Phosphoramidate Anions. The Preparation of Carbodiimides, Ketenimines, Isocyanates, and Isothiocyanates[1]

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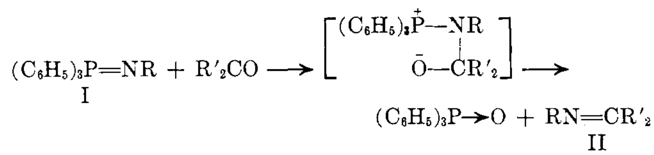
Dialkyl N-alkylphosphoramidate anions have been found to react with isocyanates to give carbodiimides, carbon dioxide to give isocyanates and carbodiimides, ketenes to give ketenimines, carbon disulfide to give isothiocyanates, and with aldehydes to give imines. These syntheses utilize readily available starting materials and proceed under unusually mild reaction conditions.

The phosphinimines (I) were discovered some 40 years ago by Staudinger and are, in principle, extremely interesting intermediates for synthesis of a wide variety of unsaturated nitrogen compounds.[2,3] Their utility, like that of the Wittig reagents to which they bear a formal analogy, is based on the fact that they react with a number of carbonyl-containing molecules to give phosphine oxides and an unsaturated nitrogen compound, II. In many cases, however, phosphinimines require relatively tedious procedures for their preparations.



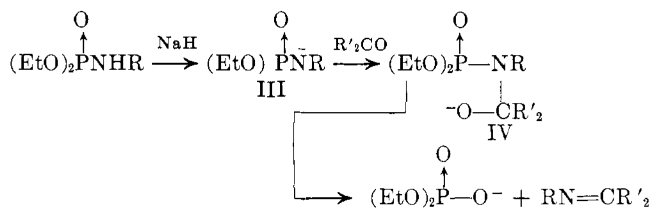
As an extension of our interest in the usefulness of phosphonate carbanions in olefin synthesis,[4] we have examined their nitrogen analogs. The phosphoramidate anions (III) are quite analogous to the phosphinimines in their reactivity toward carbonyl groups. Because of their ready availability, they should prove to be very useful reagents for laboratory preparations of unsaturated organic nitrogen compounds. Dialkyl N-alkylphosphoramidates may be conveniently prepared by the classical reaction of an amine with the commercially available dialkyl phosphorochloridates. An alternate and frequently superior synthesis is based

$$(EtO)_2\overset{O}{\overset{\uparrow}{P}}Cl + RNH_2 \longrightarrow (EtO)_2\overset{O}{\overset{\uparrow}{P}}NHR$$

$$(EtO)_2\overset{O}{\overset{\uparrow}{P}}H + 2RNH_2 + CCl_4 \longrightarrow (EtO)_2\overset{O}{\overset{\uparrow}{P}}NHR + RNH_3{}^+Cl^- + HCCl_3$$

on the reaction of a dialkyl phosphite with amines in the presence of carbon tetrachloride.[5]

Phosphoramidates react smoothly with sodium hydride as a 50% oil dispersion to form stable anions (III) in either benzene or glyme solvents. Reaction of these compounds with active carbonyl groups is quite rapid and normally takes place at room temperature. This synthesis in all probability proceeds stepwise through an adduct such as IV and is based on the ex-



cellence of diethyl phosphate as a leaving group. The sodium diethyl phosphate normally precipitates from the reaction medium after the reaction is complete and can be conveniently removed at that time. Indeed, the ease in which the products prepared by this synthesis are isolated constitutes a major advantage over the phosphinimine route. The major drawback of this method is that it cannot be employed very successfully for materials which are unstable in the presence of an alkaline medium.

The preparation of carbodiimides by reaction of the phosphoramidate anions with isocyanates is a particularly useful variant of the anion synthesis. In contrast to other syntheses of carbodiimides,[6,7] this method is preferred for unsymmetrically substituted products. Its limitation lies in the tendency of many isocyanates, particularly where R′ is a primary alkyl group, to polymerize in basic solution.[8] In

$$(EtO)_2\overset{O}{\overset{\uparrow}{P}}\bar{N}R + R'N{=}C{=}O \longrightarrow R'N{=}C{=}NR + (EtO)_2\overset{O}{\overset{\uparrow}{P}}{-}\bar{O}$$

these cases the yields are much lower. Our experience with carbodiimide synthesis is summarized in Table I. Those carbodiimides which had not previously been

TABLE I
CARBODIIMIDES
RN=C=NR′

R′	R	Yield, %
t-Octyl	Cyclohexyl	84
Phenyl	Cyclohexyl	60
t-Octyl	Dimethylamino	60
t-Butyl	Dimethylamino	60

described in the literature were in all cases characterized by hydrolysis to the ureas. N-*t*-Octyl-N′-dimethylaminocarbodiimide (V) is of some special interest. While it is a distillable liquid, on standing it crystallizes to a dimer (VII) of unknown structure. This phenomenon is reversible in that the dimer can be thermally cracked to give monomer. The monomer (V) can also be alkylated with benzyl chloride to give

(1) A portion of this work has been reported as a communication: W. S. Wadsworth, Jr., and W. D. Emmons, *J. Am. Chem. Soc.*, **84**, 1316 (1962).

(2) H. Staudinger and E. Hauser, *Helv. Chim. Acta*, **4**, 861 (1921).

(3) H. Zimmer and G. Singh, *J. Org. Chem.*, **28**, 483 (1963). Other leading references are cited in this article.

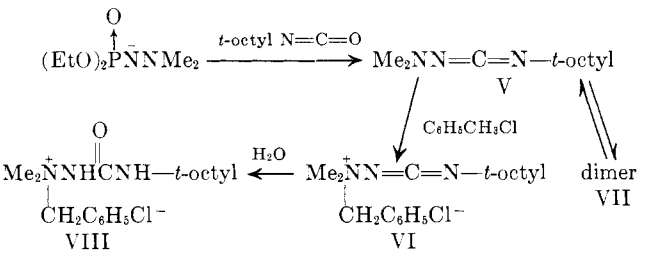
(4) W. S. Wadsworth, Jr., and W. D. Emmons, *J. Am. Chem. Soc.*, **83**, 1733 (1961).

(5) F. Atherton, H. Openshaw, and A. Todd, *J. Chem. Soc.*, 660 (1945).

(6) H. Khorana, *Chem. Rev.*, **53**, 145 (1953).

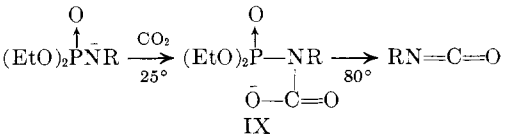
(7) T. W. Campbell, J. J. Monagle, and V. S. Foldi, *J. Am. Chem. Soc.*, **84**, 3673 (1962).

(8) U. Shashoua, W. Sweeney, and R. Tietz, *ibid.*, **82**, 866 (1960).



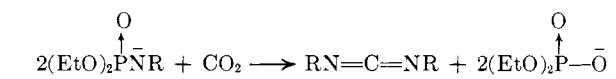
a stable water-soluble carbodiimide which on standing several hours in water is converted to a quaternary carbazide (VIII). The structure of VIII was verified by independent synthesis from the parent carbazide and benzyl chloride. The water-soluble carbodiimide (VI) should presumably be of some use in peptide synthesis since it is easy to make and is not rapidly hydrolyzed.[9]

Phosphoramidate anions react smoothly with CO_2 at room temperature and atmospheric pressure to give a carbamate (IX) which when heated to an appropriate temperature (usually 80°) yields an isocyanate, normally in good yield. The fragmentation to give isocyanate is, however, subject to pronounced steric accelera-



tion and proceeds very smoothly when R is a secondary or tertiary alkyl group. When R was primary, *i.e.*, *n*-butyl, an intermediate, presumably the carbamate, could be isolated by removal of solvent. The intermediate, which liberated CO_2 when acidified, did not decompose until temperatures of over 150° were reached. At this stage an extremely small amount of distillate containing isocyanate and carbodiimide (*via* infrared) was obtained. It was apparent from the volume of CO_2 given off at this temperature and the quantity of phosphoramidate recovered from the residue that the main reaction in this instance was the reversal of carbamate formation.

If the reaction of carbon dioxide with a branched N-alkylphosphoramidate is initially carried out at a temperature of 80°, the carbamate fragments, possibly concurrently with its formation, and the liberated isocyanate reacts with a second mole of the anion to give carbodiimide as the major product. These results



are summarized in Table II. It is apparent from these data that some fragmentation of the carbamate to give isocyanate takes place even at low temperatures when the substituent group is bulky and in the case where it is phenyl. The absence of phenyl isocyanate in the reaction mixture from CO_2 and the N-phenylphosphoramidate anion may simply reflect the facile polymerization of phenyl isocyanate in basic medium.[10]

The phosphoramidate synthesis can conveniently be employed for the preparation of ketenimines. Although other procedures for ketenimine synthesis

(9) J. Sheehan and J. Halvka, *J. Org. Chem.*, **21**, 439 (1956).
(10) H. Khorana, *Chem. Rev.*, **57**, 47 (1957).

TABLE II

REACTION OF CARBON DIOXIDE WITH N-ALKYLPHOSPHORAMIDATE

R	Temp. of initial CO_2 addition, °C.	Isocyanate, %	Carbodiimide, %
s-Butyl	25	75	0
Cyclohexyl	25	70	0
Cyclohexyl	80	24	53
t-Butyl	10	62	5
t-Butyl	80	7	59
Phenyl	10	0	39

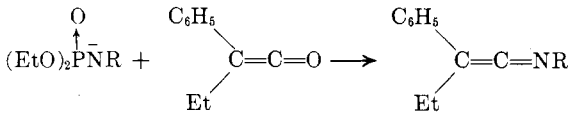
TABLE III

SYNTHESIS OF ISOTHIOCYANATES

RN=C=S

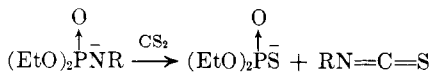
R	Yield, %
n-Butyl	75
Cyclohexyl	71
t-Butyl	56
Phenyl	30

have been described,[11-13] they suffer from low yields or lack of generality. Three phosphoramidate anions, when treated with phenylethylketene and with R as phenyl, cyclohexyl, and *n*-butyl, respectively, gave ketenimines in yields of 62, 58, and 18%. The keten-

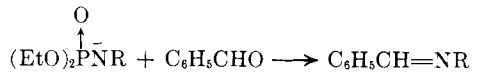


imines were in every case characterized by hydrolysis to a known amide. It was also found that optimum yields were obtained when a twofold excess of ketene over the phosphoramidate anion was employed.

A convenient synthesis of isothiocyanates can also be based on phosphoramidate anions. The anions react smoothly with carbon disulfide to give the isothiocyanates in moderately good yields. These results are summarized in Table III. This synthesis is, of course, facilitated by the fact that isothiocyanates do not react under ordinary conditions with phosphoramidate anions.



Finally, in contrast to the phosphinimines which Staudinger reported to be unreactive to benzaldehyde,[2] phosphoramidate anions react with benzaldehyde to give benzaldimines in good yield. Thus in the case of N-phenyl-, N-dimethylamino-, and N-methoxyphos-



phoramidate anions the imines were obtained in yields of 83, 80, and 82%, respectively. While this synthesis is of little preparative value, it again illustrates the broader scope of the phosphoramidate anion synthesis over the phosphinimine route.

(11) H. Staudinger and E. Hauser, *Helv. Chim. Acta*, **4**, 887 (1921).
(12) C. Stevens and J. French, *J. Am. Chem. Soc.*, **75**, 657 (1953).
(13) M. Newman, T. Fukumaga, and T. Miwa, *ibid.*, **82**, 873 (1960).

TABLE IV

DIETHYL N-ALKYLPHOSPHORAMIDATES

$$(EtO)_2\overset{\overset{O}{\uparrow}}{P}NHR$$

R	B.p. (mm.) or m.p., °C.	Yield, %	$n^{25}D$	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
n-C_4H_9	107 (0.35)	73.3	1.4260	45.93	9.97	6.69	45.97	9.51	6.72
t-C_4H_9	95 (1.0)	88.0	1.4290	45.93	9.57	6.69	45.81	9.57	6.62
C_6H_{11}	101–102	80.2		51.03	9.35	5.95	49.94	9.45	5.96
C_6H_5[a]	95–96	87.6							
CH_3O	107 (0.5)	77.5	1.4275	32.78	7.64	7.65	32.79	7.55	7.59
$(CH_3)_2N$	102 (0.55)	61.0	1.4300	36.73	8.67	14.28	36.62	8.54	14.37
CH_3[b]	130 (15)	86.0	1.4215						

[a] F. Atherton and A. Todd, *J. Chem. Soc.*, **1106**, (1948). [b] H. McCombie, B. Saunders, and G. Stacey, *ibid.*, **921** (1945).

Experimental

The diethyl N-alkylphosphoramidates were prepared by the procedure outlined by Todd, *et al.*[5] A primary amine was added slowly to a solution containing diethyl hydrogen phosphite, carbon tetrachloride, and xylene. After the addition, the mixture was filtered by suction and the solvent was removed under reduced pressure. The product was recovered by distillation or recrystallization of the residue. (See Table IV.)

N-Phenyl-N′-cyclohexylcarbodiimide.—Diethyl N-cyclohexylphosphoramidate, 11.8 g. (0.05 mole), was dissolved in 50 ml. of dry 1,2-dimethoxyethane, and the solution was added under nitrogen to a slurry of 50% sodium hydride,[14] 2.4 g. (0.05 mole), in 100 ml. of dry 1,2-dimethoxyethane. After the dropwise addition was completed and hydrogen evolution had ceased, the mixture was heated at 70° for 0.5 hr. The solution was cooled to room temperature and phenyl isocyanate, 11.8 g. (0.10 mole), dissolved in 20 ml. of dry dimethoxyethane was added dropwise at approximately 25°. After the addition, the solution was heated at 70° for 15 min.

The mixture was stripped and the residue was distilled, giving 6.0 g. (60%) of clear distillate, b.p. 116–120° (0.35 mm.). The product became cloudy on standing. The freshly distilled material showed strong absorption at 2150 cm.$^{-1}$ which is characteristic of carbodiimides.[15]

Anal. Calcd. for $C_{13}H_{16}N_2$: C, 78.00; H, 8.00; N, 14.00. Found: C, 77.04; H, 8.05; N, 13.84.

The product was stirred with 20 ml. of dilute HCl for 0.5 hr. after which time it had crystallized. The product was recrystallized twice from ethanol giving a nearly quantitative yield of N-phenyl-N′-cyclohexylurea, m.p. 183–184°. The infrared spectrum of the urea was identical with that of an authentic sample prepared from phenylisocyanate and cyclohexylamine. A mixture melting point was undepressed.

N-(*t*-Octyl)-N′-cyclohexylcarbodiimide.—Diethyl N-cyclohexylphosphoramidate anion, 0.10 mole, was prepared as described in the above procedure. The solution containing the anion was cooled to room temperature and *t*-octyl isocyanate,[16] 15.5 g. (0.10 mole), was added dropwise at approximately 25°. After the addition the mixture was heated at 70° for 0.5 hr. Upon cooling, a gummy precipitate was formed. The precipitate was removed by decantation and the mother liquor was stripped under reduced pressure. The residue was distilled giving 10.0 g. (84%) of product, b.p. 78° (0.15 mm.), $n^{25}D$ 1.4756.

Anal. Calcd. for $C_{15}H_{28}N_2$: C, 76.31; H, 11.85; N, 11.84. Found: C, 76.17; H, 11.72; N, 11.46.

The product was characterized by its infrared spectrum, strong absorption at 2150 cm.$^{-1}$, and by hydrolysis with dilute HCl to give a quantitative yield of N-*t*-octyl-N′-cyclohexylurea, m.p. 152° (from acetonitrile). The urea had an infrared spectrum identical with that of the product obtained by adding cyclohexyl amine to *t*-octyl isocyanate. A mixture melting point was undepressed.

N-(*t*-Octyl)-N′-dimethylaminocarbodiimide.—Diethyl N-dimethylaminophosphoramidate, 39.2 g. (0.2 mole), was added dropwise at approximately 25° to a slurry of 50% sodium hydride in 100 ml. of dry 1,2-dimethoxyethane. After the addition and hydrogen evolution had ceased, *t*-octyl isocyanate, 31.0 g. (0.2 mole), was added dropwise at 25°. On heating the mixture at 60° for 15 min. a heavy, gummy precipitate was produced. After cooling, the mother liquor was decanted from the precipitate and stripped at reduced pressure. The residue was distilled giving 23.5 g. (59.6%) of product, b.p. 115° (15 mm.), $n^{25}D$ 1.4585. It absorbed strongly at 2090 cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{23}N_3$: C, 67.08; H, 11.61; N, 21.30. Found: C, 67.70; H, 11.74; N, 20.48.

The distillate was easily hydrolyzed in quantitative yield to the urea by warming a dilute HCl slurry. The urea was extracted with ether and recrystallized from isooctane, m.p. 75°. Its spectrum proved to be identical with that of an authentic sample prepared from *t*-octyl isocyanate and unsymmetrical dimethylhydrazine, mixture melting point undepressed.

Although the carbodiimide is stable towards heat, it slowly deposited crystals on standing at room temperature. After standing for approximately 1 month, the product completely solidified. The crystalline dimer was recrystallized twice from isooctane, m.p. 89–90°. The product absorbed strongly at 1730 and 1620 cm.$^{-1}$.

Anal. Calcd. for $C_{22}H_{46}N_6$: C, 67.08; H, 11.61; N, 21.30; mol. wt., 394. Found: C, 66.96; H, 11.87; N, 21.55; mol. wt., 401 (ebulliometric).

The dimer, when heated past its melting point, took on a blue hue. An infrared spectrum of material heated above 130° showed it to have decomposed to monomer.

N-(*t*-Butyl)-N′-dimethylaminocarbodiimide.—The *t*-butyl analog was prepared in 60% yield using a method identical with that described for the previous procedure, b.p. 65° (15 mm.), $n^{25}D$ 1.4435. It absorbed strongly at 2090 cm.$^{-1}$.

Anal. Calcd. for $C_7H_{15}N_3$: C, 59.57; H, 10.64; N, 29.79. Found: C, 59.61; H, 10.59; N, 29.82.

The product was hydrolyzed to the urea in quantitative yield by warming the distillate with dilute HCl. The urea was extracted with ether and recrystallized from isooctane, m.p. 62°. A mixture melting point with the urea obtained by adding unsymmetrical dimethyl hydrazine to *t*-butyl isocyanate showed no depression. The infrared spectra of the two ureas were identical.

N-(*t*-Octyl)-N′-benzyldimethylammonium Chloride Carbodiimide.—N-(*t*-Octyl)-N′-dimethylaminocarbodiimide, 1.97 g. (0.01 mole), and benzyl chloride, 1.26 g. (0.01 mole), were added together with stirring and the solution was allowed to stand for 48 hr. The mixture which had solidified was taken up in benzene and filtered by suction. The precipitate was washed well with benzene and air-dried, m.p. 135–136°, 2.0 g. (62.5%).

Anal. Calcd. for $C_{18}H_{30}ClN_3$: C, 66.71; H, 9.26; Cl, 10.96; N, 12.92. Found: C, 66.50; H, 9.23; Cl, 11.19; N, 12.88.

The product showed strong absorption at 2130 cm.$^{-1}$ indicative that the carbodiimide functionality persisted.

The quaternary carbodiimide was hydrolyzed to N-*t*-octyl-N′-benzyldimethylammonium chloride urea by dissolving a sample in water and allowing the aqueous solution to stand for 48 hr. The gummy residue which precipitated during this time was extracted with methylene chloride. The methylene chloride extract was dried over $MgSO_4$ and stripped. The gummy residue which defied crystallization showed strong absorption in the infrared at

(14) Sodium hydride, 50% in mineral oil, was supplied by Metal Hydrides, Inc. The solvents were dried over calcium hydride prior to their use and the anions were prepared under an atmosphere of nitrogen in order to exclude moisture.

(15) L. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1958, p. 267.

(16) N. Bortnick, L. Luskin, M. Hurwitz, and A. Rytina, *J. Am. Chem. Soc.*, **78**, 4358 (1956).

1710 cm.$^{-1}$. The spectrum was identical with that of a gummy residue obtained by refluxing equivalent amounts of N-(*t*-octyl)-N′-dimethylaminourea and benzyl chloride in isooctane for 2 hr.

N-(*t*-Butyl)-N′-benzyldimethylammonium Chloride Carbodiimide.—This quaternary carbodiimide was prepared in a manner identical with that used for the *t*-octyl analog, m.p. 128–129° (69%).

Anal. Calcd. for $C_{14}H_{22}ClN_3$: C, 62.92; H, 8.24; N, 15.73. Found: C, 62.97; H, 8.16; N, 15.81.

A gummy product which defied crystallization was obtained upon hydrolysis of the quaternary carbodiimide. The product was extracted with methylene chloride. It had an infrared spectrum identical with that of the gummy product obtained by refluxing N-(*t*-butyl)-N′-dimethylaminourea with benzyl chloride in isooctane.

Reaction of Sodium Diethyl N-(*n*-Butyl)phosphoramidate with CO_2.—Diethyl N-(*n*-butyl)phosphoramidate, 41.8 g. (0.2 mole), was added dropwise with stirring at 40° to a slurry of 50% sodium hydride, 9.6 g. (0.2 mole), in 100 ml. of dry benzene. After hydrogen evolution had ceased, the mixture was cooled to 10° and CO_2 was passed slowly through the solution at such a rate that the temperature of the mixture did not rise above room temperature. After the absorption of CO_2 had ceased, the mixture was stripped under reduced pressure (20 mm.) giving a white crystalline product which could not be recrystallized and which liberated copious amounts of CO_2 when treated with dilute HCl.

The dry solid did not decompose until temperatures of 150–160° were reached. At this point a small amount of distillate, 2 g., was collected which was not purified further. The distillate which showed strong absorption at 2100 and 2250 cm.$^{-1}$ apparently contained a mixture of di-*n*-butylcarbodiimide and *n*-butyl isocyanate.

The residue was taken up in water; the aqueous solution was acidified with dilute HCl and extracted with ether. The ether extract was dried over $MgSO_4$ and stripped giving 26.0 g. (62%) of the starting diethyl N-*n*-butylphosphoramidate.

Reaction of Sodium Diethyl N-Cyclohexylphosphoramidate with CO_2 at 80°.—Diethyl N-cyclohexylphosphoramidate, 23.5 g. (0.1 mole), was added to a slurry of 50% sodium hydride, 4.8 g. (0.1 mole), in 100 ml. of dry 1,2-dimethoxyethane with stirring at a temperature below 30°. The mixture was stirred at room temperature until it became homogeneous and gas evolution had ceased. The solution was warmed to 80° and CO_2 gas was slowly bubbled through the hot solution with stirring for 1 hr. During this period a gummy precipitate was formed. The mixture was cooled and the mother liquor was decanted from the residue and stripped. The residue was distilled giving two fractions. The infrared spectrum of the first fraction, b.p. 70–71° (15 mm.), was identical with the spectrum of an authentic sample of cyclohexyl isocyanate, 3.0 g. (24%). The infrared spectrum of the second fraction, b.p. 100–102° (0.25 mm.), was identical with that of authentic dicyclohexyl carbodiimide, 5.5 g. (53%).

Reaction of Sodium Diethyl N-Cyclohexylphosphoramidate with CO_2 at 25°.—Diethyl N-cyclohexylphosphoramidate anion was prepared as in the previous experiment. CO_2 gas was passed slowly through the homogeneous solution at approximately 25° by means of ice-bath cooling. When the absorption of CO_2 had ceased, the mixture was heated at 80° for 30 min., giving rise to a gummy precipitate. Indeed the formation of the gummy precipitate was a good index for determining the optimum temperature for the fragmentation of carbamate to isocyanate. The mixture was then cooled and the solvent was decanted from the precipitate. The precipitate was washed with solvent and the solvent layers were combined. Removal of solvent by distillation gave a residue which when distilled gave 8.7 g. (70% yield) of cyclohexyl isocyanate, b.p. 170° (760 mm.). No dicyclohexylcarbodiimide was detected by infrared.

Diphenylcarbodiimide.—Diethyl N-phenylphosphoramidate, 22.8 g. (0.1 mole), was added slowly to a slurry of 50% sodium hydride, 4.8 g. (0.1 mole), in 100 ml. of benzene. After the addition, which was conducted at 30°, the mixture was warmed gently to 60° where the temperature remained until the theoretical amount of gas had been evolved. The mixture was cooled to 10° and CO_2 gas was passed through slowly giving rise to a viscous precipitate. When gas absorption had ceased, the mixture was allowed to come slowly to room temperature under a CO_2 atmosphere. Solvent was decanted from the precipitate and stripped under reduced pressure (20 mm.) giving a liquid residue. The residue when fractionated gave 7.5 g. (39% yield) of diphenylcarbodiimide, b.p. 106° (0.25 mm.). The infrared spectrum of the product was identical with that of an authentic sample. The spectra of the residue and distillate gave no indication of any isocyanate.

Phenylethylketene Phenylimine.—Diethyl N-phenylphosphoramidate, 11.5 g. (0.05 mole), dissolved in 50 ml. of dry 1,2-dimethoxyethane was added slowly with stirring to a slurry of 50% sodium hydride, 2.4 g. (0.05 mole), at approximately 30°. After the addition, the solution was stirred until gas evolution ceased. Phenylethylketene, 14.6 g. (0.1 mole), was added dropwise at room temperature and the solution was warmed at 50° for 0.5 hr. The reaction mixture was stripped and distilled giving 6.8 g. (62%) of crude product, b.p. 125–130° (0.35 mm.), $n^{25}D$ 1.5904. It proved impossible by repeated distillations to obtain an analytically pure sample. The distillate absorbed strongly at 2010 cm.$^{-1}$ which is characteristic of ketenimines.[12]

Anal. Calcd. for $C_{16}H_{15}N$: N, 6.33. Found: N, 6.23.

The product was shaken with dilute HCl and the mixture was allowed to stand for 48 hr. A crystalline product, m.p. 80–81° (from alcohol), 6.3 g. (86%), was obtained by extracting the aqueous solution with ether and evaporating the ether extract. The product proved to be identical in its physical properties and spectrum with N-phenyl-α-phenylbutyramide prepared by treating α-phenylbutyryl chloride with aniline, m.p. 81°; mixture melting point was undepressed.

Phenylethylketene Cyclohexylimine.—Diethyl N-cyclohexylphosphoramidate, 11.7 g. (0.05 mole), dissolved in 50 ml. of 1,2-dimethoxyethane was added slowly to a slurry of 50% sodium hydride, 2.4 g. (0.05 mole), in 100 ml. of 1,2-dimethoxyethane. After the addition, which was carried out at room temperature, the solution was stirred until gas evolution ceased and the solution became homogeneous. Phenylethylketene, 14.6 g. (0.1 mole), was added dropwise at room temperature. While stirring the mixture for 48 hr. at room temperature, a gummy precipitate was produced. The mother liquor was decanted from the precipitate and stripped at reduced pressure; the residue was distilled giving 6.2 g. (58%) of straw-yellow liquid, b.p. 122–124° (0.5 mm.). The infrared spectrum showed strong absorption at 2000 cm.$^{-1}$.

Anal. Calcd. for $C_{16}H_{21}N$: C, 84.53; H, 9.25; N, 6.17. Found: C, 84.36; H, 9.28; N, 5.95.

The ketenimine was shaken with dilute HCl and the product, m.p. 116–117° (from isooctane), was extracted with ether. The product, obtained in 91% yield, proved to have a spectrum identical with that of the amide obtained by adding cyclohexylamine to α-phenylbutyryl chloride, m.p. 116–117°; mixture melting point was undepressed.

Phenylethylketene *n*-Butylimine.—Diethyl N-*n*-butylphosphoramidate 20.9 g. (0.1 mole), dissolved in 50 ml. of 1,2-dimethoxyethane was added slowly to a slurry of 50% sodium hydride, 4.8 g. (0.1 mole), in 100 ml. of 1,2-dimethoxyethane. After the addition, which was carried out at room temperature, the solution was stirred until gas evolution ceased. Phenylethylketene, 29.2 g. (0.2 mole), was added dropwise at room temperature. After stirring the solution for 48 hr. at room temperature, a gummy precipitate was produced. The mother liquor was decanted from the precipitate, stripped at reduced pressure, and the residue was distilled giving 3.6 g. (18%) of yellow liquid, b.p. 87–92° (0.2 mm.). The infrared spectrum of the product showed strong absorption at 2000 cm.$^{-1}$.

Anal. Calcd. for $C_{14}H_{19}N$: N, 6.96. Found: N, 6.61.

The product was hydrolyzed with dilute HCl. After extracting the aqueous mixture with ether and stripping the extract, a viscous liquid product remained, b.p. 132° (0.1 mm.), $n^{25}D$ 1.5129. The physical properties of this product were identical with those of the amide obtained by adding *n*-butylamine to α-phenylbutyryl chloride. Their infrared spectra were superimposable.

***n*-Butyl Isothiocyanate.**—Diethyl N-*n*-butylphosphoramidate, 20.9 g. (0.1 mole), was added dropwise at room temperature to a slurry of 50% sodium hydride, 4.8 g. (0.1 mole), in 100 ml. of 1,2-dimethoxyethane. After the addition, the mixture was stirred at room temperature until gas evolution ceased. Carbon disulfide, 7.6 g. (0.1 mole), was added and the solution was refluxed gently for 0.5 hr. The mixture, which darkened during the heating, was stripped and the residue was distilled giving 8.7 g. (75%) of liquid distillate, b.p. 169–170°. The infrared spectrum of the distillate was identical with that of an authentic sample of *n*-butyl isothiocyanate.

Cyclohexyl Isothiocyanate.—Diethyl N-cyclohexylphosphoramidate, 23.6 g. (0.1 mole), dissolved in 50 ml. of 1,2-dimethoxyethane was added slowly at room temperature to a slurry of 50% sodium hydride, 4.8 g. (0.1 mole), in 100 ml. of 1,2-dimethoxyethane. The mixture was stirred until gas evolution ceased and the solution had become homogeneous. Carbon disulfide, 7.6 g. (0.1 mole), was added dropwise at room temperature after which the solution was heated at 70° for 0.5 hr. The solution was cooled, decanted from a gummy residue, stripped, and distilled. The infrared spectrum of the distillate, 9.5 g. (71%), b.p. 117–118° (10 mm.), was identical with that of an authentic sample of cyclohexyl isothiocyanate.

O-Methylbenzaldoxime.[17]—Diethyl N-methoxyphosphoramide, 9.85 g. (0.05 mole), was added dropwise to a slurry of 50% sodium hydride, 2.4 g. (0.05 mole), in 100 ml. of 1,2-dimethoxyethane. The solution was stirred at room temperature until gas evolution ceased. Benzaldehyde, 5.3 g. (0.05 mole), was added slowly at approximately 25°. After the addition, the mixture was warmed at 60° for 0.5 hr. and cooled. The solution was decanted away from a gummy precipitate and stripped; the residue was distilled giving 5.5 g. (82%) of clear liquid distillate, b.p. 90° (15 mm.).

(17) K. V. Auwer and B. Ottens, *Ber.*, **57**, 456 (1924).

New Methods of Introducing the Carbo-*t*-butoxy Amino-Protecting Group. Preparation and Use of *t*-Butyl Cyanoformate and *t*-Butyl Iminodicarboxylate[1]

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A new route to the potentially useful carbo-*t*-butoxylating agent, *t*-butyl cyanoformate (I), is described which involves treatment of a *t*-butyl α-alkoxyacetate with N-bromosuccinimide followed by hydrolysis of the intermediate α-bromo ester (IV) and reaction of the resulting glyoxylate solution with hydroxylamine to yield *t*-butyl oximinoacetate (II). Dehydration of the oxime by means of acetic anhydride and triethylamine gave the cyanoformate (I). As an approach to the synthesis of various biscarbo-*t*-butoxylated amino compounds the preparation of several precursors was examined. Treatment of ethyl *t*-butyl oxalate with hydrazine gave *t*-butyl oxalyl hydrazide (VII) which on diazotization gave the unstable *t*-butyl oxalyl azide (VIII). The pure axide (VIII) could not be isolated but was converted directly to *t*-butyl iminodicarboxylate (IX) by warming with *t*-butyl alcohol. It was shown that the sodium salt of the imino compound (IX) reacted with alkyl halides to give the biscarbo-*t*-butoxylated amino derivatives which by hydrogen chloride cleavage were converted to the corresponding primary amines. Amination of the sodium salt of IX by means of mesitoxyamine gave *t*-butyl hydrazine-1,1-dicarboxylate (XI).

In view of the increasing importance of the carbo-*t*-butoxy group as an amino-protecting function, studies are continuing aimed at the development of new carbo-*t*-butoxylating agents having special advantages over those currently available.[2] To date, the acylating agent of choice from the point of view of availability, acylating power, and shelf stability is *t*-butyl azidoformate.[3] A related acylating agent, *t*-butyl cyanoformate (I), which has been described recently,[4] was first

$$\underset{\text{I}}{NC\text{–}COOCMe_3} \qquad \underset{\text{II}}{HON{=}CHCOOCMe_3}$$

obtained by the dehydration of *t*-butyl oxamate by means of trifluoroacetic anhydride. In the present paper we report a more convenient route to this potentially useful cyanoformate, namely dehydration of the corresponding oxime, *t*-butyl oximinoacetate (II). The oxime (II) was obtained through the corresponding glyoxylate. Previously the most convenient routes to alkyl glyoxylates involved the oxidative cleavage of dialkyl tartrates[5] and the reaction of alkyl bromoacetates with dimethyl sulfoxide.[6] Since *t*-butyl bromoacetate is readily obtainable, numerous attempts were made to oxidize this compound by the method of Hunsberger and Tien.[6] Although this method has been shown to give ethyl glyoxylate in 70–75% yields, the results were unsatisfactory with the *t*-butyl analog. Some aldehydic material was indeed obtained as shown by isolation of small amounts of the phenylhydrazone of *t*-butyl glyoxylate from the reaction mixture. A number of potential routes to *t*-butyl glyoxylate through the corresponding dichloroacetate were also found to lack promise. It was eventually found that *t*-butyl α-alkoxyacetates undergo ready bromination in the α-position on treatment with N-bromosuccinimide in carbon tetrachloride in the presence of benzoyl peroxide. The α-bromo-α-alkoxyacetates (IV) proved to be satisfactory intermediates in the synthesis of glyoxylate derivatives. Both *t*-butyl α-methoxy- (III, R = CH_3; R′ = *t*-Bu) and α-*t*-butoxyacetate (III, R = R′ = *t*-Bu) were converted easily to the desired oximinoacetate (II). The best yields were obtained using the α-methoxyacetate. It was not necessary to isolate the intermediate bromo ester (IV) or the glyoxylate derived therefrom. Bromoacetates such as IV undergo hydrolysis extremely readily on contact with water.[7,8] In order to avoid cleavage or hydrolysis of

$$\underset{\text{III}}{ROCH_2COOR'} \qquad \underset{\text{IV}}{ROCH(Br)COOR'}$$

(1) Supported by a grant (GM-09706-02) from the National Institutes of Health.

(2) For references to earlier work, see L. A. Carpino, *J. Org. Chem.*, **28**, 1909 (1963).

(3) L. A. Carpino, C. A. Giza, and B. A. Carpino, *J. Am. Chem. Soc.*, **81**, 955 (1959).

(4) L. A. Carpino, *ibid.*, **82**, 2725 (1960). NOTE ADDED IN PROOF (AUG. 11, 1964).—M. Leplawy and W. Stec [*Bull. acad. polon. sci., ser. sci. chim.*, (6) **12**, 21 (1964); *Chem. Abstr.*, **61**, 1933 (1964)] have shown that *t*-butyl cyanoformate can be obtained by reaction of *t*-butyl alcohol with carbonyl cyanide. These investigators also showed the cyanoformate to be generally useful in the carbo-*t*-butoxylation of amino acid derivatives.

(5) F. J. Wolf and J. Weijlard, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p. 124.

(6) J. Tien and I. M. Hunsberger, *Chem. Ind.* (London), 88 (1959).

(7) A. Bendich and G. C. Clements, *J. Am. Chem. Soc.*, **75**, 4075 (1953).

(8) R. Quelet and J. Gavarret, *Bull. soc. chim. France*, 1075 (1950).