

THE STABILITY OF SALSALATE IN OCTANOL SOLUTION

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As part of a bioavailability study, it was required to find a 1-octanol-soluble drug which could be administered and detected at a low enough concentration to cause no harmful pharmacological effects. Preliminary reading and experiments indicated that salsalate (salicyl salicylate) fitted these criteria, but when precise solubility determinations were attempted, the uv spectrum changed with time. It was suspected that transesterification to octyl salicylate was taking place, and the subsequent investigation is described below.

A sample of octyl salicylate was prepared by direct room temperature esterification of salicylic acid with octanol in the presence of dicyclohexyl carbodiimide and 4-dimethylaminopyridine (Hassner and Alexian, 1978). Distillation at 5 mm yielded a fraction at 120° which gave mass, nmr and ir spectra consistent with octyl salicylate. This was submitted to glc on a 6 ft column of $\frac{1}{8}$ in diameter glass containing 3% OV-17 on acid washed dimethyldichlorosilane Chromosorb W, 80-100 mesh, programmed from 140 to 300° at 20° min⁻¹. The chromatogram gave a single major peak plus a minor (4%) octanol peak. The fraction, corrected for the octanol impurity, was used to construct a calibration curve for octyl salicylate. 1.5% solutions of salsalate in octanol were stored at room temperature and 100°, and aliquots removed from time to time. These gave glc peaks corresponding to octyl salicylate, and were used to assess the rates of reaction. Rectilinear log plots of octyl salicylate concentration against time were obtained at 100°, giving a half life of 3.6 h. The results at room temperature suggested a half life of 7 to 8 days. The uv spectra corresponded to those obtained with synthetic mixtures of salsalate, octanol and octyl salicylate.

The fact that salsalate, whose ester group is protected by bulky substituents, reacts so rapidly suggests that transesterification may be commonplace in solutions of esters in octanol, and the observed half lives indicate that within the period of time required to measure a partition coefficient, an ester solute could change its identity considerably.

Hassner, A. and Alexian, V. (1978). *Tetrahedron Letters* 46 4475-4478

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