SYNTHESIS AND STRUCTURAL CONFIRMATION OF 5,6-CYCLOPENTENO-5-DEAZAPTERIN

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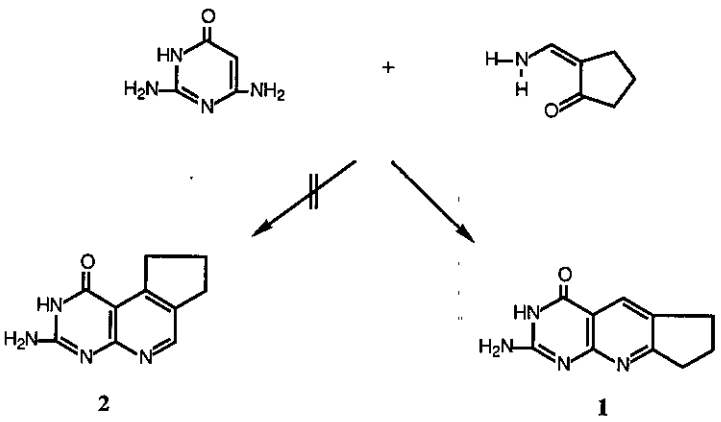
Abstract - Condensation of 2,4-diamino-6(1H)-pyrimidinone with 1-formyl-1-cyclopentene in 60% acetic acid gives 5,6-cyclopenteno-5-deazapterin (**2**). The 2-pivaloyl derivative of **2** was then synthesized in an unequivocal manner by Diels-Alder cycloaddition of 2-pivaloylamino-7-methylthio-6-azapterin (**3**) with 1-(N-morpholino)cyclopentene to give 5,6-cyclopenteno-2-pivaloylamino-7-methylthio-5-deazapterin (**4**), followed by Raney nickel desulfurization.

In 1973 Stark and Breitmaier described the condensation of 2,4-diamino-6(1H)-pyrimidinone with 2-(aminomethylene)cyclopentanone to give the 5,6-annulated-5-deazapterin **2**[1]. The equivocal regiochemistry of this reaction prompted reports by our group in 1984[2] and by Ganjee and coworkers (with the cyclohexeno annulated homolog) in 1985[3] and with a tetrahydropyridine annulated derivative) in 1987[4] that the product actually formed was the 6,7-annulated-5-deazapterin **1**.

Our assignment of structure **1** to the Stark and Breitmaier condensation product was based upon an independent and unequivocal synthesis. We now describe an unambiguous synthesis of **2**. In a recent communication[5] we reported the cycloaddition of various pyrimido[4,5-e]-1,2,4-triazines (6-azapteridines) with enamines to give 5-deazapterins. Thus, heating 2-pivaloylamino-7-methylthio-6-azapterin (**3**) with 1-(N-morpholino)cyclopentene in refluxing dioxane gave 5,6-cyclopenteno-2-pivaloylamino-7-methylthio-5-deazapterin (**4**). We have now found that Raney nickel desulfurization of **4** affords the pivaloyl protected derivative **5** of the previously unknown annular compound **2**.

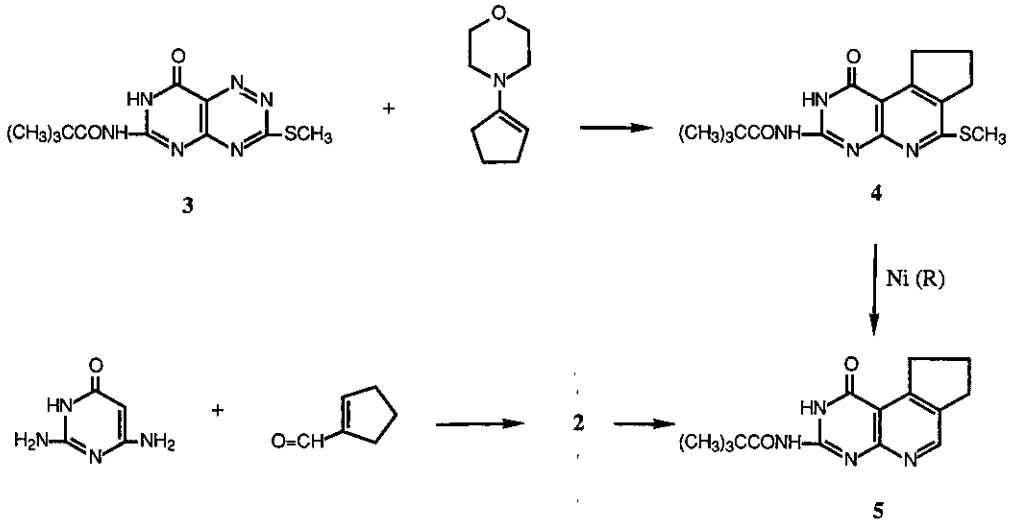
Using a modification of the method described by Wood et al.[6], we were then able to synthesize **2** in good yield by the condensation of 1-formyl-1-cyclopentene[7] with 2,4-diamino-6(1H)-pyrimidinone in 60% acetic acid. The intermediate dihydro compound underwent spontaneous oxidation under the reaction conditions. Treatment of **2** thus formed with pivalic anhydride in the presence of pyridine then gave **5**, identical in all respects with **5** prepared by the Diels-Alder route. We are currently investigating the utilization of functionalized 5-membered carboxyclic and heterocyclic α,β-unsaturated aldehydes for the preparation of biologically significant 5,6-annulated-5-deazapterins[5].

Since small variations in the nature of the pyrimidine, the bis-electrophile and even the solvent can have unpredictable effects on the regiochemistry of these cyclocondensation reactions[8], it would seem prudent to confirm all structural assignments by independent synthesis.



2 **1**

Scheme 1



3 **4** **5**

Scheme 2

EXPERIMENTAL

5,6-Cyclopenteno-5-deazapterin (**2**). A mixture of 2,4-diamino-6(1H)-pyrimidinone (1.33 g, 9.2 mmol) and 1-formyl-1-cyclopentene[7] (0.71 g, 3.6 mmol) was heated at reflux in 10 ml of 60% aqueous acetic acid containing 1 drop of pyrrolidine for 3.5 h. The initial heterogeneous reaction mixture rapidly became clear. The precipitate which had formed after 2 h was collected by filtration, washed with hot water, methanol and finally ether; yield 0.35 g (47%) of **2** as a white microcrystalline solid, mp >300 °C; ^{1}H nmr (d-TFA) δ 1.99 (q, 2 H, J = 7.6 Hz), 2.73 (t, 2 H, J = 7.6 Hz), 3.25 (t, 2 H, J = 7.6 Hz), 8.02 (s, 1 H). High ms: Calcd for $C_{10}H_{10}N_4O$: m/z 202.0854. Found 202.0833.

5,6-Cyclopenteno-7-methylthio-2-pivaloylamino-5-deazapterin (**4**). A mixture of 2-pivaloylamino-6-methylthio-6-azapterin[5] (0.24 g, 0.82 mmol) and 1-(N-morpholino)cyclopentene (0.50 g, 3.3 mmol) in 10 ml of dioxane was heated under reflux and under nitrogen for 2.5 h. The reaction mixture was then cooled to room temperature and the solvent was removed under reduced pressure. Trituration of the residual dark solid with ethanol gave a gray powder which was taken up in chloroform and filtered through a silica gel plug, with chloroform as the eluant. Evaporation of the combined chloroform filtrates under reduced pressure gave 0.12 g (44%) of **4** as a white solid, mp 268-270 °C; ^{1}H nmr ($CDCl_3$) δ 1.30 (s, 9 H), 2.19 (q, 2 H, J = 7.6 Hz,), 2.66 (s, 3 H), 2.80 (t, 2 H, J = 7.6 Hz), 3.43 (t, 2 H, J = 7.6 Hz), 8.22 (br s, 1 H), 11.51 (br s, 1 H). High ms: Calcd for $C_{16}H_{20}N_4O_2S$: m/z 332.1307. Found 332.1276.

5,6-Cyclopenteno-2-pivaloylamino-5-deazapterin (**5**). Method A. A mixture of 5,6-cyclopenteno-5-deazapterin (**2**) (0.10 g, 0.5 mmol), pivalic anhydride (0.40 g, 2.2 mmol) and pyridine (0.50 g, 6.3 mmol) was heated at 140 °C for 5 h. The reaction mixture was allowed to cool to r.t. overnight, and the precipitated solid was collected by filtration and washed with aqueous ethanol. Recrystallization from aqueous methanol gave 0.13 g (92%) of **5** as a white solid, mp 247-248 °C; ^{1}H nmr ($CDCl_3$) δ 1.34 (s, 9 H), 2.23 (q, 2 H, J = 7.6 Hz), 3.00 (t, 2 H, J = 7.6 Hz), 3.49 (t, 2 H, J = 7.6 Hz), 8.36 (br s, 1 H), 8.66 (s, 1 H), 11.97 (br s, 1 H). High ms:Calcd for $C_{15}H_{18}N_4O_2$: m/z 286.1429. Found 286.1427.

Method B. A mixture of 5,6-cyclopenteno-7-methylthio-2-pivaloylamino-5-deazapterin (**4**)[5] (0.12 g, 0.36 mmol) and ca. 5.0 g of Raney nickel (Aldrich, washed with water and ethanol) in 25 ml of ethanol was stirred at room temperature for 120 h. The mixture was filtered through Celite, which was then rinsed with hot chloroform. Evaporation of the combined filtrates left 0.009 g (9%) of a white solid which was identical in every respect with **5** prepared by Method A.

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