

## The Mechanisms [1]

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## Dedicated to Professor Ernest E. Campaigne on the occasion of his 75th Birthday

The mechanisms involved in various stages of the Kindler Reaction are discussed, with particular attention especially to its most unusual feature: the movement of a carbonyl group from methylene carbon to methylene carbon in an unbranched alkyl chain, or around a cycloalkyl ring. The first step is the reversible formation of an enamine, which is attacked by a catalyst generated from sulfur and the amine solvent to form a highly reactive intermediate with a sulfur-containing heterocyclic ring. The natures of the catalytically active species and the reactive intermediates are proposed. Other steps involved in the Kindler Reaction are also discussed, as is the relationship of the Willgerodt Reaction to the Kindler Reaction.

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The numerous variants of the Willgerodt and Kindler Reactions have been reviewed in the preceding paper of this series [1] and in reviews by Carmack and Spielman [2] and by Brown [3]. As synthetic routes to carboxamides, thiocarboxamides, and derivatives of these, these old reactions have been useful, but their mechanisms have remained obscure. It is also evident that not all variants can be explained by common mechanisms. In this paper we shall consider principally the Kindler modification in which ketones having a least one unbranched *n*-alkyl chain react with sulfur and a secondary amine to form an *N,N*-disubstituted thiocarboxamide. Acetylenes with one *n*-alkyl substituent also react similarly.

The feature of the Willgerodt and Kindler Reactions [1] that is hardest to explain is the isomerization of a carbon group along a chain of methylene groups or around a ring; *e.g.*,  $R-CO(CH_2)_n-R' \rightarrow RCH_2CO-(CH_2)_{n-1}R'$ , *etc.* In the preceding paper we presented evidence that the secondary amine typically used in the Kindler Reaction reacts first, reversibly and rapidly, to form an enamine. The amine also reacts with elemental sulfur, or alternatively with other forms of sulfur, to form catalytically active species, the nature of which will be proposed. The simplest compound which we have found to be an effective catalyst is **dithio-bis-4,4'**-morpholine.

## Summary of Experimental Evidence Relating to the Isomerization.

Some of the experimental findings [1a] in the studies of the Kindler Reaction that must be reconciled with an overall mechanistic scheme can be summarized:

•Evidence that enamines are intermediates in the migration of the carbonyl group along a chain of methylene groups is provided by experiments in which the enamines themselves have been isomerized by elemental sulfur alone or, better, in the presence of free secondary amine,

without the presence of water (which would produce free ketones). The process of enamine formation was shown to occur rapidly and reversibly when the appropriately substituted ketones were warmed in secondary amine; the enamine formation occurs slowly even at room temperature.

•Tertiary amines, *e.g.*, *N*-methylmorpholine, are unable to cause isomerization of the ketone function, no matter in what form the sulfur is introduced into the medium.

•The secondary amine can be varied considerably; among effective ones are morpholine, piperidine, pyrrolidine, dimethylamine; there must be at least one hydrogen on nitrogen.

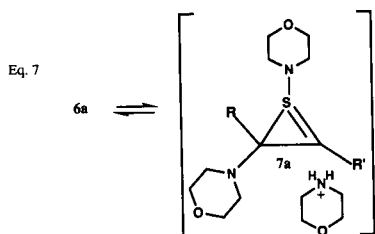
•With a suitable ketone and a medium consisting of an appropriate secondary amine, the sulfur can be introduced in many different forms: elemental rhombic sulfur ( $S_8$ ), sulfur polysulfides, polythiosulfenamides, *e.g.*,  $R_2N-S(S)_n-NR_2$ . In the latter example of the sulfenamides, *n* must have a value of at least 1 (*i.e.*, there must be at least two sulfur atoms), since in experiments using  $R_2N-S-NR_2$ , no isomerization could be achieved.

•The isomerization reaction catalyzed by sulfur derivatives must involve highly reactive (energy-rich) intermediates, since, under certain experimental conditions when water is present, more than 98-99% of the total mole equivalents of starting ketone can be accounted for in the form of an isomeric ketone mixture throughout the course of the reaction by use of direct infrared observations. In non-aqueous starting amine, up to half of the ketonic material disappears into crypto-intermediates not observable in the infrared region of the ketone group; the ketones reappear, however, when water is added.

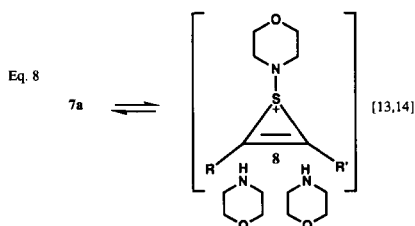
•At some point during the isomerization reaction, a mechanism must show the elimination of an amino group from one carbon atom and the attachment of an equivalent amino function to its neighbor. That central interme-



and other electrophiles [7-12], forming first an addition complex having tetravalent sulfur, which subsequently dissociates. In Eq. 6 we show our proposed intermediate **5a** closing a three-membered ring intermediate—a sulfiliminium ion, **6a**. (Sulfilimines and related derivatives are reviewed in the excellent monograph by Oae and Furukawa, [13]). The reaction would be analogous with the proposed intermediate steps in the addition of sulfur halides and sulfenyl halides to olefins [7-12] and acetylenes. Through both its strained ring character and its highly polar functional group, the proposed intermediate **6a** should exhibit high reactivity. We propose (Eq. 7) that the hydrogen on the small ring will now be quite acidic and would undergo deprotonation by the solvent, morpholine, leading to an unstable unchanged intermediate, **7a**. It will be noted that in order to accommodate the electron pair released in the deprotonation of **6a** it is necessary for the sulfur to expand to a ten-electron valence shell. This should favor the expulsion of the ring morpholino group, and its elimination would be assisted by acceptance of the proton handed off from the ring *via* a solvent morpholine molecule.



We now reach (Eq. 8) the midpoint of the proposed isomerization sequence with intermediate **8**, an S-4-morpholino-thiirenium cation. Its structure would be analogous to

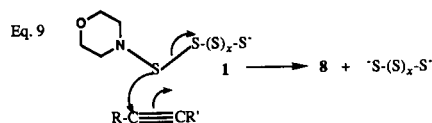


the known thiirene S-oxides [14]. In this central intermediate, the oxidation state of the two carbons that were previously carbonyl and methylene subunits have now become equivalent in oxidation level. Since all steps leading from **3a** to **8** have been postulated to be readily reversible, a natural consequence is that the readdition of morpholine to **8** could occur at either the 2- or the 3-ring position, which differ only to the extent that R and R' differ. Thus, the starting ketone, **3a**, would be reformed, or attachment to the other carbon of **8** would result in an isomer, **3b**, of **3a**. The evidence is that all intermediate steps can and do occur rapidly and reversibly, and with little loss due to side reactions, except when steric effects or possibilities

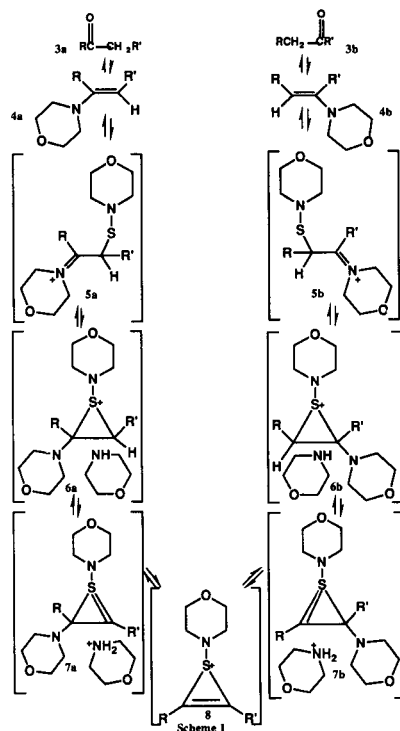
for aromatization are present. A critical point is the assumption that sulfide ion, polysulfide ion, or polythio-sulfenamide ion are capable recapturing the sulfur function of **5a** or **5b**, to regenerate enamines and active forms of catalyst. The conservation of active forms of the sulfur catalyst is necessary to explain some of the experimental findings in Paper 6 [1].

Scheme 1 combines all the proposed steps leading from ketone **3a** through **8** to ketone **3b**, and *vice versa*.

The central intermediate **8** common to both legs of Scheme 1 offers a possible explanation of the ability [15] of aliphatic acetylenes to participate in the Kindler and Willgerodt Reactions. Eq. 9 shows the possible addition of **1** to an unsymmetrically substituted acetylene. The nucleophilic reaction of the acetylenic function with the sulfenamide sulfur atom of **1** or **2**, with displacement of the extra sulfur chain could generate Intermediate **8** directly, and subsequent reactions would follow the pathways of Scheme 1.



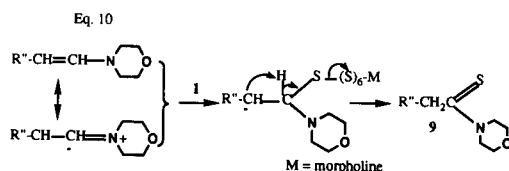
It should be noted that the proposed Intermediate **8** in Equation 8 is a structural analog of the thiirene 1-oxide family of interesting heterocyclic compounds [14], with a nitrogen atom replacing oxygen on sulfur. The thiirene 1-oxides are reportedly "surprisingly stable compounds," and examples of both aryl- and alkyl-substituted derivatives have been prepared as stable crystalline compounds. Much has been written concerning their possible "aroma-



tic" or "antiaromatic" character. The experimental verification of derivatives of the proposed Intermediate **8**, and in particular the determination whether it represents an isolable class of new heterocyclic derivatives, would open up interesting theoretical as well as preparative possibilities.

#### The Terminal Thioamide Formation of the Kindler Reaction.

The situation in a ketone with a *n*-alkyl chain is unique when the enamine reaches the terminal methyl group and, in the well-known Kindler synthesis, irreversibly produces an *N,N*-disubstituted thiocarboxamide. The presence of the extra hydrogen on the methyl group gives the potential for the terminal oxidation to occur at the expense of a sulfur atom. A possible sequence is shown in Eq. 10.



#### The Willgerodt Reaction.

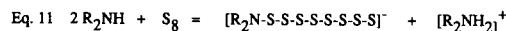
The Willgerodt Reaction was originally carried out with aqueous ammonium polysulfide at temperatures above 200° in sealed glass tubes. Later modifications [2,3] used simply elemental sulfur, aqueous ammonia, and a solvent such as dioxan or pyridine to increase the mutual miscibility or organic and inorganic components; under these conditions, reaction temperature and time were both decreased and yields improved.

The interesting experiments of Cerwonka, Anderson, and Brown [16] involving the deuterium labeling of methylene groups in a typical Willgerodt Reaction can now be explained in terms of a scrambling of the chain hydrogens with the aqueous ammonia solution's hydrogens as the ketone group is free to isomerize back and forth along the chain.

Numerous publications by Asinger and co-workers [17] and by Mayer and co-workers [18] have shown that the reactions of ketones with ammonia and sulfur can be extremely rapid and complex, even below room temperature. There are hints that some of the reactions involve direct attack upon the enolic forms of the carbonyl compound. There are mechanistic features of the Willgerodt Reaction that can probably be formulated in pathways similar to those of the Kindler Reaction, especially in the isomerization of the ketone group along a methylene chain, and the terminal oxidation to a carboxamide function. The reaction of ammonia with sulfur appears to have greater complexity than even the reactions of secondary amines with sulfur, and it will not be dealt with further in this review.

#### Redox Reactions as a Feature of the Kindler Reaction.

Mention has been made of the fact that the aminolysis of elemental sulfur in its common 8-ring form involves both formal oxidation and reduction: The polythiosulfenamide is a derivative of a hypothetical acid:



HO-SSSSSSSS-H, in which one terminal sulfur atom has been oxidized and the other terminal sulfur reduced. Because of the very facile nucleophilic displacement of sulfur by sulfur in disulfides and polysulfide chains, the long-chain polysulfides can undergo disproportionation reactions to form statistical mixtures of different chain length. The aminolysis of **1** in Eq. 2, and the reaction of **4a** with **2** in Eq. 4 represent a further oxidation stage for one sulfur in the sulfenamide **5a** and a reduction of the sulfur in **6**. The sulfur atoms in the intermediates **6a** and **7a** represent still higher valence states of sulfur, and **7a** requires a 10-electron shell for the sulfur atom. We believe that the changes in the valence state of sulfur are a fundamental contributing factor to its extraordinary catalytic capabilities. In the families of compounds represented by the formulas  $\text{R}_2\text{N-S}(\text{S})_x\text{-S}^-$  and  $\text{R}_2\text{N-S}(\text{S})_x\text{-NR}_2$ , there exists a finely graded series of sulfur valency levels, depending upon the values of *x*. A minimum requirement for the catalysis of the isomerization of the carbonyl function appears to be  $\text{R}_2\text{N-S-S-G}$ . We have demonstrated that catalysis is achieved in the case where *G* = *N*-morpholino. Whether *G* may be any of the higher polysulfides or polythiosulfenamides cannot readily be proved because of the lability of these functions. Clearly, further studies of the polythiosulfenamides should be expected to yield interesting results.

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