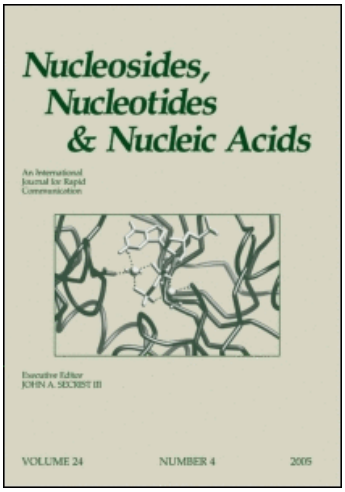

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Structure Determination of 4-Chloro-DRB

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STRUCTURE DETERMINATION OF 4-CHLORO-DRB

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Abstract: 'Chloro-DRB' (1-β-D-ribofuranosyl-4,5,6-trichlorobenzimidazole) was prepared in the 1950's and shown to be more potent than DRB as an inhibitor of RNA synthesis. The ambiguous location of the third chlorine atom has been determined by nOe studies to be at the 4-position.

* * * *

From the first report of DRB[1] (1-β-D-ribofuranosyl-5,6-dichloro-benzimidazole) in the 1950's to the 2,5,6-trichloro analog[2] (TCRB) prepared in the 1990's, halogenated benzimidazole nucleosides have been shown to be inhibitors of processes involving nucleic acid derivatives. Sehgal *et al.*[3] have shown DRB and related halogenated derivatives to be specific inhibitors of RNA synthesis[4,5,6] in mammalian cells; most severely affected were heterogeneous nuclear RNA (hnRNA), cytoplasmic mRNA and ribosomal RNA. Of particular interest is the fact that these nucleosides apparently need no phosphorylation to the corresponding nucleotide derivative in order to express their biological activity[5]. Other activities of DRB are also reported including antiviral activity[1,4], superinduction of interferon[7], interference with topoisomerase II[8], and inhibition of casein kinases I and II (may mediate directly or indirectly RNA polymerase II inhibition)[9,10].

Included in the first description of the synthesis of DRB[11] by Dr. Clifford H. Shunk of the then Merck Sharp & Dohme Research Laboratories was the characterization of other halogenated benzimidazole nucleosides. The most

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[Dedicated to the memory of Dr. Roland K. Robins]

interesting of these was a trichloro derivative (either 4,5,6 or 5,6,7 substitution), whose activity exceeded the activity of DRB in every system examined: RNA synthesis inhibition[12], anti-influenza activity[13,14] and casein kinase inhibition[15]. The original material prepared by C. H. Shunk was used in all investigations of biological activity. The structural ambiguity of the active chloro-DRB is additionally clouded by the fact that detailed experimentals were not provided in the original publications; therefore a resynthesis of the trichloro material today would not provide absolute assurance that the product obtained would be identical to the original material used in the experiments of decades past.

Chloro-DRB was prepared by the mercuric salt method using preformed 4,5,6-trichlorobenzimidazole; literature review suggests it is not possible to predict with certainty whether glycosylation would proceed at N-1 or N-3 (only one product was isolated).

The residue of Dr. Shunk's original samples were obtained and the nuclear magnetic resonance spectrum was taken as well as an nOe difference spectrum, irradiated at the 1' position.

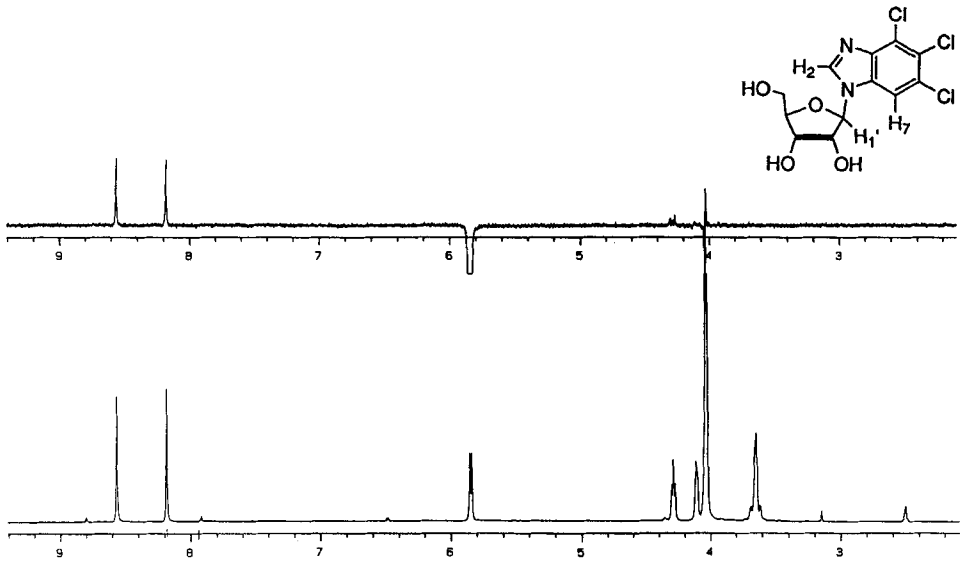

FIGURE 1. Nuclear magnetic resonance spectrum (400MHz, DMSO) of 'chloro-DRB' (bottom) and nOe difference spectrum, irradiated at H-1' (top)

Both of the aromatic H resonances show strong nOe enhancement [δ8.58 (H-2) and δ8.18 (H-4 or H-7 based on chemical shift)], which is only possible for the situation where the chlorine atom is located at C-4. In a parallel experiment, DRB showed three aromatic protons at δ8.57 (H-2), δ8.20 (H-4) and δ7.94 (H-7); under identical conditions nOe was only seen for H-2 and H-7, not H-4. Therefore, the structure of 'chloro-DRB' is 1-β-D-ribofuranosyl-4,5,6-trichlorobenzimidazole.

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