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The Preparation and Properties of a New Polymorphic Form of (α-Bromoisovaleryl)urea

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(α-Bromoisovaleryl)urea has two polymorphic forms (I and II: leaflet crystals and needle crystals, respectively) but another form (III) of fine crystals, which shows different transition and melting properties from the conventional forms, was found in commercial (α-bromoisovaleryl)urea of JP grade. These fine crystals are transformed to parallelogramic plates at about 110° and melt at 142°.

Suitable conditions for the preparation of form III were examined and its properties were studied. Form III was obtained as columnar crystals from methanol on standing for 2 days at −20°. The crystals are very fragile and show an X-ray diffraction pattern and infrared spectrum different from those of the conventional polymorphs.

The transition and melting properties of these columnar crystals are the same as those of the fine crystals found in commercial (α-bromoisovaleryl)urea. It was found that form III is more stable at 4° or below than the conventional leaflet crystals (form I), though the relative stability of these polymorphic forms is reversed at room temperature.

Keywords——(α-bromoisovaleryl)urea; polymorph; transition; melting property; X-ray diffraction; thermomicroscopy

In connection with the bioavailability of solid pharmaceuticals, polymorphism has an important effect on the dissolution rate and solubility of crystals. It has become apparent that (α-bromoisovaleryl)urea (Bromisovalum, (2-bromo-3-methylbutyryl)urea), which has been used widely as a sedative or hypnotic, has two polymorphic forms, leaflet crystals and needle crystals, according to Watanabe.[2] The former is stable at lower temperature (form I), and the latter at higher temperature (form II). Form I is transformed to form II at about 96° by heating[3] and form II melts at 152—153°.

A study of the transition and melting properties of commercial (α-bromoisovaleryl)urea (JP grade) by thermomicroscopy indicated the presence of fine crystals which were transformed to parallelogramic plates instead of needles, and melted at 142°. These fine crystals (form III) appeared to be different from the conventional form I or form II.

Crystallization of pure form III was attempted in the present work, and columnar crystals of (α-bromoisovaleryl)urea were obtained by crystallization from cold methanol (−20°). When these crystals were ground and observed by thermomicroscopy, they showed the same

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[2] A. Watanabe, *Yakugaku Zasshi*, **58**, 565 (1938).

[3] A. Watanabe, Yumiko Tanaka, and Yoko Tanaka, *Chem. Pharm. Bull.*, **25**, 2239 (1977).

transition and melting properties as the fine crystals in commercial (α-bromoisovaleryl)urea. The X-ray diffraction pattern and infrared absorption spectrum of form III were different from those of the conventional form I or form II. The preparation and properties of this new form of (α-bromoisovaleryl)urea are discussed in this study.

Materials and Methods

Preparation of the Polymorphic Forms of (α-Bromoisovaleryl)urea——Form I: Form I was obtained by the method of Watanabe[2] as follows: (α-bromoisovaleryl)urea of JP grade (Nippon Shinyaku Co., Kyoto) was dissolved in hot MeOH and recrystallized at room temperature.

Form II: Form II was obtained by a modification of Watanabe's method[2] as follows: form I obtained as described above was ground to a powder and heated for 1 hr at 110—120°. However, this was done under dried N_2 gas, because the crystals colored due to oxidation during heating if Watanabe's original method was used.

Form III: Form III was obtained as follows: form I obtained above was dissolved in MeOH and left in a freezer at −20°. The crystals that initially crystallized out from MeOH at −20° were form I, but they were transformed into form III on standing for 2 days or longer. Therefore, the conditions for crystallization or transition were studied. The crystallization or transition was examined at 20° (room temperature), +4° (refrigerator), and −20° (freezer), at two initial concentrations of (α-bromoisovaleryl)urea in MeOH. Some transition experiments were carried out on a large scale. The effect of storage time at each temperature was also studied.

Confirmation of Polymorphic Forms——X-Ray Diffraction: Each form was ground to a powder and the X-ray diffraction patterns were measured with a Rigaku Denki Geigerflex 2012 (Cu-K_α radiation, Ni filter). Infrared (IR) spectroscopy: IR spectra were measured by the Nujol mull method with a JASCO IRA spectrophotometer.

Thermomicroscopy and Photomicrograms: The transition and melting properties were observed with a thermomicroscope (Yazawa Kagaku Co., Tokyo) and photomicrographs were taken with a photomicrographic system made by Olympus Co., Tokyo.

Results and Discussion

Form I appears as leaflet crystals and form II as needle crystals, as mentioned previously. Photomicrographs of these polymorphic forms are shown in Fig. 1-a and b, respectively. Form III obtained in this experiment appears as columnar crystals which are very fragile. A photomicrograph of this new polymorphic form is shown in Fig. 1-c.

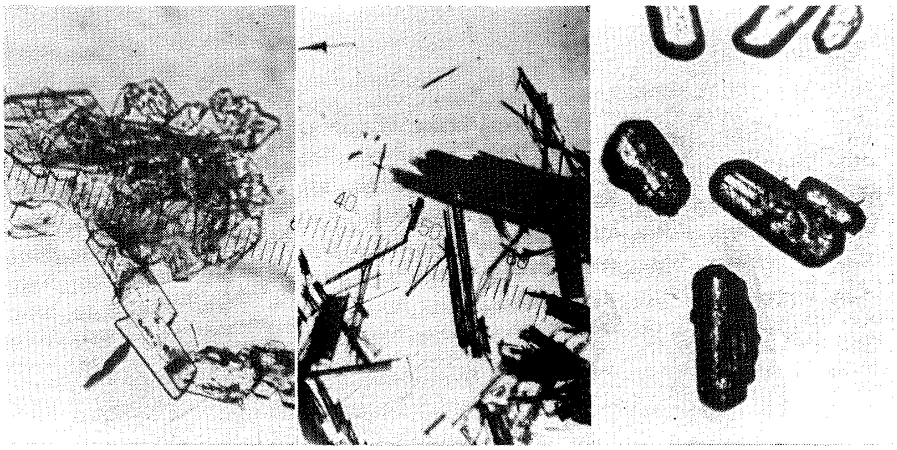
(a) Form I (b) Form II (c) Form III

Fig. 1. Photomicrographs of the Three Forms of (α-Bromoisovaleryl)urea (×67)

IR spectra of these forms are shown in Fig. 2. The spectra of form I and II are the same as those reported by Ohba *et al.*[4] The spectrum of form III was different from that of form

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[4] T. Ohba, Y. Tada, and Y. Oyama, *Eisei Shikenjo Hokoku*, **82**, 33 (1964).

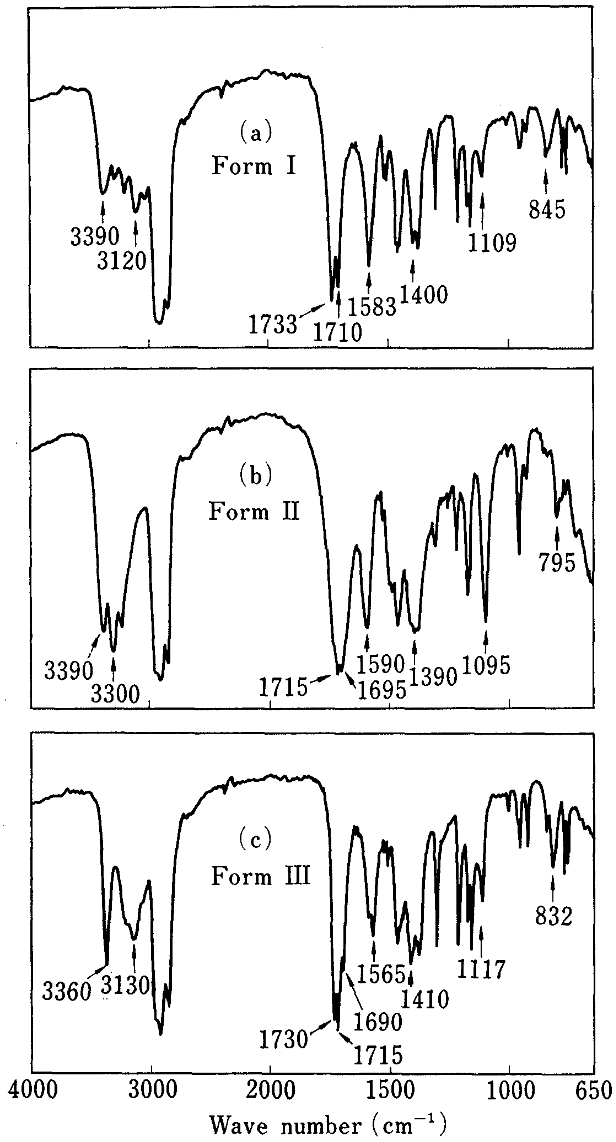

Fig. 2. IR Absorption Spectra of the Three Forms of (α-Bromoisovaleryl)urea in Nujol Mulls

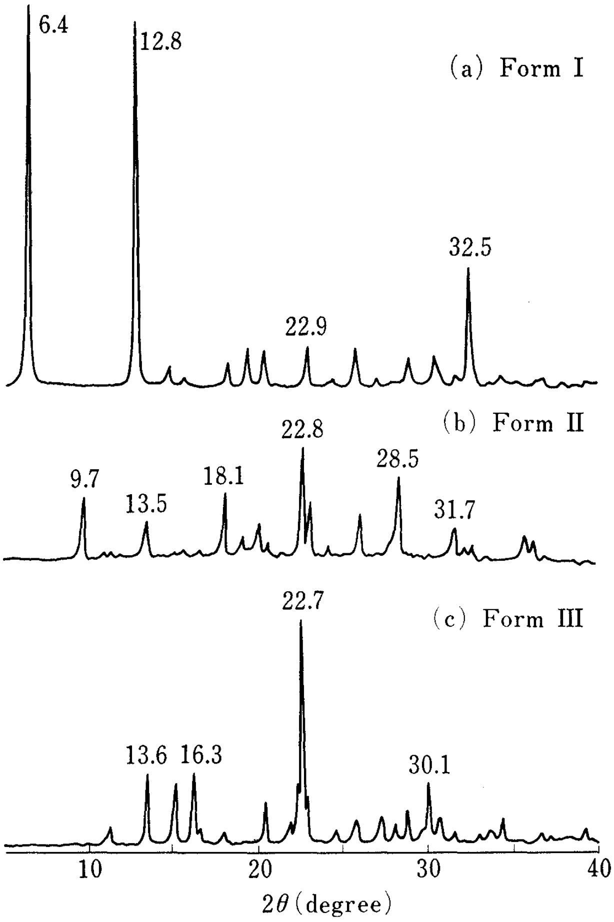

Fig. 3. X-Ray Diffraction Patterns of the Three Forms of (α-Bromoisovaleryl)urea

I or II. In particular, the absorption patterns in the high wave number region were different, and the absorption peaks were shifted in the finger-print region as shown in Fig. 2.

The X-ray diffraction patterns of the three forms are shown in Fig. 3. In the diffraction pattern of form I shown in Fig. 3-a, very high diffraction peaks were observed at $2\theta=6.4°$ and 12.8°. The disappearance of these two peaks indicated completion of the transition from form I to form II or form III. As shown in Fig. 3-c, in the diffraction pattern of form III, the highest peak was observed at 22.7° and specific diffraction peaks were also observed at 13.6°, 16.3°, 30.1°, 34.3°, 39.2°, and elsewhere. Therefore, it appears that form III is a new polymorphic or pseudopolymorphic modification of (α-bromoisovaleryl)urea.

The results of elemental analysis are shown in Table I, supporting the view that form III is a new polymorphic form.

Table II shown the conditions for the formation of form III. When 5 g of form I was dissolved in 30 ml of methanol and kept at room temperature (20°), no crystals were obtained. (α-Bromovaleryl) urea was recrystallized from methanol at the same concentration in a refrigerator (+4°) or a freezer (−20°). In both cases, crystals obtained after 3 hr showed form

Table I. Elemental Analysis Data for the Three Forms of (α-bromoisovaleryl)urea

	Elemental analysis (%)		
	C	H	N
Calcd.	32.30	4.97	12.56
Form I	32.48	5.00	12.34
Form II	32.47	4.90	12.31
Form III	32.52	4.96	12.40

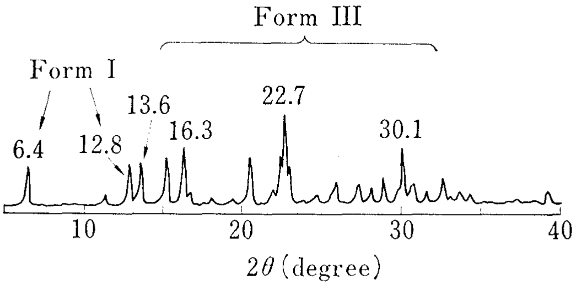

Fig. 4. X-Ray Diffraction Pattern of the Crystals obtained after 1 Day at 4°

I-type X-ray diffraction patterns, as shown in Table II. Therefore, it is considered that the initial crystals formed are in form I even at low temperature, and that they do not undergo transition within 3 hr. The crystals taken from the refrigerator after 1 day also showed the form I-type diffraction pattern, but the crystals from the freezer after 1 day showed a mixed pattern of forms I and II, as shown in Fig. 4.

In the diffraction pattern of the crystals kept for 2 days at −20°, the characteristic peaks of form I (6.4° and 12.8°) had disappeared and a form III-type pattern was seen, as shown in Fig. 3-c. The crystals at 4° remained in form I after 3 days, but they showed the X-ray diffraction pattern of form III after 1 month.

Table II. Crystal Forms obtained under Various Conditions

Time	Concentration[a)] 5 g/30 ml Temp. (°C)		10 g/30 ml Temp. (°C)			20 g/120 ml Temp. (°C)	
	4	−20	20	4	−20	4	−20
3 hr	I	I	—	I	I	—	—
1 Day	I	I+Ⅲ	—	—	I+Ⅲ	—	I+Ⅲ
2 Days	—	Ⅲ	—	I	Ⅲ	I	Ⅲ
3 Days	I	Ⅲ	I	—	—	—	—
1 Month	Ⅲ	—	I	—	—	—	—

a) (α-Bromoisovaleryl) urea (g) dissolved in methanol (ml).
Crystal forms: I, formI; III, form III; I+III, mixture of form I and form III.

On the basis of these results, it is considered that seed crystals of form I are initially generated in cold methanol, and grow, then these form I crystals are slowly transformed into form III. This transition is completed in about 2 days at −20°, while it proceeds so slowly at 4° as to be indetectable by the X-ray diffraction method after 3 days. It is concluded that form III is stable as crystals and that form I is metastable as crystals between 4° and −20°, but the transition from metastable to stable form in methanol is much slower at 4° than at −20°.

Similar experiments were carried out at different concentrations or scales in order to see whether this transition is influenced by the amount of crystals deposited or by the initial temperature of the crystallization. The results of experiments with 10 g of (α-bromoisovaleryl)urea in 30 ml of methanol and 20 g of (α-bromoisovaleryl)urea in 120 ml of methanol are also shown in Table II.

As shown in this talbe, no difference was found at the lower temperature compared with the results of the experiment with 5 g of (α-bromoisovaleryl)urea in 30 ml of methanol. Recrystallization occurred at room temperature, but no transition was seen at a high concentration in 1 month, as shown in Table II. When form III was obtained by recrystallization from methanol at −20° for 2 days, then kept at room temperature for 10 days without separation from methanol, it retransformed into form I completely. These results show that form I is more stable than form III at room temperature. When form III was kept at room temperature and form I was kept at −20° for 1 month without a solvent, no transition to form I or form III, respectively, was observed. Therefore, it is suggested that such a transition proceeds during the processes of dissolution and recrystallization in a solvent.

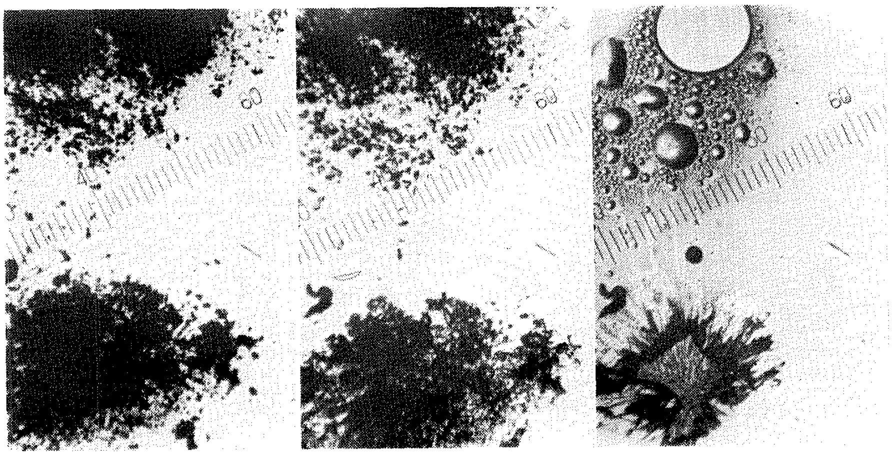
(a) RoomTemp. (b) 120° (c) 150°

Fig 5. Photomicrographs of Powdered Forms I and III of (α-Bromoisovaleryl)-urea at Various Temperatures (×67)

The upper powder is form III and the lower powder is form I in each case.

As mentioned previously, form III, the new polymorphic form of (α-bromoisovaleryl) urea obtained in this study, formed columnar crystals as shown in Fig. 1-c. When they were ground to a powder and observed by thermomicroscopy, they were transformed into parallelogramic plates at about 110°, and then melted at 142°. Form I was transformed to form II (needles), as mentioned previously, but partially untransformed form I melted at 142° and crystallized immediately to give needle crystals (form II), which melted at 152°. Therefore, it is assumed that the parallelogramic plated are the same form as form I.

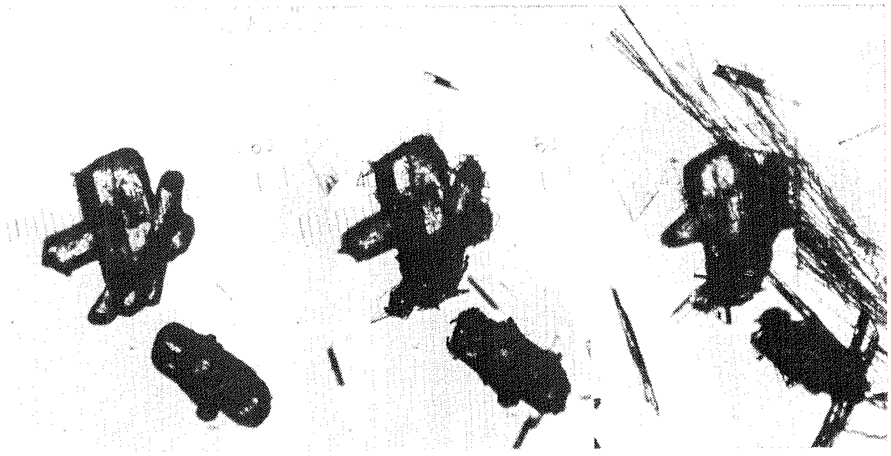
(a) Room Temp. (b) 120° (c) 135°

Fig. 6. Photomicrographs of Form III at Various Temperatures (×67)

The transition and melting properties of the ground forms I and III as determined by thermomicroscopy are shown in Fig. 5. As shown in these photographs, form I was transformed into needles but form III melted at 142° without transformation into needles. When columnar crystals were heated without grinding, though transition to the parallelogramic plates was observed, they often also transformed into fine needles, as shown in Fig. 6, and these needle crystals melted at 148—156°.

The thermal properties, solubility, and interactions of (α-bromoisovaleryl)urea polymorphs in relation to the bioavailability are now being studied in this laboratory.