788. *Interaction between Carbonyl Groups and Biologically Essential Substituents. Part II.*[1] *Further Observations on the Effect of Ketones on Optically Active α- and β-Amino-esters.*

By F. Bergel and (Miss) J. Butler.

The effects of diketones on the rotatory behaviour of amino-esters have been investigated. A condensation product of acetylacetone and L-tyrosine ethyl ester is described. The absolute configuration of (+)-β-amino-β-phenylpropionic acid has been established and the mutarotation of its ethyl ester in ketonic solvents studied.

In extension of our studies [1] of the rotatory behaviour of optically active α-amino-esters and of (+)-amphetamine in ketonic solvents, we obtained additional results with diketones and a β-amino-ester.

The situation with the diketones so far used, namely biacetyl, acetylacetone and two cyclohexane-1,3-diones, is not as simple as that with monoketones. For the latter, Table 1

[1] Part I, Bergel, Lewis, Orr, and Butler, *J.*, 1959, 1431.

illustrates the rotatory behaviour of α-amino-esters in a homologous series of cyclic ketones in comparison with their specific rotation in ethanol.

TABLE 1.

Maximal $[\alpha]_D$ at 18—25°.

Ethyl esters of	Ethanol	Cyclobutanone	Cyclopentanone	Cyclohexanone	Cycloheptanone
L-Tyrosine (*c* 3·25)	+17°	−143°	−161° [1]	−124° [1]	−106°
D-Phenylalanine (*c* 3·0)	−22	+125 †	+153 [1]	+137 [1]	—
L-Valine (*c* 2·25)	−29	—	−229	−178	−121
D-Valine (*c* 2·25)	+29	—	+216	+175	+121

† Cyclobutanone–ethanol 1 : 1 (v/v).

In contrast, no mutarotation occurred with L-tyrosine ethyl ester in cyclohexane-1,3-dione or dimedone (Table 2). This could be explained if the preferred state of the molecules were the monoenolic form (see Meek *et al.*[2]). Both these cyclic diketones are sufficiently strong acids (K_a 0·55 × 10^{-5} and 0·71 × 10^{-5} respectively [3]) to protonate the amino-group of the ester and hence to prevent azomethine formation.[1]

TABLE 2.

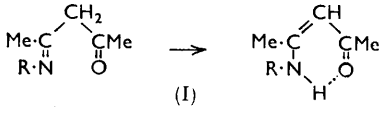
Maximal $[\alpha]_D$ at 18—25°.

	L-Tyrosine Et ester (*c* 3·25)	L-Tyrosine Et ester (*c* 3·25, ethanol + 2 equiv. of dione)	Phenylalanine Et ester (*c* 3·0)
Acetylacetone	−266°	−195°	L −271°
Biacetyl–ethanol (1 : 1 v/v)	−140		D +148
Cyclohexane-1,3-dione		+22·5	
Dimedone		+24	

Acetylacetone, on the other hand, with K_a 1·5 × 10^{-6},[4] is not sufficiently acidic to prevent the formation of a product which gave analyses for a monoazomethine. But this compound, in contrast to *N*-cyclopentylidenetyrosine ester, described in Part I,[1] did not show an infrared absorption band in the 1650 cm.$^{-1}$ region (for C=N of acyclic substances [5]). This, according to Henecka,[6] is due to the isomerisation of the azomethine to a pseudo-aromatic enamine (I; R = *p*-HO·C_6H_4·CH_2·CH·CO_2Et).

Rotatory-dispersion measurements (cf. Figure), while showing only a plain curve without Cotton effect [7] down to 300 mμ, gave a value of $[M]_{350}$ = −12,000° in comparison with $[M]_{350}$ = −1000° for *N*-cyclopentylidenetyrosine ethyl ester.

Reverting to Table 2, one can see there that the maximal specific rotations of tyrosine and L-phenylalanine esters in acetylacetone are similar in magnitude and that in biacetyl–ethanol a similar relation has been noted between D-phenylalanine (opposite sign) and tyrosine ethyl ester.

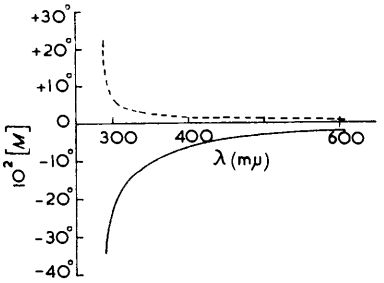


(I)

For the purpose of investigating the rotatory behaviour of a β-amino-ester with known absolute configuration in ketonic solvents, DL-β-amino-β-phenylpropionic acid was

[2] Meek, Turnbull, and Wilson, *J.*, 1953, 2891.
[3] von Schilling and Vorländer, *Annalen*, 1899, **308**, 190, 193.
[4] Guinchant, *Ann. Chim. Phys.*, 1918, **9**, 139.
[5] Cf. Jones and Sandorfy in "Chemical Application of Spectroscopy," Vol. IX of "Technique of Organic Chemistry," ed. West, Interscience Publ. Inc., New York, 1956, p. 532.
[6] Henecka, "Chemie der Beta-Dicarbonyl Verbindungen," Springer-Verlag, Berlin, 1950, p. 189.

resolved in the form of its *N*-formyl derivative by the method of Fischer *et al.*[8] The (+)-formamido-acid was transformed into the amino-ester hydrochloride, and after *N*-acetylation the ester was converted into an azide. This compound was submitted to a Curtius degradation, followed by acid hydrolysis which gave the L-(−)-phenylethylenediamine dihydrochloride. Arpesella *et al.*[9] had related the configuration of this diamine to L-(+)-α-aminophenylacetic acid, therefore (+)-β-amino-β-phenylpropionic acid belongs to the L-series. After the experiments had been carried out it came to our knowledge that Lukeš *et al.*[10] had reached the same conclusion, using a different method of degradation.



Rotatory dispersion curves (by courtesy of Professor W. Klyne) for (– – –) L-tyrosine ethyl ester and (——) *N*-cyclopentylidene-L-tyrosine ethyl ester.

Mutarotation measurements of the ethyl ester of L-(+)-β-amino-β-phenylpropionic acid in a number of monoketones showed that interaction produced a positive shift of $[\alpha]_D$ (Table 3). This effect is the opposite to that found for L-α-amino-esters. Balenović,[11]

TABLE 3.

Maximal $[\alpha]_D$ at 22° ± 2° (*c* 3·0, except for ethanol where *c* 2·0).

Ethanol	+8°	Instantaneous	Cyclohexanone	+68°	After 3 min.
Diethyl ketone	+23	,,	Cycloheptanone	+61	,, 60 min.
Cyclopentanone	+73	After 8 min.	Acetylacetone	−600	,, 45 min.

when extending the studies of Lutz and Jirgensons[12] who had found a positive shift of $[\alpha]_D$ with L-α-amino-acids in presence of hydrochloric acid, came to the conclusion that this shift with L-β-amino-acids was in a negative direction.

The only observation which remains puzzling is the behaviour of L-β-amino-β-phenylpropionic ester in presence of acetylacetone. Unexpectedly a high lævorotation was noticed ($[M]_{350}$ −13,000°) which cannot be caused solely by formation of a pseudoaromatic product (I; R = C_6H_5·$\overset{|}{C}$H·CH_2·CO_2Et).

EXPERIMENTAL

Physical Measurements.—Optical rotations were obtained as described in Part I.[1] Rotatory dispersions were measured with a Rudolph spectropolarimeter by courtesy of Professor W. Klyne. Infrared absorption measurements were carried out on a Perkin–Elmer model 12C spectrometer, by courtesy of Dr. R. L. Jones.

Solvents and Ketones.—For polarimetry, ethanol was dried as described in Part I.[1] Cyclobutanone was purchased from Aldrich Chemical Company and used without further purification. Cycloheptanone, distilled through a fractionating column, had b. p. 178—179°. Biacetyl, distilled through a fractionating column, had b. p. 88°. Acetylacetone, similarly distilled, had b. p. 136—137°. Cyclohexane-1,3 dione, recrystallised from benzene, had m. p. 107—108°.

[7] Djerassi and Klyne, *Proc. Chem. Soc.*, 1957, 55.
[8] Fischer, Scheibler, and Groh, *Ber.*, 1910, **43**, 2020.
[9] Arpesella, La Manna, and Grassi, *Gazzetta*, 1955, **85**, 1354.
[10] Lukeš, Kovář, Kloubek, and Bláha, *Coll. Czech. Chem. Comm.*, 1958, **23**, 1367.
[11] Balenović in "Amino Acids and Peptides with Antimetabolic Activity," Ciba Found. Symp., J. & A. Churchill, London, 1958, p. 5.
[12] Lutz and Jirgensons, *Ber.*, 1930, **63**, 448.

5,5-Dimethylcyclohexane-1,3-dione was used without purification. Other ketones were purified as described in Part I.[1]

Amino-esters.—α-Amino-esters were obtained as described in Part I.[1]

Product from L-Tyrosine Ethyl Ester and Acetylacetone.—L-Tyrosine ethyl ester was dissolved in the minimum volume of acetylacetone and set aside at room temperature. The precipitated N-(1-*methyl*-3-*oxobutylidene*)-L-*tyrosine ethyl ester* was filtered off, washed with dry ether, and recrystallised from benzene; it had m. p. 147·5—149°, $[\alpha]_D^{20}$ −265·5° (*c* 2·0 in EtOH) (Found: C, 65·6; H, 7·2; N, 4·85. $C_{16}H_{21}NO_4$ requires C, 65·95; H, 7·3; N, 4·8%).

Ethyl D- *and* L-β-*Amino*-β-*phenylpropionate.*—DL-β-Amino-β-phenylpropionic acid was prepared by Mr. J. Johnson, by Johnson and Livak's method,[13] and treated with 2 : 1 (v/v) mixture of 98% formic acid and acetic anhydride at room temperature. After removal of the solvents the residue was recrystallised from water, giving DL-β-formamido-β-phenylpropionic acid, m. p. 126—128°. This compound was resolved by the method of Fischer *et al.*,[8] giving (+)-, m. p. 135·5—136°, $[\alpha]_D^{27}$ +113·5° (*c* 2·0 in EtOH), and (−)-β-formamido-β-phenylpropionic acid, m. p. 133·5—136°, $[\alpha]_D^{25}$ −114·5° (*c* 2·0 in EtOH). The formyl group was removed and the carboxyl group esterified simultaneously by treatment with ethanolic hydrogen chloride at 50°. The (+)-formamido-acid gave ethyl (−)-β-amino-β-phenylpropionate hydrochloride, m. p. 122—123°, $[\alpha]_D^{26}$ −15·0° (*c* 2·0 in EtOH). The free-amino-ester, which was liberated with aqueous sodium hydrogen carbonate, was an oil having $[\alpha]_D^{24}$ +8·0° (*c* 2·0 in EtOH). (−)-β-Formamido-β-phenylpropionic acid gave the (+)-ester hydrochloride, m. p. 118—120°, $[\alpha]_D^{24}$ +14·5° (*c* 2·0 in EtOH).

Degradation of (+)-β-*Amino*-β-*phenylpropionic acid.*—Ethyl (−)-β-amino-β-phenylpropionate hydrochloride with acetic anhydride, acetic acid, and anhydrous sodium acetate at 50° gave the *N*-acetyl derivative as a yellow oil. This (1·6 g.) was warmed in methanol with hydrazine hydrate (2 ml.) at 50° and left overnight. The solvents were removed and the solid residue was recrystallised twice from the minimum volume of water to give (+)-β-*acetamido*-β-*phenylpropionhydrazide* (1·2 g., 80%), m. p. 205·5—207°, $[\alpha]_D^{31}$ +74° (*c* 1·0 in H_2O) (Found: C, 59·2; H, 7·0; N, 19·1. $C_{11}H_{15}N_3O_2$ requires C, 59·7; H, 6·8; N, 19·0%).

The hydrazide (0·9 g.), in ice-water (2·5 ml.), N-hydrochloric acid (5 ml.), and sufficient acetic acid to give a clear solution was treated with sodium nitrite (0·37 g.) in water (1 ml.) at 0°. The mixture was extracted with cold benzene, and the organic layer was washed (in the cold) with water, sodium hydrogen carbonate solution, and water, dried (Na_2SO_4), and refluxed for 1·5 hr. The solvent was removed *in vacuo*, leaving a crystalline residue which was presumably 3-acetyl-4-phenylimidazolid-2-one.[14] This residue was refluxed in concentrated hydrochloric acid (5 ml.) for 2 hr.[15] After removal of the solvent *in vacuo*, the solid residue was recrystallised from ethanol–dry ether, to give L-(−)-phenylethylenediamine dihydrochloride (0·35 g., 41% based on hydrazide), m. p. 285° (decomp.), $[\alpha]_D^{26}$ −28·3° (*c* 3·0 in EtOH). Arpesella *et al.*[9] give $[\alpha]_D^{19}$ −17·6° (*c* 2·25 in H_2O); Lukeš *et al.*[10] give for the D-isomer $[\alpha]_D^{21}$ +28·9° (*c* 8·86 in H_2O). The diamine afforded its *NN'*-diacetyl derivative, m. p. 172—173°, $[\alpha]_D^{23}$ +82°, $[M]_D^{23}$ +180° (*c* 2·0 in EtOH), $[\alpha]_D^{23}$ +102°, $[M]_D^{23}$ +224° (*c* 1·0 in dioxan). Reihlen *et al.*[16] give m. p. 174°, $[M]_D^{20}$ +178° in ethanol, $[M]_D^{20}$ +237° (in dioxan).

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[13] Johnson and Livak, *J. Amer. Chem. Soc.*, 1936, **58**, 301.
[14] Rodionov and Bezinger, *Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk*, 1952, 962.
[15] Kanevskaya, *J. prakt. Chem.*, 1932, **132**, 335.
[16] Reihlen, Weinbrenner, and von Hessling, *Annalen*, 1932, **494**, 143.