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Pyrimidine Derivatives and Related Compounds. XXIV.[1] Synthesis of N-Substituted 6-Formyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]-pyrimidine Derivatives and Related Compounds[2]

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N-Substituted 2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidines (**1**) undergo the Vilsmeier and Mannich reactions at the 6-position to give the 6-formyl derivatives (**3**) *via* the Vilsmeier intermediates (**2**) and the Mannich-base (**4**), respectively. The intermediates (**2**) allow to react with amines and active methylene compounds to afford the corresponding Schiff's bases (**10a—e**) and condensation products (**11—13**), respectively. Treatment of **3** with hydrazines and hydroxylamine give the hydrazones (**10f—j**) and oxime (**10k**). Cyclization of 6-ethoxycarbonylmethylamino-5-formyluracil (**18**) gives 6-ethoxycarbonylpyrrolo[2,3-*d*]pyrimidine (**20**), which is hydrolized to yield the 6-carboxylic acid (**21**).

Since the pyrrolo[2,3-*d*]pyrimidine ring system is a skeleton of antibiotics such as tubercidin,[4] toyocamycin,[5] and sangivamycin,[6] a large number of investigations have been reported on the syntheses and reactions of these derivatives.[7] Previously we reported[8] the synthesis of N-substituted 2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidine derivatives (**1**) which may be regarded as a 7-deaza analogue of xanthine. In this paper, the electrophilic displacement reactions, particulary the Vilsmeier and Mannich reactions, of the pyrrolo[2,3-*d*]pyrimidines (**1**) are described, and the compounds prepared by these reactions are examined for their potential antibacterial activities.

The pyrrole ring of **1** is considered to be very reactive at the α- and β-positions toward electrophiles; in fact, nitration and bromination of **1** caused resinification, so that the products have not been able to be isolated and purified. The Vilsmeier reaction of **1a—j** using N-dimethyl formamide (DMF)-$POCl_3$ as an electrophile gave stable intermediates (**2a—j**), which were readily hydrolyzed to yield the formyl compounds (**3a—j**) (Table I and II). In this reaction, the compounds (**1k, l**) having a phenyl group at 1-position gave directly **3k, l** without isolation of the corresponding intermediates.

In another electrophilic reaction, the 1,3-dimethyl compound (**1a**) was allowed to react with formalin and dimethylamine in acetic acid to give the hydrochloride of a Mannich base

1) Part XXIII: S. Senda and K. Hirota, *Chem. Pharm. Bull.* (Tokyo), **22**, 2593 (1974).
2) This work was presented at the Sixth Congress of Heterocyclic Chemistry, Nagoya, 1973, Abstract of Paper, p. 171.
3) Location: *492-36, Mitahora, Gifu.*
4) T.B. Johnson, *J. Am. Chem. Soc.*, **33**, 758 (1911); K. Anzai, G. Nakamura, and S. Suzuki, *J. Antibiotics* (Tokyo), **10A**, 201 (1957).
5) H. Nishimura, K. Katagiri, K. Sato, M. Mayama, and N. Shimaoka, *J. Antibiotics* (Tokyo), **9A**, 60 (1956); K. Ohkuma, *ibid.*, **13A**, 361 (1960).
6) K.V. Rao and D.W. Renn, *Antimicrobial Agents and Chemotherapy*, **1963**, 77 (1964).
7) *a*) D.H. Kim and A.A. Santilli, *J. Heterocycl. Chem.*, **6**, 819 (1969) and references cited therein; *b*) R.A. West and L. Beauchamp, *J. Org. Chem.*, **26**, 3809 (1961); *c*) R.A. West, *ibid.*, **26**, 4959 (1961); *d*) *Idem, ibid.*, **28**, 1991 (1963); *e*) G. Westphal and H.-H. Stroh, *Ann. Chem.*, **711**, 124 (1968); *f*) H. Ogura, M. Sakaguchi, and K. Takeda, *Chem. Pharm. Bull.* (Tokyo), **20**, 404 (1972); *g*) K. Senga, S. Nishigaki, M. Higuchi, and F. Yoneda, *ibid.*, **20**, 1473 (1972); *h*) F. Yoneda and M. Higuchi, *Bull. Chem. Soc. Japan*, **46**, 3849 (1972).
8) *a*) S. Senda and K. Hirota, *Chem. Letters*, **1972**, 367; *b*) S. Senda and K. Hirota, *Chem. Pharm. Bull.* (Tokyo), **22**,, 1459 (1974).

(**4**), which was also obtained by catalytic hydrogenation of the Vilsmeier-intermediate (**2a**) in autoclave under 10 atm. In order to determine the reaction site of **1** in the Vilsmeier and Mannich reactions, the following experiments were carried out. Thus, **4** was further hydrogenated catalytically under 50 atm to obtain a methyl compound (**5**). This compound was identified as 1,3,6-trimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidine (**5**) which was obtained also by cyclization of 6-isopropylenehydrazino-1,3-dimethyluracil (**6**) with heating.[8] On the other hand, the formyl compound (**3a**) was catalytically hydrogenated under 45 atm, but the methyl compound (**5**) was not obtained, only producing 6-hydroxymethyl-1,3-dimethyl-2,4-dioxo-1,2,3,4,5,6-hexahydropyrrolo[2,3-*d*]pyrimidine (**7**).

It was therefore established that the electrophilic attack in the Vilsmeier and Mannich reactions on this pyrrolopyrimidine was on the α-pyrrole carbon. This is controversial to the

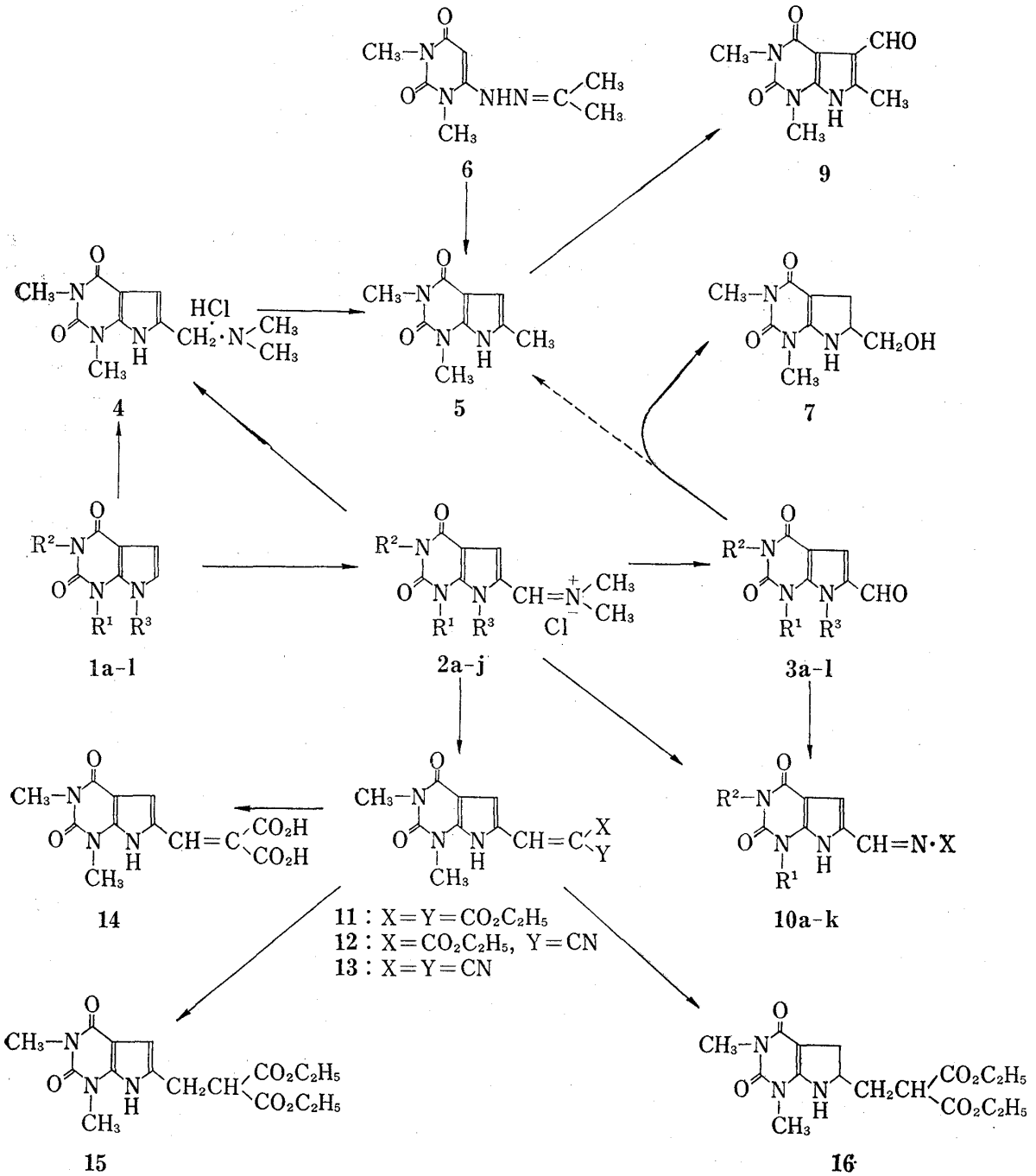
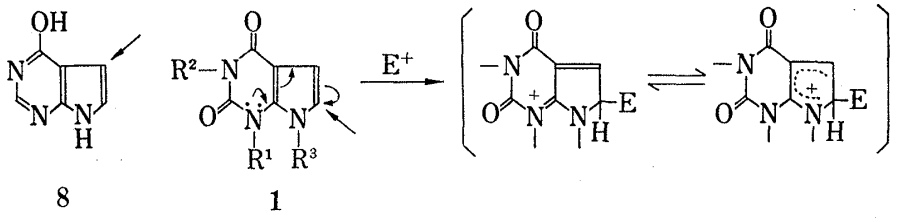


Chart 1

result reported by West[7c] that the Mannich reaction of 4-hydroxypyrrolo[2,3-*d*]pyrimidine (**8**) proceeded at 5-position. This discrepancy is considered to be due to that the electron density at the 6-position is increased by the electron-donating nitrogen atom at the 1-position and that the transition state for attack at the 6-position is of lower energy (due to greater resonance stabilization) than that at the 5-position (Chart 2).



8 1

Chart 2

The Vilsmeier reaction of the 6-methyl compound (**5**) in which the reactive 6-position is blocked by a methyl group gave 5-formyl compound (**9**) but with the 6-formyl compound (**3**) or 6-ethoxycarbonyl compound (**19**, described later), in which the 6-position is substituted by an electron-attracting group, the Vilsmeier reaction did not proceed only recovering the starting material.

This type of the Vilsmeier-intermediates (**2**) has higher reactivity than the formyl compound (**3**), and reacted with a variety of amines producing the corresponding Schiff's bases (**10a—e**). Treatment of the formyl compounds (**3**) with hydrazines and hydroxylamine gave the hydrazones (**10f—j**) and oxime (**10k**), respectively (Table III). The compound **2a** reacted with active methylene compounds such as diethyl malonate, ethyl cyanoacetate, and malononitrile to give the condensation products (**11**, **12**, and **13**). Alkaline hydrolysis of the diester compound (**11**) gave a dicarboxylic compound (**14**).

When the compound **11** was reduced in the presence of Pd-C catalyst at 80° under 10 atm in an autoclave there was obtained the compound (**15**) in which only the double bond in the side chain on the 6-position was reduced, while, reduction of **11** at 120° under 45 atm gave 1,2,3,4,5,6-hexahydropyrrolo[2,3-*d*]pyrimidine (**16**) in which the 5, 6 double bond in the pyrrolo ring was further reduced.

The synthesis of the 6-carboxypyrrolo[2,3-*d*]pyrimidine derivatives was studied. First, the 6-formyl compound (**3a**) was treated with H_2O_2, $KMnO_4$ or other oxidizing agents, but the compound **3a** strongly resisted to the attempted oxidation recovering only the starting material. Then a new synthetic route involving cyclization of a pyrrole ring was developed. Thus, 6-ethoxycarbonylmethylamino-1,3-dimethyluracil (**17**)[9] was treated with the Vilsmeier reagent (DMF-$POCl_3$) in DMF to give 6-ethoxycarbonylmethylamino-5-formyl compound (**18**) which was also obtained by displacement of 6-chloro-5-formyl-1,3-dimethyluracil (**19**)[10] with glycine ethyl ester hydrochloride in the presence of triethylamine. Heating **18** in the presence of potassium carbonate yielded 6-ethoxycarbonylpyrrolo[2,3-*d*]pyrimidine (**20**). The nuclear magnetic resonance (NMR) spectrum of this compound showed a doublet at 7.33 ppm due to coupling of the aromatic proton on the 5-position with NH, which was converted into a singlet by addition of deuterium oxide, revealing the characteristic behavior of this type of compounds. Hydrolysis of **20** under alkaline conditions gave 6-carboxy-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidine (**21**), which was heated at 280—290° to afford the decarboxylated pyrrolo[2,3-*d*]pyrimidine (**1a**).

Studies on the antibacterial, antiviral, coccidiostatic and antimycoplasmic activities of the compounds **3**, **4** and **10—16**, which were prepared here, are under way.

9) W. Pfleiderer, *Chem. Ber.*, **90**, 2604 (1957).
10) S. Senda, K. Hirota, G.-N. Yang, and M. Shirahashi, *Yakugaku Zasshi*, **91**, 1372 (1971).

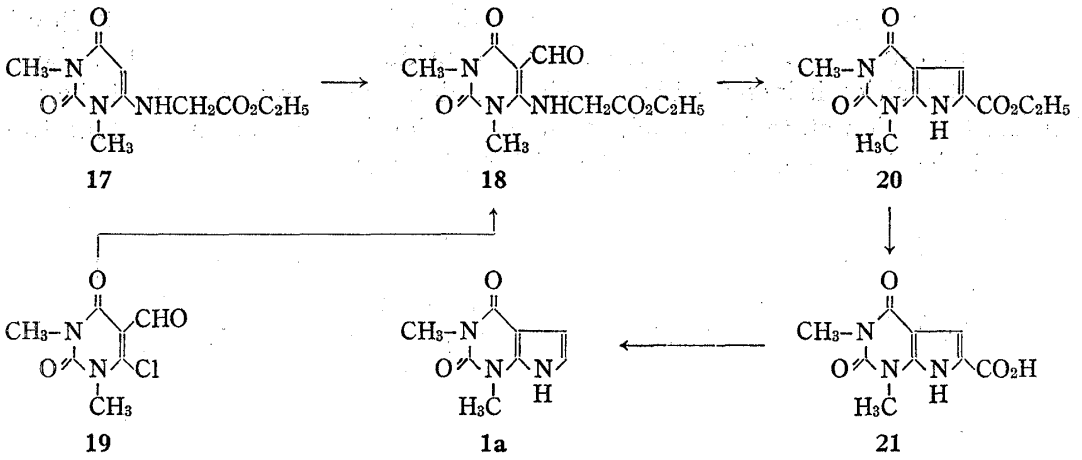
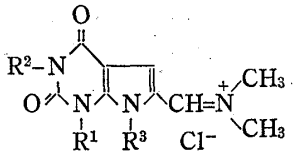


Chart 3

Experimental[11]

The Vilsmeier Intermediates (2) of N-Substituted 2,4-Dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidines (1) (Table I)——To a solution of 2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidine (**1a**—**j**)[8b] (0.01 mole) in 10—30 ml of DMF was added 0.01 mole of $POCl_3$ dropwise with stirring. The temperature was kept between 40° and 60°. After cooling, the resulting precipitate was filtered and washed with acetone to give a crystalline product which required no further purification.

Table I. The Vilsmeier Intermediates (2) of N-Substituted 2,4-Dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidines (1)



Compd. No.	R^1	R^2	R^3	mp (°C) (decomp.)	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	N
2a	Me	Me	H	296—298	90	$C_{11}H_{15}O_2N_4Cl$	48.80 (49.01)	5.58 (5.75)	20.70 (20.68)
2b	Me	Me	Me	246—249	90	$C_{12}H_{17}O_2N_4Cl$[a]			
2c	Et	H	H	>300	74	$C_{11}H_{15}O_2N_4Cl$	48.80 (48.45)	5.58 (5.86)	20.70 (20.38)
2d	Et	Me	H	265—270	95	$C_{12}H_{17}O_2N_4Cl$	50.61 (50.83)	6.02 (6.32)	19.68 (19.78)
2e	Et	Et	H	260—265	33	$C_{13}H_{19}O_2N_4Cl$[a]			
2f	Pr	H	H	270—275	94	$C_{12}H_{17}O_2N_4Cl$	50.61 (50.43)	6.02 (6.15)	19.68 (19.42)
2g	$CH_2CH=CH_2$	H	H	277—280	87	$C_{12}H_{15}O_2N_4Cl$	50.98 (50.75)	5.34 (5.62)	19.82 (19.67)
2h	$CH_2CH=CH_2$	Me	H	245—248	83	$C_{13}H_{17}O_2N_4Cl\cdot H_2O$	49.60 (49.46)	6.08 (6.24)	17.80 (18.22)
2i	$CH_2CH=CH_2$	Me	Me	222—225	78	$C_{14}H_{19}O_2N_4Cl$	54.10 (54.22)	6.16 (6.37)	18.01 (17.81)
2j	Bu	Me	H	195—200	87	$C_{14}H_{21}O_2N_4Cl$[a]			

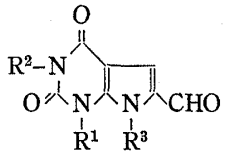
a) This compound, which is impure for elemental analysis, was hydrolized to give the formyl compound (**3** in Table II).

11) All melting points were measured with a Yanagimoto Micro Melting Point Apparatus and are uncorrected. NMR spectra were recorded on a Hitachi Perkin-Elmer Model R-20B spectrometer using tetramethylsilane as an internal reference.

N-Substituted 6-Formyl-2,4-dioxo-1,2,3,4-tetrahydro[2,3-*d*]pyrimidines (3a—l in Table II)——a) A mixture of **2a—j** (0.01 mole) and H_2O (50 ml) was heated at 70—80° for a few min. After cooling, the resulting precipitate was filtered, washed with H_2O, and then recrystallized from an appropriate solvent. NMR (DMSO-d_6) δ: **3a**; 3.22 and 3.47 (each 3H, each s, $NCH_3\times2$), 7.38 (1H, s, 5-H), 9.48 (1H, s, CHO) 12.50—12.80 (1H, br, NH). **3b**; 3.23, 3.73, and 4.18 (each 3H, each s, $NCH_3\times3$), 7.45 (1H, s, 5-H), 9.48 (1H, s, CHO).

b) To a solution of 2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidine (**1k, l**)[8b] (0.01 mole) in 20—30 ml of DMF was added 0.01 mole of $POCl_3$ dropwise with stirring. The solution was further stirred for 10 min and evaporated under reduced pressure. H_2O (40 ml) was added to the residue and the mixture heated at 70—80° for 5 min. After cooling, the resulting precipitate was filtered, washed with H_2O, and recrystallized from EtOH to give **3k, l**.

Table II. N-Substituted 6-Formyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidines (3)



Compd. No.	R^1	R^2	R^3	mp (°C)	Recryst. solvent	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	N
3a	Me	Me	H	284	H_2O	95	$C_9H_9O_3N_3$	52.17 (52.38)	4.38 (4.55)	20.28 (20.11)
3b	Me	Me	Me	231—233	H_2O	73	$C_{10}H_{11}O_3N_3$	54.29 (54.56)	5.01 (5.09)	19.00 (18.91)
3c	Et	H	H	>300	DMF	85	$C_9H_9O_3N_3$	52.17 (52.32)	4.38 (4.79)	20.28 (19.94)
3d	Et	Me	H	>300	EtOH–H_2O	92	$C_{10}H_{11}O_3N_3$	54.29 (54.11)	5.01 (5.30)	19.00 (19.14)
3e	Et	Et	H	274	EtOH–H_2O	76	$C_{11}H_{13}O_3N_3$	56.16 (56.35)	5.57 (5.70)	17.86 (17.63)
3f	Pr	H	H	>300	EtOH–H_2O	95	$C_{10}H_{11}O_3N_3$	54.29 (54.41)	5.01 (5.36)	19.00 (18.64)
3g	$CH_2CH{=}CH_2$	H	H	>300	EtOH–H_2O	89	$C_{10}H_9O_3N_3$	54.79 (54.98)	4.14 (4.39)	19.17 (10.30)
3h	$CH_2CH{=}CH_2$	Me	H	>300	EtOH–H_2O	98	$C_{11}H_{11}O_3N_3$	56.65 (56.73)	4.75 (4.99)	18.02 (18.13)
3i	$CH_2CH{=}CH_2$	Me	Me	210	EtOH–H_2O	87	$C_{12}H_{13}O_3N_3$	58.29 (58.38)	5.30 (5.27)	17.00 (16.92)
3j	Bu	Me	H	240	AcOEt	90	$C_{12}H_{15}O_3N_3$	57.82 (57.92)	6.07 (6.28)	16.86 (17.13)
3k	Ph	Me	H	>300	EtOH	63	$C_{14}H_{11}O_3N_3$	62.45 (62.62)	4.12 (4.35)	15.61 (15.88)
3l	Ph	Me	Me	211	EtOH	85	$C_{15}H_{13}O_3N_3$	63.59 (63.49)	4.63 (4.88)	14.83 (14.89)

6-Dimethylaminomethyl-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidine Hydrochloride (4)——a) To a solution of **1a** (1.8 g, 0.01 mole) in 20 ml of AcOH were added 37% formalin (0.9 g) and 40% aq. solution of Me_2NH (1.2 g). The solution was allowed to stand for 1 hr, and then evaporated under reduced pressure. The residue was dissolved into a large amount of acetone, an equivalent of conc. HCl was added thereto, and the resulting precipitate was filtered. Recrystallization from EtOH gave 1.5 g (55%) of the hydrochloride (**4**), mp 230° (decomp.). NMR (D_2O) δ: 3.01 (6H, s, $N(CH_3)_2$), 3.27 and 3.53 (each 3H, each s, $NCH_3\times2$), 4.45 (2H, s, $-CH_2N\langle$), 6.78 (1H, s, 5-H). *Anal.* Calcd. for $C_{11}H_{16}O_2N_4\cdot HCl$: C, 48.44; H, 6.28; N, 20.54. Found: C, 48.59; H, 6.42; N, 20.29.

b) A solution of **2a** (2.35 g) in 400 ml of abs. EtOH was hydrogenated in an autoclave at 10 atm and 75° using Pd–C (0.3 g) as a catalyst. After 6 hr, activated charcoal was added to the reaction solution and the catalyst was removed by filtration. The filtrate was evaporated under reduced pressure, and then

the residue was recrystallized from EtOH to give 1.0 g (43%) of the hydrochloride (**4**), mp 230° (decomp.), identical with the compound (**4**) prepared above.

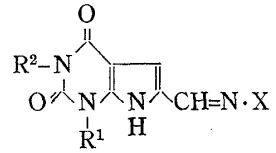
1,3,6-Trimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidine (5)——A solution of **4** (2.4 g) and Et_3N (2 ml) in 120 ml of EtOH was hydrogenated in an autoclave at 100 atm and 80° for 5 hr using Pd–C (0.5 g) as a catalyst. Activated charcoal was added to the reaction solution, the catalyst was removed by filtration, and the filtrate was evaporated under reduced pressure. H_2O was added to the residue and the crude product was filtered, and then recrystallized from EtOH to give 1.0 g (59%) of colorless leaflets, mp>300°, identical with an authentic sample.[8]

6-Hydroxymethyl-1,3-dimethyl-2,4-dioxo-1,2,3,4,5,6-hexahydropyrrolo[2,3-*d*]pyrimidine (7)——A solution of **3a** (2 g) in 400 ml of EtOH was hydrogenated in an autoclave at 45 atm and 120° for 6 hr using Pd–C (0.3 g) as a catalyst. After the reaction, the solution was treated as described in the preparation (b) of **4**. The crude product was recrystallized from PrOH to give 1 g (49%) of colorless plates, mp 224—226°. *Anal.* Calcd. for $C_9H_{13}O_3N_3$: C, 51.17; H, 6.20; N, 19.90. Found: C, 51.38; H, 6.39; N, 20.08.

5-Formyl-1,3,6-trimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidine (9)——To a solution of **5** (1.0 g, 0.005 mole) in 10 ml of DMF was added 0.6 g of $POCl_3$ dropwise with stirring. The solution was heated on a water bath for 10 min and evaporated under reduced pressure. H_2O was added to the residue and the solution was heated at 70—80° for 5 min. After cooling, the resulting precipitate was filtered, washed with H_2O, and recrystallized from EtOH to give 0.56 g (51%) of **9**, mp>300°. NMR (CF_3CO_2H) δ: 2.87 (3H, s, 6-CH_3), 3.79 and 3.88 (each 3H, each s, $NCH_3\times2$), 9.87 (1H, s, CHO). *Anal.* Calcd. for $C_{10}H_{11}O_3N_3$: C, 54.29; H, 5.01; N, 19.00. Found: C, 54.13; H, 5.04; N, 18.79.

The Shiff's Bases (10a—e) of N-Substituted 6-Formyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidines (3) (Table III)——To a suspension of **2** (0.01 mole) in 20 ml of abs. EtOH was added 0.01 mole of amine (methylamine, allylamine, benzylamine, or aniline). The mixture was stirred for 30 min and evaporated under reduced pressure. H_2O was added to the residue and the resulting crude product was filtered, and then recrystallized from an appropriate solvent.

Table III. The Schiff's Bases, Hydrazones, and Oxime (**10**) of N-Substituted 6-Formyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidines (**3**)



Compd. No.	R^1	R^2	X	mp (°C)	Recryst. solvent	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	N
10a	Me	Me	Me	270	DMF	89	$C_{10}H_{12}O_2N_4$	54.54 (54.66)	5.49 (5.66)	25.44 (25.67)
10b	Me	Me	CH_2–CH=CH_2	211—212	EtOH	72	$C_{12}H_{14}O_2N_4$	58.52 (58.31)	5.73 (5.90)	22.75 (22.75)
10c	Me	Me	CH_2Ph	131—132	AcOEt	61	$C_{16}H_{16}O_2N_4\cdot H_2O$	61.13 (61.48)	5.77 (6.01)	17.83 (18.01)
10d	Me	Me	Ph	292	MeOH	90	$C_{15}H_{14}O_2N_4\cdot HCl$	56.52 (56.75)	4.74 (4.88)	17.57 (17.69)
10e	$CH_2CH=CH_2$	H	CH_2Ph	283	EtOH	88	$C_{17}H_{16}O_2N_4$	66.22 (66.18)	5.23 (5.47)	18.17 (18.43)
10f	Me	Me	NHMe	251—252	EtOH	85	$C_{10}H_{13}O_2N_5$	51.05 (51.29)	5.57 (5.84)	29.77 (29.25)
10g	$CH_2CH=CH_2$	H	NHMe	271	DMF	97	$C_{11}H_{13}O_2N_5$	53.43 (53.57)	5.30 (5.57)	28.33 (28.54)
10h	$CH_2CH=CH_2$	H	NHPh	271	EtOH	74	$C_{16}H_{15}O_2N_5$	62.12 (61.93)	4.89 (5.11)	22.64 (22.91)
10i	$CH_2CH=CH_2$	Me	NHMe	212	AcOEt	84	$C_{12}H_{15}O_2N_5$	55.16 (55.31)	5.79 (5.90)	26.81 (26.96)
10j	$CH_2CH=CH_2$	Me	NHPh	253	EtOH	73	$C_{17}H_{17}O_2N_5$	63.14 (63.36)	5.30 (5.42)	21.66 (21.45)
10k	Me	Me	OH	276	DMF–H_2O	77	$C_9H_{10}O_3N_4$	48.65 (48.92)	4.54 (4.81)	25.22 (25.41)

The Hydrazones (10f—j) of N-Substituted 6-Formyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidines (3) (Table III)——A solution of **3** (0.01 mole) and hydrazine (0.01 mole) (methylhydrazine or phenylhydrazine) in 20 ml of DMF was heated at 100° for 10 min. The solution was evaporated under reduced pressure and H_2O was added to the residue. The crude product was filtered and recrystallized from an appropriate solvent.

The Oxime (10k) of 6-Formyl-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidine (3a) (Table III)——A mixture of **3a** (2.1 g, 0.01 mole), hydroxylamine hydrochloride (0.8 g), Et_3N (1.2 g) and DMF (20 ml) was heated at 100° for 10 min. After cooling, the resulting precipitate was filtered, washed with H_2O, and recrystallized from DMF–H_2O to give 1.7 g of **10k**. NMR (DMSO-d_6) δ: 3.22 and 3.50 (each 3H, each s, $NCH_3\times2$), 6.62 (1H, s, 5-H), 7.97 (1H, s, –CH=N–), 10.83 (1H, s, =NOH), 11.90—12.03 (1H, br, NH).

6-(2,2-Bisethoxycarbonylvinyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidine(11)——In 210 ml of abs. EtOH were dissolved Na (1.5 g) and diethyl malonate (9.6 g). The solution was allowed to stand for 30 min, and then 8.4 g (0.03 mole) of **2a** was added thereto. The mixture was stirred for 30 min and evaporated under reduced pressure. The residue was dissolved in 90 ml of H_2O and the solution was neutralized with AcOH. The resulting precipitate was filtered and recrystallized from DMF–EtOH to give 9.8 g (93%) of yellow needles, mp 252°. NMR (CF_3CO_2H) δ: 1.48 (6H, t, 7.2 Hz, $OCH_2C\underline{H}_3\times2$), 3.65 and 3.82 (each 3H, each s, $NCH_3\times2$), 4.54 (4H, q, 7.2 Hz, $OC\underline{H}_2CH_3\times2$), 7.34 (1H, d, 2.4 Hz, 5-H), 7.83 (1H, s, –CH=C〈). *Anal.* Calcd. for $C_{16}H_{19}O_6N_3$: C, 55.01; H, 5.48; N, 12.03. Found: C, 55.11; H, 5.60; N, 12.07.

6-(2-Cyano-2-ethoxycarbonylvinyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidine (12)——In 70 ml of abs. EtOH were added Na (0.5 g) and ethyl cyanoacetate (2.3 g), the solution was allowed to stand for 30 min, and 2.7 g of **2a** was added thereto. The mixture was treated as described in the preparation of **11**. Recrystallization of the crude product from AcOEt gave 1.9 g (63%) of yellow needles, mp 259°. NMR (CF_3CO_2H) δ: 1.50 (3H, t, 7.2 Hz, $OCH_2C\underline{H}_3$), 3.63 and 3.81 (each 3H, each s, $NCH_3\times2$), 4.54 (2H, q, 7.2 Hz, $OC\underline{H}_2CH_3$), 7.89 (1H, d, 2.5 Hz, 5-H), 8.39 (1H, s, –CH=C〈). *Anal.* Calcd. for $C_{14}H_{14}O_4N_4$: C, 55.62; H, 4.67; N, 18.54. Found: C, 55.55; H, 4.60; N, 18.43.

6-(2,2-Dicyanovinyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidine (13)——In 70 ml of abs. EtOH were added Na (0.5 g) and malononitrile (1.3 g), the solution was allowed to stand for 30 min, and 2.7 g of **2a** was added thereto. The mixture was treated as described in the preparation of **11**. Recrystallization of the crude product from MeOH gave 1.7 g (64%) of yellow needles, mp 297° (decomp.). NMR (CF_3CO_2H) δ: 3.63 and 3.80 (each 3H, each s, $NCH_3\times2$), 7.90—8.00 (2H, multiplets, 5-H and –CH=C〈). *Anal.* Calcd. for $C_{12}H_9O_2N_5\cdot1/2H_2O$: C, 54.54; H, 3.81; N, 26.51. Found: C, 54.24; H, 4.09; N, 26.33.

6-(2,2-Dicarboxyvinyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidine (14)——To 20 ml of 10% aq. solution of NaOH was added 3.5 g of **11**. The mixture was heated on a water bath for 30 min, and then neutralized with AcOH to give a crude product, which was recrystallized from H_2O to give 1.6 g (52%) of light yellow powder, mp>300°. *Anal.* Calcd. for $C_{12}H_{11}O_6N_3\cdot H_2O$: C, 46.31; H, 4.21; N, 13.50. Found: C, 45.97; H, 4.51; N, 13.26.

6-(2,2-Bisethoxycarbonylethyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidine(15)——A solution of **11** (3.5 g) in 600 ml of MeOH was hydrogenated in an autoclave at 10 atm and 80° for 6 hr using Pd–C (0.5 g) as a catalyst. After the reaction, activated charcoal was added thereto, the catalyst was removed by filtration, and the filtrate was evaporated under reduced pressure. Recrystallization of the residue from H_2O gave 1.5 g (43%) of colorless leaflets, mp 172°. NMR ($CDCl_3$) δ: 1.25 (6H, t, 7.2 Hz, $OCH_2C\underline{H}_3\times2$), 3.17 (2H, d, 6.5 Hz, $-C\underline{H}_2CH$〈), 3.42 and 3.54 (each 3H, each s, $NCH_3\times2$), 3.74 (1H, t, 6.5 Hz, $-CH_2C\underline{H}$〈), 4.21 (4H, q, 7.2 Hz, $OC\underline{H}_2CH_3\times2$), 6.28 (1H, d, 2.5 Hz, 5-H), 9.80—10.05 (1H, br, NH). *Anal.* Calcd. for $C_{16}H_{21}O_6N_3$: C, 54.69; H, 6.02; N, 11.91. Found: C, 54.41; H, 5.89; N, 12.14.

6-(2,2-Bisethoxycarbonylethyl)-1,3-dimethyl-2,4-dioxo-1,2,3,4,5,6-hexahydropyrrolo[2,3-*d*]pyrimidine (16)——A solution of **11** (3.5 g) in 600 ml of EtOH was hydrogenated in an autoclave at 45 atm and 120° for 6 hr using Pd–C (0.5 g) as a catalyst. The reaction solution was treated as described in the preparation of **15** to give a crude product. Recrystallization from benzene-ligroin gave 1.1 g (32%) of **16**, mp 134°. *Anal.* Calcd. for $C_{16}H_{23}O_6N_3$: C, 54.38; H, 6.56; N, 11.89. Found: C, 54.30; H, 6.69; N, 12.01.

6-Ethoxycarbonylmethylamino-5-formyl-1,3-dimethyluracil (18)——a) To a solution of 6-ethoxycarbonylmethylamino-1,3-dimethyluracil (17)[9] (1.4 g) in 20 ml of DMF was added 0.9 g of $POCl_3$ dropwise with stirring at room temperature. The solution was allowed to stand for 1 hr and evaporated under reduced pressure. H_2O was added to the residue, the solution was neutralized with 10% Na_2CO_3 solution to give 1.1 g (63%) of a crude product. Recrystallization from EtOH gave colorless needles, mp 200°. NMR ($CDCl_3$) δ: 1.32 (3H, t, 7.2 Hz, $OCH_2C\underline{H}_3$), 3.35 and 3.52 (each 3H, each s, $NCH_3\times2$), 4.26 (2H, d, 6 Hz, NCH_2CO), 4.29 (2H, q, 7.2 Hz, $OC\underline{H}_2CH_3$), 9.99 (1H, s, CHO), 11.03—11.40 (1H, br, NH). *Anal.* Calcd. for $C_{11}H_{15}O_5N_3$: C, 49.07; H, 5.62; N, 15.61. Found: C, 49.20; H, 5.55; N, 15.43.

b) To a mixture of 6-chloro-5-formyl-1,3-dimethyluracil (19)[10] (2 g, 0.01 mole), glycine ethyl ester hydrochloride (1.4 g, 0.01 mole), and DMF (10 ml) was added triethylamine (2 g, 0.02 mole) dropwise with stirring at room temperature. After 30 min, the resulting crude product was filtered, washed with H_2O, and recrystallized from EtOH to give 1.3 g (48%) of **18**, mp 200°, identical with the compound (**18**) prepared above.

6-Ethoxycarbonyl-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidine (20)——A mixture of **18** (1.35 g, 0.005 mole), anhydrous K_2CO_3 (0.9 g), and DMF (10 ml) was heated at 100° for 5 hr. The reaction solution was evaporated under reduced pressure, the residue was dissolved in H_2O, and neutralization of the solution with AcOH gave a crude product. Recrystallization from EtOH afforded 0.7 g (56%) of colorless needles, mp 280°. NMR ($CDCl_3$) δ: 1.38 (3H, t, 7.2 Hz, $OCH_2C\underline{H}_3$) 3.43 and 3.62 (each 3H, each s, $NCH_3 \times 2$), 4.34 (2H, q, 7.2 Hz, $OC\underline{H}_2CH_3$), 7.33 (1H, d, 2.4 Hz, 5-H), 9.90—10.07 (1H, br, NH). *Anal.* Calcd. for $C_{11}H_{13}O_4N_3$: C, 52.58; H, 5.22; N, 16.73. Found: C, 52.32; H, 5.17; N, 16.62.

6-Carboxy-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidine (21)——A mixture of **20** (1.25 g, 0.005 mole) and 5% NaOH solution (20 ml) was heated at 100° for 10 min. After cooling, the solution was neutralized with conc. HCl to 0.9 g (91%) of a crude product. Recrystallization from DMF–EtOH gave colorless needles, mp 282° (decomp.). *Anal.* Calcd. for $C_9H_9O_4N_3$: C, 48.43; H, 4.06; N, 18.83. Found: C, 48.17; H, 4.32; N, 18.63.

Decarboxylation of 6-Carboxy-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidine (21)——The carboxylic acid (**21**) (0.45 g, 0.002 mole) was heated at 280—290° for 5 min. After cooling, the crude product was recrystallized from H_2O to give 0.29 g (80%) of 1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrrolo[2,3-*d*]pyrimidine (**1a**), mp 300°, identical with an authentic sample.[8b]