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Studies on 4-Chloropyrido[2,3-*d*]pyrimidine and Pyrido[2,3-*d*]pyrimidine

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Ketone carbanion reacted as nucleophilic reagent with 4-chloropyrido[2,3-*d*]pyrimidine (I).

Reaction of I in the presence of sodium amide with acetophenone and acetone gave 2-(4-pyrido[2,3-*d*]pyrimidinyl)acetophenone (III) and 1-(4-pyrido[2,3-*d*]pyrimidinyl)-2-propanone (IV), respectively. The reaction with propiophenone, 3-pentanone and 2-butanone afforded 4-ethylpyrido[2,3-*d*]pyrimidine (V). The reaction with 2-pentanone gave 1-(4-pyrido[2,3-*d*]pyrimidinyl)-2-pentanone (VII) and 4-propylpyrido[2,3-*d*]pyrimidine (VI).

Quinazoline (XIII) has been shown to add several nucleophilic reagents across the 3,4-position. These investigation have now been extended to pyrido[2,3-*d*]pyrimidine (X).

The reaction of X with methylmagnesium iodide, benzylmagnesium chloride and phenylmagnesium bromide afforded 4-methyl- (XIVa), 4-benzyl- (XIVb) and 4-phenyl-3,4-dihydropyrido[2,3-*d*]pyrimidine (XIVc), respectively. These compounds was derived to 4-methyl- (IX), 4-benzyl- (XVII) and 4-phenyl-pyrido[2,3-*d*]pyrimidine (XVIII), respectively, by oxidation with potassium ferricyanide in alkali medium.

The reaction with acetophenone in sodium methoxide solution afforded 2-(3,4-dihydro-4-pyrido[2,3-*d*]pyrimidinyl)acetophenone (XV).

The reaction with hydrogen cyanide afforded 3,4-dihydro-4-pyrido[2,3-*d*]pyrimidinecarbonitrile (XVI) which was derived to 4-pyrido[2,3-*d*]pyrimidinecarbonitrile (XIX). XIX was also derived to 4-methoxypyrido[2,3-*d*]pyrimidine (XX) and 4(3*H*)-pyrido[2,3-*d*]pyrimidinone, respectively from the reaction with methoxide and hydroxide ion.

It may be concluded through the foregoing experimental results that the addition is occured across the 3,4-position as similar as that of XIII already reported.[5]

Reaction of 4-Chloropyrido[2,3-*d*]pyrimidine (I) with Ketone Carbanions

It has been reported by T. Higashino and his co-workers that the reaction of 4-chloroquinazoline (II) with several ketones in the presence of sodium amide afforded (quinazolinyl) methyl alkyl (or phenyl) ketone (A) and 4-alkylquinazoline (B) accompanied with elimination of chloride ion shown in Chart 1.[2]

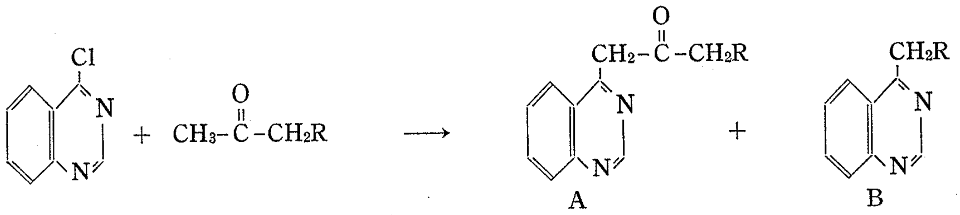

Chart 1

It seemed to be expected that similar reaction might be proceeded by applying this reaction to I. In fact, reaction of I with acetophenone, acetone, respectively afforded 2-(4-pyrido[2,3-*d*]pyrimidinyl)acetophenone (III) and 1-(4-pyrido[2,3-*d*]pyrimidinyl)-2-propanone (IV). Reaction of I with propiophenone and 3-pentanone gave 4-ethylpyrido[2,3-*d*]pyrimidine (V) and with 2-pentanone afforded 4-propylpyrido[2,3-*d*]pyrimidine (VI) and 1-(4-pyrido[2,3-*d*]-

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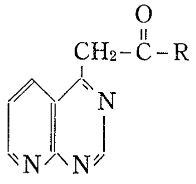
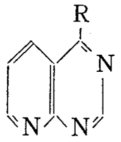
[1] Location: *160, Oshika, Shizuoka-shi.*

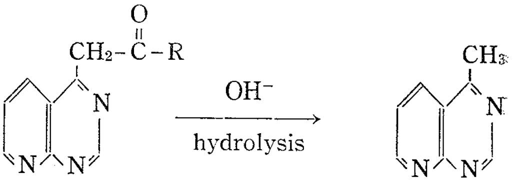
[2] T. Higashino, Y. Tamura, K. Nakayama, and E. Hayashi, *Chem. Pharm, Bull.* (Tokyo), **18**, 1262 (1970).

pyrimidinyl)-2-pentanone (VII). It might be supposed the formation of V and 1-(4-pyrido-[2,3-*d*]pyrimidinyl)-2-butanone (VIII) from the reaction of I with 2-butanone but it resulted only formation of V and we could not isolated VIII. The results were shown in Table I.

Table I. Reaction of I with Ketone Carbanions

Ketones	Reaction products	
	 R:	 R:
$CH_3CO-C_6H_5$	$-C_6H_5$ (III)	
CH_3COCH_3	$-CH_3$ (IV)	
$C_2H_5CO-C_6H_5$		$-C_2H_5$ (V)
$C_2H_5COC_2H_5$		$-C_2H_5$ (V)
$CH_3COC_3H_7$	$-C_3H_7$ (VII)	$-C_3H_7$ (VI)
$CH_3COC_2H_5$		$-C_2H_5$ (V)

The structure of III, IV and VII should be respectively postulated to be 2-(4-pyrido[2,3-*d*]-pyrimidinyl)acetophenone, 1-(4-pyrido[2,3-*d*]pyrimidinyl)-2-propanone and 1-(4-pyrido[2,3-*d*]-pyrimidinyl)-2-pentanone through the following facts; correspondence of their elemental analytical values to $C_{15}H_{11}ON_3$, $C_{10}H_9ON_3$ and $C_{12}H_{13}ON_3$, respectively, and the formation of 4-methyl-pyrido[2,3-*d*]pyrimidine (IX) from their hydrolysis with sodium hydroxide solution.



III: R=$-C_6H_5$
IV: R=$-CH_3$
VII: R=$-C_3H_7$

IX

Chart 2

Identity of V and IX was established to be 4-ethyl- and 4-methyl-pyrido[2,3-*d*]pyrimidine through the following data. i) Their elemental analytical values corresponded to $C_9H_9N_3$ and $C_8H_7N_3$, respectively. ii) Their absorption peaks approximated to those of pyrido[2,3-*d*]-pyrimidine (X) in their ultraviolet (UV) spectra as shown in Table II. iii) The presence of marked absorption bands were recognized due to the 4-ethyl, 4-methyl group respectively, and to the protone of the 2-position in pyrido[2,3-*d*]pyrimidine molecule in thier nuclear magnetic resonance (NMR) spectra. Moreover, they gave a splitting of AMX pattern due to the three protons at the position of 5, 6 and 7 as shown in Table III.

VI corresponding the elemental analytical values to $C_{10}H_{11}N_3$ showed the absorption peaks approximated to those of 4-alkylpyrido[2,3-*d*]pyrimidine as shown in Table II. So VI should be postulated to be 4-propylpyrido[2,3-*d*]pyrimidine.

Table II. UV Spectra of 4-Alkylpyrido[2,3-*d*]pyrimidine

Compounds	UV λ_{max}^{EtOH} mμ (log ε)					
V	246 (3.59)	254 (3.58)	264 (3.48)	288 (3.68)[a]	294 (3.77)	305 (3.78)
VI	248 (3.54)	256 (3.54)	264 (3.45)	289 (3.59)[a]	296 (3.70)	307 (3.69)
IX	248 (3.57)	257 (3.56)	266 (3.47)	290 (3.64)[a]	296 (3.74)	307 (3.73)
X	246 (3.54)	254 (3.53)	264 (3.44)	290 (3.68)[a]	293 (3.73)	304 (3.73)

[a] shoulder

Table III. NMR Spectra of 4-Alkylpyrido[2,3-*d*]pyrimidine

Compounds	NMR (τ) in $CDCl_3$							Coupling constant (cps)		
	2-H	4-H	5-H	6-H	7-H	$4-CH_3$	$4-C_2H_5$	J_{5-6}	J_{5-7}	J_{6-7}
V	0.62^s		1.48^q	2.40^q	0.77^q		8.55^t 6.66^q	8.4	1.9	4.2
IX	0.60^s		1.48^q	2.35^q	0.72^q	6.98^s		8.6	1.9	4.4
X[3]	0.43^s	0.43^s	1.56^q	2.28^q	0.67^q			8.3	1.9	4.2

s: singlet, t: triplet, q: quartet

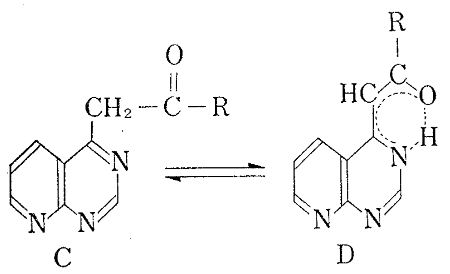


Chart 3

III, IV and VII will exist to be one form or the other of two tautomeric isomers, C and D as shown in Chart 3.

These compounds showed low frequency shift of the carbonyl absorption in their infrared (IR) spectra as shown in Table IV, longer wave length shift in contrast with 4-alkylpyrido[2,3-*d*]pyrimidine in their UV spectra as shown in Table V, and the presence of broading band due to strong desielding of internal hydrogen bonding at range -4.5—-7.0 τ which was equivalent just to one proton and of one olefinic proton as sharp singlet at range 3.0—4.0 τ in their NMR spectra.

From these spectrophotometric data it was well concluded that these compounds should be existed as enol form (D) constituting a conjugate chelation system due to the same reason as described in previous paper.[2]

Table IV. IR Spectra of III, IV and VII

Compounds	IR ν_{max}^{KBr} cm^{-1} (C=O)
III	1608
IV	1623
VII	1624

Table V. UV Spectra of III, IV and VII

Compounds	UV λ_{max}^{EtOH} mμ (log ε)					
III	237(3.90)[a]		288(3.94)		402(4.54)	423(4.46)
IV		269(3.98)	277(4.08)	386(4.38)	404(4.23)	
VII		270(3.97)	277(4.07)	387(4.34)	403(4.20)	

a) shoulder

Reaction of X with Nucleophilic Reagent

The preparation of the starting X was made by the modified method. 4(3*H*)-Pyrido-[2,3-*d*]pyrimidinone (XI) was derived to the chloro compound (I), which was purified by passing through alumina column, and submitted to catalytic reduction in neutral medium, at ordinary temperature, using a catalyst of palladium on magnesium oxide carrier, affording X in 37.9% yield. X here-by formed was identified by its synthesis by ring closure of 2-formamidonicotinaldehyde (XII) in saturated methanolic ammonia.[4]

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3) W.L.F. Armarego and T.J. Batherham, *J. Chem. Soc.*, (*B*), **1966**, **750.**

4) W.L.F. Armarego, *J. Chem. Soc.*, **1962**, 4094.

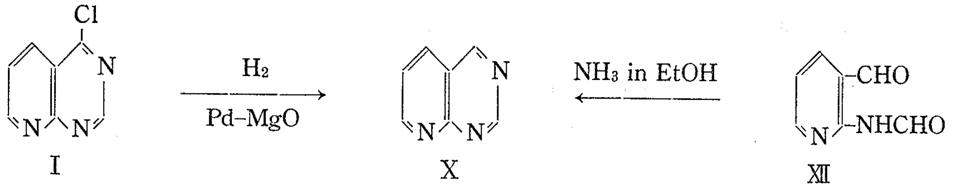

Chart 4

Quinazoline (XIII) has been shown to add several nucleophilic reagents across the 3,4-position of pyrimidine ring.$^{5)}$ This reactivity has been explained due to overlapping of -M and -E effect of nitrogen atoms of the ring and the effect of the fused benzene ring. Following are representative reactions by which addition is occured across the 3,4-position by application of nucleophilic reagent to XIII as shown in Chart 5.

(a) Reaction with Grignard reagent.$^{5)}$
(b) Reaction with the carbanion of acetophenone.$^{5)}$
(c) Reaction with hydrogen cyanide.$^{5)}$

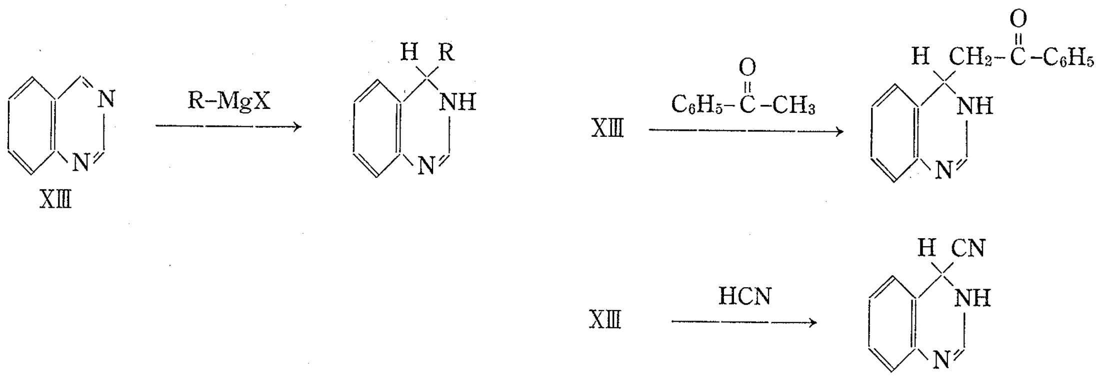

Chart 5

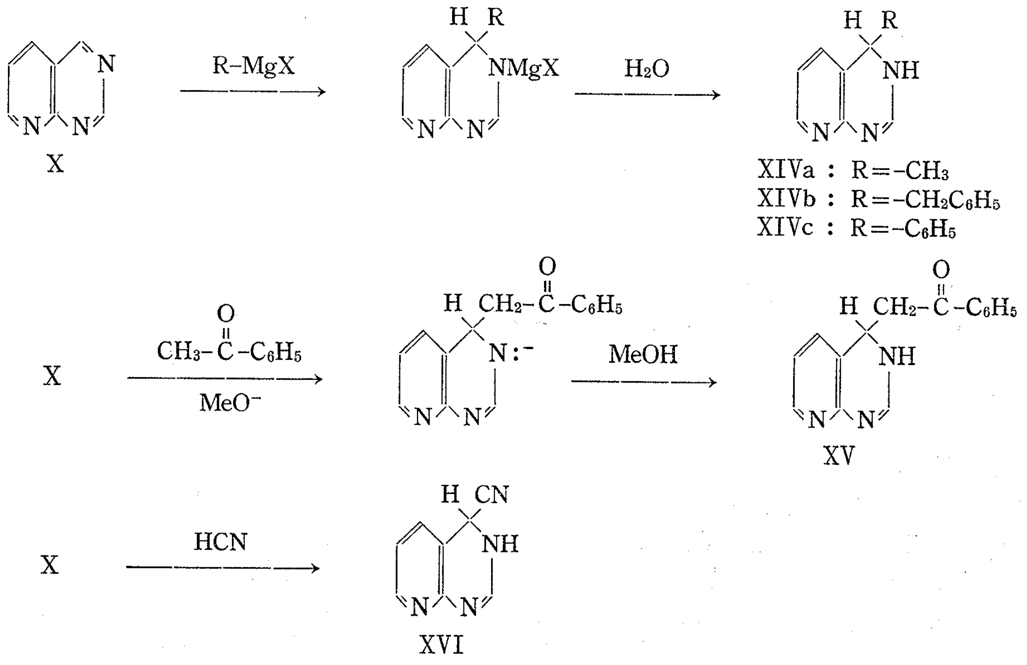

Chart 6

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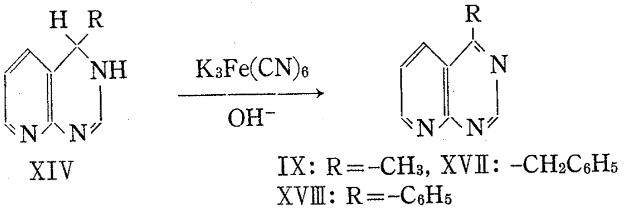
5) T. Higashino, *Yakugaku Zasshi*, **80**, 245 (1960); E. Hayashi and T. Higashino, *Chem. Pharm. Bulll.* (Tokyo), **12**, 1111 (1964).

As a similar effect should be expected on the 3,4-position of X, these investigation have now been extended to X.

Application of these reaction to X resulted in the formation of the desired addition product across the 3,4-position, the reaction with a, b and c producing 4-alkyl (or phenyl)-3,4-dihydropyrido[2,3-*d*]pyrimidine (XIV), 2-(3,4-dihydro-4-pyrido[2,3-*d*]pyrimidinyl)acetophenone (XV) and 3,4-dihydro-4-pyrido[2,3-*d*]pyrimidinecarbonitrile (XVI), respectively.

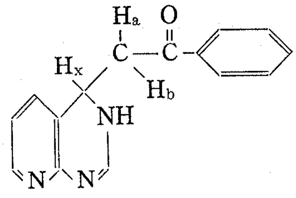
The structure of XIVa, XIVb and XIVc was respectively determined to be 4-methyl-, 4-benzyl- and 4-phenyl-3,4-dihydropyrido[2,3-*d*]pyrimidine through the following reaction. The oxidation of XIVa, XIVb and XIVc with potassium ferricyanide in alkali medium gave IX, 4-benzyl- (XVII) and 4-phenyl-pyrido[2,3-*d*]pyrimidine (XVIII), respectively.



XIV

IX: R=$-CH_3$, XVII: $-CH_2C_6H_5$
XVIII: R=$-C_6H_5$

Chart 7



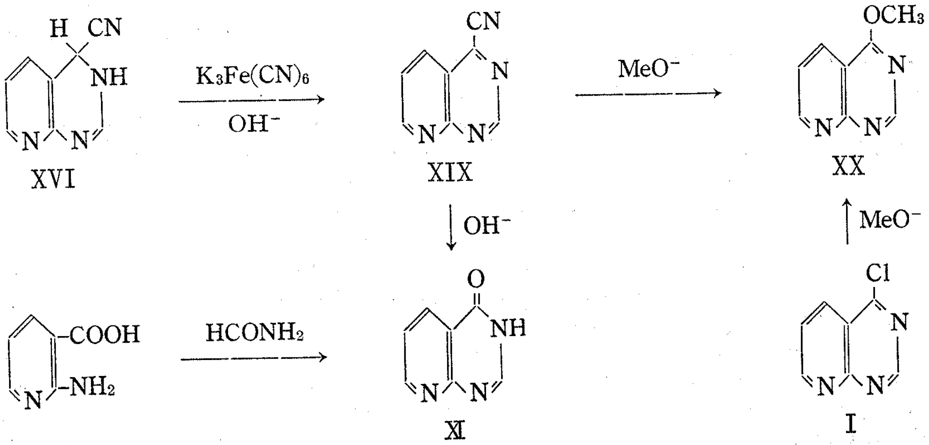
XV

Chart 8

XV showed a *m/e* 251 peak which just corresponded to that of its molecular ion (M^+) in its mass spectrum and a marked absorption band at 1650 cm^{-1} for carbonyl group in its IR spectrum. In UV spectrum the two absorption peaks were located at 244 and 304 mμ. The former approximated to that of acetophenone (242 mμ)[6] and the latter did to that of XIVc (305 mμ). Bands of Ha and Hb shown in Chart 8 constituted the eight expected peaks in AB portion of ABX pattern. The two methylene protons were coupled with each other (τ: 6.70, Ha, τ: 6.44, Hb, J_{a-b}=21.0 cps) in its NMR spectrum.[7] The nonequivalence of the two methylen protons might be due to the presence of three different substituents on the neighbouring assymetric ring carbon atom or to restricted rotation. (τ: 4.57 (1H, triplet, J_{a-x} $=J_{b-x}$=7.0 cps, Hx)).

These data should indicate XV to be 2-(3,4-dihydro-4-pyrido[2,3-*d*]pyrimidinyl)acetophenone.

It was very unstable and failed to purify it in various way so that XVI was submitted to an oxidation with potassium ferricyanide in alkali medium to result in formation of 4-pyrido-



XVI XIX XX XI I

Chart 9

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[6] J. Tanaka, S. Nagakura, and M. Kobayashi, *J. Chem. Phys.*, **24**, 311 (1956).

[7] $CDCl_3$ was used as solvent.

[2,3-*d*]pyrimidinecarbonitrile (XIX). XIX showed a *m/e* 156 peak which just corresponded to its molecular ion (M^+) in its mass spectrum was derived to 4-methoxypyrido[2,3-*d*]pyrimidine (XX) and XI, respectively, from the reaction with methoxide and hydroxide ion. XX and XI⁸⁾ was identified its structure on admixture with the corresponding specimen prepared from another rout.

It may be concluded through the foregoing experimental results that the 4-position of X is active to nucleophilic reagents and the addition is occured across the 3,4-position as similar as that of quinazoline already reported.⁵⁾

Experimental⁹⁾

UV spectra were measured in 99.5% EtOH on a Hitachi Spectrophotometer Model ESP-2U.

IR spectra were recorded with a Hitachi Spectrophotometer Model EPI-G2.

NMR spectra were measure at 60 Mc and 23° on a Japan Electron Optics Lab. Spectrophotometer Model JNM-C-60H. Tetramethylsilane was used as internal standard.

Mass spectra were recorded on a Hitachi RMS-4 single focusing mass spectrometer. The ionisation energy normally used was 80 eV. Samples were vaporised in an all glass inlet system for the compounds having melting point below 150° and direct inlet system for that above 150°.

Reaction of I with Acetophenone——To a mixture of 5 ml of acetophenone and 0.50 g of $NaNH_2$, a solution of 10 ml of acetophenone and 0.50 g of I was gradually added at ordinary temperature with vigorous stirring. After stirring was continued for 2 hr, the reaction mixture was poured onto an excess of ice-H_2O mixture and extracted with $CHCl_3$. The $CHCl_3$ solution was extracted with 2N HCl to separate out the HCl salt. The HCl salt was collected by suction and neutralized with conc. ammonia water to separate the free base which was dissolved in $CHCl_3$. After drying over anhyd. Na_2SO_4 the $CHCl_3$ solution was passed through a column of alumina to remove impurities. The crystallization from EtOH-$CHCl_3$ mixture gave yellow needles in 45.3% yield (0.34 g), mp 248°. *Anal.* Calcd. for $C_{15}H_{11}ON_3$ (2-(4-pyrido[2,3-*d*]pyrimidinyl)acetophenone): C, 72.27; H, 4.45; N, 16.86. Found: C, 72.28; H, 4.46; N, 16.57. NMR (in $CDCl_3$) τ: 3.22 (1H, singlet, olefinic H), 1.5—2.8 (9H, multiplet, aromatic H), −7.0 (1H, broading, hydrogen bonding H).

Reaction of I with Acetone——To a mixture of 0.50 g of $NaNH_2$ and 5 ml of acetone, a solution of 0.50 g of I and 10 ml of acetone was gradually added with vigorous stirring. Then exothermic reaction took place. After stirring for 1.5 hr the reaction mixture was poured onto an excess of ice-H_2O mixture, neutralized with dil.AcOH and extracted with $CHCl_3$. The $CHCl_3$ solution was extracted with 2N HCl. The HCl layer was neutralized with conc. ammonia water and extracted with $CHCl_3$. The crude solid obtained from the extracte was purified by passing through a column of alumina by use of benzene. The crystallization from EtOH gave yellow needles in 21.0% yield (0.12 g), mp 216°. *Anal.* Calcd. for $C_{10}H_9ON_3$ (1-(4-pyrido-[2,3-*d*]pyrimidinyl)-2-propanone): C, 64.16; H, 4.85; N, 22.45. Found: C, 64.12; H, 4.79; N, 22.26. NMR (in $CDCl_3$) τ: 7.76 (3H, singlet, $-CH_3$), 3.99 (1H, singlet, olefinic H), 1.6—2.9 (7H, multiplet, aromatic H), −4.5 (1H, broading, hydrogen bonding H).

Reaction of I with Propiophenone——A mixture of 0.50 g of I, 0.50 g of $NaNH_2$ and 10 ml of propiophenone was allowed to stand for 3 hr at ordinary temperature with stirring. The exothermic reaction took place. The reaction mixture was poured onto an excess of ice-H_2O mixture, neutralized with AcOH and extracted with $CHCl_3$. The $CHCl_3$ layer was then extracted with 2N HCl. The HCl layer was neutralized with conc. ammonia water and extracted with $CHCl_3$. The crude solid from the extracte was dissolved in benzene and passed through a column of alumina. The first fraction was necessary. Recrystallization from petr.ether gave pale yellow needles in 10.4% yield (0.05 g), mp 100°. *Anal.* Calcd. for $C_9H_9N_3$ (4-ethylpyrido[2,3-*d*]pyrimidine): C, 67.90; H, 5.70; N, 26.40. Found: C, 68.90; H, 5.84; N, 26.32.

Reaction of I with 3-Pentanone——A mixture of 0.50 g of I, 0.50 g of $NaNH_2$ and 10 ml of 3-pentanone was stirred at ordinary temperature for 3.5 hr. The exothermic reaction took place. V was obtained in 33.3% yield (0.16 g) according as similar treatment as the reaction of I with propiophenone.

Reaction of I with 2-Butanone——A mixture of 0.50 g of I, 0.50 g of $NaNH_2$ and 3 ml of 2-butanone in 10 ml of benzene was stirred for 1 hr at ordinary temperature. V was obtained in 52.0% yield (0.25 g) according as similar treatment as the reaction of I with propiophenone.

Reaction of I with 2-Pentanone——A mixture of 0.50 g of I, 0.50 g of $NaNH_2$ and 3 ml of 2-pentanone in 10 ml of benzene was stirred for 1.5 hr at ordinary temperature. The reaction mixture was poured onto an excess of ice-H_2O mixture, neutralized with AcOH and extracted with $CHCl_3$. The $CHCl_3$ layer was then extracted with 2N HCl and the HCl layer was neutralized with conc. ammonia water and extracted with $CHCl_3$. After drying over anhyd. Na_2SO_4 the extracte was passed through a column of alumina. From

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8) R.K. Robins and G.H. Hitchings, *J. Am. Chem. Soc.*, 77, 2256 (1955).

9) All melting points were not corrected.

the first fraction low melting substance was obtained in 19.2% yield (0.10 g). *Anal.* Calcd. for $C_{10}H_{11}N_3$ (4-propylpyrido[2,3-*d*]pyrimidine): C, 69.34; H, 6.40; N, 24.26. Found: C, 69.14; H, 6.23; N, 24.13.

From the second fraction VII was obtained as yellow needles in poor yield (trace), mp 232° (from benzene). *Anal.* Calcd. for $C_{12}H_{13}ON_3$ (1-(4-pyrido[2,3-*d*]pyrimidinyl)-2-pentanone): C, 66.95; H, 6.09; N, 19.25. Found: C, 66.94; H, 6.11; N, 19.03.

Hydrolysis of III, IV and VII——A mixture of 0.10 g of III and a solution of 0.50 g of NaOH dissolved in 5 ml of H_2O was refluxed for 40 min. After cooling the reaction mixture was extracted with $CHCl_3$. Neutralization of the H_2O layer with conc. HCl gave white plate in 60.0% yield (0.03 g) which was undepressed on admixture with benzoic acid, mp 122°.

After drying over anhyd.Na_2SO_4 the extracte was passed through a column of alumina to remove impurities. Recrystallization from benzene–petr.ether mixture gave slightly pale yellow plate in 33.3% yield (0.02 g), mp 139°. *Anal.* Clacd. for $C_8H_7N_3$ (4-methylpyrido[2,3-*d*]pyrimidine): C, 66.19; H, 4.86; N, 28.95. Found: C, 65.87; H, 4.51; N, 29.11.

Hydrolysis of IV and VII by the same method as above afforded IX in 30—40% yield.

4-Chloropyrido[2,3-*d*]pyrimidine (I)——This compound was prepared essentially according to the directions of R.K. Robins and G.H. Hitchings.[8])

To a 35 ml of $POCl_3$ was added 2.0 g of XI[8]) and the solution was refluxed for 1 hr (There remained a small amount of tarry material which did not dissolve with longer refluxing). The excess of $POCl_3$ was removed under reduced pressure and the sirupy residue was poured onto an excess of ice. The reaction mixture was then extracted with $CHCl_3$ and washed with H_2O. After drying over anhyd.Na_2SO_4 the extracte was passed through a column of alumina to remove impurities. Evaporation of $CHCl_3$ gave I as white crystals in 48.9% yield (1.1 g), mp 134° (decomp.). A small amount was recrystallized from benzene–petr. ether mixture to rise melting point to 137° (decomp.).

Reduction of I: A Pd catalyst prepared from 10 ml of 1% $PdCl_2$ solution and 1.0 g of MgO was added to a solution of 1.0 g of I dissolved in a mixture of 40 ml of benzene and 15 ml of H_2O and the mixture was shaken in H_2 stream. After rapid absorption of 130 ml of H_2, the catalyst was filtered off, the filtrate was evaporated to dryness under reduced pressure and the residue was dissolved in 15 ml of H_2O. The H_2O solution was neutralized with 10% NaOH and separated $Mg(OH)_2$ was filtered off and the filtrate which was salted out with anhyd. K_2CO_3 to separate X was extracted with $CHCl_3$. The $CHCl_3$ solution was passed through a column of alumina to remove impurities. Recrystallization from benzene gave colourless needles in 37.9% yield (0.3 g), mp 107—108°. This compound was undepressed on admixture with pyrido[2,3-*d*]pyrimidine (X), mp 107—108° prepared from another route.[4])

Reaction of X with Methylmagnesium Iodide——Methylmagnesium iodide was prepared by the usual method from 0.40 g of MeI and 0.10 g of Mg in 10 ml of anhyd.ether. This solution was gradually added to a warm solution of 0.30 g of X dissolved in 40 ml of benzene and 10 ml of anhyd. ether mixture. After the reaction mixture was refluxed for 2 hr, 15 ml of 2N HCl was added and the solution was neutralized, saturated with anhyd.K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ solution was dried over anhyd.K_2CO_3. Evaporation of $CHCl_3$ gave XIVa as yellow oil in 77.4% yield (0.26 g).

Reaction of X with Benzylmagnesium Chloride——Reaction of 0.30 g of X with benzylmagnesium chloride (prepared from 0.40 g of benzyl chloride and 0.10 g of Mg in 10 ml of anhyd. ether) in a solution of 20 ml of benzene and 10 ml of anhyd. ether by the same method as described in the reaction of X with methylmagnesium iodide afforded XIVb as viscous oil in 78.4% yield (0.40 g).

Reaction of X with Phenyl Magnesium Bromide——Reaction of 0.30 g of X with phenylmagnesium bromide (prepared from 0.40 g of bromobenzene and 0.10 g of Mg in 10 ml of anhyd.ether) in a solution of 40 ml of benzene and 10 ml of anhyd. ether by the same method as described in the reaction of X with methylmagnesium iodide afforded XIVc as colourless prisms in 83.5% yield (0.40 g), mp 195° from benzene–MeOH mixture. *Anal.* Calcd. for $C_{13}H_{11}N_3$ (4-phenyl-3,4-dihydropyrido[2,3-*d*]pyrimidine): C, 74.62; H, 5.30; N, 20.08. Found: C, 75.00; H, 5.17; N, 20.25. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3182 (NH). UV $\lambda_{\max}^{\text{EtOH}}$ mμ (log ε): 225 (3.96 shoulder), 305 (3.90). Mass Spectrum *m/e*: 209 (M^+).

Oxidation of XIVa——A solution of 1.8 g of $K_3Fe(CN)_6$ dissolved in 6 ml of H_2O was gradually added to a mixture of a solution of 0.30 g of XIVa dissolved in 20 ml of benzene and 1 ml of 33% KOH with shaking at ordinary temperature. Exothermic reaction took place. After shaking the reaction mixture 1.5 hr separated the benzene solution was dried over anhyd. Na_2SO_4. Benzene was evaporated from the extracte to dryness and the residue which dissolved a solution benzene and $CHCl_3$ (1:1) was passed through a column of alumina to remove impurities. Recrystallization from benzene–petr.ether mixture gave IX in 13.5% yield (0.04 g), mp 139°.

Oxidation of XIVb——Reaction used 0.40 g of XIVb dissolved in 20 ml of benzene, 1 ml of 33% KOH and a solution of 1.8 g of $K_3Fe(CN)_6$ dissolved in 6 ml of H_2O by the same method as described in the oxidation of XIVa afforded XVII as colourless liquid in 25.2% yield(0.10 g). Recrystallization of its picrate from MeOH gave yellow needles, mp 169°. *Anal.* Calcd. for $C_{20}H_{14}O_7N_6$ (4-benzylpyrido[2,3-*d*]pyrimidine picrate): C, 53.34; H, 3.13; N, 18.66. Found: C, 52.99; H, 3.51; N, 18.42.

Oxidation of XIVc——Reaction used 0.20 g of XIVc in 20 ml of benzene, 2 ml of 15% KOH and a solution of $K_3Fe(CN)_6$ in 6 ml of H_2O by the same method as described in the oxidation of XIVa afforded XVIII as white needles in 75.7% yield (0.15 g), mp 128—129° from benzene–petr.ether mixture. *Anal.* Calcd. for $C_{13}H_9N_3$ (4-phenylpyrido[2,3-*d*]pyrimidine): C, 75.34; H, 4.38; N, 20.28. Found: C, 75.33; H, 4.28; N, 20.12. UV λ_{max}^{EtOH} mμ (log ε): 225 (4.20 shoulder), 282 (3.87), 312 (4.02). Mass Spectrum *m/e*: 207 (M^+). NMR (in $CDCl_3$) τ: 1.8—2.4 (6H, multiplet, aromatic H), 1.23 (1H, quartet, $J_{5-6}=9.0$ cps, $J_{5-7}=2.2$ cps, H-5), 0.18 (1H, singlet, H-2).

Reaction of X with Acetophenone——A solution of 0.30 g of X, 0.30 g of acetophenone and 6 ml of sodium methoxide solution (0.10 g of Na dissolved in 6 ml of MeOH) was allowed to stand over night at ordinary temperature. The reaction mixture was neutralized with dil.AcOH and MeOH was removed under reduced pressure. The residue was recrystallized from benzene to give orange needles in 34.8% yield (0.20 g), mp 146—147°. *Anal.* Calcd. for $C_{15}H_{13}ON_3$ (2-(3,4-dihydro-4-pyrido[2,3-*d*]pyrimidinyl)acetophenone): C, 71.69; H, 5.21; N, 16.72. Found: C, 71.86; H, 5.19; N, 17.07. UV λ_{max}^{EtOH} mμ (log ε): 244 (4.17), 304 (3.88).

Reaction of X with HCN——A solution of 0.50 g of X and 1 ml of HCN dissolved in 3 ml of H_2O was allowed to stand over night under cooling with ice. Separated crystals were collected by suction and washed with H_2O. The crude XVI wsa obtained in 66.3% yield (0.41 g).

Oxidation of XVI——A solution of 1.8 g of $K_3Fe(CN)_6$ dissolved in 6 ml of H_2O was gradually added to a mixture of 0.40 g of XVI, 2 ml of 50% K_2CO_3 and 20 ml of $CHCl_3$ with shaking at ordinary temperature. After shaking the reaction mixture for 1.5 hr separated the $CHCl_3$ solution was dried over anhyd. Na_2SO_4. Removing $CHCl_3$ gave slightly yellow needles in 38.0% yield (0.15 g), mp 119—120° from benzene–petr. ether mixture. *Anal.* Calcd. for $C_8H_4N_4$ (4-pyrido[2,3-*d*]pyrimidinecarbonitrile): C, 61.53; H, 2.58; N, 35.88. Found: C, 61.64; H, 2.65; N, 35.49. UV λ_{max}^{EtOH} mμ (log ε): 247 (3.54), 255 (3.56), 264 (3.55), 299 (3.73 shoulder), 307 (3.80), 320 (3.68). Mass Spectrum *m/e*: 156 (M^+).

Reaction of XIX with Methoxide Ion——A solution of 0.30 g of XIX and sodium methoxide solution (0.05 g of Na dissolved in 2 ml of MeOH) was refluxed for 20 min. MeOH was removed under reduced pressure and H_2O was added to the residue. The H_2O solution was saturated with anhyd. K_2CO_3 and extracted with $CHCl_3$. After drying over anhyd. Na_2SO_4 the extracte was passed through a column of alumina to remove impurities. Recrystallization from petr. ether gave colourless needles in 61.5% yield (0.19 g), mp 119—120°. *Anal.* Calcd. for $C_8H_7ON_3$ (4-methoxypyrido[2,3-*d*]pyrimidine): C, 59.62; H, 4.38; N, 26.07. Found: C, 59.85; H, 4.42; N, 25.70. UV λ_{max}^{EtOH} mμ (log ε): 217 (4.34), 256 (3.66), 266 (3.59 shoulder), 288 (3.69 shoulder), 298 (3.76), 308 (3.62 shoulder). NMR (in $CDCl_3$) τ: 5.76 (3H, singlet, OCH_3), 2.45 (1H, quartet, $J_{5-6}=8.3$ cps, $J_{6-7}=4.3$ cps, H-6), 1.44 (1H, quartet, $J_{5-7}=2.0$ cps, H-5), 0.96 (1H, singlet, H-2), 0.79 (1H, quartet, H-7).

Reaction of I with Methoxide Ion——A solution of 0.30 g of I and sodium methoxide solution (0.05 g of Na dissolved in 2 ml of MeOH) was refluxed for 20 min. MeOH was removed under reduced pressure and H_2O was added to the residue. The H_2O solution was saturated with anhyd. K_2CO_3 and extracted with $CHCl_3$. After drying over anhyd.Na_2SO_4 the extract was passed through a column of alumina to remove impurities. Recrystallization from petr. ether gave colourless needles in 61.6% yield (0.18 g), mp 119—120°. *Anal.* Calcd. for $C_8H_7ON_3$ (4-methoxypyrido[2,3-*d*]pyrimidine): C, 59.62; H, 4.38; N, 26.07. Found: C, 59.54; H, 4.45; N, 25.79.

Reaction of XIX with Hydroxide Ion——A mixture of 0.10 g of XIX and 1 ml of 10% NaOH solution was allowed to stand over night at ordinary temperature with stirring. The reaction mixture was neutralized with AcOH to separate XI which was collected by suction. Recrystallization from H_2O gave colourless plate, mp 258°, in 31.9% yield (0.03 g).

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