Molecules **2007**, *12*, 1623-1631

molecules

ISSN 1420-3049

www.mdpi.org/molecules

Full Paper

o-Quinonoid Heterocycles: Synthesis and Crystal Structure of 2,3-Dicyano-5,7-bismethylthieno[3,4-*b*]pyrazine

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Received: 1 June 2007; in revised form: 20 July 2007 / Accepted: 20 July 2007 / Published: 30 July 2007

Abstract: 2,3-Dicyano-5,7-bismethylthieno[3,4-*b*]pyrazine (**5**), has been obtained as a minor product from reactions of *S*-nucleophiles with 5,6-di(1-bromoethyl)pyrazine-2,3-dicarbonitrile (**3**), or from a condensation of 4-hydroxy-2,5-dimethyl-2,3-dihydrothiophen-3-one (**4**) with diaminomaleonitrile. The molecular structure of compound **5** has been confirmed by X-ray diffraction. A partial separation of charge causes a donor-acceptor type arrangement of the planar molecules in uniform parallel stacks with an interplanar spacing of 3.334(2) Å at 100 K.

Keywords: Thieno[3,4-*b*]pyrazine; *o*-quinonoid heterocycles; pyrazine-dicarbonitrile; di(1-bromoethyl)pyrazine; crystal structure.

Introduction

Several years ago we reported studies on 5,6-bis(bromomethyl)pyrazine-2,3-dicarbonitrile as a potential synthon for substituted azaphthalocyanines (AzaPcs) [1]. Due to its extremely labile "benzylic" hydrogens, the dicarbonitrile was found to be too reactive towards base to be of general use. The branched 1-bromoethyl group, expected to be less reactive towards base, might be a good

substitute for the bromomethyl group, but pyrazines with chiral side chains would result from reactions with nucleophiles.

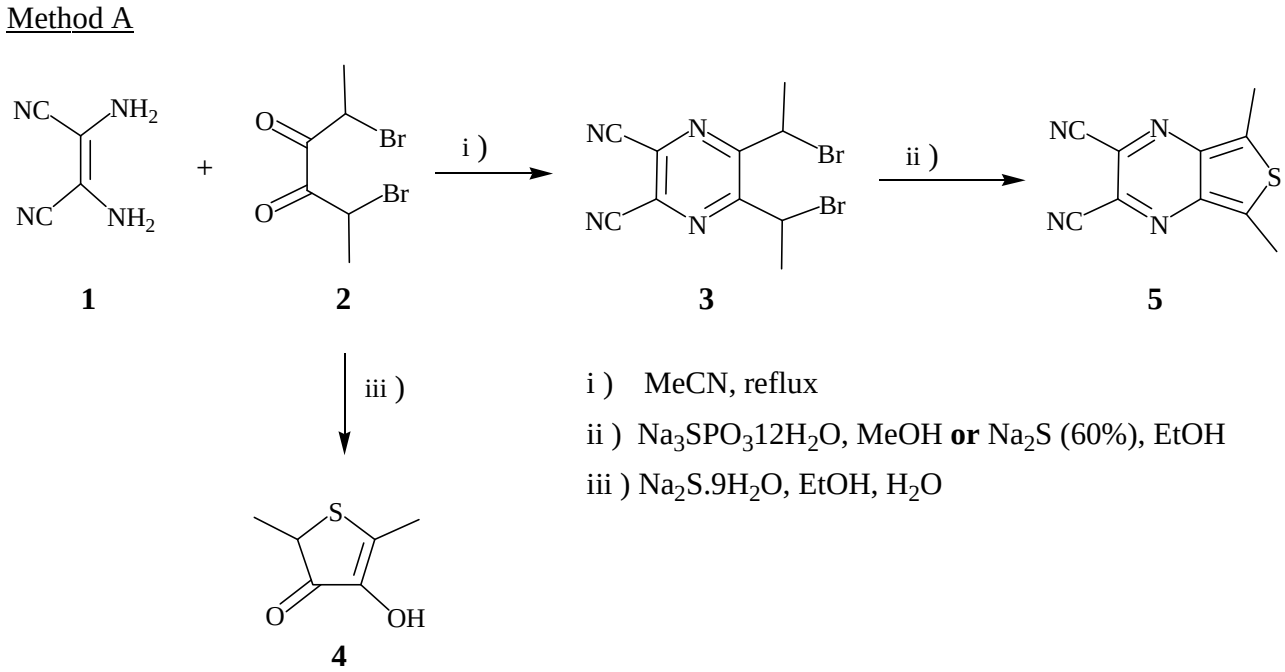
The objective of the present work was to prepare and explore 5,6-bis(1-bromoethyl)pyrazine-2,3-dicarbonitrile (**3**) as a synthon for octa-substituted AzaPcs. Reactions of **3** with sodium sulfide followed by oxidation, were expected to give **5** *via* the corresponding dihydrothiophene derivative.

Results and Discussion

Syntheses

A reaction between diaminomaleonitrile (**1**) and 2,5-dibromohexane-3,4-dione (**2**) [2], gave 5,6-di(1-bromoethyl)pyrazine-2,3-dicarbonitrile (**3**) in approximately 83 % crude yield (Scheme 1). This product was a mixture of 5-(1-bromoethyl)-6-ethyl-pyrazine-2,3-dicarbonitrile and the two diastereomers of **3**. NMR spectroscopy does not allow determination of absolute configuration, but single or double signals for the hydrogens at a chiral centre will tell whether one or two diastereomers are present. One diastereomer of the pure compound **3** was obtained (48 %) upon chromatography on silica with benzene elution. Sharp proton and carbon NMR signals for **3** support this conclusion, which is in accord with studies of the analogous compound 1,2-bis(1-bromoethyl)benzene by Wyatt *et al*. [3].

Scheme 1. Synthesis of 2,3-Dicyano-5,7-bismethylthieno[3,4-*b*]pyrazine (**5**).



As anticipated, compound **3** is more stable towards base than 5,6-bis(bromomethyl)pyrazine-2,3-dicarbonitrile [1], but it still decomposes in pyridine after a couple of hours. In fact, the latter

compound decomposes immediately in methanol solutions of sodium sulphide or trisodium thiophophate dodecahydrate, wheras **3** is relatively stable towards these reagents. Thus, it is obvious that the secondary "benzylic" hydrogens of **3** are less reactive towards base, both due to steric hindrance, and as well to inductive electron donation from the attached methyl groups.

Trisodium thiophosphate dodecahydrate, a reagent used for base sensitive substrates [4], gave an unexpected reaction with compound **3**. A small amount (8 %) of a crimson red powder was obtained, identified as 2,3-dicyano-5,7-bismethylthieno[3,4-*b*]pyrazine (**5**). We were not able to isolate any of the expected dihydroanalogues of **5** from the tarry reaction mixture. A reaction where a solution of **3** in ethanol was added slowly to an ethanol solution of 60 % powdered sodium sulphide yielded 15 % of compound **5**. In another experiment where the two reactants were mixed at once a slightly lower yield (11 %) of **5** was obtained. Other reaction products were polar compounds which could not be properly characterized due to slow decomposition. We were not able to convert any of these products to **5**. Reactions of **3** with sodium sulfide in other solvents, i.e. 1-propanol, 1-butanol or quinoline gave lower yields of **5**.

An alternative method for preparation of **5**, or its dihydro analogue, would be a reaction of 4-hydroxy-2,5-dimethyl-2,3-dihydrothiophen-3-one (**4**) with **1**. Compound **4**, a flavour enhancing substance for baked breads, has been reported in patents [5,6]. However, although we found that phase transfer conditions were superior to the reported method of preparation, **4** was not in any instance obtained as a crystalline compound, as reported [6]. A reaction of compound **4** with **1** gave compound **5** in low yield (3 %).

Although the thieno[3,4-*b*]pyrazine system is known, previous synthetic methods are based on condensations of 3,4-diamino-thiophenes with *o*-dicarbonyl compounds [7,8]. The analogous thieno[3,4-*b*]quinoxaline system has been studied by Cava and his group [9,10].

Crystal structure of compound **5**

Compound **5** crystallized in space group $P2_1/m$. With *b* as the unique axis this space group has mirror planes at y = ¼ and ¾. The asymmetric (unique) unit of **5** is one half molecule related to the other half through the crystallographic mirror planes. Figure 1 displays the mirror symmetry of the molecule, and confirms the assignment of its conformation from spectroscopy. All the non-hydrogen atoms are nearly confined to one plane, the thiophene and pyrazine rings are significantly coplanar. There is a small out-of-plane bending of the nitrile goups, the deviations of C(4) and N(2) from the common ring plane are 0.012(2) and 0.036(2) Å, respectively, the methyl C(5) atom is displaced by 0.021(2) Å to the opposite side of this plane. The structure of **5** thus conforms very closely to two orthogonal mirror planes, of which one is exact, the line of intersection runs through the midpoint of the C(3) – C(3') bond and the S atom. There is no strong anisotropy in the ADPs of the non-H atoms, hence, no indication of disorder at 100 K. The strong colour indicates an extended π electron delocalization.

The CSD data base contains structure data for two related compounds: 2,3-dimethylthieno[3,4-*b*]pyrazine (*A*) [11] and 2,3-dimethyl-5,7-bis(2-thienyl)thieno[3,4-*b*]pyrazine (*B*) [12]. There are similarities in the bonding parameters of **5**, *A* and *B*, notably a very large asymmetry in the two C─N bond lengths of the pyrazine ring; mean values and ranges for the three compounds are 1.372 ± 0.005

Å for C(2)─N(1) and 1.307 ± 0.006 Å for C(3)─N(1). In comparison the unsubstituted delocalized pyrazine ring has four equal C─N bonds of intermediate length 1.336 Å [13]. The largest structural difference between **5** and compounds *A* and *B* appears in the pyrazine C─C bonds; C(2)─C(2'), 1.451(2) Å and C(3)─C(3'), 1.446(2) Å, in **5** are of similar magnitude, vs. 1.423 ± 0.005 Å and 1.465 ± 0.005Å, respectively, in *A*/*B*. In the parent pyrazine structure there are two equivalent C─C bonds of length 1.405 Å. The value 1.423 Å corresponds very closely to the C─C bond length in thiophene [13]. The thiophene ring of compound *B* exhibits a much stronger degree of delocalization than **5** and *A* due to the two thienyl side groups.

Both the pyrazine ring and the two CN groups are electron attractive, causing a partial separation of charge, with excess positive charge on the S atom (or the thiophene ring) and excess negative charge on the pyrazine N atoms and the CN groups.

Figure 1. Molecular conformation of compound **5**. A few atoms generated by mirror symmetry have been labelled (primed numbers). ADP ellipsoids correspond to a 50 % probability.

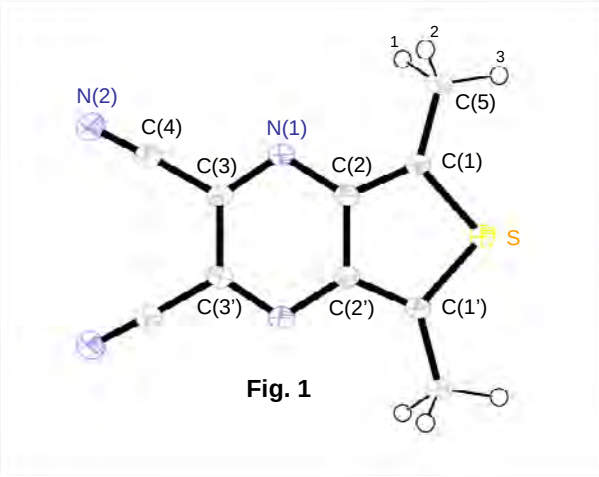
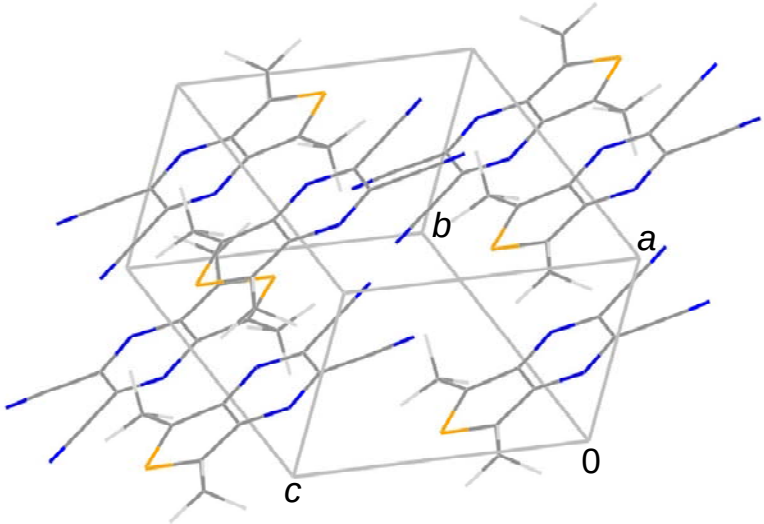


Figure 2. Crystal structure showing the arrangement of planar molecules in stacks with alternating orientation along **b**. Within each stack there is strong intermolecular interaction. Colour code: S: orange, N: blue, C: grey, H: light grey.



The crystal structure of **5** is shown in Figure 2. The molecules form uniform stacks, all molecular planes are parallel and very nearly lying in the (1 0 1) planes. Molecules in neighbour stacks along **b** have their long axis turned in opposite directions. All molecules within a stack have the same orientation. The thiophene ring is directly facing the fragment containing ½ pyrazine ring and the cyano groups of the adjacent molecule of the same stack in a donor-acceptor like arrangement, promoted by the charge separation within the molecule. The interplanar distance is only 3.334(2) Å, which is comparable to the parent distance in the common hexagonal graphite, 3.354 Å (= *c*/2) at room temperature [14], or 3.341 Å at 100 K, calculated from the thermal expansion coefficient *a*(*T*) along **c** in [14]. The short interplanar distance in **5** relays a significant electrostatic character of the intrastack interaction. The shortest lateral S····N contacts, S····N(2) and S····N(2'), 3.366(2) Å, both N of the molcule at *x*-1, *y*, *z*+1, are normal van der Waals contacts connecting neighbour stacks along **c**. The cohesion in the **b** direction is much weaker. The shortest contacts in this direction are two of the type C─H····N, at 2.77 and 2.71 Å, involving both N(1) and N(2) in two different molecules of the nearest stack along **b**. Contacts involving H have been calculated with the C─H bonds normalized to 1.10 Å.

Experimental

General

Mass spectra were obtained on an AEI MS-902 spectrometer at 70 eV electron energy. IR spectra were obtained on a Nicolet 20-SXC FT-IR spectrometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker Avance DPX 400 NMR spectrometer at 399.65 MHz and at 100.40 MHz, respectively, with tetramethylsilane (TMS) as internal standard. UV-Vis spectra were obtained on a Cary 50 UV-vis spectrophotometer. Melting points were obtained on a Büchi 530 melting point apparatus and are uncorrected. Merck Kieselgel 60F 254 was used for TLC and Merck silica 63-200 :m was used for column chromatography.

Syntheses

2,5-Dibromohexane-3,4-dione (**2**)

2,5-Dibromohexane-3,4-dione (**2**) was prepared [2] by bromination of hexane-3,4-dione and purified by chromatography on silica with dichloromethane (DCM) as eluent; R_f ($CHCl_3$) = 0.75. ^{1}H- NMR ($CDCl_3$) δ 1.82 (6H, m), 5.27 (2H, m).

5,6-Di(1-bromoethyl)pyrazine-2,3-dicarbonitrile (**3**)

A mixture of diaminomaleonitrile (**1**, 4.32 g, 40 mmol) and 2,5-dibromohexane-3,4-dione (**2**, 10.9 g, 40 mmol) in acetonitrile (70 mL) was heated under reflux for 1.5 h. The solvent was removed under reduced pressure and the solid residue was chromatographed on silica with DCM to give 11.5 g (approx. 83 %) of the title compound; m.p. 135–149 °C. This solid was chromatographed on silica with benzene and 6.5 g (48 %) of pure product were obtained; m.p. 160–162 °C; ^{1}H-NMR ($CDCl_3$) δ

2.14 (6H, d, J = 6.6 Hz), 5.55 (2H, q, J = 6.6 Hz); ^{13}C-NMR ($CDCl_3$) δ 21.55 (CH_3), 40.12 (CH), 112.57 (CN), 131.35 (C-5, C-6), 157.10 (C-2, C-3); MS *m/z* (% rel. int.) 346 (1.5), 344 (M, 3.3), 342 (1.6), 265 (49.8), 264 (7.8), 263 (50.8); Calc. for $C_{10}H_8{}^{79}Br^{81}BrN_4$: 343.9095. Found: 343.9090.

4-Hydroxy-2,5-dimethyl-2,3-dihydrothiophen-3-one (**4**)

Compound **4** has been prepared by other workers from **2** and sodium sulfide nonahydrate in ethanol [6]. A solution of **2** (2.72 g, 10 mmol) in DCM (40 mL) was mixed with a solution of sodium sulfide nonahydrate (3.6 g, 15 mmol) in water (20 mL) and the phase transfer catalyst methyl-trioctylammonium chloride ("Aliquat", 0.1 g). The mixture was stirred vigorously at ambient temperature for 2 h. The reaction was monitored by TLC with chloroform on silica. The organic phase was dried over magnesium sulfate, and the solvent was removed under reduced pressure to yield a yellow semisolid, 1.1 g (76 %). Lit [6] m.p. 77–79 °C. Attempts to recrystallise the product were unsuccessful, and compound **4** seemed slightly unstable even when kept in the dark at 5 °C. ^{1}H-NMR ($CDCl_3$) δ 1.57 (3H, d, J = 7 Hz), 2.27 (3H, s), 3.69 (1H, q, J = 7 Hz), 6.20 (1H, broad s); ^{13}C-NMR ($CDCl_3$) δ 14.92, 16.99, 45.50, 141.37, 147.93, 197.98.

2,3-Dicyano-5,7-bismethylthieno[3,4-b]pyrazine (**5**): Method A with trisodium thiophosphate dodecahydrate

To a solution of **3** (0.52 g, 1.5 mmol) in methanol (15 mL) was added a suspension of trisodium thiophosphate dodecahydrate (0.59 g, 15 mmol) in methanol (15 mL). The reaction mixture was heated under reflux for 19 h, concentrated to about 5 mL and extracted with DCM (3 x 15 mL). The red DCM extracts were chromatographed on silica eluting with DCM. The first red fractions were combined, evaporated and the residue was filtered with diethyl ether to yield 0.02 g (8 %) of a crimson red powder, m.p. 275 – 278 °C (dec.); ^{1}H-NMR ($CDCl_3$) δ 2.91 (6H, s); ^{13}C-NMR ($CDCl_3$) δ 11.94 (CH_3), 114.02 (CN), 126.90, 134.18, 137.04; IR (KBr) < 2228 (CN), (1385, 1327, 1247, C=N or C=C), 1116 (C-S) cm^{-1}; UV-vis [CH_2Cl_2 (,)] 340 (4 900), 484 (1 500) nm; MS *m/z* (% rel. int.) 216 (5.8), 215 (15.4), 214 (M, 100), 213 (74.8); Calc. for $C_{10}H_6N_4S$: 214.0313. Found 214.0311.

Method A with sodium sulfide

Finely ground 60 % sodium sulfide (0.10 g, 0.7 mmol) was dissolved in ethanol (20 mL). A solution of compound **3** (0.21 g, 0.6 mmol) in ethanol (20 mL) was added dropwise during 30 min, and the orange solution was stirred at ambient temperature for 48 h. The solvent was removed under reduced pressure, and the residue was extracted with benzene (2 x 10 mL). Removal of the benzene gave a glassy red residue (0.09 g) which was chromatographed on silica eluting with benzene. The fractions with R_f (benzene) = 0.3 were combined to give 0.03 g of a red solid, which was recrystallized from benzene to yield 0.02 g (15 %) of compound **5**, m.p. 263–265 °C (dec.). The rest of the benzene soluble material was eluted from the column with acetone and gave 0.06 g of a glassy solid, R_f ($CHCl_3$) = 0, R_f(benzene) = 0. This material decomposed slowly when kept in chloroform solution. ^{1}H-NMR ($CDCl_3$) δ 1.3 – 2.0 and 2.6 – 2.9 (broad unresolved multiplets), 4.5 (weak, broad s). UV-vis (acetone)

329 nm. The benzene insoluble material was extracted with acetone and 0.05 g of a glassy brown solid was obtained from the acetone extract. This material was insoluble in water, but decomposed slowly in air. UV-vis (acetone): 330 nm.

Method B

A solution of **1** (1.08 g, 10 mmol) and **4** (1.44 g, 10 mmol) in acetonitrile (25 mL) was heated under reflux for 6 h, then heated at 45 ^{0}C for 5 days. The solvent was removed under reduced pressure, and the residue chromatographed on silica with DCM. The first fractions yielded 0.06 g (3 %) m.p. 190 – 300 ^{0}C (dec); ^{1}H- and ^{13}C-NMR spectra were identical to those of **5** obtained by Method A. The silica column was emptied with acetone and compound **1**, 0.5 g (46 %) m.p. 175 – 184 °C (dec) was obtained from the oily residue with diethyl ether.

*X-ray structure study of **5***

Compound **5** produced by Method A with Na_2S was obtained as an intergrowth of crimson red crystals by slow evaporation from a benzene solution. A small single crystal of size about 75 × 55 × 25 mm was cut from a larger specimen and used for the diffraction study. Intensity data were collected at 100 K on an Oxford Diffraction 6-circle diffractometer equipped with an Onyx CCD detector using synchrotron radiation. Frames of data were collected by 0.6^o scans in ω for a range of crystal orientations and detector 2θ settings so as to obtain a good coverage of reciprocal space out to a resolution of d = 0.75 Å (sinθ/λ = 0.667 Å^{-1}). The data were corrected for Lorentz and polarization effects and merged. Structure solution was by direct methods as coded in the SHELX97 program package [15]. In the subsequent full-matrix least-squares refinement based on F^2 the non-H atoms were treated with anisotropic atomic displacement parameters (ADPs), the H atoms with isotropic ADPs. No restraints on parameters were necessary. A survey of the data collection and structure refinement is given in Table 1.

Table 2 contains the crystal data. Supplementary crystallographic data has been deposited with the Cambridge Crystallographic Data Centre as CCDC 647482. These data can be obtained free of charge from CCDC via www.ccdc.cam.ac.uk/conts/retrieving.html.

Acknowledgements

The measurement of X-ray diffraction data was carried out on Station A of the Swiss-Norwegian Beamlines (SNBL) at ESRF, Grenoble. One of us (FM) gratefully acknowledges support from the Norwegian Research Council (NFR) through Grant 173962/V30.

Table 1. Summary of data collection and refinement.

Resolution, s_{max}, sinθ λ^{-1} (Å^{-1})	0.667
Coverage within s_{max}	81.3 %
Total no. reflections	6443
Total no. unique reflections	1172
Unique reflections (F_o> 4σ(F_o)) (*NO*)	1002
R_{merge}(all)	0.0287
No. variables (*NV*)	82
***R*(*F*) (all)**	0.049
***R*(*F*) (F_o> 4σ(F_o))**	0.042
$R_w(F^2)$	0.121
Goodness-of-fit (*GOF*)	1.112
Extrema in final diff. electron density (e Å^{-3})	- 0.36 to 0.56
Extrema corresponding to bonding (e Å^{-3})	≥ 0.05

$w = 1 / [\sigma^2(F_o^2) + (0.07140 * P)^2 + 0.24030 * P]$ where $P = (\text{Max} (F_o^2, 0) + 2 * F_c^2) / 3$

$R(F) = \Sigma | | F_o| - | F_c| | / \Sigma | F_o|$

$R_w(F^2) = \{ \Sigma [w(F_o^2 - F_c^2)^2] / \Sigma [w(F_o^2)^2] \}^{1/2}$

$GOF = [\Sigma w(F_o^2 - F_c^2)^2 /(NO - NV)]^{1/2}$

Table 2. Crystal data for compound **5.**

Composition	$C_{10}H_6N_4S$	**M.p.(K)**	536-538 (dec.)
***M*$_r$**	214.252	***T*(K)**	100
Space group	$P2_1/m$	***Z***	2
***a*(Å)**	4.6878(2)	**λ(Å)**	0.70916(10)
***b*(Å)**	14.7977(10)	***D*$_x$(Mg·m^{-3})**	1.476
***c*(Å)**	7.2631(5)	**Size(μm)**	~ 75×55×25
β(°)	106.866(7)	**μ(mm^{-1})**	0.276
***V*(Å^3)**	482.16(5)		

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Sample Availability: Samples of compounds **3** and **5** are available from the authors.