Trimethoprim crystal forms

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Many examples of drug polymorphism have been described (Mewada, Parikh & Somasekhara, 1973; Pearson & Varney, 1973; Bettinetti, Giordano & others, 1974) and research in this direction is stimulated by the way in which different polymorphic forms can affect mechanical and physical characteristics of powders (Conte, Colombo & others, 1975; Kuhnert-Brandstaetter, 1973) and bioavailability (Khalafallah, Khalil & Moustafa, 1974; Shozo, Takaichi & others, 1974).

Trimethoprim (2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine, TMP) is a widely used broad spectrum antibacterial administered in combination with sulphonamides.

We have therefore investigated whether TMP exists in polymorphic forms. TMP was crystallized from various solvents and the crystal forms investigated with infrared spectrophotometry and X-ray diffraction techniques.

The most frequently encountered crystal form of TMP which can be obtained from various common organic solvents and here denoted as form I, is triclinic and shows the following crystal data (Philips PW 1100 computer-controlled four-circles diffractometer, Cu-Kα and Mo-Kα radiation): a = 10·505 Å; b = 10·545 Å; c = 8·057 Å; $\alpha = 100°31'$; $\beta = 112°14'$; $\gamma = 107°26'$; space group P1 or $\bar{P}1$; U = 742·69 Å^3; Z = 2; D_m = 1·305 g cm^{-3}; D_c = 1·300 g cm^{-3}; M = 290·32. This material was crystallized from methanol, mp. 200°.

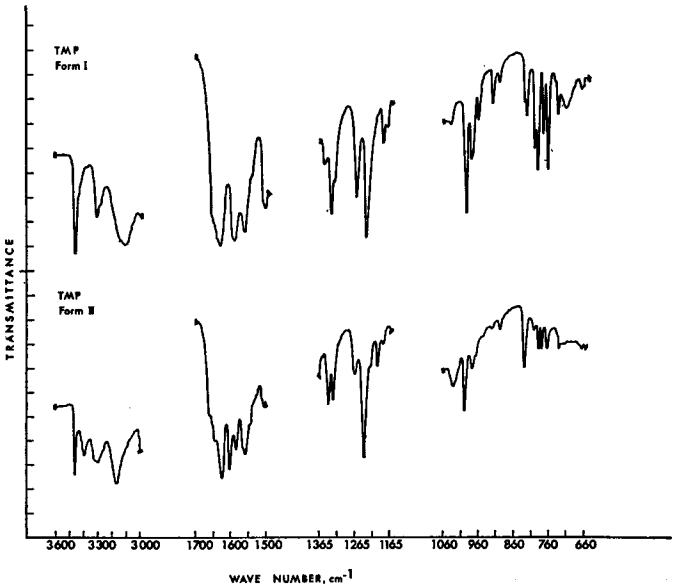
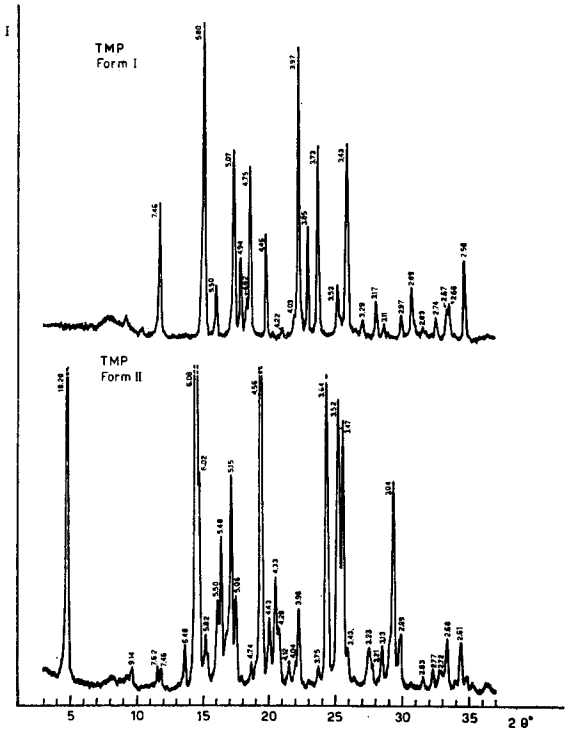


FIG. 1. Main bands of infrared spectra (Nujol mulls) of forms I and II.



2. X-ray diffraction patterns (powder method) of forms I and II.

Preliminary results suggest that TMP can exist as a second polymorph, form II, when crystallized from toluene (or methyl-isobutylketone).

TMP form II is monoclinic and its crystal data are: a = 18·164 Å; b = 6·054 Å; c = 12·900 Å; $\beta = 92°51'$; space group $P2_1/c$; U = 1416·73 Å^3; Z = 4; D_m = 1·362 g cm^{-3}; D_c = 1·361 g cm^{-3}; M = 290·32. Form II changes to form 1 by heating to 170° and consequently has the same melting point, 200°.

Significant differences were also observed in infrared spectra (Perkin-Elmer 421 spectrophotometer; KBr discs and Nujol mulls) and X-ray diffraction patterns (powder method; (Philips PW 1050/25 diffractometer, Cu-Kα radiation) between forms I and II (see Figs. 1 and 2).

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