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# SYNTHESIS OF ASPEROPTERIN-B AND SOME ANALOGUES

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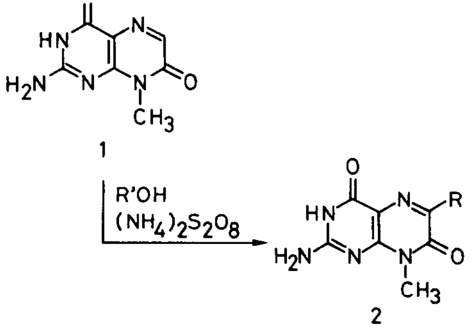
Summary: Homolytic 1-hydroxyalkylation on 8-methylisoxanthopterin by a primary or secondary alcohol and ammonium peroxydisulfate in a pH 5-6 phosphate buffer gave two naturally occuring pteridines, Asperopterin-B and 6-(1-hydroxypropyl)-8-methylisoxanthopterin, and several analogues.

The formation of a carbon-carbon linkage is a long seeked and one of the most important process in organic synthesis. However, the chemistry of pteridine and analogous heterocycles has little recorded the carbon-carbon bond formations, because their extreme low solubility in common organic solvents prevented the application of the recent synthetic techniques. Since many of the biologically important pteridines possessing a carbon functional group at the C(6) position are synthesized with great difficulties, it is significant to develop a new method to introduce a carbon side chain to the readily available pteridines. We have recently reported a general C(6) acylation of the pteridine nuclei in the chemical synthesis of Deoxysepiapterin.[1] Here is described another general procedure to introduce a 1-hydroxyalkyl group to the pteridine ring.



| compound | R | yield/% |
|---|---|---|
| **2a** | $CH_2OH$ | 53 |
| **2b** | $CH(OH)CH_3$ | 36 |
| **2c** | $CH(OH)CH_2CH_3$ | 54 |
| **2d** | $CH(OH)CH_2CH_2CH_3$ | 41 |
| **2e** | $C(OH)(CH_3)_2$ | 45 |
| **2f** | $C(OH)(CH_3)CH_2CH_3$ | 22 |

Heating a mixture of 8-methylisoxanthopterin (**1**), ammonium peroxydisulfate,[2,3] and methanol in a pH 5-6 phosphate buffer gave 6-hydroxymethyl-8-methylisoxanthopterin (**2a**), a natural pteridine named Asperopterin-B isolated from Aspergillus oryzae.[4] In lower (pH <3.0)[2,3] or higher (>9) pH conditions, the product **2a** was converted into unknown nonfluorecent compounds. Naturally occurring 6-(1-hydroxypropyl)-8-methylisoxanthopterin (**2c**), which was obtained from firefly [Photinus pyralis][5] and synthesized from **1** by acylation,[6] was synthesized by the reaction of **1** and 1-propanol. Ethanol and 1-butanol were also employed to the hydroxyalkylation. The reaction using a secondary alcohol, like 2-propanol and 2-butanol, proceeded similarly but more slowly to give the 1-hydroxyalkylated products **2e** and **2f**, respectively.

The following is the general procedure: a suspension of **1** (600 mg, 3.1 mmol) in a 1:2 mixture (100 ml) of an alcohol and 0.5 M ammonium phosphate buffer, pH 5-6, was heated under reflux. Solid $(NH_4)_2S_2O_8$ (4.6 g, 20 mmol) was added to the mixture and refluxing was continued for 10-120 min till **1** was not detected on Cellulose TLC. The solution was concentrated to about a quater volume, adjusted to pH 2-3 with HCl, and then applied to a column of activated charcoal (5 g) and Celite (15 g). The column was washed thoroughly with water and the product was eluted by a 1:1:2 mixture of 5% aqueous ammonia, pyridine, and ethanol. Evaporation of the eluate and crystallization from water gave **2** which gave satisfactory elemental analyses and $^1$H NMR.[7]

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7. $^1$H NMR ($CD_3SOCD_3$): **2a**, 7.07 (1H, br), 4.7 (1H, br), 4.43 (2H, br), 3.40 (3H, s); **2b**, 7.10 (1H, br), 4.85 (1H, q, 6.6 Hz), 3.75 (2H, br), 3.58 (3H, s), 1.32 (3H, d, 6.6 Hz); **2c**, 7.08 (1H, br), 4.63 (1H, dd), 3.46 (3H, s), 1.72 (2H, m), 0.85 (3H, t, 7.3 Hz); **2d**, 7.10 (1H, br), 4.70 (1H, br), 3.30 (3H, s), 1.8-1.0 (4H, m), 0.92 (3H, t, 6.4 Hz); **2e**, 7.08 (1H, br), 3.45 (3H, s), 3.25 (2H, br), 1.43 (6H, s); **2f**, 7.12 (1H, br), 3.39 (3H, s), 3.3 (2H, br), 1.80 (2H, q, 7.8 Hz), 1.39 (3H, s), 0.67 (3H, t, 7.7 Hz).

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