	165
XIII	NaBr		**XII**	95	211

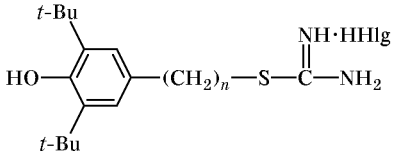
[a] The reaction was carried out in 1-butanol in an open system.
[b] The reaction was carried out in ethanol in a sealed ampule.

of the products. With the above reactant ratio, compounds **XI**–**XIII** and **XVII**–**XX** were obtained in 77–95% yield (see table).

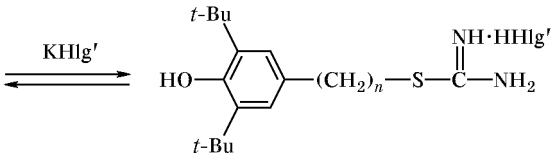
A considerable advantage of using relatively low-boiling solvents was that they can readily be removed from the reaction mixture. On the other hand, higher temperature ensures higher reaction rate. Therefore, it was interesting to carry out the reaction of alkyl halides with thiourea in a closed system [9] in order to take advantage of both high temperature and low-boiling solvent. The effect of the reaction conditions on the yield of the target product in a closed system was studied with compound **XI** as an example. The reaction was performed in ethanol in a sealed ampule, the reactant ratio, temperature, and reaction time being varied. The best yields of isothiuronium chloride **XI** (88–94%) were obtained at a thiourea–alkyl halide ratio of 1 : 1.2, temperature 120–125°C, and reaction time 4–7 h. Under the same conditions, compounds **XIV**–**XVI** were synthesized in 80–89% yield.

From the viewpoint of antioxidant activity, the most interesting are *S*-alkylisothiuronium iodides, for iodide ion itself is an antioxidant. At the same time, ω-(4-hydroxyphenyl)alkyl iodides are the most difficultly accessible among the other halogen derivatives, since their syntheses include many stages. It seemed reasonable to obtain *S*-alkylisothiuronium iodides via ion-exchange reactions from the corresponding chlorides and bromides (Scheme 2). Such

Scheme 2.



XI–**XIII**



XI–**XIII**

transformations occur fairly readily, since the bond between the isothiuronium fragment and the halogen is strongly ionized. The solubilities of compounds **XI**–**XIII** in water are comparable (0.28–0.45 g/100 g of H_2O at 25°C); therefore, addition of a large excess of metal halide (sevenfold) displaces the equilibrium toward the desired isothiuronium halide. We thus obtained target isothiuronium salts **XI**–**XIII** in 92–96% yield.

EXPERIMENTAL

The ^{1}H NMR spectra were obtained on a Bruker spectrometer operating at 500 MHz; the solvent used was D_2O (compounds **XI**, **XIII**, **XV**–**XVII**, and **XIX**) or CD_3OD (compounds **XII**, **XIV**, **XVIII**, and **XX**); tetramethylsilane was used as external reference. The IR spectra were recorded on a Vector 22 Fourier spectrometer; samples were prepares as KBr pellets (150 : 1).

Reaction of alkyl halides with thiourea. *a.* To a mixture of 15 mmol of alkyl halide **I**–**III** or **VII**–**X** and 12.5 mmol of thiourea we added 30 ml of 1-butanol, and the mixture was refluxed for 3–5 h (see table). The solvent was distilled off on a rotary evaporator, the residue was washed with warm pentane or hexane, and the precipitate was filtered off and dried. Isothiuronium salts **XI**–**XIII** and **XVII**–**XX** were thus obtained.

b. A 50-ml heat-resistant glass ampule was charged with 15 mmol of alkyl halide **I** or **IV**–**VI**, 12.5 mmol of thiourea, and 6 ml of ethanol. The ampule was sealed, placed in a thermostat equipped with a shaking device, and heated at 120–125°C for a time specified in table. The ampule was then cooled and opened, the solvent was distilled off on a rotary evaporator, the tarry residue was treated with pentane (or hexane), and the crystals were filtered off, washed with warm pentane (or hexane), and dried. We thus obtained isothiuronium salts **XI** and **XIV**–**XVI**.

Reaction of isothiuronium salts with sodium (or potassium) halides. Isothiuronium salt **XI**–**XIII**, 8 mmol, was dissolved on heating in 50 ml of water. A saturated solution of 56 mmol of appropriate sodium (or potassium) halide was prepared separately. On mixing the hot solutions, a solid precipitated. The mixture was cooled, and the precipitate was filtered off, washed on a filter with three portions of cold water, and dried first in air and then in a Fischer drying apparatus over toluene. Isothiuronium salts **XI**–**XIII** were thus obtained.

***S*-[3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)propyl]-isothiuronium chloride (XI).** ^{1}H NMR spectrum, δ, ppm: 1.430 s (18H, *t*-Bu), 2.048 m (2H, $ArCH_2C\mathbf{H}_2$), 2.726 t (2H, $ArCH_2$), 3.123 t (2H, CH_2S), 7.146 s (2H, H_{arom}). IR spectrum, ν, cm^{-1}: 3644 (OH), 3263 and 3062 (NH_2^+), 2955 (CH), 1650 (NH_2^+). Found, %: C 59.89; H 8.92; Cl 9.74; N 7.52; S 8.71. $C_{18}H_{31}ClN_2OS$. Calculated, %: C 60.22; H 8.70; Cl 9.88; N 7.80; S 8.93.

***S*-[3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)propyl]-isothiuronium bromide (XII).** ^{1}H NMR spectrum, δ, ppm: 1.430 s (18H, *t*-Bu), 2.000 m (2H, $ArCH_2C\mathbf{H}$), 2.690 t (2H, $ArCH_2$), 3.139 t (2H, CH_2S), 6.993 s (2H, H_{arom}). IR spectrum, ν, cm^{-1}: 3607 (OH), 3294 and 3032 (NH_2^+), 2953 (CH), 1648 (NH_2^+). Found, %: C 53.68; H 7.82; Br 19.81; N 6.76; S 8.01. $C_{18}H_{31}BrN_2OS$. Calculated, %: C 53.59; H 7.75; Br 19.81; N 6.04; S 7.95.

***S*-[3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)propyl]-isothiuronium iodide (XIII).** ^{1}H NMR spectrum, δ, ppm: 1.430 s (18H, *t*-Bu), 2.049 m (2H, $ArCH_2C\mathbf{H}_2$), 2.736 t (2H, $ArCH_2$), 3.120 t (2H, CH_2S), 7.166 s (2H, H_{arom}). IR spectrum, ν, cm^{-1}: 3611 (OH), 3204 and 3094 (NH_2^+), 2952 (CH), 1641 (NH_2^+). Found, %: C 47.69; H 7.14; I 28.35; N 5.93; S 7.29. $C_{18}H_{37}IN_2OS$. Calculated, %: C 48.00; H 6.94; I 28.17; N 6.22; S 7.12.

***S*-[2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)ethyl]-isothiuronium chloride (XIV).** ^{1}H NMR spectrum, δ, ppm: 1.430 s (18H, *t*-Bu), 2.909–2.938 t (2H, $ArCH_2$), 3.366–3.395 t (2H, CH_2S), 7.041 s (2H, H_{arom}). IR spectrum, ν, cm^{-1}: 3628 (OH), 3287 and 3095 (NH_2^+), 2959 (CH), 1640 (NH_2^+). Found, %: C 58.93; H 8.62; Cl 10.04; N 8.36; S 9.57. $C_{17}H_{29}ClN_2OS$. Calculated, %: C 59.19; H 8.47; Cl 10.28; N 8.12; S 9.30.

***S*-[4-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)butyl]-isothiuronium chloride (XV).** ^{1}H NMR spectrum, δ, ppm: 1.430 s (18H, *t*-Bu), 1.782 m (4H, $ArCH_2C\mathbf{H}_2C\mathbf{H}_2$), 2.582 t (2H, $ArCH_2$), 3.224 t (2H, CH_2S), 7.055 s (2H, H_{arom}). IR spectrum, ν, cm^{-1}: 3630 (OH), 3269 and 3050 (NH_2^+), 2957 (CH), 1653 (NH_2^+). Found, %: C 61.47; H 8.58; Cl 9.41; N 8.32; S 8.83. $C_{19}H_{33}ClN_2OS$. Calculated, %: C 61.18; H 8.92; Cl 9.50; N 7.51; S 8.60.

***S*-[3-(3-*tert*-Butyl-4-hydroxyphenyl)propyl]isothiuronium chloride (XVI).** ^{1}H NMR spectrum, δ, ppm: 1.418–1.453 s (9H, *t*-Bu), 2.030–2.059 m (2H, $ArCH_2CH_2$), 2.724–2.754 t (2H, $ArCH_2$), 3.106–3.135 t (2H, CH_2S), 6.883–6.899 d (1H, H_{arom}), 7.027–7.057 d (1H, H_{arom}), 7.254–7.258 s (1H, H_{arom}). IR spectrum, ν, cm^{-1}: 3281 and 3082 (NH_2^+), 2945 (CH), 1651 (NH_2^+). Found, %: C 55.53; H 7.47;

Cl 12.28; N 8.99; S 10.32. $C_{14}H_{23}ClN_2OS$. Calculated, %: C 55.52; H 7.65; Cl 11.71; N 9.25; S 10.59.

***S*-[3-(4-Hydroxyphenyl)propyl]isothiuronium chloride (XVII).** ^{1}H NMR spectrum, δ, ppm: 2.030 m (2H, $ArCH_2C\mathbf{H}_2$), 2.725 t (2H, $ArCH_2$), 3.114 t (2H, CH_2S), 6.893–6.910 d (2H, H_{arom}), 7.185–7.203 d (2H, H_{arom}). IR spectrum, ν, cm^{-1}: 3334 and 3125 (NH_2^+), 2959 (CH), 1650 (NH_2^+). Found, %: C 48.78; H 6.21; Cl 15.06; N 11.57; S 12.78. $C_{10}H_{15}ClN_2OS$. Calculated, %: C 48.67; H 6.13; Cl 14.37; N 11.35; S 12.99.

***S*-[3-(4-Hydroxyphenyl)propyl]isothiuronium bromide (XVIII).** ^{1}H NMR spectrum, δ, ppm: 2.128 m (2H, $ArCH_2C\mathbf{H}_2$), 2.834 t (2H, $ArCH_2$), 3.289 t (2H, CH_2S), 6.884–6.907 d (2H, H_{arom}), 7.186–7.203 d (2H, H_{arom}). IR spectrum, ν, cm^{-1}: 3228 and 3129 (NH_2^+), 2937 (CH), 1646 (NH_2^+). Found, %: C 41.79; H 5.09; Br 27.42; N 9.47; S 11.40. $C_{10}H_{15}BrN_2OS$. Calculated, %: C 41.25; H 5.19; Cl 27.44; N 9.62; S 11.01.

***S*-[3-(4-Methoxyphenyl)propyl]isothiuronium chloride (XIX).** ^{1}H NMR spectrum, δ, ppm: 2.015–2.045 m (2H, $ArCH_2C\mathbf{H}_2$), 2.724–2.754 t (2H, $ArCH_2$), 3.100–3.129 t (2H, CH_2S), 3.855 s (3H, OCH_3), 6.990–7.008 d (2H, H_{arom}), 7.242–7.259 d (2H, H_{arom}). IR spectrum, ν, cm^{-1}: 3208 and 3083 (NH_2^+), 2913 (CH), 1650 (NH_2^+). Found, %: C 50.33; H 6.43; Cl 13.46; N 10.92; S 12.71. $C_{11}H_{17}ClN_2OS$. Calculated, %: C 50.66; H 6.57; Cl 13.59; N 10.74; S 12.29.

3-(4-Methoxyphenyl)propylisothiuronium bromide (XX). ^{1}H NMR spectrum, δ, ppm: 2.001–2.031 m (2H, $ArCH_2C\mathbf{H}_2$), 2.723–2.753 t (2H, $ArCH_2$), 3.148–3.177 t (2H, CH_2S), 3.786 s (3H, OCH_3), 6.869–6.886 d (2H, H_{arom}), 7.148–7.165 d (2H, H_{arom}). IR spectrum, ν, cm^{-1}: 3212 and 3073 (NH_2^+), 2915 (CH), 1647 (NH_2^+). Found, %: C 42.94; H 5.60; Br 27.29; N 8.87; S 10.43. $C_{11}H_{17}BrN_2OS$. Calculated, %: C 43.29; H 5.61; Br 26.18; N 9.18; S 10.50.

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