

Synthesis of the Selenopyrimidine Nucleosides 2-Seleno- and 4-Selenouridine (I)

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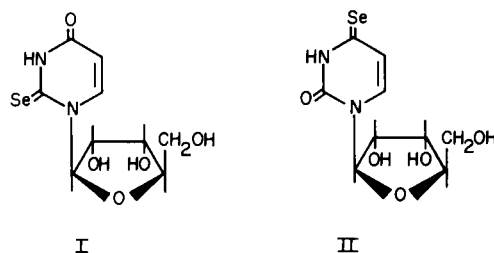
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Received November 21, 1972

Sir:

The isolation and characterization (2) of a minor nucleoside from t-RNA (*E. coli*) as 4-thiouridine created considerable interest in the chemistry and biological implications of this minor nucleoside. The isomeric nucleoside (2-thiouridine), also isolated (3) from t-RNA (*E. coli*), prompted additional investigations and reports involving the isolation of not only the above sulfur containing nucleosides from various t-RNA's but also the presence of several other closely related thiopyrimidine nucleosides. This has resulted in numerous reports (4) on the biological and chemotherapeutic activity, chemical synthesis, and the possible role that these sulfur containing minor nucleosides have on the tertiary structure of t-RNA. It has been recently reported (5) that the growth of *E. coli* in a medium containing selenite [^{75}Se] resulted in the incorporation of ^{75}Se into undesigned heterocyclic moieties of the t-RNA. It has also been shown (6) that selenomethionine will function as effectively as methionine during aminoacyl t-RNA synthesis of *E. coli* which prompted the assumption (5) that selenium probably follows a biosynthetic pathway into t-RNA which is very similar to that of sulfur. Therefore, the two most probable minor nucleosides in this ^{75}Se t-RNA are 2-selenouridine and 4-selenouridine. We have been involved in the chemical synthesis of selenonucleosides in several areas (7) and this report (5) has prompted us to communicate some of the ongoing research in our lab involving the chemical synthesis of selenopyrimidine nucleosides which are closely related to the sulfur containing minor nucleosides from t-RNA.

The silylation of 2-selenouracil (8) was accomplished with hexamethyldisilazane at reflux temperature and this silyl derivative was then condensed (9) with 2,3,5-tri-*O*-benzoyl-1-*O*-acetyl- β -D-ribofuranose, in 1,2-dichloroethane in the presence of stannic chloride, to furnish nucleoside material. The blocking groups were removed with sodium methoxide in methanol at room temperature and the resulting residue purified by dry-column chromatography (SilicAR CC7; chloroform-methanol, 10:1). The nucleoside was recrystallized from chloroform-methanol (10:1)



to furnish a colorless crystalline product (30%) which was characterized as 2-selenouridine (I) ($\text{C}_9\text{H}_{12}\text{N}_2\text{O}_5\text{Se}$; Calcd.: C, 35.2; H, 3.94; N, 9.12. Found: C, 34.9; H, 4.29; N, 8.83); m.p. 197° dec.; uv λ max (pH 1) 308 nm; λ max (methanol) 312 nm; λ max (pH 11) 237, 293 nm; pmr (dimethyl sulfoxide- d_6) doublet at δ 8.12 ($J = 8.2$ Hz, C-6 proton); a doublet at δ 6.22 ($J = 8.2$ Hz, C-5 proton), a doublet at δ 6.74 ($J_{1,2} = 3.5$ Hz, anomeric proton) and the characteristic pattern usually observed (10) for the remaining protons of a ribofuranose moiety. The anomeric configuration and actual site of ribosylation was established by treatment of I with dilute base to afford a nucleoside which was identical with an authentic sample of uridine.

Treatment of 4-chloro-1-(2,3,5-tri-*O*-benzoyl- β -D-ribofuranosyl)pyrimidin-2-one (11) with selenourea in methanol at reflux temperature for 2 hours under a nitrogen atmosphere effected a facile nucleophilic displacement of the 4-chloro group as determined by thin-layer chromatography. The benzoyl groups were then removed from the nucleoside material with sodium methoxide in methanol at room temperature. The resulting residue was recrystallized from chloroform to furnish bright yellow crystals of 4-selenouridine (II); m.p. $150\text{--}151^\circ$ dec.; ($\text{C}_9\text{H}_{12}\text{N}_2\text{O}_5\text{Se}$; Calcd.: C, 35.2; H, 3.94; N, 9.12. Found: C, 35.31; H, 3.91; N, 9.06); uv λ max (pH 1) 259, 366 nm; λ max (methanol) 265, 371 nm; λ max (pH 11) 236, 283, 338 nm; pmr (dimethyl sulfoxide- d_6) doublet at δ 8.04 ($J = 7.4$ Hz, C-6 proton), a doublet at δ 6.74 ($J = 7.4$ Hz, C-5 proton), a doublet at δ 5.82

($J_{1,2} = 3.6$ Hz, anomeric proton), and the characteristic pattern usually observed for the remaining protons of a ribofuranose moiety.

These selenopyrimidine nucleosides have not been isolated from naturally occurring sources, however, this is probably due to hydrolysis during isolation since we have found that the seleno group of I and II is very labile. A modification of the current isolation procedures should provide several selenopyrimidine nucleosides as minor components of certain t-RNA species.

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