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The Crystal Structure of 3′-(β-Methylaminoethyl)spiro(cyclopentane-1,1′-indene) Hydrochloride

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The title compound, $C_{16}H_{21}N.HCl$, which is a new sympathomimetic drug, is monoclinic with $a=7\cdot338$, $b=13\cdot957$, $c=14\cdot979$ Å, $\beta=95\cdot79°$ and $D_x=1\cdot15$ g cm^{-3}. The space group is $P2_1/c$ and $Z=4$. The crystal structure has been determined by the Patterson method and refined to an R of 0·055 for 1482 observed reflexions collected by diffractometry. The structure consists of infinite bimolecular layers in which strong N–H···Cl hydrogen bonds (3·07 and 3·11 Å) connect the side chains of the molecules. These bilayers are lined by the hydrophobic rings and adjacent layers are held together by van der Waals forces only. The plane of the maximally extended side chain makes an angle of 80·3° with the indene plane and the cyclopentane ring has an envelope conformation.

Introduction

The title compound, hereinafter referred to as KABI 1847, is a new sympathomimetic amine which has been synthesized and pharmacologically tested by the pharmaceutical company AB Kabi, Sweden (Jönsson, Merenyi, Dahlander & Sparf, 1976). The present study forms part of a research project on biologically active amines. As no good crystals could be obtained from the free base (a common feature of this class of compounds) a salt was used for the investigation.

Experimental

The material obtained from Kabi AB was recrystallized by slow evaporation of an aqueous solution at room temperature. The monoclinic crystals were very thin, often slightly curved, plates elongated along **a**. More than 20 carefully selected crystals had to be rejected before one was found giving reflexions nearly free from streaks caused by strain or disorder. This crystal was trimmed to an almost circular plate, 0·35 mm in diameter with a thickness of 0·10 mm, and was mounted about **b**. Preliminary unit-cell dimensions and systematic absences were determined from Weissenberg photographs while accurate cell parameters were obtained from diffractometer measurements.

Crystal data

3′-(β-Methylaminoethyl)spiro(cyclopentane-1,1′-indene) hydrochloride, $C_{16}H_{21}N.HCl$. $a=7\cdot338$, $b=13\cdot957$, $c=14\cdot979$ Å, $\beta=95\cdot79°$. F.W. 263·81; $V=1526\cdot3$ Å^3; $D_x(Z=4)=1\cdot148$ g cm^{-3}; $F(000)=568$. Systematic extinctions: $h0l$ absent with h odd and $0k0$ absent with k odd indicating the space group $P2_1/c$ (C_{2h}^5).

Integrated intensities were recorded on a linear diffractometer (Pailred) with graphite-monochromated Mo $K\alpha$ radiation (0·7107 Å) for the layers $h0l$ through $h18l$ within $\sin\theta/\lambda\leq0\cdot65$. Altogether 3527 independent reflexions were recorded within a quarter sphere. Of these only 1482 differed significantly from the background level. The net intensities were corrected for

Table 1. *Final fractional coordinates and their standard deviations* (*in parentheses*)

	x	y	z
Cl	0·3437 (1)	0·1315 (1)	0·0113 (1)
C(1)	0·4150 (6)	0·5026 (3)	0·2574 (3)
C(2)	0·2777 (6)	0·5678 (3)	0·2306 (3)
C(3)	0·2825 (9)	0·6572 (4)	0·2717 (4)
C(4)	0·4175 (11)	0·6777 (4)	0·3369 (5)
C(5)	0·5561 (8)	0·6154 (4)	0·3640 (4)
C(6)	0·5536 (6)	0·5251 (3)	0·3241 (3)
C(7)	0·6825 (6)	0·4429 (4)	0·3387 (3)
C(8)	0·7053 (9)	0·4018 (5)	0·4353 (4)
C(9)	0·8861 (13)	0·3503 (6)	0·4426 (6)
C(10)	0·9990 (10)	0·3930 (7)	0·3737 (6)
C(11)	0·8839 (7)	0·4649 (5)	0·3225 (4)
C(12)	0·5958 (7)	0·3712 (3)	0·2723 (3)
C(13)	0·4449 (6)	0·4045 (3)	0·2268 (3)
C(14)	0·3278 (6)	0·3562 (3)	0·1520 (3)
C(15)	0·3642 (5)	0·3973 (3)	0·0614 (3)
N	0·2532 (4)	0·3482 (2)	−0·0119 (2)
C(16)	0·2881 (8)	0·3831 (3)	−0·1025 (4)
H(2)	0·176 (6)	0·552 (4)	0·180 (3)
H(3)	0·188 (6)	0·698 (4)	0·254 (3)
H(4)	0·407 (6)	0·732 (4)	0·362 (3)
H(5)	0·654 (6)	0·636 (4)	0·407 (3)
H(8*A*)	0·613 (7)	0·357 (4)	0·450 (4)
H(8*B*)	0·713 (7)	0·460 (4)	0·475 (3)
H(9*A*)	0·946 (8)	0·371 (5)	0·500 (4)
H(9*B*)	0·874 (8)	0·283 (5)	0·434 (3)
H(10*A*)	1·118 (8)	0·415 (5)	0·398 (4)
H(10*B*)	1·034 (8)	0·338 (5)	0·328 (4)
H(11*A*)	0·915 (7)	0·532 (4)	0·340 (4)
H(11*B*)	0·893 (7)	0·462 (4)	0·257 (4)
H(12)	0·645 (6)	0·313 (4)	0·265 (3)
H(14*A*)	0·197 (6)	0·363 (4)	0·156 (3)
H(14*B*)	0·349 (6)	0·284 (4)	0·155 (3)
H(15*A*)	0·338 (6)	0·466 (4)	0·057 (3)
H(15*B*)	0·487 (6)	0·394 (4)	0·053 (3)
H(N*A*)	0·126 (7)	0·351 (4)	−0·010 (3)
H(N*B*)	0·268 (7)	0·290 (4)	−0·005 (3)
H(16*A*)	0·261 (7)	0·448 (4)	−0·098 (3)
H(16*B*)	0·414 (7)	0·362 (4)	−0·110 (3)
H(16*C*)	0·228 (7)	0·343 (4)	−0·139 (3)

Lorentz and polarization factors but not for absorption owing to the low μ value (μ for Mo $K\alpha=2{\cdot}3$ cm^{-1}). The structure amplitudes were put on an approximately absolute scale by Wilson statistics but the different layers were, in the subsequent refinement, given individual scale factors.

Determination and refinement of the structure

The position of the chlorine atom was found from a three-dimensional Patterson function. A Fourier synthesis based on the signs determined by the chlorine atom only, gave maxima which could easily be interpreted as the 17 non-hydrogen atoms constituting the KABI 1847 molecule. The refinement was carried out by a full-matrix least-squares procedure. After one cycle of isotropic and one cycle of anisotropic refinement of the non-hydrogen atoms the conventional R was 0·099. A difference synthesis revealed the positions of all hydrogen atoms. After two cycles of anisotropic refinement of the non-hydrogen atoms and with the hydrogen atoms locked in the positions derived from the difference maps R dropped to 0·070. Weights were applied to $|F_o|$ according to $w=1/(a+|F_o|+b|F_o|^2)$ with $a=10{\cdot}0$ and $b=0{\cdot}02$. The positional parameters of the hydrogen atoms were refined in an additional cycle in which they were given individual temperature factors ranging from 4·5 to 10·0 Å^2. A final cycle of refinement of the non-hydrogen atoms resulted in an R of 0·055 for the 1482 observed reflexions. In the last cycle the average parameter shifts expressed as fractions of the e.s.d.'s were 0·41. The final atomic fractional coordinates and the β's of the non-hydrogen atoms are given in Tables 1 and 2 respectively.* The scattering factors for chlorine, nitrogen and carbon were from *International Tables for X-ray Crystallography* (1962) while that for the hydrogen atoms was taken from Stewart, Davidson & Simpson (1965). The computations were performed on an IBM 360/75 using our program system (Bergin, 1971) and the stereo picture of the molecule was produced by *ORTEP* (Johnson, 1965).

Description of the structure

The geometry of the molecule

A schematic representation of the KABI 1847 molecule with the atomic numbering is seen in Fig. 1 and a stereo view of the molecule is given in Fig. 2. The molecule contains three planar parts: (1) the atoms of the indene nucleus, (2) the atoms C(8)–C(11) of the cyclopentane ring and (3) the ethylamine side chain. The deviations of the atoms from these planes are given in Table 3. As in earlier determinations of indene derivatives (Andrianov, Kemme, Tarnopol'skii & Shibaeva, 1969; Rodesiler, Hall Griffit & Amma, 1972; Dreissig, Luger, Rewicki & Tuchscherer, 1973) the indene ring system is planar within the limits of error. However, the exocyclic atom C(14) is 0·06 Å out of the ring plane. The cyclopentane ring exhibits approximately C_s symmetry, an arrangement characteristic of an envelope conformation (Eliel, 1962). The four atoms C(8)–C(11) are thus nearly coplanar while C(7) is 0·53 Å out of the plane. The indene plane and the plane of the cyclopentane ring are nearly perpendicular to one another (90·6°). The ethylamine side chain involving the atoms C(13)–C(15) and N is very nearly planar but the terminal methyl carbon atom, C(16), is 0·06 Å out of the plane. The plane of the chain is inclined 80·3° to the indene plane, a conformation found in the majority of biologically active phenethylamines and indoleamines (Carlström, Bergin & Falkenberg, 1973).

The bond lengths and angles, uncorrected for thermal motion, are given in Table 4 and Fig. 1. Generally

Table 2. *Thermal parameters* ($\times 10^4$) *and standard deviations* (*in parentheses*)

β_{ij} are the coefficients in the expression: $\exp\,[-(h^2\beta_{11}+k^2\beta_{22}+l^2\beta_{33}+hk\beta_{12}+hl\beta_{13}+kl\beta_{23})]$.

	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
Cl	175 (2)	42 (4)	107 (1)	−19 (2)	79 (2)	−17 (1)
C(1)	216 (9)	49 (4)	55 (3)	−23 (7)	87 (8)	10 (4)
C(2)	258 (10)	59 (5)	69 (3)	22 (8)	93 (9)	9 (4)
C(3)	366 (15)	64 (5)	84 (4)	60 (10)	115 (13)	12 (5)
C(4)	523 (21)	51 (5)	101 (5)	11 (12)	216 (16)	−23 (6)
C(5)	355 (14)	68 (5)	68 (3)	−92 (10)	87 (10)	−30 (5)
C(6)	256 (10)	53 (5)	57 (3)	−41 (8)	85 (9)	9 (4)
C(7)	253 (11)	74 (5)	55 (3)	−20 (9)	45 (9)	−2 (4)
C(8)	441 (18)	105 (6)	50 (3)	−49 (14)	26 (12)	25 (6)
C(9)	574 (27)	127 (7)	106 (5)	141 (21)	−87 (20)	67 (9)
C(10)	333 (16)	152 (8)	128 (6)	108 (17)	−3 (16)	48 (10)
C(11)	237 (11)	114 (6)	92 (4)	−21 (12)	27 (11)	6 (7)
C(12)	287 (11)	52 (4)	66 (3)	28 (9)	70 (9)	9 (4)
C(13)	220 (9)	56 (5)	50 (2)	−18 (7)	55 (8)	3 (4)
C(14)	231 (9)	55 (5)	68 (3)	−26 (7)	62 (8)	14 (4)
C(15)	171 (8)	41 (4)	64 (3)	−1 (6)	61 (7)	7 (4)
N	160 (7)	44 (4)	67 (2)	1 (5)	43 (6)	7 (3)
C(16)	351 (14)	58 (5)	68 (3)	−14 (9)	101 (10)	−7 (5)

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* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 31725 (10 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

they are close to expected values (Sutton, 1965). However, the large thermal motion of the atoms C(3) and C(4) of the phenyl ring and, above all, the atoms C(9) and C(10) of the cyclopentane ring makes the positions of these atoms somewhat uncertain. The bonds involving these atoms are found to be slightly shorter than the standard values. Due to the non-isometric shape and the relatively poor quality of the crystal the calculated e.s.d.'s given in the tables are presumably considerable under-estimates.

Hydrogen bonds and molecular packing

The chloride ions and the positively charged nitrogen atoms of the molecules form layers coinciding with the (001) planes. Although the chlorine and nitrogen atoms are not perfectly coplanar, the deviations from (001) are rather small, ±0·17 and ±0·18 Å for the two atomic species respectively (Fig. 3). Within each layer the chloride ions form a distorted squared network with distances of 4·36, 4·94, 4·94 and 6·22 Å between the corner atoms. The similarly arranged nitrogen atoms are at distances of 4·58, 4·58, 5·56 and 5·67 Å from each other. Since the two nets are intermeshed so that each nitrogen atom is more or less at the centre of a chlorine 'square' the nitrogen atoms will be surrounded by four chlorine atoms at distances of 3·07, 3·11, 4·02 and 4·32 Å. The first two of these represent strong hydrogen bonds with N–H···Cl angles of 172·3 and 173·5° respectively. The side chains of the KABI 1847 molecules are thus firmly locked by a hydrogen-bonding system which forms meander-like chains running parallel to the *a* axis throughout the structure. On the other hand there are no short intermolecular contacts between the cyclic, hydrophobic part of adjacent molecules, the closest C···C, C···H and H···H approaches being 3·62, 3·00 and 2·48 Å, respectively, *i.e.* well above the sum of the atomic radii. The blade shape of the crys-

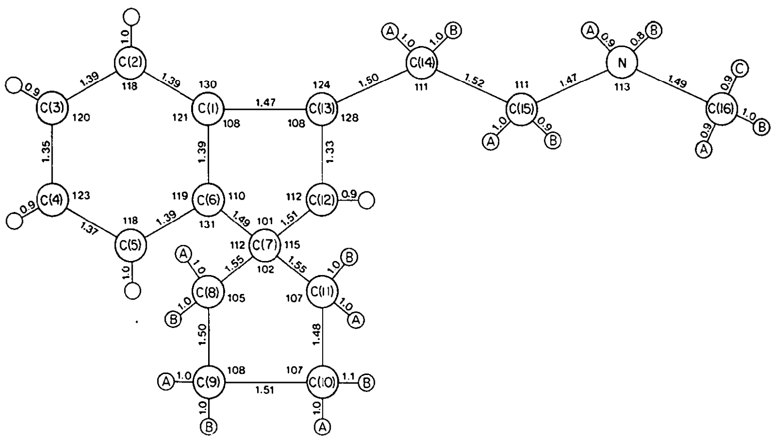

Fig. 1. Schematic drawing of the KABI 1847 molecule showing the numbering of the atoms. Distances in Å, angles in degrees.

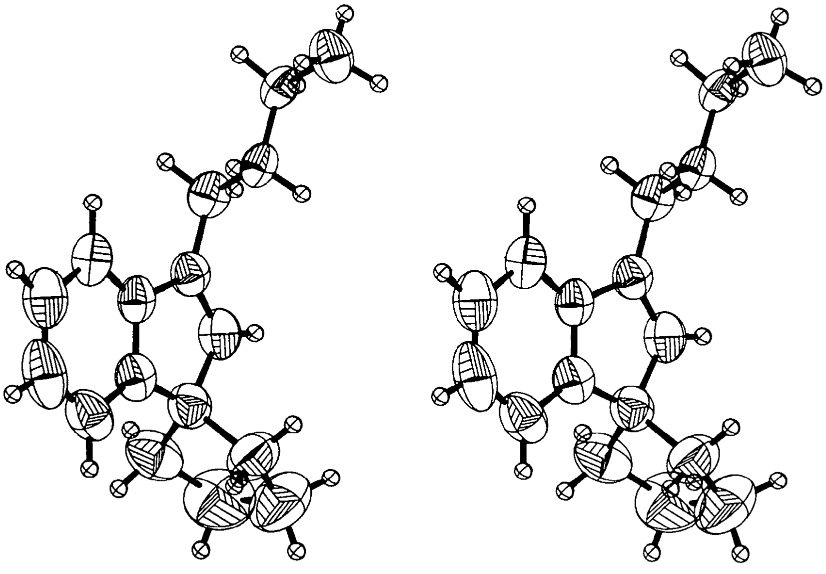

Fig. 2. Stereoscopic drawing of the KABI 1847 molecule. Heavy atoms are represented by thermal ellipsoids of 50% probability. Hydrogen atoms are depicted as small spheres.

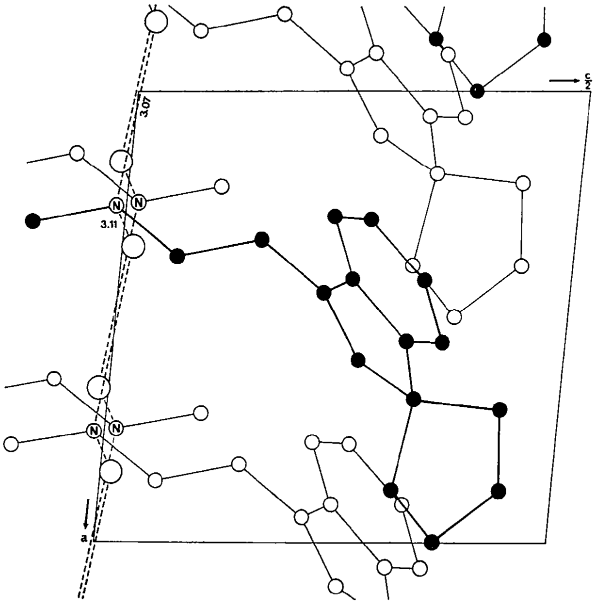

Fig. 3. A packing diagram showing half a unit cell of KABI 1847 seen along **b**. Dashed lines represent hydrogen bonds, distances in Å. Hydrogen atoms are omitted for clarity.

Table 3. *Least-squares planes and deviations in Å of individual atoms*

The equations of the planes are in the form $AX+BY+CZ=D$, where X, Y, Z are coordinates in orthogonal ångström space. Asterisks indicate atoms not included in the calculation of the planes.

Plane of indene rings

$$0{\cdot}6230X+0{\cdot}3584Y-0{\cdot}6953Z=1{\cdot}5008$$

C(1)	+0·001	C(6)	−0·007	H(2)	+0·03*
C(2)	+0·003	C(7)	+0·006	H(3)	−0·02*
C(3)	+0·007	C(12)	+0·002	H(4)	−0·07*
C(4)	−0·011	C(13)	−0·007	H(5)	+0·06*
C(5)	+0·006	C(14)	+0·061*	H(12)	+0·02*

Plane of cyclopentane ring

$$0{\cdot}3054X+0{\cdot}6976Y+0{\cdot}6481Z=9{\cdot}4853$$

C(8)	+0·011	C(11)	−0·011
C(9)	−0·018	C(7)	−0·528*
C(10)	+0·018		

Plane of side chain

$$0{\cdot}7345X-0{\cdot}6753Y-0{\cdot}0669Z=-1{\cdot}9013$$

C(13)	+0·009	N	+0·009
C(14)	−0·009	C(16)	+0·059*
C(15)	−0·009		

tals is reflecting the direction of weak and strong binding forces within the crystal. The thin dimension of the crystals is thus along **c*** in which direction the structure is held together by weak van der Waals forces only, whereas the long dimension of the crystals corresponds to the direction of the hydrogen bonds.

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Table 4. *Intramolecular bond distances* (Å) *and bond angles* (°) *with estimated standard deviations in parentheses*

C(1)–C(2)	1·386 (6)	C(9)—C(10)	1·510 (12)
C(2)–C(3)	1·391 (7)	C(10)–C(11)	1·475 (11)
C(3)–C(4)	1·350 (9)	C(11)–C(7)	1·553 (6)
C(4)–C(5)	1·368 (8)	C(7)—C(12)	1·506 (7)
C(5)–C(6)	1·394 (7)	C(12)–C(13)	1·325 (6)
C(6)–C(1)	1·388 (6)	C(13)–C(1)	1·468 (6)
C(6)–C(7)	1·489 (6)	C(13)–C(14)	1·501 (6)
C(7)–C(8)	1·548 (7)	C(14)–C(15)	1·522 (6)
C(8)–C(9)	1·503 (11)	C(15)–N	1·469 (5)
		N——C(16)	1·488 (6)

C(2)—C(1)—C(6)	121·3 (4)
C(2)—C(1)—C(13)	130·5 (4)
C(6)—C(1)—C(13)	108·3 (4)
C(1)—C(2)—C(3)	118·4 (5)
C(2)—C(3)—C(4)	119·6 (6)
C(3)—C(4)—C(5)	123·3 (6)
C(4)—C(5)—C(6)	118·1 (5)
C(1)—C(6)—C(5)	119·3 (4)
C(1)—C(6)—C(7)	109·9 (4)
C(5)—C(6)—C(7)	130·8 (5)
C(6)—C(7)—C(8)	115·5 (5)
C(6)—C(7)—C(11)	115·2 (5)
C(6)—C(7)—C(12)	101·2 (4)
C(8)—C(7)—C(11)	101·8 (5)
C(8)—C(7)—C(12)	111·7 (4)
C(11)–C(7)—C(12)	111·9 (5)
C(7)—C(8)—C(9)	104·9 (6)
C(8)—C(9)—C(10)	107·6 (7)
C(9)—C(10)–C(11)	107·3 (7)
C(7)—C(11)–C(10)	106·8 (6)
C(7)—C(12)–C(13)	112·5 (4)
C(1)—C(13)–C(12)	108·1 (4)
C(1)—C(13)–C(14)	124·1 (4)
C(12)–C(13)–C(14)	127·7 (4)
C(13)–C(14)–C(15)	110·9 (4)
C(14)–C(15)–N	110·9 (4)
C(15)–N——C(16)	113·3 (4)

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