SYNTHESIS OF THEOPHYLLINE NUCLEOSIDES FROM 6-AMINO-1,3-DIMETHYL-5-*N*-GLYCOSYLIDENEIMINOURACIL

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Abstract - A new synthesis for 7-glycosyl-theophylline from 6-amino-1,3-dimethyl-5-*N*-*D*-glycosylideneiminouracil and diethoxymethyl acetate is proposed. The structures of obtained theophylline nucleosides are described.

Xanthines and xanthine nucleosides are compounds of an interest on account of their biological activity.[1] A number of alkylxanthines, such as theophylline and derivatives, became interesting as adenosine receptors antagonist.[2] 1,3-Dialkyl-7-ribosylxanthines has been found to be a partial agonist at A3 adenosine receptor.[3] Contrary to alkylxantine bases, their nucleosides are less studied both from the chemical and biological viewpoints. Our group has lately been concerned with the preparation of theophylline and thiotheophylline nucleosides. In previous works we synthesized 7-glycosyl-8-methyltheophylline, where sugar moieties attached to position 7 are *D*-gluco, *D*-galacto,[4] *D*-xylo,[5] *D*-arabino and *D*-ribo[6] derivatives.

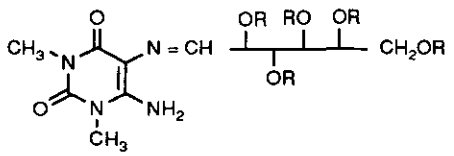
The preparation of 7-glycosyltheophylline has been carried out by several methods *via* condensation of the base and glycosyl derivatives since the first synthesis by Fischer.[7] No alternative syntheses for construction of the base from either glycosylimidazole derivatives or glycosylaminopyrimidine derivatives have, to the best of our knowledge, been reported to date. In this paper we propose a new synthesis for 7-glycosyltheophylline by constructing the purine ring from a diaminopyrimidine derivative.

6-Amino-1,3-dimethyl-5-*N*-*D*-glucosylideneiminouracil (**1**) has previously been used as starting material to prepare theophylline nucleosides: 8-(*D*-glucopentaacetoxypentyl)theophylline (**4**) was synthetized from 6-amino-1,3-dimethyl-5-*N*-*D*-(2', 3', 4', 5', 6'-penta-*O*-acetyl)glucosylideneiminouracil (**2**),[8] and 7-β-*D*-gluco pyranosyl-8-methyltheophylline (**5**) has been synthetized from 6-amino-5-(2', 3', 4', 5'-tetra-*O*-acetyl-*N*-β-*D*-glucopyranosyl)acetylamino-1,3-dimethyluracil (**3**).[4]

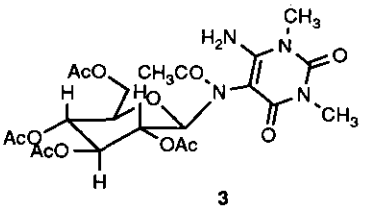
Compound (**3**) is prepared by reaction of **1** with acetic anhydride in an acid medium.[9] This reaction probably involves the initial attack of the electrophilic reagent (in this case CH_3CO^+) on N-5, followed by that of the hydroxyl group at C-5' on C-1' to close the sugar moiety into pyranose ring that is then thoroughly acetylated to **3**.

Diethoxymethyl acetate (DEMA) has been used to prepare 9-alkylpurines by reaction with 4-alkylamino-5-aminopyrimidine.[10] Likewise carbocyclic nucleosides have been prepared from 5-amino-6-chloro-4-

cyclopentylaminopyrimidine.[11] Although compound (**1**) is not a diamino derivative, it can be expected that, as



1, R = H
2, R = Ac



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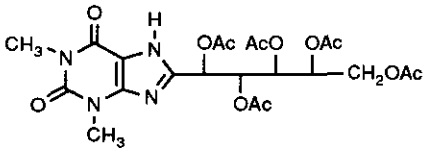

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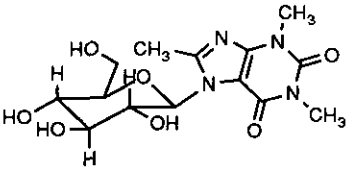

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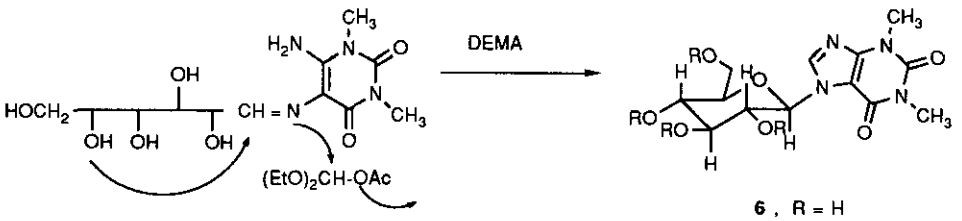
in acetylation in an acid medium, DEMA should react by initially attacking N-5 and then cyclizing the sugar moiety to the pyranose form, followed by attack of the amino group at C-6 on the formyl group at N-5 to close the imidazole ring and yield 7-glycosyltheophylline.

Treatment of **1** with DEMA afforded 7-β-*D*-glucopyranosyltheophylline (**6**) in 60 % yield, which is quite good taking into account that the starting material was obtained in almost quantitative yield from the readily accessible 5,6-diamino-1,3-dimethyluracil and the corresponding sugar.



1

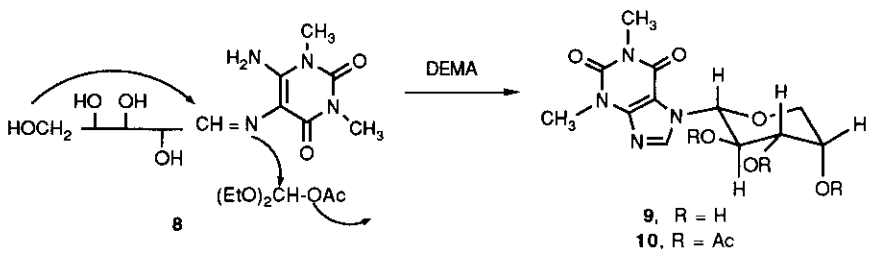
6, R = H
7, R = Ac

Mp and optical rotation of compound (**6**) are coincident with reported values.[12] The spectral data of **6** (mass spectrum, ^{1}H-nmr, and ^{13}C-nmr) also are in accord with the proposed structure.

Treatment of **6** with acetic anhydride in pyridine afforded 7-(2',3',4',6'-tetra-*O*-acetyl-β-*D*-glucopyranosyl) theophylline (**7**). Mp, optical rotation, and ^{1}H-nmr of **7** are coincident with reported values.[12,13]

Similarly, 7-α-*L*-arabinopyranosyltheophylline (**9**) was obtained from 6-amino-1,3-dimethyl-5-*N*-*L*-arabino sylideneiminouracil (**8**). The structure of **9** was assigned on the basis of the spectral data (see Experimental). There are two salient features in the structure of **9**, first, the pyranose form of the sugar moiety, and second, the conformation of α-anomer $^1C_4$. Compound (**8**) can close the sugar either by attack of HO-C4' on C-1' to give a furanose form or by attack of HO-C5' to give a pyranose form. The chemical shift for C-4' (69.5 ppm) in the ^{13}C-nmr spectrum indicates a pyranose form. The furanose form is excluded since the chemical shift for

C-4' must be between 82 and 88 ppm.[14] On the other hand, $J_{1',2'}$ (9.1 Hz) and $J_{2',3'}$ (9.1 Hz) indicate a *trans*



diaxial arrangement of H-1' and H-2' with the theophylline substituent equatorially arranged. These observed data therefore verify the α-configuration of a pyranose form with a $^1C_4$ conformation for compound (**9**).

Acetylation of **9** with Ac_2O in pyridine yields 7-(2',3',4'-tri-*O*-acetyl-α-*L*-arabinopyranosyl)theophylline (**10**). ^{1}H-nmr, ^{13}C-nmr, and mass spectra support the proposed structure (see Experimental). In ^{1}H-nmr, the signals corresponding to H-1' and H-2' protons, as in the gluco derivative(**7**), are broadened. The broadening effect arose from an equilibrium between two conformers owing to molecular crowding and restricted rotation about the glycoside bond.[15]

Mps and optical rotations for **10** and **9** are consistent with those reported by Pryde and Willians[16] for the condensation product between tri-*O*-acetyl-*L*-arabinopyranosyl bromide and the silver salt of theophylline and its deacetyl derivative. Although they suggested the structure of 7-β-*L*-arabinopyranosyltheophylline, they provided no data about the configuration at C-1' and the conformation of sugar moiety.

The reaction was also extended to the *D*-arabinosylideneimino derivative. As expected, the physical data and spectra obtained were identical with those for the *L*-arabino derivatives except for the specific rotation which was of the same absolute value but opposite sign.

In conclusion, a novel synthesis of theophylline nucleosides from 6-amino-1,3-dimethyl-5-*N*-*D*-glycosylidene iminouracil by treatment with DEMA was developed. Although the same reagent has been used to obtain purine derivatives from 5,4-diaminopyrimidines, imino groups had never been used. This method works because of the occurrence of a nucleophilic atom at suitable position for attacking the carbon atom of the imino group.

EXPERIMENTAL

Melting points were determined on a Gallenkamp instrument and are given uncorrected. Optical rotations were measured by using a Perkin-Elmer Model 241 polarimeter. Mass spectrometry was carried out on a HP-MS 5988A instrument using the direct injection and electron-impact (EI) modes. The nmr spectra were obtained on Bruker WP-200 SY instrument at 200 MHz for ^{1}H and 50 MHz for ^{13}C. ^{1}H Chemical shifts (δ_H) are given either relative to residual $CHCl_3$ (δ 7.27) in deuteriochloroform or residual HOD (δ 4.8) in dideuterium oxide. ^{13}C Chemical shifts (δ_C) are given either relative to $CDCl_3$ (δ_C 77.0) in deuteriochloroform or CD_3COCD_3 (δ_C 29.8) in dideuterium oxide, and were assigned by HCORR experiments.

7-β-*D*-Glucopyranosyltheophylline (6)

Compound **(1)** (1 g, 3 mmol) was treated with 6 ml of DEMA at R.T. for 20 h. The reaction mixture was concentrated at a low pressure; then, 10 ml of water was added to the residue, followed by evaporation to dryness. The residue was treated with 20 ml of NaOMe-MeOH (0.05M) for 1 h and neutralized with IR 120 resin. After filtration, the solvent was removed at a low pressure and the resulting white solid foam was recrystallized from ethanol to give **6** (620 mg, 60%). Mp 272-274 °C (lit.,[11] mp 272-277 °C), $[\alpha]_D^{24}$ - 44° (c 1, water) (lit.,[11] $[\alpha]_D$ - 45°).

7-(2',3',4',6'-Tetra-*O*-acetyl-β-*D*-glucopyranosyl)theophylline (7)

Compound **(6)** (200 mg) was dissolved in a freshly prepared solution of acetic anhydride (3 mL) and pyridine (1 mL). The reaction mixture was kept at room temperature for 24 h. The solvents were removed at a low pressure; then 5 mL of water was added to the residue, followed by evaporation to dryness. The same procedure was carried out twice with methanol in order to obtain a solid foam. Recrystallization from ethanol gave the title compound **(7)** (232 mg, 78%). Mp 145-147 °C (lit.,[11] mp 146-148 °C), $[\alpha]_D^{24}$ -17° (c 1 $CHCl_3$) (lit.,[11] $[\alpha]_D$ - 17°).

7-α-*L*-Arabinopyranosyltheophylline (9)

Compound **(9)** was obtained from **8** following the same procedure described for **6**. Yield 58%. Mp 280-283 °C, $[\alpha]_D^{25}$ + 37.5° (c 1, water). Ms (EI) *m/z*: 312 (M^+, 7%), 180 (Th-H^+, 100%). ^{1}H-Nmr (D_2O) δ: 8.3 (1H, s, H-8), 5.67 (1H, d, *J* 9.1 Hz, H-1'), 4.25 (1H, pt, *J* 9.1-9.1 Hz, H-2'), 4.10 (1H, m, H-4'), 4.05 (1H, dd, *J* 9.1-1 Hz, H-3'), 3.94-3.81 (2H, m, H-5'$_{ax}$ and H-5'$_{eq}$), 3.48 and 3.29 (6H, 2s, 2 N-$\underline{CH_3}$). ^{13}C-Nmr (D_2O) δ: 155.7 (C-6), 152.5 (C-2), 149.1 (C-4), 142.3 (C-8), 107.0 (C-5), 85.7 (C-1'), 73.1 (C-3'), 70.1 (C-2'), 69.5 (C-4'), 68.9 (C-5'), 30.2 ($\underline{C}H_3$-N1), 28.5 ($\underline{C}H_3$-N3).

7-(2',3',4'-Tri-*O*-acetyl-α-*L*-arabinopyranosyl)theophylline (10)

Compound **(10)** was obtained from **9** following the same procedure described for **7**. Yield 80%. Mp 210-212 °C, $[\alpha]_D^{25}$ +38.5° (c 1, $CHCl_3$). Ms (EI) *m/z*: 438 (M^+, 8%), 259 (87%, triacetylarabinose moiety), 180 (Th-H^+, 37%), 157 (46%, 259 - $C_4H_6O_3$), 139 (87%, 259 - 2AcOH), 97 (100%, 139 - CH_2CO). ^{1}H-Nmr ($CDCl_3$) δ: 7.93 (1H, s, H-8), 6.07 (1H, bd, *J* 9 Hz, H-1'), 5.71 (1H, bt, *J* 9 Hz, H-2') [both broadened signals became narrower in the spectrum recorded at 313 K], 5.48 (1H, m, H-4'), 5.21 (1H, dd, *J* 9-3 Hz, H-3'), 4.12 (1H, dd, *J* 9-1.5 Hz, H-5$_{ax}$), 3.92 (1H, dd, *J* 9-0.5 Hz, H-5$_{eq}$), 3.62 and 3.43 (6H, 2 s, 2 N-$\underline{CH_3}$), 2.21, 2.02 and 1.92 (9H, 3 s, 3 CO$\underline{CH_3}$). ^{13}C-Nmr ($CDCl_3$) δ: 169.9-169.1 (3 $\underline{C}$O-CH_3), 154.8 (C-6), 151.4 (C-2), 148.8 (C-4), 140.0 (C-8), 106.4 (C-5), 82.9 (C-1'), 70.9 (C-3'), 68.2 (C-2'), 67.8 (C-4'), 67.2 (C-5'), 29.9 ($\underline{C}H_3$-N1), 28.0 ($\underline{C}H_3$-N3), 20.6-20.1 (3 CO-$\underline{C}H_3$).

REFERENCE AND NOTES

1 "Comprehensive Medicinal Chemistry. The rational design, mechanistic study and therapeutic application of chemical compounds," (C. Hansch, P. C. Sammes, and J. B. Taylor, general editors), Pergamon Press, 1991.

2 K. A. Jacobson, P. J. M. van Galen, and M. Williams, *J. Med. Chem.*, 1992, **35**, 407

3 a) H. O. Kim, X. D. Ji, N. Melman, M. E. Olah, G. L. Stiles, and K. A. Jacobson, *J. Med. Chem.*, 1994, **37**, 4020; b) P. J. M. van Galen, A. H. van Bergen, C. Gallo Rodríguez, N. Melman, M. E. Olah, A. P. Ijzerman, G. L. Stiles, and K. A. Jacobson, *Mol. Pharmacol.*, 1994, **45**, 1101.

4 A. Fernández-Fernández, M. Melgarejo-Sampedro, R. Robles-Díaz, A. Sánchez-Rodrigo, and R. Rico-Gómez, *J. Carbohydr. Nucleosides. Nucleotides*, 1981, **8**, 325.

5 R. Rico-Gómez, *Heterocyles*, 1982, **19**, 633.

6 R. Rico-Gómez and J. Ríos-Ruiz, *An. Quim., C*, 1983, **79**, 36.

7 E. Fischer and B. Helferich, *Ber.*, 1914, **47**, 210.

8 M. Sakaguchi, Y. Miyata, H. Ogura, K. Gonda, S. Koga, and T. Okamoto, *Chem. Pharm. Bull.*, 1979, **27**, 1094; H. Ogura, M. Sakaguchi, T. Okamoto, K. Gonda, and S. Koga, *Heterocycles*, 1979, **12**, 359.

9 M. Melgarejo-Sampedro and R. Rico-Gómez, *An. Quím.*, 1976, **72**, 998.

10 J. A. Montgomery and C. Temple Jr., *J. Am. Chem. Soc.*, 1958, **80**, 409 .

11 R. Vince and S. Daluge, *J. Org. Chem.*, 1980, **45**, 531.

12 A. J. Freestone, L. Hough, and A.C. Richardson, *Carbohydr. Res.*, 1973, **28** 378.

13 K. Onodera, S. Hirano, N. Kashimura, F. Masuda, T. Yajima, and N. Miyazaki, *J. Org. Chem.*, 1966, **31**, 1291.

14 J. B. Stothers, "Carbon-13 Nmr Spectroscopy", p. 472, Pergamon Press, 1972.

15 Two conformers seem to be subject to less marked steric interactions about the dihedral angle τ [H(1')-C(1')-N(7)-C(8)] *viz.* the *syn* conformer, with τ = 0° where H-1' and C-8 are in a *syn*-coplanar arrangement, and *anti* conformer, with τ = 180° where H-1' and C-8 are in an *anti*-coplanar layout. Variable temperature ^{1}H-nmr experiments and molecular mechanics calculations confirmed the occurrence of two *syn* and *anti* conformers in a ratio of 20/80 for both **7** and **10**. A detailed study of this and others nucleosides will be published in the near future.

16 J. Pryde and T. Willians, *J. Chem. Soc.*, 1933, 640.

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