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Pyrimidine Derivatives and Related Compounds. XIII.[1] The Synthesis of N-Substituted Pyrazolo[3.4-*d*]pyrimidines from Pyrazole Derivatives[2]

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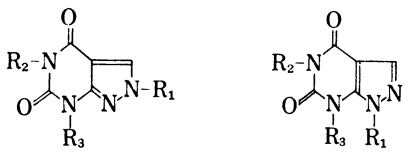
An alkylation of 3-amino-4-ethoxycarbonylpyrazole (**1**) under various conditions was investigated. Alkylated pyrazoles (**2, 3a, b**) were condensed with isocyanates or isothiocyanate to yield pyrazolylurea derivatives (**4a—f, 10**). Ring closure of these intermediates was carried out in a solution of sodium ethoxide and the resulting 2,5 (or 1,5)-disubstituted pyrazolo[3,4-*d*]pyrimidines (**5a—f, 11a, b**) were alkylated to give 2,5,7 (or 1,5,7)-trisubstituted pyrazolo[3,4-*d*]pyrimidines (**6a—e, 12a, b**) or 2,5-disubstituted 6-methylmercaptopyrazolo[3,4-*d*]pyrimidines (**7a, b**). Instead of the use of isocyanates, another methods by fusing ureas with methylpyrazole were also investigated. Furthermore, debenzylation of 2-benzylpyrazolo[3,4-*d*]pyrimidines (**6c, d**) was carried out with 35 atm of hydrogen in an autoclave at 220° over palladium on carbon to give debenzylated compounds (**13a, b**).

Many xanthine and purine derivatives show various biological activities, and therefore, pyrazolo[3,4-*d*]pyrimidine derivatives have hitherto been studies as their antagonists by many investigators. Although many reports on such pyrazolopyrimidine derivatives were presented recently, derivatives bearing substituents at nitrogen atoms of pyrimidine nucleus have rarely been reported.

The present investigation was undertaken in order to synthesize such N-substituted compounds, *i.e.*, 2,5,7-trisubstituted 4,6-dioxo-4,5,6,7-tetrahydropyrazolo[3,4-*d*]pyrimidines (**A**) and 1,5,7-trisubstituted 4,6-dioxo-4,5,6,7-tetrahydropyrazolo[3,4-*d*]pyrimidines (**B**) (Chart 1), from N-alkylpyrazole compounds.

It had been reported[4] that alkylpyrazoles such as 1-alkyl-5-amino-4-ethoxycarbonylpyrazole (**2**) and 1-alkyl-3-amino-4-ethoxycarbonylpyrazoles (**3**) were prepared by condensing ethyl ethoxymethylenecyanoacetate with alkylhydrazines, but there has been no report as to an alkylation of pyrazole derivatives to give alkylpyrazole compounds (**2, 3**). Therefore, we studied an alkylation of 3-amino-4-ethoxycarbonylpyrazole (**1**)[5] under various conditions (Table I).



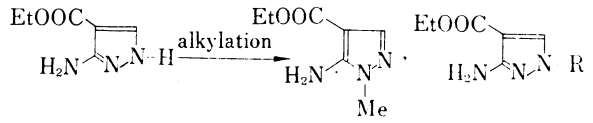
A **B**

Chart 1

With regard to the methylation, method A in which **1** was treated with diazomethane in ether and tetrahydrofuran gave 5-amino-4-ethoxycarbonyl-1-methylpyrazole (**2**) in 18.3% together with the recovering of 40% of the starting **1**. The method B in which **1** was methylated with dimethyl sulfate in an aqueous alkaline solution gave a mixture of **2** and 3-amino-4-ethoxycarbonyl 1-methylpyrazole (**3a**). Nuclear magnetic resonance (NMR) spectrum

1) Part XII: S. Senda, K. Hirota, G. -N. Yang and M. Shirahashi, *Yakugaku Zasshi*, **91**, 1372 (1971).
2) This work was presented at the 91th Annual Meeting of the Pharmaceutical Society of Japan, Fukuoka, April 1971.
3) Location: *492-36, Mitahora, Gifu.*
4) P. Schmidt, K. Eichenberger, M. Wilhelm and J. Druey, *Helv. Chim. Acta*, **42**, 349 (1959).
5) P. Schmidt and J. Druey, *Helv. Chim. Acta*, **39**, 986 (1956).

Table I. The Alkylation of 3-Amino-4-ethoxycarbonylpyrazole (**1**)



1 **2** 3a: R=Me
3b: R=$CH_2C_6H_5$

Method	Alkylating agent	Medium	Product	Yield (%)
A	CH_2N_2	ether, THF	**2**	18.3
B	Me_2SO_4	NaOH, H_2O	**3a**	50.8
C	MeI	NaOMe, MeOH	**3a**	40.0
D	MeI	DMF, K_2CO_3	**3a**	36.6
E	$C_6H_5CH_2Cl$	NaOEt, EtOH	**3b**	43.0
F	$C_6H_5CH_2Cl$	DMF, K_2CO_3	**3b**	24.5

of the mixture showed that the producing ratio of **2**: **3a** is about 1: 4. Repeated recrystallizations of the mixture from petroleum benzin could separate **3a**. Similar results were obtained in method C or D where methyl iodie in methanolic sodium methoxide or that in N,N-dimethylformamide (DMF) was used, respectively. The infrared (IR) and ultraviolet (UV) spectra of **2** and **3a** obtained above were identical with those of authentic samples.[4]

As to a benzylation using benzyl chloride, either method E which was carried out in ethanolic solution of sodium ethoxide or method F carried out in potassium carbonate and DMF gave 3-amino-1-benzyl-4-ethoxycarbonylpyrazole (**3b**). From above results, it is evident that the predominant product in alkylation of **1** was 1-alkyl-3-amino-4-ethoxycarbonylpyrazole (**3a, 3b**) except in method A.

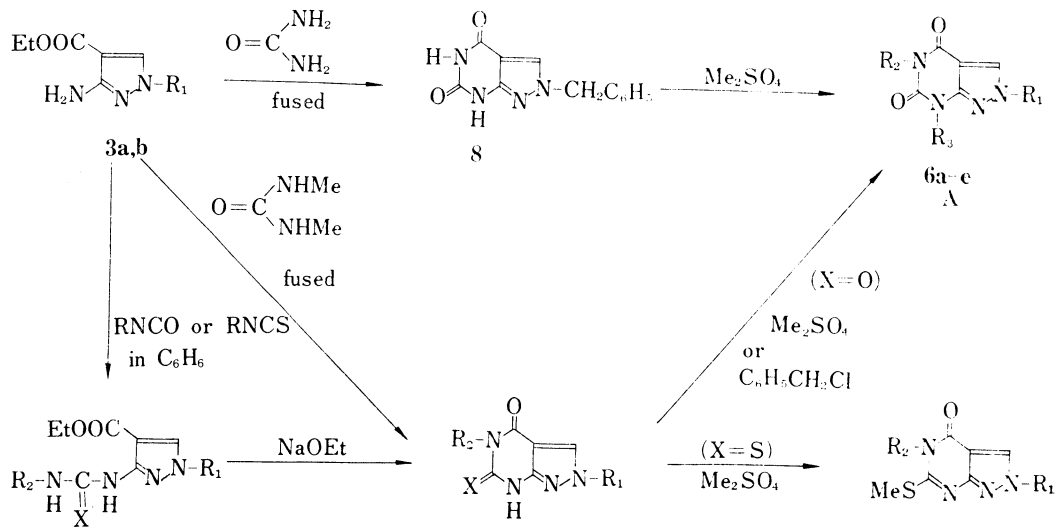
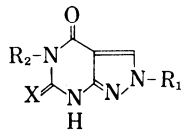


Chart 2

2,5,7-Trisubstituted 4,6-dioxo-4,5,6,7-tetrahydropyrazolo[3,4-*d*]pyrimidines (**A**) were synthesized from **3a** or **3b** by modified procedures of Schmidt's method[4] (Chart 2). Thus,

3a and **3b** were treated with phenyl isocyanate, methyl isocyanate or phenyl isothiocyanate in benzene to give pyrazol-3-ylurea derivatives (**4a**—**f**) (Table IV) which were easily converted to ring-closed compounds, *i,e.*, 2,5-disubstituted 4,6-dioxo-4,5,6,7-tetrahydropyrazolo[3,4-*d*]pyrimidines (**5**) in the presence of sodium ethoxide (Table II). Then **5a**—**d** (X=O) were

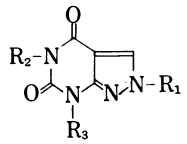
TABLE II. 2,5-Disubstituted 4,6-Dioxo-4,5,6,7-tetrahydropyrazolo[3,4-*d*]pyrimidines (**5a**—**f**)[a]



Compd.	R_1	R_2	X	Yield (%)	mp (°C)	UV λ_{max}^{EtOH} mμ (ε)	Formula		Analysis (%) C	H	N
5a	Me	Me	O	96.6	>300[b]	240 (4500) 260 (5450)	$C_7H_8O_2N_4$	Calcd. Found	46.66 46.89	4.48 4.50	31.10 31.13
5b	Me	C_6H_5	O	91.0	>300	241 (3000) 262 (4500)	$C_{12}H_{10}O_2N_4$	Calcd. Found	59.50 59.30	4.16 4.22	23.13 22.93
5c	$CH_2C_6H_5$	Me	O	90.5 42.9[c]	270—271	242 (3000) 264 (4800)	$C_{13}H_{12}O_2N_4$	Calcd. Found	60.93 61.04	4.72 4.63	21.87 22.04
5d	$CH_2C_6H_5$	C_6H_5	O	97.6	>300	242 (6500) 262 (7500)	$C_{18}H_{14}O_2N_4$	Calcd. Found	67.91 68.16	4.43 4.38	17.60 17.39
5e	Me	C_6H_5	S	71.4	>300	234 (11150) 250 (12000) 278 (10750)[d] 298 (19000)	$C_{12}H_{10}ON_4S$	Calcd. Found	55.84 55.95	3.90 4.07	21.70 21.48
5f	$CH_2C_6H_5$	C_6H_5	S	95.2	256—258	234 (11250) 251 (9900) 278 (9000)[d] 300 (16750)	$C_{18}H_{14}ON_4S$	Calcd. Found	64.66 64.81	4.22 4.32	16.76 16.99

a) All compounds are colorless prisms (from EtOH). *b*) lit.[4] mp 342—344°
c) prepared from **3b** with dimethylurea *d*) shoulder

TABLE III. 2,5,7-Trisubstituted 4,6-Dioxo-4,5,6,7-tetrahydropyrazolo[3,4-*d*]pyrimidines (**6a**—**e**)[a]



Compd.	R_1	R_2	R_3	Yield (%)	mp (°C)	UV λ_{max}^{EtOH} mμ (ε)	Formula		Analysis (%) C	H	N
6a	Me	Me	Me	75.2 34.8[c]	202—203[b]	240 (2875) 264 (4750)	$C_8H_{10}O_2N_4$	Calcd. Found	49.88 49.45	5.19 5.36	28.85 29.12
6b	Me	C_6H_5	Me	96.0 56.8[d]	265—266	241 (3675) 265 (4750)	$C_{13}H_{12}O_2N_4$	Calcd. Found	60.93 60.69	4.72 4.81	21.87 21.60
6c	$CH_2C_6H_5$	Me	Me	95.4 5.6[e]	190—192	243 (2650) 266 (5100)	$C_{14}H_{14}O_2N_4$	Calcd. Found	62.21 62.24	5.22 5.33	20.73 20.89
6d	$CH_2C_6H_5$	C_6H_5	Me	90.6	214—215	242 (3500) 266 (5750)	$C_{19}H_{16}O_2N_4$	Calcd. Found	68.66 68.89	4.85 4.97	16.86 16.83
6e	$CH_2C_6H_5$	C_6H_5	$CH_2C_6H_5$	45.6	201—202	244 (8200) 265 (7000)	$C_{25}H_{20}O_2N_4$	Calcd. Found	73.51 73.31	4.94 4.83	13.72 13.72

a) All compounds are colorless needles (From MeOH). *b*) lit.[4] mp 199—200°
c) prepared from **13a** *d*) prepared from **13b** *e*) prepared from **8**

then treated with dimethyl sulfate or benzyl chloride to give **A**-type compounds (**6**) in good yields (Table III). From **5e** and **5f** (X=S) were obtained S-methyl derivatives, 2-methyl-6-methylmercapto-4-oxo-5-phenyl-4,5-dihydropyrazolo[3,4-*d*]pyrimidine (**7a**) and 2-benzyl-6-methylmercapto-4-oxo-5-phenyl-4,5-dihydropyrazolo[3,4-*d*]pyrimidine (**7b**) respectively. Further attempts to remove S-methyl group of them by Raney nickel in ethanolic solution were unsuccessful. On the other hand, it was failure to chlorinate **5c** (R_1=$CH_2C_6H_5$, R_2=Me, X=O) and **5d** (R_1=$CH_2C_6H_5$, R_2=C_6H_5, X=O) with phosphorus oxychloride by the usual procedure. It was also unsuccessful to prepare their thio-derivatives by using phosphorus pentasulfide in pyridine.

Another synthetic method of **6** was also investigated. Thus, **3b** was fused with urea at 180° to 190° and the resulting 2-benzyl-4,6-dioxo-4,5,6,7-tetrahydropyrazolo[3,4-*d*]pyrimidine (**8**) was methylated with excess dimethyl sulfate in the presence of alkali to lead to a formation of **6c**. When **3b** was fused with N,N'-dimethylurea, **5c** was obtained.

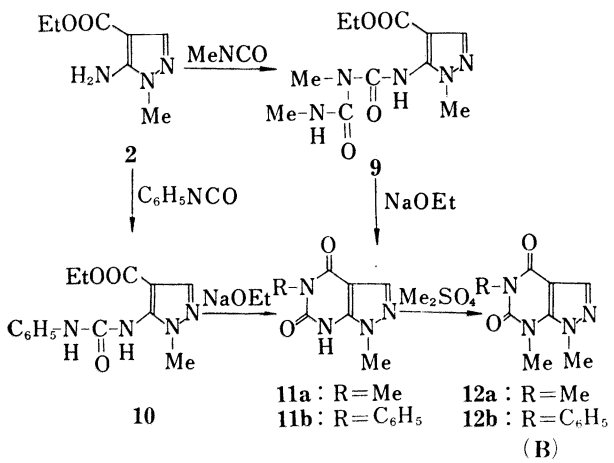


Chart 3

1,5,7-Trisubstituted 4,6-dioxo-4,5,6,7-tetrahydropyrazolo[3,4-*d*]pyrimidines (**B**) were similarly synthesized from **2**. It is interesting that **2** was condensed with two equivalent moles of methyl isocyanate giving N-(4-ethoxycarbonyl-1-methylpyrazol-5-yl)-N'-carbamoyl-N'-methylurea (**9**).[4,6] When **2** was condensed with phenyl isocyanate, an equimolar reaction proceeded, resulting in the formation of N-(4-ethoxycarbonyl-1-methylpyrazol-5-yl)-N'-phenylurea (**10**). Then, **9** and **10** were treated in the presence of sodium ethoxide to give 1,5-disubstituted 4,6-dioxo-4,5,6,7-tetrahydropyrazolo[3,4-*d*]-pyrimidines (**11a**,[4] **11b**), which were further methylated to **B**-type compounds (**12a**[6], **12b**) (Chart 3).

1-Benzyl-5,7-dimethyl-4,6-dioxo-4,5,6,7-tetrahydropyrazolo[3,4-*d*]pyrimidine was easily debenzylated on a treatment with hydrogen over palladium on carbon at an atmospheric pressure at 40°.[4] On the other hand, the debenzylation of 2-benzyl-4,6-dioxo-4,5,6,7-tetrahydropyrazolo[3,4-*d*]pyrimidine derivatives (**6c**, **6d**) were carried out with hydrogen over palladium on carbon in acetic acid solution at 35 atm, 220°, namely at a temperature higher than the melting point of **6c** and **6d** to give 5,7-dimethyl-4,6-dioxo-4,5,6,7-tetrahydropyrazolo[3,4-*d*]-pyrimidine (**13a**)[7] and 7-methyl-5-phenyl-4,6-dioxo-4,5,6,7-tetrahydropyrazolo[3,4-*d*]pyrimidine (**13b**) respectively (Chart 4). Further methylation of **13a** and **13b** with dimethyl sulfate gave the corresponding 2-methylated derivatives, namely **6a** and **6b** respectively. For a direct preparation of **13a** and **13b** without a debenzylation step, **1** was allowed to react with methyl isocyanate or phenyl isocyanate in a similar manner as described above. Expected pyrazolylureas (**14a**, **14b**) were not obtained, but resulted in the formation of 1-carbamoylpyrazole derivatives (**15a**,[8] **15b**) which were independently synthesized from ethyl ethoxymethylenecyanoacetate and 4-methyl or 4-phenyl semicarbazide respectively.

6) P. Schmidt, K. Eichenberger and J. Druey, *Helv. Chim. Acta*, **41**, 1052 (1958).
7) W. Pfeiderer and K. -H. Schündehütte, *Ann. Chem.*, **615**, 42 (1958).
8) L. Capuano, M. Welter and R. Zander, *Chem. Ber.*, **102**, 3698 (1969).

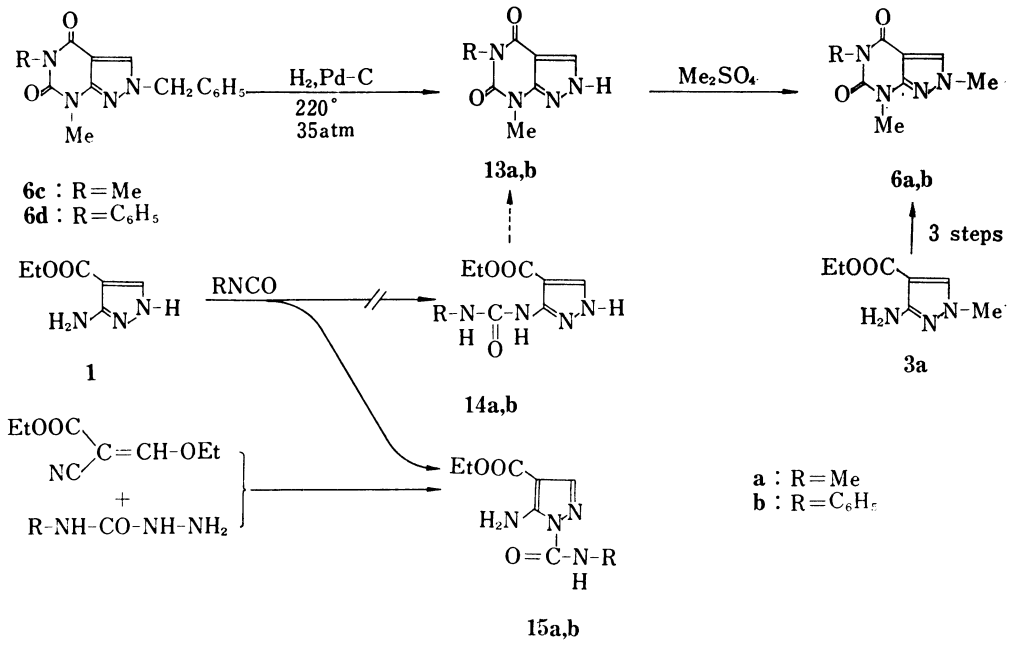


Chart 4

Experimental

The Alkylation of 3-Amino-4-ethoxycarbonylpyrazole (1) (Table I)——Method A: To a magnetically stirred and ice-chilled ethereal solution of CH_2N_2 (prepared from 10 g of N-nitrosomethylurea) was added dropwise **1** (5 g, 0.032 mole) in 60 ml of THF and 40 ml of ether. After the mixture was stirred at 0° for 1 hr and at room temperature for an additional 1 hr, it was allowed to stand overnight. The solvent was then evaporated *in vacuo* and the resulting residue was subjected to an alumina chromatography with $CHCl_3$. From the first fraction, colorless needles of 5-amino-4-ethoxycarbonyl-1-methylpyrazole (**2**) (1 g, 18.3%) were obtained, mp 100—101°. UV λ_{max}^{EtOH} mμ (ε): 226 (10450), 257 (10550). From the rest of the fractions was recovered **1** (2 g, 40%).

Method B: **1** (4.7 g, 0.03 mole) was dissolved in a solution of NaOH (1.5 g) in 20 ml of H_2O. The solution was kept cold with cold water from the outside, Me_2SO_4 (4.2 g, 0.033 mole) was added dropwise thereto at such a rate that the inner temperature did not rise above 25°. The mixture was kept at room temperature until the pH of it became 7. The water contained therein was distilled away *in vacuo*. The residual paste was extracted by boiling it with three 100 ml portions of C_6H_6. The combined extracts were dried ($MgSO_4$) for 12 hr and the solvent was evaporated. To the resulting pasty substance was added ether (3 ml) and the mixture was cooled to give a white solid. Recrystallization of it from ether gave 3.2 g of white needles, mp 60—65°. Although the elemental analysis of this product agreeded with the formula of $C_7H_{11}O_2N_3$, its NMR spectrum showed that it was a mixture of **2** and 3-amino-4-ethoxycarbonyl-1-methylpyrazole (**3a**). On a repeated recrystallization from petroleum benzin, **3a** (2.6 g, 50.8%), mp 90—91°, could be separated. UV λ_{max}^{EtOH} mμ (ε): 270 (3650).

Method C: In 50 ml of absolute MeOH were dissolved Na (0.8 g), **1** (4.7 g, 0.033 mole) and MeI (4.7 g, 0.033 mole) successively. The solution was refluxed on a water bath for 1 hr. After evaporating the solvent *in vacuo* from it, ether (3 ml) was added to the residue. On cooling, a white solid was obtained. Repeated recrystallization of this solid from petroleum benzin gave **3a** (2 g, 40%).

Method D: A stirring mixture of **1** (4.7 g, 0.03 mole), anhydrous K_2CO_3 (4.5 g), DMF (5 ml) and MeI (4.7 g, 0.033 mole) was warmed at 60° for 1 hr, filtered and the filtrate was evaporated *in vacuo*. The resulting residue was dissolved in EtOH (20 ml) and the solvent was evaporated. The residue was mixed with ether (3 ml) and the mixture was cooled to give a brown semisolid. Recrystallization from petroleum benzin gave **3a** (1.8 g, 36%).

The IR and UV absorption spectra of all the compounds which were obtained in methods A, B, C, and D were identical with those of authentic samples.[4]

Method E: To 100 ml of absolute EtOH were added Na (1.9 g), **1** (12.4 g, 0.08 mole) and $C_6H_5CH_2$-Cl (10 g, 0.08 mole) successively. The mixture was refluxed on a water bath for 1 hr and was filtered when

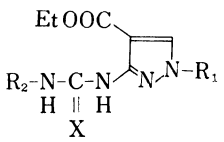
it was still hot so that NaCl was removed. The filtrate was concentrated to about 1/4 of the original volume and cooled until crystals appeared. The crystals were collected and washed with ether. Recrystallization from EtOH–H_2O gave 3-amino-1-benzyl-4-ethoxycarbonylpyrazole (**3b**) (10.7 g, 43.7%), colorless needles, mp 111—113°. *Anal.* Calcd. for $C_{13}H_{15}O_2N_3$: C, 63.66; H, 6.16; N, 17.13. Found: C, 63.74; H, 6.11; N, 17.37. UV λ_{max}^{EtOH} mμ (ε): 270 (5750). IR ν_{max}^{Nujol} cm^{-1}: 3475, 3320, 1690, 1605, 1100. NMR ($CDCl_3$) δ: 7.56 (1H, singlet, pyrazole ring-H), 7.31 (5H, multiplet, C_6H_5), 5.06 (2H, singlet, N-CH_2-C_6H_5), 4.58 (2H, broad peak, NH_2), 4.26 (2H, quartet, J=7 cps, O-CH_2-Me), 1.30 (3H, triplet, J=7 cps, CH_3).

Method F: A mixture of $C_6H_5CH_2Cl$ (4.2 g, 0.0335 mole), **1** (5.2 g, 0.0335 mole), anhydrous K_2CO_3 (4.6 g) and DMF (5 ml) was heated at 95° for 2 hr. After separation of K_2CO_3, water was added to the solution until no more crystals were formed. The crystals were collected and washed with H_2O to give white needles, mp 107—110°. Recrystallization from ether–MeOH yielded **3b** (2 g, 24.4%), colorless needles, mp 111—113°. IR spectra showed that the product by method E and F were identical.

N-Substituted N′-(4-Ethoxycarbonyl-1-methylpyrazol-3-yl)-urea Derivatives (**4**) (Table IV)——a) MeNCO (22.8 g, 0.4 mole) and Et_3N (5 ml) were added to a solution of **3a, b** (0.1 mole) in 150 ml of C_6H_6. The solution was refluxed on an oil bath at 100—120° for 8 hr. The solvent was removed *in vacuo*. The resulting residue was mixed with 10 ml of ether and cooled. It was filtered and the crystals were washed with ether to give **4a** and **4c**.

b) A solution of **3a, b** (0.1 mole) and C_6H_5NCO or C_6H_5NCS (0.18—0.2 mole) in 200 ml of C_6H_6 was refluxed on an oil bath at 160—170° for 2 hr. The reaction mixture was concentrated to about 40 ml. The concentrate was cooled, filtered and resulting white crystals were washed with 15 ml of MeOH to give **4b** and **4d—f**.

Table IV. Pyrazol-3-ylureas (**4a—f**)[a,b]



Compd.	R_1	R_2	X	Yield (%)	mp (°C)	Formula		Analysis (%) C	H	N
4a	Me	Me	O	65.0	118—119[c]	$C_9H_{14}O_3N_4$				
4b	Me	C_6H_5	O	60.8	135—137	$C_{14}H_{16}O_3N_4$	Calcd.	58.32	5.59	19.44
							Found	58.47	5.63	19.41
4c	$CH_2C_6H_5$	Me	O	75.5	108—109	$C_{15}H_{18}O_3N_4$	Calcd.	59.59	6.00	18.53
							Found	59.80	6.24	18.52
4d	$CH_2C_6H_5$	C_6H_5	O	68.6	135—136	$C_{20}H_{20}O_3N_4$	Calcd.	65.95	5.53	15.38
							Found	65.79	5.58	15.16
4e	Me	C_6H_5	S	17.3	162—163	$C_{14}H_{16}O_2N_4S$	Calcd.	55.25	5.30	18.41
							Found	55.37	5.45	18.36
4f	$CH_2C_6H_5$	C_6H_5	S	80.6	138—139	$C_{20}H_{20}O_2N_4S$	Calcd.	63.15	5.30	14.73
							Found	62.87	5.53	14.72

a) All compounds are colorless prisms.
b) recrystallization solvent: **4a** from C_6H_6, **4b—f** from MeOH
c) lit.[4] mp 119°

2,5-Disubstituted 4,6-Dioxo-4,5,6,7-tetrahydropyrazolo[3,4-*d*]pyrimidines (5a—d) and 2,5-Disubstituted 4-Oxo-6-thio-4,5,6,7-tetrahydropyrazolo[3,4-*d*]pyrimidines (5e, f) (Table II)——a) The following is a general procedure. An equimolar mixture of pyrazolylurea (or pyrazolylthiourea) (**4**) and NaOEt in EtOH was refluxed for 1 hr, and the solvent was removed *in vacuo*. The residue was dissolved in a sufficient volume of water and the aqueous solution was neutralized with AcOH. The precipitate formed was collected by filtration and successively washed with H_2O and EtOH. Recrystallization of it from EtOH gave colorless prisms of **5**.

b) **3b** (2.5 g, 0.01 mole) was fused with N,N′-dimethylurea (1.8 g, 0.02 mole) at 220° for 1 hr. To the resulting oily substance was added 5 ml of EtOH. Crystals that formed were collected and washed with EtOH to give **5c** (1.1 g, 42.9%), colorless prisms (from EtOH), mp 270—271.° The IR spectrum of this compound was identical with that of the product obtained above.

2,7-Dialkyl-5-methyl(or phenyl)-4,6-dioxo-4,5,6,7-tetrahydropyrazolo[3,4-*d*]pyrimidines (**6**)[Table III]——a) The following preparation illustrates a general procedure. In an aqueous solution of NaOH (0.5 g)

in 20 ml of H_2O was dissolved **5**(0.01 mole). This alkaline solution was cooled and added dropwise with Me_2SO_4 (1.4 g). The mixture was shaken for several minutes, heated on a water bath for 5 min, cooled, filtered and washed with cold water to give white crystlas (**6a—d**).

b) A mixture of **5d** (2.2 g, 0.007 mole), $C_6H_5CH_2Cl$ (1g, 0.0077 mole) and NaOH solution (0.35 g in 15 ml of H_2O) was heated on a water bath for 1 hr. The resulting crystals were collected to yeidl **6e** (1.3 g).

c) **8** (2g, 0.01 mole) was dissolved in an aqueous solution of NaOH (5.3 g) in 65 ml of H_2O. Me_2SO_4 (12.3 g) was added dropwise to the resulting alkaline solution which was cooled with cold water. The reaction mixture was then heated on a water bath for 1 hr and extracted with three 50 ml portions of $CHCl_3$. The combined extracts were dried ($MgSO_4$) and evaporated to give **6c** (0.1 g), colorless needles (from EtOH), mp 190—192°. The identity of this product with that prepared from **5c** was shown by a mixture melting point and IR spectra comparisons.

d) Debenzylated compounds (**13a** and **13b**) were methylated with Me_2SO_4 as described above to give **6a** and **6b** respectively. The IR spectra showed that these two products were identical with those synthesized from **5a** and **5b** respectively.

2-Methyl-6-methylmercapto-5-phenyl-4-oxo-4,5-dihydropyrazolo[3,4-*d*]pyrimidine (**7a**)——**5e** was methylated with Me_2SO_4 as described above to give S-methylated compound, **7a**(92.1%), colorless needles (from MeOH), mp 214—216°. *Anal.* Calcd. for $C_{13}H_{12}ON_4S$: C, 57.35; H, 4.44; N, 20.58. Found: C, 57.58; H, 4.69; N, 20.41. UV λ_{max}^{EtOH} mμ (ε): 230 (16300), 238 (14250, shoulder), 271 (8750).

2-Benzyl-6-methylmercapto-5-phenyl-4-oxo-4,5-dihydropyrazolo[3,4-*d*]pyrimidine(**7b**)——**5f** was methylated as described above to give **7b**(89.4%), colorless needles (from MeOH), mp 221—223°. *Anal.* Calcd. for $C_{19}H_{16}ON_4S$: C, 65.51; H, 4.63; N, 16.08. Found: C, 65.74; H, 4.88; N, 16.11. UV λ_{max}^{EtOH} mμ(ε): 232 (19000), 240 (17650, shoulder), 270 (11400).

2-Benzyl-4,5-dioxo-4,5,6,7-tetrahydropyrazolo[3,4-*d*]pyrimidine(**8**)——**3b** (12.3 g, 0.05 mole) was fused with urea (9 g, 0.015 mole) at 220° for 2 hr. The resulting solid was cooled and ground to a fine powder, and the powder was washed with hot EtOH to give **8** (5 g, 41.3%), white powder, mp>300°. This product was hardly soluble in organic solvents and in NaOH solution. Recrystallization from AcOH gave an analytically pure sample. *Anal.* Calcd. for $C_{12}H_{10}O_2N_4$: C, 59.50; H, 4.16; N, 23.13. Found: C, 59.61; H, 4.33; N, 23.20.

N-(4-Ethoxycarbonyl-1-methylpyrazol-5-yl)-N′-carbamoyl-N′-methylurea (**9**)——This compound was preprared according to Schmidt, *et al.*[4] We obtained it in 66.4% yield, mp 152—153° (lit. mp 148—149°). NMR ($CDCl_3$) δ: 7.83 (1H, singlet, pyrazole ring-H), 6.17 (2H, two broad peaks, NH-CO-N(Me)-CO-NH-), 4.21 (2H, quartet, J=7 cps, O-CH_2-Me), 3.67 (3H, singlet, pyrazole ring CH_3), 2.80 (6H, doublet, J=5 cps, two CO-NCH_3), 1.26 (3H, triplet, J=7 cps, O-C-CH_3).

N-(4-Ethoxycarbonyl-1-methylpyrazol-5-yl)-N′-phenylurea (**10**)——**2** (5 g, 0.03 mole) and C_6H_5NCO (4 g, 0.033 mole) were condensed in C_6H_6 (50 ml) as described in the synthesis of **4b** to give **10** (4 g, 51.3%), colorless needles (from MeOH–ether), mp 167—169°. *Anal.* Calcd. for $C_{14}H_{16}O_3N_3$: C, 58.32; H, 5.59; N, 19.44. Found: C, 58.42; H, 5.70; N, 19.42.

1,5-Dimethyl-4,6-dioxo-4,5,6,7-tetrahydropyrazolo [3,4-*d*]pyrimidine (**11a**)——As described in the synthesis of series **5**, the ring closure of **9** gave **11a** (49.8%), colorless prisms (from EtOH), mp>300°. *Anal.* Calcd. for $C_7H_8O_2N_4$: C, 46.66; H, 4.48; N, 31.10. Found: C, 46.72; H, 4.70; N, 31.35.

1-Methyl-5-phenyl-4,6-dioxo-4,5,6,7-tetrahydropyrazolo[3,4-*d*]pyrimidine (**11b**)——According to the same procedure which was described above, **11b** was obtained as colorless prisms, in 92% yield, mp>300°. *Anal.* Calcd. for $C_{12}H_{10}O_2N_4$: C, 59.50; H, 4.16; N, 23.13. Found: C, 59.14; H, 4.36; N, 23.36. UV λ_{max}^{EtOH} mμ (ε): 251 (8000).

1,5,7-Trimethyl-4,6-dioxo-4,5,6,7-tetrahydropyrazolo[3,4-*d*]pyrimidine (**12a**)——This compound was prepared according to Schmidt, *et al.*[6] We obtained it in 36.6% yield, mp 237—238° (lit. mp 229—231°). *Anal.* Calcd. for $C_8H_{10}O_2N_4$: C, 49.48; H, 5.19; N, 28.85. Found: C, 49.42; H, 5.21; N, 28.92.

1,7-Dimethyl-5-phenyl-4,6-dioxo-4,5,6,7-tetrahydropyrazolo[3,4-*d*]pyrimidine (**12b**)——**11b** was methylated with Me_2SO_4 as described in the preparation of **6a—d** to give **12b** as colorless needles (from MeOH) in 94.9% yield, mp 209—211°. *Anal.* Calcd. for $C_{13}H_{12}O_2N_4$: C, 60.93; H, 4.72; N, 21.87. Found: C, 60.63; H, 4.62; H, 22.14. UV λ_{max}^{EtOH} mμ (ε): 239 (3670), 254 (4750).

5,7-Dimethyl-4,6-dioxo-4,5,6,7-tetrahydropyrazolo[3,4-*d*]pyrimidine (**13a**)——10% Pd-C (1.2 g) was added to a solution of **6c** (5.4 g, 0.02 mole) in 65 ml of AcOH and the mixture was allowed to hydrogenate in an autoclave at 220° for 4 hr with 35 atm of H_2. The reaction mixture was filtered and the solvent was evaporated *in vacuo* to result in the formation of the crystals. Recrystallization from MeOH gave **13a** (1 g, 27.7%), colorless needles, mp 277—279° (lit.[7] mp 279°). *Anal.* Calcd. for $C_7H_8O_2N_4$: C, 46.66; H, 4.48; N, 31.10. Found: C, 46.70; H, 4.71; N, 31.30. UV λ_{max}^{EtOH} mμ (ε): 238 (3750), 259 (3925). Mass Spectrum *m/e*: 180 (M^+).

7-Methyl-5-phenyl-4,6-dioxo-4,5,6,7-tetrahydropyrazolo[3,4-*d*]pyrimidine (**13b**)——**6d** (5 g, 0.015 mole) was reduced in the presence of 10% Pd-C (1.2 g) under the same conditions as described above to give **13b** (3 g, 83.3%), colorless needles (from MeOH), mp >300°. *Anal.* Calcd. for $C_{12}H_{10}O_2N_4$: C, 59.50; H, 4.16; N, 23.13. Found: C, 59.46; H, 4.43; N, 23.05. UV λ_{max}^{EtOH} mμ (ε): 237 (3500), 259 (3400). Mass Spectrum *m/e*: 243 (M^+).

5-Amino-4-ethoxycarbonyl-1-methylcarbamoylpyrazole (15a)——a) **1** (3.1 g, 0.02 mole) was condensed with MeNCO (1.2 g, 0.02 mole) as described in the synthesis of **4a** to yield **15a** (3.1 g, 73.1%), colorless needles (from EtOH), mp 133—134° (lit.[8] mp 133°). *Anal.* Calcd. for $C_8H_{12}O_3N_4$: C, 45.28; H, 5.70; N, 26.40. Found: C, 45.26; H, 5.58; N, 26.58. NMR ($CDCl_3$) δ: 7.60 (1H, singlet, pyrazole ring-H), 6.90 (3H, broad peak, -NH- and $-NH_2$), 4.26 (2H, quartet, $J=7$ cps, O-CH_2-Me), 2.96 (3H, doublet, $J=5$ cps, N-CH_3), 1.34 (3H, triplet, $J=7$ cps, O-C-CH_3). UV λ_{max}^{EtOH} mμ (ε): 265 (7750).

b) MeNCO (1.2 g) was added into a solution of 80% of hydrazine hydrate (1.3 g) in MeOH (5 ml). The mixture was let stand at room temperature for 1 hr. Solid substance formed was removed by filtration. The solvent in the filtrate was evaporated *in vacuo* to give colorless oily substance which upon cooling solidified to give 4-methyl semicarbazide (1.3 g, 73.5%), mp 126—129°. A solution of 4-methyl semicarbazide (1 g, 0.0112 mole) and ethyl ethoxymethlenecyanoacetate (1.9 g, 0.0112 mole) in EtOH (15 ml) was let stand at room temperature for 2 hr. Crystals which formed were collected, and recrystallized from H_2O to give **15a** (0.8 g, 33.7%) as colorless needles, mp 133—134°. The IR spectra showed that this product was identical with that synthesized above.

5-Amino-4-ethoxycarbonyl-1-phenylcarbamoylpyrazole (15b)——a) **1** (3.1 g, 0.02 mole) was condensed with C_6H_5NCO (2.6 g, 0.022 mole) as described in the preparation (a) of **15a** to give **15b** (4 g, 73%), colorless plates (from EtOH), mp 130—131°. *Anal.* Calcd. for $C_{13}H_{14}O_3N_4$: C, 56.93; H, 5.15; N, 20.43. Found: C, 57.17; H, 5.18; N, 19.99. NMR ($CDCl_3$) δ: 8.93 (1H, broad peak, -NH-), 7.66 (1H, singlet, pyrazole ring-H), 7.35 (5H, multiplet, C_6H_5), 6.95 (2H, broad peak, $-NH_2$), 4.27 (2H, quartet, $J=7$ cps, O-CH_2-Me), 1.35 (3H, triplet, O-C-CH_3). UV λ_{max}^{EtOH} mμ (ε): 248 (29150).

b) Ethyl ethoxymethylenecyanoacetate (2 g, 0.0118 mole) and 4-phenyl semicarbazide (2 g, 0.0118 mole) were dissolved in 20 ml of EtOH. The solution was let stand at room temperature until the crystals were precipitated. After the addition of 10% HCl (4 ml) to it, the mixture was refluxed on a water bath for 20 min. The solvent was evaporated *in vacuo*. The pasty residue was dissolved in 20 ml of MeOH and the solution was cooled. Solid substance formed was removed by filtration, and the filtrate was neutralized with 10% NaOH, boiled for 5 min and cooled. Crystals formed were collected and washed with H_2O. Recrystallization from EtOH gave **15b** (0.5 g, 15.6%). The IR spectra showed that this compound was identical with that synthesized above.