N-GLUCOSYL-5-AMINO-4-CARBAMOYL- AND 4-ETHOXYCARBONYLIMIDAZOLES AS POTENTIAL PRECURSORS OF 4-OXOIMIDAZO[4,5-c]-1,2,6-THIADIAZINE 2,2-DIOXIDES

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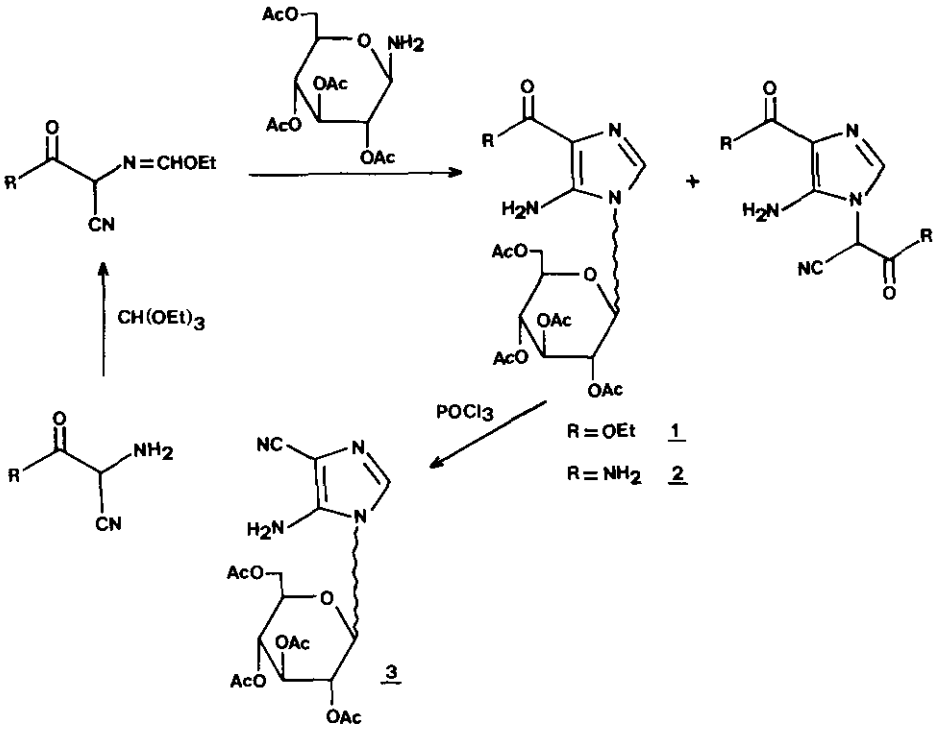
Abstract -The syntheses of 1-(tetra-O-acetyl-β-D-glucopyranosyl)-5-amino-4-ethoxy-carbonylimidazole and 1-(tetra-O-acetyl-α and β-D-glucopyranosyl)-5-amino-4-carbamoylimidazoles are described. Conversion of the latter to the corresponding 4-cyano derivative is also reported. Related N-substituted 5-amino-4-ethoxycarbonylimidazole derivatives have been cyclized to imidazo[4,5-c]-1,2,6-thiadiazine 2,2-dioxides upon treatment with sulfamoyl chloride.

N-Glucosyl-5-aminoimidazoles bearing suitable functional groups at position 4 can be considered as valuable key intermediates for the preparation of glucosyl purines[1] and related nucleosides. In the present paper, we wish to report the preparation of 1-glucosyl-5-aminoimidazoles 1 and 2 and the conversion of the latter to the 4-cyano derivative 3.[2] The conditions for the cyclization of these compounds with sulfamoyl chloride to imidazo[4,5-c]-1,2,6-thiadiazine 2,2-dioxide derivatives have been studied. New substituted derivatives of this ring system[3] have thus been prepared starting from the corresponding 5-amino-4-ethoxycarbonylimidazoles.

1-(Tetra-O-acetyl-β-D-glucopyranosyl)-5-amino-4-ethoxycarbonylimidazole (1) and an anomeric mixture of 1-(tetra-O-acetyl-D-glucopyranosyl)-5-amino-4-carbamoylimidazoles (2) were prepared from 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosylamine and ethyl N-(cyano-N-ethoxycarbonylmethyl) and (N-carbamoylmethyl)formimidate respectively, following the method described by Shaw.[4] Both reactions afforded complex mixtures from which 1 and 2 could be isolated, together with the products derived

from the condensation of ethylaminocyanoacetate and the corresponding imidate[5] (see Scheme I).



Scheme I

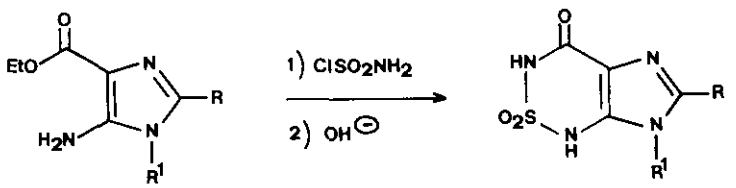
The structures of both nucleosides have been studied by 300 MHz ^{1}H-nmr spectroscopy. The anomeric configuration of 1 was established as β on the basis of the value of the coupling constant $J_{1',2'}$ = 9.3 Hz, consistent with a trans disposition of H-1' and H-2'. The signals of all the protons have been assigned and the measured coupling constants are gathered in the experimental part. The 5-amino group appears as two broad signals as a result of the hindered rotation around the C-N bond.[6]

Compound 2 was isolated as an anomeric mixture (β:α = 90:10). The signal corresponding to the β anomeric proton appears, unexpectedly, at lower field than that belonging to the α, a fact which has been found in some related ribosides.[3] Nevertheless, the signal with the larger coupling constant ($J_{1',2'}$ = 9.3 Hz) has been assigned to the β whereas that with $J_{1',2'}$ = 8.7 Hz to the α anomer.

Compound 2 could readily be converted into the corresponding 4-cyano derivative 3 by treatment with $POCl_3/CHCl_3$.[7] This compound had previously been prepared by a multi-step reaction sequence starting from 4(5)-bromo-5(4)-nitroimidazole.[2]

In order to obtain glucosyl derivatives of imidazo[4,5-c]-1,2,6-thiadiazine 2,2-dioxide which can be regarded as sulfur dioxide analogs of purine nucleosides, imidazole derivatives 1 and 3 were treated with sulfamoyl chloride.[8] The N-sulfonylamino derivatives thus obtained turned out to be too unstable to be isolated and were therefore subjected to several cyclization reactions which included different acid and basic media, treatment with $CF_3COOH/(CF_3CO)_2O$ and HPO_4Na_2.[9] However, all these attempts of ring closure failed, giving rise to decomposition products.

Nevertheless, other related 5-amino-4-ethoxycarbonylimidazole derivatives could successfully be cyclized to the corresponding imidazo[4,5-c]-1,2,6-thiadiazine derivatives.



$R = H, CH_3$

$R^1 = H, C_6H_{11}, CH_2C_6H_5$

$R = H$	$R^1 = C_6H_{11}$	4
$R = H$	$R^1 = CH_2C_6H_5$	5
$R = CH_3$	$R^1 = H$	6

Thus, 1-cyclohexyl-, and 1-benzyl-5-amino-4-ethoxycarbonylimidazole reacted with sulfamoyl chloride in anhydrous benzene[10] or methylene chloride. Ring closure was achieved in 12.5% aqueous sodium hydroxide affording 7-cyclohexyl- and 7-benzyl-4-oxo-1H,3H-imidazo[4,5-c]-1,2,6-thiadiazine 2,2-dioxide 4 and 5 respectively. In the case of 5-amino-4-ethoxycarbonyl-2-methylimidazole it was necessary to activate the amino group by silylation.[11] A similar reaction sequence afforded the 6-methylimidazo[4,5-c]-1,2,6-thiadiazine derivative 6.

The structures of the new compounds have been established according to their analytical and spectroscopic data. In the ^1H-nmr spectra of 4 and 5 the H-6 appears as a singlet at 8.9 and 9.0 ppm respectively.

In conclusion, 5-amino-4-ethoxycarbonylimidazoles can be considered useful precursors of sulfur dioxide analogs of purines. However, glycosyl derivatives seem too labile to resist the drastic reaction conditions needed for the cyclization.

EXPERIMENTAL

Melting points were determined on a capillary apparatus and are uncorrected. Ir spectra were recorded on a Perkin-Elmer 257 spectrophotometer. The uv spectra were measured on a Perkin-Elmer 350 spectrophotometer. Column chromatography was performed on Merck silica-gel 60 (70-230 mesh), and preparative thin layer chromatography was performed on 20 x 20 cm glass plates coated with a 2 mm layer of silicagel PF_{254} (Merck). Compounds were detected with uv light (254 nm) or by spraying the plate with ethanol: sulphuric acid (3:1) and heating.
^{1}H-nmr spectra were recorded at 293°K on a Varian XL-300 instrument operating at 300 MHz (1, 2) or on a Varian EM-390 operating at 90 MHz (4, 5, 6), using TMS as internal standard.

1-(Tetra-O-acetyl-β-D-glucopyranosyl)-5-amino-4-ethoxycarbonylimidazole (1)

To a solution of ethyl N-(cyanoethoxycarbonylmethyl)formimidate[12] [prepared from 2.5 g (0.019 mol) of ethyl aminocyanoacetate[13] by reaction with 2.8 g (0.019 mol) of ethyl orthoformate] in 50 ml of dry acetonitrile, 4.7 g (0.019 mol) of 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosylamine were added. The mixture was heated for 4 h, evaporated to dryness and the residue was purified by silica-gel column chromatography, using chloroform:methanol 25:1 as eluent. The fraction containing the desired product, was dissolved in ethanol (5 ml) and cooled overnight. The solid was collected by filtration and recrystallized from benzene to give 1.5 g (27 %) of 1 as white needles, mp: 198°C (decomp.). Ir (ν, cm^{-1}, Nujol): 3400 (NH_2), 1750, 1700 (C = O). uv λnm (ε) MeOH: 266 (15000). ^{1}H-nmr ($CDCl_3$, 300 MHz) δ: 7.27 (s, 1H, H-2), 5.57 (t, 1H, $J_{1',2'}$ = 9.3 Hz, H-2'), 5.37 (bs, 1H, exchangeable with D_2O, NH), 5.35 (t, 1H, $J_{2',3'}$ = 9.5 Hz, H-3'), 5.34 (bs, 1H, exchangeable with D_2O, NH), 5.29 (d, 1H, $J_{1',2'}$ = 9.3 Hz, H-1'), 5.25 (t, 1H, $J_{3',4'}$ = 9.7 Hz, H-4'), 4,34 (q, 2H, J = 7.1 Hz, OCH_2), 4.32 (dd, 1H, $J_{5',6'}$ = 4.8 Hz, $J_{6',7'}$ = -12.6 Hz, H-6'), 4.16 (dd, 1H, $J_{5',7'}$ = 2.2 Hz, $J_{6',7'}$ = -12.6 Hz, H-7'), 3.95 (dq, 1H, $J_{5',7'}$ = 2.2

Hz, $J_{5',6'}$ = 4.8 Hz, $J_{4',5'}$ = 9.7 Hz, H-5'), 2.11 (s, 3H, $COCH_3$), 2.07 (s, 3H, $COCH_3$), 2.03 (s, 3H, $COCH_3$), 1.93 (s, 3H, $COCH_3$), 1.38 (t, 3H, J = 7.1, CH_3).
Anal. Calcd. for $C_{20}H_{27}N_3O_{11}$: C, 49.48; H, 5.56; N, 8.65. Found: C, 49.18; H, 5.30; N, 8.76.

1-(Tetra-O-acetyl-α and β-D-glucopyranosyl)-5-amino-4-carbamoylimidazoles (2)

To a solution of ethyl N-(cyanocarbamoylmethyl)formimidate [prepared from 0.5 g (0.004 mol) of aminocyanoacetamide[15] by reaction with 0.58 g (0.001 mol) of ethyl orthoformate] in dry acetonitrile (50 ml), 1.75 g (0.005 mol) of 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosylamine was added. The reaction mixture was refluxed for 2 h, after that the solvent was evaporated under reduced pressure and the residue was dissolved in ethanol (5 ml). The solution was cooled one day, the solid collected by filtration and recrystallized from ethanol to yield 0.7 g (31%) of 2 as white needles, mp: 150-152°C (decomp.). Ir (ν, cm^{-1}, Nujol): 3480, 3360 (NH_2), 1700 (C = O). uv λnm (ε) MeOH: 265 (10200). ^{1}H-nmr ($CDCl_3$, 300 MHz) δ: 7.03 (s, 1H, H-2), 5.55 (t, 1H, $J_{1',2'}$ = 9.3 Hz, H-2'β), 5.36 (t, 1H, $J_{2',3'}$ = 9.3 Hz, H-3'β), 5.29 (d, 1H, $J_{1',2'}$ = 9.3 Hz, H-1'β), 5.25 (t, 1H, $J_{3',4'}$ = 9.6 Hz, H-4'β), 5.23 (t, $J_{1',2'}$ = 8.9 Hz, H-2'α), 5.19 (bs, 2H, exchangeable with D_2O, NH_2), 5.11 (t, $J_{2',3'}$ = 9.4 Hz, H-3'α), 4.96 (t, $J_{3',4'}$ = 9.9 Hz, H-4'α), 4.66 (d, $J_{1',2'}$ = 8.7 Hz, H-1'α), 4.31 (dd, 1H, $J_{5',6'}$ = 4.5 Hz, $J_{6',7'}$ = -12.7 Hz, H-6'β), 4.28 (dd, $J_{5',6'}$ = 4.7 Hz, $J_{6',7'}$ = -12.6 Hz, H-6'α), 4.17 (dd, $J_{5',7'}$ = 2.2 Hz, $J_{6',7'}$ = -12.6 Hz, H-7'α), 4.16 (dd, 1H, $J_{5',7'}$ = 2.4 Hz, $J_{6',7'}$ = -12.7 Hz, H-7'β), 3.94 (dq, 1H, $J_{5',7'}$ = 2.4 Hz, $J_{5',6'}$ = 4.5 Hz, $J_{4',5'}$ = 9.6 Hz, H-5'β), 3.80 (dq, $J_{5',7'}$ = 2.2 Hz, $J_{5',6'}$ = 4.7 Hz, $J_{4',5'}$ = 9.9 Hz, H-5'α) 2.11 (s, $COCH_3$α), 2.10 (s, 3H, $COCH_3$β), 2.08 (s, $COCH_3$α), 2.07 (s, 3H, $COCH_3$β), 2.03 (s, $COCH_3$α), 2.03 (s, 3H, $COCH_3$β), 2.01 (s, $COCH_3$α), 1.94 (s, 3H, $COCH_3$β).
Anal. Calcd. for $C_{18}H_{24}N_4O_{10}\cdot H_2O$: C, 45.56; H, 5.48; N, 11.81. Found: C, 45.74; H, 5.48; N, 11.96.

1-(Tetra-O-acetyl-α and β-D-glucopyranosyl)-5-amino-4-cyanoimidazoles (3)

Compound 2 (1.1 g, 0.002 mol) was dissolved in chloroform (25 ml). The solution was cooled to 0°C and triethylamine (2.10 ml) was added, followed by the dropwise addition of $POCl_3$ (0.25 ml) at 0°C. After complete addition, the reaction mixture

was stirred at room temperature for 3 h and diluted by the addition of chloroform (50 ml). This was washed with a 10% aqueous solution of sodium bicarbonate followed by water, and the organic layer was dried over sodium sulphate. Evaporation of the solvent under reduce pressure left a residue wich was crystallized from ethanol to give 0.4 g (38%) of 3 as white needles, mp: 186 °C (Lit[2]. 186-187 °C).

7-Cyclohexyl-4-oxo-1H,3H-imidazo[4,5-c]-1,2,6-thiadiazine 2,2-Dioxide (4)

To a stirred solution of 0.5 g (0.002 mol) of 5-amino-4-ethoxycarbonyl-1-cyclohexylimidazole[5] and 0.5 g (0.004 mol) of sulfamoyl chloride in 25 ml of methylene chloride, triethylamine was added dropwise until pH became 7. The solution was heated for 4 h. After cooling the mixture to room temperature, 12.5% aqueous sodium hydroxide (25 ml) was added, and stirring was continued for 3 h. The aqueous phase was separated, the organic layer was washed with 2 x 15 ml of water, and the combined aqueous layers were acidified with hydrochloric acid. The solid was collected, dissolved in 8 ml of 1% aqueous sodium hydroxide and acidified with concentrated hydrochloric acid, to yield 0.26 g (46%) of 4 as white leaflets, mp: 268-269 °C (decomp.). Ir (ν, cm^{-1}, Nujol) 3250, 3150 (NH), 1680 (C=O), 1310, 1140 (SO_2). Uv λnm (ε) MeOH: 218 (6500), 248 (2100), 293 (4800). ^{1}H-nmr (DMSO-d_6) δ: 8.9 (s, 1H, H-6), 1.9-1.3 (m, 5H, C_6H_{11}).
Anal. Calcd. for $C_{10}H_{14}N_4O_3S$: C, 44.44; H, 5.18; N, 20.74; S, 11.85. Found: C, 44.21; H, 5.25; N, 20.46; S, 11.65.

7-Benzyl-4-oxo-1H,3H-imidazo[4,5-c]-1,2,6-thiadiazine 2,2-Dioxide (5)

A stirred solution of 0.25 g (0.001 mol) of 5-amino-1-benzyl-4-ethoxycarbonylimidazole[16] and 0.23 g (0.002 mol) of sulfamoyl chloride in 25 ml of methylene chloride was refluxed for 4 h. After cooling the solution, 25 ml of 12.5% aqueous sodium hydroxide was added and the stirring was continued for 2 h. The aqueous layer was separated and was acidified with concentrated hydrochloric acid. The solid was collected by filtration, dissolved in 5 ml of 1% aqueous sodium hydroxide and acidified with hydrochloric acid, to yield 0.1 g (35%) of 4 as white needles, mp: 254-255 °C (decomp.). Ir (ν, cm^{-1}, Nujol): 3360 (CH), 1720 (C=O), 1300, 1190 (SO_2). Uv λnm (ε) MeOH: 228 (4100), 250 (2000), 293 (4200). ^{1}H-nmr (DMSO-d_6) δ: 9.0 (s, 1H, H-6), 7.4 (m, 5H, Ph), 5.2 (s, 2H, CH_2).

Anal. Calcd. for $C_{11}H_{10}N_4O_3S$: C, 47.48; H, 3.59; N, 20.14. Found: C, 47.37; H, 3.38; N, 20.02.

6-Methyl-4-oxo-1H,3H-imidazo[4,5-c]-1,2,6-thiadiazine 2,2-Dioxide (6)

A suspension of 0.5 g (0.003 mol) of 5-amino-4-ethoxycarbonyl-2-methylimidazole[17] in 10 ml of hexamethyldisilazane was refluxed for 6 h under nitrogen and then evaporated to dryness. The residue was dissolved in 50 ml of dry benzene and, after the addition of 0.78 g (0.006 mol) of sulfamoyl chloride, the mixture was refluxed for 1 h. After cooling the mixture to room temperature, 25 ml of 25% aqueous sodium hydroxide was added, and stirring was continued for 2 h. The aqueous phase was separated and acidified with concentrated hydrochloric acid. After chilling, the solid was collected and recrystallized from water to yield 0.1 g (17%) of 6 as red needles, mp:210-212 °C (decomp.). Ir (ν,cm^{-1}, Nujol): 3420, 3150 (NH), 1650 (C=O), 1300, 1170 (SO_2). Uv λnm (ε) MeOH: 221 (4500), 246 (2600), 292 (5500). ^{1}H-nmr (DMSO-d_6) δ: 2.2 (s, 3H, CH_3).
Anal. Calcd. for $C_5H_6N_4O_3S.\ H_2O$: C, 27.27; H, 3.63; N, 25,45. Found: C, 27.03; H, 3.71; N, 25.37.

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