A Novel Synthesis of 3,9-Dialkyl and 8-Aryl-3,9-dimethylxanthines

Shaker Youssif,* Azza El-Kafrawy, Besheer Bayoumy, and Said El-Bahaie

Department of Chemistry, Faculty of Science, Zagazig University, Zagazig, Egypt
Received September 6, 2001

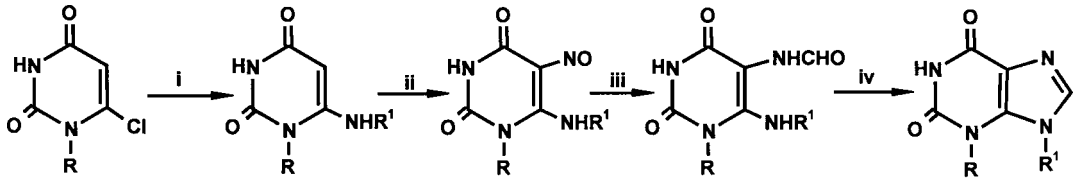
Several compounds of 3,9-dialkylxanthines were prepared from 1-methyl-6-chlorouracil *via* nucleophillic reactions with different aliphatic amines, followed by nitrosation, reduction, formaylation and finally dehydrocyclization. On the other hands, a series of 8-aryl-3,9-dimethylxanthines were synthesized by dehydrocyclization of 5-arylamido-1-methyl-6-methylaminouracils either by fussion or oxidation of 5-arylidine-amino-1-methyl-6-methylaminouracils using sodium periodate. Phosphoryl chloride was found to be uneffective reagent for dehydrocyclization that, gave another products from 1,3-oxazolo[5,4-d] pyrimidines.

Keywords : 3,9-Dialkylxanthines, 5-Arylidineamino-, 5-Arylamidouracils, 8-Aryl-3,9-dimethylxanthines, Oxazolopyrimidine-6-one.

Purine derivatives and their analogues have critical roles in various biological processes and considerable attention has been given to the field of purine chemistry in a search for potential antagonists.[1,2] The syntheses of purines generally involved the condensation-cyclization of 6-amino-5-nitrosopyrimidines with several carbon sources, such as benzylideneaniline,[3,4] aromatic aldehydes,[5] quarternized Mannich bases.[6] Vilsmeier reagents[7] and amide acetals[8] or by the reaction of 6-anilinouracils with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD)[9] as nitrogen source. 3,9-dimethylxanthines has been prepared by various methods.[10-13] 8-Arylpurines have been synthesized either by dehydrocyclization of 4-amino-5-arylamidopyrimidines with phosphoryl chloride,[14,15] phosphoric acid[16] and by dry heating,[17] or by cyclization of Schiffs base analogues using ferric chloride,[18] nitrobenzene,[19] or bisulfite adduct of aldehydes.[20] We report herein the synthesis of some purine analogues, namely 3,9-dimethyl-, and 8-aryl-3,9-dimethylxanthines.

The sequence starting from 6-chloro-1-methyluracil (**1a**)[21,22] is the most favored method for the synthesis of 3,9-dimethylxanthine. The treatment of 6-chloro-1-methyl- and/or 6-chloro-1-propyluracil (**1a**, **b**) with different alkyl amines such as methyl-, isopropyl-, *n*-butyl-, neopentylamine in ethanol were heated under reflux for a short period to afford 1-alkyl-6-alkylaminouracil **2a-h**. The nitrosation of compounds **2a-h** using sodium nitrite in acetic acid at room temperature gave 5-nitroso derivatives **3a-g** which on reductive formylation gave **4a-g**. The dehydrocyclization of 5-formamidouracils **4a-g** using a mixture of formamide/formic acid led to the formation of **5a-g** as shown in (Scheme 1) in a moderate yields. ^{1}H-nmr data were shown in Tables 1, 2 and 3.

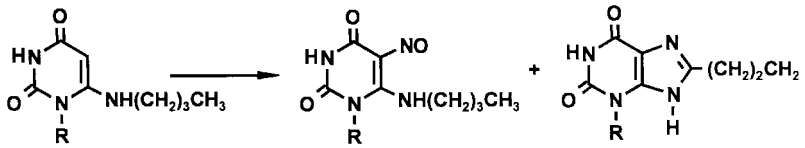
In the course of nitrosation step for the preparation of **3c**, **g** the 3,8-dialkylxanthine derivatives **6a**, **b** were formed simultaneously. The structures were confirmed by ^{1}H-nmr (DMSO-d_6) at δ 13.1 (s, 1H, NH(3)), 11.07 (s, 1H, NH(9)) and MS: m/z (%) = M^- 208 (70), M-CH_2CH_3 179 (63), 137



i) alkylamine, EtOH; ii) $NaNO_2$/AcOH; iii) Zn/ HCOOH; iv) $HCONH_2$/ HCOOH

Compd. No.	R	R^1
5a	CH_3	CH_3
5b	CH_3	$CH(CH_3)_2$
5c	CH_3	$(CH_2)_3CH_3$
5d	CH_3	$CH_2C(CH_3)_3$
5e	$CH_2CH_2CH_3$	CH_3
5f	$CH_2CH_2CH_3$	$(CH_2)_3CH_3$
5g	$CH_2CH_2CH_3$	$CH_2C(CH_3)_3$

Scheme 1



2c,g **3c,g** **6a,b**

Where R = CH_3, $CH_2CH_2CH_3$

Table 1. ^{1}H-nmr spectral data for **2b-h**, δ-values in DMSO-d_6

Compd. no.	δ-ppm				
	N_1-alkyl	N_3-H	C_5-H	C_6-NH	another signal
2b	3.18 (s, 3H, CH_3)	10.41 (s, 1H)	4.5 (s, 1H)	6.19 (d, 1H)	3.5 (m, 1H, CH), 1.5 (d, 6H, $2CH_3$)
c	3.18 (s, 3H, CH_3)	10.41 (s, 1H)	4.47 (s, 1H)	6.67 (t, 1H)	3.02 (q, 2H, CH_2), 1.51 (m, 2H, CH_2), 1.32 (m, 2H, CH_2), 0.88 (t, 3H, CH_3)
d	3.25 (s, 3H, CH_3)	10.43 (s, 1H)	4.66 (s, 1H)	6.38 (t, 1H)	2.88 (d, 2H, CH_2), 0.92 (s, 9H, $3CH_3$)
e	3.71 (t, 2H, CH_2)	10.42 (s, 1H)	4.41 (s, 1H)	6.94 (q, 1H)	1.52 (m, 2H, CH_2), 0.92 (t, 3H, CH_3)
f	3.79 (t, 2H, CH_2)	10.40 (s, 1H)	4.5 (s, 1H)	6.18 (d, 1H)	3.51 (m, 1H, CH), 1.45 (m, 2H, CH_2), 1.14 (d, 6H, $2CH_3$), 0.83 (t, 3H, CH_3)
g	3.72 (t, 2H, CH_2)	10.39 (s, 1H)	4.45 (s, 1H)	6.70 (t, 1H)	3.02 (m, 2H, CH_2), 1.48 (m, 4H, $2CH_2$), 1.28 (m, 2H, CH_2), 0.86 (2t, 6H, $2CH_3$)
h	3.84 (t, 2H, CH_2)	10.39 (s, 1H)	4.65 (s, 1H)	6.46 (t, 1H)	2.88 (d, 2H, CH_2), 1.51 (m, 2H, CH_2), 0.85 (s, 9H, $3CH_2$)

Table 2. ^{1}H-nmr spectral data for compounds (**3a-g**) in DMSO-d_6

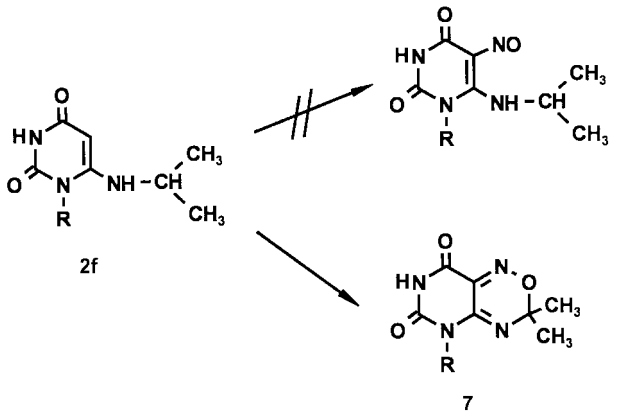
Compd. no.	δ-ppm				
	N_1-alkyl	N_3-H	C_6-NH	C_6-N-alkyl	another signal
3a	3.41 (s, 3H, CH_3)	15.29 (s, 1H)	11.28 (q, 1H)	3.13 (d, 3H, CH_3)	-
b	3.43 (s, 3H, CH_3)	13.82 (s, 1H)	11.30 (s, 1H)	3.07 (m, 1H, CH)	1.08 (d, 6H, $2CH_3$)
c	3.43 (s, 3H, CH_3)	13.84 (s, 1H)	10.97 (t, 1H)	3.5 (s, 2H, CH_2)	0.87 (t, 3H, CH_3), 1.66 (m, 2H, CH_2), 2.65 (m, 2H, CH_2)
d	3.38 (s, 3H, CH_3)	16.01 (s, 1H)	10.98 (s, 1H)	3.56 (d, 2H, CH_2)	0.98 (s, 9H, $3CH_3$)
e	3.73 (t, 2H, CH_2)	13.88 (s, 1H)	11.26 (q, 1H)	3.07 (d, 3H, CH_3)	1.55 (m, 2H, CH_2), 0.78 (t, 3H, CH_3)
f	3.69 (t, 2H, CH_2)	13.86 (s, 1H)	11.27 (q, 1H)	3.19 (p, 2H, CH_2)	1.48 (m, 4H, $2CH_2$), 1.27 (m, 2H, CH_2), 0.79 (m, 6H, $2CH_3$)
g	3.78 (t, 2H, CH_2)	13.92 (s, 1H)	11.32 (t, 1H)	3.12 (d, 2H)	1.62 (m, 2H, CH_2), 0.85 (t, 3H, CH_3), 0.89 (s, 9H, $3CH_3$)

Table 3. ^{1}H-nmr spectral data for (**4a-g**), δ-values in DMSO-d_6

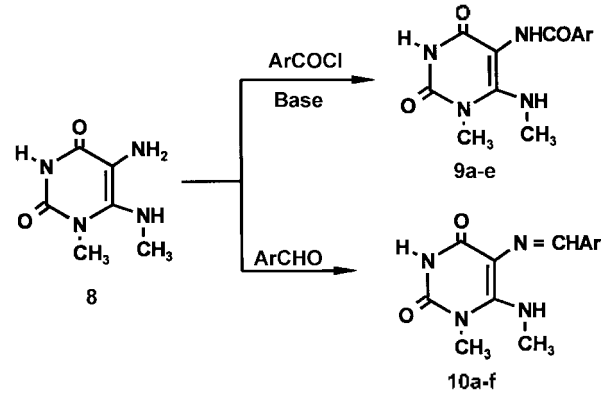
Compd. no.	δ-ppm					
	N_1	N_3-H	5-NH	6-NH	5-CHO	another signals
13a	3.24 (s, 3H, CH_3)	10.78s	8.68d	6.58q	8.33d	2.87(d, 3H)
			8.01d	6.39q	7.76d	
b	3.28 (s, 3H, CH_3)	10.87s	8.74d	6.59q	8.1d	1.12 (d, 6H),
			8.22d	6.28q	7.76d	3.28 (m, 1H)
c	3.28 (s, 3H, CH_3)	10.8s	8.68d	6.12q	8.08d	0.85 (t, 3H)
		10.24s	8.24d	5.97q	7.74d	1.26 (m, 2H)
						1.43 (m, 2H)
d	3.35 (s, 3H, CH_3)	10.98d	9.00d	5.85q	8.10d	0.84 (s, 9H)
				5.45q	7.74d	2.98 (d, 2H)
e	3.74 (t, 2H, CH_2)	10.81s	8.64d	6.46t	8.07d	0.84 (t, 3H)
		10.72s	8.28d	6.32t	7.73d	1.94 (m, 2H)
f	3.78 (t, 2H, CH_2)	10.77s	8.71d	6.34t	8.07d	0.84 (2t, 6H)
			8.28d	6.13t	7.75d	1.21 (m, 2H)
						1.45 (m, 4H)
g	3.8 (t, 2H, CH_2)	10.97s	8.96d	5.68t	8.09d	0.83 (3t, 3H)
			8.35d	8.39t	7.72d	1.56 (m, 2H)
						2.9 (d, 2H)

(22), 98 (7), 48 (100), 29 (49).

The nitrosation of compound **2f** did not give the expected 5-nitroso analogue, but instead gave 3,3-dimethyl-5-propyl-6,8-dioxo-5,6,7,8-tetrahydro-3H-pyrimido[5,4-c]-1,2,5-oxadiazine (**7**), upon stirring with sodium nitrite and acetic acid for 12h at room temperature. The structure of the compound 7 was confirmed by ^{1}H-nmr, mass and uv spectra. Its uv spectrum was identical to that of the analogous 3,3,5,7-tetramethyl-6,8-dioxo-5,6,7,8-tetrahydro-3H-pyrimido[5,4-c]-1,2,5-oxadiazine, prepared by Goldner.[23] The mass spectrum of the compound 7 showed MS: m/z = M^- 238, M^+-CH_3 223, M^+-CH_3CN 197, M^--CH_3NCO 181 and other fragment ions.



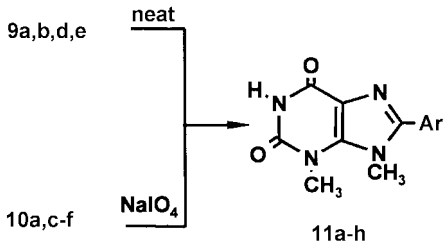
Treatment of 5-amino-1-methyl-6-methylaminouracil (**8**), (which was prepared by the hydrogenolysis of 1-methyl-6-methylamino-5-nitrosouracil (**3a**)[11]) with aroyl chlorides under proper conditions (benzoyl chloride, 4-methyl-, 2-chlorobenzoyl chloride in 1 N NaOH at 0 °C, with 4-nitrobenzoyl chloride in ethyl acetate in presence of sodium bicarbonate at 0 °C, or with 4-triflouromethylbenzoyl chloride in pyridine at room temperature) afforded the corresponding 5-arylamido-1-methyl-6-methylaminouracils (**9a-e**) in a good yields (Scheme 2). The uv spectra of these compounds showed close resemblance of absorptions between 204 and 265 nm.



No.	Ar
10a	C_6H_5
10b	4-$CH_3OC_6H_4$
10c	2-$NO_2C_6H_4$
10d	3-$NO_2C_6H_4$
10e	4-Pyridyl
10f	2-Furyl

No.	Ar
9a	C_6H_5
9b	4-$CH_3C_6H_4$
9c	2-Cl.C_6H_4
9d	4-$NO_2C_6H_4$
9e	4-$CF_3C_6H_4$

Scheme 2



No.	Ar.	No.	Ar.
11a	-C_6H_5	11e	2-NO_2.C_6H_4
11b	4-CH_3.C_6H_4	11f	3-NO_2.C_6H_4
11c	2-Cl.C_6H_4	11g	4-pyridyl
11d	4-CF_3.C_6H_4	11h	2-furyl

Scheme 3

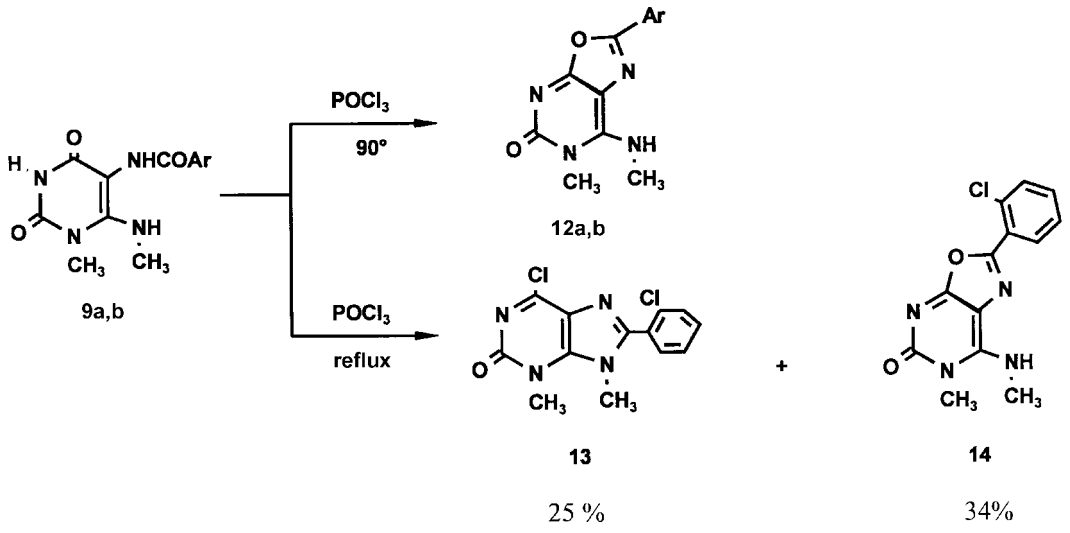
Reaction of compound **8** with different aromatic aldehydes namely, benzaldehyde, 4-anisaldehyde, 2-nitro-, 3-nitrobenzaldehyde, pyridine-4-caboxaldehyde and 2-furaldehyde with stirring at room temperature for 15-60 min gave the corresponding Schiffs bases 5-arylidineamino-6-methylaminouracils (**10a-f**) in good yields (Scheme 2).

Dehydrative cyclization of the compounds **9a-e** by heating at 280-320 °C and oxidation of compounds **10a-f** by refluxing with sodium periodate in absolute ethanol for 3-36h gave the corresponding 8-aryl-3,9-dimethylxanthines (**11a-i**) (Scheme 3). The structures of these compounds were proved by elemental analyses, uv spectral data which were similar to those of 8-arylpurines[16] except the compounds **11c** and **11f** which exhibit a hypsochromic shift due to the planarity of 8-aryl with the xanthine ring.

An attempt was made to prepare 8-arylpurines by the action of freshly distilled phosphoryl chloride on compounds 9, but 2-aryl-5-methyl-4-methylamino-1,3-oxazolo[5,4-d] pyrimidine-6-one (**12a, b**) were formed instead on heating with phosphoryl chloride at 90 °C in an oil bath. (Scheme 3) ^{1}H nmr for compound **12a** shows doublet for the methyl group of $NHCH_3$(6) at δ = 3.39, quartet for NH at δ = 8.11 and the absence of NH(3) group. On the other hand, when **9b** was heated under reflux with phosphoryl chloride for 3.5 h two products: 2,6-dichloro-9-methyl-8-(2-chlorophenyl)-purine (**13**) and 2-(2-chlorophenyl)-5-methyl-4-methylamino-1,3-oxazolo[5,4-d]pyrimidine-6-one (**14**) were isolated. (Scheme 4). We conclude that the $POCl_3$ at 90 °C acts as dehydrocyclizing agent but at higher temperature acts as a halogenated and dehydrocyclizing agent.

Experimental Section

All melting points were recorded on an electrothermal gallenkamp apparatus and are uncorrected. The ^{1}H nmr



Scheme 4

spectra were recorded on a Bruker AC 250 spectrometer in d (ppm) and with tetramethylsilane as the internal standard. The UV spectra were determined with Perkin Elmer, Lambda 5 or 15 spectrophotometer: λ_{max} in nm (log ε). The microanalyses were performed in the microanalytical laboratory of the Faculty of Chemistry, Konstanz University, Germany.

1-Methyl-, or 1-propyl-6-chlorouracil (1a, b).[21,22] These compounds were prepared according to the reported method[21,22]

1-Alkyl-6-alkylaminouracil (2a-h). A mixture of **1a** and/or **1b** (25.5 mmol) in absolute ethanol (15 mL) and alkylamines (150 mmol) (40% ethanolic methylamine, isopropyl, 50% ethanolic *n*-butyl and neopentylamine) were heated under reflux for 15 min. After cooling, the precipitated product was collected by filtration, dried in the oven and recrystallised from appropriate solvent into colourless crystals (Table 1).

2a:[11] m.p. 275-77°; 77% yield; R_f(SG) = 0.33A; uv (methanol): 265 (4.35), 203 (4.15). Recrystallized from water. Anal. Calcd. for $C_6H_9N_3O_2$: C, 46.44; H, 5.85; N, 27.08. Found: C, 46.51; H, 6.12; N, 26.78.

2b: m.p. 266-68°; 84% yield; R_f(SG) = 0.39A; uv (methanol): 267 (4.33), 204 (4.20). Recrystallized from water. Anal. Calcd. for $C_8H_{13}N_3O_2$: C, 52.45; H, 7.15; N, 22.93. Found: C, 51.85; H, 7.03; N, 22.48.

2c: m.p. 212-14°; 96% yield; R_f(SG) = 0.70B; uv (methanol): 267 (4.37), 204 (4.22); Recrystallized from water. Anal. Calcd. for $C_9H_{15}N_3O_2$: C, 54.81; H, 7.66; N, 21.30. Found: C, 54.41; H, 7.66; N, 21.37.

2d: m.p. 237°; 69% yield: R_f(SG) = 0.18A; uv (methanol): 268 (4.27), 203 (3.90); Recystallized from methanol. Anal. Calcd. for $C_{10}H_{17}N_3O_2$: C, 56.85; H, 8.11; N, 19.89. Found: C, 56.73; H, 8.17; N, 19.98.

2e: m.p. 215°; 71% yield: R_f(SG) = 0.43A; uv (methanol): 266 (4.33), 204 (4.09). Recrystallized from methanol. Anal. Calcd. for $C_8H_{13}N_3O_2$: C, 52.44; H, 7.14; N, 22.90. Found: C, 54.45; H, 7.15; N, 23.45.

2f: m.p. 219°; 83% yield: R_f(SG) = 0.59A; uv (methanol): 268 (4.36), 203 (4.20). Recrystallized from acetone. Anal. Calcd. for $C_{10}H_{17}N_3O_2$: C, 56.86; H, 8.11; N, 19.89. Found: C, 56.49; H, 8.20; N, 20.25.

2g: m.p. 212-13°; 88% yield; R_f(SG) = 0.46A; uv (methanol): 267 (4.36), 203 (4.19). Recrystallized from ethanol. Anal. Calcd. for $C_{11}H_{19}N_3O_2$: C, 58.68; H, 8.49; N, 18.66. Found: C, 58.70; H, 8.34; N, 18.88.

2h: m.p. 202-03°; 83% yield: R_f(SG) = 0.62A; uv (methanol): 269 (4.29), 204 (4.11). Recrystallized from methanol. Anal. Calcd. for $C_{12}H_{21}N_3O_2$: C, 60.23; H, 8.83; N, 17.56. Found: C, 60.12; H, 8.91; N, 17.74.

1-Alkyl-6-alkylamino-5-nitrosouracil (3a-g). Compound **2a-e** and/or **2g, h** (19 mmol) was dissolved in water (40 mL), then sodium nitrite (22 mmol) and acetic acid (70 mmol) were added with stirring for 3h in an ice bath. There was generally a color changes in these reactions to either red, pink or violet. The precipitated product was collected by filtration, washed with ether and dried in the dessicator for 48h to afford **3a-g**.

The mother liquor of compound **3c, g** was evaporated in vacuo till dryness, water (10 mL) added and the precipitate collected by filtration, dried in the oven and recrystallized from ethanol to give compounds **6a** and **6b** respectively.

3a: m.p. 180°; 88% yield: R_f(SG) = 0.49A; uv (methanol): 314 (3.80), 230 (4.11).

3b: m.p. 140°; 34% yield; R_f(SG) = 0.30F; uv (methanol): 315 (3.50), 228 (3.80) Anal. Calcd. for $C_8H_{12}N_4O_3$: C, 45.28; H, 5.70; N, 26.40. Found: C, 45.12; H, 5.71; N, 25.94.

3c: m.p. 128°; 40% yield; R_f(SG) = 0.70A; uv (methanol): 317 (3.99), 229 (4.25) Anal. Calcd. for $C_9H_{14}N_4O_3$: C, 47.78; H, 6.23; N, 24.76. Found: C, 48.01; H, 6.02; N, 24.82.

3d: m.p. 137°; 71% yield: R_f(SG) = 0.77A; uv (methanol): 318 (3.90), 230 (4.20) Anal. Calcd. for $C_{10}H_{16}N_4O_3$: C, 49.99; H, 6.71; N, 23.32. Found: C, 49.96; H, 6.73; N, 23.05.

3e: m.p. 152°; 72% yield; R_f(SG) = 0.55A; uv (methanol): 314 (3.80), 230 (4.11) Anal. Calcd. for $C_8H_{12}N_4O_3$: C, 45.28; H, 5.69; N, 26.41. Found: C, 45.07; H, 5.70; N, 26.31

3f: m.p. 76°; 72% yield; R_f(SG) = 0.52A; uv (methanol): 314 (3.70), 229 (4.10). Anal. Calcd. for $C_{11}H_{18}N_4O_3$: C, 51.95; H, 7.12; N, 22.03. Found: C, 51.86; H, 6.95; N, 21.96.

3g: m.p. 105°; 63% yield; R_f(SG) = 0.38B; uv (methanol): 312 (3.60), 230 (4.09). Anal. Calcd. for $C_{12}H_{20}N_4O_3$: C, 53.71; H, 7.51; N, 20.88. Found: C, 53.67; H, 7.51; N, 20.60.

6a: m.p. 320-22°; 24% yield; R_f(SG) = 0.65B; 1H nmr: δ 13.11 (s, 1H, NH(3)), 11.08 (s, 1H, NH(9)), 3.35 (s, 3H, CH_3 (1)), 2.58 (t, 2H, CH_2), 1.07 (m, 2H, CH_2), 0.09 (t, 3H, CH_3). Anal. Calcd. for $C_9H_{12}N_4O_2$: C, 51.91; H, 5.81; N, 27.01. Found: C, 51.93; H, 5.81; N, 26.83.

6b: m.p. >320°; 26% yield; R_f(SG) = 0.59B. Anal. Calcd. for $C_{12}H_{18}N_4O_2$: C, 57.58; H, 7.24; N, 22.38. Found: C, 57.47; H, 7.26; N, 22.16.

1-Alkyl-6-alkylamino-5-formamidouracil (4a-g). A mixture of compounds **3a-g** (5 mmol), zinc dust (30 mmol) and formic acid (0.58 mmol) were heated under reflux for 15 min. The reaction mixture was filtered on hot and the filterate was evaporated *in vacuo* till dryness, then ethanol (10 mL) was added. The precipitated product was filtered, dried in the oven and recrystallized from appropriate solvent.

4a: m.p. 321°; 61% yield; uv (methanol): 271 (4.22), 205 (4.12).

4b: m.p. 240°; 72% yield; R_f(SG) = 0.67B; uv (methanol): 272 (4.00), 206 (3.95); recrystallized from methanol; Anal. Calcd. for $C_9H_{14}N_4O_3$: C, 47.78; H, 6.19; N, 24.77. Found: C, 47.69; H, 6.24; N, 25.05.

4c: m.p. 223°; 75% yield; R_f(SG) = 0.79E; uv (methanol): 272 (4.01), 207 (4.01); recrystallized from methanol; Anal. Calcd. for $C_{10}H_{16}N_4O_3$: C, 50.00; H, 6.71; N, 23.32. Found: C, 49.81; H, 6.62; N, 23.68.

4d: m.p. 215°; 82% yield; R_f(SG) = 0.32A; uv (methanol): 275 (4.20), 207 (4.18); recrystallized from methanol; Anal. Calcd. for $C_{11}H_{18}N_4O_3$: C, 51.98; H, 7.10; N, 22.04. Found: C, 51.80; H, 7.13; N, 21.66.

4e: m.p. 195°; 74% yield; R_f(SG) = 0.50E; uv (methanol): 272 (4.23), 202 (4.19); recrystallized from ethanol; Anal. Calcd. for $C_9H_{14}N_4O_3$: C, 47.78; H, 6.23; N, 24.76. Found: C, 48.02; H, 6.70; N, 23.37.

4f: m.p. 184-86°; 36% yield; R_f(SG) = 0.70A; uv (methanol): 273 (4.24), 204 (4.18); recrystallized from methanol; Anal. Calcd. for $C_{12}H_{20}N_4O_3$: C, 53.71; H, 7.49; N, 20.88. Found: C, 53.11; H, 7.53; N, 20.96.

4g: m.p. 190-92°; 57% yield; R_f(SG) = 0.72B; uv (methanol): 274 (4.38), 203 (4.34); recrystallized from ethanol; Anal. Calcd. for $C_{13}H_{22}N_4O_3$: C, 55.30; H, 7.80; N, 19.72. Found: C, 54.83; H, 7.74; N, 19.50.

3,9-Dimethylxanthines (5a-g). A mixture of compound **4a-g** (2 mmol), formamide (3.0 mL), water (0.25 mL) and formic acid (0.25 mL) were heated at 160° for 30 min. After cooling, the precipitated crystal was collected by filtration, dried in the oven and recrystallized from appropriate solvent to give **5a-g**.

5a: m.p. 336°; 46% yield; R_f(SG) = 0.72B; uv (methanol): 265 (3.72), 235 (3.71), 202 (4.02); recrystallized from water.

5b: m.p. 198-99°; 49% yield; R_f(SG) = 0.65E; uv (methanol): 268 (3.94), 237 (3.83), 201 (4.25); recrystallized from methanol. Anal. Calcd. for $C_9H_{12}N_4O_2$: C, 51.91; H, 5.81; N, 26.91. Found: C, 51.72; H, 5.80; N, 26.70.

5c: m.p. 126°; 44% yield; R_f(SG) = 0.60B; uv (methanol): 268 (3.96), 237 (3.86), 202 (4.25); recrystallized from ethanol. Anal. Calcd. for $C_{10}H_{14}N_4O_2$: C, 54.04; H, 6.35; N, 25.21. Found: C, 54.01; H, 6.35; N, 24.83.

5d: m.p. 262-64°; 70% yield; R_f(SG) = 0.41A; uv (methanol): 265 (3.95), 235 (3.96), 203 (4.24); recrystallized from ethanol. Anal. Calcd. for $C_{11}H_{16}N_4O_2$: C, 55.92; H, 6.82; N, 23.71. Found: C, 55.46; H, 6.78; N, 23.69.

5e: m.p. 256-58°; 50% yield; R_f(SG) = 0.51E; uv (methanol): 266 (3.95), 237 (3.83), 202 (4.15); recrystallized from ethanol. Anal. Calcd. for $C_9H_{12}N_4O_2$: C, 51.91; H, 5.81; N, 26.91. Found: C, 52.08; H, 5.83; N, 27.65.

5f: m.p. 189-90°; 64% yield; R_f(SG) = 0.46A; uv (methanol): 265 (3.88), 236 (3.85), 202 (4.20); recrystallized from water. Anal. Calcd. for $C_{12}H_{18}N_4O_2$: C, 57.58; H, 7.24; N, 22.38. Found: C, 57.36; H, 7.05; N, 22.44.

5g: m.p. 229-30°; 19% yield; R_f(SG) = 0.50A; uv (methanol): 266 (3.95), 236 (3.94), 202 (4.26); recrystallized from ethanol. Anal. Calcd. for $C_{13}H_{20}N_4O_2$: C, 59.07; H, 7.62; N, 21.99. Found: C, 59.20; H, 7.62; N, 21.18.

3,3-Dimethyl-5-propyl-6,8-dioxo-5,6,7,8-tetrahydro-3H-pyrimido[5,4-c]-1,2,5-oxadiazine (7). Compound **2f** (2 mmol) was suspended in water (10 mL) with stirring in ice bath, then acetic acid (8.7 mmol) and sodium nitrite (4.0 mmol) were added, a pink color appeared which changed to white precipitate with continuous stirring. The reaction mixture kept in refrigerator for two days. The precipitate was collected by filtration, dried in the oven and recrystallized from methanol (15 mL) to afford 7 with m.p. 190°; 43% yield; uv (methanol): 281 (4.12), 208 (4.11); Anal. Calcd. for $C_{10}H_{14}N_4O_3$: C, 50.41; H, 5.92; N, 23.51. Found: C, 50.51; H, 5.98; N, 23.74.

5-Amino-6-methylamino-1-methyluracil (8).[18] This compound was prepared as a reported method.[18]

5-Arylamido-1-methyl-6-methylaminouracils (9a-c). Compound **8** (3.0 g, 17.6 mmol) was dissolved in a solution of 1 N sodium hydroxide (30 mL) and an equimolar quantity of the aroyl chloride, benzoyl, 4-methylbenzoyl or 2-chlorobenzoyl chloride was added dropwise over a period of 0.5 h with stirring at 0 °C. The mixture was stirred for an additional 1h, and the pH of the solution was adjusted to 5 by adding conc. hydrochloric acid. The precipitate was filtered, washed with water, dried in the oven and recrystallised from ethanol (150 mL).

9a: m.p. 274 °C; 56% yield; R_f(SG) = 0.73B; uv (methanol): 271 (4.25), 222 (4.12), 209 (4.18). ^{1}H nmr: 10.75 (s, 1H, NH(C-3)), 9.03 (s, 1H, NH(C-5)), 7.90 (dd, 2H, aromatic), 7.43 (m, 3H, aromatic), 6.43 (q, 1H, NH(C-6), 3.25 (s, 3H, NMe(1)), 2.83 (d, 3H, NHMe(C-6)). Anal. Calcd. for $C_{13}H_{14}N_4O_3$: C, 56.93; H, 5.14; N, 20.42. Found: C, 56.80; H, 5.19; N, 21.00.

9b: m.p. 289°C; 64% yield; R_f(SG) = 0.24A; uv (methanol): 271 (4.28), 232 (4.29), 205 (4.52). ^{1}H nmr: 10.75 (s, 1H, NH(3)), 8.95 (s, 1H, NH(C-5)), 7.82 (d, 2H, aromatic),

7.27 (d, 2H, aromatic), 6.41 (q, 1H, NH(C-6)), 3.25 (s, 3H, NMe(1)), 2.83 (d, 3H, NHMe(C-6)), 2.34 (s, 3H, P-Me)). Anal. Calcd. for $C_{14}H_{16}N_4O_3$: C, 58.32; H, 5.58; N, 19.43. Found: C, 58.33; H, 5.63; N, 19.55.

9c: m.p. 303-304 °C; 58% yield; R_f(SG) = 0.48A; UV (methanol): 271 (4.19), 208 (4.27). ^{1}H nmr: 10.76 (s, 1H, NH(3)), 8.96 (s, 1H, NH(C-5)), 7.39-7.95 (m, 3H, aromatic), 6.46 (q, NH(C-6)), 3.25 (s, 3H, NMe(1)), 3.0 (d, 3H, NHMe (C-6)). Anal. Calcd. for $C_{13}H_{13}ClN_4O_3$: C, 50.57; H, 4.24; N, 18.15. Found: C, 50.62; H, 4.24; N, 18.60.

1-Methyl-6-methyl amino-5-(4-nitrobenzamido)uracil (9d). Compound **8** (2.0 g, 11.7 mmol) was dissolved in sodium bicarbonate solution (1.0 g in 32 mL of water) with stirring at 0 °C. 4-nitrobenzoyl chloride (2.2 mL) in ethylacetate (30 mL) was added dropwise. The reaction mixture was stirred for an additional 2 h. The formed precipitate was filtered, washed with ether, dried in the oven and recrystallised from ethanol (100 mL). m.p. 306-308 °C; 46% yield; R_f(SG) = 0.09A; uv (methanol): 270 (4.02), 235 (4.69), 204 (3.96). ^{1}H nmr: 10.82 (s, 1H, NH(3)), 9.41 (s, NH(C-5)), 8.33 (d, 2H, aromatic), 8.13 (d, 2H, aromatic), 6.50 (q, 1H, NH(C-6)), 3.26 (s, 3H, NMe(1)), 2.85 (d, 3H, NHMe(C-6)). Anal. Calcd. for $C_{13}H_{13}N_5O_5$: C, 48.90; H, 4.10; N, 21.93. Found: C, 48.95; H, 4.14; N, 22.00.

1-Methyl-6-Methylamino-5-(4-trifluoromethylbenzamido)-uracil (9e). Compound **8** (3.0 g, 17.6 mmol) was dissolved in pyridine (110 mL) and 4-trifluoromethylbenzoyl chloride (2.0 mL, 13.0 mmol) was added dropwise with stirring at room temperature for 5 h. The reaction mixture was poured on ice (150 g) and the precipitated product was collected by filtration, washed with ether, and dried to give **9e** (2.54 g). The mother liquor was evaporated *in vacuo* till dryness, water (30 mL) was added with stirring. The formed precipitate was filtered, washed with ether and dried to give an additional yield of **9e** (0.79 g). The product was (3.33 g) which recrystallized from a mixture of water/ethanol 2 : 1 to afford a colorless crystals, m.p. 283 °C; 58% yield; R_f (SG) = 0.48A; uv (methanol): 271 (4.25), 216 (4.24), 204 (4.31). ^{1}H nmr: 10.80 (s, 1H, NH(3)), 8.31 (s, 1H, NH), 8.09 (d, 2H, aromatic), 7.87 (d, 2H, aromatic), 6.50 (q, 1H, NH(C-6)), 3.26 (s, 3H, NMe(1)), 2.84 (d, 3H, NHMe(C-6)).

Anal. Calcd. for $C_{14}H_{13}F_3N_4O_3$: C, 49.13; H, 3.82; N, 16.36. Found: C, 49.06; H, 3.83; N, 16.20.

1-Methyl-5-arylidineamino-6-methylaminouracil (10a-f). Compound **8** (2.0 g, 1 l.7 mmol) was dissolved in water (100 mL) and a variety of equimolar amounts of aromatic aldehydes like benzaldehyde, 4-anisaldehyde, 2-nitro-, 3-nitrobenzaldehyde, pyridine-4-carboxaldehyde or 2-furaldehyde, was added with stirring at room temperature for 30 min. The precipitated product was collected by filtration, washed with methanol then ether, dried in the oven and recrystallized from a mixture of methanol/water 2 : 1.

10a: m.p. 235-237 °C; 57% yield; R_f(SG) = 0.64A; uv (methanol): 344 (4.17), 298 (4.13), 231 (4.02), 204 (4.20). ^{1}H nmr: 10.83 (s, 1H, NH(3)), 9.60 (s, 1H, CH(C-5)), 7.72 (dd, 2H, aromatic), 7.36 (m, 3H, aromatic), 6.92 (q, 1H, NH(C-6)), 3.26 (s, 3H, NMe(1)), 3.25 (d, 3H, NHMe(C-6)). Anal. Calcd for $C_{13}H_{14}N_4O_2$: C, 60.45; H, 5.46; N, 21.69. Found: C, 60.34; H, 5.41; N, 21.63.

10b: m.p. 224-226 °C; 43% yield: R_f(SG) = 0.76A; uv (methanol): 345 (4.36), 298 (4.27), 212 (4.27), 205 (4.26). ^{1}H nmr: 10.80 (s, 1H, NH(3)), 9.52 (s, 1H, CH(C-5)), 7.67 (d, 2H, aromatic), 6.95 (d, 2H, aromatic), 6.82 (q, 1H, NHMe(C-6), 3.80 (s, 3H, OMe(p)), 3.21 (s, NMe(1)), 3.19 (d, 3H, NHMe(C-6). Anal. Calcd for $C_{14}H_{16}N_4O_3$: C, 58.32; H, 5.59; N, 19.43. Found: C, 58.30; H, 5.52; N, 19.38.

10c: m.p. 231 °C; 52% yield: R_f(SG) = 0.78B; uv (methanol): 357 (3.99), 293 (4.15), 215 (4.25), 205 (4.34). ^{1}H nmr: 10.90 (s, 1H, NH(3)), 9.90 (s, 1H, CH(C-5)), 8.12 (d, 1H, aromatic), 7.92 (d, 1H, aromatic), 7.70 (t, 1H, aromatic), 7.50 (t, 1H, aromatic), 7.09 (q, 1H, NHMe(C-6)), 3.32 (s, 3H, NMe(1)), 3.25 (d, 3H, NHMe(C-6)).

Anal. Calcd for $C_{13}H_{13}N_5O_4$: C, 51.48; H, 4.32; N, 23.09. Found: C, 51.44; H, 4.28; N, 23.02.

10d: m.p. 249-250 °C; 76% yield: R_f(SG) = 0.59A; uv (methanol): 351 (3.70), 291 (3.70), 215 (3.81). ^{1}H nmr: 10.90 9s, 1H, NH(3)), 9.72 (s, 1H, CH(C-5)), 8.45 (s, 1H, aromatic), 8.13 (d, 2H, aromatic), 7.66 (t, 3H, aromatic), 7.10 (q, 1H, NHMe(C-6)), 3.23 (s, 3H, NMe(1)), 3.29 (s, 3H, NHMe(C-6)). Anal. Calcd for $C_{13}H_{13}N_5O_4$: C, 51.48; H, 4.32; N, 23.09. Found: C, 51.28; H, 4.30; N, 22.98.

10e: m.p. 245-246 °C; 55% yield: R_f(SG) = 0.48A; uv (methanol): 368 (3.93), 291 (3.85), 237 (3.74), 203 (3.86). ^{1}H nmr: 10.92 (s, 1H, NH(3)), 9.61 (s,1H, CH(C-5)), 8.56 (d, 2H, aromatic), 7.62 (d, 2H, aromatic), 7.16 (q, 1H, NHMe(C-6)), 3.32 (s, 3H, NMe(1), 3.29 (d, 3H, NHMe(C-6)). Anal. Calcd for $C_{12}H_{13}N_5O_2$: C, 55.59; H, 5.05; N, 27.01. Found: C, 55.51; H, 4.94; N 26.99.

10f: m.p. 223-225 °C; 19% yield; R_f(SG) = 0.80A; uv (methanol): 349 (4.40), 301 (4.27), 203 (4.19). ^{1}H nmr: 10.81 (s, 1H, NH(3)), 9.44 (s, 1H, CH(C-5)), 7.71 (d, 1H, aromatic), 6.83 (q, 1H, NH(6)), 6.75 (d, 1H, aromatic), 6.56 (d, 1H, aromatic), 3.30 (s, 3H, NMe(1)), 3.26 (d, 3H, NHMe (6)). Anal. Calcd for $C_{11}H_{12}N_4O_3$: C, 53.22; H, 4.87; N, 22.56. Found: C, 53.21; H, 4.85; N, 22.30.

8-Aryl-3,9-dimethylxanthine (11a-h).

Method A: Compound **9a**, **b**, **d**, **e** (1.7 mmol) were heated near their melting points for 1 h. The products were dissolved in 0.5 N of sodium hydroxide (30 mL) and filtered on boiling water (30 mL) and acidified with acetic acid (5 mL). After cooling, the precipitates were collected by filtration, washed with ether, dried and recrystallized from methanol to give **11a-d**.

Method B: To a suspensions solution of compound **10a**, **c-f** (1.0 mmol) in ethanol (15 mL), a solution of sodium periodate (4.0 mmol) in water (5 mL) was added. The mixtures were refluxed with stirring for 4h. After cooling, the precipitates were collected by filtration, washed with water, dried in the oven and recrystallized from methanol.

11a: m.p. 312-313 °C; 28% Yield; R_f(SG) = 0.36 A; uv (0.1 N HCl): 282 (3.82), 255 (3.90), 202 (4.29). ^{1}H nmr: 11.15 (s, 1H, NH(1)), 7.52+7.61 (m, 5H, aromatic), 3.85 (s, 3H, NMe(9)), 3.65 (s, 3H, NMe(3)). Anal. Calcd for $C_{13}H_{12}N_4O_2$: C, 60.92; H, 4.72; N, 21.86. Found: C, 60.88; H, 4.68; N, 21.82.

11b: m.p. > 330 °C; 85% Yield; R_f(SG) = 0.35 A; uv (0.1 N HCl): 287 (4.23), 249 (4.08), 203 (4.43). ^{1}H nmr: 11.19 (s. 1H, NH(1)), 7.54+7.50 (dd. 4H, aromatic). 3.83 (s, 3H. NMe(9)). 3.64 (s, 1H. NMe(3)). 2.37 (s, 3H. Me(p)). Anal. Calcd for $C_{14}H_{14}N_4O_2$: C. 62.21: H. 5.22; N, 20.72. Found: C. 62.02: H, 5.19; N. 20.88.

11c: m.p. 231 °C; 33% Yield: R_f(SG) = 0.71 A; uv (0.1 N HCl): 272 (4.30), 233 (4.12), 208 (4.44). ^{1}H nmr: 11.23 (s. 1H, NH(1)). 7.56+7.67 (m, 4H. aromatic). 3.66 (s. 3H. NMe (9)). 3.39 (s, 3H. NMe(3)). Anal. Calcd for $C_{13}H_{11}ClN_4O_2$: C. 53.71: H. 3.81; N, 19.27. Found: C. 35.70: H. 3.79; N, 19.31.

11d: m.p. 321 °C: 64% Yield: R_f(SG) = 0.46 A; uv (0.1 N HCl): 285 (3.96), 214 (4.29), 202 (4.16). ^{1}H nmr: 11.23 (s. 1H, NH(1)). 7.85-7.93 (dd. 4H. aromatic). 3.89 (s, 3H, NMe (9)). 3.65 (s. 3H, NMe(3)). Anal. Calcd for $C_{14}H_{11}F_3N_4O_2$: C, 51.85: H. 3.41; N, 17.27. Found: C. 51.80: H. 3.42; N, 17.25.

11e: m.p. 310-312 °C: 60% Yield; R_f(SG) = 0.57B; uv (0.1N HCl): 260 (4.20), 241 (4.20). 203 (4.53). ^{1}H nmr: 11.23 (s. 1H, NH(1)). 8.23 (d, 1H. aromatic), 7.87 (m, 2H. aromatic), 7.70 (d, 1H. aromatic). 3.73 (s. 3H. NMe(9)). 3.67 (s. 3H. NMe(3)). Anal. Calcd for $C_{13}H_{11}N_5O_4$: C. 51.82: H. 3.68: N, 23.24. Found: C, 51.78: H, 3.64; N. 23.21.

11f: m.p. 312-314 °C; 30% Yield: uv (0.1 N HCl): 328 (4.28). 300 (4.17), 275 (4.04). 204 (4.35). ^{1}H nmr: 11.26 (s. 1H, NH(1)), 8.42 (s. 1H, aromatic). 8.35 (d, 1H, aromatic). 8.10 (d. 1H, aromatic), 7.84 (t. 1H, aromatic), 3.91 (s. 3H. NMe(9)), 3,65 (s, 3H, NMe(3)). Anal. Calcd for $C_{13}H_{11}N_5O_4$: 51.82: H, 3.68: N. 23.24. Found: C, 51.80: H, 3.62: N, 23.19.

11g: m.p. 319 °C; 40% Yield: R_f(SG) = 0.25 A; uv (0.1 N HCl): 351 (4.23), 267 (4.02), 202 (4.42). ^{1}H nmr: 11.26 (s. 1H, NH(1)), 8.73+7.64 (dd, 4H, aromatic). 3.92 (s. 3H, NMe (9)). 3.65 (s. 3H. NMe(3)). Anal. Calcd for $C_{12}H_{11}N_5O_2$: C. 56.02: H. 4.31; N, 27.22. Found: C, 55.98: H. 4.29; N, 27.21.

11h: m.p. 305-307 °C; 20% Yield; R_f(SG) = 0.31 A; uv (0.1 N HCl): 291 (4.22), 234 (4.02). 207 (4.18). ^{1}H nmr: 11.25 (s, 1H, NH(1)). 7.91+6.70 (m. 3H. aromatic). 3.97 (s, 3H, NMe(9)), 3.64 (s, 3H. NMe(3)). Anal. Calcd for $C_{11}H_{10}N_4O_3$: C, 53.65: H. 4.09; N, 22.75. Found: C. 53.64: H. 3.99; N, 22.63.

2-Aryl-6-methyl-7-methylamino-1,3-oxazolo[5,4-d]pyrimidin-5-one (12a, b). A mixture of compound **9a**, **b** (2.0 mmol) and phosphoryl chloride was heated at 90 °C for 0.5h. The excess of phosphoryl chloride was evaporated *in vacuo* and the residue was poured on ice (15 g) with shaking. The precipitate was collected by filtration, washed with ether, dried in the oven and recrystallised from methanol.

12a: m.p. 320 °C, 89% yield. R_f = 0.62 in 1 : 9 methanol : chloroform. Anal. Calcd. for $C_{13}H_{12}N_4O_2$: C. 60.93; H. 4.71: N. 21.86. Found: C. 60.99: H, 4.77; N, 22.92.

12b: m.p. > 330 °C. 60% yield. R_f = 0.53 in 1 : 9 methanol : chloroform. ^{1}H nmr: 8.12 (q. 1H, NH(4)), 7.92-7.51 (m. 4H, aromatic). 3.41 (d, 3H. NHMe(4)). 3.32 (s, 3H. NMe(5)). Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C. 62.21; H, 5.21: N. 20.94. Found: C. 61.97: H, 5.17; N, 20.94.

2,6-dichloro-9-methyl-8-(2-chlorophenyl)purine (13) and 2-(2-chlorophenyl)-5-methyl-4-methylamino-1,3-oxazolo-[5,4-d] pyrimidine-6-one (14). A mixture of compound **9a** (1.0 g. 3.0 mmol) and redistilled phosphoryl chloride (30 mL) was heated under reflux for 3.5h (the color changed to dark brown after 1h from refluxing). The reaction mixture was poured on ice (20 g) with strong shaking. The precipitate was collected by filtration. dried and recrystallized from water (20 mL) giving compound **13**. m.p. 295-298 °C, yield (0.23 g. 25%) and R_f = 0.49 (CH_3OH : $CHCl_3$ 1 : 9). Anal. Calcd. for $C_{12}H_7Cl_3N_4$: C. 45.96: H, 2.24; N, 17.86. Found: C, 45.95: H, 2.30; N. 18.00.

The mother liquor was left standing overnight The precipitate was collected by filtration, dried in the oven and recrystallized from methanol (20 mL) to give compound **14**, m.p. 193 °C, yield (0.35 g. 34%) and R_f = 0.84 (CH_3OH: $CHCl_3$ 1 : 9). ^{1}H nmr: 8.19 (q. 1H, NH(4)), 7.96+7.47 (m. 4H. aromatic), 3.41 (d. 3H, NMe(4)). 3.36 (s. 3H, NMe(5)). Anal. Calcd. for $C_{13}H_{11}ClN_4O_2$: C. 53.71; H, 3.81; N, 19.27. Found: C, 52.80: H, 3.90; N. 19.00.

Where A: $CH_3OH/CHCl_3$ (1 : 9) B; $CH_3OH/CHCl_3$ (1 : 4) E: $CH_3OH/CHCl_3$ (3 : 7) F; CH_2Cl_2/CH_3OH (20 : 1).

Acknowledgment. The author wishes to thank Prof. Dr. W. Pfleiderer, Faculty of Chemistry. University of Konstanz, Germany, for many helpful discussions and to carry out this work in his laboratories.

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