placed continuously by fresh *t*-butyl alcohol from the dropping funnel and each hour another 1-g. portion of sodium *t*-butoxide was added to the reaction mixture through the neck of the reaction flask that held the dropping funnel. After a total of 11.5 g. (0.12 mole) of the butoxide had been added over a period of ten hours all of the *t*-butyl alcohol was distilled off—the last traces were removed under diminished pressure—and the residue dissolved in 100 ml. of water. The exact amount of dilute hydrochloric acid to react with the sodium *t*-butoxide that was used then was added to the aqueous solution. From this neutralized solution 0.9 g. (10%) of 5-ethyl-5-(2-pyridyl)-barbituric acid,[5] m. p. 257–258°, crystallized on standing. This compound may be recrystallized from dilute alcohol.

Anal. Calcd. for $C_{11}H_{11}O_3N_3$: N, 18.03. Found: N 18.07.

The aqueous solution from which the barbituric acid was filtered was evaporated to dryness and the residue extracted with hot ethyl acetate. From the ethyl acetate 4.6 g. (55%) of α-(2-pyridyl)-butyrylurea (II), m. p. 122–123°, was obtained.

Anal. Calcd. for $C_{10}H_{13}O_2N_3$: N, 20.30. Found: N, 19.95.

A 0.4132-g. sample of this ureide yielded on quantitative hydrolysis[6] 0.0645 g. of ammonia (calcd. 0.0679).

Summary

The preparation of 5-ethyl-5-(2-pyridyl)-barbituric acid by the condensation of ethyl-2-pyridylmalonic ester with urea in the presence of sodium *t*-butoxide in *t*-butyl alcohol is described.

This barbituric acid appears to have no hypnotic or anesthetic action.

MADISON, WISCONSIN RECEIVED AUGUST 5, 1943

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(5) The preparation of this barbituric acid is reported (*Chem. Zentr.*, **108**, I, 2405 (1937)) in an abstract of a French patent. However, this abstract repeats a typographical error in the text of the patent. The structure of the barbituric acid that is shown in the patent indicates it to be 5-ethyl-5-(4-pyridyl)-barbituric acid, which is the compound that would be expected from the reactants (4-pyridylpyridinium bromide hydrobromide and 5-ethylbarbituric acid) that were used. No properties of this barbituric acid are listed in the patent.

(6) McElvain, THIS JOURNAL, **57**, 1303 (1935).

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Halogenation of Pyridine

BY S. M. MCELVAIN AND M. A. GOESE

In connection with some investigations in progress in this Laboratory it became necessary to prepare the 2- and 3-bromopyridines in fairly large (300–500 g.) quantities. Work along this line started as an evaluation of the various methods that have been described in the literature and then progressed into the development of improved and, in certain respects, novel procedures for the preparation and isolation of the desired compounds. This paper reports the details of these procedures together with the results of the application of one of them to other halogens and to the three picolines.

2-Bromopyridine.—While this compound may be prepared from such 2-substituted pyridines as 2-aminopyridine[1a] or 1-methyl-2-pyridone,[1b] it seemed that the direct bromination procedure of Wibaut and Den Hertog[2] would be more suitable for its preparation in quantity. This latter procedure involves a vapor phase reaction of bromine and pyridine at 500° and is carried out by passing the vapors of the reactants through a tube that is maintained at this temperature. The yield of the 2-bromopyridine is about 48%. This procedure was found in the present work to be quite satisfactory although somewhat slow, but it was possible to improve it in this latter respect by preheating the vapors of the reactants and packing the reaction tube with short lengths of glass tubing. An apparatus and procedure in which the rate of passage of the reactants through the reaction tube may be increased five-fold over that used by Wibaut and Den Hertog, and with which it is possible to prepare 400–500 g. of 2-bromopyridine in about five hours are described in the Experimental Part. In addition to the 2-bromopyridine, 2,6-dibromopyridine is obtained in 17% yields by this procedure.

3-Bromopyridine.—The preparation of this compound, together with some of the 3,5-dibromopyridine, by heating for six to eight hours at 230–250° the crystalline pyridine hydrobromide perbromides—obtained by crystallization from glacial acetic acid—has been described in an earlier paper[3] from this Laboratory. Yields of 36–38% of 3-bromopyridine and 30–36% of 3,5-dibromopyridine were obtained. Since this work was reported the vapor phase bromination of pyridine to 3-bromopyridine in 39% yields has been described.[2] This bromination was carried out in a pumice packed tube at 300°. Somewhat later, Maier-Bode[4] obtained 34–42% yields of 3-bromopyridine when bromine vapor was passed through fused pyridine hydrochloride at 215° in the presence of mercuric chloride.

Since the vapor phase bromination of pyridine had proved satisfactory for the preparation of 2-bromopyridine it was used at first for the preparation of 3-bromopyridine. The yields of this product were approximately those reported by Wibaut but the rate at which the reaction could be run was so low that it seemed impracticable for the preparation of the product in any considerable quantity. For example, with the apparatus shown in Fig. 1 that had proved quite efficient in

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(1) (a) Craig, THIS JOURNAL, **56**, 231 (1934); (b) Fischer, *Ber.*, **32**, 1297 (1899).

(2) Wibaut and Den Hertog, *Rec. trav. chim.*, **51**, 381 (1932).

(3) Englert and McElvain, THIS JOURNAL, **51**, 863 (1929).

(4) Maier-Bode, *Ber.*, **69**, 1534 (1936).

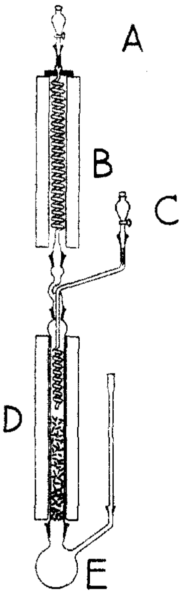
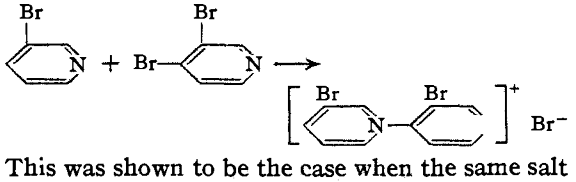


Fig. 1.—Apparatus for the preparation of 2-bromopyridine.

the production of 2-bromopyridine it was not possible to prepare more than 25 g. of 3-bromopyridine per hour. This bromination procedure suffers from the additional disadvantage that the reaction tube becomes plugged periodically with a black solid, the nature of which is discussed below, and which is the major reaction product when bromine and pyridine vapors interact at 300–350°, particularly if an excess of pyridine is present.

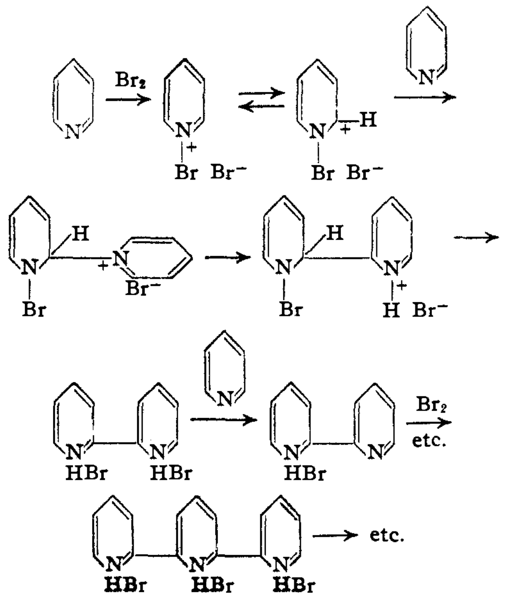
The direct bromination of pyridine also was attempted in the liquid state at temperatures lower than those used in the above mentioned vapor phase bromination. Bromine and pyridine react exothermically in equimolecular amounts at ordinary temperatures to form a stable, orange-red, crystalline perbromide. When this perbromide was heated to 250–260°, it underwent autobromination to yield some brominated products but about half of the pyridine was converted to the same type of black material that plugged the reaction tube and was the major reaction product in the vapor phase reaction of bromine and pyridine. Fractionation of the brominated pyridines from this reaction yielded about 27% of the theoretical quantity of a fraction that boiled within the range (61–63° at 15 mm.) of 3-bromopyridine, a small amount of an intermediate fraction from which a solid product, m. p. 70–71° and thought to be 3,4-dibromopyridine, was isolated and about a 2% yield of 2-bromopyridine (b. p. 92–93° at 25 mm.). The 3-bromopyridine fraction, however, was far from being a pure product; on standing for a few days this colorless liquid became filled with an orange-yellow solid which when filtered off showed the properties of a quaternary salt. It was water-soluble, melted at 165–167° and contained approximately 20% ionic bromine. These data led to the conclusion that the 3-bromopyridine fraction contained a considerable amount of the dibromopyridine fraction and that the quaternary salt resulted from the interaction of these two compounds, thus



This was shown to be the case when the same salt was produced by allowing a mixture of 3-bromopyridine and the solid product of m. p. 70–71° to interact.

The filtrate from which this salt was removed, on standing for several months, again became filled with a solid. This product also was very soluble in water, but in other respects its properties were distinctly different from those of the salt described above. The salt that formed on longer standing was greenish-yellow in color, melted in the neighborhood of 300° and contained about 32% of ionic bromine. These properties indicate that it is the result of a rather considerable polycondensation between the brominated pyridine molecules. A small amount of a product with properties similar to this salt also formed after a few months, in samples of 3-bromopyridine prepared by the vapor phase reaction.

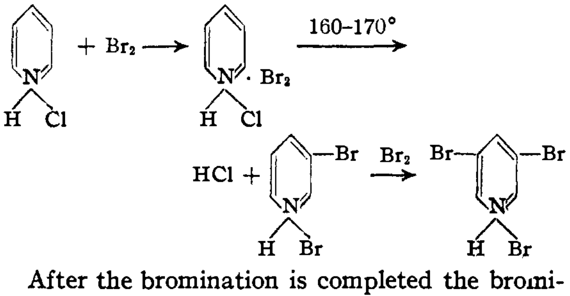
When the orange-colored pyridine perbromide was heated with more pyridine a violent, exothermic reaction occurred at about 70° and the reaction mixture turned into a black tar similar to that obtained as the major reaction product in the other bromination reactions. With the excess of pyridine this black material is the sole reaction product. As it is formed in the reaction mixture it is a hydrobromide salt and is quite soluble in water. The free base that is obtained by the decomposition of this salt with alkali contains no halogen, has no melting point and, depending upon the extent to which the original mixture of bromine and pyridine was heated, is quite insoluble in non-acidic solvents. If the reaction of bromine with an excess of pyridine is carried out in a bomb at 200–250° the black free base that is obtained is practically insoluble; if, however, the mixture of bromine and pyridine is heated under a reflux for half an hour at the boiling point of pyridine after the initial reaction subsides about half of the water-insoluble free base that is obtained dissolves in alcohol. This material gives a deep red alcoholic solution. These facts, together with the



elementary analysis (72.2% C, 5.2% H, 17.0% N), indicate that this black product has a polypyridylene type of structure, the formation of which from bromine and an excess of pyridine may be represented as follows (for the sake of simplicity all of the linkages are shown at the 2-position of the pyridine nucleus; of course, some of the linkages may be at the 4-position).

It may be seen from the above reactions that the formation of the black polymer involves an oxidative condensation of a number of pyridine molecules by bromine. If it is assumed that all of the bromine is used to bring about this type of condensation, the weight of the polymer that is obtained from a given amount of bromine is a measure of the extent of polymerization since one bromine molecule is required to add each pyridine nucleus to the chain. The amount of the water-insoluble free base that was formed during the low temperature polymerization mentioned above indicated that the average polymer molecule contained four pyridine nuclei.

The difficulties encountered in the direct bromination of pyridine led to a study of the bromination of pyridine salts. It was soon found that the hydrochloride is the most suitable salt for this purpose. Liquid bromine and solid pyridine hydrochloride react at room temperature to form a perbromide which partially liquefies from the heat of reaction and which may be heated at atmospheric pressure without loss of bromine and converted into a mixture of the 3-bromo- and 3,5-dibromopyridine. This auto-bromination reaction occurs at 160–170°. In order to obtain maximum yields of the monobromo compound it is advisable to use two molecular equivalents of the hydrochloride for each mole of bromine. As the bromination proceeds hydrogen chloride rather than hydrogen bromide is evolved from the reaction mixture. The process may be illustrated in the following manner



After the bromination is completed the brominated products are separated from the unchanged pyridine salt by distillation under diminished pressure. At 190–220° and 25 mm. pressure the bromopyridines distil rapidly from the reaction mixture. The 3,5-dibromopyridine, as the free base, comes over first; it is followed by the hydrochloride of 3-bromopyridine. These products as they collect in the receiver, are solids and are practically free of any unchanged pyridine or its salt. The brominated pyridines are obtained from the solid distillate by treatment with alkali. The yields of the 3-bromopyridine, b. p. 61–63° (15 mm.), vary from 35–40% while the yield of the 3,5-dibromopyridine, m. p. 110–111°, amounts to about 27% of the theoretical. 3-Bromopyridine prepared in this manner has remained free from solid material after standing for over a year.

The residue in the reaction flask contains none of the black polymer that forms so readily during the bromination of pyridine. Practically all of the pyridine that is not brominated may be recovered when this reaction residue is made alkaline.

The Use of Other Salts.—The hydrobromide may be used instead of the hydrochloride in the above procedure. However, it is necessary to heat the perbromide of the hydrobromide to 230–250° before the bromination occurs. This temperature corresponds to that used when the crystalline pyridine hydrobromide perbromide was heated.[3] The yields of 3-bromo- and 3,5-dibromopyridine are about the same as those obtained with the hydrochloride. Pyridine sulfate cannot be substituted for the halogen acid salts in this preparation because it does not form a stable perbromide. When a mixture of two moles of pyridine sulfate and one mole of bromine is heated the bromine distils out when its boiling point is reached.

The Use of Other Halogens.—Earlier attempts to chlorinate pyridine and pyridine hydrochloride[5] resulted in polychlorinated products. More recently Wibaut and Nicolai[6] reported the gas phase chlorination of pyridine. At 270° they obtained a good yield (31–46%) of 2-chloropyridine together with a small amount of the 2,6-dichloropyridine. Lower temperature chlorination (at 200°) in an effort to bring about chlorination in the 3-position, took place very slowly and yielded none of the monochloro derivative but instead a mixture of 3,5-dichloro-, 3,4,5-trichloro- and pentachloropyridines. These authors studied the chlorination of fused pyridine hydrochloride and found that at 170° the main products were 3,5-dichloro- and 3,4,5-trichloropyridines with only a small amount of the 3-chloropyridine. They also noted that mercuric chloride had no effect on the yields and course of these chlorinations (*cf.* ref. 4).

In the present work an attempt was made to apply the procedure that was used for the preparation of the 3-bromopyridine to the preparation of the corresponding 3-chloro derivative. Two equivalents of pyridine hydrochloride slowly absorbs approximately one equivalent of chlorine at room temperature to form a semi-solid perchloride which completely melts at about 90° but which loses chlorine when heated above 100°. However, if the heating is rapidly continued to 160–180°, some chlorination occurs and it is possible

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(5) Sell and Dootson, *J. Chem. Soc.*, **73**, 442 (1898); **75**, 979 (1899).

(6) Wibaut and Nicolai, *Rec. trav. chim.*, **58**, 709 (1939).

to isolate 3-chloropyridine and 3,5-dichloropyridine, each in about 4% yields. These products may be separated from the unchanged pyridine hydrochloride by distillation under diminished pressure in the same manner as described for the 3-bromo-derivative.

The direct iodination of pyridine has been reported by Rodewald and Plazek.[7] They found that treatment of fused pyridine hydrochloride at 280° with iodine gave a small yield of pentaiodopyridine. The same product along with a smaller amount of 3,5-diiodopyridine was formed in the vapor phase reaction of iodine and pyridine at 300–500°. In the presence of an oxidizing agent, such as fuming sulfuric acid, these authors reported an 18% yield of 3-iodopyridine from the direct iodination of pyridine.

In the present work it was found that iodine and pyridine hydrochloride react to form a very stable periodide which melts at about 150° and retains its iodine at temperatures up to 280°. Between 280 and 290° hydrogen iodide is evolved rapidly from the periodide. When the reaction mixture is subjected to diminished pressure, pentaiodopyridine, m. p. 106°, distils over. The yield of this product amounts to 37% of the theoretical.

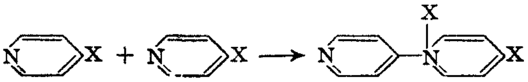
Pyrolysis of Perbromides of Picoline Hydrochlorides.—When the procedure described above for the bromination of pyridine was applied to the picolines, interesting and unexpected results were obtained. Bromine forms a stable perbromide with the hydrochlorides of each of the picolines but when these perbromides were heated they lost hydrogen chloride at 120–130° and passed into the corresponding picoline perbromides

$$CH_3C_5H_4NHCl \cdot Br_2 \longrightarrow HCl + CH_3C_5H_4N \cdot Br_2$$

These picoline perbromides, in contrast to pyridine perbromide which is stable up to 250–260°, underwent a vigorous polymerization reaction when heated above 135° and passed into black polymers similar in properties to the ones obtained from the reaction of bromine with pyridine. However, there was no evidence of any nuclear bromination products that could be separated from the reaction mixture by steam distillation from alkaline solution.[8]

Only in the case of α-picoline was there any evidence of nuclear bromination of the salt. During the time (fifteen hours) that was required for all of the halogen acid to be expelled from the perbromide of the hydrochloride at 120–130°, a small amount of the salt was brominated and a bromopicoline, probably the 2-methyl-5-bromopyridine, was isolated in 3% yields from the reaction mixture.

The results of the work that are now reported indicate that 2-bromopyridine may be satisfactorily prepared by the interaction of bromine with pyridine in the gas phase at 500°. Wibaut and Nicolai[6] have reported that 2-chloropyridine may be prepared similarly at 270°. Bromine appears to be the only halogen that can be used to prepare a 3-halogenopyridine in satisfactory yields and this preparation involves the bromination of a pyridine salt. For completeness it should be mentioned that the 4-halogenopyridines cannot be prepared by direct halogenation. The 4-chloro- and 4-bromopyridines have been made by the action of the corresponding phosphorus pentahalide on 4-hydroxypyridine[9] which is obtained by the hydrolysis of 4-pyridylpyridinium dichloride.[10] These 4-halogenopyridines, however, are not particularly valuable as synthetic agents because of the high reactivity of the halogen toward the amino nitrogen.[9] The 4-bromo compound rapidly passes into a solid quaternary compound at 0° while the 4-chloro compound undergoes a similar change more slowly at room temperature. These salts are of indefinite composition, but undoubtedly are the result of a polycondensation the first step of which is the formation of N-(4-pyridyl)-4-halogeno-pyridinium halide.



It is this behavior of the 4-halogenopyridines that led to the conclusion in the present work that the solid material that separates from certain of the samples of 3-bromopyridine, prepared by the direct bromination of pyridine, is due to the presence of some 3,4-dibromopyridine in the product. In contrast to this behavior, 2-bromopyridine, although it contains a quite reactive halogen, does not react with itself or with 3-bromopyridine to form a quaternary salt.

Experimental Part

Preparation of 2-Bromopyridine.—The furnaces used for this preparation are shown in Fig. 1. The spiral in furnace B for preheating the pyridine vapor was 60 cm. in length and was constructed from 6 meters of 10-mm. glass tubing. The spiral in furnace D for preheating the bromine vapor was 12 cm. in length and was constructed from 1.5 meters of 5-mm. glass tubing. The reaction portion of the tube in furnace D was 3.5 cm. in diameter and 40 cm. long and was filled to within 2 cm. of the lower end of the spiral with 0.5-cm. lengths of 6-mm. Pyrex glass tubing. The receiver E was a 1-liter flask fitted with an air condenser through which the vapors of hydrogen bromide were led to a hood. Rheostats controlling the heating of the furnaces were adjusted to maintain a temperature of 500°, as measured by a thermocouple in the disconnected furnaces, around spiral in furnace B and *within* the reaction tube of furnace D. After this adjustment the thermocouple was removed, the furnaces connected and the reaction started.

From the dropping funnel A a total of 480 g. (6 moles) of pyridine and from funnel C a total of 1440 g. (9 moles) of bromine were simultaneously dropped into the furnaces

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(7) Rodewald and Plazek, *Ber.*, **70**, 1159 (1937).

(8) Also there was no evidence of a lachrymator that would indicate bromination of the methyl group of the picolines. In this connection it should be noted that β-picolyl bromide may be prepared by the bromination of β-picoline in concentrated hydrochloric acid solution at 150° (Dehnel, *Ber.*, **33**, 3498 (1900); Kuhn and Richter, This Journal, **57**, 1927 (1935)).

(9) Wibaut, *et al.*, *Rec. trav. chim.*, **54**, 807 (1935); **58**, 885 (1939).

(10) Koenigs and Greiner, *Ber.*, **64**, 1049 (1931).

over a period of five hours. The rates of passage of the reactants through the furnace should be such that no vapors of bromine appear in the receiver. The excess of bromine was found by Wibaut and Den Hertog[3] and also in the present work to be necessary for maximum yields of the monobromo compound. The dark brown, viscous reaction product that collected in receiver E then was made basic with an aqueous sodium hydroxide solution and steam distilled until a total of 3 liters of distillate was collected. The water-insoluble oil was separated and the aqueous portion of the distillate extracted with 200 ml. of benzene and this extract combined with the separated oil. Fractional distillation of this mixture yielded 440 g. (46%) of 2-bromopyridine, b. p. 90–92° (25 mm.). The solid residue that remained in the distilling flask was steam distilled again and from this distillate 235 g. (17%) of 2,6-dibromopyridine, m. p. 118–119°, was separated by filtration.

Neither 2-bromopyridine nor 2,6-dibromopyridine gave any evidence of quaternary salt formation when treated with methyl iodide or methyl *p*-toluenesulfonate in the manner described below for the preparation of derivatives of 3-bromopyridine and 3,5-dibromopyridine.

Preparation of 3-Bromopyridine from Pyridine Hydrochloride.—The apparatus used in this preparation is shown in Fig. 2. In the 3-liter reaction flask, A, was placed 1155 g. (10 moles) of pyridine hydrochloride. Through a dropping funnel that temporarily replaced the tube leading to the manometer in the side arm of the reaction flask 800 g. (5 moles) of bromine was run onto the pyridine hydrochloride; enough heat was generated during this addition to cause the red perbromide that was formed to partially liquefy and if the mixture was stirred—the mechanical stirrer was turned by hand at first—the bromine could be added over a period of five minutes without loss. The separatory funnel then was replaced by the manometer connection and, with the stirrer running, the mixture was heated in an oil or metal bath. At about 100° the mixture was completely liquid and at 160° the evolution of hydrogen chloride started. This gas passed through flasks B and C (each of 1-liter capacity) and was absorbed in flask D which had a capacity of 5 liters. After about an hour at 160–170° the evolution of hydrogen chloride diminished noticeably. Then the temperature of the heating bath was raised to 195–200°. After another hour at this temperature the evolution of hydrogen halide practically ceased. Titration of an aliquot of the aqueous acid in flask D showed that 4.4 moles of halogen acid had been absorbed. This acid was shown to be hydrochloric acid by the boiling point (108–109°) and the acid content (about 20%) of the constant boiling mixture obtained by fractionation of the aqueous solution of the absorbed acid.

The exit tube of flask D, which up to this time had remained open, then was connected to a water pump and, with stirring continued, the pressure inside the system reduced. At the same time cooling water was run over the receiver, B. The 3,5-dibromopyridine which rapidly distilled from the reaction mixture solidified in flask B and, to some extent, in flask C and the connecting air condensers. As the dibromo compound was removed from the reaction mixture and the pressure in the system dropped to about 25 mm., the temperature of the heating bath was raised to about 220°. After about an hour at this temperature and pressure all of the 3-bromopyridine in the form of its hydrochloride distilled out of the reaction mixture and solidified in flask B and the air condenser leading to it. Occasional application of a free flame to this air condenser was necessary to force the solid condensate into receiver B. After this hydrochloride was removed the reaction mixture in flask A changed to a thick slush and stirring became difficult.

The distilled reaction products in receivers B and C were treated with a solution of 200 g. of sodium hydroxide in 1 liter of water and extracted with benzene. Fractionation of this extract yielded 300 g. (37%) of 3-bromipyridine, b. p. 61–63° (15 mm.) and a residue of 144 g. (26%) of 3,5-dibromopyridine which melted at 110–111° after redistilling with steam. These percentage yields are based upon the bromine put into the reaction; if the unused pyridine in the reaction residue were recovered by making this residue alkaline, extracting with benzene and fractionating, the yield of 3-bromopyridine was 44% of the theoretical based upon the pyridine not recovered.

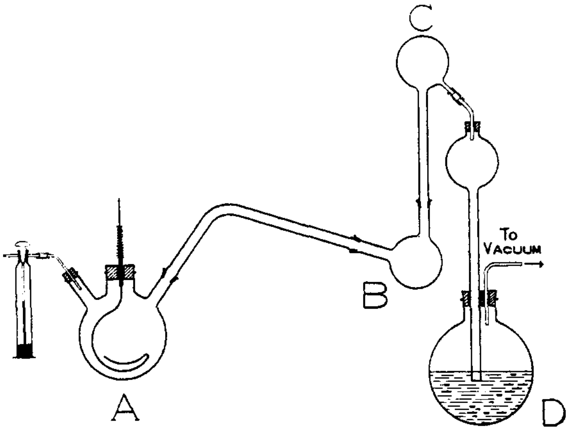

Fig. 2.—Apparatus for the preparation of .3-bromopyridine.

When a ratio of pyridine hydrochloride to bromine of 1.5 to 1 was used, the mono and dibromo derivatives were obtained in 26 and 38% yields, respectively; with a ratio of 3 to 1 the yields were practically the same as those obtained above with the 2 to 1 ratio of the reactants.

The hydrobromide instead of the hydrochloride may be used in the above preparation, but in this case the fused perbromide must be heated to 230–250° before the bromonation and the accompanying evolution of halogen acid starts. The brominated products may be distilled out of the reaction mixture as described above and the yields are practically the same. The sulfate salt, however, cannot be used. When bromine is mixed with pyridine sulfate there is no evidence of any reaction and when the mixture is heated the bromine distils out.

3-Bromopyridine Hydrochloride.—This salt is stable in aqueous solution and may be obtained by the evaporation of a solution of 3-bromopyridine in dilute hydrochloric acid. The salt melts at 158–159° and, if placed in a distillation apparatus and heated in an oil-bath at 175–190°, it distils rapidly when the pressure in the system is reduced to 20–25 mm. The solid distillate also melts at 158–159° and its melting point is not changed by recrystallization from alcohol.

Anal. Calcd. for C_5H_5NClBr: Cl, 18.25. Found: Cl, 18.12.

In contrast to this behavior, pyridine hydrochloride under the same pressure does not distil until the temperature of the heating bath reaches 250°. 3,5-Dibromopyridine forms a hydrochloride in anhydrous ether but this salt is immediately hydrolyzed by water and dissociated into its components by heating to 180–200°.

Methiodides and Methyl *p*-Toluenesulfonates of 3-Bromopyridine and 3,5-Dibromopyridine.—A 1-g. sample of each of these brominated pyridines in ether solution was treated with 3 g. of methyl iodide and allowed to stand for forty-eight hours. The precipitated salts were recrystallized from alcohol. The methiodide of 3-bromopyridine melts at 164–165°; the methiodide of 3,5-dibromopyridine melts at 273–274°.

Anal. Calcd. for C_6H_7NBrI: I, 42.3. Found: I, 42.2. Calcd. for $C_6H_6NBr_2I$: I, 33.4. Found: I, 33.3.

The methyl *p*-toluenesulfonates of these bromopyridines were prepared by heating 5-g. samples of each of the amines dissolved in 25 cc. of benzene with equivalent quantities of methyl *p*-toluenesulfonate on the steam-bath for three hours. After recrystallization from alcohol the 3-bromopyridine methyl *p*-toluenesulfonate melted at

156–157° and the corresponding derivative of 3,5-dibromopyridine melted at 219–221°.

Anal. Calcd. for $C_{13}H_{14}O_3NBrS$: C, 45.34; H, 4.07. Found: C, 45.52; H, 4.28. Calcd. for $C_{13}H_{13}O_3NBr_2S$: C, 36.86; H, 3.1. Found: C, 36.69; H, 3.25.

Vapor Phase Bromination of Pyridine at 300–350°.—The preheating spiral and the reaction chamber of the furnace shown in Fig. 1 were heated to 350° and 108 g. (1.36 moles) of pyridine and 280 g. (1.75 moles) of bromine allowed to pass through the reaction tube during a period of three hours. A more rapid rate of passage of the reactants showed unreacted bromine vapor in the receiver; any increase in the amount of pyridine relative to the bromine caused excessive formation of the black polymeric material that soon plugged the reaction tube. A viscous red-brown liquid condensed in the receiver. This reaction product was made distinctly basic with sodium hydroxide and steam distilled until about 700 ml. of distillate was collected. After separation of the heavy oil and white solid in the distillate, the aqueous portion was saturated with sodium chloride and extracted with ether. This extract was combined with the separated oil and solid and, after drying over solid sodium hydroxide, fractionated. After about 5 g. of pyridine distilled over, 78 g. (36%) of 3-bromopyridine, b. p. 61–63° (15 mm.), was collected. The yield of 3,5-dibromopyridine, obtained from the residue of this distillation and melting at 110–111°, amounted to 66 g. (20%).

The alkaline solution from which the brominated products were steam distilled was quite clear and colorless after the insoluble, black polymer was filtered off. This product is the form in which practically all of the unbrominated pyridine is recovered from this reaction. The polymer does not melt but sinters slowly when heated on a spatula in a flame. It is insoluble in all of the common inert solvents, but is readily soluble in dilute aqueous acids.

The Preparation and Pyrolysis of Pyridine Perbromide.—To 300 g. (3.8 moles) of pyridine in a 3-liter round-bottom flask was added 606 g. (3.8 moles) of bromine over a period of about fifteen minutes. This addition must be accompanied by vigorous swirling of the contents of the flask and cooling under a tap to 20–25° to prevent the heat of the reaction from starting the polymerization of the pyridine—this starts at about 70° and is violently exothermic—to the black polymer previously mentioned. The orange crystalline perbromide began to appear as the last portions of bromine were added. The flask then was fitted with an air reflux condenser and heated in a metal bath. At about 100° the perbromide liquefied and at 240–250° a vigorous evolution of hydrogen bromide began. After two and one-half hours at this temperature no more halogen acid was evolved. The reaction mixture then was cooled, treated with 900 ml. of 20% aqueous sodium hydroxide solution and the resulting alkaline mixture steam distilled until 2.5 liters of distillate was collected. The alkaline residue from which this distillate was distilled contained a large amount of the same type of black polymer that remained after the steam distillation of the reaction product from the vapor phase bromination.

The distillate consisted of a heavy oil that contained some white crystalline material and the aqueous portion. Most of the aqueous layer was decanted off, saturated with sodium chloride, and extracted with ether. The heavy oil was separated from the water that remained with it by ether extraction. These ether extracts were combined, dried and distilled. The following fractions were obtained: (a) 70 g. of pyridine, b. p. 114–115°; (b) 165 g. of a bromopyridine fraction, b. p. 61–63° (15 mm.); (c) 5 g. of an intermediate fraction, b. p., 65–75° (15 mm.), m. p. 70–71° after recrystallization from alcohol; (d) 10 g. of 2-bromopyridine, b. p. 75–78° (15 mm.); (e) a residue of 55 g. of 3,5-dibromopyridine, m. p. 110–111°.

Fraction (b), which at first was thought to be 3-bromopyridine, on standing for a few days became filled with an orange solid which, when filtered off and recrystallized from alcohol, melted at 165–167°, was water-soluble, and contained 21.2% of bromine that could be precipitated as silver bromide. This amount of ionic bromine indicated a quaternary salt formed from the addition of a dibromopyridine, such as one that contained a reactive 4-bromo substituent, to 3-bromopyridine. In fact the solid material obtained from fraction (c) yielded this same quaternary salt when it was mixed with a sample of pure 3-bromopyridine. Samples of fraction (b) from which this orange salt had or had not been separated appeared to solidify completely on long standing (six to ten months). There was, however, considerable liquid mixed with the solid as was shown by the amount that dissolved in a non-polar solvent, such as ether or benzene. The salt which remained undissolved in such a solvent was greenish-yellow in color, melted at about 300°, was water-soluble and contained about 32% titratable bromide ion.

The Reaction of Pyridine Perbromide with an Excess of Pyridine.—To 22 g. (0.28 mole) of pyridine 11 g. (0.07 mole) of bromine was carefully added with cooling and the resulting red solution heated under a reflux. At about 70° the solution became black and the heat of reaction caused the excess pyridine to reflux. As this initial reaction subsided the pyridine solution was refluxed over a burner for thirty minutes. The resulting reaction mixture then was treated with an aqueous solution of sodium hydroxide, steam distilled to remove the excess pyridine and the remaining black insoluble material filtered from the red colored alkaline solution after cooling. This black solid after drying weighed 7.4 g. Approximately half of it dissolved to give a deep red solution when shaken with 50 ml. of alcohol. Both the alcohol-soluble and alcohol-insoluble materials are soluble in dilute aqueous acids but have no melting points. If the structure of this black product is of the polypyridylene type shown in the introductory part and it is quantitatively formed, the yield of 7.4 g. from 11 g. of bromine indicates an average of 4 pyridine nuclei per molecule of polymer.

An excess of α-picoline showed a similar behavior with its perbromide. The initial reaction set in at about 90° and proceeded with even more vigor than the reaction in which pyridine was used.

Pyrolysis of Pyridine Hydrochloride Perchloride.—In an apparatus similar (except that a 1-liter reaction flask was employed) to that used for the preparation of 3-bromopyridine from pyridine hydrochloride was placed 250 g. (2.1 moles) of this salt. Chlorine was passed into the salt by means of an inlet tube that extended through the salt to the bottom of the reaction flask. Approximately 50 g. of chlorine was taken up rapidly and the resulting product, which was partially liquefied at room temperature, was completely molten when heated to 100°. Further absorption of chlorine was very slow but an additional 15 g.—to make a total of 65 g. (0.92 mole)—was absorbed if the chlorine was passed through the molten salt held at 90–100° for an hour. However, as the temperature of the heating bath was raised this absorbed chlorine began to be expelled, but at 160–180° there was a noticeable evolution of hydrogen chloride and a slow evolution of this gas continued for about thirty minutes at this temperature. Then the products of the reaction were isolated in the same manner as described in the preparation of the corresponding bromo compounds. Only 4.1 g. (4%) of 3-chloropyridine, b. p. 146–148°, and 3 g. (4%) of 3,5-dichloropyridine, m. p. 67–68° after recrystallization from alcohol, were obtained.

Pyrolysis of Pyridine Hydrochloride Periodide. Pentaiodopyridine.—In the same apparatus used above for the chlorination of pyridine hydrochloride a mixture of 173 g. (1.5 moles) of this salt and 190 g. (0.75 mole) of iodine was heated in a metal bath with stirring. The mixture liquefied at about 150° and at 280° began to give off hydrogen iodide. After one and one-half hours at 280–290° the evolution of this gas stopped. The reaction mixture then was subjected to diminished pressure whereupon 40 g. (37%) of pentaiodopyridine, m. p. 105–106° after recrystallization from alcohol, distilled out and was collected.

Pyrolysis of α-Picoline Hydrochloride Perbromide.—In a 1-liter 3-neck flask, equipped with an air condenser and stirrer, 160 g. (1 mole) of bromine was mixed with 130 g. (1 mole) of α-picoline hydrochloride. The resulting red liquid was heated at 120–130° for fifteen hours during which time the hydrogen halide that was evolved was collected in water. Titration of an aliquot of this acid solution indicated that 1 mole of hydrogen chloride had been driven from the perbromide. If the remaining reaction mixture was treated with cold, dilute aqueous sodium hydroxide the orange-colored, solid picoline perbromide separated and could be filtered off. If this product or the original reaction product was warmed carefully to 50–60° with a 20% aqueous solution of sodium hydroxide until the red color disappeared, an insoluble oil separated. This oil was taken up in benzene. Fractionation of this benzene solution yielded 70 g. (75%) of unchanged α-picoline and 5 g. of a nuclear monobrominated product, b. p. 73–74° (17 mm.); n^{25}_{D} 1.5580; d^{25}_{4} 1.5584.

Anal. Calcd. for C_6H_6NBr; N, 8.14. Found: N, 7.98.

This monohalogen compound had an odor and chemical behavior similar to 3-bromopyridine with no indication of lachrymatory properties that would be expected if the bromine had entered the methyl group. An attempt was made to determine the position of the halogen in this compound by converting it to the corresponding nitrile by means of cuprous cyanide. While this method is very satisfactory for the preparation of nicotinonitrile from 3-bromopyridine,[11] no nitrile could be obtained from the bromo-α-picoline. The reaction product was a tar from which nothing could be distilled.

Heating the α-picoline hydrochloride perbromide for a longer time (forty-eight hours) did not increase the yield of the brominated product, a fact that shows the bromination reaction involves the hydrochloride and is competitive with the pyrolysis to the α-picoline perbromide and hydrogen chloride. When the α-picoline hydrochloride perbromide was heated to higher temperatures (140–200°), the only reaction product was black polymeric material similar to that obtained below when the picoline perbromide was heated. At these temperatures, apparently, the picoline perbromide undergoes oxidative polymerization as rapidly as it forms from the pyrolysis of the perbromide of the hydrochloride.

Similar experiments in which β-picoline and γ-picoline were used instead of α-picoline gave practically the same results, except that it was not possible to isolate any nuclear bromination product from either of these picolines.

Pyrolysis of α-Picoline Perbromide.—An orange, crystalline perbromide of α-picoline was obtained by carefully mixing equivalent amounts of bromine (34.4 g.) and α-picoline (20 g.). This perbromide was carefully heated in an oil-bath; it melted completely at a bath temperature of 95°. At 135° a violent exothermic reaction took place, the bromine color disappeared, and a viscous black solid remained in the reaction flask. From the reaction product was isolated 3 g. of unchanged α-picoline through a steam distillation from a basic solution, saturating the distillate with sodium hydroxide and extracting with 25 cc. of ether. The weight of non-volatile, black polymer that was insoluble in both water and alcohol amounted to 11.6 g.

Reaction of α-Picoline Perbromide with an Excess of α-Picoline.—Twenty grams of α-picoline (0.22 mole) and 10 g. of bromine (0.06 mole) were carefully heated in a round-bottom flask equipped with a reflux condenser and thermometer extending below the surface of the liquid. On raising the temperature to 90° an extremely violent exothermic reaction took place resulting in considerable loss of material through the reflux condenser. The temperature of the reaction mixture rose to 250°. The reaction product, after removal of the excess α-picoline by steam distillation, consisted of the same black polymeric material that was obtained in the previous experiment.

Summary

The rate of the vapor phase bromination of pyridine at 500° to form 2-bromopyridine is found to be substantially increased by preheating the vapors of the reactants.

Various methods for the preparation of 3-bromopyridine have been studied and evaluated and a procedure by which this compound may be prepared in relatively large quantities and in 35–40% yields by the pyrolysis of pyridine hydrochloride perbromide has been developed.

The properties of some of the other products that are formed along with or instead of 3-bromopyridine in the various bromination procedures are described and the probable structures discussed.

Extension of the preferred bromination procedure to chlorine and iodine indicates that 3-bromopyridine is the only one of the 3-halogenopyridines that may be prepared satisfactorily by direct halogenation of pyridine.

The behavior of the three picolines and their hydrochlorides in this bromination procedure is described and compared to that of pyridine.

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[11] McElvain and Goese, THIS JOURNAL, **63**, 2283 (1941).

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Sulfonation of Pyridine and the Picolines

BY S. M. MCELVAIN AND M. A. GOESE

O. Fischer[1] and his collaborators first obtained pyridine-3-sulfonic acid in varying yields by heating pyridine with concentrated sulfuric acid in sealed tubes at 300–350° for twenty-four hours or at the boiling point of the reaction mixture for from thirty hours to twenty days. Later workers used fuming sulfuric acid in combination with aluminum,[2] vanadyl[3] and mercuric[4] sulfates as catalysts for the sulfonation. With these catalysts higher yields of pyridine-3-sulfonic acid were obtained in considerably shorter periods of reaction. Mercuric sulfate was particularly valuable as a catalyst because it caused the sulfonation to occur at lower reaction temperatures; using it with fuming sulfuric acid, Wulff reported 37% yields of sulfonic acids from pyridine and the α- and γ-picolines after three and one-half hours at

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[1] Fischer *et al.*, *Ber.*, **15**, 62 (1882); **16**, 1183 (1883); **17**, 763 (1884).

[2] Weidel and Murmann, *Monatsh.*, **16**, 751 (1895).

[3] (a) Meyer and Ritter, *ibid.*, **35**, 765 (1914); (b) Craig, THIS JOURNAL, **55**, 2855 (1933).

[4] (a) French Patent 685,062, *Chem. Zentr.*, **101**, II, 2576 (1930); (b) Wulff, German Patent 541,036, *Chem. Abs.*, **26**, 1945 (1932); (c) Wulff, U. S. Patent 1,880,646, *ibid.*, **27**, 515 (1933); (d) van Gastel and Wibaut, *Rec. trav. chim.*, **53**, 1031 (1934); (e) Machek, *Monatsh.*, **72**, 77 (1938).