The Crystal Structure of *dl*-1,2,3,4,5,6-Hexahydro-6,11,12,12-tetramethyl-2,6-methano-3,11-propano-3-benzazocine Hydrochloride Monohydrate

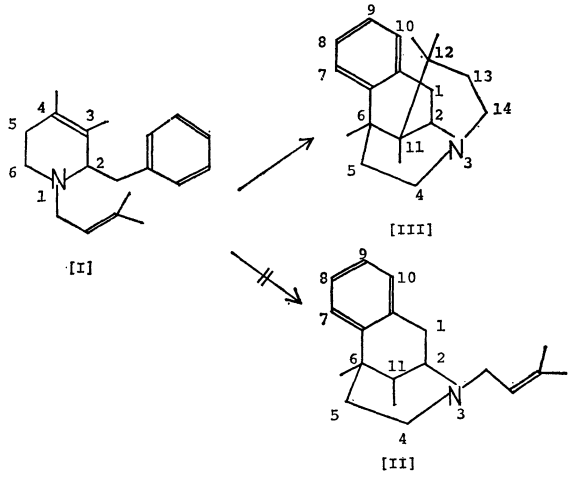
Michio KIMURA, Takesi NAKAJIMA, Shigeho INABA, and Hisao YAMAMOTO

Takarazuka Research Laboratories, Sumitomo Chemical Co., Ltd., Takatsukasa, Takarazuka, Hyogo 665

(Received December 26, 1973)

The structure of the title crystal ($C_{19}H_{27}N \cdot HCl \cdot H_2O$) has been determined by X-ray diffraction method. The racemate crystallizes in monoclinic, space group $P2_1/c$ with $a=14.30$, $b=15.74$, $c=7.79$ Å, $\beta=98°58'$ and $Z=4$. The reflection intensities were measured visually from equi-inclination integrating Weissenberg photographs taken with Cu$K\alpha$ radiation. The structure was solved by the direct method of phase determination. The final R factor was 0.113. The molecules are linked in endless chains along c-axis by $N^+\cdots Cl^-$ and $Cl^-\cdots H_2O\cdots Cl^-$ hydrogen bonds. Two piperidine rings in the molecule have the chair conformation. This product which shows analgesic activity has a new molecular structure having a four-ring system, part of which is a benzomorphan nucleus.

In several synthetic studies of 6,7-benzomorphan derivatives,[1] it has been reported that the cyclization of 1-allyl-1,2,5,6-tetrahydro-2-benzyl-3,4-dimethylpyridine or the corresponding 1-(3′-methylallyl) derivatives with Lewis acid gives the 6,7-benzomorphan derivatives. We have discovered that cyclization of 1-(3′,3′-dimethylallyl) derivatives [I] with P_2O_5-85% H_3PO_4 does not give 3-(3′,3′-dimethylallyl)-1,2,3,4,5,6-hexahydro-6,11-dimethyl-2,6-methano-3-benzazocine [II], but another product in high yield, which shows analgesic activity. We failed to determine the molecular structure of the product by NMR, IR and Mass spectra. An X-ray diffraction investigation for its hydrochloride has been undertaken, and the chemical structure of the product established is [III].



[I] [III] [II]

Experimental

Preparation of 1,2,3,4,5,6-Hexahydro-6,11,12,12-tetramethyl-2,6-methano-3,11-propano-3-benzazocine[III]. A mixture of 40 g of [I], 262 g of phosphorus pentoxide and 329 g of 85%-phosphoric acid was kept at 135~140 °C (bath temperature 150~160 °C) for 20 hours under nitrogen atmosphere, cooled, poured into 500 ml of ice-water and basified with concentrated ammonium hydroxide. The oily product was extracted three times by 500 ml of ether and dried over anhydrous sodium sulfate. After removal of ether, the residue was distilled under reduced pressure. Bp: 144~147 °C (0.25~0.28 mmHg); Mp: 72~74 °C (uncorr.). Anal. Calcd for $C_{19}H_{27}N$: C(84.70); H(10.10); N(5.20%). Found: C (84.65); H(9.97); N(5.16%). IR: ν_{max}^{Neat} 2850~3050, 1600, 1580, 1480, 1440, 760, 740, 710, 700 cm^{-1}. NMR ($CDCl_3$);

Table 1. Crystal data

Crystal system	monoclinic
Systematic absence	$h0l$ with odd l, $0k0$ with odd k
Space group	$P2_1/c$
a	14.30±0.08 Å
b	15.74±0.09
c	7.79±0.06
β	98°58′±45′
V	1731.0 Å^3
Z	4
ρ_c	1.257 g/cm^3
ρ_o	1.251

Table 2. Initial set

H	$\lvert E_h \rvert$	sign or symbol
2 2 7	3.88	+
3 11 3	3.42	+
11 2 1	3.25	+
5 8 4	2.87	a
$\bar{2}$ 0 6	2.85	b
$\bar{3}$ 6 3	2.77	c
$\bar{7}$ 6 5	2.78	d

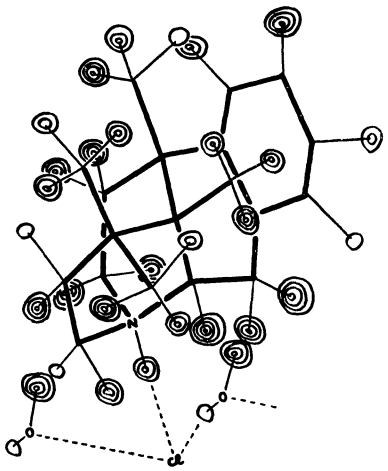


Fig. 1. Difference map projected along the b axis. The contours are drawn at equal intervals on an arbitrary scale.

Table 3. Final atomic parameters with their standard deviations (in parentheses).

(a) Atomic coordinates ($\times 10^4$) for non-hydrogen atoms

Atom	x/a	y/b	z/c	Atom	x/a	y/b	z/c
Cl	5392(6)	8702(6)	2959(12)	C (9)	2248(22)	474(20)	3192(40)
N	3512(19)	9613(18)	2087(34)	C (10)	1503(21)	9752(20)	2758(39)
O	4557(30)	6944(30)	4238(54)	C (11)	1753(24)	9243(23)	1218(41)
C (1)	1557(21)	9140(20)	4289(38)	C (12)	2795(25)	8949(24)	1460(43)
C (2)	754(24)	8668(23)	4557(47)	C (13)	3717(27)	229(26)	742(47)
C (3)	795(27)	8098(24)	5911(52)	C (14)	2857(28)	778(26)	216(47)
C (4)	1653(31)	7990(26)	7000(49)	C (15)	2383(25)	1143(23)	1754(47)
C (5)	2476(29)	8436(24)	6722(44)	C (16)	1997(26)	930(24)	4816(44)
C (6)	2417(23)	9011(21)	5370(38)	C (14)	454(25)	57(25)	2344(49)
C (7)	3319(24)	9491(23)	5202(42)	C (18)	1447(30)	1581(28)	910(62)
C (8)	3251(22)	68(21)	3662(39)	C (19)	3056(31)	1844(25)	2534(59)

(b) Anisotropic temperature factors ($\times 10^4$) for non-hydrogen atoms in the form of $\exp\{-(B_{11}h^2+B_{22}k^2+B_{33}l^2+B_{12}hk+B_{13}hl+B_{23}kl)\}$

Atom	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
Cl	34(1)	29(1)	158(2)	6(1)	−1(1)	−6(1)
N	29(2)	24(2)	86(6)	2(1)	14(2)	2(2)
O	96(4)	95(3)	264(13)	−44(3)	−36(6)	52(6)
C (1)	29(2)	18(1)	86(6)	1(1)	19(3)	−6(3)
C (2)	41(2)	22(2)	165(9)	−2(2)	31(3)	−3(4)
C (3)	55(3)	19(2)	198(10)	−2(2)	58(4)	0(4)
C (4)	70(3)	25(2)	134(9)	5(2)	50(4)	8(4)
C (5)	62(3)	24(2)	96(7)	2(2)	19(4)	6(3)
C (6)	37(2)	20(1)	68(6)	2(1)	10(3)	1(3)
C (7)	34(2)	28(2)	91(7)	0(2)	−3(3)	8(3)
C (8)	28(2)	24(2)	84(7)	1(1)	9(3)	2(3)
C (9)	27(2)	19(1)	91(7)	0(1)	7(3)	−2(3)
C (10)	26(2)	19(1)	86(7)	0(1)	8(3)	−5(3)
C (11)	35(2)	29(2)	82(7)	−1(2)	8(3)	−14(3)
C (12)	37(2)	30(2)	104(8)	0(2)	12(3)	−22(3)
C (13)	52(3)	36(2)	128(8)	4(2)	35(4)	19(4)
C (14)	49(3)	36(2)	118(8)	1(2)	20(4)	21(4)
C (15)	37(2)	21(2)	134(8)	0(2)	11(4)	11(3)
C (16)	43(2)	25(2)	106(8)	−1(2)	19(4)	−16(3)
C (17)	26(2)	31(2)	149(9)	4(2)	−1(4)	−3(4)
C (18)	43(3)	32(2)	222(13)	12(2)	9(5)	32(5)
C (19)	56(3)	23(2)	210(12)	−9(2)	10(5)	5(4)

δ 7.0∼7.4(m, 4H, aromatic); 1.7∼3.4 (m, 11H, methylene); 1.6 (s, 3H, methyl); 1.2 (s, 3H, methyl); 1.1 (s, 3H, methyl); 0.8(s, 3H, methyl).

Preparation of the Hydrochloride of III. To the ethereal solution of III was bubbled anhydrous hydrogen chloride gas at 0∼5 °C for 10 minutes. The resulting crystals were filtered and recrystallized from acetone at room temperature. Colorless prisms, $C_{19}H_{27}N\cdot HCl\cdot H_2O$. Mp: 243.5∼244.5 °C (uncorr.). Anal. Calc. for ($C_{19}H_{30}ONCl$): C(70.43); H (9.35); N(4.32); Cl(10.95%). Found: C(70.40); H(9.31); N(4.30); Cl(10.91%). IR: ν_{max}^{Nujol} 3500, 3450, 2500, 1640, 780, 740 cm^{-1}. $[\alpha]_D^{20°}$: 0°(c=1.316, MeOH).

The thermogravimetric analysis(TGA) scan showed a 5.20 % weight loss in the temperature region 65—149 °C (in comparison with 5.562% calculated for one water molecule of the monohydrate).

X-Ray Analysis of $C_{19}H_{27}N\cdot HCl\cdot H_2O$. Single crystals suitable for X-ray analysis were shaped to rectangular prism elongated along the c axis, by dissolving with methanol. The unit cell dimensions were calibrated with NaCl powder patterns superposed on Weissenberg photographs. The density was measured by flotation in a mixture of benzene and carbon tetrachloride. Crystal data was listed in Table 1. Crystal specimens of dimensions 0.44×0.40×0.51 mm and 0.24×0.29×0.52 mm were selected for data collection around the b and c axes respectively. Weissenberg photographs for layers of $h0l$-$h12l$ and $hk0$-$hk5$ were taken with nickel-filtered Cu$K\alpha$ radiation. Intensities were esitmated visually, and corrected for Lorentz and polarization factors and for absorption. But no correction for spot shapes was applied. An absolute scale and overall temperature factor (B=3.122 Å^2) were determined by Wilson plot[2] and a total of 3211 independent reflections were obtained.

Solution and Refinement of the Structure

A symbolic addition procedure[3,4] was used to solve the phase problem. Normalized structure factors, $|E_h|$

TABLE 4. BOND DISTANCES AND ANGLES IN [III]

(a) Bond distances

	Distance (Å)		Distance (Å)		Distance (Å)		Distance (Å)
C (1)-C (2)	1.409	C (11)-C (12)	1.544	C (6)-C (7)	1.520	C (15)-C (9)	1.572
C (2)-C (3)	1.379	C (12)-N	1.491	C (7)-C (8)	1.495	C (9)-C (16)	1.545
C (3)-C (4)	1.388	N-C (8)	1.516	C (8)-C (9)	1.560	C (10)-C (17)	1.558
C (4)-C (5)	1.417	N-C (13)	1.491	C (9)-C (10)	1.558	C (15)-C (18)	1.558
C (5)-C (6)	1.381	C (13)-C (14)	1.505	C (10)-C (1)	1.526	C (15)-C (19)	1.526
C (6)-C (1)	1.393	C (14)-C (15)	1.575	C (10)-C (11)	1.530		

(b) Bond angles

	Angle (deg.)		Angle (deg.)
C (2)-C (1)-C (6)	119.8	C (8)-C (9)-C (16)	108.7
C (2)-C (1)-C (10)	120.4	C (16)-C (9)-C (15)	110.0
C (6)-C (1)-C (10)	119.8	C (16)-C (9)-C (10)	106.1
C (1)-C (2)-C (3)	121.2	C (10)-C (9)-C (15)	119.4
C (2)-C (3)-C (4)	118.4	C (8)-C (9)-C (15)	103.3
C (3)-C (4)-C (5)	121.5	C (9)-C (10)-C (1)	109.9
C (4)-C (5)-C (6)	119.1	C (1)-C (10)-C (17)	106.6
C (5)-C (6)-C (1)	120.0	C (17)-C (10)-C (11)	109.5
C (5)-C (6)-C (7)	116.1	C (11)-C (10)-C (9)	108.4
C (1)-C (6)-C (7)	123.9	C (9)-C (10)-C (17)	111.2
C (6)-C (7)-C (8)	114.9	C (1)-C (10)-C (11)	107.0
C (7)-C (18)-C (9)	112.3	C (10)-C (11)-C (12)	113.7
C (7)-C (8)-N	111.6	C (11)-C (12)-N	115.4
C (9)-C (8)-N	109.7	C (12)-N-C (8)	110.8
C (9)-C (8)-N	109.7	C (12)-N-C (8)	110.8
C (8)-C (9)-C (10)	109.1	C (12)-N-C (13)	115.2
C (8)-N-C (13)	111.1	C (18)-C (15)-C (9)	113.8
N-C (13)-C (14)	108.9	C (9)-C (15)-C (19)	109.9
C (13)-C (14)-C (15)	115.6	C (19)-C (15)-C (14)	104.4
C (14)-C (15)-C (18)	106.5	C (14)-C (15)-C (9)	111.4
C (19)-C (15)-C (18)	107.3		

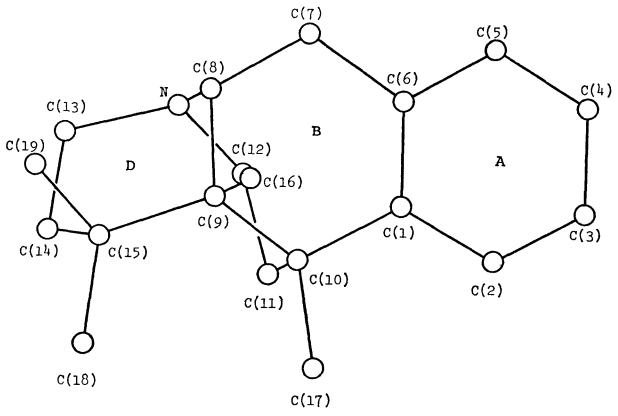


Fig. 2. The molecule viewed normal to the benzene ring plane.

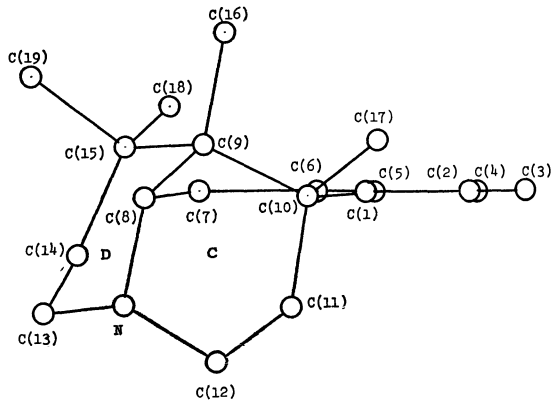


Fig. 3. The molecule viewed along the benzene ring plane.

were calculated and a set of Σ_2 relationships was tabulated. Three origin defining reflections and four reflections given symbols were selected by consideration of the magnitudes of the $|E_h|$ and the number of high probability Σ_2 relationships for each reflection, shown as in Table 2. The signs or symbols of 293 reflections out of 486 with $|E_h| \geq 1.4$ were determined by Σ_2 relationships. An E map was calculated based on these 293 signed E's with a=d=(+) and b=c=(−), and 21 of the 22 non-hydrogen atoms were located. The oxgen atom of water was revealed on a subsequent difference Fourier map. The R value, $\Sigma||F_o|-$

$|F_c||/\Sigma|F_0|$, at this stage was 0.469 with all 22 atoms assumed as carbon atoms. Refinement of the structure was done first by diagonal and then block-diagonal least-squares until $R=0.134$. A difference Fourier map using all reflections, indicated the positions of all 30 hydrogen atoms, which is shown in Fig. 1. The hydrogen atom coordinates used in further refinement, however, were calculated from geometrical considerations and were not refined. All hydrogen atoms were given isotropic temperature factors which were those of the atoms to which they are attached. The final R was 0.113 for all observed reflections. The final atomic parameters are shown in Table 3. Atomic scattering factors were taken from "International Tables for X-ray Crystallography".[5]

A list of the observed and calculated structure factors is kept by the office of the Chemical Society of Japan, (Document No. 7415). All calculations were done on a CDC 3600 and IBM 370 computers using the UNICS programs and those written by the present authors.

Results and Discussion

The molecule [III] consists of a four-ring system, the rings being named as A, B, C and D in Figs. 2 and 3. The molecular structure shown in Figures is one of the racemic paires. The bond distances and angles are shown in Table 4. The standard deviations in the distances and angles are estimated to be 0.049 Å and 2.8° respectively. The molecule of [III] is a new molecular skeleton, but it can be considered as a segment of morphine molecule,[6] since the corresponding parts (rings A, B and C) have the same configuration as the latter. The bond distances and angles are in good agreement with those in cyclazocine,[7] 2-allyl-2'-hydroxy-5,9-dimethyl-6,7-benzomorphan (AHDB).[8] The product [III] has analgesic activity as well as AHDB and cyclazocine. The averages of the aromatic C–C, saturated C–C and C–N bonds are 1.395, 1.541, and 1.499 Å respectively. The ring B attached to the benzene ring has a slightly distorted half-chair conformation with C(9) lying 0.66 Å above the benzene ring plane (Table 5). Two piperidine rings (C and D) assume a nearly regular chair form, and the conformations about the ten single bonds in C and D are staggered. The methyl groups C(16), C(17) and C(18) are in equatorial positions with re-

Table 5. The deviation of individual atoms from least-squares plane of the benzene ring

$(-0.334X+0.727Y+0.600Z=11.856)$

Where X, Y, and Z in Å are referred to the axes a*, b, c respectively.

Atom	Distance (Å)	Atom	Distance (Å)
C (1)	0.01	C (6)	0.00
C (2)	0.01	C (7)	0.03
C (3)	0.00	C (8)	0.05
C (4)	0.01	C (9)	0.66
C (5)	0.01	C (10)	0.03

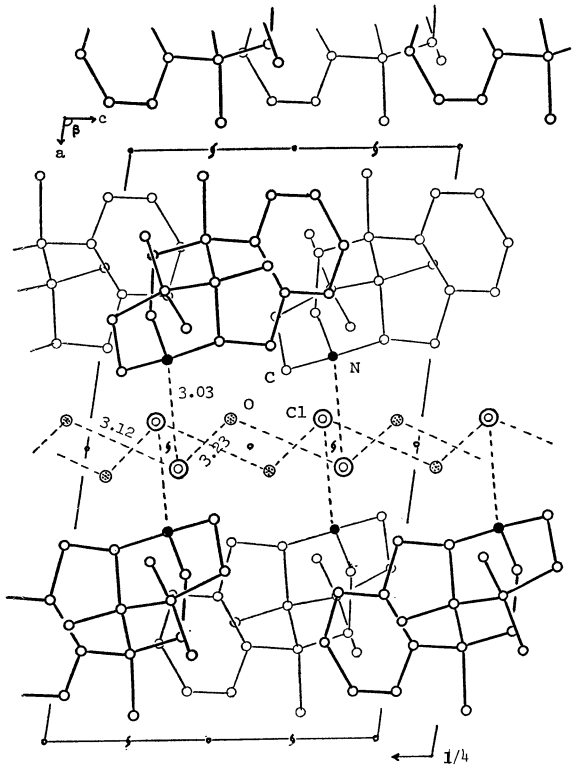


Fig. 4. Projection of the structure along the b axis.

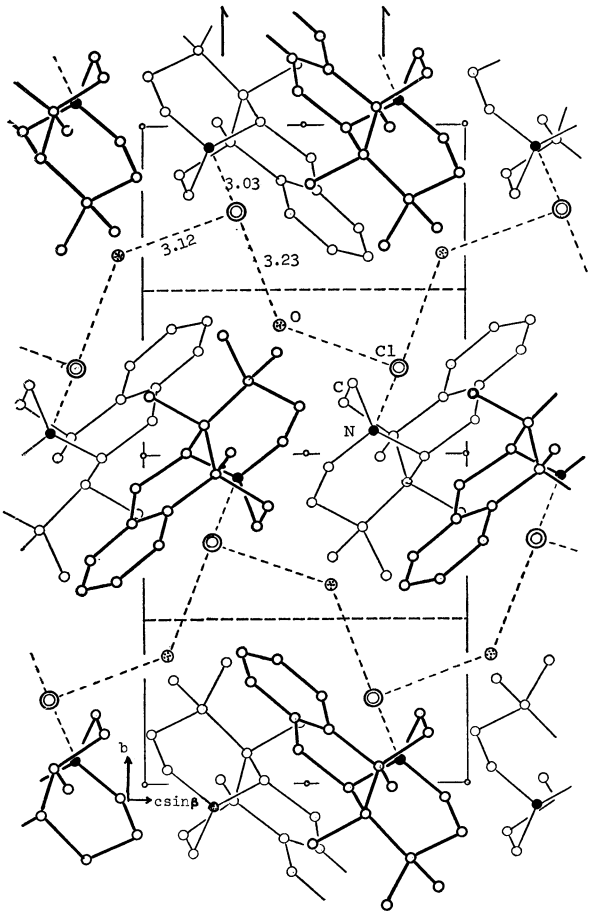


Fig. 5. Projection of the structure along the c axis.

TABLE 6. INTERMOLECULAR DISTANCES (<4 Å).

		Distance (Å)			Distance (Å)
C (2) ··· C (17)	d	3.76	C (17) ··· C (2)	d	3.76
C (3) ··· C (2)	b	3.98	C (17) ··· C (3)	d	3.77
C (3) ··· C (11)	b	3.93	C (19) ··· Cl	c	3.94
C (3) ··· C (17)	d	3.77	C (19) ··· O	f	3.88
C (4) ··· C (1)	b	3.81	Cl ····· C (7)	c	3.57
C (4) ··· C (2)	b	3.64	Cl ····· C (8)	c	3.59
C (4) ··· C (3)	b	3.86	Cl ····· C (16)	c	3.91
C (4) ··· C (11)	b	3.57	Cl ····· C (19)	e	3.94
C (4) ··· C (12)	b	3.52	Cl ····· C (13)	f	3.73
C (5) ··· C (12)	b	3.79	Cl ····· C (14)	f	3.87
C (7) ··· Cl	c	3.57	Cl ····· O	b	3.23
C (8) ··· Cl	c	3.59	O ····· C (13)	f	3.66
C (13) ··· Cl	f	3.73	O ····· C (19)	f	3.88
C (13) ··· O	f	3.66	N ····· Cl	a	3.03
C (14) ··· Cl	f	3.87	O ····· Cl	a	3.12
C (16) ··· Cl	c	3.91			

Symmetry code	Symmetry operation		
a	x	y	z
b	x	$\frac{3}{2}-y$	$\frac{1}{2}+z$
c	$1-x$	$2-y$	$1-z$
d	$-x$	$2-y$	$1-z$
e	$1-x$	$-\frac{1}{2}+y$	$\frac{1}{2}-z$
f	$1-x$	$2-y$	$-z$

spect to the piperdine ring C and/or D. C(19) is in axial positions with respect to D. Figures 2 and 3 show the molecule viewed normal to and parallel to the benzene ring plane respectively. These figures show that the benzomorphan nucleus is approximately shaped. Intermolecular distances (<4 Å) are shown in Table 6. Hydrogen bonds exist between the N^+ and Cl^- ions and between the Cl^- ion and the water molecule, so that endless chains along c-axis are formed as seen from Figs. 4 and 5.

The authors wish to express their thanks to professor Kenji Osaki of the Pharmaceutical Department of Kyoto Univ. for discussions about this manuscript and to the staffs of Sumitomo Chemical Computer Center for computing.

References

1) T. Kametani and K. Kigasawa, *Yuki Gosei Kagaku Kyokai Shi* **29**, 227 (1971), T. Kametani *et al.*, *J. Heterocyclic Chem.* **6**, 43 (1969), N. F. Albertson and W. F. Wetterau, *J. Med. Chem.* **13**, 302 (1970), T. Kametani *et al.*, *ibid.*, **12**, 694 (1969), Sumitomokagaku, Jap. Pat. 45—31664 (1970), Ger. Pat. 1,927,724 (1970), T. Kametani *et al.*, *J. Heterocyclic Chem.* **9**, 1057, 1065 (1972), **8**, 769 (1971).

2) A. J. C. Wilson, *Nature*, **50**, 151 (1942).

3) I. L. Karle and J. Karle, *Acta Crystallogr.*, **16**, 969 (1963), **21**, 894 (1966).

4) W. H. Zachariasen, *ibid.*, **5**, 68 (1952).

5) "International Tables for X-ray Crystallography", vol. III, Kynoch Press, Birmingham (1962), pp. 202—203.

6) M. MacKay and D. C. Hodgkin, *J. Chem. Soc.*, **1955** 3261.

7) I. L. Karle, R. D. Gilardi, A. V. Fratini, and J. Karle, *Acta Crystallogr.*, **B25**, 1469 (1969).

8) W. Fedeli, G. Giacomello, S. Cerrini, and A. Vaicago, *J. Chem. Soc., B*, **1970**, 1190.