identical with that of reference anabasine. The m.p. (204–206°) and the mol. wt (620·06—by non-aqueous titration) of the dipicrate furnished a further evidence of the alkaloid identity. The presence of nicotine in the plant was confirmed by its identical R_F values on t.l.c. (Table 1) with that of reference nicotine.

Literature review has indicated that this is the first report on the occurrence of nicotine in the genus Haloxylon and most likely within the Chenopodiaceae.

The percentage of total alkaloids in the powdered dried plant was determined by non-aqueous titration (B.P. 1973) and found to be 5·4% (calculated as anabasine).

The alkaloidal content of this plant which is mostly anabasine (as shown by fractional distillation) is therefore very much higher than those reported for the other plants used as commercial sources of anabasine such as *Anabasis aphylla L.* which contains 0·62–1·3% anabasine, used in the U.S.A. (Smith, 1935; Webb, 1948). Moreover, the plant is widely distributed throughout the Kingdom of Saudi Arabia. It is a large shrub that attains a height of 2 m and is of very low moisture content. All the alkaloidal bases of the plant were obtained by steam distillation and these are most probably of the same chemical class.

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Anomalous behaviour of some hydroflumethiazide crystal samples

During an investigation of the dissolution properties of thiazide diuretics anomalous dissolution properties of four samples of hydroflumethiazide were observed. The samples were prepared as follows:

(i) hydroflumethiazide was dissolved in heated acetone, the solvent was allowed to slowly evaporate at room temperature (20°) and the material was then dried at 37°;
(ii) excess hydroflumethiazide was dissolved in boiling absolute ethanol, filtered, allowed to crystallize at 45° and the crystals produced harvested and dried at 45°;
(iii) hydroflumethiazide was dissolved in absolute ethanol, filtered, rapidly cooled to 2–3°, the needle crystals thus produced were harvested and dried at 100°;
(iv) hydroflumethiazide was dissolved in absolute ethanol, filtered, rapidly cooled to 2–3° and the needle crystals thus obtained were dried at room temperature under a vacuum of 1 mm Hg for 24 h, and stored in a dessicator containing silica gel.

Infrared spectroscopy (Perkin-Elmer 157 NaCl Infrared Spectrophotometer), elemental analysis and chemical assay failed to indicate differences between crystals prepared by methods (i), (ii) and (iii). X-ray powder diffraction patterns (Phillips PW 1050/25) obtained using nickel filtered copper radiation indicated minor differences in line intensities between samples prepared by methods (i) and (ii). Samples prepared by method (iii) exhibited similar peaks but of lower and differing intensities. The differences observed between samples prepared by methods (i), (ii) and (iii) were not sufficient to indicate polymorphism.

Infrared and X-ray diffraction patterns of crystals prepared by method (iv) were different from each of the other samples. Distinct differences in infrared spectra were observed in the high frequency N–H stretching region between 3000 cm^{-1} and 3500 cm^{-1}, in the C–C stretching region around 1600 cm^{-1} and in the 1500 cm^{-1} to 1540 cm^{-1} region. The X-ray diffraction pattern of crystals prepared by method (iv) before and after exposure to air is shown in Fig. 1. It is evident that this sample is unstable and in the presence of air converts to crystals similar to those prepared by method (iii). Elemental analysis, chemical assay and estimation of alcohol content by gas chromatography (Perkin-Elmer FII) indicated that sample (iv) is a 1:1 alcoholate of hydroflumethiazide. The converted crystals, similar to those prepared by method (iii), were found to contain 0·6–0·7% ethanol.

Intrinsic dissolution rates for each sample were determined using the beaker method of Levy & Procknal (1964). Weighed quantities of each sample were compressed into discs (13 mm diam. at 375 MN m^{-2}) under vacuum in a hydraulic punch die assembly (RIIC Hydraulic Press C30). The dissolution profiles, obtained in 0·1N HCl at 37° (stirring speed 59 rev min^{-1}), appeared non-linear in all cases during the first 20 min, despite the fact that sink conditions operated. The initial intrinsic dissolution rates are listed in Table 1.

Solubilities of each sample were determined using a method similar to that of Shefter & Higuchi (1963). Samples (iii) and (iv) showed peak solubilities after about 2 min, the solubility then decreasing with time to that of sample (ii) indicating conversion to this form. The rate of transformation was greater with crystals prepared by method (iv). The peak solubilities obtained for samples (iii) and (iv) together with the

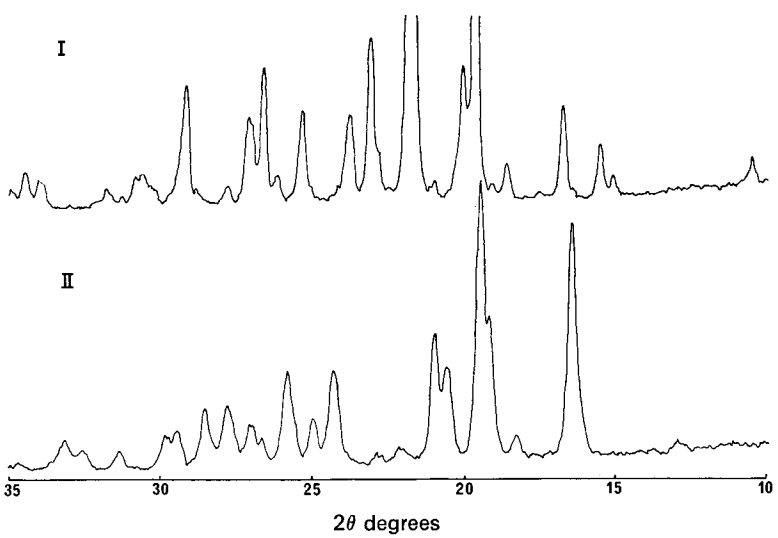

FIG. 1. X-ray diffraction patterns: I sample of hydroflumethiazide alcoholate; II same sample following exposure to air.

Table 1. *Initial dissolution rate and maximum solubility for hydroflumethiazide samples in 0·1N HCl at 37°.* All values are the means of 3 or more determinations. All values were within ±2·5% of the mean.

Sample	Dissolution rate mg cm^{-2} h^{-1}	Solubility mg ml^{-1}
(i)	2·48	0·538
(ii)	2·83	0·605
(iii)	3·48	0·859*
(iv)	3·27	0·712*

* Represent peak solubilities.

equilibrium solubilities for samples (i) and (ii) are included in Table 1. These solubilities are in rank order agreement with the dissolution data. The crystal transformation observed during solubility determinations of samples (iii) and (iv) is consistent with the non-linearity of the dissolution profiles. However, the non-linear dissolution profiles of samples (i) and (ii) cannot be ascribed to the same cause. Preliminary studies on the relation between solubility and compression pressure indicate that compression may be involved in the non-linearity observed in each case.

Polyvinylpyrrolidone (PVP) has been shown to inhibit crystal growth and phase transformations in suspensions (Simonelli, Mehta & Higuchi, 1970). Solubilities of samples (iii) and (iv) were therefore determined in 0·1N HCl containing 1% PVP at 37°. The presence of PVP prevented the transformation observed with sample (iii) and delayed it with sample (iv). The plateaux solubilities observed were 0·919 mg ml^{-1} and 3·05 mg ml^{-1} for samples (iii) and (iv) respectively. The solubility of the stable form (sample (ii)) in the solution containing 1% PVP was slightly reduced (0·582 mg ml^{-1}), an effect of PVP which has been reported for other drugs (Breuninger & Goettsch, 1965; Gibaldi & Weintraub, 1968). These results indicate that the alcoholate is approximately five times more soluble than the stable form.

In conclusion, it would appear that crystals prepared by methods (i) and (ii) belong to the same polymorphic form, the differences in solubilities being possibly due to crystal imperfection. Pearson & Varney (1973) have recently reported similar effects for batches of oxyclozanide crystals. Crystals prepared by method (iii) appear to be an example of a desolvated crystal species; such species have been reported for other drugs by Pfeiffer, Yang & Tucker (1970). Preparation by method (iv) yields an alcoholate of hydroflumethiazide, which, under normal atmospheric conditions, converts to the desolvated crystal losing all except a small fraction of solvent from the crystal lattice.

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