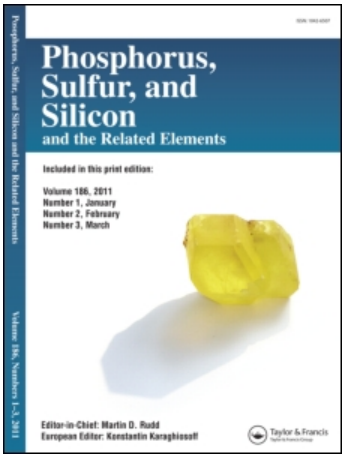

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SYNTHESIS AND STRUCTURE OF SOME PHOSPHONYLATED OXIMES RELATED TO ORGANOPHOSPHATE NERVE AGENTS

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SYNTHESIS AND STRUCTURE OF SOME PHOSPHONYLATED OXIMES RELATED TO ORGANOPHOSPHATE NERVE AGENTS

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Oximes, and in particular oximate salts, can be useful nucleophiles for the treatment of organophosphate nerve agent poisoning and decontamination of chemical warfare agents. In this paper, the reactions of phosphonochloridate analogues of the chemical warfare nerve agents VX, GB, and GA and the oximes 2-butanone oxime, 2,3-butanedione monoxime, and its potassium salt (KD), are examined. Under controlled conditions, (0°C, 1 molar eq. KD), the major product is the O-(O-alkyl phosphonyl)oxime; with excess oximate KD, the intermediate phosphonylated oximes containing an α-carbonyl undergo a "second-order" Beckmann rearrangement to give (*E*)-mono(O-acetyloxime)-2,3-butanedione.

Key words: Organophosphorus nerve agent; phosphonylated oximes; oximes; sarin; tabun; Beckmann rearrangement

INTRODUCTION

Oximes, and in particular pyridinium aldoximes, are useful reactivators of organophosphate inhibited acetylcholinesterase (AChE). However, it has been reported that some phosphonylated oximes, the initial reaction products of pyridinium aldoximes and phosphonofluoridates, are in themselves toxic.[1] These compounds have been shown to be powerful inhibitors of AChE; obidoxime phosphonylated by sarin (GB) was found to have a very large inhibitory rate constant of $1.7 \times 10^{-9}\ M^{-1}\ min^{-1}$ (pH 7.5, 25°C), larger than that of sarin itself[1e] $1.24 \times 10^{-7}\ M^{-1}\ min^{-1}$.

2-Butanone oxime (**1**), 2,3-butanedione monoxime (**2**, DAM), and potassium 2,3-butanedione monoximate (**3**, KD) are potential reactive nucleophiles for the chemical destruction, or "decontamination," of chemical warfare (CW) agents. Should these oximes be used as decontaminants, it is expected that phosphonylated oximes would be formed from the reaction of **1**, **2**, or **3** and an organophosphate nerve agent. Authentic samples of these proposed decontamination intermediates are thus needed for the complete identification of the reaction products between such oximes and organophosphate CW agents as well as for toxicological studies.

Phosphonylated oximes are generally unstable and prepared *in situ* by direct reaction of the oxime and the organophosphate nerve agent of interest.[1a,2] Few phosphonylated oximes have been reported as synthetic products in the literature. However, these compounds were often unstable and difficult to isolate[3] and the spectroscopic data of phosphonylated oximes are limited to a Yugoslavian paper which reports some infrared and nuclear magnetic resonance spectra for a series

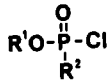
of methylphosphonyl oximes of sarin, soman, and GF.[4] In this paper, the synthesis, chemistry, and structure of some novel phosphonylated oximes related to the organophosphate nerve agents sarin (**4**, GB), VX (**5**) and tabun (**6**, GA) are described.†

RESULTS

The procedures selected for the synthesis of the phosphonylated oximes were chosen so that, in addition to providing authentic samples of the phosphonylated oximes, they would also provide data regarding the possible reaction products of an organophosphate nerve agent with a decontaminant such as KD (**3**). For this study, the alkyl phosphonochloridates **7a–c** were used as chemical analogues of the parent CW agents (Table I) thus avoiding the use of the more toxic CW agents themselves. Two procedures were utilized: 1) the direct reaction of KD (**3**), an

TABLE I

Phosphonochloridates as nerve agent analogues



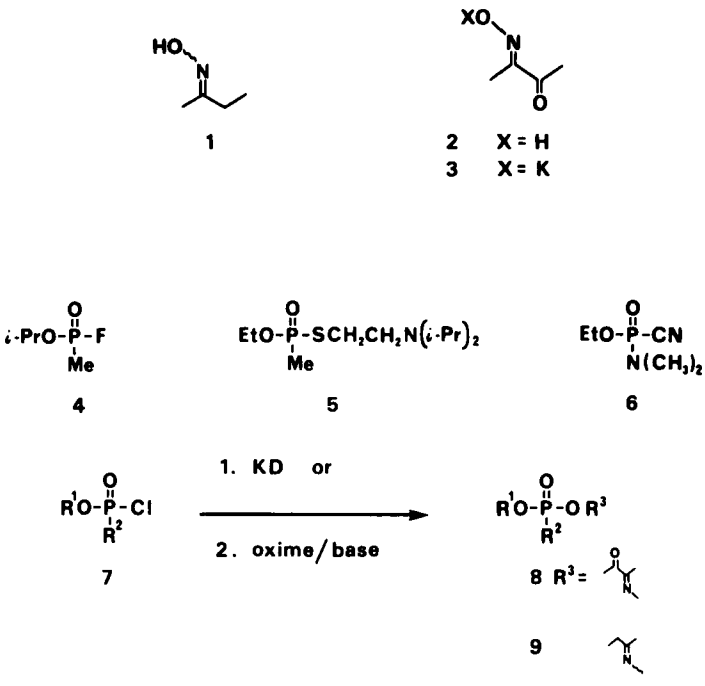
7

Phosphonochloridate **7**			
	R^1	R^2	Parent Agent
7a	CH_3CH_2	CH_3	VX
7b	$(CH_3)_2CH$	CH_3	GB
7c	CH_3CH_2	$(CH_3)_2N$	GA

oximate salt, and a phosphonochloridate and 2) the reaction of an oxime (**1** or **2**) and a phosphonochloridate in the presence of a suitable base (Scheme 1).

The heterogeneous reaction of a suspension of KD (**3**) in toluene and ethyl methylphosphonochloridate (**7a**) was used as a model for the nucleophilic destruction of nerve agents, and VX (**5**) in particular. Gas chromatographic-mass spectrometric (GC-MS) analysis of the crude reaction mixture, after workup, showed that the major product was not the phosphonylated oxime as expected but a non-organophosphorus compound with the phosphonylated oxime **8a** being only a minor product (Figure 1). The EI mass spectrum of the major product had a base ion of m/z 101 and was similar to the EI-MS of 2,3-butanedione monoxime (**2**, Figure 2). This product was isolated and the 60 MHz ^1H NMR spectrum showed only three

† The *in vivo* and *in vitro* toxicology of these compounds has been investigated and will be reported in a separate publication. T. W. Sawyer, M. T. Weiss, C. A. Boulet, and A. S. Hansen, *Fund. Appl. Toxicol.*



Scheme 1

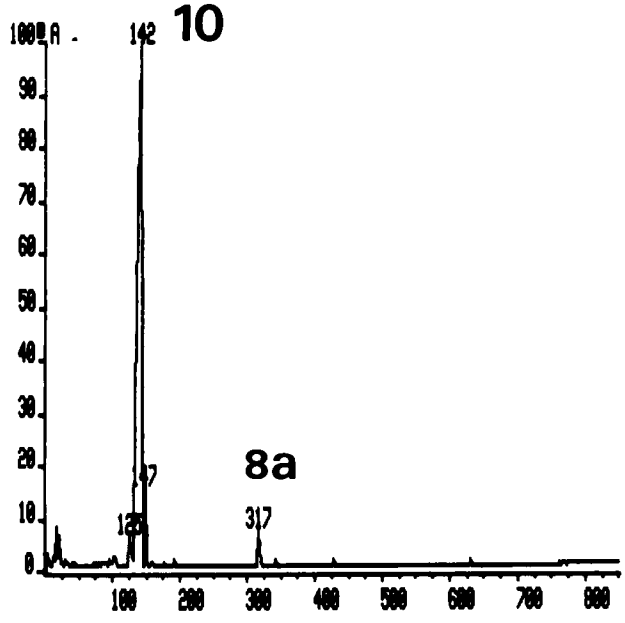


FIGURE 1 Total ion current GC-MS chromatogram of the crude product mixture from the reaction of ethyl methylphosphonochloridate (**7a**) and KD (**3**). The major product observed is the acetylated oxime **10**.

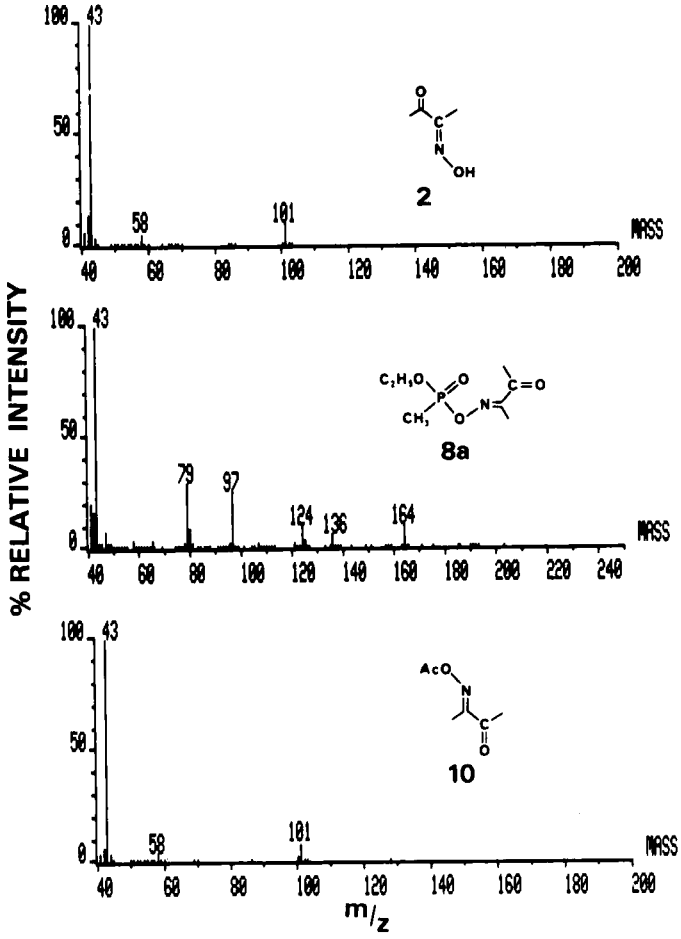
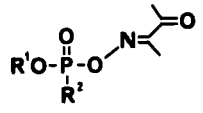


FIGURE 2 EI-MS spectra of 2,3-butanedione monoxime (**2**), (*E*)-2,3-butanedione mono[O-(O-ethyl methylphosphonyl)oxime] (**8a**) and the acetylated oxime **10**.

TABLE II

Phosphonylated derivatives of 2,3-butanedione monoxime (**2**)



8

	R^1	R^2
8a	CH_3CH_2	CH_3
8b	$(CH_3)_2CH$	CH_3
8c	CH_3CH_2	$(CH_3)_2N$

singlets of equal intensity at 2.1, 2.3, and 2.6 ppm. A molecular weight of 143 was confirmed during ammonia chemical ionization MS analysis of this product. From this data the structure of the major compound was assigned as mono(O-acetyloxime)-2,3-butanedione (**10**). This product was later found to be identical to an authentic sample of **10** prepared by the method of Gass and Bope.[5]

The phosphonylated oximes **8a** and **8b** (Table II), derivatives of VX (**5**) and GB (**4**) respectively, were prepared by reacting the corresponding phosphonochloridates **7a** and **7b** with 2,3-butanedione monoxime (**2**) in the presence of triethylamine (TEA) at low temperature. With this procedure acetylated oxime **10** was a minor product (Figure 3). However the isolated yields of products from these reactions were only moderate due to decomposition of the products during distillation. At room temperature, the major product was again the acetylated oxime **10**.

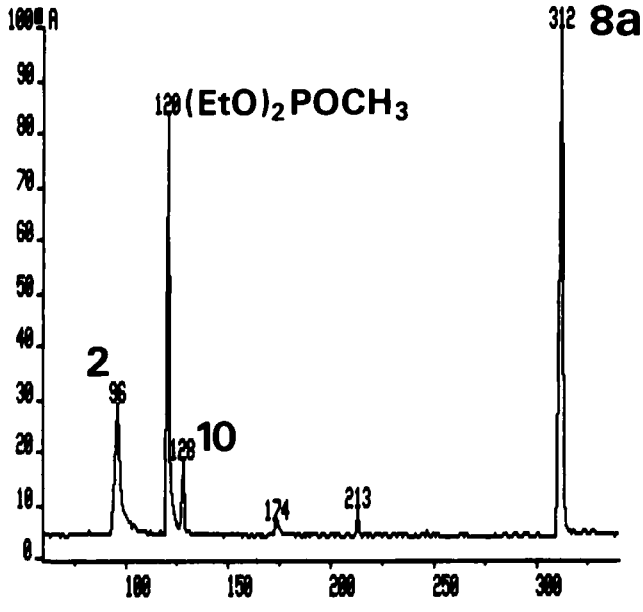
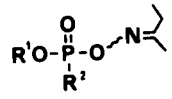


FIGURE 3 Total ion current GC-MS chromatogram of the crude product mixture from the reaction of ethyl methylphosphonochloridate (**7a**) and 2,3-butanedione monoxime (**2**)/TEA.

TABLE III
Phosphonylated derivatives of 2-butanone oxime (**1**)



9

	R^1	R^2
9a	CH_3CH_2	CH_3
9b	$(CH_3)_2CH$	CH_3
9c	CH_3CH_2	$(CH_3)_2N$

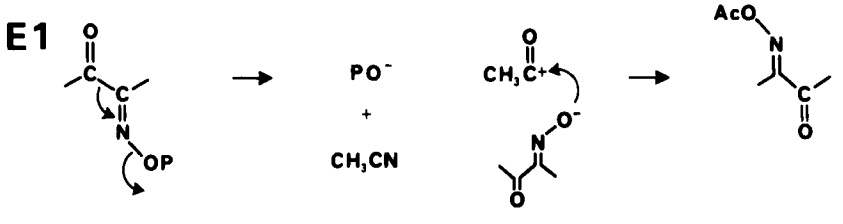
A small quantity of 2,3-butanedione mono[O-(O-ethyl dimethylamidophosphonyl)oxime] (**8c**), the phosphonylated derivative of GA (**6**), was prepared from **7c** using the more reactive oxime KD (**3**) due to the decreased reactivity of phosphoramides[6] (Route 1, Scheme 1). Although the major product of this reaction was the acetylated oxime, a small amount of desired product was isolated after preparative thin layer chromatography. Immediate analysis of the phosphonylated oximes **8a–c** by ^{1}H and ^{13}C NMR and GC-MS analysis showed that the isolated products corresponded to the proposed structures. However, these compounds proved unstable upon standing necessitating repeated Kugelrohr purifications between analyses. Satisfactory combustion analyses could not be obtained for compounds **8a** and **8c**.

The phosphonylated derivatives of 2-butanone oxime (**1**), compounds **9a–c** (Table III), were also prepared by the reaction of the oxime and the phosphonochloridates **7a–c** in the presence of TEA (Route 2, Scheme 1). No evidence of the acetylated oxime **10** was observed in these reactions.

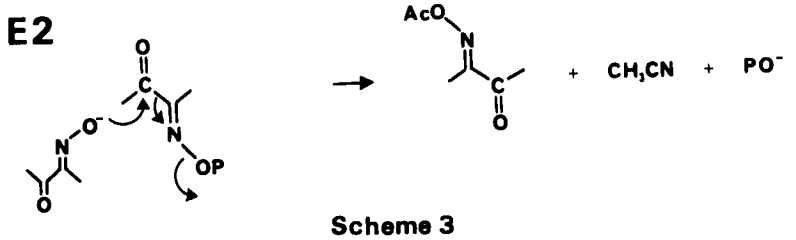
DISCUSSION

Reaction of Phosphonylated Oximes with Excess 2,3-Butanedione Monoxime

The major product isolated from the reaction of KD (**3**) and the phosphonochloridates **7a–c** was found to be the acetylated oxime **10**. This product was apparently formed by the rearrangement of the intermediate phosphonylated oxime, as suggested by Green and Saville, although neither the phosphonylated oxime nor were the acetylated oximes isolated[7] in that study. The acid catalyzed rearrangement of ketoximes and aldoximes to amides (or amines) via the Beckmann rearrangement is well understood.[8] Under non-isomerizing conditions, in the absence of a Bronsted



Scheme 2



Scheme 3

acid, the rearrangement is stereospecific with the group anti to the -OR migrating. Monoximes of α-diketones can also undergo a fragmentation, or second-order Beckmann rearrangement, to give nitriles.

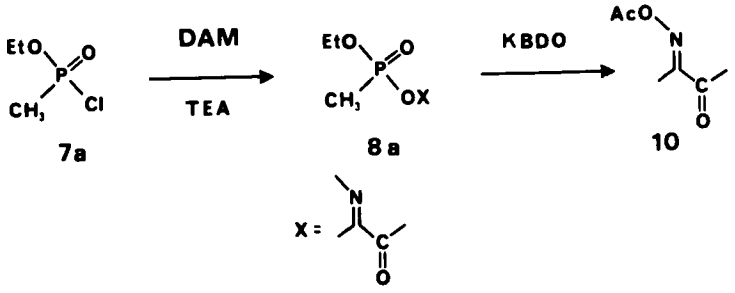
The mechanism of the second-order Beckmann rearrangement has not been clearly established and two mechanisms have been proposed for the fragmentation of α-ketomonoximes. In the E1 type reaction (Scheme 2), the fragmentation occurs first to produce an acyl carbonium ion which can combine with solvent or the oximate anion to give an acylated nucleophile. A second possibility is an E2 type mechanism where the second-order Beckmann rearrangement is initiated by nucleophilic attack of the oximate anion at the carbonyl carbon with concerted fragmentation to give a nitrile and an alkoxide (Scheme 3).

Ferris[9] has presented considerable evidence for the ionization mechanism for the Beckmann rearrangement under conditions which strongly favor the E1 type mechanism but do not exclude the E2 mechanism. These conditions include aqueous media, high acid concentration, and steric hindrance of the carbonyl (which can also increase the stability to carbonium ion). Clearly the E2 mechanism is still possible in the presence of a good nucleophile, a non-hindered carbonyl, and a non-polar solvent.[10]

The intermediacy of 2,3-butanedione mono[O-(O-ethyl methylphosphonyl)-oxime (**8a**) in the formation of acetylated oxime **10** was confirmed by two separate experiments. Treatment of **8a** with either TEA or the oxime **2** alone (in refluxing toluene) gave quantitative recovery of starting material. When treated with either KD (**3**) or 2,3-butanedione monoxime (**2**)/TEA, **8a** was converted to the acetylated oxime (Scheme 4). This suggests that the mechanism is an E2-type and that nucleophilic attack at the carbonyl carbon initiates the fragmentation. The other two products of the second-order Beckmann reaction, namely acetonitrile and ethyl methylphosphonate, were not observed under the preparative and analytical conditions of these experiments.

A second series of phosphonylated oximes (**9a–c**) were prepared from 2-butanone oxime (**1**) and the phosphonochloridates **7a–c**. These reactions gave no evidence of either the normal or second-order Beckmann rearrangement products.

These experiments, in part, confirm the general reaction scheme and kinetics developed by Ford and Watts for the reaction of sarin and 1-phenylbutane-1,2,3-trione-2-oxime.[3] Although these reactions had been explored in aqueous media, reactions under non-aqueous conditions have permitted the isolation of the unstable phosphonylated oxime and show that it too undergoes a second-order Beckmann



Scheme 4

rearrangement via an E2 type to acetylated oxime **10**. From the kinetic data of Ford and Watts, the intermediate phosphonylated oxime is three times more reactive towards excess oxime than is GB and very much more subject to alkaline hydrolysis. The relative differences in rates would be even greater in the case of dimethylphosphoramido oximes thus explaining the difficulty in achieving good yields of the phosphonylated GA derivative because any phosphonylated oxime is immediately consumed by excess nucleophile.

Stereochemistry of Phosphonylated Oximes

Methods for the assignment of geometric configuration of the imino group in oximes have included utilization of the Beckmann rearrangement, thermal isomerization and spectroscopic techniques. The known stereospecificity of the Beckmann rearrangement and ^{13}C NMR analysis of the products and reference compounds allows for the complete assignment of the ^{1}H and ^{13}C NMR spectra of the phosphonylated oximes.

The stereochemistry of 2,3-butanedione monoxime (**2**) and potassium 2,3-butanedione monoximate (**3**) had previously been shown to be exclusively *E*, consistent with the assignment of stereochemistry for oximes with a quaternary α-carbon.[11] Aliphatic oximes such as 2-butanone oxime (**1**) exist as a mixture of *E*- and *Z*-stereoisomers. 2-Butanone oxime is a ratio of approximately 75:25 *E*:*Z*; ratios of 72:28[12] and 74:26[13] have been reported. The ratio of stereoisomers of the phosphonylated 2-butanone oximes was determined from the ratio of integrals for the well resolved H-3 methylene quartets at 2.11 (*E*) and 2.25 (*Z*) ppm and found to be approximately 74:26.

The chemical shift assignments of the ^{1}H NMR of phosphonylated 2,3-butanedione oxime derivatives **8a–c** (Table IV) were based on comparison to the parent 2,3-butanedione monoxime (**2**). Assignment of the ^{13}C NMR (Table V) signals was slightly more complex due to the heteronuclear $^{13}C-^{31}P$ couplings. One, two, and three $^{13}C-^{31}P$ couplings were observed for phosphonylated oximes and are reported as absolute values in Hz. The one and three-bond couplings of alkyl phosphonates are known to be positive whereas the two bond couplings are negative.[14] The typical $^{1}J_{CP}$, $^{2}J_{CP}$, and $^{3}J_{CP}$ are in the 125–165, 6–7, and 5–6 Hz ranges, respectively. The couplings observed for compound **8a** are typical: $^{1}J_{CP}$ = 142 Hz and $^{2}J_{COP}$ = 6.7 Hz. A slightly higher $^{3}J_{CNOP}$ of 12.9 Hz was measured. Three bond couplings as high as 47 Hz have been observed in bicyclic phosphine oxides with hindered conformations.[15]

The stereochemistry of these compounds is readily assigned as *E* when referenced to the chemical shift assignments of the parent oxime **2**. The reaction of an oxime and a phosphonochloridate does not lead to isomerization of the oxime, and the *E*-stereochemistry is retained in the product. Other assignments were made from the analysis of coupling and carbon-proton shift correlation experiments.

The phosphonylated derivatives of 2-butanone oxime (**9a–c**) are excellent examples for illustrating the influence of geometric isomerism on ^{13}C chemical shifts.[16] The *E*- and *Z*-isomers show a large steric compression shift difference for the C-1 and C-3 carbons adjacent to the ketoxime (Table VI). This large difference, in which the C-1 methyl of the *Z*-isomer is deshielded by approximately 6 ppm relative

TABLE IV

[1]H NMR data for phosphonylated 2-butanone oxime and 2,3-butanedione monoxime derivatives[a]

PROTON	COMPOUND									
	8a	8b	8c	9a		9b		9c	
				(Z)	(E)	(Z)	(E)	(Z)	(E)
H-1 (s)	1.93	1.91	2.05	1.77	1.76	1.77	1.76	1.76[b]	1.76
H-3 (q)	--	--	--	2.11	2.25	2.11	2.25	2.11	2.24
				(7.5)	(7.5)	(7.5)	(7.5)	(7.5)	(7.5)
H-4	2.29 (s)	2.29 (s)	2.43 (s)	0.92 (t)	0.89 (t)	0.93 (t)	0.90 (t)	0.94 (t)	0.91 (t)
				(7.5)	(7.5)	(7.5)	(7.5)	(7.5)	(7.5)
H-5 (d)	1.56	1.55	2.80	1.39		1.39		2.53	
	(17.7)	(17.8)	(11)	(17.51[c])		(17.51)		(10.1)	
H-6 (cm)	4.17	4.75	4.22	3.95		4.65		3.90	
H-7	1.21	1.23, 1.17	1.40	1.12		1.15, 1.10		1.15	
	(t, 7.0)	(d, 6.2)	(dt 57.0 1.1[d])	(t, 7.5)		(dd, 6.6, 1.72)		(dt, 7.1, 0.5)	

[a] Chemical shifts, δ, in ppm ($CDCl_3$ reference, 7.27 ppm); J_{HH} and J_{PC} (Hz) are shown in brackets. For structure numbering see, for example, Figure 4.

[b] Not resolved.

[c] J_{HP}

[d] Long range J_{HP}

TABLE V

^{13}C NMR data for phosphonylated 2,3-butanedione monoxime derivatives **8a–c** and related compounds[a]

	COMPOUND				
CARBON	**2**	**8a**	**8b**	**8c**	**10**
1	8.10	9.48	9.47	8.92	8.65
2	156.9	162.4	162.2	161.8	160.42
	--	(12.2)	(12.2)	(13.6)	--
3	197.9	193.8	195.0	194.9	196.7
4	25.0	25.16	25.18	24.92	24.60
5	--	10.05	10.51	36.33	--
	--	(142)	(142)	(3.0)	--
6	--	62.16	71.37	62.94	--
	--	(6.8)	(7.0)	(6.0)	--
7	--	16.01	23.46, 23.73	15.67	--
	--	(5.7)	(5.2)	(6.8)	--

[a] Chemical shifts, δ, in ppm ($CDCl_3$ reference); P–C coupling constants (J) are shown in brackets and are given as absolute values in Hz.

TABLE VI

^{13}C NMR data for 2-butanone oxime (1) and related phosphonylated oximes (9a–c)[a]

	COMPOUND							
	1		9a		9b		9c	
CARBON	(Z)	(E)	(Z)	(E)	(Z)	(E)	(Z)	(E)
1	18.60	12.73	18.75	14.24	18.75	14.32	18.84	14.01
2	159.4	159.0	167.84	167.14	167.53	166.84	167.61	166.90
			(12.0)	(12.0)	(12.8)	(12.5)	(12.9)	(12.5)
3	21.62	28.73	22.82	28.61	22.87	28.64	22.67	28.78
4	9.47	10.63	9.59	10.52	9.60	11.01	9.62	10.14
5	--		9.82		10.3		36.45	
			(141)		(141)		(3.2)	
6	--		61.15		69.97		62.34	
			(6.7)		(6.7)		(5.6)	
7	--		15.88		23.68, 23.32		15.77	
			(5.1)		(4.8, 5.6)		(5.6)	

[a] Chemical shifts, δ, in ppm ($CDCl_3$ reference); P–C coupling constants (J) are shown in brackets and are given as absolute values in Hz.

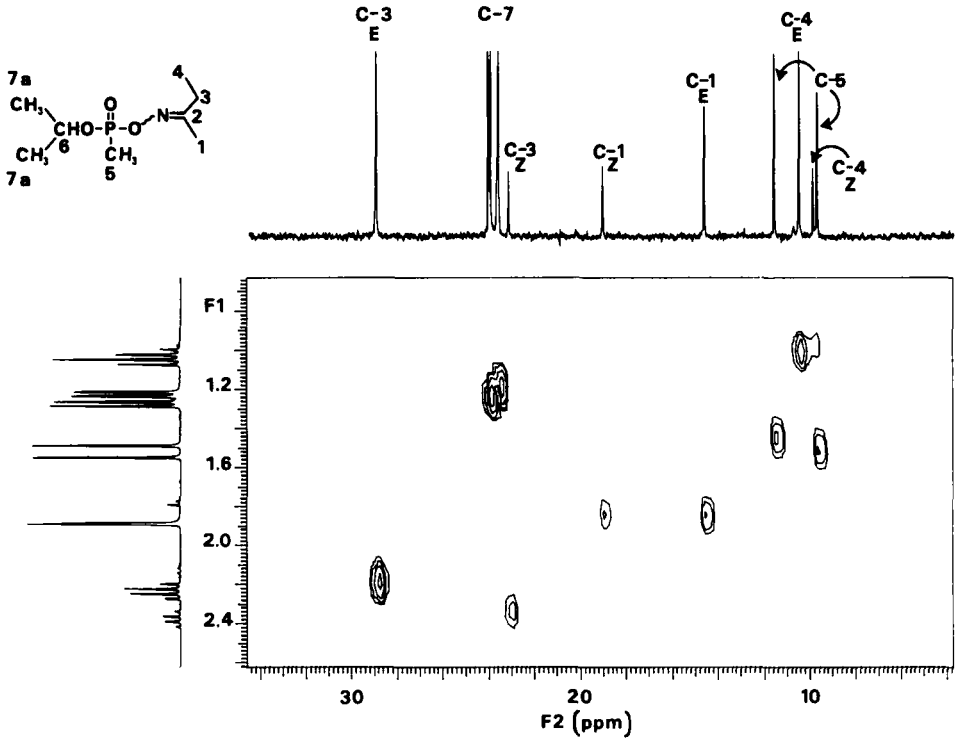


FIGURE 4 Carbon-proton heteronuclear correlation NMR spectrum of the aliphatic region of 2-butanone O-(O-isopropyl methylphosphonyl)oxime (**9b**) which exists as a mixture of *E*- and *Z*-stereoisomers.

to the *E*-isomer is readily visible in the ^{1}H-^{13}C heteronuclear correlation experiment of 2-butanone O-(O-isopropyl methylphosphonyl)oxime (**9b**) illustrated in Figure 4. This gamma-gauche effect gives a distinct pattern to the ^{1}H and ^{13}C spectra where a doubling of the proton peaks and six carbon signals were observed for the three aliphatic carbons of the 2-butanone oxime fragment.

CONCLUSIONS

This paper reports the synthesis and structure of six phosphonylated oxime derivatives related to the chemical warfare nerve agents GA, GB, and VX. These compounds were prepared in non-aqueous solvents by reacting a phosphonochloridate with either 2,3-butanedione monoxime, potassium 2,3-butanedione monoximate or 2-butanone oxime. These conditions enabled the identification of (*E*)-mono(O-acetyloxime)-2,3-butanedione as a second-order Beckmann rearrangement product of phosphonylated α-ketoximes.

EXPERIMENTAL

General. All reactions, unless otherwise indicated, were performed under a positive pressure of dry N_2. All solvents employed were reagent grade or better; anhydrous solvents were prepared according

to standard methods: anhydrous ether and tetrahydrofuran (THF) were distilled from Na and K/benzophenone ketyls respectively. Triethylamine (TEA) was distilled from NaOH. Ether refers to diethyl ether. Organic extracts were dried over anhydrous $MgSO_4$. Potassium 2,3-butanedione monoximate (Raylo Chemicals, Edmonton, Alberta Lot 1363-A-1) and 2,3-butanedione monoxime (Aldrich) were used without further purification. Preparative thin-layer chromatography was done with E. Merck Silica Gel 1 mm 60F-254. The term *in vacuo* refers to removal of solvent by Buchi Rotavapor at water evaporator vacuum followed by 0.1 mm Hg vacuum. Reactions were monitored by ^1H NMR using a Varian EM 360A. ^1H and ^{13}C NMR spectra of purified products were recorded on a Bruker AM 400 (Agricultural Research Station, Lethbridge) or Bruker ACP 300 (Bruker Spectrospin). Heteronuclear correlation experiments were performed on a Varian VXR 300S spectrometer using Varian supplied pulse sequences. IR spectra were recorded on a Beckmann IR 4260 as thin films. Capillary column GC/MS analyses were performed over a 400 to 40 u mass range with a VG 70/70E double focusing mass spectrometer equipped with a Varian 3700 GC. GC analyses were performed with a J+W 15 m × 0.32 mm I.D. capillary column coated with a 0.25 μm DB-1 film. Microanalyses were performed by D. Mahlow, University of Alberta. The following abbreviations are used: h (hours), min (minutes), rt (room temperature), s (singlet), d (doublet), t (triplet), q (quartet), cm (complex multiplet).

(E)-2,3-Butanedione Mono[O-(O-ethyl methylphosphonyl)oxime] (**8a**). *Procedure 1: Reaction of KD* (**3**) *and Ethyl Methylphosphonochloridate* (**7a**). Potassium 2,3-butanedione monoximate (**3**, 0.472 mole, 65.6 g) was suspended in dry toluene (200 mL) and approximately 50 mL was removed by azeotropic distillation to ensure anhydrous conditions. To this rapidly stirred suspension was added ethyl methylphosphonochloridate (**7a**, 0.472 mole, 67.0 g) in toluene (100 mL) over a 30 min period. The reaction was vigorously exothermic and was moderated by cooling with an ice bath. After the addition of the chloridate was complete, reflux was maintained by heating for a further 30 min, and then the reaction mixture was allowed to cool to rt. The mixture was filtered, washed with brine (2 × 500 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The oil was purified by Kugelrohr distillation (110°C, 0.3 mm Hg) to give 8.27 g (12.3% yield based on initial KD) of a colourless oil: GC/MS, EI (70 eV) m/z (relative intensity, 101 (7), 43 (100), 42 (5), 41 (3); IR (thin film), 1790, 1710, 1365, 1185 cm^{-1}, NMR (60 MHz, δ, ppm) 2.5, 2.3, 2.1 (each s, 3H). The product was identical to an authentic sample of mono-(O-acetyloxime)-2,3-butanedione.

Procedure 2: Reaction of 2,3-Butanedione Monoxime (**2**) *with Ethyl Methylphosphonochloridate* (**7a**). Ethyl methylphosphonochloridate (**7a**, 0.16 mole, 22.7 g) was dissolved in anhydrous ether and cooled to ice bath temperature. A mixture of 2,3-butanedione monoxime (**2**, 0.16 mole, 16 g) and TEA (2.3 mL) in ether (20 mL) was added dropwise over 40 min. The reaction mixture was stirred at ice bath temperature for 1 h then at rt overnight. The precipitate was removed by filtration and the filtrate was concentrated *in vacuo* to give 3.21 g of a pale yellow oil. The oil was purified by Kugelrohr distillation (125–140°C/0.25 mm Hg) to give 41.4% (1.37 g) of **8a**: GC/MS EI (70 eV), m/z (relative intensity), 164 (9), 136 (5), 124 (9), 97 (24), 79 (28), 43 (100), 42 (15), 41 (20); IR (thin film) 1710, 1250, 1050, 950 cm^{-1}; ^1H NMR, Table IV; ^{13}C NMR, Table V.

Anal. Calculated for $C_7H_{14}NO_4P$: C, 40.56; H, 6.81; N, 6.76. Found: C, 40.07; H, 7.04; N, 6.02.

Second-order Beckmann Rearrangement of **8a**. *Treatment of* **8a** *with 2,3-butanedione monoxime*. The oxime **2** (240 mg, 2.4 mmole in 10 mL ether) was added dropwise to a stirred solution of phosphonylated oxime **8a** (500 mg, 2.4 mmole in 20 mL ether) at rt. The reaction mixture was heated to reflux overnight, cooled and concentrated *in vacuo* to give 720 mg of an oil. Analysis by NMR showed this oil to be a mixture of the two starting materials; no acetylated oxime was observed. The crude mixture, isolated above, was treated with TEA (1 mL in 20 mL ether). The product was isolated as described to give 180 mg acetylated oxime **10**.

Treatment of **8a** *with potassium 2,3-butanedione monoximate*. Phosphonylated oxime **8a** (500 mg, 2.4 mmole in 10 mL ether) was added to stirred suspension of KD (**3**, 334 mg, 2.4 mmole) in 25 mL toluene. The suspension was heated to reflux for 2 h, cooled, and filtered, and the filtrate was concentrated *in vacuo* to give 240 mg of acetylated oxime **10**.

(E)-2,3-Butanedione Mono[O-(O-isopropyl methylphosphonyl)oxime] (**8b**). Isopropyl methylphosphonochloridate (**7b**, 0.05 mole, 7.8 g) in ether (50 mL) was added dropwise to a stirred solution of 2,3-butanedione monoxime (**2**, 0.05 mole, 5.1 g) and TEA (0.05 mole, 5.1 g) in ether (150 mL). The reaction mixture was heated to reflux for 2 h then cooled to rt. The precipitate was removed by filtration and the filtrate was concentrated *in vacuo* to give a pale yellow oil. The oil was taken up in dichloromethane (50 mL) and washed with water (2 × 50 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to give an oil which was purified by distillation to give 68% (7.5 g) of **8b** (bp 90–94°C/0.05 mm Hg): GC/MS, EI (70 eV) m/z (relative intensity), 136 (16), 123 (5), 97 (24), 79 (16),

43 (100), 42 (12), 41 (16); IR (thin film) 1700, 1355, 1255, 1000, 900 cm^{-1}; ^1H NMR, Table IV; ^{13}C NMR, Table V.

Anal. Calculated for $C_8H_{16}NO_4P$: C, 43.44; H, 7.29; N, 6.33. Found: C, 43.09; H, 7.45; N, 6.02.

(E)-2,3-Butanedione mono[O-(O-ethyl dimethylamidophosphonyl)oxime] (**8c**). Ethyl dimethylamidophosphonochloridate (**7c**, 0.050 mole, 8.6 g) in toluene (20 mL) was added dropwise to a vigorously stirred suspension of KD (**3**, 0.050 mole, 6.9 g). The reaction mixture was heated at 40°C for 2 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo* to give a pale yellow oil. This product was distilled (bp 110–115°C/0.02 mm Hg) to give 2.0 g of a mixture of acetylated and phosphonylated oximes. A portion of this mixture was purified by preparative thin layer chromatography: 500 mg of the mixture dissolved in 0.5 mL dichloromethane was spotted on a 1 mm silica gel plate (Merck silica gel 60 F254) and developed with ethyl acetate/hexane 1:1 solvent system. The band at rf 0.2 (UV visualization) was removed, extracted with ethyl acetate, and concentrated *in vacuo* to give a colorless oil. This procedure was repeated and the combined products were purified by Kugelrohr distillation (130°C/0.1 mm Hg) to give 750 mg of **8c**: GC/MS, EI (70 eV), m/z (relative intensity), 153 (8), 124 (6), 108 (5), 44 (53), 43 (100), 42 (20), 41 (8); IR (thin film) 1700, 1310, 1260, 1120, 1045 cm^{-1}; ^1H NMR, Table IV; ^{13}C NMR, Table V.

Anal. Calculated for $C_8H_{17}N_2O_4P$: C, 40.68; H, 7.25; N, 11.86. Found: C, 41.00; H, 7.47; N, 10.06.

General Method for the Synthesis of Phosphonylated 2-Butanone Oximes. 2-Butanone O-(O-ethyl methylphosphonyl)oxime (**9a**). Ethyl methylphosphonochloridate (**7a**, 0.011 mole, 1.55 g) was dissolved in THF (20 mL) and cooled to ice bath temperature. A mixture of 2-butanone oxime (**1**, 0.11 mole, 0.96 g) and TEA (0.12 mole, 1.12 g) in THF (10 mL) was added dropwise over 15 min. The mixture was stirred at ice bath temperature then was allowed to slowly warm to rt overnight. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The oil was purified by Kugelrohr distillation (125°C/0.2 mm Hg) to give 1.0 g of a 2.87:1 [72% (*E*)] mixture of 2-butanone [(*E*)-O-(O-ethyl methylphosphonyl)oxime] and 2-butanone [(*Z*)-O-(O-ethyl methylphosphonyl)oxime]: GC/MS EI (70 eV) (*E*)-isomer, m/z (relative intensity, 97 (17), 79 (35), 70 (37), 69 (13), 68 (9), 42 (100), 41 (13); IR (thin film) 1310, 1250, 1040, 920, 730 cm^{-1}; ^1H NMR, Table IV; ^{13}C NMR, Table VI.

Anal. Calculated for $C_7H_{16}NO_3P$: C, 43.52; H, 8.35; N, 7.25. Found: C, 43.49; H, 8.58; N, 7.28.

2-Butanone O-(O-isopropyl methylphosphonyl)oxime (**9b**). The compound was prepared from isopropyl methylphosphonochloridate (**7b**, 0.05 mole, 7.8 g) and 2-butanone oxime (**1**, 0.05 mole, 4.35 g) as described above. The crude oil was dissolved in CH_2Cl_2 (25 mL) and washed with water (2 × 25 mL); the organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The oil was purified by distillation to give 3.6 g (35%) of a 3.15:1 [76% (*E*)] mixture of (*E*) and (*Z*)-isomers: bp 64–66°C/0.2 mm Hg; GC/MS, EI (70 eV) (*E*)-isomer, m/z (relative intensity), 137 (6), 97 (28), 87 (11), 79 (16), 70 (34), 69 (18), 68 (8), 43 (21), 42 (100), 41 (18); IR (thin film) 1455, 1370, 1305, 1250, 1000, 920 cm^{-1}; ^1H NMR, Table IV; ^{13}C NMR, Table VI.

Anal. Calculated for $C_8H_{18}NO_3P$: C, 46.37; H, 8.76; N, 6.76. Found: C, 46.38; H, 8.96; N, 7.04.

2-Butanone O-(O-ethyl dimethylamidophosphonyl)oxime (**9c**). Ethyl dimethylamidophosphonochloridate (**7c**, 0.05 mole, 8.53 g) in toluene (25 mL) was added dropwise to a vigorously stirred (mechanical stirrer) suspension of potassium 2-butanone oximate [potassium 2-butanone oximate was prepared *in situ* by the reaction of 0.05 mole (4.35 g) of **1** and 1.95 g potassium metal] in toluene (50 mL). The reaction mixture was heated to reflux for 2 h and then allowed to cool to rt. The precipitate was removed by filtration and concentrated *in vacuo* to give a pale yellow oil. The oil was redissolved in dichloromethane (25 mL), washed with water (2 × 25 mL) and the organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The oil was purified by distillation to give 4.8 g (43%) of a 3.6:1 [78% (*E*)] mixture (*E*)- and (*Z*)-isomers: bp 98–100°C/0.2 mm Hg; GC/MS, EI (70 eV), (E)-isomer, m/z (relative intensity), 152 (21), 124 (15), 108 (8), 70 (45), 44 (39), 43 (10), 42 (100), 41 (9); IR (thin film) 1310, 1255, 1045, 1000, 900 cm^{-1}; ^1H NMR, Table IV; ^{13}C NMR, Table VI.

Anal. Calculated for $C_8H_{19}N_2O_3P$: C, 43.23; H, 8.62; N, 12.61. Found: C, 43.59; H, 8.69; N, 12.55.

(E)-Mono(O-acetyloxime)-2,3-butanedione (**10**). Acetyl chloride (0.1 mole, 7.85 g) was slowly added to a cooled (ice bath) solution of 2,3-butanedione monoxime (**2**, 0.1 mole, 10.1 g) and TEA (0.12 mole, 12 g) in ether (200 mL). The reaction mixture was stirred for 1 h at ice bath temperature then 2 h at

rt. The suspension was filtered and the filtrate was concentrated *in vacuo*. The crude product was distilled under vacuum to give 12.05 g of a clear liquid (bp 46–51°C/2.5 mm Hg); GC/MS, EI (70 eV), m/z (relative intensity), 100 (7), 43 (100), 42 (5), 41 (3); IR (thin film), 1790, 1710, 1365, 1180, 995 cm^{-1}, ^1H NMR (60 Mz), 2.5, 2.3, 2.1 ppm (each s, 3H); ^{13}C NMR Table V.

REFERENCES

1. (a) B. E. Hackley Jr., G. M. Steinberg and J. C. Lamb, *Arch. Biochem. Biophys.*, **88,** 211 (1959); (b) J. B. Barstad, G. Lilleheil and T. Skobba, *Arch. Int. Pharmacodyn.*, **179,** 352 (1969); (c) O. Rogne, *Biochem. Pharmacol.*, **16,** 1853 (1967); (d) K. Schoene, *Biochem. Pharmacol.*, **22,** 2997 (1973); (e) M. Nenner, *Biochem. Pharmacol.*, **23,** 1255 (1974); (f) L. P. A. De Jong and D. I. Ciulin, *Biochem. Pharmacol.*, **27,** 857 (1978).
2. J. C. Lamb, G. M. Steinberg and B. E. Hackley Jr., *Biochem. Biophys. Acta*, **89,** 174 (1964).
3. B. W. Ford and P. Watts, *J. Chem. Soc. Perkin Trans.*, **2,** 1009 (1974).
4. D. Minic, M. Cosic, D. Rakin, M. Orlov and Z. Binenfeld, *Naucno-Technicki Pregled*, **27,** 3 (1977).
5. L. Gass and F. W. Bope, *J. Am. Chem. Soc.*, **48,** 186 (1959).
6. J. R. Cox Jr. and B. Ramsay, *Chem. Rev.*, **64,** 317 (1964).
7. A. L. Green and B. Saville, *J. Chem. Soc.*, 3887 (1956).
8. (a) L. G. Donarume and W. H. Heldt, *Organic Reactions*, **11,** 1 (1960); (b) P. A. S. Smith, *Molecular Rearrangements* (P. de Mayo Ed., Wiley, New York, 1963) Vol. 1, pp. 483–506; (c) C. G. McCarty, *The Chemistry of the Carbon-Nitrogen Double Bond* (S. Patai Ed., Wiley-Interscience, New York, 1970) pp. 363–464.
9. (a) A. F. Ferris, *J. Org. Chem.*, **25,** 12 (1960); (b) A. F. Ferris, G. S. Johnson and F. E. Gould, *J. Org. Chem.*, **25,** 1813 (1960).
10. J. P. Freeman, *J. Org. Chem.*, **26,** 3507 (1961).
11. G. E. Hawkes, K. Herwig and J. D. Roberts, *J. Org. Chem.*, **39,** 1017 (1974).
12. K. D. Berlin and S. Rengaraju, *J. Org. Chem.*, **36,** 2912 (1971).
13. R. R. Fraser, R. Capoor, J. W. Bovenkamp, B. N. Lacroix and J. Pagotto, *Can. J. Chem.*, **61,** 2616 (1984).
14. E. Breitmaier and M. Voelter, *Carbon-13 NMR Spectroscopy*, (VCH, New York, 1987) 3rd ed., pp. 160–162.
15. R. B. Wetzel and G. L. Kenyon, *J. Chem. Soc., Chem. Comm.*, 287 (1973).
16. F. W. Wehrli and T. Wirthlin, *Interpretation of Carbon-13 NMR Spectra* (Heyden, London, 1976) pp. 187–188.