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Adenine reacts slowly with 2,5-dimethoxytetrahydrofuran (**3**) in a dilute acetic acid solution in methanol-water, to give 6-(pyrrol-1-yl)purine (**4**). Under more acidic conditions, **4** is partly transformed to 6-(indol-1-yl)purine (**5**) and other unidentified products. The reaction may be used for the preparation of 9-glycosides of **4** from the corresponding adenine derivatives provided their 9-glycosyl linkage is somewhat resistant to acid hydrolysis.

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We have recently described the synthesis of 6-(3-methylpyrrol-1-yl)-9- β -D-ribofuranosylpurine (**1**), a new metabolite of the plant hormone derivative zeatin riboside, and of its aglycone **2** [1]. These two compounds were the first representatives of the 6-(pyrrol-1-yl)purine heterocyclic system.

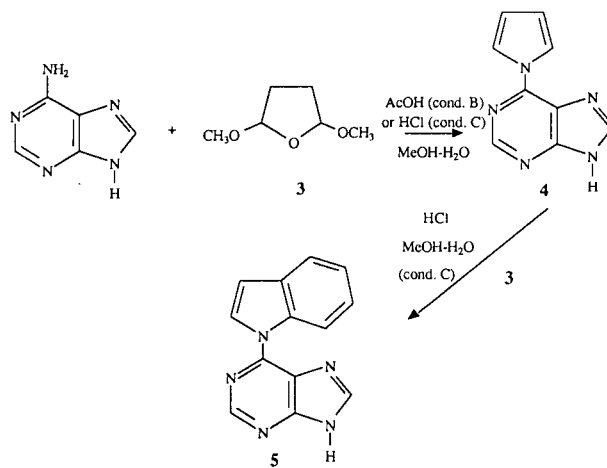
Since *N*-alkyl and *N*-arylpyrroles are known to be easily prepared from the corresponding alkyl or aryl primary amines and 2,5-dimethoxytetrahydrofuran (**3**) [2], we have studied the reaction of adenine and of some of its 9-glycosides with **3**, in order to synthesize the *nor*-derivative **4** of the methylpyrrolyl purine **2**, and to have an access to new nucleosides analogues.

Results and Discussion.

Under standard conditions [2], in acetic acid at reflux or at 80°, with an equimolar amount of **3** (conditions A), adenine gave rise to a mixture in which hplc analysis revealed the presence of at least 4 products, besides unreacted adenine. In contrast, the expected 6-(pyrrol-1-yl)purine (**4**) was selectively obtained by using a dilute solution of acetic acid in a water-methanol (50-50) mixture and a large excess of **3**, and heating at reflux for several days (conditions B) (Scheme 1). The reaction was very slow in the absence of water, and an excess of **3** was necessary to offset its partial polymerization resulting from prolonged heating.

A faster reaction was observed when hydrochloric acid was used as a catalyst instead of acetic acid in ethanol solution (conditions C). However, pyrrole **4** was further partially transformed into a new product, which was identified as 6-(indol-1-yl)purine **5** (Scheme 1). Compounds **4** and **5** were identified to the major products detected by hplc in the reaction mixture obtained in conditions A.

Some examples of the formation of indoles from pyrroles and **3** have been described in the literature. 1-Methylindole has been found as an intermediate of the preparation of 1-methylcarbazole from 1-methylpyrrole,

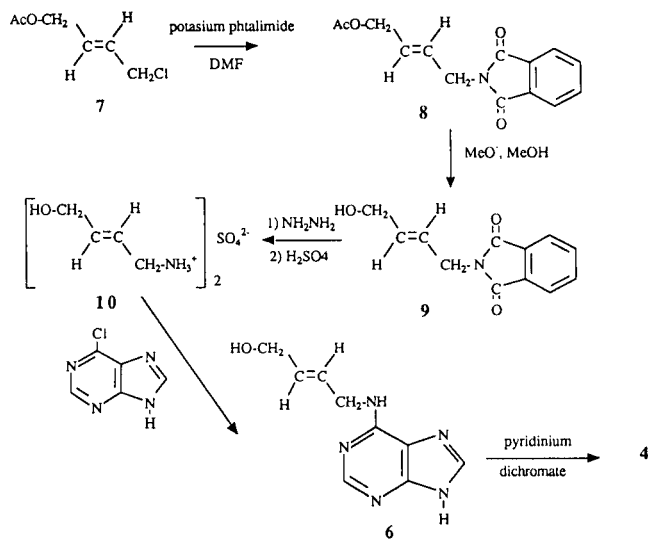


Scheme 1

catalyzed by hydrogen chloride in benzene containing a small amount of water [3]. A mechanism was proposed. Similarly, 2-nitrophenylhydrazines have given rise to corresponding pyrroles, indoles and carbazoles by heating at reflux in ethanolic hydrogen chloride [4]. Thus it is clear that indoles and further carbazoles may be obtained from pyrroles and **3**, upon catalysis by acids. The proposed mechanism [3] should be modified, by taking into account of this acid catalysis. A large variety of electrophilic (cationic) intermediates may be generated in acidic protic media from **3**, by protonation of an oxygen atom, and cleavage of a neighbouring C-O bond, a general reaction of acetals. Solvent, unprotonated amine molecules, and also the pyrrole, which is prone to electrophilic substitutions [5], may all compete to attack these intermediates. The reaction of nucleophilic amines with **3** is generally fast and no indoles are observed from subsequent reaction of the obtained pyrroles [2]. Nucleophilic substitution of adenine occurs only on the ring nitrogen atoms [6]. Thus, it behaves as a poor nucleophilic primary amine. Protonation also occurs on the ring nitrogen atoms, mainly at N-1 and N-3 [7], and the nucleophilicity of the 6-NH₂ in protonated adenine is expected to be lower than in the neutral molecule. In dilute acetic acid, adenine is pro-

tonated at a small extent. Under these conditions, the relative rates of the reactions of adenine and of the corresponding pyrrole **4** becomes more favourable to adenine than in strongly acidic medium, and only pyrrole **4** may be observed as the product, but at the expense of the reaction time.

For identification purpose, 6-(pyrrol-1-yl)purine (**4**) was also obtained by oxidation of *nor*-zeatin (**6**) by pyridinium dichromate (Scheme 2), through a similar reaction as for the preparation of its methyl derivative **2** from zeatin [1]. *Nor*-zeatin (**6**) was prepared from the chloroacetate **7** [8], using a similar method to that used for the synthesis of zeatin [9] (Scheme 2).

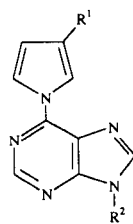


Scheme 2

The presence of a pyrrole ring in **4** was evidenced through spectroscopic studies. The ¹H-nmr spectrum exhibited two triplets for the protons of the expected pyrrole ring (A₂X₂ spectrum). An identical coupling constant was measured between H-2 and H-3, and between H-2 and H-4 (2.25 Hz), which was close to that found in pyrrole (2.1 Hz) [10]. Furthermore, the mass spectrum of **4** exhibited a base peak at m/z 159 (M-26) corresponding to the loss of an acetylene molecule, a characteristic fragmentation observed in pyrrole and *N*-phenylpyrrole [11].

Adenosine reacted in a similar manner as adenine with **3** under conditions B, giving the pyrrolyl-purine riboside **11**. No hydrolysis of the ribosyl moiety was observed, and **11** was obtained in good yield. 9-β-D-arabinofuranosyladenine gave a similar reaction, but some hydrolysis occurred, and **4** was obtained as well as the expected product **12**. The pyrrolyl analogue of deoxyadenosine cannot be prepared by this method, the deoxyribosyl group being quickly removed by hydrolysis.

In conclusion, *N*-pyrrolyl derivatives of adenine may be obtained by condensation of this compound with **3**, but



- | | |
|-----------|---|
| 1 | R ¹ = Me, R ² = β-D-ribofuranosyl |
| 2 | R ¹ = Me, R ² = H |
| 4 | R ¹ = R ² = H |
| 11 | R ¹ = H, R ² = β-D-ribofuranosyl |
| 12 | R ¹ = H, R ² = β-D-arabinofuranosyl |

Formulas

under less acidic conditions than the usual reaction of aliphatic or aromatic amines, and the reaction requires heating for a long period. Despite the acidic conditions of the reaction, this method may be applied to some nucleoside analogues of adenine where the 9-*N*-glycosyl linkage is few sensitive to acid hydrolysis.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage and are uncorrected. The ¹H nmr spectra were recorded on a Varian EM 360 or Bruker (200 MHz) spectrometers using tetramethylsilane as an internal standard. Mass spectra were obtained from a Varian MAT 112 spectrometer equipped with an electron impact ionization source (ei-ms - 70 eV). Elemental analyses were performed by the Service Central d'Analyses du CNRS, Vernaison, France. The uv spectra were recorded on a Kontron Uvikon 810 spectrometer, from 95% ethanol solutions, and ir spectra on a Perkin Elmer 117 apparatus, in nujol suspensions. Hplc analyses were performed on Lichrosorb RP 18 (10 μm) columns (25 cm x 4.1 mm ID), using eluents containing variable proportions of water and methanol. The chromatograph was from Waters (M 6000A pump, U6K injector and M440 uv detector working at 254 nm).

Reaction of Adenine with 2,5-Dimethoxytetrahydrofuran (**3**).

Conditions A.

Adenine (100 mg, 0.74 mmole) and **3** (100 mg, 0.76 mmole) were dissolved in 3.5 ml of glacial acetic acid, and the solution was heated at 80° overnight. Hplc (methanol-water, 70:30) from the reaction mixture gave a chromatogram which exhibited five major peaks [retention times: 2.4 minutes (adenine), 3.2, 4.1, 9.0 and 10.5]. The mixture was not separated.

Conditions B.

Adenine (1 g, 7.4 mmoles) was suspended in a mixture of 50 ml of methanol and 50 ml of water. Acetic acid (1 ml, 15 mmoles) was added, followed by **3** (10 g, 76 mmoles). The mixture was heated to reflux (80°) for 7 days (hplc, eluent methanol-water, 70:30, one peak at 4.1 minutes). After cooling, the solvent was removed *in vacuo*, and the residue was chromatographed through silica gel (eluent dichloromethane-ethanol, 9:1). The fractions containing the 6-(pyrrol-1-yl)purine (**4**) were collected, and the solvent was evaporated. Addition of some drops of dichloromethane to the residue initiated the crystallization to a white solid, which was dried, 700 mg (51%), mp 299°; ¹H nmr (200 MHz, DMSO-d₆): δ 6.40 (t, J = 2.5 Hz, 2H, pyrrole C2 and C5-H), 8.29 (t, J = 2.5 Hz, 2H, pyrrole C3 and C4-H),

8.55 and 8.68 (2s, 2 x 1H, purine C2 and C8-H); ms: m/z 185 (M^+), 184 ($M^+ -H$), 159 ($M^+ -C_2H_2$, base peak), 131 ($M^+ -2 HCN$), 119 ($M^+ -C_4H_4N$), 92, 65; uv (hydrochloric acid, 0.1M): λ max 297 nm (ϵ 17,100), 288 (18,700), 224 (sh, 8,900); (neutral): λ max 297 nm (ϵ 18,000), 288 (19,300), 224 (sh, 9,800); (sodium hydroxide, $10^{-3} M$): λ max 307 nm (sh, ϵ 12,000), 299 (14,700), 224 (13,100).

Anal. Calcd. for $C_9H_7N_5$: C, 58.37; H, 3.81. Found: C, 58.04; H, 3.55.

Conditions C.

Adenine (1 g, 7.4 mmol) and **3** (4 g, 38.8 mmol) were added to a solution of hydrogen chloride (50 mmol) in 100 ml of ethanol. The solution was heated to 80° for 48 hours [hplc, eluent methanol-water, 70:30, 3 peaks at 2.4 minutes (adenine), 4.1 (**4**), and 10.5]. After cooling, the mixture was filtered. The filtrate was evaporated to dryness under reduced pressure. The residue was treated with 50 ml of methanol-water (4:1). After filtration, the solid was recrystallized in methanol-water (1:1) and dried under reduced pressure at 100°, giving 6-(indol-1-yl)purine (**5**), 500 mg (28%), mp 285-290°; hplc (methanol-water, 70:30): tr 10.5 minutes; 1H nmr (60 MHz, DMSO- d_6): δ 6.85 (d, 1H, indole C2-H), 7.22 (d, 1H, indole C3-H), 7.26-7.79 (m, 4H, phenyl-Hs), 8.53 and 8.78 (2s, 2 x 1H, purine C2 and C8-H); ms: m/z 235 (M^+), 234 ($M^+ -H$), 208 ($M^+ -HCN$), 180, 134, 117, 90, 89; uv (neutral): λ max 322.5 nm, 270.5.

Anal. Calcd. for $C_{13}H_9N_5 \cdot 0.5 H_2O$: C, 63.92; H, 4.13. Found: C, 64.19; H, 4.21.

N-[(*E*)-4-Acetoxybut-2-enyl]phthalimide (**8**).

(*E*)-4-acetoxy-1-chlorobut-2-ene (**7**) [8] (7.42 g, 0.05 mole) was dissolved in DMF (10 ml) and the solution was added to a solution of potassium phthalimide (11.17 g, 0.06 mole) in 60 ml of DMF. The mixture was stirred overnight at room temperature. Water (80 ml) was added. The mixture was extracted with diethyl ether (3 x 100 ml). The combined extracts were washed with 50 ml of sodium hydroxide 1 M and with water (100 ml). After drying over sodium sulfate, the solvent was evaporated. The residue was recrystallized from petroleum ether leaving a white solid (10.8 g, 82%), mp 70°; 1H nmr (60 MHz, carbon tetrachloride): δ 2.00 (s, 3H, CH_3), 4.12 (m, 2H, CH_2-N), 4.25 (m, 2H, CH_2O), 5.81 (m, 2H, $CH=CH$), 7.8 (m, 4H, phenyl-Hs); ir: ν 1740 cm^{-1} (ester C=O), 1770, 1700 (phthalimide C=O), 1610 (C=C), 970 (*trans* $CH=CH$).

Anal. Calcd. for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.74; H, 5.00; N, 5.44.

N-[(*E*)-4-Hydroxybut-2-enyl]phthalimide (**9**).

The phthalimide **8** (4.3 g, 16 mmol) was added to 60 ml of a solution of sodium methanolate (1.3 mmol). The mixture was left at room temperature overnight. Lewatit S1080 cation exchanger (H^+ form - 400 mg, 1.6 mEq) was added, and the suspension was stirred for 2 hours. After filtration, the solvent was removed *in vacuo*, leaving a white solid, 2.75 g (80%), mp 110°; 1H nmr (60 MHz, deuteriochloroform): δ 2.70 (s, 1H, OH), 4.1 (dd, $^3J = 4$ Hz, $^4J = 1$ Hz, 2H, CH_2N), 4.3 (dd, 2H, CH_2O), 5.85 (m, 2H, $CH=CH$), 7.8 (m, 4H, phenyl-Hs); ir: ν 3300 cm^{-1} (OH), 1770, 1700 (C=O), 1610 (C=C), 955 (*trans* $CH=CH$).

Anal. Calcd. for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.20; H, 4.91; N, 6.64.

(*E*)-4-Hydroxybut-2-enylammonium Sulfate (**10**).

The phthalimide **10** (3.5 g, 16 mmol) was dissolved in 15 ml of methanol, and 1 ml (20.6 mmol) of hydrazine hydrate was added. The solution was heated to reflux for 2.5 hours. After cooling, 10 ml of water was added. The solvents were partly evaporated to half volume. Sulfuric acid (0.79 g, 8 mmol) was added and a white precipitate was obtained. After addition of 50 ml of water, the suspension was filtered. The filtrate was evaporated to dryness under reduced pressure. The oily residue crystallized in ethanol giving a hygroscopic white solid (2.3 g, 52%) which was not further purified; 1H nmr (60 MHz, DMSO- d_6): δ 3.4 (m, 2H, CH_2N), 3.95 (m, 2H, CH_2O), 5.8 (m, 2H, $CH=CH$).

6-[(*E*)-4-Hydroxybut-2-enylamino]purine (*nor*-Zeatin) (**6**).

The ammonium sulfate **9** (1.5 g, 5.4 mmol), 6-chloropurine (1 g, 6.4 mmol) and 5 ml of triethylamine were added to 40 ml of ethanol. The mixture was heated to reflux for 24 hours. The solvent was removed *in vacuo*, and the residue was recrystallized from water and dried under reduced pressure to give a white solid, 400 mg (45%), mp 245°; 1H nmr (60 MHz, DMSO- d_6): δ 3.85 (m, 2H, CH_2N), 4.1 (dd, 2H, CH_2O), 5.7 (m, 2H, $CH=CH$), 8.1 and 8.2 (2s, 2 x 1H, purine C2 and C8-H); ms: m/z 205 (M^+), 188 ($M^+ -OH$), 186, 174 ($M^+ -CH_2OH$), 162, 160, 148, 135, 119.

Anal. Calcd. for $C_9H_{11}N_5O$: C, 52.67; H, 5.40; N, 34.13. Found: C, 52.46; H, 5.31; N, 34.40.

6-(Pyrrol-1-yl)purine (**4**) from *nor*-Zeatin (**6**).

Nor-zeatin (**6**) (160 mg, 0.78 mmol) was dissolved in 2 ml of DMF, and pyridinium dichromate (0.36 g, 0.95 mmol) was added. The mixture was stirred at room temperature for 5 days. The solvent was removed *in vacuo*, and the residue was chromatographed through a silica gel column (eluent dichloromethane-methanol, 9:1). A fraction containing 15 mg (10%) of a compound which co-chromatographed (tlc and hplc) with **4**, and gave identical mp, uv and nmr spectra as **4**, was isolated.

6-(Pyrrol-1-yl)-9- β -D-ribofuranosylpurine (**11**).

This compound was prepared similarly as **4** from adenosine (conditions B). After the reaction, the residue obtained after evaporation of the solvent was chromatographed on silica gel (eluent chloroform-methanol, 9:1) and the product was recrystallized from water, yielding after drying under reduced pressure, 696 mg from 1 g of adenosine, (58%), mp 162-165°; 1H nmr (200 MHz, DMSO- d_6): δ 3.6-4.3 (m, 2H, C3' and C4'-H), 3.63 (m, 2H, CH_2), 4.58 (m, 1H, C2'-H), 5.99 (d, 1H, C1'-H), 6.38 (t, $J = 2.5$ Hz, 2H, pyrrole C3 and C4-H), 8.02 (t, $J = 2.5$ Hz, 2H, pyrrole C2 and C5-H), 8.65 and 8.76 (2s, 2 x 1H, purine C2 and C8-H); ms: m/z 317 (M^+), 228, 214, 185 ($M^+ -ribosyl$), 158; uv (hydrochloric acid, 0.1 M): λ max 298 nm (ϵ 17,800), 289 (19,500), 221 (11,200); (neutral): λ max 298 nm (ϵ 17,600), 288 (18,900), 221 (11,200); (sodium hydroxide, $10^{-3} M$): λ max 298 (17,600), 289 (19,000), 218, sh (10,900).

Anal. Calcd. for $C_{14}H_{15}N_5O_4 \cdot 0.5 H_2O$: C, 51.53; H, 4.91; N, 21.47. Found: C, 51.12; H, 4.89; N, 21.19.

6-(Pyrrol-1-yl)-9- β -D-arabinofuranosylpurine (**12**).

This compound was prepared similarly as **4** and **11** from 9- β -D-arabinofuranosyladenine (conditions B). After the reaction, the residue obtained after evaporation of the solvent was chro-

matographed through a Lichroprep RP 18 (40-63 μm) 310 x 25 mm glass column, with a linear elution gradient (methanol-water, 30:50 to 50:50 over 1 hour). The fractions containing the product **12** were collected, and the solvents were evaporated leaving a white solid which was dried at 100° under reduced pressure, 200 mg (34%), mp 208-210°; ^1H nmr (200 MHz, DMSO- d_6): δ 3.69 (m, 2H, CH_2), 3.84 (q, J = 4.4 Hz, 1H, C2'-H), 4.18 (q, J = 5.0 Hz, 1H, C3' or C4'-H), 4.26 (q, J = 5.2 Hz, 1H, C3' or C4'-H), 5.13 (t, J = 5.3 Hz, 1H, C5'-OH), 5.59 (d, J = 4.5 Hz, 1H, C2'-OH), 5.69 (d, J = 5.2 Hz, 1H, C3'-OH), 6.43 (d, J = 5.2 Hz, 1H, C1'-H), 6.45 (t, J = 2.2 Hz, 2H, pyrrole C3 and C4-H), 8.30 (t, J = 2.2 Hz, 2H, pyrrole C2 and C5-H), 8.69 and 8.74 (2 s, 2 x 1H, purine C2 and C8-H); ms: m/z 317 (M^+), 228, 214, 185 (M^+ - arabinosyl), 158; uv (neutral): λ max 298 nm, 287, 220 (sh).

Anal. Calcd. for $\text{C}_{14}\text{H}_{15}\text{N}_5\text{O}_4 \cdot \text{H}_2\text{O}$: C, 50.15; H, 5.11; N, 20.88. Found: C, 50.41; H, 5.15; N, 20.79.

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