Communications to the Editor

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Chemistry of Kanamycin. VI.*1 Deamination Reaction of Methyl 3-Glucosaminide with Nitrous Acid

Deamination of monocyclic aminopyranose sugars with nitrous acid has been attempted by many workers.[1] Similar reactions were carried out in this laboratory during the study on the structure of the antibiotic, kanamycin, indicating that the amino group of methyl 6-glucosaminide, a component of kanamycin, was predominantly replaced with hydroxyl group.[2]

The deamination of methyl 3-glucosaminide which was the first example of the rupture of C-C bond resulting in the contraction of the ring on the same treatment of amino sugar is reported herein.

Methyl 3-amino-3-deoxy-α-D-glucopyranoside[2] (I), when reacted with sodium nitrite and acetic acid under ice-cooling, yielded a deaminated product (II) which was isolated as crystalline *p*-ethoxyanilide, m.p. 156~156.5° (*Anal.* Calcd. for $C_{15}H_{21}O_5N$: C, 61.0; H, 7.1; N, 4.8; OCH_3, 21.0. Found : C, 60.8; H, 7.1; N, 4.7; OCH_3, 19.9.). The deaminated product (II) was formed on treating the *p*-ethoxyanilide with dil. acetic acid and purified by paper chromatography (solvent system; *n*-BuOH-AcOH-H_2O=4:1:2.5 v/v; ascending method; color reagent, aniline hydrogen phthalate). (II) was collected by elution of the spot at Rf 0.69 from paper strips, crystallized after standing for 2 weeks, and showed no content of α-epoxy group*2 by quantitative measurement, and a weak shoulder at 270 mμ (in MeOH). The presence of aldehyde group in (II) was supported by the color reactions (aniline hydrogen phthalate and fuchsin-sulfurous acid tests), by the formation of *p*-ethoxyanilide, and finally by its derivation to the corresponding carboxyl group by hypoiodite oxidation as follows : By potassium hypoiodite oxidation under the usual condition employed in the oxidation of aldoses to aldonic acids,[3] (II) consumed 86% of the theoretical amount of iodine, while D-glucose showed 100% consumption. The crude oxidation product was directly paper-chromatographed (solvent system; *n*-BuOH-AcOH-H_2O=4:1:2.5 v/v) showing a new spot of lactone (III) at Rf 0.77 (detection reagent, NH_2OH-$FeCl_3$), which was removed from paper strips and recrystallized from ether, m.p. 78~80° (Kofler block), $[\alpha]_D^{32}$ +88°→+97° (after 5 days)(c=0.753, in H_2O). $[\alpha]_D^{32}$ +245° (c=0.740, in 0.01*N* NaOH) (*Anal.* Calcd. for $C_7H_{10}O_5$: C, 48.4; H, 6.2; eq. wt. 174. Found : C, 48.8; H, 6.1; saponification eq. 166). (III) was neutral in aqueous solution and did not reduce red tetrazolium. Infrared spectra of (III) in KBr and CCl_4 showed bands at 3430 and 3535 cm^{-1} attributable to hydroxyl group, and bands at 1760 and 1794 cm^{-1} indicative of γ-lactone. (III) consumed cold NaOH-MeOH and the resulting product showed bands at 1585 and 1410 cm^{-1} (in Nujol), typical for carboxylate ion group. By the attempted periodate oxidation, the Na salt of (III) showed no appreciable consumption of the reagent. Thus, these observations support the γ-lactone structure for (III) and hence the structure (II) for the deaminated product. That the IR band for aldehyde carbonyl in (II) was

*1 Part V : J. Antibiotics, **A11**, 168(1958).

1) F. Shafizadeh : "Advances in Carbohydrate Chemistry," **13**, 43(1958), Academic Press Inc., New York.

2) H. Ogawa, T. Ito, S. Kondo, S. Inoue : Bull. Agr. Chem. Soc. Japan, **23**, 289(1959).

3) (a) M. Macleod, R. Robison : Biochem. J., **23**, 517(1929). (b) R. Kuhn, I. Löw : Chem. Ber., **86**, 1032(1953).

*2 The formation of α-epoxy group might be expected from the deamination of diaxial *trans*-α-amino alcohol.

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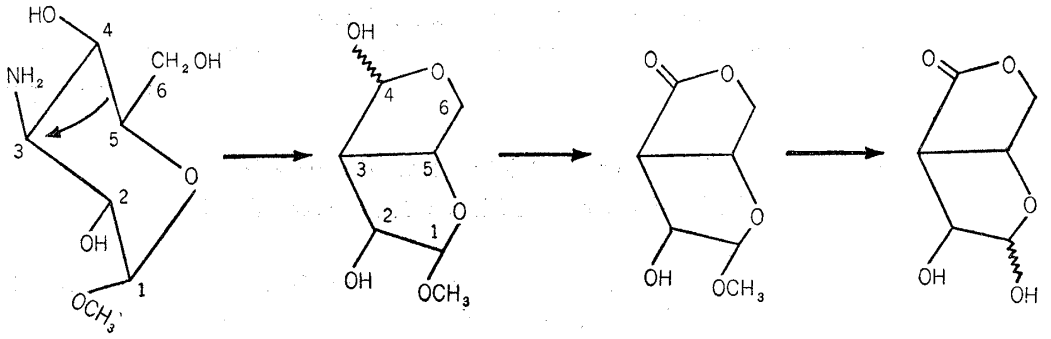

(I) (II) (III) (IV)

found to be very weak, seems to be due to the existence of (II) mainly in 4,6-hemiacetal form.

Further evidences were added for the structure (III) by the formation of demethyl-lactone (IV) and examination of the periodate oxidation product. By refluxing in *N* sulfuric acid for 1.5 hr., (III) was converted to (IV), which showed a single spot (Rf 0.60), positive to lactone and reducing sugar tests, on paper chromatogram (*n*-BuOH-AcOH-H_2O=4:1.2.5 v/v). (IV) melted at 132° (Kofler block) and was highly sensitive to red tetrazolium (less than 50 μg./cc.), characteristic to ketol structure, and consumed 1 mole of $NaIO_4$ within 2 hours accompanied with the formation of 1 mole of acid. IR spectrum of (IV) in Nujol showed a band at 1747 cm^{-1} (γ-lactonic carbonyl).

The mechanistic explanation of reactions and configurational assignments were given as follows: In the preferred conformation of (I), in which the pyranose ring is rigidly stabilized by the methoxyl group at 1-position, as seen in the diagram, the departing group ($-NH_2$) and the migrating group (C-5) are in the antiparallel coplanarity which, as is well known in the cyclohexane series,[4] favors ring contraction with inversion at C-3 and with retention at C-5 to give (II). As a consequence of this stereospecific reaction course, the fusion of two rings, tetrahydrofurans, in (II) might occur in *cis*- and, accordingly, the ring junction in its oxidation product (III) is placed in the same relationship which was experimentally supported by the ready regeneration of the γ-lactone (III) from its sodium salt in an acid medium, because the *trans*-fusion of two five-membered rings would cause their distortion.[5]

Under mild conditions, such as used in this case, the configuration at C-1 and C-2 in (I) is probably retained in the reaction course affording (II) and then (III). Thus, the configuration of (II) is assigned as methyl 3-deoxy-3-C-formyl-α-D-ribofuranoside which is illustrated in the diagrams including other reaction products, (III) and (IV).

It will be of interest for further investigation that 1,2-shift from 5—4 to 5—3 bond preferred over the shift from 1—2 to 1—3 bond which is also in coplanarity with the amino group.

Full details will be published elsewhere.

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4) W. Klyne: "Progress in Stereochemistry," **I**, 72(1954), Butterworths Scientific Publications, London.
5) J. A. Mills: "Advances in Carbohydrate Chemistry," **10**, 17(1955), Academic Press Inc., New York.

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