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A NEW METHOD FOR THE SYNTHESIS OF SOME 9-β-D-ARABINOFURANOSYLPURINES BY A COMBINATION OF CHEMICAL AND ENZYMATIC REACTIONS[1)]

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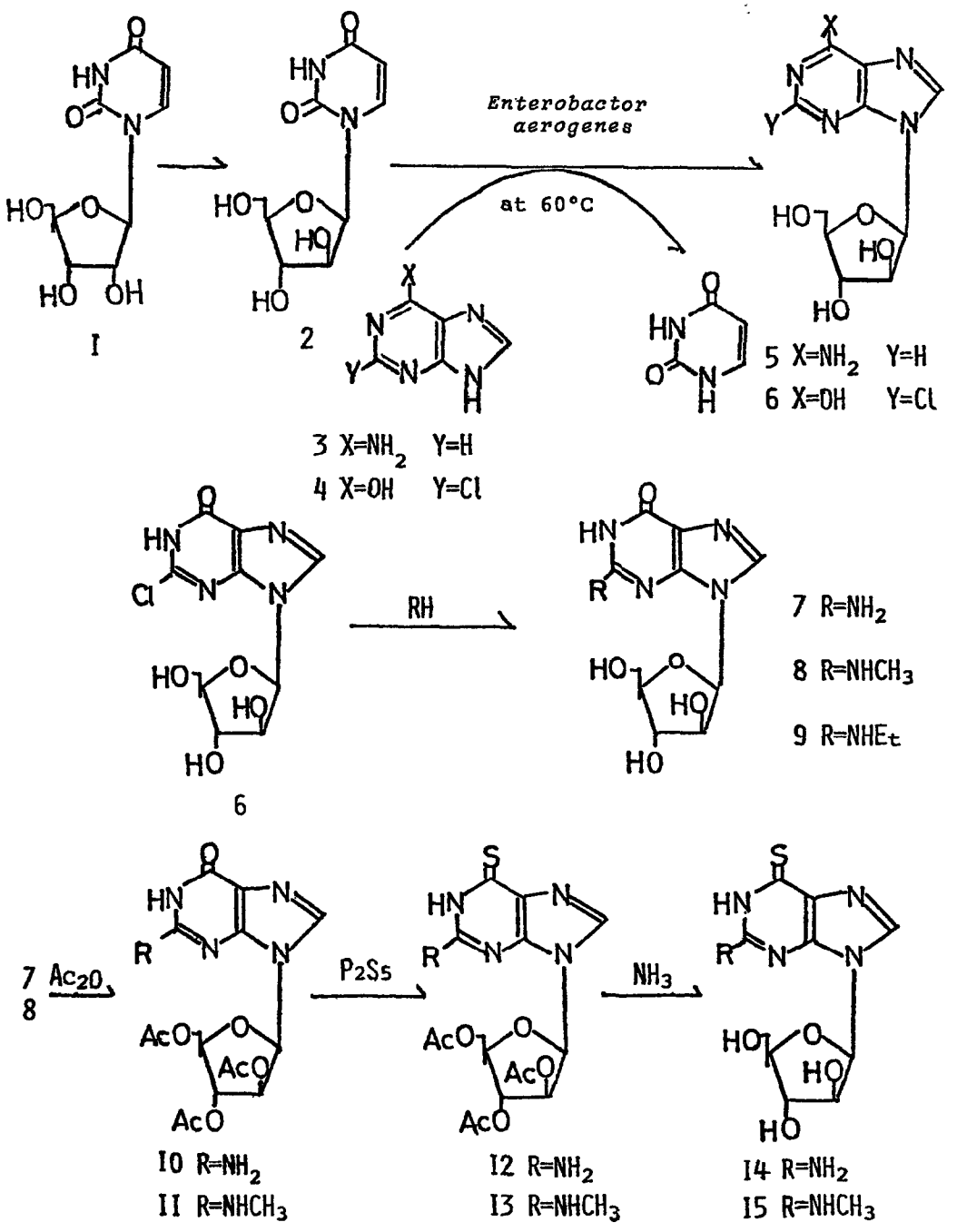
Summary: An enzymatic transarabinosylation between 2-chlorohypoxanthine and 1-β-D-arabinofuranosyluracil gave 9-β-D-arabinofuranosyl-2-chlorohypoxanthine which was chemically converted to 9-β-D-arabinofuranosylguanine and its derivatives.

The antiviral or antitumor activity of 9-β-D-arabinofuranosylpurines or the corresponding nucleotides has generated considerable interest.[2)] Although the syntheses of 9-β-D-arabinofuranosylpurines have been achieved by a sugar-base coupling reaction,[3)] by a cleavage reaction of 8,2'-anhydro-8-oxy-9-β-D-arabinofuranosylpurines[4)] or by a transformation of oxazolidinethione derivative,[5)] there remain some definite practical limitations in these approaches because of low-yielding, laborious and time-consuming process.

We now report a new strategy for the utilization of enzymes as catalysts in the synthetic process of 9-β-D-arabinofuranosylpurines. More recently we have shown[6)] that the antiviral agent, 9-β-D-arabinofuranosyladenine (5, ara-A), can be easily obtained by a novel enzymatic transarabinosylation between adenine (3) and 1-β-D-arabinofuranosyluracil (2). This procedure was extended successfully to the synthesis of 9-β-D-arabinofuranosyl-2-chlorohypoxanthine (6), which was important as an intermediate for the preparation of biologically interesting 9-β-D-arabinofuranosylpurines.

When 2-chlorohypoxanthine (4) (0.1 mol) and compound 2 (0.3 mol), readily obtained via 2,2'-anhydro -β-D-arabinofuranosyluracil[7)] from uridine (1), were incubated with intact cells of Enterobactor aerogenes (500 g as wet paste) in 10 ℓ of 25 mM potassium phosphate buffer (pH 7.0) for 12 hours at 60°C, compound 6 was produced specifically and, after removing the bacterial cells, isolated by column chromatography (Dowex 1 X 4) in 34% yield (based on 4). This compound had m.p. 208-209°C (dec.) and showed nmr [(DMSO-d_6) δ 8.06 (H-8), 6.02 (H-1', $J_{1',2'}$=4.5 Hz)] and UV spectra [$\lambda_{max}^{pH\ 1}$ 253 nm (ε=12000), $\lambda_{max}^{pH\ 13}$ 257 nm (ε=13600)], the latter of which was identical with those previously reported.[8)]


Enterobactor aerogenes
at 60°C
I
2
3 X=NH2 Y=H
4 X=OH Y=Cl
5 X=NH2 Y=H
6 X=OH Y=Cl
RH
6
7 R=NH2
8 R=NHCH3
9 R=NHEt
7 Ac2O
8
P2S5
NH3
I0 R=NH2
II R=NHCH3
I2 R=NH2
I3 R=NHCH3
I4 R=NH2
I5 R=NHCH3

Compound 6 was treated with methanolic ammonia in an autoclave at 150°C for 4 hours to give 9-β-D-arabinofuranosylguanine (7, ara-G) in 85% yield, which had m.p. >300°C (darkens at 275°C), nmr [(DMSO-d_6) δ 7.77 (H-8), 6.04 (H-1′, $J_{1',2'}$=3.9 Hz)] and UV spectra [$\lambda_{max}^{pH\ 1}$ 257 nm (ε=12900), 278 nm (sh. ε=8700), $\lambda_{max}^{pH\ 13}$ 259 nm (ε=12100), 267 nm (ε=12300)], which were the same with those reported earlier.[4b,8,9] Compound 7 has been reported to have a significant antiviral activity.[2a]

Substitution of methylamine and ethylamine for ammonia in the synthesis of ara-G similarly afforded 9-β-D-arabinofuranosyl-N^2-methylguanine (8) and -N^2-ethylguanine (9) in 47 and 58% yields, respectively. Compound 8 had m.p. >300°C; nmr (DMSO-d_6) δ 7.86 (H-8), 6.08 (H-1′, $J_{1',2'}$=4.2Hz), 2.83 (N-CH_3); UV $\lambda_{max}^{pH\ 1}$261 nm (ε=13800), 284 nm (sh. ε=7400), $\lambda_{max}^{pH\ 13}$259 nm (ε=11600), 272 nm (sh. ε=10400). Compound 9 had m.p. 216-217°C; nmr (DMSO-d_6) δ 7.60 (H-8), 5.90 (H-1′, $J_{1',2'}$=4.2 Hz), 3.33 (N-CH_2-CH_3), 1.16 (N-CH_2-CH_3); UV $\lambda_{max}^{pH\ 1}$261.5nm (ε=14400), 285 nm (sh. ε=7400), $\lambda_{max}^{pH\ 13}$260 nm (ε=12000), 272 nm (sh. ε=10700).

Acetylation of 7 with acetic anhydride in pyridine gave the corresponding triacetate (10) (m.p. 216-218°C) in 88% yield, which was further heated with phosphorus pentasulfide in pyridine for 4 hours, affording 6-thio derivative (12) (m.p. 247-248°C) in 72% yield. Deacetylation of 12 with methanolic ammonia gave 9-β-D-arabinofuranosyl-6-thioguanine (14) in 60% yield, which has been reported to show a potent antitumor activity.[10] This compound had m.p. 250°C dec. (darkens at 210°C) and showed nmr [(DMSO-d_6) δ 7.95 (H-8), 5.95(H-1′, $J_{1',2'}$=4.2 Hz)] and UV spectra [$\lambda_{max}^{pH\ 1}$ 264 nm (ε=7800), 351 nm (ε=20700), $\lambda_{max}^{pH\ 13}$ 252 nm (ε=12000), 270 nm (sh. ε=7000), 320.5 nm (ε=17900)]. Although λ_{max} (351 nm at pH 1) of 14 was slightly different from that previously reported,[10] it was the same with that of thioguanosine.

By the same manner, 9-β-D-arabinofuranosyl-N^2-methyl-6-thioguanine (15) was also obtained *via* the triacetate (11) (m.p. 281-283°C) of 8 and its 6-thio derivative (13), m.p. 290°C (dec.), in 33% overall yield. Compound 15 had m.p. >300°C (darkens at 235°C); UV $\lambda_{max}^{pH\ 1}$ 270 nm (ε=10200), 356 nm (ε=18700), $\lambda_{max}^{pH\ 13}$ 258 nm (ε=14000), 277 nm (sh. ε=9400), 324 nm (ε=14500); nmr (DMSO-d_6) δ 7.90 (H-8), 6.05 (H-1′, $J_{1',2'}$=4.2 Hz), 2.85 (N-CH_3).

Thus the present methodology by a combination of chemical and enzymatic reactions seems to be very promising to synthesize biologically important 9-β-D-arabinofuranosylpurines with ease and on a large scale.

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