Synthesis of O,O-Dimethyl S-(1,2-Dicarbethoxy)ethyl Phosphorothioate (Maloxon) and Related Compounds from Trialkyl Phosphites and Organic Disulfides

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Bis(carbalkoxyalkyl) disulfides are cleaved by trialkyl phosphites to give O,O-dialkyl S-carbethoxymethyl, S-2-carbethoxyethyl, and S-(1,2-dicarbalkoxy)ethyl phosphorothioates. S-Alkyl carbalkoxyalkyl sulfides are obtained as coproducts. The reaction is shown to proceed more readily than the corresponding reaction with unsubstituted alkyl disulfides. The reactivities of the disulfides are apparently related to the pK_a values of the parent mercaptans.

O,O-Dimethyl S-(1,2-dicarbethoxy)ethyl phosphorothioate (II), the oxo analog[1] of the well-known insecticide, malathion (I), has been demonstrated to occur among the metabolic products of malathion in both the cockroach and the mouse.[2] Its synthesis was first accomplished by Johnson[3] by oxidation of malathion with nitric acid. The reaction was difficult to control and variations in product quality were encountered.

$$\underset{\text{I}}{(CH_3O)_2P(S)SCH(CO_2Et)CH_2CO_2Et} \xrightarrow{HNO_3} \underset{\text{II}}{(CH_3O)_2P(O)SCH(CO_2Et)CH_2CO_2Et} \quad (1)$$

Reactions of O,O-dimethyl phosphorothioate salts with esters of bromosuccinic and chloroacetic acids have been used to prepare authentic samples of phosphorothioates II and V of Table I.[4] The yields in these reactions (30–40%) were lower than might have been expected from the literature.[5] Low yields by such routes may arise from the following side reaction.[6]

$$\underset{\text{III}}{(CH_3O)_2POS^-} + \text{II} \longrightarrow (CH_3O)_2P(O)SCH_3 + \underset{CH_3O}{\overset{-O}{\diagdown}}\!\!>P(O)SCH(CO_2Et)CH_2CO_2Et \quad (2)$$

$$\underset{\text{IV}}{}$$

Because these previous routes were unsatisfactory, the method of Morrison[7] for the reaction of trialkyl phosphites with sulfenyl chlorides was investigated for the preparation of maloxon. In the reaction of trimethyl phosphite with 1,2-dicarbethoxyethylsulfenyl chloride, quantitative conversion of the sulfenyl chloride occurred in toluene solution at −30° on slow addition of the phosphite. The by-product, methyl chloride, escaped on warming to room temperature, and the phosphorothioate was subsequently distilled. However, the product was contaminated with chlorinated by-products. Subsequently, the work of Jacobson, Harvey, and Jensen[8a] on the splitting of ethyl disulfide with triethyl phosphite led to consideration of the following reaction with bis(carbalkoxyalkyl) disulfides as a method for preparation of maloxon and related compounds.

$$(RO)_3P + R'SSR' \longrightarrow [(RO)_3\overset{+}{P}SR'\ RS^-] \longrightarrow RSR' + (RO)_2P(O)SR' \quad (3)$$

R and R′ = radicals shown in Table I

It was recognized that, because of the instability of maloxon at the high temperatures which Jensen, *et al.*, had employed, reduced temperatures would have to be investigated. However, the literature suggested that lower temperatures would not yield the desired product. The reactions of trialkyl phosphites with unsubstituted alkyl disulfides have been explored[8,9] and mechanisms have been proposed for the formation of the observed products. The reactions may be formulated as in eq. 3 and 4. Reaction 3 (R = C_2H_5) is an ionic reaction

$$(RO)_3P + R'SSR' \longrightarrow (RO)_3P(S) + R'SR' \quad (4)$$

$$\downarrow$$

$$(RO)_2P(O)SR \quad (5)$$

which has been observed at temperatures of 140°[8] and higher.[9] Reaction 4 (R = C_2H_5) is a radical reaction observable at temperatures as low as 60° in the presence of dialkyl peroxide catalysts and light and produces a phosphorothionate.[9] When R is CH_3 (see Experimental section), this reaction is observable in the absence of added catalysts at temperatures below 100°. The isomerization of trimethyl phosphorothionate,[10] known to occur at appreciable rates above 130°,[9,10] did not seem likely to interfere at the temperatures employed in our study.

The reaction of trialkyl phosphites with bis(carbalkoxyalkyl) disulfides in the absence of solvent was found to proceed exothermally when initiated at steam-bath temperature. The ease with which this reaction proceeds was surprising in view of the results with alkyl disulfides.[8] Careful fractionation of the product gave a 90% yield of maloxon (II). In simi-

(1) The compound has been referred to in the literature as malaoxon or maloxon by various investigators to recall its relationship to malathion.

(2) R. D. O'Brien, *J. Econ. Entomol.*, **50**, 159 (1957).

(3) G. A. Johnson, U. S. Patent 2,713,018 (1953); *Chem. Abstr.*, **50**, 2113*h* (1956).

(4) Unpublished results of Mrs. S. DuBreuil Curry and Dr. G. Berkelhammer of this laboratory.

(5) G. Schrader [German Patent 942,988 (1956); *Chem. Abstr.* **50**, 16825*h* (1956)] reports the formation of O,O-diethyl S-(1,2-dicarbethoxy)ethyl phosphorothioate (VIII) in 83% yield from ammonium diethyl phosphorothioate and diethyl bromosuccinate.

(6) G. Berkelhammer, S. DuBreuil, and R. W. Young [*J. Org. Chem.*, **26**, 2281 (1961)] describe an analogous reaction.

(7) D. C. Morrison, *J. Am. Chem. Soc.*, **77**, 181 (1955).

(8) (a) H. I. Jacobson, R. G. Harvey, and E. V. Jensen, *ibid.*, **77**, 6064 (1955); (b) R. G. Harvey, H. I. Jacobson, and E. V. Jensen, 139th National Meeting of the American Chemical Society, St. Louis, Mo., March 1961, Abstract, p. 44-O; (c) R. G. Harvey, H. I. Jacobson, and E. V. Jensen, *J. Am. Chem. Soc.*, **85**, 1618 (1963).

(9) C. Walling and R. Rabinowitz, *ibid.*, **81**, 1243 (1959).

(10) G. Hilgetag, G. Schramm, and H. Teichmann, *J. prakt. Chem.*, **8**, 73 (1959).

TABLE I

O,O-DIALKYL S-CARBALKOXYALKYL PHOSPHOROTHIOATES

$(RO)_2P(O)SR'$

No.	R	R'	Yield, %	B.p., °C. (mm.)	$n^{25}D$	Formula	Calcd., % C	H	P	S	Found, % C	H	P	S
V	Me	CH_2CO_2Et	48.5	97–103 (0.07)	1.4645	$C_6H_{13}O_5PS$	31.58	5.74	13.57	14.51	31.25	5.68	13.56	13.97
VI	Me	$CH_2CH_2CO_2Et$	45.4	108–113 (0.07)	1.4770	$C_7H_{15}O_5PS$	34.71	6.24	12.79	13.26	*a*			
VII	Me	$CH(CO_2Me)CH_2CO_2Me$	79.0	126–132 (0.12)	1.4690	$C_8H_{15}O_7PS$	33.57	5.28	10.82	11.20	33.86	5.41	11.07	11.03
II	Me	$CH(CO_2Et)CH_2CO_2Et$	89.3	132 (0.10)	1.4666	$C_{10}H_{19}O_7PS$	38.21	6.09	9.86	10.20	38.37	6.23	9.87	10.30
VIII	Et	$CH(CO_2Et)CH_2CO_2Et$	74.0	133–137 (0.15)		$C_{12}H_{23}O_7PS$	42.10	6.77	9.05	9.37	*b*			

[a] Analytically pure samples of the major primary products, VI and X (Table II), claimed in this reaction were not obtained (see Experimental section). [b] Lit.[5] b.p. 114–115° (0.02 mm.)

TABLE II

ALKYL CARBALKOXYALKYL SULFIDES

RSR'

No.	R	R'	Yield, %	B.p., °C. (mm.)	$n^{25}D$	Formula	Calcd., % C	H	S	Found, % C	H	S	Ref.
IX	Me	CH_2CO_2Et	96.0	75–80 (21)	1.4542	$C_5H_{10}O_2S$	44.74	7.51	23.89				*a, b*
X	Me	$CH_2CH_2CO_2Et$	21.6	77–89 (13)	1.4560	$C_6H_{12}O_2S$	48.62	8.16	21.63				*c, d*
XI	Me	$CH(CO_2Me)CH_2CO_2Me$	80.0	63–65 (0.08)	1.4664	$C_7H_{12}O_4S$	43.74	6.29	16.68	43.62	6.35	16.28	
XII	Me	$CH(CO_2Et)CH_2CO_2Et$	80.5	77–88 (0.30)	1.4586	$C_9H_{16}O_4S$	49.07	7.32	14.57	48.87	7.06	14.50	
XIII	Et	$CH(CO_2Et)CH_2CO_2Et$	76.0	92–94 (0.70)	1.4577	$C_{10}H_{18}O_4S$	51.26	7.74	13.68	51.36	7.76	13.47	*e*

[a] T. Yamanishi, Y. Obata, and M. Sano [*J. Agr. Chem. Soc. Japan*, **26**, 660 (1952); *Chem. Abstr.*, **49**, 2301*a* (1955)] give b.p. 62° (13 mm.). [b] M. Protiva, *et al.*, *Cesk. farm.*, **6**, 425 (1957); *Chem. Abstr.*, **52**, 9944*h* (1958). [c] Lit.[b] b.p. 57° (8 mm.). [d] J. L. Szabo and E. T. Stiller [*J. Am. Chem. Soc.*, **70**, 3667 (1948)] give b.p. 88° (18 mm.). [e] Fitger (Dissertation, University of Lund, 1924, p. 44) and F. K. Beilstein ("Handbuch der Organischen Chemie," Vol. III, 3rd Ed., 1942, p. 288) give b.p. 145° (15 mm.).

lar fashion there were obtained 50–90% yields of other phosphorothiolates (V–VIII) with the properties given in Table I, and yields of 76–96% of alkyl sulfide by-products (IX–XIII, Table II). These represent the first instances of phosphorothioates formed from dialkyl disulfides at temperatures below 115°. The reactions of trimethyl phosphite with diethyl dithiodiacetate and diethyl 3,3'-dithiodipropionate were studied in order to determine the relative effects of α- and β-carbalkoxy groups on reactivities of disulfides. In the case of diethyl dithiodiacetate, reaction is quite vigorous at 82 and 112°, requiring the use of solvents (benzene and toluene, respectively) to control the temperature. With diethyl 3,3'-dithiodipropionate, reaction was much less vigorous even without solvent. Decomposition of the product became evident after 28 hr. at 110–112°.

The relative reaction rates with trimethyl phosphite of the bis(1,2-dicarbalkoxy)ethyl disulfides, judged by observations of the rates of rise in temperature, appear to lie between the rates for diethyl dithiodiacetate and diethyl 3,3'-dithiodipropionate. It is most noteworthy that in all cases the principal products were phosphorothiolates.

Discussion

The reactivities of disulfides toward trialkyl phosphites, as noted above, appear to be related inversely to the pK_a values of the parent mercaptans (Table III).

TABLE III

pK_a OF MERCAPTO COMPOUNDS AND MERCAPTO ESTERS

Compd.[a]	Structure	pK_a	Ref.
Thiophenol	PhSH	7.78	*b*
		6.52	*c*
Methyl mercaptoacetate	$MeOCOCH_2SH$	7.68	*b*
Ethyl mercaptoacetate	$EtOCOCH_2SH$	7.96, 7.93	*c*
Ethyl mercaptan	EtSH	10.50	*b*
		10.9	*c*
n-Butyl mercaptan	*n*-BuSH	10.66	*c*

[a] The pK_a values of ethyl 3-mercaptopropionate and of dimethyl and diethyl mercaptosuccinate are not reported in the literature. [b] J. P. Danehy and C. J. Noel, *J. Am. Chem. Soc.*, **82**, 2511 (1960). [c] M. M. Kreevoy, E. T. Harper, R. E. Duvall, H. S. Wilgus, III, and L. T. Ditsch, *ibid.*, **82**, 4899 (1960).

This dependence supports the ionic mechanism proposed by Jacobson, *et al.*[8] (eq. 3). Our observations indicate that diethyl dithiodiacetate approaches phenyl disulfide in reactivity and gives only the thiol ester and no thionophosphate. Tetraethyl dithiodisuccinate and diethyl 3,3'-dithiodipropionate, on the other hand, are somewhat less reactive and traces of thionophosphate have been detected by gas–liquid chomatography (g.l.c.) in the reaction products.[11] A radical mechan-

(11) C. G. Moore and B. R. Trego [*J. Chem. Soc.*, 4205 (1962)] have reported reaction of trialkyl phosphite with alkenyl disulfides to proceed slowly at 80° with the formation of triethyl phosphorothionate and allylically rearranged monosulfides. The mechanism appears to differ from the radical chain reaction and to involve the allyl group in a special way. It thus differs from both the free-radical and ionic reactions observed for other dialkyl disulfides.

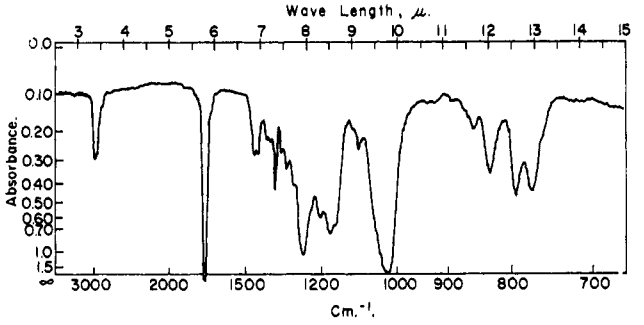

Figure 1.—Infrared spectrum of maloxon; sodium chloride cell, 0.005 mm. thick.

ism, such as that used to explain the alkyl disulfide reactions with trialkyl phosphites,[9,12] may make a small contribution to the over-all reaction of the less reactive disulfides.

Maloxon prepared by the Johnson process,[3] as reported by O'Brien,[2] showed extraneous absorptions in its infrared spectrum at 1570 and 1625 cm.$^{-1}$ characteristic of nitration products. It also failed to show the distinctive absorption at 1260 cm.$^{-1}$ due to P=O. The phosphorothioates described in this paper all show the latter band. Maloxon (Figure 1) and all the compounds possessing the $(MeO)_2P(O)S$– structure are distinguished from the corresponding $(MeO)_2P(S)S$– compounds, *e.g.*, malathion, by narrow bands at 770 and 795 cm.$^{-1}$ and by the narrowness of the bands at 830 and 860 cm.$^{-1}$.

Experimental

Materials.—Reagents and solvents were commercial products used without purification unless specifically mentioned. Trimethyl and triethyl phosphites, obtained from the Virginia Carolina Corp., were usually redistilled before use. Trimethyl phosphite for the large-scale preparation of II was treated with metallic sodium for the removal of acidic contaminants before distillation. Ethyl and *n*-butyl disulfides, ethyl mercaptoacetate, and β-mercaptopropionic acid were Eastman Kodak Co. products. Thiomalic acid from four sources was used: Evans Chemetics, Eastman, National Aniline Division of Allied Chemical Corp., and the acid hydrolysis of a sample of O,O-diethyl dithiophosphatosuccinic anhydride.[13] Diethyl dithiodiacetate[14] was obtained in 60% yield, b.p. 112–116° (0.3 mm.), $n^{25}D$ 1.4950,[15] by oxidation of ethyl mercaptoacetate with an alcoholic solution of iodine in the presence of potassium acetate buffer.

Diethyl 3,3′-Dithiodipropionate.—β-Mercaptopropionic acid was oxidized in 92% yield to 3,3′-dithiodipropionic acid, m.p 155–157°, with ferric chloride by the procedure of Westerman and Rose.[16] The dithio acid was converted to the diethyl ester[17] in 60% yield, b.p. 124–131° (0.05 mm.), $n^{27}D$ 1.4912, by the usual esterification procedures[18] using either sulfuric acid or hydrogen chloride.

Anal. Calcd. for $C_{10}H_{18}O_4S_2$: C, 45.09; H, 6.81; S, 24.07. Found: C, 45.01; H, 7.32; S, 24.02.

Dimethyl Mercaptosuccinate.—Thiomalic acid was esterified by the method of Barry, *et al.*,[19] in 40% yield, b.p. 80–85° (0.65 mm.), $n^{26}D$ 1.4672.

Anal. Calcd. for $C_6H_{10}O_4S$: C, 40.44; H, 5.66; S, 17.99. Found: C, 41.32; H, 5.95; S, 17.66.

Diethyl mercaptosuccinate[19] was similarly prepared in 88% yield, b.p. 108–110.5° (3 mm.),[20] $n^{25}D$ 1.4571.

Tetramethyl dithiodisuccinate was prepared by iodine oxidation of dimethyl mercaptosuccinate in 92% yield, $n^{25}D$ 1.4998.

Anal. Calcd. for $C_{12}H_{18}O_8S_2$: C, 40.67; H, 5.12; S, 18.10. Found: C, 41.12; H, 5.57; S, 17.60.

Tetraethyl dithiodisuccinate was prepared by oxidation of diethyl mercaptosuccinate both by alcoholic iodine with potassium acetate buffer, yield 96.5%, $n^{25}D$ 1.4822, d^{25} 1.183; and by aqueous iodine and potassium iodide, yield 96.2%, $n^{25}D$ 1.4824.

Anal. Calcd. for $C_{16}H_{26}O_8S_2$: C, 46.81; H, 6.38; S, 15.62. Found: C, 47.15; H, 6.02; S, 15.85.

A small sample was distilled at 198–204° (1.2 mm.).

1,2-Dicarbethoxy Ethyl Sulfenyl Chloride.—Sulfenyl chlorides were prepared by procedures adapted from Brintzinger, *et al.*[21] Sulfuryl chloride, 30.2 g. (0.22 mole), in 30 ml. of benzene was added during 15 min. to a stirred solution of 41.2 g. (0.2 mole) of diethyl mercaptosuccinate in 160 ml. of benzene. Gas was evolved and the temperature rose to 37°. The solution was stirred and heated at 50–58° for 2 hr. with steady evoluton of gas and was allowed to stand overnight. Removal of solvent and volatile materials by distillation to a final pot temperature of 60° (0.7 mm.) left 46 g. of deep golden yellow oil which was calculated to contain 70.2% of the desired sulfenyl chloride on the basis of analysis for Cl. Distillation of a 5-g. sample of the product gave 2.7 g. (44.7%), b.p. 101–104° (0.9 mm.), $n^{25}D$ 1.4760.

Anal. Calcd. for $C_8H_{13}ClO_4S$: Cl, 14.73; S, 13.32. Found: Cl, 14.76; S, 13.41.

The residue from distillation, 2.86 g., $n^{25}D$ 1.4885, was believed to be largely tetraethyl dithiodisuccinate. Reaction of this material with sulfuryl chloride was also used to produce the sulfenyl chloride.

O,O-Dimethyl S-(1,2-Dicarbethoxy)ethyl Phosphorothioate (II). A.—Tetraethyl dithiodisuccinate, 631 g. (1.535 moles), was stirred and warmed on the steam bath to 90°. No special precautions were taken to exclude light. Trimethyl phosphite, 229 g. (1.862 moles), warmed to about 60°, was added rapidly. A mildly exothermic reaction occurred which was controlled between 100–115° by occasional cooling during the first 40 min. of a 191-min. reaction period. The final temperature was 96° and the material was allowed to cool and to stand overnight. Sampling at intervals for observations by infrared spectra showed that reaction was substantially complete at 2 hr. (observations of increases in absorptions at 770, 795, 830, and 1260 cm.$^{-1}$, and of decreases in those at 730, 750, and 2800 cm.$^{-1}$).

A similar preparation, from 41.0 g. (0.10 mole) of the disulfide and 24.4 g. (0.2 mole) of the phosphite, was made and the material was combined with that above for isolation of the products.

Volatile materials were removed by distillation on the steam bath to a final pressure of 0.35 mm. at 95°. The reaction products were then resolved into two major components by a series of distillations using an Asco Rota-Film molecular still at a pressure of 1 μ with a Thermocap Relay to control the jacket temperature. The more volatile component, S-methyl diethylthiomalate, 291 g., was recovered at 65–70°. Redistillation through a vacuum-jacketed Vigreux column gave a main cut of 195 g. with the properties and analysis given in Table II.

The less volatile component, O,O-dimethyl S-(1,2-dicarbethoxy)ethyl phosphorothioate, 459 g., was obtained at 100°. Yield, physical properties, and analysis are given in Table I.

The other phosphorothioates and alkylmercapto compounds listed in Tables I and II were obtained by the above procedure.

B.—1,2-Dicarbethoxy ethyl sulfenyl chloride, prepared from 277 g. (0.673 mole) of tetraethyl dithiodisuccinate and 110 g. (0.81 mole) of sulfuryl chloride, in 1000 ml. of toluene was chilled to −40°. Trimethyl phosphite, 200 g. (1.61 moles) in 200 ml. of toluene, was added during 30 min., maintaining the temperature at −30 to −27°. When 70% of the phosphite solution (1.12 moles, 84% yield based on starting disulfide) had been added, the yellow color of the sulfenyl chloride faded suddenly, indicating completion of the reaction. Removal of volatile products and solvent by distillation under reduced pressure to a

(12) P. J. Bunyan and J. I. G. Cadogan, *J. Chem. Soc.*, 2953 (1962).

(13) F. M. Cowen, U. S. Patent 2,729,675 (1956); *Chem. Abstr.*, **50**, 12103e (1956).

(14) (a) T. S. Price and D. F. Twiss, *J. Chem. Soc.*, **93**, 1645 (1908); (b) *ibid.*, **101**, 1259 (1912).

(15) Lit.[14] b.p. 164° (14 mm.), $n^{25}D$ 1.49701.

(16) B. D. Westerman and W. C. Rose [*J. Biol. Chem.*, **75**, 534 (1927)] give m.p. 154–155°.

(17) Lit.[14] b.p. 194° (17 mm.), $n^{16}D$ 1.49650.

(18) J. F. Mulvaney, J. G. Murphy, and R. L. Evans, *J. Am. Chem. Soc.*, **70**, 1069 (1948).

(19) V. C. Barry, L. O'Rourke, and D. Twomey, *Proc. Roy. Irish Acad.*, **51B**, 223 (1947); *Chem. Abstr.*, **42**, 4134a (1948).

(20) Lit.[19] b.p. 132–136° (14 mm.).

(21) (a) H. Brintzinger, K. Pfannstill, H. Koddebusch, and K. E. Kling, *Chem. Ber.*, **83**, 87 (1950); (b) H. Brintzinger and H. Ellwanger, *ibid.*, **87**, 300 (1954).

final pot temperature of 80° (2.5 mm.) recovered methyl chloride in Dry Ice traps and left 399 g. of slightly hazy, light yellow oil, $n^{25}D$ 1.4704. Distillation of a sample of this product gave 75.7%, b.p. 140–151° (0.55–0.21 mm.), $n^{25}D$ 1.4652, from which the yield was calculated as 71.7%. The product was molecularly distilled at 68° (0.05 mm.); 95.6 g. of distillate was collected leaving a rather large undistilled residue which contained about 30% of unchanged tetraethyl dithiodisuccinate. The distillate was found to contain about 2.6% chlorine corresponding to 25% of an O,O-dimethyl S-(1,2-dicarbethoxy)-*x*-chloroethyl phosphorothioate.

Anal. Calcd. for 75% $C_{10}H_{19}O_7PS$ plus 25% $C_{10}H_{18}ClO_7PS$: Cl, 2.54. Found: Cl, 2.60.

O,O-Dimethyl S-Carbethoxymethyl Phosphorothioate (V).—A mixture of 15.0 g. (0.063 mole) of diethyl dithiodiacetate and 15.6 g. (0.126 mole) of trimethyl phosphite in 35 ml. of toluene was heated at 110–112° for 5.5 hr. with stirring. Samples of the reaction mixture were taken at intervals for examination by g.l.c. [A Perkin-Elmer vapor fractometer, Model 154, with 2-ft. column of 20% Carbowax 20M on Chromosorb W, at 145°, with helium carrier gas at 200 ml./min. was used. Retention times were for IX, 0.9 min.; V, 29.5 min.; $(SCH_2CO_2C_2H_5)_2$, 33.0 min.] Reaction was estimated to be 50% complete in 1.5 hr. In a similar experiment in benzene at 80–82°, reaction was 50% complete in about 8 hr.

In an experiment in which no solvent was used, 27.0 g. (0.113 mole) of the disulfide was warmed to 97° on the steam bath. Addition of 28.1 g. (0.226 mole) of the phosphite caused an exothermic reaction which carried the temperature to 160° before cooling was applied. With steam on again, the temperature rose to only 105° for a few minutes, thus showing that the reaction was over. The products V and IX were isolated from this experiment. Yields were estimated by g.l.c. assay of the crude reaction product after distillation to remove excess phosphite.

O,O-Dimethyl S-(2-Carbethoxyethyl) Phosphorothioate (VI).—A reaction mixture containing 26.6 g. (0.1 mole) of diethyl 3,3′-dithiodipropionate and 24.8 g. (0.2 mole) of trimethyl phosphite without solvent was heated at 110–112° for 47 hr. with stirring. G.l.c., using the vapor fractometer with column described above at 165°, showed these retention times: X, 0.6 min.; VI, 16.7 min.; $(SCH_2CH_2CO_2C_2H_5)_2$, 28.1 min. Sampling for gas–liquid chromatography showed that the reaction was 50% complete in about 11 hr. After 28 hr., it was evident that residual disulfide was not reacting and that the phosphorothioate was being decomposed. From a similar experiment in which 13.3 g. (0.05 mole) of the disulfide and 12 g. (0.1 mole) of the phosphite were heated overnight on the steam bath, the products VI (76% pure by g.l.c.) and X (90%) were obtained by fractional distillation, washing, and redistillation. Their identities were confirmed by infrared spectra.

Reaction of Trimethyl Phosphite with Unsubstituted Alkyl Disulfides. A.—A mixture of 24.2 g. (0.2 mole) of ethyl disulfide and 49.6 g. (0.4 mole) of freshly distilled trimethyl phosphite (Matheson Coleman and Bell) was stirred and heated at 80–82° with sampling at 0, 22, and 42 hr. for examination by gas–liquid chromatography. An Aerograph gas chromatograph with a GE SF96 silicone column was used with helium carrier gas at 50 ml./min., column temperature 85–92°, injection port temperature 99°. At 22 hr., a component was observed which was found to cochromatograph with an authentic sample of trimethyl phosphorothionate. At 42 hr., this component appeared to have increased slightly in amount. No component was observed in the region in which an authentic sample of O,O,S-trimethyl phosphorothioate appeared. Thus, neither this material nor the S-ethyl homolog appeared to have been formed. After 42 hr., the major components were still unchanged starting materials. Ethyl sulfide was not positively identified. Quantitative estimates were not made.

B.—A mixture of 25 g. (0.14 mole) of *n*-butyl disulfide and 34.8 g. (0.238 mole) of trimethyl phosphite (85% pure by g.l.c. assay) was heated on the steam bath for 17 hr. Distillation, redistillation, and combination of products on the basis of boiling points and refractive indexes gave five cuts which were assayed by g.l.c. The major components were unreacted trimethyl phosphite and *n*-butyl disulfide with estimated recoveries of 68.5 and 66.0%, respectively. Yields of trimethyl phosphorothionate and *n*-butyl sulfide of 20 and 22%, respectively, were estimated. No components were observed with retention times expected for O,O,S-trimethyl phosphorothioate or O,O-dimethyl S-*n*-butyl phosphorothioate.

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Studies of Nucleosides and Nucleotides. XXVII.[1] Synthesis of α-Adenosine-5′-monophosphate

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A mixture of α and β anomers of N-benzoyl-9-(5′-diphenylphosphoryl)-D-ribofuranosyladenine 2′,3′ cyclic carbonate was obtained by the condensation of N^6-benzoyladenine chloromercury salt with 5-diphenylphosphoryl-D-ribofuranosyl bromide 2′,3′ cyclic carbonate. Removal of protecting groups by refluxing methoxide and subsequent incubation with snake venom gave α-adenosine-5′-monophosphate.

As part of a program of synthesizing various nucleoside phosphates for the investigation of substrate specificity of several enzyme systems[2,3] we synthesized α-adenosine-5′-monophosphate.

In 1958, Wright, *et al.*,[4] successfully synthesized α-adenosine, but did not attempt to phosphorylate this product. In their study cyclic carbonate protection on the 2′- and 3′-OH groups of ribofuranosyl bromide was shown to be suitable for obtaining the α anomer. In the synthetic work on α-D-ribofuranose-1-pyrophosphate-5-phosphate,[5] it was also found that a bulky substituent existing at C-5 position (on the upper side of the furanose ring) exerted an inhibitory effect against attack of the entering group at C-1 from the same side of the ring. Considering these

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