

POTENTIAL INHIBITORS OF CANCEROUS GROWTH IV
NITROSYL CHLORIDE ADDITION PRODUCTS OF GLYCALs

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Although nitrosyl chloride is a well known reagent for unsaturation tests (1), especially in cyclic terpenes, the synthetic possibilities of the corresponding reaction in the carbohydrate field have apparently not been studied.

Preliminary experiments conducted in conjunction with our studies on D-ribose derivatives as anti-cancer compounds, have shown that highly crystalline NOCl - adducts may be obtained from various acetylated glycal. These products serve as suitable precursors for the synthesis of the corresponding amino compounds required in this laboratory in fairly large quantities for a study of D-ribose (2, 3), and other sugar derivatives (4) as "carrier molecules" in the development of new anti-cancer compounds.

Nitrosyl chloride reacts smoothly with 3,4,6-tri-O-acetyl-D-glucal in CCl_4 medium at $0^\circ C$ to form a crystalline adduct (I), m.p. $115-119^\circ$ (decomp), $[\alpha]_D^{25} + 170$ (C 6.0 chloroform).

Under similar conditions, 3,4-di-O-acetyl-D-arabinal yields a crystalline product (II), m.p. $116-121^\circ$ (decomp),

$[\alpha]_D^{25}$ -203.2 (C 5.0, chloroform).

Satisfactory C,H, and N analyses and qualitative tests confirmed that the compounds are nitroso sugar derivatives. Both products are soluble in the usual organic solvents and may be recrystallized from ethyl acetate-petroleum ether (40-60°C.).

N.M.R. spectroscopy indicated that the products are acetylated 1-chloro-2-nitroso-1,2-dideoxy sugars and also revealed that, contrary to expectation, the secondary nitroso compounds do not rearrange to the corresponding iso-nitroso structures. The existence of the secondary nitroso structures is also indicated by the chemical instability of the products as well as by their thermochromic behavior in solution. Solutions of the adducts in CCl_4 are colourless at room temperature but assume a progressively more intense sea-green hue at higher temperatures. At 50-55°C, thermal decomposition occurs as indicated by the development of a brown colour ascribable to the formation of nitrogen oxides.

N.M.R. spectroscopic analysis leaves little doubt that the reaction of NOCl under these conditions occurs by means of a cis-addition; this result, although in conflict with currently held views (5) on the mechanism and stereochemistry of NOCl addition, serves to confirm the recent findings of Meinwald *et al* (6) and suggests a radical mechanism for the reaction.

The product obtained from 3,4,6-tri-O-acetyl-D-glucal therefore appears to be 3,4,6-tri-O-acetyl-2-nitroso-2-deoxy-D-glucopyranosyl chloride (I), while that obtained

from 3,4-di-O-acetyl-D-arabinal is 3,4-di-O-acetyl-2-nitroso-2-deoxy- β -D-arabinopyranosyl chloride (II).

Both I and II react smoothly with silver acetate in glacial acetic acid at room temperature to yield the calculated amount of silver chloride. The chlorine-free nitrogen-containing products of such reactions could not be crystallized. These are assumed to be 1,3,4,6-tetra-O-acetyl-2-nitroso-2-deoxy-D-glucopyranose (III) and 1,3,4-tri-O-acetyl-2-nitroso-2-deoxy-D-arabinopyranose (IV).

Reduction of I with zinc-copper in glacial acetic acid yields a colourless, crystalline chlorine-free product (V), m.p. 204-205°C, $[\alpha]_D^{17} + 24$ (C5.0, chloroform) λ_{max} : 3.28, 5.69, 7.28, 8.95, 9.39, 9.56 (SH) μ .

N.M.R. spectroscopic data and elemental analysis led us to assume V to be 1,3,4,6-tetra-O-acetyl-2-amino-2-deoxy-D-glucopyranose (V). Deacetylation of V with barium methylate in metanol yields a product VI identified as D-glucosamine, by means of paper and thin layer chromatography. The same material may be obtained by reduction and deacetylation of III.

A white, crystalline product (VII), m.p. 195-196°C, $[\alpha]_D^{17} - 31.2$ (C 5.0 chloroform), λ_{max} : 3.28, 5.69, 7.22, 8.90, 9.10, 9.56 μ . may be obtained by the reduction of II with zinc-copper in glacial acetic acid which was shown to be 1,3,4-tri-O-acetyl-2-amino-2-deoxy arabino-pyranose in a similar way.

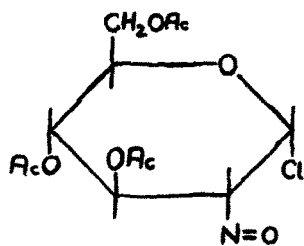
In view of the fact that, in all of the NOCl adducts

obtained by us, the halogens are easily replaceable by nucleophiles, the reaction presents a direct method for the synthesis of 2-deoxy-2-amino pyranose nucleosides.

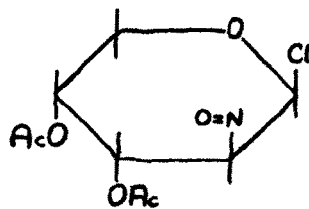
The feasibility of obtaining an NOCl adduct from a furanoseglycal (8), is at present being investigated. We have obtained evidence to suggest that the route to the synthesis of the hitherto unknown 2-deoxy-2-amino nitroso nucleosides has been opened.

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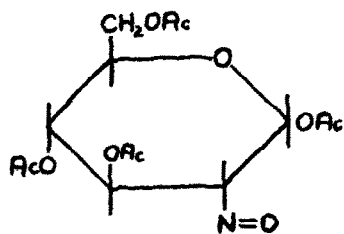
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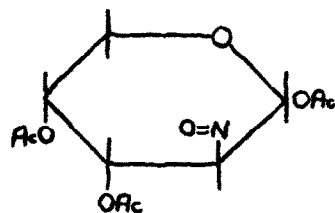
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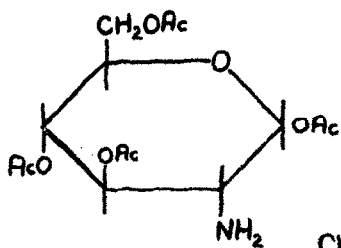
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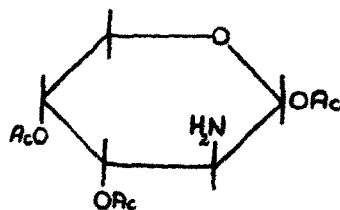
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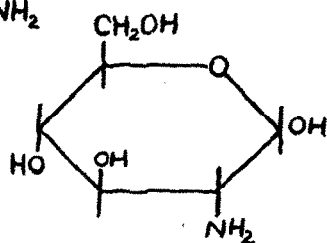
IV



V



VII



VI