

Structure of the Diastereoisomeric Salt of (+)-4-*o*-Chlorophenyl-2-hydroxy-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinane and (1*R*,2*S*)-(-)- α -[(1-Methylamino)ethyl]benzyl Alcohol

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Abstract. $C_{21}H_{29}ClNO_3P$, $M_r = 441.89$, monoclinic, $P2_1$, $a = 19.6588$ (13), $b = 7.2079$ (11), $c = 7.9206$ (5) Å, $\beta = 100.728$ (5)°, $V = 1102.7$ Å³, $Z = 2$, $D_x = 1.331$ Mg m⁻³, Cu $K\alpha$ radiation (graphite-crystal monochromator, $\lambda = 1.54178$ Å), $\mu(\text{Cu } K\alpha) = 2.507$ mm⁻¹, $F(000) = 468$, $T = 290$ K, final conventional R factor = 0.030, wR = 0.041 for 3487 'observed' reflections and 351 variables. The crystal structure is stabilized by a network of N—H···O and O—H···O hydrogen bonds. The phosphorinane ring is in the usual chair conformation. The ephedrine, however, is in an unusual *cis* configuration (folded form).

Introduction. The present compound, denoted CLINAM, is the third of a series of crystal structure investigations on phosphorinane ephedrine salts. The other compounds (INAM, INAP, CLINAP) are presented in two preceding papers and one following paper. These structural investigations are part of a study on crystallization properties of diastereoisomers. CLINAM is the chlorine derivative of the first compound INAM (Kok, Wynberg, Smits, Beurskens & Parthasarathi, 1987; paper I). CLINAM and the following compound CLINAP (Kok, Wynberg, Parthasarathi, Smits & Beurskens, 1987; paper IV) form a pair of diastereoisomers. The title compound has been prepared from (+)-phosphorinane and (−)-ephedrine (see Fig. 1). The salt was recrystallized from ethanol/ethyl acetate before use. The melting point, 492.6 K, and the enthalpy of fusion, ΔH° , 48.95 kJ mol⁻¹, were measured with DSC. The solubility of this *n*-salt at 298 K in 100% and 50% ethanol is 5.6 and 8.6 (g/100 g solution) respectively. A comparison of structural results will be presented in paper IV.

Experimental. Nearly all X-ray experiments and calculations were performed as described in paper I and will not be repeated here. The differences are: size of irregularly shaped crystal 0.06 × 0.11 × 0.54 mm,

7505 reflections measured, 3788 unique ($R_{\text{int}} = 0.019$) of which 3487 observed; $h-9\rightarrow9$, $k-8\rightarrow5$, $l/0\rightarrow23$; drift: 1.00–1.05; absorption correction range: 0.80–1.00; DIFABS range: 0.88–1.16; Bijvoet coefficient: 0.991 (2). The structure was solved using DIRDIF (Beurskens *et al.*, 1983), which gave all non-hydrogen atoms, with the Cl and P positions from the best MULTAN solution as input (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980).

Discussion. Final positional and thermal parameters are given in Table 1.* Molecular geometry data are collected in Table 2. A stereoview of the molecule, showing the molecular configuration, is given in Fig. 1. In this figure the moieties are treated as separate entities and the ephedrine moiety is given in a projection along C(1)–H(1). The crystallographic numbering scheme is, except for the chlorine atom Cl(1), identical to that in paper I.

Table 2 also gives the hydrogen bonds. The structure contains phosphorinane cations and ephedrine anions which are linked in a three-dimensional network by N—H···O and O—H···O hydrogen bonds. Fig. 2 shows the crystal packing projected along the *c* axis. This figure clearly shows the nature of the packing: bilayers, parallel to the *bc* plane, held together internally by van der Waals contacts, mainly between the phenyl rings, and externally by the hydrogen bonds mentioned earlier.

The phosphorinane ring is in the usual chair conformation. The ephedrine, however, is in an unusual folded form (*cis* configuration). A table of torsion angles, showing the configuration of the ions, is

* Lists of structure factors, anisotropic thermal parameters and H-atom parameters not involving hydrogen bonds have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 43810 (18 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. Positional and equivalent isotropic thermal parameters with e.s.d.'s in parentheses

| | x | y | z | $U_{eq}(\text{\AA}^2 \times 100)$ |
|--------|-------------|-------------|-------------|-----------------------------------|
| Cl(1) | 0.03217 (4) | 0.9139 (1) | 0.8158 (1) | 5.61 (2) |
| P(2) | 0.22674 (2) | 0.51845 | 0.58562 (6) | 3.00 (2) |
| O(1) | 0.26816 (7) | 0.4671 (3) | 0.7728 (2) | 3.99 (5) |
| O(21) | 0.24371 (8) | 0.3723 (3) | 0.4670 (2) | 4.05 (5) |
| O(22) | 0.23907 (9) | 0.7146 (3) | 0.5459 (2) | 4.75 (6) |
| O(3) | 0.14846 (6) | 0.4888 (2) | 0.6043 (2) | 2.71 (4) |
| C(4) | 0.1254 (1) | 0.5829 (3) | 0.7468 (3) | 2.77 (6) |
| C(5) | 0.1686 (1) | 0.5143 (4) | 0.9183 (3) | 3.47 (6) |
| C(6) | 0.2447 (1) | 0.5575 (4) | 0.9156 (3) | 4.31 (8) |
| C(41) | 0.04803 (9) | 0.5530 (3) | 0.7218 (2) | 2.81 (6) |
| C(42) | 0.0022 (1) | 0.6938 (3) | 0.7470 (3) | 3.45 (7) |
| C(43) | -0.0689 (1) | 0.6674 (4) | 0.7132 (3) | 4.62 (9) |
| C(44) | -0.0951 (1) | 0.4960 (5) | 0.6613 (3) | 4.69 (9) |
| C(45) | -0.0515 (1) | 0.3524 (4) | 0.6385 (3) | 4.36 (8) |
| C(46) | 0.0196 (1) | 0.3825 (3) | 0.6665 (3) | 3.33 (7) |
| C(51) | 0.1601 (2) | 0.3060 (5) | 0.9436 (4) | 4.76 (9) |
| C(52) | 0.1489 (1) | 0.6195 (5) | 1.0678 (3) | 4.95 (9) |
| C(1) | 0.3889 (1) | 0.2023 (4) | 0.3827 (3) | 3.41 (7) |
| O(10) | 0.3412 (1) | 0.3215 (3) | 0.2811 (3) | 5.72 (7) |
| N(2) | 0.30644 (9) | 0.0303 (3) | 0.5313 (2) | 3.59 (6) |
| C(2) | 0.3571 (1) | 0.0127 (4) | 0.4109 (3) | 3.54 (6) |
| C(20) | 0.3383 (2) | 0.0635 (5) | 0.7137 (4) | 5.2 (1) |
| C(3) | 0.3204 (2) | -0.0752 (6) | 0.2455 (4) | 6.7 (1) |
| C(11) | 0.4509 (1) | 0.1790 (3) | 0.2963 (3) | 3.56 (7) |
| C(12) | 0.5130 (1) | 0.1140 (4) | 0.3902 (4) | 4.62 (8) |
| C(13) | 0.5706 (1) | 0.0929 (4) | 0.3115 (5) | 5.8 (1) |
| C(14) | 0.5661 (1) | 0.1352 (4) | 0.1420 (5) | 5.7 (1) |
| C(15) | 0.5049 (2) | 0.2021 (5) | 0.0479 (4) | 5.8 (1) |
| C(16) | 0.4477 (1) | 0.2239 (4) | 0.1255 (4) | 4.69 (8) |
| *H(10) | 0.308 (2) | 0.340 (6) | 0.343 (5) | 6.0 |
| *H(21) | 0.275 (2) | 0.134 (5) | 0.497 (4) | 6.0 |
| *H(22) | 0.280 (2) | -0.078 (5) | 0.524 (4) | 6.0 |

* Hydrogen atoms involved in hydrogen bridges.

Table 2. Selected distances (Å) and angles (°) with e.s.d.'s in parentheses

| | | | |
|------------------|-----------|------------------|-----------|
| Cl(1)–C(42) | 1.743 (3) | P(2)–O(3) | 1.588 (1) |
| P(2)–O(1) | 1.597 (2) | C(4)–C(5) | 1.543 (3) |
| P(2)–O(21) | 1.490 (2) | C(5)–C(6) | 1.531 (3) |
| C(2)–C(3) | 1.512 (4) | C(1)–C(11) | 1.516 (3) |
| O(3)–C(4) | 1.459 (2) | N(2)–C(2) | 1.507 (3) |
| C(1)–O(10) | 1.408 (3) | P(2)–O(22) | 1.479 (2) |
| C(5)–C(51) | 1.528 (4) | O(1)–C(6) | 1.453 (3) |
| C(5)–C(52) | 1.516 (3) | C(4)–C(41) | 1.513 (2) |
| N(2)–C(20) | 1.483 (3) | C(1)–C(2) | 1.536 (3) |
| C(1)–H(1) | 0.94 (3) | C(4)–H(4) | 0.92 (4) |
| N(2)–H(22) | 0.94 (3) | O(10)–H(10) | 0.90 (4) |
| C(6)–H(62) | 1.04 (3) | N(2)–H(21) | 0.97 (3) |
| C(2)–H(2) | 0.94 (3) | C(6)–H(61) | 0.98 (4) |
| C(1)–C(42)–C(43) | 117.1 (2) | C(1)–C(42)–C(41) | 121.1 (2) |
| C(2)–C(1)–C(11) | 110.5 (2) | P(2)–O(1)–C(6) | 116.0 (1) |
| O(10)–C(1)–C(2) | 112.4 (2) | O(10)–C(1)–C(11) | 108.4 (2) |
| C(1)–C(2)–N(2) | 110.6 (2) | C(1)–C(2)–C(3) | 112.9 (2) |
| N(2)–C(2)–C(3) | 108.6 (2) | C(2)–N(2)–C(20) | 114.9 (2) |
| O(1)–P(2)–O(21) | 106.6 (1) | O(1)–P(2)–O(22) | 110.1 (1) |
| O(1)–P(2)–O(3) | 102.6 (1) | O(21)–P(2)–O(22) | 118.5 (1) |
| O(21)–P(2)–O(3) | 107.4 (1) | O(22)–P(2)–O(3) | 110.4 (1) |
| P(2)–O(3)–C(4) | 117.1 (1) | O(3)–C(4)–C(5) | 109.4 (2) |
| O(3)–C(4)–C(41) | 106.4 (2) | C(5)–C(4)–C(41) | 116.4 (2) |
| C(4)–C(5)–C(51) | 112.0 (2) | C(4)–C(5)–C(52) | 110.4 (2) |
| C(4)–C(5)–C(6) | 107.6 (2) | C(51)–C(5)–C(52) | 109.8 (2) |
| C(6)–C(5)–C(51) | 109.4 (2) | C(6)–C(5)–C(52) | 107.5 (2) |
| O(1)–C(6)–C(5) | 111.8 (2) | | |
| C(2)–N(2)–H(21) | 110 (2) | C(2)–N(2)–H(22) | 109 (2) |
| C(20)–N(2)–H(21) | 106 (2) | C(20)–N(2)–H(22) | 109 (2) |
| H(21)–N(2)–H(22) | 108 (3) | C(1)–O(10)–H(10) | 105 (3) |

Possible hydrogen bonds.

Primed atoms: $-x, -0.5+y, -z$; D: donor atom; A: acceptor atom

| D | H | A | Angle | $D-H$ | $H-A$ | $D-A$ |
|----------------|--------|-----|--------|---------|---------|---------|
| N(2)–H(21)... | O(21) | | 159.6° | 0.973 Å | 1.826 Å | 2.761 Å |
| N(2)–H(22)... | O(22') | | 170.1 | 0.936 | 1.718 | 2.646 |
| O(10)–H(10)... | O(21) | | 176.1 | 0.899 | 1.752 | 2.650 |

presented and compared with other structures in paper IV.

All distances and angles are in the expected range. The shortest fourth-neighbour intramolecular contacts are C(46)–C(51): 3.240 (5) and P(2)–C(51): 3.672 (3) Å.

The shortest intermolecular contacts, excluding H atoms and apart from the contacts involved in hydrogen bonds, of which the longest is 2.761 (3) Å, are between O(1), O(21), O(22) and C(1), C(20) and range from 3.286 (3) to 3.306 (3) Å. The shortest contact between phenyl rings is C(42)–C(46): 3.498 (4) Å. Besides this, the bulky chlorine atom takes part in many van der Waals contacts, of which the shortest is Cl(1)–C(46): 3.572 (4) Å.

Although the structure differs from the structure of INAM (paper I), the same number of hydrogen bonds is found, which is in accordance with the fact that the

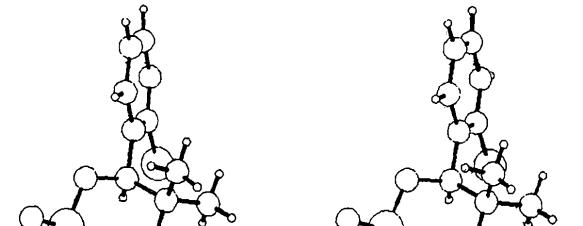


Fig. 1. Stereoview of the molecule, showing the molecular configuration. Top: (+)-dioxaphosphorinane moiety, bottom: (-)-ephedrine moiety. The ephedrine moiety is given as a projection along C(1)–H(1).

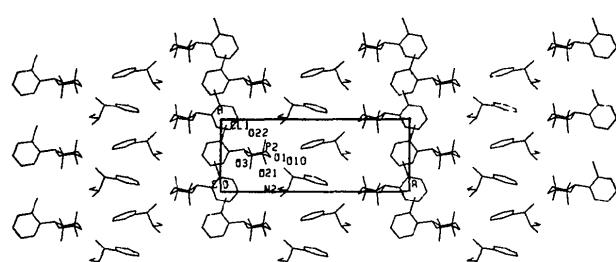


Fig. 2. Projection of the structure along the c axis.

salt-forming centres are the same. Comparison of Fig. 2 with the corresponding figure in paper I makes clear that, although different in detail, the packing is essentially the same.

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References

BEURSKENS, P. T., BOSMAN, W. P., DOESBURG, H. M., VAN DEN HARK, TH. E. M., PRICK, P. A. J., NOORDIK, J. H., BEURSKENS, G., GOULD, R. O. & PARTHASARATHI, V. (1983). *Conformation in Biology*, edited by R. SRINIVASAN & R. H. SARMA, pp. 389–406. New York: Adenine Press.

KOK, A. M. G., WYNBERG, H., PARTHASARATHI, V., SMITS, J. M. M. & BEURSKENS, P. T. (1987). *Acta Cryst. C43*, 1336–1341.

KOK, A. M. G., WYNBERG, H., SMITS, J. M. M., BEURSKENS, P. T. & PARTHASARATHI, V. (1987). *Acta Cryst. C43*, 1328–1331.

MAIN, P., FISKE, S. J., HULL, S. E., LESSINGER, L., GERMAIN, G., DECLERCQ, J.-P. & WOOLFSON, M. M. (1980). *MULTAN80. A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data*. Univs. of York, England, and Louvain, Belgium.

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Structure of the Diastereoisomeric Salt of (+)-4-*o*-Chlorophenyl-2-hydroxy-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinane and (1*S*,2*R*)-(+)- α -[(1-Methylamino)ethyl]benzyl Alcohol

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Abstract. $C_{21}H_{29}ClNO_5P$, $M_r = 441.89$, monoclinic, $P2_1$, $a = 13.8421$ (11), $b = 8.3808$ (6), $c = 9.8118$ (9) Å, $\beta = 99.672$ (7)°, $V = 1122.1$ Å³, $Z = 2$, $D_x = 1.308$ Mg m⁻³. Cu $K\alpha$ radiation (graphite-crystal monochromator, $\lambda = 1.54178$ Å), $\mu(\text{Cu } K\alpha) = 2.464$ mm⁻¹, $F(000) = 468$, $T = 290$ K, final conventional R factor = 0.043, wR = 0.057 for 3259 'observed' reflections and 348 variables. The structure contains phosphorinane cations and ephedrine anions which are linked in a three-dimensional network by N–H…O and O–H…O hydrogen bonds. The phosphorinane ring is in the usual chair conformation. The ephedrine is in the usual extended form. Related 1,3,2-dioxaphosphorinane and ephedrine compounds are compared.

Introduction. The present compound, denoted CLINAP, is the fourth of a series of crystal structure investigations on phosphorinane ephedrine salts. The other compounds (INAM, INAP, CLINAM) are presented in the three preceding papers [Kok, Wynberg, Smits, Beurskens & Parthasarathi (1987) (paper I); Smits, Beurskens, Kok & Wynberg (1987) (paper II);

Smits, Beurskens, Parthasarathi, Rijk, Kok & Wynberg (1987) (paper III)]. These structural investigations are part of a study on crystallization properties of diastereoisomers. CLINAP is the chlorine derivative of the second compound INAP (paper II), with which it was found to be isomorphous and isostructural except for the chlorine atom. CLINAP and the preceding compound CLINAM (paper III) form a pair of diastereoisomers.

The synthesis of the dioxaphosphorinane, a novel chiral acidic resolving agent, has recently been described by ten Hoeve & Wynberg (1985). The crystal structure of the diastereoisomeric *p*-salt with ephedrine has been determined in order to discover significantly different structural features as an aid in a resolution protocol. Studies related to this subject have been published by Briano (1981) and by Gould & Walkinshaw (1984).

The title compound has been prepared from (+)-phosphorinane and (+)-ephedrine (see Fig. 1). The salt was recrystallized from a mixture of ethanol and ethyl acetate before use. The melting point, 489.4 K, and the enthalpy of fusion, ΔH° , 41.42 kJ mol⁻¹, were