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OPTICAL ROTATORY DISPERSION OF *TRANS*-CYCLANE-1,2-DICARBOXYLIC ACID THIONAMIDE[1]

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Abstract—Anomalous rotatory dispersion curves of thionamides derived from optically active *trans*-cyclane-1,2-dicarboxylic acids involving 3, 4, 5 and 6-membered rings were investigated. The thionamide derivatives showed pronounced Cotton effects associated with their n–π* absorption bands. The (*R*:*R*)-acid derivatives of the 3,5 and 6-membered rings exhibited negative Cotton effects and on the basis of this empirical correlation, (−)-*trans*-cyclobutane-1,2-dicarboxylic has been assigned the (1*R*:2*R*)-configuration.

GENERALLY, optically active carboxylic acids exhibit only plain ORD curves in the 300–700 mμ region.[2-4] Djerassi *et al.* demonstrated that acylthiourea and N-substituted thionamide derivatives of α-substituted (α-asymmetric) mono-carboxylic acids produced anomalous rotatory dispersion curves which correspond to the low extinction UV absorption maxima at 340 and 320–360 mμ respectively.[5-7] Although not without exception, the general conclusion from this work was that the acylthiourea derivatives of α-substituted mono-carboxylic acids of (*R*)-configuration exhibit positive Cotton effects whereas the N-methylthionamide derivatives exhibit negative ones. Potentially, these type of derivatives may provide a convenient and useful means of relating absolute configurations of acids.

In connection with some other work, we were interested in establishing the absolute configuration of (−)-*trans*-1,2-cyclobutanedicarboxylic acid (III). The extension of Djerassi's work to dicarboxylic acids seemed a promising means of doing so. Since such extensions and extrapolations are fraught with danger it was decided to first apply this method to cyclic dicarboxylic acids of known configuration. For the 3-membered ring we chose (−)-(1*R*:3*R*)-*trans*-caronic acid[8] (I) and (+)-(1*S*:2*S*)-*trans*-1,2-cyclopropanedicarboxylic acid[9] (II). As an example of the 6-membered dicarboxylic acid we selected (+)-(1*S*:2*S*)-*trans*-1,2-cyclohexanedicarboxylic acid.[10] Unfortunately, the absolute configuration of the 5-membered homolgue, *trans*-1,2-

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[1] This study was supported by Grant 1240-A4 from the Petroleum Research Fund and in part by Public Health Service Grant CA-4065, from the National Cancer Institute.

[2] W. Kuhn, *Tetrahedron* **13**, 1 (1961).

[3] A. Fredga, J. P. Jenning, W. Klyne, P. M. Scopes, B. Sjöberg and S. Sjöberg *J. Chem. Soc.* 3928 (1965).

[4] J. C. Craig and S. K. Roy, *Tetrahedron* **21**, 391 (1963).

[5] C. Djerassi, K. Undheim and A. M. Weidler, *Acta Chim. Scand.* **16**, 1147 (1962).

[6] C. Djerassi, H. Wolf and E. Bunnenberg, *J. Am. Chem. Soc.* **84**, 4552 (1962).

[7] J. V. Burakevich and C. Djerassi, *J. Am. Chem. Soc.*, **87**, 51 (1965).

[8] L. Crombie and S. H. Harper, *J. Chem. Soc.* 470 (1954).

[9] Y. Inouye, T. Sugita and H. M. Walborsky, *Tetrahedron* **20**, 1965 (1964).

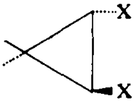
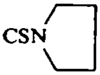
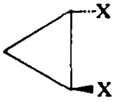
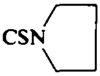
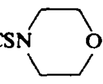
[10] H. M. Walborsky, L. Barash and T. C. Davis, *Tetrahedron* **19**, 2333 (1963).

cyclopentanedicarboxylic acid, had not been established. However, the absolute configuration of (−)-*trans*-cyclopentanediacetic acid had been determined as 1*S*:2*S*.[11] It was, therefore, only necessary to convert (−)-*trans*-1,2-cyclopentanedicarboxylic acid (IV), by the Arndt–Eistert procedure, into the known homolgue in order to establish its configuration as 1*R*:2*R* (Experimental).

RESULTS AND DISCUSSION

The spectropolarimetric data are summarized in Table 1. As can be seen, all the substituted thionamides exhibit a pronounced Cotton curve corresponding to the low extinction UV absorption band of the C=S chromophore at 320–350 mμ.

TABLE 1. SPECTROPOLARIMETRIC DATA FOR THIONAMIDE DERIVATIVES OF CYCLANE-1,2-DICARBOXYLIC ACIDS

		Extrema				Amplitude	UV	
Thionamide	$[\alpha]_D$(MeOH)	$[\phi]$	λ(mμ)	$[\phi]$	λ(mμ)	× 10^{-2}	λ(mμ)	ε
	(R:R)—I							
I-a	72	−985	385	6020	310	−70·1	330	160
(X:CSNH$_2$)								
I-b	36·3	−2830	370	10300	315	−131	335	138
(X:CSNHCH$_3$)								
I-c	91	−3470	385	9980	322	−134·5	344	102
(X:CSNMe$_2$)								
I-d	75·4	−2430	381	5960	327	−83·9	336·5	112
(X:CSN )								
	(S:S)—II							
II-a	906	14700	351	2260	341	124	330	196s
(X:CSNH$_2$)								
II-b	834	18400	345	5450	316	130	325	122s
(X:CSNHMe)								
II-c	470	7400	358	5053	336	23·5	338	149s
(X:CSNMe$_2$)								
II-d	500 D	9130	358	7110	340	20·2	337	113s
(X:CSN )								
II-e	310	5900	366	4480	345	14·2	348	183s
(X:CSN  O)	339 D	5760	370	4380	352	13·8	356	148
II-f	119	4260	366	2120	343	21·4	347	160s
(X:CSN—Pr$_2$)								

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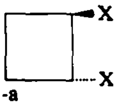
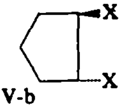
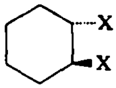
[11] P. M. Bourn and W. Klyne, *J. Chem. Soc.* 2044 (1960).

TABLE 1.—*continued*

Thionamide	$[\alpha]_D$(MeOH)	Extrema				Amplitude × 10^{-2}	UV	
		$[\phi]$	λ(mμ)	$[\phi]$	λ(mμ)		λ(mμ)	ε
	(R:R)—III							
III-a (X:$CSNH_2$)	−200	−2870	374	−1070	331	−18·0	330	151
III-b (X:CSNHMe)	−180	−3240	359	−1150	318	−20·9	331	107
	(R:R)—IV							
IV-b (X:CSNHMe)	−110	−2920	364	−360	318	−25·6	329	101
	(S:S)—V							
V-b (X:CSNHMe)	28	400	368	60	332	3·40	350	100s

D: dioxan
s: shoulder

Moreover, the N,N-dimethylthionamides can be used to determine the absolute configurations of optically active *trans*-cyclane-1,2-dicarboxylic acids. The (*R*:*R*)-N,N-dimethylthionamides derived from the corresponding acids showed negative and the (*S*:*S*)-derivatives positive Cotton curves. These data are consistent with the results of Djerassi[7] on the mono-carboxylic acids and the same empirical correlation obtains. On this basis one may assign the (*R*:*R*) configuration to (−)-*trans*-1,2-cyclobutanedicarboxylic acid (III).

It should also be noted that the Brewster method of conformational asymmetry[12] (Table 2) is also in agreement with the above assignment.

TABLE 2. CALCULATED AND FOUND MOLECULAR ROTATIONS FOR TRANS-CYCLANE-1,2-DICARBOXYLIC ACIDS

Acid	M.p.	$[\alpha]_D^{25}$(MeOH)	$[\phi]_D$ obs.	$[\phi]_D$ calc'd.	$[\alpha]_D$ (MeOH)*
(−)-(1*R*:3R)—I	208	−35·5	−52·5	−45	−64·5
(+)-(1S:2S)—II	156–65	+200	+260	+135	+295
(−)-(1*R*:2*R*)—III	113–4	−158	−223	−135	−249
(−)-(1*R*:2*R*)—IV	180–1	−85·9	−138	−135	−174
(+)-(1*S*:2*S*)—V	179–80	+21·5	+37	+135	+31·3

* N-methylamide derivative.

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[12] J. H. Brewster, *J. Am. Chem. Soc.* **81**, 5475, 5483 (1959).

Returning to Table 1, one observes that there is an additivity in the contribution of the thionamide chromophore to the molecular extinction coefficient at the n-π* transition band. The values (100–138) found for the N-methylthionamide derivatives of the dicarboxylic acids are about twice that reported for the N-methylthionamides of mono-carboxylic acids[7] (41–72). This may indicate that each chromophore contributes independently to the low extinction absorption and that the excited state n–π* orbital is involved mainly with the dissymmetric environment at the α-position and is largely independent of the other dissymmetric center beta to it.

Djerassi[7] observed both a change in sign and an increase in amplitude as the N-substituent of the thionamide of (*S*)-2-methylbutyric acid was changed from hydrogen to methyl, dimethyl, pyrrolidino and morpholino. This was interpreted as being due to a change in rotamer composition. In this connection, thionamides of acids I and II were prepared and the N,N-substituents varied. In contrast to the above observation, the sign of the Cotton curves did not change and the amplitude reduced rather than increased with greater bulkiness of the substituents. This suggests that the main contributing conformation of these systems is kept relatively constant and that one might be able to extend the Octant Rule to this system as it has been applied to carbonyl derivatives in which the chromophore is locked in a rigid molecular skeleton.[13]

For the conformational analysis of these systems, the free rotations about the exocyclic single bond between the ring carbon and the thiocarbonyl carbon, and about the single bond connecting the thiocarbonyl carbon with the amidonitrogen are of greatest importance. Of the two, the rotation about the C–N bond is considerably more restricted due to the partial double bond character acquired by the conjugation of the π-electron on C=S with the non-bonding electrons on the nitrogen.[14] On this basis, one might view the thionamide moiety as existing essentially in a planar conformation.

Conformational analysis of the thionamide derivatives of 1,2-cyclopropanedicarboxylic acid (II) is of particular interest. The endo-orbitals of the cyclopropane ring are $sp^{4.12}$ hybridized and the bent bonds lie in the plane of the ring.[15] The high p-character of these orbitals permits them to overlap to some extent with the adjacent π-orbital of the C=S in the thionamide moiety.[16] The overlap in this case would not be expected to be as great as that between the non-bonding electrons on nitrogen and the C=S. It is therefore suggested that it is the rotation about the cyclopropyl carbon and the C=S carbon which will determine the important conformations of this system. Granting this assumption, then the most stable conformation may be either *cisoidal* or *transoidal*, in which the plane of the thionamide group bisects the adjacent annular bond angle. In these conformations one obtains the maximum overlap of the cyclopropane endo-orbitals, π of the C=S and non-bonding electrons (p-orbital) of the amide nitrogen (Fig. 1). The choice of *cisoidal* or *transoidal* conformation may be decided by steric and environmental factors such as bulkiness of N,N-substituents and the degree and type of solvation. In caronic acid (I), supplemental

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[13] W. Moffit, R. B. Woodward, A. Moscowitz, W. Klyne and C. Djerassi, *J. Am. Chem. Soc.* **83**, 4013 (1961).

[14] L. Skulski, G. C. Palmer and M. Calvin, *Tetrahedron Letters* 1773 (1963).

[15] L. L. Ingraham, in M. S. Newman's *Steric Effects in Organic Chemistry* pp. 518–521. Wiley, New York (1956).

[16] R. Hoffmann, *Tetrahedron Letters* 3819 (1965); E. M. Kosower and M. Ito, *Proc. Chem. Soc.* 25 (1962).

considerations must be made for the steric interaction of the geminal dimethyl groups on the ring.

The greater amplitude in the Cotton curves of the cyclopropane derivatives as compared with the higher homologues may be attributed to both the absence of conformational mobility of the ring system itself and the overlap of the cyclopropyl ring orbitals with the thionamide chromophore. The latter leads to a relatively fixed conformation, either *cisoidal* or *transoidal*, which is the main contributor to the rotation. The ring-chromophore resonance is reduced as one goes to the higher membered rings. This type of interaction may still be of some importance in the 4-membered ring where the hybridization of the endocyclic orbitals is $sp^{3.31}$ but should virtually disappear in the 5 and 6-membered rings.[17] A further complication in the higher homologues is an increased flexibility of the ring systems which introduces further conformational effects. Nevertheless, the observation that the sign of the Cotton curves of the thionamide derivatives of I and II did not change upon introduction of bulkier N-substituents suggests that important conformational changes are probably not occurring in these cases and that the *cisoidal* conformation is preferred over the *transoidal*. Steric considerations would lead one to conclude that bulky N,N-substituents would increase severely non-bonded interactions with the ring if the system was in a *transoidal* conformation. Accepting the *cisoidal* conformation as a reasonable model (Fig. 2) and with knowledge of the absolute configurations one finds that the Octant Rule is applicable. In these cases the thionamide moiety is looked upon as forming a spiran ring system[18] with the other ring and this would place, for example, the portion of the 3-membered ring which contains the

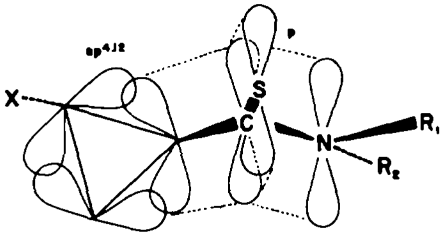

FIG. 1. Orbital overlap of thionamide grouping with cyclopropane ring.

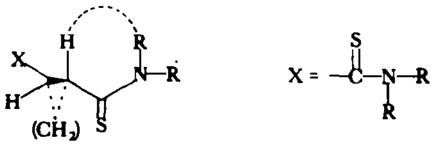

FIG. 2. Model for extended octant rule.

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[17] K. Mislow, *Introduction to Stereochemistry* p. 49. Benjamin, New York (1965).

[18] C. Djerassi, W. Klyne, T. Norin, G. Ohloff and E. Klein, *Tetrahedron* **21**, 163 (1965).

TABLE 3. PHYSICAL PROPERTIES AND ANALYTICAL DATA FOR THIONAMIDE DERIVATIVES

Compound	M.p.	Empirical formula	Calc.			Found			IR-bands characteristic of chromophore (cm^{-1})					
			C%	H%	N%	C%	H%	N%						
I-a	210	$C_7H_{12}N_2S_2$	—	—	14·88	—	—	14·62	3300	3140	1637[a]	1416	1368	
I-b	148·5–149	$C_9H_{16}N_2S_2$	49·95	7·45	12·94	50·31	7·53	13·20		3240	1542[a]	1438	1366	
I-c	208	$C_{11}H_{20}N_2S_2$	54·05	8·24	11·46	53·92	8·22	11·70			1506[a]	1455	1385	
I-d	219–220	$C_{15}H_{24}N_2S_2$	60·77	8·16	9·45	60·70	8·24	9·45	3500		1470[a]	1445		
II-a	184–186 (decomp.)	$C_5H_8N_2S_2$	37·47	5·03	17·48	37·49	4·97	17·65	3320		1625[a]	1434	1300	
II-b	196 (decomp.)	$C_7H_{12}N_2S_2$	44·65	6·42	14·88	44·77	6·48	14·50	3300		1530[a]	1445	1365	
II-c	134–134·5	$C_9H_{16}N_2S_2$	49·95	7·45	12·94	49·89	7·21	12·82	3450		1512[a]	1390	1275	
II-d	233	$C_{13}H_{20}N_2S_2$	58·16	7·51	10·43	58·36	7·85	10·44			1480[a]	1445	1400	1328
II-e	154	$C_{13}H_{20}N_2S_2O_2$	51·97	6·71	9·36	51·68	6·64	9·60	3450		1476[a]	1438		
II-f	173–173·5	$C_{17}H_{32}N_2S_2$	—	—	8·52	—	—	8·63	3450		1476[a]	1457	1368	1346
III-a	165–167 (decomp.)	$C_6H_{10}N_2S_2$	—	—	16·07	—	—	15·89	3300		1630[a]	1420	1310	
III-b	87·5–88	$C_8H_{14}N_2S_2$	47·48	6·97	13·85	47·40	6·88	14·05	3220		1545[a]	1435	1367	
IV-b	158–159	$C_9H_{16}N_2S_2$	49·95	7·45	12·94	49·89	7·47	12·65	3500		1550[a]	1450	1378	
V-b	166–168	$C_{10}H_{18}N_2S_2$	—	—	12·16	—	—	12·30	3450		1480[a]	1430		

[a] C=S stretching.

other thionamide grouping in the far upper left octant. When applied to the thionamide derivative of (+)-(1S:2S)-1,2-cyclopropanedicarboxylic acid (II) a positive Cotton curve is predicted and found. This same model seems to be applicable to the higher homologues as well.

EXPERIMENTAL

All amides and thionamides of cyclane-1,2-dicarboxylic acids in this work were prepared by the same procedure employed by Djerassi[8] with a small modification. Details are illustrated by one typical example.

All ORD curves were measured on a Yanagimoto spectropolarimeter model-III. MeOH solns were used unless otherwise indicated.

Preparation of (+)-(R:R)-N,N-*dimethylthionamide of caronic acid* (Ib). A 156 mg quantity of caronic acid, m.p. 208–208·5, $[\alpha]_{546}$ −34·5°, was converted to N,N-dimethylamide by treatment of the acid chloride with methylamine in chloroform: m.p. 219°, $[\alpha]_D^{12}$ −64·5°, yield 250 mg. The amide was warmed to refluxing gently with 600 mg of sulfurated potash and 1 g P_2S_5 in 10 ml of dry benzene, to give after drying and washing with MeOH, and recrystallization from benzene, colorless prisms, (I-b), m.p. 148–149°, $[\alpha]_D^{15}$ 36·3° (c 2·0 MeOH): λ_{max} 335 mμ, ε, 138; typical IR-bands 3240, 1542, 1438, and 1366 cm^{-1}. (Found: C, 50·31, H, 7·53; N, 13·20; Calc. for $C_9H_{16}N_2S_2$ C, 49·95; H, 7·45; N, 12·94%).

Correlation of (−)-trans-*cyclopentane*-1,2-*dicarboxylic acid to* (−)-(S:S)-trans-*cyclopentane*-1,2-*diacetic acid*. A 600 mg quantity of (−)—V,[19] $[\alpha]_D$ −22°, was refluxed with 5 g $SOCl_2$ for 1 hr. The soln of the acid chloride (b.p. 69–70°/3 mm) in 5 ml of dry ether was added to an excess of diazomethane in ether and the mixture was kept at room temp overnight. Ether was removed and the residue was diluted in 20 ml of abs EtOH. Ag_2O (50 mg) was added to the soln and the mixture was heated until the evolution of N ceased. Another portion of Ag_2O (100 mg) was added and the mixture was again refluxed for additional 1·5 hr. Ag_2O was filtered off and the solvent was removed under reduced press. The oily residue was distilled to give (−)-cyclopentane-1,2-diacetate: b.p. 110–119°/0·3 mm, n_D^{15} 1·4722, yield 350 mg. The ester was hydrolysed in 30% HCl (10 ml) to give (−)-(*S*:*S*)-*trans*-cyclopentane-1,2-diacetic acid,[20] m.p. 136–138°, $[\alpha]_D^{25}$ −3·0° (MeOH).[21]

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[19] L. J. Goldsworthy and W. H. Perkin, *J. Chem. Soc.* 2639 (1914).

[20] J. W. Barret and R. P. Linstead, *J. Chem. Soc.* 1069 (1935).

[21] It would appear from the observed rotation that racemization was encountered in the Arndt-Eistert reaction. This is probably not the case since we started with 25% optically pure acid (V) the resultant low optically purity is probably due to our isolation procedure.