Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²)*

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

	x	y	z	U_{eq}
O1	0.9148 (3)	1.1588 (2)	0.26522 (5)	0.0707 (4)
C1	0.7392 (3)	1.1986 (3)	0.30940 (6)	0.0500 (4)
C2	0.6462 (3)	0.9447 (3)	0.33149 (6)	0.0452 (4)
C3	0.4614 (3)	0.9713 (3)	0.37993 (6)	0.0443 (4)
C4	0.3659 (3)	0.7150 (3)	0.40273 (6)	0.0433 (4)
C5	0.1863 (3)	0.7417 (3)	0.45223 (6)	0.0439 (4)
C6	0.0898 (3)	0.4864 (3)	0.47527 (5)	0.0433 (4)

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

O1—C1	1.413 (2)	C4—C5	1.521 (2)
C1—C2	1.499 (2)	C5—C6	1.520 (2)
C2—C3	1.515 (2)	C6—C6^i	1.520 (2)
C3—C4	1.521 (2)		
O1—C1—C2	110.1 (1)	C3—C4—C5	113.7 (1)
C1—C2—C3	113.3 (1)	C4—C5—C6	114.0 (1)
C2—C3—C4	113.8 (1)	C5—C6—C6^i	113.9 (2)

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

All non-H atoms were refined anisotropically by full-matrix least-squares methods. H atoms were fixed in idealized positions.

Data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1992). Cell refinement: *MSC/AFC Diffractometer Control Software*. Data reduction: *TEXSAN* (Molecular Structure Corporation, 1995). Program(s) used to solve structure: *SHELXS86* (Sheldrick, 1990). Program(s) used to refine structure: *TEXSAN*. Software used to prepare material for publication: *TEXSAN*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: TA1172). Services for accessing these data are described at the back of the journal.

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[3-(4-Bromophenyl)-1-(4-methoxyphenyl)-pyrazol-5-yl]acetonitrile†

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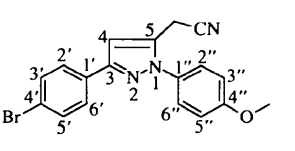
Abstract

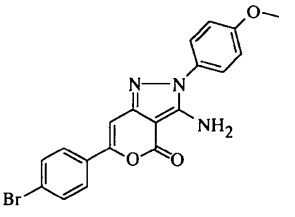
The title compound, $C_{18}H_{14}BrN_3O$, is one of the products obtained from the reaction of 6-(4-bromophenyl)-4-methylthio-2-oxo-2*H*-pyran-3-carbonitrile with 4-methoxyphenylhydrazine hydrochloride. The bromophenyl and methoxyphenyl groups are oriented with dihedral angles of 14.4 (2) and 53.8 (1)°, respectively, with respect to the pyrazole ring.

Comment

Pyrazoles have found applications in the areas of medicine and agriculture, and also in synthetic chemistry (Weily & Wiley, 1964; Taki *et al.*, 1992). Because of their widespread uses, intensive research efforts have been directed towards the development of new and improved synthetic routes for the preparation of pyrazole derivatives. We have synthesized several diphenylpyrazoleacetonitriles in order to extend the series for structure–activity studies.



(I)



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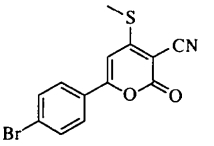

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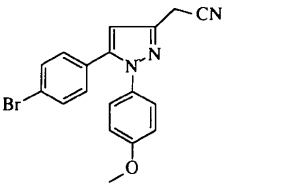

(IV)

† Alternative systematic name: 5-(4-bromophenyl)-2-(4-methoxyphenyl)-3-pyrazoleacetonitrile.

In this context, we prepared two different compounds, (I) and (II), each containing the pyrazole moiety, from the single-stage treatment of 6-(4-bromophenyl)-4-methylthio-2-oxo-2*H*-pyran-3-carbonitrile, (III), with 4-methoxyphenylhydrazine hydrochloride in pyridine; an analogue of (I) has previously exhibited a strong anti-invasive activity against solid tumours (Parmar *et al.*, 1997). The molecular structure of (I) has been determined in order to assign its constitution unambiguously since the isomeric structure (IV) could not easily be excluded on the basis of spectroscopic data alone.

The molecular structure of the title compound is illustrated in Fig. 1. Bond lengths and angles are unexceptional; specifically, the acetonitrile group is 'well behaved' with a C—C—N bond angle of 179.0 (4)°. The bromophenyl and methoxyphenyl groups are aligned with dihedral angles of 14.4 (2) and 53.8 (1)°, respectively, with respect to the pyrazole ring. Presumably the larger angle is due to a steric interaction between the methoxyphenyl group and the adjacent $-CH_2CN$ substituent in the pyrazole ring; similar observations have been reported for [3-(4-methylphenyl)-1-phenylpyrazole-5-yl]acetonitrile (Singh *et al.*, 1995). The methoxy group is oriented slightly out of the plane of its attached phenyl group as shown by the C7″—O1—C4″—C5″ torsion angle of −9.1 (5)°. There are no unusual intermolecular interactions.

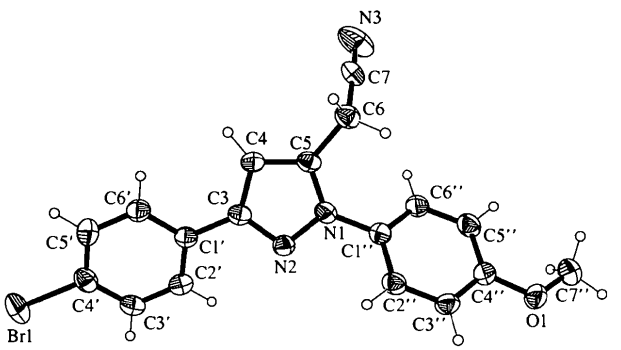

Fig. 1. View of the title molecule showing the atomic numbering. Displacement ellipsoids are drawn at the 50% probability level and H atoms have small arbitrary radii for clarity.

Experimental

A solution of 6-(4-bromophenyl)-4-methylthio-2-oxo-2*H*-pyran-3-carbonitrile [(III); 3.22 g, 0.01 mol] in dry pyridine (40 ml) was heated at 335 K for 15 min on an oil bath. 4-Methoxyphenylhydrazine hydrochloride (3.48 g, 0.02 mol) was then added and the reaction mixture refluxed for 5 h at 389 K. After the reaction was complete, pyridine was distilled off at reduced pressure and the residue was taken up in ethyl acetate, washed with water and dilute HCl, and dried over anhydrous Na_2SO_4. On removal of ethyl acetate, the crude reaction mixture was chromatographed on silica gel; compound (I) eluted with chloroform–petroleum (1:4) and crystallized from acetone as fine needles (1.4 g, 38% yield; m.p. 380–381 K). IR (nujol) ν_{max}: 2950, 2270 (C≡N), 1620, 1510, 1450, 1310, 1260, 1110, 1020, 970, 845 and 620 cm^{-1}; UV (MeOH) λ_{max}: 291, 266 and 242 nm; ^1H NMR (250 MHz, $CDCl_3$): δ 3.71 (*s*, 2H, $-CH_2CN$), 3.86 (*s*, 3H, $-OCH_3$), 6.77 (*s*, 1H, H-4), 7.02 (*d*, 2H, J = 9.0 Hz, H-2″ and H-6″), 7.36 (*d*, 2H, J = 9.0 Hz, H-3″ and H-5″), 7.52 (*d*, 2H, J = 8.6 Hz, H-2′ and H-6′) and 7.70 (*d*, 2H, J = 8.6 Hz, H-3′ and H-5′); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 16.01 (CH_2CN), 55.6 (OCH_3), 104.60 (C-4), 114.79 (C-3″ and C-5″), 115.53 (CH_2CN), 122.14 (C-4′), 126.86 (C-2″ and C-6″), 127.22 (C-3′ and C-5′), 131.15 (C-1′), 131.44 (C-1″), 131.78 (C-2′ and C-6′), 133.16 (C-3), 150.74 (C-5) and 160.06 (C-4″); EIMS *m/z* (% int.): 368/370 ([M + 1]$^+$, 37/20), 367/369 ([M^+], 100/98), 352/354 (9/8), 339/341 (6/7), 273 (6), 245 (4) and 131 (6).

Crystal data

$C_{18}H_{14}BrN_3O$
M_r = 368.23
Monoclinic
$C2/c$
a = 29.896 (2) Å
b = 4.1678 (4) Å
c = 28.487 (2) Å
β = 117.742 (2)°
V = 3141.4 (2) Å^3
Z = 8
D_x = 1.557 Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 4117 reflections
θ = 1.62–28.64°
μ = 2.625 mm^{-1}
T = 180 (2) K
Needle
0.47 × 0.20 × 0.19 mm
Colourless

Data collection

Siemens SMART CCD area diffractometer
ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996)
T_{min} = 0.607, T_{max} = 0.854
9246 measured reflections

3688 independent reflections
2691 reflections with $I > 2\sigma(I)$
R_{int} = 0.053
θ_{max} = 28.64°
h = −39 → 29
k = −5 → 3
l = −34 → 37

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.050
$wR(F^2)$ = 0.112
S = 1.156
3688 reflections
209 parameters
H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.0269P)^2 + 8.5584P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.002
$\Delta\rho_{max}$ = 0.56 e Å^{-3}
$\Delta\rho_{min}$ = −0.58 e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected geometric parameters (Å, °)*

Br1—C4′	1.905 (3)	N1—C1″	1.432 (4)
O1—C4″	1.370 (4)	N2—C3	1.338 (4)
O1—C7″	1.423 (4)	N3—C7	1.133 (5)
N1—N2	1.360 (3)	C3—C4	1.408 (4)
N1—C5	1.365 (4)	C4—C5	1.374 (4)
N2—N1—C5	112.4 (2)	C5—C4—C3	105.6 (3)
C3—N2—N1	104.5 (2)	N1—C5—C4	106.2 (3)
N2—C3—C4	111.3 (3)	N3—C7—C6	179.0 (4)
C4—C3—C1′—C6′	−13.6 (5)	C7″—O1—C4″—C5″	−9.1 (5)
N2—N1—C1″—C6″	126.6 (3)		

The temperature of the crystal was controlled using an Oxford Cryosystems Cryostream Cooler (Cosier & Glazer, 1986). Data were collected over a hemisphere of reciprocal space by a combination of three sets of exposures. Each set had a different φ angle for the crystal and each exposure of 10 s covered 0.3° in ω. The crystal-to-detector distance was 5.01 cm. Coverage of the unique set was over 90% complete to at least 28° in θ. Absence of crystal decay was established by repeating the initial frames at the end of the data collection and analyzing the duplicate reflections. H atoms were added at calculated positions and refined using a riding model. Anisotropic displacement parameters were used for all non-H atoms; H atoms were given isotropic displacement parameters equal to 1.2 (or 1.5 for methyl H atoms) times the equivalent isotropic displacement parameter of the atom to which they are attached.

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: *SHELXL97* (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, McMeeking & Parkin, 1996) for access to the Cambridge Structural Database (Allen & Kennard, 1993).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: BM1183). Services for accessing these data are described at the back of the journal.

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(–)-Formoterol,† a Selective β_2-Adrenoreceptor Agonist

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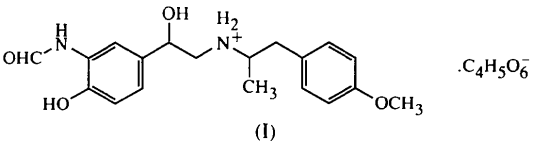
Abstract

The crystal structure of (−)-formoterol [2-hydroxy-5-(hydroxy-2-{[2-(*p*-methoxyphenyl)-1-methylethyl]-amino}ethyl)formanilide (+)-tartrate, $C_{19}H_{25}N_2O_4^+ \cdot C_4H_5O_6^-$] has been determined in order to elucidate its configuration relative to that of (+)-tartrate. The result is consistent with the configuration proposed on the basis of the chemical correlation experiments.

Comment

Formoterol, one pair of enantiomers of 2-hydroxy-5-[(1*RS*)-1-hydroxy-2-{[(1*RS*)-2-(*p*-methoxyphenyl)-1-methylethyl]amino}ethyl]formanilide, is a long-acting β_2-adrenoreceptor agonist (Ida, 1976*a*,*b*) and its fumarate (YM-08316) has been clinically used for the treatment of asthma. The pharmacological properties of formoterol have been extensively evaluated in several review papers (Faulds, Hollingshead & Goa, 1991; Anderson, 1993; Tattersfield, 1993).

In the search for selective β-adrenoreceptor-stimulating compounds, we synthesized 2-hydroxy-5-[(1*RS*)-1-hydroxy-2-{[(1*RS*)-2-(*p*-methoxyphenyl)-1-methylethyl]-amino}ethyl]formanilide, which was then separated into two racemic compounds, formoterol and the other, by selective crystallization (Murase *et al.*, 1977). Each racemate was further separated into its optical isomers using the (+) and (−) forms of tartaric acid as the resolving agents (Murase *et al.*, 1978). Among these four isomers, (−)-formoterol showed the most potent bronchodilatory activity. We have now determined the crystal structure of (−)-formoterol (+)-tartrate, (I), in order to confirm its configuration.



(I)

† Systematic name: [2-(4-methoxyphenyl)-1-methylethyl][2-(3-formylamino-4-hydroxyphenyl)-2-hydroxyethyl]ammonium tartrate.