NONGLYCOSIDE ANALOGS OF NUCLEOTIDES

COMMUNICATION 7.* CHIRAL 2,3-DIHYDROXYPROPYL DERIVATIVES OF NUCLEIC BASES

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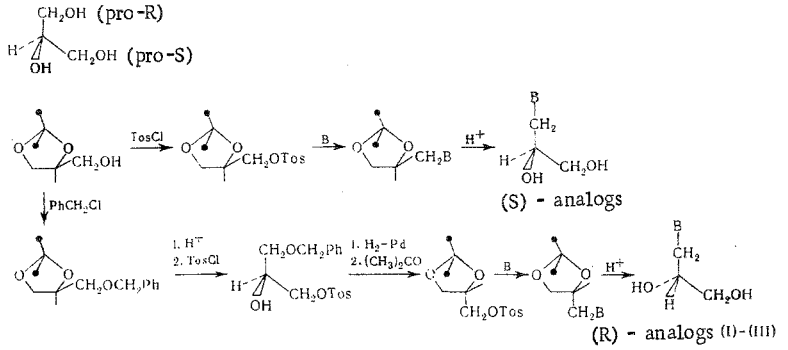
Racemic 9-(2',3'-dihydroxypropyl)adenine is an inhibitor of protein synthesis in a ribosomal system [2]. We synthesized the optically active 2,3-dihydroxypropyl derivatives of some nucleic bases. The prochiral properties of glycerol represent an interesting possibility for obtaining such compounds. Replacing the hydroxy group in a pro-R- or pro-S-enantiotropic hydroxymethyl group by a base leads directly to both enantiomers. The synthesis was accomplished by the following scheme:



B = 1-Uracil (I); 1-Cytosine (II); 9-Adenine (III)

The structure of the obtained compounds was proved by the NMR spectra and by comparison with the racemic derivatives.†

The circular dichroism (CD) spectra of the obtained compounds were studied (Fig. 1). Although the synthesized compounds have a total of one chiral center, still the amplitude of the Cotton effect is very close to that for the natural nucleosides that contain at least three chiral C atoms. In addition, the dihydroxypropyl derivatives with a natural configuration at C-2' have a CD spectrum with the opposite sign. Finally, closure of the five-membered ring in the isopropylidene derivatives leads to a twofold decrease in the absolute value of the molar ellipticity, similar to the isopropylidene derivatives of the natural nucleosides. Usually this is associated with a shift of the conformational equilibrium relative to the glycoside linkage toward the syn conformation [4, 5]. The results obtained by us place in doubt the existence of a similar correlation.

EXPERIMENTAL

The NMR spectra were taken on a BS-487C spectrometer (Czechoslovakia). The CD spectra were recorded on a Roussel Jouan II dichrograph. The TLC was carried out on Silufol UV-254 plates in a

*See [1] for Communication 6.

†The synthesis of (S)-(2',3'-dihydroxypropyl)uracil and the thymine derivative was described [3] at the time the present work was being completed.

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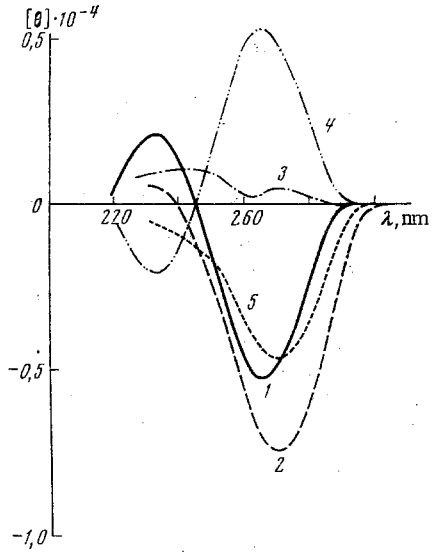

Fig. 1. CD spectra at pH 7 and 20°: 1) (S)-(I); 2) (S)-(II); 3) (S)-(III); 4) (R)-(I); 5) (S)-2',3'-O-isopropylidene-(II).

$MeOH-CHCl_3$ mixture (ranging from 3 to 30% MeOH).

(R)-1,2-O-Isopropylideneglycerol was obtained as described in [6], and then was tosylated as described in [7]. The benzylation of (R)-1,2-O-isopropylideneglycerol with subsequent removal of the isopropylidene protection, tosylation, and removal of the benzyl group by hydrogenolysis were carried out as described in [8]. The obtained (S)-1-tosylglycerol was converted to the isopropylidene derivative as described in [8]. The nucleic bases were alkylated with the (R)- and (S)-1-tosyl-2,3-O-isopropylideneglycerols as described in [9]. The protective groupings were removed in a similar manner.

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CONCLUSIONS

The optically active 2,3-dihydroxypropyl derivatives of uracil, cytosine, and adenine were synthesized and their circular dichroism spectra were measured.

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