

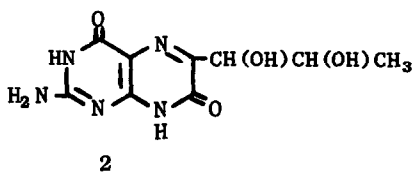
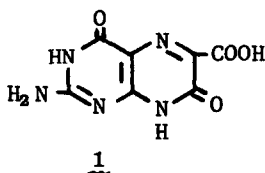
A NEW AND UNEQUIVOCAL SYNTHESIS OF ISOXANTHOPTERIN-6-CARBOXYLIC ACID (CYPRINO-POURPRE B)^{1,2}

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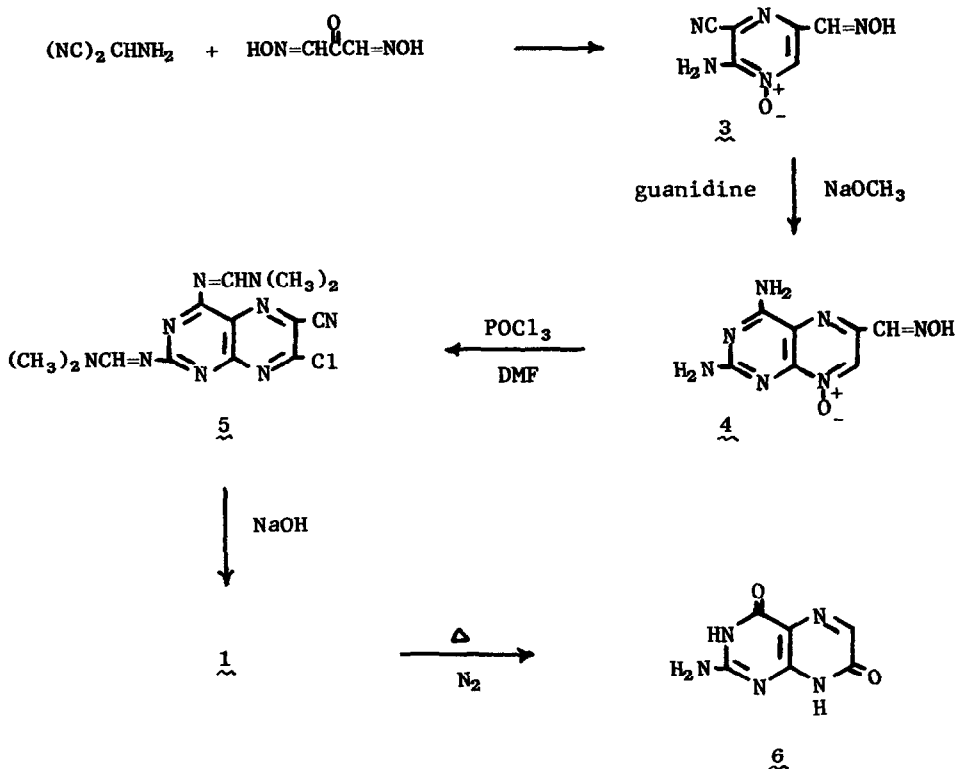
One of the major pteridine constituents of the scales and skin of fresh water fishes, the Cyprinidae, is Cyprino-Pourpre B, which has been identified as isoxanthopterin-6-carboxylic acid (1).⁴ It is believed that 1 arises by biological oxidation of ichthyopterin (2), another of the common pteridine fish-skin pigments.⁵ Although 1 has been synthesized twice previously (by condensation of 2,4,5-triamino-6(1H)-pyrimidinone with diethyl oxomalonate⁶



or with alloxan in alkaline solution⁷), both procedures are inherently ambiguous and, indeed, lead to concomitant formation of varying amounts of the isomeric xanthopterin-7-carboxylic acid. As part of our program directed towards the utilization of pteridine 8-oxides as intermediates for the synthesis of the pteridine natural products,⁸⁻¹⁰ we have achieved a synthesis of isoxanthopterin-6-carboxylic acid (1), totally free of its isomer, by a route which unambiguously positions the substituents in the pyrazine ring.

Thus (see Scheme 1), condensation of aminomalononitrile tosylate with dioximinoacetone gave 2-amino-3-cyano-5-oximinomethylpyrazine 1-oxide (3), which was readily cyclized with guanidine to 2,4-diamino-6-oximino-methylpteridine 8-oxide (4).¹¹ Heating a solution of 4 in a mixture of POCl₃/DMF for 2 hr at 65° resulted in the separation of 5 (93%), which upon 24 hr reflux with 10% aqueous sodium hydroxide solution, followed by

acidification, gave isoxanthopterin-6-carboxylic acid (**1**) (89%), identical both chromatographically and spectroscopically with naturally occurring Cyprino-Pourpre B.



Scheme 1

When **1** was heated at 260° in a current of dry nitrogen, decarboxylation readily occurred (judged complete in 30 min). Dissolution of the dark grey residue in 1 N NaOH followed by decolorization with charcoal and acidification afforded pure isoxanthopterin (**6**), identical in all respects with an authentic sample.

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11. We have previously described the condensation of dioximinoacetone with ethyl α -aminocyanoacetate to give 2-amino-3-ethoxycarbonyl-5-oximino-methylpyrazine 1-oxide, which was a key intermediate in the synthesis of pterin-6-carboxaldehyde (see ref. 9).