

Research Laboratories, Parke, Davis and Co.

Sugar Lactams. I. 5-Amino-5-deoxy-D-ribonolactam and Related Products

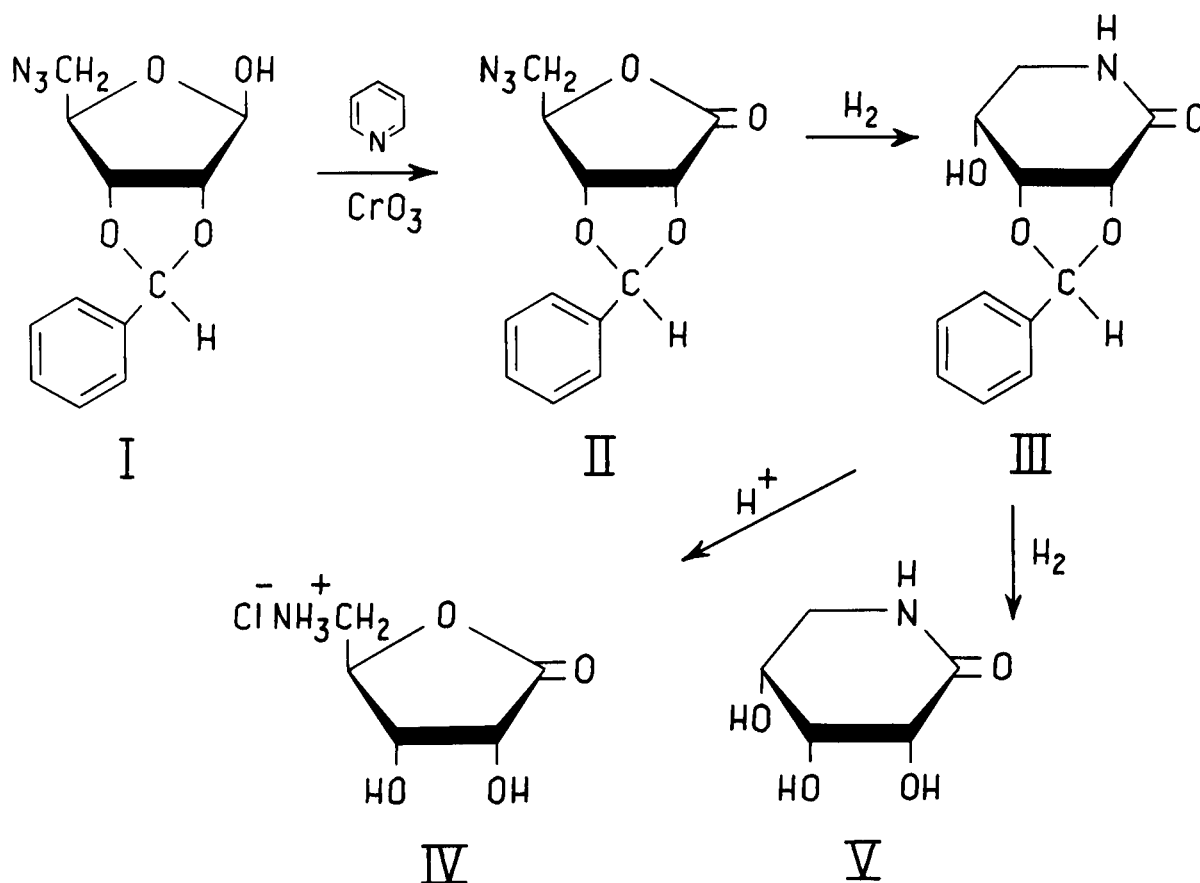
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Sir:

The synthesis of sugar derivatives containing nitrogen as the ring atom has been recently reported from several laboratories (1-5). These reports have included the synthesis of 5-acetamido-5-deoxypentoses which are formed as a mixture of furanose and pyranose ring forms, the latter containing the nitrogen function in a six-membered ring.

We wish to report the synthesis of a novel crystalline sugar having a six-membered lactam structure (V). In connection with this work, it was found that the oxidation of an aldofuranose derivative having a free hydroxyl group at C-1 with the pyridine-chromium trioxide complex (6) afforded the corresponding aldonolactone in one step and high yield. Oxidation of a secondary hydroxyl group in an acyclic system (7-9) or in an exocyclic side chain attached to a cyclic structure (10-11), proceeds more readily than in the case of hydroxyl groups attached directly to a pyranoid ring (12, 13). The oxidation of a secondary hydroxyl group in a furanoid ring has been hitherto unsuccessful (13-15). The facile oxidation of the C-1 hydroxyl group in the aldofuranose derivative described herein is due to the greater reactivity at the anomeric site.

Treatment of 5-azido-2,3-O-benzylidene-5-deoxy- β -D-ribofuranose (4) (I) with the pyridine-chromium trioxide complex overnight at room temperature gave crystalline 5-azido-2,3-O-benzylidene-5-deoxy-D-ribono- γ -lactone (II) (80%), m.p. 146-7°, $[\alpha]_D^{23}$ -13° (c., 0.71 in acetone) (Calcd. for $C_{12}H_{11}N_3O_4$: C, 55.17; H, 4.24; N, 16.09. Found: C, 55.14; H, 4.26; N, 16.13) (16). This compound could be detected by a lactone test (17) on paper or thin layer chromatograms and showed a band at 1795 cm^{-1} in the infrared spectrum. The n.m.r. spectrum in dimethyl sulfoxide at 60 mc. showed peaks consistent with the structure. Hydrogenation of II at room temperature and atmospheric pressure over Pd-C in methanol or over PtO_2 in ethyl acetate afforded 5-amino-2,3-O-benzylidene-5-deoxy-D-ribonolactam (III) as colorless needles in almost quantitative yield, m.p. 203-4°, $[\alpha]_D^{23}$ +48.5° (c., 0.7 in dimethyl sulfoxide) (Calcd. for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.96; OH, 7.25. Found: C, 61.18; H, 5.66; N, 5.85; OH, 10.72). The lactam III could not be detected with the hydroxylamine reagent (17). The infrared spectrum showed a band at 1650 cm^{-1} but no amide II band indicating the cyclic nature of the amide function (18). The n.m.r. spectrum in dimethyl sulfoxide showed peaks consistent with the proposed structure. The presence of one hydroxyl group as a result of the ring expansion was confirmed by an hydroxyl determination. The lactam structure was further ascertained by reduction of III with lithium aluminum hydride in ether-tetrahydrofuran to give an oil which was devoid of carbonyl absorption bands in the infrared spectrum. Hydrolysis of the benzylidene group in III with Amberlite IR-120 (H^+) (19) (2 hrs. on a steam bath) gave a



product that was retained on the resin. Elution of the resin with 2*N* hydrochloric acid followed by evaporation of the eluate afforded crystalline 5-amino-5-deoxy-D-ribo- γ -lactone hydrochloride (IV) (30-35%), m.p. 185-7° (dec.), $[\alpha]_D +68^\circ$ (c., 0.35 in MeOH) (Calcd. for $C_5H_{10}NO_4Cl$: N, 7.65; Cl, 19.28. Found: N, 7.20; Cl, 19.38). The infrared spectrum showed bands at 2800-2400 cm^{-1} and 1920 cm^{-1} due to amine hydrochloride function and at 1770 cm^{-1} due to the carbonyl function. Hydrogenolysis of III over Pd-C in 95% ethanol containing acetic acid afforded crystalline 5-amino-5-deoxy-D-ribonolactam (V) (42%), m.p. 193-5° (dec.); $[\alpha]_D +33^\circ$ (c., 0.29 in H_2O). Spectral studies showed the absence of aromatic absorption in V.

The sequence II — III — IV illustrates an interesting example of ring tautomerism involving internal O to N and N to O acyl shifts. In the aldose series, the formation of 5-acetamido-5-deoxy-D-ribofuranose seemed to be favored over the heterocyclic pyranose isomer under neutral, acidic or alkaline conditions (4).

The oxidation of aldose derivatives having a free OH at C-1 with the pyridine-chromium trioxide reagent to the corresponding lactones, is presently being investigated in these laboratories.

Acknowledgment.

Optical rotations and spectral studies were performed by Dr. J. M. Vandenbelt and associates. Microanalyses

were done by Mr. C. E. Childs and associates of Parke, Davis and Co. The authors thank Dr. H. M. Crooks, Jr., for valuable discussions and Misses J. I. Balfe and S. C. Addington for technical assistance.

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Received November 10, 1963

Ann Arbor, Michigan