

## Heteroaromatic Boron Compounds

### III. On the Nitration of Some Derivatives of Borazarothienopyridines

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Some derivatives of 4,5-borazarothieno[2,3-c]pyridine, (II), and 7,6-borazarothieno[3,2-c]pyridine (III) have been nitrated under various conditions. Nitration of 7-hydroxy-7,6-borazarothieno[3,2-c]pyridine (IIIa), 7-hydroxy-6-methyl-7,6-borazarothieno[3,2-c]pyridine (IIIb), and of 7-methyl-7,6-borazarothieno[3,2-c]pyridine (IIIc) with fuming nitric acid in sulphuric acid led to the 3-nitro derivatives as the only detectable isomers, while the nitration of 4-hydroxy-4,5-borazarothieno[2,3-c]pyridine (IIa) yielded the 3- and 2-mono nitro derivatives in the ratio 8:1, and 4-hydroxy-5-methyl-4,5-borazarothieno[2,3-c]pyridine (IIb) yielded the 3- and 2-mono nitro derivatives in the ratio 4:1.

For comparison 3-formyl-2-thiopheneboronic acid and 2-formyl-3-thiopheneboronic acid were nitrated under similar conditions, as it was not possible to obtain defined products from the corresponding dimethyl hydrazones. Only the 5-nitro isomer was obtained in the nitration of 3-formyl-2-thiopheneboronic acid, giving additional evidence for the aromatic nature of III.

Nitration of II and III with fuming nitric acid in acetic anhydride (acetyl nitrate) yielded only nitration in the boron-nitrogen containing ring giving the 7- and 4-nitro derivative, respectively.

Structure determinations were carried out by chemical degradations and NMR-spectroscopy. A characteristic long-range coupling between the 3- and 7-hydrogen of II was identified.

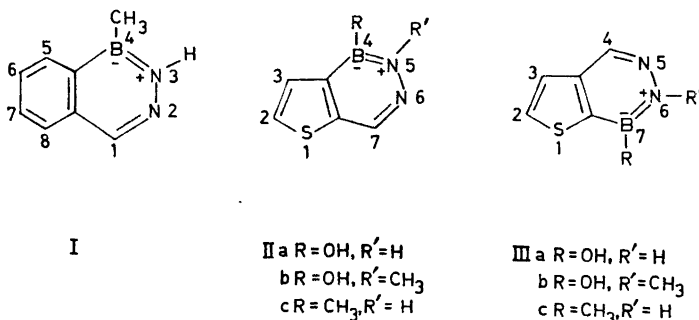
The chemistry of heteroaromatic boron compounds has attracted considerable interest during recent years (for review *cf.* Ref. 1).

In part I<sup>2</sup> and II<sup>3</sup> of this series it was shown that starting from thiophene derivatives certain boron heteroaromatics such as 4,5-borazarothieno[2,3-c]pyridines\* (II) and 7,6-borazarothieno[3,2-c]pyridines\* (III) are easily

† Deceased.

\* According to *Chemical Abstracts* nomenclature, the ring-system in II should be called 1,2-dihydro thieno[3,2-d][1,2,3]diazaborine and III 1,2-dihydro thieno[2,3-d][1,2,3]diazaborine. However, for reasons discussed by Dewar and Dietz<sup>4</sup> we prefer the nomenclature suggested by the latter authors.

accessible. The NMR-spectra and hydrolytic stability of these compounds have been studied. Some electrophilic substitution reactions have been carried out with this new heteroaromatic system.



Nitration <sup>5</sup> of I in sulphuric acid led to substitution in position 8, while nitration <sup>6</sup> of IIc in acetic acid by acetic anhydride-nitric acid led to substitution in position 7. This difference in substitution pattern may seem somewhat surprising at first glance, but it must be remembered that quite different nitration conditions were used in these two reactions.

It has also been found, contrary to earlier statements,<sup>5</sup> that I is brominated by molecular bromine in acetic acid in the 1-position <sup>7</sup> and IIc in the analogous 7-position.<sup>6</sup>

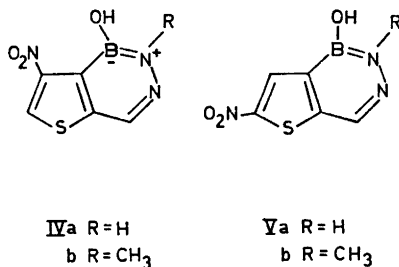
In order to determine whether nitration of systems II and III in sulphuric acid led to substitution in the thiophene ring in analogy with system I, and to investigate the effect of different substituents in the boron-nitrogen containing ring of systems II and III on the substitution path, the nitration of some derivatives of systems II and III has been carried out under various conditions.

Nitration of IIa in sulphuric acid yielded two nitro products in the ratio 8:1. The products were separated by preparative TLC on silica gel with chloroform as eluent. Elementary analysis indicated the products to be mono nitro derivatives in both cases. The NMR-spectrum of the main product shows four bands at  $\tau = -0.92, 0.90, 1.62$  and  $2.92$  with the intensities 1:1:1:1. The band at  $-0.92 \tau$  can be assigned to the NH-hydrogen. To assign the other bands is difficult as the spectrum shows no coupling, but this fact indicates that the substitution must have occurred in the thiophene ring. Oxidation of this nitro product by alkaline permanganate gave 4-nitro-2-thiophenecarboxylic acid, which definitively shows the product to be 4-hydroxy-3-nitro-4,5-borazathieno[2,3-c]pyridine (IVa).

The other nitro product is the 2-nitro derivative, 4-hydroxy-2-nitro-4,5-borazathieno[2,3-c]pyridine (Va) since the elementary analysis indicates a mono nitro derivative and both the NMR- and IR-spectrum are quite different from the two other mono nitro derivatives of IIa. The NMR-spectrum in DMSO shows four bands with the same intensity. The NH-hydrogen occurred at  $-0.80 \tau$ . A band at  $1.42 \tau$  shows a splitting of  $0.5 \text{ c/s}$  which assigns

this band to the 3- or 7-hydrogen. The other bands at 1.26  $\tau$  and 1.66  $\tau$  are rather broad.

Nitration of IIb in sulphuric acid gave again two nitro products, but now in the ratio 4:1. The products were separated by preparative TLC on silica gel. Elementary analysis indicated in both cases mono nitro products. The NMR-spectrum of the main product shows four bands with no coupling, and oxidation by alkaline permanganate gave 4-nitro-2-thiophenecarboxylic acid. This shows the product to be the 3-nitro derivative, (IVb). The NMR-spectrum

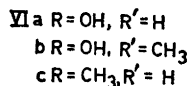


of the other product also shows four bands with intensities 1:1:1:3 at  $\tau=0.95$ , 1.38, 1.69, and 6.37, respectively. But in this case the bands at  $\tau=1.38$  and  $\tau=1.69$  show a splitting of 0.7 c/s which shows that these two bands must belong to the 3- and 7-hydrogens. The bands at  $\tau=0.95$  and  $\tau=6.37$  can be assigned to the OH- and CH<sub>3</sub>-hydrogens, respectively.

It is thus evident that the two 2-nitro derivatives of system II, Va and Vb, show a long-range coupling between the 3- and 7-hydrogens.

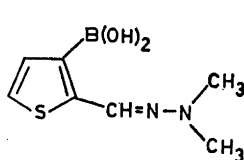
Earlier it has been reported<sup>2</sup> that the NMR-spectrum of IIa in DMSO shows a long-range coupling from the 7-hydrogen to one of the thiophene-hydrogens, but to which was an open question. From the observation above we can now conclude that the long-range coupling occurred to the 3-hydrogen, and that it follows the pattern of the straightest zig-zag path<sup>8</sup> and not the coupling pattern observed in 2-thiophene aldoxime<sup>9</sup> and 2-thiophene aldehyde<sup>9</sup> where the side-chain hydrogen is coupled to the 5-hydrogen.

Nitration of the three derivatives of system III gave in each case only one nitro product. In no case did the NMR-spectra of the nitro product show any couplings, which indicates that the substitution must have occurred in the thiophene ring, but the position of substitution was not evident from the spectra. Oxidation of the nitro products by alkaline permanganate gave the same nitrothiophenecarboxylic acid. The NMR-spectrum of this acid shows in the aromatic area two bands at  $\tau=1.38$  and  $\tau=1.75$  with the same intensity with a coupling of 3.6 c/s, characteristic for 3,4-disubstituted thiophenes.<sup>10</sup> The acid is therefore 4-nitro-3-thiophenecarboxylic acid, which shows that the nitration of the derivatives of system III in sulphuric acid occurred in the 3-position, yielding the compounds VIa—c.

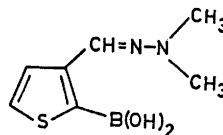


It is of interest to compare the isomer distributions obtained upon nitration of II and III with those obtained with the closest non-cyclic analogues in order to obtain additional information on the aromaticity of these systems and their similarity to thianaphthene and thiophene analogues of isoquinoline.

There were also some indications in our earlier work that some derivatives of II and III could exist in strongly acidic solutions in part as a protonated hydrazone boronic acid.<sup>3</sup> The simplest open analogues are the dimethyl hydrazones VII and VIII of the corresponding formylthiopheneboronic acids which cannot ringclose. These compounds were easily obtained in high yield by



VII



VIII

the reaction of dimethyl hydrazine with 2-formyl-3-thiopheneboronic acid and 3-formyl-2-thiopheneboronic acid, respectively. However, it was not possible to obtain any well-defined nitration products upon using the same conditions as for II and III. Also at  $-45^{\circ}\text{C}$  mainly decomposition products were obtained. We therefore chose the formyl thiopheneboronic acids as models, assuming that the directing effect of a C=O and a C=N double bond are of some similarity. Another complication in a comparison between the cyclic systems and the aldehyde boronic acids is that the free boronic acid group is "meta"-directing, but a boron-containing group which no longer is strongly electron-deficient, such as a  $-\overset{\ominus}{\text{B}}=\overset{\oplus}{\text{N}}-$ , is strongly "ortho"-directing, as is observed in the nitration of boronic acids in acetic anhydride.<sup>11</sup> Our hypothesis is therefore, that if ring-closure did not lead to aromatic stabilization, similar isomer distributions should be obtained in the nitration of II and 2-formyl-3-thiopheneboronic acid in sulphuric acid and in the nitration

of III and 3-formyl-2-thiopheneboronic acid, and that the boron-containing group should be "meta"-directing in both the cyclic and open systems.

The nitration of 3-formyl-2-thiopheneboronic acid yielded a mono nitro product in good yield. The NMR-spectrum in DMSO shows three bands with intensities 1:1:2 at  $\tau = -0.35$ , 1.75, and 4.24, respectively. The band at  $\tau = -0.35$   $\tau$  is assigned to the aldehydic hydrogen resonance. The band at 1.75  $\tau$  belonged to an aromatic hydrogen and the band at 4.24  $\tau$  belonged to the  $B(OH)_2$  hydrogens. Protodeboronation in acetic acid gave 5-nitro-3-thiophene aldehyde, which demonstrates that the nitration product is 3-formyl-5-nitro-2-thiopheneboronic acid. This substitution path is not unexpected, as nitration of 3-thiophene aldehyde<sup>12</sup> in sulphuric acid occurs in the 5-position. The  $\alpha$ -directing effect of the sulphur and the 5-directing effect of the formyl group predominate over the 4-directing effect of the  $B(OH)_2$  group. To study the 4-directing effect of the  $B(OH)_2$  group, nitration of 2-thiopheneboronic acid in sulphuric acid has been attempted, but no nitro-2-thiopheneboronic acid could be found, only 2,4-dinitrothiophene, which demonstrates the stabilization effect of the formyl group on the carbon-boron bond.

Nitration of 2-formyl-3-thiopheneboronic acid gave 2-formyl-5-nitro-3-thiopheneboronic acid and 4-nitro-2-thiophene aldehyde in 22 % and 57 % yield, respectively. Our structural proof for the first product is elementary analysis and an NMR-spectrum in DMSO which shows an aldehyde hydrogen at  $-0.40$   $\tau$ , one aromatic hydrogen at 1.65  $\tau$  and two hydrogens at 3.70  $\tau$  which belong to the  $B(OH)_2$  group. Protodeboronation in acetic acid gave 5-nitro-2-thiophene aldehyde.

The formation of the other product is rather difficult to explain. If the protodeboronation had occurred before the nitration, one should expect a mixture of 5-nitro- and 4-nitro-2-thiophene aldehyde in the ratio 1:3. This is the case in nitration<sup>13</sup> of 2-thiophene aldehyde in sulphuric acid itself. But neither the IR-spectrum nor the NMR-spectrum gave any indication of the presence of 5-nitro-2-thiophene aldehyde. Another explanation is that the nitration gave a mixture of the 4-nitro- and 5-nitro-2-formyl-3-thiopheneboronic acid isomers and that a nitro group "ortho" to the borono group caused a rapid protodeboronation due to neighbouring group participation. Such an effect of a nitro group in protodeboronation has never been reported, but the observation that no nitrothiophene aldehydes could be detected in the nitration of 3-formyl-2-thiopheneboronic acid, which protodeboronated faster than 2-formyl-3-thiopheneboronic acid in conc. hydrochloric acid,<sup>3</sup> seems to support this explanation. For in this case it is not possible to have a nitro group "ortho" to the borono group. Some experiments to test this explanation are in preparation, but here we will conclude with, that the nitration of 2-formyl-3-thiopheneboronic acid occurred in 4- and 5-position in the ratio 3:1, being the same as in the nitration of 2-thiophene aldehyde. This result is perhaps somewhat unexpected as the "meta"-directing  $B(OH)_2$  should deactivate the 4-position. However, as Gronowitz<sup>14</sup> has pointed out, a -I-M-substituent in the 3-position deactivates its 4-position to a much lesser extent than its 2-position.

The marked difference in orientation obtained in the nitration of III, which yields only 3-substitution, and the nitration of 3-formyl-2-thiopheneboronic acid, which yields only 5-substitution, gives additional evidence for the aromatic nature of III and also eliminates the possibility that the protonated boronic acid hydrazone obtained upon reversible hydrolytic ring-opening is the substrate. On the other hand, the isomer distribution in the nitration of II and of 2-formyl-3-thiopheneboronic acid are so similar that in this case conclusions regarding the aromaticity of II cannot be drawn from this experiment.

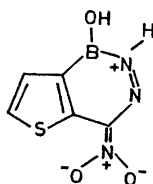
It has long been known that in thianaphthene the  $\beta$ -position is most reactive in electrophilic substitution in contrast to thiophene itself. In a recent investigation<sup>15</sup> of the nitration of thianaphthene with fuming nitric acid in acetic acid it was found that 60–65 % of 3-nitrothianaphthene was formed together with 10–15 % of 2-nitrothianaphthene and 20–30 % of other components, mainly 4-nitrothianaphthene. Halogenation was more selective and led to predominant formation of the 3-isomers. In other work (nitration in acetic anhydride) it is claimed that 5-nitrothianaphthene is the second isomer formed.<sup>16</sup> Although the nitrating conditions are not quite comparable, it is thus evident that at least in III, the 3-position is attacked more selectively than in thianaphthene. This has also been found to be the case with thieno[3,2-c]-pyridine.<sup>17</sup>

Nitration in acetic acid by acetic anhydride-nitric acid, in which case acetyl nitrate is probably the nitrating agent, caused a quite different substitution pattern, as stated earlier.<sup>6</sup> In all the derivatives of systems II and III the nitration occurred in the boron-nitrogen containing ring. This is perhaps not so surprising when we know the substitution path in the B-methyl case of system II, as it is known that in a pyridine-type ring a hydroxyl group will activate the ring in electrophilic substitution. Thus nitration of 4-isoquinolinol<sup>18</sup> gives the 3-nitro derivative, while nitration of isoquinoline<sup>19</sup> itself causes substitution in the 8- and 5-positions under the same nitration conditions, namely nitric acid in conc. sulphuric acid.

Our structural proof is based on elementary analysis, which indicates a mono nitro product, and NMR-spectroscopy. The NMR-spectra of the nitro products in THF solution show one singlet and two doublets in the aromatic area when R=OH. The coupling in the doublets is 5 c/s, characteristic for 2,3-disubstituted thiophenes.<sup>10</sup> The singlet migrated on addition of water, which indicates that the band must belong to the OH-hydrogen.

Also a chemical proof for substitution in the boron-nitrogen containing ring was obtained. While IIa, b, and c were stable in the presence of 2 N sodium hydroxide, and IIIa, b, and c were quite instable and protodeboronated completely, the nitro products of IIa, IIb as well as those of IIIa and IIIb were instable in the presence of alkali. Protodeboronation occurred and the products were 2- and 3-thiophenecarboxylic acid, respectively. These results prove that the nitro group is not in the thiophene ring.

The decreased stability of this nitro product toward alkali is probably due to decreased stabilization of the borono-nitrogen bond due to the contribution of resonance structures such as IX.



## IX

This is also probably the reason for the hydrolysis of the B-methyl to the B-hydroxyl observed earlier in the nitration of IIc by acetic anhydride-nitric acid.<sup>6</sup> A similar hydrolysis was also found earlier, when 10-methyl-10,9-borazaro-phenanthrene was nitrated by acetic anhydride-nitric acid.<sup>20</sup>

The yield of nitro products is rather low when R'=H, but neither the NMR-spectra nor TLC of the crude nitro products on silica gel gave any indication of mixtures.

We see that nitration in sulphuric acid and in acetic acid by acetic anhydride-nitric acid led to quite different isomer distributions. If nitration by acetic anhydride-nitric acid is a real electrophilic substitution, one explanation for the difference can be that the substitution in the boron-nitrogen containing ring arises from attack on the neutral molecules, while in sulphuric acid the substitution arises from attack on the conjugate acid. However, according to Dewar<sup>5</sup> protonation would not be expected to alter the orientation of substitution, only the reactivity. It has also been shown that it is the conjugate acids of quinoline<sup>21,22</sup> and isoquinoline<sup>22</sup> which are attacked in nitration in sulphuric acid.

Similar differences in substitution pattern has been found in nitration of quinoline. Nitration in sulphuric acid gave the 5-nitro- and 8-nitro derivatives,<sup>19</sup> while nitration by acetic anhydride-nitric acid gave the 3-, 6-, and 8-nitro derivatives.<sup>23</sup> Dewar has suggested that this orientation path arises from a primary addition of acetyl nitrate at the 1,2-bond, thereby forming a substituted aniline which undergoes further substitution. The detailed mechanisms of these reactions are not known, but it has been shown that bromination<sup>24</sup> at low acidities of the *N*-cyano-quinolinium ion gave 3-bromo-3,6-dibromo- and 3,6,8-tribromo-quinoline, and that the 3-substitution occurred by an addition-elimination mechanism, which seems to support Dewar's mechanism for the formation of 3-nitro derivatives of quinoline.

Addition of acetyl nitrate to the C=N bond in nitrogen heterocyclic compounds has been found in the nitration<sup>25</sup> of 4-phenylpyrimidine by acetic anhydride-nitric acid.

An addition-elimination mechanism to explain the substitution in nitration by acetic anhydride-nitric acid of the boron compounds does not fit well, for then one must postulate an intermediate with a nitro group on the carbon atom and an acetoxy group on the nitrogen atom, which is opposite to the orientation in the known case of addition in 4-phenylpyrimidine and Dewar's postulated intermediate for the 3-substitution of quinoline. Such an inter-

mediate has also been assumed in certain electrophilic reactions of isoquinoline in order to explain 4-substitution,<sup>26</sup> but it is difficult to see how it can explain 1-substitution.

If one views the ring-systems II and III as modified hydrazones, substitution at the 1-position is not without precedence. Thus nitration of aryl phenyl hydrazones with amyl nitrite<sup>27</sup> as well as bromination in acetic acid<sup>28</sup> occurs at the azomethine bond.

Molecular-orbital calculations<sup>29</sup> by the  $\omega$ -method<sup>30</sup> for the free base of the boron compound indicate that electrophilic substitution should occur in the thiophene ring part.

However, only the  $\pi$ -electron densities are in accordance with greater reactivity at the 3- than at the 2-position. Both superdelocalizability and localization energies predict the opposite reactivities. These calculations might also indicate that the nitration in acetic anhydride hardly is a direct electrophilic substitution.

It is evident that more detailed theoretical and experimental studies are necessary for a deeper understanding of the isomer distributions obtained in nitrations of these boron-containing heterocyclics.

#### EXPERIMENTAL

The NMR spectra were obtained on a Varian A-60 NMR spectrometer using tetramethyl silane as internal standard. The IR spectra were obtained on a Perkin-Elmer 257 grating infrared spectrophotometer. The elementary analyses were carried out by Miss Ilse Beetz, Mikroanalytisches Laboratorium, Kronach. All crude nitration products were analysed by NMR and TLC for isomers.

*2-Formyl-3-thiopheneboronic acid dimethylhydrazone.* To a solution of 4.68 g (0.03 mole) of 2-formyl-3-thiopheneboronic acid in 200 ml of ether was added 5.0 ml of dimethylhydrazine. The residue after evaporation on a boiling water bath crystallized from ethanol-water giving 5.0 g (84 %) of the title compound, m.p. 90–100°C. NMR (DMSO):  $\tau_{\text{OH}}$  1.63,  $\tau_{\text{CH}}$  2.03,  $\tau_{2,3}$  2.63–2.78,  $\tau_{\text{CH}_2}$  7.05;  $J_{23} = 5.1$  c/s. (Found: C 42.74; H 5.50; N 14.26. Calc. for  $\text{C}_7\text{H}_{11}\text{BN}_2\text{O}_2\text{S}$  (198.1): C 42.44; H 5.60; N 14.13).

*3-Formyl-2-thiopheneboronic acid dimethylhydrazone.* From 1.56 g (0.01 mole) of 3-formyl-2-thiopheneboronic acid and 2.0 ml of dimethylhydrazine the title compound was prepared as described for the isomeric compound above. Recrystallization from ethanol-water yielded 1.3 g (66 %), m.p. 90–100°C. NMR (DMSO):  $\tau_{2,3,\text{CH}}$  2.50,  $\tau_{\text{OH}}$  3.25,  $\tau_{\text{CH}_2}$  7.06. (Found: C 42.48; H 5.56; N 14.30. Calc. for  $\text{C}_7\text{H}_{11}\text{BN}_2\text{O}_2\text{S}$  (198.1): C 42.44; H 5.60; N 14.13).

*2-Thiopheneboronic acid.* To 366 ml of 0.75 N butyllithium in ether 21 g of thiophene in 100 ml of dry ether was added under stirring and nitrogen. After refluxing for 15 min, the mixture was cooled to  $-70^\circ\text{C}$  and 150 g butyl borate in 200 ml of dry ether was added all at once. After stirring at  $-70^\circ\text{C}$  for 4 h, the mixture was allowed to warm to  $0^\circ\text{C}$  and then 200 ml of 2 N hydrochloric acid was added and the mixture stirred further for one hour. The water phase was extracted with ether and the combined ether phases extracted with 1 N sodium hydroxide. Upon acidification with 4 N hydrochloric acid 15 g of 2-thiopheneboronic acid separated out. Recrystallization from methanol-water yielded 10 g (32 %) of the title compound, m.p. 133–134°C. (Lit.<sup>31</sup> 134–135°C).

*Nitration of 2-thiopheneboronic acid.* To a mixture of 25 ml of conc. sulphuric acid and 1.70 ml of fuming nitric acid ( $d$  1.5, 0.04 mole) cooled to  $-20^\circ\text{C}$ , 2.5 g (0.02 mole) of the title compound was added in portions under vigorous stirring. After stirring for one hour at the same temperature, the mixture was poured onto 400 g of ice, and extracted with ether. The combined ether phases were dried over magnesium sulphate and evaporated *in vacuo*, giving 2.0 g (58 %) of 2,4-dinitrothiophene. M.p. after recrystallization from methanol-water 51–53°C. (Lit.<sup>32</sup> 51–52°C).



*Nitration of 3-formyl-2-thiopheneboronic acid.* To a solution of 25 ml of conc. sulphuric acid and 0.85 ml of fuming nitric acid ( $d$  1.5, 0.02 mole) cooled to  $-20^{\circ}\text{C}$  1.56 g (0.01 mole) of 3-formyl-2-thiopheneboronic acid in portion was added with vigorous stirring. After stirring for 45 min at the same temperature, the mixture was poured onto 200 g of ice, which caused precipitation of white crystals. The crystals were filtered off, washed with water and dried. The crude product weighed 1.8 g. Recrystallization from ethanol-water gave 1.4 g (70 %) of 3-formyl-5-nitro-2-thiopheneboronic acid, m.p.  $150-155^{\circ}\text{C}$ . NMR (DMSO):  $\tau_{\text{CHO}}$   $-0.35$ ,  $\tau_1$  1.75,  $\tau_{\text{B(OH)_2}}$  4.24. (Found: C 30.15; H 1.86; N 6.91. Calc. for  $\text{C}_5\text{H}_4\text{BNO}_5\text{S}$  (201.0): C 29.88; H 2.01; N 6.97).

*Degradation of the nitroproduct.* 0.5 g (0.0025 mole) of the nitroproduct was refluxed with 25 ml of acetic acid for 3 h. The mixture was then evaporated *in vacuo* and the residue was taken up in ether. The ether solution was washed with 25 ml of 2 N sodium carbonate, dried over magnesium sulphate and evaporated *in vacuo*, which gave a crystalline residue. The IR spectrum of the residue was identical with that of an authentic sample of 5-nitro-3-thiophene aldehyde. Yield 0.35 g (89 %). M.p. after one recrystallization from petroleum-ether ( $80-120^{\circ}\text{C}$ )  $81-83^{\circ}\text{C}$ . (Lit.<sup>12</sup>  $82.5-83.5^{\circ}\text{C}$ ).

*Nitration of 2-formyl-3-thiopheneboronic acid.* To a solution of 50 ml of conc. sulphuric acid and 1.70 ml of fuming nitric acid ( $d$  1.5, 0.04 mole), cooled to  $-20^{\circ}\text{C}$  3.12 g (0.02 mole) of 2-formyl-3-thiopheneboronic acid was added with vigorous stirring. After stirring at the same temperature for 45 min, the mixture was poured onto 200 g of ice and extracted with  $3 \times 100$  ml of ether. The combined ether phases were extracted with  $3 \times 50$  ml of 2 N sodium carbonate. The water phases were at once acidified to pH 1 with 4 N hydrochloric acid which caused precipitation of white crystals. The crystals were filtered off and dried; the crude product weighed 1.2 g (A). Recrystallization of product A from ethanol-water yielded 0.9 g (22 %) of 2-formyl-5-nitro-3-thiopheneboronic acid, m.p.  $125-130^{\circ}\text{C}$ . NMR (DMSO):  $\tau_{\text{CHO}}$   $-0.40$ ,  $\tau_1$  1.65,  $\tau_{\text{B(OH)_2}}$  3.70. (Found: C 30.59; H 1.99; N 7.19. Calc. for  $\text{C}_5\text{H}_4\text{BNO}_5\text{S}$  (201.0): C 29.88; H 2.01; N 6.97).

The ether extract was dried over magnesium sulphate and evaporation *in vacuo* yielded 2.0 g of a crystalline residue. Recrystallization from petroleum-ether ( $80-120^{\circ}\text{C}$ ) yielded 1.8 g (57 %) of 4-nitro-2-thiophenealdehyde, m.p.  $56-60^{\circ}\text{C}$  (Lit.<sup>33</sup>  $61^{\circ}\text{C}$ ). NMR (acetone):  $\tau_{\text{CHO}}$   $-0.08$ ,  $\tau_3$  1.47,  $\tau_5$  0.97;  $J_{35} = 1.6$  c/s,  $J_{5-\text{CHO}} = 1.4$  c/s.

*Degradation of nitroproduct A.* 0.5 g (0.0025 mole) of the nitro product was refluxed 48 h with 25 ml of acetic acid and worked up as described above. The IR spectrum of the product (0.25 g, 64 %) was identical with the spectrum of an authentic sample of 5-nitro-2-thiophenealdehyde. M.p. after recrystallization from petroleum-ether ( $80-120^{\circ}\text{C}$ )  $72-75^{\circ}\text{C}$ . (Lit.<sup>33</sup>  $74^{\circ}\text{C}$ ).

*Nitration of 7-hydroxy-7,6-borazarothieno[3,2-c]pyridine (IIIa) in conc. sulphuric acid.* To a solution of 40 ml conc. sulphuric acid and 0.85 ml of fuming nitric acid ( $d$  1.5, 0.02 mole), cooled to  $0^{\circ}\text{C}$  3.04 g (0.02 mole) of the B-hydroxy compound was added with vigorous stirring. After stirring for 2 h at the same temperature, the reaction mixture was poured onto 500 g of ice. Neutralization of the solution with solid sodium bicarbonate caused precipitation of 3.5 g (89 %) of brown crystals. Recrystallization from ethanol-water gave 2.8 g (71 %) of 7-hydroxy-3-nitro-7,6-borazarothieno[3,2-c]pyridine, m.p.  $265-270^{\circ}\text{C}$ . NMR (DMSO):  $\tau_{\text{NH}}$   $-0.66$ ,  $\tau_{\text{OH}_{2,4}}$  0.75, 1.20 and 1.38. (Found: C 30.94; H 1.65; N 21.22. Calc. for  $\text{C}_5\text{H}_4\text{BN}_3\text{O}_3\text{S}$  (197.0): C 30.48; H 2.05; N 21.32).

*Oxidation of the nitro product.* To a stirred solution of 1.0 g potassium permanganate in 50 ml of 2.5 N sodium hydroxide was added 0.5 g (0.0025 mole) of the nitro product at room temperature. After one hour 1.0 g of sodium bisulphite was added, the manganese dioxide was filtered off, and the filtrate was acidified to pH 1 with conc. hydrochloric acid and extracted with ether. The ether extract was dried over sodium sulphate and evaporated *in vacuo* giving 0.32 g (74 %) of 4-nitro-3-thiophenecarboxylic acid. M.p. after recrystallization from water  $169-172^{\circ}\text{C}$ . NMR (DMSO):  $\tau_{\text{COOH}}$  0.37,  $\tau_{2,5}$  1.38-1.75;  $J_{25} = 3.6$  c/s. (Found: C 34.99; H 2.21; N 7.98; S 18.66. Calc. for  $\text{C}_5\text{H}_3\text{NO}_4\text{S}$  (173.1): C 34.69; H 1.75; N 8.09; S 18.53).

*Nitration of 7-hydroxy-6-methyl-7,6-borazarothieno[3,2-c]pyridine (IIIb) in sulphuric acid.* To a mixture of 10 ml of conc. sulphuric acid and 0.42 ml of fuming nitric acid ( $d$  1.50, 0.01 mole), cooled to  $-20^{\circ}\text{C}$  1.66 g (0.01 mole) of the title compound was added in small portions. After stirring for one hour at the same temperature, the reaction mixture was poured onto 200 g of ice and neutralized with solid sodium bicarbonate to pH 7, which caused precipitation of brown crystals. The crude nitro product weighed

1.4 g (66 %). Recrystallization from acetone-water yielded 1.3 g (62 %) of 7-hydroxy-6-methyl-3-nitro-7,6-borazarothieno[3,2-c]pyridine. M.p. 215–228°C. NMR (DMSO):  $\tau_{3,4,\text{OH}}$  0.77, 0.81, 1.53,  $\tau_{\text{CH}_3}$  6.42. (Found: C 34.14; H 2.84; N 19.48. Calc. for  $\text{C}_6\text{H}_6\text{BN}_3\text{O}_3\text{S}$  (211.0): C 34.15; H 2.87; N 19.91).

*Oxidation of the nitro product.* 0.3 g (0.0014 mole) of the nitro product was oxidized in the way as described earlier, giving 0.205 g (90 %) of 4-nitro-3-thiophenecarboxylic acid, m.p. 169–172°C.

*Nitration of 7-methyl-7,6-borazarothieno[3,2-c]pyridine (IIIc) in sulphuric acid.* To a mixture of 10 ml of conc. sulphuric acid and 0.42 ml of fuming nitric acid (*d* 1.5, 0.01 mole), cooled to 0°C 1.50 g (0.01 mole) of the title compound was added with vigorous stirring. After 2 h at the same temperature the reaction mixture was poured onto 200 g of ice and neutralized by solid sodium bicarbonate to pH 7, which caused precipitation of brown crystals. The crude nitro product weighed 1.90 g (97 %). Recrystallization from ethanol-water yielded 1.35 g (70 %) of 7-methyl-3-nitro-7,6-borazarothieno[3,2-c]pyridine, m.p. 177–179°C. NMR (DMSO):  $\tau_{\text{NH}}$  –1.83,  $\tau_{3,4}$  0.67, 1.12,  $\tau_{\text{CH}_3}$  9.15. (Found: C 37.02; H 2.92; N 21.74. Calc. for  $\text{C}_6\text{H}_6\text{BN}_3\text{O}_3\text{S}$  (195.0): C 36.95; H 3.10; N 21.54).

*Oxidation of the nitroproduct.* 0.5 g (0.0026 mole) of the nitro product was oxidized by the same procedure as described earlier, giving 0.290 g (64 %) of 4-nitro-3-thiophenecarboxylic acid, m.p. 169–172°C.

*Nitration of 4-hydroxy-4,5-borazarothieno[2,3-c]pyridine (IIa) in sulphuric acid.* 3.04 g (0.02 mole) of the title compound was nitrated as described earlier for the isomeric compound. The crude nitro product weighed 3.6 g (92 % yield). TLC on silica gel with chloroform as eluent showed two bands. 100 mg of the crude nitro product was put on 2 mm 20 × 20 cm plates and eluted 6 times (drying between each time). Extraction of each of the bands with acetone gave 71 mg of the compound (A) which moved most rapidly and 9 mg of the compound (B) which moved slower. The compound A was 4-hydroxy-3-nitro-4,5-borazarothieno[2,3-c]pyridine. M.p. after recrystallization from ethanol-water 200–205°C NMR (DMSO):  $\tau_{\text{NH}}$  –0.92,  $\tau_{3,7,\text{OH}}$  0.90, 1.62 and 2.92. (Found: C 30.50; H 2.00; N 20.86. Calc. for  $\text{C}_6\text{H}_4\text{BN}_3\text{O}_3\text{S}$  (197.0): C 30.48; H 2.05; N 21.32).

The nitro product B was 4-hydroxy-2-nitro-4,5-borazarothieno[2,3-c]pyridine. M.p. after recrystallization from ethanol-water 288–296°C. NMR (DMSO):  $\tau_{\text{NH}}$  –0.08,  $\tau_{3,7,\text{OH}}$  1.26, 1.42 and 1.66;  $J_{3,7} = 0.5$  c/s. (Found: C 32.27; H 2.01; N 21.51. Calc. for  $\text{C}_6\text{H}_4\text{BN}_3\text{O}_3\text{S}$  (197.0): C 30.48; H 2.05; N 21.32).

*Oxidation of the nitro product A.* 0.5 g (0.0025 mole) of the nitro product A was oxidized by the same procedure as described earlier, giving 0.20 g (46 % yield) of a crystalline product. The IR spectrum of this product was identical with the spectrum of an authentic sample of 4-nitro-2-thiophenecarboxylic acid, prepared by oxidation of 4-nitro-2-thiophene aldehyde diacetate<sup>33</sup> with hydrogen peroxide.<sup>34</sup>

*Nitration of 4-hydroxy-5-methyl-4,5-borazarothieno[2,3-c]pyridine (IIb) in sulphuric acid.* 1.66 g (0.01 mole) of the title compound was nitrated in the same way as the isomeric compound, described earlier, giving 1.3 g (62 %) of nitro products. TLC on silica gel with chloroform as eluent showed two yellow bands. By working on 2 mm 20 × 20 cm plates, eluting with chloroform 6 times (drying between each time) and extracting the two bands with acetone, these two nitro products could be isolated. In a typical run, 100 mg of crude nitro product was chromatographed, which gave 76 mg of the product which moved fastest (A) and 19 mg of the product which moved more slowly (B). Product A was 4-hydroxy-5-methyl-3-nitro-4,5-borazarothieno[2,3-c]pyridine. M.p. 155–158°C after recrystallization from ethanol-water. NMR (DMSO):  $\tau_{3,7,\text{OH}}$  0.88, 1.69 and 2.78,  $\tau_{\text{CH}_3}$  6.40. (Found: C 34.17; H 2.71; N 19.42. Calc. for  $\text{C}_6\text{H}_6\text{BN}_3\text{O}_3\text{S}$  (211.0): C 34.15; H 2.87; N 19.91).

Product B was 4-hydroxy-5-methyl-2-nitro-4,5-borazarothieno[2,3-c]pyridine. M.p. 232–257°C after recrystallization from ethanol-water. NMR (DMSO):  $\tau_{\text{OH}}$  0.95,  $\tau_{3,7}$  1.38–1.69,  $\tau_{\text{CH}_3}$  6.37;  $J_{3,7} = 0.7$  c/s. (Found: C 34.60; H 2.61; N 19.77. Calc. for  $\text{C}_6\text{H}_6\text{BN}_3\text{O}_3\text{S}$  (211.0): C 34.15; H 2.87; N 19.91).

*Oxidation of nitro product A.* 0.3 g (0.0014 mole) of nitro product A was oxidized by the same procedure as described earlier, giving 0.05 g (21 %) of 4-nitro-2-thiophenecarboxylic acid, identified by comparison of the IR spectrum with the spectrum of an authentic sample prepared as described above.

*Nitration of 7-hydroxy-7,6-borazarothieno[3,2-c]pyridine (IIIa) in acetic anhydride-nitric acid.* To a solution of 1.52 g (0.01 mole) of the title compound in 50 ml of acetic

acid a mixture of 10 ml acetic anhydride and 0.85 ml fuming nitric acid ( $d$  1.5, 0.02 mole) was added dropwise at room temperature. After stirring for 6 h, the reaction mixture was poured onto 100 g of ice and neutralized with solid sodium bicarbonate, which caused precipitation of yellow crystals (0.9 g, 46 %). Recrystallization from ethanol-water and drying in a drying pistol at 80°C over phosphorus pentoxide yielded (0.43 g, 22 %) of 7-hydroxy-4-nitro-7,6-borazarothieno[3,2-*c*]pyridine, m.p. 225–243°C. NMR (THF):  $\tau_{\text{NH}}$  -0.38,  $\tau_{\text{OH}}$  1.96,  $\tau_{2,3}$  1.91–2.01;  $J_{23}$  = 4.8 c/s. (Found: C 30.84; H 1.96; N 21.51. Calc. for  $\text{C}_6\text{H}_4\text{BN}_3\text{O}_3\text{S}$  (197.0): C 30.48; H 2.05; N 21.32).

*Degradation of the nitro product.* 0.4 g (0.002 mole) of the nitro product was refluxed with 25 ml of 2 N sodium hydroxide for 2 h. After cooling to room temperature the mixture was extracted with ether, the water phase acidified to pH 1 with conc. hydrochloric acid and extracted 3 times with 50 ml of ether. The combined ether phases were dried over sodium sulphate and evaporated *in vacuo*, giving 71 mg (28 %) of 3-thiophenecarboxylic acid identified by comparison of the IR spectrum with the spectrum of an authentic sample prepared according to Gronowitz.<sup>35</sup>

*Nitration of 7-hydroxy-6-methyl-7,6-borazarothieno[3,2-*c*]pyridine (IIIb) in acetic anhydride-nitric acid.* To a solution of 1.66 g (0.01 mole) of the title compound and 20 ml of acetic acid a mixture of 10 ml acetic anhydride and 0.42 ml of fuming nitric acid ( $d$  1.5, 0.01 mole) was added dropwise. After stirring for 2 h, the reaction mixture was worked up as described earlier, giving 1.6 g (76 %) of the crude nitro product. Recrystallization from ethanol-water yielded 1.3 g (62 %) of 7-hydroxy-6-methyl-4-nitro-7,6-borazarothieno[3,2-*c*]pyridine, m.p. 140–155°C. NMR (THF):  $\tau_{\text{OH}}$  1.38;  $\tau_{2,3}$  1.97–2.03;  $J_{23}$  = 5.0 c/s. (Found: C 34.45; H 2.78; N 19.59. Calc. for  $\text{C}_6\text{H}_5\text{BN}_3\text{O}_3\text{S}$  (211.0): C 34.15; H 2.87, N 19.91).

*Degradation of the nitro product.* 0.3 g (0.0014 mole) of the nitro product was treated in the same way as described earlier, giving 0.060 g (33 %) of 3-thiophenecarboxylic acid, identified as above.

*Nitration of 7-methyl-7,6-borazarothieno[3,2-*c*]pyridine (IIIc) by acetic anhydride-nitric acid.* To a solution of 1.50 g (0.01 mole) of the title compound and 20 ml of acetic acid a mixture of 5 ml acetic anhydride and 0.85 ml of fuming nitric acid ( $d$  1.5, 0.02 mole) was added dropwise at room temperature. After stirring for 2 h, the reaction mixture was worked up as described earlier, giving 0.7 g (36 %) of the crude nitro product. Recrystallization from acetone-water yielded 0.4 g (21 %) of 7-methyl-4-nitro-7,6-borazarothieno[3,2-*c*]pyridine, m.p. 210–214°C. NMR (THF):  $\tau_{2,3}$  1.80–1.95,  $\tau_{\text{CH}_3}$  9.00;  $J_{23}$  = 5.10 c/s. (Found: C 37.14; H 2.82; N 21.49. Calc. for  $\text{C}_6\text{H}_6\text{BN}_3\text{O}_3\text{S}$  (195.0): C 36.95; H 3.10; N 21.54).

*Nitration of 4-hydroxy-4,5-borazarothieno[2,3-*c*]pyridine (IIa) in acetic anhydride-nitric acid.* 1.52 g (0.01 mole) of the title compound was nitrated under the same condition as described earlier for the isomeric compound, giving 0.9 g (46 %) of the crude nitro product. Recrystallization from ethanol-water and drying in a drying pistol at 80°C over phosphorus pentoxide yielded 0.6 g (30 %) of 4-hydroxy-7-nitro-4,5-borazarothieno[2,3-*c*]pyridine, m.p. 265–288°C. NMR (THF):  $\tau_{\text{NH}}$  -0.50,  $\tau_{\text{OH}}$  1.52,  $\tau_{2,3}$  2.12–2.28;  $J_{23}$  = 5.2 c/s. (Found: C 31.14; H 1.84; N 22.05. Calc. for  $\text{C}_6\text{H}_4\text{BN}_3\text{O}_3\text{S}$  (197.0): C 30.48; H 2.05; N 21.32).

*Degradation of the nitro product.* The nitro product (0.40 g, 0.02 mole) was treated in the same way as described earlier, giving 0.080 g (31 %) of 2-thiophenecarboxylic acid, identified by comparison of the IR spectrum with that of an authentic sample prepared according to Gilman.<sup>36</sup>

*Nitration of 4-hydroxy-5-methyl-4,5-borazarothieno[2,3-*c*]pyridine by acetic anhydride-nitric acid.* 1.66 g (0.01 mole) of the title compound was nitrated as described earlier for the isomeric compound, giving 1.3 g (62 %) of a crude nitro product. Recrystallization from ethanol-water yielded 0.9 g (43 %) of 4-hydroxy-5-methyl-7-nitro-4,5-borazarothieno[2,3-*c*]pyridine, m.p. 260–265°C. NMR (THF):  $\tau_{\text{OH}}$  1.50,  $\tau_{2,3}$  2.20–2.42;  $J_{23}$  = 5.2 c/s. (Found: C 34.38; H 2.60; N 20.09. Calc. for  $\text{C}_6\text{H}_5\text{BN}_3\text{O}_3\text{S}$  (211.0): C 34.15; H 2.87; N 19.91).

*Degradation of the nitroproduct.* The nitro product (0.42 g, 0.002 mole) was treated in the same way as described earlier, giving 0.097 g (38 %) of 2-thiophenecarboxylic acid, identified as above.

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