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# THE SYNTHESIS OF 4-AMINO-8-(β-D-RIBOFURANOSYL)AMINOPYRIMIDO[5,4-d]PYRIMIDINE FROM A PURINE NUCLEOSIDE: A NOVEL REARRANGEMENT OF THE PURINE RING

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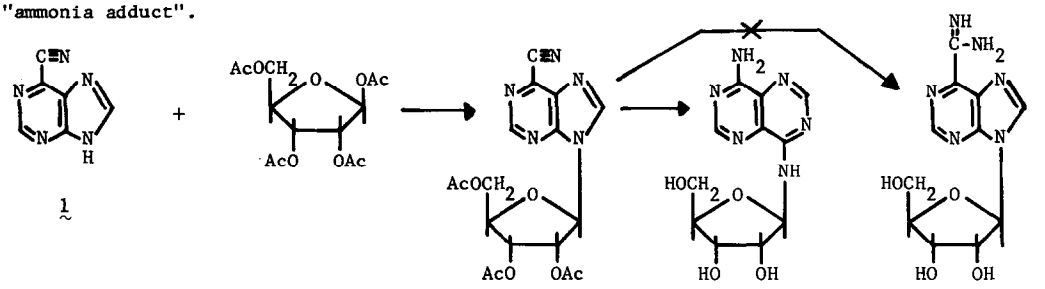
Several years ago Ishido and co-workers[1] described formation of an "equimolar adduct of ammonia and 6-cyano-D-ribofuranosylpurine" by deacetylation of 6-cyano-9-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)purine (2) with methanolic ammonia (Scheme I). We were interested in studying nucleophilic addition to the cyano moiety of 2 and sought to investigate the structure of this "ammonia adduct".



1 2 4 3

Preparation of 2 by the acid catalysed fusion[2] of 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose with 6-cyanopurine (1) followed by deacetylation with methanolic ammonia afforded the "ammonia adduct", mp 214-216° (lit[1] 210-213°). Elemental analysis (C, H, N) was consistent with the empirical formula $C_{11}H_{14}N_6O_4$. It seemed reasonable that this compound could be 9-β-D-ribofuranosylpurine-6-carboxamidine (3); however, an inspection of the pmr spectrum revealed several anomalies. The signal for the anomeric proton ($H_{1'}$) was a quartet centered at δ5.88 (in $d_6$ DMSO, DSS standard, on a Hitachi Perkin-Elmer R20A nmr) and suggested a possible anomeric mixture. By other criteria (mp, chromatography) this compound was homogeneous. When $D_2O$ was added to exchange the active hydrogens, the quartet collapsed to a doublet at δ5.88. A closer inspection

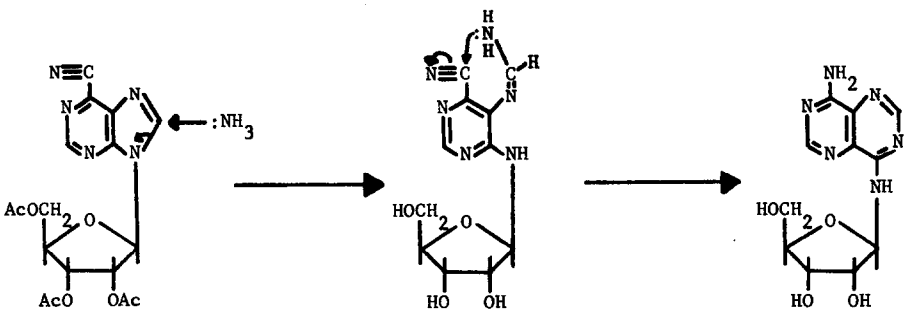
of the spectrum suggested that the anomeric proton was coupled with an active hydrogen which exhibited a signal at $\delta$8.4 as a doublet with a 9 Hz coupling constant. This supposition was corroborated by spin decoupling of the signal centered at $\delta$8.4 which caused collapse of the quartet at $\delta$5.88 to the doublet at $\delta$5.88 (vide supra). A second unexpected property of this compound is that the ultraviolet spectrum in $H_2O$ gave four maxima: 292 nm ($\epsilon$16,000), 303 nm ($\epsilon$14,100), 319 nm ($\epsilon$12,400) and 334 nm ($\epsilon$8,500) which is unusual for uv spectra of purines.

In order to resolve these data, it was decided to determine the structure crystallographically. The crystal belongs to the space group P1 with one molecule per unit cell. The cell dimensions are a = 5.434Å, b = 12.269Å, c = 4.574Å, $\alpha$ = 92.3°, $\beta$ = 94.0°, and $\gamma$ = 95.3°. The volume of the cell was 302.6Å$^3$. The crystal utilized to collect three dimensional data was a rectangular plate, 0.4 X 0.5 X 0.05 mm. 1123 Data were collected on a Syntex automated diffractometer with monochromatic Cu $K_\alpha$ [$\lambda(CuK_\alpha)$=1.5418] radiation using the $\theta$ - 2 $\theta$ scan technique. The structure was determined by direct methods and refined by full-matrix least-squares with the hydrogen atoms treated isotropically and all others anisotropically. The final refinement resulted in a residual, $R_1$ of 0.071 and a weighted R value of 0.108.

Our results show that the actual structure of the "ammonia adduct" is 4-amino-8-($\beta$-D-ribofuranosyl)aminopyrimido[5,4-d]pyrimidine (4). Review of the physical data in the light of structure 4 reveals that H of the 8-amino group is coupled to the adjacent anomeric ($H_{1'}$) proton and produces the quartet signal centered at $\delta$5.88 ($H_{1'}$).

The ribose ring remains in the $\beta$-D-ribofuranosyl configuration and shows the unusual O1' endo conformation. Moreover, a consequence of this puckering is that O2' and O3' are eclipsed rather than staggered with respect to one another.

Formation of 4 from 2 can be rationalized if scission of the bond between C-8 and N-9 occurs in basic media. Several relevant examples of alkaline cleavage of this bond in the imidazole ring of purines have been noted,[3-8] leading to formation of 5-formylaminopyrimidine derivatives. However, with our work ring opening is caused by ammonia and is followed by ring closure involving the cyano group to afford 4-amino-8-$\beta$-D-ribofuranosylaminopyrimido[5,4-d]-pyrimidine (4), possibly as depicted below.



The detailed study of this novel reaction is now in progress.

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