

Cortisone acetate crystal forms

SIR,—Different crystalline forms of cortisone acetate have been distinguished by several workers (see Table 1). Unfortunately the various methods used to investigate them have often prevented correlation with previous work, so that a single form may have received several different designations. This is exemplified by the hydrated form recently described by Carless, Moustafa & Rapson (1968a, b) as form IV*, apparently on the basis of similarities between its infrared spectrum and that of their form IV. In fact, examination of this spectrum (Moustafa & Rapson, personal communication) showed it to be identical with that of a form described as form VI (Mesley, 1966), the X-ray diffraction pattern of which agrees with one listed in the X-ray Powder Data File as form γ (card 10-559) and with form V of Williams (1961) and form 5 of Majek (1951, 1954). The method of preparation and the rather sparse X-ray data given by Magerlein, Dale & Wachtel (1958) for their form A suggest that this again is the same form, although this is denied in the patent specification. Table 1 represents an attempt to correlate all those forms about which data have been published.

TABLE 1. CRYSTAL FORMS OF CORTISONE ACETATE PREVIOUSLY REPORTED

a	b	c	d	e	f	g	Solvent
I	III	III	α	2	II		—
II	II	II	β	1	I	B	—
III	I	I		3		C	—
IV	IV	IV	E				ethanol
IV*		VI	γ	5	V	A	water
V	V	V	F				methanol
		VII					tetrahydrofuran/water?
		VIII	δ				dimethylacetamide
					VI		acetone
					VII		dimethylformamide

Notes

- a Carless, Moustafa & Rapson (1966, 1968a).
 b Callow & Kennard (1961).
 c Mesley & Johnson (1965); Mesley (1966).
 d X-ray Powder Data File (methods of preparation of E & F transposed).
 e Majek (1951, 1954).
 f Williams (1961).
 g Magerlein, Dale & Wachtel (1958).
 Other solvated forms have been obtained from methyl ethyl ketone, n-propanol, isopropanol, glacial acetic acid, dioxan and diethyl ether (Kuhnert-Brandstätter & Grimm, 1968).

It is generally accepted that many of these forms contain solvent and are therefore not strictly polymorphic modifications. Recently, however, Kuhnert-Brandstätter & Grimm (1968) have prepared a large number of solvated forms and have disputed earlier results relating to some of them. In particular they claim that forms IV and V, stated by Callow & Kennard (1961) and by Carless & others (1966) to be hydrated, in fact contain ethanol and methanol respectively, and that form III of the latter workers (Callow's form I) is a hydrate. The assertions regarding forms IV and V appear to be correct: these forms have been prepared using anhydrous ethanol and methanol respectively, and the vapours evolved on heating have been examined by infrared spectroscopy, using a multi-reflection gas cell of one metre pathlength; in each instance the vapour was found to be the pure alcohol. The molecular weight and elemental composition quoted by Callow & Kennard (1961) would be consistent with one molecule of solvent per molecule of cortisone acetate in each form.

The statement by Kuhnert-Brandstätter & Grimm (1968) that form III is a hydrate, apparently based solely on the evolution of bubbles when the crystals were heated in silicone oil, cannot be supported. This form has been prepared

by recrystallization from 30% water in acetone, giving a product with an infrared spectrum identical with that of Carless & others (1966) and an X-ray pattern agreeing with that of Callow & Kennard (1961). Differential scanning calorimetry confirmed the findings of Carless & others in showing no transition consistent with evolution of water; a small, very broad, endothermic transition below 55°C was confirmed by infrared examination of the vapour as being due to removal of traces of acetone from the surface of the crystals (there was no evidence for the presence of the acetone solvated form in this sample).

Several other solvated forms have been prepared, and found to agree with previously published data. However the material obtained by recrystallization from, or evaporation of, a tetrahydrofuran solution is apparently different from that reported by Kuhnert-Brandstätter & Grimm (1968). These workers reported infrared absorptions due to OH and C=O groups at 3375, 1750, 1725 and 1708 cm^{-1} , whereas our material, previously designated form VII (Mesley, 1966) had absorptions at 3290, 1739, 1724 and 1701 cm^{-1} . In addition, when obtained by evaporation of tetrahydrofuran solution in a current of air, a peak at 3640 cm^{-1} was present; this frequency is improbably high for an organic hydroxyl group in a crystalline solid, and is attributed to inclusion of water molecules in a clathrate type of structure. Whether this form also contains tetrahydrofuran has not been established with certainty.

It was noted during this work that some of the solvated forms were unstable after grinding with liquid paraffin. In particular the forms obtained from acetone, tetrahydrofuran and isopropanol solutions, when examined as Nujol mulls, showed spectral changes over a period of 30 min or less. This phenomenon has been observed occasionally with other polymorphic substances, but despite this the Nujol mull method is still considered to be preferable to the alkali halide disc method for examining polymorphic substances.

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