# Synthesis of Furfuryl and Nitrofurfuryl Derivatives of Adenine and Uracil

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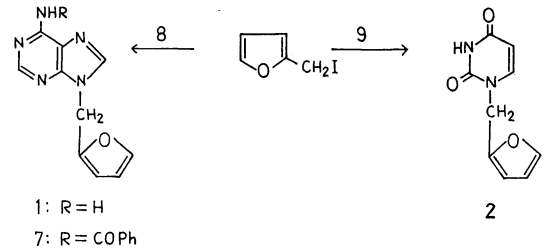
Condensation of 5-nitrofurfuryl iodide with uracil in dimethylformamide in the presence of lithium hydride gave 1-(5′-nitrofurfuryl)uracil. When the iodide was treated with adenine, 3-substituted adenine was mainly obtained, whereas the analogous reaction of benzamidopurine gave 9-substituted adenine. These compounds showed antitumor and broad antibacterial activity. Furfuryl derivatives were also described.

Since the introduction of nitrofurazone (5-nitrofurfural semicarbazone) as an antibacterial agent, many nitrofuran derivatives have been prepared in an effort to increase and to modify activity. Among the derivatives, 5-nitrofurfuryl derivatives of pyrazolopyrimidines have been prepared by Burch[1] and found to possess excellent antibacterial activity. Furthermore, the 5-nitrofurfuryl derivative of a tetrahydropyrimidine compound prepared by Hurst *et al.*[2] has been found to be antiviral but not antibacterial. On the other hand, a series of furfuryl pyrimidines and purines have been prepared by Hull[3] in connection with kinetine which is an adenine derivative and a cell division stimulator.

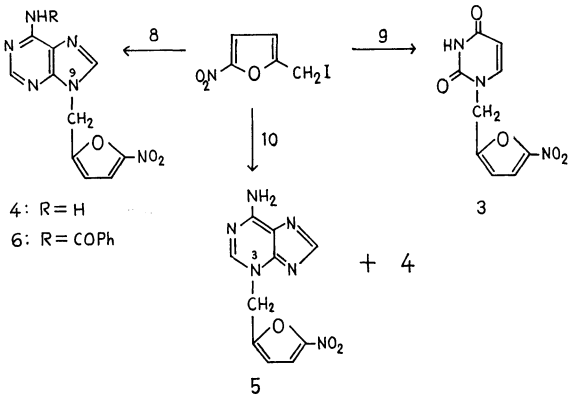
In the course of an investigation of the synthesis of nucleoside-related compounds, we have recently reported[4] the synthesis of some reversed nucleosides of pyrimidine and purine bases. As a part of this investigation, it seemed of interest to synthesize further nitrofurfuryl and furfuryl analogs in which the furanose structure is replaced by furan. This paper describes the preparation of 9-furfuryl-, 9-(5′-nitrofurfuryl)-, and 3-(5′-nitrofurfuryl)adenine(**1**, **4**, and **5**) and 1-furfuryl- and 1-(5′-nitrofurfuryl)uracil (**2** and **3**).

In the previous paper,[4] the authors have shown that the condensation of terminal iodo-sugars with pyrimidine bases in dimethylformamide smoothly occurred in the presence of lithium hydride or sodium hydride. This reaction was extended in the present synthesis, using furfuryl and 5-nitrofurfuryl iodide.

Furfuryl iodide, which was prepared by the reaction of triphenyl phosphate methiodide with furfuryl alcohol according to the method of Lanauer and Rydon,[5] was, *in situ*, condensed with 6-benzamidopurine (8) in the presence of sodium hydride to afford 6-benzamido-9-furfurylpurine (**7**) in 51% yield. Ammonolysis of the benzamido derivative with methanolic ammonia gave 9-furfuryladenine (**1**) (Scheme 1), which showed a melting point corresponding with that reported for the substance prepared by a entirely different method by Hull.[3] An analogous reaction of furfuryl iodide with uracil (9) in the presence of lithium hydride gave 1-furfuryluracil (**2**).




Scheme 1.




Scheme 2.

Likewise, 5′-nitrofurfuryl derivatives have been prepared from 5-nitrofurfuryl iodide[6] and uracil, adenine (10) and 6-benzamidopurine (Scheme 2).

The condensation of the iodide with uracil in the presence of lithium hydride afforded 1-(5′-nitrofurfuryl)uracil (**3**).

Analogous reaction of the iodide with adenine and 6-benzamidopurine (benzoyladenine) led to different derivatives. It has been found that the reaction using 6-benzamidopurine followed by hydrolysis gave 9-(5′-nitrofurfuryl)adenine (**4**), while the reaction using adenine mainly gave 3-(5′-nitrofurfuryl)adenine (**5**).

3- and 9-subsitutions on adenine and 1-substitution on uracil have been established by comparison of the ultraviolet spectra (Table 1) of the products with substituted adenines and uracils of known structure.[7-10] The structures of the above described products have further been supported by their IR and NMR spectra by reference to the compilations by Jackman[11] and Bhacca *et al.*[12]

In preliminary experiments to assess the biological activity of the above products, it has been observed that the nitrofurfuryl derivatives **3**, **4**, and **5** interestingly showed antitumor activity. All these compounds also

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Table 1. Ultraviolet spectral data

**3**: 1-(5′-nitrofurfuryl)uracil **4**: 9-(5′-nitrofurfuryl)adenine **5**: 3-(5′-nitrofurfuryl)adenine

| Solvent | 3 | | 4 | | 5 | |
|---|---|---|---|---|---|---|
| | max ($\varepsilon$) | min ($\varepsilon$) | max ($\varepsilon$) | min ($\varepsilon$) | max ($\varepsilon$) | min ($\varepsilon$) |
| 0.1N HCl | 262 (10300) | 230 (5500) | 258 (15650) | 230 (6720) | 276 (17700) | 237 (6140) |
| | 318 (10750) | 286 (6000) | 315 (11700) | 286 (6870) | 313 (10150) | 300 (9240) |
| water | 263 (10300) | 233 (5800) | 259 (15600) | 227 (6250) | 276 (15050) | 244 (6430) |
| | 318 (10950) | 285 (6200) | 317 (11700) | 284 (5600) | 310 (10500)[b] | |
| 0.1N NaOH | 225 (14000) | 308 (4700) | 258 (15100)[a] | 226 (5550)[a] | 285 (10700)[a] | 248 (6230)[a] |
| | | | 317 (11300)[a] | 283 (5100)[a] | | |

a) pH 9.0; The UV absorption (315 m$\mu$) by the nitrofuran moiety of **3** and **5** disappear, being decomposable by alkali.
b) Shoulder.

showed wide antimicrobial spectra against bacteria and fungi.

## Experimental

*9-Furfuryladenine (1).* A solution of furfuryl alcohol (1.01 g, 10.3 mmol) and methyltriphenoxyphosphonium iodide (5.27 g, 11.6 mmol) in dry ether (15 ml) was stirred at room temperature for 1 hr. To the solution, a solution of 6-benzamidopurine (2.43 g, 10.2 mmol) and sodium hydride (270 mg, 11.3 mmol) in dry dimethylformamide (30 ml) was added and the mixture was heated at 80—83 °C (bath temperature) for 5 hr and evaporated to dryness at 40 °C. The residue was dissolved in chloroform (120 ml) and the solution was washed with two 40 ml portion of water, dried with sodium sulfate, filtered, and evaporated to sirup. The residue (6.4 g) was chromatographed on a short column (2.5×30 cm) of alumina (Merck, acid washed, 110 g) and eluted successively with benzene, benzene–ethyl acetate (1: 1), ethyl acetate, ethyl acetate–methanol (1: 1) and methanol. The condensation product (**7**) was eluted with ethyl acetate–methanol (1: 1), being recognized by ultraviolet absorption. The fractions were combined and evaporated to dryness. The residue was crystallized from ethanol, 1.64 g (51%) of needles of 6-benzamido-9-furfurylpurine (**7**), mp 192.5—193.5 °C, UV: $\lambda_{max}^{MeOH}$ 331 m$\mu$($\varepsilon$ 15000).

Found: C, 64.05; H, 4.33; N, 21.87%. Calcd for $C_{17}H_{13}N_5O_2$: C, 63.94; H, 4.10; N, 21.93%.

A sample of **7** (1.64 g) was dissolved in 40 ml of methanolic ammonia (saturated at 0 °C) and kept at 0 °C for 16 hr. The solution was evaporated *in vacuo* to dryness. The residue was crystallized from hot water to give 9-furfuryladenine (**1**), 0.48 g (21.5%) of needles, mp 193.5—194 °C (lit,[3] mp 191—192 °C), UV $\lambda_{max}^{0.1N\ HCl}$ 260 m$\mu$ ($\varepsilon$ 17800), $\lambda_{max}^{H_2O}$ 261 m$\mu$ ($\varepsilon$ 17700), $\lambda_{max}^{0.1N\ NaOH}$ 261 m$\mu$($\varepsilon$ 18100).

Found: C, 56.30; H, 4.58; N, 31.93%. Calcd for $C_{10}H_9N_5O$: C, 55.81; H, 4.22; N, 32.54%.

*1-Furfuryluracil (2).* Uracil (0.810 g, 7.2 mmol) and lithium hydride (52 mg, 8.0 mmol) dissolved in 20 ml of dry dimethylformamide by heating to 120—130 °C was added to a solution of triphenyl posphate methiodide (3.61 g, 8.0 mmol) and furfuryl alcohol (0.70 g, 7.2 mmol) in ether (10 ml). After heating at 110—120 °C for 45 min, the solution was evaporated *in vacuo* and the dark sirup was extracted with hot water (40 ml). The extract was evaporated to dryness *in vacuo* and chromatographed over 80 g of silica gel (Mallineckrodt) using benzene–methanol (4: 1) to give crystals of **2**, 0.28 g (20.2%), which was recrystallized from water; colorless needles, mp 117—119 °C.

Found: C, 56.25; H, 4.20; N, 14.58%. Calcd for $C_9H_8N_2O_3$: C, 56.05; H, 4.64; N, 14.51%.

UV: $\lambda_{max}^{0.1N\ HCl}$ 266 m$\mu$ ($\varepsilon$ 6860), $\lambda_{min}^{0.1N\ HCl}$ 238 m$\mu$ ($\varepsilon$ 2250), $\lambda_{max}^{H_2O}$ 265 m$\mu$ (9800), $\lambda_{min}^{H_2O}$ 240 m$\mu$ ($\varepsilon$ 2680), $\lambda_{max}^{0.1N\ NaOH}$ 264 m$\mu$ ($\varepsilon$ 6840), $\lambda_{min}^{0.1N\ NaOH}$ 245 m$\mu$($\varepsilon$ 4600).

*1-(5′-Nitrofurfuryl)uracil (3).* To a mixture of uracil (1.68 g, 15 mmol) and lithium hydride (0.12 g, 15 mmol) dissolved in dry dimethylformamide (100 ml) by heating to 80 °C, 5-nitrofurfuryl iodide (2.68 g, 10 mmol) was added and stirred at 80 °C for 80 min. The reaction mixture was condensed to 15 ml and filtered. To the filtrate, water (80 ml) was added and the mixture was shaken with benzene (50 ml×2). The benzene layer was evaporated to dryness *in vacuo* to give a dark residue which was chromatographed over silica gel (Mallineckrodt, 70 g) using benzene–methanol (9: 1) as the eluent. The main fractions were evaporated to dryness *in vacuo* to yield 0.447 g (20%) of crude 1-(5′-nitrofurfuryl)uracil. Recrystallization from ethanol or water–ethanol gave pale yellow needles. Mp 209—210 °C (decomp.).

Found: C, 45.74; H, 3.25; N, 17.30%. Calcd for $C_9H_7N_3O_5$: C, 45.57; H, 2.98; N, 17.72%.

IR: $\nu_{max}^{KBr}$ 1500, 1360 cm$^{-1}$ (-$NO_2$). NMR (DMSO-$d_6$): $\delta$ 5.12 (2H singlet, -$CH_2$-), $\delta$ 5.74 (1H doublet, $J$=8 Hz, $H_5$), $\delta$ 6.90 and 7.74 (1H each doublet, $J$=4 Hz, $H_3'$ and $H_4'$), $\delta$ 7.85 (1H doublet, $J$=8 Hz, $H_6$), $\delta$ 11.41 (1H, 3-NH).

*9-(5′-Nitrofurfuryl)adenine (4).* To a sample of **6** (116 mg) dissolved in hot methanol (40 ml) was added 2 M hydrochloric acid (40 ml) and the mixture was refluxed on boiling water bath for 2 hr. After concentration *in vacuo* to about 27 ml and subsequent washing with ethyl ether (20 ml×3), the solution was further concentrated to give fine needles of 9-(5′-nitrofurfuryl)adenine hydrochloride (82.5 mg, 88%). It decomposed at >216 °C.

Found: C, 40.03; H, 3.69; N, 27.90; Cl, 11.54%. Calcd for $C_{10}H_9N_6O_3Cl$: C, 40.49; H, 3.06; N, 28.32; Cl, 11.95%.

The crystals gave a single spot ($R_f \simeq 0.5$) (tlc with butanol saturated with water). IR: $\nu_{max}^{KBr}$ 1700, 1610 (-N=C=), 1510, 1350 (-$NO_2$), 1235, 1225 cm$^{-1}$ (furan ring).

A sample of the hydrochloride (73.2 mg, 0.25 mmol) was dissolved in a mixture of hot water (45 ml) and methanol (5 ml) and the solution was cooled to room temperature. To the solution, sodium carbonate (14.5 mg, 0.13 mmol) was added to give pale yellow needles of **4** (51.7 mg, 80.5%). It decomposed at >235 °C.

Found: C, 46.66; H, 3.55; N, 32.65%. Calcd for $C_{10}H_8N_6O_3$: C, 46.16; H, 3.10; N, 32.30%.

IR: $\nu_{max}^{KBr}$ 1645, 1595 (-N=C=), 1500, 1350 (-$NO_2$), 1240 cm$^{-1}$ (furan ring). NMR (DMSO-$d_6$): $\delta$ 6.56 (2H, -$CH_2$-), $\delta$ 7.34 (2H, -$NH_2$), $\delta$ 6.90 and 7.70 (each 1H, $H_4'$ and $H_3'$), $\delta$ 8.27 and 8.34 (each 1H, $H_2$ and $H_8$).

*3-(5′-Nitrofurfuryl)adenine (5).* To a mixture of adenine (1.06 g, 8 mmol) and lithium hydride (64 mg, 8 mmol) dis-

solved in dry dimethylformamide (40 ml) by heating to 55 °C, 5-nitrofurfuryl iodide (2.14 g, 8 mmol) was added and the mixture was stirred at 50—55 °C for 2 hr. The mixture was concentrated and the dark residue was chromatographed on a column of silica gel (90 g, Mallineckrodt), being washed with benzene (300 ml) and eluted with ethyl acetate–methanol (4: 1). Evaporation of the initial fractions followed by crystallization from water–methanol gave 9-(5′-nitrofurfuryl)-adenine (**4**), 42.1 mg (2.2%). From the middle fractions, 3-(5′-nitrofurfuryl)adenine (**5**) was obtained, colorless crystals, 344 mg (16.5%), mp 214 °C (decomp.).

Found: C, 46.34; H, 3.31; N, 32.34%. Calcd for $C_{10}H_8N_6O_3$: C, 46.16; H, 3.10; N, 32.30%.

IR: $\nu_{max}^{KBr}$ 1495, 1345 $cm^{-1}$ ($-NO_2$). MNR (DMSO-$d_6$): $\delta$ 5.77 (2H, $-CH_2-$), $\delta$ 6.99 and 7.68 (each 1H, $H_4'$ and $H_3'$), $\delta$ 7.83 and 8.56 (each 1H, $H_8$ and $H_2$), $\delta$ 8.19 (2H, $-NH_2$).

*6-Benzamido-9-(5′-nitrofurfuryl)purine (**6**).* To a mixture of 6-benzamidopurine (2.524 g, 10.6 mmol) and lithium hydride (80 mg, 10.1 mmol) dissolved in dry dimethylformamide (100 ml) by heating to 80 °C, 5-nitrofurfuryl iodide (2.680 g, 10.6 mmol) was added and the mixture was heated at 78—85 °C for 3 hr. The reaction mixture was evaporated to dryness *in vacuo* and the residue was dissolved in methanol (10 ml). The solution was chromatographed on a column of silica gel (200 g, Mallineckrodt, 100 mesh), being washed with benzene (900 ml) and eluted with benzene–methanol (15: 1). The middle fractions gave crude 6-benzamido-9-(5′-nitrofurfuryl)purine (yield 24.6%). Analytical sample was obtained as colorless needles by recrystallization from 2-propanol. Mp 171—172.5 °C.

Found: C, 56.15; H, 3.63; N, 22.88%. Calcd for $C_{17}H_{12}N_6O_4$: C, 56.04; H, 3.32; N, 23.07%.

UV: $\lambda_{max}^{MeOH}$ 282 m$\mu$ ($\varepsilon$ 28000). IR: $\nu_{max}^{KBr}$ 1695 (C=O), 1500, 1360, 1330 ($-NO_2$), 1240 $cm^{-1}$ (C–O–C). NMR (DMSO-$d_6$): $\delta$ 5.80 (2H, $-CH_2-$), $\delta$ 7.00 and 7.7 ($H_4'$ and $H_3'$), $\delta$ 8.69 and 8.84 (each 1H, $H_8$ and $H_2$).

*Bioassay.* It is interesting that compounds **3**, **4**, and **5** showed significant antitumor activity against Yoshida *sarcoma ascites*. The inhibition % of **3**, **4**, and **5** at concentrations 10 mcg/ml and (100 mcg/ml) were 66.3 (83.0), 78.1 (78.7) and 75.7 (83.7) %, respectively. (Control: 6-mercapto-9-$\beta$-D-ribofuranosylpurine at 10 mcg/ml and (100 mcg/ml): 49.4 (77.8) %.

Compounds **3**, **4**, **5**, and **6** also showed broad antibacterial and antifungal activity. Their minimum inhibitory concentrations (mcg/ml) were 1.0—7.8 against Gram-positive bacteria tested, 31.2—62.4 against *E. coli* K-12 and 15.6—31.2 against some fungi tested.

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