EDINGTON, P. & HARDING, M. M. (1974). *Acta Cryst.* **B30**, 204–206.
Enraf–Nonius (1979). *Structure Determination Package.* Enraf–Nonius, Delft, The Netherlands.
FINKELSTEIN, A. V. & PTITSYN, O. B. (1977). *Biopolymers*, **16**, 469–495.
FUESS, H., HOHLWEIN, D. & MASON, S. A. (1977). *Acta Cryst.* **B33**, 654–659.
GORBITZ, C. H. (1989). *Acta Cryst.* **B45**, 390–395.
HARADA, Y. & IITAKA, Y. (1977). *Acta Cryst.* **B33**, 250–252.
HERBSTEIN, F. H. & KAPON, M. (1979). *Acta Cryst.* **B35**, 1614–1619.
ITOH, H., YAMANE, T., ASHIDA, T. & KAKUDO, M. (1977). *Acta Cryst.* **B33**, 654–659.
IUPAC-IUB COMMISSION ON BIOCHEMICAL NOMENCLATURE (1970). *J. Mol. Biol.* **52**, 1–17.
JANIN, J., WODAK, S., LEVITT, M. & MAIGRET, B. (1978). *J. Mol. Biol.* **125**, 357–386.
JEFFREY, G. A. & MALUSZYNSKA, H. (1990). *Acta Cryst.* **B46**, 546–549.
KIM, S.-H. & RICH, A. (1967). *Science*, **158**, 1046–1048.
KISTENMACHER, T. J., HUNT, D. J. & MARSH, R. E. (1972). *Acta Cryst.* **B28**, 3352–3361.
LEHMANN, M. S., KOETZLE, T. F. & HAMILTON, W. C. (1972). *Int. J. Pept. Protein Res.* **4**, 229–239.
MADDEN, J. J., MCGANDY, E. L. & SEEMAN, N. C. (1972). *Acta Cryst.* **B28**, 2377–2382.
MADDEN, J. J., MCGANDY, E. L., SEEMAN, N. C., HARDING, M. M. & HOY, A. (1972). *Acta Cryst.* **B28**, 2382–2389.
MARTINEZ-CARRERA, S. (1966). *Acta Cryst.* **20**, 783–789.
MITRA, J. & RAMAKRISHNAN, C. (1977). *Int. J. Pept. Protein Res.* **9**, 27–48.
ODA, K. & KOYAMA, H. (1972). *Acta Cryst.* **B28**, 639–642.
PFEIFFER, D., RECK, G. & OEHLKE, J. (1985). *Crystallogr. Res. Technol.* **20**, 1345–1350.
PONDER, J. W. & RICHARDS, F. M. (1987). *J. Mol. Biol.* **193**, 775–791.
PRASAD, N. & GOVIL, G. (1980). *Proc. Indian Acad. Sci. Chem. Sci.* **89**, 253–262.
ROMAN, P., GUTIERREZ-ZORRILLA, J. M., LUQUE, A. & VEGAS, A. (1987). *J. Crystallogr. Spectrosc. Res.* **17**, 585–595.
SHELDRICK, G. M. (1985). *SHELX86. Crystallographic Computing* 3, edited by G. M. SHELDRICK, C. KRUGER & R. GODDARD, pp. 175–189. Oxford Univ. Press.
STEWART, R. F., DAVIDSON, E. R. & SIMPSON, W. T. (1965). *J. Chem. Phys.* **42**, 3176–3187.
SURESH, C. G. & VIJAYAN, M. (1985). *Int. J. Pept. Protein Res.* **26**, 329–336.
VOET, D. & RICH, A. (1970). *Prog. Nucleic Acid Res. Mol. Biol.* **10**, 183–265.

Acta Cryst. (1991). **B47**, 511–521

Structural Comparison of a *gem*-Dichlorodiarylcyclopropane Antiestrogen and Three of its Derivatives

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Abstract

The pure antiestrogenic activity of compound (1) gave the impetus to synthesize a series of its derivatives (2)–(4). Structural features of these compounds are compared. Compound (1): 1,1-dichloro-*cis*-2,3-diphenylcyclopropane, $C_{15}H_{12}Cl_2$, $M_r = 263{\cdot}2$, orthorhombic, *Pbca*, $a = 19{\cdot}627$ (7), $b = 19{\cdot}460$ (6), $c = 6{\cdot}670$ (2) Å, $V = 2547{\cdot}5$ Å^3, $Z = 8$, $D_x = 1{\cdot}372$ g cm^{-3}, λ(Mo $K\alpha$) = 0·71069 Å, μ(Mo $K\alpha$) = 4·3 cm^{-1}, $F(000) = 1088$, $T = 138$ K, $R = 0{\cdot}026$ for 1923 observed reflections. Compound (2): 1,1-dichloro-*cis*-2,3-bis(4-methoxyphenyl)cyclopropane, $C_{17}H_{16}Cl_2O_2$, $M_r = 323{\cdot}2$, monoclinic, $P2_1/c$, $a = 16{\cdot}540$ (1), $b = 7{\cdot}4749$ (7), $c = 12{\cdot}333$ (3) Å, $\beta = 91{\cdot}53$ (2)°, $V = 1524{\cdot}2$ Å^3, $Z = 4$, $D_x = 1{\cdot}408$ g cm^{-3}, λ(Cu $K\alpha$) = 1·54178 Å, μ(Cu $K\alpha$) = 37·0 cm^{-1}, $F(000) = 672$, $T = 163$ K, $R = 0{\cdot}031$ for 2919 observed reflections. Compound (3): 1,1-dichloro-*cis*-2-(4-benzyloxyphenyl)-3-phenylcyclopropane, $C_{22}H_{18}Cl_2O$, $M_r = 369{\cdot}3$, monoclinic, $P2_1/a$, $a = 21{\cdot}064$ (3), $b = 14{\cdot}749$ (2), $c = 5{\cdot}8222$ (8) Å, $\beta = 95{\cdot}48$ (2)°, $V = 1800{\cdot}5$ Å^3, $Z = 4$, $D_x = 1{\cdot}362$ g cm^{-3}, λ(Cu $K\alpha$) = 1·54178 Å, μ(Cu $K\alpha$) = 31·5 cm^{-1}, $F(000) = 768$, $T = 163$ K, $R = 0{\cdot}032$ for 3256 observed reflections. Compound (4): 1,1-dichloro-*trans*-2-(4-acetoxyphenyl)-3-phenylcyclopropane, $C_{17}H_{14}Cl_2O_2$, $M_r = 321{\cdot}2$, monoclinc, $P2_1/n$, $a = 16{\cdot}555$ (4), $b = 12{\cdot}297$ (2), $c = 7{\cdot}439$ (1) Å, $\beta = 98{\cdot}31$ (2)°, $V = 1498{\cdot}5$ Å^3, $Z = 4$, $D_x = 1{\cdot}423$ g cm^{-3}, λ(Mo $K\alpha$) = 0·71069 Å, μ(Mo $K\alpha$) = 3·8 cm^{-1}, $F(000) = 664$, $T = 163$ K, $R = 0{\cdot}034$ for 2474 observed reflections. The crystal structure determinations show that the relative conformation of the two aryl rings in all four structures are quite similar. In this conformation one of the phenyl rings is in a

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bisecting position with respect to the cyclopropane ring, while the other is in a perpendicular position. In each of the four molecules the cyclopropane ring shows significant bond-length asymmetry with $d[C(2)—C(3)] > d[C(1)—C(3)] > d[C(1)—C(2)]$. The average ring C—C distances in the three *cis* compounds, 1·516 (15) in (1), 1·521 (13) in (2) and 1·514 (16) Å in (3), are all longer than that in the *trans* compound, (4), 1·508 (7) Å. A modified additive scheme for the substituent effects on the asymmetry of the bond length in the cyclopropane ring has been adopted which explains both qualitatively and quantitatively the geometrical results of the present study. The two Cl—C distances in each of the *cis* compounds differ by about 0·02 Å while in the *trans* compound the difference is about 0·01 Å. Energy-minimization calculations with the molecular mechanics program *MM*2 show that the crystal structures of the three *cis* compounds (1)–(3) closely resemble the corresponding energy-minimized structures, but the conformation of the minimum-energy structure of the *trans* compound (4) is different from its crystal structure. Steric energy profiles of various conformers of compounds (1) and (4) have been explored.

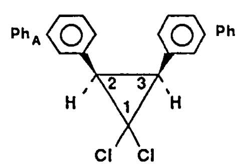
Introduction

Antiestrogens are compounds which prevent estrogens from expressing their full effects on a variety of estrogen target tissues (Horowitz & McGuire, 1978). Of these, the triarylethylenes are the best known, represented by tamoxifen, (*Z*)-1,2-diphenyl-1-{4-[2-(dimethylamino)ethoxy]phenyl}-1-butene, which is in current use for the treatment of hormone-dependent breast cancer (Sutherland & Jordan, 1981; Jordan, 1983; Furr & Jordan, 1984). However, the ethylenic antiestrogens are associated with partial estrogen agonist properties, which compromises their effectiveness as antagonists.

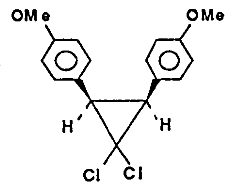
It is reported that the cyclopropane ring shares some of the chemical and spectroscopic properties of the ethylenic double bond since the σ electrons in the C—C bond of the ring tend to exhibit the characteristics associated with the mobile π electrons (Rogers & Roberts, 1946). X-ray crystallographic studies demonstrate that the phenyl rings in tamoxifen are rotated out of the plane of the double bond by more than 50° (Precigoux, Courseille, Geoffre & Hospital, 1979; Cutbush, Neidle, Foster & Leclercq, 1982). Consequently, there is no conjugation between the phenyl rings and the ethylenic double bond, as confirmed by NMR (Bedford & Richardson, 1966), or between the phenyl rings themselves. The introduction of a cyclopropane ring should not disturb any electronic effect in the stilbene-type nucleus, but could produce some steric changes.

The preparation of compounds related to variations of diethylstilbestrol (DES) in which the central ethylenic double bond is replaced with a cyclopropyl ring was carried out to determine if these changes influenced the estrogen agonist activity of the diarylethylenes. While some of these agents proved to be profoundly weaker estrogens than DES, one, analog II (1,1-dichloro-*cis*-2,3-diphenylcyclopropane), (1), (Magarian & Benjamin, 1975) showed measurable antiestrogen activity. Although a weaker antiestrogen than tamoxifen, (1) is unique in that it is devoid of intrinsic estrogen agonist activity (Pento, Magarian, Wright, King & Benjamin, 1981).

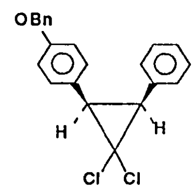
A search for stronger antiestrogens without estrogen activity led to the synthesis and biological testing of several derivatives of (1). We report in this study the molecular structures of four of these compounds, including (1).



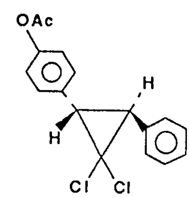
(1)



(2)



(3)



(4)

Crystal structure determinations of these compounds were undertaken to elucidate their stereochemical features. The relative orientation of the two aryl rings with respect to the cyclopropane ring is of particular interest. Energy-minimization calculations were conducted using the molecular mechanics program *MM*2 (Burkert & Allinger, 1982; Allinger, 1985) to find energetically preferred conformations of the diarylcyclopropanes.

The structural results of these four cyclopropane derivatives provided an opportunity to investigate the effect of mixed donor–acceptor substitution on the cyclopropane ring geometry. In recent years extensive studies have been carried out on the substituent-induced asymmetry in the cyclopropane ring (Lauher & Ibers, 1975; Jason & Ibers, 1977; Jason, Gallucci & Ibers, 1981; Maas, 1983; Tinant, Declercq & Van Meerssche, 1985; Tinant, Wu, Declercq, Van Meerssche, Masamba, De Mesmaeker & Viehe, 1988; Schrumpf & Jones, 1987*a*; Romming & Sydnes, 1987). From a collection of geometrical

Table 1. *Intensity data collection and refinement parameters*

	(1)	(2)	(3)	(4)
No. of reflections for cell parameters	48	48	48	66
2θ range (°)	$22 < 2\theta < 30$	$46 < 2\theta < 88$	$40 < 2\theta < 60$	$20 < 2\theta < 41$
Crystal size (mm)	0·20 × 0·23 × 0·47	0·24 × 0·27 × 0·30	0·09 × 0·12 × 0·48	0·17 × 0·27 × 0·30
Radiation	Mo $K\alpha$ (graphite monochromator)	Cu $K\alpha$	Cu $K\alpha$	Mo $K\alpha$ (graphite monochromator)
$2\theta_{max}$ (°)	50	150	150	53
hkl range	$0 \le h \le 22$	$-20 \le h \le 20$	$-26 \le h \le 26$	$-20 \le h \le 20$
	$0 \le k \le 22$	$0 \le k \le 9$	$0 \le k < 18$	$0 \le k < 15$
	$0 \le l \le 10$	$0 \le l \le 7$	$0 \le l \le 9$	$0 \le l \le 9$
Unique data	2220	3135	3708	3083
Observed data [$I \ge 2\sigma(I)$]	1923	2919	3256	2474
Scan type	θ–2θ	θ–2θ	θ–2θ	θ–2θ
Scan width (°)	0·90 + 0·20tanθ	0·80 + 0·20tanθ	0·80 + 0·20tanθ	0·80 + 0·35tanθ
Horizontal aperture (mm)	2·50 + 0·86tanθ	3·5 + 0·86tanθ	3·0 + 0·86tanθ	4·0 + 0·86tanθ
T_{max} (s)	120	90	90	90
Max. monitor variation (%)	3	3·8	7·4	6·7
Max. and min. transmission		0·5738, 0·4438	0·7717, 0·4856	—
Final R	0·026	0·031	0·032	0·034
wR	0·036	0·048	0·045	0·040
S	1·52	2·04	1·65	1·47
Max. shift/σ	0·041	0·005	0·022	0·023
Max. and min. peaks in final difference maps (e Å^{-3})	±0·20	±0·30	±0·25	±0·30

data through to 1980, Allen (1980) has shown that π-acceptor substituents shorten the distal bond and lengthen the vicinal bonds, while the particular donor groups like Cl and F have the reverse effect, that is, of lengthening the distal bond and shortening the vicinal bonds. Allen proposed an additive scheme for the bond-length variations in which it is assumed that the bond-length asymmetry in cyclopropanes is the sum of the asymmetries induced by each individual substituent. The proposed additivity of bond-length asymmetry is found to be applicable mostly for pure acceptor substitution and for selective donor substituents. There were insufficient data for Allen to test the additivity scheme for mixed donor–acceptor substituents, such as the halogen-phenyl substituents. The complex nature of the phenyl-substitution effect and its dependence on the conformation of the phenyl ring has been discussed by Jason & Ibers (1977). The validity of the additivity principle for donor–acceptor-substituted cyclopropanes has been questioned as it failed to explain the asymmetry observed in 1,1-dichloro-2,2-diphenylcyclopropane and some of its related compounds (Jason *et al.*, 1981). On the other hand, Tinant *et al.* (1988) concluded from the results of 11 substituted cyclopropanes that the effects of substituents on the ring bond lengths are additive even in the case of mixed donor–acceptor substitution. The present work provides some experimental results dealing with the effect of multiple substitution on the geometry of the cyclopropane ring, in particular for the mixed *gem*-dichloro and phenyl substituents. An additive scheme similar to that formalized by Allen (1980), but modified to incorporate the understanding that the substituent effect of the phenyl ring depends on their conformation, has been applied to analyze the geometry of the present structures.

Experimental

Crystal data, intensity data collection parameters and refinement results are summarized in Table 1. All X-ray measurements were made on an Enraf–Nonius CAD-4 automatic diffractometer equipped with a liquid N_2 low-temperature device; cell parameters by least-squares fit of $\pm 2\theta$ for a number of reflections [48 for (1), (2), (3) and 66 for (4)] measured at low temperature using Mo $K\alpha_1$ (λ = 0·70926 Å) for compounds (1) and (4), and Cu $K\alpha_1$ (λ = 1·54051 Å) for compounds (2) and (3); space groups were determined from systematic absences; intensity data were collected in each case by applying the θ–2θ scan technique with variable scan width and variable horizontal aperture size; for each compound three standard reflections were monitored every 2 h of X-ray exposure, and three orientation control reflections checked every 200 measurements; intensities were corrected for Lorentz and polarization factors, and for absorption [for compounds (2) and (3) only] by using a numerical method (Sheldrick, 1976). Structures were determined by direct methods using the program *MULTAN*80 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980) and refined by a full-matrix least-squares routine, *SHELX*76 (Sheldrick, 1976), in which the quantity $\sum w(|F_o| - |F_c|)^2$ was minimized, $w = 1/\sigma_F^2$, σ_F from counting statistics. All hydrogen atoms were located from the difference Fourier map, final refinements with anisotropic thermal parameters for the non-hydorgen atoms and isotropic thermal parameters for the hydrogen atoms; atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV, pp. 55, 99, 149).

Molecular mechanics calculations were performed using the program *MM*2 (Burkert & Allinger, 1982;

Allinger, 1985). All four structures were subjected to energy minimization. Steric energy profiles of the various conformers of compounds (1) and (4) were explored for minimum energy regions by using idealized symmetric models of (1) (*cis* model) and (4) (*trans* model). In the *trans* model, the acetoxy group of (4) was stripped off and replaced by a hydrogen atom. A total of 13 × 13 conformers of each of the two model compounds were built on an Evans and Sutherland PS390 graphic system by rotating each of the phenyl rings Ph_A and Ph_B in turn through 0–180° in steps of 15°. The steric energy of each of these conformers was calculated by utilizing the 'initial energy only' option in *MM*2. For each compound, the calculated relative energies ($E_r = E - E_{min}$) were plotted against the torsion angles, φ_A [C(3)—C(2)—C(21)—C(26)] and φ_B [C(2)—C(3)—C(31)—C(32)] in the form of a contour map. Normal force-field parameters as given in *MM*2 were used along with the following additional parameters for atom types 12 (Cl), 22 (cyclopropane C) and 2 (benzene C): (i) torsional parameters 12—22—22—22 (0·000, −0·250, 0·550), 5—22—22—12 (0·000, 0·000, 0·406), 2—22—22—12 (0·000, 0·000, 0·406); (ii) stretching parameters 2—2 (6·000, 1·390), 12—22 (3·230, 1·795); (iii) bending parameters 12—22—22 (0·560, 118·0), 12—22—12 (1·080, 111·7). These parameters were obtained by comparing those given in the *MM*2 parameter tables for closely related interactions and by trial energy minimization that gave proper geometries for the molecules.

Results

General description

The final atomic parameters of the four structures are listed in Table 2.* Stereoviews of single molecules of (1), (2), (3) and (4) are shown in Figs. 1(*a*), 1(*b*), 1(*c*) and 1(*d*) respectively along with the numbering schemes. In each case, the cyclopropane ring carbon, to which the bisecting phenyl is attached, is arbitrarily assigned as C(3). The selected bond distances, bond angles and torsion angles for the four structures are listed in Table 3.

The most striking structural feature is the relative conformation of the two phenyl rings, which is closely similar in all four structures. In this conformation, the phenyl ring Ph_B is very close to the bisecting position with respect to the cyclopropane ring, while the phenyl ring Ph_A is very near the

* Lists of structure amplitudes, anisotropic thermal parameters, hydrogen-atom parameters, all bond lengths and angles, and least-squares-planes parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 53939 (57 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. *Atomic parameters with e.s.d.'s in parentheses*

$$U_{eq} = (1/6\pi^2)\sum_i\sum_j\beta_{ij}\mathbf{a}_i.\mathbf{a}_j.$$

	x	*y*	*z*	U_{eq} (Å^2)
(*a*) 1,1-Dichloro-*cis*-2,3-diphenylcyclopropane (1)				
Cl(1)	0·34583 (2)	0·16503 (2)	0·61048 (6)	0·0259 (1)
Cl(2)	0·22365 (2)	0·20521 (2)	0·39736 (6)	0·0277 (1)
C(1)	0·29868 (8)	0·15472 (7)	0·3896 (2)	0·0211 (4)
C(2)	0·33151 (8)	0·14631 (8)	0·1893 (2)	0·0217 (5)
C(3)	0·29270 (8)	0·08581 (8)	0·2867 (2)	0·0215 (5)
C(21)	0·40630 (8)	0·14465 (8)	0·1489 (2)	0·0220 (5)
C(22)	0·45071 (8)	0·19472 (8)	0·2213 (2)	0·0248 (5)
C(23)	0·51847 (8)	0·19501 (9)	0·1624 (3)	0·0300 (5)
C(24)	0·54274 (9)	0·1453 (1)	0·0315 (3)	0·0335 (6)
C(25)	0·49938 (9)	0·0950 (1)	−0·0401 (3)	0·0333 (6)
C(26)	0·43139 (9)	0·09427 (9)	0·0185 (2)	0·0275 (5)
C(31)	0·32497 (8)	0·02020 (7)	0·3531 (2)	0·0203 (4)
C(32)	0·38693 (8)	0·01481 (8)	0·4552 (2)	0·0239 (5)
C(33)	0·41168 (8)	−0·04930 (9)	0·5130 (3)	0·0281 (5)
C(34)	0·37628 (8)	−0·10868 (9)	0·4657 (3)	0·0287 (5)
C(35)	0·31573 (9)	−0·10414 (8)	0·3603 (2)	0·0268 (5)
C(36)	0·28988 (8)	−0·04042 (8)	0·3066 (2)	0·0229 (5)
(*b*) 1,1-Dichloro-*cis*-2,3-bis(4-methoxyphenyl)cyclopropane (2)				
Cl(1)	0·71436 (2)	0·30620 (5)	0·53854 (3)	0·0279 (1)
Cl(2)	0·77473 (2)	0·33783 (5)	0·32192 (3)	0·0300 (1)
O(1)	0·49900 (7)	0·9721 (2)	0·7029 (1)	0·0367 (4)
O(2)	0·98698 (6)	0·5986 (2)	0·88616 (9)	0·0274 (3)
C(1)	0·75753 (9)	0·4508 (2)	0·4450 (1)	0·0227 (4)
C(2)	0·73314 (9)	0·6448 (2)	0·4417 (1)	0·0222 (4)
C(3)	0·81938 (9)	0·5893 (2)	0·4801 (1)	0·0213 (4)
C(21)	0·67064 (8)	0·7228 (2)	0·5129 (1)	0·0221 (4)
C(22)	0·58884 (9)	0·6809 (2)	0·4961 (1)	0·0285 (5)
C(23)	0·52926 (9)	0·7609 (2)	0·5570 (1)	0·0299 (5)
C(24)	0·55114 (9)	0·8847 (2)	0·6368 (1)	0·0274 (4)
C(25)	0·63227 (9)	0·9292 (2)	0·6529 (1)	0·0286 (4)
C(26)	0·69086 (9)	0·8500 (2)	0·5914 (1)	0·0254 (4)
C(31)	0·85896 (8)	0·5997 (2)	0·5900 (1)	0·0200 (4)
C(32)	0·82139 (8)	0·5731 (2)	0·6891 (1)	0·0217 (4)
C(33)	0·86585 (9)	0·5744 (2)	0·7856 (1)	0·0220 (4)
C(34)	0·94939 (9)	0·6034 (2)	0·7864 (1)	0·0210 (4)
C(35)	0·98768 (9)	0·6339 (2)	0·6893 (1)	0·0229 (4)
C(36)	0·94240 (9)	0·6319 (2)	0·5928 (1)	0·0216 (4)
C(4)	0·4155 (1)	0·9268 (3)	0·6929 (2)	0·0439 (6)
C(5)	1·0732 (1)	0·6170 (2)	0·8899 (1)	0·0297 (5)
(*c*) 1,1-Dichloro-*cis*-2-(4-benzyloxyphenyl)-3-phenylcyclopropane (3)				
Cl(1)	0·12544 (2)	−0·00738 (3)	0·99398 (6)	0·0349 (1)
Cl(2)	0·10241 (2)	0·06684 (3)	0·53448 (7)	0·0453 (1)
O(1)	−0·03056 (5)	−0·38377 (8)	1·1424 (2)	0·0398 (4)
C(1)	0·11581 (8)	−0·0333 (1)	0·6987 (3)	0·0331 (5)
C(2)	0·08284 (8)	−0·1177 (1)	0·6107 (3)	0·0355 (5)
C(3)	0·15552 (7)	−0·1063 (1)	0·6020 (3)	0·0324 (5)
C(21)	0·05393 (7)	−0·1854 (1)	0·7603 (3)	0·0338 (5)
C(22)	0·01363 (7)	−0·1596 (1)	0·9237 (3)	0·0361 (5)
C(23)	−0·01433 (8)	−0·2230 (1)	1·0597 (3)	0·0368 (5)
C(24)	−0·00338 (7)	−0·3152 (1)	1·0287 (3)	0·0342 (5)
C(25)	0·03723 (7)	−0·3422 (1)	0·8639 (3)	0·0374 (5)
C(26)	0·06506 (8)	−0·2782 (1)	0·7336 (3)	0·0384 (5)
C(31)	0·20610 (7)	−0·1604 (1)	0·7368 (3)	0·0294 (4)
C(32)	0·20000 (8)	−0·2019 (1)	0·9487 (3)	0·0330 (5)
C(33)	0·24890 (8)	−0·2561 (1)	1·0509 (3)	0·0378 (5)
C(34)	0·30413 (8)	−0·2690 (1)	0·9463 (4)	0·0415 (5)
C(35)	0·31152 (8)	−0·2260 (1)	0·7392 (3)	0·0406 (5)
C(36)	0·26295 (8)	−0·1720 (1)	0·6371 (3)	0·0330 (5)
C(4)	−0·07207 (8)	−0·3588 (1)	1·3146 (3)	0·0362 (5)
C(41)	−0·11304 (7)	−0·4390 (1)	1·3599 (3)	0·0318 (4)
C(42)	−0·16176 (8)	−0·4641 (1)	1·1925 (3)	0·0333 (5)
C(43)	−0·20271 (8)	−0·5338 (1)	1·2335 (3)	0·0379 (5)
C(44)	−0·19652 (9)	−0·5788 (1)	1·4435 (3)	0·0427 (6)
C(45)	−0·1481 (1)	−0·5552 (1)	1·6096 (3)	0·0432 (6)
C(46)	−0·10635 (9)	−0·4857 (1)	1·5680 (3)	0·0385 (5)
(*d*) 1,1-Dichloro-*trans*-2-(4-acetoxyphenyl)-3-phenylcyclopropane (4)				
Cl(1)	0·27873 (3)	0·45469 (4)	0·34654 (7)	0·0264 (1)
Cl(2)	0·10173 (3)	0·44987 (7)	0·28476 (7)	0·0259 (1)
O(1)	−0·06423 (7)	0·1843 (1)	−0·4038 (2)	0·0256 (4)
O(2)	0·02173 (8)	0·1132 (1)	−0·5799 (2)	0·0296 (5)
C(1)	0·1919 (1)	0·3730 (1)	0·2899 (3)	0·0193 (5)
C(2)	0·1955 (1)	0·2831 (1)	0·1558 (3)	0·0191 (5)
C(3)	0·1912 (1)	0·2567 (1)	0·3539 (2)	0·0183 (5)
C(21)	0·1260 (1)	0·2580 (2)	0·0102 (3)	0·0195 (6)
C(22)	0·1075 (1)	0·3284 (2)	−0·1368 (3)	0·0229 (6)
C(23)	0·0449 (1)	0·3047 (2)	−0·2765 (3)	0·0238 (6)
C(24)	0·0021 (1)	0·2089 (2)	−0·2692 (3)	0·0207 (5)

Table 2 (*cont.*)

	x	y	z	U_{eq} (Å^2)
C(25)	0·0187 (1)	0·1381 (2)	−0·1255 (3)	0·0231 (6)
C(26)	0·0806 (1)	0·1635 (1)	0·0157 (3)	0·0204 (5)
C(31)	0·2583 (1)	0·2064 (2)	0·4831 (3)	0·0184 (5)
C(32)	0·3388 (1)	0·1999 (2)	0·4490 (3)	0·0242 (6)
C(33)	0·3986 (1)	0·1551 (2)	0·5768 (3)	0·0267 (6)
C(34)	0·3794 (1)	0·1159 (2)	0·7393 (3)	0·0264 (6)
C(35)	0·2994 (1)	0·1198 (2)	0·7734 (3)	0·0276 (6)
C(36)	0·2393 (1)	0·1650 (1)	0·6454 (3)	0·0227 (6)
C(4)	−0·0464 (1)	0·1298 (1)	−0·5536 (3)	0·0216 (6)
C(5)	−0·1234 (1)	0·0948 (2)	−0·6698 (3)	0·0316 (7)

perpendicular position. In (2), the methoxy groups lie on the plane of the respective phenyl groups, while in (3), the benzyloxy group is nearly perpendicular to the phenyl ring Ph_A, with the dihedral angle between the planes being 80°. In the *trans* compound (4), the plane of the acetoxy group is nearly perpendicular to the phenyl ring (the dihedral angle is 83°).

In all four structures the cyclopropane ring is distinctly asymmetric with C(2)—C(3) being consistently the longest bond and C(1)—C(2) the shortest bond. The asymmetry is more pronounced in the three *cis* compounds. The average C—C ring distances of 1·516 (15) in (1), 1·521 (13) in (2) and 1·514 (16) Å in (3) are all longer than the average for the *trans* compound (4), 1·508 (7) Å. The mean C—C ring distance of 1·515 (6) Å for all four compounds compares well with the mean C—C distance [1·510 (2) Å] cited by Allen (1980) for a large number of cyclopropane derivatives, and that of 1·513 (1) Å observed in a series of 11 cyclopropane derivatives by Tinant *et al.* (1988). The endocyclic C—C—C angles in the *trans* compound are nearly equal while in the *cis* compounds the average C(2)—C(1)—C(3) angle of 61·9 (1)° is appreciably larger than the average of the other two C—C—C angles, 59·0 (2)°. Despite the various substitutions on the phenyl ring at C(2), the two bridging C—C distances connecting the cyclopropyl ring and phenyl rings show little difference and range between 1·491 (2) and 1·495 (2) Å. The steric strain experienced by the phenyl ring Ph_B due to its bisecting position is reflected in the large difference between angles C(3)—C(31)—C(32) and C(3)—C(31)—C(36) which is over 10° in (2) and about 5° in (4) (Table 3).

The mean Cl—C distances of 1·762 (2) in (1), 1·757 (2) in (2), 1·761 (2) in (3) and 1·759 (2) Å in (4), are in good agreement with the average Cl—C distance of 1·758 Å reported in the survey of *gem*-dichlorocyclopropane structures (Allen, 1980), and with the average value of 1·747 Å observed in the structure of hexachlorocyclopropane (Schrumpf & Jones, 1987*b*) and the corresponding gas-phase value in 1,1-dichlorocyclopropane [1·756 (2) Å] (Hedberg,

Table 3. *Selected bond distances* (Å), *bond angles* (°) *and torsion angles* (°) *with e.s.d.'s in parentheses*

	(1)	(2)	(3)	(4)
Cl(1)—C(1)	1·752 (2)	1·747 (2)	1·754 (2)	1·754 (2)
Cl(2)—C(1)	1·771 (2)	1·767 (2)	1·768 (2)	1·763 (2)
C(1)—C(2)	1·492 (2)	1·506 (2)	1·492 (2)	1·496 (3)
C(1)—C(3)	1·511 (2)	1·511 (2)	1·505 (2)	1·508 (3)
C(2)—C(3)	1·545 (2)	1·547 (2)	1·546 (2)	1·521 (2)
C(2)—C(21)	1·493 (2)	1·493 (2)	1·493 (2)	1·495 (2)
C(3)—C(31)	1·492 (2)	1·491 (2)	1·493 (2)	1·493 (2)
Cl(1)—C(1)—Cl(2)	110·6 (1)	110·5 (1)	110·2 (1)	111·1 (1)
Cl(1)—C(1)—C(2)	122·5 (1)	120·0 (1)	121·7 (1)	118·2 (1)
Cl(1)—C(1)—C(3)	121·7 (1)	121·4 (1)	120·4 (1)	120·7 (1)
Cl(2)—C(1)—C(2)	116·5 (1)	119·1 (1)	117·8 (1)	119·8 (1)
Cl(2)—C(1)—C(3)	116·2 (1)	116·8 (1)	117·4 (1)	118·0 (1)
C(1)—C(2)—C(3)	59·6 (1)	59·3 (1)	59·4 (1)	59·9 (1)
C(1)—C(3)—C(2)	58·4 (1)	59·0 (1)	58·5 (1)	59·2 (1)
C(2)—C(1)—C(3)	61·9 (1)	61·7 (1)	62·1 (1)	60·9 (1)
C(1)—C(2)—C(21)	126·1 (1)	123·3 (1)	124·0 (1)	122·3 (1)
C(3)—C(2)—C(21)	123·0 (1)	124·9 (1)	123·5 (1)	121·3 (2)
C(1)—C(3)—C(31)	126·3 (1)	125·0 (1)	125·4 (1)	123·9 (1)
C(2)—C(3)—C(31)	124·6 (1)	130·0 (1)	125·7 (1)	125·2 (2)
C(2)—C(21)—C(22)	122·5 (1)	120·5 (1)	121·8 (2)	120·0 (2)
C(2)—C(21)—C(26)	118·2 (1)	121·3 (1)	120·5 (1)	121·0 (2)
C(3)—C(31)—C(32)	125·3 (1)	126·3 (1)	125·4 (1)	123·3 (2)
C(3)—C(31)—C(36)	116·5 (1)	116·1 (1)	116·5 (1)	118·1 (2)
Cl(1)—C(1)—C(2)—C(21)	0·7 (2)	−2·1 (2)	−1·7 (2)	−138·6 (2)
Cl(2)—C(1)—C(2)—C(21)	142·3 (1)	139·5 (1)	139·9 (1)	2·6 (2)
Cl(1)—C(1)—C(3)—C(31)	−0·7 (2)	10·0 (2)	1·6 (2)	6·7 (3)
Cl(2)—C(1)—C(3)—C(31)	−140·4 (1)	−130·0 (1)	−137·5 (1)	−135·5 (1)
C(3)—C(2)—C(21)—C(26)	61·2 (2)	41·0 (2)	60·4 (2)	−38·2 (2)
C(2)—C(3)—C(31)—C(32)	42·6 (2)	35·6 (2)	26·9 (7)	14·8 (2)
C(21)—C(2)—C(3)—C(31)	0·9 (2)	−0·2 (4)	−0·5 (2)	136·3 (2)
**M*12—C(3)—C(31)—C(32)	6·7 (2)	−3·6 (2)	−9·5 (2)	−22·2 (2)
†*M*13—C(2)—C(21)—C(22)	−89·2 (2)	−107·9 (2)	−86·2 (2)	108·4 (2)

* *M*12 is the mid-point of the bond C(1)—C(2).
† *M*13 is the mid-point of the bond C(1)—C(3).

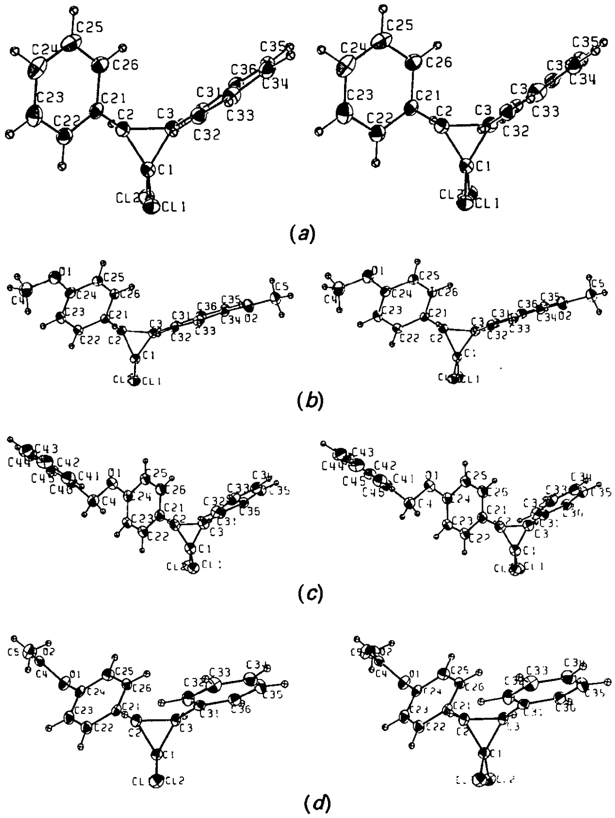


Fig. 1. Stereoviews of a single molecule of compounds (*a*) (1) (*b*) (2), (*c*) (3) and (*d*) (4). Atom numbering is also shown.

Hedberg & Boggs, 1982). The two Cl—C distances in each of the structures are noticeably unequal. In the three *cis* compounds the mean Cl(1)—C—C angle of 121·3 (4)° is significantly larger than the mean Cl(2)—C—C angle of 117·3 (4)°. The corresponding mean angles in the *trans* compound are nearly equal, 119·5 (1) and 118·9 (1)°. The Cl—C—Cl angles in the present four structures range between 110·2 (1) and 111·1 (1)°, and are slightly smaller than that observed in hexachlorocyclopropane (112·2°) and also that of 1,1-dichlorocyclopropane [112·6 (2)°] (Hedberg *et al.*, 1982). Some of these geometrical features are analyzed in detail in separate sections.

Cyclopropane ring geometry

A close scrutiny of the ring C—C distances shows that the asymmetries induced by the substituents in all four compounds are quite significant. The differences between the C(2)—C(3) distance and the other two C—C bonds in the ring range between 0·034 and 0·054 Å in the three *cis* compounds, and are 0·013 and 0·025 Å in the *trans* compound. The small but systematic difference between C(1)—C(2) and C(1)—C(3) bond distances which ranges between 0·005 in (2) and 0·019 Å in (1), seems to be quite interesting. As both compounds (1) and (2) have symmetrical substituents, a simple additive scheme of substituent effects as formalized by Allen (1980) would be inadequate to explain such observed asymmetries. As shown in Fig. 2(*a*), such a scheme should lead to an exactly symmetrical ring with equivalent C(1)—C(2) and C(1)—C(3) distances in both (1) and (2). A modified additive scheme (as outlined in Table 4) based on the assumption that the phenyl ring at a bisecting conformation has the strongest conjugative interaction with the cyclopropane ring and hence the maximum effect on the bond lengths, seems to explain the observed asymmetries in the present structures. In this modified scheme, the asymmetry parameter δ_2 is replaced by $\delta_2\cos\theta$, where the angular parameter θ is defined following Jason & Ibers (1977). θ is the acute angle between the distal bond vector and the normal of the substituent phenyl-ring plane (Fig. 2*b*) and is such that $\theta = 0°$ for bisecting and $\theta = 90°$ for perpendicular conformations. Table 4 gives a comparison of the observed bond distances with the expected distances according to the modified scheme. The agreement between the observed values and the predicted values is quite remarkable. An even better set of expected distances is obtained (Table 4, column 3) with $\delta_2 = 0·013$ (average asymmetry parameter obtained from the observed bond distances).

The proposed modified additive scheme seems to explain most of the available experimental results on the bond asymmetry induced by mixed donor–acceptor substitution in the cyclopropane ring. However, several factors still need to be mentioned. The C(2)—C(3) distance in the three *cis* compounds is appreciably longer than that in the *trans* compound suggesting that part of the bond increment in the *cis* compounds must be due to steric crowding. We suggest that the additive scheme is essentially valid for most substituents but the undetermined steric effect may not be negligible. From our analysis, we can further conclude that the phenyl (or other π-acceptor substituent) in the bisecting conformation contributes most to the bond-length asymmetry and that even if some conjugation occurs at the perpendicular conformation its effect on the bond length is probably negligible. The effect of the phenyl ring may indeed be influenced by the other substituents and as a result a constant δ (asymmetry parameter) for phenyl substituents may not be appropriate in all situations. It is quite apparent that the bond-length asymmetries in a polysubstituted cyclopropane are complex sums of electronic, hybridization and steric constraints, but an additive approach seems quite adequate to explain most cases.

Cl—C distance

The average Cl—C distance of 1·758 (3) Å is significantly shorter than typical Cl—C single bonds

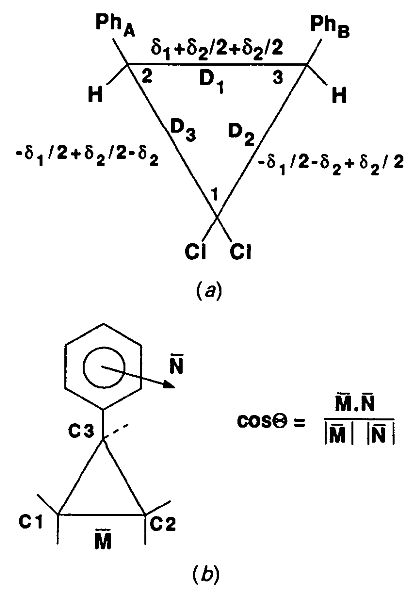
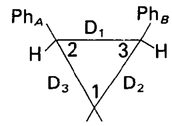


Fig. 2. (*a*) Additive scheme for the substitution-induced bond-length asymmetry in the cyclopropane ring. δ_1 gives the asymmetry parameters for Cl substitution and δ_2 is the asymmetry parameter for the phenyl ring (Allen, 1980). (*b*) The conformational parameter, θ, for describing phenylcyclopropane geometry. **N** is the normal to the phenyl ring and **M** represents the C(1)—C(2) vector.

Table 4. *Cyclopropane ring-bond asymmetry: comparison of observed and predicted ring bond lengths (D)* (Å)



$D_1(\text{calc.}) = \Delta + \delta_1 + \frac{1}{2}\delta_2\cos\theta_A + \frac{1}{2}\delta_2\cos\theta_B$ $\quad D_2(\text{calc.}) = \Delta - \frac{1}{2}\delta_1 - \delta_2\cos\theta_A + \frac{1}{2}\delta\cos\theta_B$ $\quad D_3(\text{calc.}) = \Delta - \frac{1}{2}\delta_1 + \frac{1}{2}\delta_2\cos\theta_A - \delta_2\cos\theta_B$

where $\Delta = (D_1 + D_2 + D_3)/3$, δ_1 = asymmetry parameter for Cl_2 substituents, δ_2 = asymmetry parameter for phenyl substituents, θ_A = conformation angle of Ph_A (see Fig. 2*b*), θ_B = conformation angle of Ph_B.

	(1)			(2)			(3)			(4)		
	Obs.	Calc.*	Calc.†	Obs.	Calc.*	Calc.†	Obs.	Calc.*	Calc.†	Obs.	Calc.*	Calc.†
D_1	1·545 (2)	1·551	1·543	1·547 (2)	1·557	1·553	1·546 (2)	1·549	1·546	1·521 (2)	1·544	1·540
D_2	1·511 (2)	1·510	1·508	1·511 (2)	1·513	1·511	1·505 (2)	1·508	1·506	1·508 (2)	1·499	1·498
D_3	1·492 (2)	1·487	1·493	1·506 (2)	1·493	1·498	1·492 (2)	1·485	1·490	1·496 (3)	1·481	1·486

* Calc. $\delta_1 = 0{\cdot}025$, $\delta_2 = 0{\cdot}018$.
† Calc. $\delta_1 = 0{\cdot}025$, $\delta_2 = 0{\cdot}013$.

(1·790–1·810 Å), indicating that there is some degree of conjugation between the chlorine atoms and the cyclopropane ring. In the three *cis* compounds the mean of the difference between Cl(1)—C(1) and Cl(2)—C(1) distances (Δr) is 0·018 Å which is twice as large as that in the *trans* compound (Δr = 0·009 Å). In contrast, the two Cl—C distances in 1,1-dichloro-2,2-diphenylcyclopropane (Lauher & Ibers, 1975) are virtually equal. These results suggest that a correlation possibly exists between the asymmetric Cl—C distances and uneven charge distribution on the two surfaces of the cyclopropane ring resulting from the substituent (in particular phenyl) conformation. A survey of Cl—C distances in some of the *gem*-dichlorocyclopropane structures with phenyl substituents (Table 5) shows further evidence for such a correlation. In most of these structures it is also seen that the shorter Cl(1)—C(1) bond is bent away from the cyclopropane ring more than the longer Cl(2)—C(1) bond (given by angles ψ_1 and ψ_2). In five of the structures (1)–(5), the bending away of Cl(1) can be explained in terms of steric crowding caused by the bisecting phenyl ring and is reflected by the close Cl(1)—H[C(32)] contacts (Table 5). The results from compounds (6) and (7), which show significant asymmetry in Cl—C distances but not in their disposition, are in a way consistent with our assumption. In each compound, there is only one phenyl substituent which is in a perpendicular conformation and the shorter Cl—C bond lies on the side of the phenyl ring. Significant asymmetry in the two Cl—C bonds has also been seen in other *gem*-dichlorocyclopropane derivatives without any phenyl substituent (Baker & Pauling, 1972; Zukerman-Schpector, Castellano, Oliva, Brocksom & Canevarolo, 1984).

Table 5. Cl—C *distances* (Å) *and other related parameters* (Å,°) *in some gem-dichlorocyclopropanes*

ψ_1 = *M*23—C(1)—Cl(1); ψ_2 = *M*23—C(1)—Cl(2) and *M*23 is the midpoint of the bond C(2)—C(3).

Compound*	Cl(1)—C	Cl(2)—C	Δr	ψ_1	ψ_2	Cl(1)—H[C(32)]
(1)	1·752 (2)	1·771 (2)	0·019	128·3 (1)	121·1 (1)	2·66
(2)	1·747 (2)	1·767 (2)	0·020	126·5 (1)	123·1 (1)	2·76
(3)	1·754 (2)	1·768 (2)	0·014	127·0 (1)	122·8 (1)	2·89
(4)	1·754 (2)	1·763 (2)	0·009	124·8 (1)	124·5 (1)	3·04
(5)	1·752 (2)	1·763 (2)	0·011	126·7 (2)	123·0 (1)	2·77
	1·757 (2)	1·763 (2)	0·007	126·3 (1)	123·2 (1)	2·80
(6)	1·741 (1)	1·751 (1)	0·010	123·9 (1)	123·4 (1)	
(7)	1·747 (4)	1·760 (5)	0·013	124·7 (3)	125·3 (3)	
(8)	1·753 (2)	1·755 (2)	0·002	124·9 (2)	124·3 (2)	

* (1)–(4) Present work, (5) 1,1-dichloro-2,3-diphenyl-2-(4-methoxyphenyl)-cyclopropane (Li *et al.*, 1991), (6) 2,2-dichloro-1-(4-ethoxyphenyl)-1-cyclopropanecarboxylic acid (Poppleton, 1986), (7) 2,2-dichloro-1-phenyl-1-cyclopropanephosphate (Maas, 1983), (8) 1,1-dichloro-2,2-diphenylcyclopropane (Lauher & Ibers, 1975).

Conformation of the two substituent phenyl rings

The values of conformational parameters, θ, and the dihedral angles between the various ring planes for all the four structures are listed in Table 6. θ_B ranges from 4·8 to 9·8° for the three *cis* compounds and is 22·2° in the *trans* compound, while θ_A ranges between 75 and 86°. The conformation of (4) is in sharp contrast to that observed in 1,1-dibromo-*trans*-2,3-diphenylcyclopropane and 1,1-dibromo-*trans*-2,3-bis(4′-nitrophenyl)cyclopropane (Jason & Ibers, 1977) where the two phenyl rings are symmetrically oriented with $\theta_A = \theta_B$ = 48·3° for the first compound and $\theta_A = \theta_B$ = 52·2° for the latter one. For the three *cis* compounds, the observed asymmetric conformation is probably the sterically more favorable one, but it is intriguing to see the *trans* compound deviate from the symmetrical conformation observed in its bromo analogs. The structure of a related triarylcyclopropane also has a similar conformation with the phenyl ring at C(3) in the bisecting position while the two phenyl rings at C(2) are both in the perpendicular conformation (Li, Hossain, Ji, van der Helm, Magarian & Day, 1991). It appears that the *para* substitution on Ph_A in compounds (3) and (4) did not seem to have much effect on the conformation of the two aryl rings.

Table 6. *Ring conformation*

(*a*) Dihedral angles between various planes

Plane	Atoms included in the plane
*P*1	C(1), C(2), C(3)
*P*2	C(21), C(22), C(23), C(24), C(25), C(26)
*P*3	C(31), C(32), C(33), C(34), C(35), C(36)
*P*4	C(41), C(42), C(43), C(44), C(45), C(46)

Compound	Dihedral angle (°) (e.s.d.'s range from 0·1 to 0·3°) ∠*P*1–*P*2	∠*P*1–*P*3	∠*P*2–*P*3	∠*P*1–*P*4
(1)	44·2	87·1	58·4	
(2)	48·7	86·0	47·7	
(3)	48·8	81·9	50·7	80·0
(4)	51·6	78·1	56·8	

(*b*) Angle between a plane and a vector (°)
θ_A is the angle between plane *P*2 and vector C(1)—C(3) and θ_B is the angle between plane *P*3 and vector C(1)—C(2) (e.s.d.'s range from 0·2 to 0·4°)

	Crystal structure		Minimum-energy structure	
Compound*	θ_A	θ_B	θ_A	θ_B
(1)	81·6	4·8	86·1	4·4
(2)	75·1	8·9	86·6	8·1
(3)	82·3	9·8	85·0	7·5
(4)	74·6	22·2	67·4	57·2
(9)	48·3	48·3		
(10)	52·2	52·2		
(11)	89·5	10·7		

*(1)–(4) Present work, (9) 1,1-dibromo-*trans*-2,3-diphenylcyclopropane (Jason & Ibers, 1977), (10) 1,1-dibromo-2,3-bis(4-nitrophenyl)cyclopropane (Jason & Ibers, 1977), (11) 1,1-dichloro-2,3-diphenyl-2-(4-methoxyphenyl)-cyclopropane (Li *et al.*, 1991).

The predominance of this skew symmetric conformation (one bisecting and one perpendicular phenyl ring) in the solid state suggests that this is probably the most favorable conformation for 2,3-diphenylcyclopropanes.

The phenyl-ring conformations in the present structures are compared with those observed in the stilbene-type compounds (two phenyl rings bridged by an ethylenic double bond) in Fig. 3(*a*), which shows a stereoview of the stilbene skeletons of five *cis*-stilbene derivatives superimposed on the corresponding fragment in (1). Fig. 3(*b*) shows a view of the superimposed molecules of tamoxifen and compound (1). The striking match of the phenyl-ring orientations in all these structures shows clearly that the skew conformation observed in the present structures is equivalent to the propeller conformation in stilbene derivatives and that the introduction of the cyclopropane ring in place of an ethylenic double bond had virtually no effect on the phenyl-ring conformations.

Energy-minimization calculations

All four crystal structures were subjected to energy-minimization calculations by using the molecular mechanics program *MM*2. Figs. 4(*a*)–4(*d*) show the superimposed drawing of the crystal structure and the respective minimum-energy structure for all the four compounds. The energy-minimized structures of the three *cis* compounds are conformationally very close to their respective crystal structures. The conformational parameters, θ_A and θ_B, of the energy-minimized structures are within 10° of that for the corresponding crystal structures (Table 6). This suggests that the skew symmetric conformation of the two phenyl rings (one bisecting and one perpendicular) is the energetically most favorable one for the *cis*-diarylcyclopropanes. For the *trans* compound (4), the energy-minimized structure has a somewhat different conformation than its crystal structure. The phenyl ring, Ph_B, is rotated away from the near bisecting position in its crystal structure by about 35°, and the overall conformation of the minimum-energy conformer (θ_A = 67·4 and θ_B = 57·2°) is closer to the symmetric conformation observed in its bromo analog (Jason & Ibers, 1977). However, the energy difference between the crystal structure and the energy-minimized structure is small [0·2 kcal mol^{-1} (1 kcal = 4·184 J)].

The steric energy profiles for the idealized models of compounds (1) and (4) are shown in Figs. 5(*a*) and 5(*b*) respectively. For the *cis* model, there are two lowest energy regions, *A* and *B*, of equivalent energy with minima near $\varphi_A \sim 60$, $\varphi_B \sim 30°$ and $\varphi_A \sim 150$, $\varphi_B \sim 120°$. These two conformers closely correspond to the skew symmetric conformations $\theta_A = 90$, $\theta_B = 0°$ and $\theta_A = 0$, $\theta_B = 90°$ observed in the crystal struc-

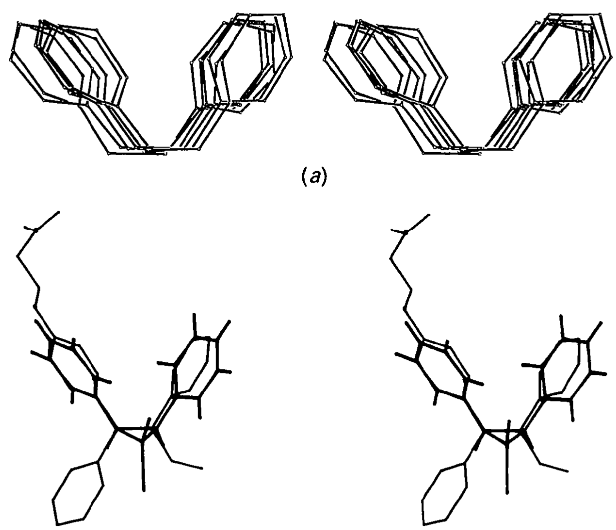
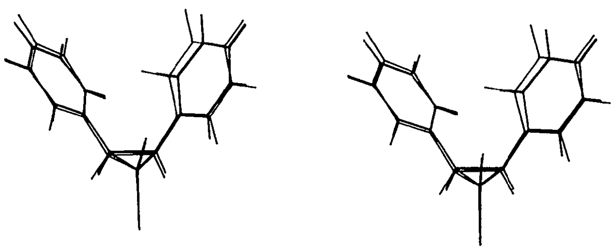


Fig. 3. (*a*) Stereoview of the stilbene skeleton in (1) superimposed with those of five *cis*-stilbene derivatives; each structure is given a translation for visual clarity. From left to right: compound (1) (present work); (*Z*)-5-(methoxymethyl)-3-[4-(phenylethenyl)-phenyl]-2-oxazolidinone (Durant, Lefevre, Norberg & Evrard, 1982); *cis*-4,5-diphenylhex-4-en-2-yne (Churchill & Julis, 1981); *cis*-tetrachlorostilbene (Norrestam, Hovmoller, Palm, Gothe & Wachtmeister, 1977); *cis*-4-nitro-α-cyano-β-methylstilbene (Tinant, Touillaux, Declercq, Van Meerssche, Leroy & Weiler, 1983); tetra-*n*-butylammonium bis(stilbenedithiolato)nickelate-(II) (Mahadevan, Seshasayee, Kuppusamy & Manoharan, 1984). (*b*) Stereosuperposition of compound (1) and the tamoxifen molecule.

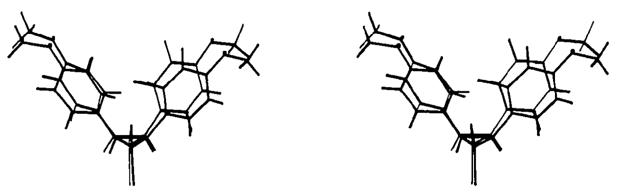
tures of the *cis* compounds. A third low-energy region, *C*, with minima near $\varphi_A \sim 70$, $\varphi_B \sim 110°$ has about 3 kcal mol^{-1} higher energy. This conformer is close to the position where both the phenyl rings are in perpendicular positions ($\theta_A = 90$, $\theta_B = 90°$). For the *cis* model, the energy minima are narrow ($\sim 10 \times 15°$ within 1 kcal mol^{-1}) with a steep barrier to rotation of the phenyl rings.

For this *trans* model, Fig. 5(*b*), there is only one low-energy region which is very broad ($\sim 60 \times 60°$ within 1 kcal mol^{-1}) with its lowest energy near $\varphi_A \sim 150$, $\varphi_B \sim 150°$ which corresponds to a symmetrical conformation with $\theta_A \sim 67$, $\theta_B \sim 67°$.

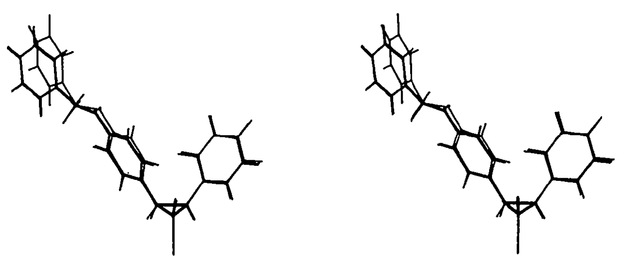
Several conclusions can be drawn from these energy contour maps: (i) that the *cis* arrangement of the two aryl rings is not as flexible as with the *trans* arrangement; (ii) that for *cis*-diarylcyclopropane the



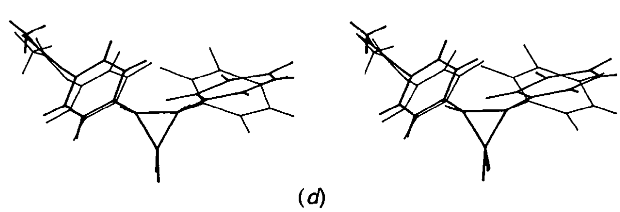
(*a*)



(*b*)

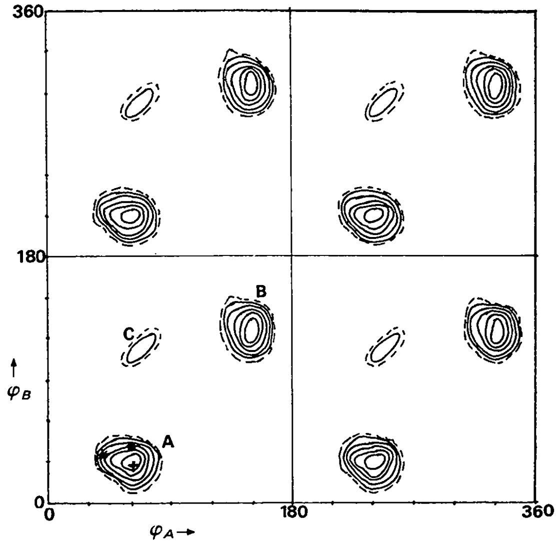


(*c*)

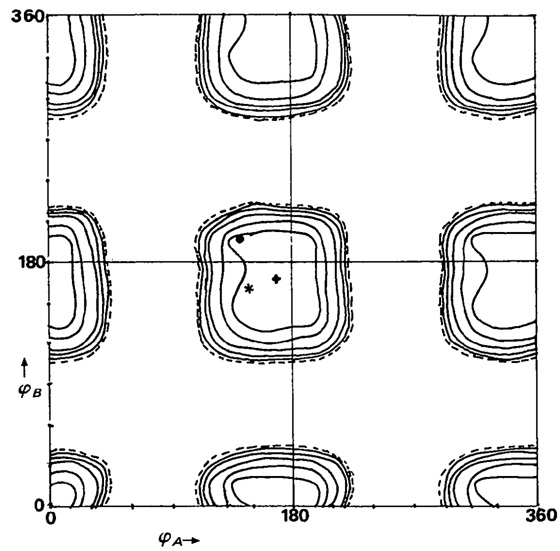


(*d*)

Fig. 4. Stereoviews of the crystal structure (thick lines) and minimum-energy structure (thin lines) for (*a*) (1), (*b*) (2), (*c*) (3) and (*d*) (4).



(*a*)



(*b*)

Fig. 5. Two-dimensional energy plot for the *cis* (*a*) and *trans* model (*b*). In each drawing, the horizontal axis designates increments of φ_A torsion angles, and the vertical axis corresponds to increments of φ_B torsion angles. The conformational parameter, θ, has an approximately linear relationship with φ. For the *cis* model, $\varphi_A \sim 143$, 53° corresponds to $\theta_A = 0$, 90°, and $\varphi_B \sim 37$, 127° corresponds to $\theta_B = 0$, 90° respectively. For the *trans* model, φ_A (or φ_B) ~ 37, 127° corresponds to θ_A (or θ_B) 0, 90° respectively. Relative energies, $E_r = E - E_{min}$, where E_{min} is the energy of the global minimum, are plotted. Contours are drawn at the low-energy regions starting at 1 kcal mol^{-1} at an interval of 1 kcal mol^{-1}. The dashed line represents the highest energy plotted (6 kcal mol^{-1}). The maps are extended to 360/360° to show symmetries between all possible conformers. In (*a*) positions ●, * and + indicate the crystal structures of (1), (2) and (3) respectively. In (*b*) positions ●, * and + indicate the crystal structure of (4), the energy-minimized structure of (4) and the bromo analog of (4) respectively.

lowest energy conformer is one with one ring in a bisecting position and the other in a perpendicular position, conformers where both the rings are near a perpendicular position have higher energy (~3 kcal mol^{-1}), and the conformer with both the rings in bisecting positions is sterically impossible; (iii) that for *trans*-diarylcyclopropane, the lowest energy conformer is one with the symmetrically oriented phenyl rings. The broader minima in (4) also explains the small difference in energy (0·2 kcal mol^{-1}) between its crystal structure and the energy-minimized structure, although their conformational difference (~35°) is quite appreciable.

Structure–activity relation

Early antiestrogenic studies of (1) and its *trans* isomer have shown that: (i) compound (1) is a weaker antiestrogen than tamoxifen but is devoid of intrinsic agonist activity (Magarian & Benjamin, 1975; Pento *et al.*, 1981); (ii) compound (1) and tamoxifen were equally effective in reducing the growth of established 7,12-dimethylbenz[*a*]-anthracene (DMBA)-induced rat mammary tumors, but (1) induced greater reduction in the occurrence of new tumors (Pento, Magarian & King, 1982; King, Pento, Magarian & Brueggemann, 1985; King, Magarian, Terao & Brueggemann, 1985); (iii) the *trans* isomer of (1) is devoid of any biological action (Pento *et al.*, 1981).

Recently compounds (2), (3) and (4) were evaluated for their *in vivo* estrogenic and antiestrogenic behavior and all were found to be inactive estrogens and antiestrogens (Griffin, 1989), *In vitro* human breast cancer cell suppressive effects of (1), (2), (3) and (4) were also studied (Griffin, 1989), and the results show that compound (2) had a moderate and compound (3) a weak inhibitory effect on the growth of the MFC-7 human mammary carcinoma cell line, while the *trans* compound (4) had a negligible effect. In contrast, (1) had a significant inhibitory effect on MFC-7 cell proliferation which is comparable to that of tamoxifen (Day, Magarian, Jain, Pento, Mousissian & Meyer, 1991).

Although it is difficult to make structure–activity conclusions based on this limited series of analogs, the results of these studies indicate that: (i) the *cis* compounds are more active than the *trans* form, which is consistent with the findings of Duax and coworkers for tamoxifen (Weeks, Griffin & Duax, 1977); (ii) the present series of derivatives (2) and (3), from (1), are far less active than the parent compound (1). Crystal structure determination showed remarkable similarities in the diaryl conformation and geometries of (2) and (3) with those of (1) and subsequent energy-minimization studies have shown that these stereochemical features are energetically preferred and stable. It is quite apparent from these results that the substitution patterns in (2) and (3), instead of enhancing have in fact reduced the activity of compound (1). This suggests a need for a different substitution pattern on (1) (perhaps a basic side chain and/or a third aryl substitution as in tamoxifen) to find derivatives with enhanced nonestrogen antiestrogencity. Work is in progress in this direction.

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References

ALLEN, F. H. (1980). *Acta Cryst.* **B36**, 81–96.
ALLINGER, N. L. (1985). *MM2 Program.* Quantum Chemistry Program Exchange, Univ. of Indiana, Bloomington, USA.
BAKER, R. W. & PAULING, P. J. (1972). *J. Chem. Soc. Perkin Trans.* 2, pp. 1451–1453.
BEDFORD, G. R. & RICHARDSON, D. N. (1966). *Nature (London)*, **212**, 733–734.
BURKERT, V. & ALLINGER, N. L. (1982). *Molecular Mechanics.* ACS Monograph No. 177. Washington, DC: American Chemical Society.
CHURCHILL, M. R. & JULIS, S. A. (1981). *Cryst. Struct. Commun.* **10**, 1375–1380.
CUTBUSH, S. Q., NEIDLE, S., FOSTER, A. B. & LECLERQ, F. (1982). *Acta Cryst.* **B38**, 1024–1027.
DAY, B. W., MAGARIAN, R. A., JAIN, P. T., PENTO, J. T., MOUSISSIAN, G. K. & MEYER, K. L. (1991). *J. Med. Chem.* **34**, 842–851.
DURANT, F., LEFEVRE, F., NORBERG, B. & EVRARD, G. (1982). *Cryst. Struct. Commun.* **11**, 983–990.
FURR, B. J. A. & JORDAN, V. C. (1984). *Pharmacol. Ther.* **25**, 127–205.
GRIFFIN, M. T. (1989). PhD Dissertation, Univ. of Oklahoma, USA.
HEDBERG, L., HEDBERG, K. & BOGGS, J. E. (1982). *J. Chem. Phys.* **77**, 2996–3002.
HOROWITZ, K. B. & MCGUIRE, W. L. (1978). *Breast Cancer: Advances in Research and Treatment*, Vol. 2, edited by W. L. MCGUIRE, pp. 155–204. New York: Plenum Press.
JASON, M. E., GALLUCCI, J. C. & IBERS, J. A. (1981). *Isr. J. Chem.* **21**, 95–104.
JASON, M. E. & IBERS, J. A. (1977). *J. Am. Chem. Soc.* **99**, 6012–6021.
JORDAN, V. C. (1983). *Breast Cancer Res. Treat.* **3**(S), S73–S86.
KING, M. M., MAGARIAN, R. A., TERAO, J. & BRUEGGEMANN, G. L. (1985). *J. Natl Cancer Inst.* **74**, 447–451.
KING, M. M., PENTO, J. T., MAGARIAN, R. A. & BRUEGGEMANN, G. L. (1985). *Nutr. Cancer*, **7**, 239–249.
LAUHER, J. W. & IBERS, J. A. (1975). *J. Am. Chem. Soc.* **97**, 561–567.
LI, D., HOSSAIN, M. B., JI, X., VAN DER HELM, D., MAGARIAN, R. A. & DAY, B. W. (1991). *Acta Cryst.* Submitted.
MAAS, G. (1983). *Phosphorus Sulfur Relat. Elem.* **14**, 143–150.
MAGARIAN, R. A. & BENJAMIN, E. J. (1975). *J. Pharm. Sci.* **64**, 1626–1632.
MAHADEVAN, C., SESHASAYEE, M., KUPPUSAMY, P. & MANOHARAN, P. T. (1984). *J. Cryst. Spectrosc. Res.* **14**, 179–191.
MAIN, P., FISKE, S. J., HULL, S. E. LESSINGER, L., GERMAIN, G., DECLERCQ, J.-P. & WOOLFSON, M. M. (1980). *MULTAN80. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data.* Univs. of York, England, and Louvain, Belgium.

NORRESTAM, R., HOVMOLLER, S., PALM, T.-B., GOTHE, R. & WACHTMEISTER, C. A. (1977). *Acta Cryst.* B**33**, 370–376.

PENTO, J. T., MAGARIAN, R. A. & KING, M. M. (1982). *Cancer Lett.* **15**, 261–269.

PENTO, J. T., MAGARIAN, R. A., WRIGHT, R. J., KING, M. M. & BENJAMIN, E. J. (1981). *J. Pharm. Sci.* **70**, 399–403.

POPPLETON, B. J. (1986). *Acta Cryst.* C**42**, 879–881.

PRECIGOUX, G., COURSEILLE, C., GEOFFRE, S. & HOSPITAL, M. (1979). *Acta Cryst.* B**35**, 3070–3072.

ROGERS, M. T. & ROBERTS, J. D. (1946). *J. Am. Chem. Soc.* **68**, 843–846.

ROMMING, C. & SYDNES, L. K. (1987). *Acta. Chem. Scand. Ser. B*, **41**, 717–723.

SCHRUMPF, G. & JONES, P. G. (1987*a*). *Acta Cryst.* C**43**, 1182–1185.

SCHRUMPF, G. & JONES, P. G. (1987*b*). *Acta Cryst.* C**43**, 1185–1187.

SHELDRICK, G. M. (1976). *SHELX76*. Program for crystal structure determination. Univ. of Cambridge, England.

SUTHERLAND, R. L. & JORDAN, V. C. (1981). Editors. *Non-Steroidal Antiestrogens*. Sydney: Academic.

TINANT, B., DECLERCQ, J.-P. & VAN MEERSSCHE, M. (1985). *Acta Cryst.* C**41**, 597–599.

TINANT, B., TOUILLAUX, R., DECLERCQ, J.-P., VAN MEERSSCHE, M., LEROY, G. & WEILER, J. (1983). *Bull Soc. Chim. Belg.* **92**, 101–110.

TINANT, B., WU, S., DECLERCQ, J.-P., VAN MEERSSCHE, M., MASAMBA, W., DE MESMAEKER, A. & VIEHE, H. G. (1988). *J. Chem. Soc. Perkin Trans.* 2, pp. 1045–1052.

WEEKS, C. M., GRIFFIN, J. F. & DUAX, W. L. (1977). Am. Crystallogr. Assoc. Summer Meet., Abstract PB6.

ZUKERMAN-SCHPECTOR, J., CASTELLANO, E. E., OLIVA, G., BROCKSOM, T. J. & CANEVAROLO, E. T. (1984). *Can. J. Chem.* **62**, 570–573.

Acta Cryst. (1991). B**47**, 521–527

X-ray Analysis of Cubic Crystals of the Complex Formed Between Ribonuclease T_1 and Guanosine-3′,5′-bisphosphate

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Abstract

The complex formed between ribonuclease T_1 (RNase T_1) and guanosine-3′,5′-bisphosphate (3′,5′-pGp) crystallizes in the cubic space group *I*23 with $a = 86{\cdot}47$ (4) Å. X-ray data were collected on a four-circle diffractometer to 3·2 Å resolution and the structure was determined by molecular-replacement methods [*ULTIMA*; Rabinovich & Shakked (1984). *Acta Cryst.* A**40**, 195–200] based on the RNase T_1 coordinates taken from the complex with guanosine-2′-phosphate. Refinement converged at 16·6% for 1540 data with $|F_o| > 1\sigma(|F_o|)$ with acceptable stereochemistry. The RNase T_1 conformation is comparable to that in other complexes which crystallize preferentially in space group $P2_12_12_1$ except for side chains that interact intermolecularly. The guanine of 3′,5′-pGp is bound to the recognition site in the same way as in other guanine-containing complexes except for its interaction with Glu46. The side-chain carboxylate of this amino acid does not form hydrogen bonds to N1H and N2H of guanine but is rotated so as to permit insertion of two water molecules which replace its acceptor functions. In contrast to other guanosine derivatives which are bound to RNase T_1 in the *syn* form, 3′,5′-pGp is *anti*. This conformation positions the two phosphate groups 'outside' the protein, with hydrogen-bonding contacts only to water molecules; the active site is filled by water. The RNase T_1–3′,5′-pGp complex probably has biological significance as it may represent the enzyme–product complex before dissociation.

Introduction

Although ribonuclease T_1 (RNase T_1) from the fungus *Aspergillus oryzae* with a chain length of only 104 amino acids is one of the smallest known enzymes, it is highly specific (Takahashi & Moore, 1982; Heinemann & Hahn, 1989). It cleaves RNA at the 3′-phosphate position of guanosine, yielding through transesterification oligonucleotides with terminal guanosine-2′,3′-cyclic phosphates which are ultimately hydrolyzed to oligonucleotides with a terminal 3′-guanylic acid. The reaction is catalyzed by Glu58, Arg77, His92; His40 appears to serve as an activator for Glu58 (Heinemann & Saenger, 1982). The specific recognition between RNase T_1 and guanine is through a combination of hydrogen bonds formed between Asn43N$^{\delta}$H···N7, Asn44NH···O6, Tyr45NH···O6, Glu46O$^{\epsilon 1}$···HN1, Glu46O$^{\epsilon 2}$···H$_1$N2, Asn98O···H$_2$N2, and stacking interactions whereby guanine is sandwiched between the side chains of Tyr42 and Tyr45 (Arni, Heinemann, Tokuoka & Saenger, 1988).

This detailed knowledge was obtained by spectroscopic and, notably, by crystallographic studies in

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