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OPTICAL PROPERTIES OF DIMEDONYL DERIVATIVE OF AROMATIC AMINES AND AMINO ACIDS

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Abstract—It is shown that the Cotton effect associated with the dimedone condensates of amino compounds depends on the relative position of the vinylogous amide group and other chromophores present in the molecule. The chirality of the homoconjugated chromophore, in these partially rigid structures, strongly affects the sign of their ORD curves which are opposite in the derivatives of aromatic and aliphatic amino acids having the same configuration at the asymmetric C atom. On this assumption, some results published previously have been corrected. The inversion of the Cotton effect observed in the derivatives of secondary amines has been explained by means of a conformational change.

IT HAS been shown that the product of the reaction of an amine with dimedone yields the vinylogous amide chromophore —CO—CH═C—NH—, which absorbs in the 280 nm region (dioxan).[1] When situated in an asymmetric surrounding, this chromophore becomes optically active and shows a Cotton effect.

In this paper we report some recent results obtained with the dimedone condensates of some arylkylamines and aralkylamino acids. It is shown that the situation is more complicated than was anticipated earlier.[1,2] More precisely, it appears that the presence of a chromophoric group on the amino moiety, as well as the conformation of the derivative, strongly affects the sign of the Cotton effect.

A reinvestigation of the optical properties associated with the dimedone condensates indicates some similarity with those reported for some N-[2-pyridyl-N-oxide]-amino derivatives whose ORD curves seem to depend on the rotational interaction between the pyridyl-N-oxide group and other chromophores present in the molecule.[3]

The planar vinylogous amide group, having hindered internal rotation around C—N bond,[4] should tend to give preferential rotamers like those indicated in A and B since the H atom on the asymmetric carbon has smaller steric requirements than R_1 and R_2 group.

In respect to the group outside of the plane of the vinylogous amide chromophore, the rotamers A and B are mirror images, hence they should give opposite Cotton effects; their absolute values depend on the nature of the two substituents R_1 and R_2.

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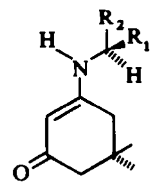
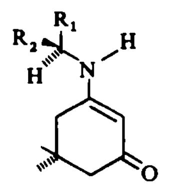


A



B

When R_1 and R_2 are two alkyl groups of comparable size, both the rotamers A and B have analogous probability of existence, then the partial compensation leads to ORD curves of low amplitude.

In fact, low amplitude ORD curves have been obtained (Table 1)[1] for 2-aminopentane (I), 2-amino-3-methylbutane (II) and 1,3-dimethylbutylamine (III) dimedone adducts.

Table 1. Optical properties of dimedonyl derivatives of aliphatic and alicyclic amines

Dimedonyl condensation compound Amine	Molecular amplitude*	Ref. for configuration
(*S*)-2-amino pentane (I)	−23	*a*
(*S*)-2-amino-3-methyl butane (II)	−8	*a*
(*S*)-1,3-dimethyl-butylamine (III)	−21	*a*
3-(*R*)-α-amino-5α-pregnane (IV)	+62	*b*
3-(*S*)-β-amino-5α-pregnane (V)	−70	*b*
3-(*S*)-β-amino-17β-hydroxy-5α-androstane (VI)	−84	*c*
17-(*R*)-α-amino-3β-hydroxy-5α-androstane (VII)	+957	*d*
17-(*S*)-β-amino-3β-hydroxy-5α-androstane (VIII)	−607	*d*

* in dioxan

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

[b] M. M. Janot, Q. Khuong-Huu, X. Lusinchi and R. Goutarel, *Bull. Soc. Chim. Fr.* 1669 (1960)

[c] M. M. Janot, Q. Khuong-Huu and R. Goutarel, *Bull. Soc. Chim. Fr.* 1640 (1960)

[d] M. Davis, E. W. Parnell and D. Warburton, *J. Chem. Soc.* (C) 1688, 1698 (1966)

On the other hand, an increase in the molecular amplitude of the ORD curves has been observed when the following situations are encountered. Firstly, when the nature of the substituent R_1 and/or R_2, or the nature of the solvent favours one conformation over others. This is the case with the dimedone derivatives of steroids in which there is less conformational freedom than in simple alkyl amino adducts. In addition, the dimedonyl derivatives of the 17-aminosteroids, where the conformation of the dimedonyl group is rather frozen, exhibit higher molecular amplitudes than dimedonyl derivatives at position 3 (Table 1). Secondly, when the substituents R_1 or R_2 contain a chromophoric group. In this case, either in rotamer A if the chromophoric group is in R_1 or in rotamer B if the chromophoric group is in R_2, there is a geometry suitable for an electronic interaction between this chromophore and the vinylogous amide. This homoconjugated chromophore[5] constitutes an extended π-system, in which the chirality is opposite in the two rotamers. In such a situation, the sign of the ORD curves depends on the relative geometry of the two chromophores, even if the electronic interaction only occurs in the less favorable conformation. Finally, when both substituents R_1 and R_2 contain a chromophore, then significant electronic interactions are operative in both rotamers. Since the homoconjugated chromophore in the two rotamers has opposite chirality leading to Cotton effects of opposite signs, the resultant sign of the ORD curve will essentially depend on the relative population of conformers A and B and on the absolute value of the molecular amplitude associated with each of them.

The experimental Cotton effects obtained with several dimedone derivatives of amines of known configuration allows one to establish the sign of the contribution to the optical properties, due to the homoconjugated system. If the chromophoric group is R_1 it will make a negative contribution to the Cotton effect associated with rotamer A. Conversely, if the chromophoric group is R_2, a positive contribution will be associated with the Cotton effect exhibited by rotamer B.

In fact, the amplitude of the dimedone derivative of 3β-amino steroids containing a double bond at position 4 or 5, is higher than that of a saturated steroid. Furthermore, the Cotton effect is negative for all derivatives from (*S*) alkyl amino esters (R_1 = $COOCH_3$; R_2 = alkyl), whereas it is positive for the derivatives prepared from aromatic amino esters (R_1 = $COOCH_3$; R_2 = aryl or aralkyl) having the same absolute configuration (Table 2).

TABLE 2. OPTICAL PROPERTIES OF DIMEDONYL DERIVATIVES OF AMINES CONTAINING A CHROMOPHORIC GROUP

Dimedonyl condensation compounds Amine	Molecular amplitude*	Ref. for configuration
3-(*S*)-β-amino-20 hydroxy-pregn-5-ene (IX)	−183	*a*
3-(*S*)-β-amino-pregn-5-ene-20-one (X)	−192	
(*S*)-alanine methyl ester (XI)	−224	*b*
(*S*)-alanine thiophenyl ester (XII)	−785	*b*
(*S*)-valine methyl ester (XIII)	−401	*c*
(*S*)-valine thiophenyl ester (XIV)	−1018	*c*
(*S*)-leucine methyl ester (XV)	−275	*c*
(*S*)-leucine thiophenyl ester (XVI)	−646	*d*
(*S*)-cyclohexyl alanine methyl ester (XVII)	−238	*b*
(*S*)-phenylalanine methyl ester (XVIII)	+436	*e*
(*S*)-tyrosine O-benzyl methyl ester (XIX)	+582	*e*

* in dioxan

[a] M. M. Janot, A. Cavé and R. Goutarel *Bull. Soc. Chim. Fr.* 896 (1959)

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

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

[d] A. Deer, J. H. Fried and B. Halpern *Austral. J. Chem.* **20** 797 (1967) and preceding papers.

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

This inversion in the sign of the Cotton effect, which is also observed in the dimedone adduct of phenylalanine methyl ester (XVIII) and in its dihydroresorcinol analogue, may be attributed to the contribution of rotamer B, in which the interaction between the phenyl and the dimedonyl chromophores originates a positive Cotton effect, whose absolute value is greater than that produced by interaction between the methyl ester and the dimedonyl chromophores. This assumption is supported by the fact that the amplitude of a thiophenylester derivative is greater than that of the equivalent amino acid alkylester.

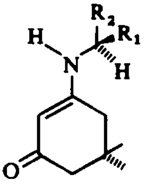
The results published earlier associated the sign of the Cotton effect with the conventional *R* and *S* configuration. In some compounds an inversion of the Cotton effect was observed when a methylene group was introduced between the asymmetric C atom and the phenyl ring.[1,2]

However, more recent observations seem to indicate that this methylene group should influence only the degree of rotational freedom of the phenyl ring in respect to the dimedonyl moiety, but should not affect the chirality of the homoconjugated chromophore originated from their interaction. Consequently, the sign of the Cotton effect should remain the same and only the amplitude should vary.

In order to check this assumption the dimedone derivative of α-benzylethylamine (XXI), α-phenylethylamine (XXII), phenylalanine methyl ester (XVIII) and phenylglycine methyl ester (XXIV) have been re-examined. Their ORD curves show that the absolute configurations assigned previously[1,2] to α-benzylethylamine and phenylglycine methyl ester dimedone derivatives exhibiting positive Cotton effect, have to be revised.

Table 3, where the correct results are reported, clearly shows that the sign of the Cotton effect cannot be related to the *R* and *S* conventional sequence rule; in fact

TABLE 3. OPTICAL PROPERTIES OF DIMEDONYL DERIVATIVES OF AMINE CONTAINING AN AROMATIC CHROMOPHORE



Dimedonyl condensation compound			Molecular amplitudes*		Ref. for configuration
	R_2	R_1	dioxan	methanol	
R-XX	$-\mathrm{CH_2OH}$	$-\mathrm{CH_2}-\mathrm{C_6H_5}$	−186	−283	*a*
S-XXI	$-\mathrm{CH_3}$	$-\mathrm{CH_2}-\mathrm{C_6H_5}$	−286	−258	*a*
S-XXII	$-\mathrm{CH_3}$	$-\mathrm{C_6H_5}$	−510	−682	*b*
S-XXIII	$-\mathrm{CH_3}$	$-1-\mathrm{C_{10}H_7}$	−1517	−1540	*b*
R-XVIII	$-\mathrm{COOCH_3}$	$-\mathrm{CH_2}-\mathrm{C_6H_5}$	−483	−385	*a*
R-XXIV	$-\mathrm{COOCH_3}$	$-\mathrm{C_6H_5}$	−273	−233	*c*

* For compounds XX, XXII, the ORD curves were actually taken for the antipodes

[a] P. Karrer and K. Ehrhardt, *Helv. Chim. Acta* **34** 2202 (1951)
J. Cymerman Craig, R. P. K. Chan, and S. K. Roy, *Tetrahedron* **23** 3573 (1967)

[b] W. Leithe, *Chem. Ber.* **64** 2827 (1931)
H. Wolf, E. Bunnenberg and C. Djerassi, *Chem. Ber.* **97** 533 (1964)

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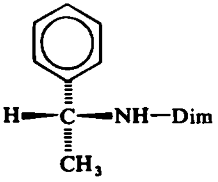
dimedonyl derivatives of *S*-amines (XXI, XXII and XXIII) present Cotton effects opposite to those shown by dimedonyl derivatives of *S*-aromatic amino ester (XVIII and XXIV) or amino alcohol (XX). The sign of the Cotton effect does not change when the mutual relationship between the aromatic chromophore and the dimedonyl group is the same.

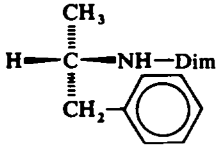
It is also worth mentioning that in the compounds containing two chromophoric groups, e.g. phenylglycine and phenylalanine methyl ester, the absolute value of the Cotton effect of their dimedone derivatives reflect the different population of the rotamers A and B. Whereas the amplitude of the Cotton effect increases if one goes from the α-benzylethylamine (XXI) to the α-phenylethylamine derivative (XXII), in the amino ester case the amplitude of the derivative (XXIV) is smaller than that of XVIII, this behaviour might be explained by a greater participation of rotamer A in the (S)-phenylglycine case in respect to the (S)-phenylalanine methyl ester derivative. A similar conformational change would account for the different amplitudes found for dim-α-benzyl ethylamine (XXI) and dim-phenylalaninol (XX).

In the dimedonyl derivatives of amines, lacking other functional groups, it is reasonable to assume that the rotamer population is comparable. Hence, the ORD curve of the dimedonyl derivative of (*R*)-(−)-1,2-diphenylethylamine (XXV)[6] should have the same sign as that shown by (*R*)-(+)-phenylethylamine (XXII). The positive Cotton effect observed experimentally for this substance is in agreement with the molecular amplitude calculated by algebraic summation of the Cotton effect associated with the (*R*)-(+)-α-phenylethylamine and (*S*)-(−)-α-benzylethylamine derivatives (Table 4).

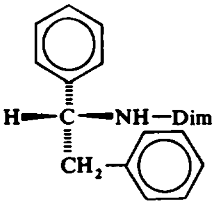
TABLE 4. AMPLITUDES (a) IN ORD CURVES OF DIMEDONYL DERIVATIVES PREPARED FROM OPTICALLY PURE AMINES


(*R*)-XXII

a_1


(*S*)-XXI

a_2


(*R*)-XXV

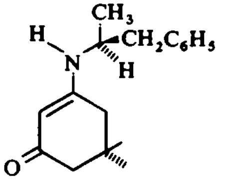
a_3

Solvent	a_1	a_2	a_3	
			Calc.: a_1 + a_2	Observed
Methanol	+682	−258	−682 + 258 = + 424	+393
Dioxan	+510	−286	−510 + 286 = + 224	+242

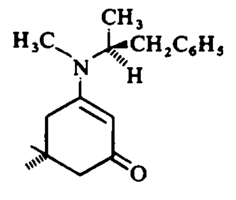
These results become meaningful if one considers that in these dim-amino-derivatives, which have similar rotameric composition, the Cotton effect is mainly due to the interaction of the dimedonyl group with the phenyl group in compound (*R*)-XXII through rotamer B and with the benzyl group in compound (*S*)-XXI through rotamer

A. Since in structure (*R*)-XXV this interaction is present in both rotamers A and B, the amplitude of its Cotton effect should be approximately the algebraic summation of the amplitudes of (*R*)-XXII and (*S*)-XXI.

Moreover, we have observed that the dimedone derivative of *S*-(+)-N-methyl-α-benzylethylamine (XXVI) has a Cotton effect opposite in sign to that of (*S*)-(+)-α-benzylethylamine (XXI). Other secondary amines (namely N-methyl-α-phenylethylamine, N-methyl-α-naphtylethylamine and the corresponding N-ethyl derivatives) do not react with dimedone even if they are refluxed for several hours in benzene. Consequently, the Cotton effect inversion observed for compounds XXI and XXVI can not be generalized. However, it seems reasonable to admit that the introduction of an alkyl group on the amino N atom could induce a conformational change in the plane of the vinylogous amide like that indicated in the rotamers A and C; the presence of a NH group could stabilize rotamer A by interaction with the solvent or through the formation of a dimer due to intermolecular H-bonding.



A



C

In these conformers, the homoconjugated chromophores originated by the interaction of the phenyl and dimedonyl groups have opposite chirality and could be then responsible for the opposite Cotton effect experimentally observed.

In conclusion, we propose that the sign of the Cotton effect associated with these dimedone condensation compounds reflects the relative position of the vinylogous amide with the other chromophores present in the molecule such as an aromatic ring and/or carboxyl group, etc. The relative position of the two chromophoric groups, will then depend on the configuration and the conformation of the molecule.

These results and observations may find a theoretical support in the general coupled-oscillator treatment applied by Mason[7] to some rigid structures.

EXPERIMENTAL

The preparations were performed as indicated previously.[1,2] The ORD curves were taken with an automatic recording Cary spectropolarimeter, Mod. 60. Concentrations are expressed in mg/ml of solution. Only new compounds and corrected data are reported below. For other data, references 1 and 2 should be consulted.

N-(*5,5-Dimethyl-2-cyclohexen-*1*-on -3-yl*) (R)-(−)-1,2-*diphenyl ethylamine* (R)-XXV. (*R*)-(−)-1,2-Diphenylethylamine, as the free base ($[\alpha]_D$ −11°) was treated as described.[1] After crystallization from benzene, the dimedone condensate (*R*)-XXV exhibited: m.p. 167–168°; $[\alpha]_D$ +35° (dioxan); λ_{max} 279 nm (log ε 4·41); ν_{max} 3250, 1580, 1540 cm^{-1}; ORD (*c*, 0·14; dioxan); $[\Phi]_{350}$ + 6100°, $[\Phi]_{330}$ + 7900°, $[\Phi]_{310}$ + 9700°, $[\Phi]_{300}$ + 13,600°, $[\Phi]_{295}$ + 15,500°, $[\Phi]_{290}$ + 13,600°. $[\Phi]_{280}$ ± 0°, $[\Phi]_{273}$ − 7500°, $[\Phi]_{270}$ − 6400°, *a* = +230. (*c*, 0·17; MeOH) $[\Phi]_{350}$ + 5200°, $[\Phi]_{330}$ + 8400°, $[\Phi]_{310}$ + 19,200°, $[\Phi]_{307}$ + 20,500°, $[\Phi]_{300}$ + 11,900°, $[\Phi]_{295}$ ± 0°, $[\Phi]_{290}$ − 10,500°, $[\Phi]_{280}$ − 16,900°, $[\Phi]_{270}$ − 11,600°, *a* = +374. (Found: C, 82·79; H, 7·97; N, 4·34. Calcd. for $C_{22}H_{25}NO$: C, 82·72; H, 7·89; N, 4·38%).

N-(5,5-*Dimethyl-2-cyclohexen-1-on-3-yl*) (S)-*deoxyephedrine* (S)-XXVI. ORD (c = 0·11; dioxan): $[\Phi]_{350}$ +4400°, $[\Phi]_{330}$ +6600°, $[\Phi]_{320}$ +8100°, $[\Phi]_{310}$ +12,800°, $[\Phi]_{300}$ +18,100°, $[\Phi]_{290}$ +5800°, $[\Phi]_{286}$ ±0°, $[\Phi]_{280}$ −8100°, $[\Phi]_{272}$ −13,000°, $[\Phi]_{270}$ −12,400°, $[\Phi]_{260}$ −5000°, a = +311. (c, 0·14; MeOH): $[\Phi]_{350}$ +3600°, $[\Phi]_{330}$ + 6100°, $[\Phi]_{320}$ +8500°, $[\Phi]_{310}$ +11,000°, $[\Phi]_{300}$ +2700°, $[\Phi]_{297}$ ±0°, $[\Phi]_{290}$ −4200°, $[\Phi]_{280}$ −7300°, $[\Phi]_{272}$ −8200°, $[\Phi]_{270}$ −7600°, $[\Phi]_{260}$ −3900°, a = +192.

N-(5,5-*Dimethyl-2-cyclohexen-1-on-3-yl*) (R)-*phenylglycine methyl ester* (R)-XXIV. The configuration of *D*-(−)-phenylglycine methyl ester was checked by GLC of the N-TFA-S-prolyl-D-(−)-phenylglycine methyl ester.[8] D-(−)-Phenylglycine behaved as all methyl ester of D-amino acids. Retention time: SR (4·1); SS (4·6), compared with phenylalanine methyl ester SR (8·1); SS (8·4) (SR = LD). This shows D-(−)-phenylglycine methyl ester to have the (R) absolute configuration.

The dimedonyl derivative was prepared as in ref. 2. m.p. 118°; $[\alpha]_D$ −208° (dioxan); ORD (c, 0·14; dioxan). $[\Phi]_{330}$ −5200°, $[\Phi]_{310}$ −8800°, $[\Phi]_{295}$ −18,300°, $[\Phi]_{286}$ −22,500°, $[\Phi]_{280}$ −14,000°, $[\Phi]_{274}$ ±0°, $[\Phi]_{265}$ +13,100°, $[\Phi]_{259}$ +16,400°, $[\Phi]_{250}$ +11,400°, a = −389. (c, 0·13; MeOH): $[\Phi]_{330}$ −7800°, $[\Phi]_{310}$ −14,400°, $[\Phi]_{300}$ −17,700°, $[\Phi]_{290}$ −10,200°, $[\Phi]_{283}$ ±0°, $[\Phi]_{280}$ +8500°, $[\Phi]_{267}$ +11,100°, $[\Phi]_{260}$ +9100°, $[\Phi]_{250}$ +3300°, a = −288.

N-(5,5-*Dimethyl-2-cyclohexen-1-on-3-yl*)-(S)*phenylalaninol* (S)-XX. (S)-Phenylalaninol,* as the free base ($[\alpha]_D$ −23°; EtOH) was treated as described.[1] After crystallization from acetone, the dimedone condensate (S)-XX exhibited. m.p. 135–136°; $[\alpha]_D$ +59° (dioxan); λ_{max}280 nm (log ε 4·41) ν_{max} 3300, 1580, 1520 cm^{-1}; ORD (c, 0·14; dioxan): $[\Phi]_{310}$ +1600°, $[\Phi]_{300}$ +3400°, $[\Phi]_{292}$ +6200°, $[\Phi]_{282}$ ±0°, $[\Phi]_{270}$ −10,200°, $[\Phi]_{260}$ −12,400°, $[\Phi]_{250}$ −9600°, a = +186. (c, 0·13; MeOH); $[\Phi]_{330}$ +1300°, $[\Phi]_{320}$ +3600°, $[\Phi]_{310}$ +9600°, $[\Phi]_{305}$ +11,200°, $[\Phi]_{300}$ +6300°, $[\Phi]_{296}$ ±0°, $[\Phi]_{290}$ −9900°, $[\Phi]_{280}$ −17,100°, $[\Phi]_{270}$ −14,800°, $[\Phi]_{260}$ −11,800°, $[\Phi]_{250}$ −9600°, a = +283. (Found: C, 74·65; H, 8·47; N, 5·15. Calcd. for $C_{17}H_{23}NO_2$. C, 74·69; H, 8·48; N, 5·12%).

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* Prepared from L-Phenylalanine by reduction with LAH.[9] *cf* O. Vogl and M. Pohm, *Monatsh. Chem.* **83**, 541 (1952).