[CONTRIBUTION FROM THE STAMFORD LABORATORIES OF THE CENTRAL RESEARCH DIVISION, AMERICAN CYANAMID CO.]

Phosphonium Compounds. I. Elimination Reactions of 2-Cyanoethyl Phosphonium Salts. Asymmetric Phosphines and Alkylenediphosphines

BY MARTIN GRAYSON, PATRICIA TARPEY KEOUGH AND GERALD A. JOHNSON

RECEIVED MARCH 28, 1959

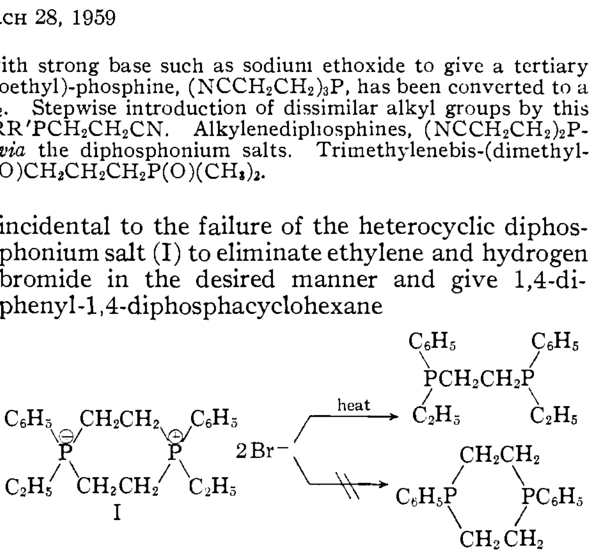
Phosphonium salts containing a 2-cyanoethyl group react with strong base such as sodium ethoxide to give a tertiary phosphine and 3-ethoxypropionitrile. In this way, tris-(2-cyanoethyl)-phosphine, $(NCCH_2CH_2)_3P$, has been converted to a series of alkyl bis-(2-cyanoethyl)-phosphines, $RP(CH_2CH_2CN)_2$. Stepwise introduction of dissimilar alkyl groups by this method permits the preparation of asymmetric phosphines, $RR'PCH_2CH_2CN$. Alkylenediphosphines, $(NCCH_2CH_2)_2P(CH_2)_{2-3}P(CH_2CH_2CN)_2$, have been prepared from dihalides *via* the diphosphonium salts. Trimethylenebis-(dimethylphosphine) was prepared and isolated as the dioxide, $(CH_3)_2P(O)CH_2CH_2CH_2P(O)(CH_3)_2$.

Introduction

Studies of base-promoted elimination (E_2) reactions of phosphonium salts have been limited in the past to the 2-phenylethyl system and have been only of theoretical interest.[1] Thermal decomposition of phosphonium halides to the tertiary phosphine and organic halide also has received some attention.[2] Although this procedure offers an alternative synthetic approach to compounds of the general type discussed here, it is a severely limited method.[3] Successful synthetic application has been made only with elimination of groups such as ethyl in the presence of phenyl which is at the other extreme of the cleavage order.[2,4]

Recent developments in this Laboratory have made tris-(2-cyanoethyl)-phosphine readily available as an organic intermediate.[5] We have found that the base-promoted elimination reaction of phosphonium salts derived from this phosphine proceeds readily with loss of a 2-cyanoethyl group. With this technique we have developed useful synthetic procedures for the preparation of asymmetric phosphines and alkylenediphosphines.

Alkylenediphosphines are of interest from a practical as well as a theoretical standpoint in view of the powerful coördination properties of trivalent phosphorus. Aside from 1,2-arylenediphosphines,[6] compounds of this type are virtually unknown materials. Recently, however, Wagner and Burg's procedure[7] for alkylation of sodium phosphide in liquid ammonia has been applied to the preparation of unsubstituted ethylene- and trimethylendiphosphines,[8] ethylenebis-(dimethylphosphine),[9] aryl-substituted phosphorus heterocycles[4] and the alkylenediphosphine, ethylenebis-(ethylphenylphosphine).[10] The preparation of the latter was incidental to the failure of the heterocyclic diphosphonium salt (I) to eliminate ethylene and hydrogen bromide in the desired manner and give 1,4-diphenyl-1,4-diphosphacyclohexane



I

Results and Discussion

We have found that tertiary phosphines containing the group R can be prepared from tris-(2-cyanoethyl)-phosphine by quaternization with the alkyl halide, RX, followed by base-promoted elimination of a 2-cyanoethyl group. This replacement of the 2-cyanoethyl group may be carried out again with a second alkyl halide, R'X, to give the unsymmetrical tertiary phosphine $RR'PCH_2CH_2CN$. Some of the phosphonium salts prepared in this investigation are described in Table I and the tertiary phosphines derived from them in Table II. The alkylenediphosphonium salts and alkylenediphosphines are described in the Experimental part.

$$(NCCH_2CH_2)_3P + RX \longrightarrow [(NCCH_2CH_2)_3P - R]^{\oplus}X^{\ominus}$$

$$[(NCCH_2CH_2)_3P{-}R]^{\oplus}X^{\ominus} + NaOEt \xrightarrow{EtOH} (NCCH_2CH_2)_2P{-}R + EtOCH_2CH_2CN + NaX$$

In this paper we report the first known case of a successful double elimination reaction of a simple acyclic ethylenediphosphonium salt to give an ethylenediphosphine. Ethylenebis-[bis-(2-cyanoethyl)-phosphine] was prepared from tris-(2-cyanoethyl)-phosphine and ethylene dibromide in two steps.

$$2(NCCH_2CH_2)_3P + BrCH_2CH_2Br \longrightarrow [(NCCH_2CH_2)_3\overset{\oplus}{P}CH_2CH_2\overset{\oplus}{P}(CH_2CH_2CN)_3]2Br^{\ominus}$$

$$[(NCCH_2CH_2)_3\overset{\oplus}{P}CH_2CH_2\overset{\oplus}{P}(CH_2CH_2CN)_3]2Br^{\ominus} + 2NaOEt \xrightarrow{EtOH} (NCCH_2CH_2)_2PCH_2CH_2P(CH_2CH_2CN)_2 + 2NaBr + 2EtOCH_2CH_2CN$$

Past attempts to prepare ethylenediphosphines by double elimination reactions with simple ethylenediphosphonium salts have resulted in rupture of the alkylenephosphorus bond.[11] This cleavage

---

[1] G. W. Fenton and C. K. Ingold, *J. Chem. Soc.*, 2342 (1929); L. Hey and C. K. Ingold, *ibid.*, 531 (1933).

[2] J. Meisenheimer, J. Casper, M. Horing, W. Lauter, L. Lichtenstadt and W. Samuel, *Ann.*, **449**, 213 (1926); G. W. Fenton, L. Hey and C. K. Ingold, *J. Chem. Soc.*, 989 (1933).

[3] G. M. Kosolapoff. "Organophosphorus Compounds," John Wiley and Sons, Inc., New York, N. Y., 1950, p. 84.

[4] F. G. Mann, I. T. Millar and H. R. Watson, *J. Chem. Soc.*, 2516 (1958).

[5] M. M. Rauhut, I. Hechenbleikner, Helen A. Currier, F. C. Schaefer and V. P. Wystrach, THIS JOURNAL, **81**, 1103 (1959); I. Hechenbleikner and M. M. Rauhut, U. S. Patent 2,822,376 (Feb. 4, 1958).

[6] F. A. Hart and F. G. Mann, *J. Chem. Soc.*, 3939 (1957).

[7] R. I. Wagner and A. B. Burg, THIS JOURNAL, **75**, 3869 (1953).

[8] A. J. Leffler and E. G. Teach, presented before the Division of Organic Chemistry, 133rd Meeting of the American Chemical Society, San Francisco, Calif., 1958.

[9] C. E. Wymore, Ph.D. Thesis, University of Illinois, 1957.

[10] C. H. S. Hitchcock and F. G. Mann, *J. Chem. Soc.*, 2081 (1958).

[11] A. W. Hofmann, *Ann. Suppl.*, **1**, 145 (1861).

TABLE I

PREPARATION OF 2-CYANOETHYLPHOSPHONIUM HALIDES

$$(NCCH_2CH_2)_2{-}PR' + RX \xrightarrow{\text{solvent}} [(NCCH_2CH_2)_2{-}PRR']^{\oplus}X^{\ominus}$$

RX	R′	Solvent	Reflux time, hr.	Yield, %	M.p., °C.	X,[a] %, Calcd.	X,[a] %, Found
CH_3I[b]	CH_2CH_2CN	CH_3COOH	15[c]	97	239–240	40.81	41.74[d]
C_2H_5I	CH_2CH_2CN	n-C_4H_9OH	15[e]	100	269–270	36.34	35.25[d]
$CH_2{=}CHCH_2I$	CH_2CH_2CN	n-C_4H_9OH	15[c]	98.5	177–178	35.15	34.10
CH_3I	CH_3	CH_3OH	0.5	91.5	194–195	41.04	41.52
C_2H_5I	CH_3	C_2H_5OH	0.5	78	210–211	40.91	41.19
$NCCH_2CH_2CH_2Br$	CH_3	n-C_4H_9OH	15	96	116–125	26.44	26.10

[a] Unless otherwise noted the Volhard technique was used, and phosphonium salts were not recrystallized before titration. [b] Prepared by M. Rauhut; see ref. 5. [c] Reaction temperature was 40–45° for first two hours, room temperature remaining time. [d] Recrystallized from acetonitrile once. [e] One hour at reflux, remaining time at room temperature.

TABLE II

PREPARATION OF TERTIARY PHOSPHINES

$$[RR'P^{\oplus}{-}(CH_2CH_2CN)_2]X^{\ominus} + NaOC_2H_5 \xrightarrow[C_2H_5OH]{} RR'{-}P{-}CH_2CH_2CN + C_2H_5OCH_2CH_2CN + NaX$$

R	R′	X	Yield, %	B.p., °C.	B.p., Mm.	$n^{25}D$	Carbon, %, Calcd.	Carbon, %, Found	Hydrogen, %, Calcd.	Hydrogen, %, Found	Nitrogen, %, Calcd.	Nitrogen, %, Found	Phosphorus, %, Calcd.	Phosphorus, %, Found
CH_3	CH_2CH_2CN	I	50–57	159–160	0.35	1.5030	54.52	54.94	7.19	7.24	18.17	17.99	20.09	19.88
C_2H_5	CH_2CH_2CN	I	43.5	153–155	0.55	1.5040	56.99	56.90	7.79	7.64	16.66	16.44	18.42	18.51
$CH_2{=}CHCH_2$	CH_2CH_2CN	I	49–64	178–179	1.65	1.4980	59.98	59.53	7.27	7.75	15.55	15.02	17.19	15.02[a]
$CH_2{=}CHCH_2$	CH_2CH_2CN	I	32.4[b]	201–202	1.95	1.4970	56.59[c]	56.44	8.08	8.39	13.20	13.46	14.60	14.08
CH_3	CH_3	I	45[b]	34–35	0.10	1.4800	52.17	52.16	8.76	8.77	12.17	12.16	26.91	27.15
C_2H_5	CH_3	I	56	68–70	1.75	1.4805	55.77	56.03	9.37	9.57	10.84	10.55	23.98	23.62
$NCCH_2CH_2CH_2$	CH_3	Br	61	174	1.30	1.4995	57.13	57.25	7.79	7.79	16.66	16.26	18.42	18.18

[a] Product most probably contaminated by trace amounts of ethoxypropylbis-(2-cyanoethyl)-phosphine. [b] Sodium methoxide was used as the base and methanol as the solvent. [c] Theoretical C, H, N and P calculated for bis-(2-cyanoethyl)-methoxypropylphosphine.

reaction also was observed by Hitchcock and Mann in their above-mentioned preparation of ethylenebis-(ethylphenylphosphine).[10] In this case two alkylene groups were present in the original cyclic diphosphonium salt, but only one remained in the product.

We too observed alkylene-phosphorus bond cleavage in our attempt to prepare ethylenebis-(dimethylphosphine) from ethylenebis-(2-cyanoethyldimethylphosphonium bromide). 2-Cyanoethyldimethylphosphine was the only product isolated.[12]

$$[NC\overset{\beta}{C}H_2CH_2(CH_3)_2\overset{\oplus}{P}\overset{\beta'}{C}H_2\overset{\beta'}{C}H_2\overset{\oplus}{P}(CH_3)_2CH_2\overset{\beta}{C}H_2CN]2Br^{\ominus} \xrightarrow[\text{EtOH}]{\text{2NaOEt}} (CH_3)_2PCH_2CH_2CN\ 46\% +$$
$$[(CH_2{=}CH{-}\overset{\oplus}{P}(CH_3)_2CH_2CH_2CN)Br^{\ominus}\ \text{derived tars}]$$

The activation to beta attack by base provided by the positive phosphorus centers (at β') evidently greatly exceeds the activation provided by the nitrile groups (at β). Our successful preparation of ethylenebis - [bis - (2 - cyanoethyl) - phosphine], therefore, no doubt was due to the presence of three nitrile groups for each phosphonium center. This result may also have been favored to a small extent by steric blocking of the acidic alkylene hydrogens.

Alkylenebis-(dialkylphosphines) can be prepared, however, if at least three methylene groups separate the phosphorus atoms. The elimination reaction was quite sluggish with trimethylenebis-(2-cyanoethyldimethylphosphonium bromide) and required 72 hours of refluxing in 1-butanol with sodium n-butoxide to force a small yield of product. The product was isolated as trimethylenebis-(dimethylphosphine oxide), probably because of exposure to air and oxidation. This type of compound is quite susceptible to atmospheric oxidation in contrast to the reported inertia of the ethylenediphosphines to such attack.[9] Elimination of the 2-cyanoethyl group in the presence of the 3-cyanopropyl group in bis-(2-cyanoethyl)-3-cyanopropylmethylphosphonium bromide provides a further structural analogy to the preparation of the trimethylenebis-(dialkylphosphines). The simplest

$$[(NCCH_2CH_2)_2\overset{\oplus}{P}(CH_3)CH_2CH_2CH_2CN]Br^{\ominus} + NaOEt \longrightarrow$$
$$NCCH_2CH_2P(CH_3)CH_2CH_2CH_2CN + NaBr +$$
$$EtOCH_2CH_2CN$$

route to compounds of this type, $R_2P(CH_2)_{3+n}PR_2$, appears to be by means of the base-catalyzed addition of acrylonitrile to the appropriate secondary phosphine.[5] However, the substituted homolog

$$R_2PH + CH_2{=}CHCN \longrightarrow R_2PCH_2CH_2CN$$
$$2R_2PCH_2CH_2CN + X(CH_2)_{3+n}X \longrightarrow$$
$$[NCCH_2CH_2\overset{\oplus}{P}(R)_2(CH_2)_{3+n}\overset{\oplus}{P}(R)_2CH_2CH_2CN]2X^{\ominus}$$
$$[NCCH_2CH_2\overset{\oplus}{P}(R)_2(CH_2)_{3+n}\overset{\oplus}{P}(R)_2CH_2CH_2CN]2X^{\ominus} \xrightarrow{\text{base}}$$
$$R_2P(CH_2)_{3+n}PR_2$$

trimethylenebis-[bis-(2-cyanoethyl)-phosphine] was prepared by us in good yield from tris-(2-cyanoethyl)-phosphine and 1,3-dibromopropane.

The yields of the alkylenebis-[bis-(2-cyanoethyl)-phosphines] were about 70–75%. In view of the bifunctional nature of the reactions, this was considerably higher than yields of the low molecular

---

(12) G. Wittig, H. Eggers and P. Duffner, *Ann.*, **619**, 10 (1958), report attempted preparation of $(C_6H_5)_3P{=}CHCH{=}P(C_6H_5)_3$ from $(C_6H_5)_3\overset{\oplus}{P}CH_2CH_2\overset{\oplus}{P}(C_6H_5)_3$ and $2C_6H_5Li$ gives only 46% of $(C_6H_5)_3P$. With aqueous caustic, however, they obtained 44% $(C_6H_5)_3P$ and products derived from $[(C_6H_5)_3\overset{\oplus}{P}CH{=}CH_2]OH^{\ominus}$ such as ethylene, benzene and $(C_6H_5)_3PO$.

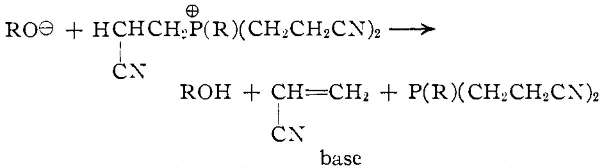
weight liquid phosphines reported in Table II which ranged from 40 to 60%. The improvement may be attributed to the ease of isolation of the solid diphosphines.

As noted in Table II, the elimination reaction with the allylphosphonium salt in ethanol gave an impure product. With methanolic sodium methoxide, this decomposition gave exclusively bis-(2-cyanoethyl)-methoxypropylphosphine and none of the expected allylbis-(2-cyanoethyl)-phosphine.

$$[CH_2{=}CHCH_2P(CH_2CH_2CN)_3]^{\oplus}I^{\ominus} \xrightarrow[CH_3OH]{CH_3ONa} (CH_3OC_3H_6)P(CH_2CH_2CN)_2 + CH_3OCH_2CH_2CN + NaI$$

The position of the ether linkage has not been determined. The addition of ethanol was evidently a slower process and gave both ether and olefin. Presumably the addition takes place before elimination and activation is provided by the phosphonium group. Attempts to add methanol to simple olefins such as cyclohexene in the presence of sodium methoxide and tributylphosphine were unsuccessful.

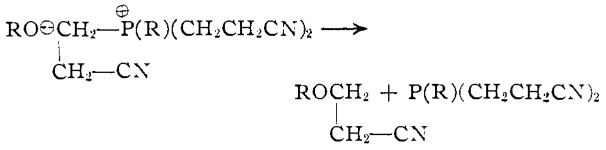
We refer throughout the discussion to the elimination of the 2-cyanoethyl group. To be precise, we feel it is likely that loss of the 2-cyanoethyl group proceeds by a normal E_2 mechanism[13] with subsequent rapid, base-catalyzed formation of a 3-alkoxypropionitrile by addition of solvent alcohol to acrylonitrile.



$$RO^{\ominus} + H\underset{CN}{C}HCH_2\overset{\oplus}{P}(R)(CH_2CH_2CN)_2 \longrightarrow ROH + \underset{CN}{CH}{=}CH_2 + P(R)(CH_2CH_2CN)_2$$

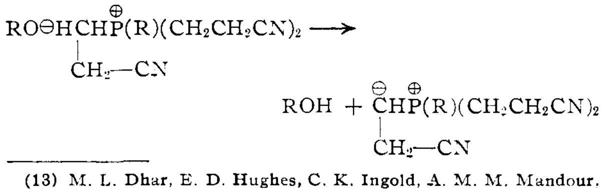
$$ROH + CH_2{=}CHCN \xrightarrow{base} ROCH_2CH_2CN$$

A conceivable alternative path leading to ether formation would involve direct nucleophilic displacement of the tertiary phosphine by attack of alkoxide ion on the methylene group adjacent to phosphorus. However, ether formation has not



$$RO^{\ominus}CH_2{-}\overset{\oplus}{P}(R)(CH_2CH_2CN)_2 \longrightarrow ROCH_2 + P(R)(CH_2CH_2CN)_2$$
$$\quad\;\; \underset{}{CH_2{-}CN} \qquad\qquad\qquad\qquad\qquad\qquad\quad CH_2{-}CN$$

been observed in alkoxide promoted elimination reactions with other phosphonium salts of various types.[1] In addition, when solid tris-(2-cyanoethyl)-methylphosphonium iodide was heated in a vacuum system with solid sodium cyanide, we observed formation of larger amounts of acrylonitrile than of succinonitrile. Direct nucleophilic attack of alkoxide ion on the methylene group adjacent to phosphorus would probably result in phosphinomethylene formation by removal of hydrogen rather than displacement as indicated above.

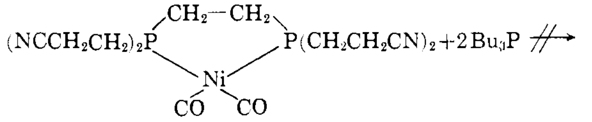


$$RO^{\ominus}H\underset{CH_2-CN}{C}H\overset{\oplus}{P}(R)(CH_2CH_2CN)_2 \longrightarrow ROH + \overset{\ominus}{\underset{CH_2-CN}{C}}H\overset{\oplus}{P}(R)(CH_2CH_2CN)_2$$

It is not likely that phosphinomethylenes were formed, however, since these are known to give tertiary phosphine oxides in water[14] and careful examination of the aqueous layer after work-up of these reactions failed to give evidence of tertiary phosphine oxides. A complete decomposition of phosphinomethylene by an α,β-elimination[15] to give the observed products cannot be excluded, although the temperatures involved here are probably rather low for this path to be followed.

Except for the above-described sodium cyanide experiment, attempts to employ other bases to effect the elimination reaction were not encouraging. Sodium acetylide in toluene and triethylamine in acetonitrile failed to react with tris-(2-cyanoethyl) methylphosphonium iodide. In both of these reactions, solubility of the iodide salt was limited. Dibutylamine in excess gave dibutyl-2-cyanoethylamine and tars. Sodium amide in liquid ammonia did cause the reaction to take place and in yields comparable to those obtained with alkoxides. The product, however, was yellow and of higher refractive index than the normal, pure material even when excess phosphonium salt was employed. The nature of the impurity present in the product is being investigated.

Preliminary examination of the chelating power of the alkylenediphosphines gives some indication of the expected stability imparted by ring formation. The complex of nickel carbonyl and ethylenebis-[bis-(2-cyanoethyl)-phosphine] does not exchange with tributylphosphine. In contrast, the complex with tris-(2-cyanoethyl)-phosphine exchanges readily.[16]



$$[(NCCH_2CN_2)_3P]_2Ni(CO)_2 + 2Bu_3P \longrightarrow 2(NCCH_2CH_2)_3P + (Bu_3P)_2Ni(CO)_2$$

Experimental[17]

Preparation of Phosphonium Halides.—The reaction of alkyl halides with tris-(2-cyanoethyl)-phosphine were generally carried out in hot 1-butanol which provides some solubility for the phosphine. Lower alcohols could be used with bis-(2-cyanoethyl)-alkylphosphines which are more soluble and more reactive than tris-(2-cyanoethyl)-phosphine. Volatile reagents such as methyl iodide are preferably allowed to react at lower temperatures in a better solvent for tris-(2-cyanoethyl)-phosphine such as acetic acid, acetonitrile or acetone. A large excess of alkyl halide is preferred and iodides or bromides give best results since quaternization is a reversible process. Tris-(2-cyanoethyl)-phosphine is stable in air, but reactions were generally carried out in a nitrogen atmosphere. Liquid alkyl 2-cyanoethylphosphines were handled in an inert atmosphere.

Preparation of Tertiary Phosphines.—In general, the elimination reactions of the 2-cyanoethylphosphonium halides were carried out using either sodium ethoxide or methoxide. In one case, the preparation of bis-(2-cyanoethyl)-methylphosphine, a series of reactions was run using a variety of bases and basic conditions. These latter experiments are described below in detail. The standard sodium alkox-

---

[13] M. L. Dhar, E. D. Hughes, C. K. Ingold, A. M. M. Mandour, G. A. Maw and L. J. Woolf, *J. Chem. Soc.*, 2093 (1948).

[14] D. D. Coffman and C. S. Marvel, THIS JOURNAL, **51**, 3496 (1929); G. Wittig, *Experientia*, **12**, 41 (1956).

[15] F. Weygand, H. Daniel and H. Simon, *Ber.*, **91**, 1691 (1958); G. Wittig and R. Polster, *Ann.*, **599**, 13 (1956).

[16] L. S. Meriwether and M. Fiene, private communication.

[17] Melting points are uncorrected.

ide procedure is given only for the preparation of bis-(2-cyanoethyl)-methylphosphine and 2-cyanoethylethylmethylphosphine. Data for all other tertiary phosphine preparations and for the phosphonium salts from which they were synthesized are summarized in Tables I and II.

Bis-(2-cyanoethyl)-methylphosphine.—Tris-(2-cyanoethyl)-phosphine (386.4 g., 2.0 moles) was dissolved in five liters of warm (40°) glacial acetic acid. Approximately 670 g. (4.65 moles) of methyl iodide was added with some external cooling to maintain a temperature of 40–45°. After storage at room temperature overnight, the solid was filtered and dried to give 615 g. (97%) of tris-(2-cyanoethyl)-methylphosphonium iodide, m.p. 239–240°.[18]

Sodium methoxide (70.5 g., 1.31 moles) was dissolved in 750 ml. of absolute methanol and the solution was added to a refluxing mixture of 438 g. (1.31 moles) of tris-(2-cyanoethyl)-methylphosphonium iodide in 750 ml. of methanol. After two hours, the methanol was removed under reduced pressure, 600 ml. of water was added and the mixture was extracted with 300 ml. of benzene in three portions. The benzene solution was dried and freed of solvent and 3-methoxypropionitrile (b.p. <27° at 0.25 mm.). The residual liquid distilled at 159–160° at 0.35 mm. and weighed 116.5 g. (57.5%), n^{25}D 1.5030.[19]

Sodium Cyanide Preparation of Bis-(2-cyanoethyl)-methylphosphine.—Solid tris-(2-cyanoethyl)-methylphosphonium iodide (33.5 g., 0.1 mole) and 4.9 g. (0.1 mole) of sodium cyanide were carefully mixed together in a well ventilated hood and then heated under reduced pressure in a simple distillation apparatus to a pot temperature of 250°. Bis-(2-cyanoethyl)-methylphosphine distilled as a yellow liquid boiling at 185–210° at 3 to 12 mm., n^{25}D 1.5033, in 35.8% yield (5.5 g.), leaving a large quantity of pot tars. Mass spectroscopy analysis indicated that the volatile by-products of this reaction, collected in the cold trap, contained a two-to-one ratio of acrylonitrile to succinonitrile with trace amounts of hydrocyanic acid.

Attempted Sodium Acetylide Preparation of Bis-(2-cyanoethyl)-methylphosphine.—A slurry of tris-(2-cyanoethyl)-methylphosphonium iodide (167.7 g., 0.50 mole) mixed with 24.0 g. (0.50 mole) of sodium acetylide and 250 ml. of dry toluene was warmed to 80° briefly and then stirred overnight at room temperature without any noticeable gas evolution. The mixture was filtered and 191 g. of starting materials was recovered.

Sodium Amide Preparation of Bis-(2-cyanoethyl)-methylphosphine.—Approximately one liter of liquid ammonia was poured into a vermiculite insulated reaction flask from an inverted cylinder and 19.5 g. (0.50 mole) of sodium amide was added under nitrogen. The clear, slightly colored solution was stirred and 85.3 g. (0.25 mole) of tris-(2-cyanoethyl)-methylphosphonium iodide was added in portions at −33°. A slight exotherm was observed and the clear solution became dark red after stirring for 2.5 hr. Solid ammonium chloride (16.5 g., 0.3 mole) was added in small portions with a color change from red to light brown. The excess ammonia was allowed to evaporate and the residue was treated with 500 ml. of water and extracted with chloroform. The chloroform extract was dried, concentrated and distilled to give 21.8 g. (57%) of slightly yellow bis-(2-cyanoethyl)-methylphosphine, b.p. 153° at 0.55 mm., n^{25}D 1.5109.

Attempted Triethylamine Preparation of Bis-(2-cyanoethyl)-methylphosphine.—Solid tris-(2-cyanoethyl)-methylphosphonium iodide (167.7 g., 0.50 mole) was added at once to a stirred solution of 55.5 g. (0.50 mole) of triethylamine in 250 ml. of acetonitrile, and heated to reflux for 20 hr. The mixture containing undissolved solid was cooled to room temperature and upon filtering yielded 160 g. of unreacted tris-(2-cyanoethyl)-methylphosphonium iodide (m.p. 242–243°). Distillation of the filtrate yielded an azeotrope of acetonitrile and triethylamine of b.p. 69–70° which contained about 50 volume per cent. triethylamine.

Attempted Dibutylamine Preparation of Bis-(2-cyanoethyl)-methylphosphine.—Tris-(2-cyanoethyl)-methylphosphonium iodide (83.8 g., 0.25 mole) was added at once to an excess (129.2 g., 1.0 mole) of dibutylamine and the mixture was heated to reflux. At a liquid temperature of 160° the solid was completely melted and formed a dark red lower phase which was dispersed by stirring. Refluxing was continued for two hours and then the mixture was cooled to room temperature and the two liquid phases were separated. Distillation of the upper phase yielded 66 g. (51% recovery) of dibutylamine, b.p. 60° at 19.5 mm., n^{25}D 1.4157, and 11 g. (20%) of dibutyl-2-cyanoethylamine, b.p. 130–135° at 0.5 mm., n^{25}D 1.4685. The lower, liquid phase could not be distilled in vacuum at bath temperature up to 240° and was viscous and tar-like in nature.

2-Cyanoethylethylmethylphosphine.—Bis-(2-cyanoethyl)-methylphosphine (23.0 g., 0.15 mole) was dissolved in 75 ml. of absolute ethanol at room temperature and 52 g. (0.33 mole) of ethyl iodide was added. The mixture was refluxed in a nitrogen atmosphere for 15 minutes, cooled and the solid filtered and dried, to give 35.5 g. (78%) of bis-(2-cyanoethyl)-ethylmethylphosphonium iodide, m.p. 210–211°.[18]

Metallic sodium (2.3 g., 0.10 g. atom) was dissolved in 150 ml. of absolute alcohol and 31.0 g. (0.10 mole) of bis-(2-cyanoethyl)-ethylmethylphosphonium iodide was added. The mixture was heated to dissolve the solid and the excess alcohol was evaporated in vacuum. The remaining paste was extracted with benzene, and the liquid remaining after removing the benzene was distilled; b.p. 68–70° at 1.8 mm., 7.2 g. (56%), n^{25}D 1.4805.[19]

Preparation of Alkylenediphosphines, a. Ethylenebis-[bis-(2-cyanoethyl)-phosphine].—Tris-(2-cyanoethyl)-phosphine (193.2 g., 1.0 mole) was dissolved in 400 ml. of refluxing butanol. When solution was complete, 84.5 g. (0.45 mole) of 1,2-dibromoethane was added slowly with stirring to the refluxing solution. The mixture was heated for a total of 24 hours and then filtered while hot. The white crystalline diphosphonium salt which had precipitated during refluxing was collected, dried and then recrystallized from acetonitrile to yield 238 g. (92.5%) of ethylenebis-[tris-(2-cyanoethyl)-phosphonium bromide], m.p. >300°.

Anal. Calcd. for $C_{20}H_{28}N_6P_2{\cdot}2Br$: Br, 27.83. Found: Br, 26.49.[20]

Metallic sodium (4.6 g., 0.2 g. atom) was dissolved in 250 ml. of absolute ethanol and the solution was cooled to 25°. Fifty-eight grams (0.1 mole) of ethylenebis-[tris-(2-cyanoethyl)-phosphonium bromide] was added to the sodium ethoxide solution and the mixture was refluxed for two hours. At the end of this time the reaction mixture was concentrated and cooled. The ethylenebis-[bis-(2-cyanoethyl)-phosphine] separated as a granular solid and was washed with ice-water to remove sodium bromide. Upon recrystallization from aqueous acetone, it yielded 22.8 g. (74.6%) of the diphosphine, m.p. 101–102°.

Anal. Calcd. for $C_{14}H_{20}N_4P_2$: C, 54.90; H, 6.58; N, 18.29; P, 20.23. Found: C, 54.71; H, 6.66; N, 18.32; P, 20.32.

b. Trimethylenebis-[bis-(2-cyanoethyl)-phosphine].—The diphosphonium salt, trimethylenebis-[tris-(2-cyanoethyl)-phosphonium bromide], was prepared from 130.7 g. (0.68 mole) of 1,3-dibromopropane by the technique used for the ethylene salt described above. The diphosphonium salt was obtained in 86.5% yield (152.6 g.), m.p. 83–85°.

Anal. Calcd. for $C_{21}H_{30}N_6P_2{\cdot}2Br$: Br, 27.16. Found: Br, 26.09.[20]

This diphosphonium salt was treated as in example (a) above with a methanol solution of 6.7 g. (0.292 g. atom) of sodium. The resulting crystalline trimethylenebis-[bis-(2-cyanoethyl)-phosphine] was recrystallized from aqueous acetic acid to give 32.5 g. (69.1%) of product, m.p. 53–54°.

Anal. Calcd. for $C_{15}H_{22}N_4P_2$: C, 56.24; H, 6.95; N, 17.49; P, 19.34. Found: C, 56.21; H, 7.02; N, 17.24; P, 19.26.

c. Attempted Preparation of Ethylenebis-(dimethylphosphine).—2-Cyanoethyldimethylphosphine (27.5 g., 0.247 mole) was mixed with 150 ml. of 1-butanol under nitrogen and 1,2-dibromoethane was added slowly at room temperature. The mixture was refluxed overnight. The crystalline diphosphonium salt which separated was collected and dried. It weighed 31.3 g. (75%) and had m.p. 249–252°.

Anal. Calcd. for $C_{12}H_{24}N_2P_2{\cdot}2Br$: Br, 38.22. Found: Br, 35.63.[20]

Metallic sodium (3.2 g., 0.14 g. atom) was dissolved in 100 ml. of absolute ethanol and 29.3 g. (0.07 mole) of ethyl-

---

[18] Analysis reported in Table I.

[19] Analysis is reported in Table II.

[20] Volhard analysis run on crude material.

enebis-(2-cyanoethyldimethylphosphonium bromide) was added all at once to the resulting ethoxide solution. The mixture was heated to reflux briefly and then kept at room temperature overnight. The excess alcohol was removed and the residue was treated with 100 ml. of water and extracted with benzene. Upon distillation, the benzene extract yielded 5 g. (0.032 mole) of 2-cyanoethyldimethylphosphine (b.p. 70–72° at 1.5 mm., $n^{25}{}_D$ 1.4762). Concentration of the original aqueous reaction mixture gave only brown tars.

d. Preparation of Trimethylenebis-(dimethylphosphine Oxide).—The phosphonium salt, trimethylenebis-(2-cyanoethyldimethylphosphonium bromide), was prepared by the procedure described for ethylenebis-(2-cyanoethylphosphonium bromide) from 30.6 g. (0.266 mole) of 2-cyanoethyldimethylphosphine and 20.2 g. (0.1 mole) of 1,3-dibromopropane. The desired phosphonium salt was obtained in 98% yield, m.p. 175–176°.

Anal. Calcd. for $C_{14}H_{26}N_2P_2{\cdot}2Br$: Br, 36.98. Found: Br, 34.48.[20]

This diphosphonium salt (36.6 g., 0.085 mole) was treated with 9.2 g. (0.170 g.-atom) of sodium in 200 ml. of methanol and refluxed for three hours under nitrogen. Upon working up the reaction mixture 71.5% of trimethylenebis-(2-cyanoethyldimethylphosphonium bromide) was recovered.

This reaction was repeated using 26.2 g. (0.062 mole) of the diphosphonium salt with sodium (2.82 g., 0.124 g.-atom) in 100 ml. of butanol and refluxing for approximately 72 hours. After distilling the excess solvent, the reaction residue was treated with 100 ml. of water and extracted with 100 ml. of benzene. The benzene extract after accidental exposure to air during work-up yielded a small amount of a very hygroscopic solid which was identified by infrared and mass spectroscopy as trimethylenebis-(dimethylphosphine oxide).

This material was distilled under reduced pressure, b.p. 115° at 0.20 mm.

Anal. Calcd. for $C_7H_{18}O_2P_2$: P, 31.58; mol. wt., 196. Found: P, 32.09, 32.12; mol., wt., 196 (determined by mass spectroscopy).

Acknowledgments.—Microanalyses were carried out under the supervision of Dr. J. A. Kuck and Mrs. E. C. Grim. Interpretation of infrared spectra was provided by Norman Colthup and mass spectrometer data by Rosemarie Herberich and A. H. Struck. McGill Valentine prepared bis-(2-cyanoethyl)-methoxypropylphosphine.

STAMFORD, CONN.

[CONTRIBUTION FROM THE RESEARCH DIVISION, BRISTOL LABORATORIES, INC.]

Synthesis of Trifluoromethylated Compounds Possessing Diuretic Activity[1]

BY CHARLES T. HOLDREGE, RICHARD B. BABEL AND LEE C. CHENEY

RECEIVED APRIL 3, 1959

4-Amino-6-trifluoromethyl-*m*-benzenedisulfonamide (VI) was synthesized from 4-chloro-3-nitrobenzotrifluoride. Compound VI reacted with formic acid to give 7-sulfamyl-6-trifluoromethyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (VII). Cyclization of VI with formaldehyde produced 3,4-dihydro-7-sulfamyl-6-trifluoromethyl-2H-1,2,4-benzothiadiazine 1,1-dioxide (VIII). Reaction of VI with a variety of aldehydes and ketals gave 3-substituted dihydrobenzothiadiazine dioxides. Compounds VII and VIII were found to be potent orally active diuretic agents.

The synthesis of a series of compounds containing the trifluoromethyl group was carried out as part of a program aimed at developing useful oral diuretic and hypotensive agents. The compounds were prepared by the route illustrated in Chart I.

4-Chloro-3-nitrobenzotrifluoride was converted to I by a modification of the literature procedure.[2] Conversion of I to II was accomplished by chlorination of a suspension of I in aqueous acetic acid.[3] Compound II could not be prepared by chlorination of I in a mixture of concentrated hydrochloric and nitric acids at 80°.[4] It was interesting to note that Caldwell and Sayin[5] could not satisfactorily prepare the isomeric 4-nitro-2-trifluoromethylbenzenesulfonyl chloride by either procedure.

Crude II was converted to III[6] either by reaction with concentrated ammonium hydroxide or by treatment of a toluene solution with an excess of anhydrous ammonia at 0–4°. In addition to III there was obtained a complex mixture of by-products which made the purification of III tedious.

Reduction of the nitro group of III to give IV was best carried out with either iron and acetic acid or, preferably, with iron and ammonium chloride. Catalytic hydrogenation of III at low pressure with Raney nickel catalyst gave yields of IV in the range of 76–80% provided that III was carefully purified.

The preparation of V[7] by the chlorosulfonation of IV was carried out by an adaptation of the procedure of Lustig and Katscher.[8] The heating period of several hours at 150°, used by these authors, was found to be excessive in the present case. With 20–90-g. quantities of IV the best results were obtained with a heating period of 15–20 minutes at a bath temperature of 150°. Substantially longer heating periods increased the amount of tarry by-products and drastically reduced the yield of V. If sodium chloride was omitted the desired product was not obtained. A major side reaction in the chlorosulfonation was judged to be an attack on the trifluoromethyl group, a supposition supported by the work of LeFave[9] and Scheurer.[10]

---

(1) Presented in part at the 135th Meeting of the American Chemical Society, Division of Medicinal Chemistry, April 5–10, 1959, at Boston, Mass.

(2) A. I. Kiprianov and L. M. Yagupol'skiĭ, *Zhur. Obshchei, Khim.*, **22**, 2209 (1952); *C. A.*, **47**, 4769 (1953).

(3) H. J. Barber, *J. Chem. Soc.*, 101 (1943).

(4) E. Wertheim, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 471.

(5) W. T. Caldwell and A. N. Sayin, THIS JOURNAL, **73**, 5125 (1951).

(6) Some sensitive individuals developed a dermatitis while working with this reaction mixture.

(7) Compound V has been alternatively prepared by the chlorosulfonation of *m*-aminobenzotrifluoride. This reaction will be the subject of a future publication from our laboratories.

(8) O. Lustig and E. Katscher, *Monatsh.*, **48**, 87 (1927).

(9) G. M. LeFave, THIS JOURNAL, **71**, 4148 (1949).

(10) P. G. Scheurer and G. M. LeFave, *ibid.*, **72**, 3308 (1950).