Part I. Silicon Tetrachloride as a Coupling Reagent for Amide Bond Formation.

Part II. Synthesis of Benzophosphole.

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Abstract

Part I. Silicon tetrachloride was found to be an efficient coupling reagent for the formation of amides from simple carboxylic acids and amines. The reaction appears to be quite general for all aliphatic and aromatic acids and amines. The use of this reagent for peptide synthesis was also investigated. A number of phthaloyl-, benzoyl- and acetyl-aminoacids were condensed with various methyl or ethyl aminoesters to give moderate yield of dipeptides. Benzyloxycarbonyl-aminoacids reacted with amino-esters to give poor yield of dipeptides. The extent of racemization during peptide synthesis by this method was examined and compared with existing methods.

Part II. A potentially general synthesis of 1-hetero-indene was developed and applied to the preparation of 1-phenyl-1-benzophosphole, a novel heterocyclic system.

Short Title:

PART I. SILICON TETRACHLORIDE
PART II. BENZOPHOSPHOLE

PART I

SILICON TETRACHLORIDE AS A COUPLING REAGENT FOR AMIDE BOND FORMATION

PART II

SYNTHESIS OF BENZOPHOSPHOLE

by

L. T. L. Wong

A thesis submitted in conformity with
the requirements for the degree of
Doctor of Philosophy

McGill University

March 1971

ACKNOWLEDGMENTS

The author wishes to thank Dr. T. H. Chan, his research director, for his guidance and aid. Thanks are also due to Mr. Peter Currie for recording the mass spectra.

The author is grateful for financial assistance from the National Research Council of Canada by the award of a Studentship in 1968-1970.

CONTRIBUTION TO ORIGINAL KNOWLEDGE

This thesis contains two separate parts. Part I deals with the use of silicon tetrachloride, a novel coupling reagent, for the formation of amide bond. The coupling method is found to be quite general for the preparations of simple amides. It has been modified for the syntheses of dipeptides. In Part II, a potentially general synthesis of 1-heteroindene has been developed. It has been applied to the preparation of 1-phenyl-1-benzophosphole, a novel heterocyclic system.

PART I

SILICON TETRACHLORIDE AS A COUPLING REAGENT FOR AMIDE BOND FORMATION

TABLE OF CONTENTS

INTRODUCTION

The atom silicon, having a normal valence of four as carbon and occupying a space in the second row of the periodic table, shows a few characteristic features that differentiate its organic chemistry quite remarkably from that of carbon:

(1) The low electronegativity of silicon:- Table I shows the electronegativity values and their differences (ΔEl with respect to Si) of a number of elements. These data are taken from Eaborn[1]. As can be seen, silicon is more electropositive in comparison with

TABLE I

Element	Electronegativity	ΔEl
Si	1.8	-
C	2.5	0.7
H	2.1	0.3
Cl	3.0	1.2
Br	2.8	1.0
O	3.5	1.7
N	3.0	1.2

carbon or hydrogen. Consequently, the chemical behavior of the Si-H bond in relation to the C-H bond can be quite different. The Si-H bond would be expected to polarize into $Si^{\delta+}-H^{\delta-}$ and react as a re-

ducing agent in contrast to the inert property of the C-H bond. Indeed most organosilanes resemble metal hydrides in their reductive ability. Because of the very low electronegativity of silicon, many silicon linkages to other heteroatoms also have rather pronounced ionic character. An example would be the silicon-halogen bond which is more ionizable (30% ionic character[1]) than a carbon-halogen bond.

(2) Availability of the silicon d-orbitals:- The silicon atom, although it is generally tetravalent, can expand its octet to accomodate more than eight electrons by using the 3d-orbitals. Pentacovalent[2] and hexacovalent[3] silicon compounds are known to exist. There are also some evidence to suggest that the silicon 3d-orbitals are involved in compounds of the type Si-X where X has a lone pair of p electrons to form $p\pi$-$d\pi$ bonding[4]. The subject of $p\pi$-$d\pi$ bonding is however controversial[5].

(3) The great stability of the silicon-oxygen bond:- Table II shows the average bond energies of various bonds of silicon or carbon with a few elements. The data are obtained from Cottrell[6]. It must be emphasized that these bond energies are average values only and take no account of the effects of substituents.

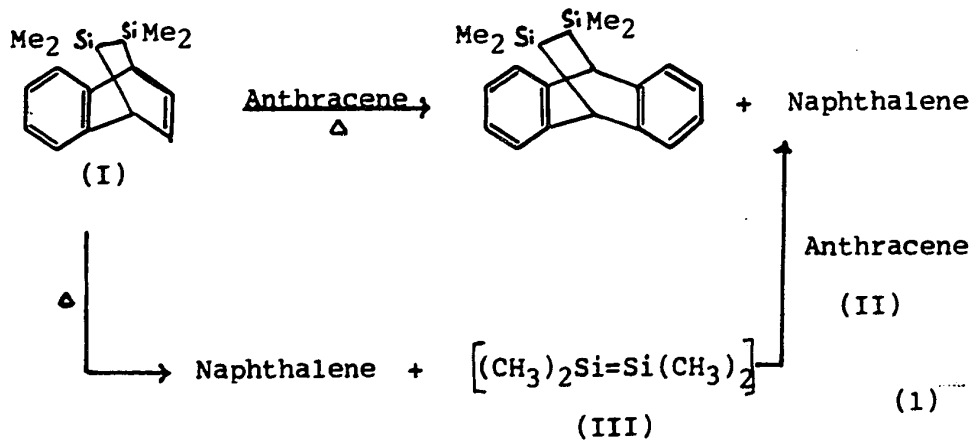
TABLE II

Bond	Bond Energy (Kcal/mole)	Bond	Bond Energy (Kcal/mole)
Si-Si	53	C-Si	76
Si-C	76	C-C	83
Si-H	76	C-H	99
Si-O	108	C-O	86
Si-N	- [a]	C-N	73
Si-Cl	91	C-Cl	81
Si-Br	74	C-Br	68

a) Eaborn[1] gave a value of 77Kcal/mole.

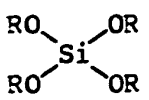
One may observe the high value for Si-O bond as compared to C-O and this accounts for the great stability of silica and silicones.

(4) Unwillingness of silicon to form $p\tilde{\pi}$-$p\tilde{\pi}$ multiple bond:- No well-authenticated case of $p\tilde{\pi}$-$p\tilde{\pi}$ multiple bond for silicon is known. Recently Peddle and co-workers[7] published an interesting paper entitled '7,8-Disilabicyclo[2.2.2.]-2,5-octadienes. An approach to Tetramethyldisilene.' It was found that the tetramethyldisilyl bridge of the disilabicyclo[2.2.2.]-2,5-octadiene compound (I) could be quantitatively transferred to another diene (e.g.II) when these were heated together at high temperature. (Eq. 1) The reaction was proposed to proceed via initial retrodiene reaction of the disilabicyclo compound to form tetramethyldisilene (III) followed by a Diels-Alder addition of



this to the diene (II). The disilene however was found to be only a transient species and could not be isolated. In the absence of diene as trapping agent, it polymerized quickly to give a mixture of organosilicon compounds. Up to the present time, no stable compounds with Si=Si, Si=O or Si=C multiple bonds have been isolated. While the reasons for this are not clear, it is often attributed to the decrease in the overlap integral for the $3p\pi$-$3p\pi$ bond because of increased internuclear separation[8]. This property of silicon resembles other second row elements, e.g. phosphorus. It allows for the relative stability of silicon compounds with multiple functional groups attaching to the same silicon atom. Examples like tetra-

alkoxysilane (IV)[17], tetraacyloxysilane (V)[17] and tetraaminosilane (VI)[57] are known stable compounds.



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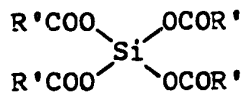

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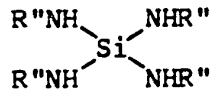
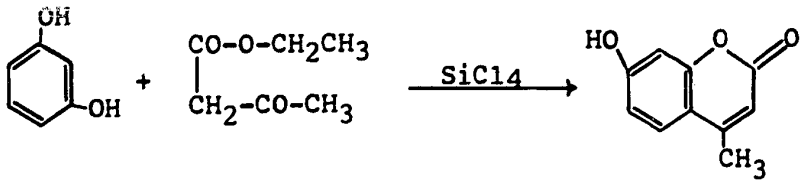


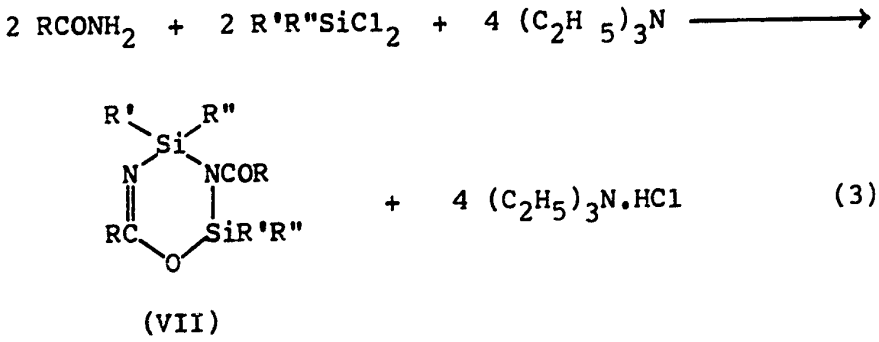
(VI)

There are a large number of organosilane reactions which occur because of these characteristic features mentioned above. To briefly cite a few, the reduction of phosphine oxides[9] and sulfoxides[10] by silanes and perchloropolysilanes[11]; the synthesis of olefins and ketones from carbonyl compounds and carbanions alpha to silicon[12]; the reductive silylation of carbonyl compounds[13] and carboxylic acids[14] are novel examples. The driving force of these reactions is the formation of the highly stable Si-O bond. Another type of reaction is the dehydrating action of organohalosilanes. Trivedi[15] found that resorcinol condensed with ethyl acetylacetate with silicon tetrachloride as the condensation reagent to form coumarin (Eq. 2); the author did not give mechanistic details of the reaction. More recently, Klebe[16] studied the properties of disilaoxadiazines (VII) which were formed from the reactions of dichlorosilanes with N-unsubstituted amides in the presence of base (Eq. 3). When these disilaoxadiazines were heated neat or in solution,



(2)

they decomposed to give the corresponding nitrile and siloxane (Eq. 4). The overall reaction can be looked upon as a mild method for the dehydration of amide to nitrile, the driving force being again the formation of Si-O bond.



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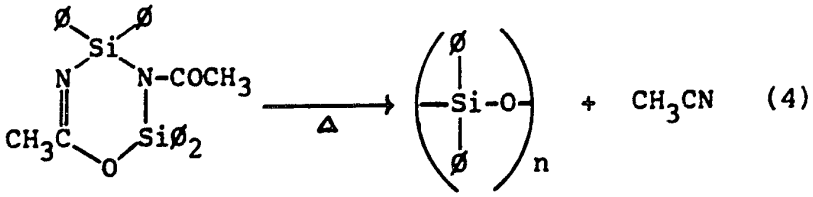


(4)

Although the use of halosilanes as dehydrating reagents is known, the field has not been fully explored. For example, silicon tetrachloride is known to react vigorously with water to form silica[58]; however, there has been no report in the chemical literatures on the use of silicon tetrachloride as dehydrating agent for the

coupling of amide bond from carboxylic acid and amine. It is the purpose of this research project to investigate the possible use of silicon tetrachloride as coupling agent for amide and peptide formation.

AMIDE FORMATION

Theory

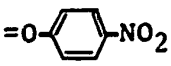
The condensation between a carboxylic acid and an amine generally does not take place because of the interference of a proton-transfer reaction (Eq. 5). To overcome this, a number of reagents have been developed. Essentially they involved the activation of the carboxylic acid to either an acid chloride, an acid anhydride, or an active ester (Eq. 6).

$$RCOOH + H_2NR' \longrightarrow RCOO^- + H_3\overset{+}{N}R' \qquad (5)$$

$$RCOX + H_2NR' \longrightarrow RCONHR' + HX \qquad (6)$$

X=Cl

=OCOR"

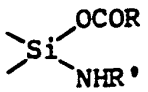
=O-  -NO_2

The use of silicon tetrachloride as dehydrating agent for amide bond formation appears to be quite feasible from theoretical consideration. Halosilanes are known to react exothermically with carboxylic acid[17] and amine[18] to form acyloxy and aminosilanes respectively together with the evolution of hydrogen chloride gas (Eq. 7,8). In the case of silicon tetrachloride which contains more than one

$$\equiv Si\text{-}Cl + RCOOH \longrightarrow \equiv Si\text{-}OCOR + HCl \quad (7)$$

$$\equiv Si\text{-}Cl + H_2NR' \longrightarrow \equiv Si\text{-}NH\text{-}R' + HCl \quad (8)$$

active Si-Cl bonds, formation of the intermediate (VIII) having an acyloxy and an amino group attaching to the same silicon atom is possible. Intermediate of this kind would be expected to decompose according to Eq. 9 leading to the formation of highly stable silica and amide. A calculation on the heat of reaction with values from Table II gives $\Delta H = E_{C-O} + E_{Si-n} - E_{Si-O} - E_{C-n} = -18$Kcal/mole. It would be difficult to estimate the entropy change for this reaction, but it is expected to be a positive value because of an overall increase in the number of particles in the reaction. There would be a decrease in free energy for the whole process.



(VIII)

$$\longrightarrow RCONHR' + (-Si\text{-}O\text{-})_n \quad (9)$$

Results

To test the prediction, experiments were carried out by reacting a carboxylic acid and an amine with silicon tetrachloride using pyridine both as solvent and as base to capture the hydrogen chloride released. Thus, to two moles of benzoic acid and two moles of aniline in pyridine was added one and a half moles of silicon tetrachloride. A

white precipitate was formed instantly with much evolution of heat in the reaction mixture. The precipitate appeared to redissolve gradually after continuous stirring for thirty minutes. The mixture was refluxed for one hour and then hydrolysed with ice-water. The precipitate was filtered and extracted with ethanol to give benzanilide in 70% yield. The compound was identified by comparison with an anthentic sample. In this manner, a number of amides could be prepared (Table III).

This mode of amide formation using silicon tetrachloride in pyridine as coupling reagent appears to be quite simple and efficient. The overall reaction can be depicted by Eq.(10). The reaction is usually quite clean as the other product in the reaction mixture is silica which is insoluble in all common organic solvents. Hence the problem of product contamination with side products can be avoided.

$$2\ RCOOH + 2\ R'NH_2 + SiCl_4 \xrightarrow{\text{Pyridine}} 2\ RCONHR' + (-SiO_2-)_n + 4\ HCl \qquad (10)$$

Reaction Conditions: In general, the reaction was carried out in pyridine by heating the mixture at 110° for one to two hours. Good yield of product was usually obtained under these conditions. The reaction was also found to proceed at room temperature. Although a longer reaction time was

TABLE III

AMIDE FORMATION FROM CARBOXYLIC ACID AND AMINE WITH SILICON TETRACHLORIDE-PYRIDINE AS COUPLING REAGENT.

Acid	Amine	Conditions	Product, yield
Acetic	Aniline	r.t., 16 hrs	Acetanilide, 59%
Stearic	Aniline	r.t., 16 hrs	Stearanilide, 70%
Benzoic	Aniline	reflux, 1 hr	Benzanilide, 70%
p-Toluic	Aniline	r.t., 16 hrs	p-Toluanilide, 36%
p-Toluic	Aniline	reflux, 1 hr	p-Toluanilide, 70%
Benzoic	Cyclohexylamine	r.t., 16 hrs	N-Cyclohexylbenzamide, 25%
Benzoic	Cyclohexylamine	reflux, 1 hr	N-Cyclohexylbenzamide, 90%
Benzoic	t-Butylamine	reflux, 1 hr	N-t-Butylbenzamide, 68%
Benzoic	2,4,6-Mesidine	reflux, 1 hr	N-2,4,6-trimethyl-phenylbenzamide, 80%
2,4,6-Mesitoic	Aniline	reflux, 2 hrs	2,4,6-Trimethyl-benzanilide, 23%
Acetic	N-Methylaniline	40-50°, 1 hr,N	N-Methylacetanilide, 75%

necessary, the yield of amide was, at best, fair. For example, in the reaction between p-toluic acid and aniline, the yield of p-toluanilide varied from 36% to 70% as the temperature increased.

Solvent-Base System: The use of pyridine as both the solvent and the base was found to be the most efficient for this reaction. Pyridine is miscible with water and the amide could usually be isolated by precipitation from the reaction mixture by pouring it onto crushed ice. Any unreacted acid would remain in the salt form which is soluble in the aqueous phase. Pyridine also has the advantage that it is quite volatile and can be evaporated off readily as this was found to be necessary sometimes during isolation. Other bases such as 2-picoline and triethylamine could also be used although the latter is quite immiscible with water and causes some difficulties during the isolation of product. The reaction was also found to proceed in neutral solvent such as acetonitrile or benzene. In this case, a stoichiometric amount of a base was added to trap the hydrogen chloride evolved during the reaction.

Variation of Stoichiometry of $SiCl_4$: Although the theoretical amount of silicon tetrachloride needed in the reaction is one mole per two moles each of acid and amine used, the yield of amide in general was found to be fair

only with this stoichiometry. The yield however could be increased by increasing the amount of the coupling reagent. High yield of product was usually obtained when a molar excess of silicon tetrachloride was used in the reaction.

Scope of Reaction: The reaction appears to be quite general for all simple carboxylic acids and amines. It was found that aliphatic, aromatic and fatty acids coupled with aniline to give good yields of the corresponding anilide. The reaction also occurred smoothly between benzoic acid and various primary alkyl, aryl and secondary amines (Table III). It is of interest to note that this method also coupled sterically hindered acids and amines quite effectively. t-Butylamine and 2,4,6-trimethylaniline reacted with benzoic acid to give N-t-butylbenzamide (68%) and N-2,4,6-trimethylphenylbenzamide (80%) respectively. On the other hand, highly steric hindered 2,4,6-trimethylbenzoic acid reacted with aniline to give 23% yield of 2,4,6-trimethylbenzanilide. Attempts to couple 2,4,6-trimethylbenzoic acid with 2,4,6-trimethylaniline failed. Both starting materials could be recovered quantitatively. This may indicate that the steric hinderance in the reaction is too great for it to occur to any significant extent.

PROPOSED MECHANISM OF REACTION

Although this coupling reaction using silicon tetrachloride in pyridine appears to be quite effective in the formation of amide bond, its mechanism is far from being clear. The observation of instantaneous precipitation during the addition of silicon tetrachloride is most likely due to the formation of $SiCl_4.Py_2$ complex which is known to form between silicon tetrachloride and pyridine[19]. This crystalline compound is insoluble in toluene, benzene, ether, dioxane and chloroform, but reacts violently with water with evolution of hydrogen chloride. It would appear that the initial step in the coupling reaction involves the decomposition of this complex into its components by the acid and the amine. The observation of gradual dissolution of the precipitate after complete addition of silicon tetrachloride seems to be in agreement with this decomposition step. The reaction would then proceed via displacement reactions to form acyloxy[17] or aminosilanes[18] (p. 8). This interpretation suggests that the complex itself has no bearing on the formation of the amide bond. The finding that this reaction also proceeds in base such as 2-picoline which is known not to complex with silicon tetrachloride[3] supports this interpretation.

The exact mode of condensation between the acyloxy and the aminosilanes to form the amide bond is not known. There are at least four different mechanisms which can be proposed and these are outlined below:

(a) The condensation can proceed via the acid chloride which conceivably could be formed from nucleophilic attack of Cl^- on the acyloxysilane (Eq. 11). Reaction between acid chloride and amine (or aminosilane) to form amide is well-documented.

$$\equiv Si\text{-}O\text{-}\overset{\overset{O}{\|}}{C}\text{-}R \longrightarrow R\text{-}\overset{\overset{O}{\|}}{C}\text{-}Cl \xrightarrow[(\text{or } \equiv Si\text{-}NHR')]{R'NH_2} R\text{-}\overset{\overset{O}{\|}}{C}\text{-}NH\text{-}R' \qquad (11)$$

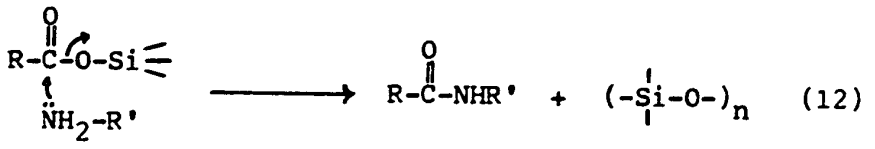
(b) The condensation can proceed via the acid anhydride which may be formed during the reaction. Recently Benkeser[44] reported that the reaction between trichlorosilane and benzoic acid in refluxing benzene gave good yield of benzoic anhydride. It may be postulated that this anhydride is formed from the thermal decomposition of benzoyloxysilanes as follows:

$$2\ \geq Si\text{-}OCO\phi \longrightarrow \phi\text{-}COOCO\text{-}\phi + (-\overset{|}{Si}\text{-}O\text{-})_n$$

$$\rangle Si(OCO\phi)_2 \longrightarrow \phi\text{-}COOCO\text{-}\phi + (-\overset{|}{Si}\text{-}O\text{-})_n$$

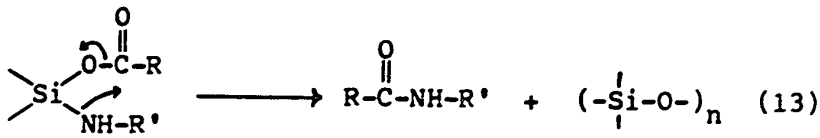
In the present condensation reaction, similar acyloxysilanes can also decompose to yield the corresponding anhydride which couples with the amine (or aminosilane) to give the amide.

(c) The condensation may proceed via a direct nucleophilic attack of the amine (or aminosilane) on the acyloxysilane which can be considered as a mixed anhydride of carboxylic acid and silicic acid. (Eq. 12)



(12)

(d) The condensation may proceed via the proposed intermediate (VIII) which has an acyloxy and an amino group attached to the same silicon. The occurrence of an intramolecular four-centered reaction between the groups can lead to amide formation (Eq. 13).



(13)

Mechanism (a) which involves the formation of acid chloride is very improbable. Silicon tetrachloride has so far not been observed to act as chlorinating agent in reaction with carboxylic acids. This is quite in contrast to

phosphorus tri- and pentachlorides which are well-known chlorinating agents. Mechanism (b) involving the acid anhydride is also unlikely. It must be mentioned that the reaction between trichlorosilane and benzoic acid reported by Benkeser[59] occurred only under thermal condition*. Decomposition of the acyloxysilane to the anhydride is not likely to take place at room temperature#. It would seem therefore that if the present condensation reaction were to proceed through the acid anhydride, amide bond formation should not have been observed when the reaction was carried out at room temperature. However the fact that the reaction does proceed at rather mild conditions (although the yield in general is lower) suggests the need to have other mechanisms to explain the formation of product+.

Mechanism (c) and (d) are the more probable ones by which the present condensation reaction may proceed. Although it appears quite difficult to present an unambiguous

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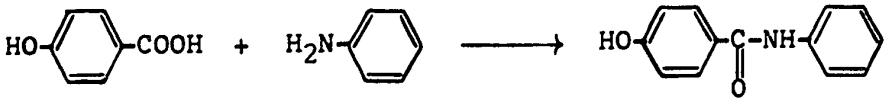
* Even though Benkeser reported that good yield of benzoic anhydride was formed by heating the mixture in benzene solution (80°C), he was not sure whether the anhydride was actually formed under the refluxing condition or at the distillation of product which must involve a higher temperature. It might very well be that the decomposition of acyloxysilanes to the anhydride does not take place at 80°C.

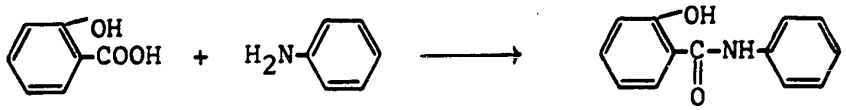
For example, Dandegaonker[33] reported that tetraacyloxysilanes decompose only at > 200° to give good yields of anhydrides.

+ This anhydride mechanism cannot be totally ruled out for the present reaction when carried out at refluxing pyridine.

distinction between these two alternatives, nevertheless there is evidence to believe that mechanism (d) prevails. This is based on two experimental observations:-

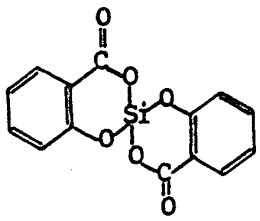


(50%)



(<1%)

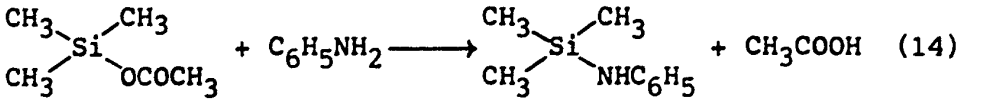
(i) The coupling between p-hydroxybenzoic acid and aniline with silicon tetrachloride proceeded smoothly to give 50% yield of p-hydroxybenzanilide. The same reaction carried out with salicylic acid however gave less than one percent of salicylanilide. The result is explicable if it is realized that salicylic acid reacts with silicon tetrachloride to form silicon disalicylate[17] (IX) whereas the corresponding spiro-compound cannot



(IX)

be formed with p-hydroxybenzoic acid. Formation of silicon disalicylate thus prevents the formation of intermediate VIII for coupling reaction. On the other hand, if the reaction were to go through mechanism (c) which involves a nucleophilic attack of the amine (or aminosilane) on the acyloxysilane, then it would be difficult to see why such an attack on the carbonyl of silicon disalicylate cannot take place to give salicylanilide. From this argument, mechanism (d) is the favored one.

(ii) The second evidence is based on the reactions between acetoxysilanes and aniline. Mehrotra[17] reported that the following reactions (Eq. 14-16) occurred exothermically and quantitatively:



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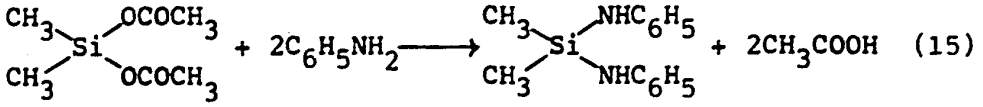


(15)

$$Si(OCOCH_3)_4 + 4C_6H_5NH_2 \longrightarrow Si(NHC_6H_5)_4 + 4CH_3COOH \quad (16)$$

However it would appear that in reactions 15 and 16, the initial displacement of an acetoxy group by a mole of aniline would result in the formation of an inter-

mediate similar to VIII (ie, one which has an acyloxy group and an amino group attaching to the same silicon atom). As mentioned previously (p. 9), this intermediate should decompose favorably to give amide and polysiloxane (or silica). The argument suggests that acetanilide rather than the aminosilanes should be formed from these reactions. From this consideration, it was decided to reinvestigate the reaction between acetoxysilanes and aniline. The results are shown below (Eq. 17, 18):

$$(CH_3)_2Si(OCOCH_3)_2 + C_6H_5\text{-}NH_2 \longrightarrow CH_3\text{-}CO\text{-}NH\text{-}C_6H_5 + \left(\begin{array}{c} CH_3 \\ | \\ -Si-O- \\ | \\ CH_3 \end{array}\right)_n \qquad (17)$$

$$Si(OCOCH_3)_4 + C_6H_5\text{-}NH_2 \longrightarrow CH_3\text{-}CO\text{-}NH\text{-}C_6H_5 + (SiO_2)_n \qquad (18)$$

We found that acetanilide formation (yield: 50-80%) was actually observed in both cases. It is not clear to us why the present results should be different from that reported by Mehrotra. However this finding seems to strengthen considerably the belief that mechanism (d) is indeed the mechanism of choice for the inter-

pretation of amide bond formation from reactions involving acyloxy and aminosilanes.

It should be mentioned that no detail investigation was made on the stoichiometry of aniline for the above reactions. Brief studies on reaction 18, using two and four moles of aniline, resulted in the isolation of two molar yields of acetanilide from both cases. Most probably this reaction proceeds with the elimination of two moles of acetic acid according to the following representation (Eq. 19):

$$Si(OCOCH_3)_4 + 2\ C_6H_5\text{-}NH_2 \longrightarrow$$

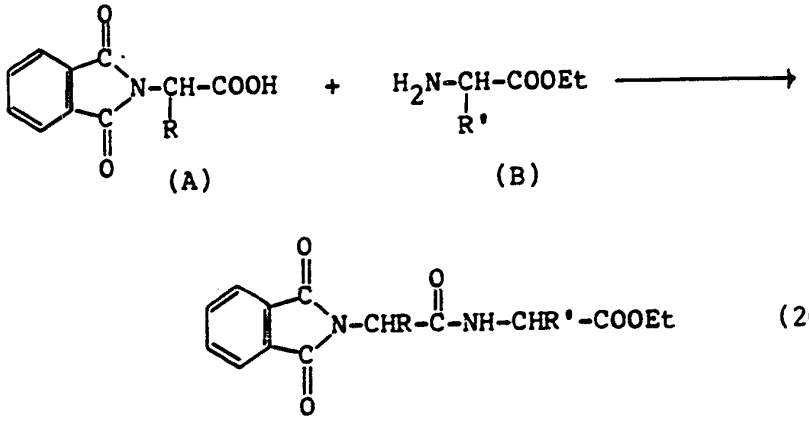
$$2\ CH_3CO\text{-}NH\text{-}C_6H_5 + 2\ CH_3COOH + (SiO_2)_n \qquad (19)$$

No further studies were made in greater depth on the mechanism of this coupling reaction. Instead, attention was turned to the investigation on the application of this novel coupling procedure in the field of peptide synthesis. Even though a large number of coupling methods are now available for linking peptide bonds, no one method can be applied universally for all purposes. Therefore it appears worthwhile to us to study the feasibility of using silicon tetrachloride for effecting peptide bond formation.

PEPTIDE SYNTHESIS

Historical Background

Perhaps the most important use of amide bond formation is illustrated in the field of peptide synthesis where α-amino acids are linked together. An α-amino acid has two functional groups, viz, an amino group and an acid group. To join up a peptide systematically, one of the functional group is usually blocked during the coupling reaction and then deblocked afterwards[20]. A general representation is shown in Eq. 20 where the amino function of the amino acid A is protected by the phthaloyl group



(A) (B)

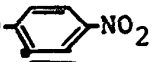
(20)

(Phth) and the acid function of amino acid B is being converted into an ester (-OEt). Other common amino protecting

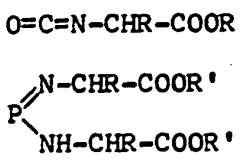
groups include the trifluoroacetyl (Tfa), formyl (For), trityl (Tri), benzyloxycarbonyl (Z) and t-butyloxycarbonyl (Boc) groups. The acetyl (Ac) and benzoyl (Bz) groups are less employed because they can only be removed under drastic conditions which could cleave other amide linkages as well. However they are used extensively for racemization studies. The esters, e.g. methyl, ethyl and benzyl esters, are often used as acid protecting groups.

In a peptide synthesis, the appropriately protected amino acids are joined together by a coupling reagent. A brief summary of the numerous coupling methods reported in the literature can be mentioned[20]. They can generally be classified into three categories:-

(a) Reactive derivatives of the carbonyl component: The carboxylic acid function is being activated into the

X-NH-CHR-CO-N_3	azide
X-NH-CHR-CO-Cl	acid chloride
X-NH-CHR-COOCO-R'	acid anhydride
X-NH-CHR-COO- 	active ester
X-NH-CHR-CO- 	active amide

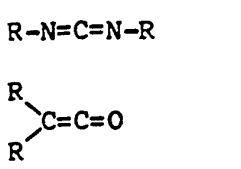
(b) Reactive derivatives of the amino component: These include the



isocyanate

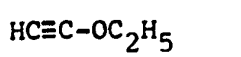
phosphazo intermediate

(c) Coupling reagents: These are compounds which on addition to a mixture of an acid and an amine afford the formation of amide bond. This class includes the



carbodiimide

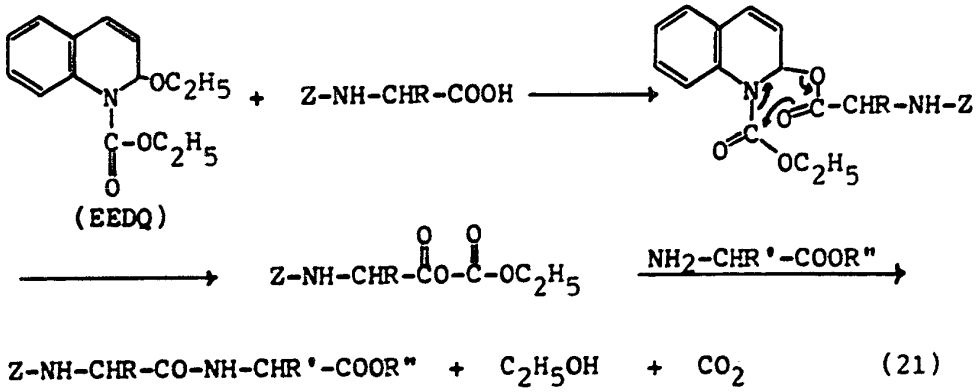
ketene



ethoxyacetylene

cyanoacetylene

Recently there are numerous novel coupling methods reported. A new and useful coupling reagent is N-ethoxy-carbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ), discovered by Belleau[22]. Peptide condensation with this reagent is believed to proceed through the acid anhydride intermediate



(EEDQ)

(21)

according to Eq. 21. Mukaiyama and co-workers[23] reported a new oxidation-reduction condensation method for peptide synthesis using sulfenamide, acid copper salt and triphenylphosphine (Eq. 22). This method was later extended

$$(RCOO)_2Cu + 2\ R'\text{-}S\text{-}NR''_2 + 2\ (C_6H_5)_3P \longrightarrow 2\ R\text{-}CO\text{-}NR''_2 + (R'S)_2Cu + 2\ (C_6H_5)_3P{=}O \quad (22)$$

into a more convenient preparative procedure using dipyridinedisulfide and triphenylphosphine along with the appropriately protected amino acids[56] (Eq. 23). Kenner

$$X\text{-}NH\text{-}CHR'\text{-}COOH + H_2N\text{-}CHR''\text{-}COOY + (C_6H_5)_3P + \left(\text{N}\!\!\diagup\!\!\text{S-}\right)_2 \longrightarrow X\text{-}NH\text{-}CHR'CONH\text{-}CHR''COOY + (C_6H_5)_3P{=}O + 2\ \text{N(H)}\!\!=\!\!\text{S} \quad (23)$$

and co-workers[24] was also able to effect peptide bond formation by employing acyloxyphosphonium salts as acylating agents (Eq. 24).

$$(Me_2N)_3\overset{+}{N}\text{-}O\text{-}\overset{+}{P}(NMe_2)_3.2TsO^- \xrightarrow{RCOO^-} RCOO\text{-}\overset{+}{P}(NMe_2)_3.TsO^- \xrightarrow{R'NH_2} RCO\text{-}NHR' + (Me_2N)_3P{=}O \quad (24)$$

Very recently, Pelter[45] reported a new amide forming reaction involving, for the first time, boron reagent. The acyloxydialkoxyborane (X) was found to react with amine to give amide. However, application of this coupling method

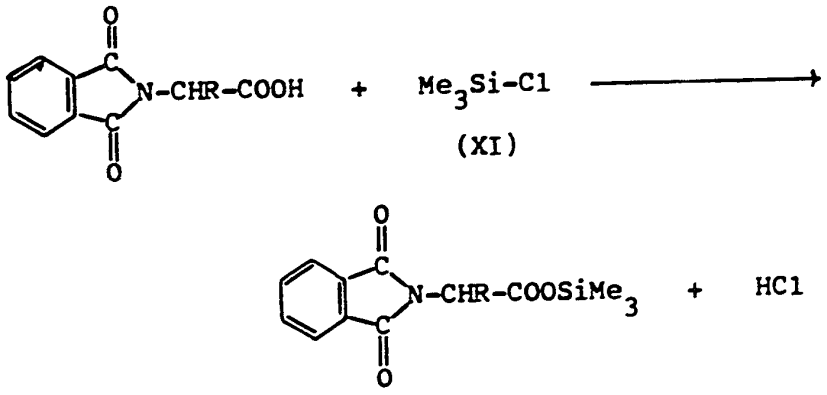
for peptide synthesis afforded dipeptide only in low yield (Eq. 25). The low conversion achieved therefore does not make this approach of value, in practice.

$$RCOOB(OMe)_2 \xrightarrow{\text{amine}} \text{Amide}$$

(X)

$$PhCONH\text{-}CH(CH_2CH(CH_3)_2)\text{-}COO^-Na^+ + ClB(OMe)_2 \longrightarrow \left[PhCONH\text{-}CH(CH_2CH(CH_3)_2)\text{-}COOB(OMe)_2\right] \xrightarrow{H_2N\text{-}CH_2\text{-}COOEt} PhCONH\text{-}CH(CH_2CH(CH_3)_2)\text{-}CO\text{-}NH\text{-}CH_2\text{-}COOEt \quad (25)$$

Organosilicon compounds, such as trimethylchlorosilane (XI)[46], hexamethyldisilazane (XII)[25] and bis(trimethylsilyl)-acetamide (XIII)[26], have been used extensively in peptide chemistry as silylating agents (Eq. 26-28).



(26)

$$H_2N\text{-}CHR\text{-}COOH + Me_3Si\text{-}NH\text{-}SiMe_3 \longrightarrow \underset{(XII)}{} \quad R\text{-}\underset{\underset{NH\text{-}SiMe_3}{|}}{CH}\text{-}COOSiMe_3 + HCl \qquad (27)$$

$$CH_3\text{-}\underset{\underset{OH}{|}}{CH}\text{-}\underset{\underset{NH_2}{|}}{CH}\text{-}COOH + CH_3\text{-}\underset{\underset{NSiMe_3}{\|}}{C}\text{-}OSiMe_3 \ (XIII) \longrightarrow$$

$$CH_3\text{-}CH(OSiMe_3)\text{-}\underset{\underset{NHSiMe_3}{|}}{CH}\text{-}COOSiMe_3 \qquad (28)$$

Silylated amino acids are readily volatile and can be analysed by gas chromatography. Birkofer and co-workers[47] also reported the use of silylated amino acids for peptide synthesis (Eq. 29). Peptides with as many as five α-amino acids were synthesized in this way with high yield of product per step.

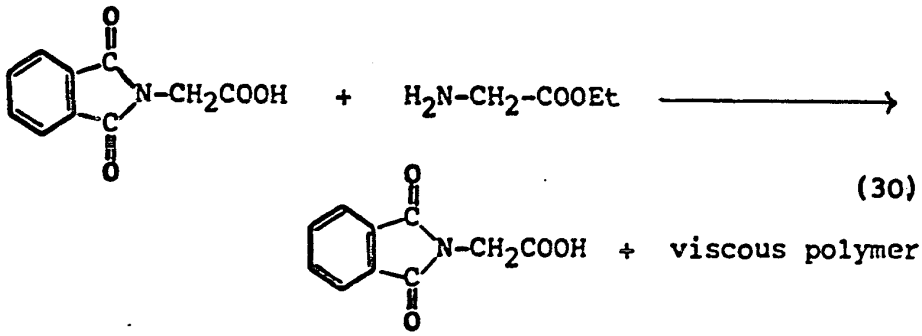
$$X\text{-}NH\text{-}CHR\text{-}COOH + ClCOOEt \longrightarrow X\text{-}NH\text{-}CHR\text{-}COOCOEt$$
$$\underline{TMS\text{-}NH\text{-}CHR\text{-}COOTMS} \rightarrow X\text{-}NH\text{-}CHR\text{-}CONHCHR'\text{-}COOTMS + CO_2 + C_2H_5OTMS \qquad (29)$$

However thus far, there has no report in the literature on the practical application of organosilicon compounds as coupling reagents for peptide formation. In view of our finding that silicon tetrachloride can effect the coupling of amide bonds from simple carboxylic acids and amines, ex-

periments were carried out to test the validity of this reagent for peptide synthesis.

Results

In preliminary work, the reaction between phthaloyl-DL-phenylalanine (Phth-DL-Phe), aniline and $SiCl_4$ was carried out by refluxing the mixture for two hours in pyridine. Phthaloyl-DL-phenylalanine-anilide was obtained in 57% yield. Using the same conditions, the reaction between benzoic acid and ethyl glycinate however failed to give any benzoylglycine ethyl ester (Bz-Gly-OEt). Benzoic acid was recovered quantitatively from the reaction mixture after hydrolysis. Attempt to recover the starting amino ester was unsuccessful, but instead, a viscous polymeric compound was obtained. Coupling between phthaloylglycine and ethyl glycinate was also tried, the dipeptide again was not obtained. The starting phthaloylglycine could be recovered, but attempt to obtain the amino ester failed (Eq. 30). It seems that in the above

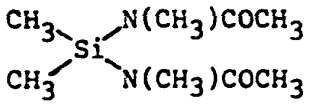


(30)

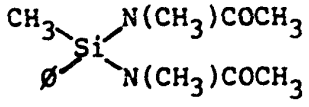
reactions involving ethyl glycinate, the amino ester was being polymerized by silicon tetrachloride to polyglycine. Therefore normal peptide bond formation was not observed in these reactions. Such a polymerization reaction has also been reported by Birkofer and Ritter (Eq. 31)[27].

$$H_2N\text{-}CH_2COOEt + SiCl_4 \longrightarrow Si(OC_2H_5)_4 + (\text{-}NH\text{-}CH_2CO\text{-})_n \quad (31)$$

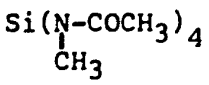
It becomes quite clear that silicon tetrachloride itself cannot be used to couple dipeptide because of the facile polymerization of the amino ester. Work was then carried out to modify this amide coupling procedure for peptide synthesis. Recently, Klebe and Finkleiner[28] prepared compounds (XIV) and (XV) from the corresponding chlorosilane and N-methylacetamide in the presence of triethylamine.The acetamide group can be replaced easily by either an acyloxy group or an amino group in a stepwise manner. It appeared therefore reasonable to expect that a compound such as (XVI) can replace silicon tetrachloride as the coupling reagent. The acetamide formed during the reaction



(XIV)



(XV)



(XVI)

should in no way affect the coupling reaction. However attempts to prepare compound (XVI) by reaction of one mole

of silicon tetrachloride with four moles of N-methylacetamide in the presence of triethylamine were not successful. No characterizable compound could be isolated from the reactions.

Another approach to the problem is to make use of tetraacyloxysilane as the acylating agent (p. 21). It was observed that tetraacetoxysilane reacted with aniline to give acetanilide (Eq. 19). Tetraacetoxysilane was also found to react with DL-leucine methyl ester (DL-Leu-OMe) to yield 54% of acetyl-DL-leucine methyl ester (Ac-DL-Leu-OMe). Hence it should be feasible to synthesize peptide according to the following equation (Eq. 32):

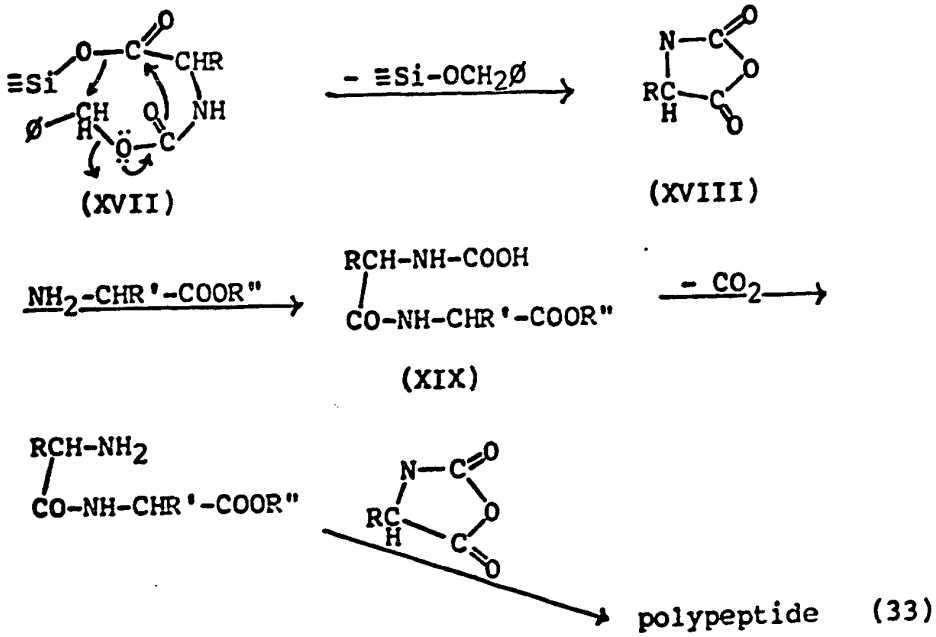
$$\begin{aligned} &\text{X-NH-CHR-COOH} + \text{SiCl}_4 \longrightarrow (\text{X-NH-CHR-COO})_4\text{Si} \\ &\underline{\text{NH}_2\text{-CHR'-COOCH}_3} \longrightarrow \text{X-NH-CHR-CONH-CHR'COOCH}_3 \end{aligned} \qquad (32)$$

Indeed, it was found that dipeptide could be obtained by this stepwise procedure in fair to good yields. The appropriately N-protected amino acid was converted to the tetraacyloxysilane by heating four moles of the amino acid with one mole of silicon tetrachloride in pyridine for thirty minutes to two hours. The resultant tetraacyloxysilane was not isolated and was allowed to react <u>in situ</u> immediately. To the reaction mixture, the amino ester was added and the mixture was stirred at room temperature overnight. The

solvent was evaporated in vacuo at 40° and the residue was decomposed with water. The organic material was extracted with ethyl acetate. The ethyl acetate solution, after washing with dilute aqueous hydrochloric acid and sodium bicarbonate solutions, was evaporated to yield the crystalline dipeptide. The yields were moderate in most cases, however there was no effort to optimise the conditions. In this way, a number of phthaloyl-(Phth), benzoyl-(Bz) and acetyl-(Ac) amino acids were condensed with various methyl and ethyl amino esters (Table IV).

The use of benzyloxycarbonyl-(Z) as N-protecting group was found to offer considerable difficulties due to its instability in the presence of silicon tetrachloride. By carrying out the tetraacyloxysilane formation at lower temperature (50-60°), benzyloxycarbonylglycine coupled smoothly with various amino esters to give fair yields of the corresponding dipeptide. However, with other benzyloxycarbonyl-amino acids e.g. Z-alanine, Z-leucine, the yields of dipeptides in general were found to be very low. Careful isolation of products in all cases gave, aside from the expected dipeptide, a polymeric material and another product identified as tetrabenzyloxysilane. The formation of tetrabenzyloxysilane can only arise from the cleavage of the Z-group from the Z-amino acids. This cleavage was at first thought to be caused by the hydrogen chloride released in

the reaction. It appeared reasonable since the Z-protecting group is usually removed by hydrochloric[48] or hydrobromic[49] acids. In order to avert this cleavage, tetraacyloxysilane formation was performed by refluxing the sodium salts of the Z-amino acids with silicon tetrachloride in acetonitrile:benzene solvent mixture. However the same cleavage of the Z-group occurred. While the mode of formation of both the polymer and tetrabenzyloxysilane is not very clear, it is likely that the benzyloxycarbonyl-amino acid-silylester (XVII) upon heating decomposed to give benzyloxysilane and the Leuchs' anhydride (XVIII). The latter compound is known to react with amino ester to give the



(XVII) (XVIII) (XIX) (33)

carbamate intermediate (XIX) which on losing carbon dioxide regenerates a free amino group that reacts further with the Leuch's anhydride to form polypeptide (Eq. 33).

Our studies show that silicon tetrachloride can be employed for peptide synthesis through the initial formation of tetraacyloxysilane intermediate. The discovery, however, that benzyloxycarbonyl-protecting group undergoes cleavage during the reaction causes a set back to the general utility of the present coupling procedure. The benzyloxycarbonyl-(Z) substituent can be considered as the most satisfactory amino-protecting group in peptide synthesis. Not only can the group be easily introduced before and removed after the reaction, but most important of all, it shows little or no tendency to induce the racemization of the amino acid during peptide synthesis.

TABLE IV

DIPEPTIDE FORMATION WITH SILICON TETRACHLORIDE

Acid	Amine	Dipeptide	Conditions of tetra-acyloxysilane formation	Yield
Phth-Gly	L-Leu-OMe	Phth-Gly-Leu-OMe[a]	110°, pyridine, 30 mins.	48%
Phth-Gly	Gly-OEt	Phth-Gly-Gly-OEt	110°, pyridine, 30 mins.	45%
Phth-DL-Ala	DL-Ala-OEt	Phth-DL-Ala-DL-Ala-OEt	110°, pyridine, 2 hrs.	51%
Bz-DL-Ala	DL-Ala-OEt	Bz-DL-Ala-DL-Ala-OEt	110°, pyridine, 1 hr.	58%
Bz-L-Leu	Gly-OEt	Bz-Leu-Gly-OEt[b]	110°, pyridine, 45 mins.	65%
Bz-L-Leu	Gly-OEt	Bz-Leu-Gly-OEt[b]	sodium salt, CH_3CN-C_6H_6	62%
Ac-DL-Phe	DL-Ala-OEt	Ac-DL-Phe-DL-Ala-OEt	110°, pyridine, 1 hr.	60%
Ac-L-Phe	L-Ala-OMe	Ac-Phe-Ala-OMe[c]	110°, pyridine, 1 hr.	43%
Ac-L-Ala	L-Phe-OMe	Ac-Ala-Phe-OMe[d]	110°, pyridine, 30 mins.	44%
Z-Gly	Gly-OEt	Z-Gly-Gly-OEt	60°, pyridine, 1⅓ hr.	70%
Z-Gly	DL-Ala-OEt	Z-Gly-DL-Ala-OEt	60°, pyridine, 1⅓ hr.	54%
Z-DL-Ala	Gly-OEt	Z-DL-Ala-Gly-OEt	60°, pyridine, 1½ hr.	15%

a $-[\alpha]_D^{20} = +5.9^{\circ}$ (c 3.6, $CHCl_3$)

b - complete racemic product was obtained

c - 40% D-L isomer according to NMR

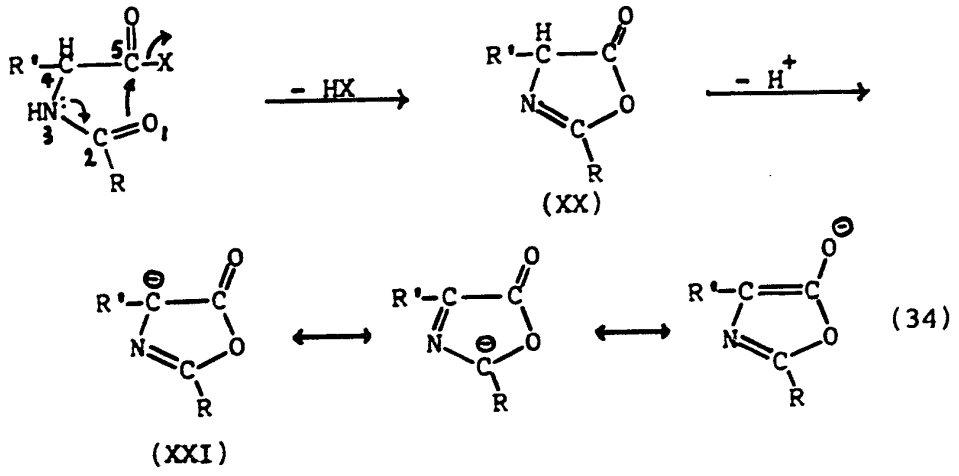
d - 50% D-L isomer according to NMR

RACEMIZATION STUDIES

Mechanisms of Racemization

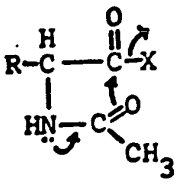
One of the greatest concern to chemist in peptide synthesis is the problem of racemization, i.e. lost of optical purity of the amino acids. There are two mechanisms put forward to explain racemization of peptide during the course of reaction. They are: (a) the formation of oxazolone (azlactone) intermediate, and (b) proton abstraction from the asymmetric alpha carbon.

Bergmaun and Zervas[29] first assumed the formation of oxazolone intermediate to explain the racemization observed during the acylation of amino acids. The mechanism can be depicted by Eq. 34. Elimination of HX, where X is

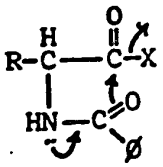


(34)

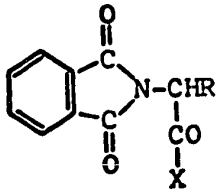
a good leaving group, leads to the oxazolone structure (XX). Oxazolone is known to racemize easily by the loss of proton at carbon 4, a reaction catalysed by base, to produce the oxazolone anion (XXI, several resonance structures indicated). This leads to the loss of optical activity. Amino-protecting groups which involve a monoacylation of the amino nitrogen generally show great tendency to form oxazolones. Examples are the acetyl (XXII) and benzoyl (XXIII) groups. On the other hand those which involve a



(XXII)

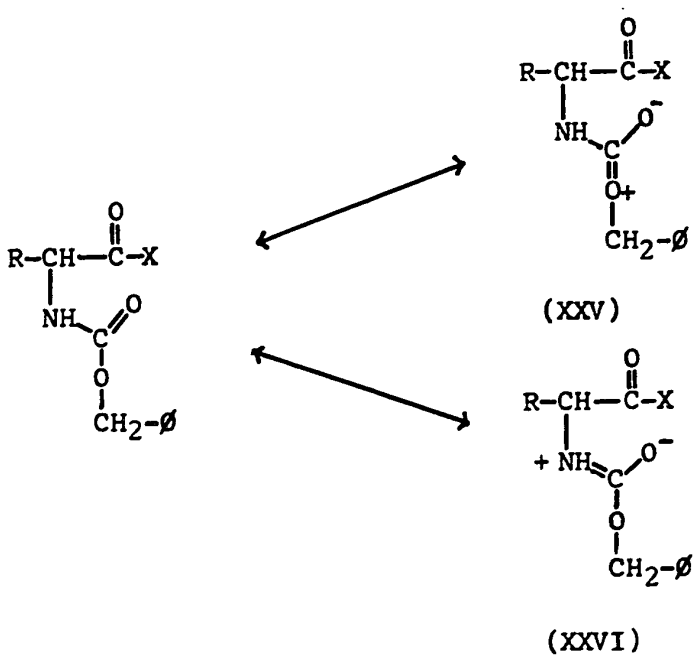


(XXIII)



(XXIV)

diacylation of the amino nitrogen show little tendency for oxazolone formation. This is exemplified by the phthaloyl protecting group (XXIV). However there is a monoacylating protecting group, the benzyloxycarbonyl group, which also shows no tendency to form oxazolone. This property may be explained by resonance consideration (Eq. 35). Of the two resonance structures XXV and XXVI, XXV is expected to be the major contribution. Since structure XXVI which can lead to oxazolone intermediate is the minor contribution, the benzyloxycarbonyl group therefore shows little tendency to cause racemization of amino acid.

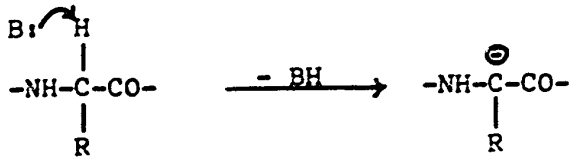


(XXV)

(XXVI)

(35)

Even though N-phthaloyl and N-benzyloxycarbonyl-amino acids show no tendency to form oxazolones, there are a number of their active esters which do undergo base catalysed racemization. This fact renders the oxazolone mechanism alone insufficient to explain the problem. An additional mechanism has been postulated which involves direct proton abstraction from the asymmetric alpha carbon atom (Eq. 36)[50-52]. It is generally accepted that either one or both mechanisms can proceed during racemization.



(36)

The problem of racemization during peptide bond formation is a very complicating and conflicting one. Indeed racemization is influenced greatly by the amino-protecting groups, the individual amino acids, and the coupling procedure employed. As mentioned above, benzyloxycarbonyl and phthaloyl amino-protecting groups are less inclined to cause racemization because they lack the tendency to form oxazolones. Amino acids with electronegative substituents in the beta position-such as cysteine, serine, phenylalanine and histidine—are the most easily racemized. Presumably the electron withdrawing effect of the substituent facilitates proton abstraction from the alpha carbon. Finally, with the exception of the azide method, all other coupling procedures can cause various degrees of racemization depending on the conditions in which they are employed. It would remain interesting to investigate if the present coupling method involving silicon tetrachloride causes racemization during peptide synthesis.

Detection of Racemization

Although acetyl and benzoyl amino-protecting groups are not commonly used in peptide synthesis, they are widely used for racemization studies. This is because they are very liable to cause racemization via oxazolone intermediates. The extent of racemization during peptide formation

using silicon tetrachloride as coupling reagent was examined by two methods:-

(i) NMR method - Recently, Halpern et al[31] proposed the use of nmr for the detection of racemization during peptide synthesis. In the coupling reaction between Ac-L-Phe and L-Ala-OMe (or Ac-L-Ala and L-Phe-OMe), the diastereoisomers of this dipeptide were shown to possess differences in their nmr spectra. The C-Me doublet signal for the L-L (or D-D) compound was found to be at lower field (7.5 Hertz) than the corresponding signal for the D-L (or L-D) isomer due to the deshielding effect of the phenyl group. By measuring the relative intensities of their nmr signals, a quantitative analysis of the diastereoisomers' ratio can be obtained without isolation. The amount of each diastereoisomer detected should therefore reflect the degree of racemization. Using this method, the Ac-Phe-Ala-OMe dipeptide obtained with silicon tetrachloride was found to contain 40% of the D-L diastereoisomer (fig. 1). Halpern[31] reported that using dicyclohexylcarbodiimide (DCC) and 2-ethyl-5-phenyl-isoxazolium-3'-sulfonate (K) as coupling reagents, the D-L isomer in the product was 50% and 6% respectively. The Ac-Ala-Phe-OMe dipeptide was also coupled using

the present procedure (fig. 2) and the percent racemization compared with that of other coupling methods (Table V). Even though silicon tetrachloride appears to give slightly better results than the well-known coupling reagent DCC, extensive racemization of product nevertheless has occurred during the reaction.

(ii) Young's test for racemization - Young[32] reported that when benzoyl-L-leucine is condensed with ethyl glycinate, the crude benzoyl-leucylglycine ethyl ester obtained has a high degree of chemical purity and is always a crystalline solid. The optically pure Bz-L-Leu-Gly-OEt has an optical rotation of -34.0° (c= 2-4, EtOH). By measuring the optical rotation of the dipeptide prepared by a coupling procedure in comparison with the value of -34.0 for pure compound, the degree of racemization during the coupling reaction can be calculated. For example, a difference of -17.0° would mean that a 50% racemization of product has occurred. Using this test, the present method of peptide synthesis gave essentially racemic Bz-Leu-Gly-OEt ($[\alpha]_D^{20} < 1^{\circ}$). This, in comparison with other coupling methods (Table VI), places the present method in an untenable position. The extensive racemization cannot be solely due to the presence of pyridine because, using the sodium salt

Fig. 1 NMR METHOD FOR DETECTION OF RACEMIZATION

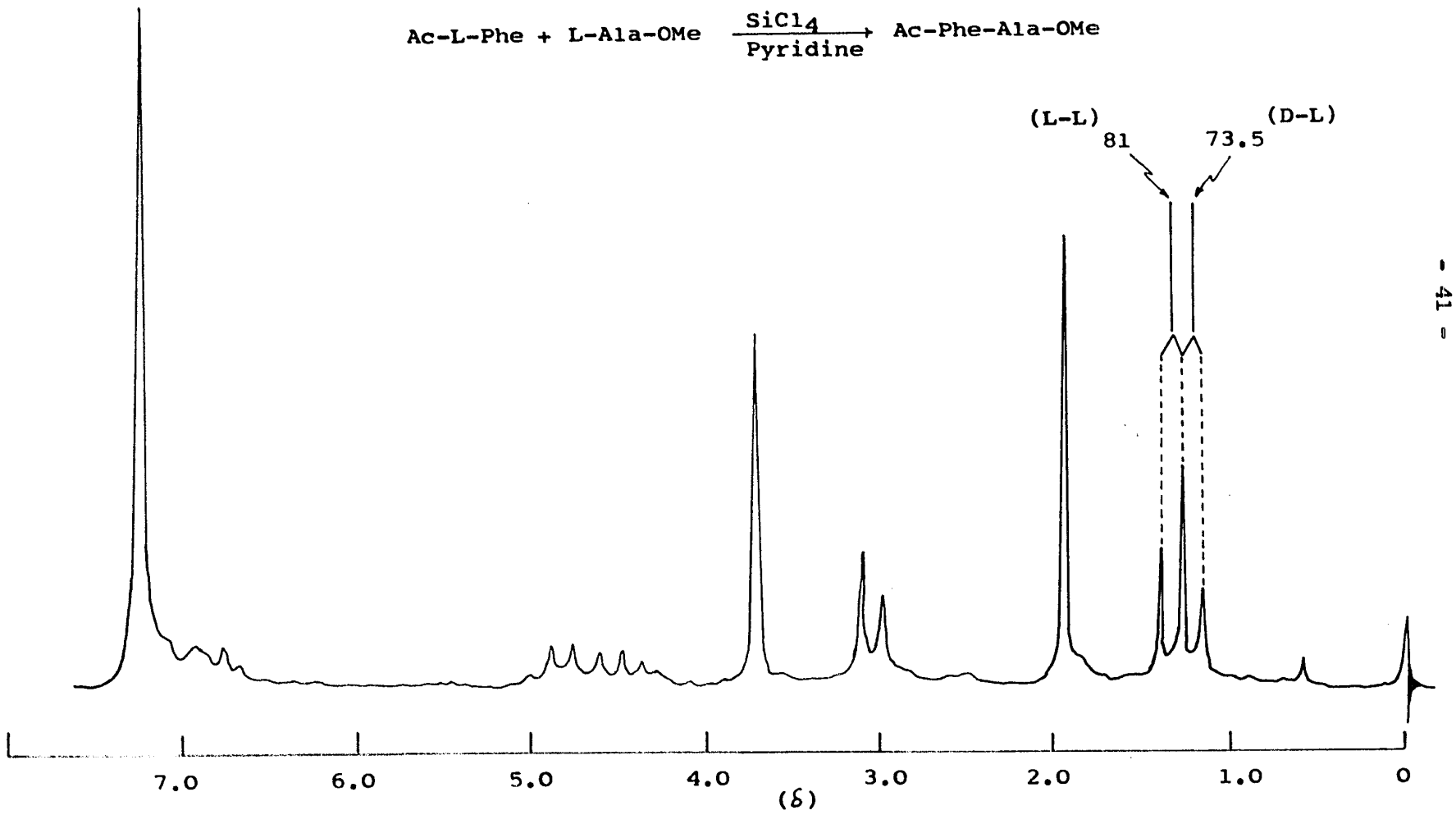


Fig.2 NMR METHOD FOR DETECTION OF RACEMIZATION

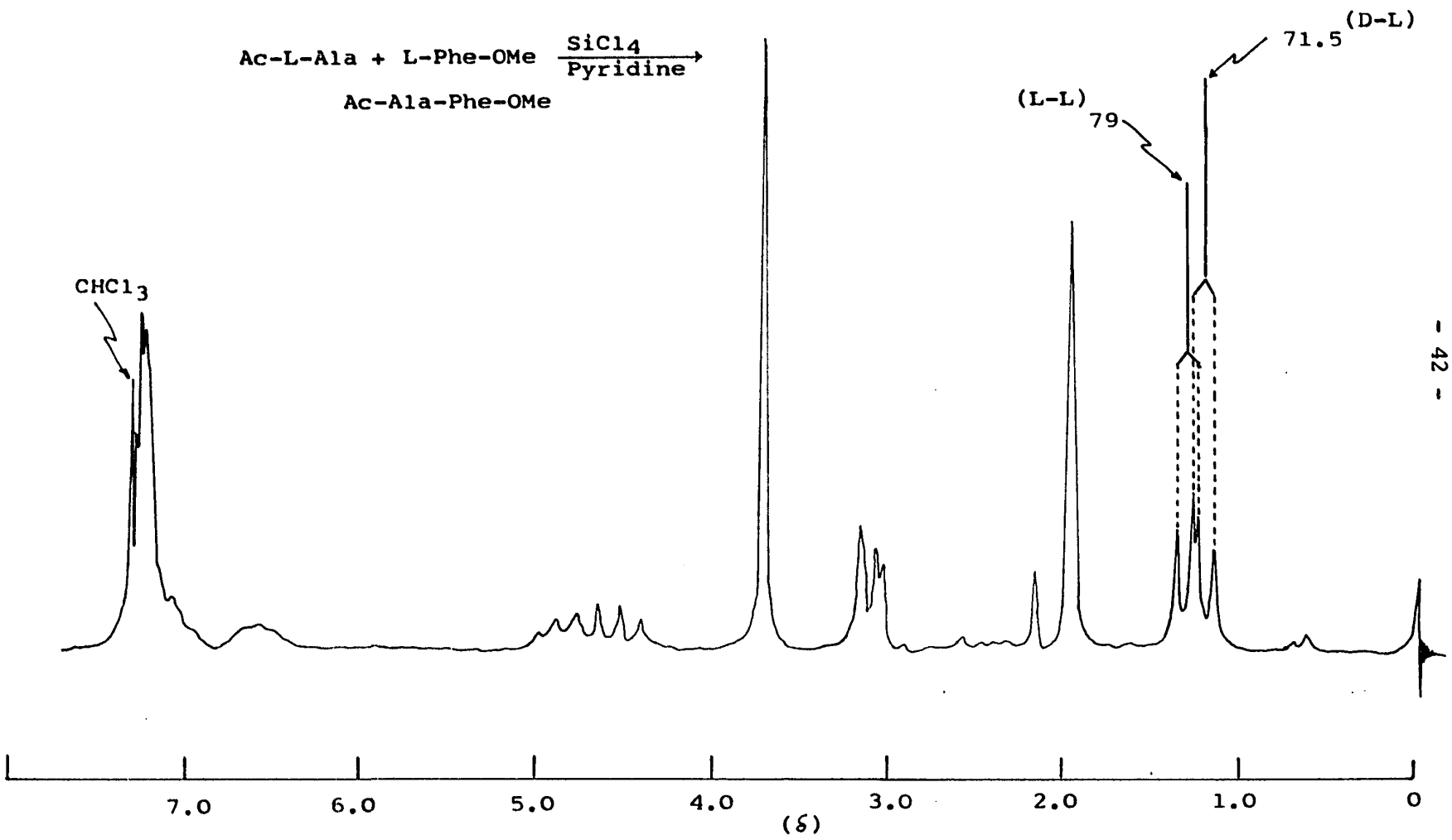


Fig. 3 NMR METHOD FOR DETECTION OF RACEMIZATION

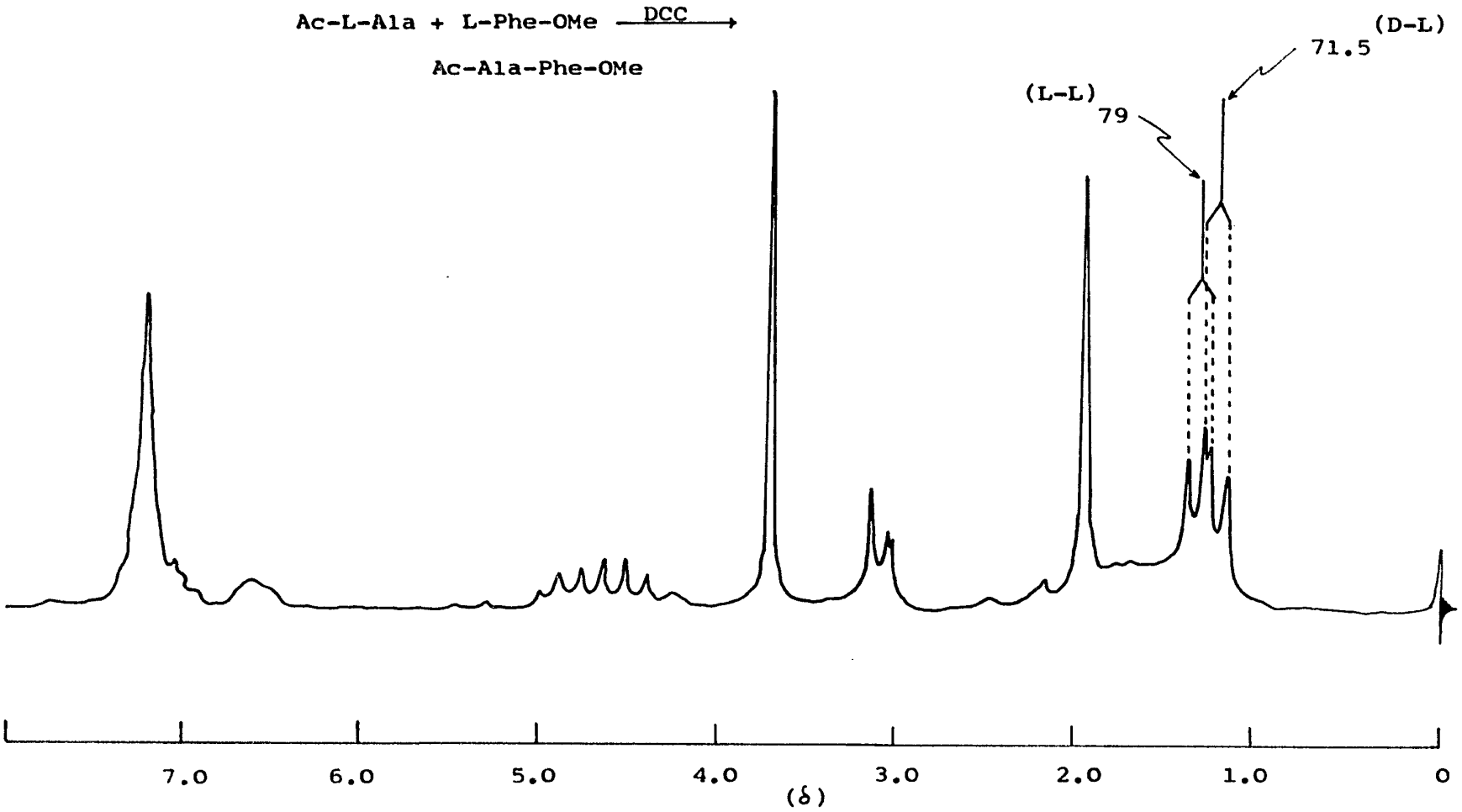


TABLE V

NUCLEAR MAGNETIC RESONANCE METHOD FOR DETECTION OF RACEMIZATION DURING PEPTIDE BOND FORMATION

Amino acid	Amino ester	% D-L(L-D) in product with coupling reagent			Methyl resonance (Hz)	
		K	DCC	$SiCl_4$	L-L	D-L
Ac-L-Phe	L-Ala-OMe	6[a]	50[a]	40	81	73.5
Ac-L-Ala	L-Phe-OMe	3[a]	50[b]	50	79	71.5

a- Data obtained from Halpern[31].

b- Halpern reported a value of 35%.

TABLE VI

YOUNG'S SUPERSENSITIVE TEST FOR RACEMIZATION DETECTION

Bz-L-Leu + Gly-OEt ⟶ Bz-Leu-Gly-OEt

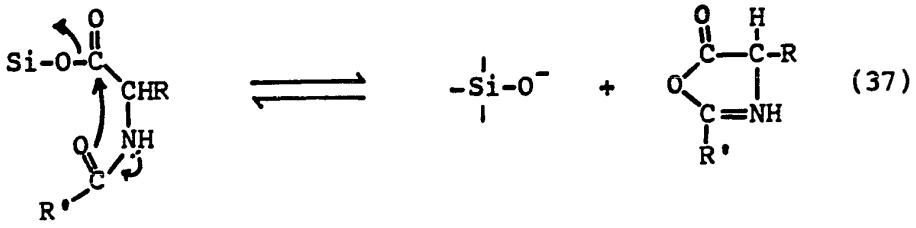
Method	$[\alpha]_D$	% L-isomer in excess of D-isomer
Dicyclohexylcarbodiimide, triethylamine	-5.5[a]	16
N-Ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline	-33.5	99
2-Ethyl-5-m-sulphonatophenyl-isoxazolium	-32.8[a]	96
Silicon tetrachloride, pyridine	-0.4	1
Phosphorus trichloride, pyridine	-0.6[a]	2

a - Data obtained from Young[32]

of Bz-L-Leu for the preparation of tetraacyloxysilane in acetonitrile:benzene (4:1 by volume), a racemic compound was also obtained.

The mode of racemization using silicon tetrachloride as coupling reagent is not very clear. However from the present studies, a few conclusions can be drawn. The basic solvent medium cannot be responsible for the racemization caused by α-proton abstraction since coupling reaction of Bz-L-Leu sodium salt with ethyl glycinate conducted in neutral solvent also gives totally racemic product. Hence in this reaction, the mode of racemization is more likely due to the intervention of oxazolone intermediate. An experiment was then attempted to isolate the oxazolone, 4-isobutyl-2-phenyloxazolone, which Young has reported to be a stable crystalline compound[30]. The tetraacyloxysilane was formed by heating benzoyl-L-leucine sodium salt with silicon tetrachloride for two hours. The solution was then cooled to room temperature and the solvent evaporated to give a residue which was triturated with hot n-hexane solution. The hexane solution was decanted and on evaporation gave a crystalline solid, m.p. 40-45°. It showed no optical activity in ethanol. It's infrared spectrum (fig. 4) in Nujol gave ρ_{max} at 1830 and 1665 cm^{-1}, in close accord with that reported by Young for 4-isobutyl-2-phenyloxazolone.

This finding indicates that racemization via oxazolone intermediates can take place in coupling reactions using tetraacyloxysilanes as acylating agents. The following equilibrium (Eq. 37) may very probably serve as the racemization mechanism:-



(37)

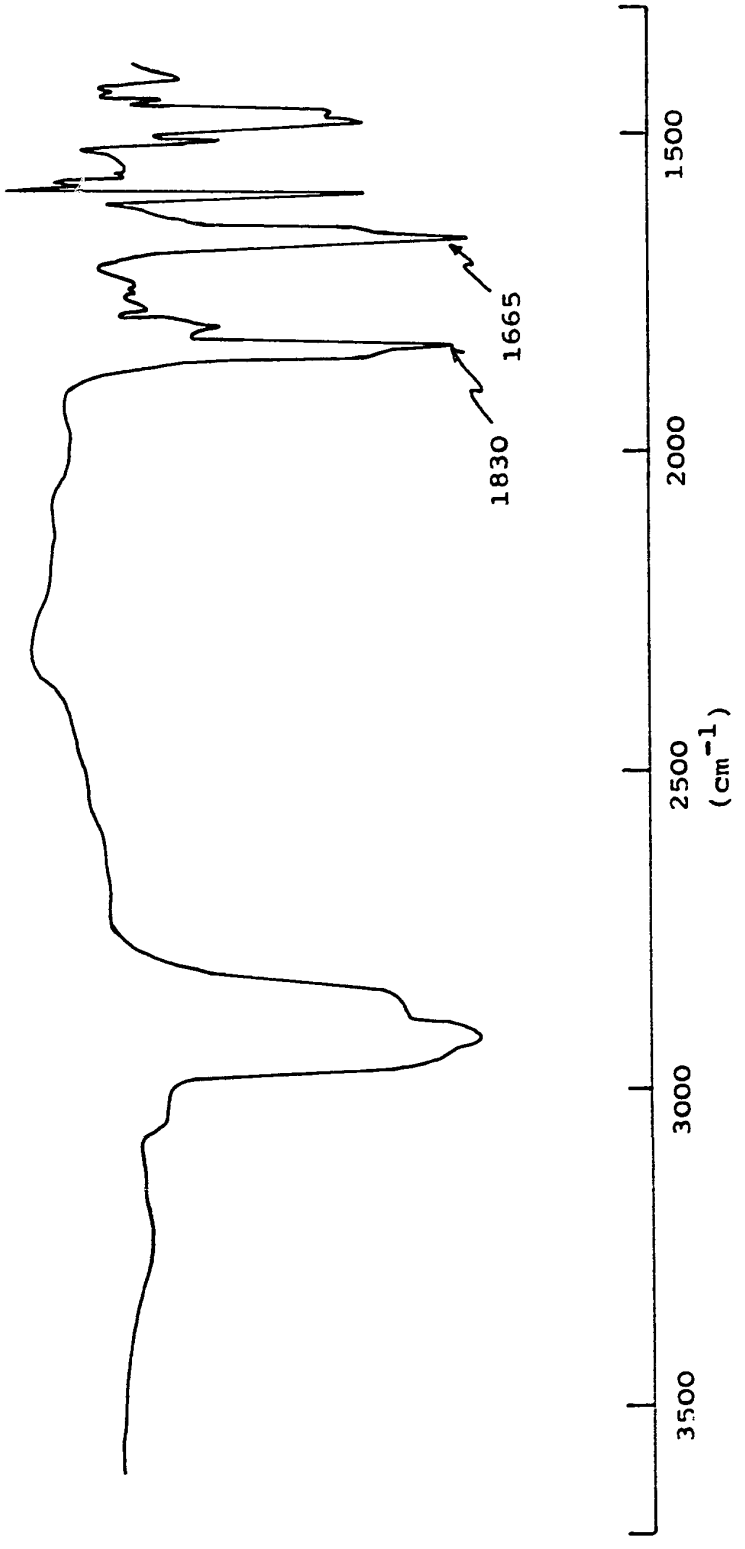


Fig.4 IR SPECTRUM OF 4-ISOBUTYL-2-PHENYLOXAZOLINE (NUJOL)

CONCLUSION

The use of silicon tetrachloride as coupling reagent for amide and peptide bond formation has been investigated. The reaction appears to be quite general for all simple aliphatic and aromatic acids and amines. Modification of this coupling method to the initial formation of tetra-acyloxysilane as acylating agent extends the use of this reagent for peptide synthesis. Coupling of dipeptides from amino acids with phthaloyl, benzoyl and acetyl as the amino protecting groups give fair to good yields of products. The use of benzyloxycarbonyl protecting group however offers considerable difficulties. The very fact that benzyloxy-carbonyl group shows instability under the reaction condition and also the extensive degree of racemization of the dipeptide produced render this coupling method not a valuable one. However some advantages of using silicon tetrachloride can be considered. The reagent itself is relatively inexpensive, and the reaction is generally clean and free of contamination with side products.

Even though this coupling procedure using silicon tetrachloride appears to be of limited value for peptide synthesis,

further work may be carried out to study kinetically the detailed mechanism of this reaction. Tetraacyloxysilanes of simple carboxylic acids are a class of well-characterized compounds which can be obtained quite readily[53,54]. Hence they may conveniently be used for model studies for this purpose. Tetraacyloxysilanes formed from amino acids on the other hand have never been isolated. In the present peptide synthesis, these acyloxysilanes were presumed to be formed from reactions between N-protected amino acids and silicon tetrachloride. Further work can therefore be carried out in this area to isolate and characterize a new class of tetraacyloxysilanes.

EXPERIMENTAL SECTION

1. All reactions with silicon tetrachloride were carried out under anhydrous conditions. Pyridine was dried over potassium hydroxide pellets and was distilled immediately prior to use.
2. Literature melting points cited with no references given are found in the " Handbook of Chemistry and Physics".
3. Melting points are not corrected.
4. Nuclear Magnetic Resonance (nmr) spectra were measured on Varian A60 or T60 spectrometers, using tetramethylsilane (TMS) as an internal standard. The following abbreviations were used in reporting the spectra: s=singlet; d=doublet; t=triplet; q=quartet; m=multiplet; h=hump.
5. Infrared (ir) spectra were taken on a Perkin-Elmer Model 237B with polystyrene calibration.
6. Mass spectra were recorded using an AEI MS-902 instrument.
7. Microanalyses were performed by Dr, C. Daesslé, Montreal.

AMIDE FORMATION, REACTION AND MECHANISM

Benzanilide: To a solution of 10 g. (0.082 mole) benzoic acid and 7.6 g. (0.082 mole) aniline in 100 ml. dry pyridine was added 10.5 g. (0.061 mole) silicon tetrachloride. The mixture was refluxed for two hours. The solution was cooled and poured into 200 ml. of ice water. The precipitate which contained benzanilide and silica was filtered and extracted with hot ethanol. Evaporation of the organic solution to dryness gave 11.2 g. (70%) benzanilide. Recrystallization from ethanol gave solid m.p. 165-166°. (Lit. m.p. 163-165°). IR absorption-ν_{max} 3345 cm^{-1} (N-H), 1660cm^{-1} (C=O), 1530, 1320 cm^{-1} (N-H, C-N).

Acetanilide: To a solution of acetic acid (2.5 g., 0.041 mole) and aniline (3.8 g., 0.041 mole) in anhydrous pyridine (50 ml.), silicon tetrachloride (4.0 g., 0.024 mole) was introduced. The mixture was stirred at room temperature overnight and then poured onto crushed ice. The precipitate (silica) was filtered and the filtrate was concentrated to an oil. On addition of a few drop of water, 3.3 g. (59%) of crystalline acetanilide precipitated out, m.p. 113°.

(Lit. m.p. 113-114°). IR absorption-ν_{max} 3265 cm^{-1} (N-H), 1660 cm^{-1} (C=O), 1540, 1320 cm^{-1} (N-H, C-N).

p-Toluanilide: To a solution of 4 g. (0.029 mole) p-toluic acid and 2.7 g. (0.029 mole) aniline in 50 ml. pyridine was added 3.8 g. (0.022 mole) of silicon tetrachloride. The solution was left stirring at room temperature overnight and then poured into 100 ml. of ice water. The precipitate which contained p-toluanilide and silica was filtered and extracted with ethanol to give 2.2 g. (36%) of product. Recrystallization from ethanol-water gave p-toluanilide, m.p. 138-141° (Lit. m.p. 140°). IR absorption-ν_{max} 3350 cm^{-1} (N-H), 1655 cm^{-1} (C=O), 1528, 1325 cm^{-1} (N-H, C-N).

A similar experiment was carried out, but the solution was refluxed for two hours after the addition of silicon tetrachloride. Isolation yielded 4.3 g. (70%) of p-toluanilide whose infrared spectrum was identical with that of the compound obtained above.

Stearanilide: To a solution of 10 g. (0.035 mole) stearic acid and 3.3 g. (0.035 mole) of aniline in 100 ml. of pyridine was added 3.75 g. (0.022 mole) of silicon tetrachloride. The mixture was stirred overnight at room temperature and then poured into 200 ml. of ice water. The precipitate was filtered and extracted with benzene. The organic solution

was dried and evaporated to dryness to yield 10 g. of crude product. Recrystallization from ethanol-water gave 8.8 g. pure stearanilide (70%), m.p. 93-94°. (Lit. m.p. 94°). IR absorption-μ_{max} 3320 cm^{-1} (N-H), 1660 cm^{-1} (C=O), 1540, 1320 cm^{-1} (N-H, C-N).

N-Cyclohexylbenzamide: To a solution of 1.22 g. (0.01 mole) benzoic acid and 1.0 g. (0.01 mole) cyclohexylamine in 20 ml. of dry pyridine was added 2 g. (0.012 mole) of silicon tetrachloride. The mixture was stirred overnight and then poured into ice water. The precipitate was filtered and extracted with ethanol. Evaporation to dryness gave 0.5 g. (25%) N-cyclohexylbenzamide, m.p. 150°. (Lit. m.p. 149°). IR absorption-μ_{max} 3240 cm^{-1} (N-H), 1630 cm^{-1} (C=O), 1550, 1330 cm^{-1} (N-H, C-N).

A similar experiment was performed, but after the addition of silicon tetrachloride the solution was refluxed for one hour. Isolation after hydrolysis gave 1.8 g. (90%) N-cyclohexylbenzamide whose infrared spectrum was identical with that of the compound obtained above.

N-t-Butylbenzamide: To a solution of 1 g. (0.008 mole) benzoic acid and 0.6 g. (0.008 mole) t-butylamine in 30 ml. of dry pyridine was added 1.0 g. (0.006 mole) of silicon tetrachloride. The mixture was refluxed for one hour, poured

into 50 ml. of ice water and the precipitate was filtered. Extraction of the precipitate with ethanol yielded 0.5 g. (38%) N-t-butylbenzamide, m.p. 134-136°. (Lit. m.p. 134°). The filtrate was evaporated to dryness to an oil which on addition of a few drops of water crystallized out. Recrystallization of the solid from ethanol-water gave second crop of product, 0.4 g. (30%). Total yield was 68%. IR absorption- ρ_{max} 3320 cm^{-1} (N-H), 1640 cm^{-1} (C=O), 1530, 1310 cm^{-1} (N-H, C-N).

N-2,4,6-Trimethylbenzanilide: To a solution of 1 g. (0.008 mole) benzoic acid and 1.1 g. (0.008 mole) 2,4,6-mesidine in 30 ml. dry pyridine was added 1.4 g. (0.008 mole) silicon tetrachloride. The resulting mixture was refluxed for one hour and poured onto crushed ice. The precipitate which contained both the product and silica was filtered and extracted with acetone. Evaporation of the organic solution to dryness yielded 1.6 g. (80%) N-2,4,6-trimethylbenzanilide, m.p. 206°. (Lit. m.p. 204°). IR absorption- ρ_{max} 3270 cm^{-1} (N-H), 1640 cm^{-1} (C=O), 1515, 1290 cm^{-1} (N-H, C-N).

2,4,6-Trimethylbenzanilide: To a solution of 1 g. (0.006 mole) 2,4,6-trimethylbenzoic acid and 0.57 g. (0.006 mole) aniline in 20 ml. dry pyridine was added slowly 1.1 g. (0.006 mole) silicon tetrachloride. The mixture was refluxed

for one hour and then poured onto crushed ice. The brown precipitate was filtered and extracted with hot ethanol. Evaporation of the solvent gave 0.35 g. (23%) 2,4,6-trimethylbenzanilide which after recrystallization from ethanol-water had m.p. 168-170°. IR absorption-ν_{max} 3260 cm^{-1} (N-H), 1660 cm^{-1} (C=O), 1540, 1320 cm^{-1} (N-H, C-N). Analysis: Calcd. C, 80.3; H, 7.1; N, 5.9. Found C, 80.2; H, 7.0; N, 6.2.

N-Methylacetanilide: To a solution of 1 g. (0.017 mole) acetic acid and 1.8 g. (0.017 mole) N-methylanilide in 20 ml. dry pyridine stirring under an atmosphere of nitrogen was added 2.8 g. (0.017 mole) silicon tetrachloride. The solution turned pink after addition of the silane. On warming, the color turned to dark brown. The mixture was left stirring at 40-50° for one hour and then hydrolysed with ice water. The precipitate was filtered and the filtrate concentrated to yield 1.88 g. (75%) crude N-methylacetanilide. Recrystallization from ligroin gave white crystal, m.p. 100-102°. (Lit. m.p. 102°). IR absorption-ν_{max} 1660 cm^{-1} (C=O).

Attempted preparation of N-2,4,6-trimethylphenyl-2,4,6-mesitamide: To a solution of 1.0 g. (0.006 mole) 2,4,6-mesitoic acid and 0.83 g. (0.006 mole) 2,4,6-mesidine in 25 ml. pyridine was added 1.1 g. (0.006 mole) silicon tetrachloride. The mixture was refluxed for one hour and poured

onto crushed ice. The precipitate was filtered and extraction of the precipitate with hot ethanol failed to give any product. The filtrate was concentrated to dryness to recover quantitatively both starting materials.

Coupling between p-hydroxybenzoic acid and aniline: To a solution of 1.0 g. (0.007 mole) p-hydroxybenzoic acid and 0.67 g. (0.007 mole) aniline in 20 ml. pyridine was added 0.9 g. (0.005 mole) silicon tetrachloride. The mixture was heated at 100° for one hour and poured into ice water. The precipitate was filtered and extracted with ethanol. Evaporation of the alcohol solution to dryness gave 0.85 g. (50%) p-hydroxybenzanilide, m.p. 202°. (Lit. m.p. 201-202°). The filtrate was evaporated to give an oily residue which on recrystallization from ethanol-water yielded 0.35 g. of a solid identified to be the starting acid. IR absorption of p-hydroxybenzanilide- ν_{max} 3320 cm^{-1} (N-H, OH), 1650 cm^{-1} (C=O), 1530, 1320 cm^{-1} (N-H, C-N).

Coupling between o-hydroxybenzoic acid and aniline: To a solution of 1.0 g. (0.007 mole) o-hydroxybenzoic acid and 0.67 g. (0.007 mole) aniline in 20 ml. pyridine was added 0.9 g. (0.005 mole) silicon tetrachloride. The mixture was heated at 100° for one hour and hydrolysed with ice water. The precipitate was filtered and extracted with hot water. Evaporation to dryness yielded 10 mg. (<1%) salicylanilide,

m.p. 135°. (Lit. m.p. 134-135°). The filtrate was evaporated to give a solid residue. Recrystallization from water gave crystals m.p. 159°, whose infrared spectrum was identical with that of the starting acid.

Reaction between tetraacetoxysilane and aniline:

(a) Preparation of tetraacetoxysilane. A solution of 7.2 g. (0.12 mole) acetic acid and 5.1 g. (0.03 mole) silicon tetrachloride in 25 ml. dry n-pentane was heated to reflux. The hydrogen chloride evolved was trapped in a solution of potassium carbonate. After the evolution of gas had ceased (5 to 6 hrs.), the solvent was evaporated off and the product washed three times with pentane. The crystal was dried in vacuo to give 6.9 g. (88%) yield of tetraacetoxysilane, m.p. 112°. (Lit. m.p. 110-112°[33]). NMR- δ 2.2 (s, $COC\underline{H}_3$). Mass Spect.- m/e 205 (M^+-AcO), m/e 163 (205-CH_2CO), m/e 121 (163-CH_2CO), m/e 79 (121-CH_2CO).

(b) Reaction with two moles aniline. To 2.0 g. (0.007 mole) tetraacetoxysilane dissolved in 20 ml. pyridine was added slowly 1.42 g. (0.015 mole) pure aniline. An exothermic reaction ensured and on continued stirring for about ten minutes, there was observed a gradual geling of the reaction mixture. After the mixture was left stirring at room temperature overnight, it was poured onto crushed ice. The

precipitate was filtered and the filtrate evaporated to dryness to yield, after recrystallization, 1.7 g. (84%) acetanilide, m.p. 112°.

(c) Reaction with four moles aniline. Reaction was carried out similar to (b) using 2.8 g. (0.03 mole) aniline. Work up in the same way yielded 1.65 g. (41% based on aniline) of acetanilide, m.p. 112°.

PEPTIDE SYNTHESIS

Phthaloyl-DL-phenylalanine-anilide: To a solution of 3 g. (0.01 mole) phthaloyl-DL-phenylalanine[34] and 0.93 g. (0.01 mole) aniline in 50 ml. dry pyridine was added 1.2 g. (0.007 mole) silicon tetrachloride. The mixture was refluxed for two hours and then poured onto crushed ice. The precipitate was filtered and extracted with hot ethanol. Evaporation to dryness gave 2.1 g. (57%) phthaloyl-DL-phenylalanine-anilide. Recrystallization from ethanol gave solid, m.p. 210-213°. IR absorption-ν_{max} 3275 cm^{-1} (N-H), 1780, 1725 cm^{-1} (C=O, imide), 1672 cm^{-1} (C=O, amide), 1550, 1327 cm^{-1} (N-H, C-N). Analysis: Calcd. C, 74.6; H, 4.9; N, 7.6. Found C, 74.4; H, 5.1; N, 7.8.

Preparation of ethyl glycinate: Ethyl glycinate hydrochloride (10 g., 0.07 mole) was suspended in 100 ml. chloroform and triethylamine (7.25 g., 0.07 mole) was added. The solution was stirred for one hour and then evaporated to dryness. On addition of 200 ml ether to the residue, the triethylamine hydrochloride salt precipitated out and was filtered. The filtrate was concentrated to give a light yellow oil which distilled at 66°/35mm to yield 4.5 g. (64%)

ethyl glycinate (Lit. b.p. 148-149°). The compound deposited crystals on standing overnight probably due to self-dimerization to form 2,5-diketopiperazine[21].

Attempted coupling between benzoic acid and ethyl glycinate with silicon tetrachloride: To a solution of 1 g. (0.008 mole) benzoic acid and 0.84 g. (0.008 mole) ethyl glycinate in 25 ml. pyridine was added 1.0 g. (0.006 mole) silicon tetrachloride. The mixture was refluxed for thirty minutes and hydrolysed with water. A viscous brown product separated out on standing overnight and was filtered. Extraction of the viscous solid with ethyl acetate failed to give any amide. The filtrate was concentrated to recover 0.9 g. of benzoic acid. The viscous compound was likely a polymer.

Attempted coupling between phthaloylglycine and ethyl glycinate with silicon tetrachloride: To a solution of 2.05 g. (0.01 mole) phthaloylglycine and 1.03 g. (0.01 mole) ethyl glycinate in 30 ml. pyridine was added 1.2 g. (0.007 mole) silicon tetrachloride. The mixture was heated at 100° for thirty minutes and then poured into ice water. A sticky brown product separated out and was filtered. The filtrate was evaporated to dryness to recover 1.9 g. starting acid. No dipeptide was detected on thin layer chromatography by comparison with an authentic sample. The sticky product was likely a polymer.

Reaction between tetraacetoxysilane and DL-leucine methyl ester: To a solution of 1 g. (0.004 mole) tetraacetoxysilane in 10 ml. pyridine was added 1.37 g. (0.008 mole) DL-leucine methyl ester hydrochloride. No exothermic reaction occurred. Triethylamine, 0.77 g. (0.008 mole), was then added and a gel appeared a few minutes later. The mixture was stirred at room temperature overnight and poured onto crushed ice. The silica was filtered and the filtrate concentrated to give a solid residue which was extracted with ether. Evaporation of the organic solution yielded 0.9 g. oily product. Slow recrystallization of the oil from cyclohexane gave 0.75 g. (54%) acetyl-DL-leucine methyl ester, m.p. 75-76°. (Lit. m.p. 77°[35]). IR absorption- ν_{max} 3280 cm^{-1} (N-H), 1750 cm^{-1} (C=O, ester), 1660 cm^{-1} (C=O, amide), 1550 cm^{-1} (N-H). NMR- δ 1.0 (d,6,-CH($\underline{CH_3}$)$_2$); 1.65 (m,3,-$\underline{CH_2}$$\underline{CH}$($CH_3$)$_2$); 2.07 (s,3,-COC$\underline{H_3}$); 3.8 (s,3,-OC$\underline{H_3}$); 4.7 (m,1,-NH-C$\underline{H}$-); 6.2 (h,1,-N$\underline{H}$-).

Acetyl-DL-leucine: The above ester was further characterized by hydrolysis to the acid. Acetyl-DL-leucine methyl ester (0.5 g.) was hydrolysed at room temperature with N NaOH (2 ml.) in water (2 ml.) for two hours. The solution was acidified with dilute hydrochloric acid to Congo red and filtered. The acid (0.36 g., 75%) after recrystallization from ethyl acetate-pet. ether, had m.p. 159-160°. (Lit. m.p. 161°[36]). IR absorption- ν_{max} 3330 cm^{-1} (N-H), 2500-

2700 cm^{-1} (OH stretching), 1710 cm^{-1} (C=O, acid), 1630 cm^{-1} (C=O, amide), 1565 cm^{-1} (N-H).

Phthaloylglycyl-glycine ethyl ester: To a solution of 2.43 g. (0.012 mole) phthaloylglycine in 20 ml. dry pyridine, a solution of 0.5 g. (0.003 mole) silicon tetrachloride in 5 ml. benzene was added slowly with stirring. The mixture was heated at 110° for thirty minutes. To the cooled mixture, 0.61 g. (0.006 mole) ethyl glycinate was added and the solution was stirred overnight at room temperature. The mixture was then evaporated under vacuum at 50° and the residue was hydrolysed with water and extracted with ethyl acetate. The organic phase was washed with dilute hydrochloric acid, water, dilute sodium bicarbonate solution and then water. The organic solution was dried and evaporated to give 0.76 g. (45%) phthaloylglycylglycine ethyl ester which on recrystallization from ethyl acetate-hexane gave colorless solid, m.p. 193-195°. (Lit. m.p. 194-195°(37)). IR absorption-ν_{max} 3200 cm^{-1} (N-H), 1775-1700 cm^{-1} (C=O, imide, ester), 1640 cm^{-1} (C=O, amide), 1550 cm^{-1} (N-H). NMR-δ1.35 (t,3,-$OCH_2\underline{CH_3}$), 4.2 (d,2,-NH-$\underline{CH_2}$-), 4.35 (q,2,-$O\underline{CH_2}CH_3$), 4.55 (s,2,-$N\underline{CH_2}$-), 6.6 (h,1,-$\underline{NH}$), 7.9 (m,4,$C_6\underline{H_4}$-).

Phthaloylglycyl-L-leucine methyl ester: To a solution of 4 g. (0.02 mole) phthaloylglycine in 40 ml. pyridine was

added 0.85 g. (0.005 mole) silicon tetrachloride dissolved in 5 ml. benzene. The mixture was stirred for thirty mins. and then refluxed for an additional thirty minutes. To the cooled solution was added 1.4 g. (0.01 mole) L-leucine methyl ester* and the mixture stirred overnight at room temperature. The pyridine was evaporated under vacuum at 50° and the residue hydrolysed with water and extracted with ethyl acetate. After successive washings of the organic layer with dilute hydrochloric acid, water, dilute sodium bicarbonate solution and water, it was dried with magnesium sulfate and evaporated to dryness to yield 1.55 g. (48%) dipeptide. Recrystallization from chloroform-hexane gave solid, m.p. 134-138°. $[\alpha]_D^{20}$ = +5.9° (c= 3.6, $CHCl_3$). IR absorption-ν_{max} 3320 cm^{-1} (N-H), 1788, 1730 cm^{-1} (C=O, imide), 1745 cm^{-1} (C=O, ester), 1674 cm^{-1} (C=O, amide), 1550 cm^{-1} (N-H). NMR-δ 1.0 (d,6,-CH($C\underline{H}_3$)$_2$), 1.7 (m,3, -$C\underline{H}_2C\underline{H}(CH_3)_2$), 3.8 (s,3,-O$C\underline{H}_3$), 4.46 (s,2,-N$C\underline{H}_2$-), 4.7 (m,1,-NHC$\underline{H}$-), 6.5 (d,1,-N$\underline{H}$-), 7.86 (m,4,$C_6\underline{H}_4$-). Analysis: Calcd. C, 61.5; H, 6.0; N, 8.4. Found C, 61.6; H, 6.2; N, 8.6.

Phthaloyl-DL-alanyl-DL-alanine ethyl ester: A solution of 0.5 g. (0.003 mole) silicon tetrachloride in 5 ml. dry

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* Prepared by neutralizing an aqueous solution of L-leu-OMe.HCl to pH 9 with K_2CO_3 and subsequent extraction into ether.

benzene was added slowly to 2.6 g. (0.012 mole) phthaloyl-DL-alanine dissolved in 20 ml. pyridine. The mixture was refluxed for two hours and then cooled to room temperature. DL-Alanine ethyl ester*, 0.7 g. (0.006 mole), was added and the solution kept overnight. The pyridine was evaporated under vacuum and the oily residue hydrolysed with water and extracted with ethyl acetate. The organic layer, after suitable washings, was dried (sodium sulfate) and concentrated to give 0.97 g. (51%) dipeptide. Recrystallization from ethanol-water yielded solid, m.p. 107-109°. IR absorption- ν_{max} 3160 cm^{-1} (N-H), 1775-1700 cm^{-1} (C=O, imide, ester), 1630 cm^{-1} (C=O, amide), 1525 cm^{-1} (N-H). NMR- δ 1.27 (t,3,-$OCH_2\underline{CH_3}$), 1.42 (d,3,-CH-$\underline{CH_3}$), 1.75 (d,3,-CH-$\underline{CH_3}$), 4.25 (q,2,-OCH_2-), 4.8 (m,2,2-$\underline{CH}$-), 6.8 (d,1,-$\underline{NH}$-), 7.9 (m,4, $C_6\underline{H_4}$).

Analysis: Calcd. C, 60.4; H, 5.7; N, 8.8. Found C, 60.2; H, 5.8; N, 9.0.

Preparation of benzoyl-DL-alanine: DL-Alanine (5 g., 0.056 mole) was dissolved in a solution containing 4.5 g. NaOH in 50 ml. water. The mixture was cooled to 5-10° and benzoyl chloride (7.9 g., 0.056 mole) was added over thirty minutes. After stirring for one hour, the solution was acidified with dilute hydrochloric acid to Congo red and

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* Prepared similar to ethyl glycinate.

the precipitate filtered. The product was washed three times with water and recrystallized from ethyl acetate-pet. ether to yield 7.7 g. (71%) benzoyl-DL-alanine, m.p. 165°. (Lit. m.p. 166°).

Benzoyl-DL-alanyl-DL-alanine ethyl ester: To a solution of 2.3 g. (0.012 mole) benzoyl-DL-alanine in 20 ml. pyridine was added 0.5 g. (0.003 mole) silicon tetracholride dissolved in 5 ml. benzene. The mixture was heated at 110° for one hour and cooled to room temperature. DL-Alanine ethyl ester, 0.7 g, (0.006 mole) was added and the solution stirred at room temperature overnight. The pyridine was evaporated and the residue hydrolysed with water. Extraction with ethyl acetate followed by suitable washings of the organic layer yielded 1.0 g. dipeptide (58%). Recrystallization from chloroform-hexane gave solid, m.p. 125-130°. IR absorption-ν_{max} 3270, 3100 cm^{-1} (N-H), 1733 cm^{-1} (C=O, ester), 1670, 1625 cm^{-1} (C=O, amide), 1570, 1530 cm^{-1} (N-H, amide). NMR-δ 1.2 (2t,3,-$OCH_2\underline{C}H_3$), 1.38, 1.45 (2d,6,2CH-$C\underline{H}_3$), 4.12 (2q,2,-$OC\underline{H}_2CH_3$), 4.6 (m,2,2 -$C\underline{H}$-CH_3), 7.6 (m,7,2-$N\underline{H}$ & $C_6\underline{H}_5$).
Analysis: Calcd. C, 61.7; H, 6.9; N, 9.6. Found C, 61.5; H, 6.7; N, 9.5.

Acetyl-DL-phenylalanyl-DL-alanine ethyl ester: To a solution of 2.5 g. (0.012 mole) acetyl-DL-phenylalanine*

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* Obtained from Mann Research Labs., Inc., N.Y.

in 20 ml. pyridine was added 0.5 g. (0.003 mole) silicon tetrachloride in 5 ml. benzene. The mixture was heated at 110° for one hour and cooled to room temperature. DL-Alanine ethyl ester, 0.70 g. (0.006 mole), was added and the mixture stirred overnight. The pyridine was evaporated and the residue hydrolysed with water. Extraction with ethyl acetate followed by suitable washings yielded 1.1 g. (60%) acetyl-DL-phenylalanyl-DL-alanine ethyl ester. Recrystallization from chloroform-hexane gave crystals, m.p. 186-188°. IR absorption- ν_{max} 3150 cm^{-1} (N-H), 1730 cm^{-1} (C=O, ester), 1620 cm^{-1} (C=O, amide), 1540 cm^{-1} (N-H). NMR- δ 1.3 (t and d overlap,6,-CH-C$\underline{H}_3$ & -OCH$_2$C$\underline{H}_3$), 1.98 (s,3,C$\underline{H}_3$CO-), 3.1 (d,2,C$\underline{H}_2$-Ø), 4.2 (q,2,-OC$\underline{H}_2$CH$_3$), 4.6 (m,2,2-NHC$\underline{H}$-), 6.7 (2d overlap,2,2-N$\underline{H}$CH-), 7.35 (s,5,C$_6\underline{H}_5$-). Anal. Calcd. C, 62.8; H, 7.2; N, 9.2. Found C, 62.5; H, 7.1; N, 9.1.

Benzyloxycarbonylglycyl-glycine ethyl ester: To a solution of 2.5 g. (0.012 mole) benzyloxycarbonylglycine in 20 ml. pyridine heated at 60° was added over forty-five minutes 0.5 g. (0.003 mole) silicon tetrachloride dissolved in 15 ml. benzene. The mixture was kept at 60° for thirty minutes and cooled to room temperature. Ethyl glycinate, 0.61 g. (0.006 mole) was added and the solution stirred overnight. The pyridine was evaporated and the residue hydrolysed with

water and extracted with ethyl acetate. After suitable washings, the organic solvent was evaporated to give 1.2 g. (70%) product. Recrystallization from chloroform-hexane gave solid, m.p. 80° (Reported m.p. 80-81° [38]). NMR- δ 1.27 (t,3,-$OCH_2\underline{C}H_3$), 3.94, 4.02 (2d overlap as t, 4,2-NH-$C\underline{H}_2$-), 4.2 (q,2,-$OC\underline{H}_2CH_3$), 5.15 (s,2,-$C\underline{H}_2$-Ø), 5.92 (t,1,N$\underline{H}$-), 7.0 (t,1,N$\underline{H}$-), 7.35 (s,5,$C_6\underline{H}_5$-).

Benzyloxycarbonylglycyl-DL-alanine ethyl ester: To a solution of 2.5 g. (0.012 mole) benzyloxycarbonylglycine in 20 ml. pyridine heated at 60° was added 0.5 g. (0.003 mole) silicon tetrachloride in 10 ml. benzene over forty-five minutes. The mixture was kept at 60° for thirty minutes and cooled to room temperature. DL-Alanine ethyl ester, 0.7 g. (0.006 mole), was added and the mixture stirred overnight. On working up the usual way, there was isolated 1.0 g. benzyloxycarbonylglycyl-DL-alanine ethyl ester, m.p. 52-54°. (Lit. m.p. 53-55° [39]). NMR- δ 1.27 (t,3,-$OCH_2\underline{C}H_3$), 1.40 (d,2,-$CH\underline{C}H_3$), 3.94 (d,2,-$NH\underline{C}H_2$-), 4.2 (q,2,-$OC\underline{H}_2CH_3$), 4.55 (m,1,-$C\underline{H}CH_3$), 5.15 (s,2,$C\underline{H}_2$-Ø), 6.1 (t,1,N$\underline{H}$), 7.2 (d,1,N$\underline{H}$), 7.35 (s,5,$C_6\underline{H}_5$-).

Preparation of benzyloxycarbonyl-DL-alanine: To a solution of 4.45 g. (0.05 mole) DL-alanine in 12.5 ml. of 4N sodium hydroxide chilled to 5° was added alternately drop by drop over a period of thirty minutes 16 ml. 4N NaOH and 9.5 g.

(0.056 mole) benzyloxycarbonylchloride with vigorous shaking. The mixture was stirred for two hours and then extracted with 100 ml. ether to remove the excess benzyloxycarbonylchloride. The aqueous fraction was acidified slowly to Congo red with 5N HCl acid with cooling in an ice bath. After further stirring for about one hour, the product which precipitated out was filtered and dried. Recrystallization from ether-pet. ether gave 7.6 g. product (70%), m.p. 113-115° (Lit. m.p. 115°[40]).

Benzyloxycarbonyl-DL-alanyl-glycine ethyl ester: To a solution of 2.6 g. (0.012 mole) benzyloxycarbonyl-DL-alanine in 20 ml. pyridine heated at 60° was added 0.5 g. (0.003 mole) silicon tetrachloride in 10 ml. benzene over thirty minutes. The mixture was kept at 60° for one hour and cooled to room temperature. Ethyl glycinate, 0.61 g. (0.006 mole) was added and the solution stirred overnight. The pyridine was evaporated and the residue hydrolysed with water and extracted with ethyl acetate. The organic phase, after suitable washings, was concentrated to yield 0.5 g. oily product. Recrystallization twice from chloroform-pet. ether gave 0.25 g. (~15%) benzyloxycarbonyl-DL-alanyl-glycine ethyl ester, m.p. 80°. (Lit. m.p. 81°[41]). NMR- δ 1.27 (t,3,$-OCH_2\underline{C}H_3$), 1.4 (d,2,$-CH\underline{C}H_3$), 4.02 (d,2, $NH\underline{C}H_2-$), 4.2 (q,2,$-O\underline{C}H_2CH_3$), 4.55 (m,1,$-\underline{C}HCH_3$), 5.15 (s,2, $-\underline{C}H_2-\emptyset$), 5.7 (d,1,$N\underline{H}$), 7.0 (h,1,$N\underline{H}$), 7.35 (s,5,$C_6\underline{H}_5-$).

Preparation of tetrabenzyloxysilane: To a solution of 2.2 g. (0.008 mole) tetraacetoxysilane in 20 ml. dry benzene was added 3.5 g. (0.032 mole) benzyl alcohol. A slight exothermic reaction ensued. The mixture was heated at reflux for one hour and the solvent evaporated. The residue was distilled to yield 2.5 g. (64%) tetrabenzyloxysilane, b.p. 225-230°/0.05mm (Lit. b.p. 259-260°/1mm[55]). NMR- δ 4.33 (s,8,-$OC\underline{H}_2$-Ø), 6.75 (s,20,-$OCH_2C_6\underline{H}_5$).

Isolation of tetrabenzyloxysilane from the reaction of benzyloxycarbonyl-DL-alanine with silicon tetrachloride: To a solution of 1.3 g. (0.006 mole) benzyloxycarbonyl-DL-alanine in 10 ml. pyridine was added 0.25 g. (0.0015 mole) silicon tetrachloride and the mixture heated at 110° for two hours. After cooling the pyridine was distilled and the residue was chromatographed on column (silica gel) with benzene. The first product collected was identified by comparison with an authentic sample to be tetrabenzyloxysilane (0.41 g., 60%).

RACEMIZATION STUDIES

(a) Nuclear Magnetic Resonance Method

Preparation of N-acetyl-L-alanine: L-Alanine, 2.0 g. (0.023 mole) suspended in 10 ml. of water was acetylated with 7 g. (0.069 mole) acetic anhydride and 6.4 g. (0.16 mole) sodium hydroxide dissolved in 10 ml. water over a period of two hours. The mixture was kept slightly alkaline all the time with vigorous stirring and cooling at 5°. After the reaction was complete, the solution was acidified to Congo red and extracted four times with ethyl acetate. The organic layer was dried with magnesium sulfate and concentrated to give a sirup which on standing *in vacuo* overnight crystallized out. After purification by repeated incomplete solution in ethyl acetate and addition on benzene (three times), acetyl-L-alanine, m.p. 124-127°, was obtained. $[\alpha]_D^{25}$ -60° (c=3, H_2O). [Lit. m.p.[42] 122-123°, $[\alpha]_D^{23}$= -62° (c=3, H_2O); m.p.[43] 130-132°, $[\alpha]_D$ = -60° (c=1, H_2O)].

Preparation of L-alanine methyl ester hydrochloride: To a solution of 10 g. L-alanine suspended in 150 ml. absolute methanol was bubbled through rapidly a stream of dry HCl gas. After all amino acid had dissolved, the hot solution

was cooled to 0° and the introduction of gas continued until saturation. The mixture was then left at room temperature for four hours and concentrated to dryness in vacuo below 50° to give a syrup. Slow crystallization from dry ether gave a crystalline suspension which was filtered off and washed four times with dry ether. After drying overnight in vacuo over sodium hydroxide pellets to remove excess hydrogen chloride, the product was recrystallized from methanol-ether to yield 11 g. (71%) L-alanine methyl ester hydrochloride, m.p. 109-110°. (Lit. m.p. 109-110°(44)).

Acetylphenylalanyl-alanine methyl ester: To a solution of 2.5 g. (0.012 mole) acetyl-L-phenylalanine* in 20 ml. pyridine was added 0.5 g. (0.003 mole) silicon tetrachloride in 10 ml. benzene. The mixture was heated at 110° for one hour and cooled to room temperature. To the mixture, L-alanine methyl ester hydrochloride (0.83 g., 0.006 mole) was added followed by triethylamine (0.6 g., 0.006 mole). The mixture was left overnight at room temperature. The pyridine was evaporated and the residue hydrolysed with water and extracted with ethyl acetate. The organic phase, after washings with dilute acid and base, was dried and concentrated to give 0.75 g. (43%) solid product. Its n.m.r. spectrum ($CDCl_3$) showed the methyl resonance as two

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* Obtained from Mann Research Labs., Inc., New York.

overlapping doublets at 81 and 73.5 Hz. downfield from TMS with relative intensities of 60:40.

Acetylalanyl-phenylalanine methyl ester: A solution of 0.2 g. (0.0012 mole) silicon tetrachloride in 5 ml. benzene was added to a solution of 0.62 g. (0.0047 mole) acetyl-L-alanine in 10 ml. pyridine. The mixture was heated at 110° for thirty minutes and cooled to room temperature. L-Phenylalanine methyl ester hydrochloride*, 0.51 g. (0.0024 mole) was added followed by 0.25 g. (0.0025 mole) triethylamine and the mixture stirred overnight. The pyridine was evaporated and the residue hydrolysed with water and extracted with chloroform. The organic phase was washed with dilute acid and base and concentrated to yield 0.3 g. (44%) crude dipeptide. Its n.m.r. spectrum ($CDCl_3$) showed the methyl resonance as two doublets at 79 and 71.5 Hz. downfield from TMS with relative intensities of 50:50.

Acetylalanyl-phenylalanine methyl ester using DCC as coupling reagent: To 0.48 g. (0.002 mole) L-phenylalanine methyl ester hydrochloride suspended in 5 ml. dry methylene chloride was added 0.23 g. (0.002 mole) triethylamine followed by 0.29 g. (0.002 mole) acetyl-L-alanine. The mixture was cooled to 0° and 0.46 g. (0.002 mole) dicyclohexylcarbodiimide was added. The reaction mixture was stirred

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* Obtained from Aldrich Chemical Co.

at 0° for thirty minutes and kept in the refrigerator overnight. The precipitate was filtered and the filtrate washed with dilute acid and bicarbonate solutions. Evaporation of the filtrate gave 0.42 g. (70%) of crude dipeptide. Its n.m.r. spectrum ($CDCl_3$) showed the methyl resonance as two doublets at 79 and 71.5 Hz. downfield from TMS with relative intensities of 50:50.

(b) Young's supersensitive test for racemization

Preparation of benzoyl-L-leucine[32]: To a solution of 13.1 g. L-leucine in 50 ml. 2N sodium hydroxide was added at 0° alternately 11.6 ml. benzoyl chloride and 60 ml. 2N sodium hydroxide over a period of one hour with vigorous stirring. After further stirring for fifteen minutes, the solution was extracted with 100 ml. ether. The aqueous layer was acidified to Congo red and the oily product extracted in ether. To the combined ether extract, cyclohexylamine (10 ml.) was added to give 25.5 g. (77%) benzoyl-L-leucine cyclohexylamine salt. Recrystallization from methanol-ether gave needles of m.p. 145-146°. The salt, (24 g.) was suspended in 200 ml. ethyl acetate and shaken with 200 ml. 2N hydrochloric acid. After separation, the aqueous layer was extracted with ethyl acetate and the combined organic phase was dried and concentrated to a small volume. Addition of petroleum ether with ice cooling

gave crystalline benzoyl-L-leucine (16 g., 89%). The product was recrystallized once from chloroform-pet. ether and dried in vacuo for two to three days to give a solid, m.p. 105-107°. $[\alpha]_D^{17} = -4.6^\circ$ (c=10.3 EtOH). [Lit. m.p. 106°, $[\alpha]_D^{23} = -4.9^\circ$ (c=10.3 EtOH)(32)].

Benzoyl-leucyl-glycine ethyl ester: To a solution of 2.62 g. (0.0112 mole) benzoyl-L-leucine in 20 ml. pyridine was added 0.47 g. (0.0028 mole) silicon tetrachloride in 5 ml. ether. The mixture was heated at 110° for forty-five minutes and cooled to room temperature. A solution of 0.57 g. (0.0056 mole) ethyl glycinate in 1 ml. ether was added and the mixture stirred overnight. The pyridine was evaporated and the residue hydrolysed with water and extracted with ethyl acetate. After suitable washings, the solvent was evaporated to give 1.16 g. (65%) benzoyl-leucyl-glycine ethyl ester, m.p. 137-145°. $[\alpha]_D^{17} = < -0.5^\circ$ (c=3.01 EtOH). NMR-δ 0.92 (d,6,$-CH(C\underline{H}_3)_2$), 1.25 (t,3,$OCH_2C\underline{H}_3$), 1.75 (m,3,$-C\underline{H}_2C\underline{H}(CH_3)_2$), 4.0 (d,2,$-NH-C\underline{H}_2-$), 4.19 (q,2,$-OC\underline{H}_2CH_3$), 4.85 (m,1,-NH-C$\underline{H}$-), 7.4, 7.9 (m,7, 2N$\underline{H}$ & $C_6\underline{H}_5$).

Benzoyl-leucyl-glycine ethyl ester from sodium acid salt: To 2.6 g. (0.0112 mole) benzoyl-L-leucine dissolved in 30 ml. dry acetonitrile was added slowly 0.5 g. (53.7% in paraffin, 0.0112 mole) sodium hydride and the mixture stirred for one hour. To this was added 20 ml. acetonitrile

and 15 ml. benzene and then 0.47 g. (0.0028 mole) silicon tetrachloride. The solution was refluxed for two hours and cooled to room temperature. Ethyl glycinate, 0.57 g. (0.0056 mole) was added and the mixture left stirring overnight. The solvent was evaporated and the residue hydrolysed with water and extracted into ethyl acetate. Work up in the usual way yielded 1.1 g. (62%) dipeptide. Recrystallization from ethyl acetate-pet. ether gave solid, m.p. 136-142°. $[\alpha]_D^{17} = -0.5^\circ$ (c=3 EtOH).

Benzoyl-L-leucyl-glycine ethyl ester using EEDQ as coupling reagent: To a solution of 2.6 g. (0.0112 mole) benzoyl-L-leucine and 1.15 g. (0.0112 mole) ethyl glycinate in 50 ml. dry benzene was added 2.84 g. (0.0115 mole) N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline* and the mixture was stirred at room temperature for 7 hr. The solvent was evaporated and the residue crystallized from ethyl acetate-petroleum ether to give Bz-Leu-Gly-OEt (92%), m.p. 155-157°, $[\alpha]_D^{17} = -32.2^\circ$ (c 3, EtOH). [Lit. m.p. 157-158°, $[\alpha]_D^{25}$ -33.5° (c 3, EtOH)[22]].

Isolation of 4-isobutyl-2-phenyloxazolone: To a solution of 2.78 g. (0.012 mole) benzoyl-L-leucine in 30 ml. acetonitrile was added 0.53 g. (53.7% in paraffin, 0.012 mole) sodium hydride. The mixture was stirred for one hour. The

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* Obtained from Aldrich Chemical Co.

suspension was diluted with 20 ml. acetonitrile and 15 ml. benzene and then 0.5 g. (0.003 mole) silicon tetrachloride in 5 ml. benzene was added. The mixture was heated at reflux for two hours and cooled to room temperature. The solvent was evaporated <u>in vacuo</u> to give a residue which was triturated with hot n-hexane. The hexane solution on evaporation gave a crystalline solid m.p. 40-45°. It weighted 0.29 g. (11.3%) and showed in infrared absorption (Nujol) ν_{max} 1830 and 1665 cm^{-1}. It showed no optical activity. $[\alpha]_D^{18} = 0°$ (c 2, EtOH).

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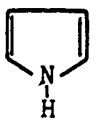
PART II

SYNTHESIS OF BENZOPHOSPHOLE

TABLE OF CONTENTS

INTRODUCTION

The chemistry of pyrrole (I) and derivatives has been known for many decades and has been investigated quite extensively. However the related phosphole (II) system has been comparatively little explored until recently and the first phosphole derivative, dibenzophosphole (IV), was not prepared till 1953[1]. These two classes of compounds can-



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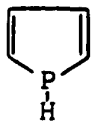

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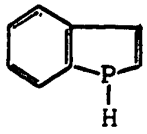

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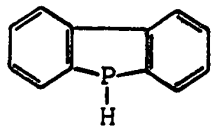


(IV)

not be expected to possess the same chemical and physical behaviors because of the great contrast in properties between nitrogen and phosphorus. The electron configuration (only the outer valence shell is considered) of nitrogen is $2s^2 2p^3$ and that of phosphorus is $3s^2 3p^3$. Tervalent phosphorus is known usually not to form double bonds either with itself ($3p\pi$-$3p\pi$) or carbon ($3p\pi$-$2p\pi$) or nitrogen[2]. Phosphorus has the ability to expand its valence shell to include 3d orbitals (i.e. to form pentaorganophosphorus compounds), a property unknown to nitrogen. The single-bond covalent

radius[3] of phosphorus is 1.1Å which is 0.4Å larger than that of nitrogen. The bond length of phosphorus is generally observed to be greater than that of nitrogen due to greater bulk of the phosphorus atom[2]. The typical bond angle of phosphorus compound is 100±1° while that of nitrogen is 106-108°[2]. The inversion frequencies of pyramidal phosphorus compounds are very low in great contrast to amines and this large energy barrier of inversion makes possible the isolation of optically active phosphines[4,5].

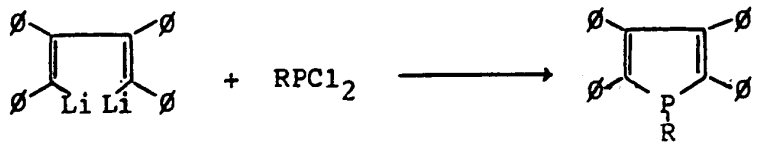
The main interest of the phosphole system lies in its potential aromatic character and behavior as secondary or tertiary phosphine. The question that is often asked is whether phosphole and derivatives behave like their nitrogen analogs in making the lone electron pair available for the formation of an aromatic system of 6$\tilde{\pi}$-electrons. During the past decade, a great deal of work has been done in attempting to solve this problem. However the answer at present still remains inconclusive.

The field of phosphole chemistry can be divided generally into: (1) simple phosphole, (2) dibenzophosphole and (3) benzophosphole.

Simple phosphole: synthesis

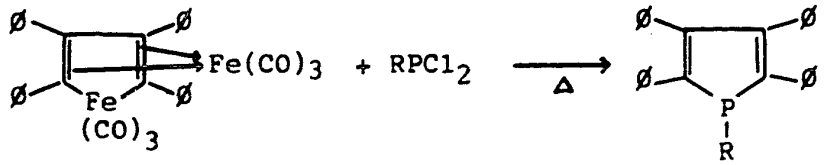
The synthesis of phosphole (II) itsely is unknown. All

simple phospholes prepared thus far contain at least one substituent. The first simple phosphole derivative was reported in 1959. The question whether such a system could exist was answered when Hubel and Braye[6] and Leavitt[7] discovered about simultaneously that 1,4-dilithio-1,2,3,4-tetraphenylbuta-1,3-diene (V) reacted with alkyl or aryl dichlorophosphine to give P-alkyl or aryl-2,3,4,5-tetraphenylphospholes (Eq. 1). A subsequent synthesis was re-



(V) (1)

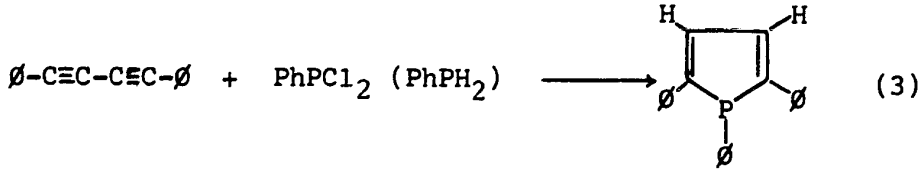
ported by Hubel[6] who found that iron carbonyl diphenylacetylene complex $Fe_2(CO)_6(Ph\text{-}C{\equiv}C\text{-}Ph)_2$, obtained from the reaction of $[Fe(CO)_4]_3$ with diphenylacetylene in boiling petroleum ether, could be used instead of the dilithio-compound. The iron carbonyl-tolan complex contains



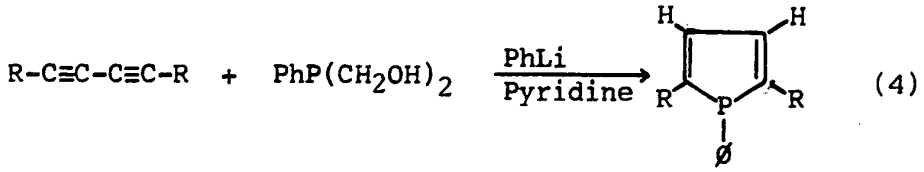
(2)

a cis-butadienoid system bonded to an iron atom and reacted similarly as V with dichlorophosphine (Eq. 2). Campbell and co-workers[8] later discovered that 1,2,5-triphenyl-

phosphole could be prepared simply by reacting diphenyl-buta-1,3-diene with phenyldichlorophosphine or phenyl-phosphine (Eq. 3). Markl[9] also reported similarly on



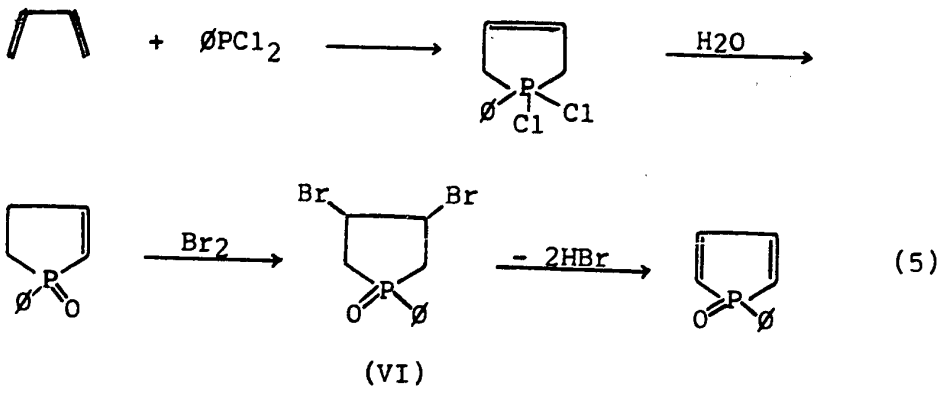
(3)



(4)

this reaction but using bis(hydroxymethyl)-phenylphosphine instead in pyridine containing catalytic amount of phenyl lithium (Eq. 4).

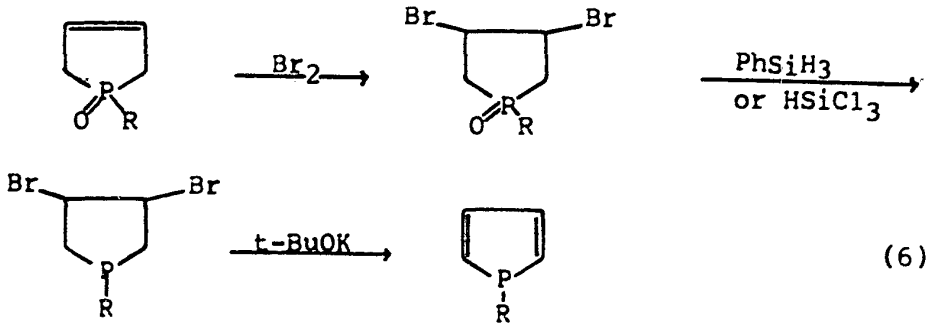
The above preparative methods are generally useful for the preparation of highly phenylated phospholes. Less phenylated compounds, on the other hand, can be synthesized by another approach which involves the dehydrohalogenation of phospholane intermediates. Thus Donadio and Howard[10] prepared 1-oxy-1-phenylphosphole by the addition of bromine to 1-oxy-1-phenyl-2-phospholene followed by dehydrobromination of the dibromophospholane VI (Eq. 5). The oxy-phenylphospholene was prepared according to the method of McCormack[11] by the addition of phenyldichlorophosphine to butadiene and hydrolysis of the adduct. The oxy-phenylphosphole obtained



(5)

(VI)

was found to be extremely reactive and dimerize readily at room temperature. Markl[12] and Quin[13] recently used similar approaches for the syntheses of 1-phenylphosphole (VIIa) and 1-methylphosphole (VIIb) respectively. In each case bromine was added to the appropiate 3-phospholene oxide[11] to give the corresponding dibromophospholane oxide which was reduced either with phenylsilane or trichlorosilane and then followed by dehydrobromination to give the corresponding phosphole (Eq. 6). The 1-methylphosphole prepared by Quin is the simplest phosphole known to date.

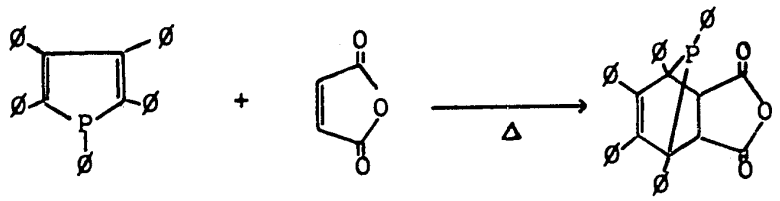


(6)

(VIIa) R= Ø (VIIb) R= CH_3

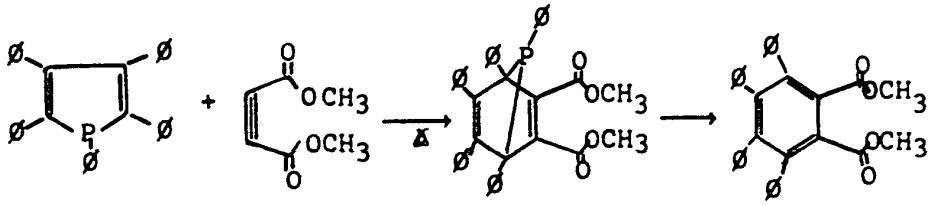
Properties of simple phosphole

As mentioned at the beginning (p. 2), the main interest of phosphole derivatives lies in the possible aromatic character of these compounds. The extent of delocalization of the lone pair of electrons on phosphorus in this system however has not been well defined experimentally. From the chemical behaviors of substituted phospholes, the ring appears to show little parallel to that of common heterocyclopentadienes, particularly pyrrole. Thus pentaphenylphosphole undergoes normal Diels-Alder addition[6,7] with maleic anhydride to give adduct VIII (Eq. 7). Reaction



(7)

(VIII)



(8)

(VIIIa)

with dimethyl acetylenedicarboxylate on the other hand gives good yield of dimethyl tetraphenylphthalate which must have resulted from the aromatization of compound VIIIa according

to Eq. 8. The ease in which the phosphole ring undergoes Diels-Alder reaction is not characteristic of aromatic system. Pentaphenylphosphole also forms stable addition products with iron carbonyls, similar to those formed by conjugated dienes[6,7]. Furthermore, phosphole derivatives react like tertiary phosphines at the phosphorus atom to form oxides, sulfides, selenides and quaternary salts. Phosphole oxides are normally prepared by treatment of phospholes with hydrogen peroxide[6,8,12,14] and sulfides and selenides are obtained in high yields by heating with sulfur or selenium[6,12,14]. Quaternary salts are formed relative easily by reactions with alkylbromide or iodide[13,14]. These reactions may indicate the readily availability of the non-bonding electron pair and hence rule out its delocalization into the ring.

This apparent non-aromatic behavior in the chemical sense can perhaps be misleading. Brown[15] has pointed out that the formation of oxides and quaternary salts for pyrrole and phosphole systems would involve going from a pyramidal to a tetrahedral arrangement about the hetero-atom. The fact that pyrrole undergoes these reactions less readily is because the difference in energy between the two arrangements is much greater for nitrogen than for phosphorus. Brown furthermore calculated and found that the planar configuration of phosphole has a substantial conjugation energy which is

close to that of pyrrole. Mortimer and co-workers[16], using thermochemical measurements, obtained a value of 39 Kcal/mole as the resonance stabilization energy for pentaphenylphosphole. This value was estimated from the difference in heat of formation of pentaphenylphosphole oxide and triphenylphosphine oxide and may be taken as a measure of the conjugation energy of the phosphole system relative to its oxide.

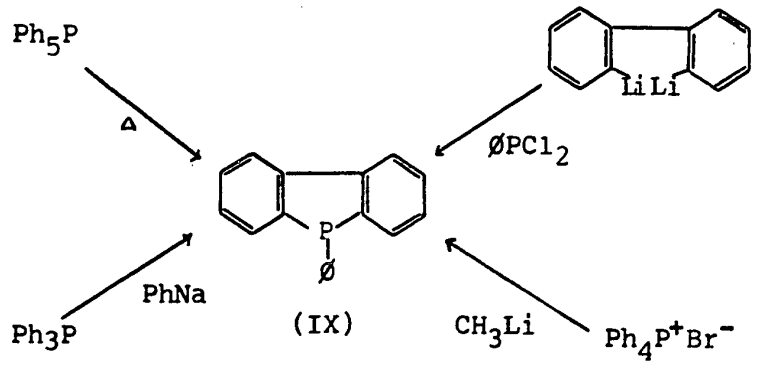
Recent support to the theory of aromatic phosphole is provided by Markl who did some nmr studies on this system. In the compound 1-phenyl-2,5-dimethylphosphole[9], the low-field position of the ring protons at 6.39 δ indicates deshielding which is characteristic of aromatic rings. 1-Phenylphosphole[12] also shows nmr spectrum with the ring protons resonate in the normal aromatic range as the corresponding N-phenylpyrrole. Finally Quin[13] also observed striking similarities between 1-methylphosphole and its N-analog in their nmr, uv and mass spectra.

Dibenzophosphole; synthesis

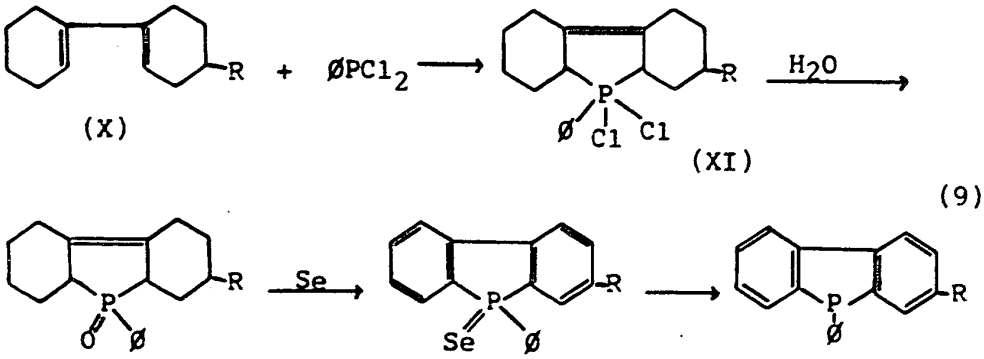
The first dibenzophosphole, 9-phenyl-9-phosphafluorene (IX), was synthesised by Wittig[1] in 1953 by four different methods although the yield in each case was low. These are summarized in Scheme I. These routes were later improved and led to the preparation of a large number of dibenzo-

phosphole derivatives with substituents such as $-N(CH_3)_2$, $-CH_3$ etc. on the ring[17-21].

Scheme I

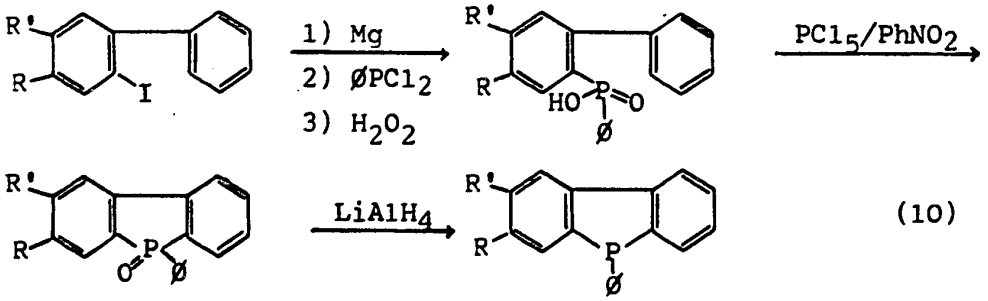


A more conventional approach to the synthesis of dibenzophosphole was that of Campbell[14] which was based on the McCormack's diene-halophosphine reaction.[11] Phenyldichlorophosphine was allowed to react with the biscyclohexyl compound (X) to yield an adduct (XI) which was hydrolysed to the phospholene oxide. Dehydrogenation with selenium followed by reduction gave the dibenzophosphole (Eq. 9). Campbell's second approach[22] to dibenzophosphole synthesis involved cyclization of 2-biphenylphenylphosphinic

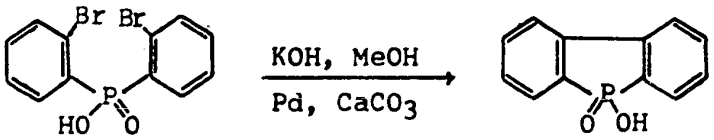


(9)

acids according to Eq. 10. The starting phosphinic acid could easily be obtained from Grignard reaction of the appropriate iodobiphenyl with phenyldichlorophosphine. Freedman and co-workers[23-24] also used cyclization approach for the preparation of phosphafluorinic acids from substituted diphenylphosphinic acids (Eq. 11).

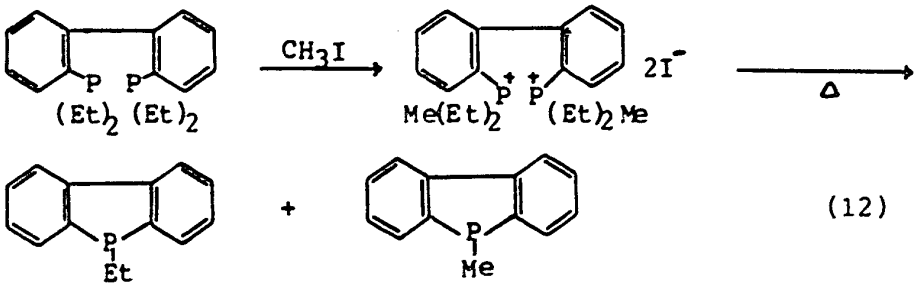


(10)



(11)

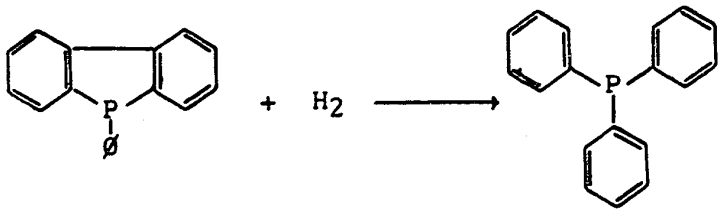
More recently a novel synthesis of dibenzophosphole system was reported by Millar[25] which involved pyrolysis of diphosphine quaternary salts derived from diphosphines by quaternization with alkyl iodide or bromide (Eq. 12). The yield of product however was not reported and the mechanism of the reaction remains unknown.



(12)

Properties of dibenzophosphole

In general dibenzophosphole behaves similarly as simple phosphole in reactions at the phosphorus atom. Thus dibenzophosphole reacts with hydrogen peroxide, sulfur and selenium to give dibenzophosphole oxide, sulfide and selenide respectively. Reaction with alkylbromide or iodide yields the corresponding quaternary salt. These reactions, as in the case for simple phosphole, indicate again the ready availability of the free electron pair and cast doubt on the aromaticity at the phosphorus ring. However from thermochemical measurements, Mortimer et al[26] obtained a value of +8.4 Kcal/mole for the heat of hydrogenation of 9-phenyl-9-phosphafluorene. This, in comparison with the calculated value:

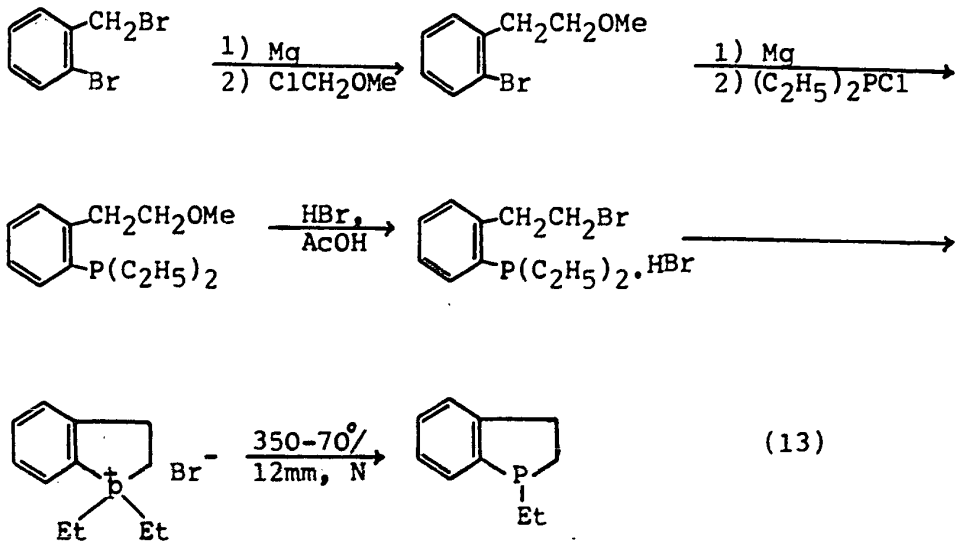


$\Delta H_{hyd.} = +8.4$ Kcal/mole

$\Delta H_{hyd.} = E_{C-C} + E_{h-h} - 2E_{C-h} = -10.6$ Kcal/mole, gives the resonance energy as 19 Kcal/mole for dibenzophosphole. Although this value is much lower than that of simple phosphole (39 Kcal/mole), nevertheless it shows resonance stabilization in the dibenzophosphole system.

Benzophosphole

There has been no report on the synthesis and properties of 1-benzophosphole (III) or its 1-substituted derivatives in the chemical literature thus far. A 2,3-dihydro-1-benzophosphole derivative has been prepared by Millar[27] via a 5-step synthesis (Eq. 13). Another 1-benzophosphole derivative (the only other prepared) that has been reported is the cyclic ylid XII. It was obtained[28] by a long synthetic route with the final stage involving the dehydrohalogenation of the cyclic phosphonium salt (XIII) with potassium t-butoxide (Eq. 14).



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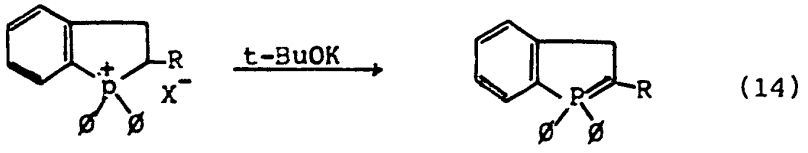


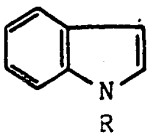
(XIII) (XII) (14)

It is apparent from the above discussion that although phosphole and dibenzophosphole are well known and have been investigated quite extensively, the chemistry of 1-benzophosphole is almost completely unknown. This is very surprising in view of the following two facts. First, the problem of aromaticity of phosphole and derivatives is of much current interest and the benzophosphole system can provide the chemist with yet another system to study on. Second, the lack of report on benzophosphole makes the series of phosphole chemistry incomplete. This lack may be due to the fact that there exists no easy synthetic scheme for its preparation. Benzophosphole is unsymmetrical unlike phosphole and dibenzophosphole and therefore cannot be expected to be prepared similarly from the many preparative pathways of phosphole and dibenzophosphole.

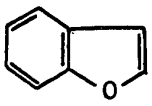
RESULTS AND DISCUSSION

General approach to 1-heteroindene

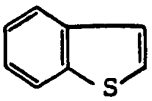
Heteroindenes like indole (XIV), benzofuran (XV) and benzothiophene (XVI) have been known for many decades. Of these, indole and its derivatives have been investigated much more thoroughly than the oxygen and sulfur analogs because of the higher incidence of indoles occurring in



(XIV)

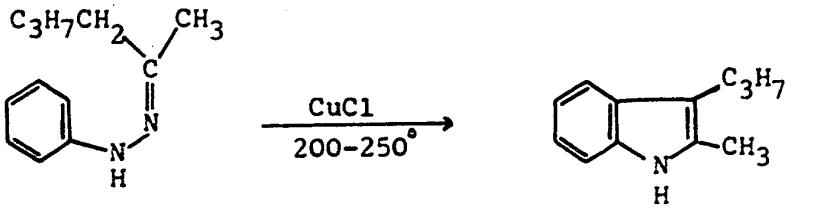


(XV)



(XVI)

nature products and because of the intensive studies effected on the dyestuff indigo. The majority of the more general methods for the synthesis of 1-heteroindenes involve procedures which form the heterocyclic ring through ring closure. These are illustrated by examples in Eq. 15-18.



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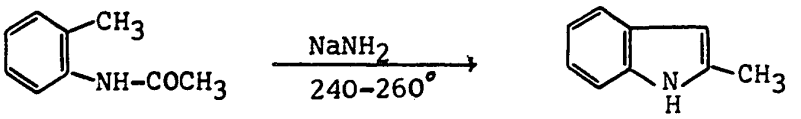

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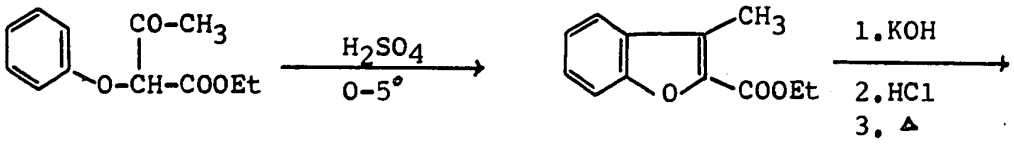

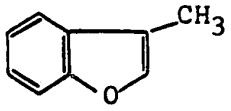

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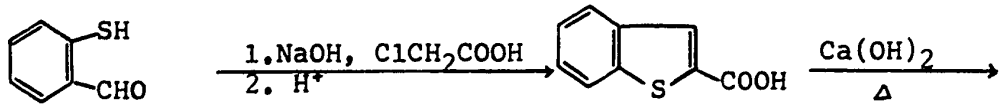
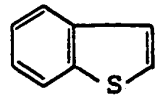
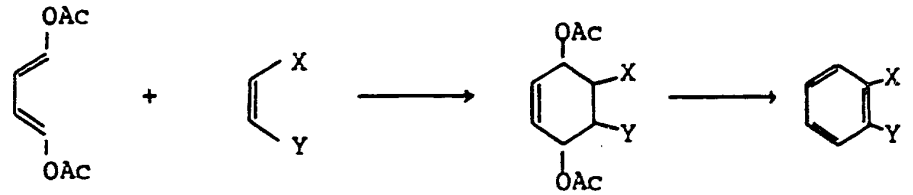




(18)

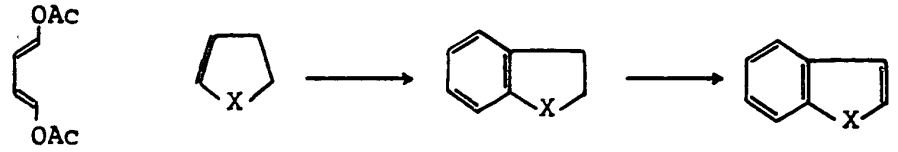
A new approach to the synthesis of 1-heteroindenes may be to involve construction of the phenyl ring instead. Recently a simple and direct method for forming a benzene ring was reported by Hill and Carlson[29]. The synthesis is based on the addition of trans,trans-1,4-diacetoxybutadiene (XVII) to dienophiles. Diels-Alder adduct of structure XVIII was found to aromatize either thermally or when treated with a base to yield the corresponding phenyl compound (Eq. 19). This synthesis of aromatic ring appears



(19)

(XVII) (XVIII)

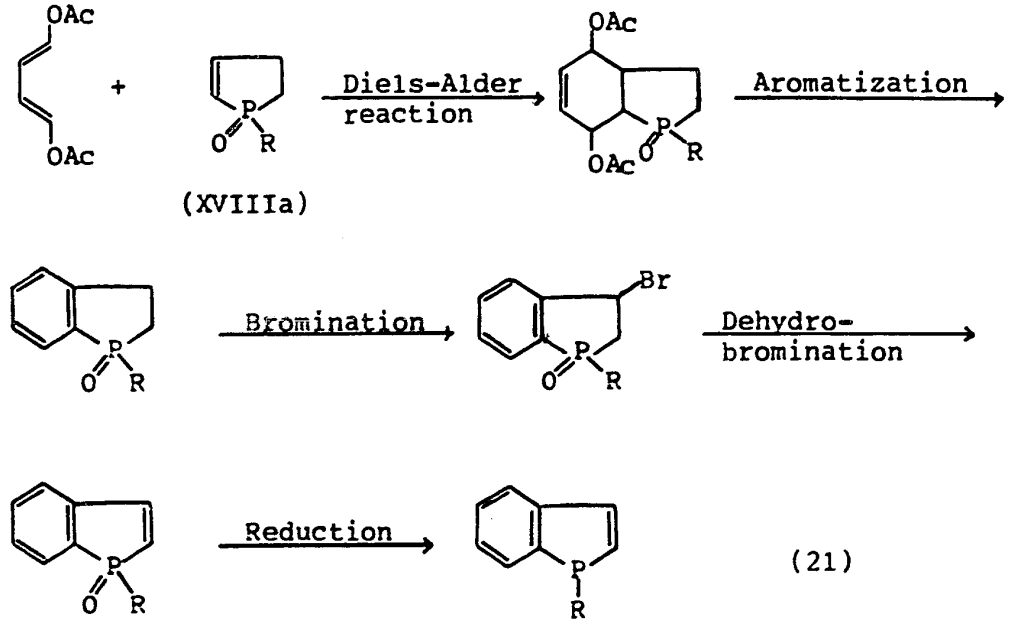
to be general for many dienophiles[30]. Hence it may be applied for the syntheses of 1-heteroindenes according to the following representation (Eq. 20):



(20)

X= N-R, O, S

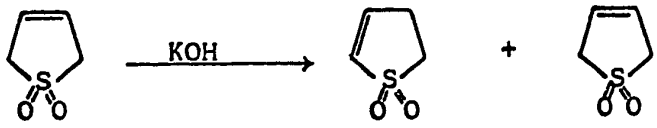
The success of this synthetic scheme can also lead to a simple preparation of the 1-benzophosphole system. As mentioned in the introduction (p. 13), the chemistry of benzophosphole is virtually unreported in the literature. Therefore it is the main interest of this research project to investigate on the synthesis of this system by the following proposed preparative scheme (Eq. 21):



(21)

Benzothiophene-1,1-dioxide

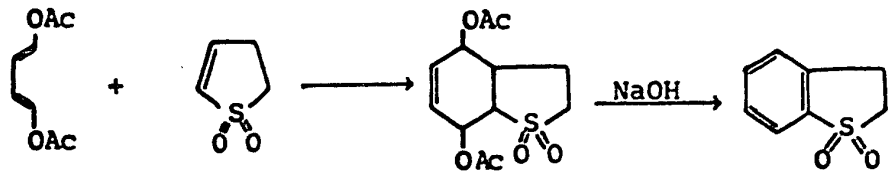
As a model compound for the study of this synthetic scheme, benzothiophene-1,1-dioxide was chosen to be prepared. The dienophile required in the reaction, 2,3-dihydrothiophene-1,1-dioxide (XIX), was prepared according to the method of Bailey and Cummins[31] by isomerization of butadiene sulfone with potassium hydroxide and fractional distillation of the two isomers (Eq. 22). When a mixture



(22)

(XIX)

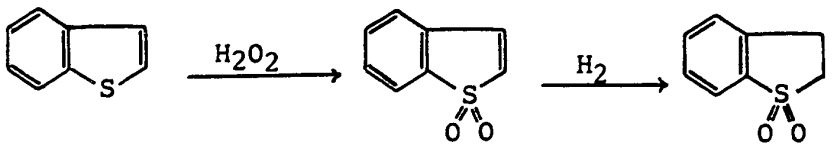
of equal molar quantities of 1,4-diacetoxybutadiene and 2,3-dihydrothiophene-1,1-dioxide was heated in a sealed ampule at 150-160° for 7 days, a new compound (XX) was formed in low yield as revealed by thin layer chromatography. The black reaction mixture was refluxed in an alcoholic sodium hydroxide solution and on isolation there was obtained, apart from the starting materials, a 20% yield (based on reacted dienophile) of 2,3-dihydrobenzothiophene-1,1-dioxide (Eq. 23). The product was identified



(23)

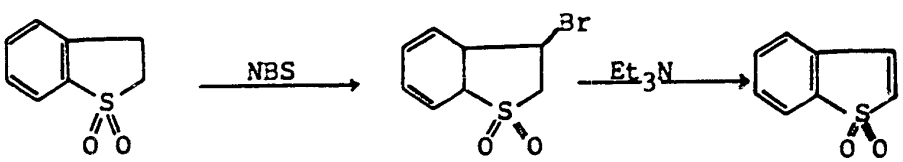
(XX)

by comparison with an authentic sample prepared from benzothiophene (Eq. 24). Compound XX, although not identified, was undoubtly the diacetoxy-adduct which did not aromatize thermally under the reaction condition.



(24)

Radical bromination of 2,3-dihydrobenzothiophene-1,1-dioxide with N-bromosuccimide did not take place under photolytic conditions. However the reaction proceeded smoothly by refluxing with a catalytic amount of benzoyl peroxide. The monobromo-substituted compound (XXI) was isolated as an oil in over 80% purity (as indicated by glc) and identified by mass spectrum. Although its structure was not absolutely identified, it was most likely to be the 3-bromo-compound since radical bromination is more liable to take place at the benzylic position. Treatment of XXI with triethylamine induced instant dehydrobromination to yield quantitatively benzothiophene-1,1-dioxide (Eq. 25), again identified with an authentic sample.

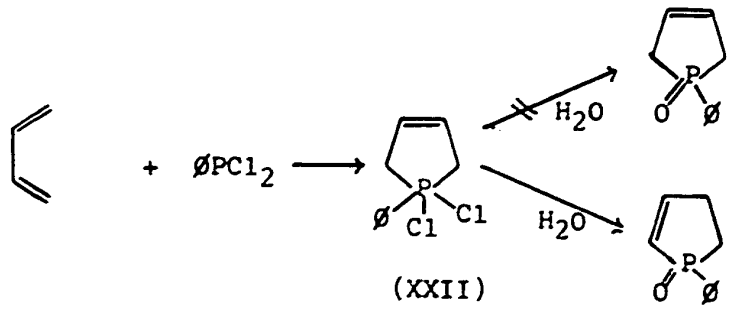


(XXI)

(25)

1-Phenyl-1-oxy-2,3-dihydrobenzophosphole

The successful synthesis of benzothiophene-1,1-dioxide indicates that this scheme could possibly be used for the preparation of other heteroindenes. Although the yield in the Diels-Alder step was low, no attempt was made to optimize it. Work was then proceeded to attempt a similar synthesis of 1-phenyl-1-benzophosphole, chosen to represent the benzophosphole series because the required dienophile for its synthesis, 1-phenyl-1-oxy-2-phospholene, could be secured easily from the McCormack reaction[11]. It should be mentioned in here that although the preparation of 1-phenyl-1-oxy-2-phospholene from butadiene and phenyldichlorophosphine has been known for many years, the compound was originally reported in the literature as the 3-isomer (Eq. 26). It was pointed out[45] later and proved[46] from nmr studies by Korte that the compound was actually the 2-isomer. Quin[43] recently also did some nmr studies on similar systems. The reason why the phosphonium salt (XXII) should hydrolyse to the 2- and not 3-isomer is not exactly known. It might be that due to the electron withdrawing effect



(XXII) (26)

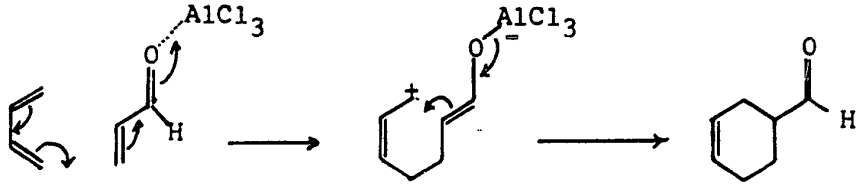
of the phenyl group attaching to the phosphorus, there is an increase in tendency for the loss of α-proton. In this connection, it was found that hydrolysis of diene-methylphosphonous dichloride adduct proceeded without rearrangement[32]; the electron-releasing methyl group has replaced the electron-attracting phenyl group.

The Diels-Alder reaction between 1,4-diacetoxybutadiene and 1-phenyl-1-oxy-2-phospholene was carried out in a sealed tube at 150° for 14 days. A new compound was isolated in 50% yield (crude, based on 2-phospholene reacted) by column chromatography and identified as 1-phenyl-1-oxy-2,3-dihydrobenzophosphole (XXIV) by nmr spectrum, mass spectrum and elemental analysis. Thermal elimination of acetic acid from the Diels-Alder adduct XXIII has apparently occurred in this case in contrast to the sulfur analog.

Conditions of reaction. The above Diels-Alder reaction fails to proceed when carried out in refluxing solvents such as benzene, xylene or tetralin. Reaction seems to proceed very slowly below 130° in the sealed tube. On the other hand a high reaction temperature (200° or higher) causes extensive polymerization of the diacetoxybutadiene. Therefore the optimum temperature is at 150-160°. Also the reaction appears to stop after 10-14 days as continuous heating to over three weeks fails to increase the yield

in any appreciable amount.

Catalysts. In an effort to increase the yield of the reaction, catalysts such as $AlCl_3$, $ZnCl_2$ and Cu_2O were used in the reaction. It has been reported[33] that these catalysts may increase dramatically the rate of Diels-Alder reactions with strong electrophilic dienophiles, e.g. α,β-unsaturated aldehydes or ketones. The mechanism[34] involves initial co-ordination of the catalyst with the dienophile's electron-withdrawing function followed by a Michael type of addition of the diene to the activated dienophile. Ring formation with a short-lived zwitterionic intermediate (XXV) gives the Diels-Alder adduct (Eq. 27).



(XXV) (27)

α,β-Unsaturated phosphonic acids and phosphates give infrared and ultraviolet spectra similar to the corresponding olefin indicating that these compounds possess no $p\pi$-$p\pi$ conjugation between the olefinic and phosphoryl bonds[35]. Compounds of this kind are tetrahedral at the phosphorus atom and are in contrast to the planar carbonyl compounds, in which an α,β-olefinic linkage conjugates strongly with the carbonyl group. However this conclusion is different

from that reached on chemical grounds which shows vinyl phosphates and similar compounds undergo rapid nucleophilic addition to the olefinic bond. This observation has been interpreted to be due to conjugation of the carbon-carbon double bond with the phosphoryl bond.

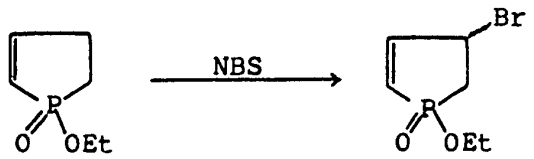
If this phenomenon of non-coplanar conjugation does exist, then in the present reaction involving 2-phospholene oxide as dienophile similar activation by catalyst could be expected to occur. However reactions carried out with incoporation of $AlCl_3$, $ZnCl_2$ or Cu_2O failed to show any increase in rate. Instead these catalyst caused facile polymerization of the diene and polymerization was observed even at low reaction temperature.

Variation of stoichiometry of diene. Since the Diels-Alder reaction is a reversible one, another approach to increase the yield of this reaction may involve using excess of one component to drive the reaction further to product. However experiments performed with 1,3 and 5 molar excess of diene under the same reaction conditions failed to show any appreciable increase in yield.

1-Phenyl-1-oxybenzophosphole

The 2,3-dihydrobenzophosphole (XXIV) on bromination with N-bromosuccinimide (NBS) yielded a new compound (XXVI)

as indicated by t.l.c. This was reacted <u>in situ</u> with excess triethylamine to give triethylamine-hydrobromide salt and 1-phenyl-1-oxybenzophosphole (XXVII), identified by nmr, uv and mass spectra. Although compound XXVI was not characterized, it is likely to be the monobromination product which dehydrobrominates quickly on treatment with base. Bromination is more likely to occur at the 3-position of the benzophosphole ring (benzylic) similar to that observed by Westheimer[36] for 1-oxy-1-ethoxy-2-phospholene (Eq. 28)



(28)

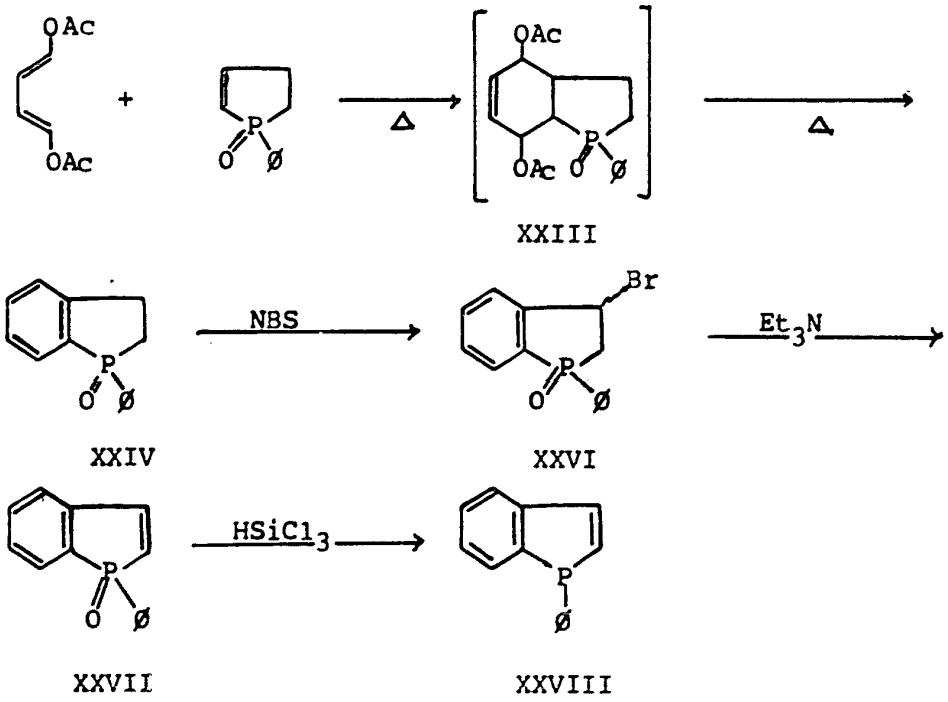
<u>1-Phenyl-1-benzophosphole</u>

The final step of the synthesis involves the reduction of the benzophosphole oxide to the benzophosphole. Silanes which can act as reducing agents, e.g. phenylsilane[37], trichlorosilane[38] are found to be the most effective for this purpose. The reduction of 1-phenyl-1-oxybenzophosphole with excess trichlorosilane gave 35% yield of the expected 1-phenyl-1-benzophosphole (XXVIII), identified again by nmr, uv and mass spectra. Mislow[39] recently reported that perchloropolysilanes could also be used for the reduction of phosphine oxides and these generally give higher

yields of products. In the present case however, the use of hexachlorodisilane was found to yield 30% of the reducing product.

The successful synthesis of 1-phenyl-1-benzophosphole (Scheme II) marks the first compound prepared for the benzophosphole series. This scheme can undoubtly be extended to the syntheses of other P-substituted benzophospholes by simply varying the dienophile used in the reaction. However in the present studies, it would be more interesting to look into the properties of 1-phenyl-1-benzophosphole and its oxide and see if they could shed some light on the possible aromaticity of the benzophosphole system.

Scheme II



Properties of 1-phenyl-1-benzophosphole and derivatives

Infrared spectrum. The infrared spectrum of 1-phenyl-1-benzophosphole (fig. 1) is relatively simple and shows strong phenyl bands at 1440, 1100 and 700-800 cm^{-1}. The band at 1100 cm^{-1} is probably due to aromatic vibration involving some P-C stretching[40]. The spectra of its oxide XXVII (fig. 2) and the 2,3-dihydro-1-oxy-compound XXIV (fig. 3) each shows a characteristic strong P=O stretching band near 1190 cm^{-1}. This is comparable with the P=O band of triphenylphosphine oxide which also stretches at that frequency.

Ultraviolet spectrum. 1-Phenyl-1-oxy-2,3-dihydrobenzophosphole (XXIV) shows an uv spectrum (fig. 4) which has a high intensity primary band at 225 $m\mu$ and a low intensity secondary band showing fine vibrational structure with maxima at 272 $m\mu$. The spectrum greatly resembles that of triphenylphosphine oxide[47]. The longer wavelength of the 225 $m\mu$ band is assigned to correspond to the ^1L_a band of benzene at 203 $m\mu$, displaced by substitutions. The low intensity secondary band on the other hand corresponds to the ^1L_b band of benzene at 256 $m\mu$. The fine vibrational structure shown in the secondary band indicates that this compound, like triphenylphosphine oxide[41], has unperturbed or weakly perturbed benzene rings. Hence it may be concluded that the

phenyl rings in this compound do not show appreciable conjugation with one another.

The spectra of 1-phenyl-1-benzophosphole (fig. 5) and its oxide (fig. 6) each shows an additional low intensity band centering at 313 mμ. The interpretations of these spectra however are of considerable difficulty. The uv spectra of heteroindenes like benzofuran, indole and benzothiophene have not been successfully interpreted and correlated so far. This is because of their inherently complicated nature and the problem of even distinguishing between vibrational structure and separate electronic transitions. One feature of the spectra of these heterocyclics is their general resemblance to each other and to the corresponding fused-ring hydrocarbon naphthalene[54] indicating participation or delocalization of the lone pair at the heteroatom into the ring. In this respect, the spectrum of 1-phenyl-1-benzophosphole was compared with that of N-phenylindole and found to be of close similarity (Table I, fig. 7). This could perhaps sug-

Table I. Ultraviolet absorption spectra of 1-phenyl-1-benzophosphole and N-phenylindole

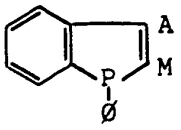
Compounds	λ_{max} (mμ)	log ε
1-Phenyl-1-benzophosphole	223, 260, 306, 316	4.39, 4.05, 3.56, 3.56
N-Phenylindole	217, 258, 291, 297	4.41, 4.26, 3.91, 3.89

gest similar electronic excitations occurring for the two ring systems.

Nuclear magnetic resonance spectrum. The ^1H nmr spectrum of 1-phenyl-1-oxy-dihydrobenzophosphole (fig. 8) shows two 2H multiplets at 2.4 and 3.3 δ for the two methylene groups, a 9H multiplet at 7.5 δ for the aromatic protons, all in accord with structure. The complexity of the spectrum is due to splittings by the phosphorus atom. The nmr spectrum of 1-phenyl-1-oxybenzophosphole (fig. 9) shows only vinylic and aromatic hydrogens at 6.5 and 7.4 δ respectively. The splitting of the vinylic group is partly obstructed by the phenyl resonance. The spectrum of 1-phenyl-1-benzophosphole (fig. 10, 100 MHz; fig. 11, 220 MHz) shows the vinylic and phenyl protons all group around 7.2 δ but are well separated. The vinylic splitting contains 8 lines and could be considered as part of the AMX system (X=P). The phenyl group appears less complex in this case in contrast to the oxide.

The nmr parameters for the phosphole ring protons of 1-phenyl-1-benzophosphole are given in Table II. The α-proton is assigned to M and the β-proton to A. In acyclic organophosphorus compounds, $J_{PH\alpha}$ is generally less than $J_{PH\beta}$[55]. But our assignments would make $J_{PH\alpha}$ considerably greater than $J_{PH\beta}$ for 1-phenyl-1-benzophosphole. A comparison with related systems however shows that the value of J_{AX} is close

Table II. Nmr Parameters for Phosphole Ring Protons of 1-Phenyl-1-benzophosphole



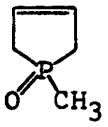
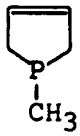
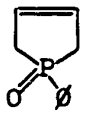
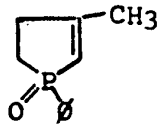
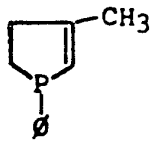
$\delta A = 7.49$; $\delta M = 6.80$
$J_{PH\beta}$ (J_{AX}) = 16.2 Hz
$J_{PH\alpha}$ (J_{MX}) = 38.0 Hz
$J_{H\alpha H\beta}$ (J_{AM}) = 7.2 Hz

to values of 12.5 and 13.77 Hz obtained for $J_{PH\beta}$ in 2,5-dimethyl-1-phenylphosphole[9,12] and 1-methylphosphole[13] respectively. Also, in 3-methyl-1-phenyl-2-phospholene, $J_{PH\alpha}$ is 42 Hz[43], and in selenophene $J_{SeH\alpha}$ and $J_{SeH\beta}$ have been reported[57] as 48 and 9.5 Hz respectively. These similarities strongly suggest that M is the α-proton and A is the β-proton.

An important difference that can be observed between the nmr spectra of 1-phenyl-1-benzophosphole and its oxide is in the position of the vinyl protons. In general phosphine oxides and phosphonium salts show a shift of the alkyl, aryl or vinyl substituent protons towards lower field in comparison with the parent phosphines. This shift has been interpreted to be associated with the positive charge on the phosphorus atom in phosphine oxide and phos-

phonium salt[41]. Table III shows some of the shifts of phospholene compounds in this connection. A comparison

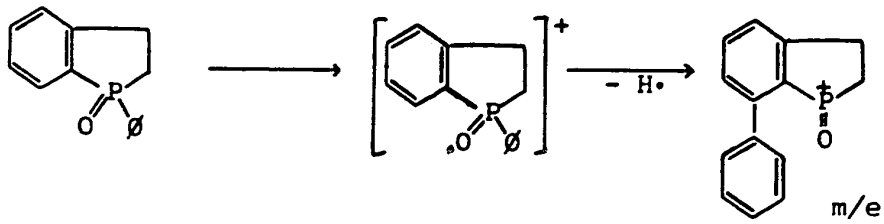
Table III. Pmr Spectra of Phospholenes and Oxides[a]

Compound	P-Ø	$P-CH_3$	CH_2	=CH	$C-CH_3$
	-	1.61	3.31	5.83	-
	-	0.81	1.75-2.75	5.72	-
	7.32-7.95	-	2.74	6.02	-
	6.80-7.40	-	1.80-2.80	5.50	-
	-	-	1.80-3.10	5.97	2.08
	-	-	1.50-2.80	5.68	1.80

a - Data given in δ (ppm)

between the spectra of 1-phenyl-1-benzophosphole and its oxide however reveals that the vinylic protons of the former are at lower field (a shift of 0.4 ppm), in complete reverse to the examples cited in Table III. Furthermore these protons are likely aromatic since they resonate well below 3.5δ, in the region of aromaticity. This observation may be interpreted to be due to delocalization of the lone pair at phosphorus and thereby imposing aromatic character on the phosphole ring.

Mass spectrum. The mass spectrum of 1-phenyl-1-oxy-2,3-dihydrobenzophosphole (fig. 12) shows a strong molecular ion (M^+) at 228. The only other prominent peak in the spectrum is the (M^+-1) ion at 227 which may arise from the loss of a hydrogen radical by rearrangement (Eq. 29). This



(29)

fragmentation pattern is quite different from that of the dienophile 1-phenyl-1-oxy-2-phospholene, which shows a strong tendency to eliminate ethylene instead (fig. 13). The (M^+-C_2H_4) ion is actually the base peak of the spectrum.

The mass spectrum of 1-phenyl-1-oxybenzophosphole (fig. 14)

is of considerable interest. Its prominent peaks and their relative abundance are shown in Table IV. The interesting features are the fragmentation peaks at m/e 178 and 179. Exact mass measurements show that these fragments have molecular formulae of $C_{14}H_{10}$ and $C_{14}H_{11}$ respectively. Most probably they arise from the loss of P=O fragment as shown in Scheme III. The observation of a metastable ion at m/e 151

Scheme III

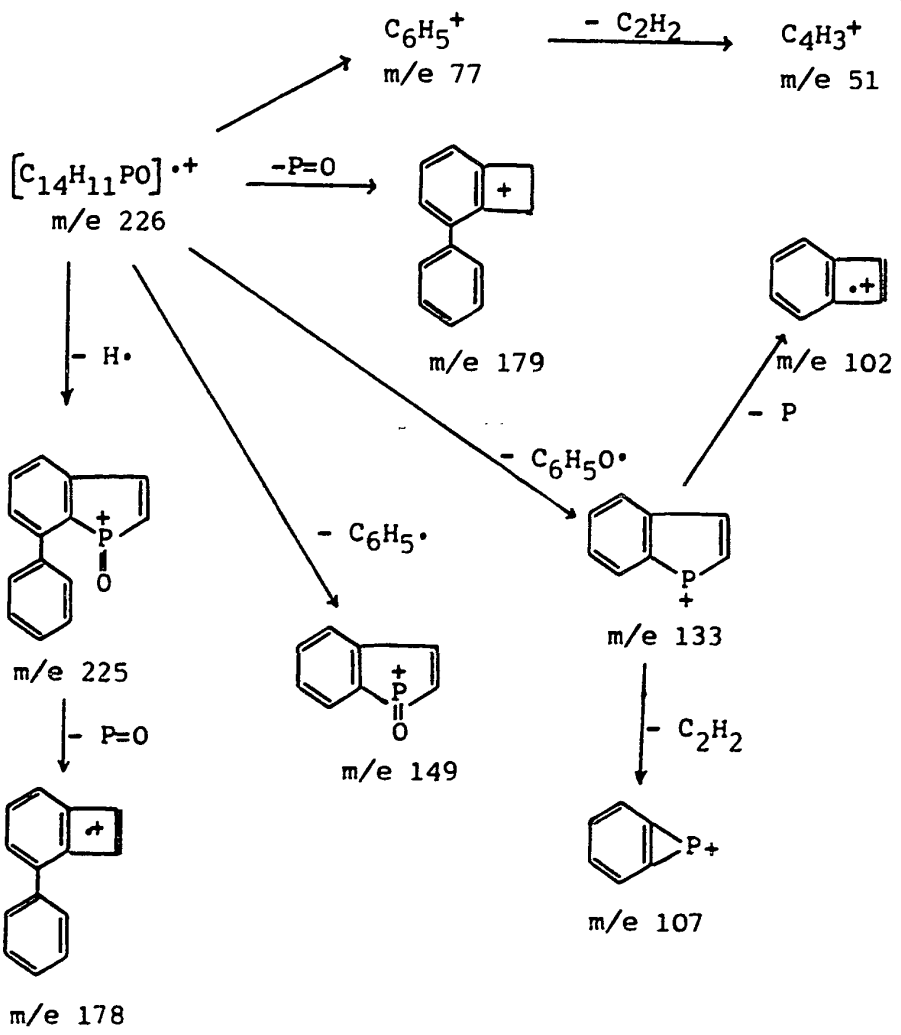


Table IV. Prominent Peaks in the Mass Spectrum of 1-Phenyl-1-oxybenzophosphole

m/e	Molecular Fragment	Exact Mass		Abundance
		Calcd	Found	
227 (M^++1)	$C_{14}H_{12}PO$			40
226 (M^+)	$C_{14}H_{11}PO$			100
225 (M^+-1)	$C_{14}H_{10}PO$			35
179	$C_{14}H_{11}$	179.0856	179.0860	84
178	$C_{14}H_{10}$	178.0776	178.0782	56
149	C_8H_6PO	149.0148	149.0156	60
133	C_8H_6P	133.0197	133.0207	30
121	C_7H_6P	121.0203	121.0207	28
107	C_6H_4P			15
102	C_8H_6			24
77	C_6H_5			35
51	C_4H_3			34
47	PO			20

indicates the direct fragmentation of mass 179 from the molecular ion by this kind of P=O elimination. The other fragments in the spectrum can be accounted for quite easily. Peaks at m/e 149 and 133 are derived from the loss of $C_6H_5\cdot$ and $C_6H_5O\cdot$ respectively from M^+. Elimination of acetylene from m/e 133 gives the m/e 107 ion whereas on the other hand loss of P produces the m/e 102 fragment.

The mass spectrum of 1-phenyl-1-benzophosphole (fig. 15) shows similar fragmentation pattern as its oxide. Table V gives the prominent peaks and their relative abundance. The most abundant ion is the molecular peak (M^+) of m/e 210. Strong M^+ peaks are characteristic of the related hetero-

Scheme IV

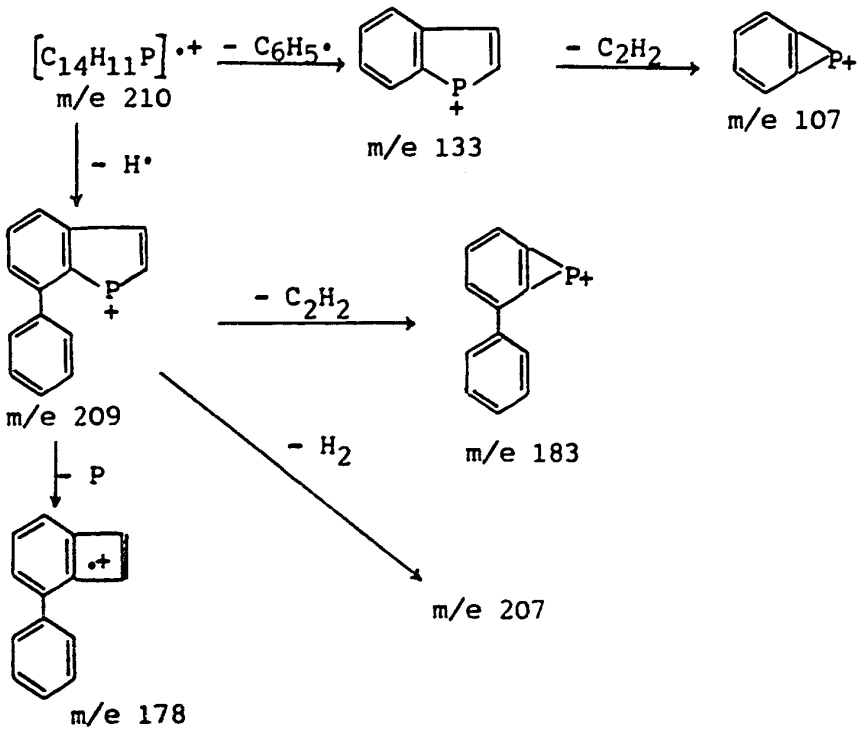


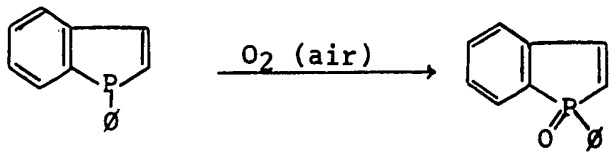
Table V. Prominent Peaks in the Mass Spectrum of 1-Phenyl-1-benzophosphole

m/e	Molecular Fragment	Exact Mass		Abundance
		Calcd	Found	
211 (M^++1)	$C_{14}H_{12}P$			16
210 (M^+)	$C_{14}H_{11}P$	210.0591	210.0598	100
209 (M^+-1)	$C_{14}H_{10}P$			17
207 (M^+-3)	$C_{14}H_8P$			16
183	$C_{12}H_8P$	183.0354	183.0364	13
178	$C_{14}H_{10}$	178.0779	178.0782	72
133	C_8H_6P	133.0197	133.0207	10
107	C_6H_4P			12

aromatics[58], attest to the stability of the ring system. The next abundant ion is the peak at m/e 178. Exact mass measurement gives the formula $C_{14}H_{10}$ which could arise only by elimination of P from the m/e 209 peak. Loss of acetylene from the same peak on the other hand gives the m/e 183 ion. Fragment at m/e 133 is resulted from direct loss of $C_6H_5\cdot$ from M^+. Further elimination of acetylene from this produces the m/e 107 ion.

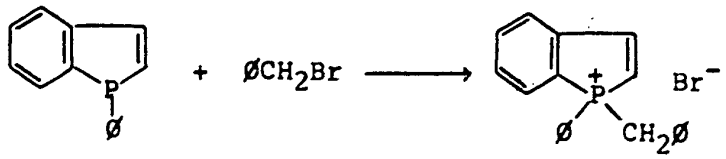
Chemical properties of 1-phenyl-1-benzophosphole

Oxidation. Like all phosphines, 1-phenyl-1-benzophosphole is very susceptable to oxidation. A pure sample left



standing in contact with air was completely converted to the oxide. The product that was obtained gave identical spectroscopic properties as that of compound XXVII.

Phosphonium salt. 1-Phenyl-1-benzophosphole undergoes



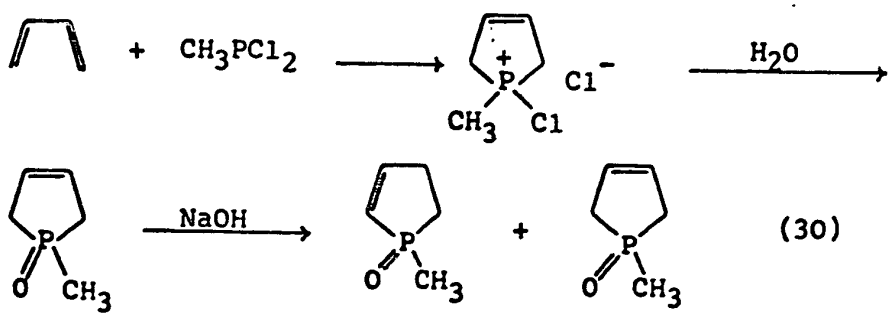
another typical phosphine reaction, reacting with alkyl

halide to form quaternary salt. Thus its reaction with benzyl bromide gave phenylbenzylbenzophospholephosphonium bromide (XXIX), m. p. 225°.

CONCLUSION

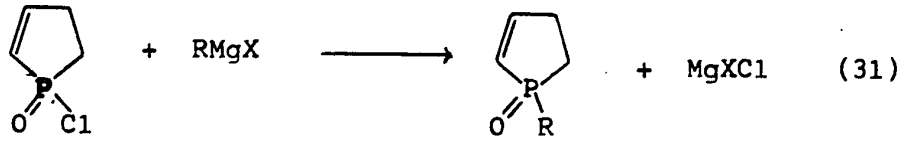
In this research project, a simple synthetic route has been developed for the synthesis of 1-phenyl-1-benzophosphole. The spectroscopic properties of this compound has been examined and uv and nmr interpretations give evidence of aromaticity of the benzophosphole system. This finding is in close accord with that of Quin[13] who also reported similarly on the aromaticity of 1-methylphosphole.

From the synthetic point of view, this route can be extended for the preparations of other 1-substituted-benzophospholes. The required dienophiles may be prepared similarly from the McCormack reaction[11]. For example the 1-methyl compound has been prepared by Quin[42] according to Eq. 30.



Another more versatile way of obtaining the dienophile

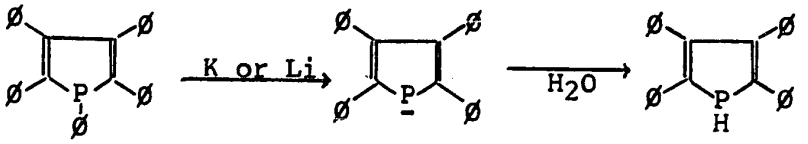
may involve the use of 1-chloro-1-oxy-2-phospholene (XXX). Quin reported recently that the reaction[43] between 1-chloro-3-methyl-2-phospholene oxide and phenyl Grignard reagent gave 1-phenyl-3-methyl-2-phospholene oxide. It is conceivable that this reaction could also be applied for 1-chloro-1-oxy-2-phospholene and various Grignard reagents (Eq. 31). The success of this alternate route of preparation



(31)

can eliminate the need of having to start from a particular alkyl or aryldichlorophosphine in the McCormack reaction which is sometimes difficult to obtain.

The synthesis of the parent 1-benzophosphole (III) by this present method appears to be more difficult since the required dienophile, 1-oxy-2-phospholene (XVIIIa, R=H), cannot be easily prepared. It has been reported that P-unsubstituted phosphole[50] and dibenzophosphole[51] derivatives could be prepared from metallic cleavage of the corresponding P-phenyl compound followed by hydrolysis (Eq. 32-33). Hence it would appear that the parent 1-benzophosphole could also be obtained similarly (Eq. 34).



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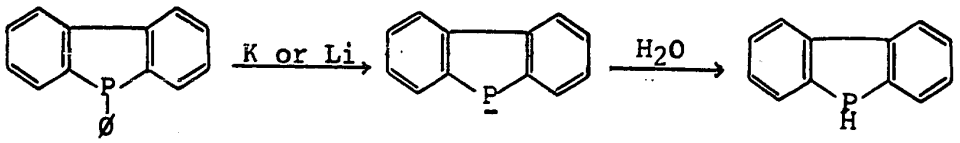

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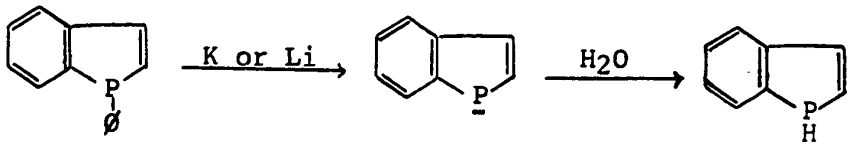
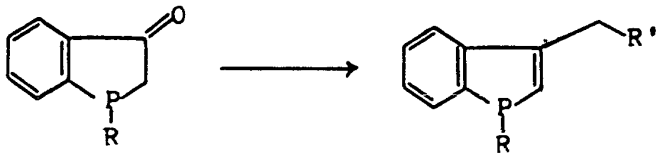


(34)

Finally further synthesis could be extended on the benzophosphole system and derivatives. For example, introduction of an active functional group like a ketone in the 3-position of 2,3-dihydrobenzophosphole could lead to the preparations of a large number of phosphorus analogs of indole (Eq. 35). Simple indole alkaloids like gramine, tryptamine and serotonin are an important class of compound



(35)

which shows pronounced physiological activities. It would remain interesting to synthesize the phosphorus analogs of these compounds and compare their activities (if any) with that of the corresponding indole.

EXPERIMENTAL SECTION

1. Benzene was dried over sodium and was distilled immediately prior to use.
2. All melting points are not corrected.
3. Infrared (ir) spectra were taken on a Perkin-Elmer Model 237B with polystyrene calibration.
4. Ultraviolet (uv) spectra were recorded using an Unicam SP 800A UV Spectrophotometer.
5. Nuclear magnetic resonance (nmr) spectra were measured on Varian A60 or T60 spectrometers, using tetramethylsilane (TMS) as an internal standard. The 220 MHz spectrum was obtained from the 220 MHz laboratory, Sheridan Park, Ontario.
6. Mass spectra were recorded using an AEI MS-902 instrument.
7. Microanalyses were performed by Microanalyses Lab., Denmark.

trans,trans-1,4-Diacetoxybutadiene. The method of Hill and Carlson[29] was modified slightly to obtain purer intermediate compound 7,8-diacetoxybicyclo[4.2.0]-octadiene-(2,4) as follows: To 80 g. (0.25 mole) of mercuric acetate stirring in 200 ml. glacial acetic acid was added 26 g. (0.25 mole) cyclooctatetraene. The white precipitate formed after 15 minutes was decomposed by heating in an oil bath at 70° for about 2 hours. The warm mixture was poured into 2 l. of water and stood overnight. The greyish-brown precipitate was filtered and extracted into acetone. Mercury was separated off and the organic solvent evaporated to yield crude 7,8-diacetoxybicyclo[4.2.0]-octadiene-(2,4) which was air dried overnight; yield 45 g., 82%.

A solution of 44.5 g. (0.2 mole) 7,8-diacetoxybicyclo-[4.2.0]-octadiene-(2,4) and 28.4 g. (0.2 mole) dimethyl acetylenedicarboxylate in 150 ml. benzene was refluxed for 6 hours. The solvent was evaporated and the residue distilled at reduced pressure. A mixture of 1,4-diacetoxybutadiene and dimethyl phthalate started to distil at 130°(7mm) from which the diacetoxybutadiene precipitated out in the cooled receiver. When no more precipitation was observed to form, the distillation was stopped. The solid was triturated with petroleum ether and filtered. Recrystallization from acetone-petroleum ether gave 16 g. (47%) colorless needles, m.p. 103-104°(Lit.[52] m.p. 103-104°)

Reaction of 1,4-diacetoxybutadiene with 2,3-dihydrothiophene-1-dioxide: A mixture of 0.2 g. (0.001 mole) diacetoxybutadiene, 0.14 g. (0.001 mole) 2,3-dihydrothiophene-1-dioxide[31] and a pinch of hydroquinone was heated in a sealed tube at 150° for 7 days. The tube was opened and the reaction mixture was taken up in 10 ml. of 95% ethanol. Sodium hydroxide (0.4 g.) was added and the mixture refluxed for 4 hrs. The solution was cooled, acidified with 10% sulfuric acid and then extracted 5 times with chloroform. The organic solvent was evaporated and the residue was chromatographed on silica gel, with ether as the eluent. From this was obtained 0.2 g. (20% based on reacted 2,3-dihydrothiophene-1-dioxide) of 2,3-dihydrobenzothiophene-1-dioxide (m.p. 89-91°) whose infrared spectrum was identical with that of an authentic sample*.

Benzothiophene-1-dioxide: A mixture of 0.1 g. (0.0006 mole) 2,3-dihydrobenzothiophene-1-dioxide, 0.11 g. (0.0006 mole) N-bromosuccinimide and a few grains of benzoyl peroxide in 10 ml. of dry benzene was refluxed for 2 hrs. The solvent was evaporated and the residue separated by preparative t.l.c. From this was obtained 0.085 g. (58%) of the monobromobenzothiophene-1-dioxide as an oil. The compound was dissolved in 5 ml. benzene and treated with 0.1 g. triethylamine. The triethylamine hydrobromide was filtered and the solvent was

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* Prepared by oxidation of thionaphthene to its 1-dioxide followed by hydrogenation[59], m.p. 91-92°.

evaporated to give 0.048 g. (84%) of benzothiophene-1-dioxide, m.p. 141-143°. A mixed melting point determination of the compound with an authentic sample was undepressed.

Preparation of 1-phenyl-1-oxy-2-phospholene. The compound was prepared according to the method reported by McCormack[11]: A charge of 38 g. (0.21 mole) phenyldichlorophosphine, 11.6 g. (0.21 mole) butadiene (cooled) and 0.2 g. copper-stearate[53] was placed in a pressure bottle and stored at room temperature for 2 months. The bottle was opened and the brown viscous adduct was hydrolysed with 400 ml. of ice water. The pH of the solution was adjusted to 6.5 with 30% sodium hydroxide. The solution was then saturated with sodium chloride and extracted with three 200 ml. portions of chloroform. The combined extract was dried with $MgSO_4$ and the solvent evaporated. Vacuum distillation of the residue gave 12 g. (32%) of 1-phenyl-1-oxy-2-phospholene, b.p. 140-144°/0.05mm; m.p. 73-76° (Lit.[11] b.p. 153-5°/0.2mm; m.p. 67-75°).

Reaction of 1,4-diacetoxybutadiene with 1-phenyl-1-oxy-2-phospholene: A mixture of 1 g. (0.006 mole) diacetoxybutadiene, 1 g. (0.006 mole) 1-phenyl-1-oxy-2-phospholene and a pinch of hydroquinone was heated in a sealed tube at 150° for 14 days. The tube was opened and the dark reaction mixture was chromatographed on silica gel, eluting with

ethyl acetate. From this there was obtained 0.28 g. (22%) of crude 1-phenyl-1-oxy-2,3-dihydrobenzophosphole as a brownish oil which solidified under vacuo overnight. Purification by subliming at 100°/0.1mm gave colorless hygroscopic solid m.p. 97-101°. An analytical sample was obtained by repeated sublimation (3 times). Anal.- Calcd. C, 73.65; H, 5.70. Found C, 73.3; H, 6.1.

1-Phenyl-1-oxybenzophosphole: To a solution of 0.16 g. (0.0007 mole) 1-phenyl-1-oxy-2,3-dihydrobenzophosphole in 20 ml. dry benzene was added 0.13 g. (0.0007 mole) N-bromo-succinimide and a few grains of benzoyl peroxide.The mixture was refluxed for 3 hrs. and cooled to room temperature. To this was added 0.1 g. of triethylamine and the resulting mixture was left stirring overnight. The triethylamine hydrobromide salt was filtered off and the filtrate evaporated to dryness. The residue was chromatographed on silica gel, eluting with ethyl acetate. From this there was obtained 0.12 g. crude 1-phenyl-1-oxybenzophosphole which was purified by subliming at 120°/0.1mm. The yield of pure product was 0.08 g. (50%), m.p. 84-88°. Anal.- Calcd. C, 74.3; H, 4.9. Found C, 73.9; H, 5.0.

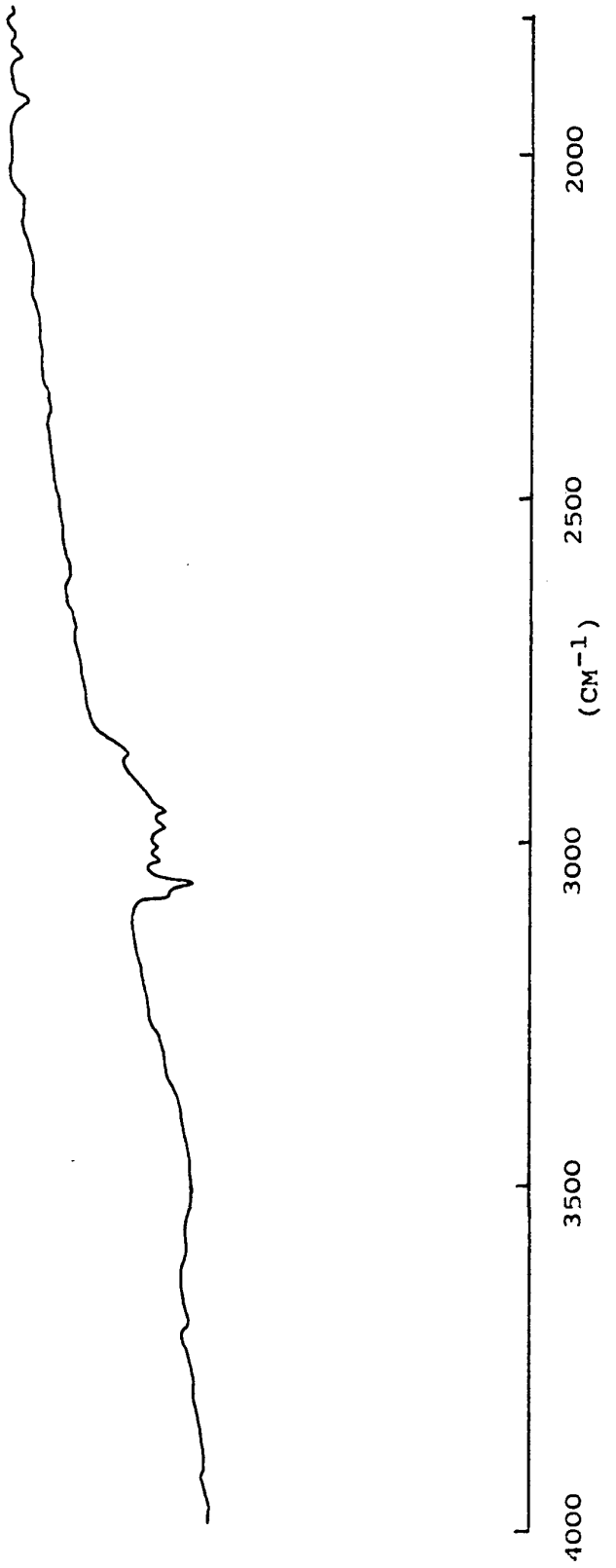
Reduction of 1-phenyl-1-oxybenzophosphole with trichlorosilane: To a solution of 0.11 g. (0.0005 mole) 1-phenyl-1-oxybenzophosphole in 10 ml. dry benzene was added 0.2 g.

(0.0015 mole) trichlorosilane. The mixture was refluxed for 2 hrs, cooled and hydrolysed with 30% NaOH solution. The silica was filtered off and the filtrate washed twice with water. The organic solution was dried with $MgSO_4$ and evaporated to yield a solid residue. Purification by subliming at 30-35°/1mm gave 0.032 g. (35%) 1-phenyl-1-benzophosphole, m.p. 66-68°. Anal.- Calcd. C, 80.0; H, 5.2. Found C, 79.9; H, 5.4.

Reduction of 1-phenyl-1-oxybenzophosphole with hexachlorodisilane: To a solution of 0.11 g. (0.0005 mole) 1-phenyl-1-oxybenzophosphole in 10 ml. dry benzene was added 0.09 cc (134 mg., 0.0005 mole) hexachlorodisilane. The mixture was refluxed for 2 hrs., cooled and hydrolysed with 30% NaOH solution. Work up the similar way gave 0.028 g. (30%) 1-phenyl-1-benzophosphole, m.p. 66-68°.

Figure 1

Infrared Spectrum of 1-Phenyl-
1-benzophosphole


4000
3500
3000
2500
2000
(CM-1)

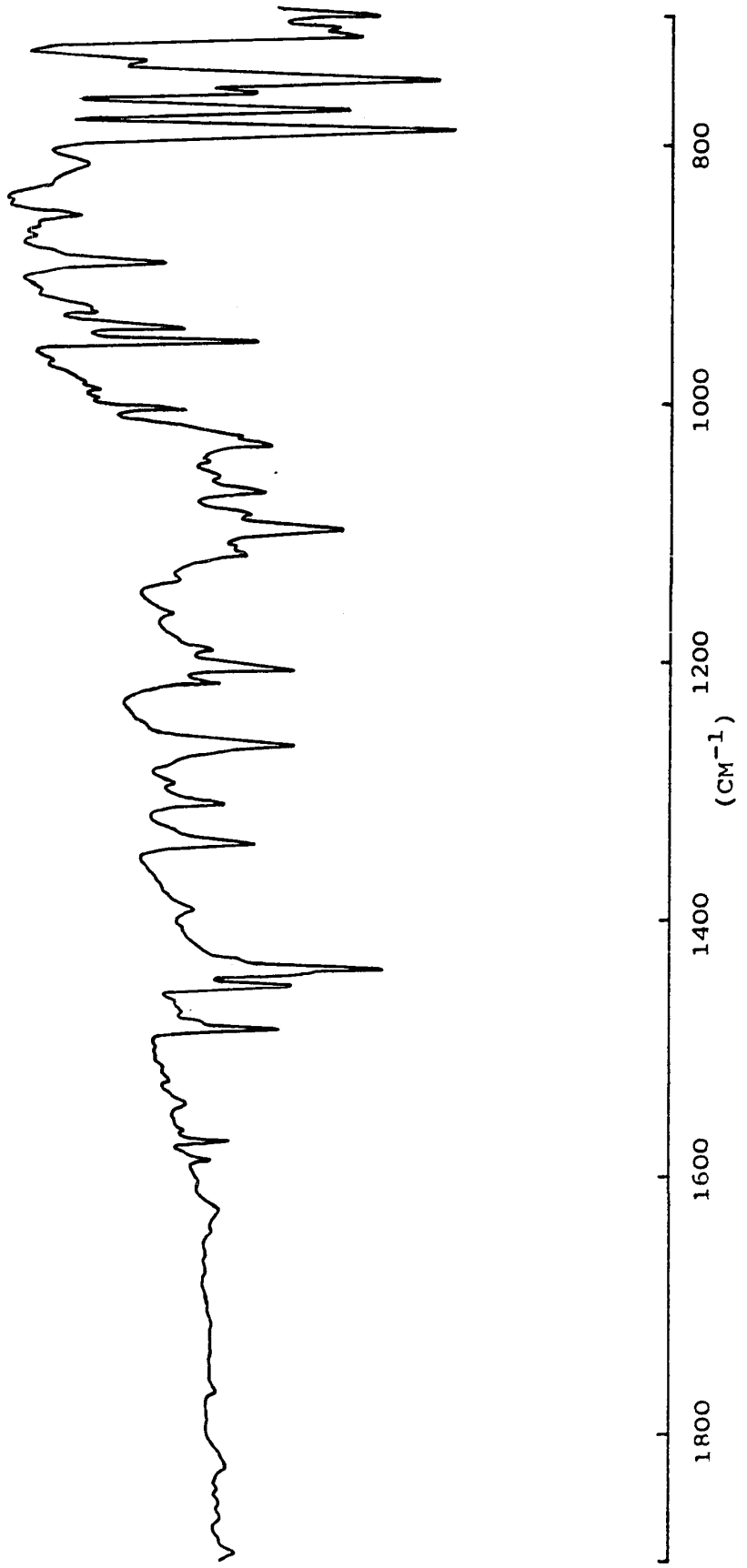
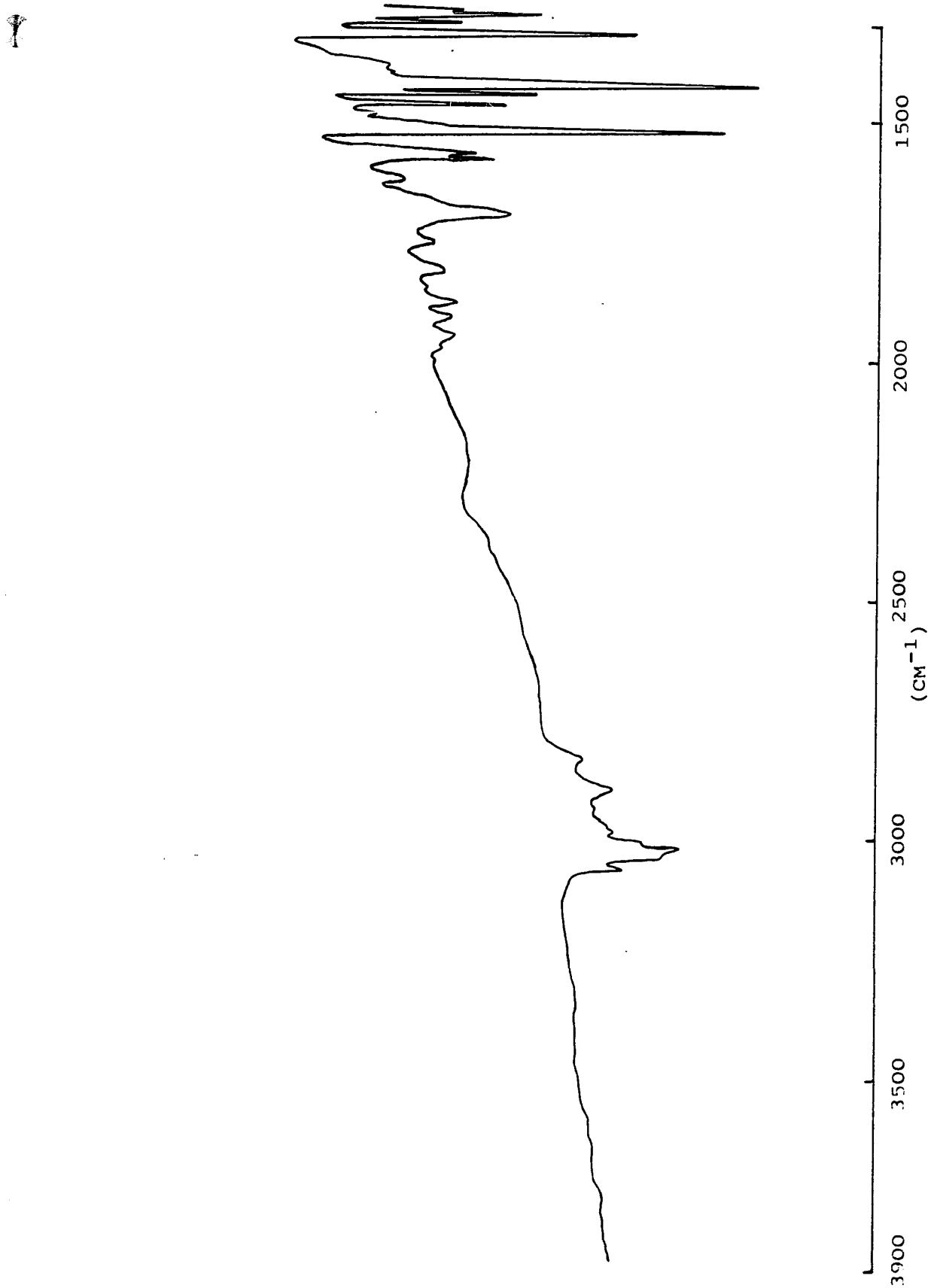

800
1000
1200
1400
1600
1800
(CM-1)

Figure 2

Infrared Spectrum of 1-Phenyl-
1-oxybenzophosphole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3500
3000
2500
2000
1500
(CM-1)

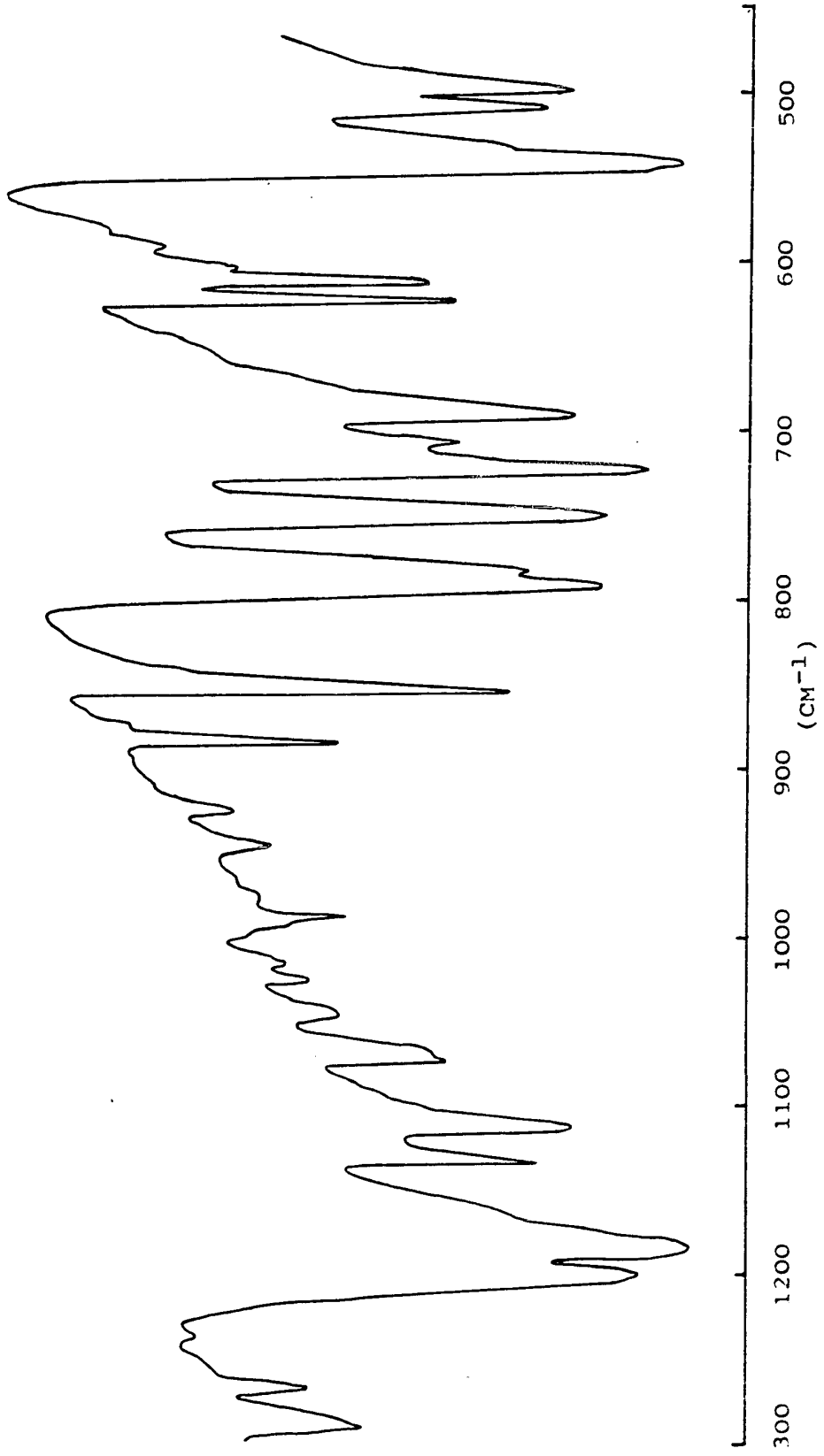
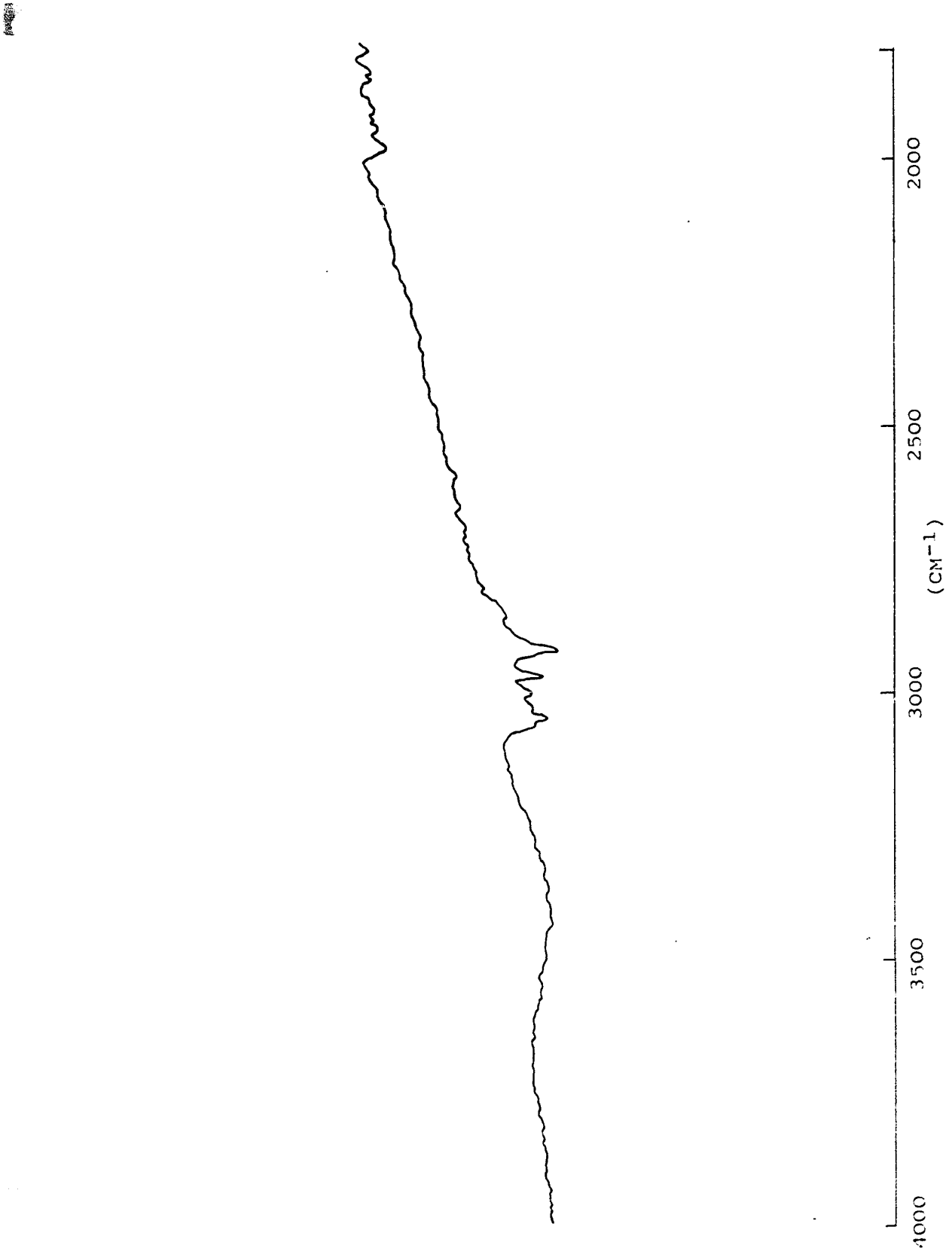

500
600
700
800
900
1000
1100
1200
1300
(CM-1)

Figure 3

Infrared Spectrum of 1-Phenyl-1-oxy-2,3-dihydrobenzophosphole


4000
3500
3000
2500
2000
(CM-1)

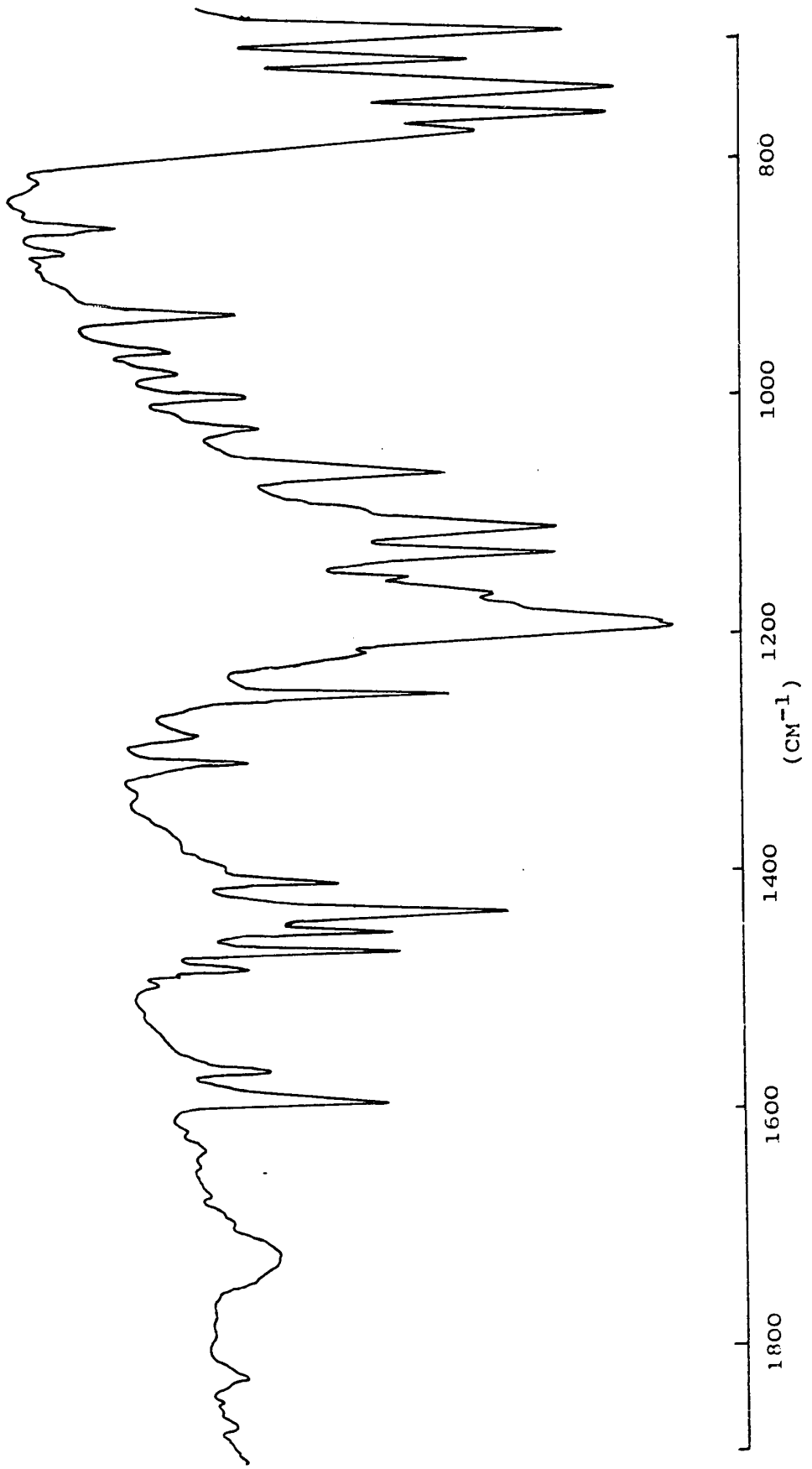

800
1000
1200
1400
1600
1800
(CM-1)

Figure 4

Ultraviolet Spectrum of 1-Phenyl-1-oxy-2,3-dihydrobenzophosphole

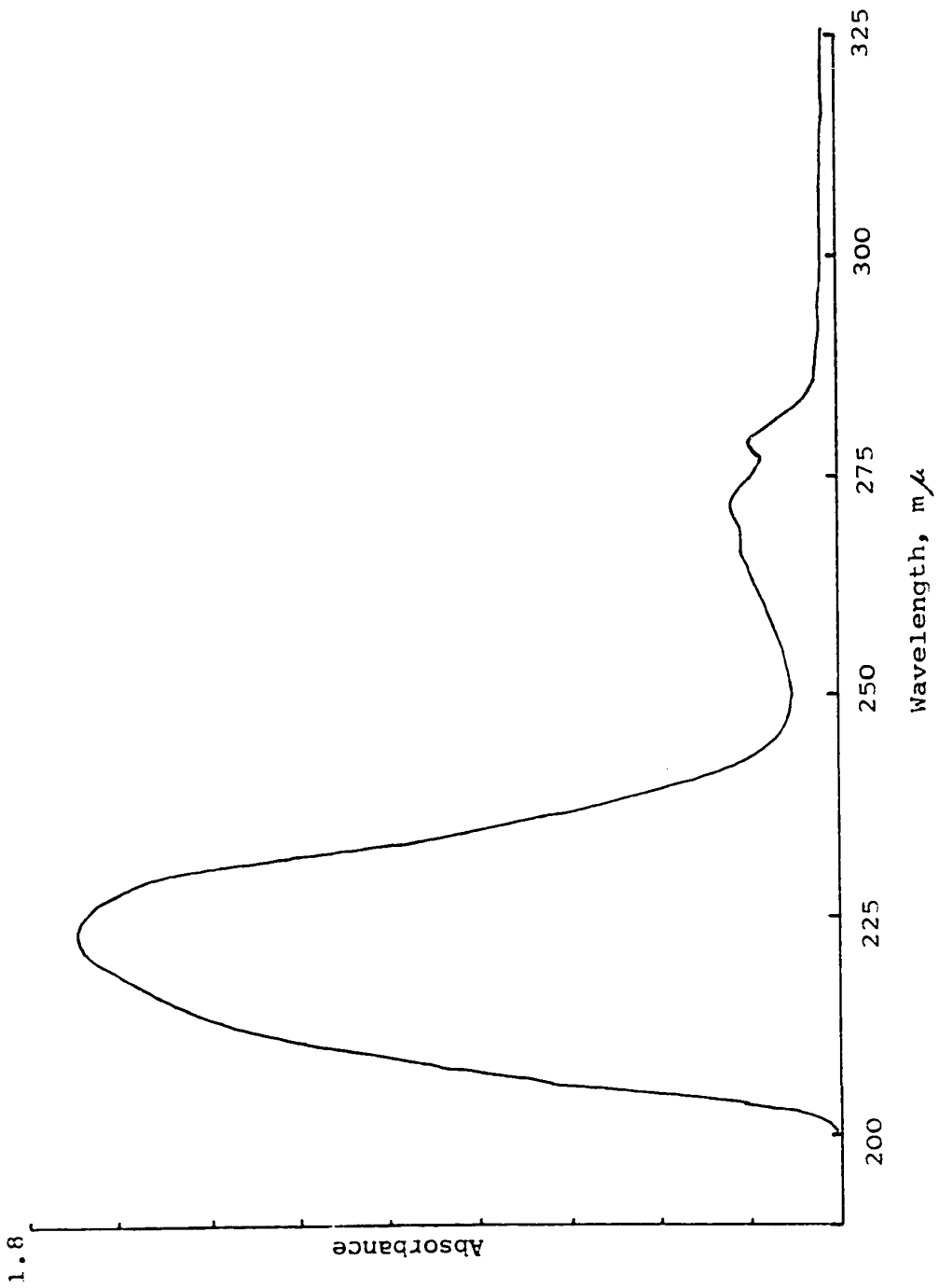

1.8
Absorbance
200
225
250
275
300
325
Wavelength, mμ

Figure 5

Ultraviolet Spectrum of 1-Phenyl-
1-benzophosphole

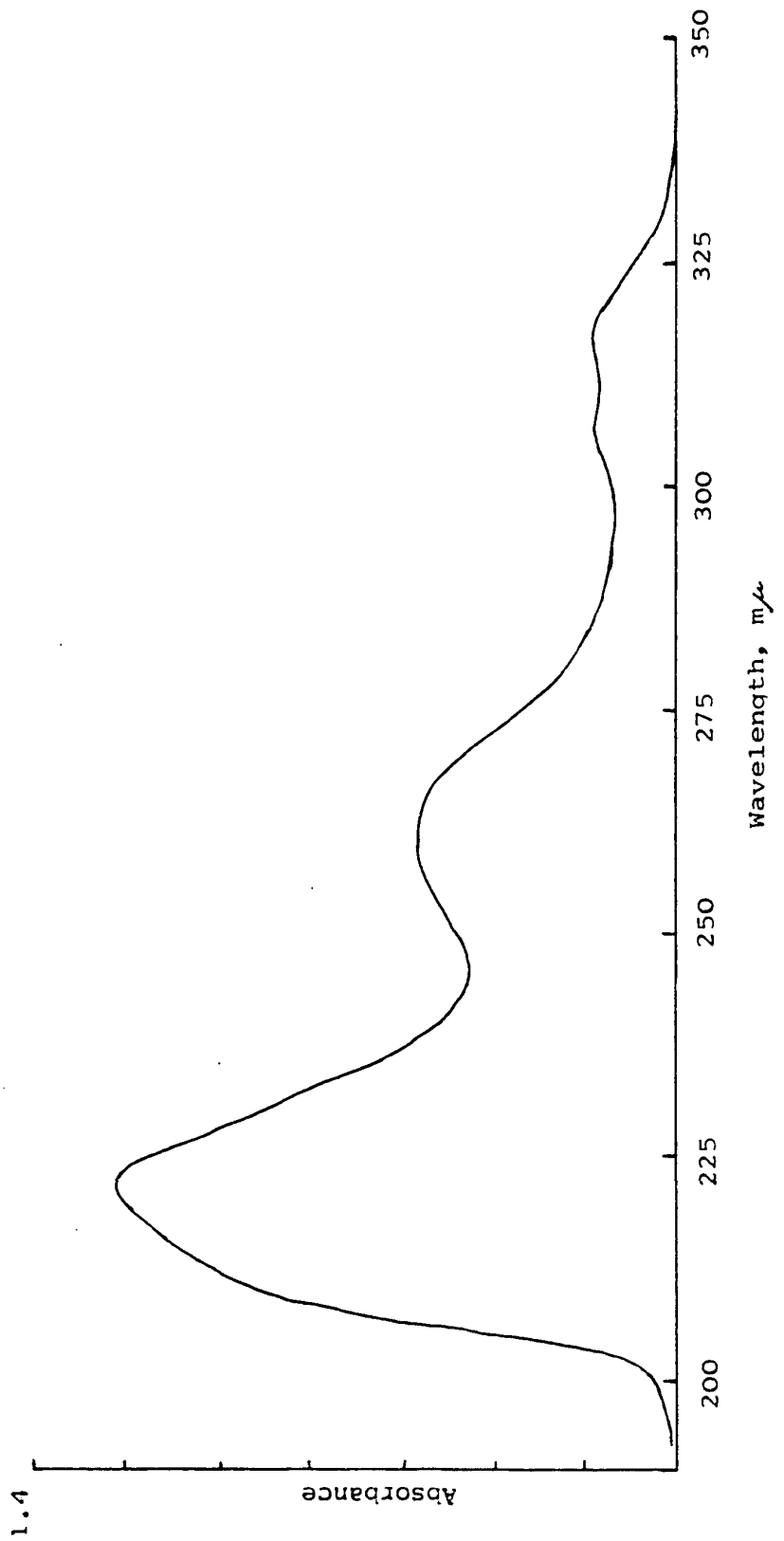

1.4
Absorbance
200
225
250
275
300
325
350
Wavelength, mμ

Figure 6

Ultraviolet Spectrum of 1-Phenyl-1-oxybenzophosphole

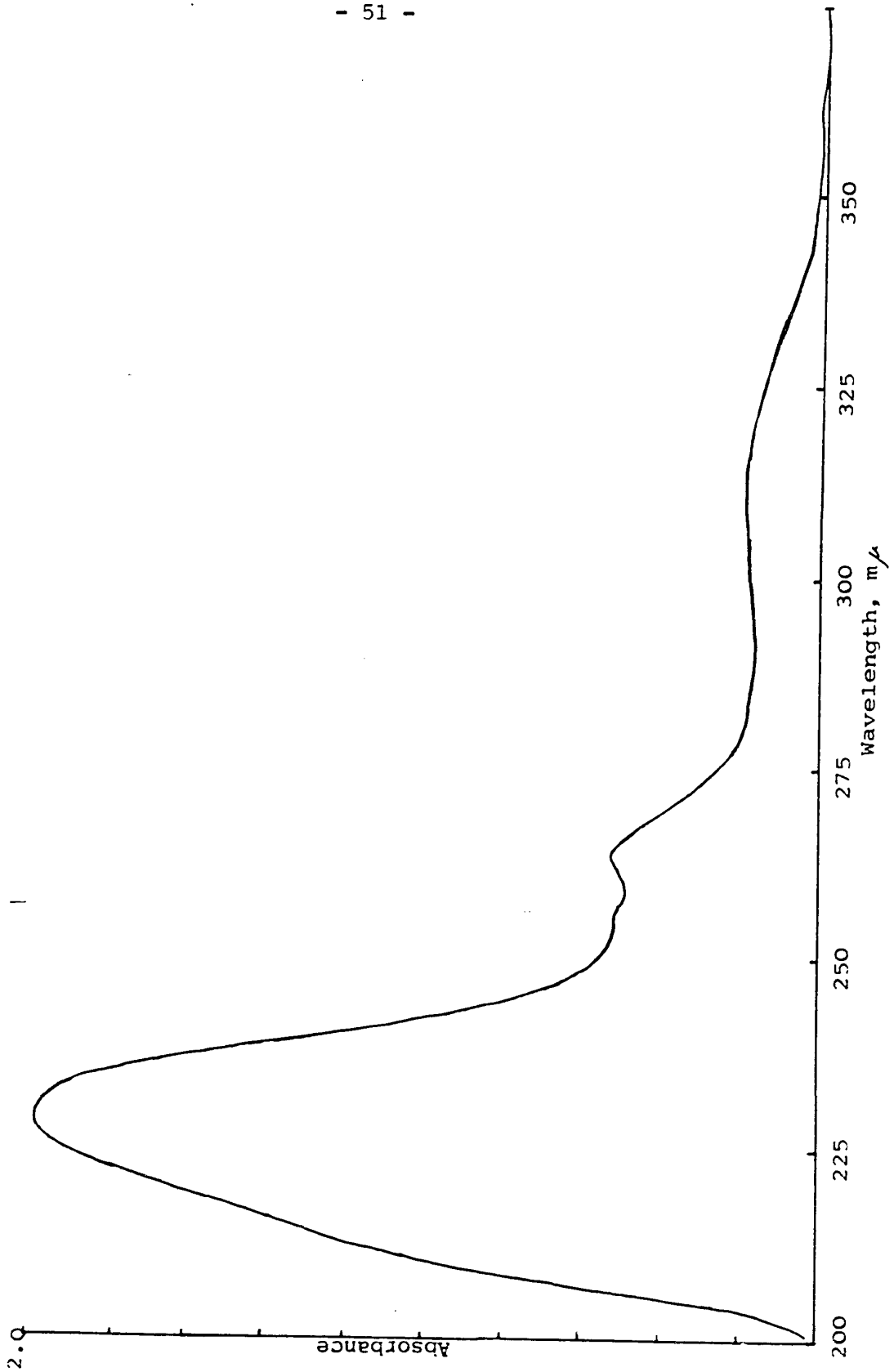

2.0
Absorbance
200
225
250
275
300
325
350
Wavelength, mμ

Figure 7

Ultraviolet Spectra of 1-Phenyl-
1-benzophosphole—·—·—·—·—·—·—·—;
1-Phenylindole——————————.

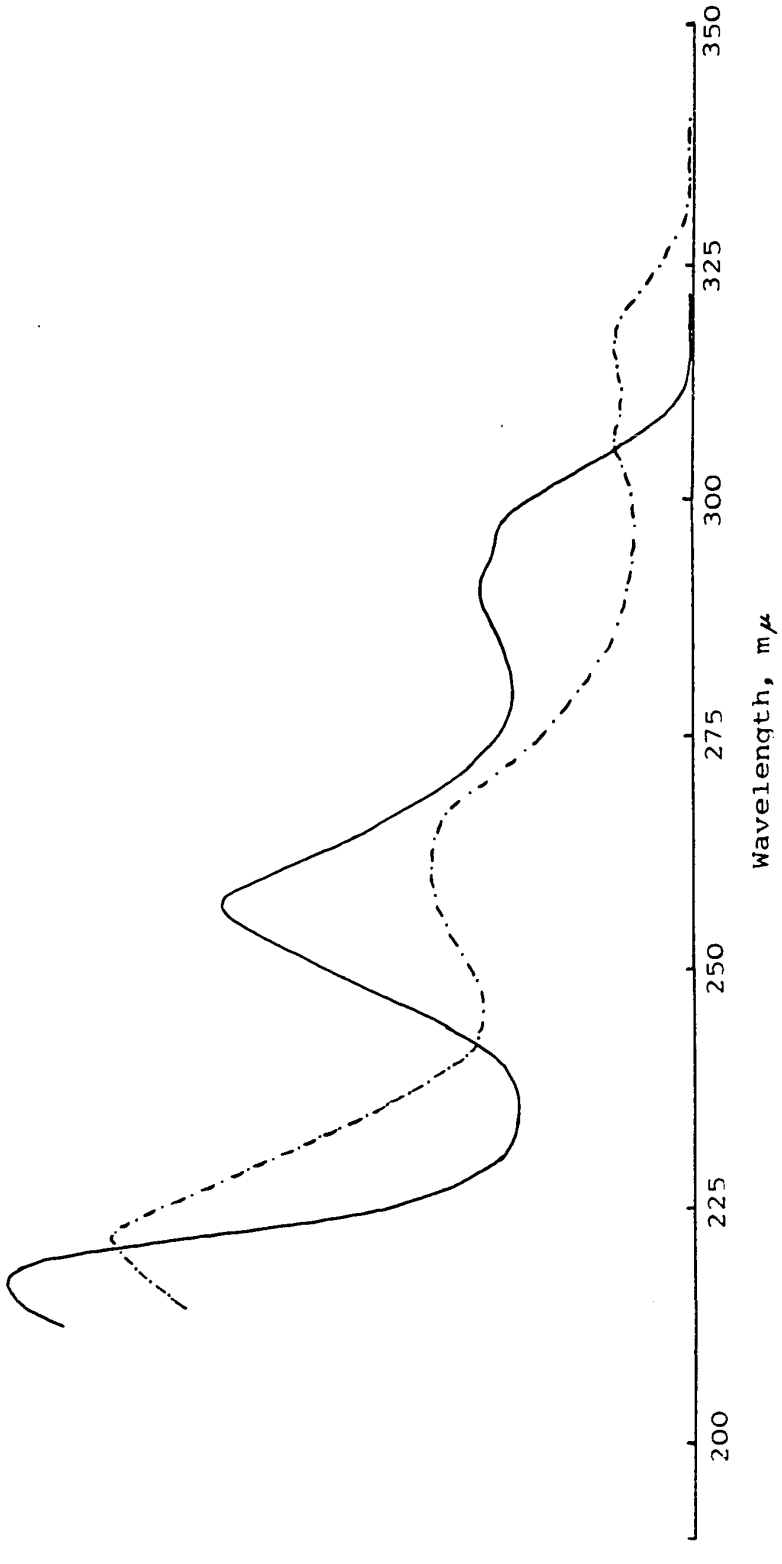

200
225
250
275
300
325
350
Wavelength, mμ

Figure 8

60 MHz NMR Spectrum of 1-Phenyl-1-oxy-2,3-dihydrobenzophosphole

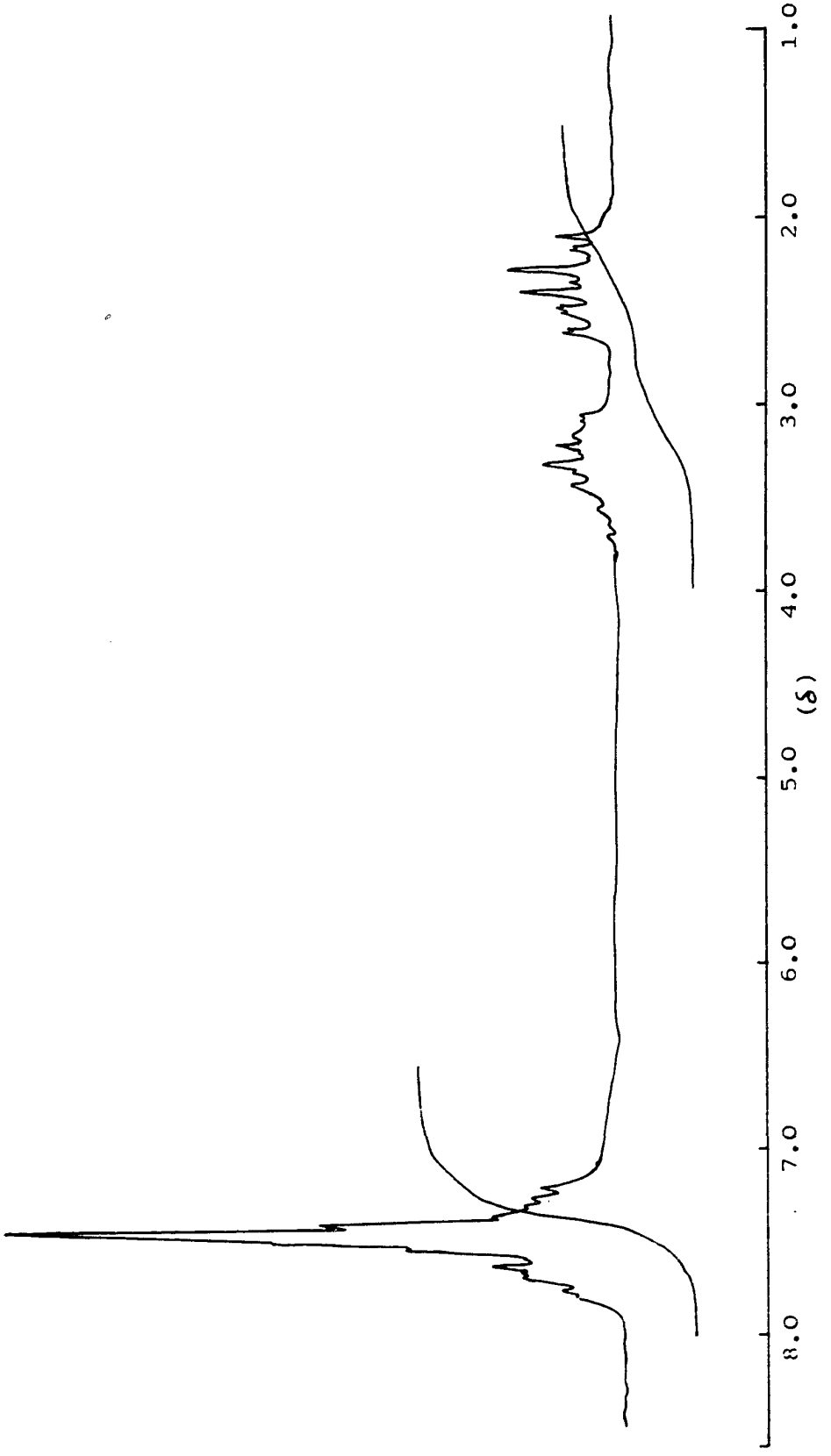

8.0
7.0
6.0
5.0
(δ)
4.0
3.0
2.0
1.0

Figure 9

100 MHz NMR Spectrum of 1-Phenyl-1-oxybenzophosphole

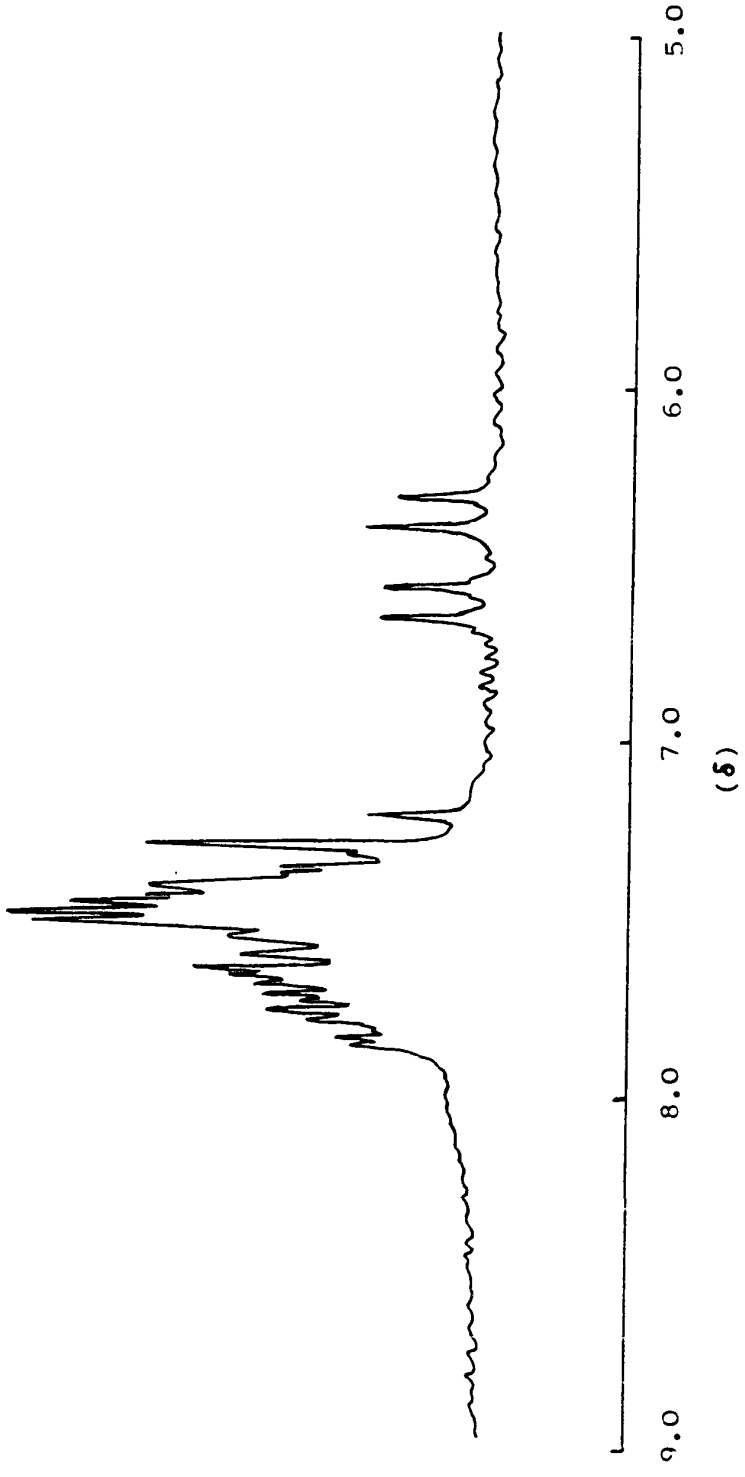

5.0
6.0
7.0
8.0
9.0
(δ)

Figure 10

100 MHz NMR Spectrum of 1-Phenyl-1-benzophosphole

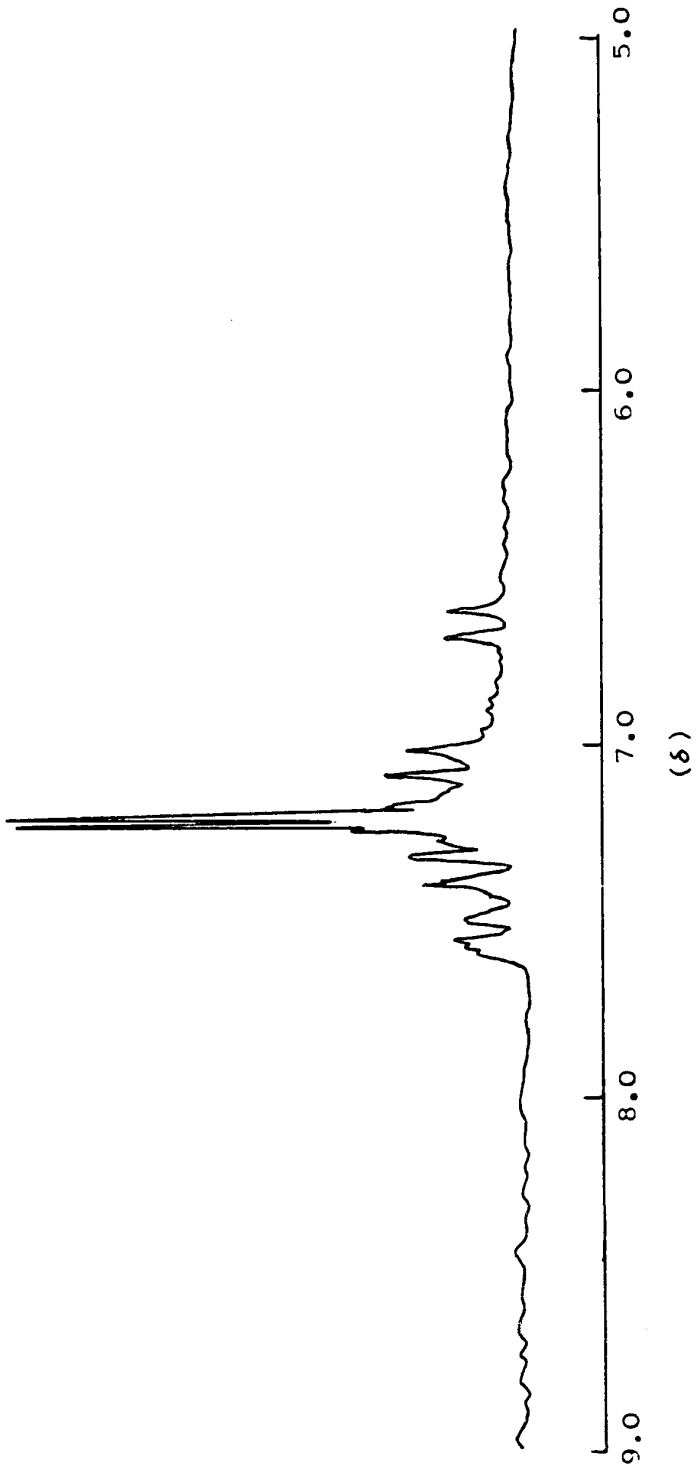

5.0
6.0
7.0
8.0
9.0
(δ)

Figure 11

220 MHz NMR Spectrum of 1-Phenyl-1-benzophosphole

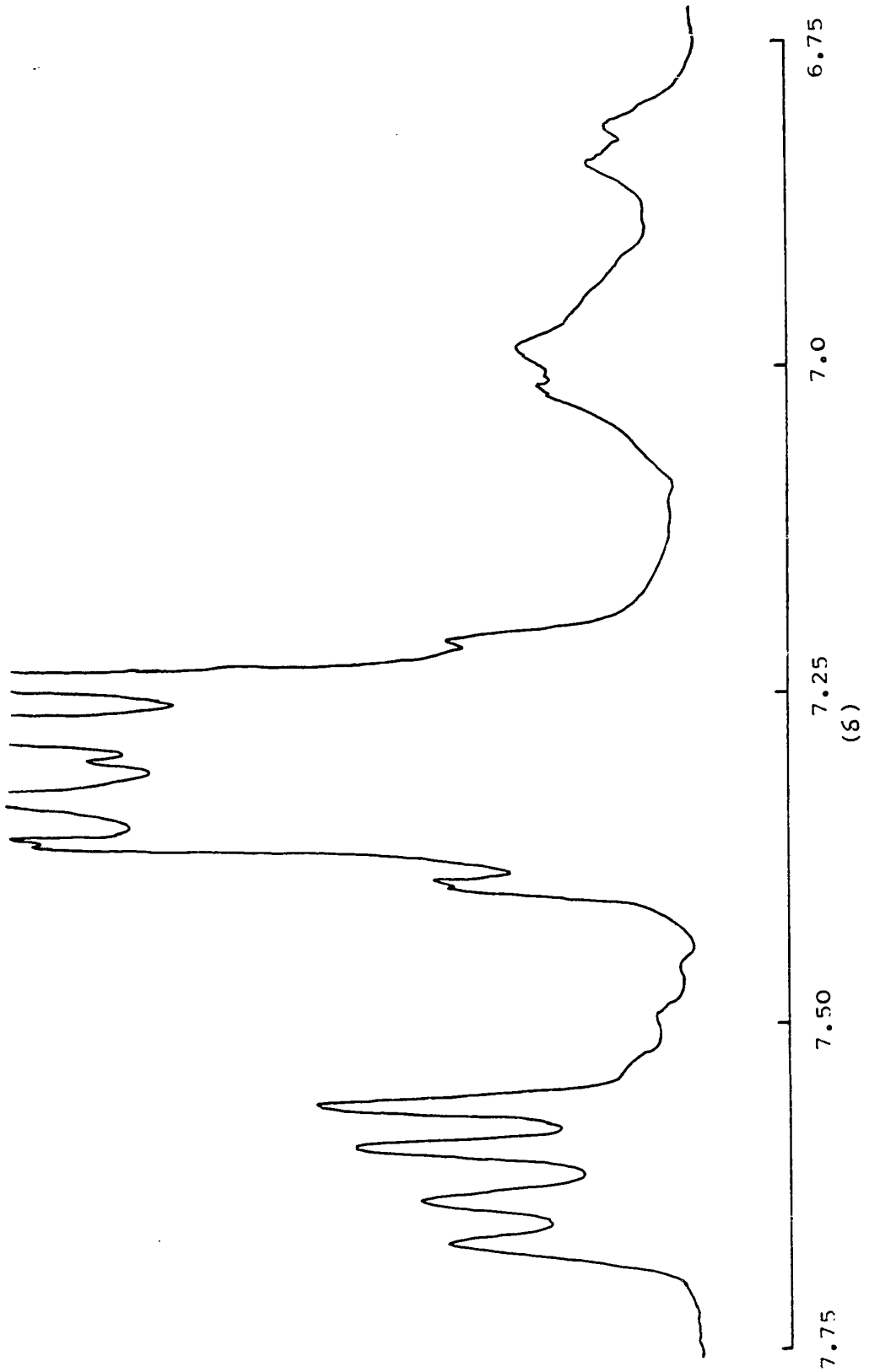

7.75
7.50
7.25
(δ)
7.0
6.75

Figure 12

Mass Spectrum of 1-Phenyl-1-oxy-
2,3-dihydrobenzophosphole

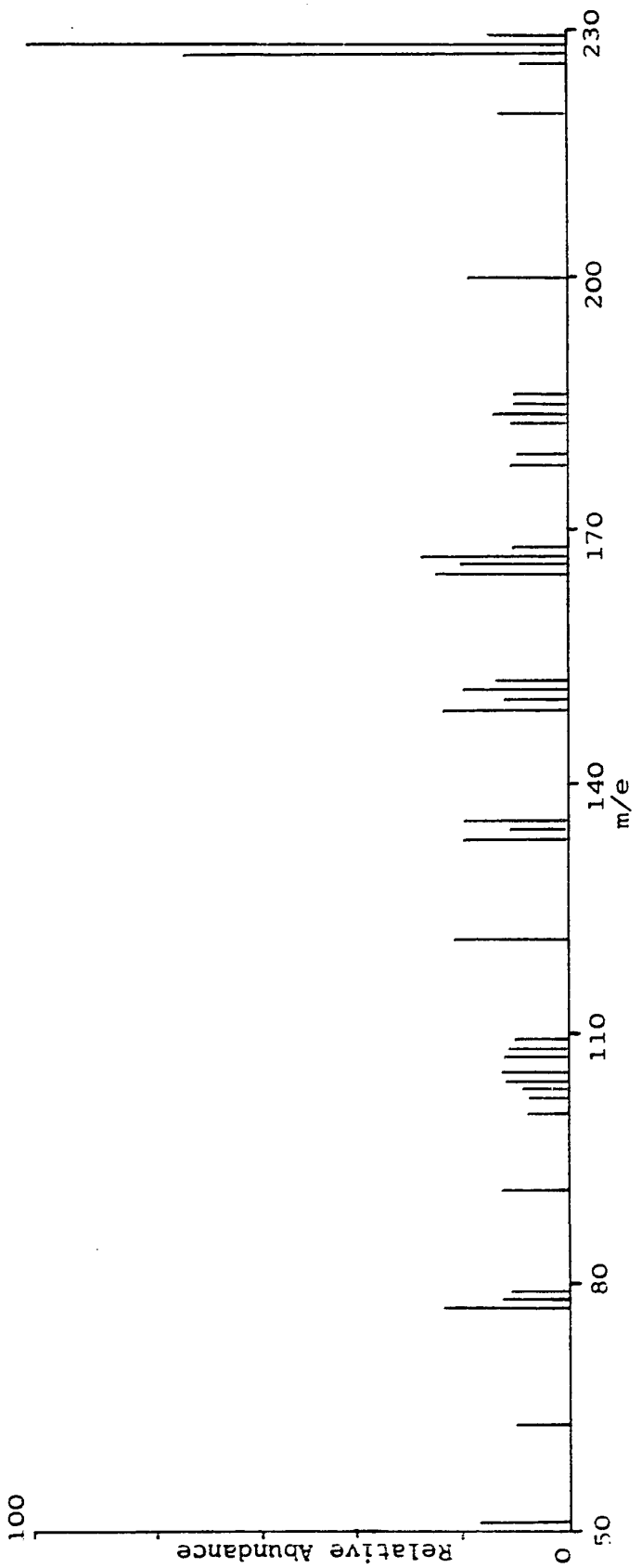

Relative Abundance
100
0
50
80
110
140
170
200
230
m/e

Figure 13

Mass Spectrum of 1-Phenyl-1-oxy-
2-phospholene

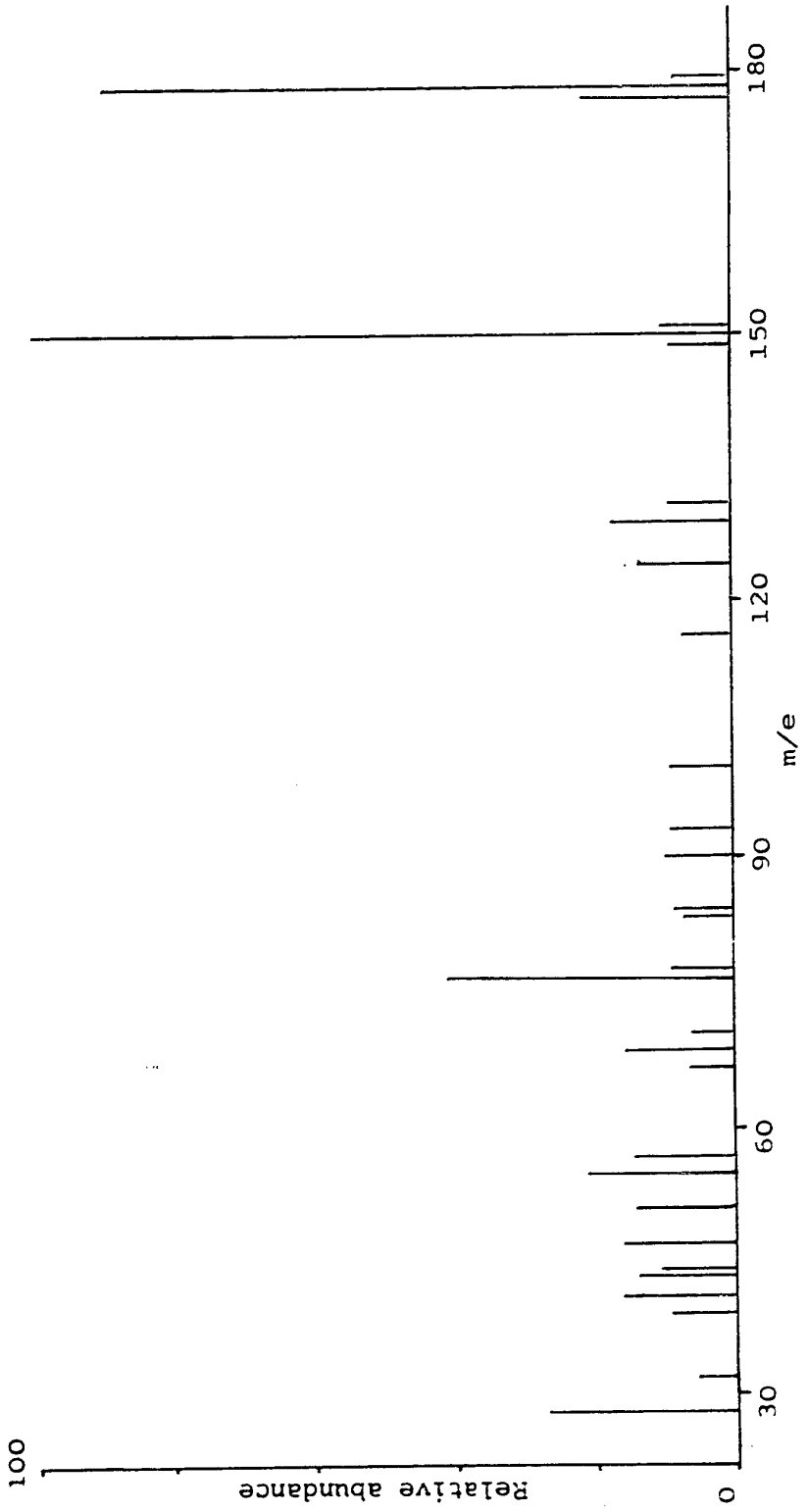

Relative abundance
100
0
30
60
90
120
150
180
m/e

Figure 14

Mass Spectrum of 1-Phenyl-
1-oxybenzophosphole

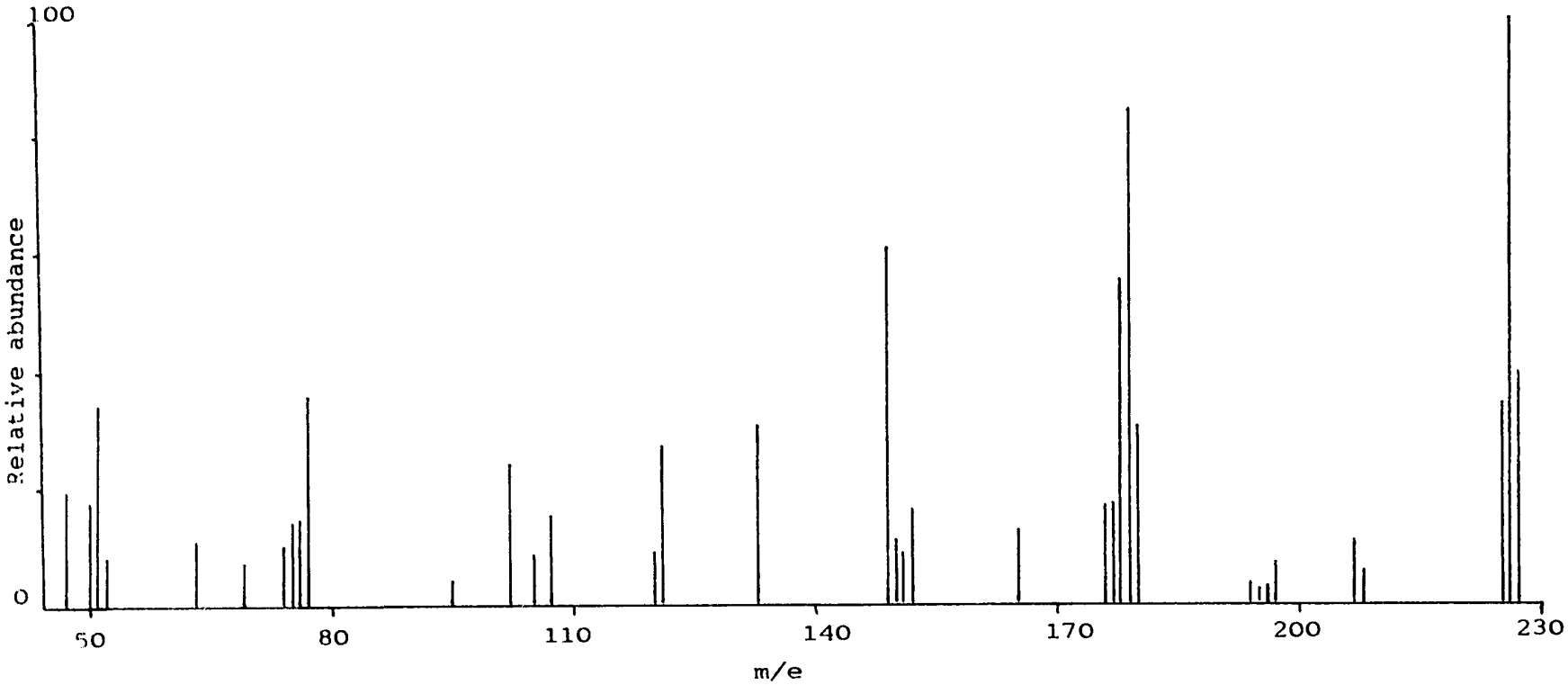
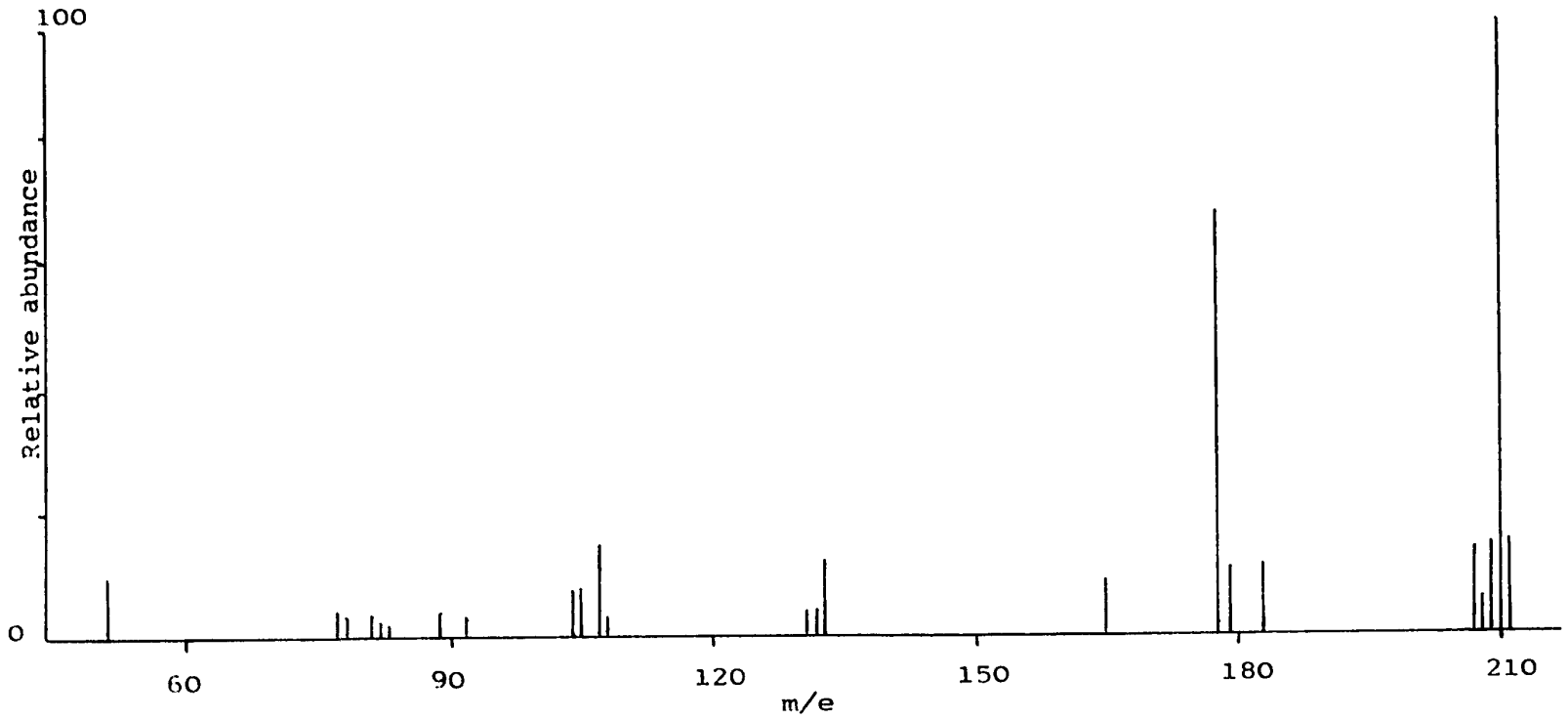

100
Relative abundance
0
50
80
110
140
170
200
230
m/e

Figure 15

Mass Spectrum of 1-Phenyl-
1-benzophosphole


100
Relative abundance
0
60
90
120
150
180
210
m/e

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