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# 5, 5′-Diuracil 및 몇가지 유도체의 합성

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# The Synthesis of 5. 5′-Diuracil and Its Derivatives

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요 약. 5-Uracildiazonium salt에 구리를 촉매로 한 축합반응으로 5, 5′-diuracil을 합성하고 이것의 몇가지 유도체를 만들어 그 구조를 확인하였다.

**Abstract.** Through the copper catalyzed coupling reaction a uracil dimer, 5, 5′-diuracil was synthesized from 5-uracildiazonium salt. Several derivatives of above diuracil dimer were also synthesized. The structure of the dimer was determined from their spectral data.

## Introduction

Uracil, 2, 4-dihydroxypyrimidine(I), is a physiologically very important compound which is a constituent base of RNA. Although large number of its derivatives have been thoroughly investigated, very few studies have been made on its dimers. So far only one example could be found in the literatures concerning this matter. Smietanowska and Shuger[1] reported that uracil is dimerized in aqueous solution in very poor yield (200 $\gamma$ from 900 mg of uracil after irradiation for 40 min.) by UV irradiation. The uracil dimer was quite stable in acid and rather stable in dilute alkali at the room temperature, but easily decomposed in 0.1 $N$ NaOH solution at 100 °C. It showed UV absorption maxima at 235 nm., a bathochromic shift of about 17 nm. from uracil. They proposed a doubly bridged structure(II) for this dimer.

The authors obtained a new uracil dimer which differs from II in many aspects and proposed a 5-5′ singled bridged structure(III) for this dimer. This was obtained by copper catalyzed coupling of 5-uracildiazonium salt in an acidic solution. It is very stable even in strongly alkaline solution at elevated temperature.

Several derivatives of this dimer were synthesized and examined to clarify the structure of this dimer.

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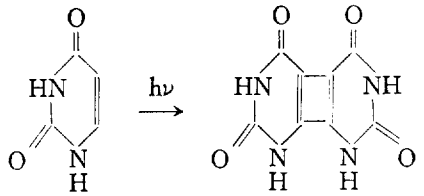
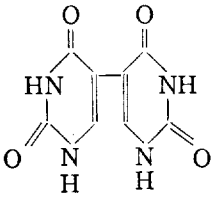


I II



III

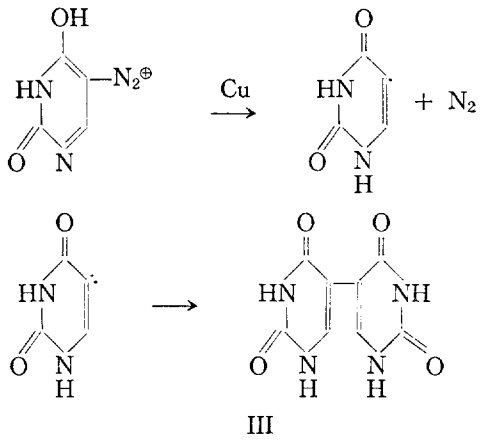
## Results and Discussion

Adding freshly prepared copper powder to the acidic suspension of 5-uracildiazonium salt[2] at low temperature, a spontaneous reaction occurs with vigorous evolution of a gas. After completion of the reaction, 5, 5′-diuracil is filtered and obtained as colorless microcrystalline. This diuracil is not soluble either in water or in any organic solvent even on heating. It can be purified through dissolving in dilute alkali and reprecipitating by adding an acid to the resulting alkaline solution. It decomposes above 350°C without melting. It is thermally so stable that it does not give any recognizable mass peak in the mass-spectrum even when the oven temperature is kept at 300 °C. The molecular weight is determined from the mass-spectrum of its tetramethyl derivative, which is identified as *N*, *N*′, *N*″, *N*‴-tetramethyldiuracil(IV), synthesized through methylation of III with dimethyl sulfate in an alkaline media.

IV can be recrystallized from hot water and melts at 252 °C with decomposition. Upon the mass-spectrscopy of IV, the molecular ion peak is observed as the prominent peak at m/e=278 which is in well agreement with the calculated value from the formula, $C_{12}H_{14}N_4O_4$, for the singly bridged uracil dimer. The high melting point, poor solubility in every kind of solvents, and the high intensity of the molecular ion peak in the mass-spectrum indicates the presence of very strong intermolecular hydrogen-bonding or dipole-dipole attraction in the diuracil(III) and its tetramethyl derivative(IV). This fact means that IV is a *N*-methyl derivative rather than the *O*-methyl derivative.

The UV absorption maximum of III in dilute alkaline solution(pH=12) is shifted bathochromically about 12 nm. from that of uracil. Since Smietanowska[1] reported a bathochromic shift of about 17 nm for their doubly bridged diuracil(II), it is not likely that III be the same compound. Rather small shift and large extinction coefficient in III also support that III would be a singly bridged dimer rather than the doubly bridged one.

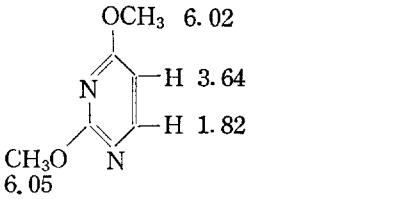
The dimerization reaction is supposed to proceed as follows by analogy of the reaction mechanism of benzenediazonium salts.

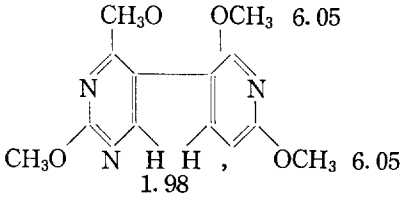


III

It is concluded that the bridge bond between two uracil unit in III would most likely be at between 5-5′ position from the above mechanism This is proved from the nmr spectrum of *O*-methylated diuracil, 2, 2′, 4, 4′-tetramethoxy -5, 5′-dipyrimidine(VI). Only one signal due

to the nuclear hydrogen is observed at $\tau$=1.98 as singlet. In the uracil derivative, the resonance signals of two nuclear C—H protons appear as two doublets at $\tau$=1.82 and $\tau$=3.64 respectively[3]. The signal at $\tau$=1.82 is assigned to the proton on the carbon atom adjacent to the nitrogen atom.

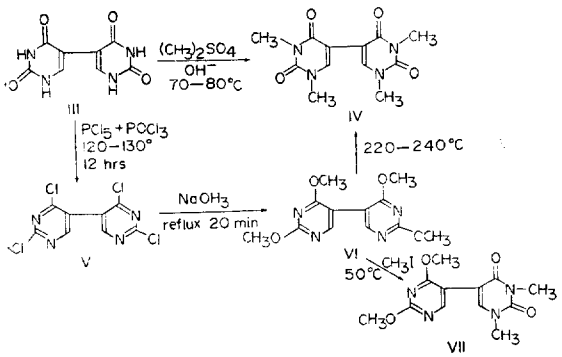



VI

Therefore the absence of the signal at the neighborhood of $\tau$=3.5 in VI also confirms the 5, 5′-bridged structure.

The position substituted by methyl groups in IV is determined by comparing with VI synthesized through tetrachlorodipyrimidine(V), obtained by chlorination of III with phosphorous pentachloride. Through this comparison, IV is identified as *N*-tetramethylated diuracil rather than the *O*-tetramethylated one. VI is converted into IV by heating at 220~240 °C in an oil bath.




By heating with methyl iodide in a sealed tube. VI is also converted into another tetramethyl derivative of diuracil, which is assumed to be 1, 3-dimethyl-2, 4-dioxo-2′, 4′-dimethoxy-5, 5′-dipyrimidine (VII) from the nmr data.

The structures and some physaicl and spectral data are listed in *Table* 1.

## Experimental

**5, 5′-Diuracil(III).** To the suspension of 5-uracildiazonium salt prepared by usual procedure[2] from 100 mg of uracil, 100 mg of freshly prepared copper powder[4] was added in one portion with stirring. Vigorous evoltion of a gas

*Table* 1.

| Uracil deriv. | | Diuracil deriv. |
|---|---|---|
| (I) | | (III) |
| 338 °C (decomp.) | m.p | over 360° (decomp.) |
| 218(ε=2500), 259(ε=2800) | UV(pH 12) | 230 (ε=11400), 293.5 (ε=14000) |
| 61 °C | m.p | 133 °C (V) |
| 222(ε=1600), 259(ε=2200) | UV(EtOH) | 230(ε=9300), 259(ε=4900) |
| 17.5 °C<br>222 °C | m.p.<br>b.p. | 174 °C (VI) |
| (in $CDCl_3$) a: 1.82(d)<br>b: 3.64(d)<br>c,d: 6.02(s)<br>6.05(s) | nmr(τ) | ($CCl_4$) a: 1.98(s)<br>b: 6.05(s) |
| 19 °C<br>224 °C<br>259 mμ | m.p.<br>b.p.<br>UV(EtOH) | 139 °C (VIII)<br>263.5 mμ |
| 123 °C<br>264.5 mμ | m.p.<br>UV(MeOH) | 252 °C (decomp.) (IV)<br>288 |
| 149 °C | m.p<br>UV(95% EtOH)<br>nmr(τ) in $D_2O$ | 243 °C (VII)<br>286(ε=22000)<br>235(ε=34000)<br>6.64(s), 6.52(s), 6.47(s)<br>6.06(s), 2.26(s), 2.11(s) |

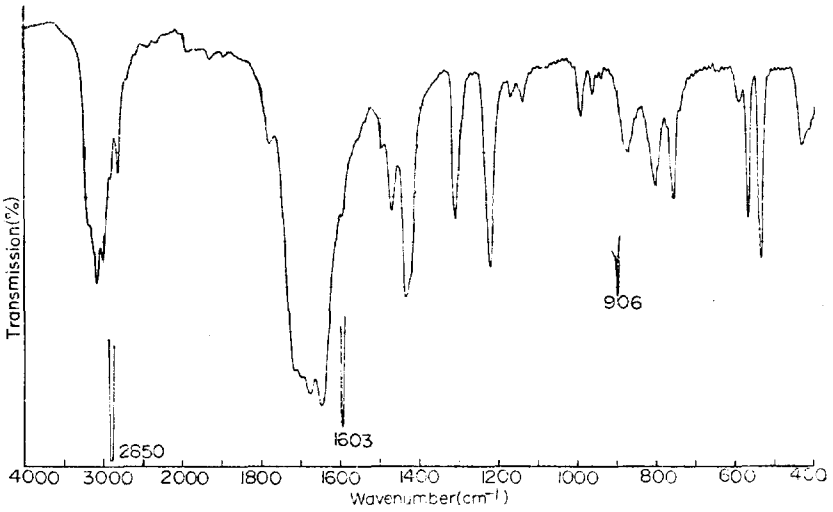



*Fig.* 1.

was observed. The temperature of the solution was kept at 0~5 °C and the stirring was continued for 40 min. Then the reaction mixture was kept overnight in a refrigerator. To the reaction mixture, an excess of $Na_2CO_3$ solution was added to dissolve diuracil. The unreacted copper powder was filetred off and washed with water. The filtrate was treated with 50 mg of Norit and acidified. III was separated out as white microcrystalline. Since the diuracil was practically insoluble in water and any organic solvents, it was purified through dissolving in aqueous alkali and reprecipitating by neutrallization.

Overall yield from 5-Aminouracil is 48 % (42 mg), mp., 360 °C. *Anal.*, found N, 23.6 ; calc. for $C_8H_6N_4O_4$, 25.2. $\lambda$max at pH=12, 230 nm($\epsilon$=11,400); 293.5 nm($\epsilon$=14,000). ir, 1725 and 1675 $cm^{-1}$(heterocyclic ketone).

**1, 1′, 3, 3′-Tetramethyl-5, 5′-diuracil (IV).** III (150 mg) was dissolved in a solution of NaOH (150 mg) in 10 m*l* of distilled water. Dimethyl sulfate(3 m*l*) was added into this solution with stirring at 0 °C. Then the temperature was raised to 80 °C and kept at this temperature for 1 hr. On cooling colorless cystarals were obtained. Recrystallized from ethanol. Yield, 130 mg(70 %). mp., 252 °C. $\lambda_{max}$, (EtOH) 288 nm. ir, 1695, 1650 $cm^{-1}$ (heterocyclic ketone). nmr, $\tau$=6.55(*s*), 6.67(*s*), 2.29(*s*) ; ratio, 3 : 3 : 1

**2, 2′, 4, 4′-Tetrachloro-5, 5′-dipyrimidine (V).** III(100 mg) was mixed with 1.5 g. of $PCl_5$ and 0.5 m*l*. of $POCl_3$ and heated under reflux at 110~120 °C for two hrs. in an oil bath. The temperature was raised to 130 °C and kept at this temperature for further 10 hr. A dark brown solution was resulted. The excess $POCl_3$ was removed under reduced pressure and the remaining $PCl_5$ was destroged carefully by slow addition of water. The solution was extracted three times with ether. The ether extract was washed firstly with dil. $Na_2CO_3$ solution to remove mineral acid and finally with water. The ether solution was dried over anhyd. $CaCl_2$ and evaporated under reduced pressure. The residue was recrystallized from methanol. Yellow platelet. Yield, 80 mg. (60 %). mp., 133.0-

133.5 °C. $\lambda_{max}$(95 % EtOH), 230 nm. ($\epsilon$=9, 300) ; 259 nm. ($\epsilon$=4,900). Mass-spectra : prominent peak at m/e=75 (=100) parent peak 294 (6.5), $p$+2 296 (6.8), $p$+4 298 (4.0) ; Calc. for $C_8H_2N_4Cl_4$, 294. ir, absortion band at 1725 and 1675 $cm^{-1}$. due to the hetrocyclic ketone group disappeared and two new absorption bands due to C—Cl bond appeared at 776 and 694 $cm^{-1}$.

**2, 2′, 4, 4′-Tetramethoxy-5, 5′-dipyrimidine (VI).** V(100 mg.) was dissolved in 5 m*l*. of absolute MeOH. A solution of metallic Na(200 mg.) in 5 m*l*. of absolute MeOH was added into the above solution and refluxed for 20 min. On cooling pale yellow needles were separated out. The precipitate was filtered and washed with water until no more chloride ion was detected in the washing. Recrystallized from MeOH. White needles, mp., 174~175 °C. Yield, 70 %. $\lambda_{max}$(95 % EtOH), 262 nm($\epsilon$=9,700). nmr, $\tau$=1.89(s), 6.05(s) ; ratio, 1 : 6. ir, no carbonyl group band between 1,800 ~1,600 $cm^{-1}$, bands at 776 and 694 $cm^{-1}$(C—Cl) disappeared.

**2, 2′, 4, 4′-Tetraethoxy-5, 5′-dipyrimidine (VIII).** Same procedure was employed as VI. Absolute EtOH was used in the place of absolute MeOH. White fibrous crystals. Yield, 70 %, mp., 139.0~139.5 °C. $\lambda_{max}$ (95 % EtOH), 263.5($\epsilon$=12,000). nmr, $\tau$=1.99($s$), 5.6($q$), 8.6($t$) ; ratio, 1 : 4 : 6.

**1, 3-Dimethyl-2, 4-dioxo-2′, 4′-dimethoxy-5, 5′-dipyrimidin (VII).** IV(100 mg.) and 2 m*l* of freshly distilled $CH_3Cl$ was heated in a sealed tube at 50°C for 5 hrs. After cooling the precipitate was filtered and washed with ether and recrystallized from hot water. Pale yellow crystals, yield, 85 %. mp., 243 ~244 °C. *Anal.* found : C, 51.05 : H, 5.31 : N, 20.80 ; Calc. for $C_{12}H_{14}N_4O_4$ : C, 51.80 ; H, 5.07 ; N, 20.14 ; —$OCH_3$ by modified Zeisel method[5] : Found, 20.1 ; Calcd, 22.3. $\lambda_{max}$(95 % EtOH), 235 ($\epsilon$=34,000) ; 286 nm ($\epsilon$=22,000). ir, two strong bands at 1693 and 1673 $cm^{-1}$ due to the heterocyclic ketone groop. nmr., $\tau$=6.64($s$), 6.52 ($s$), 6.47($s$), 6.06 ($s$), 2.26($s$), 2.11($s$); ratio, 3 : 3 : 3 : 3 : 1 : 1.

**Conversion of VI to IV.** VI(100 mg.) was heated in a small test tube on an oil bath. The resulting brown residue was dissolved in sufficient amount of hot water and treated with Norit. Upon evaporation, colorless platelet crystals were obtained. Yield, 80 %. This was matched in every respect with the directly methylated product from III.

## Acknowledgement

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