In attempting to prepare the 2,4,5,8-isomer the cyclodehydration procedure of Adams and Campbell yielded neither the quinoline nor its sulfate when applied to the appropriate imine. However, it was observed that, by slowly distilling the imine, a slightly higher boiling fraction was obtained at the end of the distillation, which formed colorless crystals upon cooling. This material proved to be the quinoline in an impure state and had been formed in small yield by cyclodehydration induced solely by heating the imine around 110° at about 1 mm. pressure. Recrystallization from 95% ethanol gave white crystals of the quinoline, which still contained large amounts of the imine. Further purification was not successful. By comparing the infrared spectra of the imine, and the quinoline contaminated with imine, the following wave lengths, in microns, were determined to be characteristic of the quinoline: 11.67(m), 12.23(s), 12.69(m), 12.77(m) and 14.25(m).

4-(2,3-Dimethylbenzimino)-pentan-2-one, apparently previously unreported, consisted of white crystals, m.p. 88.0° (*Anal.* Calcd. for $C_{13}H_{17}NO$: C, 76.81; H, 8.43. Found: C, 76.92; H, 8.45.)

The physical constants of the synthesized polymethylquinolines are listed in Table II.

Infrared Spectra of Quinolines.—A Perkin-Elmer model 21 spectrophotometer, equipped with sodium chloride optics, was used to obtain the spectra. The slit opening at 2.0 $\mu$ was 3 $\mu$, on Resolution Schedule 927. Under these conditions, good resolution with an acceptable noise level was obtained. Matched 0.498-mm. sodium chloride cells were used. An average concentration of about 1.0% quinoline in Baker analyzed carbon disulfide was used in obtaining the infrared spectra.

**Acknowledgments.**—The authors are indebted to Theodore L. Yarboro of this Laboratory for purification of some quinolines and determination of all atmospheric boiling points, to Glenn L. Cook for infrared spectra of alkylpyridines, and to A. L. Lochte for a trimethylquinoline sample.[15]

(15) Presented before the Division of Organic Chemistry, American Chemical Society, San Francisco, Calif., April, 1958.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

# The Action of Heterocyclic N-Oxides on 2-Bromopyridine. Oxidative Brominations Involving N-Oxide Hydrobromides

BY FAUSTO RAMIREZ AND PETER W. VON OSTWALDEN[1]

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The action of pyridine-1-oxide and of the three isomeric picoline-1-oxides on 2-bromopyridine was investigated. The main products of these reactions have the skeleton of 1-(2′-pyridyl)-2-pyridone, in which the pyridone moiety is derived from 2-bromopyridine and the pyridyl group is derived from the N-oxide. The 1-(2′-pyridyl)-3-bromo-2-pyridones and the 3,5-dibromoanalogs also isolated under certain conditions were shown to originate from secondary oxidative brominations involving the N-oxide hydrobromides, $\geqslant \overset{(+)}{N}\text{—}\overset{(-)}{O}HBr$. It is suggested that this manifestation of the oxidative power of heterocyclic N-oxides: $\geqslant \overset{(+)}{N}\text{—}\overset{(-)}{O}YX \rightarrow \geqslant N{:}XOY$ may play a wider role in N-oxide chemistry.

Nucleophilic attack on heterocyclic systems by heterocyclic N-oxides[2] would open attractive synthetic possibilities.[3] This type of reaction is implicit in a recent report by Takeda, Hamamoto and Tone.[4] These authors obtained 1-(2′-pyridyl)-2-pyridone (III), pyridine and a substance $C_{10}H_7ON_2Br$ (m.p. 129°) of unknown structure, from the reaction of pyridine 1-oxide (I) with 2-bromopyridine (II) at 100°. Pyridine 1-oxide was found to react also with 2-bromoquinoline[4] and, later,[5,6] the reaction was extended to quinoline 1-oxide.[7] No satisfactory reaction mechanism was advanced.

We have studied[1] the reaction of pyridine 1-oxide and of the three isomeric picoline 1-oxides with 2-bromopyridine. The reactions were carried out: (1) in the absence of solvent and (2) in toluene solution containing a small amount of hydrogen bromide. In the absence of solvent and of initiator, the reactions were explosively exothermic after a relatively long induction period at 100°. The induction period was virtually eliminated by the initial addition of small amounts of mineral acid. Small amounts of free radical inhibitors did not seem to influence the reaction, but the presence of piperidine had a marked inhibitory effect. No reaction was detected between 2,6-lutidine 1-oxide and 2-bromopyridine.

In our hands, the reaction of pyridine 1-oxide (I) with 2-bromopyridine (II) at 100° yielded 1-(2′-pyridyl)-2-pyridone (III) and 1-(2′-pyridyl)-3-bromo-2-pyridone (V) in about equal amounts (each in 20–30% yield). The reaction also produced pyridine and traces of 2-pyridone (VI). Compound V appeared to be identical with the bromo compound reported by Takeda.[4]

In toluene solution with hydrogen bromide–acetic acid catalyst, the N-oxide and the bromopyridine reacted smoothly to give 1-(2′-pyridyl)-2-pyridone (III) in 53% yield. No bromo compound V or pyridine could be detected under these conditions.

The reaction between 2-bromopyridinium hydrobromide (II·HBr, prepared separately) and pyridine 1-oxide (I), proceeded as expected, without

(1) From part of the Ph.D. Thesis of P. W. von Ostwalden; preliminary communication in *Chemistry & Industry*, 46 (1957).

(2) For a recent review see A. R. Katritzky, *Quart. Revs.*, **10**, 395 (1956).

(3) Nucleophilic attack on alkyl halides by heterocyclic N-oxides has been known for some time; see, *e.g.*, M. Henze, *Ber.*, **70**, 1270 (1937).

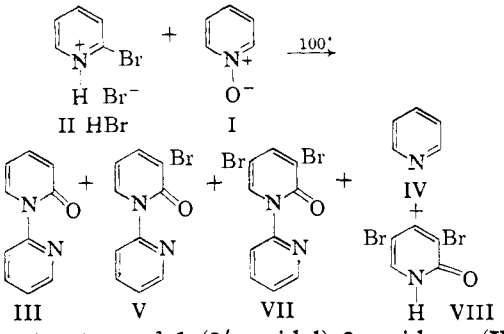
(4) K. Takeda, K. Hamamoto and H. Tone, *J. Pharm. Soc. Japan*, **72**, 1427 (1952); *C. A.*, **47**, 8071 (1953).

(5) K. Takeda and K. Hamamoto, *ibid.*, **73**, 1158 (1953); *C. A.*, **48**, 12748 (1954).

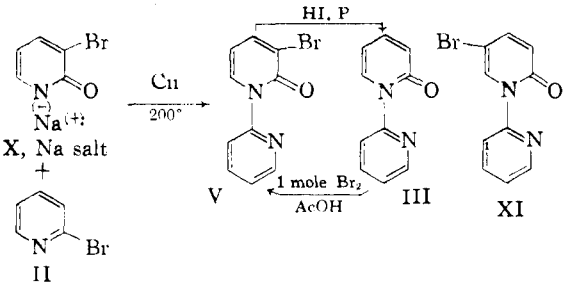
(6) See also, K. Hamamoto and T. Kubota, *ibid.*, **73**, 1162 (1953); *C. A.*, **48**, 12748 (1954).

(7) The present investigation suggests that the substance $C_{10}H_9ON_2Br$ isolated by Takeda and Hamamoto[5] from the reaction of quinoline 1-oxide with 2-bromopyridine is 1-(2′-quinolyl)-3-bromo-2-pyridone.

induction period but was vigorous. In addition to the pyridylpyridones III and V, and pyridine, small amounts of 1-(2′-pyridyl)-3,5-dibromo-2-pyridone (VII) and of 3,5-dibromo-2-pyridone (VIII)[8] were produced.

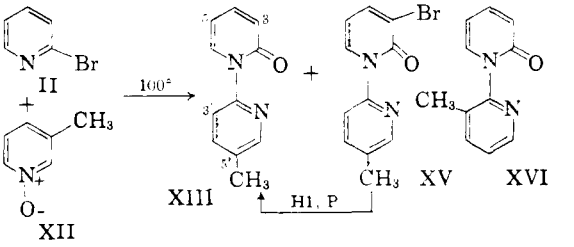



The structure of **1-(2′-pyridyl)-2-pyridone (III)** had been proved[4,6] by degradation and by synthesis from the sodium salt of 2-pyridone and 2-bromopyridine (with copper powder). We arrived at the structure of the bromo compounds as follows: The ultraviolet absorption spectra of the 129°-substance V and of the pyridone III were similar, but the 315-mμ pyridone maximum of the latter was shifted to 325 mμ in the former. Furthermore, V could be reduced to III by hydriodic acid and red phosphorus and III could be converted into V by one molar equivalent of bromine in acetic acid.[9] The 129°-substance V was shown to be *different* from 1-(2′-pyridyl)-5-bromo-2-pyridone (XI), which was synthesized from the known[10,11] 5-bromo-2-pyridone (IX) and 2-bromopyridine (II). Finally, an authentic sample of 1-(2′-pyridyl)-3-bromo-2-pyridone (V) was made from 2-bromopyridine (II) and 3-bromo-2-pyridone (X) (prepared as described elsewhere).[12]



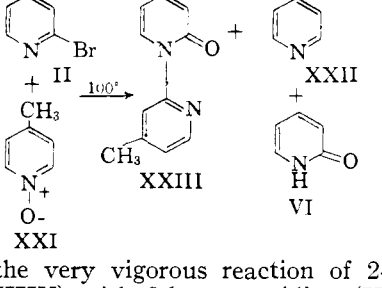

**1-(2′-Pyridyl)-3,5-dibromo-2-pyridone (VII)** was obtained by bromination of 1-(2′-pyridyl)-2-pyridone (III) in acetic acid with an excess of bromine. It is known[11] that bromination of 1-methyl-2-pyridone (XIX) under the same conditions yields 1-methyl-3,5-dibromo-2-pyridone (XX). Substance VII was also obtained by bromination of the monobromo-pyridylpyridones V and XI.

From the vigorous reaction of 2-bromopyridine (II) with 3-picoline 1-oxide (XII), in the absence of a solvent and catalyst, **1-(5′-methyl-2′-pyridyl)-2-pyridone (XIII) and 1-(5′-methyl-2′-pyridyl)-3-bromo-2-pyridone (XV)** (each *ca.* 20%), together with some 3-picoline (XIV) were isolated. In toluene solution with hydrogen bromide catalyst, 1-(5′-methyl-2′-pyridyl)-2-pyridone (XIII) (50% yield) and very small amounts of the bromo compound XV and of 3-picoline were obtained.




The reaction also could have produced **1-(3′-methyl-2′-pyridyl-2-pyridone (XVI)**, isomeric with XIII, depending on whether coupling takes place in the 2′- or 6′-position of the N-oxide moiety. No 3′-isomer (XVI) was found among the reaction products. Both isomers, XIII and XVI, were synthesized independently from sodio-2-pyridone and 2-bromo-5-methylpyridine (XVII) or 2-bromo-3-methylpyridine (XVIII), respectively. The structure of the **1-(5′-methyl-2′-pyridyl)-3-bromo-2-pyridone (XV)** was established by reduction to XIII; the assignment of position 3 to the bromine was based on spectral evidence and on the mechanistic analogy between the formation of XV and the previously discussed compound V.

The reaction of 2-bromopyridine (II) with 4-picoline 1-oxide (XXI) had the shortest of the observed induction periods (1.75 hr.) and produced **1-(4′-methyl-2′-pyridyl)-2-pyridone (XXIII)** (10%), 4-picoline (XXII) (17%) and **2-pyridone (VI)** (18%). There was no evidence of formation of a brominated pyridylpyridone. In toluene solution with HBr catalyst the pyridylpyridone (XXIII) was obtained in 30% yield, besides 4-picoline (XXII) and 2-pyridone (VI). Compound XXIII was synthesized from 2-bromo-4-methylpyridine (XXIV) and the sodium salt of 2-pyridone.




From the very vigorous reaction of 2-picoline 1-oxide (XXV) with 2-bromopyridine (II), there was isolated 1-(6′-methyl-2-pyridyl)-2-pyridone

(8) An authentic sample was prepared according to W. Koenigs and R. Geigy, *Ber.*, **17**, 589 (1884).

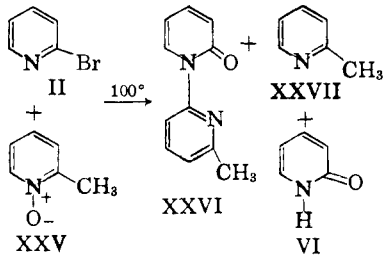
(9) There is no doubt that the bromine entered position-3 of the 1-(2′-pyridyl)-2-pyridone (III) rather than position-5. P. A. De Villiers and H. J. den Hertog [*Rec. trav. chim.*, **75**, 1303 (1956)], however, have reported that chlorination of III gave 1-(2′-pyridyl)-5-chloro-2-pyridone.

(10) A. E. Chichibabin and V. S. Tyazhelova, *J. Russ. Phys. Chem. Soc.*, **50**, 483 (1918); *C. A.*, **18**, 1495 (1924).

(11) H. Decker and A. Kaufmann, *J. prakt. Chem., N.F.*, **84**, 440 (1911).

(12) In our hands, 5-bromo-2-pyridone had m.p. 180.5–181° (from aq. ethanol); $\lambda_{max}^{EtOH}$ 315 mμ (ε 4500), 235 mμ (ε 10,000); it gave a red-brown color with ethanolic ferric chloride (*cf.* ref. 10 and H. L. Bradlow and C. A. VanderWerf, *J. Org. Chem.*, **16**, 73 (1951)). Our 3-bromo-2-pyridone had m.p. 184–185° (from aq. ethanol); $\lambda_{max}^{EtOH}$ 310 mμ (ε 7200), 234 mμ (ε 4700); it gave no color with ethanolic ferric chloride. The mixed m.p. of the two isomers was 135–150° (see W. A. Lott and E. Shaw, THIS JOURNAL, **71**, 70 (1949)).

(XXVI) (10%), 2-picoline (XXVII) (40%) and 2-pyridone (22%). No bromopyridones could be detected. This reaction had the longest induction period, nearly 8 hr. When the reaction was run at 100° in toluene solution with HBr catalyst for 10 hr., about 60% of the unreacted starting materials was recovered; furthermore, 1-(6′-methyl-2′-pyridyl)-2-pyridone (XXVI) was isolated in 6% yield. No brominated products or 2-picoline were observed under these conditions. Compound XXVI was synthesized from 2-bromo-6-methylpyridine (XXVIII) and sodio-2-pyridone.




The following mechanism (Fig. 1) is suggested for the formation of N-(2′-pyridyl)-2-pyridones from 2-bromopyridine and pyridine 1-oxide (or the picoline 1-oxides). The heterocyclic N-oxide performs a nucleophilic attack on the 2-halopyridine $\alpha$-carbon (step 1). In the intermediate A thus formed, the N-oxide becomes the substrate for an intramolecular nucleophilic attack by the halopyridine nitrogen (step 2). As a result of this molecular rearrangement *via* intermediate C (step 3) the N-oxide oxygen is transferred to the 2-halopyridine $\alpha$-carbon, while a new bond is formed between the nitrogen atom of the latter and the N-oxide $\alpha$-carbon. A similar result is obtained *via* B. The formation of hydrogen bromide in the last step suggests autocatalysis and would explain the observed induction period.

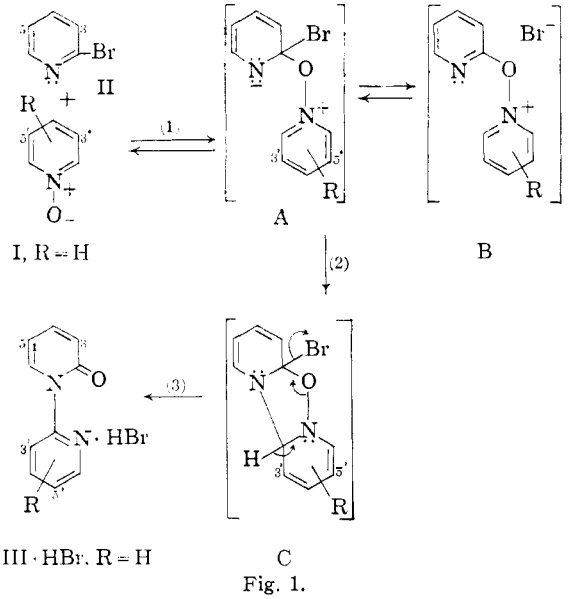



Fig. 1.

The exclusive formation of 1-(5′-methyl-2′-pyridyl)-2-pyridone (III, R = 5′-$CH_3$) from 3-picoline 1-oxide (I, R = 3′-$CH_3$) suggests a steric effect in the cyclization. Formation of the isomeric 1-(3′-methyl-2′-pyridyl)-2-pyridone (III, R = 3′-$CH_3$) would involve closure on a position *ortho* to the methyl group.

A similar mechanism could apply to the reaction of pyridine 1-oxide with 2-(*p*-toluenesulfonyloxy)-pyridine.[13]

The brominated pyridones arise as secondary products from the initially formed N-pyridylpyridones (or 2-pyridone), the unreacted N-oxide and the generated hydrogen bromide acting together as brominating agent.[14] When 1-(2′-pyridyl)-2-pyridone (III) and pyridine 1-oxide hydrobromide (I·HBr) were heated to 200°, 1-(2′-pyridyl)-3-bromo-2-pyridone (V) and pyridine were formed in good yield. Some 1-(2′-pyridyl)-3,5-dibromo-2-pyridone (VII) also was produced. Likewise, 1-methyl-2-pyridone hydrobromide (XIX·HBr) and pyridine-1-oxide gave, on heating, 1-methyl-3,5-dibromo-2-pyridone (XX). In both cases the brominated products were the same as those obtained with bromine in acetic acid solution.

The oxidative bromination, formally: $\geq\overset{+}{N}-OHBr^{(-)}\rightarrow\geq N:$ HOBr, is one source of the pyridine and of the picolines isolated in the reactions of the N-oxides with 2-bromopyridine.[15] This manifestation of the oxidizing power of heterocyclic N-oxides undoubtedly plays a role in many reactions, whenever the temperature is high enough. For instance, 3-bromo-4-pyridone and 3,5-dibromo-4-pyridone were isolated[16] when 4-nitropyridine 1-oxide and 48% aqueous hydrobromic acid[17] were heated to 160°.

**Acknowledgment.**—We are grateful to the Eli Lilly Research Grants Committee for generous support.

## Experimental

Analyses by Micro-Tech Laboratories, Skokie, Ill.

**Reaction of Pyridine 1-Oxide (I) with 2-Bromopyridine (II).**—A mixture of 9.5 g. (0.1 mole) of pyridine 1-oxide (I) and 15.8 g. (0.1 mole) of 2-bromopyridine (II) was heated to 100° under nitrogen. After 2.25 hr., a vigorous exothermic reaction ensued and the mixture reached a temperature of 250° within seconds. After the violent reaction had subsided, the mixture was kept at 100° for an additional 2-hr. period.

The reaction mixture was dissolved in dilute hydrochloric acid; the dark solution was made alkaline with sodium hydroxide and extracted with chloroform. The chloroform extract was distilled giving 0.6 g. of pyridine (IV), determined as picrate. The residue from the distillation was

(13) P. A. De Villiers and H. J. den Hertog, *Rec. trav. chim.*, **76**, 647 (1957); *cf.* footnote 9 of the present paper.

(14) As expected, pyridine-1-oxide did not produce bromine when refluxed in hydrobromic acid (*ca.* 140°). However, in the N-oxide–2-bromopyridine reaction (procedure 1) the reaction temperature reached above 200° during the exothermic phase. The absence of bromopyridones in procedure 2 is thus due to a lower reaction temperature.

(15) The 2-pyridone-(VI) isolated in these reactions may be due to hydrolysis of B (Fig. 1) during the work-up. As shown by separate experiments VI did not arise from unreacted 2-bromopyridine. No methyl-containing 2-pyridones (*e.g.*, 4-methyl-2-pyridone) could be detected.

(16) (a) E. Ochiai, T. Ito and S. Okuda, *J. Pharm. Soc. Japan*, **71**, 591 (1951); *C. A.*, **46**, 980 (1952); (b) H. J. den Hertog and W. P. Combe, *Rec. trav. chim.*, **70**, 581 (1951).

(17) A related phenomenon involving the sulfoxide function has been described: (a) H. Gilman and J. Eisch, THIS JOURNAL, **77**, 3862 (1955); (b) T. L. Fletcher, M. J. Namkung and H. L. Pan, *Chemistry & Industry*, 660 (1957).

chromatographed over alumina, eluting first with benzene and later with more polar solvent mixtures. The work-up of about 20 separate fractions gave 5.3 g. (21%) of 1-(2'-pyridyl)-3-bromo-2-pyridone (V) and 4.1 g. (24%) of 1-(2'-pyridyl)-2-pyridone (III).

Neutralization of the alkaline layer and extraction with chloroform afforded 0.1 g. of 2-pyridone (VI).

Pure III was obtained after distillation and recrystallization from hexane–petroleum ether (at −20°); white needles, m.p. 54–56°, reported[4] m.p. 55–56°; $\lambda_{max}^{EtOH}$ 315 mμ, ε 6,000; 266 mμ, ε 2,900; infrared ($CHCl_3$) bands: 1658s cm.$^{-1}$ (6.04 μ), 1594s (6.27).

The picrate of III was prepared in ether; m.p. 115–117°, reported[4] m.p. 117–117.5°.

Recrystallization from methanol afforded analytically pure 1-(2'-pyridyl)-3-bromo-2-pyridone (V); white needles, m.p. 128–129°; ultraviolet $\lambda_{max}^{EtOH}$ 325 mμ, ε 7,300; 265 mμ; ε 3,000; infrared ($CHCl_3$) bands 1658s cm.$^{-1}$ (6.04 μ), 1608s (6.21), 1592 (6.28). Insoluble in water; soluble in 5% HCl. No picrate was obtained from V in ether.

*Anal.* Calcd. for $C_{10}H_7ON_2Br$: C, 47.8; H, 2.8; N, 11.2; Br, 31.8. Found: C, 47.7; H, 2.9; N, 10.8; Br, 31.7.

**Reaction of 2-Bromopyridine (II) with Pyridine 1-Oxide (I) in Toluene Solution with HBr Catalyst.**—A solution of (I) (9.5 g.) and (II) (19.7 g.) in 100 ml. of toluene containing 5 drops of 30% hydrogen bromide in acetic acid, was heated for 6 hr. at 105°, with stirring. No violent reaction was observed. After about 2 hr., the initially clear solution had turned light brown and began to deposit a dark oil. The mixture was allowed to cool and the toluene layer was decanted from the brown oily precipitate. The toluene was extracted with dilute hydrochloric acid and the acidic extracts were combined with the oily precipitate. This solution was made alkaline and then was subjected to the separation procedure described above. The products isolated were a trace of pyridine (0.18 g. of picrate) and 9.1 g. (53%) of 1-(2'-pyridyl)-2-pyridone (III) (m.p. 53–54° after one recrystallization). No evidence for the formation of the bromo compound V was obtained.

**Reaction of 2-Bromopyridinium Hydrobromide (II·HBr) with Pyridine 1-Oxide (I).**—A mixture of I (4.75 g., 0.05 mole) and II·HBr (m.p. 200–202°, 12 g., 0.05 mole) was heated to 100° for a total time of 4 hr. As soon as the reactants had melted, the expected violent reaction took place. The cooled mixture was dissolved in dilute acid, made alkaline, and extracted with chloroform. The chloroform extract was subjected to the usual separation procedure and the following products isolated: 1.3 g. (33%) of pyridine, 0.5 g. (3%) of **1-(2'-pyridyl)-3,5-dibromo-2-pyridone (VII)**, 1.5 g. (12%) of 1-(2'-pyridyl)-3-bromo-2-pyridone (V), and 0.3 g. (3.5%) of 1-(2'-pyridyl)-2-pyridone (III). The alkaline solution was neutralized and extracted with chloroform; evaporation of the extract left 0.6 g. (5%) of **3,5-dibromo-2-pyridone (VIII)** (soluble in 5% NaOH; recrystallized from benzene; m.p. and mixed m.p. with authentic (VIII) 207–209°).

An analytical sample of 1-(2'-pyridyl)-3,5-dibromo-2-pyridone (VII) was obtained by recrystallization from 95% ethanol; white needles, m.p. 157–158°; insoluble in 5% NaOH; ultraviolet $\lambda_{max}^{EtOH}$ 340 mμ, ε 7,100; 223 mμ, ε 21,400 infrared ($CHCl_3$) bands 1660s cm.$^{-1}$ (6.03 μ), 1608s (6.23), 1575 (6.35), 1500m (6.68), 1466m (6.82), 1432m (6.98).

*Anal.* Calcd. for $C_{10}H_6ON_2Br_2$: C, 36.4; H, 1.8; N, 8.5; Br, 48.4. Found: C, 36.6; H, 1.7; N, 8.3; Br, 48.8.

**Bromination of 1-(2'-Pyridyl)-2-pyridone (III) with One Molar Equivalent of Bromine.**—To a solution of 0.3 g. (1.74 millimoles) of pure III in 40 ml. of glacial acetic acid was added a solution of 0.3 g. (1.88 millimoles) of bromine in 20 ml. of acetic acid, gradually and in the cold. The clear, yellow mixture was let stand at room temperature for 2 days. After this, it was diluted with an equal volume of water, containing a trace of sodium bisulfite, made alkaline with sodium hydroxide, and extracted with chloroform. The dried chloroform extract, on evaporation, left 0.4 g. (92%) of crude 1-(2'-pyridyl)-3-bromo-2-pyridone (V), readily crystallizing oil, crude m.p. 85–100°; ultraviolet $\lambda_{max}^{EtOH}$ 325 mμ, 265 mμ. Two recrystallizations from hexane–benzene yielded the practically pure compound; white leaflets, m.p. 125–127°; ultraviolet $\lambda_{max}^{EtOH}$ 325 mμ, ε 7,600, 265 mμ.

**Reduction of 1-(2'-Pyridyl)-3-bromo-2-pyridone (V) to 1-(2'-Pyridyl)-2-pyridone (III).**—A mixture of (V) (1 g., 4 millimoles), 57% hydriodic acid (20 ml.) and red phosphorus (1.2 g.) was refluxed for 18 hours. After cooling, the mixture was filtered, the clear filtrate made alkaline with sodium hydroxide, and extracted with chloroform. Removal of the chloroform left 0.5 g. (72%) of (III) (m.p. 53–55° after one recrystallization).

**Bromination of III with Excess of Bromine.**—To a solution of 0.3 g. (1.74 millimoles) of III in 10 ml. of acetic acid was added a solution of 1.0 g. (6.25 millimoles) of bromine in 10 ml. of acetic acid, and the mixture was kept at room temperature for 2 hr. The mixture was diluted with water and made alkaline. Compound VII precipitated as fine needles (m.p. 156–158° after one recrystallization).

**Bromination of (V).**—One-half gram of V was dissolved in 10 ml. of acetic acid. To this was added a solution of 1 g. of bromine in 10 ml. of the same solvent and the resulting mixture was let stand at room temperature for 1 day. Addition of alkali to the mixture and isolation of the resulting precipitate yielded 0.22 g. (33%) of VII, m.p. 154–156°.

**Bromination of XI.**—1-(2'-Pyridyl)-5-bromo-2-pyridone (XI) was brominated in precisely the same manner as described for the 3-bromo compound. A 79% yield of VII was obtained.

**Action of Pyridine 1-Oxide Hydrobromide (I·HBr) on 1-(2'-Pyridyl)-2-pyridone (III).**—One gram (5.8 millimoles) of 1-(2'-pyridyl)-2-pyridone (III) and 2.05 g. (11.6 millimoles) of pyridine 1-oxide hydrobromide (I·HBr) were heated under nitrogen to 200–210° for 1 hour. The reaction mixture was taken up in water, made alkaline, and extracted with chloroform. The chloroform extract was fractionated and chromatographed in the usual manner to yield 0.84 g. of pyridine picrate (corresponding to 0.27 g. of pyridine), 0.1 g. (5%) of 1-(2'-pyridyl)-3,5-dibromo-2-pyridone (VII), and 0.8 g. (55%) of 1-(2'-pyridyl)-3-bromo-2-pyridone (V), m.p. 124–126°.

**Reaction of 1-Methyl-2-pyridone Hydrobromide (XIX·HBr) with I.**—Five grams (0.026 mole) of XIX·HBr and 2.5 g. (0.026 mole) of pyridine 1-oxide (I) were heated to 200–210° for 4 hr. The usual separation yielded the picrate corresponding to 1.0 g. (50%) of pyridine and 0.2 g. of 1-methyl-3,5-dibromo-2-pyridone (XX), m.p. 181–182°.[11] (Additional oily products of this reaction were not investigated.)

**Reaction of 2-Bromopyridine (II) with 3-Picoline 1-Oxide (XII).**—A mixture of 3-picoline 1-oxide (XII) (10.9 g., 0.1 mole) and of 2-bromopyridine (II) (23.7 g., 0.15 mole) was heated to 100°. After 2.5 hr. a very vigorous reaction ensued. The mixture was kept at 100° for a total time of 4 hr. The dark residue was dissolved in warm water, the solution was made alkaline, and extracted with chloroform. Removal of the chloroform left a residue which was fractionally distilled. The forerun contained a small amount of 3-picoline (0.35 g., 4%; identified as picrate). The main fraction (collected at 125–165° (0.2 mm.)) was a viscous oil which slowly crystallized (10.9 g.). This material was chromatographed. Elution, first with benzene and then with methanol, afforded 5.4 g. (20%) of **1-(5'-methyl-2'-pyridyl)-3-bromo-2-pyridone (XV)** and 3.3 g. (18%) of **1-(5'-methyl-2'-pyridyl)-2-pyridone (XIII)**. The analytical sample of the bromopyridone (XV) was obtained by recrystallizing the crude several times from benzene–hexane; white needles, m.p. 151–152°; ultraviolet $\lambda_{max}^{EtOH}$ 325 mμ (ε 8,300), 271 mμ (ε 3,900); infrared ($CHCl_3$) bands 1650s cm.$^{-1}$ (6.06 μ), 1608m (6.22), 1511w (6.61); 1470s (6.80). No picrate was formed in ether.

*Anal.* Calcd. for $C_{11}H_9ON_2Br$: C, 49.8; H, 3.4; N, 10.6; Br, 30.2. Found: C, 50.1; H, 3.4; N, 10.4; Br, 30.5.

The analytical sample of 1-(5'-methyl-2'-pyridyl)-2-pyridone (XIII) was obtained by reclromatography and several recrystallizations from cyclohexane and hexane alternately; white needles, m.p. 93–94°. Ultraviolet $\lambda_{max}^{EtOH}$ 316 mμ (ε 6,400), 272 mμ (ε 3,700), 221 mμ (ε 13,000), infrared ($CHCl_3$) bands 1658s cm.$^{-1}$ (6.04 μ), 1612s (6.20), 1594s (6.27), 1532m (6.52), 1474s (6.78). No picrate was obtained from XIII in ether.

*Anal.* Calcd. for $C_{11}H_{10}ON_2$: C, 70.9; H, 5.4; N, 15.0. Found: C, 70.4; H, 5.4; N, 14.8.

**Reaction of 2-Bromopyridine (II) with 3-Picoline 1-Oxide (XII) in Toluene Solution with HBr Catalyst.**—A

solution of XII (10.9 g.) and II (23.7 g.) in 100 ml. of toluene containing 5 drops of a 30% solution of hydrogen bromide in acetic acid was heated to 110° for 4 hr. with stirring. After 1.5 hr., the previously clear solution had become turbid and brown. The heat of the reaction kept the solution boiling smoothly for some time and a dark viscous oil separated. The toluene was removed under reduced pressure, the residue dissolved in warm water, the solution made alkaline, and extracted with chloroform. Distillation of the extract gave a forerun which was shown to contain 3-picoline (0.5 g., 5%). The main fraction (15.3 g.), collected at 125–165° (0.2 mm.), after chromatography yielded 9.5 g. (51%) of 1-(5′-methyl-2′-pyridyl)-2-pyridone (XIII), and 1.2 g. (4.5%) of 1-(5′-methyl-2′-pyridyl)-3-bromo-2-pyridone (XV).

**Reduction of 1-(5′-Methyl-2′-pyridyl)-3-bromo-2-pyridone (XV) to 1-(5′-Methyl-2′-pyridyl)-2-pyridone (XIII).**—A mixture containing 0.25 g. (0.95 millimole) of XV, 6 ml. of 57% hydriodic acid and 1 g. of red phosphorus was refluxed for 18 hours. The filtered solution was made alkaline (NaOH) and extracted with chloroform. Removal of the chloroform left 0.14 g. (80%) of crystalline XIII (m.p. 94–95° after one recrystallization from hexane).

**Reaction of Bromopyridine (II) with 4-Picoline 1-Oxide (XXI).**—A mixture of XXI (10.9 g., 0.1 mole) and II (15.8 g., 0.1 mole) was heated to 100° under nitrogen for a total time of 4 hr. After 1.75 hr., a very vigorous reaction occurred. The black-brown reaction mixture was subjected to the usual separation procedure, including chromatography (see the corresponding reaction of pyridine 1-oxide). The chloroform extract, on distillation, yielded 4.5 g. of picrate (m.p. and mixed m.p. with authentic 4-picoline picrate 165–167°; corresponds to 1.6 g. (17%) of 4-picoline) and 1.85 g. (10%) of crystalline 1-(4′-methyl-2′-pyridyl)-2-pyridone (XXIII). No bromo compounds were detected. Several recrystallizations from hexane of the crude XXIII afforded an analytical sample; white, coarse crystals, m.p. 113.5–114.5°; ultraviolet $\lambda_{max}^{EtOH}$ 314 mμ, ε 6,300, 264 mμ, ε 2,700; infrared ($CHCl_3$) bands 1658s cm.$^{-1}$ (6.04 μ), 1612s (6.20), 1594s (6.27), 1535m (6.51), 1474 (6.78); 1447w (6.91).

*Anal.* Calcd. for $C_{11}H_{10}ON_2$: C, 70.9; H, 5.4; N, 15.0. Found: C, 70.9; H, 5.2; N, 14.7.

**The picrate of XXIII** precipitated slowly when ether solutions of the two components were mixed; fine, yellow needles, m.p. 125–126° (from chloroform).

*Anal.* Calcd. for $C_{11}H_{10}ON_2 \cdot C_6H_3O_7N_3$: C, 49.2; H, 3.2; N, 16.9. Found: C, 49.1; H, 3.1; N, 17.4.

From the alkaline layer, 1.7 g. of crude 2-pyridone was isolated.

**Reaction of 2-Bromopyridine (II) with 4-Picoline 1-Oxide (XXI) in the Presence of a Solvent and Catalyst.**—A solution of (XXI) (10.9 g.) and (II) (15.8 g.) in 100 ml. of toluene, containing 2 ml. of a 30% solution of hydrogen bromide in acetic acid, was heated for a total time of 6 hr. at 100° under nitrogen and with stirring. The usual separation afforded about 1% of 4-picoline (as picrate), 5.6 g. (30%) of 1-(4′-methyl-2′-pyridyl)-2-pyridone (XXIII) and 3.0 g. (32%) of 2-pyridone (VI).

**Action of 4-Picoline 1-Oxide Hydrobromide (XXI·HBr) on 1-(4′-Methyl-2′-pyridyl)-2-pyridone (XXIII).**—A mixture of 1.5 g. of (XXIII) and 1.6 g. of (XXI·HBr) (m.p. 133–136°) was made and heated to 200° for 1 hr. The usual separation procedure afforded 0.24 g. (11%) of 1-(4′-methyl-2′-pyridyl)-3-bromo-2-pyridone (XXIX) and 0.75 g. (50%) of (unreacted) 1-(4′-methyl-2′-pyridyl)-2-pyridone (XXIII). The bromo compound XXIX was recrystallized from hexane–benzene: white crystals, m.p. 118.5–119.5° and (after resolidification) 127–128°. Ultraviolet $\lambda_{max}^{EtOH}$ 324 mμ, ε 8,800; 362 mμ (shoulder, ε 4,200). Infrared ($CHCl_3$) band: 1658 cm.$^{-1}$ (6.04 μ). No picrate was obtained from (XXIX).

*Anal.* Calcd. for $C_{11}H_9ON_2Br$: C, 49.8; H, 3.4; N, 10.6. Found: C, 49.7; H, 3.4; N, 11.0.

**Reaction of 2-Bromopyridine (II) with 2-Picoline 1-Oxide (XXV).**—21.8 g. (0.2 mole) of 2-picoline 1-oxide (XXV) and 31.6 g. (0.2 mole) of 2-bromopyridine (II) were kept at 100°, under nitrogen, for a total time of 9 hr. After 7 hr. 45 min., a very vigorous reaction took place with a sudden temperature rise to 255°. The reaction mixture was dissolved in dilute hydrochloric acid, made alkaline and extracted with chloroform. Distillation of the chloroform extract afforded 7.4 g. (40%) of 2-picoline (as picrate). Chromatography of the residue gave an oil which after distillation afforded 3.7 g. (10%) of 1-(6′-methyl-2′-pyridyl)-2-pyridone (XXVI) (viscous oil, b.p. 130–135° (0.2 mm.), $n^{26}D$ 1.6135, ultraviolet $\lambda_{max}$ 313 mμ). Crystalline XXVI, m.p. 53–54° (hexane), was obtained after further chromatography; $\lambda_{max}^{EtOH}$ 315 mμ (ε 6,400), 270 mμ (ε 4,100); infrared ($CHCl_3$) bands 1658s cm.$^{-1}$ (6.04 μ), 1608s (6.23).

*Anal.* Calcd. for $C_{11}H_{10}ON_2$: C, 70.9; H, 5.4; N, 15.0. Found: C, 70.8; H, 5.1; N, 15.4.

The picrate of XXVI precipitated slowly from a chloroform–ether solution; yellow needles, m.p. 148.5–149.5°.

The alkaline layer contained 4.2 g. (22%) of 2-pyridone (VI).

**Reaction of 2-Bromopyridine (II) with 2-Picoline 1-Oxide (XXV) in Toluene Solution with HBr Catalyst.**—A mixture of 10.9 g. of XXV, 15.8 g. of II, 100 ml. of toluene and 4 ml. of a 30% solution of hydrogen bromide in acetic acid was stirred at 100° for 10 hr. The reaction mixture had no 2-picoline; 9.1 g. (58%) of unreacted 2-bromopyridine and 6.9 g. (63%) of unreacted 2-picoline 1-oxide were recovered by distillation.

The residue (3.7 g.) after the distillation was chromatographed to give 1.1 g. (6%) of 1-(6′-methyl-2′-pyridyl)-2-pyridone (XXVI).

**Attempted Reaction of 2-Bromopyridine (II) with 2,6-Lutidine 1-Oxide.**—A mixture of 2,6-lutidine 1-oxide, 2-bromopyridine and some 30% hydrogen bromide in acetic acid was heated to 100° for 10 hr. Only a darkening of the color of the mixture was observed; that no reaction had taken place was demonstrated by comparison of the infrared spectrum and $n_D$ with those of a freshly prepared mixture.

**Reaction of Sodium 2-Pyridones with 2-Bromopyridines.**—A mixture of the two components and some copper powder was heated to 200°. The product was treated with dilute hydrochloric acid and the filtered solution was made alkaline and extracted with chloroform. The pyridyl-2-pyridones were purified by chromatography and recrystallization (see Table I). The starting materials were prepared as previously described: 3-bromo-2-pyridone (X),[12] 5-bromo-2-pyridone (IX),[10,12] 2-bromo-5-methylpyridine (XVII),[18] 2-bromo-3-methylpyridine (XVIII),[19] 2-bromo-4-methylpyridine (XXIV),[20] 2-bromo-6-methylpyridine.[21]

TABLE I

| 2-Pyridones | M.p[a]., °C. |
|---|---|
| 1-(2′-Pyridyl)-3-bromo- (V) | 126–128 |
| 1-(2′-Pyridyl)-5-bromo- (XI)[b] | 133–134 |
| 1-(5′-Methyl-2′-pyridyl)- (XIII) | 94–95 |
| 1-(3′-Methyl-2′-pyridyl)- (XVI)[c] | 107–108 |
| 1-(4′-Methyl-2′-pyridyl)- (XXIII) | 113–115 |
| 1-(6′-Methyl-2′-pyridyl)- (XXVI) | 50–53 |

[a] Solvent: hexane, alone or mixed with benzene. [b] $\lambda_{max}^{EtOH}$ 330 mμ (ε 4,900), 225–230 mμ (shoulder). Calcd. for $C_{10}H_7ON_2Br$: C, 47.8; H, 2.8; N, 11.2; Br, 31.8. Found: C, 47.8; H, 2.9; N, 10.8; Br, 32.0. [c] $\lambda_{max}^{EtOH}$ 306 mμ (ε 5,800), 268 mμ (shoulder), 263 mμ (ε 4,200). Calcd. for $C_{11}H_{10}ON_2$: C, 70.9; H, 5.4; N, 15.1. Found: C, 70.9; H, 5.4; N, 15.2.

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