Rotamers and Isomers in the Fulgide Series. Part 3.† Structures of the Bis(4-methoxy-3-methylbenzylidene)succinic Anhydrides

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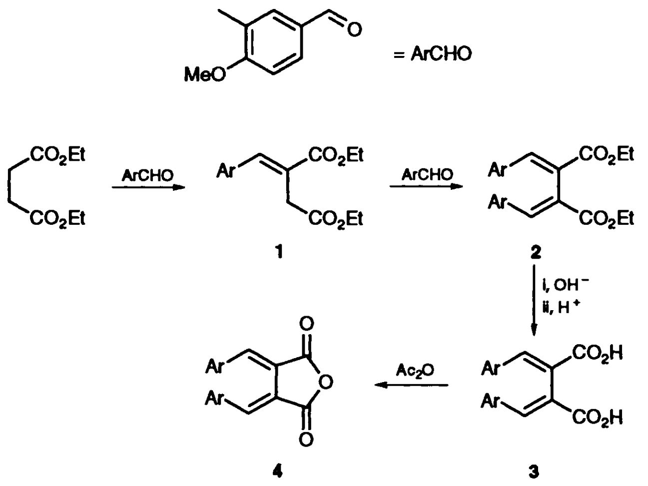
The conformation of bisarylsuccinic anhydrides is a function of steric interaction between the aryl rings and the reactivity of the substituents that they carry. To explore the second factor a methyl group has been introduced for the present study. For the first time a stable *E,Z*-isomer has now been isolated as a result. The structures of the *E,E*- and *Z,Z*-isomers have been determined crystallographically. Crystals of the *E,E*-isomer have $a = 7.835(1)$, $b = 8.966(1)$, $c = 25.725(3)$ Å, space group $P2_12_12_1$, $Z = 4$; and for *Z,Z* $a = 25.506(5)$, $b = 7.896(1)$, $c = 20.058(3)$ Å, $\beta = 102.75(1)°$, space group $C2/c$, $Z = 8$. All efforts to obtain sufficiently large crystals of the *E,Z*-product have failed, but it has been characterised in terms of NMR evidence. The dehydrogenation product from ring closure of the *E,Z*-isomer has been characterised from its NMR spectrum and confirmed crystallographically, $a = 13.132(4)$, $b = 8.239(1)$, $c = 17.242(7)$ Å, $\beta = 100.84(3)°$, space group $P2_1/c$. Atomic coordinates from this structure are used to optimize the *E,Z*-structure by molecular modelling.

Previous experience[1,2] indicates that fulgide molecules are likely to adopt one of three arrangements with appreciably different stabilities. The *Z,Z*-rotamer, as a virtually strain-free arrangement is the most likely, and predicted to be the most stable. This variant is usually readily available as single-crystal material and has been well studied in the past. The next most common modification is the *E,E*-isomer with a substantial measure of steric repulsion between the aryl rings. In the case of unsymmetrically substituted aryl groups two enantiomers may stabilise into substantially different configurations, not related by mirror symmetry. It is one of the objectives of this on-going investigation to isolate both of these modifications for the same compound, as yet without success. The third, *E,Z*-rotamer is the hardest to come by, because of the favourable disposition for chemical reaction to produce a naphthalene derivative *via* dehydrogenation. Isolation of the elusive *E,Z*-intermediate is the second major objective of the work.

The stereochemistry and rotameric preferences of the *E,E*- and *Z,Z*-isomers of substituted fulgides (dimethylenesuccinic anhydrides) have so far been studied in this laboratory for the cases of the 3,4-dimethoxy-[1] and the *p*-methoxy-phenyl[2] substituents. In the case of the *p*-methoxy derivative the *E,E*-anhydride was converted to the *Z,Z*-isomer by irradiation at 366 nm,[2] while in the case of the electronically more activated 3,4-dimethoxy derivative simple exposure to silica gel effected this conversion.[1] In neither case was an *E,Z*-isomer obtained, although such an intermediate equilibrium stage must be assumed. Similarly, irradiation of the 3,4-dimethoxyfulgenic acid at 366 nm led to the formation of isomers from which, after cyclisation to the anhydrides, only the *Z,Z*-isomer was obtained; when the irradiation of the fulgenic acid was prolonged, cyclisation of the products led to the isolation of some dehydrogenation product, the substituted 1-phenylnaphthalene-2,3-dicarboxylic anhydride, thus also indicating the transient occurrence of an *E,Z*-isomer.

The present study concerns the reactivities of such isomers for the case of 4-methoxy-3-methylphenyl substituents. Here the 3-methoxy group is replaced by a methyl group, thus involving a decrease in the dipolar moment in the substituent bond towards the aromatic ring by a factor of *ca.* 4. At the same time it has been shown that the stereochemical effectiveness of a methyl group in conformationally flexible (*e.g.* cyclohexane) systems is some three times that of a methoxy group[3] so that different reactivities may here be at issue.

The *E,E*-fulgenic acid (**3**) on cyclisation afforded the *E,E*-anhydride **4**, m.p. 155–156 °C, and the detailed disposition of the substituents could be demonstrated to be as in **5** by X-ray diffraction (see below).



When the diacid **3** was irradiated at 366 nm the course of the isomerisation could be followed by TLC and silylation–GLC and the acids obtained now yielded the *E,Z*-fulgide **6** after cyclisation. This compound, m.p. 165–166 °C, was invariably obtained as microcrystalline needles, so that a single-crystal study was not possible. The detailed analysis of its NMR characteristics however demonstrates the separate *E*- and *Z*-double bond relationships within the molecule. The typical low-frequency chemical shift of the olefinic proton, on passing from the *E,E* to the *Z,Z* configuration, together with the high-frequency shift of the isolated *ortho* aromatic proton here found by decoupling experiments, are in accord with the relevant data for the full series of these fulgides; the relevant data are in Table 1.

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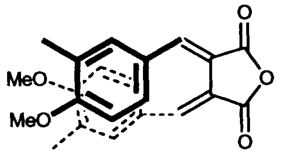
† Part 2, ref. 2.

Table 1 Chemical shift assignments (ppm) for specific protons of isomeric fulgides

	E,E		*Z,Z*		*E,Z*			
					E-branch		*Z*-branch	
Aryl substituents	Olefinic	Isolated *ortho*	Olefinic	Isolated *ortho*	Olefinic	Isolated *ortho*	Olefinic	Isolated *ortho*
p-MeO[a]	7.86	6.74	7.33	8.11	—	—	—	—
3,4-$(MeO)_2$[b]	7.84	6.46	7.35	8.25	—	—	—	—
3-Me-4-MeO	7.82	6.58	7.31	7.89	8.00	7.46	7.61	7.74[c]

[a] From ref. 2. [b] From ref. 4. [c] The availability of rotameric alternatives for the bond to the aryl substituents in the case of the *E*- and *Z*-configurations in the *E,Z*-isomer is demonstrated for the solid state by Fig. 3, and is reflected in the different anisotropies effected by the two aryl rings on each other in solution, as shown here.

Both the *E,E*-fulgide **5** and its *E,Z*-isomer **6** could be isomerised on heating (see Experimental section) to the *Z,Z*-isomer (**7**), orange prisms of m.p. *ca.* 188 °C. The crystallographic structure is reported below. The *E,E*-fulgide **5** on prolonged heating in acetonitrile solution at 200 °C afforded the dehydrogenation product, 7-methoxy-6-methyl-1-(4′-methoxy-3′-methylphenyl)naphthalene-2,3-dicarboxylic anhydride (**8**), m.p. 222 °C, whose structure was demonstrated by detailed analysis of its NMR characteristics (see Experimental section), while a single crystal afforded acceptable confirmation of its structure by X-ray diffraction analysis.



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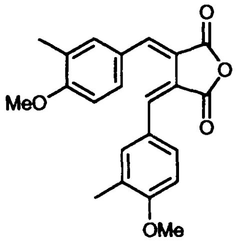

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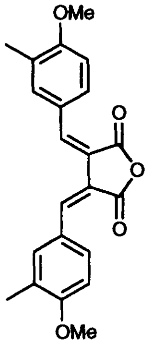

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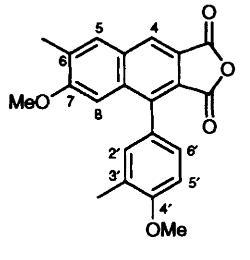

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Experimental

Measurements and routine procedures were as reported before,[1,2] except that analytical GLC was over a column (2.1 × 0.002 m) of OV17 (1% on Anakrom Q).

E,E-*Bis*(4-*methoxy*-3-*methylbenzylidene*)*succinic Acid* (**3**).—The Stobbe condensation of 3-methyl-anisaldehyde with diethyl succinate, carried out in the presence of sodium hydride[5] as before[1,2] gave a mixture of the diesters of itaconic acid (**1**) and the fulgenic acid **2**. This mixture was converted to the mixed diethyl esters which were again[6] treated in the same manner and then hydrolysed to afford the fulgenic acid **3** as yellow needles, m.p. 210–214 °C from acetic acid–formic acid (1 : 1, v/v); by silylation–GLC analysis the product was quite pure (ET_{233} 267 °C, 99%); δ(200 MHz, CD_3CN) 7.77 (2 H, s, olefinic), 7.41 (2 H, dd, *J* 8.5 and 2.2, ArH), 7.33 (2 H, d, *J* 2.4, ArH), 6.83 (2 H, d, *J* 8.5, ArH), 3.79 (6 H, s, OMe) and 2.09 (6 H, s, Me). Its stereochemistry follows from the detailed structure of its anhydride **4** = **5** below.

E,E-*Bis*(4-*methoxy*-3-*methylbenzylidene*)*succinic Anhydride* (**4**).—This was prepared from the diacid **3** and acetyl chloride as before[1] and crystallised from acetone as deep yellow prisms, m.p. 155–156 °C, δ(200 MHz, $CDCl_3$) 7.82 (2 H, s, olefinic), 6.67 (2 H, dd, *J* 2.1 and 8.4, ArH), 6.58 (2 H, d, *J* 2.1, ArH), 6.33 (2 H, d, *J* 8.5, ArH), 3.75 (6 H, s, OMe) and 1.85 (6 H, s, Me); TLC in benzene–ethyl acetate (39 : 1, v/v) showed only one spot at hR_F 31.

E,Z-*Bis*(4-*methoxy*-3-*methylbenzylidene*)*succinic Anhydride* (**6**).—The diacid **2** (501 mg) in acetone (50 cm^3) was irradiated at 366 nm and the progress of the reaction followed by TLC in benzene–ethyl acetate–formic acid (18 : 2 : 1, v/v) and by silylation of aliquot samples followed by GLC. After 2 h the solution contained two main products, *viz.* unchanged starting material (hR_F 25, and ET_{233} 267 °C) and a new product (hR_F 20 and ET_{233} 272 °C) in the ratio 2 : 1. Chromatography over silica gel afforded this mixture (395 mg), which (90 mg) was kept in acetyl chloride (6.5 cm^3) at 55 °C for 17 h. The recovered product (86 mg) afforded the fulgide **6** as yellow felted microneedles (23 mg), m.p. 165–166 °C (from acetone), δ(200 MHz, $CDCl_3$) by double irradiation shown to have two sets of aromatic and olefinic protons at 8.00 (1 H, s), 7.93 (1 H, dd, *J* 2.2 and 7.6), 7.74 (1 H, d, *J* 2.3) and 6.86 (1 H, d, *J* 7.8) and at 7.61 (1 H, s), 7.52 (1 H, dd, *J* 2.0 and 8.3), 7.47 (1 H, d, *J* 2) and 6.87 (1 H, d, *J* 8.4) and also resonances at 3.91 (3 H, s) and 3.90 (3 H, s) for OMe, and at 2.22 (6 H, s) for ArMe. The structure, simulated by molecular mechanics is reported below.

Isomerisation of E,Z-*fulgide* (**6**).—The *E,Z*-fulgide (**6**, 33 mg) in acetone (1 cm^3) in an evacuated sealed tube was heated at 120 °C for 120 h. The recovered product was fractionally crystallised from acetonitrile to afford some small but massive crystals (2 mg), m.p. 189–190 °C, which by X-ray diffraction analysis were found to be the *Z,Z*-fulgide **7** (below).

Z,Z-*Bis*(4-*methoxy*-3-*methylbenzylidene*)*succinic Anhydride* (**7**).—The *E,E*-fulgide (**5**, 50 mg) was spread on silica gel (2.5 g) and heated under nitrogen at 120 °C for 88 h. By chromatography over silica gel (25 g) in benzene–ethyl acetate (39 : 1 v/v) frontal yellow fractions afforded a mixture (6 mg) which on TLC in the same solvent showed some starting material at hR_F 31 and a major new spot at hR_F 42. Crystallisation from acetonitrile afforded the *Z,Z*-isomer (**7**) as orange prisms, m.p. 186–188 °C, δ(200 MHz, $CDCl_3$) 8.09 (2 H, dd, *J* 2.4 and 8.6, ArH), 7.89 (2 H, d, *J* 2.3, ArH), 7.31 (2 H, s, olefinic), 6.91 (2 H, d, *J* 8.7, ArH), 3.92 (6 H, s, OMe) and 2.27 (6 H, s, Me).

A selected prism afforded the *Z,Z*-structure (**7**) of the anhydride by X-ray diffraction analysis.

Table 2 Crystal data and summary of data collection parameters and structure refinement

Compound	4	7	8
Formula	$C_{22}H_{20}O_5$	$C_{22}H_{20}O_5$	$C_{22}H_{18}O_5$
M_r	364.42	364.42	362.40
Crystal size/mm	0.12 × 0.25 × 0.31	0.19 × 0.43 × 0.90	0.60 × 0.22 × 0.31
Temperature/°C	25	25	25
Number of reflections for cell constants	25	25	25
Θ range for cell constants/deg	16–18	17–20	3–12
a/Å	7.835(1)	25.506(5)	13.132(4)
b/Å	8.966(1)	7.896(1)	8.239(1)
c/Å	25.725(3)	20.058(3)	17.242(7)
β/deg	90	102.75(1)	100.84(3)
V/Å^3	1807.14	3630.97	1832.066
D_c/g cm^{-3}	1.339	1.333	1.321
μ/cm^{-1}	0.9	0.9	0.9
Scan mode	ω–2Θ	ω	ω–2Θ
Vertical aperture/mm	4.0	4.0	4.0
Horizontal aperture/mm	1.3	1.3	1.3
Scan speed/deg min^{-1}	0.97–5.49	1.37 – 5.49	0.72–3.30
Θ range/deg	2–30	2–30	2.5–25
Standard reflection decay/%	10.4	15.0	1.1
Number of measured data	3027	11081	3588
Space group	$P2_12_12_1$	$C2/c$	$P2_1/c$
z	4	8	4
F(000)	768	1536.00	760.00
Internal consistency, R		0.021	0.037
Cut-off criterion	$F > 3\sigma(F)$	$F > 3\sigma(F)$	$F > 2\sigma(F)$
Observed reflections	1527	2763	1173
Number of parameters	135	247	135
Residual density/e Å^{-3}			
Maximum	0.32	0.32	0.63
Minimum	−0.32	−0.37	−0.66
Weighting scheme	$2.1604/\sigma^2(F)$	$2.3640/\sigma^2(F)$	$3.1430/\sigma^2(F)$
R	0.075	0.087	0.200
R_w	0.061	0.076	0.145
R_g	0.051	0.068	0.114

Dehydrogenation of the E,E-*Fulgide* (**5**).—The *E,E*-fulgide (**5**, 51 mg) in acetonitrile (1 cm^3) in an evacuated sealed tube was heated at 200 °C for 24 h. The product (24 mg prisms from acetonitrile, m.p. 220–221 °C after undergoing a phase change at 185 °C) on further crystallisation showed a constant m.p. 222 °C as before; it was shown to be 7-methoxy-6-methyl-1-(4′-methoxy-3′-methylphenyl)-naphthalene-2,3-dicarboxylic anhydride (**8**) by NMR spectroscopy with decoupling experiments, δ(200 MHz, $CDCl_3$) 8.34 (1 H, s, 4-H), 7.85 (1 H, s, 5-H), 7.25 (1 H, dd, *J* 0.5 and 8.2, 6′-H), 7.22 (1 H, d, *J* 0.5, 2′-H), 7.2 (1 H, m, 8-H), 7.01 (1 H, d, *J* 8.3, 5′-H), 3.95 and 3.79 (6 H, 2 × s, 7-OMe and 4′-OMe), 2.43 (3 H, s, 6-Me) and 2.31 (3 H, s, 3′-Me). A crystal was found which afforded confirmation of this structure by X-ray diffraction analysis.

Crystallographic Analysis.—Four crystalline products were isolated experimentally, but in only two cases were diffraction quality crystals obtained. Well-refined structures of **4** and **7** are described. Crystals of **8** were of low quality, in line with previous experience.[1] Efforts to improve the data by low-temperature crystallography failed to produce better resolution.

Crystal data and a summary of data collection parameters for compounds **4**, **7** and **8** are given in Table 2. All measurements were made on an Enraf-Nonius CAD4 single-crystal diffractometer with an incident beam graphite-crystal monochromator [λ(Mo-Kα) 0.7104 Å]. Fixed scan and aperture widths were used while the scan speed was varied. Crystal decay and orientation were monitored during data collection. Decay corrections (using standard Enraf-Nonius software) were carried out for crystals of **4** and **7**. Data reduction consisted of correction for background and Lp effects. No absorption corrections were applied as the compounds have low absorption coefficients.

All computing was done on an IBM-compatible PC using the programs SHELX[7] for structure solution and refinement, SCHAKAL88[8] for plotting structure diagrams and XANADU[9] for mean plane calculations. The structures were solved using direct methods and refined by full-matrix least squares. Weighting schemes based on counting statistics were employed where $R_w = \Sigma(\sqrt{w}|\Delta F|)/\Sigma(wF_0)$ and $R_g = [\Sigma w(|\Delta F|)^2/\Sigma(w_0F_0{}^2)]^{\frac{1}{2}}$. All hydrogen atoms were placed in geometrically calculated positions and refined in a riding mode with common isotropic temperature factors.

Structure **8** did not refine as well as the other two, even though the residual electron density was not large enough to indicate any disorder or presence of solvent molecules. At the termination of refinement the conventional R was disappointingly high, although the index R_g was almost respectable. Such a large discrepancy between R and R_g is very likely symptomatic of disorder.[10] This may also explain the poor crystal quality. A summary of the structure refinements can be seen in Table 2 and the atomic numbering scheme is shown in Fig. 1. Stereoscopic views of the structures can be seen in Figs. 2–4. Full lists of atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.*

Results

Crystal Structure.—The two aryl rings in compound **4** are not parallel. The angle between the normals to their planes is 15.5°. These rings are rotated by almost the same amount from the

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* For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 2*, 1993, issue 1.

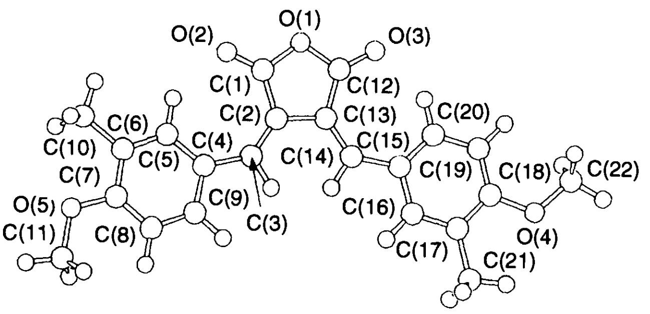

Fig. 1 Atomic numbering scheme for non-hydrogen atoms

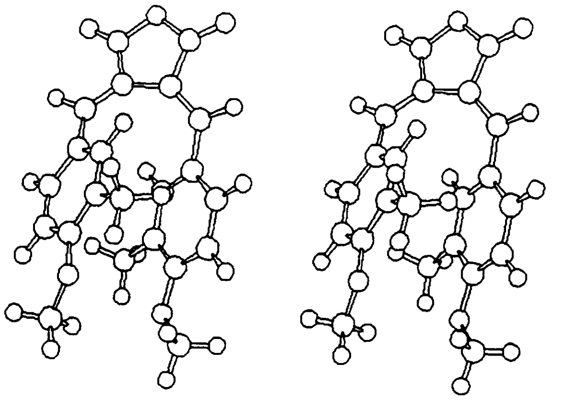

Fig. 2 Stereoscopic view of the structure of compound **4**

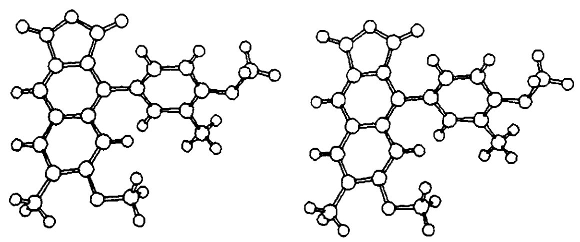

Fig. 4 Stereoscopic view of the structure of compound **8**

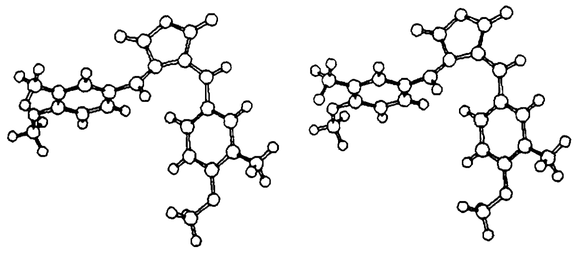

Fig. 5 Stereoscopic view of the molecular mechanics structure of compound **6**

Table 3 Selected torsion angles in compounds **4** and **7**

Angle	4	7
C(3)–C(2)–C(13)–C(14)	31.94°	2.38°
C(4)–C(3)–C(2)–C(13)	0.81°	178.74°
C(2)–C(13)–C(14)–C(15)	3.25°	177.69°

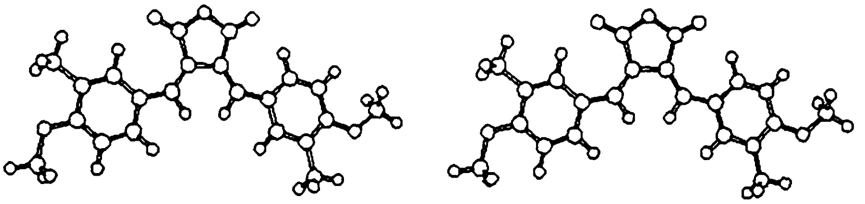

Fig. 3 Stereoscopic view of the structure of compound **7**

plane of the anhydride ring with angles between the plane normals of 32.3° and 29.3°. In the open compound **7** there is no steric crowding and so it is not unexpected to find that the aryl rings are coplanar. The angle between their plane normals is 1.3°. Once again the two aryl rings are rotated from the plane of the anhydride ring by almost the same amount, although not as pronounced as in compound **4**. The angles between the plane normals of the anhydride ring with those of the two aryl rings are 8.3° and 7.3°. Another means of visualising these rotations in terms of the torsion angles is shown in Table 3.

In compound **8** the naphthalene and anhydride rings are planar. The normal to the mean plane of this part of the molecule makes an angle of 58.4° to the normal of the mean plane at the aryl ring. This is similar to that seen in the bis(3,4-dimethoxybenzylidene)succinic anhydride previously studied.[2]

Molecular Mechanics.—A variety of fulgide structures have been simulated by molecular mechanics before[1,2] and the details of the force field are well established. The only requirement to ensure correct simulation of an unknown structure is therefore a starting configuration that would not refine into a false minimum. The overall strain energy of the fully refined structure should, however, provide reliable guidance in this respect. It was argued that the formation of the dehydrogenation product proceeds *via* the *E*,*Z* arrangement **6**, suggesting the crystallographic structure of **8** as a suitable starting point. The strategy consisted of treating the bond [C(14)–C(9)], responsible for fusing the rings, as a non-bonded contact until these atoms have moved apart to about 3.5 Å. Hydrogen atoms were then added in geometrically calculated positions and the refinement was allowed to proceed to completion. The final structure is shown stereoscopically in Fig. 5. There are no unusual structural features and it very likely represents the true structure. The region around the central C–C bond in the five-membered ring is of special importance since this is the region of largest difference between the *E*,*E* and *Z*,*Z* structures. It is fair to expect the dissymmetry between the two sides of the molecule to mirror the differences between the symmetrical *E*,*E* and *Z*,*Z* arrangements. This comparison is made graphically in Figure 6 showing the relevant bond angles. Bond lengths and torsion angles are less useful in this context. The close parallel observed is interpreted as a strong indication that the observed variation in structure is due in all instances to steric factors characteristic of the various geometrical isomers. The calculated strain in the molecule (29 kcal mol^{-1}) is very close to the values calculated before for other *E*,*E* and *Z*,*Z* isomers in the series. There was no ambiguity in the way in which the generated structure responded during refinement since the aryl substituent in **8** is not co-planar with the naphthalene part.

All attempts to characterise the *E*,*Z* product crystallographically, including powder diffraction, were unsuccessful.

Discussion

The three families of fulgides examined as part of this series to date, differ only through the nature of their *meta* substituents, being R = MeO, H, CH_3 respectively. Some interesting crystallographic differences are observed. (i) Only the dimethoxy *Z*,*Z*-rotamer has two-fold symmetry. The two other *Z*,*Z*-rotamers have pseudo two-fold axes in the solid state because of the relative orientation of their aryl substituents. A 180° rotation of any aryl group around its connecting single bond is required to restore the full symmetry. (ii) All of the *E*,*E*-rotamers have two-fold symmetry. An additional asymmetrical isomer with rotated aryl groups occurs for the *p*-methoxy compound only. (iii) Only the methyl derivative occurs as a stable *E*,*Z*-rotamer.

Acknowledgements

Professor G. W. Perold warmly thanks Dr. R. J. Highet (NIH, Bethesda, MD) for the hospitality of his laboratory during exploratory stages of this study. We also thank Dr. L. Carlton and Mrs. S. Heiss for NMR spectral assistance.

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Paper 2/06715C
Received 18*th December* 1992
Accepted 25*th February* 1993