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Pyrimidine Derivatives and Related Compounds. XVIII.[1] Studies in the Synthesis and Pharmacological Activities of 2,4-Dioxo-1,2,3,4,6,7-hexahydro-5*H*-cyclopenta[*d*]pyrimidine Derivatives

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Syntheses of 3-substituted 2,4-dioxo-1,2,3,4,6,7-hexahydro-5*H*-cyclopenta[*d*]pyrimidines (3-substituents: methyl, cyclohexyl, phenyl) from 2-ethoxycarbonylcyclopentanone were investigated. These compounds were alkylated in 1-position to give 1,3-disubstituted pyrimidine derivatives (1-substituents: CH_3, CH_2COOR, CH_2CONR_2, $CH_2CH_2NR_2$). Their acute toxicities and analgetic, antipyretic, and antiinflammatory activities were tested.

The authors previously synthesized 5,6-dialkyluracil derivatives (A) and investigated their analgetic and sedative actions.[3] Further to the above, we have now studied a method for synthesizing 2,4-dioxo-1,2,3,4,6,7-hexahydro-5*H*-cyclopenta[*d*]pyrimidine derivatives (B) which have a close relation with A in such a respect that alkyl groups at 5- and 6- positions of A form a cyclopentane ring. We have also studied the relation of chemical structures of B with their pharmacological activities.

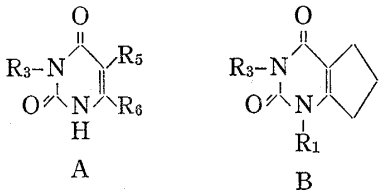


Chart 1

As to the synthesis of 3-substituted 2,4-dioxo-1,2,3,4,6,7-hexahydro-5*H*-cyclopenta[*d*]pyrimidine derivatives, there was a report in which a dehydration-condensation of 2-ethoxycarbonylcyclopentanone (**1**) with alkylurea was carried out by refluxing in benzene or dioxane in the presence of small amounts of phosphoric acid, *p*-toluenesulfonic acid, *etc.*[4] We modified the above method. Thus, a small amount of hydrochloric acid was added to a mixture of **1** and a monosubstituted urea (substituents: methyl, cyclohexyl, phenyl), subjected to a condensation by allowing stand at a room temperature for 10 to 20 days, the resulting N-substituted N'-(2-carbethoxypentenyl)-urea [substituents: methyl (**2**), cyclohexyl (**3**), phenyl(**4**)] was hydrolyzed with or dissolved in a sodium hydroxide solution, and acidified with hydrochloric acid to synthesize 3-substituted 2,4-dioxo-1,2,3,4,6,7-hexahydro-5*H*-cyclopenta[*d*]pyrimidine [substituents: methyl (**5**), cyclohexyl (**6**), phenyl (**7**)]. In order to improve the above ring closure reaction, we have also attempted the dehydration-condensation of **1** with a phenylurea in a mixture of DMF and acetic anhydride whereupon the reaction time could be shortened to 4 to 5 days and the yield increased.

Another route to synthesize **7** was also studied. Thus heating of **1** with aniline in xylene gave 2-(N-phenylcarbamoyl)cyclopentanone (**8**), which was made to react with ammonia. The resulting 1-amino-2-(N-phenylcarbamoyl)cyclopentene (**9**) was treated with ethyl chlorocarbonate to give 1-ethoxycarbonylamino-2-(N-phenylcarbamoyl)cyclopentene (**10**). Treatment of **10** with 10% alcoholic potassium hydroxide gave **7**.

1) Part XVII: S. Senda, K. Hirota, and J. Notani, *Chem. Pharm. Bull.* (Tokyo), **20**, 1389 (1972).
2) Location: *493-36, Mitahora, Gifu.*
3) S. Senda, M. Honda, K. Maeno, and H. Fujimura, *Chem. Pharm. Bull.* (Tokyo), **6**, 490 (1958).
4) E.J. Soboczenski, U.S. Patent 3235360 [*C.A.*, **64**, 14196 (1966)].

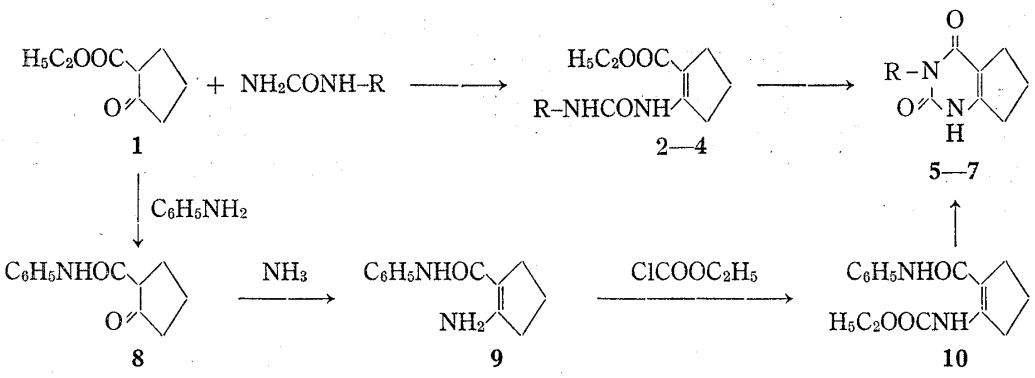


Chart 2

Methylation of **5**—**7** with dimethyl sulfate in a methanolic sodium hydroxide solution gave the corresponding 3-substituted 1-methyl-2,4-dioxo-1,2,3,4,6,7-hexahydro-5*H*-cyclopenta-[*d*]pyrimidine [substituents: methyl (**11**), cyclohexyl (**12**), phenyl (**13**)]. Further, compounds (**5**—**7**) were similarly treated with ethyl monochloroacetate to give 3-substituted 1-carbethoxy-methyl-2,4-dioxo-1,2,3,4,6,7-hexahydro-5*H*-cyclopenta[*d*]pyrimidine [substituents: methyl (**14**), cyclohexyl (**15**), phenyl (**16**)].

When compounds (**14**—**16**) were hydrolyzed by refluxing with 20% hydrochloric acid, the corresponding 3-substituted 1-carboxymethyl-2.4-dioxo-1,2,3,4,6,7-hexahydro-5*H*-cyclopenta-[*d*]pyrimidines [substituents: methyl (**17**), cyclohexyl (**18**), phenyl (**19**)] were obtained. Treatment of **14**—**16** with NH_4OH or hydrazine hydrate in methanol gave compounds (**20**—**24**), respectively, in which a carbethoxymethyl group at 1-position was changed to carbamoylmethyl or hydrazinomethyl group (Table II).

When compounds (**5**—**7**) in ethanol were made to react with N,N-dimethylchloroacetamide, N,N-diethylchloroacetamide, N-butylchloroacetamide or β-diethylaminoethyl chloride in the presence of sodium ethoxide, they gave 3-substituted 1-(N,N-dialkylcarbamoylmethyl)-2,4-dioxo-1,2,3,4,6,7-hexahydro-5*H*-cyclopenta[*d*]pyrimidines (**25**—**33**) and 3-substituted 1-(β-diethylaminoethyl)-2,4-dioxo-1,2,3,4,6,7-hexahydro-5*H*-cyclopenta[*d*]pyrimidines (**34**, **35**), respectively (Table III).

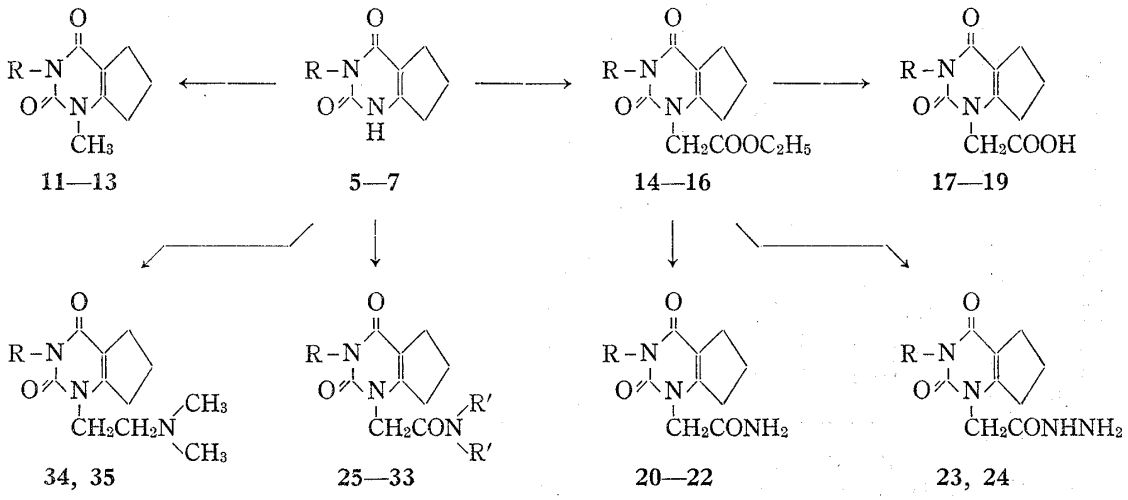


Chart 3

We have then attempted to synthesize 1-methyl-2,4-dioxo-1,2,3,4,6,7-hexahydro-5*H*-cyclopenta[*d*]pyrimidine (**40**). Thus 2,4-dioxo-1,2,3,4,6,7-hexahydro-5*H*-cyclopenta[*d*]-pyrimidine (**36**)[5] was heated to reflux in phosphorus oxychloride, the resulting 2,4-dichloro-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (**37**) was made to react with 2 moles of sodium

methoxide in methanol, the resulting 2,4-dimethoxy-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (**38**) was treated with methyl iodide by letting stand for 2 to 3 days at a room temperature, and the resulting 1-methyl-4-methoxy-2-oxo-1,2,6,7-tetrahydro-5*H*-cyclopenta[*d*]-pyrimidine (**39**) was hydrolyzed by refluxing in 20% hydrochloric acid to give the desired compound (**40**). Methylation of **36** with 1 mole of dimethyl sulfate in a sodium hydroxide solution also gave **40**.

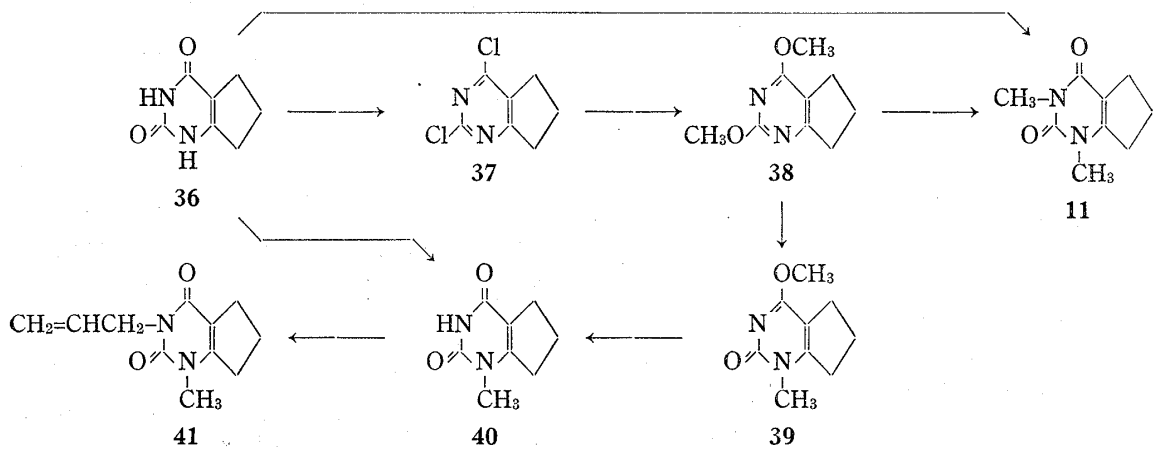
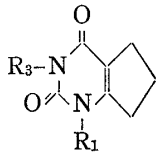


Chart 4

TABLE I. Pharmacological Activities of 1,3-Disubstituted 2,4-Dioxo-1,2,3,4,6,7-hexahydro-5*H*-cyclopenta[*d*]pyrimidines



Compd. No.	R_1	R_3	Acute toxicity[a] LD_{50} (mg/kg)	Analgetic[b] activity ED_{50} (mg/kg)	Antiinflammatory[c] (%) 50	100 (mg/kg)
11	CH_3	CH_3	430	201	35	45
12	CH_3		308	125		34
13	CH_3	C_6H_5	692	133		28
41	CH_3	$CH_2CH=CH_2$	340	236		
19	CH_2COOH	C_6H_5	1600	—		
21	CH_2CONH_2		1200	—		
22	CH_2CONH_2	C_6H_5	1080	—		
25	CH_2CONM_{e2}	CH_3	1050	—		
27	CH_2CONMe_2	C_6H_5	380	93		
34	$CH_2CH_2NEt_2$	CH_3	1100	—		
35	$CH_2CH_2NEt_2$	C_6H_5	350	—		
Aminopyrine			280	135	43	48

a) in mice (*i. p.*)
b) Modified Haffner's method (*i. p.*)[6]
c) Inhibitory effect (%) on the rat paw edema induced by carrageenin in male rats.[7]

5) *a*) L.O. Ross, L. Goodman, and B.R. Baker, *J. Am. Chem. Soc.*, **81**, 3108 (1959); *b*) G.D. Stevens, A. Halamandaris, P. Wenk, R.A. Mull, and E. Schlitter, *Arch. Biochem. Biophys.*, **83**, 141 (1959) [*C.A.*, **54**, 1528 (1960)]; *c*) G. Biglino, Farmaco (Pavia), *Ed. Sci.*, **17**, 377 (1962) [*C.A.*, **58**, 5684 (1963)]; *d*) R.W. Lamon, *J. Heterocycl. Chem.*, **5**, 837 (1968).
6) H. Fujimura and K. Nakajima, *Bull. Inst. Chem. Res.* (Kyoto Univ.), **25**, 36 (1951).
7) C.A. Winter and G.W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962).

Treatment of **40** with allyl bromide in an ethanolic potassium hydroxide solution gave 3-allyl-1-methyl-2,4-dioxo-1,2,3,4,6,7-hexahydro-5*H*-cyclopenta[*d*]pyrimidine (**41**). Heating of 2,4-dimethoxy-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (**38**) at 250—270° gave 1,3-dimethyl-2,4-dioxo-1,2,3,4,6,7-hexahydro-5*H*-cyclopenta[*d*]pyrimidine (**11**). As to the synthesis of **11**, the methylation of **36** with methyl iodide and potassium carbonate in abs. ethanol was superior to the method described above.

Pharmacology

Acute toxicities [LD_{50} in mice (*i.p.*)], analgetic activities [according to Haffner's method with a threshold dose of morphine in mice (*i.p.*)],[6] antiinflammatory activities [inhibitory effect on rat hind paw edema induced by carrageenin (*p.o.*)][7] and antipyretic activities [febrile rats by Brewer's yeast (*p.o.*)] of the above compound were tested (Table I).

Analgetic and sedative activities of the tested compounds were generally weaker than those of 5,6-dialkyluracils (A), while antiinflammatory activity of the compound (**8**) was nearly same as that of aminopyrine. None of the tested compounds exhibited antipyretic activities.

Experimental

N-(2-Carbethoxycyclopentenyl)-N′-methylurea (**2**)——To a mixture of 10.4 g of 2-ethoxycarbonylcyclopentanone (**1**), 5.2 g of methylurea and 3 ml of abs. EtOH were added 2—3 drops of conc. HCl. The mixture was stirred well and kept for 10—20 days over conc. H_2SO_4 in a vacuum desiccator, stirred from time to time, and powdered to facilitate drying. The crude product (13.5 g) was recrystallized from EtOH to give colorless prisms of mp 209°. *Anal.* Calcd. for $C_{10}H_{16}O_3N_3$: C, 56.59; H, 7.60; N, 13.20. Found: C, 56.82; H, 7.76; N, 13.13.

N-(2-Carbethoxycyclopentenyl)-N′-cyclohexylurea (**3**)——A mixture of 14.2 g of cyclohexylurea and 15.7g of **1** was treated as described above to give 27.5 g of crude products. Recrystallization from MeOH gave colorless leaflets of mp 138—138.5°. *Anal.* Calcd. for $C_{15}H_{24}O_3N_2$: C, 64.26; H, 8.63; N, 9.99. Found: C, 64.07; H, 8.63; N, 10.18.

N-(2-Carbethoxycyclopentenyl)-N′-phenylurea (**4**)——A mixture of 13.6 g of phenylurea and 15.7 g of **1** was treated as described above to give crude products. Recrystallization from EtOH–H_2O to give colorless needles of mp 127—128°. *Anal.* Calcd. for $C_{15}H_{18}O_3N_2$: C, 65.67; H, 6.61; N, 10.21. Found: C, 65.79; H, 6.86; N, 10.44.

3-Methyl-2,4-dioxo-1,2,3,4,6,7-hexahydro-5*H*-cyclopenta[*d*]pyrimidine (**5**)——To a solution of 4.4 g of NaOH in 60 ml of H_2O was added 12 g of **2**, the mixture was warmed for 1 hr on a water bath. The solution was cooled and acidified with conc. HCl. The precipitate was filtered off, washed with H_2O, and recrystallized from MeOH to give 7.3 g of colorless prisms, mp 244°. *Anal.* Calcd. for $C_8H_{10}O_2N_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.97; H, 6.16; N, 16.59.

3-Cyclohexyl-2,4-dioxo-1,2,3,4,6,7-hexahydro-5*H*-cyclopenta[*d*]pyrimidine (**6**)——To a solution of 6 g of NaOH and 150 ml of MeOH was added 25 g of **3**. The mixture was refluxed for 1 hr, and acidified with conc. HCl. The reaction solution was condensed, the precipitate was filtered off, washed with H_2O, and recrystallized from MeOH or dioxan to give 17.6 g of colorless needles, mp>290°. *Anal.* Calcd. for $C_{13}H_{18}O_2N_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.92; H, 7.91; N, 12.25.

2,4-Dioxo-3-phenyl-1,2,3,4,6,7-hexahydro-5*H*-cyclopenta[*d*]pyrimidine (**7**)——a) To a solution of 6 g of NaOH and 150 ml of MeOH was added 24.5 g of **4**. The mixture was refluxed for 1 hr, and treated as described above. Recrystallization from MeOH gave 16 g of colorless needles, mp 288°. *Anal.* Calcd. for $C_{13}H_{12}O_2N_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.71; H, 5.06; N, 12.37.

b) A mixture of 1.8 g (0.05 mole) of phenylurea, 15.6 g (0.1 mole) of **1**, 10 ml of DMF, 8 ml of Ac_2O and 2 drops of conc. H_2SO_4 was allowed to stand at room temperature for 4 days, the reaction solution was dissolved in NaOH solution (40 g of NaOH in 240 ml of H_2O) at 60° with stirring. The mixture was allowed to stand overnight at room temperature and acidified with conc. HCl. The precipitate was filtered off, and recrystallized from MeOH to give 10 g of colorless needles, mp 288°. It was confirmred by infrared (IR) spectra to be identical with the compound **7** obtained above.

c) To a solution of KOH (10 g of KOH in 100 ml of EtOH) was added 1 g of 1-ethoxycarbonylamino-2-(N-phenylcarbamoyl)cyclopentene (**10**), the mixture was heated until **10** was dissolved in solution, cooled, and acidified with conc. HCl. The precipitated product was filtered, washed with H_2O, and recrystallized from MeOH to give 0.6 g of colorless needles, mp 288°. It was confirmed by IR spectra to be identical with the compound (**7**) obtained above.

2-(N-Phenylcarbamoyl)cyclopentanone (**8**)——To a solution of 50 ml of xylene and 2—3 drops of pyridine was added 62.4 g of **1**, the mixture was heated at 140°, and solution of 37.2 g of aniline, 43 ml of xylene

and 2—3 drops of pyridine was added thereto dropwise for 2 hr. The ethanol given off by the reaction is continuously distilled and collected with xylene in a Dean Stark trap. After the dropping, the mixture was further heated for 1 hr, allowed to stand overnight. The precipitated product was filtered and recrystallized from MeOH to give 58 g (71%) of colorless columns, mp 103°. *Anal.* Calcd. for $C_{12}H_{13}O_2N$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.67; H, 6.37; N, 6.91.

1-Amino-2(N-phenylcarbamoyl)cyclopentene (9)——Into 200 ml of benzene was dissolved 20 g of **8**, ammonia gas was passed thereinto for 2 hr. After the introduction of ammonia, the precipitated products was filtered, and recrystallized from MeOH to give 4.0 g of colorless needles, mp 209°. *Anal.* Calcd. for $C_{12}H_{14}ON_2$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.30; H, 6.83; N, 13.88.

1-Ethoxycarbonylamino-2-(N-phenylcarbamoyl)cyclopentene (10)——To a mixture of 2 g of **9**, 0.8 g of pyridine and 20 ml of acetone was added 1.1 g of ethyl chlorocarbonate. The mixture was warmed for 1 hr. Acetone was distilled, H_2O was added to the residue, the insoluble product was filtered, and recrystallized from MeOH to give 2.3 g of colorless needles, mp 144°. *Anal.* Calcd. for $C_{15}H_{18}O_3N_2$: C, 65.67; H, 6.61; N, 10.21. Found: C, 65.93; H, 6.91; N, 10.28.

1,3-Dimethyl-2,4-dioxo-1,2,3,4,6,7-hexahydro-5*H*-cyclopenta[*d*]pyrimidine (11)——a) In an aq. solution of KOH (3.0 g of KOH in 30 ml of H_2O) was dissolved 3.7 g of **5**, 7 g of dimethyl sulfate was added dropwise thereinto, and the mixture was heated on a water bath for 4 hr. After the reaction was completed, the solution was extracted with $CHCl_3$, the extract was recrystallized from petroleum ether to give 2.4 g of colorless needles, mp 78—79°. *Anal.* Calcd. for $C_9H_{12}O_2N_2$: C, 59.98; H, 6.71; N, 15.55. Found: C, 60.30; H, 7.07; N, 15.83.

b) 2,4-Dimethoxy-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (**38**) was heated on an oil bath (250—270°) for 3 hr. The crude product was distilled *in vacuo* to give 2 g of colorless oil, bp_7 163—165°. Recrystallization from petroleum ether gave colorless needles of mp 84—85°. It was confirmed to be identical by a mixed melting point with the compound (**11**) obtained above.

c) To 80 ml of abs. EtOH were suspended 3 g (0.02 mole) of **36**[5] and 5.5 g (0.04 mole) of K_2CO_3, 14.2 g (0.1 mole) of methyl iodide was added thereto. The mixture was refluxed for 20 hr. After the reaction, the precipitate was removed by filtration, the filtrate was evaporated under reduced pressure, and a small amount of ether was added thereto. The product was filtered and recrystallized from ligroin to give 3.4 g (94%) of colorless needles, mp 81—82°. It was confirmed to be identical by a mixed melting point with the compound (**11**) obtained above.

3-Cyclohexyl-1-methyl-2,4-dioxo-1,2,3,4,6,7-hexahydro-5*H*-cyclopenta[*d*]pyrimidine (12)——In a solution of 1 g of NaOH and 40 ml of MeOH was dissolved 10 g of **6**, and 6 g of dimethyl sulfate was added dropwise thereinto. The mixture was refluxed for 5 hr. After the reaction was completed, the mixture was concentrated *in vacuo*, H_2O was added to the residue. The precipitated product was filtered off, and recrystallized from petroleum ether to give 7.2 g of colorless prisms, mp 107—108°. *Anal.* Calcd. for $C_{14}H_{20}O_2N_2$: C, 67.71; H, 8.12; N, 11.28. Found: C, 68.00; H, 8.07; N, 11.36.

1-Methyl-2,4-dioxo-3-phenyl-1,2,3,4,6,7-hexahydro-5*H*-cyclopenta[*d*]pyrimidine (13)——Into a solution of 1 g of NaOH and 20 ml of MeOH was dissolved 4.7 g of **7**, and 3.1 g of dimethyl sulfate was added thereto. The mixture was treated as described above. Recrystallization from EtOH gave 3.7 g of colorless prisms, mp 196—197°. *Anal.* Calcd. for $C_{14}H_{14}O_2N_2$: C, 69.40; H, 5.83; N, 11.56. Found: C, 69.61; H, 5.99; N, 11.09.

1-Carbethoxymethyl-3-methyl-2,4-dioxo-1,2,3,4,6,7-hexahydro-5*H*-cyclopenta[*d*]pyrimidine (14)——To a solution of NaOMe (from 0.25 g of Na and 100 ml of MeOH) was added 16.6 g (0.01 mole) of **5**. The mixture was refluxed for 7 hr with 25 g of ethyl monochloroacetate. Solvent was removed under the reduced pressure, and H_2O was added to the residue. The precipitate was filtered, and the crude product was recrystallized from ligroin to give 7.8 g of colorless needles, mp 111—113°. Anal. Calcd. for $C_{12}H_{16}O_4N_2$: C, 57.12; H, 6.39; N, 11.11. Found: C, 57.32; H, 6.64; N, 11.40.

3-Cyclohexyl-1-carbethoxymethyl-2,4-dioxo-1,2,3,4,6,7-hexahydro-5*H*-cyclopenta[*d*]pyrimidine (15)——**6** (23.4 g, 0.1 mole) was treated with ethyl monochloroacetate (25 g) as described above, the crude product was distilled *in vacuo* to give 22.4 g of light yellow oil, bp_7 233—235°. *Anal.* Calcd. for $C_{17}H_{24}O_4N_2$: C, 63.73; H, 7.55; N, 8.74. Found: C, 63.51; H, 7.39; N, 8.94.

1-Carbethoxymethyl-2,4-dioxo-3-phenyl-1,2,3,4,6,7-hexahydro-5*H*-cyclopenta[*d*]pyrimidine (16)——**7** (22.8 g, 0.1 mole) was treated with ethyl monochloroacetate (25 g) as described in the preparation of **14**. The crude product was recrystallized from MeOH to give 16.9 g of colorless prisms, mp 176°. *Anal.* Calcd. for $C_{17}H_{18}O_4N_2$: C, 64.95; H, 5.77; N, 8.91. Found: C, 64.73; H, 5.96; N, 9.22.

1-Carboxymethyl-1-methyl-2,4-dioxo-1,2,3,4,6,7-hexahydro-5*H*-cyclopenta[*d*]pyrimidine (17)——To 45 ml of 20% HCl was added 4 g of **14**, and the mixture was refluxed for 2 hr. After the reaction, the mixture was cooled on standing, the precipitate was filtered off, and dissolved into 10% aq. solution of Na_2CO_3. The filtrate was acidified with conc. HCl, and the separate crystals were recrystallized from H_2O to give 3.0 g of colorless needles ,mp 212°. *Anal.* Calcd. for $C_{10}H_{12}O_4N_2$: C, 53.57; H, 5.39; N, 12.50. Found: C, 53.43; H, 5.62; N, 12.63.

1-Carboxymethyl-3-cyclohexyl-2,4-dioxo-1,2,3,4,6,7-hexahydro-5*H*-cyclopenta[*d*]pyrimidine(18)——To 60 ml of 20% HCl was added 4.8 g of **15**, the mixture was refluxed for 3 hr, and treated as described above.

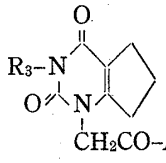
The crude product was recrystallized from H_2O–MeOH to give 3.9 g of colorless plates, mp 108—110°. *Anal.* Calcd. for $C_{15}H_{20}O_4N \cdot H_2O$: C, 58.05; H, 7.15; N, 9.00. Found: C, 58.15; H, 7.30; N, 9.29.

1-Carboxymethyl-2,4-dioxo-3-phenyl-1,2,3,4,6,7-hexahydro-5*H*-cyclopenta[*d*]pyrimidine (19)——To 50 ml of 20% HCl was added 4.7 g of **16**, the mixture was refluxed for 3 hr, and treated as described in preparation of **17**. The crude product was recrystallized from H_2O to give 2.5 g of colorless plates, mp 208—210°. *Anal.* Calcd. for $C_{15}H_{14}O_4N_2$: C, 62.93; H, 4.93; N, 9.79. Found: C, 62.85; H, 5.09; N, 9.49.

3-Substituted 1-Carbamoylmethyl (or Hydrazidomethyl)-2,4-dioxo-1,2,3,4,6,7-hexahydro-5*H*-cyclopenta[*d*]pyrimidine (20—24) (Table II)——a) To a solution of MeOH (30 ml) and conc. NH_4OH (25 ml) was added 0.025 mole of **17**—**19**, and the mixture was heated at 100° for 15—20 hr in a sealed tube. After the reaction, the mixture was cooled, the precipitated product was filtered, and recrystallized from H_2O or MeOH.

b) To a solution of hydrazine hydrate (3 ml) and MeOH (30 ml) was added 0.025 mole of **17** or **19**. The mixture was refluxed for 2 hr, and cooled on standing. The precipitated crystals were filtered off, and recrystallized from MeOH.

TABLE II. 1,3-Disubstituted 2,4-Dioxo-1,2,3,4,6,7-hexahydro-5*H*-cyclopenta[*d*]pyrimidine



Compd.[a] No.	R_3	A	mp (°C)	Yield (%)	Recryst. solvent	Formula		Analysis (%) C	H	N
20	CH_3	NH_2	270	36	H_2O	$C_{10}H_{13}O_3N_3$	Calcd.	53.80	5.87	18.83
							Found	53.57	6.15	18.67
21		NH_2	237	41	MeOH	$C_{15}H_{21}O_3N_3$	Calcd.	61.84	7.27	14.42
							Found	61.60	7.53	14.19
22	C_6H_5	NH_2	226	56	H_2O	$C_{15}H_{15}O_3N_3$	Calcd.	63.15	5.30	14.73
							Found	63.37	5.50	14.95
23	CH_3	NH-NH_2	239	72	MeOH	$C_{10}H_{14}O_3N_4$	Calcd.	50.42	5.92	23.52
							Found	50.52	6.15	23.31
24	C_6H_5	NH-NH_2	222	62	MeOH	$C_{15}H_{16}O_3N_4$	Calcd.	59.99	5.37	18.66
							Found	59.75	5.63	18.95

a) Apprearance: All compounds are colorless needles.

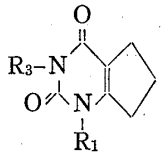
3-Substituted 1-(N,N-Dialkylcarbamoylmethyl)-2,4-dioxo-1,2,3,4,6,7-hexahydro-5*H*-cyclopenta[*d*]pyrimidine (25—33) and 3-Substituted 1-(*β*-Diethylaminoethyl)-2,4-dioxo-1,2,3,4,6,7-hexahydro-5*H*-cyclopenta[*d*]pyrimidine (34, 35) (Table III)——Each 0.04 mole of **5**—**7** was dissolved in EtOH solution of NaOEt (0.04 mole of Na in 100 ml of abs. EtOH), and 0.04 mole of N,N-dimethylchloroacetoamide (5 g), N,N-diethylchloroacetoamide (6 g) or *β*-diethylaminoethyl chloride (5.5 g) was added thereto. The mixture was refluxed for 10—14 hr. After the reaction, the solution was concentrated, and H_2O was added to the residue. The precipitated product was filtered off, and recrystallized.

2,4-Dichloro-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (37)——To 250 ml of $POCl_3$ was added 45 g of 2,4-dioxo-1,2,3,4,6,7-hexahydro-5*H*-cyclopenta[*d*]pyrimidine (**36**),[5] and the mixture was refluxed for 6.5 hr. After the reaction was completed, the solution was concentrated *in vacuo*, ice was added to the residue. The mixture was extracted with ether, the extract was washed with aq. solution of 5% NaOH and further with H_2O. Solvent was evaporated, and the residue was distilled *in vacuo* to give 45 g of oil, bp_{10} 142—143°. Recrystallization from ligroin gave colorless plates of mp 81—82° (lit.[5a] mp 69—70°, lit.[5e] mp 76°). *Anal.* Calcd. for $C_7H_6N_2Cl_2$: C, 44.47; H, 3.20; N, 14.82. Found: C, 44.68; H, 3.40; N, 15.00.

2,4-Dimethoxy-6,7-dihydro-5*H*-cyclopenta[*d*]pyrimidine (38)——In 400 ml of MeOH was dissolved 28.3 g of **37**, a solution of NaOEt (6.9 g of Na in 100 ml of MeOH) was added thereinto, and the mixture was allowed to stand for a day. After the reaction, MeOH was evaporated, aq. solution of 5% NaOH was added to the residue, the mixture was extracted with ether. The extract was distilled *in vacuo* to give 24.8 g of oil, bp_{13} 119—124°. *Anal.* Calcd. for $C_9H_{12}O_2N_2$: C, 59.98; H, 6.71; N, 15.55. Found: C, 60.06; H, 6.94; N, 15.57.

4-Methoxy-1-methyl-2-oxo-1,2,6,7-tetrahydro-5*H*-cyclopenta[*d*]pyrimidine (39)——A mixture of **38** (9 g, 0.05 mole) and methyl iodide (14.2 g, 0.1 mole) was heated at 60—70° for 2—3 hr in a sealed tube. The reaction was evaporated and recrystallized from H_2O to give 7.5 g of colorless needles, mp 161—163°. *Anal.* Calcd. for $C_9H_{12}O_2N_2$: C, 59.98; H, 6.71; N, 15.55. Found: C, 59.79; H, 6.61; N, 15.21.

Table III. 1,3-Disubstituted 2,4-Dioxo-1,2,3,4,6,7-hexahydro-5*H*-cyclopenta[*d*]pyrimidine



Compd. No.	R_1	R_3	mp (°C)	Yield (%)	Appearance (recryst. solv.)	Formula		Analysis (%) C	H	N
25	$-CH_2CONMe_2$	CH_3	150	66	prisms (AcEt)	$C_{12}H_{17}O_3N_3$	Calcd.	57.35	6.82	16.72
							Found	57.08	7.04	16.61
26	$-CH_2CONMe_2$		203	46	prisms (acetone)	$C_{17}H_{25}O_3N_3$	Calcd.	63.92	7.89	13.16
							Found	63.79	7.95	13.37
27	$-CH_2CONMe_2$	C_6H_5	195	42	plates (AcEt)	$C_{17}H_{19}O_3N_3$	Calcd.	65.16	6.11	13.41
							Found	65.44	6.30	13.32
28	$-CH_2CONEt_2$	CH_3	166	33	needles (acetone)	$C_{14}H_{21}O_3N_3$	Calcd.	60.19	7.58	15.04
							Found	60.20	7.73	14.97
29	$-CH_2CONEt_2$		130	60	powders (ligroin)	$C_{19}H_{29}O_3N_3$	Calcd.	65.68	8.41	12.10
							Found	65.52	8.65	12.40
30	$-CH_2CONEt_2$	C_6H_5	153	28	needles (AcEt)	$C_{19}H_{23}O_3N_3$	Calcd.	66.84	6.79	12.31
							Found	67.05	6.89	12.44
31	$-CH_2CONHBu$	CH_3	163	44	needles (AcEt)	$C_{14}H_{21}O_3N_3$	Calcd.	60.19	7.58	15.04
							Found	60.00	7.82	15.33
32	$-CH_2CONHBu$		124	73	needles (ether)	$C_{19}H_{29}O_3N_3$	Calcd.	65.68	8.41	12.10
							Found	65.71	8.38	12.27
33	$-CH_2CONHBu$	C_6H_5	188	51	needles (AcEt)	$C_{19}H_{23}O_3N_3$	Calcd.	66.84	6.79	12.31
							Found	67.10	6.83	12.15
34	$-CH_2CH_2NEt_2$	CH_3	186	70	plates (MeOH-ether)	$C_{14}H_{23}O_2N_3 \cdot HCl$	Calcd.	55.71	8.02	13.92
							Found	55.81	8.25	14.10
35	$-CH_2CH_2NEt_2$	C_6H_5	91	61	prisms (ligroin)	$C_{19}H_{25}O_2N_3$	Calcd.	69.90	7.70	12.84
							Found	69.68	7.78	12.97

1-Methyl-2,4-dioxo-1,2,3,4,6,7-hexahydro-5*H*-cyclopenta[*d*]pyrimidine (**40**)——a) To 40 ml of 20% HCl was added 4 g of **39**, the mixture was refluxed for 2 hr, and cooled on standing. The precipitated product was filtered, and recrystallized from H_2O to give 2.4 g colorless leaflets, mp 247° (lit.,[5d] mp 248—249°). *Anal.* Calcd. for $C_8H_{10}O_2N_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.63; H, 6.32; N, 17.07.

b) Into 100 ml of 10% NaOH solution was dissolved 31 g (0.2 mole) of **36**,[5] 33.4 g (0.2 mole) of dimethyl sulfate was dropped thereinto with stirring, and the mixture was stirred until the reaction solution become neutral. The precipitated product was filtered off, washed with H_2O, and recrystallized from MeOH to give 13 g of colorless leaflets, mp 245—246°. It was confirmed by IR spectra to be identical with the compound (**40**) obtained above.

3-Allyl-1-methyl-2,4-dioxo-1,2,3,4,6,7-hexahydro-5*H*-cyclopenta[*d*]pyrimidine (**41**)——Into a solution of KOH (2 g of KOH in 30 ml of EtOH) was dissolved 5.5 g of **40**, 7.5 g of allyl bromide was added thereto. The mixture was refluxed for 6 hr, and concentrated *in vacuo*. The resulting residue was washed with H_2O, and recrystallized from petroleum ether to give 3.5 g of colorless needles. *Anal.* Calcd. for $C_{11}H_{14}O_2N_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 64.32; H, 7.12; N, 13.62.