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Chiroptical Properties of Anilides of (+)- β -Methylhydrocinnamic Acid

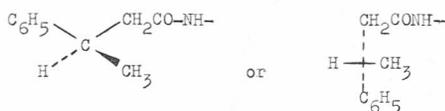
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A series of substituted anilides of (+)- β -methylhydrocinnamic acid were synthesized and their CD- and UV-spectra were measured. All compounds (with the exception of para-nitro- and ortho-methyl-substituted) show positive Cotton effects at about 240 and 210 nm, which were attributed, respectively, to the anilide and aromatic chromophores interacting with each other.

The chiroptical properties of simple amides have been thoroughly investigated. At the same time there are few works concerning the chiroptical properties of anilides¹⁻⁴. It was shown that the anilide absorption band at about 240 nm was optically active. For a detailed study of the chiroptical properties of the anilide chromophore and its interaction with an aromatic one we have synthesized a series of anilides of (S) (+)- β -methylhydrocinnamic acid (*Ia-m*) and measured their UV- and CD-spectra in the 400—200 nm region in ethanol and dioxane.



- I : a, X = H; b, X = 4-CH₃; c, X = 4-OCH₃; d, X = 4-OH;
 e, X = 4-Br; f, X = 4-NO₂; g, X = 2-CH₃; h, X = 2-OCH₃;
 i, X = 2-OH; j, X = 2-Cl; k, X = 2-Br; l, X = 3-OH;
 m, X = 3-NO₂.

The unsubstituted anilide of (+)- β -methylhydrocinnamic acid (*Ia*) shows a strong Cotton effect (CE) at about 240 nm. Furthermore, there are two more CEs: a strong positive one at 210 nm due to the ¹L_a transition and a very weak positive one in the longwave region (290—270 nm) due to the ¹L_b transition of aromatic chromophore⁵. The longwave-length CE is considerably obscured by the more intense CE at about 240 nm, like in the case of the parent acid⁶.

The position of the 240 nm CE does not depend on the solvent, but its magnitude increases in dioxane in comparison with ethanol (Figure 1).

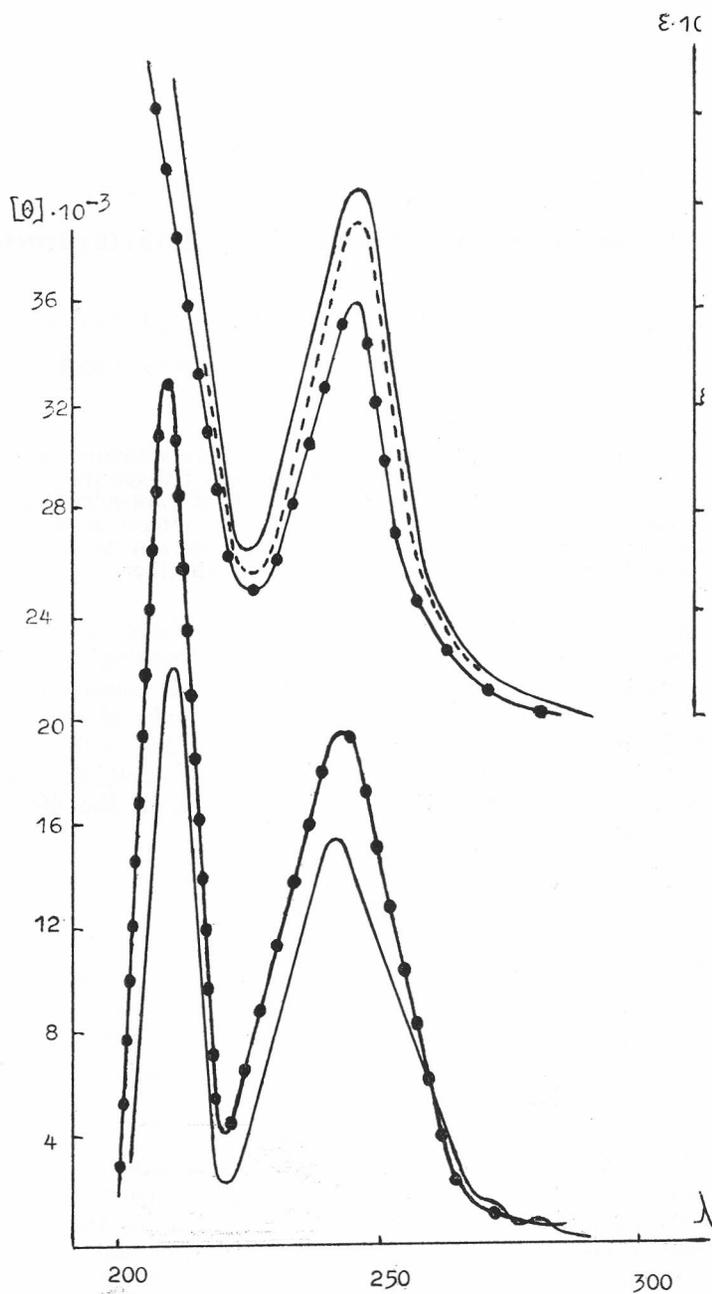


Figure 1. CD- and UV-spectra of Ia in ethanol (—), in dioxane (---) (UV-spectrum of IIb in ethanol (—)).

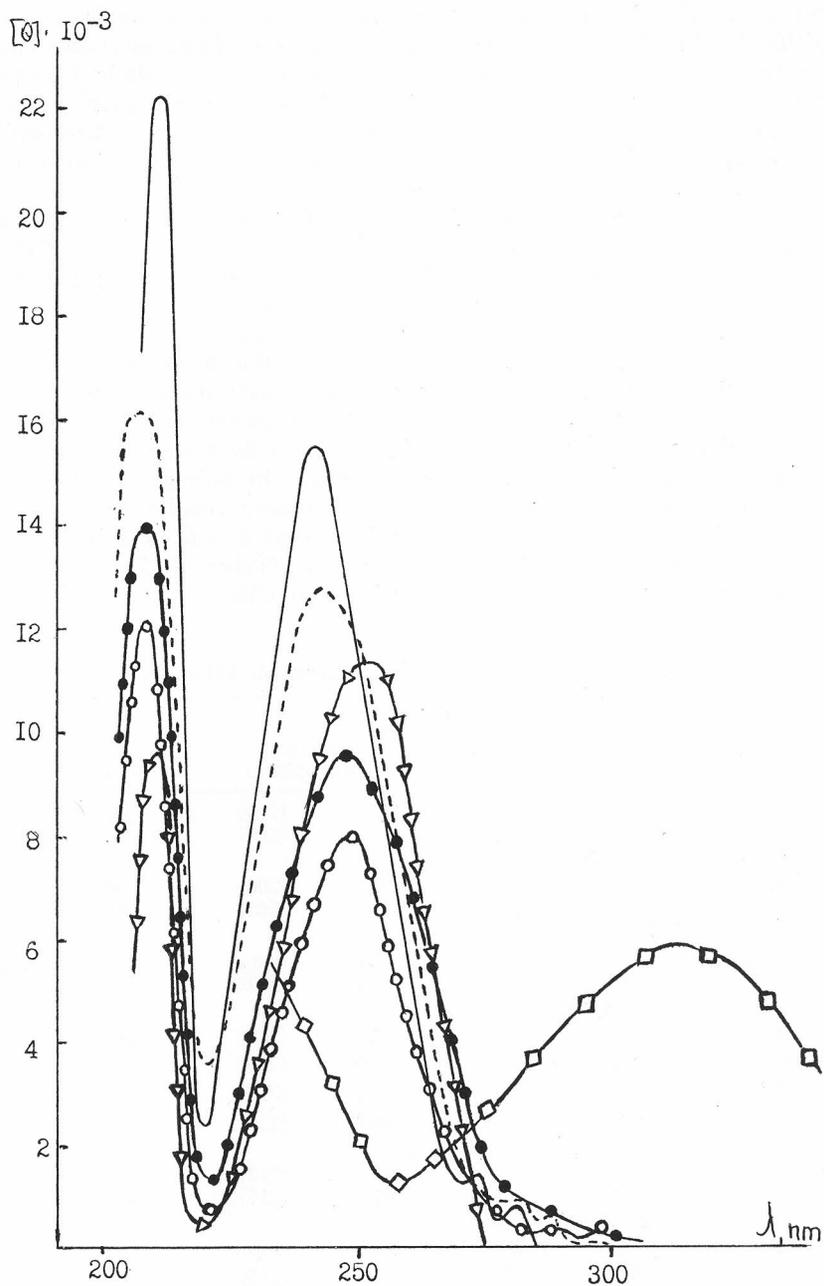


Figure 2. CD-spectra of p-substituted anilides (in ethanol): *Ib* (-----) *Ic* (—●—●—●—), *Id* (—○—○—○—), *Ie* (—△—△—△—), *If* (—□—□—□—), *Ia* (—).

The para-substituted anilides (*Ib-e*) exhibit two positive CEs at 250–240 nm and about 210 nm (Figure 2). A change of the solvent leads to a negligible shift (1–2 nm) of the 240 nm CES and its magnitude increases slightly. The position of the observed CEs is in accordance with their UV-spectra. Anilides *Ib, d* show a very weak CE in the 300–280 nm region, caused by the 1L_b band of the aromatic chromophore, like in the case of unsubstituted anilide *Ia*. This CE is not observed for anilides *Ic, e*, perhaps because it is masked by the intense CE at about 240 nm.

The *p*-nitroanilide *If* differs from the other members of the studied series. We were able to measure only the positive CE at 315 nm (Figure 2), which is due to the electronic transition in nitrobenzene chromophore and is in accordance with the UV-spectra. It was not possible to measure the shortwave CE because of a very low signal-to-noise ratio.

From the comparison of the CD-spectra of the unsubstituted (*Ia*) and the para-substituted anilides (*Ib-j*) it can be seen that there is no correlation between the donor-acceptor properties of the para-substituent in the anilide moiety and the position and magnitude of the CEs caused by the anilide and aromatic chromophores. The introduction of the substituent (CH₃, OCH₃, OH, Br) into the para-position of the anilide moiety results in a bathochromic shift of the CE in the anilide absorption region and in a hypsochromic shift of the 1L_a CE (with the exception of Br) (Table I). Para-substituents slightly decrease the magnitudes of the observed CEs.

TABLE I
UV- and CD-data of Anilides Ia-m (in Ethanol)

I	X	[θ] · 10 ⁻³ (λ /nm)				λ_{\max} /nm (ϵ)	
		Anilide chromophore		Aromatic chromophore			
<i>a</i>	H	15.4	(241)	22.1	(210)	242	(12000)
		19.4	(243)	32.9	(209)	240	(10700)
<i>b</i>	4-CH ₃	12.7	(243)	16	(206)	250	(15000)
		15.4	(244)	22.3	(205)	250	(13500)
<i>c</i>	4-OCH ₃	9.5	(247)	13.8	(208)	253	(12200)
		9.2	(249)	15.5	(220!)		
		(dioxane)					
<i>d</i>	4-OH	7.9	(249)	12.1	(208)	254	(14400)
<i>e</i>	4-Br	11.3	(252)	9.5	(210)	255	(18500)
<i>f</i>	4-NO ₂			5.8	(315)	323	(14500)
<i>g</i>	2-CH ₃	10.5	(231, shoulder)	29.4	(211)	236	(6300, shoulder)
<i>i</i>	2-OCH ₃	1.6	(244)	65	(213)	246	(28200)
		1.4	(244)	67	(217)	246	(26500)
		(dioxane)					
<i>j</i>	2-OH	5.8	(241)	21	(218!)	246	(12200)
	2-Cl	9	(236)	34.2	(215)	242	(24400)
<i>k</i>	2-Br	6.8	(239)	43	(217)	238	(26200, shoulder)
<i>l</i>	3-OH	9.3	(248)			250	(11200)
<i>m</i>	3-NO ₂	50.2	(241)	14	(224)	247	(21200)

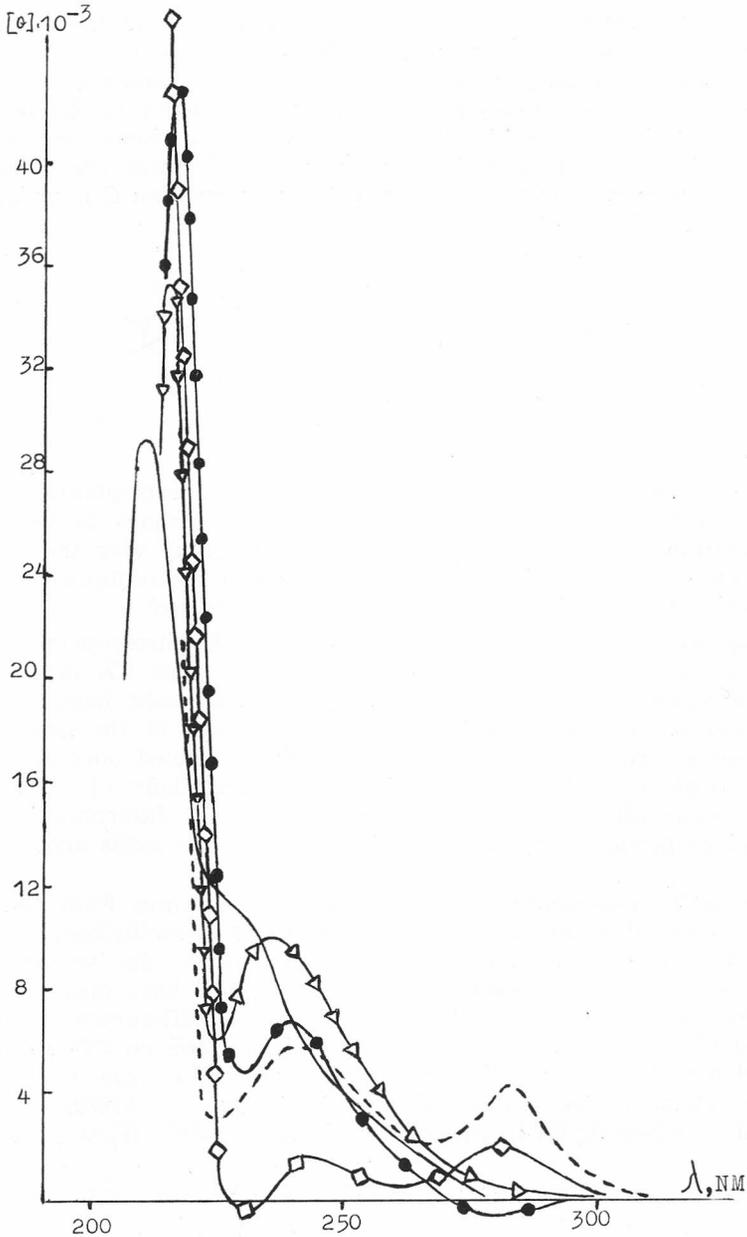


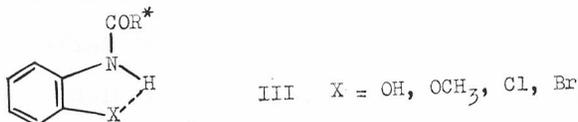
Figure 3. CD-spectra of *o*-substituted anilides (in ethanol): *Ig* (—), *Ih* (—□—□—□—), *Ii* (---), *Ij* (—△—△—△—), *Ik* (—●—●—●—).

disappearance of the anilide chromophore. Due to the steric hindrance of the ortho-methyl group in *Ig*, the amido-group adopts a position out of plane of the aromatic ring, so there is no conjugation between phenyl and amido groups in this compound. Consequently, we must regard the interaction of

the aromatic chromophore of the acid moiety mainly with the amide chromophore but not with the anilide one. It was shown earlier that β -methylhydrocinnamic acid amide exhibited a CD-band only in the 220 nm region⁶.

The ortho-substituted anilides *Ih-k* show two positive CEs: one in the 240 nm region and the second at about 210 nm. The blue shift of the 230–240 nm band for the *o*-Br-substituted anilide and the red shift for the *o*-HO- and *o*-CH₃O-substituted anilides (*Ik, i, h*) appear in comparison with the bands of the unsubstituted analogue *Ia* (Table I).

The CE at 210 nm can be attributed to the ¹L_a aromatic band, like in the case of the unsubstituted anilide *Ia*. The *o*-methoxy- and *o*-hydroxy-substituted anilides (*Ih, k*) show weak positive CEs near 280 nm, which can be assigned to the ¹L_b aromatic band. The 240 nm CE is associated with the anilide chromophore. The formation of the cyclic structure *III* for such anilides due to the intramolecular hydrogen bond was reported¹⁰



The intramolecular hydrogen bond between the amide proton and an ortho-substituent of the aromatic ring brings the amide group and the aromatic ring into coplanarity, thus retaining the anilide chromophore in contrast to the ortho-methyl analogue in which such hydrogen bonding is impossible. Structure *III* is confirmed for *Ih* by its ¹H NMR-spectrum in which the remaining ortho-proton of the anilide moiety is seen due to its deshielding by amide carbonyl (δ 8.30 ppm, 1H).

Introduction of the metha-substituent (compounds *Il, m*) causes no steric effect and the CD-curves of these anilides are very similar to that of the unsubstituted (in the case of *Im*, up to 220 nm) or para-substituted (*Il*) anilides.

EXPERIMENTAL

CD-spectra were measured with a JASCO spectropolarimeter model *J-20* in cells of 0.1 and 0.05 cm path lengths. Concentrations were about 0.1–1.0 mg/ml. UV-spectra were recorded with a Specord spectrometer.

The optically active anilides (*Ia-m*) were synthesized by the reaction of (+)- β -methylhydrocinnamoyl chloride with the corresponding anilines (Table II).

The anilide of (+)-2-methylbutyric acid (*Ia*) was prepared from its chloride and aniline, yield 63%, m. p. 96–97 °C (benzene-dioxane).

Anal. C₁₁H₁₅NO calc'd: C 74.53; H 8.47. Found: C 74.20; H 7.85.

ORD (in ethanol): 375 nm (+470), 290 (+1460), 240 (+1800);

(in dioxane): 375 (+183), 290 (+668), 240 (+950).

The anilide of (+)-3-methylvaleric acid (*Ib*) was prepared from its chloride and aniline, yield 70%, m. p. 68–87 °C (benzene-dioxane).

Anal. C₁₂H₁₇NO calc'd: C 75.7; H 9.01.

Found: C 75.97; H 9.01.

UV-spectra (in ethanol): λ_{\max} 241 nm (ϵ 11800).

ORD (in ethanol): 350 (+76), 290 (+142), 240 (+212);

(in dioxane): 375 (+36), 290 (+54), 245 (+86).

TABLE II
 Substituted Anilides of (+)- β -Methylhydrocinnamic Acid

I	X	Yield %	M. p. °C	IR-spectrum $\nu_{\text{NH}}/\text{cm}^{-1}$		Formular	Anal. % C	Calcd. Found % H
				Amide I	Amide II			
a	H	90	145—146	3252		C ₁₆ H ₁₇ NO	80.30	7.16
				1656	1560		79.91	7.24
b	4-CH ₃	69	117—117.5	3330		C ₁₇ H ₁₉ NO	80.63	7.56
				1664	1550		80.62	7.39
c	4-OCH ₃	80	138—139	3320		C ₁₇ H ₁₉ NO ₂	75.81	7.11
				1680	1575		75.88	7.28
d	4-OH	76	152—153	3450		C ₁₆ H ₁₇ NO ₂	75.30	6.66
				1700	1530		75.30	6.68
e	4-Br	85	142—143	3315		C ₁₆ H ₁₆ NOBr	60.39	5.07
				1670	1545		60.49	5.04
f	4-NO ₂	65	100—101	3308		C ₁₆ H ₁₆ N ₂ O ₃	67.59	5.67
				1660	1542		67.45	5.60
g	2-CH ₃	72	113—113.5	3463		C ₁₇ H ₁₉ NO	80.63	7.56
				1715	1567		80.85	7.58
h	2-OCH ₃	77	71—72	3439, 3395		C ₁₇ H ₁₉ NO ₂	75.81	7.11
				1700	1540		75.96	6.86
i	2-OH	68	103—105	3434, 3400		C ₁₆ H ₁₇ NO ₂	75.30	6.66
				1675	1510		75.35	7.14
j	2-Cl	70	83—84	3432		C ₁₆ H ₁₆ NOCl	74.00	6.16
				1605	1560		73.91	6.60
k	2-Br	65	95—96	3294		C ₁₆ H ₁₆ NOBr	63.13	5.26
				1665	1540		63.43	5.69
l	3-OH	61	122—123	3318		C ₁₆ H ₁₇ NO ₂	75.30	6.66
				1660	1570		75.02	7.02
m	3-NO ₂	70	68—70	3300		C ₁₆ H ₁₆ N ₂ O ₃	67.59	5.67
				1670	1540		67.18	5.76

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SAŽETAK**Kiroptička svojstva anilida (+)- β -metoksihidrociniamske kiseline**

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Pripravljen je niz supstituiranih anilida (+)- β -metilhidrociniamske kiseline i izmjereni njihovi CD- i UV-spektri. Svi spojevi, s izuzetkom p-nitro i o-metil-supstituiranih derivata, pokazuju pozitivne Cottonove efekte oko 240 nm i 210 nm, koji se pripisuju anilidu i aromatskim kromoforima u interakciji.