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CARDOPATINE AND ISOCARDOPATINE, TWO NOVEL CYCLOBUTANE SUBSTANCES FROM *CARDOPATIUM CORYMBOSUM*

ANTONIO SELVA†, ALBERTO ARNONE†, ROSANNA MONDELLI†, VINCENZO SPRIO‡, LEOPOLDO CERAULO‡, SALVATORE PETRUSO‡, SALVATORE PLESCIA‡ and LILIANA LAMARTINA‡

†Istituto di Chimica, Politecnico di Milano, Piazza L. da Vinci 32, 20133-Milano, Italy*; ‡Istituto di Chimica Farmaceutica e Tossicologica, Università di Palermo, 90123-Palermo, Italy

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Key Word Index—*Cardopatium corymbosum*; Compositae; cardopatine; isocardopatine; thiophenes; cyclobutane conformation; ^{13}C NMR; mass spectra.

Abstract—Two new natural substances containing a cyclobutane unit, cardopatine and isocardopatine, the *trans* and *cis* isomers respectively of 5,5″ (cyclobut-1,2-ylene-diethynylene)*bis* 2,2′-bithiophene), together with the known α-terthienyl and 5-(but-3-en-1-ynyl)-2,2′-bithienyl, have been isolated from the roots of *Cardopatium corymbosum*. Evidence is given that the novel cyclobutane substances are not the products of a spontaneous dimerization of a bithienyl monomeric unit. Structure determination and conformational analysis are reported.

INTRODUCTION

The present paper deals with the identification and structure elucidation of four natural substances isolated from the roots of *Cardopatium corymbosum* DC (Chamaleon niger Dioscoridis, tribe Cynareae, subtribe Carlineae) [1]. Two of them, **1** and **2**, have previously been isolated from some other species of Compositae [2–4], while substances **3** and **4**, named cardopatine and isocardopatine, are new and present an uncommon cyclobutane ring structure.

RESULTS AND DISCUSSION

Neutral extracts of the roots gave in addition to the known compounds **1** [5] and **2** [2–4] two new thiophenes, named cardopatine **3** and isocardopatine **4**, which gave the same molecular formula $C_{24}H_{16}S_4$ and showed very similar IR, UV, MS and NMR spectra. The data suggested that **3** and **4** were stereoisomeric (or regioisomeric) dimers of **2**, such as 1,2-(or 1,3) disubstituted cyclobutanes, likely originating by a natural head to head (or head to tail) cycloaddition, involving the ethylene bond. The 70 eV MS of both **3** and **4** showed an easy cycloreversion process, leading to the dominant half-mass fragment ions (*m/e* 216) [6–11], the structure of which can be assumed to be identical to that of **2**, according to the practically identical relative intensities of the metastable peaks for three competitive decomposition reactions [12].

The NMR spectra showed a pair of equivalent α-monosubstituted thiophene rings and another pair of equivalent α,α′-disubstituted thiophene rings, which was also suggested by the presence of IR bands at 840 and 800 cm^{-1}, respectively. The six remaining protons were at high field and arranged in a AA′BB′XX′ pattern. The ^{13}C NMR spectra showed 12 separated signals which corresponded to 24 carbon atoms. The 8 signals at low field were completely analysed and attributed to the thiophene rings. Chemical shifts, one-bond and long-range coupling constant values are given in Table 1 and are in accord with those reported for **2** [13]. As the high field portion of the spectra, corresponding to the saturated fragment of the molecules, consisted of two identical triplets (27.4 ppm) and two identical doublets (31.8 ppm), two methylenes and two methyne groups must be arranged in a cyclobutane unit. Moreover the shifts of the signals in the 70–90 ppm region and the absence of one-bond interactions indicated the presence of acetylenic quaternary carbon atoms. That the bithienyl chromophore was conjugated with an unsaturated system analogous to that of **2** followed from the UV spectra. The suggested structures of **3** and **4** were confirmed by the following reactions (see Scheme 1).

Table 1 ^{13}C NMR chemical shifts of **3** and **4***

	3		**4**
C-2	138.0†‡		138.4†
C-3	123.9	*ddd* (167.0, 5.6, 9.2)	124.2
C-4	127.8	*ddd* (168.7, 4.5, 4.5)	128.3
C-5	124.6	*ddd* (187.2, 10.6, 7.3)	124.8
C-2′	122.2	*dd* (5.8, 11.0)	123.0
C-3′	132.2	*dd* (170.7, 5.0)	132.5
C-4′	123.2	*dd* (167.5, 5.0)	123.6
C-5′	136.7†‡		137.4†
C_α	76.2‡		78.3
C_β	96.0‡		95.9
CH	33.7	*d*§ (142.0)	31.8
CH_2	26.9	*t*§ (140.0)	27.4

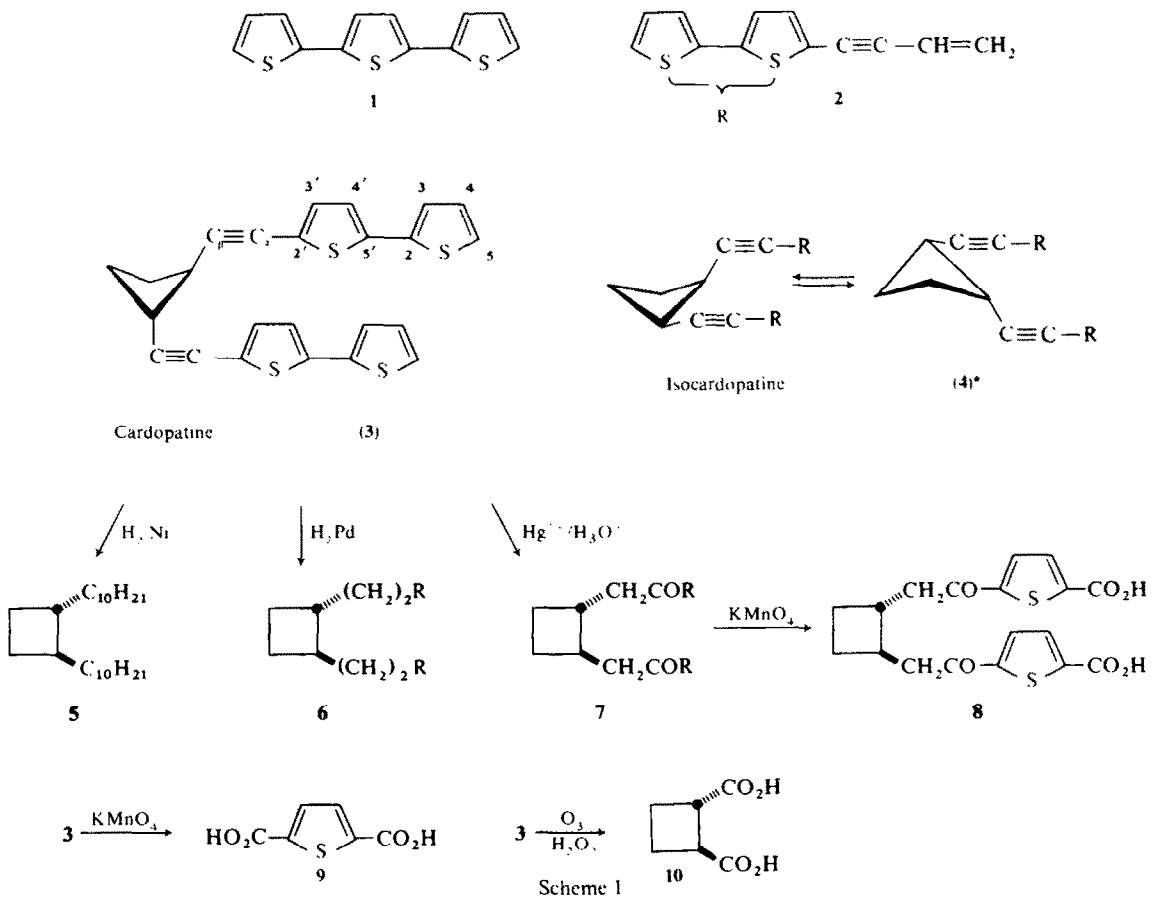
*In ppm (δ) obtained from $CDCl_3$ solution relative to internal TMS. The values in parentheses are one-bond, two-bond and three-bond coupling constants in that order.

†These values may be reversed.

‡Multiplet without one bond interaction.

§Broad.

*Centro di Studio del Consiglio Nazionale delle Ricerche per le Sostanze Organiche Naturali.



Scheme 1

*The same reactions with **4** afforded **5a**, **6a**, and **10a**; all compounds are racemic

(i) Oxidation with $KMnO_4$ of **3** and **4** gave thiophene-2,5-dicarboxylic acid **9**, characterized as the dimethyl ester, proving the presence of an α,α'-disubstituted thiophene partial structure.

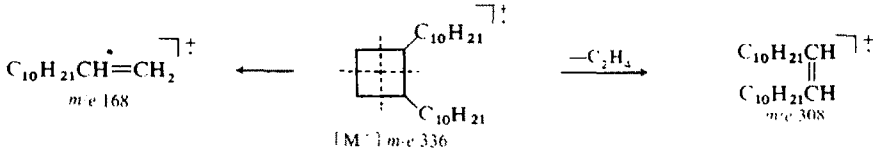
(ii) Catalytic hydrogenation in ether with Pd/C (10%) of both the acetylenic bonds of either **3** and **4** gave octahydro-derivatives **6** and **6a** ($C_{24}H_{24}S_4$).

(iii) Hydration of **3** in the presence of mercuric salts afforded the diketone **7** ($C_{24}H_{20}O_2S_4$), which led to a dicarboxylic acid **8** ($C_{18}H_{10}O_6S_2$) by oxidation with $KMnO_4$ of the terminal thiophene rings.

(iv) Hydrogenation of **3** and **4** with Ni-Raney gave monocyclic hydrocarbons **5** and **5a** ($C_{24}H_{48}$), respectively, as the major products. After purification by preparative GC, the MS of these compounds were very similar and showed a metastable ion which supported loss of ethylene (*m/e* 308) and formation of $M/2^+$ (*m/e* 168) from the molecule ions (M^+, *m/e* 336) (Scheme 2), according to the 1,2-disubstituted cyclobutane structures.

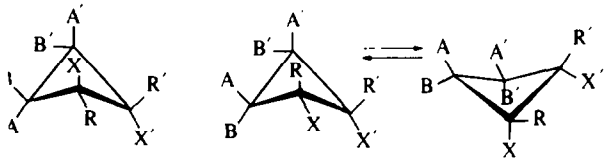
The presence of the 1,2-disubstituted cyclobutane moiety and the relative configuration of the side chains on the four-membered ring were both unequivocally proved by ozonolysis, followed by oxidation with H_2O_2 (Scheme 1). *Trans*- and *cis*-1,2-cyclobutanedicarboxylic acids, **10** and **10a**, respectively, were obtained from **3** and **4**, and were identified as dimethylesters by GC–MS, comparing MS and retention times with those of authentic samples.

Finally, LAOCN3 analysis of the AA'BB'XX' portion of the PMR spectra originating from the six protons of the cyclobutane ring of cardopatine **3** and isocardopatine **4** was carried out in order to obtain information about the relative stereochemistry and the preferred conformation of the four-membered ring [14–16]. Since the AA'BB' part of the six-spin system was very complex, owing to the small relative shift between A and B, trial calculations were performed without iterative refinement, using as input parameters the coupling constant values of substituted cyclobutanes [14–17], and taking account of



Scheme 2. Metastable supported transitions.

Table 2. Coupling constant values (Hz) of the AA'BB'XX' portion of the PMR spectrum for 3 and 4.



3 4

	3	4
$^2J_{AB} = {}^2J_{A'B'}$	−10.9	−10.9
$^3J_{AA'}$	10.7	8.7
$^3J_{BB'}$	2.3	6.3
$^3J_{AB'} = {}^3J_{A'B}$	8.7	5.9
$^3J_{AX} = {}^3J_{A'X'}$	9.6	7.9
$^3J_{BX} = {}^3J_{B'X'}$	8.7	
$^3J_{XX'}$	9.2	7.0
$^4J_{AX'} = {}^4J_{A'X}$	0.0	−1.1
$^4J_{BX'} = {}^4J_{B'X}$	−1.0	2.6

the possible different conformations, i.e. planar, twisted or rapidly interconverting structures. Firstly, by varying J_{AX}, $J_{AX'}$, J_{BX}, $J_{BX'}$ and $J_{XX'}$ a good fit was obtained for the X pattern of 3 and 4 at 3.37 ppm and 3.54 ppm, respectively. Variation of A and B chemical shifts and slight modifications of the remaining couplings led to the values reported in Table 2, which gave a good fit with the experimental spectra. The coupling constant values, in particular $^3J_{XX'}$ and the four-bond cross-ring interactions (sign and magnitude) [14–16] indicated a *trans* and *cis* configuration for cardopatine 3 and isocardopatine 4, respectively. Actually for 3, the 9.2 Hz of $^3J_{XX'}$ and the *ca* zero value [17] of the cisoid couplings $^4J_{AX'}$ and $^4J_{A'X}$ show that protons X and X' were *trans* axially oriented. From these results and also from the 9–10 Hz values of the vicinal couplings $^3J_{AA'}$, $^3J_{AX}$ and $^3J_{A'X'}$ (*ax,ax* interactions) and from the small magnitude of $^3J_{BB'}$ (*eq,eq*), it followed that the cyclobutane ring of cardopatine 3 existed preferentially in a twisted conformation. On the contrary for isocardopatine 4 the fit was obtained only by considering an average between two equivalent and rapidly interconverting structures. In particular (i) the values of $^3J_{XX'}$, $^3J_{AB'}$, $^3J_{AX}$ and $^3J_{A'X'}$ denote *ax,eq* interactions or an average between *eq,eq* (*ca* 2.5 Hz) and *ax,ax* (9–10 Hz) [17] interactions; (ii) the positive sign of the identical four-bond couplings $^4J_{BX'}$ and $^4J_{B'X}$ is characteristic of cisoid coupling and the magnitude of 2.6 Hz indicated an average between *eq,eq* (*ca* +5 Hz) and *ax,ax* (*ca* zero) [17] interactions. The negative value of *ca* 1 Hz for both stereoisomers 3 and 4 indicated a transoid coupling between *axial* and *equatorial* protons.

Anemonine [18], hoveine [19], truxilic and truxinic acids [20] are the only other natural substances with a non-fused cyclobutane ring. The first, anemonine, is the product of a spontaneous dimerization of a monomeric unit. Since in our case the optical inactivity of the *trans* isomer 3, would be in favour of a similar dimerization process, the conditions of extraction were accurately checked and some specific dimerization reactions of the monomeric compound 2 were carried out. As cardopatine 3 and isocardopatine 4 have been detected by TLC in a sample obtained without heating the fresh roots, and attempts to dimerize in mild conditions the monomer 2 were unsuccessful (see Experimental), we must conclude that they are not artifacts obtained during manipulation of the extracts, but are present in the fresh roots. However a photochemical and/or enzyme catalysed cycloaddition of 2 in the roots cannot be excluded.

EXPERIMENTAL

Mps are uncorr. UV spectra were measured in isooctane, optical rotations in EtOH, IR spectra KBr discs or film, NMR spectra in $CDCl_3$. PMR spectra were recorded at 100 MHz and FT ^{13}C NMR spectra at 25.18 MHz. Chemical shifts are in pp, (δ) from TMS as internal reference, coupling constants are in Hz. ^{13}C frequencies assignments were made by ^1H noise decoupling gated undecoupled spectra and by single frequency selective heteronuclear decoupling. The analyses of the 2nd order six-spin system AA'BB'XX' were performed using the LAOCN3 programe [21]. Electron impact MS were run at 70 eV (80 μA). CC and TLC were performed with Si gel, micropack column for HPLC with Si-10/25 cm.

Isolation. Ground small roots (1.2 kg) were extracted with petrol for 12 hr. Chromatography of the extract over a Si gel column gave in order 5-(but-3-en-1-ynyl)-2,2'-bithienyl 2 (0.6 g) and 2,2':5'2''-terthienyl 1 (1.9 g). UV, IR and NMR as reported in the literature [2–4]. Further elution with cyclohexane-C_6H_6 (9:1) 1.8 l. and (8:2) 0.9 l. gave in order cardopatine 3 and isocardopatine 4 *cis* and *trans* isomers respectively of 5,5'' (cyclobut-1,2-ylenediethynylene) *bis*-2,2'bithiophene. (Found for 3: C, 66.80; H, 3.89; S, 28.54. Found for 4: C, 66.82; H, 3.89; S, 29.30. $C_{24}H_{16}S_4$ requires: C, 66.67; H, 3.73; S, 29.60%).

Cardopatine 3. Yellow plates mp 123–125° (EtOH). UV λ_{max} nm: 340, 242 (log ε 4.82, 4.33); $[\alpha]_D^{20} = 0$; IR λ_{max} cm^{-1}: 840 (2-thienyl), 810 (thiophen-2,5-diyl). PMR: δ 7.14 (H-3, *dd*), 6.98 (H-4, *dd*), 7.19 (H-5, *dd*), ($J_{3,4} = 3.7$, $J_{3,5} = 1.2$, $J_{4,5} = 5.0$), 7.03 and 6.98 (H-3', *d*, H-4' *d*, $J_{3',4'} = 3.8$). AA'BB'XX' pattern, δ_A 2.15 (2H, *m*, CH_2), δ_B 2.29 (2H, *m*, CH_2), δ_X 3.37 (2H, *m*, CH), for the complete analysis see Table 2. ^{13}C NMR: see Table 1. MS (probe) *m/e* (rel. int.): 432 [M^+] (9), 216 [$M^+/2$] (100), 171 [$M^+/2$ − CHS] (13), 95 (6).

Isocardopatine 4. Light yellow plates mp 79–80° (EtOH). UV λ_{max} nm: 340, 242 (log ε 4.82, 4.33); IR ν_{max} cm^{-1}: 840 (2-thienyl), 810 (thiophen-2,5-diyl). PMR: δ 7.12 (H-3, *dd*), 6.97 (H-4, *dd*), 7.18 (H-5, *dd*), ($J_{3,4} = 3.7$, $J_{3,5} = 1.3$, $J_{4,5} = 5.0$), 7.06 and 7.00 (H-3' *d*, H-4' *d*, $J_{3',4'} = 3.8$), AA'BB'XX' pattern, δ_A 2.28 (2H, *m*, CH_2), δ_B 2.33 (2H, *m*, CH_2), δ_X 3.54 (2H, *m*, CH), for the complete analysis see Table 2. ^{13}C NMR: see Table 1. MS (probe) *m/e* (rel. int.): 432 [M^+] (12), 216 [$M^+/2$] (100), 171 [$M^+/2$ − CHS] (13), 95 (7).

Assay for dimerization of 2. Cardopatine 3, isocardopatine 4 and bithienyl 2 were detected by TLC in the Me_2CO–petrol extracts (room temp. for *ca* 10 min) of the fresh ground roots. The relative amount of these 3 components (measured by HPLC) did not change appreciably when the roots were extracted for 4 days, or when the original soln was adsorbed on a Si gel column for 24 hr. On the other hand, dimerization reactions of the monomeric compound 2 have been carried out. Exposure to UV light for a short time without/with a trace of acid did not induce compound 2 to dimerize. Traces of the dimers 3 and 4 were detected only when a soln of pure monomer 2 was adsorbed on a Si gel column for 24 hr, or the same soln adsorbed on a TLC plate was exposed to a UV lamp.

Hydrogenation of 3 *with* Ni-*Raney*. A soln of 3 (400 mg) in EtOH (300 ml) was hydrogenated for 12 hr over Ni-Raney W_2 (1 g) at room temp. and 3–4 atm pres. Removal of the catalyst and purification by CC (hexane) gave *trans* 1,2-didecylcyclobutane (5) as a colourless oil (yield 50%). PMR: δ 0.88 (6H, degenerate *t*, 2Me); 1.2–1.4 (36 H, CH_2 of the side-chains), 1.4–2.0 (6 H of the cyclobutane ring). MS (all glass inlet system heated at 200°) *m/e*: 336 [M^+] (3), 308 [$M^+ - C_2H_4$] (3), 168 [$M^+/2$] (4), 55 (100). High resolution measurement: *m/e* 336.376 (±0.002), m* (336 → 308), (336 → 168). (Found: C, 85.66; H, 14.36. $C_{24}H_{48}$ requires: C, 85.63; H, 14.37%).

Hydrogenation of 4 *with* Ni-*Raney*. The same procedure used

for **3** gave the colourless oil *cis* 1,2-didecylcyclobutane (**5a**). PMR: δ 0.88 (6 H, degenerate *t*, 2 Me), 1.2–1.4 (36 H, CH_2 of the side chains), 1.5–2.4 (6 H of the cyclobutane ring). MS (all glass inlet system heated at 200°) *m/e*: 336 [M^+] (2), 308 [$M^+ - C_2H_4$] (1), 168 [$M^+/2$] (2.5), 55 (100), m* (336 → 308), (336 → 168). (Found: C, 85.53; H, 13.66. $C_{24}H_{48}$ requires: C, 85.63; H, 14.37%).

Hydrogenation of **3** *with* Pd/C. A soln of **3** (350 mg) in Et_2O (200 ml) was hydrogenated for 6 hr over Pd/C (10%) at room temp. and 3–4 atm pres. This gave, after purification by chromatography, a yellow viscous oil (yield 75%), *trans* 5,5″(cyclobut-1,2-ylene diethylene) *bis* [2,2′-bithiophene] (6), which solidified on standing at room temp. mp 53–54°. UV λ_{max} nm: 308, 244 (log ε 4.11, 3.77), IR ν_{max} cm^{-1}: 840 (2-thienyl), 800 (thiophen-2,5-diyl). MS (probe) *m/e*: 440 [M^+] (26), 220 (3.5), 2.18 (9), 193 (2), 192 (3), 181 (9.5), 180 (13), 179 (100). (Found: C, 65.83; H, 5.31. $C_{24}H_{24}S_4$ requires: C, 65.44; H, 5.49%).

Hydrogenation of **4** *with* Pd/C. The same procedure used for **3** gave a yellow viscous oil, *cis* 5,5″(cyclobut-1,2-ylenediethylene) *bis* [2,2′-bithiophene] (**6a**), which showed identical UV and IR as for **6**.

Hydration of **3**. A soln of **3** (500 mg) in MeOH (300 ml), with H_2SO_4 10% (10 ml) and $HgSO_4$ (500 mg), was refluxed for 12 hr. Filtration and concn gave a yellow crystalline product *trans* 5,5″[cyclobut-1,2-ylene *bis* (methylenecarbonyl)] *bis* [2,2′-bithiophene] (7) mp 168–171° (EtOH) (yield 62%). UV λ_{max}^{EtOH} nm: 349, 244, 252 sh (log ε 4.54, 3.94, 3.84); IR ν_{max} cm^{-1}: 1620, 1640 (2 × CO), 840 (2-thienyl), 800 (thiophen-2,5-diyl); PMR: δ 7.27 (H-3 and H-5, *m*), 7.03 (H-4, *dd*), ($J_{3,4}$ = 3.5, $J_{3,5}$ = 1.2, $J_{4,5}$ = 5.0, values obtained from C_6H_6 soln), 7.13 and 7.57 (H-3′ *d*, H-4′ *d*, $J_{3',4'}$ = 4.0), 3.18, 2.98 (4 H two q_{AB}, $^2J_{AB}$ = 15.5, CH_2CO), 2.60 (2H, *m*, CH cyclobutane), 1.6–2.3 (4H, *m*, CH_2 cyclobutane). MS(probe) *m/e*: 468 [M^+] (10), 260 (30), 280 (100).

Oxidation of **7**. A soln of **7** (500 mg) in Me_2CO (150 ml), with 5% $KMnO_4$ (100 ml), and 2N H_2SO_4 (50 ml), was stirred at room temp. until the oxidation was completed. Filtration, evapn, extraction with Et_2O (3 × 100 ml), extraction with 10% $NaHCO_3$ (4 × 50 ml) and acidification gave *trans* 5,5″[cyclobut-1,2-ylene *bis* (methyne carbonyl)] di-2-thiophenecarboxylic acid (8) mp 250 252° (yield 60%). The dimethylester had mp 170–171° (MeOH): IR ν_{max} cm^{-1}: 830 (thiophen-2,5-diyl), 1640, 1660 (2 CO ketones), 1720 (CO ester); PMR: δ 7.75 and 7.62 (H-3′ *d*, H-4′ *d*, $J_{3',4'}$ = 4.0), 3.14 and 3.05 (4 H, two q_{AB}, J_{AB} = 15.5, $COCH_2$), 2.60 (2 H, *m*, CH cyclobutane), 1.6–2.3 (4 H, *m*, CH_2 cyclobutane), 3.91 (6 H, 2 OMe). (Found: C, 57.68; H, 4.77; S, 14.65. $C_{20}H_{20}O_6S_2$ requires: C, 57.14; H, 4.73; S, 15.23%). MS (probe), *m/e*: 392 [M^+] (3), 374 (5), 222 (37), 170 (38) 155 (100)

Oxidation of **3**. 500 mg of **3** were oxidized with $KMnO_4$ as described for **7**. Extraction with Et_2O of the acidified soln and sublimation *in vacuo* of the residue gave 2,5-thiophendicarboxylic acid (**9**) (54%). The dimethylester had mp and mmp 144 146° (lit. 148° [22]); PMR: δ 3.90 (6 H, s, 2 OMe), 7.78 (2 H, s, thiophene); MS (glass inlet), *m/e*: 200 [M^+] (34), 169 (100).

Ozonolysis of **3**. Ozone (5 l. hr) was bubbled for 2 hr through a CO_2–EtOH cooled soln of **3** (100 mg) in EtOAc (25 ml). Evapn, addition of H_2O (30 ml) and H_2O_2 (0.5 ml), heating to boiling, leaving 24 hr at room temp., extraction with Et_2O, washing with 5% K_2CO_3, acidification of the aq. layer with 2N H_2SO_4 and extraction with Et_2O gave a soln of *trans* cyclobutane-1,2-dicarboxylic acid (**10**) which was directly added to CH_2N_2 in Et_2O. Evapn gave methyl *trans*-cyclobutane-1,2-dicarboxylate identical (GC–MS) with an authentic sample. MS (GC) *m/e*: 141 [M^+ – OMe] (41), 140 [M^+ – MeOH] (57), 113 [M^+ – COOMe] (100), 112 (74), 85 (20), 81 (49), 71 (50), 59 (52), 55 (77), 53 (35).

Ozonolysis of **4**. Similar treatment of **4** gave the dimethyl ester of *cis* cyclobutane-1,2-dicarboxylic acid (**10a**) identified as above. MS (GC) *m/e*: 141 [M^+ – OMe] (58), 140 [M^+ – MeOH] (39), 113 [M^+ – COOMe] (100), 112 (23), 85 (16), 81 (55), 71 (31), 59 (45), 55 (64), 53 (28).

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