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Studies on Ketene and Its Derivatives. XXXIX.[1] Reaction of Diketene with Semicarbazone

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Reaction of aromatic ketone semicarbazone, such as propiophenone semicarbazone (VIIa), acetophenone semicarbazone (VIIb) and benzophenone semicarbazone (VIIc), with diketene in glacial acetic acid gave the N-alkylidene aminouracil derivatives (VIIIa—c) in good yield. Hydrolysis of VIIIa—c with 10% hydrochloric acid afforded 1-amino-6-methyluracil (IX). Similarly, benzaldehyde semicarbazone (VIId) reacted with diketene to give 1-benzalamino-6-methyluracil (VIIId), which, on catalytic reduction, was reduced to 1-benzylamino-6-methyluracil (XIV). Reaction of aliphatic ketone semicarbazone, such as acetone semicarbazone (VIIe), methylethylketone semicarbazone (VIIf), and cyclohexanone semicarbazone (VIIg), did not afford the VIII-type compounds, but gave IX.

In 1908 Chick and Wilsmore[3,4] reported the reaction of diketene with the carbonyl reagent such as phenylhydrazine (Ia) or semicarbazide (Ib) to give the phenylhydrazone of acetoacetic phenylhydrazide (IIa) or the semicarbazone of acetoacetic semicarbazide (IIb), respectively. Some 36 years later Lecher and co-workers[5] re-investigated the reaction of phenylhydrazine (Ia) with diketene under various conditions and stated that at low temperature the reaction gave IIa in good yield, but heating of IIa in glacial acetic acid or aqueous mineral acid afforded 1-phenyl-3-methyl-5-pyrazolone (III, R=C_6H_5) or 1-phenyl-5-methyl-3-pyrazolone (III′, R=C_6H_5), respectively.

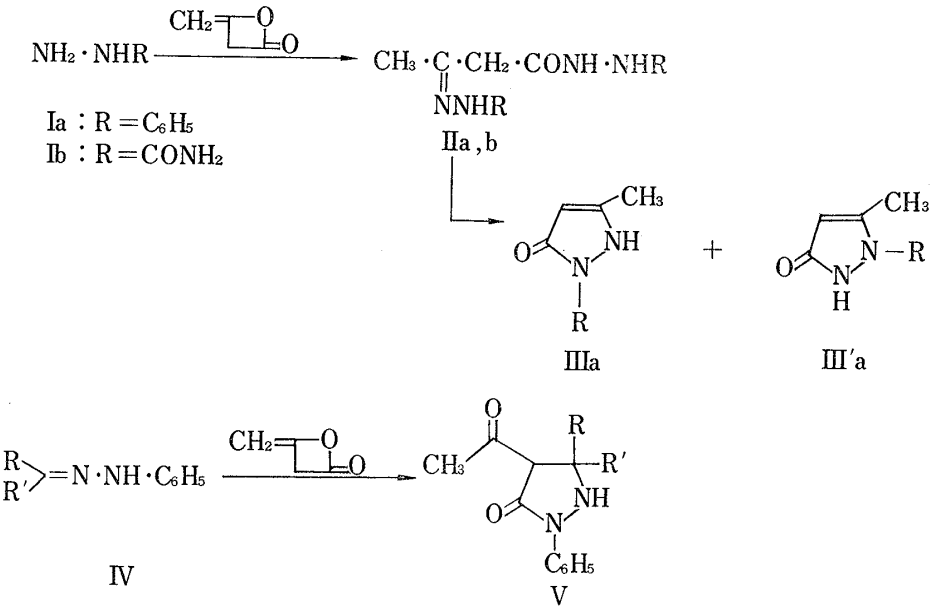

Chart 1

1) Part XXXVIII: T. Kato and N. Katagiri, *Chem. Pharm. Bull.* (Tokyo), **18**, 2269 (1970).
2) Location: *Aobayama, Sendai.*
3) F. Chick and N.T.M. Wilsmore, *J. Chem. Soc.*, **93**, 946 (1908).
4) F. Chick and N.T.M. Wilsmore, *J. Chem. Soc.*, **97**, 1478 (1910).
5) H.Z. Lecher, R.P. Parker, and R.C. Conn, *J. Am. Chem. Soc.*, **66**, 1959 (1944).

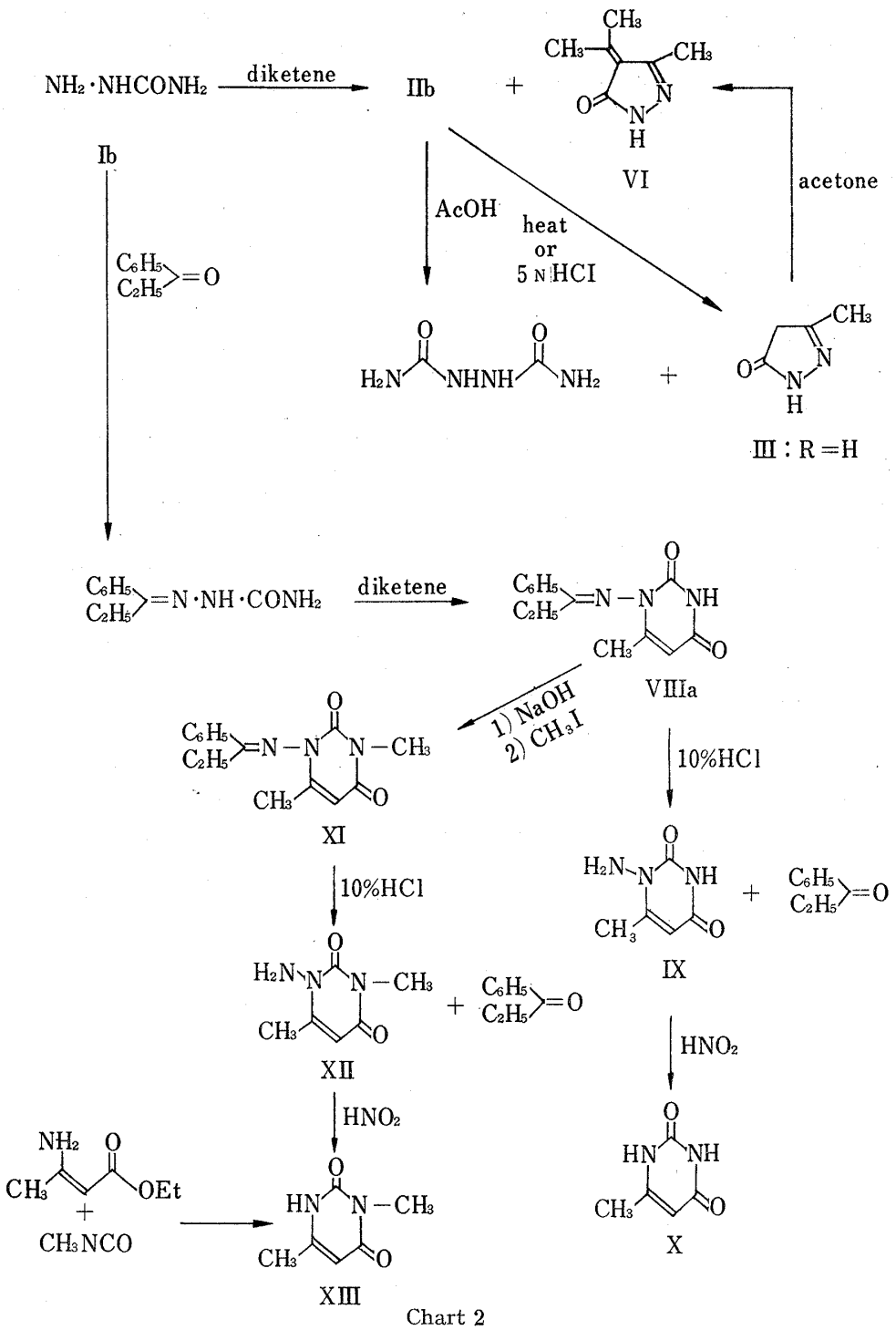

Chart 2

On the other hand, in the previous paper of this series[1] we have reported the reaction of the phenylhydrazone (IV) with diketene giving the 3-pyrazolidone derivatives (V). The continuing investigation was undertaken in an effort to prepare the N-carbamoyl-3-pyrazolidone derivative (V, $C_6H_5 \rightarrow CONH_2$) by the reaction of diketene with the semicarbazone (VII). However, we found that the reaction did not afford the pyrazolidones (V), but gave the N-aminouracil derivatives (VIII). In addition we re-tested the reaction of Ib with diketene, which is also the subject of the present paper.

According to the litrature reported by Chick[4] treatment of semicarbazide with diketene afforded the semicarbazone of acetoacetic semicarbazide (IIb) as a main product with the formation of colorless prisms as a by–product, which was identified with 4-isopropylidene-5-

methyl-3-pyrazolone (VI) by comparison of infrared spectra with an authentic sample.[6] Heating of IIb in glacial acetic acid gave syn-N,N′-dicarbamoylhydrazine[7] and 5-methyl-3-pyrazolone (III, R=H), which was treated with acetone giving VI. Hydrolysis of IIb with 5N hydrochloric acid gave III (R=H) in 59% yield. When IIb was heated under reduced pressure, III (R=H) was sublimed in 44% yield.

Heating of a mixture of propiophenone semicarbazone (VIIa) and diketene in glacial acetic acid gave 1-(N-(1-phenyl)propylidene)amino-6-methyluracil (VIIIa) in good yield. The infrared (IR) spectrum of VIIIa indicates the presence of NH at 3360 and the carbonyl absorption at 1708 and 1675 cm^{-1}. In the nuclear magnetic resonance (NMR) spectrum of VIIIa signals of methyl protons (2.06 ppm, 3H, singlet), ethyl protons (0.97 ppm, 3H, triplet, J=8 cps and 2.66 ppm, 2H, quartet, J=8 cps), olefinic proton (5.59 ppm, 1H, singlet), benzene ring protons (7.3—8.0 ppm, 5H, multiplet), and NH proton (11.34 ppm, 1H, broad) can be observed.

Hydrolysis of VIIIa with 10% hydrochloric acid afforded 1-amino-6-methyluracil (IX) and propiophenone. Treatment of IX with nitrous acid gave 6-methyluracil (X).

Reaction of VIIIa with methyl iodide gave 1-(N-(1-phenyl)propylidene)amino-3,6-dimethyluracil (XI), which, on treatment with 10% hydrochloric acid, was hydrolyzed to 1-amino-3,6-dimethyluracil (XII) and propiophenone. Treatment of XII with nitrous acid gave 3,6-dimethyluracil (XIII), whose IR spectrum was identical in every respect with that of an authentic sample prepared from ethyl β-aminocrotonate and methylisocyanate.

These data described above are consistent with the structure of the product as 1-(N-(1-phenyl)propylidene)amino-6-methyluracil (VIIIa).

Similarly, acetophenone semicarbazone (VIIb) and benzophenone semicarbazone (VIIc) reacted with diketene to give 1-(N-(1-phenyl)ethylidene)amino-6-methyluracil (VIIIb) and 1-(N-benzhydrylidene)amino-6-methyluracil (VIIIc), respectively. Both VIIIb and VIIIc were hydrolyzed with 10% hydrochloric acid to the same product, 1-amino-6-methyluracil (IX).

Reaction of benzaldehyde semicarbazone (VIId) with diketene in glacial acetic acid afforded 1-benzalamino-6-methyluracil (VIIId). The infrared spectrum of VIIId showed the absorptions of the NH streching (3120 cm^{-1}) and the carbonyl groups (1705, 1660 cm^{-1}). Its NMR spectrum indicated the signals due to 6-methyl protons (2.22 ppm, 1H, singlet),

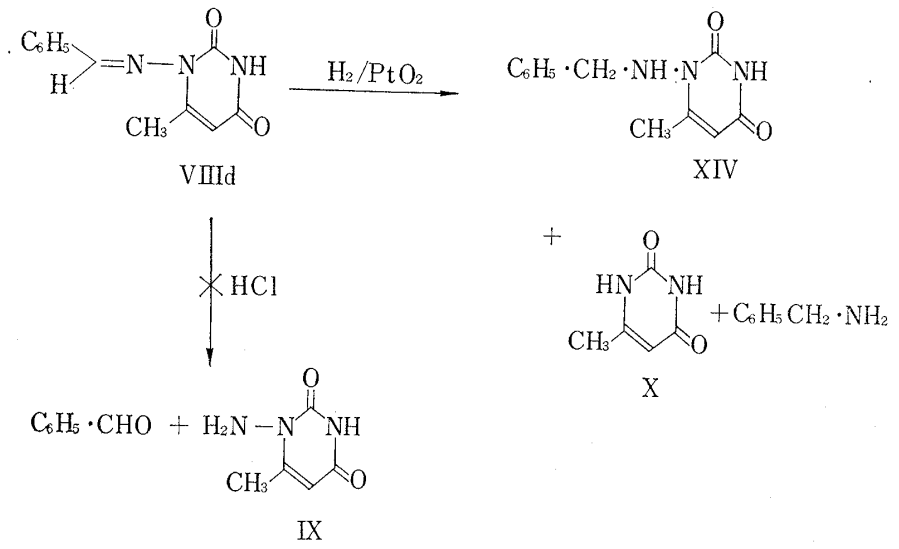

Chart 3

6) L. Wolf, *Ber.*, **38**, 3041 (1905).
7) Th. Curtius and K. Heidenreich, *J. prakt. Chem.*, (2), **52**, 468 (1905).

a proton at 5-position (5.51 ppm, 1H, singlet), an olefinic proton (8.95 ppm, 1H, singlet), benzene ring protons (7.4—8.0 ppm, 5H, multiplet), and an NH proton (11.42 ppm, 1H, singlet).

Both acid and alkali hydrolysis of VIIId afforded a resinous product, from which 1-amino-6-methyluracil (IX) was not detected. Catalytic reduction of VIIId with platinum dioxide in methanol gave 1-benzylamino-6-methyluracil (XIV), 6-methyluracil (X), and benzylamine. These observations are consistent with the structure of VIIId as 1-benzalamino-6-methyluracil.

Reaction of aliphatic ketone semicarbazone, such as acetone semicarbazone (VIIe), methylethylketone semicarbazone (VIIf), and cyclohexanone semicarbazone (VIIg), did not afford the VIII-type compounds, but gave 1-amino-6-methyluracil (IX).

Experimental

Reaction of Semicarbazide (Ib) with Diketene——To a solution of Ib (11.1 g) and sodium acetate (16.4 g) in H_2O (150 ml) was added diketene (10.1 g) dropwise with cooling. The mixture was stirred for 1 hr at room temperature, and crystals separated were collected by filtration. Recrystallization from H_2O gave colorless prisms (IIb), mp 217—219° (decomp.). Yield, 5.7 g (53%). *Anal.* Calcd. for $C_6H_{12}O_3N_6$ (IIb): C, 33.33; H, 5.59; N, 38.88. Found: C, 33.06; H, 5.74; N, 39.08.

The filtrate was condensed under reduced pressure to dryness, and the residue was extracted with EtOH. The EtOH fraction was evaporated to give a crystalline residue, which, after washing with a small amount of H_2O, was purified by recrystallization from MeOH–AcOEt to colorless prisms (VI), mp 210—213° (decomp.), whose IR spectrum was identical with that of an authentic sample prepared from III (R=H) and acetone according to the literature.[6] *Anal.* Calcd. for $C_7H_{10}ON_2$ (VI): C, 60.85; H, 7.30; N, 20.28. Found: C, 60.89; H, 7.52; N, 20.09.

Reaction of IIb with Glacial Acetic Acid——A solution of IIb (2.2 g) in glacial AcOH (10 ml) was heated at reflux for 30 min. The mixture was cooled and crystals separated were collected. Recrystallization from H_2O gave colorless prisms, mp 247—248° (decomp.) (lit. mp 245—246°).[7] Yield, 0.8 g (67%). *Anal.* Calcd. for $C_2H_6O_2N_4$(*syn*-N,N′-dicarbamoylhydrazine): C, 20.34; H, 5.12; N, 47.44. Found: C, 20.39; H, 5.31; N, 47.59.

The filtrate was condensed *in vacuo* to dryness, and the residue was purified by recrystallization from EtOH to colorless prisms, mp 210° (decomp.). Yield, 0.4 g (41%). Its IR spectrum was identical in every respect with that of an authentic specimen of 5-methyl-3-pyrazolone (III, R=H) prepared from ethyl acetoacetate and hydrazine according to the literature.[8]

Hydrolysis of IIb with 5N HCl to give 5-Methyl-3-pyrazolone (III, R=H)——A suspension of IIb (1.5 g) in 5N HCl (20 ml) was heated at reflux for 1 hr. The mixture was evaporated under reduced pressure to dryness. The residue was neutralized with 10% Na_2CO_3, and filtered. Recrystallization from EtOH–H_2O gave colorless prisms (III, R=H). Yield, 0.4 g (59%).

Vacuum Distillation of IIb——One gram of IIb was placed in a distilling flask, and heated at 210° under reduced pressure (5 mmHg). White crystals sublimed was collected, and recrystallized from EtOH–H_2O to colorless prisms (III, R=H). Yield, 0.2 g (44%).

1-(N-(1-Phenyl)propylidene)amino-6-methyluracil (VIIIa)——A mixture of propiophenone semicarbazone (VIIa) (3.8 g) and diketene (3.4 g) in AcOH (13 ml) was heated under reflux for 1 hr. The reaction mixture was condensed by distillation *in vacuo* to give a residue, to which MeOH was added and rubbed with a glass rod. Crystals separated were collected and purified by crystallization from EtOH to colorless needles, mp 194—196° (VIIIa). Yield, 4 g (78%). *Anal.* Calcd. for $C_{14}H_{15}O_2N_3$ (VIIIa): C, 65.34; H, 5.88; N, 16.33. Found: C, 65.54; H, 6.03; N, 16.64. IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 3360 (NH), 1708, 1678 (CO). NMR (DMSO-d_6, ppm): 2.06 (6-CH_3), 5.59 (5-H), 11.34 (NH).

1-(N-(1-Phenyl)ethylidene)amino-6-methyluracil (VIIIb)——A mixture of acetophenone semicarbazone (VIIb) (3.5 g) and diketene (3.4 g) in AcOH (15 ml) was heated under reflux for 1.5 hr. After cooling, crystals separated were collected by suction, and washed with ether. Purification by recrystallization from EtOH gave colorless leaves, mp 215° (decomp.). Yield, 4.2 g (88%). *Anal.* Calcd. for $C_{13}H_{13}O_2N_3$ (VIIIa): C, 64.18; H, 5.39; N, 17.28. Found: C, 63.94; H, 5.43; N, 17.32. IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 3360 (NH), 1705, 1680 (CO). NMR (DMSO-d_6, ppm): 2.68 (6-CH_3), 5.58 (5-H), 11.33 (NH).

1-(N-Benzhydrylidene)amino-6-methyluracil (VIIIc)——A solution of benzophenone semicarbazone (VIIc) (4.8 g) and diketene (3.4 g) in AcOH (20 ml) was refluxed for 1 hr. The solution was concentrated *in vacuo*. After washing with ether, the crystalline residue was purified by crystallization from $CHCl_3$ to colorless needles (VIIIc), mp 214—216° (decomp.). Yield, 5.0 g (82%). *Anal.* Calcd. for $C_{18}H_{15}O_2N_3$

8) Th. Curtius and R. Jay, *J. prakt. Chem.*, (2), 39, 52 (1889).

(VIIIc): C, 70.80; H, 4.95; N, 13.76. Found: C, 71.02; H, 5.11; N, 13.89. IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 3360 (NH), 1705, 1675 (CO). NMR (DMSO-d_6, ppm): 2.22 (6-CH_3), 5.47 (5-H), 11.02 (NH).

1-Benzalamino-6-methyluracil (VIIId)——A mixture of benzaldehyde semicarbazone (VIId) (2.9 g) and diketene (3 g) in AcOH (14 ml) was refluxed for 1 hr. After cooling, crystals separated were collected, washed with ether, and purified by crystallization from $CHCl_3$ to colorless prisms, mp 236° (decomp.). Yield, 3.5 g (85%). *Anal.* Calcd. for $C_{12}H_{11}O_2N_3$ (VIIId): C, 62.87; H, 4.84; N, 18.33. Found: C, 63.11; H, 5.13; N, 18.40.

1-Amino-6-methyluracil (IX)——1) Hydrolysis of VIIIa: A mixture of VIIIa (2.6 g) and 10% HCl (15 ml) was heated under reflux for 1 hr. After cooling, the mixture was washed with ether. The ether washing was dried over Na_2SO_4, condensed to give 1.3 g (almost quantitative yield) of propiophenone. The HCl soluble fraction was condensed *in vacuo* to give a crystalline residue, which was purified by recrystallization from EtOH yielding pale yellow prisms (IX), mp 242—244° (decomp.). Yield, 1.1 g (76%). *Anal.* Calcd. for $C_5H_7O_2N_3$ (IX): C, 42.55; H, 5.00; N, 29.78. Found: C, 42.38; H, 5.08; N, 30.27. IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 3320, 1720, 1640. NMR (CF_3CO_2H, ppm): 2.37 (6-CH_3), 6.07 (5-H).

Similarly, hydrolysis of VIIIb (2.4 g) with 10% HCl (15 ml) gave acetophenone (1 g, 83%) and IX (1.2 g, 86%). The same treatment of VIIIc (3.1 g) with HCl gave benzophenone (1.8 g, 99%) and IX (1.2 g, 84%), but from VIIId none of benzaldehyde nor IX was detected.

2) Reaction of Aliphatic Ketone Semicarbazone (VIIe,f,g) with Diketene: A solution of acetone semicarbazone (VIIe) (1.2 g) and diketene (1.7 g) in AcOH (8 ml) was heated under reflux for 1.5 hr, and then H_2O (5 ml) was added. The mixture was heated for an additional 0.5 hr, condensed *in vacuo* to dryness, and the resulting residue was purified by recrystallization from EtOH to pale yellow prisms (IX). Yield, 0.8 g (57%).

Similar treatment of methylethylketone semicarbazone (VIIf) (1.3 g) and cyclohexanone semicarbazone (VIIg) (1.9 g) with diketene (1.7 g) afforded the same product (IX) in 43% (0.6 g) and 32% (0.45 g) yield, respectively.

1-(N-(1-Phenyl)propylidene)amino-3,6-dimethyluracil (XI)——To a solution of NaOH (0.4 g) in H_2O (4 ml)–EtOH (20 ml) was added VIIIa (2.6 g), and the mixture was stirred until in solution. Ether (60 ml) was added to the solution giving a precipitate, which was collected, dried in a desiccator overnight, and then dissolved in abs. EtOH (20 ml). CH_3I (0.9 ml) was added to the solution, and the mixture was refluxed for 30 min. The solvent was distilled off *in vacuo*, and the residue was extracted with benzene. The benzene extract was purified by crystallization from petroleum benzine–$CHCl_3$ to colorless needles (XI), mp 115°. Yield, 1.7 g (63%). *Anal.* Calcd. for $C_{15}H_{17}O_2N_3$ (XI): C, 66.40; H, 6.32; N, 15.49. Found: C, 66.37; H, 6.50; N, 15.80. IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 2980, 1695, 1660. NMR ($CDCl_3$, ppm): 2.14 (6-CH_3), 3.40 (3-CH_3), 5.70 (5-H).

1-Amino-3,6-dimethyluracil (XII)——A solution of XI (1.35 g) in 10% HCl (10 ml) was heated under reflux for 0.5 hr. The mixture was extracted with ether. From the ether soluble fraction 0.6 g (90%) of propiophenone was obtained. The ether insoluble layer was neutralized with Na_2CO_3, condensed to dryness under reduced pressure, and the residue was extracted with hot acetone. The acetone extract was purified by crystallization from acetone to colorless needles (XII), mp 151—152°. Yield, 0.6 g (78%). *Anal.* Calcd. for $C_6H_9O_2N_3$ (XII): C, 46.44; H, 5.85; N, 27.08. Found: C, 46.35; H, 5.79; N, 27.43. IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 3300, 1695, 1660. NMR ($CDCl_3$, ppm): 2.34 (6-CH_3), 3.36 (3-CH_3), 4.52 (NH_2), 5.54 (5-H).

3,6-Dimethyluracil (XIII)——To a solution of XII (0.77 g) in 20% HCl (5 ml) was added $NaNO_2$ with ice-cooling. Crystals separated were collected, washed with H_2O, and purified by recrystallization from EtOH to colorless needles (XIII), mp 262° (decomp.), whose IR spectrum was identical with that of an authentic sample of 3,6-dimethyluracil.[9] Yield, 0.5 g (71%).

6-Methyluracil (X)——A solution of IX (1.4 g) in 20% HCl (10 ml) was treated with $NaNO_2$ (0.8 g) with ice-cooling. Crystals separated were collected, and recrystallized from EtOH to colorless needles, mp 300° (decomp.), whose IR spectrum was identical with that of an authentic sample of 6-methyluracil.[10] Yield, 1 g (80%).

1-Benzylamino-6-methyluracil (XIV)——A mixture of VIIId (2.3 g) and PtO_2 (0.1 g) in MeOH (100 ml) was shaken in H_2 until 280 ml of H_2 had been absorbed (1.3 equivalent amount at 20°). The time required was 8 hr. The catalyst was removed by filtration, and the filtrate was condensed to give a crystalline solid. Recrystallization from EtOH gave 0.8 g (66%) of 6-methyluracil (X).

The mother liquor was condensed, and the residue was purified by alumina chromatography using petroleum ether and MeOH as solvents. From the petroleum ether eluent an oily substance was obtained, which was heated with Ac_2O to yield colorless needles of mp 60°, undepressed on admixture with an authentic sample of N-benzylacetamide. From the MeOH eluent colorless needles (EtOH) of mp 195—197° were obtained. Yield, 0.2 g (9%). *Anal.* Calcd. for $C_{12}H_{13}O_2N_3$ (XIV): C, 62.32; H, 5.67; N, 18.17. Found:

9) A. Pinner, *Ber.*, **18**, 759 (1885).
10) A. Boese, *Ind. Eng. Chem.*, **32**, 16 (1940).

C, 62.48; H, 5.96; N, 18.56. IR $\nu_{max}^{CHCl_3}$ (cm^{-1}): 3380, 1710, 1680, 1620. NMR (CF_3CO_2H, ppm): 2.35 (6-CH_3), 4.23 (C_6H_5 CH_2), 5.96 (5-H).

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