The Stereochemistry of Asymmetric Phosphorus Compounds: The Correlation of the Configurations of O-Ethyl and O-Isopropyl Methylphosphonothioic Acids

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THE STEREOCHEMISTRY OF ASYMMETRIC PHOSPHORUS COMPOUNDS: THE CORRELATION OF THE CONFIGURATIONS OF O-ETHYL AND O-ISOPROPYL METHYLPHOSPHONOTHIOIC ACIDS.

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U. S. ARMY
Chemical Corps Research and Development Command
CHEMICAL RESEARCH AND DEVELOPMENT LABORATORIES
Army Chemical Center, Maryland
FOREWORD

The work described in this report was performed under Task 4C08-03-016-07, New Agent Research (U). The experimental data are recorded in notebooks 4950, 6035, 6098, 6105, 6190, and 6508. The work was started in March 1958 and was completed in April 1959.

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When this document has served its purpose, DESTROY it. DO NOT return the document to U. S. Army Chemical Research and Development Laboratories.
A part of a study of the basic stereochemistry of organophosphorus compounds, the objective of this work was to correlate the configurations of the resolved isomers of O-isopropyl methylphosphonothioic acid and O-ethyl methylphosphonothioic acid by a physical and a chemical method. The physical method was based upon a quasi-racemate formation between dicyclohexylamine salts of the acids, the chemical method upon an alkoxide ion displacement at the asymmetric phosphorus atom of the S-methyl esters of these acids to form the common optically active ethyl isopropyl methylphosphonate.

Based on the physical and the chemical evidence presented for the correlation of the configurations of O-ethyl and O-isopropyl methylphosphonothioic acid, it is concluded that the two levo enantiomers possess the same configuration. This conclusion agrees with that previously reached on the basis of the biochemical evidence.
I. INTRODUCTION.

The resolution of a series of O-alkyl alkylphosphonothioic acids has been described. That the levo enantiomers of these acids all possess the same configuration was concluded from the fact that optically active derivatives synthesized from these levo enantiomers were more potent inhibitors of cholinesterase enzymes than were those synthesized from the corresponding dextro enantiomers. We have now correlated the configurations of two of these resolved acids by a physical and a chemical method, and the results thus obtained are in agreement with the conclusion earlier reached on the basis of the biochemical evidence.

O-Isopropyl methylphosphonothioic acid (I) and O-ethyl methylphosphonothioic acid (II) were selected for this study. The physical method used to correlate their configurations is based on the quasi-racemate method. Here, melting points observed for mixtures of the dicyclohexylamine salts of (+)-I and (-)-I (table 1) indicate that a quasi-racemic compound, mp 159° to 161°C, is formed in this system, and, hence, these two compounds are of opposite configuration. The melting points of mixtures of the dicyclohexylamine salts of (-)-I and (-)-II were also determined (table 2). Here, a depression of the respective melting points indicates the absence of any quasi-racemate formation.

The chemical method used for the correlation is based upon the principle that if two optically active compounds of the opposite configuration, which possess the substituents a, b, c, x and a, b, c, y, respectively, have a common group c replaced by y and x, respectively, then the identical product will be obtained from both compounds.

II. RESULTS.

In our study, the configuration of I was related to that of II by converting both compounds into ethyl isopropyl methylphosphonate (V). The conversions that were carried out and the signs of the rotations obtained are outlined in the following reaction scheme.*

* The assigned structural formulas are intended to depict merely the probable relative configurations of these compounds. Absolute configurations in this series have not been established.
### TABLE 1

**MIXED MELTING POINTS OF MIXTURES OF THE DICYCLOHEXYLAMINE SALTS OF THE (+)-I AND (-)-II ACIDS**

<table>
<thead>
<tr>
<th>(+)-I Salt in mixture (mole %)</th>
<th>Melting point °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>123 - 125</td>
</tr>
<tr>
<td>2.4</td>
<td>123 - 125</td>
</tr>
<tr>
<td>6.1</td>
<td>124 - 135</td>
</tr>
<tr>
<td>14.8</td>
<td>124 - 145</td>
</tr>
<tr>
<td>37.3</td>
<td>124 - 159</td>
</tr>
<tr>
<td>49.0</td>
<td>159 - 161</td>
</tr>
<tr>
<td>69.5</td>
<td>142 - 158</td>
</tr>
<tr>
<td>81.4</td>
<td>122 - 152</td>
</tr>
<tr>
<td>93.4</td>
<td>122 - 130</td>
</tr>
<tr>
<td>97.3</td>
<td>122 - 126</td>
</tr>
<tr>
<td>100</td>
<td>123 - 124</td>
</tr>
</tbody>
</table>

### TABLE 2

**MIXED MELTING POINTS OF MIXTURES OF THE DICYCLOHEXYLAMINE SALTS OF THE (-)-I AND (-)-II ACIDS**

<table>
<thead>
<tr>
<th>(-)-I Salt in mixture (mole %)</th>
<th>Melting point °C</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>123 - 125</td>
</tr>
<tr>
<td>14.4</td>
<td>114 - 121</td>
</tr>
<tr>
<td>49.1</td>
<td>104 - 120</td>
</tr>
<tr>
<td>69.7</td>
<td>104 - 119</td>
</tr>
<tr>
<td>100</td>
<td>121.5 - 123</td>
</tr>
</tbody>
</table>
As may be seen from this scheme, if (+)-I and (-)-II are of opposite configurations (as shown), then conversion of these two acids into their corresponding S-methyl esters by treatment of their sodium salts with methyl iodide (with retention of configuration), followed by a displacement of the methyl mercaptide group with ethoxide in the case of III, and isopropoxide in the case of IV, will give rise to superimposable forms, and, hence, the identical ethyl isopropyl methylphosphonate. This conclusion is independent of the steric course (i.e., retention or inversion) by which the mercaptide group is displaced by the alkoxide anions, but it does depend upon the reasonable assumption that the same steric course is followed in both cases. A steric course with inversion of configuration has been depicted for the displacement reactions in this scheme.

The reactions outlined above were carried out first on optically inactive materials, and the synthetic procedures thus worked out were then used for the optically active syntheses.
In this manner, (+)-I, \([a]_D^\text{D} +13.91^\circ\) (neat, 1 dm), was converted into (+)-O-isopropyl S-methyl methylphosphonothioate (III), \([a]_D^\text{D} +114.4^\circ\) (neat, 1 dm), which in turn was converted into (-)-V, \([a]_D^\text{D} -0.90^\circ\) (neat, 1 dm), on treatment with sodium ethoxide in ethanol.

Similarly, (-)-II, \([a]_D^\text{D} -13.50^\circ\) (aq base), was converted into (-)-O-ethyl S-methyl methylphosphonothioate (IV), \([a]_D^\text{D} -120.2^\circ\) (neat, 1 dm), which in turn was converted into (-)-V, \([a]_D^\text{D} -0.86^\circ\) (neat, 1 dm), on treatment with sodium isopropoxide in isopropyl alcohol.

As a result of the relatively low rotations observed for the optically active V, however, the synthetic procedures were doublechecked for their internal consistency by converting (-)-I and (+)-II by means of the same series of reactions into (+)-V via their (-)-III and (+)-IV intermediates, respectively. In addition, it was shown that under the conditions of the (+)-III-ethoxide product run, the starting material would be optically stable in the presence of the mercaptide ion product. Also, the (-)-V product would have racemized only about 5% by the excess ethoxide ion used, and little, if at all, by the excess isopropoxide ion used.

The rates of the conversion of (-)-III into (+)-V by ethoxide ion and of (+)-IV into (+)-V by isopropoxide ion were measured polarimetrically at varying concentrations of the reactants, and second-order reaction-rate constants \((k_2)\) were calculated. The results are summarized in tables 3 and 4. As may be seen from table 4, the reaction of (+)-IV with sodium isopropoxide showed no ionic-strength effects over the concentration range studied, and the constancy of the \(k_2\) values obtained indicates that here a bimolecular mechanism is operative. Although the reaction of (-)-III with sodium ethoxide (table 3) satisfied a second-order rate expression for the individual rate runs, an increase in the calculated rate constants was obtained with increasing ethoxide concentrations. This observation was confirmed by duplicate runs (not reported here) at 0.07-, 0.14-, and 0.34-molar ethoxide concentrations, respectively. In one run (table 3, run 5), with added salt (sodium iodide), a marked decrease in the reaction rate was observed. This apparently anomalous result was not further investigated.

The fact that nearly equal rotations were observed for the (-)-V product obtained from both the (+)-III and (-)-IV systems, the demonstrated optical stability of the starting material and the product under the experimental conditions used, and the indicated bimolecular nature, at least of the IV-isopropoxide system, suggest that the low rotation observed for the (-)-V obtained from these reactions is inherently characteristic of the compound itself.
TABLE 3

KINETICS OF THE REACTION OF (-)-O-ISOPROPYL S-METHYL METHYLPHOSPHONOTHIOATE (III) WITH SODIUM ETHOXIDE IN ETHANOL

<table>
<thead>
<tr>
<th>Run</th>
<th>(-)-III</th>
<th>NaOEt</th>
<th>Temp °C (±0.2°)</th>
<th>$k_2$ liter mole⁻¹ min⁻¹</th>
<th>Reaction followed %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.0448</td>
<td>0.0700</td>
<td>29.8</td>
<td>0.095 ±0.002</td>
<td>8 - 75</td>
</tr>
<tr>
<td>2</td>
<td>0.0472</td>
<td>0.142</td>
<td>28.9</td>
<td>0.109 ±0.001</td>
<td>11 - 85</td>
</tr>
<tr>
<td>3</td>
<td>0.0854</td>
<td>0.142</td>
<td>28.9</td>
<td>0.108 ±0.005</td>
<td>8 - 95</td>
</tr>
<tr>
<td>4</td>
<td>0.0924</td>
<td>0.318</td>
<td>30.6</td>
<td>0.147 ±0.004</td>
<td>43 - 99</td>
</tr>
<tr>
<td>5</td>
<td>0.0944</td>
<td>0.142*</td>
<td>29.8</td>
<td>0.071 ±0.002</td>
<td>24 - 64</td>
</tr>
<tr>
<td>6</td>
<td>0.22</td>
<td>0.78</td>
<td>ca. 26**</td>
<td>0.180 ±0.004</td>
<td>37 - 97</td>
</tr>
</tbody>
</table>

* Plus 0.192 mole/liter of added sodium iodide.
** (+)-III product run at room temperature.

TABLE 4

KINETICS OF THE REACTION OF (+)-O-ETHYL S-METHYL METHYLPHOSPHONOTHIOATE (IV) WITH SODIUM ISOPROPOXIDE IN ISOPROPYL ALCOHOL

<table>
<thead>
<tr>
<th>Run</th>
<th>(+)-IV</th>
<th>NaOiPr</th>
<th>Temp °C (±0.2°)</th>
<th>$k_2$ liter mole⁻¹ min⁻¹</th>
<th>Reaction followed %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.0300</td>
<td>0.0802</td>
<td>29.7</td>
<td>1.09 ±0.04</td>
<td>35 - 93</td>
</tr>
<tr>
<td>2</td>
<td>0.0590</td>
<td>0.0830</td>
<td>29.9</td>
<td>1.04 ±0.09</td>
<td>37 - 99</td>
</tr>
<tr>
<td>3</td>
<td>0.0540</td>
<td>0.160</td>
<td>29.8</td>
<td>1.12 ±0.04</td>
<td>76 - 97</td>
</tr>
<tr>
<td>4</td>
<td>0.103</td>
<td>0.164</td>
<td>29.9</td>
<td>1.01 ±0.07</td>
<td>50 - 99</td>
</tr>
<tr>
<td>5</td>
<td>0.0890</td>
<td>0.214</td>
<td>29.8</td>
<td>1.03 ±0.03</td>
<td>69 - 99</td>
</tr>
</tbody>
</table>
The fact that (-)-V was obtained from both (+)-I and (-)-II proves that antipodes of the acids I and II, which are of opposite rotation, are also of opposite configuration. As indicated above, this proof depends upon the assumption that the steric course by which mercaptide is displaced by ethoxide and by isopropoxide is the same in the two systems studied. The fact that the stereochemical correlation obtained by the chemical method is in agreement with that obtained by the quasi-racemate method, and with the conclusion reached earlier on the basis of the biochemical evidence, proves that these two systems do react in a stereochemically analogous fashion.

III. EXPERIMENTAL.

A. Mixed-Melting-Point Data for Correlation of Configurations.

Mixtures of the dicyclohexylamine salts of the (+)-I and (-)-II acids and the (-)-I and (-)-II acids were prepared by weighing, grinding, and mixing the samples in small test tubes. The results are given in tables 1 and 2.

B. (+)-O-Isopropyl S-Methyl Methylphosphonothioate (III).

(+)-O-Isopropyl methylphosphonothioic acid (I) (5.0 gm, 0.033 mole), \( \alpha_{\text{obsd}}^{25} +13.91 \pm 0.01^\circ \) (neat, \(*1\) dm), was neutralized with 50 ml of freshly prepared 0.66 N methanolic sodium methoxide, and an excess of methyl iodide (14 gm, 0.1 mole) was added. The solution was gently refluxed for 5 hr on the steam bath and the excess methyl iodide and the methanol were then distilled off. The residue was taken up in ether, filtered, concentrated, and distilled, to give 4.0 gm (0.024 mole, 73%) of (+)-III, bp 73° to 75°C (4 mm), \( n_D^{25} 1.4712, \alpha_{\text{obsd}}^{25} +114.40 \pm 0.03^\circ \) (neat, 1 dm), \( [\alpha]_D^{28} +87.8 \pm 0.1^\circ \) (benzene, 2 dm, \( C ** 3.280), \alpha_{\text{obsd}}^{26} +91.4 \pm 0.1^\circ \) (ethanol, 2 dm, \( C 14.80). \)

In a preliminary experiment, the dl-III, \( n_D^{25} 1.4714, \) was similarly prepared in ethanol solution.

C. (-)-Ethyl Isopropyl Methylphosphonate (V) From (+)-III.

(+)-III (3.70 gm, 0.022 mole) was mixed with a freshly prepared solution of sodium (1.8 gm, 0.078 mole) in ethanol, then diluted to 100 ml with absolute ethanol. The reaction was followed polarimetrically from the

* All the neat rotations were measured using the sodium D line.
** \( C = \) Concentration milligrams per milliliter.
first recorded rotation of $+8.34^\circ$ (3 min after mixing) to $-0.20^\circ$ (53 min from the time of mixing). After a total of 90 min, the reaction mixture was brought to pH 7 with aqueous hydrochloric acid. The ethanol was distilled off, and the residual aqueous solution was saturated with sodium chloride, then extracted with ether. The ether solution was dried (Drierite) and concentrated, and the residue was distilled to give 1.7 gm (0.010 mole, 47%) of (-)-V, bp 60$^\circ$C (3.5 mm), $n^25_\text{D} 1.4096$, $\alpha_{\text{obsd}} -0.90 \pm 0.02^\circ$ (neat, 1 dm).

In a preliminary run, dl-V, bp 72$^\circ$ to 73$^\circ$C (4 mm), $n^25_\text{D} 1.4095$, was obtained from dl-III and sodium ethoxide after 16 hr in ethanol at room temperature.

Anal. Calcd. for C$_6$H$_{15}$O$_3$P: C, 43.4; H, 9.1. Found: C, 42.9; H, 9.0.

D. (-)-O-Ethyl S-Methyl Methylphosphonothioate (IV).

(-)-O-Ethyl methylphosphonothioic acid$^2$ (II) (6.7 gm, 0.048 mole), $[\alpha]^{\text{D}}_28.5 -12.6^\circ$ (aq base, 2 dm, C 2.844), was neutralized with an equivalent amount of sodium methoxide in methanol, then refluxed with excess methyl iodide for 4 hr. Water (ca. 50 ml) was added, and the excess of methyl iodide and the methanol were distilled off through a short helix filled column. The aqueous mixture was saturated with potassium chloride, then extracted with ether. The ether solution was dried (Drierite), filtered, and concentrated. The residue was distilled to give 4.8 gm (0.031 mole, 65%) of (-)-IV, bp 88$^\circ$C (3.5 mm), $n^25_\text{D} 1.4790$, $\alpha_{\text{obsd}} -120.20^\circ$ (neat, 1 dm), $[\alpha]^{\text{D}}_{30} -91.3 \pm 0.2^\circ$ (benzene, 2 dm, C 3.160). A forerun of 0.5 gm, $n^25_\text{D} 1.4775$, was also collected.

Anal. Calcd. for C$_4$H$_{11}$O$_2$PS: C, 31.2; H, 7.2. Found: C, 31.0; H, 7.0.

In a preliminary experiment, dl-IV, bp 86$^\circ$ to 87$^\circ$C (4 mm), $n^25_\text{D} 1.4784$, was prepared from dl-II by this procedure.


E. (-)-Ethyl Isopropyl Methylphosphonate (V) From (-)-IV.

(-)-IV (ca. 4.6 gm, 0.030 mole) was mixed with a freshly prepared solution of sodium (1.43 gm, 0.062 mole) in 200 ml of isopropyl alcohol, then diluted to 250 ml with isopropyl alcohol. The reaction was followed polarimetrically from the first recorded rotation of $-1.00^\circ$ (13 min after mixing) to
-0.021 ± 0.009° (105 min after mixing). After an additional 45 min, a value of -0.021 ± 0.014° was recorded. The reaction mixture was then worked up as described above for the preparation of (-)-V from (+)-III to give 1.25 gm (0.0075 mole, 25%) of (-)-V, bp 69°C (3 mm), \( n^D_{25} 1.4095 \), \( \alpha_{\text{obsd}} -0.86 ± 0.01° \) (neat, 1 dm).

Anal. Calcd. for C\(_{6}\)H\(_{15}\)O\(_{3}\)P: C, 43.4; H, 9.1. Found: C, 43.1; H, 9.2.

In a preliminary run, dl-V, bp 72°C (4 mm), \( n^D_{25} 1.4095 \), was obtained from dl-IV and sodium isopropoxide after 18 hr in isopropyl alcohol at room temperature.

Anal. Calcd. for C\(_{6}\)H\(_{15}\)O\(_{3}\)P: C, 43.4; H, 9.1. Found: C, 43.5; H, 9.1.

F. (-)-O-Isopropyl S-Methyl Methylphosphonothioate (III).

(-)-O-Isopropyl methylphosphonothioic acid\(^2\) (I), (4.4 gm, 0.029 mole), \( \alpha_{\text{obsd}} -12.94 ± 0.01° \) (neat, 1 dm), was treated essentially according to the procedure described above for the preparation of (+)-III from (+)-I, to give 3.24 gm (0.0193 mole, 67%) of (-)-III, bp 76°C (4.5 mm), \( n^D_{25} 1.4705 \), \( [\alpha]_{D}^{25} -83.5 ± 0.1° \) (benzene, 2 dm, C 3.070), \( [\alpha]_{D}^{25} -86.6 ± 0.1° \) (ethanol, 2 dm, C 11.36).

Anal. Calcd. for C\(_{5}\)H\(_{13}\)O\(_{2}\)PS: C, 35.7; H, 7.8. Found: C, 35.4; H, 7.8.

G. (+)-Ethyl Isopropyl Methylphosphonate (V) From (-)-III.

(-)-III (2.84 gm, 0.017 mole), \( [\alpha]_{D}^{27} -86.6° \) (ethanol), was treated with sodium ethoxide (0.069 mole) in 100 ml absolute ethanol as described above for the preparation of (-)-V from (+)-III. After 150 min, the mixture was worked up to give 1.78 gm (0.0107 mole, 63%) of (+)-V, bp 62°C (4.5 mm), \( n^D_{25} 1.4092 \), \( \alpha_{\text{obsd}} +0.82 ± 0.01° \) (neat, 1 dm).

Anal. Calcd. for C\(_{6}\)H\(_{15}\)O\(_{3}\)P: C, 43.4; H, 9.1. Found: C, 43.2; H, 9.3.

H. (+)-O-Ethyl S-Methyl Methylphosphonothioate (IV).

(+)-O-Ethyl methylphosphonothioic acid\(^2\) (II), \( \alpha_{\text{obsd}}^{28.5} +9.565 ± 0.003° \) (neat, 1 dm), was converted into (+)-IV, bp 72° to 73°C (3 mm), \( n^D_{25} 1.4790 \).
I. (+)-Ethyl Isopropyl Methylphosphonate (V) From (+)-IV.

(+)-IV (3.75 gm, 0.0244 mole) was treated with sodium isopropoxide (0.046 mole) in 250 ml isopropyl alcohol as described above for the preparation of (-)-V from (-)-IV. After 150 min, the mixture was worked up to give 1.34 gm (0.0081 mole, 33%) of (+)-V, bp 54°C (2.7 mm), $n_D^25 1.4096$, $\alpha_{\text{obsd}}^{29} +0.659 \pm 0.008^\circ$ (neat, 1 dm). In addition, a forerun of 0.36 gm, $n_D^25 1.2087$, was also collected.

J. (-)-III in the Presence of 0.15 N Sodium Mercaptide in Ethanol.

A solution of sodium mercaptide was prepared by saturating a 0.3244 N solution of ethanolic sodium ethoxide with methyl mercaptan. Then, 11.5 ml of this solution were added to (-)-III (0.366 gm, 0.00217 mole), $[\alpha]_D^{30} -89.2 \pm 0.10^\circ$ (ethanol, 2 dm, C 3.080), and the resulting solution was brought up to volume in a 25-ml volumetric flask, then transferred to a stoppered 2-dm jacketed polarimeter tube at 30°C. The initially observed rotation of -2.705 $\pm 0.005^\circ$ did not show any detectable change during 17.5 hr. The rotation then began to fall at a gradually accelerating rate until an observed rotation of -1.709 $\pm 0.005^\circ$ was recorded after 114 hr.

K. (+)-V in the Presence of 1.05 N Sodium Ethoxide in Ethanol.

Partially racemic (+)-V (1.061 gm, 0.00639 mole), $\alpha_{\text{obsd}}^{29} +0.659 \pm 0.008^\circ$ (neat, 1 dm), in a 5-ml volumetric flask was brought up to volume with 3.87 ml of freshly prepared 1.36 N ethanolic sodium ethoxide solution, then transferred to a 2-dm polarimeter tube, and the change of the observed rotation was recorded with time. The initial value of +0.822 $\pm 0.007^\circ$ (10 min after mixing) fell off to +0.477 $\pm 0.008^\circ$ in 6.25 hr according to a calculated pseudo-first-order rate expression where $k = (1.41 \pm 0.08) \times 10^{-3}$ min$^{-1}$ at a temperature of 29.5°C $\pm 0.4^\circ$.

L. (+)-V in the Presence of 0.165 N Sodium Isopropoxide in Isopropyl Alcohol.

(+)-V (0.8342 gm, 0.00502 mole), $\alpha_{\text{obsd}}^{29} +0.82 \pm 0.014^\circ$ (neat, 1 dm), was brought up to volume in a 5-ml volumetric flask with 4.15 ml of freshly prepared 0.199 N sodium isopropoxide in isopropyl alcohol solution. The observed rotation of this solution was +0.618 $\pm 0.012^\circ$ (2 dm) at a room temperature of 23.8°C. After 4 hr, a value of +0.600 $\pm 0.0130^\circ$ (2 dm) at a
A temperature of 25.5°C was recorded.

IV. CONCLUSIONS.

Based on the physical and chemical evidence presented for the correlation of the configurations of O-ethyl and O-isopropyl methylphosphonothioic acid, it is concluded that the two levo enantiomorphs possess the same configuration. This conclusion agrees with that previously reached on the basis of the biochemical evidence.
LITERATURE CITED


The configurations of the resolved isomers of O-isopropyl methylphosphonothioic acid and O-ethyl methylphosphonothioic acid have been correlated by a physical and a chemical method. The conclusion that the levo isomers possess the same configuration agrees with that previously reached on the basis of some biochemical evidence.