Phosphorus Pentoxide in Organic Synthesis; XI[1]. A New Synthetic Approach to 7-Deazahypoxanthines

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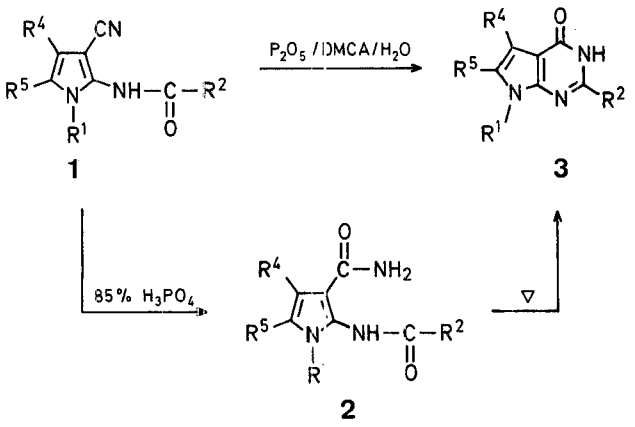
Pyrrolo[2,3-*d*]pyrimidines (7-deazapurines) have aroused considerable interest due to the discovery of their presence in many natural products[2,3]. The hypoxanthine isosters pyrrolo[2,3-*d*]pyrimidin-4-ones have been found to occur as heterocyclic bases in a number of antibiotics[4,5]. Further, some deazapurin-6-one derivatives have been reported[6] to possess diuretic, cardiac, and central nervous system-stimulating activities.

Different synthetic routes to deazahypoxanthines have been reported[7]. However, little has been mentioned regarding their synthesis via pyrrole intermediates. 7-Deazahypoxanthines are considered as useful starting materials for the production of other pyrrolo[2,3-*d*]pyrimidine derivatives. For example, the biologically important pyrrolo[2,3-*d*]pyrimidin-4-amines are obtained through transformation of the oxo group to an amino group[8,9].

We present here a new one-step synthesis of a number of substituted deazahypoxanthines starting from pyrrole derivatives. The deazahypoxanthines **3** are now obtained by a one-step cyclisation of the corresponding 2-acylamino-3-cyanopyrrole derivatives **1**. The reaction is carried out by heating compounds **1** in a mixture of phosphorus pentoxide, *N*,*N*-dimethylcyclohexanamine (DMCA), and water. The reaction proceeds smoothly at temperatures ranging from 180–200 °C, and is complete within 1–3 hours.

We investigated the use of reaction mixtures of different compositions and found that the molecular ratio P_2O_5/DMCA/H_2O = 1/1/1.5 is the most suitable one and affords the best yields. When a mixture of the composition 1/1/0.75 was used, i.e., a mixture containing only half the amount of water, the dimeric condensation product **4** was obtained as the main product along with low yields of both the starting material **1** and the expected deazahypoxanthine. Compound **4** was characterised by analytical data, mass, I.R., and N.M.R. spectrometry.

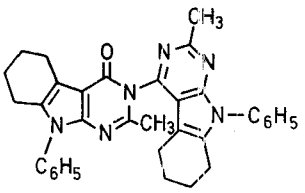


1 3

2

DMCA = c-C6H11-N(CH3)2

1,2,3	R^1	R^2	R^4	R^5
a	H	CH_3	CH_3	H
b	H	CH_3	C_6H_5	H
c	H	CH_3	CH_3	$CH_2-C_6H_5$
d	H	CH_3	CH_3	$i\text{-}C_4H_9$
e	C_6H_5	CH_3	CH_3	CH_3
f	C_6H_5	CH_3	$-(CH_2)_4-$	
g	C_6H_5	C_6H_5	CH_3	CH_3
h	C_6H_5	CF_3	CH_3	CH_3
i	C_6H_5	OC_2H_5	CH_3	CH_3



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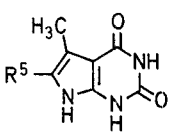
It is worthy of note that only in the case of the 3-cyano-2-trifluoroacetylaminopyrrole **1h** was the cyclization product isolated as the sodium salt from which the free compound **3h** could be obtained by treatment with acid. This particular behavior of compound **3h** may be attributed to the enhanced acidity of the NH group due to the presence of the trifluoromethyl group.

It has been reported[10] that some deazaxanthines of the type **5** could be prepared from the corresponding 3-cyano-2-ethoxycarbonylaminopyrroles (**1**, $R^2 = OC_2H_5$) by a two-step sequence. However, attempts to obtain the corresponding deazaxanthine **3i** by similar treatment of the 2-ethoxycarbonylaminopyrrole derivative **1i** with the $P_2O_5/DMCA/H_2O$ reagent were not successful.



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The deazahypoxanthine structure assigned to the products **3a–h** is based on analytical as well as mass, I.R., and N.M.R. spectral data. The I.R. spectra of compounds **3** show the NH stretching vibrations in the region $\nu = 3150-3200\ cm^{-1}$ characteristic of cyclic secondary amides, in addition to the amide I band near $\nu = 1670\ cm^{-1}$. The mass and ^1H-N.M.R. spectra of products **3** are also in fair agreement with their structures.

It is believed that the formation of compounds **3** proceeds through the intermediacy of the amides **2** resulting from hydrolysis of the cyano function in **1** followed by intramolecular cyclodehydration under the reaction conditions. This assumption was supported by an independent two-step synthesis of products **3**. The 3-cyano derivatives **1a–g**, were converted into the corresponding amides **2a–g** by heating in 85% phosphoric acid for 5–10 minutes. Mere heating of amides **2** above their melting points afforded the deazahypoxanthines **3**. It is of interest to note that in case of the 2-(trifluoroacetylamino)-pyrrole **1h**, the corresponding 7-deazahypoxanthine derivative **3h** was directly produced without isolation of the amide **2h**. This result may also be attributed to the presence of the above-mentioned trifluoromethyl group. The structure of amides **2a–g** was established on the basis of analytical and spectral data.

Comparison of the two methods employed in this work for the production of 7-deazahypoxanthines **3a–h** clearly shows the superiority of the new easy one-step synthesis which affords products **3** in 57–76% yields whereas the overall yields obtained by the other route do not exceed 43%.

The 2-acylamino-3-cyanopyrroles **1a, c**[11], **1b**[12], **1d**[13], and **1e, f, g**[14] were prepared as previously described. Derivative **1h** was prepared by acylation of the corresponding 2-aminopyrrole.

The 3-cyanopyrrole **1b** showed herbicide activity in post-emergent tests against *Solanum lycopersicum, Sinapis alba, Stellaria media*, and *Phaseolus vulgaris* at 4 kg/ha. Only the two 7-deazahypoxanthines **3e** and **3f** were tested; both of them showed plant regulatory activity. The latter activity was also found for compound **1b**[15].

3-Cyano-4,5-dimethyl-2-trifluoroacetylamino-1-phenylpyrrole (1h): 2-Amino-3-cyano-4,5-dimethyl-1-phenylpyrrole[16] (21.1 g, 0.1 mol) is dissolved in trifluoroacetic acid (25 ml) and then trifluoroacetic anhydride (23.1 g, 0.11 mol) is added while stirring at room temperature. The solution is refluxed for 20 min, cooled, and poured onto crushed ice (500 g). The solid formed is collected by suction, dried, and recrystallized from ethanol; yield: 12.6 g (41%); m.p. 163–164°C.

$C_{15}H_{12}F_3N_3O$	calc.	C 58.64	H 3.93	N 13.67
(307.3)	found	58.60	3.91	13.40

M.S.: *m/e* = 307 (M^+, 62%); 210 (100).

I.R. (KBr): ν = 3180 (NH); 2225 (C≡N); 1735 cm^{-1} (C=O).

^1HN.M.R. ($CDCl_3/TMS_{int}$): δ = 1.96 (s, 3H); 2.13 (s, 3H); 7.04–7.50 (m, 5H); 8.78 ppm (s, 1H).

4-Oxo-3,4-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidines (7-Deazahypoxanthines, 3a–h); General Procedure:

Water (5.4 g, 0.3 mol) is added dropwise to a cooled and stirred mixture of phosphorus(V) oxide (28.4 g, 0.2 mol) and *N,N*-dimethylcyclohexanamine (25.2 g, 0.2 mol). The mixture is then gradually heated to 200°C on an oil bath until a clear mixture is obtained. The temperature is adjusted to 180–200°C (see Table 1), the 2-acylamino-3-cyanopyrrole **1a–h** (0.05 mol) is added, and stirring and heating is continued for 1–3 h (see Table 1). The mixture is then allowed to cool to 100°C and 2 molar sodium hydroxide solution (250 ml) is added till alkaline pH reaction. Stirring is continued 30 min at room temperature and the precipitate formed is collected by suction, washed with water, dried, and recrystallized from a suitable solvent (Table 1).

Table 1. Preparation of 4-Oxo-3,4-dihydro-7*H*-pyrrolo[2,3-*d*]pyrimidines (7-Deazahypoxanthines, **3**)

3	Reaction 1 → 3			Reaction 2 → 3	m.p. [°C] (solvent)	Molecular Formula[a]	M.S. *m/e* (%)	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. (60 MHz, DMSO-d_6/TMS$_{int}$, 82 °C) δ [ppm]
	Conditions [°C]	[h]	Yield [%]	Yield [%]					
a	200°	2	76	61	> 360° (DMF)	$C_8H_9N_3O$ (163.2)	163 (M^+, 100)	3220 (NH); 1660 (C=O)	2.26 (s, 6H); 6.59 (s, 1H); 11.10 (br. s, 2H)
b	200°	3	75	43	> 360° (DMF)	$C_{13}H_{11}N_3O$ (225.2)	225 (M^+, 100)	3175 (NH); 1660 (C=O)	2.32 (s, 3H); 7.2 (s, 1H); 7.6 (m, 5H)
c	200°	3	76	59	360° (DMF)	$C_{15}H_{15}N_3O$ (253.3)	253 (M^+, 100)	3200 (NH); 1670 (C=O)	2.22 (s, 3H); 2.25 (s, 3H); 3.88 (s, 2H); 7.22 (m, 5H); 11.07 (br. s, 2H)
d	200°	1	70	64	302–303° (ethanol)	$C_{12}H_{17}N_3O$ (219.3)	219 (M^+, 19); 176 (100)	3200 (NH); 1660 (C=O)	0.86 (d, 6H); 1.92 (m, 1H); 2.19 (s, 3H); 2.25 (s, 3H); 2.29 (d, 2H); 10.75 (br. s, 1H)
e	180°	2	75	64	328° (DMSO)	$C_{15}H_{15}N_3O$ (253.3)	253 (M^+, 100)	3240 (NH); 1660 (C=O)	2.02 (s, 3H); 2.19 (s, 3H); 2.30 (s, 3H); 7.29–7.56 (m, 5H); 11.42 (br. s, 1H)
f	180°	2	62	70	302–303° (ethanol)	$C_{17}H_{17}N_3O$ (279.3)	279 (M^+, 100)	3250 (NH); 1660 (C=O)	1.79 (m, 4H); 2.21 (s, 3H); 2.45 (m, 2H); 2.68 (m, 2H); 7.3–7.5 (m, 5H); 11.41 (br. s, 1H)
g	200°	3	57	42	321–322° (dioxan)	$C_{20}H_{17}N_3O$ (315.4)	315 (M^+, 100)	3200 (NH); 1660 (C=O)	2.10 (s, 3H); 2.36 (s, 3H); 7.35–8.05 (m, 10H)
h	200°	3	65[b]	48[c]	299–301° (ethanol)	$C_{15}H_{12}F_3N_3O$ (307.3)	307 (M^+, 100)	3210 (NH); 1680 (C=O)	2.16 (s, 3H); 2.40 (s, 3H); 7.6 (m, 5H)

[a] The microanalyses showed the following maximum deviations from the calculated values: C ± 0.4, H ± 0.04, N ± 0.4.

[b] Isolated as the sodium salt; m.p. 328–330 °C.
$C_{15}H_{11}F_3N_3ONa \cdot H_2O$ (347.3) calc. C 51.88 H 3.77 N 12.10
found 52.27 4.01 12.22

[c] Obtained by treatment of **1h** with 85% H_3PO_4.

Table 2. Preparation of 2-Acylaminopyrrole-3-carboxamides (**2**)

2	Yield [%]	m.p. [°C] (solvent)	Molecular Formula[a] or m.p. [°C] reported	M.S. *m/e* (%)	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. (60 MHz, DMSO-d_6/TMS$_{int}$) δ [ppm]
a	47	228–230° (toluene)	$C_8H_{11}N_3O_2$ (181.2)	181 (M^+, 68); 122 (100)	3490, 3450, 3380, 3330, 3240, 1660, 1630	2.13 (s, 3H); 2.20 (s, 3H); 6.30 (s, 1H); 6.77 (s, 2H, NH_2); 10.93 (s, 1H); 11.16 (s, 1H)
b	58	193–195° (methanol)	192–193°[17]	243 (M^+, 72); 184 (100)	3460, 3380, 3340, 1660, 1640	2.17 (s, 3H); 6.5 (s, 3H); 7.1 (m, 5H); 10.80 (s, 1H)
c	73	259–261° (DMF)	$C_{15}H_{17}N_3O_2$ (271.3)	271 (M^+, 100), 212 (35)	3490, 3380, 3320, 3250, 1660, 1640	2.13 (s, 3H); 2.20 (s, 3H); 4.00 (s, 2H); 6.8 (s, 2H); 7.5 (m, 5H); 11.13 (s, 2H)
d	67	243–245° (toluene)	$C_{12}H_{19}N_3O_2$ (237.3)	237 (M^+, 40); 194 (100)	3460, 3380, 3300, 3160, 1660, 1640	0.82 (d, 6H); 2.0 (m, 1H); 2.18 (s, 6H); 2.50 (d, 2H); 6.93 (s, 2H); 10.3 (s, 2H)
e	62	261–218° (ethanol)	$C_{15}H_{17}N_3O_2$ (271.3)	271 (M^+, 42); 212 (100)	3420, 3390, 3280, 1660, 1630	1.83 (s, 3H); 1.97 (s, 3H); 2.23 (s, 3H); 6.90 (s, 2H); 7.66 (m, 5H); 9.60 (s, 1H)
f	40	163–165° (methanol)	$C_{17}H_{19}N_3O_2$ (297.4)	297 (M^+, 34); 238 (100)	3440, 3320, 3260, 1665, 1640	1.77 (m, 4H); 2.3 (m, 5H); 2.53 (m, 2H); 6.66 (s, 2H); 7.20–7.43 (m, 5H); 9.4 (s, 1H)
g	55	218–220° (toluene)	$C_{20}H_{19}N_3O_2$ (333.4)	333 (M^+, 27); 316 (100); 212 (24); 211 (68)	3420, 3320, 3260, 1660, 1640	1.96 (s, 3H); 2.20 (s, 3H); 6.80 (s, 2H); 7.2–7.9 (m, 10H); 9.9 (s, 1H)

[a] The microanalyses showed the following maximum deviations from the calculated values: C ± 0.4, H ± 0.04, N ± 0.4.

2-Acylaminocarbonylpyrrole-3-carboxamides (2a–g); General Procedure:

A suspension of the 2-acylamino-3-cyanopyrrole 1a–g (0.05 mol) in 85% phosphoric acid (100 ml) is immersed in an oil bath preheated to 130 °C, and heating is continued until a clear solution is obtained (5–10 min). After cooling, the mixture is poured onto crushed ice (500 g). After the ice has melted, the product **2** is isolated by suction, washed with water, air-dried, and recrystallized from a suitable solvent (Table 2).

Application of the above procedure to educt 1h affords the deazahypoxanthine **3h**.

Thermal Cyclodehydration of Compounds 2a–g to 7-Deazahypoxanthines 3a–g; General Procedure:

The carboxamide **2a–g** (0.01 mol) is heated for 3–5 min in an oil bath preheated at a temperature 50 °C above the melting point of **2**. Melting occurs with decomposition. In some cases, the melt resolidified quickly and in others it solidified on cooling. The solidified melt is triturated with a few ml of methanol and the separated solid is isolated by suction, washed with methanol, dried, and recrystallized.

The identity of the products **3a–g** thus obtained with compounds **3a–g** obtained directly from **1a–g** was established by determination of melting points and mixture melting points as well as by comparison of the ^{1}H-N.M.R. spectra and of the R_f values obtained on silica gel plates using chloroform/methanol (19/1) as eluent.

2-Methyl-3-(2-methyl-9-phenyl-5,6,7,8-tetrahydro-9*H*-pyrimido[4,5-*b*]indol-4-yl)-4-oxo-9-phenyl-3,4,5,6,7,8-hexahydro-9*H*-pyrimido[4,5-*b*]indole (4):

Water (2.7 g, 0.15 mol) is added to a stirred mixture of phosphorus(V) oxide (28.4 g, 0.2 mol) and *N,N*-dimethylcyclohexanamine (25.2 g, 0.2 mol). The mixture is heated on an oil bath at 180 °C until a clear mixture is obtained. The pyrrole derivative **1f** (13.9 g, 0.05 mol) is added and the temperature is kept at 180 °C for 2 h. The mixture is then allowed to cool to ~100 °C and cold 2 normal sodium hydroxide solution (250 ml) is added. Stirring is continued for a further 30 min and the separated solid is isolated by suction, washed with water, and dried. The product (10 g) is recrystallized from dioxan (100 ml), the mother liquor being saved for isolation of product **3f**; yield of **4**: 6.8 g (43%); m.p. 291–293 °C.

$C_{34}H_{32}N_6O \cdot C_4H_8O_2$ (dioxan)	calc.	C 72.58	H 6.41	N 13.36
(540.65 + 88.1) [628.8]	found	72.35	6.44	13.45

M.S.: *m/e* = 540 (M^+, 100%).

I.R. (KBr): ν = 1690 cm^{-1} (C=O).

^{1}H-N.M.R. ($CDCl_3$/TMS_{int}): δ = 1.83 (m, 8H); 2.20 (s, 3H); 2.53 (m, 4H); 2.77 (s, 3H); 3.0 (m, 4H); 3.70 (s, 8H, 1 mol dioxan); 7.47 ppm (m, 10H).

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