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The Crystal and Molecular Structures of (+)-Pseudoephedrine and (+)-Pseudoephedrine Hydrochloride

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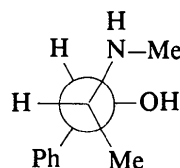
The crystal structures of (+)-pseudoephedrine, I, and (+)-pseudoephedrine hydrochloride, II, have been determined by X-ray diffraction techniques. Both compounds form orthorhombic crystals, with the space group $P2_12_12_1$, and four molecules per unit cell. The unit-cell dimensions are $a = 7.337$ (4), $b = 8.646$ (5) and $c = 16.113$ (7) Å for I and $a = 25.358$ (11), $b = 6.428$ (5) and $c = 6.901$ (5) Å for II. The structures were solved by direct methods and refined by least-squares techniques to R values of 0.065 for I and 0.075 for II. We have demonstrated that protonation does not alter molecular shape since the conformations in I and II are virtually identical. Both molecules, I and II, are in an extended form which is similar to that found in various ephedrines and related phenethylamines.

Introduction

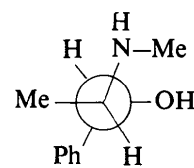
The relation between molecular structure and biological activity is intriguing. The possibility of defining the stereochemical requirements of a receptor site by considering the geometry of active drugs has stimulated both theoretical [*e.g.* Pullman, Coubeils, Courrière & Gervois (1972) and Kier (1968*a*) and references therein] and experimental studies. For example, Portoghesi (1967) has studied the conformation of ephedrine isomers in solution by NMR techniques, while Hearn, Freeman & Bugg (1973) have reviewed the X-ray work on phenylethanamines. However, a persistent problem is whether the conformation found by a given physical method is the same as that found at the receptor site. This question is frequently raised in X-ray diffraction studies despite the fact that the drug–receptor interactions are closely related to solid-state effects. An additional complication is introduced if the drug can exist in protonated or deprotonated forms, in which case the conformation may be pH dependent. Obviously, the above questions will only be answered by the multifaceted approach. As part of our broad program of studies of antihistamines and bronchodilators, we have undertaken an X-ray study of

(+)-pseudoephedrine and (+)-pseudoephedrine hydrochloride.

Ephedrine and pseudoephedrine can exist as various conformers, and the preferred conformation has been the subject of much controversy. Portoghesi (1967) used NMR techniques to assign the conformation 1 to ephedrine and 2 to pseudoephedrine. The crystal structures of various ephedrine salts have been determined and the conformation 1 was found in all cases: the hydrochloride by Bergin (1971), the monohydrogen phosphate by Hearn, Freeman & Bugg (1973) and the dihydrogen phosphate by Hearn & Bugg (1972). However, there are no data on either ephedrine or pseudoephedrine free base or salts of pseudoephedrine. Therefore, we undertook a study of pseudoephedrine free base, I, and pseudoephedrine hydrochloride, II, to



(1)



(2)

determine the conformation and to compare the salt and free-base conformations. In addition, a comparison of our results with other ethanolamine structures would be informative in assessing the steric and electronic requirements of activity.

Experimental

(+)-Pseudoephedrine was purchased from Sigma Chemical Company, St. Louis, MO. Suitable crystals were grown from an ethyl alcohol solution by slow evaporation. Preliminary precession photographs indicated orthorhombic symmetry. The systematic absences of $h00$ for $h = 2n + 1$, $0k0$ for $k = 2n + 1$ and $00l$ for $l = 2n + 1$ indicated that the most probable space group was $P2_12_12_1$.

A crystal was shaped into a sphere approximately 0.3 mm in diameter by slowly rotating a larger crystal in an alcohol-water mixture. The spherical crystal was used for the measurement of the cell constants and intensity data. The crystal was coated with an aeroplastic dressing since the free base is somewhat hygroscopic. All measurements were made on a Syntex $P\bar{1}$ diffractometer with graphite-monochromatized Mo $K\alpha$ radiation. The details are similar to those given by Dymock & Palenik (1974). The four standard reflections which were measured after every 96 measurements decreased in intensity by about 11% during data

collection. Although the standards were used to rescale the data, we decided nevertheless to collect a second data set. A second crystal was ground to a 0.23 mm sphere and used for a second set of measurements with Cu $K\alpha$ radiation and a Ni filter. The standard reflections decreased by only 3% during the data collection in this case. The various details are summarized in Table 1. The two data sets were reduced to structure amplitudes by standard procedures. No absorption corrections were made.

Table 1. *Crystal data for pseudoephedrine, I, and pseudoephedrine hydrochloride, II*

	I		II
Formula	$C_{10}H_{15}NO$		$C_{10}H_{16}ClNO$
Molecular weight	165.24		201.70
Crystal system	Orthorhombic		Orthorhombic
Space group	$P2_12_12_1$		$P2_12_12_1$
Radiation	Cu	Mo	Mo
$a(\text{\AA})$	7.337 (4)	7.322 (3)	25.358 (11)
$b(\text{\AA})$	8.646 (5)	8.659 (3)	6.428 (5)
$c(\text{\AA})$	16.113 (7)	16.120 (7)	6.901 (5)
Volume (\AA^3)	1022.1	1022.0	1124.9
Z	4	4	4
D_c (g cm^{-3})	1.074		1.191
D_m (g cm^{-3})	1.07		1.19
Number of unique reflections	839	1078	1900
Number of 'reliable' reflections	685	664	547
2θ range ($^\circ$)	0-110	0-50	0-60

Table 2. *The final parameters ($\times 10^4$) of the non-hydrogen atoms in pseudoephedrine with the estimated standard deviations in parentheses*

The temperature factor is of the form: $\exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + \beta_{12}hk + \beta_{13}hl + \beta_{23}kl)]$. The first line gives the parameters from the Cu data set and the second line those from the Mo data set.

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
O(1)	-309 (5)	5813 (4)	2321 (2)	259 (9)	245 (7)	73 (2)	14 (15)	56 (8)	114 (7)
	-305 (6)	5818 (6)	2320 (3)	300 (12)	263 (9)	77 (3)	37 (19)	19 (10)	109 (9)
N(1)	-1016 (6)	8571 (5)	1640 (2)	380 (14)	146 (6)	47 (2)	8 (19)	-18 (9)	-10 (7)
	-1001 (7)	8560 (6)	1641 (3)	329 (15)	169 (8)	46 (2)	43 (23)	-31 (11)	-6 (8)
C(1)	2603 (8)	5440 (6)	1627 (3)	316 (14)	150 (8)	42 (2)	-52 (22)	-11 (10)	34 (8)
	2655 (10)	5439 (7)	1627 (4)	338 (17)	154 (10)	41 (3)	-33 (28)	-61 (13)	26 (10)
C(2)	2065 (8)	4135 (6)	1185 (3)	388 (17)	154 (9)	56 (3)	-48 (23)	-4 (12)	8 (9)
	2073 (9)	4122 (7)	1175 (4)	290 (17)	183 (11)	52 (3)	-67 (26)	-4 (13)	26 (11)
C(3)	3411 (10)	3102 (6)	902 (4)	664 (27)	146 (9)	61 (3)	135 (28)	4 (16)	1 (9)
	3418 (12)	3087 (8)	916 (5)	617 (30)	169 (11)	68 (4)	179 (35)	189 (20)	-5 (12)
C(4)	5218 (9)	3365 (7)	1072 (4)	435 (21)	263 (12)	79 (3)	275 (30)	59 (15)	84 (13)
	5244 (12)	3342 (9)	1046 (6)	500 (28)	272 (15)	104 (5)	334 (39)	216 (21)	139 (17)
C(5)	5756 (9)	4634 (7)	1497 (4)	345 (18)	255 (12)	89 (4)	44 (30)	10 (14)	46 (12)
	5748 (11)	4606 (9)	1495 (6)	374 (24)	245 (15)	124 (6)	162 (39)	54 (21)	83 (17)
C(6)	4478 (9)	5667 (6)	1787 (3)	377 (17)	202 (10)	57 (3)	-28 (27)	17 (12)	5 (10)
	4484 (9)	5658 (8)	1785 (4)	307 (19)	231 (13)	67 (3)	-86 (32)	-122 (15)	39 (14)
C(7)	1202 (7)	6575 (6)	1960 (3)	334 (16)	145 (8)	41 (2)	23 (22)	4 (11)	-2 (7)
	1220 (10)	6582 (7)	1950 (4)	365 (19)	147 (10)	51 (3)	-41 (29)	18 (15)	10 (10)
C(8)	426 (9)	7616 (5)	1272 (3)	416 (17)	117 (7)	40 (2)	1 (23)	-15 (11)	-2 (8)
	439 (10)	7607 (7)	1272 (3)	412 (21)	125 (9)	43 (3)	7 (29)	53 (13)	-7 (10)
C(9)	1901 (9)	8629 (6)	898 (3)	582 (23)	150 (8)	57 (3)	60 (27)	142 (14)	40 (9)
	1862 (12)	8639 (8)	903 (5)	616 (30)	160 (11)	64 (4)	46 (35)	174 (18)	37 (12)
C(10)	-2234 (9)	9265 (7)	1032 (4)	510 (21)	245 (11)	69 (3)	287 (30)	-102 (14)	-22 (12)
	-2253 (12)	9257 (9)	1035 (5)	531 (26)	276 (16)	72 (4)	322 (39)	-77 (19)	-43 (16)

(+)-Pseudoephedrine hydrochloride was also purchased from Sigma Chemical Company. Crystals were grown from water and preliminary photographs also indicated the space group $P2_12_12_1$. Intensity measurements were made on a GE XRD-6 diffractometer with Zr-filtered Mo $K\alpha$ radiation. The measurements were made at the University of Waterloo by procedures described by Palenik (1972), but the structure determination was made at the University of Florida. Those reflections with $I(\text{intensity}) \geq 1.2$ times the background were considered reliable and used in the analysis. Details are given in Table 1.

Structure determination and refinement

Both structures were solved by direct methods with *MULTAN* (Germain, Main & Woolfson, 1971). The R index $[= \Sigma |F(\text{obs})| - |F(\text{calc})| / \Sigma |F(\text{obs})|]$, after all the atoms had been located, was 0.22 for the free base for both data sets and 0.21 for the hydrochloride. After three least-squares cycles with the full matrix and individual isotropic thermal parameters, the R values were 0.13 and 0.11 for I and 0.089 for II. A difference Fourier synthesis was used to locate all the H atoms in both compounds. Two least-squares cycles with the block approximation reduced R to 0.076 for both data sets of I and to 0.084 for II. The H atom parameters were now allowed to vary and two further block-diagonal least-squares cycles reduced R to 0.065 for the Cu data set of I, 0.073 for the Mo data set of I and 0.075 for II and refinement was terminated. The shifts of the non-hydrogen parameters in the last cycle were all less than one-fourth of an estimated standard deviation. The final atomic parameters are given in Tables 2, 3, 4 and 5.

The quantity minimized in the least-squares calculation was $\Sigma w[|F(\text{obs})| - |F(\text{calc})|]^2$. The weighting scheme was $w = F(\text{obs})^2/F(\text{low})^2$ if $|F(\text{obs})| < F(\text{low})$,

$w = 1$ if $F(\text{low}) \leq F(\text{obs}) \leq 2F(\text{low})$ and $w = 4F(\text{low})^2/F(\text{obs})^2$ if $F(\text{obs}) > 2F(\text{low})$. The values of $F(\text{low})$ were 7.0 and 20.0 for I and II respectively. The

Table 3. *The final parameters for the hydrogen atoms in pseudoephedrine with their estimated standard deviations in parentheses*

The first line for each atom gives the values obtained from the Cu data set and the second line those from the Mo data set. The hydrogen atom is given followed by the atom to which it is bonded in brackets, the bond distance (Å), the positional parameters ($\times 10^3$) and the isotropic thermal parameter.

Atom [bonded to]	Distance	x	y	z	$B(\text{Å}^2)$
H(1) O(1)	0.86 (5)	17 (7) 27 (8)	515 (6) 517 (7)	266 (3) 267 (4)	8.8 (15) 5.2 (18)
H(2) N(1)	0.93 (4)	-174 (6) -174 (7)	803 (5) 799 (7)	201 (3) 204 (4)	7.1 (13) 4.2 (16)
H(3) C(2)	1.07 (5)	63 (6) 68 (8)	398 (5) 402 (7)	112 (3) 112 (4)	7.6 (12) 5.4 (17)
H(4) C(3)	1.06 (5)	265 (7) 277 (9)	224 (6) 217 (8)	58 (3) 63 (5)	8.5 (14) 6.9 (20)
H(5) C(4)	1.15 (6)	634 (7) 637 (10)	260 (7) 261 (9)	78 (4) 83 (6)	11.3 (18) 10.5 (26)
H(6) C(5)	1.16 (6)	722 (8) 721 (11)	506 (8) 506 (10)	164 (4) 161 (5)	12.1 (18) 9.6 (23)
H(7) C(6)	1.07 (4)	484 (7) 496 (9)	657 (5) 653 (7)	221 (3) 219 (4)	7.8 (14) 6.3 (20)
H(8) C(7)	1.09 (4)	169 (6) 168 (8)	743 (5) 741 (8)	240 (3) 239 (4)	6.3 (12) 6.0 (18)
H(9) C(8)	1.08 (4)	-4 (5) -7 (8)	690 (5) 691 (7)	76 (2) 79 (4)	5.4 (11) 5.9 (18)
H(10) C(9)	0.93 (5)	173 (7) 176 (8)	923 (8) 922 (7)	43 (3) 44 (4)	9.6 (16) 6.6 (20)
H(11) C(9)	1.09 (6)	233 (8) 245 (9)	950 (7) 952 (8)	135 (3) 136 (4)	11.0 (17) 7.5 (21)
H(12) C(9)	1.09 (5)	315 (6) 309 (8)	812 (6) 811 (8)	66 (3) 67 (4)	8.2 (14) 5.9 (19)
H(13) C(10)	1.16 (6)	-154 (7) -152 (9)	1015 (7) 1007 (9)	59 (3) 69 (5)	10.8 (17) 9.3 (24)
H(14) C(10)	0.95 (5)	-328 (6) -318 (9)	965 (6) 966 (9)	131 (3) 133 (4)	8.3 (15) 7.3 (22)
H(15) C(10)	1.15 (6)	-306 (7) -304 (9)	835 (7) 841 (8)	68 (4) 69 (5)	11.2 (17) 7.5 (22)

Table 4. *The final parameters ($\times 10^4$) of the non-hydrogen atoms in pseudoephedrine hydrochloride with the estimated standard deviations in parentheses*

The temperature factor is of the form: $\exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + \beta_{12}hk + \beta_{13}hl + \beta_{23}kl)]$.

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
Cl	1783 (1)	3436 (5)	2776 (5)	30 (1)	276 (7)	307 (8)	4 (8)	3 (6)	17 (24)
O(1)	3131 (3)	3452 (15)	4316 (9)	27 (2)	637 (32)	244 (20)	24 (21)	36 (11)	-296 (72)
N(1)	2889 (3)	2964 (14)	513 (11)	29 (2)	358 (37)	162 (22)	40 (15)	-11 (12)	30 (60)
C(1)	4032 (4)	2351 (20)	3970 (15)	20 (2)	510 (57)	284 (31)	-53 (20)	4 (16)	-91 (79)
C(2)	4025 (4)	301 (19)	4812 (14)	28 (3)	294 (40)	215 (30)	4 (20)	-32 (17)	25 (70)
C(3)	4466 (5)	-442 (21)	5655 (18)	35 (3)	475 (54)	299 (37)	96 (23)	-12 (21)	-19 (95)
C(4)	4937 (4)	562 (27)	5624 (17)	16 (2)	1101 (94)	335 (36)	13 (28)	13 (18)	-265 (121)
C(5)	4959 (5)	2513 (27)	4693 (18)	33 (3)	991 (85)	398 (42)	-174 (29)	12 (23)	-233 (112)
C(6)	4501 (4)	3329 (25)	3922 (15)	27 (3)	515 (49)	289 (32)	-3 (29)	8 (17)	-74 (106)
C(7)	3561 (4)	3250 (20)	2937 (17)	37 (3)	304 (36)	343 (37)	-21 (28)	-29 (19)	-14 (107)
C(8)	3360 (4)	1919 (18)	1213 (15)	30 (3)	318 (40)	290 (31)	10 (22)	-38 (16)	-24 (76)
C(9)	3799 (4)	1767 (27)	-264 (14)	31 (3)	768 (66)	140 (26)	52 (31)	22 (16)	-54 (101)
C(10)	2611 (5)	1623 (18)	-974 (14)	45 (3)	170 (27)	220 (27)	43 (27)	-80 (18)	-78 (78)

Table 5. *The final parameters for the hydrogen atoms in pseudoephedrine hydrochloride*

The estimated standard deviations are given in parentheses. The hydrogen atom is given followed by the atom to which it is bonded, the bond distance (Å), the positional parameters ($\times 10^3$) and the isotropic thermal parameter.

Atom [bonded to]	Distance	x	y	z	B (Å ²)
H(1)[O(1)]	1.11 (9)	317 (3)	392 (16)	586 (13)	11 (3)
H(2)[N(1)]	1.00 (9)	260 (3)	286 (14)	150 (13)	9 (3)
H(3)[N(1)]	1.33 (10)	290 (3)	420 (17)	-103 (14)	14 (3)
H(4)[C(2)]	1.27 (9)	353 (3)	-12 (16)	476 (15)	10 (3)
H(5)[C(3)]	1.29 (10)	444 (3)	-232 (16)	630 (13)	10 (4)
H(6)[C(4)]	1.39 (11)	529 (4)	-103 (18)	604 (15)	13 (4)
H(7)[C(5)]	1.13 (11)	535 (4)	337 (22)	471 (19)	17 (4)
H(8)[C(6)]	1.07 (13)	449 (4)	495 (20)	360 (14)	13 (4)
H(9)[C(7)]	0.96 (9)	359 (3)	466 (14)	246 (15)	8 (3)
H(10)[C(8)]	1.11 (9)	326 (3)	44 (13)	196 (12)	7 (3)
H(11)[C(9)]	1.11 (11)	371 (4)	71 (19)	-150 (14)	13 (4)
H(12)[C(9)]	1.24 (10)	419 (3)	83 (17)	39 (15)	13 (4)
H(13)[C(9)]	1.25 (10)	396 (3)	299 (18)	-153 (12)	9 (3)
H(14)[C(10)]	1.03 (12)	271 (3)	8 (19)	-88 (14)	12 (3)
H(15)[C(10)]	1.28 (9)	215 (3)	239 (14)	-67 (13)	11 (3)
H(16)[C(10)]	0.80 (11)	258 (3)	178 (16)	-212 (16)	11 (3)

scattering factor for Cl⁻ was from Doyle & Turner (1968). The C, N, and O scattering factors were from Hanson, Herman, Lea & Skillman (1964). The H scattering factor was that of Stewart, Davidson & Simpson (1965). All calculations were carried out on an IBM-370/165 computer.*

Discussion

The thermal ellipsoids and atomic numbering for the free base and the cation are illustrated in Figs. 1 and 2

* A list of structure factors for both compounds has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32149 (16 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

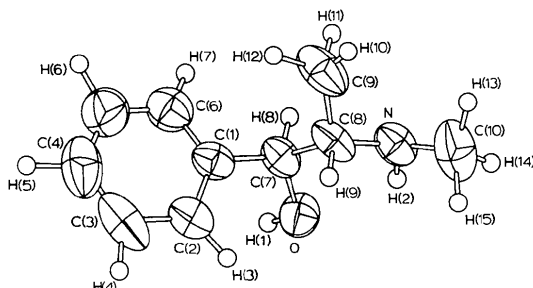


Fig. 1. An ORTEP drawing of the pseudoephedrine molecule showing the atomic numbering and thermal ellipsoids. The parameters are from the Cu $K\alpha$ data set. The hydrogen atoms are illustrated as small spheres for simplicity.

respectively. The individual distances and angles are given in Table 6. The distances and angles in the free base obtained from the two data sets are in good agreement. The only significant differences [by the criteria of Cruickshank & Robertson (1953)] are between the C(6)–C(1) bond distances ($t_0 = 2.81$) and between the C(3)–C(4)–C(5) bond angles ($t_0 = 2.90$).

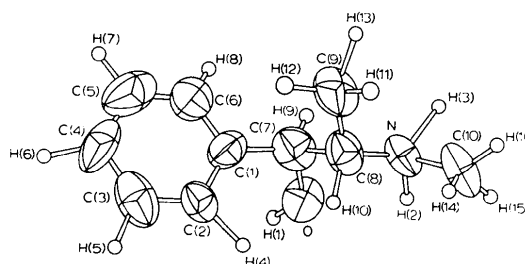


Fig. 2. An ORTEP drawing of the pseudoephedrine cation showing the atomic numbering and thermal ellipsoids. The chloride ion has not been included and the hydrogen atoms are illustrated as small spheres for simplicity.

Table 6. *Bond distances and angles in pseudoephedrine, I, and pseudoephedrine hydrochloride, II*

The estimated standard deviations are in parentheses. The column headed by Cu refers to the Cu $K\alpha$ data set, while the Mo $K\alpha$ data set is headed by Mo.

	I-Cu	I-Mo	II
Bond distances (Å)			
C(1)–C(2)	1.392 (7)	1.419 (9)	1.440 (17)
C(2)–C(3)	1.407 (9)	1.395 (10)	1.347 (16)
C(3)–C(4)	1.373 (10)	1.371 (12)	1.359 (18)
C(4)–C(5)	1.352 (9)	1.364 (12)	1.410 (23)
C(5)–C(6)	1.377 (9)	1.380 (11)	1.382 (18)
C(6)–C(1)	1.413 (8)	1.377 (10)	1.345 (16)
C(1)–C(7)	1.520 (7)	1.534 (9)	1.506 (17)
C(7)–O	1.414 (6)	1.429 (8)	1.452 (13)
C(7)–C(8)	1.538 (7)	1.519 (9)	1.551 (16)
C(8)–C(9)	1.517 (8)	1.496 (10)	1.513 (15)
C(8)–N	1.467 (7)	1.464 (8)	1.454 (13)
N–C(10)	1.455 (8)	1.470 (10)	1.515 (13)
Bond angles (°)			
C(1)–C(2)–C(3)	118.8 (5)	117.3 (6)	119.3 (10)
C(2)–C(3)–C(4)	120.5 (6)	122.6 (7)	123.7 (12)
C(3)–C(4)–C(5)	121.2 (6)	118.3 (8)	117.7 (13)
C(4)–C(5)–C(6)	120.0 (6)	121.9 (8)	118.7 (13)
C(5)–C(6)–C(1)	120.7 (5)	119.9 (7)	123.9 (12)
C(6)–C(1)–C(2)	118.8 (5)	119.9 (6)	116.6 (16)
C(6)–C(1)–C(7)	120.3 (5)	120.9 (6)	120.7 (16)
C(2)–C(1)–C(7)	120.9 (5)	119.1 (6)	122.2 (10)
C(1)–C(7)–O	112.0 (4)	112.2 (5)	108.6 (9)
C(1)–C(7)–C(8)	112.0 (4)	113.0 (5)	114.3 (10)
C(8)–C(7)–O	106.2 (4)	106.1 (5)	107.8 (9)
C(7)–C(8)–N	107.7 (4)	108.0 (5)	105.7 (9)
C(7)–C(8)–C(9)	111.1 (4)	111.9 (5)	108.1 (9)
C(9)–C(8)–N	110.5 (4)	109.1 (5)	114.3 (9)
C(8)–N–C(10)	113.7 (4)	114.3 (5)	110.2 (8)

The phenyl rings are planar, with an average C—C distance of 1.386 (9) in I-Cu, 1.384 (8) in I-Mo and 1.381 (16) Å in II. The estimated standard deviation of the averaged value is given by $\sigma(\text{average}) = [\Sigma(X_i - \bar{X})^2 / N(N - 1)]^{1/2}$, where \bar{X} is the average value and X_i is the i th value of the N 'equivalent' measurements. The C—C—C bond angles in the phenyl rings all average 120.0° (as expected for a planar hexagon), with $\sigma(\text{average})$ equal to 0.4, 0.8 and 1.3° for I-Cu, I-Mo and II respectively.

The C—C distances in the side chains, C(1)—C(7), C(7)—C(8) and C(8)—C(9), of the cation and free base are not significantly different and are similar to the dimensions found in the various ephedrine derivatives

by Bergin (1971), Hearn & Bugg (1972), and Hearn, Freeman & Bugg (1973). Similarly, the C—O distances in the pseudoephedrines [average 1.432 (11) Å] are not significantly different from those reported by these authors in the ephedrines [average 1.418 (3) Å]. The only difference in bond lengths between the various pseudoephedrine and ephedrine derivatives appears to involve the N—C(8) and N—C(10) distances in pseudoephedrine hydrochloride, II, which are significantly different ($t_0 = 3.31$). In pseudoephedrine free base, I-Cu, I-Mo, the two C—N distances are not significantly different [average 1.464 (3) Å]. The fact that protonation of the N atom might alter the C—N bond lengths is not unreasonable. The situation in the

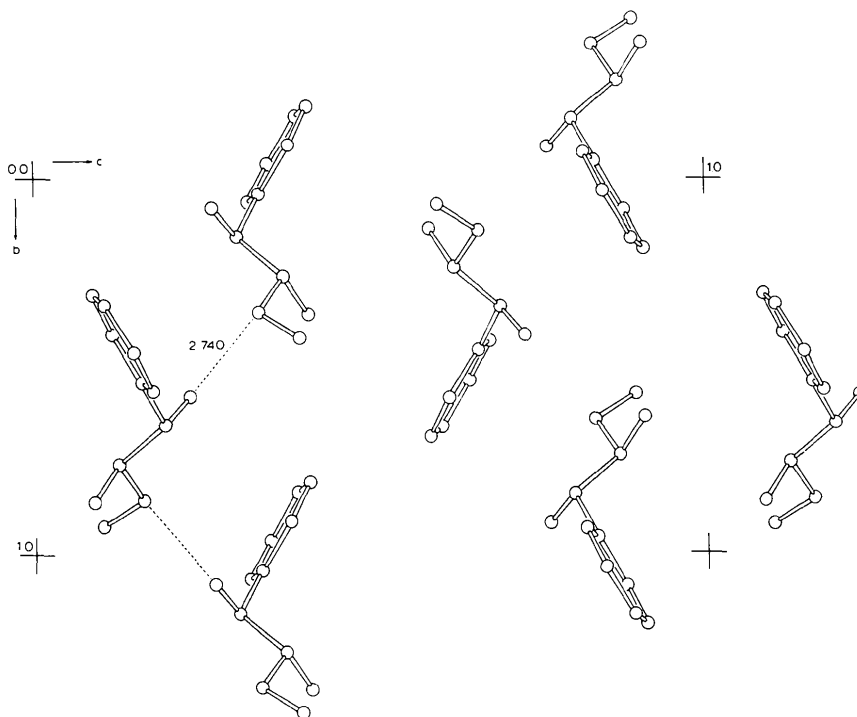


Fig. 3. A packing diagram for pseudoephedrine free base as viewed down *a*. The O—H...N hydrogen bond is shown by a dotted line.

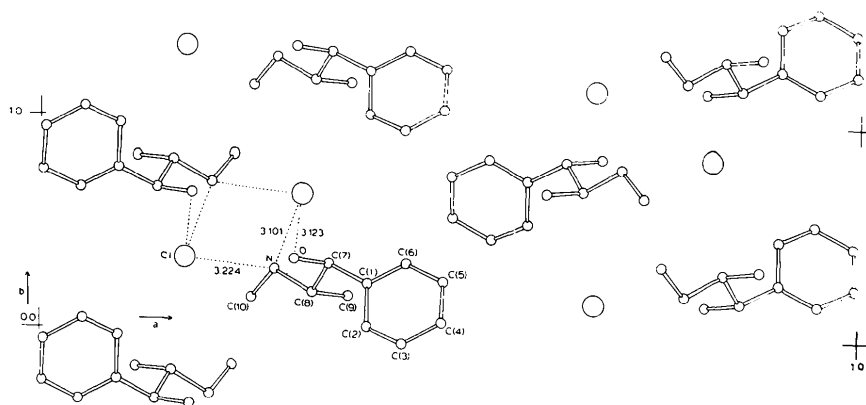


Fig. 4. A packing diagram for pseudoephedrine hydrochloride as viewed down *c*. The three hydrogen bonds are illustrated by dotted lines.

ephedrine derivatives is somewhat more complicated since, when chloride and dihydrogen phosphate are the anions, the C–N bonds are different while, when monohydrogen phosphate is the anion, the distances are equivalent in the two crystallographically unique molecules. These differences may reflect to some extent the different hydrogen-bonding patterns in the various compounds.

The hydrogen-bonding and molecular packing are illustrated in Figs. 3 and 4 for the free base and hydrochloride respectively. The dimensions of the hydrogen bonds have been summarized in Table 7. In the free base there is one strong intermolecular hydrogen bond involving O–H···N which links the molecules into infinite chains around the screw axis. There is a short intramolecular contact between N and O, but the N–H(2)···O angle of 108° is not very favorable for hydrogen-bond formation. In the various salts the hydrogen-bonding usually involves the anion. In the hydrochloride, II, there are three hydrogen bonds to the chloride ion which is similar to the situation reported by Bergin (1971) in ephedrine hydrochloride. In both ephedrine and pseudoephedrine the hydrogen bonds link the cations in a helical fashion around the screw axis.

Both the free base, I, and the cation, II, exist in an essentially fully extended conformation in the solid state. The torsion angle C(1)–C(7)–C(8)–N [called τ_2 by Carlström, Bergin & Falkenberg (1973)] is 175.9° in I and 176.1° in II, compared with 180° for a fully extended side chain. Carlström, Bergin & Falkenberg (1973) had noted that all biogenic monoamines have the anti-periplanar τ_2 torsion angle (*i.e.* $\tau_2 = 180^\circ$). Kier (1968*b*) had suggested, on the basis of extended Huckel calculations, that pseudoephedrines would have a synclinal τ_2 torsion angle ($\tau_2 = \pm 60^\circ$). His conclusion is obviously incorrect. A comparison of the conformation of the pseudoephedrines I and II with other phenylethanamines can also be made by consideration of the four torsion angles (τ, ω, χ, ψ) defined by Hearn, Freeman & Bugg (1973). The angles are also defined in Table 8 where the values for the various pseudoephedrine and ephedrine derivatives have been tabulated. The angle ψ shows a large variation in the various compounds and most likely reflects the different hydrogen-bonding and packing patterns. The

angle χ is very close to $\pm 180^\circ$ in all cases and also illustrates the extended nature of the side chain. The angles τ and ω are dependent on the enantiomer which is chosen for the calculation. That is, if the coordinates in Tables 2–5 are inverted, the signs of all the torsion angles also change. Although an attempt was made to determine the absolute configuration of the free base, the results were inconclusive. If one assumes that the configurations deduced by Portoghesi (1967) are correct, then the coordinates in Tables 2–5 should be inverted. The question of the relation between structure and activity has been discussed by Portoghesi (1967) and Carlström, Bergin & Falkenberg (1973) and will not be reiterated here. Knowledge of the absolute configuration is essential to an understanding of the varying activities of the various ephedrine and pseudoephedrine derivatives. Therefore, a discussion of the points will be deferred until the completion of our studies of the absolute configurations of these derivatives. The important conclusion from our study is the fact that the free base, I, and the cation, II, have the same conformation. Consequently, protonation and hydrogen-bonding appear to play minor roles in determining the conformation of the molecule in the solid state.

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Table 8. Comparison of some torsion angles in various ephedrine and pseudoephedrine derivatives

The torsion angles are identical to those defined by Hearn, Freeman & Bugg (1973): τ is C(2)–C(1)–C(7)–O(1); ω is O(1)–C(7)–C(8)–N; χ is R–N–C(8)–C(7); and ψ is H[on O(1)]–O(1)–C(7)–C(8).

	τ	ω	χ	ψ
Pseudoephedrine	44	52	–162	174
Pseudoephedrine hydrochloride	63	55	–171	162
Ephedrine hydrochloride	–21	–70	–170	175
Ephedrine dihydrogen phosphate	–21	–73	177	128
Ephedrine monohydrogen phosphate A	–36	–57	–168	85
B	–11	–69	–169	85

Table 7. Hydrogen bonds

D–H···A	Position of A	D–H (Å)	H···A (Å)	D···A (Å)	$\angle D-H\cdots A$ (°)	$\angle H-D\cdots A$ (°)
Pseudoephedrine (I-Cu)						
O–H(1)···N	$-x, y - \frac{1}{2}, \frac{1}{2} - z$	0.86 (5)	1.88 (5)	2.740 (5)	174 (5)	4 (3)
N–H(2)···O	x, y, z	0.93 (4)	2.25 (5)	2.675 (5)	108 (3)	53 (3)
Pseudoephedrine hydrochloride, II						
O–H(1)···Cl	$\frac{1}{2} - x, 1 - y, \frac{1}{2} + z$	1.11 (9)	2.16 (9)	3.123 (9)	144 (7)	24 (7)
N–H(2)···Cl	x, y, z	1.01 (9)	2.27 (9)	3.224 (8)	157 (7)	16 (7)
N–H(3)···Cl	$\frac{1}{2} - x, 1 - y, \frac{1}{2} + z$	1.33 (9)	1.91 (10)	3.101 (9)	146 (7)	20 (7)

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The Crystal and Molecular Structure of *cis*-1,2-Dimethoxycarbonyl-1,2-bis(4-nitrophenyl)cyclobutane

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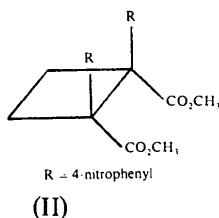
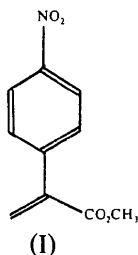
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cis-1,2-Dimethoxycarbonyl-1,2-bis(4-nitrophenyl)cyclobutane, C₂₀H₁₈O₈N₂, crystallizes in space group *P*₂₁/*c* with *Z* = 4 and cell parameters *a* = 10.158 (1), *b* = 25.598 (3), *c* = 8.206 (1) Å, β = 110.169 (4)°. Data were collected on an automatic four-circle diffractometer with Cu Kα radiation, and the structure has been refined by full-matrix least squares to a residual *R* = 0.045 for 2516 independent significant reflexions. The cyclobutane ring is puckered with a dihedral angle of 21.4° and contains a C–C bond of length 1.606 (3) Å between the two *cis*-substituted atoms.

Introduction

Schauble, Freed & Swerdloff (1971) have shown that upon irradiation crystalline methyl α-(4-nitrophenyl)-

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acrylate (I) dimerizes to give dimethoxycarbonylbis(4-nitrophenyl)cyclobutane.

On the basis of NMR and chemical evidence, these authors proposed that the photodimerization had occurred in a head-to-head manner to give the *cis*-1,2-disubstituted isomer (II). We report here the results of an X-ray diffraction study of this compound.

Experimental

A sample of the photodimer was supplied by Professor Schauble of the Villanova University, Pennsylvania. Slow cooling of a saturated methanol solution yielded colourless hexagonal plates perpendicular to [010]. A prismatic cleavage fragment measuring 0.2 × 0.2 ×