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

**VI.\* (–)-(1R,5R,9R,13R)-2'-Hydroxy-5,9 $\alpha$ -dimethyl-2-(tetrahydrofurfuryl)-6,7-benzomorphan and (–)-(1R,5R,9R,13S)-2'-Hydroxy-5,9-dimethyl-2-(tetrahydrofurfuryl)-6,7-benzomorphan Tartrate Monohydrate**

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## Abstract

(–)-(1R,5R,9R,13R)-N-(Tetrahydrofurfuryl)normetazocine [2'-hydroxy-5,9 $\alpha$ -dimethyl-2-(tetrahydrofurfuryl)-6,7-benzomorphan],  $C_{19}H_{27}NO_2$ ,  $M_r = 301.43$ , crystallizes in the orthorhombic space group  $P2_12_12_1$  with  $a = 9.0022$  (5),  $b = 12.2825$  (3) and  $c = 14.840$  (1) Å,  $V = 1640.9$  Å<sup>3</sup>,  $D_m = 1.23$ ,  $D_c = 1.22$  Mg m<sup>-3</sup>,  $Z = 4$ ,  $\lambda(Cu K\alpha) = 1.5418$  Å,  $\mu = 0.623$  mm<sup>-1</sup>. The final  $R$  value is 0.046 for 1524 observed reflections. (–)-(1R,5R,9R,13S)-N-(Tetrahydrofurfuryl)normetazocine tartrate monohydrate,  $C_{19}H_{28}NO_2 \cdot C_4H_5O_6 \cdot H_2O$ ,  $M_r = 469.54$ , has monoclinic symmetry, space group  $P2_1$ , with  $a = 9.033$  (4),  $b = 16.106$  (7),  $c = 7.821$  (3) Å,  $\beta = 92.58$  (4)°,  $V = 1136.7$  Å<sup>3</sup>,  $D_m = 1.38$ ,  $D_c = 1.37$  Mg m<sup>-3</sup>,  $Z = 2$ ,

$\lambda(Mo K\alpha) = 0.71069$  Å,  $\mu = 0.113$  mm<sup>-1</sup>. The structure was refined to  $R = 0.038$  for 1689 observed reflections. Both structures were solved using direct methods of phase determination. Potential-energy calculations, using the structural data, suggest that the different action profiles of the diastereomers could be the result of an additional drug–receptor binding.

## Introduction

Since it was shown (Merz & Stockhaus, 1979) that some  $N$ -[tetrahydrofuryl(alkyl)]normetazocines‡ possess action profiles distinctly different from that of morphine and other classical opiates, it seemed worthwhile, as part of our investigation into the relationship between molecular structure and physio-

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‡ *Chemical Abstracts* name for normetazocine: 1,2,3,4,5,6-hexahydro-2,6-methano-6,11-dimethyl-3-benzazocin-8-ol.

logical properties of morphine-related compounds, to solve the crystal structures of the diastereomers  $(-)-(1R,5R,9R,13R)-$  and  $(-)-(1R,5R,9R,13S)-[2'$ -hydroxy-5,9 $\alpha$ -dimethyl-2-(tetrahydrofurfuryl)-6,7-benzomorphan], hereafter abbreviated by their code numbers Mr 1526 and Mr 2034 respectively.

final cycle was 0.09 and 0.15 $\sigma$ . Difference syntheses computed at this stage showed no significant features

Table 1. Atomic coordinates ( $\times 10^4$ ) and equivalent isotropic temperature factors ( $\text{\AA}^2$ ) with e.s.d.'s in parentheses

$$B_{eq} = \frac{1}{3} \sum_i \sum_j \beta_{ij} a_i \cdot a_j$$

Experimental	x	y	z	$B_{eq}$	
	Mr 1526				
	O(2')	2514 (1)	3258 (1)	1885 (1)	4.18 (5)
	C(1')	5078 (2)	3441 (2)	1592 (1)	2.86 (5)
	C(2')	3806 (2)	3806 (2)	2028 (1)	3.13 (5)
	C(3')	3896 (2)	4722 (2)	2576 (1)	3.37 (6)
	C(4')	5244 (2)	5246 (2)	2679 (1)	3.26 (6)
	C(1)	9339 (2)	4920 (2)	2070 (1)	2.95 (5)
	N(2)	9920 (2)	4081 (1)	2705 (1)	2.60 (4)
	C(3)	8940 (2)	3127 (1)	2801 (1)	2.84 (5)
	C(4)	8512 (2)	2657 (2)	1899 (1)	3.12 (6)
	C(5)	7845 (2)	3515 (2)	1249 (1)	2.99 (5)
	C(6)	6444 (2)	3969 (1)	1693 (1)	2.52 (5)
	C(7)	6524 (2)	4896 (1)	2247 (1)	2.66 (5)
	C(8)	7950 (2)	5526 (1)	2380 (1)	3.24 (6)
	C(9)	9041 (2)	4406 (2)	1145 (1)	3.32 (6)
	C(10)	8645 (3)	5270 (3)	444 (2)	4.93 (8)
	C(11)	7530 (3)	2958 (3)	351 (2)	4.53 (8)
	C(12)	10239 (2)	4558 (2)	3595 (1)	3.04 (5)
	C(13)	11175 (3)	3842 (2)	4206 (1)	3.44 (6)
	O(14)	10238 (2)	3096 (1)	4691 (1)	5.02 (6)
	C(15)	10702 (4)	3040 (3)	5608 (2)	5.36 (9)
	C(16)	12155 (4)	3641 (2)	5672 (2)	4.97 (8)
	C(17)	12009 (3)	4464 (2)	4928 (2)	4.73 (8)
	Mr 2034				
	O(2')	4072 (2)	223 (1)	7033 (3)	3.16 (6)
	C(1')	5973 (3)	1262 (2)	6991 (4)	2.54 (8)
	C(2')	4528 (4)	1007 (2)	6662 (4)	2.64 (8)
	C(3')	3491 (4)	1557 (2)	5923 (5)	3.12 (9)
	C(4')	3948 (4)	2343 (2)	5470 (5)	3.17 (10)
	C(1)	7406 (4)	3726 (2)	5738 (4)	2.85 (9)
	N(2)	7417 (3)	4146 (1)	7480 (3)	2.48 (7)
	C(3)	6977 (4)	3554 (2)	8857 (4)	2.79 (9)
	C(4)	7907 (4)	2778 (2)	8867 (5)	2.84 (9)
	C(5)	7976 (4)	2354 (2)	7100 (4)	2.65 (9)
	C(6)	6419 (3)	2059 (2)	6565 (4)	2.37 (8)
	C(7)	5415 (4)	2602 (2)	5760 (4)	2.74 (9)
	C(8)	5878 (4)	3440 (2)	5117 (5)	3.29 (10)
	C(9)	8507 (4)	3014 (2)	5821 (5)	3.10 (10)
	C(10)	8722 (6)	2661 (3)	4025 (6)	5.32 (14)
	C(11)	9112 (4)	1650 (2)	7262 (6)	3.57 (10)
	C(12)	6476 (4)	4914 (2)	7404 (5)	3.18 (10)
	C(13)	6833 (4)	5557 (2)	8738 (5)	3.25 (10)
	O(14)	8194 (3)	5948 (2)	8360 (5)	5.12 (9)
	C(15)	8129 (5)	6801 (3)	8635 (8)	5.45 (15)
	C(16)	6602 (5)	7006 (2)	9255 (6)	4.32 (12)
	C(17)	5708 (4)	6253 (2)	8708 (5)	3.56 (10)
	O(18)	10337 (2)	4958 (2)	5612 (3)	3.99 (8)
	C(19)	11580 (3)	4838 (2)	6171 (4)	2.60 (8)
	O(20)	12648 (2)	4534 (2)	5294 (3)	3.86 (7)
	C(21)	12083 (3)	5040 (2)	8007 (4)	2.65 (8)
	O(22)	11354 (3)	5732 (1)	8631 (3)	3.49 (7)
	C(23)	11844 (3)	4278 (2)	9128 (4)	2.72 (8)
	O(24)	10318 (2)	4166 (2)	9325 (3)	3.78 (7)
	C(25)	12711 (4)	4358 (2)	10854 (4)	2.70 (8)
	O(26)	14073 (2)	4460 (1)	10813 (3)	3.37 (7)
	O(27)	11958 (3)	4316 (2)	12154 (3)	3.97 (7)
	O(28)	8861 (3)	4745 (2)	12182 (3)	4.94 (9)

#### Determination and refinement of the structure

Both structures were solved by direct methods with *MULTAN* (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980) and refined with *XRAY* (Stewart, Machin, Dickinson, Ammon, Heck & Flack, 1976) by block-diagonal least squares, first with isotropic temperature factors and finally anisotropically. H atoms were located in a difference synthesis and included in the refinement in fixed positions with isotropic temperature factors (isotropic temperature factor of their parent atoms in Mr 1526; one overall temperature factor in Mr 2034). The refinements converged to  $R$  0.046 for Mr 1526 and 0.038 for Mr 2034. The weighting scheme was  $w = (A + |F_o| + B|F_o|^2 + C|F_o|^3)^{-1}$  with  $A = 150$  and 10.0,  $B = 0.01$  and 0.001, and  $C = 0.0025$  and 0.0, respectively. The average parameter shift during the

(maximum electron density 0.14 and 0.18 e Å<sup>-3</sup>).  
Final atomic coordinates are listed in Table 1.\*

\* Lists of structure factors, anisotropic thermal parameters and H-atom coordinates have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 38061 (33 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

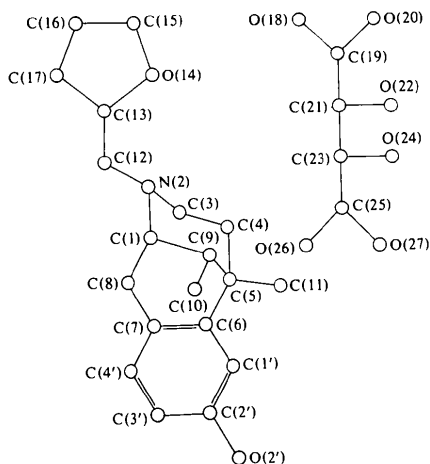


Fig. 1. Atomic-numbering scheme.

Table 2. Bond lengths (Å)

	Mr 1526	Mr 2034
O(2')—C(2')	1.360 (3)	1.363 (4)
C(1')—C(2')	1.389 (3)	1.381 (5)
C(1')—C(6)	1.399 (3)	1.390 (5)
C(2')—C(3')	1.391 (3)	1.396 (5)
C(3')—C(4')	1.382 (3)	1.382 (6)
C(4')—C(7)	1.387 (3)	1.399 (5)
C(1)—N(2)	1.490 (3)	1.522 (6)
C(1)—C(8)	1.526 (3)	1.514 (5)
C(1)—C(9)	1.536 (3)	1.517 (5)
N(2)—C(3)	1.474 (3)	1.505 (4)
N(2)—C(12)	1.473 (3)	1.500 (5)
C(3)—C(4)	1.508 (3)	1.506 (5)
C(4)—C(5)	1.549 (3)	1.545 (5)
C(5)—C(6)	1.529 (3)	1.525 (5)
C(5)—C(9)	1.543 (3)	1.550 (5)
C(5)—C(11)	1.524 (4)	1.531 (5)
C(6)—C(7)	1.406 (3)	1.390 (5)
C(7)—C(8)	1.512 (3)	1.505 (5)
C(9)—C(10)	1.528 (4)	1.535 (6)
C(12)—C(13)	1.519 (3)	1.494 (5)
C(13)—O(14)	1.437 (3)	1.424 (5)
C(13)—C(17)	1.515 (4)	1.512 (6)
O(14)—C(15)	1.426 (3)	1.393 (6)
C(15)—C(16)	1.504 (5)	1.519 (7)
C(16)—C(17)	1.504 (4)	1.509 (6)
O(18)—C(19)	—	1.203 (4)
C(19)—O(20)	—	1.304 (4)
C(19)—C(21)	—	1.521 (4)
C(21)—O(22)	—	1.394 (4)
C(21)—C(23)	—	1.530 (5)
C(23)—O(24)	—	1.405 (4)
C(23)—C(25)	—	1.536 (4)
C(25)—O(26)	—	1.243 (4)
C(25)—O(27)	—	1.250 (4)

## Results and discussion

The atomic-numbering scheme is given in Fig. 1. Bond lengths, bond angles and selected torsion angles are listed in Tables 2, 3 and 4, respectively. Mean-plane calculations are in Table 5. ORTEP stereopairs (Johnson, 1965) are shown in Fig. 2. Compared with the values in previously determined benzomorphan compounds (Gelders, De Ranter & Kokkes, 1980, and references therein) the bond lengths and angles are within the expected limits. It may be noted that the C—N bonds are on average longer by 0.03 Å in the

Table 3. Bond angles (°)

	Mr 1526	Mr 2034
C(2')—C(1')—C(6)	121.7 (2)	120.8 (3)
O(2')—C(2')—C(1')	118.2 (2)	121.9 (3)
O(2')—C(2')—C(3')	122.8 (2)	118.2 (3)
C(1')—C(2')—C(3')	119.0 (2)	119.9 (3)
C(2')—C(3')—C(4')	119.5 (2)	119.0 (3)
C(3')—C(4')—C(7)	122.3 (2)	121.6 (3)
N(2)—C(1)—C(8)	115.7 (2)	113.0 (3)
N(2)—C(1)—C(9)	110.0 (2)	108.7 (2)
C(8)—C(1)—C(9)	109.1 (2)	111.7 (3)
C(1)—N(2)—C(3)	113.7 (1)	111.6 (2)
C(1)—N(2)—C(12)	111.1 (1)	110.5 (2)
C(3)—N(2)—C(12)	110.3 (1)	112.6 (2)
N(2)—C(3)—C(4)	111.8 (2)	111.4 (3)
C(3)—C(4)—C(5)	113.0 (2)	114.0 (3)
C(4)—C(5)—C(6)	107.5 (1)	108.0 (2)
C(4)—C(5)—C(9)	106.0 (2)	107.5 (3)
C(4)—C(5)—C(11)	108.1 (2)	107.9 (3)
C(6)—C(5)—C(9)	111.1 (2)	110.2 (3)
C(6)—C(5)—C(11)	112.8 (2)	113.4 (3)
C(9)—C(5)—C(11)	111.1 (2)	109.6 (3)
C(1')—C(6)—C(5)	120.7 (2)	119.7 (3)
C(1')—C(6)—C(7)	118.9 (2)	120.0 (3)
C(5)—C(6)—C(7)	120.3 (2)	120.2 (3)
C(4')—C(7)—C(6)	118.6 (2)	118.6 (3)
C(4')—C(7)—C(8)	119.1 (2)	119.3 (3)
C(6)—C(7)—C(8)	122.3 (2)	122.0 (3)
C(1)—C(8)—C(7)	114.0 (1)	115.4 (3)
C(1)—C(9)—C(5)	108.9 (2)	108.9 (3)
C(1)—C(9)—C(10)	111.3 (2)	110.5 (3)
C(5)—C(9)—C(10)	113.5 (2)	113.1 (3)
N(2)—C(12)—C(13)	114.4 (2)	116.0 (3)
C(12)—C(13)—O(14)	110.0 (2)	108.8 (3)
C(12)—C(13)—C(17)	113.9 (2)	112.2 (3)
O(14)—C(13)—C(17)	105.0 (2)	104.7 (3)
C(13)—O(14)—C(15)	109.7 (2)	111.2 (3)
O(14)—C(15)—C(16)	106.9 (2)	108.0 (3)
C(15)—C(16)—C(17)	102.0 (2)	102.5 (3)
C(13)—C(17)—C(16)	102.9 (2)	104.0 (3)
O(18)—C(19)—O(20)	—	124.8 (3)
O(18)—C(19)—C(21)	—	122.9 (3)
O(20)—C(19)—C(21)	—	112.4 (2)
C(19)—C(21)—O(22)	—	112.1 (2)
C(19)—C(21)—C(23)	—	109.0 (3)
O(22)—C(21)—C(23)	—	111.1 (2)
C(21)—C(23)—O(24)	—	109.3 (2)
C(21)—C(23)—C(25)	—	110.9 (3)
O(24)—C(23)—C(25)	—	112.2 (2)
C(23)—C(25)—O(26)	—	117.1 (2)
C(23)—C(25)—O(27)	—	115.8 (2)
O(26)—C(25)—O(27)	—	127.1 (2)

Table 4. Selected torsion angles (°)

	Mr 1526	Mr 2034
<b>Ring A</b>		
C(7)–C(6)–C(1')–C(2')	–0.3 (4)	–1.5 (5)
C(6)–C(1')–C(2')–C(3')	0.2 (4)	–1.2 (6)
C(1')–C(2')–C(3')–C(4')	–0.4 (4)	2.5 (6)
C(2')–C(3')–C(4')–C(7)	0.6 (4)	–1.0 (6)
C(3')–C(4')–C(7)–C(6)	–0.7 (4)	–1.7 (6)
C(4')–C(7)–C(6)–C(1')	0.5 (3)	3.0 (6)
<b>Ring C</b>		
C(8)–C(1)–C(9)–C(5)	–66.1 (3)	–61.0 (4)
C(1)–C(9)–C(5)–C(6)	54.9 (3)	57.1 (4)
C(9)–C(5)–C(6)–C(7)	–24.4 (3)	–32.8 (5)
C(5)–C(6)–C(7)–C(8)	4.2 (4)	10.7 (5)
C(6)–C(7)–C(8)–C(1)	–14.9 (3)	–12.8 (5)
C(7)–C(8)–C(1)–C(9)	45.2 (3)	38.3 (5)
<b>Ring E</b>		
C(9)–C(1)–N(2)–C(3)	–55.9 (2)	–60.5 (4)
C(1)–N(2)–C(3)–C(4)	51.0 (2)	53.2 (4)
N(2)–C(3)–C(4)–C(5)	–53.0 (3)	–51.3 (4)
C(3)–C(4)–C(5)–C(9)	58.1 (3)	54.5 (4)
C(4)–C(5)–C(9)–C(1)	–61.5 (2)	–60.4 (4)
C(5)–C(9)–C(1)–N(2)	61.8 (2)	64.4 (4)
<b>N side chain</b>		
C(1)–N(2)–C(12)–C(13)	–165.8 (2)	–156.6 (3)
C(3)–N(2)–C(12)–C(13)	67.3 (3)	77.9 (4)
N(2)–C(12)–C(13)–O(14)	–85.9 (3)	72.1 (4)
N(2)–C(12)–C(13)–C(17)	156.5 (2)	–172.5 (3)
C(12)–C(13)–O(14)–C(15)	–136.9 (2)	138.9 (4)
C(13)–O(14)–C(15)–C(16)	–9.4 (4)	0.2 (4)
O(14)–C(15)–C(16)–C(17)	28.8 (4)	–18.8 (5)
C(15)–C(16)–C(17)–C(13)	–36.2 (3)	29.1 (4)
C(16)–C(17)–C(13)–O(14)	31.6 (3)	–29.8 (4)
C(16)–C(17)–C(13)–C(12)	152.0 (2)	–147.7 (4)

tartrate salt Mr 2034. The same effect was observed in cyclazocine [2-(cyclopropylmethyl)-2'-hydroxy-5,9-dimethyl-6,7-benzomorphan] and its HBr salt (Karle, Gilardi, Fratini & Karle, 1969). From Tables 4 and 5 it can be seen that in both substances the aromatic *A* ring [rings are named in the same way as in morphine (Gylbert, 1973)] is almost planar, the hydroaromatic *C* ring has the sofa form and the piperidine *E* ring has a slightly distorted chair conformation. The acute angles between the mean planes of rings *A* and *E*, and *C* and *E* confirm the general 'T' shape of the rigid morphine-derived analgesics. In Mr 1526 the molecules are linked by a single hydrogen bond between N and the phenolic O forming endless chains parallel to *a*. In Mr 2034, due to the presence of the tartrate ion and the water molecule, an extensive network of hydrogen bonds is formed.

Hydrogen-bond parameters are given in Table 6 and the packing of the molecules can be seen in Fig. 3. To obtain a plausible explanation for the different pharmacological behaviour of the diastereomers [Mr 1526 nalorphine-like agonist–antagonist; Mr 2034 ketazocine-like agonist (Merz & Stockhaus, 1979)] a

Table 5. Mean-plane calculations

(a) Deviations of atoms from planes ( $\text{\AA} \times 10^3$ ). Atoms marked with an asterisk define the plane. E.s.d.'s are *ca* 0.005  $\text{\AA}$  for Mr 1526 and 0.007  $\text{\AA}$  for Mr 2034

	Mr 1526	Mr 2034	Mr 1526	Mr 2034
<b>Ring A</b>				
O(2')	–22	–60	C(1)	316
C(1')*	0	0	C(5)	80
C(2')*	0	–14	C(6)*	1
C(3')*	–2	13	C(7)*	–2
C(4')*	3	2	C(8)	–25
<b>Ring C</b>				
C(1)*	80	30	C(7)*	50
C(5)*	–56	–3	C(8)*	–102
C(6)*	28	–28	C(9)	–700
<b>Ring E</b>				
C(1)*	–250	–284	C(4)*	227
N(2)*	193	227	C(5)*	–280
C(3)*	–184	–191	C(9)*	294
<b>Tetrahydrofuran (THF) ring</b>				
C(13)*	31	0	C(16)*	–30
O(14)*	–52	1	C(17)	542
C(15)*	50	–1		–472

(b) Interplanar angles (°)

	Mr 1526	Mr 2034
<i>A</i> – <i>E</i>	85.3 (2)	85.2 (3)
<i>C</i> – <i>E</i>	88.5 (2)	89.9 (3)
<i>A</i> –THF ring	73.0 (2)	43.4 (3)
<i>C</i> –THF ring	78.3 (2)	48.6 (3)
<i>E</i> –THF ring	21.8 (2)	61.6 (3)

conformational-energy study was performed using the program *EENY* (Motherwell, 1974) and empirical constants from Giglio (1969). The energy maps (Fig. 4) show the regions of minimum energy for the tetrahydrofurfuryl side chain. In Mr 1526, within *ca* 9 kJ above the energy minimum, the N(2)–C(12)–C(13)–O(14) torsion angle can take any value as long as C(1)–N(2)–C(12)–C(13) remains in the 210–240° region. For Mr 2034 the map shows several minima with one of particular interest. In the conformation with C(1)–N(2)–C(12)–C(13) 300° and N(2)–C(12)–C(13)–O(14) 90° (*E* = 12.9 kJ *versus* the minimum energy *E* = 8.6 kJ) the tetrahydrofuryl O is in a position very near to that of the O in ketazocine (2-cyclopropyl-2'-hydroxy-5,9-dimethyl-8-oxo-6,7-benzomorphan). In this particular position one of the lone pairs on O(14) projects away from the mean plane of the molecule (ring *C*), as in ketazocine, so that a supplementary binding site to the receptor becomes available. This could explain why Mr 2034 has a ketazocine-like action profile, whereas Mr 1526, because the conformation with a near-ketazocine oxygen position is energetically unfavourable, shows only a weak agonist–antagonist action.

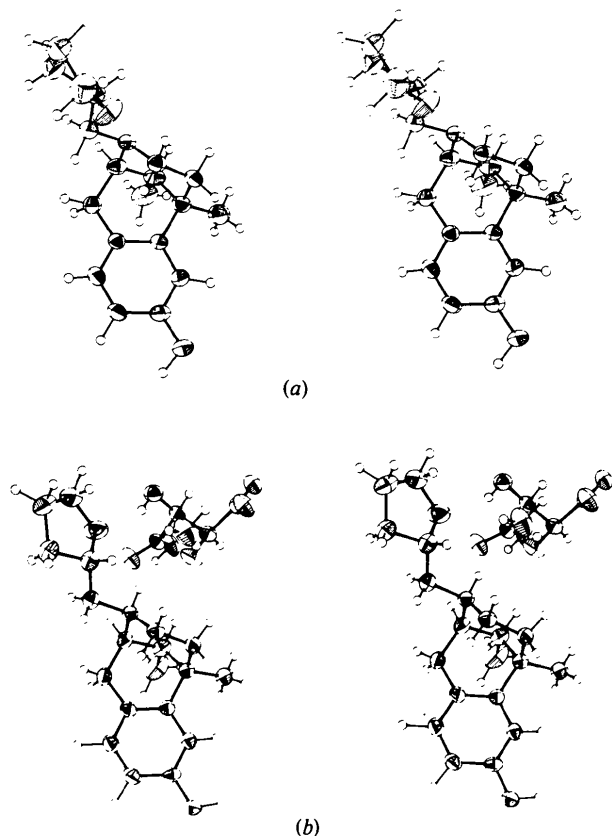


Fig. 2. Stereoscopic views with 50% probability ellipsoids for the non-hydrogen atoms of (a) Mr 1526 and (b) Mr 2034.

Table 6. Hydrogen-bond distances (Å) and angles (°)

## Mr 1526

A	B	C	AB	BC	AC	$\angle ABC$
O(2')—H(2')...N(2)			1.02	1.82	2.820 (3)	163.1

Symmetry code: none  $x, y, z$ ; (i)  $x - 1, y, z$ .

## Mr 2034

A	B	C	AB	BC	AC	$\angle ABC$
O(2')—H(2')...O(26')			0.99	1.64	2.626 (4)	169.2
N(2)—H(2)...O(24)			0.96	2.15	2.934 (4)	138.6
O(20)—H(20)...O(27 <sup>h</sup> )			1.09	1.44	2.531 (4)	175.0
O(22)—H(22)...O(14)			0.87	2.06	2.873 (4)	154.6
O(24)—H(24)...O(28)			0.95	1.90	2.803 (4)	156.5
O(28)—H(28A)...O(18 <sup>ll</sup> )			0.99	2.01	2.961 (4)	160.4
O(28)—H(28B)...O(2' <sup>lv</sup> )			0.84	2.06	2.852 (4)	159.2

Symmetry code: (i)  $-x + 2, y - \frac{1}{2}, -z + 2$ ; (ii)  $x, y, z - 1$ ; (iii)  $x, y, z + 1$ ; (iv)  $-x + 1, y + \frac{1}{2}, -z + 2$ .

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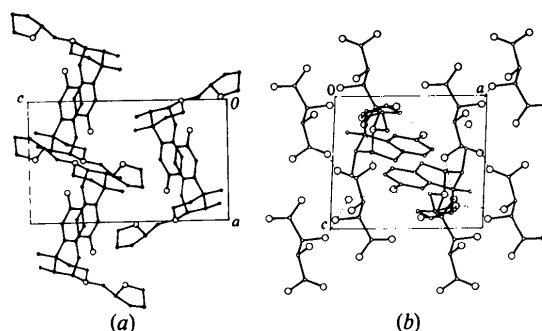


Fig. 3. Projections in the (010) plane showing the packing and the hydrogen-bond scheme for (a) Mr 1526 and (b) Mr 2034.

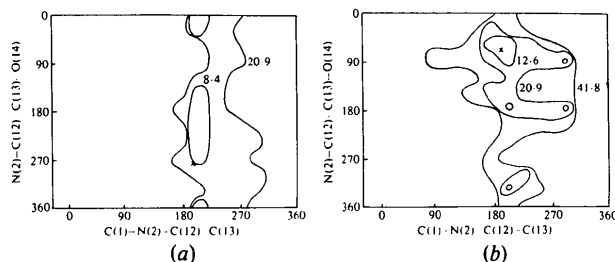


Fig. 4. Maps of the intramolecular potential-energy calculations for (a) Mr 1526 and (b) Mr 2034. The crosses indicate the experimental values; the contours are in  $\text{kJ mol}^{-1}$ .

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