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Note

On the catalysis of the Amadori rearrangement

J. Yoshimura, M. Funabashi,
Laboratory of Chemistry for Natural Products, Tokyo Institute of Technology, Meguroku, Tokyo (Japan)

and H. Simon
Chemisches Institut der Fakultät für Landwirtschaft und Gartenbau Weihenstephan, Technische Hochschule München, D 8050 Freising-Weihenstephan (Deutschland)

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Catalysis of the Amadori rearrangement[1] has been effected by a variety of acids[2-4], such compounds as ethyl malonate or phenylacetone (which contain activated methylene groups[5]), and tertiary amine salts[6]. A mechanism involving *N*-protonation of the glycosylamine, followed by prototropic shifts and loss of a proton from the tautomeric cation, has been proposed[3,7]. Other suggested mechanisms involve addition of the proton to the glycosylamine ring oxygen[8], and rearrangement of the Schiff's base of 3,4:5,6-tetra-*O*-benzoyl-*aldehydo*-D-glucose and *p*-toluidine through the corresponding 1,1-bis(*p*-toluidino) derivative. By tracer techniques, it was proved, however, that this mechanism is not valid in the case of glycosylamines having free hydroxyl groups[10].

We now report that complexes of amines with such Lewis acids as boron trifluoride and its derivatives accelerate the rearrangement, and that 1,2:5,6-di-*O*-isopropylidene-D-*arabino*-hex-3-ulose and acetoin also react with amines and different catalysts in an Amadori rearrangement.

The rates of the rearrangements of 4,6-*O*-benzylidene-*N*-phenyl- (**1**) and -*N*-(*p*-tolyl)-D-glucosylamine (**2**) in absolute *p*-dioxane at 85° in the presence of different catalysts were measured by titration with Tillman's reagent[6] under a nitrogen atmosphere. In the case of an acid–base-catalyzed rearrangement, the rate should be accelerated by the addition compounds of amines with Lewis acids. As shown in Fig. 1, triethylborane has no effect, whereas difluoro(phenyl)borane shows a weaker catalytic activity than acetic acid. The first-order rate constant of the rearrangement of glycosylamine **2** was increased from $4.2 \times 10^{-4}\ \mathrm{min}^{-1}$ to 9.0 and to $12.5 \times 10^{-4}\ \mathrm{min}^{-1}$ in the presence of difluoro(phenyl)borane by addition of pyridine and triethylamine, respectively. The rate constant ($1.3 \times 10^{-3}\ \mathrm{min}^{-1}$) for compound **1** in the presence of acetic acid was increased about 1.3 times by the addition of aniline, pyridine, or triethylamine. The linearity between the amount of product formed and the reaction time indicates that the simultaneous destructive reactions[6] are essentially being supressed under the conditions used, especially in the initial reaction stage.

As shown in Fig. 2, boron trifluoride and ethoxydifluoroborane showed stronger

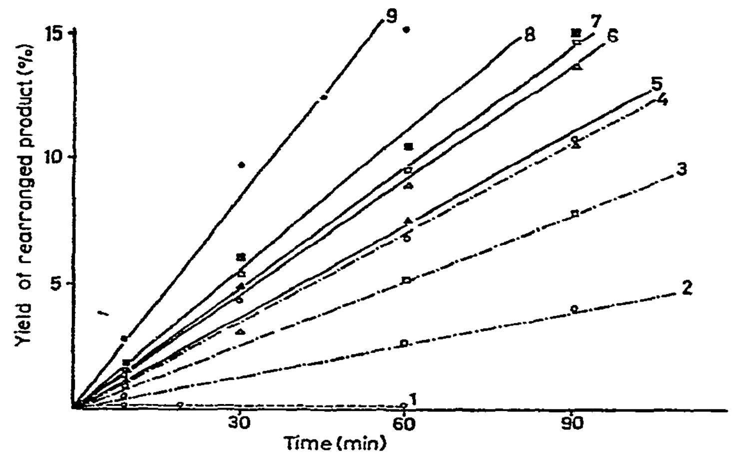


Fig. 1. Amadori rearrangement of 2 mmoles of **1** (lines 5–9) and **2** (lines 1–4) in 50 ml of *p*-dioxane at 85 ±0.5° in the presence of (1) 1 mmole of triethylborane; (2) 3 mmoles of difluoro(phenyl)-borane; (3) 9 mmoles of pyridine in addition to (2); (4) 3 mmoles of triethylamine in addition to (2); (5) 1 mmole of acetic acid; (6) 3 mmoles of triethylamine in addition to (5); (7) 4 mmoles of pyridine in addition to (5); (8) 5 mmoles of aniline in addition to (5); (9) 2 mmoles of acetic acid.

catalytic action than acetic acid in the initial reaction stage, but color formation occurred due to the destruction of glycosylamine **2** and the product. The addition of pyridine, however, caused a decrease in both the initial reaction and decomposition

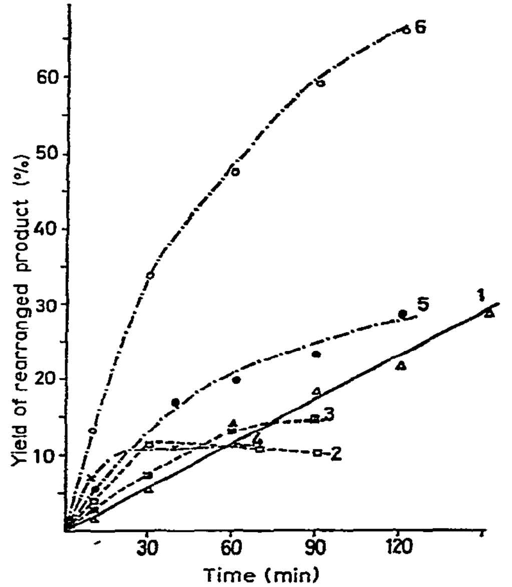
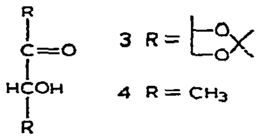


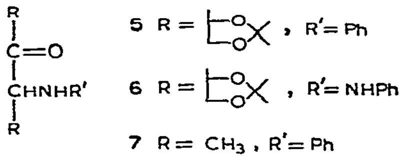
Fig. 2. Amadori rearrangement of 2 mmoles of **2** in 50 ml of *p*-dioxane at 85 ±0.5° in the presence of (1) 0.5 mmole of acetic acid; (2) 0.2 mmole of boron trifluoride; (3) 0.4 mmole of boron trifluoride and 2 mmoles of pyridine; (4) 0.5 mmole of ethoxydifluoroborane; (5) 4.75 mmoles of pyridine in addition to (4); (6) 1.7 mmoles of triethylamine in addition to (4).

rates. Triethylamine showed a remarkable acceleration of the initial rate and the suppression of decomposition reactions. From a consideration of the results mentioned above, it seems most reasonable to conclude that the Amadori rearrangement is an acid–base-catalysed reaction in which the balance of the acidity and basicity in the reaction system controls simultaneous and consecutive reactions.

On the other hand, the Amadori rearrangement is considered to be general in the reaction of α-hydroxycarbonyl compounds with amines, wherein a carbonyl group is generated in place of an α-hydroxyl group. Such a structural change has been conclusively proved in the reaction of benzoin[11] and ketoses[12] with amines. Moreover, Paulsen *et al.*[13] reported that 5-amino-5-deoxy-D-xylose rearranges easily to 1,5-dideoxy-1,5-imino-D-*threo*-pentulose hydrate through a cyclic Schiff's base structure in a neutral or acidic solution. In the course of a study of the dimerisation of *N*-arylaldimines[14], the authors obtained evidence that the Amadori rearrangement occurs with 1,2:5,6-di-*O*-isopropylidene-D-*arabino*-hex-3-ulose (3) in the reaction with amines.

By partial acetylation of 1,2:5,6-di-*O*-isopropylidene-D-mannitol, we obtained the corresponding monoacetate which was oxidized with methyl sulfoxide and acetic anhydride[15] to the 4-*O*-acetyl derivative of compound **3**, which was then deacetylated with methanolic ammonia. Because of its instability, compound **3** was used without further purification. Condensation of ketose **3** with an excess of aniline or phenylhydrazine in methanol, in the presence of ammonium chloride or acetic acid, followed by chromatography on silica gel, gave the corresponding 4-anilino-4-deoxy (**5**) or 4-deoxy-4-phenylhydrazino derivatives (**6**). Similar condensation of acetoin (**4**) and two molar equivalents of aniline gave 3-anilino-2-butanone (**7**). The structures of compounds **5**, **6**, and **7** were ascertained by the characteristic i.r. absorptions of the carbonyl group and the hydrogen atom attached to nitrogen. Direct condensation of acetoin and excess of aniline in the presence of boron trifluoride, under a nitrogen atmosphere, at higher temperature afforded *N*-(3-anilino-2-butylidene)aniline (the disubstituted derivative), which was gradually oxidized by air to the Schiff's base of biacetyl. These results, together with Carson's observation[16] that the biacetyl Schiff's base is produced in the reaction of acetoin with cyclohexylamine, indicate that other examples of the Amadori rearrangement of α-hydroxycarbonyl compounds could result from suitable selection of reaction conditions.





EXPERIMENTAL

Melting points are uncorrected. Solutions were evaporated under diminished pressure at a bath temperature not exceeding 40°. Optical rotations were measured in a 0.5-dm tube. Triethylborane[17], difluoro(phenyl)borane[18], and ethoxydifluoroborane[19] were prepared according to the literature procedures. Boron trifluoride etherate was a commercial product. 4,6-*O*-Benzylidene-*N*-phenyl-D-glucosylamine[20] had m.p. 145.5–147°, $[\alpha]_D$ −75.2° (*c* 0.5, *p*-dioxane), and the corresponding *N*-(*p*-tolyl) derivative had m.p. 144.5–145°, $[\alpha]_D$ −89° (*c* 0.5, pyridine); lit.[21] m.p. 142–143°.

Measurement of the rate of the Amadori rearrangement. — A solution of glycosylamine **1** or **2** (2 mmoles) in absolute *p*-dioxane[22] (50 ml) was kept at 85 ±0.5° under dry nitrogen. After addition of the catalysts, a 5-ml aliquot was transferred at intervals (usually, 10, 30, 60, 90, and 120 min) to a flask which was immersed in an ice–water bath. The surface of the solution was covered with nitrogen, 5 ml of 0.2N sodium hydroxide was added, and the solution was then immediately titrated with dichlorophenyl-indophenol (Tillman's reagent)[6]. The mean value of two titrations, differing usually less than 1%, was adopted. The Tillman's reagent was checked before each experiment by titration of 1 mg of the standard sample of 1-anilino-4,6-*O*-benzylidene-1-deoxy-D-fructose[4] or 4,6-*O*-benzylidene-1-deoxy-1-(*p*-toluidino)-D-fructose[21]. The results were shown in Figs. 1 and 2.

*3-O-Acetyl-1,2:5,6-di-O-isopropylidene-*D*-mannitol.* — Acetic anhydride (6.5 ml, 69 mmoles) was added dropwise during 25 min to a solution of 1,2:5,6-di-*O*-isopropylidene-D-mannitol (18 g, 69 mmoles) in pyridine (30 ml). After standing overnight at room temperature, the reaction mixture was poured into ice–water. The resulting crystals (5.0 g; 20%), m.p. 125°; lit.[23] m.p. 123°; were the corresponding diacetate. The filtrate was extracted with methylene chloride, and the extract was evaporated. Distillation of the residue gave the title compound (14.5 g, 66.7%), b.p. 144–150°/4 mm, $[\alpha]_D^{28}$ 2.4° (*c* 3.34, methanol).

Anal. Calc. for $C_{14}H_{24}O_7$: C, 55.25; H, 7.95. Found: C, 54.94; H, 8.13%.

*4-O-Acetyl-1,2:5,6-di-O-isopropylidene-*D-arabino*-hex-3-ulose* (**3**). — A solution of the above monoacetate (14.5 g, 48 mmoles) in methyl sulfoxide (150 ml) and acetic anhydride (100 ml) was kept overnight at room temperature, poured into ice–water, and neutralized with sodium hydrogen carbonate. The solution was extracted with methylene chloride, and the extract was washed twice with water, dried, and evaporated. Distillation of the resulting syrup gave a fraction (9.3 g, 64.2%), b.p. 126–128°/1 mm, $[\alpha]_D^{28}$ −5.1° (*c* 1.77, methanol), which showed no i.r. absorption band for hydroxyl groups.

Anal. Calc. for $C_{14}H_{22}O_7$: C, 55.62; H, 7.34. Found: C, 55.50; H, 7.86%.

*4-Anilino-4-deoxy-1,2:5,6-di-O-isopropylidene-*D-arabino- *(and/or* D-lyxo)*-hex-3-ulose* (**5**). — A solution of the above hexulose (9.3 g, 38 mmoles) in 60 ml of methanol saturated with dry ammonia was kept for 2 h at room temperature, and evaporated. The syrup obtained was immediately mixed with toluene (30 ml), aniline (7.8 g, 84 mmoles), and ammonium chloride (0.5 g), and the mixture was refluxed for 4 h and then evaporated. The resulting syrup was fractionated on a column packed with 150 g of silica gel (Wakogel 100) by eluting with benzene–acetone of successively increasing concentration in acetone. The fraction eluted with solvent ratios of 10:1 and 10:2 was rechromatographed in the same manner to give the title compound as a pale-brown syrup (2.4 g, 20.6%); t.l.c., R_F 0.42 (benzene–ligroin–acetone, 3:1:1); $[\alpha]_D^{22}$ $-44.5°$ (*c* 0.72, methanol); $\nu_{\max}^{\text{NaCl}}$ 3350 (N–H), 1742 and 1670 cm^{-1} (C=O).

Anal. Calc. for $C_{18}H_{25}NO_5 \cdot H_2O$: C, 58.20; H, 7.87; N, 4.07. Found: C, 58.50; H, 7.79; N, 3.77%.

*4-Deoxy-1,2:5,6-di-*O*-isopropylidene-4-phenylhydrazino-*D-arabino(*and/or* D-lyxo)-*hex-3-ulose* (6). — A solution of ketose 3 (2.5 g, 9.6 mmoles) and phenylhydrazine (3.1 g, 28 mmoles) in 10 ml of methanol was refluxed for 3 h in the presence of a few drops of acetic acid. The syrup obtained by evaporation was chromatographed on a silica gel column by elution, in turn, with benzene–ligroin, benzene, benzene–acetone, and acetone. Evaporation of the last fraction gave compound 6 as a pale-brown syrup (1.8 g, 54.5%); $[\alpha]_D^{22}$ $-70°$ (*c* 1.08, methanol); $\nu_{\max}^{\text{NaCl}}$ 3350 and 3250 (N–H), 1740 and 1680 cm^{-1} (C=O).

Anal. Calc. for $C_{18}H_{26}N_2O_5$: C, 61.70; H, 7.48; N, 8.00. Found: C, 61.40; H, 7.49; N, 8.12%.

3-Anilino-2-butanone (7). — A solution of acetoin (4.4 g, 50 mmoles), aniline (9.9 g, 106 mmoles), and one drop of boron trifluoride etherate in ethanol (30 ml) was refluxed for 2 h and evaporated. Distillation of the residual syrup gave compound 7 (2.7 g, 33.4%) as a pale-yellow liquid; b.p. 114–115°/1 mm; $\nu_{\max}^{\text{NaCl}}$ 3350 (N–H), 1710 and 1690 cm^{-1} (C=O).

Anal. Calc. for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.08. Found: C, 73.59; H, 8.36; N, 8.15%.

N-(3-Anilino-2-butylidene)aniline. — A mixture of acetoin (4.4 g, 50 mmoles), aniline (18.6 g, 200 mmoles), and one drop of boron trifluoride etherate was refluxed for 3 h under nitrogen, and immediately distilled to give the title compound as a pale-yellow liquid (2.9 g, 24.3%); b.p. 162–163°/2 mm; $\nu_{\max}^{\text{NaCl}}$ 3360 (N–H) and 1663 cm^{-1} (C=N).

Anal. Calc. for $C_{16}H_{18}N_3$: C, 80.63; H, 7.61; N, 11.76. Found: C, 80.06; H, 7.72; N, 11.67%.

Gradual oxidation of this liquid by air produced the Schiff's base of biacetyl[24], m.p. and mixed m.p. 138°.

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