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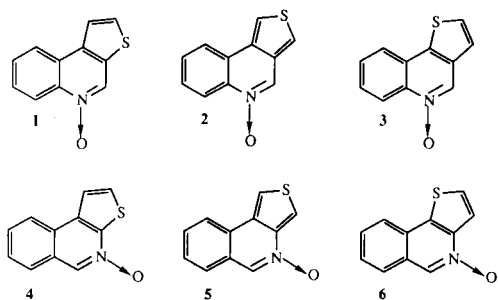
The synthesis of the two remaining isomeric monothiophene analogues of phenanthridine *N*-oxide, thieno[3,2-*c*]quinoline *N*-oxide and thieno[3,2-*c*]isoquinoline *N*-oxide, is described. The ^1H and ^{13}C nmr spectra of all six isomeric thieno-fused quinoline and isoquinoline *N*-oxides are discussed.

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Introduction.

For a number of years we have been interested in studying the effect of the annelation of thiophene rings in tricyclic heterocyclic systems on the chemical and spectroscopic properties. We have previously described a convenient synthesis of some thieno-fused analogues of phenanthridine *N*-oxide, consisting of the Pd(0)-catalysed coupling of *o*-bromonitrobenzene with *o*-formylthiopheneboronic acids to give *o*-formyl-3-(2-nitrophenyl)thiophenes, which upon reduction with ammoniacal ferrous sulfate ring-closed to thieno-fused quinoline *N*-oxides **1** and **2**. Similarly, from *o*-formylbenzeneboronic acid and *o*-bromonitrothiophenes, thieno-fused isoquinolines **4** and **5** were obtained *via* *o*-nitro-3-(2-formylphenyl)thiophenes [1]. In this way, four of the six isomeric monothiophene analogues of phenanthridine *N*-oxide could be prepared (Scheme I). A similar strategy was previously used for the synthesis of six of nine isomeric dithiophene analogues of phenanthridine *N*-oxides [2].

Scheme I



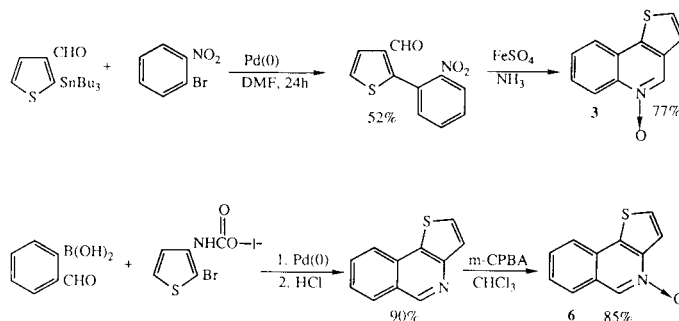
Synthesis.

The synthesis of thieno[3,2-*c*]quinoline *N*-oxide (**3**) by this approach failed due to the easy hydrolysis of 3-formyl-2-thiopheneboronic acid under the weakly alkaline reaction conditions, while the attempted coupling of *o*-formylbenzeneboronic acid with 2-bromo-3-nitrothiophene to thieno[3,2-*c*]isoquinoline *N*-oxide (**6**) failed due to the high reactivity and instability of the latter compound [1].

We have previously found that the coupling of tin deriv-

atives under neutral conditions can be successful, when the coupling with boronic acid fails [2]. We therefore reacted 2-tributylstannyl-3-thiophenecarboxaldehyde [3] with *o*-bromonitrobenzene under Pd(0)-catalysis, which gave 2-(2-nitrophenyl)-3-thiophenecarboxaldehyde in 52% yield. Reduction with ammoniacal ferrous sulfate then gave **3** in 77% yield (Scheme II).

Scheme II



Attempts to couple *o*-tributylstannylbenzaldehyde, or the less sterically crowded *o*-trimethylstannylbenzaldehyde, with 2-bromo-3-nitrothiophene also failed due to the decomposition of 2-bromo-3-nitrothiophene. The missing thieno[3,2-*c*]isoquinoline *N*-oxide (**6**) was therefore prepared in 85% yield through oxidation of thieno[3,2-*c*]isoquinoline with *m*-chloroperbenzoic acid, which was prepared in 90% yield in a one-pot procedure, through the Pd(0) catalyzed coupling of *o*-formylbenzeneboronic acid and *t*-butyl-*N*-(2-bromo-3-thienyl)carbamate [4].

NMR Spectra.

We have now undertaken a detailed study of ^1H and ^{13}C spectra of all six isomers, in order to be able to study aromatic substitution reactions of these heterocycles.

^1H NMR Spectra.

Assignments of ^1H chemical shifts and coupling constants of these compounds are given in Tables I and II. The ^1H nmr spectra of the six thieno[*c*]quinoline and thieno[*c*]isoquinoline *N*-oxides were in accordance with their structures. The characteristic feature of these spec-

tra is that the azomethine protons (H_4 and H_5) are more deshielded than other protons, owing to the adjacent nitrogen atom. The thiophene hydrogens appear as an AB quartet with normal thiophenic 2,3-coupling constants (5-5.5 Hz) and 2,5-coupling constants (2.8-3.5 Hz) [5]. Unambiguous shift assignments of the thiophene hydrogens were based on the 1H - ^{13}C HETCOR spectra (Figure 1).

Table I. 1H nmr chemical shifts (δ , ppm) of the thieno(c)isoquinoline and thieno(c)quinoline N-oxides [a]

Compound	1H	2H	3H	4H	5H	6H	7H	8H	9H
1	7.82	7.74		8.90		8.83	7.70	7.70	8.20
2	7.77		8.08	8.70		8.74	7.70	7.70	8.17
3		7.62	7.39	8.96		8.87	7.74	7.74	8.08
4	7.70	7.84			8.80	8.19	7.65	7.65	7.84
5	8.11		8.37		8.48	8.10	7.54	7.54	7.68
6		7.99	7.65		8.75	7.90	7.65	7.65	7.81

[a] The numbering is analogous to that given in Table IV.

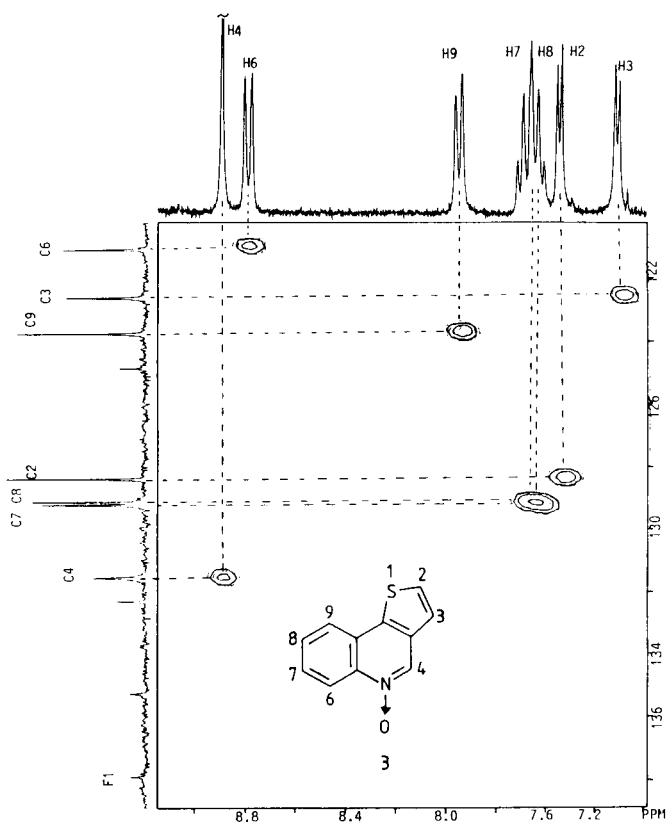


Figure 1. 1H - ^{13}C HETCOR spectrum of compound 3.

Table II. 1H nmr coupling constants (J , Hz) for the thieno(c)isoquinoline and thieno(c)quinoline N-oxides

Compound	J_{12}	J_{23}	J_{13}	J_{67}	J_{68}	J_{78}	J_{79}	J_{89}
1	5.3			7.8	1.8	6.8	1.7	7.4
2			2.8	6.1	2.6	6.5	2.2	6.1
3		5.3		8.2	1.5	6.7	1.5	7.4
4	5.5			8.1	1.6	6.7	1.7	7.8
5			3.5	7.1	1.3	6.8	1.4	7.6
6		5.5		7.9	1.3	7.1	1.4	8.2

The coupling constants of the benzene parts are in the intervals of 6.1-8.2 Hz and 1.3-2.6 Hz, which are characteristic for J_{ortho} and J_{meta} in benzene [6].

^{13}C Chemical Shift Assignments.

Unambiguous assignments of the ^{13}C nmr signals of these systems are given in Table III. Assignments were based on proton-decoupled ^{13}C spectra, proton-coupled ^{13}C spectra and 1H - ^{13}C HETCOR spectra. The HETCOR spectrum of compound 3 is shown in Figure 1. In the parent thiophene ring, the ^{13}C chemical shift of the α -carbon is smaller than that of the β -carbon [7], while in all fused systems this shift is larger than that of the β -carbon. The azomethine carbons (C_4 and C_5) are more shielded than these carbon atoms in the parent compounds [8].

This general trend in these systems arises on N -oxidation, which results in shieldings of the adjacent carbon atoms, and clearly indicates the high electron density of these positions in the ring. This has also been observed in quinoline and isoquinoline [9].

Table III. The chemical shifts ($\delta^{13}C$, ppm) of the thieno(c)isoquinoline and thieno(c)quinoline N-oxides [a]

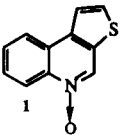
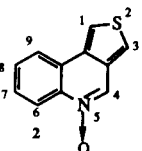
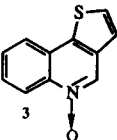
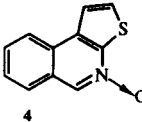
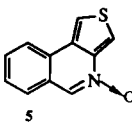
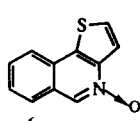
Compound	C1	C2	C3	C4	C5	C6	C7	C8	C9
1	121.3	130.2		130.4		120.5	128.7	128.9	123.8
2	118.5		120.7	129.7		120.2	129.3	128.0	123.5
3		128.4	121.1	131.4		122.6	129.0	129.2	123.8
4	121.4	127.6			132.2	122.6	127.6	128.8	125.5
5	115.8		119.1		132.8	122.7	127.7	129.1	125.8
6		127.0	120.0		133.6	122.4	128.1	129.2	125.9

[a] Containing only the CH carbons.

^{13}C - 1H Coupling Constants.

Unambiguous assignments of the carbon-proton coupling constants are given in Table IV. The assignments were based on the proton-coupled ^{13}C nmr spectra. In addition to the large splitting, $^1J_{CH}$, each of the proton-bearing carbons, except for C_4 in compound 1 and 3, appears as two doublets or quartets due to long-range couplings. The one-bond 1H - ^{13}C coupling constants in the benzene part fell in the range 160-168 Hz. The C_{α} - H_{α} coupling constants range from 180 Hz to 192 Hz in the thiophene subunits, while the C_{β} - H_{β} coupling constants in the thiophene part have the values of 169-172 Hz, which are ca 20 Hz smaller than the values of $J_{C_{\alpha}H_{\alpha}}$. This large difference should be very useful for the structure determination of α - or β -mono-substituted derivatives. J_{CH4} in thieno[c]quinoline N -oxides and J_{CSH5} in thieno[c]isoquinoline N -oxides range from 184 Hz to 188 Hz. The long-range C_{α} - H_{β} coupling constants in the thiophene ring range from 5.4 Hz to 7.4 Hz, which are 2 Hz larger than the coupling constants of $C_{\beta}H_{\alpha}$ (2.1 Hz-5.1 Hz). Long-range couplings over three bonds are observed not only in the thiophene part, but also in the isoquinoline systems between C_5 and H_6 .

Table IV The J_{CH} values (Hz) in thieno(c)isoquinoline- and thieno(c)quinoline *N*-oxide

	$^1J_{CH}$	$^2J_{CH}$	$^3J_{CH}$
	C1H1 171 C2H2 188 C4H4 188 C6H6 168 C7H7 163 C8H8 162 C9H9 163	C1H2 4.1 C2H1 6.5 C6H7 7.0 C9H8 7.4	
	C1H1 187 C3H3 192 C4H4 188 C6H6 167 C7H7 162 C8H8 164 C9H9 162	C6H7 8.1 C9H8 8.1	C1H3 5.3 C3H1 4.9 C3H4 2.1 C4H3 2.2
	C2H2 188 C3H3 173 C4H4 185 C6H6 169 C7H7 164 C8H8 162 C9H9 160	C2H2 6.1 C3H2 6.9	
	C1H1 172 C2H2 188 C5H5 187 C6H6 161 C7H7 162 C8H8 162 C9H9 164	C1H2 2.1 C2H1 5.4 C6H7 7.2 C9H8 7.2	C5H6 5.4
	C1H1 196 C3H3 190 C5H5 184 C6H6 161 C7H7 163 C8H8 162 C9H9 163	C6H6 7.0 C9H8 7.5	C1H3 3.6 C3H1 5.5 C5H6 4.5
	C2H2 188 C3H3 178 C5H5 184 C6H6 162 C7H7 164 C8H8 161 C9H9 164	C2H3 7.5 C3H2 5.1 C6H7 7.1 C9H8 6.5	C5H6

EXPERIMENTAL

Melting points are uncorrected. The 1H nmr spectra were recorded with a Varian XL-300 spectrometer in deuteriochloroform solution. The mass spectra were recorded on a Finnigan 4021 spectrometer. The glc analyses were carried out on a Varian 3700 gas chromatograph using an OV-17, 3%, 2 m column.

2-(2-Nitrophenyl)-3-thiophenecarboxaldehyde.

A 250 ml three-necked flask equipped with condenser, magnetic stirrer, thermometer and nitrogen inlet, was charged with 8.0 g (0.02 mole) of 2-tributylstannyl-3-thiophenecarboxaldehyde [3], 4.0 g (0.02 mole) of *o*-bromonitrobenzene, 0.69 g (0.6 mmole) of tetrakis(triphenylphosphine) palladium(0) [10], and 90 ml of anhydrous dimethylformamide. The mixture was stirred at 100° for 24 hours. After cooling the mixture to room temperature, it was evaporated and the residue diluted with water. The water phase was extracted three times with ether and the combined organic phases were dried over magnesium sulfate. After removal of the solvent the residue was recrystallized from ethanol to give 2.42 g (52%) of the title compound as yellow needles, mp 79-80°. 1H nmr (deuteriochloroform): δ = 9.71 (d, 1H, -CHO), 8.09 (m, 1H, H_3), 7.76 (m, 1H, H_5), 7.70 (m, 1H, H_4), 7.55 (d, 1H, H_2), 7.52

(m, 1H, H_6), 7.41 (dd, 1H, H_7), $J_{H_4-H_5}$ = 5.2 Hz, J_{CHO-H_5} = 0.71 Hz. Anal. Calcd. for $C_{11}H_7NO_3S$: C, 56.65; H, 3.02; N, 6.01. Found: C, 56.54; H, 3.12; N, 6.12.

Thieno[3,2-c]quinoline *N*-Oxide (3).

This compound was prepared according to the procedure described in ref [1], from 2.1 g (0.009 mole) of 2-(2-nitrophenyl)-3-thiophenecarboxaldehyde, 23 g (0.08 mole) of ferrous sulfate in 60 ml of water, nine drops of 2 *N* hydrochloric acid and 25 ml of aqueous ammonia. After workup, the residue was recrystallized from acetonitrile to give 1.4 g (77%) of the title compound, mp 187-188°.

Anal. Calcd. for $C_{11}H_7NOS$: C, 65.65; H, 3.51; N, 6.96. Found: C, 65.34; H, 3.48; N, 6.84.

Thieno[3,2-c]isoquinoline *N*-Oxide (6).

To a stirred solution of 1.0 g (0.0054 mole) of thieno[3,2-c]isoquinoline [4] in 25 ml of chloroform, 1.2 g (0.0069 mole) of *m*-chloroperbenzoic acid (Aldrich, 80-90%) was added, in small portions over a period of 2 hours. Stirring at room temperature was continued for two days. The solution was extracted twice with 10 ml of 5% aqueous sodium hydroxide. The organic layer was dried (sodium sulfate) and evaporated. The solid residue was recrystallized from ethanol to give 0.9 g (83%) of the title compound, mp 182-183°.

Anal. Calcd. for $C_{11}H_7NOS$: C, 65.65; H, 3.51; N, 6.96. Found: C, 65.13; H, 3.28; N, 6.75.

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