7q, 79409-71-5; **7r**, 79409-72-6; **7s**, 79409-73-7; **9a**, 79409-74-8; **9b**, 79409-75-9; **9c**, 79409-76-0; **9d**, 79409-77-1; **9e**, 79409-78-2; **9f**, 79409-79-3; **9g**, 79409-80-6; **9h**, 79409-81-7; **9i**, 79409-82-8; **10r**, 79420-94-3; **15**, 79409-83-9; **16**, 79409-84-0; **17**, 79409-85-1; **18**, 79409-86-2; **19**, 79409-87-3; 1-(phenylthio)-2-propene, 5296-64-0; 1-(phenylthio)-3-(trimethylsilyl)-1-propene, 79409-88-4; isopropyl iodide, 75-30-9; 1-bromo-3-phenylbutane, 5801-17-2; cycloheptyl bromide, 2404-35-5; benzyl bromide, 100-39-0; cyclohexylmethyl bromide, 2550-36-9; *trans*-cinnamyl bromide, 26146-77-0; cyclopentyl bromide, 137-43-9; *n*-hexyl bromide, 111-25-1.

Phase-Transfer-Catalyzed Michaelis–Becker Reaction

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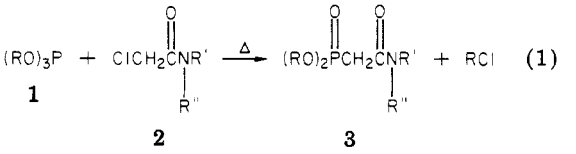
Dialkyl hydrogen phosphonates or dialkylphosphine oxides are conveniently and efficiently alkylated by alkyl chlorides to produce dialkyl alkylphosphonates or trialkylphosphine oxides, respectively, by aqueous sodium hydroxide in a liquid–liquid phase-transfer-catalyzed reaction. Despite the hydrolytic instability of dialkyl hydrogen phosphonates, their reaction with chloroacetamides in the two-phase system can provide dialkyl (carbamoylmethyl)phosphonates $(RO)_2P(O)CH_2C(O)NR'R''$ in 90% yields and crude purities. Many of these products have unique utility as solvent extraction reagents for the fractionation of hazardous radionuclides. The new route is not plagued by the side reactions typical of conventional Arbuzov or Michaelis–Becker syntheses, which seriously limit yields and crude product purities. It does not require anhydrous conditions or the use of alkali metals, alkoxides, or hydrides and provides access to products outside the scope of conventional routes.

The general utility of the reaction of the conjugate bases of dialkyl hydrogen phosphonates, $(RO)_2P(O)H$, and dialkylphosphine oxides, $R_2P(O)H$, with alkylating agents (i.e., the Michaelis–Becker reaction) is limited by the requirement of a strong anhydrous base (e.g., alkali metals, alkoxides, or hydrides) for conjugate base formation. Since such bases are reactive directly with alkylating agents, it is necessary to prepare these reactive organophosphorus alkali metal salts in stoichiometric quantities prior to exposure to the desired alkylating agent. A stepwise procedure such as this which results in high concentrations of these strong nucleophiles can lead to undesirable side reactions (vide infra).

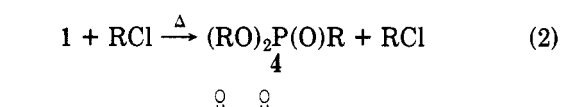
It has been reported that diethyl hydrogen phosphonate reacts with benzyl chloride in the presence of potassium carbonate and a crown ether at 100 °C to afford diethyl benzylphosphonate in 66% yield.[1] This reaction likely proceeds by proton abstraction on the surface of the solid carbonate but demonstrates the capability of a properly activated weak base for this reaction.

This study was undertaken to develop a simple and facile route to elusive dialkyl (carbamoylmethyl)phosphonates **3**, which are unique reagents for the fractionation of radionuclides from nuclear process streams by solvent extraction.[2-9] We now report a convenient method for high-yield preparations of these compounds as well as novel tertiary (carbamoylmethyl)phosphine oxides **10** via a Michaelis–Becker reaction facilitated by liquid–liquid phase-transfer catalysis (PTC),[10,11] a route which substantially relieves the limitatioins described above.

Siddall found the reaction of trialkyl phosphites (**1**) with *N,N*-dialkylchloroacetamides (**2**, eq 1) to be sluggish, requiring forcing conditions.[12] The reactivity of **1** in this example of the Arbuzov reaction is further reduced when R is large, such as when **3** is designed as a solvent extraction reagent and must be very hydrophobic. The reaction is plagued by typical Arbuzov side reactions (eq 2 and 3), and poor yields (40–50%) of difficulty purifiable products inevitably result.[13]



(1)



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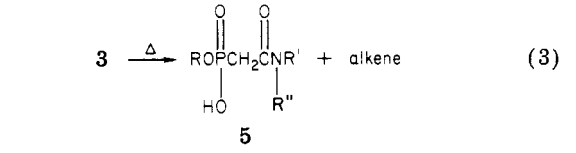
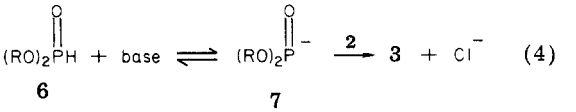


(3)

The nucleophilic displacement involving **2** and alkali metal salts (**7**) of dialkyl hydrogen phosphonates (**6**, eq 4),



(4)

an example of the Michaelis–Becker reaction, occurs under considerably milder conditions.[14] However, the previously

(1) Fedorynski, M.; Wojciechowski, K.; Matacz, Z.; Makosza, M. *J. Org. Chem.* **1978**, *43*, 4682. In this article, the text reports the use of potassium carbonate with a crown ether, while Table I reports the use of sodium carbonate with tetrabutylammonium bromide.
(2) Schulz, W. W. Report No. ARH-SA-203; Atlantic Richfield Hanford Co.: Richland, WA, 1974.
(3) Schulz, W. W.; McIsaac, L. D. Report No. ARH-SA-217; Atlantic Richfield Hanford Co.: Richland, WA, 1975.
(4) McIsaac, L. D.; Baker, J. D.; Tkachyk, J. W. Report No. ICP-1080; Idaho Chemical Programs, Allied Chemical: Idaho Falls, ID, 1975.
(5) Shulz, W. W. U.S. Patent 3 993 728, 1976.
(6) Hagen, P. G.; Navratil, J. D. Report No. RFP 2708; Rockwell Atomics International: Rocky Flats, Golden, CO, 1978.
(7) Shoun, R. R.; McDowell, W. J.; Weaver, B. *CIM Spec. Vol.* **1979**, *21*, 101.
(8) Schulz, W. W.; McIsaac, L. D. *CIM Spec. Vol.* **1979**, *21*, 619.
(9) Navratil, J. D.; Thompson, G. H. *Nucl. Technol.* **1979**, *43*, 136.
(10) Weber, W. P.; Gokel, G. W. "Phase Transfer Catalysis in Organic Synthesis"; Springer-Verlag: New York, 1977.
(11) Starks, C. M.; Liotta, C. "Phase Transfer Catalysis: Principles and Techniques"; Academic Press: New York, 1978.
(12) Siddall, T. H., III. *J. Inorg. Nucl. Chem.* **1963**, *25*, 883.
(13) Schroeder, N. C.; McIsaac, L. D.; Meikrantz, D. H.; Krupa, J. F.; Baker, J. D. *J. Inorg. Nucl. Chem.* **1980**, *42*, 1029.
(14) Siddall, T. H., III. *J. Inorg. Nucl. Chem.* **1964**, *26*, 1991.

0022-3263/81/1946-5188$01.25/0

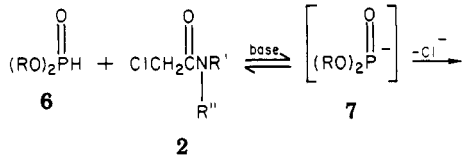
Table I. Summary of PTC Preparative Data for Products 3 and 10[a]

product	temp, °C	time, h	crude yield, %	crude purity, %[b]
3b	5–10	5	100	91
3c	10–15	2.5	100	81
3d	15–20	3	79	84
3e	15–20	4.5	90	83
3g	20–25	4	97	88
3h	20–25	5.5	100	85
3j	10–15	3.5	94	79
3k	15–20	3	89	57
3l	25–30	8	50	91
3m	10–15	9.5	51	71
10b	40–42	6	104	84
10f	40–42	3	82	77
10i	40–42	4.5	102	85

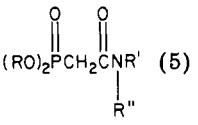
[a] The conditions, yields, and products reported are the result of single runs and are not to be considered optimized. [b] Minimum weight percent obtained by GLC.

discussed limitations of this route lead to a product of similar quality to that obtained by the Arbuzov route.

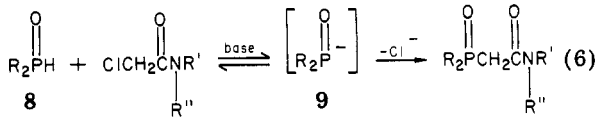
It is generally known that dialkyl hydrogen phosphonates are vulnerable to hydrolysis in aqueous environments, whether acidic or basic.[15] We have discovered, however, that 6, where R is sufficiently hydrophobic to afford good organic solubility (R ≥ C_3H_7), exhibits reasonable stability in an organic-aqueous two-phase system. This observation permits the application of phase-transfer catalysis with aqueous sodium hydroxide to the Michaelis–Becker reaction. With proper conditions to favor nucleophilic displacement (eq 5) relative to consumption of 6 by hydrolysis, excellent yields of 3 are obtained under very mild and convenient conditions (Table I).



6 2 7



3 (5)



8 2 9 10 (6)

a, R = n-C_4H_9, R′ = R″ = C_2H_5; b, R = R′ = R″ = n-C_4H_9; c, R = n-C_6H_{13}, R′ = R″ = C_2H_5; d, R = $(CH_3)_3CCH_2C(CH_3)HCH_2$, R′ = R″ = CH_3; e, R = n-$C_4H_9C(C_2H_5)HCH_2$, R′ = R″ = CH_3; f, R = n-C_8H_{17}, R′ = R″ = CH_3; g, R = n-$C_4H_9C(C_2H_5)HCH_2$, R′,R″ = $(CH_2)_4$; h, R = n-$C_4H_9C(C_2H_5)HCH_2$; R′ = R″ = C_2H_5; i, R = n-C_8H_{17}, R′ = R″ = C_2H_5; j, R = $(CH_3)_3CCH_2C(CH_3)HCH_2CH_2$, R′ = R″ = CH_3; k, R = i-C_9H_{19}, R′ = R″ = CH_3; l, R = $(CH_3)_2CH(CH_2)_3C(CH_3)HCH_2$, R′ = R″ = CH_3; m, R = R′ = n-$C_4H_9C(C_2H_5)HCH_2$, R″ = H

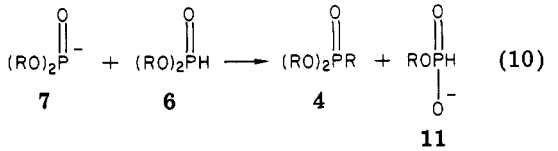
Agitation of a two-phase system comprised of an aqueous sodium hydroxide solution and an organic phase made up of a solvent such as methylene chloride, the reactants 2 and 6, and a catalytic amount of a quaternary ammonium or phosphonium chloride (QCl) enables ion exchange to occur at the phase interface with distribution of the resultant base, QOH, to the organic phase (eq 7).[16] There,

$$QCl(org) + NaOH(aq) \rightleftharpoons QOH(org) + NaCl(aq) \quad (7)$$

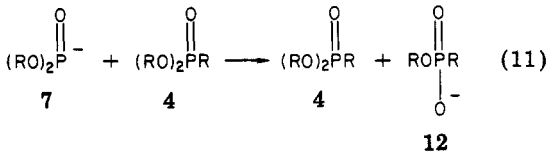
$$QOH(org) + 6(org) \rightleftharpoons (RO)_2P(O)Q(org) + H_2O \quad (8)$$

$$(RO)_2P(O)Q(org) + 2(org) \rightarrow 3(org) + QCl(org) \quad (9)$$

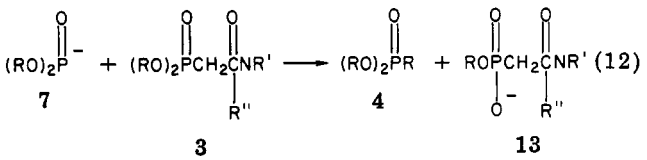
it is a sufficiently strong base to deprotonate the dialkyl hydrogen phosphonate 6 (eq 8). The nucleophilic dialkyl phosphonate anion 7 reacts as it is formed with 2 to produce the product, 3, directly (eq 9). The avoidance of high concentrations of 7 is likely a primary reason (along with the mild conditions) that side products typical of conventional Michaelis–Becker reactions[17] (eq 10–12) are substantially avoided by this technique.



7 6 4 11 (10)



7 4 4 12 (11)



7 4 3 13 (12)

Hydrophobic aliphatic quaternary catalysts promote favorable organic phase distribution of QOH, a requirement for effective hydroxide transfer (eq 7). They also enhance organic phase distribution of 7 (eq 8 and 9), minimizing hydrolytic degradation (vide infra). The structural features of the catalysts which are conducive to PTC activity in general[10,11] apply to this technique.

Chloride is preferred for both the catalyst counterion and for the leaving group of 2. It exchanges readily with other anions such as hydroxide, promoting a favorable equilibrium constant for eq 7. Anions such as Br^-, I^-, or RSO_3^- associate more strongly with Q^+ in the organic phase[18] and diminish its ability to transfer hydroxide ion, so catalyst "poisoning" can result in the presence of such anions.

If the catalyst, QCl, is replaced by a tertiary amine such as tri-n-butylamine, only hydrolysis of 6 is observed. Clearly, tertiary amines do not catalyze the desired reaction, and either their alkylation by 2 is slow under these conditions or the resulting quaternary ammonium chloride is not a phase-transfer catalyst.

Removal of the catalyst from the product can be accomplished by known techniques.[19,20] Alternatively, the

(15) Kosolapoff, G. M.; Maier, L. "Organic Phosphorus Compounds"; Wiley-Interscience: New York, 1973; Vol. 5, pp 41–2.

(16) It is debatable whether the hydroxide ion actually enters the organic phase and a strong argument can be made for a heterogeneous deprotonation (Dehmlow, E. V.; Slopianka, M.; Heider, J. *Tetrahedron Lett.* **1977**, 2361). However, our qualitative observations that this reaction is facilitated by very hydrophobic catalysts (e.g., methyltricaprylylammonium chloride relative to tetrabutylammonium chloride) and that the rate of reaction is independent of the stirring rate above about 200 rpm suggest that, in this case, the relatively polar organic media (a solution of the dipolar aprotic amides 2 and 3 or 10 in CH_2Cl_2) and a high $[OH^-]$ favor hydroxide transfer to the organic phase as QOH_{org}.

(17) Petrov, K. A.; Maklyaev, F. L.; Bliznyuk, N. K. *J. Gen. Chem. USSR (Engl. Transl.)* **1960**, *30*, 1604.

(18) Reference 11, p 67.

(19) Reference 11, p 55.

(20) Rafecas, L.; Artus, J. J. *Tetrahedron Lett.* **1980**, *21*, 977.

quaternary ion can be immobilized on an insoluble polymer matrix to form a solid–liquid–liquid triphase catalysis system[21] in which the solid catalyst is easily removed by filtration.

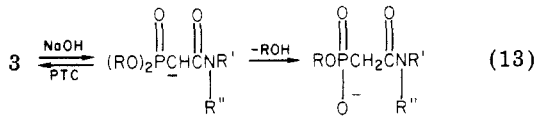
The degree of agitation is important to the success of the reaction. When a conventional laboratory mechanical paddle stirrer is used, the rate of reaction is qualitatively proportional to the rate of stirring below about 200 rpm, likely a mass transfer effect. Above this point, however, the rate of reaction is independent of stirring rate, a common feature of PTC reactions. The rate of hydrolysis, however, continues to increase rapidly with increased agitation, so it is advantageous to maintain the stirring speed near 200 rpm to minimize hydrolysis relative to the desired displacement reaction.

High aqueous phase base concentrations favor hydroxide transfer (eq 7) and reduce aqueous phase distribution of all the organic species, reducing the tendency toward hydrolysis. This also reduces the amount of water available for hydration of the organic ions in the organic phase. Commercial 50% sodium hydroxide is the aqueous phase of choice; more dilute solutions lead to measurable hydrolysis.

Although the use of an organic solvent is not necessary, best results have been obtained with the use of methylene chloride. This solvent appears to facilitate hydroxide transfer, diminishes organic ion hydration in the organic phase, and provides favorable distribution coefficients for the organic species involved.

Hydrophobic R groups naturally improve the organic distribution of **6**, of **7**, and of the product **3** reducing the chance for hydrolysis. This feature makes this technique ideally suited for the preparation of solvent extraction reagents for which such hydrophobicity is required.

Although under the properly chosen conditions excellent yields of **3** are obtained, excessive reaction times are to be avoided because product hydrolysis can occur. It has not yet been established whether this decomposition results from conventional phosphonate or carboxamide hydrolyss or from an E1cB-type (eq 13) hydrolysis,[22] although the



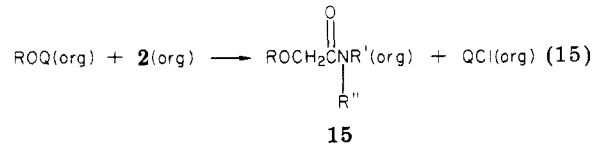
(13)

14 13

latter appears unlikely on the basis of our inability to trap intermediate **14** with alkylating agents.

If hydrolysis occurs to any extent during the reaction, regardless of whether the hydrolyzed species is the starting dialkyl hydrogen phosphonate, **6**, conjugate base, **7**, or product, **3**, a product is the alcohol, ROH. In the PTC system, the corresponding alkoxide is formed (eq 14) which

$$\mathrm{ROH(org) + QOH(org) \rightleftharpoons ROQ(org) + H_2O} \quad (14)$$



(15)

15

competes for remaining chloroacetamide, **2**, to form irreversibly another side product, **15** (eq 15).[23] It is also very likely that the organophosphorus hydrolysis product anion

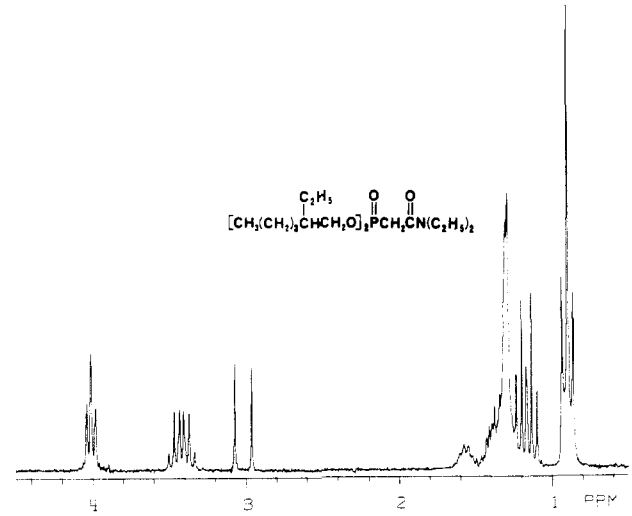


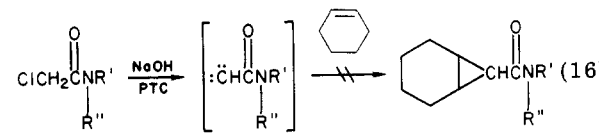
Figure 1. ^{1}H NMR spectrum of bis(2-ethyl-1-hexyl) (*N*,*N*-diethylcarbamoylmethyl)phosphonate (**3h**).

strongly associates in the organic phase with Q^+. Such catalyst "poisoning" (vide supra) results in reaction failure. The overall result is that the PTC route to **3** either works exceptionally well or fails. Clearly, hydrolysis must be avoided.

When the products **3** are used for solvent extraction applications, the presence of dealkylated products such as **5** or **13** cause serious problems.[14,24,25] Their very high extractant strength interferes with proper selective stripping. These impurities are present in products **3** prepared by conventional routes (eq 3 and 12) and can also result from thermal or radiolytic decay during operation. The substantial avoidance of these byproducts by the PTC route relative to conventional techniques is a significant advantage.

The new method provides a route to novel tertiary (carbamoylmethyl)phosphine oxides (**10**) which promise to be stronger extractants than **3** and whose structure precludes hydrolysis, which in **3** can lead to the troublesome impurities **5** and **13**. Sodium salts of dialkylphosphine oxides **9** are known to be very insoluble, a problem which generally precludes the use of the Michaelis–Becker reaction for the synthesis of trialkylphosphine oxides.[26] However, no difficulties with precipitation are encountered during the PTC reaction (eq 6), as the quaternary ammonium salts of **9** are converted as they form alkylated products **10**. Although dialkylphosphine oxides are less reactive than corresponding dialkyl hydrogen phosphonates, the hydrolytic stabilities of the former and of the resulting products, **10**, permit higher reaction temperatures.

Use of cyclohexene as the reaction solvent leads to normal PTC formation of **3b**. No products indicative of the intermediacy of a carbene resulting from geminal dehydrochlorination of **2** could be detected (eq 16).



(16)

2

(21) Regen, S. L. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 421.
(22) Broxton, T. J.; Duddy, N. W. *J. Org. Chem.* **1981**, *46*, 1186.
(23) Freedman, H. H.; Dubois, R. A. *Tetrahedron Lett.* **1975**, 3251.
(24) Bahner, C. T.; Shoun, R. R.; McDowell, W. J. Report No. ORNL/TM-5878; Oak Ridge National Laboratory: Oak Ridge, TN, 1977.
(25) Katz, S.; Bond, W. D. *J. Inorg. Nucl. Chem.* **1979**, *41*, 1781.
(26) Siddall, T. H., III; Davis, M. A. *J. Chem. Eng. Data* **1965**, *10*, 303. This article reports an alternative route to trialkylphosphine oxides.
(27) Schimmelschmidt, K.; Kleiner, H. British Patent 1 298 156, 1972.

Table II. Summary of Analytical Data for Products 3 and 10

product	$\delta(^1HCH_2)^a$	$\delta\,^{31}P^b$	$J(^{31}PCH)^c$	sample purity[d]	anal. calcd, found, % C	H	N	P
3a[e]	3.02	22.12	22.1	81	54.71, 54.80	9.84, 9.71	4.56, 4.25	10.08, 9.97
3b[f]	3.01	22.25	22.1	94	59.48, 59.69	10.54, 10.26	3.85, 3.92	8.52, 8.38
3c[f]	3.01	22.12	22.1	95	59.48, 59.50	10.54, 10.36	3.85, 3.74	8.52, 8.50
3d[f]	3.06	21.54	22.1	97	61.35, 61.28	10.81, 11.02	3.58, 3.47	7.91, 8.13
3e[f]	3.06	21.86	22.1	95	61.35, 61.22	10.81, 11.00	3.58, 3.68	7.91, 7.99
3g[f]	2.99	22.10	22.1	96	63.28, 63.53	10.52, 11.10	3.35, 3.99	7.42, 7.36
3h[f]	3.01	22.14	22.2	94	62.98, 63.13	11.05, 11.05	3.34, 3.27	7.38, 7.39
3j[f]	3.05	21.97	22.1	96	62.98, 63.05	11.05, 10.98	3.34, 3.28	7.38, 7.41
3k[f]	3.06	21.97	22.1	88	62.98, 63.09	11.05, 11.20	3.34, 3.39	7.38, 7.38
3l[f]	3.00	19.17	21.4	91	62.98, 63.02	11.05, 11.05	3.34, 3.39	7.38, 7.34
3m[f]	2.84	24.34	20.1	91	65.65, 65.56	11.44, 11.51	2.95, 3.01	6.51, 6.33
10b[f]	2.96	48.27	15.1	91	65.22, 66.35	11.56, 11.56	4.23, 4.15	9.34, 8.87
10f[g]	2.96	47.61	14.0	100	66.81, 66.94	11.77, 11.64	3.90, 3.87	8.61, 8.71
10i[h]	2.97	48.30	14.8	85	68.18, 68.00	11.96, 12.01	3.61, 3.53	7.99, 7.98

[a] ^1H NMR chemical shift (parts per million) of methylene protons signal (center of observed doublet) relative to tetramethylsilane. [b] ^{31}P NMR chemical shift (parts per million) of the phosphorus atom (decoupled) downfield from 85% phosphoric acid. [c] ^1H NMR coupling constant (hertz) for the splitting of the methylene protons signal by the ^{31}P atom. [d] Minimum weight percent obtained by GLC. [e] Prepared by reported method;[12] double distilled through a 10-cm length Vigreux column. [f] Flash distilled (10^{-3} mmHg, Kugelrohr apparatus). [g] Recrystallized from pentane; mp 38.5–40.5. [h] Undistilled crude product.

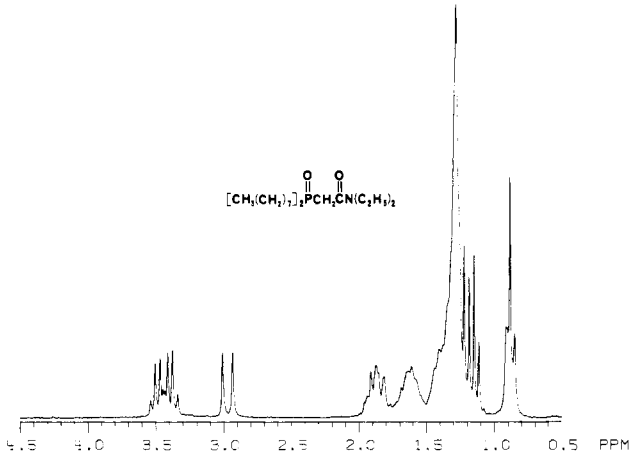


Figure 2. ^1H NMR spectrum of (*N,N*-diethylcarbamoylmethyl)di-*n*-octylphosphine oxide (10i).

The ^1H NMR spectra of 3 and 10 are unambiguous (Figures 1 and 2), the CH_2 signal appearing as a sharp doublet (Table II). This signal is overlapped with the higher field amide methyl signal when R′ = R″ = CH_3. The proton-decoupled ^{31}P spectra consists of a sharp singlet (Table II) affording an excellent method of determining phosphorus-containing impurities.

Experimental Section

A Perkin-Elmer Sigma 1 gas chromatograph with a flame-ionization detector was used routinely for reaction monitoring and product analysis. A 6 ft × $^1/_8$ in. stainless-steel column packed with 3% SE-30 on Chromsorb Q 80/100 was used with helium as the carrier. Carefully fractionated, chromatographically pure dibutyl phthalate was used as an internal standard for the quantitative analyses. NMR spectra were obtained from 10% solutions in $CDCl_3$ with a Nicolet NT-200 spectrometer operated at 200.067 MHz for ^1H and at 80.98 MHz for ^{31}P. Methyltricaprylylammonium chloride was a commercial product of Ashland Chemicals, reported to be an 85% solution. Dibutyl hydrogen phosphonate and bis(2-ethylhexyl) hydrogen phosphonate were products of Mobil Chemicals and were 93.8% and 93.6% pure by GLC. Dialkyl hydrogen phosphonates (6) which were not commercially available were prepared by known procedures (Table III). *N,N*-Diethylchloroacetamide was obtained from ICN/K&K Life Sciences and was 97.7% pure by GLC. Di-*n*-butylphosphine oxide was obtained from Organometallics, Inc., and was 90% pure by GLC. Di-*n*-octylphosphine oxide was obtained from Specialty Organics, Inc., and was chromatographically pure. All other organics utilized were available from common sources and were of reagent quality. Elemental analyses were performed by Galbraith Labs., Inc.

Table III. Summary of Preparative Data for Dialkyl Hydrogen Phosphonates 6 and Chloroacetamides 2

product	bp, °C (mmHg)	yield,[a] %	purity,[b] %
6c[c]	90–92 (0.1)	79	97
6d[d]	94–97 (0.01)	82	96
6j[d]	99–101 (0.001)	77	95
6k[d]	84–91 (0.001)	71	95
6l[d]	83–96 (0.0005)	49	99.5
2b	103–110 (0.7)	94	99.5
2d	58 (0.05)	79	99.2
2g	100–105 (1.3)[e]	88	99.5
2m	103–116 (0.8)	97	99.5

[a] Distilled. [b] Minimum weight percent obtained by GLC. [c] Prepared by the method described in ref 15, p 40. [d] Prepared by the method described in ref 27. [e] Mp 43–6 °C.

The following general experimental procedures are to be considered illustrative.

Preparation of Dialkyl (Carbamoylmethyl)phosphonates (3). Into a 500-mL, three-necked, round-bottomed flask equipped with a thermowell, a 125-mL pressure-equalizing addition funnel, a mechanical stirrer, inert gas fittings, and a septum was placed a solution of 0.10 mol of the chloroacetamide and 0.5 g of methyltricaprylylammonium chloride in 75 mL of methylene chloride along with 100 mL of 50% sodium hydroxide. The solution was stirred at 200 rpm under a gentle purge of nitrogen and maintained at the appropriate reaction temperature (Table I) while a solution of 0.11 mol of the dialkyl hydrogen phosphonate and 0.5 g of methyltricaprylylammonium chloride in 75 mL of methylene chloride was added dropwise. Analytical samples were removed by syringe every 30 min for GLC analysis to monitor disappearance of starting material and formation of product. The addition was complete after 1 h. After 2 h additional dialkyl hydrogen phosphonate (0.01 mol) was added, the stirring was continued for the remainder of the reaction time (Table I), and the phases were separated. The aqueous layer was extracted with 50 mL of pentane and the combined organic layers were washed with three 50-mL portions of 50% by volume aqueous methanol followed by one 50-mL portion of saturated sodium chloride solution. After the mixture was dried over anhydrous potassium carbonate and filtered, the filtrate was evaporated in vacuo [80 °C (2 mmHg)]. Product data for 3 are summarized in Tables I and II.

Sacrificial Study of PTC Route Conditions Leading to Hydrolysis. A reaction was conducted by the same general procedure as the PTC route (vide supra) to prepare dibutyl

(*N,N*-dibutylcarbamoylmethyl)phosphonate (**3b**). However, the reaction temperature was increased to 25 °C and the stirring rate to 500 rpm. The first product observed (20 min) by monitoring the progress of the reaction was **3b**. However, as the reaction proceeded, a new product, eluting earlier than **3b**, steadily grew in concentration. A large amount of precipitate began to accumulate which eventually precluded syringe sampling. After a reaction time of 16 h, 100 mL of water was slowly added to aid dissolution of the accumulated precipitate. The phases were separated, and the aqueous layer was washed with 100 mL of methylene chloride. The organic layers were combined and worked up as previously described to yield only 12.7 g of an amber oil which was analyzed by GLC and found to be predominantly comprised of the new product (59%) and **3b** (4%). Distillation yielded a fraction [7.9 g; bp 105–106 °C (0.35 mmHg)] of a colorless oil which was the new product in 93% purity. NMR, IR, and GC/M identified the product as *N,N*-dibutyl-*n*-butoxyacetamide (**15b**). No products resulting from alkylation of possible intermediate **14b** could be detected.

Preparation of Tertiary (Carbamoylmethyl)phosphine Oxides 10. Into a 500-mL, three-necked, round-bottomed flask equipped with a thermowell, a mechanical stirrer, a condenser, and a septum was placed a solution of 0.11 mol of the chloroacetamide, 1.0 g of tetra-*n*-hexylammonium chloride, and 0.10 mol of the dialkylphosphine oxide in 150 mL of methylene chloride along with 100 mL of 50% sodium hydroxide. The solution was stirred at 300 rpm under a gentle reflux until GLC analysis of removed aliquots indicated the consumption of the starting materials. Workup as before (vide supra) produced the product, **10**, data for which are summarized in Tables I and II.

Preparation of Chloroacetamides 2. An adaptation of the Schotten–Baumann procedure was found most suitable. Thus, into a three-necked, round-bottomed flask equipped with a thermowell, a mechanical stirrer, a 250-mL pressure-equalizing addition funnel, and inert gas fittings was placed a solution of 0.10 mol of the amine in 100 mL of methylene chloride along with 100 mL of 20% by weight sodium hydroxide solution. With the temperature maintained at −25 °C under a gentle nitrogen purge and a stirring rate of 150 rpm, a solution of 12.4 g (0.11 mol) of chloroacetyl chloride in 50 mL of methylene chloride was added dropwise. When the addition was complete, the reaction mixture was allowed to stir an additional 15 min and then was transferred to a 500-mL separatory funnel. The phases were separated, and the aqueous layer was washed with three 50-mL portions of methylene chloride. The combined organic layer was washed with a solution comprised of 100 mL of saturated sodium chloride and 5 mL of concentrated hydrochloric acid, dried ($MgSO_4$), concentrated, and distilled under reduced pressure (Table III).

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Registry No. 2b, 2567-59-1; **2d**, 2675-89-0; **2g**, 20266-00-6; **2m**, 32461-85-1; **3a**, 7439-68-1; **3b**, 66258-30-8; **3c**, 7369-66-6; **3d**, 79373-07-2; **3e**, 79373-08-3; **3g**, 79391-52-9; **3h**, 66258-31-9; **3j**, 79373-09-4; **3k**, 79373-10-7; **3l**, 79373-11-8; **3m**, 79391-53-0; **6b**, 1809-19-4; **6c**, 6151-90-2; **6d**, 79373-12-9; **6e**, 3658-48-8; **6f**, 1809-14-9; **6j**, 79373-13-0; **6k**, 79373-14-1; **6l**, 13086-87-8; **8b**, 15754-54-8; **8f**, 3011-82-3; **10b**, 79373-15-2; **10f**, 79391-54-1; **10i**, 79391-55-2; chloroacetyl chloride, 79-04-9; *N*-butyl-1-butanamine, 111-92-2; *N*-methylmethanamine, 124-40-3; pyrrolidine, 123-75-1; 2-ethyl-1-hexanamine, 104-75-6.

Marine Natural Products: Halogenated Acetylenic Ethers from the Sea Hare *Aplysia Dactylomela*[1]

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From the extracts of a Caribbean sea hare, *Aplysia dactylomela*, one new halogenated sesquiterpene ether, **8**, isodeodactol ($C_{15}H_{25}O_2Br_2Cl$), and two isomeric pairs of new C_{15}-halogenated ethers having straight-chain carbon skeletons have been isolated: **3** and **4** ($C_{15}H_{20}OBrCl$); **5** and **6** ($C_{15}H_{20}O_2BrCl$). Compounds **3–6** belong to a class of fatty acid derived ethers characterized by ether rings of various sizes and a terminal enyne moiety. X-ray analysis confirmed that **3**, (3*E*)-12-*epi*-obtusenyne, contains a nine-membered ether ring with a trans terminal enyne group. Spectral analysis and chemical correlation established that **4** differs from **3** only in having a cis terminal enyne group. Ether **5** was found by X-ray analysis to have a cis-fused 1,5-dioxodecalin skeleton and a trans terminal enyne group. Detailed spectral analyses confirmed that ether **6** is the 3*Z* isomer of **5**. The structure of isodeodactol, **8**, was established by spectral analysis.

In previous work with extracts of the sea hare *Aplysia dactylomela*, we have isolated a variety of compounds[2] including the two halogenated ethers dactylyne (**1**)[3] and isodactylyne (**2**)[4] (Chart I). These ethers are representatives of a group of related ethers[5] of algal origin characterized by a straight-chain C_{15} carbon skeleton and a terminal enyne functionality. The extracts from *A. dactylomela* are rich in organics, and in this paper we describe the isolation of five new halogenated ethers, **3–6** and **8**, four of which belong to the group represented by **1** and **2**. All of the *Aplysia* isolates are considered to be of algal origin since such a dietary source has been established for

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