Data collection

Enraf–Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
Absorption correction: none
6690 measured reflections
3819 independent reflections
2610 reflections with $I > 2\sigma(I)$
$R_{int} = 0.052$
$\theta_{max} = 27.46°$
$h = -13 \rightarrow 13$
$k = -10 \rightarrow 10$
$l = 0 \rightarrow 26$
3 standard reflections
frequency: 60 min
intensity decay: <1%

Refinement

Refinement on F^2
$R(F) = 0.048$
$wR(F^2) = 0.137$
$S = 1.043$
3819 reflections
221 parameters
H atoms: see text
$w = 1/[\sigma^2(F_o^2) + (0.0796P)^2 + 0.0235P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.225$ e Å^{-3}
$\Delta\rho_{min} = -0.177$ e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected geometric parameters (°)*

H3A—O3—H3B	107 (3)	N2—C14—C8	114.49 (12)
C9—C1—C11	126.53 (13)	O2—C17—C18^i	135.51 (16)
C9—C8—C14	126.26 (12)	O2—C17—C18	133.88 (16)
C1—C9—C8	127.62 (12)	O1—C18—C17^i	135.98 (16)
N1—C11—C1	114.01 (12)	O1—C18—C17	134.63 (16)
C9—C1—C11—N1	−83.48 (18)	C9—C8—C14—N2	67.50 (18)
C11—C1—C9—C8	6.1 (2)	C14—C8—C9—C1	4.1 (2)

Symmetry code: (i) $1 - x, -y, 1 - z$.

Table 2. *Hydrogen-bonding geometry (Å, °)*

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1A···N2	0.97 (3)	1.72 (3)	2.671 (2)	167 (3)
N2—H1B···N1	0.86 (10)	1.83 (10)	2.671 (2)	165 (8)
O3—H3A···O2^i	0.87 (3)	1.95 (3)	2.753 (3)	153 (3)
O3—H3B···O1	0.86 (3)	2.11 (3)	2.877 (3)	149 (3)
C13—H13A···O2^{ii}	0.96	2.25	3.188 (3)	166
C16—H16A···O2^{ii}	0.96	2.42	3.341 (3)	161
C16—H16C···O3	0.96	2.54	3.384 (3)	146

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

The H atoms bonded to N and O atoms have been located on a difference Fourier map; their coordinates have been subsequently introduced as parameters in the refinement. A two-site disorder model was introduced for the [N—H···N]$^+$ moiety; the occupation factor for atom H1*A* refined to 0.75 (4). All other H atoms have been introduced at calculated positions riding on their carrier atoms. The isotropic atomic displacement factor of the H atoms is related to the equivalent isotropic displacement of the carrier atoms by a factor of 1.5 for ammonium, water and methyl-H atoms and 1.2 for all other H atoms.

Data collection: locally modified *CAD-4 Software* (Enraf–Nonius, 1989). Cell refinement: *SET4* (de Boer & Duisenberg, 1984). Data reduction: *HELENA* (Spek, 1997). Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1985). Program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997). Molecular graphics: *PLATON* (Spek, 1990). Software used to prepare material for publication: *PLATON*.

Diffraction data were kindly collected by A. M. M. Schreurs.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: GD1043). Services for accessing these data are described at the back of the journal.

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3′-(2,3-Dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl)-5-fluorospiro[3*H*-indole-3,2′-thiazolidine]-2(1*H*),4′-dione

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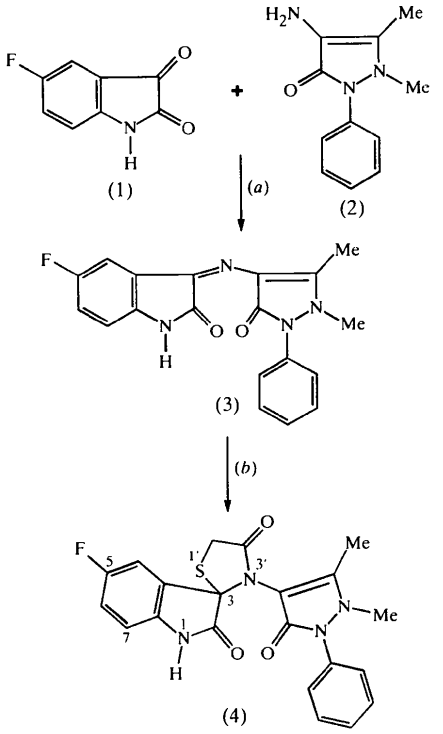
Abstract

The synthesis and structure of the title compound, $C_{21}H_{17}FN_4O_3S$, is described. It is a novel spiro-indole in which the sp^3 spiro-C atom is linked to S and N atoms. The pyrazole ring is aligned at 76.8 (1)° with respect to the attached phenyl ring and at 87.7 (1)° with respect

to the best plane through the spiro ring. Molecules are linked to form infinite chains by N—H···O hydrogen bonds, with N···O = 2.7002 (15) Å.

Comment

The chemistry of spiro-indoles in which an indole ring is joined to sulfur- and nitrogen-containing heterocycles at the C-3 position through a spiro-C atom is of great interest due to their physiological and biological activities. Spiro[indole–thiazolidine]diones are used in pharmaceuticals because of their anti-inflammatory (Rovnyak *et al.*, 1977), fungistatic and bacteriostatic (Kirichenko *et al.*, 1981), and anticonvulsant (Rajopadhye & Popp, 1984) activities. The significance of these compounds can be judged from the fact that most of the references to spiro-indoles in the literature are patents. Furthermore, incorporation of fluorine in the indole ring, as in the title compound, (4), enhances the biological activity by increasing solubility in lipoid material and fat deposits in the body (Whittle & Yound, 1963).



(*a*) C_2H_5OH (dry), room temperature
(*b*) $HSCH_2COOH$, $C_6H_5CH_3$ (dry), reflux

In the course of our research (Jain *et al.*, 1996, 1997) into the development of new spiro-indoles *via* molecular modification, we now report the synthesis of a novel spiro heterocyclic, *viz.* spiro[indole–pyrazolinylthiazolidine], containing three biodynamic heterocyclic moieties along with fluorine. Condensation of 5-fluoroindole-2,3-dione, (1), with 4-amino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one, (2), gave a potent intermediate 3-indolylimine, (3), in 92% yield. Indolylimines represent a novel class of anti-HIV agents which appear to act by inhibiting virus-dependent cell fusion (Smallheer *et al.*, 1993). Cycloaddition of mercaptoacetic acid to imine (3), in toluene under reflux with azeotropic removal of water, gave the title compound (4); the structure of this novel compound has been confirmed by X-ray crystallographic analysis and is illustrated in Fig. 1.

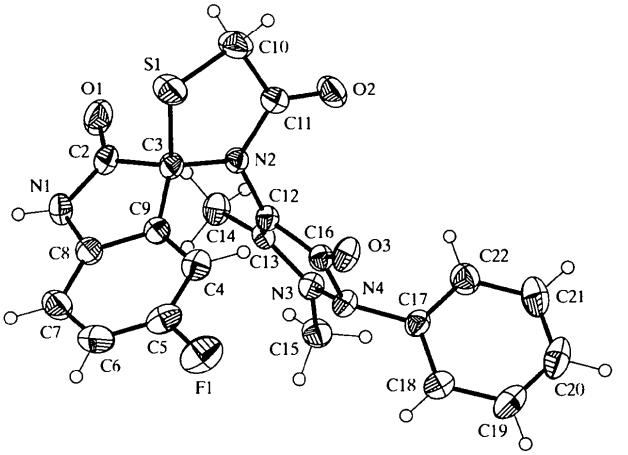


Fig. 1. View of the title molecule showing the atomic numbering. Displacement ellipsoids are drawn at the 50% probability level for non-H atoms. H atoms are shown as spheres of arbitrary radii.

The best planes through the phenyl and various heterocyclic rings are aligned at large angles with respect to adjacent planes. For example, the pyrazole ring (C12, C13, C16, N3 and N4; r.m.s. deviation 0.024 Å) is aligned at 76.8 (1)° with respect to the attached phenyl ring and at 87.7 (1)° with respect to the best plane through the spiro ring (C3, C10, C11, N2 and S1; r.m.s. deviation 0.117 Å). As anticipated, the spiro-C3 atom is essentially sp^3 hybridized, with bond angles in the range 102.9 (1)–118.8 (1)°; this results in the best plane through the spiro ring being inclined at 86.1 (1)° to the indole ring system. The bond lengths and angles are largely unexceptional (Table 1).

Only two other structures containing the same spiro-indole core appear to have been reported (Allen & Kennard, 1993; Fletcher *et al.*, 1996); these compounds are 1-benzyl-3′-(4″-chlorophenyl)-2,4′-dioxospiro[indoline-3,2′-thiazolidine]-5′-acetic acid (Popp *et al.*, 1987) and 5-chloro-3′-(4-fluorophenyl)spiro[3*H*-indole-3,2′-thiazolidine]-2,4′(1*H*)-dione (Sehgal *et al.*, 1994). Both of these compounds have spiro-C bond-angle ranges which are very close to those reported for the title compound and are 103.0–117.0 and 102.2–117.3°, respectively; all three structures have their adjacent planar subsections arranged at high angles with respect to each other. Molecules are linked to form infinite chains by N—H···O hydrogen bonds, with N···O = 2.7002 (15) Å (Table 1).

Experimental

A mixture of 5-fluoroindole-2,3-dione [(1); 1.65 g, 0.01 mol] and 4-amino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one [(2); 2.03 g, 0.01 mol] was stirred in absolute ethanol at room temperature for 5 min. The precipitate of the Schiff base (3) that was obtained was filtered off, dried and crystallized from methanol–chloroform as orange–red crystals (3.22 g, 92% yield). IR (KBr) ν_{max}: 3481, 3094, 2928, 2868, 1726, 1651, 1619, 1574, 1479, 1455, 1317, 1263, 1130, 1095, 1072, 913, 820, 749 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6): δ 2.01 (*s*, 3H, CH_3), 3.10 (*s*, 3H, N—CH_3), 7.80–6.81 (*m*, 8H, aromatic H), 10.51 (*s*, 1H, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 11.1, 35.6, 38.8, 40.9, 78.3, 111.2, 119.1, 122.4, 134.4, 137.8, 148.5, 159.8, 165.6, 171.7, 176.9; EIMS (electron impact MS, *m/z*): 350 (M^+), 231, 167, 125, 111, 97, 85, 71, 57. A mixture of (3) (1.75 g, 0.005 mol) and mercaptoacetic acid (0.506 g, 0.005 mol) was taken up in dry toluene and the contents refluxed for 8 h with azeotropic removal of water. The solvent was removed using a rotatory evaporator and the residue was treated with a saturated solution of sodium bicarbonate to remove excess acid. The remaining solid was filtered off, dried and crystallized from a methanol–chloroform mixture to give colourless crystals of (4) (1.35 g, yield 63%). IR (KBr) ν_{max}: 3200, 1736, 1718, 1655, 1550, 1495, 1400, 1380, 1280, 860, 780, 745, 690, 620 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6): δ 2.2 (*s*, 3H, CH_3), 3.1 (*s*, 3H, N—CH_3), 3.81 and 4.26 (2*d*, 2H, J = 14.8 Hz, $-CH_2-$), 6.73–7.82 (*m*, 8H, aromatic H), 10.52 (*s*, 1H, NH); ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 10.5, 32.5, 34.9, 110.9, 115.3, 115.8, 117.3, 117.7, 124.3, 124.6, 125.1, 127.3, 129.1, 134.4, 137.8, 153.7, 156.2, 159.9, 170.7, 171.7, 176.9.

Crystal data

$C_{21}H_{17}FN_4O_3S$
M_r = 424.45
Monoclinic
$P2_1/n$
a = 10.1159 (5) Å
b = 15.5291 (7) Å
c = 13.3630 (6) Å
β = 110.744 (1)°
V = 1963.12 (16) Å^3
Z = 4
D_x = 1.436 Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 7633 reflections
θ = 2.09–28.44°
μ = 0.206 mm^{-1}
T = 180 (2) K
Block
0.46 × 0.36 × 0.28 mm
Orange

Data collection

Siemens SMART CCD area-detector diffractometer
ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)
T_{min} = 0.908, T_{max} = 0.944
11 442 measured reflections
4600 independent reflections

3566 reflections with $I > 2\sigma(I)$
R_{int} = 0.020
θ_{max} = 28.44°
h = −13 → 13
k = −20 → 19
l = −8 → 17
Intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.037
$wR(F^2)$ = 0.097
S = 1.030
4600 reflections
273 parameters
H atoms constrained
$w = 1/[\sigma^2(F_o^2) + (0.0503P)^2 + 0.2465P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.247 e Å^{-3}
$\Delta\rho_{min}$ = −0.295 e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected geometric parameters and hydrogen-bonding geometry (Å, °)*

S1—C10	1.7867 (17)	O3—C16	1.2406 (16)
S1—C3	1.8388 (13)	N2—C11	1.3686 (18)
F1—C5	1.3685 (18)	N2—C12	1.4149 (16)
O1—C2	1.2159 (18)	N2—C3	1.4494 (17)
O2—C11	1.2114 (17)		
C10—S1—C3	92.51 (7)	N2—C3—S1	105.30 (9)
N2—C3—C9	118.80 (11)	C9—C3—S1	108.91 (9)
N2—C3—C2	113.08 (11)	C2—C3—S1	107.39 (9)
C9—C3—C2	102.93 (11)		
C3—N2—C12—C13	98.02 (17)	N3—N4—C17—C22	54.56 (17)
C3—N2—C12—C16	−97.79 (16)	C16—N4—C17—C22	−81.31 (17)
C16—N4—C17—C18	96.09 (16)		

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N1—H1A···O3^i	0.88	1.85	2.7002 (15)	161

Symmetry code: (i) $\frac{5}{2} - x, \frac{1}{2} + y, \frac{1}{2} - z$.

The temperature of the crystal was controlled using an Oxford Cryosystems Cryostream Cooler (Cosier & Glazer, 1986).

Data collection: *SMART* (Siemens, 1994*a*). Cell refinement: *SAINT* (Siemens, 1995). Data reduction: *SAINT*. Program(s) used to solve structure: *SHELXTL/PC* (Siemens, 1994*b*). Program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997). Molecular graphics: *SHELXTL/PC*. Software used to prepare material for publication: *SHELXTL/PC*.

We wish to acknowledge the use of the EPSRC's Chemical Database Service at Daresbury Laboratory (Fletcher *et al.*, 1996) for access to the Cambridge Structural Database (Allen & Kennard, 1993).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: CF1329). Services for accessing these data are described at the back of the journal.

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5-Acetoxy-2,3-diphenylisoxazolidine and 5-acetoxy-3-(4-nitrophenyl)-2-phenylisoxazolidine

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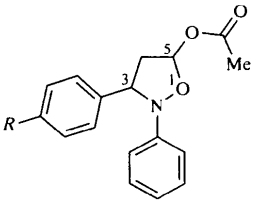
Abstract

The configurations of the isoxazolidine rings in the title compounds, 2,3-diphenylisoxazolidin-5-yl acetate ($C_{17}H_{17}NO_3$), (I), and 3-(4-nitrophenyl)-2-phenylisoxazolidin-5-yl acetate ($C_{17}H_{16}N_2O_5$), (II), are compared. The 2-phenyl group is in an equatorial position, the 5-acetoxy group is axial whilst the C3 substituent occupies a bisectional position. The angle between the phenyl groups in (I) is 80.95 (6)°, but in (II) it is 64.85 (8)°.

Comment

Reactions generally classified as 1,3-dipolar cycloaddition have been extensively employed in the synthesis of a diverse array of heterocyclic compounds (Huisgen, 1968; Hammer & Macaluso, 1964). Cycloadditions are not only ring-forming, but also proceed with a high degree of stereoselectivity. During the course of synthetic studies, a variety of isoxazolidines were prepared in our laboratory by [3+2] cycloadditions of nitrones with olefins (Cum *et al.*, 1968). It was critical to the success of this project that the configuration of the cycloadducts be firmly established. However, analysis of the ^{1}H NMR coupling constants of various isoxazolidines did not result in the unambiguous assignment of configuration because of the limitations of applying the Karplus equation to five-membered ring systems. In order to unambiguously assign the structures of the title compounds, their X-ray crystal structures were determined.



(I) R = H
(II) R = NO_2

The molecular structures of the title compounds are illustrated in Figs. 1 and 2; in each case the space groups are consistent with the presence of both enantiomers and for ease of comparison the illustrations show molecules with the same chirality at atoms C3(*S*) and C5(*R*). The internal bond angles in the isoxazolidine rings range from 102.7 (2) to 106.9 (2)° in (I) and from 103.3 (2) to 106.1 (2)° in (II); in both cases the smallest angle is N2—C3—C4 and the largest is O1—C5—C4. Corresponding bond lengths are the same within experimental error, except for O1—N2 [1.4809 (18) and 1.453 (3) Å for (I) and (II), respectively] and N2—C3 [1.479 (2) and 1.491 (3) Å, respectively]. Very few comparable isoxazolidine structures are available in the literature; the structures of 2,3-diphenyl-5-fluoromethyl-5-methoxy-4-(*p*-tolylsulfinyl)isoxazolidine (Bravo *et al.*, 1993) and 4-ethoxycarbonyl-5-trifluoromethyl-3-phenylisoxazolidin-5-ol (Bonnet-Delpon *et al.*, 1996) have been reported, but we were unable to reach any useful conclusions from an examination of corresponding bonds and angles.

The ring conformations for the isoxazolidine rings may be defined by the Cremer–Pople puckering parameters (Cremer & Pople, 1975); for compound (I) these are q_2 = 0.376 Å and φ_2 = 20.84° , whilst for (II) they are q_2 = 0.360 Å and φ_2 = 2.97°. These values imply that the puckering in (I) is best described as a half-chair structure twisted on O1—N2, but for (II) the structure approximates an envelope conformation (Spek, 1998).

The most important aspect of these structure determinations, in the context of our chemical studies, is the relative stereochemistry of the substituents in the isoxazolidine ring. In both structures the phenyl group at N2 is in an equatorial position [the angles to the Cremer–Pople plane normals are 65.92 and 60.60° for (I) and (II), respectively], the acetoxy group at C5 is axial (at 18.18 and 12.58°, respectively) whilst the substituent at C3 occupies a bisectional position (at 53.25 and 46.28°, respectively). Finally, the angle between the aromatic planes is 80.95 (6)° in compound (I); in (II) this angle is only 64.85 (8)°, whilst the plane of the nitro group