

## Derivatives of orotic acid as potential reagents for the alkali metals

There are few satisfactory reagents for the precipitation of the alkali metal ions and even fewer which have any real degree of selectivity within the alkali metal group. The double uranyl acetate reagents have many advantages for the selective precipitation of sodium, but lack high sensitivity. 5-Benzaminoanthraquinone-2-sulphonic acid<sup>1</sup> has an unusually high sensitivity towards sodium ions but no selectivity. Other organic reagents, such as dihydroxytartaric acid<sup>2</sup> and lithium tetra-*p*-tolylborate<sup>3</sup>, are somewhat limited in their application. This situation lends general interest to the reactions of the pyrimidine derivative, uracil-4-carboxylic acid, otherwise known as orotic acid, which has recently been recommended by SELLERI AND CALDINI<sup>4</sup> as a precipitant for sodium and potassium. These workers have established the optimal conditions for the quantitative precipitation of these ions from solutions of their salts using as reagents the alcohol-soluble dialkylethanolammonium salts of orotic acid. The precipitations are done in a strongly methanolic or ethanolic medium (about 80%, v/v); this lowers the solubility of the sodium and potassium orotates to a suitable level for quantitative work. The advantages claimed for these orotate reagents are: (i) no interference from lithium, the alkaline-earth metals, iron (III), aluminium, cobalt, copper and nickel; (ii) the determinations can be done on solutions of a wide range of common salts containing sodium and potassium including phosphates, thiosulphates, oxalates, and tartrates; and (iii) the ammonium ion does not interfere under the prescribed conditions.

These important aspects of orotic acid as an alkali metal precipitant have led in the present work to a study of the behaviour of a number of other pyrimidines related to orotic acid in order to establish whether these new compounds show improved characteristics with respect to the precipitation of the alkali metal ions. An increase in both sensitivity and selectivity would be particularly desirable for the wider application of this type of reagent in alkali metal analysis.

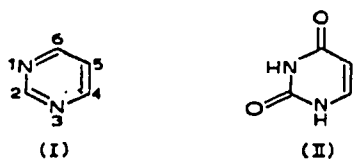
Of the other alkali metals, SELLERI AND CALDINI mention only lithium as a non-interference in the precipitation of sodium and potassium when operations are done in an aqueous medium. A qualitative examination of the behaviour of the dimethylethanolammonium orotate reagent towards solutions of Li<sup>+</sup>, Na<sup>+</sup>, K<sup>+</sup>, Rb<sup>+</sup> and Cs<sup>+</sup> indicated that the reagent lacked any useful degree of selectivity and could probably be used for the determination of the last two ions. During the course of the present investigation, BABBIE AND WAGNER<sup>5</sup> actually described the use of the dimethylethanolammonium salt in methanol for the quantitative precipitation of rubidium and caesium, which conclusively indicates the completely unselective behaviour of these orotic acid reagents.

In the present study, several derivatives of orotic acid and other related compounds have been synthesised in order to establish whether or not substitution in the orotate molecule would give rise to a new series of more selective reagents.

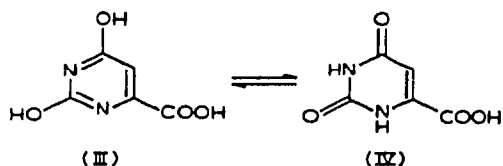
In view of the differences which exist in the numbering of the pyrimidine ring system, the following convention for pyrimidine (I) has been used.

On this basis, uracil (II) is 1,3-dihydro-2,6-dioxypyrimidine and orotic acid is 2,6-dihydroxypyrimidine-4-carboxylic acid (III), the oxo-form, uracil-4-carboxylic acid (IV) predominating in neutral aqueous solution.

The orotic acid derivatives which have been examined can be divided into two



main groups: (a) the N-substituted orotic acids and (b) the C<sub>5</sub>-substituted orotic acids. In addition, the isomeric uracil-5-carboxylic acid has also been studied. These



compounds have in general been prepared both by total synthesis and by appropriate substitution in orotic acid itself. The latter method has greatest application in the preparation of the C<sub>5</sub>-substituted acids, because the 5-position is not so electron-deficient as the 2-, 4- or 6-positions. Thus the 5-position is reasonably reactive towards

TABLE I  
REACTIONS OF THE ALKALI METALS WITH PYRIMIDINECARBOXYLIC ACIDS

Compound	NH <sub>4</sub> <sup>+</sup>	Li <sup>+</sup>	Na <sup>+</sup>	K <sup>+</sup>	Rb <sup>+</sup>	Cs <sup>+</sup>
Orotic acid	—	+	+	+	+	+
Uracil-5-carboxylic acid	—	+	+	+	+	+
5-Methylorotic acid	—	—	+	+	+	+
5-Ethylorotic acid	—	—	+	—	—	—
5-Ethoxyorotic acid	—	—	+	+	+	+
5-Isopropylorotic acid	—	—	—	—	—	—
5-Butylorotic acid	—	—	—	—	—	—
5-Phenylorotic acid	—	—	+	+	+	+
5-Phenoxyorotic acid	—	—	+	+	+	—
5-Fluoroorotic acid	—	—	+	+	+	+
5-Chloroorotic acid	—	—	+	+	+	+
5-Bromoorotic acid	—	—	+	+	+	+
5-Iodoorotic acid	—	—	+	+	+	+
5-Nitroorotic acid	—	—	+	+	+	+
5-Aminoorotic acid	—	—	+	+	+	+
5-Benzaminoorotic acid	—	—	+	+	+	+
5-Cyclohexylaminoorotic acid	—	+	+	+	+	+
1-Phenylorotic acid	—	—	—	—	—	—
1-Phenyluracil-5-carboxylic acid	—	—	+	+	—	—
1-Methylorotic acid	—	—	+	+	+	—
3-Methylorotic acid	—	—	+	—	—	—
1,3-Dimethyluracil-5-carboxylic acid	—	+	+	+	—	—
1-Methyluracil-5-carboxylic acid	—	+	+	+	+	—
Uracil-3-acetic acid	—	+	—	—	—	—
5-Methyluracil-3-acetic acid	—	—	—	+	—	—

electrophilic reagents, especially if other electron-releasing groups are also present anywhere in the ring. These acids, in the form of their *N,N*-dimethylethanolammonium salts, were tested qualitatively on solutions of lithium, sodium, potassium, rubidium, caesium and ammonium chlorides. The results of these tests are given in Table I. By a careful observation of the formation of a precipitate, and the time taken for the precipitation to be completed, an approximate indication of the comparative solubilities of the various alkali metal salts can be obtained. With the more promising reagents, absolute measurements of the solubilities of the individual salts have been made; these are given in Table II.

TABLE II  
SOLUBILITIES OF ALKALI METAL SALTS OF VARIOUS PYRIMIDINECARBOXYLIC ACIDS (g/l at 25°)

Reagent	Li		Na		K		Rb		Cs	
	80% <sup>a</sup>	90% <sup>b</sup>	80%	90%	80%	90%	80%	90%	80%	90%
Orotic acid	1.08	0.33	0.08 <sup>c</sup>	0.03 <sup>c</sup>	0.07 <sup>c</sup>	0.03 <sup>c</sup>	0.21 <sup>d</sup>	0.15 <sup>d</sup>	1.55 <sup>d</sup>	0.22 <sup>d</sup>
Uracil-5-carboxylic acid	0.54	0.19	0.08	0.03	0.14	0.06	0.32	0.08	0.63	0.21
5-Methylorotic acid	—	—	0.91	0.26	1.57	0.78	3.47	1.41	2.81	0.85
1-Phenyluracil-5-carboxylic acid	—	—	1.25	0.48	0.46	0.11	—	—	—	—
5-Aminoorotic acid	—	—	0.14	0.08	0.15	0.07	0.34	0.09	—	—
5-Chloroorotic acid	—	—	1.15	0.33	0.65	0.14	1.15	0.20	1.58	0.32
5-Bromoorotic acid	—	—	3.34	0.78	1.09	0.44	1.05	0.26	1.33	0.28
5-Iodoorotic acid	—	—	2.41	1.54	1.44	1.01	1.48	0.86	0.99	0.36

<sup>a</sup> Solubilities in 80% ethanolic solution. <sup>b</sup> Solubilities in 90% ethanolic solution. <sup>c</sup> Solubility in water (25°) is 2.94 g/l for sodium orotate and 2.57 g/l for potassium orotate<sup>1</sup>. <sup>d</sup> Solubility in water (20°) is 5.59 g/l for rubidium orotate, and 30.82 g/l for caesium orotate; in 70% methanol, the corresponding figures are 0.49 and 3.83 g/l, and for 100% methanol, the values are<sup>5</sup> 0.08 and 0.31 g/l.

### Experimental

*Preparation of reagents.* Orotic acid and uracil-5-carboxylic acid were obtained commercially. Full details of the preparation of the other substances are given elsewhere<sup>6</sup>. The reagents were used in the form of their *N,N*-dimethylethanolammonium salts, prepared in the manner described by SELLERI AND CALDINI. Each reagent solution was 0.1 *M* in ethanol (80%, v/v).

*Alkali metal solutions.* Solutions containing 10 mg/ml were prepared by dissolving the appropriate weight of pure, dry alkali metal chloride in water.

*Method of test.* To 1 ml of the aqueous solution of alkali metal chloride, 5 ml of 0.1 *M* reagent solution were added. The solution was mixed thoroughly and examined for formation of a precipitate.

*Determination of solubilities.* Solutions of each reagent (40 ml of 0.1 *M*) (Table II) in ethanol were placed in 100-ml conical flasks and solutions of the appropriate alkali metal chloride (ca. 0.5 g) dissolved in 10 ml of water were added. The resultant precipitates were aged for several hours at 3° and were then filtered off on

sintered glass crucibles. The precipitates were washed 4-5 times with 2-ml portions of 70% ethanol and twice more with 2-ml portions of 95% ethanol. The precipitates were then dried at 105° for 1 h. The composition of the precipitates was determined by ultimate analysis and sulphated ash. In every case, the normal salt was indicated.

An excess of the alkali metal precipitates was suspended in 80 and 90% ethanol in 50-ml stoppered flasks. The flasks were placed in a constant-temperature water-bath at  $25 \pm 0.2^\circ$ . The flasks were thoroughly shaken at intervals and kept under these conditions for at least four days to allow equilibrium to take place. The supernatant liquid in each flask was decanted off and filtered, and a 20-ml aliquot was transferred to a tared evaporating dish. The solutions were evaporated to dryness on a water-bath; the residues were dried in the oven at 105° for 1 h, cooled and weighed. The solubilities of the respective salts were calculated from the weights of these residues.

### Discussion

Very few of the compounds show any useful degree of selectivity or sensitivity in their action towards the alkali metals. However, uracil-3-acetic acid gives a selective reaction with lithium, 5-ethylorotic acid with sodium, and 5-methyluracil-3-acetic acid with potassium. This last reagent is especially interesting because of its ability to distinguish very readily between potassium and rubidium. A serious disadvantage of the use of these three reagents is that precipitation occurs only in solutions containing about 90% ethanol. In fact, the solubilities of their salts in solutions of lower ethanol concentration are far too high for any quantitative analytical use to be possible.

The solubility measurements, together with the observations made during the qualitative precipitation tests, have shown that none of the derivatives of orotic acid is as sensitive as orotic acid itself towards the alkali metals and that substitution in the orotic acid molecule usually results in an all-round increase in the solubility of the corresponding alkali metal salts; any increase in selectivity is gained only at the expense of sensitivity, and this only to an undesirable extent from the standpoint of analytical utility.

Of the reagents that are not substituted orotic acids, uracil-5-carboxylic acid and its derivatives seem to show promise. Uracil-5-carboxylic acid appears to be only slightly inferior to orotic acid for the precipitation of sodium, potassium and rubidium, but should prove rather better for the determination of lithium and caesium. It has the disadvantage of being less readily available than orotic acid.

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Department of Chemistry,  
The University,  
Birmingham 15 (Great Britain)

B. C. LEWIS  
W. I. STEPHEN

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