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New Polymorphic Forms of Phenobarbital[1)]

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Two new polymorphic forms, form II-Ba and form III-Cy, were obtained by recrystallization of phenobarbital in the presence of a small quantity of barbital or cyclobarbital, respectively. The two forms could be discriminated by X-ray diffraction or infrared (IR) absorption measurements.

The transition temperature and the heat of transition between form II-Ba and form II, and between form III-Cy and form II were determined to be 84 °C and 0.23 kcal/mol, and 44 °C and 0.68 kcal/mol, respectively, by solubility measurements. The dissolution rate of form II-Ba was higher than that of form II, whereas the dissolution rate of form III-Cy was lower than that or form II.

Keywords——phenobarbital; polymorph; barbital; cyclobarbital; recrystallization; dissolution behavior; transition temperature

Many pharmaceuticals can exist in different polymorphic forms and the differences in molecular arrangement can affect the physicochemical properties and bioavailability. One method to alter the properties of a compound is to change the crystal habit or form by recrystallizing it in the presence of a small amount of a compound structurally very similar to the base material.[2-4)]

In the case of phenobarbital, more than thirteen different polymorphic forms have been reported.[5-7)] In the present study, phenobarbital was recrystallized in the presence of similar compounds. As a result, form II-Ba was obtained by addition of 7.5% barbital; this form showed a higher dissolution rate than form II. Form III-Cy was obtained by addition of 7% cyclobarbital, and this form showed a lower dissolution rate than form II. The dissolution behavior and thermal properties of the three polymorphs (form II, form II-Ba and form III-Cy) were studied in this work.

Experimental

Materials——1) Form II: Phenobarbital of JP grade (Hoei Yakuko Co., Ltd.) was dissolved in ethyl acetate and recrystallized.

2) Form II-Ba: 30 g of phenobarbital of JP grade was dissolved in 140 ml of ethyl acetate at 80 °C and then 2.2 g of barbital (Sanko Seiyaku Kogyo Co., Ltd.) was also dissolved. The mixture was maintained for 3 d at room temperature.

3) Form III-Cy: 30 g of phenobarbital of JP grade was dissolved in 800 ml of chloroform at 70—75 °C and then 2.1 g of cyclobarbital (Tokyo Kasei Kogyo Co., Ltd.) was also dissolved. The mixture was maintained for 2 d in a freezer (−20 °C). The quantity of barbital in form II-Ba and the quantity of cyclobarbital in form III-Cy, were both about 1% as determined by high performance liquid chromatography.[8)]

Elemental analysis data are shown in Table I.

Characterization of Crystal Forms——Crystal forms were characterized by infrared (IR) spectrophotometry (JASCO IRA-1 grating IR spectrophotometer), X-ray diffraction (Rigaku Denki Geigerflex 2012, Ni-filter, Cu-$K\alpha$ radiation, 35 kV, 15 mA), and differential scanning calorimetry (DSC, Rigaku Denki, CN. 80, 85-DI).

Solubility Determination[9)]——Distilled water (400 ml) in a 600 ml beaker was maintained at a constant

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TABLE I. Elemental Analysis Data for the Three Forms of Phenobarbital

	Elemental analysis (%)		
	C	H	N
Calcd	62.06	5.21	12.06
Form II	62.03	5.19	12.01
Form II-Ba	61.97	5.20	12.10
Form III-Cy	62.50	5.45	11.81

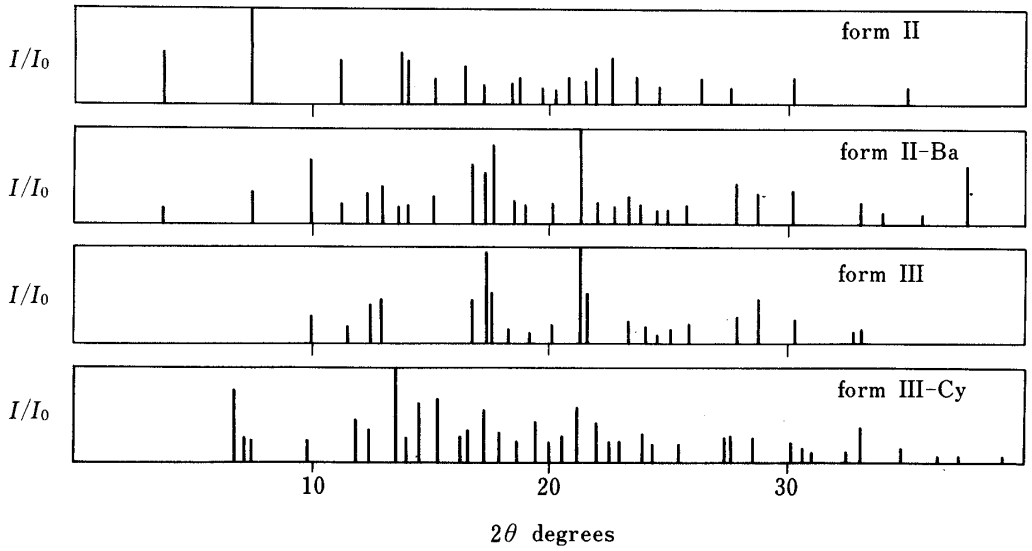

Fig. 1. X-Ray Diffraction Patterns of the Polymorphic Forms of Phenobarbital

temperature (20, 25 or 30 °C), and a sample powder of 210—250 μm size range was added in an amount corresponding to approximately twice the saturated concentration. The suspension was stirred at 200 rpm. A liquors of 1 ml were taken at appropriate intervals using a cotton-filter-equipped pipette, and after dilution of the sample with borate buffer at pH 9.5,[10] the concentration of phenobarbital was determined at $\lambda_1 = 260$ nm and $\lambda_2 = 238$ nm using a dual-wavelength spectrophotometer (Hitachi 356).

Results and Discussion

Effects of the Addition of Barbital and Cyclobarbital

Generally, in order to alter the crystal form, a compound is recrystallized in the presence of another similar compound at a level of 0.1—5%.[2] Form II is obtained by recrystallization of phenobarbital from ethyl acetate, but some change can be seen in the X-ray diffraction pattern when the recrystallization is carried out in the presence of a little barbital. In order to determine a suitable amount of barbital, it was added in amounts varying from 1 to 10% at the time of recrystallization, and the greatest change was seen in the presence of 7 or 7.5% barbital. This crystal form was designated form II-Ba. The form II-Ba thus obtained was stable for one month at room temperature. Form III is obtained by recrytallization of phenobarbital from chloroform, but form III-Cy was obtained in the presence of 7% cyclobartital at the time of recrystallization, in the same way as above.

Characterization of Crystal Forms by X-Ray Diffraction, DSC and IR Measurements

The X-ray diffraction patterns are shown in Fig. 1. Those of form II and form III agreed with those reported by Huang,[11] and a slight change was seen in the patterns of

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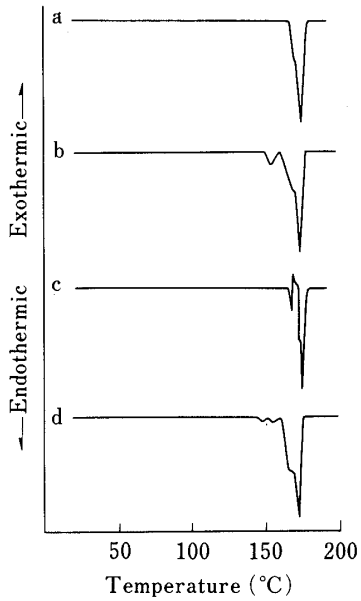

Fig. 2. Thermograms of the Polymorphic Forms of Phenobarbital Obtained by DSC (Heating Rate: 10 K/min)

a, form II; b, form II-Ba; c, form III; d, form III-Cy.

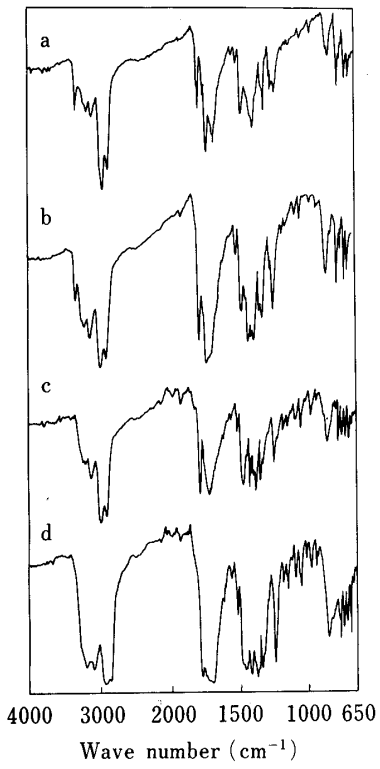

Fig. 3. IR Spectra of the Polymorphic Forms of Phenobarbital in Nujol

a, form II; b, form II-Ba; c, form III; d, form III-Cy.

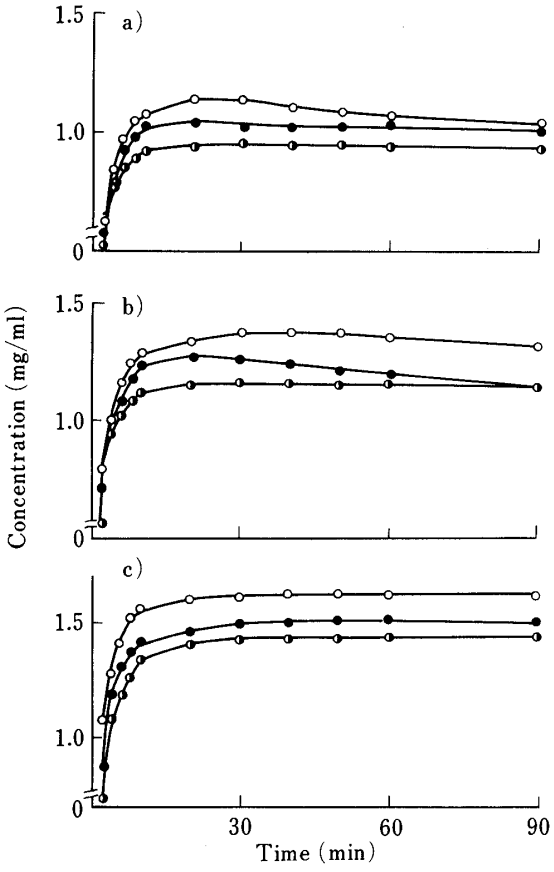

Fig. 4. Concentration–Time Curves for the Dissolution of the Polymorphic Forms of Phenobarbital in Water

●—●, form II; ○—○, form II-Ba; ◑—◑, form III-Cy. a) 20 °C. b) 25 °C. c) 30 °C.

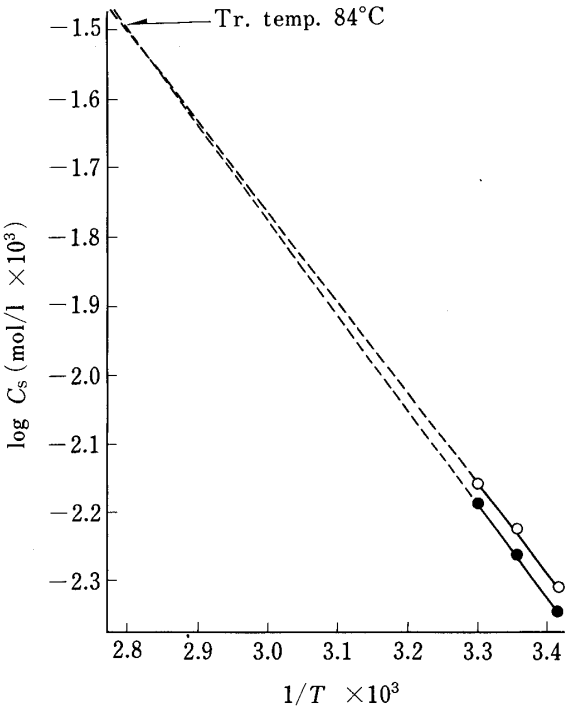

Fig. 5. van't Hoff Plots for Form II and Form II-Ba of Phenobarbital in Water

●—●, form II; ○—○, form II-Ba.

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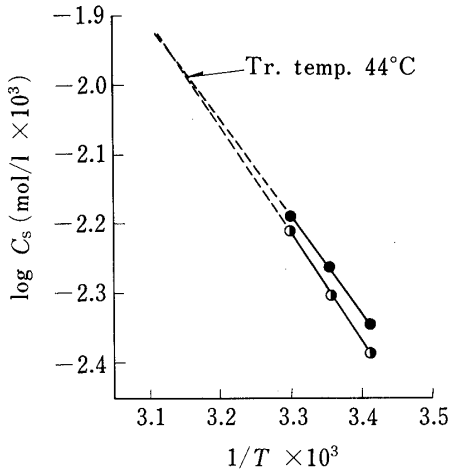

Fig. 6. van't Hoff Plots for Form II and Form III-Cy of Phenobarbital in Water
●—●, form II; ◑—◑, form III-Cy.

TABLE II. Solubilities of Form II, Form II-Ba and Form III-Cy of Phenobarbital at Various Temperatures

Temp. (°C)	Exptl. soly., (mg/ml)		
	Form II	Form II-Ba	Form III-Cy
20	1.05	1.14	0.96
25	1.28	1.39	1.17
30	1.51	1.62	1.44

TABLE III. Thermodynamic Values Calculated for Form II, Form II-Ba and Form III-Cy of Phenobarbital

	Transition temperature[a] (°C)	Heat of solution (kcal/mol)	Heat of transition[a] (kcal/mol)
Form II	—	6.36	—
Form II-Ba	84	6.13	0.23
Form III-Cy	44	7.04	0.68

a) Calculated for the conversion to Form II.

form II-Ba and form III-Cy compared with those of form II and form III, respectively. As shown in Fig. 2, the DSC curve of form II-Ba exhibits a new endothermic peak at 155 °C before the endothermic peak of form II at 175 °C, while the DSC curve of form III-Cy exhibits new endothermic peaks at 148 and 154 °C before the endothermic peak of form III at 168 °C, and the exothermic peak which is seen with form III is not observed. IR spectra are shown in Fig. 3. Some differences are apparent between form II and form II-Ba and between form III and form III-Cy.

Dissolution Behavior

Solubility values determined from the dissolution curves of phenobarbital polymorphs (form II, form II-Ba and form III-Cy) at different temperatures (20, 25 and 30 °C) are shown in Fig. 4 and Table II.

The thermodynamic parameters[12-15] calculated from van't Hoff plots (Figs. 5 and 6) of the solubility data for form II, form II-Ba and form III-Cy are listed in Table III.

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The solubility of form II-Ba obtained in the present study is very much higher than that of form II, and the solubility of form III-Cy is lower than that of form II.

References and Notes

1) Relationship between Polymorphism and Bioavailability of Drugs IV. Part III: Y. Kato, Y. Okamoto, S. Nagasawa, and T. Ueki, *Chem. Pharm. Bull.*, **29**, 3410 (1981).
2) Shionogi Seiyaku Co., Ltd., Japan. Patent 44-287 (1969).
3) K. Kuroda, T. Yokoyama, T. Umeda, Y. Kita, A. Konishi, and T. Kuroda, *Yakugaku Zasshi*, **99**, 745 (1979).
4) Yamanouchi Seiyaku Co., Ltd., Japan. Patent 48-5917 (1973).
5) B. Cleverley and P. P. Williams, *Tetrahedron*, **7**, 277 (1959).
6) R. J. Mesley, R. L. Clements, B. Flaherty, and K. Goodhead, *J. Pharm. Pharmacol.*, **20**, 329 (1968).
7) H. M. EL-Banna, A. R. Ebian, and A. A. Ismail, *Pharmazie*, **30**, 455 (1975).
8) S. J. Soldin and J. G. Hill, *Clin. Chem.*, **22**, 856 (1976).
9) Y. Kato and F. Watanabe, *Yakugaku Zasshi*, **98**, 639 (1978).
10) L. N. Mattson, *J. Am. Pharm. Assoc.*, **43**, 22 (1954).
11) T. Y. Huang, *Acta Pharm. Int.*, **2**, 43 (1951).
12) A. J. Aguiar and J. E. Zelmer, *J. Pharm. Sci.*, **58**, 983 (1969).
13) K. Sekiguchi, M. Kanke, N. Nakamura, and Y. Tsuda, *Chem. Pharm. Bull.*, **23**, 1347 (1975).
14) J. Matsunaga, N. Nambu, and T. Nagai, *Chem. Pharm. Bull.*, **24**, 1169 (1976).
15) T. Yokoyama, T. Umeda, K. Kuroda, T. Nagafuku, T. Yamamoto, and S. Asada, *Yakugaku Zasshi*, **99**, 837 (1979).

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