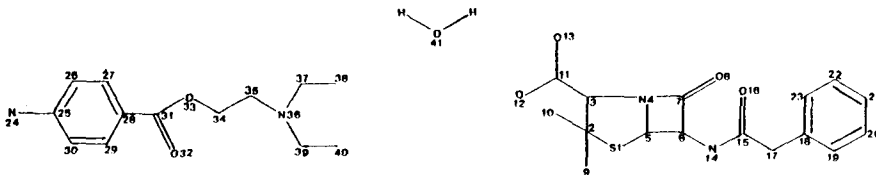


## CRYSTAL STRUCTURE OF PROCAINE BENZYL PENICILLIN MONOHYDRATE

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Procaine penicillin is therapeutically valuable because penicillin is released slowly from the stable and relatively insoluble crystals. To explain the stability of the crystals we undertook a structure determination by X-ray diffraction methods.



We were able to obtain large well-formed crystals from aqueous methanol (Rose, 1955). From Weissenberg photographs and two-circle diffractometer readings we derived unit cell dimensions  $a = 10.70(1)$ ,  $b = 10.42(1)$ ,  $c = 14.41(1)$  Å,  $\beta = 104.74(8)^\circ$ , volume  $1554$  Å<sup>3</sup>, and space group  $P2_1$ , and collected 2962 structure amplitude data. Direct methods revealed three thiazolidine ring atoms, Patterson superpositions yielded a trial structure, and least-squares refinement of the structure has so far reduced the discrepancy between observed and calculated structure factors to  $R = 5.3\%$  (structure LS). Very recently Dexter and van der Veen (1978) published the structure of procaine benzylpenicillin monohydrate crystallised from ethanol, also finding space group  $P2_1$  with a unit cell volume of  $1552.4$  Å<sup>3</sup>, and refining their structure to  $R = 7.3\%$  for 2718 data (structure DV).

Structures LS and DV agree well except for a discrepancy exceeding  $30\sigma$  in the  $y$ -coordinate of O(12), which we attribute to a typographical error in the DV paper. Hydrogen bonds N(36)-H...O(12) between procaine and penicillin, O(41)-H...O(12) joining water and penicillin, N(24)-H...O(41) between procaine and two water molecules, and N(14)-H...O(13) joining adjacent penicillins, create a firmly linked structure and contribute to the relatively low solubility as suggested by DV.

Patented methods for preparing procaine penicillin use solvents as polar as water (Sumner & Grenfell, 1955) and as nonpolar as butyl acetate (Bardolph, 1956). It would be reassuring to know that the material precipitated from the various solvents is identical. This hypothesis can be tested for the polar methanol-water and the less polar ethanol by constructing a half-normal probability plot (Abrahams & Keve, 1971) from the coordinate data of LS and DV. Such a plot gives a straight line of slope 1.7. The most reasonable interpretation is that the errors in both structure determinations have been somewhat underestimated but the crystalline material is indeed the same.

We thank Glaxo for the sample, the SRC Microdensitometer Service for film evaluation, and Dr T.A. Hamor for diffractometer time.

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