THE SYNTHESIS AND RESOLUTION OF COMPOUNDS OF TETRACOVALENT PHOSPHORUS

by

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May, 1955

ACKNOWLEDGEMENT

I wish to express my appreciation to Dr. W. E. McEwen and Dr. C. A. Vanderwerf whose guidance made this research successful. I also wish to thank my parents whose foresight made my education possible.

This thesis is dedicated to my wife.

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INTRODUCTION

Although investigations of the stereochemistry of phosphorus compounds have not been nearly so extensive as investigations of the stereochemistry of carbon compounds and nitrogen compounds, there is nevertheless considerable evidence that phosphorus possesses a tetrahedral configuration in its stable, tetracovalent compounds. Up to the present time, at least one compound representative of each of three classes of organophosphorus compounds--phosphine oxides, phosphine sulfides and quaternary phosphonium salts--has been resolved, either completely or partially.

The purpose of this research was to synthesize and resolve asymmetric compounds of tetracovalent phosphorus having a different structural type than those resolved by previous workers. This thesis contains a description of the first successful resolution of an asymmetric phosphinate, methyl methyl-p-dimethylaminophenylphosphinate (LI). This asymmetric phosphinate is readily synthesized and the resolution is easily reproduced. Of the resolutions of organophosphorus compounds reported by previous workers, only one, that of the phosphine sulfide, is readily reproducible. However, even in the case of this phosphine sulfide, the enantiomorphs were obtained only as oils and could not be purified by crystallization.

This work was undertaken for several reasons. First,

the racemic and optically active forms of methyl methyl-p-dimethylaminophenylphosphinate (LI) will be tested for anticholinesterase activity, and may reveal interesting differences in activity between the racemic modification and the dextro and levo forms. Secondly, the successful resolution of a variety of organophosphorus compounds will pave the way for mechanism studies of the reactions of these compounds. Thirdly, it is of theoretical interest to determine the structural factors which limit the optical resolution of phosphorus compounds.

HISTORICAL

Only four successful resolutions of organophosphorus compounds which contain an asymmetric phosphorus atom and no other asymmetric atom in the molecule have been reported prior to the present work. Two involved phosphine oxides, one a phosphine sulfide, and the fourth a phosphonium salt.

A far greater number of unsuccessful attempts at resolution of organophosphorus compounds have been recorded in the literature. Most of these have been with phosphonium salts. The two main reasons reported for these failures were that many of the phosphorus compounds did not form crystalline salts with appropriate resolving agents, and that some tended to form partial racemates with the resolving agents. When these partial racemates were less soluble than either of the diastereoisomers, resolution was impossible. Some of the resolutions attempted were doomed to failure from the start because the compounds were phosphorus acids. The compounds were not asymmetric because ionization leads to an anion which is a resonance hybrid in which the oxygen atoms are equivalent.

Previous workers have made resolution studies on the following classes of compounds:

1. Phosphine Oxides
2. Quaternary Phosphonium Salts

3. Phosphine Sulfides

4. Derivatives of Phosphorus Acids

The methods of synthesis of the various asymmetric compounds of tetracovalent phosphorus as well as the experimental methods used in attempting their resolutions, are of interest. The following account will describe the syntheses of the four phosphorus compounds, resolution of which has been reported. The methods of their resolution and their important physical constants will be given. An account will also be presented of many of the unsuccessful attempts at resolution of phosphorus compounds recorded in the literature.

Phosphine Oxides

The phosphine oxides were the first class of phosphorus compounds to be resolved. The dextro and levo enantiomorphs of two phosphine oxides, methylethylphenylphosphine oxide (VI) and methylphenylbenzylphosphine oxide (XI), have been isolated in pure form. Both successful resolutions were due to Jacob Meisenheimer and his co-workers (1,2).

Basing his work on the analogy between the structures of phosphine oxides and amine oxides, of which asymmetric derivatives had previously been resolved (3), Meisenheimer was able to resolve methylethylphenylphosphine oxide (VI) and methylphenylbenzylphosphine oxide (XI).

The basic oxygen of the P → O bond was involved in the combination with optically active sulfonic acids. However, Meisenheimer encountered considerable experimental difficulty in the retarded crystal growth of salts of the phosphine oxides with optically active sulfonic acids. Long periods of time were required to obtain seed crystals of each of the pure diastereoisomers. Once the proper seed crystals had been obtained, however, fractional crystallization of the mixture of diastereoisomers yielded the pure diastereoisomers. Decomposition of the pure diastereoisomers with base yielded the optically active phosphine oxides.

Meisenheimer obtained the asymmetric phosphine oxides used in his resolution studies from appropriately substituted quaternary phosphonium salts. Methylethylphenylphosphine oxide (VI), for example, was synthesized by the following series of steps: Phenyldichlorophosphine (I), obtained from benzene and phosphorus trichloride, was reacted with diphenylmercury at 230°C under a carbon dioxide atmosphere. This reaction mixture yielded, after distillation, diphenylchlorophosphine (II). The action of ethylmagnesium bromide on this compound gave ethyldiphenylphosphine (III). The latter compound afforded the quaternary crystalline methiodide (IV) on reaction with methyl iodide. The action of silver hydroxide on this methiodide gave the intermediate quaternary phosphonium hydroxide (V)

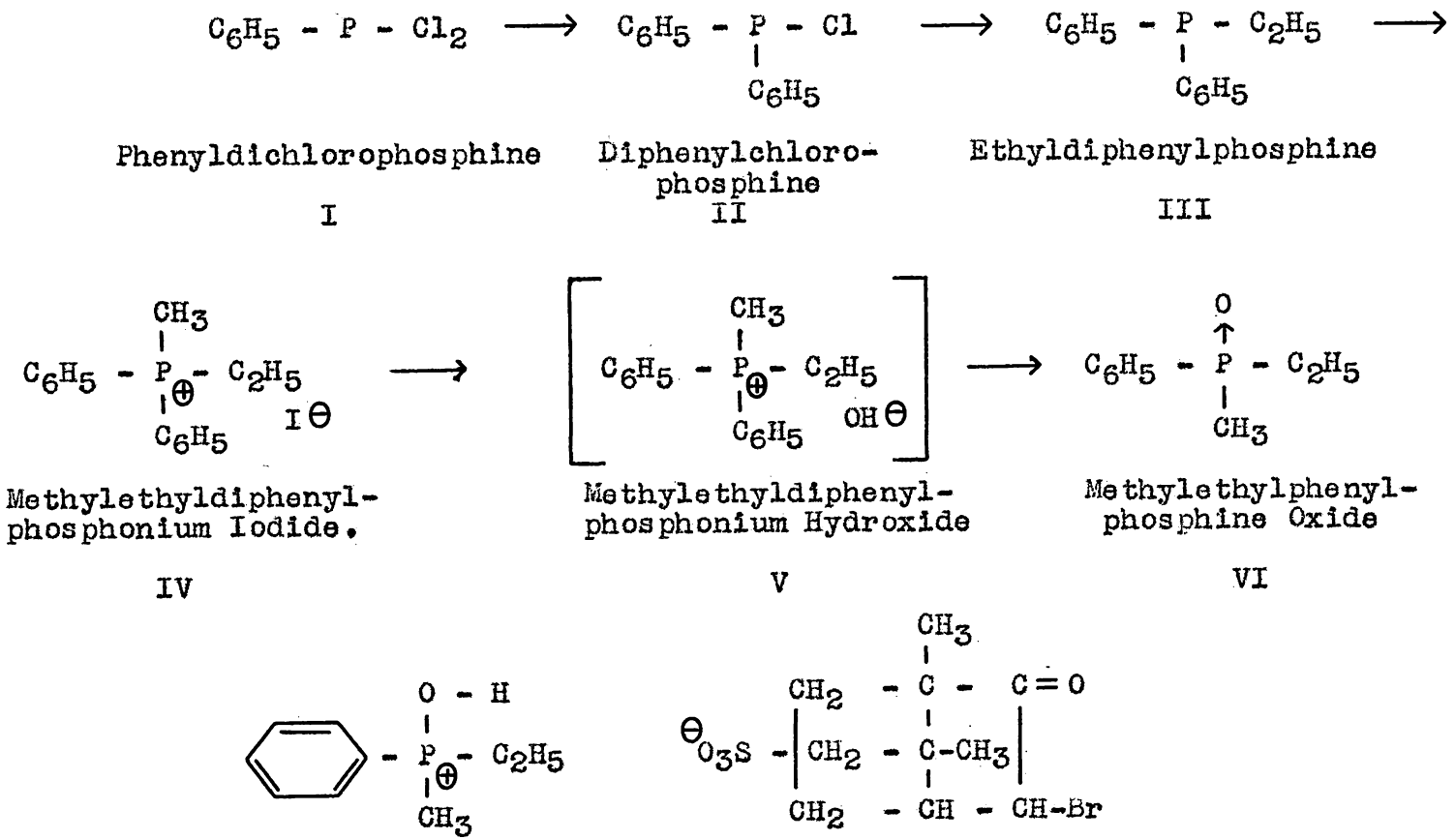


FIG. 1 SYNTHESIS AND RESOLUTION OF METHYLETHYLPHENYLPHOSPHINE OXIDE.

which was not isolated in pure form. Thermal decomposition of the quaternary base gave benzene and the asymmetric phosphine oxide, methylethylphenylphosphine oxide (VI).

The resolution of the phosphine oxide was accomplished through the stable crystalline salt which it formed with d-bromocamphorsulfonic acid. Reaction of the phosphine oxide with an equivalent quantity of d-bromocamphorsulfonic acid gave, after months of standing, suitable seed crystals to induce crystallization in bulk of the diastereoisomers. On fractional crystallization of the mixture of diastereoisomers from ethyl acetate, one of the pure diastereoisomers having a melting point of 94° and $[M]_D$ +321° was obtained. The pure diastereoisomer was decomposed with ammonia, the ammonium salt of d-bromocamphorsulfonic acid precipitating in quantitative yield. The optically active phosphine oxide was purified by distillation, b.p.$_8$ 159°, $[M]_D$ +38°.

The pure levo enantiomorph of methylethylphenylphosphine oxide (2) was obtained in a similar manner. Years were required to obtain seed crystals of the diastereoisomeric l-methylethylphenylhydroxylphosphonium l-bromocamphorsulfonates (VII). The pure diastereoisomer, m.p. 94-95°, $[M]_D$ -313°, obtained by fractional crystallization, gave the levo enantiomorph of methylethylphenylphosphine oxide, $[M]_D$ -39°, on decomposition with ammonia.

Synthesis and resolution of the second phosphine

oxide resolved, methylphenylbenzylphosphine oxide (XI), was accomplished through similar techniques by Meisenheimer. Phenyldichlorophosphine (I), on reaction with benzylmagnesium chloride, gave phenyldibenzylphosphine (VIII). The quaternary phosphonium salt, methylphenyldibenzylphosphonium iodide (IX), was then obtained by reaction of phenyldibenzylphosphine with methyl iodide. As with the other phosphonium salt, treatment with silver hydroxide gave the intermediate quaternary phosphonium hydroxide (X), which was decomposed thermally. The products were toluene and the asymmetric phosphine oxide, methylphenylbenzylphosphine oxide (XI). Salts were made by reaction of d-and l-camphorsulfonic acid with the phosphine oxide. Years were required to obtain seed crystals of the diastereoisomers. Fractional crystallization of the respective diastereoisomeric mixtures gave the two pure diastereoisomers, l-methylphenylbenzylhydroxylphosphonium d-camphorsulfonate and d-methylphenylbenzylhydroxylphosphonium l-camphorsulfonate (XII). Decomposition of each of these salts with aqueous ammonia gave the l-oxide, m.p. 135°, $[M]_D$ -167°, and the d-oxide, m.p. 135°, $[M]_D$ +168°, respectively.

Meisenheimer also attempted the resolution of three other phosphine oxides (2). The d-bromocamphorsulfonate and d-camphorsulfonate of d,l-methylpropylphenylphosphine oxide (XIII) were obtained as oils from ethyl acetate, water

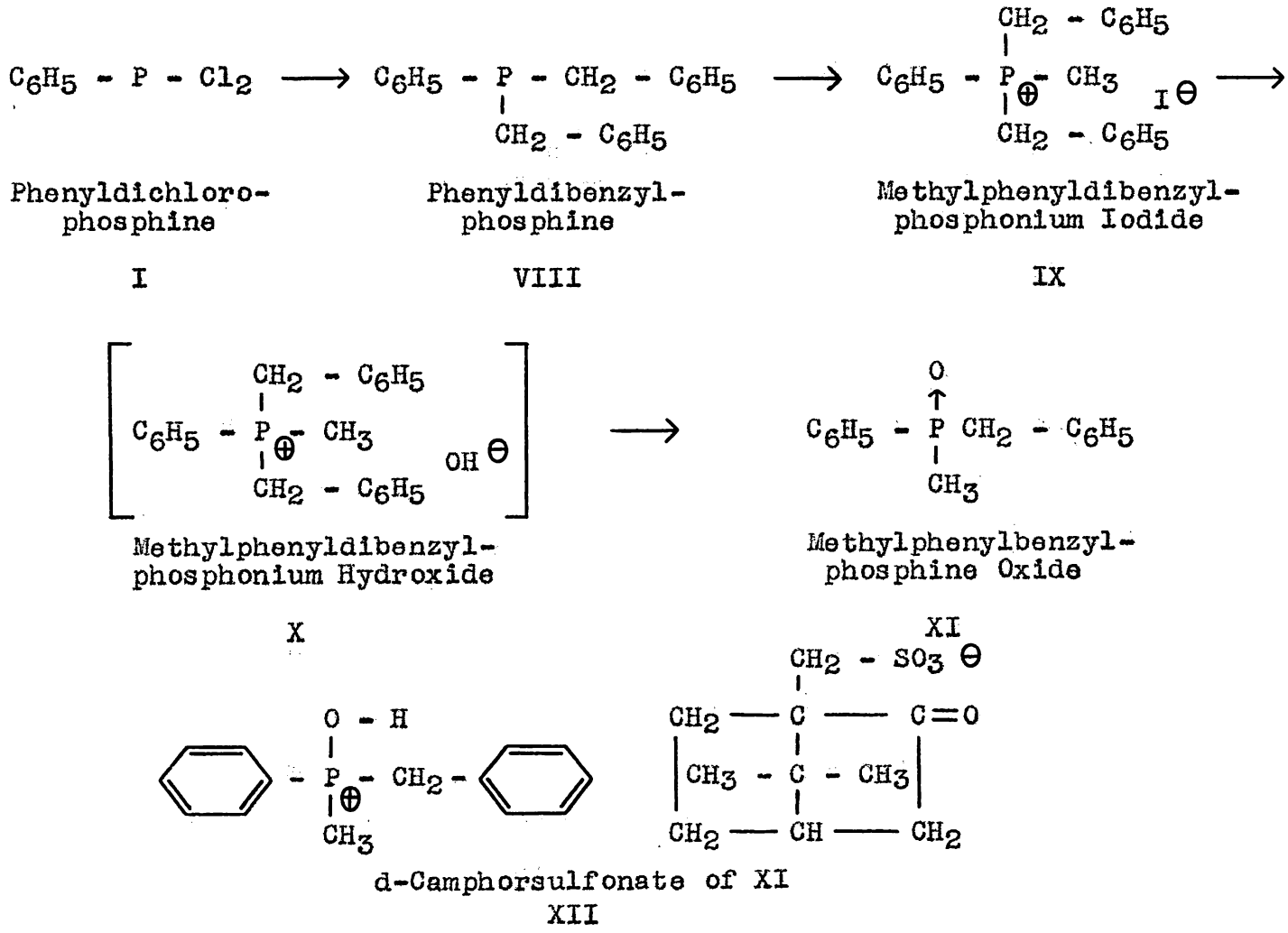
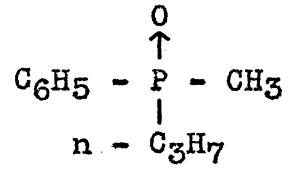
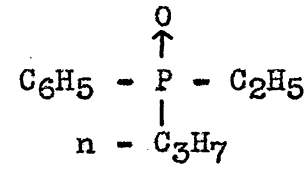


FIG. 2 SYNTHESIS AND RESOLUTION OF METHYLPHENYLBENZYLPHOSPHINE OXIDE.



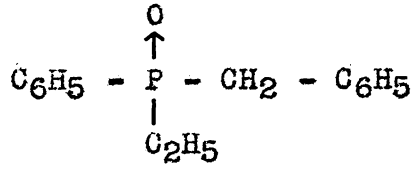
Methylpropylphenyl-
phosphine Oxide

XIII



Ethylpropylphenyl-
phosphine Oxide

XIV



Ethylphenylbenzyl-
phosphine Oxide

XV

FIG. 3 PHOSPHINE OXIDES WHICH FORM NON-CRYSTALLINE DIASTEREOISOMERS.

and ethyl alcohol. The oils would not crystallize even after standing for a year. The d-camphorsulfonate and d-bromocamphorsulfonate of d,l-ethylpropylphenylphosphine oxide (XIV) could not be obtained in crystalline form. d,l-Ethylphenylbenzylphosphine oxide (XV) also failed to form crystalline salts with optically active acids.

Quaternary Phosphonium Salts

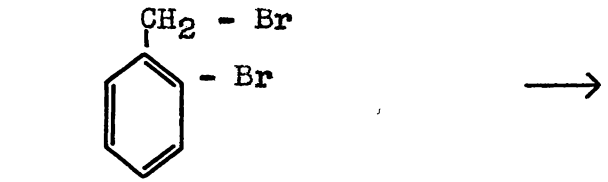
There have been more attempts at the resolution of asymmetric phosphonium salts than any other class of tetracovalent phosphorus compounds. These attempts have met with only minor success. On one occasion only has there been any indication of the resolution of an asymmetric phosphonium salt. Holliman and Mann (4), in 1947, isolated the dextro enantiomorph of 2-phenyl-2-p-hydroxy-phenyl-1,2,3,4-tetrahydroisophosphinolinium bromide (XXI, X = Br). However, they could not reproduce this result.

The success of Holliman and Mann in resolving an asymmetric arsonium salt, 2-phenyl-2-p-chlorophenacyl-1,2,3,4-tetrahydroisoarsinolinium bromide (5), prompted them to attempt the resolution of a quaternary phosphonium salt, 2-phenyl-2-hydroxyphenyl-1,2,3,4-tetrahydroisophosphinolinium bromide (XXI, X = Br). They attributed the successful resolution of the arsonium salt to the fact that the arsenic atom of the arsinolinium salt was in a

heterocyclic ring. There would then be little tendency for a dissociation equilibrium: [abcd As] I $\rightleftharpoons$ abc As + dI. Other arsonium salts which had been resolved showed rotations in solution which slowly disappeared. This was believed due to this dissociation equilibrium, especially since some of the radicals attached to the asymmetric arsonium salt were aliphatic. No phosphonium salts had been resolved previous to the work described above. This, as with the fleeting rotation of arsonium salts, was believed to be due to a dissociation equilibrium [abcdP] I $\rightleftharpoons$ abc P + dI which caused racemization of the phosphonium salt. On the other hand, there has been some evidence that phosphonium salts do not undergo dissociation as postulated above (6,7).

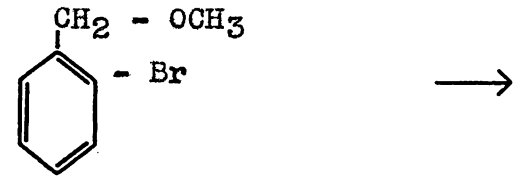
Another possible reason put forth by Holliman and Mann for the failure to resolve phosphonium salts is partial racemate formation in which the two diastereoisomers formed from a racemic phosphonium salt and a resolving agent are not separable by fractional crystallization. Thus, on decomposition of the diastereoisomers, only inactive products are obtained.

The phosphonium salt, 2-phenyl-2-p-hydroxylphenyl-1,2,3,4-tetrahydroisophosphinolinium bromide was synthesized by Holliman and Mann according to the following series of reactions: o-Bromobenzyl bromide (XVI) when treated with sodium methoxide in methanol gave o-bromo-



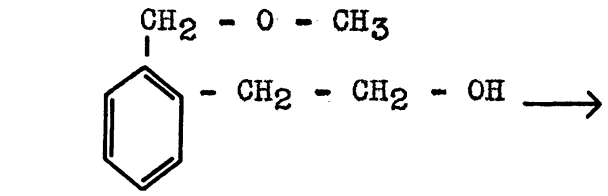
O-Bromobenzylbromide

XVI



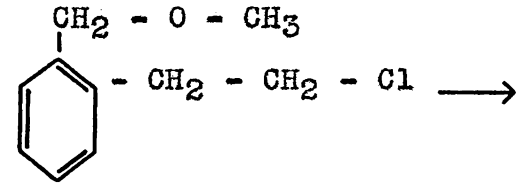
O-Bromobenzyl Methyl Ether

XVII



O-2-Hydroxyethylbenzyl Methyl Ether

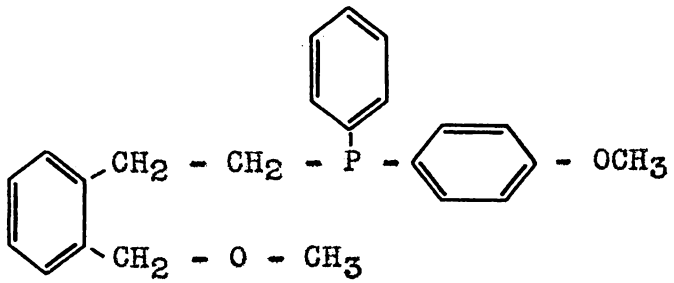
XVIII



O-2-Chloroethylbenzyl Methyl Ether

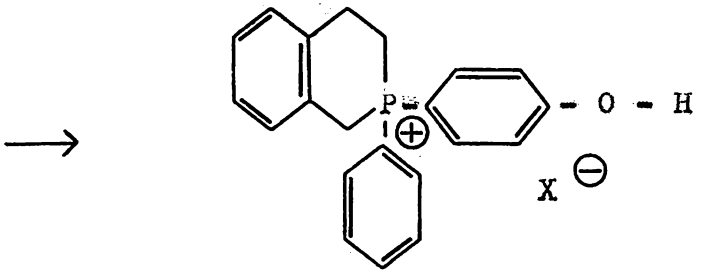
XIX

FIG. 4 SYNTHESIS AND RESOLUTION OF 2-PHENYL-2-p-HYDROXYPHENYL-1,2,3,4-TETRAHYDROISOPHOSPHINOLINIUM BROMIDE.



Phenyl-p-anisyl-2-(o-methoxy-methylphenyl)ethylphosphine

XX



2-Phenyl-2-p-hydroxyphenyl-1,2,3,4-tetrahydroisophosphinolinium Bromide

XXI

$X = Br^{\ominus}$,

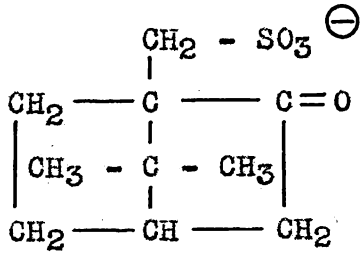


FIG. 4 (CONTD.) SYNTHESIS AND RESOLUTION OF 2-PHENYL-2-p-HYDROXYPHENYL-1,2,3,4-TETRAHYDROISOPHOSPHINOLINIUM BROMIDE.

benzyl methyl ether (XVII), which was in turn converted to the Grignard reagent. Reaction of this Grignard reagent with ethylene oxide gave o-2-hydroxyethylbenzyl methyl ether (XVIII). By the use of thionyl chloride in the presence of pyridine, o-2-chloroethylbenzyl methyl ether was obtained (XIX). Conversion of the chloro-compound to the Grignard reagent, followed by treatment with phenyl-p-anisylchlorophosphine, gave phenyl-p-anisyl-2-(o-methoxymethylphenyl) ethylphosphine (XX). When the tertiary phosphine was heated in a mixture of hydrobromic acid and glacial acetic acids, the three stages necessary to complete the synthesis, i.e., cleavage of the ether grouping, bromination and ring closure, were accomplished in one operation, giving the isophosphinolinium salt (XXI, X = Br).

The isophosphinolinium salt was resolved by the following method: The silver salt of d-bromocamphorsulfonic acid, on reaction with the phosphonium salt, gave the d-bromocamphorsulfonate of the phosphonium compound (XXI, X = d-bromocamphorsulfonate ion). This salt was readily obtained in crystalline form. Repeated crystallization from a variety of solvents failed to produce any indication that resolution was proceeding. The melting point was essentially constant at 145-152°, and the rotation was constant, $[M]_D$ + 300°. Conversion of this salt to the phosphonium bromide gave only the inactive salt.

A different resolving agent was used in attempts to

effect resolution. Preparation of the d-camphorsulfonate gave the d,l-phosphonium d-camphorsulfonate (XXI, X= d-camphorsulfonate ion), m.p. 153-158°, $[M]_D$ +102°. Recrystallization from alcohol-ethyl acetate gave the optically active d-phosphonium d-camphorsulfonate of m.p. 174-175°, $[M]_D$ +113.5°. Treatment of the optically pure d-camphorsulfonate with an alcoholic solution of calcium bromide furnished the d-isophosphinolinium bromide, m.p. 268-270°, $[M]_D$ +32.9°. (d,l-m.p. 287-87.5°).

In an attempt to obtain the l-isophosphinolinium bromide, the racemic isophosphinolinium bromide was converted to the l-camphorsulfonate, m.p. 170-172°, $[M]_D$ -102°. Recrystallization of this salt failed to change the optical rotation. Decomposition of the l-camphorsulfonate salt gave only the inactive bromide, m.p. 286-288°. Numerous additional attempts to obtain the active bromide were of no avail.

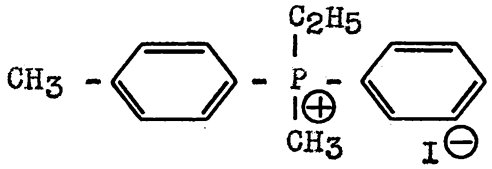
The most striking fact is that repeated attempts by these workers to reproduce their first success, the isolation of the dextro rotatory isophosphinolinium bromide, were not successful. They prepared the d-camphorsulfonate salt of the phosphinolinium compound again, but no change in the initial rotation or melting point could be obtained by fractional crystallization. Decomposition of the diastereoisomeric salt gave only the inactive bromide. This failure to reproduce their results was also reflected in their failure to obtain the levo

rotatory isophosphinolinium bromide. Holliman and Mann attributed their failures to the formation of partial racemates.

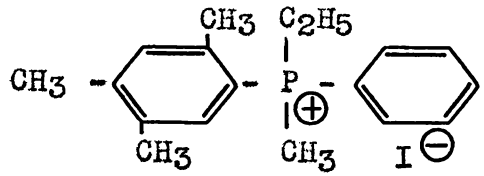
A far greater number of unsuccessful attempts to resolve asymmetric phosphonium salts are recorded in the literature. These failures have been due to partial racemate formation of the diastereoisomers and to inability to obtain crystalline diastereoisomers.

Historically, Michaelis (8), in 1901, was the first chemist to attempt the resolution of tetracovalent phosphorus compounds. He synthesized two asymmetric phosphonium salts, p-tolylphenylethylmethylphosphonium iodide (XXII) and 2,4,5-trimethylphenylphenylethylmethylphosphonium iodide (XXIII). The resolution attempts were unsuccessful with these compounds. The phosphonium d-hydrogentartrates were not crystalline, and bacteria had no effect on the racemic compounds.

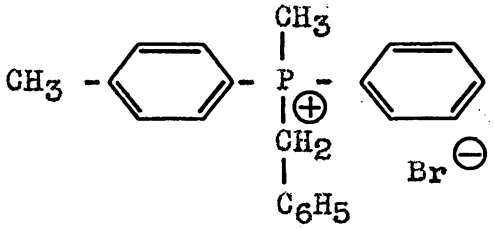
Pope and Gibson (9) synthesized two asymmetric phosphonium salts for the purpose of resolution studies; phenyl-p-tolylbenzylmethylphosphonium bromide (XXIV) and phenyl-p-tolylmethylallylphosphonium bromide (XXV). The d,l-phenyl-p-tolylbenzylmethylphosphonium d-α-bromocamphor-π-sulfonate, on successive recrystallizations from ethyl acetate-acetone, showed no change from the initial rotatory power of $[M]_D$ +269° and m.p. 129-131°. This indicated that the phosphonium salt was not resolved



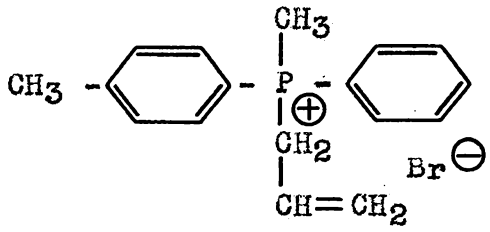
p-Tolylphenylethylmethyl-
phosphonium Iodide
XXII



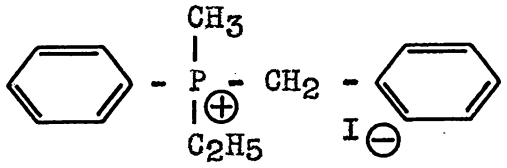
(2,4,5-Trimethylphenyl)phenylethyl-
methylphosphonium Iodide
XXIII



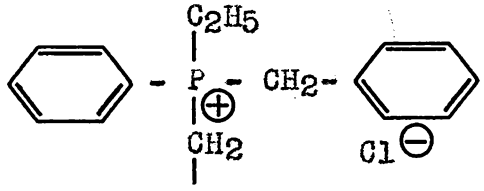
Phenyl-p-tolylbenzylmethyl-
phosphonium Bromide
XXIV



Phenyl-p-tolylmethylallyl-
phosphonium Bromide
XXV

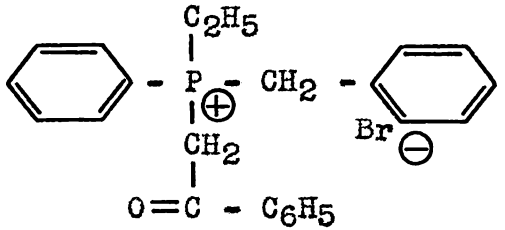


Methylethylphenylbenzyl-
phosphonium Iodide
XXVI

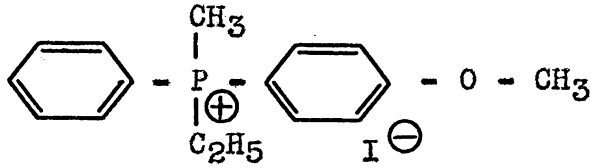


Phenylethylbenzylacetonyl-
phosphonium Chloride
XXVII

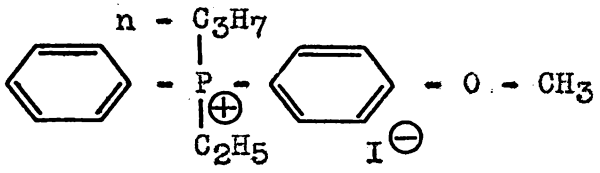
FIG. 5 ASYMMETRIC PHOSPHONIUM SALTS WHICH FORM NON-CRYSTALLINE DIASTEREOISOMERS OR PARTIAL RACEMATES.



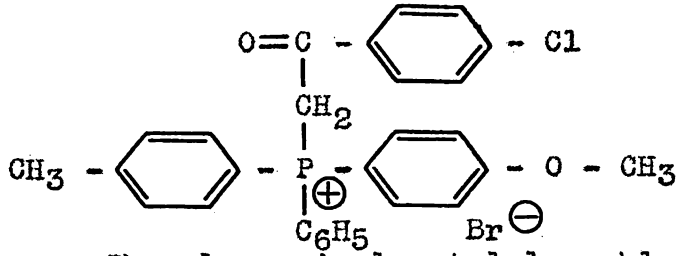
Phenylethylbenzylphenacyl-
phosphonium Bromide
XXVIII



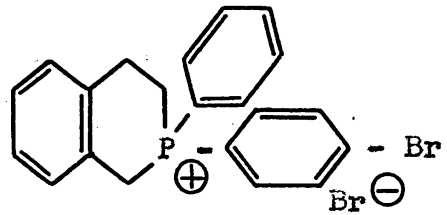
Phenyl-p-anisylmethylethyl-
phosphonium Iodide
XXIX



Phenyl-p-anisylethyl-n-propyl-
phosphonium Iodide
XXX



Phenyl-p-anisyl-p-tolyl-p-chloro-
phenacylphosphonium Bromide
XXXI



2-Phenyl-2-p-bromophenyl-1,2,3,4-
tetrahydroisophosphinolinium Bromide
XXXII

FIG. 5 (CONTD.) ASYMMETRIC PHOSPHONIUM SALTS WHICH FORM NON-CRYSTALLINE DIASTEREOISOMERS OR PARTIAL RACEMATES.

into optically active components. Conversion of the sulfonate to the phosphonium iodide gave only inactive products. Similarly, formation of the d-camphor-β-sulfonate gave only the d,l-phosphonium d-camphor-β-sulfonate on fractional crystallization. The melting point and rotation were constant at 134-137° and $[M]_D$ +49°. Conversion to the phosphonium iodide gave only the inactive iodide.

Phenyl-p-tolylmethylallylphosphonium bromide (XXV), on reaction with the silver salts of d-camphor-β-sulfonic acid, d-α-bromocamphor-π-sulfonic acid and d-α-bromocamphor-β-sulfonic acid, gave only viscous residues which could not be converted to crystalline forms.

Wedekind (6) attempted the resolution of phenyl-p-tolylmethylethylphosphonium iodide (XXII) (a compound which Meisenheimer also synthesized and attempted to resolve) by preparing the corresponding d,l-phosphonium d-camphorsulfonate. The diastereoisomeric salt was obtained in crystalline form, m.p. 128°, $[M]_D$ +103.9°. Due to the lack of sufficient material for resolution studies, Wedekind did not pursue the resolution further.

The resolution of p-tolylphenylmethylallylphosphonium iodide (XXV) was also attempted by Radcliffe and Brindley (10). They prepared the d,l-phosphonium d-bromocamphorsulfonate by the usual method. They were unable to obtain the salt in crystalline form. Resolution was, therefore, impossible.

Meisenheimer, who successfully resolved two phosphine oxides, tried to resolve methylethylphenylbenzylphosphonium iodide (XXVI) by formation of the d-bromocamphorsulfonate (2). Fractional crystallization of the salts from ethyl acetate showed little change in the initial melting point or rotatory power, m.p. 129-130°, $[M]_D$ +278°. A conversion to the phosphonium iodide was not attempted since the physical constants of the diastereoisomeric salt were not significantly changed on fractional crystallization. Evidently, resolution was not taking place.

A Russian chemist, Kamai, prepared two phosphonium salts and attempted their resolutions (11). Phenylethylbenzylacetonylphosphonium chloride (XXVII) and phenylethylbenzylphenacylphosphonium bromide (XXVIII) were converted to their bromocamphorsulfonates. The salts were obtained as non-crystallizable syrups.

In addition to their studies on the synthesis and resolution of phosphine sulfides, Davies and Mann (12) prepared three asymmetric phosphonium halides for optical resolution experiments. Phenyl-p-anisylmethylethylphosphonium iodide (XXIX), phenyl-p-anisylethyl-n-propylphosphonium iodide (XXX) and phenyl-p-anisyl-p-tolyl-p-chlorophenacylphosphonium bromide (XXXI) were synthesized and converted to their d-camphorsulfonates and d-α-bromocamphorsulfonates. However, the salts could not be obtained in crystalline form.

Holliman and Mann (4) tried to resolve 2-phenyl-2-p-bromophenyl-1,2,3,4-tetrahydroisophosphinolinium bromide (XXXII) *via* its d-bromocamphorsulfonate, d-hydrogentartrate and l-N-l-phenylethylphthalamate salts. All of these salts were obtained as non-crystallizable oils. The d-camphorsulfonate was obtained in crystalline form, m.p. 206-212°, $[M]_D$ + 98.7°. The melting point and rotation were not significantly changed upon recrystallization from ethyl alcohol-ether.

Phosphine Sulfides

The phosphine sulfides are similar to the phosphine oxides as a class of tetracovalent phosphorus compounds. The phosphine sulfides are not as basic as the phosphine oxides, and therefore the P → S bond cannot be utilized for combination with optically active sulfonic acids to effect optical resolution. Rather, a functional group must be placed on one of the radicals attached to the thiophosphoryl group. The compound may then be resolved *via* this functional grouping.

The only recorded successful resolution of a phosphine sulfide was by Davies and Mann in 1944 (12). They obtained the dextro and levo forms of phenyl-p-(carboxymethoxy) phenyl-n-butylphosphine sulfide (XXXVIII). This success came about only after their failure to resolve three other phosphine sulfides.

Phenyl-p-(carboxymethoxy)phenyl-n-butylphosphine sulfide (XXXVIII) was synthesized by Davies and Mann by the following method: p-anisyldichlorophosphine (XXXIII), obtained from anisole and phosphorus trichloride with aluminum trichloride as catalyst, was converted by diphenylmercury into phenyl-p-anisylchlorophosphine (XXXIV). Phenyl-p-anisyl-n-butylphosphine (XXXV) was prepared by the action of the chlorophosphine on n-butylmagnesium bromide. Treatment of the phosphine with hydriodic acid (to cleave the ether grouping) and then with base and benzoyl chloride, gave phenyl-p-benzoyloxyphenyl-n-butylphosphine (XXXVII). This phosphine reacted readily with sulfur to form phenyl-p-benzoyloxyphenyl-n-butylphosphine sulfide. Alkaline hydrolysis furnished phenyl-p-hydroxyphenyl-n-butylphosphine sulfide. The sodium derivative of this compound condensed readily with ethyl bromoacetate and the product, on alkaline hydrolysis, yielded the sodium salt of phenyl-p-carboxymethoxyphenyl-n-butylphosphine sulfide (XXXVIII).

The racemic phosphine sulfide was resolved by the following method: Treatment of the sodium salt of the phosphine sulfide with the hydrochloride of d-α-phenylethylamine gave the crystalline d-α-phenylethylammonium salt of phenyl-p-(carboxymethoxy)-phenyl-n-butylphosphine sulfide. Fractional crystallization of this salt raised the melting point from 195-201°C to 209-210°, which was that of the pure d-amine l-acid salt. Rotation measure-

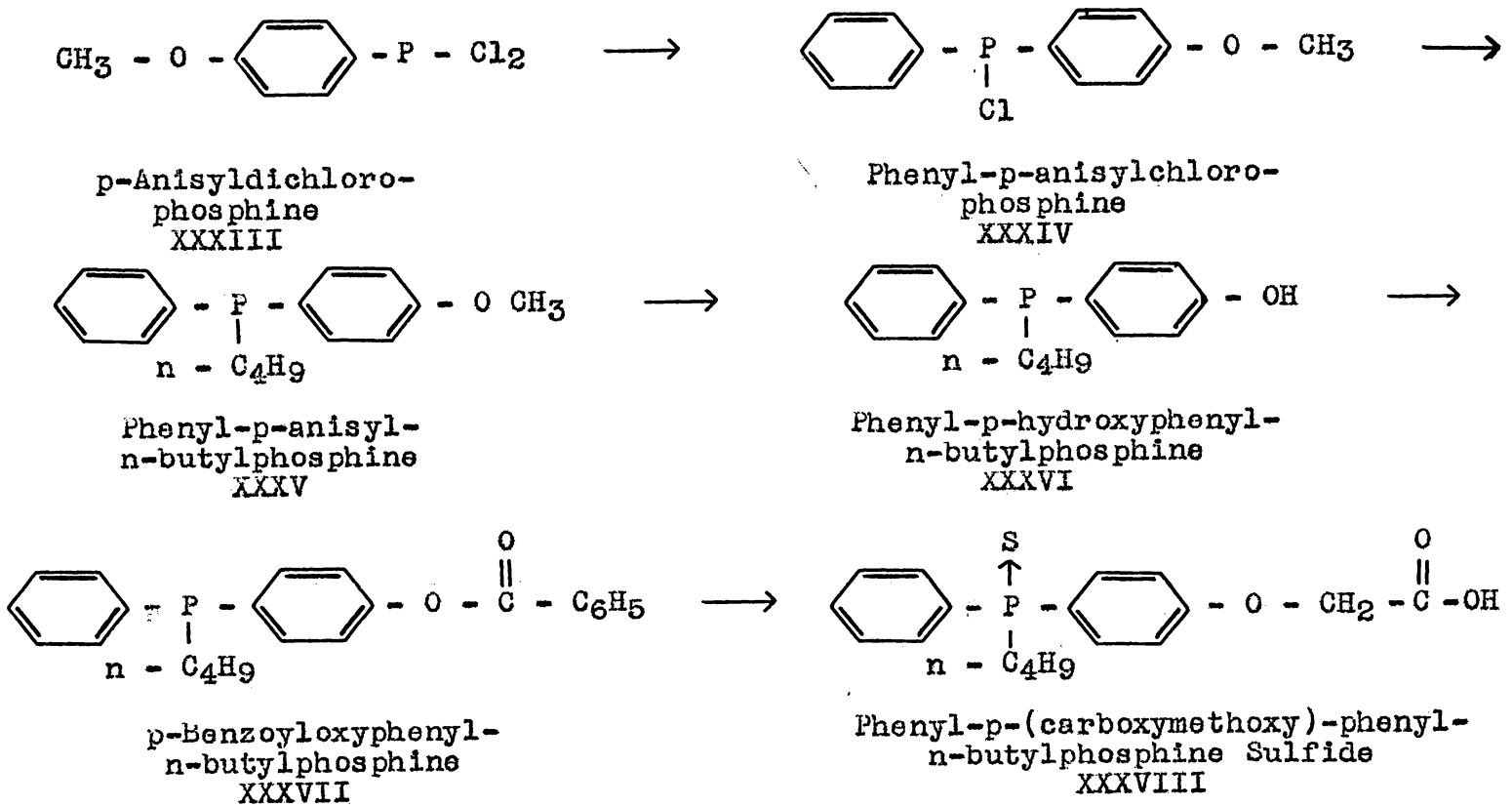


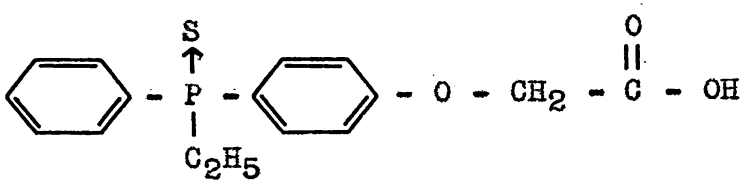
FIG. 6 SYNTHESIS OF PHENYL-p-(CARBOXYMETHOXY)PHENYL-n-BUTYLPHOSPHINE SULFIDE

ments were not made on this salt due to its poor solubility in any of the common solvents. The pure diastereoisomer was decomposed by dilute sulfuric acid. Extraction of the acid solution with benzene gave a solution of 1-phenyl-p-carboxymethoxyphenyl-n-butylphosphine sulfide having $[M]_D$ -9.7°. This enantiomorph could not be obtained in crystalline form.

In a similar manner, the racemic acid was converted into the 1-α-phenylethylammonium salt. Fractional crystallization raised the melting point from 193-200° to 209-210°. Decomposition of this pure diastereoisomer, the 1-amine d-acid salt, gave the d-phosphine sulfide having $[M]_D$ +9.6° in benzene solution. This enantiomorph also could not be obtained in crystalline form.

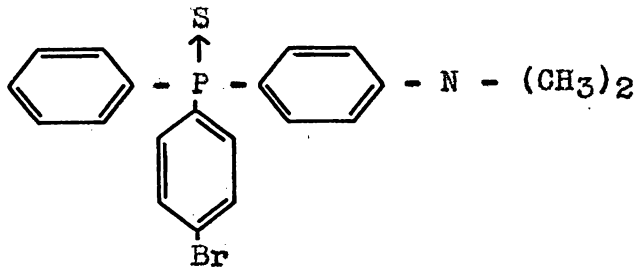
Davies and Mann (12) attempted the resolution of two other phosphine sulfides. Strikingly enough, the ethyl homologue of the above resolved phosphine sulfide could not be resolved. Phenyl-p-carboxymethoxyphenylethylphosphine sulfide (XXXIX) gave salts with 1-α-phenylethylamine, d-sec-butylamine and d-α-aminocamphor. However, repeated crystallization of these salts gave no sign of optical resolution.

Phenyl-p-bromophenyl-p-dimethylaminophenylphosphine sulfide (XL) gave a crystalline metho-d-camphorsulfonate, m.p. 224-226°, but fractional crystallization of this salt from various solvents displayed no evidence of resolution. The metho-d-bromocamphorsulfonate was also obtained in



Phenyl-p-carboxymethoxy-
phenylethylphosphine
Sulfide

XXXIX



Phenyl-p-bromophenyl-
p-dimethylaminophenyl-
phosphine Sulfide

XL

FIG. 7 PHOSPHINE SULFIDES WHICH FORMED PARTIAL RACEMATES.

crystalline form, m.p. 198-199°, but repeated recrystallization did not effect the initial rotation of the salt. As with the metho-d-camphorsulfonate, conversion to the methobromide gave only the inactive salt.

Two other asymmetric phosphine sulfides, each possessing a substituent group suitable for salt formation, specifically the 2-pyridyl and 3-pyridyl groups, were prepared by Davies and Mann. (12). These groups were so weakly basic that salts could not be formed with optically active sulfonic acids. The methiodide of the 2-pyridyl compound could only be obtained in poor yield and the methiodide of the 3-pyridyl compound could not be obtained. Thus, resolution studies on these compounds were discontinued.

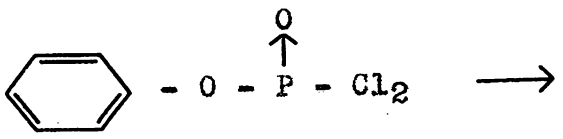
Derivatives of Phosphorus Acids

Kipping and co-workers (13,14) studied the resolution of asymmetric phosphoramidates which contained an asymmetric carbon atom as well as an asymmetric phosphorus atom. By the use of l-hydrindamine and l-menthylamine, they were able to obtain the two diastereoisomers of each of the three phosphoramidates; N-d-hydrindyl O-phenyl O-p-tolyl d-and l-phosphoramidates (XLIII), N-l-menthyl O-phenyl O-p-tolyl d-and l-phosphoramidates (XLIV), and N-l-menthyl O-p-tolyl O-2-naphthyl d-and l-phosphoramidates (XLV). Each of these mixtures of diastereoisomers were separated into two pure forms by fractional crystallization. Of course, decomposition of these optically active amides

to the acid would only give the inactive acids. The acids would not be asymmetric because ionization leads to an anion which is a resonance hybrid in which the oxygen atoms are equivalent.

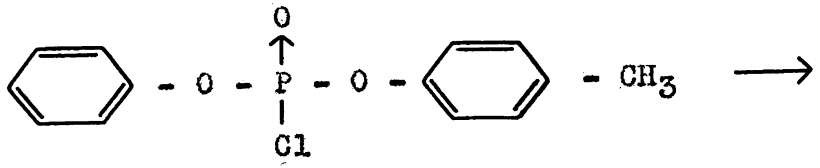
All three amides were obtained from similar starting materials. The synthesis of N-d-hydrindyl O-phenyl O-p-tolyl d-and l-phosphoramidate will serve as a typical example. Phenyl phosphorodichloridate (XLI), on treatment with the sodium salt of p-cresol in ether solution, gave phenyl p-tolyl phosphorochloridate (XLII). The acid chloride was next treated with d-hydrindamine. The product, on fractional crystallization from aqueous methyl alcohol, gave the α-isomeride, the N-d-hydrindyl d-phosphoramidate (XLIII). The most soluble fraction obtained from the mother liquor was crystallized from petroleum ether. The most soluble portion from this solvent was then crystallized from aqueous methyl alcohol to give the slightly impure β-isomer, N-d-hydrindyl l-phosphoramidate.

There have been a variety of attempts to resolve phosphorus acids which appear to be asymmetric by virtue of their structural formulas (13,14,15,24). These have been of the following type, (NH-R) (NH-R') (OH) P→O, (OR) (OR') (OH)-P→O, and (R) (R') (OH) P→O. Combination of these acids with optically active bases gave salts which did not show signs of resolution on fractional crystallization. This was due to resonance of the anion formed, which causes the phosphorus compound to be incapable of resolution.



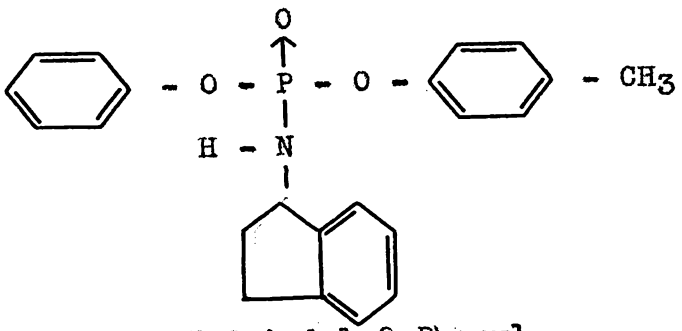
Phenyl Phosphorodichloridate

XLI



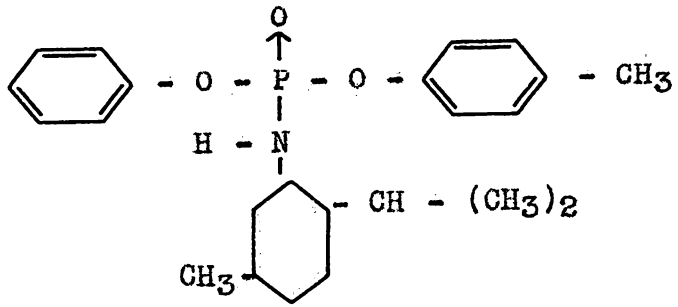
Phenyl p-Tolyl Phosphorochloridate

XLII



N-d-Hydrindyl O-Phenyl O-p-Tolyl d-and l-Phosphoramidates

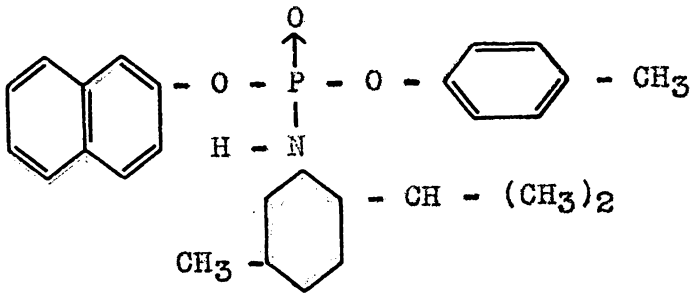
XLIII



N-l-Menthyl O-Phenyl O-p-Tolyl d-and l-Phosphoramidates

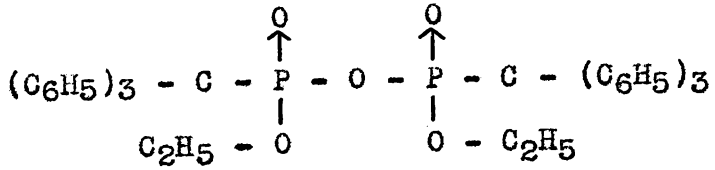
XLIV

FIG. 8 SYNTHESIS OF COMPOUNDS CONTAINING MORE THAN ONE ASYMMETRIC ATOM.



N-l-Menthyl O-p-Tolyl O-2-Naphthyl
d-and l-Phosphoramidates

XLV



Ethyl Triphenylmethylpyrophosphonate

XLVI

FIG. 9 COMPOUNDS CONTAINING MORE THAN ONE ASYMMETRIC ATOM.

Hatt (16) isolated the two pure diastereoisomeric forms of ethyl triphenylmethylpyrophosphonate (XLVI), m.p. 222-223° and m.p. 228-231°. One was undoubtedly the meso and the other the racemic modification. Both, on hydrolysis, gave the same acid. Asymmetry is lost in the acid as a result of resonance in the ion.

EXPERIMENTAL DISCUSSION

One of the first compounds selected as a model tetracovalent phosphorus compound of a different structural type than those studied by previous workers was the asymmetric phosphinate, methyl methylphenylphosphinate. The compound gave promise of rather ready accessibility and of a reasonable possibility of resolution. Although the phosphinate did not possess a conventional acidic or basic functional group, it was believed that the P→O bond would be basic enough to form crystalline addition compounds with resolving acids.

Methyl methylphenylphosphinate (XLVIII) was prepared according to the method of Arbuzov (17). Phenyldichlorophosphine (I), obtained from benzene and phosphorus trichloride with aluminum chloride as catalyst, was reacted with methyl alcohol in ether solution containing dimethylaniline as a hydrogen chloride acceptor. This gave a mixture of two esters, dimethyl phenylphosphonite (XLVII) and methyl methylphenylphosphinate (XLVIII). Dimethyl phenylphosphonite was treated with a catalytic amount of methyl iodide. After undergoing a Michaelis-Arbuzov isomerization, this afforded the isomeric phosphinate, methyl methylphenylphosphinate (XLVIII).

In attempts to effect resolution, methyl methylphenylphosphinate (XLVIII) was treated with equivalent quantities of resolving acids in a variety of solvents. No crystalline

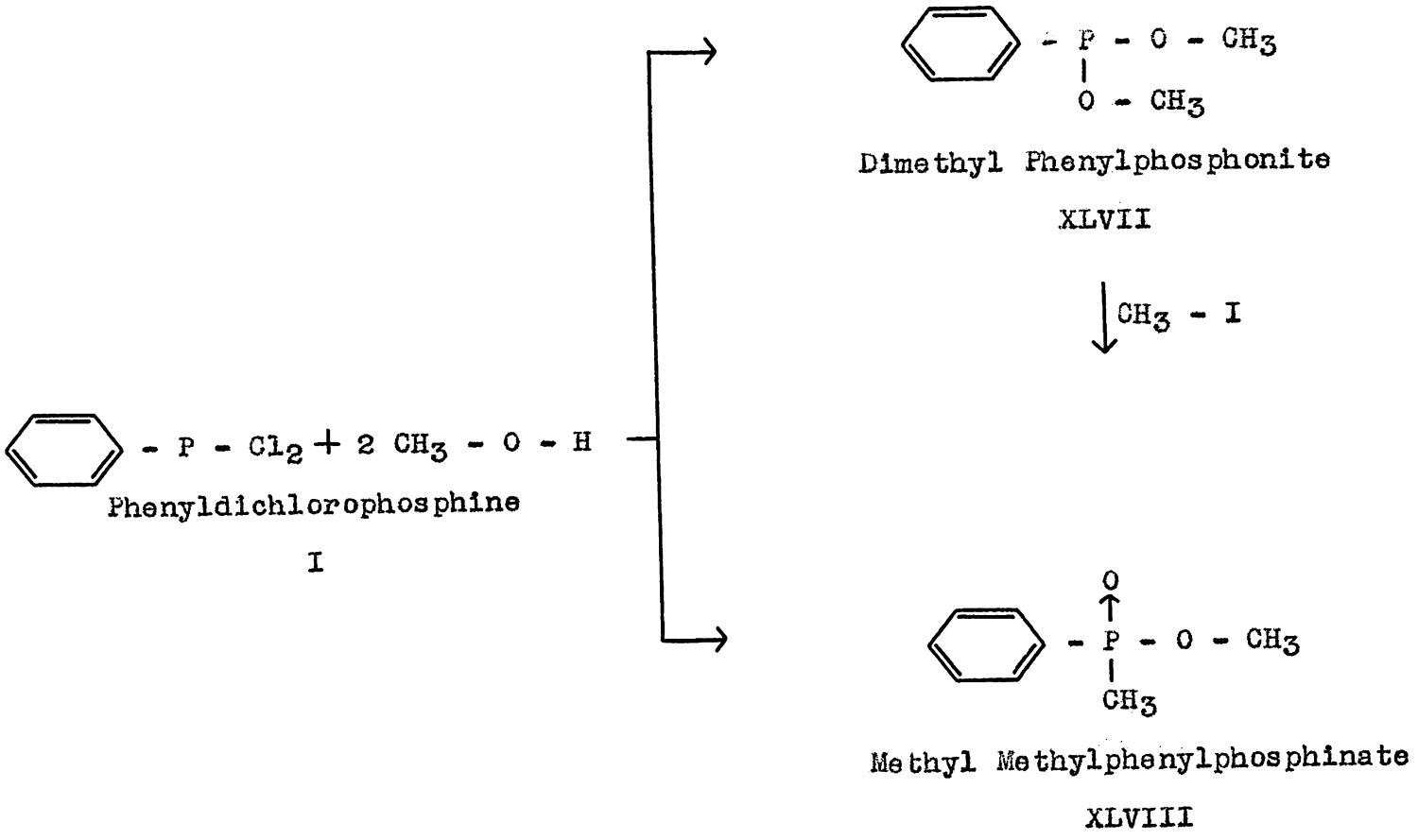


FIG. 10 SYNTHESIS OF METHYL METHYLPHENYLPHOSPHINATE.

salts were formed. Failure of the compound to form crystalline salts with resolving acids was ascribed to the fact that the oxygen present is at best a relatively weak basic center. This suggested that, for purposes of resolution, a more basic functional group should be incorporated into the molecule. On the basis of this hypothesis, methyl methyl-p-dimethylaminophenylphosphinate (LI) was synthesized.

Methyl methyl-p-dimethylaminophenylphosphinate (LI) was obtained by a series of steps. The synthesis began with the preparation of p-dimethylaminophenyldichlorophosphine (XLIX) from phosphorus trichloride and dimethylaniline, according to the method of Michaelis (18,19). Next, p-dimethylaminophenyldichlorophosphine was treated with sodium methoxide in methanol. This gave a mixture of two isomers, dimethyl p-dimethylaminophenylphosphonite (L) and methyl methyl-p-dimethylaminophenylphosphinate (LI). The phosphonite (L) was treated with a catalytic amount of methyl iodide to effect a Michaelis-Arbuzov isomerization. This afforded the isomer, methyl methyl-p-dimethylaminophenylphosphinate (LI). Further reaction with methyl iodide gave the crystalline methiodide of the phosphinate (LII).

Reaction of silver d-hydrogentartrate with the methiode of methyl methyl-p-dimethylaminophenylphosphinate (LII) gave the metho-d-hydrogentartrate of the phosphinate as

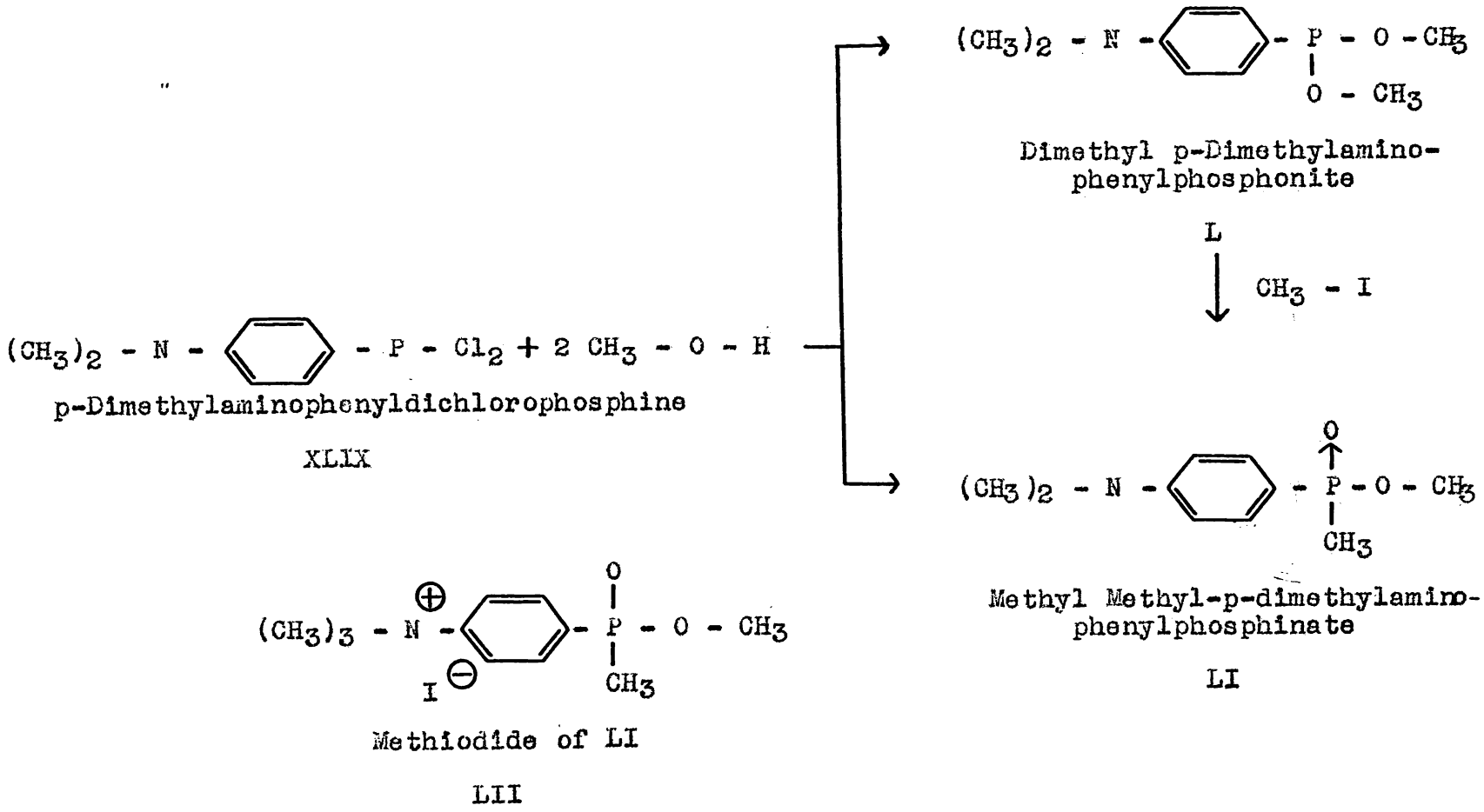


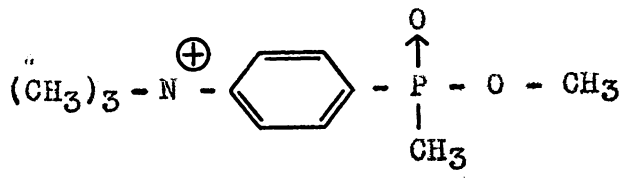
FIG. 11 SYNTHESIS OF METHYL METHYL-p-DIMETHYLAMINOPHENYLPHOSPHINATE.

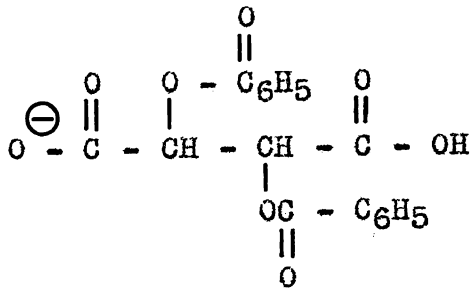
an oil. The salt could not be obtained in crystalline form.

Reaction of silver dibenzoyl-d-hydrogentartrate with the methiodide (LII) gave the d,l-methodibenzoyl-d-hydrogentartrate of methyl methyl-p-dimethylaminophenylphosphinate as a crystalline solid. Fractional crystallization of the mixture of diastereoisomers from methanol gave one of the diastereoisomers, the l-methodibenzoyl-d-hydrogentartrate of methyl methyl-p-dimethylaminophenylphosphinate (LIII), having a melting point of 139.2° and $[\alpha]_D^{25}$ -89°. Treatment of this pure diastereoisomer with picric acid in methanol solution afforded the l-methopicrate of methyl methyl-p-dimethylaminophenylphosphinate (LIV) having a specific rotation of -22°. Treatment of the diastereoisomer with potassium iodide in 95% ethanol gave the optically active methiodide (LV), $[\alpha]_D^{25}$ -29°.

Similarly, reaction of the racemic methiodide (LII) with silver dibenzoyl-l-hydrogentartrate gave the crystalline d,l-methodibenzoyl-l-hydrogentartrate of methyl methyl-p-dimethylaminophenylphosphinate. Fractional crystallization of this mixture of diastereoisomers from methanol gave the second diastereoisomer (LVI), m.p. 139.2°, $[\alpha]_D^{25}$ +88°. As with the other diastereoisomer, the action of picric acid and potassium iodide yielded the enantiomorph of the phosphinate in the form of the dextro methopicrate (LVII) and methiodide (LVIII), respectively.

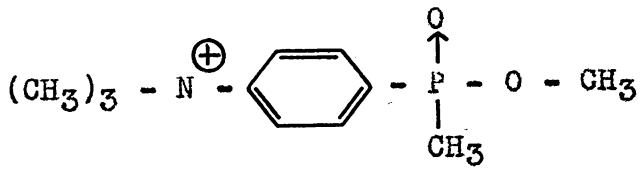
Table I gives a summary of the physical constants

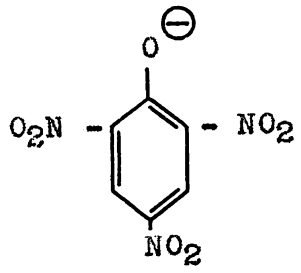


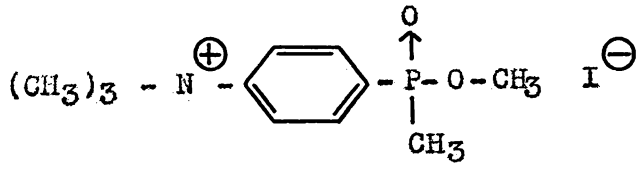


1-Methodibenzoyl-d-hydrogentartrate of LI

LIII







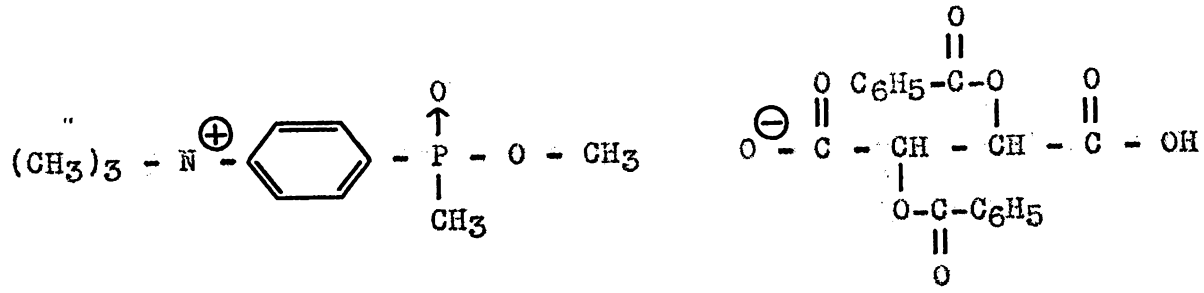
1-Methopicrate of LI

LIV

1-Methiodide of LI

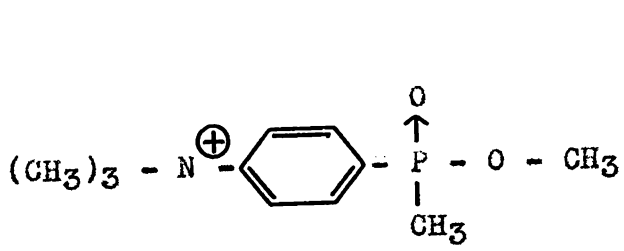
LV

FIG. 12 RESOLUTION OF METHYL METHYL-p-DIMETHYLAMINOPHENYLPHOSPHINATE.



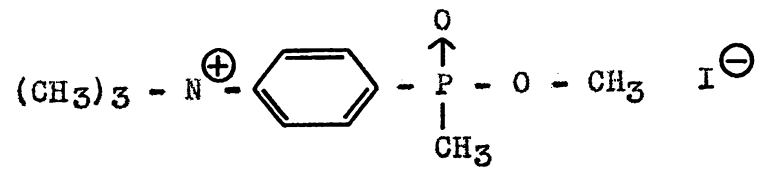
d-Methodibenzoyl-l-hydrogentartrate of LI

LVI



d-Methopicrate of LI

LVII



d-Methiodide of LI

LVIII

FIG. 13 RESOLUTION OF METHYL METHYL-p-DIMETHYLAMINOPHENYLPHOSPHINATE.

of the racemic modifications and optically active forms of the methopicrate and methiodide of methyl methyl-p-dimethylaminophenylphosphinate.

TABLE I

PHYSICAL PROPERTIES OF THE DEXTRO AND LEVO ENANTIOMORPHS

	Methopicrate		Methiodide	
	$[\alpha]_D^{25}$	M.P.	$[\alpha]_D^{25}$	M.P.
Racemic Mixture	0	176.0-176.6	0	161.0
Dextro Enantiomorph	22	170.5-171.5	28	155.6-156.4
Levo Enantiomorph	- 22	170.5-171.5	- 29	155.8-156.4

EXPERIMENTAL PROCEDURE*

Phenyldichlorophosphine--This compound was prepared by the method of Michaelis (20) with the modification suggested by Dye (21).

In a 1-l., 3-necked flask fitted with a thermometer, mercury-sealed stirrer and reflux condenser connected to a hydrogen chloride trap, were placed 312 g. (4.00 moles) of dry benzene, 556 g. (4.00 moles) of phosphorus trichloride and 186 g. (1.40 moles) of anhydrous aluminum chloride. The mixture was stirred and heated under gentle reflux for eight hours. At the end of this time, the mixture was cooled below 40° and 216 g. (1.40 moles) of phosphorus oxychloride was added slowly. The benzene and excess phosphorus oxychloride were distilled *in vacuo*. The reaction mixture was again cooled below 40°C. and 3 volumes of petroleum ether (b.p. 80-90°) was added and shaken well with the reaction mixture to insure efficient extraction. The ether layer was decanted from a greenish mass. The petroleum ether was distilled and the remaining liquid fractionated at reduced pressure through a 15 cm. Vigreux column. Phenyldichlorophosphine was collected at 109°/23mm., 163 g. (0.910 mole, 23%).

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*All melting points are corrected. Analyses by Clark Microanalytical Laboratory, Urbana, Ill. and Schwarzkoph Microanalytical Laboratory, Woodside, L.I., N.Y.

Dimethyl Phenylphosphonite(17)--In a 1-l., 3-necked flask fitted with a mercury sealed stirrer, a reflux condenser with an attached calcium chloride tube, and an addition funnel, were added 90.0 g. (0.744 mole) of dimethylaniline in 300 ml. of dry ether and 90.0 g. (0.503 mole) of phenyldichlorophosphine. To this mixture was added dropwise, with stirring, 33.0 g. (1.03 moles) of methyl alcohol. A slow reflux of ether was maintained by regulation of the rate of addition of alcohol. Stirring was continued for one hour after completion of the addition of methanol in order to insure completion of the reaction. The precipitated hydrochloride of dimethylaniline was filtered, the ether distilled and the residue fractionated through a short Vigreux column. Two fractions were obtained: (1) dimethyl phenylphosphonite, b.p. 105-110°/ 22 mm., 24.0 g. (0.141 mole) and (2) methyl methylphenylphosphinate, b.p. 147°/ 22 mm., 38.0 g. (0.224 mole), n_D^{20} 1.5216.

Methyl Methylphenylphosphinate(17)--The crude dimethyl phenylphosphonite was placed in a 100-ml. flask fitted with a reflux condenser. Two ml. of methyl iodide was added and the mixture heated slightly on the steam bath. A vigorous reaction ensued with evolution of heat. The product was fractionated through a 15 cm. Vigreux column affording 16.0 g. (0.094 mole) of methyl methylphenylphosphinate, b.p. 147°/ 22 mm., n_D^{20} 1.5216.

Attempted Resolution of Methyl Methylphenylphosphinate--Solutions of methyl methylphenylphosphinate and several resolving acids in a variety of solvents were prepared in attempts to obtain crystalline diastereoisomers. In no case were crystalline salts formed. Evaporation of the solvents yielded only oils which could not be induced to crystallize. Table II summarizes these experiments.

p-Dimethylaminophenyldichlorophosphine--This compound was prepared by the procedure of Michaelis and Schenk (18,19).

In a 3-necked flask fitted with a mercury-sealed stirrer and a reflux condenser with a calcium chloride tube, were placed 400 g. (2.91 moles) of freshly distilled phosphorus trichloride and 285 g. (2.35 moles) of dimethylaniline. The mixture was cooled by immersion of the flask in an ice bath. With vigorous stirring, 80.0 g. (0.600 mole) of anhydrous aluminum chloride was added in 20.0 g. batches at 15 minute intervals. The mixture was then heated on the steam bath for two hours with slight refluxing. The reaction mixture was extracted three times with 300-ml. portions of petroleum ether (b.p. 80-90°). Distillation of the petroleum ether and fractionation of the residue through a short Vigreux column gave 103.5 g. (0.466 mole, 20%) of p-dimethylaminophenyldichlorophosphine, b.p. 155-158° (2.5 mm.), m.p. 55-60°. Redistillation at reduced pressure gave a product of m.p. 64-65° (reported, 66° (18,19)).

TABLE II
ATTEMPTED RESOLUTION OF METHYL METHYLPHENYLPHOSPHINATE

Run	Weight of Phosphinate	Resolving Acid and Amount	Mole Ratio Acid to Ester	Solvent	Amount of Solvent
1	10.0 g.	a-13.6 g.	1	ethyl acetate	210 ml.
2	5.0 g.	a-6.8 g.	1	acetone	30 ml.
3	5.0 g.	a-6.8 g.	1	benzene	100 ml.
4	5.0 g.	a-6.8 g.	1	ethyl acetate	30 ml.
5	2.0 g.	b-1.6 g.	1	"	40 ml.
6	4.0 g.	b-1.6 g.	2	"	40 ml.
7	2.0 g.	b-1.6 g.	1	ether	50 ml.
8	2.0 g.	b-1.6 g.	1	methyl alcohol	10 ml.
9	2.0 g.	a-2.7 g.	1	"	10 ml.
10	5.0 g.	a-6.8 g.	1	benzene petr. ether	100 ml.
11	2.0 g.	c-1.8 g.	1	ethyl acetate	100 ml.
12	4.0 g.	c-1.8 g.	2	methyl alcohol	20 ml.
13	2.0 g.	c-1.8 g.	1	"	20 ml.
14	4.0 g.	c-1.8 g.	2	ethyl acetate	75 ml.
15	2.0 g.	a-2.7 g.	1	dioxane	10 ml.
16	2.0 g.	b-1.6 g.	1	"	10 ml.
17	4.0 g.	b-1.6 g.	2	"	10 ml.
18	4.0 g.	b-1.6 g.	2	benzene	30 ml.

a - d-camphorsulfonic acid
b - l-malic acid
c - d-tartaric acid

Dimethyl p-Dimethylaminophenylphosphonite-- A solution of sodium methoxide was prepared by addition of 20.4 g. (0.888 mole) of sodium to 400 ml. of methyl alcohol contained in a 3-necked flask fitted with a reflux condenser having an attached calcium chloride tube, a mercury sealed stirrer and a dropping funnel. A solution of 98.3 g. (0.444 mole) of p-dimethylaminophenyldichlorophosphine in 200 ml. of dry benzene was added dropwise with stirring under a nitrogen atmosphere. The reaction mixture was cooled by immersion of the flask in a salt-ice bath. The mixture was stirred for an hour after the addition of the chlorophosphine had been completed. The sodium chloride was filtered off and the solvents distilled. The oily residue was filtered and then distilled at reduced pressure through a 15 cm. Vigreux column. Two fractions were obtained, (1) dimethyl p-dimethylaminophenylphosphonite, b.p. 112-114°/ 0.35 mm., 43.7 g. (0.205 mole, 46%) and (2) methyl methyl-p-dimethylaminophenylphosphinate, b.p. 159-163°/ 0.35 mm., m.p. 64-72°, 23.5 g. (0.110 mole, 25%).

Fractional distillation of (1) through a packed column gave 28.4 g. of dimethyl p-dimethylaminophenylphosphonite, b.p. 119-120°/ 0.8 mm., n_D^{30} 1.5940.

Anal. Calcd. for $C_{10}H_{16}O_2NP$: C, 56.28; H, 7.57; N, 6.57; P, 14.53. Found: C, 56.12; H, 7.50; N, 6.60; P, 14.77.

Recrystallization of (2) from dry ether gave 13.8 g. of methyl methyl-p-dimethylaminophenylphosphinate, m.p. 81.0-82.0°C.

Anal. Calcd. for $C_{10}H_{16}O_2NP$: C, 56.28; H, 7.57; N, 6.57; P, 14.53. Found: C, 56.48; H, 7.46; N, 6.89; P, 14.52.

Methyl Methyl-p-dimethylaminophenylphosphonite--Dimethyl p-dimethylaminophenylphosphonite, 35.6 g. (0.167 mole), was dissolved in 100 ml. of dry benzene and placed in a 300-ml. flask equipped with a reflux condenser. Approximately 1 ml. of methyl iodide was added. The mixture was heated to reflux on the steam bath with caution because the reaction was exothermic. The mixture was refluxed for a 1-hr. period. The solution was then cooled and filtered. Distillation of the benzene gave 29.4 g. (0.138 mole) of d,l-methyl methyl-p-dimethylaminophenylphosphinate, m.p. 74-78°C. Recrystallization from dry ether gave 25.0 g. of material of m.p. 81.0-82.0°C.

Methiodide of d,l-Methyl Methyl-p-dimethylaminophenylphosphinate--A solution of 25.6 g. (0.120 mole) of methyl methyl-p-dimethylaminophenylphosphinate and 25.0 g. (0.176 mole) of methyl iodide in 100 ml. of benzene was refluxed for 48 hours. Filtration of the mixture gave 40.3 g. (0.113 mole) of the methiodide of methyl methyl-p-dimethylaminophenylphosphinate, m.p. 161.0° (dec.).

Anal. Calcd. for $C_{11}H_{19}O_2NPI$: C, 37.19; H, 5.39; N, 3.94; P, 8.73; I, 35.73. Found: C, 37.10; H, 5.38; N, 3.98; P, 8.74; I, 35.37.

Methopicrate of d,l-Methyl Methyl-p-dimethylaminophenylphosphinate--A solution of 1.0 g. (0.00282 mole) of the methiodide of methyl methyl-p-dimethylaminophenylphosphinate in 10 ml. of methyl alcohol was treated with 0.71 g. (0.00282 mole) of sodium picrate. The solution was boiled for a few minutes to insure completion of reaction. On cooling, 0.70 g. (0.0015 mole) of the methopicrate of methyl methyl-p-dimethylaminophenylphosphinate was obtained which, on further recrystallization from methyl alcohol, gave yellow crystals, m.p. 176.0-176.6°.

Anal. Calcd. for $C_{17}H_{21}O_9N_4P$: C, 44.74; H, 4.64; N, 12.28; P, 6.79. Found: C, 44.70; H, 4.86; N, 11.99; P, 6.99.

Silver d-Hydrogentartrate--A solution of 15.0 g. (0.100 mole) of tartaric acid in 44 ml. of 2.27 N ammonium hydroxide solution (1 eq.) was treated with 17.0 g. (0.100 mole) of silver nitrate in 100 ml. of distilled water with vigorous stirring. The white flocculent precipitate was filtered, washed with water, and air dried. A yield of 16.0 g. of the silver salt was obtained.

d,l-Metho-d-hydrogentartrate of Methyl Methyl-p-dimethylaminophenylphosphinate--A solution of 5.0 g. (0.0141 mole)

of the methiodide of d,l-methyl methyl-p-dimethylamino-phenylphosphinate in 35 ml. of methyl alcohol was treated with 3.6 g. (0.0141 mole) of silver d-hydrogentartrate. The solution was boiled for 1/2 hour and the silver iodide filtered. The mother liquor was then concentrated to 15 ml. The solution was cooled in an ice-salt bath and an attempt made to induce crystallization by scratching of the flask. No crystals were formed. The solution was heated to boiling and ethyl acetate added until the cloud point was reached, then cooled and allowed to stand. No crystals formed.

Dibenzoyl-d-tartaric Acid-Monohydrate--Dibenzoyl-d-tartaric acid was prepared by the method of Butler and Cretcher (22).

A mixture of 150 g. (1 mole) of tartaric acid and 450 g. (3.2 moles) of benzoyl chloride was heated in a 500-ml. Erlenmeyer flask with stirring until the temperature rose to 150°. The main reaction occurred around 135°. The product was allowed to cool and then ground in a mortar. This solid was washed with two 300-ml. portions of benzene by heating just below the boiling point, allowing the mixture to cool to room temperature and filtering. The resulting crude dibenzoyl-d-tartaric anhydride was boiled with 1500 ml. of distilled water for 30 minutes, during which time the acid precipitated as an oil. The oil solidified on standing overnight. It was ground, air dried and washed with cold benzene. The

yield of acid was 245 g. (0.651 mole, 65%), m.p. 88-90°, $[\alpha]_D^{25}$ -114.8° (C 1.27 in methanol) (reported, m.p. 88-89°, $[\alpha]_D^{20}$ -116° (22).

Dibenzoyl-l-tartaric Acid-Monohydrate--This compound was prepared by the same procedure used by Butler and Cretcher for dibenzoyl-d-tartaric acid.

A mixture of 50.0 g. (0.333 mole) of l-tartaric acid and 150 g. (0.107 mole) of benzoyl chloride in a 250-ml. Erlenmeyer flask was heated slowly to 150°. Hydrogen chloride was evolved vigorously from 100-110°, the main reaction taking place in this temperature region. The crude dibenzoyl-l-tartaric anhydride thus obtained was purified by the addition of 100 ml. of benzene, heating to just below the boiling point, and cooling to room temperature and filtering. This process was repeated. The anhydride was hydrolyzed by boiling with 500 ml. of distilled water. The acid precipitated as an oil, which then solidified on standing overnight. It was ground in a mortar, air dried, and washed with cold benzene. The yield was 115 g. (0.306 mole, 92%), m.p. 84-86°, $[\alpha]_D^{25}$ +109 (C 1.80 in ethanol) (reported m.p. 85°, $[\alpha]_D^{25}$ +103 (23)).

Silver Dibenzoyl-d-hydrogentartrate--A slurry of 10.0 g. (0.0266 mole) of dibenzoyl-d-tartaric acid monohydrate in 300 ml. of distilled water was treated with 28.8 ml.

of 0.925 N ammonium hydroxide. The solution was heated to 85-90° to dissolve the unreacted acid and ammonium salts, and then allowed to cool to 45-50°. A solution of 4.52 g. (0.0266 mole) of silver nitrate in 75 ml. of distilled water was added dropwise with stirring. Filtration of the flocculent precipitate and air drying gave an average yield of 6.5 g. of silver dibenzoyl-d-hydrogentartrate.

Silver Dibenzoyl-l-hydrogentartrate--This salt was prepared by the identical process used for the preparation of silver dibenzoyl-d-hydrogentartrate.

l-Methodibenzoyl-d-hydrogentartrate of Methyl Methyl-p-dimethylaminophenylphosphinate--Fifteen g. (0.0310 mole) of silver dibenzoyl-d-hydrogentartrate was treated with 11.0 g. (0.0310 mole) of the methiodide of d,l-methyl methyl-p-dimethylaminophenylphosphinate in 30 ml. of boiling methyl alcohol. The theoretical quantity of silver iodide was filtered from the reaction mixture. On cooling overnight, 9.3 g. (0.0159 mole) of the d,l-methodibenzoyl-d-hydrogen tartrate of methyl methyl-p-dimethylaminophenylphosphinate was obtained, m.p. 116-119° (dec.), $[\alpha]_D^{25}$ -78 (C 1.08 in methanol). Seven successive recrystallizations from methyl alcohol gave 0.95 g. of the optically pure l-methodibenzoyl-d-hydrogentartrate of methyl methyl-p-dimethylaminophenylphosphinate, m.p. 139.2° (dec.), $[\alpha]_D^{25}$ -89° (C 0.490 in methanol).

Anal. Calcd. for $C_{29}H_{32}O_{10}NP$: C, 59.48; H, 5.51; N, 2.39; P, 5.29. Found: C, 59.21; H, 5.48; N, 2.35; P, 5.24.

Table III gives the amounts, specific rotations, and melting points obtained during the fractional crystallization.

TABLE III

RESOLUTION OF METHYL METHYL-p-DIMETHYLAMINO-PHENYLPHOSPHINATE

Crop.	Methodibenzoyl-d-hydrogentartrate			
	M.P. (dec.)	$[\alpha]_D^{25}$ (C in Methanol)		Weight, g.
1.	116-119	-78	1.08	9.3
2.	115-121	-80	1.25	7.3
3.	118-122	-84	1.67	6.1
4.	123-127	-86	1.58	4.4
5.	117-120	-88	0.997	3.2
6.	117-122	-89	1.14	2.4
7.	139.2	-88	0.761	1.4
8.	139.2	-89	0.980	0.95

l-Methopicrate of Methyl Methyl-p-dimethylaminophenylphosphinate--Treatment of 0.30 g. (0.00051 mole) of the pure diastereoisomer, l-methodibenzoyl-d-hydrogentartrate of methyl methyl-p-dimethylaminophenylphosphinate

with 0.12 g. (0.00053 mole) of picric acid gave 0.16 g. (0.00035 mole) of the methopicrate of methyl methyl-p-dimethylaminophenylphosphinate, m.p. 170.5-171.5°, $[\alpha]_D^{25}$ -22° (c 0.873 in methanol).

Anal. Calcd. for $C_{17}H_{21}O_9N_4P$: C, 44.74; H, 4.64; N, 12.28; P, 6.79. Found: C, 44.99; H, 4.57; N, 12.21; P, 6.91.

l-Methiodide of Methyl Methyl-p-dimethylaminophenylphosphinate--A solution of 0.88 g. (0.00150 mole) of the l-methodibenzoyl-d-hydrogentartrate of methyl methyl-p-dimethylaminophenylphosphinate in 5 ml. of boiling 95% ethyl alcohol was treated with 0.25 g. (0.00151 mole) of potassium iodide in 5 ml. of ethyl alcohol. A precipitate of 0.55 g. (0.00139 mole) of potassium dibenzoyl-d-hydrogentartrate was filtered off and the mother liquor diluted, while hot, with 10 ml. of ether. This was stored in the ice chest. Filtration gave 0.49 g. (0.0014 mole) of the impure methiodide, m.p. 144-148°. Four recrystallizations from absolute ethyl alcohol gave 0.17 g. of the pure methiodide, m.p. 155.8-156.4°, $[\alpha]_D^{25}$ -29° (c 1.70 in methanol).

Anal. Calcd. for $C_{11}H_{19}O_2INP$: C, 37.19; H, 5.39; N, 3.94; P, 8.73; I, 35.73. Found: C, 37.43; H, 5.26; N, 3.87; P, 8.80; I, 36.03.

d-Methodibenzoyl-l-hydrogentartrate of Methyl Methyl-

p-dimethylaminophenylphosphinate--This diastereoisomer was prepared by the same procedure used for the preparation of the l-dibenzoyl-d-hydrogentartrate of methyl methyl-p-dimethylaminophenylphosphinate.

A solution of 9.5 g. (0.0268 mole) of the methiodide of d,l-methyl methyl-p-dimethylaminophenylphosphinate in 30 ml. of boiling methyl alcohol was treated with 13.0 g. (0.0268 mole) of silver dibenzoyl-l-hydrogen tartrate. The solution was stirred and boiled for 30 minutes. Filtration of the hot solution gave the theoretical quantity of silver iodide. The mother liquor was stored in an ice chest overnight and 10.7 g. (0.0183) mole) of crystals of the methodibenzoyl-l-hydrogentartrate of d,l-methyl methyl-p-dimethylaminophenylphosphinate, m.p. 101-105° (dec.), $[\alpha]_D^{25}$ +81° (C 1.05 in methanol), were obtained. Seven recrystallizations from methyl alcohol yielded 1.30 g. of the pure diastereoisomer, d-methodibenzoyl-l-hydrogentartrate of methyl methyl-p-dimethylaminophenylphosphinate, m.p. 139.2° (dec.), $[\alpha]_D^{25}$ + 88° (C 0.650 in methanol).

Anal. Calcd. for $C_{29}H_{32}O_{10}NP$: C, 59.48; H, 5.51; N, 2.39; P, 5.29. Found: C, 59.16; H, 5.63; N, 2.38; P, 5.12.

Table IV gives the amounts and physical properties of the intermediate fractions obtained during the fractional recrystallizations.

TABLE IV

RESOLUTION OF METHYL METHYL-p-DIMETHYL-AMINOPHENYLPHOSPHINATE

Crop.	Methodibenzoyl-l-hydrogentartrate			
	M.P.(Dec.)	$[\alpha]_D^{25}$	(C in Methanol)	Weight, g.
1.	101-105	+81	1.05	10.7
2.	121-125	+82	1.36	7.8
3.	114	+85	1.34	6.2
4.	123-125	+88	1.51	4.9
5.	123-127	+91	1.69	4.3
6.	125-128	+89	1.03	3.0
7.	137.5-138.5	+88	0.910	2.2
8.	139.2	+91	0.714	1.8
9.	139.2	+88	1.30	1.3

d-Methopicrate of Methyl Methyl-p-dimethylaminophenylphosphinate--Treatment of 0.30 g. (0.000514 mole) of the pure diastereoisomer, d-methodibenzoyl-l-hydrogentartrate of methyl methyl-p-dimethylaminophenylphosphinate, in 5 ml. of boiling methyl alcohol with 0.12 g. (0.000526 mole) of picric acid gave 0.14 g. (0.000307 mole) of the d-methopicrate of methyl methyl-p-dimethylaminophenylphosphinate, m.p. 170.5-171.5°, $[\alpha]_D^{25}$ +22° (C 0.843 in methanol).

Anal. Calcd. for $C_{17}H_{21}O_9N_4P$: C, 44.74; H, 4.64; N, 12.28; P, 6.79. Found: C, 44.99; H, 4.34; N, 12.00; P, 6.82.

d-Methiodide of Methyl Methyl-p-dimethylaminophenylphosphinate--A solution of 1.0 g. (0.00171 mole) of the d-methodibenzoyl-l-hydrogentartrate of methyl methyl-p-dimethylaminophenylphosphinate in 5 ml. of boiling 95% ethyl alcohol was treated with a solution of 0.28 g. (0.00171 mole) of potassium iodide in 5 ml. of 95% ethyl alcohol. A precipitate of 0.61 g. of potassium dibenzoyl-l-hydrogentartrate was filtered off and the mother liquor diluted with 10 ml. of ether to precipitate the methiodide. Filtration gave 0.53 g. (0.00149 mole) of the methiodide, m.p. 135-150° (dec.). Four crystallizations from absolute ethyl alcohol gave 0.28 g. of the pure d-methiodide, m.p. 155.6-156.4° (dec. 156.4), $[\alpha]_D^{25}$ +28° (C 1.92 in methanol).

Anal. Calcd. for $C_{11}H_{19}O_2INP$: C, 37.19; H, 5.39; N, 3.94; P, 8.73; I, 35.73. Found: C, 37.42; H, 5.60; N, 4.23; P, 8.58; I, 35.77.

FIG. 14 INFRARED ABSORPTION SPECTRA

A. Methyl Methyl-p-dimethylaminophenylphosphinate (in chloroform)

B. Dimethyl p-Dimethylaminophenylphosphonite (in chloroform)

C. p-Dimethylaminophenyldichlorophosphine (in chloroform)

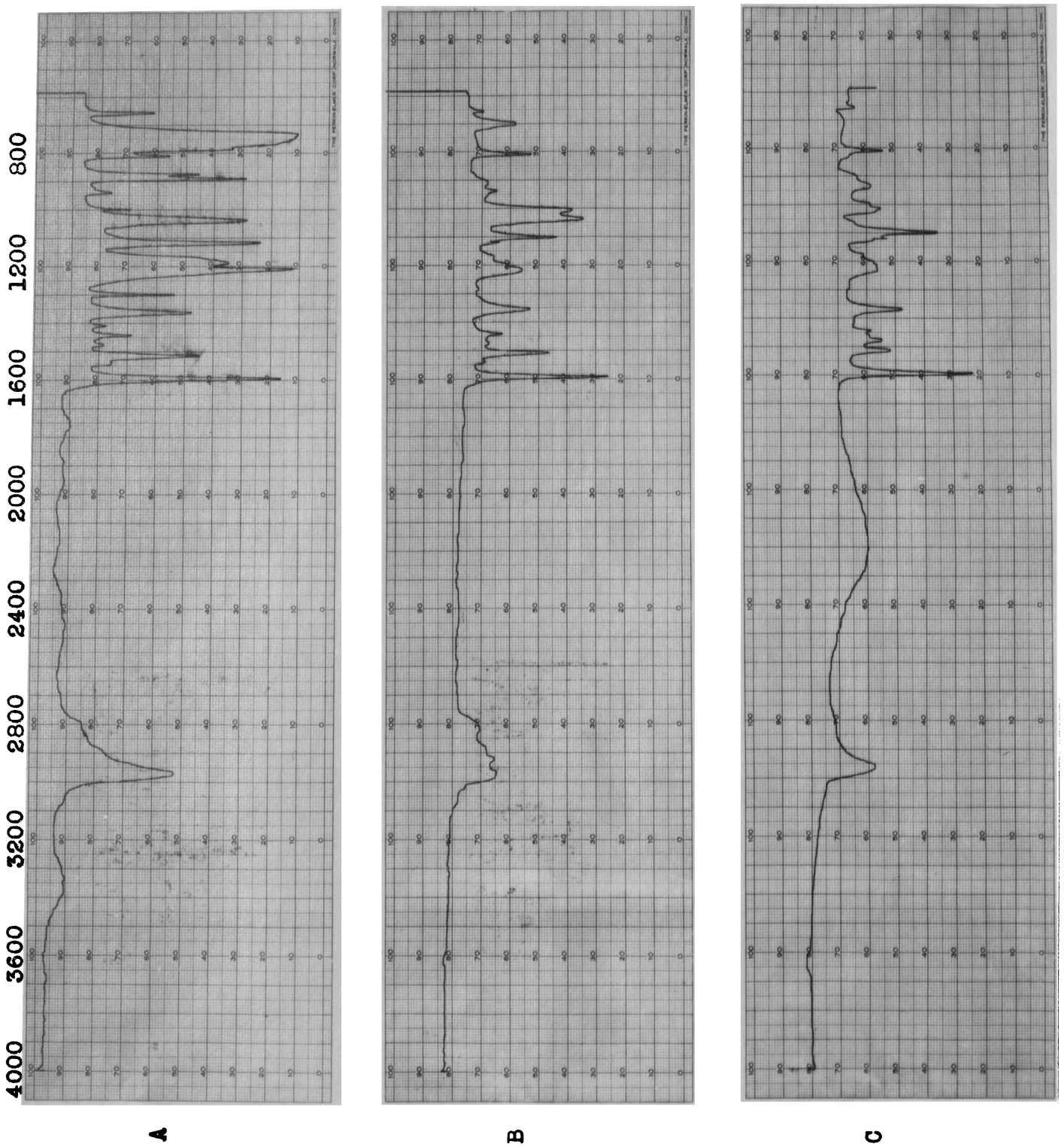
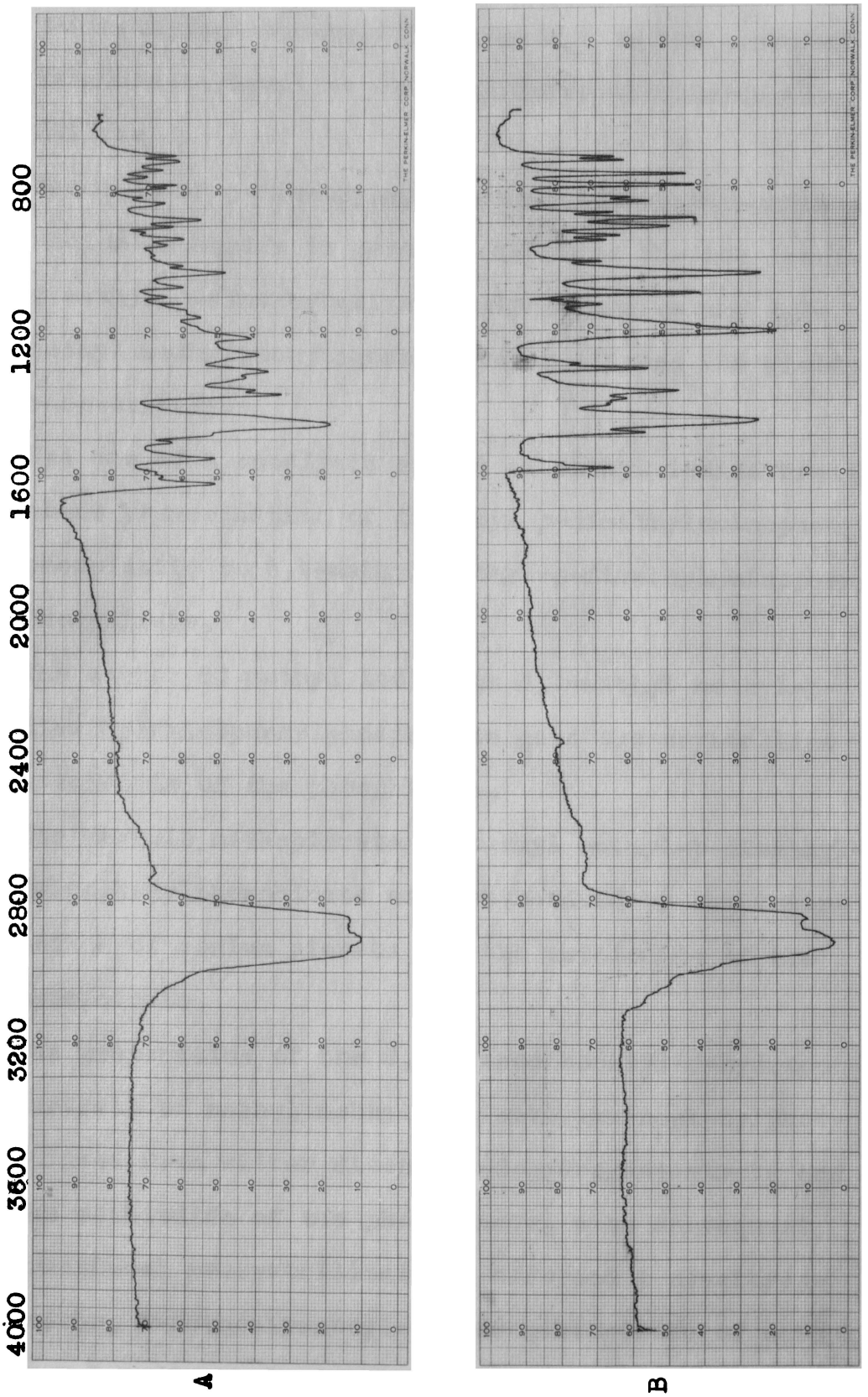


FIG. 15 INFRARED ABSORPTION SPECTRA

A. Methopicrate of Methyl Methyl-p-dimethylaminophenyl-phosphinate (Nujol Mull)

B. Methiodide of Methyl Methyl-p-dimethylaminophenyl-phosphinate (Nujol Mull)



SUMMARY

1. p-Dimethylaminophenyldichlorophosphine was prepared from dimethylaniline and phosphorus trichloride in 20% yield.
2. Reaction of p-dimethylaminophenyldichlorophosphine and sodium methoxide in methanol afforded the two isomers dimethyl p-dimethylaminophenylphosphonite and d,l-methyl methylphenylphosphinate in 46% and 25% yields, respectively.
3. The use of a catalytic amount of methyl iodide brought about isomerization of dimethyl p-dimethylaminophenylphosphonite to d,l-methyl methyl-p-dimethylaminophenylphosphinate.
4. The action of methyl iodide on d,l-methyl methyl-p-dimethylaminophenylphosphinate gave the crystalline methiodide of the phosphinate.
5. The racemic methopicrate of methyl methyl-p-dimethylaminophenylphosphinate was synthesized by the interaction of sodium picrate and the methiodide of the phosphinate.
6. The preparation of the d,l-methodibenzoyl-d-hydrogentartrate of methyl methyl-p-dimethylaminophenylphosphinate from silver dibenzoyl-d-hydrogentartrate and the methiodide of the phosphinate, with subsequent fractional recrystallization, afforded a diastereoisomer, l-methodibenzoyl-d-hydrogentartrate of methyl methyl-p-dimethylaminophenylphosphinate.

7. Combination of picric acid and the l-methodibenzoyl-d-hydrogentartrate of the phosphinate gave the l-methopicrate of methyl methyl-p-dimethylaminophenyl-phosphinate, $[\alpha]_D^{25}$ -22°.

8. The l-methiodide of methyl methyl-p-dimethylamino-phenylphosphinate, $[\alpha]_D^{25}$ -29° was prepared by the action of potassium iodide on the l-methodibenzoyl-d-hydrogentartrate of the phosphinate.

9. The synthesis of the d,l-methodibenzoyl-l-hydrogen-tartrate of methyl methyl-p-dimethylaminophenylphos-phinate from silver dibenzoyl-l-hydrogentartrate and the racemic methiodide of the phosphinate, with sub-sequent recrystallization, afforded a diastereoisomer, the d-methodibenzoyl-l-hydrogentartrate of the phos-phinate.

10. The d-methopicrate of methyl methyl-p-dimethylamino-phenylphosphinate $[\alpha]_D^{25}$ +22° was obtained by the interaction of potassium iodide and the d-methodiben-zoyl-l-hydrogentartrate of the phosphinate.

11. The action of potassium iodide on the d-methodibenzoyl-l-hydrogentartrate of the phosphinate afforded the d-methiodide of methyl methyl-p-dimethylaminophenyl-phosphinate, $[\alpha]_D^{25}$ +28°.

RECOMMENDATIONS FOR FUTURE RESEARCH

1. Asymmetric phosphorus compounds considered for optical resolution studies should contain strongly acidic or basic functional groups *via* which the compounds may be resolved.
2. A large number of the unsuccessful attempts at resolutions of phosphorus compounds utilized optically active camphorsulfonic acid derivatives. On the basis of the ready resolution of methyl methyl-p-dimethylaminophenylphosphinate *via* its methodibenzoyl-d-and l-hydrogen tartrates, it is suggested that dibenzoyl-d and l-tartaric acid be used as the resolving agent in further attempts to resolve these compounds.
3. It is suggested that the racemic and optically active forms of methyl methyl-p-dimethylaminophenylphosphinate be applied in the study of the mechanisms of reactions of organophosphorus compounds.

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