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*Acta Cryst.* (1980). **B36**, 1141–1146

### Structural Studies of Substituted 6,7-Benzomorphan Compounds.

#### IV. ( $\pm$ )-5-Ethyl-2'-hydroxy-9,9-dimethyl-2-phenethyl-6,7-benzomorphan Hydrobromide (Dimephen) and ( $\pm$ )-2'-Hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan (Phenazocine) Hydrobromide Hemihydrate

BY Y. G. GELDERS AND C. J. DE RANTER\*

*Laboratorium voor Analytische Chemie en Medicinale Fysicochemie,  
Instituut voor Farmaceutische Wetenschappen, KU Leuven, Van Evenstraat 4, B-3000 Leuven, Belgium*

AND M. KOKKES

*Laboratorium voor Kristallografie, Universiteit van Amsterdam, Nieuwe Achtergracht 166, Amsterdam,  
The Netherlands*

(Received 22 September 1979; accepted 1 January 1980)

#### Abstract

Dimephen,  $C_{24}H_{32}NO^+.Br^-$ , crystallizes in the monoclinic space group  $P2_1/c$  with  $a = 11.472$  (1),  $b = 16.933$  (1),  $c = 11.793$  (1) Å,  $\beta = 113.019$  (9)° and  $Z = 4$ . The structure was solved from a Patterson synthesis and refined to  $R = 0.046$  for 1993 independent reflections. Phenazocine hydrobromide hemihydrate,  $C_{22}H_{28}NO^+.Br^-.\frac{1}{2}H_2O$ , has triclinic symmetry,  $P\bar{1}$ , with  $a = 10.263$  (1),  $b = 14.307$  (1),  $c = 15.835$  (2) Å,  $\alpha = 72.506$  (8),  $\beta = 72.976$  (8),  $\gamma = 69.020$  (6)° and  $Z = 4$ . A Patterson synthesis revealed the structure which was refined to  $R = 0.041$  for 4480 independent reflections. Hydrogen bonds between Br, O and N atoms link the molecules in the crystals of both compounds. The structural data, confirmed by potential-energy calculations, indicate that the conformation of the phenethyl substituent is not critical for the narcotic activity of the compounds considered.

\* To whom correspondence should be addressed.

#### Introduction

( $\pm$ )-5-Ethyl-2'-hydroxy-9,9-dimethyl-2-phenethyl-6,7-benzomorphan hydrobromide, hereafter abbreviated as dimephen,<sup>†</sup> and ( $\pm$ )-2'-hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan hydrobromide hemihydrate, further referred to by its generic name phenazocine,<sup>‡</sup> are both opiate narcotics showing increased analgesic activities of respectively 20 $\ddagger$  and 10 times that of morphine (Janssen & Van der Eycken, 1968). As the benzomorphan skeleton remains essentially unchanged (Gelders & De Ranter, 1980, and preceding papers in this series), the analgesic activity is largely determined by the nature of the substituents. Animal studies have shown that phenethyl substitution on the nitrogen

<sup>†</sup> *Chemical Abstracts* name for dimephen: ( $\pm$ )-6-ethyl-1,2,3,4,5,6-hexahydro-2,6-methano-11,11-dimethyl-3-phenethyl-3-benzazocin-8-ol hydrobromide; for phenazocine: 1,2,3,4,5,6-hexahydro-2,6-methano-6,11-dimethyl-3-phenethyl-3-benzazocin-8-ol.

<sup>‡</sup> Private communication from ACF Chemiefarma NV.

consistently enhances the potency of rigid opiates with a common 6,7-benzomorphan nucleus (Loew & Berkowitz, 1975, and references therein). A striking difference between both compounds is the methyl substitution in the 9 position.

For these reasons it seemed worthwhile to solve the crystal structures of both compounds.

### Experimental and structure determination

Crystal data are given in Table 1. Prismatic crystals of dimephen and phenazocine hydrobromide hemihydrate were obtained from solutions in methanol/water. The space group of dimephen was determined as  $P2_1/c$  from photographs which showed monoclinic symmetry and systematic absences for  $0k0$  and  $h0l$  with  $k$  and  $l$  odd respectively. The triclinic symmetry of phenazocine.HBr. $\frac{1}{2}$ H $_2$ O was also obtained from photographs.

Cell parameters were obtained from a least-squares calculation of the setting angles of 30 reflections measured on a Nonius CAD-4 automatic diffractometer using Cu  $K\alpha$  radiation ( $\lambda = 1.54178 \text{ \AA}$ ) and a  $\theta$ - $2\theta$  scan. For dimephen, 2768 reflections were collected of which 775 were rejected because of their low intensities [ $I < 3\sigma(I)$ ]. They were corrected for Lorentz and polarization factors but not for absorption. A Patterson synthesis and a superposition (minimum function) gave the coordinates of the non-hydrogen atoms of the molecule. Subsequent isotropic and anisotropic refinements by block-diagonal least squares using the XRAY program system (Stewart, Kruger, Ammon, Dickinson & Hall, 1976) lowered the  $R$  value to 0.073. A difference synthesis at this stage revealed the coordinates of the H atoms, which were given the isotropic thermal parameters of their adjacent atoms. Although not refined, they were included in the final

calculations which yielded an  $R$  value of 0.046 for 1993 contributing reflections.

For phenazocine.HBr. $\frac{1}{2}$ H $_2$ O, 4480 reflections were above the  $3\sigma$  level. They were also corrected for Lorentz and polarization factors but not for absorption. The structure of phenazocine.HBr. $\frac{1}{2}$ H $_2$ O was solved by a Patterson synthesis and by subsequent Fourier syntheses starting from the positions of the two bromide ions in the asymmetric unit. The two enantiomeric molecules of the asymmetric unit were refined in the same way as dimephen and the coordinates of the H atoms were determined in a difference synthesis at an  $R$  index of 0.067. They were included in the subsequent calculations with fixed positions and the isotropic temperature factors of their carrier atoms. The atomic coordinates and  $B_{eq}$  temperature factors for both compounds are given in Table 2.\* For dimephen the coordinates of the (-) molecule of the racemate are given. They were checked for consistency with the gemazocine molecule, for which the absolute configuration has already been determined (Gelders, De Ranter & Schenk, 1979).

### Discussion

The proper atomic numbering systems of dimephen and phenazocine are given in Figs. 1 and 2 together with the bond lengths of the molecules, but in the subsequent discussion the atomic numbering of dimephen will be used as reference. *ORTEP* stereopairs (Johnson, 1965) of the levorotatory cations of dimephen and phenazocine are shown in Fig. 3 and bond angles are given in Table 3. As can be deduced

\* Lists of structure factors and anisotropic thermal parameters for both compounds have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 35075 (49 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. Crystal data

	Dimephen	Phenazocine
Formula	C $_24$ H $_{32}$ NO $^+$ .Br $^-$	C $_{22}$ H $_{28}$ NO $^+$ .Br $^-$ . $\frac{1}{2}$ H $_2$ O
$M_r$	430.44	411.39
Crystal system	Monoclinic	Triclinic
Space group	$P2_1/c$	$P\bar{1}$
Unit cell $a$	11.472 (1) $\text{\AA}$	10.263 (1) $\text{\AA}$
$b$	16.933 (1)	14.307 (1)
$c$	11.793 (1)	15.835 (2)
$\alpha$		72.506 (8) $^\circ$
$\beta$	113.019 (9) $^\circ$	72.976 (8)
$\gamma$		69.020 (6)
$V$	2108 $\text{\AA}^3$	2025 $\text{\AA}^3$
$Z$	4	4
$D_c$	1.359 Mg m $^{-3}$	1.349 Mg m $^{-3}$
$D_m$ (floatation)	1.362	1.353
$F(000)$	904	840
$\mu(\text{Cu } K\alpha)$	3.033 mm $^{-1}$	3.146 mm $^{-1}$

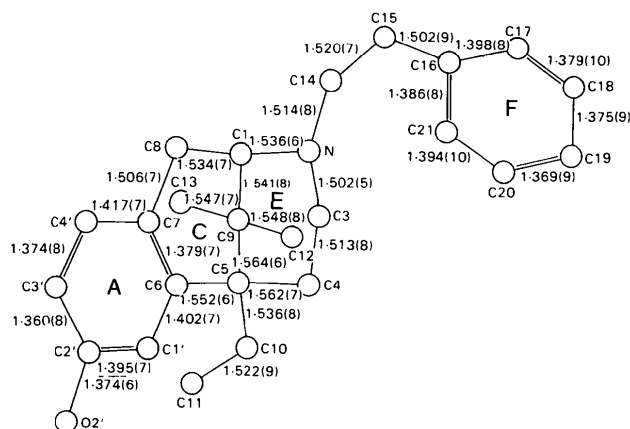


Fig. 1. Atomic numbering of dimephen and bond lengths ( $\text{\AA}$ ) with e.s.d.'s in parentheses.

Table 2. Atomic coordinates ( $\times 10^4$ ) and temperature factors ( $\text{\AA}^2$ ) with e.s.d.'s in parentheses for the refined parameters

	x	y	z	$B_{\text{eq}}$ or $B_{\text{iso}}$ ( $\text{\AA}^2$ )		x	y	z	$B_{\text{eq}}$ or $B_{\text{iso}}$ ( $\text{\AA}^2$ )
<b>Dimephen</b>					C(1)	1769 (4)	6432 (2)	6983 (2)	3.02 (12)
Br	1392 (0)	765 (0)	2236 (0)	5.42 (2)	N(A)	256 (3)	7125 (2)	6996 (1)	2.78 (9)
O(2')	-5639 (3)	649 (2)	3456 (4)	5.25 (13)	C(3)	-561 (4)	6753 (2)	6575 (2)	3.38 (12)
C(1)	-1743 (4)	3611 (2)	4307 (4)	2.85 (14)	C(4)	-514 (4)	5648 (2)	7043 (2)	3.34 (12)
N	-2108 (3)	3890 (2)	2972 (3)	3.03 (11)	C(5)	1001 (4)	4915 (2)	7081 (2)	2.64 (11)
C(3)	-3384 (4)	3595 (2)	2116 (4)	3.06 (14)	C(6)	1848 (4)	4865 (2)	6115 (2)	2.58 (11)
C(4)	-4407 (4)	3721 (2)	2606 (4)	2.86 (14)	C(7)	2555 (4)	5589 (2)	5619 (2)	2.74 (11)
C(5)	-4048 (4)	3427 (2)	3956 (4)	2.60 (13)	C(8)	2654 (4)	6395 (2)	6034 (2)	3.30 (12)
C(6)	-3838 (4)	2522 (2)	3953 (4)	2.50 (13)	C(9)	1710 (4)	5369 (2)	7539 (2)	2.85 (12)
C(7)	-2660 (4)	2219 (2)	4145 (4)	2.90 (14)	C(10)	862 (4)	3870 (3)	7662 (2)	3.87 (14)
C(8)	-1493 (4)	2718 (3)	4431 (4)	3.64 (16)	C(11)	3189 (4)	4686 (3)	7684 (2)	4.14 (14)
C(9)	-2779 (4)	3843 (2)	4771 (4)	3.01 (14)	C(12)	116 (4)	8244 (2)	6604 (2)	3.59 (13)
C(10)	-5179 (4)	3658 (2)	4276 (4)	3.45 (15)	C(13)	538 (5)	8730 (3)	7161 (2)	4.77 (15)
C(11)	-5275 (5)	3354 (3)	5451 (5)	4.81 (18)	C(14)	436 (4)	9839 (2)	6721 (2)	3.46 (13)
C(12)	-2286 (4)	3584 (3)	6136 (4)	4.19 (17)	C(15)	1622 (4)	10176 (3)	6514 (2)	4.36 (14)
C(13)	-2909 (5)	4753 (2)	4754 (5)	4.00 (17)	C(16)	1532 (5)	11198 (3)	6109 (3)	5.58 (17)
C(14)	-1166 (4)	3686 (3)	2407 (4)	3.52 (15)	C(17)	299 (5)	11875 (3)	5908 (2)	5.35 (17)
C(15)	219 (4)	3862 (3)	3174 (4)	3.81 (16)	C(18)	-888 (5)	11559 (3)	6105 (2)	4.68 (15)
C(16)	906 (4)	3715 (2)	2340 (4)	3.24 (15)	C(19)	-843 (4)	10547 (3)	6520 (2)	4.17 (14)
C(17)	972 (4)	4304 (3)	1537 (5)	4.40 (17)	C(1')	1872 (4)	4116 (2)	5713 (2)	3.18 (12)
C(18)	1469 (5)	4145 (3)	669 (5)	5.45 (19)	C(2')	2608 (4)	4081 (2)	4825 (2)	3.09 (12)
C(19)	1924 (5)	3405 (3)	586 (5)	5.11 (19)	C(3')	3276 (4)	4812 (3)	4323 (2)	3.13 (12)
C(20)	1898 (5)	2821 (3)	1378 (5)	4.57 (18)	C(4')	3267 (4)	5559 (3)	4731 (2)	3.29 (12)
C(21)	1382 (4)	2977 (3)	2246 (5)	3.86 (16)	H(1)	2250	6732	7342	2.80
C(1')	-4863 (4)	2004 (2)	3697 (4)	2.81 (14)	H(NA)	-89	7049	7651	2.67
C(2')	-4684 (4)	1190 (2)	3673 (4)	3.32 (15)	H(3,1)	-1596	7203	6657	3.42
C(3')	-3521 (5)	892 (2)	3866 (4)	3.81 (16)	H(3,2)	-51	6740	5917	3.42
C(4')	-2509 (4)	1391 (2)	4099 (4)	3.47 (15)	H(4,1)	-1172	5735	7635	3.06
H(1)	-831	3888	4869	2.91	H(4,2)	-985	5364	6751	3.06
H(N)	-2117	4391	3123	2.96	H(8,1)	2542	7099	5569	3.52
H(3,1)	-3500	3949	1355	3.09	H(8,2)	3812	6179	6101	3.52
H(3,2)	-3303	2933	2002	3.09	H(9)	989	5374	8191	3.04
H(4,1)	-4483	4338	2584	2.98	H(10,1)	350	3863	8280	3.78
H(4,2)	-5085	3363	2049	2.98	H(10,2)	340	3650	7393	3.78
H(8,1)	-914	2610	4043	3.77	H(10,3)	1840	3339	7649	3.78
H(8,2)	-809	2730	5364	3.77	H(11,1)	3877	4477	7045	3.95
H(10,1)	-5449	4330	4280	3.66	H(11,2)	3636	5115	7817	3.95
H(10,2)	-5881	3547	3614	3.66	H(11,3)	3194	3949	8066	3.95
H(11,1)	-5149	2707	5500	5.20	H(12,1)	710	8298	5964	3.76
H(11,2)	-4559	3540	6165	5.20	H(12,2)	-799	8601	6430	3.76
H(11,3)	-6029	3450	5320	5.20	H(13,1)	-128	8614	7871	4.97
H(12,1)	-2059	2991	6330	4.32	H(13,2)	1690	8302	7153	4.97
H(12,2)	-1380	3745	6467	4.32	H(15)	2612	9745	6550	4.68
H(12,3)	-2793	3750	6536	4.32	H(16)	2501	11368	5938	4.91
H(13,1)	-2080	4973	5285	4.20	H(17)	31	12697	5684	5.11
H(13,2)	-3330	5016	3827	4.20	H(18)	-1940	12058	5975	4.71
H(13,3)	-3284	4991	5325	4.20	H(19)	-1750	10200	6729	4.15
H(14,1)	-1298	3106	1927	3.78	H(1')	1384	3546	6029	2.85
H(14,2)	-1470	3960	1499	3.78	H(2')	3230	3334	3949	4.21
H(15,1)	293	4416	3399	3.77	H(3')	3870	4861	3666	3.30
H(15,2)	588	3542	3999	3.77	H(4')	3852	6108	4276	3.42
H(17)	441	4797	1499	4.37	<b>Phenazocine (B)</b>				
H(18)	1499	4582	0	5.12	Br(B)	2433 (0)	1196 (0)	123 (0)	5.47 (2)
H(19)	2206	3332	-166	4.97	O(W)	8649 (3)	7075 (2)	8705 (2)	6.56 (12)
H(20)	2067	2210	1272	4.68	O(2'B)	3365 (2)	3930 (1)	1033 (1)	3.76 (9)
H(21)	1480	2518	3054	3.92	C(1)	2058 (3)	8896 (2)	-60 (2)	2.10 (10)
H(1')	-5780	2229	3366	3.02	N(B)	3543 (3)	9018 (2)	-502 (1)	2.25 (9)
H(2')	-6470	938	3332	4.57	C(3)	4675 (3)	8023 (2)	-343 (2)	2.58 (11)
H(3')	-3349	196	3949	3.91	C(4)	4564 (4)	7542 (2)	648 (2)	2.84 (12)
H(4')	-1523	1238	4239	3.60	C(5)	3065 (4)	7427 (2)	1136 (2)	2.29 (11)
<b>Phenazocine (A)</b>					C(6)	2773 (3)	6690 (2)	736 (2)	2.23 (11)
Br(A)	4928 (0)	7096 (0)	7338 (0)	4.44 (1)	C(7)	2125 (4)	7079 (2)	-13 (2)	2.67 (11)
O(2'A)	2624 (3)	3294 (2)	4489 (1)	4.34 (9)	C(8)	1679 (4)	8206 (2)	-458 (2)	2.77 (11)

Table 2 (cont.)

	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i> <sub>eq</sub> or <i>B</i> <sub>iso</sub> (Å <sup>2</sup> )		<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i> <sub>eq</sub> or <i>B</i> <sub>iso</sub> (Å <sup>2</sup> )
C(9)	1997 (4)	8502 (2)	954 (2)	2.30 (11)	H(8,1)	2200	8249	-1220	2.83
C(10)	3058 (4)	7024 (2)	2155 (2)	3.13 (12)	H(8,2)	562	8460	-412	2.83
C(11)	444 (4)	8572 (3)	1458 (2)	3.07 (12)	H(9)	2329	8942	1280	2.11
C(12)	3695 (4)	9543 (2)	-1494 (2)	2.91 (12)	H(10,1)	3946	6335	2304	3.25
C(13)	4991 (5)	9920 (4)	-1815 (2)	5.53 (17)	H(10,2)	3100	7597	2423	3.25
C(14)	5173 (4)	10452 (3)	-2797 (2)	3.22 (12)	H(10,3)	2037	6953	2488	3.25
C(15)	4843 (5)	11496 (3)	-3068 (3)	5.00 (16)	H(11,1)	-192	9337	1262	2.96
C(16)	5058 (5)	11964 (4)	-4006 (4)	7.70 (22)	H(11,2)	93	8148	1248	2.96
C(17)	5601 (6)	11353 (5)	-4613 (3)	9.27 (25)	H(11,3)	344	8323	2179	2.96
C(18)	5922 (6)	10338 (5)	-4345 (3)	8.96 (24)	H(12,1)	3532	9071	-1830	2.87
C(19)	5721 (5)	9873 (3)	-3450 (3)	5.11 (16)	H(12,2)	2730	10227	-1549	2.87
C(1')	3195 (4)	5641 (2)	1082 (2)	2.59 (11)	H(13,1)	4887	10432	-1406	5.22
C(2')	2962 (4)	4975 (2)	702 (2)	2.87 (12)	H(13,2)	6025	9430	-1614	5.22
C(3')	2260 (4)	5354 (3)	-10 (2)	4.14 (14)	H(15)	4350	12000	-2630	5.01
C(4')	1866 (4)	6392 (3)	-365 (2)	3.88 (13)	H(16)	4819	12706	-4120	7.07
H(W1)	1452	2501	889	5.66	H(17)	5734	11801	-5400	7.97
H(W2)	1934	3332	1111	5.66	H(18)	6370	9850	-4842	8.20
H(1)	1395	9656	-192	2.31	H(19)	5920	9004	-3302	5.49
H(NB)	3626	9516	-155	2.10	H(1')	3827	5333	1615	2.75
H(3,1)	4513	7574	-681	2.38	H(2')	3798	3750	1601	3.85
H(3,2)	5694	8080	-595	2.38	H(3')	2123	4929	-450	3.94
H(4,1)	4810	7969	964	2.84	H(4')	1302	6646	-928	3.81
H(4,2)	5356	6759	807	2.84					

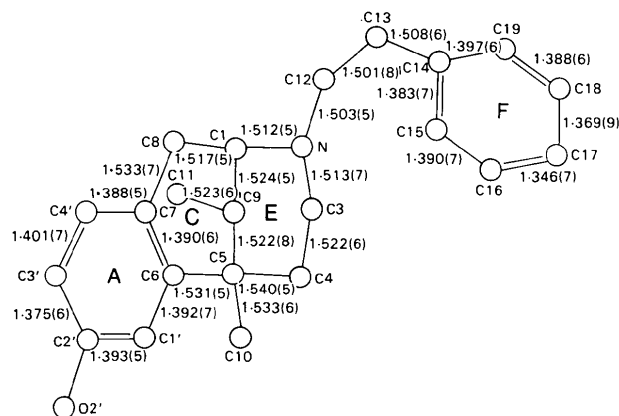


Fig. 2. Atomic numbering of phenazocine and bond lengths (Å) with e.s.d.'s in parentheses.

from the torsion angles in Table 4, the conformation of the benzomorphan nucleus is the same as in previously determined benzomorphan compounds (Gelders, De Ranter & Overbeek, 1979, and references therein). The differences between the two molecules appear in the steric conformation of the phenethyl substituent. Whereas the attachment of the side chain on the N atom is very similar [synclinal conformation for C(1)–N–C(14)–C(15) and antiperiplanar conformation for N–C(14)–C(15)–C(16)], the terminal phenyl ring *F* has a slightly different orientation. The difference in torsion angle of approximately 30° in the C(14)–C(15)–C(16)–C(17) or the C(14)–C(15)–C(16)–C(21) chains was examined for its significance by potential-energy calculations using

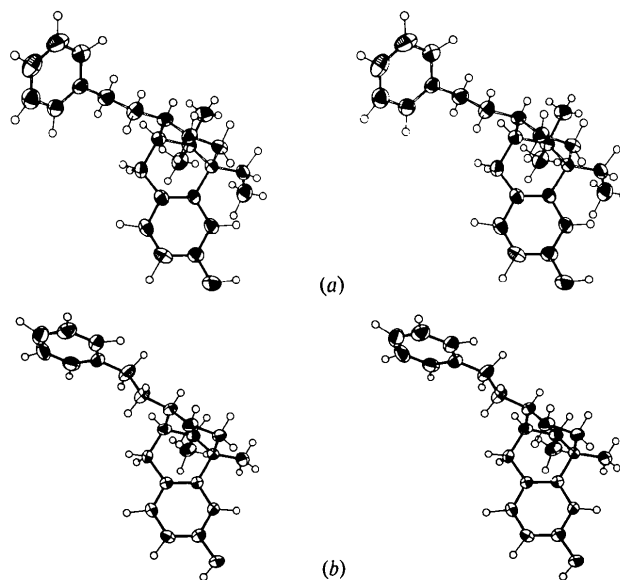


Fig. 3. Stereoscopic views of the levorotatory cations with 50% probability thermal ellipsoids for the non-hydrogen atoms for (a) dimephen, (b) phenazocine.

the program *EENY* (Motherwell, 1974) and empirical constants from Giglio (1969). From these calculations it resulted that within 8 kJ mol<sup>-1</sup> the terminal phenyl ring *F* can have any orientation, given that the N–C(14)–C(15)–C(16) torsion angle remains in its antiperiplanar conformation of about 180°. An additional point of interest in the energy considerations of the side chain is given in Fig. 4, which shows the re-

Table 3. Bond angles ( $^{\circ}$ ) with *e.s.d.*'s in parentheses using the atomic-numbering system of dimephen

	Dimephen	Phenazocine (A)	Phenazocine (B)
N-C(1)-C(8)	111.5 (4)	113.1 (3)	113.1 (3)
N-C(1)-C(9)	110.3 (4)	108.2 (3)	107.4 (3)
C(8)-C(1)-C(9)	111.1 (4)	111.8 (3)	112.1 (3)
C(1)-N-C(3)	112.9 (4)	112.0 (3)	111.4 (3)
C(1)-N-C(14)	115.2 (4)	115.0 (3)	113.3 (3)
C(3)-N-C(14)	107.7 (4)	110.9 (3)	112.1 (2)
N-C(3)-C(4)	113.2 (4)	109.8 (3)	111.5 (3)
C(3)-C(4)-C(5)	114.2 (4)	114.0 (4)	113.2 (4)
C(4)-C(5)-C(6)	106.9 (4)	109.0 (3)	108.4 (3)
C(4)-C(5)-C(9)	107.0 (4)	107.2 (3)	106.7 (3)
C(4)-C(5)-C(10)	104.9 (4)	107.8 (3)	107.8 (4)
C(6)-C(5)-C(9)	109.8 (3)	109.5 (3)	110.8 (4)
C(6)-C(5)-C(10)	113.5 (4)	113.1 (3)	112.1 (3)
C(9)-C(5)-C(10)	114.1 (4)	110.0 (3)	110.8 (3)
C(5)-C(6)-C(7)	120.7 (4)	120.4 (4)	119.4 (3)
C(5)-C(6)-C(1')	120.0 (4)	120.2 (4)	120.9 (4)
C(7)-C(6)-C(1')	119.2 (4)	119.3 (3)	119.6 (4)
C(6)-C(7)-C(8)	123.8 (4)	122.3 (3)	123.4 (4)
C(6)-C(7)-C(4')	119.2 (4)	119.7 (4)	118.4 (3)
C(8)-C(7)-C(4')	116.9 (4)	117.9 (4)	118.2 (4)
C(1)-C(8)-C(7)	114.5 (4)	115.0 (4)	114.8 (4)
C(1)-C(9)-C(5)	109.2 (4)	109.5 (3)	109.8 (3)
C(1)-C(9)-C(12)	106.2 (4)	110.5 (4)	109.7 (3)
C(1)-C(9)-C(13)	109.5 (4)		
C(5)-C(9)-C(12)	112.6 (4)	113.4 (4)	114.8 (3)
C(5)-C(9)-C(13)	112.3 (4)		
C(12)-C(9)-C(13)	106.8 (4)		
C(5)-C(10)-C(11)	120.4 (4)		
N-C(14)-C(15)	117.0 (4)	113.4 (3)	110.4 (4)
C(14)-C(15)-C(16)	105.8 (4)	111.3 (4)	112.0 (4)
C(15)-C(16)-C(17)	120.4 (5)	120.0 (4)	121.8 (4)
C(15)-C(16)-C(21)	121.7 (5)	121.4 (4)	119.4 (4)
C(17)-C(16)-C(21)	117.5 (6)	118.6 (4)	118.8 (4)
C(16)-C(17)-C(18)	120.7 (5)	120.2 (4)	119.8 (5)
C(17)-C(18)-C(19)	120.7 (6)	120.9 (5)	118.6 (4)
C(18)-C(19)-C(20)	120.0 (6)	119.9 (4)	121.3 (5)
C(19)-C(20)-C(21)	119.5 (5)	120.8 (4)	121.1 (6)
C(20)-C(21)-C(16)	121.6 (5)	119.6 (5)	120.5 (5)
C(6)-C(1')-C(2')	120.3 (5)	120.6 (4)	120.6 (4)
O(2')-C(2')-C(1')	123.3 (5)	117.0 (4)	121.9 (4)
O(2')-C(2')-C(3')	116.2 (4)	122.7 (3)	117.8 (4)
C(1')-C(2')-C(3')	120.4 (5)	120.3 (4)	120.2 (4)
C(2')-C(3')-C(4')	120.1 (5)	119.1 (4)	119.2 (5)
C(7)-C(4')-C(3')	120.7 (5)	120.9 (4)	121.8 (4)

sults of the energy mapping for variations of C(1)-N-C(14)-C(15) and N-C(14)-C(15)-C(16) performed in steps of  $30^{\circ}$  for each torsion angle. These difference maps also show that even within the small energy interval of  $41.8 \text{ kJ mol}^{-1}$  a quite broad region of torsion angles is covered, confirming the fairly high flexibility of the side chain.

The small difference in narcotic activity between the two compounds thus cannot arise from the phenethyl substituent alone, but is probably due to a different method of interaction at the drug-receptor interface, caused by the mono- or dimethyl substitution on C(9).

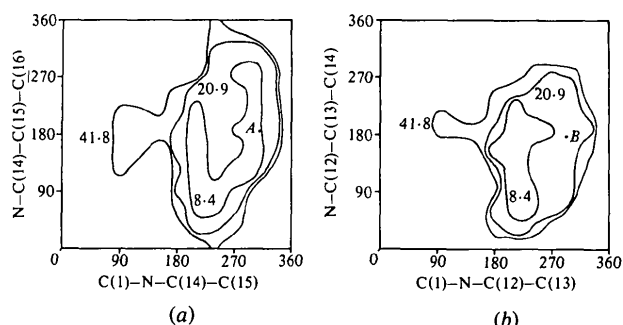


Fig. 4. Maps of the intramolecular potential-energy calculations for (a) dimephen and (b) phenazocine. The dots A and B indicate the experimental values and the contours are in  $\text{kJ mol}^{-1}$ .

Table 4. Torsion angles ( $^{\circ}$ ) with *e.s.d.*'s in parentheses, using the atomic-numbering system of dimephen

	Dimephen	Phenazocine (A)	Phenazocine (B)
<b>Ring A</b>			
C(7)-C(6)-C(1')-C(2')	1.8 (8)	0.7 (6)	-1.0 (5)
C(6)-C(1')-C(2')-C(3')	-1.6 (8)	-2.5 (6)	-2.1 (6)
C(1')-C(2')-C(3')-C(4')	0.6 (9)	3.2 (6)	3.4 (6)
C(2')-C(3')-C(4')-C(7)	0.2 (6)	-2.2 (6)	-1.5 (6)
C(3')-C(4')-C(7)-C(6)	0.0 (8)	0.4 (6)	-1.6 (6)
C(4')-C(7)-C(6)-C(1')	-1.0 (8)	0.3 (6)	2.8 (5)
<b>Ring C</b>			
C(8)-C(1)-C(9)-C(5)	-62.4 (4)	-61.3 (4)	60.4 (4)
C(1)-C(9)-C(5)-C(6)	55.2 (5)	58.2 (3)	-56.6 (4)
C(9)-C(5)-C(6)-C(7)	-26.6 (7)	-31.4 (4)	27.3 (4)
C(5)-C(6)-C(7)-C(8)	3.2 (8)	6.3 (6)	-0.4 (5)
C(6)-C(7)-C(8)-C(1)	-8.7 (8)	-7.5 (5)	3.1 (5)
C(7)-C(8)-C(9)-C(1)	38.2 (6)	35.0 (5)	-33.1 (4)
<b>Ring E</b>			
C(9)-C(1)-N-C(3)	-55.0 (5)	-61.5 (4)	60.5 (4)
C(1)-N-C(3)-C(4)	48.5 (5)	55.1 (4)	-55.3 (5)
N-C(3)-C(4)-C(5)	-49.9 (5)	-53.9 (4)	53.6 (5)
C(3)-C(4)-C(5)-C(9)	55.2 (5)	55.2 (4)	-55.6 (5)
C(4)-C(5)-C(9)-C(1)	-60.5 (5)	-60.0 (4)	61.2 (5)
C(5)-C(9)-C(1)-N	61.8 (5)	63.9 (4)	-64.4 (4)
<b>N side chain</b>			
C(1)-N-C(14)-C(15)	-47.6 (6)	-67.9 (4)	163.1 (3)
C(3)-N-C(14)-C(15)	-174.6 (4)	163.7 (3)	69.7 (5)
N-C(14)-C(15)-C(16)	-172.1 (4)	177.7 (3)	179.7 (3)
C(14)-C(15)-C(16)-C(17)	84.5 (5)	-122.6 (5)	104.2 (6)
C(14)-C(15)-C(16)-C(21)	-89.0 (5)	57.8 (5)	-77.4 (5)

The bond lengths and bond angles of the two compounds are within the expected limits. The only remark concerns the high thermal parameters in the phenyl ring F of the (+)-phenazocine molecule, which are probably due to the terminal position of this group. In the (-)-phenazocine molecule and in dimephen the effect is less pronounced. In both crystals the molecules are linked by hydrogen bonds between Br, O and N atoms, as shown in the packing schemes of Fig. 5; the hydrogen-bond data and numbering are given in Table 5. The dimephen molecules form endless parallel chains

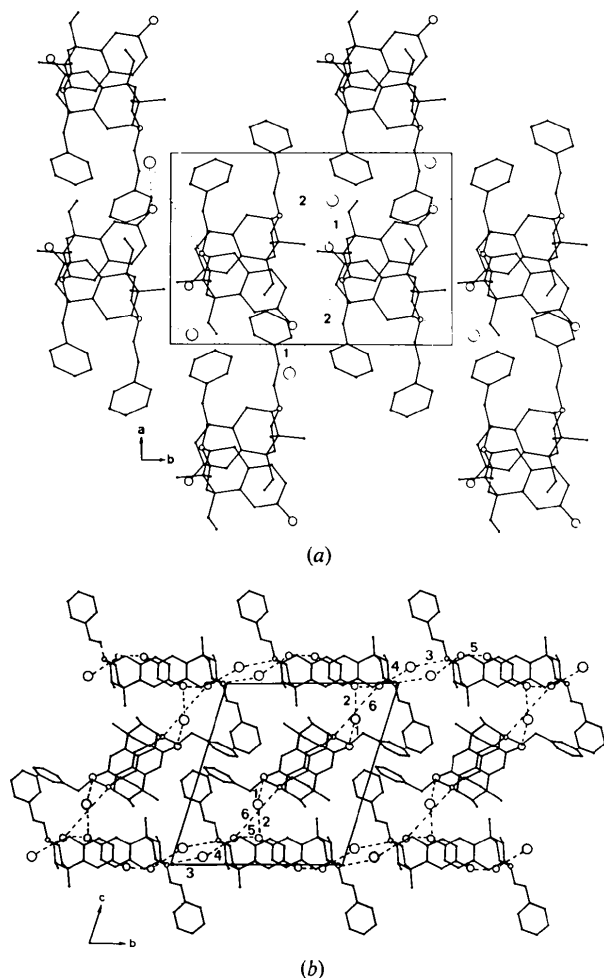


Fig. 5. Packing of the molecules and hydrogen-bonding schemes (a) for dimephen in the (001) plane and (b) for phenazocine.HBr. $\frac{1}{2}$ H<sub>2</sub>O in the (100) plane. Large, medium and small circles represent Br, O and N atoms respectively. The bond numbering refers to Table 5.

along the *a* axis; they are linked by hydrogen bonds to give V forms with the Br ions at the tips, and run mainly along the *b* axis. In phenazocine.HBr. $\frac{1}{2}$ H<sub>2</sub>O the network of hydrogen bonds is extended by the presence of one molecule of water for every two phenazocine molecules per asymmetric unit. The packing of the molecules in this crystal consists of two differently oriented chains in which the molecules are grouped two by two. Both types of chains are linked by

Table 5. *Hydrogen-bond distances (Å) and angles (°)*

Number used in Fig. 5	<i>D</i> -H... <i>A</i>	Angle	<i>D</i> -H	H... <i>A</i>	<i>D</i> ... <i>A</i>
<b>Dimephen</b>					
1	O(2')-H(O2')...Br	138.1	1.03	2.30	3.141 (4)
2	N-H(N)...Br	145.4	0.87	2.56	3.313 (4)
<b>Phenazocine</b>					
1	O(2'A)-H(O2'A)...Br(A)	163.2	0.90	2.40	3.273 (3)
2	O(2'B)-H(O2'B)...Br(A)	161.7	1.04	2.22	3.225 (3)
3	N(B)-H(NB)...Br(B)	139.4	1.06	2.38	3.262 (3)
4	O(W)-H(W1)...Br(B)	159.2	0.97	2.29	3.221 (4)
5	O(W)-H(W2)...O(2'B)	163.2	0.91	1.90	2.792 (6)
6	N(A)-H(NA)...O(W)	157.9	0.98	1.79	2.721 (4)

hydrogen bonds to the interlying Br ions and water molecules.

We thank Mr D. Heijdenrijk for making the X-ray measurements and Mr J. P. Van Cuyck for technical assistance. We acknowledge ACF Chemiefarma NV, The Netherlands, for supplying the sample of dimephen with its pharmacological data and Janssen Pharmaceutica, Belgium, for providing the sample of phenazocine.HBr. $\frac{1}{2}$ H<sub>2</sub>O. Two of the authors (YGG and CJDR) are indebted to the FGWO for financial support (project No. 3.0013.76).

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