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Studies on the Pyridazine Derivatives. XIV.[1] Synthesis and Reaction of Pyrimido[4,5-*c*]pyridazines[2]

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New pyrimido[4,5-*c*]pyridazines were synthesized by cyclization of 3-amino-4-carbamoylpyridazines(IV,VII) and 3-chloro-4-ethoxycarbonylpyridazine(II). When 3-chloro-5-hydroxypyrimido[4,5-*c*]pyridazine(XVI) was treated with phosphorous oxychloride and N,N-dimethylaniline, 1,4-dihydro-3,5-dichloro-4-(4′-N,N-dimethylaminophenyl)pyrimido-[4,5-*c*]pyridazine(XX) was obtained, the structure was established by nuclear magnetic resonance spectra of dechlorination and hydrolysis products. Amination of XX afforded 3-chloro-5-amino compounds.

Investigation on the pyrimido[4,5-*c*]pyridazine ring system has been limited to the synthesis of a few compounds. Jones[4] reported the synthesis of this ring system by Hofmann rearrangement of 3,4-dicarbamoylpyridazines at first time. More recently, Nakagome and Castle[5] developed this method. In this paper is reported an extension of the synthetic chemistry of pyrimido[4,5-*c*]pyridazines utilizing 3-amino-4-carbamoylpyridazines(IV,VII) as the starting materials.

Chlorination of 3-hydroxy-4-ethoxycarbonyl-6-chloropyridazine[6] (I) afforded 3,6-dichloro compound(II) which was converted to 3,6-dichloro-4-carbamoylpyridazine(III) with aqueous ammonia. When compound III was treated with ethanolic ammonia, a mixture of three compounds was obtained, namely 3-amino-4-carbamoyl-6-chloropyridazine(IV) as major product in 56% yield, 3-chloro-4-carbamoyl-6-aminopyridazine(V) and 3-ethoxy-4-carbamoyl-6-chloropyridazine(VI) were isolated by means of alumina column chromatography in 11% and 21% yield, respectively. In order to establish the structure of these compounds, the compounds were dechlorinated with hydrogen over palladium on charcoal, the nuclear magnetic resonance (NMR) spectra showed *ortho* coupling constant in compound VII(J=5 cps) and IX(J=5cps), *meta* coupling in VIII(J=2 cps).

On the other hand, a slightly different result was obtained when methanolic ammonia was used instead of ethanolic ammonia. The structure of XII was established to 3-methoxy-4-carbamoyl-6-chloropyridazine by comparison of ultraviolet spectrum with that of VI. Compound XIII was converted by Hofmann rearrangement to XV which was different from 3-methoxy-4-amino-6-chloropyridazine,[7] so that XIII was 3-chloro-4-carbamoyl-6-methoxypyridazine. Compound XIV was identified with 3-hydroxy-4-carbamoyl-6-chloropyridazine[6] by comparison of infrared spectrum.

Thiocarbamoyl compounds(X,XI) were obtained by reaction of corresponding compound with phosphorous pentasulfide in pyridine solution, respectively.

1) Part XIII: M. Yanai, T. Kinoshita, S. Takeda, M. Mori, H. Sadaki and H. Watanabe, *Chem. Pharm. Bull.* (Tokyo), **18**, 1685 (1970).
2) Part of this paper was presented at Kyushu Branch Meeting of Pharmaceutical Society of Japan, Nagasaki, Sept. 28, 1968.
3) Location: *1-14 Bunkyo-machi, Nagasaki, 852, Japan.*
4) R. G. Jones, *J. Org. Chem.*, **25**, 956 (1960).
5) T. Nakagome and R.N. Castle, *J. Heterocyclic Chem.*, **5**, 523 (1968).
6) T. Kuraishi, *Pharm. Bull.* (Tokyo), **5**, 587 (1957).
7) M. Yanai, T. Kuraishi and T. Kinoshita, *Yakugaku Zasshi*, **81**, 708 (1961).

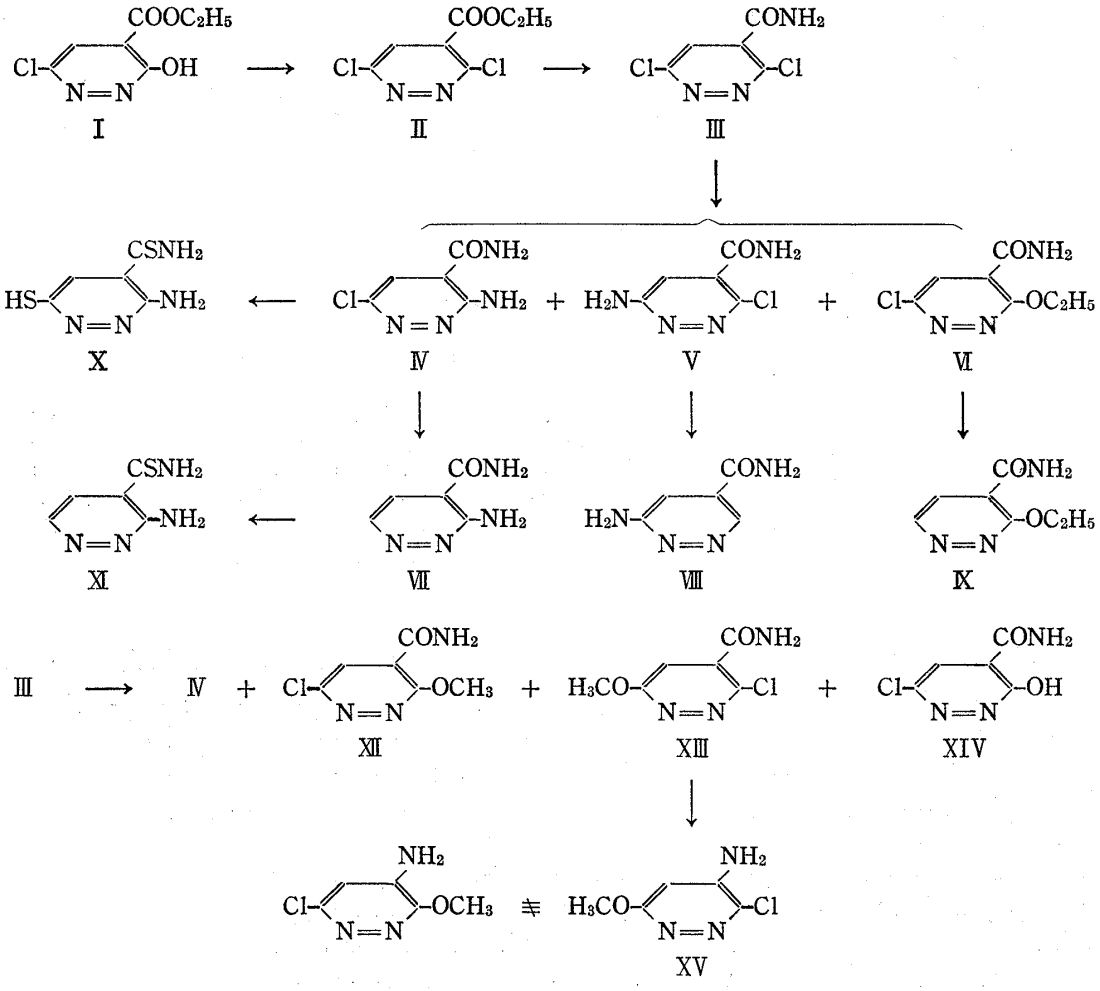

Chart 1

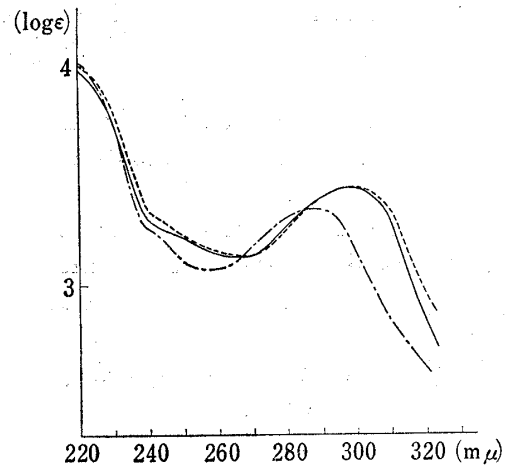

Fig. 1. Ultraviolet Spectra of XII (——), VI (------) and 3-Chloro-4-carbamoyl-6-methoxypyridazine (———), (in 95 % Ethanol)

Reaction of compound IV or VII with ethyl orthoformate afforded corresponding 3-chloro-5-hydroxy-(XVI) or 5-hydroxypyrimido-[4,5-*c*] pyridazine (XVII). 5,7-Dihydroxypyrimido[4,5-*c*]pyridazine(XVIII) was obtained by fusion of VII with urea, this compound have been synthesized *via* other route.[5]

Unfortunately the chlorination of 3-chloro-5-hydroxypyrimido[4,5-*c*]pyridazine(XVII) under a variety of chlorinating conditions was unsuccessful except phosphorous oxychloride and N,N-dimethyl(diethyl)aniline method. When XVI was treated with these reagents, the resultant was not 3,5-dichloropyrimido[4,5-*c*]-pyridazine but XXa(XXb). Compound XXa (XXb) has a melting point 230°(165°) and the elemental analysis was equivalent to $C_{14}H_{15}N_5Cl_2$($C_{16}H_{17}N_5Cl_2$), also high resolution mass spectrum agreed this component (M^+: Calcd. for $C_{14}H_{13}N_5Cl_2$: 321.055. Found: 321.055). The NMR(all signals are given in δ value) spectrum(in $CDCl_3$) shows signals at 9.05(disappear in addition of D_2O), 8.45, 7.07(J=8 cps),

6.63(J=8 cps), 4.81 and 2.90, two doublet of 7.07 and 6.63 split into AB type and coupling constant indicate *ortho* coupling. In order to obtain further information, XXa was dechlorinated over 5% palladium on charcoal to XXIa which corresponded to $C_{14}H_{15}N_5$ by elemental analysis and high resolution mass spectrum(M^+: Calcd. for $C_{14}H_{15}N_5$: 253.134. Found: 253.133). In the NMR spectrum (in DMSO-d_6) new two doublet signals appear at 6.85 (J =3 cps) and 4.69(J=3 cps), these doublets change to singlets by double irradiation to each signal. From this observation and comparison with the NMR spectra of XXa and 1,4-

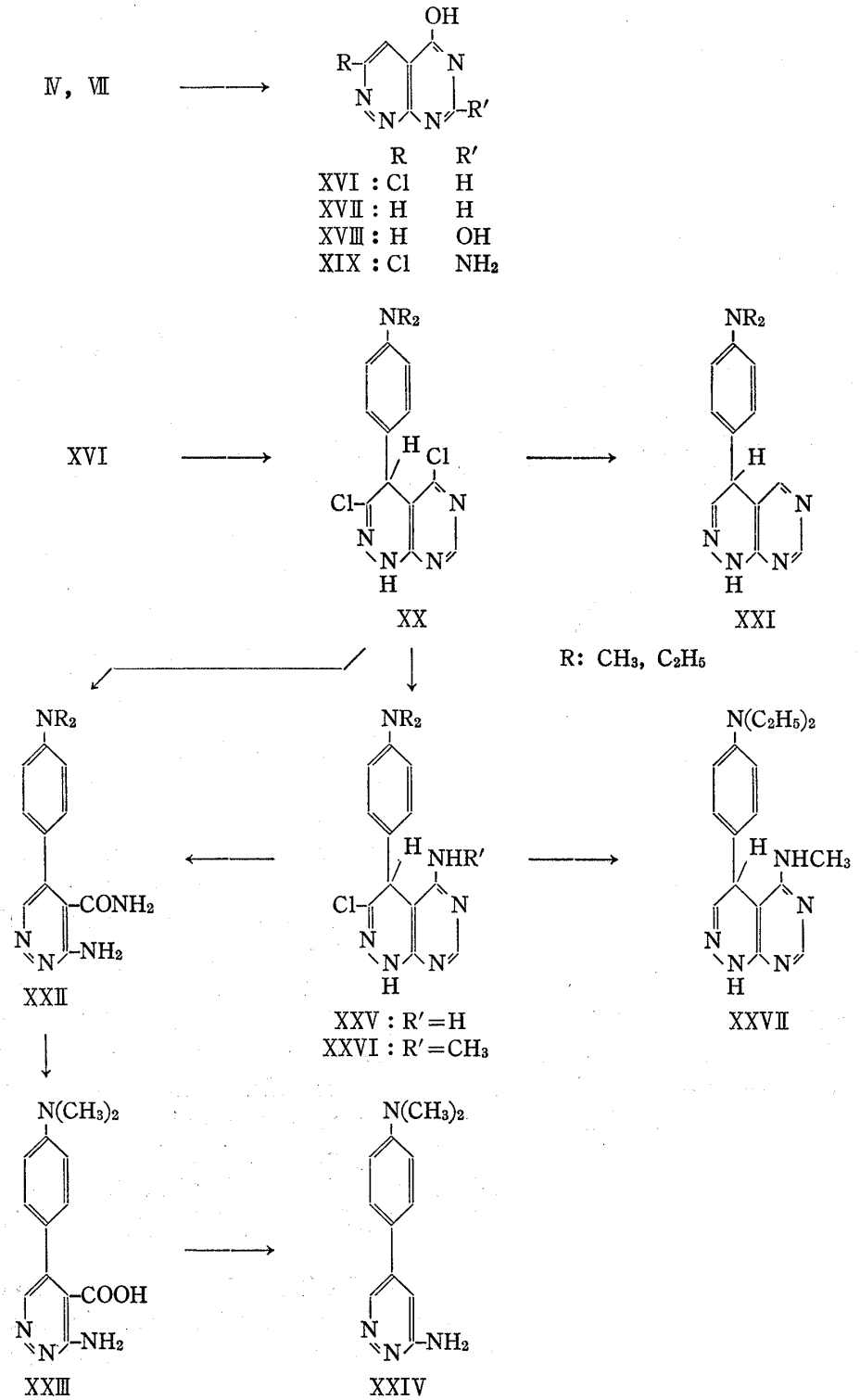

Chart 2

dihydrocinnolines,[8] the signals are assignable to position 3 and 4 hydrogen, respectively. Also other signals are assignable to NH(1H, 10.78, disappear in addition of D_2O), position 5(1H, 8.48), 7(1H, 8.03), phenyl (4H, two doublets 6.98 and 6.68) and N-methyl (6H, 2.86), respectively.

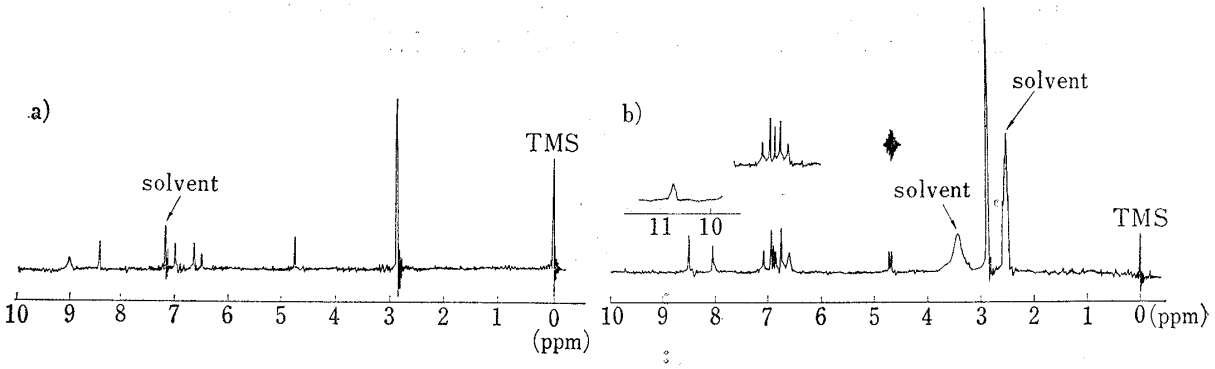

Fig. 2. Nuclear Magnetic Resonance Spectra of XXa(a) and XXIa(b) at 60Mcps

These results presume that compound XXIa is 1,4-dihydro-4-(4'-N,N-dimethylaminophenyl)pyrimido[4,5-*c*]pyridazine, so that XXa should be 1,4-dihydro-3,5-dichloro-4-(4'-N,N-dimethylaminophenyl)pyrimido[4,5-*c*]pyridazine. Also compound XXb is presumed to 1,4-dihydro-3,5-dichloro-4-(4'-N,N-diethylaminophenyl)pyrimido[4,5-*c*]pyridazine by comparison of ultraviolet spectra with that of XXa, by similarity of reaction products.

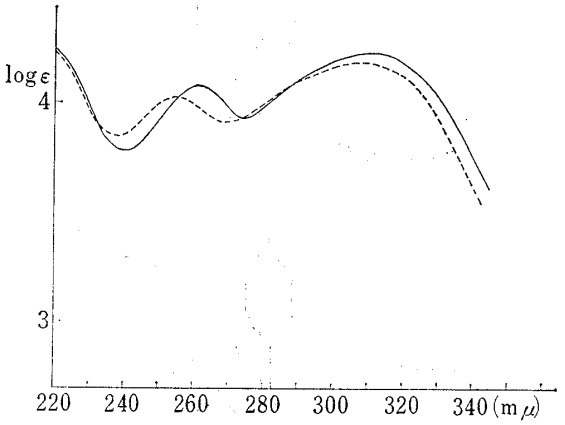

Fig. 3. Ultraviolet Spectra of XXa (——) and XXb (------), (in 95% Ethanol)

Besides this structure is supported by connection with that of compound XXIV. The NMR spectrum (in trifluoroacetic acid) of compound XXIV shows two doublets at 7.98 and 8.81, these coupling constant is 2 cps, respectively, which indicate *meta* coupling, so that XXIV is established in 3-amino-5-(4'-N,N-dimethylaminophenyl)-pyridazine. Compound XXIV was obtained by hydrolysis of XXa, followed by decarboxylation. Namely, compound XXa was hydrolyzed to 3-amino-4-carbamoyl-5-(4'-N,N-dimethylaminophenyl)-pyridazine (XXII) with 20% sodium hydroxide and ethanol, this hydrolysis included aromatization in part of dihydropyridazine ring which meaned 1,3-elimination of hydrogen chloride and migration of hydrogen. Moreover carboxamide (XXIIa) was hydrolyzed with 50% sodium hydroxide and ethanol in a sealed tube to carboxylic acid (XXIII) which was converted to XXIV with only heating over its melting point.

As mention above novel products are obtained by chlorination of XVI with phosphorous oxychloride and N,N-dimethyl(diethyl)aniline. Reaction mechanism is not clear, though this reaction is probably nucleophilic reaction of N,N-dimethyl(diethyl)aniline to 4 position of 3,5-dichloropyrimido[4,5-*c*]pyridazine.

When 3,5-dichloro compounds (XX) were treated with amines, mono amino compounds (XXV, XXVI) were obtained. In order to prove which chlorine is more active than the other, one of the amino cmpound (XXVIb) was dechlorinated to XXVII over 5% palladium on

8) L.S. Besford, G. Allen and J.M. Bruce, *J. Chem. Soc.*, **1963**, 2867.

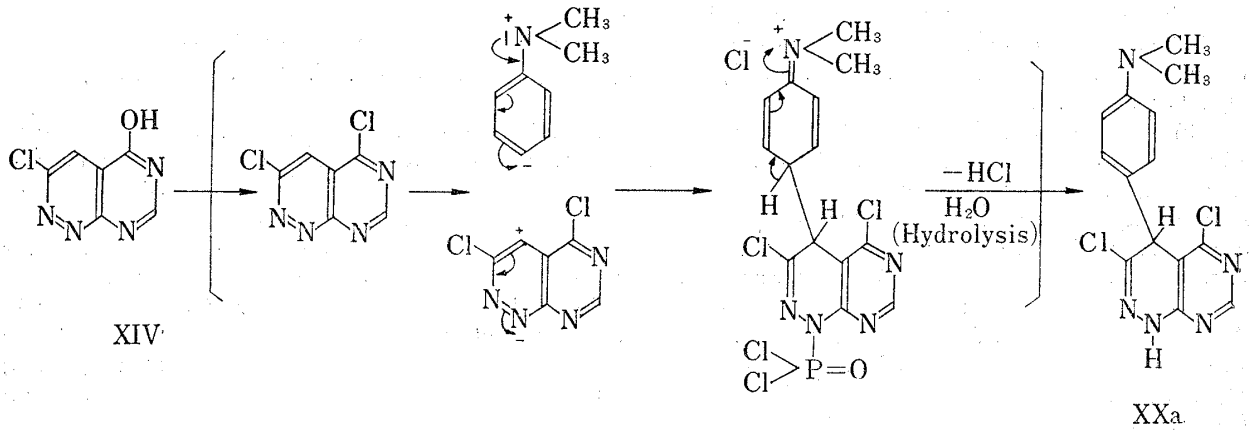

Chart 3

barium sulfate. The NMR spectrum of XXVII is complex as shown in Fig. 4, namely two signals double in two parts. when double resonance technique is employed to 4.2—4.3 region, doublet 2.85(J=6 cps) change to singlet and 6.67 change to different doublet. In addition of deuterium oxide doublet 2.85 change to singlet; and 8.17 and one proton of 4.2—4.3 region disappear, no change at 6.5—6.9. These observation suggested that one proton of 4.2—4.3 region is an NH group of methylamine and other protons couple to one proton of 6.5—6.9 in which two signals double.

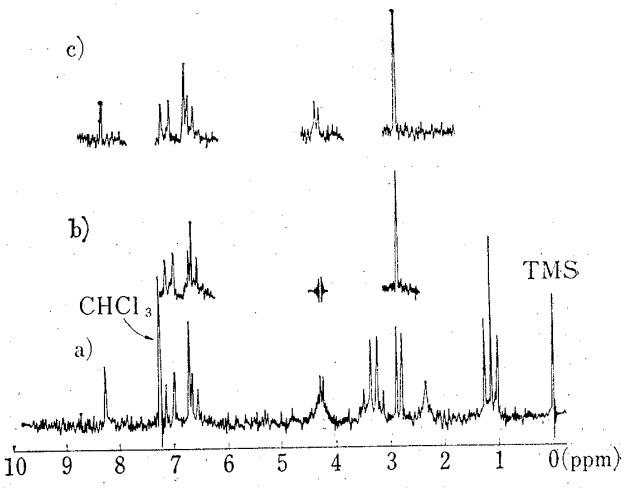

Fig. 4. Nuclear Magnetic Resonance Spectrum of XXVII at 60Mcps (in $CDCl_3$) a): original; b): spin decoupling; c): addition of D_2O

By those suggestion and comparison with NMR spectrum of compound XXI, the structure of XXV and XXVI are established to 1,4-dihydro-3-chloro-4-(4′-N,N-dialkylaminophenyl)-5-aminopyrimido[4,5-*c*]pyridazines. Definite distinctive chlorine atoms in compound XX supported that structure.

Experimental

3,6-Dichloro-4-ethoxycarbonylpyridazine(II)——A mixture of 15 g of I and 100 ml of $POCl_3$ was refluxed for 1.5 hours. After removal of $POCl_3$ *in vacuo*, the residue was poured in crushed ice and alkalized with Na_2CO_3. The mixture was extracted with $CHCl_3$, dried over $MgSO_4$ and evaporated to dryness. The residue was distilled under reduced pressure to give 13.4 g (82%) of colorless liquide, $bp_{1.3}$ 116—118°.

3,6-Dichloro-4-carbamoylpyridazine(III)——A mixture of 13 g of II and 87 ml of 28% aq. ammonia was allowed to stand in a refrigerator overnight and separated crystalline mass was collected by suction. The crude product was recrystallized from EtOH to give 10.5 g of colorless prisms, mp 178—179°. *Anal.* Calcd. for $C_5H_3ON_3Cl_2$: C, 31.25; H, 1.56; N, 21.35. Found: C, 31.13; H, 1.57; N, 21.14.

Ammonolysis of 3,6-Dichloro-4-carbamoylpyridazine(III)——a) In Ethanolic Ammonia: A mixture of 3 g of III and 20 ml of ethanolic ammonia was heated at 100° for 2 hours in a sealed tube. Separated crystalline mass was collected and recrystallized from pyridine to give 1.5 g of pale yellow needles, mp 258—259° (decomp.). *Anal.* Calcd. for $C_5H_5ON_4Cl$(IV): C, 34.78; H, 2.89; N, 32.46. Found: C, 34.44; H, 2.74; N, 32.40. The mother liquor of reaction mixture was evaporated to dryness, the residue was extracted with acetone and poured on an alumina column for chromatography.

The First Fraction: White crystals were obtained and recrystallized from EtOH to give 0.7 g of colorless plates, mp 155—156°. *Anal.* Calcd. for $C_7H_8O_2N_3Cl$(VI): C, 41.69; H, 3.97; N, 20.84. Found: C, 41.42; H, 3.91; N, 20.69.

The Second Fraction: Small amount of IV was obtained.

The Third Fraction: White crystals were obtained and recrystallized from EtOH to give 0.3 g of colorless needles, mp 245—246°. *Anal.* Calcd. for $C_5H_5ON_4Cl$(V): C, 34.78; H, 2.89; N, 32.46. Found: C, 35.15; H, 2.93; N, 32.28.

b) In Methanolic Ammonia: A mixture of 3 g of III and 25 ml of methanolic ammonia was heated at 100° for 2 hours in a sealed tube. The reaction mixture was concentrated and separated crystalline mass was collected by suction. The crude material was recrystallized from pyridine to give 0.6 g of pale yellow needles, mp 258—259°. This compound was identified with IV by comparison of infrared spectrum of an authentic specimen. The mother liquor of reaction mixture was evaporated to dryness, the residue was extracted with acetone. The extract was poured on an alumina column for chromatography.

The First Fraction: White crystalline mass was obtained, mp 120—180°, the mass was dissolved in AcOEt to repeat alumina chromatography. From the first fraction colorless needles were obtained, mp 145—147° (AcOEt). *Anal.* Calcd. for $C_6H_6O_2N_3Cl$ (XII): C, 38.40; H, 3.20; N, 22.40. Found: C, 38.26; H, 2.88; N, 21.85. From the second fraction colorless plates were obtained, mp 210.5—211.5° (decomp.) (AcOEt). *Anal.* Calcd. for $C_6H_6O_2N_3Cl$ (XIII). Found: C, 38.67; H, 3.12; N, 21.91.

The Second Fraction: Colorless needles were obtained, mp 253—254° (MeOH). *Anal.* Calcd. for $C_5H_4O_2N_2Cl$·(XIV): C, 34.63; H, 2.30; N, 24.20. Found: C, 34.66; H, 2.29; N, 24.54.

3-Amino-4-carbamoylpyridazine (VII)——IV (3.45 g) in a mixture of 28% aq. ammonia and 450 ml of MeOH was hydrogenated over 1 g of 5% Pd-C. The catalyst was filtered and washed with hot MeOH. Filtrate and washing were combined, concentrated and separated crystalline mass was recrystallized from MeOH to give 1.95 g (71%) of pale yellow needles, mp 244—245°. *Anal.* Calcd. for $C_5H_6ON_4$: C, 43.47; H, 4.38; N, 40.56. Found: C, 43.20; H, 4.64; N, 40.95. NMR[9] (in DMSO-d_6): δ 8.54 (position 6, doublet, J=5 cps), δ 7.58 (position 5, doublet, J=5 cps).

3-Amino-5-carbamoylpyridazine (VIII)——V (0.3 g) in 30 ml of MeOH was hydrogenated over 0.5 g of 5% Pd-C. The catalyst was filtered, the filtrate was evaporated to dryness *in vacuo* and the residue was recrystallized from water to give 0.18 g (75%) of needles, mp 308—310°. *Anal.* Calcd. for $C_5H_6ON_4$: C, 43.47; H, 4.38; N, 40.56. Found: C, 43.17; H, 4.66; N, 40.09. NMR (in DMSO-d_6): δ 8.72 (position 6, doublet J=2 cps), δ 7.09 (position 4, doublet, J=2 cps).

3-Ethoxy-4-carbamoylpyridazine (IX)——VI (2 g) in a mixture of 60 ml of EtOH and 1 ml of 28% aq. ammonia was hydrogenated over 0.5 g of 10% Pd-C. The catalyst was filtered and the filtrate was evaporated to dryness *in vacuo*. The residue was extracted with acetone and the extract was concentrated. Separated crystals were recrystallized from acetone to give 1.3 g (80%) of colorless prisms, mp 154—155.5°. *Anal.* Calcd. for $C_7H_9O_2N_3$: C, 50.29; H, 5.43; N, 25.14. Found: C, 50.40; H, 5.57; N, 24.97. NMR (in $CDCl_3$): δ 9.04 (position 6, doublet, J=5 cps), δ 8.13 (position 5, doublet, J=5 cps).

3-Amino-4-thiocarbamoyl-6-mercaptopyridazine (X)——IV (6 g) was suspended in 120 ml of dry pyridine, to this suspension 3 g of P_2S_5 was added and refluxed for 1.5 hours. After removal of pyridine, to the dark brown tarry residue 500 ml of water was added and heated on a free flame for 30 minutes after warmming on a water bath. Insoluble material was filtered, the filtrate was concentrated and separated crystalline mass was recrystallized from water to give 4 g (66%) of reddish brown needles, mp 228° (decomp.). *Anal.* Calcd. for $C_5H_6N_4S_2$: C, 32.26; H, 3.25; N, 30.10. Found: C, 32.47; H, 3.49; N, 30.03.

3-Amino-4-thiocarbamoylpyridazine Hydrochloride (XI)——VII (3 g) was suspended in 75 ml of dry pyridine, to this suspension 3 g of P_2S_5 was added. The mixture was refluxed at 140° for one hour. After removal of pyridine *in vacuo*, to the red residue 150 ml of 3N HCl was added and refluxed for 30 minutes. Insoluble material was filtered and the filtrate was evaporated to dryness *in vacuo*. To the tarry residue MeOH was added and separated crystalline mass was recrystallized from MeOH to give 2.3 g (56%) of yellow plates, mp 248—249° (decomp.). *Anal.* Calcd. for $C_5H_6N_4S$·HCl: C, 31.47; H, 3.67; N, 29.39. Found: C, 31.58; H, 3.62; N, 29.01.

Hofmann Rearrangement of 3-Chloro-4-carbamoyl-6-methoxypyridazine (XIII)——To a mixture of 0.3 g of XIII and 5 ml of 10% NaOH, 0.3 g of Br_2 was added dropwise with ice cooling under stirring. The mixture was allowed to stand at room temperature for 30 minutes and warmed on a boiling water bath for 20 minutes. The solution was cooled and neutralized with AcOH. The deposited crystals were collected and recrystallized from benzene to give 0.2 g of colorless plates, mp 161—162°. *Anal.* Calcd. for $C_5H_6ON_3Cl$: C, 37.63; H, 3.79; N, 26.33. Found: C, 37.66; H, 3.59; N, 25.99.

3-Chloro-5-hydroxypyrimido[4,5-*c*]pyridazine (XVI)——A mixture of 2.3 g of IV, 23 ml of ethyl orthoformate and 46 ml of DMF was refluxed for 2 hours. The mixture was evaporated to dryness *in vacuo* and the residue was recrystallized from MeOH to give 2 g (80%) of pale brown plates, mp 250—251°. *Anal.* Calcd. for $C_6H_3ON_4Cl$: C, 39.45; H, 1.65; N, 30.68. Found: C, 39.35; H, 1.83; N, 30.59. UV $\lambda_{max}^{95\%EtOH}$ mμ (log ε): 270 (4.18), 335 (3.90). IR cm^{-1}: $\nu_{C=O}$ 1695 (KBr).

5-Hydroxypyrimido[4,5-*c*]pyridazine (XVII)——A mixture of 1.7 g of VII, 17 ml of ethyl orthoformate and 34 ml of DMF was refluxed for 30 minutes. The reaction mixture was evaporated to dryness *in vacuo*

9) Tetramethylsilane is used as internal standard in all NMR spectra.

and recrystallized from water to give 1.3 g (70%) of yellowish brown prisms, mp >300°. *Anal.* Calcd. for $C_6H_4ON_4$: C, 48.65; H, 2.72; N, 37.83. Found: C, 48.46; H, 2.88; N, 37.49. UV $\lambda_{max}^{95\%EtOH}$ mμ (log ε): 264 (4.00), 314 (3.86). IR cm^{-1}: $\nu_{C=O}$ 1700 (KBr).

5,7-Dihydroxypyrimido[4,5-*c*]pyridazine (XVIII)——A mixture of 0.5 g of VII and 0.5 g (2.2 eq.) of urea was heated at 160—200° for 2 hours. To the reaction mixture, 20 ml of water was added, heated at boiling point and filtered to take off insoluble materials. The filtrate was concentrated, separated crystalline mass was recrystallized from water to give 0.3 g (50%) of yellow prisms, mp >300°. *Anal.* Calcd. for $C_6H_4O_2N_4$: C, 43.91; H, 2.46; N, 34.14. Found: C, 43.60; H, 2.53; N, 33.96. UV $\lambda_{max}^{95\%EtOH}$ mμ (log ε): 237 (shoulder), 323 (3.56). IR cm^{-1}: $\nu_{C=O}$ 1700 (KBr).

3-Chloro-5-hydroxy-7-aminopyrimido[4,5-*c*]pyridazine (XIX)——A mixture of 16.5 g of II and 25 g of guanidine carbonate (3.7 eq.) was heated at 160° for 30 minutes. The reaction mixture was dissolved in 800 ml of hot water and treated with activated carbon. After filtration the filtrate was acidified with 10% HCl to pH 5, separated crystals were collected. The crystals were dissolved in 300 ml of 2% NaOH, yellow needles of sodium salt were obtained by concentration. After filtration, sodium salt was poured in hot 3N AcOH. The separated crystalline mass was collected, purification was repeated to give 5.4 g (30%) of crystals, mp >300°. *Anal.* Calcd. for $C_6H_4ON_5Cl$: C, 36.54; H, 2.03; N, 35.53. Found: C, 36.70; H, 2.32; N, 35.04.

1,4-Dihydro-3,5-dichloro-4-(4′-N,N-dimethylaminophenyl)pyrimido [4,5-*c*]pyridazine (XXa)——A mixture of 1.3 g of XVI, 65 ml of $POCl_3$ and 2.6 ml of N,N-dimethylaniline was heated at 130° for one hour. The mixture was evaporated to dryness *in vacuo*, the residue was poured in crushed ice and allowed to stand for one hour. The mixture was alkalified with 10% NaOH and extracted with $CHCl_3$. Chloroform layer was dried over Na_2SO_4 and evaporated to dryness, the residue was recrystallized from acetone to give 1.9 g (83%) of colorless prisms, mp 229—230°. *Anal.* Calcd. for $C_{14}H_{13}N_5Cl_2$: C, 52.17; H, 4.04; N, 21.74. Found: C, 51.97; H, 4.07; N, 21.79. UV $\lambda_{max}^{95\%EtOH}$ mμ (log ε): 256 (4.04), 310 (4.20).

1,4-Dihydro-3,5-dichloro-4-(4′-N,N-diethylaminophenyl)pyrimido[4,5-*c*]pyridazine (XXb)——A mixture of 1.34 g of XVI, 60 ml of $POCl_3$ and 1 ml of N,N-diethylaniline was refluxed for 1.5 hours. Same treatment were employed as above method. The residue was recrystallized from ether to give 2.1 g (80%) of colorless plates, mp 163—165°. *Anal.* Calcd. for $C_{16}H_{17}N_5Cl_2$: C, 54.85; H, 4.86; N, 20.20. Found: C, 54.75; H, 4.86; N, 19.75. UV $\lambda_{max}^{95\%EtOH}$ mμ (log ε): 261 (4.08), 310 (4.22). Mass Spectrum M$^+$ Calcd. for $C_{16}H_{17}N_5Cl_2$: 349.086. Found: 349.083. NMR (in $CDCl_3$): δ 9.64 (1H, singlet, NH), δ 8.45 (1H, singlet, 7), δ 7.02 (2H, doublet, J=8 cps, phenyl), δ 6.55 (2H, doublet, J=8 cps, phenyl), δ 4.78 (1H, singlet, 4), δ 3.27 (4H, quartet, J=7 cps, $C\underline{H}_2CH_3$), δ 1.12 (6H, triplet, J=7 cps, $CH_2C\underline{H}_3$).

1,4-Dihydro-4-(4′-N,N-dimethylaminophenyl)pyrimido[4,5-*c*]pyridazine (XXIa)——XXa (1 g) in a mixture of 350 ml of MeOH and 0.5 ml of 28% aq. ammonia was hydrogenated over 0.7 g of 5% Pd-C. After filtration of the catalyst, the filtrate was evaporated to dryness *in vacuo* and the residue was extracted with hot AcOEt. The extract was evaporated to dryness *in vacuo* and the residue was recrystallized to give 0.45 g of colorless scales, mp 235° (decomp.). *Anal.* Calcd. for $C_{14}H_{15}N_5 \cdot 1/10H_2O$: C, 65.92; H, 6.01; N, 27.45. Found: C, 65.85; H, 6.04; N, 27.26.

1,4-Dihydro-4-(4′-N,N-diethylaminophenyl)pyrimido[4,5-*c*]pyridazine (XXIb)——XXb (0.5 g) in a mixture of 250 ml of MeOH and 0.24 g of 28% aq. ammonia was hydrogenated over 0.5 g of 5% Pd-$BaSO_4$. After filtration of the catalyst, the filtrate was evaporated to dryness *in vacuo* and the residue was extracted with hot $CHCl_3$. The extract was concentrated and passed through an alumina column. The elution was evaporated to dryness and the residue was recrystallized from ether to give 0.2 g (50%) of yellowish orange plates, mp 134—135°. *Anal.* Calcd. for $C_{16}H_{19}N_5$: C, 68.31; H, 6.81; N, 24.89. Found: C, 68.52; H, 7.05; N, 24.48. Mass Spectrum M$^+$ 281. NMR (in $CDCl_3$): δ 8.83 (1H, broad, NH), δ 8.60 (1H, singlet, 5 or 7), δ 8.01 (1H, singlet, 7 or 5), δ 7.00 (2H, doublet, J=9 cps, phenyl), δ 6.81 (1H, doublet, J=3 cps, 3), δ 6.63 (2H, doublet, J=9 cps, phenyl), δ 4.48 (1H, doublet, J=3 cps, 4), δ 3.31 (4H, quartet, J=8 cps, $C\underline{H}_2CH_3$), δ 1.15 (6H, triplet, J=8 cps, $CH_2C\underline{H}_3$).

3-Amino-4-carbamoyl-5-(4′-N,N-dimethylaminophenyl)pyridazine (XXIIa)——a) A mixture of 0.25 g of XXVa, 10 ml of EtOH and 5 ml of 20% NaOH was refluxed for 45 minutes. The mixture was evaporated to dryness *in vacuo*, to the residue a small amount of water was added and neutralized with AcOH. The precipitated crystalline mass was collected and recrystallized from EtOH to give 0.1 g (50%) of pale yellow needles, mp 275° (decomp.). *Anal.* Calcd. for $C_{13}H_{15}ON_5 \cdot 1/6H_2O$: C, 59.95; H, 5.94; N, 26.91. Found: C, 60.18; H, 5.95; N, 26.32. Mass Spectrum M$^+$ Calcd. for $C_{13}H_{15}ON_5$: 257.128. Found: 257.127. NMR (in DMSO-d_6): δ 8.53 (1H, singlet, 3), δ 7.7 (2H, broad, NH_2), δ 7.37 (2H, doublet, J=8 cps, phenyl), δ 6.75 (2H, doublet, J=8 cps, phenyl), δ 5.97 (2H, singlet, NH_2), δ 2.94 (6H, singlet, CH_3).

b) A mixture of 1.5 g of XXa, 75 ml of EtOH and 25 ml of 20% NaOH was refluxed for 2 hours. Same treatment were employed above methods, 0.9 g (75%) of pale yellow needles were obtained, mp 275° (decomp.). This compound was identified with above compound by comparison of infrared spectrum.

3-Amino-4-carbamoyl-5-(4′-N,N-diethylaminophenyl)pyridazine (XXIIb)——A mixture of 0.3 g of XXb, 15 ml of EtOH and 5 ml of 20% NaOH was refluxed for 2 hours. The mixture was evaporated to dryness *in vacuo*, to the residue, small amount of water was added and neutralized with AcOH. The separated crystalline mass was recrystallized from MeOH to give 0.2 g (83%) of yellow needles, mp 223—224°. *Anal.*

Calcd. for $C_{15}H_{19}ON_5 \cdot 1/4H_2O$: C, 62.15; H, 6.78; N, 24.16. Found: C, 62.19; H, 6.78; N, 24.17. UV $\lambda_{max}^{95\%EtOH}$ mμ (log ε): 240 (shoulder), 278 (4.01), 320 (3.79), 372 (4.17). Mass Spectrum M^+ Calcd. for $C_{15}H_{19}ON_5$: 258.159. Found: 258.157.

3-Amino-4-carboxy-5-(4′-N,N-dimethylaminophenyl)pyridazine (XXIII)——A mixture of 0.5 g of XXIIa, 20 ml of 50% NaOH and 20 ml of EtOH was heated at 120° for 13 hours in a sealed tube. The EtOH layer was separated from NaOH layer and NaOH layer was washed with EtOH. The EtOH layer and washing were combined and evaporated to dryness *in vacuo*. The residue was washed with small amount of water. The insoluble materials were dissolved in 10 ml of hot water, after cool, the solution was neutralized with 10% AcOH and separated crystalline mass was recrystallized from water to give 0.4 g (80%) of red prisms, mp 231—232° (decomp.). *Anal.* Calcd. for $C_{13}H_{14}O_2N_4$: C, 60.46; H, 5.46; N, 21.69. Found: C, 60.20; H, 5.48; N, 21.29. NMR (in trifluoroacetic acid): δ 8.54 (1H, singlet, 6), δ 7.84 (4H, phenyl), δ 3.59 (6H, singlet, CH_3).

3-Amino-5-(4′-N,N-dimethylaminophenyl)pyridazine (XXIV)——XXIII (0.3 g) was heated on a free flame in a small test tube and the resultant was recrystallized from MeOH to give 0.1 g of yellow prisms, mp 275—277°. *Anal.* Calcd. for $C_{12}H_{14}N_4$: C, 67.27; H, 6.59; N, 26.15. Found: C, 66.98; H, 6.65; N, 25.72. NMR (in trifluoroacetic acid): δ 8.81 (1H, doublet, J=2 cps, 6), δ 8.02 (4H, phenyl), δ 7.87 (1H, doublet, J=2 cps, 4), δ 3.61 (6H, singlet, CH_3).

1,4-Dihydro-3-chloro-4-(4′-N,N-dimethylaminophenyl)-5-aminopyrimido[4,5-*c*]pyridazine (XXVa)——A mixture of 0.6 g of XXa and 15 ml of ethanolic ammonia was heated at 100° for 7 hours in a sealed tube. Separated crystalline mass was collected and recrystallized from MeOH to give 0.4 g (71%) of orange needles, mp 285° (decomp.). *Anal.* Calcd. for $C_{14}H_{15}N_6Cl$: C, 55.53; H, 4.96; N, 27.76. Found: C, 55.22; H, 5.12; N, 26.30.

1,4-Dihydro-3-chloro-4-(4′-N,N-diethylaminophenyl)-5-aminopyrimido[4,5-*c*]pyridazine (XXVb)——A mixture of 0.5 g of XXb and 7 ml of ethanolic ammonia was heated at 100° for 5 hours in a sealed tube. After concentration of the reaction mixture, separated crystalline mass was collected and recrystallized from MeOH to give 0.25 g (50%) of yellow needles, mp 260—261°. *Anal.* Calcd. for $C_{16}H_{19}N_6Cl$: C, 58.09; H, 5.75; N, 25.41. Found: C, 57.88; H, 5.75; N, 25.03. UV $\lambda_{max}^{95\%EtOH}$ mμ (log ε): 255.5 (4.19), 298 (4.09).

1,4-Dihydro-3-chloro-4-(4′-N,N-dimethylaminophenyl)-5-methylaminopyrimido[4,5-*c*]pyridazine (XXVIa)——A mixture of 0.6 g of XXa, 10 ml of MeOH and 1 g of 30% methylamine was heated at 100° for 6 hours in a sealed tube. After concentration of the reaction mixture, separated crystalline mass was collected and recrystallized from MeOH to give 0.45 g (76%) of colorless needles, mp 231—232°. *Anal.* Calcd. for $C_{15}H_{17}N_6Cl$: C, 56.87; H, 5.37; N, 26.54. Found: C, 56.77; H, 5.54; N, 26.12. UV $\lambda_{max}^{95\%EtOH}$ mμ (log ε): 251 (4.30), 290 (4.08). NMR (in $CDCl_3$): δ 8.8 (1H, broad, NH), δ 8.23 (1H, singlet, 7), δ 7.08 (2H, doublet, J=9 cps, phenyl), δ 6.63 (2H, doublet, J=9 cps, phenyl), δ 4.44 (1H, singlet, 4), δ 4.2 (1H, broad, $N\underline{H}CH_3$), δ 2.92 (6H, singlet, CH_3), δ 2.83 (3H, doublet, J=5 cps, $NHC\underline{H}_3$).

1,4-Dihydro-3-chloro-4-(4′-N,N-diethylaminophenyl)-5-methylaminopyrimido[4,5-*c*]pyridazine (XXVIb)——A mixture of 1 g of XXb, 20 ml of MeOH and 2 g of 25% methylamine was heated at 100° for 5 hours in a sealed tube. After concentration of the reaction mixture, separated crystalline mass was collected and recrystallized from MeOH to give 1 g (90%) of pale yellow needles, mp 208—209°. *Anal.* Calcd. for $C_{17}H_{21}N_6Cl$: C, 59.21; H, 6.09; N, 24.39. Found: C, 59.11; H, 6.13; N, 24.47. UV $\lambda_{max}^{95\%EtOH}$ mμ (log ε): 258 (4.31), 297 (4.18). Mass Spectrum M^+ 344. NMR (in $CDCl_3$): δ 8.95 (1H, singlet, NH), δ 8.26 (1H, singlet, 7), δ 7.05 (2H, doublet, J=9 cps, phenyl), δ 6.60 (2H, doublet, J=9 cps, phenyl), δ 4.43 (1H, singlet, 4), δ 4.25 (1H, broad, $N\underline{H}CH_3$), δ 3.30 (4H, quartet, J=7 cps, $C\underline{H}_2CH_3$), δ 2.84 (3H, doublet, J=5 cps, $NHC\underline{H}_3$), δ 1.15 (6H, triplet, J=7 cps, $CH_2C\underline{H}_3$).

1,4-Dihydro-4-(4′-N,N-diethylaminophenyl)-5-methylaminopyrimido[4,5-*c*]pyridazine (XXVII)——XXVIb (0.4 g) in a mixture of 200 ml of MeOH and 0.12 ml of 28% aq. ammonia was hydrogenated over 0.6 g of 5% Pd-$BaSO_4$. After filtration of catalyst, the filtrate was evaporated to dryness *in vacuo* and the residue was recrystallized from MeOH to give 0.2 g of plates, mp 192—193°. *Anal.* Calcd. for $C_{17}H_{22}N_6$: C, 65.78; H, 7.14; N, 27.08. Found: C, 65.75; H, 6.99; N, 26.84. UV $\lambda_{max}^{95\%EtOH}$ mμ (log ε): 255.5 (4.28), 291 (4.16).