PHOLCODINE TARTRATE AND RELATED SALTS

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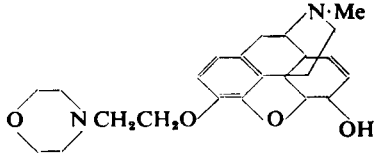
Pholcodine gives stable hydrated salts, crystallisable from water, with a series of dibasic hydroxy acids, the most important salt being the tartrate. The preparation and analysis of these salts is described.

PHOLCODINE, 3:2′-morpholinoethylmorphine (I), is a cough suppressant[1], and is described in the 1957 Supplement of the British Pharmaceutical Codex. Though soluble in dilute acids it is sparingly soluble in water. It would often be convenient in the manufacture of formulations of pholcodine to have it available as a stable crystalline salt.

Pholcodine salts of most acids are so very soluble in water that they cannot be crystallised from aqueous solution; the sulphate, for instance, is soluble in 1·5 parts of water at room temperature[2]. The formation of salts *crystallisable from water*[3], now described, appears to be confined to one particular class of organic acids of general formula (II): of especial



(I)

$$HOOC{\cdot}(CHOH)_n{\cdot}COOH$$

(II)

interest in this class are tartronic acid ($n = 1$) and tartaric acid ($n = 2$); the higher members of the class are di-acids derived from sugars, e.g., mucic acid ($n = 4$), and are not so readily available. Oxalic acid ($n = 0$), which might perhaps be considered in this class, also gives a crystalline salt with pholcodine, but this oxalate is much more soluble in water than are the other members of the series; moreover, oxalic acid is a poison and pholcodine oxalate is thus of no practical importance.

The salts may be readily prepared by dissolving pholcodine base in an equivalent amount of a 50 per cent aqueous solution of the appropriate acid at 50–70° and collecting the salt which crystallises on cooling. The salts so prepared contain two molecules of acid per molecule of base and are hydrated. Air-drying to constant weight at 35–40° affords the trihydrate with the tartrate and the tetrahydrate with the tartronate, though indefinite forms containing less water of crystallisation have been obtained on drying at higher temperatures or over a desiccant. These salts on heating dissolve in their own water of crystallisation, thus appearing to melt. They decompose when heated at 100°.

EXPERIMENTAL

Preparative

Pholcodine tartronate was prepared by dissolving pholcodine (21 g.) in aqueous tartronic acid (25 ml. of 50 per cent w/v) at 60°, stirring, and allowing the homogeneous solution to cool. After recrystallisation from water and air-drying at 35–40°, the tartronate (about 25 g.) had an apparent m.p. of 60–65°. (Found: C, 48·3; H, 6·5; N, 3·75, $C_{23}H_{30}O_4N_2$, $2C_3H_4O_5$,$4H_2O$ requires C, 49·0; H, 6·5; N, 3·95 per cent). It lost on drying *in vacuo* 9·9 per cent of its weight ($4H_2O$ requires 10·15 per cent). The tartronate tetrahydrate formed as colourless needles, stable to light, which, in the open, slowly absorbed a small variable amount of water (depending on ambient temperature and humidity).

Pholcodine tartrate similarly prepared apparently melted at about 85°. (Found: C, 49·4; H, 6·4; N, 3·9. $C_{23}H_{30}O_4N_2$,$2C_4H_6O_6$,$3H_2O$ requires C, 49·5; H, 6·4; N, 3·7 per cent). It lost 7·2 per cent of its weight on drying *in vacuo* ($3H_2O$ requires 7·2 per cent). Solubility of the colourless needles in water at 20° is about 1 in 8. It has $[\alpha]_D^{20}$–33° ($c = 1$ in water) and the pH of a 0·1 M solution in CO_2-free water is 3·1–3·5. The ultraviolet absorption of an aqueous solution shows a maximum at 283 mμ, ($\epsilon = 1650$); this corresponds well with the known value for the base. It may be obtained anhydrous by drying for seven hours over P_2O_5 at 78° and 2 mm. Hg pressure; it then has m.p. 120–122° (sealed capillary) and is hygroscopic.

Pholcodine mucate was less readily obtained. The base (7·5 g.) and mucic acid (7·6 g.) were dissolved in water (11 ml.) by warming to 75°, and the mixture was allowed to cool; the salt crystallised slowly over several days. It was best recrystallised from 50 per cent aqueous ethanol. Drying at 40° over phosphorus pentoxide in a vacuum desiccator gave the monohydrate of m.p. 133–135° (with decomposition). (Found: C, 49·4; H, 7·15; N, 3·25. $C_{23}H_{30}O_4N_2$, $2C_6H_{10}O_8$,H_2O requires C, 50·25; H, 6·15; N, 3·35 per cent).

Analytical

Determination of pholcodine base. The salt (about 0·5 g.) accurately weighed, is dissolved in water (20 ml.) and dilute ammonia solution added until the mixture is distinctly alkaline to litmus. The liberated base is then completely extracted with six 25-ml. portions of chloroform, each extract being washed with the same 5-ml. portion of water. The chloroform is evaporated, the residue dissolved in 95 per cent ethanol (5 ml., previously adjusted to pH 4·8) and the ethanol removed by evaporation. The residue is dried at 105° for 15 minutes and dissolved in 0·1N sulphuric acid (50 ml.). The excess of acid is titrated potentiometrically with 0·1N sodium hydroxide (the end point being near pH 4·8). Each ml. of 0·1N sulphuric acid is equivalent to 0·01993 g. of $C_{23}H_{30}O_4N_2$.

Alternatively a spectrophotometric method of assay may be used. Thus, e.g. anhydrous pholcodine tartrate (about 25 mg. accurately weighed) is dissolved in water and diluted to 100 ml. The extinction of

the solution is determined in a 1-cm. cell at 283 mμ. The E (1 per cent, 1 cm.) of the anhydrous salt at 283 mμ is 24·6.

Determination of moisture content. The salt is dried to constant weight in a "drying pistol" at 78° at a pressure not exceeding 5 mm. The value thus obtained is reproducible; that obtained by drying at 105° is affected by the decomposition of the salts.

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References

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