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SYSTEMATIC SYNTHESIS OF PURINE 8,5'-IMINO AND SUBSTITUTED IMINO CYCLONUCLEOSIDES

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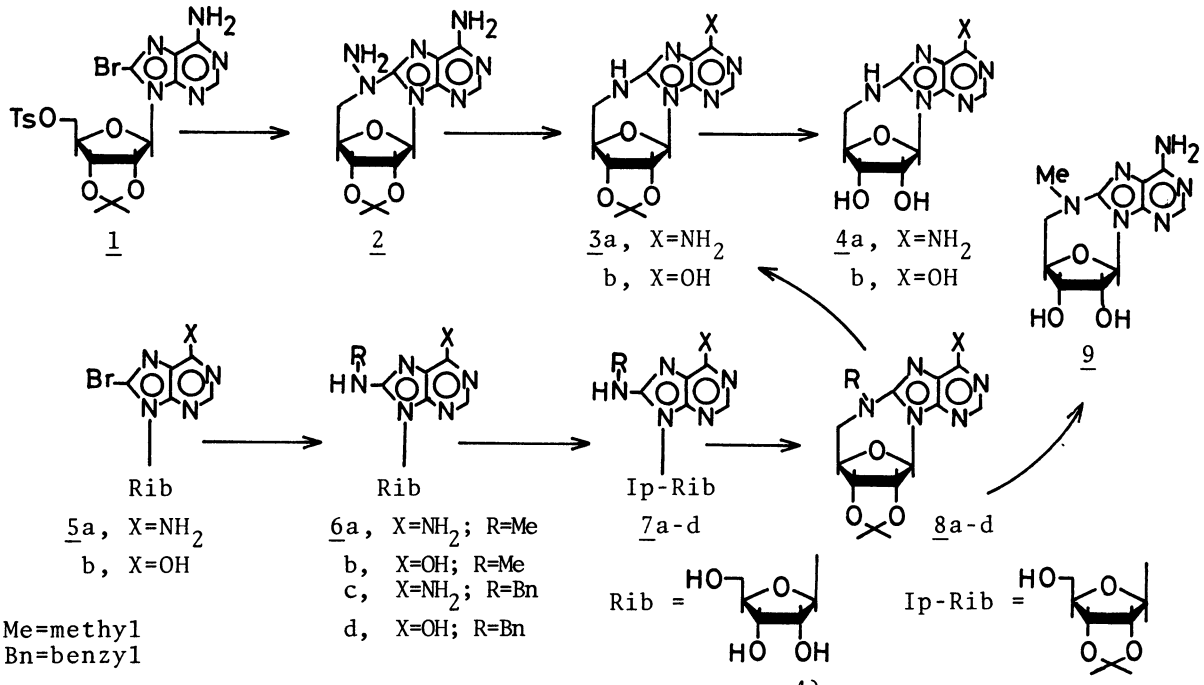
A systematic synthesis of some purine 8,5'-imino and substituted imino cyclonucleosides has been introduced. Thus, 2',3'-O-isopropylidene derivatives of 8-methylaminoadenosine, 8-methylaminoinosine, 8-benzylaminoadenosine and 8-benzylaminoinosine with excess diphenyl carbonate/Et_3N in DMF gave the corresponding 8,5'-substituted imino cyclonucleosides. These were converted to the debenzylated derivatives or to 8,5'-methylimino cycloadenosine.

A recent report[1] from this laboratory has described the synthesis of 8,5'-imino-9-(5'-deoxy-β-D-ribofuranosyl)adenine (4a) and its hypoxanthine analogue (4b) as the first 8,5'-imino cyclonucleosides. Success of this synthesis depends essentially on the use of strongly nucleophilic hydrazine as a nitrogen source: a reaction of 2',3'-O-isopropylidene-5'-O-tosyl-8-bromoadenosine (1) with an excess amount of hydrazine gave the 8,5'-aminimino cyclonucleosides (2) at room temperature, checking the notorious intramolecular quaternization at N^3 by 5'-carbon in 1 to a minimum. It was another boon to us that the N-amino group in 2 was easily removed by oxidation with iodine pentoxide or nitrous acid to give a compound 3a or 3b in quantitative yields. Analogous 8,5'-bridging with the use of hydrazine was also achieved in the guanosine series.[2] Largely due to the various biological activities claimed for 8-amino and 8-substituted amino purine nucleosides,[3] we have exploited and describe here a more direct systematic synthesis of 8,5'-N-cyclonucleosides which could serve as biological or optical models.

Reactions of 8-bromoadenosine (5a) and 8-bromoinosine (5b) with excess methylamine, as well as benzylamine, gave the corresponding 8-methylamino and 8-benzyl-



amino purine nucleosides (6a-d) in 70 to 100% yields.[4] Compounds 6a-d can be acetonated to the corresponding 2',3'-O-isopropylidene derivatives (7a-d) in high yields. Treatment of 7a-d with 1.5 equiv. diphenyl carbonate and 2-3 equiv. triethylamine in DMF at 135° for 30 min gave, in each case, two products roughly in equal amounts in terms of TLC. After having removed the solvent, each mixture was directly subjected to preparative TLC using silica gel plates and a chloroform-methanol mixture (methanol content ranged from 10 to 20% depending on the mobility of the product in each case). Generally, the more polar products proved to be the desired 8,5'-N-cyclonucleosides (8a-d) (yields:30-40%).[5] Repeated attempts to isolate the less polar ones by TLC resulted in their partial decomposition, invariably regenerating the starting materials (7a-d). Elongation of the reaction time did not change the product distributions, and hence these less polar products seem to be phenoxycarbonyl compounds other than the precursors destined for cyclization, carrying this group on 8-nitrogen or 5'-oxygen.[6] Actual intermediates for the formation of 8a-d are uncertain at present. Treatment of 8a with 90% trifluoroacetic acid yielded 8,5'-methylimino-9-(5'-deoxy-β-D-ribofuranosyl)adenine (9)[7] in a good yield, while the usual reductive debenzylation[8] of 8c,d with naphthalene anion in THF gave 3a,b[1] in over 50% isolated yields (this debenzylation must have proceeded quantitatively as judged by TLC).

Although the deep-seated mechanism for the cyclization is unknown at present,

this systematic method seems to be promising in that there is no need for precursors with a leaving group at C_5, which are generally prone to form a N^3,5'-cyclonucleoside even at room temperature and that variously substituted imino bridges can be constructed between the C_8 and $C_{5'}$, and especially in view of the fact that the direct amination of the 8-position of purine bases with ammonia is excluded,[3a,9] whereas alkyl or aralkyl substituted amines can easily replace bromine at the C_8 of purines as shown above and described.[3d,9] Elaboration of the reaction conditions for optimizing the yields in this cyclization and extension to the guanosine series are under way.

References

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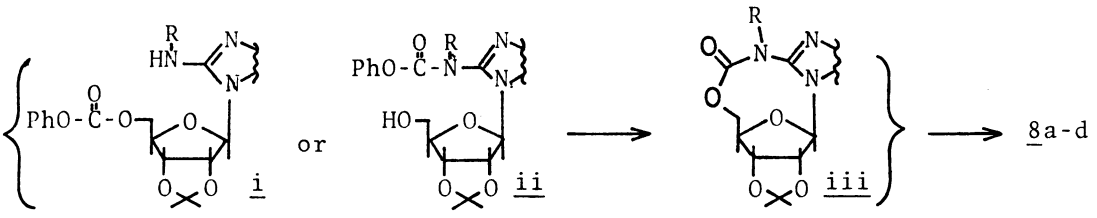
3) a) R. E. Holmes and R. K. Robins, J. Am. Chem. Soc., 87, 1772 (1965); b) R. E. Holmes and R. K. Robins, ibid., 86, 1242 (1964); E. J. Reist, D. F. Calkins, L. V. Fisher, and L. Goodman, J. Org. Chem., 33, 3651 (1974); d) R. A. Long, R. K. obins, and L. B. Townsend, J. Org. Chem., 32, 2751 (1967).
4) See Ref. 3d and 9 for compound 6a and Ref. 9 for 6c.
5) 8a: mp 263-265°C; λmax (MeOH) 273 nm (ε 20200); ^{1}H NMR (DMSO-d_6) δ 3.03 (3H, s, Me), 3.20 (1H, dd, J_{gem}=14.4 Hz, $J_{5'a,4'}$=4.4 Hz, $H_{5'a}$), 3.49(1H, dd, J_{gem}=14.4 Hz, $J_{5'b,4'}$=3.6 Hz, $H_{5'b}$), 4.61 (1H, d, $J_{3',2'}$=6.0 Hz, $H_{3'}$), 4.65 (1H, dd, $J_{4',5'a}$=4.4 Hz, $J_{4',5'b}$=3.6 Hz, $H_{4'}$), 4.95 (1H, d, $J_{2',3'}$=6.0 Hz, $H_{2'}$), 6.15 (1H, s, $H_{1'}$), 6.83 (2H, br s, NH_2), 8.05 (1H, s, H_2).
8b: mp above 300°C; λmax (MeOH) 264 nm (ε 17200); ^{1}H NMR (DMSO-d_6) δ 2.97 (3H, s, Me), 3.15 (1H, d, J_{gem}=13.2 Hz, $H_{5'a}$), 3.46 (1H, dd, J_{gem}=13.2 Hz, $J_{5'b,4'}$=4.0 Hz, $H_{5'b}$), 4.64 (2H, m, $J_{4',5'b}$=4.0 Hz, $J_{3',2'}$=6.0 Hz, $H_{4'}$ and $H_{3'}$), 4.95 (1H, d, $J_{2',3'}$=6.0 Hz, $H_{2'}$), 6.09 (1H, s, $H_{1'}$), 7.98 (1H, s, H_2), 12.28 (1H, s, lactam NH).
8c: mp 247-249°C; λmax (MeOH) 275.5 nm (ε 30600); ^{1}H NMR (DMSO-d_6) δ 3.12 (1H, d, J_{gem}=14.0 Hz, $H_{5'a}$), 3.32 (1H, dd, J_{gem}=14.0 Hz, $J_{5'b,4'}$=2.4 Hz, $H_{5'b}$), 4.37 (1H, d, J_{gem}=14.4 Hz, PhC$\underline{H}_a$-), 4.48 (1H, d, $J_{2',3'}$=6.0 Hz, $H_{2'}$), 4.59 (1H, d, $J_{4',5'b}$=2.4 Hz, $H_{4'}$), 4.74 (1H, d, $J_{3',2'}$= 6.0 Hz, $H_{3'}$), 5.02 (1H, d, J_{gem}=14.4 Hz, PhC$\underline{H}_b$-), 6.16 (1H, s, $H_{1'}$), 6.89 (2H, s, NH_2), 7.32-7.45 (5H, m, Ph), 8.07 (1H, s, H_2).
8d: dec. above 190°C, mp above 300°C; λmax (MeOH) nm (ε) 264 (16900) and 289 (8000, sh); ^{1}H NMR (DMSO-d_6) δ 3.07 (1H, d, J_{gem}=14.0 Hz, $H_{5'a}$), 3.30 (1H, d, J_{gem}=14.0 Hz, $J_{5'b,4'}$=2.8 Hz, $H_{5'b}$), 4.37 (1H, d, J_{gem}=14.4 Hz, PhC$\underline{H}_a$-), 4.53 (1H, d, $J_{2',3'}$=6.0 Hz, $H_{2'}$), 4.59 (1H, d, $J_{4',5'b}$=2.8 Hz, $H_{4'}$), 4.76 (1H, d, $J_{3',2'}$=6.0 Hz, $H_{3'}$), 4.90 (1H, d, J_{gem}=14.4 Hz, PhC$\underline{H}_b$-), 6.11 (1H, s, $H_{1'}$), 7.28-7.58 (5H, m, Ph), 8.01 (1H, s, H_2), 12.36 (1H, br s, lactam).
6) We postulate a sequential mechanism, i or ii ⟶ iii ⟶ 8a-d, for the time



being as in the formation of 2,2'-anhydrouridine from uridine and diphenyl carbonate in the presence of sodium bicarbonate.[10] To add, we have recently isolated and characterized 2',3'-O-isopropylidene-5'-O-phenoxycarbonyluridine in an attempt to cyclize 2',3'-O-isopropylideneuridine to its 2,5'-anhydro derivative using the same reagents (unpublished data).

7) Mp 269-272°C; ^{1}H NMR (DMSO-d_6) δ 3.21 (1H, dd, J_{gem}=13.6 Hz, $J_{5'a,4'}$=4.4 Hz, $H_{5'a}$), 3.43 (1H, dd, J_{gem}=13.6 Hz, $J_{5'b,4'}$=3.2 Hz, $H_{5'b}$), 3.99 (1H, t, $J_{2',3'}$=$J_{2',2'\text{-OH}}$=6.8 Hz, $H_{2'}$), 4.28 (1H, t, $J_{3',2'}$=$J_{3',3'\text{-OH}}$=6.8 Hz, $H_{3'}$), 4.48 (1H, dd, $J_{4',5'a}$=4.4 Hz, $J_{4',5'b}$=3.2 Hz, $H_{4'}$), 5.22 (1H, d, J=6.8 Hz, D_2O-exchangeable, 3'-OH), 5.50 (1H, d, J=6.8 Hz, D_2O-exchangeable, 2'-OH), 6.08 (1H, s, $H_{1'}$), 6.79 (2H, s, D_2O-exchangeable, NH_2), 8.04 (1H, s, H_2).

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