(0.1 g.), gradually absorbing about 2 moles of H_2 (131 cc., 20°) during 40 hrs. After removal of the catalyst, the solution was evaporated to leave a residue, about one-half of which crystallized. The crystals were collected, washed with MeOH, dissolved in dil. HCl, washed with ether, basified with Na_2CO_3, and extracted with ether. Evaporation of the ether left a crystalline residue (0.37 g.), m.p. 93~96°, which was recrystallized from petr. ether to colorless rods, m.p. 97~97.5°. This substance showed a brown yellow color with $C(NO_2)_4$, but did not decolorize a Br_2-AcOH solution or $KMnO_4$-acetone solution, and absorbed no more H_2 in AcOH over Adams' Pt-catalyst. It did not give carbonyl derivatives and carbonyl absorption in its ultraviolet spectrum. *Anal.* Calcd. for $C_{18}H_{31}O_2N$: C, 73.67: H, 10.65: N, 4.77. Found: C, 73.68; H, 10.72; N, 4.81. $[\alpha]_D^{13}$ +42.0° (l=1, c=2.407, 95% EtOH). I.R. $\lambda_{max}^{Nujol}\mu$: 5.85 ($COOCH_3$), 2.94, 3.02(NH).

Benzoate: Oil. $[\alpha]_D^{23}$ −22.6° (l=1, c=3.235, $CHCl_3$). I.R. $\lambda_{max}^{Nujol}\mu$: 5.795 ($COOCH_3$), 6.11(>NCO-), no NH.

N-Methylpiperidine Derivative (IVc)—The above piperidine derivative (0.38 g.), m.p. 97.0~97.5°, was dissolved in a mixture of HCO_2H (90%, 2.8 cc.) and HCHO (30%, 1 cc.), and the solution was heated on a water bath for 6 hrs. After addition of dil. HCl, the solution was evaporated, the residue was dissolved in water, washed with ether, basified with Na_2CO_3, extracted with ether, and dried over Na_2SO_4. The crystalline residue (m.p. 76~79°) was recrystallized from petr. ether to colorless prisms, m.p. 86.5~87.0°. *Anal.* Calcd. for $C_{19}H_{33}O_2N$: C, 74.22; H, 10.81; N, 4.56. Found: C, 74.49; H, 10.96; N, 4.45.

Summary

The ketol (II'), obtained by ozonolysis of dimethyl agathenedicarboxylate, was converted to the pyridine derivative (III), which was reduced with sodium and ethanol to several stereoisomeric imino-esters (IVa) and imino-alcohols (Va). One of the imino-esters was obtained directly by catalytic reduction of the ketol (II') in methanolic ammonia.

(Received April 9, 1958)

UCD 547.854.4

91. Shigeo Senda and Akio Suzui: Uracil Derivatives and Related Compounds. I. Condensation of Monosubstituted Urea and Ethyl Acetoacetate.

(*Gifu College of Pharmacy**)

Synthesis of 6-methyluracil by the condensation of urea and ethyl acetoacetate[1] is well known. Such ring closure reaction of uracil derivatives using monosubstituted ureas (substituents: phenyl, cyclohexyl, and methyl) instead of urea was examined in the present series of work.

For the condensation of phenylurea with ethyl acetoacetate, a mixture of the two compounds was stored over sulfuric acid in a vacuum desiccator until the mixture became dry and powdered, the mixture was dissolved in hot aqueous solution of sodium hydroxide, and the solution was acidified with hydrochloric acid, affording crystals of m.p. 203° in a good yield. This product was not the anticipated uracil compounds but a condensate product of 1 mole of ethyl acetoacetate with 2 moles of phenylurea, indicated by the elemental analysis. Same treatment of a mixture of phenylurea and ethyl 3-(3-phenylureido)-crotonate (I),[2] prepared from ethyl 3-aminocrotonate and phenyl isocyanate, and hydrolysis of its product gave 1-[3-(3-phenylureido)crotonoyl]-3'-phenylurea (II). The above-mentioned product of m.p. 203° was found to be identical with (II). Methylation of (II) with dimethyl sulfate gave 1,6-dimethyl-3-phenyluracil (III), liberating phenylurea which combined with carboxyl group and undergoing ring closure.

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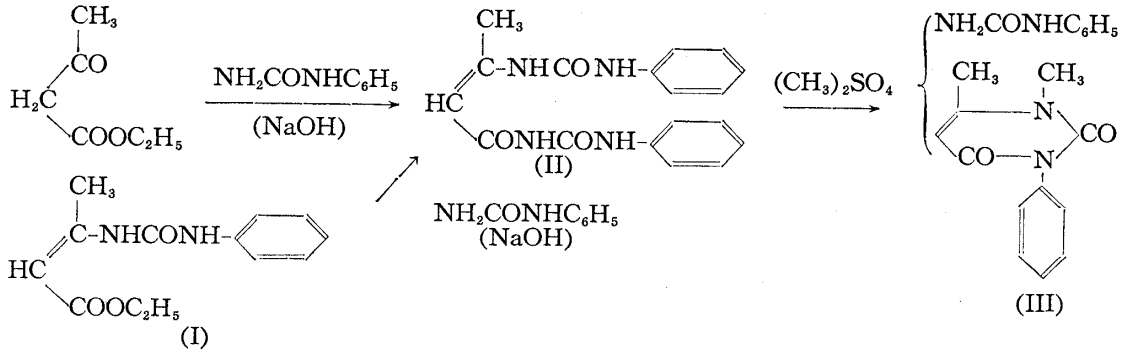
1) Org. Syntheses, Coll. Vol. II, 422(1948).

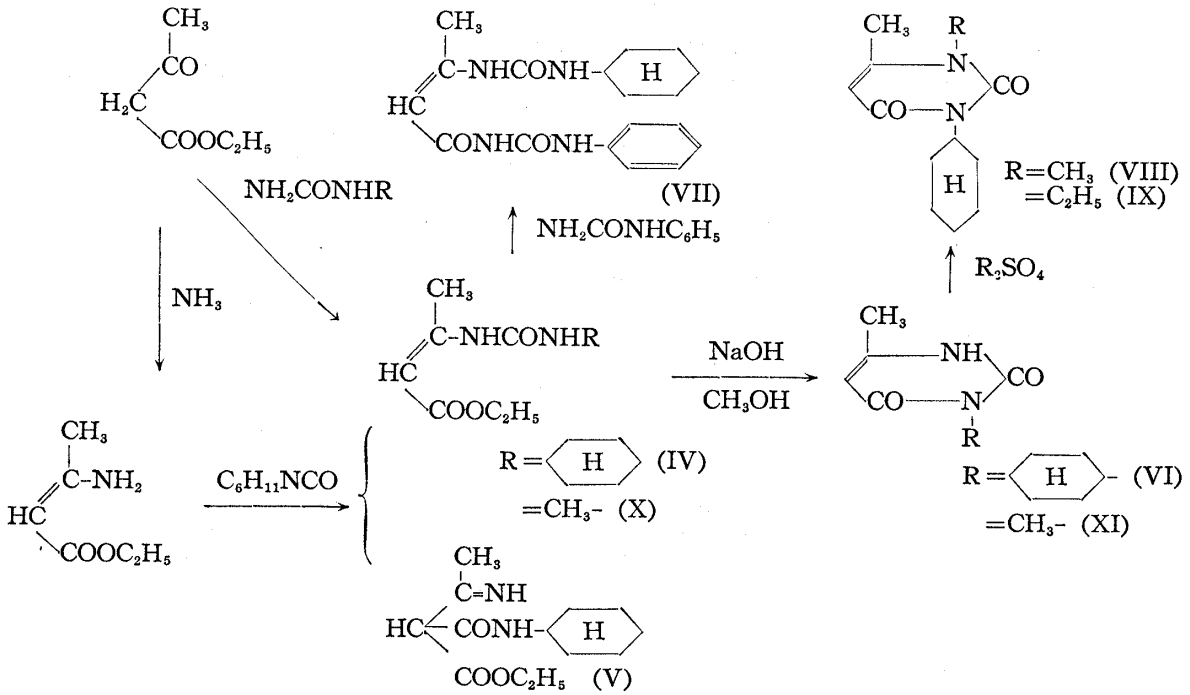
2) A. Michaelis: Ann., **366**, 377(1909); R. Behrend, F. C. Meyer: Ber., **33**, 622(1900).



For the condensation of cyclohexylurea with ethyl acetoacetate, the two compounds were treated similarly as described above to give crystals of m.p. 129°. This was also not the uracil derivative but a condensate of 1 mole each of cyclohexylurea and ethyl acetoacetate. Ethyl 3-(3-cyclohexylureido)crotonate (IV), prepared by the condensation of ethyl 3-aminocrotonate[3] and cyclohexyl isocyanate, was found to be identical with the above-mentioned product (IV) of m.p. 129°. The product of m.p. 108~109°, obtained as a by-product in the above reaction, decomposed with evolution of ammonia when it was heated with aqueous solution of sodium hydroxide and, therefore, it was assumed to be ethyl N-cyclohexyl-2-(1-iminoethyl)malonamate (V). (IV) was not hydrolyzed on heating with aqueous solution of sodium hydroxide but easily gave 3-cyclohexyl-6-methyluracil (VI) when it was heated with methanolic sodium hydroxide.

When (IV) was hydrolyzed in the presence of cyclohexylurea, (VI) was formed by cyclization to uracil without further alteration; but when 1 mole of phenylurea was added to (IV), the formation of uracil ring did not occur and gave 1-[3-(3-cyclohexylureido)crotonoyl]-3-phenylurea (VII), which was analogous to (II) in its structure.

Methylation of (VI) with dimethyl sulfate gave 1,6-dimethyl-3-cyclohexyluracil (VIII), and ethylation with diethyl sulfate gave 1-ethyl-3-cyclohexyl-6-methyluracil (IX).



Condensation of methylurea and ethyl acetoacetate gave 3,6-dimethyluracil (XI)[4] via ethyl 3-(3-methylureido)crotonate (X), similarly as in the case of cyclohexylurea.

3) A. Michaelis: Ann., **366**, 377(1909).
4) H. L. Wheeler, McFarland: Am. Chem. J., **42**, 107(1911).

From the above-mentioned experimental results, it was found that all the products obtained by the condensation of monosubstituted urea and acetoacetic ester were 3-substituted 6-methyluracil derivatives, but when phenylurea was applied, the ring closure reaction did not take place by the hydrolysis of the intermediate condensate but at the methylation.

The alkyluracils described in this report were synthesized in order to offer some intermediates for pharmaceutics.

The authors express their gratitude to Dr. Etsuo Miyamichi, President of this College, for giving continued encouragement. The authors are also indebted to Miss Hideko Iwata of the Analysis Center, University of Kyoto, for elemental analyses.

Experimental

1-[3-(3-Phenylureido)crotonoyl]-3-phenylurea (II)—(i) To a mixture of 13 g. (0.1 mole) of ethyl acetoacetate, 14 g. (0.1 mole) of phenylurea, and 3 cc. of dehyd. EtOH, 1 drop of conc. HCl was added, mixed well, placed in an evaporating dish, and kept for 7~10 days over H_2SO_4 in a vacuum (80 mm. Hg) desiccator. The reaction mixture was stirred from time to time and powdered to facilitate drying. When finely powdered, the mixture was dissolved in hot NaOH solution (8 g. of NaOH in 120 cc. of water), the solution was acidified with HCl, and the separated product was collected. The precipitate was washed with water and recrystallized from MeOH to 16.8 g. of (II) as colorless needles, m. p. 203°. *Anal.* Calcd. for $C_{18}H_{18}O_3N_4$: C, 63.89; H, 5.36; N, 16.56. Found: C, 63.78; H, 5.45; N, 16.64.

(ii) A mixture of 0.25 g. of ethyl 3-(3-phenylureido)crotonate (I) and 0.14 g. of phenylurea was boiled in NaOH solution (0.06 g. of NaOH in 2 cc. of H_2O) for 2 hrs., acidified with HCl, and the separated product was recrystallized form water to give 0.25 g. of (II) as colorless needles, m. p. 203°, undepressed on admixture with the product obtained by the above method (i).

The mother liquor of the above recrystallization was evaporated to dryness and the residue was recrystallized from water to recover 7.6 g. of colorless needles, m. p. 147°, identified by admixture as phenylurea.

1,6-Dimethyl-3-phenyluracil (III)—To KOH solution (24.5 g. of KOH in 90 cc. of water) was added 29.5 g. of (II), and 55 g. of Me_2SO_4 was dropped with shaking. The reaction was exothermic and, after (II) had completely dissolved, new crystals began to appear. When the solution became no longer alkaline, the separated product was collected and recrystallized from MeOH to 14.3 g. of (III) as colorless prisms, m.p. 205°. *Anal.* Calcd. for $C_{12}H_{12}O_2N_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.87; H, 5.47; N, 13.02.

Ethyl 3-(3-Cyclohexylureido)crotonate (IV)—To a mixture of 182 g. (1.4 moles) of ethyl acetoacetate, 199 g. (1.4 mole) of cyclohexylurea, and 50 cc. of dehyd. EtOH, 14 drops of conc. HCl were added and the mixture was stored in a desiccator at a reduced pressure for 20 days. When the reaction mixture became well-powdered, 10 g. of the crude condensate (297 g.) obtained was recrystallized from 50% MeOH to give 2 g. of (IV) as colorless prisms, m.p. 129°. *Anal.* Calcd. for $C_{13}H_{22}O_3N_2$: C, 61.39; H, 8.72; N, 11.02. Found: C, 61.93; H, 8.45; N, 11.06.

Condensation of Ethyl 3-Aminocrotonate with Cyclohexyl Isocyanate (Separation of (IV) and (V)).—A mixture of 23 g. of ethyl 3-aminocrotonate and 22 g. of cyclohexyl isocyanate was heated in an oil bath (120°) for 12 hrs., allowed to cool, and extracted with 50 cc. of ether. The residue was recrystallized from MeOH to 0.3 g. of 1,3-dicyclohexylurea as colorless plates, m.p. 226°. *Anal.* Calcd. for $C_{13}H_{24}ON_2$: C, 69.60; H, 10.78; N, 12.49. Found: C, 69.66; H, 10.94; N, 12.92.

The ether solution was evaporated and the residue was extracted with 200 cc. of petr. ether to give sandy crystals of m. p. 90~115°. A repeated fractional recrystallization of the crude crystals from petr. ether gave, from the part sparingly soluble in petr. ether, 0.5 g. of ethyl N-cyclohexyl-2-(1-iminoethyl)-malonamate (V), m. p. 108~109°. *Anal.* Calcd. for $C_{13}H_{22}O_3N_2$: C, 61.39; H, 8.72; N, 11.02. Found: C, 61.26; H, 8.81; N, 11.13.

From the portion comparatively soluble in petr. ether, 0.1 g. of ethyl 3-(3-cyclohexylureido)-crotonate (IV) was obtained as colorless prisms, m. p. 129°. *Anal.* Calcd. for $C_{13}H_{22}O_3N_2$: C, 61.39; H, 8.72; N, 11.02. Found: C, 61.40; H, 8.93; N, 11.06. The mixed m.p. of this product with the compound (m. p. 129°) obtained by the previous method was not lowered. (V) decomposed with evolution of ammonia when it was heated with NaOH solution but (IV) was not decomposed by this treatment and was recovered unchanged.

3-Cyclohexyl-6-methyluracil (VI)—(i) The crude condensation product (IV) (287 g.) of ethyl acetoacetate and cyclohexylurea was boiled with MeOH-KOH (126 g. of KOH and 800 cc. of MeOH) for 30 mins., cooled, and acidified with HCl. The separated product was collected and recrystallized from 50% MeOH to 202 g. (69%) of (VI) as colorless prisms, m.p. 225°. *Anal.* Calcd. for $C_{11}H_{16}O_2N_2$: C, 63.44; H, 7.74; N, 13.45. Found: C, 63.36; H, 7.42; N, 13.48.

(ii) The condensation product (mixture of (IV) and (V)) of ethyl 3-aminocrotonate and cyclohexyl isocyanate was hydrolyzed with MeOH-KOH (9.7 g. of KOH and 70 cc. of MeOH), when the substance dissolved with evolution of NH_3 and treated similarly as described in (i) to give 7.7 g. (40%) of (VI),

colorless prisms, m. p. 223~225°.

(iii) A mixture of 0.7 g. of cyclohexylurea and 1.3 g. of (IV) was boiled in MeOH-KOH solution (0.6 g. of KOH and 50 cc. of MeOH) and acidified with HCl. The separated mass was collected and recrystallized from MeOH to afford 0.6 g. of (VI) as colorless prisms, m.p. 225°. Both compounds obtained in (ii) and (iii) were found by admixture to be identical with (VI) obtained in (i).

1-[3-(3-Cyclohexylureido)crotonoyl]-3'-phenylurea (VII)—A mixture of phenylurea (0.68 g.) and 1.27 g. of (IV) in EtOH-KOH (0.56 g. of KOH in 50 cc. of EtOH) was refluxed on a water bath, cooled, and acidified with HCl. The separated product was collected, washed with water, and recrystallized from 50% MeOH to give 0.9 g. of (VII) as colorless needles, m.p. 178°. *Anal.* Calcd. for $C_{18}H_{24}O_3N_4$: C, 62.77; H, 7.02; N, 16.27. Found: C, 62.53; H, 6.96; N, 16.33.

1, 6-Dimethyl-3-cyclohexyluracil (VIII)—To NaOH solution (27.7 g. of NaOH in 270 cc. of H_2O) was added 110 g. of (VI), and 86.5 g. of Me_2SO_4 was dropped gradually under stirring and cooling. When the reaction mixture became acidic, the separated mass was collected, washed with water, and recrystallized from 50% MeOH to give 116 g. of (VIII) as colorless plates, m.p. 139°. *Anal.* Calcd. for $C_{12}H_{18}O_2N_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.85; H, 8.02; N, 12.82.

1-Ethyl-3-cyclohexyl-6-methyluracil (IX)—To NaOH solution (5.6 g. of NaOH in 28 cc. of H_2O) was added 15 g. of (VI), and ethylated with 21.6 g. of Et_2SO_4 to give 16 g. of (IX) as colorless needles (from petr. ether), m.p. 109~112°. *Anal.* Calcd. for $C_{13}H_{20}O_2N_2$: C, 66.07; H, 8.53; N, 11.86. Found: C, 66.35; H, 8.73; N, 11.73.

3, 6-Dimethyluracil (XI)—To 13 g. of ethyl acetoacetate and 7.4 g. of methylurea in 2.5 cc. of dehyd. EtOH 2 drops of conc. HCl was added and the mixture was treated as for (II). A part of the crude product was recrystallized from petr. ether to give ethyl 3-(3-methylureido)crotonate (X) as colorless prisms, m. p. 49°. *Anal.* Calcd. for $C_8H_{14}O_3N_2$: C, 51.60; H, 7.58; N, 15.04. Found: C, 51.57; H, 7.82; N, 14.83.

The crude (X) was hydrolyzed with NaOH solution (5 g. of NaOH in 60 cc. of water), acidified with HCl, and the separated mass was recrystallized from water to give 6.4 g. of (XI) as colorless needles, m. p. 262°. *Anal.* Calcd. for $C_6H_8O_2N_2$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.40; H, 5.66; N, 20.30.

Summary

All of the compounds derived from the condensation of monosubstituted ureas (substituents: phenyl, cyclohexyl, methyl) and ethyl acetoacetate were 3-substituted 6-methyluracil derivatives. In the case of phenylurea, the hydrolysis of the condensation product gave 1-[3-(3-phenylureido)crotonoyl]-3-phenylurea without the formation of a uracil ring, and when the condensation product was methylated, the ring closure occurred to afford 1,6-dimethyl-3-phenyluracil. In the case of cyclohexylurea or methylurea, 5-alkyl-6-methyluracil was obtained in a good yield via ethyl 3-(3-alkylureido)crotonate.

(Received February 11, 1958)

UDC 547.854.4

92 Shigeo Senda and Akio Suzui: Uracil Derivatives and Related Compounds. II.[1] Alkylation of 6-Methyl-2-thiouracil Derivatives.

(*Gifu College of Pharmacy**)

The present study was carried out to investigate the alkylation reaction of 6-methyl-2-thiouracil derivatives in detail and also to use the alkyluracils so obtained as the intermediate for pharmaceutics.

Methylation of 6-methyl-2-thiouracil[2] (I) with 2 moles of dimethyl sulfate afforded 2-methylthio-3,6-dimethyl-4-pyrimidone[3] (II) in a good yield and a small amount of 1,6-dimethyl-2-methylthio-4-pyrimidone (III) as a by-product. The hydrolysis of (II) or (III)

* 3 Kokonoe-cho, Gifu (千田重男, 鈴井明男).

1) Part I: This Bulletin, **6**, 476(1958).
2) Org. Syntheses, Coll. Vol. II, 422(1948).
3) H. L. Wheeler, McFarland: Am. Chem. J., **42**, 105(1911).