

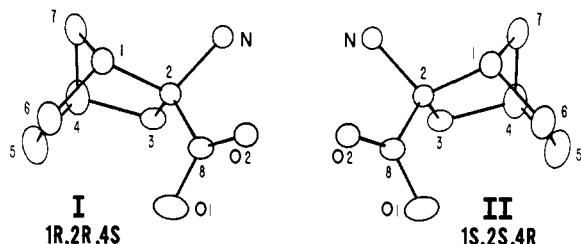
# Crystal Structure and Absolute Configuration of the Hydrobromide Salt of (-)-2-*exo*-Aminonorbornane-2-carboxylic Acid

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**Abstract:** The configuration of one of the four isomers of 2-aminonorbornane-2-carboxylic acid ( $C_8H_{13}O_2N$ ) has been determined to be (1*R*,2*R*,4*S*) by X-ray crystallography, utilizing anomalous scattering. The hydrobromide salt of this isomer, (-)-2-*exo*-aminonorbornane-2-carboxylic acid, crystallizes in space group  $P2_12_12_1$  with four molecules per unit cell of dimensions  $a = 6.986$ ,  $b = 22.669$ , and  $c = 6.150$  Å. The structure was determined by the heavy atom method and refined *vs.* 923 unique observed reflections to a final *R* factor of 0.04. The bond angles and distances in the bicycloheptane ring agree well with those observed in other norbornane compounds, but the location of the carboxyl group in the endo position is counter to certain chemical predictions. Determination of the absolute configuration relates this norbornane amino acid to (-)-norbornanone (1*R*).

The unnatural amino acid, 2-aminonorbornane-2-carboxylic acid, or BCH,<sup>1</sup> has been prepared by both the Strecker and the Bucherer syntheses,<sup>2</sup> and shown to possess several interesting biological activities. BCH inhibits the  $Na^+$ -independent transport of non-polar amino acids across cell membranes;<sup>2</sup> like leucine, it acts as an insulin-releasing factor in the rat,<sup>3</sup> and it inhibits the flavoprotein amino acid oxidases.<sup>4</sup> The chemical syntheses from ( $\pm$ )-norbornanone yield a mixture of four isomers, the (-) and (+) enantiomers of the *exo*-amino (I and II) and *endo*-amino forms. The



geometric isomers have been separated by column chromatography,<sup>2,5</sup> the isomer eluted first being designated a-BCH. Resolution of the enantiomorphs of both a- and b-BCH has permitted the demonstration that the biological potency of these compounds depends on both the geometric and absolute configurations of the molecule.<sup>4</sup> Although the insulin-releasing activity and the uptake into *Escherichia coli* cells are restricted to the levorotatory b-BCH, the stereospecificity displayed by other bioassay systems is not absolute.<sup>4,6</sup>

Efforts to establish the geometric configurations of the a- and b-BCH isomers by degradation to the known norbornane carboxylic acids<sup>7</sup> proved unsuccessful.<sup>6</sup> The assignments of configuration in the analogous cy-

clohexane amino acids, based on *pK* values, spectra, and reactivities, have been the subject of some disagreement.<sup>8,9</sup> Moreover, the differences in *pK* and in reactivity between *exo*-amino- and *endo*-amino-BCH are not large.<sup>4</sup> We therefore undertook the crystal structure analysis of one of the a-BCH isomers in order to determine its configuration. For comparison with the amino acids whose activity is mimicked by BCH, the absolute configuration is also essential, and has been determined by the use of anomalous scattering. To ensure that the observed intensity differences would be sufficiently large, a good anomalous scatterer was incorporated into the structure by conversion of (-)-a-BCH to the hydrobromide salt, which was prepared and crystallized for us by H. Tager.

The initial Fourier map of a-BCH, based on phases calculated from the bromine positions, showed that, contrary to the predictions from the *pK* values for the carboxyl and amino groups, a-BCH possesses an endo carboxyl group. The absolute configuration of (-)-a-BCH has been established as structure I (1*R*,2*R*,4*S*); refinement of this structure resulted in a final *R* factor of 0.04. In the accompanying paper,<sup>4</sup> Tager and Christensen report the identification of the two isomers of b-BCH.

## Experimental Section

Unit cell parameters and other physical data are included in Table I. The *hkl* and Friedel-related *hkl* intensities were measured using a diffractometer with Weissenberg geometry. Integrated intensities were calculated from counts accumulated during stepwise  $\varphi$  scans, and background correlations were reduced by employing balanced filters. An intensity was considered to be unobserved whenever contiguous counts in the peak region were not significantly greater than the adjacent background noise level.<sup>10</sup> Corrections for relative absorption were computed from measurements of the crystal dimensions.<sup>11,12</sup> As a final check on the absolute configuration, intensities of a selected set of reflections were also determined with a four-circle diffractometer (Table VI).

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(1) 2-Aminobicyclo[2.2.1]heptane-2-carboxylic acid.  
(2) H. N. Christensen, M. E. Handlogten, I. Lam, H. S. Tager, and R. Zand, *J. Biol. Chem.*, **244**, 1510 (1969).

(3) H. N. Christensen and A. M. Cullen, *ibid.*, **244**, 1521 (1969).

(4) H. S. Tager and H. N. Christensen, *J. Amer. Chem. Soc.*, **94**, 968 (1972).

(5) H. S. Tager and R. Zand, *Anal. Biochem.*, **34**, 138 (1970).

(6) H. N. Christensen and H. S. Tager, private communication.

(7) J. A. Berson and D. A. Ben-Efraim, *J. Amer. Chem. Soc.*, **81**, 4083 (1959).

(8) L. Munday, *J. Chem. Soc.*, 4372 (1961).

(9) R. J. W. Cremlyn and M. Chisholm, *ibid.*, 2269 (1967).

(10) J. C. Hansen, Ph.D. Thesis, University of Michigan, Ann Arbor, Mich., 1969.

(11) C. Burnham, an IBM 709/7090 computer program for computing transmission factors for crystals of essentially arbitrary shape. Geophysical Laboratory, Carnegie Institution of Washington.

(12) W. R. Busing and H. A. Levy, *Acta Crystallogr.*, **10**, 180 (1957).

Table I. Physical Data for C<sub>8</sub>H<sub>13</sub>O<sub>2</sub>N·HBr

Space group	P2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>
Mol wt	236.1
a, Å	6.988 ± 0.005
b, Å	22.673 ± 0.01
c, Å	6.150 ± 0.004
ρ <sub>calcd</sub> (Z = 4), g cm <sup>-3</sup>	1.609
Habit	Tabular {010}
Crystal size, mm	0.44 × 0.34 × 0.18
Radiation	Mo Kα (Zr-filter)
No. of unique reflections	1024 (sin θ/λ = 0.593)
μ, cm <sup>-1</sup>	43.825

<sup>a</sup> Cell dimensions were determined from the angular settings of 12 reflections, using the computer-controlled Syntex 4-circle diffractometer.

assign the absolute configuration. The weighted *R* factor for the set of parameters corresponding to II was 0.108 and that for structure I was 0.096. This difference is significant at a confidence level of much less than 0.005.<sup>15</sup> The unweighted *R* factors were 0.075 for II and 0.064 for I. Difference Fourier maps calculated including anomalous scattering corrections for the bromine atoms<sup>16</sup> yielded the positions of the fourteen hydrogen atoms. Full-matrix refinement of all parameters was then carried to a point where the ratio of parameter shift to estimated error was less than 0.25 for all but six of the parameters. Only the hydrogen parameters and the bromine thermal parameters had larger relative shifts. At the conclusion of the computations, the unweighted *R* factor was 0.040 and the weighted *R* factor was 0.043. The final parameters<sup>17</sup> and their standard deviations are given in Tables II and III; interatomic distances and bond angles appear in Tables IV and V. Figure 1 shows a stereoscopic view of the molecule including possible hydrogen-bonded atoms.

To examine the agreement between the observed and calculated

Table II. Fractional Coordinates and Thermal Parameters of Nonhydrogen Atoms<sup>a,b</sup>

Atom	<i>x</i>	<i>y</i>	<i>z</i>	β <sub>11</sub>	β <sub>22</sub>	β <sub>33</sub>	β <sub>12</sub>	β <sub>13</sub>	β <sub>23</sub>
C1	0.9229 (0.3)	0.1588 (0.1)	0.4115 (0.3)	0.0225 (15)	0.0015 (2)	0.0168 (20)	-0.0001 (3)	-0.0009 (14)	-0.0003 (5)
C2	0.8341 (8)	0.1002 (3)	0.3308 (12)	0.0154 (11)	0.0014 (1)	0.0186 (18)	0.0004 (3)	-0.0007 (14)	0.0002 (5)
C3	0.7649 (9)	0.1150 (4)	0.0992 (11)	0.0157 (14)	0.0021 (2)	0.0158 (17)	-0.0003 (4)	0.0003 (13)	-0.0003 (4)
C4	0.8214 (13)	0.1803 (4)	0.0740 (13)	0.0392 (24)	0.0017 (3)	0.0160 (21)	-0.0009 (5)	0.0021 (18)	0.0013 (5)
C5	0.6889 (19)	0.2174 (5)	0.2142 (17)	0.0489 (34)	0.0021 (3)	0.0257 (29)	0.0039 (7)	-0.0026 (24)	0.0014 (7)
C6	0.7636 (15)	0.2047 (4)	0.4492 (14)	0.0356 (24)	0.0018 (2)	0.0229 (22)	0.0017 (6)	0.0011 (22)	-0.0005 (6)
C7	0.0099 (12)	0.1820 (4)	0.1957 (14)	0.0320 (19)	0.0015 (2)	0.0220 (25)	-0.0021 (5)	0.0029 (23)	-0.0003 (7)
C8	0.6843 (8)	0.0737 (4)	0.4836 (11)	0.0154 (12)	0.0020 (2)	0.0151 (17)	-0.0002 (4)	-0.0017 (11)	0.0004 (5)
N	0.9933 (7)	0.0550 (3)	0.3232 (12)	0.0164 (10)	0.0013 (1)	0.0221 (17)	0.0002 (3)	0.0034 (13)	-0.0008 (6)
O1	0.5176 (7)	0.0994 (3)	0.4663 (12)	0.0194 (11)	0.0038 (2)	0.0383 (23)	0.0026 (4)	0.0037 (14)	0.0054 (6)
O2	0.7220 (7)	0.0345 (2)	0.6049 (8)	0.0181 (9)	0.0018 (1)	0.0227 (14)	0.0001 (3)	0.0028 (10)	0.0017 (4)
Br	0.2252 (0.8)	0.0645 (0.4)	0.8229 (1)	0.0187 (2)	0.0028 (0.2)	0.0191 (2)	0.0015 (0.4)	0.0042 (1)	0.0003 (0.6)

<sup>a</sup> The temperature factor is of the form exp[-(β<sub>11</sub>h<sup>2</sup> + β<sub>22</sub>k<sup>2</sup> + β<sub>33</sub>l<sup>2</sup> + 2β<sub>12</sub>hk + 2β<sub>13</sub>hl + 2β<sub>23</sub>kl)]. <sup>b</sup> Estimated standard deviation × 10<sup>4</sup> in parentheses.

Table III. Fractional Coordinates and Thermal Parameters for Hydrogen Atoms<sup>a</sup>

Bonded to	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i> <sup>b</sup>
C1	0.989 (9)	0.153 (3)	0.531 (12)	1.00
C3	0.632 (10)	0.113 (3)	0.095 (13)	1.00
C3	0.816 (9)	0.092 (3)	0.007 (12)	1.00
C4	0.812 (10)	0.194 (3)	0.922 (11)	1.00
C5	0.545 (11)	0.207 (4)	0.230 (14)	4.1 (2.2)
C5	0.679 (24)	0.251 (8)	0.197 (25)	5.7 (3.6)
C6	0.655 (14)	0.194 (4)	0.553 (16)	0.7 (1.3)
C6	0.812 (19)	0.237 (5)	0.518 (20)	3.7 (2.5)
C7	0.114 (10)	0.151 (3)	0.143 (12)	1.00
C7	0.055 (9)	0.219 (3)	0.211 (12)	1.00
N	0.100 (9)	0.063 (4)	0.216 (13)	1.00
N	0.974 (9)	0.025 (3)	0.296 (12)	1.00
N	0.048 (16)	0.046 (5)	0.455 (19)	4.2 (2.8)
O1	0.450 (15)	0.095 (5)	0.567 (20)	10.9 (5.4)

<sup>a</sup> Estimated standard deviations in parentheses, × 10<sup>3</sup> for coordinates, × 1 for *B*'s. <sup>b</sup> Where *B* = 1.00, the value was held constant for refinement.

**Determination of the Structure.** The structure was solved by the heavy atom method. In the initial Fourier map based on bromine phases, positions of all the nonhydrogen atoms of a-BCH were clearly seen. The carboxyl group was in the endo configuration, demonstrating that (-)-a-BCH corresponds to either I or II. Parameters from the initial refinements of all nonhydrogen atoms (weighted *R* factor = 0.102)<sup>13</sup> were used as input in a refinement to

(13) The function minimized<sup>14</sup> was Σ<sub>H</sub> w<sub>H</sub> (|F|<sub>obsd</sub> - G|F|<sub>calcd</sub>)<sup>2</sup> where *G* is the scale factor which places |F|<sub>calcd</sub> on the same scale as the observed structure factor, |F|<sub>obsd</sub>, and w<sub>H</sub> is determined from counting statistics.<sup>10</sup> The weighted *R* factor is Σ<sub>H</sub> w<sub>H</sub><sup>1/2</sup> ||F|<sub>obsd</sub> - |F|<sub>calcd</sub> / Σ<sub>H</sub> w<sub>H</sub><sup>1/2</sup> |F|<sub>obsd</sub>. For unweighted *R* factors w<sub>H</sub> = 1.

(14) J. W. Schilling, "Crystallographic Computing," Munksgaard, Copenhagen, 1970, p 201.

Table IV. Intramolecular Distances in Ångströms<sup>a</sup>

C1-C2	1.550	C1-C7	1.551
C2-C3	1.541	C7-C4	1.516
C3-C4	1.541	C2-N	1.512
C4-C5	1.518	C2-C8	1.529
C5-C6	1.564	C8-O1	1.307
C6-C1	1.540	C8-O2	1.189

<sup>a</sup> Interatomic distances were corrected for interdependence of atomic vibrations by allowing bonded atoms to ride on one another;<sup>21</sup> W. R. Busing and H. A. Levy, *Acta Crystallogr.*, **17**, 142 (1964). This correction amounts to ca. 0.05 Å. The estimated standard deviations in the bond lengths ranged from 0.009 to 0.014 Å.

values of the anomalous scattering differences, structure factors. |F<sub>+</sub>| and |F<sub>-</sub>| were calculated for I using the parameters of Tables II and III. The differences ||F<sub>+</sub>calcd| - |F<sub>-</sub>calcd|| were greater than 10% of (|F<sub>+</sub>| + |F<sub>-</sub>|)/2 for 113 reflections. The signs of the anomalous differences agreed with the assignment of (-)-a-BCH as structure I for 80% of these 113 reflections. Table VI provides a quantitative comparison of the calculated and observed differences for selected reflections whose Bijvoet ratios were predicted to be large.

**Hydrogen Bonding.** Each molecule makes four independent hydrogen bonds. Table VII presents the distances and angles between each of the possible hydrogen bonded pairs. There are four potential acceptor atoms, O2 III, Br II, Br III, and Br IV (Figures 1 and 2) situated about the nitrogen atom at distances ac-

(15) W. C. Hamilton, *Acta Crystallogr.*, **18**, 502 (1965).

(16) Anomalous dispersion corrections were taken from International Tables of Crystallography, Vol. III, Kynoch Press, Birmingham, England, 1965, pp 213-216; atomic scattering factors from H. L. Cox, Jr., and R. A. Bonham, *J. Chem. Phys.*, **47**, 2599 (1967).

(17) A listing of the structure factors will appear following these pages in the microfilm edition of this Journal. Single copies may be obtained from the Reprint Department, ACS Publications, 1155 16th St., N.W., Washington, D. C. 20036, by referring to author, title of article, volume, and page number. Remit check or money order for \$3.00 for photocopy or \$2.00 for microfilm.

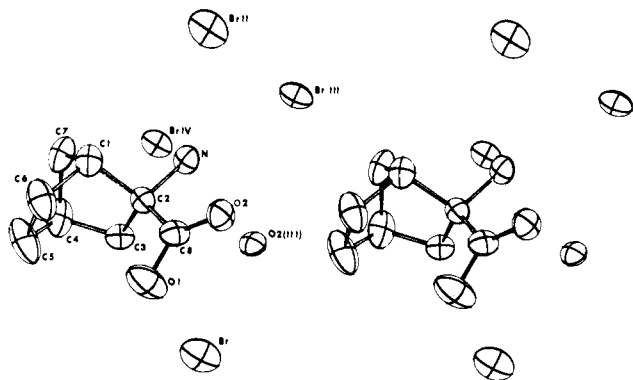


Figure 1. Stereoscopic drawing of  $(-)\text{-}\alpha\text{-BCH}$ . This drawing was prepared by the program ORTEP.<sup>21</sup> Thermal ellipsoids are scaled to enclose 50% probability. Hydrogen bonds connect O1 with Br and N with O2 III, Br II, and Br IV.

ceptable for hydrogen bonding. The C2-N-acceptor angle is nearly tetrahedral for the acceptors carbonyl oxygen O2 III, Br II, and Br IV whereas the C2-N-Br III angle is  $168^\circ$ . In addition, the angles N-H-acceptor lie between  $144^\circ$  and  $161^\circ$  for the first

Table V. Bond Angles in Degrees<sup>a</sup>

C2-C1-C6	109.8	C3-C4-C5	108.6
C2-C1-C7	100.0	C3-C4-C7	101.4
C6-C1-C7	100.5	C5-C4-C7	103.6
C1-C2-C3	103.6	C4-C5-C6	102.7
C1-C2-N	107.2	C1-C6-C5	103.1
C1-C2-C8	114.5	C1-C7-C4	94.2
N-C2-C3	110.5	C2-C8-O1	112.6
N-C2-C8	104.9	C2-C8-O2	121.8
C8-C2-C3	116.0	O1-C8-O2	125.6
C2-C3-C4	102.8		

<sup>a</sup> The central atom is the vertex. The estimated standard deviations in the angles ranged from 0.5 to 0.8 degrees.<sup>17,21</sup>

Table VI. Comparison of Observed and Calculated Anomalous Differences for Selected Reflections

Reflection <i>h k l</i>	$( F_+  -  F_- )/( F_+  +  F_- )$ Observed	Calculated	$ F_+ _{\text{calcd}}$
1 7 1	0.124	0.124	21.21
1 18 1	-0.217	-0.687	0.72
2 3 2	0.234	0.234	14.58
2 5 1	-0.103	-0.114	19.86
2 7 1	-0.104	-0.116	17.22
2 11 2	-0.061	-0.117	11.33
2 12 3	0.185	0.144	6.00
2 16 1	0.142	0.271	4.87
3 7 1	0.122	0.102	15.03
4 5 1	-0.104	-0.088	17.13

three acceptors but vary from  $90$  to  $124^\circ$  for any of the three possible N-H...Br III interactions. Therefore the atoms to which nitrogen is hydrogen bonded are O2 III, Br II, and Br IV; Br III is an atom of close approach.<sup>18</sup> The other hydrogen bond is between the hydroxyl oxygen O1 and the Br of the same asymmetric unit. Figures 2a and 2b show the crystal structure viewed down the  $a$  and  $-c$  axes, respectively. The molecules are laid down in hydrogen-bonded sheets perpendicular to the  $b$  axis. The sheets themselves are held together only by van der Waals forces.

## Discussion

Comparison of the bond distances and angles in I with those determined for other norbornane structures

(18) J. Donohue, *J. Phys. Chem.*, **56**, 502 (1952).

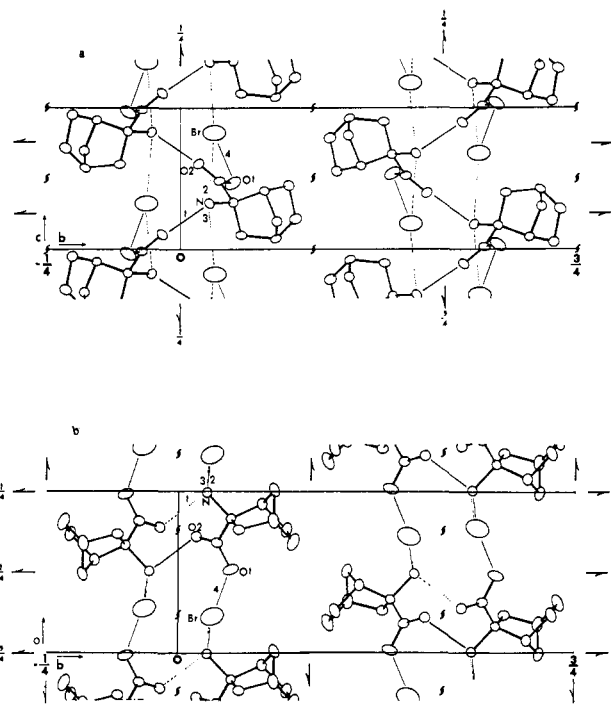


Figure 2. The molecular packing in a unit cell of  $(-)\text{-}\alpha\text{-BCH}$ . The molecule with labels corresponds to the coordinates of Table II. The bonds numbered 1-4 correspond to the hydrogen bonds in Table VII. (a) View down the  $a$  axis. A dotted ( $\cdots$ ) line indicates a hydrogen bond formed in the  $+a$  direction (out of the page); a dashed ( $---$ ) line, one in the  $-a$  direction. (b) View down the  $-c$  axis. A dotted ( $\cdots$ ) line indicates a hydrogen bond formed in the  $-c$  direction (out of the page); a dashed ( $---$ ) line, one in the  $+c$  direction.

by electron<sup>19</sup> and X-ray diffraction<sup>20</sup> reveals no strikingly unusual features in  $\alpha\text{-BCH}$ . Thus the parameters in Tables IV and V<sup>21</sup> lie within the expected ranges. The one-carbon bridge angle found in  $\alpha\text{-BCH}$ ,  $94.2^\circ$ , is comparable with the values  $93.2$  to  $96^\circ$  reported in a recent summary.<sup>22a</sup> The four two-carbon bridge angles determined here vary between  $102.7$  and  $103.6^\circ$  and the bridgehead angles, C6-C1-C2 and C3-C4-C5, are  $109.7$  and  $108.6^\circ$ , respectively. These angles are in good agreement with those observed in 3-(*N*-benzyl-*N*-methylaminomethyl)-2-norbornanol<sup>20b</sup> and differ but marginally from the values determined for norbornane and 1,4-dichloronorbornane by electron diffraction.<sup>19</sup> Recently it has been recognized that asymmetric substitution of the norbornane nucleus often produces a twist about the C1...C4 vector and thereby destroys the  $C_{2v}$  symmetry of the bicycloheptane ring system.<sup>22a</sup> In  $(-)\text{-}\alpha\text{-BCH}$  the loss of symmetry is just detectable in the bond lengths and angles, which differ by approximately  $2\sigma$  across the mirror planes through the norbornane nucleus. For  $(-)\text{-}\alpha\text{-BCH}$  HBr the twist is  $S(-,-)$ ; the magnitude of the phase angle of pseudorotation,  $\Delta$ ,<sup>22b</sup> for the ring C1-C2-C3-C4-C7-C1

(19) J. F. Chiang, C. F. Wilcox, Jr., and S. H. Bauer, *J. Amer. Chem. Soc.*, **90**, 3149 (1968).

(20) (a) A. C. MacDonald and J. Trotter, *Acta Crystallogr.*, **19**, 456 (1965); (b) A. V. Fratini, K. Britts, and I. L. Karle, *J. Phys. Chem.*, **71**, 2482 (1967).

(21) Computations used the ORFE and ORTEP programs, obtained from the Oak Ridge National Laboratory, and written by W. R. Busing, K. O. Martin, and H. A. Levy, and by C. K. Johnson, respectively.

(22) (a) C. Altona and M. Sundaralingam, *J. Amer. Chem. Soc.*, **92**, 1995 (1970); (b) C. Altona, H. J. Geise, and C. Romers, *Tetrahedron*, **24**, 13 (1968).

Table VII. Possible Hydrogen Bonding Pairs<sup>a</sup>

	Donor (D)	Acceptor (A)	Symmetry operation on A	Length, Å	Angle, deg, C-D-A
1	N	O2 III	$3/2 - x, -y, -1/2 + z$	2.862	96.2
2	N	Br II	$1 + x, y, z$	3.482	105.9
3	N	Br IV	$1 + x, y, -1 + z$	3.483	109.1
	N	Br III	$3/2 - x, -y, -1/2 + z$	3.349	168.4 <sup>b</sup>
4	O1	Br	$x, y, z$	3.098	114.5

<sup>a</sup> The estimated standard deviation in the bond lengths ranged from 0.006 to 0.008 Å; those for the bond angles from 0.4° to 0.5°. <sup>b</sup> This is an atom of close approach (see text).

is 1.2° and that for ring C1-C7-C4-C5-C6-C1 is 4.7°.

The conformation and interactions of the amino and carboxyl groups are in accord with observations on other amino acid hydrohalides. The hydroxyl and carbonyl oxygens can be clearly distinguished by their bond lengths.<sup>23</sup> The angles at the carboxyl carbon follow the pattern of other amino acids, with the O-C-O angle near 125°, and the two O-C-C angles unequal,<sup>24</sup> although the disparity between the latter two angles is somewhat greater than the average. The extensive hydrogen bonding observed in crystalline a-BCH·HBr is typical of amino acid salts. The hydrogen-bonded O···N distance of 2.86 Å is close to the "normal"<sup>24</sup> value of 2.90 Å and the N···Br distances (Table VII) may be compared with the 3.36 and 3.32 Å reported for leucine hydrobromide.<sup>23</sup> The torsion angles about the C<sub>α</sub>-C(carboxyl) bond have been examined in several amino acids and peptides. The absolute value of the dihedral angle O-C-C<sub>α</sub>-N varies from 0° to about 70°, with a cluster of angles not far from zero.<sup>24</sup> In a-BCH, this angle is 16°. As a result, the plane of the carboxyl group is approximately perpendicular to the plane defined by C1-C2-C3 of the norbornane nucleus; the interplanar angle is 80° 21'. The carboxyl proton points away from the bicycloheptane ring. The hydrogen bonds to Br<sup>-</sup> and to the amino N of a neighboring molecule undoubtedly stabilize this orientation of the carboxyl group in crystalline a-BCH.

The *exo*- and *endo*-norbornane carboxylic acids and amines were originally prepared and characterized by Alder and coworkers.<sup>25</sup> Subsequent identification of *exo* and *endo* substituents has relied on the initial assignments and used a variety of techniques, especially ir, and more recently, nmr. Solvolysis rates of *exo*- and *endo*-norbornyl chlorides differ by several orders of magnitude<sup>25c</sup> and can therefore be used to distinguish these epimers. On the other hand, saponification rates of the acid phthalates of *exo*- and *endo*-norborneol,<sup>25d</sup> like the hydrolysis rates of *exo*- and *endo*-*N*-formyl-BCH,<sup>4</sup> are almost identical. In general, *endo* isomers of norbornyl compounds prove to be less stable, and the properties of *endo* substituents are more perturbed by the ring system.<sup>26</sup> On this basis, the p*K* values of a- and b-BCH would suggest the tentative conclusion

that the a isomer possesses an *exo*-carboxyl group.<sup>4</sup> However, the structure analysis demonstrates that the carboxyl group is *endo* and emphasizes the difficulties of prediction in this series of compounds, especially when the 2 position is disubstituted.

The absolute configurations of a number of norbornane derivatives, including the *exo*- and *endo*-carboxylic acids and the *endo*-amine, have been assigned by chemical conversions relating them to other terpenoids and ultimately to glyceraldehyde.<sup>27a</sup> Several previous crystal structure analyses of monoterpene derivatives<sup>27b</sup> have included the determination of absolute configuration. Further configurational assignments have depended on application of the octant rules.<sup>28</sup> By the latter method, (-)-norbornanone (norcamphor) was identified as 1*R*, in agreement with the chemical assignment.<sup>29</sup> A similar analysis of the ORD and CD spectra of salicylidene derivatives of *exo*-3-phenyl-*endo*-2-norbornaneamines has established configurations for these compounds and hence for the 3-phenyl-2-carboxylic acids,<sup>30</sup> and chemical reactions have referred the phenyl-substituted series to norbornanone.<sup>31</sup> The present paper establishes that (-)-2-*endo*-carboxyl-2-*exo*-aminonorbornane has the 1*R* configuration and therefore unequivocally relates this amino acid to (-)-norbornanone (1*R*). Chemical data reported in the accompanying paper<sup>4</sup> demonstrate that (-)-2-*exo*-carboxyl-2-*endo*-aminonorbornane is also derived from (-)-norbornanone. L-Leucine, D-valine, or D-isoleucine can assume conformations which resemble (-)-a-BCH. Given suitable restrictions of the rotation angles, any of these carbon skeletons can be exactly superimposed on 1: e.g., if C<sub>α</sub> of D-isoleucine coincides with C2, then C<sub>β</sub> coincides with C1, the ethyl group with C5 and C6, and the methyl with C7. The relative biological activities of the BCH isomers may be partly rationalized on the basis of such comparisons.<sup>4</sup>

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