N-{4-(Methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidinyl}-*N*-phenylpropanamide: Sufentanil

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Abstract. $C_{22}H_{30}N_2O_2S$, $M_r = 386 \cdot 6$, triclinic, $P\bar{1}$, $a = 9 \cdot 053$ (2), $b = 9 \cdot 289$ (4), $c = 12 \cdot 984$ (5) Å, $\alpha = 79 \cdot 84$ (4), $\beta = 81 \cdot 29$ (3), $\gamma = 82 \cdot 46$ (3)°, $Z = 2$, $F(000) = 416$, $D_c = 1 \cdot 21$, $D_m = 1 \cdot 20$ Mg m^{-3}; final residual $R = 0 \cdot 096$. The thienyl ring is present in two different orientations.

Introduction. The present study forms part of an investigation on the structure–activity relationship of narcotic analgesics [*e.g.* substituted 6,7-benzomorphans (Gelders, De Ranter & Schenk, 1979; Gelders, De Ranter & Overbeek, 1979)]. Among these analgesics the 4-anilinopiperidines, with fentanyl as the prototype, are of particular interest, because it has been shown that substitution at the 4 position of the piperidine ring adds to the potency (Van Daele, De Bruyn, Boey, Sanczuk, Agten & Janssen, 1976). For instance, the title compound (I) has a rapid onset of action and is 4521 times more potent than morphine at the time of peak effect; it has a relatively short duration of action which is comparable to that of fentanyl and it is characterized by an unusually high safety margin (Van Bever, Niemegeers, Schellekens & Janssen, 1976).

(I)
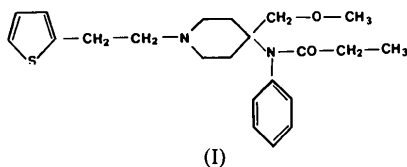
Transparent, colourless crystals were obtained by slow evaporation from a solution in petroleum ether. The space group was determined from rotation and Weissenberg photographs. Intensities were measured on a Nonius CAD-4 computer-controlled diffractometer with graphite-monochromatized Cu $K\alpha$ radiation ($\lambda = 1 \cdot 5418$ Å) using the θ–2θ scan technique ($\theta_{max} = 65°$). Cell dimensions were obtained by least-squares

analysis from the setting angles of 20 reflections. 3583 independent reflections were measured and 2830 with $I > 2 \cdot 5\sigma(I)$ were considered as observed. The data were corrected for Lorentz and polarization effects but not for absorption ($\mu = 1 \cdot 46$ mm^{-1}).

The structure was solved by direct methods with *MULTAN* (Main, Woolfson, Lessinger, Germain & Declercq, 1974). The set with the best figure of merit revealed the positions of all the non-hydrogen atoms, except for one atom of the thienyl ring. The missing atom was obtained from a Fourier synthesis with the known phases. Refinement of the model obtained to an R value of $0 \cdot 145$ gave high thermal parameters and abnormal distances in the thienyl ring [S(1)–C(2) 1·64, C(2)–C(3) 1·49, C(3)–C(4) 1·41, C(4)–C(5) 1·31 and C(5)–S(1) 1·67 Å]. A difference Fourier synthesis showed an electron density of about 2 e Å^{-3} in a region near C(3) and at 1·68 Å from C(2). These facts can be explained by the presence of two distinct conformations of the thienyl ring, related to each other by ~180° rotation about C(2)–C(6). Starting again from the C(2) and S(1) positions originally found, the positions of the remaining atoms in the first thienyl ring were calculated theoretically using mean literature values (Cynkier, 1976). Inverting the ring gave the second conformation and both were refined as separate groups. The group refinement was performed with the program *NUCLS* [J. A. Ibers's version of *ORFLS* (Busing, Martin & Levy, 1962)] in which the non-group atoms were refined anisotropically and the group atoms isotropically. The population parameters of the groups were also refined and amounted to 0·65 and 0·35 for conformations *A* and *B* respectively. The resulting R was 0·165. The structure was further refined (fixed positional and population parameters of the group atoms) by anisotropic block-diagonal least-squares analysis to an R of 0·118. A difference Fourier map at this stage revealed the H atoms, except for those of the thienyl rings; the latter were calculated. In the final stages of refinement the H atoms were included (fixed positions and isotropic temperature factors of their adjacent atoms) and the reflections were weighted as

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Table 1. *Final coordinates* ($\times 10^4$) *with standard deviations in parentheses*

The population parameters of atoms $S(1A) - C(5A)$ and $S(1B) - C(5B)$ are 0·65 and 0·35 respectively.

	x	y	z		x	y	z
S(1A)	8248	5010	1275	H(3A)	4916	6845	2494
C(2A)	6474	5136	1931	H(4A)	6899	8638	1743
C(3A)	5981	6533	2102	H(5A)	9307	7368	863
C(4A)	7070	7512	1690	H(6A)	6358	2810	1979
C(5A)	8361	6835	1218	H(6B)	5257	3700	2975
C(6)	5698 (5)	3714 (5)	2169 (4)	H(7A)	3606	4844	1722
C(7)	4279 (5)	3798 (5)	1664 (4)	H(7B)	4495	3760	853
N(8)	3330 (4)	2647 (4)	2194 (3)	H(9A)	1379	3981	2103
C(9)	1829 (4)	2958 (4)	1882 (4)	H(9B)	1875	2991	1075
C(10)	796 (4)	1842 (4)	2490 (4)	H(10A)	652	2023	3256
C(11)	1409 (4)	236 (4)	2386 (3)	H(10B)	−255	2089	2297
C(12)	3033 (4)	7 (4)	2632 (4)	H(12A)	2997	0	3453
C(13)	3981 (4)	1182 (4)	1988 (4)	H(12B)	3510	−1033	2418
N(14)	483 (3)	−790 (3)	3174 (3)	H(13A)	5000	889	2203
C(15)	1234 (4)	−2015 (4)	3824 (3)	H(13B)	4135	989	1186
C(16)	1571 (5)	−1821 (5)	4792 (4)	H(16)	1318	−697	5085
C(17)	2302 (6)	−2982 (6)	5416 (4)	H(17)	2367	−2638	6158
C(18)	2679 (6)	−4327 (6)	5080 (5)	H(18)	3178	−5264	5429
C(19)	2324 (6)	−4535 (5)	4124 (5)	H(19)	2604	−5441	3728
C(20)	1596 (5)	−3368 (5)	3487 (4)	H(20)	1319	−3409	2682
C(21)	−1053 (4)	−679 (4)	3214 (3)	H(23A)	−1694	−2842	3828
O(22)	−1740 (3)	232 (3)	2610 (3)	H(23B)	−1375	−1876	4812
C(23)	−1867 (5)	−1768 (5)	4052 (4)	H(24A)	−3998	−1887	4914
C(24)	−3542 (6)	−1297 (7)	4250 (5)	H(24B)	−3775	−272	4500
C(25)	1339 (5)	−72 (5)	1282 (4)	H(24C)	−3929	−1266	3478
O(26)	1942 (6)	−1535 (4)	1188 (3)	H(25A)	226	−116	1101
C(27)	2463 (8)	−1806 (8)	203 (5)	H(25B)	1932	639	723
S(1B)	5782	6712	1761	H(27A)	3128	−1181	−242
C(2B)	6739	5004	1820	H(27B)	3033	−2865	262
C(3B)	8247	5057	1575	H(27C)	1533	−1753	−206
C(4B)	8625	6515	1335	H(3B)	9037	4123	1566
C(5B)	7395	7532	1404	H(4B)	9734	6782	1126
				H(5B)	7433	8676	1256

Fig. 1. Bond lengths (Å) and angles (°). The e.s.d.'s for distances and angles involving non-hydrogen atoms are in the ranges 0·005–0·01 Å and 0·3–1·0°.

$w = (5·00 + |F_o| + 0·0250|F_o|^2)^{-1}$. The refinement converged to $R = 0·096$.*

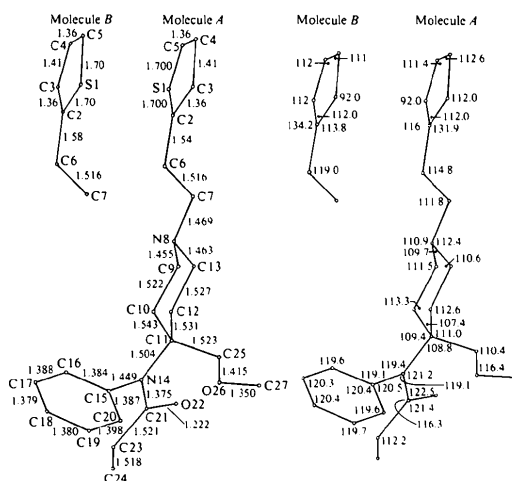The final coordinates are listed in Table 1. Fig. 1 gives bond lengths and angles and the atomic numbering scheme.

Discussion. The structure determination confirms the rotational flexibility of the terminal rings in 4-anilino-piperidines: the thienyl ring is present in two different orientations related to each other by a 164° rotation about C(2)—C(6) [dihedral angles S(1A)—C(2A)—C(6)—C(7) −118·3° and S(1B)—C(2B)—C(6)—C(7) 46·0°].
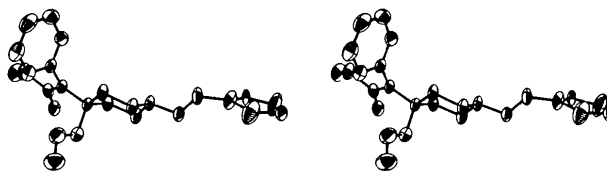
A stereoscopic view of conformation *A* is given in Fig. 2. Conformation *A* closely resembles the conformation of *N*-[4-(methoxymethyl)-1-(2-phenylethyl)-4-piperidinyl]-*N*-phenylpropanamide (Koch, De Ranter, Rolies & Dideberg, 1976), as can be seen from the

Table 2. *Torsion angles* (°) *in the title compound* (*T*)
and in the phenylethyl homologue (*P*)

	T	P
S(1A)—C(2A)—C(6)—C(7)	−118·3 (5)	−80·2 (10)
C(2A)—C(6)—C(7)—N(8)	−160·2 (5)	169·9 (8)
C(6)—C(7)—N(8)—C(9)	165·8 (4)	164·2 (8)
C(6)—C(7)—N(8)—C(13)	−71·0 (5)	−76·5 (9)
C(7)—N(8)—C(9)—C(10)	−175·4 (4)	−178·3 (7)
C(13)—N(8)—C(9)—C(10)	59·8 (5)	61·0 (8)
N(8)—C(9)—C(10)—C(11)	−55·9 (5)	−58·6 (9)
C(9)—C(10)—C(11)—C(12)	50·1 (5)	53·2 (8)
C(9)—C(10)—C(11)—N(14)	168·9 (4)	170·6 (6)
C(9)—C(10)—C(11)—C(25)	−71·1 (5)	−70·3 (8)
C(10)—C(11)—C(12)—C(13)	−51·6 (5)	−53·2 (8)
N(14)—C(11)—C(12)—C(13)	−170·2 (4)	−171·2 (6)
C(25)—C(11)—C(12)—C(13)	69·8 (5)	69·2 (8)
C(11)—C(12)—C(13)—N(8)	59·0 (5)	59·5 (8)
C(12)—C(13)—N(8)—C(7)	174·8 (4)	179·4 (6)
C(12)—C(13)—N(8)—C(9)	−61·3 (5)	−61·5 (7)
C(10)—C(11)—N(14)—C(15)	−132·5 (4)	−122·0 (7)
C(12)—C(11)—N(14)—C(15)	−15·1 (5)	−5·3 (9)
C(25)—C(11)—N(14)—C(15)	106·1 (4)	117·2 (7)
C(10)—C(11)—N(14)—C(21)	54·2 (5)	60·3 (9)
C(12)—C(11)—N(14)—C(21)	171·6 (4)	177·1 (7)
C(25)—C(11)—N(14)—C(21)	−67·1 (4)	−60·5 (9)
C(11)—N(14)—C(15)—C(20)	−90·3 (5)	−82·7 (9)
C(21)—N(14)—C(15)—C(20)	83·1 (5)	95·0 (8)
C(11)—N(14)—C(21)—O(22)	1·1 (7)	−1·2 (12)
C(11)—N(14)—C(21)—C(23)	−179·3 (4)	177·7 (7)
C(15)—N(14)—C(21)—O(22)	−172·1 (4)	−178·9 (7)
C(15)—N(14)—C(21)—C(23)	7·4 (6)	0·0 (9)
N(14)—C(21)—C(23)—C(24)	163·4 (4)	−174·4 (7)
O(22)—C(21)—C(23)—C(24)	−17·0 (7)	4·5 (11)
C(10)—C(11)—C(25)—O(26)	178·4 (4)	177·4 (6)
N(14)—C(11)—C(25)—O(26)	−61·2 (4)	−62·8 (7)
C(12)—C(11)—C(25)—O(26)	59·2 (5)	56·9 (8)
C(11)—C(25)—O(26)—C(27)	−156·3 (5)	−178·3 (7)

corresponding torsion angles in Table 2. The amide
group is planar and forms an angle of 87·0° with the
mean plane of the benzene ring. The angle between the
mean plane of the piperidine ring and that of the
benzene ring is 73·4°. As in the phenylethyl homologue
the orientation of the phenyl group relative to the
piperidine ring is different from that found in the rigid
analgesics (*e.g.* benzomorphans; Gelders, De Ranter &
Schenk, 1979). According to some authors this

Fig. 2. Stereoscopic view of conformation *A*.

orientation is related to analgesic activity (Beckett &
Casy, 1962; Belleau & Morgan, 1974).

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