New Synthesis Routes to 2-Halopyridines. II. 2-Bromopyridine

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The use of bromine chloride (equilibrium mixture) in substitution reactions has been extended to heterocyclic substrates. The vapor phase bromination of pyridine (I) with bromine chloride at temperatures as low as 375° (carbon tetrachloride diluent) gave the following product distribution: 2-bromopyridine (IV) (75%) > 2-chloropyridine (VI) (21%) > 3-bromopyridine (II) (2.0%) $\cong$ 2,6-dibromopyridine (VI) (1.5%). In contrast, when bromine was employed in place of bromine chloride (450°; carbon tetrachloride diluent), product orientation was significantly altered to give nearly equal quantities of 3-bromopyridine (II) (17%) and 2-bromopyridine (IV) (22.7%).

Bromine chloride consists of an equilibrium mixture under ambient conditions (Equation A):

$$\text{(A)} \quad 2 \text{ BrCl} \rightleftharpoons \text{Br}_2 + \text{Cl}_2$$
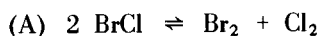
At 25°, the degree of dissociation is 43.2% (carbon tetrachloride solvent; K = 0.145) (2). Thermodynamic constants under gas phase conditions (absence of carbon tetrachloride) up to 800° have been determined (3).

Bromine chloride (i.e. equilibrium mixture) has served as a synthetic tool for addition reactions (4), as well as a powerful brominating agent (5) in substitution reactions. The latter category encompasses a wide variety of classes: aliphatics such as chlorinated- and fluorinated-methanes (6), dodecane (7), silanes (8), ethyl diazoacetate (9); cycloaliphatics such as cyclohexane (8); and, a broad spectrum of aromatics including benzene and other alkylated aromatics (8, 10), nitroaromatics (10c), phenols (11), substituted benzoic acids (10c,d,11), anisole (10c) and 2-phenylacetophenone (10d).

Only scattered observations have been reported for reactions involving bromine chloride and heterocyclic substrates such as pyridine (I). Williams obtained a solid, $C_5 H_5 N \cdot BrCl$, m.p. 107-108°, from pyridine and bromine chloride (carbon tetrachloride solvent) (12). Recently, infrared spectral studies on the bromine chloride-pyridine system in chloroform were reported by Zingaro and Witmer (13). (These investigators stated that, while bromine chloride was actually an equilibrium mixture of bromine and chlorine, the addition of an amine donor, e.g., pyridine, causes the equilibrium mixture to exist almost quantitatively in the form of the complex, B:BrCl (B = amine donor molecule)). Finally, Taylor treated pyridine hydrochloride with equimolar quantities of bromine and chlorine at 225° and obtained 3-bromopyridine (II) and 3,5-dibromopyridine (III) (14,15).

The present investigation concerns the gas phase reaction of pyridine (I) and the bromine chloride equilibrium mixture (16). Thus, when these reactants were heated at 375-450° (carbon tetrachloride diluent; unpacked reactor), 2-bromopyridine (IV) was obtained in 75% yield; the remaining products were 2-chloropyridine (VI) (21% yield), 3-bromopyridine (II) (2.0% yield) and 2,6-dibromopyridine (VI) (1.5% yield) (Equation B). The yield of 2-bromo-
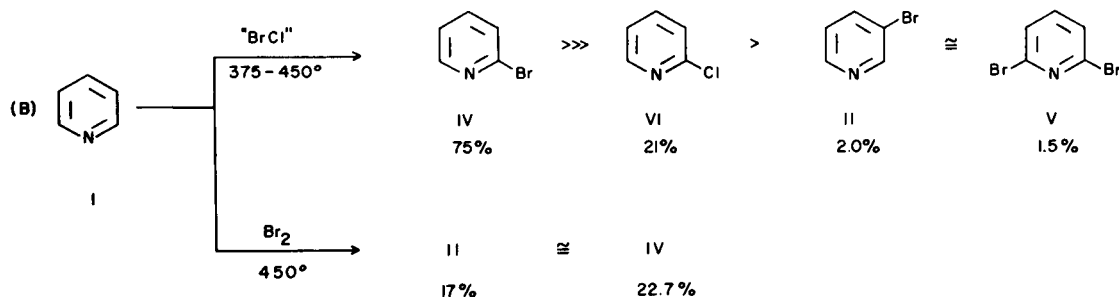
TABLE I

Isomer Distribution

Temp. (°C)	Halogen	% 2-Br-Py IV	% 3-BrPy II	% 2,6-DiBrPy V	% 3,5-DiBrPy III	Ref.
300-320°	Br_2	+	36-53	+	13-20	(17)
360-400°	Br_2	+	+	+	+	(19)
450°	Br_2	22.4	17.1	±	±	This study
500°	Br_2	46-48	±	17-36	±	(17, 18)
375-400°	BrCl	55-69	1.8-2.5	±	±	This study
450°	BrCl	66-93	1.6-2.4	1.5	±	This study

+ = Formed in unspecified quantities. ± = Not formed or possible trace.

pyridine (IV) represents an approximate two-fold increase in yield over that previously achieved from the reaction of pyridine (I) and bromine at 500°: 46-48% and 17-36% yields of 2-bromopyridine (IV) and 2,6-dibromopyridine (V), respectively (17, 18). (The latter reactions were conducted without diluent; unpacked reactors (17a) or packed with glass chips (17e), pumice (17a, 18), charcoal (17a), or ferrous bromide (18)).

The predominant substitution by the bromine-chlorine system at the α-position of pyridine is to be contrasted with the corresponding reaction with bromine at 450° (carbon tetrachloride diluent; unpacked reactor) where nearly equimolar quantities of 3-bromopyridine (II) (17.1% yield) and 2-bromopyridine (IV) (22.4% yield) were obtained. (Equation B). The mixed isomer distribution with bromine at 450° is not surprising, since the gas phase bromination of pyridine (I) has been found to be temperature-dependent (Table I): at 300°, β-substitution predominates; while, at 500°, orientation reverses to give largely α-substitution. Thus, bromination at 300° gives 3-bromopyridine (II) and 3,5-dibromopyridine (III) as the predominant products (17). At 360-400°, both α- and β-bromination occur to give a mixture of II, III, IV and V (19). At 500°, 2-bromopyridine (IV) and 2,6-dibromopyridine (V) represent the main products (17, 18).

The altered product orientation for the bromination (bromine) of pyridine with temperature has been attributed to a change from electrophilic (300°) to a radical-type bromination (500°) (20). Thus, at 300°, bromonium cation attacks the β-position of pyridine; while, at 500°, bromine atoms are involved. To account for the selective attack by the radical reagent at the α-position, Wheland (20) has provided a rationalization based on molecular orbital calculations. (Another suggestion is that the relative

thermodynamic stability of 2- and 3-bromopyridine, respectively, may partly determine such orientation at 500° (21)).

In light of the above discussion, it does not appear likely that the mechanism for the predominant formation of 2-bromopyridine (IV) from pyridine and the bromine chloride equilibrium mixture involves a polar mechanism featuring bromonium cation. Instead, a mechanism involving free radicals as suggested by Walling (22) for the bromination of toluene, cyclohexane, fluorinated methanes and silanes with bromine chloride may also be applicable for the corresponding reaction with pyridine (Equations C and D):

$$(C) \quad Cl\cdot + RH \rightarrow R\cdot + HCl$$

$$(D) \quad R\cdot + Br - Cl \rightarrow RBr + Cl\cdot$$
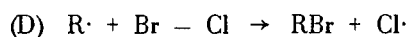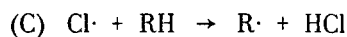
The formation of 2-chloropyridine (VI) may be expected based on the composition of the equilibrium mixture (See Equation (A); (3), (23)). Orientation during the relatively facile chlorination of pyridine is also temperature dependent: below 270°, β-substitution occurs; above 270°, α-substitution to give 2-chloropyridine (VI) predominates (19b).

EXPERIMENTAL

A. Analytical.

Known reference standards in carbon tetrachloride were prepared for VPC analysis of reaction products.

Beckman Gas Chromatograph, Model GC-2A: 2 meter; 0.25 in. o.d. aluminum column, packed with XF 1150 General Electric Nitrile Silicone (50% substituted) on Chromosorb W (80-100 mesh); column temp., 137°; helium pressure, 50 psi.; sample size, 5.0 μ;

detector current, 350 ma. The following retention times (minutes) were noted: carbon tetrachloride, 0.32; pyridine (Reilly Tar and Chemical) 1.45; 3-chloro- and/or 4-bromopyridine (Aldrich), 2.5; 3-bromopyridine (Matheson, Coleman and Bell) 7.90; 2,6-dichloropyridine (K and K Laboratories), 11.00; 2,6-dibromopyridine (K and K Laboratories), 32.00. (Retention times for ten isomeric bromopyridines with a column packed with tritolylphosphate on Chromosorb have recently been described (24)).

B. Bromination of Pyridine with Bromine Chloride.

1. At 375-400°.

Pyridine (5.80 moles) was introduced from a dropping funnel into a glass pre-heater coil (6 ft. x 3/8 in. i.d.) which was immersed in sodium nitrite-sodium nitrate salt bath heated to 375°. A solution of bromine (0.78 mole; Malinckrodt) dissolved in 1.56 moles of carbon tetrachloride (Diamond Alkali) was metered into a second coil immersed in the salt bath; concurrently, chlorine (0.95 mole, Matheson), sparged through carbon tetrachloride maintained at 64.5° (to give 2:1 molar ratio of carbon tetrachloride/chlorine), was also introduced into the halogen feed line. The gas streams emerging from the two pre-heater coils were conducted into a 12 in. unpacked glass reactor (volume, 138 ml.) maintained at 375-400° (residence time, 0.9 second.) The reactor effluent was collected in ice water, made basic (pH 9) with 20% aqueous sodium hydroxide and extracted with carbon tetrachloride. VPC analysis of the latter showed the following product distribution: pyridine, 12.7 wt. % (18% conversion); 2-bromopyridine, 3.60 wt. % (69% corrected yield); 2-chloropyridine, 0.60 wt. % (16% corrected yield); 3-bromopyridine, 0.13 wt. % (2.5% corrected yield); 3-chloro- and/or 4-bromopyridine, 0.03 wt. %; and, 2,6-dibromopyridine, trace.

2. At 450°.

To insure a more constant feed source, a weighed solution of bromine (0.46 mole), chlorine (0.46 mole) and carbon tetrachloride (1.84 moles) was introduced into the halogen feed coil, while pyridine (3.34 moles) was added to the other coil. At a reaction temperature of 450° (1.6 seconds residence time), the following product distribution was obtained: pyridine, 11.7 wt. % (22% conversion); 2-bromopyridine, 3.98 wt. % (79% corrected yield); 2-chloropyridine, 0.95 wt. % (26% corrected yield); 2,6-dibromopyridine, 0.16 wt. % (1.5% corrected yield); 3-bromopyridine, 0.08 wt. % (1.6% corrected yield). Lesser amounts of· the following were also noted: 3-chloro- and/or 4-bromopyridine, 0.04 wt. %; 2,6-dichloropyridine, 0.01 wt. %; and unknowns at 16 and 19 minutes, 0.01 and 0.05 wt. %, respectively (25).

C. Bromination of I with Bromine.

By the procedure described above, pyridine (5.6 moles), and a solution of bromine (1.6 moles) dissolved in carbon tetrachloride (3.4 moles) were separately passed through the pre-heater (450°) and then mixed in the coiled reactor at 450° (residence time, 0.8 second). The organic layer (wt. 395 g.) was processed in the manner described previously and was found by VPC to consist of: pyridine, 11 wt. % (14% conversion); 2-bromopyridine, 0.67 wt. % (22.4% corrected yield); 3-bromopyridine, 0.51 wt. % (17.1% corrected yield); and 3-chloro- and/or 4-bromopyridine, 0.04 wt. % (13% corrected yield).
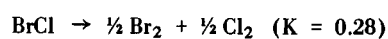
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$$BrCl \rightarrow \tfrac{1}{2} Br_2 + \tfrac{1}{2} Cl_2 \quad (K = 0.28)$$

$$Br_2 \rightarrow 2 Br \cdot \quad (K = 1.39 \times 10^{-9})$$

$$BrCl \rightarrow Br \cdot + Cl \cdot \quad (K = 5.30 \times 10^{-12})$$

$$Cl_2 \rightarrow 2 Cl \cdot \quad (K = 4.16 \times 10^{-13})$$

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