[Chem. Pharm. Bull. 30(5)1588—1593(1982)]

Studies on 1,2,3,4-Tetrahydroisoquinolines. IV.[1] β-Adrenoceptor Activity and Absolute Stereochemistry of (—)-5,7-Dihydroxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline

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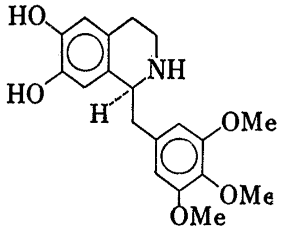
(Received September 18, 1981)

Racemic 5,7-dihydroxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline [(±)-1], a positional isomer of trimetoquinol (TMQ) with respect to its dihydroxy moiety, has been optically resolved. The bronchodilating activity in anesthetized cats (*i.v.* administration) was found to reside in the levorotatory enantiomer [(−)-1]. The absolute stereochemistry of the active enantiomer [(−)-1] was determined to be *S* by X-ray crystallographic analysis.

Keywords——1,2,3,4-tetrahydroisoquinolines; β-adrenoceptor activity; bronchodilator; optical resolution; anesthetized cat; *i.v.* administration; absolute stereochemistry; X-ray analysis

In our previous paper of this series,[2,3] we reported that (±)-5,7-dihydroxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline [(±)-1], a positional isomer of trimetoquinol (TMQ) with respect to its dihydroxyl moiety, exhibits more potent bronchodilating activity and longer duration of action than (±)-TMQ on intraduodenal administration (Chart 1).


TMQ

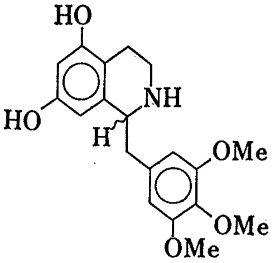

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Chart 1

The activity of (±)-TMQ is known to be highly stereoselective and to reside only in the (*S*)-(−)-enantiomer.[4,5] This result prompted us to obtain the levorotatory isomer of (±)-1. This paper describes the optical resolution of (±)-1 and the bronchodilating activity of the enantiomers [(+)-1 and (−)-1]. The absolute stereochemistry of the active enantiomer [(−)-1] was also determined by X-ray crystallographic analysis.

Chemistry

Optical resolution of (±)-1 was effected with *N*-carbobenzyloxy-D-glutamic acid and then with *N*-carbobenzyloxy-L-glutamic acid.

The (−)- and (+)- glutamates, obtained in 56.8% and 23.2% yields, respectively, were converted into their hydrochlorides. Physical data for the hydrochlorides of (−)- and (+)-1 thus obtained are summarized in Table I.

Table I

Compound	mp (dec.)	$[\alpha]_D^{20}$ ($c=2$, MeOH)	Formula	Analysis (%) Calcd (Found)			
				C	H	N	Cl
(−)-**1**·HCl	240—243	−39.2	$C_{19}H_{23}NO_5 \cdot HCl$	59.76	6.34	3.67	9.29
				(59.90	6.40	3.65	9.15)
(+)-**1**·HCl	240—243	+38.1	$C_{19}H_{23}NO_5 \cdot HCl$	59.76	6.34	3.67	9.29
				(59.83	6.32	3.61	9.30)

Table II. Bronchodilating Activities of Optical Isomers of (±)-**1** after Intravenous Administration in Anesthetized Cats

Compound	ED_{50} (μg/kg) (Geometric mean)	Potency ratio
(±)-**1**·HCl	0.143	1
(−)-**1**·HCl	0.077	1.9
(+)-**1**·HCl	358	0.0004

Table III. Final Atomic Parameters with Estimated Standard Deviations in Parentheses

Atom	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
Cl(A)	3277(2)	2078(1)	6102(3)	494(14)	154(5)	794(28)	13(8)	25(19)	−59(11)
Cl(B)	1622(2)	2887(1)	−899(3)	370(12)	178(5)	944(31)	39(7)	−10(18)	−105(12)
C (1A)	929(7)	2516(5)	4948(13)	369(52)	106(17)	814(118)	17(26)	277(71)	65(38)
C (3A)	965(8)	1910(4)	6836(13)	529(65)	105(19)	888(140)	−39(28)	−197(85)	−21(43)
C (4A)	1147(9)	1406(5)	5988(13)	652(77)	127(20)	874(147)	−95(33)	17(95)	−11(48)
C (5A)	1214(7)	1128(4)	3619(12)	363(52)	61(14)	993(140)	−72(24)	−88(71)	−96(39)
C (6A)	1318(8)	1203(5)	2208(13)	340(54)	203(26)	846(138)	18(31)	−18(75)	−34(51)
C (7A)	1299(7)	1709(4)	1721(12)	268(48)	120(18)	856(130)	67(24)	142(69)	−13(40)
C (8A)	1192(7)	2144(5)	2609(11)	329(50)	161(21)	595(111)	10(28)	−77(64)	8(43)
C (9A)	1079(6)	2060(4)	3970(11)	241(42)	148(19)	834(123)	−41(26)	101(64)	−110(45)
C (10A)	1127(6)	1549(4)	4487(12)	279(47)	54(15)	1029(137)	−57(21)	159(68)	−81(38)
C (11A)	1185(7)	3073(4)	4432(11)	399(55)	143(21)	637(117)	−56(27)	141(72)	−73(41)
C (12A)	963(7)	3526(4)	5355(12)	331(49)	60(15)	901(136)	−23(22)	39(69)	−42(38)
C (13A)	1671(8)	3826(4)	5887(12)	374(54)	128(19)	991(145)	7(27)	281(83)	52(46)
C (14A)	1464(8)	4273(4)	6677(14)	467(60)	61(15)	1253(155)	12(26)	−289(86)	−54(42)
C (15A)	631(8)	4405(4)	6997(12)	544(63)	70(17)	755(133)	14(27)	62(76)	14(39)
C (16A)	−30(8)	4106(4)	6518(12)	582(68)	93(17)	807(129)	−47(30)	26(84)	−90(44)
C (17A)	132(7)	3638(4)	5735(13)	291(48)	128(20)	1088(153)	−56(25)	135(74)	−90(47)
C (18A)	2957(12)	4503(6)	6809(23)	893(111)	130(25)	2820(355)	−86(44)	−31(171)	36(82)
C (19A)	232(15)	4855(6)	8947(15)	1553(163)	167(26)	866(165)	−104(57)	445(152)	27(55)
C (20A)	−1541(11)	4004(7)	6262(23)	518(80)	245(35)	3328(409)	1(46)	−10(168)	−157(104)
N (2A)	1324(6)	2390(3)	6254(10)	263(38)	88(14)	1057(116)	−48(19)	−57(58)	−12(34)
O (5A)	1236(6)	628(3)	4135(9)	720(53)	120(14)	1054(111)	−8(23)	22(69)	−40(33)
O (7A)	1389(7)	1781(3)	391(8)	825(58)	159(15)	414(77)	−55(77)	−10(60)	−52(28)
O (14A)	2095(6)	4580(4)	7208(12)	532(51)	196(19)	2124(175)	−77(26)	−107(81)	−181(52)
O (15A)	501(7)	4891(4)	7626(10)	873(62)	95(14)	1044(110)	−81(26)	317(76)	−38(32)
O (16A)	−819(6)	4271(3)	6830(11)	454(44)	138(15)	1879(154)	32(22)	319(70)	−109(40)
C (1B)	3568(7)	2360(4)	467(12)	268(47)	129(19)	922(129)	14(24)	−213(68)	−73(42)
C (3B)	4163(9)	2901(5)	−1394(13)	563(69)	168(23)	943(149)	16(37)	−5(87)	43(54)
C (4B)	3999(9)	3432(5)	−685(14)	649(78)	129(21)	1155(173)	−53(33)	560(101)	66(50)
C (5B)	3958(8)	3778(4)	1710(12)	424(57)	102(18)	754(127)	42(26)	−218(73)	62(41)
C (6B)	3857(7)	3714(4)	3044(11)	312(51)	89(17)	845(128)	21(24)	−181(67)	−120(39)
C (7B)	3650(7)	3218(4)	3590(12)	275(46)	103(17)	970(140)	1(25)	−110(68)	23(41)
C (8B)	3547(7)	2785(3)	2740(12)	394(52)	13(13)	1152(136)	2(21)	−15(75)	−33(35)
C (9B)	3661(6)	2844(4)	1373(10)	248(39)	62(14)	561(101)	−23(21)	13(54)	−42(32)

Atom	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
C (10B)	3878(8)	3351(4)	814(14)	441(59)	90(18)	1172(160)	−50(26)	−132(87)	−41(45)
C (11B)	4307(8)	1960(4)	671(14)	441(61)	113(21)	1396(185)	26(29)	−196(94)	−191(51)
C (12B)	4351(8)	1507(4)	−357(12)	580(68)	106(18)	628(130)	−95(30)	−299(78)	−66(41)
C (13B)	3616(7)	1195(4)	−599(12)	248(46)	104(17)	1074(142)	−2(23)	−126(70)	−89(42)
C (14B)	3648(9)	769(4)	−1423(13)	604(70)	81(17)	978(151)	−54(29)	24(87)	−4(42)
C (15B)	4448(8)	593(4)	−1929(12)	489(60)	90(18)	692(128)	14(27)	50(74)	53(39)
C (16B)	5167(7)	922(4)	−1709(13)	251(46)	93(17)	1239(161)	9(24)	120(75)	−64(45)
C (17B)	5128(7)	1358(4)	−603(14)	362(53)	94(18)	1252(162)	−7(25)	102(82)	6(47)
C (18B)	2193(9)	516(6)	−1115(17)	499(73)	268(34)	1636(230)	−53(41)	95(110)	−348(76)
C (19B)	4808(14)	96(6)	−3922(16)	1341(147)	194(30)	1028(188)	−64(56)	409(151)	−45(62)
C (20B)	6705(8)	963(5)	−1665(17)	249(52)	146(22)	2213(233)	−3(29)	51(102)	−48(63)
N (2B)	3469(5)	2509(4)	−991(10)	240(37)	139(16)	1011(114)	−43(22)	−41(59)	−31(38)
O (5B)	4148(7)	4253(3)	1120(10)	847(62)	122(15)	1398(135)	−78(26)	−77(80)	6(38)
O (7B)	3571(6)	3184(3)	4954(8)	650(51)	208(17)	449(78)	−21(26)	96(55)	−16(32)
O (14B)	2996(5)	424(3)	−1801(9)	439(41)	149(15)	1256(117)	−16(21)	91(59)	−92(37)
O (15B)	4520(6)	120(3)	−2580(9)	643(49)	71(12)	895(96)	−13(20)	193(62)	−72(27)
O (16B)	5932(6)	708(4)	−2162(10)	415(42)	222(19)	1326(123)	6(24)	45(63)	−196(42)

Positional parameters are multiplied by 10^4.
Anisotropic temperature factors are multiplied by 10^5.
Anisotropic temperature factors are in the form
$T=\exp[-(\beta_{11}h^2+\beta_{22}k^2+\beta_{33}l^2+2hk\beta_{12}+2kl\beta_{23}+2lh\beta_{13})]$.

TABLE IV. Bond Distances (Å) and Angles (°) with Estimated Standard Deviations in Parentheses

	Mol. A	Mol. B		Mol. A	Mol. B
C (1)-N (2)	1.475(16)	1.507(15)	C (11)-C (12)	1.501(15)	1.530(17)
N (2)-C (3)	1.446(14)	1.513(16)	C (12)-C (13)	1.435(16)	1.407(16)
C (3)-C (4)	1.545(17)	1.528(18)	C (13)-C (14)	1.405(16)	1.347(16)
C (4)-C (10)	1.537(17)	1.519(19)	C (14)-C (15)	1.377(18)	1.415(18)
C (10)-C (5)	1.370(15)	1.399(16)	C (14)-O (14)	1.356(16)	1.386(16)
C (10)-C (9)	1.381(15)	1.428(14)	C (15)-C (16)	1.360(17)	1.407(16)
C (5)-C (6)	1.427(17)	1.349(16)	C (15)-O (15)	1.384(13)	1.356(13)
C (5)-O (5)	1.356(13)	1.359(14)	C (16)-C (17)	1.430(16)	1.356(16)
C (6)-C (7)	1.357(17)	1.392(15)	C (16)-O (16)	1.332(16)	1.383(14)
C (7)-C (8)	1.413(16)	1.386(15)	C (17)-C (12)	1.378(16)	1.379(17)
C (7)-O (7)	1.344(14)	1.368(14)	O (14)-C (18)	1.413(21)	1.444(17)
C (8)-C (9)	1.385(16)	1.382(15)	O (15)-C (19)	1.385(19)	1.412(19)
C (9)-C (1)	1.520(17)	1.517(14)	O (16)-C (20)	1.425(20)	1.450(15)
C (1)-C (11)	1.538(16)	1.539(17)			
C (1)-N (2)-C (3)	111.8(9)	110.1(9)	N (2)-C (1)-C (11)	112.4(9)	111.4(9)
N (2)-C (3)-C (4)	112.8(10)	108.8(10)	C (1)-C (11)-C (12)	114.9(9)	115.3(11)
C (3)-C (4)-C (10)	109.8(9)	111.1(10)	C (11)-C (12)-C (13)	116.5(10)	119.3(11)
C (4)-C (10)-C (9)	125.4(10)	122.1(10)	C (11)-C (12)-C (17)	122.6(10)	120.3(11)
C (4)-C (10)-C (5)	115.7(9)	120.9(10)	C (12)-C (13)-C (14)	116.6(10)	120.9(11)
C (10)-C (5)-O (5)	118.3(10)	114.4(11)	C (13)-C (14)-O (14)	120.3(11)	129.2(12)
C (10)-C (5)-C (6)	122.2(10)	121.8(10)	C (13)-C (14)-C (15)	122.5(11)	119.8(12)
C (10)-C (9)-C (1)	117.8(10)	120.0(9)	C (14)-O (14)-C (18)	120.0(12)	114.0(10)
C (10)-C (9)-C (8)	120.0(11)	120.7(9)	O (14)-C (14)-C (15)	117.1(10)	110.7(10)
O (5)-C (5)-C (6)	119.5(10)	123.9(10)	C (14)-C (15)-O (15)	117.0(10)	121.0(10)
C (5)-C (6)-C (7)	118.2(11)	121.3(10)	C (14)-C (15)-C (16)	120.0(10)	117.5(10)
C (6)-C (7)-C (8)	119.8(11)	119.1(11)	C (15)-O (15)-C (19)	114.7(10)	121.1(10)
C (6)-C (7)-O (7)	118.4(10)	117.7(10)	C (15)-C (16)-O (16)	116.5(10)	114.0(10)
O (7)-C (7)-C (8)	121.7(10)	123.2(10)	O (15)-C (15)-C (16)	122.2(11)	121.4(11)
C (7)-C (8)-C (9)	120.8(10)	120.2(9)	C (15)-C (16)-C (17)	120.5(11)	121.9(10)
C (8)-C (9)-C (1)	122.2(10)	119.3(8)	C (16)-C (17)-C (12)	119.0(10)	119.5(10)
C (9)-C (10)-C (5)	118.8(11)	116.9(11)	C (16)-O (16)-C (20)	119.3(11)	115.7(10)
C (9)-C (1)-N (2)	109.9(9)	112.7(8)	O (16)-C (16)-C (17)	123.0(11)	123.0(10)
C (9)-C (1)-C (11)	115.3(10)	111.7(9)	C (17)-C (12)-C (13)	120.8(10)	119.7(10)

Biological Results

The bronchodilating activities[6,7] of the enantiomers [(+)-**1** and (—)-**1**] thus obtained and the racemate [(±)-**1**] were tested in anesthetized cats using the methods described in the previous paper.[2] As can be seen from Table II (*i.v.* administration), the bronchodilating activity of the levo isomer [(—)-**1**] was approx. twice that of (±)-**1**, while that of (+)-**1** was less than 1/2500th of that of (±)-**1**.

This result parallels the reported observation on the β-adrenoceptor activity of TMQ[4] (levo isomer).

X-Ray Analysis

Crystals of (—)-**1**·HCl suitable for X-ray analysis could be grown from a mixture of isopropanol and isopropylether. The final atomic parameters with their standard deviations are listed in Table III. The bond lengths and bond angles calculated from these parameters are given in Table IV. Fig. 1 illustrates the numbering system used in this crystallographic analysis. Fig. 2 shows stereoscopic views of (—)-**1**·HCl and indicates that the asymmetric unit of this crystal contains two molecules differing in the conformation of ring II.

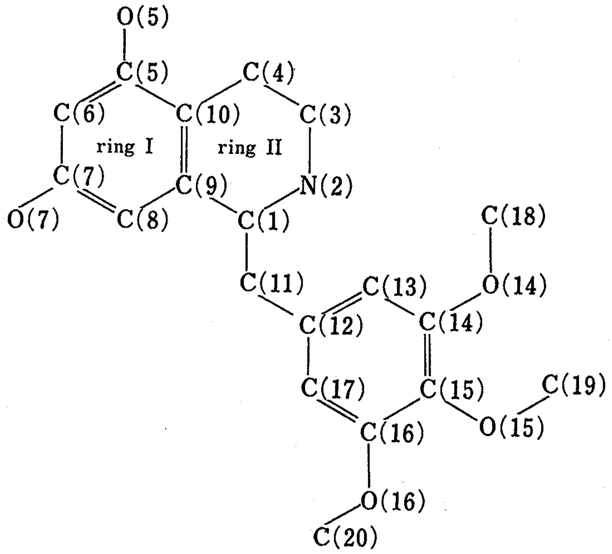

Fig. 1. The Numbering System used in the Crystallographic Analysis

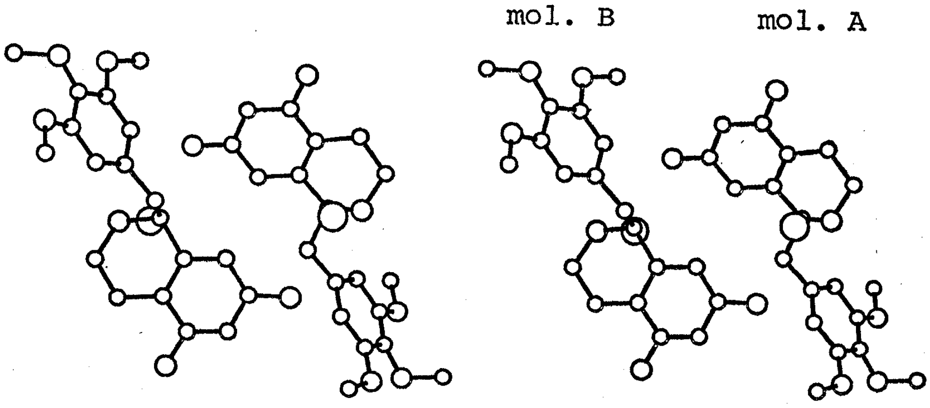

Fig. 2. Stereoview showing the Absolute Configurations of (—)-**1**

In molecule A, this ring is in a slightly deformed half-chair conformation, and the N(2) and C(3) atoms lie 0.67 Å and 0.10 Å above the plane of ring I, respectively. On the other hand, ring II in molecule B is in a twisted half-chair conformation in which the N(2) and C(3) atoms are located 0.35 Å below and 0.45 Å above the plane of ring I, respectively. Consequently, the trimethoxybenzyl groups in molecules A and B are oriented quasi-equatorially and quasi-axially, respectively. The absolute configuration of (—)-**1**·HCl, as determined from the anomalous dispersion effect of the chlorine atom, proved to be *S* and is also shown in Fig. 2.

Experimental

Melting points are uncorrected. Infrared (IR) spectra were recorded with a Hitachi IR-215 spectrometer, nuclear magnetic resonance (NMR) spectra with an FX-100 spectrometer with tetramethylsilane (TMS) as an external standard, and mass spectra with an RMU-6M spectrometer.

Resolution of (±)-5,7-Dihydroxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline [(±)-1]——$NaHCO_3$ (4.4 g, 0.053 mol) and *N*-cbz-D-glutamic acid (14.9 g, 0.053 mol) were added to a mixture of (±)-**1**·HCl (38.2 g, 0.1 mol), H_2O (500 ml), and EtOH (140 ml), and the whole was allowed to stand for 3 d at room temperature. The crystalline precipitates were collected by filtration and recrystallized three times from H_2O–MeOH (1: 2) to give the (−)-**1** glutamate (17.8 g, 56.8%) as colorless needles, mp 165—167°C (dec.), $[\alpha]^{20}_{D}$ −25.1° (*c*=2, MeOH). This salt was treated with 10% ethanolic HCl, the solution was concentrated *in vacuo*, and the residue was crystallized from EtOH–Et_2O under reflux for 1 h to afford (−)-**1**–HCl (10 g, 52.3%), mp 240—243°C (dec.), $[\alpha]^{20}_{D}$ −39.2° (*c*=2, MeOH). IR ν_{max}^{Nujol} cm^{-1}: 2400—2800. MS *m/e*: 181, 164. NMR (D_2O) δ: 2.78—3.80 (m, 6H), 3.95 (3H, s, OCH_3), 3.98 (6H, s, $OCH_3 \times 2$), 6.25 and 6.48 (1H each, d, *J*=2 Hz, H(6) and H(8)), 6.69 (2H, s, H(2′) and H(6′)).

$NaHCO_3$ (4.4 g, 0.053 mol) and *N*-cbz-L-glutamic acid (14.9 g, 0.053 mol) were added to the mother liquor (aq. EtOH) from the (−)-**1** glutamate, and the mixture was allowed to stand for 3 d at room temperature. The resulting crystals were filtered off and recrystallized four times from H_2O–MeOH (1: 2) to give the (+)-**1** glutamate (7.25 g, 23.2%), mp 164—165°C (dec.), $[\alpha]^{20}_{D}$ +24.8° (*c*=2, MeOH). This (+)-**1** salt was converted into (+)-**1**·HCl (4.1 g, 21.4%), mp 240—243°C (dec.), $[\alpha]^{20}_{D}$ +38.1° (*c*=2, MeOH), as described above for the preparation of (−)-**1**·HCl.

X-Ray Crystallographic Analysis of (−)-5,7-Dihydroxy-1-(3,4,5-trimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline–HCl [(−)-1·HCl]——Transparent, needlelike crystals of (−)-**1**·HCl were grown from a mixture of isopropanol and isopropylether. The unit-cell dimensions and the space group were determined from Weissenberg photographs. The former values were subsequently refined by measurements on a four-circle diffractometer. The crystal data were: $C_{19}H_{24}O_5NCl$ (M.W.=381.86), orthorhombic, a=15.573 (3) Å, b=25.043 (3) Å, c=9.965 (2) Å, V=3886 (1) Å^3, Dc=1.305 g/cm^3, Z=8, space group $P2_12_12_1$. The intensity data were collected on an AFC-3 automatic diffractometer (Rigaku) using Cu$K\alpha$ radiation (1.5418 Å) monochromated by a graphite plate. The total number of reflections measured was 3889, of which 2182 had intensities above the 3σ (I) level. Intensities were corrected for Lorentz and polarization factors, but no absorption corrections were applied. The structure was solved by means of the MULTAN[8] program and was refined by the block-diagonal least-squares method assuming anisotropic thermal parameters for the non-hydrogen atoms and isotropic ones for the hydrogen atoms. The weighting function used in the final cycles had the form $1/(a+b|Fo|+c|Fo|^2)$, where $a=2|Fo(\min)|$, $b=1.0$, $c=2|Fo(\max)|$. The final R factor was 0.074. The absolute configuration of (−)·1–HCl was determined by the anomalous dispersion method. Dispersion corrections used for the chlorine scattering factor for Cu$K\alpha$ radiation were $\Delta f'=0.348$ and $\Delta f''=0.702$.[9] A comparison of the Bijivoet ratios of 30 reflections with $|Fc(hkl)|$ differing from $|Fc(h\bar{k}l)|$ by more than 5% indicated that the assumed configuration was actually the antipode of the true structure (Table V). Thus, the absolute configuration of (−)-**1**·HCl was determined to be *S* as shown in Fig. 2. All the calculations were performed on a UNIVAC 1108 computer.

TABLE V. Calculated and Observed Bijvoet Ratios

h	*k*	*l*	R_c	R_o	*h*	*k*	*l*	R_c	R_o
1	2	1	0.780	1.156	3	5	2	0.935	1.018
1	3	1	0.949	1.075	4	7	2	1.136	0.931
1	11	1	1.091	0.894	4	9	2	1.107	0.840
2	7	1	0.873	1.104	5	13	2	0.930	1.107
4	4	1	0.830	1.245	6	2	2	1.098	0.945
5	1	1	0.939	1.020	2	11	3	1.055	0.932
5	4	1	1.185	0.874	8	5	3	1.059	0.966
5	16	1	1.065	0.938	8	7	3	1.122	0.871
7	2	1	0.922	1.075	2	2	4	1.079	0.909
7	4	1	0.932	1.073	4	2	4	1.062	0.928
10	2	1	1.052	0.972	4	5	4	1.070	0.948
10	3	1	1.094	0.888	4	9	4	0.918	1.028
1	13	2	1.055	0.918	5	1	4	0.944	1.032
2	5	2	1.054	0.942	5	4	4	0.946	1.144
2	9	2	1.123	0.912	6	2	4	0.919	1.250

$R_c=|F_c(hkl)|/|F_c(h\bar{k}l)|$ $R_o=|F_o(hkl)|/|F_o(h\bar{k}l)|$

Acknowledgement The authors are grateful to Dr. S. Sugasawa, Professor Emeritus of Tokyo University, for his encouragement, and to Dr. S. Saito, Director of the Organic Chemistry Research Laboratory, for valuable discussions. Thanks are also due to the staff of the Analytical Center of this company for spectral measurements and elemental analyses.

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