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Synthesis of Some New Imidazoles and Related Purine Derivatives

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ABSTRACT

Treatment of 5-(amino)imidazole-4-carbonitrile **1** with a mixture of acetic anhydride and acetic acid afforded, the unexpected 5-(acetylamino)imidazole-4-(N-acetyl)carboxamide **2**, but upon reacting **1** with acetic anhydride for a short time, the 5-(diacetylamino)imidazole-4-carbonitrile **4** was obtained. Reaction of **2** and **4** with hydrazine hydrate gave the condensation products **6** and **8a** respectively. Upon reacting **2** with methylamine and hydroxylamine, the 5-(amino)imidazole derivative **7** was afforded, but reaction of **4** with the same reagents gave products **8b** and **11** respectively. Cyclization of **2** and **4** in alkaline medium was carried out to afford the 2-methylpurin-6(1H)-one derivative **13**. Treatment of the latter product with phosphoryl chloride, followed by reaction with some cyclic 2^{IV} amines and amino acids gave the 6-substituted purines **15-17**. Moreover, when **1** was allowed to react with alkyl isocyanate the urea derivatives **19** were afforded. Also, the 8-substituted purines **20** and **21** were obtained from **19**.

INTRODUCTION

Synthesis and biological properties of a variety of substituted purines from their imidazole precursors has been previously reported[1-3]. Many 9-benzyl-8-purinol derivatives were reported as useful compounds for the treatment of viral diseases such as hepatitis B or C and contact skin inflammation[4]. Also, some purine derivatives were prepared as type of 2 helper T cell-selective immune response suppressors[5]. Moreover, the extracellular, adenine nucleotides exert significant biological actions on various peripheral tissues as well as in the centeral nervous system[6-11]. ATP plays a role as a neurotransmitter at neuromuscular junctions and within the centeral nervous system[12-15].

In the present investigation a suggested mechanism for transformation of a carbonitrile group to N-(acetyl)carboxamide was discussed. Synthesis of some purine derivatives was also attempted for their expected biological properties.

EXPERIMENTAL

Melting points are uncorrected. Microanalyses were carried out by the Microanalytical Lab., National Research Centre. IR spectra were recorded (KBr) by using a Jasco FT/IR-300E spectrophotometer. ^{1}H-NMR spectra were measured in DMSO-d_6 (or $CDCl_3$ whenever reported) by using Jeol Ex-270 MHz spectrometer with chemical shift in δ ppm. Mass spectra were recorded by using GC/MS Finnigan SSQ 7000 spectrometer.

5-Acetylamino-1-(p-chlorophenyl)imidazole-4-(N-acetyl)carboxamide 2:

To a mixture of acetic anhydride/acetic acid (20 ml, 1:1), compound **1** (0.01 mol) was added and the reaction mixture was heated under reflux for 10 hr. After cooling, the mixture was poured onto crushed ice. The solid product obtained was filtered off, washed with cold water and crystallzied from ethanol to give **2**, m.p. 164-5°C (68%). IR ν/cm^{-1}: 3350, 3244 (NH); 1740, 1720, 1675 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.20 (s, 3H, CH_3); 2.50 (s, 3H, CH_3); 7.00-7.50 (m, 4H, C_6H_4); 7.65 (s, 1H, H-2); 9.30 (b, 1H, NH); 9.45 (b, 1H, NH). Mass (m/e): 320 (40.44%); 322 (14.97%). Anal. Calcd. for $C_{14}H_{13}ClN_4O_3$: C, 52.42; H, 4.06; N, 17.47. Found: C, 52.64; H, 4.06; N, 17.80%.

5-(Diacetyl)amino-1-(p-chlorophenyl)imidazole-4-carbonitrile 4:

A mixture of **1** (0.01 mol) and acetic anhydride (20 ml) was heated under reflux for 1 hr and left to cool. The mixture was poured onto crushed ice. The separated precipitate was filtered off, washed with water and crystallzied from ethanol to give **4**, m.p. 150-1°C (70%). IR ν/cm^{-1}: 2235 (C≡N); 1733, 1712 (C=O). ^{1}H-NMR ($CDCl_3$) δ:2.25 (s, 6H, $2CH_3$); 7.00-7.60 (m, 4H, C_6H_4); 7.75 (s, 1H, H-2). Anal. Calcd. for $C_{14}H_{11}ClN_4O_2$:C, 55.54; H, 3.64; N, 18.51. Found: C, 55.50; H, 3.65; N, 18.77%.

5-(2-Thienylidene)amino-1-(p-chlorophenyl)imidazole-4- (N-acetyl)caboxamide 5 :

A mixture of **2** (0.01mol) and thiophene-2-aldehyde (0.011 mol) in ethanol (30 ml) containing hydrochloric acid (1/2 ml) was heated under reflux for 4 hr. The solid product obtained was filtered off and crystallized from ethanol to give **5**, m.p. 278-80°C (70%), IR ν/cm^{-1}: 3411(NH); 1701, 1651 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.95 (s, 3H, CH_3); 7.10-7.75 (m, 8H, C_6H_4, C_4H_3S, H-2); 8.00 (s, 1H, N=CH); 9.90 (b, 1H, NH). Anal. Calcd. for $C_{17}H_{13}ClN_4O_2S$: C, 54.77; H,3.49; N, 15.03. Found:C,55.00;H, 3.40; N, 15.00%.

Reaction of 2 and 4 with hydrazine hydrate and methylamine:

General procedure:

A mixture of **2** or **4** (0.01 mol) and hydrazine

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hydrate or methylamine (0.012 mol) in ethanol (30 ml) was heated under reflux for 4 hr. The solid product obtained was filtered off, and crytallized from ethanol to give **6**, **7** and **8**.

6: m.p. 258-60°C (87%). IR ν/cm^{-1}: 3411, 3320, 3268 (NH); 1699, 1655 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 1.65 (s, 6H, $2CH_3$); 4.95 (b, 2H, NH_2); 7.00-7.75 (m, 6H, C_6H_4, H-2, NH); 12.10 (b, 1H, NH). Mass (m/e): 334. Anal. Calcd. for $C_{14}H_{15}ClN_6O_2$: C, 50.22; H, 4.48; N, 25.11. Found: C, 50.28; H, 4.60; N, 24.80%.

7: m.p. 273-5°C (77%). IR ν/cm^{-1}: 3411, 3280 (NH); 1701, 1653 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 1.85 (s, 3H, CH_3); 7.15 (b, 2H, NH_2); 7.30-7.80 (m, 4H, C_6H_4); 7.95 (s, 1H, H-2); 9.80 (b, 1H, CO-NH). Mass (m/e): 278. Anal. Calcd. for $C_{12}H_{11}ClN_4O_2$: C, 51.70; H, 3.95; N, 20.11. Found: C, 51.62; H, 3.92; N, 20.40%.

8a: m.p. 211-2°C (60%). IR ν/cm^{-1}: 3410, 3314 (NH); 2270 (C≡N). Anal. Calcd. for $C_{12}H_{11}ClN_6$: C, 52.46; H, 4.01; N, 30.60. Found: C, 52.72; H, 3.85; N, 30.60%.

8b: m.p. 205-6°C (95%). IR ν/cm^{-1}: 3230 (NH); 2233 (C≡N). ^{1}H-NMR ($CDCl_3$) δ: 2.60 (s, 3H, CH_3); 3.25 (s, 3H, N-CH_3); 7.40-7.70 (m, 5H, C_6H_4, NH); 7.95 (s, 1H, H-2). Anal. Calcd. for $C_{13}H_{12}ClN_5$: C, 57.04; H, 4.39; N, 25.59. Found: C, 56.94; H, 4.20; N, 25.94%.

9-(p-Chlorophenyl)-2-methylpurin-1-oxide 11 :

A mixture of **4** (0.01 mol) and hydroxylamine hydrochloride (0.012 mol) in ethanol (30 ml) containing triethylamine (1/2 ml) was heated under reflux for 6 hr. After cooling, the solid product obtained was filtered off, washed with ethanol and crystallized from n-butanol to give **11**, m.p. 293-5°C (67%). IR ν/cm^{-1}: 3310 (NH). ^{1}H-NMR (DMSO-d_6) δ: 2.50 (s, 3H, CH_3); 7.55-8.00 (m, 4H, C_6H_4); 8.80 (s, 1H, H-8); 9.15 (b, 1H, NH); 9.85 (b, 1H, NH). Mass (m/e): 275. Anal. Calcd. for $C_{12}H_{10}ClN_5O$: C, 52.27; H, 3.63; N, 25.41. Found: C, 52.45; H, 3.80; N, 25.20%.

9-(p-Chlorophenyl)-2-methylpurin-6(1H)-one 13 :

A suspension of **2** or **4** (5 g) in sodium hydrogen carbonate solution (250 ml, 10%) was heated under reflux for 20 hr. After cooling, the reaction mixture was treated with dil HCl. The solid product was filtered off washed with water, and crystallized from n-butanol to give **13**, m.p. 360-2°C (65%). IR ν/cm^{-1}: 3446 (NH); 1685 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 2.30 (s, 3H, CH_3); 7.40-8.10 (m, 4H, C_6H_4); 8.30 (s, 1H, H-8); 12.35 (b, 1H, NH). Anal. Calcd. for $C_{12}H_9ClN_4O$: C, 55.28; H, 3.45; N, 21.50. Found: C, 55.50; H, 3.60; N, 21.30%.

6-Chloro-9-(p-chlorophenyl)-2-methylpurine 14 :

A mixture of **13** (5g) and phosphoryl chloride (50 ml) was heated under reflux for 2 hr and left to cool. The reaction mixture was poured onto crushed ice. The solid product obtained was filtered off, washed with water and crysallized from ethanol to give **14**, m.p. 198-200°C (65%). ^{1}H-NMR (DMSO-d_6) δ: 2.55 (s, 3H, CH_3); 7.60-8.00 (m, 4H, C_6H_4); 8.95 (s, 1H, H-8). Anal. Calcd. for $C_{12}H_8Cl_2N_4$: C, 51.61; H,2.87; N, 20.07. Found:C,51.50; H,2.60; N, 20.20%.

6-Substituted-9-(p-chlorophenyl)-2-methylpurine 15 :

A mixture of **14** (0.01 mol) and piperidine or morpholine (0.013 mol) in ethanol (25 ml) containing triethylamine (1/2 ml) was heated under reflux for 10 hr. After cooling, the solid product obtained was filtered off, washed with ethanol and crystallized from ethanol to give **15**.

15a: m.p. 175-6°C (68%). ^{1}H-NMR (DMSO-d_6) δ: 1.60 (s, 6H, $3CH_2$); 2.45 (s, 3H, CH_3); 4.25 (m, 4H, $2CH_2$); 7.50-8.10 (m, 4H, C_6H_4); 8.50 (s, 1H, H-8). Anal. Calcd. for $C_{17}H_{18}ClN_5$: C, 62.29; H, 5.50; N, 21.37. Found: C, 62.50; H, 5.40; N, 21.24%.

15b: m.p. 169-70°C (62%). ^{1}H-NMR (DMSO-d_6) δ: 2.45 (s, 3H, CH_3); 3.75 (m, 4H, $2CH_2$); 4.25 (m, 4H, $2CH_2$); 7.50-8.10 (m, 4H, C_6H_4); 8.50 (s, 1H, H-8). Anal. Calcd. for $C_{16}H_{16}ClN_5O$: C, 58.27; H, 4.86; N, 21.24. Found: C, 58.50; H, 5.00; N, 21.00%.

N-[9-(p-chlorophenyl)-2-methylpurin-6-yl]amino acids 16 and 17:
General procedure :

The appropriate amino acid (20 mmol) and sodium carbonate (11 m mol) were dissolved in water (20 ml), then adjasted to pH 9-9.5. The 6-chloropurine **14** (10 m mol) was added and the mixture was stirred at 100°C for 10-20 hrs with control of pH. The reaction mixture was left overnifgt at room temperature, then treated with formic acid (88%). The solid product obtained was filtered off, washed with water and purified using preparative silica gel TLC plates to give **16** and **17**.

16: m.p. 179-80°C (63%, 10 hr). IR ν/cm^{-1}: 1736 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 2.10 (m, 2H, γ-CH_2); 2.35 (d, 5H, CH_3, β-CH_2); 3.75 (m, 1H, δ-CH_2); 4.25 (m, 1H, δ-CH_2); 4.75, 5.45 (2d, 1H, α-CH); 7.50-8.35 (m, 4H, C_6H_4), 8.55 (s, 1H, H-8). Anal. Calcd. for $C_{17}H_{16}ClN_5O_2$: C, 57.06; H, 4.48; N, 19.58. Found: C, 56.90; H, 4.40; N, 19.80%.

17: m.p. 206-8°C (70%, 20 hr). IR ν/cm^{-1}: 3398 (NH); 1730 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 2.45 (s, 3H, CH_3); 3.40 (d, 2H, CH_2); 5.05 (t, 1H, CH); 5.75 (b, 1H, NH); 6.90-8.25 (m, 9H, Ar-H); 8.60 (s, 1H, H-8); 10.85 (b, 1H, NH, indole). Anal. Calcd. for

$C_{23}H_{19}ClN_6O_2$: C, 61.81; H, 4.26; N, 18.81. Found: C, 62.00; H, 4.20; N, 19.10%.

N-Substituted-N`-[1-alkyl-9-(p-chlorophenyl)-2-oxo-1,2-dihydropurin-6-yl]ureas 19 : General procedure :

A mixture of 1 (0.01 mol) and ethyl- or n-butyl isocyanate (0.02 mol) in pyridine (20 ml) was heated under reflux for 2 hr. The reaction mixture was evaporated till dryness and the obtained residue was triturated with methanol. The solid product obtained was filtered off and crystallized from n-butanol to give **19**.

19a: m.p. 288-90°C (61%). IR ν/cm^{-1}: 3242 (NH); 1730, 1693 (C=O). Anal. Calcd. for $C_{16}H_{17}ClN_6O_2$: C, 53.26; H, 4.72; N, 23.30. Found: C, 52.96; H, 4.46; N, 23.00%.

19b: m.p. 253-5°C (60%). IR ν/cm^{-1}: 3244 (NH); 1725, 1692 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 0.70 (t, 3H, CH_3); 0.85 (t, 3H, CH_3); 1.15 (m, 4H, $2CH_2$); 1.45 (m, 2H, CH_2); 1.65 (m, 2H, CH_2); 3.25 (m, 2H, CH_2-NH); 3.50 (m, 2H, CH_2N); 7.35-8.30 (m, 4H, C_6H_4); 8.90 (s, 1H, H-8); 9.90 (b, 1H, NH); 10.35 (b, 1H, NH). Mass (m/e): 416. Anal. Calcd. for $C_{20}H_{25}ClN_6O_2$: C, 57.26; H, 6.00; N, 20.17. Found: C, 58.00; H, 5.90; N, 20.00%.

N-Substituted-N`-[1-alkyl-8-bromo-9-(p-chlorophenyl)-2-oxo-1,2-dihydropurin-6-yl]ureas 20 : General procedure :

A suspension of **19** (0.01 mol) in water (150 ml) was stirred at room temperature, then a solution of bromine-water (1% Br_2 in H_2O) was added dropwise while stirring for 2hr. The whole mixture was neutralized with sodium hydroxide (2 N). The reaction mixture was then left overnight, the solid product obtained was filtered off and crystallized from DMF/H_2O (5:1) to give **20**.

20a: m.p. 225-7°C (75%). IR ν/cm^{-1}: 3300 (NH); 1706, 1683 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 0.80 (t, 3H, CH_3); 1.25 (t, 3H, CH_3); 2.90 (q, 2H, CH_2); 3.50 (q, 2H, CH_2); 7.35-8.20 (m, 4H, C_6H_4); 9.30 (b, 1H, NH); 9.80 (b, 1H, NH). Anal. Calcd. for $C_{16}H_{16}BrClN_6O_2$: C, 43.69; H, 3.64; N, 19.11. Found: C, 44.00; H, 3.43; N, 19.50%.

20b: m.p. 175-6°C (86%). IR ν/cm^{-1}: 3326, 3235 (NH); 1700, 1687 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 0.65 (t, 3H, CH_3); 0.90 (m, 5H, CH_3, CH_2); 1.25 (m, 2H, CH_2); 1.50 (m, 2H, CH_2); 1.65 (m, 2H, CH_2); 3.25 (m, 2H, CH_2); 3.45 (m, 2H, CH_2); 7.25-8.25 (m, 4H, C_6H_4); 9.85 (b, 1H, NH); 10.30 (b, 1H, NH). Mass (m/e): 495 (0.12%) . Anal. Calcd. for $C_{20}H_{24}BrClN_6O_2$: C, 48.44; H, 4.84; N, 16.95. Found: C, 48.45; H, 4.68; N, 16.91%.

N-Substituted-N`-[1-alkyl-9-(p-chlorophenyl)-8-hydrazino-2-oxo-1,2-dihydropurin-6-yl]ureas 21 : General procedure :

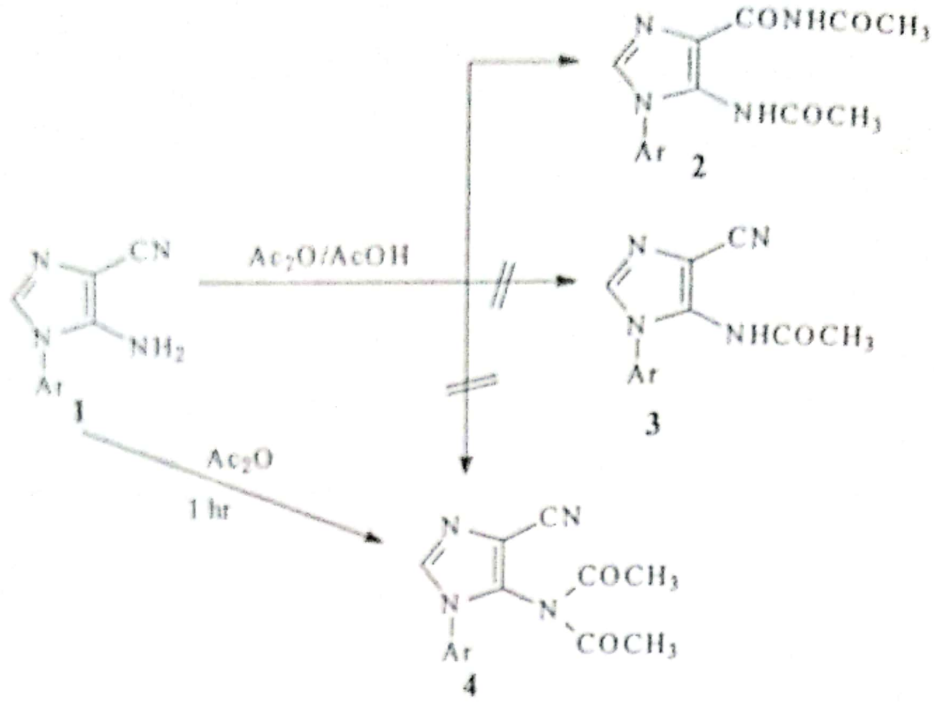
A suspension of **20** (0.01 mol) in water (100 ml) and aqueous hydrazine hydrate (50 ml, 85%) was stirred at 100°C for 2hr. The solid product obtained was filtered off, washed with water and crystallized from n-butanol to give **21**.

21a: m.p. 223-5°C (77%). IR ν/cm^{-1}: 3328, 3200 (NH); 1700, 1650 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 0.80 (t, 3H, CH_3); 1.30 (t, 3H, CH_3); 3.50 (t, 4H, $2CH_2$); 4.60 (b, 2H, NH_2); 7.35-8.30 (m, 4H, C_6H_4); 8.90 (b, 1H, NH); 9.00 (b, 1H, NH); 9.90 (b, 1H, NH). Anal. Calcd. for $C_{16}H_{19}ClN_8O_2$: C, 49.17; H, 4.87; N, 28.68. Found: C, 48.90; H, 5.02; N, 28.50%.

21b: m.p. 240-2°C (74%). IR ν/cm^{-1}: 3320, 3200 (NH); 1690, 1650 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 0.60-1.70 (m, 14H, $2CH_3$, $4CH_2$); 3.40 (m, 2H, N-CH_2); 3.50 (m, 2H, N-CH_2); 4.50 (b, 2H, NH_2); 7.00-8.00 (m, 6H, C_6H_4, 2NH); 9.90 (b, 1H, NH). Anal. Calcd. for $C_{20}H_{27}ClN_8O_2$: C, 53.75; H, 6.05; N, 25.08. Found: C, 54.00; H, 5.90; N, 25.20%.

RESULTS AND DISCUSSION:

Acetylation of the 5-amino-1-(p-chlorophenyl)-imidazole-4 carbonitrile[1,16] **1** with a mixture of acetic acid and acetic anhydride afforded the unexpected product:5-acetylamino-1-(p-chlorophenyl)-imidazole -4-(N-acetyl)carboxamide **2**, rather than the expected 5-(acetyl-amino)-; or 5-(diacetyl)imino-imidazole-4-carbonitriles **3** and **4**. Whereas, the 5-(diacetylamino)-imidazole-4-carbonitrile **4** was obtained upon boiling **1** for a short time in acetic anhydride (Scheme 1).

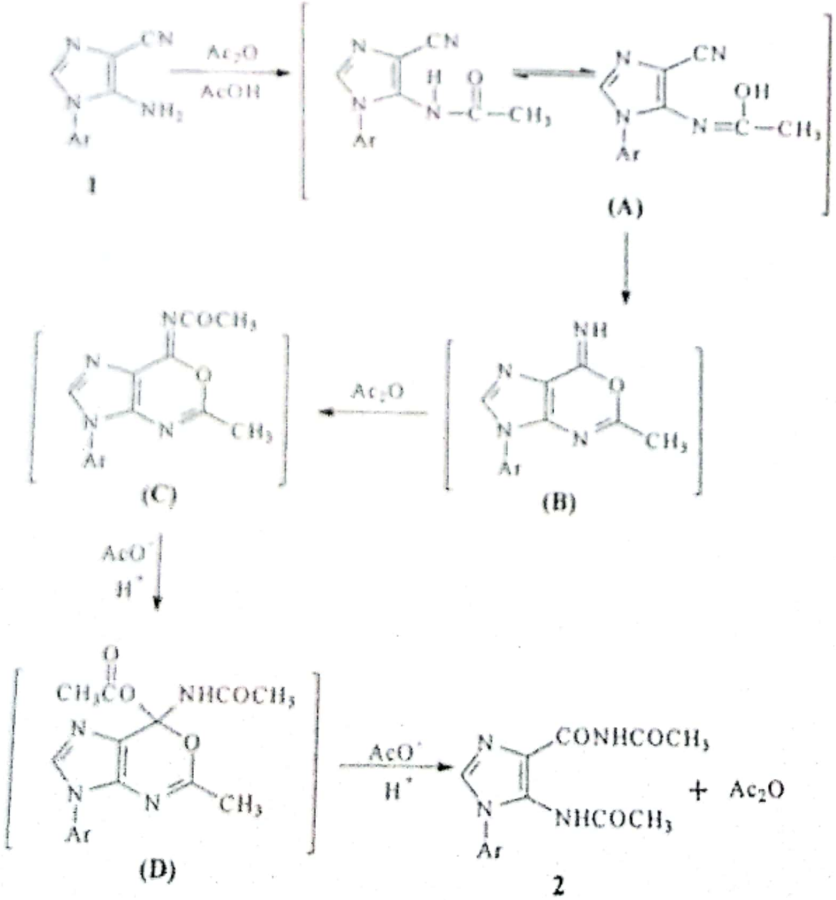


(Ar = C_6H_4Cl-p)

Scheme 1

Infrared absorption spectrum of product **2** showed lack of C=N absorption and presence of C=O (acetyl, two bands) at 1740 & 1720 cm^{-1} and C=O (amide)[17] at 1675 cm^{-1}. ^{1}H-NMR spectrum of the latter product revealed the presence of two methyl protons signals at δ 2.20 and 2.50 ppm and two proton signals (NH) at δ 9.30 and 9.45 ppm (D_2O-exchangeable). Moreover, mass spectrum accorded its proposed structure and showed m/z (M^+) at 320.

Formation of product **2** from **1** might be mechanistically illustrated in Scheme 2.



Scheme 2

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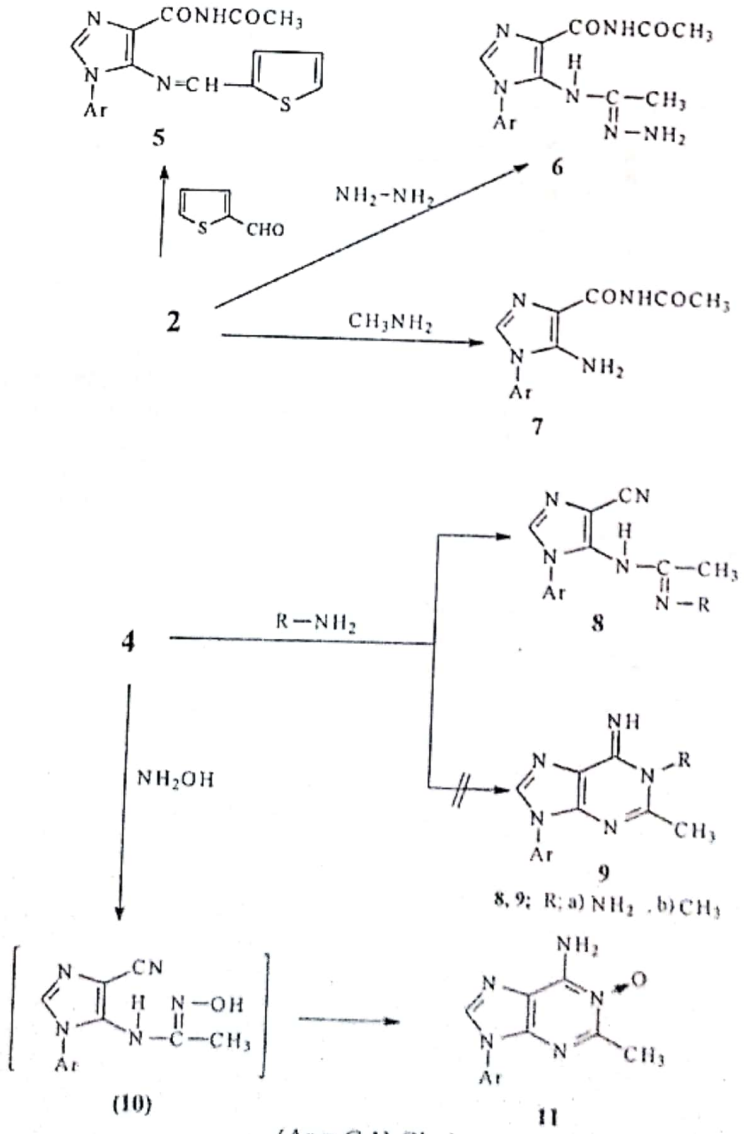
When product **2** was allowed to react with thiophene-2-aldehyde in acidic medium, the 5-(2-thienylidene)amino-1-(p-chlorophenyl)imidazole derivative **5** was obtained . The reaction might be affected by condensation with elimination of acetic acid.

Reaction of products **2** and **4** with hydrazine hydrate afforded the condensation products 6 and 8a respectively. On the other hand, when **4** was reacted with methylamine or hydroxylamine hydrochloride, the condensation product **8b** and purine-1-oxide **11** were obtained respectively. However, reaction of **2** with methylamine and hydroxylamine hydro chloride afforded the hydrolyzed product: 5-amino-1-(p-chlorophenyl)imidazole-4-(N-acetyl)carboxamide **7** (Scheme 3).

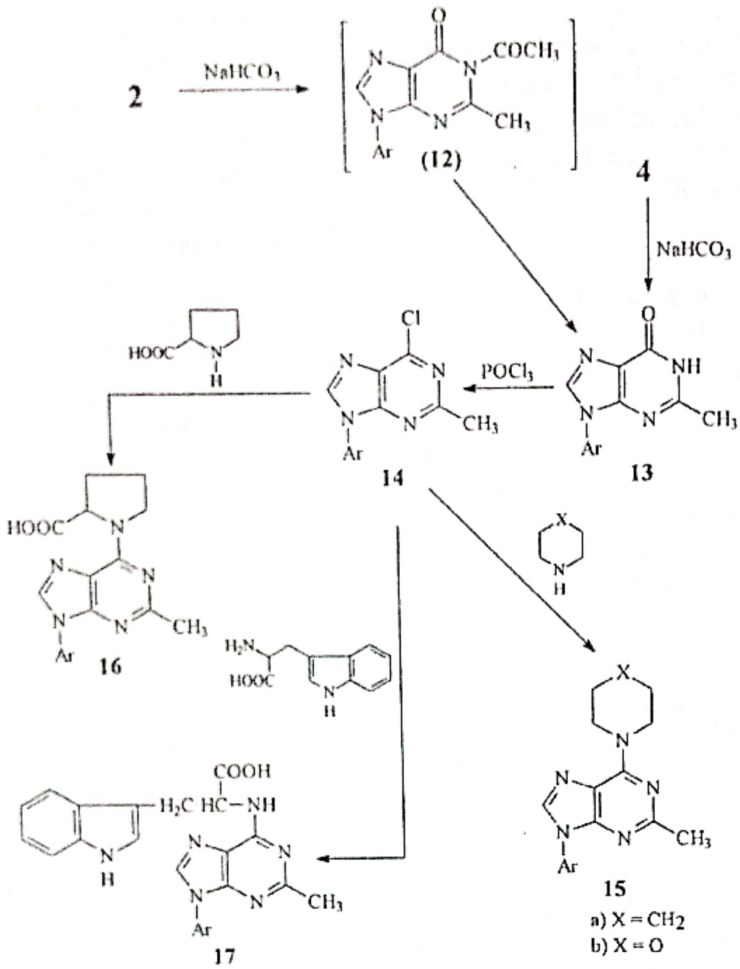
Cyclization of products **2** and **4** to 9-(p-chlorophenyl)-2-methylpurin-6(1H)-one **13** was also carried out by heating under reflux in sodium hydrogen carbonate solution (10%). Treatment of 13 with phosphoryl chloride gave the corresponding 6-chloropurine derivative **14**.

Reaction of **14** with piperidine, morpholine, L-proline or L-tryptophane gave the corresponding 6-substitutedpurine derivatives **15-17**, respectively (Scheme 4).

IR spectra of products **16** and **17** showed C=O absorption bands at 1736-1730 cm^{-1} region, the spectra showed also characteristic peaks in the 1276-1274 cm^{-1} region for COOH group[18].



Scheme 3



Scheme 4

Moreover, when **1** was reacted with ethyl or n-butyl isocyanate, the unexpected products: N-alkyl-N`-[1-alkyl-9-(p-chlorophenyl)-2-oxo-1,2-dihy - dropurin-6-yl]urea derivatives **19** were afforded without isolation of the expected 1-alkyl-6-amino-9-(p-chlorophenyl)-2-methylpurin-2-ones[19] **18**. Therefore, formation of products **19** could be achieved by incorporation of another isocyanate molecule to **18** (which might be produced in the reaction mixture as intermediates) (Scheme 5).

^{1}H-NMR spectrum of **19b** revealed the presence of two butyl protons signals, beside another two peacks (D_2O-exchangeable) which corresponded to NH protons signals. Also, the mass spectrum accorded its proposed structure.

Reaction of **19** with bromine-water was extremely rapid at room temperature, and the 8-bromo derivatives **20** were obtained as insoluble solids in high yield. On the other hand, reaction of **20** with hydrazine hydrate proceeded smoothly and afforded the hydrazino derivatives **21**.

Acknowledgment

We wish to express our gratitude to Prof. A. J. Boulton, School of Chemical Science, University of East Anglia, Norwish , U.K., for his kind useful discussion concerning the reaction mechanism of product **2**.

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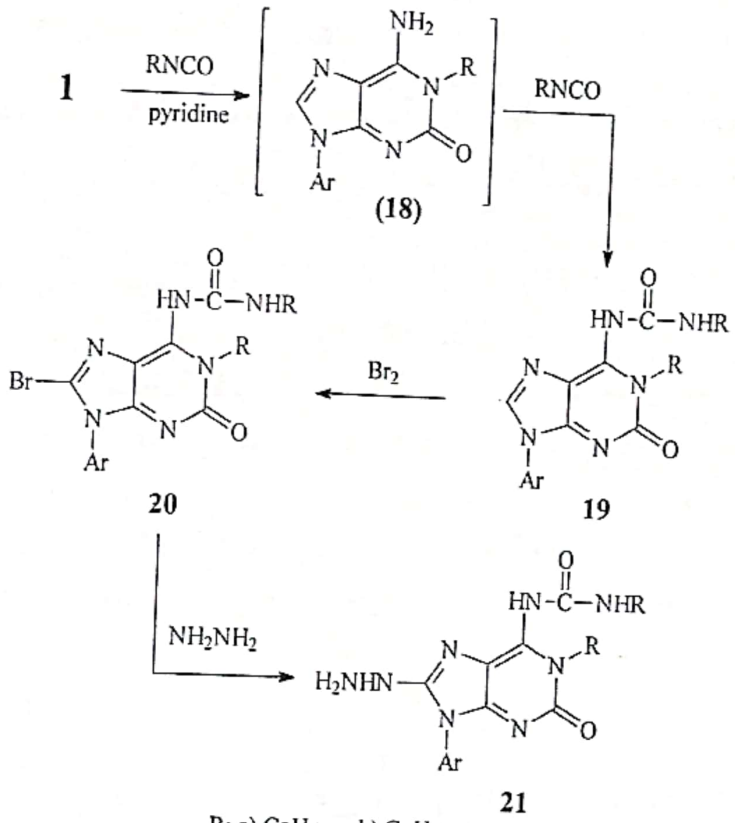

R; a) C_2H_5, b) C_4H_{9}-n

(Ar = C_6H_4Cl-p)

Scheme 5

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تشييد بعض مشتقات الاميدازول الجديدة ومشابهاتها من البيورين

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عند معاملة مشتق ٥-أمينوامیدازول-٤-كربونيتريل (١) بخليط من انهيدريد حمض الخليك وحمض الخليك نتج المركب الغير متوقع ٥-اسيتيل امينو اميدازول-٤-(ن-اسيتيل كربوكساميد) (٢) ولكن عند معاملة نفس المركب (١) بانهيدريد حمض الخليك فقط تم الحصول على المركب ٥-(ثنائى اسيتيل امينو) اميدازول (٤).

بتفاعل المركبات (٢)،(٤) مع الهيدرازين المائى تم الحصول على المشتقات (٦)، (٨أ) على التوالى. مشتق الاميدازول (٧) نتج من تفاعل المركب (٢) مع كل من الميثيل امين والهيدروكسيل امين. ولكن عند معاملة المركب (٤) مع نفس الكواشف اعطى المشتقات (٨ب)، (١١) على التوالى.

تم حلقنة المركبات (٢)،(٤) الى المركب (١٣) وذلك عند معاملتهما بالقلوى. عند تفاعل المركب (١٣) مع كلوريد الفوسفوريل متبعا بالمفاعلة مع بعض الامينات الثانوية الحلقية وكذلك الاحماض الامينية تم الحصول على مشتقات البيورين (١٥-١٧).

بالاضافة الى ماسبق عند مفاعلة المركب (١) مع بعض الايزوسيانات نتجت مشتقات اليوريا المقابلة (١٩) والتى تم الحصول منها على المشتقات (٢٠)،(٢١).