

Chiroptical Properties of *N*-Acetoacetyl- α -amino-acids, -amino-alcohols, and -amines

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N-Acetoacetyl derivatives of aliphatic and aromatic (*S*)- α -amino-acids exhibit enantiomorphic c.d. spectra in ethanolic potassium hydroxide. However, the c.d. spectra of both aliphatic and aromatic series are similar in a series of organic solvents. Similar c.d. behaviour is observed for aliphatic and aromatic *N*-acetoacetyl (*S*)- α -amino-alcohols and (*S*)-amines. Chiral shift reagent n.m.r. studies reveal that the *N*-acetoacetyl amino-acids are optically pure.

SEVERAL *N*-acetoacetyl (ACA) (*S*)- α -amino-acids (I) were needed for synthetic studies.¹ The optical rotatory properties of some aliphatic *N*-ACA- α -amino-acids and -esters have been reported recently,² but those of aromatic analogues have not been described. In view of our findings¹ that aliphatic and aromatic quinoxalinyll (*S*)-amino-acids exhibit enantiomorphic c.d. spectra, we have reinvestigated the chiroptical properties of *N*-ACA (*S*)-amino-acids and -esters (I) and *N*-ACA (*S*)-amino-alcohols and (*S*)-amines (II) by the c.d. technique. These compounds were synthesized by the reaction of keten dimer with the appropriate amines.³⁻⁶

The optical purity of a model compound (2b) was determined by the chiral lanthanide shift reagent ¹H n.m.r. technique.⁷ The acetyl methyl signal was em-

ployed as a criterion for optical purity determination using Eu(hfc)₃.† Upon addition of the shift reagent, two singlets due to diastereotopic protons, of almost the same intensity, appear in the spectrum of the (*RS*)-form, whereas the singlet of the pure (*S*) isomer suffers no change (Figure A).‡ Also the prochiral isopropyl methyl signals appear as four doublets in the spectrum of the (*RS*)-form, and as two doublets in that of (*S*)-(2b) after addition of the shift reagent (Figure A). These results indicate that (*S*)-(2b) [and by inference all the compounds (I) and (II)] is optically pure. This agrees with a report⁸ of g.l.c. results indicating the absence of racemization in the production of (2b).

The lanthanide-induced shift of the NH signals is much larger than that of the acetyl methyl or the ester methyl

† This shift reagent did not separate the ester methyl signal of (*RS*)-(2b) up to 0.6 molar ratio. Eu(tfc)₃ did not separate the acetyl methyl nor the ester methyl signals of this compound.

‡ Table A and Figure A are available as Supplementary Publication No. SUP 22034 (3 pp.). For details of Supplementary Publications see Notice to Authors No. 7 in *J.C.S. Perkin I*, 1976, Index issue.

¹ M. M. El-Abadelah, S. S. Sabri, M. Z. Nazer, and M. F. Za'ater, *Tetrahedron*, 1976, **32**, 2931.

² C. Toniolo, F. Filira, and C. Di Bello, *Biopolymers*, 1971, **10**, 2275.

³ R. N. Lacey, *J. Chem. Soc.*, 1954, 850.

⁴ H. Harris, L. V. Fischer, and K. Folkers, *J. Medicin. Chem.*, 1965, **8**, 478.

⁵ F. D'Angeli, F. Filira, V. Giormani, and C. Di Bello, *Ricerca Sci.*, 1966, **36**, 11.

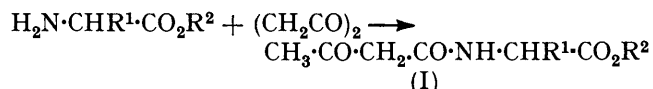
⁶ C. Di Bello, F. Filira, and F. D'Angeli, *J. Org. Chem.*, 1971, **36**, 1818.

⁷ A. F. Cockerill, G. L. O. Davies, R. C. Harden, and D. M. Racham, *Chem. Rev.*, 1973, **73**, 581.

⁸ C. Di Bello, F. Filira, V. Giormani, and F. D'Angeli, *J. Chem. Soc. (C)*, 1969, 350.

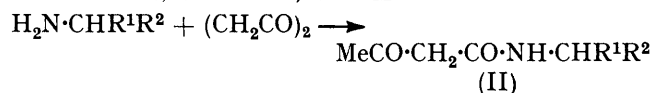
signal (Table A).† This indicates that europium preferentially complexes with the amide carbonyl rather than the acetyl or the ester carbonyl. This order of preferential complexation has been reported for related polyfunctional systems.^{7,9}

The u.v. spectra of compounds (I) and (II) show, in



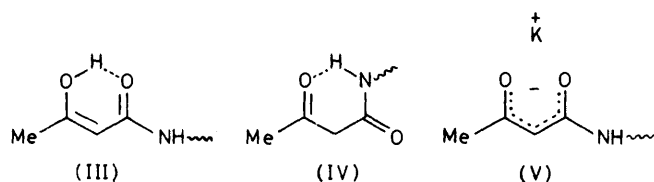
R ¹	R ¹
(1) Me	(5) Ph
(2) Pr ⁱ	(6) PhCH ₂
(3) Bu ⁱ	(7) <i>p</i> -HO·C ₆ H ₄ ·CH ₂
(4) Bu ^s	(8) indol-3-ylmethyl

a; R² = H b; R² = Me



R ¹	R ²
(9) Me	CH ₂ -OH
(10) CH ₂ Ph	CH ₂ -OH
(11) Ph	Me
(12) Et	Me

organic solvents, two major bands, characteristic of β-dicarbonyl derivatives,¹⁰ at *ca.* 245–248 and 280–290 nm (Table). The former is mainly due to the π → π* transition of the amide, and the latter is ascribed to the n → π* transition of the ketone in form (IV) and the amide in form (III). In alkaline medium, however, bands are observed at 270–275, 240–245, and 205–215 nm. These might be attributed to π → π* transitions within the hybrid *cis*-enolate anion (V). Structures similar to (V) have been postulated for enolate anions of analogous systems,¹¹ including monothio-analogues.¹²



The c.d. spectra of the aliphatic (*S*)-series (1a)–(4a) display, in organic solvents, Cotton effect bands at *ca.* 275–285 (–ve), 245–250 (–ve), and 214–217 nm (+ve) (Table and Figure 1). The aromatic (*S*)-series (5a)–(8a) exhibit a positive Cotton effect at *ca.* 214–225 nm; the bands at 280 and 245 nm were observed with certainty only for (5a), and are both of negative sign.

In alkaline medium, the c.d. spectra of the aliphatic (*S*)-series (1a)–(4a) show a positive Cotton effect at *ca.* 268–273 nm, a positive shoulder at 240–245 nm, and a negative maximum at 214–227 nm (Table and Figure 1). In alkaline medium, the c.d. spectra of the aromatic (*S*)-series (5a)–(8a) are nearly enantiomorphous to those of the aliphatic (*S*)-counterparts (Figure 1). This phenom-

⁹ M. M. El-Abadelah, S. S. Sabri, H. D. Tabbá', and H. Duddeck, unpublished work.

¹⁰ P. Markov, L. Shishkova, and A. Radashev, *Tetrahedron*, 1973, **29**, 3203; M. I. Kabachnik, S. T. Ioffe, E. M. Popov, and K. V. Vatsuro, *ibid.*, 1961, **12**, 76.

enon might be due to conformational effects and/or to differences in the 'interaction' between alkyl and aryl groups and the chromophore. Conformer (A) might be preferred for the aliphatic series, whereas conformer (B) might prevail in the aromatic series, allowing minimal

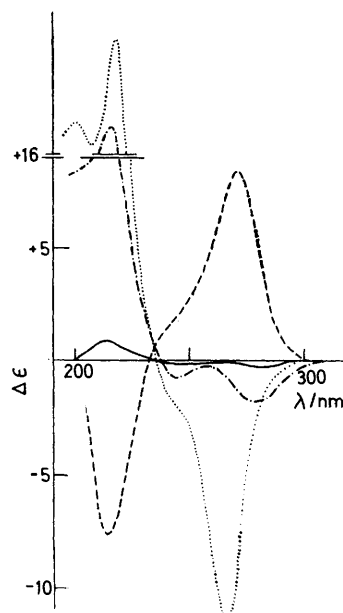
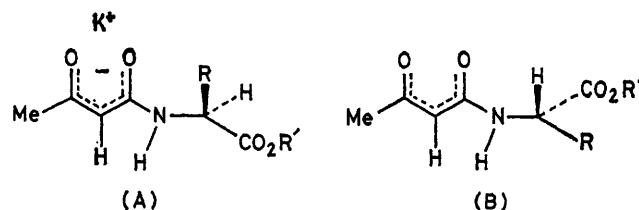


FIGURE 1 C.d. spectra of (*S*)-(4a): (—) in ethanol, (----) in ethanolic 0.1N-KOH; and of (*S*)-(5a) (— · — · —) in ethanol, (···) in ethanolic 0.1N-KOH

repulsive interaction between the aryl group and the enolate chromophore.

In alkaline medium, the aliphatic and aromatic *N*-ACA (*S*)-amino-alcohols (9) and (10) also show enantiomorphous c.d. spectra (Table and Figure 2). Similar c.d. behaviour is also observed for the *N*-ACA (*S*)-α-amines (11) and (12) (Table). These differences might be explained similarly.

The Cotton effect bands for the aromatic derivatives (5b), (6b), and (8b) are similar in sign and magnitude to those of the corresponding acids. The c.d. spectra of the



aliphatic ester derivatives (1b)–(4b) show minor differences from those of the acid derivatives (1a)–(4a). The c.d. spectra of freshly prepared alkaline solutions of the aliphatic ester derivatives (1b)–(4b) revealed a double-humped Cotton effect band (at 256 and 272 nm) that gradually collapsed (during 25 min) to a positive band at 269 nm. This change is probably due to hydrolysis of the ester, since the latter band is observed in the acid series.

¹¹ W. Müller, U. Kraatz, and F. Korte, *Tetrahedron*, 1973, **29**, 4291.

¹² J. Fabian, *Tetrahedron*, 1973, **29**, 2449.

C.d. and u.v. spectral data for the (S)-derivatives (I) and (II)

	Solvent †	C.d.		U.v. ‡	
		$\lambda_{\text{max.}}/\text{nm}$	$\Delta\epsilon$	$\lambda_{\text{max.}}/\text{nm}$	ϵ
(1a)	A	278 (-0.08), 245 (-0.20), 214 (+0.73)		284 (175), 245 (1 180)	
	E	285 (-0.20), 245 (-0.18), 217 (+0.96)		285sh (70), 245 (860)	
(1b)	E-KOH	270 (+4.80), 240sh (+1.27), 214 (-3.80)		275 (12 470), 238sh (2 400), 205 (6 235)	
	A	281 (-0.07), 248 (-0.16), 218 (+0.62)		280sh (100), 244 (1 080)	
(2a)	E	280 (-0.19), 248 (-0.22), 217 (+0.72)		277sh (150), 245 (900)	
	E-KOH	270 (+4.75), 228 (-1.82), 209 (+0.41)		276 (9 600), 241 (5 150), 210sh (4 000)	
(2b)	A	275 (-0.07), 250 (-0.14), 217 (+0.81)		276sh (80), 245 (1 080)	
	E	280 (-0.12), 247 (-0.12), 216 (+1.11)		274sh (70), 246 (800)	
(3a)	E-KOH	272 (+5.20), 245sh (+1.40), 216 (-6.20)		273 (13 250), 244sh (3 080), 207 (6 620)	
	A	284 (-0.07), 249 (-0.15), 212 (+1.01)		282sh (85), 245 (1 070)	
(3b)	E	284 (-0.17), 249 (-0.19), 211 (+0.71)		280sh (120), 245 (930)	
	E-KOH	268 (+5.18), 228 (-2.84), 211 (+0.49)		276 (14 300), 245 (5 530), 210sh (5 370)	
(4a)	A	275 (-0.17), 250 (-0.11), 216 (+1.00)		277sh (120), 245 (1 200)	
	E	280 (-0.12), 246 (-0.10), 216 (+1.11)		275sh (90), 245 (850)	
(4b)	T	284 (-0.10), 245 (-0.40), 212 (+0.85)			
	E-KOH	268 (+6.04), 240sh (+1.07), 214 (-5.40)		273 (10 900), 239sh (2 200), 208 (5 650)	
(5a)	A	284 (-0.06), 249 (-0.13), 215 (+1.28)		278sh (125), 245 (1 160)	
	E	285 (-0.20), 250 (-0.16), 215 (+1.31)		274sh (85), 245 (970)	
(6a)	E-KOH	274 (+4.74), 259 (+3.58), 229 (-2.80), 212 (+0.44)		276 (11 900), 242 (4 850), 212sh (4 850)	
	A	277 (-0.13), 249 (-0.13), 215 (+1.03)		290sh (140), 246 (1 090)	
(6b)	E	280 (-0.15), 246 (-0.12), 214 (+0.90)		285sh (230), 248 (830)	
	E-KOH	273 (+8.28), 244sh (+1.22), 217 (-7.64)		275 (15 610), 242sh (2 500), 212 (4 890)	
(7a)	A	282 (-0.07), 249 (-0.15), 212 (+1.18)		280sh (110), 245 (1 090)	
	E	283 (-0.17), 249 (-0.13), 212 (+1.01)		276sh (90), 246 (940)	
(7b)	E-KOH ^a	272 (+3.83), 256 (+2.33), 228 (-2.19), 211 (+0.71)			
	E-KOH ^b	272 (+3.92), 262 (+3.43), 228 (-2.14), 210 (+0.73)			
(8a)	E-KOH ^c	269 (+5.01), 228 (-2.68), 211 (+0.93)		277 (8 970), 244 (3 870), 211sh (3 870)	
	A	217 (+12.78)		285sh (200), 268sh (700), 251 (1 450), 247 (1 470)	
(8b)	E	280 (-1.94), 244sh (-0.89), 217 (+17.50)		268sh (1 060), 251 (2 400), 247 (2 370)	
	E-KOH	268 (-11.32), 244sh (-1.34), 218 (+21.15), 202 (+17.43)		275 (14 000), 217sh (13 000)	
(9a)	A	215 (+5.10)		285sh (200), 267sh (650), 252 (1 350), 247 (1 400)	
	E	214 (+5.85)		267sh (400), 252 (950), 247 (1 000)	
(9b)	E-KOH	270 (-9.42), 223sh (+7.43), 213 (+16.70)		275 (14 000), 218sh (10 000), 206 (14 500)	
	A	215 (+4.85)		268sh (470), 257 (1 050), 252 (1 220), 248 (1 250)	
(10a)	E	214 (+4.01)		268sh (470), 257 (950), 252 (1 080), 248 (1 090)	
	E-KOH	274 (-3.19), 238 (-1.36), 211 (+8.45)		278 (12 600), 242 (6 100), 217sh (6 300), 210sh (13 000)	
(10b)	A	225 (+4.62)		285 (1 750), 278 (2 150), 251sh (1 200), 225 (9 150)	
	E	225 (+5.70)		285sh (1 450), 278 (1 800), 252sh (1 000), 226 (10 000)	
(11a)	E-KOH	267 (-13.00), 238 (+12.55), 204 (+18.64)		303sh (2 650), 276 (14 400), 245 (17 500), 217sh (10 100), 200 (26 900)	
	A	225 (+4.95)		290 (4 450), 282 (5 200), 273 (5 000), 221 (31 400), 198 (14 650)	
(11b)	E	223 (+5.72)		290 (4 800), 282 (5 600), 274 (5 100), 221 (35 000), 198 (21 000)	
	E-KOH	273 (-7.22), 246sh (-1.21), 223 (+19.47)		290sh (11 400), 275 (20 000), 223 (36 300), 200 (16 000)	
(12a)	A	223 (+5.16)		290 (4 780), 280 (5 640), 273 (5 550), 260sh (3 350), 221 (33 800)	
	E	223 (+4.05), 204 (-3.13)		290 (5 300), 281 (6 100), 273 (5 800), 221 (36 000), 201 (22 600)	
(12b)	E-KOH	283 (-1.89), 238 (-1.17), 222 (+6.98)		290sh (2 860), 275 (4 650), 221 (9 500)	
	A	280 (+0.03), 222 (+1.71), 200 (-2.48)		244 (1 100), 195 (6 550)	
(13a)	E	219 (+0.40), 196 (-2.10)		245 (785), 193 (7 650)	
	E-KOH	278 (+1.91), 250sh (+0.60), 227 (+0.39), 200 (-3.31)		280 (16 350), 211 (7 100)	
(13b)	A	282 (+0.09), 272 (+0.10), 258 (+0.09), 253 (+0.12), 225 (+1.20)		267sh (480), 247 (1 260), 217sh (5 850), 205sh (12 200)	
	E	282 (+0.11), 265 (+0.05), 223 (+0.82), 206 (+1.75)		267sh (400), 247 (880), 217sh (6 350), 205sh (12 500)	
(14a)	E-KOH	270 (-7.51), 250sh (-2.54), 215 (+8.43), 199 (+2.10)		275 (17 250), 209 (13 600)	
	E	280 (-ve), 243 (-ve), 215 (+13.16), 197 (+26.33)		240 (2 050)	
(14b)	E-KOH	270 (-7.61), 215 (+15.93), 196 (+16.93)		270 (20 120)	
	E	294 (-0.05), 213 (+0.55)		240 (602)	
(15)	E-KOH	283 (-2.08), 273 (+0.78), 235 (-ve)		273 (10 300)	

† A = acetonitrile; E = ethanol; E-KOH = ethanolic alkali (0.1N); T = 1,1,1-trifluoroethanol. ‡ The band around 280 nm [compounds (1)–(4)] appears as an inflection on the tail of the more intense band around 245 nm.

^a Spectrum run immediately. ^b Run after 12 min. ^c Run after 25 min.

In conclusion, the position, sign, and magnitude of the Cotton effect bands of compounds (I) and (II), in alkaline medium, depend on the nature of the (S)- α -amino-compound (aliphatic or aromatic). The sign of the observed bands may thus be correlated with the configuration of

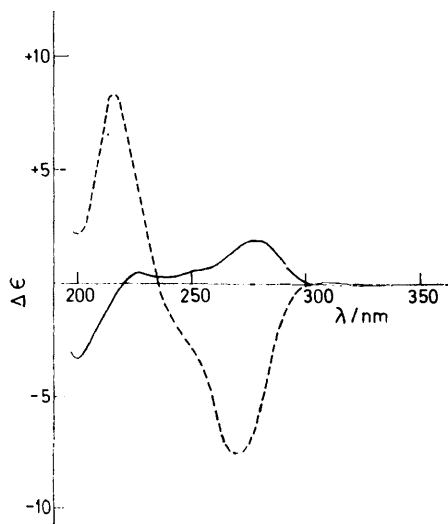


FIGURE 2 C.d. spectra of (—) in (S)-(9) in ethanolic 0.1N-KOH; (---) (S)-(10) in ethanolic 0.1N-KOH

the *N*-ACA-amino-compound provided that experimental conditions and the nature of the amino-compound are taken into consideration.

EXPERIMENTAL

(S)- α -Amino-acids, their methyl ester hydrochlorides, and chiral amines (Merck or Norse) were used without further purification. Eu(hfc)₃ and Eu(tfc)₃ were purchased from Aldrich. Optical rotations were measured at 20 °C with a Perkin-Elmer 141 polarimeter for solutions in methanol [compounds (I)] or in chloroform [compounds (II)] (*c* 1–2). C.d. spectra were recorded with a Roussel-Jouan Dichrographe II model 185; concentrations were *ca.* 2 mg ml⁻¹ and cell path lengths 0.01–0.5 cm; temperature 20 °C. U.v. spectra were recorded with a Cary 17 spectrometer in cells of 0.01 or 0.1 cm path length. ¹H N.m.r. spectra were recorded with a Varian T-60A spectrometer (solvent CDCl₃; Me₄Si as internal standard). Elemental analyses were performed by Dr. F. Pascher (Bonn).

N-Acetoacetyl (S)- α -Amino-acids and -esters (I).—The acid derivatives (Ia) were obtained by the reactions of keten

dimer with the amino-acids in 2N-sodium hydroxide.^{4–6} The m.p.s of the products agreed with literature values. The methyl esters (Ib) were prepared either from the acids (Ia) with ethereal diazomethane⁴ or by the reaction of keten dimer with the amino-esters.^{3,5} The latter were liberated from their hydrochlorides by treatment with 1 equiv. of methanolic sodium methoxide.³ The products (liquids) were purified by column chromatography [silica gel; eluants diethyl ether–light petroleum (70 : 30), followed by diethyl ether]. Values of $[\alpha]_{578}$ are reproduced here where no literature data are available, or when there are marked differences from literature values: (1a) –38.2°; (1b) –60.3°; (2b) –30.1°; (3b) –44.3°; (4a) +6.3° {lit.,⁴ $[\alpha]_{546}^{25}$ –122° (*c* 2 in MeOH)}; (4b) –16.6° {lit.,⁴ $[\alpha]_{546}^{25}$ +7° (*c* 2 in MeOH)}; (5a) +172.6°; (5b) +190.3°; (6b) +10.5°; (7a) +47.5°; (8b) +9.7°.

N-Acetoacetyl (S)- α -Amino-alcohols (9) and (10).—These were prepared by the reaction of keten dimer with the appropriate amino-alcohols [obtained by reduction (LiAlH₄) of the α -amino-acid¹³] in diethyl ether–methanol (4 : 1). 2-Acetoacetamidopropan-1-ol (9) (84%) was purified by preparative t.l.c. [Merck silica gel PF₂₅₄; 2 mm thick plates; chloroform–methanol (95 : 5)]; $[\alpha]_D$ –20.1° (Found: C, 52.35; H, 8.05; N, 8.55. C₇H₁₃NO₃ requires C, 52.8; H, 8.25; N, 8.8%). 2-Acetoacetamido-3-phenylpropan-1-ol (10) (90%) was crystallized from chloroform–light petroleum; m.p. 75°, $[\alpha]_D$ –36.6° (Found: C, 66.45; H, 7.2; N, 5.95. C₁₃H₁₇NO₃ requires C, 66.35; H, 7.3; N, 5.95%).

N-Acetoacetyl Amines (11) and (12).—These were prepared analogously by the reaction of keten dimer with the appropriate amine.¹⁴ (S)-*N*-(1-Methylpropyl)acetoacetamide (12) (74%) had b.p. 120° at 0.8 mmHg; $[\alpha]_D$ +20.7° (Found: C, 60.95; H, 9.6; N, 8.8. C₈H₁₅NO₂ requires C, 61.1; H, 9.6; N, 8.9%). The (R)-isomer (76%) had b.p. 116° at 0.5 mmHg; $[\alpha]_D$ –21.0° (Found: C, 60.6; H, 9.55; N, 8.8%). (S)-*N*-(1-Phenylethyl)acetoacetamide (11) (84%) had b.p. 180° at 0.6 mmHg; $[\alpha]_D$ +81.9° (Found: C, 70.2; H, 7.3; N, 6.85. C₁₂H₁₅NO₂ requires C, 70.2; H, 7.35; N, 6.8%). The (R)-isomer (84%) had b.p. 180° at 0.6 mmHg; $[\alpha]_D$ –82.4° (Found: C, 69.9; H, 7.5; N, 6.9%).

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¹⁴ S. I. Zavyalov, V. I. Gunar, I. A. Mikhailopulo, and L. F. Oveckina, *Tetrahedron*, 1966, **22**, 2003.