ON THE BROMINATION OF THE THREE ISOMERIC THIENO[*c*]FUSED 1,5-NAPHTHYRIDINES AND THEIR 5-*N*-OXIDES

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Abstract-Thieno[3,4-*c*]-1,5-naphthyridine (**1**) and its 5-*N*-oxide (**5**) were conveniently brominated at room temperature with tetrabutylammonium perbromide in the presence of a large excess of sodium hydrogen carbonate. Compound(**1**)gave the 1- and 3-bromo derivatives in a 4:1 ratio, while **5** was regioselectively brominated in the 3-position. Thieno[2,3-*c*]-1,5-naphthyridine (**7**), its 5-*N*-oxide (**11**) and thieno[3,2-c]-1,5-naphthyridine (**14**) did not react under these conditions, but gave products in the reaction with bromine in refluxing thionyl chloride. Compound(**7**)gave the 1-bromo derivative as main product and interestingly the 1,7-dibromo derivative as by-product. The reaction of **11** and **14** with bromine in thionyl chloride gave mainly chlorinated products.

INTRODUCTION

In connection with our interest in the effects of the mode of annelation on physical properties and reactivities of tricyclic heterocyclic systems with angular annelation, we have previously described convenient syntheses of all

nine isomeric dithieno[*b,d*]pyridines.[1-3] Experimental[4-6] and theoretical[4,7] studies of electrophilic substitution of these isomers have been undertaken. Also direct bromination,[8,9] as well as lithiation, has been studied.[10]

The same strategy as in the syntheses of the dithieno[*b,d*]pyridines was used by us in the synthesis of thieno-1,5- and -1,6-naphthyridines, namely Pd(0)-catalyzed coupling between 2- and 4-formyl-3-thiopheneboronic acids and 2-tributylstannyl-3-thiophenecarbaldehyde and 3-amino-2-bromo- and 4-acetamido-3-bromopyridines.[11] Various methods for the preparation of thieno[*c*]fused 1,5-naphthyridine-5*N*- and 9-*N*-oxides have also recently been described.[12] Nitration of some of the above-mentioned systems,[13,14] as well as nitration[15,16] of the thieno analogues of phenanthridine-*N*-oxide, has also been studied.

In the present paper, a study of the bromination of the three isomeric thieno[*c*]-fused 1,5-naphthyridines and two of their 5-*N*-oxides is described. These ring systems consist of one strongly π-deficient moiety, the 1,5-naphthyridine system, and one π-excessive moiety, the thiophene ring. Electrophilic substitution of thieno[*c*]-fused naphthyridines is therefore expected to present an interesting preparative challenge. In order to find suitable conditions for the bromination, we looked for the procedures used for the bromination of 1,5-naphthyridine and of thieno[3,2-*c*]pyridines. 1,5-Naphthyridine was first brominated by Czuba using bromine in sulfuric acid-sulfur-trioxide at 135 °C in a sealed tube. He obtained 7-10% of the 3-bromo and 30-35% of the 3,7-dibromo derivatives.[17] Later Paudler and Kress[18] applied the Eisch procedure, successfully used for the bromination of quinoline,[19] forming first a heterocyclic-bromine complex, which was decomposed by refluxing in pyridine. In this way 27% of the 3-bromo and 10% of the 3,7-dibromo derivatives were obtained. Another bromination procedure, which was applied to 1,7- and 1,8-naphthyridines, uses the hydrochlorides or hydrobromides in nitrobenzene at 175-180 °C. With excess bromine, good

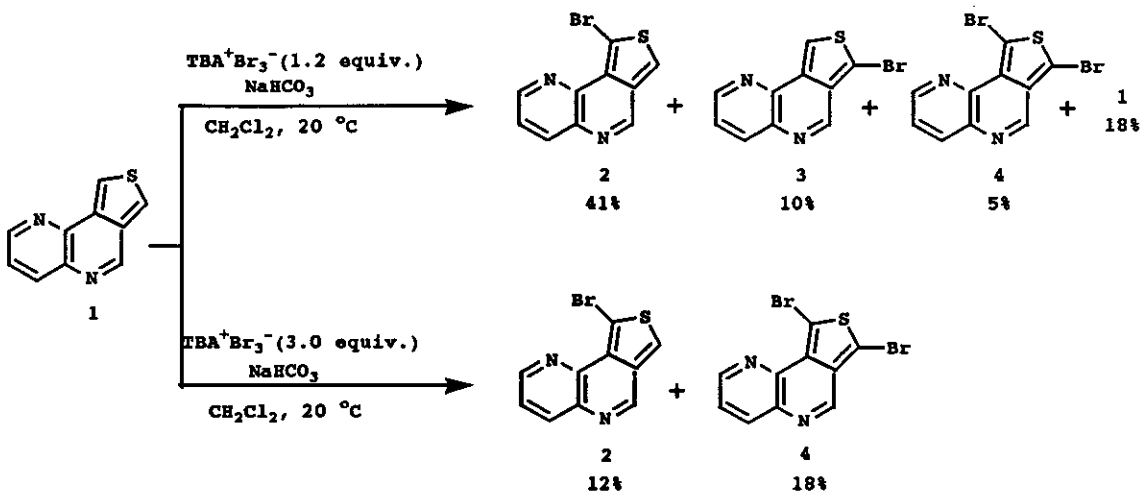
yields of dibromo derivatives were obtained.[20]

In their study of the bromination of thieno[2,3-*c*]pyridine and thieno-[3,2-*c*]pyridine, Gronowitz and Sandberg[21] found four methods which all gave the 3-bromo derivative in good yields. These were bromination with molecular bromine in 48% hydrobromic acid, the method of Garcia *et al.*[22] using bromine in thionyl chloride, the method of Derbyshire and Waters[23] using bromine in concentrated sulfuric acid-silver sulfate, and the method of Gottardi[24] using dibromoisocyanuric acid (DBI) in concentrated sulfuric acid. With more aggressive reagents, such as bromine in concentrated sulfuric acid-silver sulfate or DBI, thieno[3,2-*c*]pyridine gave appreciable amounts of the 2,3-dibromo derivative as by-product. Bromination with bromine in pyridine-carbon tetrachloride gave low yields, and mixtures of 3-bromo- and 2,3-dibromothieno[*c*]pyridines were obtained.

RESULTS AND DISCUSSION

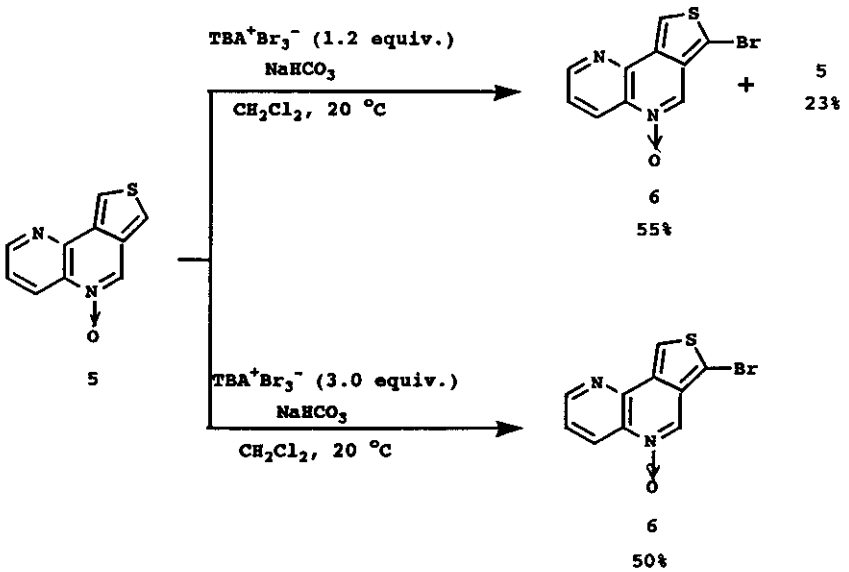
Thieno[3,4-*c*]-1,5-naphthyridine (**1**), which was expected to be the most reactive of the systems studied, gave only 8% of the 1-bromo derivative (**2**) with DBI in concentrated sulfuric acid and 45% of the starting material was recovered. The use of neutral conditions (bromine in chloroform in the presence of buffer), as described by Klemm *et al.*[25] for the bromination of thieno[*b*]pyridines, also gave low yields and a mixture of 7% of **2** and 8% of the 3-bromo isomer (**3**)were obtained. However, by using tetrabutylammonium perbromide in dichloromethane in the presence of a large excess of sodium hydrogen carbonate, **2**, **3** and 1,3-dibromothieno[3,4-*c*]naphthyridine (**4**) were obtained in 41, 10 and 5% yields, respectively. An attempted dibromination of **1**, using three equivalents of tetrabutylammonium perbromide gave low yields of products (Scheme 1).

The more reactive thieno[3,4-*c*]-1,5-naphthyridine-5-*N*-oxide (**5**) gave selective substitution in the 3-position with tetrabutylammonium perbromide



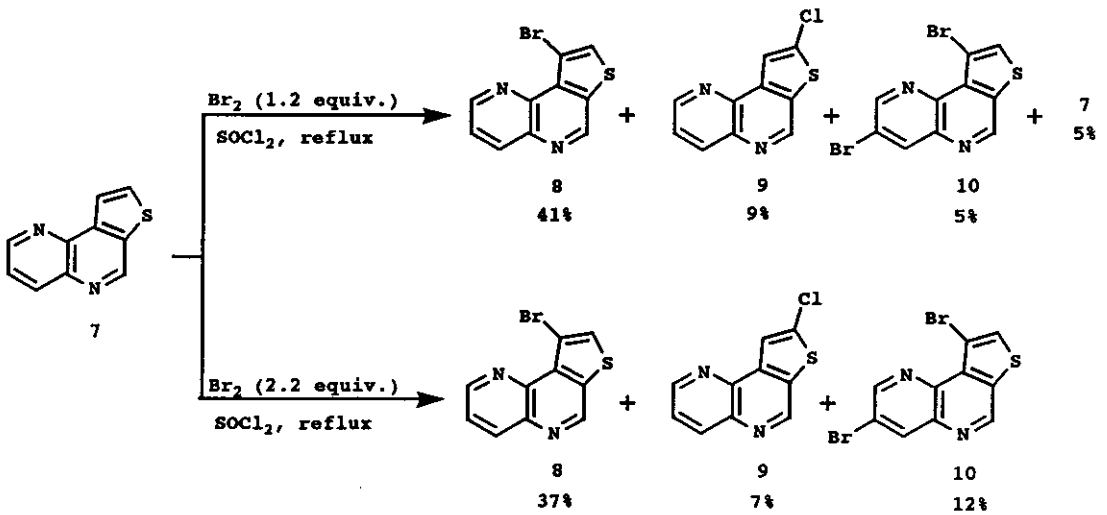
Scheme 1

yielding 55% of 3-bromothieno[3,4-*c*]-1,5-naphthyridine-*N*-oxide (**6**). The use of three equivalents of tetrabutylammonium perbromide did not lead to any dibromination (Scheme 2), which was in contrast to the easy dibromination in the thiophene part of thieno[3,4-*c*]quinoline-*N*-oxide.[16] On the other hand, thieno[2,3-*c*]-1,5-naphthyridine (**7**) and thieno[2,3-*c*]-1,5-naphthyridine-*N*-oxide (**11**) did not react with tetrabutylammonium perbromide. The use of bromine in concentrated sulfuric acid-silver sulfate was also unsuccessful, even upon heating the reaction mixture. However, by using bromine in thionyl chloride **7** gave a mixture of 1-bromothieno[2,3-*c*]-1,5-naphthyridine (**8**), 2-chlorothieno[2,3-*c*]-1,5-naphthyridine (**9**) and 1,7-dibromothieno[2,3-*c*]-naphthyridine (**10**) in 41, 9, and 5% yields, respectively. It is interesting to note that the second bromine entered into the 7-position of naphthyridine moiety, which is the most reactive position of the 1,5-naphthyridine,[18] but not the 2-position which is the case in continued bromination of 3-bromothieno[2,3-*c*]pyridine.[21] The route of formation of **9** is not obvious. It could have been formed through halogen exchange with the 2-bromo derivative or by direct reaction of **7** with thionyl chloride. The use of 2.2 equivalents of bromine led to an increase of the yield of **10** to 12% (Scheme 3).



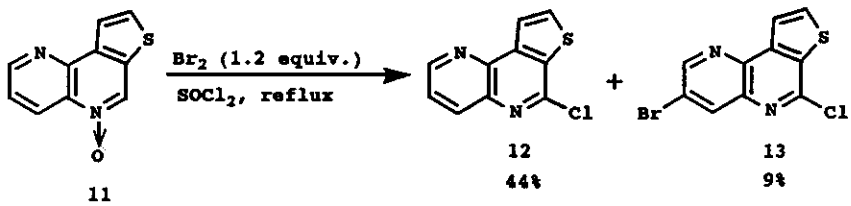
Scheme 2

The reaction of thieno[2,3-*c*]-1,5-naphthyridine-5-*N*-oxide (**11**) led to the Meisenheimer reaction with thionyl chloride, giving 44% of 4-chlorothieno[2,3-*c*]naphthyridine (**12**) and 7-bromo-4-chlorothieno[2,3-*c*]naphthyridine (**13**). The analogous Meisenheimer reaction of 1,5-naphthyridine-*N*-oxide with phosphoryl chloride gave 42% of 2-chloro-, 3% of 3-chloro and 54% of 4-chloro-1,5-naphthyridine.[18] Compound (**13**) is most probably formed by the bro-



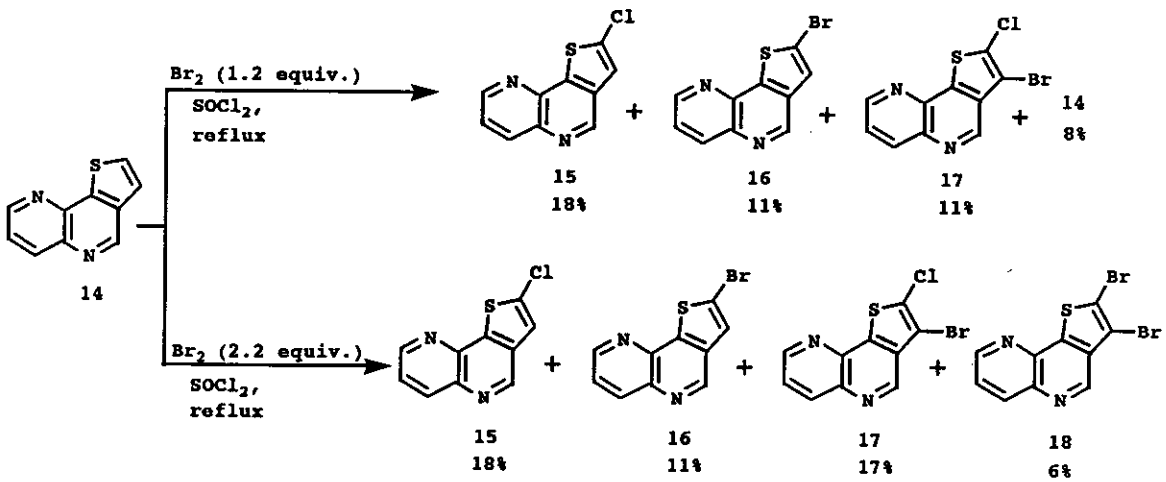
Scheme 3

mination of **12**. The substitution in the naphthyridine ring instead of the 1-position is indeed surprising (Scheme 4).



Scheme 4

The results of the bromination of thieno[3,2-*c*]naphthyridine (**14**) with bromine in thionyl chloride were disappointing. Mainly chlorinated products were obtained and the reaction gave low overall yields, in spite of the fact that this method gave good results in the bromination of thieno[3,2-*c*]pyridine.[21] Among the compounds isolated were 2-chlorothieno[3,2-*c*]naphthyridine



Scheme 5

(**15**), 2-bromothieno[3,2-*c*]-1,5-naphthyridine (**16**), 3-bromo-2-chlorothieno-[3,2-*c*]-1,5-naphthyridine (**17**) and 2,3-dibromothieno[3,2-*c*]-1,5-naphthyridine (**18**) (Scheme 5).

STRUCTURE ASSIGNEMENTS

Mass spectroscopy was valuable in establishing the number of bromine and chlorine atoms in the products. The substitution positions were proven by ^{1}H nmr spectra and proton-coupled ^{13}C nmr spectra. Correlations between carbon and proton resonances were made by ^{1}H-^{13}C HETCOR nmr spectra. Whenever

Table 1. ^{13}C Nmr chemical shifts (in ppm) of the halogenated thienonaphthyridines (**2-4,6, 8-10, 12, 13, 15** and **16**).

Compound	1C	2C	3C	4C	6C	7C	8C
2			125.3	149.3	136.7	123.4	148.6
3	119.8			148.1	137.1	123.6	149.4
4				147.7	136.8	123.8	148.8
6	121.7			129.5	129.2	123.8	151.2
8		130.4		145.6	137.4	123.5	149.6
9	122.0			144.4	137.6	123.7	150.3
10		131.5		146.7	138.6		150.5
12	123.8	133.4			136.5	123.9	150.1
13	123.7	134.0			138.1		151.0
15			122.5	145.9	138.0	123.9	150.5
16			126.4	145.8	137.9	123.9	150.5

present, long-range couplings between the thiophene ring and the azomethine linkage were used to establish the substitution positions in the thiophene ring. The magnitudes of these couplings (^{1}H-^{1}H and ^{1}H-^{13}C) were in close agreement with the couplings observed in the parent thieno[*c*]naphthyridines.[11,12] The position of the bromine atom in the thiophene ring of **8** and **10** followed from the presence of thiophenic $^{1}J_{CH}$ coupling constants of high magnitude (190.3 Hz and 191.5 Hz), characteristic of an α-CH group, and in **9** from the $^{1}J_{CH}$ coupling of 178.4 Hz.[11,16] The structure of **17** was assumed to be correct as its structure could be derived as a result of the bromination of

2-chlorothieno[2,3-*c*]1,5-naphthyridine (**15**). Unambiguous assignments of the

Table 2. J_{CH} values (Hz) of the halogenated thienonaphthyridines (**2-4,6,8-10, 12, 13, 15** and **16**).

Compound		1C	2C	3C	4C	6C	7C	8C
2	^1J			190.6	182.1	163.9	164.4	179.5
	^2J						8.8	3.2
	^3J			1.4	3.4	6.4		7.6
3	^1J	193.5			184.0	164.0	164.6	179.1
	^2J					8.7	3.0	
	^3J			6.4		7.6		
4	^1J				184.9	164.4	164.7	179.8
	^2J						8.8	3.1
	^3J					6.5		5.6
6	^1J	194.2			188.5	171.4	167.5	180.9
	^2J						8.9	3.3
	^3J					6.3		7.8
8	^1J		190.3		184.1	164.8	164.7	179.6
	^2J						9.1	3.2
	^3J					6.3		7.9
9	^1J	178.4			184.1	164.4	164.7	179.3
	^2J						9.0	3.3
	^3J					6.2		7.8
10	^1J		191.5		184.6	170.3		188.9
	^3J					4.7		5.6
12	^1J	174.8	186.0			165.6	164.9	179.5
	^2J	4.5	7.8				9.0	3.3
	^3J					6.2		7.8
13	^1J	174.5	184.8			171.0		188.3
	^2J	5.4	9.2					
	^3J					4.7		5.7
15	^1J			175.2	181.6	165.0	165.0	179.6
	^2J						8.9	3.2
	^3J			1.5	1.6	6.2		7.9
16	^1J			176.4	181.5	164.9	165.1	179.6
	^2J						9.0	3.2
	^3J			1.8	1.6	6.1		7.8

^{13}C nmr signals and the carbon-proton coupling constants of the halogenated

thieno[*c*]naphthyridines are given in Tables 1 and 2.

EXPERIMENTAL

General

Nmr spectra were recorded on a Varian XL-300 spectrometer. Deuteriochloroform was used as solvent for all substances. Sample concentrations were 5 mg/ml for the ^{1}H nmr spectra. Sample concentrations for the ^{13}C nmr and HETCOR spectra were 20-40 mg/ml. The mass spectra were recorded on a JEOL JMS-SX 102 spectrometer. The elemental analyses were carried out by Dornis und Kolbe, Mülheim, Germany. All melting points are uncorrected. Flash column chromatography was carried out using Merck silica gel 60. The columns used for hplc were a silica Dynamax column (500 x 10 mm) or a reversed phase Polygosil C_{18} column (55 x 10 mm). Thionyl chloride was purchased from Merck. Isopropyl alcohol was purchased from Sigma. Dichloromethane, heptane and ethyl acetate were distilled over molecular sieves and chloroform was distilled over phosphorous pentoxide prior to use.

Procedure for the bromination of 1 and 5 with tetrabutylammonium perbromide in dichloromethane.

A mixture of 1.0 mmol of the appropriate thieno[*c*]naphthyridine, 0.84 g (10.0 mmol) of sodium hydrogen carbonate and 0.58 g (1.2 mmol) of tetrabutylammonium perbromide[26] in 10 ml of dichloromethane was stirred at room temperature for 48 h. Water was added, the phases were separated and the aqueous phase was extracted several times with chloroform. The combined organic phases were dried over magnesium sulfate and subjected to flash chromatography. Ethyl acetate was used as eluent for the separation of the components in the reaction product of **1**. The second fraction containing the two monobromo derivatives was further separated by hplc. Chloroform/methanol (95:5) was used as eluent for the product of **5**.

1-Bromo-thieno[3,4-*c*]-1,5-naphthyridine (2).

After hplc separation using chloroform/isopropanol (98:2) as eluent 109 mg (41%) and 32 mg (12%) of **2** were obtained as pale yellow needles, mp 143-144 °C (petroleum ether, charcoal); ^{1}H nmr: δ 8.99 (s, 1H, H_4), 8.93 (dd, 1H, H_8), 8.28 (dd, 1H, H_6), 8.10 (s, 1H, H_3), 7.59 (dd, 1H, H_7), J_{67}= 8.2, J_{69}= 1.7, J_{78}= 4.5 Hz; ms: m/z 266, 264 (M^+), 185 (M^+-Br), 158 (185-HCN). *Anal.* Calcd. for $C_{10}H_5N_2BrS$: C,45.30; H,1.90; N,10.57. Found: C,45.21; H,1.95; N,10.44.

3-Bromothieno[3,4-*c*]-1,5-naphthyridine (3)

After hplc using chloroform/isopropanol (98:2) as eluent 27 mg (10%) of **3** were obtained as white needles, mp 184-186 °C (petroleum ether, charcoal); ^{1}H nmr: δ 9.02 (s, 1H, H_4), 8.83 (dd, 1H, H_8), 8.55 (d, 1H, H_1), 8.34 (dd, 1H, H_6), 7.58 (dd, 1H, H_7), J_{14}= 0.9, J_{67}= 8.2, J_{69}= 1.7, J_{78}= 4.5 Hz; ms: m/z 266, 264 (M^+), 185 (M^+-Br), 158 (185-HCN). *Anal.* Calcd for $C_{10}H_5N_2BrS$: C,45.30; H,1.90; N,10.57. Found: C,45.28; H,1.86; N,10.48.

1,3-Dibromothieno[3,4-*c*]-1,5-naphthyridine (4)

After hplc using chloroform/isopropanol (99.8/0.2) as eluent 17 mg (5%) and 62 mg (18%) of **4** was obtained as pale yellow needles, mp 164-166°C (petroleum ether, charcoal); ^{1}H nmr: δ 8.92 (s, 1H, H_4), 8.92 (dd, 1H, H_8), 8.29 (dd, 1H, H_6), 7.59 (dd, 1H, H_7), J_{67}= 8.2, J_{69}= 1.7, J_{78}= 4.5 Hz; ms: m/z (%) 346, 344, 342 (M^+), 184 (M^+-2Br), (184-HCN). *Anal.* Calcd for $C_{10}H_4N_2Br_2S$: C,34.91; H,1.17; N,8.14. Found: C,35.00; H,1.21; N,8.19.

3-Bromothieno[3,4-*c*]-1,5-naphthyridine-5-*N*-oxide (6)

After chromatography (97:3) 155 mg (55%) and 141 mg (50%) of **6** were obtained as pale yellow prisms, mp 200-202°C (acetonitrile); ^{1}H nmr: δ 8.98 (dd, 1H,

H_6), 8.92 (dd, 1H, H_8), 8.63 (broad s, 1H, H_4), 8.50 (d, 1H, H_1), 7.65 (dd, 1H, H_7), J_{14}= 0.9, J_{67}= 8.5, J_{69}= 1.6, J_{78}= 4.5 Hz; ms: m/z 282, 280 (M^+), 266, 264 (M^+-O), 201 (M^+-Br). *Anal.* Calcd for $C_{10}H_5N_2OBrS$: C,42.72; H,1.79; N,9.96. Found: C,42.64; H,1.72; N,9.87.

General procedure for the bromination of 7, 11 and 14 with bromine in thionyl chloride (Method B).

To a stirred mixture of 1.0 mmol of the appropriate thieno[*c*]naphthyridine in 2.5 ml (0.37 mol) of thionyl chloride, 0.19 g (1.2 mmol) of bromine was slowly added. The reaction mixture was stirred at reflux for 24 h, after which the thionyl chloride was distilled off. The residue was treated with saturated sodium hydrogen carbonate and extracted several times with chloroform. The combined organic phases were dried over magnesium sulfate and subjected to flash chromatography using ethyl acetate/heptane (60:40) as eluent. The second fraction containing the two monohalo derivatives was further separated by hplc.

1-Bromothieno[2,3-*c*]-1,5-naphthyridine (8)

After hplc using chloroform/isopropanol (99.6:0.4) as eluent 109 mg (41%) and 98 mg (37%) of **8** were obtained as white needles, mp 172-174 °C (petroleum ether); ^{1}H nmr: δ 9.31 (s, 1H, H_4), 9.12 (dd, 1H, H_8), 8.53 (dd, 1H, H_6), 7.90 (s, 1H, H_2), 7.72 (dd, 1H, H_7), J_{67}= 8.4, J_{68}= 1.8, J_{78}= 4.3 Hz; ms: m/z 266, 264(M^+), 239, 237(M^+-HCN), 185(M^+-Br). *Anal.* Calcd for $C_{10}H_5N_2BrS$: C,45.30; H,1.90; N,10.57. Found: C,45.19; H,1.98; N,10.46.

2-Chlorothieno[2,3-*c*]-1,5-naphthyridine (9)

After hplc using chloroform/isopropanol (99.6/0.4) as eluent 20 mg (9%) and 15 mg (7%) of **9** were obtained, mp 136-138 °C; ^{1}H nmr: δ 9.31 (s, 1H, H_4),

8.99 (dd, 1H, H_8), 8.49 (dd, 1H, H_6), 8.17 (d, 1H, H_1), 7.68 (dd, 1H, H_7), J_{14}= 0.7, J_{67}= 8.4, J_{68}= 1.6, J_{78}= 4.3 Hz; ms: m/z 222, 220 (M^+), 193 (M^+-HCN), 185 (M^+-Cl); HRms calcd for $C_{10}H_5N_2ClS$: 219.9862, found: 219.9863.

1,7-Dibromothieno[2,3-*c*]-1,5-naphthyridine (10)

After hplc using chloroform/isopropanol (99.9:0.1) as eluent 17 mg (5%) and 41 mg (12%) of **10** were obtained as white needles, mp: 230-231 °C (petroleum ether 60-70); ^1H nmr: δ 9.32 (s, 1H, H_4), 9.12 (d, 1H, H_8), 8.69 (d, 1H, H_6), 7.93 (s, 1H, H_2), J_{68}= 2.2 Hz; ms: m/z 346, 344, 342 (M^+), 265, 263 (M^+-Br), 184 (M^+-2Br), 157 (184-HCN). *Anal.* Calcd for $C_{10}H_4N_2Br_2S$: C,34.91; H,1.17; N,8.14. Found: C,35.04; H,1.23; N,8.08.

4-Chlorothieno[2,3-*c*]-1,5-naphthyridine (12)

After hplc using cloroform/isopropanol (98.5/1.5) as eluent 97 mg (44%) of **12** was obtained as white needles, mp: 188-189 °C (petroleum ether); ^1H nmr: δ 9.00 (dd, 1H, H_8), 8.44 (dd, 1H, H_6), 8.33 (d, 1H, H_1), 7.96 (d, 1H, H_2), 7.68 (dd, 1H, H_7), J_{12}= 5.4, J_{67}= 8.4, J_{68}= 1.7, J_{78}= 4.4 Hz; ms: m/z 222, 220 (M^+), 185 (M^+-Cl), 158 (185-HCN). *Anal.* Calcd for $C_{10}H_5N_2ClS$: 54.43; H,2.28; N,12.69. Found: C,54.51; H,2.22; N,12.61.

4-Chloro-7-bromothieno[2,3-*c*]-1,5-naphthyridine (13)

After hplc using cloroform/isopropanol (99.9:0.1) as eluent 27 mg (9%) of **13** was obtained, mp: 176-178 °C; ^1H nmr: δ 9.00 (d, 1H, H_8), 8.59 (d, 1H, H_6), 8.28 (d, 1H, H_1), 7.98 (d, 1H, H_2), J_{12}= 5.3, J_{68}= 2.2; ms: m/z 302, 300, 298(M^+), 256,254(M^+-CS), 219(M^+-Br), 184 (219-Cl), 157 (184-HCN) ; HRms calcd for $C_{10}H_4N_2BrClS$: 297.8968, found: 297.8964.

2-Chlorothieno[3,2-*c*]-1,5-naphthyridine (15)

After hplc using reverse phase and acetonitrile/water (35:65) as eluent 40 mg (18%) of **15** was obtained as white needles, mp 144-146 °C (petroleum ether); ^{1}H nmr: δ 9.17 (s, 1H, H_4), 8.95 (dd, 1H, H_8), 8.48 (dd, 1H, H_6), 7.67 (dd, 1H, H_7), 7.48 (s, 1H, H_2), J_{67}= 8.4, J_{68}= 1.5, J_{78}= 4.3 Hz; ms: m/z 222,220 (M^+), 185(M^+-Cl), 158(185-HCN). *Anal.* Calcd for $C_{10}H_5N_2ClS$: C,54.43; H,2.28; N,12.69. Found: C,54.28; H,2.36; N,12.58.

2-Bromothieno[3,2-*c*]-1,5-naphthyridine (16)

After hplc using reverse phase and acetonitrile/water (35:65) as eluent 29 mg (11%) of **16** was obtained, mp 149-150 °C; ^{1}H nmr: δ 9.19 (s, 1H, H_4), 8.95 (dd, 1H, H_8), 8.48 (dd, 1H, H_6), 7.67 (dd, 1H, H_7), 7.63 (s, 1H, H_3), J_{67}= 8.4, J_{68}= 1.5, J_{78}= 4.3 Hz; ms: m/z 266, 264(M^+), 185(M^+-Br),158(185-HCN); HRms calcd for $C_{10}H_5N_2BrS$: 263.9357, found: 263.9361.

3-Bromo-2-chlorothieno[3,2-*c*]-1,5-naphthyridine (17)
and 2,3-dibromothieno[3,2-c]-1,5-naphthyridine (18)

These two compounds could unfortunately not be separated by any methods available to us. The yields were estimated from the crude product using a Varian 3700 gas chromatograph, equipped with a 20 m OV-1701 capillary glass column. Peak areas were determined electronically with a Varian 4270 integrator. Mass spectra were obtained by using a JEOL JMS-SX 102 gas chromatograph/mass spectrometer. **17**: ^{1}H nmr: δ 9.23 (s, 1H, H_4), 8.98 (dd, 1H, H_8), 8.53 (dd, 1H, H_6), 7.72 (dd, 1H, H_7), J_{67}= 8.5, J_{68}= 1.6, J_{78}= 4.3 Hz; ms: m/z 300,298(M^+), 219(M^+-Br), 184(219-Cl), 157(184-HCN). **18**: ^{1}H Nmr: δ 9.19 (s, 1H, H_4), 8.98 (dd, 1H, H_8), 8.53 (dd, 1H, H_6), 7.71 (dd, 1H, H_7), J_{67}= 8.5, J_{68}= 1.6, J_{78}= 4.3 Hz; ms: m/z 346, 344, 342(M^+), 184 (M^+-2Br), 157 (184-HCN).

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REFERENCES AND NOTES

1. Y. Yang, A.-B. Hörnfeldt, and S. Gronowitz, *Chemica Scripta*, 1988, **28**, 275.
2. S. Gronowitz, A.-B. Hörnfeldt, and Y. Yang, *Chemica Scripta*, 1988, **28**, 281.
3. Y. Yang, A.-B. Hörnfeldt, and S. Gronowitz, *Syntheses*, **1989**, 130.
4. K. J. Szabo, A.-B. Hörnfeldt, and S. Gronowitz, *J. Org. Chem.*, 1991, **56**, 1590.
5. S. Gronowitz, K. J. Szabo, and J. O. Oluwadiya, *J. Heterocycl. Chem.*, 1991, **28**, 351.
6. K. J. Szabo and S. Gronowitz, *J. Heterocycl. Chem.*, 1993, **30**, 561.
7. K. J. Szabo, A.-B. Hörnfeldt, and S. Gronowitz, *J. Mol. Struct. (Theochem)*, 1992, **53**, 258.
8. K. J. Szabo, S. Gronowitz, and M. A. Hassan, *J. Heterocycl. Chem.*, 1993, **30**, 543.
9. E. Temciuc, A.-B. Hörnfeldt, and S. Gronowitz, *J. Heterocycl. Chem.*, 1993, **30**, 533.
10. S. Gronowitz, K. J. Szabo, and M. A. Hassan, *J. Org. Chem.*, 1992, **57**, 4552.
11. S. Gronowitz, J. Malm, and A.-B. Hörnfeldt, *Coll. Czech. Chem. Commun.*, 1991, **56**, 2340.
12. J. Malm, A.-B. Hörnfeldt, and S. Gronowitz, *Heterocycles*, 1993, **35**,

245.

13. S. Gronowitz, K. J. Szabo, and T. A. Olugbade, *J. Heterocycl. Chem.*, 1992, **29**, 1635.

14. K. J. Szabo, A.-B. Hörnfeldt, and S. Gronowitz, *J. Chem. Soc., Perkin Trans. 2*, **1993**, 1875.

15. S. Gronowitz and G. Timari, *Chemica Scripta*, 1992, **29**, 305.

16. S. Gronowitz and G. Timari, *J. Heterocycl. Chem.*, 1989, **29**, 309.

17. W. Czuba, *Roczniki Chem.*, 1963, **37**, 1589 (*Chem. Abstr.*, 1964, **60**, 8005).

18. W. W. Paudler and T. J. Kress, *J. Org. Chem.*, 1968, **33**, 1384.

19. J. J. Eisch, *J. Org. Chem.*, 1962, **27**, 1318.

20. H. C. van der Plas and M. Wózniak, *J. Heterocycl. Chem.*, 1976, **B13**, 961.

21. E. Sandberg and S. Gronowitz, *Arkiv Kemi*, 1970, **32**, 249.

22. E. E. Garcia, C. V. Greco, and I. M. Hunsberger, *J. Am. Chem. Soc.*, 1960, **82**, 4430.

23. D. H. Derbyshire and W. A. Waters, *J. Chem. Soc.*,**1950**, 573.

24. W. Gottardi, *Monatsh. f. Chemie*, 1969, **99**, 815.

25. L. H. Klemm, R. E. Merril, F. H. W. Lee, and C. E. Klopfenstein, *J. Heterocycl. Chem.*, 1974, **11**, 205.

26. S. Kajigaeshi, T. Kakinami, T. Okamoto, and S. Fujisaki, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 1159.

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