

***N*-[4-(Methoxymethyl)-1-(2-phenylethyl)-4-piperidiny]-*N*-phenylpropanamide**

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Abstract. $C_{24}H_{32}N_2O_2$, M.W. 380.5; triclinic, $P\bar{1}$; $a = 15.965$ (6), $b = 9.395$ (4), $c = 15.137$ (5) Å, $\alpha = 90.40$ (2), $\beta = 91.32$ (1), $\gamma = 93.18$ (2)°; 25°C; $Z = 4$.

Introduction. The 4-anilinopiperidines, of which fentanyl is the prototype, are among the most potent analgesics known. Recent work has shown that substitutions at the 4-position of the piperidine ring add to the potency (Van Daele, De Bruyn, Boey, Sanckzuck, Agten & Janssen, 1976). For instance, the title compound is 4600 times more potent than morphine. Among the analgesics the 4-anilinopiperidines form a structurally distinct class. They are topologically related to some derivatives of 1-(4-piperidyl)-2-benzimidazolinone and 1,3,8-triazaspiro[4,5]decan-4-one but the structure-activity relationships in both series are entirely different (Janssen & Van der Eycken, 1968).

Transparent, colourless crystals were obtained by slow evaporation from a solution in hexane. The space group was determined from photographs, final cell dimensions and intensities being measured on a Hilger

and Watts computer-controlled diffractometer. The experimental conditions are given in Table 1.

The intensity distribution reflects the fact that the structure is nearly monoclinic, the two molecules in the asymmetric unit being approximately related by $(-x, \frac{1}{2} + y, \frac{1}{2} - z)$.

The structure was solved with *MULTAN* (Germain, Main & Woolfson, 1971). Isotropic and anisotropic weighted block-diagonal least-squares refinement with the X-RAY program system (Stewart, Kruger, Ammon, Dickinson & Hall, 1972) gave a final R of 0.12 for all observed reflexions. The weighting scheme used in the final cycles was $w = (7.0 + |F_o| + 0.0015|F_o|^2)^{-1/2}$. The scattering factors were those of Stewart, Davidson & Simpson (1965). A final difference synthesis showed no outstanding features, except for indications of high thermal motion. The final coordinates and thermal parameters are listed in Table 2.*

Discussion. The conformation of the molecules and the numbering scheme are shown in Fig. 1 and the bond distances and angles in Table 3. The two molecules in the asymmetric unit are identical. The conformation of the 4-anilinopiperidine moiety can be compared with that of the corresponding unsubstituted fragment in *N*-{1-[3-(*p*-fluorobenzoyl)propyl]-4-piperidyl}propionanilide, FBPA (Koch & Evrard, 1974).

The only large differences in the torsion angles (Table 4) are those of C(13)-C(12)-N(18)-C(23) and C(12)-N(18)-C(23)-C(24). The amide group is planar and forms an angle of 85° with the mean plane of the benzene ring. The angle between the mean plane of the piperidine ring and the anilino group is 83°.

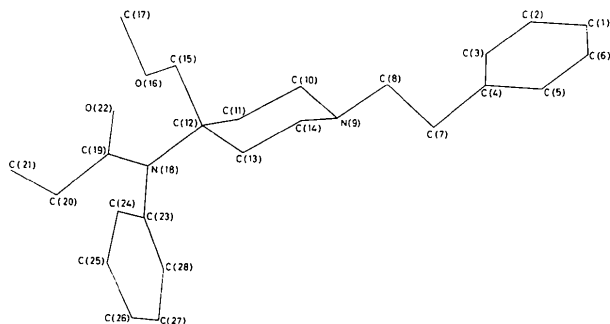
A computer program (Koch, 1973) was used to calculate the conformational energy of the molecule and

Table 1. *Experimental conditions*

Source Cu $K\alpha$, Ni-filter, $\lambda = 1.5418$ Å, ω - 2θ step scan
 $\theta_{\max} = 55^\circ$; confidence level 2.5

Total number of independent reflexions: 4199

Total observed: 3375

Fig. 1. Conformation and atomic numbering of $C_{24}H_{32}N_2O_2$.

* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 31809 (29 pp., 1 microfiche). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

of fentanyl. For the latter calculation the coordinates of the appropriate fragment of FBPA were combined with the phenylethyl chain of the title compound. The torsion angles C(13)–C(12)–N(18)–C(19) and C(12)–N(18)–C(23)–C(24) were incremented from 0 to 360° and 0 to 180°, respectively, in steps of 10°. The remaining torsion angles were fixed at their experimental values. The energy was evaluated as the sum of the torsional energy and the van der Waals interactions

between non-bonded atoms. The resulting energy map (Fig. 2) shows that the molecules are quite rigid. Obviously, the value of C(13)–C(12)–N(18)–C(19) will always be close to 90°. Thus the topological analogy with derivatives of 1,3,8-triazaspiro[4,5]decan-4-one, where this torsion angle has a value of 180° (Koch, 1973), does not correspond to any structural analogy. The orientation of the phenyl group relative to the piperidine ring is different from that found in the rigid

Table 2. Final positional and thermal parameters ($\times 10^4$) (with standard deviations in parentheses)

$$T = \exp [-2\pi^2(U_{11}h^2a^{*2} + \dots + 2U_{12}hka^*b^* + \dots)].$$

	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> ₁₁	<i>U</i> ₂₂	<i>U</i> ₃₃	<i>U</i> ₁₂	<i>U</i> ₁₃	<i>U</i> ₂₃
C(1)	−1386 (6)	3785 (6)	−4491 (6)	1213	715	1016	70	−384	97
C(2)	−532 (6)	3532 (6)	−4463 (6)	1376	867	797	−306	113	−104
C(3)	−142 (7)	3243 (10)	−3674 (6)	837	721	891	−224	115	−125
C(4)	−565 (6)	3193 (8)	−2897 (5)	705	547	556	33	−139	49
C(5)	−1420 (7)	3446 (9)	−2925 (6)	1032	610	862	10	92	−152
C(6)	−1818 (6)	3734 (6)	−3698 (6)	631	621	1733	106	−225	−173
C(7)	−135 (8)	2845 (11)	−2023 (7)	1176	816	1025	−190	−608	162
C(8)	363 (6)	4215 (9)	−1661 (6)	846	527	763	−7	−335	−14
N(9)	902 (5)	3844 (6)	−906 (4)	687	518	520	30	−148	9
C(10)	1174 (6)	5171 (9)	−427 (5)	781	553	593	79	−46	−54
C(11)	1720 (6)	4847 (9)	389 (5)	580	675	526	147	−2	−80
C(12)	2513 (5)	4054 (7)	128 (4)	556	460	378	−39	33	19
C(13)	2211 (5)	2748 (8)	−428 (5)	643	490	479	54	−99	−63
C(14)	1648 (5)	3153 (8)	−1204 (5)	563	597	549	69	−103	−32
C(15)	3136 (6)	5054 (9)	−360 (5)	763	653	530	−10	79	123
O(16)	3828 (4)	4261 (7)	−617 (4)	772	1105	836	9	267	277
C(17)	4414 (8)	5142 (15)	−1097 (8)	1032	1646	973	−198	294	192
N(18)	2950 (4)	3541 (6)	959 (4)	509	461	383	1	−9	24
C(19)	3250 (5)	4454 (8)	1594 (5)	457	621	471	−58	86	−61
C(20)	3711 (6)	3835 (10)	2392 (5)	749	810	529	−128	−112	21
C(21)	4098 (7)	5015 (11)	3027 (6)	771	1156	570	−159	−146	−158
O(22)	3172 (4)	5754 (6)	1538 (4)	805	569	712	−83	−81	−95
C(23)	3075 (5)	2049 (8)	1057 (4)	537	571	419	−37	−28	70
C(24)	3759 (6)	1469 (9)	662 (6)	704	696	740	208	−106	49
C(25)	3878 (6)	−38 (6)	755 (6)	947	938	973	387	−232	−113
C(26)	3300 (6)	−864 (6)	1240 (6)	1280	716	908	96	−410	10
C(27)	2613 (6)	−282 (6)	1636 (6)	1183	788	608	−183	−214	189
C(28)	2501 (6)	1229 (9)	1538 (5)	782	656	477	−225	−104	112
C(29)	11513 (6)	9103 (6)	9375 (6)	1558	626	1178	218	−617	−186
C(30)	10653 (6)	8751 (6)	9413 (6)	1616	829	710	541	67	60
C(31)	10200 (7)	8375 (10)	8664 (7)	1036	734	924	268	−13	109
C(32)	10574 (6)	8330 (8)	7849 (5)	816	518	578	192	−125	−54
C(33)	11440 (7)	8685 (10)	7811 (7)	1012	690	989	140	120	266
C(34)	11890 (6)	9058 (6)	8552 (6)	728	623	1937	−110	−384	202
C(35)	10042 (8)	7860 (11)	7044 (7)	1566	752	1045	433	−729	−195
C(36)	9594 (6)	9126 (8)	6639 (5)	655	554	676	42	−289	−50
N(37)	9038 (4)	8632 (6)	5897 (4)	697	540	511	72	−49	12
C(38)	8293 (6)	7852 (8)	6214 (5)	705	584	510	−179	−155	52
C(39)	7704 (6)	7306 (8)	5447 (5)	738	501	452	49	−126	19
C(40)	7419 (5)	8543 (7)	4871 (4)	600	437	369	63	14	−26
C(41)	8199 (5)	9478 (8)	4605 (5)	524	588	457	−32	−15	25
C(42)	8781 (6)	9926 (8)	5406 (5)	761	545	588	77	−86	27
C(43)	6811 (6)	9454 (8)	5394 (5)	569	560	587	3	112	−70
O(44)	6116 (4)	8555 (7)	5652 (4)	769	900	907	−21	291	−223
C(45)	5546 (8)	9323 (13)	6186 (7)	953	1334	1032	233	342	−259
N(46)	6976 (4)	7922 (6)	4059 (3)	507	406	405	64	30	−6
C(47)	6659 (5)	8758 (8)	3419 (5)	563	515	510	98	29	−11
C(48)	6199 (7)	8008 (10)	2639 (6)	888	808	621	128	−324	−27
C(49)	5787 (7)	9092 (12)	2014 (6)	835	1202	684	296	−249	6
O(50)	6736 (4)	10079 (5)	3467 (4)	828	502	711	94	−131	54
C(51)	6868 (5)	6412 (8)	3959 (4)	444	554	444	56	−24	−44
C(52)	6215 (6)	5664 (9)	4363 (5)	558	644	733	−100	−53	20
C(53)	6117 (6)	4144 (6)	4259 (6)	972	748	1042	−207	−228	138
C(54)	6690 (6)	3453 (6)	3747 (6)	1004	570	1081	18	−323	2
C(55)	7351 (6)	4209 (6)	3338 (6)	1172	707	692	307	−202	−227
C(56)	7447 (6)	5715 (9)	3442 (5)	760	675	480	244	−126	−102

Table 3. Intramolecular bond distances (Å) and angles (°) (with standard deviations in parentheses)

C(1)—C(2)	1.397 (13)	C(29)—C(30)	1.397 (13)
C(1)—C(6)	1.398 (13)	C(29)—C(34)	1.397 (13)
C(2)—C(3)	1.370 (14)	C(30)—C(31)	1.364 (14)
C(3)—C(4)	1.371 (13)	C(31)—C(32)	1.385 (13)
C(4)—C(5)	1.399 (14)	C(32)—C(33)	1.406 (15)
C(4)—C(7)	1.522 (14)	C(32)—C(35)	1.517 (14)
C(5)—C(6)	1.355 (13)	C(33)—C(34)	1.352 (14)
C(7)—C(8)	1.564 (14)	C(35)—C(36)	1.545 (14)
C(8)—N(9)	1.470 (11)	C(36)—N(37)	1.472 (11)
N(9)—C(10)	1.477 (10)	N(37)—C(38)	1.455 (11)
N(9)—C(14)	1.466 (11)	N(37)—C(42)	1.501 (10)
C(10)—C(11)	1.538 (12)	C(38)—C(39)	1.544 (11)
C(11)—C(12)	1.562 (12)	C(39)—C(40)	1.540 (10)
C(12)—C(13)	1.532 (10)	C(40)—C(41)	1.547 (11)
C(12)—C(15)	1.536 (11)	C(40)—C(43)	1.555 (11)
C(12)—N(18)	1.518 (9)	C(40)—N(46)	1.502 (9)
C(13)—C(14)	1.525 (11)	C(41)—C(42)	1.552 (12)
C(15)—C(16)	1.425 (12)	C(43)—O(44)	1.421 (11)
O(16)—C(17)	1.429 (15)	O(44)—C(45)	1.450 (14)
N(18)—C(19)	1.346 (9)	N(46)—C(47)	1.357 (9)
N(18)—C(23)	1.436 (9)	N(46)—C(51)	1.427 (9)
C(19)—C(20)	1.534 (11)	C(47)—C(48)	1.524 (12)
C(19)—O(22)	1.238 (9)	C(47)—O(50)	1.242 (9)
C(20)—C(21)	1.555 (13)	C(48)—C(49)	1.557 (14)
C(23)—C(24)	1.392 (12)	C(51)—C(52)	1.382 (12)
C(23)—C(28)	1.387 (12)	C(51)—C(56)	1.410 (11)
C(24)—C(25)	1.447 (11)	C(52)—C(53)	1.435 (10)
C(25)—C(26)	1.397 (12)	C(53)—C(54)	1.397 (12)
C(26)—C(27)	1.398 (13)	C(54)—C(55)	1.398 (12)
C(27)—C(28)	1.449 (10)	C(55)—C(56)	1.422 (10)
C(2)—C(1)—C(6)	118.1 (8)	C(30)—C(29)—C(34)	118.1 (8)
C(1)—C(2)—C(3)	120.0 (8)	C(29)—C(30)—C(31)	120.5 (8)
C(2)—C(3)—C(4)	121.9 (9)	C(30)—C(31)—C(32)	121.4 (9)
C(3)—C(4)—C(5)	118.0 (8)	C(31)—C(32)—C(33)	118.1 (9)
C(3)—C(4)—C(7)	121.9 (8)	C(31)—C(32)—C(35)	118.9 (8)
C(5)—C(4)—C(7)	120.0 (8)	C(33)—C(32)—C(35)	123.0 (8)
C(4)—C(5)—C(6)	120.9 (9)	C(32)—C(33)—C(34)	120.6 (9)
C(1)—C(6)—C(5)	121.0 (8)	C(29)—C(34)—C(33)	121.3 (8)
C(4)—C(7)—C(8)	108.9 (8)	C(32)—C(35)—C(36)	111.1 (8)
C(7)—C(8)—N(9)	109.7 (7)	C(35)—C(36)—N(37)	110.3 (7)
C(8)—N(9)—C(10)	108.3 (6)	C(36)—N(37)—C(38)	110.9 (6)
C(8)—N(9)—C(14)	111.0 (6)	C(36)—N(37)—C(42)	107.5 (6)
C(10)—N(9)—C(14)	108.7 (6)	C(38)—N(37)—C(42)	109.2 (6)
N(9)—C(10)—C(11)	110.8 (7)	N(37)—C(38)—C(39)	111.9 (7)
C(10)—C(11)—C(12)	111.4 (7)	C(38)—C(39)—C(40)	111.4 (6)
C(11)—C(12)—C(13)	107.4 (6)	C(39)—C(40)—C(41)	109.0 (6)
C(11)—C(12)—C(15)	110.9 (6)	C(39)—C(40)—C(43)	110.0 (6)
C(11)—C(12)—N(18)	109.2 (6)	C(39)—C(40)—N(46)	108.3 (6)
C(13)—C(12)—C(15)	112.7 (6)	C(41)—C(40)—C(43)	110.0 (6)
C(13)—C(12)—N(18)	108.4 (6)	C(41)—C(40)—N(46)	109.8 (6)
C(15)—C(12)—N(18)	108.1 (6)	C(43)—C(40)—N(46)	109.7 (6)
C(12)—C(13)—C(14)	111.7 (6)	C(40)—C(41)—C(42)	112.8 (6)
N(9)—C(14)—C(13)	111.7 (6)	N(37)—C(42)—C(41)	110.2 (7)
C(12)—C(15)—O(16)	108.5 (7)	C(40)—C(43)—O(44)	108.5 (6)
C(15)—O(16)—C(17)	110.5 (8)	C(43)—O(44)—C(45)	111.3 (7)
C(12)—N(18)—C(19)	121.8 (8)	C(40)—N(46)—C(47)	121.9 (6)
C(12)—N(18)—C(23)	119.3 (6)	C(40)—N(46)—C(51)	119.5 (6)
C(19)—N(18)—C(23)	118.9 (6)	C(47)—N(46)—C(51)	118.6 (6)
N(18)—C(19)—C(20)	117.8 (7)	N(46)—C(47)—C(48)	117.2 (7)
N(18)—C(19)—O(22)	121.7 (7)	N(46)—C(47)—O(50)	121.6 (7)
C(20)—C(19)—O(22)	120.5 (7)	C(48)—C(47)—O(50)	121.2 (7)
C(19)—C(20)—C(21)	112.3 (7)	C(47)—C(48)—C(49)	111.5 (8)
N(18)—C(23)—C(24)	119.3 (7)	N(46)—C(51)—C(52)	120.5 (7)
N(18)—C(23)—C(28)	118.5 (7)	N(46)—C(51)—C(56)	118.1 (7)
C(24)—C(23)—C(28)	122.2 (8)	C(52)—C(51)—C(56)	121.5 (7)
C(23)—C(24)—C(25)	119.1 (8)	C(51)—C(52)—C(53)	119.8 (8)
C(24)—C(25)—C(26)	118.7 (8)	C(52)—C(53)—C(54)	118.8 (8)
C(25)—C(26)—C(27)	122.2 (8)	C(53)—C(54)—C(55)	121.5 (8)
C(26)—C(27)—C(28)	118.5 (7)	C(54)—C(55)—C(56)	119.7 (8)
C(23)—C(28)—C(27)	119.3 (7)	C(51)—C(56)—C(55)	118.8 (7)

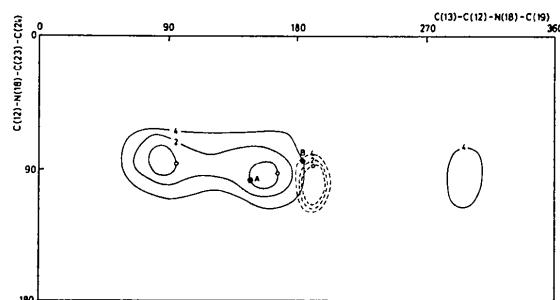
Fig. 2. Results of the conformational calculation for fentanyl (A: —) and for the title compound (B: - - - -). The dots (A, B) indicate the experimental values. The contours are in kcal mol⁻¹.

Table 4. Torsion angles in the title compound (A) and in FBPA

	A	FBPA
C(12)—C(13)—C(14)—N(9)	-59.5°	-58.2°
C(12)—C(11)—C(10)—N(9)	58.7	58.9
C(14)—C(13)—C(12)—N(18)	171.1	-176.7
C(13)—C(12)—N(18)—C(23)	5.3	-43.8
C(12)—N(18)—C(23)—C(24)	82.7	102.6
C(12)—N(18)—C(19)—O(22)	1.3	-2.5
C(12)—N(18)—C(19)—C(20)	-177.7	-179.8
N(18)—C(19)—C(20)—C(21)	174.5	-173.1

analgesics (e.g. morphine). This orientation is one of the important factors which determine activity according to theories on analgesic activity (Beckett & Casy, 1962; Belleau & Morgan, 1974). Thus it is clear that since the 4-anilino piperidines are rigid molecules their mode of interaction with analgesic receptors must be different from the classical analgesics.

References

- BECKETT, A. H. & CASY, A. F. (1962). *Progress in Medicinal Chemistry*, edited by G. P. ELLIS & G. B. WEST, p. 43. London: Butterworths.
- BELLEAU, B. & MORGAN, P. (1974). *J. Med. Chem.* **17**, 907-908.
- GERMAIN, G., MAIN, P. & WOOLFSON, M. M. (1971). *Acta Cryst.* **A27**, 368-376.
- JANSSEN, P. A. J. & VAN DER EYCKEN, C. A. M. (1968). *Drugs Affecting the Central Nervous System*, Vol. 2, edited by A. BURGER, pp. 25-60. New York: Marcel Dekker.
- KOCH, M. H. J. (1973). *Acta Cryst.* **B29**, 379-382.
- KOCH, M. H. J. & EVRARD, G. (1974). *Acta Cryst.* **B30**, 237-239.
- STEWART, J. M., KRUGER, G. J., AMMON, H. L., DICKINSON, C. & HALL, S. R. (1972). The X-RAY system - version of June 1972. Tech. Rep. TR-192. Computer Science Center, Univ. of Maryland, College Park, Maryland.
- STEWART, R. F., DAVIDSON, E. & SIMPSON, W. (1965). *J. Chem. Phys.* **42**, 3175-3187.
- VAN DAELE, P. G. H., DE BRUYN, M. F. L., BOEY, J. M., SANCKZUCK, S., AGTEN, J. T. M. & JANSSEN, P. A. J. (1976). *Arzneimittel-Forsch.* In the press.