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Destruction of Chemical Warfare Agents VX and Soman by α-Nucleophiles as Oxidizing Agents

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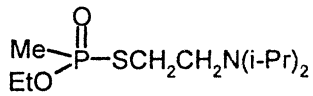
ABSTRACT: *Reactions of O-ethyl S-(2-diisopropylamino)ethyl methylphosphonothiolate, VX* **1**, *were investigated with five oxidizing agents. In all the cases, the formation of the VX N-oxide* **7** *was observed prior to the subsequent oxidation and hydrolysis into the nontoxic O-ethyl methylphosphonate* **2.** *Magnesium monoperoxyphthalate (MMPP) is probably one of the most active reagents to achieve the complete detoxification of VX* **1**. *The decontamination using MMPP was also extended with success to soman* **13**, *a G-type agent*. © 2001 John Wiley & Sons, Inc. Heteroatom Chem 12:485–490, 2001

INTRODUCTION

The exceedingly toxic *O*-ethyl *S*-(2-diisopropylamino)ethyl methylphosphonothiolate VX **1**, an irreversible inhibitor of acetyl cholinesterase enzyme (AchE), has been used as a chemical warfare nerve agent. [1] Such a compound is relatively easy to synthesize, but its detoxification is still a question of interest. [1] Therefore, a major effort must be made to achieve its inactivation: the simple hydrolysis in aqueous alkaline media gives no satisfactory decontamination because of the formation of a stable and still toxic hydrolysis product **3**. [3]



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On the contrary, the combination of hydrolysis with an oxidation reaction seems to be effective to reach the complete destruction of VX agent **1**. α-Nucleophiles, which can react as nucleophiles and as oxidizing agents, have a real efficiency. [4] In this work, we investigated the behavior of VX agent **1** toward five α-nucleophiles: magnesium monoperoxyphthal ate (MMPP), *meta*-chloroperbenzoic acid (*m*-CPBA), potassium monopersulfate (Curox®, which is a mixture of 2 $KHSO_5$, $KHSO_4$, K_2SO_4), hydrogen peroxide (H_2O_2), and hydrogen peroxide with boric acid (H_2O_2/H_3BO_3).

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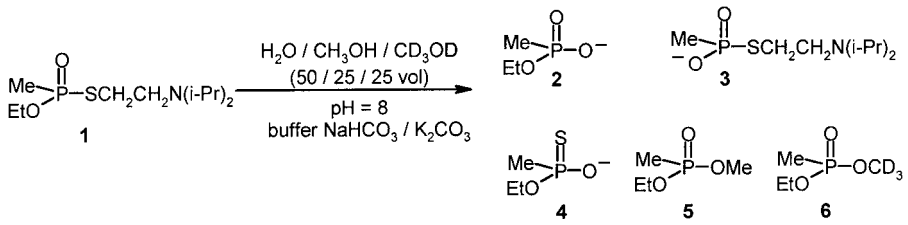

FIGURE 1 Hydrolysis of VX **1** in $H_2O/CH_3OH/CD_3OD$ solution.

All the reactions performed in this study were carried out at pH 8. This pH value was chosen because it minimizes the corrosion risk when a depollution solution is used on metallic furniture or implements.

RESULTS AND DISCUSSION

*Stability of VX **1** in MeOH/water media at pH 8*

As a blank experiment, the stability of VX **1** was first determined under the reaction conditions chosen for our investigations with oxidizing α-nucleophiles, at pH 8, in a mixture of methanol/methanol-d_4/water (25/25/50 vol). The evolution of the mixture was monitored by ^{31}P-NMR spectroscopy as a function of time. During the experiment, five phosphorus compounds (**2–5**) are detected as depicted in Figure 1.

As previously reported by Epstein [5], in aqueous solution, near neutrality, VX **1** gives three known anions as degradation products: the *O*-ethyl methylphosphonate **2**, the *S*-(2-diisopropylamino)ethyl methylphosphonothiolate **3**, and the *O*-ethyl methylthiono phosphonate **4** (tautomeric form of the phosphonothiolate compound [5]), which are formed by reaction of water with VX **1** at the phosphorus or the sulfur centers [6].

Compounds **5** and **6** are formed by the nucleophilic substitution at the phosphorus atom by MeOH or CD_3OD. In these reactions, (2-diisopropylamino) ethylthiolate acts as a nucleofuge. The $\{^1H\}^{31}$P-NMR chemical shifts and the multiplicities of **5** and **6** are respectively 36.60 ppm (singlet) and 36.61 ppm (heptuplet, $^3J_{PD} = 1.7$ Hz). The results are reported in Table 1 and Figure 2.

In order to compare our results with the literature, the first-order rate constants [7] for the hydrolysis of VX **1** in the reaction shown in Figure 1 are given in Table 1. The rate constant of VX **1** hydrolysis (4.81×10^{-3}) observed in a methanol-water solution is quite similar to that in water at pH 8. The rate constant of formation of **5** and **6** ($16.1\ 10^{-3}$) and the rate constant of **2** (11.0×10^{-3}) have the same order of magnitude. Under these reaction conditions, the nucleophilic strength of methanol and water is comparable.

TABLE 1 First-Order Kinetic Constant [7] and Chemical Shifts of VX **1** Hydrolysis

	$K_{obs} \times 10^3$ (h^{-1})		
Compound	*Literature*	*Experimental*	δ^{31} *P*
VX **1**	5.56	4.81	61.0
2	11.6	11.0	26.6
3	12.2	13.4	75.9
4		13.9	75.9
5 and **6**		16.1	36.6

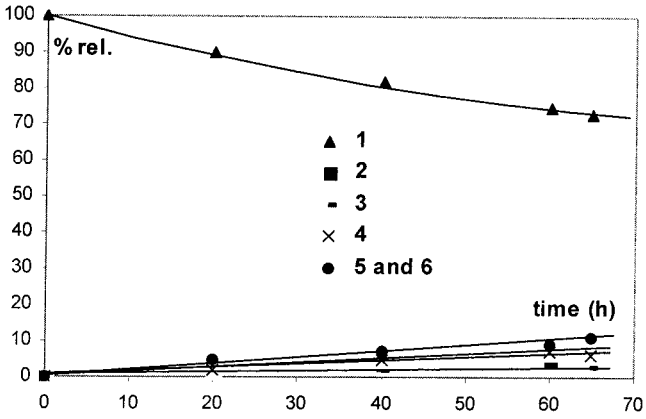

FIGURE 2 Relative percentage of VX **1** hydrolysis products versus time.

*Reaction of VX **1** with Some α-Nucleophiles*

VX **1** solution (2.8×10^{-2} M, MeOH-d_4) has been treated with an excess of oxidizing agents (2.8×10^{-1} M, initial pH = 8) in CD_3OD MeOH H_2O (25 25 50) solution. According to earlier observations, peroxy compounds are decomposed in aqueous solutions.Their degradation depends on the nature and the concentration (ionic strength) of alkali-metal ions. Therefore, the oxidizing agents were used in ten-fold excess, and the ionic strength was standardized by addition of a $NaHCO_3/K_2CO_3$ (0.4 M) buffer in water.

All the possible intermediates are given in Figure 3 [8]. VX **1** is quickly oxidized into its *N*-oxide **7**,

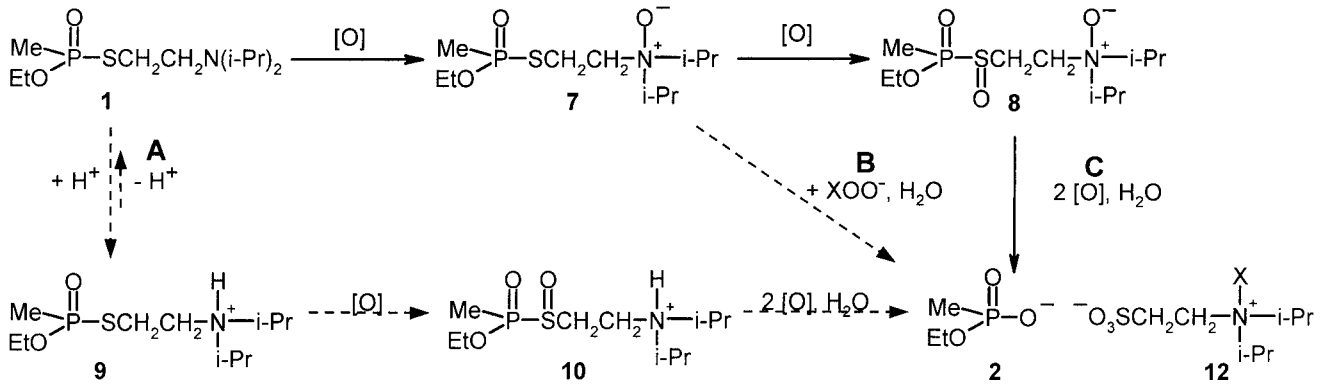

FIGURE 3 Reaction products of VX **1** with oxidizing agents.

which was clearly identified by ^{31}P NMR spectroscopy ($\delta = 54.95$ ppm) in all the experiments. The protonation of VX **1** to afford **9** (chemical path **A**) can be excluded at pH 8 due to the pK_a of the amino function, and the VX *N*-oxide **7** must be considered as only the first possible intermediate.

Reaction of MMPP with VX **1** gave exclusively the cleavage of the P(O)–S bond, leading to the formation of phosphonate **2** as the final product. Using 10 equivalents of MMPP (Figure 4), the rate of degradation of VX *N*-oxide **7** was initially high and decreased gradually to zero after 2 hours. The action of *m*-CPBA (see Figure 5) led, in 2 minutes, to the quantitative formation of VX *N*-oxide **7**, which was subsequently oxidized into the phosphonate **2**. However, after 60 minutes, the reaction did not evolve further, and 50% of *N*-oxide **7** still remained unchanged. Then, the behavior of *m*-CPBA in the reaction is very much like that of MMPP, and its instability in basic media explains its incomplete reaction with VX *N*-oxide **7**.

Reaction of hydrogen peroxide (see Figure 6) was quite similar, but some VX **1** (less than 10%) persisted even after 2 hours. However, we were not able to detect VX **1** after 48 hours. As with MMPP and *m*-CPBA, the reaction was not complete, and only 50% of nontoxic phosphonate **2** was formed.

As depicted in Figure 7, the mixture hydrogen peroxide/boric acid also gave the VX *N*-oxide **7** followed by the phosphonate **2**, but the reaction evolved continuously and no plateau was observed, even after 2 hours.

Use of the Curox reagent gave instantaneously a white precipitate that was attributed to the potassium salt of phosphonate **2** by ^{31}P-NMR evaluation. Unfortunately, it is almost impossible to follow the kinetic degradation of VX **1** under these conditions. However, after 48 hours, a ^{31}P-NMR spectrum of the liquid phase showed the presence of phosphonate **2** as the single product.

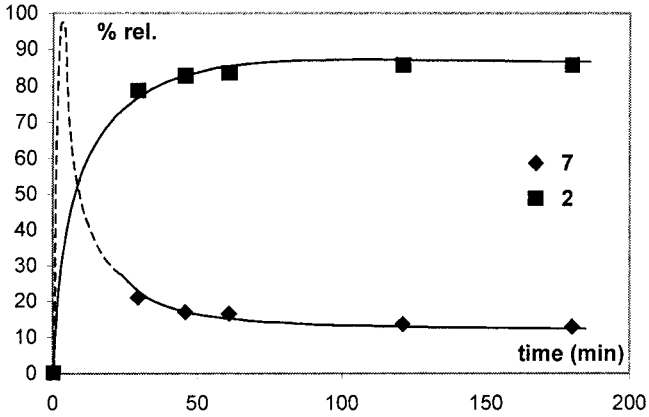

FIGURE 4 Products of **1** and MMPP (10 equivalents).

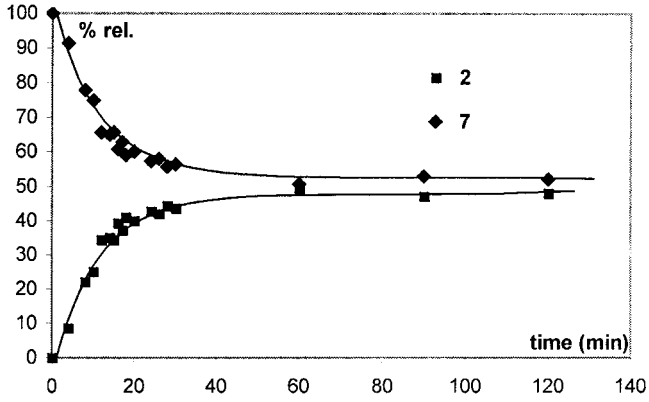

FIGURE 5 Products of **1** and *m*-CPBA (10 equivalents).

If we consider the degradation of the toxic VX *N*-oxide **7**, the half-times (see Table 2) that we observed for this reaction were between 5 and 60 minutes. The best decontaminating agent is probably MMPP, even if it is not completely stable at pH 8. As other peroxygenated reagents, the decomposition of MMPP is a second-order reaction [9]. The rate of

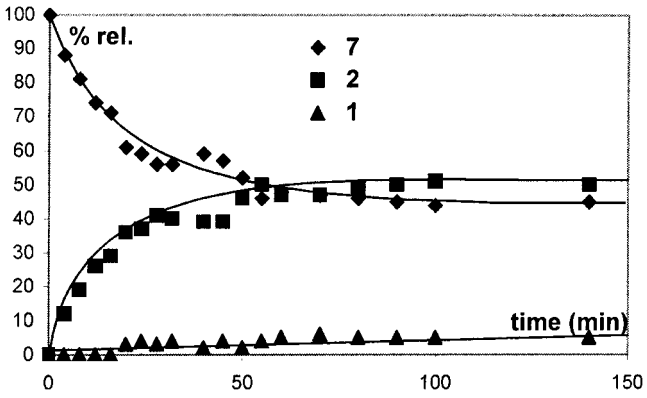

FIGURE 6 Products of **1** and H_2O_2 (10 equivalents).

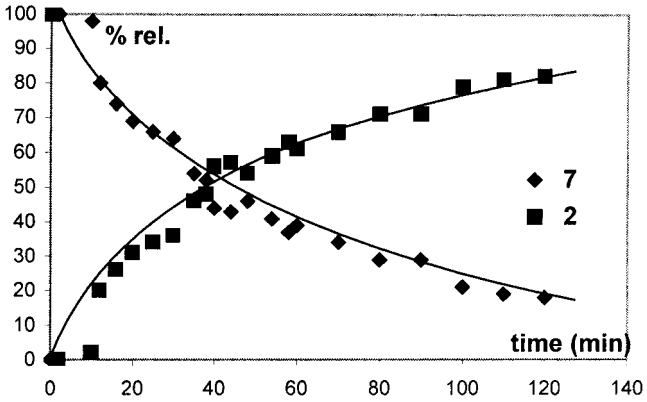

FIGURE 7 Products of **1** and H_2O_2/H_3BO_3 (10 equivalents).

TABLE 2 Half-Times Degradation of VX N-Oxide **7**

	MMPP					
	10 equiv.	*20 equiv.*	*m-CPBA*	*Curox*	H_2O_2	H_2O_2/H_3BO_3
$T_{50\%}$ (min)	5 ± 5	5 ± 3	60 ± 5		60 ± 5	38 ± 5
Final % of **7**	15	0	50	0	45	18
Time (min)	(120)	(40)	(60)	(48 h)	(100)	(120)

degradation under our conditions was 8.0×10^{-3} mol^{-1} s^{-1} , and after 11 minutes, only 50% of MMPP still remained [10].

Therefore, in a second experiment (Figure 8), we used 20 equivalents of MMPP (rather than 10 equivalents). Under these reaction conditions, the *N*-oxide **7** underwent a quantitative degradation in 40 minutes into the nontoxic phosphonate **2**. Consequently, it seems that the decomposition of MMPP is the limiting phenomenon when only 10 equivalents are used. The cleavage of the P(O)–S bond is possible by two different reactions (chemical pathway **B** and **C**):

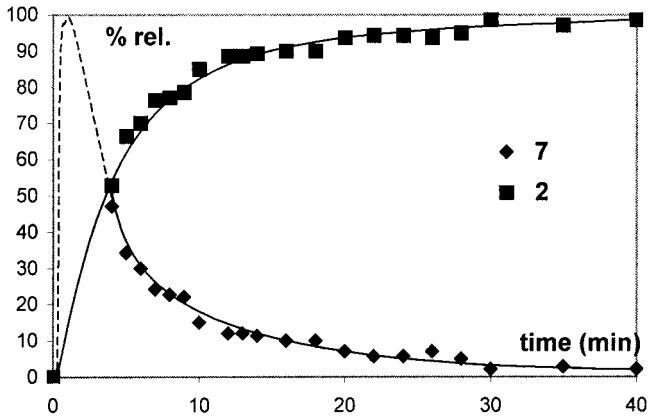

FIGURE 8 Products of **1** and MMPP (20 equivalents).

the Cope elimination reaction of *N*-oxide **7** by the pathway **B** leading directly to the phosphonate **2** can be excluded. Indeed, this reaction only needs water as the nucleophile, and we should observe in that case a complete hydrolysis of *N*-oxide **7** without the addition of an excess of MMPP. The second chemical pathway **C** implies the formation of the sulfoxide **8** or the sulfone by an oxidation reaction prior to the hydrolysis, or an hetero-Baeyer-Villiger reaction leading to the phosphate-sulfonate anhydride that is subsequently hydrolyzed. The effect of an addition of 10 more equivalents of MMPP seems to validate this path.

In order to verify the general efficiency of decontamination by MMPP toward toxic organophosphorus compounds, its reactivity was studied for G-toxic agents and particularly for soman**13**, which is chemically similar to the more volatile sarin. The decontamination experiments were realized under the same conditions used for VX **1** at pH **8**, in an aqueous methanol solution. For the G-toxic agents, the decontamination consists mainly in the cleavage of the P(O)–X bond, where X = F (soman and sarin) or CN (tabun), by a nucleophilic attack on the phosphorus center, leading to the phosphonate monoester **15** (see Figure 9).

When MMPP is added to the solution of soman, an important precipitate appears. After 20 minutes, a ^{31}P NMR examination of the liquid phase indicates the quantitative formation of the phosphonate salt **15**, which was identified by addition of an authentic sample in the NMR sample.

In basic aqueous media at pH 8.5, Epstein *et al.* [11] found the half-life of sarin was equal to 94 minutes; its degradation was also enhanced by the presence of magnesium cations ($t_{1/2}$ = 33 min). Thus, we can consider that, in less than 20 minutes, the degradation of soman is quantitative and it is

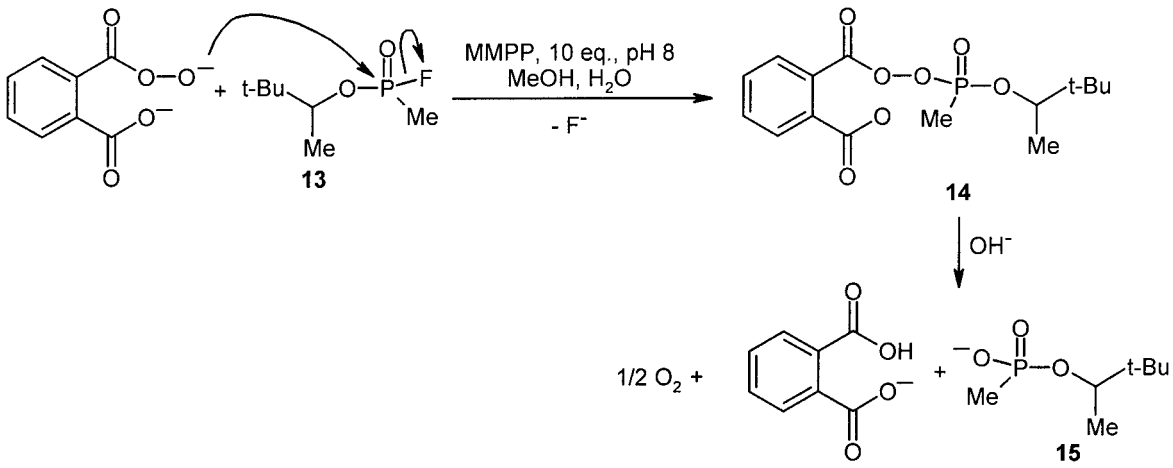

FIGURE 9 Reaction of MMPP with soman.

considerably enhanced by use MMPP rather than a simple hydrolysis.

CONCLUSION

In conclusion, the hydrolysis assay of VX 1 in water/methanol solution has shown the formation of hydrolytic compounds resulting from a nucleophilic attack of both water and methanol mainly at the phosphorus atom.

The rate of degradation of VX **1** with oxidizing α-nucleophiles is increased by a factor 200 to 2000 in comparison with the simple hydrolysis in water-methanol solution at pH 8. The reaction gave instantaneously the VX *N*-oxide **7**. However, its chemical degradation was sometimes reduced by the instability of the oxidizing agent at pH 8. Using 20 equivalents of MMPP, the best reagent of our set, we were able to reach the complete destruction of the toxic VX **1** and its *N*-oxide **7** into the inactive phosphonate **2**. The decontamination using MMPP was also extended with success to soman, a G-type agent.

EXPERIMENTAL SECTION

CAUTION: VX, soman, and some intermediates used in this experiment are extremely toxic and can only by handled in controlled environments. Therefore, all the manipulations were done in the Centre d'Études du Bouchet laboratory, which has the authorization to manipulate these chemical warfare agents.

The NMR spectra were obtained with a Bruker system at 360 MHz. The ^{31}P NMR spectra were recorded at 145.8 MHz, with H_3PO_4 as external reference. The ^{1}H NMR spectra were recorded at 200.13 MHz with tetramethylsilane as reference.

Stability Study of **1** *at pH 8*

A solution of 9.4 mg (3.5×10^{-5} mol) of **1** in 1.25 mL of MeOH-d_4/MeOH/H_2O (25/25/50) solution adjusted to pH 8 by addition of potassium carbonate and sodium hydrogenocarbonate was placed in an NMR tube. The progress of the reaction was monitored by ^{31}P NMR spectroscopy.

Synthesis of VX N-Oxide **7** *[3a]*

To a solution of 9.4 mg of VX **1** (3.5×10^{-5} mol) in 0.5 mL of MeOH, 91.0 mg of MMPP (85%, 3.13×10^{-4} mol) in 0.35 mL of MeOH was added. After 5 minutes, the mixture was concentrated.

^{31}P NMR (CD_3OD): $\delta = 54.95$ (s). lit. ref [3a] 55.4 (*t*-BuOH).

^{13}C NMR: $\delta = 14.56$ (d, $^{3}J_{PC} = 6.9$ Hz, CH_3); 17.25 (d, $^{1}J_{PC} = 108.8$ Hz, CH_3); 18.30 and 18.31 (2 s, CH_3); 29.30 (s, SCH_2); 46.23 (d, $^{3}J_{PC} = 4.7$ Hz, NCH_2); 49.10 and 49.21 (2 s, NCH); 62.69 (d, $^{2}J_{PC} = 7.1$ Hz, OCH_2).

Kinetic Study of the Decomposition of **1** *by Some α-Nucleophiles*

The solution **A** was prepared by dissolution of 96.3 mg (3.5×10^{-4} mole) of **1** in 2.5 mL of CD_3OD.

The oxidizing agent solutions **B** were prepared as listed in Table 3. The necessary quantity of commercial oxidizing agent (solution or solid) was stirred with a $NaHCO_3/K_2CO_3$ 0.4 M buffer in water/MeOH (75/25). The pH was adjusted to 8 by addition of NaOH.

The active oxygen equivalent was determined by titration with a 0.1 M solution of sodium thiosulfate with KI as the indicator. The MMPP, Curox, H_2O_2, and sodium perborate were titrated in water (by ad-

TABLE 3 Oxidizing Agents

	MMPP	*m-CPBA*	*Curox*	H_2O_2	H_2O_2/H_3BO_3
Provider	Interox	Fluka	Interox	Merck	Merck
[o] (Weight)	85%	62%	44%	9.2 M	H_2O_2 90%

dition of ammonium molybdate for H_2O_2 and sodium perborate solution) and in methanol for *m*-CPBA.

Solution A (0.25 mL, 2.8×10^{-2} M) and the appropriate oxidizing solution B (1.00 mL, 2.8×10^{-1} M) were successively introduced into a 5 mm NMR tube. Then, the tube was shaken to attain a complete mixing of the reactants before recording periodically the ^{31}P NMR spectra at 22°C.

The first-order rate constants were determined according to Epstein et al. [7] and are given in Table 1.

The soman solution was prepared by dissolution of 25.5 mg (3.5×10^{-4} mole) of **13** in 1.0 mL of CD_3OD. Soman solution (0.25 mL, 2.8×10^{-2} M) and MMPP solution (1.00 mL, 2.8×10^{-1} M) were introduced into a 5 mm NMR tube. Then, the tube was shaken to attain quickly the complete mixing of the reactants.

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