Crystal Structure and Absolute Configuration of an Anilide Hydrobromide: (+)-N-[(2-Benzylmethylamino)propyl]propionanilide Hydrobromide

By P. Singh* and F. R. Ahmed

Pure Physics Division, National Research Council of Canada, Ottawa 7, Canada
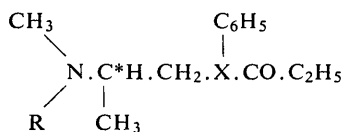
The crystal structure of (+)-N-[(2-benzylmethylamino)propyl]propionanilide hydrobromide, $C_{20}H_{27}N_2OBr$, has been determined by the heavy atom method and refined by block-diagonal least-squares to an R index of 0·049 for the 1569 observed reflexions. The unit cell is monoclinic, space group $P2_1$, with $a = 9·487$, $b = 12·071$, $c = 9·247$ Å, $\beta = 107°32'$, $Z = 2$. The six atoms of the amide group,

$$-N-\overset{\overset{\displaystyle O}{\|}}{C}-C,\quad |$$

are slightly nonplanar with a maximum deviation of 0·07 Å occurring at N, but the four atoms identified with letters are planar. The mean plane of the six atoms makes an angle of 71·3° with the adjoining phenyl ring, and only 6·0° with the second phenyl ring. The amido-nitrogen is separated from the protonated nitrogen, N^+, by only 2·972 Å which is approximately the sum of their van der Waals radii. The *s*-methyl is well removed from the phenyl rings and is not shielded by either of them. There is strong evidence in support of a hydrogen bond between N^+ and Br^-, which are 3·23 Å apart. The absolute configuration of the molecule in this hydrobromide derivative is found to be R in terms of the sequence rule nomenclature, thus confirming the absolute configuration determined chemically for the free base.

Introduction

The compound (+)-N-[(2-benzylmethylamino)propyl] propionanilide is an optically active salt of the base $I(a)$ which belongs to a group of potent analgesics discovered recently by Wright, Brabander & Hardy (1959), and known as basic anilides. The most active member of this group is diampromid, $I(b)$. Basic anilides $I(a$ and $b)$ have structural features similar to methadone, $I(c)$,

$$
\begin{array}{ccc}
CH_3 & & C_6H_5 \\
\backslash & & | \\
 & N.C^*H.CH_2.X.CO.C_2H_5 & \\
/ & | & \\
R & CH_3 &
\end{array}
$$

I (a) R = CH₂C₆H₅,   X = N
  (b) R = (CH₂)₂C₆H₅, X = N (diampromid)
  (c) R = CH₃,   X = C(C₆H₅) (methadone)

at the asymmetric carbon, C^*, since these three compounds have the groupings $>N-C^*H(CH_3)-R$. According to Beckett & Casy (1965), the more active enantiomorphs of several analgesics [including (−)-methadone] containing this structural feature relate to R-(−)-alanine, but it was found from chemical procedures by Portoghese & Larson (1964) that the more active forms of the anilides related to S-(+)–alanine, where the R and S designations refer to the 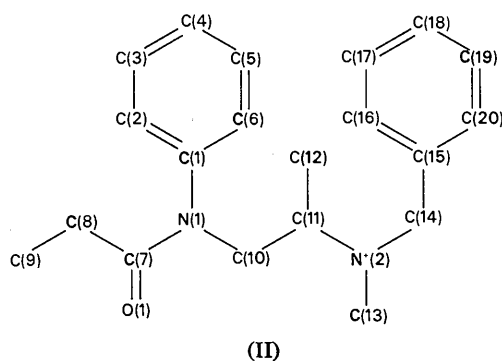absolute configuration according to the convention of Cahn, Ingold & Prelog (1956). Also, it was reported by Casy & Hassan (1967a) that methadone and the anilides differed in their stereospecificities, and it appeared likely, therefore, that 3-amino-1,1-diphenylpropyl and basic anilide analgesics differed in their modes of binding to the analgesic receptor site. A detailed structure analysis of these compounds has been considered, therefore, to be of significance in the understanding of these binding differences.

An X-ray study of the crystal structure and absolute configuration of *d*-methadone hydrobromide was carried out in this laboratory by Hanson & Ahmed (1958). A probable conformation of N-[(2-benzylmethylamino)-propyl]propionanilide hydrochloride in solution, based on spectroscopic data, was proposed by Casy & Hassan (1967b). The present X-ray crystal structure analysis of the corresponding hydrobromide derivative has been carried out in order to determine independently the molecular structure and its absolute configuration, and to provide the relevant quantitative data similar to that of methadone. A schematic drawing of the molecule giving the numbering of the atoms (Br and H excluded) is shown in II.

Crystal data

Crystals of (+)-N-[(2-benzylmethylamino)propyl]propionanilide hydrobromide are colourless, transparent, thin prisms with one of the long directions parallel to the monoclinic unique axis *b*. The chemical formula is $C_{20}H_{27}N_2OBr$ with F.W. = 391·4. The unit cell is monoclinic with dimensions $a = 9·487$, $b = 12·071$, $c =$

* National Research Council of Canada Postdoctorate Fellow.

(II)

9·247 Å ($\sigma = 0.003$ Å for each), $\beta = 107°32'$ ($\sigma = 3'$), $U = 1009.8$ Å³. The density, D_m (flotation in carbon tetrachloride, n-hexane mixture) = 1·290 g.cm⁻³ at 22 °C, and $D_x = 1.287$ g.cm⁻³ for $Z = 2$. Since the compound is optically active and the systematic absences are for $0k0$ when k is odd, the space group is uniquely determined as $P2_1$. Linear absorption coefficients are μ(Cu $K\alpha$) = 31·1 cm⁻¹ and μ(Mo $K\alpha$) = 21·7 cm⁻¹. $F(000) = 408$.

Data collection

The crystal selected for data collection was of irregular shape with approximate dimensions $0.30 \times 0.23 \times 0.05$ mm. Preliminary examination of the crystal, the unit-cell constants, and the space group was carried out with precession photographs. The cell dimensions and the intensity data were measured on a General Electric XRD 5 diffractometer equipped with a scintillation counter, with Cu radiation ($\lambda(K\alpha_1) = 1.54051$ Å, $\lambda(K\alpha_2) = 1.54433$ Å) and Ni filters. The crystal was mounted with its crystallographic b axis along the

φ axis of the instrument. The cell dimensions were measured with narrow slits ($0.02° - 0.05°$) at small take-off angles ($1.0° - 1.5°$) utilizing only the medium and high order axial reflexions. The integrated intensities were measured at a take-off angle of 2·5°, by the θ–2θ scan as described by Furnas (1957), for all the hkl and $hk\bar{l}$ reflexions within the range of the instrument ($2\theta_{max} = 165°$, $\sin\theta/\lambda = 0.64$), and the background was measured separately for each reflexion at the beginning and end of each scan. The scan was over 2° in 2θ for the low-angle reflexions and as much as 5° for the high-angle reflexions.

Appropriate attenuation of the primary beam for the very strong reflexions was achieved by reducing the X-ray tube current. The intensity of the 004 reflexion was measured every 40 to 60 minutes for scaling purposes. Of the 2319 reflexions scanned, only 1569 had a significant count above background.

The net intensity counts were reduced to the same relative scale, modified by the appropriate $(Lp)^{-1}$ corrections, and at a later stage corrected for absorption. The absorption corrections, $\exp(\mu R)$, were calculated on an IBM 360 computer with a program written by the authors in FORTRAN IV to perform the Gaussian quadrature approximation described by Busing & Levy (1957). The three-dimensional grid used in this approximation was made up of $6 \times 6 \times 6$ points. The minimum and maximum absorption corrections to the intensities were 1·15 and 2·22 for the 101 and 1,15,$\bar{1}$ reflexions, respectively. The data were not corrected for extinction but the effect of these errors on the atomic parameters was minimized by the weighting function employed in the least-squares refinement.

For the purpose of establishing the absolute configuration from violations of Friedel's law, resulting from

Table 1. *Fractional coordinates, vibration tensor componets* (Å²) *for the expression* $T = \exp\ -2\pi^2(U_{11}a^{*2}h^2 + \ldots + 2U_{23}b^*c^*kl + \ldots)$, *and their e.s.d.'s* (*all quantities* × 10⁴)

	x	y	z	U_{11}	U_{22}	U_{33}	$2U_{23}$	$2U_{13}$	$2U_{12}$
Br⁻(1)	1770 (1)	0 (2)	1351 (1)	1051 (6)	554 (4)	938 (6)	523 (12)	−114 (9)	−164 (14)
O(1)	5427 (8)	1955 (6)	1418 (7)	1585 (63)	1303 (61)	652 (37)	140 (79)	1072 (81)	615 (105)
N(1)	4681 (7)	2282 (5)	3461 (6)	704 (42)	623 (36)	475 (33)	−115 (59)	495 (59)	27 (69)
N⁺(2)	1617 (7)	2670 (5)	1472 (6)	692 (41)	622 (38)	346 (28)	95 (59)	195 (53)	147 (68)
C(1)	4704 (8)	2042 (6)	4983 (7)	592 (48)	658 (47)	387 (34)	−247 (71)	391 (64)	16 (77)
C(2)	3804 (8)	1231 (7)	5268 (8)	680 (50)	724 (51)	592 (43)	−103 (88)	382 (75)	−56 (94)
C(3)	3827 (10)	1016 (8)	6754 (9)	1066 (73)	899 (66)	676 (53)	273 (99)	748 (100)	291 (113)
C(4)	4722 (11)	1610 (9)	7930 (9)	1316 (80)	974 (72)	517 (46)	85 (95)	436 (101)	570 (133)
C(5)	5598 (11)	2423 (8)	7637 (9)	1075 (73)	990 (69)	644 (53)	−695 (101)	−101 (100)	673 (122)
C(6)	5631 (9)	2646 (7)	6170 (9)	652 (51)	820 (61)	642 (49)	−431 (88)	226 (81)	10 (89)
C(7)	5352 (9)	1648 (8)	2657 (8)	923 (61)	1005 (67)	411 (39)	−282 (85)	427 (80)	−104 (108)
C(8)	6048 (10)	552 (7)	3336 (9)	957 (67)	855 (61)	701 (53)	−122 (93)	422 (97)	248 (106)
C(9)	6747 (10)	−99 (12)	2283 (10)	1224 (75)	1106 (73)	1108 (67)	−390 (176)	1347 (119)	121 (184)
C(10)	4121 (9)	3385 (7)	2878 (9)	850 (60)	603 (49)	647 (49)	106 (82)	305 (88)	−281 (91)
C(11)	2482 (9)	3549 (7)	2532 (8)	687 (52)	695 (51)	502 (42)	129 (77)	281 (76)	−159 (86)
C(12)	2030 (10)	4747 (6)	1990 (9)	1260 (76)	443 (58)	832 (57)	103 (74)	428 (106)	−24 (89)
C(13)	1742 (12)	2791 (8)	−118 (10)	1225 (80)	896 (68)	634 (54)	−52 (101)	616 (106)	258 (123)
C(14)	1 (11)	2650 (7)	1339 (9)	1088 (72)	603 (52)	658 (51)	152 (84)	−139 (96)	271 (99)
C(15)	−289 (9)	2669 (7)	2875 (10)	677 (56)	604 (51)	905 (60)	80 (91)	167 (92)	93 (86)
C(16)	−880 (13)	3589 (8)	3358 (12)	1498 (99)	683 (62)	1124 (78)	28 (113)	1272 (146)	374 (133)
C(17)	−1112 (14)	3605 (9)	4722 (14)	1421 (101)	867 (80)	1582 (106)	−108 (152)	1178 (174)	382 (151)
C(18)	−767 (11)	2725 (11)	5705 (12)	726 (64)	1743 (127)	1090 (78)	−90 (162)	730 (117)	372 (148)
C(19)	−210 (11)	1794 (10)	5252 (13)	939 (72)	1322 (94)	1226 (82)	1103 (143)	994 (125)	703 (137)
C(20)	10 (10)	1762 (8)	3842 (11)	872 (65)	721 (56)	1060 (70)	479 (103)	740 (110)	422 (101)

the anomalous scattering by the Br atom, 19 pairs (hkl and $h\bar{k}l$)' of weak low-angle reflexions were measured. In space group $P2_1$, these violations result in the relationships: $|F(hkl)| = |F(\bar{h}k\bar{l})|$; $|F(h\bar{k}l)| = |F(\bar{h}\bar{k}\bar{l})|$; $|F(hkl)| \neq |F(h\bar{k}l)|$. The average discrepancy in the measured intensities of the equivalent reflexions (hkl and $h\bar{k}\bar{l}$, or $\bar{h}k\bar{l}$ and $h\bar{k}l$) was only 2·5%, while the average discrepancy in the intensities of the hkl and $h\bar{k}l$ resulting from the effect of the anomalous scattering was about 19%.

Structure determination and refinement

The structure was determined from Patterson and Fourier syntheses by the heavy atom method, and was refined by successive cycles of block-diagonal least-squares. The x and z coordinates of the bromine atom

Fig. 1. Perspective view of the molecules showing the unit-cell axes and the nearest bromide atom.

were deduced from the Patterson synthesis, and its y coordinate was set arbitrarily to zero since for space group $P2_1$ the origin may be chosen anywhere on the b axis. In the first Fourier synthesis which was calculated with the structure amplitudes phased by the contributions of the bromine atoms alone, there were, as expected, false mirror planes of symmetry at $y=0$ and $\frac{1}{2}$, and hence twice the true number of peaks in the asymmetric unit. It was possible, however, from consideration of reasonable bond lengths and angles to separate the peaks belonging to the same molecule from those related to them by the false mirror symmetry. The deduced structure (excluding the hydrogen atoms, and assuming $B \simeq 4$ Å^2) corresponded to an R index of 0·34 which was reduced to 0·21 after the first isotropic least-squares cycle. A Fourier synthesis, which was calculated at this stage with the new phases, confirmed the assumed model and showed no spurious peaks or false symmetries. After two isotropic and one anisotropic least-squares cycles of refinement, the R index was reduced to 0·12.

The refinement became relatively slow after this stage until the data were corrected for absorption, the absolute configuration determined, and the anomalous scattering of the bromine atom included in the structure factor calculation. About 125 generally weak reflexions with high discrepancies were remeasured and corrected, but the 001 reflexion ($|F_o| = 9·8$, $|F_c| = 20·9$) could not be improved on remeasurement and was thereafter excluded from the refinement.

At different stages of the refinement, three unsuccessful attempts were made to locate the hydrogen atoms from difference maps. The first map was evaluated before correcting the data for absorption or inclusion of the anomalous scattering, the second after correcting for absorption and the third after inclusion of the anomalous scattering. Only a few of the hydrogenn atoms could have been accepted from the maps, but it was considered more reliable to calculate the positions of 17 non-methyl hydrogen atoms, include them

Table 2. *Fractional coordinates* ($\times 10^3$) *and isotropic temperature factors* (Å^2) *of the hydrogen atoms included in the calculations, and their e.s.d.'s*

	x	y	z	B	Bonded to
H(1)	313 (6)	89 (5)	444 (6)	2·4 (1·5)	C(2)
H(2)	316 (8)	45 (6)	712 (8)	5·5 (2·2)	C(3)
H(3)	469 (7)	161 (7)	899 (8)	4·5 (1·9)	C(4)
H(4)	626 (10)	287 (8)	852 (10)	7·0 (3·0)	C(5)
H(5)	636 (7)	345 (6)	595 (7)	3·8 (1·7)	C(6)
H(6)	524 (6)	2 (8)	361 (6)	2·9 (1·3)	C(8)
H(7)	693 (8)	65 (6)	442 (8)	4·2 (1·8)	C(8)
H(8)	431 (8)	359 (6)	179 (7)	4·0 (1·8)	C(10)
H(9)	451 (7)	402 (6)	372 (7)	2·9 (1·6)	C(10)
H(10)	227 (8)	340 (6)	355 (7)	3·8 (1·7)	C(11)
H(11)	−72 (6)	174 (5)	79 (7)	2·5 (1·5)	C(14)
H(12)	−83 (8)	301 (6)	65 (8)	4·2 (1·8)	C(14)
H(13)	−130 (8)	417 (7)	265 (8)	4·6 (1·9)	C(16)
H(14)	−162 (8)	414 (7)	493 (8)	5·0 (2·0)	C(17)
H(15)	−90 (8)	261 (6)	673 (8)	4·9 (2·0)	C(18)
H(16)	5 (10)	112 (8)	596 (10)	7·0 (3·0)	C(19)
H(17)	45 (8)	109 (7)	333 (8)	5·0 (2·0)	C(20)

Table 3. *Observed and calculated structure amplitudes* ($\times 10$) *and calculated phase angles* (°)

The table lists, in repeated column groups headed K, FO, FC, ALPHA, the observed and calculated structure amplitudes and calculated phase angles for successive layers (H= 0, L= 0; H= 1, L= 0; etc.). The numerical data are arranged in multiple columns across the page.

* Indicates unobserved reflexion with threshold amplitude, $|F_{th}|$, in place of $|F_o|$.

Table 3 (*cont.*)

K	FO	FC	ALPHA
H= 1, L= 4			
1	367	371	271
2	84	72	255
3	249	258	265
4	39	42	20
5	279	285	279
6	144	136	205
7	215	221	269
8	66	66	232
9	127	135	274
10	63	70	260
11	79	85	256
12	52	51	240
13	78	75	276
14	23*	23	251
H= 1, L= -4			
0	414	409	182
1	328	321	250
2	162	181	196
3	243	252	270
4	192	201	176
5	227	244	292
6	186	197	147
7	179	192	265
8	110	123	170
9	107	108	271
10	103	101	136
11	106	105	291
12	68	63	166
13	58	60	302
14	43	42	131
H= 2, L= 4			
0	243	243	3
1	182	183	255
2	144	151	3
3	195	202	293
4	209	217	344
5	126	139	272
6	206	212	346
7	102	105	288
8	112	122	357
9	82	88	284
10	86	87	356
11	58	63	302
12	56	62	348
13	27*	18	312
H= 2, L= -4			
0	195	177	178
1	471	453	317
2	313	311	38
3	220	222	261
4	57	57	107
5	192	182	279
6	85	89	60
7	180	180	274
8	66	75	89
9	124	115	285
10	96	91	50
11	107	95	260
12	39*	35	46
13	45	44	265
14	25*	40	71
H= 3, L= 4			
0	248	239	3
1	94	101	100
2	220	219	4
3	107	114	77
4	246	245	18
5	47	42	102
6	101	103	9
7	85	86	83
8	151	149	16
9	54	45	62
10	80	82	13
11	41	38	83
12	61	57	22
13	23*	21	21
H= 3, L= -4			
0	191	196	4
1	152	141	88
2	290	300	360
3	59	58	226
4	271	267	350
5	36	42	112
6	205	204	358
7	69	69	186
8	181	184	350
9	42*	24	112
10	112	105	25
11	46	45	215
12	72	71	354
13	31*	27	186
14	22*	40	359
H= 4, L= 4			
0	35	29	0
1	198	202	97
2	55	49	182
3	152	156	83
4	34	33	139
5	170	173	99
6	69	67	75
7	133	136	78
8	38*	22	149
9	88	91	100
10	35*	22	110
11	63	63	84
12	32	24	82
H= 4, L= -4			
0	57	61	6
1	139	134	49
2	208	215	356
3	205	214	117
4	108	121	1
5	110	113	108
6	78	82	335
7	93	94	111
8	57	60	330
9	107	106	122
10	75	76	309
11	38	37	104
12	34*	34	306
13	50	47	112
14	18*	32	316
H= 5, L= 4			
0	159	160	183
1	69	70	107
2	119	121	193
3	127	124	100
4	127	130	179
5	66	59	94
6	93	88	191
7	34	32	130
8	60	60	184
9	37	37	114
10	54	52	166
11	27*	28	98
H= 5, L= -4			
0	112	116	183
1	95	98	135
2	103	113	192
3	142	137	67
4	52	99	187
5	124	116	83
6	79	92	207
7	71	68	80
8	73	71	237
9	68	64	78
10	47	40	185
11	81	74	88
12	49	38	239
13	25*	25	74
H= 6, L= 4			
0	71	82	185
1	70	64	293
2	72	69	169
3	96	89	256
4	57	57	205
5	46	41	281
6	69	65	187
7	44	45	276
8	69	65	187
9	27	25	239
10	25*	25	215
H= 6, L= -4			
0	196	202	182
1	50	49	215
2	48	57	179
3	77	71	96
4	54	97	190
5	54	51	294
6	69	75	190
7	39	44	358
8	76	72	171
9	36*	9	190
10	33*	32	156
11	30*	36	342
12	40	44	184
13	16*	19	4
H= 7, L= 4			
0	36*	4	17
1	87	87	297
2	36*	26	307
3	81	76	270
4	34*	5	57
5	65	55	271
6	32*	22	335
7	59	51	261
8	27*	13	303
9	42	34	299
H= 7, L= -4			
0	61	54	182
1	94	84	284
2	36*	23	30
3	86	88	290
4	52	44	143
5	46	52	269
6	43	48	112
7	47	44	279
8	36*	28	194
9	54	56	300
10	40	38	108
11	26*	20	253
12	19*	2	193
H= 8, L= 4			
0	62	64	3
1	33*	16	329
2	42	32	5
3	32*	20	219
4	49	43	9
5	29*	15	319
6	27*	24	6
7	23*	13	271
H= 8, L= -4			
0	38*	23	6
1	38*	40	290
2	41	42	316
3	38*	14	214
4	38*	23	114
5	38	39	276
6	41	39	19
7	36*	24	268
8	29	28	346
9	30*	13	213
10	24	20	59
11	20*	26	275
H= 9, L= 4			
0	27*	15	6
1	27*	19	89
2	26*	20	352
3	25*	20	96
4	23*	19	17
H= 9, L= -4			
0	38*	33	4
1	38*	20	50
2	42	37	352
3	38*	34	155
4	41	34	2
5	37*	23	57
6	35*	17	13
7	33*	18	191
8	29*	22	346
9	25*	11	122
10	18*	12	346
H= 10, L= -4			
0	36*	2	5
1	35*	8	37
2	35*	15	279
3	34*	14	90
4	33*	17	46
5	31*	11	146
6	29*	15	246
7	25*	14	75
8	21*	7	309
H= 11, L= -4			
0	29*	10	183
1	29*	13	45
2	28*	13	175
3	27*	6	160
4	25*	8	195
5	23*	3	61
6	19*	9	207
H= 12, L= -4			
0	18*	13	182
1	18*	1	335
2	16*	11	299
H= 0, L= 5			
0	202	196	182
1	343	342	307
2	105	99	227
3	203	203	224
4	60	69	271
5	222	225	298
6	119	120	235
7	153	160	256
8	61	66	203
9	91	88	272
10	73	77	246
11	71	74	265
12	54	59	243
13	52	49	254
H= 1, L= 5			
0	204	195	3
1	219	227	279
2	147	149	25
3	237	240	274
4	159	156	339
5	107	118	262
6	132	135	331
7	158	165	275
8	79	75	330
9	81	91	287
10	97	91	350
11	94	92	276
12	39	40	316
13	39	37	317
H= 1, L= -5			
0	224	228	184
1	89	99	274
2	187	206	167
3	53	48	34
4	309	323	181
5	88	99	308
6	139	143	150
7	55	56	69
8	220	219	204
9	76	76	304
10	82	84	166
11	69	66	41
12	82	79	186
13	30*	21	350
H= 2, L= 5			
0	187	191	4
1	32*	12	57
2	204	207	4
3	57	61	81
4	190	200	18
5	57	55	316
6	121	119	16
7	73	79	56
8	112	112	20
9	39	41	42
10	80	81	5
11	29	31	51
12	68	69	15
13	22*	18	2
H= 2, L= -5			
0	301	285	181
1	333	336	215
2	47	43	147
3	185	184	294
4	171	174	187
5	117	123	293
6	46	57	130
7	197	200	286
8	74	70	130
9	55	51	273
10	75	76	125
11	57	57	290
12	37	36	146
13	67	60	290
H= 3, L= 5			
0	34*	9	24
1	190	198	91
2	51	47	14
3	188	190	84
4	36*	23	268
5	174	175	99
6	97	100	47
7	118	121	82
8	36	28	38
9	76	75	88
10	51	51	60
11	71	65	80
12	25*	27	69
H= 3, L= -5			
0	82	89	5
1	208	198	308
2	158	157	18
3	228	221	231
4	123	126	2
5	128	114	311
6	171	179	49
7	114	115	230
8	42*	14	67
9	137	132	259
10	87	90	37
11	54	53	262
12	38	44	39
13	34	35	256
H= 4, L= 5			
0	126	134	183
1	97	106	116
2	42	38	159
3	135	129	93
4	150	152	174
5	75	73	104
6	67	57	161
7	47	51	97
8	80	78	190
9	63	63	123
10	53	50	151
11	38	38	105
H= 4, L= -5			
0	235	236	2
1	84	83	152
2	117	125	3
3	72	59	341
4	63	61	36
5	83	94	115
6	112	116	345
7	40*	35	227
8	116	105	359
9	46	46	101
10	52	47	352
11	31	31	167
12	56	50	4
13	24*	33	171
H= 5, L= 5			
0	156	151	183
1	56	54	304
2	93	88	173
3	66	64	239
4	99	98	212
5	42	36	296
6	78	72	181
7	34	32	245
8	81	80	191
9	31*	23	215
10	30	31	201
H= 5, L= -5			
0	104	105	1
1	199	203	93
2	92	92	256
3	94	106	137
4	83	80	320
5	89	95	76
6	69	57	348
7	134	130	100
8	47	46	301
9	41*	34	127
10	52	56	288
11	41	50	94
12	29*	12	260
13	20*	29	108
H= 6, L= 5			
0	37*	24	181
1	92	82	287
2	37*	20	323
3	92	87	280
4	36	30	182
5	70	61	246
6	33*	26	313
7	66	65	267
8	28*	20	247
9	43	41	288
H= 6, L= -5			
0	33*	16	344
1	72	78	169
2	45	37	201
3	102	108	22
4	93	84	183
5	77	73	127
6	36*	18	163
7	36*	27	76
8	50	50	217
9	34*	20	53
10	45	46	217
11	43	39	75
12	22*	20	236
H= 7, L= 5			
0	89	85	3
1	37	32	279
2	33	28	10
3	29	30	245
4	51	49	6
5	48	47	307
6	35	28	10
7	24*	11	298
8	27	32	5
H= 7, L= -5			
0	130	126	182
1	40	32	206
2	56	59	133
3	54	58	284
4	80	89	201
5	43	46	298
6	44	43	172
7	36*	28	26
8	42	42	161
9	30	33	284
10	28*	14	119
11	24	19	6
H= 8, L= 5			
0	28*	15	10
1	28*	18	122
2	34	32	353
3	26*	28	63
4	25*	28	11
5	22*	25	106
H= 8, L= -5			
0	37*	34	180
1	37*	8	105
2	37*	28	58
3	63	67	298
4	37*	31	229
5	37*	25	200
6	41	49	59
7	34*	15	285
8	30	29	172
9	29	30	307
10	24*	21	98
11	16*	18	266
H= 9, L= -5			
0	38*	22	4
1	38*	17	271
2	47	46	13
3	37*	16	286
4	36*	4	95
5	35*	7	286
6	33*	26	6
7	31*	16	205
8	27*	13	2
9	23*	7	224
H= 10, L= -5			
0	34*	18	3
1	34*	22	145
2	34*	18	106
3	33*	8	220
4	32*	25	296
5	30*	10	77
6	27*	12	10
7	24*	8	203
8	18*	4	15
H= 11, L= -5			
0	28*	5	181
1	28*	15	170
2	27*	2	297
3	26*	19	50
4	24*	6	27
5	21*	6	139
6	16*	8	244
H= 12, L= -5			
0	16*	10	358
1	16*	8	166
H= 0, L= 6			
0	200	197	1
1	210	215	316
2	51	53	69
3	211	209	248
4	97	98	343
5	128	135	291
6	38*	26	281
7	121	126	269
8	66	68	309
9	69	69	311
10	49	55	323
11	80	78	258
12	30*	29	280
13	19*	32	297
H= 1, L= 6			
0	142	140	5
1	84	84	166
2	173	169	330
3	124	130	308
4	162	171	23
5	47	51	4
6	153	153	344
7	38*	15	59
8	128	133	28
9	57	59	346
10	60	56	330
11	35	36	360
12	72	74	15
H= 1, L= -6			
0	135	150	183
1	144	149	88
2	106	111	222
3	190	193	68
4	130	140	193
5	94	95	168
6	120	120	239
7	218	215	51
8	42	39	201
9	72	69	77
10	94	97	221
11	66	61	90
12	31*	39	227
13	26	33	51
H= 2, L= 6			
0	162	165	2
1	135	139	65
2	65	67	73
3	161	172	91
4	72	72	6
5	98	109	99
6	69	76	68
7	95	93	93
8	62	63	16
9	71	66	57
10	50	57	51
11	50	49	85
12	30	32	71
H= 2, L= -6			
0	168	158	184
1	70	77	235
2	98	98	223
3	93	104	340
4	177	185	187
5	74	77	245
6	113	109	113
7	43*	20	27
8	128	124	213
9	64	63	291
10	86	74	164
11	39	48	347
12	58	52	183
13	21*	23	329
H= 3, L= 6			
0	154	147	182
1	189	190	127
2	37*	2	320
3	69	65	80
4	131	134	163
5	111	110	83
6	38*	18	159
7	90	87	97
8	69	68	156
9	59	63	108
10	48	46	156
11	47	48	106
H= 3, L= -6			
0	64	61	182
1	209	209	277
2	103	106	86
3	114	116	291
4	120	118	165
5	170	169	255
6	71	60	152
7	130	133	301
8	56	66	87
9	48	46	264
10	40	45	116
11	60	56	274
12	28*	32	108
13	42	37	277
H= 4, L= 6			
0	126	124	184
1	72	73	337
2	121	117	176
3	50	52	163
4	74	84	228
5	38*	3	185
6	88	82	179
7	53	58	214
8	73	72	195
9	30*	8	178
10	33	31	181
H= 4, L= -6			
0	36*	29	168
1	81	83	6
2	64	64	342
3	93	97	222
4	113	115	6
5	79	71	272
6	69	66	20
7	41*	21	212
8	59	53	51
9	30	36	256
10	63	58	39
11	46	47	241
12	28	31	24
H= 5, L= 6			
0	52	42	183
1	70	59	283
2	38*	18	12
3	136	137	265
4	62	66	176
5	45	40	283
6	43	36	268
7	78	67	252
8	32	27	204
9	39	36	289
H= 5, L= -6			
0	173	184	2
1	38*	28	130
2	67	67	37
3	102	111	45
4	138	147	4
5	103	110	159
6	55	53	288
7	41*	23	112
8	74	63	19
9	47	39	124
10	47	47	319
11	31*	11	182
12	34	32	349
H= 6, L= 6			
0	77	74	3
1	64	62	303
2	34*	19	271
3	44	37	238
4	59	56	359
5	55	54	307
6	32	27	6
7	37	32	273
8	27	27	354
H= 6, L= -6			
0	34*	28	360
1	60	50	57
2	35	44	213
3	81	82	116
4	36*	32	27
5	36*	30	264
6	66	75	253
7	77	83	77
8	34*	26	341
9	32*	24	107
10	29*	24	267
11	33	37	107
12	16*	10	286
H= 7, L= 6			
0	38	33	6
1	28*	16	108
2	48	45	8
3	27*	10	67
4	30	32	17
5	42	33	69
6	36	29	353
H= 7, L= -6			
0	51	42	184
1	98	101	178
2	76	75	200
3	99	97	44
4	37*	16	258
5	37*	30	155
6	48	35	167
7	35*	30	353
8	33*	33	188
9	21*	21	121
10	26	29	201
11	23	22	30
H= 8, L= 6			
0	20*	14	1
1	33	27	98
2	18*	8	101
H= 8, L= -6			
0	37*	27	183
1	71	74	316
2	37*	28	81
3	37*	36	119
4	36*	22	123
5	35*	37	291
6	47	41	213
7	32*	19	2
8	29*	14	118
9	25*	19	261
10	20*	9	126
H= 9, L= -6			
0	36*	4	176
1	36*	18	189
2	36*	13	218
3	35*	39	274
4	34*	3	76
5	33*	14	229
6	31*	21	52
7	28*	26	295
8	24*	6	212
9	18*	3	123
H= 10, L= -6			
0	32*	10	4
1	50	47	343
2	32*	19	292
3	31*	33	132
4	29*	21	66
5	27*	8	316
6	24*	3	316
7	20*	6	195
H= 11, L= -6			
0	26*	22	1
1	26*	7	114
2	25*	3	194
3	23*	5	219
4	21*	5	356
5	17*	12	82
H= 0, L= 7			
0	131	126	4
1	79	88	290
2	76	73	311
3	54	60	6
4	141	140	28
5	55	62	224
6	96	84	321
7	64	68	320
8	86	86	24
9	37*	26	306
10	67	55	326
11	35	42	323
12	52	51	25
H= 1, L= 7			
0	210	218	2
1	88	93	90
2	31	32	99
3	120	113	102
4	133	141	24
5	83	79	40
6	39*	37	103
7	90	86	73
8	94	91	19
9	56	50	65
10	33	41	42
11	54	49	69
H= 1, L= -7			
0	51	46	1
1	125	126	120
2	41	45	174
3	214	214	67
4	165	171	336
5	138	139	131
6	73	68	220
7	86	87	80
8	42*	38	315
9	60	53	115
10	44	40	298
11	63	57	75
12	22*	37	274
H= 2, L= 7			
0	92	97	181
1	113	114	121
2	50	45	257
3	127	124	80
4	40	44	145
5	87	85	110
6	38*	19	79
7	75	74	73
8	47	42	133
9	60	61	114
10	28*	24	141
11	45	42	105
H= 2, L= -7			
0	78	79	185
1	118	111	119
2	51	45	162
3	51	72	296
4	95	90	163
5	101	83	56
6	127	124	226
7	81	78	91
8	55	52	194
9	56	52	1
10	51	51	217
11	48	44	76
12	22*	28	203
H= 3, L= 7			
0	62	57	187
1	41	35	352
2	111	103	172
3	59	62	133
4	63	54	189
5	37*	12	171
6	104	100	181
7	44	45	178
8	46	50	199
9	31	26	179
10	41	38	173
H= 3, L= -7			
0	132	130	182
1	71	79	284
2	128	116	195
3	40*	6	44
4	77	76	216
5	60	71	287
6	85	87	123
7	63	69	311
8	70	74	202
9	37*	5	315
10	55	50	139
11	37	40	332
12	42	33	179
H= 4, L= 7			
0	64	69	183
1	47	50	304
2	38*	21	215
3	112	113	256
4	57	55	192
5	49	45	279
6	37	35	222
7	54	46	259
8	29	29	210
9	23*	15	279
H= 4, L= -7			
0	39*	9	177
1	79	73	238
2	40	52	25
3	133	132	262
4	69	66	91
5	78	87	28
6	41*	19	194
7	130	124	235
8	50	56	80
9	54	58	281
10	32*	16	90
11	26	21	277
12	33	29	86
H= 5, L= 7			
0	65	58	2
1	76	76	305
2	42	37	254
3	40	34	247
4	48	48	8
5	51	48	288
6	29*	17	334
7	46	38	268
H= 5, L= -7			
0	102	107	2
1	87	76	325
2	40*	28	89
3	76	88	183
4	54	61	1
5	68	59	305
6	45	47	28
7	48	34	261
8	38*	31	354
9	35*	27	162
10	42	46	31
11	34	26	220
H= 6, L= 7			
0	64	62	3
1	29*	4	83
2	33	35	24
3	27*	6	216
4	54	47	17
5	34	30	26
6	19*	16	330
H= 6, L= -7			
0	36*	6	157
1	93	101	137
2	56	51	283
3	37	35	316
4	62	61	17
5	75	84	91
6	35*	25	276
7	44	42	166
8	35	36	31
9	29*	7	352
10	29	30	272
11	19*	18	127
H= 7, L= 7			
0	20*	10	6
1	24	27	89
2	19*	4	319
H= 7, L= -7			
0	93	92	360
1	58	50	22
2	37*	20	156
3	52	53	101
4	36*	23	701
5	35*	10	99
6	34*	5	325
7	46	47	84
8	38	39	280
9	26*	10	69
10	21*	15	239
H= 8, L= -7			
0	58	50	182
1	86	92	172
2	35	27	269
3	37	45	310
4	34*	24	195
5	23*	10	71
6	31*	12	140
7	29*	11	305
8	26*	5	250
9	21*	4	99
H= 9, L= -7			
0	34*	20	182
1	40	44	338
2	34*	21	112
3	33*	8	161
4	32*	13	223
5	30*	10	293
6	27*	15	127
7	24*	3	137
8	19*	16	148
H= 10, L= -7			
0	30*	4	3
1	30*	28	155
2	29*	15	32
3	32	32	301
4	26*	8	171
5	24*	8	114
6	20*	4	12
H= 11, L= -7			
0	22*	4	4
1	22*	15	2
2	21*	7	262
3	19*	16	175
H= 0, L= 8			
0	140	155	2
1	91	85	135
2	40*	23	148
3	40*	23	351
4	99	98	352
5	63	58	29
6	56	60	34
7	57	57	65
8	66	61	30
9	38	25	35
10	28	26	12
H= 1, L= 8			
0	63	60	180
1	68	65	105
2	39*	26	10
3	134	134	72
4	39*	31	119
5	85	88	131
6	37*	16	105
7	64	55	77
8	32	32	103
9	38	31	99
10	21*	26	107
H= 1, L= -8			
0	77	70	4
1	64	61	137
2	123	103	352
3	63	64	144
4	66	62	75
5	48	58	36
6	71	62	316
7	58	50	152
8	67	59	5
9	45	42	137
10	44	28	312
11	27	23	132
H= 2, L= 8			
0	40	30	190
1	78	74	148
2	76	70	147
3	38*	15	60
4	63	58	190
5	36*	16	124
6	52	46	184
7	45	45	122
8	59	52	174
9	29	27	179
H= 2, L= -8			
0	42*	17	357
1	76	65	118
2	81	92	165
3	137	125	73
4	115	118	296
5	56	54	138
6	41*	24	156
7	84	77	45
8	37*	28	250
9	52	49	109
10	32	32	268
11	42	37	80
H= 3, L= 8			
0	84	85	183
1	53	49	295
2	45	40	198
3	47	46	261
4	52	48	226
5	54	47	233
6	32*	37	199
7	44	41	251
8	25*	27	212
H= 3, L= -8			
0	87	93	183
1	70	57	42
2	40	47	300
3	41*	14	60
4	120	117	159
5	38	38	68
6	47	54	258
7	45	33	92
8	33	33	189
9	43	37	356
10	42	49	202
11	20*	17	26
H= 4, L= 8			
0	41	43	1
1	54	50	266
2	33*	11	263
3	55	52	280
4	31*	7	73
5	43	38	285
6	29	20	318
7	35	27	260
H= 4, L= -8			
0	52	57	357
1	56	52	255
2	88	77	154
3	52	49	288
4	58	56	227
5	71	64	266
6	61	68	97

Table 3 (cont.)

in the refinement, and exclude the others. The most prominent peaks in the difference maps were indicative of residual thermal anisotropy of Br in the x,z plane.

In the final least-squares cycle, the R index was 0·049 for the 1569 reflexions observed above threshold, the average shift was less than 0·1σ, and the maximum shifts were 0·3$\sigma(x,y,z)$ and 0·4$\sigma(B_{ij})$. The unobserved reflexions were excluded altogether from the refinement. The quantity minimized by the least-squares procedure was $\Sigma w(|F_o| - |F_c|)^2$, where $w = 1/\{1 + [(|F_o| - p_2)/p_1]^n\}$, $|F_o| = 1·6$ to 112·5, $p_1 = 25$, $p_2 = 30$, and $n = 2$ for the early cycles and $= 4$ for the final cycles. The exponent $n = 4$ was employed in the final cycles in order to give nearly equal weights (0·5 to 1·0) to reflexions in range $5 \le |F_o| \le 55$ and much reduced weights for the others, since the very strong reflexions were likely to suffer from extinction and the very weak reflexions were inaccurate because of poor counting statistics. The scattering factor curves of Br, O, N, C, H were those given by Hanson, Herman, Lea & Skillman (1964). The curves for Br⁻ and N⁺ were derived by slight modification of the Br and N curves in order to allow for their states of ionization. The $\Delta f'$ and $\Delta f''$ components for Br were taken from International Tables for X-ray Crystallography (1962). No special allowance was made for the slight error in the curve for hydrogen.

Results

The final parameters and estimated standard deviations of the bromine and the non-hydrogen atoms of one molecule referred to a right-handed set of axes are listed in Table 1. The refined parameters and e.s.d.'s of the 17 non-methyl hydrogen atoms are given separately in Table 2, but as indicated by the high e.s.d.'s

the accuracy of these parameters is considerably lower than for the other atoms. The e.s.d.'s were calculated from the least-squares matrices by the appropriate expression given in International Tables for X-ray Crystallography (1959, p. 330). The observed and calcu-
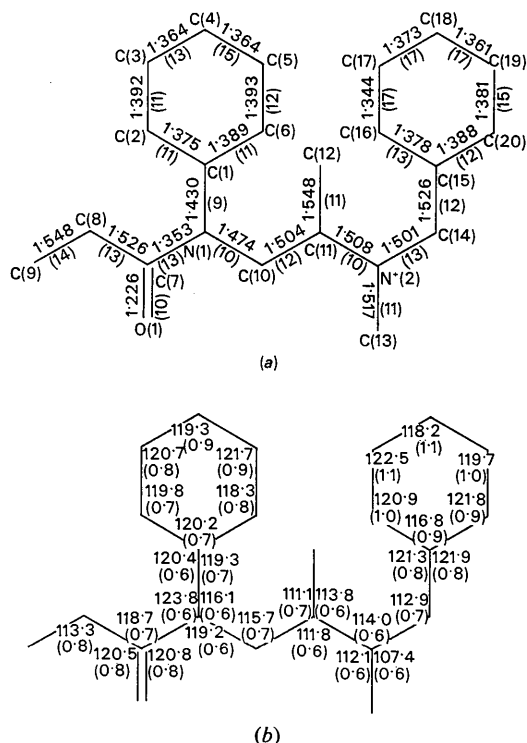

Fig. 2. (a) Bond lengths (Å) and (b) bond angles (°), with their e.s.d.'s in parentheses. E.s.d.'s of bond lengths are × 10³.

lated structure amplitudes, and the calculated phase angles based on the parameters in Table 1 and 2, are listed in Table 3. The phase angles of the $hk0$ reflexions are not exactly $0°$ or $180°$ since the anomalous scattering of the bromine atoms is included in the calculations. The discrepancies in the structure factor data are summarized in Table 4 according to the criteria described by Ahmed & Barnes (1963). The single observed reflexion listed in category 4 is the 001 reflexion, which could not be improved on remeasurement. The eight unobserved reflexions listed in categories 3 and 4 were all high-angle reflexions associated with very high background counts, resulting from unfavourable positions of the goniometer head with respect to the primary beam, and could not be measured accurately.

A perspective view of one molecule and its nearest bromine atom, relative to the unit cell axes, is presented in Fig. 1. The bond lengths and angles, not corrected for thermal vibration, and their e.s.d.'s [Ahmed & Cruickshank (1953) for the bond lengths, and *International Tables for X-ray Crystallography* (1959, p. 331) for the bond angles] are shown in Fig. 2. The mean C–H bond length is $1·05$ Å.

Discussion

Absolute configuration

The absolute configuration of the molecule has been determined from the relative intensities of 19 pairs of reflexions of the types hkl and $h\bar{k}l$. The corresponding observed and calculated structure amplitudes for the parameters given in Tables 1 and 2, and the ratios $|F_o(h\bar{k}l)|/|F_o(hkl)|$ and $|F_c(h\bar{k}l)|/|F_c(hkl)|$ are listed in Table 5. From the consistent agreement of these ratios, it should be concluded that the atomic coordinates given in Table 1 correspond to the absolute configuration of the $(+)$-N-[(2-benzylmethylamino)propyl]propionanilide in the hydrobromide derivative. For further confirmation of this conclusion, the R index for all the observed data has been found to increase from $0·049$ to $0·059$ if the absolute configuration is reversed. In this analysis, the indices and the atomic coordinates have both been chosen to correspond to a right-handed set of unit-cell axes.

The view of the molecule down the N(1)–C(7) bond, presented in Fig. 3(*a*), shows that the absolute configuration is R in terms of the sequence rule nomenclature of Cahn, Ingold & Prelog (1956). This result is in agreement with the conclusions by Portoghese & Larson (1964) regarding the absolute configuration of the molecule in the free base as derived from chemical procedures. For comparison, a similar drawing of d-methadone (the less active form of methadone) in the form of the hydrobromide derivative, based on the coordinates reported by Hanson & Ahmed. (1958) is given in Fig. 3(*b*), and its absolute configuration is shown to be S.

Interatomic distances and angles

In view of the importance of the amide and peptide groups to the structure of proteins, it would be appropriate to compare the dimensions of the amide group in this propionanilide molecule with the X-ray results (Brown & Corbridge, 1954) for acetanilide, and with the values calculated by Pauling (1960). A summary of this comparison is presented in Table 6. The two sets of results for propionanilide and acetanilide are in good agreement with each other except for one bond length, C(7)–C(8), and one angle, C(7)–N(1)–C(1), where the propionanilide results ($1·526$ Å and $123·8°$) are in better agreement with Pauling's values ($1·53$ Å and $123°$) than with the corresponding values for acetanilide ($1·476$ Å and $129·3°$).

In the propionanilide molecule, the C(10)–C(11) single bond which lies between two C–N single bonds is found to be only $1·504$ Å ($\sigma=0·012$ Å), which is rather on the short side, and its difference from the normal value of $1·54$ Å is possibly significant. The C(14)–C(15) bond of the type C–C_6H_5 which is found to be $1·526$ Å ($\sigma=0·012$ Å) in this structure is not significantly different from the average value of $1·506 \pm 0·005$ Å reported by Sutton (1965) for this type of bond. The other two C–C single bonds in the structure are $1·548$ Å each. The C–C aromatic bonds of the two phenyl rings have a weighted mean value of $1·378(\sigma_{wm}=0·004)$ Å. The apparent shortening of these bonds can be attributed, at least partly, to the omission of the corrections for thermal vibration.

Table 4. *Agreement summary*

1569 observed reflexions ($1·6 \le F_o \le 112·5$)
$R = 0·049$

Category	Limits	Number
1	$|\Delta F| \le 1·0|F_{th}|$, or $\quad |\Delta F|/|F_o| \le 0·10$	1564
2	$1·0|F_{th}| < |\Delta F| \le 2·0|F_{th}|$, or $0·10 < |\Delta F|/|F_o| \le 0·15$	4
3	$2·0|F_{th}| < |\Delta F| \le 3·0|F_{th}|$, or $0·15 < |\Delta F|/|F_o| \le 0·20$	0
4	$3·0|F_{th}| < |\Delta F| \qquad$, or $0·20 < |\Delta F|/|F_o|$	1

750 unobserved reflexions ($|F_{c\,max}| = 4·1$)

1	$|F_c| \le 1·0|F_{th}|$	687
2	$1·0|F_{th}| < |F_c| \le 1·5|F_{th}|$	55
3	$1·5|F_{th}| < |F_c| \le 2·0|F_{th}|$	7
4	$2·0|F_{th}| < |F_c| \le 2·5|F_{th}|$	1

$|F_{th}|$ = threshold amplitude = $1·3$ to $4·3$.

The three C–N+(2) bonds have a mean value of 1·509 ($\sigma_m = 0\cdot006$) Å which is significantly longer than the average value of $1\cdot479 \pm 0\cdot005$ Å reported by Sutton (1965) for the C–N bonds at a 4-covalent nitrogen. The occurrence in amino acids of C–NH₃+ bonds longer

than 1·47 Å has been discussed by Hahn (1957), where the mean value of a C–NH₃+ bond is given as 1·503 Å. Also, Hamilton, Hamor, Robertson & Sim (1962) have deduced from a similar survey of alkaloids that the $C(sp^3)$–N+ bond length is about 1·52 Å. It should,

Table 5. *Structure amplitudes and ratios of the reflexions examined for the effect of anomalous scattering by the Br atoms*

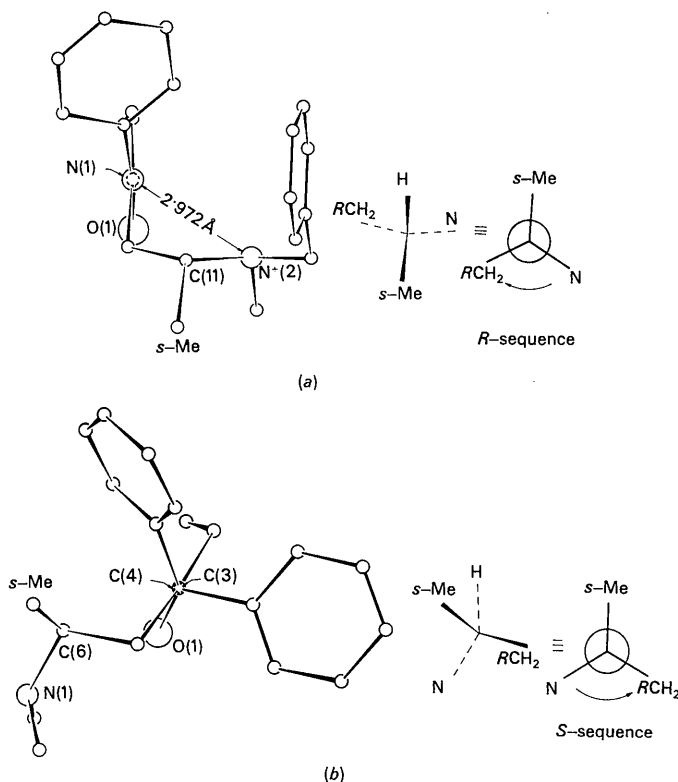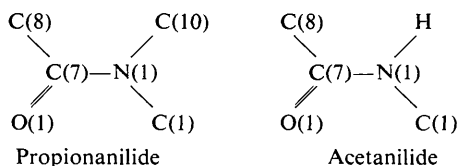| h	k	l	$\lvert F_o(hkl)\rvert$	$\lvert F_o(h\bar{k}l)\rvert$	$\lvert F_c(hkl)\rvert$	$\lvert F_c(h\bar{k}l)\rvert$	$\dfrac{\lvert F_o(hkl)\rvert}{\lvert F_o(h\bar{k}l)\rvert}$	$\dfrac{\lvert F_c(hkl)\rvert}{\lvert F_c(h\bar{k}l)\rvert}$
3	1	$\bar{1}$	11·62	9·78	11·14	9·27	0·84	0·83
4	1	$\bar{1}$	17·45	16·88	17·22	16·40	0·97	0·95
4	2	$\bar{1}$	18·41	20·62	19·35	21·72	1·12	1·12
5	1	1	2·73	2·38	1·55	1·35	0·87	0·87
1	1	$\bar{2}$	8·10	6·34	10·48	7·89	0·78	0·75
2	1	$\bar{2}$	11·99	12·48	13·42	14·50	1·04	1·08
3	2	2	10·97	10·10	11·71	10·57	0·92	0·90
4	1	$\bar{2}$	12·40	12·38	13·13	13·23	1·00	1·01
5	1	$\bar{2}$	12·69	11·93	12·86	12·11	0·94	0·94
5	2	$\bar{2}$	3·62	4·94	2·74	4·70	1·37	1·71
2	1	$\bar{3}$	10·11	9·05	9·18	7·90	0·90	0·86
2	2	3	19·62	19·48	21·26	21·18	0·99	1·00
4	2	$\bar{3}$	17·30	16·79	16·61	15·97	0·97	0·96
0	1	4	18·49	19·22	19·51	20·43	1·04	1·05
1	2	4	8·40	7·91	7·25	6·60	0·94	0·91
1	2	$\bar{4}$	16·23	15·65	18·14	17·39	0·96	0·96
3	1	$\bar{4}$	15·20	15·52	14·12	14·26	1·02	1·01
4	1	$\bar{4}$	13·89	15·22	13·43	14·98	1·10	1·11
1	2	$\bar{5}$	18·70	19·52	20·63	21·50	1·05	1·04

Fig. 3. Molecular structure and absolute configuration of (a) (+)-N-[(2-benzylmethylamino)propyl]propionanilide hydrobromide viewed along the amide bond, N(1)–C(7), (b) d-methadone hydrobromide viewed along the C(3)–C(4) bond.

Table 6. *Dimensions of the amide group*

Bond lengths in Å, angles in degrees, and e.s.d.'s in parentheses.

	Propion-anilide	Acet-anilide	Pauling's values*
C(7)–O(1)	1·226 (10)	1·226 (6)	1·24, 1·26
C(7)–C(8)	1·526 (13)	1·476 (6)	1·53
C(7)–N(1)	1·353 (11)	1·330 (6)	1·32, 1·34
C(1)–N(1)	1·430 (9)	1·426 (6)	—
C(10)–N(1)	1·474 (10)	—	1·47
C(8)–C(7)–O(1)	120·5 (8)	120·4	121
C(8)–C(7)–N(1)	118·7 (7)	117·7	114
N(1)–C(7)–O(1)	120·8 (8)	121·7	125
C(7)–N(1)–C(1)	123·8 (6)	129·3	123
C(7)–N(1)–C(10)	119·2 (6)	—	123
C(1)–N(1)–C(10)	116·1 (6)	—	114

```
      C(8)        C(10)          C(8)         H
        \        /                 \        /
         C(7)—N(1)                  C(7)—N(1)
        /        \                 /        \
     O(1)         C(1)          O(1)         C(1)

       Propionanilide              Acetanilide
```

* First values are based on the X-ray results of amino acids, simple peptides and related substances. Second values are calculated values for 40:60 resonance structures.

therefore, be concluded that the mean value of 1·509 Å which has been found in this structure is a normal length for the $C(sp^3)$–N$^+$ bonds.

An interesting intramolecular distance in the propionanilide structure is that between the two nitrogen atoms N(1) and N$^+$(2) which are separated by only 2·972 Å. This shows that the two atoms are held as
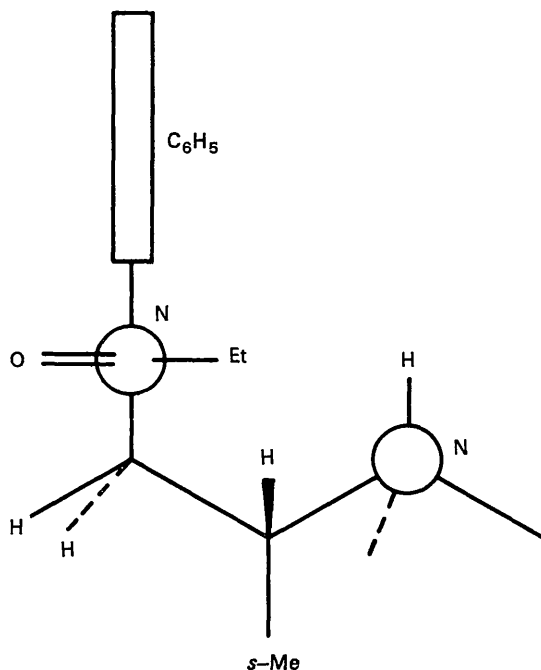

Fig. 4. The conformation proposed by Casy & Hassan (1967*b*) for *N*-[(2-benzylmethylamino)propyl]propionanilide from spectroscopic data, showing only part of the molecule.

close to each other as the van der Waals interactions between them will allow.

The Br$^-$ and N$^+$(2) ions with the coordinates listed in Table 1 are only 3·230 Å apart. Also, the Br$^-$... N$^+$(2) vector makes angles of 134·7°, 92·6°, and 92·1° with the N(2)–C(11), N(2)–C(13), and N(2)–C(14) bonds which, together with the angles of 112·1°, 107·4°, and 114·0° between the three C–N bonds, give a mean angle at N(2) of 108·8°. This evidence suggests the existence of a hydrogen bond, Br$^-$...H–N$^+$(2), with the hydrogen atom lying off the Br...N(2) vector so that the three H–N–C angles are nearer to a tetrahedral configuration than the Br–N–C angles. A similar arrangement occurs in the structure of β-prodine HCl studied by Ahmed & Barnes (1963), where the Cl–N–C angles are 125·8°, 100·0°, and 98·4°, while the H–N–C angles are 111·6°, 109·2°, and 104·3°, and the H–N–Cl angle is 14·3°.

There are no particularly short intermolecular distances in this structure. The shortest contacts not involving hydrogen atoms are 3·118 Å for C...O and 3·572 Å for C...C. The nitrogen atoms are not involved in any intermolecular distances below 4·0 Å.

Planarity of the amide group and phenyl rings

The four atoms C(8), C(7), O(1) and N(1) of the amide group are exactly planar within the accuracy of this determination. Their mean plane referred to the orthogonal set of axes $(X' = ax + cz\cos\beta$, $Y' = by$, $Z' = cz\sin\beta)$ is

$$0·7669X' + 0·4659Y' + 0·4415Z' - 5·2945 = 0 . \quad (1)$$

The displacements of the atoms from this plane are; C(8) 0·002; C(7) −0·007; O(1) 0·003; N(1) 0·002 Å, the corresponding χ^2 value is only 0·99, and $P \simeq 0·29$. Both C(1) and C(10), which are attached to N(1), lie on the same side of the plane at distances 0·151 and 0·113 Å, respectively, from it. The plane of the C(1)–N(1)–C(10) group makes a dihedral angle of 9·8° with plane (1), but the angle of rotation of this group round the N(1)–C(7) bond is only 0·6°, which is equivalent to 1·0 × e.s.d. of the angles in this structure. The angle of rotation has been calculated by the procedure described in the Appendix.

The mean plane through atoms C(8), C(7), O(1), N(1), C(1), and C(10) of the amide group is·

$$0·7940X' + 0·4468Y' + 0·4121Z' - 5·3190 = 0 . \quad (2)$$

The displacements of these atoms from plane (2) are as follows: C(8) 0·009; C(7) −0·020; O(1) 0·026; N(1) −0·070; C(1) 0·035; C(10) 0·020 Å. The corresponding χ^2 value is 171, which shows that these six atoms deviate significantly from exact planarity.

Each of the two phenyl rings is found to be exactly planar. The equations of the mean planes of C(1) to C(6), and C(15) to C(20), are

$$0·7343X' - 0·6723Y' + 0·0942Z' - 1·0165 = 0 , \quad (3)$$

and

$$0·8415X' + 0·3546Y' + 0·4077Z' - 1·2566 = 0 , \quad (4)$$

and the corresponding χ^2 values are 3·0 and 6·6, respectively. The dihedral angle between the two phenyl rings is 65·3°. Plane (2) of the amide group makes a dihedral angle of 71·3° with the adjoining phenyl ring, and a dihedral angle of 6·0° with the other phenyl ring.

Conclusions

The molecular structure shown in Figs. 1 and 3(a) as determined from this X-ray analysis, closely resembles the conformation advanced by Casy & Hassan (1967b) on the basis of spectroscopic evidence, and reproduced here in Fig. 4. The only difference between them is in the orientation of the anilo-phenyl and ethyl-carbonyl fragments relative to the aminoethyl side-chain. Their orientation is shown by the X-ray analysis to be rotated by about 90° from that assumed by Casy & Hassan. However, both models agree in the main particulars, namely, (a) the amide group and the adjoining phenyl ring are not coplanar (the angle between them has been determined as 71·3°); (b) the two nitrogen atoms are held close to each other (they are actually separated by only 2·972 Å, which is equivalent to the sum of their van der Waals radii); (c) the s-methyl, C(13), is well removed from, and is not shielded by, either of the phenyl rings.

The X-ray analysis has shown that the six atoms of the amide group are not exactly planar, and that the maximum displacement of 0·07 Å occurs at N(1). However, the four atoms C(8), C(7), O(1), and N(1) of the group are planar within the accuracy of the determination, and the C(1)–N(1)–C(10) group is tilted by 9·8° off the plane of the four atoms and is rotated round the N(1)–C(7) bond by only 0·6°. The absolute configuration which was determined through chemical procedures by Portoghese & Larson (1964) has been confirmed by this X-ray determination.

APPENDIX

Calculation of the angel of rotation round a bond

Let
$$l_1 X + m_1 Y + n_1 Z - p_1 = 0, \quad (1)$$
and
$$l_2 X + m_2 Y + n_2 Z - p_2 = 0 \quad (2)$$

represent the normal equations in cartesian coordinates of the mean planes of two groups of atoms linked together by a bond AB which lies in plane (1) and has the direction cosines (L_1, M_1, N_1). In order to calculate the angle of rotation of the second group [represented by plane (2)] round AB, define a line CD normal to AB in plane (2). The direction ratios (L'_2, M'_2, M'_2) of CD can be calculated from the following expressions:

$$L'_2 = m_2 N_1 - n_2 M_1;$$
$$M'_2 = n_2 L_1 - l_2 N_1;$$
$$N'_2 = l_2 M_1 - m_2 L_1. \quad (3)$$

The angle of rotation (φ) of the second group round the bond AB can then be calculated from the expression

$$\sin \varphi = (l_1 L'_2 + m_1 M'_2 + n_1 N'_2)/[L'^2_2 + M'^2_2 + N'^2_2]^{1/2}, \quad (4)$$

where l, m, n are assumed to be direction cosines and not direction ratios. In this treatment, the angle of rotation is defined as that between the line CD and plane (1).

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