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Studies of Thioacids and Their Derivatives

I. General Programme of the Investigation

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As an introduction to ten papers on thioacids and their derivatives a short review has been given of the approach to the problem and the main results.

Until 1944 only rather special types of thiohydrazides were known. Thiosemicarbazides have, of course, been known for a long time, and ethylxanthogenhydrazide, $C_2H_5OCSNHNH_2$, was prepared, in 1934, by Jensen [1], who also tried without success to prepare thioacethydrazide. Further some phenylhydrazides of thioacids have been prepared by Wuyts [2], who also mentions, that he had obtained a small amount of *p*-methylthiobenzhydrazide [3]. However, the first example of the more general type of thiohydrazides to be studied in detail was thiobenzhydrazide, prepared in 1943 by Holmberg [4], who carried out an extensive investigation on this compound and its derivatives [5].

In 1952 Jensen and Miquel [6] found that thiobenzhydrazide forms chelate nickel complexes of the same type as are formed by thiosemicarbazides [7] and on the basis of this observation and the hypothesis that antibacterial effects of organic compounds are often in some way connected with an ability to form chelates [8], Jensen and Jensen [9] prepared several new thiohydrazides and observed that these compounds in general possess a rather pronounced tuberculostatic and fungistatic effect. As these compounds show some similarity to two well-known tuberculostatic agents, *p*-acetamidobenzaldehyde-thiosemicarbazone (TBl) and *iso*nicotinic hydrazide(INH), it was hoped to find still more active compounds belonging to this class. A large number of thiohydrazones were prepared, and several experiments were carried out to obtain heterocyclic thiohydrazides. The thiohydrazones are rather similar to *p*-acetamidobenzaldehyde-thiosemicarbazone, but most of these compounds were very slightly soluble in water and showed no tuberculostatic activity *in vitro*. The activity of some of these compounds, especially *p*-acetamidobenzaldehyde-2-furanthiocarbohydrazone, was also tested in animal experiments, but they showed only slight activity. In our experiments the preparation of hetero-

cyclic thiohydrazides met with unusual difficulties, and in the meantime *iso*-nicotinic thiohydrazide was prepared by König *et al.*[10], but it turned out to be less active than *iso*nicotinic hydrazide against tubercle bacilli.

Thus the attempts to find new chemoterapeutics of practical importance within this class of compounds had not been too promising. On the other hand their more or less pronounced bacteriostatic effect is almost certainly connected with their ability to combine with metal ions, and we decided to investigate this property from a more fundamental point of view. The influence of thiohydrazides on the growth rate of *Aerobacter aerogenes* in the presence of various metal ions was investigated, and it was shown that certain metal ions, especially the zinc ion, show a very pronounced synergistic effect on the bacteriostatic effect of the thiohydrazides. It was also found that *NN*-dimethylthiohydrazides of certain acids, especially salicylic acid and its derivatives, had a much stronger effect than the unsubstituted thiohydrazides, and this was found also to be the case with their effect on tubercle bacilli *in vitro*. This led us to prepare a series of N-substituted thiohydrazides of salicylic acid and of *o*-alkoxysubstituted benzoic acids. At the same time the successful introduction of certain thioamides and thioureas, which are active against INH-resistent tubercle bacilli, in the therapy of tuberculosis [11] led us to some extent to consider not only thiohydrazides but also thioamides. Certain of the compounds prepared showed *in vitro* an effect which was at least as great as the effect of INH, but unfortunately their effect in animal experiments was negligible, probably because of rapid transformation of the compounds *in vivo*.

In parallel with the investigation of the antibacterial effect of the compounds prepared their complex-forming ability has been investigated. Our interest in co-ordination compounds also led us to prepare a large number of new thiosemicarbazides, although the antibacterial effect of this class of compounds was found to be much less pronounced than that of the regular thiohydrazides (with a carbon radical attached directly to the $-CSNHNH_2$ group).

Our interest in the thiohydrazides and thioamides has not only been dictated by their potential effect as antitubercular substances and their ability to form co-ordination compounds. Also from a purely organic chemical point of view these compounds are most interesting, and at the beginning of our investigation very little was known of the chemical properties of thiohydrazides. Although the chemical reactions of thiobenzhydrazide and of dithiocarbohydrazides (*i.e.* compounds of the type $RSCSNHNH_2$) have later been investigated very carefully and extensively by Holmberg [12] and by Sandström [13], our results are of a more general character, in that we have studied thiohydrazides of aliphatic, aromatic and heterocyclic acids and N-substituted thiohydrazides with many different substituents in the hydrazide group.

Accordingly our researches consist of the following parts:

1. An extensive investigation of the preparation of carboxymethyl dithioates, which are the most convenient intermediates for the preparation of the thiohydrazides (paper No. II). In connection with the preparation of these new compounds their infrared spectra have been investigated; this work has already been published [14].

2. The preparation of a large number of new thiohydrazides and thiosemicarbazides, derived not only from unsubstituted hydrazine but also from several monoalkyl- and dialkylhydrazines (papers No. III, V, and IX). Especially it was shown that the steric influence of the alkyl group determines whether monoalkylhydrazines form thiohydrazides of the type $RCSNR'NH_2$ or of the type RCSNHNHR' or a mixture of both.

3. Investigation of certain transformations of thiohydrazides and thioamides. It was found that aromatic and heterocyclic thiohydrazides can be transformed into compounds of the type $RCSN_3$, and these were proved to be thiatriazoles and not thioazides (paper No. IV). The transformation of thiohydrazides into tetrazines and thiadiazoles was investigated (paper No. VI), and during these investigations we prepared the basic 1,3,4-thiadiazole, which was prepared almost at the same time by Goerdeler [15] in a different way. The previously unknown 2-phenyl-5-thiazolone was prepared, and it was shown that it easily polymerises giving a product hitherto considered to be the thiazolone (paper No. VII). By oxidation of malonic dithiamide, salts of the dithiolenium ion were prepared [16], and it was shown that this ion constitutes a new aromatic system (paper No. VIII).

4. The ability of thiohydrazides to form co-ordination compounds, especially with metals of the first transition group, was investigated (paper No. X).

5. The antibacterial effect of the thiohydrazides and related compounds, especially as shown by the growth rate of bacteria in presence of thiohydrazides and metal ions, was investigated (paper No. XI).

Most of this work has been carried out in the years 1952—1957, but other work has delayed publication.

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