Tetrahedron Letters,Vol.28,No.44,pp 5331-5334,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

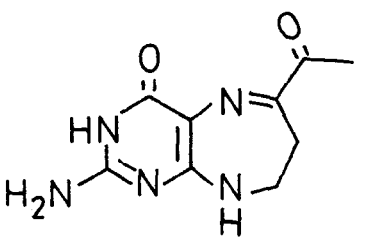
SYNTHESIS OF 6-ACETYLHOMOPTERIN. A NATURALLY OCCURRING PYRIMIDO[4,5-b][1,4]DIAZEPINE

Peter H. Boyle*, Enid M. Hughes, Hassan A. Khattab and Ronan J. Lockhart

University Chemical Laboratory, Trinity College,
University of Dublin, Dublin 2, Ireland

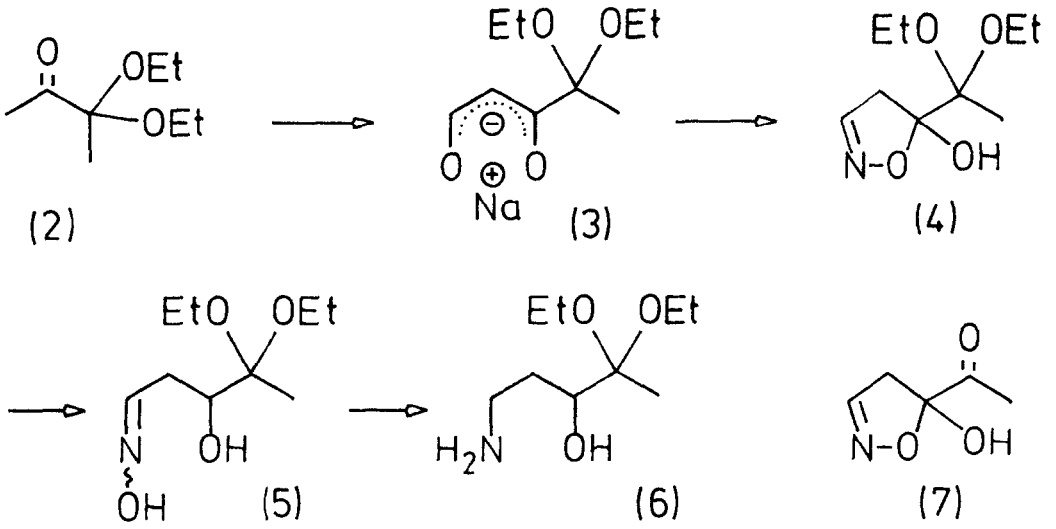
Summary: 2-amino-4-oxo-6-acetyl-3,4,7,8-tetrahydro-3H,9H-pyrimido-[4,5-b][1,4]diazepine (or 6-acetylhomopterin), has been synthesised from 1-amino-4,4-diethoxy-3-pentanol and 2-amino-4-chloro-5-nitro-6(1H)-pyrimidinone.

6-Acetylhomopterin (1) is one of only two diazepines known to occur naturally in the animal kingdom.[1] The other is the eye pigment drosopterin,[2] derived from (1) as a precursor, in Drosophila melanogaster. 6-Acetylhomopterin (1) itself is formed biosynthetically from dihydroneopterin triphosphate via 6-pyruvoyltetrahydropterin.[3] The latter is also a key intermediate in the biosynthesis of tetrahydrobiopterin,[4] which is currently the focus of great interest because of its involvement in human diseases of the central nervous system. The possibility thus arises that 6-acetylhomopterin (1) could affect some of the pteridine pathways in the metabolism of animals. At present it is available only from its natural source, however, from the eyes of Drosophila, and for this reason we wish to report an unambiguous route to its chemical synthesis.



(1)

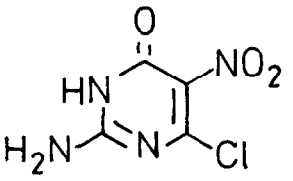
In this synthesis, four of the unfused diazepine ring atoms of the target molecule (1), together with the side chain acetyl group, were derived from the β-amino alcohol (6), and this in turn was synthesised from the mono diethyl acetal (2) of biacetyl[5] via an isoxazoline intermediate (4). The reaction sequence is shown below.



The sodium enolate (3) was readily obtained by formylation of the acetal (2) with ethyl formate and sodium hydride, and on stirring it in a buffered solution at pH 7 with hydroxylamine hydrochloride at room temperature, it afforded the 5-hydroxyisoxazoline (4) in 83% yield. It was not found possible to dehydrate (4) to the aromatic isoxazole, although it was easily converted to 5-acetyl-5-hydroxy-4,5-dihydroisoxazole (7) by acid hydrolysis of the acetal group. 5-Hydroxyisoxazolines are well known, and may exist in equilibrium with the corresponding open chain β-keto oximes, but usually they can be easily dehydrated to the corresponding isoxazoles.[6] Reduction of (4) with sodium borohydride gave (73%) a mixture of syn and anti oximes (5), which could be separated by flash chromatography. One isomer was obtained as a stable crystalline solid. The other was obtained as an oil, which on standing at room temperature equilibrated to give a mixture of the two isomers once again. The mixture of oximes (5) was reduced with lithium aluminium hydride to give the desired amino alcohol (6) in 80% yield. Alternatively, the isoxazoline (4) could be reduced directly to (6) by lithium aluminium hydride, but the overall yields by this route were lower (25%).

Condensation of the β-amino alcohol (6) with 2-amino-4-chloro-5-nitro-6(1H)-pyrimidinone (8) in ethanol solution in presence of solid sodium hydrogen carbonate, gave compound (9) in 80% yield. Mildly basic conditions were necessary for this condensation in order to preserve the acetal grouping intact. If potassium acetate was used for this purpose, yields were very much

lower, owing to competitive attack by the acetate on the active chlorine atom at position 4 of the pyrimidine. Cleavage of the acetal group in (9) occurred readily on treatment with aqueous acid, to give the hydroxy ketone (10). Oxidation of the secondary alcohol group in (9) could be accomplished without cleavage of the acetal by using dimethysulphoxide in acetic anhydride. The 2-amino group was simultaneously acetylated by this treatment, to give the 2-acetamido ketone acetal (11), but the amide group in this could be readily hydrolysed with dilute alkali to afford the desired ketone acetal (12). This latter could also be obtained directly from (9) by oxidation of the latter with chromium trioxide in pyridine. All these new compounds were fully characterised by elemental analysis and by their spectroscopic properties. Mild acid hydrolysis of (12) gave diketone (13).



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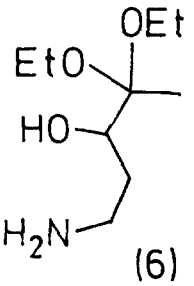

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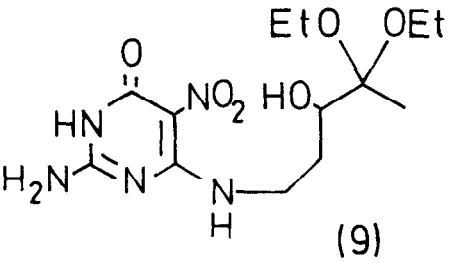

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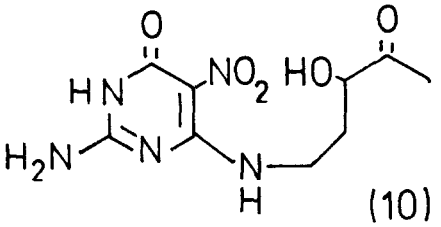

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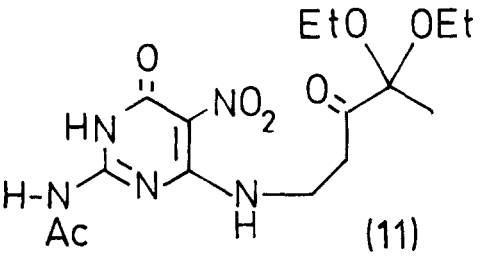

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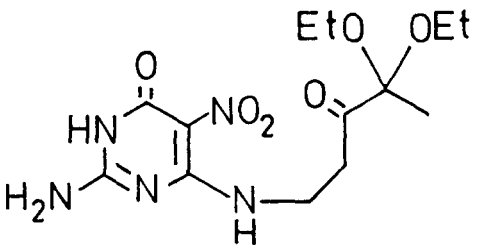

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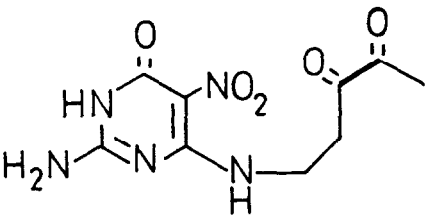

(13)

The target pyrimidodiazepine (1) was obtained from compound (12) in one step, without isolating the intermediates, by reducing (12) in alkaline aqueous dimethylformamide solution[7] with sodium dithionite. After reduction, the reaction mixture was treated with 1M barium chloride, filtered, and maintained at pH 3 at room temperature for 20 minutes. It was then neutralised to pH 7, evaporated, and the product chromatographed on a column of cellulose, eluting with 0.25% aqueous ammonium chloride solution at 4°C. On cooling, greenish yellow crystals of pure pyrimidodiazepine (1) were obtained. This product was identical on tlc and hplc with a sample of the material isolated from Drosophila, and kindly given to us by Dr. Jacobson. It analysed correctly for carbon, hydrogen, and nitrogen, and it had the same uv, ir, nmr, and ms properties as those reported[1] for the natural material. On cellulose tlc plates, the product showed a dark spot at room temperature. However, a strong fluorescence was observed at -196°, obtained by immersing the dried chromatogram in liquid nitrogen.[8]

ACKNOWLEDGEMENTS

We dedicate this work with great pleasure to Professor Wolfgang Pfleiderer on the occasion of his sixtieth birthday. We are grateful to the National Board for Science and Technology of Ireland, and to the government of the Republic of Iraq, for financial support.

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(Received in UK 22 July 1987)