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On the formation of 2,3-dihydroxyacetophenone from pentoses or hexuronic acids

Tania Ahmad, Rolf Andersson, Kjell Olsson * and Olof Theander

Department of Chemistry, Swedish University of Agricultural Sciences, S-750 07 Uppsala (Sweden)

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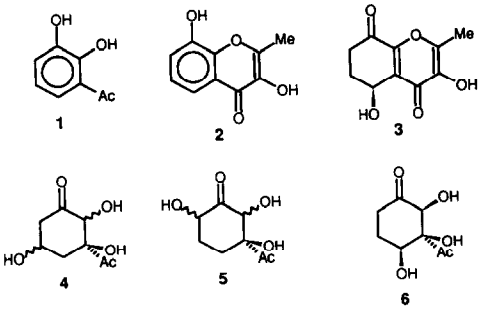
ABSTRACT

The structure of a previously isolated intermediate in the title reaction has been revised to 3-acetyl-2,3,4-trihydroxycyclohexanone by high-field ^{1}H NMR spectroscopy. The three hydroxyl groups are mutually *cis*-related.

INTRODUCTION

About 20 years ago, catechol and a number of its derivatives were obtained by degradation of pentoses or hexuronic acids in slightly acidic, aqueous solution[1,2]. Among these derivatives, 2,3-dihydroxyacetophenone (**1**) and 3,8-dihydroxy-2-methylchromone (**2**) were the most abundant. The chromone **2** was the only phenolic compound previously[3] obtained in a similar way.

A clue to the mechanism of formation of **1** and **2** was found by the trapping of alicyclic intermediates. Thus, formula 3 † was assigned to a precursor of **2**[2]. For a precursor of **1**, formulas **4**[1] and **5**[2] were proposed, without indication of the stereochemistry. In the present paper, this precursor of **1** is shown to have the structure and stereochemistry indicated by formula **6**.



* Corresponding author.

† All chiral compounds were obtained as racemic mixtures, but only one enantiomer is shown.

RESULTS AND DISCUSSION

Succinic acid had previously[2] been obtained from the precursor of **1** on borohydride reduction, followed by oxidation with lead(IV) acetate and with oxygen on platinum. This result ruled out formula **4**, but was equally consistent with **5** and **6**.

The ^{1}H NMR spectra of the originally[2] isolated precursor and its diacetate were complicated by extensive overlap, even at 400 MHz (Table I). However, in the spectrum (Fig. 1) of the diacetate, dissolved in a mixture of chloroform and acetonitrile, the signals were separated well enough to permit a clear decision between formulas **5** and **6** in favour of the latter. The symbol **6a** is therefore used for the diacetate.

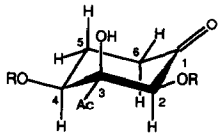
The methylene protons were readily assigned owing to the strong coupling between axial and between geminal protons. The fairly high values (δ 2.46 and 2.60, $|^2J|$ 15.0 Hz) observed for one methylene group indicated that this was adjacent to the carbonyl group. More important, when the axial proton of this methylene group was saturated, NOEs of both methine signals were observed. Hence, the methine protons were also axial. Moreover, a substantial coupling ($|^4J| \sim 1.0$ Hz) between the irradiated proton and one methine proton was observed. Such long-range coupling between axial protons implies that these are

TABLE I

^{1}H NMR data for *r*-3-acetyl-*t*-2,3,*t*-4-trihydroxycyclohexanone (**6**) in CD_3OD at 25°C and for its diacetate (**6a**) in 5:1 $CDCl_3$–CD_3CN at 60°C, see Fig. 1

H	δ		H, H	$\|J\|$ (Hz)	
	6a	**6**		**6a**	**6**
H-2	5.58	4.64	2, 6*a*	0.8 [a]	1.2
H-4	5.61	4.48	4, 5*a*	11.7	8.8
H-5*a*	2.17	2.04	4, 5*e*	5.1	7.4
H-5*e*	2.23	2.04	5*a*, 5*e*	12.7	
H-6*a*	2.60	2.57	5*a*, 6*a*	14.3	11.5
H-6*e*	2.46	2.31	5*a*, 6*e*	4.8	
Ac-3	2.27	2.35	5*e*, 6*a*	6.3	
AcO	2.00		5*e*, 6*e*	2.1	2.3
AcO	2.09		6*a*, 6*e*	15.0	14.5
HO	4.1				

[a] 1.2 Hz in pure $CDCl_3$.



6 R = H

6a R = Ac

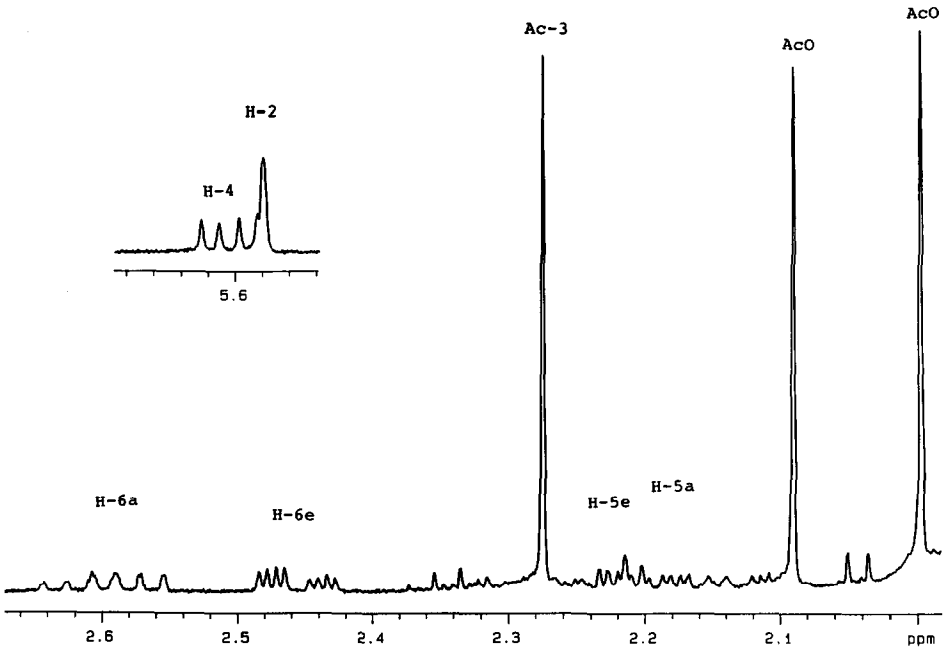
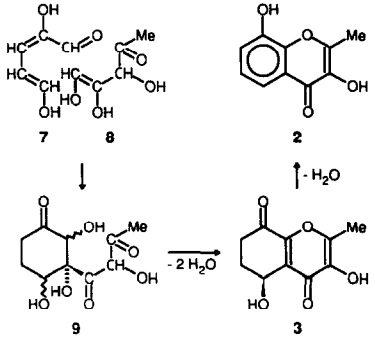


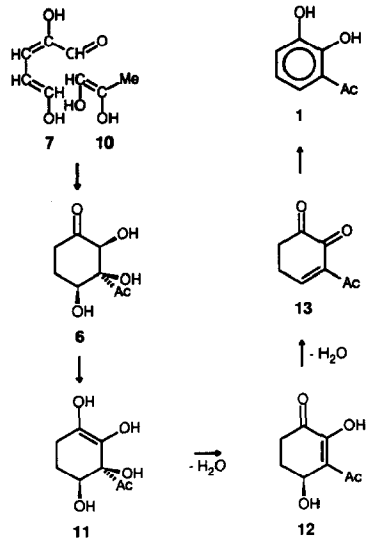
Fig. 1. 400-MHz ^{1}H NMR spectrum of compound **6a** in 5:1 $CDCl_3$–CD_3CN at 60°C.

linked through the carbonyl group[4], which is consistent with **6a** but not with a diacetate of **5**. Finally, saturation of the axial proton of the other methylene group caused an NOE of the signal from the unacetylated hydroxyl group, which was therefore axial. This was confirmed by weak NOEs of the methine signals on saturation of the *C*-acetyl protons. The various NOEs were seen most clearly in the NOE difference spectra.

A route to **2** via **3** has been proposed previously[5]. It is shown in Scheme 1 after slight modification. The key step, joining two C_5 species, is a Michael addition of



Scheme 1. Key and subsequent steps in the formation of chromone **2** via **3**.



Scheme 2. Key and subsequent steps in the formation of 2,3-dihydroxyacetophenone (**1**) via **6**.

an enediol (**8**) to an unsaturated aldehyde (**7**), followed by cyclization through aldol condensation. The subsequent steps are simple tautomerizations and β-eliminations. The route in Scheme 2 was later[6] supported by isotopic tracer techniques. Aldehyde **7** has also been proposed as a precursor of the so-called reductic acid[7].

An analogous route to **1** via **6** is shown in Scheme 2. Here, the key step joins **7** and the enediol **8** of acetol, which is a common sugar dehydration product[8]. Again, the subsequent steps are simple tautomerizations and β-eliminations. Such a simple route to **1** via **4** or **5** is not easy to imagine. In order to confirm the route in Scheme 2, we have tried to prepare **1** from acetol and some compound similar to **7** but, so far, only products related to reductic acid have been obtained[9]. Nevertheless, **7** may be a more general precursor of other phenolic products in the title reaction.

EXPERIMENTAL

The samples of **6** and **6a** were prepared in 1971[2] (and were then regarded as **5** and its diacetate). The ^{1}H NMR spectra were recorded with a Varian VXR-400 instrument and referenced to the solvent $CDCl_3$ ($CHCl_3$, δ 7.26) or CD_3OD (CHD_2OD, δ 3.31). The chemical shifts (δ) and coupling constants (J) are listed in Table I. The data for the ring protons of **6a** were obtained by spin simulation, using the standard software from Varian, VnmrS 4.1A. The spectrum of **6a**, dissolved in 5:1 $CDCl_3$–CD_3CN to minimize overlap, is shown in Fig. 1. NOE difference spectra were recorded using the same solvent mixture degassed with Ar, and a saturation time of 20 s.

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