Novel Formation of 4-Methylthiopyrene in a Hofmann Elimination Reaction Directed Toward the Synthesis of 17,19-Dioxa[2.2.3](1,2,3)cyclophanediene

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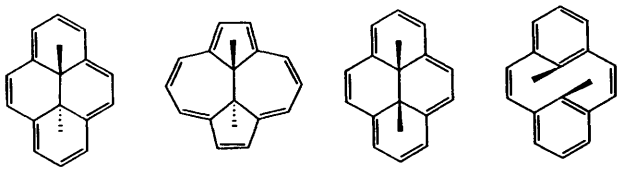
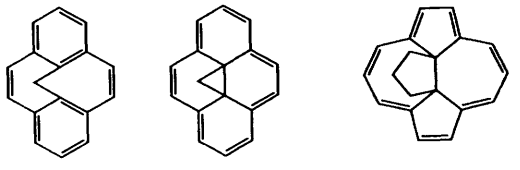
The synthesis of 17,19-dioxa[2.2.3](1,2,3)cyclophanediene was attempted *via* a Stevens rearrangement–Hofmann elimination sequence on 19,21-dioxa-2,11-dithia[3.3.3](1,2,3)cyclophane. Pyrene and 4-methylthiopyrene were, however, the isolated products. The structure of the latter was fully characterized by UV, MS, 1D and 2D ^{1}H NMR spectra. Formation of 4-methylthiopyrene was expected to involve a novel base-induced ring cyclization resulting in elimination of methanoate anion from the methylenedioxy bridge followed by a novel 1,4-hydride shift resulting in the elimination of methane.

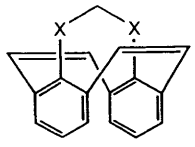
Bridged [14]annulenes **1** (δ_{Me} – 4.25)[1-3] and **2** (δ_{Me} – 4.53)[4] sustain strong induced diamagnetic ring currents and serve as



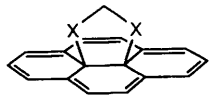
1 **2** **3** **4**



5 **6** **7**

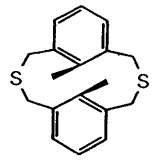


8 X = CH_2
9 X = O



10 X = CH_2
11 X = O

appropriate model compounds for various studies on aromaticity.[5,6] The *syn* isomer of **1**, namely **3** (δ_{Me} – 2.06)[3] was found to be significantly less diatropic possibly due to the deviation from planarity of the periphery. Synthetically, compound **3** was also less accessible as the route to *syn* cyclophanediene **4**, which valence isomerized to **3**, involved intermediates that readily isomerized to *anti* cyclophane systems.[3] Thus the chemistry of the *cis*-dihydropyrene **3** has not been fully explored. The centrally bridged cyclophanediene **5** retains the *syn* stereochemistry but did not lead to the isolation of the dihydropyrene system **6** due to unfavourable angle strains in the three-membered ring.[7] A synthesis of a bridged *syn* derivative of **2**, namely **7**, has however been reported.[8] The corresponding *syn* cyclophanediene **8** is thus expected to undergo valence isomerization to afford the rigid *syn* dihydropyrene system **10**. Our work however indicated that synthetically an approach to 17,19-dioxa[2.2.3](1,2,3)cyclophanediene **9** could be more readily designed. We communicate



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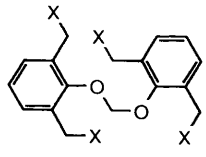
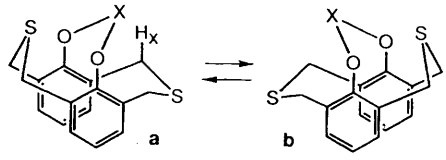


13 X = H
14 X = Br



a **b**

15 X = CH_2
16 X = CH_2CH_2

here the unexpected results obtained in our attempt toward the synthesis of the methylenedioxydihydropyrene **11**.

Results and Discussion

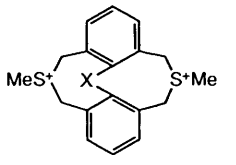
Dithiacyclophane **15**.—The *syn* dithiacyclophane **12** was used as a precursor to cyclophanediene **4**.[3] A retrosynthetic scheme suggests that the centrally bridged *syn* dithiacyclophane **15** would be an appropriate precursor required for cyclophanediene **9**. As dithiacyclophanes are readily prepared by coupling reactions of dibromides with sodium sulfide under high dilution conditions,[9] our first synthetic target was the tetrabromide **14**.

Treatment of the phenoxide ion prepared from 2,6-dimethylphenol with dibromomethane readily afforded compound **13** in >80% yield. Its simple ^{1}H NMR spectrum showed three singlets at δ 6.95, 5.22 and 2.23 corresponding to the aryl, methylene and methyl protons respectively. Free radical bromination of **13** to give **14** proved to be difficult. Mass spectral analysis of various fractions obtained from chromatography of the reaction mixture indicated mono-, di-, tri- and tetra-brominated products. The tetrabromide **14** could only be isolated in 35–40% yield after repeated chromatography. Only a very weak molecular ion was observed in its mass spectrum with the base peak at *m/z* 291 corresponding to a ready cleavage at the CH_2–O bond. The structure of **14** is however clearly supported by its ^{1}H NMR spectrum with an AB_2 system observed for the aryl protons and two singlets at δ 5.79 and 4.63 for the CH_2O and CH_2Br protons respectively.

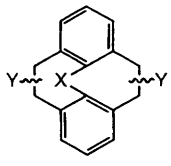
Intramolecular coupling reactions of **14** were carried out with sodium sulfide under high dilution conditions.[9] The dithiacyclophane **15** was in fact isolated in a 90% yield. The

structure of **15** is indicated by a strong molecular ion at *m/z* 316 observed in its mass spectrum. The related dithiacyclophane **16** was earlier reported[10] to exhibit the propelling conformational behaviour **16a** ⇌ **16b** at room temperature and dithiacyclophane **15** is expected to behave similarly. The relatively simple ^{1}H NMR spectrum of **15** shows an AB_2 system for the aromatic protons at δ 6.71 and 6.97 (ratio 1:2) with the B protons slightly deshielded by the anisotropic effect of the sulfur atoms. The CH_2O methylene protons appear as a singlet at δ 6.28 clearly indicating unrestricted pseudoration in the bridge. The diastereotopic CH_2S methylene protons however are observed as a well resolved AB quartet at δ 3.42 and 4.69, with the H_X protons significantly deshielded by the oxygen atoms due to a pseudo-1,3-diaxial geometry.

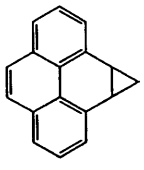
The conformational barrier for the interconversion process **16a** ⇌ **16b** was estimated at *ca.* 45 kJ mol^{-1}.[10] The conformational behaviour could be observed by monitoring the changes in the signals of CH_2O and CH_2S methylene protons in a dynamic ^{1}H NMR spectroscopic study. Results from a similar study of **15** were however discouraging. Although peak broadening was evident as the temperature of a sample of **15** was lowered to −90 °C, no coalescence of any signal was observed indicating a relatively lower energy barrier for the process **15a** ⇌ **15b**. A possible explanation is that the transition state energies in the two processes are similar but the ground state energy of **15** is relatively high resulting from more severe steric interactions between the H_X and OCH_2O protons due to their closer proximity.



17 X = OCH_2O



18 X = OCH_2O, Y = SMe
19 X = OCH_2O, Y = SMe_2^+ BF_4^-



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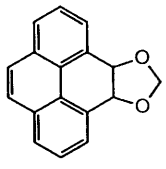

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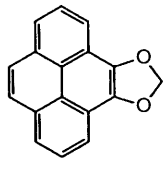

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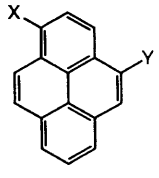
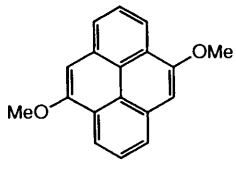


23 X = SMe, Y = H
24 X = H, Y = SMe



25

4-*Methylthiopyrene* **24**.—Treatment of dithiacyclophane **15** with dimethoxycarbonium fluoroborate[11] afforded the bis(sulfonium) salt **17** which underwent a Stevens rearrangement[12] in the presence of potassium *tert*-butoxide to give a mixture of isomers of **18**. The general structure of **18** was supported by a strong molecular ion at *m/z* 344 in the mass spectrum and a broad singlet observed at δ 2.13 characteristic of the methylthio protons in the ^{1}H NMR spectrum. The other bridge protons however appear as unresolved sets of multiplets in the range of δ

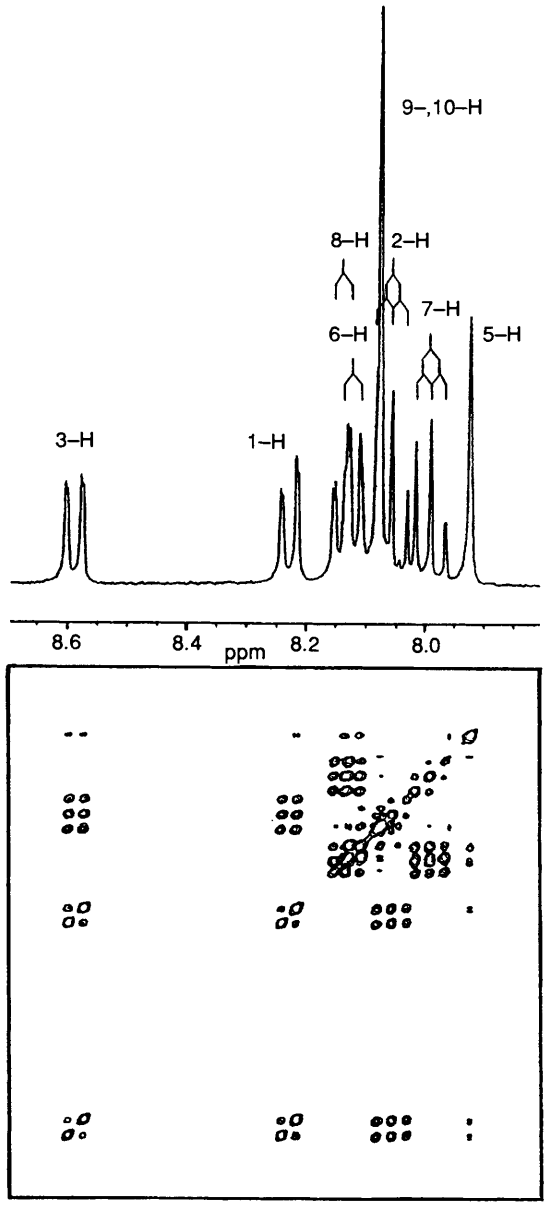


Fig. 1 1D and COSY ^{1}H NMR spectra ($CDCl_3$; 300 MHz) of 4-methylthiopyrene **24**

2.2–5.4. Remethylation of **18** with dimethoxycarbonium fluoroboroate gave the bis(sulfonium) salt **19** which was air and moisture sensitive. A Hofmann elimination of **19** to afford the cyclophanediene **9** was attempted in the presence of potassium *tert*-butoxide at room temperature. Two products were isolated after chromatography and the component eluted first was pyrene which is identical to an authentic sample.

The mass spectrum of the second component, m.p. 153 °C, indicated a molecular ion at *m/z* 248 consistent with that expected of **9** ($C_{17}H_{12}O_2$). The complicated ^{1}H NMR spectrum (Fig. 1) for the aromatic protons however suggests otherwise. A rearrangement of **5** to **20** *via* **6** as an intermediate was reported.[7] A similar reaction of **9** *via* **11** would be expected to afford **21** which is also expected to give a simple ^{1}H NMR spectrum. The electronic spectrum (Fig. 2) of the sample however suggests the structure of a pyrene derivative, consistent with the presence of a nonbonding pair substituent shifting the absoprtions slightly to longer wavelength and diminishing the fine structure. Further oxidation of **21** to form **22** was however ruled out based on mass spectral data. An elemental analysis of the sample unexpectedly

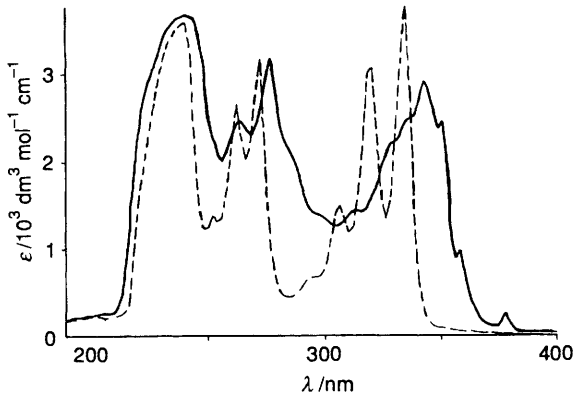
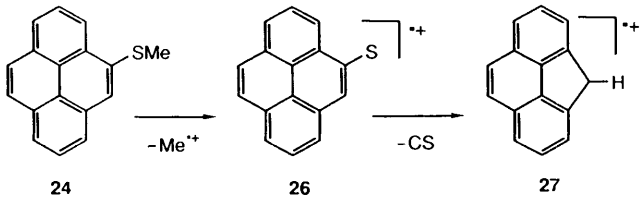


Fig. 2 UV absorption spectra of 4-methylthiopyrene **24** (——) and pyrene (– – –) taken in cyclohexane

confirmed the presence of sulfur and thus the molecular ion observed at *m/z* 248 could correspond to a molecular formula of $C_{17}H_{12}S$ instead.

The chemical shift of the methyl protons in thioanisole is at δ 2.46.[13] The singlet at δ 2.77 observed in the ^{1}H NMR spectrum of the unknown sample is consistent with a methylthiopyrene having the methythio group at C-1 or C-4. The methyl protons would thus be further deshielded by the adjacent ring. 1-Methylthiopyrene **23**, m.p. 67–68 °C,[14] has however been reported in the literature[14–16] and thus the unknown compound in our work is likely to be 4-methylthiopyrene **24**. This is well supported by the fragmentation ions at *m/z* 233 (55%) and 189 (45%) corresponding to **26** and **27** respectively in

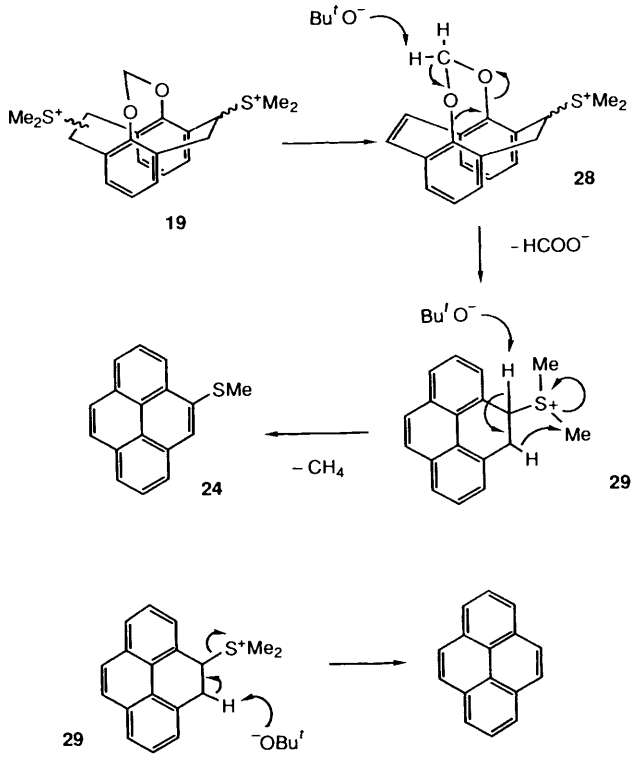


24 **26** **27**

its mass spectrum, the latter process being similar to the loss of CO from aromatic ethers to form the cyclopentadiene system.

The 1D and selected 2D ^{1}H NMR spectra of the aromatic protons of **24** are presented in Fig. 1. 3-H (δ 8.59) could be readily assigned, being significantly deshielded due to combined ring current effect of the adjacent ring and the anisotropic effect of sulfur of the methylthio group in close proximity. From the COSY spectrum, the signals at δ 8.23 and 8.05 should correspond to 1-H and 2-H respectively due to strong couplings among signals of 1-H, 2-H and 3-H. The methylthio group, being a π-donor group, shields the β-hydrogen (5-H) which appears the most upfield at δ 7.92. In an earlier report,[17] 5-, 10-H in **25** was shown to be more shielded at δ 7.2 consistent with the fact that the methoxy group is a more effective π-donor. The triplet at δ 7.99 could now be readily assigned to 7-H although assignments of 6-, 8-H are ambiguous in the 1D spectrum. From the COSY spectrum however a small through-space scalar (spin spin) coupling expected between 5-H and 6-H due to their close proximity is clearly evident which helps to confirm the broad doublet at δ 8.10 as 6-H. With 8-H observed as the signal centred at δ 8.14, all aromatic protons in **24** were then successfully assigned.

A plausible mechanism could be postulated to account for the formation of pyrene and 4-methylthiopyrene **24** in the reaction concerned. An initial Hofmann elimination in **19** would proceed as expected. Going from **19** to **28** involves the shortening of one



bridge and would result in unfavourable angle strains and electronic repulsion of the closely stacked near-parallel benzene rings. A second Hofmann elimination in **28** to afford cyclophanediene **9** would further substantiate the above unfavourable interactions. An alternative route would be a proton abstraction from the central methylenedioxy bridge followed by a ring cyclization resulting in the elimination of methanoate anion to afford **29**. Release of angle and electronic strains with simultaneous formation of a 4,5-dihydropyrene system could clearly provide the driving force for this reaction. A simple Hofmann elimination in **29** would yield pyrene. The most acidic proton in **29** is however 4-H. Abstraction of 4-H followed by a novel 1,4-hydride shift resulting in the elimination of methane would then afford 4-methylthiopyrene **24**.

Experimental

M.p.s were determined with a Sybron Thermolyne MP-12615 apparatus and are uncorrected. The ^{1}H NMR spectra were determined using $CDCl_3$ (unless otherwise stated) on a JEOL FX 90Q (90 MHz) or a Bruker ACF-300 (300 MHz) spectrometer. All the chemical shifts are reported in ppm downfield from tetramethylsilane as an internal standard. The 1D and 2D spectra determined on Bruker AC-300 were collected with 16K and 1K × 1K data points respectively. IR spectra were recorded on a Perkin-Elmer 1310 spectrometer. UV–VIS spectra were determined in cyclohexane on a Hewlett Packard 8052A Diode-array spectrometer. Mass spectra were determined on a VG Micromass 7035 spectrometer at 70 eV, electron impact ionization being used. Relative intensities are given in parenthesis. Only peaks corresponding to ^{79}Br are indicated for compound **14**. Microanalysis was performed by the Microanalytical Laboratory of the Department of Chemistry, National University of Singapore. All evaporations were carried out under reduced pressure on a rotary evaporator at *ca.* 40 °C. All organic layers were washed with water (unless otherwise stated) and dried with anhydrous sodium sulfate.

Bis(2,6-*dimethylphenoxy*)*methane* **13**.—Sodium hydroxide (9.84 g, 0.246 mol) was added to a solution of 2,6-dimethylphenol (30.0 g, 0.246 mol) in ethanol (30 cm^3). 1,2-Dibromomethane (21.4 g, 0.123 mol) was then added and the mixture was heated at gentle reflux for 12 h and then poured into water (100 cm^3) and the product extracted into dichloromethane (200 cm^3). The organic layer was washed, dried and evaporated to dryness. Chromatography on silica gel with dichloromethane–hexane (1 : 2) as eluent yielded compound **13** (25.9 g, 82%) as a thick colourless oil (Found: C, 79.8; H, 8.0. $C_{17}H_{20}O_2$ requires C, 79.65; H, 7.9%); ν_{max}(neat)/cm^{-1} 1470, 1370, 1355, 1258, 1190, 1086, 1060, 1020, 915, 810 and 765; δ_H(90 MHz) 6.95 (6 H, br s, Ph), 5.22 (2 H, s, CH_2) and 2.23 (12 H, s, CH_3); *m*/*z* 256 (M^+, 20%), 135 (100) and 105 (84).

Bis[2,6-*di*(*bromomethyl*)*phenoxy*]*methane* **14**.—This was prepared by free radical bromination of compound **13** with 4 equiv. of *N*-bromosuccinimide (NBS) in three separate attempts. In each reaction, NBS (4.45 g, 0.25 mol) was added to a solution of **13** (1.60 g, 6.25 mmol) in carbon tetrachloride (*ca.* 150 cm^3) followed by a catalytic amount of benzoyl peroxide. The mixture was then heated at reflux by irradiation from a 200 W tungsten lamp until all the NBS had reacted. The mixture was cooled and filtered. The filtrate was washed with aqueous $NaHCO_3$ and water. The organic phase was dried and evaporated to dryness. Products obtained from three separate reactions were combined. Repeated chromatography on silica gel with hexane–dichloromethane (3 : 1) as eluent yielded compound **14** (4.01 g, 38%) as colourless crystals, m.p. 130–131 °C (from EtOH) (Found: C, 35.9; H, 2.7. $C_{17}H_{16}Br_4O_2$ requires C, 35.7; H, 2.8%); ν_{max}(KBr)/cm^{-1} 1580, 1460, 1445, 1425, 1355, 1230, 1210, 1185, 1065, 1030, 970, 880, 810 and 765; δ_H(90 MHz) 7.20, 7.43 (6 H, AB_2, J_{AB} 24, Ph), 5.79 (2 H, s, CH_2O) and 4.63 (8 H, s, CH_2Br); *m*/*z* 568 (M^+, <2%), 489 (<2), 410 (<2), 291 (68), 183 (62), 133 (54), 119 (38), 105 (18) and 103 (21).

19,21-*Dioxa*-2,11-*dithia*[3.3.3](1,2,3)*cyclophane* **15**.—A solution of 95% sodium sulfide nonahydrate (1.68 g, 7.04 mmol) in 95% ethanol (200 cm^3) and a solution of compound **14** (2.00 g, 3.52 mmol) in benzene (200 cm^3) in separate rotaflow dropping funnels were added dropwise simultaneously at the same rate to nitrogen purged 95% ethanol (1 dm^3) under nitrogen. After the addition, the mixture was stirred for another 15 h and the bulk of the solvent was removed under reduced pressure. Water and dichloromethane were added to the residue and the mixture was stirred until all solids dissolved. The organic layer was separated, dried and evaporated to dryness. Chromatography on silica gel with dichloromethane–hexane (1 : 2) as eluent yielded **15** (1.01 g, 90%) as colourless crystals m.p. >300 °C decomp. (benzene–cyclohexane) (Found: C, 64.7; H, 5.0. $C_{17}H_{16}O_2S_2$ requires C, 64.55; H, 5.1%); ν_{max}(KBr)/cm^{-1} 1445, 1250, 1220, 1180, 1085, 1030, 1000, 910, 890, 800 and 760; δ_H[90 MHz; $CDCl_3$–CD_2Cl_2 (1 : 1)] 6.71, 6.97 (6 H, AB_2, J_{AB} 23, Ph), 6.28 (2 H, s, CH_2O), 3.42 and 4.69 (8 H, AB, J_{AB} 15, CH_2S); *m*/*z* 316 (M^+, 82%), 270 (36), 236 (12), 197 (54), 151 (100), 149 (10), 119 (80) and 91 (45).

Stevens Rearrangement of 2,11-*Dimethyl*-19,21-*dioxa*-2,11-*dithionia*[3.3.3](1,2,3)*cyclophane* **17**.—A solution of compound **15** (0.89 g, 2.8 mmol) in dichloromethane (5 cm^3) was added to a stirred suspension of dimethoxycarbonium fluoroborate[11] (1.36 g, 8.4 mmol) in dichloromethane (5 cm^3) kept at −30 °C under nitrogen. After the addition, the mixture was allowed to warm to room temperature and stirred for an additional 5 h. Ethyl acetate (3 cm^3) was then added and the mixture stirred for 12 h. The bis(sulfonium) salt **17**, 1.14 g (78%), was filtered, dried and used directly for the subsequent reaction.

Powdered potassium *tert*-butoxide (0.54 g, 4.08 mmol) was added to a suspension of the salt **17** (1.14 g, 2.18 mmol) in dry THF (20 cm^3) at room temperature under nitrogen. The mixture was stirred for 1 h and dilute HCl was added slowly followed by dichloromethane. The organic layer was separated, washed, dried and evaporated to dryness. Chromatography on silica gel with dichloromethane–hexane (1 : 2) as eluent yielded a mixture of isomers of dimethyl-17,19-dioxadithia[2.2.3](1,2,3)-cyclophane **18** (0.73 g, 97%), as a thick yellow oil [Found: M^+, 344.0902. $C_{19}H_{20}O_2S_2$ requires *M*, 344.0904]; ν_{max}(neat)/cm^{-1} 1430, 1300, 1245, 1200, 1085, 1020, 880, 800, 760 and 750; δ_H(300 MHz) 6.4–7.0 (6 H, m, Ph), 5.98, 5.97 (total 2 H, s, CH_2O), 3.9–4.2 (2 H, m, CHS), 2.2–2.6 (4 H, m, CH_2C) and 2.13 (6 H, br s, SCH_3); *m*/*z* 344 (M^+, 46%), 329 (24), 315 (14), 283 (78), 281 (16), 249 (32), 225 (26), 202 (45), 189 (14), 165 (100) and 119 (52).

4-*Methylthiopyrene* **24**.—The bis(sulfonium) salt **19** was obtained from compound **18** (0.41 g, 1.19 mmol) according to the procedure described for the preparation of **17**. The salt **19** was however hygroscopic and readily polymerized when exposed to air. Thus it had to be filtered from the reaction mixture under nitrogen and used immediately.

Powdered potassium *tert*-butoxide (1.44 g, 2.62 mmol) was added to a suspension of the previously obtained salt **19** in dry THF at room temperature under nitrogen. The mixture was stirred for 1 h and dilute HCl and dichloromethane were then added. The organic layer was separated, washed, dried and evaporated to dryness. Chromatography on silica gel with freshly distilled hexane as eluent yielded first pyrene (20 mg, 8%). Eluted next was 4-methylthiopyrene **24**, colourless crystals (20 mg, 7%), m.p. 153 °C (Found: C, 81.85; H, 4.6; S, 13.35. $C_{17}H_{12}S$ requires C, 82.2; H, 4.9; S, 12.9%); λ_{max}(cyclohexane)/nm 240 (ε/dm^3 mol^{-1} cm^{-1} 3670), 264 (2390), 276 (3090), 312 (1400), 330 (2180), 342 (2870), 350 (2400), 358 (910) and 378 (220); ν_{max}(KBr)/cm^{-1} 1590, 1450, 1380, 1360, 1175, 1125, 1100, 960, 900, 880, 865, 845, 825, 765 and 725; δ_H(300 MHz) 8.59 (1 H, dd, *J* 1 and 8, 3-H), 8.23 (1 H, br d, *J* 8, 1-H), 8.14 (1 H, dd, *J* 1 and 8, 8-H), 8.10 (1 H, d, *J* 8, 6-H), 8.07 (2 H, s, H-9,10), 8.05 (1 H, t, *J* 8, 2-H), 7.99 (1 H, t, *J* 8, 7-H) and 7.92 (1 H, s, 5-H); *m*/*z* 248 (M^+, 100%), 233 (55, M − CH_3), 189 (45, M − CH_3CS) and 123 (10).

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References

1 V. Boekelheide and J. B. Philips, *Proc. Natl. Acad. Sci. U.S.A.*, 1964, **51**, 550.
2 V. Boekelheide and J. B. Philips, *J. Am. Chem. Soc.*, 1967, **89**, 1695.
3 R. H. Mitchell and V. Boekelheide, *J. Am. Chem. Soc.*, 1974, **96**, 1547.
4 W. Huber, J. Lex, T. Meul and K. Müllen, *Angew. Chem., Int. Ed. Engl.*, 1981, **20**, 391.
5 R. H. Mitchell, *Adv. Theor. Interest. Molec.*, 1989, **1**, 135.
6 A. T. Balaban, M. Banciu and V. Ciorba, *Annulenes, Benzo-, Hetero-, Homo-Derivatives, and their Valence Isomers*, CRC Press, Boca Raton, Florida, 1987, vol. I, II and III.
7 J. Wirz, G. Persy, E. Rommel, I. Murata and K. Nakasuji, *Helv. Chim. Acta*, 1984, **67**, 305.
8 W. Huber, W. Irmen, J. Lex and K. Müllen, *Tetrahedron Lett.*, 1982, **23**, 3889.
9 L. Rossa and F. Vögtle, *Top. Curr. Chem.*, 1983, **113**, 1.
10 Y.-H. Lai and C.-W. Tan, *J. Org. Chem.*, 1991, **56**, 264.
11 R. F. Borch, *J. Org. Chem.*, 1969, **34**, 627.
12 R. H. Mitchell, T. Otsubo and V. Boekelheide, *Tetrahedron Lett.*, 1975, 219.

13 *The Aldrich Library of NMR Spectra*, ed. C. J. Pouchert, Aldrich Chemical Co., Milwaukee, 1983, vol. 1, p. 973.
14 V. Baliah and M. K. Pillay, *Indian J. Chem.*, 1971, **9**, 815.
15 M. K. Pillay, *Indian J. Chem., Sect. B*, 1976, **14B**, 995.
16 P. E. Hansen and A. Berg, *Acta Chem. Scand., Ser. B*, 1981, **B35**, 131.
17 S. C. Agarwal and B. L. van Duuren, *J. Org. Chem.*, 1975, **40**, 2307.

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