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SYNTHESIS AND TUBERCULOSTATIC ACTIVITY OF DERIVATIVES OF 1,2,4-TRIAZOL-3-THIONE

B. V. Trzhtsinskaya, A. E. Aleksandrova, E. V. Apakina, T. I. Vinogradova, R. A. Shchegoleva, and A. V. Afonin

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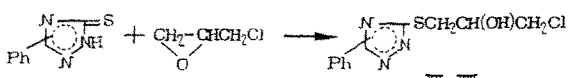
The biological activity of derivatives of 1,2,4-triazol-3-thiones (I) depends on both the nature of the substituent on the 1,2,4-triazole group and the structure of the radical attached to the exocyclic sulfur atom [1]. In an attempt to synthesize an effective tuberculostat, we prepared a series of derivatives of triazolthione I [8, 11]. The hydrazides of 5-(2-furyl)-1,2,4-triazol-3-thiocarboxylic acids are compounds possessing appreciable activity against Mycobacterium tuberculosis [11].

In a continuing systematic study of the synthesis and biological activity of derivatives of triazole I [3, 4] we studied the reaction of triazoles I, 5-methyl (II)- and 5-phenyl (III)-1,2,4-triazol-3-thione with 1-chloro-2,3-epoxypropane (CEP) [6]. It was shown that in the presence of organic bases the reaction proceeds through the cleavage of the epoxide ring and the formation of 3-(1-chloro-2-hydroxypropylthio)-5-R-1,2,4-triazoles [R = H(IV), Me(V), Ph(VI)]. The use of potassium hydroxide as catalyst leads in the resulting reaction to the corresponding 3-hydroxy-7-R-1,2,4-triazolo[2,3-b]tetrahydro-1,3-thiazines [R = Me(VII), and Ph(VIII)].

In the present work we studied the behavior of 1-phenyl(IX)-, 4-phenyl(X)- and 5-(2-furyl) (XI)-1,2,4-triazol-3-thione in this reaction.

We studied the influence of the change of the position of the phenyl substituent on the triazolethione ring. Introduction of a phenyl substituent into position 1 or 4 of the heteroring excludes the possibility of formation of diadducts and the products of heterocyclization. We have isolated the corresponding 1-phenyl(XII)- and 4-phenyl(XIII)-3(1-chloro-2-hydroxypropylthio)-1,2,4-triazole. The reaction is easily accomplished in alcohol solution at room temperature and does not require catalytic initiation.



IX, X XII, XIII

A more complex reaction takes place with the furyl-substituted triazole XI. The furyl substituent apparently activates the reaction centers on the N and S atoms to the same degree.

Institute of Organic Chemistry, Siberian Branch, Academy of Sciences of the USSR, Irkutsk; Scientific-Research Institute of Physiopulmonology, Russian Soviet Federated Republic, Leningrad. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 25, No. 3, pp. 25-27, March, 1991. Original article submitted January 16, 1990.

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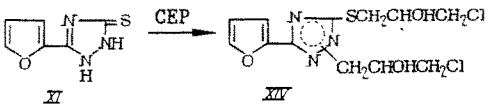
The resulting product involves the addition of 2 molecules of CEP to give 5-(2-furyl)-N-(1-chloro-2-hydroxypropyl)-3-(1-chloro-2-hydroxypropylthio)-1,2,4-triazole (XIV) as a viscous oil present, according to ^{1}H NMR data, as a mixture of isomers, involving the position of the chlorohydroxypropyl substituent on the two different N atoms.

Varying the solvents (dioxane, alcohol, acetonitrile), the catalysts (triethylamine, KOH), the temperature conditions, and the ratio of reagents did not lead to the monoadduct as the only product; on account of this we were not successful, as in [6], in obtaining the product of intramolecular heterocyclization.



XI XIV

The IR spectra of compounds XII-XIV did not show absorption bands for "thioamide I" characteristic of the starting triazolthiones IX–XI (1550, 1551, and 1530 cm^{-1}); intense absorptions at 1270 cm^{-1} appeared, indicating the vibration of the triazole ring as a result of the conversion of the primary thiocarbonyl group into the sulfide. Absorptions in the 3100–3400 cm^{-1} region are related to the valence oscillations of the hydroxyl groups.

The ^{1}H NMR spectra of compounds XII and XIII show signals for the SCH_2-groups at 3.44 and 3.35 ppm, the CH_2Cl group at 3.71 and 3.61 ppm, and the CH-groups at 4.12 and 4.07 ppm, respectively. Signals from the protons of the aromatic rings and the ring in molecule XII occur at 7.51 to 7.78 and 8.99 ppm; these same protons in molecule XIII resonated at 7.54 and 8.69 ppm, respectively. The ^{1}H NMR spectrum of the furyltriazole XIV shows signals of the furyl ring at 7.60, 6.90, and 6.55 ppm, the NCH_2 group at 4.29 ppm, the two CH-groups 4.10 and 4.15 ppm, the two CH_2Cl groups at 3.50-3.60 ppm, and the SCH_2-group at 3.40 ppm.

EXPERIMENTAL (CHEMICAL)

IR spectra were recorded on a Specord 75-IR instrument as thin films and as KBr pellets, and ^{1}H NMR spectra were obtained with a Tesla BS-497 (100 MHz) instrument at 20°C in $CDCl_3$ with TMS as internal standard. Elemental analysis data corresponded with the calculated values.

1-Phenyl-3-(1-chloro-2-hydroxypropylthio)-1,2,4-triazole (XII). A mixture of 1.8 g (0.01 mole) of triazole IX and 0.8 g (0.01 mole) of CEP in 25 ml of ethyl alcohol was stirred for 5 h at 20°C. A precipitate of 0.3 g of nonreacted IX was filtered off, and the solvent was distilled from the filtrate. The residue, a viscous oil, was dissolved in ether, which was concentrated to give a precipitate of XII, 1.6 g (59%), mp 80-81°C. $C_{11}H_{10}ClN_3OS$.

4-Phenyl-3-(1-chloro-2-hydroxypropylthio)-1,2,4-triazole (XIII) was prepared analogously to XII to give a viscous product in 100% yield, n_D^{20} 1.5868. $C_{11}H_{10}ClN_3OS$.

5-(2-Furyl)-N-(1-chloro-2-hydroxypropyl)-3-(1-chloro-2-hydroxypropylthio)-1,2,4-triazole (XIV) was prepared analogously to XII (stirred for 28 h) in 93% yield, n_D^{20} 1.5630. $C_{12}H_{15}Cl_2N_3O_2S$.

EXPERIMENTAL (BIOLOGICAL)

With the goal of studying the relationship between structure and tuberculostatic activity, the triazoles, together with the reaction products of triazoles I-III and IX-XI with CEP, and our earlier-synthesized 3-vinylthio(XV)-, 3-vinylthio-5-methyl (XVI)-, 3-vinylthio-5-phenyl (XVII)-1,2,4-triazole, and 4-vinyl-1,2,4-triazol-3-one (XVIII) [2, 3, 5, 7] were investigated. The inhibition by triazolthione II of the growth of Mycobacterium tuberculosis also was studied.

Tuberculostatic activity was studied in vitro by the two-fold dilution method in Coton liquid synthetic medium in our own modification [9] with 10% normal horse serum. As test organisms three strains of Mycobacterium tuberculosis were used: Strain H37Rv, sensitive to anti-tuberculosis preparations; Strain 25060, stable to 1 μg/ml isoniazide and to 50 μg/ml of PASC (p-aminosalicylic acid), and Strain 3714, stable to 50 μg/ml of isoniazide and 250 μg/ml of streptomycin. The density of the mycobacterial suspension was 50 million microbial cells per ml. The acute toxicity was determined on white nonhybrid mice weighing 23-25 g. The LD_{50} was calculated according to the method of [10].

TABLE 1. Tuberculostatic Activity of the Compounds

Compound	Minimal inhibitory concentration, μg/ml			LD_{50}, mg/kg
	strain $H37R_v$	strain 3714	strain 25060	
II	25	...	50	316
IV	>50	...	>50	2000
V	>50	...	...	2000
VI	>50	...	...	750
VII	>50	...	...	1000
VIII	>50	...	...	...
XII	50 (p) — 100	...	...	...
XIII	100 (p)	...	...	...
XIV	100 (p)	...	...	...
XV	>50	...	...	689
XVI	25	...	>50	292
XVII	12,5	25—50	...	450
XVIII	50	...	...	600

Notes. (p) = partial depression of the growth of Mycobacterium tuberculosis.
... — Not studied.

The results of the study of the biological activity of the test compounds are given in Table 1.

For all of the studied compounds, the highest inhibitory activity against the growth of Mycobacterium tuberculosis was shown by the vinyl derivatives XVI, XVII, and the 5-methyltriazolethione II. The relationship between structure and biological activity is clearly expressed in the vinyl derivatives of 1,2,4-triazole. Thus, the influence of the phenyl substituent in position 5 of the triazole ring of XVII leads to a two-fold strengthening of the tuberculostatic activity and a decrease on the acute toxicity by 1.5 times compared to compound XVI.

Thus, the result of this study is the discovery of compound XVII possessing moderate tuberculostatic activity and low toxicity. Systematic study in a search for potential antitubercular materials among structures analogous to that of compound XVII may expand these prospects.

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