

## Crystal Structures of Synthetic Analgetics. V. Dextromoramide

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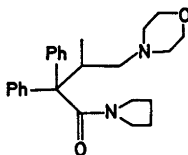
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The molecular and crystal structure of dextromoramide has been determined by X-ray methods. The crystals are orthorhombic, space group  $P2_12_12_1$  with unit cell dimensions  $a = 9.720(4)$  Å;  $b = 12.226(3)$  Å;  $c = 18.381(3)$  Å. The structure was determined by direct methods and the model refined to an  $R$ -value of 0.036 for 1788 observed reflections. The mean e.s.d.'s in bond lengths and angles are 0.004 Å and  $0.3^\circ$ , respectively.

The morpholine moiety is nearly in *anti* position relative to the quaternary carbon atom C6, the pertinent angle C6—C7—C9—N2 being  $-159.4^\circ$ . This conformation is similar to that previously reported for the bitartrate of the title compound. The pyrrolidine ring has the *envelope* conformation and the amide group is strictly planar.

The conformations of some acyclic analgetics are discussed.

Dextromoramide is a synthetic analgetics related to methadone,<sup>1</sup> and the present X-ray



crystallographic investigation was undertaken as a part of a research program in this laboratory on compounds exerting analgesic activity.

Acyclic synthetic analgetics related to methadone exhibit pharmacological activity similar to that of morphine and their activity may be dependent on a specific conformation, as proposed by Beckett *et al.*<sup>2-3</sup>

Recently the proposed molecular conformation was confirmed by X-ray crystallographic investigations on methadone.<sup>4-5</sup> The conformational flexibility of these compounds

is exemplified by the totally different conformation of methadone in the crystal structures of the hydrobromide<sup>6</sup> and of the free base.<sup>4</sup> This has encouraged the author in studying crystal structures of analgetics with the parent molecules in different environments.

In a previous paper the crystal structure of the bitartrate of the title compound<sup>7</sup> has been reported and here the X-ray analysis of the free base is presented.

### EXPERIMENTAL

Dextromoramide was prepared from the commercial dextromoramide bitartrate and crystallized readily at room temperature by slow evaporation from a diethyl ether solution. A single crystal of dimensions 0.2 mm × 0.3 mm × 0.4 mm was used for the experiments.

The crystals are orthorhombic and systematically absent reflections  $h00$ ,  $0k0$  and  $00l$  for odd indices are compatible with space group  $P2_12_12_1$ . Unit cell dimensions were determined on a Syntex PI diffractometer with graphite crystal monochromated  $\text{MoK}\alpha$ -radiation ( $\lambda = 0.71069$  Å).

Three-dimensional intensity data were collected applying the  $2\theta-\theta$  autocollection program with variable scan rate ( $2-8^\circ \text{ min}^{-1}$ ). The scan range was from  $1.0^\circ$  below  $2\theta$  ( $\alpha_1$ ) to  $1.0^\circ$  above  $2\theta$  ( $\alpha_2$ ) and the background was counted for 0.7 times the scan time. The intensities of three standard reflections were measured periodically during the collection of data; they did not show any systematic variation. E.s.d.'s in the intensities were taken as the square root of the total counts with a 2% addition for instrumental stability.

A total of 2238 independent reflections with  $\sin \theta/\lambda < 0.60$  were recorded; 1788 had a net count larger than  $2.5 \sigma_I$ .

The data were corrected for Lorentz and polarization effects.

All calculations were performed on a CYBER-74 computer utilizing the programs in Ref. 8, except for the phase determination.<sup>9</sup> Atomic form factors were those of Hanson *et al.*<sup>10</sup> for O, N and C and of Stewart *et al.*<sup>11</sup> for H.

### CRYSTAL DATA

Dextromoramide,  $C_{25}H_{32}N_2O_2$ , orthorhombic.  $a = 9.720(4)$  Å,  $b = 12.226(3)$  Å,  $c = 18.381(3)$  Å.  $V = 2184.3$  Å<sup>3</sup>,  $M = 392.55$ ,  $Z = 4$ .

$D_{obs} = 1.20$  g cm<sup>-3</sup> (floatation),  $D_{calc} = 1.19$  g cm<sup>-3</sup>  
Systematic absences:  $h00$ ,  $0k0$ ,  $00l$  for odd indices; space group  $P2_12_12_1$ .

### STRUCTURE DETERMINATION

A preliminary scale factor and an overall isotropic temperature factor ( $B = 3.7$  Å<sup>2</sup>) were derived by Wilson's statistical method and used for calculation of normalized struc-

ture factors. The phases of 400 reflections ( $E > 1.25$ ) were determined by MULTAN.<sup>9</sup> Only nine out of 35 peaks in the "best"  $E$ -map could be associated with reasonable atomic positions, and this fragment was the basis for another phase determination as proposed by Karle.<sup>12</sup> Successive fragment refinements including an increased number of atoms, eventually gave an  $E$ -map where all the 29 non-hydrogen atoms could be recognized. Anisotropic full-matrix least-squares refinements gave an  $R$ -factor of 0.10 and approximate positional parameters of all the 32 hydrogen atoms were calculated from stereochemical considerations. All the hydrogen parameters were refined, including the isotropic temperature factors, although atoms bonded to the same carbon atom were ascribed common  $B$ -values.

The refinement converged at  $R = 0.036$  ( $R_w = 0.036$ ) for the 1788 observed reflections.

Table 1. Positional and thermal parameters for the heavy atoms ( $10^5$ ) and the hydrogen atoms ( $10^4$ ) with e.s.d.'s in parentheses.

ATOM	X	Y	Z	B11	B22	B33	B12	B13	B23
C1	72617(31)	44926(25)	37884(17)	1109( 38)	822( 26)	456( 12)	239( 57)	-284( 35)	244( 38)
C2	81374(39)	84939(30)	39887(21)	1181( 41)	1045( 32)	703( 18)	-121( 78)	-392( 48)	484( 42)
C3	75905(39)	63343(29)	34172(21)	1673( 54)	869( 28)	646( 16)	-675( 65)	-899( 51)	346( 38)
C4	61578(34)	80853(23)	32489(18)	1273( 42)	588( 22)	529( 15)	-226( 52)	-162( 43)	353( 29)
C5	48757(38)	42653(21)	34178(14)	1156( 36)	429( 19)	283( 9)	115( 48)	-77( 33)	81( 23)
C6	3524(25)	47136(18)	35663(13)	987( 32)	482( 17)	231( 8)	+7( 42)	-86( 27)	55( 21)
C7	24856(28)	37787(20)	36743(13)	1126( 35)	447( 17)	234( 8)	-95( 42)	-33( 31)	48( 28)
C8	11897(32)	39684(23)	28742(14)	1314( 41)	692( 22)	287( 9)	-399( 54)	-185( 35)	87( 25)
C9	18619(38)	34771(21)	38204(14)	1212( 37)	528( 19)	263( 9)	-67( 49)	-25( 32)	-22( 22)
C10	22791(31)	15378(23)	39427(16)	1099( 37)	592( 21)	425( 12)	8( 52)	227( 36)	145( 27)
C11	16269(35)	4117(24)	3664(20)	1497( 46)	596( 22)	567( 15)	-277( 59)	425( 48)	117( 31)
C12	-4611(33)	11829(38)	42537(18)	1149( 48)	1108( 33)	398( 12)	-513( 64)	174( 38)	388( 35)
C13	1484(31)	2243(13)	43368(16)	1101( 38)	702( 23)	333( 18)	216( 53)	285( 38)	285( 26)
C14	20628(26)	56918(29)	36828(13)	945( 31)	423( 17)	242( 8)	-187( 42)	-8( 38)	94( 28)
C15	33694(29)	86487(21)	42256(14)	1183( 36)	542( 19)	256( 9)	-68( 48)	8( 31)	56( 23)
C16	27983(35)	66519(24)	46942(15)	1627( 49)	734( 24)	282( 18)	-375( 63)	151( 38)	-85( 27)
C17	18175(35)	73584(24)	43887(18)	1478( 44)	651( 22)	417( 13)	145( 59)	278( 42)	-269( 29)
C18	13887(32)	72198(23)	36892(19)	1218( 42)	631( 22)	475( 14)	274( 53)	59( 48)	7( 29)
C19	19885(36)	43988(22)	32598(14)	1178( 36)	548( 28)	294( 18)	183( 58)	-155( 33)	-3( 23)
C20	39183(27)	49153(19)	22888(14)	945( 32)	442( 18)	263( 9)	-118( 43)	-84( 38)	3( 21)
C21	37878(29)	88838(21)	18888(14)	1181( 35)	514( 19)	274( 9)	-252( 46)	-83( 32)	45( 23)
C22	48776(32)	59535(24)	11448(16)	1321( 48)	741( 24)	265( 18)	-834( 56)	-93( 35)	121( 27)
C23	45375(34)	58468(29)	7741(16)	1508( 44)	974( 38)	258( 18)	-685( 62)	123( 37)	16( 31)
C24	47428(35)	48833(26)	11399(17)	1558( 47)	889( 26)	325( 11)	-374( 62)	369( 39)	-137( 30)
C25	44449(32)	40238(22)	18741(16)	1387( 42)	585( 21)	354( 11)	-118( 51)	171( 36)	23( 25)
N1	59844(23)	49184(17)	34819(13)	929( 27)	535( 16)	378( 8)	139( 38)	-184( 28)	198( 28)
N2	12513(22)	23769(16)	38127(11)	988( 28)	532( 18)	252( 7)	-141( 37)	182( 28)	52( 18)
O1	49424(23)	33218(15)	36243(12)	1497( 29)	475( 14)	588( 9)	69( 36)	-434( 29)	
O2	5385(22)	2748(17)	3719(12)	1442( 29)	789( 16)	475( 9)	-294( 38)		

ATOM	X	Y	Z	B	ATOM	X	Y	Z	B
H1C1	7772(38)	3866(25)	3427(14)	6,3( .5)	H1C11	2237(38)	-75(28)	3985(17)	8,9( .6)
H2C1	6987(29)	4111(22)	4284(15)	6,3( .2)	H2C11	1189(34)	268(26)	3389(17)	8,9( .6)
H1C2	9067(37)	5399(25)	3935(18)	10,1( .7)	H1C12	-1198(27)	1806(21)	4613(13)	5,8( .4)
H2C2	7685(39)	5676(29)	4453(19)	10,1( .3)	H2C12	-724(27)	1618(21)	3748(13)	5,8( .9)
H1C3	8858(44)	8187(34)	2948(20)	11,1( .8)	H1C13	523(28)	2292(23)	4844(13)	5,4( .5)
H2C3	7859(43)	7897(32)	3474(20)	11,1( .2)	H2C13	-819(26)	2739(21)	4268(13)	5,4(1, .1)
H1C4	8642(38)	6477(28)	3582(18)	9,1( .7)	H1C15	4879(22)	8316(18)	4434(11)	3,6( .5)
H2C4	8898(38)	6289(28)	2818(19)	9,1( .2)	H2C15	3133(27)	6738(21)	8182(12)	5,8( .5)
H1C7	2949(22)	3181(17)	2894(18)	3,8( .5)	H1C17	1387(26)	7935(21)	4698(13)	5,8( .7)
H1C8	1415(27)	4158(23)	2885(14)	5,9( .4)	H1C18	686(29)	7738(22)	3459(14)	6,3( .7)
H2C8	688(28)	4644(21)	2691(14)	5,9( .2)	H1C19	1611(21)	6389(18)	2738(11)	2,8( .5)
H3B8	523(27)	3319(23)	2616(14)	5,9( .2)	H2C21	3458(21)	6829(17)	2131(11)	3,6( .5)
H1C9	1187(21)	3999(17)	3979(18)	3,1( .3)	H2C22	3978(24)	6694(19)	896(11)	4,2( .5)
H2C9	2597(22)	3543(17)	4173(18)	3,1( .2)	H2C23	4745(21)	5112(21)	238(13)	5,3( .9)
H1C10	2687(25)	1648(28)	4482(12)	4,6( .4)	H2C24	8171(29)	3364(24)	888(14)	6,8( .7)
H2C10	3837(25)	1617(19)	3892(12)	4,6( .2)	H2C25	4615(22)	3368(18)	2128(11)	3,6( .5)

Table 2. Interatomic distances (Å) and angles (°).

DISTANCE	(Å)	DISTANCE	(Å)	DISTANCE	(Å)
C1 - N1	1,474( 4)	C1 - C2	1,587( 4)	C2 - C3	1,466( 4)
C3 - C4	1,473( 3)	C4 - N1	1,478( 3)	C5 - N1	1,345( 3)
C5 - O1	1,218( 3)	C5 - C6	1,582( 4)	C6 - C7	1,576( 3)
C7 - C8	1,521( 4)	C7 - C9	1,531( 4)	C9 - N2	1,478( 3)
N2 - C10	1,482( 3)	C10 - C11	1,522( 4)	C11 - O2	1,428( 4)
C12 - O2	1,428( 4)	C12 - C13	1,581( 4)	C13 - N2	1,453( 3)
C6 - C14	1,538( 3)	C14 - C15	1,399( 3)	C15 - C16	1,386( 4)
C16 - C17	1,378( 4)	C17 - C18	1,383( 4)	C18 - C19	1,398( 4)
C19 - C14	1,395( 4)	C8 - C20	1,582( 3)	C20 - C21	1,377( 3)
C21 - C22	1,384( 4)	C22 - C23	1,378( 4)	C23 - C24	1,371( 4)
C24 - C25	1,382( 4)	C25 - C26	1,399( 4)		

ANGLE	(°)	ANGLE	(°)
C1 - N1 - C4	110,7( 2)	N1 - C1 - C2	104,4( 2)
C1 - C2 - C3	106,0( 3)	C2 - C3 - C4	108,0( 3)
C3 - C4 - N1	105,1( 3)	C1 - N1 - C5	119,4( 2)
C4 - N1 - C5	129,9( 2)	N1 - C5 - O1	120,0( 3)
N1 - C5 - C6	119,4( 2)	O1 - C5 - C6	120,9( 3)
C5 - C6 - C7	108,5( 2)	C5 - C6 - C14	110,8( 2)
C5 - C6 - C20	104,3( 2)	C7 - C6 - C14	100,5( 2)
C7 - C6 - C20	106,9( 2)	C14 - C6 - C20	117,4( 2)
C6 - C7 - C8	114,2( 2)	C6 - C7 - C9	114,9( 2)
C8 - C7 - C9	108,4( 2)	C7 - C9 - N2	109,9( 2)
C9 - N2 - C10	111,5( 2)	C9 - N2 - C13	113,8( 2)
C13 - N2 - C10	107,9( 2)	N2 - C10 - C11	109,7( 2)
C10 - C11 - O2	110,8( 3)	C11 - O2 - C12	109,8( 2)
O2 - C12 - C13	111,4( 2)	C12 - C13 - N2	109,9( 2)
C5 - C19 - C15	119,7( 2)	C6 - C14 - C19	121,4( 2)
C14 - C19 - C16	121,2( 3)	C15 - C16 - C17	121,2( 3)
C16 - C17 - C18	118,9( 3)	C17 - C18 - C19	120,1( 3)
C18 - C19 - C14	121,9( 3)	C19 - C14 - C15	116,6( 2)
C6 - C20 - C21	126,7( 2)	C6 - C20 - C25	116,7( 2)
C20 - C21 - C22	121,9( 3)	C21 - C22 - C23	120,8( 3)
C22 - C23 - C24	119,8( 3)	C23 - C24 - C25	119,8( 3)
C24 - C25 - C26	122,8( 3)	C25 - C26 - C21	116,5( 2)

Table 3. Torsional angles (°).

DIMEDRAL ANGLE	(°)	DIMEDRAL ANGLE	(°)
C1 - C2 - C3 - C4	23,8( 4)	C1 - N1 - C5 - O1	-2,3( 4)
C4 - N1 - C5 - O1	179,1( 3)	C1 - N1 - C5 - C6	-179,6( 2)
C4 - N1 - C5 - C6	1,7( 5)	N1 - C5 - C6 - C14	-61,8( 3)
N1 - C5 - C6 - C20	85,4( 3)	C5 - C6 - C14 - C19	-28,6( 3)
C5 - C6 - C20 - C25	58,7( 3)	C19 - C14 - C6 - C7	98,5( 3)
C21 - C20 - C6 - C7	121,1( 3)	C14 - C6 - C7 - C8	75,4( 3)
C20 - C6 - C7 - C8	-52,2( 3)	C14 - C6 - C7 - C9	-58,9( 3)
C20 - C6 - C7 - C9	-178,4( 2)	C6 - C7 - C9 - C2	-159,4( 2)
C7 - C9 - N2 - C10	87,8( 3)	C7 - C9 - C2 - C13	-156,8( 2)
C9 - N2 - C10 - C11	-175,7( 2)	C9 - N2 - C13 - C12	177,0( 2)
N2 - C10 - C11 - O2	-68,8( 3)	N2 - C13 - C12 - O2	58,0( 3)
C10 - C11 - O2 - C12	56,6( 3)	C11 - O2 - C12 - C13	-58,9( 3)

The final parameters are listed in Table 1, where the anisotropic temperature factor is given by

$$\exp - (B_{11}h^2 + B_{22}k^2 + B_{33}l^2 + B_{12}hk +$$

$$B_{13}hl + B_{23}kl)$$

A complete list of the observed and calculated structure factors may be obtained from the author on request.

## DISCUSSION

Interatomic distances and bond angles are listed in Table 2. Table 3 gives some dihedral angles. The e.s.d.'s are calculated from the correlation matrix.

Fig. 1 shows the dextromoramide molecule as seen along the *a*-axis.

The pyrrolidine ring has the *envelope* conformation with C2 being displaced by 0.31 Å out of a plane through the other ring atoms. This is about half the displacement found in moramide bitartrate (0.61 Å),<sup>7</sup> both values being in the range of displacements reported for proline-peptides.<sup>13</sup> A considerable thermal motion of the ring atoms C2 and C3 is probably the main reason for the short C-C single bonds of the ring.

The peptide unit -C6-C5(O1)-N1-(C1, C4) is strictly planar. Suggestions were made upon the influence of intramolecular repulsions being responsible for the slightly non-planar peptide group in the structure of dextromoramide bitartrate.<sup>7</sup> However, the planarity of this group in the present structure indicates that effects from crystal packing may

Table 4. Torsional angles ( $\tau$ ) and absolute configurations at  $C_\alpha$  or  $C_\beta$  of the most active enantiomer of some acyclic analgetics.

Compound	$\tau$ ( $^\circ$ )	Configuration	Ref.
1. (+)-Propoxyphene <sup>a</sup>	-176.6	R ( $C_\beta$ )	16
2. (+)-Moramide <sup>b</sup>	-166.5	R ( $C_\beta$ )	7
3. (+)-Propoxyphene	-174.2	R ( $C_\beta$ )	17
4. (+)-Moramide	-159.4	R ( $C_\beta$ )	Present work
5. (-)-Isomethadone <sup>a</sup>	-152.5	S ( $C_\beta$ )	18
6. (-)-Methadone	-68.5	R ( $C_\alpha$ )	4
7. (-)-Methadone	-69.8	R ( $C_\alpha$ )	5
8. (-)-Methadone <sup>c</sup>	-146.3 <sup>d</sup>	R ( $C_\alpha$ )	6
9. (+)-Methadol <sup>a</sup>	-116.1 <sup>d</sup>	R ( $C_\alpha$ ) <sup>e</sup>	18
10. (-)-Acetylmethadol <sup>a</sup>	-146.2	R ( $C_\alpha$ )	18

<sup>a</sup> Hydrochloride. <sup>b</sup> Bitartrate. <sup>c</sup> Hydrobromide.

<sup>d</sup> The sign has been changed to perform a direct comparison with the other values. <sup>e</sup> The configuration of the less active enantiomer.

also be responsible for the non-planarity of the bitartrate salt. The small lengthening of the C5-N1 bond, 1.356(3) Å, as compared to the accepted value (1.325 Å),<sup>14</sup> is in agreement with earlier reported values for similar peptide units.<sup>7,15</sup> The asymmetry of the bond angles around N1 agrees well with that of the bitartrate.

Earlier structure investigations on diphenylpropylamine analgetics have established the significance of non-bonded interactions on bond distances and angles.<sup>4,7,16-18</sup> The molecular distortions at the quaternary carbon atom (C6) (see Table 2) are similar in the

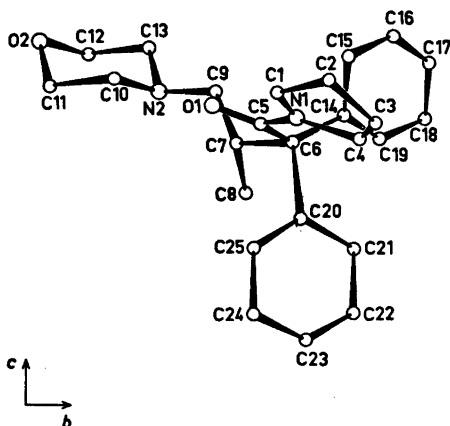


Fig. 1. The dextromoramide molecule with the numbering of the atoms indicated.

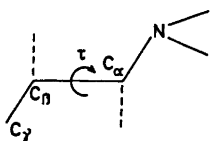
present structure. C-C single bonds involving C6 are increased by 0.04 Å as compared to their normal values,<sup>19-20</sup> and the C-C6-C bond angles vary from 104.3(2) to 117.4(2) $^\circ$ .

C6 is displaced by 0.12 Å and 0.11 Å from the planes of the two phenyl rings, respectively. These planes form an angle of 40.6 $^\circ$  which is far below the values found in methadone (80.6 $^\circ$ ) and moramide bitartrate (55.2 $^\circ$ ). The rather large angles C14-C6-C20 (117.4 $^\circ$ ), C6-C14-C19 (123.4 $^\circ$ ) and C6-C20-C21 (126.7 $^\circ$ ) are effecting a separation of the two rings to compensate non-bonded interactions between the rings. The hydrogen atoms at C19 (HC19) and C21 (HC21) are only 2.12 Å apart and there is another short intramolecular distance between the hydrogen atoms bonded to C7 and C25 (2.16 Å).

The propylamine chain with the morpholine moiety has the *extended* form, the dihedral angle C6-C7-C9-N2 being -159.4 $^\circ$ . This conformation is similar to the one found in the bitartrate, where the corresponding angle is -166.5 $^\circ$ . Thus the free base of moramide has a conformation different from that of methadone, which has a "folded" propylamine chain in the solid state.

An interesting conformational feature of the various acyclic analgetics studied by X-ray crystallographic methods so far, is the variation of the torsional angle,  $\tau$ , as defined below.

This torsional angle defines the position



of the amino group with respect to the quaternary carbon atom  $C_\gamma$  ( $C_6$  in the present paper). At present, there are ten crystal analyses available, which are listed in Table 4. The torsional angles refer to the analgetically more potent enantiomer, except for methadol which displays inversion of configurational selectivity at the receptor.<sup>21-22</sup> The compounds may be divided into two distinct classes, those having the *s*-Me group at  $C_\beta$  (Nos. 1-5, the isomethadone series) and the second class comprising those being substituted at the  $\alpha$  carbon atom (the methadone series).

The table reveals that the torsional angles may be divided into the same two classes. The variation of  $\tau$  among the first five compounds is comparatively small (roughly  $-165 \pm 12^\circ$ ) and thus shows the molecules in this class to be more rigid than the others. For the second group, including methadone, the table indicates a lack of conformational similarity. The difference in conformational flexibility of the compounds in the two classes confirms earlier suggestions.<sup>17,23</sup>

The crystal structure of dextromoramide is visualized in Fig. 2 and the crystal packing may be compared to that in the bitartrate. The moramide layers along the *b*-axis in the present structure resemble the chains parallel to the *c*-axis in the latter structure. The difference is mainly an expansion of about 8 Å in the *c* repeat unit of the bitartrate. Roughly,

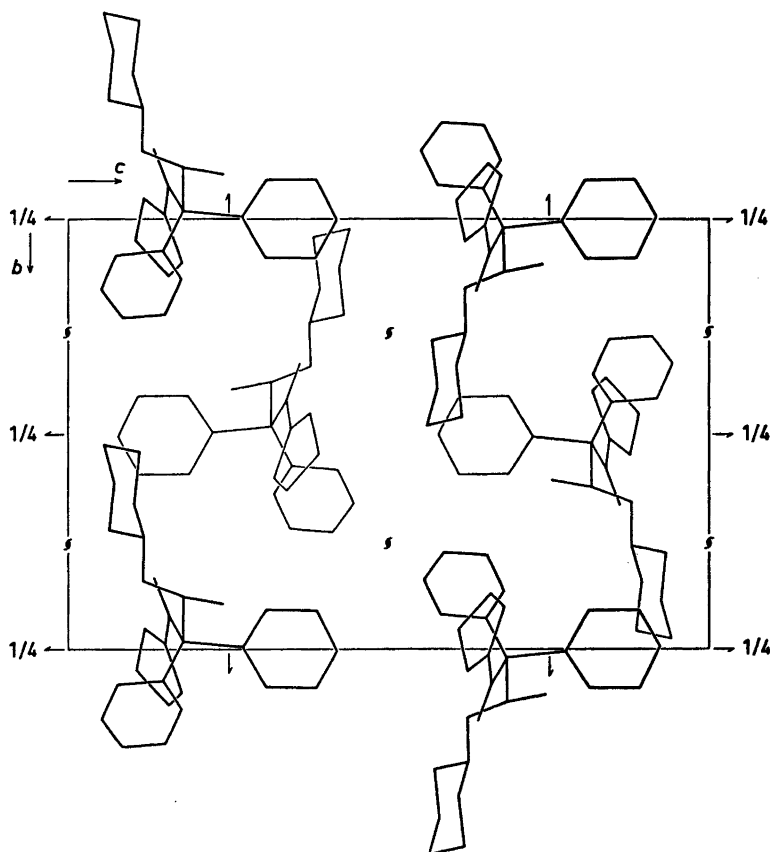


Fig. 2. The crystal structure of dextromoramide as seen along the *a*-axis.

this expansion seems to be the only modification necessary when comparing the structure of the moramide with that of the moramide bitartrate, to satisfy the crystal space requirements of the infinite chains of bitartrate ions along the *a*-axis.

There are no exceptionally short intermolecular distances in the present structure.

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