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Thieno[2,3-*c*]-1,5-naphthyridine (**3**), thieno[2,3-*c*]1,5-naphthyridine 5-oxide (**7**), thieno[3,2-*c*]-1,5-naphthyridine (**5**) and thieno[3,2-*c*]-1,5-naphthyridine 5-oxide (**9**) could conveniently be brominated at room temperature using dibromoisocyanuric acid in fuming sulfuric acid. Bromination occurred in good to moderate yields at the  $\beta$  position in the thiophene ring. Thieno[2,3-*c*]-1,5-naphthyridine 9-oxide (**12**) and thieno[3,2-*c*]-1,5-naphthyridine 9-oxide (**13**) also gave substitution in the thiophene ring at 95°. It was also found that **12** was deoxygenated under these reaction conditions. Direct oxidation of the brominated thieno[*c*]naphthyridines with *m*-chloroperbenzoic acid gave the 5-oxides in high yield.

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## Introduction.

In connection with our work on the effects of the mode of annelation on physical properties and reactivities of tricyclic heterocyclic systems with phenanthrene annelation pattern (for review *cf.* ref. [1]), we have previously described convenient one-pot procedures involving Pd(0)-catalyzed cross couplings for the synthesis of thieno[*b,c*]-quinolines and isoquinolines [2-5], dithieno[*b,d*]pyridines [6-9] and thieno[*b,c*]naphthyridines [10,11].

Extensive experimental studies and theoretical calculations of electrophilic substitution of many of the isomeric dithienopyridines [12,13] as well as the six thieno analogues of phenanthrene *N*-oxide [14,15], have been carried out.

In a recent article we described the bromination of the three isomeric thieno-*c*-fused-1,5-naphthyridines and two of their 5-*N*-oxides [16]. Thieno[3,4-*c*]-1,5-naphthyridine and its 5-*N*-oxide could conveniently be brominated in the thiophene ring at room temperature with tetrabutylammonium perbromide in dichloromethane in the presence of a large excess of sodium hydrogen carbonate. Regioselective mono-bromination of the 5-oxide at the 3-position could be achieved in fair yields under these reaction conditions. Thieno[2,3-*c*]-1,5-naphthyridine, its 5-oxide and thieno[3,2-*c*]-1,5-naphthyridine did not react under these conditions, but gave products in the reaction with bromine in refluxing thionyl chloride. However, chlorinated products were also formed with thionyl chloride, giving mixtures that were difficult to separate and only low to moderate yields of brominated products were obtained.

We therefore searched for better methods for the bromination of the thieno[2,3-*c*]- and thieno[3,2-*c*]fused systems.

These ring systems consists of one strongly  $\pi$ -deficient moiety, the 1,5-naphthyridine system, and one  $\pi$ -excessive moiety, the thiophene ring. Electrophilic substitution of thieno[*c*]-fused naphthyridines is therefore expected to

present an interesting preparative challenge and harsh methods might be needed. Some of the most aggressive reagents for the bromination of aromatic and heteroaromatic compounds are those of Derbyshire and Waters [17], using bromine in concentrated sulfuric acid-silver sulfate, and of Gottardi [18], using dibromoisocyanuric acid (DBI) in concentrated sulfuric acid. However, these methods gave very low yields of brominated products or completely unchanged starting material, when tried on the thieno[*c*]naphthyridines.

On the other hand, it had been demonstrated by Gottardi that the reaction time for the bromination with DBI of strongly deactivated aromatics is greatly decreased by changing the solvent from concentrated sulfuric acid to fuming sulfuric acid. For example, perbromination of nitrobenzene could be achieved in 1 minute at room temperature using fuming sulfuric acid, compared with 1 hour in concentrated sulfuric acid [19].

Another example of increase in reactivity by changing the solvent from concentrated sulfuric acid to fuming sulfuric acid is the study of Gronowitz and Sandberg [20] on the bromination of thieno[2,3-*c*]pyridine and thieno[3,2-*c*]pyridine, where high yields of the dibromo derivative could be obtained by the use of DBI in fuming sulfuric acid.

The bromination of pyridine *N*-oxide in fuming sulfuric acid has also been thoroughly studied by van Ammers, den Hertog and Haase [21].

In the present paper, the scope and limitations of the use of DBI in fuming sulfuric acid as a brominating agent on thieno[2,3-*c*]-1,5-naphthyridine, thieno[3,2-*c*]-1,5-naphthyridine and their 5- and 9-oxides are described.

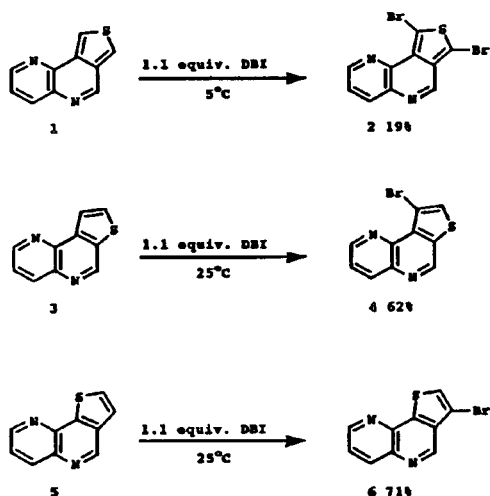
## Results and Discussion.

In a preliminary study, bromination of thieno[3,4-*c*]-1,5-naphthyridine (**1**) with equimolar amounts of DBI in fuming sulfuric acid gave 10% yield of 1,3-dibromo-

thieno[3,4-*c*]-1,5-naphthyridine (**2**) at room temperature without any starting material being recovered. This could be compared with previous results on the bromination of **1** with DBI in concentrated sulfuric acid when no dibromo derivative was formed and 45% of the starting material was recovered [16]. However, by use of 1.1 equivalents of DBI at 5°, the yield of **2** was approximately doubled (Scheme 1). This method was clearly detrimental for the [3,4-*c*]-fused system, due to the formation of tarry products, and no further efforts were made to optimize the yield. A similar observation had previously been made in the case of thieno[3,4-*c*]quinoline *N*-oxide, which decomposed under acidic conditions [15].

Thieno[2,3-*c*]-1,5-naphthyridine (**3**) and thieno[3,2-*c*]-1,5-naphthyridine (**5**) both gave regioselective substitution in the β-position with 1.1 equivalents of DBI at room temperature. The products were 1-bromothieno[2,3-*c*]-1,5-naphthyridine (**4**) and 3-bromothieno[3,2-*c*]-1,5-naphthyridine (**6**), in 62% and 71% yields, respectively (Scheme 1). The use of equimolar amounts of DBI gave lower yields and some recovered starting material. Interestingly, no trace of dibromo compounds could be detected, even with the use of a large excess of DBI, a result in sharp contrast to the easy dibromination of the thieno[*c*]pyridines [20]. It may also be noted that dibrominated compounds were obtained from the reaction of **3** and **5** with bromine in refluxing thionyl chloride [16].

Scheme 1



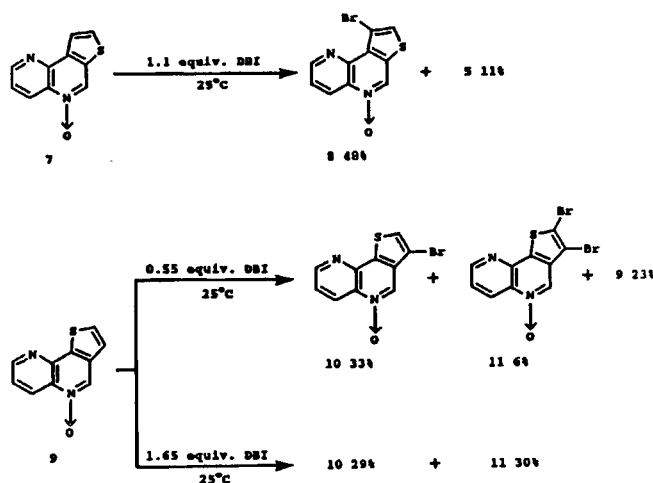
The *N*-oxide analogues of **3** and **5**, which were expected to be the most reactive of the systems studied, gave to our disappointment only modest yields of brominated products.

With equimolar amounts of DBI, thieno[2,3-*c*]-1,5-naphthyridine 5-oxide (**7**) gave a mixture of 1-bromo-

thieno[2,3-*c*]-1,5-naphthyridine 5-oxide (**8**) and **5** in 48% and 11% yields. Some decomposition of the starting material or of the products might explain the low yield, as the mixture turned dark upon standing. Again, no trace of dibromo compounds could be isolated, even with the use of a large excess of DBI.

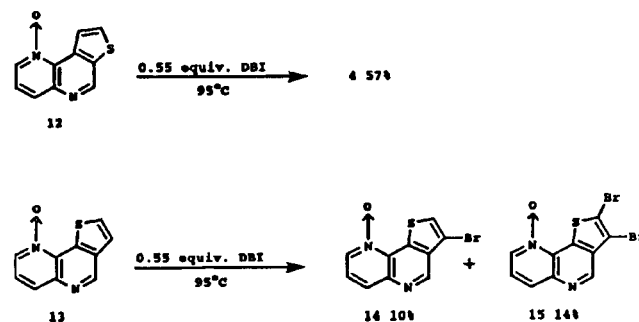
On the other hand, thieno[3,2-*c*]-1,5-naphthyridine 5-oxide (**9**) gave a mixture of 3-bromothieno[3,2-*c*]-1,5-naphthyridine 5-oxide (**10**), 2,3-dibromothieno[3,2-*c*]-1,5-naphthyridine 5-oxide (**11**) and **9** in 33%, 6% and 23% yields, respectively. The use of 1.65 equivalents of DBI led to an increase in the yield of **11** to 30% (Scheme 2).

Scheme 2



Bromination of both thieno[2,3-*c*]-1,5-naphthyridine 9-oxide (**12**) and thieno[3,2-*c*]-1,5-naphthyridine 9-oxide (**13**) at elevated temperatures gave substitution in the thiophene ring (Scheme 3). It was not possible to obtain any brominated products at lower reaction temperatures. Interestingly, the oxygen atom in **12** is lost under these reaction conditions, giving **4** in fair yield. An analogous event had previously been observed by us in the nitration of **12** in fuming sulfuric acid at elevated temperatures [22].

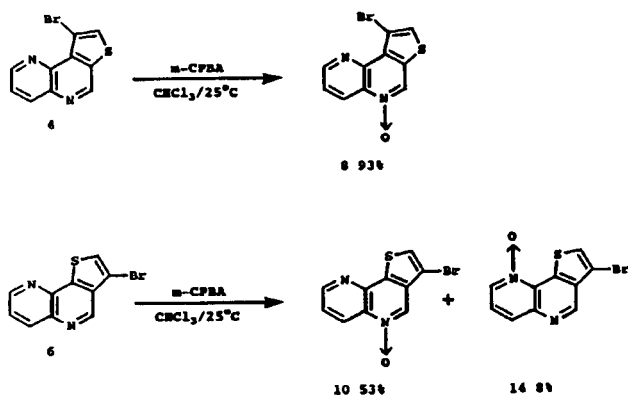
Scheme 3



As an alternative and possibly more profitable route to brominated *N*-oxides, we also investigated the direct oxidation of the bromothiено[*c*]naphthyridines. Indeed, with *m*-chloroperbenzoic acid (*m*-CPBA) at room temperature, an excellent yield of **8** could be obtained from **4**. Upon treatment of **6** with *m*-CPBA, a mixture of the 5- and 9-oxide was obtained (Scheme 4).

It is interesting to note that both the brominated thieno[*c*]naphthyridines gave higher total yields upon *N*-oxidation than their parent thieno[*c*]naphthyridines, and that the fractions of 5-oxides were increased (**3** and **5** are *N*-oxidated at the 5-position in 70% and 48% yields, respectively [cf. 10b]).

Scheme 4



### Structure Assignments.

Mass spectroscopy was valuable in establishing the number of bromine atoms in the products and the presence of the *N*-oxide. The substitution positions were determined by  $^1\text{H}$  nmr spectra and proton coupled  $^{13}\text{C}$  nmr spectra. Correlation between carbon and proton resonances were made by  $^1\text{H}$ - $^{13}\text{C}$  HETCOR nmr spectra. The chemical shifts and the magnitudes of the  $^1\text{H}$ - $^1\text{H}$  and  $^1\text{H}$ -

Table I  
 $^{13}\text{C}$  NMR Chemical Shifts (in ppm) of  
the Thienonaphthyridines **6**, **8**, **10**, **11**, **14**, **15**

Compound	2C	4C	6C	7C	8C
<b>6</b> [a]	126.4	146.6	138.1	124.3	150.6
<b>8</b> [b]	135.0	134.5	127.5	124.8	151.4
<b>10</b> [c]	128.5	132.0	129.5	124.9	152.5
<b>11</b> [c]		131.7	129.8	125.0	152.5
<b>14</b> [a]	130.1	148.6	127.7	122.5	135.5
<b>15</b> [a]		148.1	127.8	122.2	135.4

[a] Deuteriochloroform was used as the solvent. [b] A 1:1 mixture of dimethyl sulfoxide- $d_6$  and formic acid was used as the solvent. [c] A 9:1 mixture of deuteriochloroform and methanol- $d_4$  was used as the solvent.

Table II  
 $J_{\text{CH}}$  Values (Hz) of the Thienonaphthyridines **6**, **8**, **10**, **11**, **14**, **15**

Compound [a]	2C	4C	6C	7C	8C
<b>6</b>					
$^1J_{\text{CH}}$	191.2	183.5	165.3	165.0	179.9
$^2J_{\text{CH}}$				9.0	3.2
$^3J_{\text{CH}}$			6.4		7.9
<b>8</b>					
$^1J_{\text{CH}}$	194.8	194.2	172.9	170.1	183.8
$^2J_{\text{CH}}$				9.1	3.4
$^3J_{\text{CH}}$			6.4		7.9
<b>10</b>					
$^1J_{\text{CH}}$	192.2	189.6	174.2	168.6	182.2
$^2J_{\text{CH}}$				9.0	3.6
$^3J_{\text{CH}}$			6.7		8.1
<b>11</b>					
$^1J_{\text{CH}}$		190.0	173.8	168.6	182.2
$^2J_{\text{CH}}$				9.0	3.6
$^3J_{\text{CH}}$			6.6		8.1
<b>14</b>					
$^1J_{\text{CH}}$	188.4	184.4	171.0	168.3	186.1
$^2J_{\text{CH}}$				3.9	3.7
$^3J_{\text{CH}}$			6.7		8.5
<b>15</b>					
$^1J_{\text{CH}}$		185.3	171.2	168.4	186.1
$^2J_{\text{CH}}$				3.9	3.7
$^3J_{\text{CH}}$			6.6		8.5

[a] The same solvents as given in Table I were used.

$^{13}\text{C}$  coupling constants were generally of the same magnitude as in the parent thieno[*c*]naphthyridines [10]. The position of the bromine atom in the thiophene ring of **6**, **8**, **10** and **14** followed from the presence of thiophenic  $^1J_{\text{CH}}$  coupling constants (191.2, 194.8, 192.2 and 188.4 Hz), characteristic of an  $\alpha$ -CH group [14,15,16]. Compound **4** had been assigned previously [16]. Unambiguous assignments of the  $^{13}\text{C}$  signals and the carbon coupling constants of the brominated thieno[*c*]naphthyridines are given in Tables I and II.

### EXPERIMENTAL

The nmr spectra were recorded on a Varian XL-300 spectrometer. The mass spectra were recorded on a JEOL JMS-SX 102 spectrometer (70 eV). The elemental analyses were carried out by Dornis und Kolbe, Mulheim, Germany. All melting points are uncorrected. *m*-Chloroperbenzoic acid was purchased from Merck and recrystallized from dichloromethane prior to use.

Fuming sulfuric acid (30% sulfur trioxide) was purchased from Merck. Chloroform was distilled over phosphorous pentoxide and ethyl acetate over molecular sieve prior to use. Other solvents were purchased from commercial sources in analytical grade and used without further purification. The substances were purified by flash chromatography on silica gel 60 (purchased from Merck) or by chromatography on a silica gel Dynamax HPLC column, 500 x 10 mm.

General Procedure for the bromination of Thienonaphthyridines with Dibromoisocyanuric Acid in Fuming Sulfuric Acid.

To a stirred solution of 1 mmole of the appropriate thienonaphthyridine in fuming sulfuric acid, dibromoisocyanuric acid (DBI) [18] was carefully added in portions at 0°. The amounts of DBI used are given in the Schemes and when 152 mg (0.55 mmole), 304 mg (1.1 mmoles) or 456 mg (1.65 mmoles) of DBI were used, 2 ml, 4 ml and 6 ml of fuming sulfuric acid were used, respectively. Stirring at the appropriate temperature was continued for 24 hours, except for **1** and **9** (with 1.65 equivalents of DBI) which mixtures were stirred for 48 hours and 72 hours, respectively. The solution was neutralized with 2 *N* sodium hydroxide and solid sodium hydrogen carbonate and was extracted several times with chloroform. The organic phase was dried over magnesium sulfate and finally subjected to chromatography.

#### 1,3-Dibromothieno[3,4-*c*]-1,5-naphthyridine (**2**).

This compound was purified by hplc using chloroform/2-propanol: 99.5/0.5 as eluent, to give 66 mg (19%) of the title compound, with identical <sup>1</sup>H nmr and melting point as in [16].

#### 1-Bromothieno[2,3-*c*]-1,5-naphthyridine (**4**).

This compound was purified by flash chromatography using ethyl acetate as eluent, to give 164 mg (62%) of the title compound, with identical <sup>1</sup>H nmr and melting point as in [16].

#### 3-Bromothieno[3,2-*c*]-1,5-naphthyridine (**6**).

This compound was purified by flash-chromatography using ethyl acetate/*n*-heptane: 90/10 as eluent and gave 188 mg (71%), mp 165-166°; ms: *m/z* 266, 264 (M<sup>+</sup>), 185 (M<sup>+</sup>-Br), 158 (185-HCN), 141 (185-CS); <sup>1</sup>H nmr (deuteriochloroform): δ 9.28 (s, 1H, H<sub>4</sub>), 8.98 (dd, 1H, H<sub>8</sub>), 8.55 (dd, 1H, H<sub>6</sub>), 7.70 (dd, 1H, H<sub>7</sub>), 7.68 (s, 1H, H<sub>2</sub>), J<sub>6,7</sub> = 8.5, J<sub>6,8</sub> = 1.6, J<sub>7,8</sub> = 4.3.

*Anal.* Calcd. for C<sub>10</sub>H<sub>5</sub>BrN<sub>2</sub>S: C, 45.30; H, 1.90; N, 10.57. Found: C, 45.24; H, 1.98; N, 10.44.

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

This compound was purified by flash-chromatography using chloroform/methanol: 95/5 as eluent and gave 134 mg (48%). Since this compound was unstable when kept for extended periods at room temperature, no elemental analysis was attempted, mp 260° dec; ms: *m/z* 282, 280 (M<sup>+</sup>), 266, 264 (M<sup>+</sup>-O), 201 (185-Br), 173; <sup>1</sup>H nmr (deuteriochloroform/perdeuterio-methanol:90/10): δ 9.14 (dd, 1H, H<sub>8</sub>), 9.08 (dd, 1H, H<sub>6</sub>), 9.00 (s, 1H, H<sub>4</sub>), 7.84 (s, 1H, H<sub>1</sub>), 7.76 (dd, 1H, H<sub>7</sub>), J<sub>6,7</sub> = 8.8, J<sub>6,8</sub> = 1.7, J<sub>7,8</sub> = 4.3; hrms Calcd. for C<sub>10</sub>H<sub>5</sub>BrN<sub>2</sub>OS (M<sup>+</sup>-1): 279.9306 Found: 279.9306.

#### 3-Bromothieno[3,2-*c*]-1,5-naphthyridine 5-Oxide (**10**).

This compound was purified by hplc using chloroform/2-propanol: 98/2 as eluent and gave 92 mg (33%) and 81 mg (29%), respectively when 0.55 and 1.65 equivalents of DBI was

used, mp 231-235°; ms: *m/z* 282, 280 (M<sup>+</sup>), 266, 264 (M<sup>+</sup>-O), 201 (185-Br), 173; <sup>1</sup>H nmr (deuteriochloroform/perdeuterio-methanol:90/10): δ 9.07 (dd, 1H, H<sub>6</sub>), 9.00 (dd, 1H, H<sub>8</sub>), 8.92 (s, 1H, H<sub>4</sub>), 7.75 (dd, 1H, H<sub>7</sub>), 7.74 (s, 1H, H<sub>2</sub>), J<sub>6,7</sub> = 8.7, J<sub>6,8</sub> = 1.5, J<sub>7,8</sub> = 4.2.

*Anal.* Calcd. for C<sub>10</sub>H<sub>5</sub>BrN<sub>2</sub>OS: C, 42.72; H, 1.79; N, 9.96. Found: C, 42.66; H, 1.87; N, 9.84.

#### 2,3-Dibromothieno[3,2-*c*]-1,5-naphthyridine 5-Oxide (**11**).

This compound was purified by hplc using chloroform/2-propanol: 98/2 as eluent and gave 22 mg (6%) and 109 mg (30%), respectively when 0.55 and 1.65 equivalents of DBI was used, mp 295-298°; ms: *m/z* 362, 360, 358 (M<sup>+</sup>), 344 (M<sup>+</sup>-O), 281, 279 (M<sup>+</sup>-Br), 200 (M<sup>+</sup>-2Br); <sup>1</sup>H nmr (deuteriochloroform/perdeuterio-methanol:90/10): δ 9.08 (dd, 1H, H<sub>6</sub>), 9.01 (dd, 1H, H<sub>8</sub>), 8.89 (s, 1H, H<sub>4</sub>), 7.76 (dd, 1H, H<sub>7</sub>), J<sub>6,7</sub> = 8.7, J<sub>6,8</sub> = 1.5, J<sub>7,8</sub> = 4.2.

*Anal.* Calcd. for C<sub>10</sub>H<sub>4</sub>Br<sub>2</sub>N<sub>2</sub>OS: C, 33.36; H, 1.12; N, 7.78. Found: C, 33.29; H, 1.47; N, 7.57.

#### 3-Bromothieno[3,2-*c*]-1,5-naphthyridine 9-Oxide (**14**).

This compound was purified by hplc using chloroform/methanol: 98/2 as eluent and gave 27 mg (10%), mp 227-230°; ms: *m/z* 282, 280 (M<sup>+</sup>), 266, 264 (M<sup>+</sup>-O), 185 (266, 264-Br), 173, 146; <sup>1</sup>H nmr (deuteriochloroform): δ 9.39 (s, 1H, H<sub>4</sub>), 8.70 (dd, 1H, H<sub>8</sub>), 8.26 (dd, 1H, H<sub>6</sub>), 7.85 (s, 1H, H<sub>2</sub>), 7.64 (s, 1H, H<sub>7</sub>), J<sub>6,7</sub> = 8.7, J<sub>6,8</sub> = 0.9, J<sub>7,8</sub> = 6.3.

*Anal.* Calcd. for C<sub>10</sub>H<sub>5</sub>BrN<sub>2</sub>OS: C, 42.72; H, 1.79. Found: C, 42.84; H, 1.92.

#### 2,3-Dibromothieno[3,2-*c*]-1,5-naphthyridine 9-Oxide (**15**).

This compound was purified by hplc using chloroform/methanol: 98/2 as eluent and gave 52 mg (14%), mp 260-263°; ms: *m/z* 362, 360, 358 (M<sup>+</sup>), 344 (M<sup>+</sup>-O), 200 (M<sup>+</sup>-2Br); <sup>1</sup>H nmr (deuteriochloroform): δ 9.29 (s, 1H, H<sub>4</sub>), 8.68 (dd, 1H, H<sub>8</sub>), 8.24 (s, 1H, H<sub>6</sub>), 7.65 (dd, 1H, H<sub>7</sub>), J<sub>6,7</sub> = 8.7, J<sub>6,8</sub> = 0.8, J<sub>7,8</sub> = 6.2.

*Anal.* Calcd. for C<sub>10</sub>H<sub>4</sub>Br<sub>2</sub>N<sub>2</sub>OS: C, 33.36; H, 1.12; N, 7.78. Found: C, 33.28; H, 1.16; N, 7.67.

General Procedure for the Reaction of Bromothienonaphthyridines **4** and **6** with *m*-CPBA.

To a stirred solution of 265 mg (1 mmole) of the appropriate bromothienonaphthyridine in 10 ml of chloroform, 260 mg (1.5 mmoles) of *m*-CPBA was added in small portions over a period of 15 minutes at room temperature. After 4 hours the reaction mixture was diluted with 200 ml of chloroform, washed with 25 ml of 2 *N* sodium hydroxide, 25 ml of water and finally dried over magnesium sulfate. After evaporation the residue was subjected to chromatography. 1-Bromothieno[2,3-*c*]-1,5-naphthyridine 5-oxide (**8**) was purified as above and 262 mg (93%) was obtained. 3-Bromothieno[3,2-*c*]-1,5-naphthyridine 5-oxide (**10**) and 3-bromothieno[3,2-*c*]-1,5-naphthyridine 9-oxide (**14**) were obtained in a mixture and separated by hplc using chloroform/2-propanol: 95/5 as eluent. This gave 150 mg (53%) and 22 mg (8%) of **10** and **14**, respectively.

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