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PHOSPHORUS PENTOXIDE IN ORGANIC SYNTHESIS – I

PHOSPHORUS PENTOXIDE–AMINE HYDROCHLORIDE MIXTURES AS REAGENTS IN A NEW SYNTHESIS OF HYPOXANTHINES

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Abstract—A series of 23 new 1,7-dihydro-6*H*-purin-6-ones, **3a–3w**, have been prepared by heating ethyl 4-acylamino-1*H*-imidazole-5-carboxylates, **2a–2f** and **2h**, with primary amine hydrochlorides and phosphorus pentoxide in *N,N*-dimethylcyclohexylamine. Imidazo[4,5-d][1,3]oxazin-7(1*H*)-ones **6** were similarly obtained from ethyl 1*H*-imidazole-5-carboxylates **2g–2i** which had bulky 4-acylamino groups. The starting materials **2** were made by acylation of the corresponding ethyl 4-amino-1*H*-imidazole-5-carboxylates **1**. The results from pesticide and anticancer screenings are included.

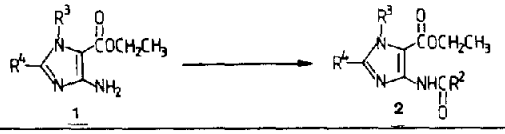
Because of the fundamental role of purines in nucleic acid chemistry and cellular biochemistry, the potential use of purine derivatives as chemotherapeutic agents in the treatment of malignant diseases was investigated as early as 1935.[1] Since then, many purines have been claimed to possess numerous useful biological activities. For example hypoxanthine derivatives are reported to have antiviral,[2] bactericidal and fungicidal[3] activities, and they are useful as anticoccidium agents, anthelmintics, plant growth regulators, and food additives.[4]

Recently, the P_2O_5-amine hydrochloride mixture was found to be a versatile reagent in ring closure reactions of *N*-acylanthranilates to yield 2,3-disubstituted 4(3*H*)-quinazolinones.[5] It was therefore of interest to investigate whether that procedure could be extended to ring closure reactions of ethyl 4-acylamino-1*H*-imidazole-5-carboxylates **2** in order to obtain polysubstituted hypoxanthines **3** with potential biological activity.

RESULTS AND DISCUSSION

Ethyl 4-acylamino-1*H*-imidazole-5-carboxylates **2** were easily obtained in high yields (58–91%) by acylation of the appropriate amines **1a**,[8] **1b**,[9] **1c**,[10] and **1d–1f**[11] (Table 1). **2a** has been prepared previously in a moderate yield.[12]

Table 1. Synthesis of ethyl 4-acylamino-1*H*-imidazole-5-carboxylates



	R^2	R^3	R^4	Yield [%]	m.p. [°C]	Analyses [%] C	H	N
2a	CH_3	H	H	91	225–227 (217–218)[12] (EtOH)			
2b	CH_3	CH_3	CH_3	80	117–118.5 (Diisopropylether/EtOH)	Calc. 53.32	6.71	18.66
						Found 53.03	6.74	18.55
2c	CH_3	CH_3	SCH_3	76	127–128 (Toluene)	Calc. 46.67	5.88	16.33
						Found 46.83	5.96	16.50
2d	CH_3	C_6H_5	H	77	127–128 (Ethyl acetate)	Calc. 61.52	5.53	15.38
						Found 61.82	5.56	15.17
2e[a]	CH_3	C_6H_5	SCH_3	84	101–102 (Light petroleum/EtOH)	Calc. 56.41	5.37	13.16
						Found 56.60	5.35	13.40
2f	CH_3	4-ClC_6H_4	H	58	193.5–194.5 (Ethyl acetate)	Calc. 54.64	4.59	13.65
						Found 54.26	4.50	13.59
2g	C_6H_5	CH_3	CH_3	70	106–107 (Diisopropylether)	Calc. 62.70	5.97	14.63
						Found 62.55	5.93	14.60
2h	C_6H_5	C_6H_5	H	90	195–196 (EtOH)	Calc. 68.04	5.11	12.53
						Found 67.74	5.05	12.76
2i	3,4,5-$(CH_3O)_3C_6H_2CH{=}CH$	C_6H_5	H	79	188.5–189.5 (EtOH)	Calc. 63.85	5.58	9.31
						Found 63.52	5.62	9.28

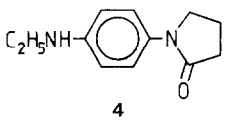
[a] Calc. S, 10.04; Found S, 10.21

Heating of ethyl 4-acetylamino-1*H*-imidazole-5-carboxylates **2a–2b, 2d** and **2f** with primary amine hydrochlorides in the molar ratio 1 : 4 in a mixture of phosphorus pentoxide (P_2O_5) and *N, N*-dimethylcyclohexylamine gave the corresponding 1,7-dihydro-6*H*-purin-6-ones **3** in 11–70% yields, Table 2.

The free amines were used instead of their hydrochlorides in the preparation of **3q** and **3s–u** without affecting the yields except for **3s**, which was isolated in only 11%, possibly because of side reactions during the prolonged reaction time. In addition to **3s** there was obtained a small amount of 1-[4-(ethylamino)phenyl]-2-pyrrolidone **4**, which originates from ethylation of the starting amine by **2d**. Low yields were also obtained with amine hydrochlorides containing thermally unstable or reactive substituents as in the preparation of **3p** and **3r**.

In the reaction of **2d** with 4-amino-1-diethylaminopentane the carbethoxy group was split off and **5** was obtained as the only product in 20% yield.

In the reaction of 2-methylthioimidazole derivative **2c** with P_2O_5 and ethylamine hydrochloride in *N,N*-dimethylcyclohexylamine at 150° for 2.5 hr, the *S*-demethylated compound **3c** was obtained in fair yield (42%). When the reaction time was reduced to 15 min, it



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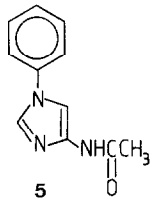

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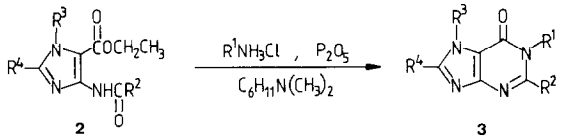
was possible to isolate 15% of the expected *S*-methylated product **3d**. Similarly the *S*-demethylated product **31** could be obtained in low yield from the complex product mixture in the reaction of **2e** with aniline hydrochloride in P_2O_5 and *N,N*-dimethylcyclohexylamine for 2.25 hr at 150°. Bergmann *et al.* have also reported an *S*-demethylation reaction when the protonated form of 1,7-dihydro-7-methyl-8-(methylthio)-6*H*-purin-6-one was refluxed for 72 hr in dimethylformamide,[13] while the neutral form proved to be stable under the same conditions. It is thus evident, that the acidic conditions in the P_2O_5-amine hydrochloride mixture favours an *S*-demethylation reaction.

When imidazolecarboxylates with bulky acylsubstituents **2g–2i** ($R^2 = C_6H_5$ or 3,4,5-$(CH_3O)_3C_6H_2CH{=}CH$)

Table 2. Yields and reaction conditions in the synthesis of **3**



2 3

	R^1	R^2	R^3	R^4	Yield [%]	Time [h]	Temp. [°C]
3a	H	CH_3	C_6H_5	H	55	1	150
3b	CH_3	CH_3	C_6H_5	H	59	0.5	150
3c[a]	CH_2CH_3	CH_3	CH_3	SH	42	2.5	150
3d	CH_2CH_3	CH_3	CH_3	SCH_3	15	0.25	150
3e	CH_2CH_3	CH_3	C_6H_5	H	70	1	140
3f	$CH_2CH_2CH_3$	CH_3	C_6H_5	H	69	0.75	160
3g	$CH_2CH_2CH_2CH_3$	CH_3	4-ClC_6H_4	H	61	0.5	150
3h	$CH_2CH(CH_3)_2$	CH_3	C_6H_5	H	60	1.25	150
3i	$CH(CH_3)CH_2CH_3$	CH_3	C_6H_5	H	54	0.33	150
3j	C_6H_5	CH_3	CH_3	CH_3	46	2	150
3k	C_6H_5	CH_3	C_6H_5	H	30	0.75	130
31[a]	C_6H_5	CH_3	C_6H_5	SH	8	2.25	150
3m	C_6H_5	CH_3	4-ClC_6H_4	H	61	1.25	150
3n	$CH_2C_6H_5$	CH_3	H	H	39	1	150
3o	$CH_2C_6H_5$	CH_3	C_6H_5	H	56	1.25	150
3p	Furfuryl	CH_3	C_6H_5	H	17	1.5	150
3q[b,c]	3-Pyridyl	CH_3	C_6H_5	H	47	0.75	240
3r	4-$EtOOCC_6H_4$	CH_3	C_6H_5	H	29	0.75	150
3s[b,d]	4-$CH_2CH_2CH_2CNC_6H_4$ (O)	CH_3	C_6H_5	H	11	7	180
3t[b]	3,4,5-$(CH_3O)_3C_6H_2$	CH_3	H	H	35	1.25	150
3u[b]	3,4,5-$(CH_3O)_3C_6H_2$	CH_3	C_6H_5	H	60	1	150
3v	CH_3	C_6H_5	C_6H_5	H	17	2	150
3w	C_6H_5	C_6H_5	C_6H_5	H	30	0.33	240

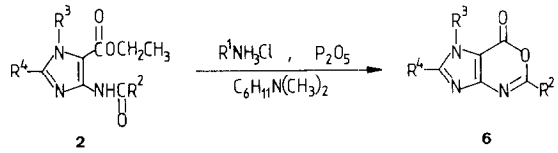
[a] Exist in the thionoform. [b] Free amine was used instead of its hydrochloride. [c] Heated 20 min at 150 °C and then 45 min at 240 °C. [d] Heated 2 h at 150 °C and then 7 h at 180 °C.

were reacted with amine hydrochlorides or ammonium chloride in P_2O_5 and *N,N*-dimethylcyclohexylamine at 150° for 1–2.5 hr, the corresponding imidazo[4,5-d]-[1,3]oxazin-7(1*H*)-ones **6** were obtained as crystalline compounds in 33–61% yields (Table 3). The formation of this fairly new heterocyclic ring system has only been reported by acylative degradation of uric acid,[6] or by treating 5 - amino - 1 - (2,3,5 - tri - O - acetyl - β - D - ribofuranosyl)imidazole - 4 - carboxylic acid with acid anhydrides.[7] The desired hypoxanthines were not isolated in our reactions with bulky R^2 substituents, except in the reaction between **2h** and methylamine hydrochloride at 150° for 2 hr, which gave a low yield of the expected 1,7 - dihydro - 2,7 - diphenyl - 1 - methyl - 6*H* - purin - 6 - one **3v**. However, when the temperature was raised to 240° for 20 min, it was possible to isolate compound **3w** in 30% yield from the dark residue in the reaction between **2h** and aniline hydrochloride. Compound **3w** was also obtained when 1,5 - diphenylimidazo[4,5 - d][1,3]oxazin - 7(1*H*) - one **6a** was treated with aniline hydrochloride under the same conditions as above.

Therefore **6** is suggested as an intermediate in the two possible alternative pathways A and B for formation of hypoxanthines **3** (Scheme 1), though **6** was not isolated in reactions with ethyl 4 - acetylamino - 1*H* - imidazole - 5 - carboxylates.

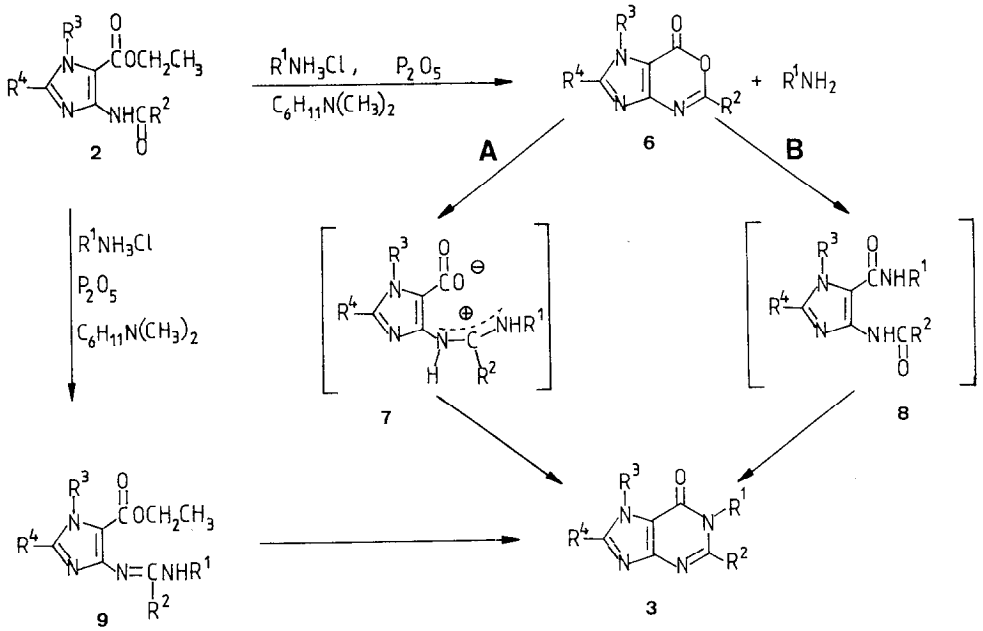
The intermediates **7** and **8** were not detected in the reaction mixture, but analogous compounds have already been isolated in the synthesis of 4(3*H*)-quinazolinones from 4*H*-3,1-benzoxazin-4-ones and primary amines.[14,15] In our laboratory a compound corresponding to the diamide intermediate **8** was also detected in the reaction product, when ethyl 2 - benzoylamino - 5 - methyl - 3 - thiophenecarboxylate was used in a mixture of P_2O_5 and amine hydrochloride[16] under conditions similar to those described in this paper. We suggest that reactions of ethyl 4-acetylamino-1*H*-imidazole-5-carboxylates (**2**, $R^2 = CH_3$) with amine hydrochlorides follow pathway A, in which **7** immediately are converted to **3** by cyclo-

Table 3. Imidazo[4,5-d][1,3]oxazin-7(1*H*)-ones **6**



2 **6**

	R^1	R^2	R^3	R^4	Yield [%]
6a	C_2H_5	C_6H_5	C_6H_5	H	61
6b	H	C_6H_5	CH_3	CH_3	56
6c	CH_3	3,4,5-$(CH_3O)_3C_6H_2CH$=CH	C_6H_5	H	33



2 **6** **7** **8** **9** **3**

Scheme 1.

dehydration in the P_2O_5-amine mixture. When R^2 is a bulky substituent (e.g. C_6H_5) the reaction is thought to follow the alternative pathway B, because steric hindrance makes attack at the imidoyl group of **6** more difficult. This is in agreement with the mechanism for the reaction of amines with 2-methyl-4*H*-3,1-benzoaxazin-4-one and 2-phenyl-4*H*-1,3-benzoxazin-4-one, respectively.[17]

The amidine **9** is also a possible intermediate for **3**, especially when $R^2 = CH_3$. Although **9** was not detected in our reactions nor in the analogous synthesis of 4(3*H*)-quinazolinones[5] and thieno[2,3-d]pyrimidin-4(3*H*)-ones,[16] we think nevertheless that this route is very attractive because we have shown that amidines can be formed from carboxamides in a mixture of P_2O_5 and an amine.[18] The intermediate **9** is also in accordance with the observation from our laboratory that secondary amides reacts faster than carboxylic esters. The stability of the carbethoxy group was also demonstrated in this investigation by the preparation of **3r**.

Biological activities. The hypoxanthines **3b** and **3k** showed low plant bactericide activity (Xanthomonas oryzae). Low insecticidal activity against Spodoptera larvae was found for **3b** and the starting material **2h**.[20] The hypoxanthines **3b, e, f, h, i, k, o–q, u** were tested against P 388 lymphocytic leukemia, but no activity was indicated.[21]

EXPERIMENTAL

^{1}H NMR spectra were recorded on a JEOL JNM-PMX 60 spectrometer. IR spectra were recorded on a Perkin–Elmer 580 IR spectrophotometer. Mass spectra were obtained on a Varian MAT 311A and a Varian MAT CH 7A. Silica gel column chromatography was performed with Waters Prep LG/SYSTEM 500 A liquid chromatograph. The microanalyses were carried out by Microanalytical Laboratory, University of Copenhagen and by Novo Microanalytical Laboratory A/S, Novo Allé, DK-2880 Bagsvaerd, supervised by Dr. R. E. Amsler.

Ethyl 4 - *acetylamino* - 1H - *imidazole* - 5 - *carboxylates* **2a–f** were prepared by heating the corresponding amines in acetic anhydride and acetic acid for 0.5–2 hr. Water was added and the mixture evaporated to give a solid, which was recrystallized from the solvents given in Table 1.

Ethyl 4 - *benzoylamino* - 1,2 - *dimethyl* - 1H - *imidazole* - 5 - *carboxylate* **2g** and *ethyl* 4 - *benzoylamino* - 1 - *phenyl* - 1H - *imidazole* - 5 - *carboxylate* **2h** were prepared according to standard procedures by treating a slurry of the corresponding amine in benzene with benzoylchloride in the presence of pyridine.

Ethyl 1 - *phenyl* - 4 - (3,4,5 - *trimethoxycinnamoylamino*) - 1H - *imidazole* - 5 - *carboxylate* **2i** was prepared by treating ethyl 4 - amino - 1 - phenyl - 1*H* - imidazole - 5 - carboxylate with 3,4,5-trimethoxycinnamoylchloride[19] in toluene in the presence of pyridine.

Amine hydrochlorides were prepared by adding the amine dropwise to 2 equivalents of cooled 4M HCl with stirring. The dry amine hydrochloride was obtained by stripping off the excess HCl.

General procedure for the preparation of 1,7-*dihydro*-6H-*purin*-6-*ones* **3a–w**. Equimolar amounts of an amine hydrochloride, *N,N*-dimethylcyclohexylamine and P_2O_5 were mixed in a three-necked flask equipped with mechanical stirring, thermometer and condenser with drying tube. The mixture was heated on a silicone–oil bath at 150° until a homogeneous mass was obtained (about 25 min). 0.01–0.04 mol of ethyl 4 - acylamino - 1*H* - imidazole - 5 - carboxylate **2** (the molar ratio of the amine hydrochloride and **2** was 4 : 1) was added, and heating at 130–240° was continued until the starting material **2** had disappeared after 0.25–7 hr (the reactions were followed by tlc or analytical liquid column chromatography). If nothing else is stated, the reaction mixture was allowed to cool to about 100° and worked up in two different routes.

Route A. 2 M NaOH was poured into the mixture until alkaline reaction (pH 8–9) and stirring was continued for 1 hr. The water phase was extracted with CH_2Cl_2 (3 × 100 ml). The organic phase was dried and CH_2Cl_2 was evaporated off. *N,N*-dimethylcyclohexylamine was distilled off at 10 mm Hg.

Route B. 2 M NaOH was poured into the mixture until neutral reaction (pH 6–8) and stirring was continued for 1 hr. The precipitated solid was filtered off, washed with water and dried.

1,7 - *Dihydro* - 2 - *methyl* - 7 - *phenyl* - 6H - *purin* - 6 - *one* **3a**. The mixture was allowed to cool to 100° and 2 M NaOH was poured into the mixture until alkaline reaction (pH 11), and stirring was continued for 1 hr. The water phase was extracted with CH_2Cl_2 (3 × 100 ml) to remove organic impurities. The water phase was adjusted to pH 7 (4 M HCl) and **3a** precipitated; m.p. 315–317° (2-butanone/2-methoxyethanol); ^{1}H NMR (DMSO-d_6) δ: 2.60 (3H, s, CH_3), 7.43–7.77 (5H, m, ArH), 8.48 (1H, s, H8), 12.53 (1H, broad s, NH); IR (KBr): 1690 (C = O) cm^{-1}; MS *m/e* (%): 227 (15), 226 (M^+, 100), 104 (10), 103 (20), 77 (19), 51 (10); (Found: C, 62.64; H, 4.45; N, 24.31. Calc. for $C_{12}H_{10}N_4O$ 1/4 H_2O: C, 62.46; H, 4.55; N, 24.28%).

1,7 - *Dihydro* - 1,2 - *dimethyl* - 7 - *phenyl* - 6H - *purin* - 6 - *one* **3b**. (*Route A*). The crude product was triturated with petroleum ether and **3b** was obtained; m.p. 185–186° (EtOH); ^{1}H NMR ($CDCl_3$) δ: 2.67 (3H, s, CH_3), 3.58 (3H, s, NCH_3), 7.48 (5H, s, ArH), 7.98 (1H, s, H8); IR (KBr): 1685 (C = O) cm^{-1}; MS *m/e* (%): 241 (16), 240 (M^+, 100), 225 (16), 212 (10), 56 (23); (Found: C, 64.76; H, 5.13; N, 23.00. Calc. for $C_{13}H_{12}N_4O$: C, 64.98; H, 5.04; N, 23.32%).

1,7,8,9 - *Tetrahydro* - 2,7 - *dimethyl* - 1 - *ethyl* - 8 - *thioxo* - 6H - *purin* - 6 - *one* **3c** was prepared from **2c**. The mixture was poured onto ice and allowed to stand until the reaction cake had dissolved. The precipitated crystals were filtered off, dissolved in 2 M NaOH and reprecipitated by 4 M HCl (pH 7–8) to yield pure demethylated product **3c**; m.p. > 310°; ^{1}H NMR (CF_3COOH) δ: 1.47 (3H, t, J = 7.0 Hz, CH_3), 2.93 (3H, s, CH_3), 4.01 (3H, s, NCH_3), 4.38 (2H, q, J = 7.0 Hz, CH_2); IR (KBr): 3140, 1700 (C = O), 1670 (sh) cm^{-1}; MS *m/e* (%): 225 (13), 224 (M^+, 100), 196 (33), 195 (13), 163 (10), 42 (49); (Found: C, 48.17; H, 5.41; N, 25.03; S, 14.43. Calc. for $C_9H_{12}N_4OS$: C, 48.19; H, 5.39; N, 24.98; S, 14.30%).

1,7 - *Dihydro* - 2,7 - *dimethyl* - 1 - *ethyl* - 8 - (*methylthio*) - 6H - *purin* - 6 - *one* **3d**. (*Route A*). The crude product **3d** crystallized from the residue by addition of diethyl ether. The ppt was filtered off and recrystallized from EtOH. Analytical pure material was obtained by sublimation; m.p. 152–153.5°; ^{1}H NMR (CF_3COOH) δ: 1.43 (3H, t, J = 7.0 Hz, CH_3), 2.90 (6H, s, C-CH_3 + S-CH_3), 4.05 (3H, s, N-CH_3), 4.36 (2H, q, J = 7.0 Hz, CH_2); IR (KBr): 1680 (C = O) cm^{-1}; MS *m/e* (%): 239 (15), 238 (M^+, 100), 223 (14), 205 (36), 195 (16), 177 (45), 164 (19), 67 (11), 42 (45); (Found: C, 50.35; H, 5.85; N, 23.56; S, 13.67. Calc. for $C_{10}H_{14}N_4OS$: C, 50.40; H, 5.92; N, 23.51; S, 13.46%).

1,7 - *Dihydro* - 1 - *ethyl* - 2 - *methyl* - 7 - *phenyl* - 6H - *purin* - 6 - *one* **3e**. (*Route B*). The ppt afforded 39% of pure **3e**. An additional amount (31% after recrystallization) was obtained by extraction of the water phase with CH_2Cl_2 (3 × 75 ml); m.p. 179.5–181° (EtOH); ^{1}H NMR ($CDCl_3$) δ: 1.33 (3H, t, J = 7.0 Hz, CH_3) 2.65 (3H, s, CH_3), 4.20 (2H, q, J = 7.0 Hz, CH_2), 7.50 (5H, s, ArH), 8.00 (1H, s, H8); IR (KBr): 1685 (C = O) cm^{-1}; MS *m/e* (%): 255 (18), 254 (M^+, 100), 227 (11), 226 (63), 212 (14), 77 (15), 42 (23); (Found: C, 66.44; H, 5.63; N, 22.10. Calc. for $C_{14}H_{14}N_4O$: C: 66.12; H, 5.55; N, 22.03%).

1,7 - *Dihydro* - 2 - *methyl* - 7 - *phenyl* - 1 - *propyl* - 6H - *purin* - 6 - *one* **3f**. (*Route A*). The crude product crystallized from EtOAc, m.p. 135–137° (EtOH); ^{1}H NMR ($CDCl_3$) δ: 1.00 (3H, t, J = 7.0 Hz, CH_3), 1.80 (2H, sext., J = 7.0 Hz, CH_2), 2.73 (3H, s, CH_3), 4.07 (2H, t, J = 7.0 Hz, CH_2), 7.52 (5H, s, ArH), 8.03 (1H, s, H8); IR (KBr): 1690 (C = O) cm^{-1}; MS *m/e* (%): 269 (14), 268 (M^+, 75), 253 (10), 227 (23), 226 (100), 77 (14), 42 (12); (Found: C, 66.95; H, 5.92; N, 20.61. Calc. for $C_{15}H_{16}N_4O$: C, 67.14; H, 6.01; N, 20.88%).

1,7 - *Dihydro* - 1 - *butyl* - 7 - (4 - *chlorophenyl*) - 2 - *methyl* - 6H - *purin* - 6 - *one* **3g**. (*Route B*). The title compound was obtained by recrystallization from EtOH using decolorizing car-

bon; m.p. 182–183° (EtOH); ^{1}H NMR ($CDCl_3$) δ: 1.00 (3H, distorted t, J = 6 Hz, CH_3), 1.17–1.93 (4H, m, $2CH_2$), 2.73 (3H, s, CH_3), 4.13 (2H, distorted t, J = 7.5 Hz, CH_2), 7.52 (4H, s, ArH), 8.03 (1H, s, H8); IR (KBr): 1690 (C = O) cm^{-1}; MS *m/e* (%): 318 (10), 316 (M^+, 30), 303 (14), 302 (10), 301 (54), 299 (37), 274 (25), 262 (35), 261 (18), 260 (100), 244 (10), 138 (10), 137 (10), 111 (13); (Found: C, 60.60; H, 5.34; N, 17.69. Calc. for $C_{16}H_{17}N_4OCl$: C, 60.66; H, 5.41; N, 17.69%).

1,7 - *Dihydro* - 2 - *methyl* - 1 - (2 - *methylpropyl*) - 7 - *phenyl* - 6H - *purin* - 6 - *one* **3h**. The mixture was cooled to 100° and 60 ml H_2O was added with stirring. After 3 hr the ppt was filtered off and dried to yield a compound with m.p. 231–236° which was probably the hydrochloride of the title compound (positive Beilstein test, solubility tests and ^{1}H NMR). The product was treated with 2 × 20 ml saturated aqueous $NaHCO_3$, washed with H_2O to neutral reaction and dried to yield **3h**; m.p. 149–150.5° (EtOH); ^{1}H NMR (DMSO-d_6) δ: 0.88 (6H, d, J = 7.0 Hz, $2CH_3$), 2.07 (1H, sext., J = 7.0 Hz, CH), 2.64 (3H, s, CH_3), 3.92 (2H, d, J = 7.0 Hz, CH_2), 7.57 (5H, s, ArH), 8.48 (1H, s, H8); IR (KBr): 1690 (C = O) cm^{-1}; MS *m/e* (%): 283 (10), 282 (M^+, 48), 227 (22), 226 (100); (Found: C, 68.18; H, 6.39; N, 19.83. Calc. for $C_{16}H_{18}N_4O$: C, 68.06; H, 6.43; N, 19.85%).

1,7 - *Dihydro* - 2 - *methyl* - 1 - (1 - *methylpropyl*) - 7 - *phenyl* - 6H - *purin* - 6 - *one* **3i**. (*Route B*). The ppt was dissolved in hot EtOH/H_2O (5 : 1), filtered hot to remove a insoluble residue, and the title compound was allowed to precipitate; m.p. 177–178° (EtOH); ^{1}H NMR ($CDCl_3$) δ: 0.87 (3H, t, J = 7.5 Hz, CH_3), 1.62 (3H, d, J = 7.5 Hz, CH_3), 1.70–2.60 (3H, m, CH + CH_2), 2.70 (3H, s, CH_3), 7.48 (5H, s, ArH), 7.97 (1H, s, H8); IR (KBr): 1690 (C = O) cm^{-1}; MS *m/e* (%): 282 (M^+, 24), 227 (27), 226 (100), 103 (10), 77 (13); (Found: C, 67.95; H, 6.32; N, 19.84. Calc. for $C_{16}H_{18}N_4O$: C, 68.06; H, 6.43; N, 19.85%).

1,7 - *Dihydro* - 1 - *phenyl* - 2,7,8 - *trimethyl* - 6H - *purin* - 6 - *one* **3j**. The mixture was allowed to cool to 100° and 2 M NaOH was poured into the mixture until alkaline reaction (pH 11) and stirring was continued for 1 hr. The water phase was extracted with CH_2Cl_2 (3 × 100 ml). After drying with Na_2SO_4, CH_2Cl_2 was evaporated and *N,N*-dimethylcyclohexylamine and excess aniline were distilled off at 0.05 mm Hg and **3j** was obtained; m.p. 192–193° (diisopropylether/EtOH with decolorizing carbon), ^{1}H NMR ($CDCl_3$) δ: 2.24 (3H, s, CH_3), 2.55 (3H, s, CH_3), 3.94 (3H, s, N–CH_3), 7.13–7.63 (5H, m, ArH); IR (KBr): 1695 (C = O) cm^{-1}; MS *m/e* (%): 255 (17), 254 (M^+, 100), 253 (28), 240 (13), 239 (85), 118 (10), 77 (50), 67 (10), 51 (11); (Found: C, 65.36; H, 5.49; N, 21.98. Calc. for $C_{14}H_{14}N_4O$: C, 66.12; H, 5.55; N, 22.04%).

1,7 - *Dihydro* - 1,7 - *diphenyl* - 2 - *methyl* - 6H - *purin* - 6 - *one* **3k**. (*Route A*). The oily residue was boiled in dilute AcOH and upon cooling and scratching with a glass rod 5.73 g crystals were obtained with m.p. 119–126° (possibly the acetate of **3k** according to ^{1}H NMR). The precipitate was recrystallized from EtOH/H_2O (1 : 2) to give pure **3k**; m.p. 186–187°; ^{1}H NMR ($CDCl_3$) δ: 2.30 (3H, s, CH_3), 7.13–7.63 (10H, s + m, ArH), 8.07 (1H, s, H8); IR (KBr): 1700 (C = O) cm^{-1}; MS *m/e* (%): 303 (22), 302 (M^+, 100), 301 (25), 288 (10), 287 (45), 77 (34); (Found: C, 71.47; H, 4.65; N, 18.55. Calc. for $C_{18}H_{14}N_4O$: C, 71.50, H, 4.67; N, 18.53%).

1,7,8,9 - *Tetrahydro* - 1,7 - *diphenyl* - 2 - *methyl* - 8 - *thioxo* - 6H - *purin* - 6 - *one* **3l** was prepared from **2e** (0.02 mol, 6.4 g). Working up was performed by cooling the mixture to 100°, then 50 ml H_2O was added under stirring and the mixture was poured onto ice. After 2 hr the ppt was filtered off and suspended in 60 ml sat. $NaHCO_3$aq., and extracted with CH_2Cl_2 (3 × 60 ml). The CH_2Cl_2 phase was dried and evaporated to give a reddish oily substance. 3.5 g crystals precipitated on addition of diisopropylether (100 ml). This precipitate was boiled in toluene (140 ml) and filtered hot to give the demethylated **3l** in low yield as an insoluble residue; m.p. 316–322° d (2-butanone); ^{1}H NMR (CF_3COOH) δ: 2.52 (3H, s, CH_3), 7.13–7.73 (10H, m, ArH); IR (KBr): 1710 (C = O), 1235 (C = S) cm^{-1}; MS *m/e* (%): 335 (25), 334 (M^+, 100), 333 (66), 202 (22), 118 (23), 77 (46), 71 (18), 57 (54), 56 (18), 51 (10); (Found: C, 64.64; H, 4.19; N, 16.92. Calc. for $C_{18}H_{14}N_4O$: C, 64.65; H, 4.22; N, 16.76%).

1,7 - *Dihydro* - 7 - (4 - *chlorophenyl*) - 2 - *methyl* - 1 - *phenyl* - 6H - *purin* - 6 - *one* **3m** (*Route B*). M.p. 225° (2-butanone); ^{1}H NMR ($CDCl_3$) δ: 2.32 (3H, s, CH_3), 7.17–7.67 (9H, m, ArH), 8.07 (1H, s, H8); IR (KBr): 1700 (C = O) cm^{-1}; MS *m/e* (%): 338 (35), 337 (29), 336 (M^+, 100), 335 (25), 323 (23), 322 (13), 321 (63), 118 (12), 77 (62); (Found: C, 63.96; H, 3.91; N, 16.41. Calc. for $C_{18}H_{13}N_4OCl$: C, 64.19; H, 3.89; N, 16.64%).

1,7 - *Dihydro* - 2 - *methyl* - 1 - *phenylmethyl* - 6H - *purin* - 6 - *one* **3n**. The procedure for preparation of **3a** was followed, m.p. 262.5–263.5° (2-butanone); ^{1}H NMR (DMSO-d_6) δ: 2.50 (3H, s, CH_3), 5.38 (2H, s, CH_2), 7.03–7.40 (5H, m, ArH), 8.14 (1H, s, H8), 13.50 (1H, br. s, NH); IR (KBr): 3185 (NH), 3140 (NH), 1675 (C = O) cm^{-1}; MS *m/e* (%): 241 (12), 240 (M^+, 62), 239 (25), 225 (11), 136 (10), 134 (15), 92 (10), 91 (100), 65 (24); (Found: C, 64.73; H, 5.06; N, 23.03. Calc. for $C_{13}H_{12}N_4O$: C, 64.98; H, 5.04; N, 23.32%).

1,7 - *Dihydro* - 2 - *methyl* - 7 - *phenyl* - 1 - *phenylmethyl* - 6H - *purin* - 6 - *one* **3o**. (*Route B*). The crude product was boiled in 100 ml EtOH, the mixture cooled and 5.35 g title compound was filtered off; m.p. 222–223° (2-butanone); ^{1}H NMR ($CDCl_3$) δ: 2.62 (3H, s, CH_3), 5.40 (2H, s, CH_2), 7.07–7.40 (5H, m, ArH), 7.53 (5H, s, ArH), 8.07 (1H, s, H8); IR (KBr): 1695 (C = O) cm^{-1}; MS *m/e* (%): 317 (12), 316 (M^+, 47), 315 (18), 142 (11), 104 (12), 92 (10), 91 (100), 77 (38), 65 (20), 51 (13); (Found: C, 71.98; H, 5.11; N, 17.69. Calc. for $C_{19}H_{16}N_4O$: C, 72.13; H, 5.10; N, 17.71%).

1,7 - *Dihydro* - 1 - (2 - *furanylmethyl*) - 2 - *methyl* - 7 - *phenyl* - 6H - *purin* - 6 - *one* **3p** was prepared from **2d** (0.03 mol, 8.2 g). (*Route B*). The residue was extracted with boiling ligroin (100–140°) (3 × 100 ml). The ligroin was evaporated and upon trituration with diethyl ether 1.26 g product was obtained. Continuous extraction with ligroin (80–100°) overnight afforded additional 0.32 g title compound; m.p. 159–161° (EtOH); ^{1}H NMR ($CDCl_3$) δ; 2.83 (3H, s, CH_3), 5.28 (2H, s, CH_2), 6.33 (2H, m, 2CH), 7.33 (1H, m, =CH–O), 7.50 (5H, s, ArH), 8.00 (1H, s, H8); IR (KBr): 1695 (C=O) cm^{-1}; MS *m/e* (%): 307 (16), 306 (M^+, 75) 277 (12), 81 (100), 77 (11), 53 (14); (Found: C, 66.44; H, 4.67; N, 17.91. Calc. for $C_{17}H_{14}N_4O_2$: C, 66.65; H, 4.61; N, 18.29%).

1,7 - *Dihydro* - 2 - *methyl* - 7 - *phenyl* - 1 - (3 - *pyridyl*) - 6H - *purin* - 6 - *one* **3q** was prepared according to the general procedure (*Route B*), except that **2d** (0.03 mol, 8.2 g), the free 3-aminopyridine (0.12 mol, 11.3 g), P_2O_5 (0.12 mol, 17 g) and *N,N*-dimethylcyclohexylamine (16 ml) were used. The temperature of the oil bath was raised from 150° to 240° after 20 min in order to make the reaction mixture homogeneous and then was heated for an additional 75 min. The crude product was treated with hot MeOH (100 ml) to yield 3.72 g of the title compound. An additional amount (0.60 g) could be obtained by extraction of the water phase with CH_2Cl_2. M.p. 291–292° (2-butanone): ^{1}H NMR (CF_3COOH) δ: 2.60 (3H, s, CH_3), 7.65 (5H, s, ArH), 8.27–9.47 (5H, m + s, PyH + H8); IR (KBr): 1700 (C=O) cm^{-1}; MS *m/e* (%): 304 (17), 303 (M^+, 100), 302 (42), 289 (10), 288 (51), 119 (10), 78 (65), 77 (31), 51 (29); (Found: C, 67.36; H, 4.39; N, 23.14. Calc. for $C_{17}H_{13}N_5O$: C, 67.31; H, 4.32; N, 23.09%).

1,7 - *Dihydro* - 1 - (4 - *carbethoxyphenyl*) - 2 - *methyl* - 7 - *phenyl* - 6H - *purin* - 6 - *one* **3r** was prepared from **2d** (0.03 mol, 8.2 g) (*Route A*). The semisolid residue (28.5 g) was subjected to silica gel column chromatography, using CH_2Cl_2 + 1% MeOH for elution and ethyl *p*-aminobenzoate (9.5 g) and crude **3r** (9.25 g) were obtained. The latter was dissolved in EtOH, reprecipitated with petroleum ether and recrystallized to yield pure title compound; m.p. 167–168° (EtOH), (crystal EtOH is liberated at about 108°); ^{1}H NMR ($CDCl_3$) δ: 1.40 (3H, t, J = 7.0 Hz, CH_3), 2.30 (3H, s, CH_3), 4.42 (2H, q, J = 7.0 Hz, CH_2), 7.33–7.50 (7H, s + d, ArH), 8.10 (2H, d, J = 4.0 Hz, ArH). 8.27 (1H, s, H8); IR (KBr): 1705 (C=O) cm^{-1}; MS *m/e* (%): 375 (25), 374 (M^+, 100), 373 (17), 360 (10), 359 (36), 331 (11), 329 (11), 103 (10), 67 (17), 66 (11), 65 (14); (Found: C, 65.28; H, 5.54, N, 13.44. Calc. for $C_{23}H_{24}N_4O_4 \cdot 1\,CH_3CH_2OH$: C, 65.70; H, 5.75; N, 13.33%).

1,7 - *Dihydro* - 2 - *methyl* - 1 - [4 - (2 - *oxo* - 1 - *pyrrolidyl*)*phenyl*] - 7 - *phenyl* - 6H - *purin* - 6 - *one* **3s**, and 1 - [4 - (*ethylamino*)*phenyl*] - 2 - *pyrrolidone* **4** were prepared from **2d** (0.03 mol, 8.2 g), 1-(4-aminophenyl)-2-pyrrolidone (0.12 mol, 21.15 g), P_2O_5 (17 g), and *N,N*-dimethylcyclohexylamine (18 ml) according to the general procedure, except that the temp. of the oil bath was raised from 150° to 180° after 2 hr. 5 hr later the mixture was allowed to cool to 100° and 150 ml H_2O and 200 ml 2 M NaOH was poured into the reaction mixture. Stirring was

continued for 1 hr, and the water phase was extracted with CH_2Cl_2 (3 × 150 ml), which after drying and evaporation afforded 28.3 g dark coloured product mixture. 3 g was subjected to silica gel preparative tlc using CH_2Cl_2 + 10% MeOH for elution and the title compounds were obtained. **3s** (11%); m.p. 184–186° (EtOH); ^{1}H NMR ($CDCl_3$) δ: 2.00–2.87 (7H, s + m, CH_3 + $2CH_2$), 3.90 (2H, t, J = 7.0 Hz, CH_2), 7.22 (2H, d, J = 8.5 Hz, ArH), 7.47 (5H, s, ArH), 7.83 (2H, d, J = 8.5 Hz, ArH), 8.07 (1H, s, H8); IR (KBr): 1700 (C=O) cm^{-1}; MS *m/e* (%): 386 (25), 385 (M^+, 100), 384 (17), 370 (19), 330 (12), 77 (15); (Found: M^+, 385.1516. Calc. for $C_{22}H_{19}N_5O_2$: *m/e* 385.1539). **4** (250 mg); ^{1}H NMR ($CDCl_3$) δ: 1.20 (3H, t, J = 7.0 Hz, CH_3), 1.90–2.70 (4H, m, $2CH_2$), 3.13 (2H, q, J = 7.0 Hz, CH_2), 3.77 (2H, t, J = 7.0 Hz, CH_2) 6.53 (2H, d, J = 9.0 Hz, ArH), 7.32 (2H, d, J = 9.0 Hz, ArH); IR (KBr): 3330 (NH), 1675 (C=O) cm^{-1}; MS *m/e* (%): 205 (12), 204 (M^+, 78), 190 (15), 189 (100), 149 (19), 133 (14); (Found: M^+, 204.1238. Calc. for $C_{12}H_{16}N_2O$: *m/e* 204.1258).

1,7 - *Dihydro* - 2 - *methyl* - 1 - (3,4,5 - *trimethoxyphenyl*) - 6H - *purin* - 6 - *one* **3t**. **2a** (0.025 mol, 4.9 g) and 3,4,5-trimethoxyaniline (0.1 mol, 18.3 g) were heated with P_2O_5 (14.2 g) and *N,N*-dimethylcyclohexylamine (15 ml) for 75 min on a silicone-oil bath (150°) with stirring. The mixture was allowed to cool to 100° and 2 M NaOH was poured into the reaction mixture until alkaline reaction (pH 11), and stirring was continued for 1 hr. The water phase was extracted with CH_2Cl_2 (3 × 100 ml) to remove organic impurities, and adjusted to pH 6–7 with 4 M HCl and sat. $NaHCO_3$aq. The water phase was extracted with CH_2Cl_2 (3 × 100 ml). The combined organic layers were dried over Na_2SO_4 and evaporated to give 5.1 g crude product. Recrystallization from 96% EtOH yielded **3t**. A low-melting impurity was allowed to sublime at 200°/0.02 mm Hg and the residue was recrystallized from EtOH to give the analytical pure title compound; m.p. 248–249° (EtOH); ^{1}H NMR (DMSO-d_6) δ: 2.23 (3H, s, CH_3), 3.78 (3H, s, OCH_3), 3.82 (6H, s, $2OCH_3$), 6.80 (2H, s, ArH), 8.10 (1H, s, H8); IR (KBr): 1685 (C=O) cm^{-1}; MS *m/e* (%): 317 (16), 316 (M^+, 100), 315 (16), 301 (45), 168 (13), 147 (11), 134 (11), 133 (33); (Found: C, 56.30; H, 5.10; N, 17.62. Calc. for $C_{15}H_{16}N_4O_4$ 1/4 H_2O: C, 56.15; H, 5.18; N, 17.46%).

1,7 - *Dihydro* - 2 - *methyl* - 7 - *phenyl* - 1 - (3,4,5 - *trimethoxyphenyl*) - 6H - *purin* - 6 - *one* **3u** (*Route B*). The residue obtained was boiled in EtOH (300 ml), cooled and filtered to yield **2u**; m.p. 269–270° (toluene); ^{1}H NMR ($CDCl_3$) δ: 2.40 (3H, s, CH_3), 3.88 + 3.91 (9H, s + s, $3OCH_3$), 6.52 (2H, s, ArH), 7.52 (5H, s, ArH), 8.10 (1H, s, H8); IR (KBr): 1700 (C=O) cm^{-1}; MS *m/e* (%): 393 (29), 392 (M^+, 100), 328 (12), 327 (53), 160 (21), 159 (62), 77 (10); (Found: C, 64.12; H, 5.00; N, 14.23. Calc. for $C_{21}H_{20}N_4O_4$: C, 64.27; H, 5.14; N, 14.28%).

1,7 - *Dhydro* - 2,7 - *diphenyl* - 1 - *methyl* - 6H - *purin* - 6 - *one* **3v**. The mixture was allowed to cool to 100° and 2 M NaOH was poured into the mixture until neutral reaction (pH 7). Now it was poured onto ice to give a semisolid product mixture, which was extracted with CH_2Cl_2 (3 × 75 ml), dried over Na_2SO_4 and CH_2Cl_2 was evaporated in the usual way. The residue obtained was triturated with EtOAc and recrystallized to yield 1.04 g of the title compound; m.p. 229-232° (EtOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$): 3.50 (3H, s, CH_3), 7.52 (10 H, s, ArH), 8.05 (1H, s, H8); IR (KBr): 1690 (C=O) cm^{-1}; MS *m/e* (%): 303 (18), 302 (M^+, 92), 301 (100), 118 (23), 77 (38); (Found: C, 71.02, H, 4.46; N, 18.28. Calc. for $C_{18}H_{14}N_4O$: C, 71.51; H, 4.67; N, 18.53%).

1,7 - *Dihydro* - 1,2,7 - *triphenyl* - 6H - *purin* - 6 - *one* **3w**. (*Route A*). The black residue obtained was triturated with EtOH (50 ml), and slightly coloured crystals could be filtered off; m.p. 264–265° (2-butanone with decolorizing carbon); ^{1}H NMR ($CDCl_3$) δ: 7.03–7.67 (15H, m, ArH), 8.13 (1H, s, H8); IR (KBr): 1700 (C=O) cm^{-1}; MS *m/e* (%): 365 (23), 364 (M^+, 100), 363 (70), 287 (19), 207 (10), 186 (15), 185 (10), 180 (11), 115 (10), 77 (96); (Found: C, 75.70; H, 4.41; N, 15.49. Calc. for $C_{23}H_{16}N_4O$: C, 75.81; H, 4.43; N, 15.38%).

3w was also prepared from **6a** (0.007 mol, 2.02 g) and aniline hydrochloride (0.028 mol, 3.63 g), P_2O_5 (4.0 g), and *N,N*-dimethylcyclohexylamine (4.2 ml) by heating on a silicone-oil bath at 240° for 20 min with stirring. The mixture was allowed to cool to 100°, and 2M NaOH was poured into the mixture until neutral (pH 7). Stirring was continued for 1 hr. The water phase was extracted with CH_2Cl_2 (3 × 50 ml), the CH_2Cl_2 was evaporated off and the residue triturated with 20 ml EtOH. 1.00 g of the title compound (39%) precipitated as slightly coloured crystals; m.p. 264–265° (2-butanone), identical (m.p., R_f, IR and NMR) with the compound obtained above.

N - (1 - *Phenyl* - 1H - *imidazol* - 4 - *yl*) - *acetamide* **5**. To a mixture of 4-amino - 1 - diethylaminopentane dihydrochloride (0.12 mol, 27.7 g), P_2O_5 (17 g) and *N,N*-dimethylcyclohexylamine (36 ml) was added **2d** (0.03 mol, 8.2 g) on a silicone-oil bath at 180°. After 3 hr the mixture was allowed to cool to about 100° and 2 M NaOH was added to pH 8–9. Stirring was continued for 1 hr. The water phase was then extracted with CH_2Cl_2 (3 × 100 ml), the combined organic layers dried over $MgSO_4$ and CH_2Cl_2 was stripped off. *N,N*-Dimethylcyclohexylamine was removed *in vacuo* (oil pump), and the hygroscopic residue was extracted on a Soxhlet extractor with ligroin (100–140°) to give 1.2 g (20%) of the title compound; m.p. 191.5–193° ($CHCl_3$); ^{1}H NMR ($CDCl_3$ + DMSO-d_6) δ: 2.17 (3H, s, CH_3), 7.48 (5H, s, ArH), 7.78 (2H, s, H2 + H5), 10.63 (1H, s, NH); IR (KBr): 1675 (C=O) cm^{-1}; MS *m/e* (%): 201 (M^+, 39), 160 (12), 159 (100), 131 (13), 117 (53), 105 (13), 104 (45), 77 (53); (Found: C, 65.85; H, 5.50; N, 21.01. Calc. for $C_{11}H_{11}N_3O$: C, 65.65; H, 5.51; N, 20.88%).

1,5 - *Diphenylimidazo*[4,5 - *d*][1,3]*oxazin* - 7(1H) - *one* **6a**. The general procedure (*Route B*) for preparation of **3** was followed using **2h** (0.02 mol, 6.7 g) and the mixture was heated for 2.5 hr at 150°. The residue obtained was boiled in EtOH (80 ml), cooled and filtered off to give pure title compound in 61% yield; m.p. 203–205°; ^{1}H NMR ($CDCl_3$) δ: 7.50–7.70 (8H, s + m, ArH), 8.15 (1H, s, H2), 8.30–8.53 (2H, m, ArH); IR (KBr): 1740 (C=O) cm^{-1}; MS *m/e* (%): 290 (22), 289 (M^+, 100), 288 (10), 212 (11), 144.5 (10), 142 (15), 105 (20), 77 (30); (Found: C, 70.18; H, 3.76; N, 14.80. Calc. for $C_{17}H_{11}N_3O_2$: C, 70.58; H, 3.83; N, 14.53%).

1,2 - *Dimethyl* - 5 - *phenylimidazo*[4,5 - *d*][1,3]*oxazin* - 7(1H) - *one* **6b** was prepared from **2g** (0.01 mol, 2.87 g) at 150° for 1 hr according to the general procedure for preparation of **3**. The mixture was allowed to cool to 100° and 2 M NaOH was poured into the mixture until alkaline (pH 11), and stirring was continued for 1 hr. The ppt was filtered off, dried and recrystallized to give 56% pure title compound; m.p. 302–304° d (2-butanone); ^{1}H NMR ($CDCl_3$) δ: 2.60 (3H, s, CH_3), 4.00 (3H, s, NCH_3), 7.43–7.70 (3H, m, ArH), 8.27–8.50 (2H, m, ArH); IR (KBr): 1760 (C=O) cm^{-1}; MS *m/e* (%): 242 (16), 241 (M^+, 100), 197 (28), 164 (22), 156 (43), 105 (41), 77 (75); (Found: C, 64.58; H, 4.53; N, 17.34. Calc. for $C_{13}H_{11}N_3O_2$: C, 64.72; H, 4.60; N, 17.42%).

1 - *Phenyl* - 5 - [2 - (3,4,5 - *trimethoxyphenyl*)*ethenyl*]*imidazo*[4,5 - *d*][1,3]*oxazin* - 7(1H) - *one* **6c** was prepared from **2i** (0.015 mol, 6.8 g) according to the general procedure for preparation of **3**. The mixture was heated for 2 hr at 150°. The mixture was then allowed to cool to 100° and 2 M NaOH was added until pH 7. The mixture was poured into 200 ml water and the ppt was filtered off to give a complex mixture of products (eight spots on tlc). When the solid was boiled in EtOH (2 × 35 ml) and washed with ether, 33% of the title compound could be obtained as an insoluble residue; m.p. 210–211° (2-butanone with decolorizing carbon); ^{1}H NMR ($CDCl_3$) δ: 3.90 (9H, s, OCH_3), 6.67 (1H, d, J = 15.6 Hz, =CH) 6.80 (2H, s, ArH), 7.52 (5H, s, ArH), 7.77 (1H, d, J = 15.6 Hz, =CH), 8.05 (1H, s, H8); IR (KBr): 1770 (C=O), 1636 cm^{-1}; MS *m/e* (%): 406 (26), 405 (M^+, 100), 404 (42), 390 (14), 374 (13), 291 (27), 202.5 (68), 198 (10), 104 (11), 77 (10); (Found: C, 65.26; H, 4.77; N, 10.27. Calc. for $C_{22}H_{19}N_3O_5$: C, 65.18; H, 4.72; N, 10.37%).

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