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BROMINATION OF PYRIDINE-N-OXIDE IN FUMING SULPHURIC ACID[1,2]

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Abstract—Pyridine-N-oxide has been brominated with a mixture of bromine and fuming sulphuric acid. 3-Bromopyridine-N-oxide is formed as the chief product together with 2,5- and 3,4-dibromopyridine-N-oxide in about equal amounts and small quantities of 2-bromopyridine-N-oxide and 2,3-dibromopyridine-N-oxide.

The mechanism of this reaction is discussed in relation to the bromination of pyridine-N-oxide with a mixture of bromine, 90% sulphuric acid and silver sulphate, which yields only a small amount of 2- and 4-bromopyridine-N-oxide.[3] In this connection the bromination of the isomeric monobromopyridine-N-oxides in both media has been investigated.

THERE is a remarkable discrepancy in the behaviour of pyridine-N-oxide towards electrophilic reagents. The N-oxide is nitrated easily to 4-nitropyridine-N-oxide by heating at 90° for 1½ hours with fuming nitric and sulphuric acids; above 100° the nitro group also enters into position 2.[4] Sulphonation of pyridine-N-oxide only proceeds under the extreme conditions necessary for the sulphonation of pyridine, i.e. heating with fuming sulphuric acid in the presence of mercuric sulphate as a catalyst for 20 hours above 220°. The 3-sulphonic acid is formed as the chief product, together with small amounts of the 2- and 4-isomers.[5] The course of the mercuration depends on the conditions chosen. Whereas pyridine-N-oxide reacts smoothly with mercuric acetate in acetic acid at 130° yielding derivatives substituted at positions 2 or 2 and 6, the nucleus is also attacked at the 3-position when pyridine-N-oxide is heated with mercuric sulphate in sulphuric acid solution at 170°.[6] It has now been found that also the course of bromination differs considerably when various reaction media are applied.

Pyridine-N-oxide was first brominated, only a year ago, by van der Plas in this laboratory with a mixture of bromine, 90 per cent sulphuric acid and silver sulphate.[7] The rate of bromination at 150° is very slow but at 200° and heating for 20 hours, 2- and 4-bromopyridine-N-oxide (ratio = 1:2) are formed in a yield of ~10 per cent.[3]

The N-oxide (I) undergoes 25–30 per cent conversion into a mixture of bromo derivatives when heated for 10 hours at 120° with half the molecular amount of bromine in fuming sulphuric acid (sulphur trioxide content = 65 per cent). The composition of the reaction mixture was established by reducing the N-oxides and

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[1] 21st Communication from this Laboratory on derivatives of pyridine-N-oxide.

[2] M. van Ammers, Thesis, Amsterdam (1961).

[3] Cf. H. C. van der Plas, H. J. den Hertog, M. van Ammers and Miss B. Haase, *Tetrahedron Letters* No 1, (1961).

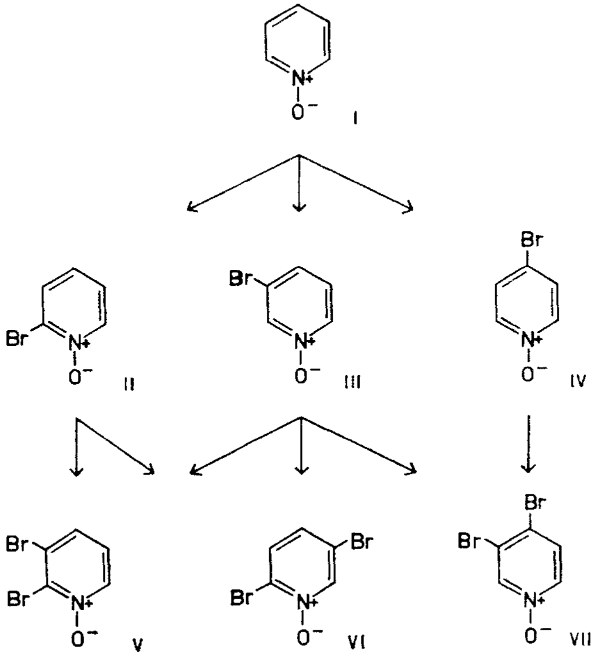
[4] [a] E. Ochiai, K. Arima and M. Ishikawa, *J. Pharm. Soc. Japan* **63**, 79 (1943); *Chem. Abstr.* **45**, 5151 (1951); [b] H. J. den Hertog and J. Overhoff, *Rec. Trav. Chim.* **69**, 468 (1950); H. J. den Hertog and W. P. Combé, *Ibid.* **70**, 581 (1951).

[5] [a] H. S. Mosher and F. J. Welch, *J. Amer. Chem. Soc.* **77**, 2902 (1955); [b] M. van Ammers and H. J. den Hertog, *Rec. Trav. Chim.* **78**, 586 (1959).

[6] [a] M. van Ammers and H. J. den Hertog, *Rec. Trav. Chem.* **77**, 340 (1958); [b] M. van Ammers, *Thesis*, Amsterdam (1961).

[7] This reagent was suggested by D. H. Derbyshire and W. A. Waters, *J. Chem. Soc.* 573 (1950).

analysing the mixture of pyridine and brominated pyridines thus formed by gas chromatography. The mixture of bromination products formed consisted of ~60 per cent of monobromo, ~35 per cent dibromo and ~5 per cent tribromo derivatives (Table 1, column 2 and 3). The amount of 3-bromopyridine-N-oxide (III) was ten times that of isomers II and IV. The mixture of dibromo compounds consisted chiefly of 2,5- and 3,4-dibromopyridine (VI and VII) in about equal amounts (15 per cent), together with a small amount (5 per cent) of 2,3-dibromopyridine-N-oxide (V), and several tribromo compounds.



Thus, in fuming sulphuric acid the bromination occurs first at position 3. This result may be explained by the fact that pyridine-N-oxide can form a stable addition product with sulphur trioxide and that in this compound the complex of sulphur trioxide and the N-oxide group deactivates the molecule especially at the 2, 4 and 6 positions (cf. formulae VIII a–d) and counteracts the attack of the nucleus at these positions by the electrophilic reagent as is the case in 90 per cent sulphuric acid.

It is remarkable that notwithstanding the deactivation of the nucleus in fuming sulphuric acid, the bromination proceeds faster in this medium than in 90 per cent sulphuric acid, possibly owing to the presence of positive bromine ions in a high concentration.[8]

It is also remarkable that the mixture of dibromopyridine-N-oxides contains chiefly the 2,5- and 3,4-isomers and that the 3,5-dibromopyridine-N-oxide is not produced in the reaction.

In this connection, the bromination of 3-bromopyridine-N-oxide (III) in fuming sulphuric acid and in 90 per cent sulphuric acid in the presence of silver sulphate was

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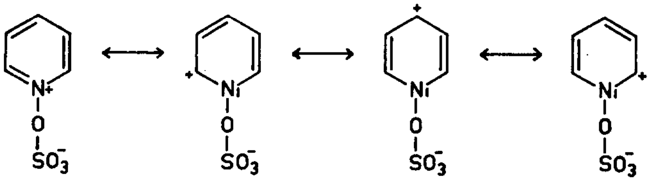
[8] Cf. the results of physical measurements by J. Arotsky, H. C. Mishra and M. C. R. Symons (*J. Chem. Soc.* 12 (1960), proving the presence of positive iodine ions in solutions of iodine in fuming sulphuric acid.

investigated (Table 1, column 7 and 8). In the second medium the rate was very slow and only 5–10 per cent bromination occurred by heating the components at 160° for 20 hours. 3,4-Dibromopyridine-N-oxide (VII) was the chief product (~65 per cent), together with 2,5- and 2,3-dibromopyridine-N-oxide (VI and V) as by-products (~35 per cent). As in the bromination of pyridine-N-oxide in 90 per cent sulphuric acid, substitution occurs mainly at the 4-position and subsequently at positions 2 or 6. When 3-bromopyridine-N-oxide was brominated in fuming sulphuric acid (120°, 10 hours), the same dibromo compounds were formed in a total yield of 25–30 per cent, but the ratio of the amounts of the isomers formed differed. The 2,5-dibromopyridine-N-oxide (VI) was the chief product while the 2,3- and 3,4-dibromo compounds (V and VII) were present in equal amounts. As in the corresponding bromination of pyridine-N-oxide no 3,5-dibromopyridine-N-oxide was formed.



VIIIa VIIIb VIIIc VIIId

In this case as well the addition product of the N-oxide and sulphur trioxide is attacked by the reagent and the orienting effect of the bromine atom already present in the nucleus surpasses that of the N-oxide group, the second bromine atom entering only in *para* and *ortho* positions to the first.

This hypothesis is confirmed by the bromination of 2-bromopyridine-N-oxide (II) in both media (Table 1, column 5 and 6). In 90 per cent sulphuric acid, 2,4- and 2,6-dibromo-pyridine-N-oxides (IX and X) are formed in low yield, and in the ratio 4·5:1 respectively. This is in agreement with the bromination of pyridine-N-oxide in the same solvent. (Table 1, column 1). In both reactions only the hydrogen atoms at the 4- or 2- (or 6-) positions are replaced while the ratio of the velocities of the replacement of these atoms is the same. The bromination of 2-bromopyridine-N-oxide in fuming sulphuric acid proceeds readily yielding only 2,5- and 2,3-dibromopyridine-N-oxide (VI and V). Here the orienting effects of the SO_3-N-oxide group and the bromine atom at the 2-position are working together.

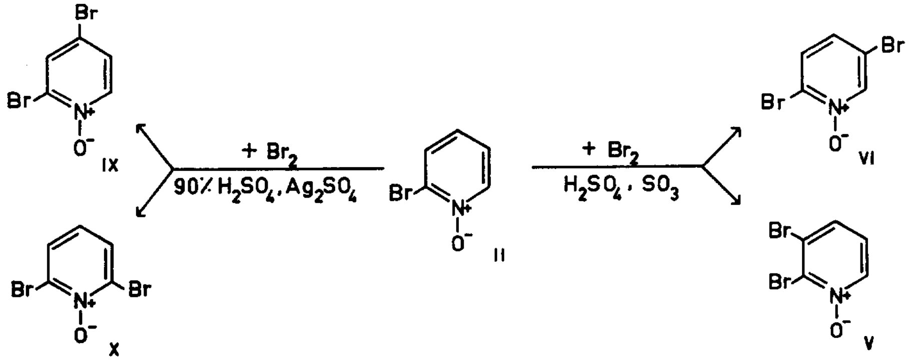


TABLE 1

	Pyridine-N-oxide				2-Bromo pyridine-N-oxide		3-Bromo-pyridine-N-oxide		4:Bromo-pyridine-N-oxide
	1	2	3	4	5	6	7	8	9
Amount of:									
N-oxide (mmoles)	50	50	26	50	30	10	22	10	10
sulphuric acid (ml)	50	30	15	30	60	15	45	15	15
sulphur trioxide (%)	—	65	65	20	—	65	—	65	65
silver sulphate (mmoles)	25	—	—	—	19	—	14	—	—
bromine (mmoles)	70	40	13	25	30	5	22	5	6
Reaction time (hr)	20	10	10	15	20	10	20	10	10
Reaction temp	180	120	120	220	160	120	160	120	120
Total yield (%)	12	30	25–30	15–20	8	70	7	25–30	60
Unchanged N-oxide (%)	80–85	65–70			80–85	5–10	70–75	65	10
Composition of the reduced reaction product (%)									
3-bromopyridine	—	58	61	38	—	—	—	—	—
4-bromopyridine	70	?	?	7	—	—	—	—	—
2-bromopyridine	30	2	3	34	—	—	—	—	—
3,5-dibromopyridine	—	—	—	—	—	—	—	—	—
3,4-dibromopyridine	—	15	16	5	—	—	64	16	84
2,4-dibromopyridine	—	—	—	4	80–85	—	—	—	—
2,5-dibromopyridine	—	17	14	6	—	66	22	61	—
2,3-dibromopyridine	—	4	3	2	—	28	14	16	—
2,6-dibromopyridine	—	—	—	2	15–20	—	—	—	—
3,4,5-tribromopyridine	—	1	1	—	—	—	—	—	10
2,4,5-tribromopyridine (?)	—	1	1	1	—	2	—	3	6
2,3,6-tribromopyridine (?)	—	2	1	1	—	4	—	4	—

In the bromination of 4-bromopyridine-N-oxide (IV) in fuming sulphuric acid the bromine atom and SO_3-N-oxide group also orientate to the same positions. 3,4-Dibromopyridine-N-oxide (VII) is formed, in fair yield, as the sole monosubstitution product together with small amounts of tribromopyridine-N-oxides, chiefly the 3,4,5-isomer (Table 1, column 9).

Comparing the bromination of 3-bromopyridine-N-oxide (III) in fuming sulphuric acid with that of pyridine-N-oxide (I), the composition of the mixtures of dibromo derivatives formed is similar, but the yield of 3,4-dibromopyridine-N-oxide (VII) from I is higher than that from III. This may be explained by assuming that VII is not only formed from I via III, but also via 4-bromopyridine-N-oxide (IV), which is converted rapidly into VII.

The investigation on the bromination of pyridine-N-oxide under varying conditions is being continued. The effect of temperature on the substitution is indicated by a preliminary experiment in which pyridine-N-oxide was brominated at 220° in fuming sulphuric acid containing 20 per cent sulphur trioxide (Table 1, column 4). In accordance with expectations, there was a shift of substitution from the 3-position to 2, 4 and 6, the reaction mixture containing even small quantities of 2,4- and 2,6-dibromopyridine-N-oxide. It is remarkable, however, that the amount of the 2-bromo compound formed exceeds that of the 4-isomer whereas in bromination above 200° in 90 per cent sulphuric acid in the presence of silver sulphate more 4- than 2-bromopyridine-N-oxide is formed.

EXPERIMENTAL

*Bromination of pyridine-*N*-oxide in fuming sulphuric acid*

Pyridine-N-oxide (4·8 g; 50 mmoles), fuming sulphuric acid containing 65% sulphur trioxide (30 ml) and bromine (2 ml; 40 mmoles) were heated in 2 sealed tubes at 120° for 10 hr. The contents were poured onto ice and neutralized with sodium hydroxide solution. No deoxidation of the N-oxide or its bromo derivatives had taken place, as proved by steam distillation of a portion of the basified reaction mixture, the distillate containing neither pyridine nor bromopyridines. From the ethereal solution obtained by continuous extraction for 16 hr of ½ the reaction mixture, 1·72 g of a semisolid was obtained. This was converted into a mixture of pyridine and bromopyridines by heating for 1 hr at 100° with 1·3 g iron powder and 10 ml acetic acid; basifying the reaction product and extraction with ether.

A portion of this mixture was analysed by gas liquid chromatography in a Becker gaschromatograph (Delft, the Netherlands) with a katharometer as detector. The analysis was carried out using a copper column (length 2 m, diameter 0·4 cm) filled with tritolyl phosphate on chromosorb (ratio = 1:5) which was kept at 165° and hydrogen (rate 60 ml/min) as carrier gas.

Relative retention times:

pyridine:	0·25
3- and 4-bromopyridine:	0·65
2-bromopyridine:	1·00[9]
3,5-dibromopyridine:	1·40
3,4-dibromopyridine:	1·95
2,4-dibromopyridine:	2·25
2,5-dibromopyridine:	2·55
2,3-dibromopyridine:	3·50
2,6-dibromopyridine:	4·15

[9] The absolute retention time of 2-bromopyridine is 5·8 min

The analysis is complicated by the fact that 4-bromo- has the same retention time as 3-bromopyridine. The ratio of the amounts of the monobromopyridines may be calculated from the chromatograms of the mixture before and after heating for 3 hr at 100–110°, as during heating 4-bromopyridine is converted into non-volatile pyridylpyridinium compounds. Thus, the first chromatogram gives the ratio of the amounts of 3- and 4-bromopyridine to that of 2-bromopyridine; the second approximately the ratio of the amounts of 3- and 2-bromopyridine.

The amount of unchanged pyridine-N-oxide is calculated from the data of the chromatographic analysis and a measurement of the absorption at 2540 Å in a Unicam S.P. 500 Spectrophotometer of the aqueous solution left after extraction with ether. The result of the analysis of the reaction mixture obtained in this experiment is given in Table 1, column 2.

*Bromination of pyridine-*N*-oxide* (I) *in* 90% *sulphuric acid*

4·8 g I (50 mmoles), dissolved in 50 ml 90% sulphuric acid, was heated in 2 sealed tubes with 8 g silver sulphate (25 mmoles) and 3·5 ml bromine (70 mmoles) for 20 hr at 180°. After cooling, the contents were poured onto ice and the precipitate (silver bromide) filtered off. The filtrate was neutralized with sodium carbonate and continuously extracted with ether for 60 hr. After evaporation, 1·48 g of 2- and 4-bromopyridine-N-oxide together with unchanged I was obtained. This mixture was reduced with iron and acetic acid and the reaction product formed subjected to gas chromatography. By measuring the absorption at 2540 A, the residual amount of unchanged I was determined.

*Bromination of the monobromo derivatives of pyridine-*N*-oxide*

The bromination of the three monobromopyridine-N-oxides in both media and the analysis of the reaction mixtures were similarly carried out.

2-Bromo- and 3-bromopyridine-N-oxide were synthesized by oxidation of the bromopyridines; 4-bromopyridine-N-oxide was prepared according to Leonard and Wajngurt by reacting 4-nitropyridine-N-oxide with hydrobromic acid.[10]

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[10] F. Leonard and A. Wajngurt, *J. Org. Chem.* **21**, 1076 (1956).