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I. THE REACTIVITY OF THE ANION DERIVED FROM 2-PROPENYL-1,3-DITHIANE. II. STUDIES DIRECTED TOWARD THE SYNTHESIS OF ILLUDIN-S. III. THE THERMAL DECOMPOSITION OF SULFONES AND SULFOXIDES.

The University of Oklahoma, Ph.D., 1974
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THE UNIVERSITY OF OKLAHOMA

GRADUATE COLLEGE

I. The Reactivity of The Anion Derived from 2-Propenyl-1,3-Dithiane

II. Studies Directed Toward The Synthesis of Illudin-S

III. The Thermal Decomposition of Sulfones and Sulfoxides

A DISSERTATION

SUBMITTED TO THE GRADUATE FACULTY

in partial fulfillment of the requirements for the

degree of

DOCTOR OF PHILOSOPHY

BY

HOWARD LEWIS TUGGLE

Norman, Oklahoma

1974

I. THE REACTIVITY OF THE ANION DERIVED FROM 2-PROPENYL-1,3-DITHIANE

II. STUDIES DIRECTED TOWARD THE SYNTHESIS OF ILLUDIN-S

III. THE THERMAL DECOMPOSITION OF SULFONES AND SULFOXIDES

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Dedication to

Janie and Johnnita

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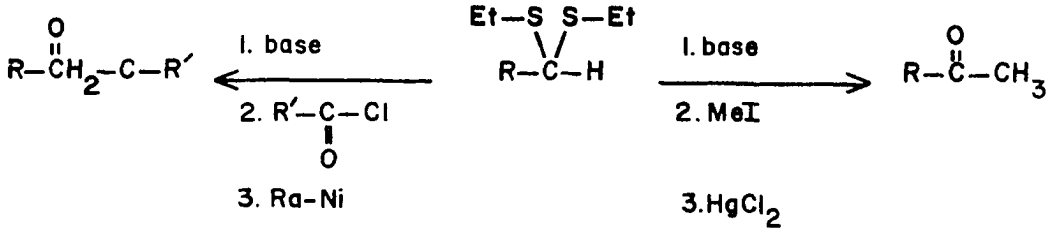
I. AN INVESTIGATION OF THE REACTIVITY OF THE ANION DERIVED FROM 2-PROPENYL-1,3-DITHIANE

History and Background

The observations by Arens,[1] Ohno[2] and Truce[3] that strong bases converted mercaptals to their corresponding anions (see scheme 1) added a new dimension to carbanion chemistry. The stability of these carbanions is attributed to the overlap between the vacant d-orbitals of the sulfur atoms and the adjacent carbanion and the inductive effect of the sulfur atoms of the mercaptal groups.

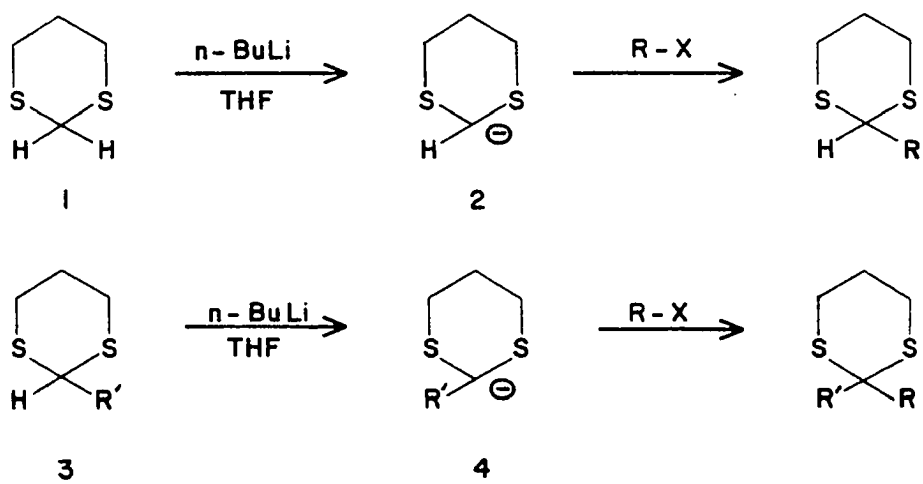
Subsequent alkylation and acylation of these anions followed by hydrolysis or desulfurization of the products provided new synthetic routes to a wide variety of functional groups. However, the yields of the products were low due to a competing reaction between the anion and the solvent, dimethylformamide. Furthermore, the synthetic utility of



Scheme 1

anions derived from mercaptals is also limited by their failure to react with secondary halides and carbonyl compounds.

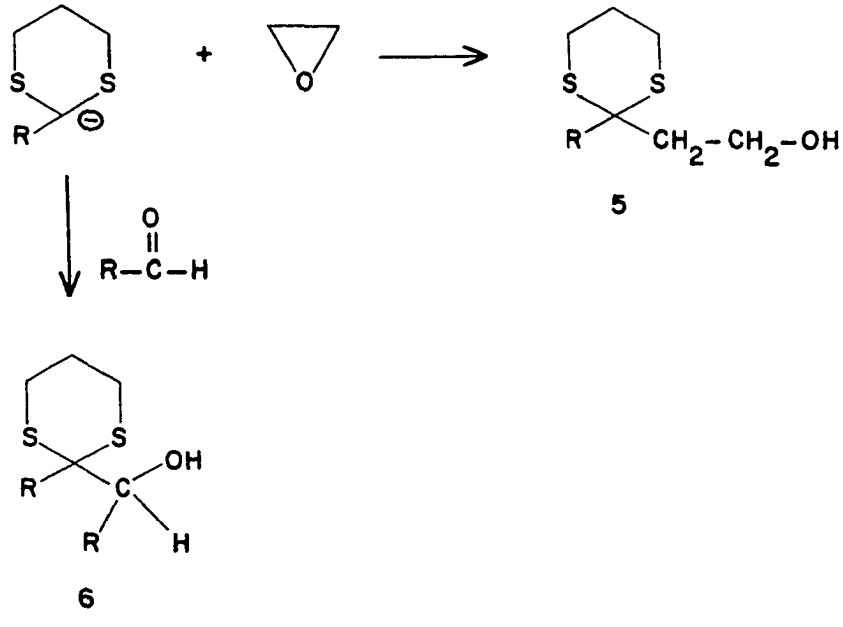
The synthetic utility of thiocarbanions suggested by the work of Arens and coworkers and Truce was greatly expanded by Corey and Seebach[4] who investigated the reactivity of anions derived from 1,3-dithiane 1 and substituted 1,3-dithianes 3.



Scheme 2

Their remarkable ease of preparation, relative stability, and exceptional reactivity established anions of type 2 and 4 as extremely useful intermediates in organic synthesis.

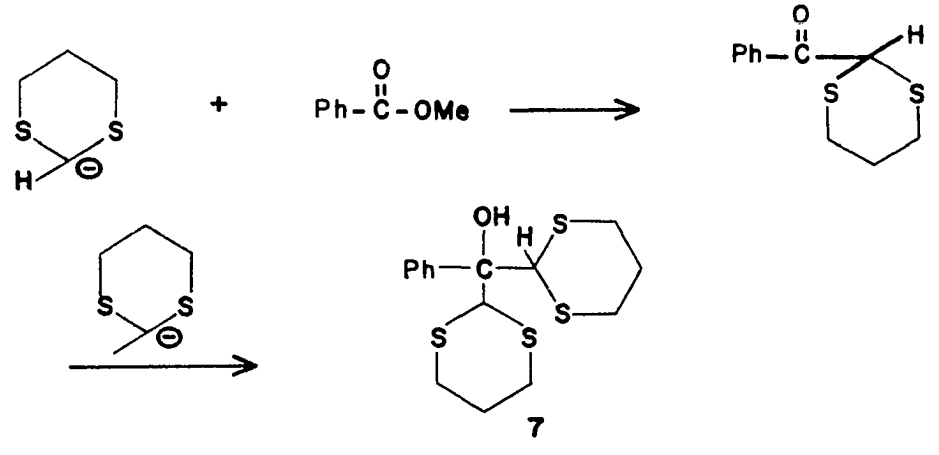
Anions of types 2 and 4 with R = primary, secondary, or t-alkyl, allyl, benzyl and aryl have been generated. They undergo alkylation with primary and secondary halides and dihalides (see scheme 2) to give excellent yields (70-90%) of purified products. The anions 2 and 4 react with epoxides (see scheme 3) to form mercaptals of β-hydroxy ketones or aldehydes, e.g. 5, in good yields; reaction with aldehydes and ketones yield mercaptals of α-hydroxy aldehydes and ketones, e.g. 6.



Scheme 3

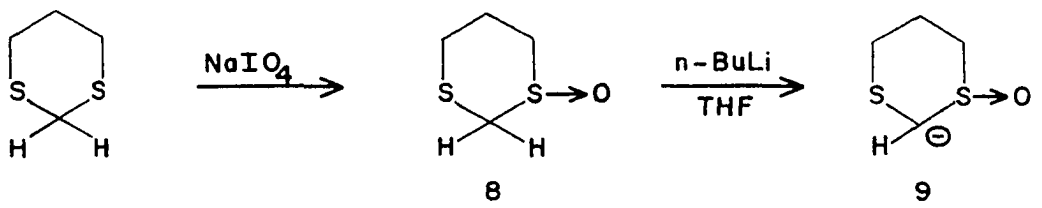
Imines, nitriles and carbon dioxide react with the anions to form products which can be subsequently hydrolyzed to the corresponding amino ketones or aldehydes, diketones or keto aldehydes and α-keto acids.

In general, acid chlorides and esters proved to be unsatisfactory as acylating agents; benzoyl chloride and methyl benzoate reacted with 2 to form the di-addition product. Even in the presence of a



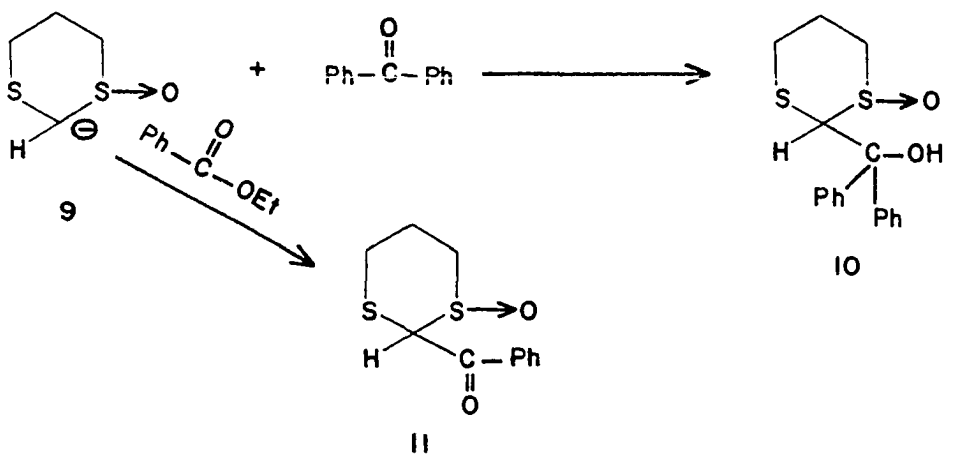
tenfold excess of methyl benzoate, the ketone formed from the initial reaction of 2 with the ester reacted further with 2 to form 7.

In addition to Corey and coworkers, Carlson and Helquist[6] have investigated the reactivity of carbanions which are stabilized by sulfur in its various oxidation states. These workers oxidized 1,3-dithiane (1) to 1,3-dithiane monoxide (8) by treatment with 1 equivalent of sodium metaperiodate. Treatment with n-butyllithium rapidly converted 8 to the anion 9.



8 9

The anion 9 exhibited behavior which is characteristic of both anion 2 and the anion of dimethyl sulfoxide as evidenced by its rapid reactions (see scheme 4) with benzophenone to form 10 and with ethyl



9 10 11

Scheme 4

benzoate to form the β-ketosulfoxide 11. The reaction of 9 with ethyl benzoate to form 11 is in sharp contrast to the reaction of 2 with ethyl benzoate which resulted in the formation of the di-addition product 7.

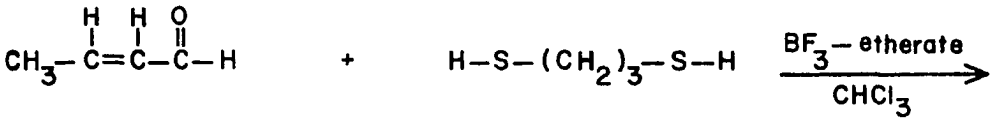
Anions derived from mercaptoles, 1,3-dithianes, and 1,3-dithiane monoxide do not undergo conjugate addition to α,β-unsaturated carbonyl systems. Both 9 and 2 react with α,β-unsaturated carbonyl systems[5,6] (Michael acceptors) in a 1,2-manner; anions derived from mercaptoles do not react in any manner with α,β-unsaturated carbonyl compounds. Otherwise, the chemical behavior of anions derived from mercaptoles, 1,3-dithianes and 1,3-dithiane monoxide is identical to the chemical behavior of other carbanions.

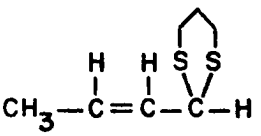
INTRODUCTION

Anions derived from the dithianes of α,β-unsaturated aldehydes present an interesting problem in that reaction can occur at either of two sites, α or γ to the geminal sulfur atoms. Since the chemical behavior of this type of anion has not been reported in the literature and since one of the reactions in a proposed synthesis (see section II of this thesis) of the natural product illudin-S entailed the reaction of such an ambident nucleophile, an investigation of the behavior of such allylic anions with alkylating and acylating reagents was undertaken. The results of this investigation will be presented in this section.

RESULTS AND DISCUSSION

The dithiane 12 used in the preliminary investigation was prepared by reacting crotonaldehyde with 1,3-propanedithiol in the presence of a catalytic amount of boron trifluoride-etherate.



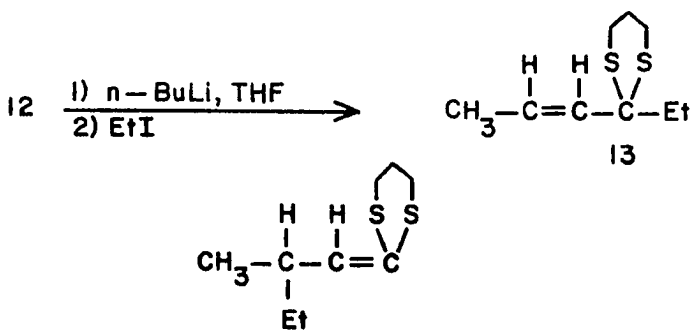


12

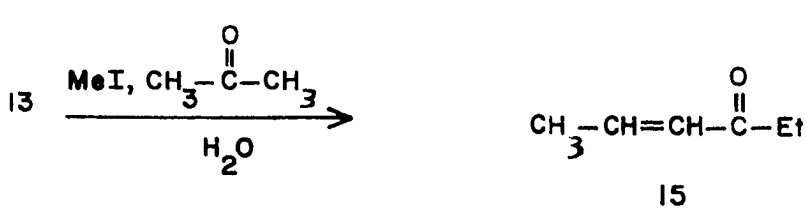
The nmr spectrum of 12 exhibits a signal at 5.0-6.2 ppm due to the two olefinic protons. This signal appears as a complex multiplet. The signal for the proton on carbon bearing the geminal sulfur atom appears as a doublet (J = 6 Hz) at 4.62 ppm. The signals for the six methylene protons of the six membered ring appear as multiplets at 2.5-3.0 and 1.8-2.3 ppm. The signal for the vinyl methyl appears as a doublet (J = 5 Hz) at 1.70 ppm.

A solution of 12 in tetrahydrofuran was treated with 1 equivalent of n-butyllithium, and the resulting anion was subsequently reacted with an excess of ethyl iodide. A single organic product 13 was obtained in 80% yields.

The mass spectrum of 13 exhibits a parent ion at m/e 188 and a base peak at m/e 85. An examination of the nmr spectrum of 13 revealed that the absorptions in the olefinic region correspond to two protons. In contrast, if the alkylation had occurred at the position γ to the geminal sulfur atoms, the resulting product 14 would exhibit only one olefinic proton absorption in its nmr spectrum rather than two as in 13. The evidence obtained from a comparison of the nmr spectra of 12 and 13 indicated that the alkylation of the anion of 12 with ethyl iodide had occurred exclusively at the position α to both sulfur atoms and thus 13 has the structure indicated.

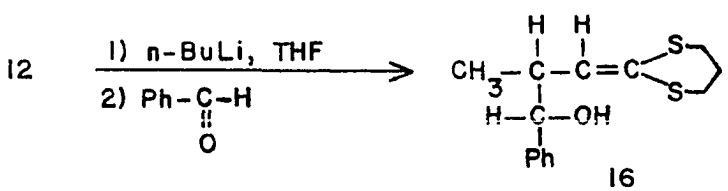


Additional evidence which further confirmed the structure of 13 was obtained from its transformation products. Raney nickel in refluxing ethanol converted 13 to hexane; when a solution of 13 and methyl iodide in aqueous acetone[7] was refluxed for twenty-four hours, ethyl propenyl ketone 15 (identified as its 2,4-dinitrophenylhydrazone) was obtained in 75-80% yields.



Several attempts to hydrolyze 13 (see Table 1) to 15 employing mercury salts were unsuccessful. Invariably, the treatment of 13 with mercuric chloride and mercuric oxide in tetrahydrofuran or acetonitrile resulted in the formation of a solid product which was not identified. Corey and coworkers[8] have observed that unsaturated dithianes cannot be successfully hydrolyzed to the corresponding unsaturated aldehydes and ketones with mercury salts due to concomitant reaction of the double bond. Thus a plausible explanation for the failure of mercury salts to convert 13 to 15 has been presented. However, when a solution of 13 in methanol was treated with mercuric chloride and mercuric oxide, a small quantity of a product (less than 1% yield) was obtained. This product was not fully characterized, but its nmr and ir spectra indicated that it was probably 5-methoxy-2-hexanone which could have resulted from the conjugate addition of methoxide ion to 15.

When the anion of 12 was treated with 1 equivalent of benzaldehyde, a mixture of the diastereoisomeric forms of 16 was obtained.



16

The mass spectrum of 16 exhibits peaks at m/e 266 (M^+) and 108 (base peak). The ir spectrum shows absorptions at 3450 cm^{-1} (OH) and 1692 cm^{-1} (C=C). The nmr spectrum of product 16 showed the following important features: two broad singlets at 7.4 and 7.2 ppm (aromatic protons), a pair of doublets at 5.25 (J = 5 Hz) and 4.5 ppm (J = 8 Hz),

TABLE 1

Some Procedures for Hydrolyzing Dithioketals

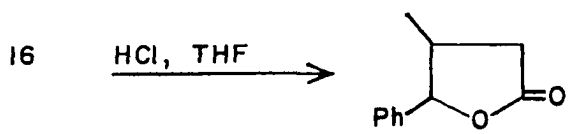
to Carbonyl Compounds

Protection Group	Moles of Reagent Per Mole of Thioketal	Aqueous Solvents (%) Experimental Conditions	Yield % of Carbonyl Product	Ref.
dithiane	NBS (6-9) $AgNO_3$ (4-4.5)	MeCN (80) or $(CH_3)_2CO$ (96) RT 10 min	75-80	8
dithiane	NCS (4.0)[a] $AgNO_3$ (4-4.5)	MeCN (80) or $(CH_3)_2CO$ (96) RT 10 min	71-100	8
dithiane	Hgo or $CdCo_3$ and $HgCl_2$ (2-3)	$(CH_3)_2CO$ (95) MeCN (90-95) Reflux	70-80	5
dithiane	BF_3-etherate HgO	THF, (15%) ACOH	30-80%	11
dithiane and dithiolane	MeI (excess)[b]	$(CH_3)_2CO$ reflux several hours	Not Reported	7
dithiolane	Chloramine-T (4)	C_2H_5OH (80)	86%	10

Methods a and b are suitable for unsaturated dithianes.

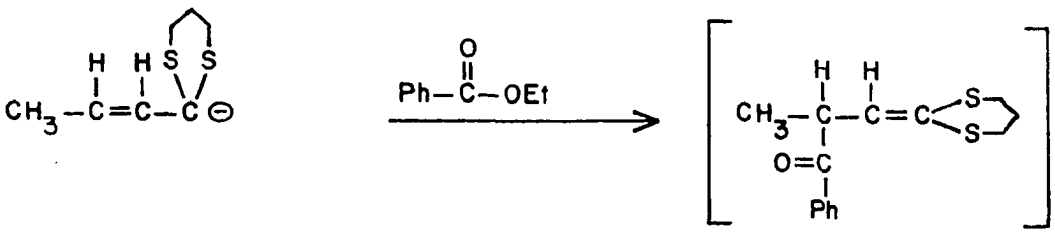
olefinic proton, and a pair of doublets at .9 (J = 5 Hz) and .6 ppm (J = 8 Hz), terminal methyl.

The evidence provided by its nmr spectrum unequivocally established 16 as a mixture of diastereoisomers. The signals for the aromatic protons, the olefinic protons and the methyl groups are clearly distinguishable for each isomer; furthermore, the ratio of the intensities of each pair of these signals is approximately (3:2). Further justification for this structural assignment was provided by the structure of the product 17 which resulted from the treatment of a solution of 16 in tetrahydrofuran with dilute hydrochloric acid. The ir spectrum of 16 exhibited a strong absorption at 1778 cm^{-1} (γ-lactone carbonyl). The mass spectrum of 17 exhibited a molecular ion at m/e 176; the nmr spectrum of 17 showed the following important features: a 5 proton multiplet at 7.1-7.9 due to the aromatic protons; signals for the benzylic proton, doublets at 5.62 (J = 5 Hz) and 4.95 ppm (J = 7 Hz) respectively; and signals for the methyl group, doublets at 1.25 (J = 7 Hz), and .7 ppm (J = 5 Hz). The signals for the remaining protons appear as a multiplet at 2.0-3.2 ppm. Thus, β-methyl-γ-phenyl-γ-butyrolactone 17 is a mixture of diastereoisomers just as its precursor, 16.

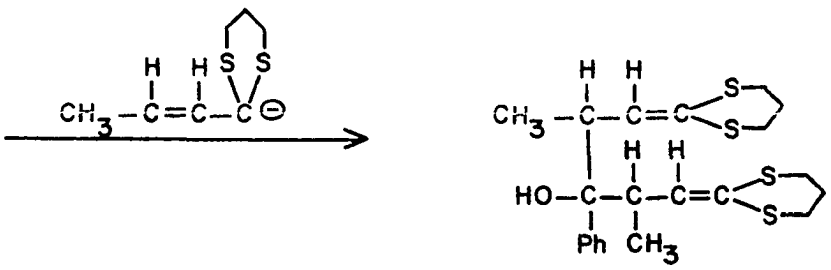


17

When the anion of 12 was treated with 1 equivalent of ethyl benzoate, a compound formulated as 18 was the only product isolated from the reaction mixture. Presumably, the anion of 12 reacted initially with ethyl benzoate to form the ketone 19 which then reacted with an additional mole of the anion of 12 to form the di-addition product 20. This is consistent with the observation of Corey and coworkers who reacted the anion of 1,3-dithiane with a tenfold excess of ethyl acetate and obtained the di-addition product; inverse addition produced the same results.



18



19

SUMMARY

Anions derived from the dithianes of α,β-unsaturated aldehydes alkylate at the position α to both sulfur atoms, acylate at the position γ to both sulfur atoms and undergo addition to carbonyl compounds (aldehydes and ketones) at the position γ to both sulfur atoms. Hydrolysis of the products resulting from the alkylation of these anions provides a new route to the synthesis of α,β-unsaturated ketones.

During this study considerable effort was devoted to the hydrolysis of the dithiane 13 to the corresponding α,β-unsaturated ketone. Procedures utilized in attempts to effect these conversions along with other procedures reported in the literature are summarized in Table 1.

EXPERIMENTAL

All metling points and boiling points are uncorrected. All solvents were redistilled prior to use. Anhydrous solvents were prepared by distillation from calcium hydride. Column chromatography supports were silicAR CC-7 (Mallinckrodt, 100/200 mesh) and silica Gel H (Merck AG, Darmstadt). Thin layer chromatography was performed on 5 x 20 cm glass plates coated with silica gel H (Merck AG, Darmstadt). The developed plates were exposed to iodine vapor for visualization of the chromatogram.

Gas chromatographic analyses were performed on a Varian Aerograph Model 1220-1 or Aerograph Model 1740-1 gas chromatograph. The infrared spectra were taken on a Beckman IR-8 spectrometer as potassium bromide pellets or in solutions of carbon tetrachloride or chloroform. Ultraviolet spectra (uv) were taken in 95% ethanol solutions with a Hitachi Perkin-Elmer, model 124 spectrometer. Nuclear magnetic resonance spectra (nmr) were taken on Varian A-60 or T-60 spectrometers using tetramethylsilane (TMS) as an internal reference. Samples were run in varying concentrations of carbon tetrachloride and deuteriochloroform. Chemical shifts are reported in δ-units (parts per million from TMS) and are followed by the multiplicity of the signal, the number of protons, the corresponding coupling constant and the assignment. The multiplicities are denoted by the symbols: s, singlet; d, doublet; dd, double doublet; t, triplet; and m, multiplet.

The mass spectra were taken on a Hitachi Perkin-Elmer RMU-7 spectrometer using perfluorokerosene as an internal reference. Major peaks and molecular ions are reported followed by percentage of the base peak.

Combustion analyses were carried out by Bernhardt Laboratories in Mülheim, West Germany.

2-propenyl-1,3-dithiane (12)

A solution of 80 g (1.14 mol) of crotonaldehyde and 108 g (1 mol) of 1,3-propanedithiol in 500 ml of chloroform was placed in a 1 l three-necked flask which was equipped with a magnetic stirring bar and an addition funnel. The flask was immersed in an ice-water bath at 0° and 15 ml of boron trifluoride-etherate was added slowly to the contents of the flask. The reaction mixture was stirred for 12 hr during which time the temperature of the bath was allowed to rise to room temperature. The chloroform solution was first washed with a 10% solution of sodium bicarbonate and then with a saturated solution of sodium bisulfite. The chloroform solution was then dried over anhydrous sodium sulfate and evaporated to yield 156.8 g (96%) of the crude dithiane. Distillation of 78 g of crude product yielded 60.4 g (80%) of 2-propenyl-1,3-dithiane as a colorless liquid, bp 77-78° (1 mm). An analytical sample was obtained by collecting a middle fraction from the distillate, bp 77-78° (1 mm); n_D^{25} 1.5771; ir (thin film) 1658 cm^{-1} (carbon-carbon double bond); 1419 cm^{-1} (carbon-sulfur stretch); nmr ($CDCl_3$) δ 5.3-6.3 (m, 3, olefinic protons), 4.65 (proton on C-2 of the dithiane ring), 2.70-2.95 (m, 4, methylene protons on carbons 4 and 6 in the dithiane ring), 1.8-2.2 (m, 2, remaining methylene protons of the dithiane ring), 1.7 (d, 3,

J = 5 Hz, vinyl methyl); mass spectrum 163 (1), 162 (19), 161 (7), 160 (69), 119 (23), 105 (12), 103 (15), 95 (16), 87 (15), 86 (47), 85 (100), 74 (25), 73 (23), 71 (11), 58 (10), 55 (13), 53 (18), 47 (16), 46 (25), 45 (68), and 41 (33).

Anal. Calcd. for $C_7H_{12}S_2$: C, 52.50; H, 7.50; S, 40.00. Found: C, 52.40; H, 7.63; S, 40.11.

2-Ethyl-2-propenyl-1,3-dithiane (13)

A solution of 24 g (.15 mol) of 2-propenyl-1,3-dithiane in 200 ml of dry tetrahydrofuran was placed in a 500 ml three-necked flask which was equipped with a mechanical stirrer, a septum cap and a nitrogen inlet. The flask was immersed in a dry ice-acetone bath at -60-70° and the solution was stirred under a nitrogen atmosphere (which was maintained throughout the experiment) while .15 mol of n-butyllithium in hexane was added to the contents of the flask. Stirring was continued for 4 hr at -50-60° and then 42.6 g (.30 mol) of ethyl iodide was added to the reaction mixture. Stirring was continued for 18 hr at 0-5°, and then the reaction mixture was acidified to a pH of 4 with 10% hydrochloric acid and extracted twice with 150 ml portions of chloroform. The chloroform solution was washed with a saturated solution of sodium bisulfite, dried over anhydrous sodium sulfate and evaporated to yield 24 g (85%) of crude product. Distillation of the crude product yielded 20.85 g (74%) of 2-ethyl-2-propenyl-1,3-dithiane as a colorless liquid, bp 96-98° (1 mm). An analytical sample was obtained by collecting a middle fraction from the distillate, bp 96-98° (1 mm), n_D^{25} 1.5570; ir (thin film) 1650 cm^{-1} (carbon-carbon double bond), 1435 cm^{-1} (carbon-sulfur stretch); nmr ($CDCl_3$) δ 5.17-6.2 (m, 2, olefinic protons), 2.3-3.1 (m, 4, methylene

protons on carbons 4 and 6 of the dithiane ring), 1.6-2.3 (complex multiplet, 7, contains discernible d at 1.8 corresponding to a vinyl methyl group; remaining signals due to methylene of ethyl group and C-5 protons of dithiane ring); .90 (t, 3, J = 6 Hz, terminal methyl); mass spectrum 189 (7), 188 (60), 164 (11), 159 (45), 135 (21), 115 (10), 114 (36), 113 (35), 107 (22), 106 (10), 99 (17), 87 (10), 86 (12), 85 (100), 84 (15), 81 (21), 73 (31), 47 (20), 45 (35), and 41 (45).

Anal. Calcd. for $C_9H_{15}S_2$: C, 57.45; H, 8.51. Found: C, 57.24; H, 8.32.

1-(1,3-propylenedithio)-3-methyl-4-hydroxy-4-phenyl-1-butene (16)

A solution of 12 g (.075 mol) of 2-propenyl-1,3-dithiane in 100 ml of dry tetrahydrofuran was placed in a 500 ml three-necked flask which was equipped with a mechanical stirrer, a septum cap and a nitrogen inlet. The flask was immersed in a dry ice-acetone bath at -70° and the solution was stirred under a nitrogen atmosphere which was maintained throughout the experiment while a solution of .075 mol of n-butyllithium in hexane was added by means of a syringe to the contents of the flask. The reaction mixture was stirred for 4 hr at -70° and 8 g (.075 mol) of benzaldehyde was added to the contents of the flask. Stirring was continued for 5 min at -70°, then the reaction mixture was acidified with 10% hydrochloric acid and extracted twice with two 100 ml portions of chloroform. The chloroform solution was washed several times with a saturated solution of sodium bisulfite and dried over anhydrous sodium sulfate. Evaporation of the solvent yielded 12.6 g (78.8%) of a diastereoisomeric mixture of 1-(1,3-propylenedithio)-3-methyl-4-hydroxy-4-phenyl-1-butene as an oily solid. Three recrystallizations from 95%

ethanol yielded an analytical sample, mp 74-77°; ir (KBr) 3440 cm^{-1} (hydroxyl), 1692 cm^{-1} (carbon-carbon double bond), 1415 cm^{-1} (carbon-sulfur stretch); nmr ($CDCl_3$) δ 7.1-7.5 (m, total 5, aromatic protons), 5.3 and 4.6 (doublets, total 1, J = 6 Hz, and J = 8 Hz, olefinic protons), 3.2-3.7 (m, 2, allylic proton and the benzylic proton), 1.8-3.0 (m, 7, protons of the dithiane ring and hydroxylic proton), 1.05 and .90 (doublets, total of 3, J = 6 Hz, and J = 7 Hz, methyl); mass spectrum 267 (2), 266 (8), 133 (11), 120 (33), 119 (20), 110 (12), 108 (100), 93 (16), 47 (11), 43 (27), and 41 (10).

Anal. Calcd. for $C_{14}H_{18}S_2O$: C, 62.95; H, 6.76; O, 6.01. Found: C, 62.95; H, 6.66; O, 5.87.

The Reaction of the Anion of 2-propenyl-1,3-dithiane (12) with Ethyl Benzoate

A solution of 2 g (12.5 mmol) of 2-propenyl-1,3-dithiane in 100 ml of dry tetrahydrofuran was placed in a 500 ml three-necked flask which was equipped with a mechanical stirrer, a gas inlet and a septum cap. The flask was immersed in a dry ice-acetone bath at -30°, and the reaction was placed under a nitrogen atmosphere which was maintained throughout the experiment. A solution of 12.5 mmol of n-butyllithium in hexane was added by means of a syringe to the contents of the flask. The reaction mixture was stirred at -30° for 4 hr and 6.75 g (45 mmol) of ethyl benzoate was added to the contents of the flask. Stirring was continued for 18 hr at 0-5°, and then the reaction mixture was acidified to a pH of 4 with a 10% hydrochloric acid and extracted twice with 100 ml portions of chloroform. The chloroform solution was dried over anhydrous sodium sulfate and evaporated to yield 8.54 g of a mixture of ethyl benzoate and

the di-addition product 20. The mixture was shaken with 25 ml of ethyl acetate and white crystals separated from the solution. The crystals were collected by suction filtration and air dried to yield 3.71 g (70%) of the di-addition compound 20, mp 138-139°. Two recrystallizations from hexane-methylene chloride yielded an analytical sample, mp 142-143°; ir (KBr) 3505 cm^{-1} (hydroxyl), 1405 cm^{-1} (carbon-sulfur stretch); nmr ($CDCl_3$) δ 7.0-7.75 (m, 5, aromatic protons), 6.3 (d, 1, J = 10 Hz, olefinic proton), 5.8-5.9 (m, 1, olefinic proton), 3.1-3.7 (m, 2, allylic protons), 1.4-3 (m, 12, all of the methylene protons of the dithiane ring), 1.90, 0.60 (doublets, total of 3, J = 5 Hz, J = 6 Hz, methyls); mass spectrum 424 (3), 266 (12), 265 (16), 264 (100), 161 (10), 160 (11), 159 (60), 132 (10), 129 (13), 115 (14), 106 (15), 105 (25), 104 (20), 86 (10), 85 (25), 84 (10), 77 (15), 73 (13), 57 (44), 56 (28), 49 (17), 44 (15), 43 (25), 42 (16) and 41 (50).

Anal. Calcd. for $C_{21}H_{28}S_4O$: C, 59.43; H, 6.60; S, 30.19. Found: C, 59.29; H, 6.64; S, 30.23.

β-Methyl-γ-phenylbutyrolactone (17)

A solution of 250 mg (.94 mmol) of 16 and 5 ml of 10% hydrochloric acid in 25 ml of tetrahydrofuran was heated at 50° for 2 hr, cooled to room temperature and extracted with 100 ml of chloroform. The chloroform solution was dried over anhydrous sodium sulfate and evaporated to yield .205 g of an oil which was a mixture of 1,3-propanedithiol and β-methyl-γ-phenylbutyrolactone (17). The oil was dissolved in 25 ml of 95% ethanol, 1 g of potassium hydroxide was added, and the reaction mixture was refluxed for 12 hr and then evaporated to dryness. The solid residue was washed several times with ether and air dried. The

residue was then treated with 5 ml of concentrated hydrochloric acid and extracted twice with 50 ml portions of ether. The ether solution was dried over anhydrous sodium sulfate and evaporated to yield 99.2 mg (60%) of β-methyl-γ-phenylbutyrolactone as a colorless oil; ir (thin film) 1785 cm^{-1}(lactone carbonyl); nmr ($CDCl_3$) δ 7.2-7.9 (m, 5, aromatic protons), 5.60, 4.90 (both doublets, total 1, J = 5 Hz, J = 8 Hz, benzylic proton on carbon bearing oxygen), 2.1-3.0 (m, remaining ring protons), 1.25, .70 (both doublets, total 3, J = 5 Hz, J = 8 Hz, methyl); mass spectrum 177 (5), 176 (45), 117 (13), 116 (5), 115 (10), 107 (100), 106 (24), 105 (99), 91 (14), 79 (15), 78 (10), 77 (36), 70 (14), 69 (11), 65 (6), 50 (18), and 40 (31).

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 75.00; H, 6.82. Found: C, 73.50; H, 6.89.

Ethyl Propenyl ketone (15)

A mixture of 1 g (5.3 mmol) of 2-ethyl-2-propenyl-1,3-dithiane (13), 5 ml of methyl iodide, 1 ml of water and 50 ml of acetone was refluxed for 24 hr and then distilled at atmospheric pressure until most of the acetone was removed. The mixture was cooled to room temperature, 3 ml of water was added and the mixture was distilled through a short path distillation column. A fraction consisting of a mixture of the ketone 15 and water was collected, bp 98-101°. The mixture was poured into 25 ml of ether and the ether layer was collected and dried over anhydrous sodium sulfate. Evaporation of the ether and subsequent distillation yielded .360 g (69%) of dry ethyl propenyl ketone, bp 81-82° (12 mm); 2,4-dinitrophenylhydrazone, mp 168-169°, n_D^{25} 1.4380 [Lit.[9] bp 76.2° (8.5 mm); 2,4-dinitrophenyhydrozone, mp 170°].

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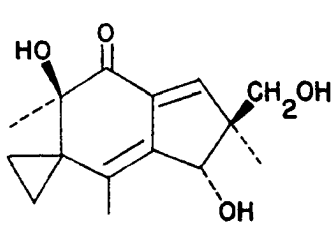
II. STUDIES DIRECTED TOWARD THE SYNTHESIS OF ILLUDIN-S

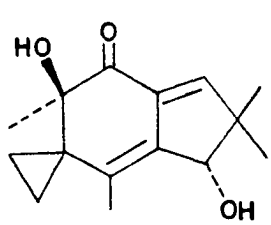
History and Background

The fungal metabolites illudin-S (1) and illudin-M (2) were first isolated from jack-o'-lantern mushrooms in 1950 by Anchel and coworkers.[1] Somewhat later, but before the structure of 1 and 2 had been published, Japanese investigators[2,3] isolated a substance which they named lampterol from the poisonous mushroom, Lampteromyces japonicus, which grows on rotten beech trees in Japan. It was later found that lampterol is identical to illudin-S, and since the latter name was the first reported in the literature, it has been retained as the family name for a group of closely related compounds.

The illudins are of considerable interest because of their antitumor activity, antibacterial activity and their possession of a unique non-isoprenoid structure. Anchel and McMorris[3] assigned structures 1 and 2 except for absolutely stereochemistry; the structure which they assigned to 1 was corroborated by an independent investigation[4] carried out in Japan.



1



2

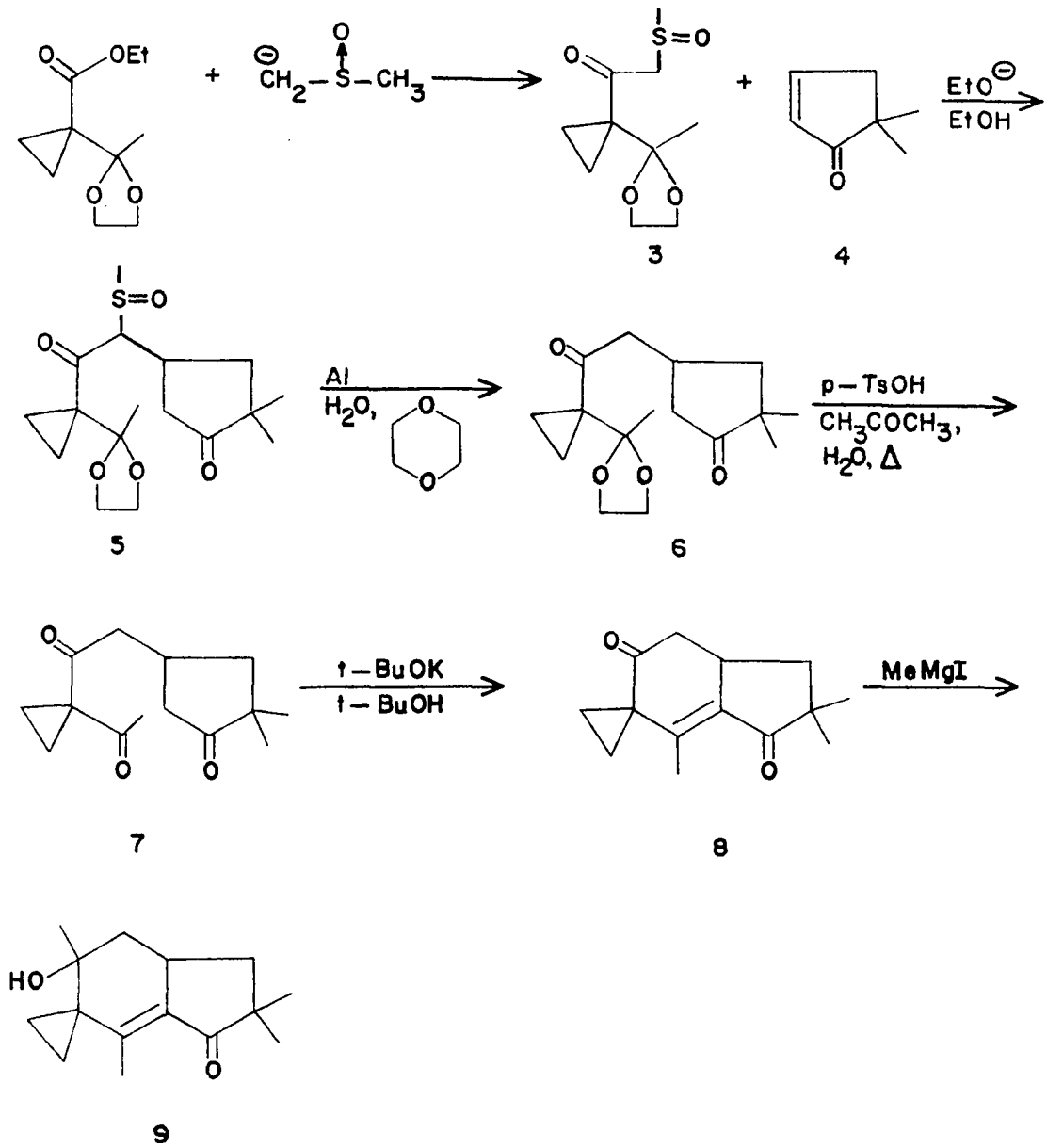
Matsumoto and coworkers[5,6] have accomplished the total synthesis of 1 and 2. In preparation for their total synthesis of 1 and 2, they conducted several preliminary investigations into the synthesis of key intermediates which possess the structural features of the illudins and the necessary functionality required for conversion to the illudins.

The first such compound to be prepared[7] was 9. The series of reactions leading to the synthesis of 9 is outlined in Scheme 1. The β-ketosulfoxide 3 required for the synthesis of 9 was prepared (see scheme 1) from methylsulfinyl carbanion and the ethylene ketal of 1-acetyl-1-carboethoxycyclopropane by the method of Corey and Chaykovsky.[8]

The Michael addition of 3 to 4 in ethanol catalyzed by sodium ethoxide afforded 5 as the only product in 60% yields. Amalgamated aluminum foil in dioxane-water at room temperature converted 5 to 6 which was transformed to the triketone 7 by p-toluenesulfonic acid in aqueous acetone. Potassium t-butoxide in t-butyl alcohol transformed 7 to the diketone 8. Methyl magnesium iodide (1 equivalent) reacted selectively with the non-conjugated carbonyl group of 8 to form 9.

After synthesizing compound 9, Matsumoto and coworkers[9] proceeded by a similar series of reactions to synthesize the more highly functionalized illudin precursor 16. The sequence of reactions leading to the synthesis of 16 is depicted in scheme 2. The series of reactions employed in the synthesis of 10, the other intermediate required for the synthesis of 15, is also shown in scheme 2.

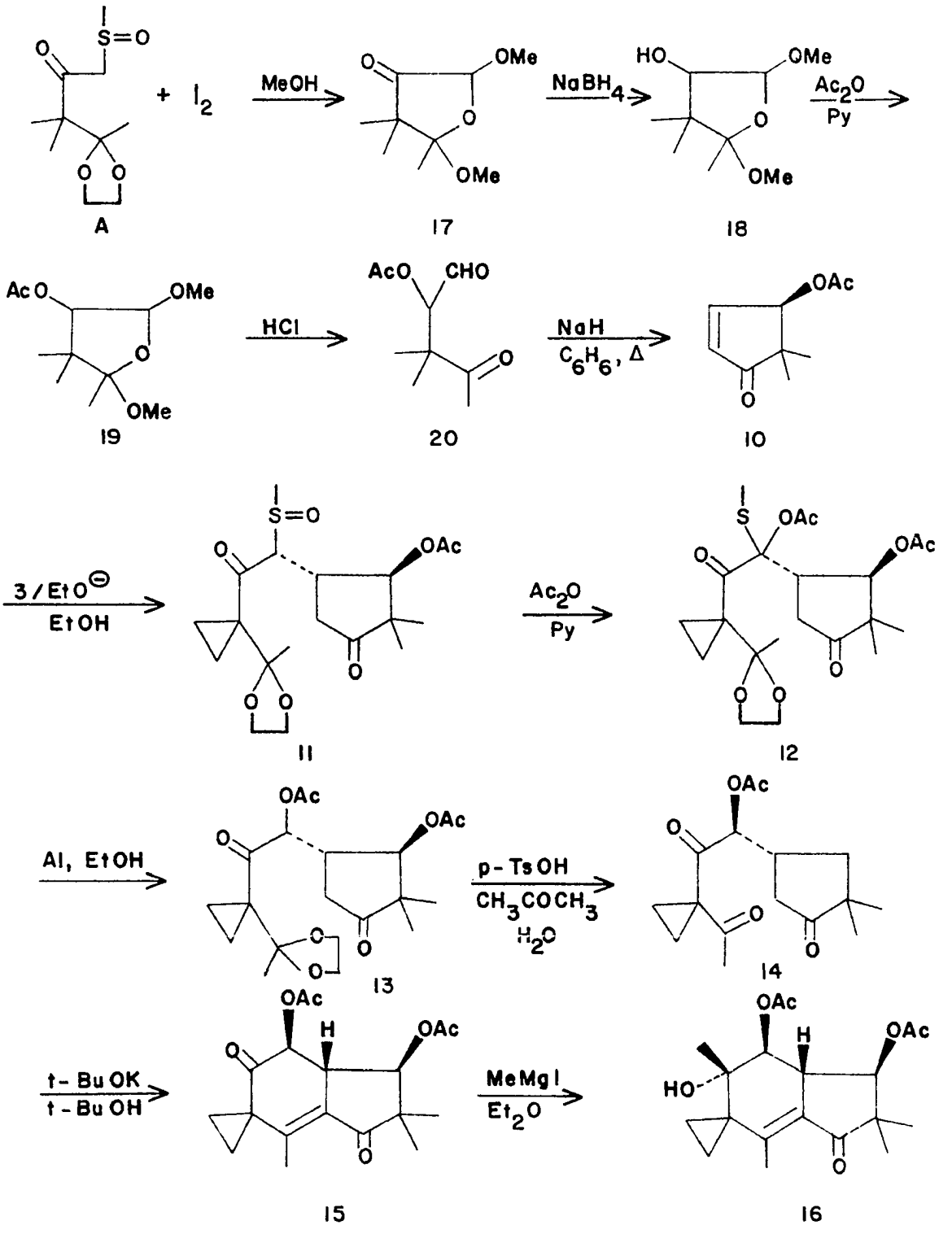
Treatment of A with iodine in methanol yielded an epimeric pair of tetrahydrofuranones 17. Sodium borohydride reduction of 17 yielded 18 (an isomeric mixture of tetrahydrofuranols) which was converted to 19



Scheme 1

by treatment with acetic anhydride in pyridine. Dilute hydrochloric acid converted 19 to the ketoaldehyde 20 which in turn was cyclized to 10 by sodium hydride in refluxing benzene.

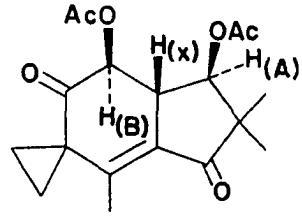
The Michael addition of 3 to 10 in ethanol catalyzed by sodium ethoxide yielded 11 as the only product. In the presence of acetic


MeOH
NaBH4
Ac2O
Py
HCl
NaH
C6H6, Δ
3 / EtO⊖
EtOH
Ac2O
Py
Al, EtOH
p-TsOH
CH3COCH3
H2O
t-BuOK
t-BuOH
MeMgI
Et2O
A
17
18
19
20
10
11
12
13
14
15
16

Scheme 2

anhydride and pyridine 11 underwent the Pummerer[10] rearrangement to form 12. Treatment of 12 with amalgamated aluminum in ethanol afforded 13 which was subsequently transformed to the triketone 14 by aqueous acetone containing a trace of p-toluenesulfonic acid.

Potassium-t-butoxide in t-butyl alcohol transformed 14 to the enone 15. Matsumoto and coworkers[9] based their stereochemical assignment in 15 on the following evidence: J_{AX} = 9 Hz, therefore, H_A and

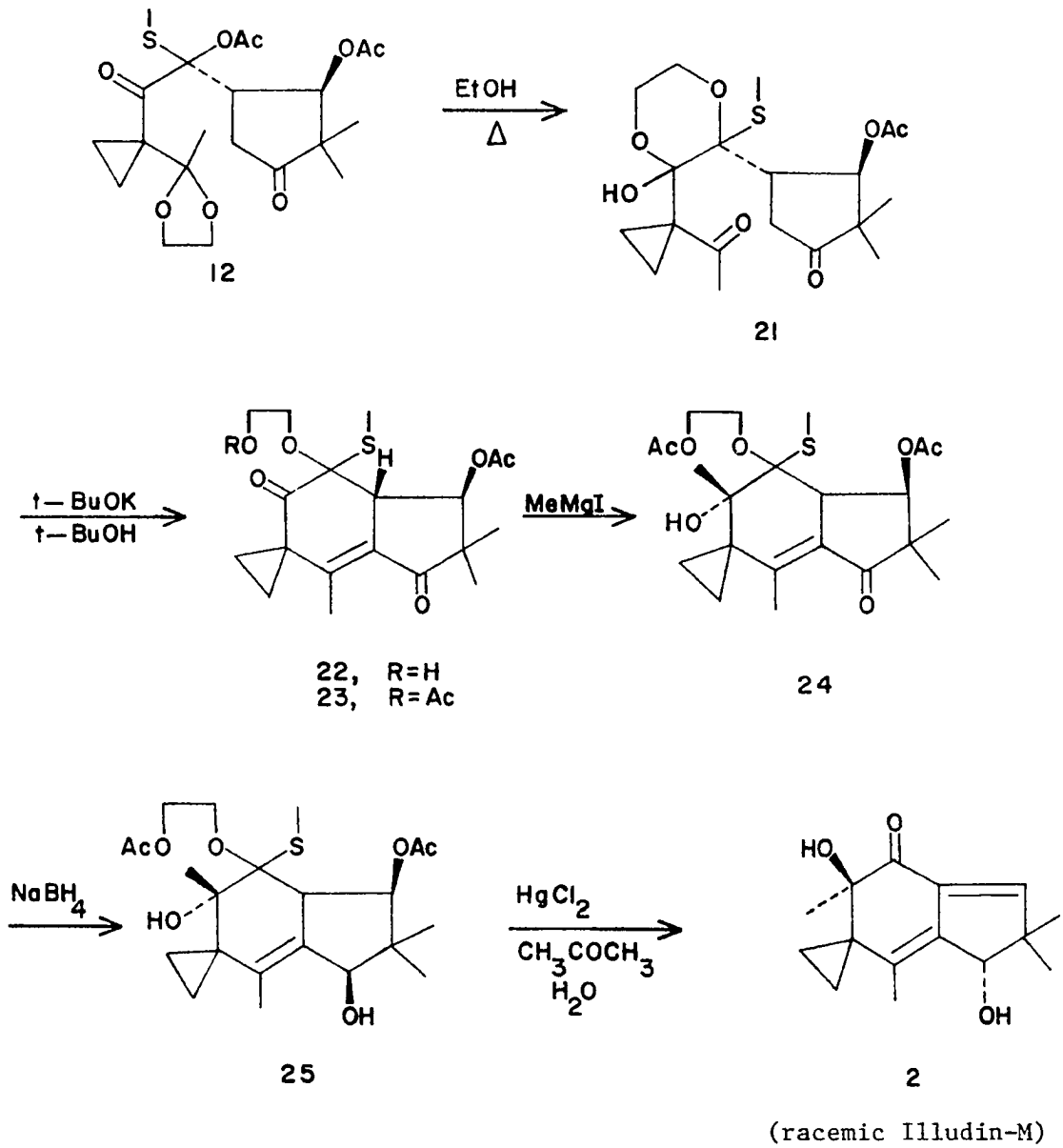


15

H_X are trans to each and axial to the cyclopentanone ring.[14] Since J_{BX} = 12 Hz, it was similarly concluded[14] that H_B and H_X are also trans to each other and axial to the cyclohexanone ring. Thus, it was concluded that 15 has the stereochemistry shown in scheme 2. Compound 15 was converted to 16 by methylmagnesium iodide which reacted selectively with the six-membered carbonyl group in a highly stereoselective manner.

The sequence of reactions leading to the synthesis of the exploratory compound 16 provided the key intermediate 12 which ultimately lead to the synthesis of illudin-M (2).[5] When 12 was heated in ethanol (see scheme 3), it rearranged to 21. Treatment of 21 with potassium-t-butoxide in t-butyl alcohol afforded 22 which was then converted to the acetate 23. Methyl magnesium iodide also reacted selectively with

the six-membered ring carbonyl group of 23 in a highly stereoselective manner to form 24. Reduction of 24 with sodium borohydride in tetrahydrofuran yielded the diol 25 as the only product. Treatment of 25



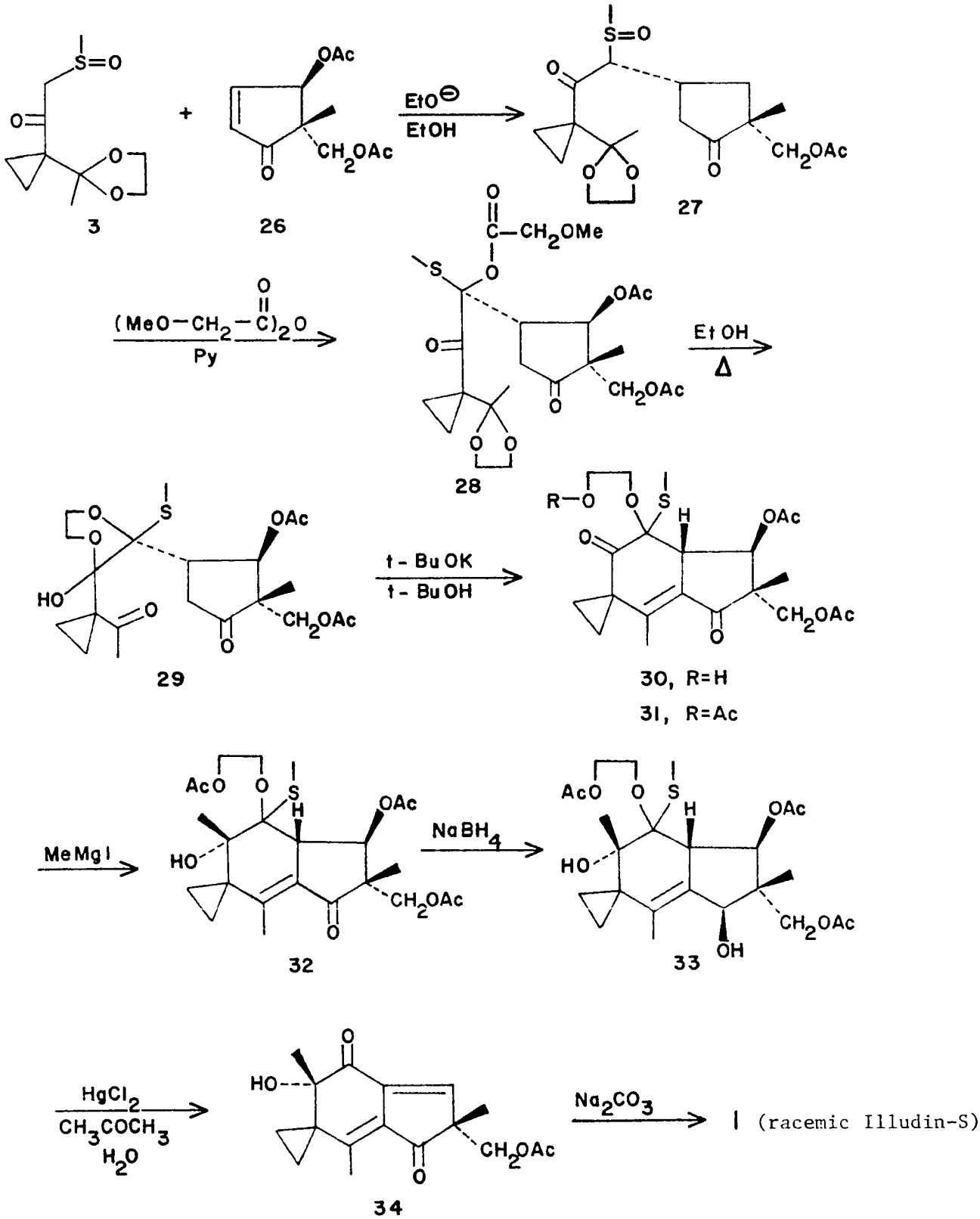
Scheme 3

with mercuric chloride in aqueous acetone afforded racemic illudin-M (2). The chemical and physical properties of the synthetic illudin-M (2) were identical in all respects to the natural occurring substance.

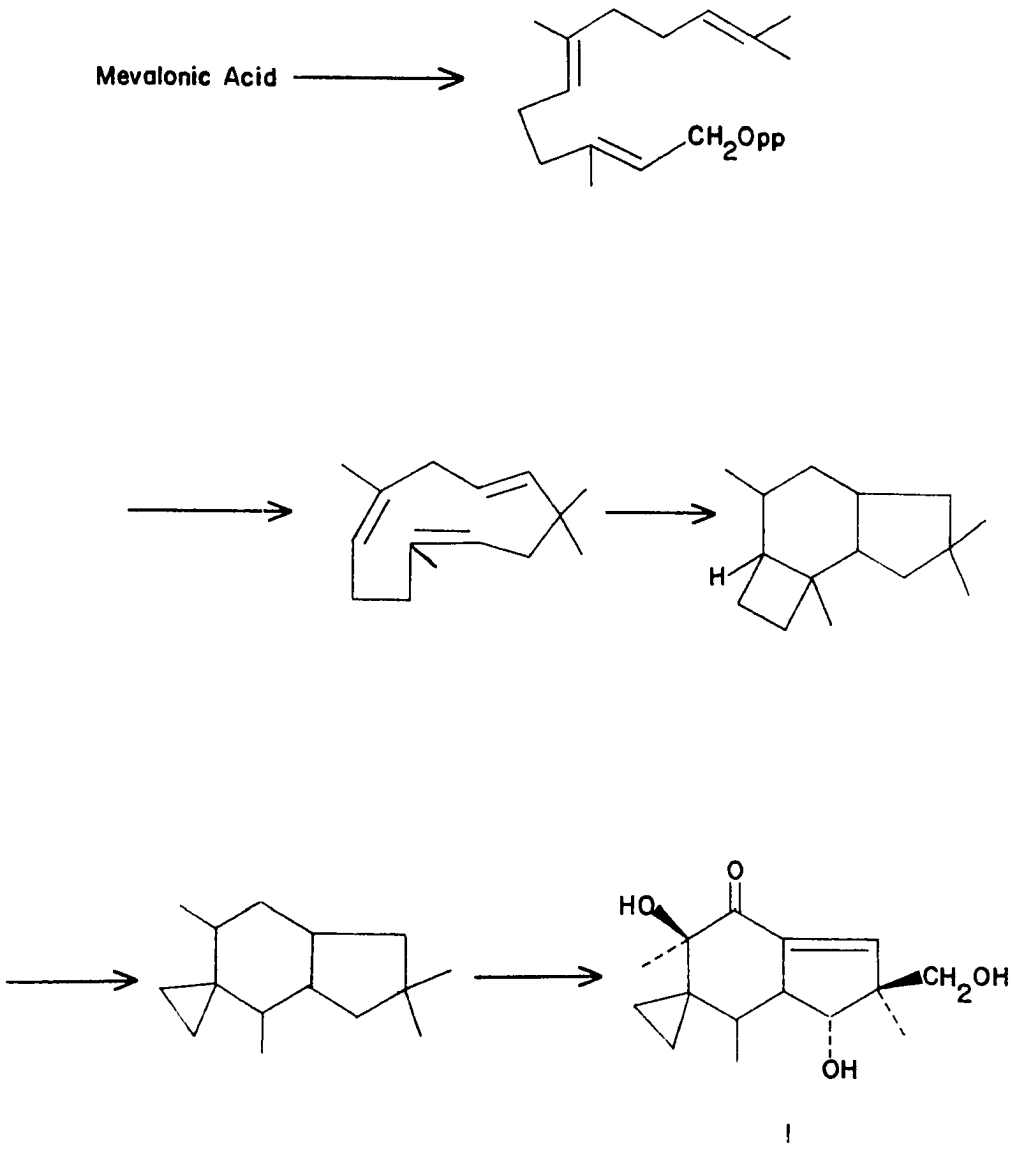
Proceeding by a similar sequence of reactions (see scheme 4), Matsumoto and coworkers[6] synthesized illudin-S (1). The treatment of 3 with potassium t-butoxide in t-butyl alcohol followed by the addition of 26 afforded the Michael adduct 27 in 70% yields. When 27 was treated with methoxyacetic anhydride, the Pummerer[10] rearrangement occurred to form 28 in quantitative yields. In the presence of ethanol, 28 was transformed to 29; potassium t-butoxide in t-butyl alcohol converted 29 to the α,β-unsaturated ketone 30. The treatment of 30 with acetic anhydride in pyridine resulted in the acetylation of the hydroxyl group to form 31.

Methyl magnesium iodide (one equivalent) reacted selectively with the six-membered ring carbonyl group of 31 to form 32; this reaction was also highly stereoselective. Sodium borohydride in tetrahydrofuran transformed 32 to 33 which in turn was converted to 34 by mercuric chloride in aqueous acetone. Compound 34 was hydrolyzed to illudin-S (1) by treatment with aqueous sodium carbonate. The physical and chemical properties of the synthetic illudin-S (1) were found to be identical in all respects to the natural occurring substance.

Illudin S has been assigned[13] the absolute configuration implied in formula 1, based on an application of the dibenzoate chirality rule to a phenolic degradation product. It has been theorized that the biogenesis of 1 and 2 from farnesyl phosphate[3,11,12] occurs in the manner indicated in scheme 5. According to that biosynthetic hypothesis, humelene serves as a precursor of the unique non-isoprenoid structure of the illudins. Investigators are conducting experiments in an effort to determine the biosynthetic sequence leading to the illudins.


3
26
EtO⊖
EtOH
27
(MeO−CH2−C)2O
Py
28
Et OH
Δ
29
t-BuOK
t-BuOH
30, R=H
31, R=Ac
MeMgI
32
NaBH4
33
HgCl2
CH3COCH3
H2O
34
Na2CO3
(racemic Illudin-S)

Scheme 4



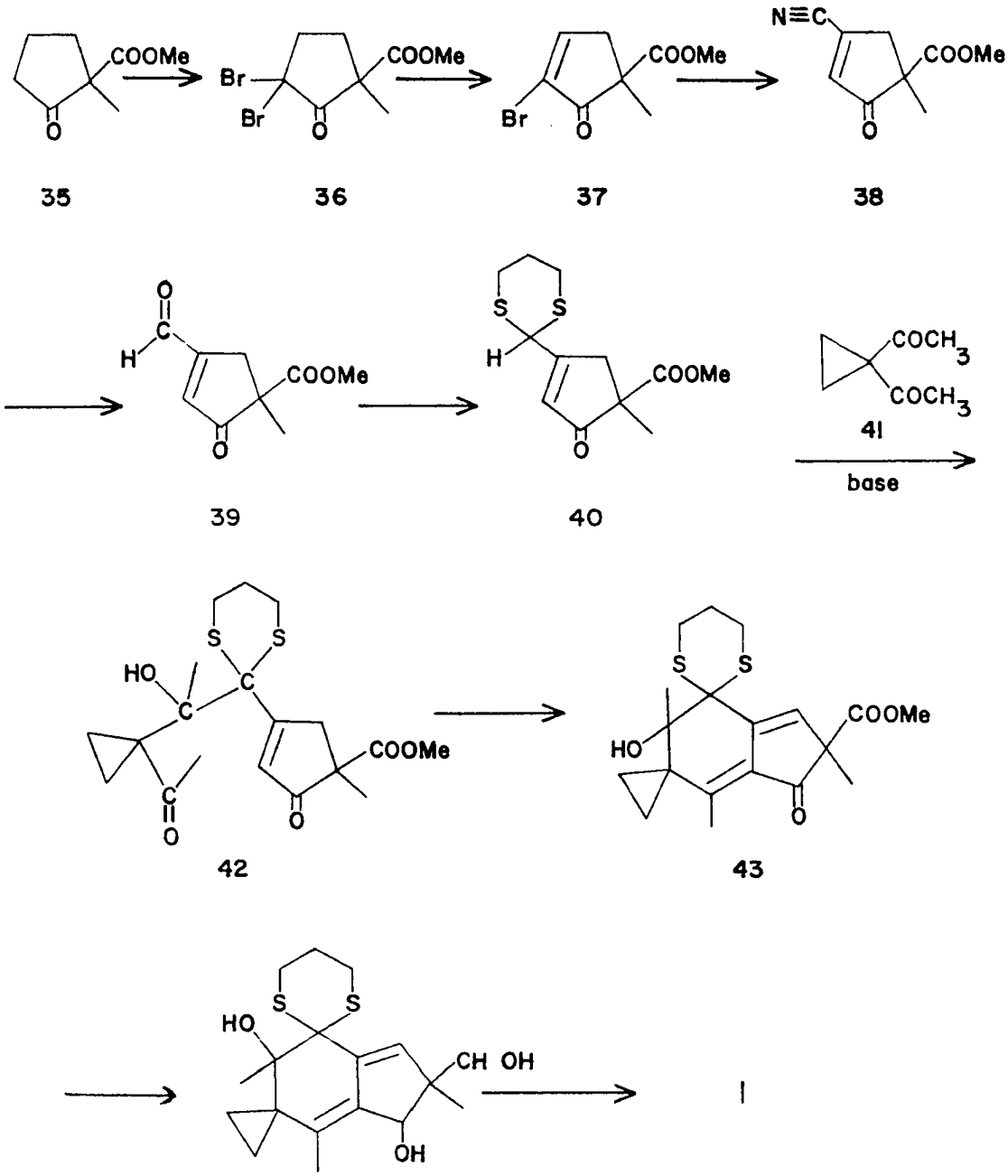
I

Scheme 5

INTRODUCTION

The objective of this study was to develop a sequence of reactions which would ultimately lead to the synthesis of the natural product illudin-S (1). The general approach to the synthesis of 1 is depicted in scheme 6 in which the principal reaction leading to the illudin skeleton involves the combination of the dithiane 40 with 1,1-diacetylcyclopropane (41). Several alternate approaches to the synthesis of the key intermediates 39 and 40 will be discussed in this section.

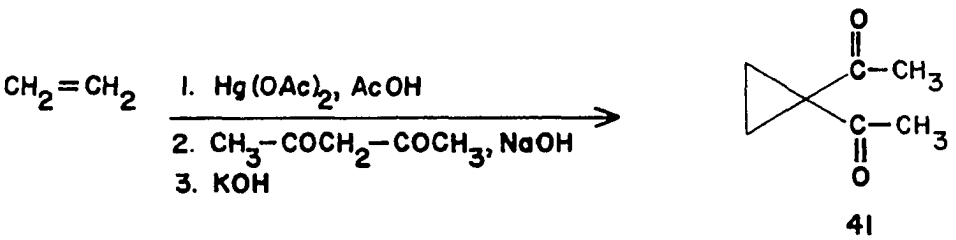
A preliminary report on the synthesis of 2[5] appeared about the time this work was initiated. An examination of the sequence of reactions employed by Matsumoto and coworkers in the synthesis of 2 revealed that the plan for synthesizing 1 and 2 laid out for evaluation in this thesis was different from that of the Japanese workers, and if successful would result in a shorter synthesis of 1 and 2. In view of the fact that the synthesis of 2 had been reported, it was decided to explore methods for synthesizing 1.


COOMe
Br
Br
COOMe
COOMe
Br
N≡C
COOMe
O
35
36
37
38
O
C
H
COOMe
O
39
S
S
H
COOMe
O
40
COCH3
COCH3
41
base
S
S
HO
C
C
C
O
COOMe
O
42
S
S
HO
COOMe
O
43
S
S
HO
CH OH
OH
I

Scheme 6

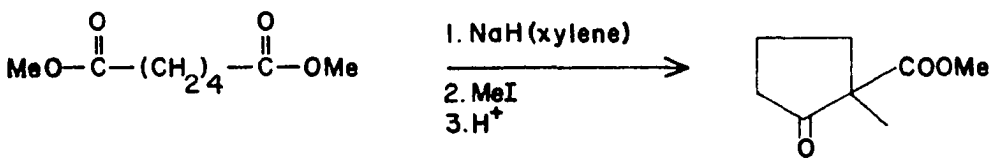
RESULTS AND DISCUSSION

Compound 41 was prepared by the method of Ichakawa and coworkers.[15]



41

2-methyl-2-carbomethoxycyclopentanone (35) was prepared by a slight modification of the procedure of Meyer and coworkers.[17]



35

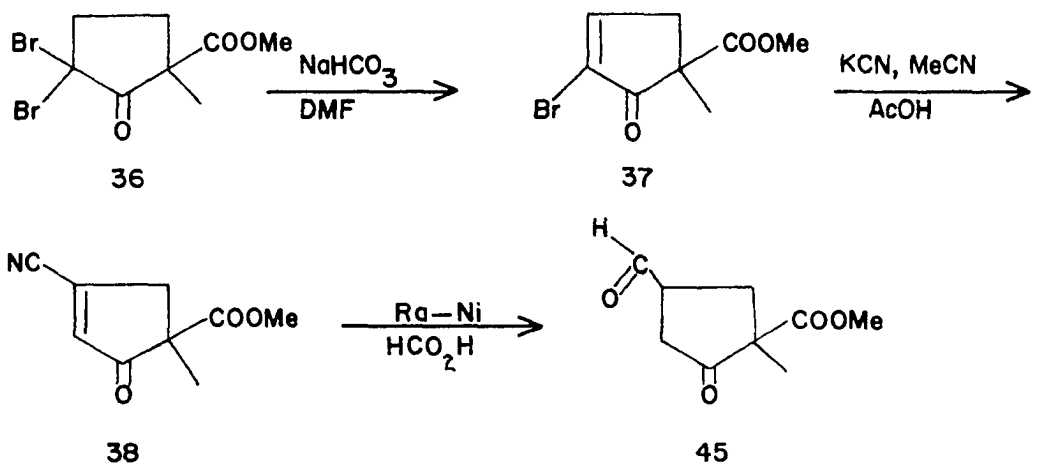
During the early stages of this reaction, the originally fluid suspension of sodium hydride in xylene turned to a thick mush as a result of the insolubility of the enolate of the β-keto ester obtained as a result of step 1. Consequently, the reaction mixture was difficult to stir by ordinary methods and as a result poor yields of the final product 35 were obtained. However, the yield of 35 was improved considerably

by rapid stirring and keeping the reaction mixture fluid by continuously adding solvent at intervals throughout the initial stage of the reaction (enolate formation).

Treatment of 35 with an excess of bromine in methylene chloride afforded 36 in 95% yield (80%) purified. The next step in the reaction sequence called for the dehydrobromination of 36 to 2-bromo-4-methyl-4-carbomethyoxycyclopentene-3-one (37). However, the possibility of the direct conversion of 36 to 38 by the action of alcoholic potassium cyanide was recognized. This conversion could take place by an initial dehydrobromination of 36 to 37 which in turn could undergo a conjugate addition of cyanide ion followed by a second dehydrobromination to give 38. When a solution of 36 in methanol was actually treated with a suspension of potassium cyanide in methanol, a dark tar was obtained. Analysis of the tar by nmr and ir spectroscopy indicated that no olefinic or nitrile groups were present in the product.

After attempts to convert 36 directly to 38 proved to be unsuccessful, attention was directed to accomplishing this conversion in a stepwise sequence, the first of which consisted of the dehydrobromination of 36. Lithium carbonate in dimethylformamide,[18] diazobicyclo [4.3.0] nonene (DBN),[19] and collidine[20] have been used to successfully convert α-haloketones to the corresponding α,β-unsaturated ketones. When a solution of 36 in benzene was treated with diazobicyclo [4.3.0]nonene, a dark tar resulted. Chromatography of the tar on silica gel yielded a small quantity of 37, the desired product. Other dehydrohalogenation procedures employed in attempts to improve the yield of 37, including lithium carbonate in acetone and collidine in acetone, were also unsuccessful. In general, tars and unaltered 36 were recovered.

The dehydrobromination of 36 (see scheme 7) was ultimately accomplished by treatment with sodium bicarbonate in dimethylformamide, whereupon 37 was obtained in 80% yields. Treatment of a solution of 37 in acetonitrile and acetic acid with potassium cyanide afforded 38 in 66-70% yields without isolation of any intermediates.



36 37 38 45

Scheme 7

The next two steps in the reaction sequence called for the conversion of 38 to the α,β-unsaturated aldehyde 39. and the conversion of 39 to the dithiane 40 (see scheme 6). Table summarizes some reported methods for converting nitriles to aldehydes. In our initial approach to the problem of converting the nitrile 38 to the α,β-unsaturated aldehyde 39, various modifications of the procedures of

TABLE 2

A Survey of Literature Procedures for Reducing Nitriles to Aldehydes

Reducing Agent	Solvent	Conditions	% Yield of Aldehyde	Ref.
DiBAH	Et_2O, $MeCl_2$ or	RT. or reflux	70-80	24
$LiAl(OEt)_3H$	Et_2O, T.H.F.	0°	80-90	22
Raney Nickel and $NaH_2PO_3 \cdot H_2O$	NCOOH, or ACOH, H_2O pyridine	R.T.	70-90	21
Raney nickel	formic acid 45-50%	80	80-90	21
HCl, $SnCl_2$	Et_2O	0°	50-90	23
Hydrazine and Raney nickel	H_2O	R.T.	75-80	33

Statsun and Backberg[21] were employed. It was assumed that the nitrile group in 38 would resemble that of benzonitrile in terms of chemical reactivity and, therefore, if benzonitrile could be successfully reduced to benzaldehyde by these procedures, the nitrile 38 could be successfully reduced to the aldehyde 39 under similar conditions. Indeed, when benzonitrile was treated with Raney nickel in formic acid, benzaldehyde was obtained in 80% yields. However, when the nitrile 38 was subjected to the same reaction conditions employed in the reduction of benzonitrile, unaltered 39 was recovered from the reaction mixture.

After several attempts to convert 38 to 39 using the procedures of Statsun and Backberg proved unsuccessful, the reaction conditions were reviewed to determine which factors could be varied in order to bring about the reduction of 38 to 39. The variables considered were the amount of Raney nickel used per gram of nitrile, the volume of formic acid,used per gram of nitrile, the amount of water in the formic acid, the reaction time, the reaction temperature, and the activity of the Raney nickel catalyst. Each of these factors was varied one at a time, but none of the reduction attempts converted 38 to the desired aldehyde 39. However, when a solution of 38 in 75% formic acid was treated with Raney nickel catalyst (1 to 1.5 grams of catalyst per gram of nitrile) at 75-80° for 1-1.5 hours, the saturated aldehyde 45 (see scheme 2) was obtained in 50-60% yields. Thus it was concluded that 38 could not be reduced to 39 by the Raney nickel procedures. It was further concluded that the amount of Raney nickel per gram of nitrile, the reaction time and the reaction temperature were critical to the reduction of 38 to the saturated aldehyde 45. (See table 3 for more details.)

TABLE 3

Results of Attempts to Reduce The Nitrile 38 to the Aldehyde 39

Moles of 38	Reducing Agent and No. of Moles	Solvent + Conditions	Product + % Yield
.0042	$Li(OEt)_3$-Al-H (.0042)	Et_2O, 0°	38 (45)
.004	$Li(OEt)_3$-Al-H (.004)	Et_2O, R.T. 1 hr	38 (80)
.011	$Li(OEt)_3$-Al-H (.001)	THF R.T. 42 hr Reflux 2 hr	38 (90)
.007	DIBAH (.007) R.T. 3 hr	Benzene R.T. 3 hr	38 (80)

Raney Nickel Procedures

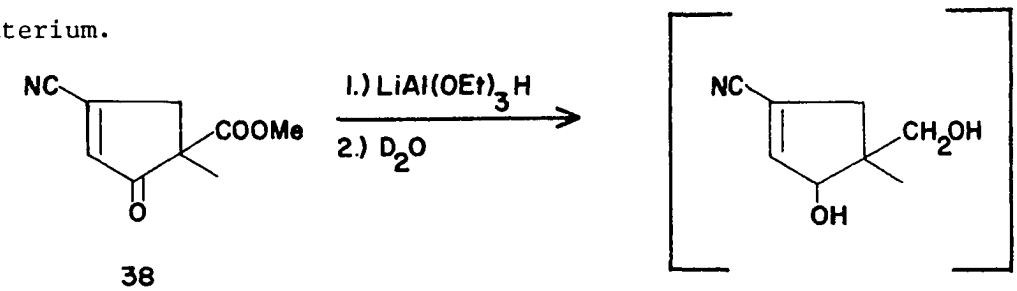
Grams of 38	Grams of Catalyst	Aqueous Solvent	Conditions	% Yield of Product
2	3	50% formic acid	60°, 2 hr	(52) saturated aldehyde 45
2	3	44% formic acid	100°, 7 min	(52) sat. ald. 45
2	2	45% formic acid, 1,2 dichloroethane	30-60° 3 hr	(60) of 45
2	6	44% formic acid	Reflux 5 min	(48) of 45
1	.5	50% formic acid	50-60° 15 min	(80) of 38
1	1.5	50% formic acid	50-60° 15 min	(55) of 45

After attempts to reduce 38 to 39 with various modifications of the Raney nickel procedures proved unsuccessful, some other procedures for the conversion of nitriles to aldehydes were explored. A search of the literature revealed that the methods of Brown,[22] Stephens,[23] Meyer[25,26] and procedures employing diisobutylaluminum hydride[24] have been used to convert nitriles to aldehydes.

The first of these procedures to be explored was the method employing lithium triethoxyaluminum hydride which was developed by Brown.[22] In an effort to develop the technique for applying this potentially useful reaction to the problem of reducing 38 to 30, it was decided that an attempt should be made to duplicate the results obtained by Brown and coworkers in one of their experiments. Accordingly, benzonitrile was treated with lithium triethoxyaluminum hydride, and benzaldehyde was obtained in 80% yields. Brown and coworkers reported a 90% yield.

Since the attempt to duplicate the experimental results of Brown and coworkers[22] proved successful, the nitrile 39 and lithium triethoxyaluminum hydride (1:1 molar ratio) were reacted under the same experimental conditions employed in the reduction of benzonitrile. However, only unaltered 38 was recovered from the reaction mixture. Similar results were obtained when a solution of 38 and triethoxyaluminum hydride (1:1 molar ratio) in tetrahydrofuran was refluxed for about four hours. Next, compound 38 was treated with a tenfold excess of lithium triethoxyaluminum hydride, and the reaction mixture worked up with deuterium oxide. The ir spectrum of the resulting product exhibited strong absorptions at 3450 cm^{-1} (hydroxyl), 2215 cm^{-1} (nitrile) and 1645 cm^{-1}

(carbon-carbon double bond) and lacked the carbonyl absorptions due to the ester and ketone functions of 38. The nmr spectrum of the product indicated that the acidic methylene protons of 38 did not exchange with deuterium.



38

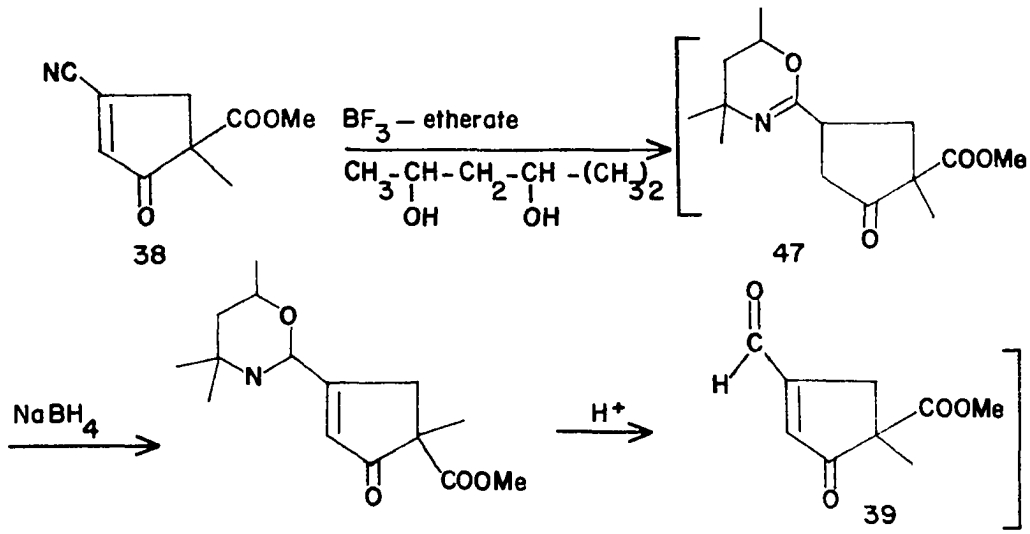
It had been postulated that the inertness of the nitrile function in 38 toward reducing agents might be due to abstraction of the ring methylene protons by the reducing agents to give an enolate that would not react further. However, the evidence presented above does not support this hypothesis.

The failure of these established reduction procedures to effect the conversion of 38 to 39 indicated that a stronger reducing agent should be employed. Accordingly, a solution of 38 and diisobutylaluminum hydride (1:1 molar ratio) in benzene was refluxed for four hours; unaltered 38 was recovered from the reaction mixture. When a solution of 38 and lithium aluminum hydride (4:1 molar ratio) in ether was stirred at -70° for one hour, the ester function of 38 was partially reduced. The ir spectrum of the product mixture exhibited absorptions at 3500 cm^{-1} (OH), 1745 cm^{-1} (ester) and 1710 cm^{-1} (ketone). Further analysis of the mixture by thin layer chromatography (tlc) and nmr spectroscopy indicated that the mixture consisted mostly of 38 and that no aldehyde was formed.

Next, the method of Stephens[23] was utilized in an attempt to reduce 38 to 39. It is reported that the Stephens method fails to

convert α,β-unsaturated nitriles to the corresponding aldehydes. Nevertheless, a mixture of 38 and stannic chloride in absolute ether was treated with dry hydrogen chloride gas; however, only unaltered 38 was recovered from the reaction mixture.

Finally, the procedure developed by Meyers and coworkers[26] was employed in an attempt to convert 38 to 39 (see scheme 8). Based on



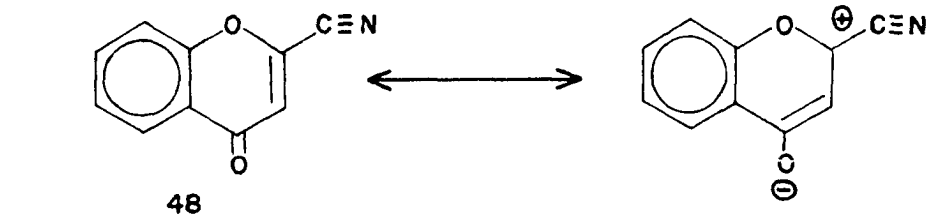
Scheme 8

the examples reported by Meyers and collaborators, it was anticipated that boron trifluoride-etherate catalyzed reaction of 38 with 2-methyl-2,4-pentanediol would result in the formation of the 1,3-oxazine 47. However, when a solution of 38, 2-methyl-2,4-pentanediol and boron trifluoride etherate in ether was maintained at 0° for 48 hours, no appreciable reaction occurred.

In view of the failures encountered in attempts to convert 38 to 39 and the fact that 38 could be successfully reduced to the saturated aldehyde 45 (see scheme 2), some methods for dehydrogenating 45 to give 39 were considered. Literature reports indicated that dichlorodicyanoquinone and selenium dioxide[32] would convert some saturated steriodal

ketones to the corresponding α,β-unsaturated ketones. When a solution of 45 and dichlorodicyanoquinone in benzene was refluxed for about two hr, a dark colored tarry product was obtained. Analysis of the reaction mixture by tlc and nmr spectroscopy indicated the presence of a complex mixture of products which exhibited no aldehyde or olefinic protons. Hence it was concluded that decarbonylation of the aldehyde 45 had taken place during the dehydrogenation attempts. Similar results were obtained when selenium dioxide was reacted with 45

Since all attempts to convert 38 to the corresponding aldehyde 39 failed, the physical data on compound 38 was re-examined. This examination revealed that the structure assigned to 38 was fully consistent with all spectra and analytical data except that the ir spectra of 38 exhibits very weak absorption in the region of 2210 cm^{-1}. A search of the literature revealed that, in general, α,β-unsaturated nitriles substituted in the β-position with a carbonyl group show virtually no absorption in the region 2210 cm^{-1}.[27,28]



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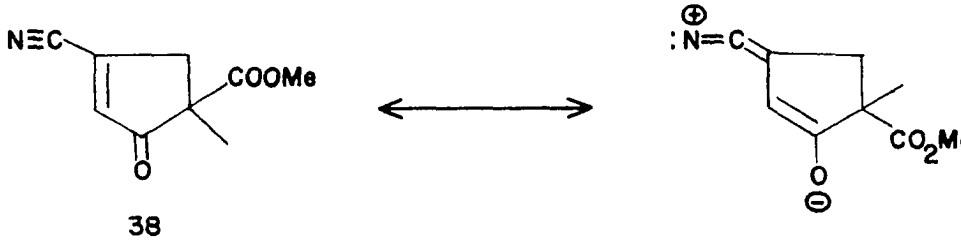


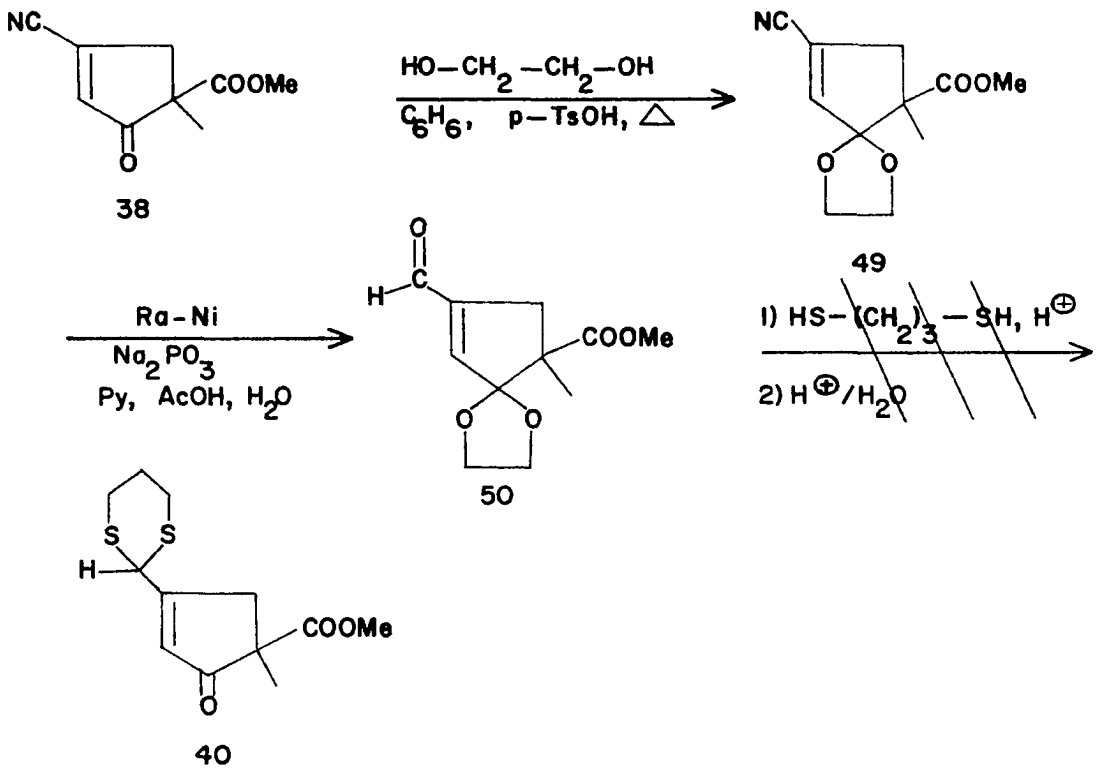
38

In order to account for this abnormality it was proposed that electrons are displaced toward the more electronegative carbonyl group in the

manner indicated for compounds 38 and 48. If the dipolar form of 38 contributes significantly to its overall electronic structure, this might explain why this compound fails to undergo reduction to the corresponding aldehyde.

In view of the fact that cyanide ion adds readily to 37 to form 38 (see scheme 2), it was believed that some other nucleophiles would undergo the Michael reaction with 37 to form precursors to 39 and 40 (see scheme 1). Accordingly the anion of nitromethane[20,30] was prepared by treating nitromethane with potassium t-butoxide in t-butyl alcohol; however, no appreciable reaction occurred when 37 was added to the anion. Attempts to catalyze the addition of nitromethane to 37 with potassium fluoride[31] in absolute ethanol were also unsuccessful. Several attempts to add the anions of 1,3-dithiane and 1,3-dithiane monoxide to 39 were also futile. As a result of these failures, the approaches to the synthesis of 39 and 40 involving the Michael reaction were abandoned and attention was again turned to compound 38.

Treatment of 38 with p-toluenesulfonic acid and ethylene glycol in refluxing benzene (see scheme 9) resulted in the ketalization of the carbonyl group of 38 to form 49 in high yields. The mass spectrum of 49 showed a molecular ion at m/e 223. In sharp contrast to compound 38, the ir spectrum of 49 showed a pronounced absorption at 2210 cm^{-1} due to the cyano group. The nmr spectrum of 49 showed the following important features: a one proton triplet at 6.1 ppm (J = 1.0 Hz), olefinic proton, and a four proton multiplet at 3.95-4.25 ppm, protons on carbons bearing oxygens. The reaction of 49 with Raney nickel and sodium hypophosphite in acetic acid, water and pyridine (1:1:2) afforded



Scheme 9

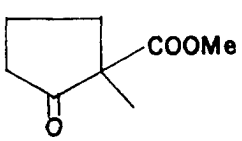
the aldehyde 50 in 60% yields. The mass spectrum of 50 exhibited a molecular ion at m/e 226. The ir spectrum showed significant absorptions at 1740 cm^{-1} (ester carbonyl) and 1685 cm^{-1} (aldehyde carbonyl). The uv spectrum showed λ_{max}^{EtOH} 218 mμ (ε, 18,000). The nmr spectrum of 50 showed the following important features: a sharp singlet at 9.5 ppm, aldehyde proton; a triplet at 6.4 ppm (J = .5 Hz) olefinic proton, and a four proton multiplet at 3.90-4.25 ppm, protons on carbon atoms bearing oxygens.

The next step in the reaction sequence called for the reaction of 50 with 1,3-propanedithiol (see scheme 4) followed by hydrolysis of ketal moiety to form the ketothioacetal 40. When this reaction was attempted using boron trifluoride-etherate as the catalyst, a mixture of products inseparable by alumina or thin layer chromatography

was isolated. This mixture exhibited practically no olefinic proton absorption in its nmr spectrum. Presumably, the 1,3-propanedithiol reacted with the carbon-carbon double bond of 50 as well as the aldehyde function under the reaction conditions (chloroform, 0°). Inverse addition (the addition of a solution of 1,3-propanedithiol and the acid catalyst) to the aldehyde produced the same results. The use of weaker acid catalysts such as p-toluenesulfonic acid, zinc chloride, and stannic chloride, as well as varying the reaction temperature from 0° to -70° were to no avail. Other attempts to circumvent the problem posed by the facile addition of 1,3-propanedithiol to carbon-carbon double bond of 50 were also futile; these attempts included hydrolysis of the ketal function and bromination of the double bond. In view of these insurmountable difficulties combined with the time and effort devoted to the project, the attempt to synthesize 1 was abandoned.

SUMMARY

Attempts to synthesize illudin-S (1) resulted in the preparation of the compounds depicted in scheme 10.



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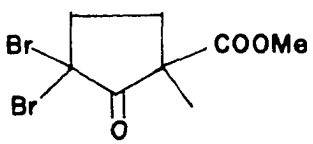

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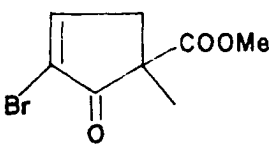

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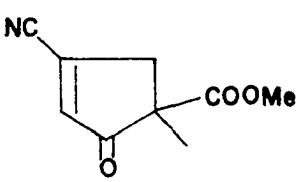

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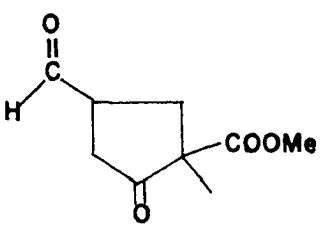

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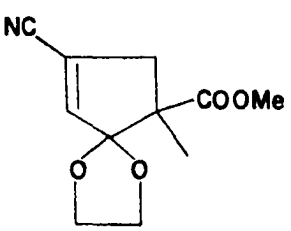

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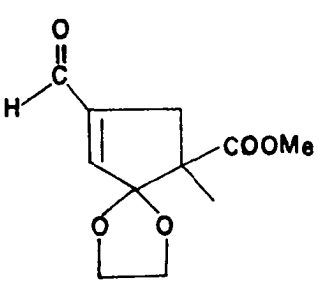

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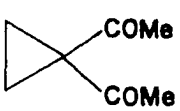

Scheme 10

EXPERIMENTAL

All melting points and boiling points are uncorrected. All solvents were redistilled prior to use. Anhydrous solvents were prepared by distillation from calcium hydride. Column chromatography supports were silicAR CC-7 (Mallinckrodt, 100/200 mesh) and silica gel H (Merck AG, Darmstadt). Thin layer chromatography was performed on 5 x 20 cm glass plates coated with silica gel H (Merck AG, Darmstadt). The developed plates were exposed to iodine vapor for visualization of the chromatogram.

Gas chromatographic analyses were performed on a Varian Aerograph Model 1220-1 or Aerograph Model 1240-1 gas chromatograph. The infrared spectra were taken on a Beckman IR-8 as potassium bromide pellets or in solutions of carbon tetrachloride or chloroform. Ultraviolet spectra (uv) were taken in 95% ethanol solutions with the Hitachi Perkin-Elmer, Model 124, spectrometer.

Nuclear magnetic resonance spectra (nmr) were taken on a Varian A-60 or T-60 spectrometers using tetramethylsilane (TMS) as an internal reference. Samples were run in varying concentrations of carbon tetrachloride and deuterochloroform. Chemical shifts are reported in δ-units (parts per million from TMS), and are followed by the multiplicity of the signal, the number of protons, the corresponding coupling constant and the assignment. The multiplicities are denoted by the symbols: s, singlet; d, doublet; dd, double doublet; t, triplet; and m, multiplet.

The mass spectra were taken on a Hitachi Perkin-Elmer RMU-7E spectrometer using perfluorokerosene as an internal reference. Major peaks and molecular ions are reported followed by percentage of the base peak.

Combustion analyses were carried out by Bernhardt Laboratories in Mülheim, West Germany, and Mr. E. Meier, Chemistry Department, Stanford University, Palo Alto, California.

2-Methyl-2-Carbomethoxycyclopentanone (35)

The procedure of Meyer and coworkers[17] was used.

To a 5-l three-necked flask which was equipped with a mechanical stirrer, a Vigrueaux column carrying a distillation head, and an addition funnel were added 24 g (1 mol) of sodium hydride as a 57% dispersion in mineral oil and 2 l of dry xylene. Under a nitrogen atmosphere (which was maintained throughout the reaction) 174 g (1 mol) of dimethyl adipate was added and the reaction mixture was stirred and the methanol xylene azeotrope was slowly distilled. After about 2 hr a thick mush formed and an additional 100-1500 ml of xylene was added to the reaction mixture. The reaction mixture was stirred rapidly and the distillation was continued until the temperature of the distillate reached 120°. The reaction mixture was cooled to room temperature, 213 g (1.5 mol) of methyl iodide was added to the reaction mixture and stirring was continued for 16 hr. An additional 71 g (.5 mol) of methyl iodide was added to the reaction mixture, stirring was continued for 24 hr and the mixture was distilled in order to remove the excess methyl iodide. The mixture was cooled to room temperature, 500 ml of 10% hydrochloric acid was added to the mixture and the layers were separated. The aqueous layer was extracted once with 500 ml of 1:1 ether-benzene, the combined organic layers were washed with a saturated solution of

sodium bisulfite and dried over anhydrous sodium sulfate. Removal of the solvents by distillation yielded 145.2 g of a mixture of the crude keto ester and mineral oil. Distillation of the mixture on a spinning band column yielded 114.5 g (78%) of 2-methyl-2-carbomethoxycyclopentanone (35) as a colorless liquid, bp 92-94° (6 mm), n_D^{25} 1.4532 [Lit[16] bp 105-106° (15 mm)]; ir (CCl_4) 1760 cm^{-1} (ketone carbonyl), 1740 cm^{-1} (ester carbonyl); nmr ($CDCl_3$) δ 3.68 (s, 3, ester methyl), 1.85-2.6 (m, 6, methylene protons), 1.23 (s, 3, quatenary methyl).

5,5-Dibromo-2-methyl-2-carbomethoxycyclopentanone (36)

A solution of 104 g (0.66 mol) of 2-methyl-2-carbomethoxycyclopentanone (35) in 350 ml of dichloromethane was placed in a one liter three-necked flask which was equipped with a magnetic stirring bar, an addition funnel, and a condenser. The contents of the flask were stirred and 224 g (1.4 mol) of bromine in 50 ml of dichloromethane was added dropwise to the flask over a 30 min period. Hydrogen bromide was evolved immediately, and stirring was continued for an additional 12 hr. The methylene chloride solution was first washed with a 10% sodium bicarbonate solution to remove the hydrogen bromide, and then with a saturated solution of sodium bisulfite to remove the excess bromine. The methylene chloride solution was then dried over anhydrous sodium sulfate and evaporated to yield 190 g (91%) of the dibromide as a yellow oil. Distillation of 10 g of the crude product yielded 8.2 g (75%) of 2-methyl-2-carbomethoxy-5,5-dibromocyclopentanone (36) as a colorless liquid, bp 98-100° (2 mm). An analytical sample was obtained by collecting a middle fraction from the distillate, bp 98-100° (2 mm), n_D^{25} 1.5198; ir (CCl_4) 1768 cm^{-1} (ketone carbonyl), 1735 cm^{-1} (ester carbonyl);

nmr (CCl_4) δ 3.73 (s, 3, ester methyl), 1.85-3.2 (m, 6, methylene protons), 1.58 (s, 3, quatenary methyl); mass spectrum 316 (13), 315 (3), 314 (20), 312 (13), 286 (28), 185 (19), 175 (34), 173 (29), 165 (21), 127 (39), 95 (23), 69 (100), 66 (25), 65 (24), 59 (25), 41 (70).

Anal. Calcd for $C_8H_{10}Br_2O_3$: C, 30.57; H, 3.19; O, 15.29. Found: C, 30.78; H, 3.34; O, 15.45.

2-Bromo-5-methyl-5-carbomethoxy-2-cyclopenten-1-one (37)

A mixture of 21 g (.25 mol) of sodium bicarbonate and 62.8 g (.20 mol) of 2-methyl-2-carbomethoxy-5,5-dibromocyclopentanone (36) and 125 ml of dimethylformamide was placed in a 500 ml three necked flask which was equipped with a magnetic stirring bar and a condenser. The flask was immersed in an oil bath, the temperature of the bath was raised to 80°, and the reaction mixture was stirred and heated for 4 hours with the temperature of the bath being maintained at 80-85°. Then the reaction mixture was allowed to cool to room temperature and poured into 500 ml of benzene. The benzene solution was filtered in order to remove the insoluble inorganic residue, and washed several times with water to remove the dimethylformamide. The benzene solution was dried over anhydrous sodium sulfate and the solvent was evaporated to yield 38.5 g (83.3%) of crude product as a dark brown oil. Distillation of the crude product yielded 2-bromo-5-methyl-5-carbomethoxy-2-cyclopenten-1-one (37) as a colorless oil (31.5 g, 70%), bp 132-134° (1 mm). The oil crystallized on cooling to form a white solid, mp 48-49°. An analytical sample was obtained by collecting a middle fraction from the distillate, bp 132-134° (1 mm), mp 48-49°. Recrystallization from hexane-methylene chloride did not change the melting point; ir (CCl_4)

1745 cm^{-1} (ester carbonyl), 1725 cm^{-1} (ketone carbonyl), 1585 cm^{-1} (carbon-carbon double bond); uv (λ_{max}^{EtOH}) 243 mμ (ε 6,857); nmr (CCl_4) δ 7.86 (t, 1, J = 2 Hz, olefinic proton), 3.68 (s, 3, ester methyl), 3.30 (dd, 1, J = 2 Hz, J = 18 Hz, methylene proton), 2.60 (dd, 1, J = 2 Hz, J = 18 Hz, methylene proton), 1.40 (s, 3, quatenary methyl); mass spectrum, 235 (2), 234 (24), 233 (3), 232 (22), 175 (15), 174 (12), 173 (14), 172 (10), 121 (100), 66 (21), 65 (32), 59 (13), 53 (11), 41 (15).

Anal. Calcd. for $C_8H_9BrO_3$: C, 41.20; H, 3.85; Br, 34.33. Found: C, 41.37; H, 3.90; Br, 34.41.

4-Methyl-1-cyano-4-carbomethoxy-2-cyclopenten-3-one (38)

Into a 500 ml three-necked flask which was equipped with an addition funel, a magnetic stirring bar and a gas inlet were placed 26 g (.4 mol) of potassium cyanide and 125 ml of acetonitrile. The gas inlet was connected to a trap containing a saturated solution of sodium hydroxide. A solution of 31 g (.13 mol) of 2-bromo-5-methyl-5-carbomethoxy-2-cyclopenten-1-one (37) in 100 ml of acetic acid was added dropwise to the mixture over a 30 min period. The reaction mixture was stirred at room temperature until all of the starting compound had reacted as indicated by nmr and thin layer chromatographic analysis (about 5 days). The reaction mixture was then poured into 300 ml of benzene and washed several times with a 10% solution of sodium bicarbonate in order to remove the acetic acid. The benzene solution was then dried over anhydrous sodium sulfate and evaporated to yield 20 g (86%) of a yellow oil. Distillation yielded 16.4 g (70%) of 4-methyl-1- -4-carbomethoxy-2-cyclopenten-3-one (38) as a light yellow oil

bp 120-122° (1 mm), mp 38-39°. Recrystallization from 1:1 hexane-methylene chloride did not change the melting point. An analytical sample was obtained by collecting a middle fraction from the distillate, bp 120-122° (1 mm), mp 38-39°; ir (CCl_4) 1755 cm^{-1} (ketone carbonyl), 1725 cm^{-1} (ester carbonyl); 1595 cm^{-1} (carbon-carbon double bond); uv (λ_{max}^{EtOH}) 250 mμ (ε 22,000); nmr (CCl_4) δ 6.75 (t, 1, J = 1.5 Hz, olefinic proton), 3.72 (s, 3, ester methyl), 3.45 (dd, 1, J = 1.5 Hz, J = 18 Hz, methylene proton), 2.75 (dd, 1, J = 1.5 Hz, J = 18 Hz, methylene proton), 1.45 (s, 3, quatenary methyl); mass spectrum, 180 (6), 179 (42), 168 (35), 164 (60), 148 (29), 147 (65), 316 (29), 121 (21), 120 (100), 119 (57), 109 (28), 108 (55), 93 (23), 92 (58), 91 (37), 81 (26), 69 (20), 66 (36), 65 (76), 59 (44), 55 (20), 51 (20), 43 (41), 41 (53).

Anal. Calcd. for $C_9H_9NO_3$: C, 60.34; H, 5.03; N, 7.82; O, 26.81. Found: C, 60.26; H, 5.16; N, 7.73; O, 26.67.

Methyl 1-methyl-4-cyano-2-ethylenedioxy-3-cyclopenten-1-carboxylate (49)

In a 500 ml one-necked flask which was equipped with a Dean Stark phase separator (carrying a reflux condenser) and a magnetic stirring bar were placed 6 g (.033 mol) 4-methyl-1-cyano-4-carbomethoxy-1-cyclopenten-3-one (38), 10 g (.16 mol) of ethylene glycol, 50 mg of p-toluenesulfonic acid and 60 ml of dry benzene. A sufficient quantity of dry benzene was placed in the phase separator in order to maintain a constant volume of benzene within the flask during the reaction and the reactiom mixture was stirred and refluxed with the continuous removal of water for a period of about 60 hr. The benzene solution was washed once with 50 ml of a 10% solution of sodium bicarbonate and dried over anhydrous sodium sulfate. The benzene was removed on the

rotary evaporator to yield 6.38 g (92%) of the cyano ketal as a yellow solid, mp 56-58°. Recrystallization from 1:1 benzene-hexane yielded 6.2 g (88%) of methyl 1-methyl-4-cyano-2-ethylenedioxy-3-cyclopenten-1-carboxylate (49) as a white crystalline solid, mp 59-60°. Two recrystallizations from benzene-hexane yielded an analytical sample, mp 60-61°; ir (KBr) 2218 cm^{-1} (nitrile stretch), 1745 cm^{-1} (ester carbonyl), 1632 cm^{-1} (carbon-carbon double bond stretch), 1075 cm^{-1} (carbon-oxygen stretch); uv (λ_{max}^{EtOH}) 215 mμ (ε 680); nmr ($CDCl_3$) δ 6.10 (t, 1, J = 1.5 Hz, olefinic proton), 3.95-4.20 (m, 4, methylene protons on carbons bearing oxygens), 3.70 (s, 3, ester methyl), 3.45 (dd, 1, 1.5 Hz, J = 18 Hz, one of the methylene protons of the five membered ring), 2.35 (dd, 1, J = 1.5 Hz, J = 18 Hz, remaining methylene proton of the five membered ring), 1.35 (s, 3, quatenary methyl); mass spectrum 224 (5), 223 (29), 208 (84), 192 (93), 191 (20), 166 (54), 164 (70), 165 (100), 151 (33), 137 (20), 136 (62), 135 (20), 134 (24), 124 (30), 121 (25), 120 (45), 119 (33), 107 (30), 123 (60), 103 (20), 93 (46), 92 (32), 91 (55), 90 (23), 86 (24), 80 (37), 79 (76), 78 (27), 77 (65), 76 (21), 69 (22), 66 (38), 65 (39), 64 (44), 63 (36), 59 (54), 53 (25), 52 (50), 51 (66), 50 (54), 40 (39).

Anal. Calcd. for $C_{11}H_{13}NO_4$: C, 59.20; H, 5.83; N, 6.78. Found: C, 59.05; H, 5.85; N, 6.41.

3-Ethylenedioxy-4-methyl-4-carbomethoxycyclopenten-1-carboxaldehyde (50)

The procedure followed was that of Staskun and Backberg.[21] A suspension of 10 g of Raney nickel catalyst (1:1 nickel-aluminum) and 200 ml of 2N sodium hydroxide were stirred at room temperature for 40 minutes in a 2-l flask. The base was decanted and the activated catalyst

was washed three times with water. Then a solution of 10 g (.045 mol) of methyl 1-methyl-4-cyano-2-ethylenedioxy-3-cyclopenten-1-carboxylate (49) in 100 ml of methanol, 400 ml of a 2:1:1 mixture of pyridine-acetic acid-water and 40 g (.30 mol) of sodium hypophosphite was added to the flask and the reaction mixture was stirred at room temperature in a nitrogen atmosphere for 12 hr. The reaction mixture was filtered with suction and the filtrate was poured into 600 ml of chloroform. The chloroform solution was washed first with a 10% solution of hydrochloric acid in order to remove the pyridine, and then a 10% solution of sodium bicarbonate to remove the acetic acid. The chloroform solution was then dried over anhydrous sodium sulfate and evaporated on the rotary evaporator to yield 6.8 g (68%) of the crude aldehyde 50 as a dark yellow solid, mp 65-66°. Recrystallization from hexane-methylene chloride (1:1) yielded 5.2 g (52%) of 3-ethylenedioxy-4-methyl-4-carbomethoxycyclopenten-1-carboxaldehyde (50) as a white solid, mp 68-69°. Two recrystallizations from benzene-hexane yielded an analytical sample, mp 69-70°; ir ($CHCl_3$) 2820 and 2715 (formyl carbon-hydrogen stretch), 1735 (ester carbonyl), 1685 (aldehyde carbonyl), and 1625 cm^{-1} (carbon-carbon double bond); uv (λ_{max}^{EtOH}) 215 mμ (ε 18,000); nmr ($CDCl_3$) δ 9.5 (s, 1, aldehyde proton), 6.4 (t, J = 1.5 Hz, 1, olefinic proton), 4.2-3.8 (m, 4, methylene protons on carbon atoms bonded to oxygens), 3.6 (s, 3, ester methyl), 3.3 (dd, 1, J = 1.5 Hz, J = 18 Hz, methylene proton of five membered ring), 2.3 (dd, 1, J = 1.5 Hz, J = 18 Hz, methylene proton of five membered ring), 1.35 (s, 3, quatenary methyl); mass spectrum 227 (3), 226 (16), 182 (30), 150 (25), 125 (16), 123 (19), 122 (26), 101 (43), 95 (32), 84 (30), 69 (55), 59 (35), 58 (28), 56 (14), 55 (20), 45 (20), 43 (41), 42 (15), and 41 (100).

Anal. Calcd. for $C_{11}H_{14}O_5$: C, 58.41; H, 6.19. Found: C, 57.71; H, 5.88.

1,3 Dithiane

In a one liter three-necked flask which was equipped with a reflux condenser, an addition funnel, and a magnetic stirring bar were placed 300 ml of chloroform and 10 ml of boron trifluoride etherate. The chloroform was refluxed gently, and 57 g (.75 mol) of freshly distilled dimethoxymethane and 54 g (.50 mol) of 1,3-propanedithiol were added slowly through the addition funnel. When the addition was completed, the heating was ceased and the reaction mixture was stirred for 12 hours at room temperature. The chloroform solution was washed twice with 50 ml of a 10% solution of sodium hydroxide, dried over anhydrous sodium sulfate and evaporated on the rotary evaporator to yield 48.3 g (80%) of 1,3-dithiane as a crystalline white solid, mp 48-49° [lit.[33] mp 54°].

1,3-Dithiane Monoxide

The procedure used was that of Carlson and Helquist.[34] A solution of 4 g (.033 mol) of 1,3-dithiane in 250 ml of methanol was placed in a 500 ml three-necked flask which was equipped with an addition funnel and a mechanical stirrer. The flask was immersed in an ice-water bath at 10°, the solution was stirred and a solution of 7.36 g (.034 mol) of sodium metaperiodate in 70 ml of water was added to the reaction mixture over a 30 min period. Stirring and cooling were continued for 30 min, and then the mixture was filtered to remove the sodium iodate. The filtrate was evaporated to near dryness on the rotary

evaporator and extracted with chloroform. The chloroform solution was dried over anhydrous sodium sulfate and evaporated to yield 3.98 g (90%) of crude 1,3-dithiane monoxide, mp 80-82°. Two recrystallizations from cyclohexane-chloroform 1:1 yielded 3.42 g (83%) of 1,3-dithiane monoxide as a white solid, mp 87-88° [Lit. mp 87°].

4-Methyl-3-oxo-4-carbomethoxycyclopentane-1-carboxaldehyde (45)

The procedure followed was a slight modification of the procedure of Staskun and Backberg.[21] A suspension of 6 g of Raney nickel alloy and 120 ml of 2N sodium hydroxide was stirred for 40 min at room temperature. The base was decanted and the activated catalyst was washed three times with water. Then 15 ml of water was added to the activated catalyst and the mixture was heated to 80° and a solution of 2 g (11 mmol) of methyl 1-methyl-4-cyano-3-ethylenedioxy-3-cyclopenten-1-carboxylate (38) in 17 ml of 88% formic acid was added to the mixture. The heating was continued at 80° for 5 min and the hot reaction mixture was then poured into 50 ml of water and extracted with 100 ml of chloroform. The chloroform solution was washed several times with a 10% solution of sodium bicarbonate and dried over anhydrous sodium sulfate. Evaporation of the solvent yielded .950 g (49%) of a mixture of the diastereomeric forms of 45 as a dark yellow oil. Bulb to bulb distillation of the oil yielded .732 g (37%) of the aldehyde as a colorless oil, bp 110-112° (.2 mm). An analytical sample was prepared by preparative gas chromatography (JXR 3%, 1.5% gas chrom. Q 8' x 3/8"); ir (CCl_4) 2705 cm^{-1} (formyl C-H), 1755 cm^{-1} (ester carbonyl), 1740-1720 cm^{-1} (ketone and aldehyde carbonyls); nmr ($CDCl_3$) δ 9.8 (bs, 1, aldehyde proton), 3.8, 3.68 (singlets, total of 3 H, ester methyl), 1.75-3.4

(m, 5, methylene protons), 1.4, 1.35 (singlets, total of 3 H, quaternary methyl); mass spectrum 184 (7), 153 (28), 127 (16), 125 (20), 124 (17), 122 (16), 121 (38), 110 (18), 100 (98), 96 (21), 95 (17), 94 (50), 93 (28), 84 (19), 83 (80), 82 (17), 81 (16), 80 (16), 77 (35), 76 (15), 73 (16), 68 (77), 67 (15), 66 (80), 65 (15), 59 (17), 58 (20), 55 (26), 54 (44), 45 (87), 44 (100), 43 (48), 42 (71), 41 (20) and 40 (90).

Anal. Calcd. for $C_9H_{12}O_4$: C, 58.66; H, 6.52. Found: C, 58.17; H, 6.47.

The attempted reaction of the anion of 1,3-dithiane with 2-bromo-5-methyl-5- carbomethoxy -2-cyclopenten-1-one (37). The apparatus was flame dried in a nitrogen atmosphere which was maintained throughout the experiment. A solution of 2.27 g (.021) of 1,3-dithiane in 100 ml of dry, freshly distilled tetrahydrofuran was placed in 250 ml three necked flask which was equipped with a septum cap, a mechanical stirrer and nitrogen inlet. The flask was flushed with nitrogen, immersed in a dry ice-acetone bath at -30° and 13.1 ml of a 1.6 molar solution of n-butyllithium in hexane was slowly added by means of a syringe to the flask. The reaction mixture was stirred for 3 hr at -30°, and a solution of 5 g (.021 mol) of 2-bromo-5-methyl-5-carbomethoxy-2-cyclopenten-1-one (37) in 25 ml of dry tetrahydrofuran was added slowly to the reaction mixture. Stirring was continued for 48 hr at 0-10°, the reaction mixture was poured into 100 ml of water and acidified to a pH of 4 with 2N hydrochloric acid. The reaction mixture was extracted twice with 100 ml portions of chloroform. The chloroform solution was dried

over anhydrous sodium sulfate and removed on the rotary evaporator to yield 5.83 g of product mixture. Analysis of the mixture by tlc and nmr spectroscopy indicated that no appreciable reaction occurred.

The attempted Michael Addition of the anion of 1,3-dithiane monoxide with 2-bromo-5-methyl-5-carbomethoxy-2-cyclopenten-1-one (37). The procedure of Carlson and Helquist[34] was used to prepare the anion of 1,3-dithiane monoxide. A nitrogen atmosphere was maintained throughout the experiment. A 250 ml three-necked flask containing a solution of 2.94 g (.216 mol) of 1,3-dithiane monoxide in 100 ml of tetrahydrofuran was immersed in a calcium chloride-ice water bath at -10° and 13.1 ml of a 1.6 molar solution of n-butyllithium was added to the flask over a 5 min period. The reaction mixture was stirred at -10° for 30 min and a solution of 5 g (.216 mol) of 2-bromo-5-methyl-5-carbomethoxy-2-cyclopenten-1-one (37) in 50 ml of tetrahydrofuran was added to the anion. Stirring was continued for 1 hr at 0° and 24 hr at room temperature. The reaction mixture was then acidified with 1N hydrochloric acid and extracted with 100 ml of chloroform. The chloroform solution was dried over anhydrous sodium sulfate and evaporated to yield a mixture of a polymeric substance and 2-bromo-5-methyl-5-carbomethoxy-2-cyclopenten-1-one (37).

The attempted Stephen Reduction of 4-methyl-1-cyano-4-carbomethoxy-1-cyclopenten-3-one (38). The procedure of Stephens[23] was used.

Preparation of the stannous chloride reducing agent. To a beaker containing 30 ml of acetic anhydride, 22.6 g (.1 mol) of stannous chloride dihydrate was slowly added. The anhydrous salt separated from

the solution immediately. The salt was collected by suction filtration and air dried under vacuum. Yield of anhydrous stannous chloride was 18.5 g (97%).

In a dry 250 ml three-necked flask which was equipped with calcium chloride tubes and a gas inlet was placed a suspension of 1.5 g (8 mmol) stannous chloride in 50 ml of absolute ether. The suspension was saturated with dry hydrogen chloride gas until a homogeneous mixture was attained. Then a solution of 1 g (5.6 mmol) of 4-methyl-1-cyano-4-carbomethoxy-1-cyclopenten-3-one in 10 ml of absolute ether was added to the reaction mixture. The reaction mixture was stirred at room temperature and after about 10 minutes a yellow oil separated from the solution. Stirring was continued for an additional 4 hr at room temperature, and the ether was decanted. The oil was collected, refluxed with 100 ml of water for 2 hr and poured into 100 ml of ether. The ether solution was dried over anhydrous sodium sulfate and removed on the rotary evaporator to yield .895 g of unaltered 38.

The reaction of 4-methyl-3-oxo-4-carbomethoxycyclopentane-1-carboxaldehyde (45) with selenious acid. The procedure of Schafer[32] was used.

A solution of 200 mg (1.12 mmol) of 45

and 200 mg of selenious acid in 10 ml of benzene was refluxed in a nitrogen atmosphere for 24 hr. Evaporation of the solvent left .358 g of a dark residue which was filtered through a column containing 20 g of activity 6 neutral alumina. Analysis of the product by thin layer chromatography and nmr spectroscopy indicated a complex mixture of products which exhibited no olefinic or aldehyde protons.

Similar results were obtained when dichlorodicyanoquinone was substituted for selenious acid in the above procedure.

The reaction of sodium cyanide with (36). A suspension of 1 g (17 mmol) of sodium cyanide and .7 g (2.2 mmol) of 5,5-dibromo-2-methyl-2-carbomethoxycyclopentanone (36) in 50 ml of methanol was refluxed in a nitrogen atmosphere for 18 hr and cooled to room temperature. The reaction mixture was concentrated on the rotary evaporator and dissolved in 100 ml of methylene chloride. The methylene chloride solution was washed several times with water and dried over anhydrous sodium sulfate. Evaporation of the methylene chloride yielded a dark tar which exhibited no olefinic or nitrile absorption when analyzed by nmr and ir spectroscopy.

The reaction of 5,5-dibromo-2-methyl-2-carbomethoxycyclopentanone (36) with 1,5-diazobicyclo[4.3.0]-5-nonene (DBN). The procedure of Oidiger[19] was used.

A solution of 8 g (.025 mol) of 5,5-dibromo-2-methyl-2-carbomethoxycyclopentanone (36) and 3.1 g (.025 mol) of DBN in 100 ml of dichloromethane was stirred in a nitrogen atmosphere at 0° for 1.5 hr. The dichloromethane solution was washed several times with a 10% solution of hydrochloric acid and dried over anhydrous sodium sulfate. Evaporation of the solvent yielded 5.2 g of a dark yellow oil. Analysis by thin layer chromatography indicated the presence of two products. The oil was chromatographed on 280 g of 100-200 mesh silic acid (50 x 4-1/2 cm column). A solution of 6.2 g of the oil was eluted with benzene and 75 ml fractions were collected. Fractions 14 + 15 were combined; evaporation of the solvent yielded .620 g of the unreacted amine. After fraction 16, the solvent was changed to 95% benzene-5%

ethyl acetate. Fractions 25 and 26 yielded 2.78 g (47%) of 2-bromo-5-methyl-5-carbomethoxy-2-cyclopenten-1-one (37) as a yellow solid, mp 48-49°.

The attempted reaction of the anion of nitromethane with 2-bromo-5-methyl-5-carbomethoxy-2-cyclopenten-1-one (37). The nitromethane was dried over anhydrous sodium sulfate and distilled from calcium hydride. The apparatus was flame-dried in a nitrogen atmosphere which was maintained throughout the experiment.

In a 250 ml three-necked flask which was equipped with a gas inlet and an addition funnel was placed a mixture of 1.3 g (.02 mol) of nitromethane, 1.16 g (.02 mol) of sodium methoxide and 50 ml of absolute methanol. The flask was immersed in an ice-water bath at 0-5°, flushed with nitrogen, and the reaction mixture was stirred for 1 hr at 0-5°. A solution of 2-bromo-5-methyl-5-carbomethoxy-2-cyclopenten-1-one (37) in 25 ml of absolute methanol was then added to the reaction mixture and stirring was continued for 12 hr at 0-10° at which time an aliquot was removed from the flask and analyzed by thin layer chromatography and nmr spectroscopy. No appreciable reaction occurred under these conditions. Similar results were obtained when the reaction was run at room temperature or refluxed.

When the above procedure was repeated using potassium-t-butoxide in t-butanol instead of sodium methoxide in methanol, only starting materials were recovered.

The attempted Michael addition of the anion of nitromethane to 2-bromo-5-methyl-5-carbomethoxy-2-cyclopenten-1-one (37) using potassium fluoride as the catalyst. A mixture of 1.8 g (.03 mol) of nitromethane, 2.33 g (.01 mol) of 2-bromo-5-methyl-5-carbomethoxy-2-cyclopenten-1-one

(37) and .1 g potassium fluoride in 50 ml of absolute ethanol was refluxed for 8 hr. The ethanol solution was poured into 100 ml of water and extracted twice with 100 ml portions of ether. The ether solution was dried over anhydrous sodium sulfate and evaporated to yield 2.25 g of the unaltered 37.

The attempted reaction of 2-methyl-2,4-pentanediol with (38). A 125 ml Erlenmeyer flask containing a solution of 1.2 g (.01 mol) of 2-methyl-2,4-pentanediol, 1 g (.006 mol) of 4-methyl-1-cyano-4-carbomethoxy-1-cyclopenten-3-one (38), and .1 ml boron trifluoride-etherate in 25 ml of absolute ether was stored in a refrigerator for 48 hr. Analysis of the mixture by tlc indicated that no reaction had occurred.

The reaction of 1,3-propanedithiol with 3-ethylenedioxy-4-methyl-4-carbomethoxycyclopenten-1-carboxaldehyde (50). A solution of 2.8 g (12 mmol) of 3-ethylenedioxy-4-methyl-4-carbomethoxycyclopenten-1-carboxaldehyde (50) in 15 ml of chloroform was placed in a 100 ml three-necked flask. The flask was placed in an ice-water bath at 0°, flushed with nitrogen and a solution of 1.23 g (12 mmol) of 1,3-propanedithiol and .1 ml of boron trifluoride-etherate in 15 ml of chloroform was added to the flask over a 10 min period. The reaction mixture was stirred for 12 hr at 0° in a nitrogen atmosphere and poured into 100 ml of chloroform. The chloroform solution was washed with a 10% solution of sodium carbonate and dried over anhydrous sodium sulfate. Evaporation of the solvent yielded 2.92 g of an oil whose nmr spectrum exhibited no olefinic proton absorptions. The above procedure was repeated using zinc chloride, stannic chloride, and p-toluenesulfonic acid as catalysts. Similar results were obtained in each case.

1,1-Diacetylcyclopropane (41)

The procedure of Ichakawa and coworkers[15] was used.

A suspension of 64 g (.2 mol) of mercuric acetate and 60 g (1 mol) of glacial acetic acid was treated with ethylene until the mixture became homogeneous. The reaction mixture was then treated successively with 10 ml of a 10% solution of sodium hydroxide, 40 g (.4 mol) of acetylacetone and 15 g of 70% perchloric acid. After standing overnight, the mixture was treated with a 10% solution of sodium chloride and white crystals separated from the solution. The crystals were collected, air dried and recrystallized from 95% ethanol to give 52 g (75%) of 3,3-diacetylpropylmercuric chloride, mp 132-133° [Lit[15] 131-132°].

A suspension of 50 g (.14 mol) of the mercury salt and 70 ml of 10% potassium hydroxide was allowed to stand at room temperature for 2 hr. The reaction mixture was filtered and the filtrate was extracted with ether. The ether solution was dried over anhydrous sodium sulfate and evaporated to yield 4.5 g of crude product. Distillation yielded 3.8 g of 1,1-diacetylcyclopropane, bp 52-53°, (2 mm) n_D^{25} 1.4524 [Lit[15] bp 74-74.5° (8 mm)].

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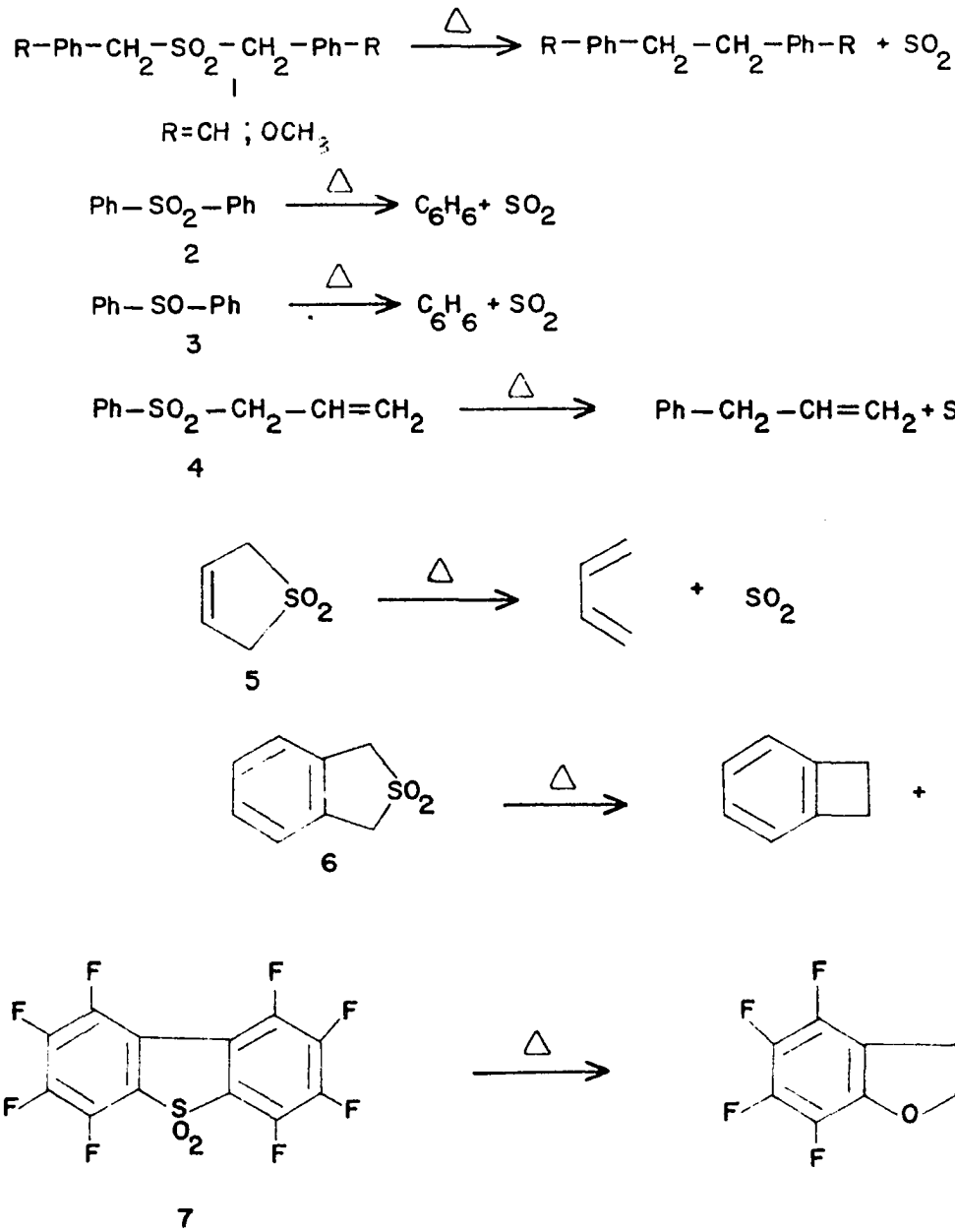
III. The Thermal Decomposition of Sulfones and Sulfoxides

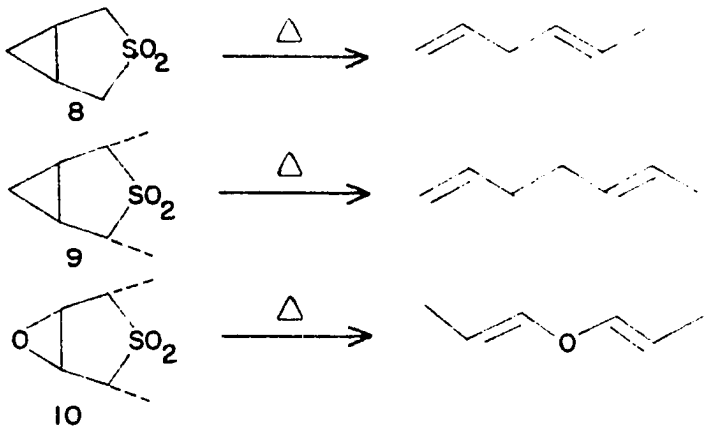
History and Background

The pyrolysis of sulfones (see scheme 1) has been used extensively in theoretical and synthetic organic chemistry. Leonard[1] pyrolyzed sulfones of type 1 at low pressures and temperatures of 600-700° and obtained good yields of symmetrical diarylethanes.



1 2 3 4 5 6 7

Scheme 1



Scheme 2

Levy and Ambrose[2] studied the kinetics of the decomposition of sulfone 2 and the sulfoxide 3. Lacombe and Stewart[3] observed that the allylic sulfone 4 lost sulfur dioxide and formed an olefin when heated at 300-400°. Cava and Deanna[4] obtained good yields of benzocyclobutene from the vapor phase pyrolysis of 6. The thermal decomposition of 6 has analogy to the well known thermal decomposition of 5.[12] Chambers and Cunningham[8] observed that the mass spectrum of 7 exhibited a peak at (M^+) - 48. This indicated that 7 could possibly eliminate sulfur monoxide when pyrolyzed. When 7 was pyrolyzed, the ether that was formed corresponded to the loss of sulfur monoxide.

Mock[5] investigated the thermal decomposition of sulfones of the type depicted in scheme 2. These reactions were found to be stereospecific in some cases and stereoselective in others and they provided a new route to the synthesis of alkenes, polyalkenes and divinyl ethers. Furthermore, Mock found these reactions were useful in elucidating the concepts of orbital symmetry.

INTRODUCTION

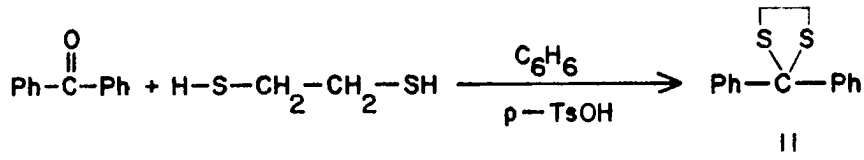
Kissick[6] prepared 1,1,3,3-tetraoxo-2,2-diphenyl-1,3-dithiolane and pyrolyzed it at 240°. Sulfur dioxide was evolved, and a mixture of the starting disulfone and another product were recovered from the reaction mixture. Somewhat later the other product was identified as benzophenone.

The objective of this investigation was to determine the scope and limitations of the reaction suggested by the work of Kissick, identify all of the reaction products and propose reasonable mechanistic pathways for their formation. Several sulfones and sulfoxides were pyrolyzed, and the results will be presented in this section.

RESULTS AND DISCUSSION

The sulfones and sulfoxides utilized in this study were prepared from compounds 11-18. The reactions employed in the preparation of compounds 11-18 are depicted in scheme 3. The dithiolanes 11-15 and the dithiane 16 were routinely prepared from the appropriate ketone (aldehyde in the case of 12) and 1,2-ethanedithiol (1,3-propanedithiol in the case of 16). The oxathiolane 17 was prepared from benzophenone and 2-mercaptoethanol by the method of Marshall and Stevenson.[9] The mercaptole 18 was prepared from benzophenone and ethanethiol by the method of Wolfrom and Karabinos.[10]

The cyclic disulfones 19-23 were prepared by oxidation of the corresponding dithiolanes (dithiane in the case of 23) with an excess of peracetic acid. In order to ensure complete oxidation of the dithiolane 11 and the dithiane 16 to the corresponding disulfones, it was necessary to carry out these oxidations in dilute solutions (ca. 1 g of the dithiolane per 25 ml of solvent). Under these conditions the reaction mixture remained homogeneous and 11 and 16 were completely oxidized to the corresponding disulfones. In contrast, when the oxidation of 11 was carried out in more concentrated solutions, a crystalline substance separated from the hot solution before the oxidation was complete. This substance was a mixture of the desired disulfone 19 and small quantity of an impurity (presumably the trioxide).



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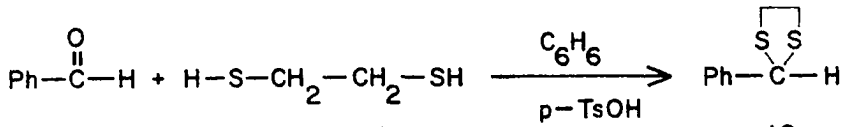

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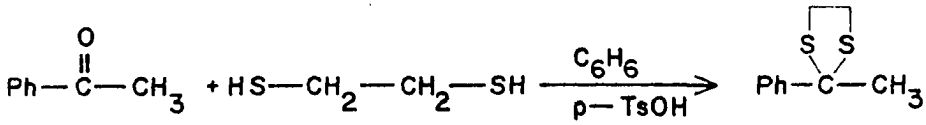

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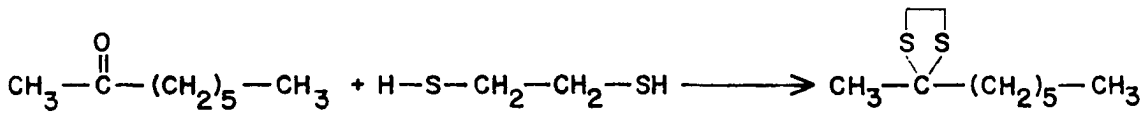

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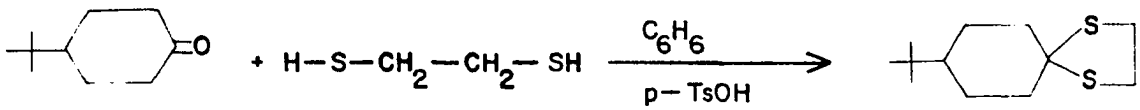

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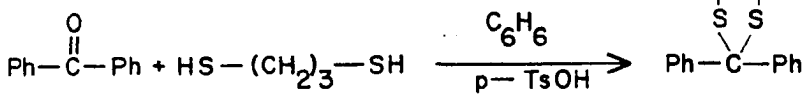

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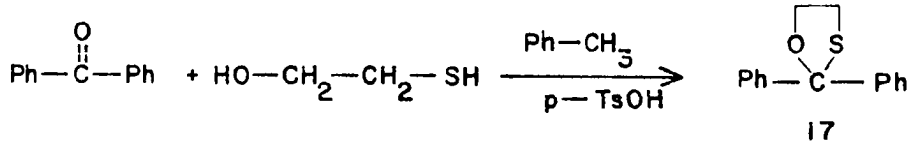

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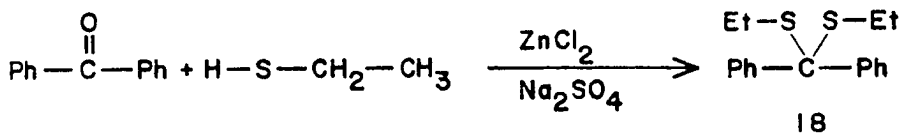

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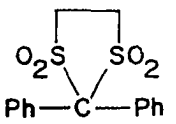
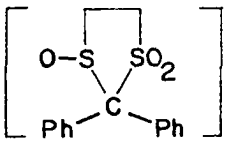
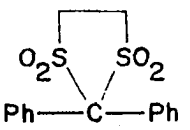
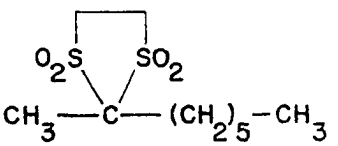
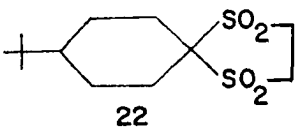
Scheme 3

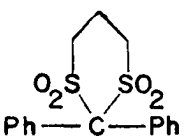
11 H_2O_2, AcOH, △ →  19

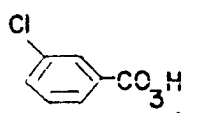
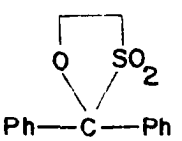
12 H_2O_2, AcOH, △ → 

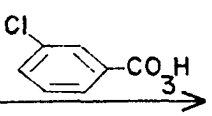
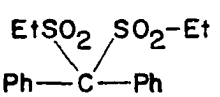
13 H_2O_2, AcOH, △ →  20

14 H_2O_2, AcOH, △ →  21

15 H_2O_2, AcOH, △ →  22

16 H_2O_2, AcOH, △ →  23

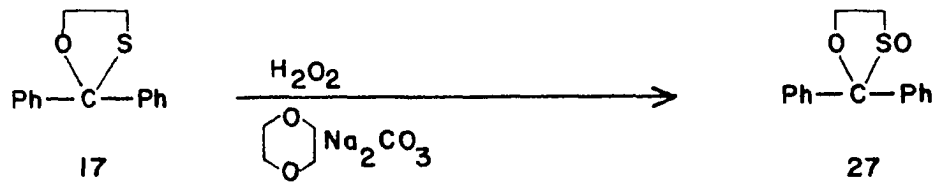
17  →  24

18  →  25

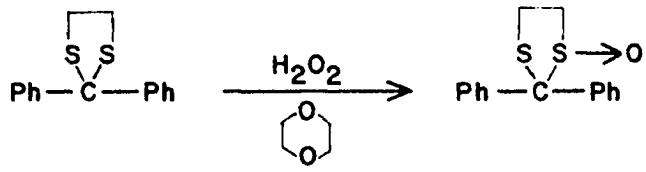
Scheme 4

Attempts to oxidize the dithiolane 12 to the corresponding disulfone by this procedure produced disappointing results. When 12 was heated with excess peracetic acid, an exothermic reaction occurred, and a crystalline substance immediately separated from the solution. The ir spectrum of this substance exhibited strong absorptions at 1310 and 1130 cm^{-1} (sulfone) and 1030 cm^{-1} (sulfoxide). The evidence obtained from the ir spectrum and tlc analysis indicated that the crystalline substance was a mixture of the trioxide (see scheme 4) and a small quantity of benzoic acid. When the mixture was treated with a dilute solution of sodium bicarbonate, the trioxide was hydrolyzed to benzaldehyde. Similar results were obtained when 12 was treated with excess m-chloroperbenzoic acid. The disulfone 25 was prepared by the oxidation of the mercaptole 18 with m-chloroperbenzoic acid. The unstable sulfone 24 was prepared by the oxidation of the oxathiolane 17 with excess m-chloroperbenzoic acid. On standing at room temperature for about 48 hours, the sulfone 24 spontaneously decomposed to give benzophenone. However, a freshly prepared sample gave satisfactory spectral data.

The sulfoxides 26 and 27 utilized in this investigation were prepared by the oxidation of 11 and 17 with hydrogen peroxide in dioxane. Hydrogen peroxide in acetone hydrolyzed 17 to benzophenone. However, a



solution of hydrogen peroxide in dioxane buffered with a 10% solution of sodium carbonate convered 17 to the sulfoxide 27.

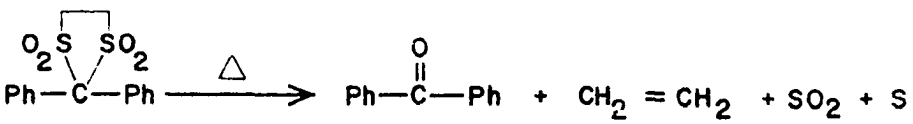


11 26

Several attempts were made to oxidize 11 to the disulfoxide, but disappointing results were obtained. Invariably, product mixtures were obtained when 11 was heated with 2 equivalents or more of hydrogen peroxide. Analysis of the mixtures by ir and mass spectroscopy indicated the presence of both the monosulfoxide and the disulfoxide. Attempts to oxidize the monosulfoxide (which was present in the mixture) to the disulfoxide resulted in the formation of a product whose ir spectrum exhibited both sulfone and sulfoxide absorptions. This product was presumably the trioxide. Theoretically, the disulfoxide or the isomeric monosulfone could result from the treatment of a dithiolane with 2 equivalents of an oxidizing agent. However, ir spectroscopy can easily distinguish between these two possibilities for the ir spectra of sulfones exhibit two strong absorptions at 1300-1330 cm^{-1} and 1010-1030 cm^{-1}, whereas the ir spectra of sulfoxides exhibit a single absorption at 1010-1030 cm^{-1}.

The primary objective of this study was to determine the scope of the reaction suggested by the work of Kissick, all of the reaction products and propose reasonable mechanistic pathways for their formation. In an effort to accomplish this objective, 1,1,3,3-tetraoxo-2,2-diphenyl-1,3-dithiolane (19) was pyrolyzed under the following conditions: at 225° and atmospheric pressure, at 225° and 2 mm of pressure, and at 225° and atmospheric pressure in the presence of a trace of benzoyl peroxide. In each instance the thermal decomposition of 19 yielded benzophenone, sulfur,

ethylene and sulfur dioxide. Under the first set of experimental conditions the product yields were as follows: benzophenone (.006 mol), sulfur (.0025 mol), ethylene (.0058 mol) and sulfur dioxide (.007 mol). Taking the yield of benzophenone as unity, this corresponds to a molar ratio of (1: .4: .96:1.16). Only the yields of benzophenone and sulfur were determined when 19 was pyrolyzed under the last two sets of conditions. The reaction products were identified by comparison of their spectral or physical pro-



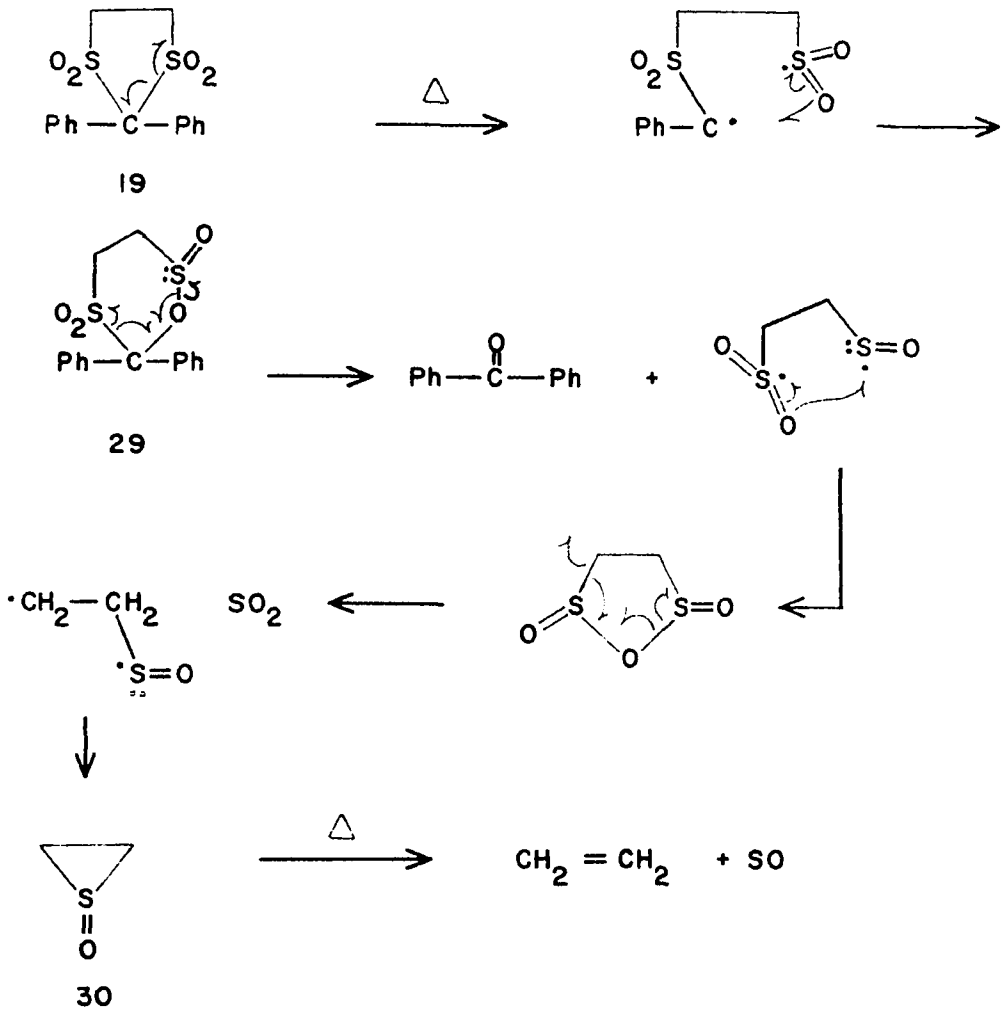
19

perties with those of authentic samples or with published data. In the cases of ethylene and sulfur dioxide, the ir spectra were compared with published ir spectra of authentic samples. Ethylene was also converted to ethylene dibromide which in turn was identified by comparing its nmr spectrum and refractive index with those of distilled samples. Benzophenone was identified by direct comparison to an authentic sample with respect to melting point, nmr and ir spectra. Sulfur was identified by its melting point.

The evidence obtained from studies of the thermal decomposition of 19 indicated that radical chains probably were not involved in the decomposition pathway since benzoyl peroxide, a powerful radical chain initiator, had no effect on the reaction. The results also established that the carbonyl oxygen atom of benzophenone came from the sulfone group since benzophenone was obtained when 19 was pyrolyzed in an evacuated system (no other source of oxygen was present in the system). This fact and the formation of all the observed products can be rationalized by the

intramolecular free radical pathway depicted in scheme 5.

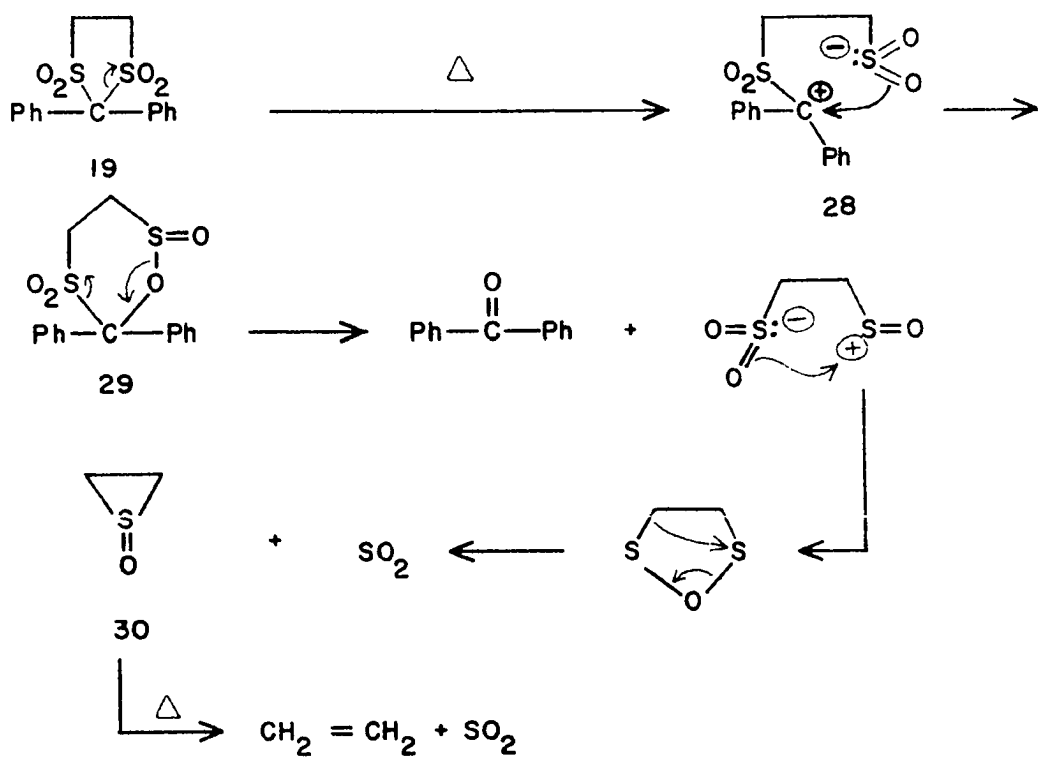
The stoichoimetry of the pathway depicted in scheme 5 requires that sulfur monoxide[8] be formed as a product from the thermal decomposition of 19. However, the instability[7] of sulfur monoxide renders its detection impossible; at all temperatures sulfur monoxide undergoes rapid disproportionation to give sulfur dioxide. Thus, the recovery of sulfur from the thermal decomposition of 19 combined with the fact that sulfur dioxide



Scheme 5

was formed in larger quantities than ethylene gives credence to the conjecture that sulfur monoxide was formed from the decomposition of 19. Therefore, the mechanism depicted in scheme 5 is fully consistent with the observed facts. The failure of benzoyl peroxide to facilitate the decomposition of 19 does not rule out an intramolecular free radical pathway such as the one outlined in scheme 5, but indicates homolytic cleavage of the disulfone is facile and does not require an external initiator.

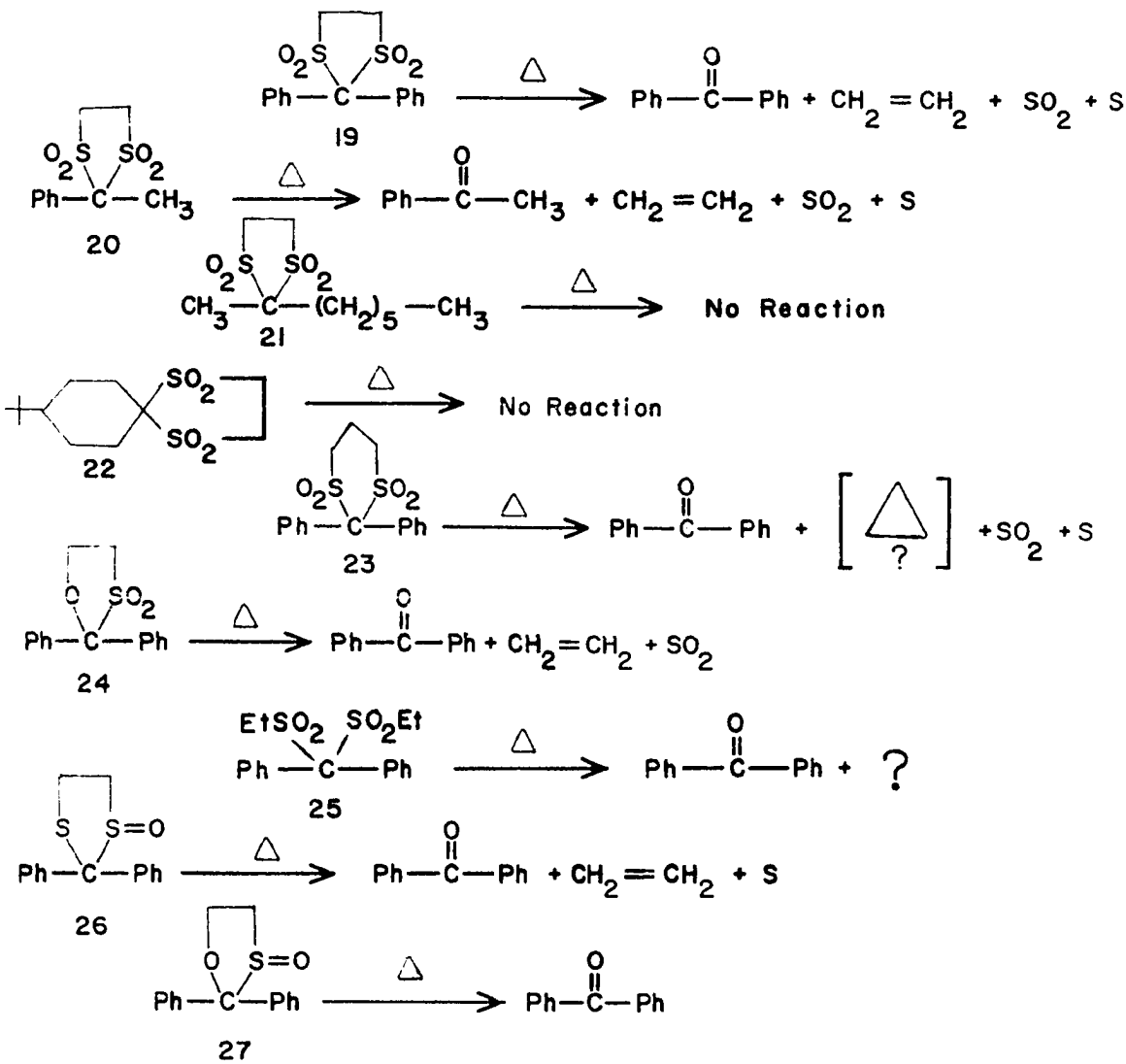
Another reasonable mechanism for the thermal decomposition of 19 is depicted in scheme 6. This proposed mechanism entails a heterolytic fission of the carbon sulfur bond of 19 to give the carbonium ion 28 which



Scheme 6

in turn cyclizes to the six-membered ring intermediate 29. The mechanistic pathways outlined in schemes 5 and 6 propose that 29 is the intermediate which gives rise to benzophenone and that the episulfoxide 30 gives rise to ethylene and sulfur monoxide. Thus, the products resulting from the thermal decomposition of 19 can reasonably be imagined to arise from a free radical pathway, a carbonium ion pathway or by competing pathways involving both carbonium ions and free radicals.

The results of the thermal decomposition of compounds 19-27 are outlined in scheme 7 and Table 4. All of the products resulting from the



Scheme 7

TABLE 4

The Results of the Thermal Decomposition

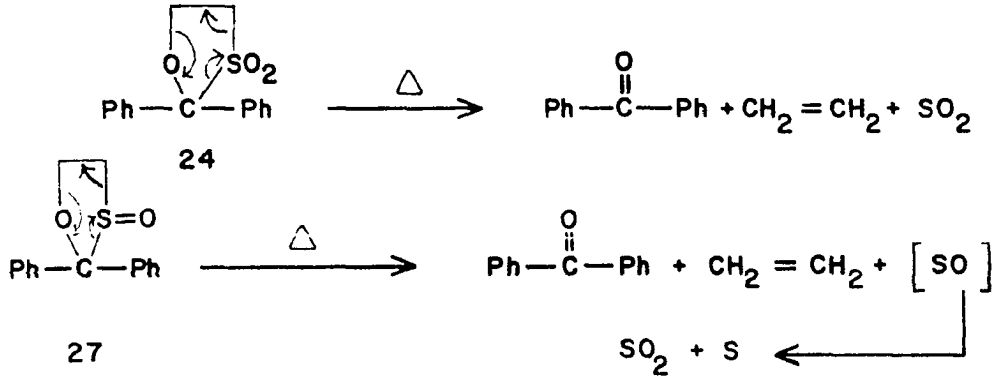
of Sulfoxides and Sulfones

Compound	Experimental Conditions	% Yield of Products
19	225° (2 mm)	benzophenone 65% sulfur 60% ethylene, sulfur dioxide
19	225° (atm. pres.)* peroxides present	benzophenone 62%, sulfur 58% ethylene and sulfur dioxide (yields no det.)
19	225° (atm. pres.)*	sulfur 60%, benzophenone 65% ethylene 60%, SO_2 66%
20	250-260° (2 mm)	Acetophenone 33%
21	200° (2 mm)	90% of 21 recovered
21	300° (2 mm)	89% of 21 recovered
22	400° (2 mm)	85% of 22 was recovered
22	500° (atm. pres.)*	88% of 22 was recovered
23	300° (atm. pres.)*	benzophenone (76.5%), sulfur 58% sulfur dioxide 55%
23	300° (2 mm)	benzophenone 70%, sulfur 62%
24	140° (2 mm)	benzophenone 65%
25	200° (5 mm)	benzophenone 70%
27	120-130° (2 mm)	benzophenone 78%
26	130-140° (atm. pres.)*	benzophenone 74%, sulfur 28% ethylene 64% no sulfur dioxide was detected.

*Pyrolyzed under a sweep of nitrogen gas.

decomposition of 19 and 26 were identified. Sulfur dioxide, sulfur, benzophenone and a product tentatively identified as cyclopropane resulted from the pyrolysis of 23. In all other instances only the ketone was fully characterized. The aliphatic disulfones 21 and 22 were found to be thermally stable at temperatures 100-200° above their melting points (68° and 252°). This may be attributable to the destabilizing effect that the sulfone group would have on the intermediate (radical or carbonium ion) that would result from the cleavage of the carbon sulfur bond. Compound 20 decomposed slowly at temperatures 120° above its melting point (131-133°).

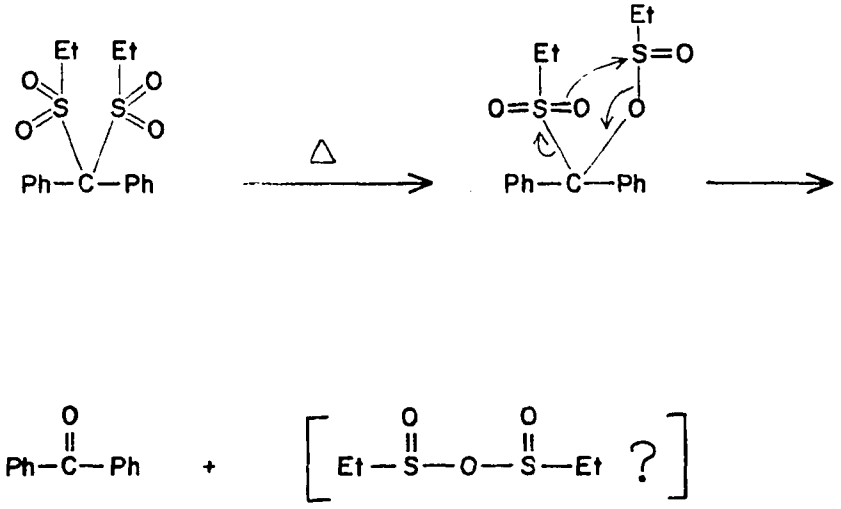
In sharp contrast to the thermal behavior of 20, 21 and 22, compounds 24 and 27 (freshly prepared samples) decompose smoothly and completely at their melting points. On standing at room temperature for about 48 hours both 24 and 27 spontaneously decomposed into benzophenone. A concerted pathway (see scheme 8) is very favorable for the thermal decomposition of 24 and 27.



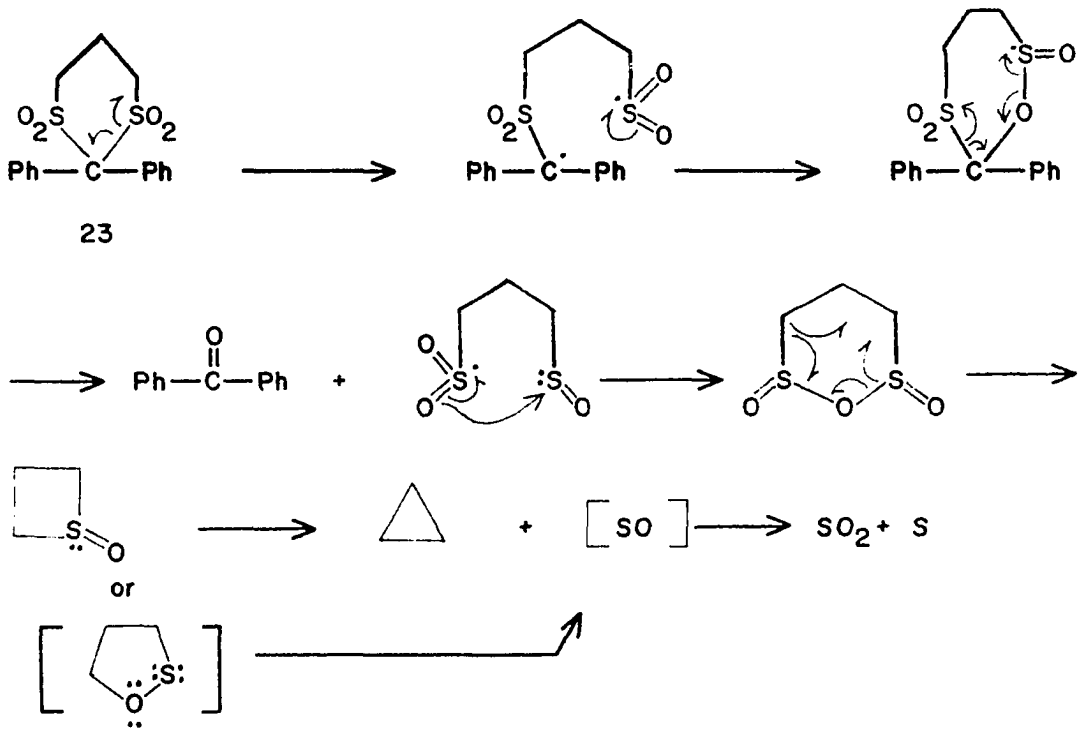
Scheme 8

Compound 23, 25 and 26 decomposed smoothly and completely at temperatures 10-20° above their melting points. The decomposition of 26 can proceed by a radical pathway similar to the one depicted in scheme 5 or the carbonium ion pathway similar to the one depicted in scheme 6.

A possible pathway for the decomposition of the non-cyclic sulfone 25 is depicted in scheme 9. However, benzophenone was the only reaction product identified from the pyrolysis of 25, and, therefore, any discussion regarding the mechanism of the decomposition of 25 in the absence of a complete identification of all of the reaction products is pure conjecture. The decomposition of 23 can proceed by the radical pathway depicted in scheme 10; however, the evidence for the formation of cyclopropane from the thermal decomposition of 23 is not yet convincing.



Scheme 9



Scheme 10

Three general pathways are proposed for the thermal decomposition of the sulfones and sulfoxides utilized in this investigation. The illustrative free radical pathway depiced in schme 5, the carbonium ion pathway depicted in scheme 6 and the concerted pathway depicted in scheme 8 are consistent with all of the observed facts. Additional experiments which would allow one to distinguish between these three mechanisms have not yet been carried out

SUMMARY

The results of this investigation indicate that disulfones derived from the dithiolanes of aliphatic ketones are themally stable, and that disulfones derived from mixed dithiolanes (one alkyl group and one aromatic ring bonded to carbonyl carbon atom of the original ketone) decompose very slowly at temperatures far above their melting points. In contrast, sulfones and sulfoxides derived from the dithiolanes, dithianes, mercaptoles and oxathiolanes of aromatic ketones undergo facile decomposition at their melting points and temperatures 10-20° above their melting points. This evidence suggests that the initial step in the decomposition pathway involves homolytic fission (see scheme 5) or heterolytic fission (see scheme 6) of the carbon sulfur bond to generate either a free radical or a carbonium ion on the carbon atom bearing the aromatic rings.

All new compounds used in this investigation gave satisfactory spectral data. The data taken on known compounds is consistent with the data reported in the literature.

EXPERIMENTAL

All melting points and boiling points are uncorrected. All solvents were redistilled prior to use. Anhydrous solvents were prepared by distillation from calcium hydride. Column chromatography supports were silicAR CC-7 (Mallinckrodt, 100/200 mesh) and silica gel H (Merck AG, Darmstadt). Thin layer chromatography was performed on 5 x 20 cm glass plates coated with silica gel H (Merck AG, Darmstadt). The developed plates were exposed to iodine vapor for visualization of the chromatogram.

Gas chromatographic analyses were performed on a Varian Aerograph Model 1220-1 or Aerograph Model 1740-1 gas chromatograph. The infrared spectra were taken on a Beckman IR-8 spectrometer as potassium bromide pellets or in solutions of carbon tetrachloride or chloroform. Ultraviolet spectra (uv) were taken in 95% ethanol solutions with a Hitachi Perkin-Elmer, Model 124 spectrometer.

Nuclear magnetic resonance spectra (nmr) were taken on the Varian XL-100, or T-60 spectrometers using tetramethylsilane (TMS) as an internal reference. Samples were run in varying concentrations of carbon tetrachloride and deuteriochloroform. Chemical shifts are reported in δ-units (parts per million from TMS) are followed by the multiplicity of the signal, the number of protons, the corresponding coupling constant and the assignment. The multiplicities are denoted by the symbols:

s, singlet; d, doublet; dd, double doublet; t, triplet; and m, multiplet.

The mass spectra were taken on a Hitachi Perkin-Elmer RMU-7E spectrometer using perfluorokerosene as an internal reference. Major peaks and molecular ions are reported followed by percentage of the base peak.

Combustion analyses were carried out by Bernhardt Laboratories in Mülheim, West Germany, and Mr. E. Meier, Chemistry Department, Stanford University, Palo Alto, California

2,2-Diphenyl-1,3-dithiolane (11)

A solution of 9.4 g (.10 mol) of 1,2-ethanedithiol, 18.2 g (.10 mol) of benzophenone and .1 g of p-toluenesulfonic acid in 200 ml of benzene was refluxed for 12 hr and cooled to room temperature. The benzene solution was washed once with 25 ml of a 10% solution of sodium bicarbonate and dried over anhydrous sodium sulfate. Removal of the benzene on a rotary evaporator and a vacuum pump yielded 25.1 g (97%) of the dithiolane as an oily solid, mp 97-99°. Recrystallization from 95% ethanol yielded 23.8 g (90%) of 2,2-diphenyl-1,3-dithiolane as a white crystalline solid, mp 101-102.5°. [lit mp[14] 102°]; ir (CCl_4) 1440 cm^{-1} (carbon-sulfur stretch); nmr ($CDCl_3$) δ 7.1-7.75 (m, 10, aromatic protons), 3.40 (s, 4, methylene protons).

1,1,3,3-Tetraoxo-2,2-diphenyl-1,3-dithiolane (19)

In a 250 ml flask was placed a mixture of 2.58 g (10 mmol) of 2,2-diphenyl-1,3-dithiolane, 10 ml of 30% hydrogen peroxide and 50 ml of acetic acid. The reaction mixture was heated on a steam bath for 12 hr and cooled to room temperature. Upon cooling, white crystals

separated from the solution. The crystals were collected by suction filtration, washed with benzene and air dried to yield 3.15 g (98%) of 1,1,3,3-tetraoxo-2,2-diphenyl-1,3-dithiolane as a white crystalline solid, mp 217-210°. Two recrystallizations from benzene yielded an analytical sample, mp 222-222.5°; ir (KBr) 1332 cm^{-1} (sulfone stretch), 1123 cm^{-1} (sulfone stretch); nmr (CF_3COOH) δ 7.35-7.75 (m, 10, aromatic protons), 4.30 (s, 4, methylene protons); mass spectrum 258 (70), 192 (12), 166 (100), 121 (20), 92 (10), 77 (75), 64 (60), 49 (12) and 43 (15).

Anal. Calcd. for $C_{15}H_{14}S_2O_4$: C, 55.90; H, 4.35; S, 19.87. Found: C, 55.81; H, 4.44; S, 19.87.

2,2-Diphenyl-1,3-dithiane (16)

In a 500 ml flask was placed 9.1 g (.05 mol) of benzophenone, 5.4 g (.05 mol) of 1,3-propanedithiol, .5 g of p-toluenesulfonic acid and 300 ml of benzene. The reaction mixture was refluxed for 12 hr and cooled to room temperature. The benzene solution was washed with a 10% solution of sodium bicarbonate and dried over anhydrous sodium sulfate. Removal of the benzene on a rotary evaporator and a vacuum pump yielded 13.5 g (99%) of the dithiane as a white solid, mp 97-98°. Two recrystallizations from 95% ethanol yielded 12.4 g (91%) of 2,2-diphenyl-1,3-dithiane as a white crystalline solid, mp 109-110°. [Lit.[15] mp 110°]; ir (CCl_4) 1440 cm^{-1} (carbon-sulfur stretch); nmr (CCl_4) δ 7.15-7.75 (m, 10, aromatic protons), 2.70 (t, 4, J = 6 Hz, methylene protons on carbon atoms bearing sulfurs), 1.8-2.1 (m, 2, remaining methylene protons).

1,1,3,3-Tetraoxo-2,2-diphenyl-1,3-dithiane (23)

In a 500 ml flask was placed a mixture of 2.72 g (.01 mol) of 2,2-diphenyl-1,3-dithiane, 10 ml of 30% hydrogen peroxide and 100 ml of

glacial acetic acid. The flask was heated on a steam bath, and after about 45 min, white crystals separated from the hot solution. The flask was stored in a refrigerator for 2 hr, and the crystals were collected by suction filtration and air dried to yield 3.11 g (92.8%) of the sulfone, mp 251-252°. Two recrystallizations from benzene yielded an analytical sample, mp 254-254.5°; ir (KBr) 1335 cm^{-1} (sulfone stretch), 1130 cm^{-1} (sulfone stretch); nmr (CF_3COOH) δ 7.35-7.90 (m, 10, aromatic protons), 3.70 (t, 4, J = 6 Hz, methylene protons on carbon atoms bearing sulfone), 2.65-2.95 (m, 2, remaining methylene protons); mass spectrum 336 (2), 209 (16), 208 (72), 207 (10), 183 (40), 182 (85), 179 (36), 167 (35), 166 (100), 165 (69), 130 (20), 105 (58), 91 (27), 90 (30), 64 (12), and 41 (19).

Anal. Calcd. for $C_{16}H_{16}S_2O_4$: C, 57.14; H, 4.76; S, 19.05. Found: C, 57.18; H, 4.79; S, 19.20.

2-(4-t-Butylspirocyclohexyl)-1,3-dithiolane (15)

A solution of 2.35 g (.025 mol) of 1,2-ethanedithiol, 3.85 g (.025 mol) of 4-t-butycyclohexanone, and .1 g of toluenesulfonic acid in 100 ml of benzene was refluxed for 12 hr and cooled to room temperature. The benzene solution was washed with 25 ml of a 10% solution of sodium bicarbonate and dried over anhydrous sodium sulfate. The benzene was removed on a rotary evaporator and a vacuum pump to yield 5.64 g (98%) of the dithiolane as white flakes, mp 64-65°. Two recrystallizations from 95% ethanol yielded an analytical sample, mp 65-65.5°; ir (KBr) 1460 cm^{-1} (carbon-sulfur stretch); nmr (CCl_4) δ 3.25 (bs, 4, methylene protons of the dithiolane ring), 2.3-1.2 (m, 9, protons of the cyclohexane ring), .9 (s, 9, protons of the t-butyl group); mass spectrum

232 (4), 231 (7), 230 (100), 133 (13), 132 (39), 131 (55), 87 (16), 81 (39), 79 (13), 62 (14), 58 (34), 56 (10), 44 (41), and 42 (26).

Anal. Calcd. for $C_{12}H_{22}S_2$: C, 62.61; H, 9.56. Found: C, 62.70; H, 9.44.

1,1,3,3-Tetraoxo-2-(4-t-butylspirocyclohexyl)-1,3-dithiolane (22)

A solution of 2.3 g (.01 mol) 2-(4-t-butylspirocyclohexyl)-1,3-dithiolane and 8 ml of 30% hydrogen peroxide in 50 ml of glacial acetic acid was heated on a steam bath for 12 hr and cooled to room temperature. White crystals (flakes) separated from the solution upon cooling. The crystals were collected by suction filtration, washed several times with benzene and air dried to yield 2.85 g (94%) of the sulfone as white flakes, mp 251-252°. Recrystallization from chloroform did not change the melting point; ir (KBr) 1298 cm^{-1} (sulfone stretch), 1122 cm^{-1} (sulfone stretch); nmr (CF_3COOH) δ 3.92 (s, 4, methylene protons of the dithiolane ring), 1.0 - 2.7 (m, 9, methylene protons of the cyclohexane ring), .95 (s, 9, protons of the t-butyl group); mass spectrum 294 (1), 234 (62), 202 (41), 141 (22), 139 (25), 139 (49), 119 (35), 97 (31), 96 (30), 95 (37), 93 (20), 91 (24), 78 (44), 77 (55), 79 (60), 75 (48), 67 (30), 65 (40), 64 (9), 56 (43), 55 (100), 54 (85), 53 (46), 51 (38), and 41 (38).

Anal. Calcd. for $C_{12}H_{22}S_2O_4$: C, 48.97; H, 7.48; S, 21.76. Found: C, 49.04; H, 7.62; S, 21.96.

2-Phenyl-2-methyl-1,3-dithiolane (13)

A solution of 7.3 g (.05 mol) of acetophenone, 9.42 g (.05 mol) of 1,2-ethanedithiol and .5 g of p-toluensulfonic acid in 250 ml of benzene was refluxed for 12 hr and cooled to room temperature. The

benzene solution was washed with 50 ml of a 10% solution of sodium bicarbonate and dried over anhydrous sodium sulfate. Removal of the benzene on a rotary evaporator and a vacuum pump yielded 10.4 g (99%) of the crude dithiolane as a clear liquid. Distillation yielded 9.7 g (83%) of 2-methyl-2-phenyl-1,3-dithiolane as a colorless liquid, bp 134-135.5° (3.5 mm): n_D^{25} 1.6158. [Lit[16] bp 131° (3 mm) n_D^{25} 1.6162.]

1,1,3,3-Tetraoxo-2-methyl-2-phenyl-1,3-dithiolane (20)

In a 250 ml flask was placed 4.2 g (.02 mol) of 2-methyl-2-phenyl-1,3-dithiolane, 15 ml of 30% hydrogen peroxide, and 60 ml of glacial acetic acid. The reaction mixture was stirred at 70-80° for 12 hr, cooled to room temperature, and poured into 500 ml of chloroform. The chloroform solution was washed several times with a 10% solution of sodium bicarbonate and dried over anhydrous sodium sulfate. Evaporation of the chloroform on a rotary evaporator and a vacuum pump yielded 5.11 g (98%) of the sulfone as a white powder, mp 128-130°. Recrystallization from hexane-dichloromethane (1:1) yielded 4.8 g (92%) of 2-methyl-2-phenyl-1,3-dithiolane as a white crystalline solid, mp 132-133°. Three recrystallizations from hexane-dichloromethane (1:1) yielded an analytical sample, mp 132-132.5°; ir (KBr) 1315 cm^{-1} (sulfone stretch), 1122 cm^{-1} (sulfone stretch); nmr ($CDCl_3$) δ 7.82-7.25 (m, 5, aromatic protons), 3.7 (s, 4, methylene protons), 2.15 (s, 3, methyl); mass spectrum 264 (4), 167 (44), 115 (17), 103 (33), 102 (100), 101 (48). 76 (39), 75 (33), 64 (2), 49 (14), and 41 (20).

Anal. Calcd. for $C_{10}H_{12}S_2O_4$: C, 46.15; H, 4.62; S, 24.62. Found: C, 46.11; H, 4.62; S, 24.47.

2-Methyl-2-hexyl-1,3-dithiolane (14)

A solution of 6.4 g (.05 mol) of 2-octanone, 4.7 g (.05 mol) of 1,2-ethanedithiol and .5 g of p-toluenesulfonic acid in 100 ml of benzene was refluxed for 12 hr and cooled to room temperature. The benzene solution was washed with 50 ml of a 10% solution of sodium bicarbonate and dried over anhydrous sodium sulfate. Removal of the benzene on the rotary evaporator yielded 10.05 g (99%) of 2-methyl-2-hexyl-1,3-dithiolane as a colorless liquid. Distillation yielded 9.25 g (90%) of the dithiolane as a colorless liquid, bp 107-109° (2.5 mm) n_D^{25} 1.5108 [Lit.[17] bp 120° (6 mm) n_D^{25} 1.5110].

1,1,3,3-Tetraoxo-2-methyl-2-hexyl-1,3-dithiolane (21)

A solution of 5 g (.024 mol) of 2-methyl-2-n-hexyl-1,3-dithiolane, 15 ml of 30% hydrogen perioxide, 50 ml of glacial acetic acid was stirred at 70-80° for 12 hr, cooled to room temperature, and poured into 500 ml of chloroform. The chloroform solution was washed several times with a 10% solution of sodium bicarbonate and dried over anhydrous sodium sulfate. Removal of the chloroform on the rotary evaporator and the vacuum pump yielded 5.79 g (90%) of crude product, mp 66-67°. Recrystallization from hexane-dichloromethane (1:1) yielded 5.25 g (81.5%) of 1,1,3,3-tetraoxo-2-methyl-2-hexyl-1,3-dithiolane as white flakes, mp 68-69°. Two recrystallizations from hexane-dichloromethane gave an analytical sample, mp 68-69°; ir (KBr) 1305 cm^{-1} (sulfone stretch), 1105 cm^{-1} (sulfone stretch); nmr ($CDCl_3$) δ 3.6 (s, 4, methylene protons of the five-membered ring), 2.3-1.9 (m, 2, methylene protons on carbons bearing the sulfonyl group), 1.7 (s, 3, quatenary methyl), 1.25-1.55 (m, 8, remaining methylene protons), .95 (t, 3, J = 3 Hz, terminal methyl);

mass spectrum 268 (2), 112 (25), 111 (10), 71 (15), 70 (44), 57 (11), 56 (100), 44 (25), 43 (11), 42 (40), and 40 (10).

Anal. Calcd. for $C_{10}H_{20}S_2O_4$: C, 44.77; H, 7.46; S, 23.87. Found: C, 44.78; H, 7.40; S, 23.98.

2,2-Diphenyl-1,3-oxathiolane (17)

The procedure of Marshall and Stevenson[9] was used.

A solution of 29 g (0.16 mol) of benzophenone, 14 g (.18 mol) of 2-mercaptoethanol and 1 g of p-toluenesulfonic acid in 250 ml of dry toluene was refluxed for 3 hr and cooled to room temperature. Upon cooling, an amorphous solid separated from the solution. The mixture was filtered with suction, and the residue was washed with 100 ml of ether. The combined filtrates were washed once with 50 ml of a 10% solution of sodium bicarbonate and dried over anhydrous sodium sulfate. Evaporation of the solvents on the rotary evaporator yielded 20.6 g of a colorless oil. The oil was filtered through a column (48 x 4.5 cm) containing a slurry of 200 g of activity 1 neutral alumina in benzene. The oil was washed down the column with 300 ml of dry benzene, and one 500 ml fraction was collected. The benzene was removed on a rotary evaporator to yield 8.5 g (22%) of the oxathiolane as a colorless oil which crystallized on cooling in a refrigerator, mp 49-51°. Recrystallization from methanol yielded 7.5 g (19%) of the oxathiolane as a white crystalline solid, mp 52-53°. [Lit.[9] mp 52°]; ir (CCl_4) 1440 cm^{-1} (carbon-sulfur stretch), 1052 cm^{-1} (carbon-oxygen stretch); nmr ($CDCl_3$) δ 7.1-7.6 (m, 10, aromatic protons), 4.18 (t, 2, J = 6 Hz, protons on carbon bearing oxygen), 3.18 (t, 2, J = 6 Hz, protons on carbon bearing sulfur).

2,2-Diphenyl-1,3-dithiolane-1-oxide (26)

A mixture of 4.0 g (15.5 mmol) of 2,2-diphenyl-1,3-dithiolane and 20 ml of dioxane and 10 ml of 30% hydrogen peroxide was stirred at room temperature for 24 hr, and poured into 100 ml of water. White crystals separated from the solution. The crystals were collected by suction filtration and air dried to yield 4.41 g (98%) of the sulfoxide, mp 122-124°. Two recrystallizations from hexane-methylene chloride (1:3) yielded an analytical sample, mp 125-125.5°. Ir (KBr) 1055 cm^{-1} (sulfoxide stretch); nmr ($CDCl_3$) δ 7.25-7.8 (m, 10, aromatic protons), 2.8-4.0 (m, 4, methylene protons); mass spectrum 274 (3) M^+, 258 (3), 192 (12), 181 (25), 163 (17), 124 (10), 121 (20), 105 (100), 77 (75), 64 (10), 60 (15), 59 (15), 50 (47), 49 (12), and 43 (15).

Anal. Calcd. for $C_{15}H_{14}S_2O$: C, 65.69; H, 5.11; S, 23.36. Found: C, 65.50; H, 5.18; S, 23.60.

3,3-Dioxo-2,2-diphenyl-1,3-oxathiolane (24)

A solution of 0.50 g (2.1 mmol) 2,2-diphenyl-1,3-oxathiolane and 1.38 g (8 mmol) of m-chloroperbenzoic acid in 50 ml of absolute ether was stirred at room temperature for 24 hr during which time a white solid precipitated from the solution. The precipitate was collected by suction filtration and washed with ether and air dried. The yield of the crude sulfone was .523 g (95%), mp 132-134°.

Recrystallization from acetone-ether yielded .493 g (90%) of 3,3-dioxo-2,2-diphenyl-1,3-oxathiolane as a white crystalline solid, mp 134-135°. Two recrystallization from acetone-ether yielded a spectral sample, mp 136-136.5°. This compound decomposed on standing at room temperature for 48 hr, therefore, no elemental analysis could be obtained;

ir ($CHCl_3$) 1309 cm^{-1} (sulfone stretch), 1130 cm^{-1} (sulfone stretch); nmr ($CDCl_3$) δ 7.2-7.9 (m, 10, aromatic protons), 4.5 (t, 2, J = 7 Hz, protons on carbon bearing oxygen), 3.22 (t, 2, J = 7 Hz, protons on carbon bearing the sulfone); mass spectrum, 274 (2), 182 (100), 105 (40), 77 (75), 64 (30), 50 (47), 49 (12) and 43 (15).

2,2-Diphenyl-1,3-oxathiolane-3-oxide (27)

A mixture of .50 g (2.1 mmol) of 2,2-diphenyl-1,3-oxathiolane, 5 ml of 10% sodium carbonate, 10 ml of 30% hydrogen peroxide and 50 ml of dioxane was heated on a steam bath for 30 min and then stirred at room temperature for 4 hr. The reaction mixture was then diluted with water, and white crystals separated from the solution. The crystals were collected by suction filtration and air dried to yield .539 g (99%) of the crude sulfoxide, mp 88-90°. Recrystallization from methylene chloride-hexane yielded .486 g (90%) of 2,2-diphenyl-1,3-oxathiolane-1-oxide as a white crystalline solid, mp 93-94°. Two recrystallizations from methylene chloride-hexane yielded a spectral sample, mp 93-94°; ir (CCl_4) 1075 cm^{-1} (sulfoxide stretch), 1059 cm^{-1} (carbon-oxygen stretch); nmr ($CDCl_3$) δ 4.65-4.92 (m, 1, proton on carbon bearing oxygen), 4.-4.45 (m, 1, proton on carbon bearing oxygen), 2.9-3.35 (m, 2, methylene protons on carbon bearing sulfoxide); mass spectrum 258 (3), 183 (24), 182 (35), 165 (10), 106 (16), 105 (100), 92 (12), 77 (75), 76 (11), 60 (15), 51 (20), and 50 (7). This compound is unstable, therefore, no satisfactory data could be obtained.

Benzophenone diethylmercaptole (18)

The procedure of Wolfrom and Karabinos[10] was used.

A mixture of 4.448 (.055 mol) of ethanethiol, 1.5 g of freshly fused zinc chloride and 2 g of anhydrous sodium sulfate was placed in a 250 ml flask. The flask was immersed in an ice-water bath at 0°, and 9.1 g (.05 mol) of benzophenone was added to the flask and the reaction mixture was stirred at 0-5° for 24 hr. The reaction mixture was then poured into 50 cc of ice water, and the organic layer was removed and washed with 50 ml of a 10% solution of sodium hydroxide and dried over anhydrous sodium sulfate. The solvent was evaporated and the crude mercaptole 14.38 g (98%) was collected and distilled to give 13.8 g (95%) of benzophenone diethyl mercaptole as a colorless liquid, bp 182-184 (.3 mm); [Lit[10] bp 146-150° (.07 mm).]

Benzophenone diethyl mercaptole tetraoxide (25)

A solution of 5.76 g (.02 mol) of benzophenone diethyl mercaptole and 20.6 g (.12 mol) of m-chloroperbenzoic acid in 100 ml of ether was stirred at room temperature, and after about 4 hrs a white solid separated from the solution. The solid was collected by suction filtration, washed with ether and air dried. The yield of crude product was 6.9 g (98%), mp 195-198°. Two recrystallizations from methylene chloride-hexane yielded an analytical sample, mp 197-197.5°; ir (KBr) 1290 cm^{-1} (sulfone stretch), 1105 cm^{-1} (sulfone stretch); nmr ($CDCl_3$) δ 7.28-8 (m, 10, aromatic protons), 3.1 (q, 4, J = 7 Hz, methylene protons of ethyl groups), 1.1 (t, 6, J = 7 Hz, terminal methyls); mass spectrum 260 (3), 259 (16), 185 (2), 84 (16), 83 (100), 166 (5), 165 (8), 164 (28), 163 (4), 162 (4), 137 (4), 115 (3), 106 (5), 105 (61) and 77 (19).

Anal. Calcd. for $C_{17}H_{20}S_2O_4$: C, 59.97; H, 5.68; S, 18.20. Found: C, 57.73; H, 5.76; S, 18.31.

The Pyrolysis of Sulfones and Sulfoxides

Description of Apparatus.

The appratus consisted of a pyrex tube 33 cm X 1.5 cm which was connected to a flask for adding solids at one end and to a trap or to a series of traps at the other end. The tube was packed with sufficient glass beads and glass wool to cover a length of approximately 4-5 cm.

Pyrolysis of 1,1,3.3-tetraoxo-2,2-diphenyl-1,3-dithiolane (19)

A. Pyrolysis at atmospheric pressure under nitrogren.

The pyrolysis tube was connected to a series of three traps. The first trap (empty) was immersed in an ice-water bath at 0°, the second trap contained 25 ml of a 1% solution of sodium hydroxide and the third trap contained a solution of 2 g of bromine in 50 ml of carbon tetrachloride. The system was swept with nitrogen, the tube was heated to 225° and 3 g (9.3 mmol) of the disulfone 19 was added slowly to the tube over a 10 min period. The temperature of the tube was maintained at 225° for 5 min and the tube was cooled to room temperature. The first trap was rinsed with chloroform, and after evaporation of the chloroform 1.203 g (72%) of benzophenone, mp 48-49° was recovered. The benzophenone was further characterized by comparing its ir and nmr spectra with the ir and nmr spectra of authentic samples. The yellow residue which remained in the first trap was dissolved in carbon disulfide; evaporation of the carbon disulfide yielded 80.1 mg of sulfur, mp 119-121°. The sodium bisulfite solution in

the second trap was heated at 80° for 24 hr with 5 ml of 30% hydrogen peroxide. The solution was cooled to room temperature and treated with excess barium hydroxide. The precipitate of barium sulfate was collected and dried in an oven at 200°. The yield of barium sulfate was 1.6310 g (.007 mol); the yield of sulfur dioxide (calculated on the basis of the barium sulfate) was .413 g (70%). The carbon tetrachloride solution in the third trap was washed with a saturated solution of sodium bisulfite, dried over anhydrous sodium sulfate and distilled at atomspheric pressure. The yield of ethylene dibromide was 1.102 g (5.3 mmol), n_D^{25} 1.5382 [Lit.[12] 1.5389]. The yield of ethylene (calculated on the basis of the ehtylene dibromide obtained) was .149 g (60%).

B. Pyrolsis In the Presence of Benzoyl Peroxide.

A trace of benzoyl peroxide and 3 g (9.3 mmol) of 19 were pyrolyzed under the conditions described above. The results are reported in Table 4 at the end of this section.

C. Pyrolysis of 19 at Reduced Pressure.

The pyrolysis apparatus was connected to a trap which was immersed in liquid nitrogen and 2 g (6.3 mmol) of 19 was pyrolyzed at 225° and 2 mm of pressure. The trap was connected to a vacuum line and the mixture was distilled into a gas ir cell at room temperature until a pressure of 4 cm was obtained. The ir spectrum of the mixture indicated the presence of sulfur dioxide and ethylene as determined by comparison of the ir spectra of the mixture with published ir spectra of sulfur dioxide and ehtylene. Benzophenone and sulfur were identified as previously described.

The yields are reported in Table 4.

The Pyrolysis of 1,1,3,3-tetraoxo-2-methyl-2-phenyl-1,3-dithiolane (20)

The pyrolysis set up was connected to a trap which was immersed in a dry ice-acetone bath and 1 g (4 mmol) of 20 was pyrolyzed at 250-260° and 2 mm of pressure. Acetophenone was recovered from the trap. See Table 4 for details.

Pyrolysis of 1,1,3,3-tetraoxo-2-methyl-2-hexyl-1,3-dithiolane (21)

To the tube was added 1 g (3.8 mmol) of 21 which was pyrolyzed at 200° and 2 mm of pressure, and in a separate experiment 1 g (3.8 mmol) of 21 was pyrolyzed at 300° and 2 mm of pressure. The results are reported in Table 4.

Pyrolysis of 1,1,3,3-tetraoxo-2-(4-t-butyl-spirocyclohexyl)-1,3-dithiolane (22)

To the tube was added 1 g (3.5 mmol) of 22 which was pyrolyzed at 400° and 2 mm of pressure, in a separate experiment 1 g (3.5 mmol) of 22 was pyrolyzed at 500° and 2 mm of pressure. The results are reported in Table 4.

Pyrolysis of 1,1,3,3-tetraoxo-2,2-diphenyl-1,3-dithiane (23)

To the tube was added 2 g (6 mmol) of 23 which was pyrolyzed under a nitrogen sweep at 300°. Sulfur dioxide, benzophenone and sulfur were collected and identified by the methods previously described. See Table

4 for more details.

To the tube was added 1 g (3 mmol) of 23 which was pyrolyzed at 300° and 2 mm of pressure. The reaction products were collected in a trap which was immersed in a liquid nitrogen bath. The ir spectrum of the gaseous mixture (taken as previous descibed) showed the presence of sulfur dioxide and a substance whose ir spectrum resembled the ir spectrum of cyclopropane. Benzophenone and sulfur were obtained. The yields are reported in Table 4.

Pyrolysis of 2,2-diphenyl-1,3-oxathiolane-1,1-dioxide (24)

To the tube was added 2.78 g (.01 mol) of freshly prepared 24 which was pyrolyzed at 150° and 2 mm of pressure. The results are reported in Table 4.

Pyrolysis of benzophenone diethyl mercaptole tetraoxide (25)

To the tube was added 0.5 g (1.4 mmol) of 25 which was pyrolyzed at 200° and 2 mm of pressure. The results are reported in Table 4.

Pyrolysis of 2,2-diphenyl-1,3-dithiolane monoxide (26)

To the tube was added 2.5 g (9.2 mmol) of 26 which was pyrolyzed at 130-140° and 1 atm of pressure. Benzophenone, sulfur and ethylene dibromide were recovered. See Table 4 for yields.

Pyrolysis of 2,2-diphenyl-1,3-oxathiolane-monoxide (27)

To the tube was added 2 g (7.8 mmol) of 27 which was pyrolyzed at 120-130° and 2 mm. The results are reported in Table 4.

2-Phenyl-1,3-dithiolane (12)

A solution of 5.3 g (.05 mol) of benzaldehyde, 4.7 g (.05 mol) of 1,2-ethanedithiol and 2 ml of boron trifluoride-etherate in 50 ml of chloroform was stirred at room temperature for 12 hr. The chloroform solution was then washed with a 10% solution of sodium bicarbonate and dried over anhydrous sodium sulfate. Evaporation of the chloroform yielded 8.9 g (98%) of crude product. Distillation yielded 8.5 g (93%) of 2-phenyl-1,3-dithiolane as a colorless liquid, bp 134-136° (3.5 mm), n_D^{25} 1.6366 [Lit.[13] bp 109.5° (.7 mm) n_D^{25} 1.6368].

The Oxidation of 2-phenyl-1,3-dithiolane

A mixture of 2 g (.011 mol) of 12, 10 ml of 30% hydrogen peroxide and 50 ml of glacial acetic acid was stirred at room temperature and after about 5 min a white solid separated from the solution. The solid was collected by suction filtration, washed with benzene and air dried to yield 1.8 g of a product whose ir spectrum exhibited absorptions at 1310, 1120 and 1030 cm^{-1} (sulfone and sulfoxide), 1710 cm^{-1} (benzoic acid).

Attempts to oxidize 12 with m-chloroperbenzoic acid produced similar results.

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