ON THE STRUCTURE OF ASYMMETRIC BENZOINS (AN OLD CONTROVERSY)

C. SIMION[1], Alina Marieta SIMION[2]

Au fost sintetizate benzoine simetrice şi asimetrice în vederea determinării structurii corecte a benzoinelor asimetrice. Structurile au fost determinate pe baza spectrelor de RMN, iar formarea lor a fost explicată prin considerente mecanicistice ţinându-se cont de efectele electronice.

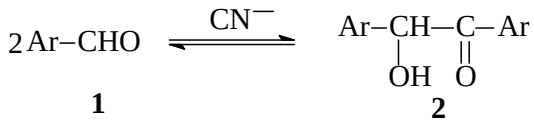
Some symmetric and asymmetric benzoins were synthesized in order to determine the correct structure of mixed benzoins. The structures were assigned by NMR analysis and they were explained by means of mechanistic consideration, taking into account the electronic effects.

Keywords: benzoin condensation, structure of asymmetric benzoins.

1. Introduction

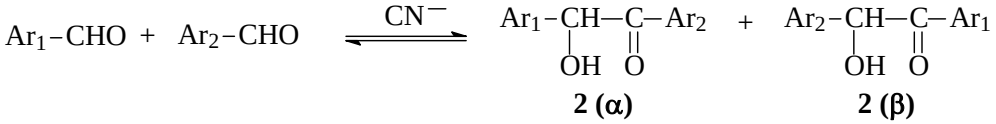
Benzoin synthesis is one of the first examples of reactions which, in a specific catalysis [1], affords the formation of a C-C bond. Benzoins could have proven to be useful intermediates in the synthesis of a large number of compounds, such as dezoxibenzoins, benzils, hydrobenzoins, stilbenes or, by condensation with compounds bearing -NH_2 group, of a wide variety of amino derivatives (*e.g.* diphenylethyl amines, hydroxy-amines, izoquinolines etc.) [2], unless the behavior of substituted benzaldehydes was not so erratic (usually, yields for substituted benzoins are lower than for benzoin itself). Benzoin condensation is usually carried out in the presence of the cyanide anion which specific catalysis is possible because it can act like a nucleophile, but also as a good leaving group and, moreover, it has a certain electronwithdrawing ability [2,3]. This reaction aroused the interest of chemists and of biochemists because it can be carried out in the presence of thiazolium functions [4] or thiazolium ions [5] yielding benzoins, but also the parent aliphatic compounds, acyloins. The general mechanism of the condensation process is similar, either using cyanide anion [3,6] or thiazolium salts [5a,b,7].

[1] Lecturer, Dept. of Organic Chemistry, University "Politehnica" of Bucharest, Romania
[2] Lecturer, Dept. of Organic Chemistry, University "Politehnica" of Bucharest, Romania



1 **2**

In the first half of 20th century, intensive studies of this reaction were carried out, due to the versatility of this new C-C bond formation method [8-10] – a great number of symmetric benzoins were obtained, but the synthesis of mixed benzoins proved to be difficult to achieve. There is however a statement from Levy and Tiffenau [11] who acknowledged that the condensation of two different aldehydes yields mixture of benzoins, but only one could be isolate from the final reaction mixture. Even in Vogel's *Practical Organic Chemistry* [12] the experimental part refering to the synthesis of 4-methoxy-benzoin describes a fractioned crystallization in order to separate the title compound from symmetric benzoin (formed as by-product). Alternative methods were used to synthesize such compounds, *e.g.* Grignard synthesis [13] or another reaction using arylglyoxal compounds as intermediates [14].



2 (α) **2 (β)**

Moreover, the structure of mixed benzoins was determined throughout chemical transformations and is not very clearly defined (there are certain contradictions regarding their structure according to different authors).

We wish to report here our investigations concerning the correct structure of some mixed benzoins.

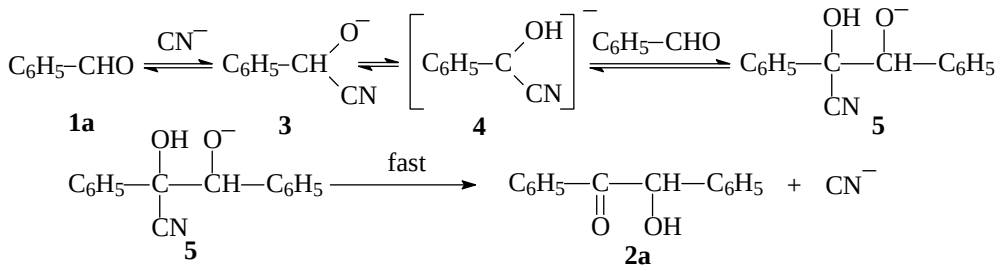
2. Experimental

The general experimental procedure used for the synthesis of benzoins was: the aldehyde (0.1 mole) and the cyanide (KCN or NaCN, 0.02 mole in 15 mL water), along with 30 mL ethanol were heated on a steam bath for 2-6 hours. The final reaction mixture was poured over icy water. The aqueous solution was extracted with methylene chloride. The organic layers were dried and slowly evaporated. On evaporation the benzoins did crystallize. The crystals were filtered off, washed with small amounts of cold methylene chloride and dried. Crude benzoins were recrystallized from ethanol. The obtained benzoins are presented in Table 1. All benzoins were analyzed by IR, ^{1}H- and ^{13}C-NMR and showed spectral data in accordance with their structure (Table 2).

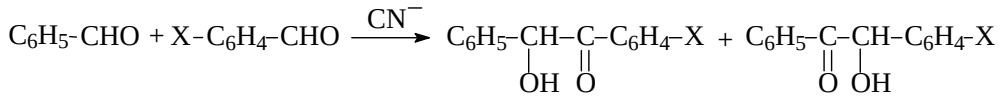
The IR spectra were registered on a FTIR Bruker – Equinox 55 spectrometer and the NMR spectra were registered on a Varian Gemini 300 apparatus at 300 MHz (^{1}H) and 75 MHz (^{13}C) using TMS as internal standard.

3. Results and discussions

The well-known mechanism proposed by Lapworth for the benzoin condensation, in the early 1900's [6a,b], was later confirmed by Schowen and coworkers [3a]. This mechanism implies two succesive nucleophile attacks and the formation of small amounts of a cyanhydrine as intermediate:



The structure of mixed benzoins was studied mainly by two groups of researchers: H. Staudinger in Germany and J.S. Buck and W.S. Ide in the U.S.A. Their results were contradictory: while Staudinger stated the formation of a β structure [8], Buck and Ide supported the α structure as main reaction product [10a,d]:



1a **1b** X = -OCH_3; **1c** X = -$N(CH_3)_2$ → **2b (α)** X = -OCH_3; **2d (α)** X = -$N(CH_3)_2$ + **2b (β)** X = -OCH_3; **2d (β)** X = -$N(CH_3)_2$

Staudinger considered the benzoin formation as a migration of a hydrogen atom from one carbonyl group to another, so he divided aldehydes in two types: A (with a reactive –CHO group and a non-mobile H atom) and B (with a non-reactive –CHO group and a mobile H atom). If type B aldehydes were characterized by their rate of auto-oxydation, the criterion for type A aldehydes was not clearly stated [8]. According to Staudinger, benzaldehyde **1a** is of type A and *p*-dimethylamino-benzaldehyde **1c** of type B, therefore the condensation product presents a β structure [8]. On the contrary, Buck and Ide, basing their assumptions on a Beckman-type process (introduced earlier by Werner and

Detscheff [15]), found that the mixed benzoins presented structures of type α [10a,d,f].

Other chemical methods of structure determination were used, such as the synthesis of mixed benzoins through Grignard reaction [13], which is anything but convenient, or other indirect approaches [10d,i,k,14], which are of limited applications.

To the best of our knowledge, there were no other attempts to determine correct structure of mixed benzoin (with the exception of synthesis by specific methods [10d,i,13,14]), especially by using modern spectral methods.

We attempted the synthesis of six different benzoins, symmetrical or mixed, by the usual condensation process using NaCN or KCN (Table 1), in order to determine their correct structures by ^{1}H- and ^{13}C-NMR.

Table 1.

Synthesized benzoins

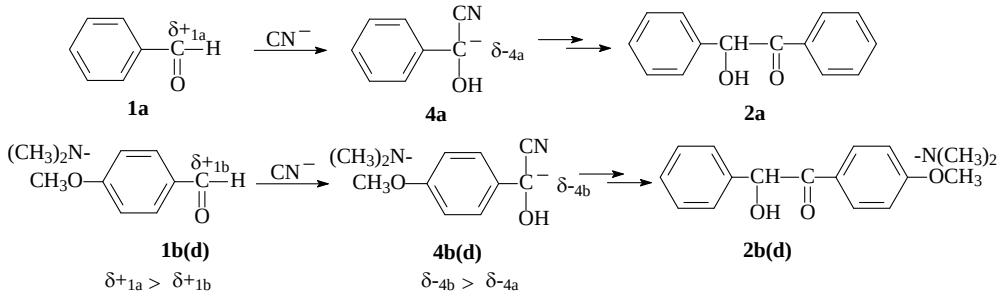
Nr.	Ar_1	Ar_2	Cpd.	Rct. time (h)	Yield (%)	m.p. (°C, lit.))
1	C_6H_5-	C_6H_5-	**2a**	2	73	134 (137, [16])
2	C_6H_5-	*p*-CH_3O-C_6H_4-	**2b (α)**	4	22	103-5 (105-6, [12])
3	*p*-CH_3O-C_6H_4-	*p*-CH_3O-C_6H_4-	**2c**	6	23	110-1 (113, [17])
4	C_6H_5-	*p*-$(CH_3)_2N$-C_6H_4-	**2d (α)**	4	36	162-3 (163-4, [8])
5	*p*-$(CH_3)_2N$-C_6H_4-	*p*-$(CH_3)_2N$-C_6H_4-	**2e**	4	0	-
6	*p*-CH_3O-C_6H_4-	*p*-$(CH_3)_2N$-C_6H_4-	**2f (α and β)**	4	17	- (144, [10b])
7	C_6H_5-	*p*-CH_3-C_6H_4-	**2g and 2a**[a]	6	52[a]	113-5 (115, [14])
8	*p*-CH_3-C_6H_4-	*p*-CH_3-C_6H_4-	**2h**	6	38	87-9 (88-9, [10a])
9	*p*-Cl-C_6H_4-	C_6H_5-	**2i, 2j and 2a**	6	28	113-16 (116, [14b])
10	*p*-Cl-C_6H_4-	*p*-Cl-C_6H_4-	**2j**	8	12	85-7 (88, [18])
11	*p*-Cl-C_6H_4-	*p*-CH_3O-C_6H_4-	**2k, 2c and 2j**	8	19	83-4 (84-5, [12k])
12	C_6H_5-	*p*-NO_2-C_6H_4-	**2l**	6	-	-[b]
13	*p*-NO_2-C_6H_4-	*p*-NO_2-C_6H_4-	**2m**	6	-	-[c]

[a] The yield represents the crude precipitate that contains both benzoins, in (according to ^{1}H-NMR spectra) an almost equimolecular mixture, which contained also small amounts of toluoin; separation of the three benzoins by means of fractioned recrystallization from ethanol was performed but proved to be very difficult to achieve, yielding finally less than 100 mg pure *p*-methyl-benzoin.
[b] A mixture of benzoin, benzoic acid and *p*-nitrobenzoic was obtained.
[c] The reaction product was *p*-nitrobenzoic acid.**Table 1.**

The nature of the correct structure of mixed benzoins (α and/or β) highly depends on the mechanism of the chemical process. As stated previously, this

mechanism implies two succesive nucleophilic attacks. The nature of the reaction product(s) depends on the electronic densities at the nucleophile as well as at the substrate.

On the first nucleophilic attack, the cyanide anion should react with the carbonyl moiety presenting the lowest electronic density: between the two reactants, benzaldehyde and anisaldehyde (or *p*-dimethylaminobenzaldehyde), due to the electrono-donor effect of the *p*-methoxy- group (or *p*-dimethylamino-), the lowest electronic density is on the >C=O group of benzaldehyde. Nevertheless, both intermediates are formed, through with a predominancy for **4a**. The next step is represented by the second nucleophilic attack between nucleophile species **4a** and **4b(d)** and substrates **1a** and **1b(d)**. Again the electrono-donor effect of the *p*-methoxy- group (or *p*-dimethylamino-) will have a key role, enhancing electron density at the carbon atom in intermediate **4b(d)**. Therefore, the pairing of nucleophile-substrate that is favored will be **4b(d)-1a** as a pair of high electronic density with normal electronic deficiency moieties. The pairing **4a**-**1a** also occurs as normal electronic density with normal electronic deficiency structures, while the pairing **4a**-**1b(d)** is totally unfavorable and does not occur. That explains why when benzaldehyde is combined with anisaldehyde in a benzoin type condensation process, two benzoin are formed and why in the asymmetric benzoin the carbonyl moiety with highest electronic deficiency will form the –CHOH– part and the carbonyl group with highest electronic density will form the >C=O part of the benzoin structure.



Consequently, the structure of the final reaction product should be a benzoin of type α as Buck and Ide concluded (**2b** and **2d**), and not of type β as indicated by Staudinger.

Table 2

Spectral characterization of benzoins

Benzoin	IR (ν, cm^{-1})	^{1}H-RMN ($CDCl_3$, δ, *J*Hz)	^{13}C-RMN ($CDCl_3$, δ, *J*Hz)
2a	1700 (C=O), 3476 (-OH)	4.54 (sl, 1H, OH), 5.72 (s, 1H, CH), 7.16 (m, 10H, $H^{arom.}$)	74.9 (CH), 113.8, 114.4, 126.2 (C_q), 128.7, 128.9, 131.5, 131.8 (C_q), 194.8 (C=O)
2b (α)	1671 (C=O), 3481 (-OH)	3.75 (s, 3H, OCH_3), 4.61 (sl, 1H, OH), 5.83 (s, 1H, CH), 6.80 (d, 2H, *8.82*, $H^{arom.}$), 7.24 (m, 5H, $H^{arom.}$), 7.85 (d, 2H, *8.89*, $H^{arom.}$)	55.5 (OCH_3), 75.8 (CH), 113.9, 126.2 (C_q), 127.7, 128.5, 128.6, 129.0, 130.1 (C_q), 131.6, 161.9 (C_q), 197.1 (C=O)
2c	1675 (C=O), 3465 (-OH)	3.76 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.60 (d, 1H, *5.44*, OH), 5.85 (d, 1H, *5.44*, CH), 6.85 (d, 2H, *8.68*, $H^{arom.}$), 6.87 (d, 2H, *9.05*, $H^{arom.}$), 7.25 (d, 2H, *8.65*, $H^{arom.}$), 7.90 (dd, 2H, *9.06*, $H^{arom.}$)	55.2 (OCH_3), 55.5 (OCH_3), 75.2 (CH), 113.8, 114.4, 129.0, 129.8 (C_q), 131.5, 132.4 (C_q), 159.6 (C_q), 163.9 (C_q), 197.3 (C=O)
2d (α)	1651 (C=O), 3421 (-OH)	3.00 (s, 6H, $N(CH_3)_2$), 4.84 (d, 1H, *6.0*, -OH), 5.87 (d, 1H, *6.0*, CH), 6.56 (d, 2H, *9.06*, $H^{arom.}$), 7.31 (m, 5H, $H^{arom.}$), 7.84 (d, 2H, *9.06*, $H^{arom.}$)	39.9 ($N(CH_3)_2$), 75.4 (CH), 110.9, 113.6, 114.4, 125.1 (C_q), 129.6, 131.8, 130.7 (C_q), 153.7 (C_q), 195.9 (C=O)
2f (α and β)	1640-70 (C=O), 3461 (-OH)	2.96 (s, 6H, $N(CH_3)_2$), 3.69 (s, 3H, OCH_3), 4.81 (d, 1H, *5.77*, OH), 5.74 (d, 1H, *5.77*, CH), 6.50 (d, 2H, *9.21*, $H^{arom.}$), 6.77 (d, 2H, *8.79*, $H^{arom.}$), 7.20 (d, 2H, *8.76*, $H^{arom.}$), 7.76 (d, 2H, *9.20*, $H^{arom.}$)	39.9 ($N(CH_3)_2$), 55.3 (OCH_3), 74.6 (CH), 111.2, 113.4, 124.6 (C_q), 130.6, 131.8 (C_q), 152.5 (C_q), 160.2 (C_q), 197.2 (C =O)
2g (α)	1688 (C=O), 3452 (-OH)	2.43 (s, 3H, CH_3), 4.72 (sl, 1H, OH), 5.95 (s, 1H, CH), 7.11 (d, 2H, *9.02*, $H^{arom.}$), 7.38 (m, 5H, $H^{arom.}$), 7.58 (d, 2H, *9.02*, $H^{arom.}$)	22.5 (CH_3), 72.8 (CH), 127.0, 129.1, 129.6, 129.7, 135.0 (C_q), 139.9 (C_q), 145.4 (C_q), 194.5 (C=O)
2h	1681 (C=O), 3433 (-OH)	2.41 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 4.69 (d, 1H, *2.41*, OH), 5.86 (d, 1H, *2.43*, CH), 7.09 (d, 2H, *8.83*, $H^{arom.}$), 7.26 (d, 2H, *9.05*, $H^{arom.}$), 7.51 (d, 2H, *8.85*, $H^{arom.}$), 7.70 (d, 2H, *9.03*, $H^{arom.}$)	22.4 (CH_3), 22.5 (CH_3), 72.5 (CH), 126.4, 128.8, 129.1, 129.5, 130.1, 134.4 (C_q), 136.9 (C_q), 139.7 (C_q), 145.1 (C_q), 194.7 (C=O)
2i (α)	1687 (C=O), 3413 (-OH)	4.51 (sl, 1H, OH), 4.92 (s, 1H, CH), 7.41 (d, 2H, *8.42*, $H^{arom.}$), 7.43 (m, 5H, $H^{arom.}$), 7.75 (d, 2H, *8.43*, $H^{arom.}$)	72.8 (CH), 128.7, 128.9, 129.6, 130.3, 133.7 (C_q), 134.3 (C_q), 136.8 (C_q), 140.9 (C_q), 191.6 (C=O)
2j	1679 (C=O), 3426 (-OH)	4.58 (d, 1H, OH), 5.06 (d, 1H, CH), 7.17 (d, 2H, *8.74*, $H^{arom.}$), 7.24 (d, 2H, *8.75*, $H^{arom.}$), 7.51 (d, 2H, *8.85*, $H^{arom.}$), 7.70 (d, 2H, *8.85*, $H^{arom.}$)	73.5 (CH), 128,5, 128,7, 129,3 (C_q), 129,8, 130,1 (C_q), 135,9 (C_q), 139,2 (C_q), 195,5 (C=O)
2k	1690 (C=O) 3450 (OH)	3.74 (s, 3H, OCH_3), 4.49 (sl, 1H, OH), 4.92 (s, 1H, CH), 6.83 (d, 2H, *8.78*, $H^{arom.}$), 7.39 (d, 2H, *8.12*, $H^{arom.}$), 7.71 (d, 2H, *8.14*, $H^{arom.}$), 7.89 (d, 2H, *8.79*, $H^{arom.}$)	55.8 (OCH_3), 73.6 (CH), 114.6, 129.6, 129.9, 131.4, 132.8 (C_q), 134.1 (C_q), 134.3 (C_q), 162.6 (C_q), 196.5 (C=O)

The ^{1}H-NMR data support this assumption: for *p*-dimethylamino-benzoin, as well as for *p*-methoxy-benzoin, the ^{1}H-NMR spectra present a strongly deshielded AB signal at 6.56 and respectively 7.84 ppm (*J* = 9.06 Hz), corresponding to both aromatic protons on *ortho*- position to the carbonyl group,

while all five protons beared by the non-substituted aromatic nuclea appear in a single multiplet (which is characteristic for aromatic nuclea linked to an aliphatic carbon) and not as two separate multiplets (like in acetophenone for instance). Same deshielded signals appear in the spectra of *p*-methoxy-benzoin as well as in the spectra of anisoin. Comparing the ^{1}H-NMR spectra of anisoin **2c** and *p*-methoxy-benzoin **2b**, it is obvious that for anisoin there are two AB signals, one at 6.85 ppm and 7.90 ppm (corresponding to the aromatic rings in the vicinity of the carbonyl group) and one at 6.84 ppm and 7.25 ppm (corresponding to the aromatic rings in the vicinity of the –CH(OH)– group). If the structure of final reaction product (*p*-methoxy-benzoin) would have been of type β, the AB signal present in the ^{1}H-NMR spectra should have shown two doublets at aproximatively 6.6 ppm and 7.3 ppm (and not 7.8 ppm). Therefore, we can conclude that the correct structure of mixed benzoins that are obtained and separated from final reaction mixture are of type α (*e.g.* **2b** and **2d**).

Single type mixed benzoin as reaction product can be obtained working with aldehydes of very different electronic densities (*e.g.* anisaldehyde and benzaldehyde or *p*-dimethylamino-benzaldehyde and benzaldehyde). Working with aldehydes of similar electron density, the mixture of both mixed benzoins is obtain (*e.g.* anisaldehyde and *p*-dimethylamino-benzaldehyde) – as demonstrated by the NMR spectra of crude reaction mixture.

4. Conclusions

We studied the synthesis of symmetrical and mixed benzoins and attributed the correct structure for the mixed benzoins. In some cases depending on the reactivity of aldehydes a mixture of benzoins was obtained. In other cases the benzoin could not be obtained. The formation of these compounds was explained through mechanistic considerations taking into account the electronic effects.

R E F E R E N C E S

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