vironmental Health Sciences and Center Grant CA 13343 from the National Cancer Institute.

Registry No.—**1**, 55400-86-7; **2**, 55400-87-8; **3**, 4371-26-0; **4**, 55400-88-9; **5**, 55400-89-0; **6**, 55400-90-3; dibenz[*a*,*h*]anthracene, 53-70-3; dimethyl sulfate, 77-78-1.

References and Notes

(1) (a) D. M. Jerina, J. W. Daly, B. Witkop, P. Zaltzman-Nirenberg, and S. Udenfriend, *J. Am. Chem. Soc.*, **90**, 6525 (1968); (b) *Biochemistry*, **9**, 147 (1970).
(2) (a) E. Boyland and P. Sims, *Biochem. J.*, **97**, 7 (1965); (b) S. H. Goh and R. G. Harvey, *J. Am. Chem. Soc.*, **95**, 242 (1973); (c) P. Dansette and D. M. Jerina, *ibid.*, **96**, 1224 (1974).
(3) (a) B. L. Van Duuren, G. Witz, and S. C. Agarwal, *J. Org. Chem.*, **39**, 1032 (1974); (b) H. Cho and R. G. Harvey, *Tetrahedron Lett.*, 1491 (1974), and ref 2c.
(4) D. B. Clayson, "Chemical Carcinogenesis", Little, Brown and Co., Boston, Mass., 1962, p 166.
(5) D. M. Jerina and J. W. Daly, *Science*, **185**, 573 (1974).
(6) B. L. Van Duuren, *Ann. N.Y. Acad. Sci.*, **163**, 633 (1969).
(7) D. M. Jerina, "Chemical Carcinogenesis", Part A, P. O. Ts'o and J. A. Di Paolo, Ed., Marcel Dekker, New York, N.Y., 1974, p 289.
(8) M. S. Newman and S. Blum, *J. Am. Chem. Soc.*, **86**, 5598 (1964).
(9) V. Mark, *J. Am. Chem. Soc.*, **85**, 1884 (1963).
(10) E. J. Moriconi, W. F. O'Connor, W. J. Schmitt, G. W. Cogswell, and B. P. Fürer, *J. Am. Chem. Soc.*, **82**, 3441 (1960).
(11) W. Lijinsky, *J. Org. Chem.*, **26**, 3230 (1961).
(12) J. A. Labudde and C. Heidelberger, *J. Am. Chem. Soc.*, **80**, 1225 (1958).
(13) E. Boyland, A. A. Levi, E. H. Mawson, and E. Roe, *Biochem. J.*, **35**, 184 (1941).
(14) R. Weitzenböck, *Monatsh. Chem.*, **34**, 193 (1913).
(15) S. Cravitt and B. L. Van Duuren, *Chem. Instrum.*, **1**, 71 (1968).
(16) M. S. Newman and W. Hung, *J. Org. Chem.*, **39**, 3950 (1974), and ref 2a.
(17) L. F. Fieser and F. Novello, *J. Am. Chem. Soc.*, **62**, 1855 (1940).

Synthetic Studies on Phosphorylating Reagent. II.[1] 2-(*N*,*N*-Dialkylamino)-4-nitrophenyl Phosphate and Its Use in the Synthesis of Phosphate Esters

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2-(*N*,*N*-Dimethylamino)-4-nitrophenyl phosphate (**6a**) and 2-(*N*,*N*-diethylamino)-4-nitrophenyl phosphate (**6b**) were prepared from 2-amino-4-nitrophenol (**4**) via three steps. These compounds were activatable in situ by the addition of an acidic catalyst and showed moderate phosphorylating ability toward various alcohols. By the comparison of their reactivities in the reaction with benzyl alcohol, **6a** was shown to be a better phosphorylating agent than **6b**. It reacted readily with an alcohol having an unprotected amino group to give the aminoalkyl phosphate without unfavorable formation of the phosphoroamidate. Reaction with a mercapto alcohol under the same condition gave the *S*-hydroxyalkylphosphorothioate as the main product.

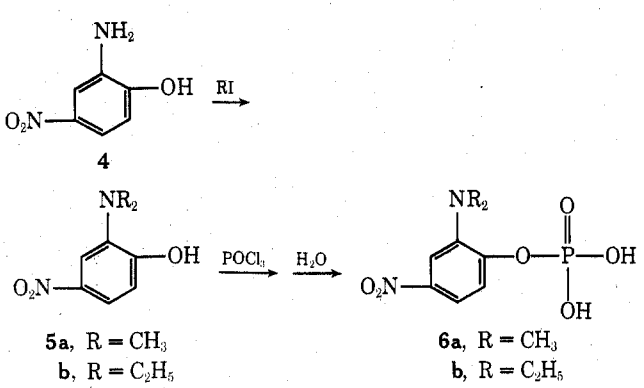
In previous papers,[1-6] we have reported the synthesis of a new phosphorylating reagent, 2-chloromethyl-4-nitrophenyl phosphorodichloridate (**1**), having an activatable protecting group and its use in the preparation of alkyl phosphates. It was shown that the reagent is very useful for the preparation of the valuable alkyl dihydrogen phosphates and dialkyl hydrogen phosphates from the corresponding alcohols. However, it could not be utilized in the phosphorylation of amino alcohols because of reaction with the amino group.

Recently, with a view to developing a milder reagent which could be used in the phosphorylation of amino alcohols, the reactivity of the inner salt of 1-(2-dihydrogenphosphoroxy-5-nitrobenzyl)pyridinium hydroxide (**3**) was investigated.[1] This reagent derived from **1** showed reduced activity and reacted satisfactorily with a *tert*-amino substituted alcohol to afford the *tert*-aminoalkyl phosphate. However, phosphorylation of alcohols which have secondary and primary amino groups resulted in the unfavorable formation of the phosphoroamidate. Another disadvantage of the reagent is its low reactivity and necessity of an excess of alcohol for completion of the reaction.

In the present study, with an aim to develop a more versatile reagent, 2-(*N*,*N*-dialkylamino)-4-nitrophenyl phosphate (**6**) was designed as a new phosphorylating agent on the following assumptions. The 2-(*N*,*N*-dialkylamino)-4-nitrophenyl group would function as a protecting group at the first stage, because the strong electron-withdrawing power of the nitro group, which exerts phosphorylating ability, is compensated by the electron-releasing effect of the dialkylamino group. However, upon addition of acidic catalyst the dialkylamino group would be converted into the positively charged ammonium group, which would enhance the electrophilicity of the phosphoryl group. Thus the reaction with a nucleophile such as alcohol and thiol would proceed smoothly. At the same time, it was expected that selective phosphorylation of the hydroxy group in an amino alcohol would be possible because of protonation of the amino group of the reactant under the conditions used.

While Amery and Corbett[7] obtained 2-(*N*,*N*-dimethylamino)-4-nitrophenol (**5a**) from 2-aminoanisole via three steps, we have attempted the preparation of 2-(*N*,*N*-dialkylamino)-4-nitrophenol by the selective dialkylation of 2-amino-4-nitrophenol (**4**). Alkylation of **4** with 2.5 molar quantities of methyl or ethyl iodide in the presence of triethylamine proceeded successfully to give the corresponding 2-(*N*,*N*-dialkylamino)-4-nitrophenol hydrochlorides **5a,b** in 58 and 19% yield, respectively (Chart I). In these al-

Chart I



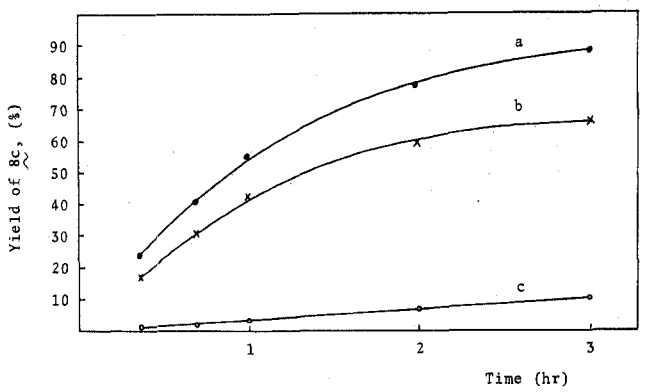


Figure 1. The yield of benzyl dihydrogen phosphate with time, in the reaction of benzyl alcohol (equimolar quantity) with phosphorylating reagents: a, 2-(*N,N*-dimethylamino)-4-nitrophenyl phosphate (**6a**); b, 2-(*N,N*-diethylamino)-4-nitrophenyl phosphate (**6b**); c, inner salt of *N*-(2-dihydrogen phosphoroxy-5-nitrobenzyl)pyridinium hydroxide (**3**).

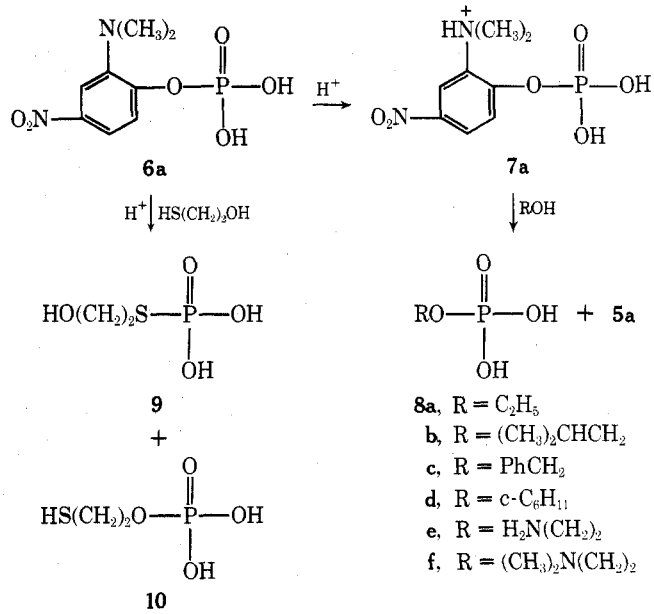
kylations, formation of other alkylated products were observed on TLC; however, their isolation was not attempted. The structure of **5a** was confirmed by NMR spectroscopy. A six-proton singlet assignable to the *N*-methyl protons appeared at 3.29 ppm and no signal attributable to the *O*-methyl protons was observed around 4.20 ppm. The phosphorylating agents **6** were readily prepared by refluxing **5** and 10 mol of phosphoryl chloride for 24 hr followed by mild hydrolysis with ice–water. Both reagents could be isolated as their crystalline ammonium salts, which could be stored in a desiccator for longer than several months without any deterioration.

Initial studies on these reagents were carried out with benzyl alcohol because the formation of product can be followed by its ultraviolet light absorption. A solution of 1 molar amount of the reagent **6**, which was converted into the triethylammonium salt before use, in anhydrous pyridine was allowed to react with an equimolar amount of benzyl alcohol in the presence of acetic acid (3 mol) and triethylamine (1 mol) under reflux for 3 hr. Aliquots were removed from the reaction mixture at various time intervals and worked up as described in the Experimental Section. The products were then chromatographed on Toyo Roshi No. 51A paper in solvent A. The ultraviolet-absorbing spot corresponding to benzyl dihydrogen phosphate[2] was eluted quantitatively and the amount of each was determined spectrophotometrically at 206 nm. The reactivity of **3** under similar reaction conditions was also traced in the same way for comparison. The results recorded in Figure 1 show that the reaction rate of **6a** is moderately faster than that of **6b** and much faster than that of **3**. The increasing reactivity would be in accord with the increasing electronegativities of the positively charged dialkylammonium and the pyridiniummethyl moieties, because they are protonated or quaternized in the reaction media. It was shown experimentally that other acidic catalysts such as H_2SO_4, CF_3CO_2H, and $BF_3{\cdot}Et_2O$ were also effective. In the absence of the acidic catalyst, the reaction was slower and reached 59% conversion under the same conditions.

Next, a series of experiments was carried out with **6a** to examine the chemical properties of the reagent and the limitations of application. The reactions with primary and secondary alcohols under similar conditions afforded the corresponding alkyl dihydrogen phosphates as monoanilinium salts in good yields. The products were identified with authentic samples prepared by known methods.[2,8] The compound **5a** formed concomitantly was easily recovered from the reaction by extraction with ethyl acetate.

Since phosphorylation of amino alcohols was our main object in this study, the reaction was attempted with 2-aminoethyl alcohols. Treatment of 2-amino- and 2-dimethylaminoethyl alcohol with **6a** in the same way gave 2-amino- (**8e**) and 2-dimethylaminoethyl dihydrogen phosphate (**8f**) in 79 and 73% yield, respectively. The use of equimolar quantities of the reagent **6a** and the reactant, and the fairly good yields, showed that no phosphoroamidate formation occurred in this case. The phosphorylation of 2-mercaptoethyl alcohol afforded a mixture of *S*-(2-hydroxyethyl) dihydrogen phosphorothioate (**9**) and 2-mercaptoethyl dihydrogen phosphate (**10**) in the ratio of 9:1 (Chart II).

Chart II



After the isolation of the mixture as the barium salt, each component was quantitatively determined according to Åkerfeldt's method.[11] It should be noted that predominant formation of the phosphorothioate **9** would be expected, owing to the strong nucleophilicity of the mercapto group.

The new reagent described here seems to have moderate phosphorylating ability toward the alcohol function of unprotected amino alcohols. Since no phosphorylating agent has been reported which does not react with primary amino groups, this procedure should provide a convenient method for the phosphorylation of compounds of biological interest such as nucleosides and aminoglycosides.

Experimental Section

Reagents. Alcohols, amines, and solvents were purified and dried by ordinary procedures. Phosphoryl chloride was freshly distilled before use.

Paper chromatography was carried out by descending technique using Toyo Roshi No. 51A paper. Solvent systems used were: A, isopropyl alcohol–concentrated ammonium hydroxide–water (7:1:2, v/v); B, 1-propanol–concentrated ammonium hydroxide–water (6:3:1, v/v). An uv lamp (254 nm) and Hanes–Isherwood reagent[12] were used for the detection of spots on paper chromatograms.

Melting points are uncorrected and were determined on a Yamato apparatus, Mp-21. The NMR spectra were determined on a Hitachi Perkin-Elmer R-20A instrument (Me_4Si). Ir spectra were determined on a Shimadzu IR-27G spectrometer, and uv spectra on a Hitachi EPS-3T spectrometer.

2-(*N,N*-Dimethylamino)-4-nitrophenol Hydrochloride (5a). To a solution of 2-amino-4-nitrophenol (**4**, 15.4 g, 0.1 mol) and triethylamine (15.1 g, 0.15 mol) in acetone (100 ml) was added drop-

wise methyl iodide (35.6 g, 0.25 mol) with stirring at room temperature for 30 min. The stirring was continued for 4 hr under reflux. Then the reaction mixture was evaporated to dryness under reduced pressure and the resulting syrup was dissolved in 2 *N* sodium acetate (100 ml). The solution was extracted with three 50-ml portions of ethyl acetate. The combined extracts were dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was dissolved in 1 *N* hydrochloric acid and the solution was filtered with charcoal (2 g). The filtrate was evaporated to dryness and the residue was crystallized with ethanol (50 ml).

Recrystallization from methanol–ethyl ether gave **5a** (12.6 g, 58%) as colorless needles: mp 215–216° dec; ν_{max} (Nujol) 2720–2300 (–$^+$NH), 1602, 1497 (Ph), 1520, 1340 cm^{-1} (NO_2); NMR (D_2O) 3.29 (s, 6, 2 CH_3), 7.36 (d, 1, C_6H), 8.28 (q, 1, C_5H), 8.63 ppm (d, 1, C_3H); λ_{max} (H_2O) (pH 6.85) 225.5 nm (ϵ 7670), 259 (5550); (pH 1.55) 223.5 (9000), 306 (9950); (pH 12.3) 279 (7550). Anal. Calcd for $C_8H_{11}N_2O_3Cl$: C, 43.95; H, 5.07; N, 12.81. Found: C, 43.72; H, 5.21; N, 12.91.

2-(*N,N*-Diethylamino)-4-nitrophenol Hydrochloride (5b). To a solution of 2-amino-4-nitrophenol (**4**, 92.5 g, 0.6 mol) and potassium carbonate (93.4 g, 0.69 mol) in acetone (500 ml) was added, dropwise, ethyl iodide (281.1 g, 1.8 mol) with stirring under reflux for 2 hr. The stirring was continued for 4 hr, and then the reaction mixture was evaporated to dryness under reduced pressure. The resulting syrup was dissolved in 2% aqueous sodium hydroxide (500 ml) and the solution was extracted with benzene (200 ml). The aqueous layer was mixed with acetic acid (50 ml) and extracted with three 100-ml portions of ethyl acetate. The combined extracts were dried over anhydrous Na_2SO_4, the solvent was removed by evaporation, and the residue was dissolved in $CHCl_3$. The $CHCl_3$ layer was passed through a column of silica gel (2.2 × 60 cm), and the product was eluted with $CHCl_3$–EtOH (10:1, v/v) and the eluates were evaporated to dryness. The residue was dissolved in ethanol (60 ml) and the solution was acidified with 35% ethanolic hydrogen chloride (80 ml). Addition of ether (300 ml) gave precipitates. The precipitates were collected by filtration and recrystallization from ethanol–ethyl ether to give **5b** (27.7 g, 19%) as pale yellow prisms: mp 220–222° dec; ν_{max} (Nujol) 2780–2300 (–$^+$NH), 1609, 1500 (Ph), 1535, 1347 cm^{-1} (NO_2); NMR (D_2O) 1.18 (t, 6, 2 CH_3), 3.80 (q, 4, 2 CH_2), 7.45 (d, 1, C_6H), 8.40 (q, 1, C_5H), 8.74 ppm (d, 1, C_3H); λ_{max} (H_2O) (pH 6.6) 387 nm (ϵ 16,800); (pH 2.0) 225.5 (8000), 305 (9300); (pH 12.5) 230 (8400), 281.5 (5500), 434 (14,800). Anal. Calcd for $C_{10}H_{15}N_2O_3Cl$: C, 48.69; H, 6.13; N, 11.36; Cl, 14.37. Found: C, 48.53; H, 6.25; N, 11.42, Cl, 14.45.

2-(*N,N*-Dimethylamino)-4-nitrophenyl Phosphate (6a). A mixture of 2-(*N,N*-dimethylamino)-4-nitrophenol hydrochloride (**5a**, 33.0 g, 0.15 mol) and phosphoryl chloride (230.4 g, 1.5 mol) was refluxed for 24 hr in the presence of a catalytic amount of potassium chloride (1.5 g) until the evolution of hydrogen chloride ceased. After removal of excess phosphoryl chloride by evaporation, anhydrous toluene (50 ml) was added, and the solution was evaporated repeatedly by adding anhydrous toluene (three 50-ml portions). The viscous residue was poured into ice–water (500 g). Pyridine (16 g) was added to the aqueous solution, which was stirred for 30 min. The solution was then passed through a column of Amberlite IR-45 resin (OH^- form, 2.2 × 50 cm) and the column was washed with water (500 ml). Concentrated ammonium hydroxide (28%) (4 ml) was added to the eluate. The solution was passed through a column of Dowex-50 (NH_4^+ form, 1.4 × 45 cm) and the column was washed with water (200 ml). The eluate was evaporated to dryness below 40°. The residue was crystallized with ethanol (200 ml) and yellow crystals were collected by filtration. Recrystallization from methanol–ethyl ether gave **6a** monoammonium salt (34.0 g, 81%) as pale yellow prisms: mp 171–172.5°; ν_{max} (Nujol) 3250–3050 (–$^+$$NH_4$), 1580, 1500 (Ph), 1510, 1352 (NO_2), 1278 (P=O), 1135, 1110 cm^{-1} (POC); NMR (D_2O) 2.97 (s, 6, 2 CH_3), 7.60 (d, 1, C_6H), 8.07 (q, 1, C_5H), 8.16 ppm (d, 1, C_3H); λ_{max} (H_2O) (pH 6.85 and 12.3) 228.5 nm (ϵ 12,400), 257 (14,400), 330 (9400); (pH 1.84) 217.5 (13,400), 283 (13,400). Anal. Calcd for $C_8H_{14}N_3O_6P\cdot O\cdot 5H_2O$: C, 33.34; H, 5.25; N, 14.58. Found: C, 33.62; H, 5.33; N, 14.60.

2-(*N,N*-Diethylamino)-4-nitrophenyl Phosphate (6b). In a similar manner as described for **6a**, **6b** was obtained from 2-(*N,N*-diethylamino)-4-nitrophenol hydrochloride (**5b**) and phosphoryl chloride in 50% yield as a pale yellow powder: mp 161–164° (aqueous ethanol); ν_{max} (Nujol) 3250–3100 (–$^+$$NH_4$), 1585, 1495 (Ph), 1522, 1350 (NO_2), 1270 (P=O), 1171, 1120 cm^{-1} (POC); NMR (D_2O) 1.05 (t, 6, 2 CH_3), 3.24 (q, 4, 2 CH_3), 7.70 ppm (s, 3, Ph); λ_{max} (H_2O) (pH 6.6) 223 nm (ϵ 8600), 302.5 (9000); (pH 2.0) 219 (10,000), 285 (9700); (pH 12.5) 232 (7750), 261.5 (8600), 316 (7700).

Table I
Alkyl Dihydrogen Phosphates and 2-Aminoethyl Dihydrogen Phosphates 8

Compd[a]	Yield, %	Mp, °C	R_f
8a[b]	80	164–165	0.21[c]
8b[b]	86	154–156	0.53[d]
8c[b]	83	166–168	0.38[c]
8d[b]	65	170–171	0.42[c]
8e	79	234–235	0.12[c]
8f	73	78–80	0.18[c]

[a] The compounds were identified with authentic samples.[2,8-10] [b] Alkyl dihydrogen phosphates were isolated as their monoanilinium salts. [c] Solvent A. [d] Solvent B.

Anal. Calcd for $C_{10}H_{18}N_3O_6P\cdot 0.33H_2O$: C, 38.40; H, 5.76; N, 13.40. Found: C, 38.56; H, 5.98; N, 13.62.

Alkyl Dihydrogen Phosphate 8a–d. General Procedure. To a solution of **6a** monotriethylammonium salt (3.63 g, 0.01 mol) in pyridine (30 ml) was added the alcohol (0.01 mol), acetic acid (1.80 g, 0.03 mol), and triethylamine (1.01 g, 0.01 mol). The reaction mixture was refluxed for 3 hr and concentrated to dryness. The residue was dissolved in water (50 ml). The solution was passed through a column of Dowex 50 (H^+ form, 1.0 × 50 cm) and the column was washed with water. The eluate was neutralized by the addition of aniline and evaporated to dryness under reduced pressure. The residue was crystallized from ethanol. Recrystallization from 95% ethanol gave the corresponding alkyl dihydrogen phosphates monoanilinium salts **8a–d** listed in Table I.

2-Aminoethyl Dihydrogen Phosphate 8e,f. General Procedure. To a solution of **6a** monotriethylammonium salt (3.63 g, 0.01 mol) in pyridine (30 ml) was added the 2-aminoethyl alcohol (0.01 mol), concentrated sulfuric acid (1.96 g, 0.02 mol), and triethylamine (1.01 g, 0.01 mol). The reaction mixture was refluxed for 3 hr and evaporated to dryness. The residue was dissolved in water (60 ml). Barium hydroxide (10.0 g, 0.032 mol) was added to the solution, which was saturated with carbon dioxide. After removal of the precipitates by filtration, the filtrate was adjusted to pH 4 with 10% H_2SO_4 and the precipitates were again removed by filtration. The filtrate was concentrated to dryness and the residue was crystallized from ethanol. Recrystallization from aqueous ethanol gave the corresponding 2-aminoethyl dihydrogen phosphates **8e,f** listed in Table I.

Phosphorylation of 2-Mercaptoethyl Alcohol using 6a. To a solution of **6a** monotriethylammonium salt (3.63 g, 0.01 mol) in pyridine (30 ml) was added 2-mercaptoethyl alcohol (0.78 g, 0.01 mol), acetic acid (1.80 g, 0.03 mol), and triethylamine (1.01 g, 0.01 mol). The reaction mixture was heated under reflux for 3 hr and evaporated to dryness. The residue was dissolved in water (40 ml). The solution was passed through a column of Dowex 50 (H^+ form, 2.8 × 40 cm) and the column was washed with water. The eluate and the washings were combined and neutralized with barium hydroxide. The precipitates were removed by filtration, the filtrate was evaporated to dryness, and the residue was crystallized with ethanol to give the crude barium salt (0.55 g). Paper chromatography (solvent B) exhibited two spots at R_f 0.23 and 0.30 as detected by Hanes–Isherwood's spray. The higher R_f spot was positive toward nitroprusside reagent, showing that the product is a mixture of 2-hydroxyethyl dihydrogen phosphorothioate (**9**) and 2-mercaptoethyl dihydrogen phosphate (**10**).

As an attempt to separate the mixture by DEAE cellulose column chromatography failed, the ratio of the products was determined to be 9:1 (**9**:**10**) by means of iodine titration according to Åkerfeld's method.[11]

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Registry No.—**4**, 99-57-0; **5a**, 55428-48-3; **5b**, 55428-49-4; **6a** monoammonium salt, 55428-50-7; **6a** monotriethylammonium salt, 55428-52-9; **6b** monoammonium salt, 55428-53-0; **8a**, 55428-54-1; **8b**, 55428-55-2; **8c**, 55428-56-3; **8d**, 55428-57-4; **8e**, 1071-23-4; **8f**, 6909-62-2; **9**, 55428-58-5; **10**, 55428-59-6; methyl iodide, 74-88-4;

ethyl iodide, 75-03-6; phosphoryl chloride, 10025-87-3; ethanol, 64-17-5; isobutyl alcohol, 78-83-1; benzyl alcohol, 100-51-6; cyclohexanol, 108-93-0; 2-aminoethanol, 141-43-5; 2-(dimethylamino)-ethanol, 108-01-0; 2-mercaptoethyl alcohol, 60-24-2.

References and Notes

(1) Part I: Y. Taguchi, Y. Mushika, and N. Yoneda, *Bull. Chem. Soc. Jpn.*, **48**, 1524 (1975).
(2) T. Hata, Y. Mushika, and T. Mukaiyama, *J. Am. Chem. Soc.*, **91**, 4532 (1969).
(3) T. Hata, Y. Mushika, and T. Mukaiyama, *Tetrahedron Lett.*, 3505 (1970).
(4) Y. Mushika, T. Hata, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, **44**, 232 (1971).
(5) Y. Mushika and N. Yoneda, *Chem. Pharm. Bull.*, **19**, 687 (1971).
(6) Y. Mushika and N. Yoneda, *Chem. Pharm. Bull.*, **19**, 696 (1971).
(7) G. W. Amery and J. F. Corbett, *J. Chem. Soc. C*, 1053 (1967).
(8) T. Obata and T. Mukaiyama, *J. Org. Chem.*, **32**, 1063 (1967).
(9) E. Cherbuliez and J. Rabinowitz, *Helv. Chim. Acta*, **39**, 1455 (1956).
(10) E. Cherbuliez and J. Rabinowitz, *Helv. Chim. Acta*, **41**, 1168 (1958).
(11) S. Åkerfeldt, *Acta Chem. Scand.*, **16**, 1897 (1962).
(12) C. S. Hanes and F. A. Isherwood, *Nature (London)*, **164**, 1107 (1949).

Micellar Effects upon the Reactions of 2,4-Dinitrophenyl Phosphate and Ethyl *p*-Nitrophenyl Phosphate with Amines

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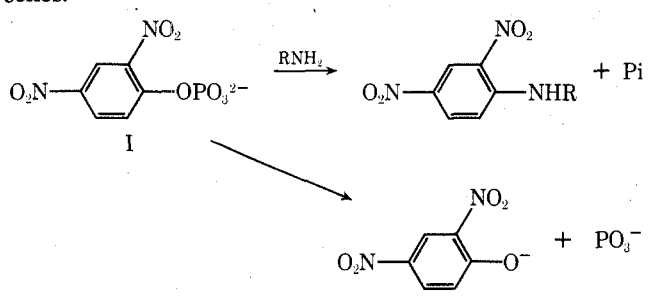
The spontaneous hydrolysis of 2,4-dinitrophenyl phosphate dianion (I) is catalyzed by cationic micelles of the choline-derived surfactant (II, n-$C_{16}H_{33}N^+Me_2CH_2CH_2OHBr^-$), but this surfactant is no more effective than cetyltrimethylammonium bromide, CTABr. Zwitterionic micelles (III, n-$C_{12}H_{25}N^+Me_2CH_2CO_2^-$) are relatively ineffective catalysts. Added primary amines increase reaction rate in the presence of micelles of CTABr or II, but much of the rate enhancement is due to attack by amine upon the aryl group. The effect of the amine increases with its chain length, but secondary amines have less effect, and no attack on the aryl group was found with tertiary amines. The reaction of ethyl *p*-nitrophenyl phosphate monoanion in the presence of CTABr or II is slightly inhibited by added primary amine. In the absence of micelles, amines increase overall reaction rate by attacking the aryl group without markedly catalyzing hydrolysis.

Micelles of cationic surfactants catalyze spontaneous hydrolyses of 2,4- and 2,6-dinitrophenyl phosphate[2,7a,b] and bimolecular nucleophilic attack upon di- and trisubstituted phosphate esters,[7b,8] and cationic surfactants containing nucleophilic[9a,b] or basic[10] groups are effective reagents for attack upon phosphoryl groups of di- and trisubstituted phosphates. Bimolecular attack upon phosphate ester dianions makes little contribution to the overall reaction in the presence or absence of micelles, except at very high pH,[7a,11-13] and in the absence of micelles amines can attack *p*-nitrophenyl phosphate upon the aryl group, as well as speed formation of *p*-nitrophenoxide ion.[14]

There are similarities between the spontaneous hydrolyses of dinitrophenyl phosphate dianions and 2,4-dinitrophenyl sulfate monoanion, in that both involve phenoxide ion elimination,[15] and are catalyzed by cationic micelles,[16] which also markedly change the relative importance of spontaneous hydrolysis of 2,4-dinitrophenyl sulfate monoanion and bimolecular attack by amines upon the aryl group.

The main aim of the present work was to investigate micellar effects upon the reactions of 2,4-dinitrophenyl phosphate dianion (I) in the presence of aliphatic amines which could in principle affect rate and products either by attacking the substrate or by changing the structure of the micelles.



The surfactants used in this work were cetyltrimethylammonium bromide (CTABr, n-$C_{16}H_{33}N^+Me_3Br^-$), *N,N*-dimethyl-*N*-2-hydroxyethylhexadecylammonium bromide (II), n-$C_{16}H_{33}N^+Me_2CH_2CH_2OHBr^-$, and *N,N,N*-dodecyldimethylglycine (III, n-$C_{12}H_{25}N^+Me_2CH_2CO_2^-$). We examined micelles of II because they are effective catalysts for attack upon di- and trisubstituted phosphate esters,[9b] and of III because they are effective catalysts for spontaneous decarboxylations.[17,18] A few experiments were made using ethyl *p*-nitrophenyl phosphate monoanion, because its reactions at high pH are catalyzed by micelles of II and CTABr.[9b]

Experimental Section

Materials. The preparation and purification of the surfactants and the phosphate esters have been described.[7,8,12] Samples of cyclohexylammonium-2,4-dinitrophenyl phosphate were 98–99% pure based on complete hydrolysis both chemically and enzymically using bacterial (*E. coli*) alkaline phosphatase.

Kinetics. The reactions were followed spectrophotometrically using a Gilford spectrophotometer with a water-jacketed cell compartment at 25.0°. The reactions of 2,4-dinitrophenyl phosphate dianion were followed at 358 nm and those of ethyl *p*-nitrophenyl phosphate monoanion were followed at 410 nm.[7-9,12] The first-order rate constants, k_ψ, are in reciprocal seconds. The rate constants for reactions in the absence of surfactants and in the presence of amines are the mean of at least duplicate measurements which agreed within 5%. All the reactions were at a sufficiently high pH that the amines were unprotonated. The substrate concentrations were ca. 2×10^{-5} *M*. The symbol C_D denotes the concentration of surfactant (detergent).

Products. The relative amounts of amine and phenoxide ion were determined after complete reaction of 2,4-dinitrophenyl phosphate by measuring the absorbance at 358 nm of the mixture of *N*-alkyl-2,4-dinitroaniline and 2,4-dinitrophenoxide ion and then reducing the pH of the solution so that the phenoxide ion was converted into phenol and the nitroaniline was unaffected. Under our conditions the difference, $\Delta\epsilon$, of the extinction coefficients of 2,4-dinitrophenoxide ion (ϵ 13,000) and 2,4-dinitrophenol (ϵ 2100) was 10,900 and was unaffected by added 0.01 *M* CTABr. We veri-