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5,5-Diethyl-1-methyl-1*H*,2*H*,3*H*,5*H*-pyrimidine-2-spiro-9′-fluorene-4,6-dione

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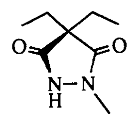
Abstract

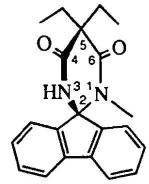
The title compound, $C_{21}H_{22}N_2O_2$, was synthesized from the corresponding pyrazolidinedione precursor by 9-fluorenyl substitution and subsequent ring expansion. The hexahydropyrimidinedione (HHPD) ring has a very flattened chair conformation and is nearly perpendicular [88.79 (13)°] to the 2-spiro-9′-fluorene ring. The two ethyl groups adopt a folded conformation and lie on opposite sides of the HHPD ring. A hydrogen-bonding scheme consisting of N—H···O═C and C—H···O═C interactions produces parallel molecular layers.

Comment

Conformational studies of cyclic dipeptides by X-ray diffraction and ^{1}H NMR spectroscopy (Gdaniec & Liberek, 1986; Liberek & Bednarek, 1978) have demonstrated that piperazinedione rings tend to assume a boat conformation with side chains folding over the ring. Some cyclic dipeptides possessing a rigid conformation are considered to be potential catalysts for asymmetric syntheses (Tanaka, Mori & Inoue, 1990).

Cyclic retro-inverso dipeptides incorporate malonic acid residues into cyclic dipeptide analogues and reverse the direction of the peptide bond. ^{1}H NMR spectra and semiempirical energy calculations indicate that the most stable conformations of hexahydropyrimidinedione (HHPD) rings with two aromatic side chains are those in which the HHPD ring adopts a planar or a boat structure (Yamazaki, Nunami & Goodman, 1991). No X-ray structure of a hexahydropyrimidine-4,6-dione has been reported previously. Here we present the crystal structure of 5,5-diethyl-1-methyl-1*H*,2*H*,3*H*,5*H*-pyrimidine-2-spiro-9′-fluorene-4,6-dione, (2), which can be regarded as an insertion product of 9-fluorenylidene into the N—N bond of the pyrazolidinedione precursor 4,4-diethyl-1-methylpyrazolidine-3,5-dione, (1). Compound (2) was realised through a ring-expansion process following the reaction of (1) with 9-bromofluorene.


(1)


(2)

An illustration of (2), together with the atom-numbering scheme, is shown in Fig. 1. An initial examination of the HHPD ring showed it to be nearly planar, the mean deviation from its least-squares plane being 0.018 Å. However, a subsequent least-squares-plane calculation using only the central portion of the ring (N1, N3, C4 and C6) exhibits near perfect planarity (mean deviation 0.001 Å) while the sp^3-hybridized C2 and C5 atoms, located at opposite ends of the ring, deviate from the central portion by −0.063 (3) and 0.049 (3) Å, respectively. Thus, the HHPD conformation can be considered to be a flattened chair form. Torsion angles C2—N3—C4—C5 of 5.5 (6)° and C2—N1—C6—C5 of −5.1 (5)° also illustrate this point. In addition, the N1 atom is slightly pyramidal as illustrated by the fact that C7 is −0.064 (5) Å out of the central portion of the HHPD ring plane and *cis* to the C2 atom. The position of H3 could not be determined with sufficient accuracy to characterize the N3 atom definitively as either trigonal planar or slightly pyramidal. Since hexahydropyrimidine itself has a flexible chair conformation and pyramidal N atoms (Armarego, 1977), the above results

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indicate the ring-flattening effect of the two carbonyl C atoms, C4 and C6, of the HHPD ring presumably arising from conjugation with N3 and N1, respectively. However, when the two carbonyl groups are introduced at the 2 and 4 positions, as in dihydrouracil, the ring becomes the twist-chair structure with C5 and C6 situated on opposite sides of a nearly coplanar N1, C2, N3 and C4 atom set (Groziak, Lin & Robinson, 1995).

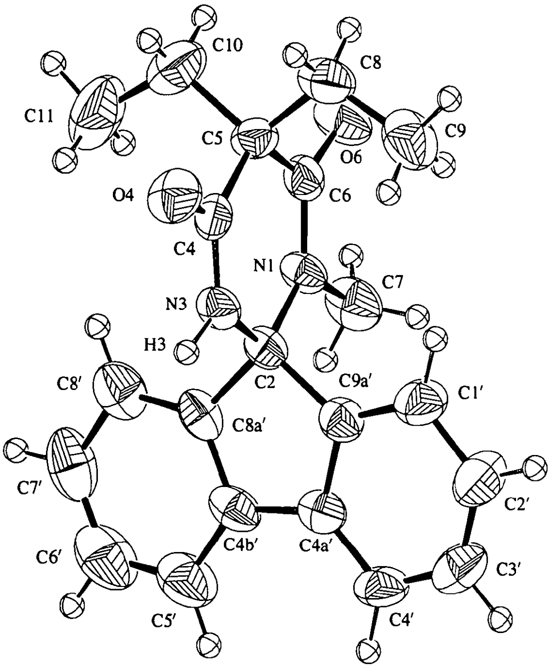

Fig. 1. Molecular structure and atom-numbering scheme for (2) with displacement ellipsoids at the 50% probability level. H atoms are shown as isotropic spheres of arbitrary radii.

The two ethyl groups of (2) fold over on opposite sides of the HHPD ring. A similar folded conformation of ethyl groups was observed in *N*-acylated 4,4-diethylpyrazolidinediones (Izydore, Bernal-Ramirez & Singh 1990). Folded rather than extended conformation of side chains seems to be a general phenomenon, as it was also observed in barbital (Hsu & Craven, 1974) and cyclic dipeptides (Gdaniec & Liberek, 1986). The fluorene ring plane is nearly parallel [2.7 (3)°] to the plane of the ethyl groups and is almost perpendicular [88.79 (13)°] to the HHPD ring.

Fig. 2 shows the hydrogen-bonding scheme of (2) in which each molecule interacts with four other molecules *via* N3—H3···O6 and C4'–H4'···O4 hydrogen bonds, producing a planar array of molecules normal to [100]. The hydrogen-bonding geometry is given in Table 3. It is unusual that one of the intermolecular hydrogen bonds involves an aromatic C—H of fluorene. The presence of a C—H···N intermolecular hydrogen bond was reported in crystalline 4,5-diazafluoren-9-one (Fun, Sivakumar, Zhu & You, 1995). However, no intermolecular contacts within the sum of van der Waals radii were reported in fluoren-9-one (Luss & Smith, 1972). Coulombic and van der Waals forces play the most important role in C—H···O and C—H···N interactions (Berkovitch-Yellin & Leiserowitz, 1984). The layered, hydrogen-bonded molecular packing provides an explanation for the high melting point and low solubility of (2).

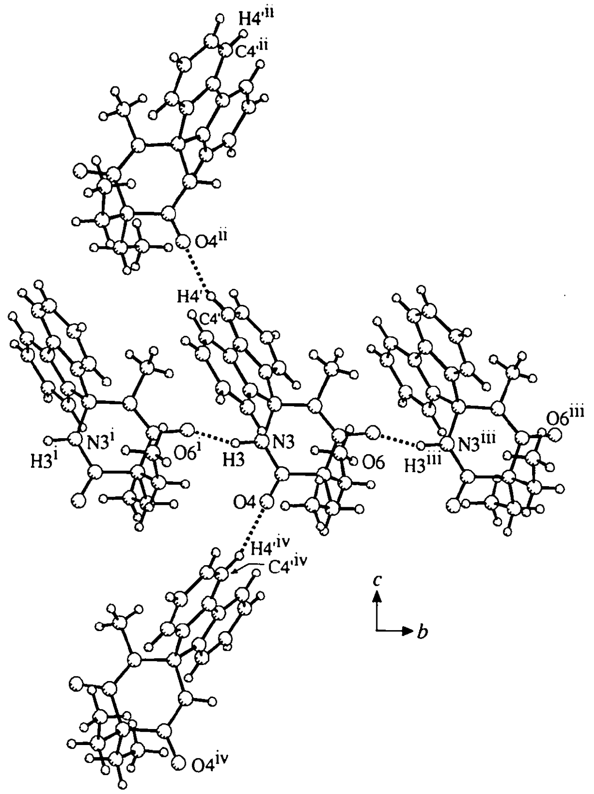

Fig. 2. Hydrogen-bonding scheme for (2) and the resultant planar molecular array. Symmetry codes: (i) $\frac{3}{2} - x, y - \frac{1}{2}, z$; (ii) $\frac{3}{2} - x, -\frac{1}{2} - y, \frac{1}{2} + z$; (iii) $\frac{3}{2} - x, \frac{1}{2} + y, z$; (iv) $\frac{3}{2} - x, -\frac{1}{2} - y, -\frac{1}{2} + z$.

Experimental

Compound (2) was prepared from 4,4-diethyl-1-methylpyrazolidine-3,5-dione in three sequential steps: deprotonation with potassium *tert*-butoxide in DMSO, treatment with 9-bromofluorene and an *in situ* ring-expansion reaction. The desired product precipitated from the DMSO solution and was recrystallized from acetone–chloroform (Bausch & Gong, unpublished work). X-ray quality crystals, m.p. 573–574 K, were obtained *via* slow evaporation of an acetone–dichloromethane solution.

Crystal data

$C_{21}H_{22}N_2O_2$	Mo $K\alpha$ radiation
$M_r = 334.42$	$\lambda = 0.71069$ Å
Orthorhombic	Cell parameters from 25 reflections
Pbcn	

$a = 15.557$ (9) Å	$\theta = 8.7$–$9.4°$
$b = 13.138$ (4) Å	$\mu = 0.073$ mm^{-1}
$c = 17.899$ (5) Å	$T = 296$ K
$V = 3658$ (4) Å^3	Bladed
$Z = 8$	0.38 × 0.28 × 0.14 mm
$D_x = 1.214$ Mg m^{-3}	Colorless

Data collection

Rigaku AFC-5S diffractometer	$R_{int} = 0.051$
ω scans (rate 3° min^{-1} in ω, maximum 3 repetitions)	$\theta_{max} = 25°$
Absorption correction: none	$h = 0 \rightarrow 18$
6535 measured reflections	$k = -15 \rightarrow 15$
3421 independent reflections	$l = -21 \rightarrow 0$
1329 observed reflections [$I > 2\sigma(I)$]	3 standard reflections monitored every 150 reflections intensity decay: 1.4%

Refinement

Refinement on F	$(\Delta/\sigma)_{max} = 0.0002$
$R = 0.048$	$\Delta\rho_{max} = 0.16$ e Å^{-3}
$wR = 0.044$	$\Delta\rho_{min} = -0.20$ e Å^{-3}
$S = 1.38$	Extinction correction: none
1329 reflections	Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV, Table 2.3.1)
226 parameters	
H-atom parameters not refined (riding, C—H 0.95 Å)	
$w = 4F_o^2/\sigma^2(F_o^2)$	

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2)*

$$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	U_{eq}
O4	0.70223 (18)	−0.1357 (2)	0.35696 (15)	0.0585 (10)
O6	0.80794 (18)	0.1469 (2)	0.49325 (15)	0.0595 (11)
N1	0.8054 (2)	−0.0089 (2)	0.54283 (17)	0.0404 (11)
N3	0.7524 (2)	−0.1508 (2)	0.47333 (16)	0.0412 (11)
C2	0.7849 (2)	−0.1172 (3)	0.5452 (2)	0.0390 (12)
C4	0.7342 (2)	−0.0951 (3)	0.4118 (2)	0.0417 (17)
C5	0.7558 (3)	0.0173 (3)	0.4122 (2)	0.0427 (14)
C6	0.7910 (2)	0.0561 (3)	0.4861 (2)	0.0407 (14)
C7	0.8387 (3)	0.0344 (3)	0.6130 (2)	0.0617 (17)
C8	0.6729 (3)	0.0768 (3)	0.3943 (2)	0.0597 (17)
C9	0.6012 (3)	0.0650 (3)	0.4512 (3)	0.0707 (17)
C10	0.8209 (3)	0.0393 (3)	0.3496 (3)	0.0703 (19)
C11	0.9065 (3)	−0.0148 (4)	0.3576 (3)	0.094 (2)
C1′	0.6383 (3)	−0.1060 (3)	0.6163 (2)	0.0577 (17)
C2′	0.5898 (3)	−0.1407 (4)	0.6762 (3)	0.0677 (19)
C3′	0.6226 (3)	−0.2088 (4)	0.7252 (2)	0.0623 (19)
C4′	0.7058 (3)	−0.2448 (3)	0.7181 (2)	0.0540 (19)
C4a′	0.7545 (3)	−0.2107 (3)	0.6579 (2)	0.0433 (14)
C4b′	0.8422 (3)	−0.2348 (3)	0.6348 (2)	0.0470 (16)
C5′	0.9032 (3)	−0.2975 (4)	0.6680 (3)	0.0720 (19)
C6′	0.9831 (4)	−0.3036 (4)	0.6360 (3)	0.082 (2)
C7′	1.0038 (3)	−0.2496 (4)	0.5723 (3)	0.072 (2)
C8′	0.9420 (3)	−0.1872 (3)	0.5384 (3)	0.0597 (19)
C8a′	0.8621 (3)	−0.1814 (3)	0.5702 (2)	0.0437 (16)
C9a′	0.7202 (2)	−0.1423 (3)	0.6071 (2)	0.0403 (14)

Table 2. *Selected geometric parameters (Å, °)*

O4—C4	1.223 (4)	C4—C5	1.514 (5)
O6—C6	1.228 (4)	C5—C6	1.519 (5)
N1—C2	1.458 (4)	C5—C8	1.542 (5)
N1—C6	1.346 (4)	C5—C10	1.538 (5)
N1—C7	1.473 (5)	C8—C9	1.517 (6)
N3—C2	1.451 (4)	C10—C11	1.518 (7)
N3—C4	1.352 (5)		
C2—N1—C6	127.2 (3)	C4—C5—C6	114.3 (3)
C2—N1—C7	115.4 (3)	C4—C5—C8	107.9 (3)
C6—N1—C7	117.2 (3)	C4—C5—C10	109.0 (3)
C2—N3—C4	129.1 (3)	C6—C5—C8	108.2 (3)
N1—C2—N3	110.3 (3)	C6—C5—C10	109.5 (3)
N1—C2—C8a′	112.0 (3)	C8—C5—C10	107.7 (3)
N1—C2—C9a′	112.1 (3)	O6—C6—N1	120.1 (4)
N3—C2—C8a′	111.3 (3)	O6—C6—C5	119.7 (3)
N3—C2—C9a′	110.3 (3)	N1—C6—C5	120.2 (3)
O4—C4—N3	120.2 (3)	C5—C8—C9	115.1 (3)
O4—C4—C5	121.3 (4)	C5—C10—C11	114.9 (4)
N3—C4—C5	118.5 (4)		

Table 3. *Hydrogen-bonding geometry (Å, °)*

D—H···A	D—H	H···A	D···A	D—H···A
N3—H3···O6^{i}	0.95	1.94	2.841 (4)	157
C4′—H4′···O4^{ii}	0.95	2.35	3.269 (5)	164

Symmetry codes: (i) $\frac{3}{2} - x, y - \frac{1}{2}, z$; (ii) $\frac{3}{2} - x, -\frac{1}{2} - y, \frac{1}{2} + z$.

Data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1988). Cell refinement: *MSC/AFC Diffractometer Control Software*. Data reduction: *PROCESS TEXSAN* (Molecular Structure Corporation, 1985). Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1985). Program(s) used to refine structure: *LS TEXSAN*. Molecular graphics: *ORTEP* (Johnson, 1965) *TEXSAN*. Software used to prepare material for publication: *FINISH TEXSAN*; *PLATON* (Spek, 1990).

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: FG1159). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Two 14-Membered Macrocycles with *trans-trans* and *trans-cis* Dienes. Trimethyl (2*E*,4*E*)-*cis*- and Trimethyl (2*Z*,4*E*)-*trans*-11,15-Dioxobicyclo[12.3.0]heptadeca-2,4-diene-7,7,14-tricarboxylate

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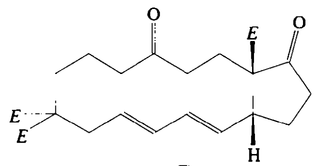
Abstract

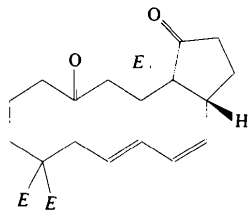
Two new isomeric 14-membered ring compounds, $C_{23}H_{30}O_8$, were synthesized based on Michael addition macrocyclization, which leads to completely controlled diene geometries, *trans-trans* and *trans-cis*. The crystal structures show the respective *trans-trans* and *trans-cis* diene geometries and their corresponding *cis* and *trans* ring junctions.

Comment

The transannular Diels–Alder cycloaddition represents a powerful approach towards the syntheses of several classes of natural products such as terpenes, triterpenes and steroids (Deslongchamps, 1991). This strategy for the construction of polycyclic macromolecules (Lamothe, Ndibwami & Deslongchamps, 1988; Marinier & Deslongchamps, 1988) involves the traditionally difficult synthesis of large rings. The conformational properties of such macrocycles change with each olefinic geometry combination and substituents as shown in earlier publications (Michel, Michel-Dewez, Roughton, Springer & Hoogsteen, 1989; Michel, Drouin, Michel-Dewez, Roughton & Deslongchamps, 1991; Drouin, Lamothe & Michel, 1992). More recently, a new series of 14-membered ring compounds have been synthesized using intramolecular Michael addition (Stork, Winkler & Saccomano, 1983), which leads to completely controlled diene geometries. Indeed, compounds (I) and (II) were obtained in low (30%) and very high (90%) yields, respectively (Crevisy, Couturier, Dugave, Dory & Deslongchamps, 1995), *via* intramolecular Michael addition involving the β-keto ester and conjugated olefinic ketone moieties.



(I)



(II)

$E = CO_2CH_3$

We present here the results of crystallographic investigations of compounds (I) and (II), undertaken to determine the ring-junction and diene geometries of these compounds as well as their exact conformations. The results clearly show that (I) and (II) have *trans-trans* and *trans-cis* olefin geometries, respectively, and their corresponding *cis* and *trans* ring junctions. Both macrocycles have carbonyl groups at C11 and at C17. Two methyl esters are attached at C1 and one at C8 in both molecules. The torsion-angle values for the olefin moieties show large deviations from ideally unstrained systems in (I). Indeed, C2—C3—C4—C5 and C4—C5—C6—C7 have respective values of −168.3 (4) and −167.9 (4)° for (I) and −178.9 (10) and −3.7 (4)° for (II). This shows that the olefinic system in (I) is severely strained compared to (II) and could explain the major difference in the yields of the two compounds. The conjugation of the diene moiety is partially broken in both molecules as shown by the C3—C4—C5—C6 torsion-angle values of 161.7 (4) and 168.2 (11)° for (I) and (II), respectively. The torsion-angle values of the 14-membered ring are similar in both compounds, which show great similarities in global conformation. Puckering analysis (Cremer & Pople, 1975) shows that the five-membered ring adopts a conformation halfway between envelope (*E*) and twist (*T*) (C_2 half chair with C17 on the twist axis).