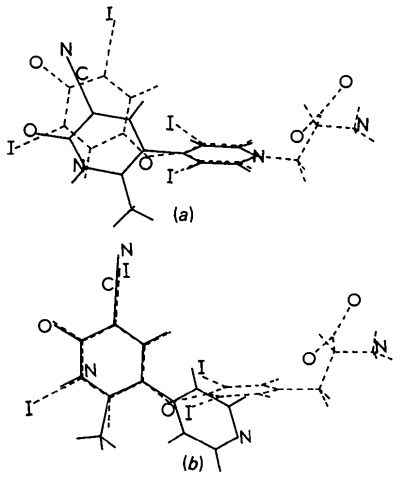

Fig. 3. (*a*) Superposition of the pyridine ring of milrinone (solid lines) on the tyrosyl ring of thyroxine (dashed lines). (*b*) Superposition of the pyridinone ring of milrinone (solid lines) on the phenolic ring of thyroxine (dashed lines). Note that the cyano group occupies the same space as the 5′-iodo group and that the keto and phenolic O atoms overlap in this orientation.

This research was supported in part by Grant AM-15051. The author thanks Walter Pangborn and Joe Luft for their technical assistance.

References

ALOUSI, A. A., FARAH, A. E., LESHER, G. Y. & OPALKA, C. J. (1979). *Circ. Res.* **45**, 666–677.

DETITTA, G. T., EDMONDS, J. W., LANGS, D. A. & HAUPTMAN, H. A. (1975). *Acta Cryst.* A**31**, 472–479.

ENDOH, M., YAMASHITA, S. & TAIRA, N. (1982). *J. Pharmacol. Exp. Ther.* **221**, 775–783.

GERMAIN, G., MAIN, P. & WOOLFSON, M. M. (1971). *Acta Cryst.* A**27**, 368–376.

International Tables for X-ray Crystallography (1974). Vol. IV. Birmingham: Kynoch Press. (Present distributor D. Reidel, Dordrecht.)

MYLOTTE, K. M., CODY, V., DAVIS, P. J., DAVIS, F. B., BLAS, S. D. & SCHOENL, M. (1985). *Proc. Natl Acad. Sci. USA*, **82**, 7974–7978.

ROBERTSON, D. W., BEEDLE, E. E., SWARTZENDRUBER, J. K., JONES, N. D., ELZEY, T. K., KAUFFMAN, R. F., WILSON, H. & HAYES, J. S. (1986). *J. Med. Chem.* **29**, 635–640.

STOUT, G. H. & JENSEN, L. H. (1968). *X-ray Structure Determination*. New York: Macmillan.

Acta Cryst. (1987). C**43**, 1328–1331

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

BY AGATHA M. G. KOK AND HANS WYNBERG

Organic Chemistry Department, University of Groningen, Nijenborgh 16, 9747 *AG Groningen, The Netherlands*

AND J. M. M. SMITS, PAUL T. BEURSKENS AND V. PARTHASARATHI

Crystallography Laboratory, University of Nijmegen, Toernooiveld, 6525 *ED Nijmegen, The Netherlands*

(*Received* 17 *September* 1986; *accepted* 23 *February* 1987)

Abstract. $C_{21}H_{30}NO_5P$, $M_r = 407{\cdot}445$, monoclinic, $P2_1$, $a = 13{\cdot}842$ (2), $b = 7{\cdot}804$ (2), $c = 10{\cdot}168$ (1) Å, $\beta = 92{\cdot}952$ (9)°, $V = 1096{\cdot}9$ Å^3, $Z = 2$, $D_x = 1{\cdot}234$ Mg m^{-3}, Cu $K\alpha$ radiation (graphite-crystal monochromator, $\lambda = 1{\cdot}54178$ Å), μ(Cu $K\alpha$) = 1·348 mm^{-1}, $F(000) = 436$, $T = 290$ K, final conventional R factor = 0·031, $wR = 0{\cdot}044$ for 2700 'observed' reflections and 342 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.

Introduction. The present compound, denoted INAM, is the first of a series of crystal structure investigations on phosporinane ephedrine salts. The other compounds (INAP, CLINAM, CLINAP) are presented in the three following papers. These structural investigations are part of a study on crystallization properties of diastereoisomers. INAM and the following compound INAP (Smits, Beurskens, Kok & Wynberg, 1987; paper II) 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 *n*-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 Brianso (1981) and Gould & Walkinshaw (1984).

0108-2701/87/071328-04$01.50

The title compound has been prepared by crystallization of the (+)-phosphorinane with (−)-ephedrine from ethanol (see Fig. 1). The melting point, 505·3 K, and the enthalpy of fusion, ΔH^f, 51·58 kJ mol^{-1}, were measured with DSC. The solubility of the *n*-salt at 298 K in 100% and 50% ethanol is 8·6 and 32·2 (g/100 g solution) respectively.

Despite the practical importance of resolutions of racemates *via* salt formation, there is no explanation or rationalization of the experimental results. We are trying to take a few, albeit uncertain, steps on the road to predicting resolution processes, using the crystal structures combined with physical data.

A comparison of structural results will be presented in paper IV of this series (with the structure report on CLINAP: Kok, Wynberg, Parthasarathi, Smits & Beurskens, 1987).

Experimental. All measurements were made at $T = 290$ K. An irregularly shaped crystal approximately 0·10 × 0·35 × 0·50 mm was used for the measurements. Throughout the experiment Cu $K\alpha$ radiation was used with a graphite-crystal monochromator on a Nonius CAD-4 single-crystal diffractometer ($\lambda = 1{\cdot}54178$ Å). The unit-cell dimensions were determined from the angular settings of 25 reflections with $22 < \theta < 42°$. The space group was determined to be $P2_1$ from the systematic absences $0k0$: $k = 2n + 1$ and the structure determination. The intensity data of 5768 reflections (half a sphere up to $\theta = 70°$ and two additional layers to be able to establish the absolute configuration) were measured, using the ω–2θ scan technique, with a scan angle of 1·50° and a variable scan rate with a maximum scan time of 15 s per reflection; h −16→16, k −2→9, l 0→12. The intensity of the primary beam was checked throughout the data collection by monitoring three standard reflections every 30 min. The final drift correction factors were between 1·00 and 1·09. Profile analysis was performed on all reflections (Lehmann & Larsen, 1974; Grant & Gabe, 1978); empirical absorption correction was applied, using ψ scans (North, Phillips & Mathews, 1968); correction factors were in the range 0·81–1·00. Lorentz and polarization corrections were applied and the data were reduced to $|F_o|$ values. Symmetry-equivalent reflections were averaged, $R_{F_{obs}} = \sum(F - \langle F \rangle)/\sum F = 0{\cdot}024$ for all reflections and 0·022 for the observed reflections only, resulting in 2884 unique reflections of which 2700 were observed with $F > 3\sigma(F)$.

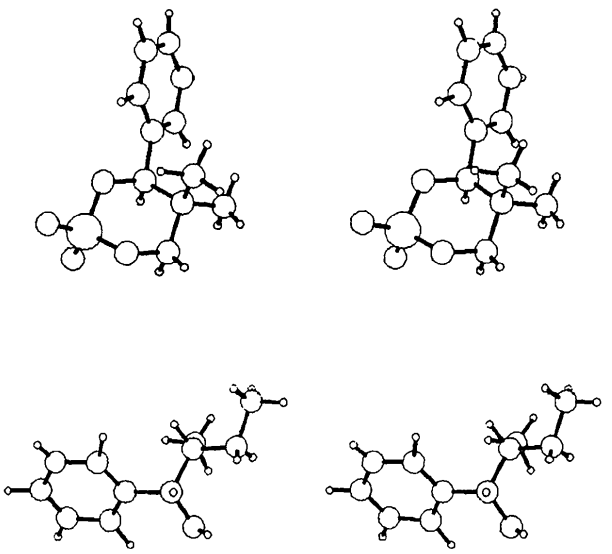

Fig. 1. Stereoview of the molecule, showing the molecular configuration. Top: (+)-dioxaphosphorinane moiety, bottom: (−)-ephedrine moiety. The ephedrine moiety is given as a projection along C(1)–H(1).

The structure was solved using the *ORIENT* option of the *DIRDIF* program system (Beurskens *et al.*, 1983) which employs the vector search methods of Nordman & Schilling (1970). With the 1,3,2-dioxaphosphorinane fragment of a related structure as input, the orientation, translation and structure expansion were performed automatically, and all non-hydrogen atoms were found.

Isotropic least-squares refinement, using *SHELX* (Sheldrick, 1976), converged to $R = 0{\cdot}116$. At this stage an empirical absorption correction was applied (Walker & Stuart, 1983), resulting in a further decrease of R to 0·103. Relative absorption correction factors were in the range 0·778–1·167. All H atoms were located from successive difference Fourier syntheses.

During the final stages of the refinement all positional parameters were refined, and the anisotropic temperature factors of all non-hydrogen atoms. The H atoms had fixed isotropic temperature factors of 0·06 Å^2.

The final conventional agreement factors were $R = 0{\cdot}031$ and $wR = 0{\cdot}044$ for 2700 'observed' reflections and 342 variables. The function minimized was $\sum w(F_o - F_c)^2$ with $w = 1/[\sigma^2(F_o) + 0{\cdot}0005F_o^2]$, $\sigma(F_o)$ from counting statistics. The maximum shift-over-e.s.d. ratio in the last full-matrix least-squares cycle was less than 0·02 for the non-hydrogen atoms and less than 0·06 for the H atoms. The final difference Fourier map showed no peaks higher than 0·20 e Å^{-3}. Near the end of the refinement the Bijvoet coefficient was calculated (Beurskens, Noordik & Beurskens, 1980). The result, $B = 0{\cdot}957$ (2) for 218 Friedel pairs, showed that the present parameter set describes the correct absolute configuration. The scattering factors used were those from *International Tables for X-ray Crystallography* (1974). Plots were drawn with *PLUTO* (Motherwell, 1976).

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

$U_{eq} = \frac{1}{3}\sum_i\sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j$

	x	y	z	U_{eq}(Å² ×100)
P(2)	0·44483 (4)	0·48155	0·25440 (5)	4·10 (1)
O(1)	0·4433 (1)	0·6221 (3)	0·1409 (2)	5·36 (5)
O(21)	0·4455 (1)	0·5711 (2)	0·3835 (1)	4·83 (5)
O(22)	0·5228 (1)	0·3554 (3)	0·2352 (2)	5·78 (6)
O(3)	0·3415 (1)	0·3925 (2)	0·2309 (1)	4·34 (4)
C(4)	0·3149 (1)	0·3306 (3)	0·0993 (2)	4·13 (6)
C(5)	0·3178 (2)	0·4793 (4)	0·0001 (2)	5·05 (6)
C(6)	0·4197 (2)	0·5557 (5)	0·0106 (2)	5·81 (8)
C(41)	0·2189 (1)	0·2415 (3)	0·1056 (2)	4·61 (7)
C(42)	0·1970 (2)	0·1030 (5)	0·0226 (3)	6·53 (9)
C(43)	0·1072 (3)	0·0232 (6)	0·0272 (4)	8·9 (1)
C(44)	0·0413 (2)	0·0761 (6)	0·1121 (4)	9·0 (1)
C(45)	0·0624 (2)	0·2104 (7)	0·1960 (4)	8·4 (1)
C(46)	0·1509 (2)	0·2936 (5)	0·1934 (3)	6·21 (9)
C(51)	0·2434 (2)	0·6165 (5)	0·0253 (3)	6·7 (1)
C(52)	0·3017 (3)	0·4095 (6)	−0·1397 (2)	7·2 (1)
C(1)	0·3026 (2)	1·0358 (4)	0·5857 (2)	4·74 (7)
O(10)	0·2977 (1)	0·8795 (4)	0·6533 (2)	7·38 (8)
N(2)	0·4206 (1)	0·9236 (3)	0·4335 (2)	4·31 (5)
C(2)	0·3222 (2)	1·0019 (4)	0·4400 (2)	4·87 (7)
C(20)	0·4694 (3)	0·9649 (5)	0·3106 (3)	6·41 (9)
C(3)	0·2489 (2)	0·8889 (6)	0·3694 (3)	7·3 (1)
C(11)	0·2115 (2)	1·1411 (5)	0·5950 (2)	5·83 (9)
C(12)	0·2098 (2)	1·3096 (5)	0·5476 (3)	7·2 (1)
C(13)	0·1270 (3)	1·4066 (8)	0·5560 (4)	9·8 (2)
C(14)	0·0464 (3)	1·342 (1)	0·6088 (5)	11·5 (2)
C(15)	0·0474 (2)	1·180 (1)	0·6552 (5)	11·6 (2)
C(16)	0·1301 (2)	1·0731 (7)	0·6507 (3)	8·4 (1)
*H(10)	0·345 (2)	0·869 (5)	0·685 (3)	6·0
*H(21)	0·418 (2)	0·823 (5)	0·438 (3)	6·0
*H(22)	0·463 (2)	0·973 (5)	0·501 (3)	6·0

* Hydrogen atoms involved in hydrogen bridges.

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. The crystallographic numbering scheme is given in Fig. 2. In these figures the moieties are treated as separate entities and the ephedrine moiety is given in a projection along C(1)—H(1).

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. 3 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 is in the usual extended

* 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 43808 (15 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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

C(1)–C(11)	1·512 (3)	P(2)–O(3)	1·5971 (1)
O(1)–C(6)	1·444 (3)	C(4)–C(5)	1·540 (4)
N(2)–C(20)	1·485 (3)	C(5)–C(6)	1·530 (3)
P(2)–O(22)	1·481 (2)	C(1)–O(10)	1·403 (4)
C(4)–C(41)	1·504 (3)	N(2)–C(2)	1·498 (3)
C(5)–C(52)	1·528 (3)	P(2)–O(21)	1·487 (2)
C(1)–C(2)	1·542 (3)	O(3)–C(4)	1·452 (2)
C(2)–C(3)	1·499 (4)	C(5)–C(51)	1·517 (4)
P(2)–O(1)	1·591 (2)		
C(1)–H(1)	0·96 (3)	C(4)–H(4)	1·01 (3)
N(2)–H(22)	0·97 (3)	O(10)–H(10)	0·72 (3)
C(6)–H(62)	1·13 (3)	N(2)–H(21)	0·79 (4)
C(2)–H(2)	1·04 (3)	C(6)–H(61)	0·88 (4)
C(2)–C(1)–C(11)	110·0 (2)	P(2)–O(1)–C(6)	114·3 (2)
O(10)–C(1)–C(2)	109·7 (2)	O(10)–C(1)–C(11)	112·3 (2)
C(1)–C(2)–N(2)	108·5 (2)	C(1)–C(2)–C(3)	114·4 (2)
N(2)–C(2)–C(3)	109·5 (2)	C(2)–N(2)–C(20)	113·7 (2)
O(1)–P(2)–O(21)	108·4 (1)	O(1)–P(2)–O(22)	110·2 (1)
O(1)–P(2)–O(3)	102·3 (1)	O(21)–P(2)–O(22)	117·2 (1)
O(21)–P(2)–O(3)	107·5 (1)	O(22)–P(2)–O(3)	110·2 (1)
P(2)–O(3)–C(4)	117·7 (1)	O(3)–C(4)–C(41)	107·3 (2)
O(3)–C(4)–C(5)	109·8 (2)	C(5)–C(4)–C(41)	115·4 (2)
C(4)–C(5)–C(51)	112·3 (2)	C(4)–C(5)–C(52)	109·5 (3)
C(4)–C(5)–C(6)	107·7 (2)	C(51)–C(5)–C(52)	109·9 (2)
C(6)–C(5)–C(51)	110·2 (3)	C(6)–C(5)–C(52)	107·1 (2)
O(1)–C(6)–C(5)	111·6 (2)		
C(2)–N(2)–H(21)	111 (2)	C(2)–N(2)–H(22)	109 (2)
C(20)–N(2)–H(21)	107 (2)	C(20)–N(2)–H(22)	103 (2)
H(21)–N(2)–H(22)	113 (3)	C(1)–O(10)–H(10)	105 (3)

Possible hydrogen bonds

Primed atoms: $1-x, 0{\cdot}5+y, 1-z$. *D*: donor atom; *A*: acceptor atom

D H *A*	Angle	*D*–H	H–*A*	*D*–*A*
N(2)–H(21)···O(21)	155·5°	0·791 Å	2·081 Å	2·822 Å
N(2)–H(22)···O(21′)	173·0	0·969	1·840	2·805
O(10)–H(10)···O(22′)	175·9	0·716	1·969	2·684

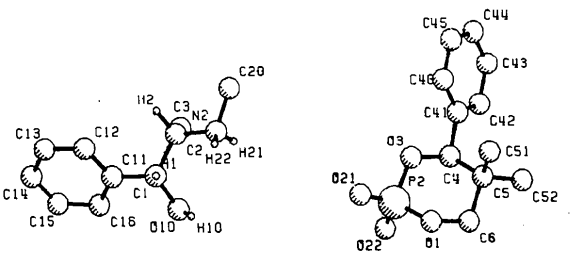

Fig. 2. Crystallographic atomic numbering scheme. The ephedrine moiety is given as a projection along C(1)—H(1).

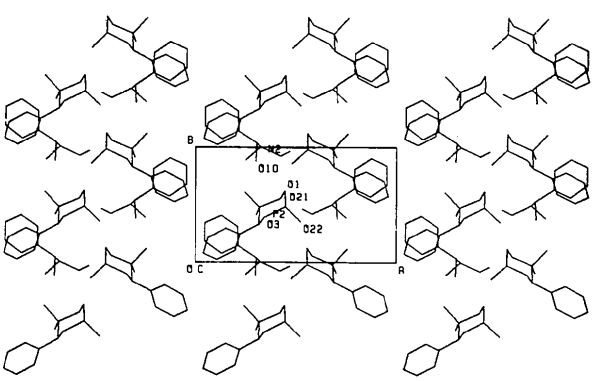

Fig. 3. Projection of the structure along the *c* axis.

form. A table of torsion angles, showing the configuration of the ions, is 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(42)···C(52): 3·285 (6), C(46)···C(51): 3·337 (6) and P(2)···C(51): 3·693 (4) Å. The shortest intermolecular contacts, excluding H atoms and apart from the contacts involved in hydrogen bonds, of which the longest is 2·822 (2) Å, are between O(21), O(22) and C(1), C(20) and range from 3·182 (3) to 3·372 (3) Å. The shortest contact between the phenyl rings of the separate moieties is 3·452 (6) Å between C(52) and C(12′) at x, $1+y$, $1+z$.

It is clear that this compound is a salt. The acidic H atom is attached to the N atom. The P—O(21) and P—O(22) bond lengths are almost the same.

This investigation was supported (in part) by the Netherlands Foundation of Technical Research (STW) with financial aid from the Netherlands Organization for the Advancement of Pure Research (ZWO). AMGK and HW gladly acknowledge close cooperation and fruitful discussions with Dr W. ten Hoeve (University of Groningen), Dr J. H. Noordik (University of Nijmegen) and with Dr A. Bruggink and co-workers of Océ-Andeno (Venlo, The Netherlands).

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.

BEURSKENS, G., NOORDIK, J. H. & BEURSKENS, P. T. (1980). *Cryst. Struct. Commun.* **9**, 23–28.

BRIANSO, N. C. (1981). *Acta Cryst.* B**37**, 618–620.

GOULD, R. O. & WALKINSHAW, M. D. (1984). *J. Am. Chem. Soc.* **106**, 7840–7842.

GRANT, D. F. & GABE, E. J. (1978). *J. Appl. Cryst.* **11**, 114–120.

HOEVE, W. TEN, & WYNBERG, H. (1985). *J. Org. Chem.* **50**, 4508–4514.

International Tables for X-ray Crystallography (1974). Vol. IV. Birmingham: Kynoch Press. (Present distributor D. Reidel, Dordrecht.)

KOK, A. M. G., WYNBERG, H., PARTHASARATHI, V., SMITS, J. M. M. & BEURSKENS, P. T. (1987). *Acta Cryst.* C**43**, 1336–1341.

LEHMANN, M. S. & LARSEN, F. K. (1974). *Acta Cryst.* A**30**, 580–584.

MOTHERWELL, W. D. S. (1976). *PLUTO*. Program for plotting molecular and crystal structures. Univ. of Cambridge, England.

NORDMAN, C. E. & SCHILLING, J. W. (1970). In *Crystallographic Computing*, edited by F. R. AHMED, pp. 110–114. Copenhagen: Munksgaard.

NORTH, A. C. T., PHILLIPS, D. C. & MATHEWS, F. S. (1968). *Acta Cryst.* A**24**, 351–359.

SHELDRICK, G. M. (1976). *SHELX*76. Program for crystal structure determination. Univ. of Cambridge, England.

SMITS, J. M. M., BEURSKENS, P. T., KOK, A. M. G. & WYNBERG, H. (1987). *Acta Cryst.* C**43**, 1331–1333.

WALKER, N. & STUART, D. (1983). *Acta Cryst.* A**39**, 158–166.

Acta Cryst. (1987). C**43**, 1331–1333

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

BY J. M. M. SMITS AND PAUL T. BEURSKENS

Crystallography Laboratory, University of Nijmegen, Toernooiveld, 6525 ED Nijmegen, The Netherlands

AND AGATHA M. G. KOK AND HANS WYNBERG

Organic Chemistry Department, University of Groningen, Nijenborgh 16, 9747 AG Groningen, The Netherlands

(*Received* 17 *September* 1986; *accepted* 23 *February* 1987)

Abstract. $C_{21}H_{30}NO_5P$, $M_r = 407{\cdot}445$, monoclinic, $P2_1$, $a = 14{\cdot}0037$ (6), $b = 8{\cdot}0948$ (7), $c = 9{\cdot}7090$ (7) Å, $\beta = 98{\cdot}904$ (5)°, $V = 1087{\cdot}3$ Å^3, $Z = 2$, $D_x = 1{\cdot}244$ Mg m^{-3}, Cu $K\alpha$ radiation (graphite-crystal monochromator, $\lambda = 1{\cdot}54178$ Å), μ(Cu $K\alpha$) = 1·360 mm^{-1}, $F(000) = 436$, $T = 290$ K, final conventional R factor = 0·039, $wR = 0{\cdot}049$ for 2782 'observed' reflections and 342 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.

Introduction. The present compound, denoted INAP, is the second of a series of crystal structure investigations on phosporinane ephedrine salts. The other compounds (INAM, CLINAM, CLINAP) are presented in the preceeding and two following papers. These structural investigations are part of a study on crystallization

0108-2701/87/071331-03$01.50