STUDY OF SUBSTITUTED FORMYLCHROMONES

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Substituted derivatives of 2- and 3-formylchromone were synthesized and studied by IR, ^{13}C and ^{1}H NMR spectroscopy and the AM1 quantum chemical method. Energy and electron distribution calculations confirm the preference of the synplanar conformation in 3-formylchromones. The calculated charges on the carbon atoms correlate well with the experimental ^{13}C chemical shifts. Substituents bonded to the aromatic nucleus have only small effect on the electron structure of the pyrone ring.

Thanks to their biological activity, chromone derivatives are the subject of considerable pharmaceutical and chemical interest[1]. In connection with prediction and preparation of biologically active compounds we synthesized some derivatives of 2- and 3-formylchromone. Whereas the derivatives of 3-formylchromone were prepared by methods described in the literature[2], the hitherto used method of preparation of 2-formylchromones[3] was modified to give better results.

Conformational analysis was performed using the AM1 quantum chemical method, the electron structure was studied by ^{13}C and ^{1}H NMR spectroscopy and the theoretical AM1 method.

EXPERIMENTAL

The melting points were determined on a Kofler block and are uncorrected. IR spectra were recorded in Nujol on a Specord 75 IR instrument (Zeiss, Jena) in the region 400 – 4 000 cm^{-1}. NMR spectra were measured on an FT NMR spectrometer Bruker AM 300 at 298 K in $CDCl_3$ with tetramethylsilane as internal standard. The resolution in the ^{1}H NMR spectra was 0.12 Hz per point. Parameters of the ^{13}C NMR spectra (75.46 MHz) are as follows: relaxation delay 3 s, pulse width 30°, digital resolution 1.6 Hz per point. The ^{13}C NMR signals were assigned using a semiselective INEPT experiment, optimized to the long-range coupling constant value J = 6 Hz.

Synthesis of Nitrones *Ia – If*. General Method

A solution of sodium ethoxide (prepared from 44 mg (2 mmol) of Na and 15 ml of ethanol) was added dropwise to a cold (–5 to 0 °C) solution of the 2-methylchromone derivative (2 mmol) and

4-nitroso-*N*,*N*-dimethylaniline (0.9 g, 6 mmol) in a minimum amount of absolute ethanol and the mixture was set aside at room temperature for 10 min. The red precipitate was collected, washed with ethanol and then with ether. The product was purified by column chromatography on silica gel in chloroform and crystallized from dioxane.

Nitrones *Ig* and *Ih*

A solution of sodium ethoxide (prepared from 44 mg (2 mmol) of Na and 15 ml of ethanol) was added dropwise at 40 °C to a solution of 2-methylchromone (0.42 g, 2 mmol) and 4-nitroso-*N*,*N*-dimethylaniline (0.9 g, 6 mmol) in a minimum amount of absolute ethanol, and the solution was stirred at 40 °C for 20 min. The precipitate was collected, washed with ethanol and then with ether. The product was purified by column chromatography on silica gel in chloroform and crystallized from dioxane.

Synthesis of 2-Formylchromone (*IIa*)

Method A. A mixture of nitrone *Ia* (0.5 g, 16 mmol) and 5 M H_2SO_4 (5 ml) was stirred at room temperature for 15 min. After dilution with water (15 ml), the resulting solution was extracted with chloroform (3 × 20 ml). The chloroform layer was washed twice with water, dried over calcium chloride and the solvent was evaporated. Crystallization of the residue from ethyl acetate afforded 0.25 g (89%) of chromone *IIa*, m.p. 161 – 162 °C (reported[3] m.p. 162 – 163 °C).

Method B. A mixture of nitrone *Ia* (0.3 g, 9.6 mmol), cyclohexane (10 ml) and *p*-toluenesulfonic acid (0.4 g, 2 mmol) was stirred at room temperature for 10 min and then at 50 °C for 20 min. Water (15 ml) was added and the stirred reaction mixture was heated at 50 °C for 1 h. After cooling, the cyclohexane layer was separated, the aqueous one was extracted with cyclohexane (2 × 10 ml) and the combined cyclohexane solutions were dried. Evaporation of the solvent afforded yellow crystals of *IIa* (0.20 g, 70%) which were crystallized from ethanol; m.p. 161 – 162 °C.

Synthesis of Substituted 2-Formylchromones *IIb* – *IIh*

A mixture of the appropriate nitrone (*Ib* – *Ih*; 16 mmol) and 5 M H_2SO_4 (5 ml) was stirred at room temperature for 15 min, diluted with water (15 ml) and allowed to stand overnight. The precipitate was collected and crystallized from ethyl acetate. For yields, analyses, melting points and IR data of the products *IIb* – *IIh* see Table I.

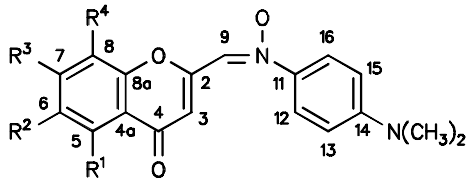
RESULTS AND DISCUSSION

Several methods of preparation of 2-formylchromones are described in the literature[3–7]. In our present study we made use of a modified method of Schmutz[3]. Condensation of substituted 2-methylchromones with 4-nitrosodimethylaniline in the presence of sodium ethoxide, followed by hydrolysis of the obtained nitrones *Ia* – *Ih* with sulfuric acid, afforded the corresponding 2-formylchromones *IIa* – *IIh* (Scheme 1).

The analytical data for nitrones *Ia* – *Ih* and 2-formylchromones *IIb* – *IIh* are given in Table I. The structure of nitrones *Ib* – *Ih* was confirmed by IR spectra (Table I), which exhibit a strong CO band of the pyrone at 1 580 – 1 623 cm^{-1} in Nujol, by ^1H NMR spectra, which display a singlet due to H-9 at δ 8.27 – 8.39 ppm and another one due to H-3 at δ 7.94 – 8.05 ppm, and also by ^{13}C NMR spectra of nitrones *Ia*, *Ib* (Table II).

TABLE I
Characteristic data of compounds *Ia – Ih* and *IIb – IIh*

Compound	Formula M.w.	M.p., °C Yield, %	Calculated/Found				IR, cm^{-1}	
			% C	% H	% N	% X	ν(C=O) pyrone	ν(HC=O)
Ia	$C_{18}H_{16}N_2O_3$	202 – 203	70.12	5.23	9.08	–	1 587	–
	308.3	58	70.23	5.28	9.12	–		
Ib	$C_{18}H_{14}Cl_2N_2O_3$	220	57.31	3.74	7.43	18.80	1 621	–
	377.2	86	57.62	3.75	7.37	18.90		
Ic	$C_{19}H_{17}ClN_2O_3$	224 – 225	63.96	4.80	7.85	9.94	1 623	–
	356.8	78	64.11	4.65	7.42	9.81		
Id	$C_{18}H_{15}BrN_2O_3$	229 – 230	55.83	3.90	7.23	20.63	1 613	–
	387.2	63	55.60	3.89	7.11	20.40		
Ie	$C_{18}H_{14}Cl_2N_2O_3$	224 – 225	57.31	3.74	7.43	18.80	1 623	–
	377.2	86	57.76	3.75	6.98	18.65		
If	$C_{19}H_{17}ClN_2O_3$	239 – 240	63.96	4.80	7.85	9.94	1 589	–
	356.8	72	63.85	4.70	7.82	9.85		
Ig	$C_{22}H_{18}N_2O_3$	219 – 221	73.73	5.06	7.82	–	1 580	–
	358.4	92	73.61	5.01	7.74	–		
Ih	$C_{22}H_{18}N_2O_3$	220 – 221	73.73	5.06	7.82	–	1 587	–
	358.4	100	73.65	5.02	7.84	–		
IIb	$C_{10}H_4Cl_2O_3$	146 – 147	49.42	1.66	–	29.17	1 659	1 708
	243.1	87	49.43	1.62	–	29.08		
IIc	$C_{11}H_7ClO_3$	169 – 170	59.35	3.17	–	15.92	1 641	1 700
	222.6	81	59.44	3.20	–	15.69		
IId	$C_{10}H_5BrO_3$	196 – 197	47.46	1.99	–	31.58	1 640	1 699
	253.1	51	47.52	1 98	–	31.83		
IIe	$C_{10}H_4Cl_2O_3$	184 – 186	49.42	1.66	–	29.17	1 639	1 700
	243.1	77	49.89	1.61	–	28.91		
IIf	$C_{11}H_7ClO_3$	190 – 191	59.35	3.17	–	15.92	1 649	1 700
	222.6	78	59.55	3.19	–	15.84		
IIg	$C_{14}H_8O_3$	196 – 197	75.00	3.60	–	–	1 633	1 707
	224.2	87	74.87	3.50	–	–		
IIh	$C_{14}H_8O_3$	216 – 217	75.00	3.60	–	–	1 644	1 707
	224.2	91	75.17	3.64	–	–		



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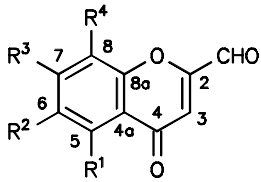

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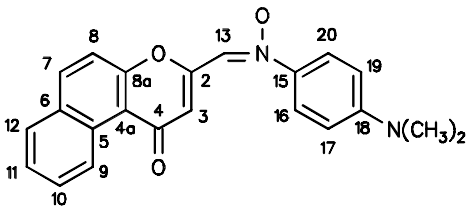
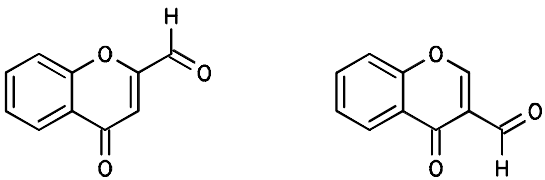


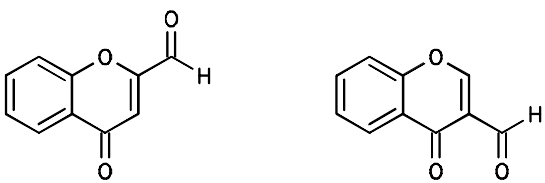
Ig

I	R^1	R^2	R^3	R^4
a	H	H	H	H
b	H	Cl	H	Cl
c	H	CH_3	H	Cl
d	H	Br	H	H
e	H	Cl	Cl	H
f	H	Cl	CH_3	H
g			H	H
h	H	H		

SCHEME 1



Synperiplanar conformation (*sp*)



Antiperiplanar conformation (*ap*)

SCHEME 2

TABLE II

^{1}H NMR spectra of the nitrones *Ia – Ih*, 2-formylchromones *IIb – IIh* and ^{13}C NMR spectra of the nitrones *Ia*, *Ib*

Compound	δ, ppm (*J*, Hz)
Ia	^{1}H NMR: 8.27 s, 1 H (H-9); 8.19 dd, 1 H, $J_{5,6}$ = 7.6, $J_{5.7}$ = 1.6 (H-5); 7.95 s, 1 H (H-3); 7.69 d, 2 H, $J_{12,13}$ = 9.3, (H-12 and H-16); 7.66 dd, 1 H, $J_{6,5}$ = 7.8, $J_{6,7}$ = 7.1 (H-6); 7.41 d, 1 H, $J_{8,7}$ = 8.2 (H-8); 7.38 ddd, 1 H, $J_{7,6}$ = 7.1, $J_{7,8}$ = 8.2, $J_{7,5}$ = 1.6 (H-7); 6.66 d, 2 H, $J_{13,12}$ = 9.3 (H-13 and H-15); 3.06 s, 6 H (CH_3) ^{13}C NMR: 155.8 (C-2), 117.7 (C-3), 179.1 (C-4), 124.4 (C-4a), 125.6 (C-5), 124.9 (C-6), 133.8 (C-7), 110.6 (C-8), 152.0 (C-8a), 124.3 (C-9), 137.4 (C-11), 122.3 (C-12), 111.0 (C-13), 155.8 (C-14), 111.0 (C-15), 122.3 (C-16), 40.2 ($N(CH_3)_2$)
Ib	^{1}H NMR: 8.27 s, 1 H (H-9); 8.10 d, 1 H, $J_{5,7}$ = 2.1 (H-5); 8.05 s, 1 H (H-3); 7.73 d, 1 H, $J_{7,5}$ = 2.1 (H-7); 7.73 d, 2 H, $J_{12,13}$ = 9.1 (H-12 and H-16); 6.71 d, 2 H, $J_{13,12}$ = 9.1 (H-13 and H-15); 3.08 s, 6 H (CH_3) ^{13}C NMR: 156.2 (C-2), 110.2 (C-3), 177.2 (C-4), 126.2 (C-4a), 123.9 (C-5), 130.6 (C-6), 133.8 (C-7), 124.2 (C-8), 150.1 (C-8a), 123.6 (C-9), 137.4 (C-11), 122.4 (C-12), 111.1 (C-13), 152.2 (C-14), 111.1 (C-15), 122.4 (C-16), 40.3 ($N(CH_3)_2$)
Ic	^{1}H NMR: 8.30 s, 1 H (H-9); 8.02 s, 1 H (H-3); 7.90 d, 1 H, $J_{5,7}$ = 2.5 (H-5); 7.71 d, 2 H, $J_{12,13}$ = 9.3 (H-12 and H-16); 7.55 d, 1 H, $J_{7,5}$ = 2.5 (H-7); 6.68 d, 2 H, $J_{13,12}$ = 9.3 (H-13 and H-15); 3.06 s, 6 H (CH_3); 2.43 s, 3 H (CH_3)
Id	^{1}H NMR: 8.32 s, 1 H (H-9); 8.28 d, 1 H, $J_{5,7}$ = 2.4 (H-5); 7.94 s, 1 H (H-3); 7.74 dd, 1 H, $J_{7,8}$ = 8.9, $J_{7,5}$ = 2.4 (H-7); 7.69 d, 2 H, $J_{12,13}$ = 7.3 (H-12 and H-16); 7.30 d, 1 H, J = 8.9 (H-8); 6.68 d, 2 H, $J_{13,12}$ = 7.3 (H-13 and H-15); 3.06 s, 6 H (CH_3)
Ie	^{1}H NMR: 8.27 s, 1 H (H-9); 8.25 s, 1 H (H-5); 8.22 s, 1 H (H-8); 7.92 s, 1 H (H-3); 7.69 d, 2 H, $J_{12,13}$ = 9.3 (H-12 and H-16); 6.67 d, 2 H, $J_{13,12}$ = 9.27 (H-13 and H-15); 3.05 s, 6 H (CH_3)
If	^{1}H NMR: 8.34 s, 1 H (H-9); 8.22 brs, 2 H (H-5 and H-8); 7.92 s, 1 H (H-3); 7.69 d, 2 H, $J_{12,13}$ = 9.3 (H-12 and H-16); 6.68 d, 2 H, $J_{13,12}$ = 9.3 (H-13 and H-15); 3.07 s, 6 H (CH_3)
Ig	^{1}H NMR: 10.08 dd, 1 H, $J_{9,10}$ = 7.9, $J_{9,11}$ = 1.0 (H-9); 8.39 s, 1 H (H-13); 8.08 d, 1 H, $J_{7,8}$ = 9.0 (H-7); 8.01 s, 1 H (H-3); 7.90 dd, 1 H, $J_{12,11}$ = 8.1, $J_{12,10}$ = 1.2 (H-12); 7.76 ddd, 1 H, $J_{10,9}$ = 7.9, $J_{10,11}$ = 6.9, $J_{10,12}$ = 1.2 (H-10); 7.72 d, 2 H, $J_{16,17}$ = 9.3 (H-16 and H-20); 7.61 ddd, 1 H, $J_{11,9}$ = 1.0, $J_{11,12}$ = 8.1 (H-11); 7.47 d, 1 H, $J_{8,7}$ = 9.0 (H-8); 6.68 d, 2 H, $J_{17,16}$ = 9.3 (H-17 and H-19); 3.08 s, 6 H (CH_3)
Ih[a]	^{1}H NMR: 8.62 – 7.50 m, 9 H (Ar-H); 8.37 s, 1 H (H-13); 6.70 d, 2 H, $J_{17,16}$ = 9.3 (H-17 and H-19); 3.06 s, 6 H (CH_3)
IIb	^{1}H NMR: 9.87 s, 1 H (CHO); 8.08 d, 1 H, $J_{5,7}$ = 2.5 (H-5); 7.82 d, 1 H, $J_{7,5}$ = 2.5 (H-7); 6.96 s, 1 H (H-3)
IIc	^{1}H NMR: 9.86 s, 1 H (CHO); 7.89 d, 1 H, $J_{5,7}$ = 2.5 (H-5); 7.67 d, 1 H, $J_{7,5}$ = 2.5 (H-7); 6.92 s, 1 H (H-3); 2.46 s, 3 H (CH_3)
IId	^{1}H NMR: 9.80 s, 1 H (CHO); 8.34 d, 1 H, $J_{5,7}$ = 2.5 (H-5); 7.86 dd, 1 H, $J_{7,8}$ = 8.9, $J_{7,5}$ = 2.5 (H-7); 7.52 d, 1 H, $J_{8,7}$ = (H-8); 6.94 s, 1 H (H-3)

TABLE II
(*Continued*)

Compound	δ, ppm (*J*, Hz)
IIe	^{1}H NMR: 9.76 s, 1 H (CHO); 8.25 s, 1 H (H-5); 8.15 s, 1 H (H-8); 7.16 s, 1 H (H-3)
IIf	^{1}H NMR: 9.76 s, 1 H (CHO); 7.97 s, 1 H (H-5); 7.84 s, 1 H (H-8); 7.11 s, 1 H (H-3); 2.48 s, 3 H (CH_3)
IIg[a]	^{1}H NMR: 9.97 dd, 1 H, $J_{9,10}$ = 8.7, $J_{9,11}$ = 1.0 (H-9); 9.84 s, 1 H (CHO); 8.19 d, 1 H, $J_{7,8}$ = 9.0 (H-7); 7.95 dd, 1 H, $J_{12,11}$ = 8.1, $J_{12,10}$ = 1.2 (H-12); 7.80 ddd, 1 H, $J_{10,9}$ = 8.7, $J_{10,11}$ = 7.0, $J_{10,12}$ = 1.2 (H-10); 7.67 ddd, 1 H, $J_{11,9}$ = 1.0, $J_{11,10}$ = 7.0, $J_{11,12}$ = 8.1 (H-11); 7.64 d, 1 H, $J_{8,7}$ = 9.0 (H-8); 7.06 s, 1 H (H-3)
IIh	^{1}H NMR: 9.90 s, 1 H (CHO); 8.10 – 7.75 m, 6 H (Ar-H); 7.25 s, 1 H (H-3)

[a] Numbering of atoms is the same as in *Ig*.

The structure of 2-formylchromones *IIa – IIh* was confirmed by IR spectra which show an aldehyde band at 1 699 – 1 708 cm^{-1} and a strong CO band of the pyrone at 1 633 – 1 659 cm^{-1}; the ^{1}H NMR spectra show an aldehyde proton signal at δ 9.76 – 9.90 ppm whereas the H-3 signal is located at δ 6.92 – 7.25 ppm (Table II). The ^{13}C NMR spectral data for aldehydes *IIa – IId* are given in Table III; the data for compound *IIa* were taken from the literature[8].

Substituted 3-formylchromones *IIIa – IIId* were prepared according to Nohara[2] by reaction of the corresponding *o*-hydroxyacetophenones with the Wilsmeier reagent. The structure of the obtained compounds and their ^{13}C NMR spectral data are listed in Table IV, the data for compound *IIIa* being again taken from the literature[8].

Compounds *IIa – IId* and *IIIa – IIId* were studied by semiempirical quantum chemical method AM1 (ref.[9]). We studied both planar arrangements of the formyl group relative to the pyrone C=C double bond: the synperiplanar, *sp*, and antiperiplanar, *ap*, arrangement (Scheme 2). We performed full optimization of the geometry for both conformations of unsubstituted 2- as well as 3-formylchromone. The thus-obtained geometries were used as input for the calculation of electron structure and energy of the substituted derivatives. The calculated charges *Q* on the carbon atoms are listed in Tables III and IV. As seen, comparison with the observed values of ^{13}C NMR chemical shifts shows a good accord. For all the carbon atoms there is a linear relationship $Q = a\ \delta(^{13}C) + b$ with regression coefficient r = 0.910 – 0.945. A change of substituent on the aromatic ring results in a relatively small shift of the δ values in ^{13}C NMR spectra and thus in a relatively small change of the calculated charge on the carbon atoms of the pyrone ring and the formyl group.

The calculated heats of formation for 3-formylchromones are about 32 kJ/mol lower than those for the corresponding isomeric 2-formylchromones.

The dependence of the heat of formation on the dihedral angle about the single bond C–CHO in 3-formylchromone and its derivatives shows that the planar *sp* conformation is more stable than the *ap* rotamer. Tsukerman and coworkers[10] on the basis of IR spectra and dipole moments of 3-formylchromones also assume the preference of *sp* conformation that may be stabilized by hydrogen bonding between the pyrone carbonyl and the hydrogen atom of the formyl group. Experimental values of dipole moments of 3-formylchromones[10] are also closer to those calculated for the *sp* conformation (Table IV).

TABLE III
Calculated and experimental characteristics of 2-formylchromone derivatives *IIa* – *IId*

Parameter	*IIa*	*IIb*	*IIc*	*IId*
$\Delta\Delta H_f$[a]	4.0	−3.3	−3.9	3.5
μ, D[b]	4.28 0.96	3.23 0.42	3.82 1.29	3.93 1.05
		Charge (chemical shift)[c]		
C-2	−17(156.7)	−15(155.9)	−14(155.7)	−18(156.0)
C-3	−219(117.8)	−219(115.1)	−221(115.2)	−216(116.8)
C-4	301(178.3)	302(176.4)	302(177.6)	301(176.9)
C-4a	−198(124.4)	−178(125.3)	−184(125.7)	−198(126.0)
C-5	−44(126.4)	−46(124.0)	−47(124.0)	−17(128.6)
C-6	−164(125.3)	−99(132.1)	−98(136.8)	−210(119.8)
C-7	−74(135.8)	−78(135.2)	−77(136.4)	−51(138.2)
C-8	−158(119.2)	−94(126.5)	−100(123.4)	−157(120.7)
C-8a	100(155.3)	97(149.9)	93(149.5)	111(154.3)
CHO	228(187.7)	228(184.5)	228(185.0)	228(185.0)
O-1	−134	−120	−122	−132
O-4	−287	−278	−284	−280
OCH	−251	−248	−250	−248
H-3[d]	186(6.91)	189(6.96)	187(6.92)	188(6.94)
HCO[d]	127(9.80)	131(9.87)	130(9.86)	128(9.80)
C=O[e]	1.856	1.863	1.858	1.861
HC=O[e]	1.950	1.954	1.952	1.953

[a] Energy difference (kJ/mol) between *ap* and *sp* conformation by AM1. [b] Calculated values for *sp* and *ap* conformation. [c] Values of AM1 charge (Q . 10^3) for *sp* conformation, ^{13}C NMR shift in parentheses. [d] ^{1}H NMR shift in parentheses. [e] Bond orders for *sp* conformation.

The relatively large energy difference between *sp* and *ap* conformation in 3-formylchromones (Table IV) can be explained by destabilization of the *ap* conformation by strong repulsion between the carbonyl oxygen of the pyrone ring and the formyl group. On the other hand, the great negative charge on the formyl oxygen atom as well as the considerable positive charge on H-2 of the pyrone ring may stabilize the *sp* conformation by an intramolecular hydrogen bond H-2 ... O(formyl). The enhanced acidity of the H-2 hydrogen atoms in 3-formylchromones is also evident from comparison of their

TABLE IV
Calculated and experimental characteristics of 3-formylchromone derivatives *IIIa* – *IIId*

Parameter	*IIIa*	*IIIb*	*IIIc*	*IIId*
$\Delta\Delta H_f$[a]	24.3	20.7	19.7	23.3
μ, D[b]	4.44 5.58 (4.76)	3.14 4.72 –	4.67 5.59 (4.97)	5.26 8.59 (6.44)
		Charge (chemical shift)[c]		
C-2	122(160.7)	119(160.3)	118(160.4)	115(160.8)
C-3	−359(120.3)	−355(120.2)	−358(120.0)	−345(120.5)
C-4	324(175.8)	325(174.1)	325(175.8)	322(174.4)
C-4a	−187(125.3)	−169(125.0)	−182(124.8)	−203(125.6)
C-5	−48(124.1)	−46(124.1)	−50(125.3)	23(122.6)
C-6	−157(126.6)	−84(132.5)	−98(136.7)	−132(145.6)
C-7	−79(134.8)	−77(134.9)	−83(135.8)	−19(129.1)
C-8	−148(118.6)	−78(127.2)	−145(118.2)	−159(120.5)
C-8a	79(156.2)	84(150.5)	76(154.3)	127(158.8)
CHO	243(188.5)	244(187.5)	244(188.5)	241(187.3)
O-1	−123	−109	−123	−117
O-4	−304	−293	−304	−282
OCH	−308	−298	−304	−296
H-2[d]	203(8.90)	206(8.60)	200(8.45)	211(8.60)
HCO[d]	130(10.16)	129(10.34)	127(10.29)	136(10.36)
C=O[e]	1.847	1.855	1.846	1.864
HC=O[e]	1.904	1.910	1.910	1.915
OC–H[e]	0.906	0.905	0.912	0.905

[a] Energy difference (kJ/mol) between *ap* and *sp* conformations. [b] Calculated values for *sp* and *ap* conformation, in parentheses the experimental values[10]. [c] Values of AM1 charge ($Q \cdot 10^3$) for *sp* conformation, ^{13}C NMR shift in parentheses. [d] ^{1}H NMR shift in parentheses. [e] Bond orders for *sp* conformation.

^{1}H NMR shifts in compounds *IIIa – IIId* with those of the H-3 atoms in substituted 2-formylchromones *IIa – IId*.

In the case of 2-formylchromone derivatives, the difference between the heats of formation for the *sp* and *ap* conformations is too small to allow determination of the preferred form (Table III). Whereas the *sp* conformation is slightly preferred in compounds *IIa* and *IId*, the presence of chlorine atom in position 8 (compounds *IIb*, *IIc*) probably reverses the energetic situation in favour of the *ap* conformer.

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