Tetrahedron. Vol 24, pp 4315 to 4326. Pergamon Press 1968 Printed in Great Britain

COTTON EFFECT OF DIMEDONE AND DIHYDRORESORCINOL CONDENSATION COMPOUNDS OF AMINO ACIDS AND PEPTIDES

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(*Received in USA* 30 *October* 1967; *accepted for publication* 24 *January* 1968)

Abstract—Dimedone and dihydroresorcinol condensation compounds of aliphatic and alicyclic amino acids having the (*R*) configuration exhibit a positive Cotton effect in the 280 mμ region. Conversely, the enantiomeric (*S*) condensates show a negative Cotton effect. The homoconjugated chromophore present in the condensation compounds of aralkylamino acids in which the asymmetric center is separated from the aromatic ring by a methylene leads to an inversion in sign of the Cotton effect. The (*R*) derivatives show negative optical rotatory dispersion curves, whereas the (*S*) antipodes present positive curves. The Cotton effect of some peptides is also discussed.

Résumé—L'examen des propriétés optiques des produits de condensation d'acides aminés aliphatiques et alicycliques avec la dimédone et le dihydrorésorcinol conduit à d'intéressantes conclusions. Les dérivés de produits de configuration absolue (*R*) montrent un effet Cotton positif dans la région de 280 mμ. Leurs antipodes (*S*) sont doués d'un effet Cotton de signe opposé. Dans le cas des produits de condensation de certains acides aminés aromatiques, le phénomène d'homoconjugaison conduit à une inversion du signe de l'effet Cotton. Enfin, on discute les propriétés de dispersion rotatoire de plusieurs peptides.

IT HAS been shown[1] that a Cotton effect is associated with the vinylogous amide grouping in the dimedonyl derivatives of optically active amines. Thus, it was anticipated that similar condensates would be useful for assignment of configuration, in the amino acid[2] and peptide series. It was therefore not surprising that dimedonyl and dihydroresorcinol condensation products of amino acids give rise to Cotton effect rotatory dispersion (RD)[3] and circular dichroism (CD)[3] curves.

Although numerous chromophoric derivatives of amino acids have already been reported,[3,4] many of these present some practical drawbacks, which induced the present study.

The N-(5,5-dimethyl-2-cyclohexen-1-on-3-yl) derivative of (*S*)[5]-alanine (*S*-**1a**), (*S*)-valine (*S*-**2a**), (*S*)-leucine (*S*-**3a**) and their methyl ester (*S*-**1b**); (*S*-**2b**), (*S*-**3b**) exhibit rather intense *negative* Cotton effects in the 275 mμ region, (Table 1), indicating that the UV transition of the vinylogous amide chromophore is optically active.

Conversely, (*R*)[5]-valine methyl ester (*R*-**2b**), (*R*)-leucine methyl ester (*R*-**3b**) and (*R*)-leucine ethyl ester (*R*-**3c**) present *positive* Cotton effect RD curves, in agreement

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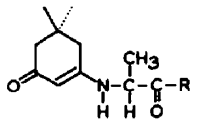
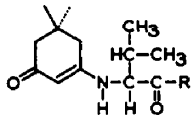
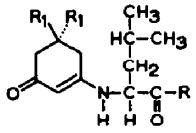
‡ This work constitutes a part of the Ph.D. Thesis presented by E. S. at the Universidad Nacional Autónoma de México, August 1967.



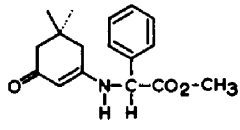
1a: R = OH
d: R = OCH_3
c: R = NH_2
b: R = $S-C_6H_5$



2a: R = OH
b: R = OCH_3
c: R = $S-C_6H_5$



3a: R = OH; R_1 = CH_3
b: R = OCH_3; R_1 = CH_3
c: R = OC_2H_5; R_1 = CH_3
d: R = OC_2H_5; R_1 = H
e: R = NH_2; R_1 = CH_3
f: R = $NHNH_2$; R_1 = CH_3
g: R = $S-C_6H_5$; R_1 = CH_3



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with what is observed with optically active amines.[1] However, the molecular amplitude characterizing the RD curves of these amino acid condensates is much more intense than in the case of aliphatic or even alicyclic amino-derivatives.[1]

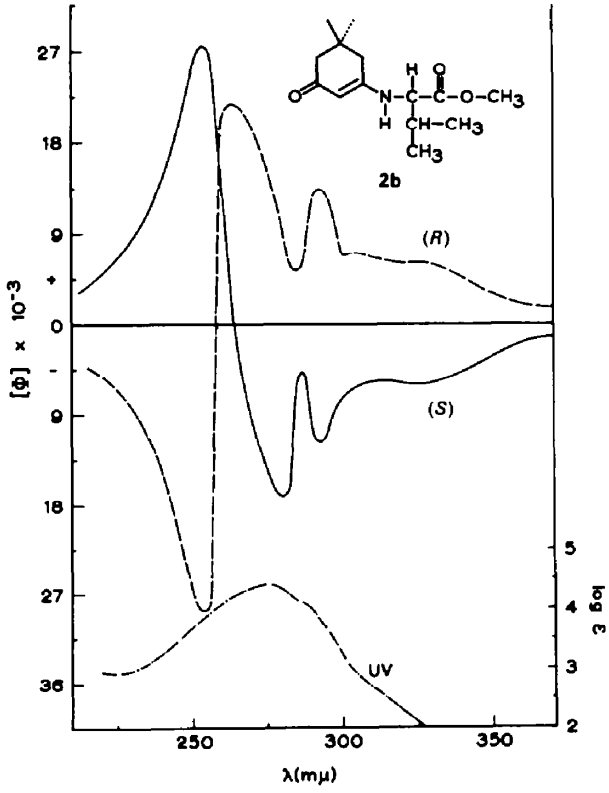


FIG. 1 RD and UV curves of N-(5,5-dimethyl-2-cyclohexen-1-on-3-yl)-(*R*)-valine methyl ester (*R*-**2b**) and its enantiomer (*S*-**2b**) in dioxan solution.

TABLE 1. ABSORPTION AND OPTICAL PROPERTIES OF DIMEDONYL AND DIHYDRORESORCINOL DERIVATIVES OF ALIPHATIC AMINO ACIDS*

Condensation compound† Amino acid	UV absorption		Cotton effect in the 280 mμ region			Ref for configuration
	λ (mμ)	log ε	First extremum [Φ] (λmμ)	Second extremum [Φ] (λ mμ)	Molecular amplitude *a*	
Dim-(*S*)-alanine (*S*-**1a**)	274	4·37	−11,750° (280)	+10,630° (250)	−224	[a]
Dim-(*S*)-alanine methyl ester (*S*-**1b**)	274	4·40	−9500° (298)	+12,870° (245)	−224	[a]
Dim-(*S*)-alanine amide (*S*-**1c**)	272	4·30	−14,300° (300)	+10,900° (254)	−252	[a]
Dim-(*S*)-alanine thiophenyl ester (*S*-**1d**)	276	4·35	−31,300° (312)	+47,200° (266)	−785	[a]
Dim-(*S*)-valine (*S*-**2a**)	274	4·30	−10,750° (281)	+22,400° (250)	−332	[b]
Dim-(*R*)-valine methyl ester (*R*-**2b**)	275	4·38	+21,598° (263)	−28,632° (255)	+502	[b]
Dim-(*S*)-valine methyl ester (*S*-**2b**)	275	4·39	−10,130° (286)	+30,000° (255)	−401	[b]
Dim-(*S*)-valine thiophenyl ester (*S*-**2c**)	276	4·31	−33,400° (313)	+68,400° (267)	−1018	[b]
Dim-(*S*)-leucine (*S*-**3a**)	274	4·32	−8750° (267)	+18,400° (240)	−272	[b]
Dim-(*R*)-leucine methyl ester (*R*-**3b**)	274	4·39	+15,200° (274)	−16,800° (259)	+320	[b]
Dim-(*S*)-leucine methyl ester (*S*-**3b**)	286 (EtOH)	4·44	−7150° (269)	+20,300° (244)	−275	[b]
Dim-(*S*)-leucine ethyl ester (*S*-**3c**)	274	4·39	−9900° (312)	+31,300° (244)	−411	[b]
Dih-(*S*)-leucine ethyl ester (*S*-**3d**)	273	4·42	−5700° (318)	+21,600° (239)	−273	[c]
Dim-(*S*)-leucine amide (*S*-**3e**)	274	4·38	−11,670° (287)	+16,970° (252)	−286	[c]
Dim-(*R*)-leucine hydrazide (*R*-**3f**)	274	4·36	+4010° (288)	−8750° (259)	+128	[c]
Dim-(*S*)-leucine hydrazide (*S*-**3f**)	275	4·35	−22,350° (280)	+20,600° (254)	−430	[c]
Dim-(*S*)-leucine thiophenyl ester (*S*-**3g**)	276	4·34	−33,000° (310)	+31,600° (264)	−646	[c]

* All spectra in dioxan, unless otherwise stated.

† Dim = dimedonyl; Dih = dihydroresorcinol

[a] W. Leithe, *Ber. Dtsch. Chem. Ges.* **64**, 2827 (1931).

[b] P. Karrer and P. Dinkel, *Helv. Chim. Acta* **36**, 122 (1953).

[c] See Ref. 10.

As indicated in Table 1, the Cotton effects of the free amino acid such as leucine (*S*-**3a**), the methyl ester (*S*-**3b**), the ethyl ester (*S*-**3c**), the amide (*S*-**3e**) and hydrazide (*S*-**3f**) are similar, which means that in these cases the ester function plays only a secondary effect on the optical properties. Furthermore, a weak optically active transition not detected on the UV curves, appears in the 325 mμ region. This is shown in Fig. 1 which reproduces the Cotton effect curves of (*R*) and (*S*)-valine methyl ester (**2b**), and could be attributed to conformational mobility existing in these substances.

In the case of thiophenyl esters of amino acids, the situation is different; although the sign remains the same, the intensity of the Cotton effect is substantially increased. As indicated in Table 1, (*S*)-alanine thiophenyl ester (*S*-**1d**) exhibits a Cotton effect which is much more intense than that of its methyl ester (*S*-**1b**) and amide (*S*-**1c**), although the UV is not affected. A similar situation is encountered in the case of the thiophenyl ester of (*S*)-valine (*S*-**2c**) and (*S*)-leucine (*S*-**3g**).

From the above observations one can conclude that the dimedone and closely related dihydroresorcinol condensates of aliphatic (*R*)-amino acids and derivatives present a positive Cotton effect in the 275 mμ region, a negative Cotton effect being associated with the (*S*)-isomers. In all compounds examined thus far the Cotton effects are much more intense than in the case of aliphatic and alicyclic amines.[1]

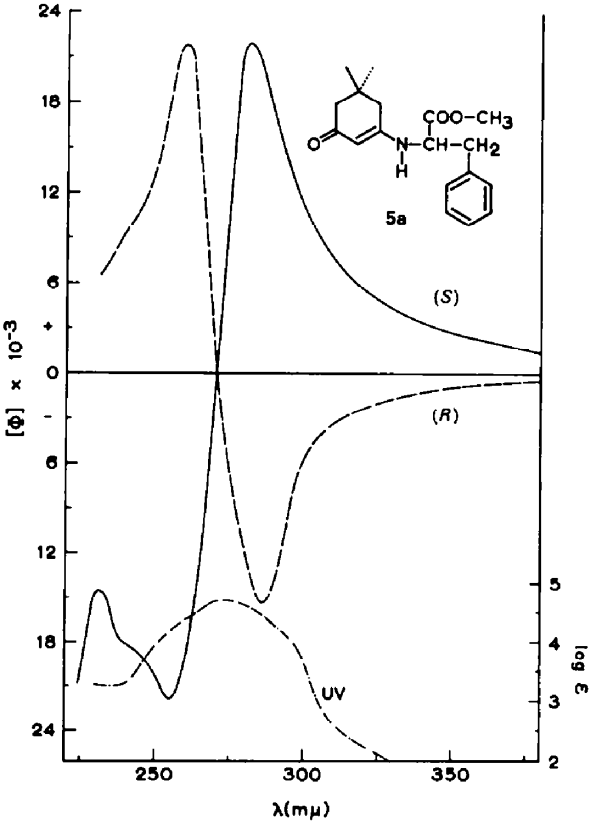


FIG. 2 RD and UV curves of N-(5,5-dimethyl-2-cyclohexen-1-on-3-yl)-(*R*)-phenylalanine methyl ester (*R*-**5a**) and its antipode (*S*-**5a**) in dioxan solution.

This enhancement in intensity is attributed to orbital overlap between the π-electrons of the vinylogous amide group and these of the carboxyl, as well as of the ester function (as in the thiophenyl ester), leading to homoconjugated chromophores. Indeed, it is well known that high optical activities are often associated with homoconjugated systems.[3,6]

In the case of some aralkylamino acids the phenomenon of homoconjugation leads to an inversion in sign of the Cotton effects, namely when a methylene group is introduced between the asymmetric carbon atom and the aromatic ring. Hence, whereas the dimedone condensate of (*S*)-phenyl-glycine methyl ester (**4**) presents a negative Cotton effect, this inversion in sign is illustrated in Fig. 2, which reproduces the UV and RD curves of the dimedone derivative of (*R*)-phenylalanine methyl ester (*R*-**5a**), as well as of its enantiomer (*S*-**5a**).* Worth noting also is the fact that these Cotton effect curves are devoid of the fine structure observed in the aliphatic and alicyclic derivatives (Fig. 1). The same properties were found for the dihydroresorcinol condensates (*R*-**5b**) and (*S*-**5b**). The confirmation that the aromatic ring is responsible

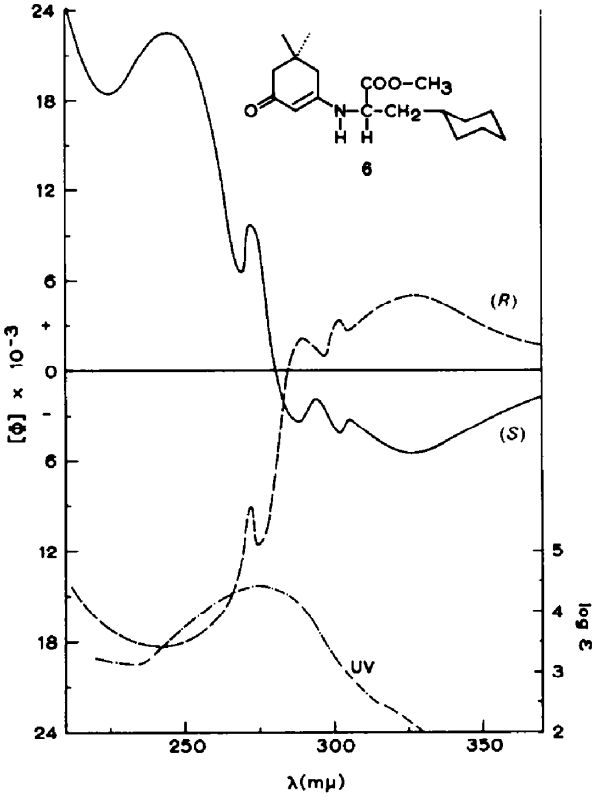
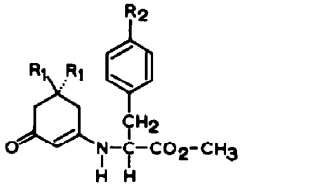


FIG. 3 RD and UV curves of N-(5,5-dimethyl-2-cyclohexen-1-on-3-yl)-(*R*)-hexahydrophenylalanine methyl ester (*R*-**6**) and its isomer (*S*-**6**) in dioxan solution.

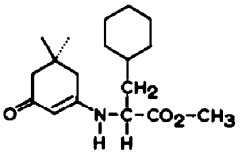
* In the course of this work, it was observed that often the (*R*) isomers or (*S*) isomers of amino acids are not 100% pure. This accounts for the quantitative difference noted in the Cotton effects of (*R*) and (*S*) enantiomers.

for the inversion of Cotton effect in these compounds (**4**, *R*-**5a**, **b**, *S*-**5a**, **b**) is deduced from the following observations. The aromatic ring of (*R*)- and (*S*)-phenylalanine was reduced catalytically to the corresponding cyclohexylalanine (hexahydrophenylalanine) compounds.[7] After methylation, the dimedone condensates were prepared and then submitted to RD. As shown in Fig. 3, a *positive* Cotton effect, centered at ca. 275 mμ is observed for the (*R*)-derivative (*R*-**6**) and a *negative* one for its antipode (*S*-**6**), as in the aliphatic amino acid derivatives discussed previously. The substantial fine structure noted in these curves is again tentatively attributed to the conformational freedom existing in the molecule (**6**).

Such an inversion in sign in going from aliphatic or alicyclic series to the aromatic compounds has also been observed with salicylidene derivatives of amino acids (phenylalanine and tyrosine).[8]



5a: $R_1 = CH_3$; $R_2 = H$
b: $R_1 = H$; $R_2 = H$
c: $R_1 = CH_3$; $R_2 = O\text{-}CH_2\text{-}C_6H_5$



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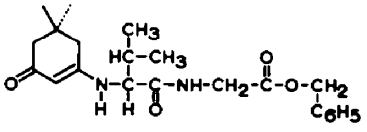

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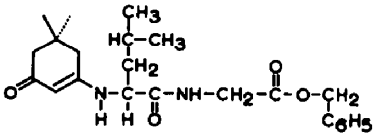

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The dimedone condensation product of the methyl ester of O-benzyl-(*S*)-tyrosine (*S*-**5c**) exhibits an intense molecular amplitude RD curve (Table 2). This increase in the Cotton effect in going from (*S*-**5a**) to (*S*-**5c**) is attributed to the substitution of the aromatic ring, in agreement with Moscowitz' observations.[9] The nature of the substituent of the aromatic ring exercises a direct influence on the rotational strength,[9] which also confirms that the chromophore under examination is the overall π-system.

The dimedonyl derivatives have been utilized in peptide synthesis.[10] In view of the optical properties just discussed, it was of interest to investigate the RD and CD curves of the dimedonyl products of some di- and tri-peptides in order to find out if the Cotton effect would allow assignment of absolute configuration of the asymmetric center in the immediate vicinity of the vinylogous amide chromophore, without interference of other amino acid moieties present in the molecule.

The dimedone condensation product of (*S*)-valine-glycine benzyl ester (*S*-**7**) exhibits a negative Cotton effect RD curve at 276 mμ. Similarly, the dimedonyl derivative of (*R*)-leucine-glycine benzyl ester (*R*-**8**) shows a positive Cotton effect at

TABLE 2. ABSORPTION AND OPTICAL PROPERTIES OF DIMEDONYL AND DIHYDRORESORCINOL DERIVATIVES OF SOME ALICYCLIC AND AROMATIC AMINO ACIDS*

Condensation compound† Amino acid	UV absorption		Cotton effect in the 280 mμ region			Ref for configuration
	λ (mμ)	log ε	First extremum [Φ] (λ mμ)	Second extremum [Φ] (λ mμ)	Molecular amplitude *a*	
Dim-(*S*)-phenylglycine methyl ester (*S*-**4**)	276	4·42	−18,784° (280)	+8495° (256)	−273	[a]
Dim-(*R*)-phenylalanine methyl ester (*R*-**5a**)	276	4·43	−15,300° (286)	+21,800° (260)	−371	[a]
Dih-(*R*)-phenylalanine methyl ester (*R*-**5b**)	274	4·43	−18,100° (284)	+25,600° (254)	−437	[a]
Dim-(*S*)-phenylalanine methyl ester (*S*-**5a**)	276	4·67	+21,800° (281)	−21,800°(255)	+436	
	288 (EtOH)	4·51				
Dih-(*S*)-phenylalanine methyl ester (*S*-**5b**)	274	4·43	+21,600° (286)	−15,800° (252)	+374	[a]
Dim-(*S*)-tyrosine O-benzyl methyl ester (*S*-**5c**)	274	4·44	+23,732° (287)	−34,451° (256)	+582	[c]
Dim-(*R*)-cyclohexylalanine methyl ester (*R*-**6**)	275	4·40	+5491° (326)	−18,905° (250)	+244	[b]
	284 ($CHCl_3$)	4·49				
	276 (Ether)	4·51				
	292 (EtOH)	4·57				
Dim-(*S*)-cyclohexylalanine methyl ester (*S*-**6**)	275	4·40	−5342° (320)	+18,420° (238)	−238	[b]

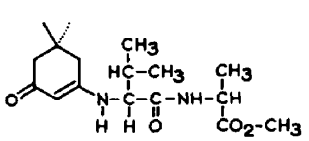
* All spectra in dioxan, unless stated otherwise.

† Dim = Dimedonyl; Dih = Dihydroresorcinol.

[a] P. Karrer and K. Ehrhardt, *Helv. Chim. Acta* **34**, 2202 (1951).

[b] W. Leithe, *Ber. Dtsch. Chem. Ges.* **64**, 2827 (1931).

[c] See Ref. 10.



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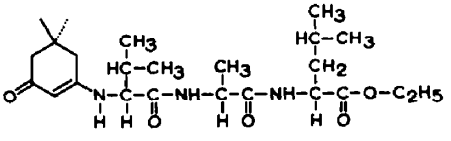

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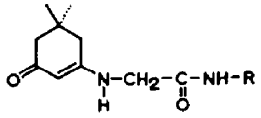

11: R = CH(CO$_2$-CH$_2$-C$_6$H$_5$)-CH(CH$_3$)-CH$_3$

12: R = CH(CO$_2$-CH$_2$-C$_6$H$_5$)-CH$_2$-CH(CH$_3$)-CH$_3$

13: R = CH(CO$_2$-CH$_3$)-CH$_2$-C$_6$H$_5$

ca. 271 mμ, whereas its enantiomer (*S*-**8**) exhibits a negative RD curve in the same region (Fig. 4).

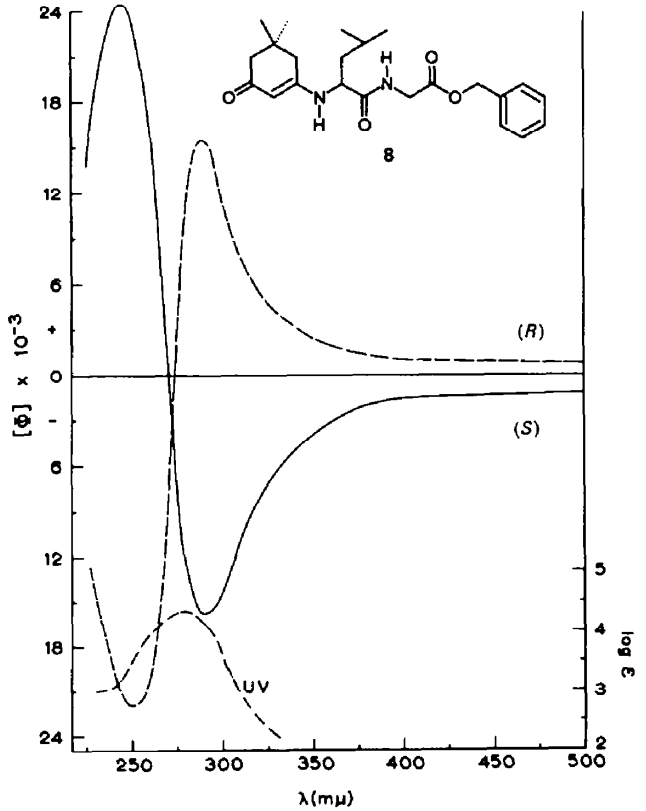

FIG. 4 RD and UV curves of N-[N^1-(5,5-dimethyl-2-cyclohexen-1-on-3-yl)-(*R*)-leucine]-glycine benzyl ester (*R*-**8**) and its enantiomer (*S*-**8**) in dioxan solution.

TABLE 3. ABSORPTION AND OPTICAL PROPERTIES OF DIMEDONYL DERIVATIVES OF PEPTIDES*

Dimedonyl condensation compound. Peptide moiety	UV absorption		Cotton effect in the 280 mμ region			Ref for configuration
	λ (mμ)	log ε	First extremum [Φ] (λ mμ)	Second extremum [Φ] (λ mμ)	Molecular amplitude *a*	
(*S*)-Valyl-glycyl benzyl ester (*S*-**7**)	278	4·40	−18,600° (290)	+33,000° (245)	−516	[a]
(*R*)-Leucyl-glycyl benzyl ester (*R*-**8**)	278	4·35	+15,600° (287)	−22,100° (253)	+377	[a]
(*S*)-Leucyl-glycyl benzyl ester (*S*-**8**)	278	4·16	−16,300° (288)	+24,500° (247)	−408	[a]
(*S*)-Valyl-(*S*)-alanyl methyl ester (**9**)	278	4·40	−28,700° (294)	+35,000° (250)	−637	[a, b]
(*S*)-Valyl-(*S*)-alanyl-(*S*)-leucine methyl ester (**10**)	278	4·43	−11,100° (289)	+29,200° (239)	−403	[a, b, c]
N-(Glycyl)-(*S*)-valine benzyl ester (**11**)	274	4·34	+11,200° (282)	−8000° (269)	+192	[c]
N-(Glycyl)-(*S*)-leucine benzyl ester (**12**)	274	4·43	+10,200° (286)	−7500° (268)	+177	[c]
N-(Glycyl)-(*R*)-phenylalanine methyl ester (**13**)	274	4·38	+2620° (300)	−3650° (266)	+63	[c]

* All spectra in dioxan, unless stated otherwise.

[a] P. Karrer and P. Dinkel, *Helv. Chim. Acta* **36**, 122 (1953).

[b] W. Leithe, *Ber. Dtsch. Chem. Ges.* **64**, 2827 (1931).

[c] See Ref. 10.

TABLE 4. PHYSICAL CONSTANTS OF DIMEDONE AND DIHYDRORESORCINOL CONDENSATION PRODUCTS OF AMINO-ACIDS, AND PEPTIDES

Compound	m.p.	$[\alpha]_D$	Analysis						
			Formula	Calculated			Found		
				C	H	N	C	H	N
S-1a[a]	214°	−128°	$C_{11}H_{17}O_3N$	—	—	6·63	—	—	6·45
S-1b	133°	−45°	$C_{12}H_{19}O_3N$	—	—	6·22	—	—	6·21
S-1d[a]	142°	−263°	$C_{17}H_{21}O_2NS$	67·33	6·93	4·62	67·31	6·67	4·48
S-2a[a]	167°	−147°	$C_{13}H_{21}O_3N$	65·24	8·85	5·85	65·53	8·92	5·87
R-2b	116–118°	+156°	$C_{14}H_{23}O_3N$	66·37	9·15	5·53	67·46	9·40	5·50
S-2b	118°	−194°	$C_{14}H_{23}O_3N$	66·37	9·15	5·53	67·55	9·43	5·41
S-2c	133°	−325°	$C_{19}H_{25}O_2NS$	68·84	7·60	4·22	68·90	7·60	4·21
R-3a[a]	198°	+132°	$C_{14}H_{23}O_3N$	66·37	9·15	5·33	66·67	9·30	5·57
R-3b	129°	+80°	$C_{15}H_{25}O_3N$	67·40	9·14	5·20	67·51	9·72	5·10
S-3b	129–130°	−80°	$C_{15}H_{25}O_3N$	67·40	9·14	—	67·61	9·50	—
R-3f	145°	+124°	$C_{14}H_{25}O_2N_3$	—	—	15·72	—	—	15·66
S-3f	160°	−186°	$C_{14}H_{25}O_2N_3$	62·89	9·43	15·72	63·10	9·51	15·72
S-3g[a]	147°	−252°	$C_{20}H_{27}O_2NS$	69·52	7·88	4·06	69·78	8·10	4·23
S-4	142°	−159	$C_{17}H_{21}O_2N$	71·05	7·37	4·87	70·95	7·25	4·80
R-5a	131°	−6°	$C_{18}H_{23}O_3N$	71·73	7·69	4·65	71·82	7·72	4·45
S-5a	131°	+2°	$C_{18}H_{23}O_3N$	71·73	7·69		71·95	7·76	—
R-5b	122°	−1°	$C_{16}H_{19}O_3N$	70·31	7·01	5·13	70·73	7·12	5·20
S-5b	122°	+6°	$C_{16}H_{19}O_3N$	—	—	5·13	—	—	5·31
S-5c	121–122°	+197°	$C_{25}H_{29}O_4N$	73·68	7·17	3·44	73·52	7·23	3·41
R-6	144–145°	+88°	$C_{18}H_{29}O_3N$	70·32	9·51	4·56	70·37	9·63	4·56
S-6	143–144°	−88°	$C_{18}H_{29}O_3N$	70·32	9·51	4·56	70·41	9·56	4·72
S-7[a]	101°	−186°	$C_{22}H_{30}O_4N_2$	68·39	7·77	7·25	68·24	7·90	7·16
S-8[a]	91°	−45°	$C_{23}H_{32}O_4N_2$	68·97	8·05	7·00	69·20	8·12	6·95
S-11[a]	123–124°	−17°	$C_{22}H_{30}O_4N_2$	68·37	7·82	7·25	68·40	7·91	7·50
S-12[a]	136–137°	−26°	$C_{23}H_{32}O_4N_2$	68·97	8·05	7·00	69·00	8·00	7·12
S-13[a]	107–108°	−11°	$C_{20}H_{26}O_4N_2$	67·02	7·31	7·82	66·90	7·52	7·81

[a] B. Halpern and L. B. James, *Nature, Lond.* **202**, 4932 (1964); B. Halpern and L. B. James, *Austral. J. Chem.* **17**, 1282 (1964); B. Halpern, *Ibid.* **18**, 471 (1965).

[b] The other compounds are described in Ref. 10.

In peptides with various asymmetric centers the sign of the Cotton effects seems to be dictated only by the absolute configuration of the carbon atom situated next to the vinylogous amide chromophore, without interference of the rest of the peptide moiety. Neither the sign nor the position of the experimental Cotton effects appear to be affected by the other asymmetric centers. This is shown in the case of (*S*)-valyl-(*S*)-alanine methyl ester (**9**)[10] and (*S*)-valyl-(*S*)-ananyl-(*S*)-leucine ethyl ester (**10**)[10] which show RD properties reminiscent of these of the simple dimedonyl condensate of valine (**2**).

When the enamine chromophore is separated from the asymmetric center by one or several atoms the sign and the shape of the 275 mμ Cotton effect curves are modified according to the nature of the amino acids forming the peptide moiety. This is illustrated in Table 3 in the case of peptides **11**, **12** and **13**, in which one notes a substantial reduction of the molecular amplitudes and inversions of the sign of the Cotton effects.

Also worth noting is the fact that the RD curves of dimedone condensates of peptides formed by aliphatic fragments do not exhibit the fine structure—and thus are much simpler—than these of dimedonyl derivatives of amino acids examined above.

One can conclude that the dimedonyl and dihydroresorcinol condensation products are not only valuable protecting groups,[10] but are also useful chromophoric derivatives in the amino acid, peptide and protein series. The sign of the Cotton effect depends on the absolute configuration of the asymmetric center situated next to the vinylogous amide chromophore. The intensity of the RD curves, as well as the position of the extrema and the shape of the curves are sensitive to the nature of the amino acid (or ester) forming the enamine system.

EXPERIMENTAL

Microanalyses were performed by Dr. A. Bernhardt, Mülheim (Germany), and m.p. (corrected) were determined with a Kofler apparatus. Rotations were measured between 16° and 22° with 1 dm tube at sodium D-light. RD curves were taken with an automatic recording JASCO/UV-5 spectropolarimeter and with a Bendix–Ericsson spectropolarimeter at the University of London, through the courtesy of Professor W. Klyne. IR spectra were recorded with a Perkin–Elmer, Model 21, NaCl prism, and UV absorption spectra were obtained with a Beckman spectrophotometer, Model D.U. We are indebted to Dr. L. Throop, Syntex Research, Palo Alto, California, for several RD curves.

General procedure for the preparation of N-(*5,5-dimethyl-2-cyclohexen-1-on-3-yl*) *and* N-(*2-cyclohexen-1-on-3-yl*) *derivatives of amino acids esters.* To a soln of dimedone (0·03M) in $CHCl_3$ (100 ml) was added the amino acid ester hydrochloride (0·03M) and the suspension neutralized by the addition of anhyd Et_3N (0·03M). The resulting clear soln was allowed to stand at room temp overnight. The soln was then washed several times with water, and the $CHCl_3$ soln dried and evaporated to dryness. The residue was then dissolved in benzene and the soln chromatographed through neutral alumina. The light yellow eluate was evaporated and the residue crystallized from benzene–hexane. For futher technical details, see Ref. 1.

The corresponding free acid derivatives were obtained by refluxing a suspension of the dimedone derivative of the amino acid ester (0·003M) in sat $NaHCO_3$aq until a clear soln resulted. After cooling to room temp, the soln was acidified to pH 4, and the ppt extracted into EtOAc. After removal of the solvent the residue was recrystallized from alcohol–ether or from EtOAc.

General procedure for the preparation of dimedone derivatives of peptide esters. To a soln of the dimedone derivative of the amino acid (0·0025M) in a neutral solvent (10 ml) cooled to 5° was added the amino acid alkyl ester hydrochloride (0·0025M), followed by dicyclohexyl carbodi-imide (0·0025M). After 16 hr at room temp the dicyclohexyl urea was filtered off and the filtrate acidified to pH 4. The product was then extracted into $CHCl_3$, and the solvent evaporated. The residue was then chromatographed through

neutral alumina and the peptide ester eluted with $CHCl_3$-benzene and usually recrystallized from EtOAc–ether.

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