A New Synthesis of Formycin *via* Nitropyrazole Derivatives

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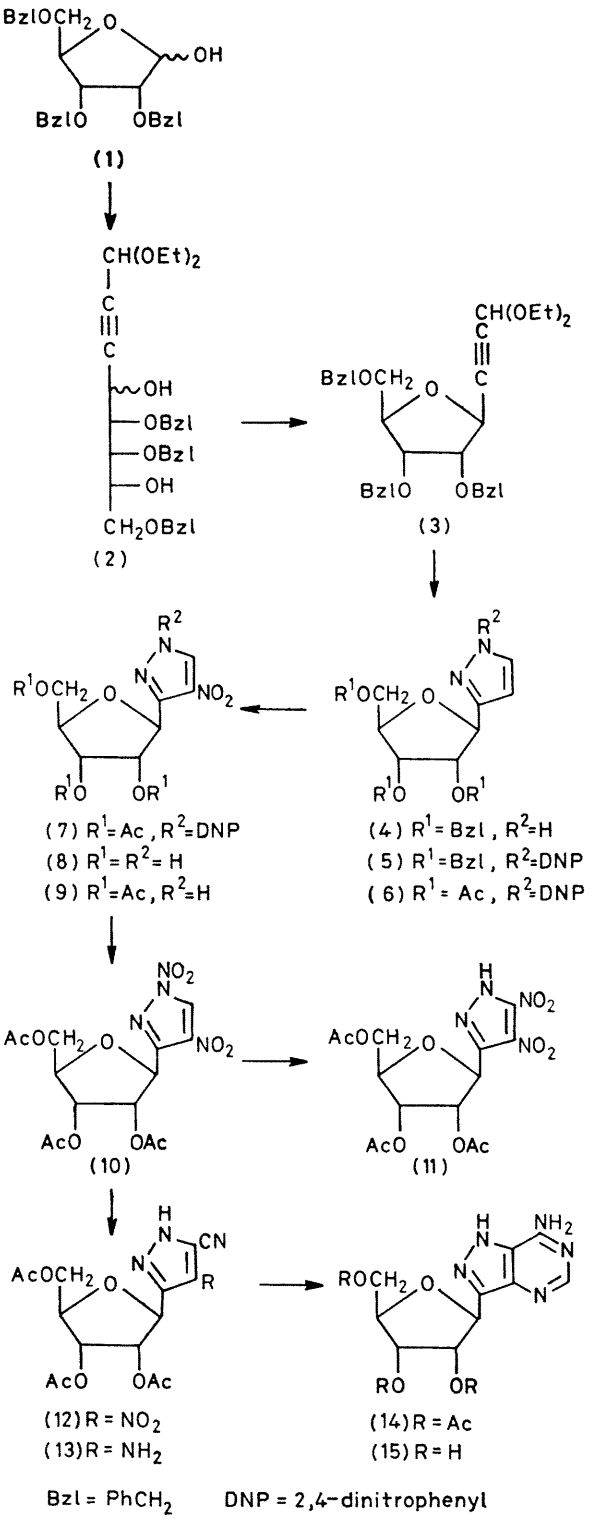
Summary 3-(2,3,5-Tri-*O*-benzyl-β-D-ribofuranosyl)pyrazole (**4**) has been converted into formycin (**15**) by a sequence involving, as the key step, *cine* substitution, by cyanide ion, of the 1-nitro group in the 1,4-dinitropyrazole (**10**).

THE *C*-nucleoside antibiotic formycin[1,2] (**15**) is a naturally occurring isomer of adenosine, containing a pyrazole in place of an imidazole ring. It has antiviral and antitumour properties and is able to replace the adenosine unit in a number of enzymic reactions at the nucleotide level. Although formycin has already been synthesised by two distinct routes[3,4] we were interested in applying our own general method,[5] which involves acetylenic intermediates, to the problem.

The ribofuranosylpyrazole[6,7] (**4**) has been prepared by an improved method. Reaction of the ribofuranose (**1**) and 3,3-diethoxyprop-1-ynylmagnesium bromide formed a mixture of D-*altro* and D-*allo* diols (**2**) which underwent ring-closure with toluene-*p*-sulphonyl chloride in pyridine[5] to give the β-D-*ribo*-isomer (**3**) [52% from (**1**)] together with the α-isomer (**8**%). Acidic hydrolysis of (**3**) followed by reaction with hydrazine gave the pyrazole (**4**) (71%) identical with that from earlier preparations.

Although nitration of a pyrazole ring normally takes place at C-4,[8] forcing conditions are required when a nitric-sulphuric acid mixture is used, owing to the formation of the pyrazolium cation. Acetyl nitrate, which acts on the neutral pyrazole ring, causes *N*-nitration. We therefore prepared the *N*-2,4-dinitrophenyl derivative (**5**) by means of 1-fluoro-2,4-dinitrobenzene and triethylamine in benzene solution.[9] The benzyl ether groups were easily removed by boron trichloride and the resulting triol was converted into the triacetate (**6**) in 80% overall yield from (**4**). Nitration of (**6**) with cupric nitrate.$3H_2O$ in acetic anhydride[10] then gave the 4-nitro-derivative (**7**) (93%); the location of the nitro group was shown by the disappearance of the characteristic signal due to H-4 in the ^1H n.m.r. spectrum. Removal of the protecting groups[9] with methanolic sodium methoxide yielded the triol (**8**) (76%) which was converted into the triacetate (**9**) (94%). *N*-Nitration[11] of (**9**) to give a single isomer (**10**) in 87% yield was achieved with the copper nitrate reagent; in the ^1H n.m.r. spectrum the signal for the pyrazole ring proton was deshielded further by the *N*-nitro group, thus establishing structure (**10**).

Habraken and Poels[12] have recently shown that 1,4-dinitropyrazoles react with secondary amines at C-5 in a *cine* substitution with expulsion of the *N*-nitro group as nitrite. When (**10**) was added to an excess of potassium cyanide in aqueous ethanol a very rapid reaction occurred at room temperature to give the key nitrile (**12**) (82%, as a crystalline benzene solvate). It may be noted, in addition, that thermal rearrangement[11] of (**10**) (in boiling anisole for 12 h) afforded the dinitropyrazole (**11**) (60%), a potential intermediate for elaboration of a fused pyrazine or other ring.



Catalytic hydrogenation of (**12**) gave the 4-aminopyrazole (**13**) (84%). Subsequent reaction of (**13**) with formamidine acetate in boiling 2-ethoxyethanol yielded formycin triacetate (**14**) (79%) which was converted by methanolysis into formycin (**15**) (90%), indistinguishable from an authentic sample.

The method described should be capable of extension to the synthesis of a number of analogues of formycin containing modifications in the sugar and heterocyclic portions.

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