Chemistry

B. G. Boldyrev, T. S. Ginzburg, and R. O. Drabkina

1957

SovietRxiv

Abstract

Full Text

Chemistry

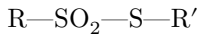
B. G. Boldyrev, T. S. Ginzburg, and R. O. Drabkina

On the Antitubercular Activity of Esters of Thiosulfonic Acids

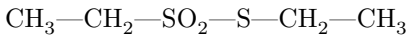
(Presented by Academician I. N. Nazarov on 12 III 1957)

The antitubercular activity of esters I of thiosulfonic acids has until now remained entirely unstudied; it is known only ([1]) that ethyl ester II of ethanethiosulfonic acid has a bacteriostatic effect on *Mycobacterium tuberculosis*, its activity being equivalent to that of analogue III of the natural antibiotic—allicin.

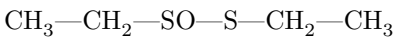
Taking into account that the structure of compounds IV has a marked effect on their antitubercular properties ([2]), we hoped, among esters I of thiosulfonic acids, to find substances with high antitubercular activity.



I



II



III

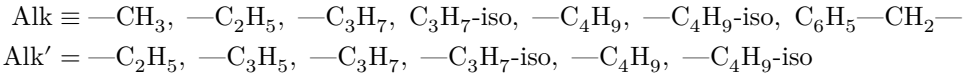
IV

Alkyl esters of alkanethiosulfonic acids

The closest in structure to allicin analogues are the alkyl esters V of alkanethiosulfonic acids, synthesized earlier by one of us with co-workers ([3–6]).

V

where



These compounds possess a broad spectrum of antibacterial action* and in *in vitro* experiments exert a bacteriostatic effect on gram-positive, gram-negative, and acid-fast bacteria, on various fungi, protozoa, etc.

In vitro experiments. The study of the antitubercular activity of esters V, carried out by T. S. Ginzburg and R. O. Drabkina, was conducted on a 10–12-day film of virulent strain no. 32 of human-type tuberculous mycobacteria, which was inoculated onto the surface of the Proskauer and Beck nutrient medium containing different concentrations of the substances under investigation. Similar experiments were carried out in the presence of 10% horse serum.

The results of the experiments were recorded at the moment when good growth of TB appeared in the control test tubes that did not contain the preparation. Bacteriostatic–

* The antibacterial properties of esters V and VI were studied by V. G. Drobotko, B. E. Aizenman, and S. I. Zelepukha at the Institute of Microbiology of the Academy of Sciences of the Ukrainian SSR.

activity was determined by the smallest amount of the substance being tested that completely inhibited the growth of TB.

All the esters tested exhibited tuberculostatic action, with the minimal inhibitory concentration for most preparations ranging within 1.0–2.0 mg%. The activity of esters V varies within narrow limits and depends little on their structure. Only certain alkyl esters of 2-methylpropanethiosulfonic acid-1 and of butanethiosulfonic acid show greater activity against TB, reaching 0.01 mg% (1 : 10 million).

Many esters of alkanethiosulfonic acids are inactivated by serum by a factor of 2–10, and some by factors of 100 and 1000. However, all esters of methanethiosulfonic acid and of propanethiosulfonic acid-2 completely retain their activity in the presence of serum, in contrast to the alkyl esters V of the other alkanethiosulfonic acids.

Experiments in vivo. The preparations most active *in vitro* were tested on animals (white mice) to determine their toxicity. The preparations were administered either subcutaneously or orally once daily. The maximum tolerated dose for most of the preparations tested (with subcutaneous administration over 4–5 days) corresponded to 1 mg. The most toxic preparations–the ethyl ester of methanethiosulfonic acid and the butyl ester of butanethiosulfonic acid–caused the death of mice already at a dose of 0.1–0.5 mg.

The least toxic substances were studied in experimental tuberculosis in order to determine their therapeutic action. For this purpose, white mice were given intravenously a culture of the same TB strain at a dose of 0.1 mg. This dose caused death of the animals from tuberculosis 3–4 weeks after infection. Treatment was begun on the day after infection and continued until the death of the control mice–infected but untreated.

All the esters tested, even those with maximum activity *in vitro*, proved ineffective in the treatment of experimental tuberculosis.

In some cases this may be explained by their ability to be sharply inactivated in the animal organism; in other cases, by their increased toxicity, which did not permit their use in *in vivo* experiments at large doses.

Alkyl esters of benzenethiosulfonic acid and its derivatives

Alkyl esters VI of benzenethiosulfonic acid and its derivatives ([6]) exert bacteriostatic and bactericidal action on the same bacterial species as the esters of alkanethiosulfonic acids; however, their activity is, as a rule, lower than that of compounds V.

$$X—C_6H_4—SO_2—S—Alk$$

where X = H—, —*n*-Cl—, *n*-CH_3O—, *n*-NO_2—, *n*-CH_3CONH—, *n*-NH_2—, *m*-NO_2—

Alk = —C_2H_5, —C_3H_5, —C_3H_7, —C_3H_7-iso, —C_4H_9, —C_4H_9-iso

Experiments in vitro. The study of the antituberculous activity of esters VI was carried out by the method described above. It was found that they possess weaker tuberculostatic activity than the alkyl esters V of alkanethiosulfonic acids: a considerable portion of them show action at a concentration of 10 mg% (dilution 1 : 10 thousand), and some only at a concentration of 20 mg%. Only individual preparations proved more active, but their action is sharply weakened by the presence of serum.

The introduction of substituents into the *n*-positions of the alkyl esters of benzenethiosulfonic acid changes the activity of the latter little: chlorine and the methoxy group slightly increase their activity, the nitro group has no noticeable effect, while the acetylamino group somewhat decreases it; deacylation of the alkyl esters

acetylthiosulfanilic acid has a favorable effect, increasing the activity of these compounds.

The mutual arrangement of substituents in the benzene nucleus is evidently not specific for esters of thiosulfo acids from the standpoint of their antitubercular properties: esters of *m*-nitrobenzenethiosulfo acid even surpass analogous compounds of the *p*-series in their activity.

As in the case of esters V, alkyl esters of benzenethiosulfo acid and its derivatives are in a number of cases inactivated by serum; however, no regular relationship between their structure and inactivation is observed.

Experiments in vivo. Three alkyl esters VI, which possessed *in vitro* activity at a concentration of 1 mg% and were not inactivated by serum, were tested for toxicity and in the treatment of experimental tuberculosis in white mice.

The maximum tolerated dose of these preparations was 5 mg. In treating the mice, a daily dose equal to 1 mg was used.

It was found that the tested preparations do not exhibit therapeutic action in the animal organism.

Thus, alkyl esters of alkanethiosulfo acids, as well as of benzenethiosulfo acid and its derivatives, possess tuberculostatic activity only *in vitro*, but do not influence the course of tuberculous infection in infected animals.

The possibility of using esters of thiosulfo acids for the treatment of external forms of tuberculosis is subject to further study.

Lviv Polytechnic Institute and
Ukrainian Scientific-Research
Institute of Tuberculosis

Received
25 II 1957

CITED LITERATURE

[1] L. Verne, D. Small, J. H. Bailey, C. J. Covallito, J. Am. Chem. Soc., **71**, 3565 (1949).
[2] L. Verne, D. Small, J. H. Bailey, C. J. Covallito, J. Am. Chem. Soc., **69**, 710 (1947).
[3] B. G. Boldyrev, A. K. Zacharchuk, DAN, **94**, 877 (1954).
[4] B. G. Boldyrev, A. K. Litkovets, DAN, **107**, 697 (1956).
[5] B. G. Boldyrev, A. K. Litkovets, T. A. Trofimova, ZhOKh, **26**, 3360 (1956).
[6] B. G. Boldyrev, Scientific Notes of the Lviv Polytechnic Institute, Chemical Technology Series, No. 2, 71 (1956).

Note: Figure translations are in progress. See original paper for figures.