Chem. Pharm. Bull. 26(3) 842—847 (1978)

UDC 547.853.1.04 : 547.574.2.04

Studies on Pyrimidine Derivatives. VI.[1] On the Reactivity of the 2-Methyl Group of 1,2,4-Trimethyl-6-oxo-1,6-dihydropyrimidine

Hiroshi Yamanaka, Hiroyuki Abe, Hidetoshi Hiranuma, and Takao Sakamoto

Pharmaceutical Institute, Tohoku University[2]

(Received August 3, 1977)

While nitrosation of 6-substituted 2,4-dimethylpyrimidines with ethyl nitrite in liquid ammonia occurred preferentially at the 4-methyl group to give the corresponding pyrimidine-4-aldoximes, the same reaction of 1,2,4-trimethyl-6-oxo-1,6-dihydropyrimidine (IV) afforded 1,4-dimethyl-6-oxo-1,6-dihydropyrimidine-2-aldoxime.

Acylation of IV with ethyl benzoate and diethyl oxalate under basic conditions also gave α-(1,4-dimethyl-6-oxo-1,6-dihydro-2-pyrimidinyl)acetophenone and ethyl 3-(1,4-dimethyl-6-oxo-1,6-dihydro-2-pyrimidinyl)pyruvate, respectively.

Keywords——1,2,4-trimethyl-6-oxo-1,6-dihydropyrimidine; 1,4-dimethyl-6-oxo-1,6-dihydropyrimidine-2-aldoxime; 1,4-dimethyl-6-oxo-1,6-dihydropyrimidine-2-carbonitrile; α-(1,4-dimethyl-6-oxo-1,6-dihydro-2-pyrimidinyl)acetophenone; ethyl α-(1,4-dimethyl-6-oxo-1,6-dihydro-2-pyrimidinyl)pyruvate; 6-substituted-2-methylpyrimidine-4-aldoximes; 6-substituted-2-methylpyrimidine-4-carbonitriles

Recently, we have reported[1,3] that side chain nitrosation and acylation of 2,4-dimethyl N-heteroaromatics such as 2,4-dimethylpyridine, 2,4-dimethylquinoline, 2,4-dimethylpyrimidine, and 2,4-dimethylquinazoline occurred preferentially at the 4-methyl groups. For instance, 2,4-dimethylpyrimidine (I) was nitrosated with ethyl nitrite and alkali amide in liquid ammonia to give 2-methylpyrimidine-4-aldoxime (II) as a sole product, and reaction of I with ethyl benzoate in the presence of sodium ethoxide in benzene afforded α-(2-methyl-4-pyrimidinyl)acetophenone (III). All the structures of the products (II, III) were confirmed by chemical methods.

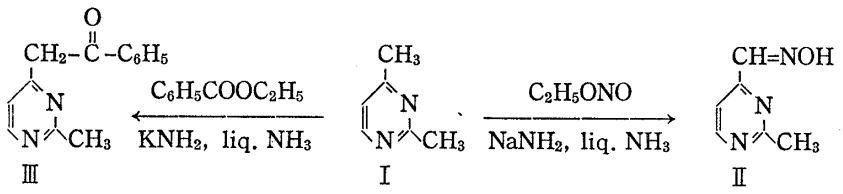

Chart 1

In this paper we wish to report the rather unexpected regioselective nitrosation and acylations of 1,2,4-trimethyl-6-oxo-1,6-dihydropyrimidine (IV) under basic conditions.

When IV was treated with potassium amide in liquid ammonia (−33°) for 1 hr, followed by the addition of ethyl nitrite, colorless crystals ($C_7H_9N_3O_2$) of mp 193—194° (V) were obtained. The infrared (IR) spectrum (KBr) of the product (V) shows an absorption band at 2780 cm^{-1} assignable to the hydroxyl group of an aldoxime. The nuclear magnetic resonance (NMR) spectrum (CF_3COOH) of the product reveals two singlets due to methyl groups at 2.61 and 3.92 ppm and a singlet assignable to the ring proton on the 5-position at 8.52 ppm. These

1) Part V: H. Yamanaka, H. Abe, and T. Sakamoto, *Chem. Pharm. Bull.* (Tokyo), **25**, 3334 (1977).
2) Location: *Aobayama, Sendai 980, Japan.*
3) H. Yamanaka, H. Abe, T. Sakamoto, H. Hiranuma, and A. Kamata, *Chem. Pharm. Bull.* (Tokyo), **25**, 1821 (1977).

observations suggest the structure of the aldoxime to be either 1,4-dimethyl-6-oxo-1,6-dihydropyrimidine-2-aldoxime (V) or 1,4-dimethyl-6-oxo-1,6-dihydropyrimidine-4-aldoxime (V'). There is no reason to draw any distinction between the 2-isomer (V) and the 4-isomer (V'), since the long range spin coupling between the C-methyl group and the ring proton is not clearly observed in this distinction.

In order to determine the structure, the aldoxime (V) was heated with phosphorus pentoxide under reduced pressure to give the nitrile (VI), mp 70—72° in 61% yield. On heating in 50% sulfuric acid the nitrile (VI) was converted to 1,4-dimethyl-2,4-dioxo-1,2,3,6-tetrahydropyrimidine (VII) which was identical with the authentic specimen prepared from 1,4-dimethyl-2-methylthio-6-oxo-1,6-dihydropyrimidine (VIII).[4] This result obviously demonstrated that the structure of the product was the 2-aldoxime (V). In this connection, replacement of a cyano group with a hydroxyl or an alkoxyl group is frequently observed on cyanopyrimidines.[5]

The reaction of IV with ethyl benzoate or diethyl oxalate in boiling benzene in the presence of sodium ethoxide afforded the corresponding monoacyl derivatives (IXa,b) in 46 and 69% yield, respectively. The benzoate (IXa) was identical with α-(1,4-dimethyl-6-oxo-1,6-dihydro-2-pyrimidinyl)acetophenone prepared by reaction of the nitrile (VI) with acetophenone and 50% aqueous sodium hydroxide. When a methanolic solution of the benzoate (IXa) was treated with aqueous ferric chloride, the pale yellow color of the solution turned to violet. The IR spectrum ($CHCl_3$) of the benzoate (IXa) reveals a characteristic absorption band at 1680 cm^{-1} owing to a carbonyl group of 4-pyrimidone, however no band assignable to a phenacyl carbonyl is observed. The NMR spectrum ($CDCl_3$) of the benzoate (IXa) exhibits signals at 2.24 ppm (3H, s), 3.40 ppm (3H, s), 5.67—5.70 ppm (1H, broad s), 5.76 ppm (1H, s), and 15.1—15.4 ppm (1H, broad) along with signals due to a phenyl group (7.40—7.70 ppm, 3H, m and 7.80—8.10 ppm, 2H, m). In this case, with the aid of double resonance

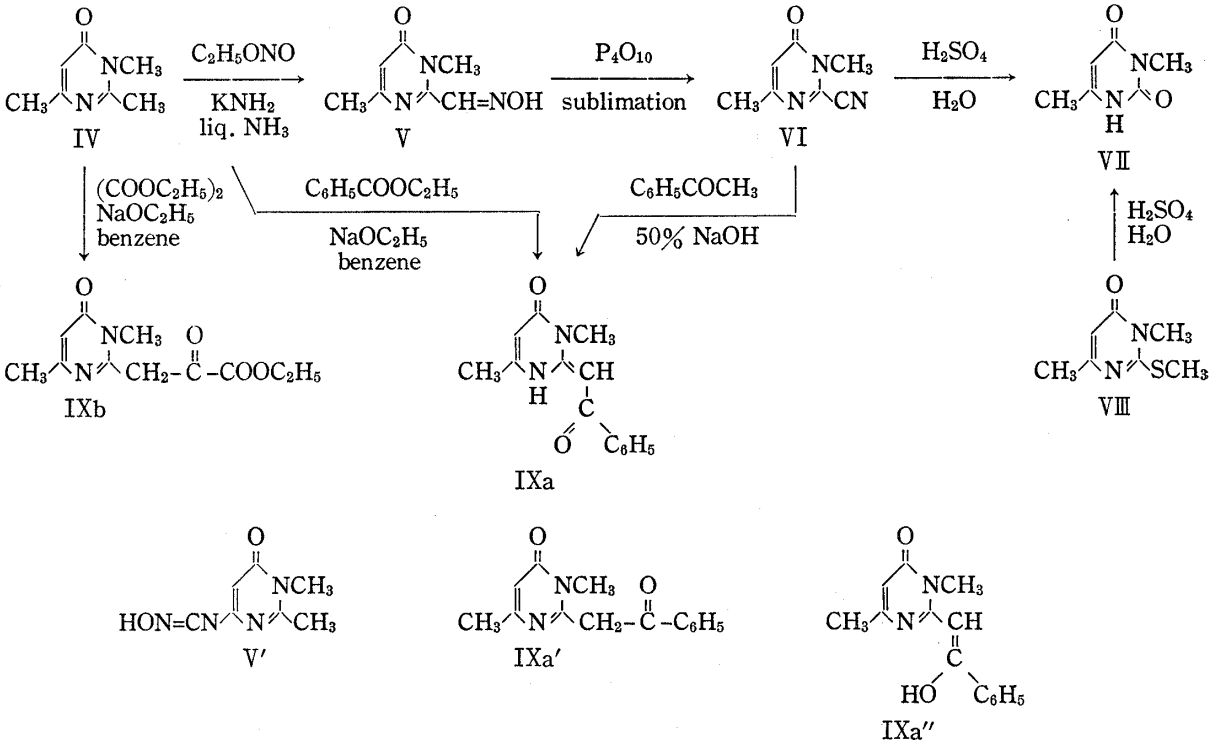

Chart 2

4) H.L. Wheeler and D.F. McFarland, *Am. Chem. J.*, **42**, 101 (1909).
5) H. Yamanaka, *Chem. Pharm. Bull.* (Tokyo), **6**, 638 (1958).

experiment the long range spin coupling between the 4-methyl group and a ring proton at the 5-position is observed (J=1.0 Hz). Furthermore it is confirmed that the same ring proton is coupled with an N-H proton.

These spectral data suggest that i) the selective benzoylation occurs at the 2-methyl group of the pyrimidone (IV), ii) the benzoate does not exist as keto form (IXa'), and an enone form (IXa) is preferential to an enol form (IXa'').

Similarly, based on the spectral data ethyl 3-(1,4-dimethyl-6-oxo-1,6-dihydro-2-pyrimidinyl)pyruvate structure was assigned to the compound IXb.

The predominant reactivity of the 2-methyl group of IV was also perceived by deuterium-hydrogen exchange reaction. When the NMR spectrum of the pyrimidone (IV) was taken in a CD_3OD–D_2O solution of sodium deuteroxide at room temperature, time dependent decrease of the areal intensity of the signal due to the 2-methyl group was immediately taken place, whereas essentially no effect was observed on the signal of the 4-methyl group. This result was consistent with that of above chemical reactions.

In order to compare with the reaction of the pyrimidone (IV), the nitrosation of some 6-substituted 2,4-dimethylpyrimidines (X) was examined. Thus, 2,6-dimethyl- (XIa),[3] 6-ethoxy-2-methyl-(XIb),[6] 2-methyl-6-phenyl- (XIc), and 6-(N,N-dimethylamino)-2-methylpyrimidine-4-aldoxime (XId) were obtained in a yield ranging from 40 to 78%, through the nitrosation of the corresponding dimethylpyrimidines (X). In all the cases, the existence of 2-isomers was not observed. Except the dimethylamino compound (XId), the structure of these aldoximes (XIa—c) were confirmed by converting them into the alkoxyl derivatives (XIIIa—c) *via* the corresponding nitriles (XIIa—c).

The authentic 6-(N,N-dimethylamino)-2-methylpyrimidine-4-carbonitrile (XIId) synthesized by the reaction of the bis-ammonium salt (XIV) with potassium cyanide in hot dimethyl sulfoxide was identical with the product (XIId).

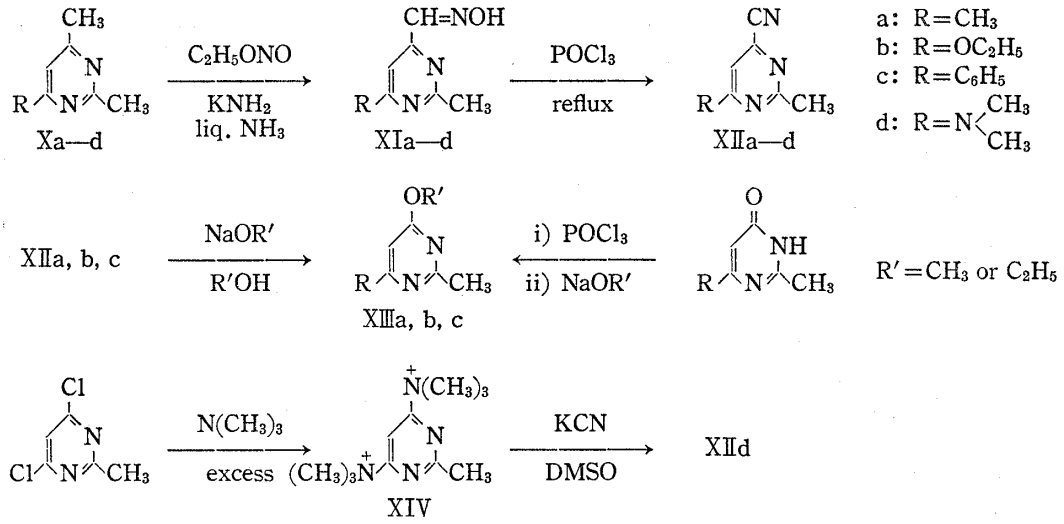

Chart 3

It is of interest that the reverse reactivity was observed on methyl groups of the N-methylpyrimidone (IV) toward those of the usual 2,4-dimethylpyrimidines (X). This is considered to be due largely to the overlapping of electron withdrawing effect of the amide carbonyl group and the azomethine bond in the ring for stabilizing the carbanion initially formed.

6) H. Yamanaka, K. Edo, and S. Konno, *Yakugaku Zasshi*, **97**, 726 (1977).

Experimental[7]

Reaction of IV and Xb—d with Ethyl Nitrite in Liquid Ammonia——General Procedure: In a 500 ml three necked flask, fitted with dry ice condenser and a mechanical stirrer, were placed 300 ml of liq. NH_3, metallic K, and a catalytic amount of anhyd. $FeCl_3$. After the formation of KNH_2, IV and Xb—d was added and the solution was stirred for 1 hr at a boiling point of liq. NH_3. Ethyl nitrite was added to the solution and the mixture was stirred for additional 1 hr. After neutralizing with NH_4Cl, the mixture was concentrated to dryness and the residue was extracted with acetone. Evaporation of the dried extracts afforded the crude products (V and XIb—d) which was purified by column chromatography (Al_2O_3–$CHCl_3$) followed by recrystallization.

The results of elemental analysis, melting points, yields, and spectral data of IV and Xb—d were summarized in Table I.

1,4-Dimethyl-6-oxo-1,6-dihydropyrimidine-2-aldoxime (V): According to the general procedure, V was obtained from IV (2.76 g, 0.02 mol), metallic K (0.86 g, 0.022 g·atom), and EtONO (3 g, 0.04 mol), as colorless prisms (2.47 g) recrystallized from acetone.

6-Ethoxy-2-methylpyrimidine-4-aldoxime (XIb): According to the general procedure, XIb was obtained from Xb (4.56 g, 0.03 mol), metallic K (1.3 g, 0.033 g·atom), and EtONO (4.5 g, 0.06 mol), as colorless prisms (3.48 g) recrystallized from MeOH.

2-Methyl-6-phenylpyrimidine-4-aldoxime (XIc): According to the general procedure, XIc was obtained from Xc (5.52 g, 0.03 mol), metallic K (4.5 g, 0.06 g·atom), and EtONO (4.5 g, 0.06 mol), as colorless needles (5.01 g) recrystallized from MeOH.

6-(N,N-Dimethylamino)-2-methylpyrimidine-4-aldoxime (XId): According to the general procedure, XId was obtained from Xd (4.53 g, 0.03 mol), metallic K (1.3 g, 0.033 g·atom), and EtONO (4.5 g, 0.06 mol), as colorless needles (3.46 g) recrystallized from MeOH.

Table I. Melting Points, Yields, Spectral Data and Elemental Analyses of V and XIb—d

Compd. No.	mp (°C)	Yield (%)	IR ν_{max}^{KBr} cm^{-1} (–OH)	NMR (CF_3COOH) ppm (–CH_3)	(–CH=N–)	(Ring proton)	Formula	Elemental analysis (%) Calcd. (Found) C	H	N
V	193—194	74	2780	2.61 (s, 3H) 3.92 (s, 3H)	8.52 (s, 1H)	6.79 (s, 1H)	$C_7H_9N_3O_2$	50.29 (50.03)	5.03 (5.29)	25.14 (24.93)
XIb	216—217	64	2780	2.93 (s, 3H)	8.20 (s, 1H)	7.10 (s, 1H)	$C_8H_{11}N_3O_2$	53.03 (53.15)	6.12 (5.95)	23.19 (23.37)
XIc	200—202	78	2760	3.12 (s, 3H)	a)	a)	$C_{12}H_{11}N_3O$	67.59 (67.73)	5.20 (5.18)	19.71 (19.88)
XId	227—228 (dec.)	64	2760	2.69 (s, 3H)	8.05 (s, 1H)	6.75 (s, 1H)	$C_8H_{12}N_4O$	53.32 (53.24)	6.71 (6.82)	31.09 (31.45)

a) The signals of these protons were not distinguished from the signals of phenyl ring protons.

1,4-Dimethyl-6-oxo-1,6-dihydropyrimidine-2-carbonitrile (VI)——A mixture of P_4O_{10} (0.43 g, 0.003 mol) and V (0.5 g, 0.003 mol) was heated at 150—200° under reduced pressure (15 mmHg) to sublime colorless prisms (0.27 g, 61%), recrystallized from ether.

Dehydration of XIb—d with $POCl_3$——General Procedure: A suspension of XIb—d in $CHCl_3$ and excess $POCl_3$ was refluxed for 1 hr. The resulting solution was concentrated under reduced pressure to give an orange red residue. The residue was poured into a mixture of 28% NH_4OH and ice. The aqueous solution was saturated with solid K_2CO_3 and extracted with benzene. After evaporating the solvent, the residue was purified by column chromatography (Al_2O_3–benzene) followed by distillation or recrystallisation to afford XIIb—d.

The results of elemental analysis, melting points, yields, and spectral data of VI and XIIb—d were summarized in Table II.

7) All melting points and boiling points are uncorrected. The IR spectra were taken with a JASCO IRA-1 spectrometer and the NMR spectra with a Hitachi R-20 spectrometer. The chemical shifts are expressed by the ppm downfield from tetramethylsilane used as an internal standard and the coupling constants by Herz (Hz). Following abbreviations are used: singlet (s), triplet (t), quartet (q), multiplet (m).

4-Ethoxy-2-methylpyrimidine-6-carbonitrile (XIIb): By the general procedure, XIIb was obtained from XIb (1.8 g, 0.01 mol), $POCl_3$ (15 g), and $CHCl_3$ (15 ml), as colorless solid (1.29 g), bp 108—110° (12 mmHg).

2-Methyl-4-phenylpyrimidine-6-carbonitrile (XIIc): By the general procedure, XIIc was obtained from XIc (2.13 g, 0.01 mol), $POCl_3$ (15 g), and $CHCl_3$ (15 ml), as colorless prisms (1.25 g) recrystallized from ether.

4-(N,N-Dimethylamino)-2-methylpyrimidine-6-carbonitrile (XIId): By the general procedure, XIId was obtained from XId (1.8 g, 0.01 mol), $POCl_3$ (15 g), and $CHCl_3$ (15 ml), as colorless needles (1.55 g) recrystallized from ether.

Table II. Melting Points, Yields, Spectral Data and Elemental Analyses of VI and XIIb—d

Compd. No.	mp (°C)	Yield (%)	IR ν_{max}^{KBr} cm^{-1} (–CN)	NMR ($CDCl_3$) ppm (–CH_3)	NMR ($CDCl_3$) ppm (Ring proton)	Formula	Elemental analysis (%) Calcd. (Found) C	H	N
VI	70— 72	61	—	2.24(s,3H) 3.60(s,3H)	6.28(s,1H)	$C_7H_7N_3O$	56.37 (56.36)	4.73 (4.73)	28.18 (27.95)
XIIb	52— 52.5	79	—	2.58(s,3H)	6.77(s,1H)	$C_8H_9N_3O$	58.88 (58.79)	5.56 (5.47)	25.75 (25.93)
XIIc	96— 98	64	—	2.80(s,3H)	7.76(s,1H)	$C_{12}H_9N_3$	73.83 (73.70)	4.65 (4.57)	21.53 (21.38)
XIId	140—141	96	2236	2.43(s,3H)	6.56(s,1H)	$C_8H_{10}N_4$	59.24 (59.40)	6.21 (6.29)	34.55 (34.87)

1,4-Dimethyl-2,4-dioxo-1,2,3,6-tetrahydropyrimidine (VII) from VI——A solution of VI (0.3 g, 0.002 mol) in 50% H_2SO_4 (10 ml) was refluxed for 2 hr. The solution was neutralized with K_2CO_3 (solid) and extracted with $CHCl_3$. After removal of the solvent, the residue was recrystallized from water to give colorless needles (0.12 g, 43%), mp 260—263°. This compound was identical with the authentic specimen.[4]

4,6-Diethoxy-2-methylpyrimidine (XIIIb) from XIIb——To a solution of NaOEt (prepared from 0.02 g·atom of metallic sodium and 10 ml of abs. EtOH) was dissolved XIIb (0.34 g, 0.002 mol) and the solution was refluxed for 2 hr. After removal of EtOH, water was added to the residue and the solution was extracted with ether. The extract was distilled under reduced pressure to give colorless liquid (0.12 g, 33%), bp 104-105° (31 mmHg). This compound was identical with the authentic specimen.[8]

4-Methoxy-2-methyl-6-phenylpyrimidine (XIIIc)——From XIIc: To a solution of NaOMe (prepared from 0.01 g·atom of metallic sodium and 5 ml of abs. MeOH) was dissolved XIIc (0.5 g, 0.0026 mol) and the solution was refluxed for 1 hr. After removal of MeOH, H_2O was added and the solution was extracted with $CHCl_3$. The extract was distilled under reduced pressure to give colorless liquid (0.28 g, 53%), bp 145—150° (22 mmHg). NMR ($CDCl_3$, ppm): 2.64 (3H, s, CH_3–), 3.93 (3H, s, CH_3–), 6.8 (1H, s, pyrimidine ring proton), 7.27—7.60 (3H, m, phenyl ring proton), 7.75—8.10 (2H, m, phenyl ring proton). *Anal.* Calcd. for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.61; H, 6.15; N, 14.34.

From 4-chloro-2-methyl-6-phenylpyrimidine: A solution of 4-chloro-2-methyl-6-phenylpyrimidine (1.0 g, 0.005 mol) and NaOMe (prepared from 0.01 g·atom of metallic sodium and 5 ml of abs. MeOH) was refluxed for 15 min. After removal of MeOH, the residue was distilled under reduced pressure to give a colorless liquid (0.55 g, 55%), bp 168—178° (28 mmHg). This compound was identical with XIIIc obtained from XIIc.

4-(N,N-Dimethylamino)-2-methylpyrimidine-4-carbonitrile (XIId) from 4,6-Dichloro-2-methylpyrimidine——Trimethylamine was bubbled into a solution of 4,6-dichloro-2-methylpyrimidine (3.3 g, 0.02 mol) in benzene (20 ml) and precipitates formed were filtered by suction. A solution of the precipitates (2.8 g, 0.01 mol) and KCN (0.65 g, 0.01 mol) in DMSO (10 ml) was stirred at room temperature for 3 hr and heated for 1 hr in a boiling water bath. The mixture was diluted with H_2O (40 ml) and extracted with $CHCl_3$. After removal of $CHCl_3$, the residue was dissolved in benzene and passed through an alumina column for decolorization and recrystallized from ether to give colorless needles (0.45 g, 28%), mp 140—141°. This compound was identical with XIId obtained from XId.

α-(1,4-Dimethyl-6-oxo-1,6-dihydro-2-pyrimidinyl)acetophenone (IXa)——i) From IV: A mixture of powdered NaOEt (prepared from metallic sodium 0.23 g, 0.01 g·atom), IV (0.69 g, 0.005 g·ation), and ethyl benzoate (1.5 g, 0.01 mol) in dry benzene was refluxed for 1 hr. The mixture was extracted with 20% HCl

8) H.C. van der Plas and H. Jongejan, *Rec. Trav. Chim.*, **89**, 680 (1970).

and H_2O layer was made alkaline with K_2CO_3 (solid) followed by extracting with $CHCl_3$. After removal of $CHCl_3$ the residue was recrystallized from benzene to pale yellow needles, mp 158—160°. Yield 0.55 g (46%). IR$\nu_{max}^{CHCl_3}$ cm^{-1}: 1680. NMR ($CDCl_3$, ppm): 2.24 (3H, s, $-CH_3$), 3.40 (3H, s, $-CH_3$), 5.67—5.70 (1H, broad s, pyrimidine ring proton), 5.76 (1H, s, $-CH=C<$), 7.40—7.70 (3H, m, phenyl ring proton), 7.80—8.10 (2H, m, phenyl ring proton), 14.80—15.10 (1H, broad, NH). *Anal.* Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.83; N, 11.56. Found: C, 69.38; H, 5.86; N, 11.79.

ii) From VI: A mixture of acetophenone (1.5 ml) and 50% NaOH (0.5 ml) was stirred for 30 min at room temperature followed by addition of VI, and stirring was continued for additional 30 min at room temperature. The mixture was acidified with 10% HCl and washed with ether. The H_2O layer was made alkaline with K_2CO_3 (solid) and extracted with $CHCl_3$. After removal of $CHCl_3$, the residue was recrystallized from ether to give colorless prisms, mp 158—160°. This compound was identical with IXa obtained from IV.

Ethyl 3-(1,4-Dimethyl-6-oxo-1,6-dihydro-2-pyrimidinyl)pyruvate (IXb)——According to the similar manner described above, IV (0.69 g, 0.005 mol), NaOEt (0.01 mol), and diethyl oxalate (1.46 g, 0.01 mol) gave pale yellow needles recrystallized from benzene, mp 164—165°. Yield 0.82 g (69%). IR$\nu_{max}^{CHCl_3}$ cm^{-1}: 1700, 1730. NMR ($CDCl_3$, ppm): 1.40 (3H, t, $J=7.0$ Hz, $\underline{CH_3}CH_2O-$), 2.29 (3H, s, $-CH_3$), 3.43 (3H, s, CH_3N), 4.48 (2H, q, $J=7.0$ Hz, $CH_3\underline{CH_2}O-$), 5.80—5.92 (1H, broad s, pyrimidine ring proton), 6.08 (1H, s, $-CH=C<$), 14.30—15.20 (1H, broad, N–H). *Anal.* Calcd. for $C_{11}H_{14}N_2O_4$: C, 55.46; H, 5.88; N, 11.76. Found: C, 55.26; H, 5.82; N, 11.48.

Hydrogen-Deuterium Exchange Reaction of IV——A D_2O solution of NaOD (40%, 0.1 ml) was added to 4 ml of CD_3OD–D_2O (3: 1) and the testing compound (*ca.* 20 mg) was dissolved in this solution containing tetramethylsilane as an internal standard. The solution was allowed to stand at room temperature in an NMR tube tightly covered by a tefron stopper. The NMR spectra were measured with a Hitachi R-20 spectrometer. The signal 2.68 ppm disappeared within 30 min after adding IV into the solution.

Acknowledgement The authors express their deep gratitude to all the staffs of the Central Analysis Room of this Institute for elemental analysis and measurement of NMR spectra.