Table III. NOE Enhancement Factors

Saturated group	Enhancement[a] H-5	N-H	H-10	H-3	H-7
Geminal dimethyl	1.00	1.16	1.00	0.95	1.23
6-Me	1.19	1.04	0.92	1.00	1.17
4-Me	1.34	0.97	0.97	1.54	1.00

[a] The enhancement ratio was determined from the ratio of the integral obtained with the secondary irradiation frequency on to the integral obtained with the secondary irradiation frequency off, both values being the average value obtained for at least five integrations.

8-Aza-4-methyl-7-morpholinocoumarin (3e). Ethyl acetoacetate (5.1 g, 40 mmol) and **27** (2.0 g, 11 mmol) were mixed and heated at reflux for 60 h to give a dark oil. The volatile materials were removed by rotoevaporation giving 3.6 g of semicrystalline black solid. This solid was washed with ether (100 mL) and twice recrystallized from benzene to give tan needles: mp 188–189 °C; IR 1735 cm^{-1} (C=O); NMR ($CDCl_3$) δ 2.36 (d, 3, J = 0.7 Hz, 4-Me), 3.76 (m, 8, morpholino protons), 6.04 (d. 1, J = 07 Hz, H-3), 6.54 (d, 1, J = 4.2 Hz, H-5), 7.69 (d, 1, J = 4.2 Hz, H-6).

10-Aza-2,8-dioxo-4,6-bis(trifluoromethyl)-2*H*,8*H*-benzo-[1,2,-*b*:5,4-*b*]dipyran (6). 2,6-Dihydroxypyridine was heated at 135 °C in excess ethyl 4,4,4-trifluoroacetoacetate (66 h). The product crystallized as colorless needles: mp 280–282 °C (Me_2SO); 5.36 g (50% yield); IR 1780 cm^{-1} (C=O); MS m/e 351, M^+; NMR (Me_2SO-d_6) δ 7.10 (s, 2, H-3 and H-7), 8.32 (broad s, 1, H-5). Anal. Calcd for $C_{13}H_3F_6NO_4$: C, 44.47; H, 0.86; F, 32.18; N, 3.99. Found: C, 44.42; H, 0.82; F, 32.18; N, 3.99.

2,6-Dihydroxypyridine (4). 2,6-Dihydroxypyridine hydrochloride (10.0 g, 68 mmol) was suspended in 400 mL of water and the pH was adjusted to 3.5 by addition of concentrated aqueous ammonia. The flocculent white solid was filtered, dried in vacuo, and used immediately without further purification.

6-Acetamido-2-pyridinol (30). This compound was prepared by the method of Buo-Hoi, Gauthier, and Xuong[18] in 50% overall yield starting from 6-amino-2-pyridinol.

Attempted Preparation of 7-Acetamido-8-aza-4-methylcoumarin (31). Ethyl acetoacetate (1.72 g; 13.2 mmol) and **30** (2.0 g; 13.2 mmol) were heated at 170 °C (oil bath) for 16 h. The pyridinol had not gone into solution. Mesytelene (5 mL) was added and the reaction mixture was heated an additional 20 h at 170 °C. Upon cooling, 2.1 g of solid separated. NMR and IR showed this to be recovered **24**, contaminated with a small amount of mesytelene.

2-Keto-4,6,8,8-tetramethyl-8,9-dihydro-2*H*-pyrano[3,2-*g*]-quinoline (8). *m*-Aminophenol (10 g; 92 mmol) and ethyl acetoacetate were mixed. Upon heating to 150 °C a clear solution was obtained. As heating continued a yellow precipitate formed. Heating was continued for a total of 6 h. The precipitate was filtered from the hot solution and washed with cyclohexane. A further 2.2 g of yellow solid was obtained from the cooled filtrate. Crystallization from methanol gave beautiful golden needles (mp 270–274 °C (lit.[8] mp 268 °C)): NMR (Me_2SO-d_6) δ 1.68 (s, 6, 8-*gem*-dimethyls), 2.29 (d, 3, J = 2 Hz, 6-Me), 2.72 (d, 3, J = 1.6 Hz, 4-Me), 5.8 (bs, 1, H-7), 6.25 (q, 1, J = 1.6 Hz, H-3), 6.71 (s, 1, H-10), 7.1 (bs, 1, NH), 7.48 (s, 1, H-5); IR 3311 (NH), 1695 cm^{-1} (C=O); MS m/e 255, M^+. Anal. Calcd: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.67; H, 6.87; N, 5.45. The nuclear Overhauser effect enhancements[19] are given in Table III. The spectra were obtained at 80 °C from a 100% Me_2SO-d_6 sample degassed by five freeze cycles and sealed under vacuum.

Registry No.—**4**, 626-06-2; **6**, 65292-88-8; **7**, 26093-31-2; **8**, 65392-09-8; **23**, 580-20-1; **24**, 58196-33-1; **25**, 61468-43-7; **26**, 65292-89-9; **27**, 65292-90-2; **28**, 7159-96-8; **29**, 58632-48-7; **30**, 770-20-7; ethyl acetoacetate, 141-97-9; ethyl 4,4,4-trifluoroacetoactate, 372-31-6; trimethyl phosphate, 512-56-1; 5-hydroxyquinoline, 578-67-6; *m*-aminophenol, 591-27-5; 2-amino-6-hydroxypyridine, 5154-00-7; 2-chloro-6-hydroxypyridine, 16879-02-0; morpholine, 110-91-8; 2-dimethylamino-6-hydroxypyridine, 65292-91-3; 2,6-dihydroxypyridine·HCl, 10357-84-3; ethyl chloroformate, 541-41-3; ethyl 2-acetopropionate, 609-14-3.

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Syntheses of [1-(Alkylthio)]- and (1-Mercapto)cycloalkanephosphonic Esters by the Reactions of Cycloalkanethiones with Trialkyl Phosphites

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Cycloalkanethiones reacted with trialkyl phosphites to give [1-(alkylthio)]- and/or (1-mercapto)cycloalkanephosphonic esters. The reaction mechanism is discussed in terms of a concerted one via the betaine intermediate. These sulfur-containing esters are easily converted to cycloalkanephosphonic esters in good yields by Raney nickel treatment.

The chemistry of thiocarbonyl compounds[1] has attracted much attention owing to their interesting reactivities and preparative significance. Especially, the reactions of thiocarbonyl compounds with organophosphorus compounds such as phosphites and phosphines have been the focus of interest in the past several years, because phosphines and phosphites

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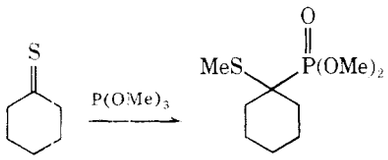
are known to demonstrate both "carbophilicity" and "thiophilicity"[2] toward organosulfur compounds. There have been several noteworthy reports on the reactions of thiocarbonyl compounds with phosphines or phosphites. Middleton and Scharkey[3] reported the reactions of hexafluorothioacetone and thiofluorenone with trialkyl phosphites to give corresponding phosphoranes. The formation of 1,3-dithiacyclohexylidenephosphorane from 1,3-dithiacyclohexane-2-thione and trimethyl phosphite was also reported by Corey and Märkl.[4] On the other hand, in his preceding papers, Corey et al.[5,6] reported the formation of olefins by the reactions of substituted ethylene trithiocarbonates and thionocarbonates with trialkyl phosphites. By similar reaction of 1,3-dithiole-2-thiones with phosphines and phosphites, many tetrathiafulvalene derivatives have been synthesized.[7] Thiocarbonyl compounds employed in those works were aromatic thiones,[3,7] perfluorothione,[3] and cyclic trithiocarbonates.[4-7] All these reactions could be explained to take place by initial thiophilic attack of phosphines and phosphites at the thiocarbonyl sulfur atom.

We have studied the reactions of cycloalkanethiones with trialkyl phosphites and succeeded in synthesizing new sulfur-containing phosphonic esters, [1-(alkylthio)]- and (1-mercapto)cycloalkanephosphonic esters. This reaction is obviously explained by carbophilic attack of phosphites at the thiocarbonyl carbon atom.

Results and Discussion

The reaction of cyclohexanethione (1) with 4 equiv of trimethyl phosphite in toluene at reflux temperature has been carried out. After a complete fading of the pink color of **1**, the workup of the reaction mixture gave a 51% yield of *O,O*-dimethyl [1-(methylthio)]cyclohexanephosphonate (**7a**). The



1 7a

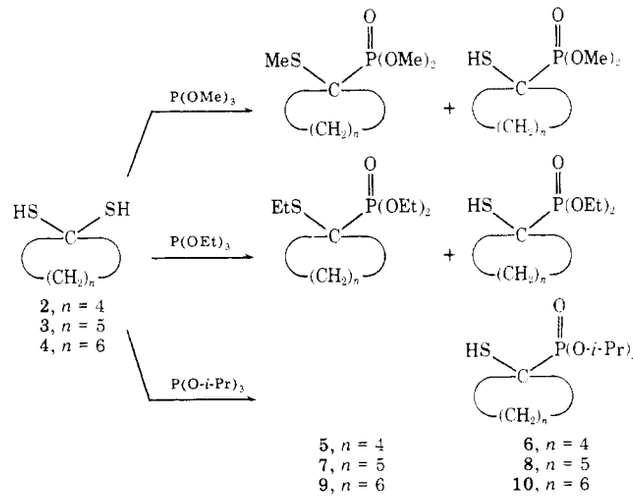
structure of **7a** was determined by the NMR and IR spectra. In the NMR spectrum of **7a**, the protons of the methyl group attaching to the sulfur atom appeared as a singlet at δ 2.20 and those attached to the oxygen atom as a doublet at δ 3.86 with J_{P-H} = 10.1 Hz. For comparison, the methyl resonances in dimethyl cyclohexanephosphonate appear as a doublet at δ 3.77 with J_{P-H} = 10.0 Hz. The infrared spectrum of **7a** revealed a strong band at 1240 cm^{-1} which is characteristic of a P=O double bond. Desulfurization of **7a** with Raney nickel in ethanol afforded dimethyl cyclohexanephosphonate, which was identical with the authentic sample.

In our preceding communication,[8] cyclohexanedithiol (**3**) was employed as a precursor of cyclohexanethione (**1**), since heating of **3** is known to afford **1** by an elimination of hydrogen sulfide. Thus, in this study *gem*-dithiols were also used in most cases as starting materials, because they are more available than cycloalkanethiones.

When a solution of cyclopentanedithiol (**2**) and 4 equiv of trimethyl phosphite in toluene was refluxed, hydrogen sulfide evolved and the color of the solution turned to pink. After the subsequent decolorization was complete, distillation gave *O,O*-dimethyl [1-(methylthio)]cyclopentanephosphonate (**5a**) in 56% yield, the formation of which was confirmed by comparing the spectral data of the product (**5a**) to those prepared from cyclopentanethione. The evolution of hydrogen sulfide and the pink coloration indicate the formation of cyclopentanethione in the reaction (Scheme I).

The reaction of **2** with triethyl phosphite gave a mixture of two sulfur-containing phosphonic esters, which were distilled

Scheme I



a, R = Me; b, R = Et; c, R = *i*-Pr

as a mixture and analyzed by gas chromatography. The second fraction was *O,O*-diethyl [1-(ethylthio)]cyclopentanephosphonate (**5b**). The structures were determined by the elemental analyses and spectral data. The NMR spectrum consisted of a quartet at δ 2.86 (2 H, J = 7.5 Hz, SCH_2CH_3), double quartets at δ 4.08 and 4.16 (4 H, J_{H-H} = 7.2 Hz, J_{P-H} = 8.5 Hz, $POCH_2CH_3$), and two triplets at δ 1.20 (3 H, J = 7.5 Hz, SCH_2CH_3) and 1.32 (6 H, J = 7.2 Hz, $POCH_2CH_3$). The infrared spectrum revealed an absorption at 1235 cm^{-1} due to a P=O double bond. These spectral features were totally consistent with the assignment of **5b.** The first fraction was *O,O*-diethyl (1-mercapto)cyclopentanephosphonate (**6b**). In the NMR spectrum of **6b,** the mercapto proton appeared as a broad singlet at δ 2.24, the methylene protons as double quartets at δ 4.11 and 4.19, and the methyl protons as a triplet at δ 1.34, respectively. The infrared spectrum of **6b** clearly exhibited an absorption at 2505 cm^{-1} assigned to the S-H stretching.

The reaction of **2** with triisopropyl phosphite gave only *O,O*-diisopropyl (1-mercapto)cyclopentanephosphonate (**6c**) in good yield (83%), but no ester having an alkylthio group. Similarly to **6b,** in the NMR spectrum the mercapto proton appeared at δ 2.28 and in the infrared spectrum a weak band at 2510 cm^{-1} assigned to the S-H stretching.

In the reactions giving mercaptophosphonic esters **6b** and **6c,** the generation of corresponding olefins was detected by a usual method.

The reaction of **3** with trialkyl phosphites was briefly reported in our preceding communication,[8] and a detailed description of the procedure and the characterization of the products were described in the Experimental Section.

The reaction of cycloheptanedithiol (**4**) with trialkyl phosphites was carried out under similar reaction conditions as mentioned above. The evolution of hydrogen sulfide and the pink coloration were also observed, and the reactions were stopped after decolorization was complete. The results are summarized in Scheme I and Table I.

As seen in Table I, the reactions proceeded rather slowly in benzene, toluene, and xylene, though the use of such solvents makes the workup of the reaction mixture easier. By addition of a small amount of ethanol to toluene, the reaction of **3** with trimethyl phosphite was accelerated to give *O,O*-dimethyl [1-(methylthio)]cyclohexanephosphonate (**7a**) together with trace of *O,O*-dimethyl (1-mercapto)cyclohexanephosphonate (**8a**). In the case of utilizing ethanol itself as a solvent, **8a** was more favorably obtained than **7a.**[18]

The mechanistic interpretation of the reactions of cycloalkanethiones (cycloalkanedithiols) with trialkyl phos-

Table I. Reaction Conditions and Yields of Products in the Reaction of Cycloalkanedithiols with Trialkyl Phosphites

Substrates (*gem*-dithiols)	Registry no.	Reactants (phosphites)	Registry no.	Reaction time, h	Solvents	Yield, % Alkylthio	Yield, % Mercapto
Cyclopentanedithiol (2)	1687-46-3	$P(OMe)_3$	121-45-9	10	Toluene	56	0
		$P(OEt)_3$	122-52-1	12	Toluene	20[a]	26[a]
		$P(O\text{-}i\text{-}Pr)_3$	116-17-6	10	Toluene	0	83
Cyclohexanedithiol (3)	3855-24-1	$P(OMe)_3$		20	Benzene	59	0
				20	Toluene	70	0
				10	Xylene	68	0
				5	Toluene (ethanol)	63	Trace
				5	Ethanol	23	39[b]
		$P(OEt)_3$		20	Toluene	20[a]	30[a]
		$P(O\text{-}i\text{-}Pr)_3$		20	Toluene	0	89
				5	Ethanol	0	85
		$P(OCr)_3$[c]	51666-84-3	20	Toluene	65	0
Cycloheptanedithiol (4)	65392-29-2	$P(OMe)_3$		48	Toluene	48	0
		$P(OEt)_3$		40	Toluene	23[a]	21[a]
		$P(O\text{-}i\text{-}Pr)_3$		48	Toluene	0	76

[a] Determined by gas chromatography. [b] 7.6% of the ethyl ester was contained. [c] Cr = $-CH_2CH{=}CHCH_3$.

phites is outlined in Scheme II. The reaction would be initiated by removal of hydrogen sulfide from cycloalkanedithiols, which might be accelerated by the action of phosphites as base. The resulting cycloalkanethiones A might immediately react with phosphites. Though trialkyl phosphites mostly behave as thiophilic reagents toward thiocarbonyl groups, in this case the phosphorus atom of phosphite seems to attack directly at the carbon atom of the thiocarbonyl group. This carbophilic attack of phosphites would form the betaine intermediate B. Addition of a small amount of polar solvent such as ethanol would stabilize the betaine intermediate B and make the reaction proceed more rapidly.

In the reaction of thiobenzophenone with trialkyl phosphites, Ogata et al.[9] suggested a reaction intermediate similar to B. The intermediate, they suggested, is not a zwitterion but a biradical, since the migration of alkylcarbonium ions in an ionic intermediate such as that of the Arbusov reaction was not observed. In our experiments, however, the intermediate should be a zwitterion type (B), because the migration of an alkyl group in an ionic intermediate occurred.

From the intermediate B the migration of the alkyl group or proton would afford the phosphonic esters containing a sulfur atom as the alkylthio or mercapto group. When phosphites were trimethyl and/or triethyl phosphites, the negatively charged sulfur atom of the betaine intermediate B would intramolecularly interact with alkyl groups from the backside and result in the formation of phosphonic esters bearing an alkylthio group. This migration is similar to that of the Arbusov reaction, in which halide anion is known to attack at the alkyl group from the backside and result in the formation of alkyl halide and phosphonic esters. However, when triethyl and/or triisopropyl phosphites were employed, these backside attacks of negatively charged sulfur would be hindered by methyl groups, and, therefore, the proton migration would take place via a concerted mechanism. In the proton migration a stepwise mechanism involving the carbonium ion also might be excluded for the following reasons: (1) in nonpolar solvents such as benzene, toluene, and xylene, the formation of the carbonium ion would unlikely take place; (2) in spite of the order of increasing stability of carbonium ions ($i\text{-}Pr^+ > Et^+ > Me^+$), the product ratios of alkylthio- to mercaptophosphonic esters decrease in this series.

In connection with the study of whether the migration took place concerted or stepwise, the reaction of **3** with tricrotyl phosphite was examined. As shown in Scheme III, the phosphite attacked at the carbon atom of the thiocarbonyl group and formed the betaine intermediate C. If the migration occurs stepwise, as the crotyl carbonium ion is known to be stable, the products must be the mercapto type phosphonic ester and/or the mixture of crotylthio and methylallylthio type esters. But, only one kind of alkylthio type phosphonic ester was obtained. In the NMR spectrum the methyl protons ap-

Scheme II

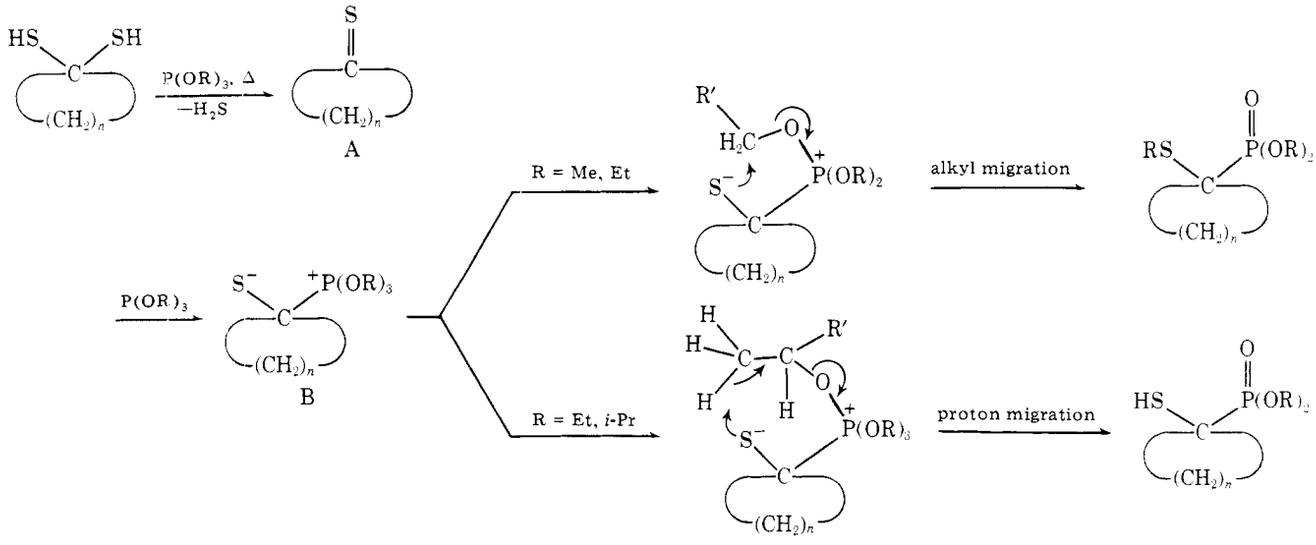
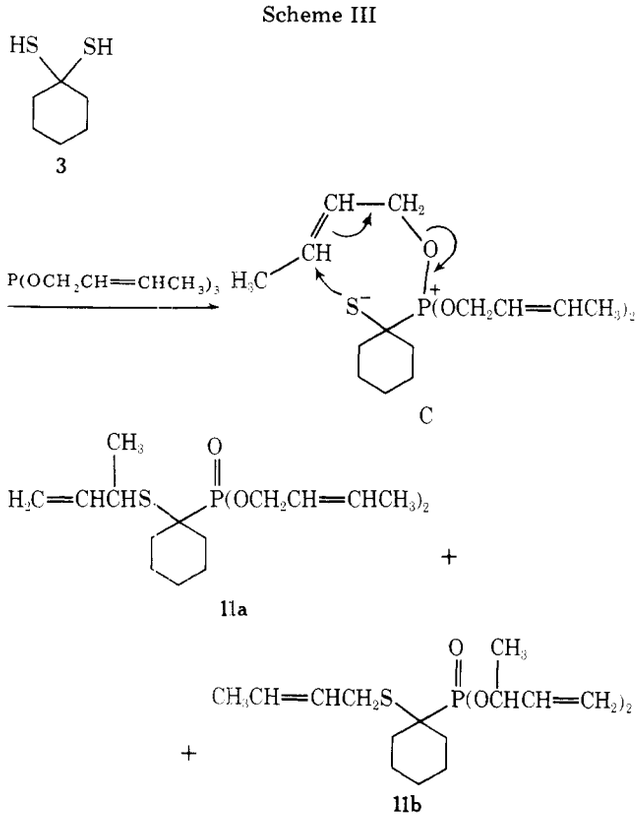


Table II. Yields of Cycloalkanephosphonic Esters by Desulfurization of [1-(Alkylthio)]- and (1-Mercapto)cycloalkanephosphonic Esters with Raney Nickel

Substrates	Registry no.	Products	Registry no.	Yield, %[a]
5a	65392-30-5	**16a**	26580-25-6	82 (46)
5b + 6b[b]	65392-31-6 (**5b**) 65392-32-7 (**6b**)	**16b**	65392-40-7	79 (37)
6c	65392-33-8	**16c**	65392-41-8	89 (74)
7a	55499-38-2	**17a**	1641-61-8	78 (55)
7b + 8b[b]	55499-40-6 (**7b**) 55499-39-3 (**8b**)	**17b**	7413-09-4	92 (46)
8c	55499-41-7	**17c**	7351-26-0	82 (73)
9a	65392-34-9	**18a**	26580-34-7	84 (41)
9b + 10b[b]	65392-35-0 (**9b**) 65392-36-1 (**10b**)	**18b**	65392-42-9	80 (33)
10c	65392-37-2	**18c**	65392-43-0	82 (63)

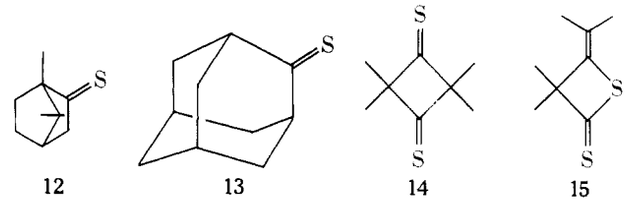
[a] Numbers in parentheses indicate the overall yield of cycloalkanephosphonic esters from *gem*-dithiols. [b] Mixtures of ethyl esters (having the ethylthio and mercapto group) were directly used.

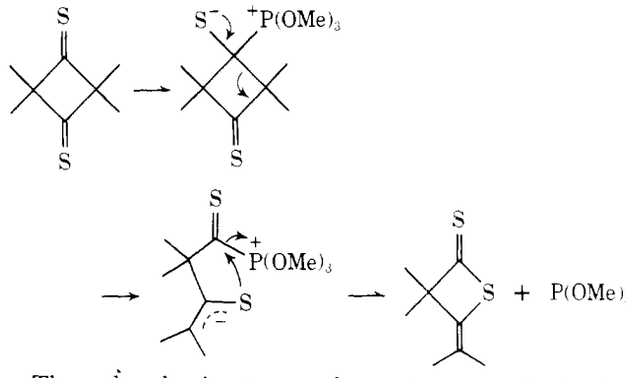
Scheme III



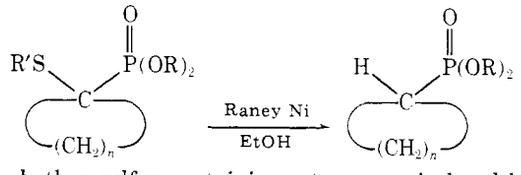
peared clearly as a doublet at δ 1.37 and the infrared spectrum revealed a characteristic band for the terminal olefin at 910 cm^{-1}, which means that the alkyl group attaching to the sulfur atom is not crotyl ($-CH_2CH{=}CHCH_3$) but methylallyl [$-CH(CH_3)CH{=}CH_2$]. Furthermore, the reaction of **3** with trimethylallyl phosphite was also examined. As expected, only one kind of alkylthio type ester was obtained. In the NMR spectrum the methylene protons appeared as a doublet at δ 3.36 (J = 7.0 Hz), which means that the alkyl group attached to the sulfur atom is not methylallyl but crotyl. Therefore, it is reasonably considered that the migration took place via a cyclic concerted mechanism. That is to say, the attack of the negatively charged sulfur atom occurred on the carbon atom of the C=C double bond, just as in the thio-Claisen rearrangement, not directly on the carbon atom adjacent to oxygen.

Though the reactions of other cycloalkanethiones such as thiocamphor (**12**), adamantanethione (**13**), and 2,2,4,4-tetramethylcyclobutane-1,3-dithione (**14**) with trimethyl phosphite were carried out, the expected reaction did not occur. In the case of the former two thiones, **12** and **13**, this is explainable by steric hindrance to attack by phosphite. The reaction of **14** gave the dithiolactone **15** quantitatively, which is different from the result of the reaction of tetramethylcyclobutanedione with trimethyl phosphite.[10] The formation of **15** from **14** is explained by the following scheme.





These phosphonic esters are the new type esters in the view of bearing sulfur as alkylthio or mercapto groups. Our sulfur-containing phosphonic esters were easily converted to cycloalkanephosphonic esters in good yields by Raney nickel desulfurization. The results are summarized in Table II. In the case of diethyl esters, the mixture of two type esters was directly used. The overall yield from *gem*-dithiols **2–4** did not



vary whether sulfur-containing esters were isolated before reduction or not. In general, the phosphonic esters have been previously prepared from alkyl halides and phosphites by the Arbusov reaction, but the yields of cycloalkanephosphonic esters are known to be low because of the side reaction (e.g., removal of hydrogen halide), especially in the use of secondary alkyl halides.[11] In our reactions, phosphonic esters were obtained in good yields as shown in Table II.

Experimental Section

The infrared spectra were recorded on a Hitachi EPI-G3 grating infrared spectrophotometer; the ^1H NMR spectra were recorded on a Varian Associates AH-100 spectrometer. The chemical shifts are given in parts per million relative to internal Me_4Si. Mass spectra were taken on a Hitachi RMU-6C mass spectrometer. Elemental analyses were carried out at the Elemental Analytical Center of Kyoto University. Gas–liquid chromatography was carried out with a Shimazu gas chromatograph Model GC-6A, using the stainless steel column packed with 20% silicone DC-550 on Celite 545.

Materials. Cyclohexanethione was prepared as described by Mayer et al.,[12] and cyclohexanedithiol and cyclopentanedithiol were prepared from 1-morpholinocyclohexene and -cyclopentene according to the literature of Djerassi and Tursch.[13] Cycloheptanedithiol was similarly prepared from 1-morpholinocycloheptene with hydrogen sulfide in 73% yield [62–63 °C (2.0 mmHg)]. Thiocamphor,[14] adamantanethione,[15] and 2,2,4,4-tetramethylcyclobutane-1,3-dithione[16] were prepared by the reported methods. Trimethyl phosphite and triethyl phosphite were commercial materials and were used after distillation. Triisopropyl and tricrotyl phosphites were prepared utilizing the procedure of Ford-Moore and Perry[17] from phosphorus trichloride and the corresponding alcohols, bp 60–61 °C (10 mmHg) and 104–105 °C (2.5 mmHg), respectively.

Reaction of Cyclohexanethione (1) with Trimethyl Phosphite. A mixture of cyclohexanethione (1.14 g) and trimethyl phosphite (5.0 g, 4 equiv) in 30 mL of toluene was heated at reflux under nitrogen overnight, producing a colorless solution. After removal of toluene and excess trimethyl phosphite, the oily residue was distilled to give 1.21 g (57%) of **7a** as a colorless liquid: bp 112–113 °C (2.5 mmHg); IR (neat) 1230 (P=O), 1180, and 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45–1.95 [m, 10 H, $-(CH_2)_5-$], 2.20 (s, 3 H, SCH_3), and 3.86 (d, 6 H, J = 10.1 Hz, $POCH_3$); MS *m/e* 238. Anal. Calcd for $C_9H_{19}O_3PS$: C, 45.37; H, 8.04; P, 13.00. Found: C, 45.08; H, 8.38; P, 13.38.

General Procedure for Reaction of the Cycloalkanedithiols 2–4 with Trialkyl Phosphites. A mixture of the 0.01 mol of the cycloalkanedithiol (**2–4**) and 0.04 mol of trialkyl phosphite in 30 mL of toluene was heated at reflux under nitrogen for 20–50 h. After removal of toluene and excess trialkyl phosphite, the residue was distilled under vacuum to give a colorless viscous liquid. In the reactions with triethyl phosphite, the distillates were [1-(ethylthio)]- and (1-mercapto)cycloalkanephosphonic esters, which were separated by gas chromatography, and yields were determined.

The boiling points, IR, ^1H NMR, and mass spectral (MS) data, and the results of elemental analyses are as follows.

***O,O*-Dimethyl [1-(methylthio)]cyclopentanephosphonate (5a):** bp 103–104 °C (4.0 mm); yield 56%; IR (neat) 1240 (P=O), 1180, and 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.47–2.26 [m, 8 H, $-(CH_2)_4-$], 2.23 (s, 3 H, SCH_3), and 3.85 (d, 6 H, J = 11 Hz, $POCH_3$); MS *m/e* 224. Anal. Calcd for $C_8H_{17}O_3PS$: C, 42.85; H, 7.64; P, 13.81. Found: C, 42.98; H, 7.84; P, 13.57.

***O,O*-Diethyl [1-(ethylthio)]cyclopentanephosphonate (5b):** bp 102–103 °C (2.5 mm) as a mixture of **5b** and **6b;** yield 20%; IR (neat) 1235 (P=O), 1162, and 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.20 (t, 3 H, J = 7.5 Hz, SCH_2CH_3), 1.32 (t, 6 H, J = 7.2 Hz, $POCH_2CH_3$), 1.5–2.2 [m, 8 H, $-(CH_2)_4-$], 2.86 (q, 2 H, J = 7.5 Hz, SCH_2CH_3), and 4.08 (dq, 4 H, J_{H-H} = 7.2 Hz, J_{P-H} = 8.5 Hz, $POCH_2CH_3$); MS *m/e* 266. Anal. Calcd for $C_{11}H_{23}O_3PS$: C, 49.61; H, 8.70; P, 11.63. Found: C, 49.36; H, 8.99; P, 11.83.

***O,O*-Diethyl (1-mercapto)cyclopentanephosphonate (6b):** yield 26%; IR (neat) 2505 (SH), 1235 (P=O), 1160, and 1030 cm^{-1}; ^1H NMR (CCl_4) δ 1.34 (t, 6 H, J = 7.1 Hz, $POCH_2CH_3$), 1.5–2.3 [m, 8 H, $-(CH_2)_4-$], 2.24 (br s, 1 H, SH), and 4.11 and 4.19 (dq, 4 H, J_{H-H} = 7.1 Hz, J_{P-H} = 8.5 Hz, $POCH_2CH_3$); MS *m/e* 238. Anal. Calcd for $C_9H_{19}O_3PS$: C, 45.36; H, 8.04; P, 13.00. Found: C, 45.36; H, 7.96; P, 13.04.

***O,O*-Diisopropyl (1-mercapto)cyclopentanephosphonate (6c):** bp 107–109 °C (3.2 mm); yield 83%; IR (neat) 2510 (SH), 1245 (P=O), and 980 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 [d, 12 H, J = 6.5 Hz, $POCH(CH_3)_2$], 1.55–2.20 [m, 8 H, $-(CH_2)_4-$], 2.28 (s, 1 H, SH), and 4.78 and 4.86 [dsep, 2 H, J_{H-H} = 6.5 Hz, J_{P-H} = 8 Hz, $POCH(CH_3)_2$]; MS *m/e* 266. Anal. Calcd for $C_{11}H_{23}O_3PS$: C, 49.61; H, 8.70; P, 11.63. Found: C, 49.30; H, 8.54; P, 11.91.

***O,O*-Dimethyl [1-(methylthio)]cyclohexanephosphonate (7a):** bp 102–104 °C (1.5 mm); yield 70%. All spectral and elemental data were identical with those of the product of the reaction of cyclohexanethione with trimethyl phosphite.

***O,O*-Diethyl [1-(ethylthio)]cyclohexanephosphonate (7b):** bp 114–115 °C (2.3 mm) as a mixture of **7b** and **8b;** yield 20%; IR (neat) 1240 (P=O), 1165, and 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (t, 3 H, J = 7.5 Hz, SCH_2CH_3), 1.35 (t, 6 H, J = 7.0 Hz, $POCH_2CH_3$), 1.45–1.98 [m, 10 H, $-(CH_2)_5-$], 2.78 (q, 2 H, J = 7.5 Hz, SCH_2CH_3), and 4.15 and 4.23 (dq, 4 H, J_{H-H} = 7.0 Hz, J_{P-H} = 8 Hz, $POCH_2CH_3$); MS *m/e* 280. Anal. Calcd for $C_{12}H_{25}O_3PS$: C, 51.41; H, 8.99; P, 11.05. Found: C, 51.01; H, 8.82; P, 11.39.

***O,O*-Diethyl (1-mercapto)cyclohexanephosphonate (9b):** yield 30%; IR (neat) 2500 (SH), 1245 (P=O), 1165, and 1025 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (t, 6 H, J = 7.0 Hz, $POCH_2CH_3$), 1.5–1.93 [m, 10 H, $-(CH_2)_5-$], 1.93 (s, 1 H, SH), and 4.18 and 4.26 (dq, 4 H, J_{H-H} = 7.0 Hz, J_{P-H} = 8.0 Hz, $POCH_2CH_3$); MS *m/e* 251. Anal. Calcd for $C_{10}H_{21}O_3PS$: C, 47.60; H, 8.39; P, 12.28. Found: C, 47.71; H, 8.64; P, 12.47.

***O,O*-Diisopropyl (1-mercapto)cyclohexanephosphonate (8c):** bp 114–115 °C (2.5 mm); yield 89%; IR (neat) 2500 (SH), 1245 (P=O), and 990 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 [d, 12 H, J = 7 Hz, $POCH(CH_3)_2$], 1.46–1.90 [m, 10 H, $-(CH_2)_5-$], 1.91 (s, 1 H, SH), and 4.67 and 4.73 [dsep, 2 H, J_{H-H} = 7 Hz, J_{P-H} = 7.5 Hz, $POCH(CH_3)_2$]; MS *m/e* 280. Anal. Calcd for $C_{12}H_{25}O_3PS$: C, 51.41; H, 8.98; P, 11.05. Found: C, 51.56; H, 9.23; P, 11.16.

***O,O*-Dicrotyl [1-(methylallylthio)]cyclohexanephosphonate (11a):** bp 149–150 °C (4.0 mm); yield 65%; IR (neat) 3080, 3015, 1675, 1630, 1245 (P=O), and 910 cm^{-1} (terminal vinyl); ^1H NMR (CCl_4) δ 1.37 [d, 3 H, J = 7.5 Hz, $SCH(CH_3)CH=CH_2$], 1.41–2.25 [m, 16 H, $-(CH_2)_5-$ and $OCH_2CH=CHCH_3$], 4.05–4.81 [m, 5 H, $OCH_2CH=CHCH_3$ and $SCH(CH_3)CH=CH_2$], 4.83–5.21 [m, 2 H, $SCH(CH_3)CH=CH_2$], 5.51–5.85 [m, 5 H, $OCH_2CH=CHCH_3$ and $SCH(CH_3)CH=CH_2$]; MS *m/e* 385. Anal. Calcd for $C_{18}H_{31}O_3PS$: C, 60.30; H, 8.71; P, 8.64. Found: C, 60.19; H, 8.85; P, 8.71.

***O,O*-Dimethylallyl [1-(crotylthio)]cyclohexanephosphonate (11b):** bp 110–111 °C (0.5 mm); yield 58%; IR (neat) 3080, 3013, 1670, 1630, 1240 (P=O), and 910 cm^{-1}; ^1H NMR (CCl_4) δ 1.38 [d, 6 H, J = 7.4 Hz, $OCH(CH_3)CH=CH_2$], 1.45–2.08 [m, 13 H, $-(CH_2)_5-$ and $SCH_2CH=CHCH_3$], 3.36 (d, 2 H, J = 7.0 Hz, $SCH_2CH=CHCH_3$), 4.15–4.67 [m, 2 H, $OCH(CH_3)CH=CH_2$], 4.57–6.23 [m, 8 H, $OCH(CH_3)CH=CH_2$ and $SCH_2CH=CHCH_3$]; MS *m/e* 385. Anal. Calcd for $C_{18}H_{31}O_3PS$: C, 60.30; H, 8.71; P, 8.64. Found: C, 60.47; H, 8.93; P, 8.50.

***O,O*-Dimethyl [1-(methylthio)]cycloheptanephosphonate (9a):** bp 126–128 °C (2.0 mm); yield 48%; IR (neat) 1240 (P=O), 1180, and 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45–1.85 [m, 12 H, $-(CH_2)_6-$], 2.21 (s, 3 H, SCH_3), and 3.81 (d, 6 H, J = 10.0 Hz); MS *m/e* 252. Anal. Calcd for $C_{10}H_{21}O_3PS$: C, 47.60; H, 8.39; P, 12.28. Found: C, 47.83; H, 8.54; P, 11.98.

***O,O*-Diethyl [1-(ethylthio)]cycloheptanephosphonate (9b):** bp 132–134 °C (2.5 mm) as a mixture of **9b** and **10b;** yield 23%; IR (neat) 1235 (P=O), 1160, and 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.24 (t, 3 H, J = 7.5 Hz, SCH_2CH_3), 1.32 (t, 6 H, J = 7.0 Hz, $POCH_2CH_3$), 1.45–1.93 [m, 12 H, $-(CH_2)_6-$], 2.78 (q, 2 H, J = 7.5 Hz, SCH_2CH_3), and 4.11 and 4.19 (dq, 4 H, J_{H-H} = 7.0 Hz, J_{P-H} = 8.0 Hz, $POCH_2CH_3$); MS *m/e* 294. Anal. Calcd for $C_{13}H_{27}O_3PS$: C, 53.04; H, 9.24; P, 10.52. Found: C, 52.75; H, 9.48; P, 10.73.

***O,O*-Diethyl (1-mercapto)cycloheptanephosphonate (10b):** yield 21%; IR (neat) 2505 (SH), 1245 (P=O), 1160, and 1038 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (t, 6 H, J = 7.0 Hz, $POCH_2CH_3$), 1.50–1.95 [m, 12 H, $-(CH_2)_6-$], 2.25 (s, 1 H, SH), and 4.19 and 4.27 (dq, 4 H, J_{H-H} = 7.0 Hz, J_{P-H} = 8.0 Hz, $POCH_2CH_3$); MS *m/e* 266. Anal. Calcd for $C_{11}H_{23}O_3PS$: C, 49.61; H, 8.70; P, 11.63. Found: C, 49.89; H, 8.96; P, 11.52.

***O,O*-Diisopropyl (1-mercapto)cycloheptanephosphonate (10c):** bp 141–142 °C (2.9 mm); yield 76%; IR (neat) 2500 (SH), 1240 (P=O), and 990 cm^{-1}; ^1H NMR (CCl_4) δ 1.32 [d, 12 H, J = 6.5 Hz, $POCH(CH_3)_2$], 1.42–2.20 [m, 12 H, $-(CH_2)_6-$], 2.11 (s, 1 H, SH), and 4.69 and 4.76 [dsep, 2 H, J_{H-H} = 6.5 Hz, J_{P-H} = 7.5 Hz, $POCH(CH_3)_2$]; MS *m/e* 294. Anal. Calcd for $C_{13}H_{27}O_3PS$: C, 53.04; H, 9.24; P, 10.52. Found: C, 53.32; H, 9.42; P, 10.61.

Reaction of Cyclohexanedithiol (3) with Trimethyl Phosphite in Ethanol. A mixture of **3** (1.48 g) and trimethyl phosphite (5.0 g) in 20 mL of ethanol was heated at reflux under nitrogen for 5 h. After concentration, the residue was distilled to afford 1.4 g of a mixture of **7a** and **8a,** which was separated by gas chromatography, and yields were determined. The yield of **7a** was 23%, and all spectral data were identical with **7a.**

***O,O*-Dimethyl (1-mercapto)cyclohexanephosphonate (8a):** mp 31–32 °C; yield 39%; IR (neat) 2510 (SH), 1230 (P=O), 1180, and 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43–1.98 [m, 10 H, $-(CH_2)_5-$], 1.93 (s, 1 H, SH), and 3.85 (d, 6 H, J = 10.0 Hz, $POCH_3$); MS *m/e* 224. Anal. Calcd for $C_8H_{17}O_3PS$: C, 42.85; H, 7.64; P, 13.81. Found: C, 42.83; H, 7.66; P, 13.68.

Reaction of 2,2,4,4-Tetramethylcyclobutane-1,3-dithione with Trimethyl Phosphite. A mixture of **14** (1.37 g) and 4 equiv of tri-

methyl phosphite in 20 mL of toluene was heated at reflux under nitrogen for 3 h. After concentration, the residue was chromatographed on silica with the elution of benzene to give 1.35 g of orange liquid, whose spectral data were all identical with the authentic sample **15**.[13]

Reduction by Raney Nickel. To a suspended solution of 10–15 g of Raney nickel (W-2 type) in 50 mL of ethanol was added a solution containing phosphonic esters **5–10** (1.5–2.0 g in 5 mL of ethanol). The reaction mixture was heated at reflux for 20 h. After filtration of nickel, the filtrate was concentrated and the residue was distilled to afford cycloalkanephosphonic esters **16–18**. The yields were summarized in Table II.

Registry No.—**1**, 2720-41-4; **8a**, 65392-38-3; **11a**, 55499-42-8; **11b**, 65392-39-4; **14**, 10181-56-3; **15**, 10181-61-0; 1-morpholinocycloheptene, 7182-08-3.

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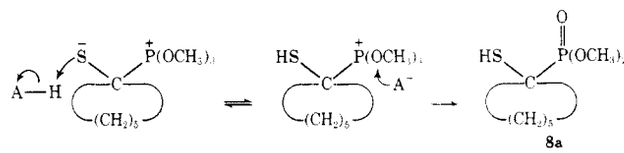
(18) When the other solvents having an active hydrogen were used in the reaction of cyclohexanedithiol with trimethyl phosphite, **8a** was also obtained in considerable yields [**7a**, 33.3%, and **8a**, 50.3% (isobutyl alcohol); **7a**, 36.8%, and **8a**, 33.8% (acetonitrile); **7a**, 29.4%, and **8a**, 35.6% (propionitrile)]. The favorable formation of **8a** might possibly be explained by the following reaction scheme.



Facile and Selective Chlorination–Cleavage of Some Cyclanones and Cyclanols with the CCl_4–KOH–*t*-BuOH Reagent. In Situ Conversion of Estrones and Estradiols into Dichlorodoisynolic Acids[1a]

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Studies of the reactions of ketones and alcohols with CCl_4–KOH–*t*-BuOH have been extended to include cyclanones and cyclanols represented by a series of estrogens. With this reagent estrone (**1**) and estrone 3-methyl ether (**4**) were rapidly and selectively converted into the corresponding 16,16-dichlorodoisynolic acids (**3**, **6**). The in situ reaction pathway consists of D-ring *gem*-α-dichlorination followed by ring cleavage. Similar treatment of estradiol (**2**) and estradiol 3-methyl ether (**5**) also provided these respective products, but at much slower rates because the initial slow oxidation step is rate determining. However, because this step involves a free-radical chain mechanism initiated by dioxygen, the conversion of **5** was greatly accelerated when contact with air was unrestricted. Reaction of **2** could not be accelerated this way because its phenolic moiety functions as a built-in inhibitor of this oxidation process.

In the course of our recent investigations of the reactions of ketones and alcohols with CCl_4-powdered KOH–*t*-BuOH, the use of estrones and estradiols as substrates was considered a valuable excursion because they represent a common class of cyclanones and cyclanols, respectively (Scheme I). It was already recognized that ketones possessing α-H's are easily α chlorinated with this reagent; rapid subsequent reactions, however, generally lead to the formation of a variety of products.[2-6] While ketones whose carbonyl function is sterically hindered, e.g., mesityl alkyl ketones, are still quite easily converted into α-chlorinated ketones, the latter do not undergo further reaction.[7] Secondary alcohols are initially oxidized with this reagent into ketones which, as already indicated, are α chlorinated in this medium.[2,5,6,8] Sterically hindered alcohols, e.g., neopentyl alcohol and di-*tert*-butylcarbinol, react slowly or not at all with this reagent at moderate temperatures.[2,6,8]

Results

Estrone (**1**) and estrone 3-methyl ether (**4**) are ketones whose carbonyl is hindered from attack mainly on one face. This degree of steric hindrance in **1** and **4** prevented neither the formation nor subsequent reaction of their α-chlorinated derivatives. Thus, both ketones underwent facile conversion with CCl_4–KOH–*t*-BuOH at 25 °C into the *gem*-α-dichloro ketones (**1a**, **4a**) which, however, could not be detected per se because they were rapidly cleaved into 16,16-dichlorodoisynolic acid (**3**) and 16,16-dichlorodoisynolic acid 3-methyl ether (**6**), respectively. Neither product has previously been reported. Within 1 h at room temperature **4** was converted into **6** in 75–80% yield; the white crystalline product, mp 157–158 °C, was analytically pure. The phenolic ketone **1**, similarly treated for 1.5 h, was converted into **3** in yields estimated to be at least 90%; however, the crystalline product, mp 155–157 °C, in this case was contaminated with material suspected to

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