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THE DIRECT UTILIZATION OF UNSATURATED SUGARS IN NUCLEOSIDE SYNTHESIS. 3-DEOXY-3-(6-CHLORO-2-METHYLTHIO-9-PURINYL)-D-ERYTHRO-HEX-1-ENOPYRANOSE, A NEW AND NOVEL TYPE OF PURINE NUCLEOSIDE (1)

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The acid catalyzed fusion procedure with acetylated glycals has been previously reported to furnish 2'-deoxypyranosylpurine nucleosides (2) and 2',3'-unsaturated pyranosylpurine nucleosides (3) in good yield. This procedure has now been found to provide a completely new type of purine nucleoside. We wish to report the isolation and characterization of a 3-deoxy-3-D-erythro-hex-1-enopyranosyl purine nucleoside from the acid catalyzed fusion of 3,4,6-tri-O-acetyl-D-glucal with 2-methylthio-6-chloropurine.

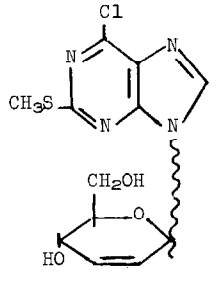
A mixture of 2-methylthio-6-chloropurine (10g) and 3,4,6-tri-O-acetyl-D-glucal (20g) was fused at 120° in the presence of catalytic amount of p-toluenesulfonic acid for 2.5 hrs under vacuum. After isolation, there was obtained 1.77 g of II (mp 214-215°), 1.36 g of I (mp 184-185°) and 1.81 g of III (mp 177-178°). The site of glycosidation for I, II and III was established as N-9 on the basis of ultraviolet absorption spectral comparisons with model compounds. However, it was established that I, II and III were different compounds on the basis of mp, tlc and pmr spectra (4).

Significant differences were noted in the pmr spectra of I, II and III in the region attributed to the carbohydrate moiety which allowed the endocyclic double bond to be assigned to either the 1,2 or 2,3 positions of the carbohydrate. The nucleoside designated as I, was assigned the structure 6-chloro-2-methylthio-9-(2,3-didehydro-2,3-dideoxy-D-erythro-hexopyranosyl)-purine on the basis of a pmr spectrum which revealed a pattern of peaks for the carbohydrate moiety very similar to that observed previously for 2-acetamido-6-chloro-9-(4,6-di-O-acetyl-2,3-didehydro-2,3-dideoxy-D-erythro-hexopyranosyl)purine (3) and certain known 4,6-di-O-acetyl-2,3-didehydro-2,3-dideoxy-D-erythro-hexosides (5,6). The pmr spectra of II and III revealed a significant change in the pattern of peaks for the carbohydrate moiety and established that II and III were very closely related to each other and definitely not 2,3-unsaturated derivatives. The

pmr spectrum of II [δ6.63 (pair of doublets), δ4.80 (pair of doublets)] and III [δ6.75 (pair of doublets), δ4.88 (overlapping pair of doublets)] revealed that these peaks occur very close to the chemical shifts reported (7) for the analogous protons of 3,4,6-tri-O-acetyl-D-glucal [δ6.53 (H1, pair of doublets), δ4.81 (H2, pair of doublets)]. These data indicate that the protons associated with the δ6.63 and δ4.80 absorption signals in the pmr spectrum of II and with the peaks at δ6.75 and δ4.88 in the pmr spectrum of III can be assigned to H1 and H2 of a hex-1-enopyranose derivative.

The assignment of the endocyclic double bond of II and III to the 1,2 position was firmly established by utilization of the double resonance technique at 100 MHz (8). Irradiation of the pair of doublets centered at δ4.80 (H2, $J_{2,1}$ = 6.0 Hz, $H_{2,3}$ = 2.0 Hz) in the pmr spectrum of II caused a collapse of the pair of doublets at δ6.63 (H1, $J_{1,2}$ = 6.0 Hz, $J_{1,3}$ = 2.0 Hz) to a doublet ($J_{1,3}$ = 2.0 Hz). The small coupling constant, $J_{1,3}$ = 2.0 Hz, results from a long-range coupling of H1 and H3. Similarly, irradiation of the pair of doublets centered at δ6.63 collapsed the pair of doublets centered at δ4.80 (H2) to a doublet ($J_{2,3}$ = 2.0 Hz). The pair of overlapping doublets centered at δ4.88 (H2, $J_{2,1}$ = 6.0 Hz, $J_{2,3}$ = 5.0 Hz) in the pmr spectrum of III were irradiated and collapsed the pair of doublets at δ6.75 (H1, $J_{1,2}$ = 6.0 Hz, $J_{1,3}$ = 1.0 Hz) to a singlet. The pair of doublets at δ4.88 (H2) were collapsed to a doublet upon irradiation of the pair of doublets centered at δ6.75 (H1). These proton decoupling results can only be accomodated in structures in which H1 and H2 are part of a 1,2-unsaturated system which corroborated the initial structural assignment of II and III as hex-1-enopyranose derivatives.

This left the actual site of purinyl attachment to the carbohydrate as the major unresolved problem. This problem was resolved by a pmr study of the diacetyl derivative (9) of II and III.



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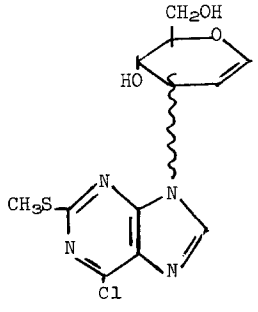

II, III

The pmr spectra of II and III revealed chemical shifts of δ4.28 and δ4.0, respectively, for the

C4 proton. The pmr spectrum of the diacetyl derivative of II showed that H4 was shifted (δ1.25) downfield to δ5.53. In a similar manner, H4 in the pmr spectrum of the diacetyl derivative of III was shifted (δ1.17) downfield to δ5.17. The $\Delta\delta$ values and direction of chemical shift are in agreement with results reported for a number of acyl and aminoacyl nucleoside esters (10,11). The significant downfield chemical shifts of H4 upon acetylation of II and III indicated that the ring hydroxyl group in II and III must obviously be a diastereoisomeric pair with the purine moiety being attached at C3 and possessing the structure shown above.

Additional studies in progress include the use of pmr spectroscopy for the unequivocal determination of configuration at C3, conformation of the carbohydrate moiety, reactions involving the 1,2-endocyclic double bond, and the use of other purines and glycals.

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4. Satisfactory analytical data (C,H,N) were obtained from Heterocyclic Chemical Corp., Harrisonville, Missouri, for all new compounds which were also found to be homogenous by tlc chromatography. All pmr spectra were determined on a Jeolco C60H nmr spectrometer at 60 MHz unless otherwise specified.

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8. We would like to thank G. D. Daves and W. Anderson of the Oregon Graduate Center, Portland, Oregon for the decoupled 100 MHz pmr spectra.

9. These derivatives were prepared by direct acetylation of II and III with acetic anhydride and pyridine.

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