

FOERST

NEWER  
METHODS  
OF  
PREPARATIVE  
ORGANIC  
CHEMISTRY

Volume  
III

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# Newer Methods of Preparative Organic Chemistry

Volume III

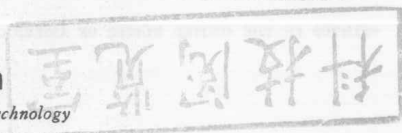
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## Preface

In this third volume of a series dealing with newer methods in preparative organic chemistry, the publishers continue to provide for the English-speaking chemist a useful survey of some of the more recent developments in this field. Like its predecessors, the volume consists of a number of selected reviews which originally appeared in *Angewandte Chemie*; these summarize a wide variety of topics in a comprehensive and authoritative manner. Detailed experimental directions are given, and the probable reaction mechanisms discussed; references to the original literature abound. This volume should, by its very nature, be of great value to all organic chemists, in both academic research institutions and industrial laboratories, who wish to keep abreast of modern techniques and developments in their field.

The translator should like to express his gratitude to Dr. N. A. Armstrong and Miss M. L. Bond for their kind assistance in the preparation of the English version of this book.

HENRY BIRNBAUM

## Foreword

This volume is intended for all synthetic organic chemists.

The first series of these articles was originally collected in one volume, which went through numerous large editions. (Several editions were reprinted in the United States during the Second World War.)

The reviews in these three volumes are in the form of monographs, and have for that reason not appeared in systematic order. We have selected what seemed to us topical and important. (Reaction mechanisms according to modern theories are postulated only where they allow the prediction of fresh applications of the reaction described.)

The up-to-date character of the reviews is due to the exceptional cooperation of the authors.

W. FOERST

*Heidelberg*

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# The Reactions of Sulfur with Araliphatic and Aliphatic Compounds

R. WEGLER, E. KÜHLE, AND WERNER SCHÄFER

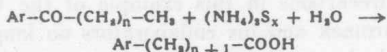
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It seems opportune at this time to give a general survey of the reactions of sulfur recently published, special emphasis being accorded to those found in the patent literature. We should like, in this respect, to restrict ourselves to reactions undergone by aliphatic compounds or groups. Reactions between sulfur and the aromatic ring (e.g. phenol or aniline) are therefore not considered; the dehydrogenation of cycloaliphatic compounds introduced by Ruzicka in 1921 has already been reviewed (1). The important problem of the vulcanization by sulfur of rubber or unsaturated polymers generally, the mechanism of which remains unelucidated, is merely touched upon, and in some reactions a possible explanation of the vulcanization is alluded to.

We ourselves have also discovered fresh information concerning the action of sulfur on alkylated heterocycles. These results appear to link individual findings of various investigators, and may at the same time be of interest in relation to the largely similar course taken by the action of sulfur on organic compounds.

## The Development of the Willgerodt Reaction

The best-known reaction between sulfur and methylene or methyl groups involving dehydrogenation or oxidation, is the so-called Willgerodt reaction (2, 3, 4). This consists in heating predominantly aromatic aliphatic ketones with an aqueous sulfur-ammonium sulfide solution in an autoclave (usually) above 200°. Carboxylic acids and their amides containing the same number of carbon atoms as the starting ketones are obtained. The reaction always proceeds, in effect, as though only the methyl group were oxidized to a carboxylic acid group, and the keto group simply converted into a methylene.



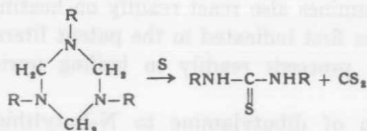
It was reasonable to expect that particularly those araliphatic ketones which can only be oxidized at one end should be conducive to a uniform



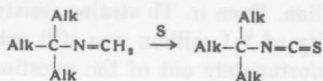
It is interesting to note moreover, as already mentioned by Willgerodt, that in the action of large quantities of sulfur or ammonium polysulfide on araliphatic ketones, the keto group may be oxidized as far as benzoic acid.

A substantial modification of the Willgerodt reaction was devised by K. Kindler. He proceeded from an observation of Wallach (12, 12a) that the action of sulfur above 180° on methylene groups adjacent to aryl groups, such as found, for example, in *p,p'*-tetramethyldiaminodiphenylmethane or even in benzylamine, results in their conversion to thiocarbonyl groups, thus forming thioketones from the former and thioamides from the latter. Kindler oxidized a series of benzylamines to thioacid amides (13, 14) (Example 3). He assumes the formation of Schiff bases as intermediates in the reaction between benzylamines and sulfur and conclusively demonstrates the ready conversion of these bases into thioamides by means of sulfur (13).

The trimeric Schiff bases of formaldehyde, existing as 1,3,5-trisubstituted hexahydro-*s*-triazines are correspondingly converted by sulfur into 1,3-disubstituted thioureas (14a).



An exception occurs in the case of the stable monomeric azomethines of tertiary alkylamines, which are converted into mustard oils on sulfurization (14a).



Not only Schiff bases, but aldehydes and ketones generally, undergo this reaction in the presence of primary and secondary amines or dry ammonia. Since the reaction takes place under anhydrous conditions, the thioacid amides are invariably obtained. This variant of the Willgerodt reaction has become generally known as the Willgerodt-Kindler reaction. The reaction is carried out at a maximum temperature of 180°.

Kindler's theoretical interpretation of the reaction, even if this does involve the initial attack of the nitrogen by sulfur, scarcely merits discussion today; the Willgerodt-Kindler method has nevertheless acquired great preparative significance and has been thoroughly developed (15). Morpholine is usually chosen as the hard-to-oxidize (16) amine com-

ponent, and the reaction proceeds at atmospheric pressure (15) (Example 4). The yields of thioamide amount to a maximum of 75%. Aliphatic ketones like methyl nonyl ketone may also be successfully subjected to the Willgerodt-Kindler reaction (8). It was even found possible to convert compounds as readily substituted in the ring as salicyl aldehyde into thioacid amides (17). Thermolabile furyl ketones, e.g. 2,5-dimethyl-3-furyl methyl ketone, could be converted into the thioamides at 100–110°, though the yields (10–27%) were rather modest. As anticipated, diketones are converted into dicarboxylic acids (17a). The Kindler method allows the surprisingly ready conversion of 1,3,5-triacetylbenzene into a 75% yield of benzenetriacetic acid (18) (Example 5).

The oxidation of benzylamines to thiobenzamides (12) is still one of the most convenient methods of synthesizing N-substituted thiobenzamides. It was subsequently more thoroughly developed by McMillan (19). Kindler's restricting the attack by sulfur to benzylamines only, though allowing its possibility in the case of, e.g. N-dimethylbenzylamine accompanied by the loss of one methyl group, has proved incorrect. Purely aliphatic amines also react readily on heating with sulfur to give thioamides, as was first indicated in the patent literature (20) (Example 6). The reaction proceeds readily in boiling pyridine at atmospheric pressure.

The oxidation of dibutylamine to N-butylthiobutyric acid amide proved to be the starting point of a more thorough elaboration, by us and by others, of oxidations effected by means of sulfur. When tested against tuberculosis in the laboratory of Prof. Domagk in Elberfeld, N-butylthiobutyric acid amide showed a specifically high tuberculostatic activity of 1:10 million. Even in Tb strains resistant to isonicotinic acid hydrazide, an activity of 1:1 million was still exhibited. Clinical use of the compound is unfortunately out of the question because of its excessive toxicity.

*p*-Nitrobenzylaniline with its highly active methylene group can be dehydrogenated to the Schiff base with sodium polysulfide at around 100°. *p*-Aminobenzaldehyde is obtained, as was already known in 1897 (21) (Example 7).

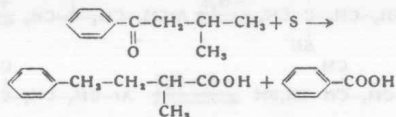
### The Mechanism of the Willgerodt Reaction

The mechanism of the Willgerodt-Kindler reaction resisted numerous investigations. Even though it has not yet been elucidated in all its details, its major steps are known with some degree of certainty.

The old concepts of Kindler whereby a phenyl group migrates during the course of the reaction with sulfur are no longer considered a serious interpretation, since no definite indication has been observed of

the isomerization of a ketone during the oxidation. Willgerodt's older hypothesis, i.e., that the oxidation of the methyl group, e.g. in acetophenone, is preceded by the reduction of the keto group, is equally improbable as the corresponding hydrocarbons will not, or hardly, react under the prevailing reaction conditions.

When advancing a mechanism, it must be borne in mind that no isomerization occurs during the oxidation, and furthermore, that ketones differing only in the position of the keto group yield identical oxidation products (9). It must also be remembered that ketones in which the carbonyl group is adjacent to a phenyl ring and which contain a quaternary carbon atom give hydrocarbons exclusively and no carboxylic acids (22). De Tar and Carmack (9) believe that a reactive group—probably the amino group—migrates along the hydrocarbon chain during the course of the Willgerodt-Kindler reaction, via addition to triple bonds. The observation, reported almost simultaneously by McMillan (10) and Carmack (9, 11, 23, 24, 25) that olefins and acetylenes (Example 8) are also converted into thioamides or acids under the conditions of the Willgerodt reaction, supports the assumption of the presence of olefins or acetylenes as intermediates. On the other hand, the same authors point out that lower yields are obtained from the Willgerodt-Kindler reaction undergone by phenylacetaldehyde and  $\beta$ -phenylpropionaldehyde than by acetophenone and propiophenone, respectively. It is concluded from this fact that it is not merely a case of a carbonyl group's migrating along the carbon chain. It must, however, also be considered that a high initial concentration of mutually reactive aldehydes is conducive to side reactions of a different type. In argument against the intermediate formation of acetylenes, the fact is adduced that branched ketones incapable of possessing a migrating triple bond can also be oxidized by sulfur (26), though the yields are, to be sure, exceedingly small.



(The ketone can be degraded further, resulting in a shortening of the chain, an observation already noted by Willgerodt (26, 27) at the commencement of his work.) The degradation of a methyl ketone group as far as a carboxylic group has also been reported by other workers (15).

The oxidation of a branched ketone appears to contradict the migration of a carbonyl group along the chain; it also does not support the intermediate formation of olefins, for in this case the poor yield would scarcely be comprehensible. More probably, the oxidation can proceed



via several mechanisms, one of which involves the olefin stage. It would, however, appear that an intermediate devoid of the possibility of migration along a branched carbon chain does provide a substantial contribution to the reaction.

McMillan (22, 28) assumes that the reaction starts with the addition of  $\text{H}_2\text{S}$  to the keto group, followed by dehydration to a thioketone, the latter's reduction to a mercaptan, elimination of hydrogen sulfide to an olefin, renewed  $\text{H}_2\text{S}$  addition which can now proceed in two directions (to give isomeric mercaptans), again elimination of  $\text{H}_2\text{S}$  to give two isomeric olefins, and so on. The thiol group thus migrates along the whole aliphatic chain, including a carbon atom linked to only one hydrogen. The primary mercaptan finally obtained is dehydrogenated to the thioaldehyde and the latter irreversibly converted into the dithio-carboxylic acid; this last step may also involve stabilization to the thio-acid amide or acid amide. Except for the conversion of the thioaldehyde into the thioacid amide, all the transformations are equilibrium reactions. It is understandable that this cycle of equilibria results in low yields in the case of compounds containing long carbon chains, since side reactions such as sulfide, or hydrocarbon formation interrupt the reaction sequence.

