Chem. Pharm. Bull. 31(3)1101—1104(1983)

Polymorphism of α-[(*tert*-Butylamino)methyl]-2-chloro-4-hydroxybenzyl Alcohol Hydrochloride (HOKU-81)

Masaru Saito,* Kugako Matsumura, Hideo Kato and Yasuo Ito

Research Laboratories, Hokuriku Seiyaku Co., Ltd, Inokuchi, Katsuyama, Fukui 911, Japan

(Received September 8, 1982)

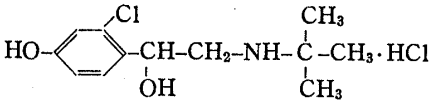
Two crystalline forms of α-[(*tert*-butylamino)methyl]-2-chloro-4-hydroxybenzyl alcohol hydrochloride (HOKU-81) were found by X-ray powder diffraction and infrared spectroscopic analyses.

By means of differential scanning calorimetry (DSC), the melting points of forms I and II were found to be 179 and 181°C, respectively. It was found by simultaneous DSC and thermogravimetry that the two polymorphs of HOKU-81 decomposed upon further heating.

Both polymorphs of HOKU-81 were very stable to humidity, heating and mechanical treatments such as grinding or compressing. These physicochemical properties of HOKU-81 are very different from those of tulobuterol hydrochloride, a pre-metabolite form of HOKU-81 in humans and an excellent bronchodilator.

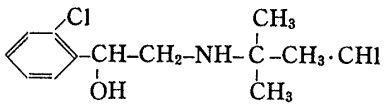
Keywords——α-[(*tert*-butylamino)methyl]-2-chloro-4-hydroxybenzyl alcohol hydrochloride (HOKU-81); polymorphism; X-ray powder diffraction; IR spectra; thermal analysis; stability

It was reported that α-[(*tert*-butylamino)methyl]-2-chloro-4-hydroxybenzyl alcohol hydrochloride (HOKU-81, Chart 1), one of the metabolites of tulobuterol hydrochloride (C-78, Chart 2) found in rat[1] and human[2] urine, possessed a much stronger bronchodilating action than C-78, which is a clinically potent and selective adrenergic β_2-stimulant.[3]



HOKU-81

Chart 1



tulobuterol hydrochloride (C-78)

Chart 2

Previously, the authors reported that three anhydrates, a monohydrate and an amorphous form of C-78 existed, and these physical forms transformed into the most stable one upon heating or mechanical treatments such as grinding or compressing.[4] It was also found that an interconversion between anhydrate and hydrate occurred by absorption or desorption of water, depending on the humidity.[5]

In this study, the crystalline form of HOKU-81 was investigated and two crystalline forms (forms I and II) were found. This article describes the preparative method, characterization and physicochemical properties of two polymorphs of HOKU-81.

Experimental

Materials——HOKU-81 was prepared by the method reported by Koshinaka *et al.*[6] HOKU-81 is highly soluble in water; one mol dissolves in *ca.* 800 ml of distilled water at 30°C.

Polymorphs of HOKU-81 were prepared as follows: Form I: HOKU-81 (10 g) was dissolved in a suitable volume of ethanol to give a saturated solution at the boiling point. The solution was allowed to cool slowly and to stand at room temperature overnight. The separated crystals were then filtered off and dried at

60°C *in vacuo*.

Form II: Form II was prepared by recrystallization from isopropanol or water in the same manner as form I.

Measurements of X-Ray Powder Diffraction Patterns and Infrared (IR) Spectra——X-Ray powder diffraction patterns were obtained on a Rigaku Geigerflex 2013 X-ray diffractometer, with Cu-$K\alpha$ radiation (λ= 1.5418 Å) and an Ni filter. IR spectra were determined using a JASCO IRA-2 grating infrared spectrophotometer (KBr method).

Thermogravimetry (TG) and Differential Scanning Calorimetry (DSC)——Simultaneous DSC and TG measurements were carried out with a Rigaku Thermoflex CN 8085-EI thermobalance and differential scanning calorimeter at 5°C/min in the solid sample pan. Temperature was calibrated with indium. N_2 gas (50 ml/min) and α-Al_2O_3 were used as the carrier gas and reference material.

Hygroscopicity——Portions of about 0.5 g of each form of HOKU-81 were stored in desiccators adjusted to various relative humidities in the range of 59 to 96% at 30°C. A sample was removed at various intervals and the change of weight was measured. The relative humidity was controlled by the use of saturated aqueous solutions of various inorganic salts.[7]

Grinding and Compressing——Grinding and compressing were done in a porcelain mortar and with a JASCO hydraulic press for KBr tablets for IR spectroscopy at 300 kg/cm² for 10 min, respectively.

Results and Discussion

Characterization of Polymorphs of HOKU-81

Two crystal forms of HOKU-81 were characterized by X-ray diffraction and IR spectroscopy. The X-ray diffraction patterns are shown in Fig. 1. The pattern of form I was distinctly different from that of form II, suggesting the existence of differences in crystal structure between the two forms. The IR spectra of forms I and II are shown in Fig. 2. It can be seen that there are differences, particularly in the 3000—3400 cm^{-1}, near 1380 cm^{-1}, 1000—1100 cm^{-1} and 800—900 cm^{-1} regions, which allow easy distinction between the two forms.

The chemical identities of two crystal forms were examined by elemental analysis, thin layer chromatography (TLC), ultraviolet (UV) absorption measurement and nuclear magnetic resonance (NMR) spectroscopy. The elemental analysis data for forms I and II coincided

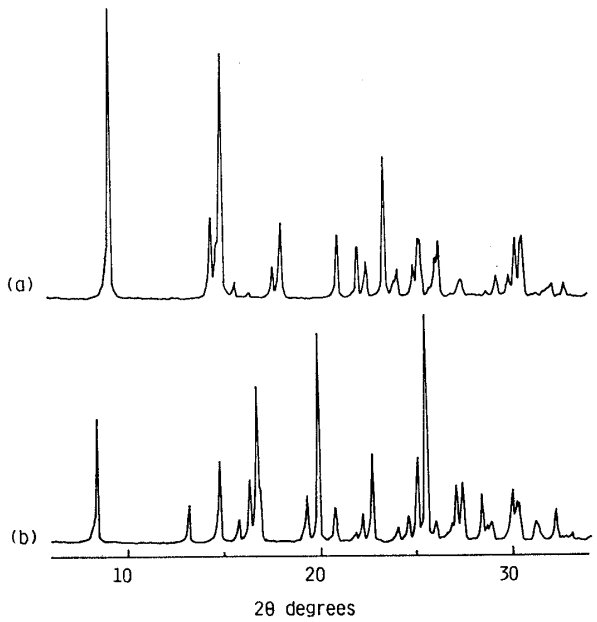


Fig. 1. X-Ray Powder Diffraction Patterns of Polymorphs of HOKU-81

(a): form I, (b): form II.

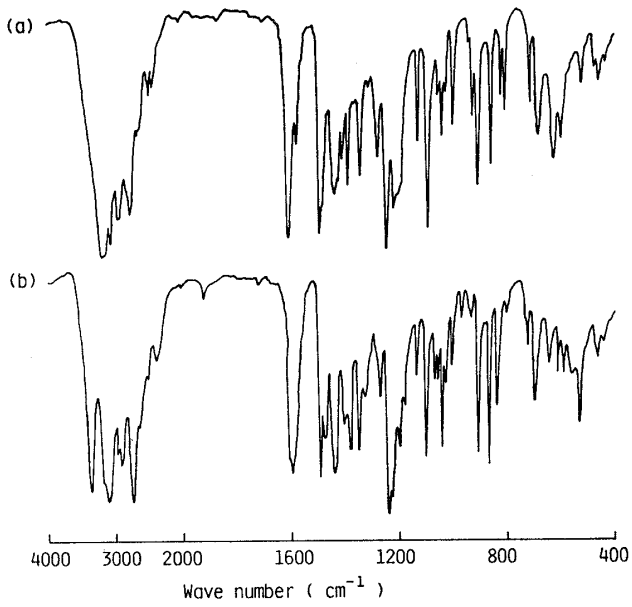


Fig. 2. Infrared Spectra of Polymorphs of HOKU-81 in KBr

(a): form I, (b): form II.

Table I. Elementary Analysis of Polymorphs of HOKU-81

Form	Formula	Calcd			Found		
		C	H	N	C	H	N
I	$C_{12}H_{18}ClNO_2 \cdot HCl$	51.44	6.84	5.00	51.36	6.98	4.89
II					51.52	6.91	4.80

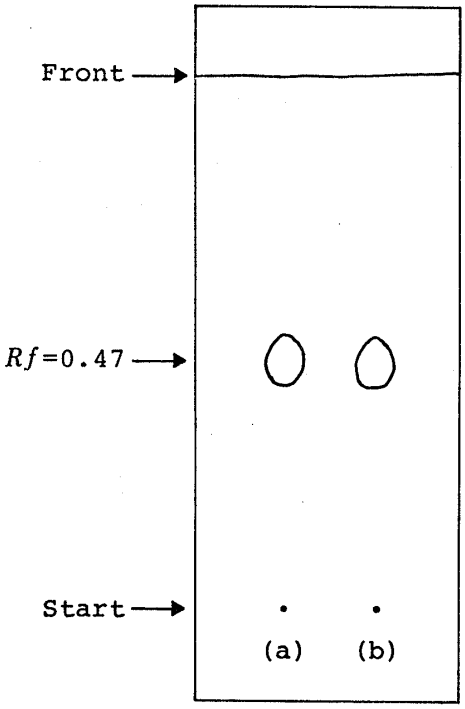


Fig. 3. Thin-Layer Chromatogram of Polymorphs of HOKU-81
(a): form I, (b): form II.

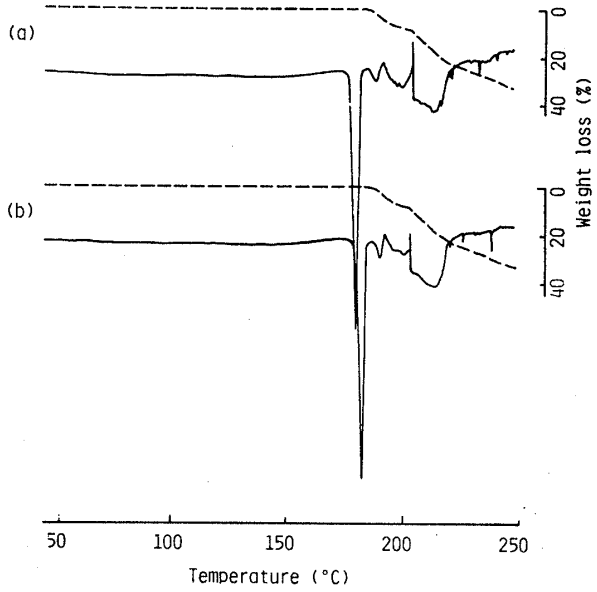


Fig. 4. Thermal Analyses of Polymorphs of HOKU-81
——: DSC curves, ----: TG curves.
(a): form I, (b): form II.

well with the theoretical values, as shown in Table I. The *Rf* values of forms I and II on chromatograms[8] coincided with each other and no other spot was detected (Fig. 3). The UV[9] and NMR[10] spectra of the two forms were also the same . These findings suggest that forms I and II of HOKU-81 had the same chemical nature in solution.

Thermal Behavior of Polymorphs of HOKU-81

The thermal behavior of polymorphs of HOKU-81 was examined by simultaneous DSC and TG measurements. The DSC and TG curves of the two forms are shown in Fig. 4. In the DSC curves, forms I and II showed only one endothermic peak corresponding to the melting point at 179 and 181°C, respectively. The heats of fusion determined by measuring the peak areas in the DSC curves were 8.31±0.23 kcal/mol and 7.89±0.13 kcal/mol for forms I and II, respectively. In the TG curves, no weight change was observed up to the temperature of fusion; however, rapid weight loss occurred on further heating. Taking into account the DSC and the TG properties, and evolution of yellow gas from an open crucible, it was assumed that the weight loss was attributable to decomposition.

Stability

The stability of polymorphs of HOKU-81 was examined under high humidity and mechanical treatments (grinding and compressing). The results showed that the two forms were

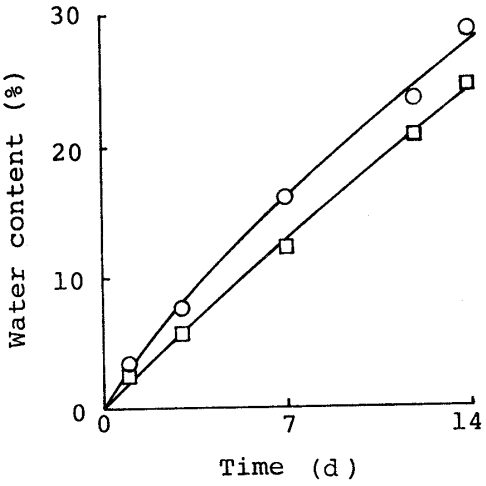


Fig. 5. Change of Water Content of Polymorphs of HOKU-81 at 30°C under 96% R.H.
—○—: form I, —□—: form II.

nonhygroscopic up to 91% R.H. at 30°C and were stable to grinding and compressing treatments. Under 96% R.H., they absorbed moisture gradually as shown in Fig. 5, but no changes in the X-ray patterns and the IR spectra were observed after 2 weeks.

Since the chemical structure of HOKU-81 is similar to that of C-78 and it possesses two hydroxy groups which could serve as water-attracting groups, it was expected that HOKU-81 might be highly hygroscopic. However, these results demonstrate that this is not the case. Furthermore, the finding that no changes occurred during heating and mechanical treatments suggested that the two polymorphs of HOKU-81 had stable crystal structures.

In the previous paper,[11] the physicochemical properties of polymorphs of C-78 were interpreted on the basis of crystal structure analyses. The difference of physicochemical properties between C-78 and HOKU-81 should also be explainable in terms of the crystal structures, and crystal structure analyses of polymorphs of HOKU-81 will be reported in subsequent papers.

Acknowledgement The authors are grateful to Professor Hideo Takenaka and Associate Professor Yoshiaki Kawashima of Gifu College of Pharmacy for helpful advice and discussions. Thanks are also due to Mr. Haruo Yabu for his assistance in the experimental work.

References and Notes

1) Y. Yamamoto, S. Higuchi, T. Fujihashi, S. Shimizu, K. Nishide and I. Uesaka, *Yakugaku Zasshi*, **97**, 244 (1977).
2) K. Matsumura, O. Kubo, T. Sakashita, Y. Adachi and H. Kato, *J. Chromatogr.*, **222**, 53 (1981).
3) *a*) Y. Gomi, H. Shirahase and H. Funato, *Jpn. J. Pharmacol.*, **29**, 515 (1979); *b*) S. Kubo I Matsubara, M. Yamazaki, S. Kasamatsu, E. Koshinaka, H. Kato, and Y. Kase, *Arzneim.-Forsch.*, **30**, 1272 (1980).
4) M. Saito, H. Yabu, M. Yamazaki, K. Matsumura and H. Kato *Chem. Pharm. Bull.*, **30**, 652 (1982).
5) M. Saito, M. Yamazaki, K. Matsumura, H. Kato, Y. Ito, Y. Kawashima and H. Takenaka, *Yakugaku Zasshi*, **103**, 336 (1983).
6) E. Koshinaka, S. Kurata, K. Yamagishi, S. Kubo and H. Kato, *Yakugaku Zasshi*, **98**, 1198 (1978).
7) S. Okano and T. Akaboshi, *Yakuzaigaku*, **17**, 96 (1957).
8) Polymorphs of HOKU-81 were spotted on the TLC plate (Kieselgel $60F_{254}$, Merck Co.) and developed in a mixture of chloroform, methanol and ammonia water (77: 22: 3).
9) An aqueous solution of HOKU-81 (1→12500) showed an absorption maximum at 276.0 nm (Perkin-Elmer 554 spectrophotometer).
10) NMR spectra were run on a Hitachi R-20B NMR spectrophotometer in deuterated methanol with Me_4Si as an internal standard.
11) Y. Harada, M. Saito, K. Matsumura, H. Kato and Y. Iitaka, *Chem. Pharm. Bull.*, **30**, 2301 (1982).