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Pyrimidine Derivatives and Related Compounds. XIV.[1] The Synthesis of N-Substituted Pyrazolo[3,4-*d*]pyrimidines from Pyrimidine Derivatives

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Reactions of 1,3-disubstituted 6-chloro-5-formyluracils (**1**) with phenylhydrazine or methylhydrazine giving 1,5,7- and 2,5,7-trisubstituted 4,6-dioxo-4,5,6,7-tetrahydropyrazolo[3,4-*d*]pyrimidines (**3**, **7** and **4**) were investigated in detail. It was found out that 5-formyl group in **1** was more reactive than that 6-chloro group. Thus, under cold condition, the reaction of **1** with phenylhydrazine yielded Schiff's bases (**2**). Upon heating, **1** with equimolar or two equivalent moles of phenylhydrazine gave isomeric compounds, **3** and **4**, which were also prepared by other routes. Reactions of methylhydrazine with **1** were also investigated. Furthermore, the Schiff's bases were made to react with other kinds of hydrazines. The reaction products showed that substituent at 1- or 2-position of the products (**4**, **7**) depended on the kind of hydrazine used later.

In the previous paper,[1] we reported synthesis of some N-substituted pyrazolo[3,4-*d*]-pyrimidines from pyrazole derivatives. In order to investigate such N-substituted compounds further, present study to synthesize them from N-substituted pyrimidine was undertaken. There have already been many papers[3] on the synthesis of pyrazolo[3,4-*d*]pyrimidines from the pyrimidine derivatives. In the present study, we have chosen 1,3-disubstituted 6-chloro-5-formyluracils (**1**) (substituents: **a**: 1,3-dimethyl; **b**: 1,3-dicyclohexyl),[4] the new compounds, as the starting pyrimidine compounds.

The reaction of **1** with phenylhydrazine or methylhydrazine giving 1,5,7- and 2,5,7-trisubstituted 4,6-dioxo-4,5,6,7-tetrahydropyrazolo[3,4-*d*]pyrimidines was investigated in detail (Chart 1). Thus, under the cold condition, 1,3-disubstituted 6-chloro-5-formyluracils(**1**) were made to react with an equimolar phenylhydrazine to give Schiff's bases, *i.e.*, 1,3-disubstituted 6-chloro-5-phenylhydrazonomethyluracils (**2**). On heating, however, the reaction led to a ring closure to afford 5,7-disubstituted 1-phenyl-4,6-dioxo-4,5,6,7-tetrahydropyrazolo-[3,4-*d*]pyrimidines (**3**). When the Schiff's base (**2b**) was heated at reflux in benzene for one hour, **3b** was also obtained.

It is interesting that when **1** was heated with two equivalent moles of phenylhydrazine, a ring closure reaction took place giving 5,7-disubstituted 2-phenyl-4,6-dioxo-4,5,6,7-tetrahydropyrazolo[3,4-*d*]pyrimidines (**4**), *i.e.*, isomeric compounds of **3**. In addition, heating of Schiff's bases (**2**) with one more equimolar phenylhydrazine in ethanol or benzene also gave **4**. It is reasonable to consider that 1,3-disubstituted 6-(2-phenylhydrazino)-5-phenylhydrazonomethyluracils (**5**) were intermediates of the reactions, in which **4** was produced from **2**, and also from **1**. Thus, the chlorine atom at 6-position of the Schiff's bases (**2**) was replaced by the second equimolar phenylhydrazine to form **5**, and their phenylhydrazono groups at 5-positions were readily released to yield the ring-closed compounds (**4**). Ultraviolet (UV) spectra were measured to distinguish between isomeric compounds **3** and **4**.

1) Part XIII: S. Senda, K. Hirota and G. -N. Yang, *Chem. Pharm. Bull.* (Tokyo), **20**, 391 (1972).
2) Location: *492-36, Mitahora, Gifu.*
3) P. Schmidt, K. Eichenberger, M. Wilhelm and J. Druey, *Helv. Chim. Acta*, **42**, 763 (1959); Robugen G. m. b. H., Ger. Patent 1186466 (1965) [*C. A.*, **62**, 13159 (1965)]; H. Bredereck, F. Effenberger and E.H. Schweizer, *Chem. Ber.*, **95**, 956 (1962); A. Dornow and K. Dehmer, *Chem. Ber.*, **100**, 2577 (1967).
4) S. Senda, K. Hirota, G. -N. Yang and M. Shirahashi, *Yakugaku Zasshi*, **91**, 1372 (1971).

In case that methylhydrazine was used, 6-chloro-1,3-dimethyl-5-methylhydrazonomethyluracil (**6a**) was obtained by the reaction of **1a** with an equimolar amount of methylhydrazine with cooling. Under the same condition, **1b** did not give the corresponding 1,3-dicyclohexyl derivative (**6b**) but 5,7-dicyclohexyl-1-methyl-4,6-dioxo-4,5,6,7-tetrahydropyrazolo[3,4-*d*]pyrimidine (**7b**) was obtained. When **1** was heated either with equimolar or two equivalent moles of methylhydrazine, 1,5,7-trimethyl-4,6-dioxo-4,5,6,7-tetrahydropyrazolo[3,4-*d*]pyrimidine (**7a**)[1,5] and **7b** were obtained but 2-methylpyrazolo[3,4-*d*]pyrimidine isomers were not formed. As same as the reaction from **2b** to **3b**, **6a** was refluxed in ethanol to give **7a**.

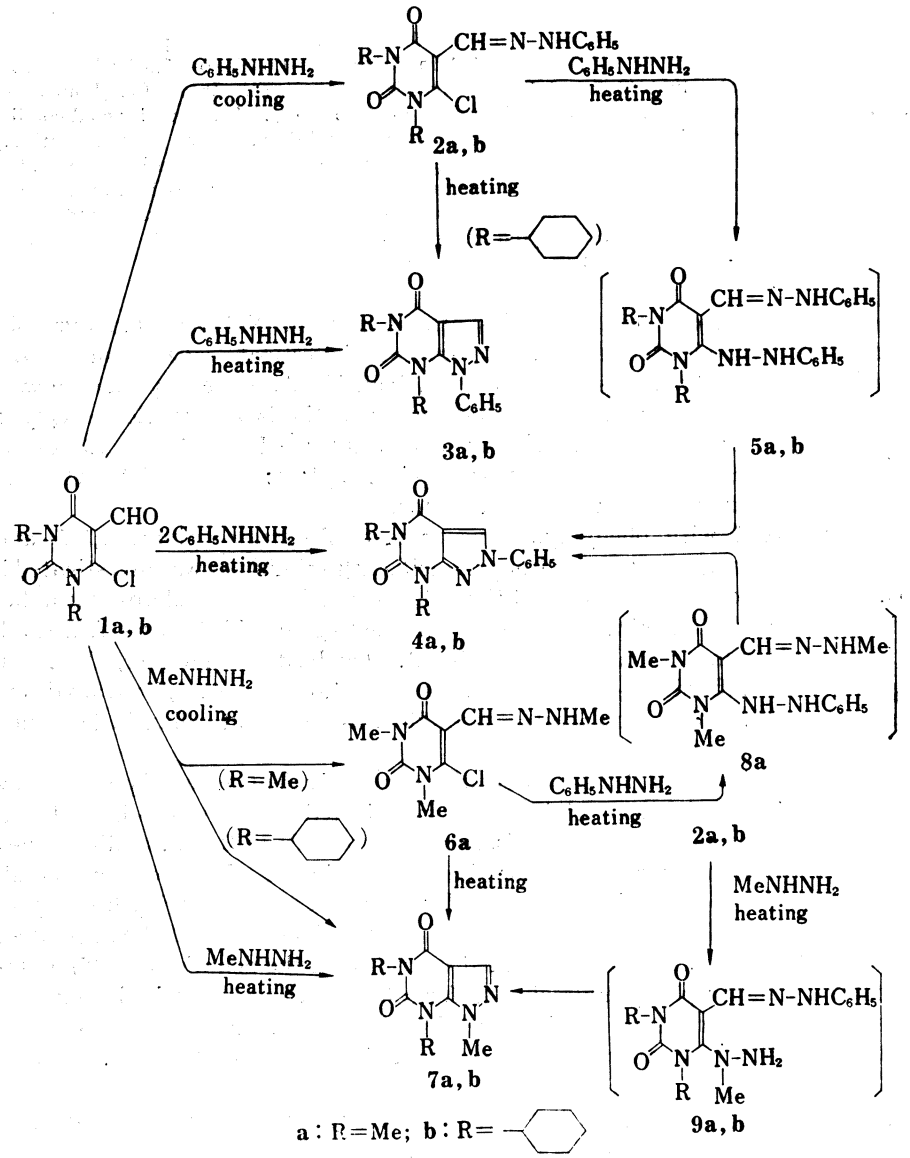

Chart 1

5) P. Schmidt, K. Eichenberger, M. Wilhelm and J. Druey, *Helv. Chim. Acta*, **42**, 349 (1959).

It is interesting that heating of **6a** with phenylhydrazine in ethanol gave **4a**, and that of **2** with methylhydrazine gave **7**. As same as the formation of **5** as described above, it is also considered that the intermediates, 1,3-dimethyl-5-methylhydrazonomethyl-6-(2-phenylhydrazino)-uracil (**8a**) and 1,3-disubstituted 6-(1-methylhydrazino)-5-phenylhydrazonomethyluracils (**9**), were formed in these reactions. Evidently, the methylhydrazino groups in **9** were attached to the pyrimidine ring in a form of 1-methylhydrazino while phenylhydrazino groups in **5** and **8a** in a form of 2-phenylhydrazino. That is why 2-methylpyrazolo[3,4-*d*]pyrimidine isomer was not formed when equimolar or two equivalent moles of methylhydrazine was used.

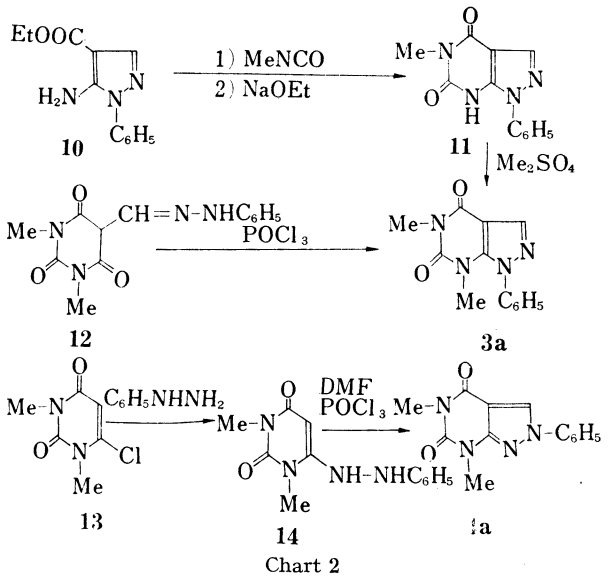

Chart 2

The isomeric compounds, **3a** and **4a**, were also prepared by other routes (Chart 2). Thus, following the modified procedures of Capuano and his co-workers,[6] 5-amino-4-ethoxycarbonyl-1-phenylpyrazole (**10**) was treated with methyl isocyanate and the product was subjected to a ring closure in the presence of sodium ethoxide to give 5-methyl-1-phenyl-4,6-dioxo-4,5,6,7-tetrahydropyrazolo[3,4-*d*]pyrimidine (**11**). Methylation of **11** with dimethyl sulfate yielded **3a**. Treatment of 1,3-dimethyl-5-phenylhydrazonomethylbarbituric acid (**12**)[4] with phosphorous oxychloride also gave **3a**. On the other hand, the replacement of 6-chloro group in 6-chloro-1,3-dimethyluracil (**13**)[7] with phenylhydrazine gave 1,3-dimethyl-6-(2-phenylhydrazino)-uracil (**14**) which was then treated with phosphorous oxychloride and N,N-dimethylformamide to afford **4a** in high yield. The infrared (IR) spectra of them showed that the products obtained in these routes were identical with those derived from **1a**.

Experimental

6-Chloro-1,3-dimethyl-5-phenylhydrazonomethyluracil (2a)——Phenylhydrazine (2.2 g, 0.02 mole) was dropped into a cold solution (0—10°) of **1a**[4] (4 g, 0.02 mole) in $CHCl_3$ (60 ml). The mixture was let stand at room temperature for 1 hr and then filtered. The resulting yellow crystals were dried in a desiccator to give dried product (3.4 g, 58%). Recrystallization of them from Me_2CO yielded yellow needles. The crystals melted at 175°; they changed to brown crystals at 176° which remelted at 200—205°. *Anal.* Calcd. for $C_{13}H_{13}O_2N_4Cl$: C, 53.34; H, 4.47; N, 19.13. Found: C, 53.57; H, 4.58; N, 19.27. IR ν_{max}^{Nujol} cm^{-1}: 3290, 1702, 1640. NMR ($CDCl_3$) δ: 7.86 (1H, singlet, -CH=N-), 7.1 (5H, multiplet, C_6H_5), 3.68 (3H, singlet, CH_3), 3.41 (3H, singlet, CH_3), 3.55 (1H, broad peak, -NH-).

6-Chloro-1,3-dicyclohexyl-5-phenylhydrazonomethyluracil (2b)——Phenylhydrazine (1.1 g, 0.01 mole) was made to react with **1b**[4] (3.4 g, 0.01 mole) at 0—10° as described in the synthesis of **2a** to give **2b** (2.6 g, 60.7%) as yellow needles (from Et_2O), mp 159—160° (decomp.), solidified again at 162—163° and re-melted at 254—257°. *Anal.* Calcd. for $C_{23}H_{29}O_2N_4Cl$: C, 64.60; H, 6.81; N, 13.06. Found: C, 64.51; H, 6.96; N, 13.19. IR ν_{max}^{Nujol} cm^{-1}: 3285, 1696, 1615. NMR ($CDCl_3$) δ: 7.89 (1H, singlet, -CH=N-), 7.15 (5H, mul-

6) L. Capuano, M. Welter and R. Zander, *Chem. Ber.*, **102**, 3698 (1969).
7) E. Bergmann and H. Heimhold, *J. Chem. Soc.*, **1935**, 955; W. Pfleiderer and K.-H. Schündehütte, *Ann. Chem.*, **612**, 158 (1957).

tiplet, C_6H_5), 4.75 (2H, broad peak, cyclohexyl-H α to N-atoms), 2.8 to 0.9 (21H, broad peaks, cyclohexyl and -NH-).

5,7-Dimethyl-1-phenyl-4,6-dioxo-4,5,6,7-tetrahydropyrazolo[3,4-*d*]pyrimidine (3a)——a) Phenylhydrazine (0.3 g, 0.0025 mole) in C_6H_6 (10 ml) was dropped into a solution of **1a** (0.5 g, 0.0025 mole) in C_6H_6 (20 ml) which was cooled with ice water, and the mixture was refluxed for 2 hr. Ten ml of MeOH was added to the brown pasty substance which was formed by removing the solvent *in vacuo* so that crystallization took place. Yellow crystals which were collected by filtration were recrystallized from MeOH to give **3a** (0.3 g, 46.9%) as yellow needles, mp 219—220°. *Anal.* Calcd. for $C_{13}H_{12}O_2N_4$: C, 60.93; H, 4.72; N, 21.87. Found: C, 60.63; H, 4.66; N, 22.13. IR ν_{max}^{Nujol} cm^{-1}: 3100, 1710, 1655, 1560, 1505. UV λ_{max}^{EtOH} mμ (ε): 230 (16520), 242 (16560). NMR ($CDCl_3$) δ: 8.80 (1H, singlet, -CH=N-), 7.52 (5H, singlet, C_6H_5), 3.43 (3H, singlet, CH_3), 3.13 (3H, singlet, CH_3).

b) In an aqueous solution of NaOH (0.6 g) in 30 ml of H_2O was dissolved **11**[6] (3.3 g, 0.0134 mole). To this alkaline solution, Me_2SO_4 (1.8 g) was added dropwise. The mixture was heated on a water bath for 30 min. Crystals which were formed on cooling were filtered and recrystallized from MeOH to give **3a** (1.3 g, 40%) as colorless needles, mp 219—220°. IR and UV spectra showed that this product was identical with that obtained by preparation (a).

c) **12**[4] (3.4 g) was heated in $POCl_3$ (15 ml) at 95° for 1 hr. The $POCl_3$ was evaporated *in vacuo*, the resulting residue was poured into ice water, the mixture was filtered, and the resulting yellow crystals were subjected to an alumina chromatography with MeOH–CCl_4 (1: 5). From the first fraction, colorless prisms of **3a** (0.6 g, 18.9%) were obtained. From the rest fractions was recovered **12** (0.1 g). Both **3a** and **12** hereby obtained, were identified by IR and UV spectra.

5,7-Dicyclohexyl-1-phenyl-4,6-dioxo-4,5,6,7-tetrahydropyrazolo[3,4-*d*]pyrimidine (3b)——a) Phenylhydrazine (0.6 g, 0.0055 mole) was made to react with **1b** (1.7 g, 0.005 mole) as described in the preparation (a) of **3a** to give 0.8 g (40%) of **3b** as colorless prisms (from MeOH), mp 268—269°. *Anal.* Calcd. for $C_{23}H_{28}O_2N_4$: C, 70.38; H, 7.19; N, 14.28. Found: C, 70.49; H, 7.33; N, 14.49. IR ν_{max}^{Nujol} cm^{-1}: 1710, 1665, 1550, 1300. UV λ_{max}^{EtOH} mμ (ε): 242 (10710), 258 (7130). NMR ($CDCl_3$) δ: 8.04 (1H, singlet, -CH=N-), 7.56 (5H, multiplet, C_6H_5), 5.0 to 0.2 (22H, broad peaks, cyclohexyl).

b) **2b** (0.5 g) in 10 ml of C_6H_6 was heated at reflux for 1 hr. The solvent of the reaction mixture was evaporated *in vacuo*. Ten ml of ether was added to the resulting residue to cause crystallization. Yellow crystals obtained by filtration and washed with ether were recrystallized from MeOH with charcoal to give **3b** (0.2 g, 44%) as colorless prisms, mp 268—269°. IR spectrum showed that the product was identical with that prepared by preparation (a).

5,7-Dimethyl-2-phenyl-4,6-dioxo-4,5,6,7-tetrahydropyrazolo[3,4-*d*]pyrimidine (4a)——a) Phenylhydrazine (0.6 g, 0.0055 mole) in EtOH (10 ml) was dropped into a solution of **1a** (0.5 g, 0.0025 mole) in EtOH (20 ml). The resulting mixture was refluxed for 2 hr and evaporated to dryness. The residue was washed with MeOH to give yellow crystals. Recrystallization of them from MeOH gave colorless prisms of **4a** (0.55 g, 85.9%), mp 285—287°. *Anal.* Calcd. for $C_{13}H_{12}O_2N_4$: C, 60.93; H, 4.72; N, 21.87. Found: C, 60.88; H, 4.86; N, 22.08. IR ν_{max}^{Nujol} cm^{-1}: 3100, 1700, 1600, 1585, 1290. UV λ_{max}^{EtOH} mμ (ε): 225 (16050), 250 (6050), 298 (15500). NMR ($CDCl_3$) δ: 8.40 (1H, singlet, -CH=N-), 7.60 (5H, multiplet, C_6H_5), 3.60 (3H, singlet, CH_3), 3.42 (3H, singlet, CH_3).

b) **2a** (2 g, 0.0068 mole) and phenylhydrazine (0.8 g, 0.0074 mole) in EtOH (160 ml) were heated at reflux for 2.5 hr. The reaction mixture was concentrated, cooled and filtered to give yellow crystals. On recrystallization of them from MeOH, **4a** (1.6 g, 92%), mp 285—287°, was obtained. The IR spectrum showed that it was identical with that obtained in preparation (a).

c) **6a** (1 g, 0.0043 mole) was made to react with phenylhydrazine (0.5 g, 0.0046 mole) in EtOH (40 ml) in a manner similar to that described in the preparation (b) to give 0.6 g (54.5%) of the product. When the reaction was carried out in $CHCl_3$ (30 ml), 0.4 g (40%) of the same product was obtained, mp 285—287°. The IR spectra of above products showed that they were identical with that obtained in preparation (a).

d) $POCl_3$ (1.9 g) was dropped into DMF (2 ml) with ice-cooling. The mixture was let stand at room temperature for 10 min. Then **14** (2.7 g) in DMF (3 ml) was added portionwise to it and the mixture was heated at reflux for 30 min. The reaction mixture was poured into ice water to give white crystals. Recrystallization of them from MeOH gave colorless prisms of **4a** (2.6 g, 92.9%), mp 285—287°. IR spectrum of it indicated that it was identical with that obtained in preparation (a).

5,7-Dicyclohexyl-2-phenyl-4,6-dioxo-4,5,6,7-tetrahydropyrazolo[3,4-*d*]pyrimidine (4b)——a) Phenylhydrazine (1.1 g, 0.01 mole) and **1b** (1.7 g, 0.005 mole) in EtOH (30 ml) were made to react in a manner similar to that described in the preparation (a) of **4a** to give pale yellow needles (from MeOH) of **4b** (1.2 g, 61.2%), mp 257—258°. *Anal.* Calcd. for $C_{23}H_{28}O_2N_4$: C, 70.38; H, 7.19; N, 14.28. Found: C, 70.64; H, 7.18; N, 14.23. IR ν_{max}^{Nujol} cm^{-1}: 3100, 1698, 1660, 1585, 1270. UV λ_{max}^{EtOH} mμ (ε): 230 (18000), 254 (7250), 310 (17000). NMR ($CDCl_3$) δ: 8.37 (1H, singlet, -CH=N-), 7.60 (5H, multiplet, C_6H_5), 4.85 (2H, broad peak, cyclohexyl-H α to N-atoms), 3.2 to 1.0 (20H, broad peaks, cyclohexyl).

b) **2b** (0.5 g, 0.00116 mole) and phenylhydrazine (0.15 g, 0.00138 mole) in EtOH (15 ml) were heated at reflux for 1 hr. The reaction mixture was concentrated and cooled to give pale yellow crystals. Re-

crystallization of them from MeOH gave **4b** (0.45 g, 98.9%), mp 256—258°. The reaction was also carried out in C_6H_6 (15 ml) instead if EtOH to give 0.1 g (22%) of the same product. The IR spectra showed that the products were identical with that synthesized in preparation (a).

6-Chloro-1,3-dimethyl-5-methylhydrazonomethyluracil (6a)——**1a** (6 g, 0.03 mole) was made to react with methylhydrazine (1.5 g, 0.03 mole) in a manner similar to that described in the synthesis of **2a** to give the crude product of **6a** (3.4 g) as yellow crystals, mp 170—180°. This product was used in the next step without further purification. Attempts to purify it let to the ring-closed compound (**7a**).

1,5,7-Trimethyl-4,6-dioxo-4,5,6,7-tetrahydropyrazolo[3,4-*d*]pyrimidine (7a)——a) **1a** (0.5 g, 0.0025 mole) was made to react with methylhydrazine (0.14 g, 0.003 mole) in a similar manner as described in the preparation (a) of **3a** to give **7a** (0.45 g, 92.8%) as colorless needles (from MeOH), mp 237—238°. The IR spectrum showed that it was identical with that of the authentic sample.[1]

b) **6a** (0.5 g) in EtOH (20 ml) was heated at reflux and worked up in a similar manner as described in the preparation (b) of **3b** to give **7a** (0.4 g, 95.5%) as colorless needles (from MeOH), mp 237—238°. The IR spectrum showed that the product was identical with that synthesized in preparation (a).

c) **2a** (1.7 g, 0.0059 mole) and methylhydrazine (0.3 g, 0.0065 mole) in C_6H_6 (40 ml) were heated at reflux for 2 hr. The reaction mixture was concentrated and cooled to give yellow crystals. Recrystallization of them from MeOH yielded **7a** (0.6 g, 52.3%), mp 237—238°. The IR spectrum showed that the product was identical with that obtained in preparation (a).

5,7-Dicyclohexyl-1-methyl-4,6-dioxo-4,5,6,7-tetrahydropyrazolo[3,4-*d*]pyrimidine (7b)——a) Methylhydrazine (0.5 g, 0.01 mole) was dropped into a cold solution (0—10°) of **1b** (3.4 g, 0.01 mole) in C_6H_6 (20 ml). The mixture was let stand at room temperature for 1 hr and then filtered to give yellow crystals. Recrystallization of them from ether yielded **7b** (2.5 g, 75.8%) as colorless needles, mp 215—216°. When the reaction mixture was evaporated to dryness, it gave 3.2 g (97%) of the same product (identified by IR spectra). *Anal.* Calcd. for $C_{18}H_{26}O_2N_4$: C, 65.43; H, 7.93; N, 16.96. Found: C, 65.65; H, 7.92; N, 16.99. IR ν_{max}^{Nujol} cm^{-1}: 1700, 1660, 1560, 1296. UV λ_{max}^{EtOH} $m\mu$ (ε): 242 (7000), 257 (7000). NMR ($CDCl_3$) δ: 7.81 (1H, singlet, -CH=N-), 4.05 (3H, singlet, CH_3), 5.1 to 0.9 (22H, broad peaks, cyclohexyl).

b) **2b** (1 g, 0.00233 mole) and methylhydrazine (0.1 g, 0.00233 mole) were made to react in a similar manner as described in the preparation (c) of **7a** to give **7b** (0.65 g, 84.5%) which was identical with the product that obtained in preparation (a).

5-Methyl-1-phenyl-4,6-dioxo-4,5,6,7-tetrahydropyrazolo[3,4-*d*]pyrimidine (11)——To a solution of 5-amino-4-ethoxycarbonyl-1-phenylpyrazole (12 g, 0.077 mole) in C_6H_6 (50 ml), Et_3N (4 ml) and MeNCO (17.1 g, 0.3 mole) were added. The mixture was heated at reflux in an oil–bath (bath temperature: 170°) for 8 hr. The solvent was then evaporated *in vacuo*. Ether (20 ml) was added to the resulting residue. The mixture was filtered to give white crystals. Recrystallization of them from MeOH gave 10.7 g of the intermediate, mp 152—154° (lit.[6] 157°). The above intermediate was refluxed with Na (1.5 g) in EtOH (60 ml) for 30 min. The solvent of the reaction mixture was evaporated *in vacuo*. The resulting residue was dissolved in H_2O. Solid substance which was formed was removed by filtration. White crystals formed by the neutralization of the filtrate with AcOH were recrystallized from EtOH to give **11** (3.3 g) as colorless needles, mp >300° (lit.[6] 296°).

1,3-Dimethyl-6-(2-phenylhydrazino)uracil (14)——A mixture of 6-chloro-1,3-dimethyluracil[7] (7.7 g, 0.05 mole) and phenylhydrazine (10.8 g, 0.1 mole) in EtOH (100 ml) was heated at reflux for 2 hr. The solvent was evaporated. The resulting residue was dissolved in hot water and reddish crystals were obtained on cooling. Recrystallization of them from MeOH with charcoal gave **14** (5 g, 40.6%) as light brown prisms, mp 206—208°. *Anal.* Calcd. for $C_{12}H_{14}O_2N_4$: C, 58.52; H, 5.73; N, 22.75. Found: C, 58.82; H, 5.92; N, 23.11.