The Willgerodt-Kindler Reactions. 6. Isomerization of the Carbonyl Group in Alkanones and Cycloalkanones [1]

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

The most unusual feature of the Willgerodt-Kindler Reactions is the facile isomerization of the carbonyl function along a chain of unbranched methylene groups, or around a cycloaliphatic ring containing several connected methylene groups. We have demonstrated that the first step in the Kindler process is the formation of enamines by reaction of the carbonyl function with secondary aliphatic amines, followed by reaction of the enamine with certain sulfur-amine catalysts to form reactive heterocyclic sulfur intermediates that facilitate the elimination-readdition of the amines reversibly along the chain. It was shown that compounds of the type R_2N-S-S-NR_2 are effective catalysts but not compounds of the type R_2N-S-NR_2. Some cyclohexanone derivatives undergo aromatization, with anomalous results in certain cases.

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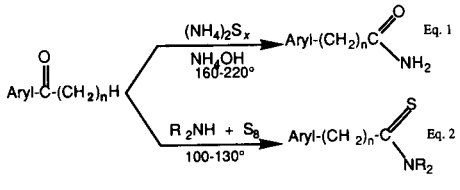
In the classic Willigerodt Reaction [2,3], and *n*-alkyl aryl ketone is heated in a sealed pressure tube at 200° or higher with aqueous ammonium polysulfide, forming an ω-arylcarboxamide (Eq. 1). The later Kindler modification [2,4] substituted a mixture of elemental sulfur and a secondary amine (originally, dimethylamine; now typically morpholine) at temperatures usually in the range of 100-130°; under these conditions the ketone is converted into an *N*-substituted thiocarboxamide (Eq. 2).



Willgerodt suggested in 1888 [3] that the oxygen of the carbonyl group wanders along the aliphatic chain to the methyl group to form the isomeric aldehyde, which then undergoes oxidation with sulfur and ammonia to the amide. Kindler later suggested [4] a mechanism which postulated a rearrangement of the aryl group on the carbon chain, but his mechanism, as well as others that involved rearrangement of the carbon skeleton, have been ruled out by later investigations. The excellent review by Brown [5] has assembled the essential data of many investigations of these reactions and their numerous variants.

The essential correctness of Willgerodt's original interpretation has been confirmed, but details of the mechanism have remained puzzling, especially as to the nature of the catalytically active form(s) of sulfur and the complete sequence of steps by which a carbonyl functional group can move from one carbon atom of a chain to another with seeming ease.

In early work in our laboratory [6], it was shown that the aryl substituents play no essential role in either the Willgerodt or Kindler synthesis, and unbranched acetylenes participate about as readily as ketones [7]. Under somewhat more vigorous conditions, olefins can also form carboxamides, as can certain easily dehydrated carbinols, some amine, imines, *etc.* [2,5].

Carmack and Spielman suggested in a 1946 review [2] that enamines may be intermediates in the isomerization of ketones and acetylenes, and they may be the common intermediate linking the reactions of these two functional types. In the same year, Carmack and DeTar [8] suggested that the then unknown thiirenes and thioketenes might be intermediates in the Willgerodt and Kindler processes and their extensions. In 1946, the state of fundamental knowledge of sulfur chemistry did not allow a convincing formulation of detailed mechanistic schemes. In 1963 we confirmed experimentally that enamines do indeed isomerize as we postulated; a reaction scheme based upon this finding was presented at a national meeting [9]. Other laboratories have confirmed the fact that enamines undergo isomerization induced by the catalytic action of sulfur.

In this paper we describe experiments focused especially upon the isomerization phase of the Kindler procedure, in both substituted and unsubstituted alkanones and cycloalkanones. We shall show that the ketonic and aldehyde functions, as well as their enamine derivatives, can be moved along chains and around rings, often with surprising ease, by the combined action of sulfur and a secondary amine.

The isomerization reaction can be useful in certain situations in which one member of a family of isomeric ketones with a common carbon skeletal structure may be readily available but others difficult to obtain; this would be

particularly true in the case of natural products. In the case of cycloalkanones, the reaction would be limited to isomerization to form a mixture of isomers that could be separated by known means. In the case of open-chain carbonyl compounds, where the terminal reaction to form carbonamide or thiocarbonamide is possible by the Willgerodt or Kindler processes, use of mild conditions could limit the extent of amide formation and still produce a mixture of carbonyl isomers in good yield.

The close study of a series of carefully selected model compounds in the sulfur-amine isomerization reaction has also yielded much new information regarding the mechanisms. It has uncovered several surprising side reactions that must be reconciled with the overall interpretation.

This Paper No. 6 will be limited largely to presentation of experimental results. Interpretation will be covered mainly in Paper 7 of this series. To follow the course of the experiments described herein, it is sufficient at this point to state that we believe the central isomerization step - the process by which the oxygen atom of a carbonyl function trades places with a pair of hydrogen atoms on an adjacent methylene group - involves highly reactive thiiranium and thiirenium intermediates. These are postulated to be formed reversibly from enamines and revert readily to isomeric enamines. Recent advances in the chemistry of sulfur compounds has made possible a rational inference as to the nature of intermediates too reactive and fugitive to be isolated.

We found that movement back and forth along a chain or ring of methylene units occurs with surprising ease and rates that compete favorably with the irreversible final Willgerodt-Kindler oxidation to form a carboxamide derivative. Only when a carbonyl group reaches a terminal methyl carbon does it create the unique situation in which the Willgerodt or Kindler processes obtain. Even then, the reverse isomerization of aldehydes back to ketones may occur more rapidly than terminal oxidation.

Isomerization of the Carbonyl Function in Alkanones.

Bible [12] appears to have been the first to report the isolation of an isomeric ketone while carrying out a Kindler-type synthesis. In the typical reaction or morpholine and sulfur with methyl 7-propionylpodocarpate, he isolated some of the 7-acetonyl isomer of the starting compound in addition to the expected β-arylpropiothiomorpholide.

Shortly after Bible's report, we observed [13] that, when phenylacetone reacts in a sulfur-morpholine solution, aliquots from the reaction mixture can be directly analyzed without separation in the infrared spectrometer: a new carbonyl absorption band appears and increases in intensity as the band of the unconjugated ketone diminishes. The sulfur-morpholine reagent is, fortunately, sufficiently transparent to allow rate studies of the isomerization of the ketonic group. While the precision of this method is not as great as might be desired, it nevertheless was adequate to permit the evaluation of some of the most important variables and to limit the range of mechanistic interpretations.

We chose for an initial study a four-carbon ketone blocked with different aryl groups at each end. With the irreversible oxidation to carboxamides typical of the Willgerodt-Kindler processes, we expected to limit the events to migration of the carbonyl function back and forth among the four possible chain positions. The choice of a four-carbon chain proved less than ideal because quantitative analysis of the mixture of similar isomers was difficult and because of competing cyclization.

The chosen ketone, 4-phenyl-1-(*p*-chlorophenyl)-1-butanone, was heated with the typical sulfur-morpholine reagent and the reaction product was chromatographically separated. Two of the possible isomers were isolated along with recovered starting ketone: 4-phenyl-1-(*p*-chlorophenyl)-4-butanone and 4-phenyl-1-(*p*-chlorophenyl)-2-butanone, but the separation was tedious and slow and the recoveries low. In a model experiment carried out with 1,4-diphenyl-1-butanone under similar conditions, the identified product was 3-(4'-morpholino)-2,5-diphenylfuran.

A much more suitable model system was found in the isomeric pair: 1,3-diphenyl-2-propanone (dibenzyl ketone) and 1,3-diphenyl-1-propanone. For convenience we shall refer to these isomers as 2-DPP and 1-DPP, respectively, hereafter. In the three-carbon chain with only two isomers, possibilities for side reactions were minimal, and a very simple analytical procedure could be used which was based upon the adequate separation in the infrared absorption of the carbonyl bands for unconjugated 2-DPP and conjugated 1-DPP, respectively: 5.82 μ and 5.91 μ. It was also found conveniently possible to observe these bands directly in the sulfur-morpholine reagent solution, which is sufficiently transparent in this region. When runs were made with water added, a more complex procedure was developed which required the separation of the ketone mixture.

Whether the reaction was started with 2-DPP or 1-DPP, we found that each would interconvert into a mixture of the two, and if the reaction time was extended sufficiently long the same steady state could be reached from either direction. The measured intensities of the carbonyl absorption bands, referred to calibration standards, followed the Beer-Lambert Law over a wide range of concentrations. The disappearance of 2-DPP and the appearance of 1-DPP could be followed as apparent first-order reactions through several half-life periods.

Because the state of sulfur in solutions of secondary

amines is very complex and little understood [14], concentrations of sulfur were expressed in terms of gram-atomic weights added to the starting reagent. In the tables and Experimental, these are expressed either as ratios of moles of ketone and amine to gram-atomic weight equivalents of sulfur, or the molar concentrations of organic ketone and amine were compared with gram-atomic equivalent weights of total sulfur per liter, without any attempt to evaluate the molecular condition of the sulfur. It is very interesting and significant that less than one gram-atomic weight of elemental sulfur per mole of ketone functions well in its catalytic role and allows the approach to a steady state. This would not be true for the classic Kindler synthesis, in which one gram-atomic weight of sulfur is irreversibly incorporated into the thiocarboxamide product.

Although the rate of isomerization increases with increasing sulfur concentration (expressed as described above), it is not a linear increase or a simple relationship. It *does appear that the sulfur plays a truly catalytic role and is not used up*, but rather is regenerated in its reactive form or forms. In our discussion of mechanism [11] we shall elaborate on our hypothesis that the reactive sulfur atom is one bonded to nitrogen in the form of a dithiosulfenamide or polythiosulfenamide. It further appears that a minimum of two sulfur atoms in this sulfenamide is required. The well-known inherent tendency of polythio chains to undergo rapid sulfur-sulfur bond displacements in basic environments, assisted by the powerful catenation tendencies of sulfur, combine to provide the means for the regeneration of catalytically active species.

When the starting reagent is anhydrous morpholine and the concentrations of both 2-DPP and 1-DPP are monitored, the sum total of both ketones falls gradually during the approach to a steady state and reaches about half the initial molar concentration of starting ketone. But, upon addition of water to such a steady-state equilibrium mixture, part, but not all, of the ketonic material that has disappeared into hidden intermediates reappears as ketone. We believe that this behavior is consistent with the proposed mechanism, and that in the absence of water (except for the small reaction-generated amount) the hidden forms of ketone represent enamine and reactive and easily hydrolyzed sulfur-containing intermediates.

Table I shows the apparent first order rate constants for isomerization of 2-DPP in anhydrous morpholine. Table II shows the dramatic effect of water; rates are in 80% morpholine-20% water. A modified analytical procedure was used. Rates are very much slower in the water-containing medium, but the total amount of 2-DPP + 1-DPP at any given time in the mixture remains rather constant at about 98-99% of the starting amount. In other words, the essential intermediates can form rapidly and effectively even in the presence of at least 20% of water, but the concentrations of reactive intermediates are much lower. This interpretation is consistent with the indications that enamines are essential intermediates.

Table I

First Order Rate Constants of Isomerization of 1,3-Diphenyl-2-propanone (2-DPP) in anhydrous Morpholine Containing Sulfur [a,b]

Run No.	[2-DPP] moles. ℓ^{-1}	$[S]_o$ [c] g at ℓ^{-1}	Temp °C	k_1 [d] hour^{-1}	Exp. $t_{1/2}$ hour	Calcd. $t_{1/2}$ hour
5	0.0800	0.240	99.59	0.164	4.3	4.2
13	0.150	0.075	"	0.079	10.8	8.8
9	"	0.300	"	0.221	3.1	3.1
17	"	1.50	"	0.386	1.9	1.8
61	0.100	0.400	"	0.236	3.0	2.9
41	0.400	"	"	0.218	3.2	3.2
133	"	"	84.58	0.106	6.5	6.5
137	"	"	"	0.106	6.7	6.5
149	"	0.000	"	[e]	∞	∞

[a] Ref 16a, p 13; Ref 16b, p 125.
[b] Anhydrous refers to the starting morpholine; enamine formation releases one water into the medium, as discussed in the text.
[c] Sulfur is expressed in terms of gram atomic weights per liter.
[d] The first order rate constant for the disappearance of 2-DPP was computed from the equation $k_1(hr^{-1}) = \frac{1}{t\ (hr)} \cdot 2.303 \log \frac{[2\text{-DPP}]_o[d]}{[2\text{-DPP}]_t}$
[e] Only a very slight change in the carbonyl absorption in the infrared region was observed, signifying neglible isomerization of 2-DPP into 1-DPP.

Table III shows the strong effect of added water in the medium, with a decrease of about one-third in rate constant for isomerization of 2-DPP in the medium starting with 1% water, as compared with starting anhydrous morpholine. If all water that would be derivable from 0.4 *M* ketone were released into the medium through enamine formation, it would produce a maximum concentration of approximately 0.7%. We have no data to indicate what the rates would be if the medium could be maintained in anhydrous state at all times. Experiments with anhydrous enamine as starting material instead of ketone show that isomerization occurs even without the possibility of ketone being present.

In view of the limited precision of the rate measurements by the infrared procedure, compounded by the uncertainties as the the state of the sulfur and its derived reactive species, the difficulty of controlling or measuring the intermediate concentrations of water, and some occurrence of irreversible side reactions (*v.i.*), we have not felt that it would be rewarding to attempt to refine these rate studies further, or to carry out interesting extensions by us of variously substituted phenyl ketones.

Table II

Rates of Reversible Isomerization of 1,3-Diphenyl-2-propanone (2-DPP) into 1,3-Diphenyl-1-propanone (1-DPP) in 80% Morpholine - 20% Water Solutions

Run No.	$[2\text{-DPP}]_o$	$[S]_o$ [a]	Temp. °C	k_1 [b] d[2-DPP]/dt hr^{-1}	$(k_1 + k_1')$ [c]	t1/2 (2-DPP) exper. (hr)	t1/2 (2-DPP) [d] calcd from [2-DPP] data	k_1 [e] d[1-DPP]/dt (column 6 -column 5)	$\frac{[1\text{-DPP}]_{eq}}{[2\text{-DPP}]_{eq}}\frac{k_1}{k_1'}$
45	0.100	0.400	99.59	0.0688	0.0969	11.2	10.2	0.0281	2.45
37	0.300	0.400	99.59	0.0699	0.1060	10.7	9.9	0.0361	1.94
33	0.400	0.400	99.59	0.0694	0.1043	10.7	10.0	0.0349	1.99
81	0.100	0.200	99.59	0.0340	0.0502	-	20.4	0.0162	2.09
77	0.100	0.100	99.59	0.0112	(0.0218) [f]	-	61.9	0.0106	1.06
41	0.400	0.400	84.58	0.0244	0.0326	-	28.4	0.0082	2.97
45	0.400	0.400	84.58	0.0209	0.0299	-	33.1	0.009	-
153	0.400	0.000	84.58	negligible changes in absorption at 5.82 μ and 5.91 μ during 12 hours					
109-A	0.400	0.400	99.59						2.89 [g]
109-B	0.400 [1-DPP]	0.400	99.59						3.02 [h]
57 [i]	0.100	(0.200) [j]	99.59	(0.0282) [k]	(0.0356) [k]			(0.0074) [k]	
89 [i]	0.100	0.200 [S] [g] 0.200 [H_2S]	99.59	0.0797	0.1356			0.0559	
121[i]	0.400	0.200 [S] [j] 0.200 [H_2S]	99.59	0.0610	0.0902			0.0292	

[a] Initial sulfur concentration is expressed in gram atomic weights/liter.[b] k_1 is the first order rate constant for disappearance of 2-DPP, calculated from the equation of $k_1 = \frac{1}{t\ (hr)} \cdot 2.303 \log \frac{[2\text{-DPP}]_o}{[2\text{-DPP}]_t}$

The constants computed from the observed changes in [1-DPP] and the equation $k = \frac{1}{t\ (hr)} \cdot 2.303 \log \frac{[2\text{-DPP}]}{[2\text{-DPP}] - [1\text{-DPP}]_t}$ were in good agreement during the first half life. The values in

Table II are from the more precise analytical data on [2-DPP]. [c] The sum of the constants, k_1 and k_1', for d[2-DPP]/dt and for d[1-DPP]/dt, respectively, were calculated in two ways (Ref 16a, p 172; Ref 16b, p 126, Eq. 16):

$$(k_1 + k_1') = \frac{1}{t\ (hr)} \cdot 2.303 \log \frac{[2\text{-DPP}] - [2\text{-DPP}]_{eq}}{[2\text{-DPP}] - [2\text{-DPP}]_e} \quad \text{and} \quad (k_1 + k_1') = \frac{1}{t} \cdot 2.303 \log \frac{[1\text{-DPP}]_{eq}}{[1\text{-DPP}]_{eq} - [1\text{-DPP}]_t}$$

The values in Table II are from data calculated by the first equation above, since [1-DPP] is in general less accurately determined than [2-DPP]. The values are in essential agreement through the first half-life, then begin to diverge, partly because irreversible side reactions remove ketones from the reaction to form unidentified side products. [d] Calculated from the equation $t_{1/2} = \frac{0.6933}{k_1}$ (Ref 16b, p 125) [e] k_1' = first order rate of isomerization of 1-DPP, calcd as $(k_1 + k_1')$ in column 6 *minus* k_1 in column 5. [f] Calculated by second eq., Footnote c. based upon observed changes in 2-DPP. [g] Average of two runs starting from 2-DPP. [h] Average of two runs starting from 1-DPP.[i] In this experiment, elemental sulfur was replaced with 4,4'-dithio-*bis*-morpholine. [j] The 0.200 *M* concentration for the catalyst consisting of 4,4'-dithio-*bis*-morpholine. Rates fall between those of experiments 81 and 77 above, in which the gram atomic weights/liter of elemental sulfur were 0.200 and 0.100, respectively. [k] Rate constants in parentheses were calculated from analytical data for 1-DPP; because these are inherently more difficult to measure than 2-DPP, the constants are regarded as less precise than in other exps. [g] The total concentration 0.400 consisted of 0.200 gram atomic weights of elemental sulfur/liter *plus* 0.200 *M* hydrogen sulfide.

Table III

Effect of Variations of Water Content in the Morpholine upon the Rates of Isomerization of 1,3-Diphenyl-2-propanone into 1,3-Diphenyl-1-propanone

Run No.	$[2\text{-DPP}]_o$	$[S]_o$ g at/ℓ^{-1}	% H_2O in solvent	k_1	$k_1 + k_1'$	k_1'	K_{eq}
61	0.100	0.400	0	0.236			
65	0.100	0.400	1	0.169			
85	0.100	0.400	5	0.119	0.185	0.066	1.8
45	0.100	0.400	20	0.0688	0.0969	0.0281	2.4

With the 2-DPP—1-DPP system as a model, we undertook a series of experiments to determine how the sulfur catalyst and the amine could be varied. The choice of the secondary amine was not critical: both pyrrolidine and piperidine were effective as well as the frequently used morpholine. The original preparative experiments of Kindler had used dimethylamine, which requires a pressure vessel.

In sharp contrast, the change from morpholine to *N*-methylmorpholine completely failed to result in any isomerization, no matter in what form the sulfur catalyst was added. Likewise, when attempts were made with open-chain alkanones to effect isomerization using *N*-methylmorpholine and sulfur, there was no sign of movement of the carbonyl or of formation of a typical Kindler thiocarboxamide.

We next investigated variations in the sulfur catalyst. All attempts to effect a Kindler-type synthesis with an open-chain ketone without any amine but using sulfur in combination with various inorganic bases failed. We tried alcoholic sodium hydroxide with sulfur and with sodium tetrasulfide, aqueous sodium tetrasulfide, and dioxane-water-sodium tetrasulfide, without any indication that isomerization occurred, or that carboxylic acid derivatives were formed.

When, however, any of the convenient secondary amines was used, the form in which the sulfur was added could be varied considerably. For example, rhombic elemental sulfur, or sodium tetrasulfide, or 4,4'-dithio-*bis*-morpholine in morpholine solution catalyzed the isomerization readily. It appears, therefore, that at least one nitrogen-hydrogen bond must be present in the amine [a few experiments in the literature involve primary amines, but these amines are themselves readily oxidized by sulfur].

In order to define the minimal requirements for sulfur, parallel experiments were carried out in which the effective catalyst dithio-4,4'-*bis*-morpholine was compared with thio-4,4'-*bis*-morpholine in combination with 4-methylcyclohexanone. While the *dithio* reagent readily caused isomerization to a mixture of 2-methylcyclohexamone, 3-methylcyclohexamone, and 4-methylcyclohexanone, the *monothio* compound was ineffective in catalyzing isomerization. We interpret this as indicating that a minimum requirement is for $R_2N\text{-}S\text{-}S\text{-}G$, where G can be a second sulfenamide group, or may be another as yet undetermined possible group. The presence of a sulfur-sulfur bond seems indicated as a minimum requirement in our experiments.

Table IV

Isomerization of 4-Heptanone and Heptanal in Morpholine-Sulfur [a] at 100° C

Run No.	Time hours	% Recovery of Ketone	Percent Isomer Distribution in Recovered Ketone		
			4-	3-	2-
1	0.17	36.5	70	21	9
2	0.5	31	58	27	5
3	1.5	17	20	49	31
4 [b]	0.33	5.5		17	83

[a] Reactants: 1 mole ketone: 1 g-at wt. S:2 moles morpholine.
[b] 4-Heptanone was used in Exps. 1-3, heptanal in Exp. 4.

The convenient use of infrared absorption in the systems with 1-DPP and 2-DPP could not be applied to purely aliphatic systems, obviously. For the study of isomerization in alkanones and cycloalkanones, a different procedure was developed. In a reaction mixture undergoing an isomerization experiment, aliquot samples of the ketone-sulfur reagent-amine were withdrawn at intervals, hydrolyzed in dilute aqueous acid to regenerate carbonyl compounds from the enamine intermediates, dried, separated from high-boiling products by short-path distillation under reduced pressure, and analyzed by gas chromatography. It was not unusual to find that the sequence of retention times of a family of isomeric ketones paralleled the order of the position of the carbonyl group with respect to the open end of the chain: the nearer to the chain end, the slower the movement.

Isomerization of simple alkanones can be observed to occur even at room temperature, although slowly. It occurs fairly rapidly in unbranched alkanones at 100°, but isomerization seems to be strongly inhibited when the carbonyl group approaches within one carbon or two from a branch in the chain. This observation is of interest in view

of the reports by Willgerodt and other later investigators [7] that aryl isoalkyl ketones form carboxamides with the same skeleton, but the yield is very low. Although the formation of branched-chain amides has been confirmed in one or two cases, chain cleavage also occurs when Willgerodt reactions are carried out with branched chain ketones under forcing conditions, and the very low yields suggest that different mechanistic pathways need to be invoked to account for the branched chain amides.

4-Heptanone and heptanal isomerization reactions are described in Table IV. They have been the subject of several previous investigations [5], and are of special interest because they provide the least complicated example in which the isomerization of the functional carbonyl can be compared with the irreversible formation of carboxamide (Kindler Reaction). When 4-heptanone was heated in the classic sulfur-morpholine reagent at 100° for only ten minutes, isomerization had already proceeded to form a ratio 70:21:9 of the 4-:3-:2-isomers. After thirty minutes of heating, the ratio of isomers had changed to 58:26:9. Prolonged heating converts any of the *n*-heptanones irreversibly into heptanothiomorpholide (Kindler Reaction).

A surprising result was observed in the experiment (Run No. 4, Table IV) starting with heptanal. Rapid reverse isomerization occurred within twenty minutes at 95-100° and the isomer mixture of 2-heptanone:3-heptanone was 83:17. The isomerization mechanism can operate, therefore, in competition with the Kindler thiomorpholide formation.

The effect of chain branching in slowing the isomerization was shown in the example of 2,6-dimethyl-4-heptanone (diisobutyl ketone). When this ketone was heated with the sulfur-morpholine reagent at 120-125° for 22 hours and then the mixture was hydrolyzed as usual in dilute acid, the ketonic mixture, after distillation, contained a ratio of 30:70 of 2,6-dimethyl-3-heptanone:2,6-dimethyl-4-heptanone. A purely statistical equilibration would produce a ratio of 2:1 of these two isomers. The movement of the ketonic group toward the methyl branches is either slower than in the open-chain 4-heptanone, or the equilibrium mixture greatly favors the less hindered 4-position. Recovery of total ketones was in the range of 35-56%.

Experiments with 6,10-dimethyl-2-undecanone (hexahydropseudoionone) and the sulfur-morpholine reagent yielded, in addition to recovered 2-isomer, two other ketonic isomers which were thought likely to be the 3- and the 4-isomers; their order of retention times in the gas chromatograph were consistent with these assignments, which were not otherwise determined. Analysis (pmr) was unable to detect the presence of the aldehyde isomer; under the conditions of the experiment it would probably have been converted into the thiomorpholide. No peak was found for a possible fourth ketone, but this would be the 5-isomer, and its formation, by analogy with previous examples, would be inhibited by the nearness to the methyl branch.

Isomerization of the Carbonyl Function in Cycloalkanones.

Alicyclic ketones offer attractive opportunities for the use of the isomerization procedure, presumably with little complication from Kindler-type oxidative processes. Actually, in many cases isomerization can be rapid and produce the expected mixture of isomeric cyclanones. But in six-ringed compounds and others in which dehydrogenation can form aromatic rings, the aromatization process takes precedence; it is possible that with the proper choice of conditions the isomerization could be achieved with a minimum of aromatization. The conditions to produce predominantly aromatized products can vary widely, and some of the products are not the obvious ones.

Horton and van den Berghe [15a] were apparently the first to heat a cyclic ketone - 1-tetralone - with the sulfur-morpholine reagent. The product was identified as 2-naphthalene-4'-morpholine, but they did not prove whether the nitrogen function entered the 2- or the 3-position with respect to the original 1-oxo group. Dauben, Ciula, and Rogen [15b] answered this question in the example of 6-methoxy-1-tetralone. They showed that their product was 6-methoxy-2-naphthalene-4'-morpholine. If it is possible to generalize from this one example, and one starts with a 1-tetralone derivative, the amino group will enter the adjacent 2-position. We found that 2-tetralone also yields 2-naphthalene-4'-morpholine. Several other substituted tetralone derivatives were studied, with the same generalization applying. These examples will be discussed in a later section of this paper.

On the basis of the analogy with the tetralone experiments, we anticipated that cyclohexanone would yield 4-phenylmorpholine. Surprisingly, when heated with the sulfur-morpholine reagent, cyclohexanone yielded up to 10% of 1,4-benzene-*bis*-4'-morpholine, apparently with no detectable *o*- or *m*-isomers. It is possible that 4-phenylmorpholine (**1**) is an intermediate in the formation of the diamine. Piperidine with sulfur and cyclohexanone yielded 1,4-benzene-*bis*-1'-piperidine (**2**), but in lower yield. When 4-methylcyclohexanone and 3-methylcyclohexanone were heated with sulfur-morpholine reagent, they both yielded the same product, 2-methylbenzene-1,4-*bis*-4'-morpholine (**3**). In at least the case of 4-methylcyclohexanone, isomerization would have had to precede aromatization.

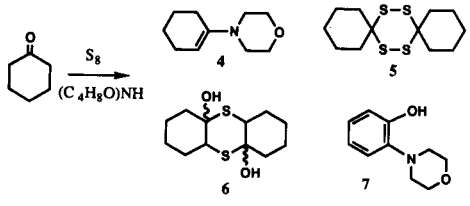
When the enamine derived from cyclohexanone and morpholine - 4-(1-cyclohexenyl)morpholine (**4**) - was used instead of cyclohexanone and dithio-*bis*-4-morpholine was used as the catalyst-reagent, either alone or with added morpholine, the sole isolated product was 1,4-benzene-*bis*-

4'-morpholine, and the yield was a maximum of 16%. Since no water was present, the improved yield of the product in comparison with the result form cyclohexanone supports the idea that the enamine is the essential intermediate in these various processes.

Since most or all of the experiments in which cyclohexanones and tetralones were aromatized to benzene or naphthalene derivatives have been carried out in vigorously boiling sulfur-amine, we desired to determine what would be formed from cyclohexanone under much milder conditions.

Accordingly, cyclohexanone was heated with sulfur-morpholine at 40-50° for 2.5 hours, after which the mixture was carefully fractionally distilled under reduced pressure. Not surprisingly, in addition to unreacted cyclohexanone, a mixture of four products was isolated: 4'-(1-cyclohexenyl)-morpholine (**4**), 7,8,15,16-tetrathiadispiro[5.2.5.2]hexadecane (**5**), the stereoisomeric mixture of dihydroxydithianes (**6**), and 2-hydroxyphenyl-4'-morpholine (**7**).

Scheme 1



Formation of the enamine **4** is consistent with and supports the concept of **4** as an essential intermediate. Compounds **5** and **6** are known [17a]. A compound analogous with **5** was isolated by Willgerodt [17b] in the mild reaction of acetone with ammonium polysulfide. It was called by him *duplodithioacetone* and was later shown to have the structure of 3,3,6,6-tetramethyl-1,2,4,5-tetrathiane [17a]. We proved the structures of **5** and **7** by comparison with authentic samples. Knowing the structures of the products did not help much to clarify the mechanisms operating, but they now appear to be consistent with the overall reaction scheme that will be presented in Paper 7 of this series. They confirm the fact that reactions of organic compounds with sulfur generally tend to be complex.

In a review, Mayer [18] stated that the first step in the Kindler Reaction requires elevated temperatures above 100°. In view of our finding that isomerization can proceed at room temperature, albeit slowly, we wished to determine whether the postulated intermediate step of enamine formation could indeed proceed rapidly at room temperature.

We found that, immediately upon mixing of equimolecular weights of cyclohexanone and morpholine, formation of the enamine begins to occur spontaneously and fairly rapidly. If no effort is made to remove the liberated water, enamine formation reaches a steady state; the composition of this equilibrium mixture varies with the amine used. Since the enamine has a strong absorption band at 6.08 μ, well separated from the band due to ketone function, the appearance of enamine can be observed directly in the infrared spectrometer. In the case of cyclohexanone-morpholine, the equilibrium is reached at approximately 20-30% conversion. Pyrrolidine and cyclopentanone react much more rapidly and with higher conversion at the steady state. Immediately upon mixing equimolecular weights of these two compounds at room temperature, a turbidity develops and two layers separate, one apparently enriched in enamine and the other containing more of the liberated water. When that reaction in tetrahydrofuran is monitored in the infrared spectrometer, the formation of enamine proceeds to the limit of approximately 75% within one to two hours. We conclude that enamine formation does not require high temperatures and may continue to completion with the further transformations under the conditions of the sulfur-amine reagent.

It is well known that enamines are very sensitive to steric influences that hinder the approach to coplanarity of the groups on nitrogen and the groups on the olefin. This fact helps to explain the difficulty in the isomerization process of moving the ketone group into proximity to a branch in the chain. Some of our more complex examples such as fused-ring systems (*e.g.*, 3-cholestanone) and bridged-ring systems (*e.g.*, camphor) are difficult to isomerize.

The example of water-free isomerization of 4'-(4-methyl-1-cyclohexenyl)morpholine by warming with one gram-atomic equivalent of sulfur at 100-110° presents an interesting situation. The progress of isomerization was evaluated after one hour by cooling, careful hydrolysis with dilute aqueous acid, and gas chromatographic analysis. The ratios of 4-:3-:2-methylcyclohexanones were 44:54:2. When 0.25 molecular equivalent of free morpholine was present in an otherwise similar experiment, the isomer ratios were 31:65:4, which changed to 35:58:6 in two hours of heating. Comparison was made with the reaction of 4-methylcyclohexanone heated with an equimolecular weight of morpholine and one gram-atomic weight of sulfur for one hour at 100-110°; here the ratio of isomers was 16:50:34. The purely statistical distribution would be 20:40:40. It is clear that steric factors operate more compellingly when the anhydrous enamine is isomerized without being able to equilibrate with ketone in the presence of some water. This observation is in accord with the sensitivity of enamines to steric influences. The isomerization also seems to be aided by a certain amount of free amine, even though there may be a small amount free even when the anhydrous enamine is isomerized, since the proposed mechanism involves the elimination and readdition of amine to the carbon skeleton.

Table V illustrates several effects of varying reaction conditions of 4-methylcyclohexanone in sulfur-morpholine reagent. Experiment 1 (Table V) shows that the isomerization proceeds slowly at room temperature: 17 hours at 25-30° produces almost the same isomer mixture as heating for 15 minutes at 80°; under these conditions, no 2-isomer showed up. In Exp. 3 (Table V), heating for 20 minutes at 85-90° finally resulted in the appearance of 6% of the 2-isomer. In the mechanism we visualize, a single cycle through one round of intermediates is sufficient to move the carbonyl group to the adjoining 3-position, while two cycles of isomerization would be necessary to produce the 2-isomer. After 30 minutes heating at 100°, an approach to a statistical distribution was observed (18:52:30), but the sterically favored 3-isomer was still greatly in excess of the hindered 2-isomer.

As little as 0.2 gram-atomic weights of sulfur can catalyze extensive isomerization of 4-methylcyclohexanone (Exp. 8, Table V) during heating for 15 minutes at 100°, but none of the 2-isomer was yet detected, and isomerization had not proceeded as far as in the comparable Exp. 4.

The effect of added water is shown in Exp. 9 (Table V), which is otherwise comparable with Exp. 7. Two molar equivalents of water had the effect of producing product ratios of 16:45:39, the nearest approach to a statistical distribution of isomers in Table V.

The reversibility of the isomerization was investigated in a limited series of experiments which started with 2-methylcyclohexanone (not included in Table V but to be compared with those results that started with 4-methylcyclohexanone). When the 2-methylcyclohexanone was heated for 15 minutes at 105-110° (compare with Exp. 4, Table V), the recovered ketonic mixture had product ratios of 4-:3-:2- of 6:24:70 in contrast to 25:58:17 starting with 4-methylcyclohexanone. During one hour at 105-110°, the isomer ratio reached 17:44:39 compared with 17:52:30 starting with 4-methylcyclohexanone. It is clearly more difficult to move the ketone group away from an adjoining methyl branch than it is to move it from a more open position.

Steric factors are also apparent in the isomerization of 4-*t*-butylcyclohexanone: even after eight hours of heating at 120° the 2-isomer did not appear and the 4-:3-isomer ratio was 76:24. After only one hour's heating the ratio was 79:21 and it leveled off at 76:24 after two hours and did not appear to change after that. It appears that in this case even the usually favored 3-position is subject to considerable steric inhibition.

3-Cholestanone was chosen as an example of an important derivative of a natural product and also typical of many polycyclic fused ring systems. Because of the lower solubility of this large molecule, the ketone:morpholine:-gram-atomic weight of sulfur was altered from the usual 1:1:1 to 1:4:1. Heating at 130-135° for four hours represented an effort to overcome the steric inhibition expected at positions 1 and 4. The liquid chromatographic separation of the resulting product mixture yielded 19.7% of recovered 3-cholestanone, 19.7% of 2-cholestanone, and 4.4% of a product that was identified as $\Delta^{4,5}$-3-cholestenone. None of the other two hoped-for isomers (1- and 4-cholestanone) was isolated.

Isomerization of the Carbonyl Function in Cyclopentanones.

In view of the ease of formation of enamines from cyclopentanone, as compared with cyclohexanone (*v.s.*), we cor-

Table V

Isomerization of 4-Methylcyclohexanone by Sulfur and Morpholine

Expt. No.	Reactant Ratios 4-MCH [a] : Morpholine: Sulfur [b]	Reaction Time, Hours	Reaction Temp, ° C	% Yield	% of Isomers 4-MCH	3-MCH	2-MCH
1	1 : 2 : 1	17	25-30	18	45.3	54.7	0
2	1 : 2 : 1	0.25	80	21.5	45.8	54.2	0
3	1 : 2 : 1	0.33	85-90	20.5	27.8	65.8	6.3
4	1 : 2 : 1	0.25	100	17	25.1	58.1	16.8
5	1 : 2 : 1	0.5	100	14.5	17.4	52.2	30.4
6	1 : 2 : 1	1.5	100	14	19.3	53.5	27.1
7	1 : 2 : 1	4.0	100	12.5	21.8	52.2	25.8
8	1 : 2 : 1/5	0.25	100	16.5	58	42	0
9	1 : 2 : 1:2(H_2O)	4	100	6	16	45.4	38.5

[a] MCH = methylcyclohexanone.
[b] Sulfur expressed in gram-atomic weights.

rectly anticipated that isomerization of methylcyclohexanones would proceed rapidly. 3-Methylcyclopentanone was heated with 1:2:1 ratio of ketone:amine:sulfur gram-atomic weights for 50-70° for only ten minutes to produce an isomer ratio of 3-MCP:2-MCP of 75:25.

The stiff bridged ketone, (+)-camphor, was stubbornly resistant to isomerization and appeared not to have changed at all under most of the reaction conditions that had previously been effective with other simpler ketones. In the typical ratio of 1:2:1 for 115-125° for 24 hours, we estimated that only 5% of the (+)-camphor had been converted into (-)-epicamphor. [It is interesting to note that when the carbonyl group is moved to its adjacent carbon atom, the resulting epicamphor is *almost but not quite a mirror image of the camphor molecule*, with the exception that the bridgehead methyl group is on the other bridgehead carbon. Because of this relationship, the circular dichroism spectra of the two camphor isomers are opposite in sign, and the compounds are very difficult to separate, as might be expected for two compounds which are close to being enantiomers.] We were able to effect the estimation of the isomer mixtures by chemical separation of derivatives, the 2,4-dinitrophenylhydrazones. It was also found that pyrrolidine was more effective than morpholine in producing isomerization: replacement of morpholine with pyrrolidine at 95-97° for 25 hours produced a ratio of 84:16 of camphor:epicamphor.

When even more strenuous conditions were used in an effort to force further conversion (130-135° for 37.5 hours), chemical reduction took place, yielding a ratio of 50 camphor:42 bornyl mercaptan:8 isobornyl mercaptan. Still more drastic heating at 145° for 39 hours only shifted this ratio to 34:56:10. These results are consistent with the postulated three-ring sulfur heterocyclic intermediate, which would add the strain of a small, reactive intermediate to the strain of the rigid bridged ring system.

Other Applications of the Isomerization Reaction.

The widespread occurrence of carbonyl compounds in nature suggests that the application of sulfur-amine isomerization could greatly enhance the numbers of interesting compounds derivable from natural sources. For example natural muscone [(-)-3-methylcyclopentadecanone] could in principle be converted into its 2-, 4-, 5-, 6-, 7- and 8-isomers, some of which would probably retain their optical activity. In this simple way, the correlation of structure-activity relationships might be done systematically in families of ketones (and their derivatives) in situations where the direct synthesis of all the isomers would be difficult or impossible.

Studies with Tetralones.

As mentioned above, we carried out a number of experiments designed to show the orientation of the newly introduced amino group when 1- and 2-tetralone derivatives were heated with sulfur and secondary amines. We confirmed that the reaction of 1-tetralone, previously investigated by Horton and van den Berghe [15] (*v.s.*), when heated with morpholine and sulfur, yielded 2-naphthalene-(4'-morpholine) (**8**). Two further experiments were carried out with 1-tetralone. In the first, piperidine replaced morpholine and the product was 2-naphthalene-1-piperidine (**9**). When pyrrolidine replaced morpholine, the product was 2-naphthalene-1-pyrrolidine (**10**). The same three products **8**, **9**, **10** also resulted when 2-tetralone was heated with the sulfur-amine reagent containing, respectively, morpholine, piperidine, and pyrrolidine. 7-Methyl-1-tetralone was heated with sulfur-amine reagents containing, respectively, morpholine, piperidine, and pyrrolidine. The resulting products of these three reactions were, respectively, 7-methylnaphthalene-2-(4'-morpholine) (**11**), 7-methylnaphthalene-2-(1-piperidine) (**12**), and 7-methylnaphthalene-2-(1-pyrrolidine) (**13**). In order to verify the correct orientation of the entering amine group, we also prepared 6-methylnaphthalene-2-(4'-morpholine) (**14**) and 6-methylnaphthalene-2-(1-pyrrolidine) (**15**). These isomers differed from those isolated from the substituted methyl-1-tetralones. It seems therefore proven beyond question that, starting with either 1- or 2-tetralone derivatives, the amine group consistently enters the adjacent 2-position. One may conclude from this that a mechanism consistent with the isomerization required for this result involves an intermediate probably involving only the 1 and 2 positions of the nucleus. We have postulated that this intermediate is a small ring containing a bridging sulfur atom.

EXPERIMENTAL

Morpholine was purified by refluxing for twenty-four hours over sodium and distillation; the process was repeated. Sulfur was purified by extraction with cyclohexane in a Soxhlet extractor and collected after crystallization. Carbonyl compounds were checked for homogeneity by gas chromatographic methods and checked for identity by unambiguous synthesis or by preparation of derivatives. Infrared absorption measurements for the rate studies with the diphenylpropanones were made in the Perkin-Elmer Model 21 Infrared Spectrometer with sodium chloride or lithium fluoride prisms. The infrared spectra were determined in Perkin-Elmer Model 137-B or 137-G instruments. The gas chromatographic analyses of mixtures of isomeric ketones and aldehydes were carried out in an F and M Scientific Corporation Model 500 Linear Programmed High Temperature Gas Chromatograph. The column was 1/8 inch × 24 feet, stainless steel, packed with 5 percent Bentone 34 and 5 percent didecyl phthalate on 60-70-mesh Chromosorb-W, acid washed. Such a column has been used for the separation of isomeric alkylbenzene and chloroacetophenones [19]. We thank Dr. Jack Gill for suggesting this type of column and providing one for our use. Melting points were recorded in open Pyrex capillaries in a circulating oil bath with total immersion of stem. PMR spectra were measured in a Varian Model A-60 NMR Spectrometer. Elemental analyses were

determined by A. Bernhardt, Mühlheim, Ruhr, West Germany, or by Midwest Microlab, Indianapolis, Indiana, or by Ms Joanna Dickey at Indiana University. Thin layer chromatography was carried out on silica-coated glass plates, with elution by benzene:ethyl acetate (95:5%).

Isomerization of Phenylacetone.

When phenylacetone was warmed in morpholine containing one gram-atomic equivalent of sulfur per mole of ketone at 70°, and the infrared absorption at 5.82 μ was observed in aliquot samples, a gradual decrease in the intensity of the absorption due to the unconjugated carbonyl group in phenylacetone was observed. Simultaneously, a new absorption band at 5.92 μ appeared and increased in intensity. When the mixture was taken up in dilute aqueous acid and the ketones isolated, the mixture was found to consist of phenylacetone and propiophenone (12.9% and 3.3%, respectively, recovered) in addition to the expected Kindler product, 3-phenylpropiothiomorpholide.

Reaction of 4-Phenyl-1-(*p*-chlorophenyl)-1-butanone with Morpholine and Sulfur.

The Grignard reagent prepared from 3-phenyl-1-bromopropane in ether was allowed to react with *p*-chlorobenzaldehyde. The purified carbinol was oxidized with aqueous potassium dichromate-sulfuric acid at 60° to yield 4-phenyl-1-(*p*-chlorophenyl)-1-butanone, mp 53.0-53.5°. This ketone (6.47 g, 0.025 mole) was heated at gentle reflux in 12.5 ml of dry morpholine containing 0.8 g (0.025 g-atomic weight) of sulfur for eight hours. The morpholine was largely removed under reduced pressure, the residue gas was treated with hot, dilute hydrochloric acid, and the neutral product was chromatographed on a column of acid-washed Merck alumina. The starting ketone was recovered in 28% yield. A second ketone eluted next in 0.216 g (3.3%) yield, mp 85.5-86.0°. The latter product was shown to be identical with 4-phenyl-1-(*p*-chlorophenyl)-4-butanone (**16**). A second isomeric ketone was eluted from the column with cyclohexane-ether (10:1) to yield 0.48% of ketone **17**, mp 62.5-63.5° after sublimation and two recrystallizations from ethanol. It was shown to be 4-phenyl-1-(*p*-chlorophenyl)-2-butanone (**17**), identified by comparison with a synthetic sample, prepared as described below. The fourth isomer - the 3-butanone isomer - was not found, although it may have been present in small amounts.

Ketone **16** was synthesized by the Grignard reaction of 3-(*p*-chlorophenyl)-1-propanemagnesium bromide with benzaldehyde and the oxidation of the resulting carbinol with acidic potassium dichromate. The product recrystallized from aqueous ethanol melted at 83-84.5° and was identical with the product described above from the isomerization reaction.

Anal. of **16**. Calcd. for $C_{16}H_{15}ClO$: C, 74.26; H, 5.85. Found: C, 74.40; H, 6.09.

Ketone **17** was synthesized by a similar Grignard synthesis starting with *p*-chlorobenzyl bromide and β-phenylpropionyl chloride, and subsequent oxidation of the carbinol. 4-Phenyl-1-(*p*-chlorophenyl)-2-butanone (**17**), mp 62-63° from 50% aqueous ethanol, was identical with the last isomer isolated from the isomerization described above.

Reaction of 1,4-Diphenyl-1-butanone with Sulfur and Morpholine.

1,4-Diphenyl-1-butanone was prepared in 77% yield by oxidation of 1,4-diphenyl-1-butanol as described by R. Stoermer and F. Schenk [*Ber.*, **61B**, 2320 (1928)]. When 22.4 g (0.10 mole) of this ketone was heated with 3.2 g (0.10 g-atomic weight) of sulfur for eight hours in gently refluxing morpholine, the ketonic material was isolated by removal of the morpholine under reduced pressure, acidic extraction of the oil, and chilling of the oil to recover 30% of the starting ketone, mp 54-55°. A basic product was recovered from the acidic washings of product oil. After chromatographic purification on Merck acid-washed alumina, a yield of 0.326 g (1.1%) of 3-(*N*-morpholino-2,5-diphenylfuran (**18**) was obtained. The product **18** was identified by comparison with a synthetic specimen synthesized in 75% yield by the ring closure of dibenzoyl-*N*-morpholinoethane in the presence of sulfuric acid and acetic anhydride according to the procedure of R. E. Lutz, P. S. Bailey, and N. H. Shearer, Jr., [*J. Am. Chem. Soc.*, **68**, 2224 (1946)].

Anal. of **18**. Calcd for $C_{20}H_{19}NO_2$: C, 78.65; H, 6.28; N, 4.59. Found: C, 78.29; H, 6.20; N, 4.59.

Rates of Isomerization of 1,3-Diphenyl-2-propanone (or 2-DPP).

1,3-Diphenyl-2-propanone (Eastman commercial dibenzyl ketone) was purified by distillation under reduced pressure and recrystallization from ether-cyclohexane (1:1), mp 39.0-39.5°. 1,3-Diphenyl-1-propanone was prepared by oxidation with acidic dichromate of 1,3-diphenyl-1-propanol, which was made by Grignard synthesis from 2-phenylethylmagnesium bromide and benzaldehyde. When recrystallized from ethanol it had mp 71.4-72.0° (reported 72° by H. Nomura [*Bull. Soc. Chim.*, **37**, 1245 (1925)]).

For the rate studies, calibration curves were made up from known mixtures of the two isomeric ketones in dry morpholine; these were scanned in a calibrated sodium chloride cell in a Perkin-Elmer Model 21 Infrared Spectrometer in the region of 5.5-6.0 μ with either a sodium chloride or lithium fluoride prism. Straight-line Beer-Lambert law plots for the two ketones in the range of 30-85% absorption were used as references for analysis.

When rates were measured in dry morpholine, 1.5-ml aliquot samples were made up to the stated concentrations at room temperature (where reactions were negligibly slow), heated at the stated temperature and time, then cooled to room temperature and measured in the carbonyl absorption region in the calibrated cell and compared with the reference standards. In those runs which included water in the morpholine, 1.0-ml aliquots were diluted with 5.00 ml of carbon tetrachloride and treated with 0.3-0.5 g of anhydrous sodium sulfate. The filtered solution was observed in the infrared cell and compared with similarly treated reference solutions.

Rate constants for disappearance of 1,3-diphenyl-2-propanone were calculated from simple first order kinetic equations. Tables I and II and III collect the data from representative runs. Footnotes refer to equations used in some of the calculations. Table II and III show the effects of water upon the rates of isomerization.

Attempted Isomerization of 1,3-Diphenyl-2-propanone in *N*-Methylmorpholine and Sulfur.

N-Methylmorpholine was substituted for morpholine in several experiments carried out otherwise exactly as in the foregoing paragraphs. For example, with ketone:amine:sulfur (gram-atomic weight) mole ratios of 1:2:1, heated at 86° for 11 hours, there was no trace in the spectrometer of an absorption corresponding to 1,3-diphenyl-1-propanone. Reference experiments showed that as little as 2.5% of the conjugated isomer could have been readily observed.

A similar experiment with *N*-methylmorpholine and the addition of one part of water in four parts of amine likewise showed no trace of isomerization.

An attempt was made to carry out a typical Kindler-like synthesis with acetophenone, *N*-methylmorpholine, and sulfur at 84.5° for 24 hours. Although it was clear that a thiomorpholide would not be expected, it was of interest to ascertain whether some other derivative(s) of phenylacetic acid might be produced. No such product was detected.

Attempted Reactions Using Inorganic Bases and Polysulfides.

1,3-Diphenyl-2-propanone was heated in dioxan-water solution with sodium tetrasulfide with no sign of any isomerization of the carbonyl group. The same ketone was heated also with ethanol-water solutions of sodium tetrasulfide, and in strong sodium hydroxide containing sodium tetrasulfide. In sharp contrast, the combination of sodium tetrasulfide in aqueous morpholine caused ready isomerization, but sodium tetrasulfide in aqueous *N*-morpholine did not lead to any isomerization.

Isomerization of 4-Heptanone in Morpholine-Sulfur Solutions.

A standardized procedure was used: 4-heptanone was heated with morpholine and sulfur in the ratio of 1 mole ketone: 2 moles amine: 1 gram-atomic weight of elemental sulfur for varying periods of time at 100°. The cooled samples were diluted with 6*N* hydrochloric acid and warmed gently to hydrolyze the enamines (and possibly other intermediates) back to ketones. The solutions were extracted with ether, the ether was dried, and distillation under reduced pressure in a short-path still was used to separate the volatile ketones from high-boiling byproducts. The mixture of carbonyl isomers was analyzed by gc on a column of Bentone-34 and 5% didecyl phthalate on 60-70 mesh Chromosorb-W (acid washed) [19]. The percentages of isomers were determined by a graphic method which was calibrated by means of known mixtures of the pure isomers. The changing distributions of isomers as a function of reaction time are shown in Table IV. Experiment 4 includes a comparison run starting with heptanal.

Isomerization of 2,6-dimethyl-4-heptanone (Diisobutyl Ketone).

Commercial diisobutyl ketone (Union Carbide) was freed from a small amount of impurity with long retension time in gc analysis, by purification through the crystalline semicarbazone. The reactant ratios were 1 mole ketone:2 moles morpholine:1 g-atomic weight of sulfur; the temperature was 120-125°; times varied from one hour to 48 hours. The isomer which formed was 2,6-dimethyl-3-heptanone (isopropyl isoamyl ketone) and was available from commercial sources as a reference standard. The results are presented in the discussion.

Isomerization of 6,10-dimethyl-2-undecanone.

The commercial hexahydropseudoionone (Aldrich Chemical) contained 6% of an impurity which was not identified but which appeared unchanged among the products of isomerization. At 125-139° in the usual 1:2:1 ratios of ketone:morpholine:sulfur reaction mixture for two hours, the products (21% recovered) showed in the gc analysis a ratio of 49:10:37:3.5 of starting ketone:Ketone **A**:Ketone **B**:inert impurity, which was mentioned above in the commercial starting ketone. No aldehydic proton was seen in the pmr spectrum. Further heating up to four hours did not significantly change the isomer ratios. The retention times of the four compounds in the product mixture were: 25.8 minutes: 22.5 minutes: 17.4 minutes. The slowest moving band was starting 2-isomer; the ketones **A** and **B** are probably the 3- and 4-ketonic isomers, respectively. The missing isomers are the aldehyde and probably the 5-ketone, based upon the experiences with other branched chain ketones, in which it was observed that the isomerization process finds it difficult or impossible to move the ketone group to the carbon next to a chain branch.

The Amination-Aromatization of Tetralones with Sulfur and Secondary Amines.

The series of reactions with both 1- and 2-tetralones followed a general procedure as follows: one molecular equivalent of the tetralone was heated with 1 to 2 molecular equivalents of a secondary amine (either morpholine, or piperidine, or pyrrolidine) and 1 gram-atomic equivalent of sulfur in a reflux apparatus in an oil bath at 135° for eights hours. The reaction mixture was cooled, taken up in 12% hydrochloric acid, clarified with charcoal, and the amine was precipitated with concentrated ammonium hydroxide. The aminonaphthalene derivatives are described individually below.

2-Naphthalene-4'-morpholine (**8**), mp 87-88°, resulted from heating 2-tetralone with morpholine. It is the same product previously described by Horton and van den Berghe [15a]; its structure was verified by repeating their experiment with 1-tetralone and showing that both products were identical.

2-Naphthalene-1-(1-piperidine) (**9**) resulted from the reaction of either 2-tetralone or 1-tetralone with piperidine and sulfur; mp 58-59°. The *picrate* melted at 190-191°, cor. An authentic sample was synthesized by the Bucherer reaction between 2-naphthol and piperidine.

Anal. of **9**. Calcd. for $C_{15}H_{17}NO$: C, 85.26; H, 8.11; N, 6.63. Found: C, 85.33; H, 8.12; N, 6.63.

Anal. of **9.picrate**. Calcd. for $C_{21}H_{20}N_4O_7$: C, 57.27; H, 4.58. Found: C, 57.52; H, 4.61.

2-Naphthalene-1-(1-pyrrolidine) (**10**) resulted from the reaction of either 1- or 2-tetralone with pyrrolidine. An authentic sample of this base was synthesized by means of the Bucherer reaction of 2-naphthol with pyrrolidine, mp 90° from ethanol. The *picrate* had mp 152-153° from ethanol.

Anal. of **10**. Calcd. for $C_{14}H_{15}NO$: C, 85.24; H, 7.66; N, 7.10. Found: C, 85.27; H, 7.63; N, 7.05.

Anal. of **10.picrate**. Calcd. for $C_{20}H_{18}N_4O_7$: C, 56.34; N, 4.25. Found: C, 56.35; H, 4.21.

7-Methylnaphthalene-2-(4'-morpholine) (**11**) was formed by the reaction of 7-methyl-1-tetralone with sulfur and morpholine, mp 125° from ethanol-water. The **11.picrate** had mp 182° from ethanol. The 7-methylnaphthalene-1-tetralone was synthesized by the cyclization of δ-(*p*-tolyl)butyric acid with polyphosphoric acid.

Anal. of **11**. Calcd. for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.16; H, 7.68; N, 6.01.

Anal. of **11.picrate**. Calcd for $C_{21}H_{20}N_4O_8$: C, 55.26; H, 4.42. Found: C, 55.31; H, 4.43.

7-Methylnaphthalene-2-(1-pyrrolidine) (**13**) resulted in the reaction of the 7-methyl-1-tetralone with sulfur in pyrrolidine; mp 110.5-111° after two recrystallizations from ethanol. The **13.picrate** had mp 175° from ethanol.

Anal. of **12**. Calcd. for $C_{15}H_{17}N$: C, 85.26; H, 8.11; N, 6.63. Found: C, 85.07; H, 8.05; N, 6.71.

Anal. of **13-picrate**. Calcd. for $C_{21}H_{20}N_4O_7$: C, 57.27; H, 4.58. Found: C, 57.27; H, 4.48.

6-Methylnaphthalene-2-(1-pyrrolidine) (**15**) was synthesized for comparison with the product obtained from 7-methyl-1-tetralone

as a possible product. It was prepared by means of a Bucherer synthesis from 6-methyl-2-naphthol and pyrrolidine. Its mp was 83° after two recrystallizations from ethanol, and was clearly not identical with the product obtained from 7-methyl-1-tetralone. The **15.picrate** had mp 133° from ethanol.

Anal. of **15**. Calcd. for $C_{15}H_{17}N$: C, 85.26; H, 8.11; N, 6.63. Found: C, 85.28; H, 8.06; N, 6.70.

Anal. of **15.picrate**. Calcd. for $C_{21}H_{20}N_4O_7$: C, 57.27; H, 4.58. Found: C, 57.35; H, 4.46.

1,4-Benzene-di-4′-morpholine (**1**) from Cyclohexanone, Morpholine, and Sulfur.

Cyclohexanone (9.34 g, 0.096 mole), morpholine (87.0 g, 1.0 mole), and sulfur (3.2 g, 0.1 gram atomic weight) were heated together under reflux at 130-135° for eight hours, then excess morpholine was removed under reduced pressure, and the mixture was neutralized with sodium hydroxide. The product crystallized and was purified by recrystallization from ethanol. The purified product, mp 194-195°, was identified as 1,4-benzene-di-4′-morpholine in 2.13 g (9%) yield. The *dipicrate* melted at 196° with darkening. An authentic sample was synthesized from *p*-phenylenediamine and *bis*-(2-chloroethyl) ether. It had mp 196° and formed an identical *dipicrate*. Both specimens of the free base gave the deep blue color characteristic of *p*-phenylenediamine derivatives when an aqueous solution was treated with one drop of aqueous ferric chloride solution. When, instead of elemental sulfur, 0.05 mole of dithio-*bis*-4,4′-morpholine was used in an otherwise similar experiment as reagent, the same product diamine was obtained in 7.4% yield. When the same sulfur reagent was used but with 0.1 mole the yield of diamine rose to 12.4%.

Anal. of **1**. Calcd as $C_{14}H_{20}N_2O_2$: C, 67.72; H, 8.11; N, 11.28. Found: C, 67.94; H, 8.21; N, 11.36.

Anal. of **1.dipicrate**. Calcd. as $C_{26}H_{26}N_8O_{16}$: C, 44.20; H, 3.71; N, 15.86. Found: C, 44.77; H, 3.66; N, 15.86.

1,4-Benzene-di-1′-piperidine (**2**) from Cyclohexanone, Piperidine and Sulfur.

In a similar experiment to the one described above with morpholine, a yield of 1% of **2** was obtained. It had mp 108-109°; **2.dipicrate** had mp 202-203°.

Anal. of **2**. Calcd. for $C_{16}H_{24}N_2$: C, 78.64; H, 9.90; N, 11.46. Found: C, 78.93; H, 9.79; N, 11.51.

Anal. of **2.dipicrate**. Calcd. for $C_{28}H_{30}N_8O_{14}$: C, 47.87; H, 4.30. Found: C, 47.92; H, 4.27.

2-Methylbenzene-1,4-di-4′-morpholine (**3**) from 3-Methylcyclohexanone.

When 0.1 mole of 3-methylcyclohexanone was heated with 0.1 g-atomic weight of sulfur in 50 ml of refluxing morpholine for 11 hours, the amine product was isolated in a procedure similar to that described for **1**. Chromatography on Merck acid-washed alumina, eluted with cyclohexane-ether, yield 1.3% of **3**, mp 104-105.5°, raised to 107-107.5° by recrystallization from ethanol. The identification was by synthesis from *o*-toluidine by *p*-nitration, reduction to 2-methyl-1,4-benzenediamine with zinc dust, and conversion to the *bis*-tertiary amine with *bis*-2-chloroethyl ether and aqueous potassium hydroxide. The product obtained in this sequence had mp 107-108° and its mp was not depressed when the two samples were mixed.

Anal. of **3**. Calcd. for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.69. Found: C, 68.62; H, 8.31; N, 10.89.

2-Methylbenzene-1,4-di-4′-morpholine (**3**) from 4-Methylcyclohexanone.

When 4-methylcyclohexanone was used instead of 3-methylcyclohexanone in a procedure similar to the previous one, the product was again **3**, mp 107-108° in 0.76% yield. No depression of mp occurred when the samples from this and the preceding experiment were admixed.

1,4-Benzene-di-4′-morpholine (**1**) from 4′-(Cyclohexenyl)-morpholine (**4**), Morpholine, and Sulfur.

The enamine **4** (0.05 mole) was heated with 0.05 g-atomic weight of sulfur in 25 ml of gently refluxing morpholine for 1.5 hours. The product was isolated as in the preceding experiments; it was identified as **1** in 16% yield. The same base **1** was also obtained when **4** was heated with dithio-*bis*-4,4′-morpholine.

Reactions of Cyclohexanone with Morpholine and Sulfur under Mild conditions.

A mixture of cyclohexanone (196 g, 2 moles), sulfur (32 g, 1 g-atomic weight), and morpholine (174 g, 2 moles) was stirred at 40-50° for two hours, after which the mixture was fractionally distilled under reduced pressure (18-25 Torr). The following fractions were collected:

Fraction 1: 98.6 g, bp 25-47°, consisted of three components, as determined by gc and infrared: cyclohexanone, morpholine, and the enamine **4**.

Fraction 2: 42.3 g, bp 47-51°, was cyclohexanone.

Fraction 3: 48 g, bp 51-100°, contained cyclohexanone and its enamine **4**, and in addition a colorless crystalline produt separated, which, after recrystallization from ethanol, had mp 131-131.5°, and was identified as having the structure 7,8,15,16-tetrathiadispiro[5.2.5.2]hexadecane (**5**), previously described by Fredga [17a]. It had uv λ max 227 nm (ε 6.7) and 266 nm (ε 255).

Fraction 4: 72 g, bp 100-200°, deposited a solid (13 g), which was separated and recrystallized from ethanol to yield a colorless, crystalline product, mp 128.5-129°. It was identified as 2-hydroxyphenyl-4′-morpholine (**7**) by elemental analysis and direct comparison with an authentic specimen made by the procedure of Campbell and Reed [20].

Anal. of **7**. Calcd. for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.92; H, 7.54; N, 7.66.

Fraction 5: the liquid portion from Fraction 4 weighed 59 g. When attempts were made to redistill the liquid under reduced pressure, a solid weighing 0.8 g separated. When recrystallized from ethanol, it had mp 175.5-176° and was identified by elemental analysis as a stereoisomeric mixture of dimers of cyclohexanone-2-thiol, or dihydroxyperhydrothianthrene (**6**), previously described by Milligan and Swan [21]. A sample obtained from Swan [we express our thanks to Dr. John Swan and the C.S.I.R.O. of Melbourne, Australia] showed an infrared spectrum that was superposable upon that of product **6**; the Swan sample had a mp of 155-164°. The difference in mp's is not surprising in view of the fact that the structure would be expected to exist as a labile mixture of diasteroisomers.

Anal. of **5**. Calcd. for $C_{12}H_{20}O_2S_2$: C, 55.35; H, 7.69; S, 24.62. Found: C, 55.42; H, 7.80; S, 24.21.

Isomerization of the Enamine, 4-Methylcyclohexenyl)-4′-morpholine, with Sulfur.

The enamine derived from 4-methylcyclohexanone and morpholine by Stork's procedure [22] was heated with sulfur in the ratio of 1 mole: 1 g-atomic weight for one hour at 100-110°. The cooled mixture was worked up as previously described with aqueous 6 *N* hydrochloric acid, extracted with ether, distilled under reduced pressure in a short-path still, and analyzed by gc. The mixture of three isomeric methylcyclohexanones had the ratios of 4-:3-:2-isomers of 44:54:2. Another experiment was carried out identically except for the addition of 0.25 molar proportion of morpholine. After one hour of heating the ratio of isomers was 31:65:4. In a third experiment, the ratios of enamine:S:morpholine were 1:1:1; after the heating for one hour at 100-110° and workup, the ratios of isomers were 16:50:34. The total recovery of ketone was 22.3%.

Attempted Isomerization of 4-Methylycyclohexanone Using Thio-*bis*-4'-morpholine.

Dithio-*bis*-4'-morpholine was shown previously to be an effective catalyst for the isomerization of 4-methylcyclohexanone, either alone or, more effectively, when free morpholine was present. In a series of experiments [by Dr. Donald Wiesler, whose contribution we acknowledge with thanks] to determine whether thio-*bis*-4'-morpholine would also function as a catalyst for the isomerization of 4-methylcyclohexanone, it was found that the *mono*-thio-*bis*-sulfenamide was ineffective. We conclude therefrom that a minimum of two sulfur atoms is essential for the occurence of isomerization; we consider this an important observation with regard to the understanding of the mechanisms involved.

Isomerization of 4-*t*-Butylcyclohexanone with Morpholine and Sulfur.

4-*t*-Butylcyclohexanone (Aldrich Chemical) showed by gc analysis the presence of 3.5% of an impurity having a retention time of 37.4 minutes compared with 27.5 minutes for the 4-ketone. The impurity appeared not to take part in the isomerization experiment, and showed up in every run as the easily identified last peak to appear. Several experiments were carried out at 120° for one hour with reactant ratios of 1:1:2 of ketone; S, and morpholine. Worked up in the usual way, the ketonic products showed three principal peaks with retention times of 25.5 minutes, 28.5 minutes, and 38.4 minutes, with a very small peak at 20.4 minutes. The slowest peak was the inert minor ingredient in the ketone; the 28.5 minute peak corresponded to the starting 4-isomer. We believe that the 25.5 minute peak was probably the 3-isomer. The 2-isomer, if represented by the very small blip, would have been formed in very small yield, too small to identify.

Isomerization of 3-Cholestanone with Morpholine and Sulfur.

A mixture of 1.93 g (0.005 mole, mp 129-139°), of 3-cholestanone, 1.74 g (0.02 mole) of morpholine, and 0.15 g (0.005 g-atomic weight) of sulfur was heated with stirring at 135-138° for four hours. The cooled mixture was warmed briefly with 6 *N* hydrochloric acid then the organic products were extracted with ether and chromatographed on a silica gel column with cyclohexane, then cyclohexane-benzene, and later benzene-chloroform as eluants. Some of the fractions were rechromatographed on Woehlm Nearly Neutral Alumina. One product was identified as 2-cholestanone (0.6 g), mp 127-129°, $[\alpha]_D^{22}$ +46° (c 1.472 chloroform) for which the reported [23] properties are mp 131°, $[\alpha]_D^{22}$ +48.4° (c 1.09 chloroform). A mixture of this ketone with the starting 3-cholestanone melted at 100-117°. Thin-layer chromatography on silica gel with benzene-ethyl acetate (95:5) indicated that some 3-cholestanone was still present in the 2-isomer, accounting for its slightly low mp. Another fraction from the main product was recrystallized from ethanol and had a mp of 80.5-81.5°. Its ultraviolet spectrum in 95% ethanol showed an α,β-unsaturated carbonyl chromophore (λ max 242 nm, log ϵ 4.22); the reported mp [23] for $\Delta^{4,5}$-3-cholestenone was 80-81° and the ir was identical with that which we observed with this product.

Isomerization of (+)-Camphor into (-)-Epicamphor.

(+)-Camphor (Eastman Kodak) was heated with morpholine and sulfur in the usual 1:2:1 ratio at 115-125° for 24 hours in a sealed glass tube. (A preliminary experiment had indicated that the camphor was unchanged in only two hours of heating.) After the usual workup with aqueous acid, extraction with ether, and sublimation, a product was isolated which gc analysis showed to consist of 95% camphor and 5% epicamphor. A third experiment with pyrrolidine substituted in place of morpholine was heated for 25 hours at 95-97°; in this case the ketonic product contained 84% camphor and 16% epicamphor. A measurement of the optical rotation of the sublimed mixture of ketones in this third experiment showed $[\alpha]_D^{29}$ +28.9° (c = 1 ethanol). The reported rotations for (+)-camphor and (-)-epicamphor are, respectively, +42.1° and −40.3°. The observed rotation is therefore consistent with the gc analysis of 16% epicamphor. The identification of the epicamphor by derivatization was difficult by the almost mirror-image relationship of the two ketones, but was achieved by chromatography on a Florisil column of the 2,4-dinitrophenylhydrazones, with cyclohexane-benzene-chloroform as eluants. The derivative of epicamphor moved more rapidly than that of the camphor. The pmr of the products after separation from the column showed slight but definite differences for the methyl hydrogens: 8.88, 8.98 and 9.08 τ for the epicamphor-DNP derivative and 8.86, 9.00, and 9.18 τ for the camphor-DNP. The epicamphor-DNP was hydrolyzed with dilute hydrochloric acid containing levulinic acid [25] and oxalic acids to liberate the epicamphor, which, after sublimation at 60°, had a mp of 167-172°. The ORD spectrum of this product was almost a mirror image of the ORD of (+)-camphor, with a negative minimum at 310 nm and a positive maximum at 270 nm.

Under forcing conditions in which (+)-camphor was heated with sulfur and pyrrolidine at 130-145° for times up to 39 hours, the combined organic reaction products were sublimed and analyzed by liquid chromatography on silica gel, monitored with tlc on silica gel, the principal products isolated were recovered camphor, a trace of camphene, bornyl mercaptan, and isobornyl mercaptan. For comparison, a specimen of bornyl mercaptan was prepared by the method of Haraszti [26], and a specimen of isobornyl mercaptan was made by the method of Subluskey and King [27]. While these products consisted mainly of the claimed isomer, each was contaminated with smaller amounts of the other. Both main synthetic products were purified by tlc and proved identical with the byproducts of the forced isomerization reaction of (+)-camphor. An even more vigorous treatment of camphor at 190° and 40 hours produced as the main product a somewhat low-melting bornyl disulfide, mp 177-178.4°. A sample for comparison was prepared by the iodine oxidation of bornyl mercaptan; it had a mp of 190-192°.

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