The solution was warmed at 60° for 30 minutes, treated with decolorizing carbon and filtered. The filtrate was extracted with chloroform. After drying over anhydrous potassium carbonate, the chloroform was removed under reduced pressure. The yellow residue melted at 137–162°. Repeated recrystallization from ligroin failed to change the melting point. A mixture of two isomers was assumed but no method has been found to separate them as yet.

N-Oxides of Imidazo-(b)-pyridines. 6-Bromoimidazo-(b)-pyridine-4-N-oxide (XXXII). A 1.2 M solution of peracetic acid was made according to the procedure of Byers and Hickenbottom.[6] 6-Bromoimidazo-(b)-pyridine[3] (3.96 g., 0.02 mole) was suspended in an equivalent amount of freshly prepared 1.2 M peracetic acid (17 ml.). The suspension was warmed at 50°. The solid dissolved and after 20 minutes a white solid precipitated. The latter was removed, dried and recrystallized from glacial acetic acid.

(6) A. Byers and W. J. Hickenbottom, *J. Chem. Soc.*, 284, (1948).

6-Chloroimidazo-(b)-pyridine-4-N-oxide (XXXIII). The *N*-oxide was prepared from 6-chloroimidazo-(b)-pyridine[3] by the procedure used for XXXII except that the suspension was warmed at 70° for 30 min.

6-Bromo-7-methylimidazo-(b)-pyridine-4-N-oxide (XXXIV). The preparation of this compound from 6-bromo-7-methylimidazo-(b)-pyridine[3] was similar to that used for XXXIII.

5-Methyl-6-bromoimidazo-(b)-pyridine-4-N-oxide (XXXV). No precipitate formed when 5-methyl-6-bromoimidazo-(b)-pyridine was warmed with the peracetic acid solution at 70° for 30 minutes. The solution was concentrated to half volume under reduced pressure. The product so obtained was purified by dissolving in glacial acetic acid and adding ether to precipitate the *N*-oxide.

5,7-Dimethyl-6-bromoimidazo-(b)-pyridine-4-N-oxide (XXXVI). The preparation of XXXVI, from the corresponding diamine,[3] was similar to that used for compound XXXII. It was purified in the same manner as XXXV.

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Reaction of Phosphine with Isocyanates

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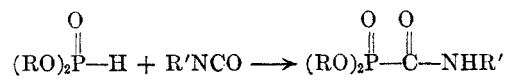
Received March 30, 1959

Phosphine reacts with three isocyanates to give derivatives of a new class of organophosphorus compounds, the tricarbamoylphosphines. Information about the hydrolytic and thermal stability of these materials is presented.

As part of a general study of the reactions of phosphine with carbonyl-containing compounds,[1a,b] we have investigated the reaction of phosphine with isocyanates.

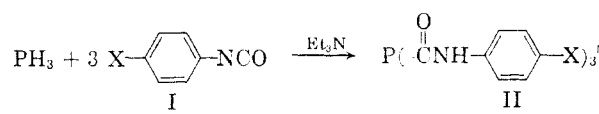
Few reports are to be found in the literature dealing with the reaction of an isocyanate with a substance having a P—H bond. Reetz *et al.* found that dialkyl phosphonates and isocyanates react in the absence of catalyst at temperatures of about 135° to give low yields of carbamoylphosphonates.[2]



Higher yields have been obtained in this reaction by the use of basic catalysts.[3–5] Other reactions of this type which give monocarbamoyl derivatives have been carried out with a monoalkylphosphinic acid,[6] an alkyl monoalkylphosphinate,[7] a dialkyl thionophosphonate,[7] and a secondary phosphine.[1b]

Although no reactions of isocyanates and phosphine have been reported, Hunter has described an unsuccessful attempt to react phosphine with phenyl isothiocyanate.[8]

In the present work we have found that phosphine reacts with isocyanates to give derivatives of a novel type of organophosphorus compound, tricarbamoylphosphine.



a. X = H
b. X = Cl
c. X = NO_2

The reactions were conducted under mild conditions (room temperature and 2–4 atmospheres of phosphine) for periods ranging from 4 hours to 4 days. The yields were 13, 55, and 100% of IIa, IIb, and IIc, respectively, based on the isocyanate charged. Judging from the yields obtained, the reactivities of the isocyanates employed were in the same order, in terms of the electronegativity of

(1) For previous reports in this field see: (a) Abstracts of Papers presented at the 134th Meeting of the American Chemical Society, Chicago, Ill., September 1958, p. 97P. (b) *J. Am. Chem. Soc.*, **80**, 6454 (1958).

(2) T. Reetz, D. H. Chadwick, E. E. Hardy, and S. Kaufman, *J. Am. Chem. Soc.*, **77**, 3813 (1955).

(3) R. B. Fox and D. L. Venezky, *J. Am. Chem. Soc.*, **78**, 1661 (1956).

(4) A. N. Pudovik and A. V. Kuznetsova, *Zhur. Obshcheĭ Khim.*, **25**, 1369 (1955).

(5) E. C. Ladd and M. P. Harvey, Can. Patent **509,034** (1955).

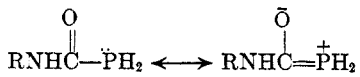
(6) R. B. Fox and W. J. Bailey, Abstracts of Papers presented at the 130th Meeting of the American Chemical Society, Atlantic City, N. J., September 1956, p. 50–0.

(7) A. N. Pudovik, I. V. Konovalova, and R. E. Krivonosova, *Zhur. Obshcheĭ Khim.*, **26**, 3110 (1956).

(8) R. F. Hunter, *Chem. News*, 50 (1930).

the substituent, as that observed toward other nucleophiles such as amines, *i.e.*, Ic>Ib>Ia.[9]

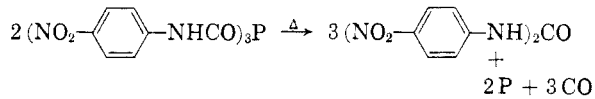
The experimental conditions for these reactions were such that approximately equimolar amounts of phosphine and isocyanate were present initially in the reaction mixtures. In spite of this trisubstituted derivatives of phosphine were the only products observed. In the reaction with phenyl isocyanate the conversion was quite low, but the bulk of the isocyanate was unaltered as indicated by infrared examination. The intermediate mono- and dicarbamoyl phosphines, $RNHCOPH_2$ and $(RNHCO)_2PH$, were not detected. If it is assumed that the tertiary amine catalyst functions in the phosphine reaction in the same way as it is thought to operate in other reactions with isocyanates, *i.e.*, by activating the isocyanate rather than removing a proton in the transition state,[9] two interesting conclusions can be drawn from these observations. First, since the intermediate addition products appear to be more reactive toward isocyanates than phosphine itself, the nucleophilic reactivity of the phosphorus atom is increased by substitution of a carbamoyl group for hydrogen in much the same way as the base strength of phosphine is increased by successive replacement of hydrogen with methyl groups.[10] Secondly, the amide type of resonance with phosphorus is probably not important in these



substances since if it were, one would expect to get monocarbamoyl derivatives such as are obtained under these conditions with ammonia and primary amines.

A limited study of reaction conditions was carried out. It was found that even with *p*-nitrophenyl isocyanate no reaction occurred in the absence of a catalyst such as triethylamine. A stronger base such as pentamethylguanidine did not improve the reaction with phenyl isocyanate, and with metallic sodium present, considerable amounts of isocyanate dimer and trimer were formed. Experiments with *p*-chlorophenyl isocyanate indicated that benzene was superior as a solvent to either acetonitrile or petroleum ether as indicated by the amount of product obtained in a given reaction time. This is similar to the solvent effect found in the reaction of phenyl isocyanate with methanol.[11] Longer reaction times and a higher temperature (60°) failed to improve the conversions obtained with phenyl and *p*-chlorophenyl isocyanate. This is probably due to inactivation of the catalyst rather than an equilibrium situation since the products are stable in the presence of triethylamine; however, this point has not been investigated further.

The tris(arylcarbamoyl)phosphines which have been prepared are thermally stable in the solid state below 200°. At somewhat higher temperatures they melt, evolve gases, and rapidly resolidify. This thermal decomposition was investigated in the case of tris(*p*-nitrophenylcarbamoyl)phosphine, and it was found that in boiling dimethylformamide or nitrobenzene this substance decomposes to give 4,4′-dinitrocarbanilide and elemental phosphorus. The gas collected from the decomposition of a sample in the absence of solvent was found to consist of a mixture of 61% CO and 39% CO_2. The following equation accounts for the major reaction observed:



The tris(arylcarbamoyl)phosphines proved to be of greater stability to hydrolysis than that reported for the monoacyl phosphines.[12] More than 90% of tris(*p*-chlorophenylcarbamoyl)phosphine was recovered unchanged after boiling in aqueous suspension for 16 hours or in 90% aqueous acetic acid solution for 15 minutes. The carbamoylphosphonates are also reported to be more stable to hydrolysis than the acylphosphonates.[2]

The reaction of 2,4-tolylene diisocyanate with phosphine was slow and no definite product was isolated. Phenyl isothiocyanate failed to react with phosphine under the conditions described for the isocyanates. Several attempts to react phosphine with the (iso)cyanic acid liberated from potassium cyanate by acids were unsuccessful. Large amounts of cyanuric acid were isolated in some cases.

EXPERIMENTAL[13]

General procedure for reaction of phosphine with isocyanates. These reactions were carried out using a standard Parr pressure reaction apparatus. Solutions of the isocyanates were prepared in pressure bottles, the catalyst was added, and the bottles were quickly attached to the apparatus. The vessel was evacuated and filled with nitrogen three times and finally filled with phosphine from the reservoir before shaking was started. After the solution was saturated, the reaction was allowed to proceed under 30–60 lb./sq. in. pressure for varying periods of time. In removing the bottle from the apparatus, the evacuation and filling with nitrogen was repeated. No significant rises in temperature were noted. Precipitation of the products was noticed soon after the reactions with *p*-chlorophenyl and *p*-nitrophenyl isocyanate were started.

Reaction with phenyl isocyanate (Ia). A solution of 17.9 g. (0.15 mole) of Ia and 0.5 ml. of triethylamine in 100 ml. of dry benzene was allowed to react with phosphine for 4 days.

(9) R. G. Arnold, J. A. Nelson, and J. J. Verbanc, *Chem. Revs.*, **57**, 47 (1957).

(10) H. C. Brown, *J. Am. Chem. Soc.*, **67**, 503 (1945).

(11) S. Ephraim, A. E. Woodward, and R. B. Mesrobian, *J. Am. Chem. Soc.*, **80**, 1326 (1958).

(12) G. M. Kosolapoff, *Organophosphorus Compounds*, John Wiley and Sons, Inc., New York, 1950, p. 14.

(13) All melting points are uncorrected. Thanks are due to the microanalytical group of this laboratory for the analyses and to Dr. John E. Lancaster for the infrared spectra.

The solution was then filtered to remove a small amount of insoluble material and concentrated to half its original volume. Fifty ml. of petroleum ether (b.p. 30–60°) was then added and the solid which deposited was collected giving 1.63 g. of material, m.p. 184–186°. Additional petroleum ether (200 ml.) was added to the filtrate and an additional 0.80 g. of material was deposited, m.p. 183–186°. The total yield of tris(phenylcarbamoyl)phosphine (IIa) was 13%. The analytical sample was prepared by recrystallization from acetic acid giving white crystalline material of m.p. 212–213° (resolidifies to an orange solid).

Anal. Calcd. for $C_{21}H_{18}N_3O_3P$: C, 64.45; H, 4.64; N, 10.74; P, 7.92. Found: C, 64.68; H, 4.86; N, 10.73; P, 8.10.

ν_{max}^{Nujol}: 3200 (w), 1665, 1605 (s), 1505, 1470, 1455 (s), 1320, 1255, 1180, 1105 (w), 1080 (w), 910 (w), 895 (w), 880 (w), 750 (s), and 685 cm.$^{-1}$

The petroleum ether–benzene filtrate was evaporated and the residual liquid was examined by infrared spectroscopy. The spectrum was virtually identical with that of phenyl isocyanate.

Reaction with p-chlorophenyl isocyanate (Ib). A solution of 15.4 g. (0.1 mole) of Ib and 0.5 ml. of triethylamine in 100 ml. of dry benzene was reacted with phosphine for 6 hr. The crystalline solid which deposited was collected to give 9.1 g. (55%) of tris(*p*-chlorophenylcarbamoyl)phosphine (IIb) which turned yellow at 235° and melted with immediate resolidification at 245°. An analytical sample was prepared by recrystallization from acetic acid. There was no change in melting point behavior.

Anal. Calcd. for $C_{21}H_{15}Cl_3N_3O_3P$: C, 50.98; H, 3.06; Cl, 21.50; N, 8.49; P, 6.26. Found: C, 50.94; H, 3.22; Cl, 21.23; N, 8.36; P, 6.55.

ν_{max}^{Nujol}: 3200 (w), 1655, 1595 (s), 1535 (s), 1495 (s), 1405, 1305, 1285 (w), 1240, 1170 (w), 1115, 1090, 1015, 875 (w), 825 (s), and 745 cm.$^{-1}$

Reaction with p-nitrophenyl isocyanate (Ic). A solution of 16.4 g. (0.1 mole) of Ic and 1.0 ml. of triethylamine in 100 ml. of dry benzene was reacted with phosphine for 4 hr. The yellow solid was collected and dried giving 17.5 g. (100%) of tris-(*p*-nitrophenylcarbamoyl)phosphine (IIc), m.p. 267–270°. It was insoluble in all common organic solvents. An analytical sample was prepared by extracting the solid with boiling acetone. Two such treatments gave 15.9 g. (91%) of IIc with a single band in the infrared carbonyl region at 1675 cm.$^{-1}$ Five melting point determinations were carried out with this material in a heated bath. In three cases the samples decomposed suddenly in the range of 245–250°. In the other two cases the samples melted at 277–278° (dec.).

Anal. Calcd. for $C_{21}H_{15}N_6O_9P$: C, 47.92; H, 2.87; P, 5.89. Found: C, 47.96; H, 2.96; P, 5.82.

ν_{max}^{Nujol}: 3200 (w), 1675, 1620, 1605, 1555 (s), 1515 (s), 1420, 1345 (s), 1310, 1260, 1190 (w), 1170, 1125, 1115, 885 (w), 860 (s), 810, 755, and 680 (w) cm.$^{-1}$

Thermal decomposition of tris(p-nitrophenylcarbamoyl)-phosphine (IIc). Five g. of IIc was suspended in 25 ml. of dimethylformamide and the mixture was heated until it boiled gently. Smooth decomposition took place, gas was evolved, and the bulk of the solid dissolved. The solution was filtered hot and the amorphous red phosphorus which formed was collected. The filtrate was allowed to cool and 3.1 g. (72%) of 4,4′-dinitrocarbanilide was obtained as shiny pale yellow plates decomposing at 323°. This material gave bright yellow needles having a similar decomposition point when recrystallized from either pyridine or nitrobenzene. Plates were again obtained when the latter was recrystallized from dimethylformamide. The two crystalline forms showed major differences in the infrared (Nujol mull). An authentic specimen was prepared by reacting *p*-nitrophenyl isocyanate and *p*-nitroaniline in refluxing benzene containing a trace of triethylamine. It showed the same behavior in recrystallization as the thermal decomposition product of IIc, and samples from both sources showed decomposition points varying from 320–330°, depending on the rate of heating. The infrared spectra were identical provided the samples were recrystallized from the same solvent. The melting points recorded for this substance vary considerably. One of the more recent reports gives a value of 310.5° (from pyridine).[14] The analysis was carried out with a sample recrystallized from dimethylformamide.

Anal. Calcd. for $C_{13}H_{10}N_4O_5$: C, 51.66; H, 3.34; N, 18.54. Found: C, 51.48; H, 3.55; N, 18.83.

IIc (1.388 g.) was placed in a small bulb connected to a gas buret filled with mercury and equipped with a leveling bulb. The system was swept with helium and the bulb was heated to 275°. The gas which formed was evolved suddenly and a total of 57.8 ml. (STP) was collected. Mass spectrographic analysis indicated that the gas consisted of 61% carbon monoxide and 39% carbon dioxide.

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(14) I. M. Kogan and D. F. Kutepov, *Zhur. Obshcheĭ Khim.*, **21**, 1297 (1951).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MICHIGAN STATE UNIVERSITY]

Tetrazole Analogs of Pyridinecarboxylic Acids[1]

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Received March 30, 1959

The isomeric 5-tetrazolylpyridines were prepared as anlogs of the pyridine carboxylic acids by interaction of the cyanopyridines with hydrazoic acid. Interaction of 2,6-dicyanopyridine and hydrazoic acid gave the tetrazole analog of dipicolinic acid. Hydrogenation of the tetrazolylpyridines gave the corresponding 5-tetrazolylpiperidines, the analogs of the several isomeric piperidine carboxylic acids.

One of the first instances of vitamin antagonism observed was the interference by pyridine-3-sulfonic acid (I) and its amide (II) with the utilization of niacin (III) and niacinamide (IV) as evidenced by inhibition of staphylococcus growth.[4] Subsequently, 3-acetylpyridine[5] and thiazole-5-

(1) Based on the doctoral thesis submitted to Michigan State University in 1958 by James M. McManus.

(2) White Laboratories Fellow, 1956–1958.

(3) Present address: Chas. Pfizer & Co., Inc., Brooklyn, N. Y.

(4) H. McIlwain, *Brit. J. Expt. Pathol.*, **21**, 136 (1940).

(5) E. Auhagen, *Z. physiol. Chem.*, **274**, 48 (1942).