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INTERNAL SOLVATION EFFECTS ON THE CONFORMATION OF ACYCLICS

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Abstract—Experiments attempting to discern internal solvation (or H—bonding) of COOH or COO^- by OH are outlined. In aqueous solutions little evidence for internal solvation exists. In basic methanol this effect appears due to poor solvation by the solvent. The origin of anomalous coupling constants in t-butyl compounds is discussed briefly.

IN CYCLOHEXANE carboxylic acids,[1] the carboxylate anion exhibits a stronger preference for the equatorial position than does the free acid itself. The ammonium ion is also more space demanding than the free amine.[2] This behaviour has been ascribed to the greater effective size of the heavily solvated ions. In the acyclic molecule, malic acid,[3] the progression from the unionized to the singly ionized and to the doubly ionized species results in increasing population of the conformer with *trans* carboxylates. Although charge repulsion and ionic size are of undoubted importance, an attractive interaction between hydroxyl and carboxylate may also help to determine conformation.

In order to study possible hydroxyl-carboxylate association more completely, several isomeric pairs of the β-hydroxypropionic acids II and esters III were prepared by the Ivanov reaction.[4, 5] The NMR data are listed in Table 1. The configurations of these acids were proved by stereospecific conversion to the *cis* or *trans* oxazolidones IV. The NMR spectra[6] of IV show *cis* or *trans* configuration, and by extrapolation, the *erythro* or *threo* configuration of II.

In addition to greater probable stability,[7] the *threo* isomers exhibit larger vicinal coupling constants,[8–13] J_{AB}, than the *erythro* isomers, with the exception of IIc. In moving from non-polar to polar solvents a slight increase in J_{AB} is observed, indicative of a growing predominance of T_T (J_{AB} *ca* 10–13 Hz) over T_{G_1} and/or T_{G_2} (J_{AB} *ca* 1–3 Hz).[14] The dihedral angles in Fig 2 are shown as 60° for convenience only.[13] In deuterochloroform, intramolecular H—bonding[8] is possible in both T_{G_2} and T_T. The observed coupling constants for the *threo* isomers (*ca* 9·5 Hz for Ia, b, d in $CDCl_3$) is thought to reflect a weighted mean of these two conformations, with T_T the stronger contributor. Infrared spectra of these *threo* isomers showed very weak free OH absorptions at low concentration.[8] Conformer T_{G_1} must therefore be comparatively unimportant. In DMSO or pyridine solutions, H—bonding to solvent becomes preferred.[9, 15] and the conformation offering minimum steric hindrance to external association (T_T) becomes somewhat more important.[16]

In $CDCl_3$ the NMR data for the *erythro* isomers (J_{AB} *ca* 7 Hz) suggest that similar populations of the conformer with *trans* protons (E_T) and the conformer(s) with *gauche* protons (E_{G_1} and/or E_{G_2}) exist. The IR spectra of the *erythro* esters III (which occupy similar conformations as the acids II) usually showed much more intense

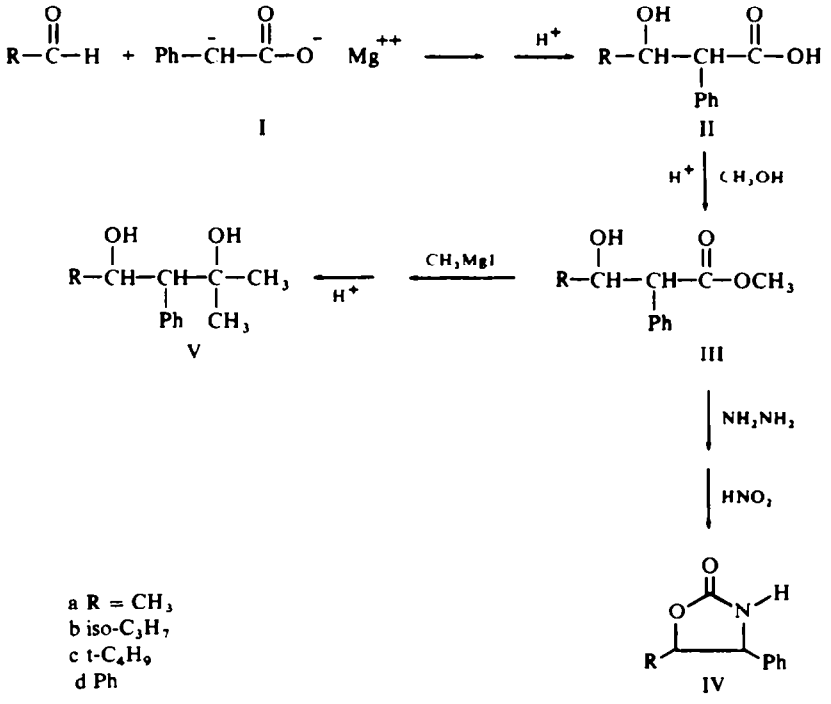


FIG 1

free OH absorption than the *threo* isomers,[8] consistent with a substantial population of E_T, which cannot undergo intra-molecular H—bonding. For the *erythro* compounds, a *substantial* increase in J_{AB} is noted upon moving from $CDCl_3$ to methanol,[9] indicative of an increase in population of E_T at the expense of E_{G_1} or E_{G_2}.[17] Intermolecular association thus eliminates much of E_{G_1} and/or E_{G_2} (which were stabilized by intramolecular association).

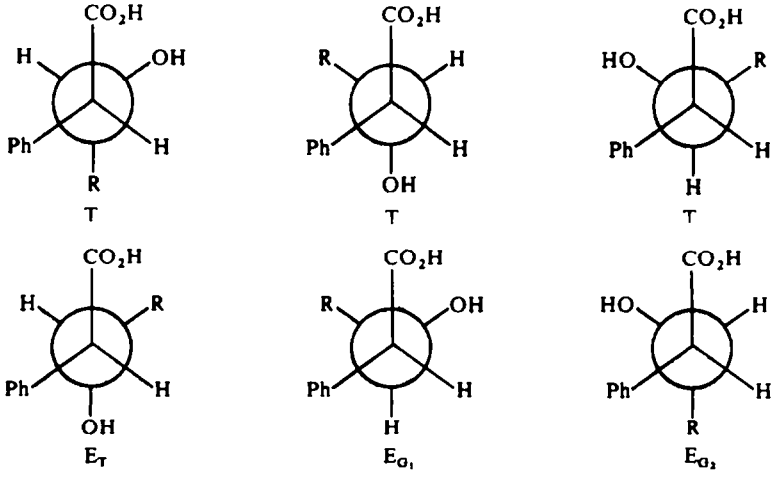
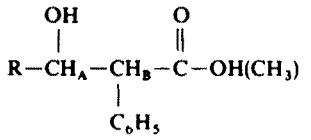


FIG 2

TABLE 1. NMR PARAMETERS[a] FOR ACIDS II AND ESTERS (III)



			Chemical shifts (ppm) in 10% Pyridine		J_{AB}(Hz)					
			H_A	H_B	$CDCl_3$[f,j]	Pyridine	$DMSOd_6$	CH_3OD[h]	CH_3O^-/CH_3OD[k]	$D_2O/CO_3^{=}$[l]
a	CH_3	*threo*	4·92	4·05	9·4 (9·4)	9·4 (9·5)	9·8 (9·5)	9·9 (9·8)	8·3	9·8
		erythro	4·90	4·06	7·0 (7·0)	7·9 (8·0)	8·1 (8·1)	8·2 (8·1)	5·9	8·5
b	iso-C_3H_7	*threo*	4·68	4·27	9·7[c] (9·6)	10·1 (10·1)	10·8 (10·8)	10·2 (10·4)	6·5	9·6
		erythro	4·55	4·23	7·1[c,d] (7·0)	8·0 (8·2)	8·7 (8·5)	8·6 (8·7)	5·7	9·3
c	t-C_4H_9	*threo*[g]	4·33	4·22	[b] (4·6)	6·6	[e] (e)	[e] (e)	1·6	2·9
		erythro	4·61	4·23	[b] (7·7)	7·0	8·2 (7·8)	8·4 (8·0)	5·1	9·4
d	C_6H_5	*threo*	5·85	4·51	[b] (9·3)	10·1 (9·9)	9·8 (10·0)	10·0 (10·0)	8·3	10·0
		erythro	5·92	4·51	7·2[d] (7·6)	8·5 (8·6)	9·6 (9·4)	9·5 (9·5)	5·8	9·0

[a] Average of several runs taken on a Varian A60-D instrument; J_{AB} values were taken from expanded spectra. The spectra were simulated by the LAOCOON III program[35] where appropriate.

[b] Insoluble.

[c] Isopropyl methine-H_A coupling constant: 2·2 Hz (*threo*), 4·1 Hz (*erythro*).

[d] Slightly heated for solubility.

[e] Superimposed resonances.

[f] A trace of trifluoroacetic acid was added to promote rapid exchange of the hydroxyl proton.

[g] Slightly impure with the *erythro* isomer.

[h] In some cases CD_3OD was used.

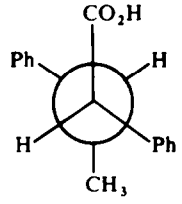
[j] Concentration *ca* 10% w/v. Several compounds tested showed essentially invariant J_{AB} values (±0·2 Hz) over a four-fold change in concentration. Other β-hydroxy esters than covered in this study were quite concentration dependent in CCl_4, however.

[k] Apparent pH *ca* 11.

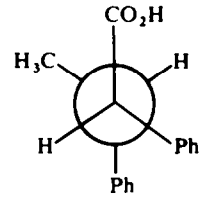
[l] pH 8·5–9·0.

The carboxylate anions, in basic aqueous media, appear to populate substantially the same conformers (T_T and E_T) as the free acids in other polar solvents. However *in methanol the anions exhibit substantially reduced values for* J_{AB}. Thus intramolecular association between hydroxyl and carboxylate reappears and is apparently more intense than in the original $CDCl_3$ solution of the free acid. The intramolecular association or internal solvation of carboxylate by hydroxyl appears in methanol and not in water due to the reduced solvating power of the methanol.[18]

A model system in which intramolecular association is not possible, *erythro* 2,3-diphenylbutanoic acid, VI, shows little change in J_{AB} (11·2 ±0·2 Hz) upon variation of the solvent from deuterochloroform to basic methanol. The *threo* isomer showed an equally large[19, 20] coupling constant in deuterochloroform that is insensitive to solvent. Thus, the conformers are favored in which two sets of *gauche* interactions exist between large groups, each set being separated by protons[9] (Fig 3).



erythro VI



threo VI

FIG 3

In an effort to determine the state of aggregation of the free acids, the apparent molecular weights of Ia–c were determined osmometrically, usually at three concentrations. The data are recorded in Table 2. The tendency for the methyl and iso-

TABLE 2. APPARENT MOLECULAR WEIGHTS *vs* CONCENTRATION IN CHLOROFORM AT *ca* 25°

	R	Calcd MW	Observed MW (concentration, [a] %)		
threo Ia	CH_3	180	360 (1·80)	300 (0·90)	[c] 264 (0·45)
erythro Ia	CH_3	180	347 (1·80)	343 (0·90)	[c] 321 (0·45)
threo Ib	iso-C_3H_7	208	404 (2·10)	333 (1·0)	[c] 310 (0·66)
erythro Ib	iso-C_3H_7	208	420 (2·10)	417 (1·0)	[c] 364 (0·40)
threo Ic	t-C_4H_9	222	insol.	320 (1·03)	[c] 300 (0·51)
erythro Ic	t-C_4H_9	222	insol.	insol.	insol.
threo VI	—	240	404 (1·86)	332 (0·93)	[c] 287 (0·46)
erythro VI	—	240	371 (2·23)	360 (1·11)	[c] 348 (0·56)

[a] These concentrations are on a weight per unit volume basis.

propyl compounds Ia and Ib to exist as dimers is notable. The *threo* isomers drop off toward monomer with decreasing concentration much more quickly than the *erythro* isomers. The more extensive and more stable intramolecular hydrogen bonding in the *threo* isomers[8, 9, 11, 12] may favor monomeric character (see, however, the concentration effect on VI). However, over most of the same concentration range, little effect was noted on the NMR J_{AB} values (±0·2 Hz). Furthermore the coupling

constants of the acids are very similar to those of the esters (Table 1). Several esters tested showed only a slight deviation from the monomeric molecular weight. Other work has shown similar esters to be intramolecularly hydrogen bonded.[8] Thus in *threo* isomers, intramolecular hydroxyl-carboxyl association seems probable even though the carboxyl function is dimerized. Fig 4 shows one possible mode of association.*

In contrast to the previous compounds, molecules with three polar groups, e.g. certain amino acids,[22, 23] show quite different coupling constants and configurations. Teddei and Pratt[24] have shown that threonine and allothreonine exhibit similar, low values for J_{AB} (*ca* 4 Hz), which were somewhat pH dependent. Similar findings occur for the isomers of phenylserine[25] VII and VIII (Table 3).

TABLE 3

				J_{AB} (Hz)					
			TFA[b]	D_2O					MeO^-/MeOH
				pH	1	6	8	13	
threo	phenylserine	VII	4·3		4·2	4·4	4·4	5·3	insol.
erythro	phenylserine[a]	VIII	2·2		4·1	4·2	4·6	5·9	7·0

[a] Some dioxane was present.
[b] Trifluoroacetic acid.

These low values for J_{AB} are suggestive of predominant conformers with *gauche* protons (Fig 5). The conformer with *trans* protons becomes somewhat more important in VIII as pH increases and the charge site shifts from nitrogen to carboxylate with consequent change in the effective size of this group. Electronegativity changes may also affect the magnitude of J_{AB} with increasing pH.

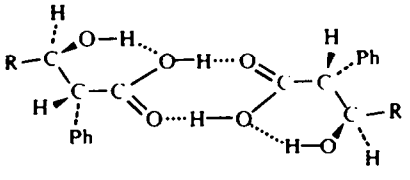


FIG 4

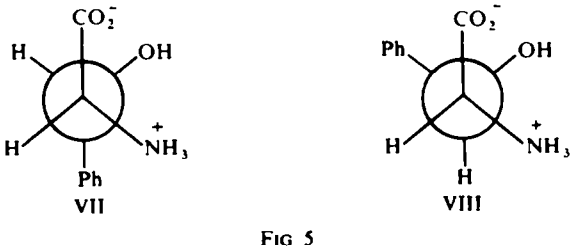


FIG 5

* Hydroxyl-n-carbonyl association is preferred, if permitted by geometry although hydroxyl-ester oxygen bonding is also observed in certain instances, as well as hydroxyl-π carbonyl association[21]

The data could be interpreted in terms of a preference of the three polar groups for a contiguous area of high solvation (i.e. a hydrophilic region). This interpretation must be approached cautiously, however, since other molecules e.g. 3-phenyl-3-acetoxy-2-methoxypropanoic acid, show similar, low coupling constants in polar or non-polar solvents.[26, 8c]

The β-hydroxy esters III have been converted to the diols V (Fig 1). The spectra of similar diols have been recently covered by Maffrand and Maroni.[27] We wish only to add the following observation. The NMR spectra of many t-butyl compounds show

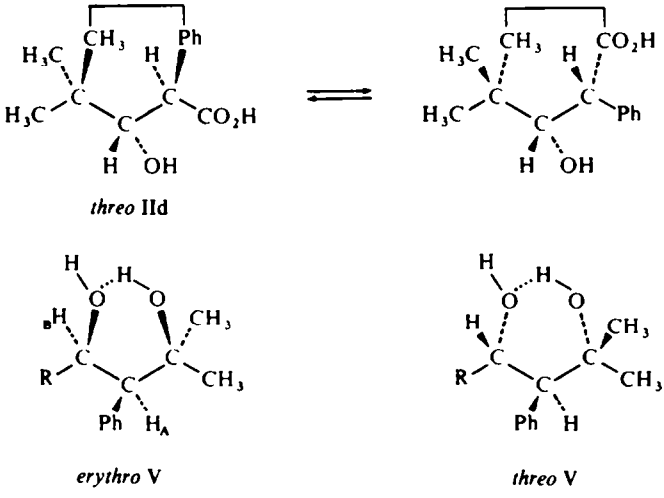


FIG 6

anomalously low J_{AB} values[28,*] (e.g. IIIc, Table 1). For *threo* IIIc, this phenomenon is now thought to be due to a different mode of relieving non-bonded interactions, which occurs in addition to internal rotation. Considerable variation of the bond angles (and/or bond distances) involving the t-butyl C—C bond, or of the methyl groups of the t-Bu group itself are considered probable as the best method available of achieving the most comfortable fit of groups. This interpretation, however, awaits a more definite proof, such as an X-ray analysis.

The dimethyl hydroxy carbinyl group of V bears obvious similarities to the t-butyl group. In both structures 1,3 interactions are unavoidable no matter what conformation is populated (Fig 6).[30] In V the 1,3 interactions involve the two hydroxyl groups and are attractive because of the strong H—bond. In V entirely "normal" values for J_{AB} are observed (Table 4), unlike the t-Bu compounds in which the 1,3 interaction is repulsive. However, the conformation shown for V (Fig 6) may also be favored by other factors than H—bonding (perhaps minimized non-bonded repulsions) †since the

* Best *et al* expresses the belief that angle variations had occured.[29] Earlier work[29a] on the basis of $J_{C^{13}-H}$ values, came to a somewhat different conclusion. The $J_{C^{13}-H}$ values are no longer considered conclusive.

† Eliel and Kaloustian [*Chem. Commun.* 290 (1970)] have suggested an attractive interaction exists between oxygen groups.

TABLE 4. NMR PARAMETERS IN THE DIASTEREOMERIC SUBSTITUTED 2-METHYL-3-PHENYL-2,4-BUTANEDIOLS V

	R		Chemical shifts[d] (ppm) H_A		H_B	J_{AB}[a] (Hz) $CDCl_3$	pyridine
Va	CH_3	*threo*	2·72		4·56	10·3	10·7
		erythro	2·38	ca	4·55	2·7	3·0
Vb	iso-C_3H_7	*threo*	2·90		4·30	10·9[b]	11·2
		erythro	2·62		3·96	2·5[c]	2·8
Vd	Ph	*threo*	3·06		5·21	10·6	11·0
		erythro	2·64		5·59	3·0	2·8

[a] 15% w/v concentration.
[b] J isopropyl methine – H_B 1·6 Hz.
[c] J isopropyl methine – H_B 8·7 Hz.
[d] Chloroform-d solution, a trace of TFA was added to promote rapid exchange.

coupling constants are but slightly different in pyridine. In pyridine intramolecular association should be at least partially destroyed.

EXPERIMENTAL

Compounds IIa–d were prepared by the method of Zimmerman and Traxler:[32] *threo* IIa, m.p. 136–137°, lit. 135–136°; *erythro* IIa, m.p. 90–91°; *threo* IIb, 139–140°; lit. 139–140°; *erythro* IIb, m.p. 174–175°, lit. 171–172°; *threo* IIc, m.p. 164–165°; *erythro* IIc, m.p. 200–201°; *threo* IId, m.p. 176–177°, lit. 177–178°; erythro IId, m.p. 142–143°; lit. 145°. The diastereomeric acids were separated by chromatography on silica gel[32] (Baker) although considerable trouble was encountered with the IIIc diastereomers which required several columns, with attempts to purify by recrystallization between columns. (Found: C, 66·91; H, 6·73. *erythro* IIa, Calcd. for $C_{10}H_{12}O_3$: C, 66·6; H, 6·66%; Found: C, 70·03; H, 8·45. *threo* IIc, Calcd. for $C_{13}H_{18}O_3$: C, 70·27; H, 8·10; Found: C, 69·83; H, 8·22. *erythro* IIc, Calcd. for $C_{13}H_{18}O_3$: C, 70·27; H, 8·10%).

The esters III were prepared from their respective acids II by the usual Fischer esterification. The spectral data are recorded in Table 1. Several of the esters were oils which were purified by extraction away from acidic materials and chromatography on silica gel and film drying the fractions whose NMR spectrum indicated high purity: *threo* IIIa, an oily solid, m.p. 50–53°; *erythro* IIIa, an oil; *threo* IIIb, m.p. 83–85°, *erythro* IIIb, an oil; *threo* IIIc, m.p. 95–96°; *erythro* IIIc, an oil; *threo* IIId, m.p. 99–100° (lit.[32] 99–100°); for *erythro* IIId the best m.p. obtained in our hands was 77–79° (lit.[32] 87–88°); the NMR spectrum showed only trace impurities. (Found: C, 69·30; H, 7·68. *threo* IIIa, Calcd. for $C_{11}H_{14}O_3$: C, 69·43; H, 7·23%; Found: C, 69·06; H, 7·19. *erythreo* IIIa, Calcd. for $C_{11}H_{14}O_3$: C, 69·43; H, 7·23%; Found: C, 70·46; H, 8·28. *threo* IIIb, Calcd. for $C_{13}H_{18}O_3$: C, 70·27; H, 8·10%; Found: C, 70·12; H, 8·34. *erythreo* IIIb. Calcd. for $C_{13}H_{18}O_3$: C, 70·27; H, 8·10%; Found: C, 71·31; H, 8·47. *threo* IIIc. Calcd. for $C_{14}H_{20}O_3$: C, 71·14; H, 8·47%; Found: C, 71·12; H, 8·21. *erythro* IIIc, Calcd. for $C_{14}H_{20}O_3$: C, 71·14; H, 8·47%).

Conversion of the above esters III to their respective oxazolidone derivatives IV, essentially followed the method of Zimmerman and Traxler.[32] Spectral and analytical data on the oxazolidones follows:

trans IVa (R = CH_3), m.p. 122–122·5°, NMR (pyridine), δ 1·48 (d, 3, J = 6·2 Hz, $C\underline{H}_3$), 4·33 (m, 1), and 4·50 (d, 1, J = 7·0 Hz). (Found: C, 67·82; H, 6·38; N, 7·69. Calcd. for $C_{10}H_{11}NO_2$: C, 67·80; H, 6·22; N, 7·91%).

For *cis* IVa (R = CH_3), m.p. 105–106°. NMR (pyridine), δ 0·89 (d, 3, J *ca* 6, extensive virtual coupling, $C\underline{H}_3$), and 5·05 (m, 2, J *ca* 8 Hz from computer simulation). (Found: C, 68·00; H, 6·22; N, 7·88. Calcd. for $C_{10}H_{11}NO_2$: C, 67·80; H, 6·27; N, 7·91%).

For *trans* IVb (R = iso—C_3H_7), m.p. 123–124°, NMR ($CDCl_3$), δ 0·96 (d, 3, J = 3·3 Hz, CH—($\underline{CH}_3$)$_2$), 1·06 (d, 3, J = 3·3 Hz, CH—($\underline{CH}_3$)$_2$), *ca* 1·9 (m, 1, $\underline{CH}$(CH_3)$_2$, 4·17 (d of d, 1, J = 5·8, J = 5·8 Hz), 4·58 (d, 1, J = 5·8 Hz), *ca* 6·07 (s, 1, $\underline{NH}$), and 7·35 (s, 5, C_6H_5). (Found: C, 70·05; H, 7·48; N, 6·90. Calcd. for $C_{12}H_{15}NO_2$: C, 70·25; H, 7·31; N, 6·83%).

For *cis* IVb (R = iso—C_3H_7), m.p. 177–178°, NMR ($CDCl_3$), δ 0·65 (d, 3, J = 6 Hz), CH—($\underline{CH}_3$)$_2$), 0·96 (d, 3, J = 6 Hz, CH—($\underline{CH}_3$)$_2$), *ca* 1·5 (m, 1, $\underline{CH}$—(CH_3)$_2$), 4·36 (d of d, 1, J = 7·3, J = 9·5 Hz), 4·73 (d, 1, J = 7·3 Hz), 6·05 (s, 1, $\underline{NH}$), and 7·32 (s, 5, C_6H_5). (Found: C, 70·06; H, 7·12; N, 6·75. Calcd. for $C_{12}H_{15}NO_2$: C, 70·25; H, 7·31; N, 6·83%).

For *trans* IVc (R = t—C_4H_9), m.p. 150–151°, NMR ($CDCl_3$), δ 0·95 (s, 9, t—$C_4\underline{H}_9$), 4·06 (d, 1, J = 5·2 Hz), 4·61 (d, 1, J = 5·2 Hz), 6·88 (s, 1, N$\underline{H}$), and 7·31 (s, 5, $\underline{C_6H_5}$). (Found: C, 71·05; H, 7·64; N, 6·23. Calcd. for $C_{13}H_{17}NO_2$: C, 71·23; H, 7·76; N, 6·34%).

For *cis* IVc (R = t—C_4H_9), m.p. 172–173°, NMR ($CDCl_3$), δ 0·73 (s, 9, t—$\underline{C_4H_9}$), 4·49 (d, 1, J = 7·0 Hz), 4·77 (d, 1, J = 7·0 Hz), and 7·31 (s, 5, $\underline{C_6H_5}$). (Found: C, 70·81; H, 7·75; N, 6·29. Calcd. for $C_{13}H_{17}NO_2$: C, 71·23; H, 7·76; N, 6·34%).

The *cis* and *trans* oxazolidones IVd are known compounds, m.p. 191–192°, lit. 193–194°; and m.p. 161–162°, lit. 161–162°, respectively.[32]

The diols V were prepared by addition of a 3 molar excess of methyl Grignard reagent to the esters III, using standard methods. The crystalline products were recrystallized to purify with petroleum ether. The salient NMR are recorded in Table 4. For *threo* Va, m.p. 109–110·5°. (Found: C, 73·96; H, 9·33. Calcd. for $C_{12}H_{18}O_2$: C, 74·24; H, 9·28%).

Erythro Va, non-crystallizable oil, contained a small amount of the *threo* isomer.

For *threo* Vb, m.p. 128–129°. (Found: C, 75·95; H, 10·15. Calcd. for $C_{14}H_{22}O_2$, C, 75·67; H, 9·91%).

For *erythro* Vb, m.p. 129–130°. (Found: C, 75·87; H, 9·87. Calcd. for $C_{14}H_{22}O_2$: C, 75·67; H, 9·91%).

For *threo* Vd, m.p. 92–93°. (Found: C, 80·03; H, 7·88. Calcd. for $C_{17}H_{20}O_2$: C, 79·68; H, 7·81%).

For *erythro* Vd, m.p. 94–95°. (Found: C, 80·12; H, 7·80. Calcd. for $C_{17}H_{20}O_2$: C, 79·68; H, 7·81%).

Repeated attempts to prepare Vc were unsuccessful. The carboxylic acids VI were prepared from hydrolysis of the nitriles available from another study. The nitriles were prepared by addition of alkyl Grignard to 1-cyano-1,2-diphenylethene. To 1·0 g of the mixed nitriles in a round bottom flask was added 7 ml conc. H_2SO_4, 7 ml conc. HCl (carefully) and 7 ml glacial acetic acid. The mixture was heated in a Woods metal bath at hard reflux for 24 hr, cooled, added to ether-water and extracted with water several times. The ether layer was dried ($MgSO_4$), evaporated and the maximum amount of the *erythro* acid crystallized out and recrystallized from EtOH, 0·20 g, m.p. 187·5–189·0°, lit.[31], m.p. 185–189°. The remaining material was chromatographed on silica gel, eluting with 2:1 hexane-ether, and a fairly good separation of *erythro* and *threo* acids was obtained, *threo* m.p. 125–130°, lit.[34] 125–130°, *ca* 0·05 g.

The phenylserines were prepared by the method of Fones and Shaw,[34] phenylserine, m.p. 194–199°, and allophenylserine dioxane complex, m.p. 184–189°. The former was shown to be slightly impure with the latter by paper chromatography; the latter was pure.

The NMR data were determined on a Varian A-60D instrument. The coupling constants were taken from expanded spectra (average of 3–4 scans). In addition, fresh solutions of the carboxylic acids and esters were run at least twice in each solvent. The essential correctness of the observed coupling constants was verified by computer simulation[35] (except AB spectra) and the fitting of a Calif. Computer Products plotter trace of the calculated spectrum with the observed spectrum. Deviations were never over ±0·2 Hz, usually less.

The molecular weight determinations were made on a Hewlett-Packard vapor pressure osmometer, standardized against benzil, using purified chloroform solutions. The paper chromatographic analyses on VI were graciously performed by Mr. Robert Cregge.

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