Synthesis and structure of anhydrodimers of salicylaldehydes

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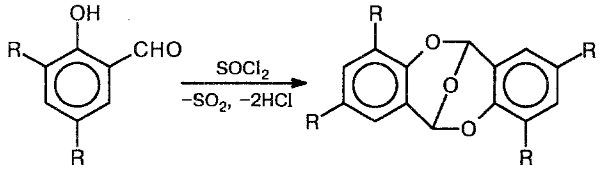
Anhydrodimers have been synthesized by reactions of salicylaldehyde and 3,5-di-*tert*-butylsalicylaldehyde with $SOCl_2$ or PCl_5. A mechanism of condensation has been proposed, and the molecular structure of dibenzo-2,6,9-trioxabicyclo[3.3.1]nona-3,7-diene has been determined by X-ray structural analysis.

Key words: salicylaldehydes, autoacetals, dibenzo-2,6,9-trioxabicyclo[3.3.1]nona-3,7-diene and its di(2,4-di-*tert*-butyl) derivative, thionyl chloride, low-nucleophilic medium, liquid phase, solid phase.

Aromatic aldehydes, including hydroxy-substituted aldehydes, are generally converted to the corresponding benzal chlorides (for example, 4-hydroxy-3,5-di-*tert*-butylbenzal chloride[1]) under the action of $SOCl_2$ and analogous reagents. The possibility of synthesizing benzal chlorides from *ortho*-hydroxy-substituted benzaldehydes is also beyond question. It is known that these compounds are postulated as intermediates in the synthesis of salicylaldehyde according to Reimer—Tiemann.[2] Formation of the corresponding benzal chlorides was observed in the reaction of 3,5-dibromosalicylaldehyde and its 4,6-dimethyl- and 4-methoxy-substituted analogs with PCl_5.[3] However, our attempts to synthesize benzal chlorides from salicylaldehyde (**1a**) and its 3,5-di-*tert*-butyl-substituted homolog (**1b**) under the action of $SOCl_2$ yielded products that contained neither halogen atoms nor hydroxyl groups and were identified as bicyclic anhydrodimers (autoacetals) (**2a,b**) (Scheme 1).

Scheme 1



1a,b **2a,b**

R = H (**a**), Me_3C (**b**)

Anhydrodimerization with the formation of **2** is a general phenomenon in chemistry of salicylaldehydes. An anhydrodimer was first prepared when a copper salt of salicylaldehyde was distilled;[4] later on, anhydrodimerization was repeatedly observed in reactions of salicylaldehydes with carboxylic acid anhydrides[5] and halides,[6] PCl_3 (see Ref. 3), and $POCl_3$ (see Ref. 8).

We have demonstrated that anhydrodimerizations of unsubstituted salicylaldehyde **1a** and of its di-*tert*-butyl-substituted analog **1b** differ substantially in rate. When **1a** reacts with an excess of $SOCl_2$, compound **2a** is formed nearly instantaneously. For the conversion **1b** → **2b**, more time is required (~20 h). Condensation of **1b** is best performed in a medium of $SOCl_2$ taken in a slight excess (~1 : 1.5). The use of other solvents (CH_2Cl_2 and benzene) inhibits the process to the point of its complete termination (ether). Concentrated H_2SO_4 and P_2O_5 are inefficient as condensing reagents. Derivatives of **1** with a protected hydroxyl group, for example *O*-acyl-substituted derivatives, lose the capacity for condensation.

Apparently, condensation proceeds as a stepwise process starting with the formation of the chlorosulfite of initial compound **1**. In the absence of an external competitor, the displaced hydroxyl group is accepted by the adjacent carbonyl group. The carbenium intermediate generated in this process reacts with the second aldehyde molecule to afford hemiacetal.

The next stages, which duplicate two previous stages, complete the formation of bicyclic system **2** (Scheme 2).

According to Scheme 2, a low nucleo(proto)philicity of the medium and a high concentration of **1** should favor this process. The role of concentration is confirmed, in particular, by data on the conversion of **1a** in an Ac_2O/H^+ medium, where anhydrodimerization was

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† Deceased.

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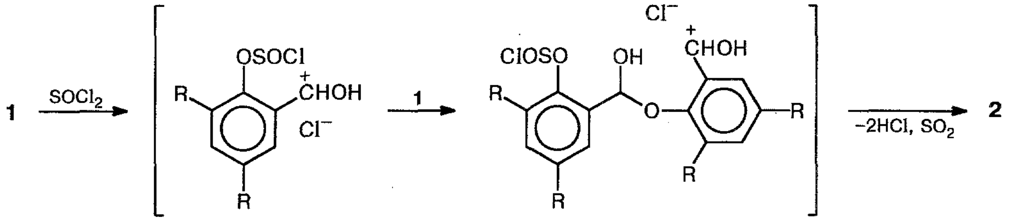
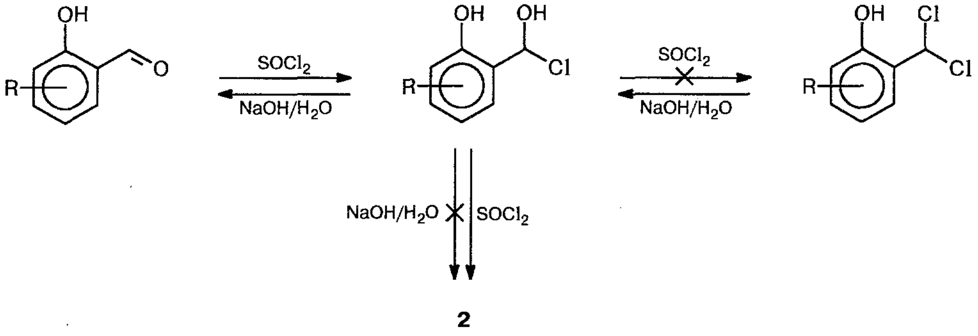
Scheme 2



Scheme 3



also observed.[5] It was established that formation of autoacetal **2a**, which occurs at a **1a** : Ac_2O ratio of 1 : 1, is inhibited when the reaction mixture is diluted; with a **1a** : Ac_2O ratio of 1 : 6, the only product of conversion of **1a** is 2-(diacetoxymethyl)phenylacetate. It is interesting to note that in the presence of inorganic acid, **1b** in Ac_2O undergoes no anhydrodimerization even with a **1b** : Ac_2O ratio of 1 : 1 (protective action of *tert*-butyl groups). In this case, 3,5-di-*tert*-butyl-*O*-acetylsalicylaldehyde is formed. Using **1b** as an example, it was demonstrated that autocondensation occurs under the action of PCl_5 in CH_2Cl_2 as well as in the solid phase (when a mixture of **1a** and PCl_5 is ground at 20 °C). The solid-phase occurrence of the process offers an alternative to the use of low-nucleophilic highly concentrated media. Previously, we observed an example of this kind with a solid-phase acid-catalyzed condensation of 2-hydroxy-3,5-di-*tert*-butylbenzyl alcohol to the corresponding dibenzyl ether.[9]

It is remarkable that when studying the Reimer—Tiemann reaction, intermediates of which are similar to the key intermediate compounds in the scheme of **1**→**2** conversion proposed by us (Scheme 3), we did not observe formation of compounds of type **2**.

Apparently, under conditions of this reaction, only solvolysis of intermediate benzylidene chloride with the participation of a nucleophilic medium occurs.

Therefore, analysis of the data in the literature and the results that we obtained demonstrate that condensation with the formation of **2** is possible only in a low-nucleophilic medium at rather high concentrations of **1**.

Though autocondensation of **1** has long been known,[4] the structure of anhydrodimers **2** was long based on data of elemental analysis and chemical conversions; the spectral characteristics of **2** have been obtained only rather recently.[10] We first performed X-ray structural analysis of anhydrodimer **2a** and confirmed the structure of dibenzotrioxabicyclo[3.3.1]nonadiene (Fig. 1, Tables 1 and 2) unambiguously. The dioxene cycles adopt a half-chair conformation: the O(1), C(6), C(1), and C(7) atoms lie in one plane; the C(7a) and O(2) atoms deviate from this plane in the opposite directions by −0.53 and 0.42 Å, respectively. Unfortunately, the poor quality of the crystals makes it impossible to discuss the values of bond lengths and bond angles in this structure in detail. In crystals of **2a**, a bifurcated hydrogen bond between the H(7) atom of the basis molecule and the O(1′) ($-x$, y, $1.5-z$) and O(2′) ($-x$, y, $1.5-z$) atoms was observed: O...H are 1.80(3) and 2.10(3) Å, respectively. In this work, compound **2b** was obtained for the first time.

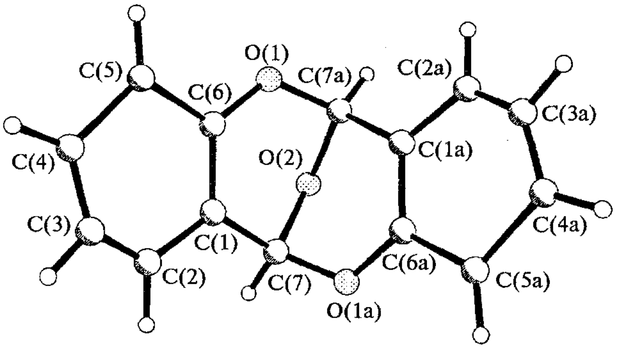


Fig. 1. Structure of **2a**.

Table 1. Atomic coordinates of nonhydrogen atoms ($\times 10^4$) in the structure of **2a**

Atom	*x*	*y*	*z*
O(1)	−746(7)	2424(7)	5692(9)
O(2)	0	3437(6)	7500(6)
C(1)	1571(8)	1959(7)	6974(9)
C(2)	2890(10)	1448(11)	7020(14)
C(3)	3121(13)	832(8)	6149(15)
C(4)	2416(12)	602(6)	4969(12)
C(5)	868(14)	1156(9)	4628(9)
C(6)	538(7)	1893(5)	5808(7)
C(7)	1270(16)	2709(12)	8135(10)

Table 2. Bond lengths and bond angles of the trioxabicyclononadiene fragment in the structure of **2a**

Bond	*d*/Å	Angle	φ/deg
O(1)—C(6)	1.342(9)	C(6)—O(1)—C(7a)	117.9(9)
C(1)—C(6)	1.355(9)	C(7)—O(2)—C(7a)	106.5(12)
O(1)—C(7a)	1.26(1)	C(6)—C(1)—C(7)	116.5(8)
C(1)—C(7)	1.47(2)	O(1)—C(6)—C(1)	124.3(7)
O(2)—C(7)	1.55(2)	O(2)—C(7)—C(1)	107.4(7)
		O(2)—C(7)—O(1a)	99.5(9)
		C(1)—C(7)—O(1a)	122.2(13)

Experimental

General procedure of synthesis of compounds 2a,b. A mixture of aldehyde **1** (5 mmol) and freshly distilled $SOCl_2$ (3 mL) was kept for 2 days at 20 °C. The reaction was monitored chromatographically. Then $SOCl_2$ was removed, the residue was extracted with hexane, and the extract was washed with water until the reaction became neutral and then dried. After freezing-out from a hexane solution, compounds **2a** (89 %) and **2b** (77 %) were isolated. When the reaction was performed in 15 mL of CH_2Cl_2 or benzene under the same conditions, the yield of **2a** and **2b** was decreased to 65 and 57 %, respectively.

Dibenzo-2,6,9-trioxabicyclo[3.3.1]nona-3,7-diene (2a): m.p. 130—131 °C (hexane—benzene). Found (%): C, 73.85; H, 4.86. $C_{14}H_{10}O_3$. Calculated (%): C, 73.67; H, 5.29. The ^1H NMR spectrum ($CDCl_3$, δ, *J*/Hz): 6.31 (2 H, CH); 6.86 (2 H, H(5), *J* = 8.2); 6.95 (2 H, H(3) and H(3′), *J* = 7.6 and 1.2); 7.23 (2 H, H(4) and H(4′)); 7.28 (2 H, H(2) and H(2′)).

Di(2,4-di-*tert*-butylbenzo)-2,6,9-trioxabicyclo[3.3.1]nona-3,7-diene (2b): m.p. 218—219 °C (acetone). Found (%): C, 79.39; H, 9.47. $C_{30}H_{42}O_3$. Calculated (%): C, 79.59; H, 9.79. The ^1H NMR spectrum ($CDCl_3$, δ): 1.24 and 1.33 (18 H, Me_3C); 6.36 (2 H, CH); 7.10 and 7.17 (4 H, H(3), H(3′), H(5), and H(5′)).

Crystals of **2a** ($C_{14}H_{10}O_3$) are monoclinic. At 20 °C, a = 9.066(3), b = 12.729(4), c = 9.120(3) Å, β = 95.19(2)°, V = 1048(1) Å^3, d_{calc} = 1.447 g cm^{-3}, space group *C*2/*c*, Z = 4. The unit-cell parameters and intensities of 359 reflections with $F > 6\sigma(F)$ were measured on an automated Siemens P3/PC diffractometer (Mo-Kα radiation, graphite monochromator, θ/2θ scanning technique, $2\theta_{max}$ = 50°).

The structure was solved by the direct method using the SHELXTL Plus program package.[11] The positions of H atoms were calculated geometrically and refined using a "riding" model with U_{iso} = 0.08 Å^2. A full-matrix least-squares refinement with anisotropic thermal parameters for nonhydrogen atoms converged to R = 0.094 (R_w = 0.094, S = 1.79). Atomic coordinates are given in Table 1.

2-Acetoxy-3,5-di-*tert*-butylbenzaldehyde. One drop of concentrated H_2SO_4 was added to a mixture of **1b** (5 mmol) and acetic anhydride (5 mmol). After 30 min, the crystalline material was dissolved on heating in hexane. Crystals of *O*-acetyl-substituted **1b** (88 %), m.p. 83—84 °C (hexane), were obtained. Found (%): C, 73.43; H, 8.87. $C_{17}H_{24}O_3$. Calculated (%): C, 73.87; H, 8.75. The ^1H NMR spectrum ($CDCl_3$, δ, *J*/Hz): 1.14 and 1.32 (18 H, Me_3C); 2.04 (3 H, Me); 7.52 and 7.67 (2 H, Ph, *J* = 2.4); 9.75 (1 H, CH).

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