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Pyrimidine Derivatives and Related Compounds. XVI.[1] Synthesis of 1,3-Disubstituted 5-Cyanouracil Derivatives and Related Compounds

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Ring closure reactions for synthesizing 1-substituted 5-cyanouracils, 3-substituted 5-cyanouracils, 1-substituted 5-carboxyuracils and 1- substituted 5-acetyluracils were investigated where substitutents were methyl, butyl, phenyl, and cyclohexyl. These compounds were then methylated in 1- or 3-position to give 1,3-disubstituted uracil derivatives which were useful as intermediates for drugs.

The present study has been undertaken in order to investigate a rational method for a synthesis of 1,3-disubstituted uracil derivatives having a cyano group in the 5-position as well as related compounds such as 5-acetyl- and 5-carboxyuracil derivatives. We paid our particular attention on the synthesis of the uracils having phenyl and cyclohexyl in 1- and 3-positions as intermediates of drugs, *e.g.* analgetics, sedatives.

As to 1-substituted 5-cyanouracil derivatives, a method of Shaw[3] or Warrener[4] (Method A) is known (Chart 1). However, the experimental details such as yields of products are ambiguous and so we have traced and checked the above method and improved to some extent. New method named "Method B" (Chart 1) has also been proposed and investigated. These two methods are illustrated below in some detail.

Thus, in Method A, N-ethoxycarbonylcyanoacetamide (**1**) was condensed with ethyl orthoformate or ethyl orthoacetate to give α-cyano-β-ethoxy-N-ethoxycarbonylacrylamide (**2**) or α-cyano-β-ethoxy-N-ethoxycarbonylcrotonamide (**3**) respectively, and each of them was made to react with aniline or cyclohexylamine.

When **2** was made to react with aniline, an intermediate β-anilino-α-cyano-N-ethoxycarbonylacrylamide (**4**) was produced and further heating of **4** in tetralin resulted in a ring closure giving 5-cyano-1-phenyluracil (**7**). Besides, the reaction of **2** with cyclohexylamine caused a direct condensation and a ring closure to afford 5-cyano-1-cyclohexyluracil (**8**) without a production of an intermediate.

When **3** was treated with aniline or cyclohexylamine, an intermediate **5** or **6**, respectively, was produced. They were heated in tetralin or subjected to a ring closure in an alkaline condition, 5-cyano-6-methyl-1-phenyluracil (**9**) and 5-cyano-1-cyclohexyl-6-methyluracil (**10**) were obtained respectively. The yield of products was higher in the latter ring closure method than in the former heating treatment.

In Method B, cyanoacetic acid was subjected to a dehydrating condensation with monosubstituted ureas (substituents: phenyl, cyclohexyl, methyl, butyl) in acetic anhydride, the resulting 1-substituted 3-cyanoacetylureas (**13**—**16**) were treated with DMF-DMS complex[5] and, *via* intermediates (**17**—**20**), the desired 1-substituted 5-cyanouracils (**7**, **8**, **11**, and **12**) were synthesized.

1) Part XV: S. Senda, K. Hirota and K. Banno, *J. Med. Chem.*, **15**, 471 (1972).
2) Location: *Mitahora, Gifu.*
3) *a*) G. Shaw, *J. Chem. Soc.*, **1955**, 1834; *b*) M.R. Atkinso, G. Shaw and R.N. Warrener, *J. Chem, Soc.*, **1956**, 4118.
4) R.N. Warrener, *Chem. Ind.*, **1966**, 381.
5) H. Bredereck, F. Effenberger and G. Simchen, *Chem. Ber.*, **96**, 1354 (1963); [DMF: $(CH_3)_2N\cdot CHO$; DMS: $(CH_3)_2SO_4$].

Yields in each step and those in total in Methods A and B are given in Table I. It is apparent that the Method A gave better results in general.

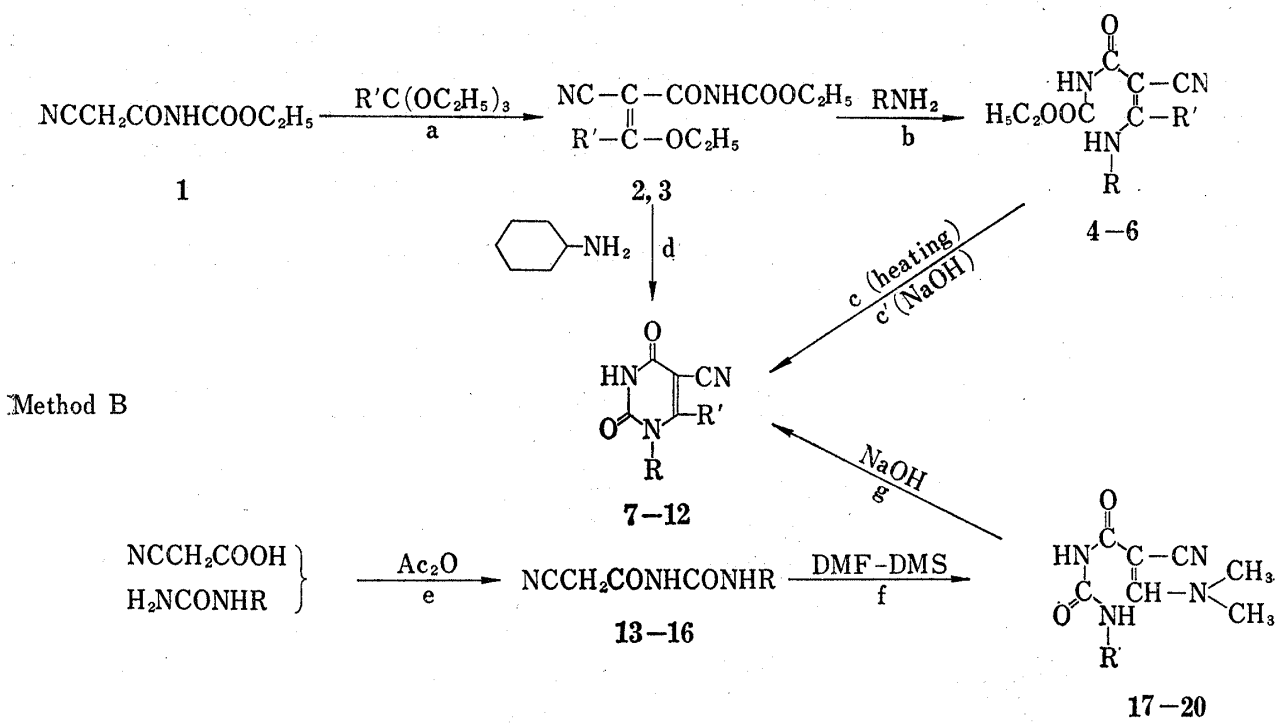
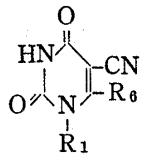


Chart 1

TABLE I. Process Yields and Total Yields of 1-Substituted 5-Cyanouracils



Method	Compd. No.	R_1	R_6	Process yeild (%) a	b	c (c')	d	Total yield (%)
A	7	C_6H_5	H	92	90	80		66
	8	⬡	H	92			93	86
	9	C_6H_5	CH_3	99	82	80 (90)		65 (73)
	10	⬡	CH_3	99	81	50 (95)		40 (76)
				e	f	g		
B	7	C_6H_5	H	90	33	80		24
	8	⬡	H	70	63	80		35
	11	CH_3	H	56	61	80		27
	12	C_4H_9	H	66	62	87		36

In synthesis of 3-substituted 5-cyanouracil derivatives, "Method C" (Chart 2) was carried out.[6] Thus, malononitrile, ethyl orthoformate and monosubstituted ureas (substituents:

6) *a*) C.W. Whitehead and J. Trauerso, *J. Am. Chem. Soc.*, 77, 5867 (1955); *b*) *idem*, *ibid.*, 75, 671 (1953).

phenyl, cyclohexyl) were heated and the resulting (3-substituted ureido)-methylenemalononitriles (**21**, **22**) were subjected to a ring closure in the presence of sodium ethoxide to give 3-substituted 5-cyanocytosines (**23**, **24**). They were hydrolyzed in HCl to afford desired 3-substituted 5-cyanouracils (**25**, **26**).

Another method (Method D) was also done (Chart 2). Thus, ethyl cyanoacetate, ethyl orthoformate and monosubstituted ureas (substituents: phenyl, cyclohexyl) were heated and the intermediate condensates (**27**, **28**) were subjected to a ring closure as in the Method C. As a result, **27** afforded 5-cyano-3-phenyluracil (**25**) and 5-ethoxycarbonyl-3-phenylcytosine (**29**) in comparatively high yields while **28** did not afford the expected products but only small amount of a side product-3-cyclohexyl-5-ethoxycarbonylcytosine (**30**) was isolated.

Yields in each step and those in total in Methods C and D are given in Table II from which the Method C seems to be a practical one.

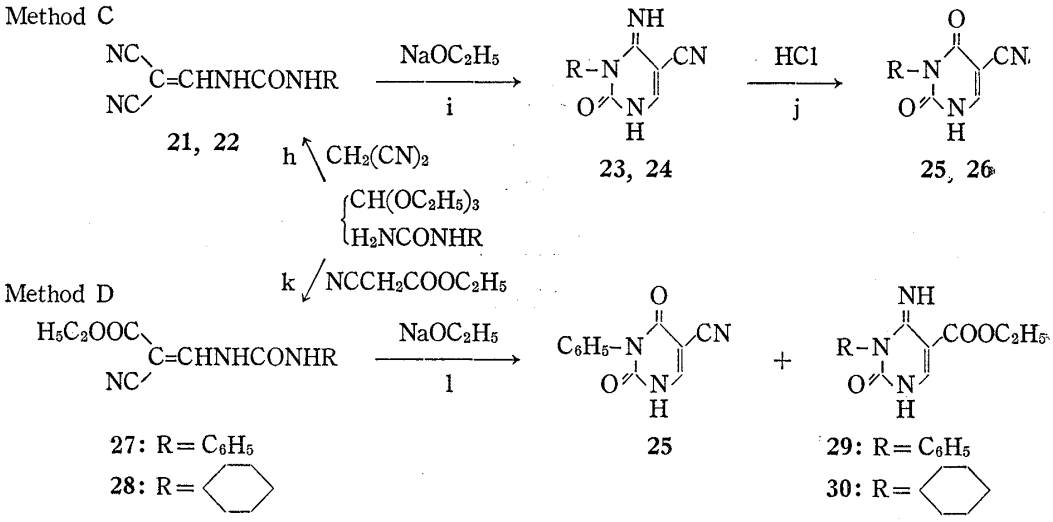
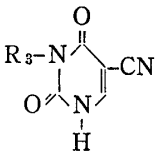


Chart 2

TABLE II. Process Yields and Total Yields of 3-Substituted 5-Cyanouracils



Method	Compd. No.	R_3	Process yield (%) h	i	j	Total yield (%)
C	25	C_6H_5	73	90	60	39
	26		82	92	42	31
			k	l		
D	25	C_6H_5	90	68		62
	26		90	0[a]		0

a) 3-Cyclohexyl-5-ethoxycarbonylcytosine (**30**) was obtained.

Synthesis of the following compounds which are related ones with the above 1- or 3-substituted 5-cyanouracil derivatives was also attempted.

Thus, for example, 1-substituted 5-carboxyluracil derivatives were synthesized as follows. Monoethyl malonate and urethane were condensed in acetic anhydride, the resulting α,N-

bis(ethoxycarbonyl)acetamide (**31**) was condensed with ethyl orthoformate and the resulting α,N-bis(ethoxycarbonyl)-β-ethoxyacrylamide (**32**) was heated with aniline or cyclohexylamine, whereupon the ring closure took place giving 1-substituted 5-ethoxycarbonyluracils (**33**, **34**). Or, ethyl β-cyclohexylaminocrotonate[7] was treated with ethoxycarbonyl isocyanate,[8] the resulting α,N-bis(ethoxycarbonyl)-β-cyclohexylaminocrotonamide (**35**) was warmed in 10% aqueous sodium hydroxide solution, and was subjected to a ring closure to give 1-cyclohexyl-5-ethoxycarbonyl-3-methyluracil (**36**).

1-Substituted 5-acetyluracil derivatives were synthesized by similar routes as reported by Shaw, *et al.*[9] Thus, α-acetyl-β-ethoxy-N-ethoxycarbonylacrylamide (**37**) was heated to reflux in ethanol with aniline, methylamine, propylamine or cyclohexylamine to give 1-substituted 5-acetyluracils (**38**—**41**) in high yields such as 83—98% (Chart 3).

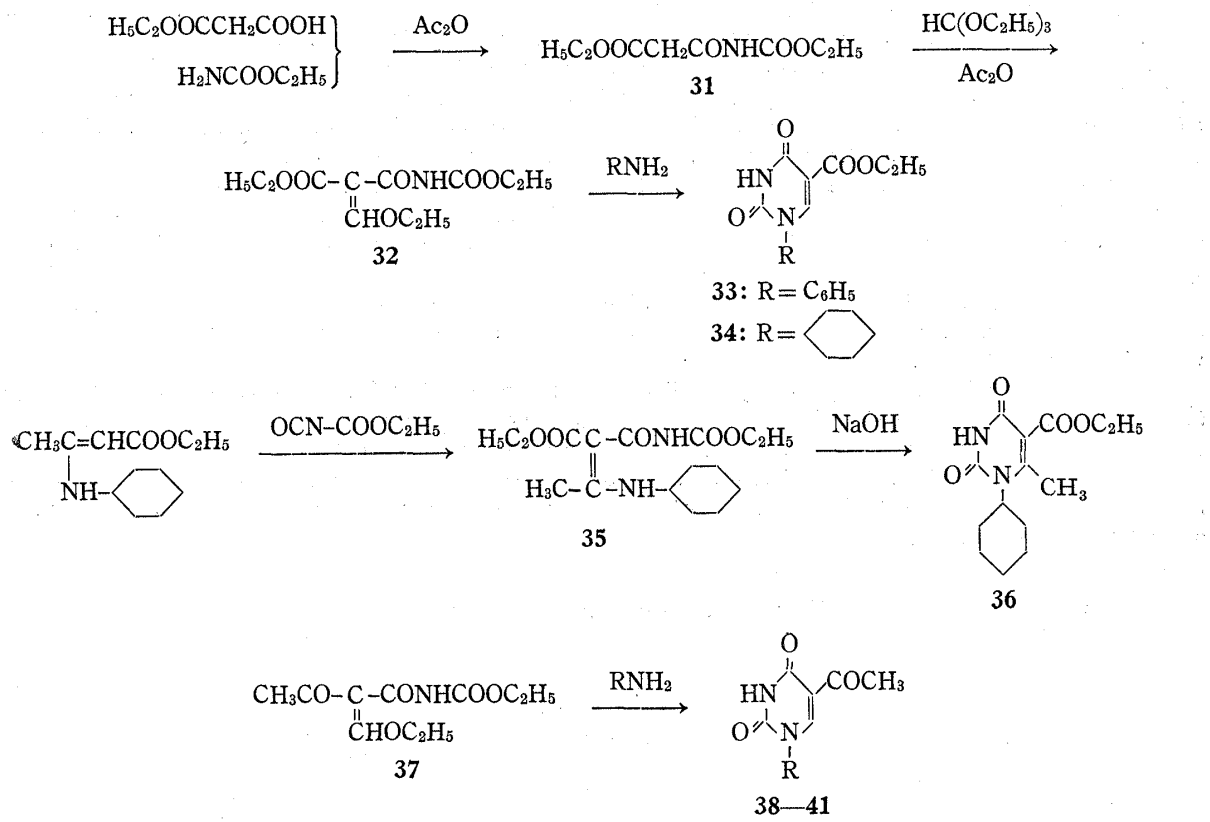


Chart 3

1-Substituted 5-cyanouracil derivatives (**7**—**11**), 3-substituted 5-cyanouracil derivatives (**25**, **26**), 1-cyclohexyl-5-ethoxycarbonyl-6-methyluracil (**36**) and 5-acetyluracil derivatives (**38**, **39**, **41**) obtained as above were methylated with dimethyl sulfate in an alkaline condition whereupon nitrogen atom at 1- or 3-position was methylated and 1,3-disubstituted uracil derivatives (**42**—**45**) (Table VII) were produced.

Experimental

α-Cyano-β-ethoxy-N-ethoxycarbonylacrylamide (**2**)——To 120 g (0.8 mole) of ethyl orthoformate and 125 g (0.8 mole) of N-ethoxycarbonylcyanoacetamide (**1**)[3b] was added 300 ml of Ac_2O, the mixture was heated to reflux for 1 hr, concentrated *in vacuo*, and the residue solidified on standing was washed with ether and filtered to give 150 g (92%) of a crude product, mp 110—115°. Recrystallization from acetone–

7) A. Skita and C. Wueff, *Ann.*, **453**, 207 (1927).
8) R.W. Lamon, *J. Heterocyclic Chem.*, **6**, 261 (1969).
9) J.H. Dewar and G. Shaw, *J. Chem. Soc.*, **1961**, 3254.

ether mixture gave colorless needles of mp 123° (lit.[3a] mp 120°). *Anal.* Calcd. for $C_9H_{12}O_4N_2$: C, 50.94; H, 5.70; N, 13.20. Found: C, 51.04; H, 5.85; N, 13.36.

α-Cyano-β-ethoxy-N-ethoxycarbonylcrotonamide (3)——A mixture of 33 g (0.2 mole) of ethyl orthoacetate and 31 g (0.2 mole) of **1** was heated to reflux for 1 hr in 100 ml of Ac_2O and treated as same as above to give 45 g (99%) of a crude product, mp 98—100°. Recrystallization from benzene gave colorless plates of mp 134°. *Anal.* Calcd. for $C_{10}H_{14}O_4N_2$: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.04; H, 6.31; N, 12.36.

β-Anilino-α-cyano-N-ethoxycarbonylacrylamide (4)——60 g (0.28 mole) of **2** was dissolved in 200 ml of EtOH, 31 g (0.3 mole) of aniline was added thereto, crystals appeared on cooling were filtered off, and washed with EtOH to give 65 g (90%) of a crude product, mp 170—180°. Recrystallization from EtOH gave colorless needles, mp 180—183° (lit.[3a] mp 170°). *Anal.* Calcd. for $C_{13}H_{13}O_3N_3$: C, 60.22; H, 5.05; N, 16.21. Found: C, 60.45; H, 5.24; N, 16.37.

β-Anilino-α-cyano-N-ethoxycarbonylcrotonamide (5)——To 50 ml of EtOH was added 22.6 g (0.1 mole) of **3**, the mixture was heated at 70—80° so that **3** was dissolved, then 9.3 g (0.1 mole) of aniline was gradually added thereto, the mixture was cooled on standing, the precipitated crystals were filtered off, washed with ether and recrystallized from AcOEt to give 20 g (82%) of colorless prisms, mp 161°. *Anal.* Calcd. for $C_{14}H_{15}O_3N_3$: C, 61.53; H, 5.53; N, 15.38. Found: C, 61.39; H, 5.35; N, 15.14.

α-Cyano-β-cyclohexylamino-N-ethoxycarbonylcrotonamide (6)——In 50 ml of EtOH was dissolved 22.6 g (0.1 mole) of **3** by the same way as above and then 9.9 g (0.1 mole) of cyclohexylamine was gradually added thereto. Recrystallization from EtOH gave 21.5 g (81%) of colorless prisms, mp 116°. *Anal.* Calcd. for $C_{14}H_{21}O_3N_3$: C, 60.19; H, 7.38; N, 15.04. Found: C, 60.02; H, 7.44; N, 15.00.

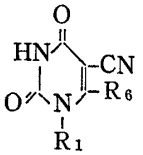
1-Substituted 5-Cyanouracils (7—12) (Table I and III)——i) Process c: To 100 ml of tetralin was added 0.1 mole of **4**, **5**, or **6** and the mixture was heated at 185—200° for 30 min, cooled on standing, filtered, the separated product was washed with ether and recrystallized from a suitable solvent to give **7**, **9** or **10** respectively.

ii) Process c′: Each 0.2 mole of **5** or **6** was dissolved in 85 ml of 10% aq. NaOH solution by heating at 80—90°, then the mixture cooled on standing, acidified with HCl, the crude product was filtered off, washed with H_2O to give **9** or **10**.

iii) Process d: 5-Cyano-1-cyclohexyluracil (**8**): In 150 ml of EtOH on heating, was dissolved **2** (55 g, 0.26 mole), thereto 27 g (0.27 mole) of cryclohexylamine was gradually added, the mixture was heated to reflux for 10 min more, cooled on standing, and filtered off to give 56 g (93%) of a crude product.

iv) Process g: Each 0.1 mole of **17—20** was added to 100 ml of 10% aq. NaOH solution, the resulting solution was made acidic with HCl on cooling at 0—10°, and the separated product (**7**, **8**, **11**, **12**) was filtered off and washed with H_2O.

Table III. 1-Substituted 5-Cyanouracils



Compd. No.	R_1	R_6	Recryst.[a] solv.	mp (°C)	Formula	Analysis(%) Calcd. C	H	N	Found C	H	N
7	C_6H_5	H	EtOH	298[b]	$C_{11}H_7O_2N_3$	61.97	3.31	19.71	62.00	3.41	19.97
8		H	dioxane	>300[c]	$C_{11}H_{13}O_2N_3$	60.26	5.98	19.15	60.46	5.96	19.17
9	C_6H_5	CH_3	AcOH	>300[d]	$C_{12}H_9O_2N_3$	63.43	3.99	18.49	63.28	4.42	18.35
10		CH_3	AcOEt	296	$C_{12}H_{15}O_2N_3$	61.78	6.48	18.02	61.68	6.60	17.92
11	CH_3	H	EtOH	267	$C_6H_5O_2N_3$	47.68	3.34	27.81	47.76	3.55	27.97
12	C_4H_9	H	AcOH	187[e]	$C_9H_{11}O_2N_3$	55.95	5.74	21.75	55.68	5.77	21.67

a) Appearance of all compounds is colorless needles. *b*) Lit.[3a] mp 290°
c) Lit.[3b] mp 324° *d*) Lit.[4] mp 332—334° *e*) Lit.[3b] mp 190°

1-Substituted 3-Cyanoacetylureas (13—16) (Tabel IV)——Ac_2O (100 ml) was added to 0.2 mole of monosubstitutedurea and 0.2 mole of cyanoacetic acid, the mixture was heated at 60° for 30 min, cooled on standing, the precipitated crystals were filtered off, washed with ether and recrystallized from a suitable solvent.

Table IV. 1-Substituted 3-Cyanoacetylureas

R-NHCONHCOCH$_2$CN

Compd. No.	R	mp (°C)	Appearance[a] (Recryst. solv.)	Yield (%)	Formula		Analysis (%) C	H	N
13	C_6H_5	223	needles (MeOH)	90	$C_{10}H_9O_2N_3$	Calcd.	59.10	4.40	20.68
						Found	59.40	4.53	20.85
14		164	prisms (AcOEt)	70	$C_{10}H_{15}O_2N_3$	Calcd.	57.40	7.23	20.03
						Found	57.52	7.21	20.19
15	CH_3	217	needles (EtOH)	56	$C_5H_7O_2N_3$	Calcd.	42.55	5.00	29.78
						Found	42.27	5.12	29.82
16	C_4H_9	156	needles (MeOH)	66	$C_8H_{13}O_2N_3$	Calcd.	52.44	7.15	22.94
						Found	52.19	7.23	23.01

a) All compounds are colorless crystals.

1-Substituted 3-Cyano-(dimethylaminomethylene)acetylureas (17—20) (Table V)——Each 0.1 mole of **13** to **16** was dissolved in 50 ml of DMF, 24 g of a complex[5] of DMF and DMS was added, the mixture was kept at 0°, and 12 g of triethylamine kept at 0—10° was gradually dropped thereinto with stirring. The mixture was stirred at room temperature for 2 hr, the precipitated crystals were filtered off, washed with ether or with benzene, and recrystallized from a suitable solvent.

Table V. 1-Substituted 3 (Dimethylaminomethylene)-cyanoacetylureas

R-NHCONHCO-C-CN
‖
CH-N(CH$_3$)$_2$

Compd. No.	R	mp (°C)	Appearance[a] (Recryst. solv.)	Yield (%)	Formula		Analysis(%) C	H	N
15	C_6H_5	152	prisms (ether–acetone)	33	$C_{13}H_{14}O_2N_4$	Calcd.	60.45	5.46	21.70
						Found	60.65	5.47	21.48
16		152	needles (MeOH–H_2O)	63	$C_{13}H_{20}O_2N_4$	Calcd.	59.07	7.63	21.20
						Found	59.18	7.58	21.02
17	CH_3	173	prisms (H_2O)	61	$C_8H_{12}O_2N_4$	Calcd.	48.97	6.17	28.56
						Found	48.74	6.14	28.80
18[b]	C_4H_9	(117)	—	(62)	$C_{11}H_{18}O_2N_4$	—	—	—	—

a) All compounds are colorless crystals.
b) During the course of purifying a curde **18**, a ring closure proceeded resulting in a production of 1-butyl-5-cyanouracil (**12**).

(3-Phenylureidomethylene)-malononitrile (21)——A mixture of 13.2 g (0.2 mole) of malononitrile, 30 g (0.2 mole) of ethyl orthoformate and 27 g (0.2 mole) of phenylurea was heated to reflux for 30—60 min. Crystals began to crystallize druring the reaction. After the reaction, the mixture was cooled on standing, the crystals were filtered off, washed with ether, and recrystallized from MeOH to give 31 g (73%) of colorless needles, mp 180—190° (decomp). *Anal.* Calcd. for $C_{11}H_8ON_4$: C, 62.25; H, 3.80; N, 26.40. Found: C, 62.32; H, 3.97; N, 26.38.

(3-Cyclohexylureidomethylene)-malononitrile (22)——A mixture of 13.2 g (0.2 mole) of malononitrile, 30 g (0.2 mole) of ethyl orthoformate and 28.4 g (0.2 mole) of cyclohexylurea was heated to reflux for 30—60 min. After the reaction, the mixture was cooled on standing, the precipitated product was filtered off, washed with ether, and recrystallized from AcOEt to give 36 g (82%) of colorless needles, mp 227° (decomp) (lit.[6b] mp 219°). *Anal.* Calcd. for $C_{11}H_{14}ON_4$: C, 60.53; H, 6.47; N, 25.67. Found: C, 60.80; H, 6.73; N, 25.60.

5-Cyano-3-phenylcytosine (23)——Na (23 g) was dissolved in 600 ml of abs. EtOH, 21 g of **21** was dissolved therein, and the mixture was heated to reflux for 30—80 min to separate out a sodium salt of the desired product. After the reaction, EtOH was removed by evaporation, the residue was dissolved in 500 ml of H_2O, the solution was neutralized with HCl or with AcOH, the precipitated crystals were filtered off, washed with H_2O and recrystallized from a mixture of DMF and H_2O to give 19 g (90%) of colorless needles, mp 290° (decomp) (lit.[6a] 275°). *Anal.* Calcd. for $C_{11}H_8ON_4$: C, 62.25; H, 3.80; N, 26.40. Found: C, 62.53; H, 3.80; N, 26.59.

5-Cyano-3-cyclohexylcytosine (24)——Na (23 g) was dissolved in 600 ml of abs. EtOH, then 22 g of **22** was dissolved therein and the mixture was treated as same as above. Recrystallization from EtOH gave 20 g (92%) of colorless plates, mp 249°. *Anal.* Calcd. for $C_{11}H_{14}ON_4$: C, 60.53; H, 6.47; N, 25.67. Found: C, 60.53; H, 6.72; N, 25.67.

5-Cyano-3-phenyluracil (25)——A suspension of **23** (21.2 g) and 12% HCl (50 ml) was heated to reflux for 5 hr, cooled on standing, the precipitated product was filtered off, washed with H_2O and recrystallized from MeOH to give 12.8 g (60%) of colorless prisms, mp >300°. *Anal.* Calcd. for $C_{11}H_7O_2N_3$: C, 61.97; H, 3.31; N, 19.71. Found: C, 62.13; H, 3.10; N, 19.53.

5-Cyano-3-cyclohexyluracil (26)——A mixture of **24** (21.8 g) and 12% HCl (50 ml) was heated to reflux for 5 hr, cooled on standing, the precipitated product was filtered off, washed with H_2O and recrystallized from MeOH to give 8.8 g (40%) of colorless needles, mp 220° (lit[6a] 231°). *Anal.* Calcd. for $C_{11}H_{13}O_2N_3$: C, 60.26; H, 5.98; N, 19.15. Found: C, 60.24; H, 5.99; N, 18.78.

Ethyl Cyano(3-phenylureidomethylene)-acetate (27)——A mixture of 11.3 g (0.1 mole) of ethyl cyanoacetate, 15 g (0.1 mole) of ethyl orthoformate and 13.5 g (0.1 mole) of phenylurea was heated to reflux for 2 hr, concentrated *in vacuo*, the concentrate was filtered off, the resulting mass was well washed with ether and recrystallized from EtOH to give 23.4 g (90%) of colorless plates, mp 225°. *Anal.* Calcd. for $C_{13}H_{13}O_3N_3$: C, 60.22; H, 5.05; N, 16.21. Found: C, 60.17; H, 5.10; N, 16.40.

Ethyl Cyano(3-cyclohexylureidomethylene)-acetate (28)——A mixture of 11.3 g (0.1 mole) of ethyl cyanoacetate, 15 g (0.1 mole) of ethyl orthoformate and 14.2 g (0.1 mole) of cyclohexylurea was heated to reflux for 2 hr, then treated as same as above and finally recrystallized from MeOH and H_2O to give 21.2 g (80%) of colorless plates, mp 163° (lit[6b] mp 156°). *Anal.* Calcd. for $C_{13}H_{19}O_3N_3$: C, 58.85; H, 7.22; N, 15.84. Found: C, 58.81; H, 7.30; N, 16.06.

5-Cyano-3-phenyluracil (25); **5-Ethoxycarbonyl-3-phenylcytosine (29)**——Na (9.2 g, 0.4 mole) was dissolved in 500 ml of abs. EtOH, 104 g (0.4 mole) of **27** was added thereto, the mixture was heated to reflux for 4 hr, EtOH was distilled off *in vacuo*, the residue was suspended in 600 ml of H_2O, the suspension was neutralized with HCl to adjust to pH 6, the resulting crude crystals were filtered off, washed with H_2O and 90 g of crude product, mp 205—222°, was obtained. It was let stand overnight with 500 ml of 48% HBr, an insoluble residue was filtered off, and washed with H_2O to give 54 g (64%) of crude 5-cyano-3-phenyluracil (**25**), mp 252—255°. Recrystallization from MeOH gave colorless prisms of mp >300°. It was compared with the **25** obtained by the Method C and confirmed to be identical with the **25** by an IR comparison.

When the filtrate after an addition of HBr in the above procedure was made weakly alkaline with satd. aq. solution of Na_2CO_3, crystals appeared. They were filtered off and washed with H_2O to give 22.5 g (22%) of crude 5-ethoxycarbonyl-3-phenylcytosine (**29**), mp 160—180°. Recrystallization from MeOH and H_2O gave colorless needles of mp 200°. *Anal.* Calcd. for $C_{13}H_{15}O_4N_3$: C, 56.31; H, 5.54; N, 15.16. Found: C, 57.04; H, 5.58; N, 14.99.

1-Cyclohexyl-5-ethoxycarbonylcytosine (30)——Na (8.0 g) was dissolved in 350 ml of abs. EtOH, 80 g (0.3 mole) of **28** was added thereto, and the mixture was heated to reflux for 2 hr. After the reaction, EtOH is evaporated *in vacuo*, the residue was dissolved in 500 ml of H_2O, the solution was neutralized with HCl and an oily product separated out. It was taken out, extracted with ether, and crude crystals which were insoluble in ether were filtered off to give 15 g (19%) of a crude product, mp 230—245°. This was dissolved in DMF, the solution was chromatographed on an active alumina and recrystallized from EtOH to give colorless needles of mp 245°. *Anal.* Calcd. for $C_{13}H_{19}O_3N_3$: C, 58.85; H, 7.22; N, 15.84. Found: C, 58.68; H, 7.14; N, 15.80.

α, N-Bis-(ethoxycarbonyl)-acetamide (31)——Ac_2O (120 ml) was added to a mixture of 89 g (1 mole) of urethane and 132 g (1 mole) of monoethyl malonate and the mixture was heated at 70—75° for 3—4 hr. After the reaction, the mixture was concentrated *in vacuo*, petroleum ether was added to an oily residue, and the mixture was let stand to give 133 g (65%) of solid crude product, mp 45—47°. Recrystallization from ligroin gave colorless needles of mp 55°. *Anal.* Calcd. for $C_8H_{13}O_5N$: C, 47.29; H, 6.45; N, 6.89. Found: C, 46.99; H, 6.21; N, 6.82.

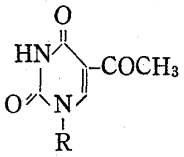
α, N-Bis-(ethoxycarbonyl)-β-ethoxyacrylamide (32)——To 10.5 g (0.05 mole) of **31** were added 7.4 g (0.05 mole) of ethyl orthoformate and 25 ml of Ac_2O, the mixture was heated to reflux for 1 hr, concentrated *in vacuo*, ligroin was added to the concentrate, and the mixture was let stand to give 7.0 g (54%) of solid crude product, mp 105—110°. Recrystallization from ligroin gave colorless needles of mp 121—122°. *Anal.* Calcd. for $C_{11}H_{17}O_6N$: C, 50.96; H, 6.61; N, 5.40. Found: C, 51.25; H, 6.80; N, 5.66.

5-Ethoxycarbonyl-3-phenyluracil (33)——To a solution of **32** (5.2 g) and 12 ml of EtOH was added 2 g of aniline and the mixture was heated to reflux for 1—2 hr. After the reaction, the mixture was cooled on standing, the precipitated crystals were filtered off, washed with EtOH and recrystallized from EtOH to give 4.4 g (85%) of colorless needles, mp 250°. *Anal.* Calcd. for $C_{13}H_{12}O_4N_2$: C, 59.99; H, 4.65; N, 10.77. Found: C, 60.28; H, 4.87; N, 10.70.

5-Ethoxycarbonyl-3-cyclohexyluracil (34)——To a solution of **32** (5.2 g) and 12 ml of EtOH was added 2 g of cyclohexylamine and the mixture was treated as same as above. Recrystallization of a crude product from EtOH gave 3.7 g (70%) of colorless needles, mp 226°. *Anal.* Calcd. for $C_{13}H_{18}O_4N_2$: C, 58.63; H, 6.81; N, 10.52. Found: C, 58.12; H, 6.82; N, 10.26.

α,N-Bis-(ethoxycarbonyl)-β-cyclohexylaminocrotonamide (35)——Ethyl β-cyclohexylaminocrotonate[7] (21.1 g, 0.1 mole) was dissolved in 100 ml of anhydrous ether and, during the solution was kept at 0° with stirring, a solution of 13.5 g (0.12 mole) of ethoxycarbonyl isocyanate[8] in 20 ml of anhydrous ether was gradually dropped thereinto. The mixture was then stirred for 2—3 hr with ice-cooling. After the reaction, ether was evaporated and the residue was washed with petroleum ether to give 32 g (99%) of solid crude product, mp 55—61°. Recrystallization from petroleum ether gave colorless prisms, mp 64°. *Anal.* Calcd. for $C_{16}H_{26}O_5N_2$: C, 58.88; H, 8.08; N, 8.58. Found: C, 58.74; H, 7.88; N, 8.79.

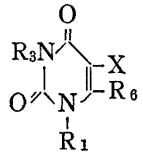
TABLE VI. 1-Substituted 5-Acetyluracils



Compd. No.	R	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
38[a]	C_6H_5	277	83	$C_{12}H_{10}O_3N_2$	62.60	4.38	12.17	62.82	4.51	12.23
39	CH_3	243[b]	98	$C_7H_8O_3N_2$	50.00	4.80	16.66	50.11	5.06	16.72
40	C_4H_9	182	67	$C_9H_{12}O_3N_2$	55.09	6.17	14.28	54.96	6.05	14.45
41		265	89	$C_{12}H_{16}O_3N_2$	61.00	6.38	11.86	61.21	6.76	11.80

a) This compound is prepared *via* a intermediate, α-acetyl-β-anilino-N-ethoxycarbonylacrylamide on referring to the report of Show[9] (lit.mp 269°). b) Lit[9] mp 234°

TABLE VII. 1,3-Disubstituted 5-Cyanouracils and Related Compounds



Compd. No.	R_1	R_3	R_6	X	Appearance[a] (Recryst. solv.)	mp (°C)	Yield (%)	Formula		Analysis (%) C	H	N
42	C_6H_5	CH_3	H	CN	needles (MeOH)	243[b]	95	$C_{12}H_9O_2N_3$	Calcd.	63.43	3.99	18.49
									Found	63.61	4.20	18.67
43		CH_3	H	CN	needles (EtOH)	180	90	$C_{12}H_{15}O_2N_3$	Calcd.	61.78	6.48	18.02
									Found	61.96	6.47	18.31
44	C_6H_5	CH_3	CH_3	CN	needles (AcOEt)	237	67	$C_{13}H_{11}O_2N_3$	Calcd.	64.72	4.60	17.42
									Found	64.84	4.80	17.48
45		CH_3	CH_3	CN	needles (MeOH)	217	77	$C_{15}H_{17}O_2N_3$	Calcd.	63.14	6.93	16.99
									Found	63.31	7.11	16.61
46	CH_3	CH_3	H	CN	needles (EtOH)	160	81	$C_7H_7O_2N_3$	Calcd.	50.91	4.27	25.46
									Found	50.86	4.31	25.40
47	CH_3	C_6H_5	H	CN	needles (MeOH)	253	98	$C_{12}H_9O_2N_3$	Calcd.	63.43	3.99	18.49
									Found	63.31	4.12	18.34
48	CH_3		H	CN	needles (AcOEt)	204[c]	85	$C_{12}H_{15}O_2N_3$	Calcd.	61.78	6.48	18.02
									Found	61.70	6.41	18.20
49		CH_3	CH_3	$COOC_2H_5$	needles (ligroin)	120	95	$C_{15}H_{22}O_4N_2$	Calcd.	61.20	7.53	9.52
									Found	61.09	7.58	9.45
50	C_6H_5	CH_3	H	$COCH_3$	needles (MeOH)	160	88	$C_{13}H_{12}O_3N_2$	Calcd.	63.92	4.95	11.47
									Found	63.86	5.15	11.56
51	CH_3	CH_3	H	$COCH_3$	needles (MeOH)	175	91	$C_8H_{10}O_3N_2$	Calcd.	52.74	5.53	15.38
									Found	52.87	5.62	15.52
52		CH_3	H	$COCH_3$	plates (EtOH)	132	80	$C_{13}H_{18}O_3N_2$	Calcd.	62.38	7.47	11.19
									Found	62.45	7.25	11.47

a) All compounds are colorless crystals. b) Lit.[3b] mp 235° c) Lit.[6a] mp 175°

1-Cyclohexyl-5-ethoxycarbonyl-6-methyluracil (36)——To 150 ml of 10% aq. solution of NaOH was added **35** (32 g), the mixture was heated at 80—90°, the resulting solution was cooled on standing, neutralized with HCl, the precipitated product was filtered off and washed with H_2O to give 20 g (72%) of crude product, mp 145—160°. Recrystallization from acetone and H_2O gave colorless needles, mp 167—169°. *Anal.* Calcd. for $C_{14}H_{20}O_4N_2$: C, 59.98; H, 7.19; N, 9.99. Found: C, 60.22; H, 7.39; N, 10.09.

5-Acetyl-1-alkyluracil (39—41) (Table VI)——α-Acetyl-β-ethoxy-N-ethoxycarbonylacrylamide (**37**) (23 g, 0.1 mole) was dissolved in 200 ml of EtOH, the solution was heated to reflux for 20—30 min with 0.1 mole of alkylamine, cooled on standing, the resulting precipitate was filtered off, and recrystallized from EtOH or AcOEt to give colorless needles.

Methylation of 5-Cyanouracil Derivatives and Related Compounds (42—52) (Tabel VII)——1-Substituted 5-cyanouracil (**7—11**), 3-substituted 5-cyanouracil (**25, 26**), 1-cyclohexyl-5-ethoxycarbonyl-6-methyluracil (**36**) or 1-substituted 5-acetyluracil (**38, 39, 41**) (each 0.1 mole) was dissolved or suspended in 80 ml of 5% NaOH solution, 12.6 g (0.1 mole) of dimethyl sulfate was dropped thereinto with stirring, and the mixture was stirred for 1—4 hr. When the reaction solution became neutral, the precipitated crystals were filtered off, washed with H_2O and recrystallized from a suitable solvent.