

Crystal Polymorphism of Pramocaine and Pramocaine-HCl

A.C. Schmidt, N. Senfter, U.J. Griesser

Institute of Pharmacy, Dept. Ph. Technology, University of Innsbruck

Pramocaine (PRC) is a local anaesthetic drug developed 1959³ with very good effectiveness against pruritus and pain on anorectal inflammations. The compound is official in the USP XXIII as the hydrochloride (**PRCHC**). The free base (**PRC-base**) is a liquid at room temperature and was reported to exist in two polymorphic forms below 25°C². No polymorphism has been reported about the hydrochloride so far, which was found to exist in three polymorphic forms. The forms have been characterized by thermomicroscopy, differential scanning calorimetry (DSC), pycnometry, FTIR- and FT-Raman-spectroscopy as well as X-ray powder- and single-crystal X-ray diffractometry and their relative thermodynamic stability was determined.

PRCHC: Modification II (mod. II) is the thermodynamic stable form at room temperature. This form is present in commercial products and crystallizes from ethanol. Mod. I and III are thermodynamically unstable at room temperature and cannot be obtained by crystallization from solvents. Mod. II exhibits an endothermic phase transition with a relatively high transition enthalpy ($\Delta_{\text{trs}}H_{\text{II-I}}$: $9.7 \pm 0.2 \text{ kJ mol}^{-1}$) at about 90°C into mod. I (T_{fus} : 171°C, $\Delta_{\text{fus}}H_{\text{I}}$: $28.8 \pm 0.6 \text{ kJ mol}^{-1}$). At about 80°C the retransformation to mod. II can be observed. According to the heat of transition rule³ the two modifications are thus enantiotropically related. On cooling of mod. II a transformation to the low temperature form (mod. III) occurs at -27°C which transforms back to mod. II on heating at -21 °C ($\Delta_{\text{trs}}H_{\text{III-II}}$: $4.3 \pm 0.1 \text{ kJ mol}^{-1}$). Hence all forms are enantiotropically related, being mod. II the stable form between -24 and 85°C. Furthermore, the XRPD-investigations indicate an isomorphous relationship between the modifications.

PRC-base: Mod. II (T_{fus} : 12.3°C, $\Delta_{\text{fus}}H_{\text{I}}$: $25.5 \pm 1.6 \text{ kJ mol}^{-1}$) is the thermodynamic stable form at low temperatures. Mod. I crystallizes from the melt (T_{fus} : 23.7°C, $\Delta_{\text{fus}}H_{\text{I}}$: $24.6 \pm 1 \text{ kJ mol}^{-1}$).

This local anaesthetic of the uncommon ether type is an example for conformational polymorphism with a very intriguing isomorphous relationship between the forms.

³ Abbott. U.S. pat. 2,870,151 (1959)

² H. Grimm. PhD Thesis. Innsbruck (1956)

³ A. Burger, R. Ramberger. Mikrochim. Acta II (1979) 259-271