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Studies on the Relationship between Physico-chemical Properties and Crystalline Forms of Tulobuterol Hydrochloride. II.[1] Crystal Structure Analyses of the Four Crystalline Forms of Tulobuterol Hydrochloride

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The crystal structures of the three forms (I, II, III) and the hydrate of tulobuterol hydrochloride (C-78) have been determined by X-ray analysis by using direct methods and refined by the block-diagonal least-squares method including anisotropic thermal parameters to final R values of 0.048, 0.057, 0.066 and 0.060 for forms, I, II, III and the hydrate, respectively. The molecular conformations in the four different crystalline forms are almost identical, though slight conformational differences are observed at the tertiary butyl terminal. The molecular packings however, are very different. Hydrogen bonds connecting the tulobuterol cations and the chloride anions form either a closed dimer-like unit in I and III or an open chain in II. In the hydrated crystal, a ribbon-like system of hydrogen bonds is formed by intervention of water molecules.

Comparison of the crystal structures among these four forms of C-78 suggests a mechanism for the phase transition in the solid state and explains their thermodynamic properties previously reported.[1]

Keywords——tulobuterol hydrochloride; polymorphism; X-ray analysis; molecular structure; crystal structure

The crystalline polymorphism and the preparation of the four crystalline forms I, II, III and the hydrate (abbreviated as Hy) as well as the amorphous form of tulobuterol hydrochloride (C-78): α-[(*tert*-butylamino)methyl]-*o*-chlorobenzyl alcohol hydrochloride have been reported previously. Their thermodynamic properties and the phase transformation were discussed on the basis of powder diffraction, infrared (IR) spectra and DSC curves, and the characterization of the five forms was accomplished. It was concluded that (i) form III, the amorphous form and Hy crystals all transform easily into form II on heating, while form I does not, (ii) form I transforms partly into form II by heating after mechanical treatments such as grinding or compression, and (iii) form II crystals obtained by crystallization from a mixture of isopropanol (or acetone) and isopropyl ether have physico-chemical properties identical with those of form II obtained by the treatment mentioned above. In order to discuss the phase relations on the basis of the structures, X-ray crystal structure determination has been carried out.

Experimental

Materials——Forms I, II, III and Hy of C-78 were prepared according to the methods reported previously. Crystals used for the X-ray analyses had dimensions of *ca.* 0.77×0.15×0.05, 0.46×0.15×0.03,

$0.4 \times 0.2 \times 0.02$ and $0.4 \times 0.3 \times 0.3$ mm for forms I, II, III and Hy, respectively. The crystals of form I had the best crystallinity but most of them were twins.

Diffraction Data Collection——The crystallographic data for the four forms are summarized in Table I. X-ray intensity data were collected on a Philips PW1100 four-circle diffractometer with the ω-2θ scan mode (3°2θ/min. for forms I and II, 4°2θ/min. for III and Hy) using graphite-monochromated Cu $K\alpha$ radiation. The data collection ranges were 6°—100° in 2θ for form I, 6°—130° for II, 6°—140° for III, and 6°—126° for Hy, giving 1817, 767, 1485 and 1988 independent reflections with $F_0 > 3\sigma(F)$, respectively. The observed intensities were corrected for Lorentz-polarization factors, but no absorption correction was applied.

Table I. Crystallographic Parameters

	Form I	Form II	Form III	Hydrate
Formula		$C_{12}H_{18}ClNO \cdot HCl$		$C_{12}H_{18}ClNO \cdot HCl \cdot H_2O$
Formula weight		264.19		282.21
Crystal system	Triclinic	Monoclinic	Monoclinic	Triclinic
Space group	$P\bar{1}$	$P2_1/n$	$P2_1/a$	$P\bar{1}$
a (Å)	15.325(5)	12.507(4)	15.815(5)	11.295(4)
b (Å)	18.581(6)	10.780(4)	8.744(3)	10.477(4)
c (Å)	7.876(3)	11.738(4)	10.633(4)	7.291(3)
α (°)	96.25(3)	—	—	105.63(3)
β (°)	101.03(3)	116.3(3)	100.38(3)	93.00(3)
γ (°)	100.01(3)	—	—	112.00(3)
U (Å^3)	2144.2	1418.8	1446.4	766.7
Z	6	4	4	2
Dm (gcm^{-3})	1.228	1.230	1.217	1.240
Dx (gcm^{-3})	1.228	1.237	1.213	1.222

Structure Determination——The structures of the four crystals were solved mainly by the direct method using the MULTAN program.[2)] Positional and thermal parameters were refined by the iteration of the difference-Fourier synthesis and the block-diagonal least-squares method to final R factors of 0.048, 0.057, 0.066 and 0.060 for forms, I, II, III and Hy, respectively. The applied weighting schemes in the refinement procedure were: $\sqrt{w}=0.8$ if $|F_0|<5.0$, $\sqrt{w}=1.0$ if $5.0 \leq |F_0|<20.0$, $\sqrt{w}=20.0/|F_0|$ if $|F_0| \geq 20.0$ for form I; $\sqrt{w}=0.8$ if $|F_0|<10.0$, $\sqrt{w}=1.0$ if $10.0 \leq |F_0|<50.0$, $\sqrt{w}=50.0/|F_0|$ if $|F_0| \geq 50.0$ for II; $\sqrt{w}=0.8$ if $|F_0|<10.0$, $\sqrt{w}=1.0$ if $10.0 \leq |F_0|<30.0$, $\sqrt{w}=30.0/|F_0|$ if $|F_0| \geq 30.0$ for III; $\sqrt{w}=0.8$ if $|F_0|<10.0$, $\sqrt{w}=1.0$ if $10.0<|F_0|<25.0$, $\sqrt{w}=25.0/|F_0|$ if $|F_0| \geq 25.0$ for Hy. Final atomic coordinates and temperature factors are listed in Tables II, III, IV and V, respectively.

Table II. Final Atomic Coordinates ($\times 10^4$) and Thermal Parameters ($\times 10^4$) with Their Estimated Standard Deviations for Non Hydrogen Atoms of Form I[a)]

Atom	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
Cl(1)	2720(3)	−1425(2)	40(5)	186(4)	61(2)	301(9)	25(2)	137(5)	12(3)
Cl(4)	3300(2)	574(2)	8515(4)	72(2)	33(1)	210(6)	23(1)	27(3)	13(2)
C(1)	2407(7)	−1510(5)	2046(13)	67(7)	23(4)	199(24)	2(4)	11(11)	9(8)
C(2)	2226(8)	−2218(6)	2502(15)	76(8)	29(4)	293(31)	5(5)	24(13)	10(9)
C(3)	2011(8)	−2282(6)	4058(16)	65(8)	30(5)	323(31)	0(5)	−9(13)	38(10)
C(4)	1954(8)	−1679(6)	5138(14)	81(8)	43(5)	206(26)	−2(5)	35(12)	47(9)
C(5)	2141(7)	−985(6)	4689(12)	55(7)	34(4)	155(22)	−6(4)	8(10)	21(8)
C(6)	2341(6)	−877(5)	3110(12)	36(5)	27(4)	169(21)	8(4)	16(9)	22(7)
C(7)	2539(6)	−106(5)	2597(13)	43(6)	26(4)	189(23)	3(4)	26(9)	25(8)
C(8)	3525(6)	223(5)	3322(13)	40(6)	29(4)	220(25)	4(4)	20(10)	35(8)
C(9)	4796(6)	1308(6)	3193(14)	34(6)	36(4)	257(27)	9(4)	21(10)	23(9)
C(10)	5369(7)	835(7)	2389(17)	26(6)	74(7)	369(34)	10(5)	36(12)	−11(12)
C(11)	4840(8)	2029(7)	2469(22)	48(8)	46(6)	695(56)	−7(5)	5(16)	107(15)
C(12)	5084(7)	1437(7)	5195(15)	53(8)	55(6)	265(29)	7(5)	20(12)	−5(10)
N(1)	3793(5)	926(4)	2640(10)	30(4)	26(3)	231(19)	9(3)	30(7)	30(6)
O(1)	1969(5)	305(4)	3299(11)	64(5)	45(3)	477(25)	30(3)	105(9)	63(7)

Atom	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
Cl(2)	3489(3)	3767(2)	11220(4)	144(3)	60(2)	238(8)	8(2)	92(4)	13(3)
Cl(5)	2226(2)	1889(1)	2359(3)	55(2)	29(1)	164(6)	15(1)	15(2)	15(2)
C(101)	3613(6)	3909(6)	9127(13)	36(6)	41(5)	219(25)	−3(4)	12(10)	27(9)
C(102)	3895(8)	4625(6)	8839(14)	64(8)	35(5)	243(27)	4(5)	11(12)	14(9)
C(103)	4008(7)	4754(6)	7198(15)	59(7)	24(4)	301(30)	1(4)	9(12)	27(9)
C(104)	3827(8)	4161(7)	5908(14)	59(8)	60(6)	203(26)	7(5)	23(11)	43(10)
C(105)	3547(7)	3456(6)	6183(13)	53(7)	38(5)	206(25)	10(5)	2(10)	14(9)
C(106)	3450(6)	3309(5)	7816(12)	26(5)	31(4)	184(22)	6(4)	4(9)	25(8)
C(107)	3153(6)	2521(5)	8163(13)	36(6)	28(4)	265(26)	9(4)	28(10)	25(8)
C(108)	2145(6)	2291(5)	7626(13)	41(6)	33(4)	231(25)	6(4)	17(10)	28(8)
C(109)	817(6)	1209(6)	7601(12)	40(6)	36(4)	135(21)	0(4)	2(9)	2(8)
C(110)	701(7)	489(6)	8410(15)	50(7)	49(5)	250(28)	−15(5)	11(11)	32(10)
C(111)	593(7)	1028(6)	5645(14)	61(7)	42(5)	204(26)	2(5)	9(11)	−13(9)
C(112)	241(7)	1725(7)	8246(17)	36(7)	60(6)	355(35)	3(5)	9(12)	−57(12)
N(2)	1806(5)	1579(4)	8236(9)	43(5)	31(3)	156(18)	9(3)	23(7)	13(6)
O(2)	3569(6)	2049(4)	7167(12)	90(6)	46(3)	505(27)	33(4)	142(11)	59(8)
Cl(3)	7028(2)	3411(2)	2797(4)	73(2)	80(2)	277(8)	−6(2)	26(3)	87(3)
Cl(6)	9351(2)	4192(2)	6460(4)	49(2)	33(1)	200(6)	−9(1)	28(2)	1(2)
C(201)	6885(7)	3636(6)	692(14)	40(6)	33(4)	226(25)	1(4)	16(10)	25(8)
C(202)	6071(7)	3325(7)	−451(15)	41(7)	51(5)	271(28)	1(5)	11(11)	29(10)
C(203)	5943(7)	3496(7)	−2135(15)	42(7)	52(5)	273(29)	9(5)	−27(11)	−4(10)
C(204)	6610(8)	3963(7)	−2626(14)	57(8)	57(6)	206(27)	15(5)	−6(11)	11(10)
C(205)	7397(7)	4271(6)	−1478(13)	43(6)	37(5)	191(24)	11(4)	14(10)	24(8)
C(206)	7569(6)	4115(5)	237(11)	37(6)	25(4)	139(20)	12(4)	7(9)	7(7)
C(207)	8457(6)	4429(5)	1488(13)	36(6)	27(4)	194(23)	4(4)	9(9)	21(7)
C(208)	9079(6)	3864(6)	1399(13)	36(6)	36(4)	201(24)	10(4)	7(10)	4(8)
C(209)	10564(7)	3542(5)	2847(13)	39(6)	34(4)	230(25)	14(4)	48(10)	31(8)
C(210)	10089(8)	2780(6)	3061(17)	73(8)	27(4)	445(37)	18(5)	95(14)	75(11)
C(211)	10910(8)	3528(7)	1126(15)	66(8)	54(6)	277(30)	21(5)	68(12)	31(10)
C(212)	11339(8)	3903(7)	4379(16)	49(8)	71(7)	291(31)	27(6)	−15(12)	27(12)
N(3)	9895(5)	4074(4)	2810(10)	32(4)	26(3)	173(17)	10(3)	19(7)	9(6)
O(3)	8846(5)	5097(4)	966(10)	63(5)	34(3)	328(20)	−3(3)	−29(8)	45(6)

a) The anisotropic temperature factors are of the form; $T=\exp[-(\beta_{11}h^2+\beta_{22}k^2+\beta_{33}l^2+2\beta_{12}hk+2\beta_{13}hl+2\beta_{23}kl)]$.

TABLE III. Final Atomic Coordinates ($\times 10^4$) and Thermal Parameters ($\times 10^4$) with Their Estimated Standard Deviations for Non Hydrogen Atoms of Form II[a]

Atom	x	y	z	$\beta_{11}(B)$	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
Cl(1)[b]	1424(3)	4745(3)	309(4)	141(4)	129(4)	212(6)	44(4)	57(4)	20(4)
Cl(2)	7035(3)	4574(2)	2551(3)	170(4)	88(2)	174(4)	55(3)	43(3)	34(3)
C(1)	2548(9)	4092(8)	1593(10)	103(11)	106(11)	197(15)	0(9)	77(11)	32(11)
C(2)	2758(10)	4585(9)	2802(10)	191(15)	93(10)	232(17)	−13(10)	160(14)	−23(12)
C(3)	3670(10)	4113(10)	3827(10)	207(17)	173(15)	143(14)	−40(13)	91(13)	−29(12)
C(4)	4333(11)	3166(10)	3732(11)	196(17)	151(14)	172(16)	52(12)	85(14)	32(13)
C(5)	4166(10)	2710(9)	2586(9)	177(14)	141(12)	94(11)	8(11)	67(10)	−13(10)
C(6)	3238(8)	3140(7)	1472(9)	103(10)	69(8)	152(13)	−6(8)	80(10)	1(8)
C(7)	3028(8)	2646(7)	189(8)	139(11)	53(8)	136(12)	−4(8)	91(10)	−3(8)
C(8)	4024(9)	3052(8)	−95(8)	138(12)	112(11)	97(11)	−20(9)	72(10)	−36(9)
C(9)	4896(7)	2429(7)	−1621(8)	100(10)	63(8)	113(11)	10(7)	60(9)	14(8)
C(10)	5794(9)	3490(9)	−1166(10)	115(12)	129(12)	156(14)	−34(10)	58(11)	−9(11)
C(11)	4408(11)	2263(11)	−3051(10)	214(17)	185(16)	124(14)	−38(13)	86(13)	−27(12)
C(12)	5420(10)	1215(9)	−905(12)	182(16)	106(12)	303(21)	77(11)	149(15)	103(13)
N	3825(6)	2758(6)	−1422(6)	83(8)	69(6)	102(9)	−17(6)	37(7)	−12(6)
O	3006(9)	1348(7)	287(8)	408(18)	123(9)	250(14)	−72(11)	199(13)	−14(9)
Cl(1′)[b]	509(1)	168(1)	254(1)	64(3)					

a) The anisotropic temperature factors are of the form; $T=\exp[-(\beta_{11}h^2+\beta_{22}k^2+\beta_{33}l^2+2\beta_{12}hk+2\beta_{13}hl+2\beta_{23}kl)]$. For Cl(1′), $T=\exp(-B\sin^2\theta/\lambda^2)$; coordinates are $\times 10^3$, B is $\times 10$ Å^2.

b) The occupancies of Cl(1) and Cl(1′) are 80% and 20%, respectively.

TABLE IV. Final Atomic Coordinates ($\times 10^4$) and Thermal Parameters ($\times 10^3$) with Their Estimated Standard Deviations for Non Hydrogen Atoms of Form III[a]

Atom	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
Cl(1)	4339(1)	3387(3)	1249(2)	4(0)	33(0)	22(0)	−2(0)	3(0)	6(0)
Cl(2)	4078(1)	8046(2)	5181(2)	4(0)	13(0)	13(0)	1(0)	1(0)	2(0)
C(1)	3228(4)	3302(7)	1135(5)	4(0)	16(1)	9(1)	−1(0)	1(0)	−1(1)
C(2)	2722(4)	4075(8)	125(6)	6(0)	18(1)	10(1)	−1(1)	1(0)	2(1)
C(3)	1844(4)	4004(8)	−2(6)	6(0)	18(1)	9(1)	1(1)	−1(0)	1(1)
C(4)	1472(4)	3216(8)	857(6)	4(0)	17(1)	11(1)	0(0)	0(0)	1(1)
C(5)	1982(4)	2465(7)	1863(5)	4(0)	14(1)	9(1)	0(0)	1(0)	1(1)
C(6)	2871(3)	2482(6)	2017(5)	4(0)	12(1)	6(0)	0(0)	0(0)	−1(1)
C(7)	3405(3)	1597(7)	3108(5)	4(0)	14(1)	7(1)	0(0)	0(0)	0(1)
C(8)	3457(4)	2485(7)	4341(5)	5(0)	13(1)	7(1)	1(0)	−1(0)	1(1)
C(9)	3986(4)	2211(7)	6773(5)	5(0)	16(1)	7(1)	1(0)	0(0)	−1(1)
C(10)	3124(4)	1706(8)	7035(6)	5(0)	21(1)	12(1)	1(1)	2(0)	2(1)
C(11)	4723(4)	1368(9)	7623(6)	6(0)	27(2)	9(1)	3(1)	−2(0)	1(1)
C(12)	4127(5)	3935(8)	6861(7)	10(1)	17(1)	12(1)	−1(1)	1(1)	−4(1)
N	4059(3)	1723(5)	5404(4)	5(0)	12(1)	6(0)	1(0)	−1(0)	0(0)
O	2985(3)	172(5)	3216(4)	8(0)	12(1)	14(1)	−2(0)	−2(0)	1(1)

a) The anisotropic temperature factors are of the form; $T=\exp[-(\beta_{11}h^2+\beta_{22}k^2+\beta_{33}l^2+2\beta_{12}hk+2\beta_{13}hl+2\beta_{23}kl)]$.

TABLE V. Final Atomic Coordinates ($\times 10^4$) and Thermal Parameters ($\times 10^3$) with Their Estimated Standard Deviations for Non Hydrogen Atoms of Hydrate[a]

Atom	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
Cl(1)	7113(1)	3728(2)	−1817(2)	20(0)	19(0)	23(0)	10(0)	12(0)	9(0)
Cl(2)	7130(1)	−555(1)	8365(2)	10(0)	16(0)	19(0)	5(0)	−1(0)	3(0)
C(1)	6769(4)	4735(4)	254(6)	7(0)	12(1)	20(1)	4(0)	3(1)	5(1)
C(2)	6721(4)	6034(5)	236(7)	9(0)	12(1)	32(1)	3(0)	2(1)	11(1)
C(3)	6449(4)	6848(5)	1845(8)	8(0)	10(1)	39(2)	3(0)	1(1)	6(1)
C(4)	6256(5)	6388(5)	3452(7)	11(1)	13(1)	29(1)	6(0)	2(1)	1(1)
C(5)	6286(4)	5079(5)	3415(6)	10(0)	14(1)	21(1)	5(0)	3(1)	4(1)
C(6)	6533(3)	4206(4)	1802(5)	6(0)	10(1)	18(1)	3(0)	1(0)	4(1)
C(7)	6574(4)	2774(4)	1806(6)	7(0)	11(1)	20(1)	3(0)	2(0)	6(1)
C(8)	7954(4)	3049(4)	2526(6)	7(0)	9(1)	28(1)	3(0)	2(1)	6(1)
C(9)	9441(4)	1816(5)	3212(7)	7(0)	12(1)	28(1)	4(0)	0(1)	6(1)
C(10)	9309(5)	277(5)	2867(7)	11(1)	14(1)	32(1)	7(1)	−1(1)	6(1)
C(11)	9817(5)	2652(6)	5407(8)	14(1)	15(1)	30(1)	5(1)	−7(1)	−1(1)
C(12)	10380(5)	2570(6)	2069(10)	8(1)	23(1)	54(2)	8(1)	9(1)	18(1)
N	8091(3)	1688(3)	2507(5)	6(0)	9(0)	20(1)	3(0)	2(0)	5(0)
O	5817(3)	2181(3)	3102(4)	8(0)	16(0)	27(1)	4(0)	4(0)	12(1)
O(w)	6450(3)	294(4)	4823(5)	21(1)	30(1)	48(1)	12(0)	12(1)	22(1)

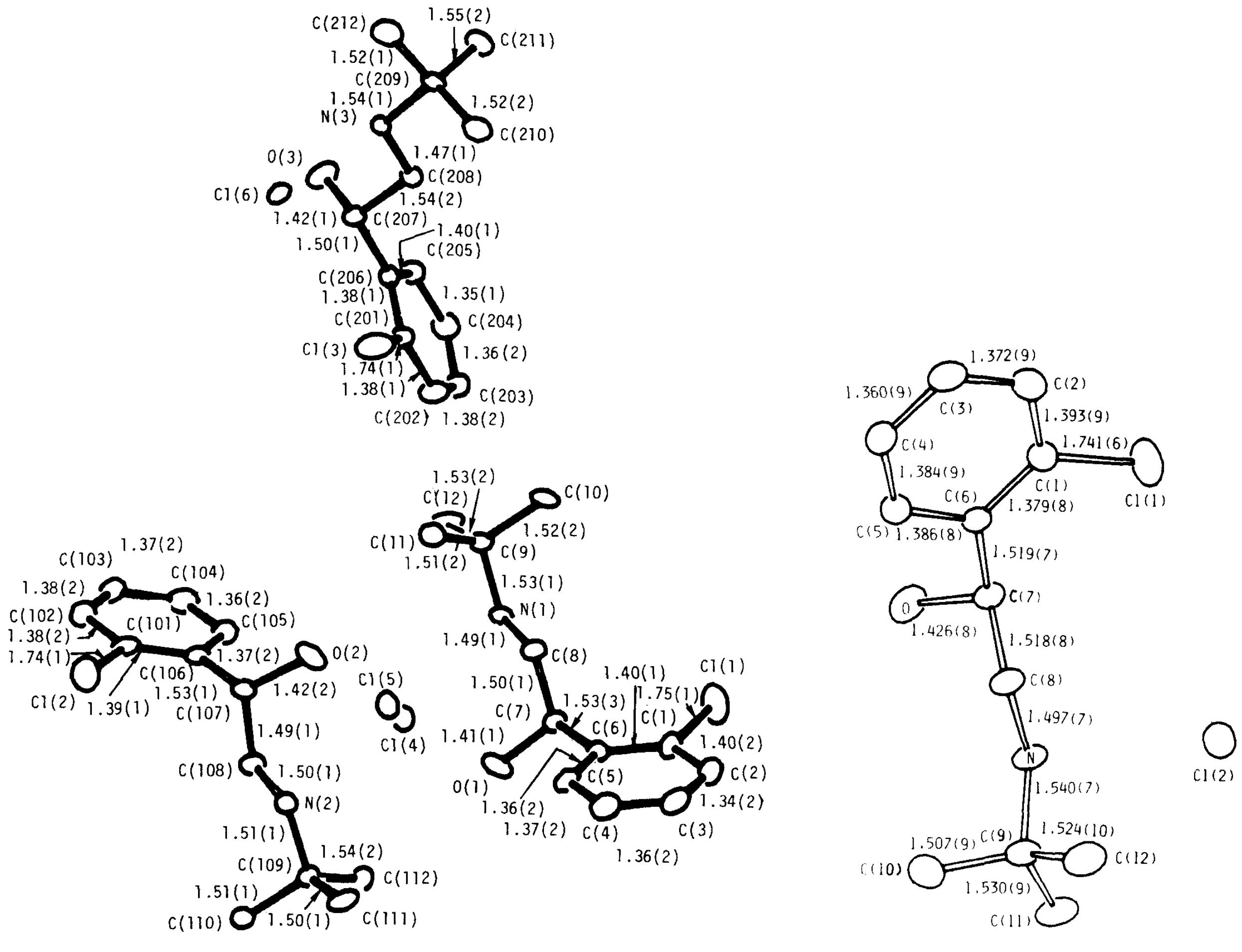
a) The anisotropic temperature factors are of the form; $T=\exp[-(\beta_{11}h^2+\beta_{22}k^2+\beta_{33}l^2+2\beta_{12}hk+2\beta_{13}hl+2\beta_{23}kl)]$.

Structure Description and Discussion

Molecular Structure

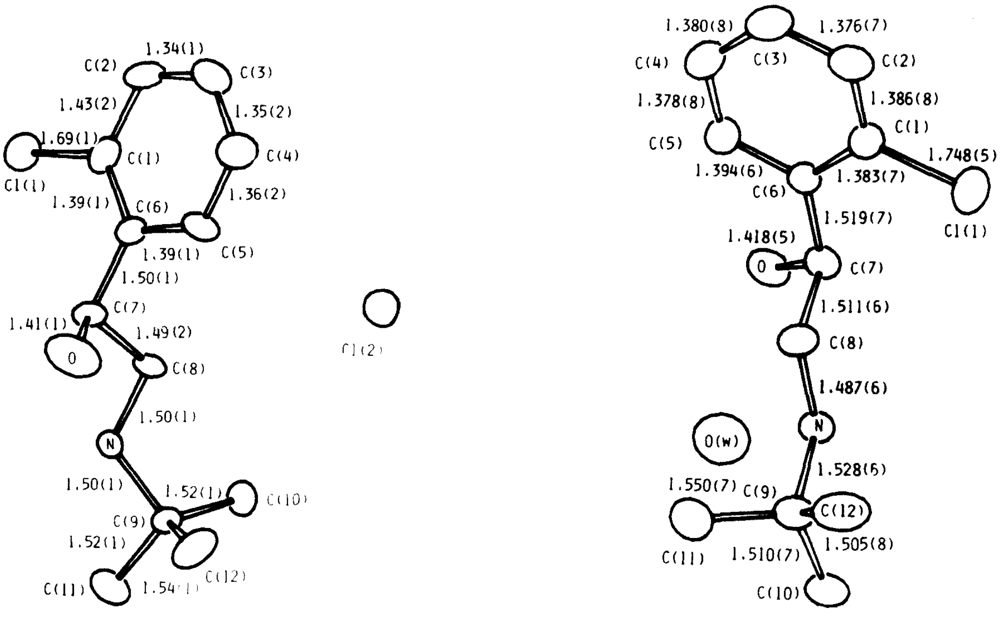
ORTEP[3] drawings of C-78 in the four crystalline forms are shown in Fig. 1 and Fig. 2 with bond lengths and angles.

The values are all chemically reasonable. As shown in Fig. 1(a), the asymmetric unit of form I involves as many as three formula unit, whereas only one unit is involved in the cases of forms II, III and Hy.



(a) form I

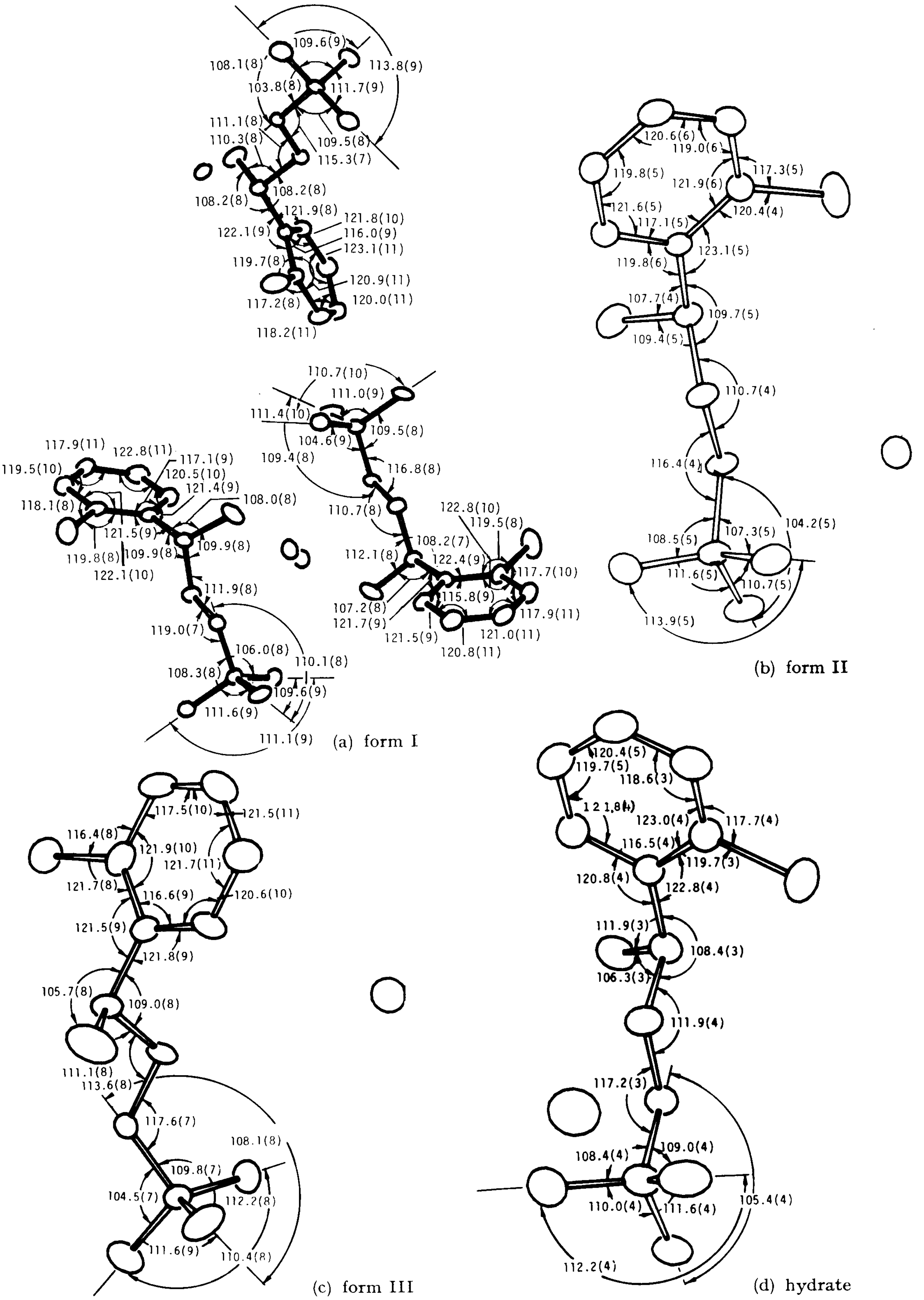
(b) form II



(c) form III

(d) hydrate

Fig. 1. Bond Lengths (Å) with Their Estimated Standard Deviations of Tulobuterol Hydrochloride in the Four Crystalline Forms



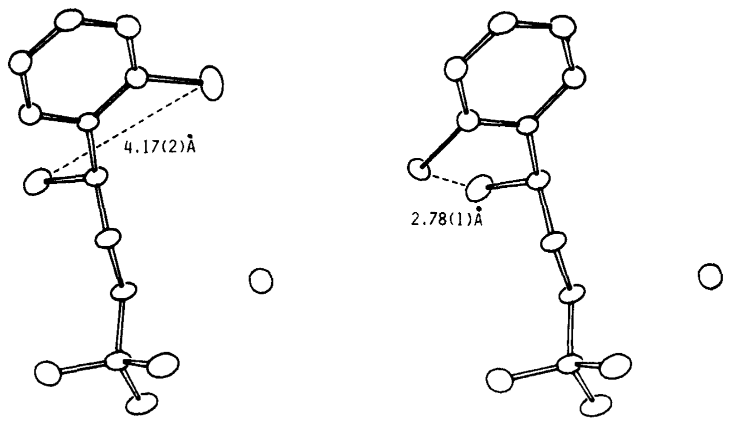
(a) form I

(b) form II

(c) form III

(d) hydrate

Fig. 2. Bond Angles (°) with Their Estimated Standard Deviations of Tulobuterol Hydrochloride in the Four Crystalline Forms

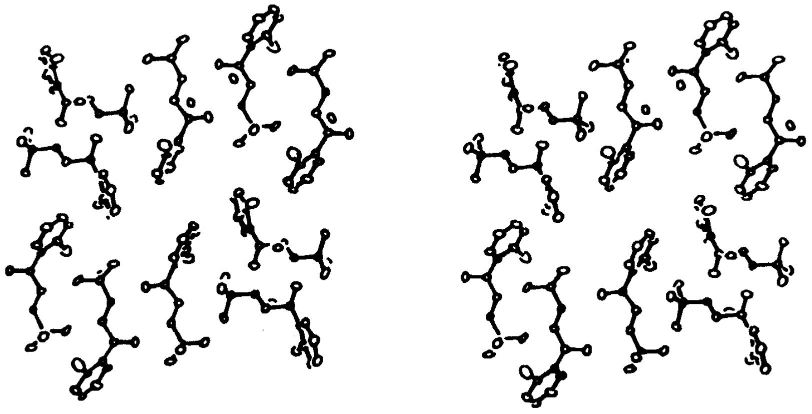


A (80%)
$\tau = 108.5°$

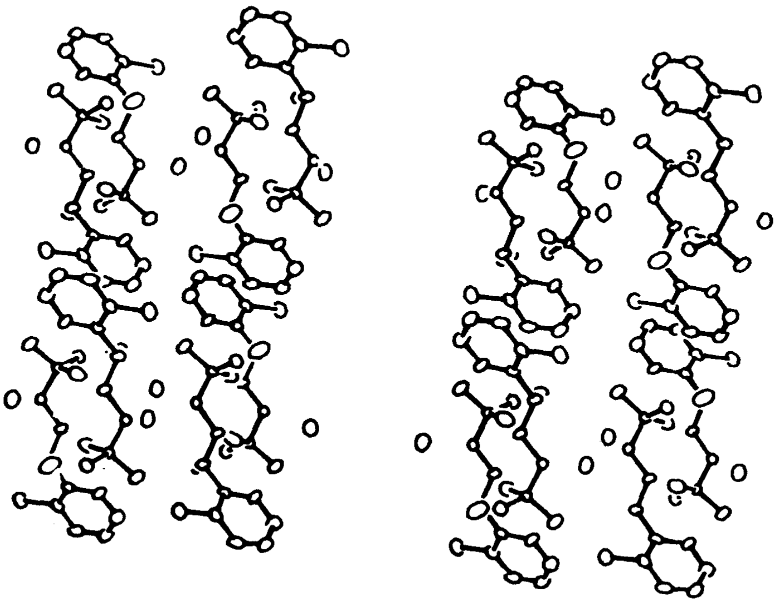
B (20%)
$\tau = -68.4°$

Fig. 3. Two Molecular Conformations derived from the Disordered Structure in Form II Crystal

The fraction and τ of the A and B conformers in form II crystal are 80%, 108.4° and 20%, −68.4°, respectively.

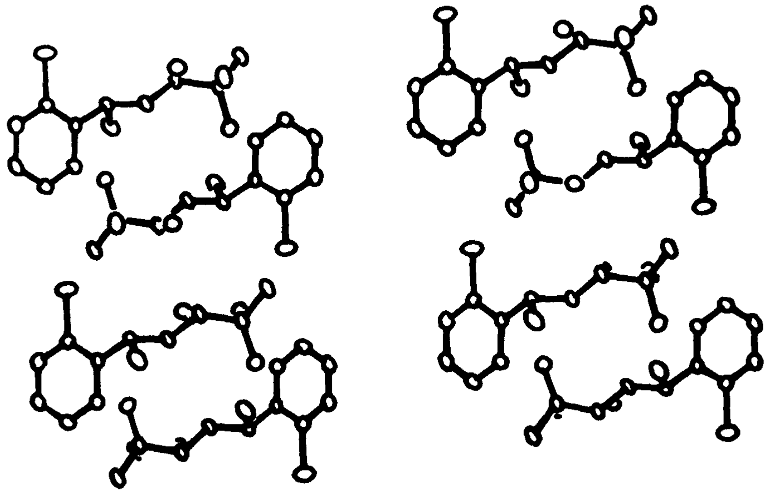


(a) form I

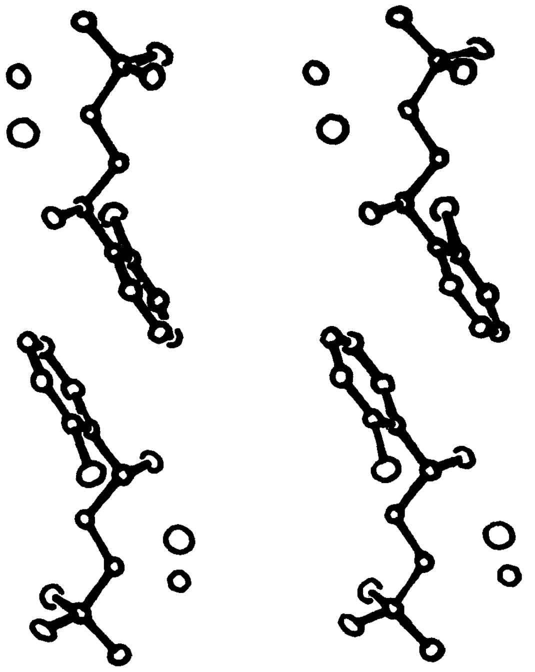


(b) form II

(continued)



(c) form III



(d) hydrate

Fig. 4. Stereoscopic Drawings of the Packing Diagrams for the Four Crystalline Forms of Tulobuterol Hydrochloride

Only in the crystal of form II did we observe disordered crystal structure, which results from a random distribution of two conformers A and B as shown in Fig. 3. These two conformers differ in the orientation of the chlorophenyl group as shown by the torsion angle about the C(6)-C(7) bond, τ[C(1)-C(6)-C(7)-C(8)], which determines the backbone conformation of the molecules. It differs by almost 180° in A and B.

Comparison of the conformations of the seven independent tulobuterol molecules in the four crystalline forms reveals that only the B conformer of form II has a different conformation.

Thus, the values of τ are $\pm 91.2°$, $\pm 96.6°$, $\pm 84.2°$ for the three crystallographically independent molecules in form I, $\pm 108.4°$ for A conformer, $\pm 68.4°$ for B conformer in II, $\pm 102.7°$ in III, and $\pm 87.2°$ in Hy (± is used because the crystals are composed of both optical enantiomers).

In all cases, the nitrogen atom is protonated and takes tetrahedral configuration.

Crystal Structure

Crystal packings of the four forms are shown in Fig. 4 by stereoscopic drawings.

It can be seen that a great difference of packing mode and a small difference of the conformation of the molecules exist. It is clear that the hydrogen bonding system determines the architecture of the crystal structure. In Table VI, all crystallographically independent hydrogen bonds are summarized.

In form I, as shown in Fig. 5, there are two types of molecular clusters named (A) and (B), each consisting of two tulobuterol molecules and two chloride anions connected by hydrogen bonds. In the cluster (A), two enantiomers related by the non-crystallographic center of symmetry (denoted by * in the figure) form a hydrogen bond system by intervention of the two chloride anions. This system is closed and planar, and the four crystallographically independent hydrogen bonds are involved. In the cluster (B), the structure is essentially the same except for the presence of the crystallographic center of symmetry instead of the non-crystallographic one.

Fig. 6 shows that, in form II, the molecules having the same chirality and related by the two-fold screw axis form a chain of hydrogen bonds incorporating chloride anions. These bonds form a spiral column along the two-fold screw axis.

In form III, as shown in Fig. 7 a pair of optical enantiomers participate in the hydrogen bond system with two chloride anions. This planar hydrogen bond scheme is almost identical

TABLE VI. Hydrogen Bond Lengths and Their Estimated Standard Deviations in Å

		d	
	Form I		
I :	$\mathrm{Cl}(4^{\mathrm{i}})$ ------ $\mathrm{N}(1^{\mathrm{ii}})$	3.16 (1) Å	<d>=3.17Å
II :	$\mathrm{Cl}(4^{\mathrm{i}})$ ------ $\mathrm{N}(2^{\mathrm{i}})$	3.19 (1)	
III:	$\mathrm{Cl}(5^{\mathrm{ii}})$ ------ $\mathrm{N}(1^{\mathrm{ii}})$	3.22 (1)	
IV :	$\mathrm{Cl}(5^{\mathrm{ii}})$ ------ $\mathrm{N}(2^{\mathrm{i}})$	3.16 (1)	
V :	$\mathrm{Cl}(6^{\mathrm{i}})$ ------ $\mathrm{N}(3^{\mathrm{i}})$	3.14 (1)	
VI :	$\mathrm{Cl}(6^{\mathrm{i}})$ ------ $\mathrm{N}(3^{\mathrm{iii}})$	3.18 (1)	
	(i) x,y,z; (ii) $x,y,z+1$; (iii) $2-x$, $1-y$, $1-z$.		
	Form II		
I :	$\mathrm{Cl}(2^{\mathrm{i}})$ ------ $\mathrm{N}^{(\mathrm{ii})}$	3.15 (1) Å	<d>=3.19Å
II :	$\mathrm{Cl}(2^{\mathrm{iii}})$ ----- $\mathrm{N}^{(\mathrm{ii})}$	3.22 (1)	
	(i) x, y, z; (ii) $1-x, 1-y, -z$; (iii) $3/2-x$, $1/2+y$, $1/2-z$; (iv) $1/2+x$, $3/2-y$, $1/2+z$.		
	Form III		
I :	$\mathrm{Cl}(2^{\mathrm{ii}})$ ------ $\mathrm{N}^{(\mathrm{i})}$	3.224 (7) Å	<d>=3.174Å
II :	$\mathrm{Cl}(2^{\mathrm{iii}})$ ----- $\mathrm{N}^{(\mathrm{i})}$	3.124 (7)	
	(i) x, y, z; (ii) $x, y-1, z$; (iii) $1-x, 1-y, 1-z$; (iv) $1-x, -y, 1-z$.		
	Hydrate		
I :	$\mathrm{Cl}(2^{\mathrm{i}})$ ------ $\mathrm{O}(w^{\mathrm{i}})$	3.097 (6) Å	
II :	$\mathrm{O}^{(\mathrm{i})}$ -------- $\mathrm{O}(w^{\mathrm{i}})$	2.880 (7)	
III:	$\mathrm{N}^{(\mathrm{i})}$ -------- $\mathrm{O}(w^{\mathrm{i}})$	2.837 (7)	
IV :	$\mathrm{Cl}(2^{\mathrm{ii}})$ ------ $\mathrm{N}^{(\mathrm{i})}$	3.121 (6)	
V :	$\mathrm{O}(w^{\mathrm{i}})$ ------ $\mathrm{O}(w^{\mathrm{iii}})$	3.137 (7)	
	(i) x, y, z; (ii) $x, y, z-1$; (iii) $1-x, -y, 1-z$.		

The capital roman number attributed to each hydrogen bonding pair corresponds to that given in Figs. 5, 6, 7 and 8, and the small roman number in parentheses represents a symmetry operation applied to each atom.

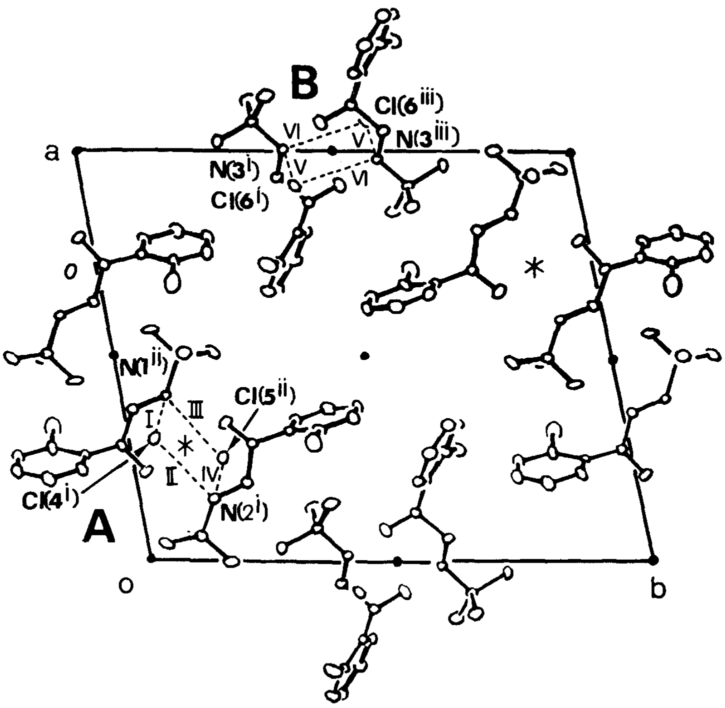


Fig. 5. The Crystal Structure of Form I viewed along the *c* Axis

Hydrogen bonds are indicated by broken lines with the capital roman numbers from I to VI. Two hydrogen bonding clusters are denoted as **A** and **B**.

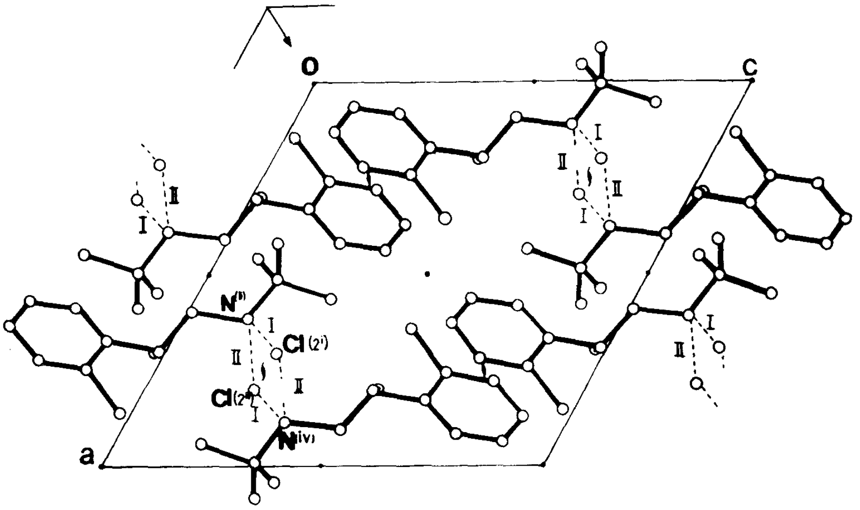


Fig. 6. The Crystal Structure of Form II viewed along the *b* Axis

Hydrogen bonds are denoted by the broken lines, and their types are distinguished by the capital roman numbers I and II.

with that found in form I crystal.

As shown in Fig. 8, the hydrogen bond system in Hy crystal, which forms a ribbon-like network along the *c* axis, is distinguished from those in the other unhydrated forms by the participation of the water molecule.

Mean hydrogen bond lengths are 3.18 Å in the cluster (A), 3.16 Å in the cluster (B) of form I, 3.19 Å in II, and 3.17 Å in III. Since the standard deviations of these hydrogen bonds are estimated to be about 0.01 Å, the differences in length may not be significant. Although a topological difference in hydrogen bonding mode is observed between the two hydrogen bonded

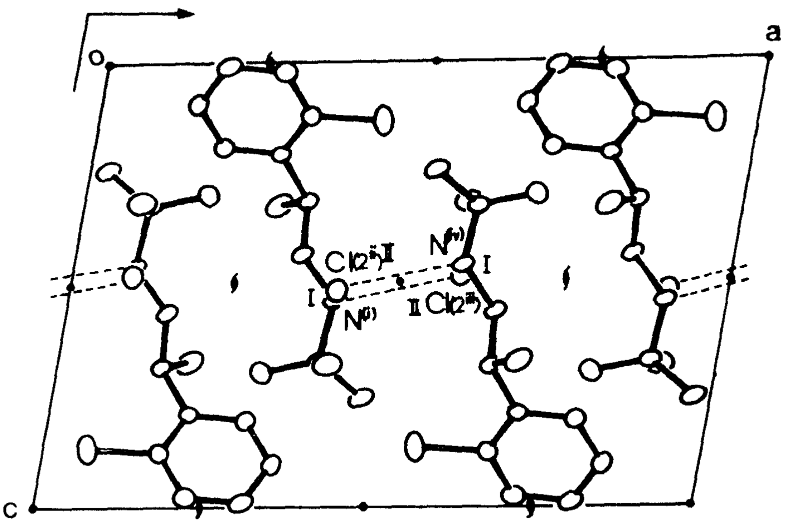


Fig. 7. The Crystal Structure of Form III viewed along the *b* Axis

Hydrogen bonds are denoted by the broken lines, and their types are distinguished by the capital roman numbers I and II.

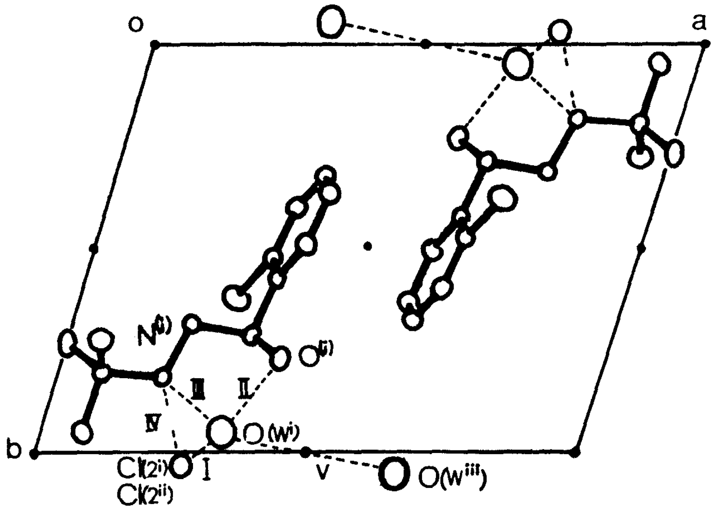


Fig. 8. The Crystal Structure of the Hydrate viewed along the *c* Axis

Hydrogen bonds are indicated by the broken lines with the capital roman numbers from I to V which distinguish the bond types.

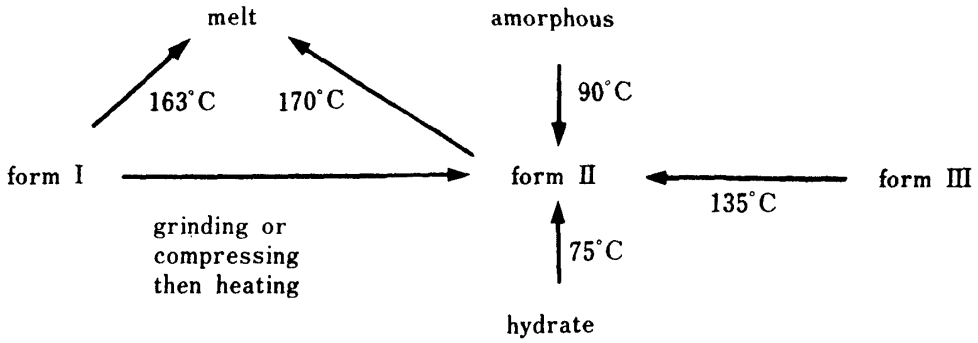


Fig. 9. Interconversion Scheme among Polymorphs of Tulobuterol Hydrochloride

clusters in form I and the chain in form II crystal, a common feature of the crystal packing still exists; the chlorophenyl and tertiary butyl groups make hydrophobic clusters in the two crystal forms.

It is difficult to visualize a pathway for the phase transition of the crystal packing from form I to form II, since the displacements of the molecules in this transition seem to be rather drastic, as can be seen in Fig. 4. In fact, rearrangement of the hydrogen bonded pair is necessary.

As shown in Fig. 9, the intercoversion scheme was established by the previous work. The above-mentioned considerations may well explain the previous experimental results on the thermodynamic properties. The previous paper reports that form III transformed easily into form II through the process of fusion and subsequent recrystallization by heating; however, the crystalline phase transition to the energetically more favored structure (form II) was not observed upon simple mechanical treatments of form I crystal, such as grinding or compression without subsequent heating.

On the other hand, by comparison of combinations of the figures (a), (b), (c), (d) in Fig. 4, the strongest structural homology of the crystal packing is recognized between the molecular arrangements of form II and form III. This can also be demonstrated by full superposition of Fig. 6 (Form II) on Fig. 7 (Form III) which is inversed and properly rotated about its origin. The transition of form III ($Dx=1.213$ gcm^{-3}) to the more compact crystal form II ($Dx=1.237$) by simple heating is well explained by this fact, although recombination of hydrogen bonded pairs by rotational displacement of tulobuterol molecules about the molecular backbone axis is neceassary.

Thus, the present investigation provides an interpretation of the phase transition of C-78 by showing a significant correlation between the crystal structures of the four forms and the thermodynamic properties as displayed in the DSC curves.

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References

1) M. Saito, H. Yabu, M. Yamazaki, K. Matsumura, and H. Kato, *Chem. Pharm. Bull.*, **30**, 652 (1982).
2) G. Germain, P. Main, and M.M. Woolfson, *Acta Cryst.*, **A27**, 368 (1971).
3) C.K. Johnson, ORTEP. Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, Tennessee.