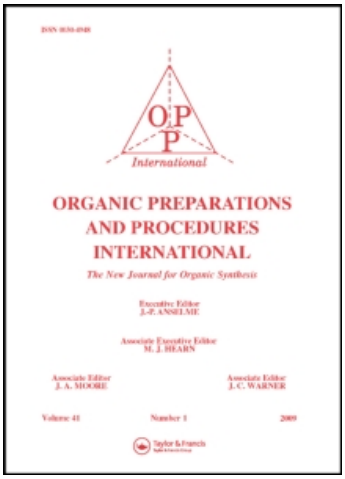

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CONVENIENT PREPARATION OF METABOLITES OF 6-*n*-PROPYLTHIOURACIL

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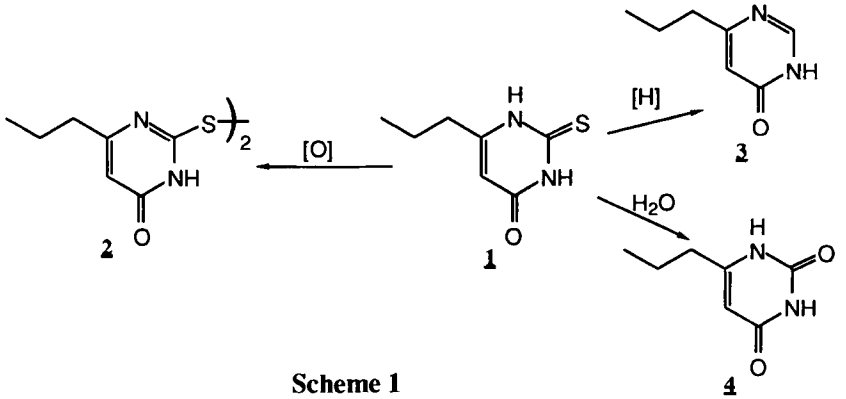
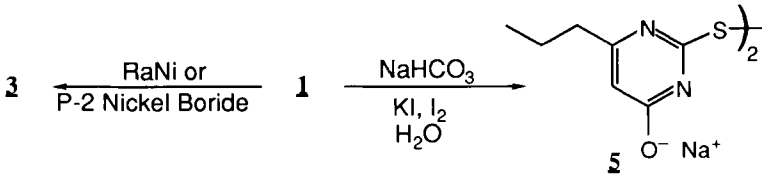
6-*n*-Propylthiouracil (PTU) **1**, is widely used clinically for the control of hyperthyroidism.[1] Recently we have been involved in the preparation of a number of potential PTU metabolites **2-4** (Scheme 1) as standards for *in vitro* and *in vivo* studies of 6-*n*-propylthiouracil metabolism.[2] To simplify our synthetic studies we sought to use commercially available PTU as a starting material for the preparation of these potential metabolites. In addition we wished to develop procedures which could be used to prepare radiolabeled derivatives from a single radiolabeled precursor, PTU. Biotransformations of drugs normally involve conversion of the drug to a more polar metabolite by oxidation, reduction or hydrolysis or by conjugation of the drug or metabolite.[3] The first three processes could lead to potential PTU metabolites such as 6-*n*-propylthiouracil disulfide **2**, 3,4-dihydro-6-*n*-propyl-4-pyrimidone **3** and 6-*n*-propyluracil **4** (Scheme 1). While no procedures exist for the direct conversion of PTU to these derivatives, similar conversions had been carried out in the unsubstituted thiouracil cases. Modifications of these procedures led to successful preparations of **2-4**.



Scheme 1

In contrast to the ready oxidation of methimazole (MMI) to its disulfide with sodium bicarbonate-iodine-KI,[4] identical treatment of propylthiouracil afforded upon work-up the sodi-

um salt of PTU as the only recognizable product despite complete decolorization of the iodine solution. Subsequently it was discovered that this disulfide is quite unstable in aqueous solution at room temperature, disproportionating to PTU and more oxidized forms of the drug. The desired PTU disulfide could however be isolated as its disodium salt **5** in crystalline form by rapid dilution of the reaction mixture with acetone and crystallization at –20°.



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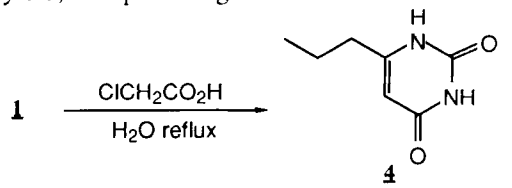
A potential reductive metabolite, 6-propyl-2-deoxyuracil **3** could be prepared directly in 20% yield by Raney Nickel desulfurization of PTU, however the material obtained from the reaction was difficult to purify. Pure **3** could be obtained most conveniently in approximately the same yield using nickel boride, a reagent we recently reported to be useful for direct reduction of the thiocarbonyl moiety of an endothiopeptide to the corresponding methylene group.[5] The P-2 nickel boride reagent is the more easily prepared and the workup is easier than that of the corresponding Raney Nickel reaction. It is likely that the low yield of reduced product in both cases was due to the strong binding of the PTU sulfur to nickel. In any case the one step reductions are far more convenient procedures for the preparation of **3** than the reported multi-step synthesis of the heterocycle.[6]

Finally, the equivalent of a hydrolytic procedure would convert PTU to 6-*n*-propyluracil **4**. While such a transformation *in vivo* would probably involve an initial oxidative step, perhaps via an intermediate disulfide **2**, a number of attempted oxidation-hydrolysis procedures on **1** did not afford **4**. Similarly the attempted alkylation of **1** with dimethyl sulfate or triethyloxonium fluoroborate to give a readily hydrolizable S-alkyl derivative was unsuccessful. Compound **1** could be converted to **4** with chloroacetic acid in water at reflux to afford **4** as a crystalline solid in 83% yield, thus providing a convenient route to the desired compound.



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Comparison of the synthetic products with those products obtained from *in vitro* thyroid peroxidase treatment of PTU showed that PTU disulfide was in fact the earliest formed major metabolite of PTU. Remarkably only very small amounts of 6-*n*-propyluracil and 3,4-dihydro-6-*n*-propyl-4-pyrimidone appear to form under these conditions,[2] in marked contrast to the metabolism of 1-methyl-2-mercaptoimidazole (MMI) where the major metabolite was shown to be the reduced derivative 1-methylimidazole.[4]

EXPERIMENTAL SECTION

Melting points were obtained on a Fisher Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer 283B spectrometer. 100 MHz ^1H NMR spectra were recorded on a JEOLCO JNM-PS-100 high resolution spectrometer. 200 MHz ^1H NMR and ^{13}C NMR spectra were recorded with a Varian XL200 spectrometer. When deuterochloroform and/or d^6-dimethyl sulfoxide was used as the NMR solvent, tetramethylsilane (TMS) was used as the internal reference; when D_2O was used as the solvent, 3-(trimethylsilyl)propanesulfonic acid, sodium salt (DSS) was used as an internal reference. Mass spectra were obtained at 70V on a Hewlett Packard 5995A gas chromatograph-mass spectrometer with an HP 9885M flexible disc drive and EI source. Samples were analyzed by direct insertion probe.

3,4-Dihydro-6-*n*-propyl-4-pyrimidone (3). Method A. Raney nickel (RaNi) alloy (Ni-Al 50/50, Alfa Products) (20.0 g) was slowly added to 80 mL of 25% NaOH solution in an ice bath with stirring (*Caution*: vigorous reaction) while keeping the temperature below 50-60 °C. After the addition was completed, the reaction mixture was heated to 90-95° for 1.5 hr. The solids were allowed to settle and the NaOH solution was decanted. Fresh 25% NaOH (80 mL) was added, and the reaction mixture was heated at 95° for 1h. After the solids settled, the NaOH solution was decanted as before. The Raney nickel (*Caution*: pyrophoric when allowed to dry) was washed with deionized water (until the washings no longer turned phenolphthalein indicator pink) followed by two portions of ethanol. Propylthiouracil (1.00 g, 5.88 mmol) was added to the RaNi suspended in ethanol (100 mL). The reaction mixture was heated to reflux for 3 hrs. The RaNi was allowed to settle, and the ethanol decanted. The RaNi was washed three more times with refluxing ethanol. The final wash was carefully filtered through Celite. Removal of the solvent afforded **3** as a tan solid which was recrystallized from ethyl acetate/hexanes to give 0.164 g (20%) of tan needles, mp. 108-111°, lit.[6] 110-112°. Method B. Sodium borohydride (0.827 g, 21.9 mmol) was added to propylthiouracil (0.155 g, 0.912 mmol) and nickel (II) chloride hexahydrate (*Caution*: suspected carcinogen) (1.733 g, 7.3 mmol) in anhydrous ethanol (10 mL) while cooling in an ice bath. After the addition was complete, the reaction mixture was allowed to come to room temperature and then heated to reflux overnight. The hot reaction mixture was filtered through Celite, and the nickel boride precipitate was washed twice with refluxing ethanol. Removal of the solvent gave a solid which was recrystallized from ethyl acetate/hexanes to afford colorless needles, mp. 108-110°, in a 20% yield. ^1H NMR ($CDCl_3$) δ 8.11 (s, 1H), 6.31 (s, 1H), 2.55 (t, 2H) 1.54-1.88 (q & bs, 3H), 0.98 (t, 3H). IR ($CHCl_3$) 3380, 1655, 1605 cm^{-1}. MS, m/e (relative intensity) 138 = M^+ (16), 110 (100).

6-*n*-Propyluracil (4). A mixture of 6-*n*-propylthiouracil (1.00 g, 5.9 mmol) and chloroacetic acid (1.11 g, 11.8 mmol) in water (65 mL) was heated to reflux overnight. Upon cooling col-

orless crystals separated which were filtered and dried affording 6-*n*-propyluracil (0.75 g, 83% yield), mp. 222-223°, lit.[7] 220°. ^{1}H NMR ($CDCl_3$,DMSO-d^6) δ 5.27 (s, 1H), 3.36 (bs, 2H), 2.27 (t, 2H), 1.59 (m, 2H), 0.93 (t, 3H). IR (KBr) 1710, 1655, 1500 cm^{-1}. (This procedure is a modification of that used for the previously described conversion of thiouracil to uracil.[8])

6-*n*-Propylthiouracil disulfide, disodium salt (5). A solution of 6-*n*-propylthiouracil (850 mg, 5 mmol) in 2M NaOH (5 mL) was treated with a solution of iodine (635 mg, 2.5 mmol) in 0.5M sodium iodide (5 mL). The mixture was stirred for 30 min. at room temperature and then added to acetone (200 mL). Upon standing overnight at –20 °C crystals formed. Drying and filtration afforded two crops of the disulfide disodium salt as colorless crystals (760 mg, 80% yield). ^{1}H NMR (D_2O) δ 5.94 (s, 1H), 2.93 (t, 2H), 1.64 (m, 2H), 0.73 (t, 3H). IR (KBr) 3350 (br), 1580, 1450 cm^{-1}. This material contained a small amount of the sodium salt of 6-*n*-propylthiouracil (HPLC, NMR). Upon standing in D_2O at room temperature **5** was converted to a mixture containing PTU, sodium salt [^{1}H NMR (D_2O) δ 5.90 (s, 1H), 2.42 (t, 2H), 1.62 (m, 2H), 0.90 (t, 3H), IR (KBr) 3450, 3200, 1650, 1605 cm^{-1}]. The PTU disulfide could be clearly distinguished from starting PTU by HPLC analysis [Reverse Phase C_{18} ultrasphere column, 20% methanol-80% 0.02 M KH_2PO_4, pH 4.8, flow rate = 0.8 mL/min., after 10 min. linear gradient over 10 min. to 90% methanol, retention times: PTU disulfide 24.9 min., PTU 19.8 min]. Under all other methods of characterization (e.g., FAB MS) PTU sodium salt was the only recognizable component. (This synthetic procedure is a modification of that reported for the conversion of thiouracil to its disulfide.[9])

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