

## OPTICAL ROTATORY DISPERSION OF DIMETHYLAMIDES OF ALDONIC ACIDS\*

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Optical rotations of dimethylamides of aldonic acids were found not to obey the Hudson amide rule in contrast to the corresponding monomethylamides and primary amides. As shown by spectropolarimetric measurements, the anomalous behaviour of dimethylamides is due to a bathochromic and hyperchromic shift of the  $\pi-\pi^*$  transition dichroic band of their amide bond.

In connection with investigations on the chemistry of lactones of dideoxyhexonic acids, numerous amides of these acids have been prepared in the Laboratory of Monosaccharides<sup>1-4</sup>. In addition to characterisation of the appropriate acids, the amides could serve to determine the configuration of starting lactones on the basis of the Hudson amide rule<sup>5,6</sup>. According to the Freudenberg modification<sup>7,8</sup> of this rule, the amide of an  $\alpha$ -hydroxy acid with D-configuration at C<sub>(2)</sub> is more dextro-rotatory than the parent acid while the corresponding amide with L-configuration at C<sub>(2)</sub> is more laevo-rotatory than the parent acid. Consequently, the difference between molecular rotations of the amide and the acid should be positive in the former case and negative in the latter. In one of our earlier papers<sup>2</sup>, we have drawn attention to the exceptional value of optical rotation (from the standpoint of the amide rule) of the dimethylamide of 4,6-dideoxy-L-xylo-hexonic acid when compared with rotations of the amide itself and monosubstituted amides. This behaviour of dimethylamides has been observed also in several other cases. It appeared therefore of interest to investigate the optical rotation of dimethylamides of aldonic acids in detail from the standpoint of the knowledge on chiroptical properties of the amide bond and in connection with investigations on amino acids<sup>9</sup> and peptides<sup>10</sup> being in progress in Department of Peptide Chemistry, Institute of Organic Chemistry and Biochemistry.

\* Dedicated to the memory of Professor R. Lukeš (deceased 1960).

Compounds of the above mentioned type do not appear frequently in the literature. Thus, several disubstituted amides of D-gluconic acid, bis(2-hydroxyethyl)amide of D-mannonic acid<sup>11</sup>, and dimethylamides of L- and D-idonic acid<sup>12</sup> have been reported. Their specific rotations, if measured, are in accordance with our observations, *i.e.*, at variance with the amide rule. For general considerations it was necessary to study disubstituted amides of aldonic acids with various configuration of the sugar residues. We have now prepared (see Table I) dimethylamides of the following

TABLE I  
Dimethylamides of Aldonic Acids

Amide	Yield %	M.p., °C (solvent)	Formula (m.w.)	Calculated/Found			$R_F$ $R_S^a$
				% C	% H	% N	
<i>I</i>	63	117–117.5 (2-propanol)	$C_7H_{15}NO_5$ (193.2)	43.52 43.46	7.83 7.85	7.25 7.11	0.39 1.39
<i>II</i>	60	114–116 (2-propanol)	$C_7H_{15}NO_5$ (193.2)	43.52 43.72	7.83 7.95	7.25 7.47	0.37 1.32
<i>III</i>	60	145–146 <sup>b</sup> (methanol–light petroleum 1 : 1)	$C_8H_{17}NO_6$ (223.4)	43.04 43.43	7.67 7.74	6.28 6.24	0.28 1.00
<i>IV</i>	80	131–132 (ethanol–acetone 1 : 1)	$C_8H_{17}NO_6$ (223.4)	43.04 43.07	7.67 7.91	6.28 6.09	0.29 1.04
<i>V</i>	81	142–143 (2-propanol)	$C_8H_{17}NO_6$ (223.4)	43.04 43.19	7.67 7.78	6.28 6.47	0.25 0.89
<i>VI</i>	81	194–195 (water–acetone 1 : 1)	$C_8H_{17}NO_6$ (223.4)	43.04 42.82	7.67 7.70	6.28 6.26	0.21 0.75
<i>IX</i>	79	197–198 (water–acetone 1 : 5)	$C_9H_{19}NO_7$ (253.3)	42.68 42.83	7.56 7.53	5.53 5.56	0.21 0.75
<i>X</i>	75	140–142 (methanol)	$C_9H_{19}NO_7$ (253.3)	42.68 42.80	7.56 7.66	5.53 5.38	0.26 0.93
<i>XI</i>	60	167–168 (2-propanol)	$C_8H_{17}NO_5$ (207.2)	46.37 46.61	8.27 8.34	6.76 6.80	0.45 1.61
<i>XII</i>	92	71–73 (dichloromethane–tetra- chloromethane)	$C_8H_{17}NO_4$ (191.2)	50.25 50.15	8.96 8.93	7.33 7.55	0.52 1.86
<i>XIII</i>	88	103.5–104.5 (chloroform–tetrachloro- methane–light petroleum 3 : 1 : 1)	$C_8H_{17}NO_4$ (191.2)	50.25 50.24	8.96 9.19	7.33 7.34	0.47 1.68
<i>XIV</i>	76	sirup	$C_8H_{17}NO_4$ (191.2)	50.25 50.24	8.96 9.13	7.33 7.38	0.52 1.86
<i>XV</i>	22	76–78 (tetrachloromethane)	$C_8H_{17}NO_4$ (191.2)	50.25 50.33	8.96 9.02	7.33 7.30	— —

<sup>a</sup>  $R_S$  values refer to the dimethylamide of D-gluconic acid (*III*); <sup>b</sup> reported<sup>13</sup>, m.p. 140–141°C [ $\alpha_D^{20} - 30.9^\circ$  (*c* 2.1, water)].

acids: D-ribonic acid (*I*), D-arabonic acid (*II*), D-gluconic acid (*III*), D-gulonic acid (*IV*), D-galactonic acid (*V*), L-mannonic acid (*VI*), D-glycero-L-manno-heptonic acid (*IX*), D-glycero-D-gulo-heptonic acid (*X*), L-rhammonic acid (*XI*), 4,6-dideoxy-L-ribo-hexonic acid (*XII*), 4,6-dideoxy-L-xylo-hexonic acid (*XIII*), 4,6-dideoxy-L-arabo-hexonic acid (*XIV*), and 4,6-dideoxy-L-lyxo-hexonic acid (*XV*). Table II contains values of specific and molecular rotations of the above amides along with rotations of parent acids and the reported data<sup>12</sup> of dimethylamides of D-idonic acid (*VII*) and L-idonic acid (*VIII*). It may be seen from Table II that the optical rotation of all dimethylamides studied is at variance with the amide rule. Since the optical rotation of the corresponding unsubstituted amides and mono-substituted amides is in accordance with this rule, it may be concluded that the anomalous behaviour of dimethylamides is due to the double substitution of the nitrogen atom.

TABLE II  
Optical Rotation of Aldonic Acids and Their Dimethylamides in Water

Compound	Configuration at C <sub>(2)</sub>	Dimethylamide			Acid <sup>a</sup>			$\Delta[\Phi]_D$	
		$[\alpha]_D$	$c(t, ^\circ\text{C})$	$[\Phi]_D$	$[\alpha]_D$	$c(t, ^\circ\text{C})$	ref.		
<i>I</i>	D	-32.8 ± 0.4	1.2 (22)	- 63.4	-17.6	0.9 (21)	-	-29.2	-34.2
<i>II</i>	L	+20.9 ± 0.6	0.9 (22)	+ 40.4	+10.5	6.0 (25)	14	+17.4	+23.0
<i>III</i>	D	-32.3 ± 0.8	1.3 (20)	- 71.0	- 6.7	2.8 (20)	15	-13.1	-58.9
<i>IV</i>	D	-17.6 ± 0.5	1.5 (22)	- 39.2	- 6.0	1.6 (20)	16	-11.8	-27.4
<i>V</i>	D	-17.5 ± 0.4	1.3 (22)	- 39.1	-13.1	- (25)	17	-25.6	-13.5
<i>VI</i>	D	-17.1 ± 0.5	1.5 (22)	- 38.2	+ 0.31	4.9 (25)	18 <sup>b</sup>	+ 0.6	-37.6
<i>VII</i>	L	+26.3	2.5 (20)	+ 58.7	+ 5.2	2.0 (20)	16	+10.2	+48.5
<i>VIII</i>	D	-26.4	2.2 (20)	- 58.9	- 5.2	2.0 (20)	16 <sup>b</sup>	-10.2	-48.7
<i>IX</i>	D	-16.7 ± 0.5	1.7 (22)	- 42.3	+2.5	1.3 (20)	19	+ 5.6	-47.9
<i>X</i>	D	-13.5 ± 0.5	1.3 (20)	- 34.2	- 8.7	2.0 (20)	20	-19.7	-14.5
<i>XI</i>	D	-10.0 ± 0.5	1.0 (20)	- 20.7	+11.0	0.9 (22)	21	+19.8	-40.5
<i>XII</i>	L	+20.1 ± 1.4	1.1 (22)	- 38.4	+ 2.6	1.1 (22)	22	+ 4.3	+34.1
<i>XIII</i>	L	+61.8 ± 0.4	0.7 (22)	+118.1	+42.3	3.0 (24)	2	+69.6	+48.6
<i>XIV</i>	D	-10.7 ± 0.6	1.8 (22)	- 20.5	- 0.84	1.0 (25)	22 <sup>c</sup>	- 1.4	-19.1
<i>XV</i>	D	+ 7.5 ± 1.3	0.6 (22)	+ 14.3	+32.1	1.0 (25)	22	+52.6	-38.3

<sup>a</sup> Optical rotation of aldonic acids is time-dependent due to the formation of lactones. In reviews there is sometimes confusion between specific rotations of acids and equilibrium values of the mixtures acid-lactone. For this reason, only those data were selected from original papers for which the time values were either near to  $t = 0$  or extrapolated to  $t = 0$ . <sup>b</sup> The reference gives the rotation of the corresponding enantiomer. <sup>c</sup> The present value represents the correction of an earlier value<sup>3</sup>.

Results of spectropolarimetric measurements are summarised in Table III. In addition to dimethylamides *I–VI* and *IX–XV*, the Table contains data concerning monomethylamides of *D*-ribonic acid (*XVI*) and 4,6-dideoxy-*L*-ribo-hexonic acid (*XVII*), primary amides of *D*-ribonic acid (*XVIII*), *D*-gluconic acid (*XIX*), 4,6-dideoxy-*L*-ribo-hexonic acid (*XX*), 4,6-dideoxy-*L*-arabo-hexonic acid (*XXI*), 4,6-dideoxy-*L*-lyxo-hexonic acid (*XXII*), and of free *D*-ribonic acid (*XXIII*) and free 4,6-dideoxy-*L*-ribo-hexonic acid (*XXIV*). The first long-wavelength Cotton effect of all above amides derived from acids with *D*-configuration at  $C_{(2)}$  carbon atom is positive; its peak is readily accessible and is located in a considerably broad range of wavelengths at 224–243 nm. The second extremum of this Cotton effect (trough) is situated in such a range where the detailed course of spectrum is difficult to be measured. ORD curves of compounds with the opposite configuration at  $C_{(2)}$  are of the enantiomeric character. All the above amides show the presence of an additional Cotton effect located at shorter wavelengths which is of an opposite sign, *i.e.*, negative, when the long-wavelength Cotton effect is positive. The additional Cotton effect is especially distinct in the case of *N,N*-dimethylamides. Owing to this effect, their molar rotations in the long-wavelength region are shifted to negative values, a negative extremum is formed by superposition at 260–280 nm, and high values of negative molar rotation are found at shortest wavelengths which should exhibit trough of the negative Cotton effect.

The long-wavelength Cotton effect is assigned to the  $n-\pi^*$  transition, the short-wavelength effect to the  $\pi-\pi^*$  transition of the amide bond. As it may be seen from Fig. 1 and from comparison of further configurationally identical compounds (*I–XVI–XVIII, III–XIX, XII–XVII–XX, XIV–XXI, XV–XXII*; see Table III),

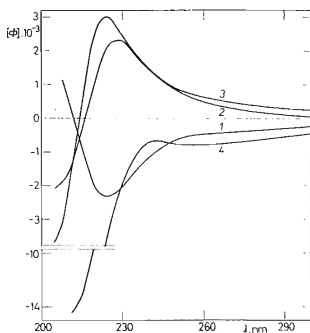


FIG. 1  
ORD Curves of *D*-Ribonic Acid and its Amides

1 Acid, 2 amide, 3 *N*-methylamide,  
4 *N,N*-dimethylamide.

the first extremum of the long-wavelength Cotton effect of dimethylamides (230 to 243 nm) is considerably bathochromically shifted in contrast to primary and mono-substituted amides (224–228 nm). However, substitution at the nitrogen atom does not affect to any considerable extent the energy and intensity of the amide  $n-\pi^*$  transition<sup>23</sup> (about 212 nm in water) which depends on excitation of the nonbonded electron of oxygen atom. On the other hand, the substitution results in a distinct bathochromic shift of the  $\pi-\pi^*$  transition<sup>23</sup>. This shift is especially remarkable in the case of monosubstituted and disubstituted amides, *e.g.*, N-methylacetamide (186 nm) and N,N-dimethylacetamide (196 nm), *cf.*<sup>23</sup>. Furthermore, the substitution causes an increase of the intensity of  $\pi-\pi^*$  transition<sup>23</sup>, and consequently an increase of the magnitude of the corresponding Cotton effect since the oscillator strength is proportional to the rotatory strength in the case of allowed transitions with an

TABLE III  
Optical Rotatory Dispersion

Compound	1st Cotton effect <sup>a</sup> $\lambda([\Phi])$	False extremum $\lambda([\Phi])$	End value $\lambda([\Phi])$
<i>I</i>	243 (– 740)	254 (– 795)	211 (– 14 500)
<i>II</i>	230 (– 1 550)	275 (+ 355)	212 (+ 18 100)
<i>III</i>	239 (+ 180)	265 (– 585)	210 (– 18 600)
<i>IV</i>	242 (– 295)	262 (– 510)	215 (– 11 300)
<i>V</i>	230 (+ 2 470)	290 (– 380)	210 (– 16 000)
<i>VI</i>	242 (– 115)	262 (– 430)	215 (– 8 100)
<i>IX</i>	242 (– 640)	259 (– 1 020)	214 (– 15 300)
<i>X</i>	240 (– 175)	280 (– 650)	215 (– 8 700)
<i>XI</i>	241 (– 175)	275 (– 600)	214 (– 14 600)
<i>XII</i>	240 (+ 220)	257 (+ 640)	216 (+ 12 500)
<i>XIII</i>	236 (– 610)	264 (+ 580)	212 (+ 23 500)
<i>XIV</i>	232 (+ 880)	280–290 (– 120)	215 (– 7 900)
<i>XV</i>	239 (+ 95)	–	215 (– 11 600)
<i>XVI</i>	224 (+ 2 990)	–	205 (– 3 700)
<i>XVII</i>	225 (– 3 980)	–	205 (+ 6 500)
<i>XVIII</i>	228 (+ 2 300)	–	205 (– 4 150)
<i>XIX</i>	226 (+ 3 490)	–	205 (– 2 500)
<i>XX</i>	229 (– 2 630)	–	205 (+ 4 200)
<i>XXI</i>	226 (+ 3 910)	–	205 (– 1 550)
<i>XXII</i>	228 (+ 3 250)	–	202 (– 4 900)
<i>XXIII</i>	224 (– 2 300)	–	–
<i>XXIV</i>	225 (+ 1 240)	–	–

<sup>a</sup> Long-wavelength extremum.

electric transition dipole moment<sup>24</sup>. Conclusively, the character of ORD curves depends on the wavelength difference of two Cotton effects of opposite signs and on the ratio of their magnitudes. A double substitution at the nitrogen atom results in a displacement of the  $\pi-\pi^*$  band to the close vicinity of the  $n-\pi^*$  band and in a simultaneous increase of its rotatory strength. The simple superposition of the small long-wavelength Cotton effect and the considerably greater short-wavelength effect results in an apparent bathochromic shift of the  $n-\pi^*$  extremum and in a change of molar rotations also in the long-wavelength region of the ORD spectrum to the values corresponding to the sign of the short-wavelength Cotton effect. Moreover, the ratio of amplitudes of both Cotton effects is influenced by structural features. Thus, e.g., when configurations at  $C_{(2)}$  and  $C_{(3)}$  carbon atoms are identical, this ratio is particularly unfavourable for the  $n-\pi^*$  Cotton effect (the first extremum is located at 239–243 nm and the whole spectrum appears on one side of the line of zero rotations); when the configurations at  $C_{(2)}$  and  $C_{(3)}$  are different, the  $n-\pi^*$  Cotton effect is considerably more distinct and the bathochromic shift of its extremum is lower.

ORD curves of the free acid *XXIII* and the dimethylamide *I* of the same absolute configuration *D* (and similarly, the pair free acid *XXIV* and dimethylamide *XII* of the absolute configuration *L*) exhibit opposite signs of both corresponding Cotton effects. The dichroic band of the  $n-\pi^*$  transition of a carboxylic group is thus negative in the case of a *D*-configuration at  $C_{(2)}$ ; the long-wavelength part of the curve is located also in the negative region. These observations are in accordance with the recently reported<sup>25</sup> ORD curves of (–)*erythro*- and (–)*threo*-2,3-dihydroxybutyric acid and the earlier reported<sup>26,27</sup> curves of monohydroxy acids. The finding that the rotation of all above dimethylamides at the sodium line is more negative (in the case of the *D*-configuration at  $C_{(2)}$ ) indicates a greater contribution of the intensive negative dimethylamide  $\pi-\pi^*$  transition to the rotation at the *D* line in contrast to the negative Cotton effect of the  $n-\pi^*$  transition of an acid but the resulting effect need not to be of a general validity. Notwithstanding, the long-wavelength parts of ORD curves of the acid and the dimethylamide of the same configuration are very close and do not permit to expect the validity of Hudson's rule. On the other hand, the absolute configuration of all dimethylamides may be reliably determined on the basis of the sign of Cotton effects.

## EXPERIMENTAL

Melting points (corrected) were taken on a heated microscope stage (Kofler block). Analytical samples were dried for 10 hours at 1 Torr/room temperature. Optical rotations were measured on the Opton apparatus in 2-decimeter polarimeter tubes. Optical rotatory dispersion was measured on a Jasco ORD/UV-5 apparatus at 25–27°C in 0.05 and 0.01 dm cells in water at concentrations of 0.06 g per 100 ml.  $R_D$  values were determined on a thin layer of silica gel (starch as binder) with the use of precoated Silufol Sheets (produced by Glasswork Kavalier, Votice, Czechoslovakia) in chloroform-ethanol 1:1. After drying, the spots were detected with the periodate–benzidine reagent<sup>28</sup>.

## Preparation of Dimethylamides of Aldonic Acids

Liquid dimethylamine (2–10 molar excess) was added in one lot to a solution or suspension (precooled to  $-20$  to  $-50^{\circ}\text{C}$ ) of the lactone (2–5 mmol) in methanol (10–20 ml). The reaction mixture was shaken at the same temperature for 15 minutes and then kept under occasional shaking at room temperature for about 40 hours. The clear solutions were evaporated to dryness under diminished pressure and the residue dried; other mixtures were concentrated to about a half of the original volume and the solid collected. In some cases, the reaction course was tested by chromatography on a thin layer of MN silicagel G (Machery & Nagel, Germany) in chloroform-ethanol 5 : 1 (the spots were detected with concentrated sulfuric acid). When the reaction mixture contained unreacted starting lactones, the whole procedure was repeated once more. Crude amides were crystallised from solvents given in Table I. In some cases, the amides were chromatographed on a column of silica gel CH (Lachema, Czechoslovakia) prior to the crystallisation. For physical constants and analytical data see Table I.

## D-Ribonic Acid (XXIII)

As reported in the case of the L-enantiomer<sup>29</sup>, the  $\gamma$ -lactone was converted in 50% yield to the acid XXIII, m.p.  $110$ – $111^{\circ}\text{C}$ ;  $[\alpha]_{\text{D}}^{21} - 17.6^{\circ}$  (5 min,  $c$  0.86, water). Reported<sup>29</sup> for the L-enantiomer, m.p.  $104$ – $105^{\circ}\text{C}$ ,  $[\alpha]_{\text{D}}^{20} + 17.6^{\circ}$  (4 min,  $c$  2.6, water). For  $\text{C}_5\text{H}_{10}\text{O}_6$  (166.1) calculated: 36.15% C, 6.07% H; found: 36.35% C, 6.10% H.

*Methylamide XVI*: The preparation was performed according to the above general procedure with the use of D-ribonic acid lactone as the starting compound. Yield, 75%, m.p.  $123$ – $124^{\circ}\text{C}$ ;  $[\alpha]_{\text{D}}^{22} + 34.3 \pm 1^{\circ}$  ( $c$  1.0, water). For  $\text{C}_6\text{H}_{13}\text{NO}_5$  (179.2) calculated: 40.22% C, 7.31% H, 7.82% N; found: 40.05% C, 7.36% H, 7.54% N.

## Other Amides

*Methylamide XVII* and amides XX, XXI, and XXII have been reported earlier<sup>1,3,4</sup>. Amides XVIII and XIX were prepared as usual from the corresponding lactones. The physical constants were in accordance with reported data.

*Elemental analyses were performed in the Department of Organic Analysis, Central Laboratories (Dr L. Helešic, Head), Institute of Chemical Technology, Prague.*

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