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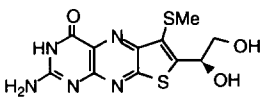
Absolute Configuration of Urothion, a Pigment of Urine : Asymmetric Synthesis of 2-Amino-6-(3,4-dihydroxybutyl)pteridin-4(3H)-one, the Desulfurization Product

Atsushi Sakurai*, Hideki Horibe, Nobuhiro Kuboyama, Yuji Hashimoto, and Yasuaki Okumura

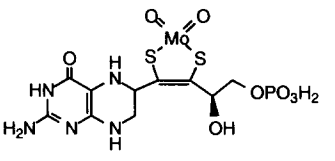
Department of Chemistry, Faculty of Science, Shizuoka University, Ohya, Shizuoka 422 Japan

ABSTRACT: In order to determine the absolute configuration of urothion, 2-amino-6-[(3*R*)-3,4-dihydroxybutyl]-pteridin-4(3H)-one and its (3*S*) compound were synthesized. Comparing the CD spectra of their tri-4-chlorobenzoates with that derived from the natural product, *R*-configuration was concluded for the secondary hydroxyl group on the side chain of urothion.

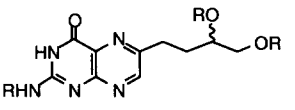
Urothion (**1**) is an optically active yellowish pigment isolated from urine.[1,2] Though its planar structure was established by syntheses,[3,4] the absolute configuration of the secondary hydroxyl group on the side chain remained elusive. Meanwhile, Johnson and Rajagopalan suggested to molybdopterin the structure **2**,[5] with the *R*-configuration for the secondary hydroxyl group.[6] Furthermore, on the basis of the metabolic study of the molybdenum cofactor, they proposed that **1** might be a urinary metabolite of **2**.[7] In order to test this proposal and to seek the biochemical significance of **1**, we determined the absolute configuration of the hydroxyl group in 2-amino-6-(3,4-dihydroxybutyl)pteridin-4(3H)-one (**3**), obtained by the Raney-Ni desulfurization of **1**.[1] The results are described herein.



1



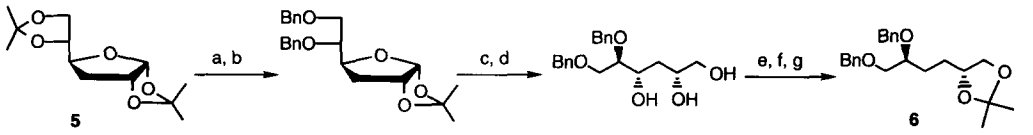
2



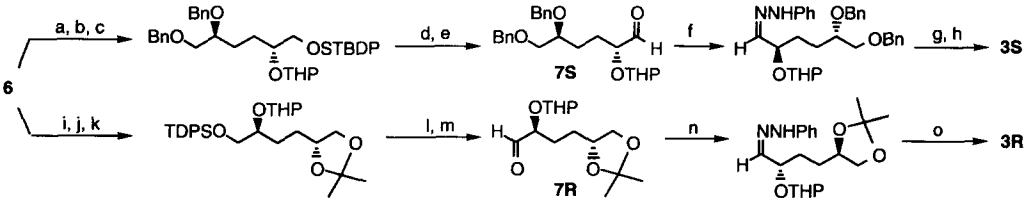
3: R = H
4: R = 4-ClC$_6$H$_4$CO-

In order to apply the exiton-chirality rule, **3** was first converted to the corresponding tri-4-chlorobenzoate **4**, CD spectrum of which exhibited a positive Cotton effect (λ_{ext} 247 and 228 nm, $\Delta\varepsilon$ +8.0 and -3.0, respectively) suggesting *S*-configuration for **3**. However, as the pteridine ring is bonded to the carbon β to the chiral center which makes the conclusion somewhat ambiguous, we decided to solve the problem by synthesis of 2-amino-6-[(3*S*)-3,4-dihydroxybutyl]pteridin-4(3H)-one (**3S**) and 2-amino-6-[(3*R*)-3,4-dihydroxybutyl]pteridin-4(3H)-one (**3R**).

The six carbon moiety in the right hand of the structure **3** including the chiral side chain was prepared from the diacetonide of 3-deoxy-D-glucofuranose **5**.[8] The optically active monoacetonide of tetraol **6** was synthesized by standard procedures as shown in Scheme 1.[9] The protected tetraol **6** was used for the preparation of two aldehydes **7S** and **7R** of the opposite chirality, and eventually converted to **3S** and **3R** as shown in Scheme 2.



Scheme 1. a. 80% AcOH, rt, overnight, 88%. b. 5 eq. NaH/THF, Ar, refl., 0.5 h; 6 eq. BnBr, 0.05 eq. Bu_4NI, Ar, refl., 1 h, quant. c. 80 AcOH, 90°C, 2.5 h, 86%. d. 0.63 eq. $NaBH_4$/EtOH, 0°C, 0.5 h and rt, 1.5 h, 84%. e. 7 eq. $(MeO)_2CMe_2$, 0.05 eq. CSA/CH_2Cl_2, r.t., 0.25 h, 60%. f. 1.5 eq. NaH, 0.05 eq. imidazole/THF, Ar, refl., 2.5 h; 5 eq. CS_2, refl., 0.5 h; 5 eq. MeI, refl., 0.5 h, 92%. g. 1.3 eq. Bu_3SnH/toluene, Ar, refl., overnight, 75%.



Scheme 2. a. 80% AcOH, rt, 2.5 h, 84%. b. 1.2 eq. TBDPSCl, 2.5 eq. imidazole/DMF, rt, 0.5 h, 87% c. 5 eq. DHP, 0.05 eq. CSA/CH_2Cl_2, rt, 10 min, 89%. d. 2 eq. Bu_4NF/THF, rt, 1 h, 94%. e. 4 eq. PDC, MS/CH_2Cl_2, rt, 14 h, 67%. f. $PhNHNH_2$•HCl, HCl/EtOH, rt, 30 min. g. 2,4,5-triaminopyrimidin-6(1H)-one•2HCl/aq EtOH (1:1), rt, 2 h and refl., 4 h; air, rt, overnight. h. H_2, 10% Pd-C/EtOH-AcOH (1:1), rt, overnight; air, rt, overnight, 14%. i. H_2, 10% Pd-C/THF, rt, 1.5 h, quant. j. same as b, 78%. k. same as c, quant. l. same as d, quant. m. same as e, 79%. n. same as f. o. same as g, 20%.

The resulted dihydroxybutylpteridines **3S** and **3R** were purified by ion exchange chromatography (Dowex 1X8, $MeCOO^-$ form, eluent: 0.05mol NH_4OAc) and recrystallization (from H_2O). Pale yellow needles obtained in both reaction sequences have UV and ^{1}H-NMR spectra identical with those of specimen **3**.[1] For the determination of absolute configuration, both **3S** and **3R** were converted to tri-4-chlorobenzoates **4S** and **4R**, and their CD spectra were compared with that of the natural derivative **4**. The spectrum of **4** was found superimposable with that of **4S**.

From these two pieces of evidence, **3** was concluded to have *S*-configuration, as was suggested from the exiton-chirality rule, and **1** to have *R*-configuration.

References and Notes.

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9. In the process e in Scheme 1, another acetonide with 6-membered ring was obtained in 35% yield. Since it can be hydrolyzed to the triol and subjected to the acetonide formation, the total yield in the process amounts to 85%.

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