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184. Torahiko Kishikawa*1 and Hidetaka Yuki*2 : Studies on Chemotherapeutic Agents. III.*3 A Synthesis of 3-Phenylpurine Derivatives.

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In the naturally occurring purine nucleosides, including some with antibiotic activity, the glycosyl linkage is generally of 9-β-D-configuration. Therefore, a host of purine derivatives substituted at the 9-position, containing many purine nucleosides, natural or unnatural have been synthesized, some of which have been demonstrated to be of considerably chemotherapeutic value.

On the other hand, recently, 3-ribosyluric acid,[1] its corresponding 5′-phosphate[2] and 3-ribosylxanthine-5′-phosphate[3] in which D-ribose was attached at the 3-position of the purine nucleus have been proved to arise in beef blood. Though the biological significance of them is unknown, the finding of the 3-ribosyl derivatives prompted the authors to attempt the preparation of 3-substituted purine derivatives. The present paper describes the synthesis of 3-phenyluric acid and its related compounds.

1-Phenylurea (I) or -thiourea (II) was allowed to react with cyanoacetylchloride in pyridine to afford 1-phenyl-3-cyanoacetylurea (III) or 1-phenyl-3-cyanoacetylthiourea (IV) (Chart 1), respectively. On treatment of III or IV with alkaline solution, cyclization was

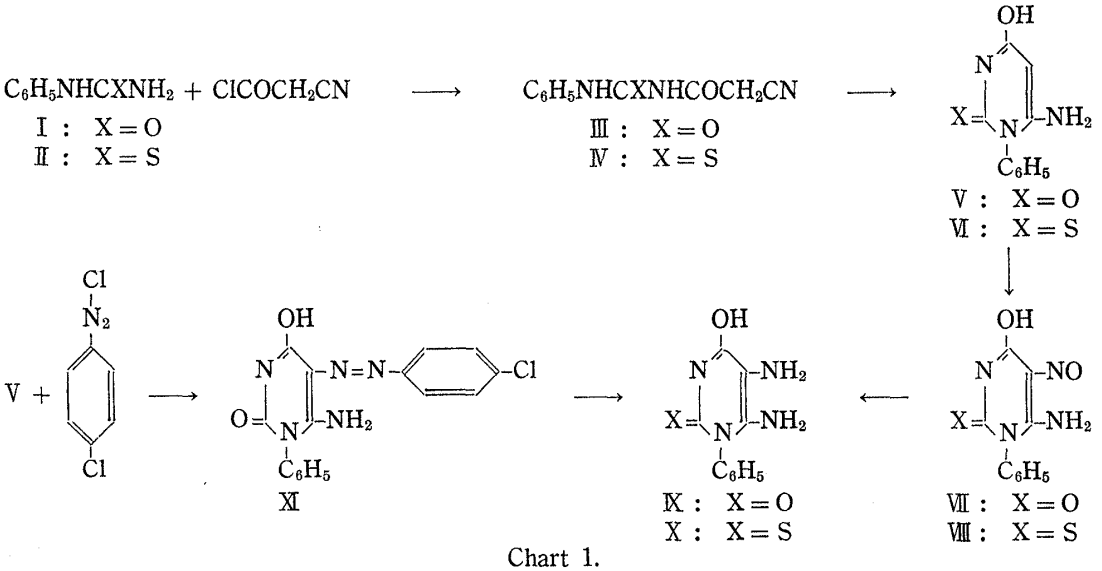

Chart 1.

effected and 1-phenyl-6-aminouracil (V) and 1-phenyl-6-amino-2-thiouracil (VI) were produced. V or VI was also obtained directly by the condensation of I or II with ethyl cyanoacetate. Nitrosation of V or VI in aqueous acetic acid with sodium nitrite smoothly took place to give 5-nitrosopyrimidines (VII) or (VIII), each of which was converted into their corresponding 5-amino derivatives (IX) or (X). In this reduction, sodium dithionite was a reagent of choice.

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*3 Part II. T. Kishikawa, H. Yuki : This Bulletin, **14**, 1360 (1966).

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1) H. S. Forrest, D. Hatfield, J. M. Lagowski : J. Chem. Soc, **1961**, 963.

2) D. Hatfield, R. Reinehart, H. S. Forrest : *Ibid*, **1963**, 899.

3) D. Hatfield, H. S. Forrest, B. Wyngaarden : Biochim. Biophys. Acta, **68**, 322 (1963).

Compound (V) was coupled with diazotized *p*-chloroaniline, giving 1-phenyl-5-(*p*-chlorophenylazo)-6-aminouracil (XI) which was reduced to the 5-amino derivative (IX). Zinc dust in acetic acid or sodium dithionite was conveniently used as reducing reagents for the azo compound.

The key intermediate, 5,6-diaminopyrimidine (IX) or (X) prepared above was fused with urea or thiourea, giving 3-phenyluric acid (XII), -2-thiouric acid (XIII), -8-thiouric acid (XIV) and -2,8-dithiouric acid (XV), respectively (Chart 2). Methylation of XIII or XIV with one mole of methyl iodide resulted in formation of 2-methylthio (XVI) or 8-methylthio derivative (XIX). On treatment of XIV with monochloroacetic acid, thiol group at 8-position was reacted to give 8-carboxymethylthio derivative (XVIII). An attempt to hydrolyze (XVIII) to (XII) was not successful.

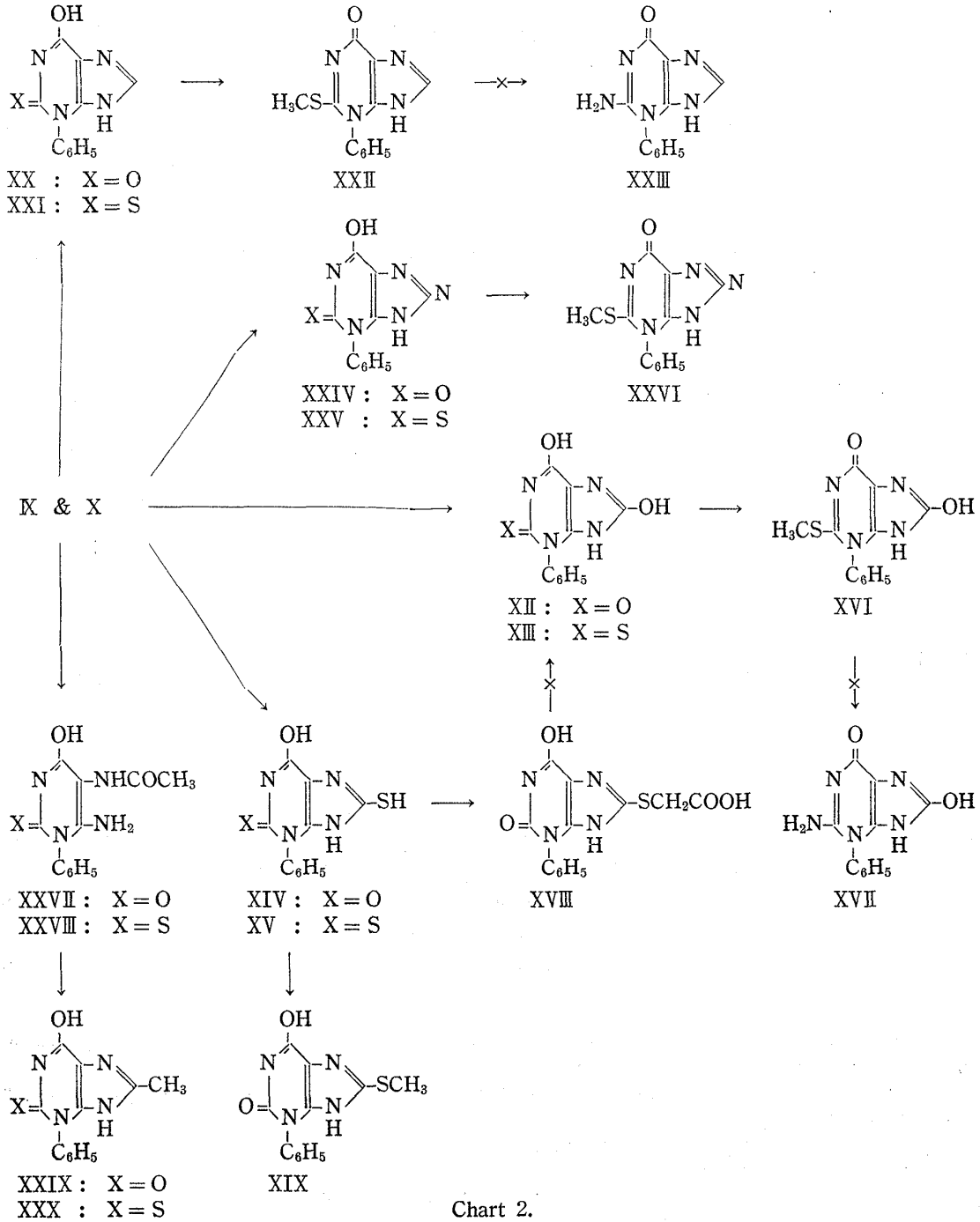

Chart 2.

By heating with formamide at 180~185°, Ⅸ or Ⅹ yielded 3-phenylxanthine (XX) or 3-phenyl-2-thioxanthine (XXI). Treatment of XXI with methyl iodide afforded XXII, methylthio group of which was not substituted with ammonia as in the case of 2-methylthio substituent of compound (XVI) under conditions investigated.

Acylation of compound (Ⅸ) or (Ⅹ) with acetic anhydride at room temperature yielded the corresponding 5-acetyl derivatives (XXVII) or (XXVIII). On heating the sodium salt of the 5-acetyl derivatives, they underwent ring closure to form 3-phenyl-8-methylxanthine (XXIX) and -2-thioxanthine (XXX).

Ⅸ or Ⅹ on treatment with nitrous acid was cyclized to yield the triazolopyrimidines (XXIV) or (XXV). Reaction of XXV with methyl iodide in alkaline solution resulted in formation of 2-methylthio derivative (XXVI).

Table I. Preliminary Anticancer Testing Results of Some 1-Phenylpyrimidine and 3-phenylpurine Derivatives Synthesized[a]

Compound No.	NSC No.	Dose	Test/Control[b]		KB cell culture ED_{50}/ml.[c]
			L 1210	Ca 755	
V	D 83723	100.0		0.78	
		100.0	1.00		
					1.0×10^2
Ⅵ	D 83724	100.0	0.93		
					1.0×10^2
XXI	D 83731	100.0		0.93	
					1.0×10^2
XXII	D 83733	100.0		0.53	
		100.0		0.66	
		100.0	1.02		
					1.0×10^2
XXIV	D 83734	100.0	0.94		
		50.0		1.05	
					1.0×10^2
XXIX	D 83732	100.0		0.55	
					1.0×10^2

a) The biological testing was performed by the screening contractors of the Cancer Chemotherapy National Service Center in U.S.A.
b) L 1210=lymphoid leukemia L 1210, Ca 755=Adenocarcinoma 755.
c) ED_{50} is the dose that inhibits growth to 50% of control growth.

Preliminary *anti*-cancer testing results of some of the compounds prepared above are given in Table I. Other compounds not listed in this Table were tested against KB cell culture. ED_{50} (γ/ml.) of all of them was more than 1.0×10^2.

Experimental[*5]

1-Phenyl-3-cyanoacetylurea (III)——To a mixture of 1-phenylurea (I, 1.2 g.) in $CHCl_3$ (20 ml.) and pyridine (0.8 g.) was added dropwise 1.0 g. of freshly distilled cyanoacetylchloride with stirring at room temperature. The reaction mixture was heated under reflux on a steam bath for 2.5 hr. Complete evaporation of the solvent afforded a residue which on recrystallization from EtOH yielded 1.0 g. of colorless needles, m.p. 209~211°. *Anal.* Calcd. for $C_{10}H_9O_2N_3$: C, 59.10; H, 4.43; N, 20.70. Found: C, 59.15; H, 4.38; N, 20.34.

1-Phenyl-3-cyanoacetylthiourea (IV)——1-Phenylthiourea (II, 1.52 g.) was dissolved in a mixture of $CHCl_3$ (20 ml.) and pyridine (0.8 g.). To this solution was added freshly distilled cyanoacetylchloride (1.1 g.) with stirring at room temperature. After gently refluxing on a water bath for about 3 hr., the solvent

*5 All melting points are uncorrected.

was removed *in vacuo* to leave a sirup which was dissolved in 10 ml. of $CHCl_3$. The $CHCl_3$ solution was extracted with 25% $NaHSO_4$, 5% $NaHCO_3$ and water three times, respectively, and dried over Na_2SO_4. The solvent was evaporated to afford a residue which on recrystallization from EtOH gave 1.2 g. of colorless needles, m.p. 185~186°. *Anal.* Calcd. for $C_{10}H_9ON_3S$: C, 54.80; H, 4.11; N, 19.17. Found: C, 54.61; H, 4.21; N, 18.83.

1-Phenyl-6-aminouracil (V)——a) One gram of III was dissolved in 15 ml. of 5% NaOH and heated on a water bath for 45 min. The reaction mixture was cooled and acidified with AcOH to give a precipitate. Recrystallization from MeOH afforded 0.8 g. of fine needles, m.p. 314~315° (decomp.). *Anal.* Calcd. for $C_{10}H_9O_2N_3$: C, 59.10; H, 4.43; N, 20.70. Found: C, 59.12; H, 4.70; N, 20.89.

b) A mixture of 1-phenylurea (6.8 g.), ethyl cyanoacetate (5.7 g.) aod Na (1.2 g.) in absolute EtOH (30 ml.) was heated under reflux on a steam bath for 8 hr. After cooling, the reaction mixture was poured into 100 ml. of cold water and acidified with AcOH. The precipitate formed was recrystallized from MeOH in fine needles, m.p. 313~315° (decomp.). The yield was 5.2 g. (51.5%).

1-Phenyl-6-aminothiouracil (VI)——VI was obtained by the same procedure described for the preparation of 1-phenyl-6-aminouracil (V) in a yield of 73% (method a) and 68% (method b). m.p. 232~233° (decomp., recrystallized from EtOH). *Anal.* Calcd. for $C_{10}H_9ON_3S$: C, 54.80; H, 4.11; N, 19.17. Found: C, 54.93; H, 4.36; N, 19.44.

1-Phenyl-5-nitroso-6-aminouracil (VII)——To a solution of 1-phenyl-6-aminouracil (V, 6.1 g.) in 100 ml. of a 1:1 mixture of water and AcOH was added dropwise $NaNO_2$ (4.1 g.) in water (10 ml.) with vigorous stirring at 10°. After addition of the nitrite, stirring was continued for further 1 hr. Water and AcOH were removed under a reduced pressure and the residue was treated with water to give violet crystals. Recrystallization from water or EtOH–water afforded 6.0 g. of violet needles, m.p. 220~221° (decomp.). *Anal.* Calcd. for $C_{10}H_8O_3N_4$: C, 51.75; H, 3.45; N, 24.10. Found: C, 51.92; H, 3.84; N, 24.06.

1-Phenyl-5-nitroso-6-amino-2-thiouracil (VIII)——1-Phenyl-6-amino-2-thiouracil (VI, 4.4 g.) was dissolved in a mixture of AcOH (100 ml.) and water (20 ml.) and the solution was cooled to 2~5° with ice water. To this solution was added $NaNO_2$ (2.7 g.) in water (5 ml.) in two portions and the reaction mixture was stirred for 1 hr. The precipitated material was filtered off, washed with water and dried. This compound was used in further reaction without purification. The crude yield was 4.2 g.

1-Phenyl-5,6-diaminouracil (IX)——a) A solution of the nitroso derivative (VII, 5.0 g.) in 80 ml. of *N*NaOH was treated with $Na_2S_2O_4$ (1.5 g.) and heated on a water bath at 50~60° for about 15 min. during which red-violet color was faded and a green precipitate was produced. Recrystallization from a 1:1 mixture of pyridine and water gave 4.0 g. of yellow-brownish crystals, m.p. 232~233°. *Anal.* Calcd. for $C_{10}H_{10}O_2N_4$: C, 55.00; H, 4.59; N, 25.70. Found: C, 55.35; H, 4.68; N, 25.76.

b) The alternative method, *via* 1-phenyl-5-(*p*-chlorophenylazo)-6-aminouracil (XI) was conveniently used. The diazotized *p*-chloroaniline (0.05 mole), free from HNO_2, was added dropwise to a vigorously stirred solution of 1-phenyl-6-aminouracil (V, 0.06 mole) in *N*NaOH at 0°. The precipitate formed was collected and washed with water. XI was used in next reaction without purification. Reduction of XI to the corresponding 5,6-diaminopyrimidine with $Na_2S_2O_4$ or Zn in AcOH was readily accomplished in usual way. The yield was 37% from 1-phenyl-6-aminouracil (V).

1-Phenyl-5,6-diamino-2-thiouracil (X)——Exactly the same procedure described above was used. m.p. 246~247° (recrystallized from a 1:1 mixture of water and DMF. *Anal.* Calcd. for $C_{10}H_{10}ON_4S$: C, 51.25; H, 4.27; N, 23.90. Found: C, 51.30; H, 4.52; N, 23.80.

3-Phenyluric Acid (XII) and 3-Phenyl-2-thiouric Acid (XIII)——The 5,6-diaminopyrimidine*6 (IX or X, 0.01 mole) and urea (0.1 mole) were well mixed and heated in an oil bath at 175~180° for 1 hr. during which the pulverized mixture went into solution and then resolidified to mass. After treatment with water, the insoluble material was dissolved in 2*N* NaOH solution followed by acidification with AcOH. The precipitate formed was recrystallized in fine crystals. XII: The yield, 63%. m.p. >300° (recrystallized from water). *Anal.* Calcd. for $C_{11}H_8O_3N_4 \cdot 1\frac{1}{2}H_2O$: C, 48.70; H, 4.06; N, 20.62. Found: C, 48.78; H, 4.25; N, 20.65. XIII: The yield, 57%. m.p. >300° (recrystallized from water-DMF). *Anal.* Calcd. for $C_{11}H_8O_2N_4S \cdot \frac{1}{2}H_2O$: C, 49.10; H, 3.34; N, 20.80. Found: C, 49.31; H, 3.20; N, 20.60.

2-Methylthio-3-phenylpurin-6,8-(3*H*,9*H*)-dione (XVI)——To a solution of 3-phenyl-2-thiouric acid (XIII, 2.6 g.) in 0.5 *N*NaOH (20 ml.) was added dropwise CH_3I (1.42 g.) with vigorous stirring at room temperature. After complete addition of CH_3I, stirring was continued for further 2 hr. followed by acidification with AcOH to give a precipitate. Recrystallization from AcOH afforded 2.2 g. of colorless crystals, m.p. >300° *Anal.* Calcd. for $C_{12}H_{10}O_2N_4S$: C, 52.55; H, 3.65; N, 20.42. Found: C, 52.30; H, 3.34; N, 20.85.

3-Phenyl-8-thiouric Acid (XIV) and 3-Phenyl-2,8-dithiouric Acid (XV)——A well-pulverized mixture of the 5,6-diaminopyrimidine (IX or X, 0.01 mole) and thiourea (0.1 mole) was heated in an oil bath at 220~225° for 30 min. during which the mixture completely melted to a fluid with an evolution of NH_3 and then resolidified to mass. After cooling, the mixture was dissolved in 10% NaOH solution followed by treatment

*6 This compound was readily converted into hemisulfate by recrystallization from NH_2SO_4 and usually used as the sulfate in further reactions.

with activated carbon and filtration. The filtrate was acidified with AcOH to give a precipitate. XIV : The yield, 53%. m.p. 309~310° (decomp.) (recrystallized from 50% AcOH in pale yellow needles). *Anal.* Calcd. for $C_{11}H_8O_2N_4 \cdot \frac{1}{2}H_2O$: C, 49.07; H, 3.34; N, 20.81. Found : C, 49.15; H, 3.34; N, 20.07. XV : The yield, 46%. m.p. 277~278° (decomp.) (recrystallized from a 1:1 mixture of H_2O and DMF in colorless needles). *Anal.* Calcd for $C_{11}H_8ON_4S \cdot HCON(CH_3)_2 \cdot \frac{1}{2}H_2O$: C, 46.92; H, 4.46; N, 19.55. Found : C, 47.19; H, 4.40; N, 19.36.

[(3-Phenyl-2,6-dioxo-1,2,3,6-tetrahydro-8-purinyl)thio]acetic Acid (XVIII)——0.5 g. of finely-powdered 3-phenyl-8-thiouric acid (XIV) was suspended in 15 ml. of water containing 1.0 g. of monochloroacetic acid and boiled for 20 min. During heating, the suspension went into clear solution and then a crystalline precipitate separated. After cooling, the precipitate was filtered off and recrystallized from water-DMF to give 0.5 g. of (XVIII), m.p. 273~274° (decomp.). An attempt was made to hydrolyze (XVIII) to 3-phenyluric acid by refluxing with 20*N* H_2SO_4, but no thioglycolic acid was formed and unchanged XVIII was recovered. *Anal.* Calcd. for $C_{13}H_{10}O_4N_4S$: C, 49.05; H, 3.14; N, 17.6. Found : C, 49.18; H, 3.48; N, 17.34.

3-Phenylxanthine (XX)——A solution of 1-phenyl-5,6-diaminouracil (IX, 2.7 g.) and HCOONa (1.2 g.) in $HCONH_2$ (25 ml.) was heated in an oil bath at 190° for 2 hr. After cooling, the reaction mixture was diluted with water. The precipitate formed was filtered off, washed with water and recrystallized from water-DMF in colorless needles, m.p. >300°. The yield was 1.8 g. *Anal.* Calcd. for $C_{11}H_8O_2N_4$: C, 57.90; H, 3.50; N, 24.57. Found : C, 57.78; H, 3.72; N, 24.51.

2-Thio-3-phenylxanthine (XXI)——1-Phenyl-5,6-diamino-2-thiouracil (X, 1.4 g.) and HCOONa (0.6 g.) were dissolved in 15 ml. of $HCONH_2$ and heated under gentle reflux in an oil bath for 1.5 hr. The $HCONH_2$ was removed *in vacuo* to give a residue which was dissolved in *N* NaOH solution. The alkaline solution was filtered off and the filtrate was brought to pH 5~6 with AcOH. The precipitate formed was recrystallized from a mixture of water and DMF in fine needles, m.p. 322~323° (decomp.). The yield was 0.7 g. *Anal.* Calcd. for $C_{11}H_8ON_4S \cdot \frac{1}{2}H_2O$: C, 52.20; H, 3.56; N, 22.15. Found : C, 52.43; H, 4.03; N, 22.62.

2-Methylthio-3-phenylhypoxanthine (XXII)[*7]——m.p. >300° (recrystallized from AcOH). *Anal.* Calcd. for $C_{12}H_{10}ON_4S$: C, 55.80; H, 3.87; N, 21.70. Found : C, 55.78; H, 4.22; N, 21.30.

3-Phenyl-8-methylthioxanthine (XIX)[*7]——m.p. >250°. *Anal.* Calcd. for $C_{12}H_{10}O_2N_4S$: C, 52.55; H, 3.65; N, 20.42. Found : C, 52.10; H, 3.45; N, 20.10.

4-Phenyl-3*H*-*v*-triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (XXIV) and 2-Thio-4-phenyl-3*H*-*v*-triazolo[4,5-*d*]pyrimidine-5,7(4*H*,6*H*)-dione (XXV)——To a suspension of the 5,6-diaminopyrimidine (IX or X, 0.01 mole) in 50 ml. of 50% AcOH was added dropwise $NaNO_2$ (0.015 mole) in water with vigorous stirring at 5~10°. After addition was complete, stirring was continued for further 1 hr. The suspension went into solution and immediately a precipitate reformed. XXIV : The yield, 92%. m.p. 265~266° (recrystallized from a mixture of H_2O and AcOH). *Anal.* Calcd. for $C_{10}H_7O_2N_5 \cdot H_2O$: C, 48.60; H, 3.64; N, 28.30. Found : C, 48.41; H, 3.78; N, 28.81. XXV : The yield, 78%. m.p. 260~261° (recrystallized from a mixture of H_2O and AcOH). *Anal.* Calcd. for $C_{10}H_7ON_5S \cdot H_2O$: C, 45.62; H, 3.42; N, 26.61. Found : C, 45.76; H, 3.56; N, 26.95.

4-Phenyl-5-methylthio-3*H*-*v*-triazolo[4,5-*d*]pyrimidin-7(4*H*)-one (XXVI)[*5]——m.p. 284~285° (recrystallized from AcOH). *Anal.* Calcd. for $C_{11}H_9ON_5S$: C, 51.00; H, 3.47; N, 27.00. Found : C, 51.01; H, 3.68; N, 26.80.

1-Phenyl-5-acetamido-6-aminouracil (XXVII) and 1-phenyl-5-acetamido-6-amino-2-thiouracil (XXVIII)——A suspension of the 5,6-diaminopyrimidine (in this case, the free base of IX or X was used, 0.01 mole) in 15 ml. of Ac_2O was heated on a steam bath for 10 min. The suspension became once clear and then a crystalline precipitate separated. XXVII : The yield, 88.1%. m.p. 239~240° (recrystallized from a 1:1 mixture of MeOH and ether). *Anal.* Calcd. for $C_{12}H_{12}O_3N_4$: C, 55.40; H, 4.62; N, 21.53. Found: C, 55.41; H, 4.31; N, 21.24. XXVIII : The yield, 80.4%, m.p. 266~267° (decomp.) (recrystallized from 80% MeOH). *Anal.* Calcd. for $C_{12}H_{12}O_2N_4S \cdot \frac{1}{2}H_2O$: C, 50.50; H, 4.56; N, 19.65. Found : C, 50.29; H, 4.54; N, 20.09.

3-Phenyl-8-methylxanthine (XXIX) and 2-Thio-3-phenyl-8-methylxanthine (XXX)——XXVII or XXVIII (0.01 mole) was dissolved in an equimolar amount of 10% NaOH solution. The solution was filtered off and the filtrate was evaporated under a reduced pressure to give a residue which was heated at 230~240° for 30 min. After cooling, water was added to dissolve the residue followed by acidification with AcOH. The precipitate formed was recrystallized from 50% EtOH in colorless needles. XXIX : The yield, 63%. m.p. >300°. *Anal.* Calcd. for $C_{12}H_{10}O_2N_4$: C, 59.50; H, 4.13; N, 23.16. Found : C, 59.62; H, 4.40; N, 23.78. XXX : The yield, 50.1%. m.p. >300°. *Anal.* Calcd. for $C_{12}H_{10}ON_4S$: C, 55.80; H, 3.88; N, 21.70. Found : C, 56.06; H, 4.19; N, 21.94.

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*7 The same procedure described for the preparation of compound (XVI) was used.

Summary

1-Phenyl-5,6-diaminouracil (IX) or -2-thiouracil (X) prepared from 1-phenyl-6-aminouracil (V) or 1-phenyl-6-amino-2-thiouracil (VI) in an usual way was fused with urea or thiourea to yield 3-phenyluric acid and 3-phenylthiouric acid derivatives (XII, XIII, XIV and XV), while it was reacted with formamide to afford 3-phenylxanthine derivatives (XX and XXI), and with nitrous acid to give triazolo-derivatives (XXIV and XXV). Acetylation of IX or X resulted in formation of the corresponding 5-acetyl derivatives (XXVII and XXVIII) which on heating at 230~240° as the sodium salts were converted into 8-methylpurine derivatives (XXIX and XXX). Preliminary *anti*-cancer testing results of the purine derivatives synthesized were described.

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185. Keiji Yoshida and Tokuo Kubota : Studies on A-Norsteroids. V.*1 Reaction of Steroidal Diosphenols with Manganese Dioxide.

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In the previous paper,[1] it was reported that treatment of 1α,2α-dihydroxy-4-en-3-oxo steroids with manganese dioxide resulted in the A-ring contraction giving the respective A-nor-3(5)-ene-1,2-dioxo steroids. During the course of further investigation on this reaction, it has been found that 2,17β-dihydroxyandrosta-1,4-dien-3-one (IIa) was also oxidized with manganese dioxide giving the A-nor-3(5)-ene-1,2-dioxo steroid. The present paper deals with this novel type of ring contraction reaction.

Rao, *et al.*[2] reported that a mixture of androst-4-ene-2β,3α,17β-triol and 2β,3β,17β-triol was readily oxidized with manganese dioxide in tetrahydrofuran giving 2,17β-dihydroxyandrosta-1,4-dien-3-one (IIa) through 2β-hydroxytestosterone. When 2β-hydroxytestosterone 17-propionate (I) was treated with manganese dioxide in acetone, occurrence of a yellow substance besides the expected diosphenol (IIb) was observed. Prolonged treatment of I with manganese dioxide led to the isolation of yellow crystals, identical with the previously obtained 17β-hydroxy-A-norandrost-3(5)-ene-1,2-dione propionate (IIIb). Since it was obvious that the formation of A-norsteroid (IIIb) proceeded through further oxidation of the diosphenol (IIb), the reaction with manganese dioxide was investigated on the diosphenol (IIa), which is easily obtainable from testosterone by acetoxylation with lead tetraacetate[3] followed by oxygen oxidation of the crude acetoxylated product in alkali medium.[4]

Although preparation of manganese dioxide followed essentially the procedure of Mancera, *et al.*,[5] the rate of ring contraction of the diosphenol (IIa) varied with a small change in the procedure. Manganese dioxide used in this investigation was prepared as described in the experimental part.

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*1 Part IV : K. Yoshida, T. Kubota : Tetrahedron, **21**, 759 (1965).
*2 Fukushima-ku, Osaka (吉田圭治, 久保田徳夫).
1) T. Kubota, K. Yoshida, F. Hayashi, K. Takeda : This Bulletin, **13**, 50 (1965).
2) P. N. Rao, L. R. Axelrod : J. Am. Chem. Soc., **82**, 2830 (1960).
3) F. Sondheimer, K. J. Romo, H. Martinez, G. Rosenkranz : *Ibid.*, **75**, 4712 (1953).
4) R. L. Clarke : *Ibid.*, **82**, 4629 (1960).
5) O. Mancera, G. Rosenkranz, F. Sondheimer : J. Chem. Soc., **1953**, 2189.