THE UNIVERSITY OF MANITOBA

Studies on Thiophene and Furan Derivatives

by

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TO

MY WIFE, SON

AND MY PARENTS

ACKNOWLEDGEMENT

I would like to thank Dr. McKinnon for his patience and guidance during the past two years, when I worked under him, and for making the experience of working under his supervision very pleasurable indeed. I would also like to take this oppertunity to thank Dr. Wong for his constant advice, which were most helpful in numerous occasions.

Abstract

The preparations of some compounds which have not appeared in literature were attempted without much success. These include: 2,2-dimethyl-3(2H)-benzo[b]thiophenone (97a); 2,2,7-trimethyl-3(2H)-benzo[b]thiophenone (93a); 2,2-dimethyl-5-phenyl-3(2H)-thiophenone (94a), and [2.2]-(2,5)thiophenophane-1,8-diene (98).

The preparation of 5,5-dimethyl-4-phenyl-2(5H)-thiophenone (95a) was considered to be successful in spite of the fact that the compound could not be purified to enable the performance of an analysis. The identity of the compound was arrived at on the basis of spectral data. 2,2-dimethyl-3(2H)-benzofuranone (97b), and 2,2,7-trimethyl-3(2H)-benzofuranone (93b) were prepared in a new fashion—by direct oxidation of 2,3-dihydro-2,2-dimethylbenzofuran (100) and 2,3-dihydro-2,2,7-trimethylbenzofuran (103) respectively. 5,5-dimethyl-4-phenyl-2(5H)-furanone (95b) was also prepared by a new method.

In the process of preparing the above compounds, some intermediates which have not appeared in literature were prepared. Some model compounds were also prepared by new methods.

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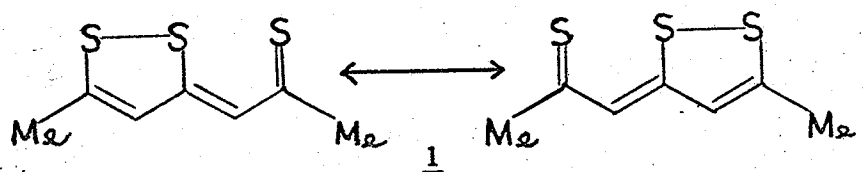
INTRODUCTION

GENERAL

The structure of the 2,5-dimethylthiothiophthene system (1) was first worked out by Bezzi, Mammi, and Garbuglio [1] by x-ray crystallography. They found that the three sulfur atoms all lay in a straight line, equally spaced at a distance of 2.36×10^{-8} cm., which is considerably greater than the normal S—S bond distance of 2.04×10^{-8} cm. found in disulfides R—S—S—R'. The C—C bond lengths were found to be between 1.37 and 1.38×10^{-8} cm. as found in aromatic systems (Fig.II). To explain these findings, they represented the system by the two following equivalent resonance structures and to this phenomenon, they gave the name single-bond—no-bond resonance (Fig.I).



1

Fig. I

An n.m.r. investigation was performed by Hertz, Traverso and Walter [2] who showed that both methyl protons and both ring protons respectively were equivalent. Further n.m.r. work by Dingwall, McKenzie and Reid [3] indicated that the ring protons were strongly deshielded due to ring current.

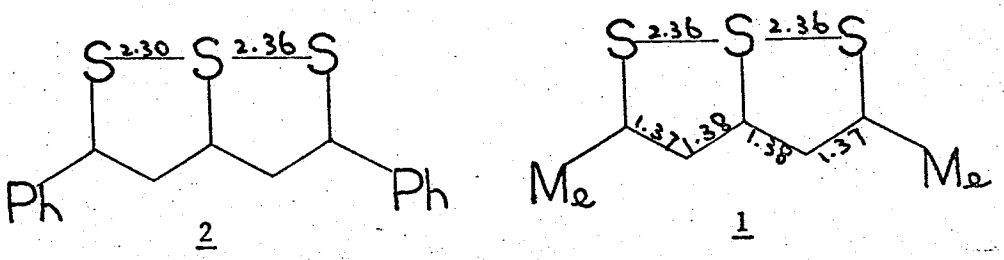
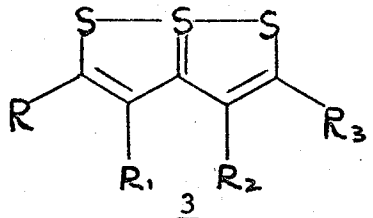


Fig. II

However, Hordvik [4] found that in the 2,5-dimethylthiothiophthene system (2), the S—S bond distances are almost, but not exactly equal (2.30×10^{-8} cm. and 2.36×10^{-8} cm.). This was attributed to slight disturbance of the molecular symmetry by the intramolecular enviroment.

Leaver and McKinnon [5] originally explained the equivalence of the methyl protons in 1 by rapid tautomerism rather than by single-bond—no-bond resonance, as proposed by Bezzi et al [1].

Theoretical calculations by Maeda [6] and by Gleiter and Hoffmann [7] showed that the thiothiophthene system is best represented by the structure 3 in which the central atom has undergone valence shell expansion and become tetravalent (Fig.III).



3

Fig. III

Maeda's calculations showed that participation of the $3P_z$ orbital of the sulfur atoms was more likely than that of $3d_{xy}$ orbitals. Gleiter and Hoffmann [7], however, showed that when 3d orbitals ars included in the calculations, the potential energy of the system shows a very flat minimum at a configuration which is almost but not quite symmetrical. Findings of Johnson and Paul [8] supported that view (Fig.IV):

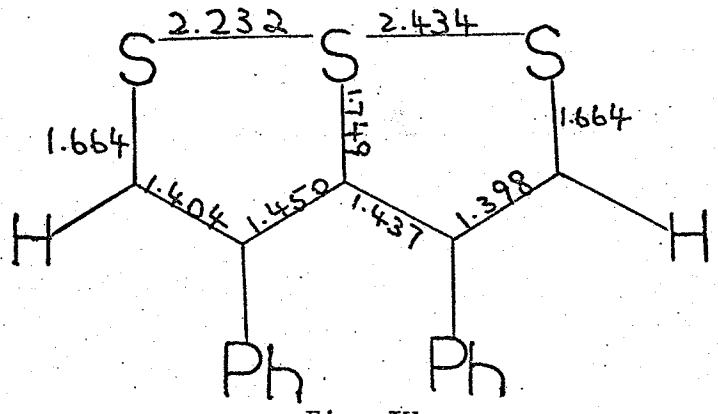
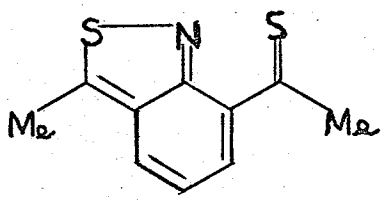


Fig. IV

Recent work by Brown, Leaver and McKinnon [9] in a reinterpretation of previous results, also agreed that the thiothiophthene system is best represented by 3.

However, irrespective of the type of phenomenon involved in the thiothiophthene system that causes the peculiar properties, it would be useful to examine related systems in which the centre atom is incapable of valence shell expansion, to determine to what extent their properties approach those of the thiothiophthene system. One such system would be 3-methyl-7-thioacetylthioanthranil (4):



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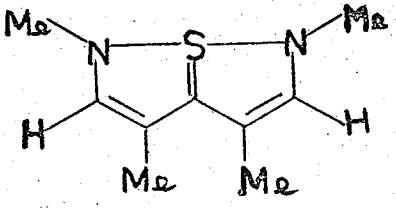
However, attempted preparation of the system failed [10] since unlike the thiothiophthene 1, the thioacetyl group was quickly hydrolysed to the acetyl during work-up, indicating that the compound did not possess any stablization akin to the thiothiophthenes. Of course valence shell expansion of the central nitrogen atom is impossible. That work indicated that a central atom capable of valence shell expansion, or at least sulfur is necessary to explain the symmetry of the thiothiophthenes. Similar phenomena have been found for an isothiazole 5 [11] and a thioxole 6 [12] derivative.



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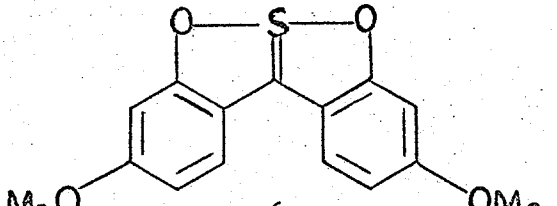
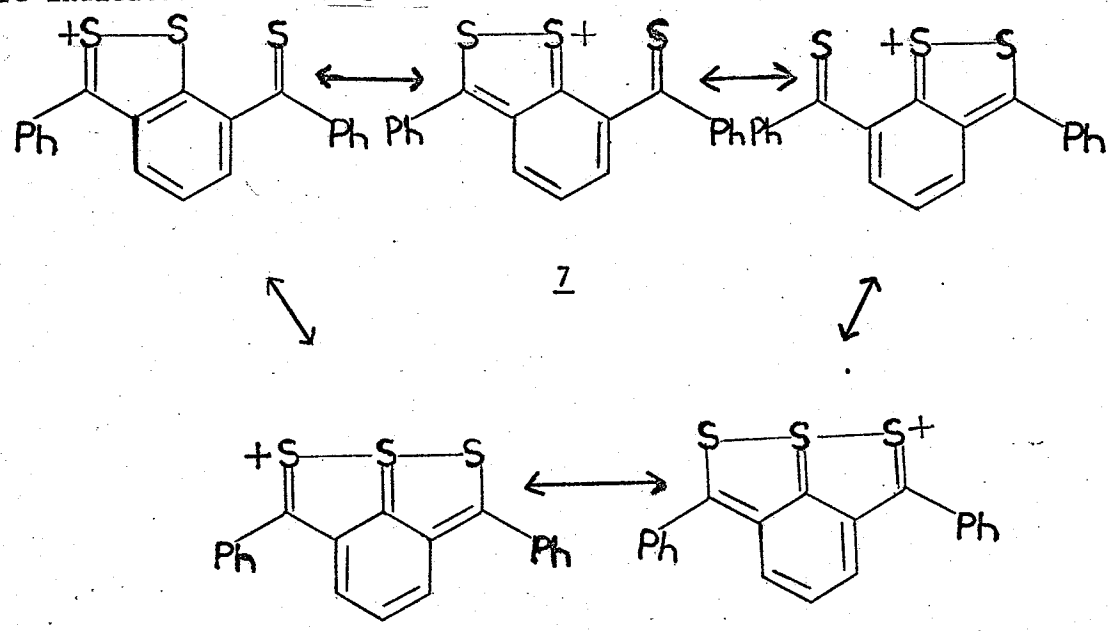


6

It was found that the chemistry of the anthranil of McKinnon and Wong [10] indicated that it might undergo tautomerism in the course of a chemical reaction, even if this was not detected by n.m.r.

The necessity of a central sulfur atom is also supported by the fact that a sulfur cation analogue of 4 was prepared and found to be stable [13]. Tetravalent sulfur contributing structures are indicated below (Fig.V).

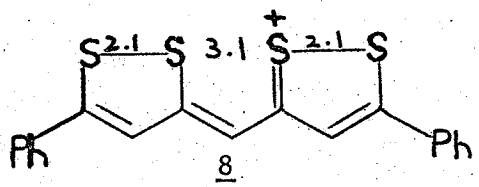


7

Fig. V

The n.m.r. of 7 showed that the phenyl groups are equivalent. Though the authors attributed this to either resonance or rapid tautomerism, in a later paper [9], they reinterpreted their results and favoured tetravalent sulfur instead.

Extending the thiothiophthene structure principle to a system containing four sulfur atoms all lying in a straight line, the cyanine system is reached. The first of these compounds was successfully synthesized by Klingsberg [14] in the form of the iodide:



8

Fig. VI

Hordvik [15] carried out the x-ray crystallographic examination of 8 and found the two internal sulfur atoms to be separated by an unusually short distance of 3.0 to 3.1x10^{-8}cm.(Fig.vi), which is far below the van der Waal's distance of 3.7x10^{-8}cm. [14,15]. Klingsberg [14] explained this by single-bond—no-bond resonance (Fig.VII).

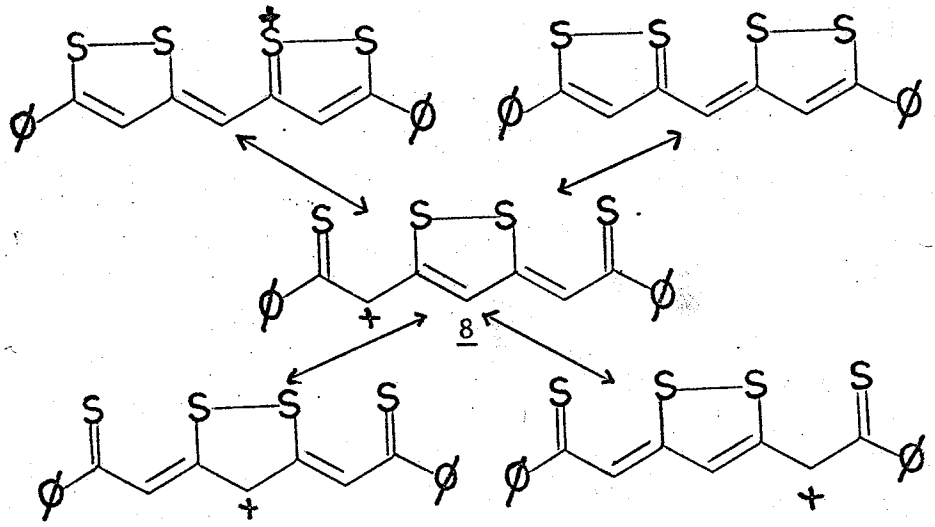
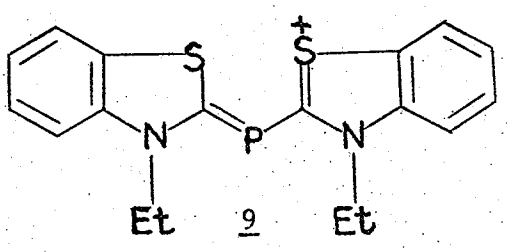


Fig. VII

However, Easton, Leaver and McKinnon [16] after successful preparation of the perchlorate of 8 argued that since (a) no evidence had yet been presented to indicate that the disulfide bonds in the dithiole nuclei were unusually long and (b) that the central S—S distance for the phosphacyanine 9 [17] is even shorter (2.95x10^{-8}cm.) and in 9, single-bond—no-bond resonance is highly improbable, they therefore, explained the findings by valence shell expansion of the internal sulfur atoms (structure 10).



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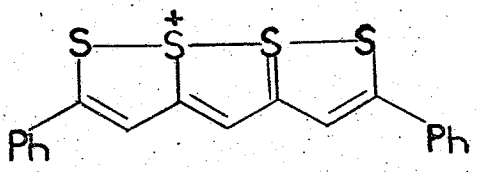

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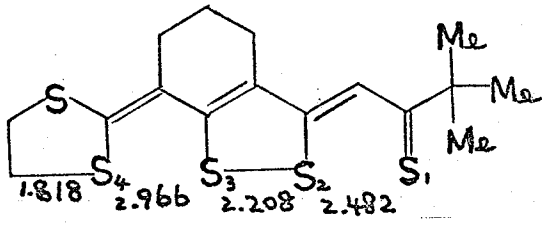
More recent findings by Sletten [18] in an x-ray study of system 11 showed that the presence of a fourth sulfur atom in the row had little influence on the bonding in the three sulfur system. There was also evidence of repulsion between S(3) and S(4).



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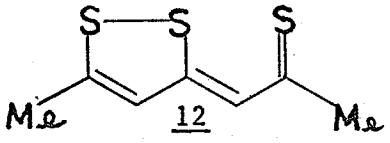


12

Fig. VIII

In a most recent communication, Gleiter and Schmidt [19] did some SCF-CI calculations, using only p orbitals as a basis for sulfur, in an attempt to explain the electronic spectrum of 2,5-dimethylthiothiophthene, found that the unsymmetrical model 12 fits best into their results. Since Gleiter and Hoffmann [7] did find that the use of d orbitals in calculations of the thiothiophthene system is favoured, on energy basis, the conclusions arrived at by Gleiter and Schmidt [19] should be treated with reservation until similar calculations involving d orbitals of sulfur are performed.

The arguments for and against the use of d orbitals of sulfur are now reviewed.

In 1939, Schomaker and Pauling [20], on the basis of the dipole moment of thiophene, postulated that structures involving an expanded shell in double bonded sulfur contribute to resonance in thiophene (Fig. IX).

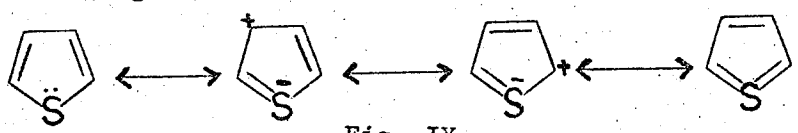
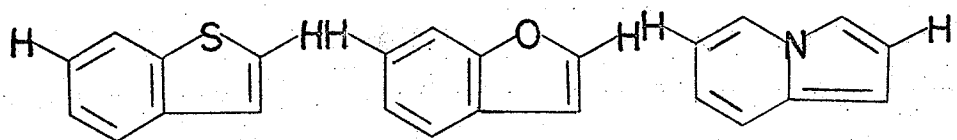


Fig. IX

In 1949, Longuet-Higgins [20a] showed that by postulating the utilization of 3d orbitals by sulfur in thiophene, one can explain the similarities of this system to benzene. Since then, a lot of experimental evidence could be explained by an expansion of the valence shell of sulfur (see review on subject by Cilento [21]). There is no doubt that in certain sulfur compounds, d orbitals are or can be utilized.

In a review by Zahradnik on "Electronic Structure of Heterocyclic Sulfur Compounds" [22], the shortcomings of theoretical calculations on the electronic structure of sulfur heterocyclic compounds when d orbitals were or were not utilized, were clearly indicated. In some cases, the use of d orbitals fitted the experimental results best and in others, the use of d orbitals failed to correlate the results with the model proposed completely.

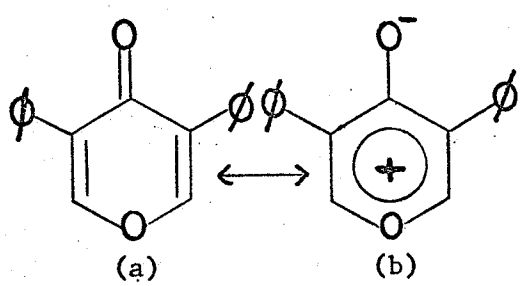
In another short review by Kiss [23], basing on u.v. absorption spectral evidence, it was concluded that the involvement of d orbitals of sulfur in open-chain compounds is unlikely though probable in sulfur heterocyclic systems. N.m.r. studies on benzo[b]-thiophene (13) [24], benzofuran (14) [25] and indolizine (15) [26], showed that couplings between the 2-proton and 6-proton in 13 and 15 is 0.5 Hz. while that in 14 could not be resolved. This was attributed to hyperconjugation through the d orbitals of sulfur in 13 and analogous through-conjugation in 15.



13 14 15

Again, the ability of sulfur to conjugate via the d orbitals can be seen in the greater $J_{2,6}$ coupling in pyrones (1.2 Hz.)

A great number of examples of the greater electron-releasing power of oxygen than sulfur [28] can be found in the literature. However, the dipole moment of γ-pyrone 16(3.82 D) [29] was found to be smaller than that of the corresponding γ-thiapyrone 17(4.40 D) [30], indicating the greater contribution of 17b to the resonance hybrid than that of 16b.



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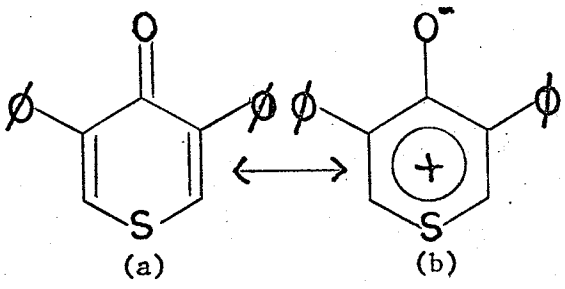

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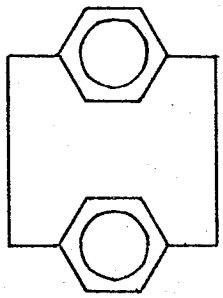
Thus, the electron-releasing ability of sulfur, in this instance, is greater than that of oxygen. This may be explained by more d orbital interaction of sulfur in a ring than in an open-chain compound, perhaps because of more favourable geometry.

In a most recent review by Salmond [31] titled "Valence-shell Expansion in Sulfur Heterocycles", it can be seen that the argument on d orbital participation of sulfur is far from settled. The only conclusion that can be drawn is that the ability of sulfur to expand its valence shell is more probable in cyclic compounds than in open-chain compounds. Thus, d orbital participation is considered to be important only when other models fail to explain the experimental results. However in some systems, especially so in thiothiophthenes, there is definite interaction between sulfur atoms, whatever the phenomena involved may be.

Cyclophanes

The [2.2]paracyclophane system (18) was first obtained in 1949 [32]. It provided a very useful model for the study of a variety of phenomena because of its unique geometry. The main interest stemmed on the fact that the two benzene rings are arranged face to face, at a maximum distance of 3.1×10^{-8}cm. apart [33]. One example of its usefulness as a model is for the theoretical treatment of transannular π-electron interactions, and the study of the effect of electronic interactions between unsaturated and unconjugated centres. Brown [34], by the x-ray diffraction method, showed that the benzene rings have been bent by eleven degrees from their normal planar state due to the large strain imposed on the system.



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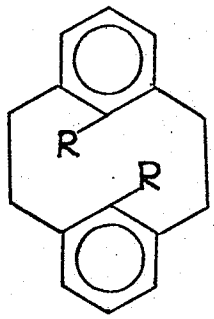
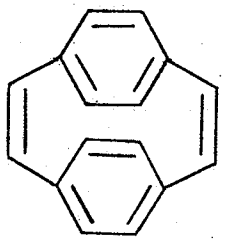


19 (a) R=H
(b) R=CH_3

Pellegrin [35] claimed to have obtained [2.2]metacyclophane (19a) by allowing m-xylylene dibromide, bromobenzene and sodium to react together. This work was repeated by Baker and co-workers [36] and confirmed that it was indeed formed in the reaction. By dehydrogenation of 19a, they obtained pyrene (25) and isolated it as the picrate [36a]. Brown [37] showed that the benzene rings in 19a are stepped and parallel. 8,16-dimethyl [2.2]metacyclophane (19b) was prepared [38] and has the same configuration as 19a, as demonstrated

by n.m.r. and x-ray structure determination [39]. Work done on 18, 19 and similar systems before 1964 had been extensively reviewed by Smith [40]. A very brief summary on the types of investigation into 18 between 1964 and 1970 can be found in a paper published by Longone and Chow [41].

Of all the cyclophanes prepared up to date, the most interesting ones are 20, 21, 22 and 23.



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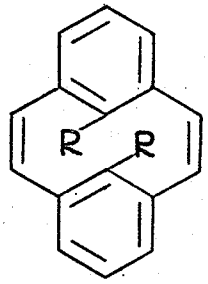
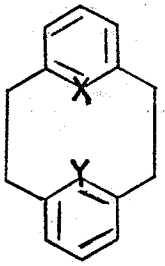


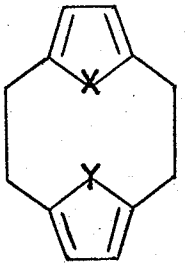
21

(a) R=H
(b) R=CH_3
(c) R=CH_2CH_3



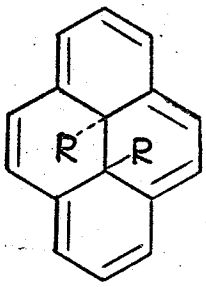
22

(a) X=N, Y=N
(b) X=N, Y=CH



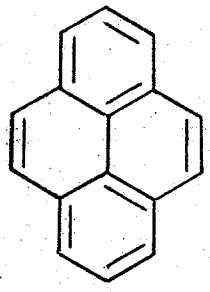
23

(a) X=O, Y=O
(b) X=S, Y=S
(c) X=O, Y=S



24

(a) R=H
(b) R=CH_3
(c) R=CH_2CH_3



25

[2.2] paracyclophane-1,9-diene (20) was first synthesized in 1958 [42]. The major object of that investigation was to find out how complete an insulation of chromophores was provided by the steric inhibition of resonance inherent in the geometry. It was found that 18, 20 and the monoolefine of 18 all had essentially the same u.v. spectra, as expected. 20 represented a system in which tremedous strain exists

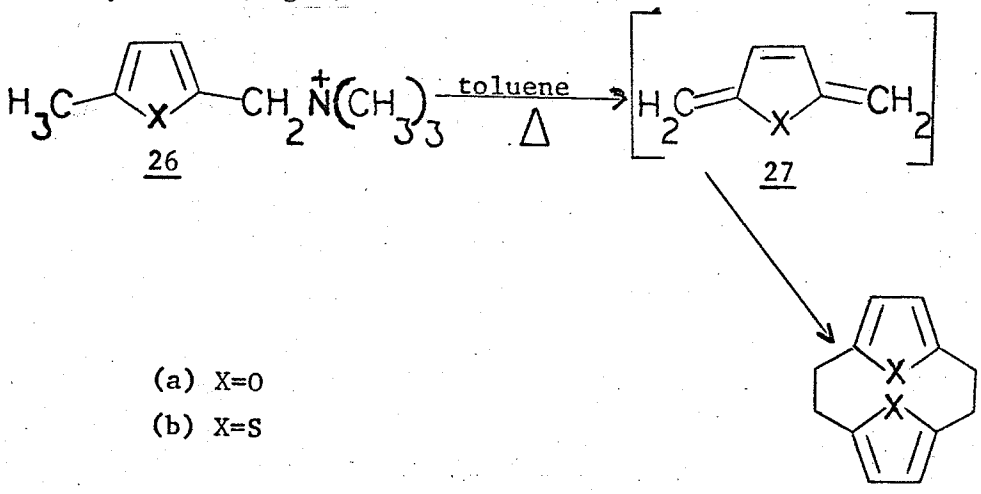
in the molecule due to the repulsion of the Π-electron clouds of the benzene rings which are forced together. As in 18, the benzene rings in 20 are bent.

System 21 is the valence tautomer of the dihydropyrene system 24. The prime interest lay in the interaction of the alkyl groups inside the Π-electron cloud, with each other and with the Π-electron cloud. Trans-15,16-dihydropyrene (24a) was synthesized by irradiation of [2.2]metacyclophane-1,9-diene (21a) with light [43]. The products formed were 24a and pyrene (25), and though 24a could not be isolated, its existence was shown n.m.r. [43]. It is surprising that 21a is stable and could be isolated pure because the corresponding 8,16-dimethyl analogue 21b undergoes spontaneous valence tautomerization at room temperature to the corresponding pyrene 24b [44]. 21c however, was found to be stable at room temperature and showed no tendency to isomerize to 24c [45]. This was attributed to the greater steric interaction of the ethyl groups with the Π-electron cloud than the methyl groups [45]. N.m.r. studies on trans-15,16-dimethyl-dihydropyrene (24b) [44] and the diethyl analogue 24c [45] indicated strong ring current in the system, and thus provided strong support for the Huckel theory of $(4n+2)\Pi$-electrons required in aromatic systems. Also, the experimental evidence showed that steric interactions between the alkyl groups and with the Π-electron cloud do play an important part in the stability of the [2.2]metacyclophane-1, 9-dienes (21).

[2.2]metacyclo-2,6-pyridinophane (22a) was first successfully prepared by Baker and co-workers [46]. I. Gault, B.J. Price and I.O. Sutherland [47] did some studies on the conformational rigidity of the system. They found that 22a has a much lower activation energy than 19a for conformational inversion. In a later paper, Fletcher

and Sutherland [48] found that the CH, N interaction in the transition state for inversion of 22b is greater than that of 22a. Thus they gave the relative magnitudes of relatively short-range interactions of this type the ascending order of N,N; CH, N and CH,CH. All these conclusions were based on n.m.r. studies at varying temperature.

[2.2](2,5)furanophane (23a) and [2.2](2,5)thiophenophane (23b) were prepared by Windberg and co-workers [49]. Both of these compounds were obtained by polymerization of the corresponding quarternary salts (Fig.X):



26 27 23

(a) X=O
(b) X=S

Fig. X

23a was obtained in an overall yield of 72% (from the quarternary iodide), while 23b was obtained in 19% yield, basing on the quarternary hydroxide. The 2,5-dihydro-2,5-dimethylene intermediate of furan 27a was isolated while that of thiophene 27b was not. 23c was obtained by Fletcher and Sutherland [48] by pyrolysing a one to one mixture of quarternary hydroxides 26. They did some n.m.r. temperature studies on 23 and found that rigidity of the system increases in the order of O,O; O,S and S,S. This was attributed to the larger size of the sulfur atom.

18 was first prepared by the low pressure pyrolysis of para-xylene [32], but was later obtained in a manner analogous to

23 [49]. However, the preparations of the other systems: 19 and 22 follow a similar pattern sumerized below (Fig.XI):-

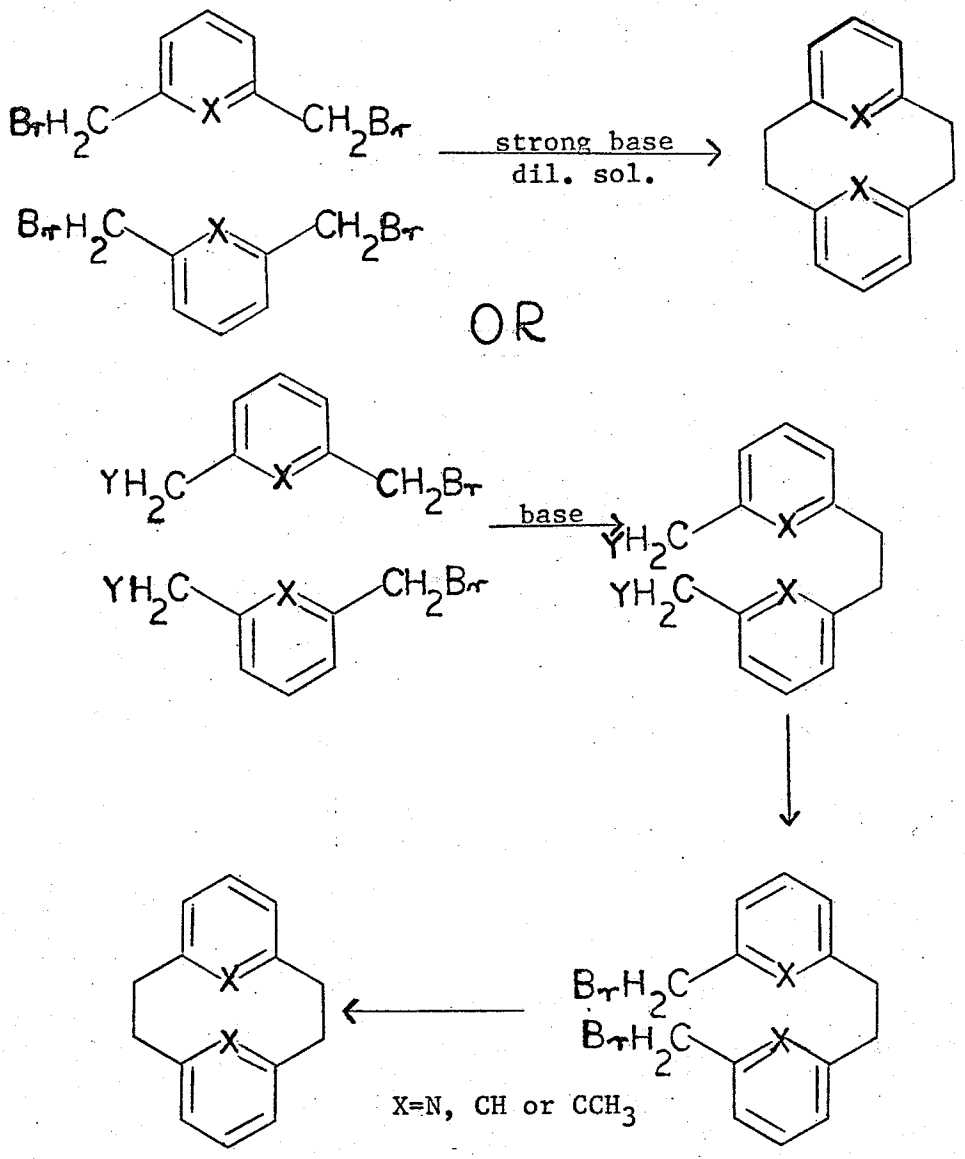


Fig. XI

The exact manner of synthesis can be found in the references and variations in the method gave different yields. It is of interest to note here that 20 was prepared by bromination of 18 with N-bromo-succinimide and subsequent elimination of HBr with potassium tertiary-butoxide while 21 was synthesized by an entirely different route (see below).

Recently, Boekelheide and co-workers developed a new synthetic path for systems 21 [50,51,43]. This involves the transformation

of a sulfide linkage into a carbon-carbon double bond (Fig.XII):

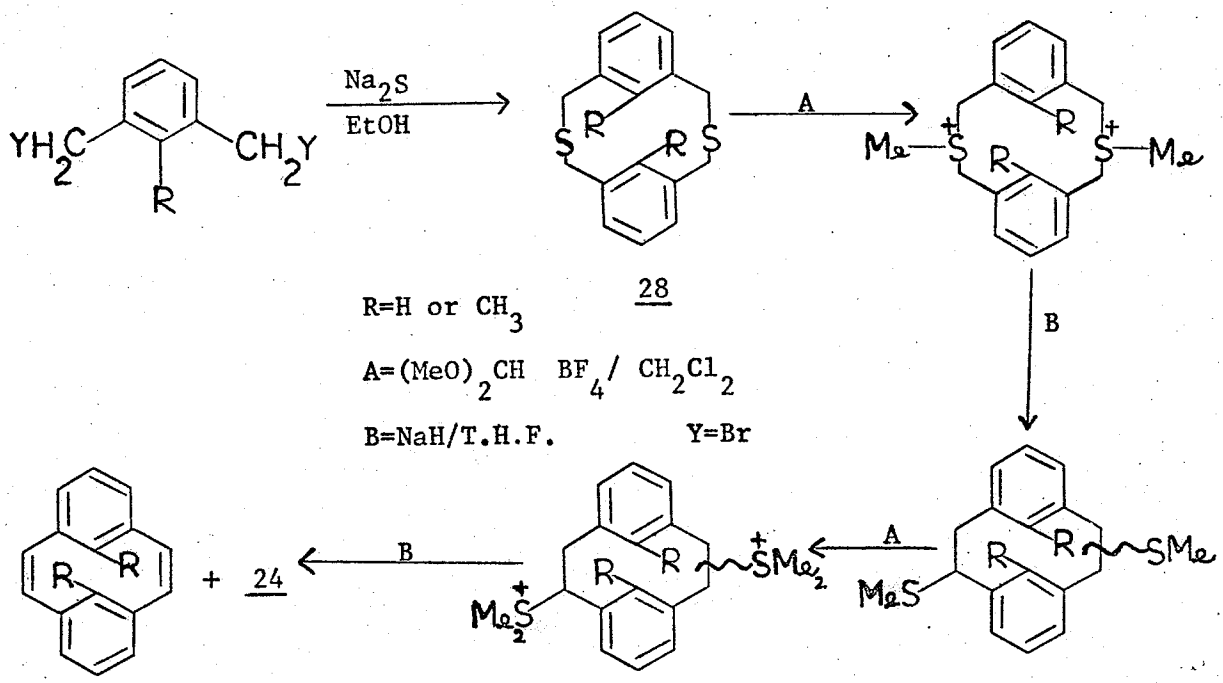


Fig. XII

28 was obtained in much better yield when the following scheme was followed [51] (Fig.XIII):

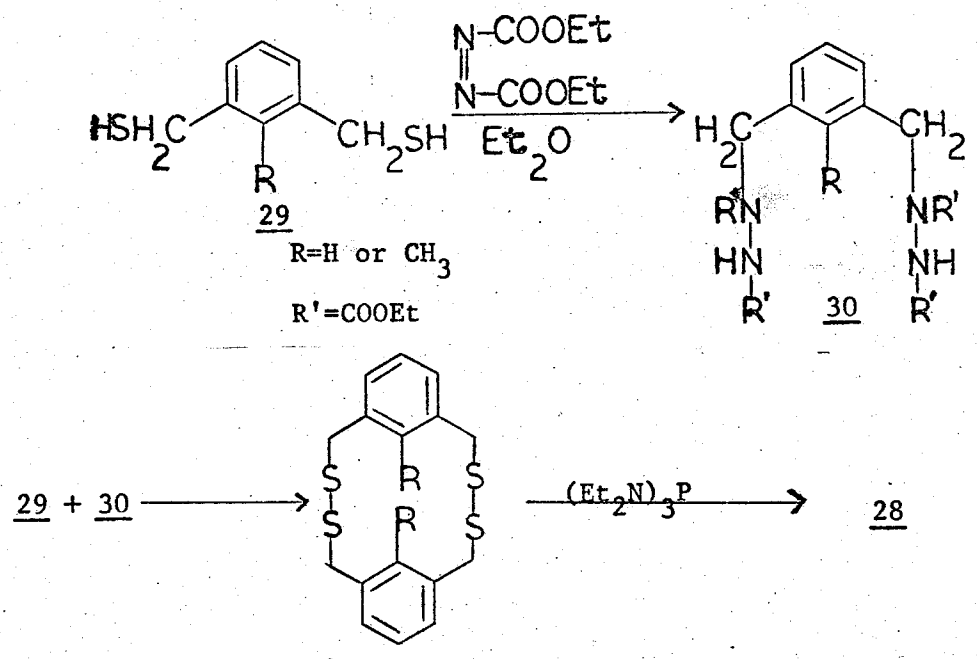
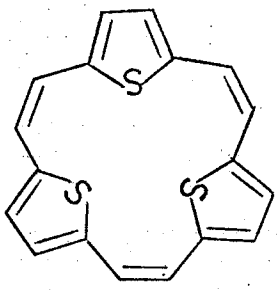


Fig. XIII

Following this procedure [2.2] metaparacyclophane-1,9-diene (31) was synthesized [52].

Finally, other heterocyclic cyclophanes of interest that

has been sythesized up to date include [18]annulene trisulfide (33) [53] and [18]annulene trioxide (34) [54]. Their properties were compared with those of [18]annulene (35).



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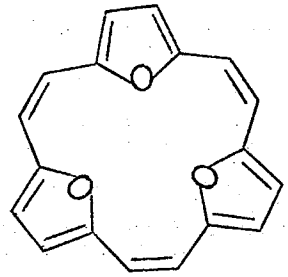
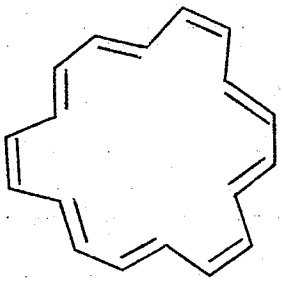
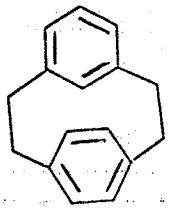


34



35

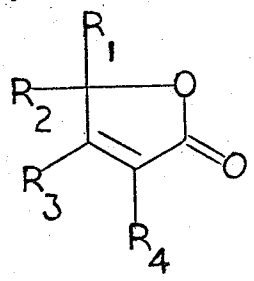


32

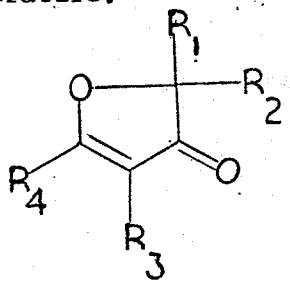
It was found that both 33 and 34 are much more stable than 35, and that while 34 is aromatic, 33 is not. From n.m.r. data, it was concluded that 33 has no significant induced ring current and thus the molecule possesses no more aromaticity than that provided by the three thienyl groups. U.V. data also supported this view. The molecule was found to be non-planar [53]. In an analogous fashion, 34 was found to have a significant induced ring current and since a planar model could be constructed, it was assumed to be planar [54].

Preparations of furanones and 3(2H)-benzofuranones

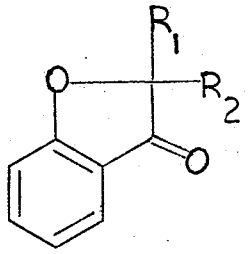
2(5H)-furanones are commonly known as α,β-unsaturated γ-lactones, They are readily formed when a γ-hydroxy-α,β-unsaturated acid is heated, or on standing at room temperature, or even in aqueous solution when the sodium salt of the acid is acidified. To illustrate the general methods employed in the synthesis of γ-lactones, and keeping in line with the object of this research, a few examples are quoted from the literature.



36

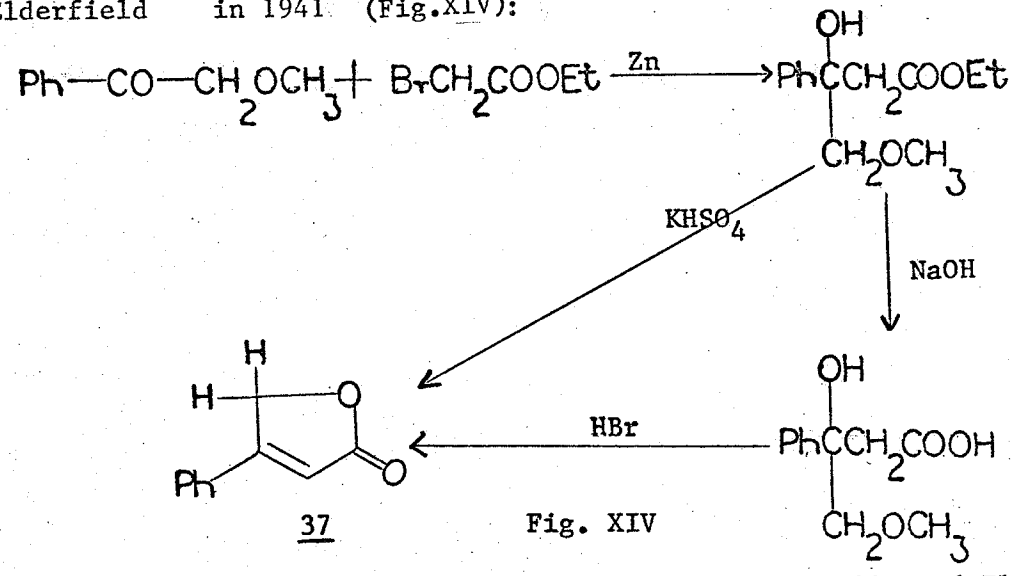


42



48

The first example is the preparation of 4-phenyl-2(5H)-furanone (37) (36, $R_1=R_2=R_4=H$, $R_3=Ph$), reported by Rubin, Paist and Elderfield [55] in 1941 (Fig.XIV):



37 Fig. XIV

In a paper immediately following the above one, Linville and Elderfield [56] reported a modified synthesis of 37 (Fig. XV).

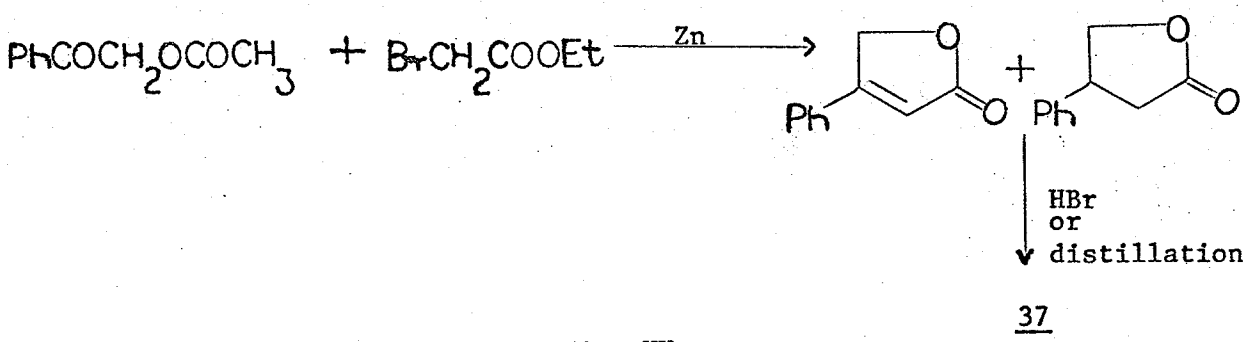


Fig. XV

The mixture of saturated and unsaturated lactones obtained in the Reformatsky reaction could not be separated and distillation or treatment with HBr in glacial acetic acid gave 37 alone. In 1943, Blout and Elderfield [57] prepared 38 (37, $R_1=R_2=R_4=H$, $R_3=C_6H_{11}$) from methyl cyclohexyl ketone (Fig. XVI):

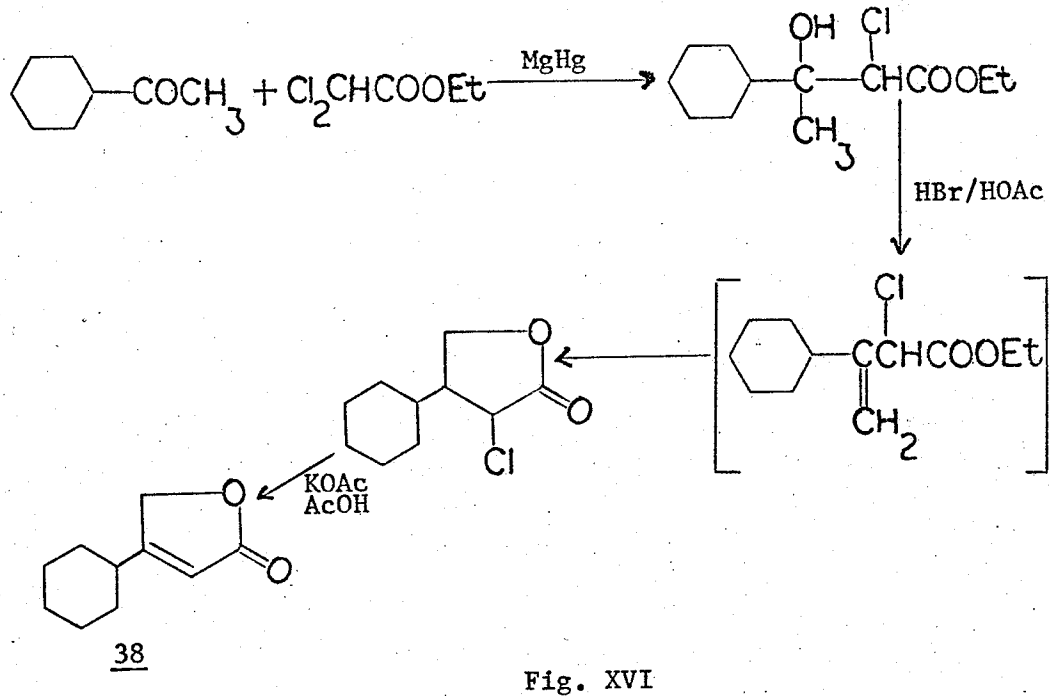


Fig. XVI

When the same synthesis was repeated with acetophenone [57], it was found that a mixture of products was obtained on treatment with HBr in acetic acid (Fig. XVII):

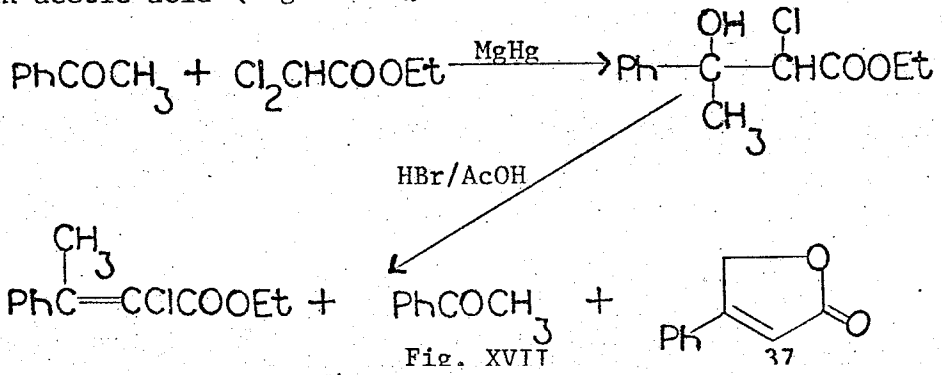


Fig. XVII

Swain, Todd and Waring [58] modified the process somewhat and by using an aldehyde, produced the same furanone 37 (Fig. XVIII):

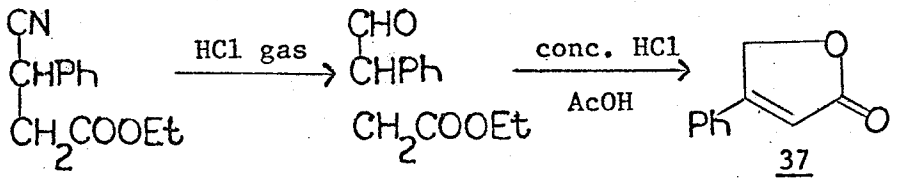


Fig. XVIII

Thus it can be seen that the same furanone 37 was synthesized from different starting materials and the same is true for a good number of 2(5H)-furanones. To illustrate the generality of the syntheses, an example below will show that by modifying the starting material, but using the same reaction path, 5,5-dimethyl-4-phenyl-2(5H)-furanone (39) (36, R_1=R_2=Me, R_3=Ph, R_4=H) [59] was prepared:

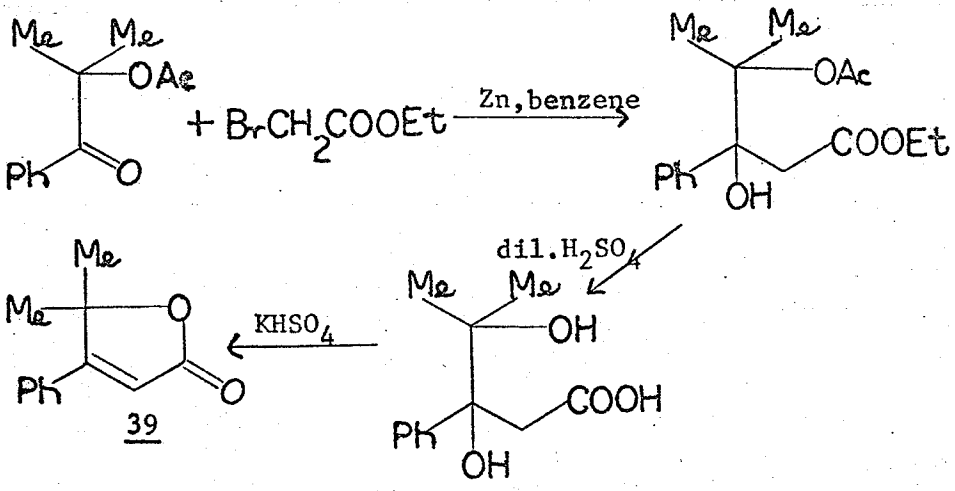


Fig. XIX

Two novel syntheses of 2(5H)-furanones are now listed to complete the picture. 40 (36, R_1=R_2=CH_3, R_3=R_4=Ph) was synthesized from isobutyrophenone [61] as shown in Fig. XX.

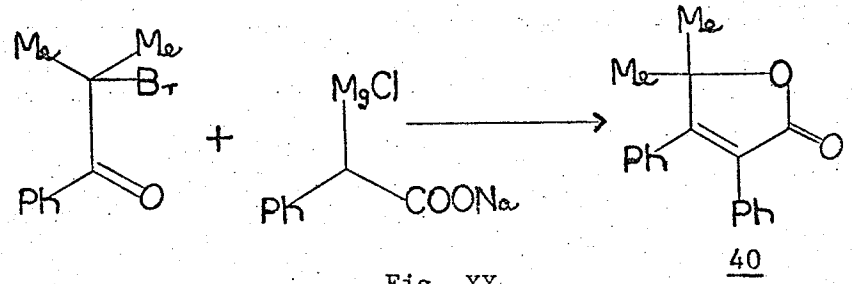
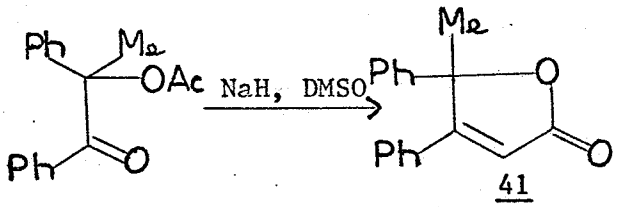


Fig. XX

The next example is the synthesis of 41 (36, R_1=Me, R_2=R_3=Ph, R_4=H) by Schering [62]:

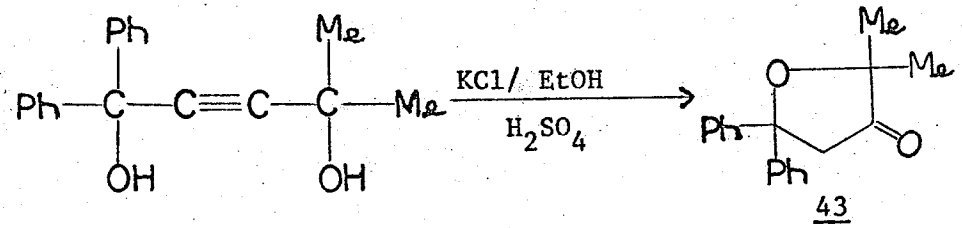


41

Fig. XXI

3(2H)-furanones 42 are not well known. However, 3-tetrahydrofuranones are just about as widely prepared as γ-lactones and 2(5H)-furanones. Their syntheses however should shed some light on the unsaturated analogue which could be obtained by introduction of a double bond. Thus, the preparation of 3-tetrahydrofuranones are reviewed instead of compounds of the type as 42.

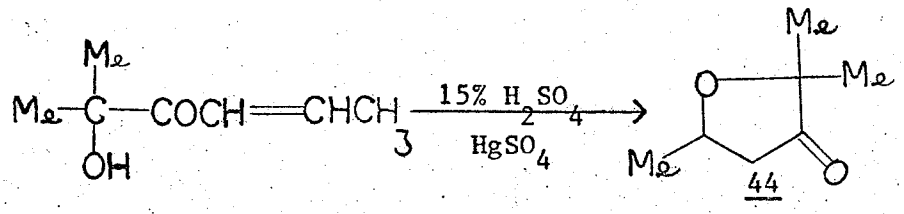
A very recent example is the preparation of 2,2-dimethyl-5, 5-diphenyltetrahydrofuran-3-one [63] (43) which involved the dehydration of diols—a general method employed.



43

Fig. XXII

The next most general method employed is the intramolecular addition of the OH group of unsaturated alcohols to the double or triple bond. The work done by Nazarov and Matsoyans [64] illustrates this (Fig. XXIII):



44

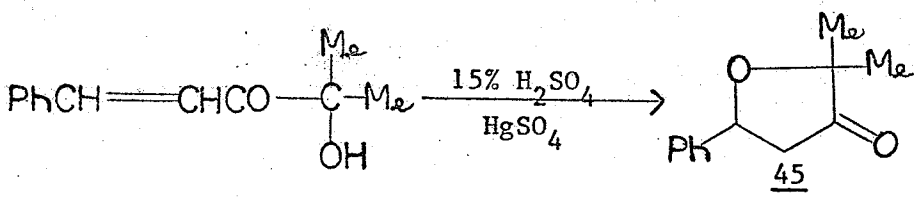


Fig. XXIII

One further example [65] is:

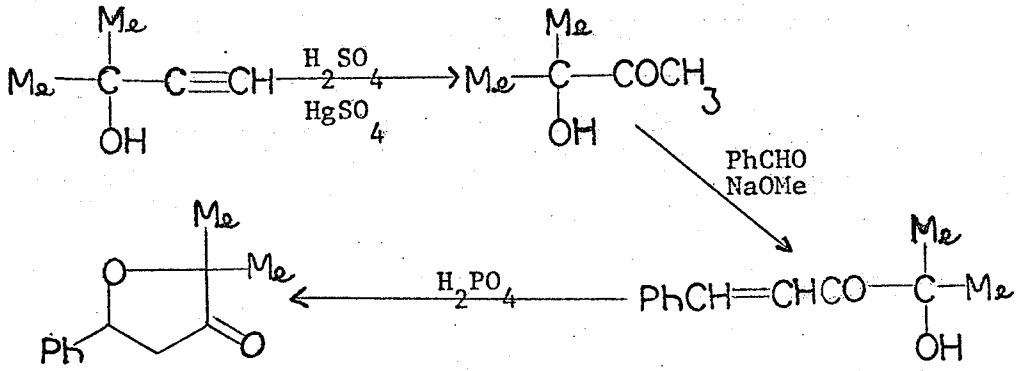


Fig. XXIV

A novel synthesis of this type of furanone can be seen in the paper published by Casnati and co-workers [60]. They prepared 45 by the hydrolysis of an isoxazolidene 46:

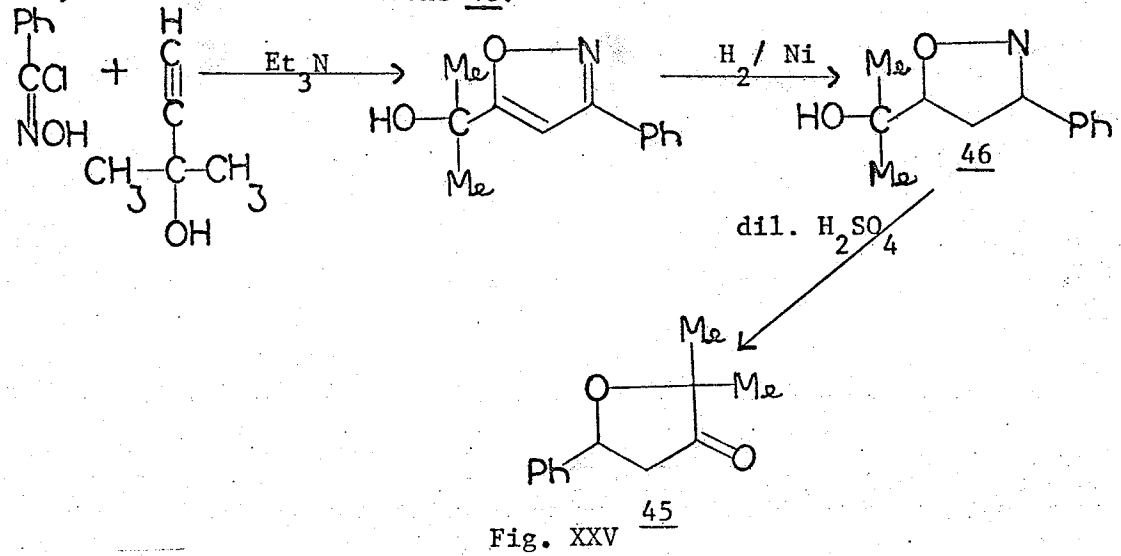
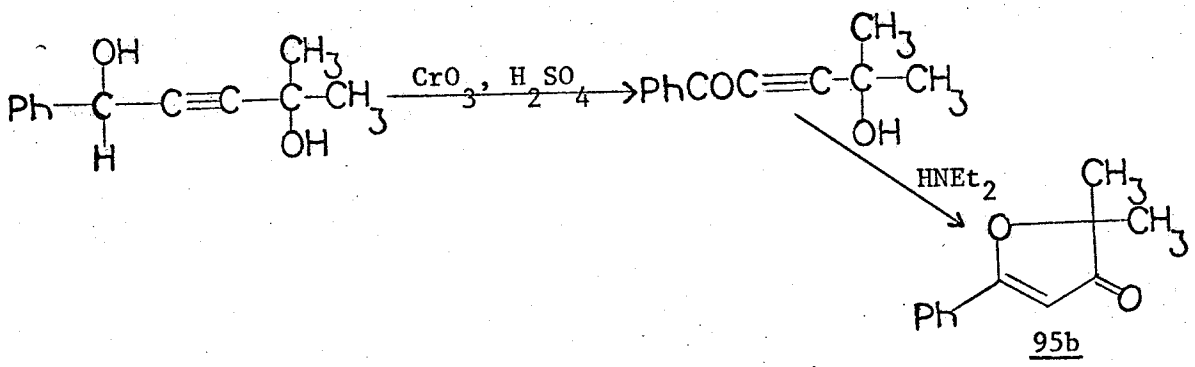


Fig. XXV

An example on the synthesis 3(2H)-furanones is the synthesis of 95b (42, $R_1=R_2=CH_3$, $R_3=H$, $R_4=Ph$) achieved by Parker and co-workers [66] (Fig. XXVI):



95b

Fig. XXVI

When a furan ring is fused to a benzene ring, we have benzofuran. 2,2-Disubstituted-3(2H)-benzofuranones 48 were prepared as early as 1914 by Auwers [67] who synthesized 2,2,5-trimethyl-3(2H)-benzofuranone (49) in the following way:

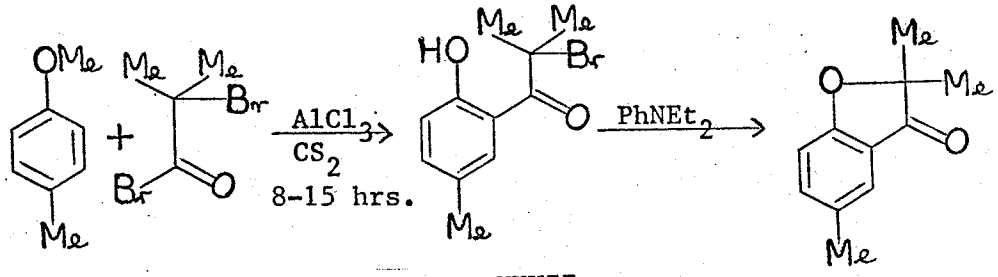


Fig. XXVII

49

Auwers [68] later reported a one step synthesis of a similar system 50 in 1920 (Fig.XXVIII):

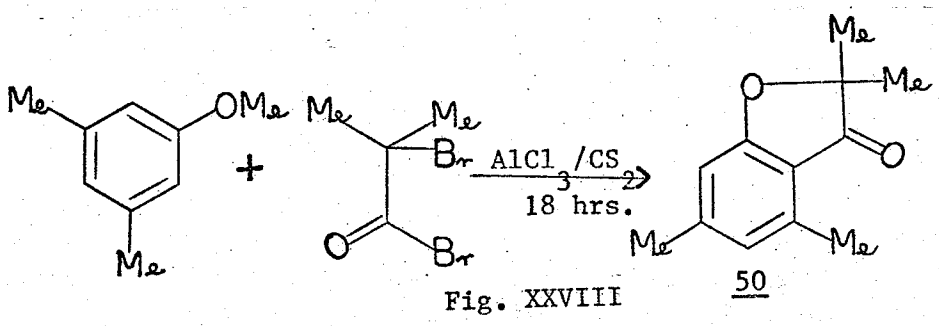


Fig. XXVIII

50

49 was also obtained by the alkylation of 51 [69]:

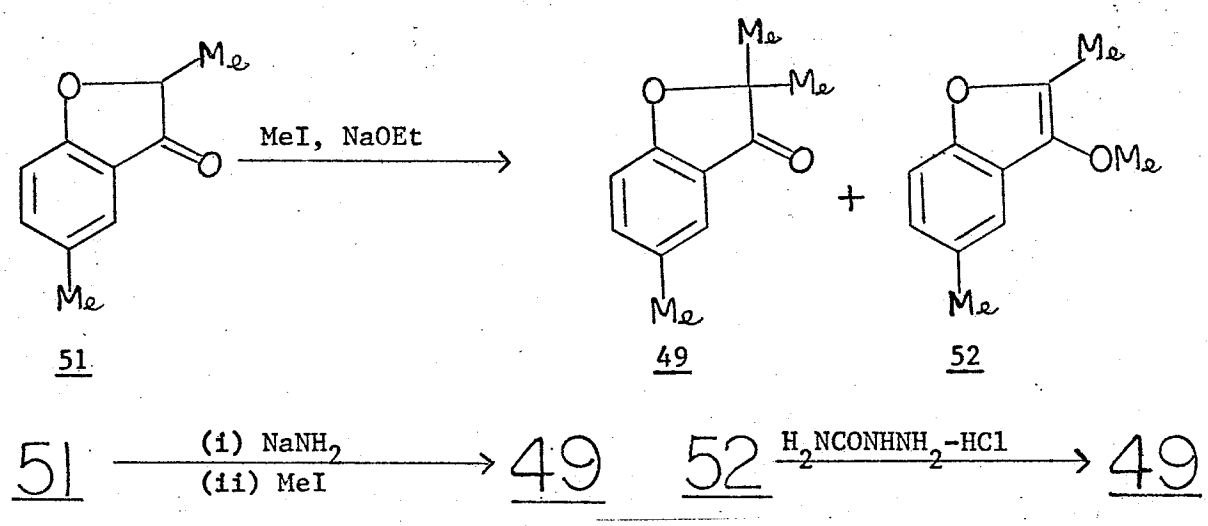


Fig. XXIX

Other methods used in the synthesis of 48 involved the novel synthesis of 2,2-diphenyl-3(2H)-benzofuranone (53) [70] (48, $R_1=R_2=Ph$):

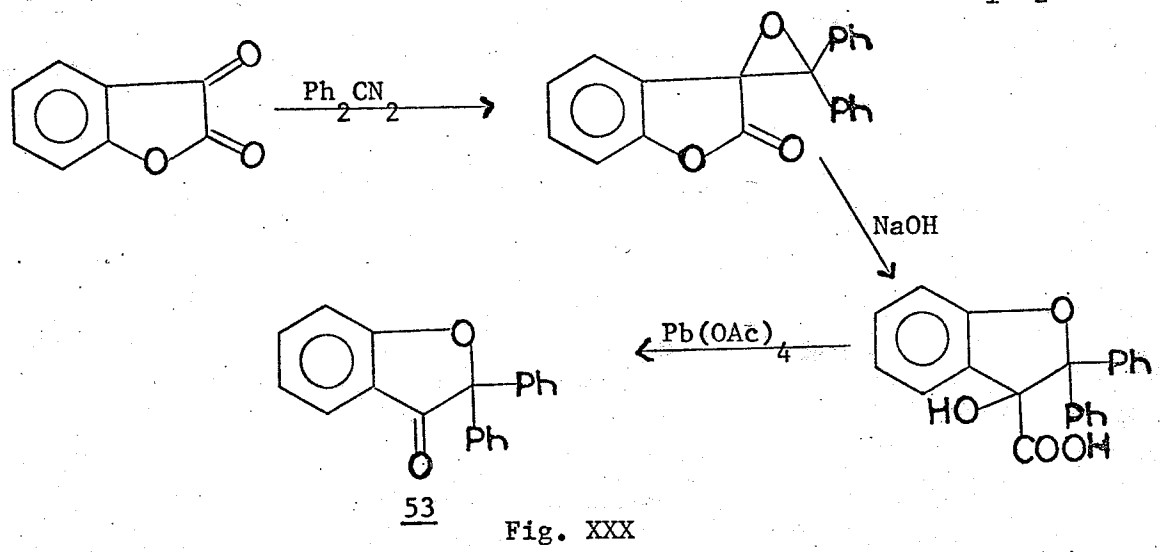
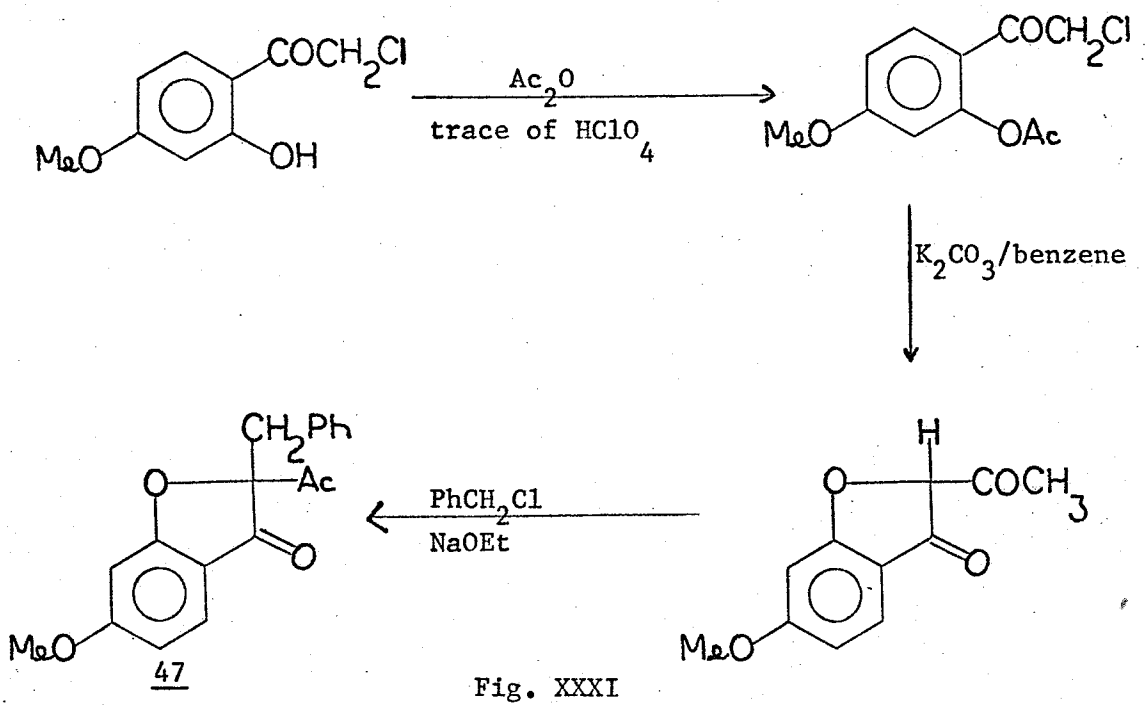


Fig. XXX

One last example on the novel synthesis of 2,2-Disubstituted-3(2H)-benzofuranones is the work done by Grover and co-workers [71]. They succeeded in preparing 2-benzyl-2-acetyl-6-methoxy-3(2H)-benzofuranone (47).



47

Fig. XXXI

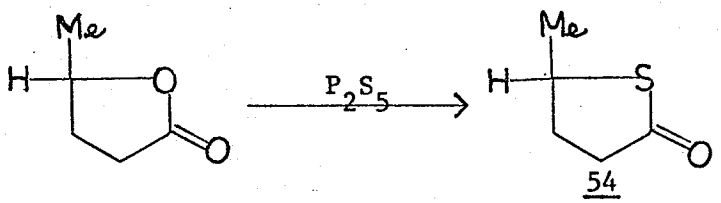
Thus, using their approach, a good number of 2-acetyl-2-R-3(2H)-benzofuranones can be obtained, simply by changing Ph-CH_2-Cl to R-Cl.

In conclusion it can be stated that furanones and benzofuranones have been widely prepared by a variety of methods. In this research, it was found that the 3-positions of benzofuranones are very reactive and a keto group can easily be introduced by direct oxidation. The approach that should be used in the syntheses of the above compounds is a matter of choice, depending on the final products required and the starting materials available.

Preparations of thiophenones and 3(2H)-benzothiophenones

2(5H)-thiophenones are commonly known as α,β-unsaturated thiolactones. They were generally prepared in the same way as 2(5H)-furanones i.e. by cyclization of the γ-mercapto acids, or by the addition of the SH group of an unsaturated thiolacid to the double or triple bond of the same molecue. Since the double bond can be introduced into the molecue with comparative ease, the preparations of 2-tetrahydrothiophenones are reviewed.

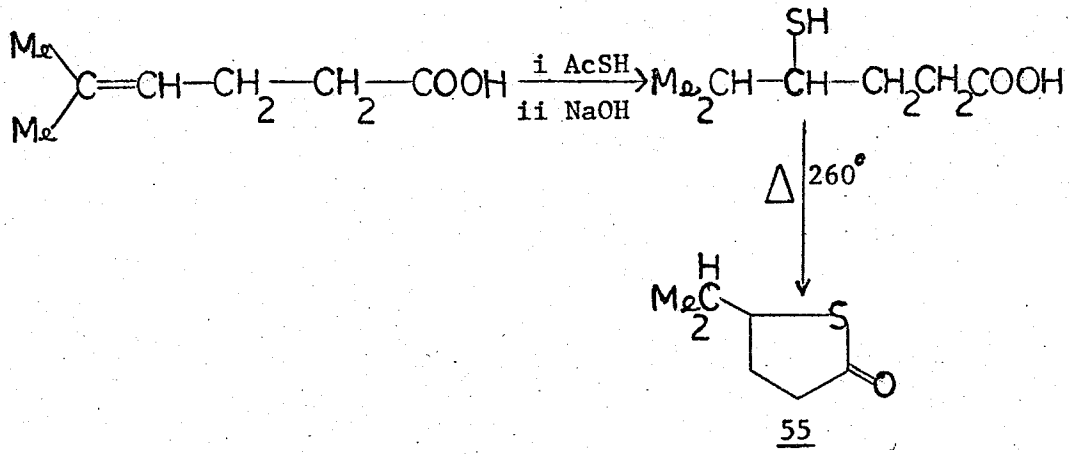
It was known as early as 1912 that sulfurization of aliphatic lactones gives thiolactones [72].



54

Fig. XXXII

The similarity of methods employed in the preparations of γ-lactones and γ-thiolactones is best illustrated by the work done by Korte and Christoph [73].



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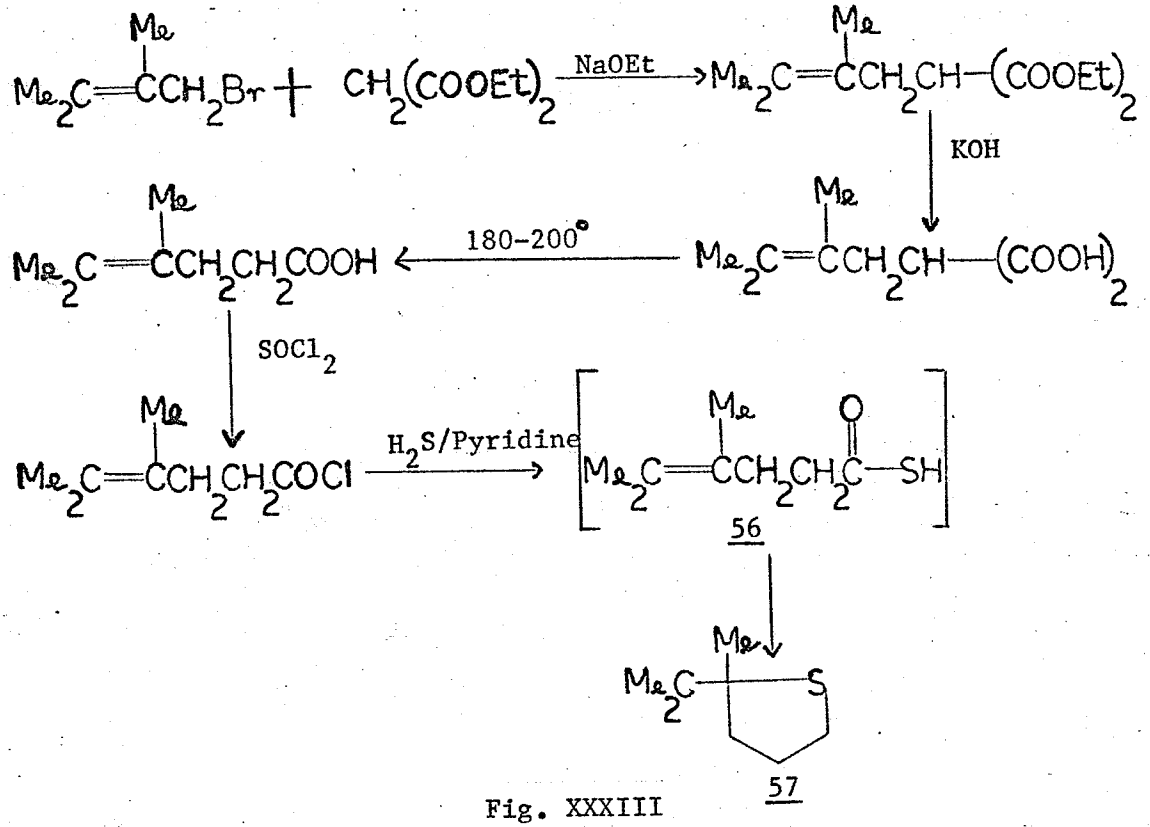


Fig. XXXIII

The thiolacid 56 spontaneously cyclized to the γ-thiolactone on acidification.

One way to prepare an unsaturated γ-thiolactone is the reaction path followed by Hornfeldt and Gronowitz in the preparation of 5-methyl-2(5H)-thiophenone (58), 5-methyl-2(3H)-thiophenone (59), and 5-benzylidene-4-bromo-2(5H)-thiophenone (60) [74]:

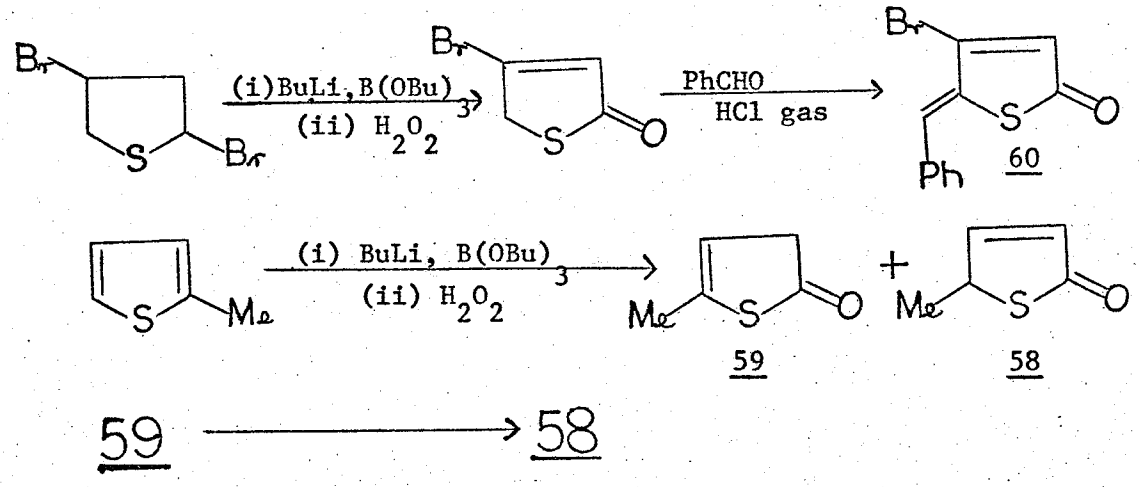
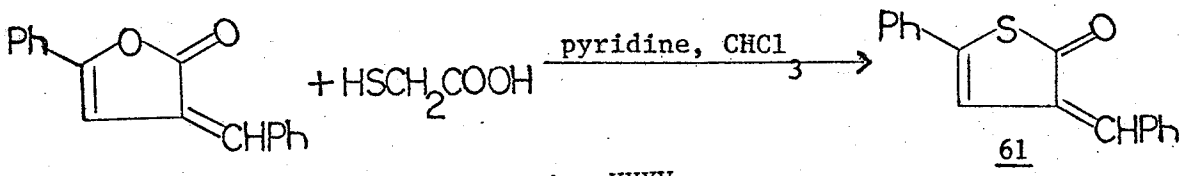


Fig. XXXIV

One further example on the preparation of 2(3H)-thiophenone is [75] :

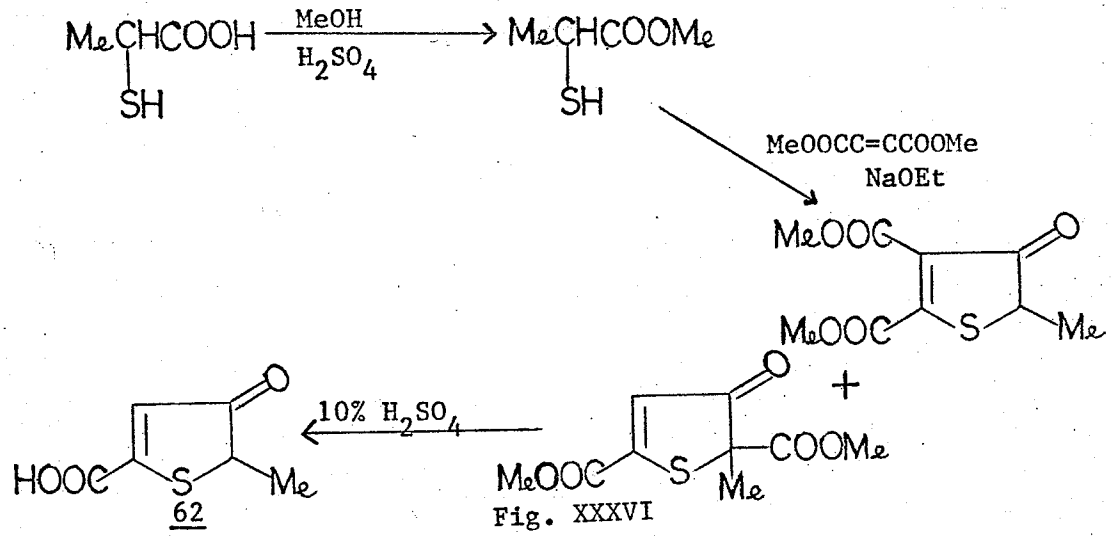


61

Fig. XXXV

Again, the preparation of 3(2H)-thiophenones and 3-tetrahydrothiophenones are very similar to those of the furan analogue.

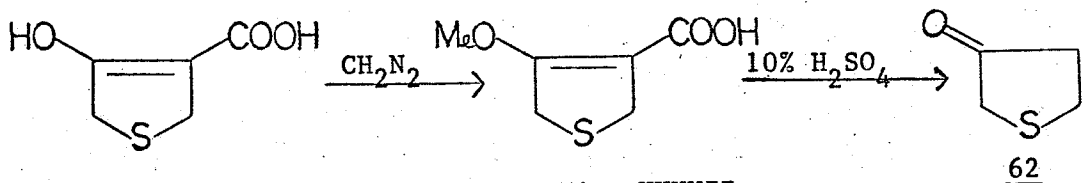
One example on the preparation of 3(2H)-thiophenone is work performed by Eugster and Allner [76] :



62

Fig. XXXVI

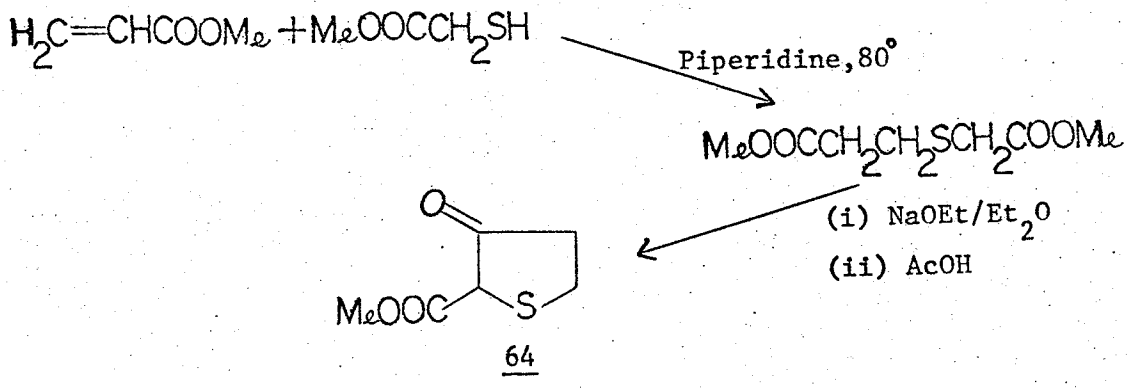
An example on the preparation of 3-tetrahydrothiophenone is [77] :



62

Fig. XXXVII

A final example on the preparation of 3-tetrahydrothiophenone is [78] :



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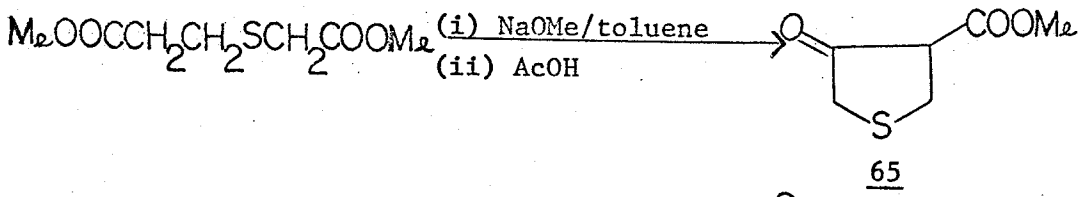


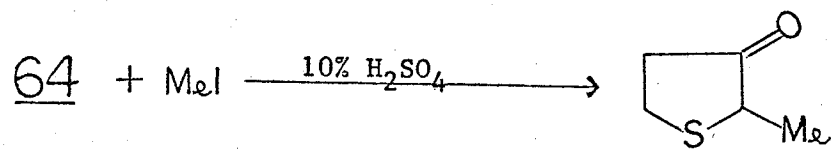
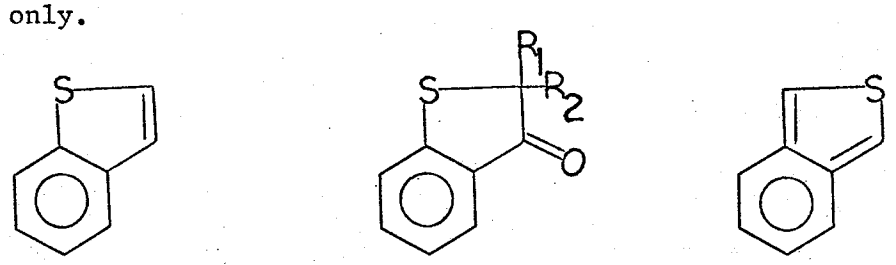


Fig. XXXVIII

The next higher homologue of thiophene is benzothiophene. There are two isomers of benzothiophene: benzo[b]thiophene (67) and benzo[c]thiophene (69). Since this research deals only with 2,2-Disubstituted-3(2H)-benzo[b]thiophenone (68), preparations of 68 are reviwed only.



67 68 69

2,2-Disubstituted-3(2H)-benzo[b]thiophenones were prepared as early as 1915 when Smiles and Ghosh [79] prepared 2,2-dibenzoyl-3(2H)-benzo[b]thiophenone (70) (68, R_1=R_2=Ph-CO-) by condensing thiosalicylic acid with dibenzoyl methane in concentrated sulfuric acid at fifty degrees.

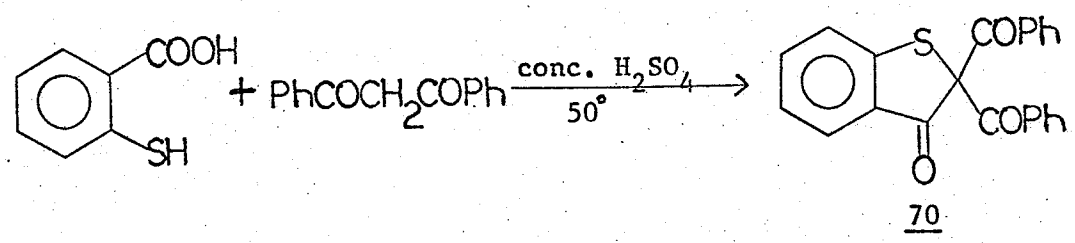


Fig. XXXIX

They tried the same reaction with acetyl acetone but were unable to isolate the 2,2-diacetyl analogue of 70.

Then Bistrzycki and Risi[80] prepared 2,2-diphenyl-3(2H)-benzo[b]thiophenone (71) by the following reaction sequence:

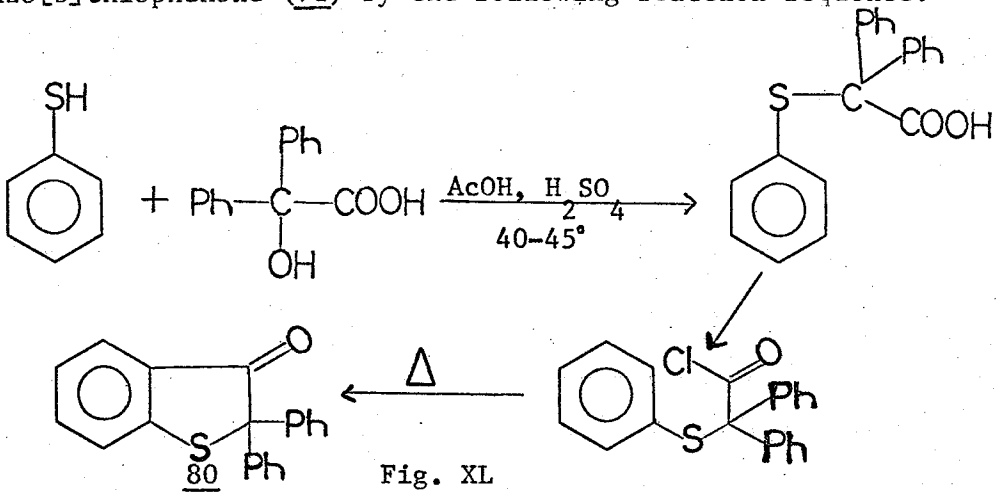


Fig. XL

They also found the Ph-CH(OH)-COOH and $(CH_3)_2C(OH)$-COOH failed to react with thiophenol and though α-4-tolylmercaptodiphenylacetic acid did give the corresponding 3(2H)-benzo[b]thiophenone, α-phenyl-mercapto-di-p-anisylacetic acid reacted in a different fashion. Thus the reaction does not seem to be a general one.

Another way to prepare 68 would be to alkylate the 2-mono-substituted compound (68, R_1 or R_2=H). Thus 81 was prepared as follows[81]:

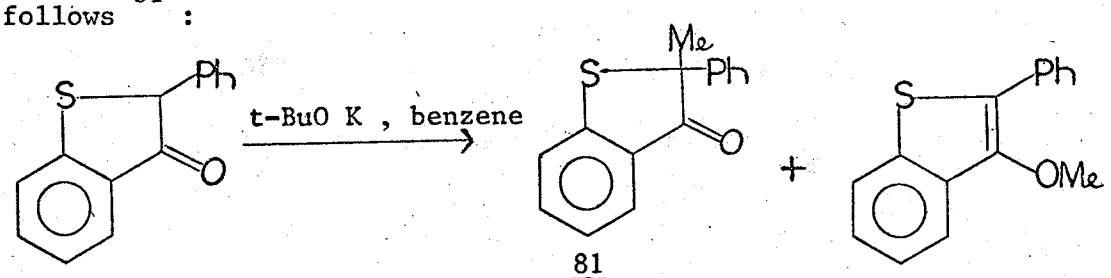


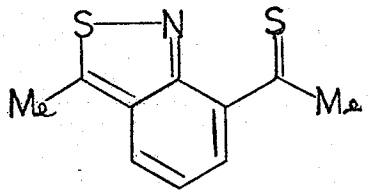
Fig. XLI

There are not many compounds analogous to 68 that have been prepared, and this is most surprising because the oxygen analogues of 68 have been widely studied and prepared. Thus, the above examples represented all the most general methods employed in the synthesis of system 68.

DISCUSSION

Object of Research

As indicated in the Introduction, systems 4, and 5, 6 and 7 are of great interest because of their differences and similarities in properties respectively with the thiothiophthene system. In trying to determine to what extent tautomerism plays a part in the structure and reactions of these compounds, it is useful to consider compounds in which the central atom is carbon.



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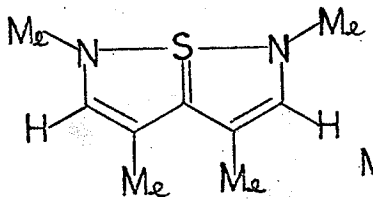

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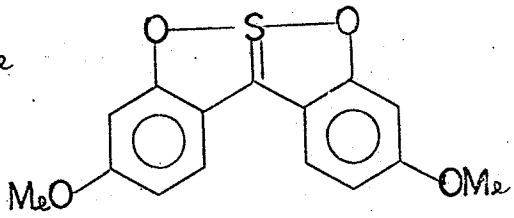

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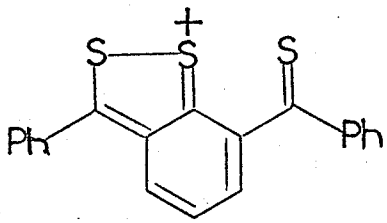
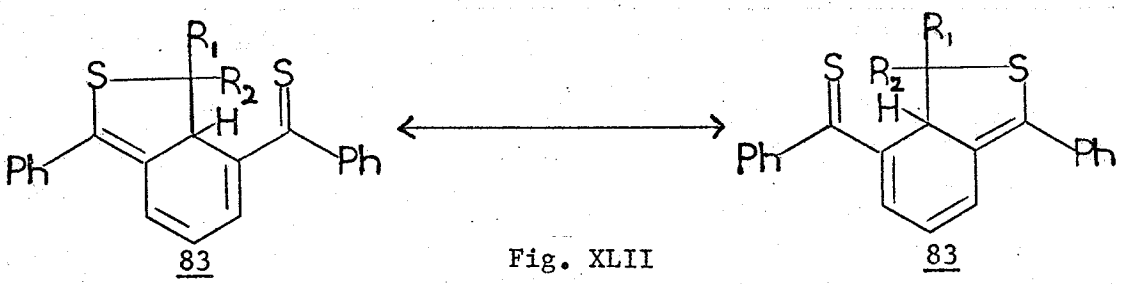


7

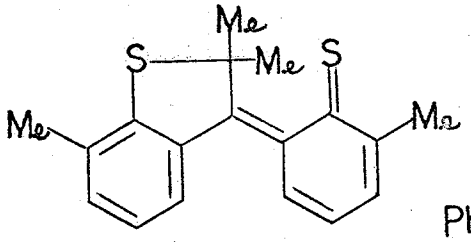
One possible compound would be 83, a carbon analogue of 7, for which two valency tautomeric structures are drawn:



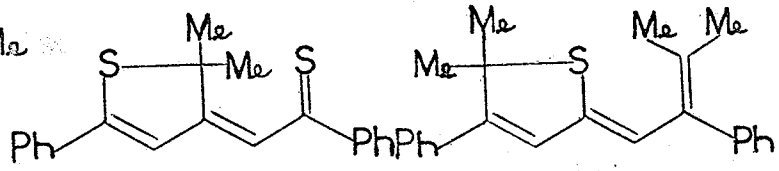
83 Fig. XLII 83

However, this is unlikely to be able to be synthesized as tautomerism would occur to benzenoid structures. However, other related systems should be suitable for investigation.

The object of this research is to prepare suitable precursors of systems 84, 85, 86 and their oxygen analogues, since these would be useful for comparative studies.



84

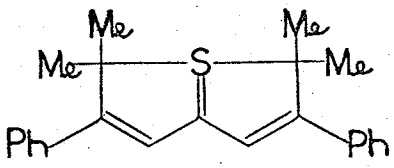


85

86

The oxygen compounds are useful not only for comparison of spectra with the sulfur analogues, but also in the study of the properties of the various systems. Since oxygen is unable to expand its valence shell as sulfur does, some differences in properties between the two analogues can be attributed to the ability of sulfur to expand its valence shell i.e. d orbital participation of sulfur.

Tautomerism of compounds 84, 85 and 86 can be envisaged that of the first two by a process analogous to an internal nucleophilic substitution at a saturated carbon atom (S_Ni reaction). Examples of this are known which are quite similar in concept to the reactions proposed. While tautomerism of 86 is a possibility, also the presence of a central sulfur atom may render symmetry possible by valence shell expansion (e.g. 87).



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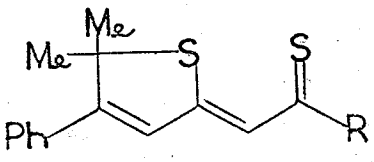
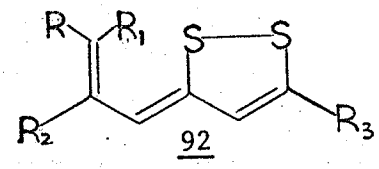
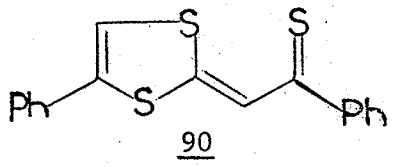


88

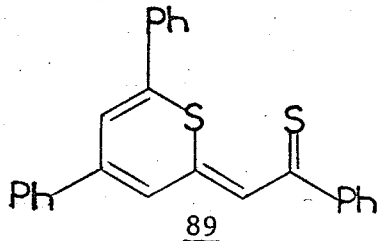
Precursors of 86 are also of interest in that they might also lead to compounds of structure 88 which are of interest in determining the extent of non-bonded sulfur to sulfur interactions, especially between thione and ring sulfur atoms such as have been studied [5], e.g. 89 and 90.



92



90



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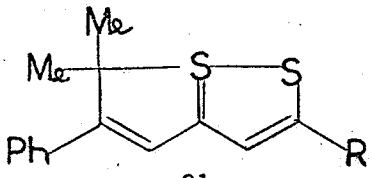
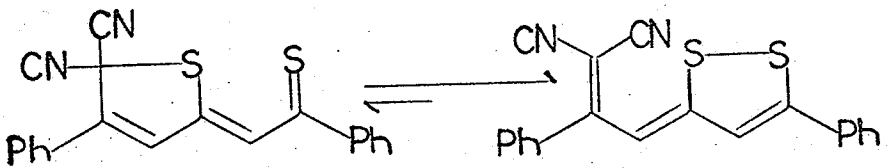


91

With a view to determine the extent of valence shell expansion in these (i.e. 91) or tautomerism to 92a (92, R=R_1=Me, R_2=Ph), a compound 92b (92, R=R_1=CN, R_2=R_3=Ph) [82] has been made. While studies failed to indicate any tautomerism of this, it would be unwise to make decisions on the basis of one compound. Further examples would be desirable. It could also be argued that tautomerism is possible, but that the equilibrium lies far to the right.

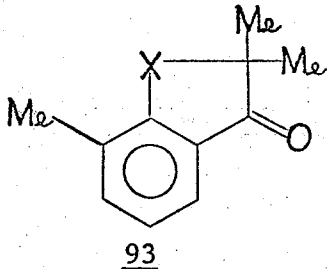


92b 92b

Fig. XLIII

It would then be desirable to attempt synthesis of the type of compound on the left, to compare their properties.

One suitable precursor of 84 would be 2,2,7-trimethyl-3(2H)-benzo[b]thiophenone (93a).



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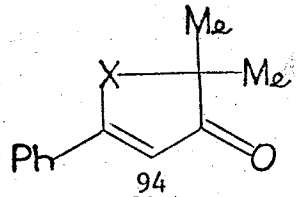

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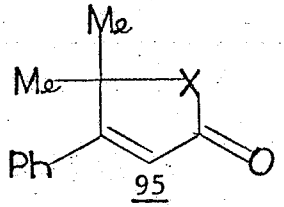
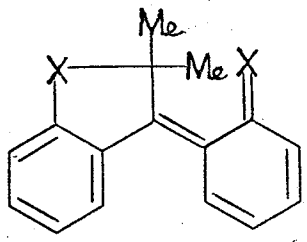


95

(a) X=S (b) X=O

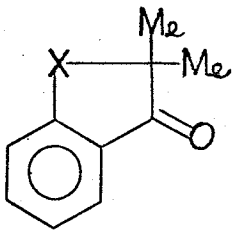
Condensation of the keto group of 93a with a suitable side chain and subsequent cyclization should give the cyclohexadienone ring with the

carbonyl and methyl groups at the required positions. Sulfurization with phosphorus pentasulfide should then give 84. Also, for comparison purposes, and to serve as model compounds, the following are useful:



96

(a) X=S



97

(b) X=O

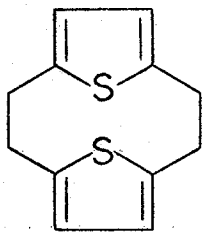
For the oxygen analogue, 2,2,7-trimethyl-3(2H)-benzofuranone (93b) would be a suitable precursor, Since the addition of the cyclohexadienone ring to 93 with the necessary methyl group and correct stereochemistry would not be easy, and would constitute a future research project or part of it.

85 and its oxygen analogue can be prepared without much difficulty if 2,2-dimethyl-5-phenyl-3(2H)-thiophenone (94a) and the corresponding furanone 94b are obtained. Condensation of 94 with a suitably substituted acetophenone or precursor, and careful adjustment of the conditions should give the right stereochemistry. Further sulfurization of the condensation product of 94a should then give the desires product 85.

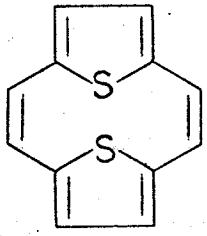
As for 86, a good precursor would be 5,5-dimethyl-4-phenyl-2(5H)-thiophenone (95a). Condensation with suitably substituted acetophenone or precursor, as in the case of 85 might then give the phenacylidene derivative of 95, depending on the reactivity of the carbonyl group to nucleophilic species. Condensation of the keto group of the phenacylidene group with isopropyl bromide, using the modified Wittig reaction would then give the desired product 86. The oxygen analogue can be prepared in the same way, using 95b.

Irrespective of the outcome of the syntheses of systems

84, 85 and 86 when 93a, 94a, and 95a are used as precursors, it would be interesting to study the interaction of two sulfur atoms when they are held very close together in a rigid system. One such system would be [2.2](2,5)thiophenophane-1,8-diene (98), the unsaturated analogue of 23b.



23b



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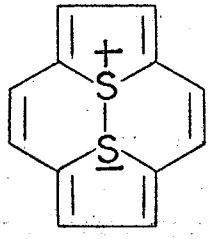


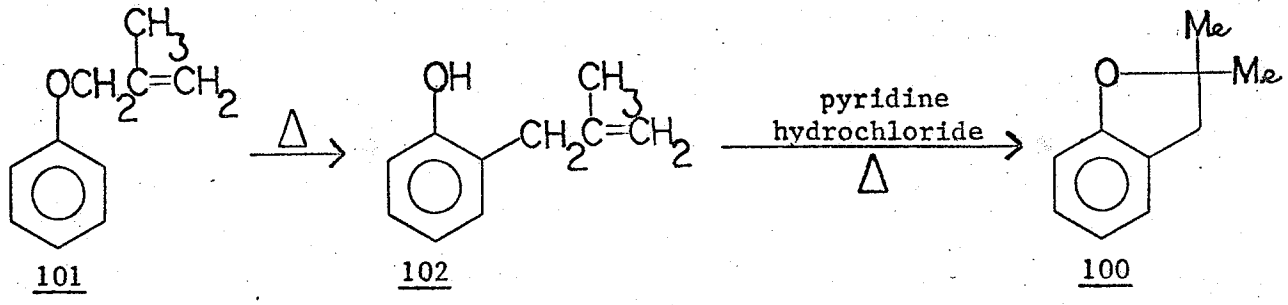
99

98 is of great interest because of the following reasons: (a). Since sulfur is very bulky, the steric repulsion between the two sulfurs in 98 would be tremendous. If the system could be prepared, it would be the only compound known that has a very short distance between two non-bonded sulfur atoms that lie in the same plane. (b). If 98 can be prepared, one can very safely assume that some type of interaction is present between the two sulfur atoms. If the type of interaction is the one shown in 99, this will serve as proof of sulfur's ability to expand its valence shell to become tetravalent. (c). Since great interest has been shown in cyclophanes in the past fifteen years or so, successful synthesis of 98 would represent the first unsaturated heterocyclophane prepared up to date.

Thus, it is also the object of this research to try to prepare 98, and some model compounds of 98.

Preparations of 2,2-dimethyl-3(2H)-benzofuranone and 2,2,7-trimethyl-3(2H)-benzofuranone

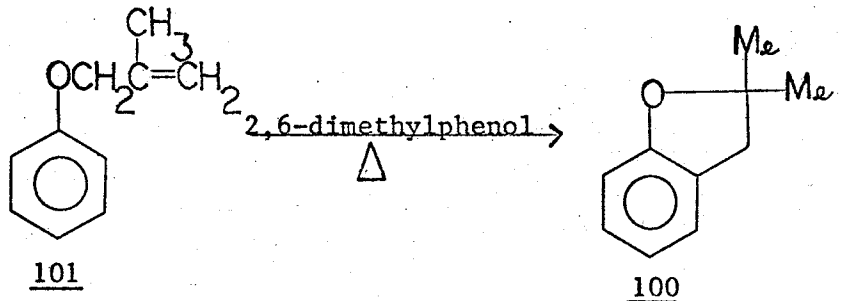
2,3-dihydro-2,2-dimethylbenzofuran (100) first appeared in literature in 1935 [83]. β-methylallyl phenyl ether (101) was rearranged to 2-methylallyl phenol (102) by heating in a bath at about 245 degrees C. for two hours. The phenol was then heated with two equivalents of pyridine hydrochloride (bath temperature 235-245 degrees C.) for two hours, and the product obtained was 100. The first reaction is a typical Claisen Rearrangement.



101 102 100

Fig. XLIV

In 1963, Shulgin and Baker [84] reported the direct conversion of 101 to 100 by heating the ether with an equal weight of 2,6-dimethylphenol at 198-9 degrees C. for three and a half hours.



101 100

Fig. XLV

2,2-dimethyl-3(2H)-benzofuranone (97b) was first prepared by Hurd and Dowbenko [65], using the following reaction scheme:

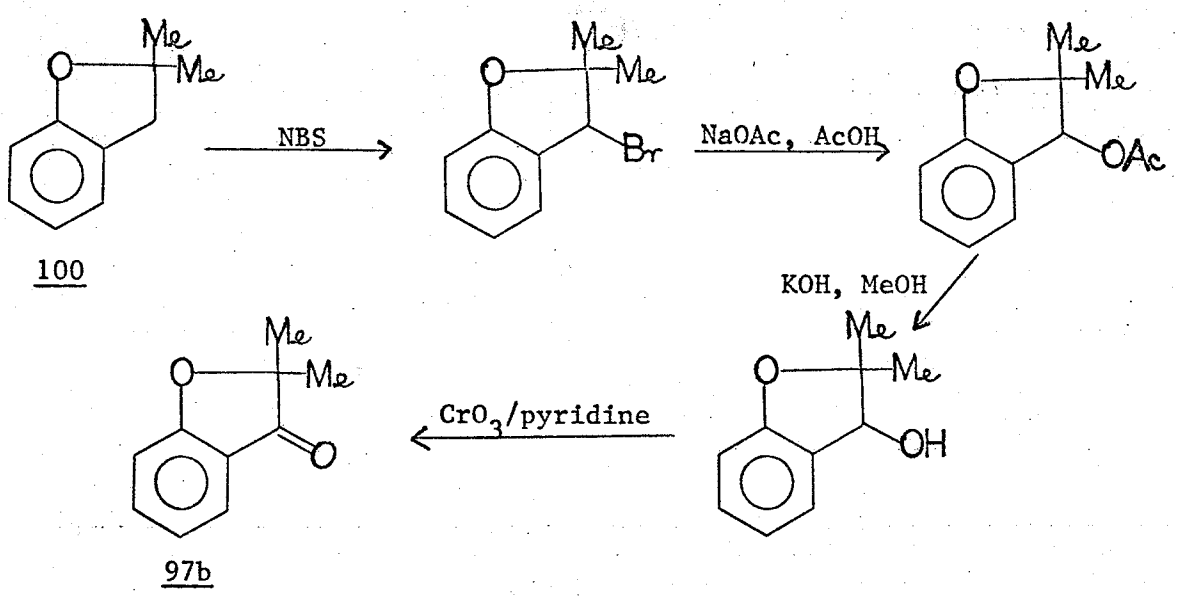


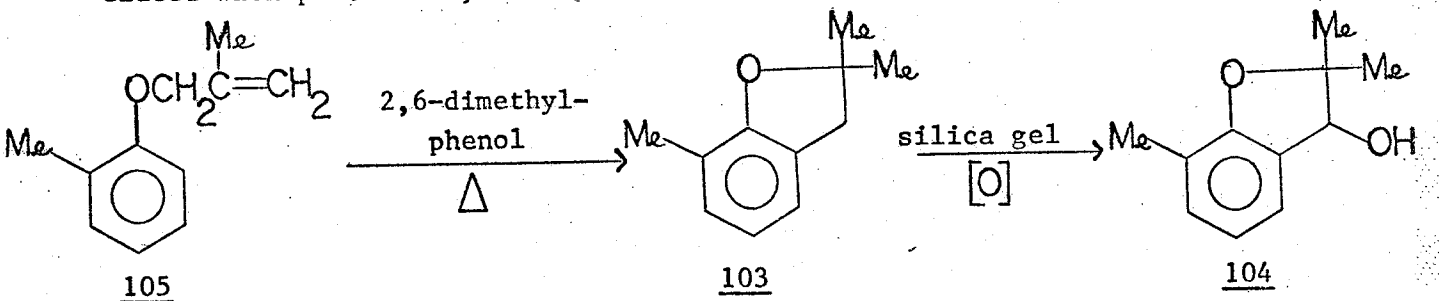
Fig. XLVI

Thus, it was decided to follow the reaction scheme of Shulgin and Baker to obtain 100 and then follow the reaction path of Hurd and Dowbenko to obtain the desired benzofuranone 97b. It was hoped that if the preparation of 97b were successful, the trimethyl analogue of 97b (i.e. 93b) could then be synthesized in the same fashion.

However, on repeating the work of Shulgin and Baker, it was found that the desired product 100 could not be isolated in a pure enough state, by distillation, to enable the performance of the next step in the reaction sequence. Then, on following the reaction scheme of Bartz and co-workers [83], it was found that the rearrangement of 101 to 102 and subsequent cyclization to 100 proceeded smoothly and gave 100 pure (checked by n.m.r.). Therefore, 100 was prepared in this fashion in spite of the low yield in the rearrangement of 101 to 102.

The synthesis of 2,3-dihydro-2,2,7-trimethyl-benzofuran (103) appeared in the same paper [83] as the 2,2-dimethyl analogue, and prepared in the same manner (Fig. XLIV). On following the reaction scheme of Shulgin and Baker (Fig. XLV), the product once again

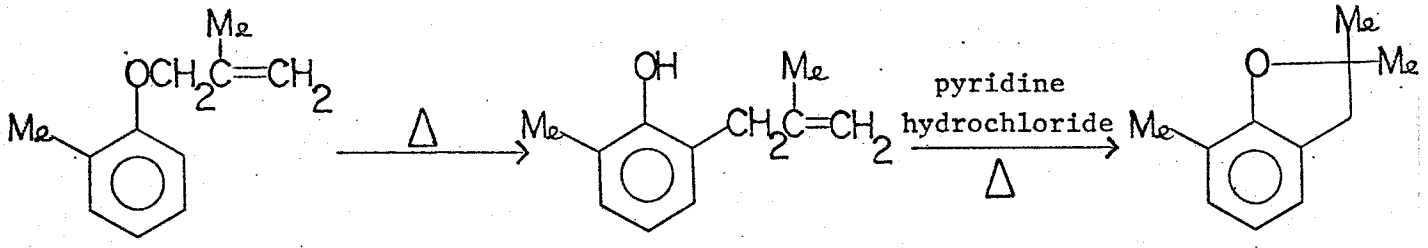
could not be purified by distillation. When the enriched fraction of 103, obtained by vacuum distillation, was put on a TLC plate, and developed with pet. ether overnight, it was found that the desired benzofuran 103 was oxidised to 2,3-dihydro-2,2,7-trimethyl-3-benzofuranol (104). When a column of silica gel was used and eluted with pet. ether, no separation was obtained.



105 103 104

Fig. XLVII

Thus, once again, 103 was prepared by rearrangement of 105 to 106 and subsequent cyclization of 106 to 103 by pyridine hydrochloride:



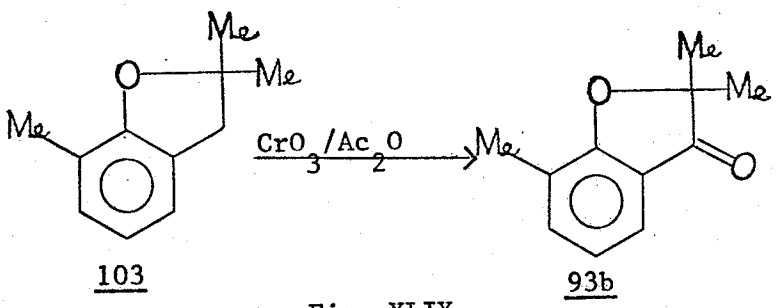
105 106 103

Fig. XLVIII

When 103 was brominated by N-bromosuccinimide in an attempt to following the reaction path of Hurd and Dowbenko to prepare 93b, no satisfactory results were obtained. The crude bromide could not be purified by distillation due to rapid polymerization and decomposition. When the crude bromide was converted to the acetate and purified by vacuum distillation, a rather impure fraction was obtained (checked by n.m.r.). TLC of the acetate did not improve the purity. Hence this approach was abandoned.

Since 103 was oxidized to 104 by silica gel with great ease, the benzilic position thus seems to be quite reactive and direct oxidation of 103 should give the desired benzofuranone 93b.

On refluxing 103 in one and a half equivalents of chromium trioxide in acetic anhydride overnight, 93b was obtained in fair yield, after purification by column chromatography.



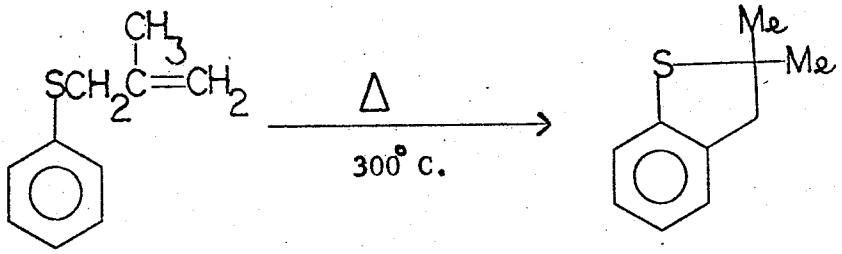
103 93b

Fig. XLIX

Thus both 93b and 97b were prepared by direct oxidation of the corresponding benzofurans, 103 and 100.

Preparation of 2,2-dimethyl-3(2H)-benzo[b]thiophenone

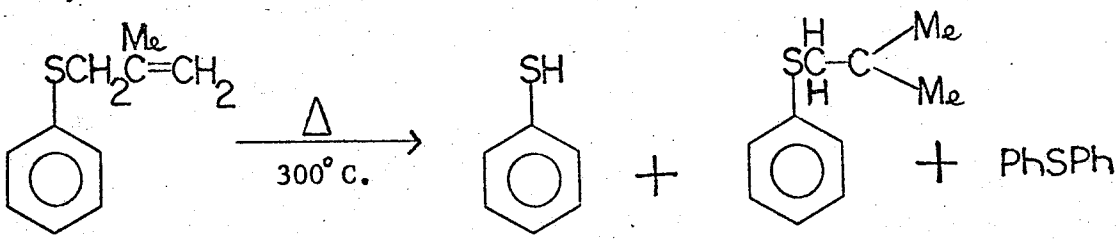
Kwart and Evans [86] first reported the synthesis of 2,3-dihydro-2,2-dimethyl-benzo[b]thiophene (107) in 1966. They pyrolysed β-methallyl phenyl sulfide (108) at 300 degrees C. in a sealed tube, in the absence of a solvent, which was thought to be essential for the Thio-Claisen Rearrangement (Fig. L).



108 107

Fig. L

However in 1967, Kwart and Cohen [87] reported that the products of such pyrolysis is really a mixture of thiophenol, phenyl isobutyl sulfide and diphenyl sulfide (fig. LI).



108

Fig. LI

In that same paper, they showed that heating 108 in quinoline under nitrogen does give 107 in varying yields, depending on the temperature.

It was intended to prepare 107 by their method, and then, following the procedures with which Hurd and Dowbenko prepared 2,2-dimethyl-3(2H)-benzofuranone (97b), to obtain 2,2-dimethyl-3(2H)-benzo[b]thiophenone (97a). However, the approach presented problems, even after the first step.

When β-methallyl phenyl sulfide (108) was refluxed with

quinoline under nitrogen, it was found that the desired product 107 was obtained in a mixture which could not be separated by distillation or any conventional method. With V.P.C., using a 5 feet column of 5% SE-30 on 60/80 Chromosorb W and running the sample through at 230 degrees C., the 2,3-dihydro-2,2-dimethyl-benzo[b]thiophene (107) obtained was mixed with phenyl isobutenyl sulfide and the two could not be separated afterwards.

Thus, the benzo[b]thiophene 107 was used as such in the next step because bromination is expected to occur in the benzilic position of 107 and phenyl isobutenyl sulfide is not expected to be brominated by N-bromosuccinimide. However, bromination followed by immediate conversion of the crude bromide to the acetate with acetic acid and sodium acetate gave the desired acetate in very impure form. Even TLC could not separate it from the other undesired products. It is believed that phenyl isobutenyl sulfide was brominated in either of the methyl groups to a certain extent. This approach was abandoned because (a) V.P.C. had to be used, and thus, could not be a useful synthetic method, and (b) the products of bromination and subsequent conversion to the acetate could not be separated.

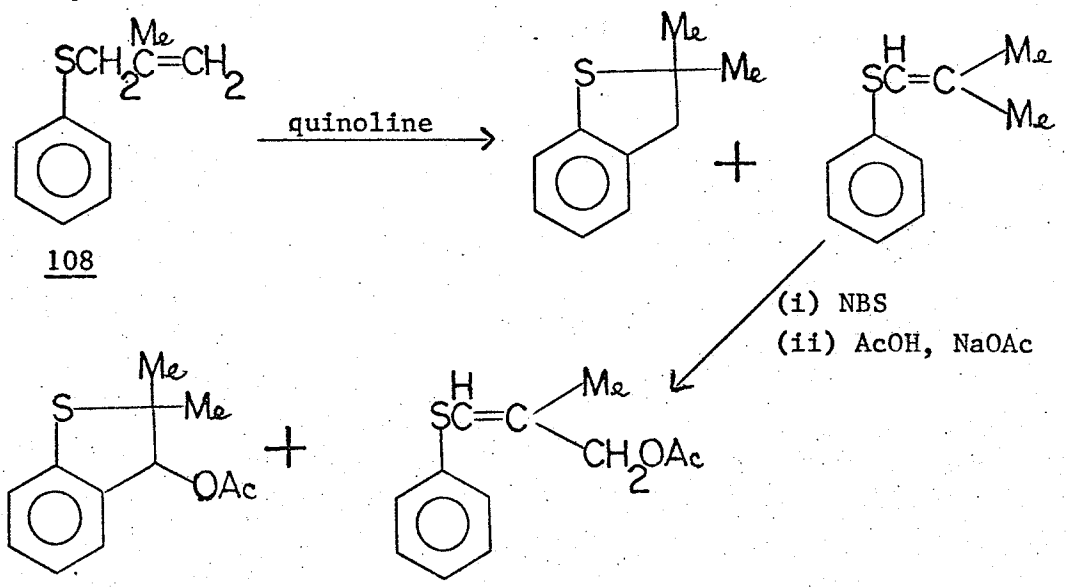
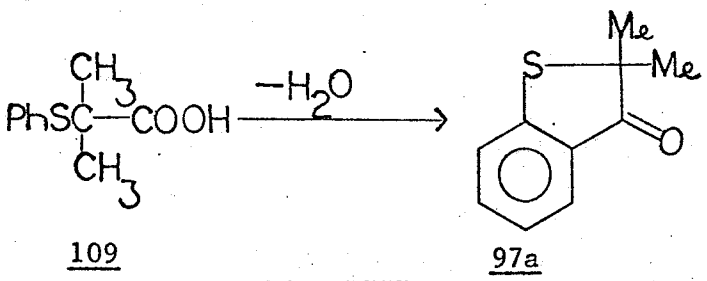


Fig. LII

It seemed then that the most reasonable approach would be to cyclize 2-methyl-2-phenylthiopropionic acid (109) by an internal dehydration:



109 97a

Fig. LIII

The acid was warmed with polyphosphoric acid and only starting material was recovered. When treated with concentrated sulfuric acid, only diphenyl disulfide and starting acid were obtained.

The failure of this approach is rather surprising since 2-phenylthioacetic acid and mono-substituted compounds are easily cyclized to the corresponding hydroxythiophenes (tautomeric dehydrothiophenones). Possibly steric hinderance by the two methyl groups is important. Fission of the sulfide bond is also likely under the acidic conditions. Possibly the inductive effect of the methyl groups also favours formation of a carbonium ion, arising from fission. This then would explain the formation of diphenyl disulfide:

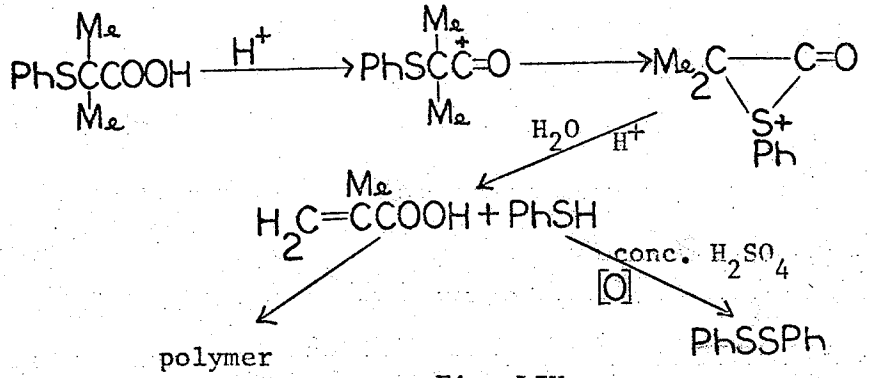


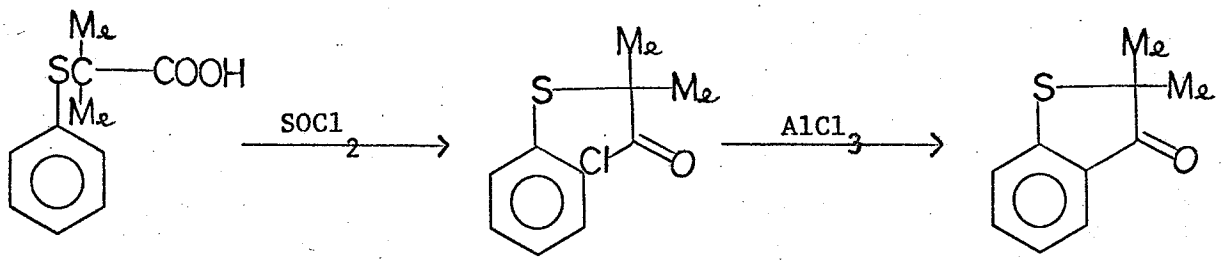
Fig. LIV

Phenyl mercaptan was oxidised by sulfuric acid to diphenyl disulfide.

When anhydrous hydrogen fluoride was used [88], and the crude product put on TLC plate, a very impure sample of 97a was

obtained (n.m.r. and i.r. suggested presence of compound). Again, when trifluoroacetic acetic anhydride was used, the product obtained could not be sufficiently purified for analysis.

It was hoped, then, that internal Friedel-Crafts acylation would work:



109 97a

Fig. LV

After converting the acid to the acid chloride, it was heated up with anhydrous aluminum chloride in dry benzene. An oil was obtained which on distillation could not be separated into definite fractions. Attempted reaction in carbon disulfide gave the same result. The crude product was then examined by TLC on silica gel and five main bands were evident. Upon treating the crude oil with 2,4-dinitrophenylhydrazine, no derivative was obtained. It was then concluded that if any desired product was formed at all, it would be present only in very low yield. On using stannic chloride, the crude oil showed a carbonyl absorption at a different position for the product obtained when aluminum chloride was used. Distillation again gave no main fraction and n.m.r. showed it to be a mixture. The acid chloride was then refluxed for two hours and the product was similar to the one obtained when stannic chloride was used in the attempted cyclization.

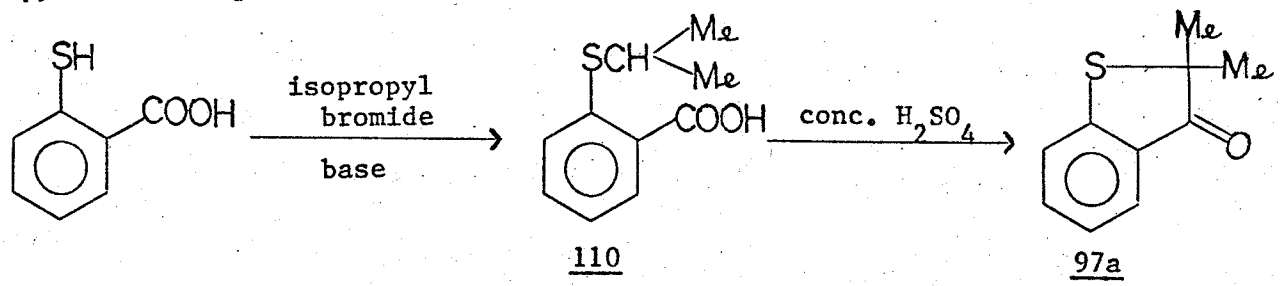
To check whether the acid chloride was rearranged when it was prepared from the acid, it was treated with methanol. The i.r. showed only one carbonyl absorption and n.m.r. gave a singlet at 8.58τ for the two methyl groups, α to the sulfur atom, a singlet

at 6.48τ for the O-methyl group and phenyl protons between 2.4-2.9τ. Therefore the acid chloride was not rearranged. Refluxing the acid chloride in toluene for 3 days gave only starting material.

The oxygen analogue of the acid was prepared and converted to the acid chloride. On treatment with aluminum chloride, the acid chloride gave a product similar to the attempted cyclization of 2-phenyl-thioisobutyrl chloride with aluminum chloride. On testing the acid chloride with methanol as before showed that no rearrangement had taken place.

It is not surprising that Friedel-Crafts Acylation would not cyclize the thio compound since Tarbell and Fukushima [88] encountered the same difficulties with m-thiocresoxyacety chloride. The presence of two methyl groups would be expected to hinder cyclization even more, due to steric interference. For the same reason, the oxygen compound failed to cyclize.

Thus, a new approach had to be used. When thiosalicylic acid was treated with isopropyl bromide under basic conditions, the sulfide 110 was formed. On treatment with concentrated sulfuric acid, a very impure sample of 97a was obtained. As in the case of anhydrous hydrogen fluoride and trifluoroacetic anhydride, the sample could not be purified enough to allow analysis (checked by n.m.r.). This approach was again abandoned.



110 97a

Fig. LVI

Finally, the following approach was taken:

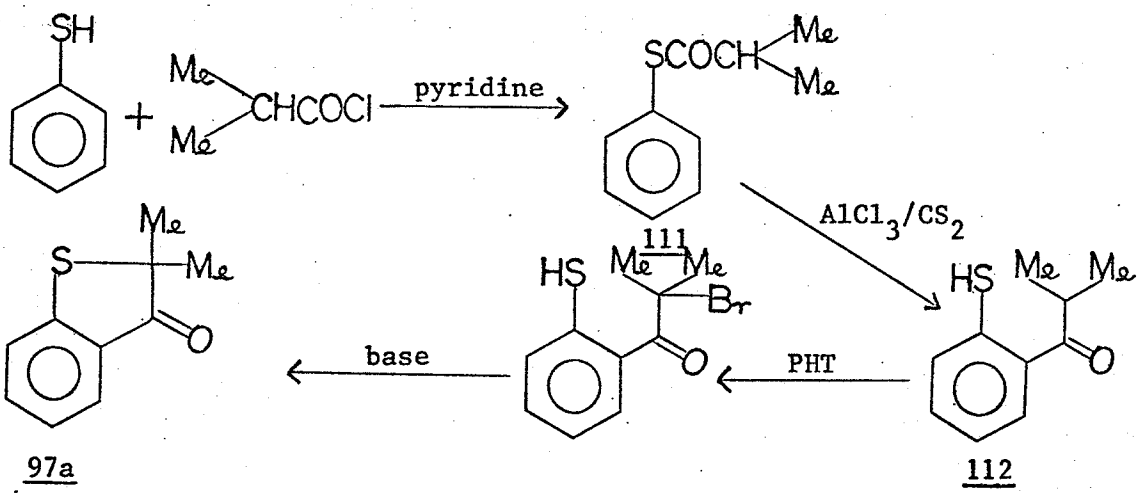


Fig. LVII

A Fries Rearrangement in carbon disulfide at room temperature failed to give 112. Therefore it seemed that either the rearrangement would not work, or more vigorous conditions are necessary to bring it about. The scheme was abandoned without trying the rearrangement under other conditions.

The attempted preparation of 2,2-dimethyl-3(2H)-benzo[b]-thiophenone (97a) failed for reasons unknown. If the Fries rearrangement can be made to work, then 97a should be readily obtainable.

Preparations of 5,5-dimethyl-4-phenyl-2(5H)-thiophenone (95a) and 5,5-dimethyl-4-phenyl-2(5H)-furanone (95b)

In an attempt to find a synthetic pathway which could be applied to the preparation of both 95a and 95b, the following reaction scheme was tried:

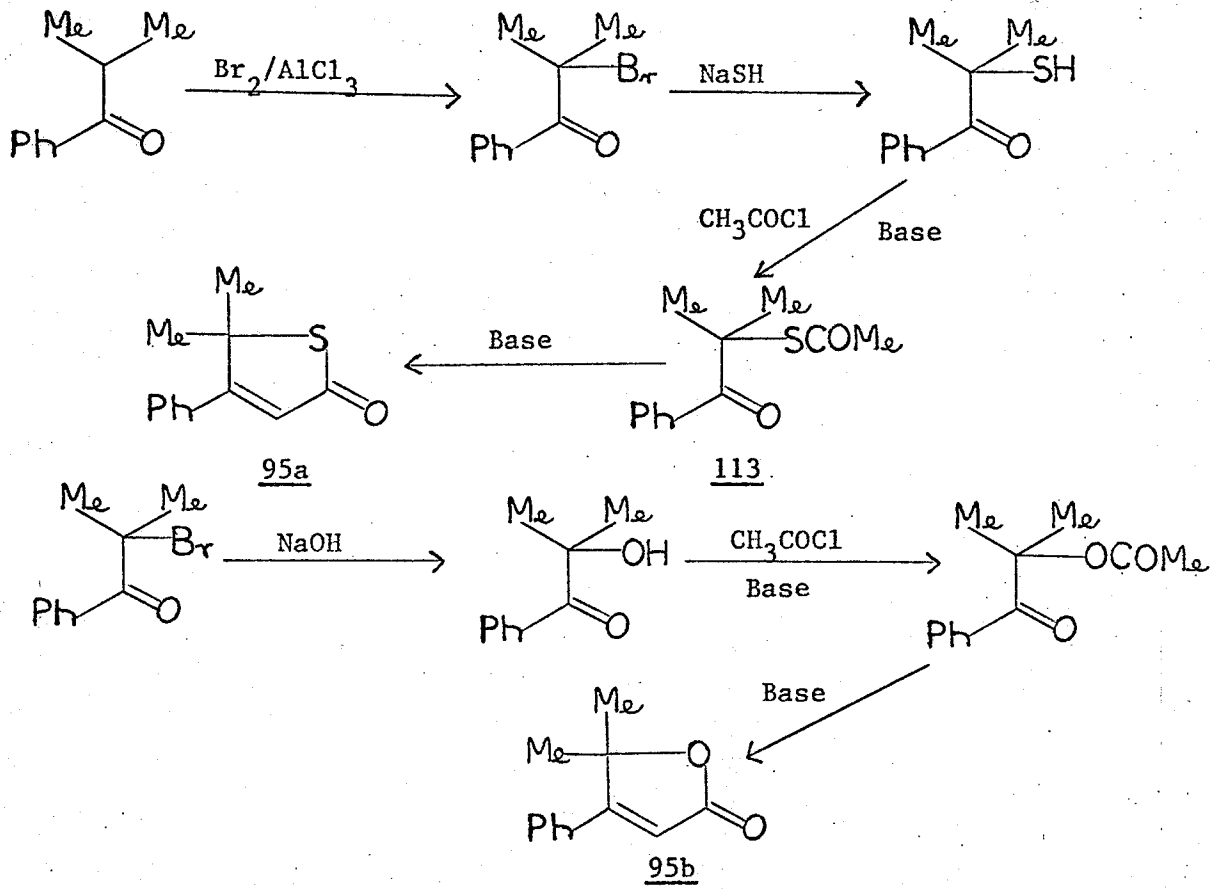
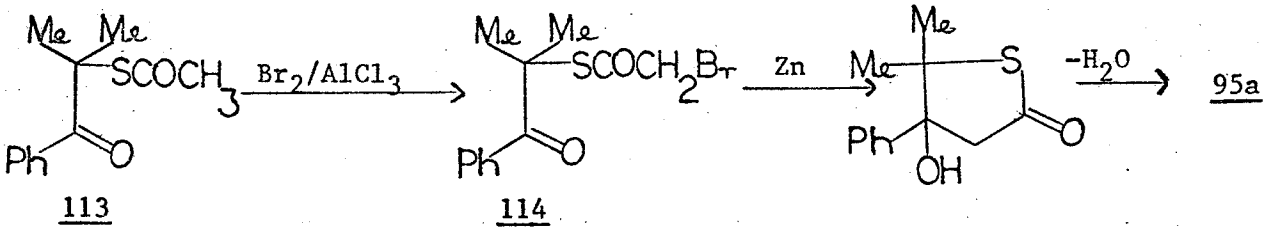


Fig. LVIII

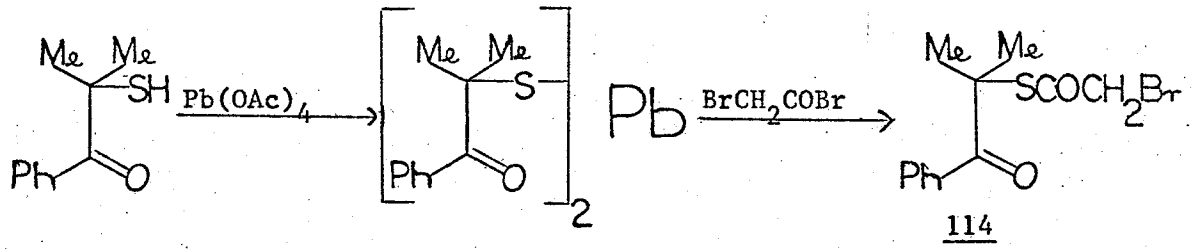
Isobutyrophenone was brominated readily to give α-bromoisobutyrophenone. However, on treatment with sodium hydrosulfide, the bromide failed to give α-mercaptoisobutyrophenone. The mercapto compound was finally obtained by following the procedures of Bose and co-workers[89]. On treatment of the mercaptan with acetyl chloride in pyridine gave the thiolester 113 in good yield. When the thiolester 113 was treated with sodium hydride in dry benzene, the compound failed to cyclize to give 95a. Thus it was hoped that by brominating the thiolester on the acetyl group to give 114 and Reformatsky reaction followed by dehydration would afford the desired compound.



113 114

Fig. LIX

When 113 was treated with bromine and aluminum chloride, no reaction occurred and when tried again under acidic conditions (in the presence of acetic acid in ether), no bromide was obtained. Stirring 113 with PTH (pyrrolidone hydrotribromide) at room temperature in dry methanol for four days gave no significant amount of desired product 114. Bromination in aqueous sodium hydroxide again failed. The apparent reason is that R—S—CO—$\bar{C}H_2$ is present in much greater quantity than R—O—CO—$\bar{C}H_2$, and thus while the oxygen compound would give the bromide, the sulfur analogue hinders bromination. Modifying the procedures once more, α-mercaptoisobutyrophenone was treated with bromoacetyl bromide in pyridine and a compound of M.W. 400 (by Mass Spec.) was obtained. Analysis showed it to be Ph—CO—$C(CH_3)_2$—S—CO—CH_2—S—$C(CH_3)_2$—CO—Ph. Then the mercaptan was treated with lead acetate and the mercaptide reacted with bromoacetyl bromide:



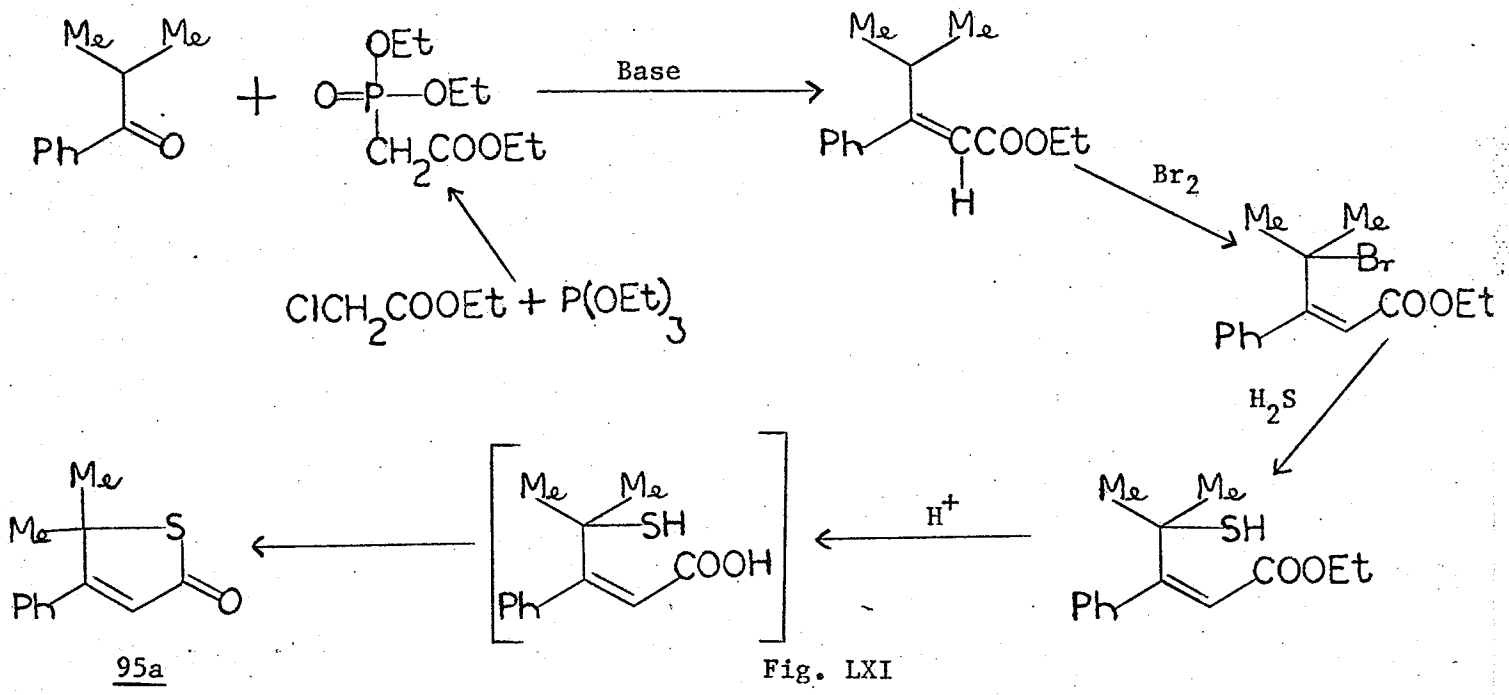
114

Fig. LX

Attempts to purify 114 failed due to its instability. TLC of 114 gave a sample for n.m.r. and decomposed on standing in the air. Thus the next step was carried out without the purification of the bromide.

On treatment with zinc in a 1:1 mixture of benzene and toluene under anhydrous conditions, gave no reaction. When dry ether was used, the same reaction failed. Thus, the bromide was not pure enough for the Reformatsky reaction to take place.

Thus, the scheme shown in Fig. LIX was abandoned and a new scheme was attempted:



95a

Fig. LXI

When isobutyrophenone was treated with the phosphonate, obtained by refluxing triethyl phosphite and ethyl chloroacetate together, in dry toluene in the presence of sodium hydride, the condensation product obtained was examined by TLC and the desired ester was present in very poor yield, and the geometry of the ester was uncertain. To eliminate the uncertainty, diethyl malonate was used. Thus, isobutyrophenone was treated with diethyl malonate in the presence of piperidine and acetic acid in benzene but no water was eliminated after 6 hours. Sodium hydride was then used instead of piperidine and AcOH. The mixture was stirred at room temperature and no product was obtained. The same was repeated in tetrahydrofuran and the same result was obtained.

In order to prepare a model compound without the phenyl group, isobutyraldehyde was condensed with diethyl malonate[90] and the product brominated:

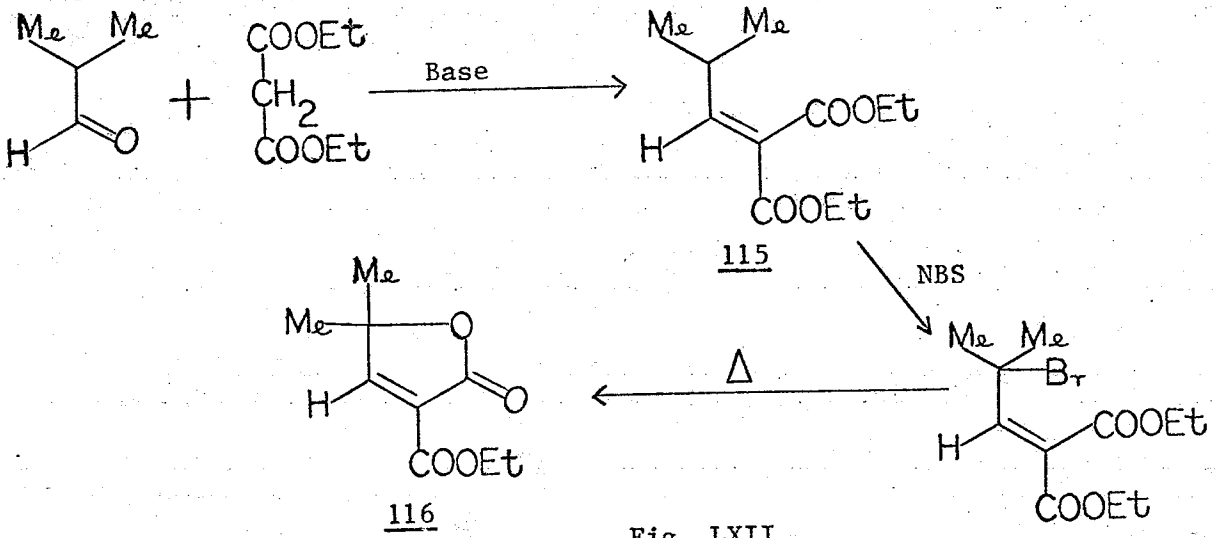


Fig. LXII

Bromination with N-bromosuccinimide was successful, but the n.m.r. of the product obtained on evaporation of solvent showed some impurity. When the bromide was purified by distillation, two fractions were obtained. The higher boiling fraction solidified in the condenser. The n.m.r. of this solid in chloroform was identical to the above impurity and showed it to be the 2(5H)-furanone 116. A possible mechanism would be:

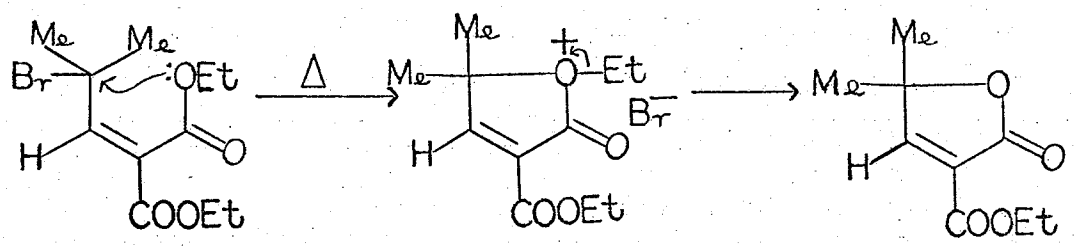


Fig. LXIII

116

To test the generality of this reaction, diethyl propylidenemalonate was brominated with N-bromosuccinimide. The product showed a satisfactory n.m.r. spectrum, but on heating the bromo compound at 190 degrees for 2½ hours, followed by distillation under reduced pressure, only a small fraction came over which partly solidified in the condenser. Treatment with acetone dissolved the bulk, leaving a small

amount of solid. On evaporation and redistillation, a colourless oil which gave no definite boiling point was obtained. The n.m.r. showed the presence of an ethyl group but no methyl. It was then concluded that the reaction was not general. This is probably facilitated by the easy ionization of the tertiary halogen, on the diethyl bromoisobutylidene malonate.

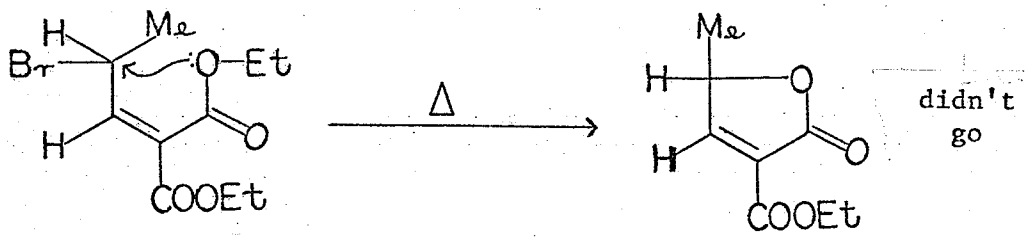


Fig. LXIV

Thus the bromide was heated at 150 degrees for three hours and then distilled under vacuum and 116 was obtained in good yield. Then 116 was treated with dilute sulfuric acid and gave in poor yield the acid of 116. The molecule was obviously unstable under these conditions. In the hope that the sulfur analogue of 116 could be obtained in a similar fashion, the bromide was treated with hydrogen sulfide and sodium in ethanol and then distilled under reduced pressure. No definite fraction was obtained and the higher boiling portion that came over up to 200 degrees at 1.5mm was cloudy and deposited sulfur. All the distillate was combined and dissolved in ethyl acetate. The sulfur that had crystallized out was filtered off, but again distillation gave no definite fractions. The n.m.r. of the distillate that came over up to 100 degrees was checked and found to be very similar to that of 115.

In the hope of preparing 95a, the following scheme was attempted:

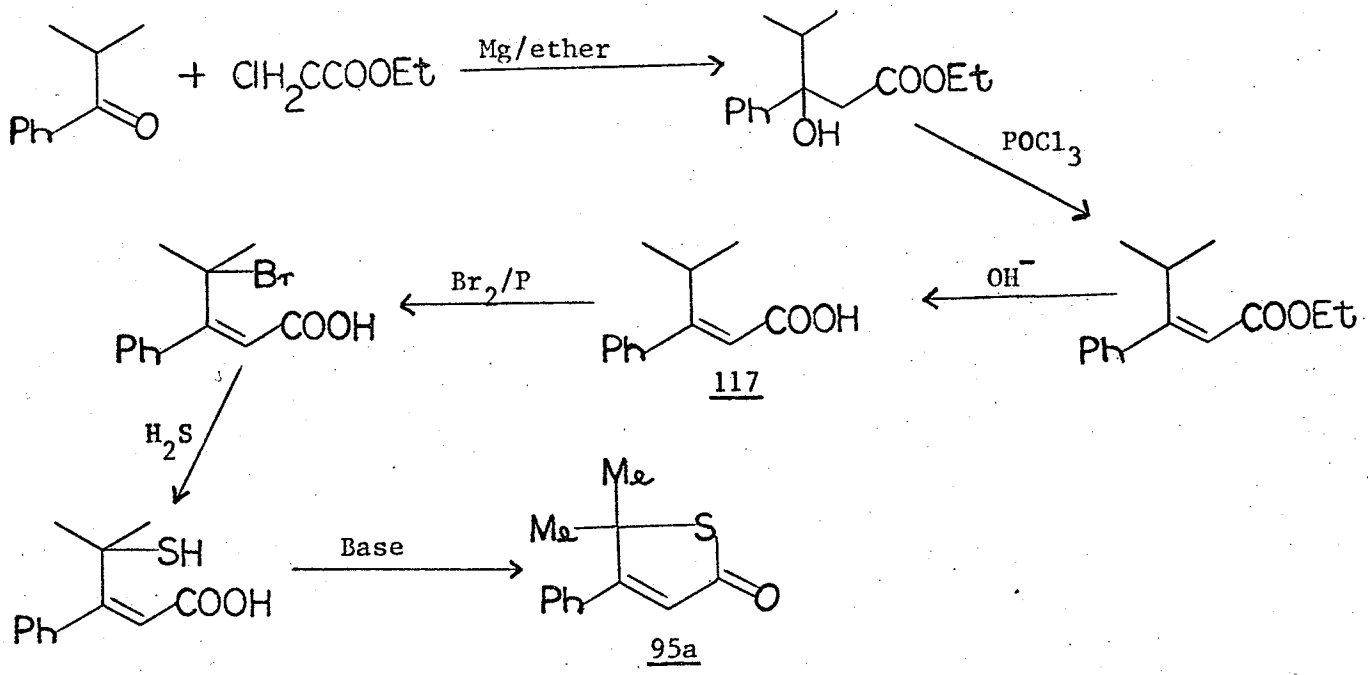


Fig. LXV

Following the procedures of Dobney and co-workers to prepare β-isopropylcinnamic acid (117), it was observed, surprisingly, that 5,5-dimethyl-4-phenyl-2-tetrahydrofuranone (118) was obtained. A mechanism for this is suggested below.

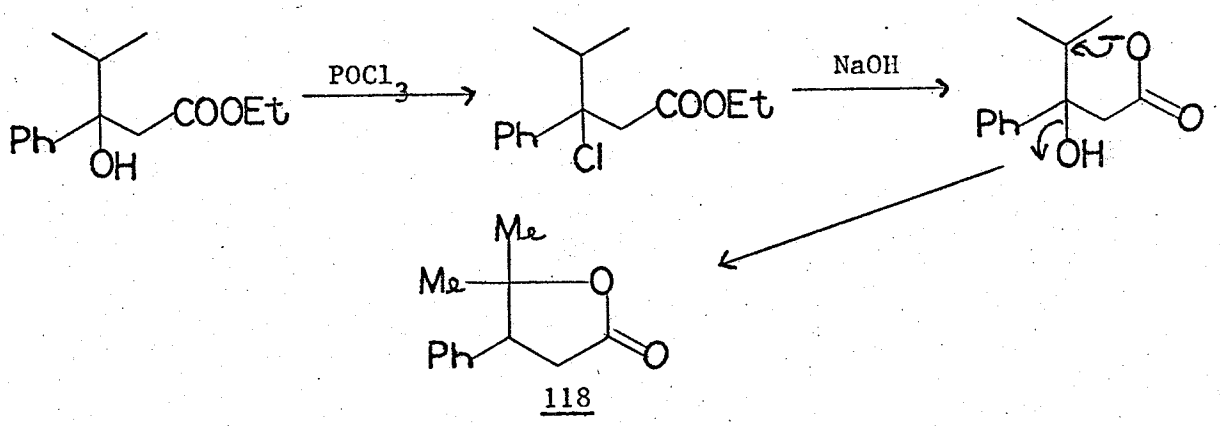


Fig. LXVI

When ρ-toluyl-benzsulfonic acid was used instead of phosphorus oxychloride, 118 was again obtained after saponification. The

mechanism of this reaction could be:

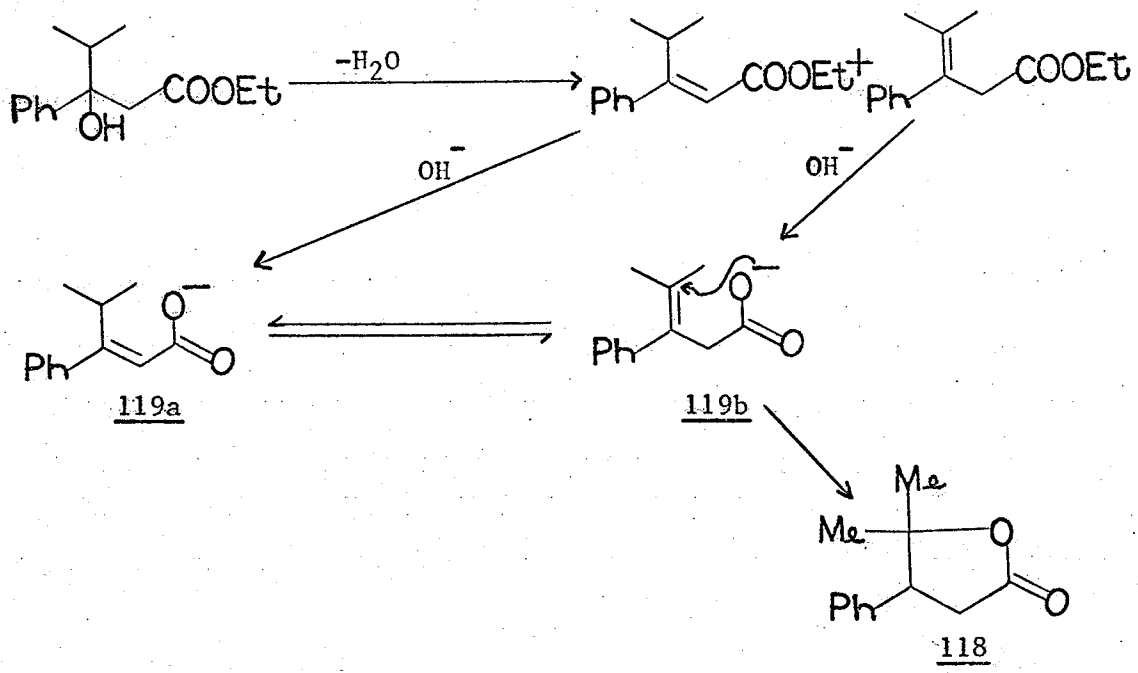


Fig. LXVII

This is consistant with the findings of Dobney and co-workers [91] who showed 119a and 119b to be in equilibrium under basic conditions.

When 118 was brominated and the product purified by a column of silica gel, it was found that hydrogen bromide was eliminated and 95b was the product obtained.

By modifying the above approach, it was hoped that 95a can be prepared:

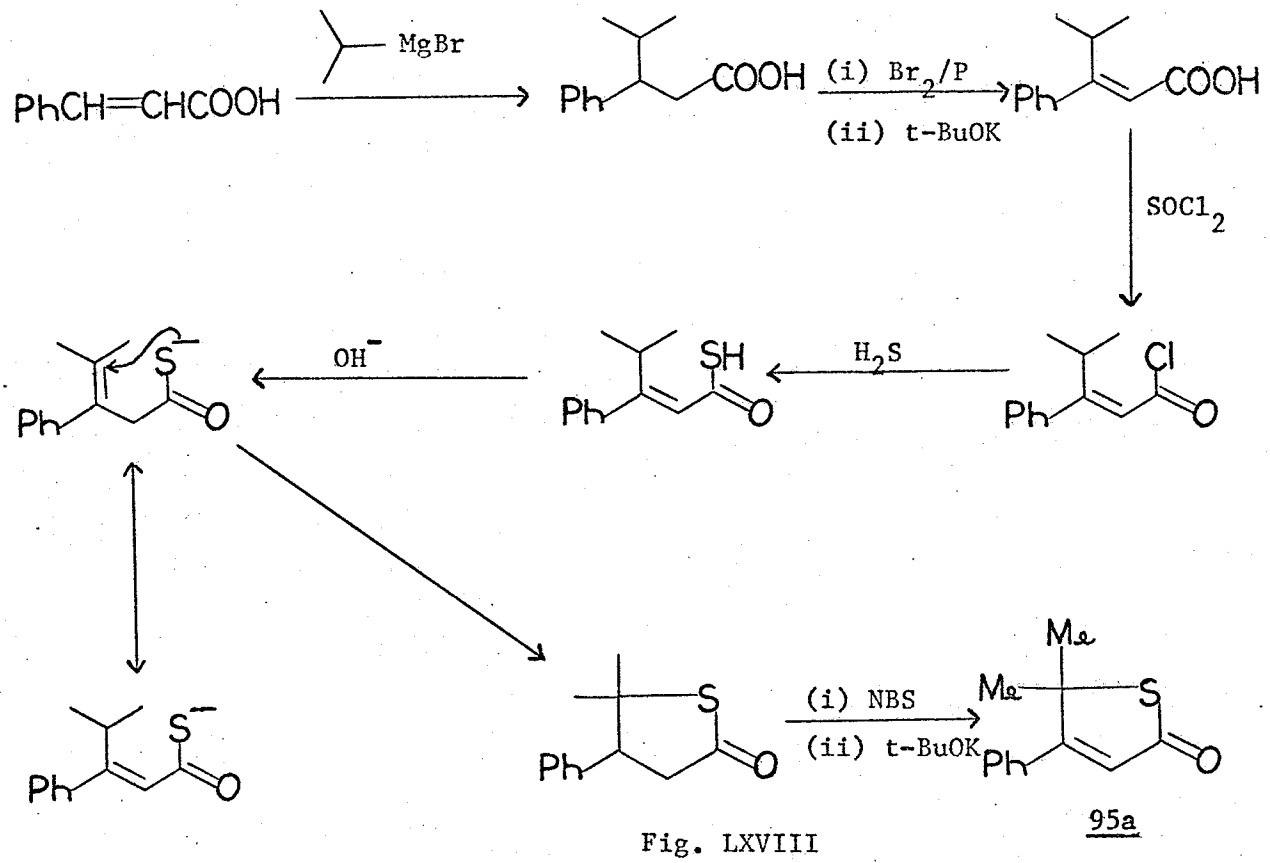


Fig. LXVIII

On repeating the work of Sorlin and Bergson [92] in an attempt to obtain β-isopropylhydrocinnamic acid failed to give the acid. Hence once again, the above approach was abandoned.

Since A.-G. Schering [62] had patented that carboxylic esters of monotertiary α-hydroxy ketones are cyclized in a dipolar aprotic solvent (DMSO) in the presence of a proton abstractor (NaH), the thiolester 113 was stirred with sodium hydride in dry dimethyl sulfoxide under nitrogen:

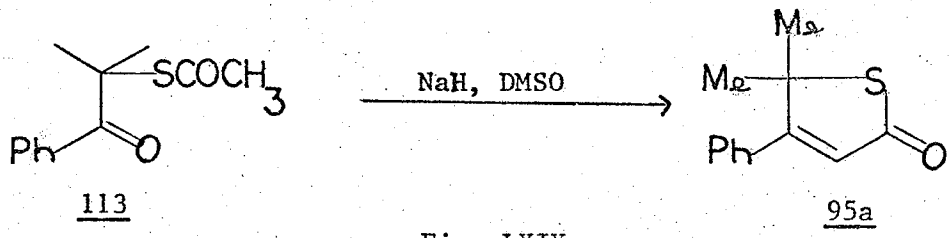


Fig. LXIX

The compound obtained, after purification by TLC, showed an extra singlet in the n.m.r. spectrum, just a little up-field from the methyl singlet of 95a. Putting the purified sample on a TLC plate once more did not succeed in getting rid of the extra peak. On comparison with the n.m.r. spectrum of the oxygen analogue 95b, the extra peak came in the same position as the singlet for the methyls in 95b. Therefore, the peak must be due to hydrolysis of the thiophenone 95a on the TLC plate by the solvent. No analysis of the compound was performed because of said reason. It is very certain, though, the compound was formed basing conclusions on n.m.r. and i.r. data.

Preparation of 2,2-dimethyl-5-phenyl-3(2H)-thiophenone

The intended pathway for the synthesis of 94a is shown below:

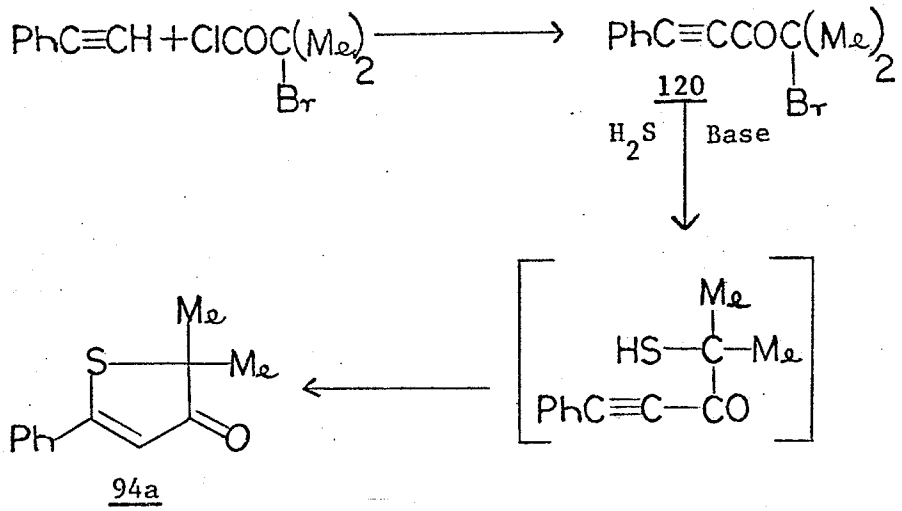


Fig. LXX

When phenylacetylene was stirred with sodium hydride and then dropped into a solution of α-bromoisobutyrl chloride, the desired product 120 was not obtained. Then phenylacetylene was treated with ethyl magnesium bromide and added to α-bromoisobutyrl chloride. Once again, 120 was not obtained. When the product of phenylacetylene and ethyl magnesium bromide was treated with cadmium chloride and then the α-bromoisobutyrl chloride again failed to give 120. The products were not analysed since i.r. gave no carbonyl peak. No reason for the failure of this reaction can be given.

A new approach was then tried:

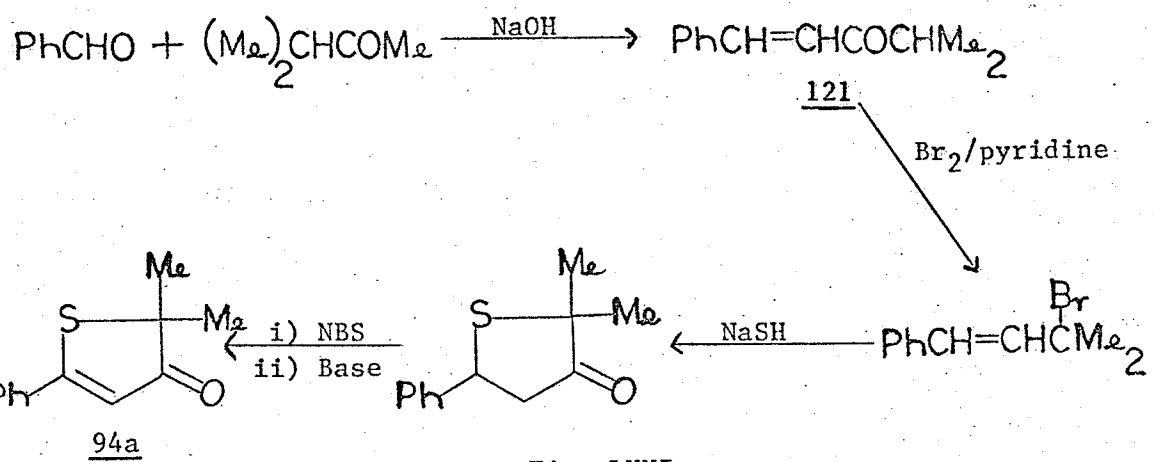


Fig. LXXI

Condensation of benzaldehyde and methyl isopropyl ketone gave the desired product 121 in good yield. 121 was then brominated with pyrrolidone hydrotribromide(PHT) and n.m.r. of product suggested it to be $(CH_3)_2CH-CO-CHBr-CHBr-Ph$. To check this, the product was treated with zinc in ethanol and 121 was formed (checked by n.m.r.).

A new approach was taken by adapting the procedures of Acheson and co-workers [93]:

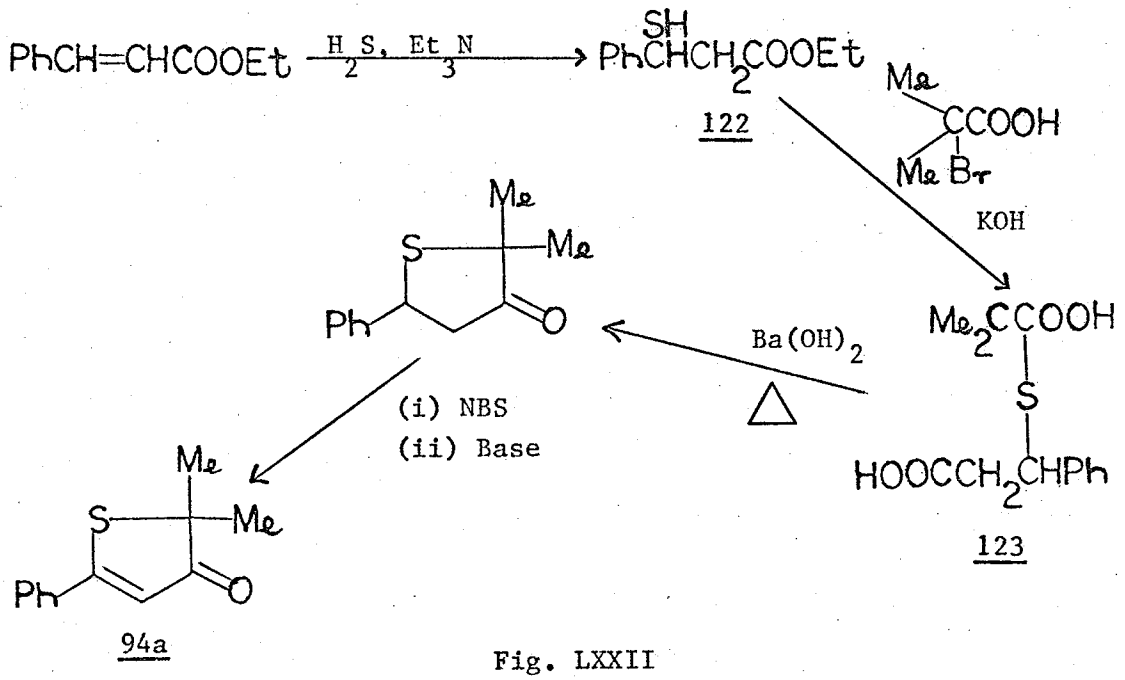


Fig. LXXII

Hydrogen sulfide was passed into an alcoholic solution of ethyl cinnamate and triethylamine. β-Mercaptohydrocinnamic acid (122) was obtained, presumably due to hydrolysis of the ester by triethylamine. The melting point of the acid was five degrees higher than that reported [95] (116-7 degrees C. compared to 111-112.5 degrees C.). N.m.r. showed a quartet for the proton on the same carbon as the SH group, a doublet for the two protons α to the carboxy group, a singlet for the OH of the acid and a singlet for the phenyl protons. The SH group showed up as a doublet, which is not inconsistant with molecules of this type. I.r. showed the presence of OH, carbonyl was in the right position, and showed monosubstitution on the ben-

zene ring. It appeared that the acid 122 was the right one. When the acid 122 was dissolved in aqueous potassium hydroxide and treated with an aqueous potassium hydroxide solution of α-bromoisobutyric acid, the required β-[α-(α-carboxyisopropyl)-mercapto]hydrocinnamic acid (123) was not obtained. It is likely due to steric hinderence of the phenyl group and the two methyl groups α to the bromine because Acheson and co-workers [93] succeeded in the following condensation:

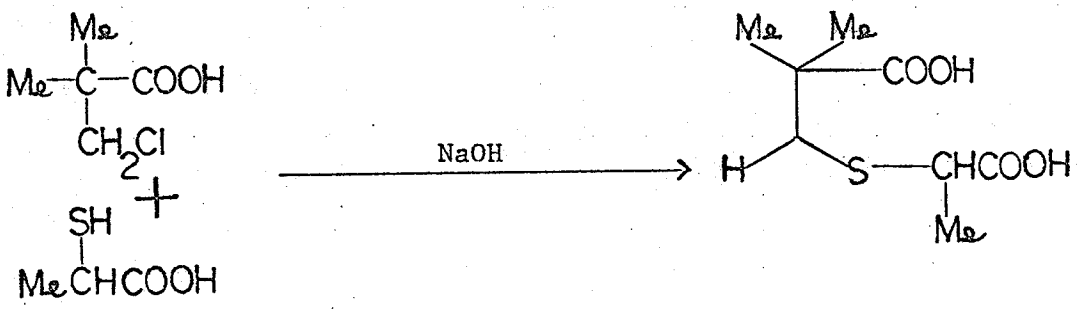


Fig. LXXIII

Preparation of 94a was not attempted any further and since 2,2-dimethyl-5-phenyl-3(2H)-furanone (94b)had been prepared [66], its preparation was not tried.

Preparation of [2,2](2,5)thiophenophane-1,8-diene

The first scheme attempted is:

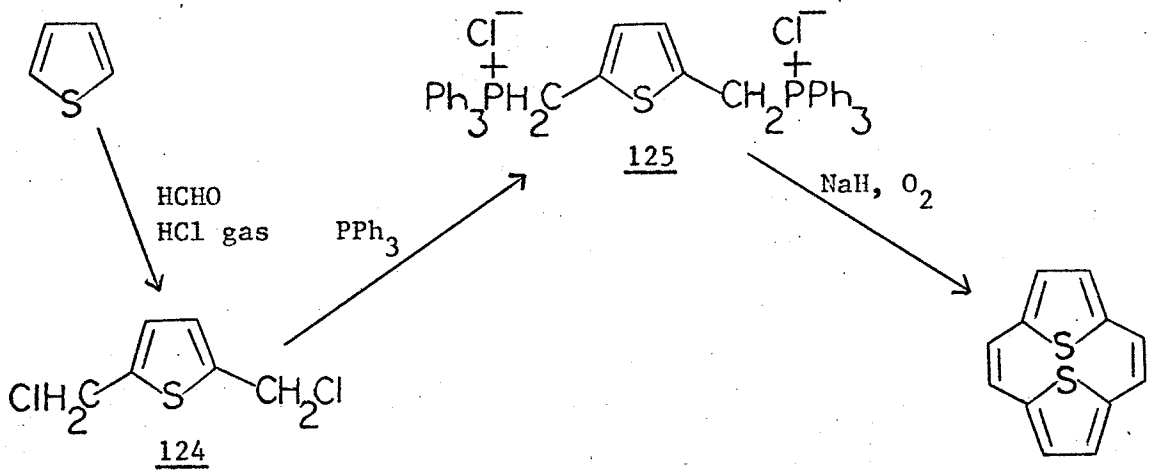
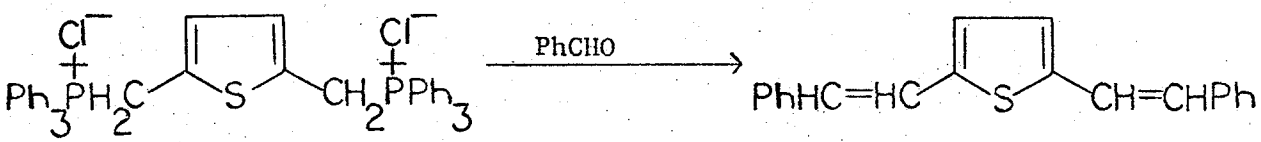


Fig. LXXIV

2,5-bischloromethylthiophene (124) was prepared in the same way as Griffing and Salisbury [94]. In treatment with triphenylphosphine in nitromethane, the diphosphonium salt 125 was obtained in good yield. On treatment with sodium hydride and with oxygen bubbling through the reaction mixture, only triphenylphosphine oxide (characterized by i.r. and n.m.r.) and polymer was obtained.

Then, it was thought that the Wittig reaction of 125 and thiophene-2,5-dicarboxyaldehyde (126) might give the diene 98. Before this was attempted, the stereochemistry of the reaction had to be ascertained. Thus, a model compound, 2,5-distyrlthiophene (127) was prepared:



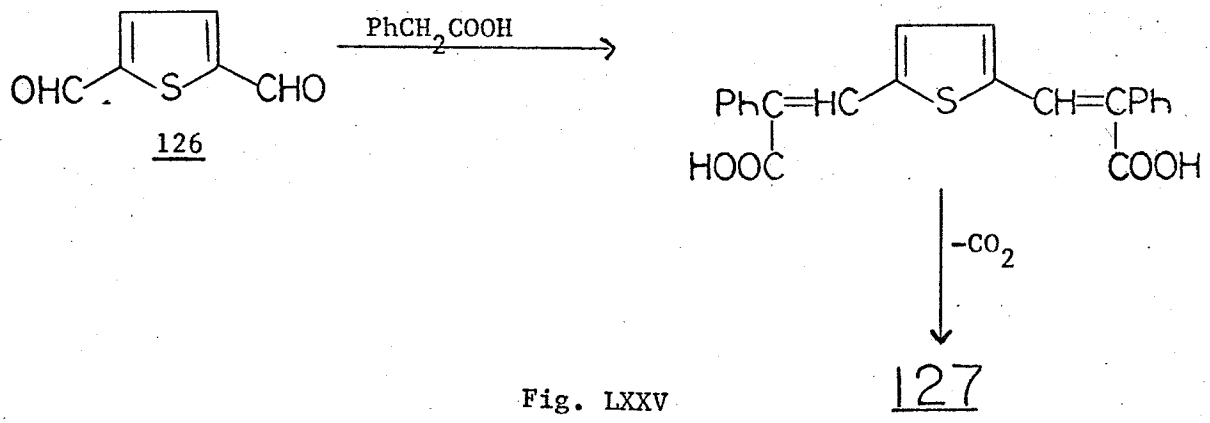


Fig. LXXV

Attempted condensation of benzaldehyde with 125 under a variety of conditions failed to give 127. These include the use of strong base —sodium hydride in polar and non-polar solvents—1,2-dimethoxy-ethane and benzene; the use of weak base—triethyl amine in ethanol and 1,2-dimethoxyethane and fairly strong base—calcium hydride in 1,2-dimethoxyethane. 2,5-distyrlthiophene (127) was finally prepared by an adaptation of Badgers precedures [53]. Thiophene-2,5-dicarboxy-aldehyde (126) was condensed with phenylacetic acid and the diacid obtained was then decarboxylated with quinoline. On examination of the product 127 with n.m.r. in an attempt to determine the stereo-chemistry of the thiophene 127, no conclusion could be arrived at.

Due to the failure of 125 to condense with benzaldehyde, therefore, instead of using 125 as the starting compound, 126 was used.

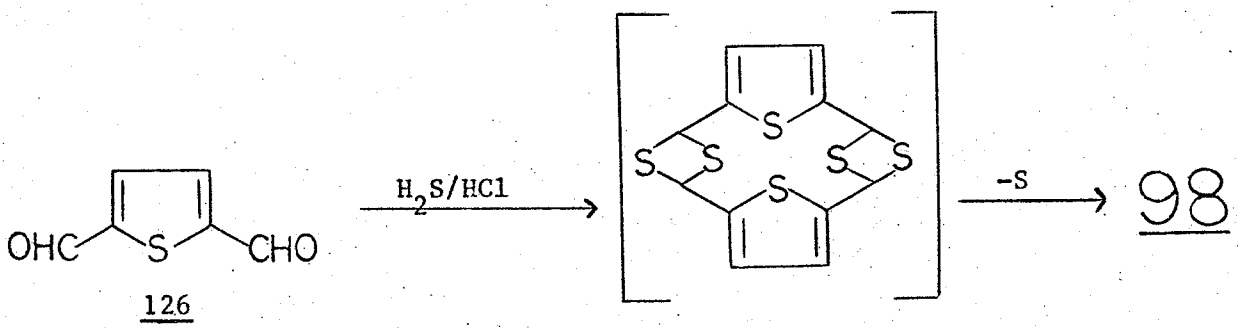
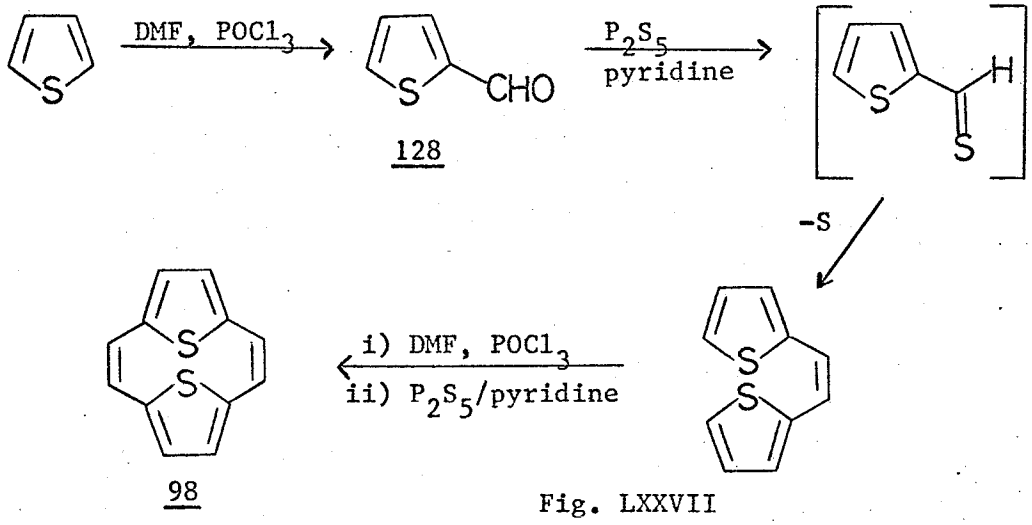


Fig. LXXVI

On passing hydrogen sulfide into a solution of 126 saturated with hydrogen chloride did not give 98, just as suspected. Condensation of 126 and 125, using sodium hydride as base in ether was performed under high dilution conditions and only polymeric material was obtained. Another starting material was used: 2-thiophencarboxaldehyde (128).

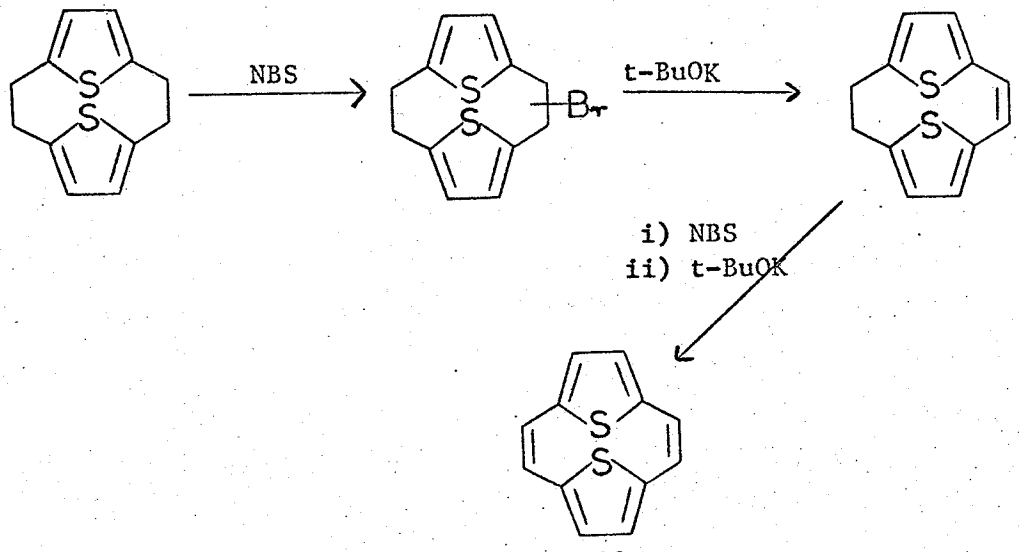


128 98

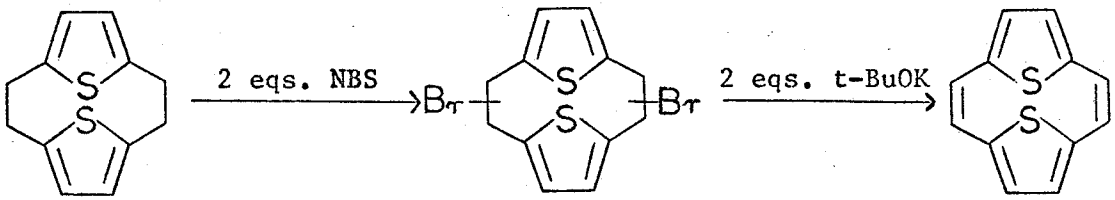
Fig. LXXVII

128 on treatment with phosphorus pentasulfide in pyridine gave only tar and the scheme was abandoned.

One last approach was tried. [2.2](2,5)thiophenophane (23b) was prepared in the same way as Winberg and co-workers[49]. It was then brominated with 2 equivalents N-bromosuccinimide:



98



98

Fig. LXXVIII

On examination of the crude reaction product by n.m.r., the protons on the bridge showed the same pattern as the starting compound 23b. The aromatic protons showed a singlet. However, ratio of the aliphatic protons to the aromatic protons became four to one. Combining with the fact that bromination took much longer time to complete than expected, the conclusion arrived at was that bromination had gone into the thiophene nuclei rather than the bridge. Bromination with one equivalent of N-bromosuccinimide also showed bromination in the thiophene nucleus rather than the bridge.

Due to the difficulties encountered, the preparation of 98 was abandoned.

Preparation of 2,2,7-trimethyl-3(2H)-benzo[b]thiophenone

Due to difficulties encountered in the preparation of 2,2-dimethylbenzo[b]thiophene (107) and its ketone 97a, preparation of 2,2,7-trimethyl-3(2H)-benzo[b]thiophenone (93a) was attempted without great hope of success.

Heating β-methallyl o-methylphenyl sulfide (129) in quinoline gave a crude reaction product which was separated by gas chromatography, using a FFAP column instead. The separation was distinctly better than 107, with 2,2,7-trimethylbenzo[b]thiophene (130) coming out essentially pure (checked by n.m.r.).

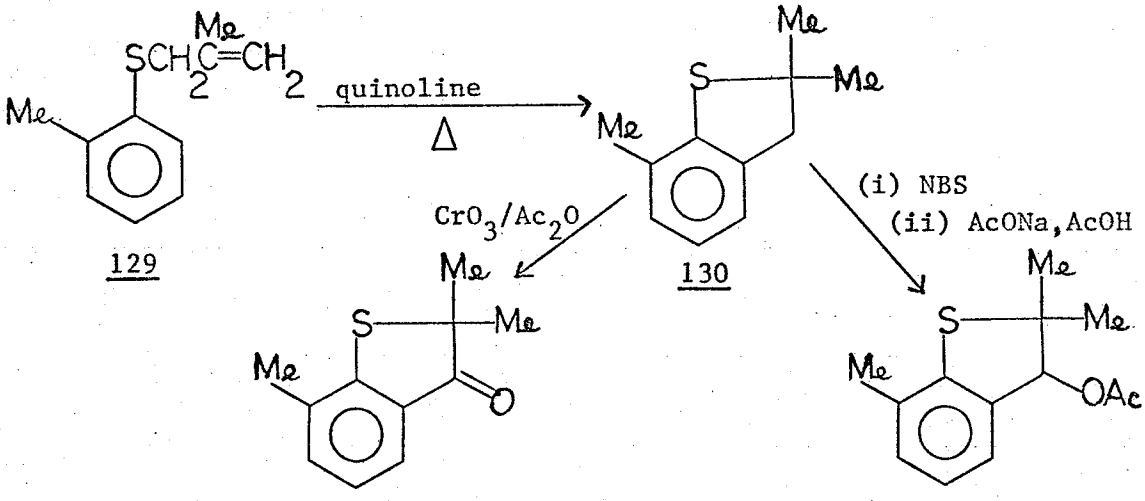


Fig. LXXIX

Bromination of 130 gave a crude product, which was immediately converted to the acetate 131. N.m.r. analysis of the crude acetate showed a mixture. TLC purification gave a mixture again. Hence, it seemed that bromination did occur in the methyl on the benzene ring. Direct oxidation of 130 failed to give 93a (examined by i.r. and n.m.r.). Products obtained were not analysed and the synthesis was abandoned.

EXPERIMENTAL

All melting points given were determined on a Fisher-Johns melting point apparatus and are corrected unless otherwise stated.

Boiling points and melting points were reported only when different from previously reported values, and when compounds were not prepared before, or were prepared by a new method.

All solutions were dried over anhydrous magnesium sulfate.

Infrared spectra were obtained on a Perkin-Elmer Model 137 Infrared Spectrometer in liquid paraffin mulls for solids, or as neat liquids, unless otherwise stated.

N.m.r. spectra were obtained on a Varian A-56/60A Spectrometer. All solutions or neat liquids contained tetramethylsilane as the internal standard. All values reported for chemical shifts of peaks are τ values.

Mass spectra were performed by Mr. D. Lin and Mr. D. Fung on a Hitachi Perkin-Elmer RMU-6D Mass Spectrometer, or by Mr. M. Arneson on a Finnegan 1015 quadrupole Mass Spectrometer.

Vapour Phase Chromatography was performed on a Varian Aerograph Series 1520 Gas Chromatograph by Mr. R. Dickenson.

Silica gel used in Column Chromatography was supplied by Fisher Scientific Company, 60-200 mesh for gas chromatography, Grade 950.

Thin Layer Chromatography was performed on silica gel DSF-5, made by Camag, obtained from Mondray Ltd., 4180 de Courtrai, Montreal.

Elemental analyses were performed by A. Bernhardt, Microanalytical Laboratory, 5251 Elback über Engelakirchen, W. Germany.

Preparations of β-methallyl o-methylphenyl ether (105) and β-methallyl phenyl ether (101)

β-methallyl o-methylphenyl ether (105) and β-methallyl phenyl ether (101) were both prepared by the method of Cope, Morrison and Field [96], by treating o-cresol and phenol respectively with β-methallyl chloride under basic conditions. Yields were 78% and 70% respectively.

Preparation of 2,3-dihydro-2,2-dimethylbenzofuran (100)

20 gms. of β-methallyl phenyl ether was heated up with 20 gms. of 2,6-dimethylphenol as described by Shulgin and Baker [84]. After the mixture had cooled down, it was dissolved in 200 mls. of pet. ether. The pet. ether solution was washed with 1N sodium hydroxide to extract the 2,6-dimethylphenol into the aqeuous layer. The pet. ether solution was then dried and the pet. ether evaporated off. The crude product was then distilled under vacuum. Three fractions were collected: 40-5 degrees/5mm., 45-50 degrees/5mm. and 50-4 degrees/5mm. Examination of each fraction by n.m.r. showed all of them to be mixtures of starting ether, desired product and other impurities.

20 gms. of β-methallyl phenyl ether was then rearranged to o-(β-methallyl)phenol and then cyclized to 2,3-dihydro-2,2-dimethylbenzofuran by heating with anhydrous pyridine hydrochloride, as described by Bartz, Miller and Adams [83]. Yield was 35% basing on starting ether. N.m.r. of neat liquid was the same as reported [84]. B.p. was 60-2 degrees/3mm (reported value was 62 degrees/8mm [83]).

Preparation of 2,3-dihydro-2,2,7-trimethylbenzofuran (103)

20 gms. of β-methallyl o-methylphenyl ether was heated up with 20 gms. of 2,6-dimethylphenol and worked up as above. Distillation under reduced pressure afforded 3 fractions: 45-9 degrees/2mm, 49-54 degrees/2mm and 54-7 degrees/2mm. N.m.r. examination

showed all 3 to be mixtures as above. The first two fractions were quite rich in the desired product. They were combined and a sample was put on a TLC plate and developed with pet. ether overnight. The plate was then left standing in the air for 1 day and the sample taken off the plate was examined by i.r. which showed the presence of a hydroxy group. On comparison with the i.r. spectrum of the desired product (obtained by the procedures described below), and since the benzilic position is the most reactive, the sample was concluded to be 2,3-dihydro-2,2,7-trimethylbenzofuran-3-ol. The combined fractions were then put through a silica gel column and eluted with pet. ether. The liquid obtained after evaporation of the pet. ether was found to be a mixture (checked by n.m.r.).

2,3-dihydro-2,2,7-trimethylbenzofuran was finally obtained in 31% yield (based on starting ether) by following the procedures of Bartz, Miller and Adams [83], just as in previous case. B.p. was 73-5 degrees/4mm (reported value was 74 degrees/8mm [83]). N.m.r. showed a singlet for the gem-dimethyl group at 8.73; singlet at 7.88 for the $ArCH_3$; singlet for the benzilic hydrogens at 7.27 and aromatic protons were spread between 3.17 and 3.61 (spectrum is that of neat liquid).

Preparation of 2,3-dihydro-2,2,7-trimethylbenzofuran-3-acetate

8.1 gms. of 2,3-dihydro-2,2,7-trimethylbenzofuran, 8.9 gms. of N-bromosuccinimide and 0.1 gm. of benzoyl peroxide were dissolved in 150 mls. of dry carbon tetrachloride. The solution was refluxed for 3 hrs., cooled and the succinimide filtered off. The filtrate was washed with water and dried. On evaporation of the carbon tetrachloride, a yellow liquid was obtained. On distillation, no definite boiling point range was obtained. The colourless distillate which came over (boiling point kept rising) soon turned pink and the residue left in the distillation flask was polymeric material. The pink distillate soon turned into dark brown on standing in the air.

Another 8.1 gms. of the benzofuran was similarly brominated with 8.9 gms. of N-bromosuccinimide as above. The crude bromide was immediately converted to the acetate by following the procedures of Hurd and Dowbenko[85]. Distillation of the crude acetate gave a fraction with b.p.=93-103 degrees/1mm. N.m.r. of this fraction showed a mixture. A sample was put on a TLC plate and developed with benzene. Examination of the sample taken off the plate by n.m.r. once again showed a mixture.

Preparations of 2,2-dimethyl-3(2H)-benzofuranone (97b) and 2,2,7-trimethyl-3(2H)-benzofuranone (93b)

1.48 gms. of 2,3-dihydro-2,2-dimethylbenzofuran, 1.0 gms. of chromium trioxide and 30 mls. of acetic anhydride were refluxed overnight. A green ppt. was formed and was filtered off after cooling. The filtrate was added to 100 mls. of water, and then extracted with ether. The ether extracts were combined and washed with 10% sodium bicarbonate solution until the evolution of carbon dioxide stopped. The ethereal solution was dried and the ether evaporated off. The crude product was then purified by a column, eluted with a 1:1 mixture of benzene and pet. ether. All attempts to crystallize 2,2-dimethyl-3(2H)-benzofuranone, obtained by evaporating the mixture of benzene and pet. ether, failed. A sample was put on a TLC plate and developed with benzene but failed to give a crystalline sample. Repeated TLC did not succeed in giving a crystalline sample. The compound rapidly turned yellow in the air. However, the sample gave a satisfactory n.m.r. and i.r. The failure of the compound to crystallize might be due to its low melting point (reported value was 39.0-39.5 degrees[85]). I.r. showed a carbonyl absorption at 5.79μ (reported 5.77μ[85]). N.m.r. in carbon tetrachloride showed a singlet at 8.58 for the gem-dimethyl

group, and aromatic protons were spread between 2.31-3.11. Yield was 31% (calculated from the weight of the compound obtained after purification by silica gel column).

1.62 gms. of 2,3-dihydro-2,2,7-trimethylbenzofuran was similarly oxidised with 1.0 gm. of chromium trioxide and worked up as before. The crude product was purified by a column of silica gel, as above. Evaporation of the benzene and pet. ether afforded colourless plates with a m.p. of 71-3 degrees. Yield was 37%. N.m.r. in carbon tetrachloride showed a singlet at 8.61 for the gem-dimethyl group; a singlet at 7.74 for the $ArCH_3$ group, and aromatic protons were spread between 2.55 and 3.33. I.r. showed a carbonyl absorption at 5.82μ.

Analysis:

Calculated for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86;

Found: C, 75.13; H, 6.70.

Preparation of 2,3-dihydro-2,2-dimethylbenzo[b]thiophene (107)

β-methallyl phenyl sulfide was prepared by an adaptation of the procedures of Cope, Morrison and Field [96], by treating thiophenol with β-methallyl chloride under basic conditions. B.p. was 82 degrees/5.5mm (reported value was 89 degrees/3.4mm [86]). Yield was 88%.

50 gms. of β-methallyl phenyl sulfide was refluxed in 140 mls. of quinoline, under nitrogen for 7 hrs. The product was dissolved in ether, washed with 10% sodium hydroxide, dil. hydrochloric acid, water and dried. Evaporation of the ether and distillation under vacuum gave two fractions. The first fraction boiled below 85 degrees/1mm and the other boiled between 85-95 degrees/1mm. N.m.r. of first fraction showed it to be mainly 2,3-dihydro-2,2-dimethylbenzo[b]thiophene and phenyl isobutenyl sulfide (by comparison with reported spectrum [87]). V.P.C. of the lower boiling fraction with a 5 ft. column of 5% SE-30

on 60/80 chromosorb W at 230 degrees gave 2,3-dihydro-2,2-dimethylbenzo[b]thiophene mixed with some phenyl isobutenyl sulfide (retention time was 6.2 min.). The higher boiling fraction gave an n.m.r. which suggested it to be mainly 3-methyl-1-thiachroman [87]. Due to overlapping of the peaks, and the fact that some of the product was inevitably lost during collection, no accurate yield could be obtained. It was estimated to be around 15%.

Preparation of 2,3-dihydro-2,2-dimethylbenzo[b]thiophene-3-acetate

8.2 gms. of the mixture of 2,3-dihydro-2,2-dimethylbenzo[b]-thiophene and phenyl isobutenyl sulfide obtained from above was dissolved in 200 mls. of dry carbon tetrachloride, together with 8.9 gms. of N-bromosuccinimide and 0.1 gm. of benzoyl peroxide. The mixture was refluxed for 3 hrs. and worked up as in the case of 103. The crude bromide was immediately converted to the acetate by following the procedures of Hurd and Dowbenko [85]. A dark brown liquid was obtained. Distillation under vacuum gave no fraction with a definite boiling point range. A sample was examined by TLC (developed by benzene) and no definite band was evident. I.r. showed the presence of two carbonyl absorptions.

Reaction of 2-methyl-2-phenylthiopropionic acid (109) with polyphosphoric acid

2-methyl-2-phenylthiopropionic acid was prepared from thiophenol, acetone and chloroform according to the procedures of Galemberti and Malandri [97]. Yield was 38%.

20 gms. of the acid was added to 100 mls. of polyphosphoric acid and warmed on a steam bath for 24 hrs. with occassional agitation. The mixture was then poured onto ice and the solid that separated was filtered off. The solid was then put into 10% sodium hydroxide solution and nearly all dissolved. The aqeuous solution was extracted with

ether and the ether layer was discarded. The aqeuous layer was acidi fied and extracted with ether. The ether layer was dried and the ether evaporated off. Examination of the product by i.r. showed it to be the starting acid.

Reaction of 2-methyl-2phenylthiopropionic acid with concentrated sulfuric acid

5 gms. of the acid was added to 50 mls. of conc. sulfuric acid and stirred while it dissolved with evolution of sulfur dioxide and reddening of the sulfuric acid. After 10 mins., the mixture was poured onto ice and the organic product extracted with ether. The ether extracts were combined and washed with water, 10% sodium hydroxide solution and dried. Evaporation of the ether and examination of the crude product by i.r. showed it to be diphenyl disulfide. The aqeuous layer was acidified with conc. hydrochloric acid. The organic layer was extracted into ether. The ether layer was washed with water and dried. Evaporation of the ether left a solid which on examination by i.r. showed it to be the starting acid.

Reaction of 2-methyl-2-phenylthiopropionic acid with anhydrous hydrogen fluoride

2.0 gms. of the acid was added to 40 mls. of anhydrous hydrogen fluoride in a polyethylene bottle. The mixture was stirred at room temperature for 12 hrs. The bottle was then put into a pan of warm water to speed up evaporation of the hydrogen fluoride. The dark brown residue was dissolved in ether. The ether solution was washed with 10% sodium bicarbonate and dried. Evaporation of the ether and examination of the crude product by i.r. showed two carbonyl absorptions. A sample was then put on a TLC plate and developed with benzene, and then with a 1:1 mixture of benzene and ether. One band gave an

i.r. identical to the starting acid. Another band gave an i.r. different from the starting acid. It showed a carbonyl absorption at 5.82μ. The n.m.r. in deuterochloroform gave a singlet up-field and a jumble of aromatic protons down-field. The integration of the protons showed a ratio of 6:5. Repeated TLC did not improve the n.m.r. spectrum.

Another 2.0 gms. of the acid was treated with 40 mls. of anhydrous hydrogen fluoride, as above, for 24 hrs. Working up as before and purification by TLC failed to give a better sample of the product (examined by n.m.r.) which had a m.p. of 118-22 degrees. The impure compound could not be proved to be 2,2-dimethyl-3(2H)-benzo[b]-thiopnenone (97a) and the dehydration of 109 to 97a was assumed to be a failure.

Reaction of 2-methyl-2-phenylthiopropionic acid with trifluoroacetic anhydride

2.0 gms. of the starting acid was refluxed with 50 mls. of trifluoroacetic anhydride for 3 days. The anhydride was evaporated off under reduced pressure. The crude product was dissolved in chloroform, and the solution was washed with saturated sodium carbonate solution and dried. The product once again resisted purification by TLC. I.r. of the purified sample was identical to the product obtained by reacting 2-methyl-2-phenylthiopropionic acid with anhydrous hydrogen fluoride.

Reaction of 2-phenylthioisobutyryl chloride with aluminum chloride

10 gms. of 2-methyl-2-phenylthiopropionic acid was treated with 10 gms. of thionyl chloride (excess) in benzene and refluxed for 1 hr. The benzene was evaporated off together with the unreacted thionyl chloride under reduced pressure. The crude 2-phenylthio-isobutyryl chloride was used as such without purification.

The acid chloride from above, was treated with 16 gms. of anhydrous aluminum chloride (excess) and the mixture heated at 60 degrees for ½ hr. and then poured into water. The organic product was extracted with ether. The ether extracts were combined and washed with water and 10% sodium hydroxide. The ether layer was dried and the ether taken off to give 5.5 gms. of oil, which did not crystallize or give a main fraction on distillation. The above reaction was repeated with more acid chloride in carbon disulfide. Identical results (checked by i.r.; identical spectra for both products) was obtained. By changing the reaction time to 5 mins. on a fresh trial did not change the results. The crude oils from all the above trials were combined and treated with 2,4-dinitrophenylhydrazine in an attempt to obtain the 2,4-dinitrophenylhydrazone derivative of 2,2-dimethyl-3(2H)-benzo[b]thiophenone if any was present in the crude oil. No such derivative was obtained. A sample of the crude oil was examined by TLC and 5 major bands were evident. Hence, it seemed that if the benzo[b]-thiophenone was present in the oil, it would be in very small quantity only. I.r. of the oil showed a carbonyl absorption at 5.83μ.

Reaction of 2-phenylthioisobutyryl chloride with stannic chloride

5 gms. of freshly prepared acid chloride was dissolved in 100 mls. of benzene and was treated with 7 gms. of anhydrous stannic chloride (slight excess). The mixture was refluxed for 16 hrs. and then poured into water. The organic product was extracted into ether, and the ether extracts were combined. The ethereal solution was then washed with dil. hydrochloric acid, 10% sodium hydroxide and water. The ether solution was dried and after evaporation of the ether, a yellow oil was obtained. Examination by i.r. showed a carbonyl absorption at 5.93μ. N.m.r. in carbon tetrachloride showed the oil

to be a mixture and distillation under vacuum failed to separate the components.

Reaction of 2-phenylthioisobutyryl chloride with methanol

The acid chloride was treated with methanol and left standing for 2 hrs. The excess methanol was evaporated off and the ester was examined by i.r. and n.m.r. N.m.r. of the neat liquid showed a singlet for the two methyl groups α to the sulfur atom at 8.58; a singlet for the O-methyl group at 6.48, and aromatic protons were spread between 2.4 and 2.9. I.r. showed a single carbonyl absorption at 5.77μ. Thus, the acid chloride was not rearranged during preparation or on standing and appear to be satiafactory in purity.

Effect of heat on 2-phenylthioisobutyryl chloride

5 gms. of the acid chloride was refluxed without a solvent for 2 hrs. Hydrogen chloride was evolved and the product gave an i.r. similar to the product obtained in the attempted stannic chloride cyclization. The carbonyl absorption was at 5.93μ. Attempted distillation under vacuum afforded no main fraction.

5 gms. of the acid chloride was refluxed in toluene for 3 days. After evaporation of the toluene, only starting material was recovered (checked by i.r.).

Reaction of 2-phenoxyisobutyryl chloride with aluminum chloride

2-methyl-2-phenoxypropionic acid was prepared by an adaptation of the procedures of Galemberti and Melandri [97], by using phenol instead of thiophenol. Yield was 24%.

20 gms. of the acid was refluxed with 20 gms. of thionyl chloride (excess) in benzene and after 1 hr., the benzene and excess thionyl chloride were evaporated off under reduced pressure. A sample of the acid chloride was treated with methanol in the same way as the sulfur analogue. Examination by i.r. and n.m.r. showed that the acid

chloride was not rearranged during preparation.

10 gms. of the acid chloride from above was dissolved in 100 mls. of benzene. 10 gms. of aluminum chloride (anhydrous and in excess) was added to the solution. The mixture was warmed on a steam bath for a further ½ hr. after effervescence stopped. The mixture was then poured onto ice and the organic product extracted with ether. The ether layer was washed with dil. hydrochloric acid, 10% sodium hydroxide and dried. Evaporation of the ether afforded an oil which failed to give a 2,4-dinitrophenylhydrazone derivative. I.r. showed a carbonyl absorption at the same position as the attempted cyclization of 2-phenylthioisobutyryl chloride with aluminum chloride (5.83μ).

Preparation of o-isopropylmercaptobenzoic acid (110)

7.7 gms. of thiosalicylic acid was dissolved in 50 mls. of ethanol containing 5 gms. of sodium hydroxide. The solution was then tested with litmus paper to ensure that it was basic. The solution was cooled with an ice-bath. Then 10 gms. of isopropyl bromide was dropped in over 15 mins. and the solution stirred for two hrs. with cooling and then stirred overnight at room temperature. Then 200 mls. of water was added and then acidified with dil. hydrochloric acid. The organic layer was extracted into ether and the ether solution was washed with water and dried. Evaporation of the ether left an oil which crystallized on standing. The acid was recrystallized from ethanol. Yield was 69%.

Reaction of o-isopropylmercaptobenzoic acid with concentrated sulfuric acid

2.0 gms. of the acid was added to 50 mls. of conc. sulfuric acid and it dissolved slowly. After stirring for 2 hrs., the acid solution was poured into 200 mls. of ice water and extracted with ether. The ether layer was washed with water, 10% sodium hydroxide

and then dried. After evaporation of the ether, a yellowish solid was obtained and it was recrystallized fron ethanol. A sample of this was put on a TLC plate and developed with benzene overnight. The major band was examined by i.r. and found to be the starting acid. A minor band gave a n.m.r. very similar to the spectra of the crude samples of products obtained in the dehydration attempts of 2-methyl-2-phenyl-thiopropionic acid.

Preparation of phenyl thiol-(2-methylpropionate) (111)

11 gms. of thiophenol was dissolved in 50 mls. of pyridine and the solution was cooled with an ice-bath. 11.8 gms. of isobutyrl chloride was dropped in over 20 mins., at the end of which time, the mixture became yery thick and a little pyridine was added to ease stirring. After stirring for 1 hr. with cooling, the mixture was poured into 300 mls. of water. The organic product was extracted into ether. The ether extracts were combined, washed with 0.6N hydrochloric acid, 10% sodium hydroxide and dried. The ether was evaporated and the liquid left behind was distilled under vacuum. Fraction boiling between 82-4 degrees/0.5mm was collected as product (reported b.p. was 108-9 degrees/7mm [100]). Yield was 89%. N.m.r. of the neat liquid showed a doublet for the methyl groups centered at 8.90 (J=7 Hz); a septet centered at 7.35 (J=7 Hz) for the proton on the same carbon atom as the two methyl groups, and aromatic protons were spread between 2.62 and 2.97. I.r. showed a carbonyl absorption at 5.88 μ.

Reaction of phenyl thiol(2-methylpropionate) with aluminum chloride

15.5 gms. of phenyl thiol-(2-methylpropionate) was dissolved in 100 mls. of carbon disulfide and 12.0 gms. of anhydrous aluminum chloride was added. The mixture was then stirred at room temperature for 3 days. The mixture was poured onto ice and extracted with ether. The ether layer was washed with water and dried. Evaporation of the

ether afforded a yellow liquid which gave an i.r. identical to the starting thiolester.

Preparation of dimethylphenacyl thiolacetate (113)

29.6 gms. of isobutyrophenone was dissolved in 150 mls. of anhydrous ether and 0.5 gm. of aluminum chloride was added. Bromine was then dropped in slowly while the mixture was cooled with ice. The bromine colour was very prominant initially, but then quickly disappeared, and finally as soon as it was added. Addition of bromine was continued until a straw colour remained after stirring for 15 mins. Then the ether was evaporated off under reduced pressure. The crude product was washed with 200 mls. of water, extracted into chloroform and then dried. The chloroform was evaporated off and the residual liquid was distilled under vacuum. The fraction boiling between 100-106 degrees/1mm was collected (reported b.p. was 130 degrees/13mm [101]). Yield was 91%.

The α-bromoisobutyrophenone obtained from above was then converted to α-mercaptoisobutyrophenone according to the procedures of Bose and co-workers [89].

The crude mercaptan from 20 gms. of α-bromoisobutyrophenone was dissolved in 100 mls. of pyridine. The solution was cooled with ice while 12 gms. of acetyl chloride was dropped in over 15 mins. with stirring. The mixture was stirred for a further 1 hr. at room temperature before added to 600 mls. of water. The mixture was extracted with three portions of 250 mls. of ether. The ether extracts were combined, washed twice with 500 mls. of water, 100 mls. of 2N hydrochloric acid and finally 100 mls. of 1N sodium hydroxide. The ether layer was dried and the ether evaporated off. The product was a pale yellow solid and recrystallization from ethanol afforded colourless leaflets with a m.p. of 67-8 degrees. Yield was 90% basing on starting bromide. N.m.r.

in carbon tetrachloride showed a singlet at 8.37 for the two methyl groups α to the sulfur atom; a singlet at 8.00 for the methyl protons of the acetyl group, and aromatic protons were found between 2.05 and 2.80. I.r. showed a carbonyl absorption at 5.93μ.

Analysis:

Calculated for $C_{12}H_{14}O_2S$: C, 64.86; H, 6.31; S, 14.14;

Found: C, 64.81; H, 6.31; S, 14.53.

Condensation of α-mercaptoisobutyrophenone with bromoacetyl bromide

18 gms. of α-mercaptoisobutyrophenone was dissolved in 100 mls. of pyridine and was cooled with ice. 22 gms. of bromoacetyl bromide was dropped in over 1 hr. while stirred. At the end of this time, the solution was poured into 600 mls. of water, and extracted with ether. The ether extracts were combined, washed with water, 1N hydrochloric acid, 1N sodium hydroxide and then dried. Evaporation of the ether left a yellow solid, which was recrystallized from ethanol. White flaky crystals were obtained. M.p. was 86-8 degrees and yield was 21%.

Elemental analysis showed the absence of bromine and mass spectral data gave a m.w. of 400 instead of 301(m.w. of dimethylphenacyl bromothiolacetate, the desired product). The compound was suspected to be $Ph-CO-C(CH_3)_2-S-CO-CH_2-S-C(CH_3)_2-CO-Ph$ (dimethylphenacyl dimethylphenacylthiolacetate), formed by the condensation of two molecues of α-mercaptoisobutyrophenone with bromoacetyl bromide. The n.m.r. in deuterochloroform supported this view: a singlet for the two methyl groups of $CO-C(CH_3)_2-S-CH_2-$ at 8.60; a singlet for the other two methyl groups at 8.35; a singlet at 6.81 for the methylene protons, and aromatic protons were found between 2.07 to 2.85 for the phenyl groups. I.r. showed two carbonyl absorptions at 5.97 and 6.07μ respectively.

Analysis:

Calculated for $C_{22}H_{24}O_3S_2$: C, 65.97; H, 6.04; S, 16.01;

Found: C, 65.93; H, 6.18; S, 16.11.

Preparation of dimethylphenacyl bromothiolacetate (114)

18 gms. of α-mercaptoisobutyrophenone was converted to the lead mercaptide by following the procedures of Borgstrom et al [99]. The yellow mercaptide was unstable. It turned black on standing in the air and hence was used right away without purification.

The mercaptide from above was dissolved in the minimum quantity of chloroform and 22 gms. of bromoacetyl bromide was dropped in slowly. The solution was stirred overnight at room temperature. At the end of this time, the yellow colour of the solution had disappeared and a white ppt. was formed. The white ppt. was filtered off and the solution was washed with water, 0.1N sodium hydroxide and dried. The chloroform was evaporated off and the residual oil soon turned from colourless to dark brown on standing. A sample was purified by TLC (developed with benzene) and the n.m.r. spectrum of the neat liquid showed a singlet at 8.33 for the methyl groups; a singlet at 6.31 for the methylene protons, and protons on the phenyl group were found between 2.04 to 2.73. Attempted distillation of the dark brown liquid resulted in polymerization only and no distillate was obtained.

Reaction of dimethylphenacyl bromothiolacetate with zinc

Freshly prepared dimethylphenacyl bromothiolacetate from 18 gms. of α-mercaptoisobutyrophenone, which had a faint colour, was dissolved in a 1:1 mixture of dry benzene and dry toluene. 6 gms. of granular zinc (cleaned with dil. hydrochloric acid, washed with water, acetone and anhydrous ether) was added to the solution. The mixture was refluxed for 24 hrs. After cooling, the zinc was filtered off

and the filtrate washed with water and dried. On weighing the zinc, it was found that none of it had reacted.

Changing the solvent to anhydrous ether gave the same result. Then zinc dust (cleaned in the same way as before) was used and the reaction performed in anhydrous ether, but once again, no reaction occurred.

Preparation of ethyl β-isopropylcinnamate from isobutyrophenone and ethyl chloroacetate

Triethylphosphite was refluxed with ethyl chloroacetate for 2 hrs. The resulting phosphonate was purified by vacuum distillation.

2.24 gms. of the phosphonate was dropped into a suspension of 0.24 gm. of sodium hydride in 50 mls. of dry toluene. The temperature was brought to 70-5 degrees, and excess sodium hydride and the sodium hydroxide formed were filtered off. Then 1.48 gms. of isobutyrophenone was dropped in and the solution stirred for 24 hrs. at 70-5 degrees. The toluene was evaporated off under reduced pressure and 100 mls. of water was added to the residue and the organic product was extracted into ether and the ether solution dried. The ether was evaporated off and 1.67 gms. of Girard-T reagent was added to the crude product, followed by 1.5 mls. of glacial acetic acid and 15 mls. of ethanol. The mixture was refluxed for 30 mins. and 100 mls. of water was added. The organic layer was extracted into ether and the ether solution was dried. Evaporation of the ether left a yellowish liquid. N.m.r. examination of the liquid showed that unreacted isobutyrophenone from the first reaction had not reacted with the Girard-T reagent. A sample was put on a TLC plate and developed with benzene. Examination of major band showed it to be isobutyrophenone. A minor band gave an i.r. spectrum which showed a carbonyl absorption at a position different from isobutyrophenone and the phosphonate.

Reaction of isobutyrophenone with diethyl malonate

30 gms. of isobutyrophenone and 32 gms. of diethyl malonate were dissolved in 100 mls. of benzene. 1.5 mls. of piperidine and 3 gms. of acetic acid were added. The mixture was refluxed for 6 hrs., at the end of which time, no water had been eliminated.

Repeating the above condensation with 5 gms. of sodium hydroxide instead of the piperidine and acetic acid, and doing it at room temperature did not give the desired product. Once again, changing the solvent to dry tetrahydrofuran and stirring at room tempera ture for 6 hrs. did not give the desired product.

Bromination of diethyl isobutylidenemalonate (115)

Diethyl isobutylidenemalonate was prepared according to the procedures of Cope and co-workers [90]. B.p. was 135-7 degrees/27mm (reported value was 122-4 degrees/10mm [90]). Yield was 63%.

42 gms. of diethyl isobutylidene malonate and 40 gms. of N-bromosuccinimide were refluxed overnight in 250 mls. of chloroform, in the presence of a small amount of benzoyl peroxide. After cooling, the succinimide was filtered off and the crude product was dissolved in pet. ether, and filtered once more. The pet. ether was evaporated off and an oil was obtained. The n.m.r. of the oil suggested incomplete bromination. Hence, the crude product was again brominated with 20 gms. of N-bromosuccinimide in carbon tetrachloride for 24 hrs. The mixture was cooled and worked up as before. The residual yellow oil was distilled under vacuum. The fraction coming over around 122 degrees/1mm was examined by n.m.r. which showed it to contain some impurity. The other small fraction that came over around 140 degrees/ 1mm solidified in the condenser and the n.m.r. spectrum showed it to be the impurity in the lower boiling fraction. Yield of the bromide was about 90%.

Effect of heat on diethyl α-bromoisobutylidenemalonate

42 gms. of the bromide from above was heated at 150 degrees for 3 hrs. and then distilled under vacuum. The fraction boiling around 130 degrees/2mm was collected. The distillate was colourless and partly solidified on the condenser and on standing. The distillate was cooled to hasten the process. The product was treated with a mixture of pet. ether and ethanol and the crystals filtered off. The crystals were then recrystallized from a mixture of acetone and pet. ether. The product 5,5-dimethyl-3-carboxyethyl-2(5H)-furanone (116) was colourless elongated prisms with a m.p. of 65-6 degrees (reported value was 68 degrees [102]). Yield was 83%. N.m.r. of the product in deuterochloroform showed a triplet centred at 8.64 (J=7 Hz) for the methyl protons of the ethyl group; a singlet at 8.43 for the two methyl groups on the ring; a quartet at 5.66 (J=7 Hz) for the methylene protons of the ethyl group, and a singlet at 1.74 for the single proton on the double bond. I.r. showed a carbonyl absorption at 5.62μ and one at 5.81μ.

Analysis:

Calculated for $C_9H_{12}O_2$: C, 58.66; H, 6.56;

Found: C, 58.52; H, 6.60.

Hydrolysis of 5,5-dimethyl-3-carboxyethyl-2(5H)-furanone

5 gms. of the furanone was refluxed with 100 mls. of 5% sulfuric acid for 1 hr. The mixture was cooled and extracted with ether. The ether extracts were combined, dried and the ether was evaporated off to give a colourless oil which rapidly crystallized on seeding. It was recrystallized from a mixture of benzene and pet. ether. Melting point was 128-30 degrees (reported value was 127 degrees [102]) and the yield was 21%. The compound effervesed with sodium bicarbonate solution and therefore was probably the correspond-

ing acid: 5,5-dimethyl-3-carboxy-2(5H)-furanone. N.m.r. in deutero-chloroform showed a singlet at 8.42 for the two methyl groups on the ring; a singlet at 1.79 for the proton on the double bond, and a singlet at 0.01 for the proton on the carboxylic group. I.r. showed a carbonyl absorption at 5.56μ and one at 5.84μ, and carboxylic absorption.

Analysis:

Calculated for $C_7H_8O_4$: C, 53.90; H, 5.12;

Found: C, 54.25; H, 4.90.

Reaction of diethyl α-bromoisobutylidenemalonate with hydrogen sulfide and sodium

28.9 gms. of the bromoester and 2.3 gms. of sodium were added to 100 mls. of ethanol. The solution was then saturated with hydrogen sulfide, allowed to stand for 3 hrs., and was then refluxed for 3 hrs. The mixture was poured into water, acidified with dil. hydrochloric acid and extracted with ether. The ether layer was dried, and the ether evaporated off. The residual yellow oil which smelled of an ester was distilled at 1.5mm and no definite fraction was evident. The oil was distilled up to 200 degrees and the later runs came over cloudy. The distillates were combined and dissolved in ethyl acetate and left standing, to enable the sulfur to crystallize out. The sulfur was filtered off, and the ethyl acetate evaporated. The residual liquid was distilled at 1.5mm. Once again, no definite fraction was obtained. The portion of the distillate that came over, up to 100 degrees, was collected and examined by n.m.r. The spectrum (carbon tetrachloride solution) was very similar to the diethyl isobutylidenemalonate spectrum.

Preparation of diethyl propylidenemalonate

58 gms. of propanal and 160 gms. of diethyl malonate were

dissolved in 500 mls. of benzene, 3 mls. of piperidene and 5 mls. of acetic acid were added. The mixture was refluxed until the calculated quantity of water had been eliminated. After cooling, the mixture was washed with water, dil. hydrochloric acid, 1N sodium hydroxide and then dried. The benzene was evaporated off and the residual liquid was distilled under vacuum. Yield was 34%.

Bromination of diethyl propylidenemalonate

19.6 gms. of the ester, 20 gms. of N-bromosuccinimide and a trace of benzoyl peroxide were added to 100 mls. of carbon tetrachloride and the mixture refluxed for 16 hrs. The mixture was cooled, and filtered. The carbon tetrachloride was evaporated off and a yellow oil was obtained. The n.m.r. of the oil in carbon tetrachloride showed two triplets for the two methyl groups of the carboxyethyl groups centered at 8.31 (J=7 Hz) and 8.33 (J=7 Hz); a doublet centered at 8.22 (J=6.5 Hz) for the methyl group α to the bromine atom; two quartets centered at 5.73 (J=7 Hz) and 5.81 (J=7 Hz) for the two methylene groups of the carboxyethyl groups; a jumble centered at 5.10 for the lone proton on the same carbon as the bromine atom; a doublet centred at 3.10 (J=11 Hz) for the proton on the double bond. The bromide was not purified.

Effect of heat on diethyl α-bromopropylidenemalonate

The crude bromide from above was heated at 190 degrees for 2½ hrs. and the resulting oil was distilled under vacuum. Only a little distilled and was in the form of a yellow oil which partly solidified in the condenser. The product was dissolved in acetone, with a little amount of solid remained insoluble and it was filtered off. The acetone was evaporated off and the oil redistilled under vacuum. A colourless oil with no definite boiling point was obtained. The n.m.r. of the oil in carbon tetrachloride showed the presence of

an ethyl group but no methyl group. Hence it could not be the desired product—3-carboxyethyl-5-methyl-2(5H)-furanone. Identity of the oil was not determined.

Preparation of 5,5-dimethyl-4-phenyl-2-tetrahydrofuranone (118)

14.8 gms of isobutyrophenone was condensed with 12.3 gms. of ethyl chloroacetate according to the procedures of Dobney et al [91]. The crude hydroxyester was treated with 5.1 gms. of phosphorus oxychloride and the mixture was refluxed for ½ hr. The mixture was cooled and 100 mls. of water added. The organic product was extracted into ether. The ethereal solution was washed with 1N sodium hydroxide, and then dried. The ether was evaporated off and the crude ester was dissolved in 100 mls. of ethanol and 10 gms. of sodium hydroxide was added. The mixture was refluxed for 2 hrs. After cooling, 300 mls. of water was added and the mixture extracted with ether. The ethereal solution was discarded and the aqeuous layer was acidified with dil. hydrochloric acid, and extracted with ether. The ether layer was washed with water and dried. The ether was evaporated off and the white solid obtained was recrystallized from ethanol. Yield was 28% basing on isobutyrophenone. M.p. was 93-4 degrees (reported value was 91-2 degrees [103]). I.r. showed a carbonyl absorption at 5.62μ. The n.m.r. in carbon tetrachloride showed a singlet at 9.00 for the methyl group that does not lie in the plane of the phenyl group; a singlet at 8.48 for the methyl group that lie in the plane of the phenyl ring; a multiplet (integration showed 3 protons) between 6.37 and 7.72 for the 3 protons on the ring, and a singlet for the phenyl protons at 2.76.

14.8 gms. of isobutyrophenone and 12.3 gms. of ethyl chloroacetate were condensed as before. The crude hydroxyester was treated with 17.2 gms. of p-toluylbenzsulfonic acid in 100 mls. of

benzene and the mixture refluxed until no more water was eliminated. The crude ester was then worked up as before. The white solid obtained was recrystallized from ethanol. Yield was 30%, basing on isobutyrophenone. M.p. and i.r. were identical to the previous product. The n.m.r. was the same and the compound was concluded to be 5,5-dimethyl-4-phenyl-2-tetrahydrofuranone.

Bromination of 5,5-dimethyl-4-phenyl-2-tetrahydrofuranone

2.3 gms. of the furanone, 2.2 gms. of N-bromosuccinimide and a small amount of benzoyl peroxide were added to 50 mls. of carbon tetrachloride and refluxed overnight. The mixture was cooled, filtered and the filtrate washed with water. After drying, the carbon tetrachloride was evaporated off, and the crude product was put through a silica gel column and eluted with a 1:1 mixture of pet. ether and benzene. Yield was 66%. The melting point was 94-6 degrees (reported value for 5,5-dimethyl-4-phenyl-2(5H)-furanone was 94-5 degrees [59]). I.r. showed a carbonyl absorption at 5.65μ. N.m.r. in carbon tetrachloride showed a singlet at 8.34 for the two methyl groups; a singlet at 3.92 for the proton on the double bond, and aromatic protons were found between 2.61 and 2.83.

Preparation of β-isopropylhydrocinnamic acid

Preparation of the title compound was attempted by following the procedures of Sorlin and Bergson [92] without success. The reaction gave only starting acid in all three attempts (checked by n.m.r.).

Preparation of 5,5-dimethyl-4-phenyl-2(5H)-thiophenone (95a)

2.2 gms. of dimethylphenacyl thiolacetate (113), 0.24 gm. of sodium hydride and 50 mls. of dry dimethyl sulfoxide were stirred under nitrogen at room temperature for 5 hrs. 100 mls. of 10% acetic acid in ice water was added and the mixture extracted with ether. The ether layer was washed with water and dried. A sample of the crude

product obtained, after evaporation of the ether, was put on a TLC plate and developed with benzene. The sample obtained failed to crystallize even after repeated TLC. N.m.r. of the sample obtained after repeated TLC (in deuterochloroform) appeared to be satisfactory for the title compound: a singlet at 8.30 for the two methyl groups; a singlet at 3.98 for the proton on the double bond and aromatic protons were spread between 2.05 and 2.82. A singlet at 8.41 was always present in the spectrum even after repeated TLC. This was attributed to the hydrolysis of the thiophenone by the solvent during TLC and formation of the corresponding furanone 95b. This was confirmed by two way TLC. I.r. of the oil after repeated TLC showed a carbonyl absorption at 5.96μ.

Condensation of phenylacetylene and α-bromoisobutyryl chloride

10 gms. of phenylacetylene in 100 mls. of anhydrous ether was stirred with 2.4 gms. of sodium hydride. After the evolution of hydrogen had stopped, the mixture was dropped into a solution of 18.6 gms. of α-bromoisobutyryl chloride in 100 mls. of absolute ether. The mixture was stirred and cooled with an ice-bath during the addition. After all the sodium phenylacetylide had been added (1 hr.), the mixture was stirred for a further 15 mins. Then 200 mls. of water was added and the ether layer was separated. The ether solution was washed with dil. hydrochloric acid, 1N sodium hydroxide and then dried. Evaporation of the ether left a dark oil which smelled of phenylacetylene. A sample was examined by TLC and only starting phenylacetylene and polymeric material were identified.

10 gms. of phenylacetylene in 100 mls. of anhydrous ether was added to ethyl magnesium bromide, prepared from 10.9 gms. of bromoethane and 2.4 gms. of magnesium turnings in 200 mls. of dry ether and the mixture refluxed for 2 hrs. 18.6 gms. of α-bromoiso-

butyryl chloride in 100 mls. of anhydrous ether was cooled with ice and stirred vigorously while the above mixture was dropped in. After the addition was complete, the mixture was stirred at room temperature for 2 hrs. and then added to 300 mls. of water. The ether layer was separated and washed with dil. hydrochloric acid, 1N sodium hydroxide and then dried. Evaporation of the ether left a dark oil smelling of phenylacetylene. The oil was put through a silica gel column and only phenylacetylene and polymeric material were identified.

10 gms. of phenylacetylene was treated with ethyl magnesium bromide as before. After refluxing for 2 hrs., 18.3 gms. of anhydrous cadmium chloride powder was added and the mixture was refluxed for a further 2 hrs. After the mixture had cooled down, it was filtered through a glass wool plug and the filtrate dropped into a solution of α-bromoisobutyryl chloride in 100 mls. of anhydrous ether as before. After working up just as before, the dark oil obtained was examined by TLC and only phenylacetylene and polymeric material were identified as before.

Condensation of methyl isopropyl ketone and benzaldehyde

60 gms. of methyl isopropyl ketone, 80 gms. of benzaldehyde, 60 gms. of 10% sodium hydroxide solution were added to 500 mls. of ethanol and the solution was stirred for 16 hrs. at room temperature. At the end of this time, the solution was poured into 1 l. of water and acidified with dil. hydrochloric acid. The mixture was extracted with ether and the ether extracts were combined. The ethereal solution was washed with water and dried. Evaporation of the ether left a liquid which was distilled under vacuum. The yield was 81%. The product was isopropyl styryl ketone.

Bromonation of isopropyl styryl ketone

7.3 gms. of the isopropyl styryl ketone and 20 gms. of

pyrrolidone hydrotribromide were dissolved in 100 mls. of methylene chloride and the mixture was stirred for 18 hrs. at room temperature. At the end of this time, the mixture became almost colourless and a white ppt. was formed. The ppt. was filtered off and the filtrate poured into 200 mls. of water. The organic layer was separated and dried. The methylene chloride was evaporated off and the colourless product was recrystallized from a mixture of benzene and pet. ether as colourless needles. Yield was 9.5 gms. and the m.p. was 99-100 degrees. I.r. showed a carbonyl absorption at 5.89μ. N.m.r. in deutero-chloroform showed a doublet for the two methyl groups centered at 8.71 (J=7 Hz); a quintet centered at 7.02 (J=7 Hz) for the hydrogen α to the two methyl groups; a quartet for the other two aliphatic protons centered at 4.77, and a singlet for the aromatic protons at 2.74.

To confirm the identity of the compound, which seemed to be 4,5-dibromo-2-methyl-5-phenyl-3-pentanone, 1 gm. of the compound was dissolved in 20 mls. of ethanol. 2 gms. of zinc (excess) was added and the mixture heated for 10 mins. and left standing for ½ hr. After filtration, the filtrate was diluted with water and extracted with ether. After drying, the ether was evaporated and a colourless oil was obtained. The n.m.r. spectrum of the oil in carbon tetrachloride was identical to that of isopropyl styryl ketone.

Analysis:

Calculated for $C_{12}H_{14}Br_2O$: C, 41.2; H, 4.00; Br, 45.8;

Found: C, 41.2; H, 4.16; Br, 45.5.

Preparation of β-mercaptohydrocinnamic acid (122)

17.6 gms. of ethyl cinnamate was dissolved in 100 mls. of ethanol and 15 mls. of triethylamine was added. Hydrogen sulfide was passed into the solution overnight. The solution turned yellow at the end of this time. The solution was poured into 300 mls. of water,

acidified with dil. hydrochloric acid and extracted with ether. The ether solution was dried and the ether evaporated off. The residual oil crystallized on standing and was recrystallized from ethanol as colourless plates. Yield was 46%. M.p. was 116-7 degrees (reported value was 111-112.5 degrees [95]). I.r. showed carboxylic absorption and a carbonyl absorption at 5.88μ. N.m.r. in deuterochloroform showed a doublet centered at 7.76 for the proton on the SH group (J=6 Hz); a doublet centered at 7.04 (J=7 Hz) for the methylene protons; a quartet centered at 5.60 (J=7 Hz) for the proton α to the phenyl group; a singlet at 2.94 for the phenyl protons, and a singlet at -0.65 for the carboxylic proton.

Condensation of β-mercaptohydrocinnamic acid and α-bromoisobutyric acid

3.74 gms. of β-mercaptohydrocinnamic acid was dissolved in the minimum quantity of 5% potassium hydroxide solution (checked by litmus paper to ensure the solution was just alkaline). Then 3.34 gms. of α-bromoisobutyric acid, dissolved in the minimum quantity of 5% potassium hydroxide solution, was added to the β-mercaptohydrocinnamic acid solution. 30 mls. of 5% potassium hydroxide solution was added and the mixture was then stirred at room temperature overnight. The mixture was then warmed on a steam bath for 1 hr. and cooled. The mixture was acidified with dil. hydrochloric acid and then extracted with ether. The ethereal solution was washed with water and dried. On evaporation of the ether, an oil was obtained and it crystallized on standing. The product was then recrystallized from ethanol. Examination by n.m.r. (in carbon tetrachloride solution) showed the presence of β-mercaptohydrocinnamic acid only.

Condensation of 2,5-bischloromethylthiophene and triphenylphosphine

2,5-bischloromethylthiophene was prepared according to the

procedures of Griffing and Salisbury [94]. Yield was 71%.

18.1 gms. of 2,5-bischloromethylthiophene was dissolved in 50 mls. of nitromethane. 26.2 gms. of triphenylphosphine was added and the mixture warmed on a steam bath for 2 hrs. The nitromethane was evaporated off under reduced pressure. The crude product was recrystallized from nitromethane as a white powder. Yield was 87%. N.m.r. in deuterochloroform showed a singlet at 7.63 for the methylene protons, and aromatic protons were found between 2.32 and 2.43. The compound started to turn brown above 210 degrees but did not melt when heated up to 300 degrees.

Analysis:

Calculated for $C_{40}H_{36}Cl_2P_2S$: C, 71.49; H, 5.11; Cl, 10.07; P, 8.79; S, 4.54.

Found: C, 71.27; H, 5.20; Cl, 10.25; P, 8.61; S, 4.57.

Preparation of 2,5-distyrylthiophene (127)

0.71 gm. of the diphosphonium salt 125 obtained from above was dissolved in 20 mls. of ethanol. 5 drops of triethylamine was added, followed by 0.21 gm. of benzaldehyde and the mixture was refluxed for 2 hrs. The mixture was then poured into water and acidified with dil. hydrochloric acid. The organic product was extracted into ether and dried. On evaporation of the ether, starting material were recovered.

Repeating the above procedures, using 1,2-dimethoxyethane as solvent instead of ethanol and refluxing the mixture for 48 hrs., gave only starting material after work up.

Changing the base to sodium hydride and doing the above reaction in both benzene and 1,2-dimethoxyethane and refluxing for 24 hrs. gave triphenylphosphine oxide and polymeric material.

Once again, the reaction was performed in 1,2-dimethoxyethane, using calcium hydride as base gave only triphenylphosphine oxide and polymeric material.

Thiophene-2,5-dicarboxyaldehyde was prepared by following the procedures of Sone [104]. 1.4 gms. of the aldehyde was added to 2.72 gms. of phenylacetic acid. 10 mls. of acetic anhydride and 10 mls. of triethylamine were added. The mixture was warmed on a steam bath for 45 mins. and then cooled. The mixture was acidified with 20 mls. of conc. hydrochloric acid and diluted with 40 mls. of water. The brown ppt. was washed thoroughly with water. Yield was 2.4 gms. The 2,5-biscarboxystyrylthiophene decomposed above 260 degrees. No n.m.r. spectrum was obtained due to difficulties encountered in trying to dissolve the compound in various solvents. I.r. showed a carbonyl absorption at 5.91 μ.

2.4 gms. of 2,5-biscarboxystyrylthiophene was added to 40 mls. of quinoline and 1 gm. of copper powder was added. The mixture was refluxed for 3 hrs. After cooling and filteration, the mixture was steam distilled to get rid of the quinoline. The yellow ppt. obtained was filtered off and purified by a column of silica gel (eluted with a 1:1 mixture of pet. ether and benzene). Yield was 87%. M.p. was 195-8 degrees (reported value was 196-8 degrees [105]). N.m.r. in deuterochloroform showed aromatic protons between 2.38 and 3.00 and nothing else. Mass spectral data confirmed the identity of the compound by giving a parent peak at 288.

Preparation of 2.2 (2,5)thiophenophane-1,8-diene (98)

1.4 gms. of the diphosphonium salt 125 was dissolved in 30 mls. of dry dimethyl sulfoxide. 0.10 gm. of sodium hydride was added to the solution. After the sodium hydride had dissolved, oxygen was passed into the solution, which was stirred at room temperature for

2 hrs. The solution was poured into 150 mls. of water and extracted with ether. The ether solution was washed twice with water and dried. Evaporation of the ether left the crude product, which was examined by TLC. Only triphenylphosphine oxide and polymeric material were identified.

1.42 gms. of the diphosphonium salt 125 was added to 50 mls. of anhydrous ether. 0.10 gm. of sodium hydride was added and the mixture was refluxed for 2 hrs. Then 150 mls. of anhydrous ether was added. 0.28 gm. of thiophene-2,5-dicarboxyaldehyde in 100 mls. of anhydrous ether was added. The mixture was refluxed under nitrogen for 48 hrs. 300 mls. of water was then added and the ether layer separated, and dried. Evaporation of the ether left only polymeric material.

Reaction of thiophene-2,5-dicarboxyaldehyde with hydrogen sulfide and hydrogen chloride

1.4 gms. of the title aldehyde was dissolved in 50 mls. of methylene chloride. The solution was cooled to -20 degrees and hydrogen chloride was passed in for 3 hrs. After that, hydrogen sulfide was passed in for 4 hrs. The solution was then stirred at room temperature overnight. The solution was poured into 100 mls. of water and the methylene chloride layer was separated, and washed with 10% sodium bicarbonate. The methylene chloride solution was dried. Evaporation of the methylene chloride left only polymeric material.

Reaction of thiophene-2-carboxyaldehyde with phosphorus pentasulfide

Thiophene-2-carboxyaldehyde was prepared by following the procedures of Emerson and Patrick[106]. Yield was 52%.

11.2 gms. of thiophene-2-carboxyaldehyde was dissolved in 100 mls. of pyridine. 25 gms. of phosphorus pentasulfide (excess) was added and the mixture refluxed for 12 hrs. After cooling, the mixture

was added to 500 mls. of water and extracted with ether. The ether layer was separated and washed with dil. hydrochloric acid and dried. Evaporation of the ether left only tar.

Bromination of [2.2](2,5)thiophenophane with N-bromosuccinimide

[2.2](2,5)thiophenophane was prepared by following the procedures of Winberg and co-workers [49]. Yield was 12%.

1.1 gm. of the thiophenophane was dissolved in 100 mls. of dry carbon tetrachloride. 1.8 gms. of N-bromosuccinimide (2 equivalents) and a trace of benzoyl peroxide were added and the mixture refluxed overnight. The mixture was cooled, filtered, and the carbon tetrachloride solution was washed with water and finally dried. Evaporation of the carbon tetrachloride left a solid which slowly turned dark brown on standing in the air. A sample was put on a TLC plate and was developed with benzene. The n.m.r. of the purified sample in deuterochloroform showed a ratio of 4:1 for the aliphatic protons to the aromatic protons. Close examination of the peaks of the aliphatic protons showed that they were nearly in the same patern as that of the parent compound. Repeated TLC gave a sample which showed the same pattern for the peaks of the aliphatic protons as that in the parent compound compound. The ratio of the aliphatic protons to the aromatic protons was 4:1. Hence, bromination occurred in the thiophene nucleus and only a small amount was brominated on the bridge, if any.

1.1 gm. of the thiophenophane was similarly brominated with 0.9 gm. of N-bromosuccinimide (1 equivalent). The crude product was dissolved in 50 mls. of t-butyl alcohol and 0.66 gm. of potassium t-butoxide was added. The mixture was warmed on a steam bath overnight. 200 mls. of water was added and the mixture was extracted with ether. The ether extracts were combined and washed with water. Evaporation of the ether left a dark brown solid. A sample was put on a TLC

plate and developed with benzene. Examination of the major band by n.m.r. (in deuterochloroform) showed a jumble of aliphatic protons, in the same pattern as the starting compound, and a singlet for aromatic protons. Hence, once again, bromination occurred in the thiophene nucleus rather than in the bridge.

Preparation of 2,3-dihydro-2,2,7-trimethylbenzo[b]thiophene (130)

59.7 gms. of o-thiocresol was condensed with 45.5 gms. of β-methallyl chloride by following the procedures of Cope, Morrison and Field [96]. Yield was 82% and b.p. was 83 degrees/1mm. N.m.r. of the neat liquid showed a doublet centered at 8.23 (J=1 Hz) for the methyl group on the double bond; a singlet at 7.72 for the methyl group on the phenyl ring; a singlet at 6.68 for the methylene protons; a singlet which showed splitting at 5.31 for the terminal methylene group on the double bond, and aromatic protons were found between 2.85 and 3.16.

10 gms. of the o-methylphenyl β-methallyl sulfide was refluxed with 10 gms. of quinoline, under nitrogen, for 5 hrs. After cooling, the mixture was dissolved in 200 mls. of pet. ether and the solution was washed with dil. hydrochloric acid, 1N sodium hydroxide and dried. The pet ether was evaporated and the crude product was purified by V.P.C., using a 10 ft. column of 8% FFAP on firebrick and running at a temperature of 200 degrees (retention time 6.6 min.). Due to overlapping of peaks and loss of product during collection, no accurate yield of the title compound was obtained. It was estimated to be around 20%. N.m.r. of the neat liquid showed a singlet at 8.57 for the gem-dimethyl group; a singlet at 7.93 for the methyl group on the phenyl ring; a singlet at 7.12 for the methylene protons, and a singlet for the aromatic protons at 3.33.

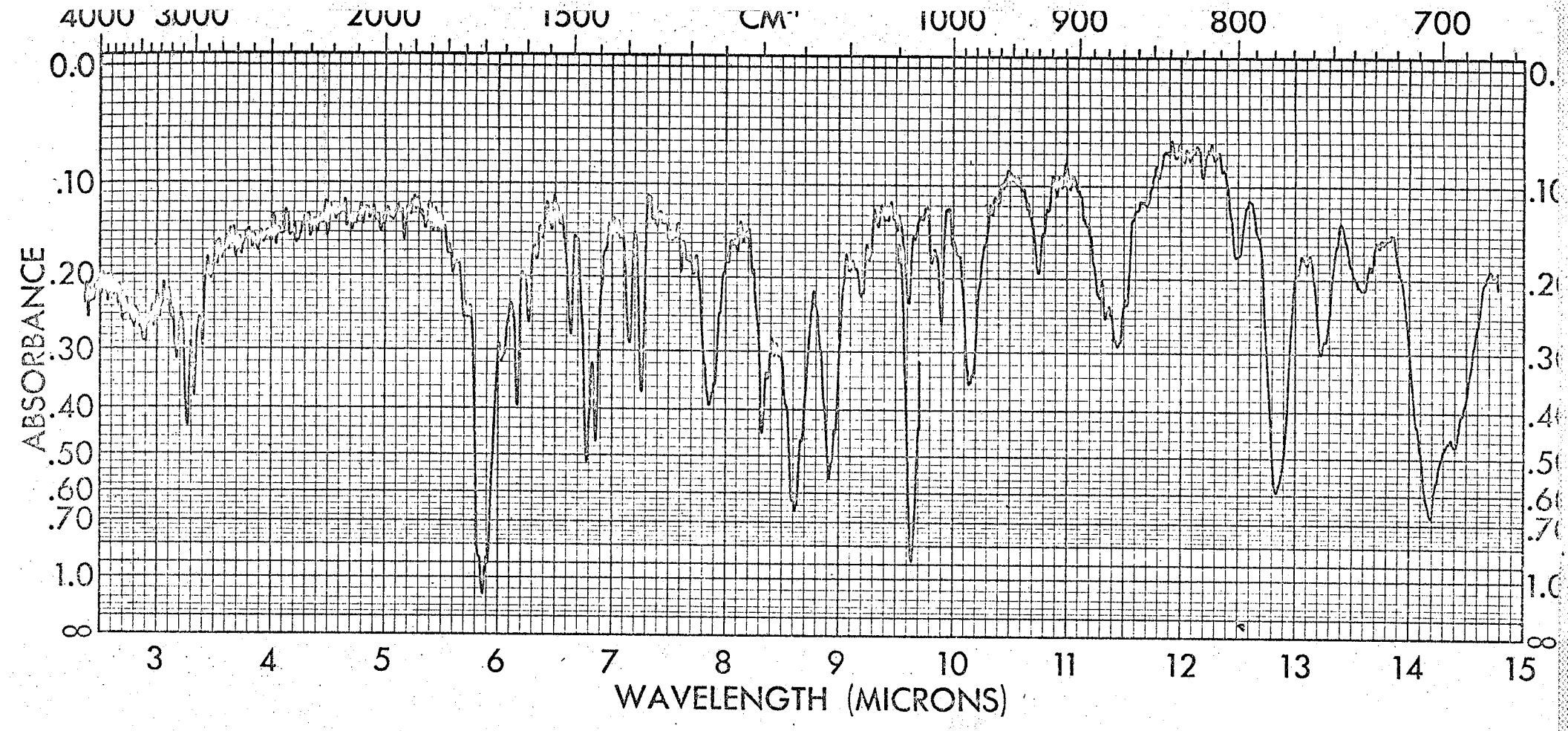
Preparation of 2,3-dihydro-2,2,7-trimethylbenzo[b]thiophene-3-acetate (131)

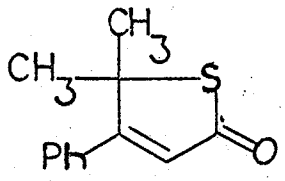
0.66 gm. of 2,3-dihydro-2,2,7-trimethylbenzo[b]thiophene was dissolved in 50 mls. of dry carbon tetrachloride. 0.72 gm. of N-bromosuccinimide with a small amount of benzoyl peroxide were added, and the mixture was refluxed for 2½ hrs. After cooling, the mixture was filtered. The filtrate was washed with water and dried. Evaporation of the carbon tetrachloride left a yellow liquid, which was immediately treated with anhydrous sodium acetate and glacial acetic acid, as described by Hurd and Dowbenko [85]. After work up, the crude product was examined by n.m.r. which showed it to be a mixture. A sample was purified by TLC (developed with benzene). Examination of the purified product once again by n.m.r. showed a mixture.

Oxidation of 2,3-dihydro-2,2,7-trimethylbenzo[b]thiophene

1.78 gms. of the title compound was dissolved in 30 mls. of acetic anhydride. 1.0 gm. of chromium trioxide was added and the mixture was refluxed overnight. The green ppt. was filtered off after the mixture had cooled down, and the filtrate was added to 200 mls. of water. The organic product was extracted into ether, and the ether layer was washed a few times with water, and then by 1N sodium hydroxide until the washing was alkaline to litmus. The ether solution was dried and the ether evaporated off. A sample of the dark brown residual liquid was examined by TLC. The desired 2,2,7-trimethyl-3(2H)-benzo[b]thiophenone was not identified.

INFRARED SPECTRA

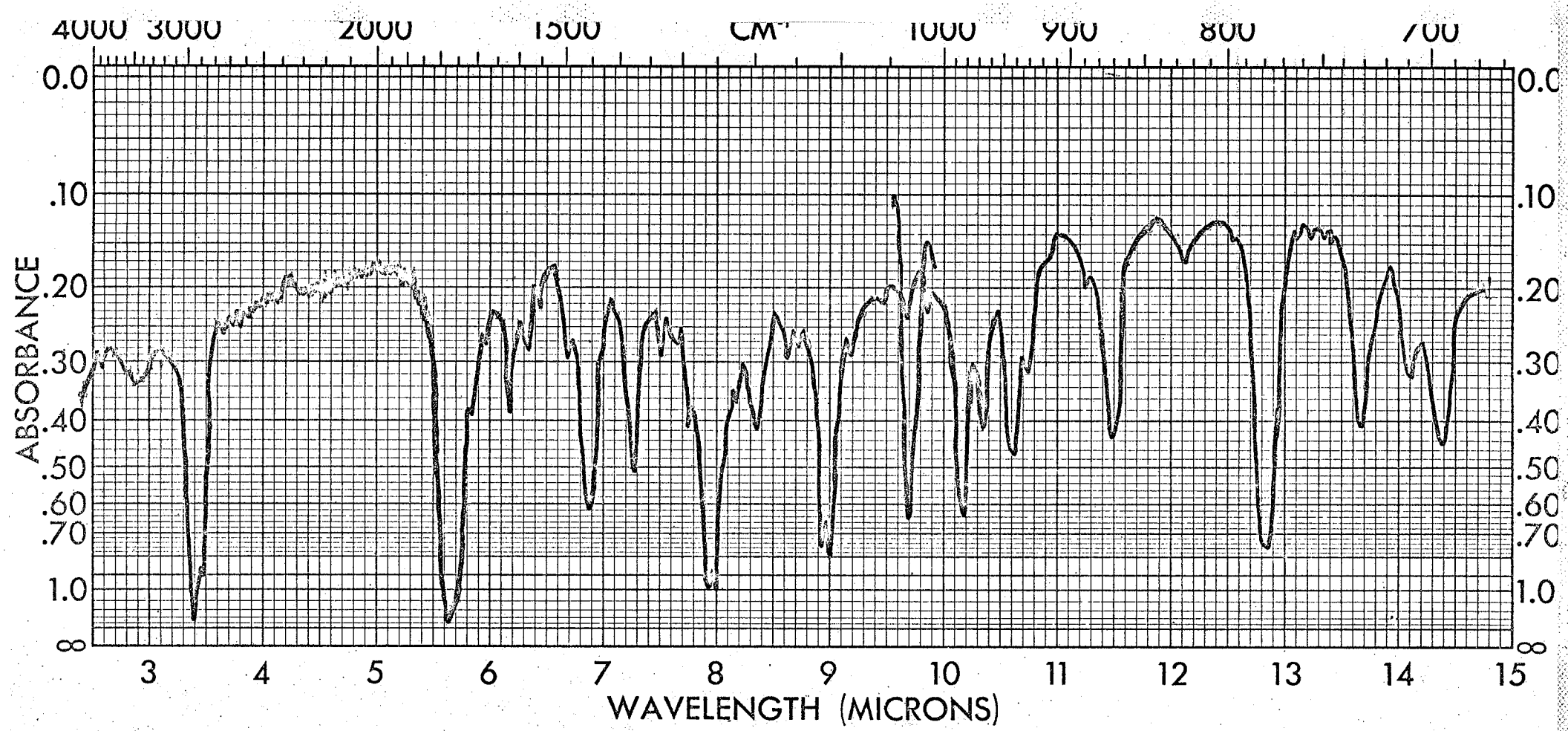


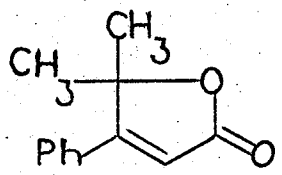


95A

PART NO.137-1280 ®

THE PERKIN-ELMER CORPORATION, NORWALK, CONN.





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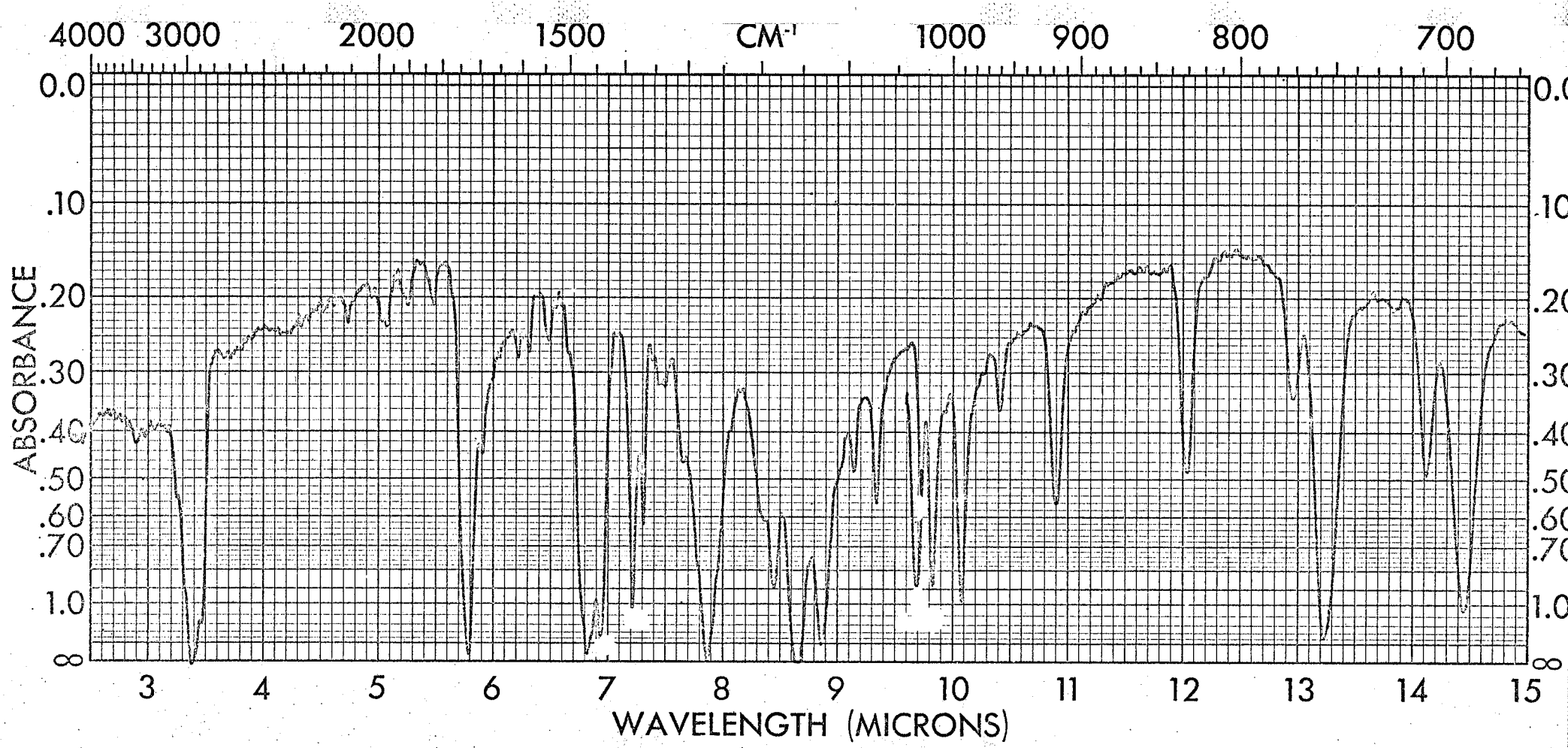
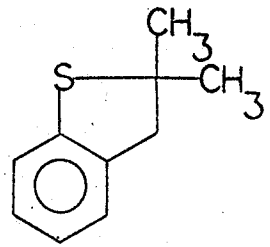
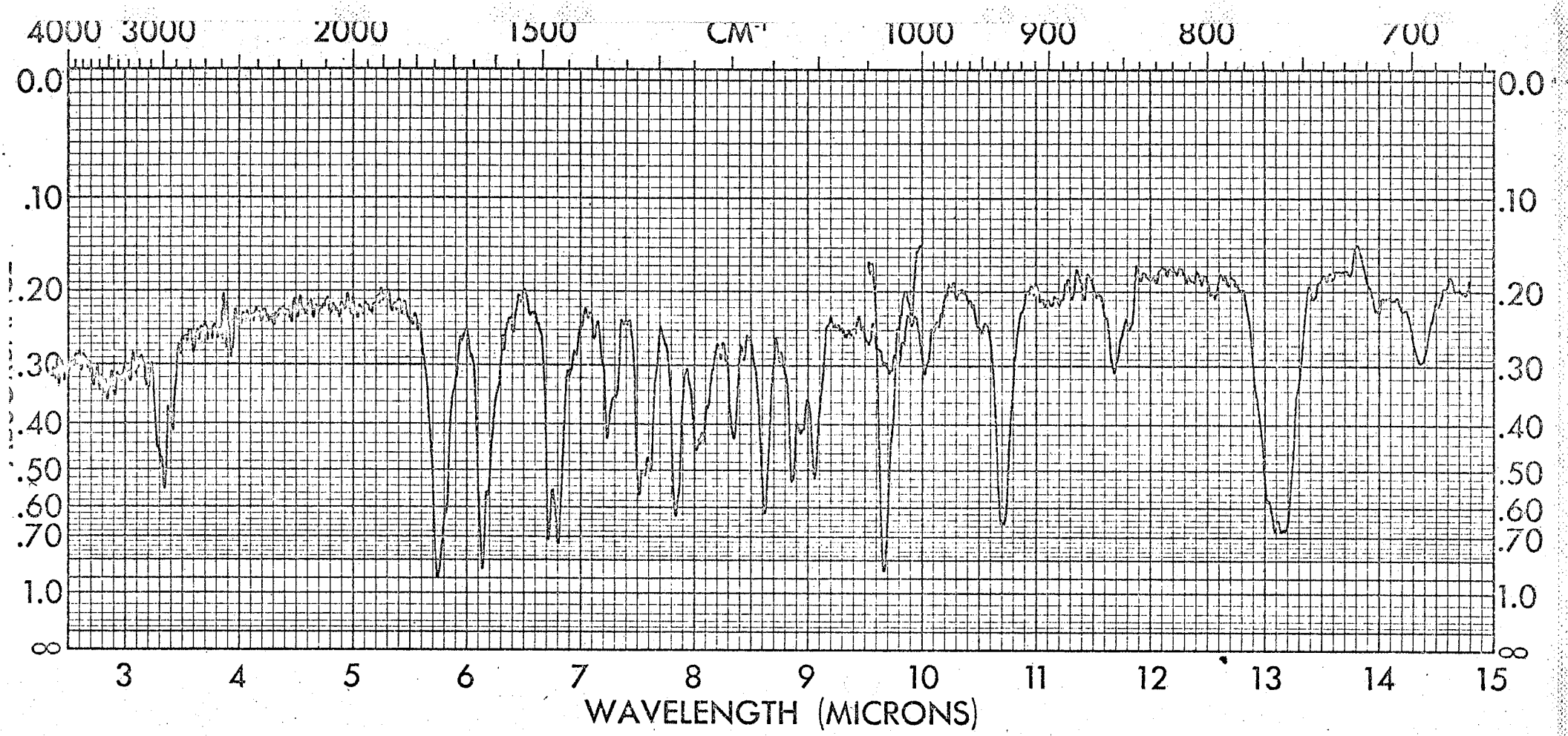
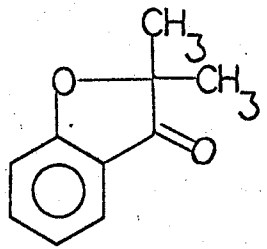




97A ?

from HF cyclization of 2-methyl-2-phenylthiopropionic acid





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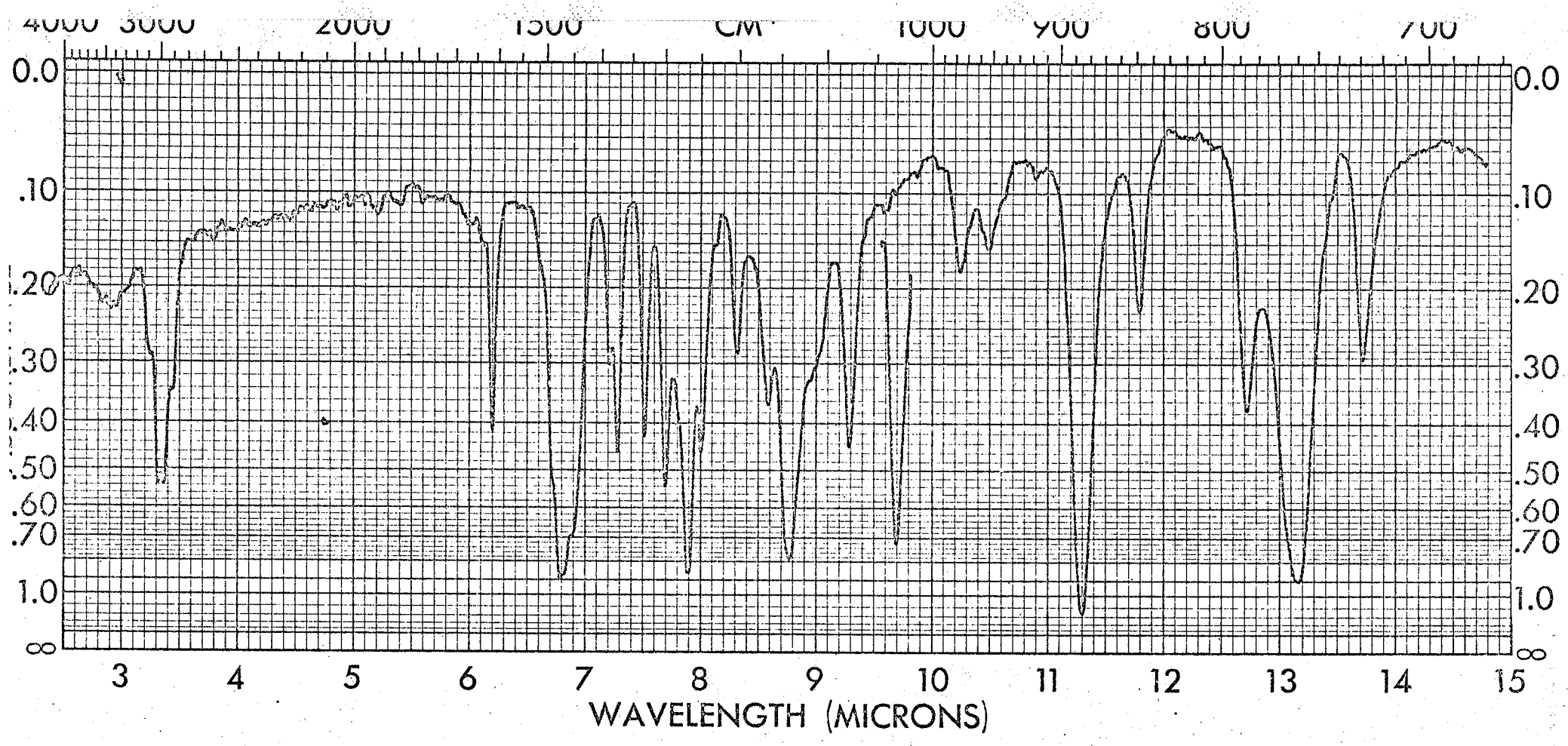
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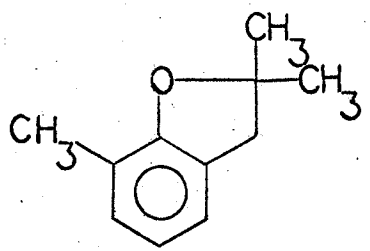
WAVELENGTH (MICRONS)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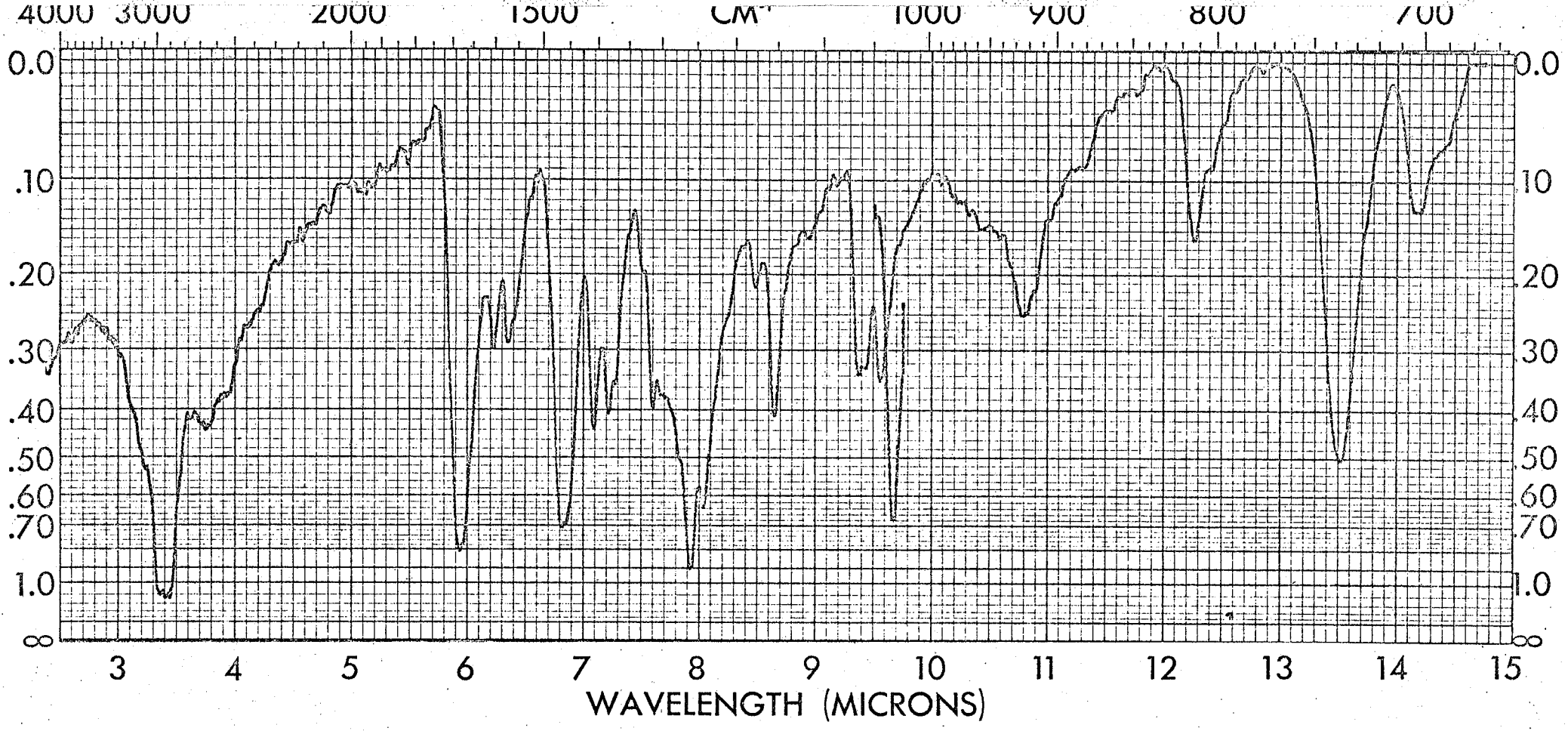
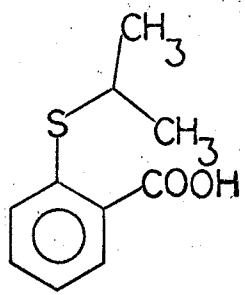
O
CH3
CH3

103

97





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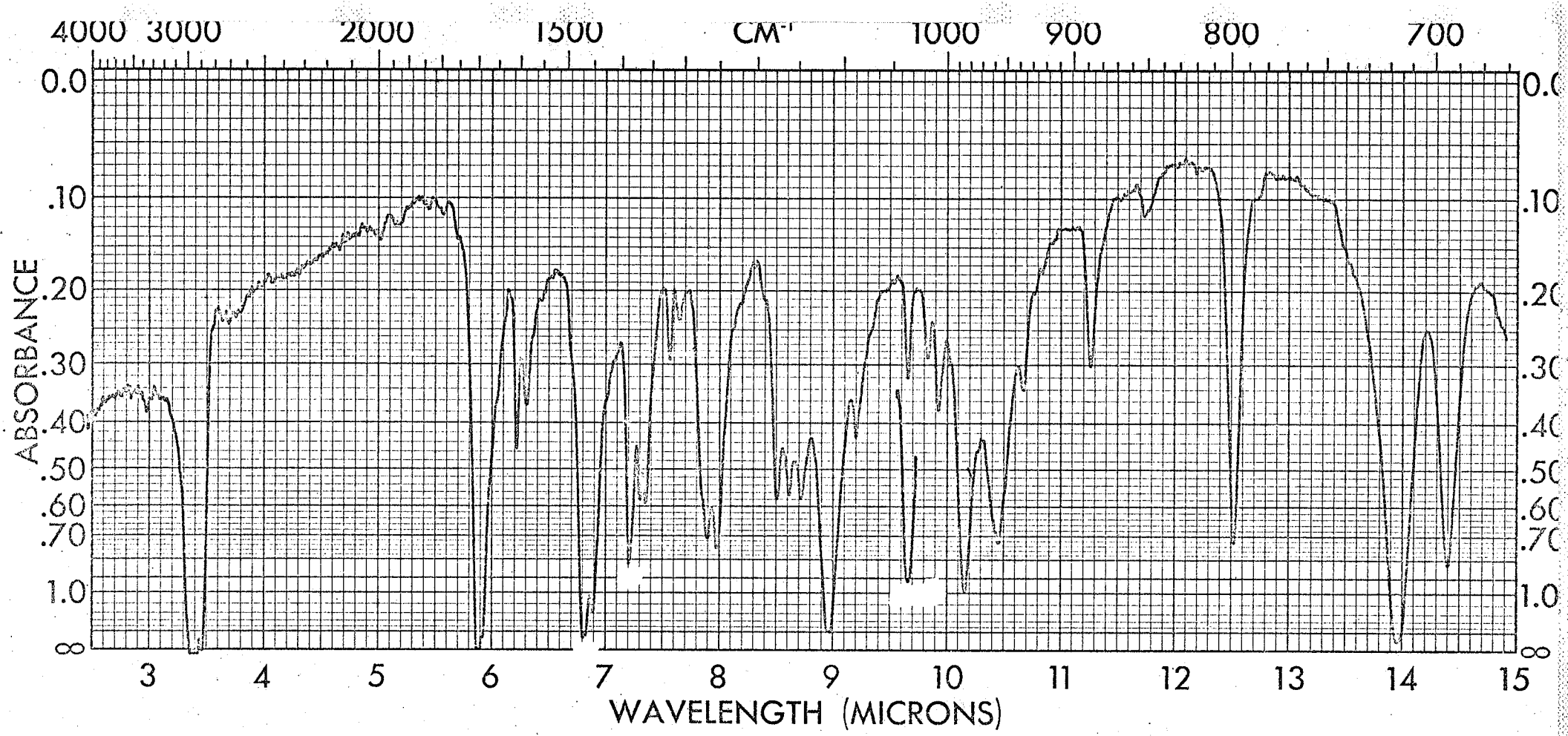

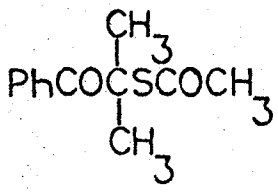

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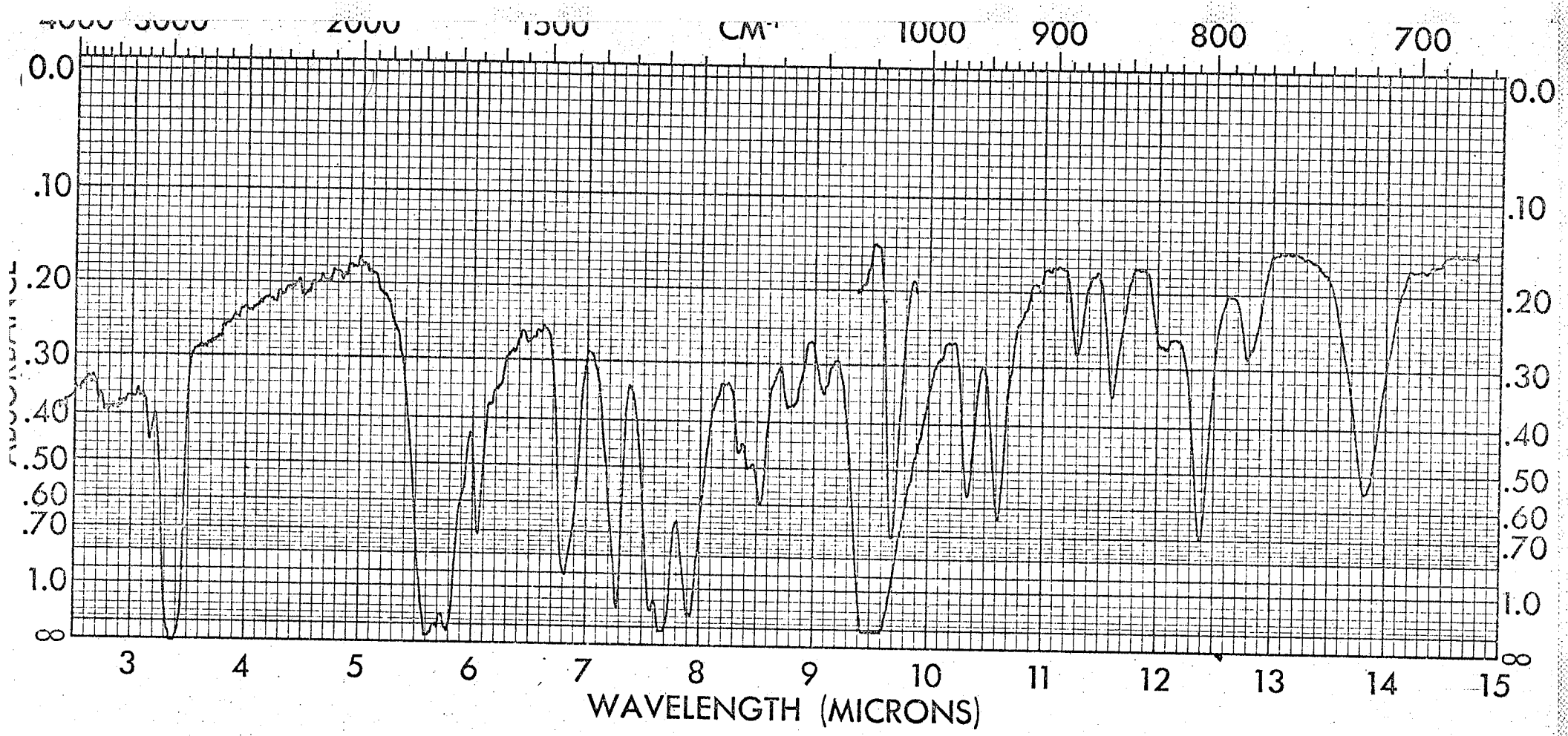
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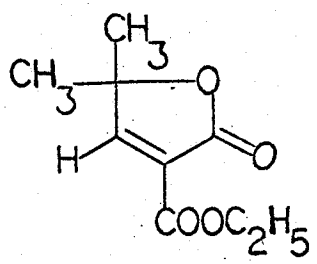
WAVELENGTH (MICRONS)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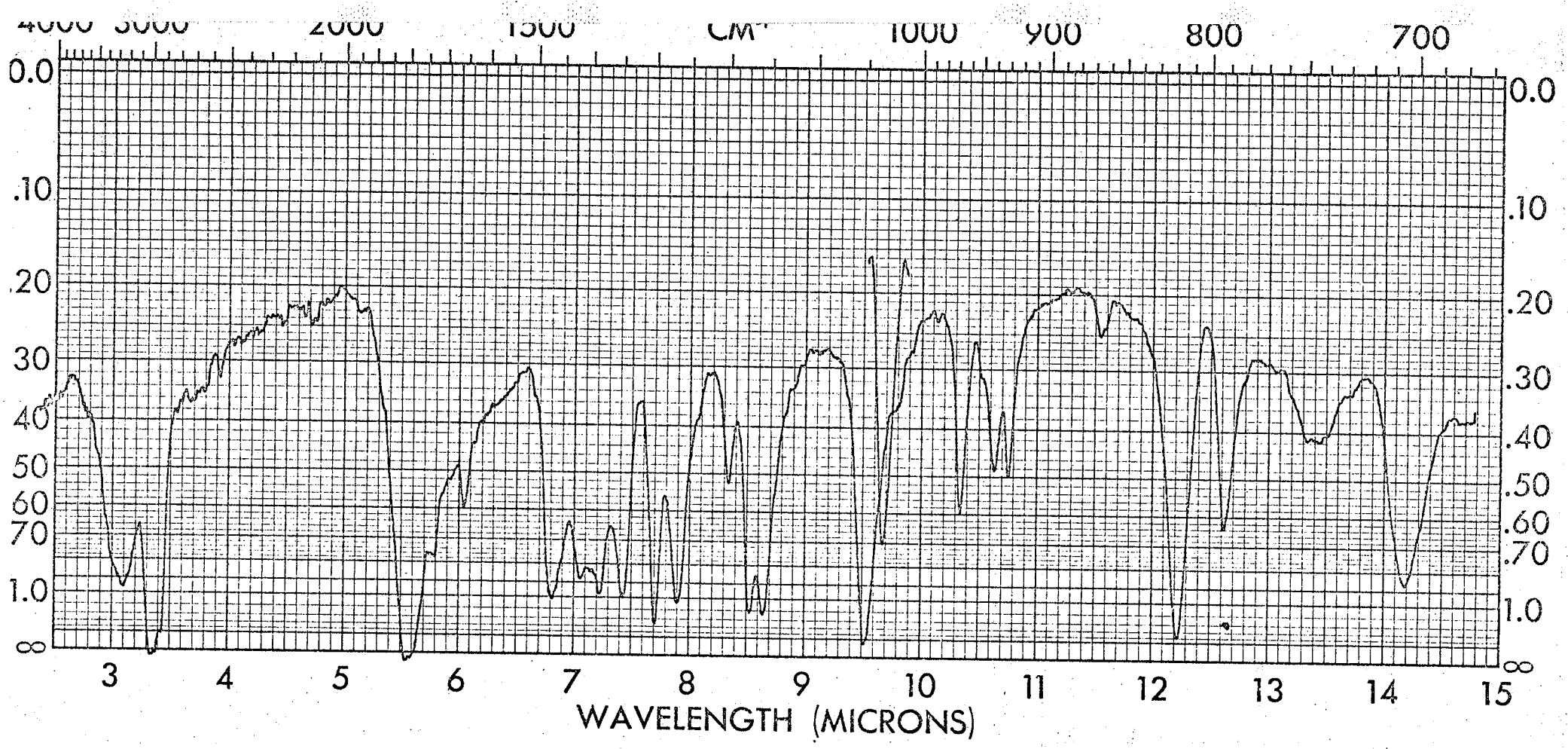
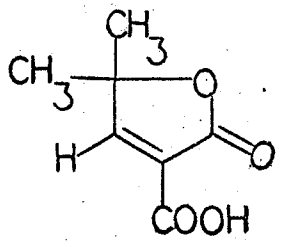
CH3
O
H
O
COOC2H5

116

100





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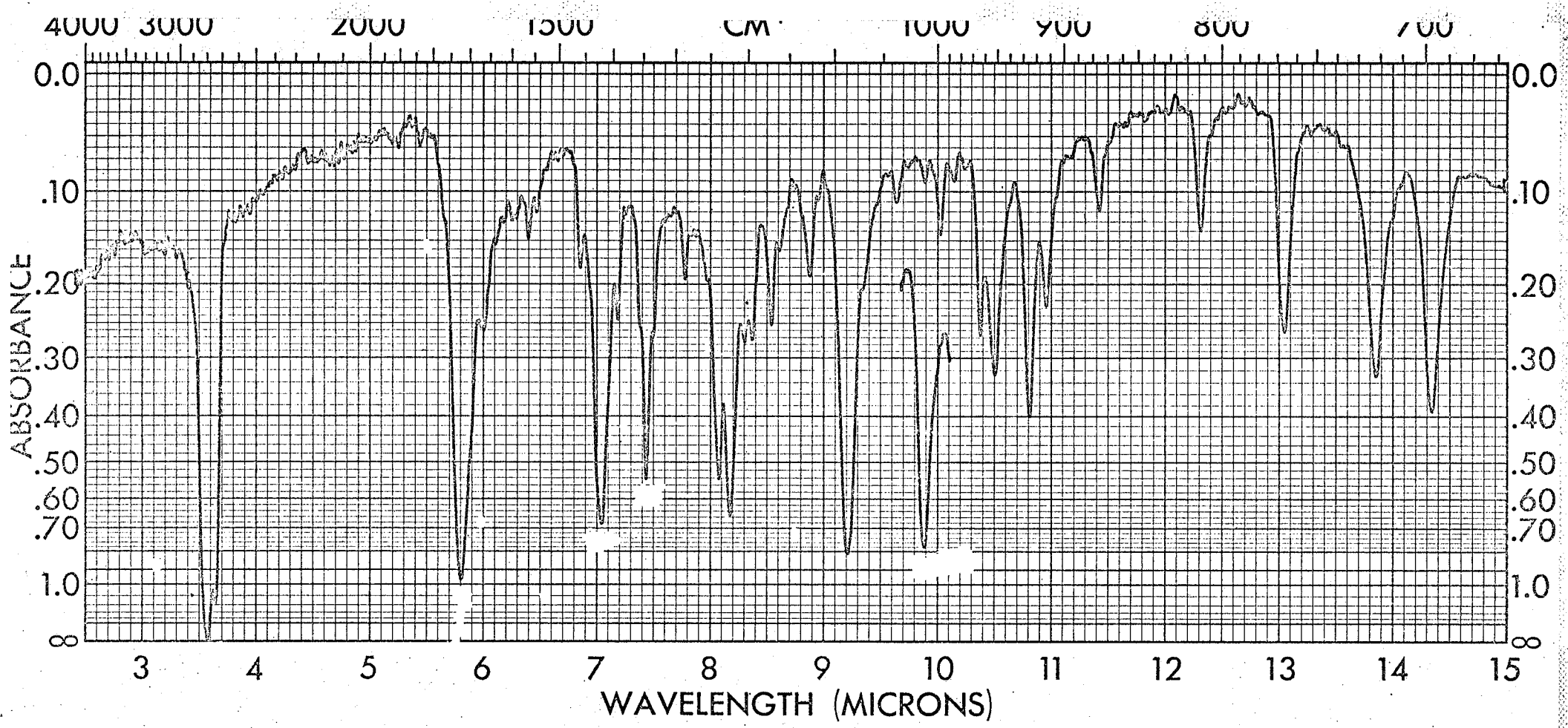

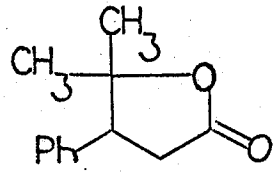

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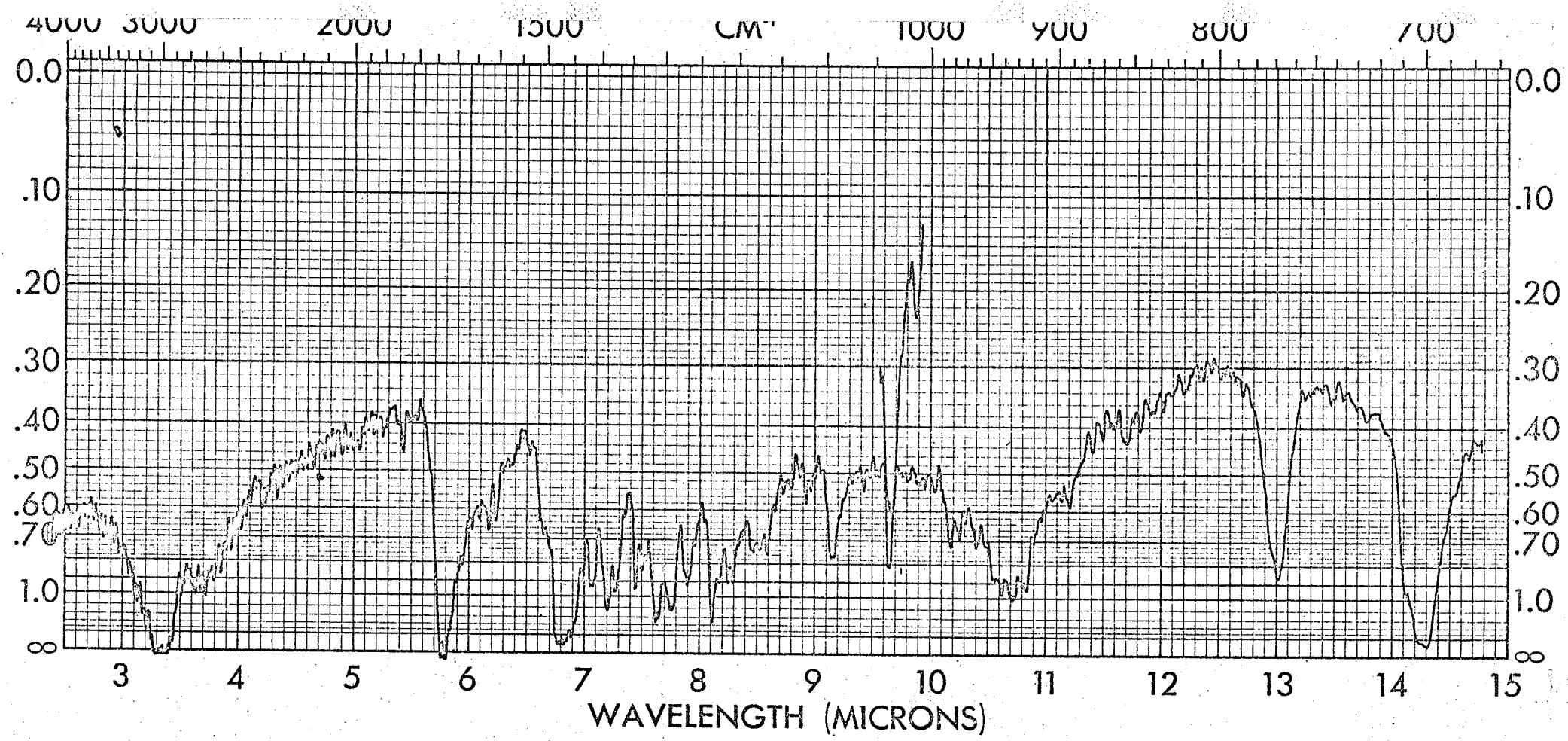

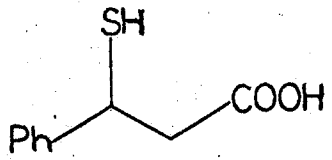

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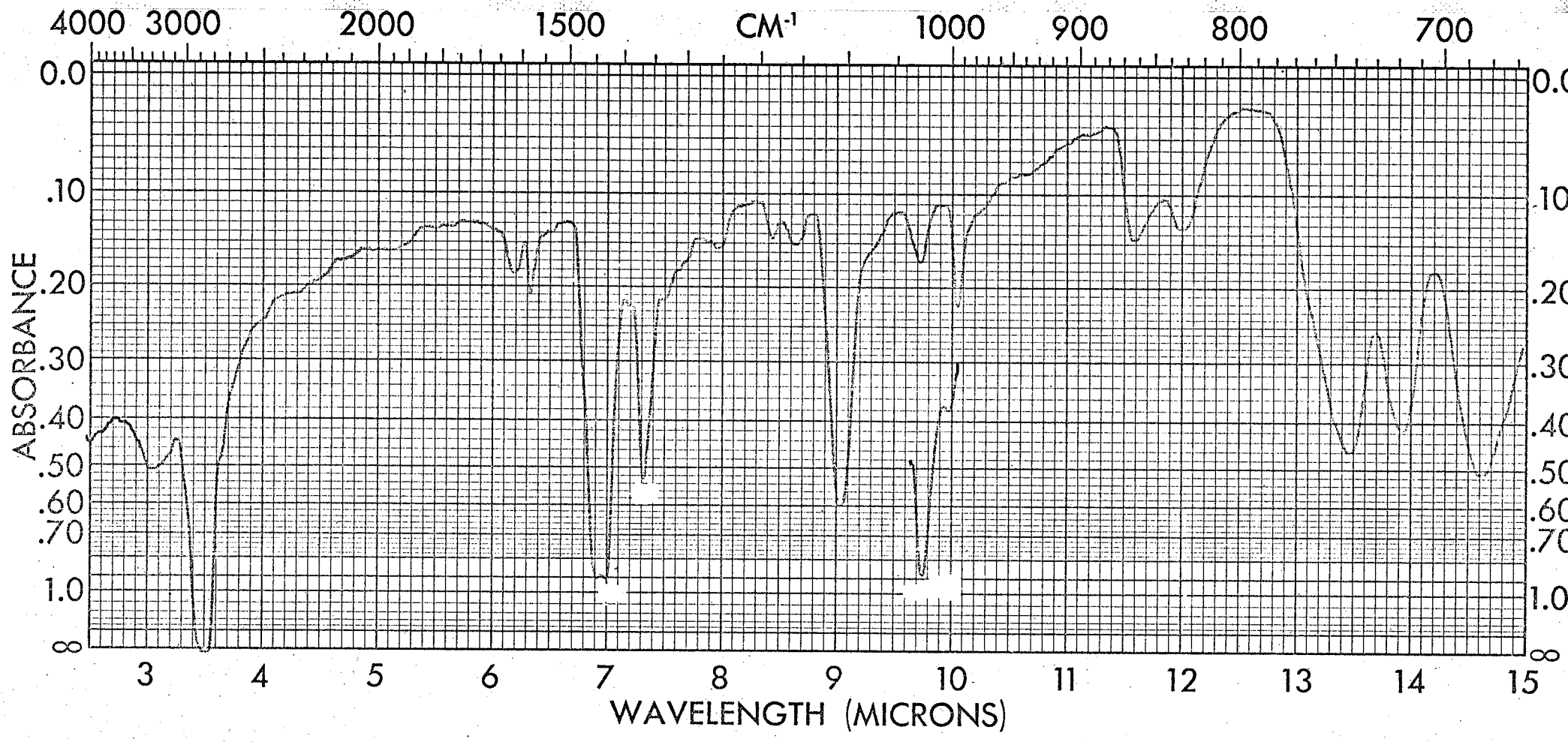

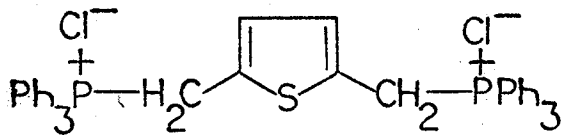

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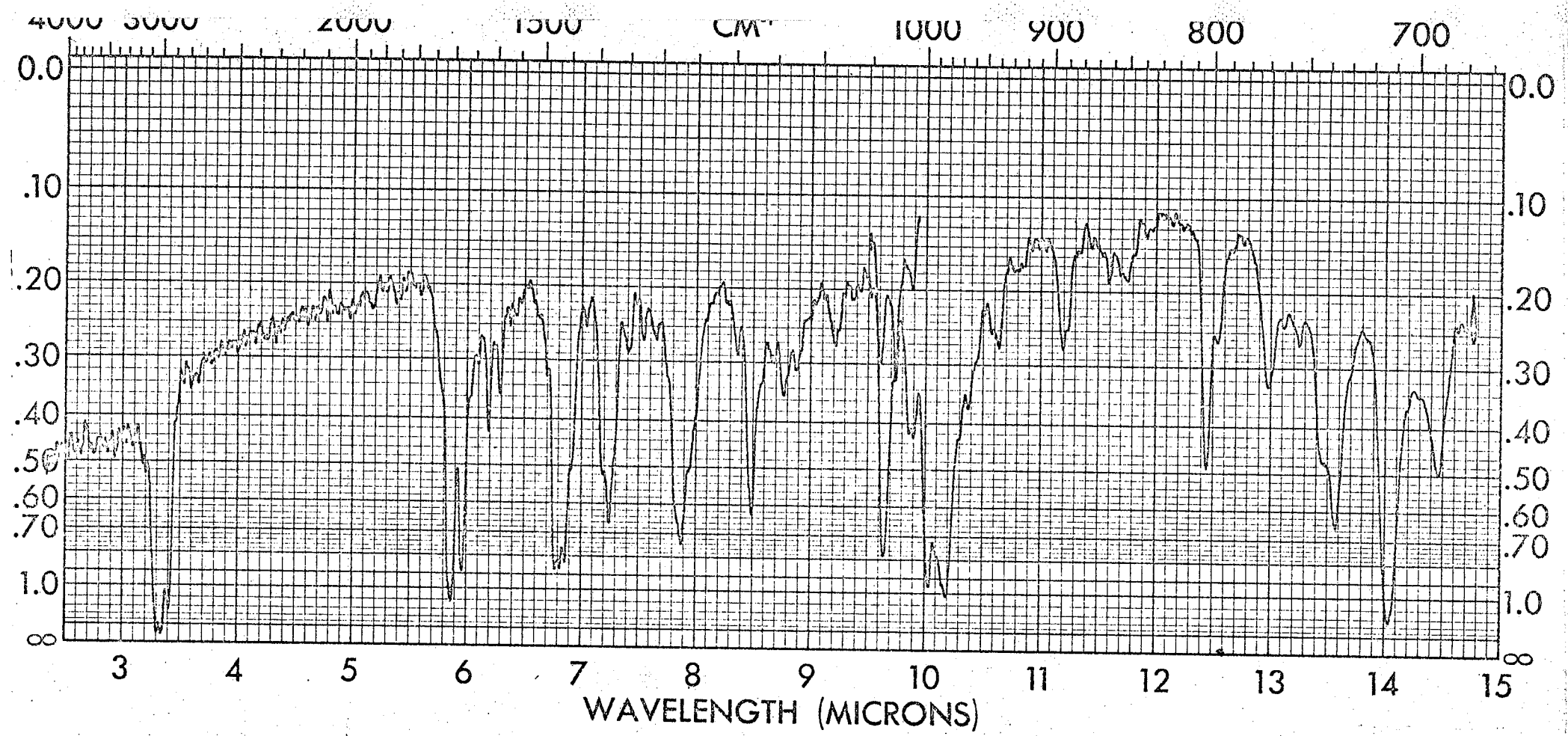

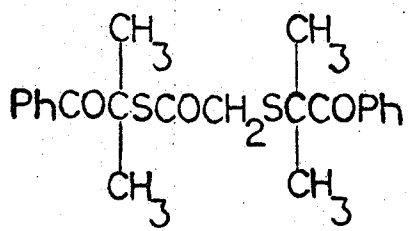

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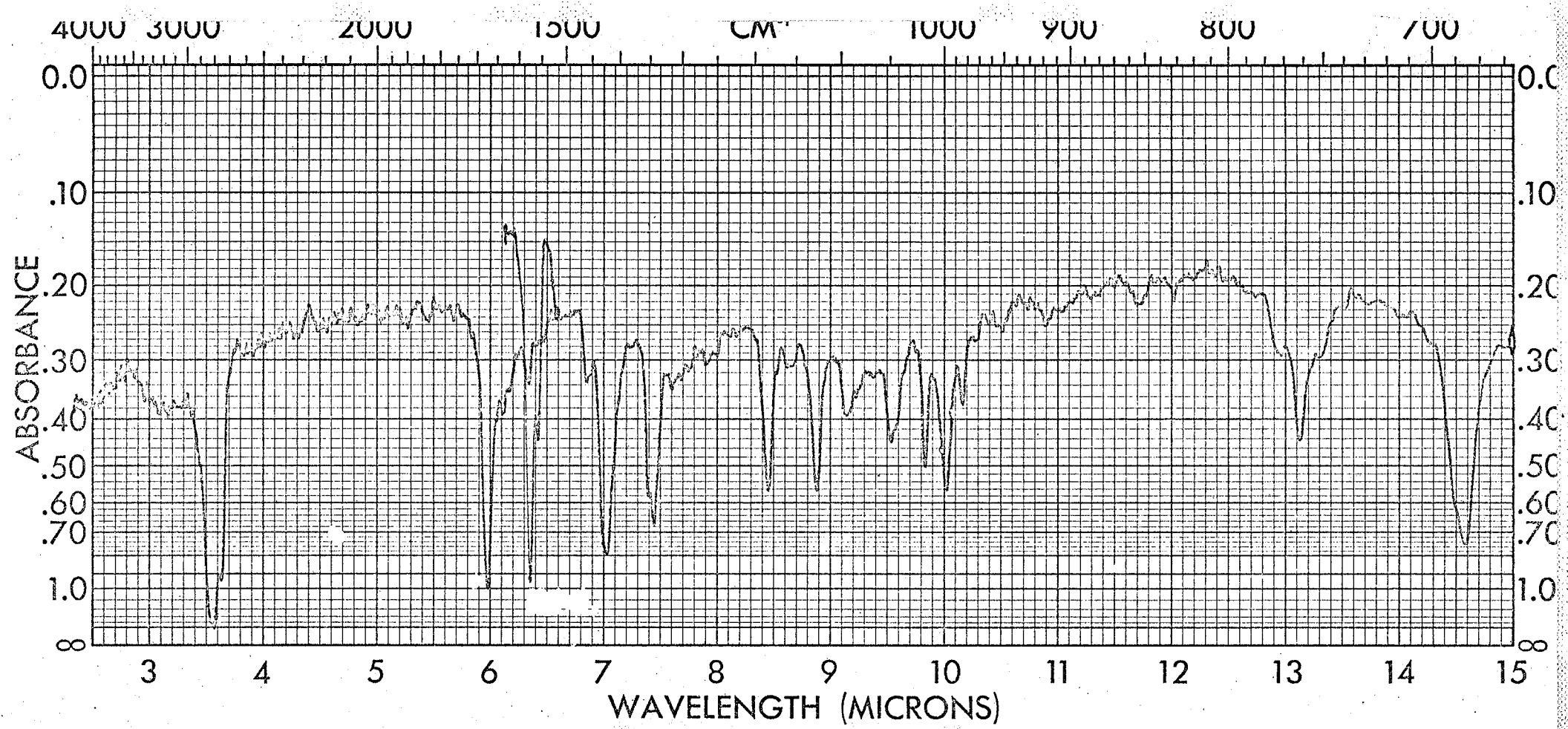
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ABSORBANCE
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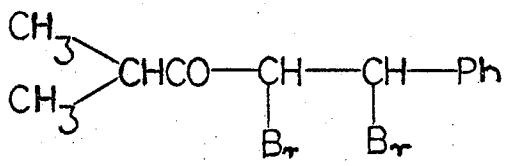
WAVELENGTH (MICRONS)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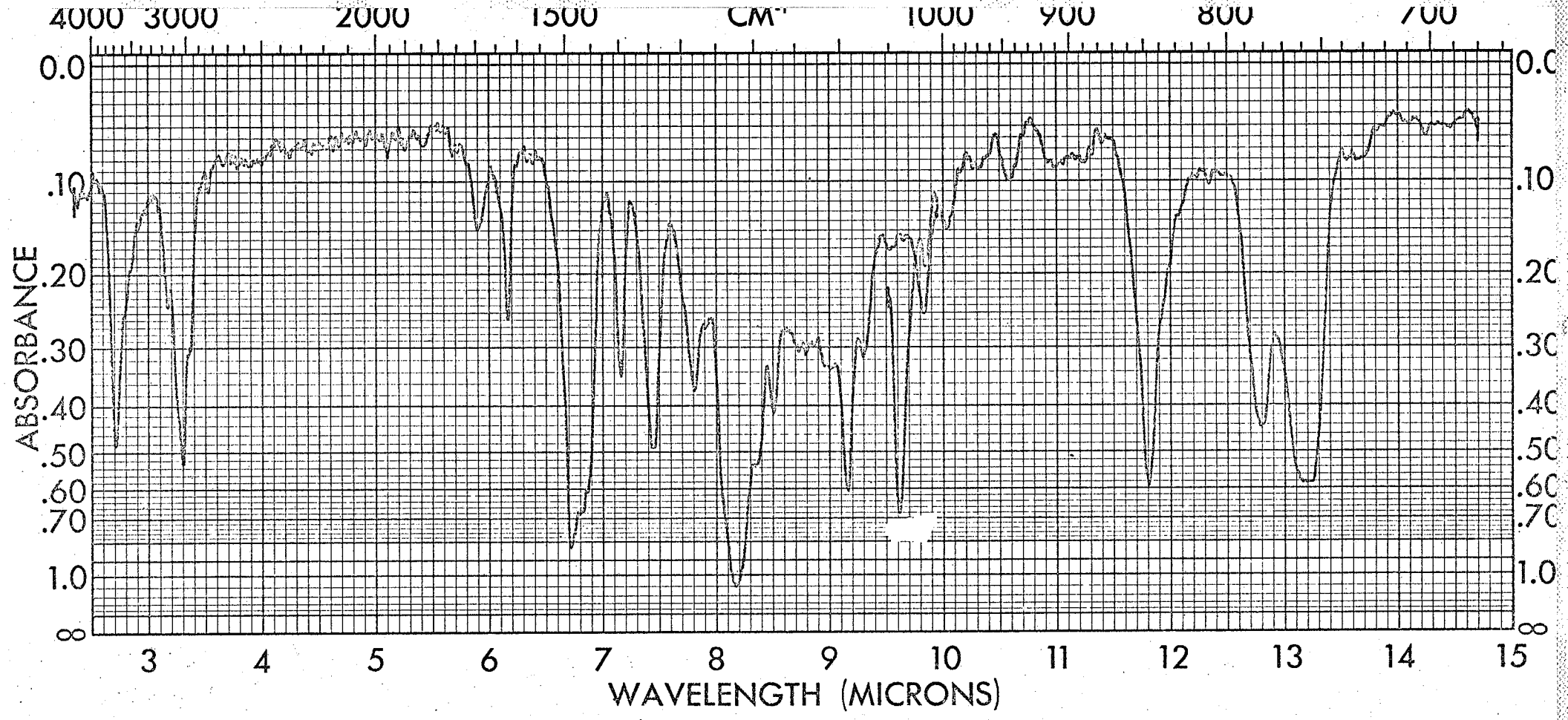
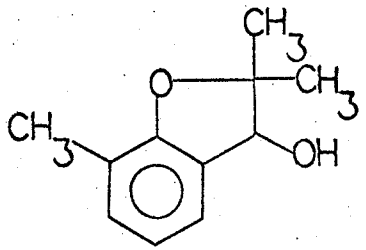
CH3
CHCO
CH
CH
Ph
Br
Br

106





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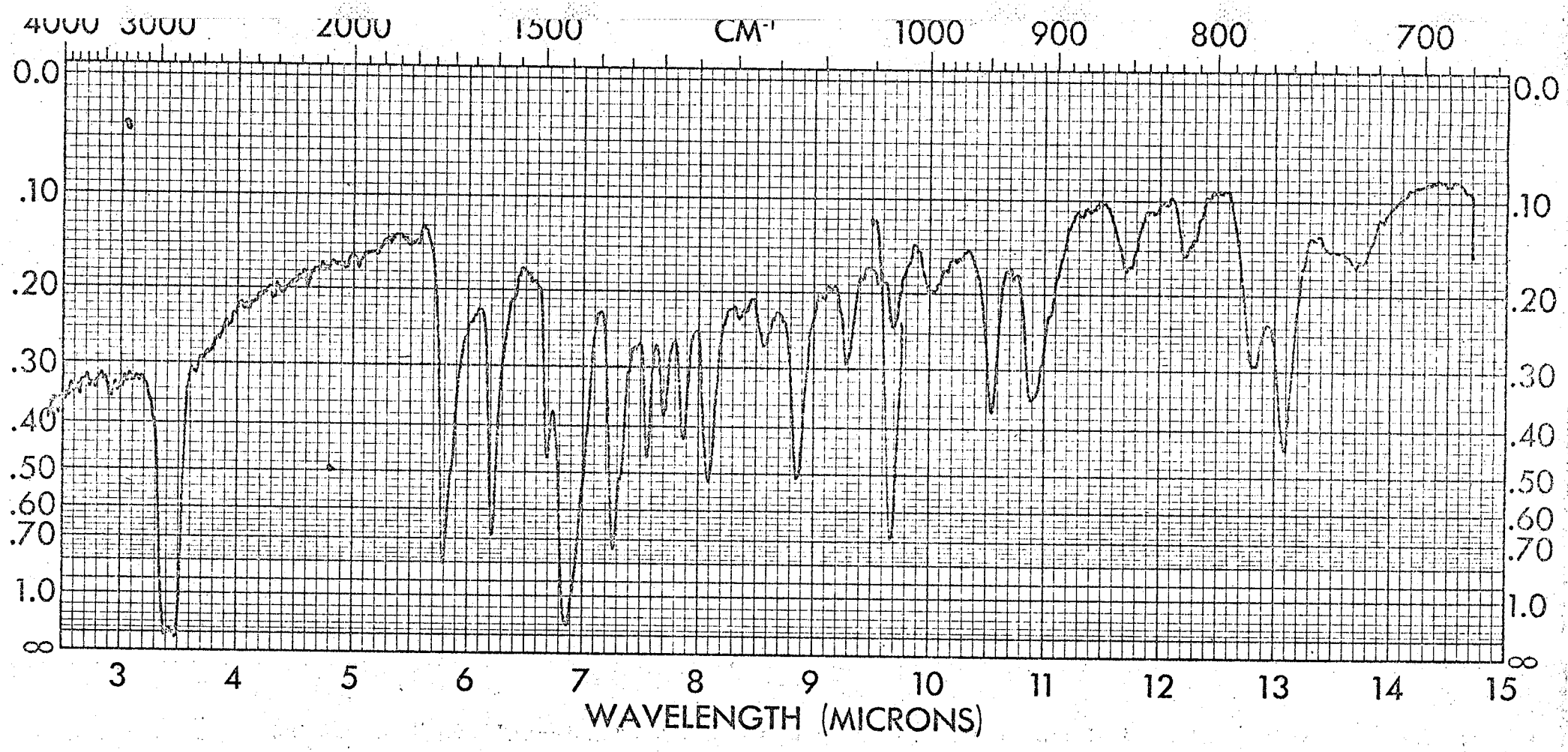

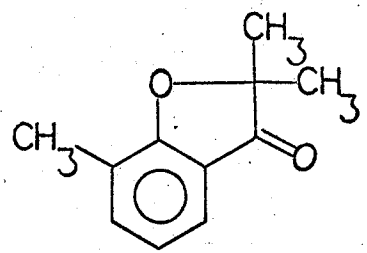

93B

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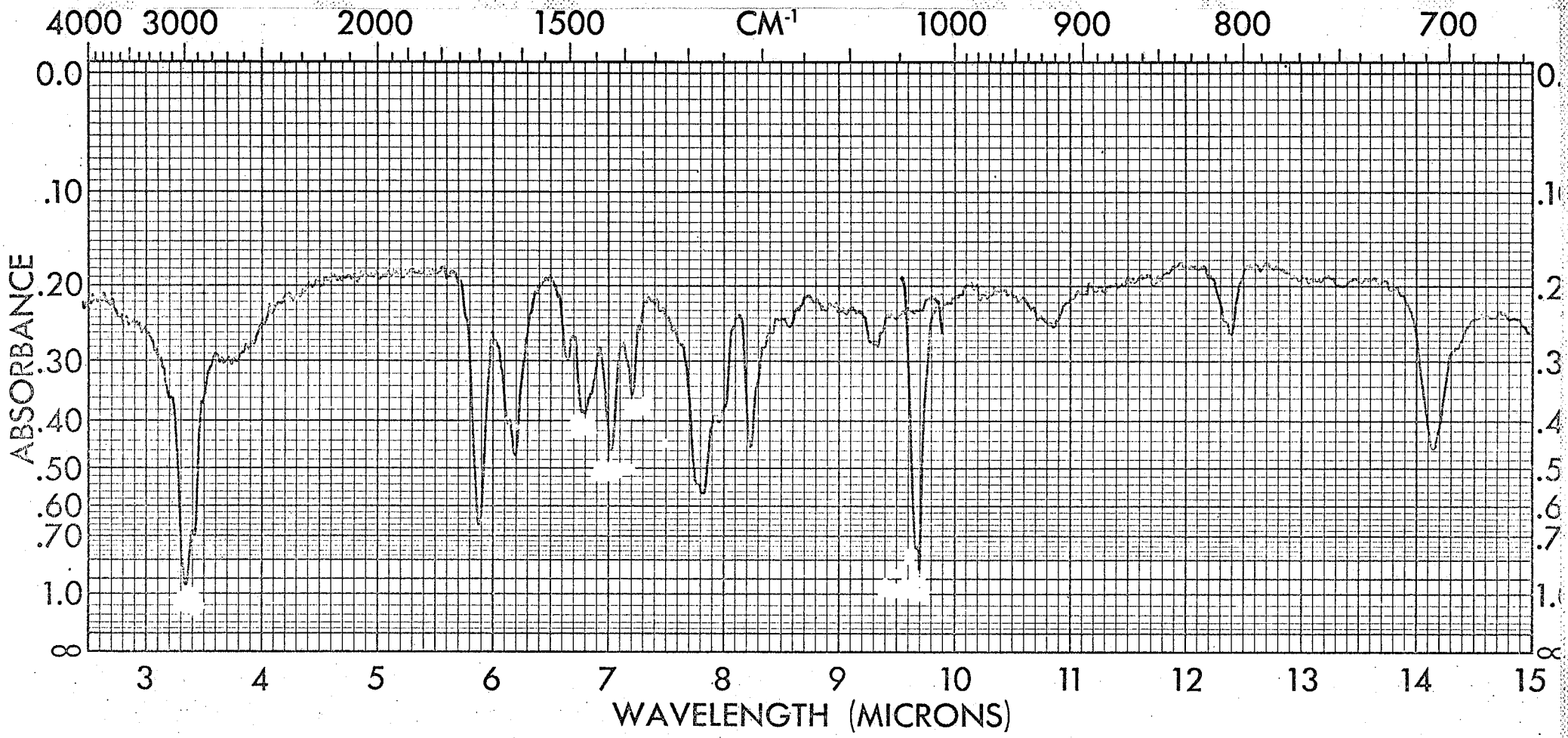
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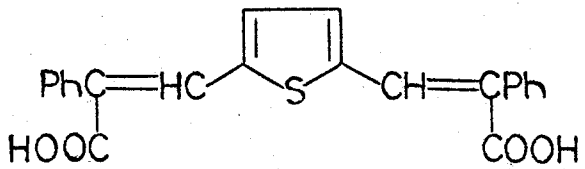
ABSORBANCE
3 4 5 6 7 8 9 10 11 12 13 14 15
WAVELENGTH (MICRONS)


PhC=HC
S
CH=CPh
HOOC
COOH

109

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