in 25 ml of benzene. Stirring was continued for an additional 4 hr. The reaction mixture was poured over ice-water, extracted with 400 ml of ether and dried (MgSO<sub>4</sub>). Evaporation of ether afforded a mixture of 13 and 14 which was separated by column chromatography over silica gel using the solvent mixture hexanetetrahydrofuran-ethyl acetate (18:1:1). The first compound emerging from the column was identified as 13, mp 123-124°, 0.8 g (7.3%).

Anal. Calcd for C6HCl3N2S: N, 11.7; Cl, 44.5; S, 13.4. Found: N, 11.8; Cl, 44.4; S, 13.2.

The second fraction consisted of the N-oxide 14: mp 144-147°; 0.4 g (3.4%); ir (KBr) 1370 cm<sup>-1</sup> (N $\rightarrow$ O).

Anal. Calcd for C6HCl8N2OS: N, 10.9; S, 12.5. Found: N, 10.5; S, 12.3.

Reaction of Diphenylglyoxime with Sulfur Monochloride. Preparation of 3,4-Diphenyl-1,2,5-thiadiazole (16) and 3,5-Diphenyl-1,2,5-thiadiazole N-Oxide (17).—Diphenylglyoxime, 30.0 g (0.125 mol), was added to a mixture of 32 ml (0.4 mol) of sulfur monochloride in 64 ml of dimethylformamide at 25° The temperature of the reaction was maintained by external cooling with the aid of an ice bath. After 2 hr, the reaction mixture was poured onto 300 g of ice water and the precipitate was filtered and dried. Thin layer chromatography indicated the presence of three compounds in addition to large amounts of sulfur. The crude mixture was resolved by column chromatography on deactivated silica gel<sup>28</sup> using the solvent mixture hexanetetrahydrofuran (9:1). Sulfur which emerged first from the column was discarded. After removal of the solvent, the second fraction was recrystallized from hexane to give 1.7 g (5.7%) of 16: colorless, crystalline solid; mp 83-84°; nmr multiplet near 7.6 ppm (phenyl H).

Anal. Calcd for C14H10N2S: N, 11.75; S, 13.45. Found: N, 11.8; S, 13.1.

The third fraction was recrystallized from hexane and afforded 1.5 g (4.7%) of 17: colorless crystalline solid; mp 124°; ir (KBr pellet): 1360 cm<sup>-1</sup> (N $\rightarrow$ O).

Notes.

# **Reactions of Trihalopropionitriles with** Trialkyl Phosphite. A Convenient Synthesis of 2-Haloacrylonitriles

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Vicinal dihalides react with trialkyl phosphites to yield either of two products, depending on the structure of the dihalide. In the absence of electron-withdrawing groups on the carbon atoms bearing the halogen atoms, phosphonate esters are formed (eq 1).<sup>1</sup>

$$(RO)_{3}P + BrCH_{2}CH_{2}Br \longrightarrow (RO)_{2}PCH_{2}CH_{2}Br + RBr (1)$$

If, however, both halogen atoms are on carbon atoms bearing electron-withdrawing groups, dehalogenation occurs (eq 2), giving a high yield of olefin.<sup>2</sup>

Anal. Calcd for C14H10N2OS: N, 11.0; S, 12.9. Found: N, 10.8; S, 12.4.

A fourth compound, possibly the corresponding di-N-oxide, did not emerge from the column and therefore was not identified.

Preparation of Acenaphtho[1,2-c]-1,2,5-thiadiatole (18) from Acenaphthoquinone Dioxime. With Sulfur Dichloride.—Sulfur dichloride (20 ml, 32.4 g, 0.315 mol) was added dropwise with stirring at 25° to a solution of acenaphthoquinone dioxime (10.6 g, 0.05 mol) in dimethylformamide (150 ml). After 2.5 hr, the mixture was poured over ice-water and filtered. The solid was dissolved in methylene chloride, charcoaled, and dried (MgSO<sub>4</sub>). Evaporation to dryness afforded a dark residual solid which was extracted with 500 ml of boiling hexane. This solution was concentrated to 150 ml and cooled to give 8.6 g (81.9%) of 18 as white solid melting at  $132-133^{\circ}$ . The nmr spectrum shows as white solid melting at 132-133°. complex lines near 7.8 ppm (aromatic H). Anal. Calcd for  $C_{12}H_6N_2S$ : N, 13.3; S, 15.3. Found: N,

13.2; 8, 15.8.

With Sulfur Monochloride .- The reaction of acenaphthoquinone dioxime (10.6 g, 0.05 mol) with sulfur monochloride (25 ml, 42.5 g, 0.315 mol) which was carried out under the same reaction conditions (see above) afforded 18 in 23% yield with recovery of about 18% of acenaphthoquinone dioxime.

**Registry No.—3,** 23431-06-3; **5**, 273-13-2; 10, 1143-73-3; 11, 23431-09-6; 13, 1982-55-4; 14, 23431-11-0; 15, 5728-20-1; 16, 4057-61-8; 17, 23431-14-3; 18, 437-40-1; 3,4,6-trichloro-o-benzoquinone, 23431-16-5; acenaphthoquinone dioxime, 1932-08-7.

Acknowledgment.-The author expresses his appreciation to Mr. G. E. Pollard and Mr. P. M. Saliman and their associates for spectral and analytical data.

$$C_{e}H_{s}CCHBr CHBrCC_{e}H_{s} + (RO)_{3}P \longrightarrow C_{e}H_{s}CCHBr CHBrCC_{e}H_{s} + (RO)_{3}P \longrightarrow C_{e}H_{s}CCH = CHCC_{e}H_{s} + (RO)_{2}PBr + RBr \quad (2)$$

In the presence of an electron-withdrawing group on only one carbon atom, the usual course of reaction with trialkyl phosphites is formation of a phosphonate ester, as illustrated by the reaction of 2,3-dichloropropionitrile with triethyl phosphite (eq 3).<sup>3</sup>

$$ClCH_2CHClCN + (EtO)_3P \longrightarrow ClCH_2CH + EtCl (3)$$

However, styrene dibromide has been found to undergo dehalogenation when allowed to react with triethyl phosphite to give styrene in 50% yield.<sup>4</sup>

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We wish to report another reaction of preparative value, where dehalogenation has been shown to occur from a system containing vicinal halide groups.

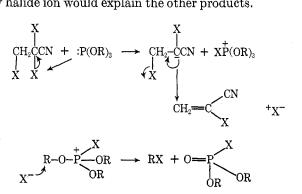
From the reaction of 2,2,3-trichloro- or tribromopropionitrile with triethyl or trimethyl phosphite below room temperature, almost quantitative yields of 2haloacrylonitriles, halophosphates, and alkyl halides can be readily isolated, (eq 4).

$$\begin{array}{c} X \\ X CH_2 CCN + (RO)_3 P \longrightarrow \\ X \\ X \\ CH_2 = C \\ CN \end{array} + (RO)_2 PX + RX \quad (4) \end{array}$$

$$R = Et$$
 or Me,  $X = Cl$  or Br

The dialkyl chlorophosphates and 2-haloacrylonitriles were characterized by their boiling points, vpc retention times, and ir and nmr spectra. The dialkyl bromophosphates could not be distilled without decomposition. The identity of these compounds was verified by conversion into their anilino derivatives according to a known method.<sup>5</sup>

These results can be explained by nucleophilic attack of phosphorus on an  $\alpha$  halogen, followed by elimination of  $\beta$  halogen from the resulting carbanion. Subsequent Arbuzov cleavage of the resultant phosphonium species by halide ion would explain the other products.



Attack by phosphorus on halogen is well established.<sup>6</sup> The intermediacy of the carbanion in these dehalogenation reactions was confirmed by reacting 2,2,3-trichloropropionitrile and triethyl phosphite in ethanol. Ethanol served as a proton donor and the reaction took the following course (eq 5).

Comparing the reactions of trialkyl phosphites with those of 2,3-dichloropropionitrile and 2,2,3-trichloropropionitrile, it appears that the phosphite can attack the  $\alpha$  carbon, giving the normal Arbuzov product (eq 3), or the  $\alpha$  chlorine, giving the dehalogenation product. Attack at the  $\alpha$  carbon is apparently favored, but is prevented in the 2,2,3-trichloro derivative presumably by the bulky geminal chlorine atoms. Attack on chlorine is, therefore, favored in the latter case.

The reaction of 2-chloro-2,3-dibromopropionitrile and triethyl phosphite also gives high yields of 2chloroacrylonitrile (eq 6), indicating that attack of trivalent phosphorus esters on bromine is favored over attack on chlorine.

$$BrCH_2CClBrCN + (EtO)_3P$$
 —

$$CH_2 = C \begin{pmatrix} CI \\ \\ CN \end{pmatrix} + (EtO)_2 PBr + EtBr \quad (6)$$

Substituted phosphines such as triphenylphosphine have also been found to react with 2,2,3-trihalopropionitriles in ether solution to give 2-haloacrylonitriles in good to moderate yields (eq 7).

$$XCH_2CX_2CN + (C_6H_5)_3P \longrightarrow$$

$$CH_2 = C X + (C_6H_5)_3 PX_2$$
 (7)

$$X = Cl \text{ or } Br$$

### **Experimental Section**

General Comments.—All the reactions were carried out in a three-necked flask equipped with magnetic stirrer assembly, dropping funnel, and a condenser connected to a cold trap. Infrared spectra were recorded on a Beckman IR 7. Nmr spectra ( $CDCl_3$ ) were obtained on a Varian A-60A instrument. Vpc analysis was carried out isothermally, using a Beckman Model 2 with a 10-ft column packed with silicon gum on Chromosorb W.

Reaction of 2,2,3-Trichloropropionitrile and Triethyl Phosphite.—Triethyl phosphite (33.0 g, 0.2 mol) was added dropwise to 2,2,3-trichloropropionitrile (32.0 g, 0.2 mol). The temperature of the reaction mixture was maintained at  $5-10^{\circ}$ by external cooling. After complete addition of the phosphite, the reaction mixture was fractionated to give ethyl chloride (12.0 g), 2-chloroacrylonitrile (16.0 g, 90%), bp 88-90°, and diethyl chlorophosphate, bp 55° (1.5 mm).

Reaction of 2,2,3-Tribromopropionitrile and Triethyl Phosphite.—The addition of triethyl phosphite (33.0 g, 0.2 mol) to 2,2,3-tribromopropionitrile (58.0 g, 0.2 mol) was carried out as described above and fractionated to give ethyl bromide (17.0 g, collected in the cold trap), 2-bromoacrylonitrile (20.0 g, 77%), bp 52-53° (85 mm), and a light yellow residue (ca. 50.0 g). This residue was identified as O,O'-diethyl bromophosphate by converting a portion of the residue into its anilino derivative as described in the literature to give diethyl anilinophosphonate, mp 93° (lit.<sup>5</sup> mp 96.5°).

Reaction of 2,3-Dibromo-2-chloropropionitrile and Triethyl Phosphite.—The reaction was carried out by slow addition of triethyl phosphite (16.6 g, 0.1 mol) to 2,3-dibromo-2-chloropropionitrile (24.5 g, 0.1 mol) at 5–10°, followed by fractionation. The reaction yielded ethyl bromide (8.0 g) and 2-chloroacrylonitrile (7.5 g, 86%), bp 84–89°. The undistilled material was converted into its anilino derivative to give diethyl anilinophosphonate, mp 93°. Reaction of 2,2,3-Trichloropropionitrile and Trimethyl Phos-

Reaction of 2,2,3-Trichloropropionitrile and Trimethyl Phosphite.—Trimethyl phosphite (24.8 g, 0.2 mol) was added to 2,2,3trichloropropionitrile (32.0 g, 0.2 mol) at 5-10°. During the course of the exothermic reaction, methyl chloride (21.0 g) was collected in the cold trap. On fractionation, the reaction mixture gave 2-chloroacrylonitrile (14.5 g, 82%), bp 86-88°.

Reaction of 2,2,3-Trichloropropionitrile and Triethyl Phosphite in the Presence of Dry Ethanol.—To an ethanol (25.0 g) solution of 2,2,3-trichloropropionitrile (16.0 g, 0.1 mol) was added

<sup>(5)</sup> H. McCombie, B. C. Saunders, and G. J. Stacey, J. Chem. Soc., 380 (1945).

<sup>(6)</sup> M. Grayson and E. Griffith, "Topics in Phosphorus Chemistry,"
Vol. 2, Interscience Publishers, Inc., New York, N. Y., 1965, pp 135-195.

triethyl phosphite (16.6 g, 0.1 mol) at 15-20°. After the complete addition of the phosphite, the reaction mixture was fractionated to give ethyl chloride (5.0 g), 2,3-dichloropropionitrile (10.5 g, 80%), bp 63-65° (35 mm), and triethyl phosphate (15.5 g), bp 85-87° (20 mm).

Reaction of 2,2,3-Trichloropropionitrile and Triphenylphosphine.—Triphenylphosphine (26.2 g, 0.1 mol) in dry ether (100 ml) was added dropwise to the 2,2,3-trichloropropionitrile (16.0 g, 0.1 mol) in dry ether (70 ml) under constant stirring. An exothermic reaction resulted and a white precipitate was formed. After complete addition of the triphenylphosphine, the white precipitate (31.0 g) was filtered. The filtrate on fractionation yielded 2-chloroacrylonitrile (6.0 g, 70%), bp 88-89°. The white precipitate, on treatment with water, gave triphenylphosphine oxide, mp 151-153° (lit.<sup>7</sup> mp 152-153°)

Reaction of 2,2,3-Tribromopropionitrile and Triphenylphosphine.-This reaction was carried out in the manner described above, using 2,2,3-tribromopropionitrile (29.2 g, 0.1 mol) in dry ether (30 ml) and triphenylphosphine (26.2 g, 0.1 mol) in dry ether (100 ml). The reaction gave 2-bromoacrylonitrile (77 g, 60%) and triphenylphosphine dibromide, which was then converted into triphenylphosphine oxide (20.0 g), mp 152-153°.

Registry No.-2,2,3-Trichloropropionitrile, 813-74-1; triethyl phosphite, 122-52-1; 2,2,3-tribromopropio-nitrile, 22929-17-5; 2,3-dibromo-2-chloropropionitrile, 22929-18-6; trimethyl phosphite, 121-45-9; triphenylphosphine, 603-35-0; triphenylphosphine oxide, 791-28-6; 2-chloroacrylonitrile, 920-37-6; diethyl chlorophosphate, 814-49-3.

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## Amino Acid Insertions in Solid-Phase Peptide Synthesis<sup>1a,b</sup>

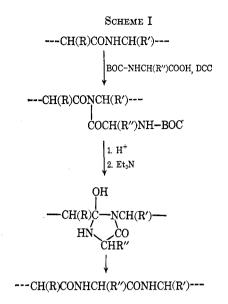
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In solid-phase peptide synthesis,<sup>2-4</sup> peptide bonds are most frequently formed through the reaction of excess N-protected amino acid and N.N'-dicvclohexylcarbodiimide<sup>5</sup> with amino acid or peptide derivatives of polystyrene. Brenner<sup>6</sup> has stated that acylation of peptide bonds, followed by aminoacyl insertion,<sup>7</sup> may be possible under such conditions (Scheme I). The occurrence of insertion reactions would yield side products closely resembling the desired product. Since the use of solid-phase peptide synthesis is increasing, $^{8-12}$  it is of interest to establish whether or not

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- (3) R. B. Merrifield, Biochemistry, 3, 1385 (1964).
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  - (7) M. Brenner, J. Cell Comp. Physiol., 54, 221 (1959).



amino acid insertions can occur in this method of

peptide synthesis. As insertion reactions should be most favored in the absence of bulky side chains (R = R' = R'' = H) a model system utilizing glycine was devised (Scheme II).

#### SCHEME II

$$Gly-O-CH_2P \xrightarrow{11 \text{ equiv of BOC Gly}}{11 \text{ equiv of DCC}} 1 \xrightarrow{1. CF_8CO_2H-CH_2Cl_2} 2$$

$$2 \xrightarrow{Et_8N-CHCl_8} 2$$

$$24 \text{ equiv of BOC Gly}, 24 \text{ equiv of DCC}$$

Large excesses of N-t-butoxycarbonylglycine<sup>13</sup> and N,N'-dicyclohexylcarbodiimide were used in both coupling reactions in an attempt to promote acylation of the peptide bond.

When a portion of product 1 was treated with trifluoroacetic acid in methylene chloride, then with triethylamine in chloroform, and finally with hydrogen bromide in trifluoroacetic acid, the products were glycine (54.8%) and glycylglycine (45.2%), as determined with an amino acid analyzer calibrated with glycine, diglycine, triglycine, and tetraglycine. Had aminoacyl insertion occurred, some triglycine would have been formed.

Product 2 was treated in the manner described for product 1 yielding glycine, diglycine, and triglycine upon paper chromatography of the cleavage products. The chromatogram from the amino acid analyzer indicated the presence of glycine (6.0%), diglycine (46.1%), triglycine (47.7%), and two trace peaks. One of these peaks emerged at the position of tetraglycine and represented 0.2% of the total products. The presence of tetraglycine would indicate that amino acid insertions can occur during solid-phase peptide synthesis when very large excesses of acylating agents are used. On the basis of these experiments it appears

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<sup>(1) (</sup>a) This work was supported in part by grants from the U. S. Public Health Service (GM-10591), the American Heart Association, the National Science Foundation, and by a Heart Research Center Grant (HE-06308). (b) The following abbreviations are used in this paper: BOC = t-butyl-oxycarbonyl; DCC = N,N'-dicyclohexylcarbodiimide; P = polystyrene-2% divinylbenzene copolymer. (c) Research Career Development Awardee of the U.S. Public Health Service.

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