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NUCLEOSIDES X[1]. SYNTHESIS OF DIPEPTIDYL AMINOSUGAR NUCLEOSIDES, STRUCTURALLY RELATED TO GOUGEROTIN

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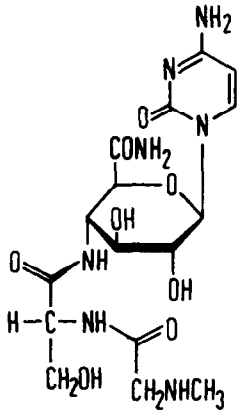
With the recent second revision of Iwasaki's formula[2] by Fox et al.[3] - prompted by findings[4] that the assignment of the 4-aminogalacto-configuration to carbohydrate degradation products[5] was incorrect - the formulation of gougerotin as 1 now appears to be firmly established, particularly in view of partial synthesis of the aminosugar[6] and nucleoside portions[7] of the molecule. Rather than seeking further verification of this structure by total synthesis, it seemed of more biochemical significance to study the influence of structural changes in the peptide, aminosugar and nucleobase moieties on the inhibitory action of peptide assembly in the 50S ribosomal subunit[8], the intricate details of which are as yet unclear. As the first results of studies directed towards this aim, we wish to report the synthesis of two sarcosyl-D-seryl-aminosugar nucleosides which differ from gougerotin in the sugar part (2) as well as in the nucleobase (3).



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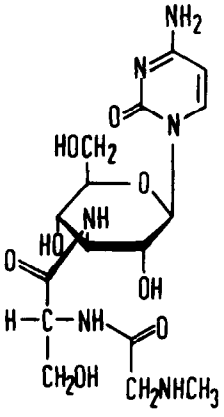

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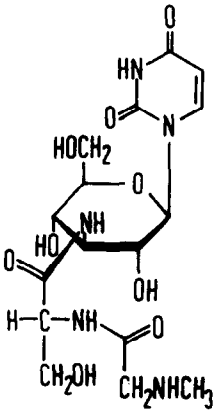
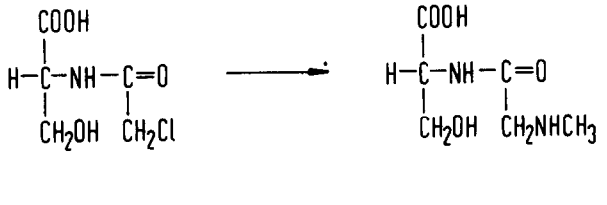


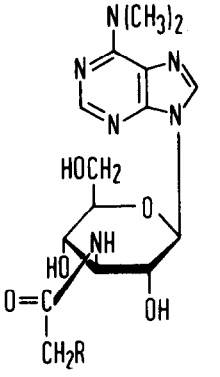
3

Peptides with an N-terminal sarcosyl-residue can be prepared by amination of chloroacetyl peptides with methylamine[9], a procedure, which on application to the N-chloroacetyl derivatives of L- and D-serine[10] respectively, gives ready access to sarcosyl-L-serine (m.p. 217-218°, dec., $[\alpha]_D^{25}$ -6.5° in water) and its D-enantiomer 5, the dipeptide in gougerotin (m.p. 220-222°, dec., $[\alpha]_D^{25}$ +6.5°). Thus, an attractive approach for

introducing a sarcosyl-seryl linkage to an aminosugar nucleoside seemed to be its N-acylation by use of an activated chloroacetyl-seryl derivative followed by amination.

However, attempts to link chloroacetyl-D-serine (4) and 9-(3-amino-3-deoxy-ß-D-glucosyl)-N,N-dimethyladenine[11] via the N,N-dicyclohexylcarbodiimide method[12] resulted in the formation of several products, among them the N-chloroacetyl derivative 6 ($[\alpha]_D^{25}$ -49° in water, dec., from 235° on), which was isolated in 22% yield and could be converted to the N-sarcosyl nucleoside hydrochloride (7), m.p. 187-190° and $[\alpha]_D^{25}$ -44° (water). Similar difficulties were encountered when employing the mixed anhydride method under conditions used successfully for linking this aminonucleoside with N-benzyloxycarbonyl-p-methoxy-L-phenylalanine[13].



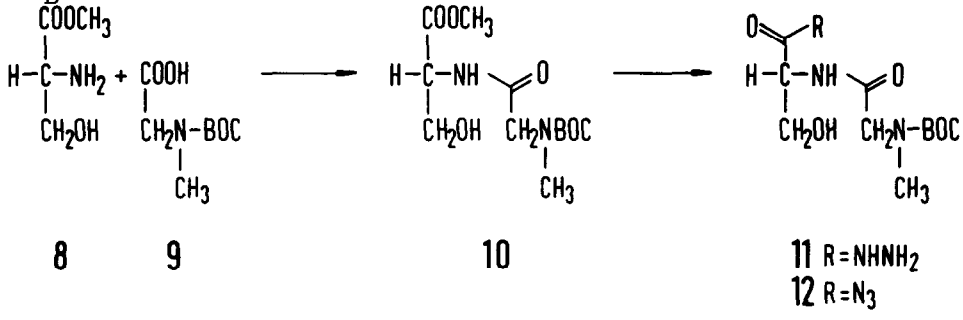


4 5 6 R=Cl 7 R=NHCH3HCl

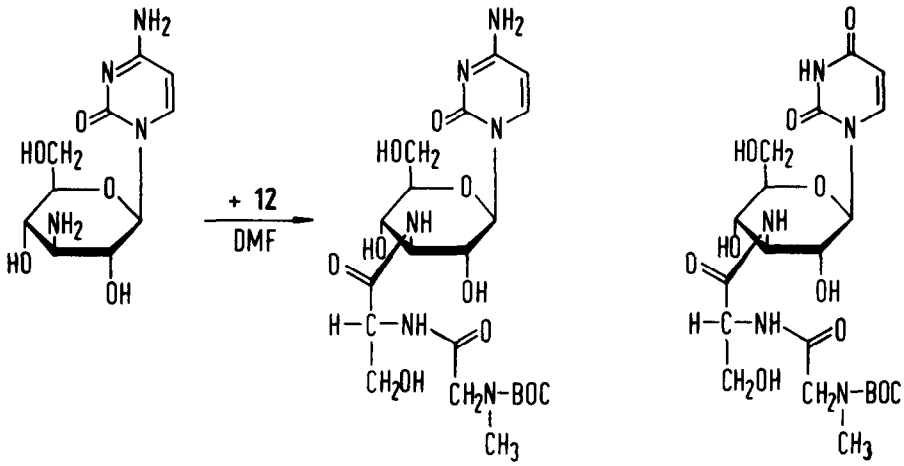
From these results and from the findings, that N-acylation of the cytosine amino group occurs using the DCC-[14,15] or the activated ester procedure[15,16], it became apparent, that none of these methods will be of general utility for linking peptidyl residues selectively to the sugar amino function of cytosine nucleosides. As an alternate approach, the azide method, as yet not evaluated for these purposes, was chosen for formation of the glyco-peptide linkage. The t-butoxycarbonyl (BOC) group was employed for N-protection, rather than the benzyloxycarbonyl moiety, to eliminate possible reduction of the aglykon[15] on removal.

N-t-Butoxycarbonyl-sarcosine (9), m.p. 84-86°, was prepared from sarcosine and t-butyl 2,4,5-trichlorophenyl carbonate using the standard procedure[17], and subsequently converted into the mixed anhydride by treatment with ethyl chloroformate/triethylamine in anhydrous tetrahydrofurane. Reaction in situ with D-serine methyl ester hydrochloride (8) afforded N-t-butoxycarbonyl-sarcosyl-D-serine methyl ester (10) in 71% yield as an analytically pure sirup of $[\alpha]_D^{25}$ +12° (methanol), which was subsequently converted (89%) to the hydrazide 11, m.p. 110-112°, $[\alpha]_D^{25}$ +21° (methanol) by treatment with aqueous

hydrazine. The azide 12, prepared *in situ* from 11 with butyl nitrite in dimethyl formamide, was coupled with 1-(3-amino-3-deoxy-ß-D-glucopyranosyl-)cytosin (13)[15] in adaptation of the procedure used by Lübke et al.[18], to give the BOC-blocked dipeptidyl nucleoside 14, m.p. 158-161°, $[\alpha]_D^{20}$ +30° (methanol), in 52% yield. Similarly, 1-(3-amino-3-deoxy-ß-D-glucopyranosyl-)uracil[19] is converted in 55% yield to 15, m.p. 158-162°, $[\alpha]_D^{20}$ +29° (methanol).



8 9 10 11 R=NHNH$_2$ 12 R=N$_3$



13 14 15

Removal of the t-BOC-protecting groups from 14 and 15, was easily accomplished by treatment with trifluoroacetic acid[20] (30 min., 25°) to afford 1-[3-(sarcosyl-D-seryl-amido)-3-deoxy-ß-D-glucopyranosyl-]cytosine (2), dec. from 220° on, $[\alpha]_D^{20}$ +20° (water) and its uracil analogue 3, m.p. 132-135°, $[\alpha]_D^{20}$ +11° (water), in nearly quantitative yield. The structures of the dipeptidyl nucleosides were in accord with UV-, IR- and NMR-spectral data[21], and were additionally verified by acid hydrolysis of 2 and 3 to the parent nucleosides, sarcosine and serine respectively.

The biological evaluation of these gougerotin analogues is pending.

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