



FFI-RAPPORT

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Synthesis of reference compounds in the 36th OPCW Proficiency Test

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Summary

The Organisation for the Prohibition of Chemical Weapons (OPCW) organizes biannual Proficiency Tests for its member states where the participating laboratories receive samples with chemicals relevant to the Chemical Weapons Convention (CWC). The Norwegian Defence Research Establishment (FFI) participated in the 36th Proficiency Test, conducted in October–November 2014. Reference compounds are usually necessary to unambiguously confirm the identity of a relevant chemical structure. Since many reference compounds are not commercially available, synthesis is often required during the 15-day test period.

The purpose of this report is to compile all technical information concerning the synthesis of reference compounds to allow for exchange of information and experience with other OPCW Proficiency Test participating laboratories. In addition, the information and experience are useful for synthesis of related compounds necessary for identification purposes in future work.

During the 36th Proficiency Test it was necessary to synthesise the following four reference compounds: bis(2-(*N,N*-diethylamino)ethyl) ethylphosphonate, 2-(*N,N*-diethylamino)ethyl ethylphosphonate, divinylsulphoxide, and 1,4-oxathiane 4-oxide. They are reportable chemicals with respect to the CWC. Isobutyl dimethylphosphinate and *O*-isobutyl dimethylphosphinothioate were synthesised to verify their structures as being non-relevant and thus non-reportable chemicals. Initial structure validation was performed using nuclear magnetic resonance (NMR) spectroscopy for all synthesised chemicals. NMR and mass spectrometric data are given for all compounds. FFI reported all spiking chemicals and achieved the best score (grade A) for its participation in this Proficiency Test.

Performing six synthesis during the 15-day test period is labour-intensive. The work includes literature studies, purchase of chemicals, preparing equipment and procedures, performing the synthesis and validating the chemical structure of the products. Some of the synthesised compounds were, however, unstable, and further work is needed to optimise such reactions.

Sammendrag

To ganger i året arrangerer Organisasjonen for forbud mot kjemiske våpen (OPCW) ferdighetstester for sine medlemsland. Her mottar deltakende laboratorier prøver med innhold av kjemiske forbindelser som er relevante for Kjemivåpenkonvensjonen (CWC). Forsvarets forskningsinstitutt (FFI) deltok i den 36. ferdighetstesten, som ble gjennomført i perioden oktober–november 2014. For å bekrefte tilstedeværelsen av en kjemisk forbindelse er det ofte nødvendig å benytte referanseforbindelser. Siden mange referanseforbindelser ikke er kommersielt tilgjengelig, må disse syntetiseres i løpet av testperioden på 15 dager.

Formålet med denne rapporten er å samle all teknisk informasjon omkring syntesene slik at informasjon og erfaringer kan deles med andre laboratorier som deltar i OPCW sine ferdighetstester. I tillegg er informasjonen og erfaringene nyttig for videre arbeid med syntese av relaterte forbindelser som er nødvendig for framtidige identifikasjonsformål.

Under den 36. ferdighetstesten var det behov for å syntetisere følgende fire referanseforbindelser: bis(2-(*N,N*-dietylamino)etyl) etylfosfonat, 2-(*N,N*-dietylamino)etyl etylfosfonat, divinylsulfoksid og 1,4-oksatan-4-oksidi. De er alle rapporterbare forbindelser med hensyn til CWC. Isobutyl dimetylfosfinat og *O*-isobutyl dimetylfosfinotioat ble også syntetisert under testen. Dette ble gjort for å verifisere strukturen til de to forbindelsene, som viste seg å være ikke relevante og derfor heller ikke rapporterbare. Under ferdighetstesten ble de første strukturoppklaringene av synteseproduktene gjort med kjernemagnetisk resonans (NMR) spektroskopi. NMR og massespektrometriske data for alle produktene er gitt i rapporten. FFI rapporterte alle de tilsatte kjemiske forbindelsene i prøvene og fikk høyeste karakter (A) for sin deltakelse i ferdighetstesten.

Det er arbeidskrevende å syntetisere seks forskjellige forbindelser i løpet av en testperiode på 15 dager. Arbeidet består i å hente inn litteratur, kjøpe utgangsstoffer og utstyr, forberede og utføre syntesene og validere de kjemiske strukturene til produktene. Noen av de syntetiserte forbindelsene var ustabile, og videre arbeid er nødvendig for å optimalisere slike reaksjonstyper.

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Preface

The authors acknowledge Fatima Ibsen, Aase Mari Opstad and Bent Tore Røen for the GC-MS and LC-MS measurements, and also Leif Haldor Bjerkeseth for synthesising one of the compounds, 2-(*N,N*-diethylamino)ethyl ethylphosphonate, during this OPCW Proficiency Test.

1 Introduction

The Organisation for the Prohibition of Chemical Weapons (OPCW) organizes biannual Proficiency Tests for its Member States [1, 2]. Laboratories seeking to become OPCW designated laboratories have to participate in these tests and accomplish successfully in three consecutive tests. The laboratories must also have a proper quality system and be accredited according to ISO/IEC 17025 to be considered for designation.

The Identification Laboratory for Chemical Warfare Agents at Norwegian Defence Research Establishment (FFI) is seeking to become a designated laboratory. The laboratory therefore participates annually in these tests.

During a Proficiency Test the participating laboratories receive samples with chemicals relevant to the Chemical Weapons Convention (CWC) [3]. The relevant chemicals are to be reported to the OPCW, while non-relevant chemicals shall not be reported. Usually the sample matrix is water, organic liquid or soil, but sometimes also other materials. The components in the samples are unknown, but the concentrations shall be between 1-100 ppm. A report describing all findings including instrumental data is to be submitted within 15 days from sample arrival.

To confirm the identity of a chemical substance in a sample a reference compound is preferred. The share number of substances relevant to the CWC makes it difficult to have all such in stock. Therefore reference compounds usually have to be synthesised during the 15 days test period. The work can consist of literature studies, buying chemicals, prepare equipment and procedures, perform the synthesis and validate the chemical structure of the products.

The 36th Proficiency Test was held in 2014 with sample dispatch 17th of October. FFI received samples 20th of October and submitted the report 3rd of November. The list of spiking chemicals in the 36th Proficiency Test is given in Appendix A.

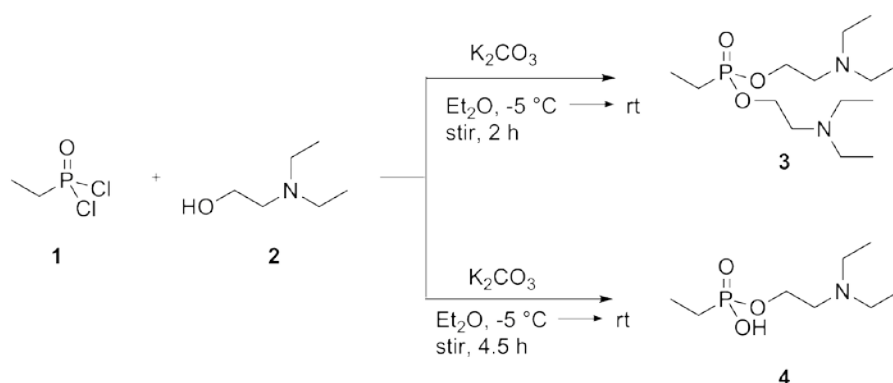
During the 36th Proficiency Test it was necessary to synthesise six different compounds. These were bis(2-(*N,N*-diethylamino)ethyl) ethylphosphonate, 2-(*N,N*-diethylamino)ethyl ethylphosphonate, divinylsulphoxide, 1,4-oxathiane 4-oxide, isobutyl dimethylphosphinate and *O*-isobutyl dimethylphosphinothioate. The first four compounds were synthesised to confirm the identity of these in the samples received and be able to report them with reference spectra. The last two compounds were synthesised to verify their structures as being non-relevant and thus non-reportable chemicals.

The report provides all technical information and experiences regarding the synthesis of reference compounds to allow exchange with other OPCW Proficiency Test participating laboratories. The report gives the synthesis results performed during this 15 days test period. It describes the discussions that were made concerning the experimental procedures and the associated challenges.

2 Results and discussion

2.1 Synthesis of bis(2-(*N,N*-diethylamino)ethyl) ethylphosphonate and 2-(*N,N*-diethylamino)ethyl) ethylphosphonate

Ethylphosphonic dichloride (**1**) and 2-(diethylamino)ethanol (**2**) were used to synthesise both bis(2-(*N,N*-diethylamino)ethyl) ethylphosphonate (**3**) and 2-(*N,N*-diethylamino)ethyl) ethylphosphonate (**4**) by two separate procedures (Scheme 1) [4]. Different equivalents of **1** and **2** were used, and the addition order was also different to facilitate the formation of either **3** or **4**.



Scheme 1 Synthesis of bis(2-(*N,N*-diethylamino)ethyl) ethylphosphonate (**3**) and 2-(*N,N*-diethylamino)ethyl) ethylphosphonate (**4**)

Triethylamine (Et_3N) is often used in this type of esterification reactions [4]. Potassium carbonate (K_2CO_3), an inorganic base, was nevertheless used in these reactions instead of triethylamine to avoid protonation of the compounds **2**, **3** and **4**. The reaction mixtures became slurry since potassium carbonate is insoluble in diethyl ether.

For **3**, the reaction mixture was carefully washed with water in an attempt to remove the salts. Still, **3** was identified in the aqueous phase by NMR and LC-MS. NMR data showed a large amount of unreacted alcohol **2**, and integration of the phosphorous NMR spectrum¹ showed a relationship of approximately 40:60 between the di- and monoester (**3**, **4**) (Appendix B.1, Figure- B.1). The product **3** was not purified or isolated, but the analysis implies that the yield of the expected diester was low.

For **4**, some non-soluble droplets in the diethyl ether solution were spotted after filtration of the reaction mixture. The droplets were dissolved in water and phosphorous NMR¹ identified **4** and large amounts of ethylphosphonic acid (EPA) in a relationship of approximately 20:80 (Appendix B.1, Figure- B.2). The product **4** was not purified or isolated, but the analysis implies that the yield of the expected monoester was low. LC-MS identified both **4** and EPA, in addition to several pyro compounds.

¹ The experiment was not performed with quantitative parameters, so the integration ratio is only semi-quantitative.

These two esters proved difficult to synthesise. Compounds of type 2-(dialkylamino)ethyl alkylphosphonochloridate (Figure 2.1), an intermediate in both esterification reactions, undergo spontaneous structural changes [4]. Xie *et al.* [5] synthesised 2-aminoethyl methylphosphonate by coupling methylphosphonic acid and *N*-trityl-2-aminoethanol (amine protected by trityl) via the Mitsunobu reaction². This could be another method for making such types of compounds in the future.

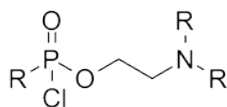
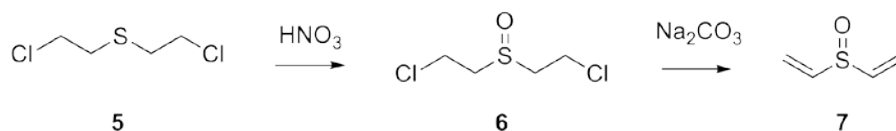


Figure 2.1 General structure of 2-(dialkylamino)ethyl alkylphosphonochloridates

2.2 Synthesis of divinylsulphoxide and 1,4-oxathiane 4-oxide

An attempt was made to synthesise divinylsulphoxide (**7**) according to the procedure described by Black *et al.* [6]. Bis(2-chloroethyl)sulphide (sulphur mustard) (**5**) was oxidized with concentrated nitric acid (HNO₃) at low temperatures to give the sulphur mustard sulphoxide (**6**). Using boiling aqueous sodium carbonate (Na₂CO₃), divinylsulphoxide (**7**) was formed by an elimination reaction from sulphur mustard sulphoxide (**6**) (Scheme 2). The last reaction was reported to give virtually quantitative yield [6].



Scheme 2 Synthesis of bis(2-chloroethyl)sulphoxide (**6**) and divinylsulphoxide (**7**) from sulphur mustard (**5**)

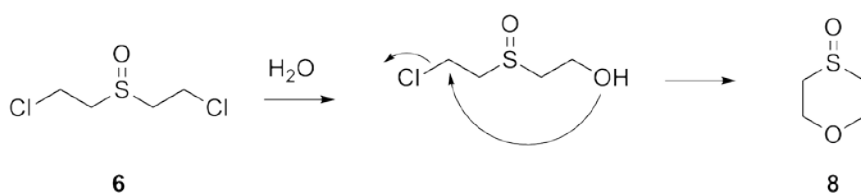
Water was added in an attempt to precipitate the sulphoxide **6**. Since this was not successful, the reaction mixture was extracted with dichloromethane. Sulphur mustard sulphoxide (**6**) was obtained as white crystals/yellowish oil and identified by NMR and GC-MS. Analytical data showed that the compound was relatively pure.

Sulphur mustard sulphoxide (**6**) dissolved in water was added sodium carbonate. Both **6** and sodium carbonate was quite poorly solvable in water at room temperature, but dissolved better at elevated temperature. According to the procedure the reflux time was 2.5 hours. Challenges with the equipment setup made it difficult to reach reflux and the reaction mixture was heated for a prolonged time (3.5 hours) at high temperatures. The mixture was allowed to cool down to room temperature and extracted with dichloromethane. After removing the solvent under reduced pressure a yellowish liquid was obtained. This consisted mainly of 1,4-oxathiane 4-

² The Mitsunobu reaction is most often used to convert alcohols into esters using triphenylphosphine and diethyl azodicarboxylate (DEAD).

oxide (**8**) and a small portion of divinylsulphoxide (**7**) identified by NMR (Appendix B.2, Figure- B.5), LC- and GC-MS. The product was neither purified nor isolated.

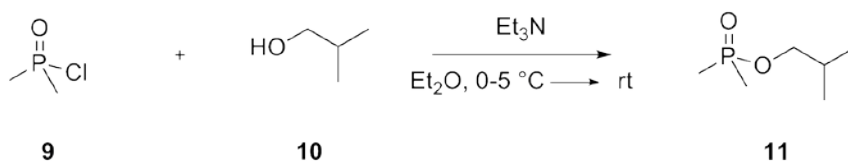
NMR data showed another vinyl compound which was formed in comparable amounts as **7** (Appendix B.2, Figure- B.6). Further structure elucidation of this compound was not performed, but 2-hydroxyethyl vinyl sulphoxide is a possibility. Formation of large amounts of the cyclic sulphoxide **8** (Appendix B.2, Figure- B.7) was probably due to the prolonged heating time. This compound **8** can be formed by a monohydrolysis of **6** followed by an intramolecular cyclization (Scheme 3). The cyclic sulphoxide **8** was one of the spiking chemicals in this Proficiency Test (Appendix A), so the formation of this compound was fortunate. Other synthetic methods for exclusively making **8** were considered [7, 8] and NMR data for **8** was found [9].



Scheme 3 Possible reaction pathway for the formation of 1,4-oxathiane 4-oxide (**8**)

2.3 Synthesis of isobutyl dimethylphosphinate

Isobutyl dimethylphosphinate (**11**) was synthesised according to a general procedure described in Pienaar *et al.* [4]. Dimethylphosphinic chloride (**9**) was reacted with isobutyl alcohol (**10**) (Scheme 4). The phosphinate **11** was obtained as a colourless liquid and identified by NMR, LC- and GC-MS, but neither purified nor isolated. Both LC-MS and ^{31}P NMR (Appendix B.1, Figure- B.3 and Figure- B.4) data showed two products with a ratio of approximately 88:12 between **11** and an unknown compound. This synthetic method appeared promising for making alkyl dialkylphosphinates, but further optimisation is necessary to increase the yield.



Scheme 4 Synthesis of isobutyl dimethylphosphinate (**11**)

2.4 Synthesis of *O*-isobutyl dimethylphosphinothioate

O-Isobutyl dimethylphosphinothioate (**13**) was synthesised by the procedure described by Arisawa and Yamaguchi in 2010 [10]. Here, butanol was used as one of the reagents and the product *O*-butyl dimethylphosphinothioate (Figure 2.2) was isolated in 72 % yield.

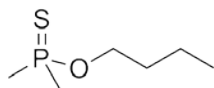
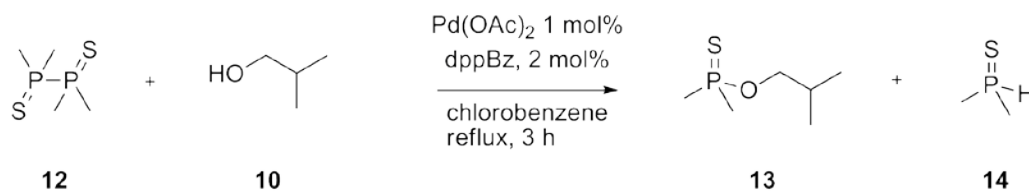


Figure 2.2 *O*-butyl dimethylphosphinothioate

An attempt was made to synthesise *O*-isobutyl dimethylphosphinothioate (**13**) using the same procedure [10] (Scheme 5). Dry reagents and solvents should have been used, but were not available at the time. The solution was heated under reflux for 3 hours. By cooling to room temperature white crystals precipitated out of the solution. The crystals were identified to be a mixture of start material 1,1,2,2-tetramethyldiphosphane-1,2-disulfide (**12**) and the by-product dimethylphosphine sulphide (**14**). *O*-Isobutyl dimethylphosphinothioate (**13**) was identified in the filtrate by NMR and LC-MS. The product **13** was not purified or isolated. Identification of the start material **12** in the crystals implies that the reaction was not completed after 3 hours.



Scheme 5 Synthesis of *O*-isobutyl dimethylphosphinothioate (**13**)

3 Conclusions

During this 36th Organisation for the Prohibition of Chemical Weapons (OPCW) Proficiency Test six different compounds had to be synthesised. The reactions performed ranged from standard esterification types using phosphonic chlorides and alcohols, to more complex reactions. Many of the synthesised products were unstable, and no attempt was made to optimise the reactions or to isolate any of the products. This was due to the limited amount of time available and the limited need for pure products for identification purposes during the test. Four of the synthesised compounds were reportable chemicals, while two were synthesised to verify their proposed structure as non-reportable chemicals. NMR and mass spectrometric data are given for all synthesised compounds.

Suggestions for improvements and alternative ways for synthesis of such reference compounds have also been described in the report. One is for making mono- and dialkyl alkyl phosphonates which proved difficult to synthesize with the applied method. The information given and the experience made during this work can be useful for synthesis of related products deemed necessary for identification purposes in future work.

FFI reported all spiking chemicals and achieved the best score (grade A) for its participation in this Proficiency Test.

4 Experimental

4.1 Chemicals

The following chemicals were purchased from Sigma-Aldrich (Munich, Germany): Diethyl ether ($\geq 99.8\%$), sodium carbonate (anhydrous 99.95-100.05%), magnesium sulphate ($\geq 99.5\%$), triethylamine ($\geq 99\%$), 2-methyl-1-propanol ($\geq 99.5\%$), dimethylphosphinic chloride (97%), 2-(diethylamino)ethanol ($\geq 99.5\%$), 1,2-bis(diphenyl phosphino)benzene (97%), palladium(II) acetate ($\text{Pd}(\text{OAc})_2$, 98%), potassium carbonate chlorobenzene, deuterium oxide (100% D_2O , 99.98% D) and chloroform-*d* (99.9%). Nitric acid (HNO_3 , 65%) and dichloromethane (J.T. Baker Ultra Resi-Analyzed) were purchased from VWR International (Darmstadt, Germany). Ethylphosphonic dichloride was purchased from Alfa-Aesar GmbH & Co.KG, and 1,1,2,2-tetramethyldiphosphane 1,2-disulfide was purchased from Tokyo chemical industry Co. LTD (TCI). Sulphur mustard (98.5%) was purchased from TNO (Rijswijk, Netherlands).

4.2 Instruments

NMR

All NMR spectra were acquired on a Bruker Avance III 600 MHz spectrometer operating at 600.23 MHz for proton and 242.98 MHz for phosphorous. The instrument is equipped with a 5 mm QNP cryoprobe with a z-gradient and automatic tuning and matching (ATMA unit) (all from BrukerBiospin, Switzerland). Experiments were performed at 25 °C using standard Bruker pulse sequences. The data were acquired and processed using TopSpin 3.2, and run under automation using IconNMR.

Standard ^1H spectra were acquired using a single pulse experiment with 30° flip angle, usually with 32 or 64 scans and 1 second relaxation delay. The transmitter frequency for proton was set to 6.2 ppm, and the spectral width was set to 21 ppm with 128 k data points. An exponential multiplication using a linear broadening of 0.3 Hz was performed prior to Fourier transform.

The $^{31}\text{P}\{^1\text{H}\}$ spectra were acquired using power-gated decoupling with a 30° flip angle, a spectral width of 350 ppm with transmitter frequency set to 50 ppm. A relaxation delay of 1.2 seconds was used with 1024 scans and 128 k data points, giving an experimental time of 35 minutes.

2D ^1H - ^{31}P HSQC-TOCSY data were acquired with 16 scans per increment and 16 dummy scans. Spectral width for proton and phosphorous was 8.8 and 103 ppm, respectively, and with transmitter frequencies set to 4.5 for proton and 50 for phosphorous. The TOCSY step was executed using a MLEV-17 pulse train with 80 ms duration. The relaxation delay was set to 1.5 seconds, and the polarisation delay optimised to $J = 14$ Hz. The 2D spectrum was acquired with 2048x256 points with a total experiment time of 2 hours and 7 seconds. The spectrum was zero

filled to 2048 and 1048 data points in the F2 and F1 dimensions respectively, and applied a QSINE window function using Sine bell shift of 2 prior to Fourier transform.

All spectra were manually phased before peak picking, integration and multiplet analysis were performed.

GC-MS

One of the gas chromatography – mass spectrometry (GC-MS) systems used during the test was a Agilent Technologies 7890A GC equipped with a 30 m x 0.25 mm i.d. Restec Rxi-5Sil MS/DB-5MS capillary column (0.25 µm film thickness) with the following temperature program: 40 °C (1 min), 10 °C/min, 280 °C (10 min). The injection was done pulsed splitless at 250 °C. The mass spectrometer was an Agilent Technologies 5975C MSD under EI conditions (70 eV) scanning from m/z 35 to 600 at 0.4 sec/scan.

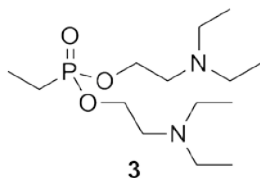
A Fisons GC 8000 was also used during the test equipped with a 30 m x 0.25 mm i.d. SGE BP-20 (wax) capillary column (0.25 µm film thickness) with the following temperature program: 40 °C (1 min), 10 °C/min, 250 °C (10 min). The injection was done splitless (1 min) at 220 °C. The mass spectrometer was a Fisons MD800 under EI conditions (70 eV) scanning from m/z 35 to 600 at 0.6 sec/scan.

LC-MS

The liquid chromatography – high resolution mass spectrometry (LC-MS) system used during the test was a Dionex Ultimate 3000 RSLC coupled to a Bruker Daltonics MicroTOF-Q III mass spectrometer with ESI ionization. Electrospray voltage was 4.5 kV, mass resolution >17500 (m/z 922) and scan range m/z 50-500. An injection volume of 2 µL was used. The mass spectrometer was used both in MS and MS/MS mode, depending on the compound of interest.

4.3 Synthetic procedures

4.3.1 Bis(2-(*N,N*-diethylamino)ethyl) ethylphosphonate

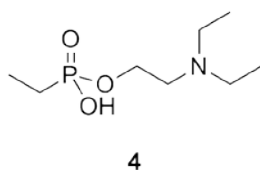


Ethylphosphonic dichloride (**1**) (1.5 g, 10 mmol) in diethyl ether (17 ml) was added dropwise to a stirred solution of 2-(diethylamino)ethanol (**2**) (2.7 g, 23 mmol) and K_2CO_3 (3.5 g, 25 mmol) in diethyl ether (10 ml) on an ice bath. Smoke was observed when the dichloride was added, and the solution became brown with white precipitates. K_2CO_3 is insoluble in diethyl ether. The reaction mixture was removed from the ice bath after 15 minutes and stirred for an additional 2

hours at room temperature. After 2 hours the pH was 14. The crude mixture was washed with water (2x10 ml). The aqueous phase became brown and the organic phase light yellow. The organic phase was dried with magnesium sulphate for 20 minutes. Diethyl ether was removed under reduced pressure and this gave an yellow oil. Bis(2-(*N,N*-diethylamino)ethyl) ethylphosphonate (**3**) was not identified in the organic phase, but in the aqueous phase by LC-MS and NMR.

MS (ESI): 309.237 [M+H]⁺, 100.116 [M-C₈H₂₀NO₃P+H]⁺, NMR (D₂O, pH 7): ³¹P δ 39.3.

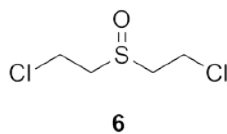
4.3.2 2-(*N,N*-diethylamino)ethyl ethylphosphonate



A mixture of 2-(diethylamino)ethanol (**2**) (1.2 g, 10 mmol) and K₂CO₃ (1.7 g, 12 mmol) dissolved in diethyl ether (10 ml) was added dropwise to ethylphosphonic dichloride (**1**) (1.5 g, 10 mmol) in diethyl ether (15 ml) on an ice bath. K₂CO₃ is insoluble in diethyl ether. The reaction mixture was removed from the ice bath after 15 minutes and stirred for additional 4.5 hours at room temperature. After filtration of the crude mixture there were some non-soluble droplets in the ether solution. These droplets were dissolved in water (5 ml) and identified as **4** by NMR. The product **4** was not purified or isolated, and the analysis implies that the yield of the expected monoester was low.

MS (ESI): 210.127 [M+H]⁺, 100.113 [M-C₂H₇O₃P+H]⁺, NMR (D₂O, pH 7): ³¹P δ 35.8.

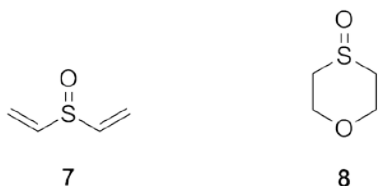
4.3.3 Bis(2-chloroethyl)sulphoxide



Sulphur mustard (**5**) (0.8 g, 4.8 mmol) was added dropwise to a stirred solution of concentrated HNO₃ (65 %) (6 ml, 8.5 g, 89 mmol) cooled with an ice-water bath. When added, the droplets of sulphur mustard turned brown-black and made a liquid film on top of the acid. The solution went from brown to greenish as it was stirred at 0-5 °C for 30 min and then allowed to warm to room temperature. Water (8 ml) was added and the solution extracted with dichloromethane (2x10 ml). The solvent was removed under reduced pressure giving a mixture of white crystals and yellowish oil containing bis(2-chloroethyl)sulphoxide (**6**).

MS (EI): m/z 158 (22%), 111 (35), 109 (91), 76 (24), 73 (25), 65 (28), 63 (100), 59 (25), 58 (18), 45 (27), NMR (CDCl₃): ¹H δ 3.97 (m, 4H, SOCH₂), 3.37-3.20 (m, 4H, CH₂Cl).

4.3.4 Divinylsulphoxide and 1,4-oxathiane 4-oxide



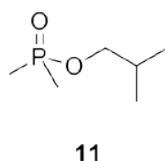
Bis(2-chloroethyl)sulphoxide (**6**) (0.6 g, 3.4 mmol) was dissolved in water (10 ml) and added Na_2CO_3 (1.1 g, 10.7 mmol). The yellowish solution was heated for 1.5 hour and refluxed for 2 hours. The reaction mixture was cooled down to room temperature and then extracted with dichloromethane (2x10 ml). The solvent was removed under reduced pressure giving a yellowish liquid containing mainly 1,4-oxathiane 4-oxide (**8**) and a small portion of divinylsulphoxide (**7**) and an unknown vinyl compound.

1,4-Oxathiane 4-oxide (**8**): MS (EI): m/z 120 (M^+ , 52%), 92 (100), 77 (40), 76 (31), 63 (25), 59 (42), 48 (34), 47 (45), 46 (28), 45 (29), 43 (76), MS (ESI): 121.033 $[\text{M}+\text{H}]^+$, NMR (CDCl_3): ^1H δ 4.38 (m, $^2J = 12.5$, $^3J_{ax,ax} = 10.2$, $^3J_{ax,eq} = 1.9$, 2H, $\text{H}_{ax-2}/\text{H}_{ax-6}$), 3.83 (m, $^2J = 12.9$, 2H, $\text{H}_{eq-2}/\text{H}_{eq-6}$), 2.93 (m, $^2J = 13.5$, $^3J_{ax,ax} = 10.0$, $^3J_{ax,eq} = 3.5$, 2H, $\text{H}_{ax-3}/\text{H}_{ax-5}$), 2.75 (m, 2H, $\text{H}_{eq-3}/\text{H}_{eq-5}$).

Divinylsulphoxide (**7**): MS (EI): m/z 102 (M^+ , 57%), 85 (33), 76 (20), 73 (32), 59 (100), 58 (40), 54 (24), 47 (28), 45 (33), NMR (CDCl_3): ^1H δ 6.58 (dd, $J = 16.6, 9.7$, 1H), 6.09 (d, $J = 16.6$, 1H), 5.91 (d, $J = 9.7$, 1H).

Unknown vinyl compound: NMR (CDCl_3): ^1H δ 6.66 (dd, $J = 16.4, 9.8$, 1H), 6.18 (d, $J = 16.5$, 1H), 6.06 (d, $J = 9.8$, 1H).

4.3.5 Isobutyl dimethylphosphinate



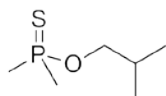
A mixture of isobutyl alcohol (**10**) (0.2 g, 2.2 mmol) and triethylamine (0.2 g, 2.3 mmol) in diethyl ether (5 ml) was added dropwise to a stirred solution of dimethylphosphinic chloride (**9**) (0.2 g, 2.0 mmol) in diethyl ether (9 ml) at 0-5 °C using an ice-water bath. After addition, the mixture was allowed to warm to room temperature and stirred for additional 2 hours. The solution was filtered and diethyl ether was removed under reduced pressure. A colourless liquid containing isobutyl dimethylphosphinate (**11**) and an unknown compound was obtained.

Isobutyl dimethylphosphinate (**11**): MS (EI): m/z 135 ($\text{M}^+ - \text{CH}_3$, 5%), 107 ($\text{M}^+ - \text{C}_3\text{H}_7$, 7), 95 (100), 78 (29), 77 (39), 57 (8), 47 (5), 41 (8), MS (ESI): 151.091 $[\text{M}+\text{H}]^+$,

NMR (D₂O): ¹H δ 3.81 (dd, *J* = 6.7, 2H, CH₂), 1.95 (sept, *J* = 6.7, 1H, CH), 1.62 (d, *J* = 14.2, 6H, PCH₃), 0.96 (d, *J* = 6.7, 6H, CH₃).

Unknown compound: MS (ESI): 171.034 [M+H]⁺, NMR (D₂O): ³¹P δ 42.5.

4.3.6 *O*-Isobutyl dimethylphosphinothioate



13

1,2-bis(diphenyl phosphino)benzene (**12**) (dppBz) (89 mg, 0.2 mmol) in chlorobenzene (20 ml) was added to a solution of 2-methyl-1-propanol (**10**) (0.8 g, 10 mmol), 1,1,2,2-tetramethyldiphosphane 1,2-disulfide (1.9 g, 10 mmol) and palladium acetate (22 mg, 0.1 mmol). The equipment was dried before use. Dry reagents and solvents were not available at the time. The solution was heated under reflux for 3 hours. Right after addition, the solution became red and after 3 hours the colour had changed to orange. The reaction mixture was cooled to room temperature and then white crystals precipitated. After filtration and evaporation of the solvent a red-yellow oil was obtained. *O*-Isobutyl dimethylphosphinothioate (**13**) was identified by LC-MS and NMR.

MS (EI): *m/z* 166 (M⁺, 1%), 111 (100), 110 (9), 95 (26), 94 (14), 93 (45), 77 (23), 65 (6), 63 (8), 41 (10), NMR (D₂O): ¹H δ 3.71 (dd, *J* = 8.3, 6.5, 2H, CH₂), n/a (1H, CH), 1.87 (d, *J* = 13.4, 6H, PCH₃), 0.86 (d, *J* = 6.7, 6H, CH₃), ³¹P δ 98.9, NMR (CDCl₃): ¹H δ 3.72 (dd, *J* = 8.5, 6.6, 2H, CH₂), n/a (1H, CH), 1.82 (d, *J* = 13.3, 6H, PCH₃), 0.93 (d, *J* = 6.8, 6H, CH₃).

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A Spiking list for the 36th OPCW Proficiency Test

Original Sample Code	Chemical ID assigned by the Laboratory	Chemical Name	CAS #	Schedule number
362-06	B-1	bis(2- <i>N,N</i> -diethylaminoethyl) disulfide	589-32-2	NSRC
362-06	B-3	bis(2- <i>N,N</i> -diethylaminoethyl) ethylphosphonate	101098-30-0	2.B.04
363-06	C-1	1,4-dithiane	505-29-3	NSRC
363-06	C-2	1,4-Oxathiane	15980-15-1	NSRC
363-06	C-3	1,4-Oxathiane 4-oxide	109-03-5	NSRC
366-06	F-1	Divinylsulfone	77-77-0	NSRC
366-06	F-2	Divinylsulfoxide	1115-15-7	NSRC

NSRC: Non-Scheduled Reportable Chemical

B NMR spectra

B.1 Phosphorous compounds

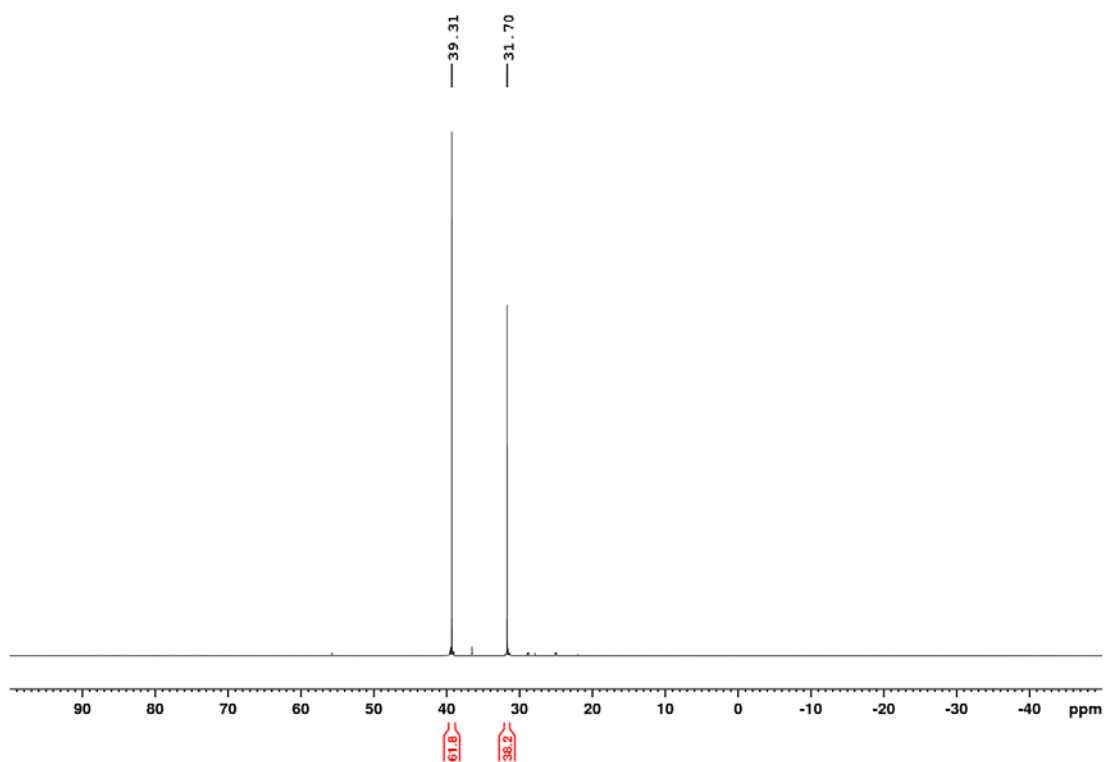


Figure B.1 $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum showing the shift values and integral ratio between bis(2-(*N,N*-diethylamino)ethyl) ethylphosphonate (**3**) and 2-(*N,N*-diethylamino)ethyl ethylphosphonate (**4**)

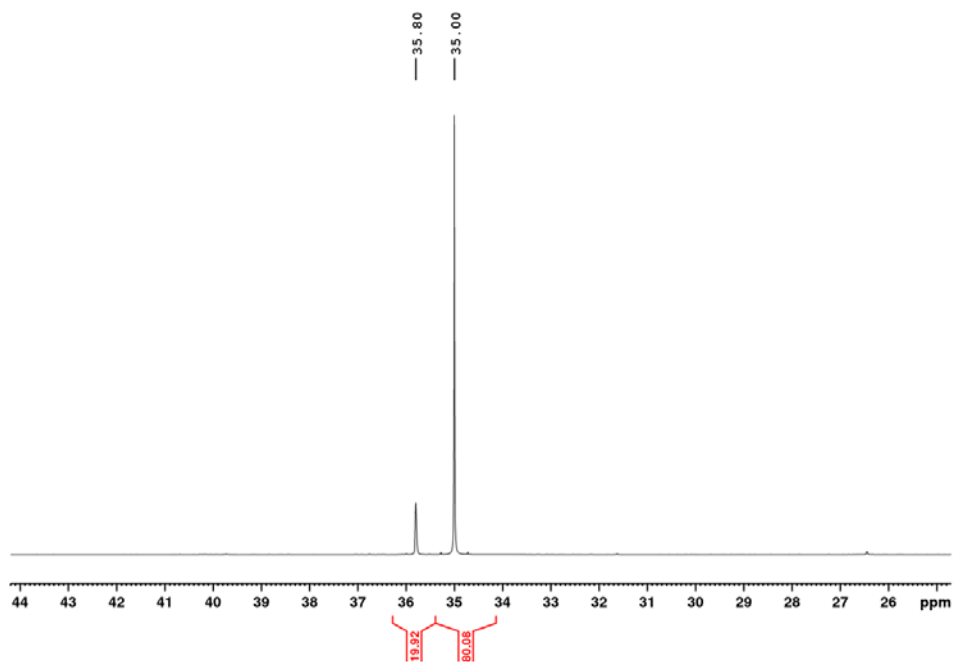


Figure B.2 $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum showing the shift values and integral ratio between 2-(*N,N*-diethylamino)ethyl ethylphosphonate (**4**) and ethylphosphonic acid (EPA)

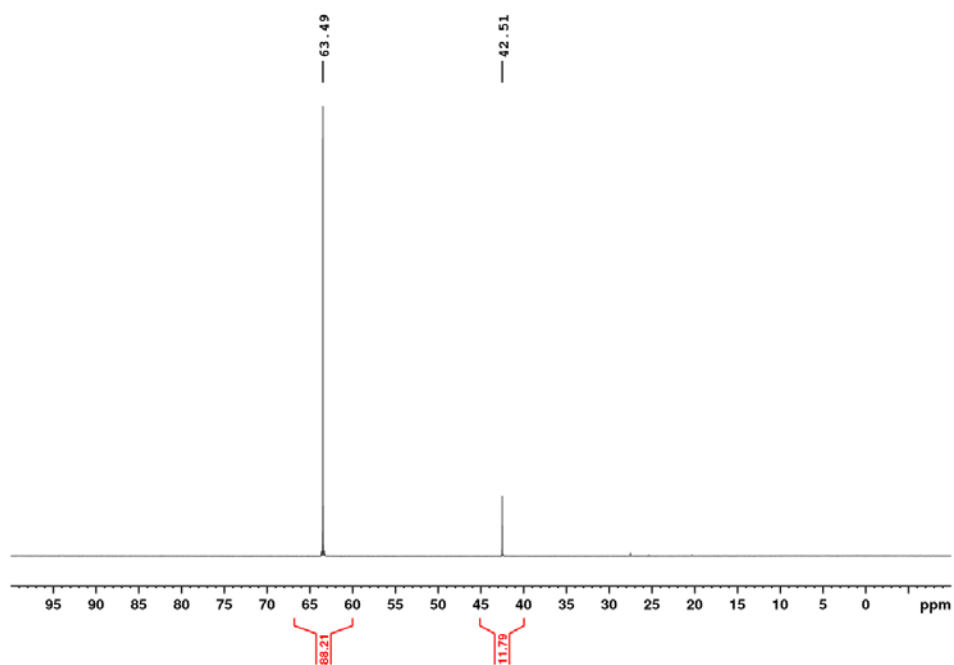


Figure B.3 $^{31}\text{P}\{^1\text{H}\}$ NMR spectrum showing the shift values and integral ratio between isobutyl dimethylphosphinate (**11**) and an unknown compound

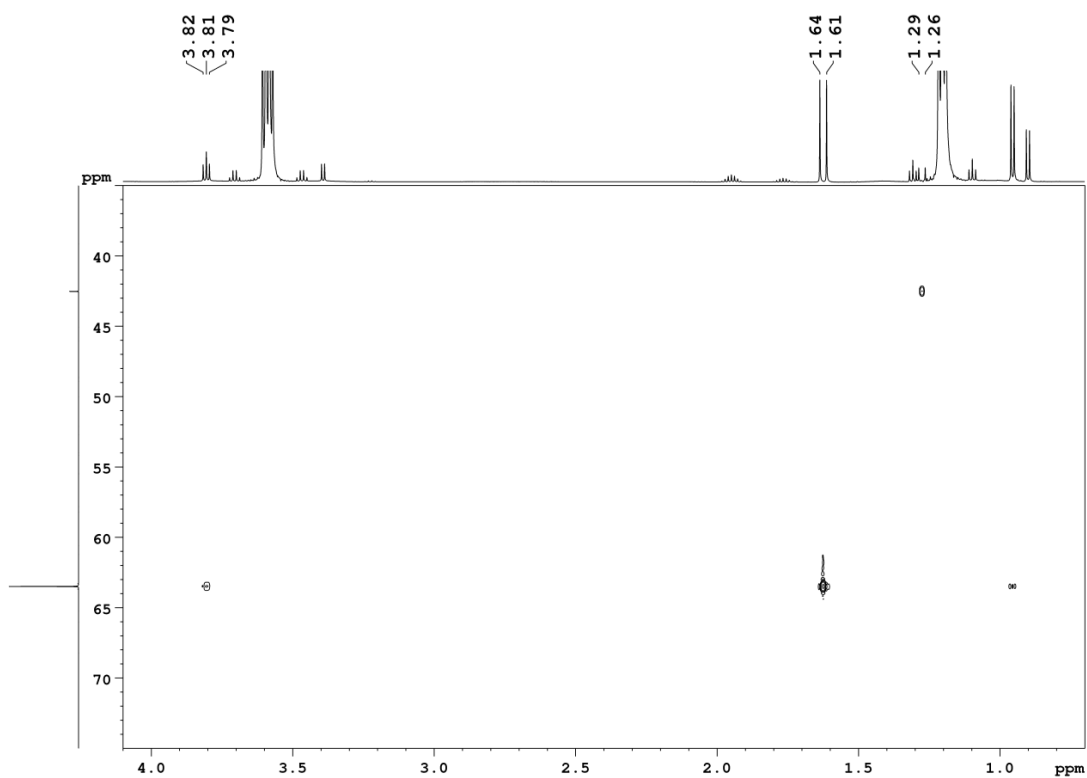


Figure B.4 $2\text{D } ^1\text{H}\text{-}^{31}\text{P}$ HSQC spectrum of isobutyl dimethylphosphinate (**II**) and an unknown compound

B.2 Sulphur compounds

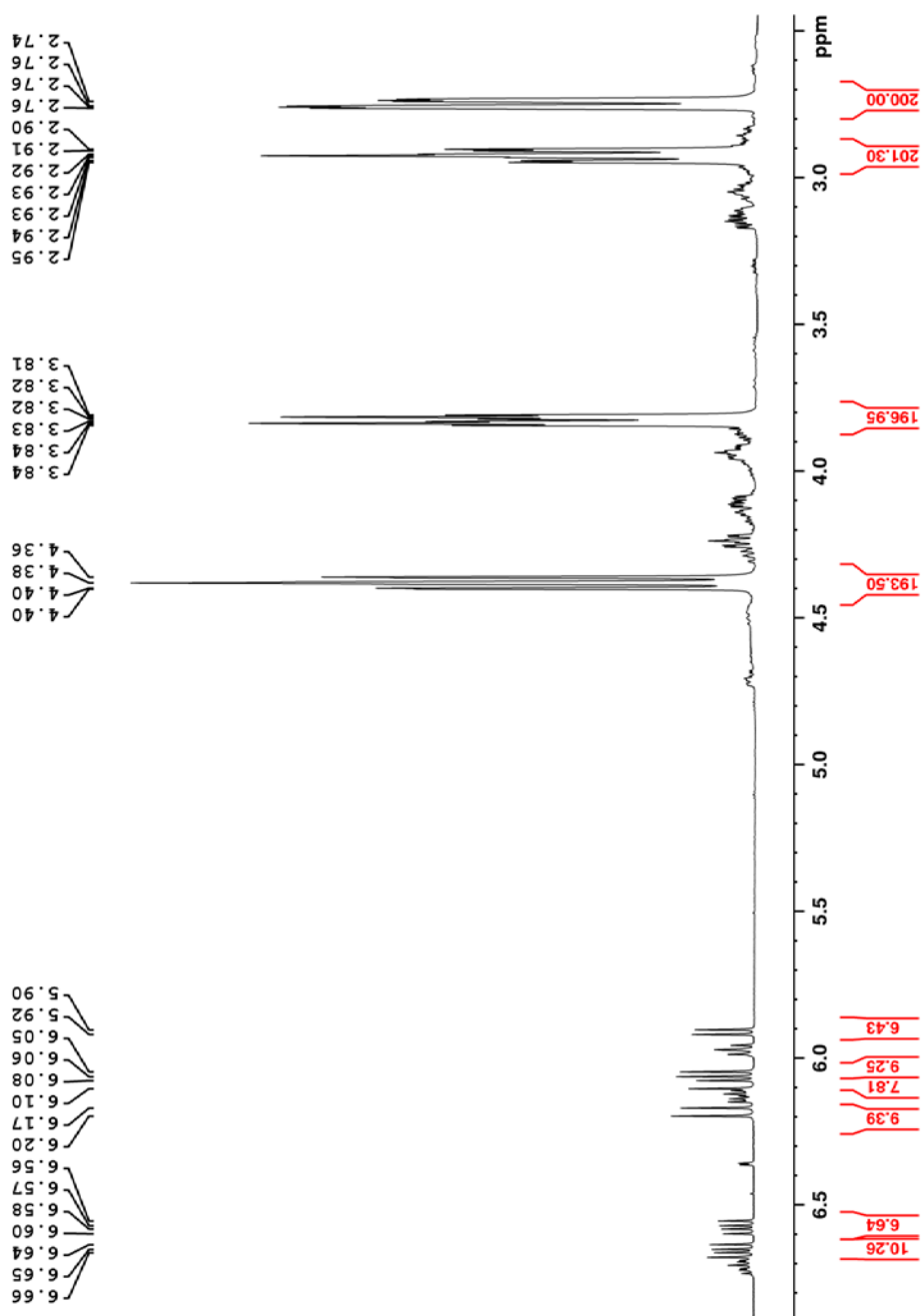


Figure B.5 ^1H NMR spectrum of divinylsulphoxide (7), 1,4-oxathiane-4-oxide (8) and an unknown vinyl compound

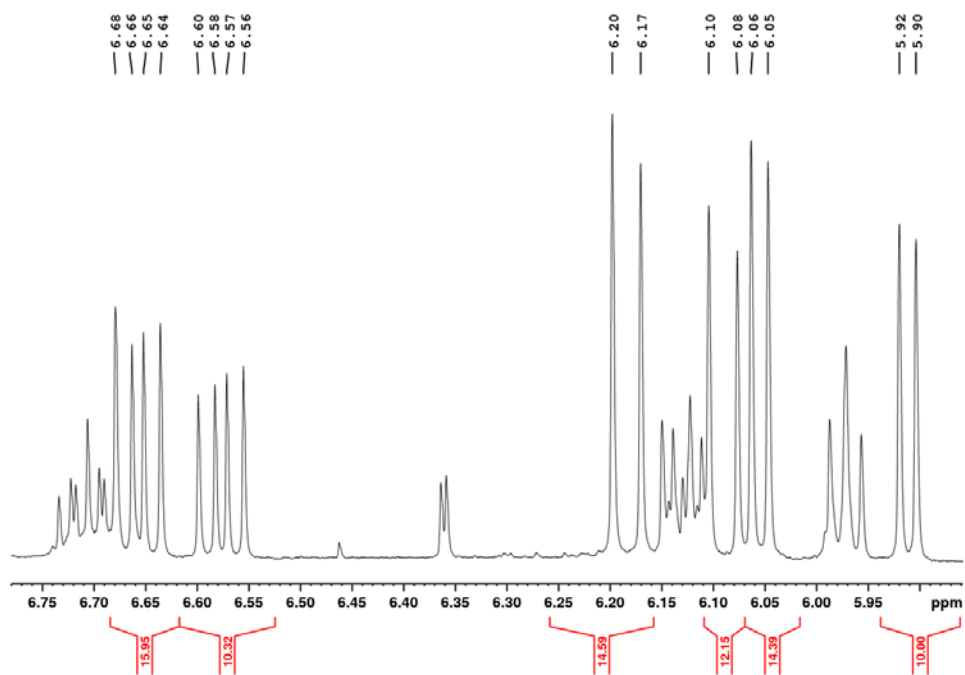


Figure B.6 ^1H NMR spectrum of divinylsulphoxide (7) and an unknown vinyl compound

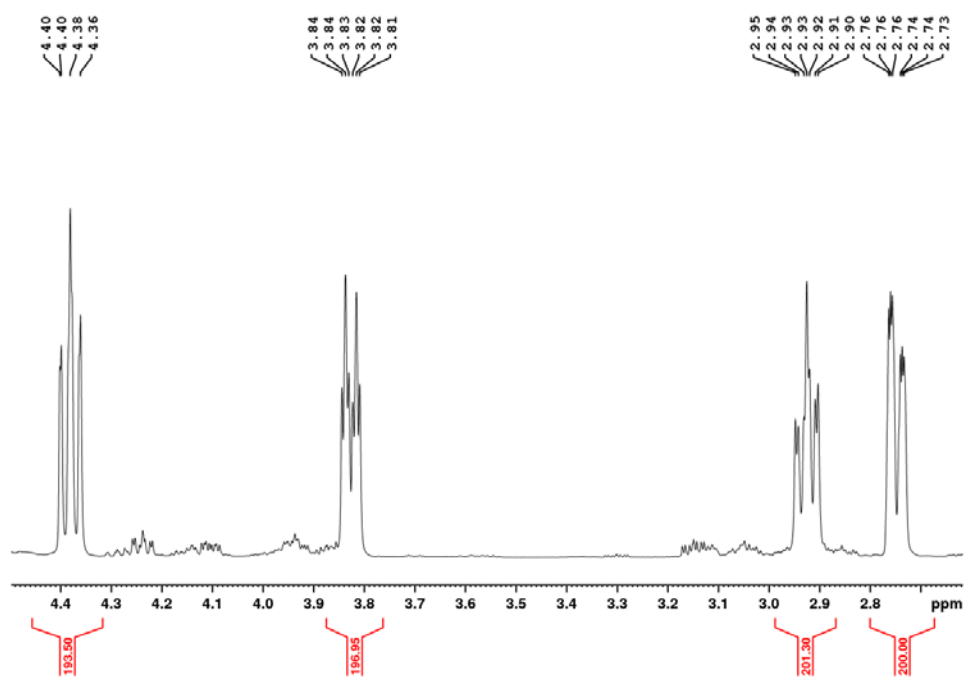


Figure B.7 ^1H NMR spectrum of 1,4-oxathiane 4-oxide (8)

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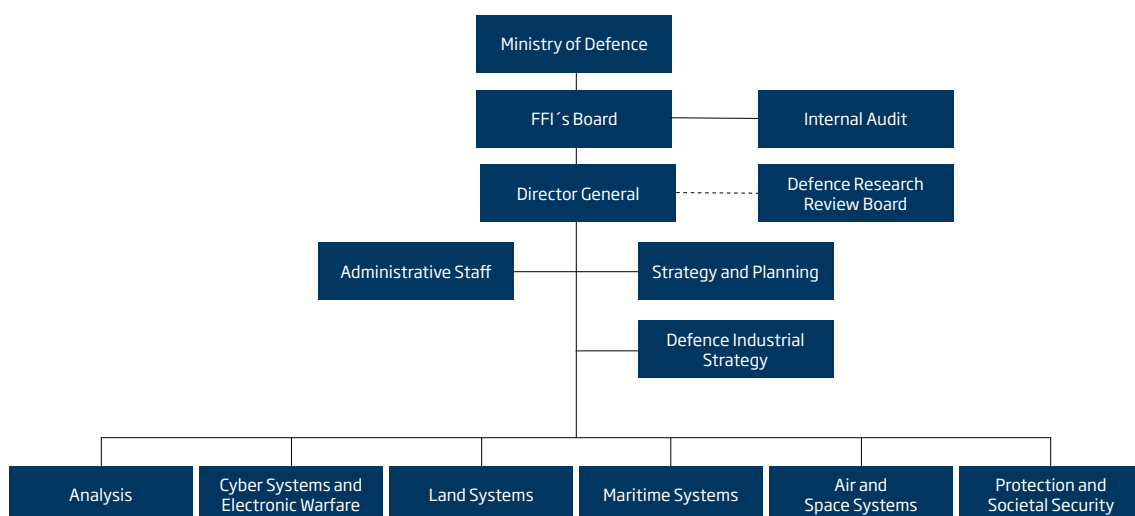
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