Carbohydrate Research, 29 (1973) 525–527

Preliminary communication

Synthesis of cordycepin-C [8-(3′-deoxy-β-D-*erythro*-pentofuranosyl)adenine]

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(Received June 28th, 1973; accepted July 5th, 1973)

The synthesis of *C*-nucleosides has attracted considerable attention since the discovery of such antibiotic substances as the formycins A and B, pyrazomycin, showdomycin, and pseudouridine C, the structures of which clearly demonstrated that antibiotic activity is not restricted to *N*-nucleosides[1].

We are involved in a program of synthesis of the *C*-nucleoside analogs of *N*-nucleoside antibiotic substances, and report here the synthesis of the *C*-nucleoside analog of cordycepin, namely, 8-(3′-deoxy-β-D-ribofuranosyl)adenine (2), which we have designated "cordycepin-C". The antibiotic cordycepin (3′-deoxyadenosine) (1) is a cytotoxic agent[2] that inhibits the growth of *Bacillus subtilis*, avian tubercle bacillus[3], Ehrlich ascites tumor-cells[4], and KB cell-cultures[5,6]. It does not inhibit synthesis of DNA, but is a strong inhibitor of that of RNA. It was considered possible that the change in the position of linkage of the furanoid ring to the adenine from N-9 to C-8 would enhance the antibiotic activity of this compound and avoid loss of activity due to enzymic hydrolysis of the nucleoside and liberation of adenine and 3-deoxy-D-*erythro*-pentose ("3-deoxy-D-ribose").

It seemed reasonable to expect that an active antibiotic substance of the *N*-nucleoside type would have a *C*-nucleoside counterpart of comparable activity, provided that the linkage between the glycosyl group and the purine moiety would allow the active sites (positions of the hydrogen bonds, etc.) to occupy the same positions in space as those in the *N*-nucleoside. Formula 3 depicts two superimposed formulas; the first belongs to natural cordycepin (1), and the second to cordycepin-C [8-(3′-deoxy-β-D-*erythro*-pentofuranosyl)adenine (2)]. The nitrogen atoms in the imidazole ring of formula 3 have been removed to avoid confusion, and the heavy lines outline bonds common to both formulas 1 and 2. It will be seen that the positions of possible hydrogen-bond formation across the double helix of a nucleic acid are the same in both cordycepin and cordycepin-C, suggesting

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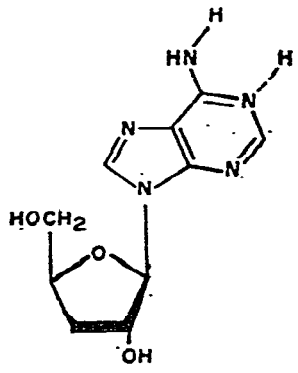

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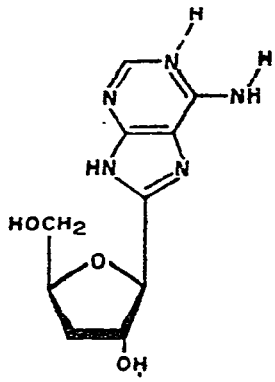

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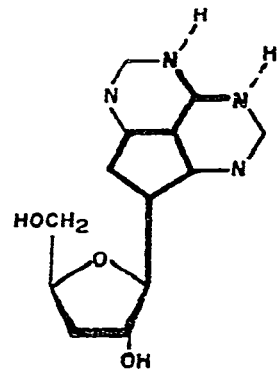

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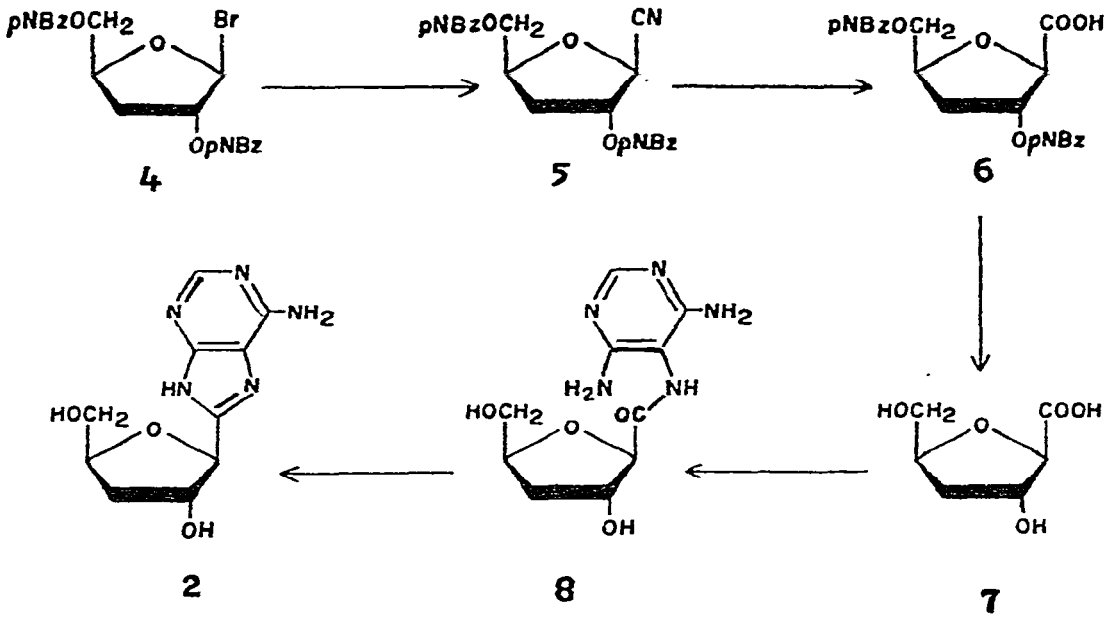
that the latter could be incorporated into the nucleic acid macromolecule or attached to an enzyme system in the same way as for the natural antibiotic.

Our approach to the synthesis of cordycepin-C was analogous to that of Bobék and Farkas[7] for the preparation of 8-(β-D-ribofuranosyl)adenine, namely, the condensation of a 2,5-anhydrohexonic acid with 4,5,6-triaminopyrimidine. The acid needed for our synthesis was 2,5-anhydro-4-deoxy-D-*ribo*-hexonic acid. The synthesis of this new carboxylic acid involved treatment of 3-deoxy-2,5-di-*O*-(*p*-nitrobenzoyl)-β-D-*erythro*-pentosyl bromide[8] (4) in nitromethane, to give 2,5-anhydro-4-deoxy-3,6-di-*O*-(*p*-nitrobenzoyl)-D-*ribo*-hexononitrile (5) in high yield. As expected from the *trans* rule[9], nitrile 5 had the β configuration. Hydrolysis of the nitrile 5 with the calculated amount of hydrogen chloride in aqueous 1,4-dioxane afforded the corresponding acid, 2,5-anhydro-4-deoxy-3,6-di-*O*-(*p*-nitrobenzoyl)-D-*ribo*-hexonic acid (6) in crystalline form. The protecting *p*-nitrobenzoyl groups were then removed by means of potassium hydroxide in aqueous 1,4-dioxane, yielding the desired 2,5-anhydro-4-deoxy-D-*ribo*-hexonic acid (7) after acidifying with Dowex 50W X-8 (H^+) ion-exchange resin and exchanging the *p*-nitrobenzoic acid liberated with acetic acid on Dowex 1 X-8 ($CH_3CO_2^-$) anion-exchange resin. Acid 7 was then condensed with 4,5,6-triaminopyrimidine monohydrochloride in aqueous solution, the reaction mixture was passed through a column of Dowex 50W X-8; and the column eluted with 2 M ammonia, to give crystalline 4,6-diamino-5-(2,5-anhydro-4-deoxy-D-*ribo*-hexonoyl)aminopyrimidine (8). Cyclization of amide 8 was achieved by heating the compound above its melting point, to give, after chromatography on silica gel, the desired *C*-nucleoside 8-(3-deoxy-β-D-*erythro*-pentofuranosyl)adenine (2).

Compounds 2, 5, 6, and 8 were all obtained in crystalline form; they gave correct elemental analyses, and had i.r. and mass spectra compatible with their assigned structures. It is also significant that the mass spectrum of cordycepin-C was found to be quite similar to that of cordycepin[10,11].



The antibiotic and carcinostatic activities of cordycepin-C are at present under evaluation.

ACKNOWLEDGMENT

This work was sponsored by the U.S. Army Medical Research and Development Command, Contract Number DADA 17-73-C-3053. This is contribution number 1197 in the Army Research Program on malaria.

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