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2-{[3-(Trifluoromethyl)phenyl]amino}-3-pyridinecarboxylic Acid* (Niflumic Acid)†

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Abstract. $C_{13}H_9F_3N_2O_2$, $P2_1/n$, $a = 5{\cdot}111\ (2)$, $b = 15{\cdot}330\ (2)$, $c = 15{\cdot}479\ (2)$ Å, $\beta = 95{\cdot}5\ (3)°$, $D_m = 1{\cdot}51$ (flotation), $D_c = 1{\cdot}55$ Mg m^{-3}, $Z = 4$. The three planar groupings in the molecule, *i.e.* the two six-membered rings and the carboxyl group, are nearly coplanar. In the crystal structure the molecules exist as hydrogen-bonded dimers. In addition, there is an intramolecular hydrogen bond connecting the carboxyl group and the N atom which bridges the two six-membered rings.

Introduction. Fenamates (mefenamic acid, meclofenamic acid, flufenamic acid and niflumic acid) constitute an important recently developed group of analgesics which are believed to act, like other anti-inflammatory analgesics, through the inhibition of prostaglandin biosynthesis (Flower, 1974). The crystal structures of mefenamic acid and flufenamic acid have been determined (McConnell, 1973, 1976). As part of a programme of X-ray studies on analgesics and their interactions (Singh & Vijayan, 1977; Krishna Murthy, Vijayan & Brehm, 1979), we report here the crystal structure of niflumic acid.

Elongated needle-like crystals of the title compound were grown from a solution in tetrahydrofuran using a sample supplied by UPSA Laboratories, Agen, France. The data were collected on a CAD-4 computer-controlled diffractometer from a specimen of dimensions $1{\cdot}0 \times 0{\cdot}3 \times 0{\cdot}2$ mm using graphite-monochromated Cu radiation up to a Bragg angle of 72°. Of the 2373 unique reflections in this range, 1426 had $I > 3\sigma(I)$ and were subsequently used for structure determination and refinement. The data were corrected for Lorentz and polarization factors. The structure was solved using *MULTAN* (Germain, Main & Woolfson, 1971) and refined by the block-diagonal least-squares method using the modified version of a program originally written by R. Shiono. The heavy atoms and the H atoms were given anisotropic and isotropic temperature factors respectively. The refinement converged at $R = 0{\cdot}080$. The weighting scheme was of the form $1/(a + bF_o + cF_o^2)$, where $a = 1{\cdot}28$, $b = -0{\cdot}034$ and $c = 0{\cdot}004$. The scattering factors for the non-hydrogen atoms and the H atoms were taken from

Table 1. *Final coordinates* ($\times 10^4$) *of the non-hydrogen atoms*

The standard deviations are given in parentheses.

	x	*y*	*z*
C(1)	8280 (19)	5434 (7)	7682 (7)
C(2)	6208 (19)	4949 (7)	7206 (8)
C(3)	4642 (21)	4432 (8)	7685 (9)
C(4)	5052 (22)	4391 (9)	8576 (9)
C(5)	7142 (24)	4871 (9)	8963 (9)
N(6)	8717 (17)	5385 (7)	8533 (6)
C(7)	5699 (20)	4992 (8)	6266 (8)
O(1)	7020 (16)	5407 (7)	5778 (5)
O(2)	3633 (16)	4529 (7)	5951 (6)
N(1)	9844 (16)	5955 (6)	7231 (6)
C(8)	11840 (19)	6546 (7)	7526 (7)
C(9)	12509 (19)	6761 (7)	8395 (7)
C(10)	14571 (21)	7353 (7)	8584 (7)
C(11)	15884 (21)	7738 (8)	7960 (8)
C(12)	15186 (22)	7533 (8)	7096 (9)
C(13)	13149 (20)	6946 (8)	6880 (7)
C(14)	15373 (22)	7556 (8)	9505 (8)
F(1)	17191 (18)	7029 (7)	9870 (6)
F(2)	13441 (17)	7527 (8)	10027 (6)
F(3)	16392 (22)	8352 (6)	9633 (6)

* The systematic chemical name for niflumic acid given in our abstract (04.6–15) communicated to the Eleventh International Congress of Crystallography, Warszawa, 3–12 August 1978, is incorrect. The error is regretted.

† Structural Studies of Analgesics and Their Interactions. VI.

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Cromer & Waber (1965) and Stewart, Davidson & Simpson (1965) respectively. The final coordinates of the non-hydrogen atoms are given in Table 1.*

Discussion. The bond lengths and angles in the molecule, and the crystal structure are shown in Figs. 1 and 2 respectively. The dimensions are similar to those observed in the other fenamates and do not merit comment.

* Lists of structure factors, thermal parameters and H atom positional parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 33958 (12 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

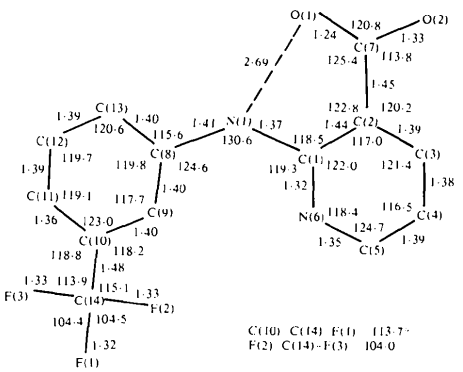

Fig. 1. Bond lengths (Å) and angles (°) in niflumic acid. The average standard deviations in bond lengths and angles are 0·015 Å and 1·0° respectively.

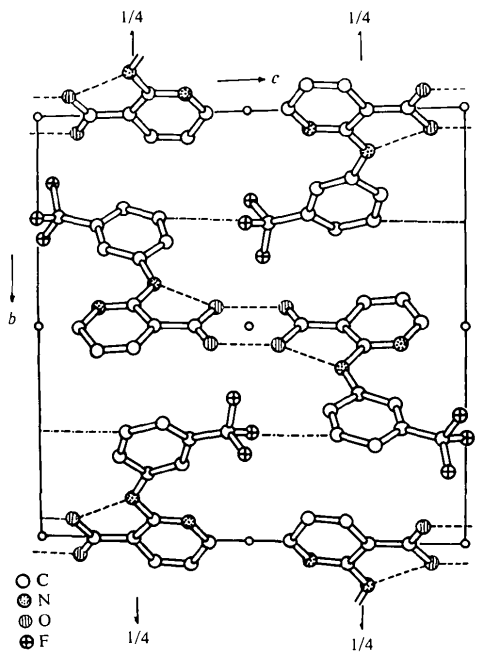

Fig. 2. Crystal structure as viewed along the *a* axis. The broken lines indicate hydrogen bonds.

Table 2. *Dihedral angles and hydrogen-bond parameters*

The primed atoms are related to the unprimed atoms by $1 - x$, $1 - y$, $1 - z$. H(O2) and H(N1) are H atoms attached to O(2) and N(1) respectively.

O(2)–C(7)–C(2)–C(1)	−177·2°
C(2)–C(1)–N(1)–C(8)	174·1
C(1)–N(1)–C(8)–C(9)	−4·5
O(2)···O(1)′	2·67 (1) Å
O(2)–H(O2)	1·1 (2)
O(1)′···O(2)–H(O2)	2 (8)°
N(1)···O(1)	2·69 (1) Å
N(1)–H(N1)	0·8 (2)
O(1)···N(1)–H(N1)	33 (12)°

The molecules of niflumic acid, like those of other fenamates, consist essentially of three planar groupings, *i.e.* the two six-membered rings and the carboxyl group, and their conformation can be described by the dihedral angles O(2)–C(7)–C(2)–C(1), C(2)–C(1)–N(1)–C(8) and C(1)–N(1)–C(8)–C(9). The values of these dihedral angles in the present structure are given in Table 2. The phenyl ring and the pyridine ring are inclined with respect to each other at 8·8° whereas the plane of the carboxyl group makes an angle of 2·3° with that of the phenyl ring. Thus, the three groups are nearly coplanar in the present structure, unlike those in mefenamic acid and flufenamic acid.

As can be seen from Fig. 2, the molecules exist as hydrogen-bonded dimers in the crystal structure – a situation similar to that found in the structures of mefenamic acid and flufenamic acid. In addition, there is an internal hydrogen bond connecting the bridging N atom and the carboxyl group. The parameters of the hydrogen bonds are given in Table 2.

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