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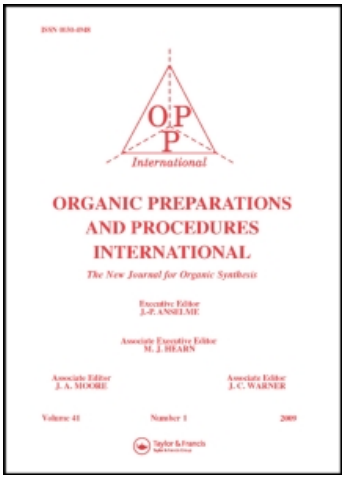

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

THE SYNTHESIS OF 6-PROPYL-2-SELENOURACIL, THE SELENIUM ANALOGUE OF THE ANTI-THYROID DRUG PTU

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To cite this Article Hu, Wei-Xiao and Guziec Jr., Frank S.(1994) 'THE SYNTHESIS OF 6-PROPYL-2-SELENOURACIL, THE SELENIUM ANALOGUE OF THE ANTI-THYROID DRUG PTU', Organic Preparations and Procedures International, 26: 6, 682 — 684
To link to this Article: DOI: 10.1080/00304949409458168
URL: http://dx.doi.org/10.1080/00304949409458168

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Acknowledgment.- The authors thank the following Brazilian agencies for financial support: CNPq, FAPESP and also International Foundation for Science.

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Submitted by (04/28/94)

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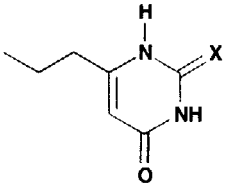
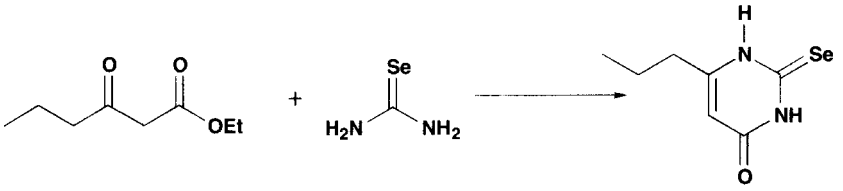
Despite the fact that thiocarbonyl compounds have often proved to be important therapeutic agents, the corresponding selenocarbonyl compounds are much less well known. One such important thiocarbonyl compound is 6-propyl-2-thiouracil (**1**), commonly referred to as PTU, a thiourylene drug useful as an anti-thyroid agent.[1] For a number of years the mechanism of action of these drugs was presumed to involve inhibition of a key thyroid enzyme, 5'-iodothyronine deiodinase, (ID-1) by formation of a mixed disulfide between a cysteine residue on the enzyme and the sulfur atom of the thiourylene.[2,3] Recently, it was discovered that ID-1 is, in fact, a seleno-enzyme containing a selenocysteine residue which is necessary for full biological activity.[4,5] Because of our interest in the chemistry of both selenocarbonyl compounds[6,7] and anti-thyroid therapeutic agents,[8] we sought to prepare 6-propyl-2-selenouracil (**2**), the selenium analogue of PTU to determine whether this compound could be a more effective inhibitor of ID-1, in particular because of the very mild conditions necessary for forming diselenide bonds.



1, X = S
2, X = Se

Initial attempts to prepare **2** by an alkylation-selenation sequence, commonly used to prepare acyclic selenoureas [7,8] failed to afford the desired selenium analogue. Compound **2** could, however, be prepared by the condensation of ethyl 3-ketohexanoate with selenourea, analogous to the published procedure for the preparation of PTU.[9] As with many selenocarbonyl compounds, 6-propylselenouracil is moderately light sensitive and easily oxidized. Decomposition can be detected by generation of finely divided red selenium, affording materials with a pale pink to red coloration.



2

Analytically pure **2** could be obtained as colorless crystals, pure by HPLC, by simple recrystallization. It should be noted that many selenocarbonyl compounds are prone to tautomerization to the *ene-selenol* form. This is often explained as being due to the poor π overlap between carbon and selenium in a double bond. The product 6-selenouracil shows the ^{13}C NMR shifts characteristic of a selenocarbonyl compound. In particular the furthest downfield signal at δ 174 is characteristic of the selenocarbonyl carbon in a carbon-selenium double bond.[9]

The successful preparation of **2** opens the possibility of the preparation of a variety of other selenium analogues. Full biological studies on the comparisons of **2** with its sulfur analogue PTU will be published separately.[10]

EXPERIMENTAL SECTION

Melting points obtained on a Fisher Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer 1600 series FTIR. 200 MHz ^1H NMR were recorded with Varian XL 200 spectrometer; 400 MHz ^{13}C NMR were recorded with a Varian Unity 400 spectrometer. Microanalysis was performed by Desert Analytics, Tucson, Arizona. All reagents were commercially available and were used without further purification.

6-Propyl-2-selenouracil (2). To selenourea (0.492 g, 4 mmol) in water (1.3 mL) and protected from light was added with stirring at room temperature ethyl 3-ketohexanoate (0.948 g, 6 mmol) along with powdered potassium hydroxide (0.336 g, 6 mmol). The mixture was stirred at room temperature for 1 hr. Water (1.3 mL) was added, and a black solid was removed by filtration. The filtrate was acidified with concentrated hydrochloric acid (1.2 mL), stirred for 30 min, and filtered. A pink solid was obtained which proved to be the selenouracil (**2**) contaminated with finely divided elemental selenium (0.25 g, 28% yield). The product was pure by HPLC μ(C -18) (CH_3CN, H_2O, AcOH - 90:20:1). An analytically pure sample could be obtained by recrystallization from glacial acetic acid, affording colorless crystals of 6-propyl-2-selenouracil (0.095 g), mp. 189-190°. IR (KBr) 3047, 2923, 1708,

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1676, 1556, 1452, 1402, 1291, 1175, 916, 631, 553 cm^{-1}, ^1H NMR (DMSO-d_6): δ 5.85 (s, 1H), 2.38 (t, 2.38), 1.93 (s, 2H), 1.57 (m, 2H), 0.90 (t, 3H), ^{13}C NMR (DMSO-d_6): δ 173.6 (C-2), 160.3 (C-4), 156.3 (C-6), 1.04.4 (C-5), 32.9 (C-7), 20.5 (C-8), 13.1 (C-9).

Anal. Calc. for $C_7H_{10}N_2OSe$: C, 38.72; H, 4.64; N 12.90. Found: C, 38.58; H, 4.66; N, 12.86

Acknowledgements.- We gratefully acknowledge the financial support of Boots Pharmaceuticals, Inc. We also thank Professor Alvin Taurog of the University of Texas Southwestern Medical Center, Dallas, TX, for helpful suggestions, and Dr. Luis Collazo for his assistance in the ^{13}C NMR studies.

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