ISSN 1070-3632, Russian Journal of General Chemistry, 2015, Vol. 85, No. 1, pp. 53–56. © Pleiades Publishing, Ltd., 2015.
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Antioxidant Activity of Isatin Acylhydrazones with Sterically Hindered Phenol Fragments

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Received October 20, 2014

Abstract—Sterically hindered phenolic isatin acylhydrazones were found to possess high antioxidant activity in model reaction with a free chromogen-radical 2,2-diphenyl-1-picrylhydrazyl (DPPH).

Keywords: isatin acylhydrazones, sterically hindered phenols, 2,2-diphenyl-1-picrylhydrazyl, antioxidant activity

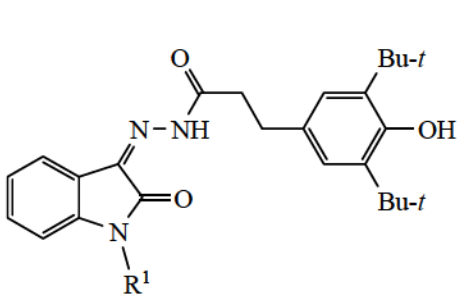
DOI: 10.1134/S1070363215010090

Sterically hindered phenols are effective antioxidants [1] widely used for correction of oxidative pathologies in living biological systems. There are data on antibacterial, anti-inflammatory, and DNA-protective activity of sterically hindered phenols [2–4]. A large number of pharmacologically active substances exhibiting a wide variety of chemotherapeutic activity [5] have been synthesized on the basis of sterically hindered phenols and various heterocyclic compounds. At the same time, data on sterically hindered phenolic derivatives of isatin are scarce. Such compounds are of considerable interest for the study of their biological activity since isatin and its derivatives, like Mannich bases, Schiff bases, and isatin hydrazones possess antibacterial, antiviral, antioxidant, anti-inflammatory, analgesic, and anti-cancer activity [6–9].

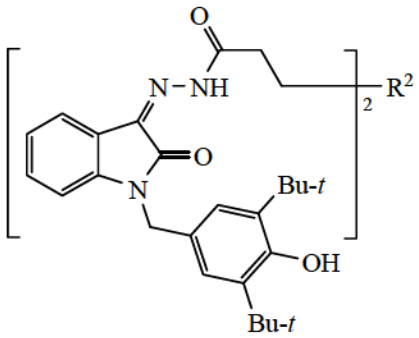
Previously, we have reported the synthesis of new isatin acylhydrazones **I**–**IV** containing sterically hindered phenol moieties [10, 11] (Scheme 1).

In the present work we evaluated antioxidant activity of compounds **I**–**IV** towards the chromogen radical 2,2-diphenyl-1-picrylhydrazyl. In [12, 13] a

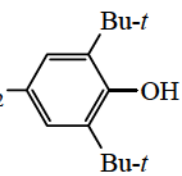
Scheme 1.



I, II

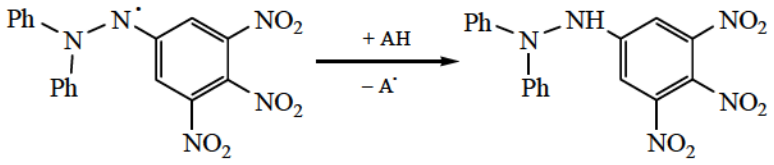


III, IV

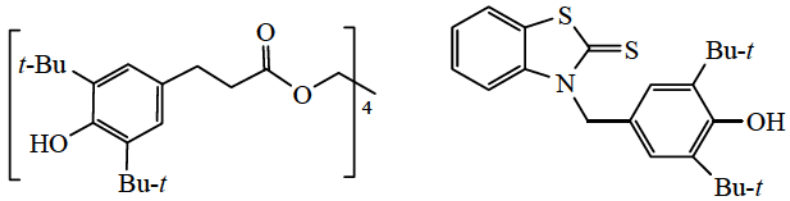


R^1 = H (**I**), CH_2 (**II**); R^2 = $(CH_2)_3$ (**III**), S (**IV**).

Scheme 2.

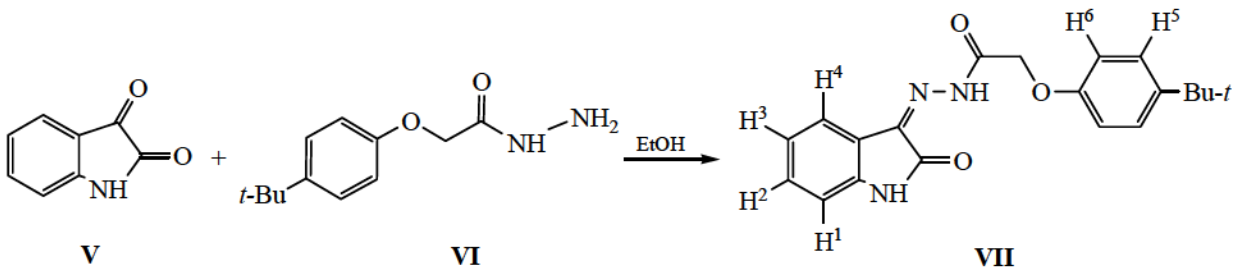


Scheme 3.



Irganox 1010 Agidol 70

Scheme 4.



V **VI** **VII**

correlation between registered antiradical and antioxidant activity was found by the example of interaction of antioxidants with 2,2-diphenyl-1-picryl-hydrazyl. Consequently, the interaction of studied isatin acylhydrazones with 2,2-diphenyl-1-picryl-hydrazyl allows a quantitative evaluation of their antioxidant activity.

The spectrum of a solution of DPPH in organic solvents contains absorption maximum in the visible region at 515–520 nm, which disappears by reacting the radical with hydrogen atom donor [14]. Measuring a decrease in time in absorbance at 520 nm of the solution of 2,2-diphenyl-1-picrylhydrazyl with an antioxidant, we calculated the rate constant for the interaction of the substance with DPPH which is a quantitative characteristic of its antioxidant activity.

The reaction of isatin acylhydrazones with DPPH was carried out at 20°C under conditions of pseudo-first order with respect to the radical in anhydrous 1,4-dioxane. In this solvent the reaction occurs predominantly by hydrogen atom transfer mechanism [15], which consists in the homolytic hydrogen abstraction from solute molecules (AH) and its transfer to the radical (Scheme 2).

The rate constants of the reaction of sterically hindered phenolic isatin acylhydrazones with DPPH are presented in the table. Pentaerythritol tetrakis-3-(3',5'-di-*tert*-butyl-4'-hydroxyphenyl)propionate (Irganox 1010) and *N*-(3,5-di-*tert*-butyl-4-hydroxybenzyl) benzotriazole (Agidol 70) were used as reference antioxidants (Scheme 3).

Furthermore, specially synthesized acylhydrazone **VII** containing no sterically hindered phenol moiety was also used as a reference antioxidant (Scheme 4).

In the ^{1}H NMR spectrum of **VII** the doubling of the proton signals of *tert*-butyl, hydroxymethylene, certain aryl and NH-groups indicates its existence in the form of *Z*- and *E*-isomers. The downfield signal of NH-proton of isatin fragment (13.71 ppm) belongs to *Z*-isomer with a strong intramolecular hydrogen bonding [10] (Scheme 5).

As can be seen from the table, sterically hindered phenolic isatin acylhydrazones **I**–**IV** show high antioxidant activity.

Isatin **V** and acylhydrazone **VII** exhibit low antioxidant activity. This fact indicates that the NH protons of the five-membered isatin ring and hydrazone fragment make a small contribution to the antioxidant effect of the test compounds. It should be noted that, according to [16], antioxidant activity of hydroxybenzaldehydes hydrazones is due to the presence of NH-group of hydrazone moiety.

The introduction of sterically hindered phenol moiety into the molecule of isatin derivatives **I**–**IV** leads to an increase in the antioxidant activity. Moreover, the presence of sterically hindered phenol moiety in the position 3 of isatin fragment [acylhydrazones **I**, **II**] provides higher antiradical activity than the exchange of NH-proton of isatin five-membered ring by analogous moiety [acylhydrazone **III**, **IV**].

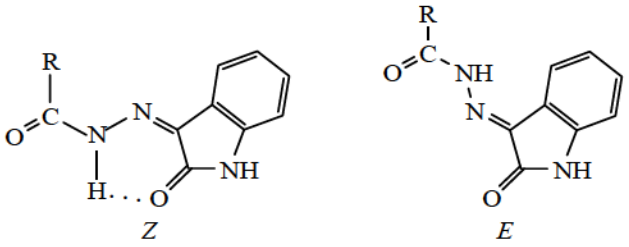
In summary, the studied sterically hindered phenolic isatin acylhydrazones **I**–**IV** are promising antioxidants whose rate constants of the reaction with DPPH are superior to heterocyclic antioxidant Agidol 70. Acylhydrazone **II** showed the highest antiradical activity among the studied compounds; its activity is comparable with highly active antioxidant Irganox 1010.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker AVANCE-600 spectrometer (600.13 MHz), the residual proton signals of the deuterated solvents serving as internal reference. Elemental analysis was performed on a Perkin Elmer PE 2400 CHNS/O-analyzer (Series 2).

The kinetics of interaction of test compounds with DPPH was studied using a PE-5300V spectrophotometer by measuring the variation of DPPH absorbance in time at 520 nm. Initial concentrations of DPPH were 0.75×10^{-4} mol/L, the concentration of the test compounds was 1.5×10^{-3} mol/L. A solution of the test compounds in 1,4-dioxane with concentration of 1.5×10^{-3} mol/L was used as a reference. It was shown in a control experiment that the concentration of a solution of DPPH in 1,4-dioxane remains unchanged under irradiating at λ 520 nm for 1 h.

Scheme 5.



Rate constants of the reaction of isatin acylhydrazones with DPPH

Compound	$k\times10^2$, mol L^{-1} s^{-1}
I	6.25±0.265
II	11.15±0.310
III	2.91±0.095
IV	3.37±0.088
V	0.23±0.044
VII	1.07±0.145
Agidol 70	2.03±0.098
Irganox 1010	12.51±0.436

Compounds **I**–**IV** were synthesized according to procedures [10, 11]. 2,2-Diphenyl-1-picrylhydrazyl (Sigma-Aldrich Chemie, Germany) as well as Irganox 1010 and 70 Agidol were used without further purification. 1,4-Dioxane was dried as described in [17].

2-(4-*tert*-Butylphenoxy)-*N*'-2-oxo-2,3-dihydro-1*H*-indol-3-ylidene)acetohydrazide (VII). A mixture of 1.47 g (0.01 mol) of isatin **V**, 2.22 g (0.01 mol) of 2-(4-*tert*-butylphenoxy)acetohydrazide **VI**, and 75 mL of ethanol was refluxed for 4 h. After cooling the formed precipitate was filtered off, washed with ethanol, and dried in air. Yield 2.98 g (85%), yellow crystals ($Z : E = 3 : 2$). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.26 s and 2.27 s (9H, Bu-*t*), 4.83 br.s and 5.08 br.s (2H, CH_2O), 6.84–7.02 m (3H, H^1, H^5), 7.05 t and 7.11 t (1H, H^3, ^3J 7.5 Hz), 7.27–7.37 m (2H, H^6), 7.40 t (1H, H^2, ^3J 7.5 Hz), 7.58 d and 8.03 br.s (1H, H^4, ^3J 7.5 Hz), 10.82 s and 13.71 s [1H, HNC(O)], 11.25 s and 11.31 br.s (1H, NH). Found, %: C 68.71; H 5.59; N 11.72. $C_{20}H_{21}N_3O_3$. Calculated, %: C 68.38; H 5.98; N 11.97.

ACKNOWLEDGMENTS

This work was financially supported by the Ministry of Education and Science of the Russian

Federation in the frame of the basic part of the governmental contract for 2014–2016.

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