die ausgeschiedenen Kristalle aus EtOH umkristallisiert. 48 mg Nadeln, Schmp. 276°. $C_9H_6O_3N_2$—Ber.: C, 56.84; H, 3.18; N, 14.73. Gef.: C, 56.56; H, 3.04; N, 14.74.

Katalytische Reduktion des Tosylates von (I)—50 mg Probe wurden in einer EtOH-Lösung mit Pd-Kohle (aus 50 mg aktiver Kohle und 6 ccm 1% $PdCl_2$ bereitet) katalytisch reduziert, wobei nach 1 Std. ca. 9 ccm H_2 aufgenommen wurden. Die Reaktionsmischung wurde vom Katalysator abfiltriert, eingeengt, der Rückstand mit Wasser verdünnt und die ausgeschiedenen Kristalle (28 mg, Schmp. 155~158°) aus Aceton umkristallisiert. Körniges Kristall vom Schmp. 160~162°. IR: $\nu_{C=O}$ 6.0 (in Nujol). C_9H_9ON—Ber.: C, 73.45; H, 6.16; N, 9.52. Gef.: C, 73.11; H, 5.89; N, 9.53.

Zusammenfassung

Bei der Chlorierung von 2-Hydroxychinolin-1-oxyd mit Phosphoroxychlorid wurde 2,4-Dichlorchinolin erhalten. 2-Hydroxychinolin-1-oxyd ergab beim Nitrieren mit Salpetersäure in Eisessig-Lösung das 6,8-Dinitroderivat. Das Acetyl-, Benzoyl- und Tosylderivate von 2-Hydroxychinolin-1-oxyd und seiner 6,8- und 3,6-Dinitroderivate wurden hergestellt. Ihre Konstitutionen wurden durch die IR-spektrographische Untersuchung als die 1-Acyloxycarbostyril-Derivate festgestellt. 1-Benzoyloxycarbostyril widersteht der Einwirkung von Benzoylnitrat, während Carbostyril dabei 6-Nitroderivat ergibt. Die katalytische Reduktion des Tosylates von 2-Hydroxychinolin-1-oxyd mit Palladium-Kohle in Äthanol-Lösung ergab 3,4-Dihydrocarbostyril.

(Eingegangen am 12. September, 1958)

UDC 547.457.1-233.07

52. Shichiro Akiya and Toshiaki Osawa: Nitrogen-containing Sugars. V.[1] Synthesis and Deamination of Methyl 4,6-Benzylidene-β-D-glucosaminide Hydrochloride.

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In 1914, Irvine and Hynd[2] reported that they obtained an amorphous powder, m.p. 144~145°, $[\alpha]_D^{20}$ −22.43°(acetone), by deamination of methyl 4,6-benzylidene-β-D-glucosaminide hydrochloride (III). They hydrolysed this compound with hydrochloric acid and condensed the debenzylated product with aniline, leading it to D-mannose anilide. From both elementary analysis and above series of reactions of this product they proposed the structure of 4,6-benzylidene-D-mannose for this deaminated product. In the preceding paper of this series,[3] it was shown that the deamination of methyl 4,6-ethylidene-3-O-methyl-α(or β)-D-glucosaminide hydrochloride did not give the expected 4,6-ethylidene-3-methyl-D-mannose but gave 2,5-anhydro-4,6-ethylidene-3-methyl-D-mannose through the cleavage of glycosidic bond and simultaneous formation of anhydro ring.

In this paper will be described the synthesis of methyl 4,6-benzylidene-β-D-glucosaminide hydrochloride (III) by a new method and the result of deamination reactions of both (III) and methyl 4,6-benzylidene-2-amino-2-desoxy-α-D-altroside hydrochloride (V). These starting sugars, the structures of which exclude any change of conformations during further deamination reactions, were treated with sodium nitrite in weak acid, and from their results a new mechanism was found for deamination of 2-amino sugars.

Irvine and Hynd synthesized (III) by condensation of methyl β-D-glucosaminide hydrochloride with benzaldehyde, but it was found that the slight solubility of methyl β-D-glucosaminide hydrochloride in benzaldehyde made the experiment tedious, with varying

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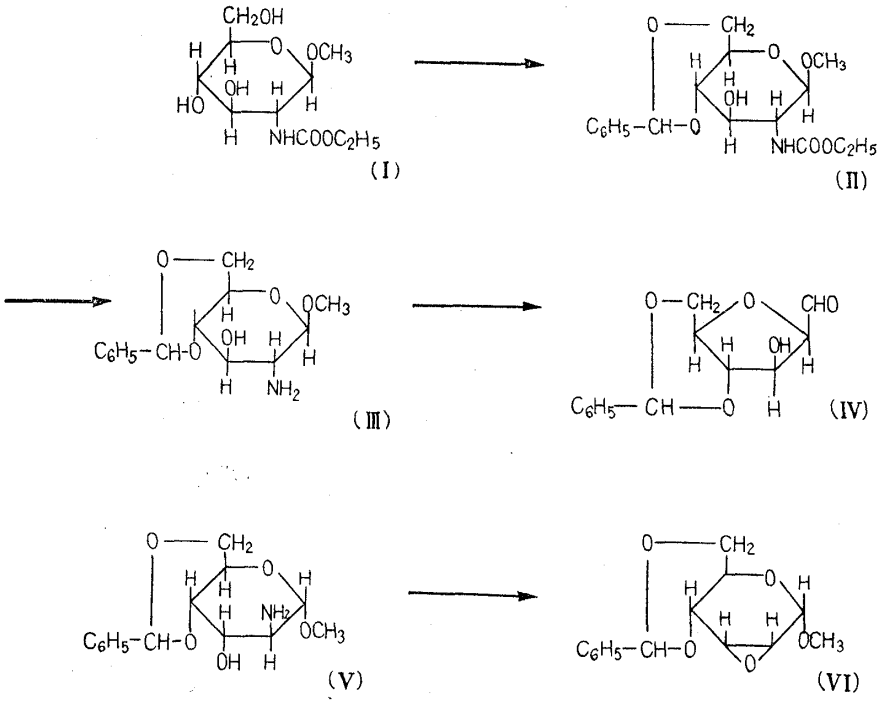
1) Part IV: Yakugaku Zasshi, **77**, 726(1957).
2) J. C. Irvine, O. A. Hynd: J. Chem. Soc., **105**, 698(1914).
3) S. Akiya, T. Osawa: Yakugaku Zasshi, **76**, 1276(1956).

yields of the product. Methyl 4,6-benzylidene-N-ethoxycarbonyl-β-D-glucosaminide (II), m.p. 228°, $[\alpha]_D^{21}$ −32.35°($CHCl_3$), was obtained by condensation of methyl N-ethoxycarbonyl-β-D-glucosaminide[1] (I) with benzaldehyde in the presence of zinc chloride as a catalyst. In general, alkoxycarbonyl group is eliminated when compounds containing it are heated in alkaline solution. It was found that the most profitable condition to eliminate the ethoxycarbonyl group of (II) was to heat the latter with barium hydroxide in 50% ethanol at 130~140°. Thus, the desired methyl 4,6-benzylidene-β-D-glucosaminide, m.p. 168~169°, $[\alpha]_D^{22}$ −72.25°($CHCl_3$), was obtained in a relatively good yield. This compound was dissolved in ethanol and converted into its hydrochloride (III), m.p. 217~218°(decomp.), $[\alpha]_D^{22}$ −64.04°(H_2O), by addition of equivalent amount of hydrochloric acid dissolved in ethanol and followed by precipitation with ether.

Deamination of (III) with sodium nitrite and acetic acid in a weak acid solution gave an amorphous powder (IV), m.p. 145~147°, $[\alpha]_D^{21}$ −22.52°(acetone). From the physical data of this product, this compound was presumed to be identical with that obtained by Irvine and Hynd. (IV) gave negative result on detection of nitrogen, had no methoxyl group, reduced Fehling's solution, and gave an odor of benzaldehyde on decomposition with acid. After hydrolysis of this compound with hydrochloric acid to remove benzylidene group, the hydrolysate was condensed with aniline according to the method of Irvine *et al.*,[4] but the product was a tarry mixture which gave no evidence of containing a trace of D-mannose anilide. Further, the hydrolysate was tested by both paper chromatography and paper ionophoresis, and in each case, no trace of D-mannose or D-glucose, but only D-chitose, 2,5-anhydro-D-mannose,[5] was detected. In independent series of experiments, no configurational change of both D-glucose and D-mannose was observed under the present condition of hydrolysis to remove the benzylidene group.



Moreover, the deaminated product showed no evidence of consuming periodate, two moles of which must be consumed if this compound had the structure of 4,6-benzylidene-D-mannose as proposed by Irvine and Hynd.

4) J. C. Irvine, D. McNicoll : J. Chem. Soc., **97**, 1449(1910).
5) S. Akiya, T. Osawa : Yakugaku Zasshi, **74**, 1259(1954); B. C. Bera, A. B. Foster, M. Stacey : J. Chem. Soc., **1956**, 4531.

From the foregoing experiments and the result of elementary analysis of the product, it was concluded that the amorphous powder obtained by deamination of (III) was 2,5-anhydro-4,6-benzylidene-D-mannose (IV). On the other hand, a similar deamination of methyl 2-amino-4,6-benzylidene-2-desoxy-α-D-altroside hydrochloride (V) with sodium nitrite gave methyl 2,3-anhydro-4,6-benzylidene-α-D-alloside (VI) in a good yield. Thus, the deamination of (V) gave (VI) without any change in glycosidic bond, contrary to the similar reaction of (III) which resulted in simultaneous cleavage of glycosidic bond and formation of anhydro ring.

Recently, communications[6] on the similar deamination reactions of *ortho*-amino alcohol were published. Thus, from 2-aminocyclohexanol (VIII) according to the *cis*-equatorial and *trans*-axial conformations of amino and hydroxyl groups of (VII), cyclopentylaldehyde and 1,2-anhydrocyclohexanol were respectively formed.

Irvine and Hynd attributed the cleavage of glycosidic bond in methyl D-glucosaminide derivatives during deamination to its betain-like structure between amino and glycosidic groups. However, it is presumed that methyl D-glucosaminide derivatives generally have C-1-conformation,[7] and therefore (III) has an equatorial amino group, and the conformation of this compound is fixed throughout the course of the deamination reaction by its *trans*-ring junction of benzylidene group. Accordingly, the deamination of (III) should cause a ring contraction as shown in Chart 1 and hemiacetal produced should easily be hydrolysed to give aldehydic group.

Or : Oxygen involved in pyranose ring

Chart 1.

In the case of (V), which was derived from methyl 4,6-benzylidene-α-D-glucoside having C-1-conformation[8] and no conformational change is conceivable in each step of synthesis, the arrangement of its amino group at C-2 and hydroxyl group at C-3 are both axial in *trans* orientation. Thus, the mechanism of the reaction which occurred during the deamination of (V) to produce an ethylene oxide ring between C-2 and C-3 positions would be represented by Chart 2.

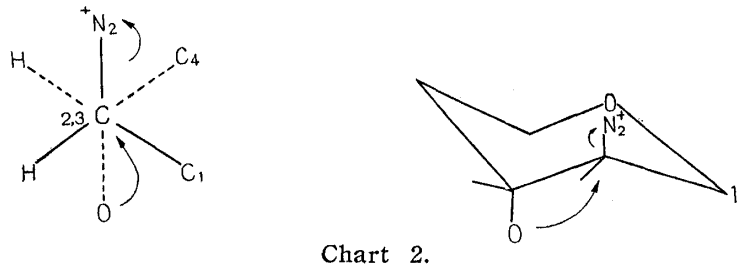


Chart 2.

Experimental

Methyl 4,6-Benzylidene-N-ethoxycarbonyl-β-D-glucosaminide (II)—To 25 g. of freshly distilled benzaldehyde, 5.0 g. of methyl N-ethoxycarbonyl-β-D-glucosaminide (I) and 10 g. of $ZnCl_2$ were added. After shaking for 7 hr., the resulting syrup was poured into water, the precipitate that formed

6) G. E. McCasland : J. Am. Chem. Soc., **73**, 2293(1951); **77**, 1105(1955).
7) G. Fodor, L. Ötväs : Chem. Ber., **89**, 701(1956).
8) R. E. Reeves : "Advances in Carbohydrate Chemistry," **6**, 107(1951).

was collected, and washed with water. Recrystallisation from EtOH gave white needles, m.p. 228°; $[\alpha]_D^{21}$ −32.35°(c=1.15, $CHCl_3$). Yield, 5.5 g. *Anal.* Calcd. for $C_{17}H_{23}O_7N$: C, 57.76; H, 6.56; N, 3.97. Found : C, 57.03; H, 6.66; N, 3.78.

Methyl 4,6-Benzylidene-β-D-glucosaminide (III)—To 50 cc. of 50% EtOH, 0.9 g. of (II) and 0.9 g. of $Ba(OH)_2$ were added and the mixture was heated for 2 hr. in a sealed tube at 130~140°. After cool, the precipitate ($BaCO_3$) was filtered off, washed with $CHCl_3$, and the filtrate was extracted with $CHCl_3$. The washings and extracts were combined, dried over Na_2SO_4, and evaporated to dryness *in vacuo*. The residue was recrystallised from 30% MeOH to white needles, m.p. 168~169°. $[\alpha]_D^{22}$ −72.25°(c=2.27, $CHCl_3$). Yield, 0.41 g. (Irvine and Hynd gave m.p. 168°, $[\alpha]_D^{20}$ −72.93°(MeOH)). Hydrochloride : The free base was dissolved in EtOH, EtOH containing equiv. amount of HCl was added, and ether was added to precipitate white needles, m.p. 217~218°(decomp.); $[\alpha]_D^{22}$ −64.04°(c=3.56, H_2O) (Irvine and Hynd gave m.p. 205°(decomp.), $[\alpha]_D^{20}$ −54.43°(MeOH)). *Anal.* Calcd. for $C_{14}H_{19}O_5N \cdot HCl$: C, 52.89; H, 6.35; N, 4.41. Found : C, 52.64; H, 5.58; N, 4.17.

2,5-Anhydro-4,6-benzylidene-D-mannose (IV)—1.0 g. of the hydrochloride of (III) was dissolved in a minimum amount of cold water, a solution of 0.9 g. of AcONa and 0.5 g. of $NaNO_2$, dissolved in a minimum amount of cold water was added, and after addition of a few drops of AcOH, this mixture was left to stand for 2 hr. in an ice bath with occasional stirring and kept aside overnight at room temperature. The white amorphous precipitate that formed was collected and washed with hot water. Yield, 0.4 g. No suitable solvent for the recrystallisation of the compound was found, but above isolated precipitate was almost pure. The compound had no methoxyl group and reduced Fehling's solution. m.p. 145~147°, $[\alpha]_D^{21}$ −22.52°(c=1.03, Me_2CO) (Irvine and Hynd gave m.p. 144~145°; $[\alpha]_D^{20}$ −22.43°(Me_2CO)). *Anal.* Calcd. for $C_{13}H_{14}O_5$: C, 62.37; H, 5.64. Found : C, 61.13; H, 5.49.

Periodate Oxidation of (IV)—To a solution of 70.0 mg. of (IV) in 10 cc. of EtOH, 5 cc. of 0.25*M* $NaIO_4$ solution was added and this mixture was brought exactly to 25 cc. by the addition of distilled water. On the other hand, the blank solution was prepared by mixing 10 cc. of EtOH, 5 cc. of 0.25*M* $NaIO_4$ solution, and 10 cc. of distilled water. To 1 cc. of each of these two solutions, 10 cc. of distilled water, 10 cc. of boric acid-borax buffer, and 0.2 g. of KI were added, and each mixture was titrated with 0.1*N* As_2O_3 solution in the usual way. Each mixture consumed 0.97 cc. of 0.1*N* As_2O_3 solution. This means that there is no consumption of periodate.

Hydrolysis of (IV)—0.1 g. of (IV) was dissolved in 20 cc. of 50% EtOH, containing 0.5% of HCl. The odor of BzH was immediately detected and the solution was maintained at 60° for 16 hr. The solution was concentrated *in vacuo* to one-half the original volume, extracted several times with ether to remove BzH, and the evaporation was continued further to a small volume.

Paper Chromatography of the Hydrolysate—The hydrolysate obtained above was tested by paper chromatography and results are summarized in Table I.

Table I. Rf Values of Hydrolysate and Related Sugars
(Toyo Roshi No. 50)

	Solvent (1)	Solvent (2)		Solvent (1)	Solvent (2)
Hydrolysate of (IV)	0.54	0.47	D-Mannose	0.32	0.26
D-Chitose	0.54	0.47	D-Glucose	0.28	0.21

(1) *n*-BuOH-pyridine-H_2O (5:3:1) (2) *n*-BuOH-AcOH-H_2O (4:1:1)
Color reagent : Aniline hydrogen phthalate

Paper Ionophoresis of the Hydrolysate—The hydrolysate obtained above was tested by paper ionophoresis and results are summarized in Table II.

Table II. Migration Distance of Hydrolysate and Related Sugars
(Toyo Roshi No. 50; 1% borax, 600 V, 1.5 hr.)

	Distance (mm.)		Distance (mm.)
Hydrolysate of (IV)	+29	D-Mannose	+47
D-Chitose	+29	D-Glucose	+56

Methyl 2,3-Anhydro-4,6-benzylidene-α-D-alloside—To a solution of 0.10 g. of methyl 2-amino-4,6-benzylidene-2-desoxy-α-D-altroside hydrochloride[9] (V) in 1 cc. of water, 0.05 g. of $NaNO_2$ in a minimum amount of cold water was added and the mixture was left to stand at room temperature for 2 hr. The white needles that precipitated were collected, washed with water, and recrystallised from hydr. Me_2CO, m.p. 198~200°; $[\alpha]_D^{15}$ +140°(c=2.67, $CHCl_3$). In admixture with authentic sample,[10] no depression of m.p. was observed. Yield, 0.07 g.

9) W. H. Myers, G. J. Robertson : J. Am. Chem. Soc., **65**, 8(1943).
10) F. G. Young, R. E. Elderfield ; J. Org. Chem., **7**, 241(1942).

Summary

Methyl 4,6-benzylidene-β-D-glucosaminide hydrochloride (III) was synthesized by a new method. Deamination of (III) with sodium nitrite in weak acetic acidity resulted in facile cleavage of glycosidic bond and simultaneous dehydration between C-2 and C-5 positions to form 2,5-anhydro-4,6-benzylidene-D-mannose. On the other hand, deamination of methyl 2-amino-4,6-benzylidene-2-desoxy-α-D-altroside hydrochloride (V) with sodium nitrite afforded methyl 2,3-anhydro-4,6-benzylidene-α-D-alloside (VI) without any change in glycosidic bond. The mechanisms of these deamination reactions were discussed.

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53. Zen-ichi Horii, Yasumitsu Tamura, Kunihiko Tanaka, and Takefumi Momose: Studies on Oxytetracycline and Related Compounds. X.*1 Synthesis of Terranaphthoic Acid.

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In previous papers concerning synthetic studies on the degradation products of oxytetracycline, the syntheses of 7-hydroxy-3-methylphthalide,[1] 6-acetylsalicylic acid,[2] decarboxyterracinoic acid,[3] and terracinoic acid[4] were described. The present report describes the synthesis of terranaphthoic acid.

Terranaphthoic acid is one of the most important degradation products of oxytetracycline and its chemical structure was shown to be 1,8-dihydroxy-4-methyl-3-naphthoic acid by Hochstein *et al.*[5] It would be interesting to synthesize terranaphthoic acid and to confirm the chemical structure by direct comparison of natural terranaphthoic acid with the synthetic material, because terranaphthoic acid plays an important role in the structural determination of oxytetracycline. However, its synthesis has not yet been accomplished.

As an exploratory experiment for the synthesis of terranaphthoic acid, the preparation of 1-hydroxy-4-methyl-3-naphthoic acid, i.e. 8-desoxyterranaphthoic acid, was carried out starting from 2-ethoxycarbonyl-3-methylindan-1-one. Based on this preliminary experiment, attempt was made to synthesize terranaphthoic acid from 2-ethoxycarbonyl-7-methoxy-3-methylindan-1-one and the acid (1,8-dihydroxy-4-methyl-3-naphthoic acid) was obtained without any difficulty during the course of processing.

Synthesis of 1-Hydroxy-4-methyl-3-naphthoic Acid (8-Desoxyterranaphthoic Acid)

2-Ethoxycarbonyl-3-methylindan-1-one (IIIa) and its 7-methoxy derivative (IIIb) were

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*1 Part IX: This Bulletin, **5**, 6(1957).

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1) Z. Horii, K. Okumura, Y. Tamura: Yakugaku Zasshi, **73**, 526(1953); F. A. Hochstein, R. Pasternack: J. Am. Chem. Soc., **73**, 5008(1951); **74**, 3905(1952); S. Kushner, J. H. Bothe, J. Morton, J. Petisi, J. H. Williams: *Ibid.*, **74**, 3710(1952).

2) Z. Horii, Y. Tamura, K. Okumura, H. Kugita: Yakugaku Zasshi, **74**, 466(1954); R. Kuhn, K. Dury: Chem. Ber., **84**, 848(1951).

3) L. H. Conover: J. Am. Chem. Soc., **75**, 4017(1953); Z. Horii, Y. Tamura, H. Kugita, K. Okumura: Yakugaku Zasshi, **74**, 150(1954).

4) Y. Tamura: Yakugaku Zasshi, **76**, 739(1956).

5) F. A. Hochstein, P. P. Regna, K. J. Brunings, R. B. Woodward: J. Am. Chem. Soc., **74**, 3706(1952); F. A. Hochstein, *et al.*: *Ibid.*, **75**, 5455(1953).