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Synthesis and Physical Studies of the Organic Salts of Pindolol: Pindolol Benzoate and Pindolol 2-Methoxyphenylacetate

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ABSTRACT

In order to investigate the formation of organic salts of drugs, two salts of pindolol were prepared using salt-forming agents which were crystalline and suitable for physical studies in the solid state. The stoichiometry of the products, pindolol benzoate and pindolol 2-methoxyphenylacetate, was established by elemental analysis. The precipitates formed were assessed by differential scanning calorimetry (DSC), thermogravimetry (TG), x-ray powder diffractometry (XRPD) and Fourier transform–infrared spectrometry (FT-IR). According to the TG and DSC curves, there was no water of crystallization in the precipitates, and the products were thermally stable. Both precipitates gave one sharp melting endotherm which differed from the endotherms of the starting compounds. The x-ray diffraction patterns of the precipitates differed clearly from those of the starting materials, acids and base. The products showed absorption by FT-IR typical of carboxylic acid salts at about 1640–1540 cm^{-1}. The carbonyl absorption indicative of the carboxylic acid group of benzoic acid or 2-methoxyphenylacetic acid was not detectable in the spectra of the precipitates. All this indicates that two new crystalline organic salts (1:1) were formed during the syntheses.

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INTRODUCTION

Bioavailability and formulation properties of acidic and basic drugs have been modified by conversion to a salt (1–4). The salt form of the drug is known to influence many physicochemical properties of the parent compound, including solubility, dissolution rate, stability, and hygroscopicity (1–14). These properties in turn affect the bioavailability and formulation possibilities of the drug. Most of the drug salts are inorganic, mainly sodium or hydrochloride salts, but the range of commercially available organic salts varies greatly.

The inorganic and organic salt-forming agents are often chosen empirically since quantitative relationships between structure and the physicochemical properties of salts are virtually nonexixtent. However, various qualitative relationships are recognized (1,2,7,11). For example, planar, high-melting aromatic sulfonic or hydroxycarboxylic acids yielded crystalline salts with a similarly high melting point, whereas flexible aliphatic strong acids yielded oils (3); and salt combinations with monocarboxylic acids are insoluble in water, while those of dicarboxylic acids confer water solubility if one carboxylic group is left free (15). Both the solubility and the stability of salts are reported to correlate with melting points of certain salts and, in general, a higher melting point is usually accompanied by a reduction in the solubility of the salt.

In general, the salt structure is poorly explained in elementary books of organic chemistry even though many organic salts of drugs are widely used in medicines. Some decision-making models have been developed to help predict salt performance (16).

Salt formation is an acid–base reaction involving either a proton-transfer or neutralization reaction. Particularly important is the relative strength of the acid or the base. There are no general guidelines indicating which organic solvent or mixture of organic solvent would be the most suitable for the precipitation medium or whether the precipitation should be made in aqueous solution. Naturally one criterion is that the acidic or basic drug should be soluble in the chosen media. The information concerning syntheses of the salts is mainly presented in patents. Some patents deal with factors which can affect the yield and certain properties of the salts such as degree of crystallinity or purity. It has been observed that, instead of forming ionic bonds with other compounds, many organic aromatic acids rather form complexes (17). Also, in the synthesis of the embonates of ampicillin, amoxicillin, and cephalexin the starting materials were precipitated as physical mixtures (18).

The present study aimed to find a physically and chemically stable organic base and acids for salt formation, and to perform structural studies in order to produce basic structures which could be used for the development of a methodology for analyzing organic salt formation.

EXPERIMENTAL

Chemicals

Pindolol (Sandoz Pharm AG, Switzerland, Ph.Eur. grade) was kindly supplied by Orion Corporation Orion–Farmos (Espoo, Finland). Benzoic acid (Merck Gmbh, Germany) and 2-methoxyphenylacetic acid (Merck Gmbh, Germany) were analytical grade. The solvents used for precipitation of salts were also analytical grade.

Preparation of the Salts

The precipitations were carried out in two media: ethanol (solvent A) and acetone and water (98 + 2) (solvent B). Pindolol (0.001 mol) was dissolved in 100 ml of medium using ultrasonic bath. The acids (0.001 mol) were added to the solutions and the reaction mixtures were stirred for 30 min at room temperature. After evaporation of the solutions to half the volume, the crystallization started. The mixtures were allowed to stand in an ice bath for 5 hr. The precipitations were filtered and washed with ice-cold precipitation medium and dried at room temperature.

Chemical Studies

Elemental Analysis

Elemental analyses were performed in the microanalytical laboratory of Ilse Beetz in Germany. The samples were dried at +60°C above P_2H_5 before analysis.

Physical Studies

Differential Scanning Calorimetry (DSC)

DSC experiments were carried out on a DSC 7 calorimeter (Perkin–Elmer). The samples (about 4 mg accurately weighed) were heated in an aluminum pan (40

μl). The measurements were carried out at a temperature range of 20° to 200°C and a heating rate of 10°C/min using nitrogen as a purge gas at a flow rate of 40 ml/min.

Thermogravimetry (TG)

TG measurements were carried out on a TGA 7 analyzer (Perkin–Elmer). The samples (about 3 mg accurately weighed) were heated in a platinic sample holder (50 μl). The measurements were carried out at a temperature range of 30° to 130°–190°C, depending on the thermal behavior of the substance. The heating rate was 10°C/min under a nitrogen purge of 40 ml/min.

X-ray Powder Diffraction (XRPD)

The diffraction patterns were measured using a Siemens D 500 x-ray powder diffraction equipment (Siemens AG, Kalsruhe, Germany). The measurements were carried out at 25°C using a copper anode x-ray tube (wavelength 0.1541 nm) operating at 1.6 kW. The x-ray beam was collimated using an automatic divergence slit and 0.05° receiving slit. The measuring range was 5–53° and the speed 1°/min.

Fourier Transform–Infrared (FT-IR) Spectrum

FT-IR spectra were recorded on a 16PC FT-IR (Perkin–Elmer) spectrophotometer using KBr disks. Spectra were recorded from 4400 cm^{-1} to 450 cm^{-1}, and the resolution was 4 nm.

RESULTS AND DISCUSSION

In order to investigate the formation of organic salts of drugs, two salts were prepared using starting compounds which were crystalline and apparently suitable for physical studies in the solid state. When choosing the starting compounds, the thermal stability was elucidated both experimentally and from the literature (19). Thermal analytical results indicated that the chosen acids and base formed sharp melting endotherms in their DSC curves (Fig. 1), and they did not decompose before their melting point (Fig. 2).

The choice of organic acids, benzoic acid and 2-methoxyphenylacetic acid, and pindolol was justified also by the significant characteristics of their IR spectra. Pindolol was regarded as a potential salt-forming agent because of the data published about its analogues, metoprolol and timolol, which were converted to salts to render them crystalline at room temperature (20,21).

Preparation methods for the organic salts of drugs have mainly been reported in the patent literature; there are no general instructions for salt formation. The precipitations were carried out in two media: ethanol and acetone and water (98 + 2), in which both of the starting compounds were dissolved. After concentration, crystallization of white precipitates started. The yield in the synthesis of pindolol 2-methoxyphenylacetate was quite poor (42%, RSD 34%; and 44%, RSD 7%, $n = 6$, respectively) in the two media. The yield of pindolol benzoate was somewhat better for the precipitate formed in a mixture of acetone–water (59%, RSD 2%, $n = 6$). Pindolol is practically insoluble in water and only slightly soluble in methanol. In general, pindolol is very poorly soluble in many commonly used precipitation media, which was the first problem when choosing solvents for the syntheses.

The compositions of the products crystallized were first established by elemental analysis. Results are given in Table 1.

The quantitation was carried out by high-performance liquid chromatography (HPLC). The HPLC method has been described elsewhere (22). The results obtained by elemental analysis agree with the results from HPLC analyses, confirming the 1:1 stoichiometry for both components in the products. Timolol maleate and metoprolol tartrate also had a 1:1 stoichiometry as determined by elemental analysis (20,21). Those salts, however, were not quantitated by HPLC. Maleic acid and tartaric acid have a very poor intrinsic UV absorption and therefore cannot be detected by a UV/VIS detector. One criterion for selecting acids for this study was their UV absorptivity.

Like the starting materials, pindolol, benzoic acid, and 2-methoxyphenylacetic acid, the products synthesized gave one sharp melting endotherm by DSC (Fig. 1). The extrapolated onset temperature and enthalpic change of the pindolol benzoate and pindolol 2-methoxyphenylacetate differed from the endotherms of the starting compounds (Table 2).

According to the DSC (Fig. 1) and TG (Fig. 2) curves, there was no water of crystallization in the precipitates, and the precipitates were thermally stable. These facts are important for the reliability of thermal analysis; dehydration at about 100°C and decomposition change the structure of the substances and lead to inaccurate melting temperature determinations (23). Also, previously mentioned organic salts, timolol maleate and

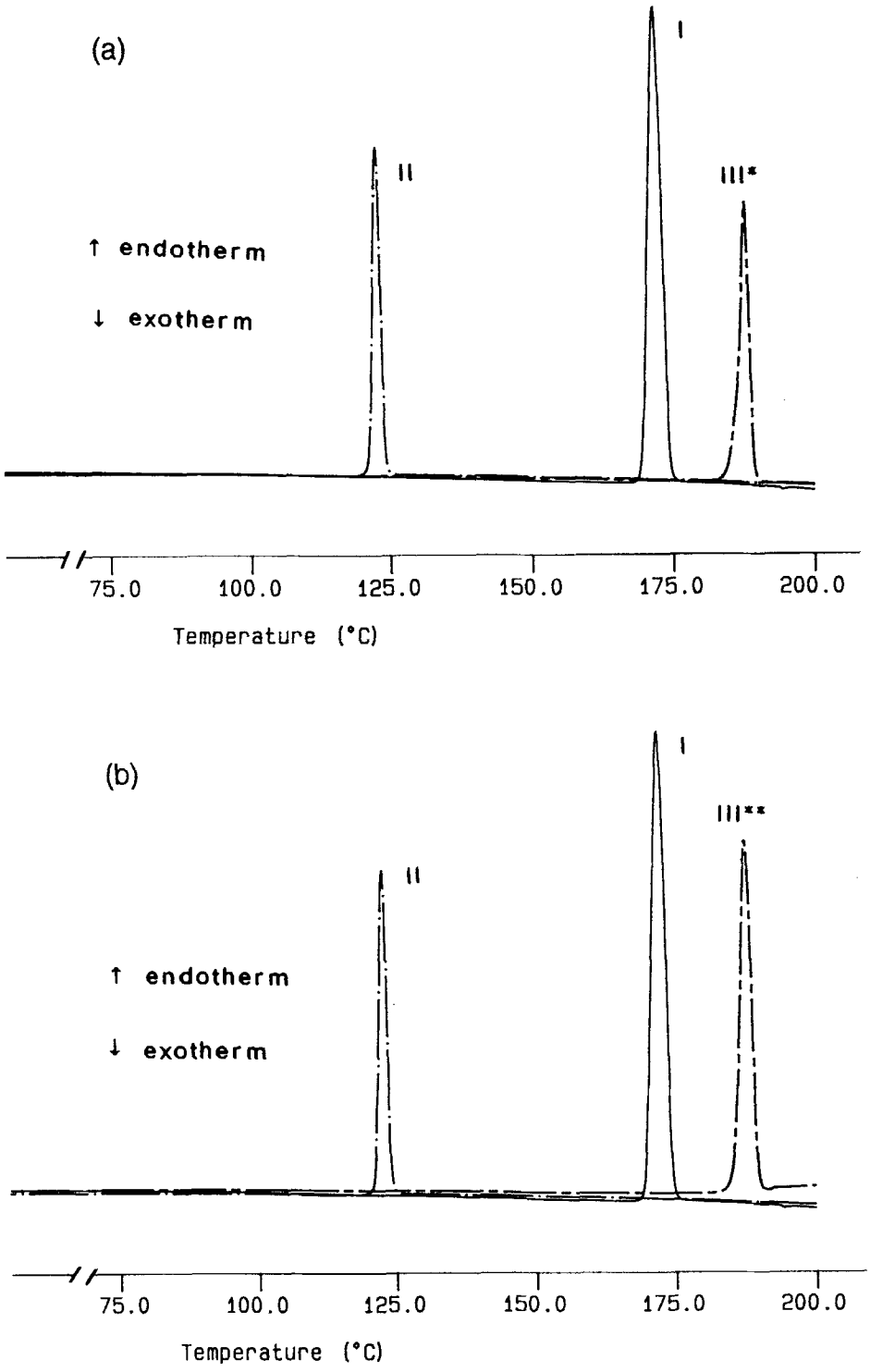
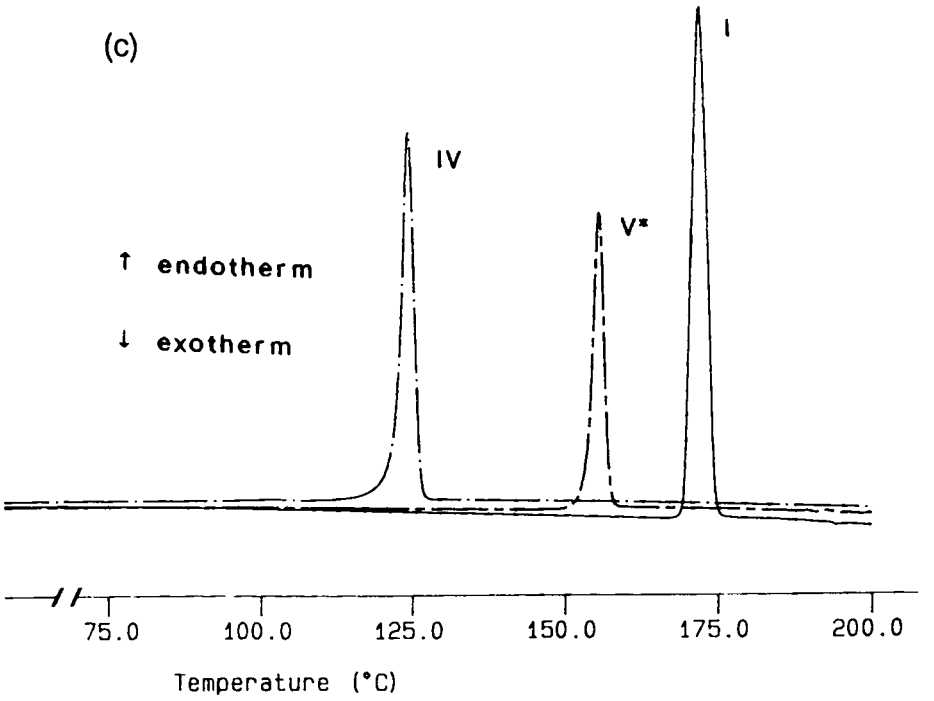
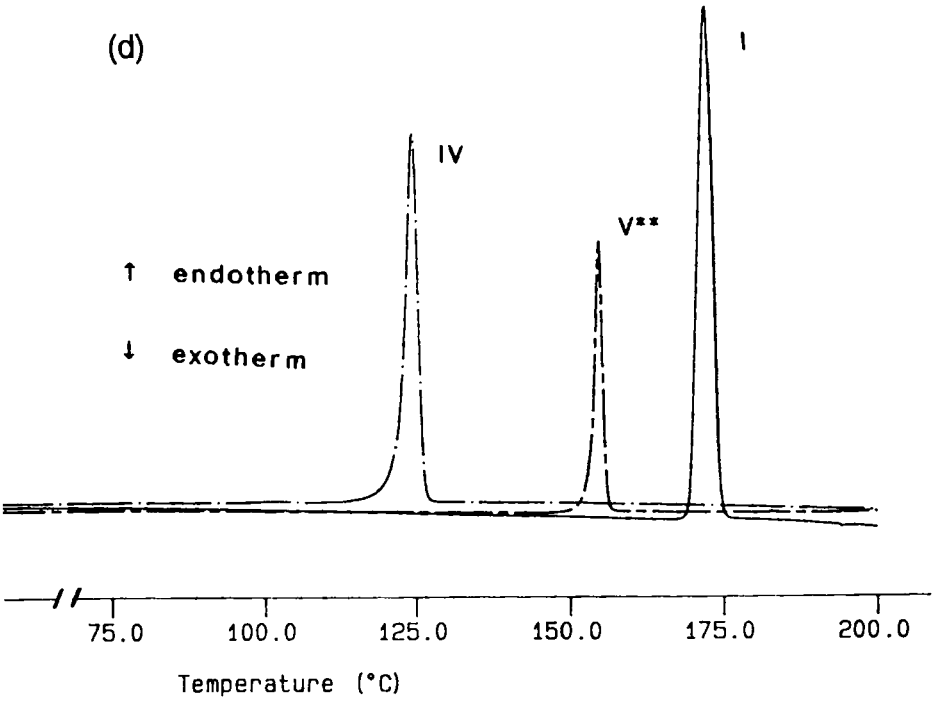


Figure 1. (a) DSC curves of pindolol (I), benzoic acid (II) and pindolol benzoate formed in solvent A (III*). (b) DSC curves of pindolol (I), benzoic acid (II) and pindolol benzoate formed in solvent B (III**). (c) DSC curves of pindolol (I), 2-methoxyphenylacetic acid (IV), and pindolol 2-methoxyphenylacetate formed in solvent A (V*). (d) DSC curves of pindolol (I), 2-methoxyphenylacetic acid (IV), and pindolol 2-methoxyphenylacetate formed in solvent B (V**).





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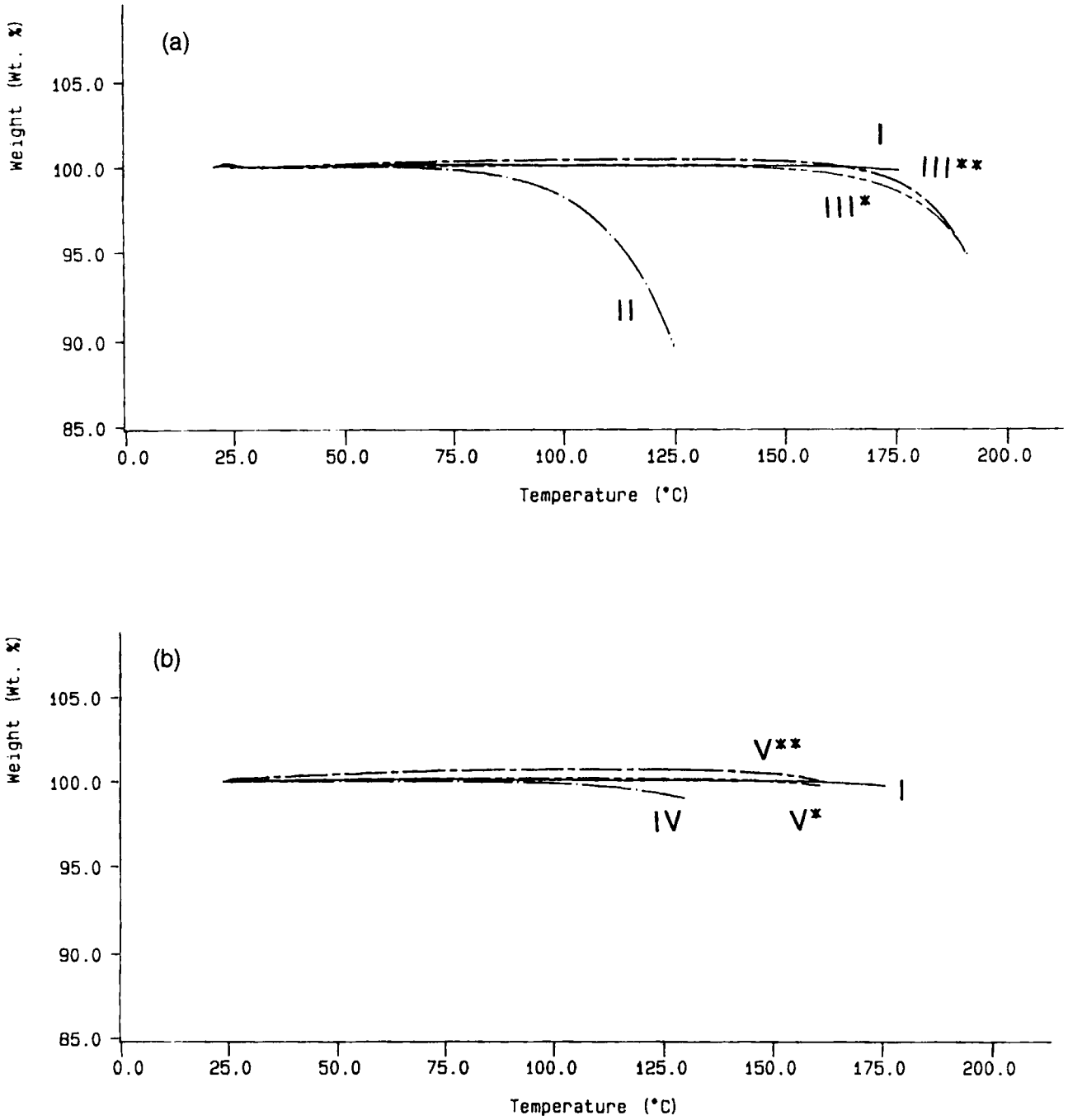


Figure 2. (a) TG curves of pindolol (I), benzoic acid (II) and pindolol benzoate [III* (formed in solvent A); III** (formed in solvent B)]. (b) TG curves of pindolol (I), 2-methoxyphenylacetic acid (IV), and pindolol 2-methoxyphenylacetate [V* (formed in solvent A); V** (formed in solvent B)].

Table 1

Elemental Analysis of Pindolol Benzoate (I) and Pindolol 2-Methoxyphenylacetate (II) (n = 2)

Compound	C (%)	H (%)	N (%)
I			
Found			
A	68.03	7.02	7.49
B	68.14	7.10	7.51
Calculated	68.09	7.07	7.56
II			
Found			
A	66.65	7.34	6.71
B	66.65	7.26	6.71
Calculated	66.65	7.30	6.76

Note. solvent A = precipitation of salt made in ethanol; solvent B = precipitation of salt made in a mixture of acetone and water (98 + 2).

metoprolol tartrate, gave one sharp DSC endotherm (20,21).

The XRPD patterns (Fig. 3) confirm the crystallinity of the products similarly to those of the starting materials. The x-ray diffractograms of the precipitates differed clearly from those of the starting materials, acids and base. The precipitates formed in different media had quite similar x-ray diffractograms, but the relative degree of crystallinity was somewhat higher for both precipitates formed in a mixture of acetone–water. The XRPD patterns obtained also showed that two new crystalline compounds were formed in the syntheses described. This result complements the results from the DSC studies. Different solvents and processes for precipitation can produce crystalline products with different physicochemical properties of, for example, one and the same salt. This indicates that the formation of organic salts must be studied using samples in the solid state where the salt structure exists.

The two precipitates formed showed absorption by FT-IR typical of carboxylic acid salts at about 1640–1540 cm^{-1} where the carboxylic acid salts display their carboxylate bands (Fig. 4). The carbonyl absorption indicative of the carboxylic acid group of benzoic acid or 2-methoxyphenylacetic acid was not detectable in the spectra of the precipitates. These results in IR studies suggest a salt character for the two products prepared. The structure of carboxylic acid salt (the carboxylate anion) was also seen at 1580 cm^{-1} in the IR spectrum of metoprolol tartrate (20). The precipitates formed in different media had similar IR spectra.

In this study on organic salt formation, different types of analytical methods were used. The results indicate that besides the stoichiometry, solving chemical analytical methods, the structure, and also the proper-

Table 2

Onset Temperature and Enthalpic Change of Pindolol, Benzoic Acid, 2-Methoxyphenylacetic Acid, Pindolol Benzoate and Pindolol 2-Methoxyphenylacetate (n = 3)

Compound	Onset (°C)	*SD*	°H (J/g)
Pindolol	169.8	0.01	249.0
Benzoic acid	121.8	0.01	143.5
2-Methoxyphenylacetic acid	122.2	0.04	144.3
Pindolol benzoate			
A	186.4	0.10	163.4
B	186.3	0.20	158.4
Pindolol 2-methoxyphenylacetate			
A	153.9	0.30	138.5
B	154.7	0.30	141.3

Note. solvent A = precipitation of salt made in ethanol; solvent B = precipitation of salt made in a mixture of acetone and water (98 + 2).

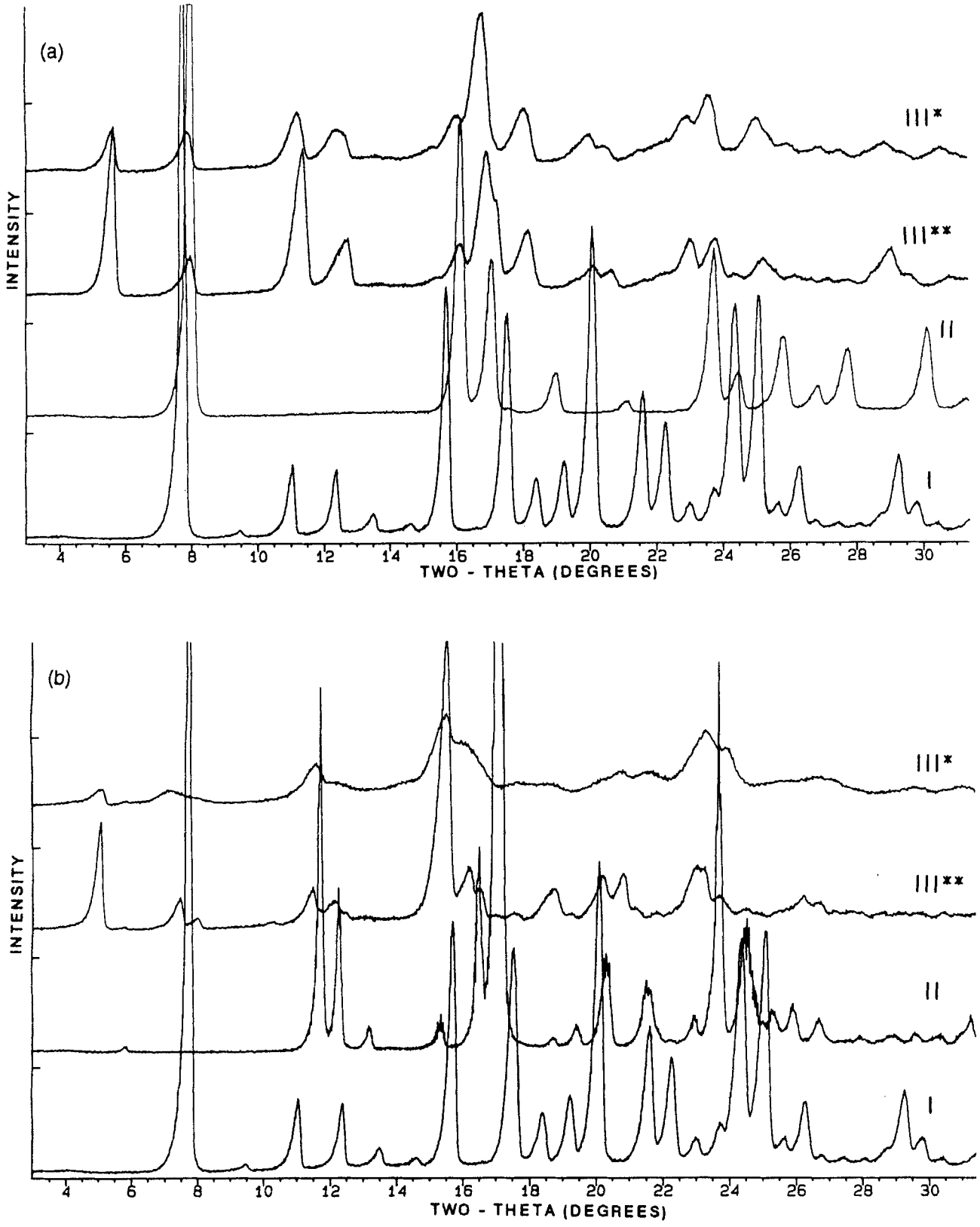
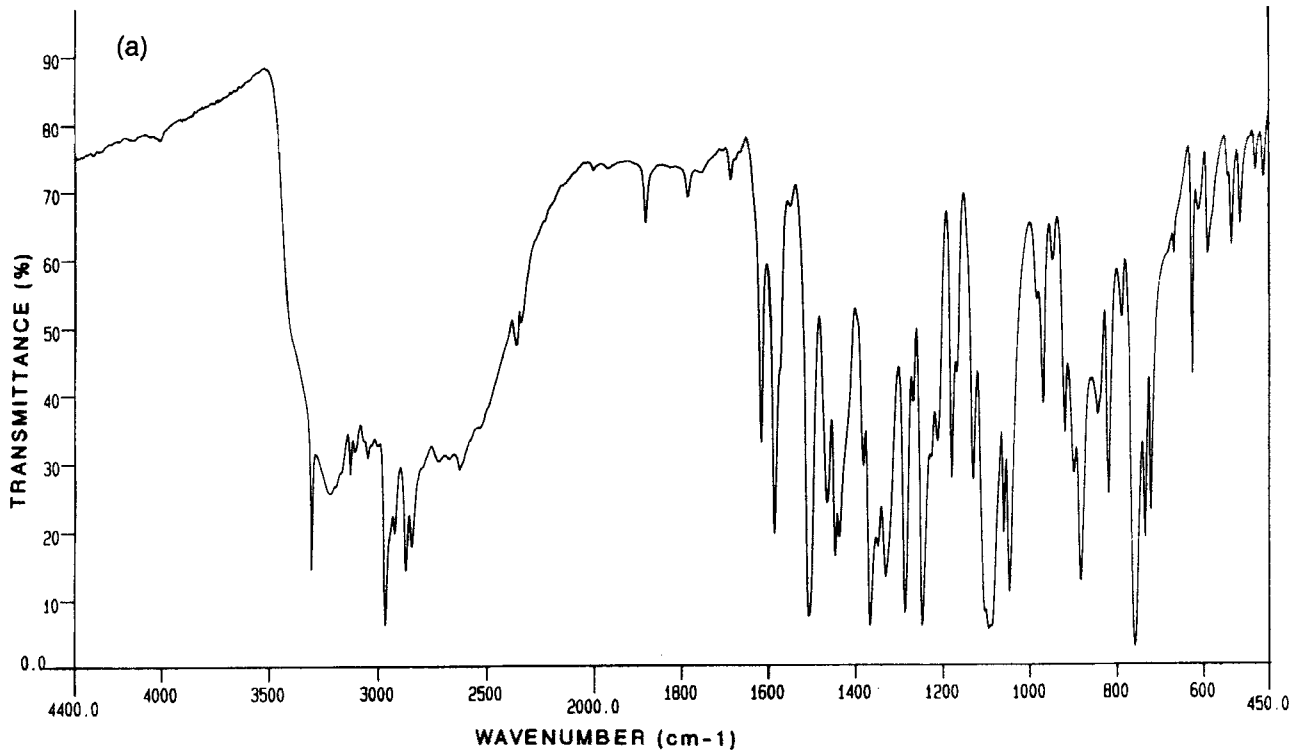


Figure 3. (a) XRPD patterns of pindolol (I), benzoic acid (II), and pindolol benzoate [III* (formed in solvent A); III** (formed in solvent B)]. (b) XRPD patterns of pindolol (I), 2-methoxyphenylacetic acid (II), and pindolol 2-methoxyphenylacetate [III* (formed in solvent A); III** (formed in solvent B)].



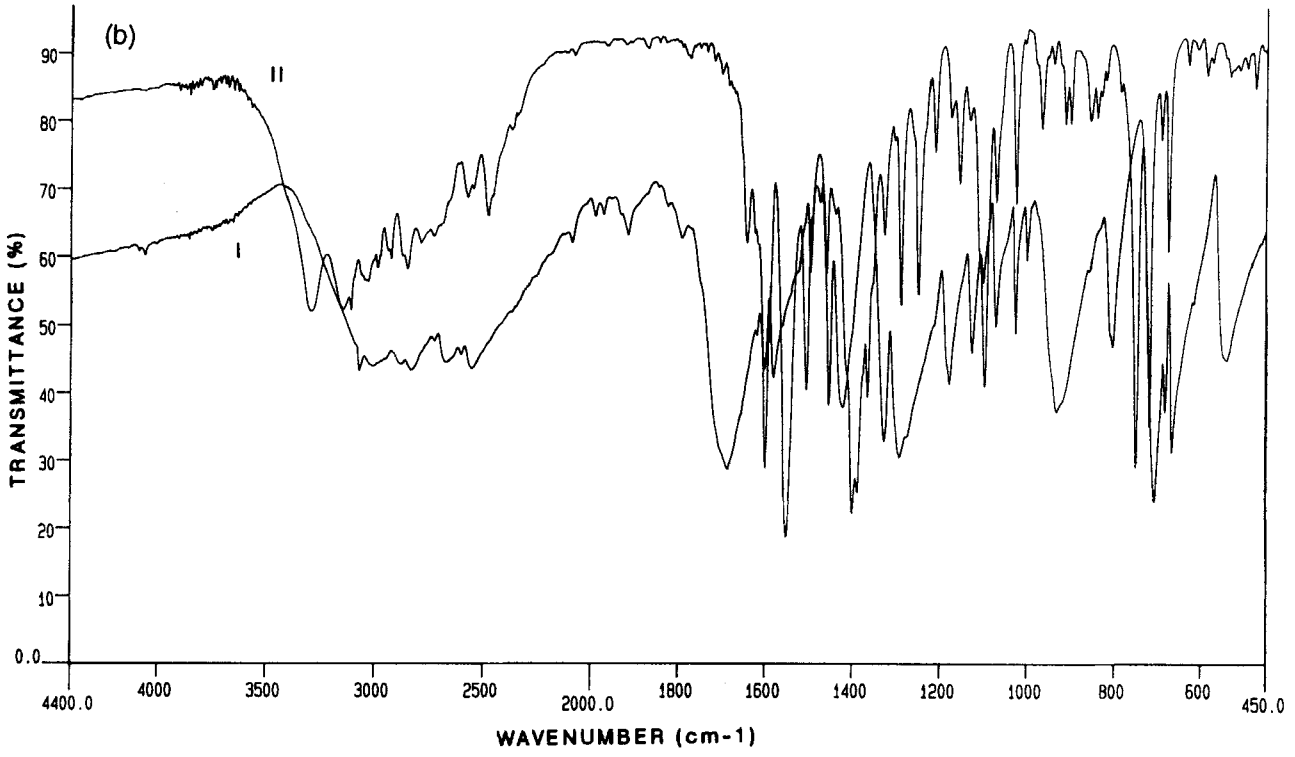


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Figure 4. (a) FT-IR spectrum of pindolol. (b) FT-IR spectrum of benzoic acid (I) and pindolol benzoate (II) (formed in solvent A). (c) FT-IR spectrum of 2-methoxyphenylacetic acid (III) and pindolol 2-methoxyphenylacetate (IV) (formed in solvent A).

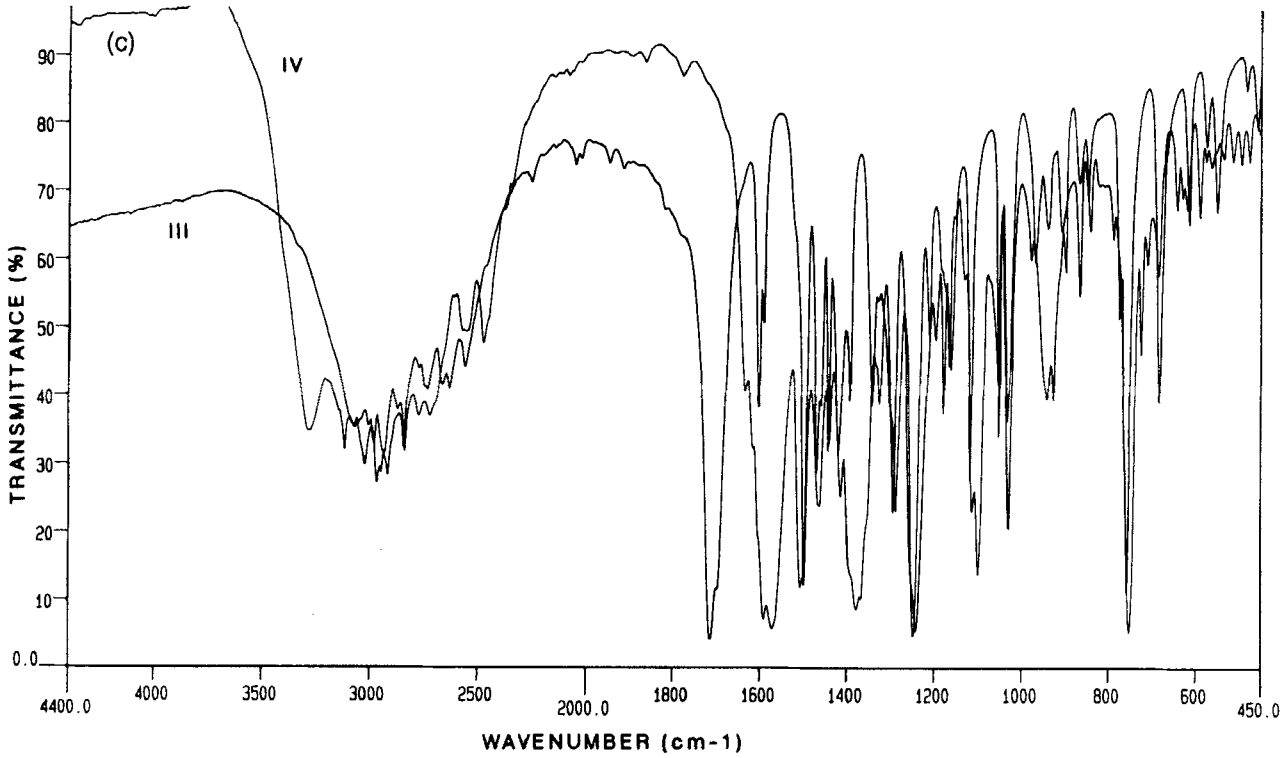

Figure 4. Continued

ties of organic salts must be established by physical methods by which the substances can be compared in the solid state in which the salt structure exists.

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