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LETTERS TO THE EDITOR

Synthesis and Structure of New Derivatives of Salicylic Acid Hydrazide

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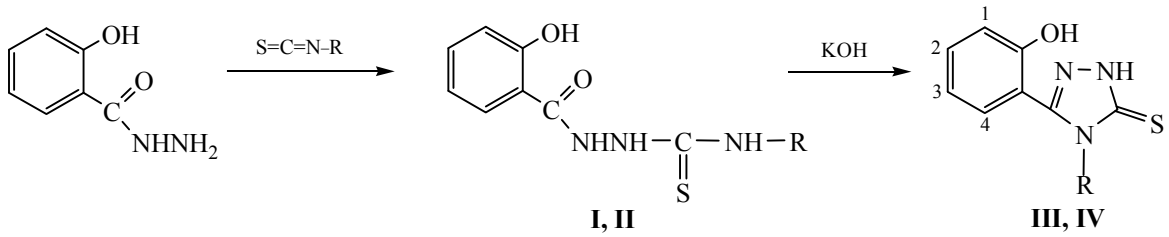
Since over 200 years salicylates have been used in medicine as analgesic, antipyretic and antiphlogistic drugs [1, 2]. Derivatives like acetylsalicylic acid (aspirin), sodium salicylate, salicylamide, methyl Salicylate are used as analgesic, antipyretic and anti-aggregation agents [4]. Some thiosemicarbazide derivatives of heterocyclic and aromatic carboxylic acids show high tuberculocidal activity [5, 6]. The modification of the structure of hydrazides and thiosemicarbazides of salicylic acid permits the preparation of new derivatives of thiazole and triazole series and the extention of the area of salicylates application.

In order to study new bioactive compounds we carried out certain convenient preparative chemical transformations of salicylic acid hydrazide resulting in 4-alkyl-5-(2-hydroxyphenyl)-1,2,4-triazole-3-thiones **III** and **IV** (Scheme 1).

The cyclization of thiosemicarbazides of salicylic acid **I** and **II** into compounds **III** and **IV** was performed at reflux for 2–3 h in aqueous potassium hydroxide solution followed by acidification with acetic acid. This method provided combinatorial libraries of compounds of type of **V** and **VI** for screening their biological activity. For example, alkylation of triazole **IV** with benzyl chloride and monochloroacetic acid in water solution in the presence of potassium hydroxide afforded 5-*S*-substituted triazoles **V** and **VI** (Scheme 2).

4-Ethyl-2-(2-hydroxybenzoyl)thiosemicarbazide (I). To a solution of 1.52 g (0.01 mol) of *o*-hydroxybenzoic acid hydrazide in 20 mL of ethanol was added dropwise 0.95 g (0.011 mol) of ethyl isothiocyanate. The reaction mixture was stirred at 50–60°C for 10 h. The reaction progress was monitored by TLC. After the reaction completed, the mixture was cooled. The formed precipitate was filtered off, washed with a small amount of cold ethanol, and recrystallized from 2-propanol. Yield 2.22 g (93%), mp 227–228°C. IR spectrum, ν, cm^{-1}: 1668 (C=O). ^1H

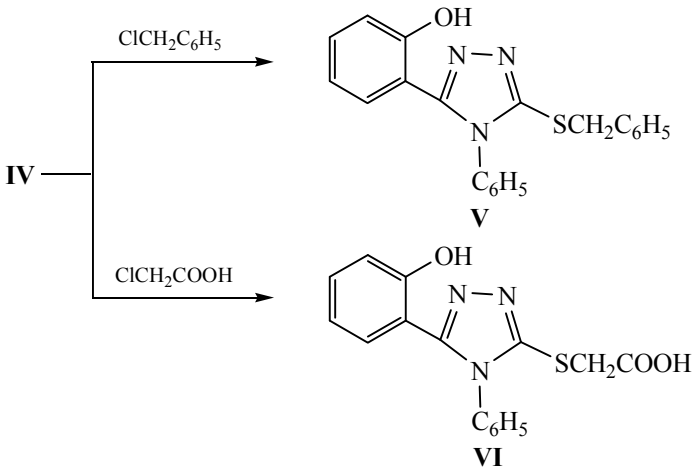
Scheme 1.



I, II **III, IV**

R = Et (**I, III**), Ph (**II, IV**).

Scheme 2.



NMR spectrum, δ, ppm (*J*, Hz): 1.02 t (3H, CH_3, *J* 7.1), 3.44 q (2H, CH_2, *J* 6.4), 6.26 d (1H, CH^1_{Ar}, *J* 8.1), 6.65 t (1H, CH^2_{Ar}, *J* 7.4), 6.48 t (1H, CH^3_{Ar}, *J* 7.5), 6.80 d (1H, CH^4_{Ar}, *J* 8.1), 8.10 s [1H, C(O)NH], 7.32 s [1H, C(S)NH], 10.02 s [1H, NHNHC(S)]. Found, %: C 50.53; H 5.74; N 17.37. $C_{10}H_{13}N_3O_2S$. Calculated, %: C 50.19; H 5.48; N 17.56.

4-Phenyl-2-(2-hydroxybenzoyl)thiosemicarbazide (II) was prepared similarly. Yield 88.8%, mp 190–191°C. IR spectrum, ν, cm^{-1}: 1670 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.23 d (1H, CH^1_{Ar}, *J* 7.5), 6.62 t (1H, CH^2_{Ar}, *J* 8.4), 6.45 t (1H, CH^3_{Ar}, *J* 8.5), 6.77 d (1H, CH^4_{Ar}, *J* 7.3), 6.72–6.80 m (5H, C_6H_5), 9.15 s [1H, C(O)NH], 7.21 s [1H, C(S)NH], 11.18 s [1H, NHNHC(S)]. Found, %: C 58.85; H 4.86; N 14.94. $C_{14}H_{13}N_3O_2S$. Calculated, %: C 58.52; H 4.56; N 14.62.

4-Ethyl-5-(2-hydroxyphenyl)-1,2,4-triazole-3-thione (III). A mixture of 2.39 g (0.01 mol) of 4-ethyl-2-(2-hydroxybenzoyl)thiosemicarbazide **I**, 0.40 g (0.01 mol) of KOH, and 30 mL of water was heated at 85°C for 2 h. After cooling the mixture was neutralized with acetic acid to pH 7. The precipitated was filtered off and recrystallized from 2-propanol. Yield 1.72 g (78%), mp 244–245°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.05 t (3H, CH_3, J_{HH} 7.1), 3.85 q (2H, CH_2, J_{HH} 7.2), 7.02 d (1H, CH^1_{Ar}, *J* 8.0), 6.95 t (1H, CH^2_{Ar}, *J* 7.4), 7.42 t (1H, CH^3_{Ar}, *J* 8.3), 7.32 d (1H, CH^4_{Ar}, *J* 7.5), 10.32 s (1H, NH), 13.80 s (1H, OH). Found, %: C 54.49; H 5.24; N 19.21. $C_{10}H_{11}N_3OS$. Calculated, %: C 54.28; H 5.01; N 18.99.

4-Phenyl-5-(2-hydroxyphenyl)-1,2,4-triazole-3-thione (IV) was prepared similarly. Yield 77%, mp 277–279°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.01 d (1H, CH^1_{Ar}, *J* 8.0), 6.09 t (1H, CH^2_{Ar}, *J* 7.3), 6.51 t (1H, CH^3_{Ar}, *J* 8.1), 6.58 d (1H, CH^4_{Ar}, *J* 7.1), 6.60–6.72 m (5H, C_6H_5), 9.18 s (1H, NH). Found, %: C 62.73; H 4.39; N 15.91. $C_{14}H_{11}N_3OS$. Calculated, %: C 62.44; H 4.12; N 15.60.

4-(5-(Benzylthio)-4-phenyl-4*H*-1,2,4-triazol-3-yl)-phenol (V). To a mixture of 0.17 g (0.003 mol) of KOH in 15 mL of ethanol and 0.95 (0.003 mol) of triazole **IV** was added 0.38 mL (0.003 mol) of benzyl chloride. Then the mixture was heated for 1 h, cooled, distilled with water and left standing overnight. The formed precipitate was filtered off and recrystallized from 2-propanol. Yield 1.17 g (93%), mp 174–175°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.41 s (2H, CH_2), 6.74 d (1H, CH^1_{Ar}, *J* 7.5), 7.22 t (1H, CH^2_{Ar}, *J* 7.8), 6.78 t (1H, CH^3_{Ar}, *J* 8.3), 7.15 d (1H, CH^4_{Ar}, *J* 7.6), 7.22–7.45 m (5H, C_6H_5), 10.19 s (1H, OH). Found, %: C 70.43; H 4.89; N 11.88. $C_{21}H_{17}N_3OS$. Calculated, %: C 70.17; H 4.77; N 11.69.

2-[(5-(4-Hydroxyphenyl)-4-phenyl-4*H*-1,2,4-triazol-3-yl]thioacetic acid (VI). A mixture of 0.5 g (0.009 mol) of KOH in 20 mL of water, 0.95 g (0.003 mol) of triazole **IV,** and 0.28 g (0.003 mol) of monochloroacetic acid was refluxed for 6 h and kept overnight. The formed precipitate was filtered off, washed with water, and recrystallized from 2-propanol. Yield 0.95 g (97%), mp 215–216°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.07 s (2H, CH_2), 6.78 d (1H, CH^1_{Ar}, *J* 7.4), 7.24 t (1H, CH^2_{Ar}, *J* 8.0), 6.80 t (1H, CH^3_{Ar}, *J* 8.2), 7.17 d (1H, CH^4_{Ar}, *J* 7.6), 7.35 m (5H, C_6H_5), 10.16 br.s (1H, OH), 12.95 br.s (1H, OH). Found, %: C 59.05; H 4.18; N 18.96. $C_{16}H_{13}N_3O_3S$. Calculated, %: C 58.70; H 4.00; N 12.84.

IR spectra were recorded on a Nicolet AVATAR-320 spectrometer from KBr pellets. ^{1}H NMR spectra of the solutions in DMSO-d_6 were registered on a Bruker DRX500 (500 MHz) and Bruker 400 (400 MHz) spectrometers, internal reference TMS. Melting points were determined on a Boetius heating block. TLC analysis was performed on Sorbfil plates eluting with 2-propanol–benzene–ammonia (10 : 5 : 2) mixture and detecting with iodine vapor.

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