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REACTION OF NUCLEIC ACID BASES WITH EPOXIDES AND LACTONE

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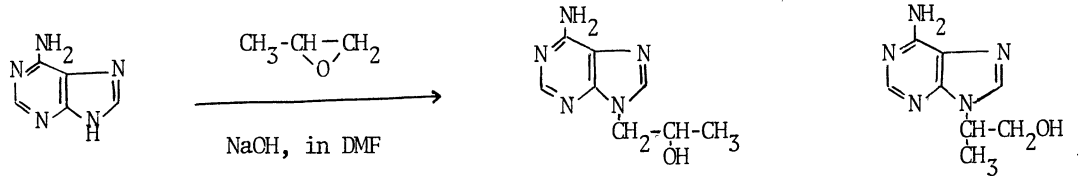
Reaction of adenine with propylene oxide and styrene oxide was found to give 9-(2-hydroxypropyl)- and 9-(2-hydroxyphenethyl)adenine, respectively. N-carboxyethylated uracil, thymine and cytosine were prepared by allowing to react the corresponding pyrimidines with propiolactone.

In order to prepare purine and pyrimidine derivatives with functional groups, reaction of purines and pyrimidines with ethylene carbonate, β-propiolactone and ethyleneimine has recently been studied, and thus the preparation of N-(2-hydroxyethyl), N-(2-carboxyethyl), and N-(2-aminoethyl) derivatives of the heterocycles has been established.[1-3]

This communication concerns with the reaction of adenine with propylene oxide and styrene oxide, as well as further preparation of N-carboxypyrimidines with β-propiolactone.

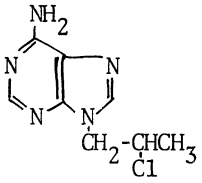
1. Reaction of adenine with epoxides

When adenine and propylene oxide were stirred at 40°C for 5 hours in dimethylformamide (DMF) solution, in the presence of catalytic amount of sodium hydroxide, 9-(2-hydroxypropyl)adenine (I) was obtained exclusively in 41 % yield (mp 187 - 189°C; λ_{max} 261 nm, ε 1.3×10^4, in H_2O), and no possible isomer (II) was formed. I was further treated with thionyl chloride to afford 9-(2-chloropropyl)adenine (III)(34 % yield, mp 173 - 175°C).

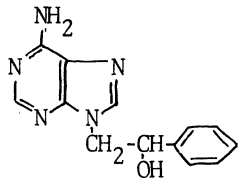


(I) (II)

The reaction of adenine with styrene oxide by refluxing them in DMF solution containing a trace of sodium hydroxide for 5 hours gave 9-(2-hydroxyphenethyl) adenine (IV) in 42 % yield (mp 237.5 - 239°C; λ_{max} 261 nm, ε 1.4×10^4, in H_2O).



(III)

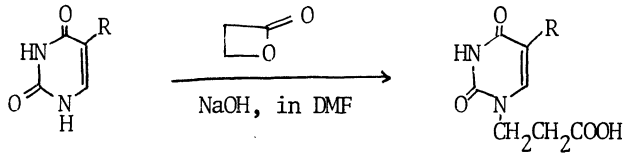


(IV)

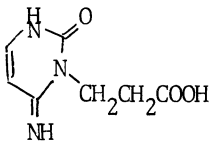
The NMR spectra of I and IV showed the doublet signal corresponding to the secondary hydroxyl group (I: τ 5.10 (O-H), IV: τ 5.82 (O-H), in DMSO-d_6), and their mass spectra had a fragment ion peak based on Ad-CH_2·$^+$ at m/e 148 (I: 193 (M^+), 178 (M^+-CH_3), 176 (M^+-OH), 148 (Ad-CH_2·$^+$), 134 (Ad·$^+$); IV: 255 (M^+), 178 (M^+-C_6H_5), 148 (Ad-CH_2·$^+$), 134 (Ad·$^+$)). These data suggest that the CH_2-O bond of propylene oxide and styrene oxide was selectively ruptured.

2. Reaction of pyrimidines with propiolactone

In a similar way as reported earlier for the synthesis of carboxylic acid derivatives of adenine and theophylline,[2] 1-(2-carboxyethyl)uracil (Va) and -thymine (Vb) were prepared by refluxing the pyrimidines with β-propiolactone in DMF solution for 5-7 hours, in the presence of sodium hydroxide (Va: 28 % yield, mp 188.5 - 189.5°C, λ_{max} 264 nm, ε 9.4×10^3; Vb: 36 % yield, mp 170 - 175°C, λ_{max} 269 nm, ε 8.8×10^3). UV data of Va and Vb suggest that the substitution was occurred exclusively in 1-position.



(Va) R=H, (Vb) R=CH_3



(VI)

Cytosine was also converted into 3-(2-carboxyethyl)cytosine (VI) under the similar reaction condition (52 % yield, mp 255 - 259°C). In the case of VI, λ_{max} in UV spectra appeared at 278 nm (ε 1.0×10^4), free NH_2 stretching bands of cytosine were lost and new =N-H band appeared in IR spectra which show the substitution at 3-position.

Carboxylic acid derivatives thus obtained were soluble in water and common organic solvents. Only the compound VI was soluble neither in water nor in DMF.

1) N.Ueda, K.Kondo, M.Kono, K.Takemoto, and M.Imoto, Makromol.Chem., 120, 13 (1968).

2) K.Kondo, M.Miyata, and K.Takemoto, Bull.Chem.Soc.Japan, 44, 2554 (1971).

3) K.Kondo, Y.Hisaoka, and K.Takemoto, Chem.Lett., 1973, 125.

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