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TECHNICAL REPORT

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CWLR 2101

STUDIES INVOLVING THE GEOMETRIC STRUCTURES OF CERTAIN 2-ALKOXYCARBONYL-1-METHYLVINYL CYCLOHEXYL METHYLPHOSPHONATES (C)

by

Charles E. Williamson
Thomas P. Dawson

FC

20 March 1957

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C. E. Williamson, T. P. Dawson

CWLR 2101, 20 Mar 57 (CONFIDENTIAL)
Project 4-08-03-016-02

Work is described in which 2-ethoxycarbonyl-1-methylvinyl 3-methylcyclohexyl methylphosphonate, EA 1576, was studied with respect to its geometric isomerism, its preparation, and its stability to heat; a general discussion of its chemistry is included. Crystalline cyclohexyl 2-methoxycarbonyl-1-methylvinyl methylphosphonate, EA 1671, is discussed with respect to its preparation, its geometric isomerism, and its similarity to EA 1576.

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STUDIES INVOLVING THE GEOMETRIC STRUCTURES OF CERTAIN 2-ALKOXYCARBONYL-1-METHYLVINYL CYCLOHEXYL METHYLPHOSPHONATES (C)

by

Charles E. Williamson
Thomas P. Dawson

Chemical Research Division

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Chemical Warfare Laboratories
Report No. 2101

APPROVED:

STUDIES INVOLVING THE GEOMETRIC STRUCTURES OF CERTAIN 2-ALKOXY-CARBONYL-1-METHYLVINYL CYCLOHEXYL METHYLPHOSPHONATES (C)

William H Summerson
WILLIAM H. SUMMERSON, Ph.D.
Director of Research

Project No.: 4-08-03-016-02
Notebook No.: 4158

Date Started: 3 June 1954
Date Completed: 1 May 1956

S. D. Silver
S. D. SILVER
Deputy Commander for
Scientific Activities

Submitted for Publication: 19 June 1956

ABSTRACT

Object.

The object of project 4-08-03-016-02 (formerly 4-08-03-005) is to obtain information on the corrosiveness, methods of stabilization and detection, and other chemical and physical properties of GB.

The object of the work described in this report was to prepare a series of phosphorus-containing compounds as part of a broad research program, directed toward the discovery of agents of greater toxicity than those already known. The geometric isomers (cis and trans forms) of certain acetoacetic ester phosphonates were to be identified and the chemistry of these compounds studied.

Results.

Two methods of preparation of 2-ethoxycarbonyl-1-methylvinyl 3-methylcyclohexyl methylphosphonate, EA 1576, were developed.

The reaction of the sodium salt of ethyl acetoacetate with 3-methylcyclohexyl methylphosphonochloridate at 80°C. produced a 90% trans-10% cis mixture.

The reaction of ethyl acetoacetate with the chloridate in the presence of triethylamine produced a 90% cis-10% trans mixture.

The cis isomer or labile form of EA 1576 was converted to the trans isomer or stable form by heat alone, or by heat in the presence of tributylamine or a catalytic amount of the sodium salt of ethyl acetoacetate.

Tentative designation as the cis isomer of the labile form of EA 1576 and as the trans isomer of the stable form was based on heat behavior of both forms, and correlations to a compound, of similar structure, capable of existing only in the cis configuration.

The anhydride of 3-methylcyclohexyl hydrogen methylphosphonate, obtained as an impurity in the preparation of EA 1576, was reconverted to EA 1576 by heating the reaction mixture in the presence of a small amount of the sodium salt of ethyl acetoacetate.

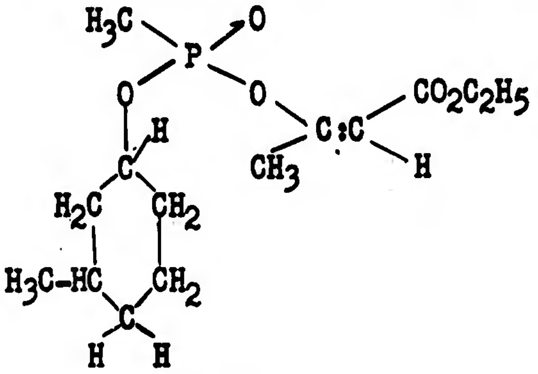
The compound, 2-methoxycarbonyl-1-cyclopentenyl 3-methylcyclohexyl methylphosphonate, closely resembling EA 1576 and capable of existing only in the cis configuration was prepared for use in infrared spectral studies.

The trans or stable form of 2-methoxycarbonyl-1-methylvinyl cyclohexyl methylphosphonate, EA 1671, was prepared and isolated by fractional crystallization, as a pure white crystalline solid of m.p. 43°C.

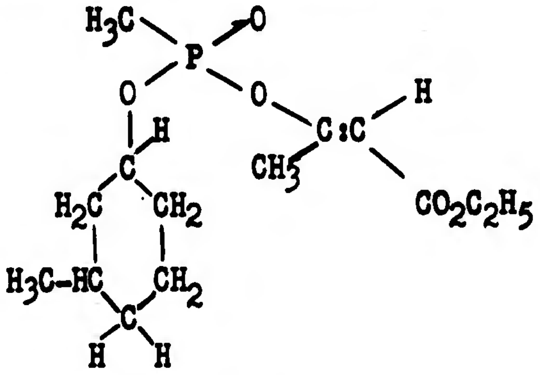
Conclusions.

1. The conditions of p. 7 give either a 90% *cis*-10% *trans* or 90% *trans*-10% *cis* mixture of EA 1576 in approximately 90% purity.

2. The labile form of EA 1576 is tentatively designated the *cis* isomer and the stable form the *trans* isomer. These designations are based on the stability to heat and correlations with a similar compound which is capable of existing only in *cis* form. The structural formulas follow:



Cis EA 1576



Trans EA 1576

3. The stable isomer of EA 1576 is more toxic in comparison with the labile isomer than was believed prior to this investigation.

4. The stable form of 2-methoxycarbonyl-1-methylvinyl cyclohexyl methylphosphonate, EA 1671, is tentatively designated as the *trans* since it showed the same characteristic infrared bonds as the stable form of EA 1576 and its infrared spectrum contained no bond attributable to the *cis* isomer. It is the most highly toxic of the series prepared to date.

5. The labile forms of 2-alkoxycarbonyl-1-methylvinyl alkylcyclohexyl methylphosphonates may be converted to the stable forms by heating them for 1 hr. at 100°C. in the presence of a small amount of the sodium salt of the corresponding alkyl acetoacetate.

Recommendations.

None, since the work was done under a continuing project.

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STUDIES INVOLVING THE GEOMETRIC STRUCTURES OF CERTAIN 2-ALKOXYCARBONYL-1-METHYLVINYL CYCLOHEXYL METHYLPHOSPHONATES (C)

I. INTRODUCTION.

A. Object.

The object of project 4-08-03-016-02 (formerly 4-08-03-005) is to obtain information on the corrosiveness, methods of stabilization and detection, and other chemical and physical properties of GB.

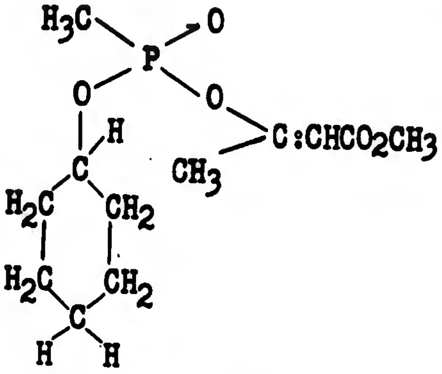
The object of the work described in this report was to prepare a series of phosphorus-containing compounds as part of a broad research program, directed toward the discovery of agents of greater toxicity than those already known. The geometric isomers (cis and trans forms) of certain acetoacetic ester phosphonates were to be identified and the chemistry of these compounds studied.

B. Authority.

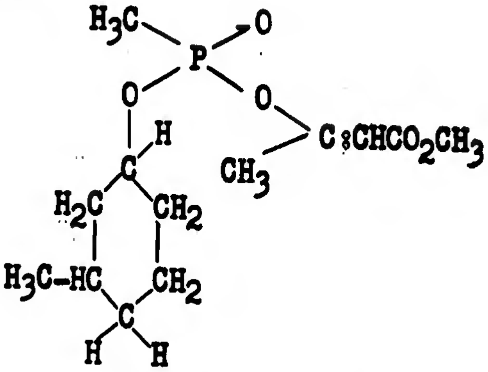
Authority for this work was contained in the project programs for fiscal years 1954 and 1955, Project 4-08-03-005, later renumbered 4-08-03-016-02, G Agents (U); the latter was approved 9 December 1954 by CCTC Item 2962.

II. HISTORICAL AND THEORETICAL.

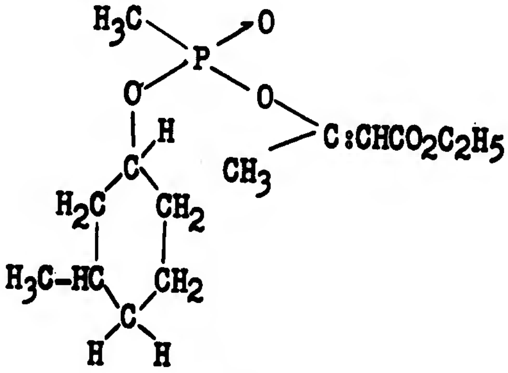
Previous work (1, 2) in the search for phosphorus containing compounds of greater toxicity than those previously known led to the discovery of several agents exhibiting a high percutaneous toxicity. Among these, cyclohexyl 2-methoxycarbonyl-1-methylvinyl methylphosphonate, EA 1671, and 2-methoxycarbonyl-1-methylvinyl 3-methylcyclohexyl methylphosphonate, EA 1598, were the most toxic compounds found. 2-Ethoxycarbonyl-1-methylvinyl 3-methylcyclohexyl methylphosphonate, EA 1576, was also quite toxic and, because of its ease of preparation, was chosen as a model compound for the purpose of studying the properties of these compounds; starting materials were readily available.



EA 1671

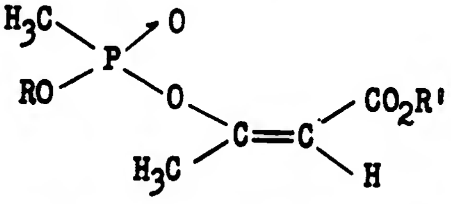


EA 1598



EA 1576

Since these compounds were of interest as possible chemical warfare agents, an attempt was made to study their properties in a more detailed manner. A number of compounds of the following general formula were synthesized in order to study the effect of changes in R and R'.



These compounds were conveniently prepared in about 90% purity. Only a few have been purified to date, since they may be obtained analytically pure only with difficulty.

III. EXPERIMENTAL.

A. Materials.

The methylphosphonic dichloride used in these studies was prepared by the Plants Division, Chemical and Radiological Laboratories, Army Chemical Center, Md. The methyl acetoacetate was obtained from Carbide and Carbon Chemicals Division, New York, N. Y. All other materials used were purchased from ordinary commercial sources.

B. Equipment.

Standard laboratory pyrex glassware was used in all experiments.

C. Preparation of Some Phosphorus-Containing Compounds.

1. The Preparation of 2-Methoxycarbonyl-1-cyclopentenyl 3-Methylcyclohexyl Methylphosphonate, EA 1659.

Methylphosphonic dichloride (13.3 g., 0.1 mole) and triethylamine (10.1 g., 0.1 mole) were dissolved in 200 ml. of benzene and 3-methylcyclohexanol (11.4 g., 0.1 mole) was added slowly while stirring. The reaction was exothermic and cooling was necessary to maintain a reaction temperature of 10°-15°C. The reaction mixture was then allowed to warm to room temperature and it was stirred for an additional hour. Triethylamine (10.1 g., 0.1 mole) was dissolved in the reaction mixture and 2-carbethoxycyclopentatone (14.2 g., 0.1 mole) was then added slowly while stirring and cooling. The reaction temperature was maintained at 35°C. After stirring for an additional hour at room temperature, the mixture was washed with a 5% aqueous sodium hydroxide solution (five 100-ml. portions) and then water (five 100-ml. washings). The solvent was removed by distillation at reduced pressure and the residue was distilled at 80°C. at 5×10^{-5} mm. Hg of pressure in a falling-film-type molecular still. A yield of 22 g. (69.5%) was obtained.

2. The Preparation of Cyclohexyl 2-Methoxycarbonyl-1-methylvinyl Methylphosphonate, EA 1671.

Methylphosphonic dichloride (33.2 g., 0.25 mole) and triethylamine (25.3 g., 0.25 mole) were dissolved in 200 ml. of benzene and cyclohexanol (25 g., 0.25 mole) was added slowly while stirring. The reaction was exothermic and cooling was necessary to maintain the reaction temperature at 10°-15°C. After stirring the reaction mixture at room temperature for an additional 2 hr., triethylamine (25.3 g., 0.25 mole) was added and then methyl acetoacetate (29 g., 0.25 mole) was added slowly while stirring and cooling. The reaction temperature was maintained at 20°C. After stirring for an additional 2 hr. at room temperature and standing overnight, the mixture containing the crude *cis* material was washed with a 5% aqueous sodium hydroxide solution (four 100-ml. volumes) and then with water (four 100-ml. washings). The solvent was removed by distillation at a reduced pressure and 2.8 g. of the sodium salt of methyl acetoacetate was added. The mixture was heated at 100°C. for 1 hr. and dissolved in 200 ml. of benzene. This solution was washed with a 5% aqueous sodium hydroxide solution (four portions of 100 ml. each) and water (four 100-ml. quantities). The solvent was then removed by distillation at a reduced pressure and the residue was distilled at 80°C. at 10^{-4} mm. Hg of pressure in a falling-film-type molecular still. A yield of 30.1 g. (43.6%) of the crude *trans* product was obtained.

Upon cooling in a dry ice-acetone bath, the product partially crystallized. These crystals were collected by filtration and were then warmed just above the melting point. The resulting liquid was allowed to cool very slowly and partially crystallize. At this point, the crystals were removed rapidly by filtration. The crystals collected in such a manner were then pressed on a porous plate. Colorless needles were obtained which melted at 43°C. Anal. Calcd. for $C_{12}H_{21}O_5P$: C, 52.2; H, 7.7; P, 11.2. Found: C, 52.2; H, 7.9; P, 11.2.

3. The Preparation of the Cis-Isomer of 2-Ethoxycarbonyl-1-methylvinyl 3-Methylcyclohexyl Methylphosphonate, EA 1576.

Methylphosphonic dichloride (132.9 g., 1.0 mole) and triethylamine (101 g., 1.0 mole) were dissolved in 1 liter of benzene contained in a 3-l. reaction flask equipped with an outlet at the bottom of the flask.

3-Methylcyclohexanol (114.2 g., 1.0 mole) was added slowly to the stirred reaction mixture. The reaction was exothermic and cooling was necessary to maintain the reaction temperature at 35°C. After stirring for an additional 30 min., triethylamine (101 g., 1.0 mole) was added and then ethyl acetoacetate (130.1 g., 1.0 mole) was added slowly while stirring and cooling. The reaction temperature was maintained at 35°C. After stirring for an additional 30 min., the reaction mixture was washed with a 5% aqueous sodium hydroxide solution (eight 150-ml. quantities) followed by water (eight portions of 100 ml. each). The benzene solution was then removed from the reaction flask and the solvent was removed by distillation at a reduced pressure. A yield of 238.7 g. (78.4%) of the crude 90% cis-10% trans material was obtained. Anal. Calcd. for $C_{14}H_{25}O_5P$: C, 55.3; H, 8.3; P, 10.2. Found: C, 55.9; H, 8.3; P, 10.1.

4. The Preparation of the Trans-Isomer of 2-Ethoxycarbonyl-1-methylvinyl 3-Methylcyclohexyl Methylphosphonate, EA 1576.

Sodium metal (3.45 g., 0.15 mole) was added to 300 ml. of xylene and the mixture was heated and stirred vigorously until the melted sodium was dispersed. Ethyl acetoacetate (19.5 g., 0.15 mole) was added and the mixture was warmed and stirred until the sodium had completely reacted. After standing overnight, the mixture was heated to 80°C. and 3-methylcyclohexyl methylphosphonochloridate was added rapidly. The reaction mixture was allowed to cool immediately after the last addition was complete. After standing overnight, it was washed with a 5% aqueous sodium hydroxide solution (six 150-ml. portions) followed by water (six 150-ml. treatments). The solvent was then removed by distillation at a reduced pressure. A yield of 36.4 g. (79.8%) of the crude 90% trans-10% cis material was obtained. Anal. Calcd. for $C_{14}H_{25}O_5P$: C, 55.3; H, 8.3; P, 10.2. Found: C, 54.8; H, 7.9; P, 10.5.

5. The Conversion of *Cis* EA 1576 to *Trans* EA 1576.

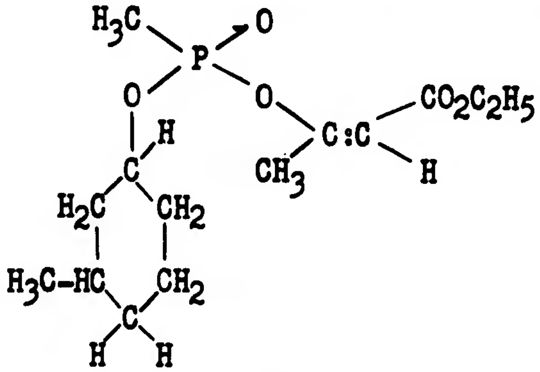
The *cis-trans* mixture of 2-ethoxycarbonyl-1-methylvinyl 3-methylcyclohexyl methylphosphonate (190.3 g., 90% *cis*-10% *trans*) was treated with 7.6 g. of the sodium salt of ethyl acetoacetate and heated in an oil bath to 100°C. for 1 hr. The mixture was then dissolved in 200 ml. of benzene and washed with a 5% aqueous sodium hydroxide solution (five 200-ml. quantities) followed by water (five 200-ml. treatments). The solvent was removed by distillation at a reduced pressure and the residue was submitted for infrared examination. A yield of 141.0 g. (74.1%) was obtained. The infrared spectrum of this material showed it to be approximately a mixture of 90% *trans*-10% *cis* isomers.

IV. RESULTS.

A. The Geometric Isomers of EA 1576 and Their Toxicity.

Toxicity tests revealed that some samples of EA 1576 were up to ten times more toxic than others, and thus the toxic component of these preparations was studied more thoroughly and attempts were made to isolate it in a pure state.

2-Ethoxycarbonyl-1-methylvinyl 3-methylcyclohexyl methylphosphonate, EA 1576, is capable of existing in two geometric structures.



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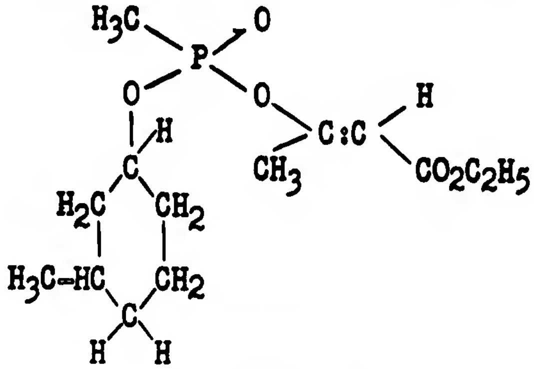


Trans II

The possibility of one isomer being more toxic than the other was investigated, and it appeared from the infrared spectra of several samples that the two isomeric forms were responsible for these variations in toxicity. Shell Development Company, Emeryville, Calif., has also shown that two forms exist in similar compounds (3).

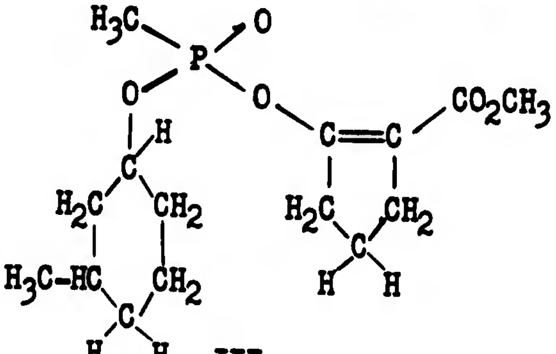
In efforts to determine which form was the more toxic, it was found that the less toxic form could be converted to the more stable toxic form by several methods, all of which involved heating the less toxic or labile form.

Heating the labile form with tributylamine at 150°C. for one hour, or heating it with the sodium salt of ethyl acetoacetate for one hour at 100°C. gave approximately 90% conversion to the stable form. Heating without a catalyst at 150°C. for two hours gave a 25% conversion, while heating to 50°C. for a period of three months gave a 90% conversion. Distillation at 106°C. at a pressure of 0.005 mm. Hg gave a 50% conversion and upon redistillation no further change was detected.

B. The Infrared Spectra of EA 1576 and Related Compounds.

Since, up to this point, the <u>cis</u> and <u>trans</u> assignments of EA 1576 and related compounds were completely dependent upon the above chemical and physical evidence, it was decided to study the infrared spectra of such compounds in a more vigorous attempt to prove their structure.

2-Methoxycarbonyl-1-cyclopentenyl 3-methylcyclohexyl methylphosphonate structure III, see below, was prepared, since it closely resembled EA 1576 and can exist only in the <u>cis</u> form.



III

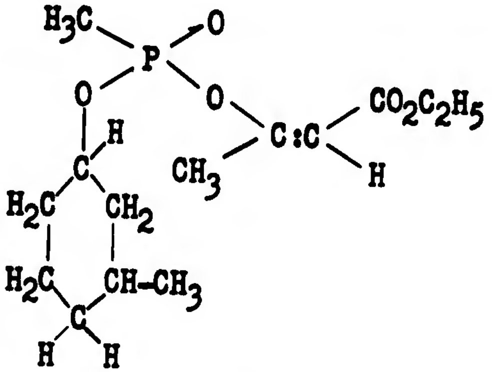
Table 1 shows the characteristic infrared bands for EA 1576 and structure III. The spectra of both the labile and stable forms are quite similar, except in the 8.0μ-9.0μ region. Both show absorptions in the C=C region (6.00μ-6.05μ).

Table 1

Infrared Spectrum Absorptions

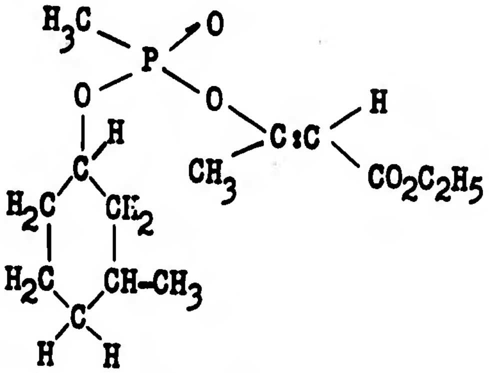
EA 1576 Labile form	EA 1576 Stable form	Compound III
8.28μ (strong) 8.7μ (medium) 8.86μ (weak)	8.86μ (strong) 8.08μ (medium) 8.28μ (weak)	8.28μ (strong) 8.7μ (medium) 8.80μ (medium-strong) None at 8.1μ None at 8.86μ

Except for the band at 8.80µ, which was not present in the spectrum of EA 1576, the spectrum of structure III seemed to confirm the structure previously proposed for the *cis* isomer. Conversely, the stable isomer would necessarily have the opposite or *trans* structure. From the information thus obtained, the labile and stable forms were tentatively assigned structures I and II respectively:



I

Cis EA 1576

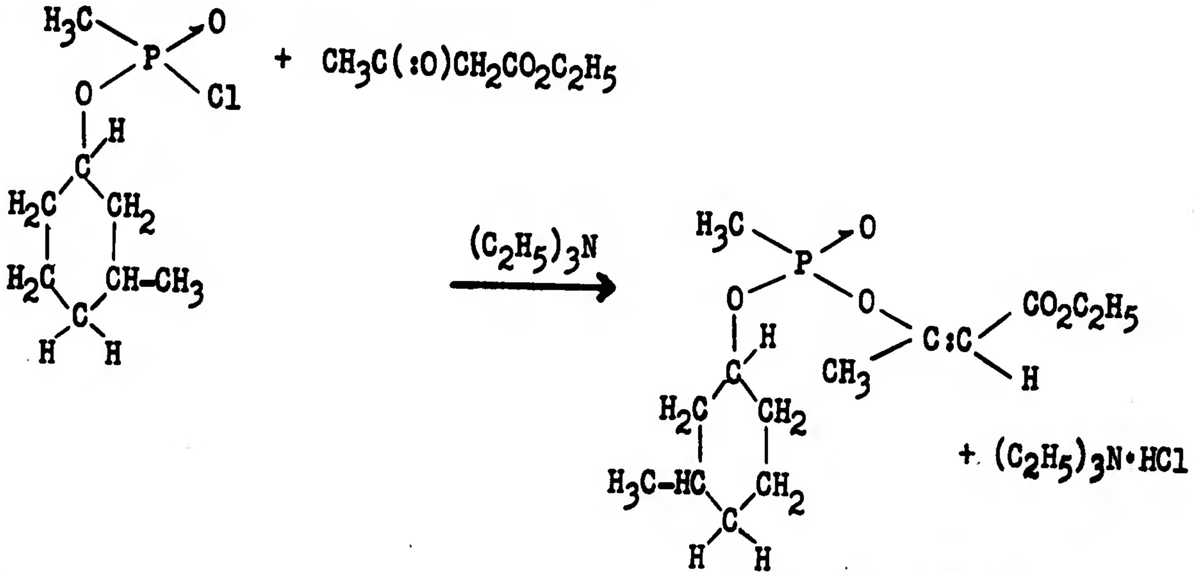


II

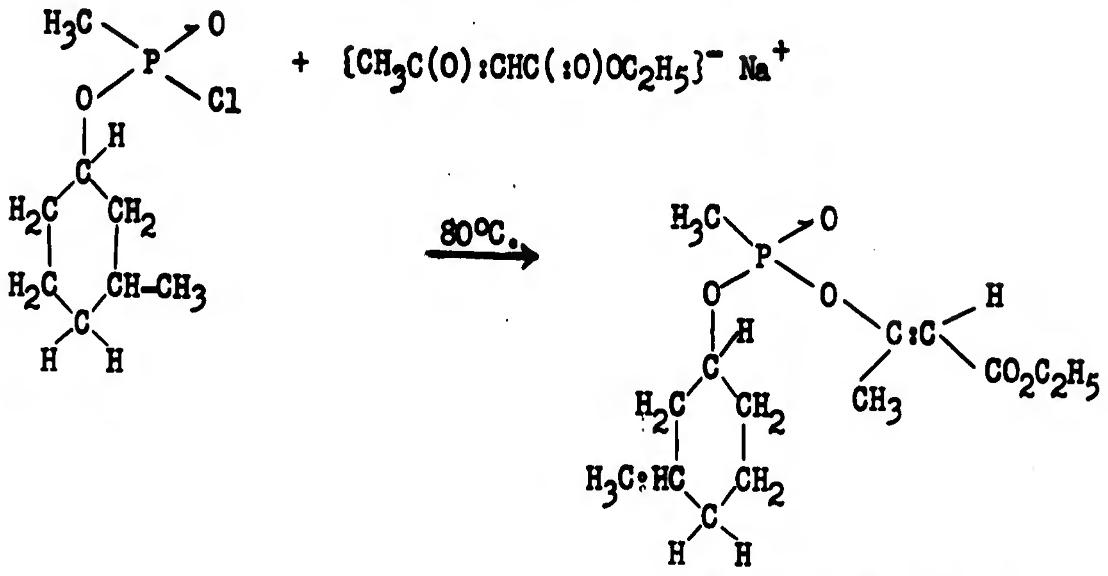
Trans EA 1576

C. General Results of the Preparation of Several Phosphorus-Containing Compounds.

Two methods of preparation were originally employed to synthesize EA 1576. After isolating the product by each method and subjecting it to infrared spectral examination, the conditions were found whereby either the 90% *cis*-10% *trans* or 90% *trans*-10% *cis* mixtures could be obtained in approximately 90% purity. The following equations indicate the methods employed to produce the desired forms:



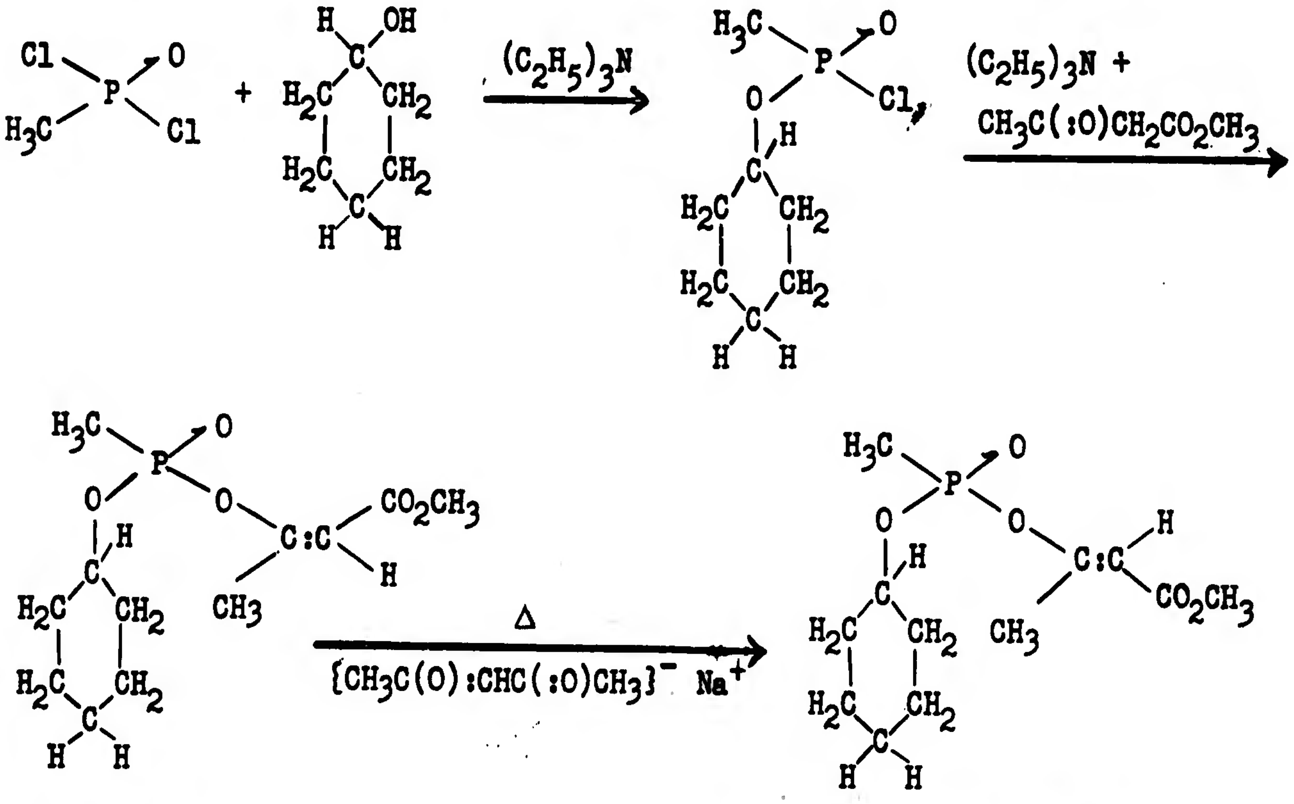
Approx. 90% *cis*
Approx. 10% *trans*



Approx. 90% <u>trans</u>

Approx. 10% <u>cis</u>

These reactions may be carried out using methyl phosphonic dichloride as a starting material and the chloridate is not isolated. As an example, cyclohexyl 2-methoxycarbonyl-1-methylvinyl methylphosphonate, EA 1671, is prepared in a single operation without the isolation of an intermediate.



<u>Cis</u> EA 1671

<u>Trans</u> EA 1671

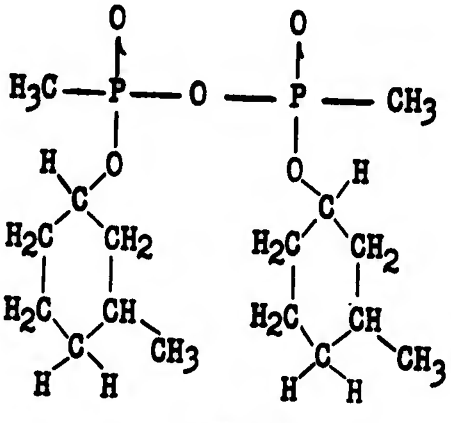
EA 1671 has been isolated in a crystalline state which is pure and exclusively trans. When subjected to infrared examination, this material exhibits the characteristic trans bands, which were found in EA 1576, but no weak band at 8.28μ. This is another indication that previous preparations which were not crystalline contained the cis isomer as an impurity. Crystalline EA 1671 is the most toxic compound of this series prepared to date, and preliminary studies indicate that it is quite stable to heat.

2-Methoxycarbonyl-1-methylvinyl 3-methylcyclohexyl methylphosphonate, EA 1598, was prepared in a similar manner without the isolation of intermediates.

D. The Purification of EA 1576.

During the preparation of EA 1576, the crude product is partially purified by washing with a 5% aqueous sodium hydroxide solution followed by water. This washing procedure, which removes triethylamine hydrochloride, free acids, and other water soluble impurities, could also be responsible for the introduction of an undesirable impurity in the final product.

Infrared examination of the washed product quite often showed a relatively strong band in the region where the P-O-P linkage of phosphonate anhydrides absorbs (approx. 10.8μ). It was found that this phosphonate anhydride IV, which is present as an impurity, could be removed by the treatment of impure cis EA 1576 with the sodium salt ethyl acetoacetate at 100°C. for 1 hr. Infrared analysis of the product obtained after such treatment showed approximately 90% trans, approximately 10% cis isomer and the complete absence of structure IV.



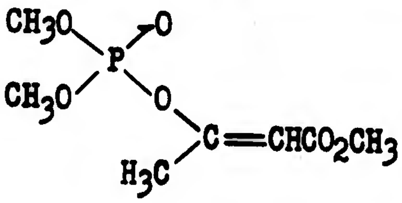
IV

V. DISCUSSION.

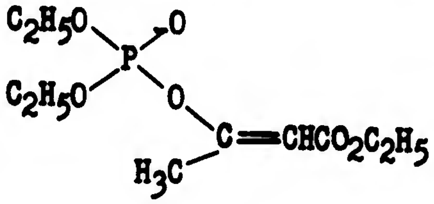
A. Effect of Heat and Ultraviolet on Cis-Trans Isomerization.

The fact that heat converted the less toxic form of EA 1576 to the more toxic form suggested in itself the first clue to its structure. In *cis-trans* isomers the *cis* form is usually of higher energy content than the *trans* form. It may be said that, in general, the *cis* forms tend to exhibit heats of combustion (4) which are higher than their corresponding *trans* isomers. Under the influence of heat, the labile form may be converted to the stable form (5). Since the less toxic form of EA 1576 is converted to the more toxic form upon heating, it appears that the toxic isomer is of a lower energy content. This isomer is normally expected to have the *trans* configuration.

Casida (6) recently reported a study of the *cis-trans* isomerism of dimethyl 2-methoxycarbonyl-1-methylvinyl phosphate structure V and diethyl 2-ethoxycarbonyl-1-methylvinyl phosphate structure VI.



V



VI

He found that the more toxic isomer was less soluble in water than the less toxic isomer. He also found that exposure to ultraviolet irradiation converted the more toxic isomer into the less toxic isomer. He further stated that ultraviolet irradiation should produce a mixture of isomers with the more stable *trans* configuration predominating, thus coming to the conclusion that the less toxic form had a *trans* configuration and the more toxic a *cis* configuration.

It should be pointed out that *cis* isomers are generally more water soluble than *trans* isomers (4), and that ultraviolet irradiation by the addition of energy to the stable form converts it into the labile modification. Ultraviolet irradiation is usually the best procedure for obtaining the labile form, since other methods such as chemical reactions and application of heat normally lead to the stable form (5). On the basis of the above empirical evidence, it appears that Casida's *cis* form exhibits properties which would lead one to believe that it actually has a *trans* configuration.

B. Weak Bands Found in the EA 1576 Labile and Stable Forms.

On the basis of the information obtained from the spectrum of structure III, it seems reasonable to believe that the weak band at 8.86μ, found in the spectrum of *cis* EA 1576, is due to the *trans* isomer which is present as an impurity, and the weak band at 8.28μ, found in the spectrum of *trans* EA 1576, is due to *cis* EA 1576 which is present as an impurity.

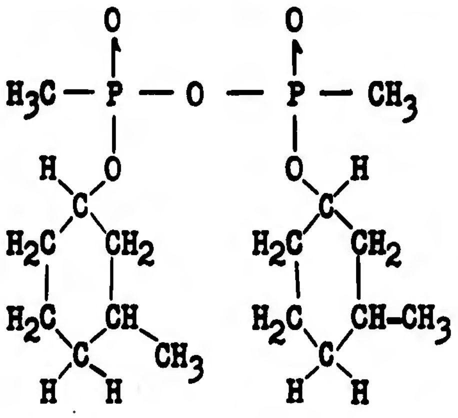
Assuming this to be the case, it would appear that the *cis* isomer is even less toxic than had been previously supposed, and that much of its toxicity may be attributed to the *trans* isomer which is present as an impurity.

C. Role of the Sodium Salt of Acetoacetic Ester.

Since the *cis* isomer is obtained, even when the reaction employing the triethylamine as a hydrogen chloride acceptor is carried out at 80°C., it appears that in this reaction the *cis* isomer is preferentially formed and even though heat is applied, in this instance, it is not sufficient to yield an appreciable amount of the *trans* material. However, if EA 1576 is produced by the reaction employing the sodium salt of ethyl acetoacetate, the product is approximately 90% *trans* when carried out at 80°C. Lower reaction temperatures resulted in an increased amount of the *cis* isomer. It appears that the sodium salt of ethyl acetoacetate acts as a catalyst in the formation of the *trans* isomer of EA 1576.

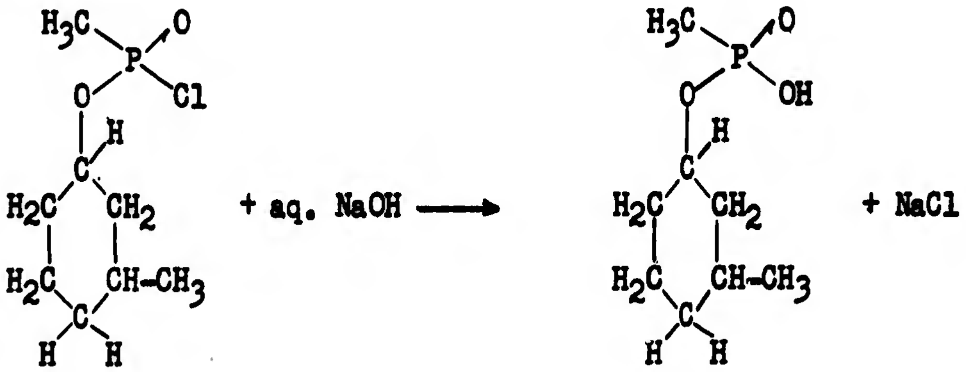
D. The 10.8μ Band: Origin of Anhydride Impurity.

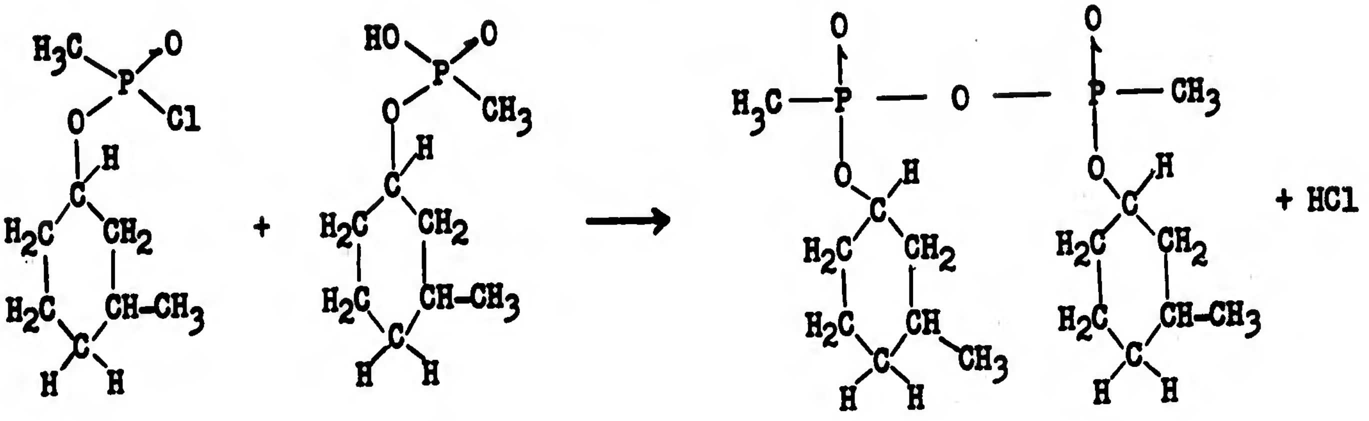
The band which is quite often found at 10.8μ in preparations of EA 1576 has tentatively been assigned to the presence of the anhydride of 3-methylcyclohexyl hydrogen methylphosphonate structure IV.



IV

It is believed that this impurity is introduced during the washing procedure through a reaction of any unreacted chloridate present according to the following equation:

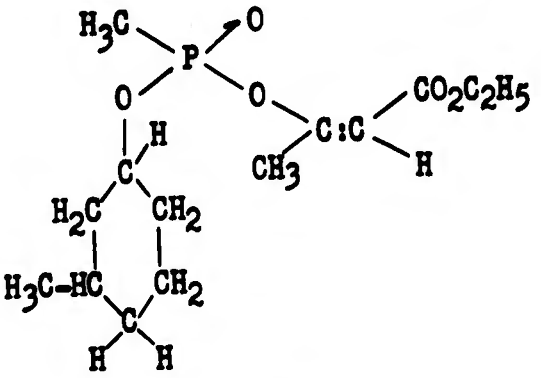




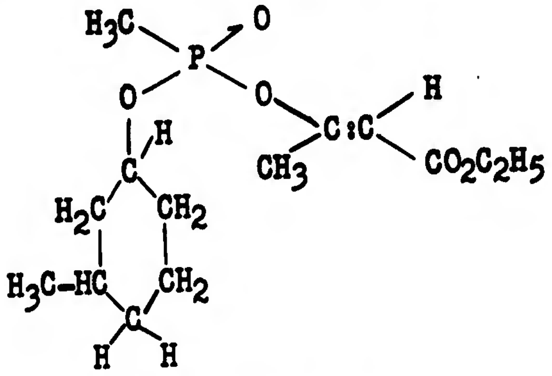
VI. CONCLUSIONS.

1. The conditions of p. 7 give either a 90% *cis*-10% *trans* or 90% *trans*-10% *cis* mixture of EA 1576 in approximately 90% purity.

2. The labile form of EA 1576 is tentatively designated the *cis* isomer and the stable form the *trans* isomer. These designations are based on the stability to heat and correlations with a similar compound which is capable of existing only in *cis* form. The structural formulas follow:



Cis EA 1576



Trans EA 1576

3. The stable isomer of EA 1576 is more toxic in comparison with the labile isomer than was believed prior to this investigation.

4. The stable form of 2-methoxycarbonyl-1-methylvinyl cyclohexyl methylphosphonate, EA 1671, is tentatively designated as the *trans* since it showed the same characteristic infrared bonds as the stable form of EA 1576 and its infrared spectrum contained no bond attributable to the *cis* isomer. It is the most highly toxic of the series prepared to date.

5. The labile forms of 2-alkoxycarbonyl-1-methylvinyl alkylcyclohexyl methylphosphonates may be converted to the stable forms by heating them for 1 hr. at 100°C. in the presence of a small amount of the sodium salt of the corresponding alkyl acetoacetate.

VII. RECOMMENDATIONS.

None, since the work was done under a continuing project.

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