

## Codeine impurity in ethylmorphine hydrochloride B.P.C.

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Ethylmorphine hydrochloride (I) is the subject of a monograph in the B.P.C. 1973. It should contain not less than 99.0% of  $C_{19}H_{24}ClNO_3 \cdot 2H_2O$  when determined by non-aqueous titration. A limit test for not more than 0.1% morphine is specified. However, limit tests for other alkaloids are not included in the monograph.

Samples of ethylmorphine hydrochloride, complying with official requirements, from three commercial sources in the United Kingdom (Ia, Evans Medical; Ib, Macfarland Smith; Ic, May and Baker) have been found to contain 1 to 5% of codeine (II). The evidence is as follows:—(i) On gas-liquid-chromatography (g.l.c.) the corresponding bases of Ia, Ib and Ic, prepared as described in the B.P.C. (1973), gave two distinct symmetrical peaks with g.l.c. retention times (Rt) of 14.4 and 16.2 min. One of these g.l.c. peaks corresponds in retention time to authentic codeine (Rt codeine 14.4 min; Rt morphine 16.8 min). The samples of I contained 1 to 5% of II when calculated from the relative peak areas (Ia and Ib 5%; Ic, 1%).

On reaction with acetic anhydride in ether the bases of I gave two acetyl derivatives (g.l.c. Rt, 21.0 and 23.7 min), one of which corresponds in g.l.c. retention time to authenticated 6-acetylcodeine (Rt 21.0 min; Rt diacetylmorphine 29.7 min). The following g.l.c. conditions were used: 2 m, 3 mm o.d. glass column, 10% OV1 on Gas-Chrom Q; nitrogen carrier gas, flow rate 60 ml min<sup>-1</sup>; oven temperature 225 °C; injection block temp. 275 °C; Perkin-Elmer F33 gas-chromatograph with a flame ionization detector.

(ii) Mass spectra of the bases of I (solid inlet, 70eV, source temperature 220 °C) exhibited molecular ions of *m/e* 313 corresponding to ethylmorphine (relative intensity 100%,  $[C_{19}H_{23}NO_3]^+$  by accurate mass measurement) and *m/e* 299 ions ( $[C_{18}H_{21}NO_3]^+$  by accurate mass measurement in the bases of Ia and Ib) which indicated the presence of codeine in the samples of I. Authentic codeine exhibited a molecular ion of *m/e* 299 (relative intensity 100%,  $[C_{18}H_{21}NO_3]^+$  by accurate mass measurement). The relative intensity of *m/e* 313 and *m/e* 299 ions in the mass spectra of the bases of I indicated a 5, 4.3 and 1% codeine impurity in Ia, Ib and Ic respectively.

Acetylated bases of I exhibited molecular ions of *m/e* 355 consistent with 6-acetylmorphine (relative intensity 100%,  $[C_{21}H_{25}NO_4]^+$  by accurate mass measurement) and *m/e* 341 ions consistent with 6-acetylcodeine ( $[C_{20}H_{23}NO_4]^+$  by accurate mass measurements in the acetylated derivatives of sample Ia and Ib). The mass spectra of authenticated 6-acetylcodeine exhibited a molecular ion of *m/e* 341 (relative intensity 100%,  $[C_{20}H_{23}NO_4]^+$  by accurate mass measurement).

(iii) Samples of I in ethanol were examined on 0.3 mm thick Silica Gel G F<sub>254</sub> coated t.l.c. plates (solvent

system, ammonia-benzene-dioxan-ethanol, 5:50:40:5). After development compounds were visualized by Dragendorff's reagent and u.v. light (254 nm). On t.l.c. all samples of I gave a single tailing spot of *R<sub>F</sub>* 0.49 (*R<sub>F</sub>* authentic codeine 0.41). After preparative t.l.c. (samples Ia and Ib) the band corresponding to codeine was scraped off, extracted with acetone and after concentration the extract re-examined on t.l.c. On t.l.c. the concentrated extract gave two distinct spots (*R<sub>F</sub>* 0.41 and 0.49) one of which corresponded to authentic codeine. Clark (1969) gives *R<sub>F</sub>* values of 0.39 and 0.46 for codeine and ethylmorphine respectively in this solvent system. G.l.c. evidence indicated that preparative t.l.c. had resulted in a mixture of approximately equal amounts of codeine and ethylmorphine.

Single recrystallizations of the samples of I and their corresponding bases from various solvents and treatment with absorbents did not reduce significantly the percentage of codeine. However repeated recrystallizations of ethylmorphine base (from sample Ic) from water eventually (5 recrystallizations) gave a sample of ethylmorphine containing less than 0.1% of codeine impurity (g.l.c. evidence). The melting point of the purified ethylmorphine and the bases of Ia, Ib and Ic were similar (ca 84–85 °C). Consequently the melting point of ethylmorphine cannot be used as a criterion of purity.

Since ethylmorphine is synthesized from morphine which does not contain codeine (Boerner et al 1974), the presence of codeine as an impurity in ethylmorphine hydrochloride is most probably attributable to an impure ethylating agent.

Ethylmorphine has been used as a standard for enzymatic *N*-demethylation in liver homogenates (George & Tephly 1968), and as a standard in the quantitative determination of other phenanthrene alkaloids (Smith & Cole 1975). As a standard for enzymatic demethylation and for the quantitative determination of codeine a 5% codeine impurity in ethylmorphine is unsatisfactory.

Since all the samples of ethylmorphine hydrochloride examined comply with official requirements (B.P.C. 1973), but contain varying amount of codeine, it is necessary to include a limit for codeine in official monographs.

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### REFERENCES

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