1957

Preparation of thiochalcone from thioacetophenone

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PREPARATION OF THIOCHALCONE FROM THIOACETOPHENONE

A Thesis

Presented to

the Faculty of the Department of Chemistry

College of the Pacific

In Partial Fulfillment

of the Requirements for the Degree

Master of Science

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by

Thomas Joseph Reilly

August 1957

APPROVED BY

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ACKNOWLEDGEMENTS

I wish to express my gratitude to Dr. Cobb for his guidance and to Dr. Wadman for criticizing and correcting this thesis.

CHAPTER I

INTRODUCTION

Since time immemorial man has sought various methods and articles for adornment, the most popular being the coloring of cloth. The colorings in plants were used extensively and this use led chemists to the discovery of their chemical constitution. The main coloring matters in plants have been found to be the flavones, which produce the light colors, and the anthocyanins, which produce the dark. They are also good tanning agents as they rid the hides of undesirable odors. This has been amplified by my research director in his doctoral thesis of natural tannins,[10] from which this thesis is an outgrowth.

Recently flavones, anthocyanins (and other dephenylated compounds of this class, the chromanones) have attained practical significance as heart stimulants,[12] sex modifiers in plants,[19] and anthelmintics.[20] It is interesting to consider what the changes in biochemical properties might be occasioned by small changes in the molecular structure. It might be also possible that the dyes would give a deeper color. Experimentation is the only means of answering such questions. Among the innumerable ways of altering the structure, the chemistry of analogy, that is the substitution of one atom for another having similar properties, was chosen.

The particular analogy chosen was based on the fact that when acetophenone and benzaldehyde are condensed by a

base or anhydrous hydrogen chloride they form benzal-acetophenone, commonly called chalcone I. This reaction is the parent reaction in the formation of flavones, which in general terms is the condensation of a thioketone with an aldehyde. The simplest of the flavones is flavone II, which is prepared in three stages. Ortho-hydroxyacetophenone and benzaldehyde are condensed, by using either of the above condensing agents, to form 2-hydroxychalcone III. Cyclizing this product yields flavanone IV. Bromination, followed by the elimination of hydrogen bromide with sodium hydroxide, produces flavone itself.[11]

Analogously, the condensation of the thioketone, thioacetophenone, V, and benzaldehyde should produce thiochalcone. In a similar manner, the o-hydroxy derivative of thioacetophenone should produce 2-hydroxy-thiochalcone VI. Bromination, followed by the elimination of hydrogen bromide, should likewise produce thioflavone VII.

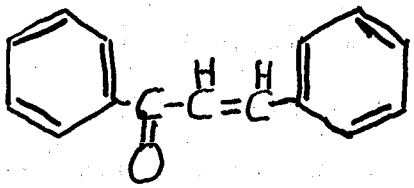
This thesis covers the practical research done on the condensation of thioacetophenone with benzaldehyde and the library research covers the chemistry of thioketones and the thioflavanones. Most of the thioketones have been made by dissolving a ketone in ethanol, usually absolute although 95 per cent was also used, saturating the solution with anhydrous hydrogen chloride at ice temperature, then admitting hydrogen sulfide for several hours. This method was first used by

Fromm and Baumann when they made thioacetophenone from acetophenone.[14] David Shirley also gives this process in his book Preparation of Organic Intermediates published by Wiley and Sons in New York. Sometimes a metallic oxide dehydration catalyst such as alumina is used.[27]

Cyclic thioketones which are trimers have been prepared from cyclopentanone, cyclohexanone, and p-methyl-cyclohexanone with hydrogen sulfide and hydrogen chloride. These cyclic thioketones will produce disulfone sulfides when they are oxidized by potassium permanganate dissolved in concentrated sulfuric acid. As an example, the ethyl mercaptol of trithiocyclohexanone, an oil which can not be distilled, even under vacuum without decomposition, can be oxidized by potassium permanganate in sulfuric acid to diethyl-sulfonecyclohexane. Its melting point is 118-9° C. Trithiocyclohexanone, itself, loses one equivalent of hydrogen sulfide and forms a compound $C_{18}H_{28}S_2$ probably cyclohexanone-dicyclohexene-mercaptol.[15]

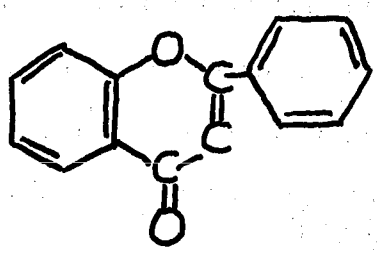
Other thioketones, such as aliphatic thioketones, have been made by action of phosphorous pentasulfide on ketones such as dimethyl ketone, methyl-ethyl ketone, diethyl ketone, dipropyl ketone, and ditertiarybutyl ketone. The solvent for these ketones was toluene. The reaction mixtures were heated on water baths for eight hours. The products obtained were usually impure despite steam distillation, drying with calcium chloride, and finally distillation of the toluene residues under vacuum.[18]

I



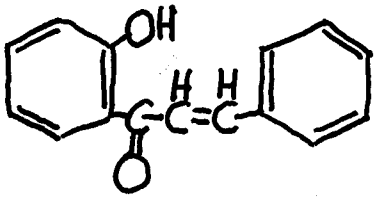
CHALCONE

II



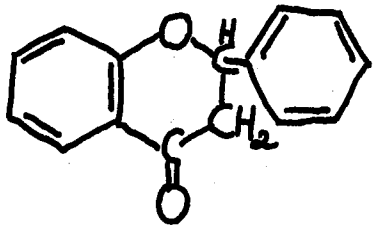
FLAVONE

III



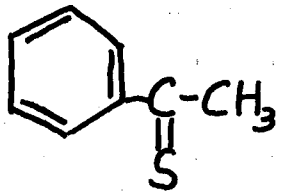
2-HYDROXYCHALCONE

IV



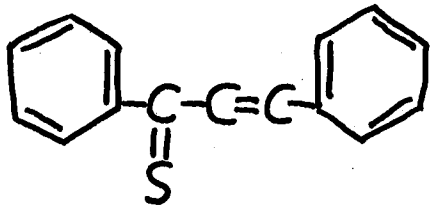
FLAVA NONE

V



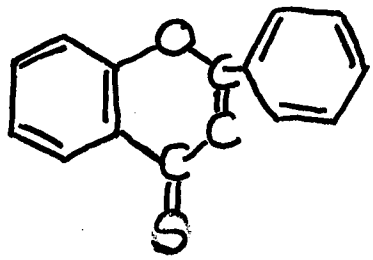
THIOACETOPHEN ONE

VI



THIOCHALCONE

VII

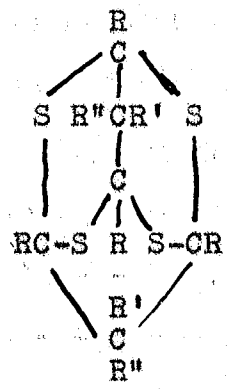


THIOFLAVONE

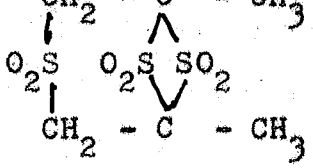
The dimeric thioketones have been made by passing carbon disulfide into a cooled solution of zinc chloride in acetone. The particular thioketone, prepared from acetone in this way, is thioacetone. Another compound, 2,6-dimethyl-2,6-endosulfidodithiane $CH_2\text{-}S\text{-}CH_2$, has been made by dis-

$$CH_3\text{-}C\text{-}S\text{-}S\text{-}C\text{-}CH_3$$
$$\quad\quad S$$

solving chloracetone in absolute ethanol and saturating the solution with hydrogen chloride. After cooling in an ice bath, carbon disulfide was then passed through the solution for five hours. The compound did not form an oxime, phenylhydrazone, or p-nitrophenylhydrazone and did not react with diazomethane, Grignard reagents, sodium amalgam in ethanol, or sodium in ether. It was oxidized to a trisulfone in small yields by using 5 per cent potassium permanganate in 96 per cent ethanol containing sulfuric acid. 1,1-phenylchloro-2-propanone, hydrogen chloride, and carbon disulfide give diphenyl-1,4, dithiene, with a melting point of 118-9° C. This agrees with that found by Growth, Chem., Abstr., 18, 1280 (1924). Chloroacetone, reacted with sodium sulfide in acetone, yields diacetonyl sulfide after being refluxed four hours.[4] Other dimeric ketones such as the aliphatic B-diketones react smoothly with hydrogen sulfide at low temperatures. Aromatic groups on the molecule, however, tend to produce tarry masses. A possible structure for the dimeric, dithio, derivatives of B-diketones is given by Fredga and Brondstrom.[13] It is



When Herbert Brintzinger and Hans-Werner Ziegler reacted chloroacetone with hydrogen chloride and hydrogen sulfide, they obtained the same compound as Böhme et al in Chem., Abstr., 37, 3435[6] (1943), that is, 2,6-endosulfido-dithiane but give the formula as $(CH_3CSCH_2)_2S$. They give the formula of the product from hydrogen chloride and diketene as CH_3COCH_2COCl. This, in turn, yields $(CH_3CSCH_2CO)_2S$ when treated with hydrogen chloride and hydrogen sulfide.[7] However, Böhme disagrees, in a later publication, with Brintzinger. Böhme believes that the structure for the sulfidodithiane which he gave previously is correct since it does not react as an ordinary thioketone and has an ultraviolet absorption maximum at twenty-seven millimicrons. This ditiane is also oxidized to a trisulfone[5] which he represents as



Thioketones have been reduced from R_2CS to R_2CSH with a direct hydrogen transfer from 1-benzyl-1,4-dihydronicotinamide

to the thioketone. Some particular thioketones used were diphenylthioketone, o-methoxy-diphenylthioketone, and p-hydroxydiphenylthioketone. These were made from diphenylmethane, o-methoxy-diphenylmethane, and p-hydroxydiphenylmethane by the action of hydrogen chloride and hydrogen sulfide with 90 per cent ethanol as solvent. The process for the reduction of R_2CS to R_2CSH was performed in a special apparatus under vacuum. This showed that the oxidation-reduction process was not affected by oxygen.[1] Some used given for thioketones are insecticides, fungicides, pesticides, and also as intermediates in organic synthesis as reagents in the textile and petroleum industries.[27] The atomic refraction of sulfur in thioketones is 9.70 and is based on the sodium D line.[6]

The thioketone used in the research was thioacetophenone. It is prepared by the hydrogen chloride-hydrogen sulfide method of Fromm and Baumann given above. J. K. Cline and coworkers[9] found that its trimer could be condensed to $PhCH_3C{:}CCH_3Ph$ by reacting it with Raney Nickel in xylene at 145-50°C under nitrogen atmosphere for ninety minutes. The product was in the trans form in 18 per cent yield. It melted at 105-6°C. Copper powder in place of nickel did not work.

The structure of trithioacetophenone seems to be a trimer in the form of a six membered ring; however, it reacts with Doctors reagent, silver nitrate, mercuric chloride

and condenses with 2,4-dinitrochlorobenzene. The presence of the thioketo group was detected by the ultraviolet spectrum of the thioacetophenone in methanol. The trimer type of structure is not the only possible one, but is believed to be in equilibrium with two other structures, the thiol and the thioketone.[17]

The purpose of the work of Arndt and coworkers was to determine if the replacement of a sulfur for the oxygen atom in the ring would produce a deepening of color similar to that of the thioindigo as compared with the oxyindigo and whether from six membered, similarly constituted sulfur containing ring systems, thioindigoid dyes could be obtained.[2] In particular, B-p-tolylmercaptohydrocinnamic acid is obtained from cinnamic acid and tolylmercaptan which are placed in acetic acid, saturated with hydrogen chloride and hydrogen bromide. The solution is heated in a sealed tube for five hours at 100°C.

B-phenylmercaptohydrocinnamic acid will produce 6-methyl-thioflavanone, melting point 96°C, when refluxed on a water bath with phosphorous oxychloride for fifteen to twenty minutes. The thioflavanone has a crimson color when dissolved in concentrated sulfuric acid. The B-p-toluol acid mentioned can give 6-methyl-thioflavanone if heated for four hours in a closed vessel with two volumes of phosphorous pentoxide.

6-methyl-thioflavanone gives a 3-benzal derivative if it is dissolved in an excess of toluene, is treated with

hydrogen chloride for ten minutes, and is allowed to stand in a closed vessel overnight. It also condenses smoothly in boiling alcohol which contains a few drops of potassium hydroxide with p-$ONC_6H_4N(CH_3)_2$ yields 6-methyl-flavanol-p-dimethylaminoanil.

Another compound, B-p-tolylmercaptopropionic acid is obtained from p-tolylmercaptan in sodium hydroxide and aqueous 3-chloropropionic acid.

Thioflavone derivatives can be obtained from thiophenol ethers. An example of this is the preparation of benzal-2-methyl-thioflavone from 3-aceto,4-thiocresyl-methylether.[3]

CHAPTER II

PREPARATION OF THIOACETOPHENONE

My experimental research consisted of two steps: (1) The preparation of thioacetophenone, (2) the condensation of it with benzaldehyde to form thiochalcone.

The procedure for step one was that of Fromm and Baumann.[14] The apparatus was composed of two gas generators, two drying flasks, two safety flasks, and a reaction flask immersed in an ice bath. The generators were fitted with dropping funnels. One flask generated hydrogen chloride by dropping concentrated sulfuric acid on salt. The other generated hydrogen sulfide by dropping hydrochloric acid (6N) onto ferrous sulfide. Both gases were then dried, the hydrogen chloride with concentrated sulfuric acid, the hydrogen sulfide with dehydrite, since the hydrogen sulfide would react with the sulfuric acid to form sulfur dioxide.

The reaction flask contained twenty-one grams of acetophenone dissolved in 150ml of ethanol. Hydrogen sulfide and hydrogen chloride were passed into the solution together for a period of fifteen to thirty hours. Substitution of undistilled acetophenone for the distilled, or 95 per cent ethanol for the absolute, neither changed the constitution of the product nor its yield. The flask was surrounded by ice for most of the reaction period but not necessarily for the complete time. The only result of this

temperature variation seemed to be the extension of reaction time. In all runs only one type of solid compound was noticed. This is shown by the melting point given below.

The crude solid was yellowish in color but whitened when washed with ethanol. It was recrystallized from a hot ethanol-acetone solution, 50 per cent of each by volume. There was only the slightest odor from the solid. After the product had been dried in air for several days, its melting point was taken and found to be 105-6°C. It was then recrystallized and dried in air for forty-eight hours then dried over phosphorous pentoxide under vacuum for another forty-eight hours. The melting point was the same. When this reaction was carried out by J. K. Cline and Company, the trimer, trithioacetophenone resulted. Its melting point was 121-2°C.[8] When my compound was heated above its melting point, it turned a deep blue in color. The filtrate, from the second crystallization, was saturated with ethanol so that more of the compound could be obtained. Water was also used, but the resultant product was sticky and hard to manipulate. The greatest amount obtained in four runs was eight grams for a 33.6 per cent yield.

Qualitative examinations were made for sulfur, chlorine, and the thiocarbonyl group, according to the procedures of Shriner and Fuson.[21] Lead acetate, in acetic acid, and sodium nitroferricyanide both gave positive identification for sulfur.[22] Beilstein's flame test[23] and the silver

nitrate test[24] gave negative results for chlorine. The thiocarbonyl test was actually the 2,4-dinitrophenylhydrazine test for the carbonyl group.[25] Both groups, however, should give a phenylhydrazone. Since the product was insoluble in the phenylhydrazine reagent but soluble in chloroform, the latter was added to the reagent containing the insoluble compound. The result was two immiscible layers but no precipitate. The test was considered as inconclusive.

Quantitative results were also inconclusive. Two methods were tried for sulfur, both based upon the oxidation of the sulfur to the sulfate ion and the precipitation of the sulfate ion as barium sulfate. The first method attempted was the Parr Bomb method, using thiourea as a control. Unfortunately, theoretical yields were not obtained with either 6 per cent hydrogen peroxide or sodium peroxide and sodium perchlorate as oxidants. The second method was oxidation by potassium permanganate in base. The inability to dissolve the manganese dioxide that was formed and to precipitate the sulfate ion raised an insurmountable difficulty.

In attempting to determine the molecular weight, further difficulties were encountered. The Rast method failed because the camphor caked after thioacetophenone was dissolved in it and hence would not powder for a capillary melting point determination. Thioacetophenone also decomposed when heated to the melting point of camphor. Phenol was next used as the solvent; but, when the control run was made with

diphenyl as the solute, its molecular weight was found to be 229 instead of the true 154.

The solution in the reaction vessel had a color of dark red. Its odor was pungent. After each of the first two runs, the solution was distilled, with the red color passing over into the distillate. The residue was a yellow oil. After washing the residue with water and placing it under refrigeration with the distillate for two weeks, the color left the distillate and it too became yellow. The aroma, however, was still strong in both the distillate and the residue. No further work was done on these constituents of the reaction.

The next step was to prepare thiochalcone from thioacetophenone.

CHAPTER III

PREPARATION OF THIOCHALCONE

Thioacetophenone was found to be insoluble in water, alcohol, and carbon tetrachloride at room temperature. It was soluble in both ethyl acetate and chloroform at room temperature but completely soluble only in chloroform after being subjected to refrigeration for twenty-four hours. Chloroform was also the best solvent for benzaldehyde at the cold temperature.

Ten grams of thioacetophenone and ten milliliters of benzaldehyde were dissolved in 125ml of chloroform and placed in the reaction apparatus, described in the last chapter, for two weeks. The resulting red solution produced red needles which whitened when washed with absolute ethanol. The crude weight of the product was two grams. The compound had to be recrystallized from hot acetone. This recrystallized product was in the form of white needles which were extremely light in weight and hygroscopic. The yield of the purified product was one-half gram in each of two runs for a 3.03 per cent yield. The melting point, after drying in air, was 222-3° C; after being dried over phosphorous pentoxide in a vacuum, it was still 222-3° C.

Thinking that the compound might be thiochalcone, qualitative tests were made for sulfur and an alkene linkage. The lead acetate method gave a positive test for sulfur.

Bromine in carbon tetrachloride[26] gave a positive test for the alkene link.

Quantitative estimation of sulfur in this compound was not obtained for the reasons given in Chapter III.

Because an alkene linkage existed, a procedure by which the alkene linkage test could be expanded into a quantitative one was suggested by Dr. William H. Wadman of the chemistry department in this college. The procedure was a molecular weight determination based upon the addition of bromine to the double bond.

If excess bromine is added to such an unsaturated compound, the portion not used for the addition to the bond is titrated indirectly with sodium thiosulfate by using potassium iodide to replace the bromine in solution, milliequivalent for milliequivalent. The iodine thus formed is titrated with the thiosulfate solution.

$$Br_2 + H_2C{=}CH_2 \rightarrow H_2BrC{-}CBrH_2 + Br_2$$

$$Br_2^- + 2I^- \xrightarrow{H^+} 2Br^- + I_2$$

$$I_2 + S_2O_3^= \rightleftharpoons S_4O_6^= + 2I^-$$

Knowing the number of milliequivalents of bromine added at the beginning and the number left unused, the number of used milliequivalents can be calculated. In practice a blank is run along with the sample so that the exact bromine concentration need not be known.

In the laboratory work this procedure was carried out on two model compounds. The first run consisted of cinnamic

acid and chalcone. Each was dissolved in twenty-five milliliters of carbon tetrachloride. Glass stoppered flasks were used to hold the compounds. Three millliliters of bromine-carbon tetrachloride solution were introduced into each flask and the blank, which contained only twenty-five millliliters of carbon tetrachloride. All three flasks were allowed to stand one hour in order to give time for the completion of the reaction. Since the solutions were red at the end of this time, bromine was considered to be in excess and the solution was acidified with ten millliliters of sulfuric acid (0.1N). Twenty-five millliliters of potassium iodide in aqueous solution were then added. Again the solutions were allowed to stand one hour. The iodine solution was then titrated with sodium thiosulfate to a starch end point. Because two insoluble layers were present, the flasks had to be shaken vigorously after each addition of the thiosulfate. The molecular weights and per cents error are given below:

Compound	M. W. (Exptl.)	M. W. (Theor.)	Error (%)
Cinnamic acid	143	148	3.3
Chalcone	198	208	4.8

In the second run two solutions of the unknown compound, one of chalcone, and the blank were used. 125 millliliters of carbon tetrachloride had to be used, in order for the unknown compound to be dissolved. The results are given below:

Compound	M. W. (Exptl.)	M. W. (Theor.)	Error (%)
Chalcone	213	208	2.4
Unknown 1	216	(224)	3.6
Unknown 2	207	(224)	7.6

If the condensation product is RCSCH=HCR, thiochalcone, where R is the phenyl group, the molecular weight should be 224.

The results of the molecular weight, together with the qualitative tests, give an indication that the unknown is thiochalcone. If this is the product, then the product, described in the last chapter, is thioacetophenone or its dimer.

CHAPTER IV

SUMMARY AND CONCLUSIONS

1. Summary

The purpose of this research project was to make a sulfur analog of chalcone. This was to be done by first preparing thioacetophenone, usually made in its trimer form, and then condensing it with benzaldehyde to form thiochalcone, the sulfur analog of chalcone.

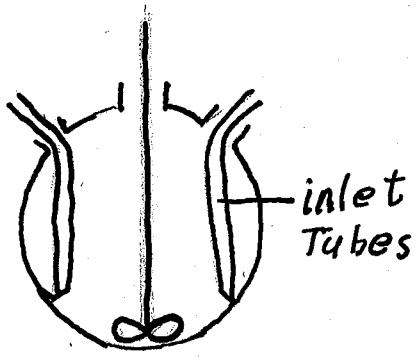
Laboratory results produced a compound which seems to be either a monomer or a dimer of trithioacetophenone. Upon condensation with benzaldehyde a new compound, probably thiochalcone, was formed.

2. Conclusions

The research revealed that the mechanisms of the two reactions might be worthy of some consideration. This idea is accentuated by the fact that the yield was low and a form of thioacetophenone was obtained different from that of earlier workers.

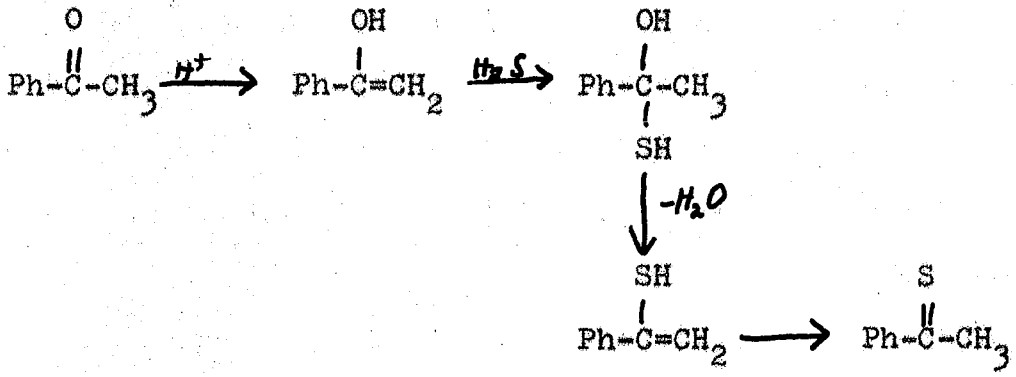
Let us first consider the possible reasons for the low yields in the first reaction. In the preparation of thioacetophenone, the ketone was reacting with hydrogen sulfide. If an insufficient amount of gas was bubbled through the solution, saturated with hydrogen chloride, then

naturally, a low yield would result. However, another possibility exists and that is the depletion of ketone concentration around the gas inlet tubes. Since the solution was stationary during each reaction time, it is quite possible that the entering gas could exhaust the concentration of the ketone around the tubes to such an extent that, the addition of more gas would result in nothing more than the gas passing through and out of the solution. A remedy for this would be to pass the solution past the inlet tubes by means of stirring. Rearrangement of the reaction flask would be necessary in order to make room for the stirrer. The stirrer probably would have to be mechanical, since the ice bath would prevent the use of a magnetic stirrer. The reaction flask could be rearranged in the following manner:

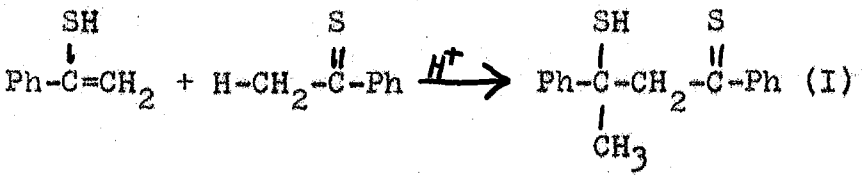


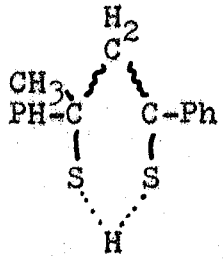
The propeller of the stirrer should be made of an inert material, such as glass, and the blades should be at such an angle, that upon rotation, they would stir the solution downward. This would aid in keeping the gas from escaping before it had a chance to react.

Now suppose the mechanism, in making the thioketone, is an enolization. This is possible, since an acid solution, in which this reaction took place, can catalyze enolization. The reaction would be,



It is also possible that an aldol condensation would be taking place at the same time. The aldolization of the ketones would naturally lower the yield of thioketone produced; however, aldolization of the thioketone could produce a dimer of thioacetophenone. This might cause a change in melting point. The process of dimerization would be as follows:

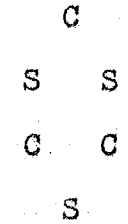




The bond between the CH_2 group and the adjacent carbon atoms would be somewhat weakened because the electrons would be

drawn away from the CH_2 group toward the sulfur atom. The pull would probably be less than if oxygen was used in place of the sulfur. As a result, the monomer could very easily be formed upon melting or dissolution in a solvent. Objection may be raised as to the stability of the SH group in (I). Why would not H_2S be formed as is water, when a carbonyl group is condensed in an acid solution, and hence form a double bond? An answer is that in order for the OH group to attract the needed hydrogen ion for water formation, it must act as a base; however, the sulfur atom, being bigger, holds its electrons more loosely and, therefore, would not attract the hydrogen ion as readily.

The formation of the dimer, instead of the usual trimer of thioacetophenone, could be due to the amount of acid in solution. Although the structure of the trimer is unknown, it is believed to be a six membered ring containing three sulfurs. The simplest structure is



If this be the structure, then the more acid present, the better the chance of the trimer not forming because acids tend to inhibit thioether formation.

Consideration of the low thiochalcone yield indicates that, since the reaction was carried out in chloroform, there

might not have been enough acid formed to catalyze the aldol type condensation. The immediate remedy for this would be to change the solvent towards one of greater polarity.

For future work this report shows that the following might be desirable:

1. Quantitative determinations of sulfur for both compounds.
2. Improvement of the yields for both compounds as noted above.
3. Production of thioflavones by the cyclization of the hydroxythiochalcones.
4. A thorough library search of the pharmacological properties of the chalcones, flavones, and related compounds, such as anthocyanins and chromanones, along with a compilation of these properties in their sulfur analogs.

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