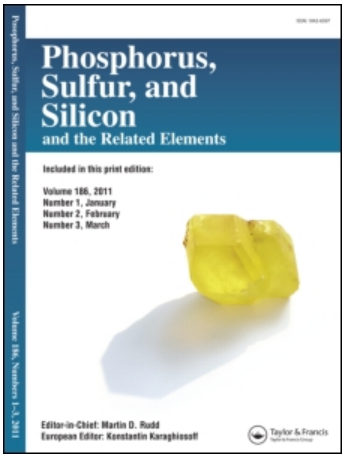

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Edmunds Lukevics[a]; Nikolai Erchak[a]; Larisa Demicheva[a]; Skaidrite Germane[a]
[a] Latvian Institute of Organic Synthesis, Riga, LATVIA

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SYNTHESIS AND NEUROTROPIC ACTIVITY OF 5-SUBSTITUTED FURFURAL THIOSEMICARBAZONES

EDMUNDS LUKEVICS, NIKOLAI ERCHAK, LARISA DEMICHEVA, SKAIDRITE GERMANE
Latvian Institute of Organic Synthesis, 21 Aizkraukles str., LV-1006, Riga, LATVIA

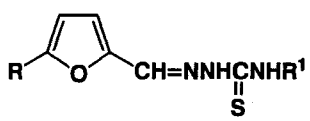
Abstract 5-Substituted-2-furaldehyde thiosemicarbazones were prepared from furfurals and thiosemicarbazide using the condensation method. The neurotropic activity of the synthesized thiosemicarbazones has been evaluated. The majority of the compounds examined has been shown to possess high or medium neurotropic activity of the depressant type. Structure-activity relationships of the titled compounds have been studied as well.

INTRODUCTION

The current paper is a continuation of the systematic study dealing with the purposeful search for biologically active substances. Cheap and available organic and elementoorganic derivatives of furfural have been chosen for our investigations. Thiosemicarbazone function appears a decisive factor for the neurotropic activity in the studied compounds.

EXPERIMENTAL

Thiosemicarbazones **1-12** were obtained usually from thiosemicarbazides and the corresponding aldehydes:



R = MeS (**1**), BuS (**2**), Me_3C (**3**), Me_3Si (**4**), $(EtO)_2CH$ (**5**), $(EtO)_2CHCH_2CH_2SiMe_2$ (**6**), $Me_3CCH_2CH_2SiMe_2$ (**7**), $NC(CH_2)_3SiMe_2$ (**8**), $ClCH_2SiMe_2$ (**9**), $Cl_2CHSiMe_2$ (**10**), HMe_2Si (**11**), R^1 = H.
R = Me_3Si, $R^1 = C_6H_5$ (**12**)

RESULTS AND DISCUSSION

The studied compounds (except for **3**, LD_{50} = 20.5 mg kg^{-1}) exhibit the moderate toxicity (~200 - 2000 mg kg^{-1}). The growth of steric hindrance and decrease of availability of elementoorganic substituent in the sulfide derivatives (compounds **1,2**) and the silyl derivatives (compounds **4,7**) lead to the increase of toxicity. The definite growth of toxicity in compounds **9,11** if compared with the trimethylsilyl derivative **4** is observed. This fact is in agreement with the character of electron effects in furylsilanes and with their possible influence on "availability" of element. Compounds **3** and **4** being the closest by structure demonstrate the largest differences in toxicity. 5-Trimethylsilylfurfural thiosemicarbazone (**4**) - the silyl analogue, is 80 times less toxic than 5-tert-butylfurfural thiosemicarbazone (**3**). The value of the neurotropic activity for these compounds differs as well. Thus, the therapeutic activity in "rotating rod", "tube", "hypothermia" tests for compound **3** is revealed in the doses close to the lethal, for compound **4** the value of the therapeutic index ($I = LD_{50}/ED_{50}$) being 2362, 2295, 3260, respectively.

The phenyl group introduced into thiosemicarbazone fragment of a molecule influences weaker on the toxicity of a compound (LD_{50} for compounds **4** and **12** of the same order). However, compound **12** is less active than compound **4**. The psychotropic activity of the compound reveals at the considerably high doses.

In general, all examined compounds, to a certain degree, possess the psychotropic activity of depriming type. It has been found that the decrease of toxicity in compounds is usually accompanied by the drop in activity (*cf* sulfide derivatives **1,2**), while among the silyl derivatives we can manage to find the highly effective compound **4c** with low toxicity.

The hypothermic action of the thiosemicarbazones studied is pronounced approximately at the same doses as their action on locomotor activity.

The examined thiosemicarbazones (except for tert-butyl- and chloromethylfuryl derivatives) at the doses of 50 mg kg^{-1} have been found to possess antihypoxic activity. Compounds **11** and **12** (25 and 40%, respectively) prolong minimally the life-span of animals. Compound **7** appears the most effective in this respect: it increases the life-span of animals by 2 times. The other compounds have moderate activity. Almost all examined compounds in the dose of 50 mg kg^{-1}, and compound **9** in the dose of 5 mg kg^{-1}, strengthen hexenal anaesthesia. Compound **7** induces the higher increase of the hexenal anaesthesia ~126%. Thiosemicarbazones **4,5,9** in the dose of 5 mg kg^{-1} do not change reliably the duration of ethanol anaesthesia. The other compounds prolong the ethanol anaesthesia by 27-125%. It has been found that the studied substances antagonize the pharmacological effects of phenamine. The methylsulfide derivative **1** being the most active decreases the central stimulating phenamine activity by 60%. It has been shown that compound **7** possesses the expressed influence on memory and training processes, improving them considerably. Compounds **7,9** prevent retrogradal amnesia, decreasing it by 60%. The other compounds lack any pronounced activity on memory processes.

The studied thiosemicarbazones (except for compounds **2,3**) reveal the marked antagonistic activity towards corazole convulsions, increasing the corazole dose needed for tonic and clonic convulsions followed by death by ~50-180%.