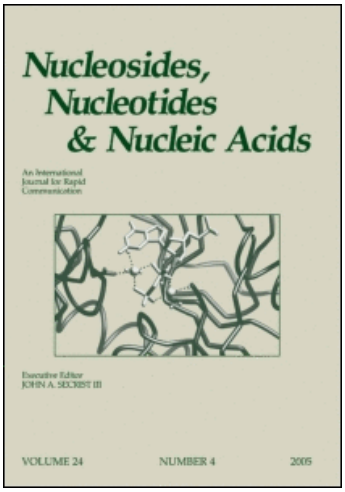

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Studies in the Protection and Selective Deprotection of 5-Amino-1-β-D-Ribofuranosylimidazole-4-Carboxamide (Aica-Riboside)

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STUDIES IN THE PROTECTION AND SELECTIVE DEPROTECTION OF 5-AMINO-1-β-D-RIBOFURANOSYLIMIDAZOLE-4-CARBOXAMIDE (AICA-RIBOSIDE)

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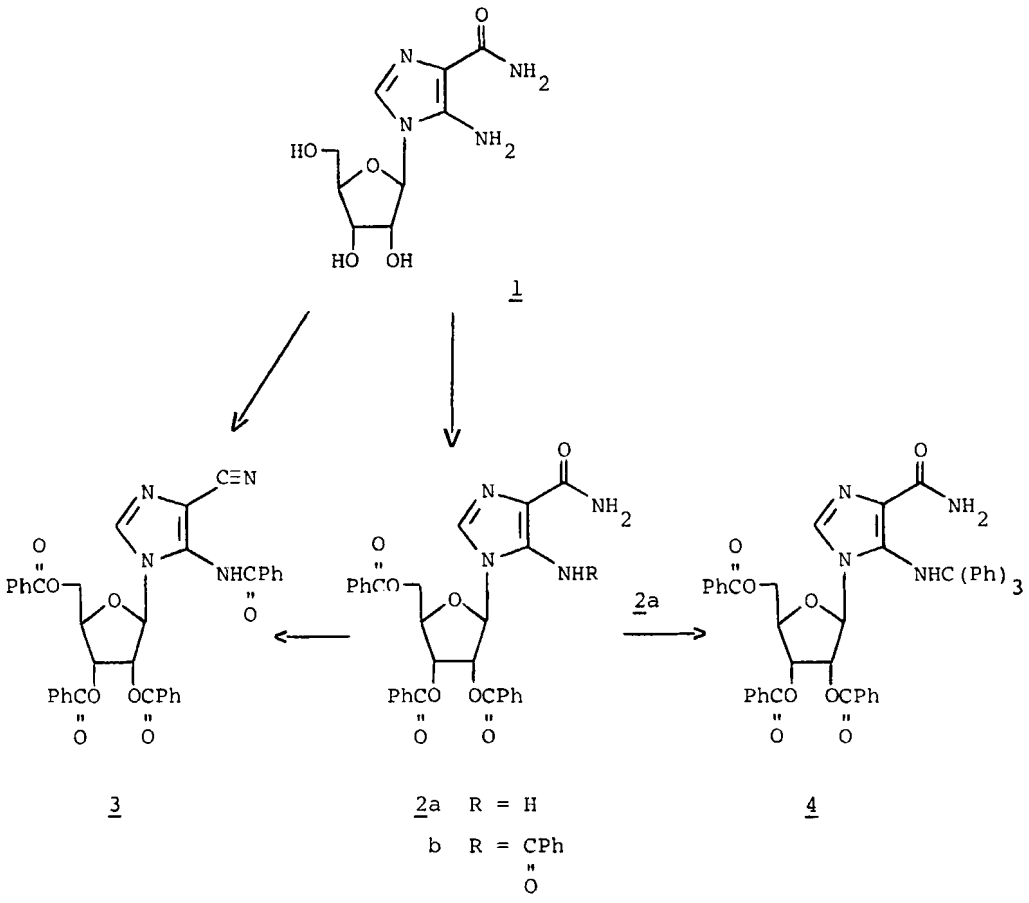
ABSTRACT: The preparation of several acylated derivatives of AICA riboside (1) and their deprotection with hydroxylaminium acetate were investigated. A facile route for the preparation of isomerically pure 2′,5′- and 3′,5′-dibenzoates of 1 is described.

In connection with our studies on imidazole nucleosides, we wished to develop methodology which would allow us easy access to partially protected derivatives, starting from the commercially available material, 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide (1). Considerable success has been claimed for the selective deprotection of peracylated purine and pyrimidine nucleosides using the reagent hydroxylaminium acetate.[1,2] We elected to extend this technique to the partial deprotection of benzoylated derivatives of 1.

Reaction of 1 with benzoic anhydride in pyridine gave an 80% yield of the tribenzoate 2a. Attempts to acylate the amino function of the nucleoside using benzoyl chloride in pyridine resulted in concomitant dehydration of the amide function. Under these conditions 3 was obtained from 1 in 42% yield, and from 2a in 65% yield. Treatment of 2a with benzoyl chloride in dichloromethane in the presence of solid sodium carbonate[3] gave a mixture of 2b and 3 in 27% and 29% yields respectively. The triphenylmethyl(trityl)derivative 4 was prepared from 2a in 67% yield without dehydration of the amide function.



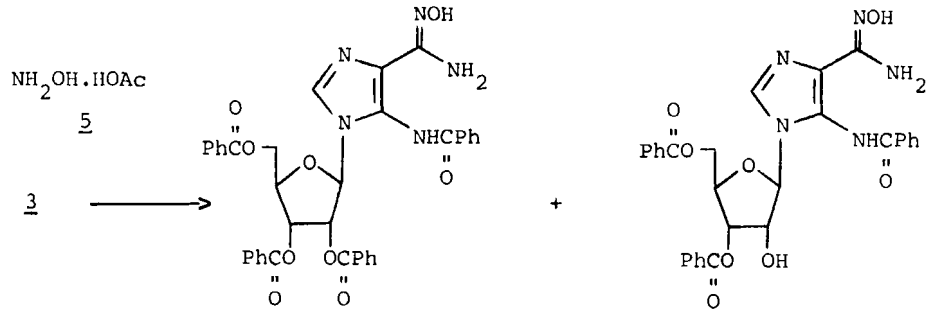
1

3

2a R = H

b R = CPh

4



5

3

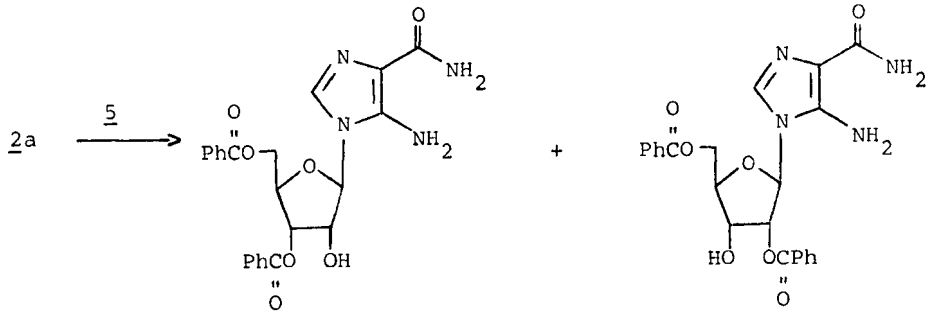
6

7

The reaction of a four fold excess of hydroxylaminium acetate (5) with the benzoates 2-4 was studied in pyridine solution. In the case of 3, the reagent 5 showed some selectivity in debenzoylation at the 2′-position, but also reacted with the 4-cyano function. The amidoximes 6 and 7 were obtained 33% and 31% yields respectively.

Reaction of 4 with 5 was complicated by detritylation, and no selectivity was observed during reaction of 5 with the tetrabenzoate 2b.

Treatment of the tribenzoate 2a with 5 gave, after 24 hours, a 70% yield of a mixture of the dibenzoates 8 and 9, in the ratio 2:1 as determined by 270MHz NMR spectroscopy. (Isomer assignments were made on the basis of ^{1}H NMR decoupling experiments).



8 9

No change in the isomer ratio was apparent on extended reaction time or on attempted equilibration of the mixture on a silica gel column.[2] Chromatographic separation of the isomers was not achieved, but, by means of a simple fractional crystallisation from ethyl acetate, both 8 and 9 were obtained in 95% isomeric purity and in 45% and 22% yields respectively.

Thus a facile method has been developed to produce, in high isomeric purity, both the 2′,5′- and 3′,5′-dibenzoates of 1, in two high yielding steps from 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide.

EXPERIMENTAL

Melting points were determined using a Reichert Kofler apparatus and are uncorrected. Infrared spectra were recorded with a Perkin Elmer 197 spectrophotometer and ^1H NMR spectra were recorded on a Jeol GX-270 MHz spectrometer. Mass spectra were recorded on a VG 70-70E mass spectrometer using fast atom bombardment with thioglycerol or p-nitrobenzylalcohol-sodium as matrix. Organic solutions of products were dried using magnesium sulphate, and chromatography was performed on Merck 7736 60H silica gel. Elemental analysis was carried out on a Carlo Erba model 1106 analyser.

5-Amino-1-β-D-2′,3′,5′-tribenzoylribofuranosylimidazole-4-carboxamide (2a)

To a suspension of compound (1) (7g, 27mmol) and dimethylaminopyridine (3.4g, 28mmol) in pyridine (70ml), was added benzoic anhydride (25g, 110mmol). The reaction mixture was stirred for 36h at room temperature then poured onto ice water (800ml) and extracted with ethyl acetate (3 x 400ml). The organic layer was separated, washed with 5 M hydrochloric acid, (3 x 100ml), neutralized with saturated sodium hydrogen carbonate solution, dried and the solvent evaporated under reduced pressure to give an oil which was chromatographed on silica gel, eluting with ethyl acetate to yield 2a (12.4g, 80%), m.p. 83-85°C (from ethyl acetate-carbon tetrachloride); ν_{max} (KBr) 3600-3100, 1730, and 1650cm^{-1}; δ_H [$(CD_3)_2SO$] 4.67-4.78 (3H, m, 4′-H and 5′-H), 5.91 (1H, m, 3′-H), 6.0-6.06 (3H, m, 2′-H and D_2O exchangeable NH_2), 6.26 (1H, d, J 6Hz, 1′-H), 6.78 (2H, br., D_2O exchangeable $CONH_2$), and 7.41-8.05 (16H, m, 3 x C_6H_5 and 2-H); (Found: C, 63.4; H, 4.5; N, 9.7%. $C_{30}H_{26}N_4O_8$ requires C, 63.2; H, 4.6, N, 9.8%).

5-Benzamido-1-β-D-2′,3′,5′-tribenzoylribofuranosylimidazole-4-carbonitrile (3)

(a) From 5-Amino-1-β-D-ribofuranosylimidazole-4-carboxamide

To an ice cooled suspension of compound (1) (3g, 12mmol) and dimethylaminopyridine (1.5g, 12mmol) in pyridine (30ml) was added benzoyl chloride (8.4ml, 73mmol), dropwise with stirring. The mixture was stirred for 15h then poured into a mixture of ice and dilute hydrochloric acid (400ml). The resulting mixture was extracted with ethyl acetate (3 x 300ml) and the organic layer separated then washed with saturated sodium hydrogen carbonate solution until neutral.

After drying the solvent was evaporated under reduced pressure to give an oil which was chromatographed on silica, eluting with acetone-hexane (1:2). The major component was collected and rechromatographed on silica gel, eluting with ethyl acetate-hexane (2:3), to give 3 (1.2g, 42%), m.p. 178-180°C (from ethanol-water); ν_{max} (KBr) 3700-3100, 2220, and 1730cm^{-1}; δ_H ($CDCl_3$) 4.64-4.92 (3H, m, 4'-H and 5'-H), 5.72-5.87 (2H, m, 2'-H and 3'-H), 6.06 (1H, d, J 3Hz, 1'-H), 7.32-8.04 (21H, m, 4 x C_6H_5 and 2-H), 8.72 (1H, s, D_2O exchangeable NH); (Found: C, 66.5; H, 4.5; N, 8.4%. $C_{37}H_{28}N_4O_8.0.5\ H_2O$ requires: C, 66.8; H, 4.4; N, 8.4%).

(b) From 2a

To an ice cooled solution of compound (2a) (2.1g, 3.7mmol) and dimethylaminopyridine (1.8g, 15mmol) in pyridine (50ml) was added benzoyl chloride (2.1g, 15mmol), dropwise with stirring. The mixture was stirred at room temperature and for 65h, then poured onto a mixture of ice and dilute hydrochloric acid (400ml). The resulting suspension was extracted with ethyl acetate (3 x 200ml), the organic layer separated, washed with dilute hydrochloric acid, and neutralized with saturated sodium hydrogen carbonate solution. After drying the organic phase the solvent was evaporated under reduced pressure to give an oil which was chromatographed on silica gel, eluting with ethyl acetate-hexane (1:1), to give 3 (1.6g, 65% after recrystallisation from ethanol-water). Spectral data were identical to those described above.

5-Benzamido-1-β-D-2',3',5'-tribenzoylribofuranosylimidazole-4-carboxamide (2b)

To a mixture of compound 2a (10.4g, 18mmol) and sodium carbonate (4.8g, 45.4mmol) in dichloromethane (200ml) was added benzoyl chloride (6.4g, 45.4mmol). The reaction mixture was heated under reflux for 15h then cooled to room temperature and poured onto ice. The organic layer was separated and the aqueous phase extracted with dichloromethane (2 x 50ml). The combined organic extracts were washed with dilute hydrochloric acid then neutralised with saturated sodium hydrogen carbonate solution. The organic layer was dried and the solvent evaporated under reduced pressure to give an oil, which was chromatographed on silica, eluting with ethyl acetate-hexane (1:1), to give, as the first component to elute, 3 (3.5g, 29%). The eluant was

changed to ethyl acetate, and further chromatography gave 2b (3.3g, 27%), m.p. 97-98°C (from ethanol-water); ν_{max} (KBr) 3700-3200, 1730, and 1650cm^{-1}; δ_H [$(CD_3)_2SO$] 4.65-4.8 (3H, m, 4'-H and 5'-H), 5.9-6.08 (3H, m, 1'-H, 2'-H and 3'-H), 7.13 (1H, s, 2-H), 7.32-8.14 (22H, m, 4 x C_6H_5 and D_2O exchangeable NH_2), and 10.36 (1H, s, D_2O exchangeable NH); (Found: C, 65.8; H, 4.8; N, 8.3%. $C_{37}H_{30}N_4O_9$ requires: C, 65.9; H, 4.5; N, 8.3%).

1-β-D-2',3',5'-tribenzoylribofuranosyl-5-triphenylmethylamino-imidazole-4-carboxamide (4)

To a solution of the compound 3 (2g, 3.5mmol) in ethyl acetate (15ml) and triethylamine (10ml) was added triphenylmethylchloride (1.5g, 5.35mmol). The mixture was stirred at room temperature for 15h then poured onto water (200ml). Ethyl acetate was added and the organic layer separated, washed with water, dried and the solvent evaporated under reduced pressure. The residual oil was chromatographed on silica gel, eluting with ethyl acetate-hexane (5:1) to give 4 (1.9g, 67%); ν_{max} (KBr) 3700-3200, 1730, and 1650cm^{-1}; δ_H [$(CD_3)_2SO$] 4.18-4.62 (3H, m, 4'-H and 5'-H), 5.63-5.9 (3H, m, 1'-H, 2'-H and 3'-H), 6.85 (1H, s, D_2O exchangeable NH), and 7.06-8.03 (3H, m, 6 x C_6H_5, 2-H and D_2O exchangeable NH_2); (Found: C, 72.6; H, 5.0; N, 6.8%. $C_{49}H_{40}N_4O_8$ requires: C, 72.4; H, 5.0; N, 6.9%).

5-Benzamido-1-β-D-2',3',5'-tribenzoylribofuranosylimidazole-4-carboxamidoxime (6) and 5-benzamido-1-β-D-3',5'-dibenzoylribofurano-sylimidazole-4-carboxamidoxime (7)

To a solution of compound 3 (500mg, 0.75mmol) in pyridine (10ml) was added hydroxylaminium acetate (280mg, 3mmol). The reaction mixture was stirred for 27h at room temperature, treated with acetone (50ml) and the solvent evaporated under reduced pressure to give an oil which was chromatographed on silica gel, eluting with chloroform-methanol (19:1). The first fraction to elute was 6 (135mg, 33%), m.p. 100-102°C (from methanol-water); ν_{max} (KBr) 3700-3100, 1730, and 1650cm^{-1}; δ_H [$(CD_3)_2SO$] 4.64-4.79 (3H, m, 4'-H and 5'-H), 5.50 (2H, s, D_2O exchangeable NH_2), 5.89-5.98 (1H, m, 3'-H), 6.0-6.04 (2H, m, 1'-H and 2'-H), 7.32-8.14 (21H, m, 4 x C_6H_5 and 2-H), 9.32 (1H, s, D_2O exchangeable NOH), 10.17 (1H, s, D_2O exchangeable NH); (Found: C, 63.5; H, 4.6; N, 9.6%. $C_{37}H_{31}N_5O_9.0.7\ H_2O$ requires: C, 63.3; H, 4.65; N, 10.0%).

The second component to elute was 7 (138mg, 31%); ν_{max} (KBr) 3700-3100, 1730, 1720, and 1670cm^{-1}; δ_H [$(CD_3)_2SO$] 4.62 (3H, m, 4′-H and 5′-H), 4.74 (1H, m, 2′-H), 5.47 (3H, br, D_2O exchangeable NH_2 and 3′-H), 5.60 (1H, d, J 4Hz, 1′-H), 6.07 (1H, d, J 6Hz, D_2O exchangeable 2′-OH), 7.46-8.04 (16H, m, 3 x C_6H_5 and 2-H), 9.29 (1H, s, D_2O exchangeable NOH), and 10.07 (1H, s, D_2O exchangeable NH); m/z (FAB) 586 ($M+1^+$).

5-Amino-1-β-D-3′,5′-dibenzoylribofuranosylimidazole-4-carboxamide (8) and 5-amino-1-β-D-2′,5′-dibenzoylribofuranosylimidazole-4-carboxamide (9)

To a solution of compound 2a (6g, 10.5mmol) in pyridine (45mL) was added hydroxylaminium acetate (3.9g, 42mmol). The mixture was stirred at room temperature for 30h, treated with acetone (60ml) and the solvent evaporated under reduced pressure to leave an oil which was chromatographed on silica, eluting with chloroform-methanol (19:1) to give a mixture of 8 and 9 (3.43g, 70%). The mixture was treated with hot ethyl acetate (10ml), cooled and filtered to give a first crop of pure 9. The filtrate was evaporated to dryness and treated with hot ethyl acetate (5ml), cooled and filtered to give a second crop of pure 9 (total recovery 1.1g, 22%), m.p. 188-192°C; ν_{max} (KBr) 3700-3000, 1725, and 1640cm^{-1}; δ_H [$(CD_3)_2SO$] 4.3-4.7 (4H, m, 3′-H, 4′-H and 5′-H), 5.59 (1H, m, 2′-H), 5.9 (3H, m, D_2O exchangeable OH and NH_2), 6.7 (2H, br, $CONH_2$), 7.41 (1H, s, 2-H), 7.53-8.12 (10H, m, 2 x C_6H_5); (Found: C, 59.2; H, 4.8; N, 12.0%. $C_{23}H_{22}N_4O_7$ requires: C, 59.2; H, 4.8; N, 12.0%).

Evaporation of the filtrate gave a pure sample of 8 as a foam (2.2g, 45%); ν_{max} (KBr) 3700-3000, 1725, and 1640cm^{-1}; δ_H [$(CD_3)_2SO$] 4.57-4.65 (3H, m, 4′-H and 5′-H), 4.78 (1H, m, 2′-H), 5.54 (1H, m, 3′-H), 5.72 (1H, d, J 7Hz, 1′-H), 5.94 (2H, s, D_2O exchangeable NH_2), 6.04 (1H, d, J 4 Hz, D_2O exchangeable OH), 6.70 (2H, br, D_2O exchangeable $CONH_2$), 7.33 (1H, s, 2-H), 7.44-8.12 (10H, m, 2 x C_6H_5); m/z (FAB) 467 ($M+1^+$), 489 ($M+23^+$); (Found: C, 58.8; H, 5.1; N, 11.9%. $C_{23}H_{22}N_4O_7$ requires: C, 59.2; H, 4.8; N, 12.0%).

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REFERENCES

1. Y. Ishido, N. Sakairi, K. Okazaki and N. Nakazaki, J. Chem. Soc. Perkin Trans. 1, **1980**, 563.
2. N. Sakairi, M.D. Rahman, K. Tamaki and Y. Ishido, Nucleosides Nucleotides, **1982**, 1, 99.
3. V.S. Mokrushin, T.A. Pospelova, V.A. Bakulev, E.F. Golivina, S.L. Nikolaeva and Z.V. Pushkareva, Khim. Geterotsiki Soedin, **1984**, 2, 247.

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