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}
N(1)	0.8698 (4)	0.0668 (5)	0.5393 (4)	0.029 (1)
N(2)	0.9187 (4)	−0.1698 (5)	0.6313 (4)	0.034 (2)
N(3)	0.8548 (4)	−0.1971 (5)	0.4900 (4)	0.035 (2)
N(4)	0.7632 (4)	−0.0224 (6)	0.2950 (5)	0.037 (2)
N(5)	0.8306 (4)	0.0998 (6)	−0.0506 (5)	0.037 (2)
N(6)	0.5843 (5)	0.2438 (6)	−0.0988 (6)	0.056 (2)
N(7)	0.5191 (5)	0.2833 (6)	−0.0280 (6)	0.053 (2)
N(8)	0.4617 (6)	0.3363 (8)	0.0346 (7)	0.084 (3)
O(1)	0.9870 (3)	0.0408 (4)	0.7854 (3)	0.033 (1)
O(2)	0.7121 (4)	−0.1335 (5)	0.2191 (4)	0.061 (2)
O(3)	0.7654 (4)	0.1121 (5)	0.2512 (4)	0.051 (2)
C(1)	0.9291 (5)	−0.0132 (6)	0.6607 (5)	0.031 (2)
C(2)	0.8294 (4)	−0.0520 (6)	0.4462 (5)	0.030 (2)
C(3)	0.7122 (5)	0.0431 (7)	−0.1560 (6)	0.043 (2)
C(4)	0.6017 (5)	0.0749 (7)	−0.1088 (6)	0.048 (2)

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

N(1)—C(1)	1.349 (6)	N(1)—C(2)	1.339 (6)
N(2)—N(3)	1.363 (5)	N(2)—C(1)	1.357 (6)
N(2)—H(N2)	0.908 (4)	N(3)—C(2)	1.305 (6)
N(4)—O(2)	1.225 (6)	N(4)—O(3)	1.224 (6)
N(4)—C(2)	1.455 (6)	N(5)—C(3)	1.484 (6)
N(6)—N(7)	1.221 (9)	N(6)—C(4)	1.455 (8)
N(7)—N(8)	1.13 (1)	O(1)—C(1)	1.275 (5)
C(3)—C(4)	1.500 (9)		
C(1)—N(1)—C(2)	100.9 (4)	N(3)—N(2)—C(1)	111.4 (4)
N(3)—N(2)—H(N2)	112.5 (4)	C(1)—N(2)—H(N2)	136.0 (4)
N(2)—N(3)—C(2)	99.4 (4)	O(2)—N(4)—O(3)	124.2 (4)
O(2)—N(4)—C(2)	118.4 (4)	O(3)—N(4)—C(2)	117.4 (4)
N(7)—N(6)—C(4)	115.5 (5)	N(6)—N(7)—N(8)	172.5 (7)
N(1)—C(1)—N(2)	108.7 (4)	N(1)—C(1)—O(1)	128.7 (4)
N(2)—C(1)—O(1)	122.7 (4)	N(1)—C(2)—N(3)	119.7 (4)
N(1)—C(2)—N(4)	121.2 (4)	N(3)—C(2)—N(4)	119.1 (4)
N(5)—C(3)—C(4)	112.5 (5)	N(6)—C(4)—C(3)	110.2 (5)
C(4)—N(6)—N(7)—N(8)	176.9 (6)	N(5)—C(3)—C(4)—N(6)	63.6 (6)
N(7)—N(6)—C(4)—C(3)	−162.1 (5)		

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

D—H···A	H···A	D···A	D—H···A
N(5)—H(N5a)···O(1^i)	2.24 (7)	2.998 (5)	146 (4)
N(5)—H(N5b)···N(1^{ii})	2.06 (8)	2.954 (6)	162 (6)
N(5)—H(N5c)···O(1^{iii})	2.03 (7)	2.815 (6)	159 (4)
N(5)—H(N2)···O(1^{iv})	1.85 (5)	2.697 (5)	154.3 (5)

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

H atoms on N(2) and N(5) were located by difference Fourier synthesis, while others were placed in calculated positions using a riding model. All H atoms were given fixed isotropic U values.

Structure solution and refinement were performed by direct methods using *SHELXTL-Plus* (Sheldrick, 1990).

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Antihypertensive 2-(1,3-Dioxolan-2-yl)-2-methyl-6-nitro-4-(2-oxo-1-pyrrolidinyl)-2H-1-benzopyran

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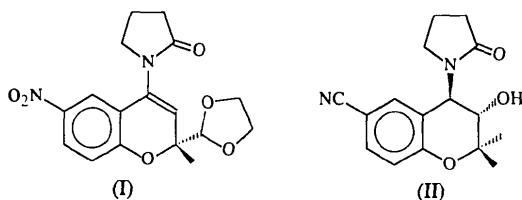
Abstract

The title compound, 1-[2-(1,3-dioxolan-2-yl)-2-methyl-6-nitro-2H-1-benzopyran-4-yl]-2-pyrrolidinone, $C_{17}H_{18}N_2O_6$, is a highly potent potassium-channel activator. The dioxolane moiety is in the pseudo-axial position. The overall conformation, in terms of the relative orientation of the oxopyrrolidine ring with respect to the benzopyran ring, is similar to that of cromakalim.

Comment

Potassium-channel activators are promising in cardiovascular therapy as antihypertensives and coronary vasodilators and consist of several structural groups including benzopyran compounds (Robertson & Steinberg, 1990). The title compound, (I), is a highly potent potassium-channel activator and shows higher (*ca* nine times) activity than cromakalim, (II), the first of this class of compounds to enter clinical trials as an antihypertensive agent (Ashwood *et al.*, 1986).

In the crystal structure of cromakalim (Cassidy *et al.*, 1989), the oxopyrrolidine ring was found to be orthogonal to the benzopyran ring. From an NMR study, it was suggested that rotation about the C—

N bond joining the oxopyrrolidine ring to the benzo-pyran moiety is prevented and cromakalim adopts a single rigid conformation in solution, similar to that observed in the crystal. The presence of another stable conformer, however, was identified from an independent NMR study by Thomas & Whitecombe (1990). In this form, the oxopyrrolidine ring is rotated by 180°. It was shown that the crystal form is lower in energy by 2.2 kcal mol^{-1} and thus predominates in solution. It was concluded that rotation about the C—N bond is rapid at ambient temperature since the energy barrier between the two conformers is in the range 11.5–13.5 kcal mol^{-1}, while a barrier to rotation of 23 kcal mol^{-1} is required for stable rotamers at 293 K (1 kcal mol^{-1} = 4.184 kJ mol^{-1}).

The present study establishes that the dioxolane moiety in (I) is in the pseudo-axial position (Fig. 1). Molecular dimensions agree well with those of related compounds. The atoms of the benzopyran ring, ex-cept for C2, form a plane with a maximum deviation of 0.072 (2) Å for the C3 atom. Atom C2 deviates by 0.292 (3) Å from the plane. The dihedral angle between the best planes of the benzopyran and oxopyrrolidine rings is 84.8 (1)° and the dihedral angle between the benzopyran ring and the nitro group is 11.1 (1)°. Atom
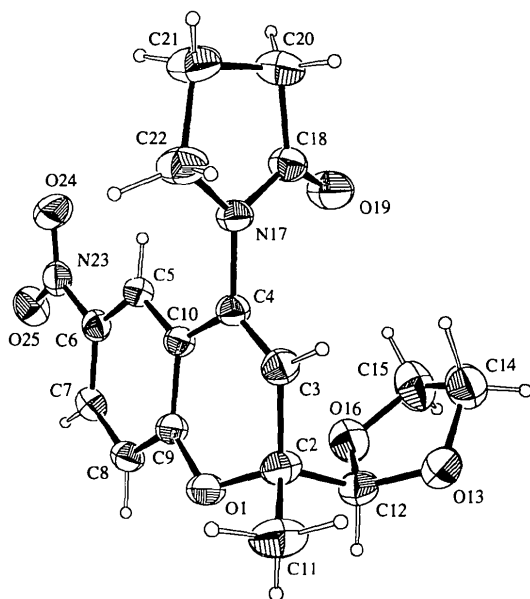
N17 deviates by 0.062 (3) Å from the plane composed of its three bonded atoms. The oxopyrrolidine and diox-olane rings are puckered significantly, with the largest ring torsion angles being −24.3 (3) and −18.6 (3)° for the C21—C22 and C14—C15 bonds, respectively. Crystal packing consists of van der Waals interactions only.

The overall conformation of (I) is similar to that found in crystalline cromakalim, with the same orien-tation of the oxopyrrolidine ring. This observation sup-ports the conclusion made for the stable conformation of cromakalim. The superimposed molecules, as found in the crystal structures of both compounds, are shown in Fig. 2. The oxo group in the oxopyrrolidine ring is essential for the activity of this class of compounds. The two oxo groups in compounds (I) and (II) are not in the same position in the superimposed structures, but are separated by 1.47 Å due to differences in the valence state of the C4 atom and the degree of rotation of the oxopyrrolidine ring.

Fig. 2. A stereoscopic view of the superimposed structures of (I) (solid line) and (II) (dotted line).

Experimental

The synthesis and biological evaluation of (I) were carried out at the Korea Research Institute of Chemical Technology. Crystals were obtained from a 2-propanol solution.

Crystal data

$C_{17}H_{18}N_2O_6$	Cu $K\alpha$ radiation
$M_r = 346.33$	$\lambda = 1.54184$ Å
Orthorhombic	Cell parameters from 25
$P2_12_12_1$	reflections
$a = 10.563 (2)$ Å	$\theta = 6.76–20.76°$
$b = 16.902 (2)$ Å	$\mu = 0.894$ mm^{-1}
$c = 9.297 (2)$ Å	$T = 295$ K
$V = 1659.8 (5)$ Å^3	Rectangular prism
$Z = 4$	$0.45 \times 0.40 \times 0.30$ mm
$D_x = 1.386$ Mg m^{-3}	Orange
$D_m = 1.345 (8)$ Mg m^{-3}	
D_m measured by flotation in sodium tartarate solution	

Data collection

Enraf–Nonius CAD-4	$R_{int} = 0.053$
diffractometer	$\theta_{max} = 64.95°$

Fig. 1. An ORTEPII (Johnson, 1976) view of (I) with the atomic numbering scheme. Displacement ellipsoids are drawn at the 25% probability level and H atoms are shown as circles of arbitrary radii.

$\omega/2\theta$ scans

Absorption correction:
none

1821 measured reflections
1635 independent reflections
1478 observed reflections
$[I > 2\sigma(I)]$

$h = 0 \to 12$
$k = 0 \to 19$
$l = 0 \to 10$
3 standard reflections
monitored every 50
reflections
intensity decay: 1%

Refinement

Refinement on F^2
$R(F) = 0.0341$
$wR(F^2) = 0.1335$
$S = 1.495$
1478 reflections
299 parameters
All H-atom parameters
refined
$w = 1/[\sigma^2(F_o^2) + (0.0671P)^2 + 0.1383P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.139$
$\Delta\rho_{max} = 0.150$ e Å^{-3}
$\Delta\rho_{min} = -0.174$ e Å^{-3}

Extinction correction:
*SHELXL*93 (Sheldrick,
1993)
Extinction coefficient:
0.0062 (7)
Atomic scattering factors
from *International Tables
for Crystallography* (1992,
Vol. C, Tables 4.2.6.8 and
6.1.1.4)
Absolute configuration:
Flack (1983) parameter =
0.2 (3)

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}
O1	0.6427 (2)	0.11895 (11)	0.0148 (2)	0.0574 (5)
C2	0.5966 (2)	0.0750 (2)	−0.1090 (3)	0.0578 (6)
C3	0.4550 (2)	0.08059 (15)	−0.1239 (3)	0.0517 (6)
C4	0.3815 (2)	0.10121 (13)	−0.0166 (2)	0.0462 (5)
C5	0.3645 (2)	0.14447 (14)	0.2419 (3)	0.0496 (6)
C6	0.4240 (2)	0.16765 (13)	0.3658 (3)	0.0520 (6)
C7	0.5551 (3)	0.17085 (14)	0.3767 (3)	0.0553 (6)
C8	0.6265 (2)	0.15212 (15)	0.2578 (3)	0.0546 (6)
C9	0.5681 (2)	0.12983 (13)	0.1314 (3)	0.0477 (5)
C10	0.4348 (2)	0.12464 (13)	0.1215 (3)	0.0459 (5)
C11	0.6653 (3)	0.1097 (3)	−0.2382 (4)	0.0830 (10)
C12	0.6380 (2)	−0.0112 (2)	−0.0824 (4)	0.0685 (8)
O13	0.5966 (2)	−0.06084 (14)	−0.1941 (3)	0.0812 (7)
C14	0.4899 (4)	−0.1047 (2)	−0.1385 (4)	0.0856 (9)
C15	0.5046 (5)	−0.1025 (2)	0.0195 (5)	0.0946 (11)
O16	0.5887 (2)	−0.03895 (13)	0.0477 (2)	0.0776 (6)
N17	0.2464 (2)	0.10444 (11)	−0.0324 (2)	0.0487 (5)
C18	0.1694 (2)	0.0433 (2)	0.0011 (3)	0.0576 (6)
O19	0.2018 (2)	−0.01711 (12)	0.0593 (3)	0.0885 (8)
C20	0.0373 (3)	0.0654 (2)	−0.0486 (4)	0.0749 (9)
C21	0.0441 (3)	0.1535 (2)	−0.0763 (5)	0.0808 (10)
C22	0.1835 (3)	0.1697 (2)	−0.1057 (5)	0.0738 (9)
N23	0.3493 (2)	0.19198 (13)	0.4888 (3)	0.0620 (6)
O24	0.2352 (2)	0.19964 (15)	0.4717 (3)	0.0856 (7)
O25	0.4021 (3)	0.20504 (14)	0.6034 (2)	0.0825 (7)

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

O1—C9	1.353 (3)	C9—C10	1.414 (3)
O1—C2	1.454 (3)	C12—O16	1.398 (4)
C2—C3	1.505 (3)	C12—O13	1.405 (4)
C2—C11	1.521 (4)	O13—C14	1.446 (5)
C2—C12	1.540 (4)	C14—C15	1.477 (6)
C3—C4	1.311 (4)	C15—O16	1.418 (4)
C4—N17	1.436 (3)	N17—C18	1.351 (3)
C4—C10	1.457 (3)	N17—C22	1.457 (3)
C5—C6	1.369 (4)	C18—O19	1.205 (3)
C5—C10	1.385 (4)	C18—C20	1.517 (4)
C6—C7	1.390 (4)	C20—C21	1.512 (5)
C6—N23	1.449 (4)	C21—C22	1.523 (4)
C7—C8	1.375 (4)	N23—O25	1.223 (3)
C8—C9	1.380 (4)	N23—O24	1.223 (3)

C9—O1—C2	120.6 (2)	C5—C10—C4	124.9 (2)
O1—C2—C3	111.9 (2)	C9—C10—C4	117.3 (2)
O1—C2—C11	105.5 (2)	O16—C12—O13	108.8 (3)
C3—C2—C11	112.1 (2)	O16—C12—C2	110.5 (2)
O1—C2—C12	105.1 (2)	O13—C12—C2	111.0 (3)
C3—C2—C12	110.9 (2)	C12—O13—C14	106.5 (3)
C11—C2—C12	110.9 (3)	O13—C14—C15	105.1 (3)
C4—C3—C2	122.4 (2)	O16—C15—C14	105.6 (3)
C3—C4—N17	121.4 (2)	C12—O16—C15	109.1 (3)
C3—C4—C10	120.9 (2)	C18—N17—C4	123.0 (2)
N17—C4—C10	117.6 (2)	C18—N17—C22	114.4 (2)
C6—C5—C10	120.3 (2)	C4—N17—C22	122.0 (2)
C5—C6—C7	122.0 (3)	O19—C18—N17	125.5 (2)
C5—C6—N23	119.7 (2)	O19—C18—C20	127.3 (2)
C7—C6—N23	118.3 (3)	N17—C18—C20	107.1 (2)
C8—C7—C6	118.6 (3)	C21—C20—C18	104.5 (2)
C7—C8—C9	120.2 (2)	C20—C21—C22	104.7 (3)
O1—C9—C8	117.4 (2)	N17—C22—C21	102.7 (2)
O1—C9—C10	121.3 (2)	O25—N23—O24	123.0 (3)
C8—C9—C10	121.2 (2)	O25—N23—C6	119.4 (2)
C5—C10—C9	117.8 (2)	O24—N23—C6	117.6 (2)

H atoms were located from a difference Fourier map and
their positions and U_{iso} values refined. The adopted absolute
configuration was confirmed by the small value of the Flack
parameter.

Data collection: *CAD-4 Software* (Enraf–Nonius, 1989).
Cell refinement: *CAD-4 Software*. Data reduction: *MolEN*
(Fair, 1990). Program(s) used to solve structure: *SHELXS86*
(Sheldrick, 1990). Program(s) used to refine structure:
*SHELXL*93 (Sheldrick, 1993). Molecular graphics: *ORTEPII*
(Johnson, 1976). Software used to prepare material for publi-
cation: *SHELXL*93.

Lists of structure factors, anisotropic displacement parameters, H-
atom coordinates, complete geometry and torsion angles have been
deposited with the IUCr (Reference: TA1029). Copies may be obtained
through The Managing Editor, International Union of Crystallography,
5 Abbey Square, Chester CH1 2HU, England.

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