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Potential Purine Antagonists: Part IX — Synthesis of 3-β-D-Ribofuranosyl-6-nitroimidazo- & Triazolo(4,5-*b*)pyridines*

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3-β-D-Ribofuranosyl-6-nitroimidazo- and triazolo[4,5-*b*]pyridines have been prepared through the chloromercury compounds and the position of the sugar residue confirmed by comparison of their UV spectra with those of authentic 3-methyl-6-nitroimidazo- and triazolo[4,5-*b*]pyridines. These compounds do not show any anticancer or antiviral activity.

IN view of the cytotoxic properties of 9-β-D-ribofuranosylpurine (nebularine)[1], the synthesis of 3-β-D-ribofuranosyl-6-nitroimidazo- and triazolo[4,5-*b*]-pyridines (Ia and IIa) has been carried out as the nitro group in position 6 of the latter would simulate the electronic character of the ring nitrogen and the ribosides Ia and IIa would thus be close analogues[2-6] of nebularine.

2-Amino-3,5-dinitropyridine, obtained[7] in almost quantitative yield by the action of ammonia on 2-chloro-3,5-dinitropyridine[8], gave 2,3-diamino-5-nitropyridine on partial reduction with sodium hydrosulphide in 58 per cent yield; m.p. 256° (lit.[9] m.p. 260°).

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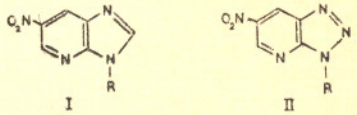

a, R = RIBOSE
b, R = H
c, R = CH_3

2,3-Diamino-5-nitropyridine gave on treatment with formic acid 6-nitroimidazo[4,5-*b*]pyridine (Ib) in 70 per cent yield, crystallized from ethanol; m.p. 297° after darkening at 265 (lit.[9], m.p. gradually sinters and decomposes above 260°), and on treatment with nitrous acid 6-nitrotriazolo [4,5-*b*]pyridine in 95 per cent yield, crystallized from water; m.p. 206-7° (decomp.) (Found: C, 36·7; H, 2·29; N, 42·08. $C_5H_3N_5O_2$ requires C, 36·36; H, 1·81; N, 42·4%).

(Ib) and (IIb) were converted to their chloromercury compounds and condensed with 2,3,5-tri-O-benzoylribofuranosyl chloride according to the method described earlier[3] to give (Ia) and (IIa). Ia crystallized from methanol-ether; yield 43 per cent; m.p. 155-7°; $[\alpha]_D^{32}$ −48 (*C*, 1 in methanol); R_f(A*), 0·66; R_f(B*), 0·74 (Found: C, 44·68; H, 4·00; N, 18·57. $C_{11}H_{12}N_4O_6$ requires C, 44·5; H, 4·05; N, 18·90%).

IIa was obtained as an amorphous powder, which was purified by preparative paper chromatography

*Paper chromatography was carried out on Whatman filter paper No. 1 by descending technique. R_f (A) and R_f (B) refer to R_f values in solvent A (*n*-butanol saturated with water) and solvent B (*n*-butanol-acetic acid-water 4:1:5, vol./vol.) respectively. The spots were located under a mineralite ultraviolet lamp.

TABLE 1 — UV SPECTRAL DATA OF VARIOUS IMIDAZO AND TRIAZOLOPYRIDINES

[UV spectra were recorded on a Unicam spectrophotometer in a concentration of 20 mg./litre]

Distilled water				0·1*N* HCl				0·1*N* NaOH			
$\lambda_{max.}^{H_2O}$	$\epsilon \times 10^{-3}$	$\lambda_{min.}^{H_2O}$	$\epsilon \times 10^{-3}$	$\lambda_{max.}^{HCl}$	$\epsilon \times 10^{-3}$	$\lambda_{min.}^{HCl}$	$\epsilon \times 10^{-3}$	$\lambda_{max.}^{NaOH}$	$\epsilon \times 10^{-3}$	$\lambda_{min.}^{NaOH}$	$\epsilon \times 10^{-3}$
3-β-D-RIBOFURANOSYL-6-NITROIMIDAZO[4,5-*b*]PYRIDINE											
237	19·60	270	3·72	229	15·48	267	3·70	240	17·64	275	4·68
305	8·03			297	6·86			310	6·27		
3-METHYL-6-NITROIMIDAZO[4,5-*b*]PYRIDINE											
237	20·96	270	4·20	226	18·46	267	4·21	240	17·14	275	3·30
305	9·23			297	8·17·			310	7·78		
3-β-D-RIBOFURANOSYL-6-NITROTRIAZOLO[4,5-*b*]PYRIDINE											
235	15·83	270	3·98	235	14·02	270	3·64	227	12·32	270	3·94
302	8·09			303	7·12			304	5·83	340	1·49
								405	3·25		
3-METHYL-6-NITROTRIAZOLO[4,5-*b*]PYRIDINE											
235	17·26	270	4·50	235	15·28	270	4·13	227	12·85	270	3·86
302	9·08			303-5	8·09			300-5	6·13	340	1·57
								405	4·76		

on Whatman No. 3 filter paper; yield 34 per cent $[\alpha]_D^{32}$ −57 (*C*, 1 in methanol), R_f(A) 0·63 (Found: C, 39·84; H, 4·21; N, 23·02. $C_{10}H_{11}N_5O_6$ requires C, 40·4; H, 3·7; N, 23·6).

In order to assign the position of sugar moiety in Ia and IIa, 3-methyl-6-nitroimidazo- and triazolo [4,5-*b*]pyridines (Ic and IIc) were prepared by a similar sequence of reactions. 2-Methylamino-3,5-dinitropyridine was obtained by the condensation[7] of methylamine with 2-chloro-2,5-dinitropyridine. It crystallized from ethanol; yield 85 per cent; m.p. 148° (Found: C, 36·53; H, 3·21; N, 28·57. $C_6H_6N_4O_4$ requires C, 36·36; H, 3·03; N, 28·2%).

2-Methylamino-3-amino-5-nitropyridine was obtained by the partial reduction[7] of 2-methylamino-3,5-dinitropyridine with ammonium sulphide. It crystallized from ethanol; yield 40 per cent; m.p. 222-4° (Found: C, 43·24; H, 5·22; N, 33·60. $C_6H_8N_4O_2$ requires C, 42·85; H, 4·70; N, 33·33%).

(Ic) and (IIc) were obtained by cyclization of 2-methylamino-3-amino-5-nitropyridine with formic acid and nitrous acid respectively. (Ic) crystallized from ethanol; yield 85 per cent; m.p. 226°; R_f(A), 0·675 (Found: C, 47·43; H, 3·62; N, 31·36. $C_7H_6N_4O_2$ requires C, 47·19; H, 3·37; N, 31·46%). (IIc) crystallized from ethanol; yield 90 per cent; m.p. 151-2°; R_f(A), 0·703 (Found: C, 40·60; H, 2·90; N, 38·83. $C_6H_5N_5O_2$ requires C, 40·2; H, 2·6; N, 39·10%).

The UV spectra (Table 1) of (Ia) and (IIa) were identical with those of the corresponding 3-methyl compounds (Ic and IIc) respectively in distilled water, 0·1*N* HCl and 0·1*N* sodium hydroxide solution. Thus the ribose moiety in these ribosides is present at position 3. The UV spectra of triazolopyridines (IIa and IIc) were interesting as in alkaline medium the solution turned yellow and besides other absorption bands gave a new peak at 405 mμ, which disappeared on neutralizing the solution thus eliminating the possibility of the triazolo ring being opened in alkaline solution. This phenomenon, therefore, seems to be due to the formation of nitronic acid species in alkaline solution.

These compounds were tested for their anticancer activity against KB cell line in the National Cancer Screening Centre, National Institute of Health, Bethesda, USA, and for their antiviral activity in tissue culture by Parke Davis & Co., and were found to be inactive in these tests.

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