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Synthesis of Dinucleoside Analog of Uracil-Uracil

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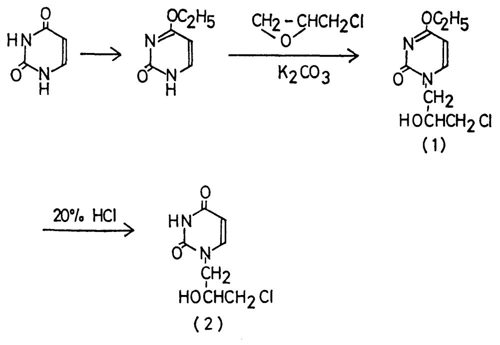
We have been attempted to prepare nucleic acid analogs in which the ribose or deoxyribose ring is replaced with an aliphatic moiety.[1-4] In order to study base-base interaction Browne, Eisinger, and Leonard[5] have studied the synthesis of dinucleotide analogs. On the other hand, Fecher *et al.*[6] synthesized the dinucleoside such as 5′-(9-adenyl)-5′-deoxy derivatives of thymidine.

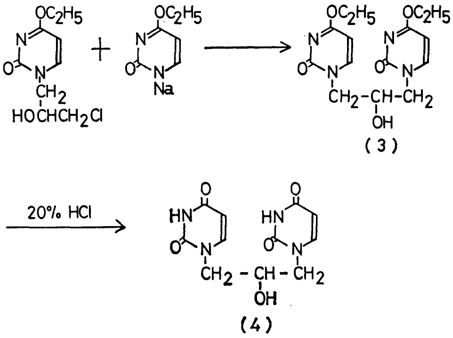
To extend this study, we have synthesized a new type dinucleoside analog of uracil-uracil.

1-(2′-Hydroxy-3′-chloropropyl)-4-ethoxy-2-pyrimidinol (**1**) was synthesized by the reaction of 4-ethoxy-2-pyrimidinol[7] with epichlorohydrin in dimethylformamide (DMF) containing potassium carbonate. The separation of product was accomplished by chromatography on silica gel using benzene–ethanol as solvent. The compound **1** was treated with 20% hydrochloric acid to give 1-(2′-hydroxy-3′-chloropropyl)uracil (**2**). Condensation of compound **1** with sodium salt of 4-ethoxy-2-pyrimidinol was carried out in DMF to give 1′,3′-bis(1-4-ethoxy-2-pyrimidinol)-2′-propanol (**3**).

When compound (**3**) was treated with 20% hydrochloric acid at 85—90 °C 1′,3′-bis(1-uracil)2′-propanol (**4**) was afforded in good yield.



Scheme 1.



Scheme 2.

The observed extinction coefficient of **4** was approximately the same value as that of 1′,3′-bis(1-uracil)-trimethylene, Ur$(CH_2)_3$Ur, shown by Browne, Eisinger, and Leonard. The compound **4** showed a small blue shift of UV when compared with the compound **2**. The compound **4** will give many derivatives through the reaction of its 2′-hydroxy group. UV data were listed in Table 1.

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1) T. Seita, K. Yamauchi, M. Kinoshita, and M. Imoto, This Bulletin, **45**, 926 (1972).

2) T. Seita, K. Yamauchi, M. Kinoshita, and M. Imoto, *Makromol. Chem.*, **154**, 255 (1972).

3) T. Seita, K. Yamauchi, M. Kinoshita, and M. Imoto, This Bulletin, **46**, 1563 (1973).

4) T. Seita, M. Kinoshita, and M. Imoto, *ibid.*, **46**, 1572 (1973).

5) D. T. Browne, J. Eisinger, and N. J. Leonard, *J. Amer. Chem. Soc.*, **90**, 7302 (1968).

6) R. Fecher, K. H. Boswell, J. J. Wittick, and T. Y. Shen, *ibid.*, **92**, 1400 (1970).

7) G. E. Hibert and E. P. Jansen, *ibid.*, **57**, 552 (1935).

TABLE 1. UV DATA OF URACIL-URACIL DIMER AND ITS RELATED COMPOUNDS

Compound	$\lambda_{\max}^{H_2O}$	ε	Ref.
2	267	10300	
4	266.5	19900	
Ur–C_3	267	10130	5
Ur–C_3–Ur	266.5	19730	5

Experimental

The melting points are uncorrected. The IR and UV spectra were measured by a JASCO Model IR-G Spectrometer and Hitachi Recording Spectrometer Model ESP-3T, respectively.

1-(2′-Hydroxy-3′-chloropropyl)-4-ethoxy-2-pyrimidinol (1). A mixture of 4-ethoxy-2-pyrimidinol (5.0 g, 36 mmol), epichlorohydrin (3.3 g, 36 mmol), and a trace of anhydrous potassium carbonate in DMF (80 ml) was stirred at 70—80 °C for 10 hr. After allowing to cool to room temperature the reaction mixture was filtered off and the filtrate was evaporated under the reduced pressure. 10 ml of ethanol was poured into the residue and kept in refrigerator overnight. The resulting white precipitate was filtered off and washed with excess ethanol. The filtrate and washing were combined, then evaporated and the oil residue was chromatographed on silica gel (Mallinckrodt). Elution with benzene–ethanol (4: 1) gave the product. The product was recrystallized from benzene to give the compound (**1**) (5.1 g (62%)) as colorless needles.

Mp 121—122 °C, UV; $\lambda_{\max}^{H_2O}$ 275 mμ, IR (Potassium bromide) 3200 (OH), 1620 (4-ethoxy-2-pyrimidinol ring); Found: C, 46.22; H, 5.19; N, 11.65%. Calcd for $C_9H_{13}N_2O_3Cl$: C, 46.44; H, 5.63; N, 12.05%.

1-(2′-Hydroxy-3′-chloropropyl)uracil (2). Compound (**1**) (0.46 g, 2 mmol) was treated in 20% hydrochloric acid, evaporated and the residue was recrystallized from benzene–ethanol (4: 1) to give compound (**2**) (0.32 g (80%)) as colorless needles.

Mp 153—156 °C; IR (Potassium bromide): 3350 (OH), 1660 (Uracil ring); Found: C, 41.28; H, 4.88; N, 13.88%. Calcd for $C_7H_9N_2O_3Cl$: C, 41.07; H, 4.44; N, 13.70%.

1′,3′-Bis(1-4-ethoxy-2-pyrimidinol)-2′-propanol (3). Mixture of compound (**1**) (3.36 g, 20 mmol) and sodium salt of 4-ethoxy-2-pyrimidinol (4.24 g, 20 mmol) was stirred in DMF at 70 °C for 2 days. The reaction mixture was filtered off and the filtrate was evaporated under reduced pressure. The resulting white precipitate was recrystallized from ethanol to give compound (**3**) (3.9 g (58%)) as colorless pales.

Mp 229—231 °C, IR (Potassium bromide); 3250 (OH), 1630 (4-ethoxy-2-pyrimidinol ring); Found: C, 53.05; H, 6.28; N, 16.37%. Calcd for $C_{15}H_{20}N_4O_5$: C, 53.55; H, 6.00; N, 16.66%.

1′,3′-Bis(1-uracil)-2′-propanol (4). Compound (**3**) (3.36 g, 10 mmol) was stirred in 20% hydrochloric acid at 90 °C for one hour, evaporating to dryness. The white precipitate was recrystallized from water to give compound (**4**) (2.68 g, (92%)) as colorless needles.

Mp 139—142 °C, IR (Potassium bromide): 3250 (OH), 1660 (Uracil ring); Found: C, 46.68; H, 4.58; N, 19.67%. Calcd for $C_{11}H_{12}N_4O_5$: C, 47.13; H, 4.32; N, 20.00%.