Synthesis, and Structural, Conformational and Pharmacological Studies of new Fentanyl Derivatives of the Norgranatane System

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A series of 9-phenethyl-3-α-(*N*-arylamido)norgranatanes have been synthesized and studied by ^1H and ^{13}C NMR spectroscopy, and the crystal structure of 9-phenethyl-3-α-(*N*-*p*-tolyl-*p*-chlorobenzamido)norgranatane has been determined by X-ray diffraction. The compounds studied display in deuteriochloroform the same preferred chair–boat conformation with the disubstituted ring in a slightly distorted boat form. This bicycle conformation is similar to that found for compound **4f** in the crystal state.

In vivo pharmacological testing demonstrated that compounds **4a–h** were inactive in the analgesic test, with the exception of compound **4b** (the *N*-*p*-tolylpropanamido derivative) which showed an ED_{50} of 100 mg kg^{-1} *p.o.*

The accentuated interest in the piperidine class of opiate agonists continues to be expressed in the pharmaceutical community; the synthesis and biological properties of these agents have also been the subject of ongoing investigations in these laboratories.

The 4-anilidopiperidine class of synthetic opioid analgesics is characterized by high potency and rapid onset of action. Fentanyl[1] is the prototype of the series. Intravenous infusion of fentanyl concurrently with a skeletal muscle relaxant and an inhalation anaesthetic is a widely accepted practice in surgical procedures.

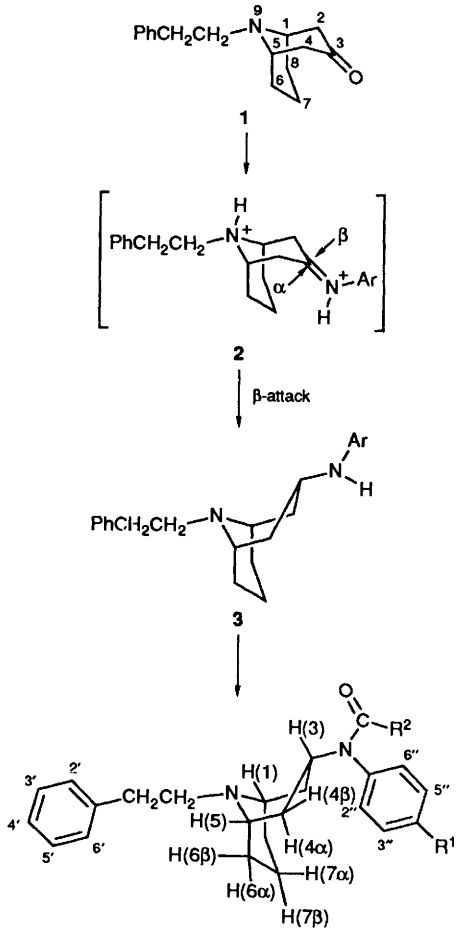
Due to the rise in the number of outpatient surgical procedures, short-acting analgesics with less severe untoward opioid side effects, such as respiratory and cardiovascular depression, are in high demand to allow patients to be ambulatory.

In an attempt to design analogues of the 4-anilidopiperidine analgesics, that would have measurable analgesic activity and would allow for a determination of conformational influences on this activity, we have undertaken a study of granatane analogues of this class of basic anilide analgesics. In this line, and in connection with our previous studies on granatane derivatives,[2–7] we report in this paper the synthesis and structural analysis, carried out with the aid of ^1H and ^{13}C NMR spectroscopy, of a series of *N*-phenethyl-3-α-(*N*-arylamido)-norgranatane derivatives **4a–h**. In order to determine their preferred conformation both in solution and in the solid state, the crystal structure of compound **4f** has also been determined. In an attempt to gain additional information concerning the effects of stereochemical factors on analgesic activity, a pharmacological study of compounds **4a–h** has been carried out.

Results and Discussion

Synthesis.—Compounds **4a–h** were prepared as shown in Scheme 1. Reaction of *N*-phenethylnorgranatan-3-one **1**[8] with the corresponding aromatic amine at pH *ca.* 6.6 in the presence of $NaBH_3CN$ led to the amines **3** *via* reductive amination.[7,9]

The most stable conformation of **1** in $CDCl_3$ solution is as represented in Scheme 1.[4] By assuming the same preferred



Compound	R^1	R^2	Compound	R^1	R^2
4a	H	Et	**4e**	H	*p*-Cl-C_6H_4
4b	Me	Et	**4f**	Me	*p*-Cl-C_6H_4
4c	OMe	Et	**4g**	OMe	*p*-Cl-C_6H_4
4d	F	Et	**4h**	F	*p*-Cl-C_6H_4

Scheme 1

Table 1 Experimental data and structure refinement procedures

Crystal data	
Formula	$C_{30}H_{33}N_2OCl$
Symmetry	Monoclinic, $P2_1/n$
Unit cell determination:	Least-squares fit from 55
Unit cell dimensions	24.9873(16), 9.1799(3), 11.6306(4), 90.0, 100.466(4), 90.0
Packing: $V(A^3)$, Z	2623.47(16), 4
Dc (g cm^{-1}), M, $F(000)$	1.1977, 473.056, 1008
μ (cm^{-1})	14.64
Experimental data	
Technique	Four circle diffractometer: Phillips PW1100. Bisecting geometry Graphite oriented monochromator: Cu-Kα $w/2\Theta$ scans, up Θmax. 65°.
Number reflections:	
Measured	4468
Observed	2810 [$2\sigma(I)$ criterion]
Range of hkl	−29 29, 0 11, 0 14
Solution and refinement	
Solution	Direct methods and Fourier synthesis
Refinement	Full-matrix L.S. on Fo
H atoms	Difference synthesis
w-scheme	Empirical as to give no trends in $\langle w\Delta F\rangle vs\langle F\text{obs}\rangle$ and $\langle \sin\Theta/\lambda\rangle$
Final F peaks	0.21 eA^{-3}
Final R and Rw	0.080, 0.077
Computer and programs	Vax 11/750, Multan80[10], X-ray System,[11] Pesos,[12] Parst.[13]
Scattering factors	Int. Tables for X-Ray Crystallography[14]
Anomalous dispersion	Int. Tables for X-Ray Crystallography[14]

Table 2 Atomic parameters for $C_{30}H_{33}ClN_2O$

Atom	x	y	z
Cl(19)	0.143 95(6)	0.402 46(18)	0.586 59(14)
O(12)	−0.039 20(17)	0.678 00(43)	0.875 24(36)
N(1)	−0.202 67(16)	0.582 19(46)	0.998 82(34)
N(10)	−0.075 25(15)	0.451 29(41)	0.853 33(32)
C(2)	−0.221 25(25)	0.571 45(84)	0.872 73(52)
C(3)	−0.171 40(25)	0.532 23(84)	0.815 35(48)
C(4)	−0.122 21(20)	0.496 05(57)	0.908 02(43)
C(5)	−0.135 95(22)	0.385 34(59)	0.994 73(47)
C(6)	−0.185 82(21)	0.436 73(56)	1.046 47(47)
C(7)	−0.231 88(28)	0.325 61(81)	1.024 79(64)
C(8)	−0.254 92(33)	0.313 99(118)	0.896 27(81)
C(9)	−0.268 17(29)	0.461 71(138)	0.839 53(74)
C(11)	−0.037 52(20)	0.553 12(57)	0.839 75(43)
C(13)	0.007 02(19)	0.507 07(53)	0.775 83(40)
C(14)	0.041 53(20)	0.392 58(60)	0.811 85(47)
C(15)	0.083 67(21)	0.360 76(63)	0.753 21(50)
C(16)	0.089 94(19)	0.444 02(60)	0.659 28(44)
C(17)	0.056 35(26)	0.556 68(72)	0.621 91(58)
C(18)	0.015 01(26)	0.588 63(69)	0.681 21(57)
C(20)	−0.079 13(18)	0.315 38(52)	0.789 49(42)
C(21)	−0.098 05(20)	0.314 73(62)	0.670 01(45)
C(22)	−0.099 75(22)	0.184 24(69)	0.609 24(51)
C(23)	−0.083 38(22)	0.054 66(62)	0.664 43(58)
C(24)	−0.065 58(23)	0.058 28(62)	0.783 46(57)
C(25)	−0.063 07(21)	0.186 63(55)	0.846 72(49)
C(26)	−0.085 14(38)	−0.083 98(89)	0.595 12(85)
C(27)	−0.240 99(28)	0.655 91(71)	1.060 56(63)
C(28)	−0.241 96(33)	0.819 87(90)	1.038 28(72)
C(29)	−0.190 73(29)	0.899 96(63)	1.088 24(54)
C(30)	−0.146 98(32)	0.901 93(73)	1.031 42(56)
C(31)	−0.099 44(39)	0.971 65(89)	1.079 85(82)
C(32)	−0.096 04(54)	1.042 15(107)	1.184 69(110)
C(33)	−0.138 81(66)	1.038 49(121)	1.240 91(91)
C(34)	−0.186 37(45)	0.968 89(96)	1.193 31(70)

Table 3 Bond lengths (Å)

Cl(19)–C(16)	1.760(5)
O(12)–C(11)	1.222(7)
N(1)–C(2)	1.459(7)
N(1)–C(6)	1.477(7)
N(1)–C(27)	1.463(9)
N(10)–C(4)	1.490(7)
N(10)–C(11)	1.357(6)
N(10)–C(20)	1.446(6)
C(2)–C(3)	1.558(9)
C(2)–C(9)	1.541(12)
C(3)–C(4)	1.517(7)
C(4)–C(5)	1.514(8)
C(5)–C(6)	1.552(8)
C(6)–C(7)	1.524(9)
C(7)–C(8)	1.505(11)
C(8)–C(9)	1.518(16)
C(11)–C(13)	1.507(7)
C(13)–C(14)	1.376(7)
C(13)–C(18)	1.375(8)
C(14)–C(15)	1.386(8)
C(15)–C(16)	1.365(8)
C(16)–C(17)	1.353(8)
C(17)–C(18)	1.374(10)
C(20)–C(21)	1.384(7)
C(20)–C(25)	1.380(7)
C(21)–C(22)	1.388(8)
C(22)–C(23)	1.378(8)
C(23)–C(24)	1.375(9)
C(23)–C(26)	1.503(11)
C(24)–C(25)	1.384(8)
C(27)–C(28)	1.527(10)
C(28)–C(29)	1.499(10)
C(29)–C(30)	1.376(11)
C(29)–C(34)	1.363(10)
C(30)–C(31)	1.377(11)
C(31)–C(32)	1.369(15)
C(32)–C(33)	1.301(21)
C(33)–C(34)	1.374(17)

conformation for **2** in solution, and on kinetic grounds, attack by the hydride anion in the β-direction is favoured [in the α-direction, the C(7) methylene group would hinder the hydride attack], and according to this assumption, in this case, compounds **3** were the only ones isolated, in agreement with studies of related systems.[2,7]

The amides **4a–h** were prepared by treatment of the corresponding amine with the appropriate acyl chloride.

Structural Study.—Description of the structure of compound **4f**.* The main crystallographic data and the structure determination procedures are given in Table 1.[10–14] Table 2 shows the atomic parameters and Tables 3 and 4 show bond lengths, and bond and torsion angles respectively. Several significant torsion angles in which hydrogen atoms are involved are also given. Fig. 1 shows the structure.[15,†]

The bicyclic system shows a distorted chair–boat conformation, as is indicated by the torsion angles. Both rings have a dominant mirror symmetry with the pseudo mirror plane passing through N(1), C(4) and C(8); this plane is also a mirror plane of the *p*-tolyl group. However, the *p*-chlorobenzoyl and phenethyl groups deviate from this symmetry.

The disubstituted ring adopts a boat conformation, N(1) and C(4) being 0.725(4) and 0.634(5) Å, respectively, from the plane

* In this description and in Tables 2, 3 and 4 numbers corresponding to those given in Figure 1 are used.

† Lists of hydrogen atom co-ordinates and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). For details of the deposition scheme see 'Instructions for Authors,' *J. Chem. Soc., Perkin Trans. 2*, 1992, issue 1.

Table 4 Bond angles and torsion angles (°)

C(6)–N(1)–C(27)	113.7(5)	C(14)–C(15)–C(16)	118.9(5)
C(2)–N(1)–C(27)	114.0(5)	Cl(19)–C(16)–C(15)	118.2(4)
C(2)–N(1)–C(6)	109.4(4)	C(15)–C(16)–C(17)	122.0(5)
C(11)–N(10)–C(20)	121.2(4)	Cl(19)–C(16)–C(17)	119.8(4)
C(4)–N(10)–C(20)	118.2(4)	C(16)–C(17)–C(18)	118.7(6)
C(4)–N(10)–C(11)	118.5(4)	C(13)–C(18)–C(17)	121.1(6)
N(1)–C(2)–C(9)	112.6(5)	N(10)–C(20)–C(25)	120.3(4)
N(1)–C(2)–C(3)	108.2(5)	N(10)–C(20)–C(21)	119.9(4)
C(3)–C(2)–C(9)	111.9(6)	C(21)–C(20)–C(25)	119.8(5)
C(2)–C(3)–C(4)	110.7(5)	C(20)–C(21)–C(22)	119.2(5)
N(10)–C(4)–C(3)	110.9(4)	C(21)–C(22)–C(23)	121.9(5)
C(3)–C(4)–C(5)	111.6(4)	C(22)–C(23)–C(26)	120.3(6)
N(10)–C(4)–C(5)	113.0(4)	C(22)–C(23)–C(24)	117.5(5)
C(4)–C(5)–C(6)	110.4(4)	C(24)–C(23)–C(26)	122.2(6)
N(1)–C(6)–C(5)	108.9(4)	C(23)–C(24)–C(25)	122.0(5)
C(5)–C(6)–C(7)	111.6(5)	C(20)–C(25)–C(24)	119.4(5)
N(1)–C(6)–C(7)	112.8(5)	N(1)–C(27)–C(28)	111.4(6)
C(6)–C(7)–C(8)	110.7(6)	C(27)–C(28)–C(29)	115.6(6)
C(7)–C(8)–C(9)	112.5(8)	C(28)–C(29)–C(34)	119.9(7)
C(2)–C(9)–C(8)	112.3(6)	C(28)–C(29)–C(30)	121.1(6)
O(12)–C(11)–N(10)	122.7(5)	C(30)–C(29)–C(34)	118.9(7)
N(10)–C(11)–C(13)	117.1(4)	C(29)–C(30)–C(31)	120.7(7)
O(12)–C(11)–C(13)	120.2(5)	C(30)–C(31)–C(32)	119.6(9)
C(11)–C(13)–C(18)	118.0(5)	C(31)–C(32)–C(33)	119.5(1.1)
C(11)–C(13)–C(14)	122.8(4)	C(32)–C(33)–C(34)	121.3(1.0)
C(14)–C(13)–C(18)	119.0(5)	C(29)–C(34)–C(33)	120.0(9)
C(13)–C(14)–C(15)	120.1(5)		
Torsion angles			
C(2)–N(1)–C(6)–C(7)	−60.09(0.60)	H(4)–C(4)–C(5)–H(51)	−58.31(5.77)
C(2)–N(1)–C(6)–C(5)	64.33(0.54)	H(4)–C(4)–C(5)–H(52)	−174.29(5.50)
C(6)–N(1)–C(2)–C(9)	57.08(0.68)	C(4)–C(5)–C(6)–N(1)	−2.80(0.57)
C(6)–N(1)–C(2)–C(3)	−67.15(0.57)	H(52)–C(5)–C(6)–H(6)	128.02(5.43)
C(4)–N(10)–C(11)–O(12)	3.39(0.72)	H(51)–C(5)–C(6)–H(6)	14.27(5.60)
C(20)–N(10)–C(11)–O(12)	166.52(0.47)	N(1)–C(6)–C(7)–C(8)	56.43(0.73)
C(11)–N(10)–C(20)–C(21)	−69.99(0.61)	H(6)–C(6)–C(7)–H(71)	45.14(5.66)
C(4)–N(10)–C(20)–C(21)	93.19(0.51)	H(6)–C(6)–C(7)–H(72)	−66.69(5.42)
C(11)–N(10)–C(20)–C(25)	108.76(0.55)	C(6)–C(7)–C(8)–C(9)	−49.43(0.92)
C(4)–N(10)–C(20)–C(25)	−88.06(0.55)	H(72)–C(7)–C(8)–H(81)	6.15(5.65)
C(4)–N(10)–C(11)–C(13)	−175.40(0.40)	H(71)–C(7)–C(8)–H(81)	−48.48(5.72)
C(20)–N(10)–C(4)–C(3)	−67.57(0.55)	H(72)–C(7)–C(8)–H(82)	−48.18(5.59)
C(11)–N(10)–C(4)–C(3)	96.07(0.53)	H(71)–C(7)–C(8)–H(82)	−163.81(5.61)
C(11)–N(10)–C(4)–C(5)	−137.84(0.45)	C(7)–C(8)–C(9)–C(2)	47.59(1.01)
C(20)–N(10)–C(4)–C(5)	58.52(0.55)	H(82)–C(8)–C(9)–H(91)	49.58(6.35)
C(20)–N(10)–C(11)–C(13)	−12.27(0.64)	H(81)–C(8)–C(9)–H(91)	−63.65(6.32)
N(1)–C(2)–C(9)–C(8)	−51.91(0.90)	H(82)–C(8)–C(9)–H(92)	168.45(5.69)
N(1)–C(2)–C(3)–C(4)	8.38(0.68)	H(81)–C(8)–C(9)–H(92)	55.21(5.72)
H(2)–C(2)–C(9)–H(91)	61.13(6.45)	N(10)–C(11)–C(13)–C(14)	−57.83(0.67)
H(2)–C(2)–C(9)–H(92)	−51.71(5.92)	O(12)–C(11)–C(13)–C(14)	123.34(0.57)
H(2)–C(2)–C(3)–H(31)	−5.91(5.86)	N(10)–C(11)–C(13)–C(18)	125.75(0.54)
H(2)–C(2)–C(3)–H(32)	−123.64(5.74)	O(12)–C(11)–C(13)–C(18)	−53.08(0.71)
C(2)–C(3)–C(4)–C(5)	50.29(0.64)	C(11)–C(13)–C(18)–C(17)	177.20(0.55)
H(32)–C(3)–C(4)–H(4)	172.53(5.75)	C(11)–C(13)–C(14)–C(15)	−176.31(0.49)
H(31)–C(3)–C(4)–H(4)	56.65(5.81)	N(10)–C(20)–C(25)–C(24)	−178.09(0.47)
C(3)–C(4)–C(5)–C(6)	−53.09(0.59)	N(10)–C(20)–C(21)–C(22)	177.75(0.47)

defined by the other four atoms. Both substituents are in an *exo* position. Ring puckering co-ordinates[16] for this ring are: Φ_2 = 2.5(5)°, Θ_2 = 86.4(4)°, q_2 = 0.788(5), q_3 = 0.049(6) and Q_T = 0.789(5).

The monosubstituted ring is in a chair conformation, with N(1) and C(8) situated 0.673(4) and 0.594(9) Å, respectively, from the plane defined by the other four atoms. The radical attached to N(1) is in the axial position. Ring puckering co-ordinates[16] for this ring are: Φ_2 = 155(6)°, Θ_2 = 173.2(8)°, q_2 = 0.064(7), q_3 = −0.538(8) and Q_T = 0.542(7).

The N(10)–C(11) bond length of 1.357(6) Å in the amide moiety, indicates a bond order between one and two, and shows a conjugation of the lone pair of the N atom with the π-electrons of the C=O group, along the N(10)–C(11)–O(12) chain.

Packing in the unit cell is due only to van der Waals forces.

Following the ideas of Desiraju[17] concerning the way in which aromatic compounds pack in molecular crystals, we have tried to investigate possible interactions between phenyl rings in the compound under study. In an attempt to rationalize the interaction pattern between two phenyl rings, a computer program has been written[18] in order to calculate some geometrical parameters which characterize the relative position and orientation of the rings. Thus, possible interactions between the *p*-chlorophenyl, [A: C(13)–C(18)], the *p*-tolyl [B: C(20)–C(25)] and phenyl [C: C(29)–C(34)] rings were analysed in the crystal, up to a chosen maximum distance between centroids of 6.5 Å. Fig. 2 shows the packing in the unit cell, as seen along the *b*-axis and Table 5 lists some relevant information concerning these interactions, the first ring being in the asymmetric unit.

There seems to be a clear interaction between rings A and C, which are orientated perpendicularly, the centroids being 4.9 Å from each other. The C(15)–H(15) bond points directly towards the centroid of ring C [H(15)–G′ = 2.6 Å], producing the typical T-shaped arrangement of the benzene dimer, which corresponds to the herringbone motif found in the crystal

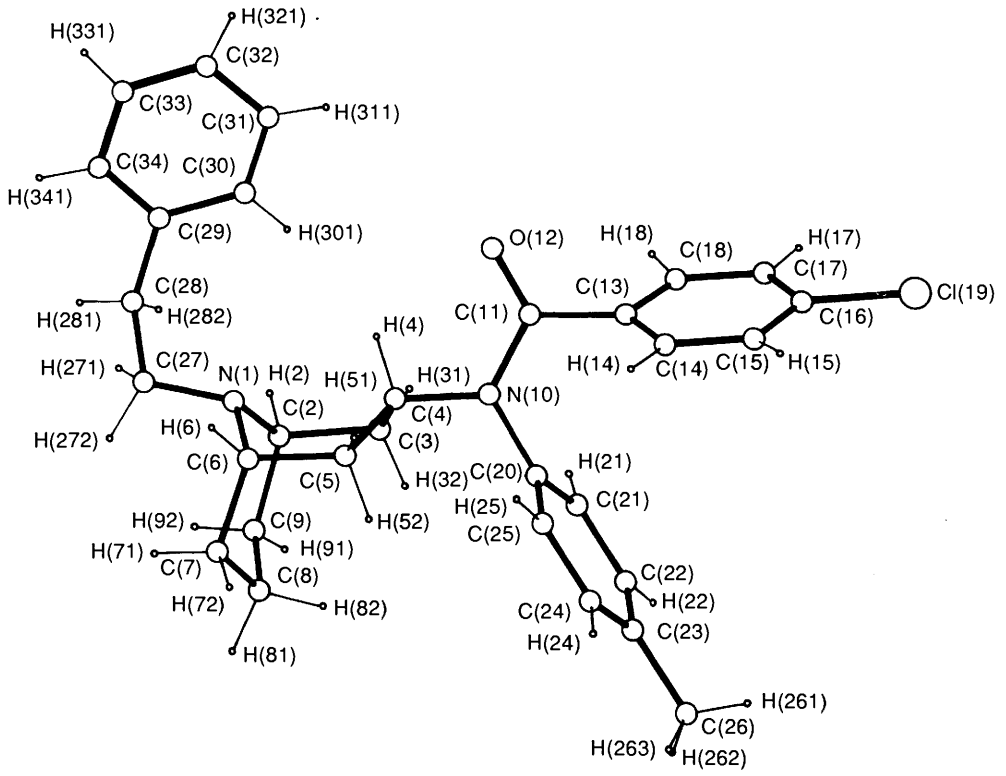


Fig. 1 PLUTO[16] view of compound **4f** showing the numbering scheme

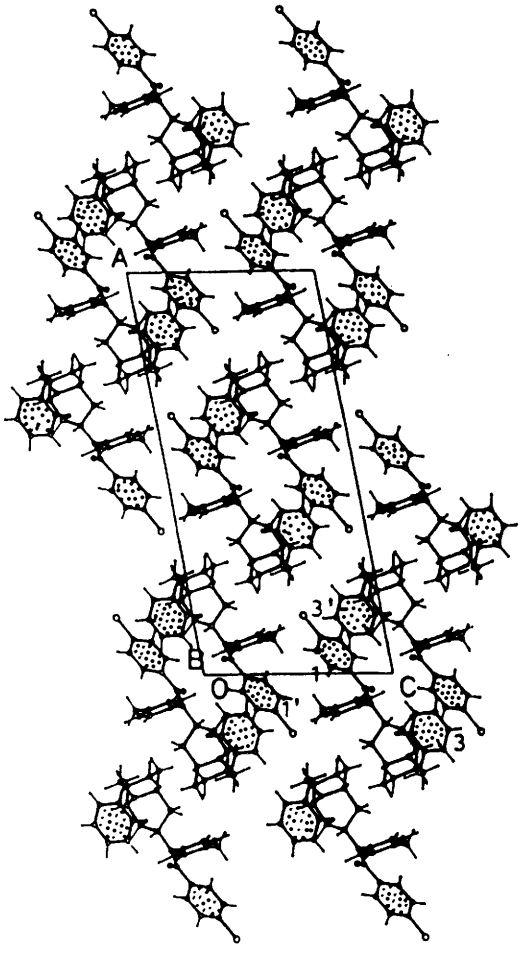


Fig. 2 Packing in the unit cell as seen along the *b*-axis

Table 5 Interaction between phenyl rings in crystal of **4f**[a]

Rings	GG′	*a*	G′P	S′G	*b*	GP′	SG′	*b*′	Symmetry
A *vs.* C′	4.9	96	0.5	4.9	77	4.8	2.6	155	−X, 1 − Y, 2 − Z
A *vs.* A′	5.2	0	3.5	3.9	111				−X, 1 − Y, 1 − Z
B *vs.* C′	5.6	93	3.3	4.1	119	3.2	4.2	111	−X, Y − 1, Z
A *vs.* C′	5.7	97	5.2	4.1	121	3.0	5.2	94	−X, 2 − Y, 2 − Z
B *vs.* C′	5.7	93	4.7	4.3	117	3.3	4.9	99	−X, 1 − Y, 2 − Z
A *vs.* B′	6.2	120	0.3	4.7	120	2.9	3.9	173	−X, 1 − Y, 1 − Z

[a] For each possible Ph · · · Ph′ interaction the following parameters are given: GG′, the distance between centroids; *a*, the angle between L.S. planes; G′P, the distance from G′ to the L.S. plane of the first ring; S′G, the distance from the closest substituent of the second ring to the centroid of the first one; *b*, the angle C′–H′ · · · G at this substituent. GP′, SG′ and *b*′ analogously for the second ring *vs.* first one. All distances are in Å and angles in degrees. The symmetry operation refers to the second ring.

structures of benzene,[19] naphthalene[20] and other aromatics. On the other hand, interaction between two type A rings through a centre of symmetry, with a 0° interplanar angle, also seems to be significant. According to Desiraju, the distance between planes, and the lateral offset of one ring with respect to the other, is in the range encountered in a survey of 110 crystal structures containing aromatic aminoacid residues, which present stacked packing patterns.[21]

These two kinds of contacts define a preferable direction of interaction along the *c*-axis in a zig-zag arrangement. The other four intermolecular contacts given in Table 5 seem to be too weak, owing to the long distances or to the unfavourable orientation of both rings.

NMR Spectra.—The ^{1}H and ^{13}C NMR data of compounds **4a–h** are summarized in Tables 6–8.

The assignment of proton and carbon resonances has been made on the basis of proton–proton and proton–carbon shift

Table 6 1H NMR chemical shifts (δ) for compounds **4a–h**[a]

H(1)[H(5)]	(brd)	3.13	3.13	3.13	3.14	3.18	3.17	3.18	3.20
H(2β)[H(4β)]	(td)	2.17	2.15	2.15	2.15	2.29	2.27	2.27	2.28
H(2α)[H(4α)]	(m)	1.36	1.34	1.31	1.30	1.65	1.59	1.55	1.60
H(3)	(tt)	5.08	5.08	5.09	5.08	5.07	5.08	5.13	5.09
H(6β)[H(8β)]		1.75 (tt)	1.75 (tt)	1.75 (tt)	1.76 (tt)	1.80 (m)	1.80 (m)	1.80 (m)	1.81 (m)
H(6α)[H(8α)]	(brd)	0.93	0.89	0.88	0.88	0.93	0.92	0.92	0.93
H(7α)	(m)	1.54	1.56	1.54	1.53	1.73	1.75	1.67	1.71
H(7β)	(m)	1.29	1.28	1.29	1.30	1.36	1.35	1.34	1.36
CH_2–Ph	(m)	2.68	2.68	2.68	2.68	2.69	2.69	2.70	2.71
CH_2–N	(m)	2.83	2.83	2.83	2.83	2.85	2.84	2.85	2.86
CH_3–Ph	(s)		2.40				2.29		
Ph	(m)	7.27	7.22	7.22	7.17	7.23	7.23	7.23	7.11
H(2″)[H(6″)]		7.27 (m)	6.96 (d)	6.91 (d)	7.17 (m)	7.10 (m)	6.87 (d)	7.74 (d)	7.11 (m)
H(3″)[H(5″)]		7.27 (m)	7.20 (d)	7.00 (d)	7.17 (m)	7.10 (m)	7.03 (d)	6.90 (d)	7.11 (m)
CH_3(Et)	(t)	1.01	1.01	1.01	1.02				
CH_2(Et)	(q)	1.91	1.92	1.92	1.91				
H(2‴)[H(6‴)]					7.18 (d)	7.18 (d)	7.18 (d)	7.11 (m)	
H(3‴)[H(5‴)]					7.08 (d)	7.09 (d)	7.10 (d)	7.11 (m)	
CH_3O	(s)			3.84				3.75	

[a] Abbreviations brd, broad doublet; m, multiplet; q, quadruplet; s, singlet; t, triplet; td, triplet of doublets; tt, triplet of triplets. δ Values were deduced from the first-order analysis of the corresponding system protons with an error of ±0.05 ppm.

Table 7 Coupling constants (J/Hz) deduced from the analysis of the ^{1}H NMR spectra of compounds **4a–h**

	4a	**4b**	**4c**	**4d**	**4e**	**4f**	**4g**	**4h**
H(2α)[H(4α)]–H(2β)[H(4β)]	12.1	12.0	12.3	11.8	12.1	12.3	12.3	11.9
H(2α)[H(4α)]–H(1)[H(5)]		2.8		2.6		2.8		
H(2α)[H(4α)]–H(3)	12.1	12.0	12.8	11.8	12.1	12.3	12.3	11.9
H(2β)[H(4β)]–H(1)[H(5)]	12.1	12.0	12.3	11.8	12.1	12.3	12.3	11.9
H(2β)[H(4β)]–H(3)	6.1	6.2	6.3	6.0	6.2	6.1	6.1	6.1
H(6β)[H(8β)]–H(6α)[H(8α)]	12.9	13.1	13.0	12.8	12.5	12.9	12.9	12.7
H(6β)[H(8β)]–H(1)[H(5)]		4.1		4.0		3.8	3.9	
H(6β)[H(8β)]–H(7α)	12.9	13.1	13.0	12.8	12.5	12.9	12.9	12.7
H(6β)[H(8β)]–H(7β)		4.1		4.0		3.8	3.9	
H(6α)[H(8α)]–H(7α)		3.9						
H(7α)–H(7β)	12.9	13.1	13.0	12.8		12.9	12.9	12.7
H(2″)[H(6″)]–H(3″)[H(5″)]		8.2	9.0			8.2	8.9	
H(2‴)[H(6‴)]–H(3‴)[H(5‴)]						8.6	8.6	8.5
CH_3–CH_2	7.3	7.4	7.4	7.3				

[a] Values deduced from the first-order analysis of the corresponding system protons. Error ±0.05 Hz.

Table 8 ^{13}C chemical shifts (δ) for compounds **4a–h** at 75 MHz[a]

	4a	**4b**	**4c**	**4d**	**4e**	**4f**	**4g**	**4h**
C(1)[C(5)]	50.17	50.14	50.23	50.09	50.11	50.12	50.28	50.10
C(2)[C(4)]	30.26	30.23	30.10	30.27	29.99	29.98	29.95	29.98
C(3)	48.05	47.70	47.65	47.87	50.85	50.41	50.28	50.61
C(6)[C(8)]	25.44	25.48	25.71	25.36	25.02	25.00	25.33	24.97
C(7)	14.20	14.19	14.06	14.16	14.28	14.26	14.18	14.18
CH_2–N	54.31	54.33	54.33	54.24	53.85	53.89	53.95	53.75
CH_2–Ph	35.92	35.91	36.02	35.90	35.70	35.70	35.59	35.54
C(1′)	140.39	141.02	140.80	140.97	140.91	140.92	140.77	140.74
C(2′)[C(6′)]	128.17[b]	128.13[b]	128.05[b]	128.16[b]	128.12[b]	128.15[b]	128.14[b]	128.15[b]
C(3′)[C(5′)]	128.89[b]	128.85[b]	128.75[b]	128.87[b]	128.81[b]	128.84[b]	128.81[b]	128.81[b]
C(6′)	125.73	125.69	125.61	125.74	125.71	125.74	125.73	125.76
CH_3		21.09				20.99		
OCH_3			55.38				55.24	
C(1″)	141.03	137.52	132.82	136.22	141.11	137.15	133.53	
C(2″)[C(6″)]	129.27[b]	129.83[b]	131.04	131.84	128.81[b]	129.59[b]	131.25	131.80
C(3″)[C(5″)]	130.24[b]	129.92[b]	114.27	116.20	130.18[b]	129.94[b]	113.98	115.81
C(4″)	128.00	137.77	158.93	161.96	127.31	137.15	158.50	161.33
C=O	173.60	173.74	173.82	173.58	169.76	169.85	169.92	169.85
CH_2(Et)	28.88	28.73	28.58	28.85				
CH_3(Et)	9.66	9.65	9.55	9.59				
C(1‴)					134.78	134.66	134.67	134.97
C(2‴)[C(6‴)]					129.60	129.47	129.51	129.47
C(3‴)[C(5‴)]					127.77	127.75	127.77	127.93
C(4‴)					135.91	136.05	136.92	135.69

[a] Directly measured on the spectra; error ±0.05 ppm. [b] These values may be interchanged.

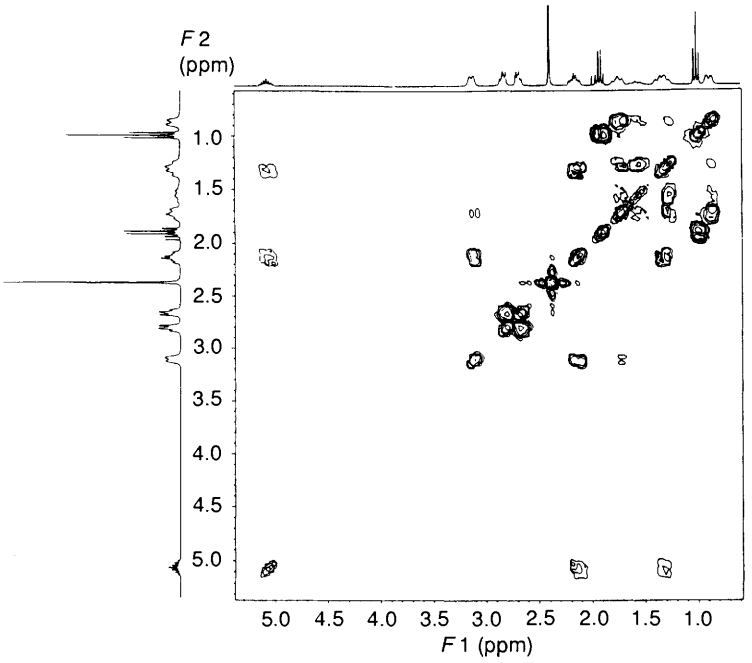


Fig. 3 Contour plots of the 300 MHz proton COSY spectrum of **4b**

correlation spectra of compound **4b**, double resonance experiments on compound **4e**, and our previous studies of related compounds.[7] The combined use of COSY and NOESY spectra of **4b** helped the conformational study.

In $CDCl_3$ at 300 MHz the signals due to H(3), H(1) [H(5)], H(2β)[H(4β)], CH_2–N, CH_2–Ph and H(6α)[H(8α)] appear well differentiated. Overlapping resonances between H(6β)-[H(8β)], H(2α)[H(4α)], H(7α) and H(7β) signals were observed. The signals corresponding to H(1)[H(5)] and H(6α)[H(8α)] appear as low resolution doublets.

The assignment of all the signals was feasible through a homonuclear 2D COSY 45° experiment. The contour plot of the 300 MHz proton COSY spectrum of compound **4b** is shown in Fig. 3 (the aromatic proton region is omitted). The cross-connectivity patterns were analysed taking into account that the lowest field triplet of triplets at 5.08 ppm, the doublet at 3.13 ppm and the doublet at 0.89 ppm can be unambiguously assigned to the H(3), H(1)[H(5)] and H(6α)[H(8α)] protons, respectively. Consideration of the correlations between H(3) and other protons allows the establishment of the following: (*i*) the triplet of doublets at 2.15 ppm correlates with H(3) and the signal at 1.34 ppm, and must correspond to H(2β)[H(4β)], (*ii*) the multiplet centred at 1.34 ppm correlates with H(2β)[H(4β)] and must correspond to H(2α)[H(4α)]. Consideration of the correlations between H(1)[H(5)] and other protons allows the establishment of the following: (*i*) signals corresponding to H(2α)[H(4α)] and H(2β)[H(4β)] (stronger correlation), (*ii*) signals corresponding to H(6α)[H(8α)] and H(6β)[H(8β)] (stronger correlation). Consideration of the correlations between H(6β)[H(8β)] and other protons allows the establishment of the signals corresponding to H(7β) and H(7α) (stronger correlation).

To strengthen these assumptions double resonance (DR) experiments were performed in $CDCl_3$ at 300 MHz on the spectrum of compound **4e**.

By irradiation of the signal at 5.07 ppm the triplet of doublets at 2.29 ppm collapses to an unresolved triplet, and the unresolved triplet at 1.65 ppm to an unresolved doublet.

On saturating the H(1)[H(5)] signal at 3.18 ppm, the signal at 2.29 ppm becomes a multiplet and the unresolved triplet of triplets at 1.80 ppm an unresolved triplet of doublets.

By saturation of the H(2β)[H(4β)] signal at 2.29 ppm, the triplet of triplets at 5.07 ppm collapses to an apparent triplet. The H(1)[H(5)] signal at 3.18 ppm collapses to a singlet, and the unresolved triplet at 1.65 ppm collapses to an unresolved doublet.

By saturation of the H(6β)[H(8β)] signal at 1.80 ppm, the doublet at 0.93 ppm collapses to a singlet.

By irradiation of the H(2α)[H(4α)] signal at 1.65 ppm the H(2β)[H(4β)] signal at 2.29 ppm collapses to an unresolved triplet.

Conformational Study.—From the ^1H and ^{13}C NMR data for **4a–h** the following general features may be deduced.

(*i*) The bicyclic system exists predominantly in a chair–boat conformation.

(*ii*) There is a pseudo-mirror plane through the granatane skeleton defined by C(3), C(7) and N(9). The unconjugated arylamino group lies nearly perpendicular to this plane, in a predominantly *trans* position with respect to H(3) (Scheme 1). In compounds **4e–h** there is a quasi-conjugation between the aminocarbonyl group and the *p*-chlorophenyl ring. In all cases there is a conjugation between the nitrogen lone pair and the carbonyl group.

(*iii*) The phenethyl group occupies a distinct axial position with respect to the chair piperidine ring.

These conclusions are supported by the following observations. (*i*) The H(1)[H(5)] signal (a broad doublet) and H(2β)[H(4β)] signal (a triplet of doublets) show a coupling constant (*ca.* 12 Hz) which is typical of eclipsed vicinal protons in piperidine systems.[22] The ^3J H(2α)[H(4α)]–H(3) value of *ca.* 12 Hz indicates a *trans* coplanar disposition of H(2α)[H-(4α)]–C–C–H(3). The ^3J H(6β)[H(8β)]–H(7α) value of *ca.* 13 Hz indicates a *trans* coplanar disposition of H(6β)[H(8β)]-C–C–H(7α).[22] The δ C(7) value of *ca.* 14.2 ppm is similar to the reported values for the corresponding amines,[7] α-granatanol (14.5 ppm)[23] and 9-(2′-hydroxyethyl)-9-azabicyclo[3.3.1]-nonan-9-α-ol (14.4 ppm)[2]; these compounds show a preferred chair–boat conformation in $CDCl_3$ solution.

(*ii*) By considering the δ ^1H and ^{13}C values of the arylamino groups, the conjugation between the N-lone pair and the π system can be disregarded. The observation of two NOESY cross-peaks at δ = 1.34/6.96 and δ = 1.92/6.96 ppm points out the following: the proximity of the H(2α)[H(4α)] protons to the

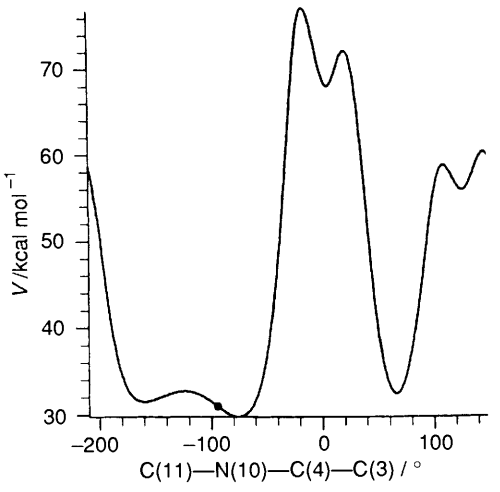


Fig. 4 Results of the conformational analysis for compound **4f**. The dot indicates the experimental value.

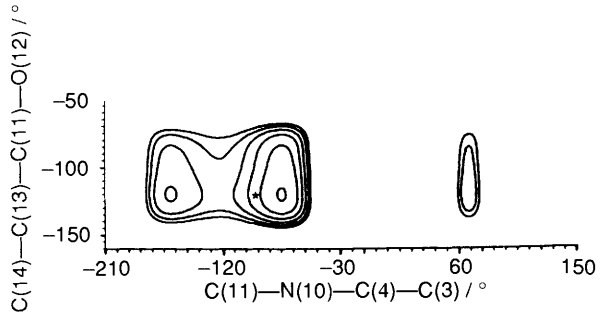


Fig. 5 Results of the conformational analysis for compound **4f**. The asterisk indicates the experimental value. The contours are in kcal mol^{-1}.

H(2″)[H(6″)] aromatic protons, and the proximity of the CH_2 propionyl protons to the H(2″)[H(6″)] aromatic protons. From the δ ^1H and ^{13}C values of the *p*-chlorophenyl group in **4e–h**, a partial conjugation between this group and the amido moiety can be proposed. In compounds **4a–d** the high field δ_H values of the methylene (propionyl) group are due to the field shielding effect exerted by the arylamino group. The δ CO values in **4a–h** indicate a conjugation between the nitrogen lone pair and the carbonyl group.

(*iii*) The δ C(6)[C(8)] values of **4a–h** are in close agreement with an axial disposition of the *N*-substituent in the chair piperidine granatane ring.[2] Moreover the AA′BB′ appearance of the methylene proton signals, and the multiplet corresponding to the phenyl protons indicates a distinct disposition of the phenethyl groups.

Summarizing, ^1H and ^{13}C data of compounds **4a–h** in solution show the same preferred chair–boat conformation, with the disubstituted ring in a slightly distorted boat form and the monosubstituted ring in a chair form. *N*-Piperidine substituents adopt an axial arrangement with respect to the chair piperidine ring. The amido substituents are in an α disposition, with the non-conjugated phenyl ring in a *trans* disposition with respect to H(3).

These results seem to be in agreement with the structure deduced from X-ray data.

Energetic calculations. In order to gain additional information concerning the conformation of these compounds a conformational analysis was undertaken.[24]

The energy of the free molecule was evaluated as a sum of the torsional energy and the van der Waals interactions between non-bonded atoms. The potential energy term used is given by eqn. (1) where *A*, *B*, *C* and *D* are constants and *r* is the distance

$$V(\text{pol}) = \frac{A.\exp(-B.r)}{r^D} - \frac{C}{r^6} \quad (1)$$

between two atoms. The torsional term takes the form of eqn. (2) for non-conjugated bonds and eqn. (3) for conjugated bonds

$$V(t) = T.(1 + \cos(3w)) \quad (2)$$

$$V(t) = T.(1 - \cos(2w))/2 \quad (3)$$

where *T* is a constant for each pair of atoms type and *w* is the torsion angle. Inclusion of the *in vacuo* electrostatic contribution in the total field did not change the position of the minima. All the torsions not considered in each study were fixed at the experimental values.

The amide moiety attached to the bicyclic C(4) was rotated through 360° about the N(10)–C(4) bond, in steps of 1°. The resulting energy plot is displayed in Fig. 4, against the value of the C(11)–N(10)–C(4)–C(3) torsion (*T*1). The minimum value corresponds to a torsion angle of −76°, which is near the experimental X-ray value of −96.1(5)°. There is a second minimum at −156° and a third one at 63°. It can be expected that the phenethyl group, which is quite bent in the experimental structure, adopts an extended conformation in solution. To assess whether this group could have any influence on the results obtained for the torsion under consideration, the energetic study was repeated removing the phenethyl part from the molecule. However, this experiment led to the same results, thus indicating, that this group does not affect the theoretical preferred conformation.

The orientation of the *p*-tolyl group in solution seems to be the same as that found experimentally. The X-ray torsion angle C(21)–C(20)–N(10)–C(4) (*T*2) of −93.2° is energetically favourable, as seen by rotating N(10)–C(4) and N(10)–C(20) simultaneously; the resulting map shows three local minima at similar values for *T*1 as the previously found, *T*2 always keeping a value of −93°.

The conformation of the *p*-chlorobenzoyl group was also studied. Fig. 5 shows the results of the simultaneous rotation about N(10)–C(4) and C(13)–C(11) bonds in steps of 1°, by plotting the value of the C(14)–C(13)–C(11)–O(12) torsion (*T*3) against *T*1. The map again corresponds very closely to that of Fig. 4; the energy reaches minimum values at *T*1 −76, −160 and 58°, *T*3 being always −120°. As happened for *T*2, *T*3 seems to be independent of the orientation of the whole amide group (*T*1), and its X-ray value of −123.3(6)° is energetically favourable.

However, as deduced by NMR analysis, there is some evidence that electronic π density of the *p*-chlorophenyl ring is partially conjugated with that of the carbonyl group in solution, thus suggesting a greater coplanarity between them. This planarity is mainly prevented by the steric impediment of the *p*-tolyl ring, as shown by the analysis carried out by removing this group from the molecule, and rotating only the C(13)–C(11) bond, which led to a theoretical *T*3 value of −151°. This apparent contradiction between the X-ray and the conclusions from NMR analysis could be explained if the conjugation along N(10)–C(11)–O(12) observed in the crystal were not so perfect in solution, therefore allowing some rotation about the N(10)–C(11) bond which would alleviate the steric effect of the *p*-tolyl group, and in this way, some kind of conjugation in the benzoyl moiety would be allowed.

Pharmacology.—Treatment with compound **4b** prevented acetic-acid-induced writhing in the mouse (ED_{50}, 100 mg kg^{-1} *p.o.*, as compared to an ED_{50} of 9 mg kg^{-1} for diclofenac) but failed to prolong reaction time in the hot plate assay in the rat. This antinociceptive activity could not be explained by an

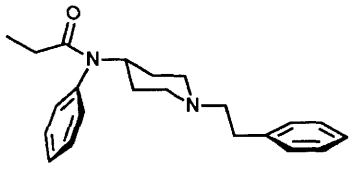


Fig. 6 Fentanyl

opioid mechanism since the compound did not inhibit electrically stimulated twitch contraction of the guinea-pig myenteric plexus preparation. All other compounds were inactive in the writhing assay and were not further evaluated.

Formation of thromboxane B_2 from arachidonic acid in rat platelets *in vitro* was also monitored, in an attempt to ascertain whether cyclooxygenase inhibition was involved in the antinociceptive effect. Surprisingly, compound **4b**, at a concentration of 0.1 mmol dm^{-3}, increased 3 times the basal production of this metabolite. Work is in progress to gain further insight into this action.

Conclusions

First-order ^1H NMR approximations of a series of *N*-substituted 4-anilidopiperidine derivatives and 3-methyl-4-propananilidopiperidines imply that the preferred conformation is that of a piperidine chair with the 4-propananilido moiety in the equatorial orientation.[25] Analysis of the crystal structure of fentanyl and its structural analogues also indicate that this is the case.[26,27] In addition, the *N*-phenethyl and propananilido moieties are extended in the crystal structure.[27] The amide function is planar and at 90° to the mean plane of the piperidine ring. Also, the amide group is nearly perpendicular to the anilido phenyl group.[23] The preferred conformation can be depicted as in Fig. 6. This conformation is also the probable solution-state conformation of fentanyl.[28]

As was deduced from the NMR studies of compounds **4a–h**, the steric requirements presented above are met in these compounds, with the exception that the fentanyl-like piperidine ring is forced to adopt a boat conformation.

In vivo pharmacological testing demonstrated that compounds **4** were inactive in the analgesic test, with the exception of compound **4b** which showed an ED_{50} of 100 mg kg *p.o.*

In the case **4f, g** the removal of the propionyl group would explain the lack of activity.[29] In the case of compounds **4c, d** the lack of activity would be due to the boat arrangement of the piperidine ring, and the C(6)–C(8) propylene unit in this part of the molecule, which would hinder an adequate binding to the opiate μ receptor.

The above reasonings together with the experimental pharmacological results support the hypothesis that the analgesic activity of **4b** cannot be accounted for by an interaction with the opiate receptor.

On the other hand, the only differences between **4b** and **4c, d** are the steric and electronic parameters of the arylanilido moiety and these latter compounds showed no antinociceptive effect. Consequently, this fact remains unclear and demands further investigations.

Experimental

All melting points were taken in open capillary tubes and are uncorrected. IR spectra were recorded on a Perkin-Elmer 883 spectrophotometer. NMR spectra were recorded on a Varian UNITY-300 spectrometer, in $CDCl_3$ with TMS as internal standard. The ^1H NMR spectra were obtained at 300 MHz using spectral width of 4000 Hz and acquisition time of 3.0 s over 64 transients. LB = −0.8, GF = 0.50 and GFS = 0.20 were used for resolution enhancement. Conventional irradiation was used for the double resonance experiments. The ^{13}C NMR spectra were recorded at 75 MHz. The spectral parameters included spectral width of 16 500 Hz, acquisition time of 1.0 s, delay time of 1.0 s and pulse width of 4 μs. The homonuclear (COSY 45°)[30,31] and heteronuclear (XHCORD)[30,32] shift correlation experiments were performed by using standard Varian pulse sequences. The NOESY[33] experiments were recorded in phase sensitive mode, using a relaxation time of 1.7 s, and a mixing time of 0.8 s.

The elemental analyses were carried out in a Perkin-Elmer Elemental Analyzer model 240 B.

Synthesis of the Amides **4a–h**.—*General procedure.* To a stirred solution of the corresponding amine (0.70 mmol) and triethylamine (1.12 mmol) in anhydrous dichloromethane (10 cm^3), was added dropwise a solution of the corresponding acyl chloride (0.84 mmol) in anhydrous dichloromethane (5 cm^3). The mixture was heated under reflux for 18 h. Then, water was added, and the resulting mixture was extracted with dichloromethane. The organic layer was dried (anhydrous magnesium sulfate), the solvent removed under reduced pressure, and the residual oil was purified on a silica gel column prepacked in hexane. Elution of the column with hexane–ethyl acetate (7:3) gave a homogeneous residue which was crystallized from hexane. NMR data for all compounds **4** are given in Tables 6 and 7 (δ_H) and Table 8 (δ_C).

N-*Phenethyl*-3-α-(N-*phenylpropanamido*)*norgranatane* (**4a**). This compound was obtained in 63% yield; m.p. 76–77 °C; ν_{max}(KBr)/cm^{-1} 1651 (CO); (Found: C, 82.95; H, 9.05; N, 4.0. Calc. for $C_{25}H_{32}NO$: C, 82.83; H, 8.90; N, 3.86%).

N-*Phenethyl*-3-α-(N-p-*tolylpropanamido*)*norgranatane* **4b**. This compound was obtained in 61% yield; m.p. 80–81 °C; ν_{max}(KBr)/cm^{-1} 1657 (CO). (Found: C, 80.05; H, 8.9; N, 7.2. Calc. for $C_{26}H_{34}N_2O$: C, 79.96; H, 8.77; N, 7.17%).

N-*Phenethyl*-3-α[N-(p-*methoxyphenyl*)*propanamido*]*norgranatane* **4c**. This compound was obtained in 59% yield; m.p. 72–73 °C; ν_{max}(KBr)/cm^{-1} 1651 (CO). (Found: C, 76.9; H, 8.55; N, 6.9. Calc. for $C_{26}H_{34}N_2O_2$: C, 76.81; H, 8.43; N, 6.89%).

N-*Phenethyl*-3-α-[N-(p-*fluorophenyl*)*propanamido*]*norgranatane* **4d**. This compound was obtained in 68% yield; m.p. 95–96 °C; ν_{max}(KBr)/cm^{-1} 1659 (CO). (Found: C, 76.4; H, 8.35; N, 7.3. Calc. for $C_{25}H_{31}FN_2O$: C, 76.10; H, 7.92; N, 7.10%).

N-*Phenethyl*-3-α-[N-*phenyl*-p-*chlorobenzamido*]*norgranatane* **4e**. This compound was obtained in 63% yield; m.p. 199–200 °C; ν_{max}(KBr)/cm^{-1} 1637 (CO). (Found: C, 75.65; H, 6.5; N, 6.35. Calc. for $C_{29}H_{31}ClN_2O$: C, 75.88; H, 6.81; N, 6.10%).

N-*Phenethyl*-3-α-[N-(p-*tolyl*)-p-*chlorobenzamido*]*norgranatane* **4f**. This compound was obtained in 61% yield; m.p. 125–126 °C; ν_{max}(KBr)/cm^{-1} 1636 (CO). (Found: C, 76.25; H, 7.15; N, 6.0. Calc. for $C_{30}H_{33}ClN_2O$: C, 76.17; H, 7.03; N, 5.92%).

N-*Phenethyl*-3-α-[N-(p-*methoxyphenyl*)-p-*chlorobenzamido*]-*norgranatane* **4g**. This compound was obtained in 67% yield; m.p. 132–133 °C; ν_{max}(KBr)/cm^{-1} 1640 (CO). (Found: C, 73.7; H, 6.9; N, 6.0. Calc. for $C_{30}H_{33}ClN_2O_2$: C, 73.68; H, 6.80; N, 5.73%).

N-*Phenethyl*-3-α-[N-(p-*fluorophenyl*)-p-*chlorobenzamido*]-*norgranatane* **4h**. This compound was obtained in 65% yield; m.p. 149–150 °C; ν_{max}(KBr)/cm^{-1} 1633 (CO). (Found: C, 73.15; H, 6.4; N, 5.9. Calc. for $C_{29}H_{30}ClFN_2O$: C, 73.02; H, 6.34; N, 5.87%).

Pharmacological Methods.—Writhing assay. For assessment of antinociceptive activity, the title compounds were suspended in aqueous 1% methoxycarbonylcellulose solution and administered *p.o.* to 15-hour-fasted male Swiss–Webster mice weighing 22–25 g (n = 5 per treatment group) followed 60 min later by *i.p.* administration of 10 cm^3 kg^{-1} of aqueous 7.5%

acetic acid.[34] Writhing was observed during a subsequent 20 min interval. A writhe was defined as abdominal stretching, downward arching of the back and full extension of the hind legs. The number of writhing responses exhibited by each animal was determined and the mean ±s.e. for each experimental group was calculated. Data were expressed as percentage of inhibition of the mean number of writhes in the vehicle-treated control group. Acetyl salicylic acid and diclofenac were used as reference drugs.

Hot plate. Mice were placed on a copper plate kept at 55 °C.[35] The pain threshold was taken as the time at which a mouse began to lick its hind forepaw.

Inhibition of thromboxane B_2 *formation* in vitro. Triplicate aliquots were analysed for thromboxane B_2 by a standardized radioimmunoassay. IC_{50} values were determined by a graded concentration–response analysis.[36]

Assessment of potential opioid properties. Female guinea-pigs (weighing 300–400 g) were killed by a blow in the head and then exsanguinated by cutting the jugular vein. Segments of distal ileum *ca.* 20 cm long were quickly removed (excision was performed *ca.* 10 cm above the ileocecal junction) and immediately placed in aerated Ringer solution of the following composition (mmol dm^{-3}): NaCl, 154; KCl, 5.66; $CaCl_2$, 2.54; $NaHCO_3$, 5.95; glucose, 2.77, and choline hydrochloride, 0.002. Strips of guinea-pig ileum myenteric plexus were mounted in an organ bath, superfused with Ringer solution, gassed with carbogen and warmed at 37 °C, following Puig *et al.*[37] The plexus was connected to an isotonic transducer under a resting tension of 0.5 g and electrically stimulated by square wave pulses (5 ms) of 70 V at frequencies of 0.15 Hz. The preparation was allowed to equilibrate for 60 min before addition of the drugs. Morphine hydrochloride was used as the reference compound.

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