[CONTRIBUTION FROM THE CHEMICAL RESEARCH DEPARTMENT, AGRICULTURAL DIVISION, AMERICAN CYANAMID CO.]

O,O-Dialkyl S-(carbamoylalkyl) phosphorodithioates

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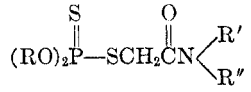
The preparation of thirty-six O,O-dialkyl S-(carbamoylalkyl) phosphorodithioates is described. Several new or improved synthetic routes are employed, most importantly one utilizing S-carboxymethyl O,O-dimethyl phosphorodithioate. The product of displacement of a phosphorothioate salt on an α-haloamide is shown to have the phosphorothiolate structure.

It has been reported[1] that a number of O,O-dialkyl S-(alkylcarbamoylmethyl) phosphorodithioates (I) exhibit activity as animal systemic insecticides.

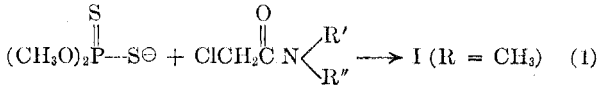


I

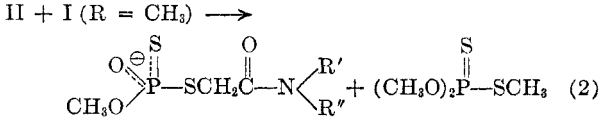
Work in these laboratories and elsewhere[2] has also established their utility as contact and systemic agents for use against insects and mites infesting plants. Many of the O,O-dimethyl esters I (R = CH_3) combine high activity with relatively low mammalian toxicity. The purpose of this paper is to record the synthesis of these and certain other members of the carbamoylalkyl phosphorodithioate series.

Thirty-six phosphorodithioates were prepared and are listed in Tables I and II. Amide nitrogen substituents include, among others: alkyl, dialkyl, aryl, heterocyclic, acyl, and sulfonyl. In addition, some variation was introduced into the phosphorus-bound alkoxyls and the alkylene group joining the phosphorodithioate and carbamoyl moieties.

Hoegberg and Cassaday[3] first prepared compounds of this class by the reaction of O,O-dialkyl phosphorodithioate salts with α-haloamides in ketonic solvents. Much of the work reported here employed variations on this technique. It was soon discovered, however, that in the syntheses of the O,O-dimethyl compounds, the method was not very satisfactory, owing to the excellent methylating ability of the products, which could successfully compete with the haloamides for the phosphorodithioate anion:

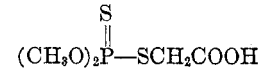


II



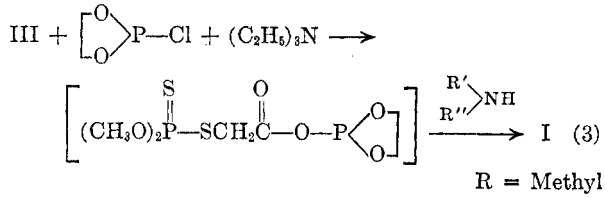
The formation of large amounts of O,O,S-trimethyl phosphorodithioate was characteristic of those reactions conducted by the conventional procedures.[3]

An effective means of shortening the synthetic route and at the same time avoiding the difficulty outlined above was discovered in the preparation and subsequent utilization of S-carboxymethyl O,O-dimethylphosphorodithioate (III). This compound, which was prepared from the reaction of II



III

(potassium salt) with chloroacetic acid, yielded only unidentifiable products when attempts were made to convert it to amides through the acid chloride. A search for milder conditions led to the discovery of the following successful route:



R = Methyl

A simple procedure which has proved valuable in the field of peptide synthesis,[4] this sequence could be carried out under mild conditions in benzene solution. It generally gave yields comparable to those obtainable from direct displacement on the chloroamides and often afforded products of superior purity.

Several other peptide-forming agents were tried in the preparation of the carbamoylalkyl phosphorodithioates, but with generally less success. In a variation of the phosphorochloridite method above, S-(*t*-butylcarbamoylmethyl) O,O-dimethyl phosphorodithioate (XVIII) was obtained impure and in low yield by treating III with IV.[4,5]

(1) R. Hewitt, A. Brebbia, and E. Waletzky, *J. Econ. Entomol.*, **51**, 126 (1958).

(2) W. J. Magee and J. C. Gaines, *J. Econ. Entomol.*, **43**, 281 (1950); E. E. Ivy, *Agr. Chem.*, **8**, 47 (1953); P. DePietri-Tonelli, *Ital. Agr.*, **1956**, No. 1.

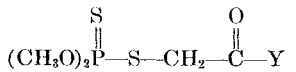
(3) E. I. Hoegberg and J. T. Cassaday, *J. Am. Chem. Soc.*, **73**, 557 (1951).

(4) R. W. Young, K. H. Wood, R. J. Joyce, and G. W. Anderson, *J. Am. Chem. Soc.*, **78**, 2126 (1956).

(5) G. W. Anderson, J. Blodinger, R. W. Young, and A. D. Welcher, *J. Am. Chem. Soc.*, **74**, 5304 (1952).

TABLE I

O,O-DIMETHYL *S*-CARBAMOYLMETHYL PHOSPHORODITHIOATES



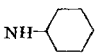
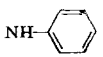
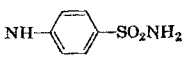
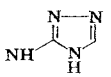
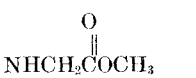
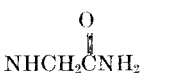
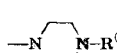
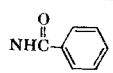
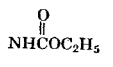
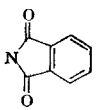
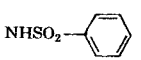
Compound	Y	Method	Recrystallization Solvent	Yield, %[a]	M.P. or n_D^{25}[b]	Calcd. C	Calcd. H	Calcd. N	Calcd. P	Found C	Found H	Found N	Found P
XII	$NHCH_3$	C	Toluene-heptane	53	50–51	26.2	5.28	6.11	13.5	26.4	5.38	6.40	13.6
XIII	NHC_2H_5	C	Toluene-heptane	67	67–68	29.6	5.80	5.76	12.7	30.0	6.19	5.85	12.6
XIV	NHC_3H_7-*n*	A	Methanol	19	63.5–64	32.7	6.27	5.44	12.0	32.8	6.29	5.73	12.1
XV	NHC_3H_7-*i*	A	Methanol-ether	28	76–77	32.7	6.27	5.44	12.0	33.0	6.18	5.16	12.4
XVI	NHC_4H_9-*n*	A	Ether (−70°)	<5	31–31.5	35.4	6.68	5.16	11.4	35.5	6.64	4.87	11.4
XVII	NHC_4H_9-*i*	A	Methanol-water	31	68.5–69	35.4	6.68	5.16	11.4	35.7	6.86	4.99	11.6
XVIII	NHC_4H_9-*t*	C[c]	Ethanol-water	53	64.5–65	35.4	6.68	5.16	11.4	35.2	6.59	4.96	11.6
XIX	NHC_8H_{17}-*n*	D	Chromatographed[d]	20	1.5136	44.0	8.01	4.28	9.46	44.1	7.82	4.23	9.45
XX	$NH-CH_2-CH=CH_2$	A	Methanol	33	57.5–58	32.9	5.53	5.49	12.1	32.8	5.73	5.64	12.3
XXI		A	Ethanol-water	37	102–103	40.4	6.78	4.71	10.4	40.4	6.86	4.56	10.7
XXII		B[e]	Methanol-water	16	83.5–84	41.2	4.84	4.81	10.6	41.2	5.03	4.79	10.6
XXIII		B[e]	Ethanol-water	19	136.5–137.5	32.4	4.08	7.56	8.36	32.5	4.31	7.43	8.07
XXIV		C	Isopropanol	<5	151–153	25.5	3.93	19.9	11.0	26.0	4.08	19.8	10.9
XXV		C	Ether	25	41–42	29.3	4.91	4.88	10.8	29.6	5.09	4.78	10.7
XXVI		B	Ethanol	31	97–97.5	26.5	4.81	10.3	11.4	26.7	5.00	10.2	11.4
XXVII	$NHOCH_3$	D	Ether	23	42.5–43.5	24.5	4.93	5.71	12.6	24.7	5.09	5.78	12.5
XXVIII	$N(CH_3)_2$	C	B.p. 106°/0.005 mm.[f]	9	1.5400	29.6	5.80	5.76	12.7	30.0	6.09	5.49	12.5
XXIX	$N(C_2H_5)_2$	C	Chromatographed[g]	<5	1.5275	35.4	6.68	5.16	11.4	35.7	6.91	5.14	11.0
XXX		D	Benzene	46	70.5–71.5	35.7	5.99	5.20	11.5	35.7	6.42	4.95	11.8
XXXI		D	Chromatographed[h]	52	1.5523	38.1	6.40	4.94	10.9	37.8	6.94	5.09	10.8
XXXII		C	Ethanol-water	61	63.5–64	33.4	6.31	4.87	10.8	33.5	6.18	4.87	10.7
XXXIII		D	Methanol	5	137.5–138.5	29.9	5.01	5.81	12.8	29.6	5.14	5.44	12.6

TABLE I (*Continued*)

Compound	Y	Method	Recrystallization Solvent	Yield, %[a]	M.P. or n_D^{25}[b]	Calcd. C	Calcd. H	Calcd. N	Calcd. P	Found C	Found H	Found N	Found P
XXXIV		B	Isopropanol	49	115–116	41.4	4.42	4.39	9.70	41.4	4.47	4.30	9.75
XXXV		B	Ether-hexane	55	57.5–58[i]	29.3	4.91	4.88	10.8	29.2	4.95	4.94	10.8
XXXVI		B[e]	CCl_4	56	106.5–107.5	26.5	4.81	10.3	11.4	26.7	4.85	10.1	11.4
XXXVII		B	$CHCl_3$—CCl_4	15	108–109	41.7	3.50	4.06	8.97	41.7	3.56	3.98	8.93
XXXVIII		B[j]	CCl_4	53	86–87	33.8	3.97		8.72	34.1	4.27		8.84

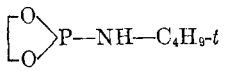
[a] Yields quoted are of analytically pure material or of material very close in melting point or refractive index to the pure compound. Losses in work-up were often high, especially in Methods A and B; and only in a few cases were efforts made to maximize yields. [b] Melting points are uncorrected. [c] A three-solvent system was used: 90 g. of water, 110 g. of toluene, and 49 g. of methanol for a 0.3 mole reaction. [d] Acid-washed unactivated alumina. Compound placed on column in benzene, eluted with benzene followed by ether and finally chloroform. [e] Acetone instead of methyl isobutyl ketone was used as solvent. The reactants were heated under reflux for from 35 min. to 3 hr., the solvent removed under vacuum, and the residue taken up in benzene, chloroform, or methyl isobutyl ketone for washing. The rest of the work-up was performed as detailed under Method B in the Experimental. [f] Molecular distillations. The boiling points listed represent the temperature of the heating jacket of the still. [g] Acid-washed unactivated alumina. Compound placed on column in benzene, eluted with chloroform followed by chloroform-ether mixtures. A fraction eluted with 60:40 chloroform: ether was rechromatographed and eluted with benzene-hexane to give the pure material. [h] Acid-washed activated alumina. Compound placed on column in benzene. Elution with benzene gave several impure fractions, but later benzene fractions, followed by fractions eluted with ether and chloroform, all had identical infrared spectra and n_D^{25} 1.5520–1.5524. [i] G. Schrader, Ger. **963,872,** reported m.p. 46°. [j] The crude product was taken up in 10% sodium bicarbonate, the solution extracted with chloroform, and the product reprecipitated with hydrochloric acid. The reprecipitated oil was dissolved in chloroform and dried over magnesium sulfate before recrystallization. [k] R = $(CH_3O)_2P(S)CH_2C(O)$—.

TABLE II

O,O-DIALKYL *S*-CARBAMOYLALKYL PHOSPHORODITHIOATES, $(RO)_2P(S)SR'C(O)NHR''$

Compound	R	R′	R″	Method	Recrystallization Solvent	Yield,[a] %	M.P. or n_D^{25}[b]	Calcd. C	Calcd. H	Calcd. N	Calcd. P	Found C	Found H	Found N	Found P
XXXIX	CH_3	$-CH(CH_3)-$	CH_3	B	Ether (−20°)	30	52.5–53	29.6	5.80	5.76	12.7	29.4	5.78	5.48	12.9
XL	CH_3	$-CH(C_2H_5)-$	CH_3	B	Heptane	5	72–73	32.7	6.27	5.44	12.0	32.8	6.29	5.39	12.2
XLI	CH_3	$-CH_2CH_2-$	CH_3	C	Ether	43	56.5–57	29.6	5.80	5.76	12.7	29.4	5.78	5.59	12.6
XLII	C_2H_5	CH_2	CH_3	B[c]	Ether-pet. ether (−70°)	83	27–28[d]	32.7	6.27	5.44	12.0	32.8	6.23	5.36	12.1
XLIII	C_2H_5	CH_2	C_2H_5	B[c]	[e]	83	1.5231			5.16	11.4			5.33	11.5
XLIV	C_2H_5	CH_2	i-C_3H_7	B[c]	[e]	93	1.5147			4.91	10.9			4.52	11.1
XLV	C_2H_5	CH_2	t-C_4H_9	A	Ether (−70°)	24	31–31.5	40.1	7.41	4.68	10.4	40.1	7.75	4.67	9.83
XLVI	C_2H_5	CH_2	$CH_3C(O)-$	B	B.p. 90–92°/0.001 mm.[f]	51	1.5300	33.7	5.65	4.91	10.9	33.9	5.88	4.84	10.8
XLVII	C_2H_5	$-CH(CH_3)-$	CH_3	B	Methanol-water	59	62–63	35.4	6.68	5.16	11.4	35.3	6.62	5.26	11.4

[a] See footnote a, Table I. [b] Melting points are uncorrected. [c] See footnote *e*, Table I. [d] Reported by Hoegberg and Cassaday[3] as an oil. [e] The crude oils proved to be analytically pure. [f] See footnote *f*, Table I.

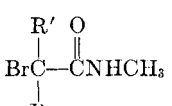


IV

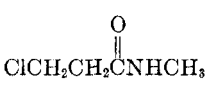
The use of dicyclohexylcarbodiimide[6] with III and either propylamine or *t*-butylamine failed to give the amides. In a single trial, the carbonic-carboxylic anhydride method using ethyl chlorocarbonate[7] did not yield any XII. Though the synthesis of peptides *via* some of the phosphite procedures is catalyzed by an equivalent of imidazole,[8] no such catalysis was detected in the preparation of the *n*-octyl compound (XIX) by the phosphorochloridite method.

A second means of reducing the consequences of reaction (2) was found in the use of a two-phase solvent system. In a toluene-water or a chloroform-water system, for example, reaction (1) occurs in the aqueous phase, while the product is immediately extracted into the organic layer as it is produced. This method was limited to those haloamides with some degree of water solubility, although in some cases, *e.g.*, compound XVIII, an unfavorable distribution of haloamide between the two phases could be overcome by the addition of a third solvent, such as methanol or ethanol.

Among those reactions carried out by direct displacement of potassium *O,O*-dimethyl phosphorodithioate on a haloamide, the effect on yields of variation in haloamide reactivity was studied.



V



VI

In the series of monoalkyl-substituted α-bromoamides, V (R′ = H), yields decreased with increasing bulk of R. Thus V (R = CH_3) gave a 30% yield of phosphorylated product after four hours at 50° in methyl isobutyl ketone whereas V (R = C_2H_5) gave a 2% yield under the same conditions, and reaction of V (R = $i-C_3H_7$) at 80° for fifteen hours resulted only in a 75% recovery of bromoamide. The tertiary bromide, V (R = R′ = CH_3), yielded no identifiable products when treated for eight hours with triethylammonium *O,O*-dimethyl phosphorodithioate in refluxing benzene. Compound VI and potassium *O,O*-dimethyl phosphorodithioate in refluxing acetone for 7.5 hours resulted in a 53% recovery of chloroamide, a 21% recovery of phosphorodithioate salt, and no desired product. On the other hand, the corresponding β-bromoamide yielded 43% of product after a considerably shorter time in refluxing toluene-water.

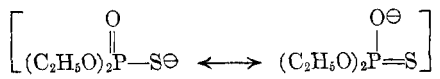
(6) J. C. Sheehan and G. P. Hess, *J. Am. Chem. Soc.*, **77**, 1067 (1955).

(7) J. R. Vaughan, Jr., and R. L. Osato, *J. Am. Chem. Soc.*, **74**, 676 (1952).

(8) G. W. Anderson, A. C. McGregor, and R. W. Young, *J. Org. Chem.*, **23**, 1236 (1958).

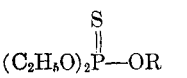
The procedures discussed above were applied to the synthesis of phosphorothioates by the reaction of potassium *O,O*-dimethyl phosphorothioate with α-haloamides.

Recently, Mandel'baum, *et al.*[9] have claimed that reaction of *O,O*-diethyl phosphorothioate salts (VII) with α-haloamides and esters have given the

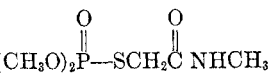


VII

phosphorothionate form of the product (VIII). In one case which we have carefully examined, the preparation of IX, spectral data conclusively



VIII



IX

show that the product has the thiol structure. Thus, the infrared spectrum shows a strong band at 1250 cm.$^{-1}$, which is characteristic of the P = O group.[10] The assignment of the thiol structure was supported by the proton magnetic resonance spectrum,[11,12,13] taken in deuterochloroform, which showed resonance peaks of 2.62 and 2.88 p.p.m., which have been assigned[11] to the CH_3OP and $PSCH_2C{=}O$ moieties respectively from observations of a number of model compounds. They have the appropriate intensity ration and appear as doublets[14] due to spin-coupling with the phosphorus nucleus. The splittings correspond to those commonly observed[11] for CH protons linked to phosphorus through oxygen or sulfur and in this compound have the values 16 c.p.s. for the CH_3OP group and 11 c.p.s. for the CH_2SP group. The formation of the phosphorothiolate isomer in this reaction is consistent with most of the work which has been reported on displacements of phosphoromonothioate salts on alkyl halides.[3,15]

A novel reaction occurred during an attempt at preparation of X. The low-melting solid, presumably X, that was initially obtained, changed on standing to a compound that melted at 170° and was water soluble. On the basis of infrared and NMR spectral data, it has been assigned the

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(10) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley & Sons, Inc., New York, 1954, p. 258.

(11) J. E. Lancaster, These Laboratories, Personal Communication.

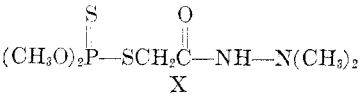
(12) S. DuBreuil and R. W. Young, 136th Meeting of the American Chemical Society, Atlantic City, N.J., Sept. 18, 1959.

(13) NMR spectra were taken with a Varian Associates V4300B high resolution spectrometer operating at 40 mc. Benzene was used as an external standard. All shifts given in this paper occur to the high field side of the benzene position.

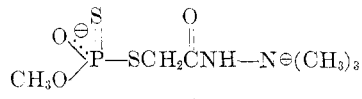
(14) T. Yamasaki, *J. Chem. Soc. Japan, Pure Chem. Sect.*, **79**, 832 (1958).

(15) M. I. Kabachnik and T. A. Mastryukova, *Zhur. Obsch. Khim.*, **25**, 1924 (1955) and references cited therein.

structure of the zwitterion XI, a product of the "internal" demethylation of X (see Experimental).



X



XI

EXPERIMENTAL[16,17]

O,O-Dialkyl carbamoylalkyl phosphorodithioates—Method A. S-(Isobutylcarbamoylmethyl) O,O-dimethyl phosphorodithioate (XVII). Triethylamine (36 g., 0.24 mole) in 20 ml. of reagent-grade benzene was added portionwise to a stirred solution of *O,O*-dimethyl hydrogen phosphorodithioate (43 g., 0.24 mole of 89% acid) in 50 ml. of benzene while maintaining the temperature between 15 and 25°. To this was added a solution of 2-chloro-*N*-isobutylacetamide (36 g., 0.24 mole) in 30 ml. of benzene, after which the reaction mixture was stirred at room temperature for 23 hr. The triethylamine hydrochloride (25 g., 75%) was removed by filtration and the filtrate was washed with 5% sodium bicarbonate until the washings were neutral or slightly basic. After washing with saturated sodium chloride solution and drying over magnesium sulfate, the solvent was removed under vacuum to give 48 g. of crude solid. Several recrystallizations from methanol-water and ethanol-water gave 20.5 g. (31%) of white crystals, m.p. 68–68.5°. The analytical sample (from methanol-water) melted at 68.5–69°.

Method B. S-(Carbamoylmethylcarbamoylmethyl) O,O-dimethyl phosphorodithioate (XXVI). To a suspension of potassium *O,O*-dimethyl phosphorodithioate[3] (20 g., 0.10 mole of salt 98.2% pure by alkaline iodine[18] titration) in 50 ml. of methyl isobutyl ketone was added *N*-carbamoylmethyl-2-chloroacetamide (15 g., 0.10 mole) in 50 ml. of methyl isobutyl ketone, followed by sodium bicarbonate[19] (8.4 g., 0.10 mole). The stirred suspension was heated at 50–60° for 5 hr. After the insoluble solids were allowed to settle, the solution was decanted or filtered and the filtrate washed with 5% sodium bicarbonate and saturated brine. Some material settled out on cooling[20] and was combined with the residue remaining after removal of the solvent under vacuum and with additional material from acetone extraction of the inorganic salts. Several recrystallizations from ethanol gave 8.5 g. (31%) of white crystalline solid, m.p. 96.5–97°. The analytical sample (from ethanol) melted at 97–97.5°.

Method C. O,O-Dimethyl S-(morpholinocarbonylmethyl) phosphorodithioate (XXXII). A solution of potassium *O,O*-dimethyl phosphorodithioate[3] (20 g. 0.10 mole of 98.2%[18] material) in 20 ml. of water was added dropwise over a 20-min. period to a rapidly stirred refluxing mixture of 4-chloroacetylmorpholine (20 g., 0.12 mole) in 20 ml. of water and 40 ml. of toluene. After an additional 5 min. stirring under reflux, the layers were separated and the aqueous layer extracted with two 10-ml. portions of fresh toluene. The combined toluene fractions were washed with 5% sodium bicarbonate and saturated sodium chloride solutions and dried over magnesium sulfate. Removal of the solvent *in vacuo* left a viscous oil, which solidified upon trituration and cooling in absolute ether; yield 20.6 g., m.p. 58–61°. Recrystallization from 20 ml. ethanol–35 ml. water gave 17.6 g. (61%) of a white crystalline solid, m.p. 63–64°.

Method D. O,O-Dimethyl S-(1-pyrrolidinylcarbonylmethyl) phosphorodithioate (XXX). Ethylene phosphorochloridite[21] (9.6 g., 0.075 mole) in about 15 ml. of reagent-grade benzene was added dropwise to a stirred, cooled solution of *S*-carboxymethyl *O,O*-dimethyl phosphorodithioate (16.2 g. 0.075 mole, see below) and triethylamine (7.6 g., 0.075 mole) in about 50 ml. of benzene in a flask protected by a drying tube. The temperature of the reaction mixture was kept below 20° during the addition. After 10 min. stirring at room temperature, the triethylamine hydrochloride (86%) was removed by filtration. Pyrrolidine (5.3 g., 0.075 mole) in about 10 ml. of benzene was added to the filtrate and the solution was heated under reflux for 30 min. The cooled solution was filtered to remove a small amount of white gum which had formed and the opalescent filtrate washed with 30 ml. of water followed by two 30-ml. portions of 20% potassium bicarbonate. After being dried over magnesium sulfate, the solvent was removed under vacuum. The residual yellow oil (12 g.) crystallized on cooling to a solid melting at 55–65°. Recrystallization from 25 ml. of benzene gave 9.4 g., (46%) of white crystals, m.p. 68.5–71.5°. The analytical sample (from benzene) melted at 70.5–71.5°.

S-(t-Butylcarbamoylmethyl) O,O-dimethyl phosphorodithioate (XVIII) *via the phosphite amide procedure.* Ethylene phosphorochloridite[21] (12.7 g., 0.1 mole) in 10 ml. of benzene was added dropwise to a stirred, cooled solution of *t*-butylamine (7.3 g., 0.1 mole) and triethylamine (10.1 g., 0.1 mole) in 20 ml. of benzene, the temperature being kept below 20°. The reaction mixture was stirred at ice temperature for 10 min. following the addition and at room temperature for an additional 5 min. The precipitated triethylamine hydrochloride (13.5 g., 99%) was filtered off and washed with fresh benzene. The filtrate was divided in half, and to each half was added 10.8 g. (0.05 mole) of *S*-carboxymethyl *O,O*-dimethyl phosphorodithioate in 20 ml. of benzene. One portion was heated under reflex for 30 min., the other for 1 hr. Each was worked up as in Method D, yielding 4.1 g. (30%) and 4.9 g. (36%), respectively, of oily solids. The 30 min. product was slurried in 50 ml. of hexane, cooled in a Dry Ice–acetone bath, filtered, and dried. The resultant oily solid (3.9 g.) exhibited an infrared spectrum virtually identical with that of analytically pure material prepared as shown in Table I.

S-Carboxymethyl O,O-dimethyl phosphorodithioate (III). A solution of 117.6 g. (0.6 mole) of potassium *O,O*-dimethyl phosphorodithioate[3] (as 124 g. of material analyzing 95% pure by Foss[18] titration) in 118 ml. of water was added over a 45-min. period, with efficient stirring, to a refluxing solution of 56.7 g. (0.6 mole) of chloroacetic acid in a mixture of 600 ml. of chloroform and 82 ml. of water. Heating under reflux and rapid stirring were continued for an additional 30 min. The reaction mixture was cooled to room temperature and the layers separated. The water layer was extracted with three 75-ml. portions of chloroform and the combined extracts and original chloroform layer washed with 40 ml. of water and dried over magnesium sulfate. Removal of the solvent under vacuum left 105 g. (81%) of an orange-brown oil, which crystallized on cooling. Three recrystallizations from 60 ml. mixtures of approximately equal volumes of carbon tetrachloride and hexane gave 71.1 g. (55%) of white crys-

(16) Because of the potential toxicity of phosphate esters, caution should be exercised when handling them.

(17) Melting points and boiling points are uncorrected. Melting points were taken on a Fisher-Johns block.

(18) The iodometric titration described by O. Foss, *Acta Chem. Scand.*, 1, 8 (1947), for phosphorothioate salts was used. Dr. D. E. Ailman of these laboratories has found it to be applicable to salts of dimethyl and diethyl phosphorodithioic acids. In the case of the dithio salts, both sulfur atoms are oxidized to sulfate.

(19) The bicarbonate was added to counteract the tendency of these reaction mixtures to become acidic.

(20) In most other preparations using this method, the product did not precipitate, and the methyl isobutyl ketone solution was dried at this point over magnesium sulfate.

(21) H. J. Lucas, F. W. Mitchell, Jr., and C. N. Scully, *J. Am. Chem. Soc.*, **72**, 5491 (1950).

talline solid, m.p. 41–43.5° (98.3% pure by potentiometric titration with alkali). The analytical sample, m.p. 42–43°, was obtained by chromatography of the crude material on unactivated acid-washed alumina (ether elution).

Anal. Calcd. for $C_4H_9O_4PS_2$: C, 22.2; H, 4.20; P, 14.3; S, 29.7. Found: C, 22.3; H, 4.35; P. 14.0; S, 29.6.

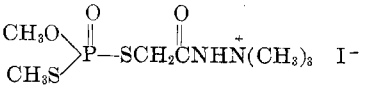
O,O-Dimethyl S-(methylcarbamoylmethyl) phosphorothioate (IX). A solution of potassium *O,O*-dimethyl phosphorothioate (111 g., 0.6 mole, 97.5% purity) and 2-chloro-*N*-methylacetamide in a chloroform-water system (200 ml. of each solvent) was rapidly stirred and heated under reflux for 2 hr. The layers were cooled and separated and the water layer extracted with two 75-ml. portions of chloroform. The combined chloroform fractions were washed with 20 ml. of 20% potassium bicarbonate solution and dried over magnesium sulfate. Removal of the solvent under vacuum left 75.4 g. of a yellow oil. Unchanged chloroamide and *O,O,S*-trimethyl phosphorothioate by-product were removed on a rotary film evaporator at a pressure of 0.4 mm. and bath temperature of 80–85°. There remained 36.9 g. of a yellow oil, which was molecularly distilled at 1 micron pressure and a jacket temperature of 100–110°. After a fore-run of liquids with low refractive index, the product (25.9 g., 20%), a straw-colored viscous oil, was collected as three fractions with n_D^{25} 1.4984, Eisenlohr-Denbigh molar refraction[22] 319.5 (Calcd. 314.3).

Anal. Calcd. for $C_5H_{16}NO_4PS$: C, 28.2; H, 5.68; N, 6.57; P, 14.5; S, 15.0. Found: C, 28.2; H, 5.65; N, 6.28; P, 14.3; S, 15.3.

2-(Mercaptomethoxyphosphinylthioacetyl)-1,1,1-trimethylhydrazonium hydroxide, inner salt (XI). *S*-Carboxymethyl *O,O*-dimethyl phosphorodithioate (38 g., 0.18 mole), ethylene phosphorochloridite (22.2 g., 0.18 mole), triethylamine (17.7 g., 0.18 mole), and anhydrous unsymdimethylhydrazine in a total of 350 ml. of benzene were allowed to react according to Method D, with the exception that following the addition of the hydrazine to the mixed anhydride the reaction mixture was stirred at room temperature for 2.5 hr. instead of being heated under reflux. A viscous oil (26 g., 59%) was obtained which had an infrared spectrum compatible with the expected hydrazide. Trituration of half the product under ether gave a white solid, m.p. 46–48°. On standing for several days this material changed to a gummy substance. Two recrystallizations from absolute ethanol gave 5 g. (23%) of a white solid, m.p. 170° dec.

Anal. Calcd. for $C_6H_{15}N_2O_3PS_2$: C, 27.9; H, 5.85; N, 10.9; P, 12.0; S, 24.8. Found: C, 27.3, 27.7, 27.6; H, 5.72, 5.98, 5.95; N, 11.0, 11.2; P, 12.3, 12.3; S, 24.9.

The zwitterionic structure was assigned on the basis of elemental analysis, the high melting point, solubility properties (soluble in water, insoluble in chloroform and benzene), and spectral evidence. The carbonyl frequency in the infrared was shifted to 1695 cm.$^{-1}$, which is about 45–50 cm.$^{-1}$ higher in frequency than the carbonyl bands of the compounds listed in Tables I and II and is in the direction to be expected for a shift caused by a proximate electron withdrawing group such as quaternary ammonium. The NMR proton spectrum[11,12,13] showed a ratio of 3 nitrogen-bound methyl groups to 1 CH_3OP group. Methylation of the product with methyl iodide gave a solid which, though it melted over a wide range and was undoubtedly impure, showed the characteristic doublet[11] of the CH_3SP group at 4.20 p.p.m. (splitting: 16 cps) in the NMR spectrum and was presumably mainly the expected methylation product of XI,



Known haloamides. The majority of the 2-chloroacetamides were prepared from chloroacetyl chloride according to the two-phase procedure of Speziale and Hamm[23] with the use of methyl isobutyl ketone instead of ethylene chloride as the nonaqueous solvent. The *N*-substituents and appropriate literature references for the known compounds prepared in this manner are as follows: ethyl,[24,25] propyl,[26] *i*-propyl,[23] butyl,[23] *i*-butyl,[26] *t*-butyl,[23] allyl,[27] phenyl,[28] and cyclohexyl.[23] *N*-(Chloroacetyl)morpholine[29] and 2-bromo-*N*-methylbutyramide[30] were similarly prepared.

The following haloamides were prepared from the corresponding haloacyl chlorides by the method described below for 3-chloro-*N*-methylpropionamide: 2-chloro-*N,N*-dimethylacetamide,[24] 2-bromo-*N*-methylpropionamide,[31,32] 2-bromo-*N*-methylisobutyramide,[30,33] and 2-bromo-*N*-methylisovaleramide.[34] The following were made by literature methods: *N*-carbamoylmethyl-2-chloroacetamide,[35] *N-p*-sulfamoylphenyl-2-chloroacetamide,[36] *N*-acetyl-2-chloroacetamide,[37] *N*-benzoyl-2-chloroacetamide,[37] *N*-chloroacetyl-*N'*-methylurea,[38] ethyl chloroacetylcarbamate,[35] and *N*-chloroacetylbenzenesulfonamide.[39] 2-Chloro-*N*-methylacetamide and 2-chloro-*N,N*-diethylacetamide were obtained commercially.

New haloamides. 2-Chloro-N-(3-triazolyl)acetamide. 3-Aminotriazole (33.6 g., 0.4 mole) and chloroacetyl chloride (56.3 g., 0.5 mole) were allowed to react according to the procedure of Speziale and Hamm[23] using methyl isobutyl ketone instead of ethylene chloride as the nonaqueous solvent. An 89% yield of solid material separated directly from the reaction mixture. Recrystallization from acetonitrile gave the analytical sample, m.p. 272° dec.

Anal. Calcd. for $C_4H_5ClN_4O$: C, 29.9; H, 3.13; N, 34.9. Found: C, 30.1 H, 3.17; N, 35.1.

N-Carbomethoxymethyl-2-chloroacetamide. A stirred, cooled (10°) slurry of methyl glycinate hydrochloride (25 g., 0.20 mole) in 300 ml. of anhydrous ether was converted to the free base by bubbling in anhydrous ammonia. The precipitated ammonium chloride (11 g., 100%) was removed by filtration and the filtrate stirred and cooled in an ice methanol bath while triethylamine (20.2 g., 0.20 mole) was added, followed by the addition of chloroacetyl chloride (22.6 g., 0.20 mole) at such a rate as to keep the temperature between −8° and −4°. The triethylamine hydrochloride was filtered off and washed with ether and chloroform. Evaporation of the combined filtrated and wash solutions gave a semi-solid mass, which was extracted with 100 ml. of hot

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(25) Ethylene chloride–water system was used.

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(31) W. E. Weaver and W. M. Whaley, *J. Am. Chem. Soc.*, **69**, 1144 (1947).

(32) M.p. 43.5–44.5°. Ref. 31 gives m.p. 40°.

(33) M.p. 59–60°. Ref. 30 gives m.p. 53–55°.

(34) A. Liebrecht, Ger. **261,877**; *Chem. Zentr.*, **84**, 395 (1913).

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(38) G. Frerichs, *Arch. Pharm.*, **237**, 288 (1899).

(39) J. von Braun and W. Rudolph, *Ber.*, **67**, 1762 (1934).

ethyl acetate. Removal of the ethyl acetate under vacuum and distillation of the residual brown oil gave 52% of material boiling at 121–127°/0.1 mm., n_D^{25} 1.4755.

Anal. Calcd. for $C_5H_8ClNO_3$: C, 36.3; H, 4.87; N, 8.46. Found: C, 36.3; H, 5.08; N, 8.21.

3-Chloro-N-methylpropionamide. Gaseous methylamine (49.0 g., 1.57 moles) was bubbled into a stirred solution of 3-chloropropionyl chloride (100 g., 0.787 mole) in 300 ml. of ethylene chloride at −15 to −10° for 1.5 hr. The thick white slurry was stirred an additional 2 hr. as it warmed to room temperature. The methylamine hydrochloride (52.2 g., 98%) was filtered off and the filtrate evaporated under vacuum to yield 100 g. of a yellow solid, m.p. 59–62°. Recrystallization from ether gave 86.4 g. (90%) of pale yellow crystals, m.p. 62–64°. The analytical sample (from ether-hexane) had m.p. 65–65.5°.

Anal. Calcd. for C_4H_8ClNO: C, 39.5; H, 6.63; Cl, 29.2; N, 11.5. Found: C, 39.6; H, 6.68; Cl, 28.9; N, 11.4.

3-Bromo-N-methylpropionamide. The same procedure utilized for 3-chloro-*N*-methylpropionamide, with the exception that liquid rather than gaseous methylamine was used, gave the 3-bromoamide from 3-bromopropionyl bromide in 52% yield as a white solid, m.p. 74–75.5°, following two recrystallizations from ethyl acetate-hexane. The analytical sample (from chloroform-hexane) melted at 78.5–79°.

Anal. Calcd. for C_4H_8BrNO: C, 28.9; H, 4.86; N, 8.44. Found: C, 29.8, 29.9; H, 5.03, 5.08; N, 8.52.

N-Chloroacetylphthalimide. The procedure of Evans and Dehn,[40] using phthaloyl chloride (101.5 g., 0.5 mole) and chloroacetamide (46.8 g., 0.5 mole) in 500 ml. of toluene, gave 30 g. (27%) of product, m.p. 170–175°, that settled out on cooling. Recrystallization from toluene, followed by chloroform, gave 10.2 g. of colorless crystals, m.p. 180–182°.

Anal. Calcd. for $C_{10}H_6ClNO_3$: C, 53.71; H, 2.71; Cl, 15.86; N, 6.26. Found: C, 53.38; H, 2.93; Cl, 15.68; N, 6.38.

Acknowledgment. We are indebted to Mrs. Melinda Kozma, who performed much of the synthetic work reported here, as well as to Dr. David Ailman, Mr. Frank Wagner, and Mrs. Ella Swartz Zonas for their contributions. We are also grateful to Dr. John Lancaster for NMR data and interpretation and to Dr. Julius Kuck and Mrs. Lee Grim for microanalyses.

STAMFORD, CONN.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE ROHM AND HAAS CO.]

The Reaction of Acrylates and Methacrylates with Organomagnesium Compounds[1]

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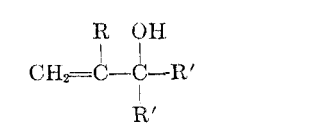
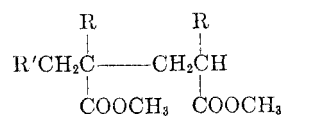
A study of the products of the reaction of methyl methacrylate, isopropyl acrylate, and methyl acrylate with various organomagnesium compounds has shown that these reactions follow a consistent pattern. The products were separated by distillation and chromatography on alumina and were identified by analysis, by infrared, ultraviolet and NMR spectroscopy and gas chromatography. In addition to the expected product (V), produced by 1,4- addition of the organomagnesium compounds to the unsaturated esters, there were products (VI and XI) produced by a combination of a 1,4- followed by a 1,2- addition of the organomagnesium compound to the unsaturated ester. There were, in addition, two unexpected products, the cyclic ketone VIII, resulting from a Dieckmann condensation, and the ketone XII, probably resulting from a combination of 1,4- and 1,2- additions followed by a reversal of the 1,2- addition.

Earlier investigators have studied the reaction of Grignard reagents with acrylic and methacrylic esters.[2–4] Various products were reported, but rarely was an attempt made to isolate and identify all the products. Lebedeva and co-workers[3] reported that the reaction of methyl methacrylate with ethylmagnesium bromide gave Ic and IIc and with isopropylmagnesium bromide gave IId. With methyl acrylate and ethylmagnesium bromide, the products were Ia, IIa, and IIIa, while with isopropyl magnesium bromide and methyl acrylate, IIb and IIIb were the products. These data are presented in Table I.



Ia. R = H; R′ = C_2H_5
b. R = H; R′ = $CH(CH_3)_2$
c. R = CH_3; R′ = C_2H_5
d. R = CH_3; R′ = $CH(CH_3)_2$



IIa. R = H; R′ = C_2H_5
b. R = H; R′ = $CH(CH_3)_2$
c. R = CH_3; R′ = C_2H_5
d. R = CH_3; R′ = $CH(CH_3)_2$

(1) Presented in part before the Division of Organic Chemistry at the 137th Meeting of the American Chemical Society, Cleveland, Ohio, April 1960.

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