On the Bromination of 1,7- and 1,8-Naphthyridine in Nitrobenzene

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Received April 12, 1976

By application of the Kress procedure for bromination it has been found that from the hydrobromide of 1,7-naphthyridine with 1.1 equivalents of bromine in nitrobenzene a mixture of 3- and 5-bromo- and 3,5-dibromo-1,7-naphthyridine is obtained in reasonable yield. With an excess of bromine 3,5-dibromo-1,7-naphthyridine is nearly exclusively formed. Similar brominations of the hydrobromide of 1,8-naphthyridine with 1.1 equivalents of bromine gave 3-bromo- and 3,6-dibromo-1,8-naphthyridine. By using an excess of bromine a high-yield conversion into 3,6-dibromo-1,8-naphthyridine is observed. Bromination of the hydrochloride salt of 1,7- and 1,8-naphthyridine affords the same bromo derivatives.

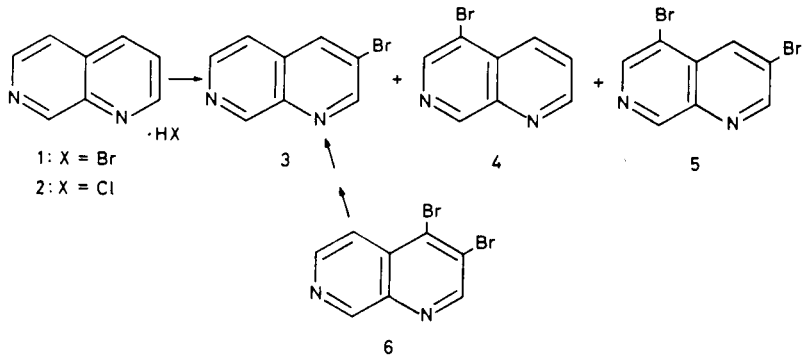
J. Heterocyclic Chem., 13, 961 (1976).

In connection with our studies on the formation of didehydroheteroarenes from heteroaryl halogenides and strong basic reagents (2) and on the formation of Meisenheimer σ-complexes between heteroaryl halogenides and amide ions (3) we became interested in the preparations of some bromo derivatives of 1,7- and 1,8-naphthyridine. There is only one report in the literature on the bromination of 1,7- and 1,8-naphthyridine (4). It describes the Eisch procedure (5) (formation of an heterocycle-bromine complex, which is decomposed by pyridine) for the preparation of 5-bromo- and 3,5-dibromo-1,7-naphthyridine and of 3-bromo and 3,6-dibromo-1,8-naphthyridine, respectively. Since the yields on these monobromo- and dibromo compounds in both reactions are low we became interested whether the recently developed method of Kress (6-9) (treatment of the hydrohalide of azine with bromine in nitrobenzene) could successfully be applied to the preparation of bromo derivatives of 1,7- and 1,8-naphthyridine.

Hydrobromides or hydrochlorides of 1,7- and 1,8-naphthyridine were heated in nitrobenzene at 175-180° with a different excess of bromine. The products present in the reaction mixture were isolated by preparative tlc or by crystallisation from different solvents; they were identified by pmr, ir, mass spectra and quantitative elemental analysis and further by comparison with reference compounds, if known. The quantitative composition of the reaction mixture was established by glc.

Bromination of the hydrobromide salt (**1**) of 1,7-naphthyridine with 1.1 equivalents of bromine affords besides unreacted starting substance, 3-bromo- (**3**), 5-bromo- (**4**) and as the main product 3,5-dibromo-1,7-naphthyridine (**5**) (See Table I). 3-Bromo-1,7-naphthyridine is an unknown compound and its structure was established by spectral data (see Experimental) and confirmed by an

Scheme I

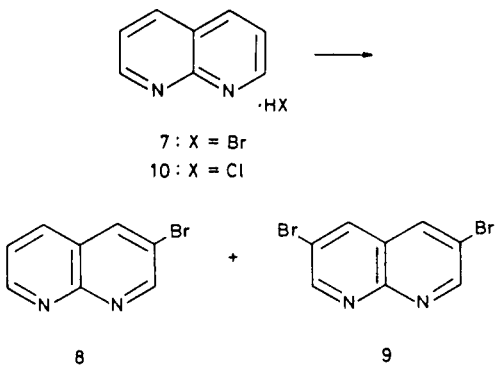


independent synthesis. It involves a reaction of 3,4-dibromo-1,7-naphthyridine (**6**) with hydrazine and a subsequent oxidation of the formed product with cuprous sulphate. Since by this method a mixture of 3-bromo-1,7-naphthyridine and 1,7-naphthyridine is obtained, it indicates that besides hydrazinolysis at position 4, also replacement of the bromine atom on position 3 has taken place.

With a small excess of bromine (2.5 equivalents) compound **5** is nearly exclusively formed in a high yield and is thus an excellent method for preparation of **5**. When instead of **1** the hydrochloride salt (**2**) of 1,7-naphthyridine was brominated with 1.1 equivalents of bromine also a mixture of **3**, **4** and **5** was obtained, **4** being the main product. However, since in addition small amounts of chloro derivatives of 1,7-naphthyridine were formed - as indicated by mass spectral analysis of the reaction product - which are very difficult to separate from the bromo derivatives, it seems preferable to use the hydrobromide salt (**1**) instead of **2** for the preparation of pure compounds **3**, **4** or **5**. Bromination of a slurry of the hydrobromide salt (**7**) of 1,8-naphthyridine in nitrobenzene with 1.1 equivalents of bromine gave in addition to unreacted starting material a mixture of 3-bromo-1,8-naphthyridine (**8**) and 3,6-dibromo-1,8-naphthyridine (**9**), being formed in nearly equal amounts (See Table II). With a small excess of bromine (2.5 equivalents) a high yield conversion of **7** into **9** was accomplished. The hydrochloride salt (**10**) of 1,8-naphthyridine gave nearly the same results as the hydrobromide salt (**7**), although the reaction products contained very small amounts of chloro derivatives of 1,8-naphthyridines, as indicated by mass spectrometry.

In summary we found that the Kress procedure for bromination of 1,7- and 1,8-naphthyridine is a far better method than the Eisch procedure.

Scheme II



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Our results are in excellent agreement with theoretical calculations of the ground-state π-electron densities of 1,7- and 1,8-naphthyridine (4), which show that the positions 3 and 5 in 1,7-naphthyridine and positions 3 and 6 in 1,8-

Table I

Glc Results of the Bromination of the Hydrohalide of 1,7-Naphthyridine

Starting Material	Amount of Bromine (Equivalent)	Amount of Nitrobenzene (ml.)	Time of Reaction (Hours)	Starting Material Recovered (%)	3-Bromo-1,7-naphthyridine (**3**) (%)	5-Bromo-1,7-naphthyridine (**4**) (%)	3,5-Dibromo-1,7-naphthyridine (**5**) (%)
1.0 g. of 1,7-Naphthyridine (7.8 mmoles), converted into its hydrobromide salt (**1**)	1.1	5	4	30.3	13.5	8.1	45.6
0.20 g. of 1,7-Naphthyridine (1.56 mmoles), converted into its hydrobromide salt (**1**)	2.5	3	6	—	<1	3.4	74.6
1.0 g. of 1,7-Naphthyridine (7.8 mmoles), converted into its hydrochloride salt (**2**)	1.1	5	4	35.2	1.5	30.9	6.4

Table II

Glc Results of the Bromination of the Hydrohalide of 1,8-Naphthyridine

Starting Material	Amount of Bromine (Equivalent)	Amount of Nitrobenzene (ml.)	Time of Reaction (Hours)	Starting Material Recovered (%)	3-Bromo-1,8-naphthyridine (**8**) (%)	3,6-Dibromo-1,8-naphthyridine (**9**) (%)
1.0 g. of 1,8-Naphthyridine (7.8 mmoles), converted into its hydrobromide salt (**7**)	1.1	5	4	26.5	32.1	29.6
0.20 g. of 1,8-Naphthyridine (1.50 mmoles), converted into its hydrobromide salt (**7**)	2.5	3	6	---	<1	72.6
1.0 g. of 1,8-Naphthyridine (7.8 mmoles), converted into its hydrochloride salt (**10**)	1.1	5	4	15.6	24.8	33.7

naphthyridine have the highest total π-electron density of all carbon positions. It can be expected that after protonation these positions still have the highest π-electron density (10) and are thus more favourable to electrophilic attack than the other carbon positions. It is of interest to note that in the reported bromination of 1,7-naphthyridine according to the Eisch procedure (4) *no* indication of the formation of 3-bromo-1,7-naphthyridine was obtained. Two comments can be made. It cannot be excluded that also in this bromination procedure besides 5-bromo- and 3,5-dibromo-1,7-naphthyridine, some 3-bromo-1,7-naphthyridine is formed, but that the applied method for separation, *i.e.*, column chromatography failed. Only by preparative glc were we able to isolate **3**. It is further questionable whether it is allowed to apply the above-mentioned calculation to substrates being involved in the Eisch procedure, since the parent heterocycle as such is not present in the reaction mixture, but a heterocycle-bromine *adduct* (7) featuring an enamine structure.

EXPERIMENTAL

Melting points (uncorrected) were determined on Kofler Plate. Pmr spectra were made in deuteriochloroform ($CDCl_3$) or deuteriotrifluoroacetic acid (CF_3COOD) using a Jeol-JNM C-60 spectrometer with TMS (τ = 10.0) as internal standard. The ir spectra were carried out in potassium bromide pellets with an Hitachi EPI-G3 or Perkin Elmer model 237 apparatus. The uv spectra were determined in ethanol with a Beckman Acta C III spectrometer. The mass spectra were recorded on an AEI MS-902 instrument.

1. Hydrobromide and Hydrochloride Salts of 1,7- and 1,8-Naphthyridine.

Through a solution of the appropriate naphthyridine (11,12) (0.2-1.0 g.) in absolute ether (30-100 ml.) dry hydrogen bromide or hydrogen chloride was bubbled for 10 minutes. The resulting precipitate was filtered, washed with absolute ether and dried in a desiccator over potassium hydroxide for 20 hours. The yields were quantitative and the following data collected:

Hydrobromide salt (**1**) of 1,7-naphthyridine, m.p. 245-247° (with sublimation and decomposition); hydrochloride salt (**2**) of 1,7-naphthyridine, m.p. 204-206° (with sublimation); hydrobromide salt (**7**) of 1,8-naphthyridine, m.p. 222-224° (with sublimation); hydrochloride salt (**10**) of 1,8-naphthyridine, m.p. 202-204° (with sublimation).

2. General Bromination Procedure.

See for specific reaction parameters, the number of mmoles of starting material and yield of the products obtained, Tables I and II. The reaction was carried out as follows: A two-neck flask provided with a dropping funnel, water condenser and a magnetic stirrer (in teflon cover) contained the appropriate hydrohalide of naphthyridine and nitrobenzene. At 175-180° bromine was added through a dropping funnel over a period of 20 minutes. Heating and stirring were continued for specified time. The mixture was cooled and the solution was diluted with three volumes of benzene. The precipitate was collected on a filter, washed with benzene and dried. The collected solid was mixed with about 50 ml. of water and made alkaline with sodium carbonate. Then the mixture was continuously extracted with chloroform for 18 hours. The chloroform solution was dried with anhydrous magnesium sulphate and filtered. From this extract the products of the reaction were isolated in the manner given below in sections 3a, 3b, 4, 5a, 5b and 6.

3. Isolation and Identification of the Products Obtained on Bromination of **1**.

a. With 1.1 Equivalents of Bromine.

The concentrated chloroform extracts (see above) were brought by an autoliner Desaga Model 121000 on four plates (20 x 40 cm) covered by a 2 mm. layer of silica gel PF_{254} (by Automatic Coater Camag 4132). The chromatograms were developed with a mixture of ethyl ether: petroleum ether (40-60°, ratio 1:1) as eluent. Three bands were obtained showing uv absorbance; they were all extracted with chloroform in a Soxhlett apparatus for 12 hours. After evaporation of the solvent from the extract of the first band (the lowest R_f) the residue was sublimed at 100°/0.5 mm, yielding 220 mg. (22%) of 1,7-naphthyridine. The residue obtained from the extract of the third band (the highest R_f) was sublimed twice at 150°/0.5 mm, yielding 420 mg. (18%) of 3,5-dibromo-1,7-naphthyridine (**5**), white needles m.p. 154-155° (Lit.

(4) 149-151°). The mass spectrum showed the characteristic 1:2:1 ratio for the peaks of m/e: 286, 288, 290. The nmr spectral data are consistent with those reported in the literature (4).

Anal. Calcd. for $C_8H_4Br_2N_2$: C, 33.4; H, 1.4. Found: C, 33.6; H, 1.6.

The chloroform extract from the second band was again subjected to tlc separation using two plates (20 x 40 cm, 2 mm layer of silica gel PF_{254}) and the chromatograms were developed 5 times with a mixture of ethyl ether:petroleum ether (40-60°), ratio 3:2 as eluent. A separation into two bands was obtained, both showing uv absorbance. Both bands were extracted with chloroform in a Soxhlett apparatus for 12 hours. After stripping of the solvent the residue was sublimed twice at 100°/0.5 mm.

From the extract of the first band (the lower R_f) 96 mg. (6.3%) of 3-bromo-1,7-naphthyridine (**3**) was obtained as white needles, m.p. 92-93°. Its structure was proven by ir identity with an authentic specimen (see section 7). From the extract of the second band (the higher R_f) 45 mg. (3.0%) of 5-bromo-1,7-naphthyridine (**4**) was obtained as white needles, m.p. 75-76° (Lit. (4) 69-70°); mass spectrum: m/e: 210 (M^+, ^{81}Br), 208 (M^+, ^{79}Br), ratio 1:1, The pmr spectrum is identical with that already reported (4).

Anal. Calcd. for $C_8H_5BrN_2$: C, 46.0; H, 2.4. Found: C, 46.1; H, 2.6.

b. With 2.5 Equivalents of Bromine.

The residue obtained by evaporation of the solvent from the chloroform extract (see section 2) was sublimed at 150°/0.5 mm and the sublimate was recrystallized from ethanol yielding 186 mg. (42%) of 3,5-dibromo-1,7-naphthyridine (**5**).

4. Isolation and Identification of the Products Obtained on Bromination of **2.**

For experimental parameters, see Table I.

The residue obtained after evaporation of chloroform (see section 2) was separated by tlc as described in section 3a. Three bands were obtained. From the first band (the lowest R_f) after sublimation at 100°/0.5 mm, 250 mg. (25%) of 1,7-naphthyridine were isolated. From the second band 190 mg. of white crystals (m.p. 69-71°) were obtained. The mass spectrum and elemental analysis showed that it is a mixture containing about 91% monobromo- and 9% monochloro-1,7-naphthyridines. Further tlc separation of this mixture by the procedure given in section 3a affords 120 mg. of 5-bromo-1,7-naphthyridine still containing some monochloro derivative and 4 mg. of a mixture of 3-bromo- and 3-chloro-1,7-naphthyridine (m.p. 82-85°). These last-mentioned products were identified by comparison of their ir spectra and retention times with reference samples (13). Extraction of the third band (the highest R_f), evaporation of the solvent and sublimation at 150°/0.5 mm of the residue obtained afforded 60 mg. of white needles at melting range 146-149°. The mass spectrum, pmr and elemental analysis clearly showed that it is a mixture of 3,5-dibromo-, bromochloro- and dichloro-1,7-naphthyridines in a ratio of about 10:3:0.5. After isolation by preparative glc 3,5-dibromo-1,7-naphthyridine (**5**) was identified by comparison of its ir spectrum and retention time with the reference sample (see section 3a).

5. Isolation and Identification of the Products of Bromination of **7.**

a. With 1.1 Equivalents of Bromine.

The general bromination procedure was carried out as described in section 2. For the experimental details, see Table II. After distilling off the chloroform the residue was dissolved in 500 ml. of boiling methanol and this solution was treated with activated carbon, filtered, concentrated to 100 ml. and cooled. The precipitate was collected (mother liquid A) and recrystallized from ethanol yielding 320 mg. (14.4%) of 3,6-dibromo-1,8-naphthyridine (white needles, m.p. > 300° (in sealed capillary), (Lit. (4) 300°). The mass spectrum showed the characteristic 1:2:1 ratio for the peaks at m/e: 286, 288, 290. The pmr spectrum in deuteriofluoroacetic acid has the following pattern: $\tau = 0.55$ (H-2, H-7); $\tau = 0.84$ (H-4, H-5); $J_{2,4} = J_{5,6} = 2.0$ cps.

Anal. Calcd. for $C_8H_4Br_2N_2$: C, 33.4; H, 1.4; N, 9.7. Found: C, 33.5; H, 1.5; N, 9.7.

From the mother liquid A the solvent was evaporated and the residue was crystallized twice from cyclohexane, yielding 120 mg. (8%) of 3-bromo-1,8-naphthyridine, white plates, m.p. 164-166° (Lit. 164-165° (15), 155-156° (4)); mass spectrum m/e: 208 (M^+, ^{79}Br), 210 (M^+, ^{81}Br), ratio 1:1. The pmr and ir spectrum are in agreement with those already reported (4,14).

Anal. Calcd. for $C_8H_5BrN_2$: N, 13.4. Found: 13.1.

From the mother liquor of the cyclohexane filtrate 1,8-naphthyridine could be recovered by evaporation of the solvent and sublimation of the residue twice at 100°/0.5 mm, yield 120 mg. (12%) of 1,8-naphthyridine.

b. With 2.5 Equivalents of Bromine.

The residue obtained by evaporation of the solvent from the chloroform extracts (see section 2) was dissolved in 200 ml. of boiling methanol and this solution was after treatment with activated charcoal, filtered, concentrated to 30 ml. and cooled. The precipitate was collected by filtration, yielding 178 mg. (40%) of 3,6-dibromo-1,8-naphthyridine.

6. Isolation of the Product of Bromination of **10.**

The products of the reaction were isolated in the same manner as described in section 5a. They were identified by comparison of their properties with those of the compounds obtained in section 5a. The mass spectrum of **8** showed the presence of about 1% monochloronaphthyridine and the mass spectrum of **9** the presence of about 2% of bromochloronaphthyridine.

7. 3-Bromo-1,7-naphthyridine (**3**) from 3,4-Dibromo-1,7-naphthyridine (**6**).

To a solution of 4.0 g. of 3,4-dibromo-1,7-naphthyridine (16) (**6**) in 550 ml. of ethanol, 10.5 ml. of 100% hydrazine hydrate were added. The solution was stirred at room temperature for 24 hours, then cooled to 0° and stirred for an additional 2 hours. The precipitate (0.6 g., m.p. 174-175° dec.) was filtered and washed with ethanol. The filtrate was concentrated quickly to 50 ml. by rotar evaporator under reduced pressure, cooled and the precipitate (2.7 g., m.p. 165-172° dec.) was collected (mother liquid A) and washed with cold ethanol. The combined precipitates (3.3 g.) were dissolved in 160 ml. of water containing 13 ml. of acetic acid; this solution was heated to boiling point. Then portions of a warm solution of 4 g. of cupric sulfate pentahydrate in 40 ml. of water were added. The resulting mixture was heated at boiling point for 15 minutes, cooled, made alkaline with a 50% aqueous sodium hydroxide solution and then continuously extracted with chloroform for 18 hours. The chloroform extracts were dried on magnesium sulfate, filtered and concentrated to about 20 ml. The mixture of compounds present in this solution was separated according to the procedure as described in section 3a. From the first band (the lowest R_f) 220 mg. of 1,7-naphthyridine were obtained. The residue obtained from the extract of the second band was sublimed twice at 100°/0.5 mm, yielding 160 mg. (5.5%) of 3-bromo-1,7-naphthyridine, m.p. 92-93°; mass spectrum m/e: 208 (M^+, ^{79}Br), 210 (M^+, ^{81}Br), ratio of both peaks 1:1; pmr

(deuteriochloroform): τ = 1.05 (H-2, doublet); τ = 1.69 (H-4, doublet); τ = 2.43 (H-5, doublet); τ = 1.36 (H-6, doublet); τ = 0.55 (H-8, singlet); $J_{5,6}$ = 6.0 Hz, $J_{2,4}$ = 2.2 Hz, $J_{5,8}$ = $J_{4,8}$ = 0.6 Hz (from the broad spectrum); ir: (cm^{-1}) 3010, 1610, 1580, 1470, 1430, 1405, 1075, 950, 925, 905, 810, 645, 635; uv: λ max = 217 nm (log ϵ = 4.18), 234 nm (log ϵ = 4.50), 268 nm (log ϵ = 3.53), 204 nm (log ϵ = 3.31), 317 nm (log ϵ = 3.27).

Anal. Calcd. for $C_8H_5BrN_2$: C, 46.0; H, 2.4. Found: C, 46.0; H, 2.5.

From the third band (the highest R_f) 180 mg. (4.5%) of starting material **6** was recovered.

When the mother liquid A was evaporated to dryness and the residue was oxidized with cupric sulfate pentahydrate only 1,7-naphthyridine (320 mg.) was isolated, total yield of 1,7-naphthyridine 540 mg. (30%).

8. Glc Analyses.

The analyses of the reaction mixture obtained by bromination of hydrohalides of 1,8-naphthyridine were carried out with a Hewlett-Packard instrument, model 5700 A with Flame-ionisation detection and nitrogen as carrier gas, using stainless steel column (length 200 cm, internal diameter 1/8 inch), filled with 9.2% OV-275 on Chromosorb W.HP 100-200 mesh. Column temperature 230°, flow rate of the carrier gas 10 ml./23 sec. Relative retention times: 1,7-naphthyridine 1.00 (used as reference); 1,8-naphthyridine 5.36; 3-bromo-1,8-naphthyridine 7.64; 3,6-dibromo-1,8-naphthyridine 10.45.

The analyses of the reaction mixtures obtained by bromination of hydrohalide of 1,7-naphthyridine were carried out with a Becker gas chromatograph, The Netherlands, with flame-ionisation detection and nitrogen as carrier gas, using the same column as described above. Column temperature: 180°.

Relative retention times were: 1,7-naphthyridine, 0.14; 5-bromo-1,7-naphthyridine, 0.19; 3-bromo-1,7-naphthyridine, 0.22; 3,5-dibromo-1,7-naphthyridine, 0.27; 1,8-naphthyridines, 1.00 (used as reference).

Acknowledgment.

We are indebted to the Ministry of Education and Science in The Netherlands for providing a fellowship to one of us (M.W.), to Dr. C. A. Landheer and Mr. W. P. Combé for measurement and interpretation of mass spectra, to Mr. W. Ch. Melger for advice on the chromatographic analyses, to Mr. A. van Veldhuizen for measurements of pmr, ir and uv spectra and to Mr. H. Jongejan for carrying out the microanalyses.

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