aration of 5,7-dimethoxybenzimidazole. The product was recrystallized from dioxane with the aid of decolorizing carbon.

2-Methyl-5,6-dimethoxybenzimidazole and 2-hydroxymethyl-5,6-dimethoxybenzimidazole were prepared by Phillips' method.[5]

*2-Chloromethyl-5,6-dimethoxybenzimidazole hydrochloride.* A mixture of 8.19 g. (0.0393 mole) of 2-hydroxymethyl-5,6-dimethoxybenzimidazole and 15 ml. of thionyl chloride was refluxed for 4 hr. The mixture was cooled and the solid removed and washed with chloroform. It was recrystallized from ethanol with the aid of decolorizing carbon.

*2-Di-n-butylaminomethyl-5,6-dimethoxybenzimidazole.* A solution of 2.63 g. (0.01 mole) of 2-chloromethyl-5,6-dimethoxybenzimidazole hydrochloride and 3.78 g. (0.03 mole) of di-*n*-butylamine in 5 ml. of ethanol was refluxed for 3 hr. The alcohol was removed by evaporation and the residue treated with water. The water solution was extracted with chloroform. The chloroform was removed and the residue dissolved in ether. The addition of petroleum ether precipitated an oil which solidified on cooling. This product was purified by forming its hydrochloride in carbon tetrachloride solution. The salt was recrystallized from ethanol and then converted to the base by treatment with sodium carbonate solution. The free base was recrystallized from carbon tetrachloride–petroleum ether.

*2-Di(β-chloroethyl) aminomethyl-5,6-dimethoxybenzimidazole.* 2-Chloromethyl-5,6-dimethoxybenzimidazole hydrochloride (3.22 g., 0.0123 mole) and 3.9 g. (0.070 mole) of diethanolamine were dissolved in 40 ml. of ethanol and the solution was refluxed for 3 hr. The ethanol was removed *in vacuo* and 100 ml. of chloroform added. A small upper layer formed and was discarded. Ten ml. of thionyl chloride was added to the chloroform layer and the solution was refluxed for 1 hr. After cooling, the precipitate was removed by filtration. It was recrystallized from ethanol with the aid of decolorizing carbon.

*5,6-Dihydroxybenzimidazole Hydrobromide.* 5,6-Dimethoxybenzimidazole (1 g., 0.0056 mole) was dissolved in 25 ml. of 48% hydrobromic acid and the solution was refluxed for 1 hr. On cooling, the product crystallized. It was recrystallized from ethanol–petroleum ether.

PHILADELPHIA, PA.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PENNSYLVANIA]

# Preparation of Pyrido-(2,3)-pyrazines, Pyrido-(3,4)-pyrazines and Imidazo-(b)-pyridines

MERVYN ISRAEL[1] AND ALLAN R. DAY

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A number of imidazopyridines and pyridopyrazines have been prepared. Imidazo-(b)-pyridines having methyl groups and/or halogen were converted to mono *N*-oxides by the action of 1.2 *M* peracetic acid. Electron attracting substituents prevented *N*-oxidation. The pyridopyrazines failed to give *N*-oxides under a variety of conditions.

A number of benzimidazoles and quinoxaline derivatives have been found to possess antimetabolite or bactericidal activity. The activity of these compounds is somewhat dependent on the nature and positions of substituent groups. Much less is known about the imidazopyridines and pyridopyrazines. It seemed desirable to prepare a number of substituted imidazopyridines and pyridopyrazines for testing purposes. Diaminopyridines were the starting materials for these preparations.[2]

2-Amino-5-chloropyridine was nitrated to form 2-amino-3-nitro-5-chloropyridine. The latter was reduced most efficiently with sodium dithionate to the corresponding 2,3-diamino compound. The diamine was converted to 6-chloroimidazo-(b)-pyridine by refluxing with formic acid and to 7-chloropyrido-(2,3)-pyrazine and 2,3-dimethyl-7-chloropyrido-(1,3)-pyrazine by treatment with glyoxal and diacetyl respectively. The diphenyl derivative was made from the diamine and benzil.

When 2-amino-3-nitro-5-chloropyridine was reduced with stannous chloride in concentrated hydrochloric acid, a dichlorinated diamine was isolated. This product was assumed to be 5,6-dichloro-2,3-diaminopyridine. It was converted to the corresponding pyridopyrazines with glyoxal and diacetyl.

2-Amino-4-methylpyridine was brominated in alcohol solution to give 2-amino-4-methyl-5-bromopyridine. The latter was nitrated to the corresponding 3-nitro compound which was then reduced with stannous chloride to 2,3-diamino-4-methyl-5-bromopyridine. The diamine was converted to 2-hydroxy-6-bromo-7-methylimidazo-(b)-pyridine by fusion with urea and to 2-mercapto-6-bromo-7-methylimidazo-(b)-pyridine by treatment with carbon disulfide in alcoholic potassium hydroxide solution. 6-Bromo-7-methylimidazo-(b)-pyridine was obtained from the diamine by heating with formic acid. This imidazo compound was oxidized to 6-bromo-7-imidazo-(b)-pyridinecarboxylic acid. 2,3-Diamino-4-methyl-5-bromopyridine was also treated with glyoxal, diacetyl and benzil, respectively, to obtain the corresponding pyridopyrazines.

The preparation of 2,3-diamino-5-bromo-6-methylpyridine from 2-amino-6-methylpyridine was completely analogous to that just described for the 4-methyl isomer. The 2,3-diamino-5-bromo-6-methylpyridine was converted to the corresponding

(1) DuPont Teaching Fellow, 1957–1958.

(2) The new compounds that were prepared during this investigation are being tested at the University of Pennsylvania. The results will be reported later.

2-hydroxy and 2-mercapto-5-methyl-6-bromoimidazo-(b)-pyridines as described for the 4-methyl isomer. Reactions with glyoxal, diacetyl and benzil gave the corresponding pyridopyrazines. Attempts to oxidize the methyl group in 5-methyl-6-bromoimidazo-(b)-pyridine to the carboxyl group were not successful. This methyl group, which is alpha to the pyridine nitrogen atom, is very resistant to oxidation.

2-Amino-4,6-dimethylpyridine was converted to 2,3 - diamino - 4,6 - dimethyl - 5 - bromopyridine by methods similar to those just described except that it was necessary to acetylate the 2-amino compound prior to bromination. Formic acid, glyoxal and diacetyl converted 2,3-diamino-4,-6-dimethyl-5-bromopyridine to the corresponding imidazole and pyrazines. When 5,7-dimethyl-6-bromoimidazo-(b)-pyridine was oxidized with potassium permanganate, the corresponding 5,7-dicarboxylic acid was obtained.

Attempts to form pyrazines from 2,3-diaminopyridine-5-sulfonic acid were unsuccessful. The imidazopyridine sulfonic acid was reported earlier.[3]

4-Aminopyridine was the starting material for another series of pyrazines. It was nitrated and reduced to form both 3,4-diamino-5-nitropyridine and 3,4,5-triaminopyridine by modifications of previously described procedures.[3] The latter was treated with glyoxal, methylglyoxal and diacetyl to form the corresponding pyrido-(3,4)-pyrazines. With methyl glyoxal, a mixture of two isomers was obtained, 2-methyl- and 3-methyl-8-aminopyrido-(3,4)-pyrazines. The 3,4-diamino-5-nitropyridine did not form pyrazines with glyoxal or methyl glyoxal and only a very low yield of 2,3-dimethyl-8-nitropyrido-(3,4)-pyrazine was obtained from the reaction with diacetyl.

In addition to the compounds noted above, five *N*-oxides of imidazo-(b)-pyridines were also prepared. Imidazo-(b)-pyridines, substituted with halogen and/or methyl groups, readily formed mono *N*-oxides when treated with peracetic acid. The *N*-oxide function has been assigned to the pyridine nitrogen rather than to a nitrogen atom in the imidazole ring for two reasons: (1) the ability of pyridines to form *N*-oxides is well known; and (2) benzimidazole under similar conditions was found to be unaffected. *N*-Oxides of imidazopyridines containing strong deactivating groups could not be prepared. Both imidazo-(b)-pyridine-6-sulfonic acid and 7-nitroimidazo-(c)-pyridine failed to form *N*-oxides.

The mono *N*-oxide of 7-bromopyrido-(2,3)-pyrazine was reported in 1948.[4] Attempts to prepare the di-*N*-oxide failed. In the present investigation, attempts were made to prepare *N*-oxides of the pyridopyrazines reported here. Although various conditions were used, the attempts were unsuccessful.

## EXPERIMENTAL

*2-Amino-3-nitro-5-chloropyridine* (I). 2-Amino-5-chloropyridine was nitrated by the method of Vaughan, Krapcho and English.[5] The yield was 70%, m.p. 191–192°.

*2,3-Diamino-5-chloropyridine* (II). The 5-nitro compound was reduced with sodium dithionate.[5] The yields were 45-50%, m.p. 172–173°.

*6-Chloroimidazo-(b)-pyridine* (III). 2,3-Diamino-5-chloropyridine was refluxed with formic acid.[5] The yield was 74%, m.p. 237–238°.

*7-Chloropyrido-(2,3)-pyrazine* (IV). A solution of 2.9 g. (0.02 mole) of 2,3-diamino-5-chloropyridine and 5 g. (0.025 mole) of 30% aqueous glyoxal in 25 ml. of 50% aqueous ethanol was refluxed for 20 minutes. Water was added to the hot solution until it became cloudy. On cooling, the product separated and was removed by filtration. It was recrystallized from ligroin.

*2,3-Dimethyl-7-chloropyrido-(2,3)-pyrazine* (V). This preparation was similar to that of IV except that diacetyl was used in place of glyoxal. The product was recrystallized from ligroin and finally from 30% ethanol.

*2,3-Diphenyl-7-chloropyrido-(2,3)-pyrazine* (VI). 2,3-Diamino-5-chloropyridine (4.0 g., 0.028 mole) was refluxed with 6.0 g. (0.028 mole) of benzil in 60 ml. of benzene for 1 hr. The solution was dried over anhydrous magnesium sulfate and the benzene removed under reduced pressure. The residue was recrystallized from ligroin and then from ethanol. The product was obtained as pale yellow needles.

*2,3-Diamino-5,6-dichloropyridine* (VII). To a solution of 76.8 g. (0.4 mole) of anhydrous stannous chloride in 200 ml. of concentrated hydrochloric acid was added 17.4 g. (0.1 mole) of 2-amino-3-nitro-5-chloropyridine in small portions. Finally, the solution was refluxed for 30 minutes. After cooling, the solution was made strongly basic with 40% sodium hydroxide solution. The mixture was stirred for 2 hr. at 90° and the yellow precipitate removed by filtration and washed with ice water. Extraction with hot water gave a white product which was then recrystallized from water, yield 32%, m.p. 167°.

*Anal.* Calcd. for $C_5H_5N_3Cl_2$: C, 33.70; H, 2.80; N, 23.59; Cl, 39.88. Found: C, 33.50; H, 2.94; N, 23.42; Cl, 39.54.

*6,7-Dichloropyrido-(2,3)-pyrazine* (VIII). This compound was prepared from VII by the same procedure that was used for compound IV. The crude product was recrystallized from 30% ethanol.

*2,3-Dimethyl-6,7-dichloropyrido-(2,3)-pyrazine* (IX). Diacetyl was used in place of glyoxal in this preparation, otherwise the method was the same as for compound IV. The crude product was recrystallized from 50% ethanol.

*2,3-Diamino-4-methyl-5-bromopyridine* (X). The starting compound for this preparation was 2-amino-4-methylpyridine. The procedure which was used is reported in reference 3. Only one modification is reported here. After the stannous chloride reduction of 2-amino-3-nitro-4-methyl-5-bromopyridine, the solution was cooled to precipitate the double tin salt of the diamine. The latter was removed and dissolved in boiling 0.3 N hydrochloric acid. Hydrogen sulfide was passed into the solution to precipitate the tin as sulfide. After removing the latter, the filtrate was adjusted to a pH of 9–10. On cooling, the diamine separated as fine crystals, yield 55–57%, m.p. 161–162°.

*2-Hydroxy-6-bromo-7-methylimidazo-(b)-pyridine* (XI). A mixture of 4.04 g. (0.02 mole) of 2,3-diamino-4-methyl-5-bromopyridine and 1.2 g. (0.02 mole) of urea was fused at 180° until no more ammonia was given off. The brown solid was dissolved in 50 ml. of hot dimethyl formamide and after

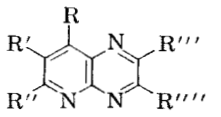
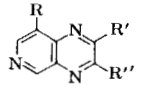
(3) H. Graboyes and A. R. Day, *J. Am. Chem. Soc.*, **79**, 6421 (1957).

(4) V. Petrow and J. Saper, *J. Chem. Soc.*, 1389 (1948).

(5) J. R. Vaughan, Jr., J. Krapcho and J. P. English, *J. Am. Chem. Soc.*, **71**, 1885 (1949).

TABLE I

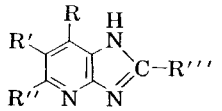
PYRIDOPYRAZINES

| | R | R′ | R″ | R‴ | R⁗ | Formula | Yield, % | M.P. °C. | Analyses: Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found | Nitrogen Calcd. | Nitrogen Found | Chlorine Calcd. | Chlorine Found | Bromine Calcd. | Bromine Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | |  | | | | | | | | | |
| | | | | | | | | | Pyrido-(2,3)-pyrazines | | | | | | | | | |
| IV | H | Cl | H | H | H | $C_7H_4N_3Cl$ | 51 | 159–160.5 | 50.77 | 50.84 | 2.45 | 2.58 | 25.37 | 25.25 | 21.40 | 21.32 | | |
| V | H | Cl | H | $CH_3$ | $CH_3$ | $C_9H_8N_3Cl$ | 72 | 152 | 55.82 | 55.67 | 4.14 | 4.20 | 21.70 | 21.51 | 18.31 | 18.12 | | |
| VI | H | Cl | H | $C_6H_5$ | $C_6H_5$ | $C_{19}H_{12}N_3Cl$ | 60 | 159–161 | 71.80 | 71.55 | 3.81 | 3.72 | 13.22 | 13.04 | 11.15 | 10.93 | | |
| VIII | H | Cl | Cl | H | H | $C_7H_3N_3Cl_2$ | 55 | 162–164d | 42.05 | 41.88 | 1.51 | 1.59 | 21.01 | 21.09 | 35.46 | 35.71 | | |
| IX | H | Cl | Cl | $CH_3$ | $CH_3$ | $C_9H_7N_3Cl_2$ | 66 | 197–199d | 47.39 | 47.60 | 3.09 | 3.03 | 18.43 | 18.52 | 31.10 | 30.96 | | |
| XIV | $CH_3$ | Br | H | H | H | $C_8H_6N_3Br$ | 82 | 204–206 | 42.88 | 43.07 | 2.70 | 2.64 | 18.76 | 18.87 | | | 35.67 | 35.76 |
| XV | $CH_3$ | Br | H | $CH_3$ | $CH_3$ | $C_{10}H_{10}N_3Br$ | 90 | 141.5–143 | 47.62 | 47.43 | 4.00 | 3.89 | 16.67 | 16.54 | | | 31.71 | 32.00 |
| XVI | $CH_3$ | Br | H | $C_6H_5$ | $C_6H_5$ | $C_{20}H_{14}N_3Br$ | 18 | 199.5–201 | 63.84 | 63.98 | 3.75 | 3.87 | 11.17 | 11.14 | | | 21.24 | 21.47 |
| XXII | H | Br | $CH_3$ | H | H | $C_8H_6N_3Br$ | 47 | 165–166d | 42.88 | 43.04 | 2.70 | 2.90 | 18.76 | 18.65 | | | 35.67 | 35.62 |
| XXIII | H | Br | $CH_3$ | $CH_3$ | $CH_3$ | $C_{10}H_{10}N_3Br$ | 84 | 161–162 | 47.62 | 47.53 | 4.08 | 4.10 | 16.67 | 16.43 | | | 31.71 | 31.81 |
| XXIV | H | Br | $CH_3$ | $C_6H_5$ | $C_6H_5$ | $C_{20}H_{14}N_3Br$ | 60 | 160d | 63.84 | 64.02 | 3.75 | 3.79 | 11.17 | 10.99 | | | 21.24 | 21.31 |
| XXV | $CH_3$ | Br | $CH_3$ | H | H | $C_9H_8N_3Br$ | 42 | 174–174.5d | 45.39 | 45.24 | 3.39 | 3.57 | 17.65 | 17.58 | | | 33.57 | 33.46 |
| XXVI | $CH_3$ | Br | $CH_3$ | $CH_3$ | $CH_3$ | $C_{11}H_{12}N_3Br$ | 68 | 166–167 | 49.63 | 49.61 | 4.55 | 4.67 | 15.79 | 15.82 | | | 30.02 | 29.93 |
| | | | | | | | | |  | | | | | | | | | |
| | | | | | | | | | Pyrido-(3,4)-pyrazines | | | | | | | | | |
| XXVIII | $NO_2$ | $CH_3$ | $CH_3$ | | | $C_9H_8N_4O_2$ | 28 | 109.5–110 | 52.94 | 52.81 | 3.95 | 3.91 | 27.44 | 27.24 | | | | |
| XXIX | $NH_2$ | H | H | | | $C_7H_6N_4$ | 54 | 149–150 | 57.55 | 57.56 | 4.14 | 4.13 | 38.36 | 38.46 | | | | |
| XXX | $NH_2$ | $CH_3$ | $CH_3$ | | | $C_9H_{10}N_4$ | 65 | 187–189 | 62.05 | 62.06 | 5.79 | 5.76 | 32.17 | 32.03 | | | | |
| XXXI | $NH_2$ | $CH_3$(H) | $CH_3$(H)[a] | | | $C_8H_8N_4$ | 62 | 137–162 | 59.99 | 59.88 | 5.04 | 5.15 | 34.97 | 34.78 | | | | |

[a] Mixture of 2-methyl and 3-methyl isomers.

TABLE II

IMIDAZOPYRIDINES

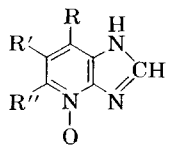


Imidazo-(b)-pyridines

| | R | R′ | R″ | R‴ | Formula | Yield, % | M.P., °C. | Analyses | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Carbon | | Hydrogen | | Nitrogen | | Bromine | | Sulfur | |
| | | | | | | | | Calcd. | Found | Calcd. | Found | Calcd. | Found | Calcd. | Found | Calcd. | Found |
| XI | $CH_3$ | Br | H | OH | $C_7H_6N_3BrO$ | 57 | >300 | 36.86 | 36.61 | 2.65 | 2.86 | 18.42 | 18.44 | 35.04 | 35.26 | | |
| XIII | $CH_3$ | Br | H | SH | $C_7H_6N_3BrS$ | 73 | >300 | 34.43 | 34.59 | 2.48 | 2.30 | 17.22 | 17.11 | 32.74 | 32.64 | 13.13 | 12.97 |
| XVII | COOH | Br | H | H | $C_7H_4N_3BrO_2$ | 61 | 254–255d | 34.73 | 34.65 | 1.67 | 1.84 | 17.36 | 17.20 | 33.00 | 32.80 | | |
| XVIII | $COOCH_2CH_2OH$ | Br | H | H | $C_9H_8N_3BrO_3$ | 47 | 208–209 | 37.78 | 37.64 | 2.82 | 2.69 | 14.69 | 14.62 | 27.94 | 28.02 | | |
| XIX | H | Br | $CH_3$ | OH | $C_7H_6N_3BrO$ | 73 | >300 | 36.86 | 37.07 | 2.65 | 2.40 | 18.42 | 18.57 | 35.04 | 35.27 | | |
| XXI | H | Br | $CH_3$ | SH | $C_7H_6N_3BrS$ | 68 | >300 | 34.43 | 34.23 | 2.48 | 2.45 | 17.22 | 17.06 | 32.74 | 32.52 | 13.13 | 13.08 |
| XXVII | COOH | Br | COOH | H | $C_8H_4N_3BrO_4$ | 58 | 244d | 33.58 | 33.30 | 1.41 | 1.62 | 14.69 | 14.68 | 27.94 | 27.78 | | |

TABLE III

IMIDAZO-(b)-PYRIDINE N-OXIDES



| | R | R′ | R″ | Formula | Yield, % | M.P., °C. | Analyses | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Carbon | | Hydrogen | | Nitrogen | | Chlorine | | Bromine | |
| | | | | | | | Calcd. | Found | Calcd. | Found | Calcd. | Found | Calcd. | Found | Calcd. | Found |
| XXXII | H | Br | H | $C_6H_4N_3BrO$ | 51 | 254d | 33.66 | 33.61 | 1.88 | 1.66 | 19.36 | 19.48 | | | 37.35 | 37.51 |
| XXXIII | H | Cl | H | $C_6H_4N_3ClO$ | 63 | >300 | 42.27 | 42.27 | 2.38 | 2.36 | 24.77 | 25.00 | 20.90 | 20.67 | | |
| XXXIV | $CH_3$ | Br | H | $C_7H_6N_3BrO$ | 90 | 263–264d | 36.86 | 36.68 | 2.65 | 2.48 | 18.43 | 18.22 | | | 35.04 | 35.24 |
| XXXV | H | Br | $CH_3$ | $C_7H_6N_3BrO$ | 60 | 263d | 36.86 | 36.80 | 2.65 | 2.85 | 18.43 | 18.31 | | | 35.04 | 35.31 |
| XXXVI | $CH_3$ | Br | $CH_3$ | $C_8H_8N_3BrO$ | 75 | 246d | 39.70 | 39.46 | 3.33 | 3.30 | 17.36 | 17.09 | | | 33.01 | 32.79 |

treatment with decolorizing carbon the product was precipitated by the addition of water. It was then recrystallized from *n*-amyl alcohol.

*1-N-Acetyl-2-acetoxy-6-bromo-7-methylimidazo-(b)-pyridine* (XII). 2-Hydroxy-6-bromo-7-methylimidazo-(b)-pyridine (1.14 g.) was refluxed for 30 minutes with 25 ml. of acetic anhydride containing one drop of concentrated sulfuric acid. The product crystallized on cooling and was purified by recrystallization from acetic anhydride. The yield was 90%, m.p. 197–198°.

*Anal.* Calcd. for $C_{11}H_{10}N_3BrO_3$: C, 42.33; H, 3.23; N, 13.47; Br, 25.61. Found: C, 42.26; H, 3.28; N, 13.40; Br, 25.47.

*2-Mercapto-6-bromo-7-methylimidazo-(b)-pyridine* (XIII). 2,3-Diamino-4-methyl-5-bromopyridine (2.02 g., 0.01 mole) was dissolved in 30 ml. of ethanol. To this solution was added 0.1 g. of potassium hydroxide and 0.8 g. of carbon disulfide. The solution was heated on the steam bath for 1 hr., during which time a yellow solid precipitated. The product was removed and recrystallized from dimethyl formamide–water.

*7-Bromo-8-methylpyrido-(2,3)-pyrazine* (*XIV*). Compound XIV was prepared from 2,3-diamino-4-methyl-5-bromopyridine by the procedure described for making compound IV. The product was recrystallized from 40% aqueous ethanol.

*2,3,8-Trimethyl-7-bromopyrido-(2,3)-pyrazine* (*XV*). Compound XV was prepared from 2,3-diamino-4-methyl-5-bromopyridine by the method described for making compound V. The product was recrystallized from 50% aqueous ethanol.

*2,3-Diphenyl-7-bromo-8-methylpyrido-(2,3)-pyrazine* (XVI). A mixture of 3.2 g. (0.016 mole) of 2,3-diamino-4-methyl-5-bromopyridine and 3.3 g. (0.016 mole) of benzil in 100 ml. of 50% aqueous ethanol was refluxed for 6 hr. After cooling, the product was removed and recrystallized from ethanol with the aid of decolorizing carbon.

*6-Bromo-7-carboxyimidazo-(b)-pyridine* (XVII). 6-Bromo-7-methylimidazo-(b)-pyridine[3] (2.12 g., 0.01 mole) was partially dissolved in 150 ml. of boiling water containing 1 g. of sodium carbonate. Four grams (0.025 mole) of powdered potassium permanganate was added, in small portions, to the refluxing solution. After 1 hr. the manganese dioxide was removed and the filtrate concentrated to one third the original volume under reduced pressure. Acidification of this solution, with 10% hydrochloric acid, gave a precipitate which was removed and recrystallized from 50% aqueous ethylene glycol.

*β-Hydroxyethyl 6-bromo-7-imidazo-(b)-pyridine carboxylate* (XVIII). 6-Bromo-7-carboxyimidazo-(b)-pyridine (0.63 g., 0.0026 mole) was suspended in 20 ml. of ethylene glycol which had been previously saturated with dry hydrogen chloride at 10°. The mixture was slowly heated to reflux temperature. The solid dissolved gradually over a period of 3 hr. After cooling, an equal volume of water was added and the pH adjusted to 7.0. On standing overnight, at −10°, the ester crystallized. The product was recrystallized from a small volume of water.

*2-Hydroxy-5-methyl-6-bromoimidazo-(b)-pyridine* (XIX). Compound XIX was prepared from 2,3-diamino-5-bromo-6-methylpyridine[2] by the method described for XI. The purification procedure, however, was not the same. The brown residue was dissolved in hot 10% sodium hydroxide. The solution was treated with decolorizing carbon and filtered. The addition of 15 ml. of 40% sodium hydroxide, to the cooled filtrate, precipitated the product as its disodium salt. The latter was dissolved in water and the solution acidified with hydrochloric acid to precipitate the product. It was recrystallized from dimethyl formamide–water.

*1-N-Acetyl-2-acetoxy-5-methyl-6-bromoimidazo-(b)-pyridine* (XX). The preparation of XX from XIX was the same as that described for compound XII. The yield was almost quantitative, m.p. 178°.

*Anal.* Calcd. for $C_{11}H_{10}N_3BrO_3$: C, 42.33; H, 3.23; N, 13.47; Br, 25.61. Found: C, 42.40; H, 3.07; N, 13.48; Br, 25.35.

*2-Mercapto-5-methyl-6-bromoimidazo-(b)-pyridine* (XXI). Compound XXI was prepared by the method used for making XIII. The product was recrystallized from ethylene glycol.

*6-Methyl-7-bromopyrido-(2,3)-pyrazine* (XXII) *and 2,3,6-Trimethyl-7-bromopyrido-(2,3)-pyrazine* (XXIII). Compounds XXII and XXIII were prepared from 2,3-diamino-5-bromo-6-methylpyridine by the procedures described for making compounds IV and V respectively.

*2,3-Diphenyl-6-methyl-7-bromopyrido-(2,3)-pyrazine* (XXIV). 2,3-Diamino-5-bromo-6-methyl-pyridine (4.04 g., 0.02 mole) and an equimolar amount (4.5 g.) of benzil were dissolved in 40 ml. of ethanol and the solution refluxed for 1 hr. The solution was evaporated, the residue taken up in chloroform, and the solution dried over anhydrous magnesium sulfate. After the chloroform was removed, the residue was recrystallized from ligroin.

*6,8-Dimethyl-7-bromopyrido-(2,3)-pyrazine* (XXV). 2,3-Diamino-4,6-dimethyl-5-bromopyridine[3] (2.2 g., 0.01 mole) and 2 g. of 30% glyoxal solution (1 equivalent of glyoxal) in 25 ml. of water were heated at 80° for 25 minutes. Crystallization occurred on cooling. The product was recrystallized from ligroin.

*2,3,6,8-Tetramethyl-7-bromopyrido-(2,3)-pyrazine* (*XXVI*). This compound was prepared from the corresponding diamine by the procedure used for making V. The product was recrystallized from ligroin.

*5,7-Dicarboxy-6-bromoimidazo-(b)-pyridine* (XXVII). 5,7-Dimethyl-6-bromoimidazo-(b)-pyridine (3 g., 0.0133 mole) was partially dissolved in 200 ml. of boiling water containing 2.5 g. of sodium carbonate. Powdered potassium permanganate (11 g., 0.07 mole) was added in small portions and the solution was refluxed for 2 hr. The manganese dioxide was removed and the filtrate was evaporated to a volume of 60 ml. under reduced pressure. The addition of concentrated hydrochloric acid precipitated a pale yellow solid. The latter was recrystallized from 40% aqueous ethylene glycol to give pale yellow needles.

*2,3-Dimethyl-8-nitropyrido-(3,4)-pyrazine* (XXVIII). 3,4-Diamino-5-nitropyridine[3] (6.2 g., 0.04 mole) was dissolved in 100 ml. of hot water. The addition of 4 ml. of diacetyl (0.045 mole) produced a very dark solution. After cooling, the solution was extracted with ether. The ether extract was dried over anhydrous magnesium sulfate, clarified with charcoal, and evaporated to dryness. The residue was extracted with hot ligroin. Yellow crystals separated from the extract on cooling. The product was recrystallized once from cyclohexane and three times from a minimum amount of ethanol and was obtained as yellow needles.

*8-Aminopyrido-(3,4)-pyrazine* (XXIX). A solution of 5.8 g. (0.025 mole) of 3,4,5-triaminopyridine trihydrochloride[3] in water was neutralized with sodium bicarbonate. The solution was warmed to 60° and 5 g. of 30% glyoxal solution (0.025 mole glyoxal) and 5.2 g. of sodium bisulfite (0.05 mole) were added. The cooled solution was made strongly alkaline with 20% aqueous sodium hydroxide and extracted with chloroform. The extract was dried over anhydrous potassium carbonate and the chloroform then removed. The residue was recrystallized from a large volume of ligroin to give orange needles.

*2,3-Dimethyl-8-aminopyrido-(3,4)-pyrazine* (XXX). An aqueous solution of 7 g. (0.03 mole) of 3,4,5-triaminopyridine trihydrochloride was neutralized with sodium bicarbonate and a slight excess of diacetyl (2.7 ml.) was added. The solution was warmed at 80° for 10 minutes. The solution was made strongly alkaline with 10% sodium hydroxide solution and on cooling brown crystals separated. The product was recrystallized from water and obtained as yellow needles.

*2-Methyl and 3-Methyl-8-aminopyrido-(3,4)-pyrazines* (XXXI). To a solution of 4.67 g. (0.02 mole) of 3,4,5-triaminopyridine trihydrochloride in 40 ml. of water at 60° was added a solution of 6 g. of 30% aqueous methyl glyoxal solution and 6.25 g. of sodium bisulfite in 30 ml. of water.

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.

PHILADELPHIA, PENNSYLVANIA

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[CONTRIBUTION FROM THE STAMFORD LABORATORIES, CENTRAL RESEARCH DIVISION, AMERICAN CYANAMID COMPANY]

# Reaction of Phosphine with Isocyanates

SHELDON A. BUCKLER

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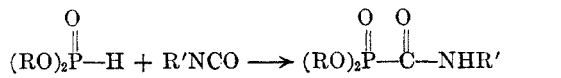
Phosphine reacts with three isocyanates to give derivatives of a new class of organophosphorus compounds, the tricarbamoylphosphines. Information about the hydrolytic and thermal stability of these materials is presented.

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.

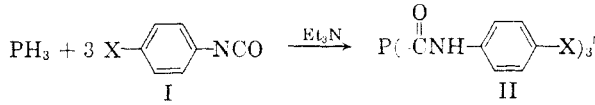
Few reports are to be found in the literature dealing with the reaction of an isocyanate with a substance having a P—H bond. Reetz *et al.* found that dialkyl phosphonates and isocyanates react in the absence of catalyst at temperatures of about 135° to give low yields of carbamoylphosphonates.[2]



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.



I II

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-O.

(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).