Crystal and Molecular Structure of (−)-*erythro*-1′-(2,5-Dimethoxyphenyl)-3′-diethylaminobutyl Acetate Hydrobromide[1]

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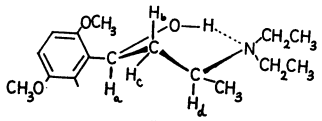
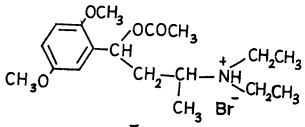
In order to determine the stereospecificity and absolute configuration of 1′-(2,5-dimethoxyphenyl)-3′-diethylamino-*n*-butanol, X-ray structure analysis of its acetate hydrobromide has been carried out. The crystal of the derivative belongs to the monoclinic space group C2, with lattice constants $a=14.21_8$, $b=8.29_0$, $c=18.18_7$Å, $\beta=108.1°$, containing four formula units of $C_{18}H_{29}O_4N\cdot HBr$ in a unit cell. The structure was solved by the heavy atom method and refined by the block-matrix least squares method to an R value of 0.06. The absolute configuration was determined by the use of the anomalous dispersion method, the configuration at the two asymmetric carbon atoms being found to be *S*.

In the course of a study on antitussives, it was found that 1′-(2,5-dimethoxyphenyl)-3′-diethylamino-*n*-butanol (I) strongly potentiates the antitussive activity of codein.[2] However, this compound has four stereoisomers and it seemed to be of importance to compare their pharmacological activities. One of us (H. H.) attempted to synthesize each isomer stereoselectively and obtained two diastereomers I_a and I_b.[3] The diastereomer, I_a, was then acetylated, being resolved by using *d*-camphorsulfonic acid. Their infrared spectra showed that the hydroxyl group forms an intramolecular hydrogen bonding to the diethylamino nitrogen. The nuclear magnetic resonance spectrum of I_a, on the other hand, showed a nuclear Overhauser effect between the protons H_a and H_d. Thus the relative configuration of I_b was presumed to be *erythro* type and that of I_b *threo* type.



I_a



II

An X-ray analysis was undertaken to establish the absolute configuration of I_a. The crystal of its levorotatory acetate hydrobromide(II) was used for the analysis.

Experimental

(−)-*erythro*-1′-(2,5-Dimethoxyphenyl)-3′-diethylamino-*n*-butyl acetate hydrobromide (II) was prepared as follows. To a solution of I_a-acetate (100 mg) in absolute ether (10 ml) was added dropwise a 2% solution of HBr in absolute ether (10 ml) at −60°. Ether was evaporated *in vacuo* to obtain a crystal (110 mg). The cyrstal was recrystallized from absolute ether–methanol mixture under exclusion of moisture. Colorless thin plates parallel to (001); mp 147—148 °C, IR (KBr) 1745, 1505, 1230, 1210, 1045 cm^{-1}. $[\alpha]_D^{20}$ −82.5° (*c* 0.627, EtOH). ORD (*c* 4.8×10^{-4}, MeOH) $[\phi]_{400}$ −116°, $[\phi]_{350}$ −168°, $[\phi]_{300}$ −402°, $[\phi]_{250}$ −2940°, $[\phi]_{233}$ −8800° (trough). Found: C, 53.16; H, 7.38; N, 3.34%. Calcd for $C_{18}H_{30}O_4NBr$: C, 53.46; H, 7.48; N, 3.46%.

The Laue symmetry and systematic extinction on the precession photographs taken with Zr-filtered Mo radiation indicated that the space group is C2 or Cm or C2/m. The density of the crystal (1.32 g cm^{-3}) measured by the flotation method is in good agreement with the calculated value of 1.317 g cm^{-3} assuming four formula units in a unit cell. The space group was taken to be C2 considering the asymmetry of the molecule.

Crystal Data. (−)-*erythro*-1′-(2,5-Dimethoxyphenyl)-3′-diethylaminobutyl acetate hydrobromide, $C_{18}H_{29}O_4N\cdot HBr$, mol wt 404.35. Monoclinic, $a=14.218\pm0.008$, $b=8.290\pm0.005$, $c=18.187\pm0.010$ Å, $\beta=108.1\pm0.1°$, $Z=4$, $D_m=1.32$ g cm^{-3}, $D_x=1.317$ g cm^3, Space group: C2.

The lattice constants and intensity data were obtained by using a four-circle X-ray differentometer with Zr-filtered Mo$K\alpha$ radiation. Intensities were measured by the θ–2θ scanning method with a scan speed of $2\theta=4°$/min. The backgrounds were counted on both sides of each diffraction peak for 10 sec. Out of about 3310 possible *hkl* and $\bar{h}kl$ reflections having a 2θ value less than 60°, 1647 structure factors were evaluated as being observed since they have net intensities greater than three times their estimated standard deviations.

Determination and Refinement of the Structure

The crystal structure was determined by the heavy atom method. The two methoxy groups attached to the benzene ring have large temperature factors and it was hard to find their exact positions on the Fourier map. One of the terminal methyl groups, C(14) of the methoxy group at C(9), could not be found and the atom was excluded from the present analysis. Refinement of the atomic parameters was carried out by the block-matrix least-squares method using the HBLS program.[4] Several cycles of calculations with anisotropic temperature factors for non-hydrogen atoms reduced the R value to 0.063 for 1647 observed structure factors. The weighting scheme used was:

$$w = 1 \text{ when } F_o > 2.5$$

$$w = 0 \text{ when } F_o \leq 2.5 \ .$$

The final atomic parameters are listed in Table 1 with their estimated standard deviations. A comparison of the observed and calculated structure factors is given in Table 2†. The final difference Fourier map showed only a trace of the peak which might be as-

† Table 2 has been deposited at the office of the Chemical Society of Japan (Document No. 7406).

Table 1. Atomic parameters and their estimated standard deviations

Temperature factors are of the form: $T=\exp\{-(\beta_{11}h^2+\beta_{22}k^2+\beta_{33}l^2+2\beta_{12}hk+2\beta_{13}hl+2\beta_{23}kl)\}$. To represent the absolute configuration, x, y and z should be referred to the left-handed coordinate system.

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
Br	0.6862(1)	0.5000(0)	1.0738(1)	0.0052(0)	0.0164(1)	0.0034(0)	-0.0000(2)	0.0012(0)	-0.0004(1)
O(1)	0.3423(5)	0.4281(10)	0.7279(5)	0.0051(4)	0.0191(14)	0.0049(3)	0.0017(6)	0.0013(3)	-0.0001(5)
O(2)	0.2213(7)	0.2465(14)	0.7196(6)	0.0072(6)	0.0337(25)	0.0079(5)	-0.0047(10)	0.0032(5)	-0.0049(10)
O(3)	0.4191(8)	-0.0148(26)	0.6926(6)	0.0110(7)	0.0304(24)	0.0070(4)	0.0024(21)	0.0002(4)	-0.0024(17)
O(4)	0.3560(9)	0.4032(26)	0.4544(6)	0.0108(8)	0.1014(73)	0.0046(4)	0.0025(19)	0.0016(5)	0.0096(14)
N	0.6264(4)	0.4968(19)	0.8853(4)	0.0034(3)	0.0108(10)	0.0040(3)	-0.0000(13)	0.0013(22)	-0.0014(11)
C(1)	0.4084(7)	0.2935(14)	0.7287(6)	0.0049(6)	0.0150(18)	0.0034(4)	-0.0006(8)	0.0008(4)	-0.0025(7)
C(2)	0.5138(6)	0.3580(13)	0.7679(6)	0.0036(5)	0.0128(16)	0.0039(4)	-0.0005(8)	0.0009(3)	-0.0011(7)
C(3)	0.5329(6)	0.3874(12)	0.8524(5)	0.0036(4)	0.0122(15)	0.0032(3)	-0.0009(7)	0.0007(3)	0.0002(6)
C(4)	0.5474(9)	0.2312(15)	0.8979(8)	0.0057(7)	0.0163(21)	0.0062(6)	-0.0014(10)	0.0018(5)	0.0010(9)
C(5)	0.2461(8)	0.3800(17)	0.7219(7)	0.0056(6)	0.0242(25)	0.0041(4)	0.0012(11)	0.0019(4)	-0.0010(9)
C(6)	0.1848(9)	0.5316(25)	0.7237(8)	0.0070(7)	0.0294(50)	0.0053(5)	0.0048(16)	0.0016(5)	-0.0007(12)
C(7)	0.3953(8)	0.2454(17)	0.6446(7)	0.0052(6)	0.0215(24)	0.0045(5)	0.0005(11)	0.0018(4)	-0.0016(9)
C(8)	0.3787(9)	0.3501(21)	0.5857(6)	0.0066(7)	0.0344(34)	0.0031(4)	0.0015(14)	0.0012(4)	0.0010(10)
C(9)	0.3717(12)	0.3006(30)	0.5122(8)	0.0090(10)	0.0525(55)	0.0043(6)	0.0056(21)	0.0007(6)	0.0016(15)
C(10)	0.3774(11)	0.1292(34)	0.5008(10)	0.0072(9)	0.0700(75)	0.0060(7)	0.0049(24)	0.0008(7)	-0.0053(21)
C(11)	0.3945(11)	0.0291(32)	0.5570(8)	0.0096(10)	0.0387(59)	0.0057(6)	0.0053(22)	0.0000(6)	-0.0064(18)
C(12)	0.4025(9)	0.0732(21)	0.6297(9)	0.0055(7)	0.0327(37)	0.0067(6)	0.0002(13)	0.0007(5)	-0.0085(12)
C(13)	0.4066(15)	-0.1911(26)	0.6718(14)	0.0126(15)	0.0231(39)	0.0142(14)	0.0017(21)	-0.0025(12)	-0.0058(21)
C(15)	0.7140(7)	0.4230(14)	0.8646(7)	0.0034(5)	0.0177(18)	0.0048(4)	0.0007(8)	0.0014(4)	-0.0025(8)
C(16)	0.8110(7)	0.5060(40)	0.9154(7)	0.0038(4)	0.0217(23)	0.0067(5)	-0.0014(17)	0.0015(4)	-0.0024(18)
C(17)	0.6113(8)	0.6707(14)	0.8624(7)	0.0056(6)	0.0126(18)	0.0050(5)	0.0002(9)	0.0018(4)	0.0001(8)
C(18)	0.5349(8)	0.7479(13)	0.8959(7)	0.0069(7)	0.0093(15)	0.0064(6)	0.0016(9)	0.0033(5)	0.0000(8)

sociated with C(14), but it was almost impossible to locate the atom.

Determination of the Absolute Configuration

The absolute configuration was determined by use of the anomalous dispersion method. The dispersion corrections for the atomic scattering factors of bromine for Mo$K\alpha$ radiation were taken to be $\Delta f'=-0.3$, $\Delta f''=2.5$.[5] The calculated values of intensity ratio between the Friedel pair of reflections agreed with those observed on the $hk0$, $hk1$ and $0kl$ precession photographs if one takes the left-handed coordinate system. A comparison of observed and calculated intensity ratios is given in Table 3. The Figures in this paper are drawn with the correct absolute configuration.

Table 3. Comparison of calculated and observed intensity ratios of Friedel pair reflections

$h\ k\ l$	$I(hkl)/I(h\bar{k}l)$ Calcd	$I(hkl)/I(h\bar{k}l)$ Obsd
0 2 0	0.88	<1
1 1 0	0.91	<1
3 1 0	0.94	<1
7 1 0	1.23	>1
8 2 0	1.07	>1
1 3 0	0.77	<1
3 3 0	0.87	<1
5 3 0	0.84	<1
3 1 1	1.80	>1
$\bar{5}$ 1 1	0.61	<1
6 2 1	0.58	<1
$\bar{2}$ 2 1	1.06	>1
5 3 1	0.79	<1
$\bar{5}$ 3 1	1.20	>1
0 2 2	1.12	>1
0 2 4	1.21	>1
0 2 6	0.92	<1
0 4 1	0.89	<1

Discussion of the Structure

Figure 1 shows a stereoscopic view of the molecule drawn by the plotter program ORTEP.[6] We see

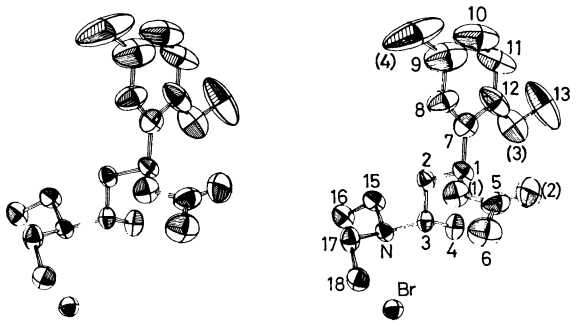


Fig. 1. Stereoscopic view of the molecule.
The ellipsoid covers the area in which the center of the atom is found with a probability 50%. The numbers in parentheses indicate those of oxygen atoms.

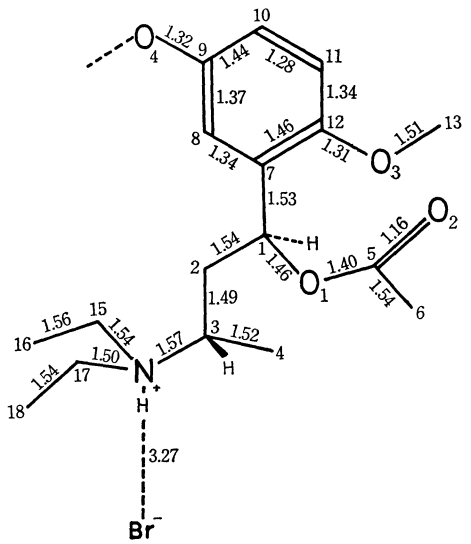


Fig. 2. Bond lengths (Å).

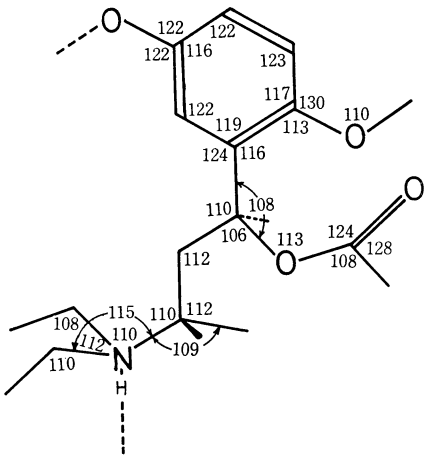


Fig. 3. Bond angles (°).

Table 4. Deviations of atoms from the least-squares plane

Benzene ring			
C(7)	0.00 Å	C(1)[a]	0.04 Å
C(8)	−0.01	O(3)[a]	0.01
C(9)	0.02	C(13)[a]	−0.26
C(10)	−0.02	O(4)[a]	0.01
C(11)	0.01		
C(12)	0.00		
Acetyl group			
O(1)	0.00 Å	C(1)[a]	0.02 Å
C(5)	−0.02		
O(2)	0.01		
C(6)	0.01		

a) Not included in the least-squares calculation.

Table 5. Internal rotation angles

A-B-C-D	τ
O(1)-C(1)-C(2)-C(3)	−70°
C(1)-C(2)-C(3)-C(4)	−74
C(1)-C(2)-C(3)-N	−164
C(2)-C(3)-N-C(15)	53
C(2)-C(3)-N-C(17)	−74
O(1)-C(1)-C(7)-C(8)	−36
C(11)-C(12)-O(3)-C(13)	13

The torsion angle τ of the bonded group A-B-C-D is defined as the angle between planes A-B-C and B-C-D. It is positive if clockwise and negative if anticlockwise from the near atom A to the further D.

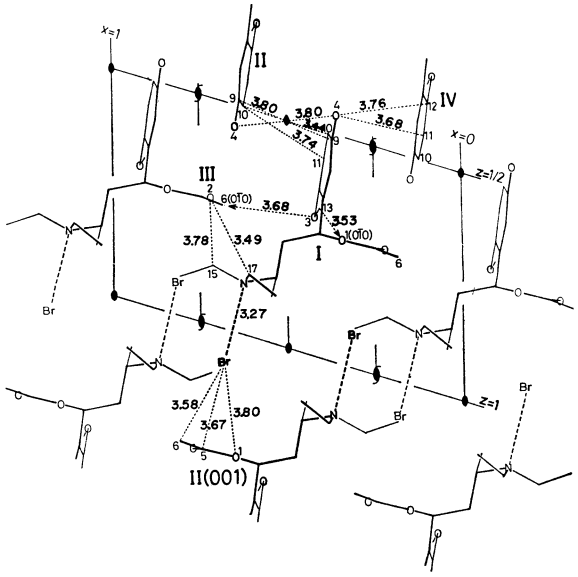


Fig. 4. Projection of crystal structure along the b axis. Intermolecular short contacts of atoms less than 3.8 Å are shown by dotted lines. The positions of the molecules are: I at x, y, z; II at $1-x$, y, $1-z$; III at $1/2+x$, $1/2+y$, z; IV at $1/2-x$, $1/2+y$, $1-z$, where x, y and z are given in Table 1. Translations are shown in parentheses, thus, II (001) be at $1-x$, y, $2-z$.

that the absolute configurations at C(1) and C(3) are both *S* configuration. The bond lengths and angles are shown in Figs. 2 and 3, respectively. The standard deviations of the values for light atoms are about 0.01—0.02 Å and 1°, respectively, except for those involving C(9), C(13), O(3) and O(4) atoms for which they are about 0.04 Å and 2°. The large values for these atoms are due to the extremely large anisotropic thermal vibrations. No abnormal lengths and angles are found in the structure. The diethylamino nitrogen is protonated and takes a tetrahedral configuration. The bromide anion is 3.27 Å apart from the nitrogen atom and a hydrogen bond is formed between them. The planarities of the benzene ring and acetyl group are shown in Table 4.

The skeleton of the butyl acetate group, C(6), C(5), O(1), C(1), C(2), C(3), and C(4), is strongly folded at C(2) and C(3). The C(6), C(5), O(1) and C(1) atoms are extended in a *trans* planar form while the C(4) atom is folded back and closer to C(1) at 3.12 Å, the internal rotation angles about the C(1)–C(2), C(2)–C(3) bonds being −70° and −74°, respectively. The reason for the *gauche* conformation about the C(2)–C(3) bond is to make the nitrogen atom *trans* with respect to C(1) and to locate the charged diethylamino group far from the acetyl group. As for the rotation about the C(1)–C(2) bond, it is easy to see that if it were a *trans* conformation, either the methyl group $C(4)H_3$ or the diethylamino group would be too close to the phenyl group. Some internal rotation angles to be noted are listed in Table 5.

The projection of the crystal structure along the b axis is shown in Fig. 4, together with short intermolecular distances less then 3.8 Å. The diethylamino nitrogen atom is protonated and forms a hydrogen bond to the bromide ion. There are many van der Waals contacts among molecules I, III and their translation equivalents along the a and b axes. The bromide ion also interacts with the acetyl group of the neighboring molecule mainly through van der Waals forces. The methoxyphenyl groups are stacked in **a** direction and several close contacts are found between them.

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