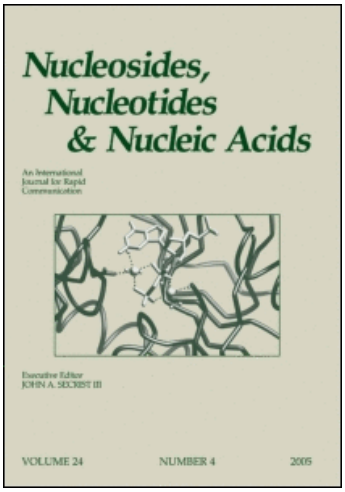

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PYRAZOLO[3,4-b]PYRIDINE NUCLEOSIDES: TOTAL SYNTHESIS OF THE GUANOSINE, ISOGUANOSINE AND XANTHOSINE ANALOGUES†

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Summary. An expeditious and total synthesis of the guanosine (3a), isoguanosine (3b) and xanthosine (3c) analogues in the pyrazolo[3,4-b]pyridine ring system has been accomplished for the first time from the precursor 5-amino-1-(2,3-O-isopropylidne-β-D-ribofuranosyl)pyrazole (8) by various ring closure procedures.

We described the rationale behind the regio- and stereoselective synthesis of certain pyrazolo[3,4-b]pyridine nucleosides (1 and 2), which are structurally related to adenosine and inosine.[1] In this report we describe the first example of 4,6-disubstituted pyrazolo[3,4-b]pyridine ribonucleosides from hitherto unreported 5-amino-1-(2,3-O-isopropylidene-β-D-ribofuranosyl)pyrazole (8) by unique ring annulation procedures.

Compound 6[2], was saponified to give 7 (98% yield), which on subsequent decarboxylation (in Ph_2O at 220° C) furnished the key starting material 8 as a crystalline compound (84% yield). The pyrazole 8 was converted to 12 in 4-steps as follows: When pyrazole 8 was heated with the sodium salt of diethyl oxalacetate in glacial AcOH, compound 9 was obtained, which on treatment with hydrazine furnished the hydrazide 10. Compound 10 was allowed to react with $NaNO_2$/AcOH to provide the azide 11, which on Curtius rearrangement afforded the isopropylidene blocked nucleoside 12 in 51% overall yield for 4-steps starting from 8.

The carboxylate 6 was reacted[3] with diethyl malonate in NaOEt/EtOH to provide nucleoside 13 in 62% yield. Blocking of 13 with 90% aq TFA gave compound 14, which on saponification and decarboxylation furnished the xanthosine analogue 3c.

Using compound 15[4], we have now prepared for the first time, the guanosine analogue 3a from the nucleoside 8. The ketene dithioacetal 15 reacted with 8 in EtOH to provide 16, which on subsequent ammonolysis in the presence of $HgCl_2$ furnished crystalline 18 (mp 172° C). Thermal cyclocondensation gave the isopropylidene derivative 19. Deblocking of 19 gave the guanosine congener 3a in ca. 9% overall yield. A similar reaction of 15 with 8 in DMF (120° C) furnished the ring annulated product 17 in one step (via the intermediate 16) in 86% yield.

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† Dedicated to Professor C.B. Reese on the occasion of his 60th Birthday.
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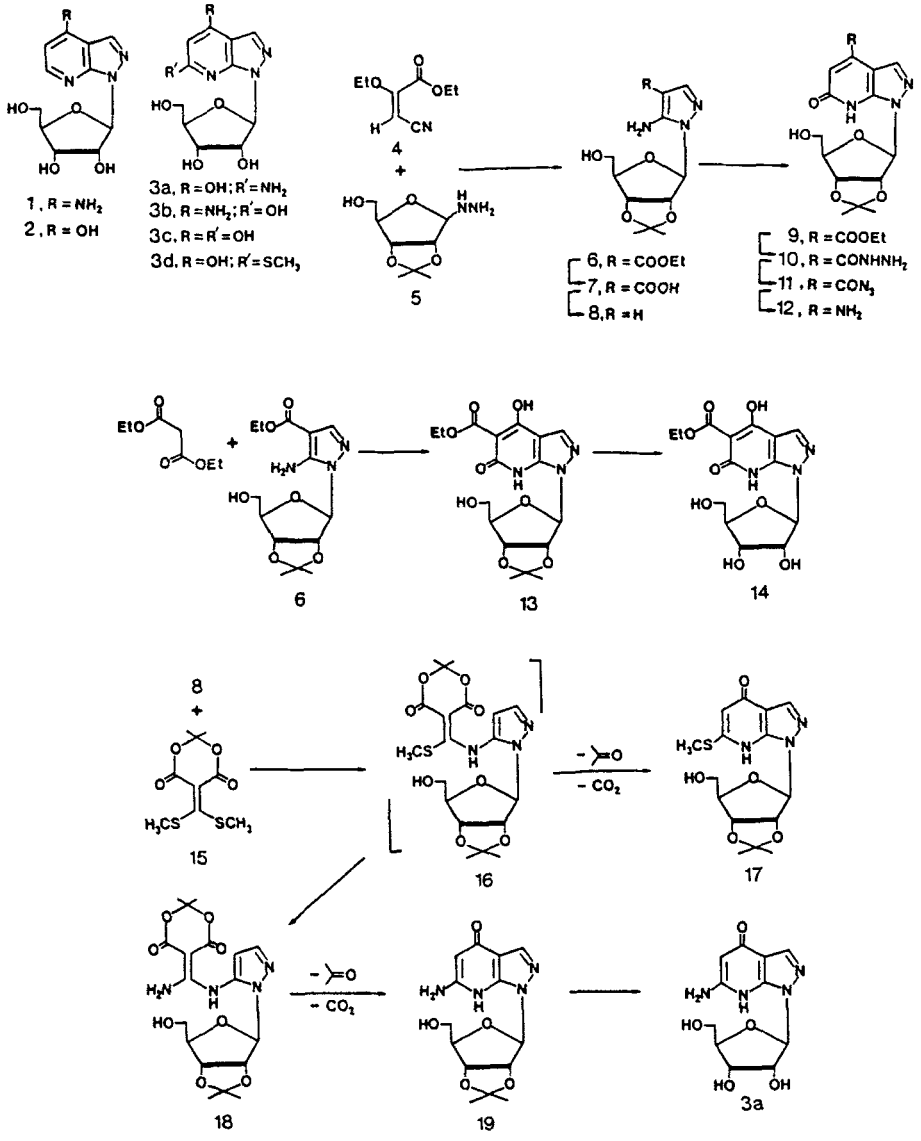

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