Simple Syntheses of Isouramil and Isobarbituric Acid†

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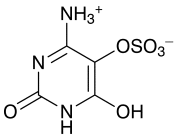
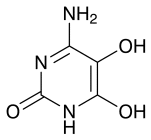
Peroxodisulfate oxidations of uracil and 6-aminouracil followed by hydrolysis led to efficient syntheses of isobarbituric acid and isouramil.

Isouramil (4-amino-5,6-dihydroxypyrimidin-2-one, **II**) is the aglycone of convicine which, together with the aglycone of vicine, are the causative agents of favism.[1,2] These pyrimidines are also reported to have therapeutic effects in the treatment of malaria and cancer.[2]

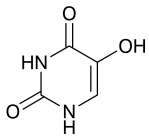
Isouramil has been synthesized by nitrosation of 2,4,5-trihydroxypyrimidine followed by reduction,[3,4] and by condensation of urea with a 2-cyano-2-alkoxyacetic acid ester.[5] The latter route is lengthy and the former requires the relatively expensive isobarbituric acid (*ca.* $50 per g). Hurst[6] attempted the synthesis of isouramil *via* the Elbs oxidation of 6-amino-2,4-dihydroxypyrimidine (*ca.* $1 per g.) He reported that the intermediate 4-amino-6-hydroxypyrimidin-2-one 5-hydrogensulfate **I** failed to give a satisfactory elemental analysis. There were also difficulties in hydrolysis of the sulfate ester.



I



II



III

Modification of Hurst's procedure has led to an easy route to isouramil. The crude sulfate ester **I** was recrystallized to give a product which had the theoretical carbon and nitrogen analyses for the trihydrate; the analysis for hydrogen was unacceptably low. The equivalent weight also suggested a trihydrate. Conversion into the potassium salt, however, yielded material which gave a satisfactory analysis. Hydrolysis of **I** to isouramil **II** cannot be carried out as usual in hot aqueous HCl because of concomitant hydrolysis of the amino group.[3] Zav'yalov and Pokhvisneva[7] reported success by using concentrated HCl at room temperature for the related pyrimidine, divicine-5-*O*-sulfonate (2,4-diamino-6-hydroxypyrimidine 5-hydrogensulfate). Isouramil-5-*O*-sulfonate **I** is insoluble in concentrated HCl. However, 48% aqueous HBr dissolves this material easily and gives a good yield of the hydrolysis product, **II**.

I also report an improved route to isobarbituric acid **III** which ought to lower its cost. Elbs oxidations of uracil (*ca.* 20 cents per g) had been previously carried out but with an overall yield of **III** of 9%[8] or without reported yield.[6] If one avoids isolation of the sulfate ester, then **III** can be obtained in crude form in about 50% yield. The impurity is uracil which is difficult to remove by crystallization. However, trituration with aqueous ammoniacal propan-2-ol extracts the uracil. Pure isobarbituric acid can then be recovered from the residue by acidification and recrystallization.

The purity of compounds **II** and **III** was established by agreement of their molar absorption coefficients with literature values.

Experimental

Isouramil-5-O-sulfonate **I**.—2 g (0.016 mol) of 4-amino-2,6-dihydroxypyrimidine (Aldrich) was dissolved in water (20 ml) containing NaOH (1.6 g, 0.04 mol). The solution was cooled on ice and then sodium peroxodisulfate (3.8 g, 0.016 mol) was added in portions over 15 min with stirring. The solution was brought to 22 °C and allowed to stand overnight. The orange solution was cooled on ice and then concentrated HCl (4 ml, 0.048 mol) was added with stirring. The precipitate which formed after a few minutes was filtered off, washed with cold water and then cold 95% ethanol to yield 2.4–2.7 g (55–62%) of crude **I** after air-drying. Crystallization from 50% ethanol yielded colorless needles, mp > 300 °C. Tests for chloride were negative. Titration with KOH gave an equivalent weight of 270 ± 5 (calc. for the trihydrate, 277) (Found: C, 17.4; H, 2.8; N, 14.9. Calc. for $C_4H_5N_3O_6S\cdot 3H_2O$: C, 17.3; H, 3.9; N, 15.1%). IR(Nujol): 3430, 3325, 3200, 1700, 1625, 1410, 1280, 1250, 1155, 1060, 840, 720 cm^{-1}. UV (λ_{max}/nm, ε/M^{-1} cm^{-1}): 224 (4700), 270 (17 100) (in 0.1 M HCl).

Potassium Salt of **I**.—Compound **I** (270 mg, 0.001 mol) was dissolved in water (5 ml). The pH was brought to about 10 with 1 M aqueous KOH. The solution was evaporated to dryness and the residue was recrystallized from 50% ethanol to yield small white crystals, mp > 300 °C (Found: C, 17.15; H, 1.24; N, 14.54. Calc. for $C_4H_{3.5}K_{1.5}N_3O_6S$: C, 17.14; H, 1.26; N, 14.99%. IR (Nujol): 3455, 3415, 3340, 3290, 3180, 1730, 1650, 1530, 1360, 1265, 1235, 1150, 1055, 840, 760, 720 cm^{-1}. UV (λ_{max}/nm, ε/M^{-1} cm^{-1}): 222 (4600), 270 (17 000) (in water). The strong IR bands around 1050 cm^{-1} are characteristic of sulfate esters.

Isouramil **II**.—Crude **I** (1 g) was dissolved in 48% aqueous HBr (10 ml). The solution was kept at 22 °C. It began to deposit crystals of isouramil after about 3 h. After 5 h the reaction mixture was cooled to 5 °C and allowed to stand overnight. The crystals were filtered off, washed with 48% HBr, water and 95% ethanol. Air-drying gave 0.38 g (60% yield) of isouramil with spectra in agreement with those reported by Bien *et al.*[4] (IR) and Davoll and Laney[5] (UV).

Isobarbituric Acid **III**.—Uracil (3.16 g, 0.028 mol) was dissolved in water (30 ml) containing NaOH (3 g). The solution was cooled on ice and then sodium peroxodisulfate (7.16 g, 0.03 mol) was added in portions with stirring during 1 h. The homogeneous solution was allowed to stand at 22 °C overnight. The pH was adjusted to about 7.5 with concentrated HCl. This solution was allowed to stand for 2–3 d at 22 °C during which time uracil slowly precipitated (1 g). After removal of the uracil by filtration, one-half volume of concentrated HCl was added and the solution heated to boiling for 10 min. Isobarbituric acid (2 g) precipitated in the cold. This crude material contained about 14% uracil. The yield of isobarbituric acid was 49% after correction for this or 71% after taking into account the uracil initially recovered. Crystallization was ineffective in separating uracil and isobarbituric acid. However, the remaining uracil can be removed by trituration with the solvent recommended for chromatographic separations in this system, propan-2-ol–concentrated ammonia–water (7:1:2)[7,8] Five-hundred milligram lots were stirred with about 10 ml of this mixture at 22 °C for 30 min. TLC on cellulose showed only uracil in the filtrate. The residue was filtered off, washed with fresh solvent and finally 95% ethanol. This material was clean by TLC and was recrystallized from dilute HCl to yield **III** in about 70% yield with spectral characteristics in agreement with the literature values.[8]

I thank Dr. G. E. Means for interesting me in isouramil.

†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research(S)*, 1998, Issue 1]: there is therefore no corresponding material in *J. Chem. Research(M)*.

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