147. A New Base-induced Rearrangement of Hexopyranuronic Acid Derivatives with Solvent Participation[1])

Preliminary Communication

by **Joseph Kiss** and **Wolf Arnold**

F. Hoffmann-La Roche & Co., Ltd., Pharmaceutical Research Department and Central Research Units, CH-4002 Basel

Dedicated to Professor *George Büchi* on the occasion of his 60th birthday

(10.IV.81)

Summary

Uronates (as pyranosides or furanosides) bearing good leaving groups (mesylates, tosylates, phosphates, *etc.*) in β- and γ-position to the alkoxycarbonyl group (*e.g.* **1**) give the epimeric β,γ-unsaturated α-alkoxy-β,γ-dideoxy-uronates **4** by treatment with organic or inorganic bases in alcoholic solution.

This new rearrangement of carbohydrates was exemplified with a D-glucosamine derivative: an alcoholic solution of methyl [*O*(1)-benzyl-2-*C*-benzyloxyformamido]-2-deoxy-3,4-bis[*O*(methylsulfonyl)]-α-D-glucopyranosiduronate **1** in the presence of KOH, DBU, or strong alkaline anion exchange resins gave the C(5)-epimeric mixture of methyl [benzyl-2-[*C*-(benzyloxy)formamido]-2,3,4-trideoxy-5-alkoxy-α-D-glycero-hex-3-enopyranosid]uronates (**4a–e**). The reaction took place with stoichiometric solvent participation using primary, secondary or tertiary alcohols. Other polyfunctional compounds having an alcoholic hydroxyl group can also participate in this reaction. Compounds obtained have been characterized in the form of their crystalline amides.

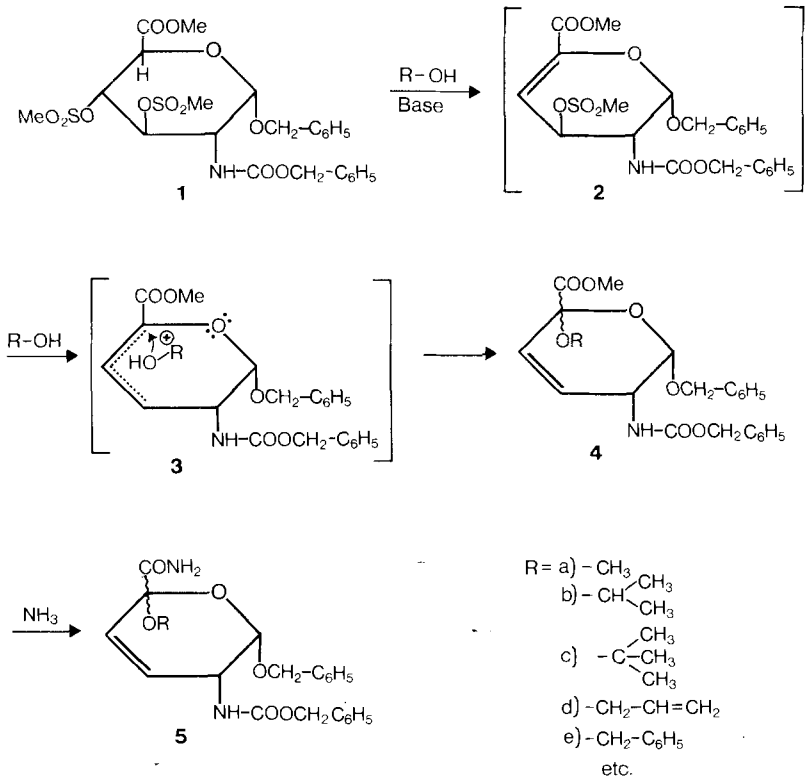
A large number of papers deal with the transformations of sulfonates in the pyranoside and also in the furanoside series[2]), but only a few examine the chemical properties of *O*-alkoxysulfonyl-uronates [2]. The reactivity of these sulfonates is strongly influenced by the carboxyl group, and surprising transformations can arise from this interference of reactivity. These transformations are not restricted solely to the *O*-alkoxysulfonyluronates: uronates with other good leaving groups (such as phosphates [3], glycopyranosides [4], *etc.*) give also similar transformations.

On investigating the reactions of *O*-alkoxysulfonyluronates, we found that 3,4-*O*,*O*-dimethanesulfonylated D-glucosamineuronates gave a new class of carbo-

[1]) Enolacetal Sugars, Part IX. Part VIII see: [2b].

[2]) For a survey on this subject see *e.g.* [1].

0018-019X/81/5/1566-04$01.00/0



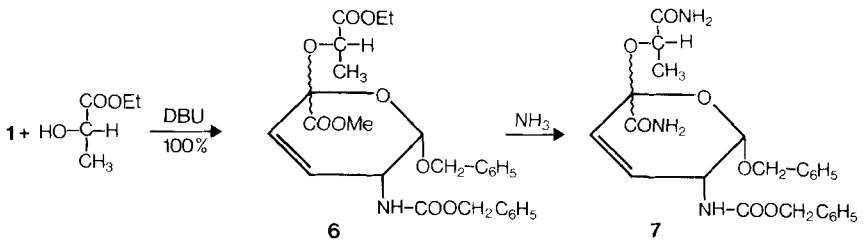
hydrates by treating the sulfonates with a strong base in alcoholic solution at room temperature. The resulting compounds were the C(5)-epimeric 2,3,4-trideoxy-5-alkoxy-2-amino-hex-3-enopyranosiduronate derivatives **4**, which were obtained in nearly theoretical yield.

By methanesulfonylation of methyl [*O*(1)-benzyl-2-*C*-(benzyloxy)formamido]-2-deoxy-α-D-glucopyranosiduronate using methanesulfonyl chloride in pyridine one obtained the starting material **1** (m.p. 145–146°, $[\alpha]_D^{25} = +100°$ ($c = 0.66$, $CHCl_3$)).

The title reaction can be carried out under very simple conditions: for example, compound **1** was dissolved in 10–20 parts of methanol and allowed to stay in the presence of 2.5–3.0 mol of methanolic KOH or DBU (= 1,5-diazabicyclo[5.4.0]-undec-5-ene) at room temperature until all starting material was consumed (monitoring by TLC. in ethyl acetate or in ethyl acetate/hexane; detection by spraying with sulfuric acid).

Bases for inducing this rearrangement other than KOH or DBU can also be used, such as alkali and alkaline earth hydroxides, trialkylamines, alkali alkoxides, anion exchange resins, *etc.*

The isolation of the new compounds is simple: after evaporation of the solvent, the excess of the base was removed by washing with diluted mineral acid (*e.g.* in



methylene chloride solution), and the C(5)-epimeric mixture **4** was obtained in nearly theoretical yield, *e.g.* the C(5)-epimeric 5-methoxy compound **4a**.

Data of compound **4a**. $[\alpha]_D^{25} = +19.8°$ ($c = 0.74$, $CHCl_3$). – ^{1}H-NMR. (100 MHz, $CDCl_3$): mixture of 2 components. *Data of the main component* (*ca.* 80%): 3.35 (*s*, CH_3O–C(5)); 3.71 (*s*, $COOCH_3$); 4.45 (*m*, H–C(2)); 4.62 and 4.91 (*AB*-pattern, $J_{gem} = 12$ Hz, $C_6H_5CH_2O$–C(1)); 5.08 (*s*, $COOCH_2C_6H_5$); 5.1 (br., HN–C(2)); 5.13 (*d*, $J(1,2) = 3.6$, H–C(1)); 5.94 (*d*×*d*, $J(3,4) = 10$, $J(2,4) = 1.2$, H–C(4)); 6.07 (*d*×*d*, $J(2,3) = 3$, H–C(3)); 7.28 and 7.30 (2 *s*, 2 C_6H_5).

$C_{23}H_{25}O_7N$	Calc.	C 64.63	H 5.90	N 3.28	OCH_3 14.52%
(427.45)	Found	„ 64.49	„ 5.90	„ 3.12	„ 14.35%

By treating of **4a** with anhydrous NH_3 in methanol the amide **5a** was received. – *Data of compound* **5a**. M.p. 157–159°, $[\alpha]_D^{20} = +7{,}0°$ ($c = 0.1$, CH_3OH). – ^{1}H-NMR. (270 MHz, $CDCl_3$): mixture of 2 components. – *Data of the main component* (*ca.* 90%): 3.33 (*s*, OCH_3); 4.32 (*m*, H–C(2)); 4,73 and 4.91 (*AB*-pattern, $J_{gem} = 12.5$, $C_6H_5CH_2O$–C(1)); 5.12 (*s*, $COOCH_2C_6H_5$); 5.17 (*d*, $J(1,2) = 3$, 1 H–C(2)); 5.28 (*d*, $J = 9$, HN–C(2)); 6.0 and 6.7 (br., $CONH_2$); 6.0 (*d*, $J(3,4) = 9.5$, H–C(4)); 6.08 (*d*×*d*, $J(2,3) = 5$, H–C(3)); 7.33 (*s*, 2 C_6H_5).

$C_{22}H_{24}O_6N_2$	Calc.	C 64.07	H 5.87	N 6.79	OCH_3 7.52%
(412.44)	Found	„ 63.79	„ 5.83	„ 6.76	„ 7.76%

The reaction described above has also been carried out with secondary (*e.g.* 2-propanol) and tertiary alcohols (*e.g.* *t*-butyl alcohol) resulting in the corresponding C(5)-epimeric 2,3,4-trideoxy-5-isopropoxy (or tert. butoxy)-2-amino-hex-3-enopyranosiduronate derivative (**4b** and **4c**).

4c: $[\alpha]_D^{20} = +36.6°$ ($c = 0.47$, $CHCl_3$). **4b** was transformed into the corresponding amide **5b**: m.p. 107–109°, $[\alpha]_D^{20} = +7.0°$ ($c = 0.1$, CH_3OH); similarly, **4c** gave the amide **5c**: m.p. 105–106°, $[\alpha]_D^{20} = +9.0°$ ($c = 0.1$, $CHCl_3$).

Allyl and benzyl alcohols react similarly according to the above reaction scheme giving **4d** and **4e**.

Hydroxy compounds other than simple alcohols can also be used in this reaction, *e.g.* ethyl (–)-L-lactate gave the corresponding 5-substituted 3,4-unsaturated glucuronide derivative **6**: $[\alpha]_D^{20} = -14.6°$, $[\alpha]_{365}^{20} = -64.3°$ ($c = 0.26$, $CHCl_3$);

$C_{27}H_{31}O_9N$	Calc.	C 63.15	H 6.08	N 2.73%
(513.54)	Found	„ 63.25	„ 6.22	„ 2.94%

The corresponding diamide 7 was obtained with anhydrous NH_3 in methanolic solution at room temperature.

Data of compound **7**. M.p. 175–176°, $[\alpha]_D^{20} = -13.2°$, $[\alpha]_{365}^{20} = -33.6°$ ($c = 0.14$, CH_3OH). – ^{1}H-NMR. (80 MHz, $CDCl_3$): 1.41 (*d*, $J = 7$, CH_3CH); 4.23 (*qa*, $J = 7$, CH_3CH); 4.35 (*m*, H–C(2)); ~4.7 and ~4.9 (*AB*-pattern, $J_{gem} = 13$, $C_6H_5CH_2O$–C(1)); 5.15 (*s*, $COOCH_2C_6H_5$); ~5.16 (*d*, $J \sim 2$–3, H–C(1)); 5.3

(br. *d*, $J \sim 8$, HN–C(2)); 5.7 and 5.96 (br., $CONH_2$); ~6.08 (*d*, $J(3,4) = 11$, 4 CH); 6.2 (*d* × *d*, $J(2,3) = 3.5$, H–C(3)); 6.83 (br., $CONH_2$); 7.38 (~*s*, 2 × C_6H_5).

$C_{24}H_{27}O_7N_3$ (469.49) Calc. C 61.40 H 5.80 N 8.95% Found C 61.27 H 5.78 N 8.82%

Although the reaction mechanism of the above described transformation has not yet been investigated thoroughly, we believe however (on the basis of our previous experiments [2a]) that the first step is the enolacetal forming β-elimination giving the reactive intermediate **2**. The sulfonate of the latter intermediate is assumed to be in a highly activated position: in the neighbourhood of a cyclic enolacetal O-atom and moreover in an allylic and vinylogous (α)-position to the uronate alkoxycarbonyle group, to give in alkaline medium the hypothetical mesomeric system **3**. Nucleophilic attack of the solvent O-atom at position 5 of the cation **3** stabilizes this system under formation of a new C,O-linkage and the 3,4 double bond.

The above described class of unsaturated carbohydrates seems also to be of preparative interest – *inter alia* – because two epimeric centers are present in one hexopyranuronate ring. In addition the functionalization of the unsaturated linkage [6] of the compound **4** proved to be easy to give various 3,4-substituted deoxy sugar derivatives, and also 5-ulosonates.

Some further types of β-eliminative rearrangement on pyranoside and furanosiduronates, and also on oligo- and polysaccharides, possessing pyranuronate residues[3]) will be described separately.

REFERENCES

[1] *L. Goodman*, Adv. Carbohydrate Chem. *22*, 109 (1067); *D.H. Ball & F.W. Parrish*, ibid. *24*, 139 (1969).

[2] a) *J. Kiss*, Adv. Carbohydrate Chem. Biochem. *29*, 229 (1974); b) *J. Kiss & P. Taschner*, J. Carbohyd. Nucleosides. Nucleotides *1*, 279 (1974).

[3] *J. Kiss & K. Noack*, Carbohyd. Res. *16*, 245 (1971).

[4] *J. Kiss*, Tetrahedron Lett. *1970*, 1983.

[5] *J. Kiss & F. Burkhardt*, Helv. Chim. Acta *52*, 2622 (1969); *K. Heyns & H. Paulsen*, Angew. Chem. *69*, 600 (1957).

[6] *S. Umezawa, T. Tsuchiya & Y. Okazaki*, Bull. Chem. Soc. *44*, 3494 (1971).

[7] *G.O. Aspinall*, 'Polysaccharides', Pergamon Press, Oxford 1970, pp. 122–124.

[3]) 3,4-Di-*O*-glycosyl-hexopyranuronate sugar units can be found *e.g.* in natural glucuronates [7].