

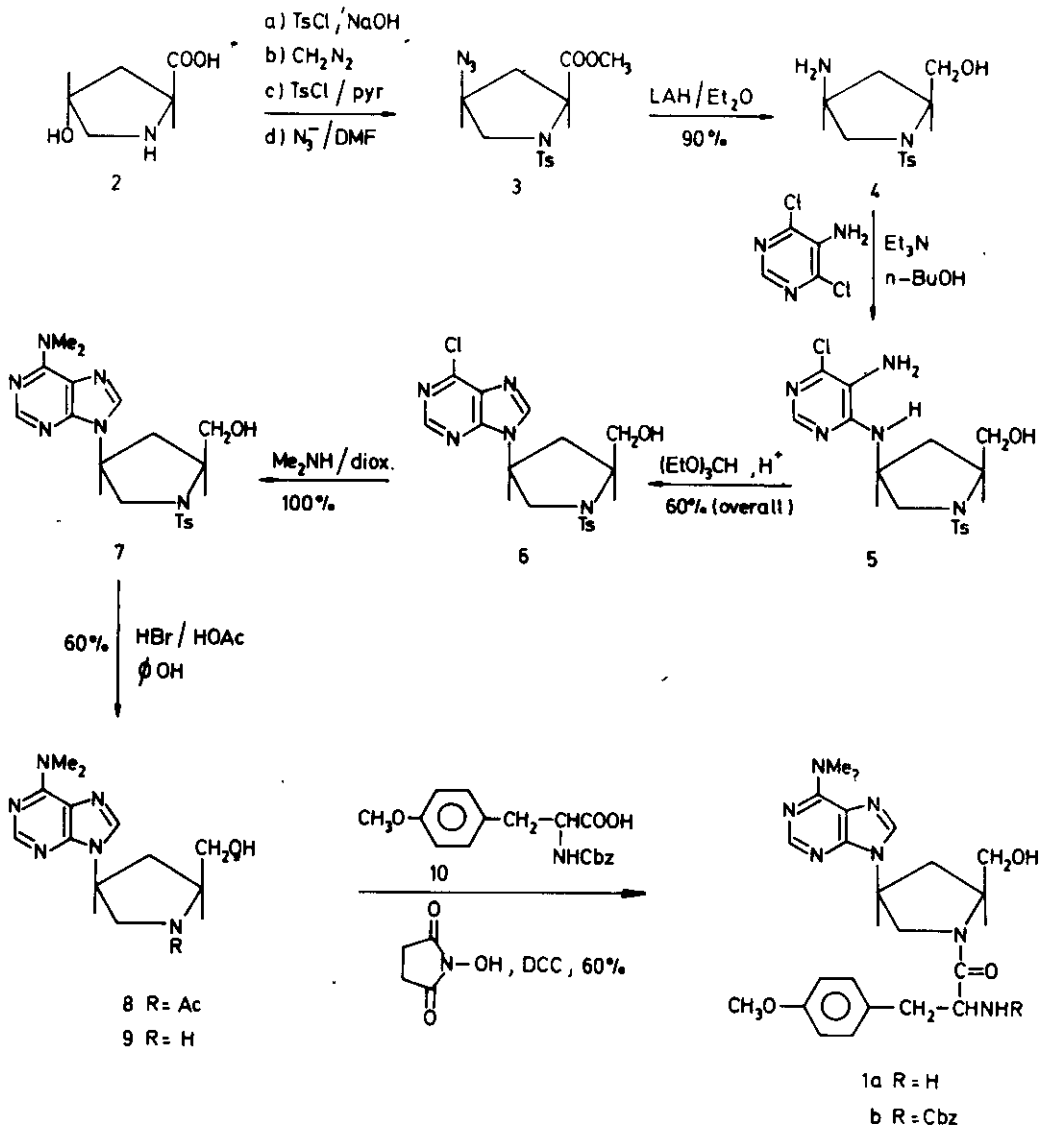
SYNTHESIS OF A NON-SACCHARIDAL ANALOG OF PUROMYCIN¹.

Frans M. Kaspersen², Hans Bieräugel and Upendra K. Pandit*
Organic Chemistry Laboratory, University of Amsterdam,
Nieuwe Achtergracht 129, Amsterdam, The Netherlands.

The synthesis of (2S,4S)-N-(p-methoxyphenyl-L-alanyl)-2-hydroxymethyl-4-[N₉-6-(dimethylamino)purinyl]pyrrolidine (1), a non-saccharidal analog of puromycin, is described.

Several non-saccharidal nucleoside analogs in which the purine and pyrimidine bases are attached to α -amino acids have been recently reported from this laboratory.^{3,4} Particular interest resides in these systems in view of their analogy to nucleo-peptide models.⁵ Amongst the natural α -amino acids L-proline possesses structural features which make it uniquely suitable as a substitute for the glycosidic moiety of the nucleoside analogs.⁶ This communication describes the synthesis of the novel puromycin analog 1a.

The commercially available optically active (-)-4-hydroxy-L-proline (2) was visualized as a convenient starting material for the synthesis of 1. N-Tosylation of 2, followed by the sequence esterification, O-tosylation and reaction with azide anion led, via stereospecific substitution (S_N2) of the O-tosyl group, to azide 3.⁷ Reduction of the azide with LiAlH₄ yielded the versatile intermediate 4, mp 119-120° (90%), in which the amino group is capable of elaboration into a desired purine or a pyrimidine derivative.⁶ Conversion of 4 into the 6-chloropurine derivative 6 [mp 174-176°; uv (C₂H₅OH) 230 nm (ϵ 16,000), 265(10,500); nmr(CDCl₃) δ 8.42, 8.69 (2H, 2 x s, purine protons⁸)] was carried out in two



steps, namely, via its condensation with 5-amino-4,6-dichloropyrimidine and subsequent cyclization of the resulting pyrrolidine derivative 5 by heating it with ethyl orthoformate (pure) in the presence of catalytic quantities of HCl.

Treatment of 6 with dimethylamine in dioxane yielded, in quantitative yield, the corresponding 6-dimethylamino derivative 7, [mp 75-85°; uv (C₂H₅OH) 218 nm (ϵ 19,500), 276 (ϵ 16,000); nmr (CDCl₃) δ 3.50 (6H-s, N(CH₃)₂), 7.81, 8.26 (2H, 2 x s, purine protons⁸)]. Attempted detosylation of 7 (HBr/HOAc, PhOH) gave, in addition to the expected free amine 9, the corresponding N-acetylated product 8 [ir 1630 cm⁻¹ (NCOCH₃); nmr (CDCl₃) δ 2.11 (3H-broad singlet NCOCH₃)]. The mixture of 8 and 9 could be smoothly converted to 9 by treatment with KOH and methanol.

The coupling of 9 with protected p-methoxyphenylalanine 10 was most satisfactorily achieved by the use of DCC and N-hydroxysuccinimide.⁹ The latter procedure is known to involve little or no racemization during peptide bond formation and has been successfully applied to the synthesis of certain puromycin analogs.⁹ When the resulting dipeptide 1b was subjected to hydrogenolysis (H₂/Pd, HOAc) the benzyloxycarbonyl (Cbz) group was readily removed to yield the puromycin analog 1a as a hygroscopic solid, mp 72-75°, [ir (KBr) 1630 cm⁻¹ (N-C=O), 1590 (purine); uv (C₂H₅OH) 277 nm (ϵ 18,500)].

The nmr spectrum of 1a in CDCl₃ (30°) exhibits two analogous sets of partly superimposed signals. When, however, the spectrum was run at 100° (d₆-DMSO), several of the bands sharpened and the double sets of signals disappeared to result in a spectral pattern typical of a single species (Table I).

TABLE I

Temp.	N(CH ₃) ₂	p-MeOC ₆ H ₄ (aromatic)	H ₂ , H ₈ (purine)
30° (CDCl ₃)	3.49 (s) ^b	6.73, 6.81; 7.05, 7.13	7.61; 8.26
30° (CDCl ₃)	3.49 (s) ^b	a 6.91; 7.09, 7.17	7.81; 8.24
100° (d ₆ -DMSO)	3.44 (s)	6.76, 6.85; 7.09, 7.18	8.03; 8.21

a. Falls under signal at δ 6.81; b. broadened singlet.

These results can be rationalized in terms of the existence at 30°, of two discrete amide configurational isomers (I and II) involving a restricted rotation about the amide bond. This type of isomerization has been well documented.¹⁰ The possibility that steric hinderance to rotation of the purine moiety (about C-N bond) may account for the two isomers can be excluded from the fact that while compounds like 6 and 7 - in which steric hinderance would be appreciable - do not exhibit such isomerism, the nmr spectrum of the N-acetyl derivative 8 is consistent with existence of two 'frozen' rotamers. The rotational barrier is, however, insufficient to maintain the integrity of the two species at higher temperatures and the observed spectrum at 100° is that of a single substance. From the integrals of the aromatic and purine protons the ratio of I:II has been determined as 2:1.¹¹ Biological investigations on the puromycin analog 1a are in progress and their results will be presented elsewhere.

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