DIRECT THIATION OF 7-THEOPHYLLINE NUCLEOSIDES

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Abstract — 8-Methyl-6-thiotheophylline nucleosides have been obtained by treatment of the corresponding 8-methyl-theophylline nucleosides with Lawesson's Reagent.

Synthesis of thionucleosides has been carried out by different sunthetic methods. The reagents classically used are either P_2S_5 or H_2S under adequated conditions depending of the nature of the nucleosides.

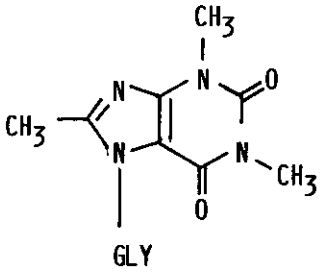
Thioxanthines can be prepared from xanthines with P_2S_5 in hot pyridine. Oxo groups in C-2 have show to be less reactive than those in C-6. Thus, xanthines give selectively 2-oxo-6-thioxanthines.[1] 2-Thioxantines require a different synthetic strategy, such as cyclization of 4,5-diamino-2-mercapto-6-hydroxy-pyrimidines to purines according to Traube's method.[2] The thiation reaction when the nitrogen atoms in the xanthines are alkylated is more difficult. Wooldridge and Slack have prepared 6-thiotheophylline and 6-thiotheobromine with P_2S_5 under refluxing dry pyridine, whereas caffeine was recovered unchanged after prolonged treatment with the same reagent.[3] These results are rationalized in terms of theophylline and theobromine having at least one enolizable oxo groups, whereas caffeine is lacking these groups. This behavior has been confirmed in our laboratory. An attempt was made to prepared 7-ß-D-(2, 3, 4, 6-tetra-O-acetyl)glucopyranosyl-8-methyl--thio-theophylline, **2a**, from 7-ß-D-(2, 3, 4, 6-tetra-O-acetyl)glucopyranosyl-8-methyl-theophylline, **1a**, by treatment with P_2S_5 in dry pyridine, but the starting material was recovered unchanged after 2 days under refluxing conditions.[4]

In 1978, Lawesson and co-workers began to study the conversion of the carbonyl groups in thiocarbonyl compounds using 2,4-(p-methoxy-phenyl)1,3-dithia-2,4-diphosphetane-2,4-disulphide.[5] The results of this study demonstrate that this reagent, now know as Lawesson's Reagent (LR), is an exceptionally good thiating compound, and as such it has been widely used.[6]

In the present paper we report the preparation of 6-thio-teophylline nucleosides from the cor-

responding theophylline nucleosides by treatment with LR in refluxing toluene.[7]

Scheme I



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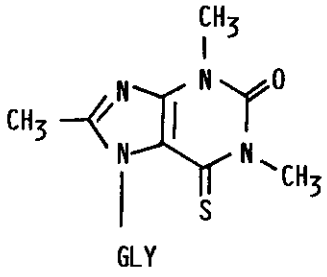

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1a and 2a, GLY = ß-D-(2, 3, 4, 6-tetra-O-acetyl)glucopyranosyl

1b and 2b, GLY = ß-D-(2, 3, 4, 6-tetra-O-acetyl)galactopyranosyl

Structure of 1a and 1b are similar to that of caffeine without enolizable oxo groups. Thus 1a, obtained according to the methods previously reported,[8] gave 7-ß-D-(2, 3, 4, 6-tetra-O--acetyl)glucopyranosyl-8-methyl-6-thio-theophylline, 2a, in a 70% yield, as a yellow solid, uv ($CHCl_3$) λ_{max} 340 nm (ε 15 000), mp 98 °C, $[\alpha]_D^{27}$ +82 (c 1, $CHCl_3$). The ms spectrum (EI 70 eV) shows M^+ = 540, which indicates the substitution of only one atom of oxigen by one atom of sulphur. The ^{1}H-nmr spectrum (200 MHz, $CDCl_3$) shows a doublet at 8.19 ppm (J = 10 Hz) assigned to H-1´. This signal appears in 1a at 6.50 ppm, which represents a down field shift of 1.69 ppm. The down field shift has been observed previously in thionucleosides and can be attributed to the anisotropic effect of the thiocarbonyl group.[9] Another charasteristic of the ^{1}H-nmr spectrum is that all of the signal are sharp, in contrast to those in the spectrum of 1a, where the signals corresponding to the sugar moiety and the signal of the methyl group on C-8 are broad. The observed peak broadening in the spectrum of 1a is due to the existence of two conformers and a partially restricted rotation along the C-1´/N-7 bond caused by the molecular steric hindrance, whereas in 2a the rotation is completelly restricted by the considerable larger volume of the sulphur atom. A detailed study of the conformations of these and related compounds will be reported in the near future.

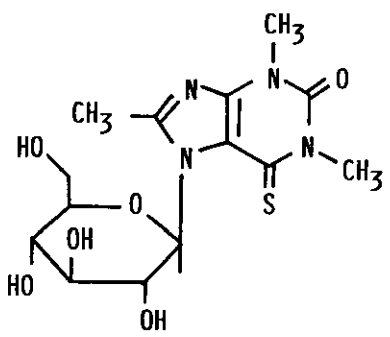
In the ^{13}C-nmr spectrum (Table I) the most significant difference between 1a and 2a is the shift of the 21,3 ppm for C-6 which proves the substitution of the oxigen atom on this carbon by sulphur.

Table I[a]

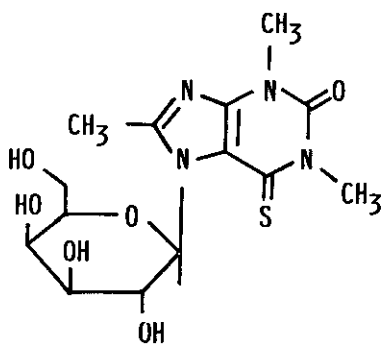
Compounds	C-2	C-3	C-5	C-6	C-8	C-1′
1a[b]	152.3	151.3	106.4	154.5	147.8	82.9
2a[b]	155.8	149.9	117.5	175.8	149.8	80.5
1b[b]	152.6	151.4	106.4	154.6	147.8	82.3
2b[b]	156.1	149.9	117.0	175.6	149.8	80.7
3a[c]	155.0	149.1	117.5	174.5	144.4	82.3
3b[c]	155.3	149.1	117.5	174.5	144.5	83.0

a) ^{13}C-nmr recorded on a Bruker WP-200 SY spectrometer (50.13 MHz); b) measured in $CDCl_3$; c) in DMSO-d_6

In the same manner, 7-ß-D-(2, 3, 4, 6-tetra-O-acetyl)galactopyranosyl-8-methyl-theophylline, **1b**, afforded 7-ß-D-(2, 3, 4, 6-tetra-O-acetyl)galactopyranosyl-8-methyl-thio-theophylline, **2b**, uv ($CHCl_3$) λ_{max} 360 nm (ε 12 200), mp 116 °C, $[\alpha]_D^{27}$ +107 (c 1, $CHCl_3$), EIMS (70 eV) m/z 540 (M^+). The ^{1}H-nmr spectrum (200 MHz, $CDCl_3$) shows H-1′ at 8.28 ppm (d, J = 10 Hz) and the ^{13}C-nmr spectrum (50 MHz, $CDCl_3$) gives a signal at 175.6 ppm corresponding to C-6 of the heterocycle which confirms the oxigen-sulphur substitution. In this case there is no peak broadening in the ^{1}H-nmr spectrum of **1b**, because the rotation along C-1′/N-7 is totally restricted due to the axial acetate on C-4′. O-deacetylation of both **2a** and **2b** with NaMeO/MeOH afforded quantitatively 7-ß-D-glucopyranosyl-8--methyl-6-thio-theophylline, **3a** [uv (MeOH) λ_{max} 350 nm (ε 19 800), mp 258 °C, $[\alpha]_D^{26}$ +155 (c 0.4, MeOH), EIMS (70 eV) m/z 372 (M^+, 2%) 210 (100%), ^{1}H-nmr (200 MHz, DMSO-d_6) 7.60 ppm (d, 1H, J = 10 Hz, H-1′)], and 7-ß-D-galactopyranosyl-8-methyl-6-thio-theophylline, **3b** [uv (MeOH) λ_{max} 350 nm (ε 18 750), mp 241 °C, $[\alpha]_D^{26}$ +181 (c 0.4, MeOH), EIMS (70 eV) m/z 372 (M^+, 4%) 210 (100%), ^{1}H-nmr (200 MHz, DMSO-d_6) 7.52 ppm (d, 1H, J = 10 Hz, H-1′)].



3a



3b

To our knowledge, this is the first report of a successful direct thiation of a purin nucleoside with non enolizable oxo groups. Further studies with 6-thio-theophylline nucleosides are in good progress.

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7 1 mM of LR for 1 mM of the nucleoside. The reaction was monitored by tlc. One more mM of LR was added in several times until complete disappearance of the starting material (48 h). The toluene was removed under reduced pressure, the residual product was separated and purified by cc on silica gel (eluent: gradient $CHCl_3$ to $CHCl_3$/MeOH 1:1), followed by crystallitation from MeOH.

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