Chemistry of Heterocyclic Compounds, Vol. 42, No. 4, 2006

MASS-SPECTRAL BEHAVIOR AND THERMAL STABILITY OF HETARYL ANALOGS OF UNSYMMETRICAL BENZOINS

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The main path in the mass-spectral dissociation of the hetaryl analogs of unsymmetrical benzoins is β-fragmentation with cleavage of the central C–C bond. Here, the strongest peak in the mass spectra of α-benzoins is the peak of the hydroxymethylhetaryl cation, and in β-benzoins it is the peak of the hetaroyl cation. The thermal α → β isomerization of the hetaryl analogs of benzoin was studied. In the case of indole and pyrrole derivatives the formation of polyheterocyclic systems is observed.

Keywords: benzoins, polyheterocycles, isomerization, mass spectrometry.

Benzoins have found widespread use as synthons in organic synthesis (e.g., see [1-8]). Of particular interest in the chemistry of benzoins in recent times has been their use as model biochemical substrates (e.g., see [9-11]). However, many problems concerning the structure and characteristics of unsymmetrical benzoins have not so far been resolved. Thus, during investigation of the spectral characteristics of unsymmetrical benzoins in order to establish their structure and their affiliation to an isomeric series (the α- or β-isomer) it was shown that electron-impact mass spectrometry is not very suitable for this purpose [12]. It was observed that the main fragmentation path was β-fragmentation with cleavage of the central C–C bond, and peaks for both aroyl and both hydroxybenzyl cations were observed in the mass spectra. It is interesting to note that such bond cleavage provides a source of radicals during polymerization, where benzoins and their alkyl ethers are used as a photosensitive material [13]. In [14] during the preparation of unsymmetrical benzoins the mass spectra were used to confirm the structure of the obtained compounds, and the main fragmentation path was also cleavage of the central C–C bond. However, it is difficult to establish any general relationship in the fragmentation and formation of the ions giving the base peaks by analyzing the mass spectral data.

Earlier during investigation of the isomerization of α-benzoins obtained by electrophilic hydroxymethylation of π-excessive heterocycles [15] we demonstrated differences in the ^{1}H NMR spectral characteristics of the α- and β-isomers [16]. In the present work we studied the differences in the mass spectral characteristics of the obtained isomeric benzoins. The spectra were recorded with direct injection of the sample into the ionization zone.

We established that the main path is β-fragmentation. Here, the charge is mainly located on the fragment in which greatest stabilization of positive charge is realized; for hetarylphenylbenzoins it is the cation containing the group from the π-excessive heterocycle. Each of the investigated series of isomers has a characteristic base peak, and this makes it possible to distinguish clearly between them: The peak of the

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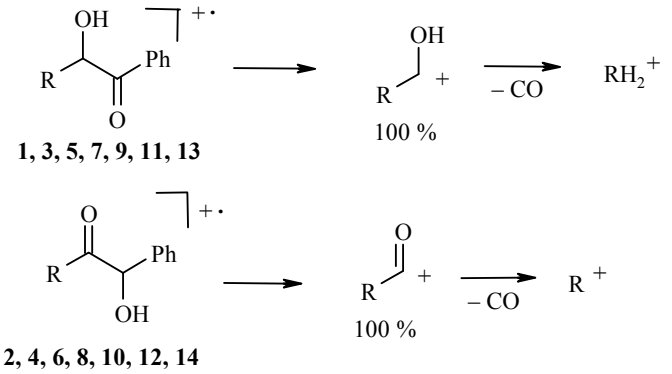
hydroxybenzoyl cation for the α-isomers; the peak of the hetaroyl cation for the β-isomer. In the case of the β-benzoin **10**, in which the fragments have approximately identical ability to delocalize the positive charge and identical mass, both types of cation are formed with approximately identical intensity.



In most cases (with the exception of the hydrazones **11-14**) in the mass spectra the second in intensity is the peak of the fragments formed during subsequent elimination of CO molecules by the ions presented above. In the case of the α-isomers this is a σ-complex. Here the intensity of the peak is probably related to the stability of this complex for the given heterocycle. Thus, the highest intensity is observed in the case of the derivatives of 1,2,5-trimethylpyrrole and indole; in the case of the furan derivatives such signals are absent altogether. In the case of the β-isomers the intensity of the hetaryl cations formed similarly by elimination of CO is lower on account of their low stability.

It should be noted that the series of isomers differ in their stability to electron impact. The α-isomers give more stable molecular ions than the β-isomers. In the case of the furans **7** and **8** the molecular ions have identical intensity, due to the small difference in the electron-donating characteristics of the phenyl and furan residues. This relationship only breaks down for the hydrazones **11-14**, in which the conjugation between the dimethylamino and carbonyl groups leads to higher stability for the molecular peaks of the β-isomers.

However, as seen from the data in Table 1, in each mass spectrum of one isomer there signals that are to a large degree characteristic for the other isomer. In our opinion this is due to the fact that some of the molecules of the substance in the ionization chamber before ionization manage to undergo thermal isomerization when heated under vacuum [17] to the enediol form, which is always present in benzoin [18]. Although measured at higher ionization chamber temperatures (up to 240°C) the patterns of the mass spectra remain practically unchanged.

The absence of a relationship in the mass-spectral data in [14] can probably be explained by chemical transformations that take place under the conditions used to record the mass spectra, i.e., the obtained mass spectra did not correspond to the data of the individual compound.

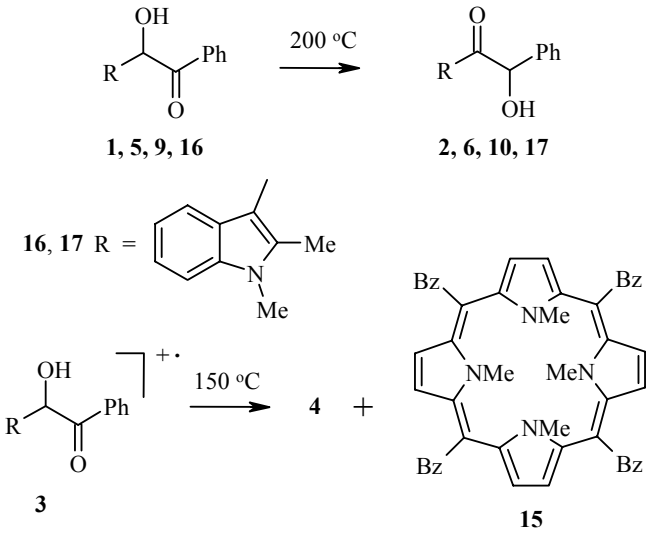
For confirmation we studied the thermal stability of unsymmetrical benzoins. Thus, α-benzoins **1**, **3**, **5**, and **9** are capable of isomerizing to the β-isomers with quantitative yields (10% for the pyrrole **3**) when heated for 10 min at 200°C (at 150°C for the pyrrole **3**) (Table 2). The yield is not reduced by increasing the heating time to 30 min. This indicates that whether thermal isomerization occurs does not depend on the structure of the benzoin, unlike α→β isomerization in a basic medium, where the transformation time depends strongly on the electronic effect of the hetaryl group [16]. Consequently, the thermal transformation takes place through the enediol form as a result of keto–enol tautomerism. In the case of the pyrrole **3** the tetramerization product the porphyrin **15** was isolated during thermal isomerization. Its structure was confirmed by spectral data. Thus, its mass spectrum contained a molecular ion peak at *m*/*z* 784. In the ^{1}H NMR spectrum there were singlets in the region of 5.41 and 6.25 ppm corresponding to the olefinic and pyrrole protons respectively.

TABLE 1. The Mass Spectra of the Benzoins **1-14***

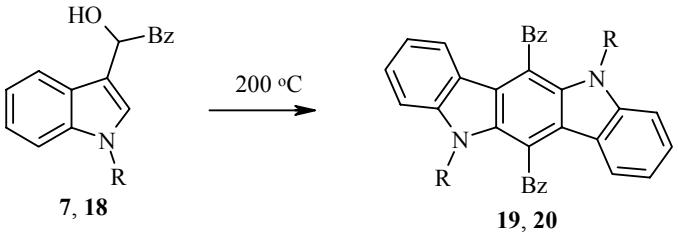
Compound	R	*m/z* (*I*, %)					*I*, %*[2]			
		M^+	$RC^+H(OH)$	RH_2^+	$RC^+=O$	R^+	$PhC^+H(OH)$	PhH_2^+	$PhC^+=O$	Ph^+
1	4-Dimethylaminophenyl	255 (8)	150 (100)	122 (8)	148 (5)	120 (7)	6	2	9	9 7
2	4-Dimethylaminophenyl	255 (7)	150 (1)	—	148 (100)	—	1	4	6	
3	1-Methyl-2-pyrrolyl	215 (9)	110 (100)	82 (22)	108 (7)	80 (3)	—	—	4	8
4	1-Methyl-2-pyrrolyl	215 (3)	110 (3)	—	108 (100)	80 (7)	5	5	1	6
5	1,2,5-Trimethyl-3-pyrrolyl	243 (12)	137 (100)	109 (58)	135 (13)	107 (7)	7	2	5	6
6	1,2,5-Trimethyl-3-pyrrolyl	243 (4)	—	—	135 (100)	107 (2)	2	1	1	2
7	3-Indolyl	251 (10)	146 (100)	118 (35)	144 (32)	116 (6)	—	1	8	11
8	3-Indolyl	251 (5)	146 (1)	—	144 (100)	116 (11)		2	—	3
9	5-Methyl-2-furyl	216 (6)	111 (100)	83 (3)	109 (2)	81 (1)	—	1	7	12
10	5-Methyl-2-furyl	216 (8)	111 (16)	83 (6)	109 (100)	81 (4)	91	44	5	25
11	5-Dimethylhydrazonomethyl-1-methyl-2-pyrrolyl	285 (16)	180 (100)	152 (2)	178 (6)	150 (4)	7	—	5	5
12	5-Dimethylhydrazonomethyl-1-methyl-2-pyrrolyl	285 (23)	—	—	178 (100)	—	4	4	1	—
13	5-Dimethylhydrazonomethyl-2-furyl	272 (14)	167 (100)	—	165 (11)	137 (1)	5	1	16	13
14	5-Dimethylhydrazonomethyl-2-furyl	272 (28)	167 (10)	—	165 (100)	137 (6)	4	9	4	11

* The odd numbers are the α-isomers RCH(OH)C(O)Ph; the even numbers are the β-isomers RC(O)CH(OH)Ph.

*[2] The intensities of the respective peaks are given.



The behavior of the indole derivatives under these conditions is more complicated. Thus, 1,2-dimethylindole **16** isomerizes with a high yield to the β-isomer **17**. At the same time the indoles **7** and **18**, not containing substituents at position 2, form the dimerization products indolo[3,2-*b*]carbazoles **19** and **20**. Here, in the case of the indole **7** strong resin formation is observed, and the dimer **20** is isolated with a small yield, whereas the N-methylindole **18** gives a high yield of the dimer **20**. The structure of the dimeric products is confirmed by the mass-spectral data, which contain the corresponding molecular ion peaks, whereas the position of the signals in the ^{1}H NMR spectra differs little from the signals of the corresponding protons in the initial α-benzoins [15].

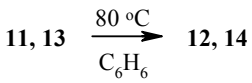


7, 19 R = H , **18, 20** R = Me

The polyheterocyclic products are probably formed by electrophilic alkylation at the *ortho* position of the heterocyclic by the benzylic hydroxyl group followed by oxidation, leading to the formation of an aromatic structure. The dimerization of α-benzoins found here is one of the new methods for the synthesis of indolocarbazoles [19].

The β-benzoins **2**, **4**, **6**, **8**, and **10** remain stable when heated, although resinification occurs after very prolonged heating (more than 2 h).

The hydrazones **11** and **13** form the β-isomers **12** and **14** respectively even in boiling benzene. However, α→β isomerization probably occurs in this case [16] under the influence of the basic dimethylamino group.



Thus, we have demonstrated that the main dissociation path in the mass spectrum of unsymmetrical benzoins is β-fragmentation with retention of the charge on the fragment with the possibility of greatest delocalization of the positive charge. The α-benzoins are capable of isomerizing thermally to the β-isomers.

TABLE 2. The Yields of the Products from Thermal Isomerization of α-Benzoins

Initial compound	Product	mp of product, °C (solvent)	Yield, %
1	**2**	167-168 (ethanol) [12]	95
3	**4**	107-108 (hexane) [16]	10
	15	217-218 (methanol)	20
5	**6**	137-138 (ethanol) [16]	96
7	**19**	299-301 (benzene)	10
9	**10**	150-151 (ethanol) [16]	97
16	**17**	185 (ethanol) [16]	89
18	**20**	213-215 (methanol)	91

EXPERIMENTAL

The ^{1}H NMR spectra were recorded in DMSO-d_6 on a Varian VXR-300 instrument (300 MHz) with TMS as internal standard. The IR spectra were obtained in tablets with potassium bromide on a UR-20 instrument. The UV spectra were obtained in DMFA on a Specord M-40 instrument with an absorbing layer 1 cm thick. The mass spectra were recorded on an MX-1321 instrument under electron impact at 70 eV with direct injection of the sample and an ionization chamber temperature of 160°C (for data on the benzoins, see Table 1). The reaction and the purity of the obtained compounds were monitored by TLC on Silufol UV-254 plates in 1:5 benzene–acetone. The benzoins **1**, **3**, **5**, **7**, **9**, **16**, **18** [15], **4**, **6**, **8**, and **10** [16] were obtained by familiar procedures. The physicochemical characteristics of the β-benzoins **2** [12], **4**, **6**, **10**, and **17** [16] agreed fully with published data.

Preparation of α-Benzoins 11 and 12 (General Procedure). To a solution of phenylglyoxal hydrate (0.76 g, 5.00 mmol) in dichloromethane (5 ml) we added a solution of furfural N,N-dimethylhydrazone or N-methylpyrrole-2-carbaldehyde (5.00 mmol) in dichloromethane (5 ml). The solution was kept at room temperature for three days, dried over sodium sulfate, filtered, and evaporated under vacuum. The residue was crystallized from hexane.

2-[5-(Dimethylhydrazinomethyl)furan-2-yl]-2-hydroxy-1-phenylethanone (11). Yield 86%, yellow powder; mp 136.5-137°C. IR spectrum, ν, cm^{-1}: 3430, 3140, 3000, 2940, 2875, 2805, 1690, 1600, 1575, 1290, 1230. UV spectrum, λ_{max}, nm (log ε): 244.9 (3.94), 308.3 (4.23). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.87 (6H, s, $N(CH_3)_2$); 5.00 (1H, d, *J* = 6.5, CHO<u>H</u>); 6.19 (1H, d, *J* = 6.5, CHO<u>H</u>); 6.32 (1H, d, *J* = 3.4, Fur H-3); 6.45 (1H, d, *J* = 3.4, Fur H-4); 7.05 (1H, s, CH=N); 7.49 (2H, t, *J* = 7.8, Ph H-3,5); 8.05 (2H, d, *J* = 7.8, Ph H-2,6). Found, %: C 66.32; H 5.81. $C_{15}H_{16}N_2O_3$. Calculated, %: C 66.16; H 5.92.

2-[5-(Dimethylhydrazonomethyl)-1-methyl-1H-pyrrol-2-yl]-2-hydroxy-1-phenylethanone (12). Yield 88%, yellow powder; mp 136-137°C. IR spectrum, cm^{-1}: 3175, 2970, 2868, 1682, 1597, 1261, 1234, 1200, 1155, 1070, 1042, 1013, 990, 952, 920. UV spectrum, λ_{max}, nm (log ε): 243.9 (4.06), 305.3 (4.20). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.30 (3H, s, Pyr CH_3); 3.81 (1H, s, $N(CH_3)_2$); 5.63 (1H, d, *J* = 7.6, CHO<u>H</u>); 5.70 (1H, d, *J* = 4.0, Pyr H-3); 6.03 (1H, d, *J* = 4.0, Pyr H-4); 6.17 (1H, d, *J* = 7.6, C<u>H</u>OH); 7.25 (1H, s, CH=N); 7.43 (2H, t, *J* = 8.6, Ph H-3,5); 7.57 (1H, d, *J* = 8.6, Ph H-4); 7.90 (2H, d, *J* = 8.06, Ph H-2,6). Found, %: C 67.36; H 6.71. $C_{16}H_{19}N_3O_2$. Calculated, %: C 67.36; H 6.71.

Thermal Isomerization (General Procedure). A 1.5-mmole sample of the α-benzoin was kept at 200°C (150°C in the case of the pyrrole **3**) for 10 min. The residue was cooled to room temperature and crystallized (Table 2). The characteristics of the polyheterocyclic products formed under the conditions of thermal isomerization and some details of the experiments are given.

Phenyl(10,15,20-tribenzoyl-21,22,23,24-tetrahydroporphyrin-5-yl)methanone (15). The compound was obtained by crystallization of the residue insoluble in acetone. IR spectrum, ν, cm^{-1}: 3085, 2965, 1705, 1610, 1470, 1425, 1320, 1225, 1015. UV spectrum, λ_{max}, nm (log ε): 284.1 (4.47). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.31 (12H, s, NCH_3); 5.41 (4H, s, Het H-7,8,17,18); 6.25 (4H, s, Het H-2,3,12,13); 7.46 (8H, t, *J* = 7.8, Ph H-3,5); 7.56 (4H, t, *J* = 7.8, Ph H-4); 7.95 (8H, d, *J* = 7.8, Ph H-2,6). Mass spectrum, *m*/*z* (I_{rel}, %): 784 $[M]^+$ (3), 488 (14), 409 (11), 291 (37), 212 (21), 173 (18), 122 (14), 105 (100), 94 (94), 77 (65). Found, %: C 79.39; H 5.10. $C_{52}H_{40}N_4O_4$. Calculated, %: C 79.57; H 5.14.

(11-Benzoyl-6,12-dihydro-6,12-diazaindeno[1,2-*b*]fluoren-5-yl)phenylmethanone (19). IR spectrum, ν, cm^{-1}: 3420, 3080, 1695, 1610, 1470, 1333, 1239, 1012. UV spectrum, λ_{max}, nm (log ε): 284.8 (4.40). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 6.90 (2H, t, *J* = 7.8, Het H-3,9); 7.30 (2H, t, *J* = 7.8, Het H-4,10); 7.31 (2H, d, *J* = 7.8, Het H-2,8); 7.45 (2H, d, *J* = 7.8, Het H-5,11); 7.57 (4H, d, *J* = 7.8, Ph H-3,5); 7.73 (2H, t, *J* = 7.8, Ph, H-4); 7.99 (4H, d, *J* = 7.8, Ph H-2,6); 11.32 (2H, s, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 464 $[M]^+$ (100), 359 (5), 245 (19), 179 (10), 105 (46), 77 (24). Found, %: C 82.70; H 4.25. $C_{32}H_{20}N_2O_2$. Calculated, %: C 82.74; H 4.34.

(11-Benzoyl-6,12-dimethyl-6,12-dihydro-6,12-diazaindeno[1,2-*b*]fluoren-5-yl)phenylmethanone (20). IR spectrum, ν, cm^{-1}: 3070, 2958, 1704, 1610, 1490, 1382, 1345, 1219, 1010. UV spectrum, λ_{max}, nm (log ε): 286.7 (4.45). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.53 (6H, s, NCH_3); 6.48 (2H, t, *J* = 7.8, Het H-3,9); 6.98 (2H, t, *J* = 7.8, Het H-4,10); 7.31 (2H, d, *J* = 7.8, Het H-2,8); 7.38 (2H, d, *J* = 7.8, Het H-5,11); 7.45 (4H, d, *J* = 7.8, Ph H-3,5); 7.73 (2H, t, *J* = 7.8, Ph H-4); 8.06 (4H, d, *J* = 7.8, Ph H-2,6). Mass spectrum, *m*/*z* (I_{rel}, %): 492 $[M]^+$ (7), 388 (11), 273 (12), 249 (14), 144 (100), 105 (21), 77 (20). Found, %: C 82.84; H 4.79. $C_{34}H_{24}N_2O_2$. Calculated, %: C 82.91; H 4.91.

Isomerization of Benzoins 11 and 12 (General Procedure). A solution of the α-benzoin (1.50 mmol) was boiled in benzene (6 ml) for 1 h 30 min. The mixture was cooled, and the precipitate was filtered off and crystallized from benzene.

1-[5-(Dimethylhydrazonomethyl)furan-2-yl]-2-hydroxy-2-phenylethanone (13). Yield 53%, yellow powder; mp 160-162°C. IR spectrum, ν, cm^{-1}: 3425, 3115, 2955, 2880, 1650, 1560, 1510, 1350, 1275. UV spectrum, λ_{max}, nm (log ε): 293.8 (3.88), 375.4 (4.14). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.99 (6H, s, $N(CH_3)_2$); 5.70 (1H, d, *J* = 5.1, CHOH); 6.06 (1H, d, *J* = 5.1, CHOH); 6.54 (1H, d, *J* = 3.6, Fur H-4); 7.09 (1H, s, CH=N); 7.28 (1H, d, *J* = 7.5, Ph H-4); 7.32 (2H, t, *J* = 7.5, Ph H-3,5); 7.47 (2H, d, *J* = 7.5, Ph H-2,6); 7.65 (1H, d, *J* = 3.6, Fur H-3). Found, %: C 66.15; H 5.89. $C_{15}H_{16}N_2O_2$. Calculated %: C 66.16; H 5.92.

1-[5-(Dimethylhydrazonomethyl)-1-methyl-1H-pyrrol-2-yl]-2-hydroxy-2-phenylethanone (14). Yield 45%, yellow powder; mp 140-141°C. IR spectrum, ν, cm^{-1}: 3390, 3136, 2940, 2885, 2800, 1616, 1568, 1494, 1446, 1400, 1360, 1340, 1297, 1207, 1180, 1056, 1000, 931, 909. UV spectrum, λ_{max}, nm (log ε): 254.1 (3.74), 367.1 (4.42). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.33 (6H, s, $N(CH_3)_2$); 3.69 (3H, s, Pyr CH_3); 5.66 (1H, d, *J* = 6.9, CHOH); 5.77 (1H, d, *J* = 6.9, CHOH); 6.31 (1H, d, *J* = 4.5, Pyr H-4); 7.17 (1H, s, CH=N); 7.23 (1H, d, *J* = 4.5, Pyr H-3); 7.30 (1H, d, *J* = 9.0, Ph H-4); 7.37 (2H, t, *J* = 9.0, Ph H-3,5); 7.46 (2H, d, *J* = 9.0, Ph H-2,6). Found %: C 67.28; H 6.59. $C_{16}H_{19}N_3O_2$. Calculated %: C 67.35; H 6.71.

The work was carried out with financial support from the Ministry of Education and Science of Ukraine (State Registration No. 0104U000476).

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