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The Anticholinergic Drug Dexetimide. The Crystal Structure and Absolute Configuration of (+)-1-Benzyl-4-(2,6-dioxo-3-phenyl-3-piperidyl)piperidine Hydrobromide Hemihydrate

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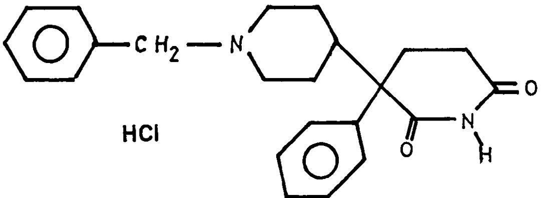
The hydrobromide of dexetimide, the pharmacological active enantiomer of (±)-benzetimide, crystallizes from 70% alcohol as the hemihydrate. The crystals are triclinic, space group $P1$, with $a=7{\cdot}390$ (2), $b=9{\cdot}073$ (1), $c=17{\cdot}284$ (2) Å, $\alpha=96{\cdot}24$ (1), $\beta=101{\cdot}78$ (2), $\gamma=81{\cdot}28$ (2)°, $Z=2$. The structure solution was initiated with a direct method based on addition modulo eight of symbolic phases, and was completed by standard Fourier techniques. Cu $K\alpha$ counter data, corrected for absorption, were refined by block-diagonal least-squares procedures to $R=0{\cdot}046$ for 4799 observed amplitudes. The absolute configuration is S. The conformations of the two independent molecules differ to fulfil the requirements for hydrogen bonding and packing. The two dexetimide.HBr molecules fit, together with a water molecule of crystallization, in a network including hydrogen bonds and Coulomb interactions. The Br ions are 'sandwiched' between two benzetimide molecules with short N–H···Br and C–H···Br contacts.

Introduction

(±)-Benzetimide-HCl, (±)-1-benzyl-4-(2,6-dioxo-3-phenyl-3-piperidyl)piperidine.HCl, (I), is a potent and persistent anticholinergic agent, acting in both the peripheral and the central nervous system. Its activity is entirely due to the (+)-enantiomer dexetimide (Janssen *et al.*, 1971). The drug is used to suppress Parkinson-like symptoms sometimes evoked in psychiatric patients being treated with neuroleptic drugs. A comparative study by van Wijngaarden, Soudijn & van der Eycken (1970) of space-filling models of agonists, dexetimide, and other antagonists of acetylcholine resulted in the correct prediction of the S configuration of dexetimide. Soudijn, van Wijngaarden & Ariëns (1973) suggested that dexetimide is bound stereospecifically to the acetylcholine receptor probably covering the acetylcholine binding site of the receptor with the hydrophilic part of the molecule. Accepting this hypothesis, it was shown that dexetimide is a useful tool for localizing acetylcholine receptors by making use of its stereospecific binding properties (Beld & Ariëns, 1974).



(I)

This paper gives an account of the structure determination of the hydrobromide of the (+)-enantiomer of (±)-benzetimide. A preliminary report of the absolute configuration, from a poorer data set, has been given (Spek, Peerdeman, van Wijngaarden & Soudijn, 1971). The purpose of the structure determination was the verification of the prediction for the absolute configuration of (+)-benzetimide (van Wijngaarden, 1970). The structure was also used as a test case for two techniques, the Symbolic Phasing Procedure (Spek, 1975) and an automated Patterson technique (Lenstra, 1973).

The structure of the free base (+)-benzetimide has been published (Koch & Dideberg, 1973). In the present paper a comparison of the results of both structure determinations is included.

Experimental

The hydrobromide of dexetimide crystallizes from 70% alcohol in thin needle- and plate-shaped transparent colourless crystals. A sample was obtained from Dr I. van Wijngaarden and Dr W. Soudijn (Janssen Pharmaceutica, Beerse, Belgium). A specimen, 0·24 × 0·26 × 0·10 mm, was mounted on a glass fibre approximately along **a**. Two sets of data were measured on this crystal. A preliminary set contained the intensities of a hemisphere of reflexions measured out to $\theta=23°$ (Mo $K\alpha$) on an Enraf–Nonius AD3 diffractometer. The resulting set of 2604 reflexions was of poor quality owing to instrumental difficulties. It was used for the solution of the structure and for preliminary refinement.

A new set was collected on an Enraf–Nonius CAD4 diffractometer with a scintillation counter and Ni-filtered Cu $K\alpha$ radiation. Cell dimensions and their standard deviations were determined on the CAD4 diffractometer by centring of 12 reflexions and a least-squares technique (Duisenberg, 1974). The Delaunay reduced cell and other data are summarized in Table 1.

Table 1. *Crystallographic and physical data for (+)-benzetimide hydrobromide hemihydrate* ($C_{23}H_{27}N_2O_2Br.\frac{1}{2}H_2O$)

F.W. 452·4
Triclinic, space group: $P1$
$Z=2$

	Delaunay reduced cell
$a=$ 7·390 (2) Å	$a'=$ 7·390 (2) Å
$b=$ 9·073 (1)	$b'=$ 9·073 (1)
$c=$ 17·284 (2)	$c'=$ 17·355 (2)
$\alpha=$ 96·24 (1)°	$\alpha'=$ 92·50 (1)°
$\beta=$ 101·78 (2)	$\beta'=$ 102·86 (2)
$\gamma=$ 81·28 (2)	$\gamma'=$ 98·72 (2)

The matrix used in the transformation to the Delaunay reduced cell is

$$\begin{pmatrix} \mathbf{a}' \\ \mathbf{b}' \\ \mathbf{c}' \end{pmatrix} = \begin{pmatrix} 1 & 0 & 0 \\ 0 & \bar{1} & 0 \\ \bar{1} & 0 & \bar{1} \end{pmatrix} \begin{pmatrix} \mathbf{a} \\ \mathbf{b} \\ \mathbf{c} \end{pmatrix}$$

$d_c=1{\cdot}343$ g cm^{-3} $F(000)=478$
μ(Cu $K\alpha$)$=29{\cdot}4$ cm^{-1} $V=1118{\cdot}4$ Å^3
λ(Cu $K\alpha$)$=1{\cdot}5418$ Å
Crystal volume$=4{\cdot}6\times10^{-3}$ mm^3
Number of observed reflexions hkl: 2419
$\bar{h}\bar{k}l$: 2793
Number with $I<2{\cdot}5\sigma(I)$: 411

The intensities for all accessible reflexions up to $\theta=55°$ were collected by the ω-scan technique with automatic scan expansion $\Delta\omega=3{\cdot}1+0{\cdot}35\tan\theta$. Each reflexion was measured at a speed designed to achieve 1000 counts above background. The measurement of a reflexion hkl was immediately followed by the measurement of the Friedel related $\bar{h}\bar{k}\bar{l}$. The data were corrected for fluctuations in the intensity (<2%) and for absorption (Duisenberg, 1968). The observed absorption factors were in the range from 1·29 to 1·75. The intensities of 4801 reflexions were measured with $I>2{\cdot}5\sigma(I)$. Another 411 reflexions were marked unobserved and excluded from further refinement.

Structure determination

The structure was solved with the Mo data. The observed structure factors were put on an absolute scale (Wilson, 1942), and normalized structure factors $|E(hkl)|$ calculated. The E statistics indicate that the space group is $P1$.

The structure determination was carried out both by direct methods and by automated Patterson techniques. The difficulties encountered in the application of the latter have been described by Lenstra (1973) and are comparable to those encountered in the application of direct methods to this structure.

The Symbolic Phasing Procedure (Spek, 1969, 1975) was used to solve the structure. 492 reflexions with $|E|>1{\cdot}3$ were selected, from which 4855 phase relations were generated. The relations were ordered according to the variance of their phase indication. The origin for the description of the structure was fixed according to the general seminvariance theory (Hauptman, 1972). The device used in this structure determination is one of the many possible, and is part of the automatic mode of the program. As a start the program chose the three reflexions $20\bar{1}$, $2\bar{1}7$ and $13\bar{1}$ that are linearly independent modulo (2,2,2). The phases of these reflexions were arbitrarily set to zero. This is not sufficient to fix the origin in $P1$. In this space group it is a necessary condition that the determinant of the three reflexions equals ±1, instead of 36 in this case. According to the seminvariance theory it is then necessary to add a few more reflexions (m) to the origin-determining set, so that the largest common divisor of the determinants that can be constructed with the $m+3$ reflexions is equal to one. In our case the reflexion $0\bar{2}1$ was chosen, and assigned a symbolic phase. In addition to these four reflexions another 25 were added with symbolic phases. All these reflexions were chosen on the basis of the usual criteria (Spek, 1975). New phases were found by insertion of the symbolic phases of the starting set, and later the derived phases, in reliable phase relations. Phases were added modulo eight, in contrast to addition modulo two as is common practice in symbolic addition procedures for centrosymmetric space groups. The phase of a reflexion was thus implicitly considered to be a multiple of 45°. After phase expansion and subsequent elimination of 23 symbols, three symbols including the one to fix the origin uniquely were left. The set of 512 solutions, obtained by assigning different phases (multiples of 45°) to the remaining symbols, was arranged according to the value of $\sum_{\mathbf{hk}}|\Delta\varphi|\,|E_{\mathbf{h}}E_{\mathbf{k}}E_{\mathbf{h}+\mathbf{k}}|$, where the summation is over all relationships and $\Delta\varphi$ the sum of the phases in a phase relation (Spek, 1975). Since we did not explicitly limit the range of phases for the symbols to fix the enantiomorph uniquely, the resulting set of solutions was degenerate under criteria ordering the solutions.

Fourier syntheses were calculated for a number of solutions with the highest probability. Some solutions were shown to be false from the number of large peaks. The ninth nontrivial solution showed only two large peaks corresponding to the two Br^- ions. In addition several flat and puckered six-membered rings could be discerned. The general pattern was, however, one of a double solution. Both the correct structure and its enantiomorph, inverted through a point in the middle between the Br positions, were suspected to be present with approximately the same weight. One of the four piperidine rings that could be detected near the Br^- ions was picked out as a starting point. The two benzyl fragments attached to this piperidine ring could also be located.

At this point some time was spent in attempts to find the rest of the structure with weighted tangent refinement techniques starting with phases calculated for the located atoms, but without success. Therefore a cycle of structure factor and Fourier map calculations was initiated. This cycle started with $R=0{\cdot}30$ for the two heavy and twenty light atoms, and R became 0·21 when all atoms, apart from the water molecule (see below), were located.

Looking at the structure determination in retrospect it is clear that we were in fact solving a nearly centrosymmetric doubled structure. This became evident after the calculation of a Fourier synthesis including only the 492 E's $> 1\cdot30$ that were used in the structure determination, with phases calculated for the refined structure. An E map was obtained, which in general appeared to be the same as the E map described above. Only the weights (2:1) of the two overlapping inversely related structures were slightly different. The contributions of the Br atoms to the large E's is apparently such that they simulate a nearly centrosymmetric structure. The deviation from this has to come from the many weak reflexions, which, however, were not included in the Fourier summation. In view of this it is also clear why the tangent refinement process did not result in a better Fourier map. Tangent refinement is a rather delicate matter in space groups like $P1$, because all the invariants $\Delta\varphi = \varphi_{\mathbf{h}} + \varphi_{\mathbf{k}} - \varphi_{\mathbf{h}+\mathbf{k}}$ tend to refine to values equal to zero unless proper precautions are taken.

Table 2. *Absolute configuration determination*

(*a*) Effect of anomalous dispersion on the agreement for the accepted configuration S (model 1) and for the enantiomorph R (model 2). Hydrogen atoms were excluded.

	Model 1	Model 2
$\sum \lvert F_o \rvert$	83770	83803
$\sum \lvert \Delta F \rvert$	4837	5549
R	0·058	0·066
R_w	0·067	0·076
$\mathscr{R} = R(2)/R(1)$	1·138	
$\mathscr{R}_w = R_w(2)/R_w(1)$	1·134	

$n = 4801$

$m = 512$

$\mathscr{R}_{b,\,n-m,\,\alpha} = \mathscr{R}_{1,\,4289,\,0.005} = 1\cdot001$

(*b*) Some Friedel-related pairs of reflexions. The intensities are corrected for absorption and on a relative scale. The $\sigma(I)$'s are given in parentheses.

h	k	l	$F_c(hkl)$		$F_c(\bar{h}\bar{k}\bar{l})$	$I_o(hkl)$		$I_o(\bar{h}\bar{k}\bar{l})$
0	1	$\bar{7}$	47·1	<	48·1	16747 (279)	<	18259 (390)
0	1	$\bar{2}$	8·1	>	6·1	2168 (86)	>	1377 (74)
0	2	6	11·9	>	10·5	1284 (50)	>	1003 (31)
0	2	15	16·3	>	15·4	923 (45)	>	649 (23)
0	6	$\overline{13}$	5·7	<	6·4	93 (9)	<	163 (30)
1	$\bar{6}$	$\bar{4}$	20·7	>	18·9	1506 (58)	>	1284 (52)
1	$\bar{3}$	7	21·5	>	20·8	2783 (58)	>	2440 (47)
1	$\bar{1}$	$\bar{1}$	4·7	<	8·5	269 (47)	<	1398 (62)
2	4	$\bar{3}$	30·1	>	27·9	7335 (175)	>	6418 (156)
4	5	$\bar{7}$	22·2	>	20·6	1664 (44)	>	1361 (54)
6	1	$\bar{7}$	21·4	>	20·5	1529 (41)	>	1225 (46)

Refinement and absolute configuration

The origin was shifted to the pseudo centre of symmetry between two Br atoms. The refinement with the Mo data did not proceed satisfactorily ($R = 0\cdot14$). Nevertheless the determination of the absolute configuration appeared to be possible, and this configuration was adopted hereafter. At this point the Cu data were obtained and refinement with this set was continued by block-diagonal least-squares procedures. Both *hkl* and $\bar{h}\bar{k}\bar{l}$ data were used. The coordinates of $\mathrm{Br(1)}_A$ were kept fixed during the refinement. Temperature motion was included with anisotropic parameters. Only non-hydrogen atoms were included at this stage. The refinement converged to $R = 0\cdot074$. A difference synthesis, including a hemisphere ($\bar{h}\bar{k}\bar{l}$) of observed reflexions, showed four peaks up to 1·5 e Å^{-3}. Only one of these positions remained stable during subsequent refinement when atoms were introduced with O scattering factors. Its position was such that it fitted in a hydrogen-bond network and so was identified as a water molecule. Its temperature motion is quite high, which is why it was not found earlier. The other peaks were no longer present in later difference syntheses. R dropped to 0·058 after insertion of the extra O atom.

A second refinement was carried out for the enantiomorphous structure to recheck the assignment of the absolute configuration. The result is summarized in Table 2. According to Hamilton's (1965) R-factor test for 4801 reflexions and 512 parameters, the discrimination between the two models is significant and the enantiomorphous model can be rejected at a level much lower than 0·005.

H atoms, except for those of the water molecule, were introduced at calculated positions and their positions corroborated by a difference synthesis. After subsequent refinement only one H atom of the water molecule could be found. Two reflexions 001 and 00$\bar{1}$ apparently suffered from secondary extinction and were excluded from the final cycles. Further refinement of all parameters, except for the isotropic temperature factors of the H atoms, which were fixed at the values of the atoms they are bonded to, converged to $R = 0\cdot046$ ($R_w = 0\cdot052$) for 4799 observed reflexions. The function minimized was $\sum[w(|F_o| - |F_c|)^2]$. R and R_w are defined as $R = \sum(|F_o| - |F_c|)/\sum|F_o|$ and $R_w = [\sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2]^{1/2}$. All observed reflexions were treated with unit weight.*

The final positional parameters are shown in Table 3. The final difference synthesis showed no significant features $> 0\cdot3$ e Å^{-3}, apart from some peaks of 0·7 eÅ^{-3} near the Br atoms, indicating that the absorption correction was not completely effective. With respect to the missing second H atom of the water molecule, no electron density peak higher than 0·1 e Å^{-3} was

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* The following data have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 31329 (42 pp., 1 microfiche): tables of (*a*) intensity statistics, (*b*) anisotropic thermal parameters, (*c*) hydrogen atom parameters, (*d*) bond distances, (*e*) least-squares planes, (*f*) structure factors; figures showing (*a*) intensity of the reflexion 014 and its Friedel-related 0$\overline{14}$ as a function of the rotation angle ψ around the reflexion normal, (*b*) Newman projections along N(2)–C(17) and C(4)–C(12), (*c*) hydrogen bonding. Copies may be obtained through The Executive Secretary. International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

found near O(3). The scattering factors for O, N and C were from Cromer & Mann (1968), for H from Stewart, Davidson & Simpson (1965) and for Br^- from *International Tables for X-ray Crystallography* (1962). The corrections for anomalous scattering by Br were $\Delta f' = -0{\cdot}96$ and $\Delta f'' = 1{\cdot}46$ (Rietveld, 1966).

Table 3. *Final fractional atomic coordinates, with estimated standard deviations in parentheses, for the non-hydrogen atoms*

Molecule *A*	*x*	*y*	*z*
Br(1)	0·7357 (0)	0·7436 (0)	0·4685 (0)
N(1)	0·3918 (10)	0·7335 (8)	0·1062 (4)
N(2)	0·2829 (8)	0·7787 (6)	0·4599 (3)
O(1)	0·6550 (1)	0·6822 (9)	0·0584 (5)
O(2)	0·1132 (8)	0·7880 (6)	0·1432 (4)
C(1)	0·5718 (13)	0·6594 (10)	0·1066 (6)
C(2)	0·6414 (12)	0·5496 (10)	0·1696 (5)
C(3)	0·5505 (11)	0·5890 (9)	0·2389 (5)
C(4)	0·3356 (10)	0·6043 (8)	0·2183 (4)
C(5)	0·2670 (12)	0·7166 (8)	0·1534 (5)
C(6)	0·2628 (10)	0·4553 (8)	0·1796 (4)
C(7)	0·3733 (12)	0·3167 (9)	0·2023 (6)
C(8)	0·3078 (14)	0·1840 (10)	0·1652 (7)
C(9)	0·1524 (14)	0·1817 (10)	0·1129 (6)
C(10)	0·0410 (13)	0·3165 (10)	0·0920 (5)
C(11)	0·1053 (10)	0·4492 (8)	0·1251 (5)
C(12)	0·2424 (10)	0·6646 (8)	0·2897 (4)
C(13)	0·2806 (11)	0·8248 (8)	0·3218 (5)
C(14)	0·2052 (11)	0·8808 (8)	0·3927 (4)
C(15)	0·2349 (10)	0·6232 (7)	0·4319 (4)
C(16)	0·3075 (11)	0·5639 (8)	0·3593 (4)
C(17)	0·2209 (11)	0·8426 (7)	0·5342 (5)
C(18)	0·3265 (11)	0·7741 (9)	0·6078 (5)
C(19)	0·4889 (13)	0·8115 (11)	0·6462 (6)
C(20)	0·5816 (15)	0·7547 (13)	0·7162 (7)
C(21)	0·4983 (20)	0·6537 (13)	0·7479 (7)
C(22)	0·3368 (23)	0·6133 (17)	0·7097 (7)
C(23)	0·2497 (17)	0·6686 (14)	0·6396 (6)
Molecule *B*			
Br(1)	1·2656 (1)	0·2565 (1)	0·5312 (1)
N(1)	1·0334 (14)	−0·0028 (8)	0·8921 (5)
N(2)	0·8259 (8)	0·2811 (6)	0·5407 (3)
O(1)	1·2967 (14)	−0·0865 (8)	0·9728 (4)
O(2)	0·7585 (11)	0·0750 (8)	0·8129 (4)
C(1)	1·2256 (16)	−0·0232 (11)	0·9120 (6)
C(2)	1·3305 (16)	0·0419 (12)	0·8638 (6)
C(3)	1·2161 (14)	0·0855 (10)	0·7847 (5)
C(4)	1·0199 (12)	0·1774 (9)	0·7900 (5)
C(5)	0·9223 (14)	0·0783 (11)	0·8289 (6)
C(6)	1·0388 (14)	0·3210 (9)	0·8457 (5)
C(7)	1·1983 (17)	0·3917 (11)	0·8601 (6)
C(8)	1·2061 (21)	0·5292 (12)	0·9070 (7)
C(9)	1·0483 (24)	0·5955 (13)	0·9358 (8)
C(10)	0·8951 (20)	0·5263 (13)	0·9256 (6)
C(11)	0·8907 (16)	0·3905 (11)	0·8780 (6)
C(12)	0·9018 (11)	0·2158 (8)	0·7104 (5)
C(13)	0·9137 (11)	0·0943 (8)	0·6426 (5)
C(14)	0·7914 (10)	0·1328 (8)	0·5664 (4)
C(15)	0·8102 (12)	0·4002 (8)	0·6067 (5)
C(16)	0·9399 (13)	0·3626 (8)	0·6821 (5)
C(17)	0·7055 (10)	0·3197 (8)	0·4639 (4)
C(18)	0·7535 (9)	0·2359 (8)	0·3937 (4)
C(19)	0·6857 (12)	0·1058 (9)	0·3609 (5)
C(20)	0·7286 (14)	0·0329 (10)	0·2938 (6)
C(21)	0·8518 (14)	0·0849 (11)	0·2547 (6)
C(22)	0·9237 (13)	0·2136 (12)	0·2864 (6)
C(23)	0·8799 (11)	0·2879 (9)	0·3545 (5)
Water			
O(3)	0·8129 (14)	0·9294 (9)	0·0110 (5)

Description and discussion of the structure

The unit cell contains two crystallographically independent molecules, *A* and *B*, which gives us the opportunity to compare the geometries of both molecules with that of the free base (Koch & Dideberg, 1973). The numbering scheme is given in Fig. 1. Bond lengths involving non-hydrogen atoms are also presented in Fig. 1 and bond angles in Table 4. The bond distances were not corrected for thermal motion.

Table 4. *Bond angles (°) for the heavier atoms including some involving hydrogen atoms*

Comparable angles for the free base (FB) studied by Koch & Dideberg (1973) are also given.

	A	*B*	FB
N(1)—C(1)—O(1)	119·6 (9)	117·2 (11)	118·9 (2)
N(1)—C(1)—C(2)	115·0 (9)	118·2 (8)	117·4 (2)
O(1)—C(1)—C(2)	125·4 (9)	124·4 (11)	123·7 (2)
C(1)—C(2)—C(3)	112·2 (7)	113·5 (9)	113·0 (2)
C(2)—C(3)—C(4)	114·0 (6)	113·9 (8)	113·4 (2)
C(3)—C(4)—C(5)	108·1 (7)	105·2 (7)	108·4 (2)
C(4)—C(5)—N(1)	116·8 (6)	116·9 (8)	117·7 (2)
O(2)—C(5)—C(4)	123·2 (8)	122·9 (9)	124·0 (3)
N(1)—C(5)—O(2)	119·9 (7)	119·9 (10)	118·2 (3)
C(1)—N(1)—C(5)	128·9 (7)	126·6 (10)	127·6 (2)
C(3)—C(4)—C(12)	113·2 (6)	114·0 (7)	112·0 (2)
C(5)—C(4)—C(6)	104·7 (5)	106·5 (7)	105·8 (2)
C(6)—C(4)—C(12)	110·3 (7)	109·7 (6)	108·5 (2)
C(3)—C(4)—C(6)	112·5 (6)	111·5 (7)	112·8 (2)
C(5)—C(4)—C(12)	107·6 (6)	109·6 (7)	109·1 (2)
C(4)—C(6)—C(7)	118·0 (6)	122·3 (9)	121·6 (3)
C(4)—C(6)—C(11)	123·9 (6)	120·1 (9)	120·4 (2)
C(6)—C(7)—C(8)	117·1 (7)	120·9 (11)	120·6 (3)
C(7)—C(8)—C(9)	123·4 (8)	118·5 (13)	120·8 (4)
C(8)—C(9)—C(10)	120·0 (9)	121·6 (11)	119·1 (4)
C(9)—C(10)–C(11)	118·1 (8)	118·3 (12)	120·8 (4)
C(6)—C(11)–C(10)	123·3 (7)	123·0 (11)	120·8 (3)
C(7)—C(6)—C(11)	118·2 (7)	117·4 (8)	117·8 (3)
C(4)—C(12)–C(13)	113·1 (7)	115·5 (6)	114·0 (2)
C(4)—C(12)–C(16)	111·8 (6)	113·6 (7)	112·7 (2)
C(13)–C(12)–C(16)	107·5 (6)	107·5 (7)	108·5 (3)
C(12)–C(13)–C(14)	114·3 (7)	114·3 (6)	109·8 (3)
N(2)—C(14)–C(13)	111·1 (6)	111·9 (6)	109·6 (3)
C(14)–N(2)—C(15)	108·7 (5)	109·2 (6)	109·0 (3)
N(2)—C(15)–C(16)	111·8 (6)	112·9 (6)	110·7 (3)
C(12)–C(16)–C(15)	114·2 (6)	111·0 (7)	111·4 (3)
C(14)–N(2)—C(17)	111·2 (5)	112·4 (5)	112·1 (3)
C(15)–N(2)—C(17)	114·7 (6)	113·8 (5)	112·8 (3)
N(2)—C(17)–C(18)	115·4 (6)	116·8 (6)	114·2 (4)
C(17)–C(18)–C(19)	123·1 (9)	124·5 (8)	118·4 (4)
C(17)–C(18)–C(23)	119·3 (8)	119·3 (7)	123·2 (4)
C(19)–C(18)–C(23)	117·5 (8)	116·3 (7)	118·3 (4)
C(18)–C(19)–C(20)	123·3 (11)	122·9 (9)	120·3 (5)
C(19)–C(20)–C(21)	117·8 (10)	120·8 (9)	120·7 (5)
C(20)–C(21)–C(22)	119·8 (11)	117·8 (9)	120·3 (5)
C(21)–C(22)–C(23)	121·3 (15)	121·5 (10)	119·8 (5)
C(18)–C(23)–C(22)	120·2 (12)	120·7 (8)	120·3 (4)
C(14)–N(2)—H(1)	107 (4)	110 (5)	–
C(15)–N(2)—N(1)	108 (4)	111 (4)	–
C(17)–N(2)—H(1)	107 (4)	100 (4)	–
C(1)—N(1)—H(27)	100 (5)	124 (5)	112 (3)
C(5)—N(1)—H(27)	127 (5)	109 (5)	120 (3)

The thermal motion of the molecules is shown in Fig. 2 (*ORTEP*, Johnson, 1970). From this it can be seen that the thermal motion of some parts of the molecules is rather anisotropic, particularly for the phenyl groups and the water molecule. The large thermal vibration of the water molecule may be explained by the weak bonding in which it is involved.

Five H atoms bonded to atoms having a relatively high thermal motion refined to chemically unreasonable distances [C–H = 1·2–1·5 Å, σ(C–H) = 0·1 Å]. The other 45 H bonded to C atoms have distances in the range 0·8 to 1·2 Å with average C–H = 0·99 (2) Å.

Estimated standard deviations were calculated taking into account both the errors in the lattice parameters and the standard deviations derived from inversion of the block-diagonal matrices. The standard deviations σ_m in the averages x_m were calculated from

$$\sigma_m = [\textstyle\sum_i (x_i - x_m)^2 / N(N-1)]^{1/2} .$$

The geometry of benzetimide

The geometry and the absolute configuration of the two independent molecules of (+)-benzetimide.HBr is shown in Fig. 2. A comparison of the bond distances in these two molecules and in the free base (+)-benzetimide is given in Fig. 1. Torsion angles (Klyne & Prelog, 1960) are in Table 5.

The central piperidine rings are in the chair conformation. The average C–N$^+$ distance is 1·509 (9) Å, comparable to the 1·497 Å found by Griffith & Robertson (1972) in parpanit. The protonation on N(2) results in an increase of the immediately surrounding bond lengths by about 0·05 Å, whereas the lengths of the next neighbouring bonds shrink by approximately

Table 5. *Torsion angles*

(FB = (+)-benzetimide, Koch & Dideberg, 1973)

	A	*B*	FB
Dioxopiperidyl moiety			
C(1)–C(2)–C(3)–C(4)	+55·7	+47·6	+48·9
C(2)–C(3)–C(4)–C(5)	−53·7	−57·6	−53·3
C(3)–C(4)–C(5)–N(1)	+24·5	+39·6	+32·4
C(4)–C(5)–N(1)–C(1)	+2·4	−13·0	−6·7
C(5)–N(1)–C(1)–C(2)	−2·4	−1·0	+0·1
N(1)–C(1)–C(2)–C(3)	−26·3	−16·5	−21·2
Asymmetric carbon C(4)			
C(3)–C(4)–C(12)–C(13)	+63·2	+38·2	+63·9
C(3)–C(4)–C(12)–C(16)	−58·4	−86·7	−60·5
C(5)–C(4)–C(12)–C(13)	−56·2	−79·4	−56·0
C(5)–C(4)–C(12)–C(16)	−177·8	+155·7	+180·0
C(6)–C(4)–C(12)–C(13)	−169·8	+164·0	−170·8
C(6)–C(4)–C(12)–C(16)	+68·6	+39·1	+64·8
C(7)–C(6)–C(4)—C(12)	−96·6	−101·2	−98·0
Benzyl moiety			
C(14)–N(2)—C(17)–C(18)	−164·7	−74·3	−160·0
C(15)–N(2)—C(17)–C(18)	+71·5	+161·0	+76·5
C(23)–C(18)–C(17)–N(2)	−100·3	−89·2	+25·7
Piperidine ring			
C(12)–C(13)–C(14)–N(2)	+58·0	+54·9	+61·2
C(13)–C(14)–N(2)—C(15)	−58·2	−53·4	−64·0
C(14)–N(2)—C(15)–C(16)	+57·1	+56·7	+62·2
N(2)—C(15)–C(16)–C(12)	−55·9	−59·5	−57·8
C(15)–C(16)–C(12)–C(13)	+50·3	+55·1	+53·5
C(16)–C(12)–C(13)–C(14)	−51·9	−54·3	−54·9

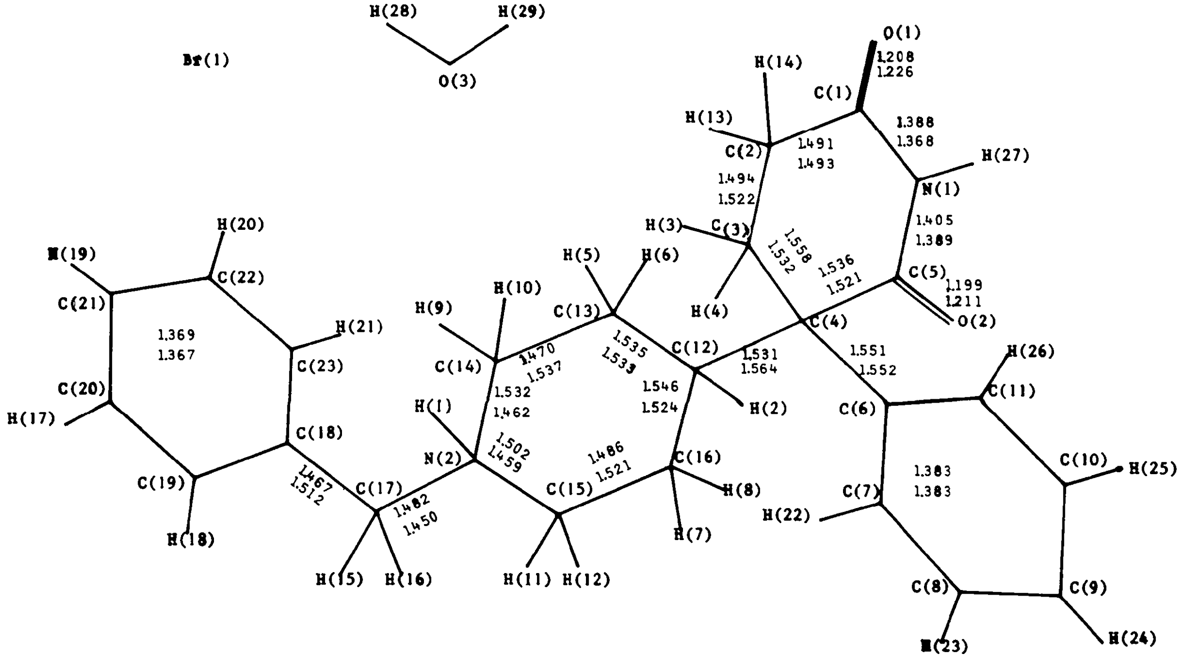

Fig. 1. Numbering scheme and bond distances involving non-hydrogen atoms. The upper values stand for the distances averaged over the two independent molecules *A* and *B* of dexetimide.HBr, the lower for the distances reported by Koch & Dideberg (1973) for the free base. Standard deviations for the present structure determination range from 0·01 to 0·02 Å.

the same amount. The other two piperidine rings are considerably flattened owing to the presence of the nearly planar imide fragment.

Most of the C–C lengths around C(4) are somewhat longer than the accepted values, C(sp^3)–C(sp^3) = 1·537 Å and C(sp^3)–C(sp^2) = 1·505 Å (Sutton, 1965), which is attributed to steric hindrance.

The average bond distance in the three left (Fig. 1) phenyl groups (*A*, *B* and free base) are 1·361 (13), 1·376 (12) and 1·367 (13) Å and in the three right phenyl groups 1·381 (19), 1·386 (10) and 1·383 (5) Å.

The average C–C distances for the two phenyl groups in each of the three molecules differ by about 0·015 Å which is, however, of the same order as the standard deviations. All the averages are less than the standard value of 1·394 (5) Å (Sutton, 1965) but are comparable to the mean value 1·374 Å reported for the benzyl moieties in tribenzylamine (Iwasaki & Iwasaki, 1972). Part of this shortening may be attributed to the lack of thermal motion correction.

The torsion angles (Table 5) show that the largest differences in *A* and *B* are the internal rotations around N(2)–C(17) and C(4)–C(12). The rotations about the first bond are equivalent but of opposite sign. The sign is presumably dependent on packing. About C(4)–C(12) the torsion angles for *A* agree well with the values found for the free base. This probably represents the conformation with the lowest free energy. The

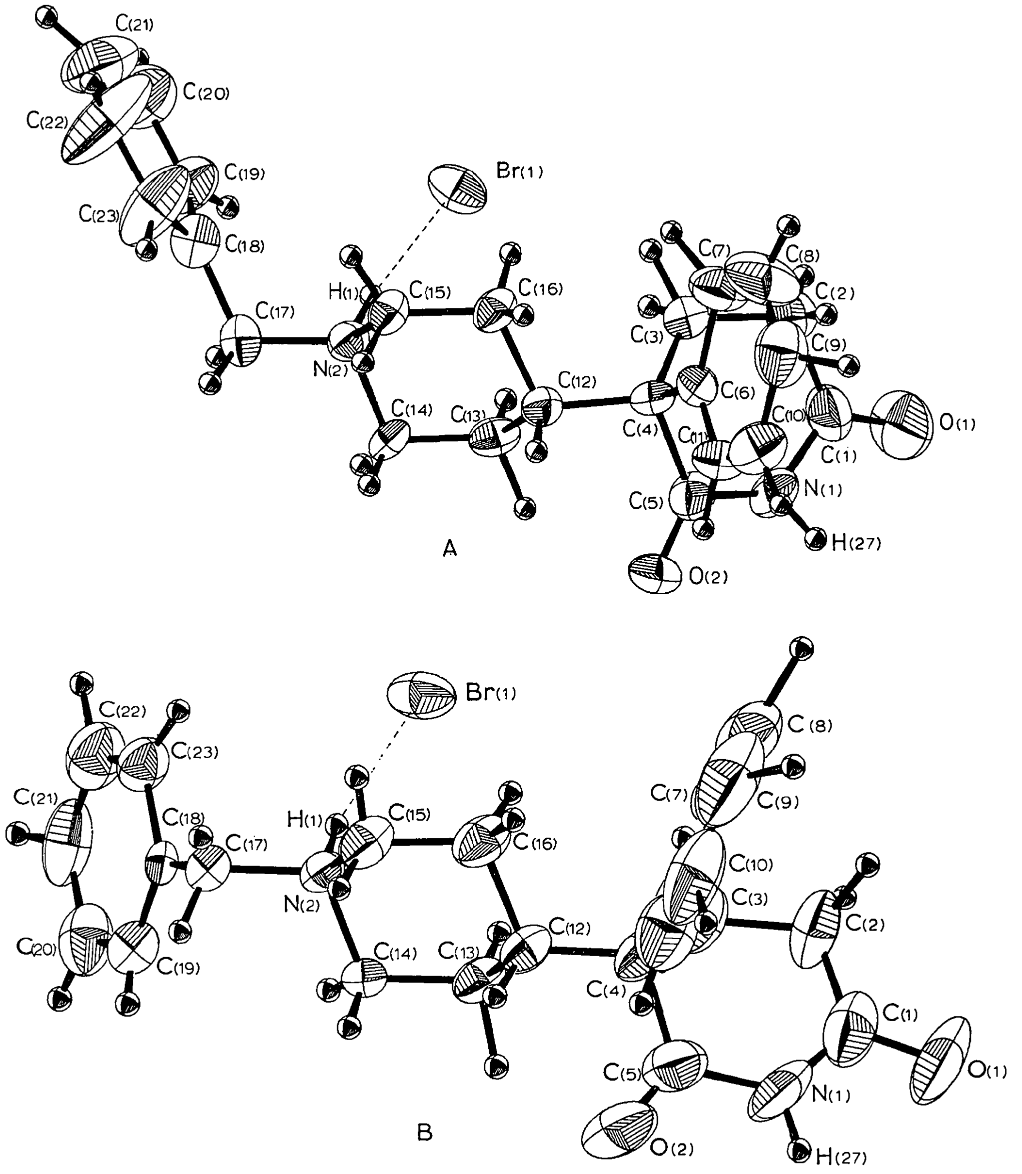

Fig. 2. *ORTEP* drawings scaled to include 50% probability. The molecules are shown with their absolute configuration. The hydrogen atoms are represented as artificially small spheres.

deviation by approximately 25° from this conformation found in *B* is necessary to fulfil the requirements for hydrogen bonding. A still larger rotation (about $-60°$) is necessary to bring the molecule into the conformation used for the prediction of the absolute configuration on the basis of receptor theory (van Wijngaarden, 1970; van Wijngaarden, Soudijn & van Eycken, 1970).

The crystal structure

The packing is shown in Fig. 3 (Kaas, 1969). Apart from weak van der Waals interactions, the molecules are held together by a network of hydrogen bonds and Coulomb interactions. Firstly there is a set of hydrogen bonds of the types N–H···O and O–H···O running as a chain in the **a** direction in the plane $z=0$. This system is shown in Fig. 3 and tabulated in Table 6. The water molecule acts as an acceptor for N(1)$_B$–H(27)$_B$ and as a donor for O(1)$_A$. Although some discussion is possible about the exact nature of the interaction O(3)–H(28)···O(1)$_A$, a point in favour of the given interpretation is that only the H atom involved in hydrogen bonding was found in the difference syntheses. The hydrogen bonding in the free

Table 6. *Geometry of the hydrogen bonds and some other short interactions involving bromine with* H···Br *less than* 3 Å

The combination *ijk* codes a lattice translation $(i-5)\mathbf{a}+(j-5)\mathbf{b}+(k-5)\mathbf{c}$.

D	H	*A*	Symmetry transformation of *A*, *ijk*	*D*–H	H···*A*	*D*···*A*	*D*–H···*A*
N(1)$_A$	H(27)$_A$	O(1)$_B$	464	0·86 (8) Å	2·06 (8) Å	2·879 (10) Å	159°
N(1)$_B$	H(27)$_B$	O(3)	546	0·96 (9)	2·08 (9)	3·034 (15)	172
O(3)	H(28)	O(1)$_A$	455	0·89 (10)	2·32 (11)	2·941 (14)	127
N(2)$_A$	H(1)$_A$	Br(1)$_A$	555	0·92 (6)	2·38 (6)	3·287 (3)	169
N(2)$_B$	H(1)$_B$	Br(1)$_B$	555	0·86 (8)	2·42 (7)	3·260 (4)	166
C(17)$_A$	H(16)$_A$	Br(1)$_A$	455	1·10 (7)	2·70 (7)	3·748 (4)	159
C(15)$_A$	H(11)$_A$	Br(1)$_A$	455	0·99 (6)	2·94 (7)	3·845 (3)	152
C(14)$_B$	H(9)$_B$	Br(1)$_A$	545	1·06 (6)	2·97 (6)	3·789 (4)	134
C(17)$_B$	H(15)$_B$	Br(1)$_B$	455	1·00 (7)	2·86 (7)	3·808 (3)	158

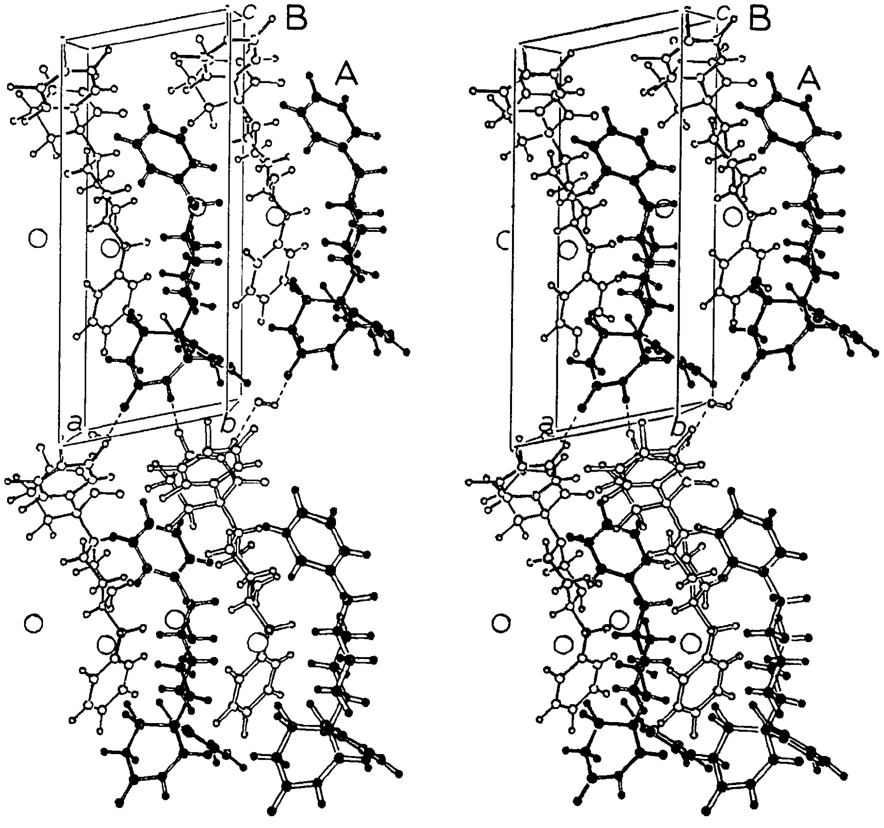

Fig. 3. Stereoscopic drawing illustrating the packing of the molecules.

base (Koch & Dideberg, 1973) is very similar, except that no water molecule is involved as an acceptor/donor bridge. In both cases one carbonyl function is not involved in hydrogen bonding.

The ionogenic interactions are concentrated in the plane $z=\frac{1}{2}$, with the Br^- ions in a 'sandwich' position between two benzetimide molecules. There are short interactions of the type N–H···Br and C–H···Br. The environments of the Br^- ions are also tabulated in Table 6 which includes all distances less than the sum of the van der Waals radii (Br = 1·95 Å, H = 1·2 Å) (Pauling, 1960). The Br^- ions are located nearly at the apex of the triad of C(14), C(15) and C(17) above N(2) at distances of 3·287 and 3·260 Å respectively. This distance is somewhat larger than in similar structures. A distance of 3·209 Å is found in (±)-β-prodine hydrobromide (Ahmed, Barnes & Di Marco Masironi, 1963) and 3·23 Å in capaurine hydrobromide (Shimanouchi, Sadasa, Ihara & Kametani, 1969). The somewhat longer N···Br distance probably indicates that the Br^- ions interact with several surrounding molecules, especially the one above along x. An indication in this respect is given by the rather long distance N–H···Br = 3·387 Å found in a configuration where the Br^- ion is surrounded by two N–H and one O–H group (Kroon & Krabbendam, 1974).

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