A New Synthesis of Pyrazofurin

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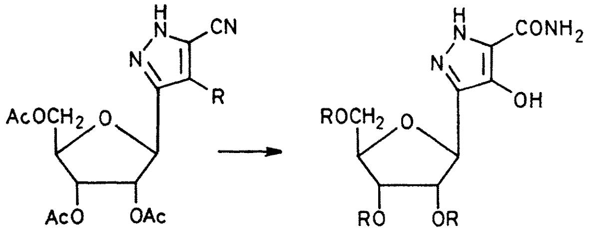
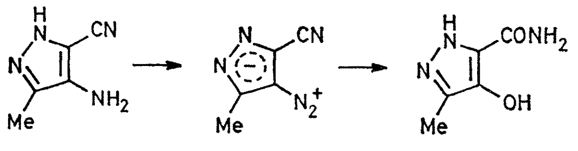
Summary Pyrazofurin (**4**) has been synthesised by a novel route, involving, as the key step, photochemical substitution of a diazopyrazole

The C-nucleoside antibiotic pyrazofurin (pyrazomycin)[1] (**4**), isolated from the culture filtrate of a strain of *Streptomyces candidus*,[2] shows activity against a number of viruses[3] and tumours,[4] and is currently undergoing clinical trials


(1),R = NH_2
(2),R = OH
(3) R = Ac
(4) R = H

Pyrazofurin has previously been synthesised by two distinct routes,[5,6] and we now report the application of our general method for C-nucleoside synthesis,[7] involving acetylenic intermediates, to the synthesis of pyrazofurin, these methods have recently been successfully applied to the synthesis of the related antibiotic formycin [8]

Our earlier work[8] had led to the synthesis of the 4-aminopyrazole (**1**) Use of this intermediate for the synthesis of pyrazofurin clearly necessitates the replacement of nitrogen with oxygen at C-4 and a sequence involving diazotisation suggested itself Use of this procedure for the synthesis of 4-hydroxypyrazoles is, however, not well documented, owing presumably to the known stability of pyrazole diazonium salts [9] Furthermore, it would be necessary to carry out a diazotisation prior to conversion of the nitrile into an amide, in order to avoid cyclisation to a pyrazolo-[4,3-*d*]triazinone [10] Diazotisation ($NaNO_2$, $MeCO_2H$, 0 °C) of the model compound 4-amino-5-cyano-3-methylpyrazole (**5**)[10], and subsequent neutralisation ($NaHCO_3$), gave the crystalline diazopyrazole (**6**) which was stable under a variety of hydrolytic conditions When a solution of (**6**) in aqueous acetone was subjected to u v photolysis[11,12] through Pyrex the 4-hydroxy compound (**7**) was produced in 62% overall yield When a similar sequence was applied to (**1**) the hydroxypyrazole (**2**) was obtained in 87% yield


(5) (6) (7)

Hydrolysis of the nitrile function was best achieved using nickel acetate tetrahydrate in boiling acetic acid,[13] to give pyrazofurin triacetate (**3**) (65%); treatment of (**3**) with ammonia in aqueous methanol produced crystalline pyrazofurin (**4**) (75%), indistinguishable from an authentic sample.

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