Synthesis, Absolute Configuration, and Circular Dichroism of the Enantiomers of Fluorosuccinic Acid

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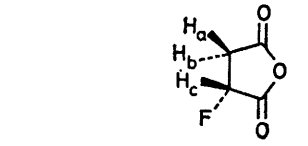
Diethylaminosulphur trifluoride (DAST) converts (2*S*)- and (2*R*)-malate esters into the enantiomeric fluorosuccinate esters. (2*S*,3*R*)-[3-$^2H_1$]Malate, obtained from fumarate by fumarase-catalysed hydration in deuterium oxide, was used to show that the reaction with DAST occurs stereospecifically with *inversion* of configuration. Conversion of (2*S*)-aspartic acid into fluorosuccinate with sodium nitrite in polyhydrogen fluoride–pyridine occurs predominantly with *retention* of configuration. The circular dichroic spectra of (2*S*)- and (2*R*)-fluorosuccinic acids and their methyl esters are ' anomalous ' and consequently the absolute configuration previously assigned to a *Pseudomonal* metabolite, (+)-fluorosuccinic acid, is shown to be erroneous.

DURING an investigation of the mechanism of action of the enzyme fumarase,[1] the need arose for (2*S*)-fluorosuccinate as an analogue of the natural substrate (2*S*)-malate. (2*RS*)-Fluorosuccinic acid has been synthesised,[2] and is a substrate for succinate dehydrogenase.[3] However no resolution of the racemate has been reported, although attempts have been made.[3] (+)-Fluorosuccinic acid was obtained as a *Pseudomonal* metabolite of *p*-fluorophenylacetic acid, but the D-configuration, assigned to it by comparison of its optical rotatory dispersion curve with those of other D-(+)-halogenosuccinic acids, cannot be regarded as secure.[4]

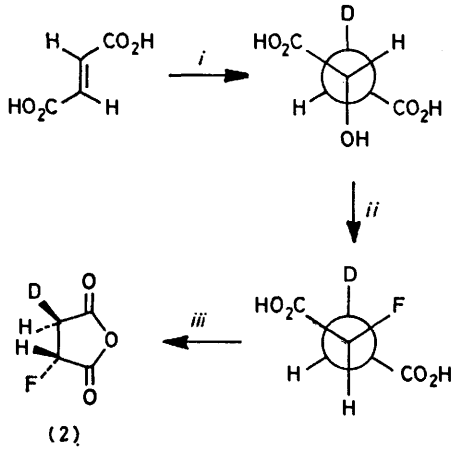
Diethylaminosulphur trifluoride (DAST) [5,6] converts alcohols into fluoro-compounds under mild conditions and with much less dehydration than is commonly encountered with other fluorinating reagents.[7] Moreover, good evidence has been provided that the reagent first forms an alkoxydiethylaminosulphur difluoride intermediate which is attacked by fluoride ion with inversion of configuration.[8] However, in an extensive investigation of the reaction of DAST with oxygenated 5α-androstanes, several examples of substitution of hydroxy-groups with fluorine occurred with retention of configuration, not all of which could be explained by neighbouring-group participation.[9]

Synthesis of (2S)- *and* (2R)-*Fluorosuccinates.*—(2*R*)- and (2*S*)-Malic acids were esterified and converted with DAST at 0 °C into the enantiomeric fluorosuccinic dimethyl esters in high yield, the only by-product being *ca.* 6% of dimethyl fumarate. The esters, after purification by preparative g.l.c., were shown to be pure enantiomers by n.m.r. spectroscopy using the chiral shift reagent tris-[3-(trifluoroacetyl)-(+)-camphorate]-europium(III).[10] The esters were hydrolysed under acidic conditions,[2] in view of the known propensity of fluorosuccinic esters to give fumarate under even mildly basic conditions.[11] The recrystallised acids had melting points virtually identical with that reported for (+)-fluorosuccinic acid.[4]

Assignment of the Absolute Configuration of the 2-*Fluorosuccinic Acids.*—In order to establish rigorously the absolute configurations of the enantiomeric fluorosuccinic acids and the stereochemical course of the DAST reaction, the synthesis was repeated with (2*S*,3*R*)-[3-$^2H_1$]malic acid which was obtained by the fumarase-catalysed hydration of fumarate in deuterium oxide.[12,13] Purification of the 2-fluoro-[3-$^2H_1$]succinic ester followed by acid-catalysed hydrolysis gave a 2-fluoro[3-$^2H_1$]-succinic acid (Scheme) 2-Fluorosuccinic acid derived from (2*S*)-malic acid was converted into its anhydride (1) by refluxing with acetyl chloride.[14] The ^{19}F n.m.r. spectrum is shown in Figure 1(a) from which the coupling constants $^3J_{H_aF}$ 13.5, $^3J_{H_bF}$ 24.9, and $^2J_{H_cF}$ 52.5 Hz can be obtained. These assignments are based on extensive literature precedent and are entirely in accord with expectation.[15] The ^{19}F n.m.r. spectrum of the 2-fluoro-[3-$^2H_1$]succinic anhydride derived from 2-fluoro-[3-$^2H_1$]succinic acid consisted of four lines [Figure 1(b), broader than those in 1(a) owing to unresolved deuterium coupling] with $^3J_{HF}$ 25 and $^2J_{HF}$ 55 Hz. The



(1)



SCHEME *Reagents: i*, fumarase, D_2O; *ii* (a) CH_2N_2, (b) DAST, (c) H_3O^+; *iii*, CH_3COCl

$^3J_{HF}$ coupling constant establishes the structure unequivocally as (2*R*,3*S*)-2-fluoro-[3-$^2H_1$]succinic anhydride (2).*

Circular Dichroism of (2S)- *and* (2R)-*Fluorosuccinic Acids and Esters*.—The anomalous behaviour of fluoroketones, when compared with chloro-, bromo-, and iodoketones is frequently but not invariably observed in circular dichroism, the phenomenon first being encountered as a violation of the axial halogeno-ketone rule.[16] The c.d. spectra of (2*S*)- and (2*R*)-fluorosuccinic acids and their dimethyl esters demonstrate their antipodal stereochemistries. The single Gaussian band with maximum at 214 nm in both acids and esters is assigned to the carbonyl $n \longrightarrow \pi^*$ transition (Figure 2; only dimethyl (2*S*)-fluorosuccinate is shown) and shows the hypsochromic shift expected by comparison with (2*R*)-chlorosuccinic acid ($\lambda_{max.}$ 224 nm) and (2*R*)-bromosuccinic acid ($\lambda_{max.}$ 236 nm).[17] The magnitude of $\Delta\varepsilon_{max.}$ for the

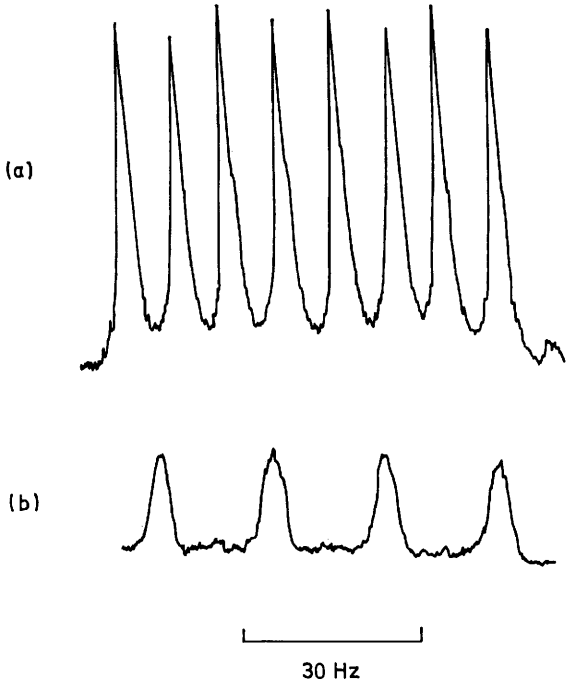


FIGURE 1 ^{19}F N.m.r. spectra at 84.6 MHz of (a) fluorosuccinic anhydride (1) and (b) (2*R*,3*S*)-2-fluoro-[3-$^2H_1$]succinic anhydride (2)

esters is similar to that of the acids, as is commonly observed (Table).[18] However the effect of fluorine on the signs of the c.d. spectra is 'anomalous,' (2*R*)-fluorosuccinic acid and its diester exhibiting negative circular dichroism, whereas (2*R*)-chloro- and (2*R*)-bromo-succinic acids have positive c.d. spectra.[17,19] This is the first example of an 'anomalous' c.d. spectrum for a fluorocarboxylic acid or ester and infringes upon the generalisations proposed for carboxylic acids.[20]

Fluorosuccinic acid has also been prepared by the diazotisation of aspartic acid in polyhydrogen fluoride–pyridine, but no comment about the stereochemistry was made and its chiroptical properties were not measured.[21] Fluorosuccinic acid made by this method from (2S)-aspartic acid showed a positive c.d. curve with $\lambda_{max.}$ 214 nm $\Delta\varepsilon$ + 0.81. Thus the transformation occurs with *retention* of configuration [(2*S*)-aspartic acid to (2*S*)-fluorosuccinic acid] presumably as a result of neighbouring carboxy-group participation. The $\Delta\varepsilon$ however is 25% lower than that of (2*S*)-fluorosuccinic

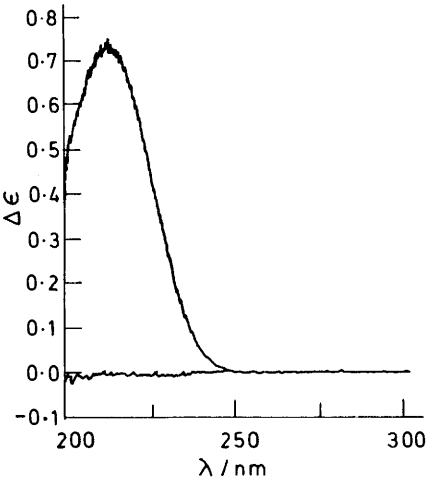


FIGURE 2 C.d. spectrum in methanol of dimethyl (2*S*)-fluorosuccinate

acid prepared by the DAST reaction, reflecting some racemisation.

The optical rotatory dispersion spectrum of a fluorosuccinic acid isolated after metabolism of *p*-fluorophenylacetic acid by a *Pseudomonas* species showed a positive Cotton effect which was interpreted, by analogy, as arising from an acid possessing the D-configuration.[4] This is now seen to be erroneous and the metabolite is actually (2*S*)-fluorosuccinic acid. A transform of the

Circular Dichroic Spectral Data for Halogenosuccinic Acids and Esters

Compound	$\lambda_{max.}$(MeOH)/ nm	$\Delta\varepsilon$	Reference
(2*S*)-Fluorosuccinic acid	214	+1.08	This work
(2*R*)-Fluorosuccinic acid	214	−0.97	This work
(2*R*)-Chlorosuccinic acid	224	+1.17	17
(2*R*)-Bromosuccinic acid	236	+2.01	17
Dimethyl (2*S*)-fluorosuccinate	214	+0.74	This work
Dimethyl (2*R*)-fluorosuccinate	214	−0.74	This work

optical rotatory dispersion curve showed it to possess a c.d. maximum at 217 nm with $\Delta\varepsilon$ approximately 78% of that of (2*S*)-fluorosuccinic acid obtained by the DAST reaction.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. ^{1}H and ^{19}F N.m.r. spectra were recorded on a Perkin-Elmer R32 spectrometer at 90 and 84.6 MHz respectively. Chemical shifts are reported in p.p.m. from tetramethylsilane and external trifluoroacetic acid respectively, ^{19}F chemical

* The change in configurational assignment at C-3 follows from the sequence rules governing the *R*,*S* notation.

shifts being quoted as positive if upfield from the reference. Mass spectra were recorded on a VG micromass high-resolution 16F spectrometer and i.r. spectra on a Unicam SP1000 spectrophotometer. Deuterium oxide was obtained from Fluorochem Ltd., fumaric acid (monosodium salt) and fumarase were obtained from Sigma Chemical Co. Ltd., and polyhydrogen fluoride–pyridine reagent and (2*R*)- and (2*S*)-malic acid were obtained from Aldrich Chemical Co. Ltd. Preparative g.l.c. was performed on a PEGA column obtained from Pye Unicam Ltd. and fitted to a Pye Unicam Series 105 Chromatograph.

Dimethyl (2S)-*Malate*.—This diester was prepared from (2*S*)-malic acid ($[\alpha]_D^{20}$ −28.3, *c* 5 in pyridine) in 64% yield by the method of Brenner and Huber.[22]

Dimethyl (2R)-*Fluorosuccinate*.—To a stirred solution of diethylaminosulphur trifluoride[7] (2.0 g, 12.4 mmol) in dry ethanol-free chloroform (10 cm^3) cooled to 0 °C was added dropwise over 15 min a solution of dimethyl (2*S*)-malate (2.0 g, 12.4 mmol) in dry ethanol-free chloroform (10 cm^3). The mixture was allowed to reach ambient temperature (30 min) and an equal volume of water added cautiously to the vigorously stirred solution. The organic layer was separated, washed with saturated sodium hydrogencarbonate solution and saturated brine, dried ($MgSO_4$), and evaporated under reduced pressure to give dimethyl (2*R*)-fluorosuccinate (1.73 g, 85%) contaminated with *ca.* 6% dimethyl fumarate (estimated from the ^{1}H n.m.r. spectrum). The pure ester was obtained by preparative g.l.c. using a PEGA column at 150 °C; τ[$(CD_3)_2CO$] 4.74 (dt, $^3J_{HH}$ 6.0, $^2J_{HF}$ 45.0 Hz, 1 H, CHF) 6.25 and 6.33 (s, 3 H each, CO_2Me), and 6.92 and 7.22 (m, 2 H, CH_2); δ_F +114.8 (dt, $^2J_{HF}$ 49.5, $^3J_{HF}$ 25.0 Hz), c.d. $\lambda_{max.}$ 214 nm, Δε −0.74.

(2R)-*Fluorosuccinic Acid*.—Dimethyl (2*R*)-fluorosuccinate (1.73 g) was refluxed with 5% sulphuric acid (10 cm^3) for 1.25 h. The solution was made strongly acidic with concentrated sulphuric acid and extracted with ether, and the extract was dried ($MgSO_4$) and the solvent removed to give (2*R*)-fluorosuccinic acid as a crystalline solid (1.02 g, 71%). Recrystallisation from ethyl acetate, or ethyl acetate–chloroform gave the pure *acid*, m.p. 130—132 °C, which could be vacuum-sublimed (*ca.* 115 °C and 0.5 mmHg); τ([$^2H_6$]DMSO) 4.8 (ddd, $^2J_{HF}$ 47.5, $^3J_{HH}$ 5 and 7 Hz, 1 H, CHF), and 7.05 and 7.33 (m, 2 H, CH_2). δ_F ([$^2H_6$]DMSO) + 110.1 (dt, $^3J_{HF}$ 25.0, $^2J_{HF}$ 47.8 Hz), c.d. $\lambda_{max.}$ 214 nm, Δε −0.97 (Found: C, 35.5; H, 3.9. $C_4H_5FO_4$ requires C, 35.3; H, 3.7%).

(2R)-*Fluorosuccinic Anhydride* (1).—(2*R*)-Fluorosuccinic acid (250 mg) was suspended in acetyl chloride (10 cm^3) and refluxed for 1.5 h. The resulting solution was evaporated under reduced pressure to give (2R)-fluorosuccinic anhydride (200 mg, 92%), $\nu_{max.}$ ($CHCl_3$) 1 810 and 1 895 cm^{-1} (CO·O·CO); τ($CDCl_3$) 4.46 (td, $^3J_{H_aH_c}$ 8.5, $^3J_{H_bH_c}$ 6.0, $^2J_{H_cF}$ 50.0 Hz, 1 H, CHF), and 6.4—7.3 (m, 2 H, CH_2); δ_F ($CDCl_3$) +117.3 (ddd, $^2J_{H_cF}$ 52.5, $^3J_{H_aF}$ 13.5, $^3J_{H_bF}$ 24.9 Hz, CHF).

(2S)-*Fluorosuccinic Acid*.—(2*R*)-Malic acid ($[\alpha]_D^{20}$ +27.0, *c* 5 in pyridine) was esterified, converted into dimethyl (2*S*)-fluorosuccinate (c.d. $\lambda_{max.}$ 214 nm Δε +0.74), and hydrolysed as above to give (2*S*)-fluorosuccinic acid, m.p. 130—132.5 °C, c.d. $\lambda_{max.}$ 214 nm, Δε +1.08.

Dimethyl (2S,3R)-[3-$^2H_1$]*Malate*.—Monosodium fumarate (410 mg) was converted into (2*S*,3*R*)-[3-$^2H_1$]malate by fumarase in deuterium oxide as described by Fisher *et al.*[12] The acid in dry methanol was treated with ethereal diazomethane. Removal of the excess of reagent and solvent gave dimethyl (2*S*,3*R*)-[3-$^2H_1$]malate (85%) with a deuterium content of 94 ± 0.7% (by mass spectrometry).

Dimethyl (2R,3S)-*Fluoro*[3-$^2H_1$]*succinate*.—Dimethyl (2*S*,3*R*)-[3-$^2H_1$]malate was converted into the dimethyl [3-$^2H_1$]-fluorosuccinate with DAST as described for dimethyl (2*R*)-fluorosuccinate, τ($CDCl_3$) 4.74 (dd, $^3J_{HH}$ 4.0, $^2J_{HF}$ 47.5 Hz), 6.20 and 6.32 (2 s, 3 H each, CO_2Me), and 7.05 (ddt, $^2J_{HD}$ 2.0, $^3J_{HH}$ 4.0, and $^3J_{HF}$ 26.5 Hz); δ_F ($CDCl_3$) +115.9 (qt, $^2J_{HF}$ 27.0, $^3J_{HF}$ 49.0, $^3J_{FD}$ 3.2 Hz).

(2R,3S)-*Fluoro*[3-$^2H_1$]*succinic Acid*.—The dimethyl ester was hydrolysed with 5% sulphuric acid as for (2*R*)-fluorosuccinic acid to give (2*R*,3*S*)-fluoro[3-$^2H_1$]succinic acid (69%), τ(D_2O) 4.65 (dd, $^3J_{HH}$ 4.0, $^2J_{HF}$ 48.0 Hz, 1 H, CHF) and 6.91 (ddt, $^2J_{HD}$ 2.0, $^3J_{HF}$ 24.0, $^3J_{HH}$ 4.0 Hz, 1 H, CHD); δ_F($CDCl_3$) +115.1 (ddt, $^2J_{HF}$ 50.0, $^3J_{HF}$ 25.0, $^3J_{FD}$ 4.0 Hz).

(2R,3S)-*Fluoro*[3-$^2H_1$]*succinic Anhydride* (2).—(2*R*,3*S*)-Fluoro[3-$^2H_1$]succinic acid (90 mg) was suspended in acetyl chloride (5 cm^3) and refluxed for 1.5 h. Evaporation under reduced pressure gave (2*R*,3*S*)-fluoro[3-$^2H_1$]succinic anhydride (65 mg, 81%); $\nu_{max.}$ ($CHCl_3$) 1 810 and 1 885 cm^{-1} (CO·O·CO); τ($CDCl_3$) 4.40 (dd, $^3J_{HH}$ 4.5, $^2J_{HF}$ 51.0 Hz, 1 H, CHF), 6.84 (ddt, $^2J_{HD}$ 3.0, $^3J_{HH}$ 4.5, $^3J_{HF}$ 25.0 Hz); δ_F ($CDCl_3$) +116.5 (dd, $^2J_{HF}$ 55, $^3J_{HF}$ 25 Hz).

(2S)-*Fluorosuccinic Acid from* (2S)-*Aspartic Acid* (*with* V. T. Jones).—Fluorosuccinic acid was prepared from (2*S*)-aspartic acid by the method of Olah and Welch.[21] The acid was purified by preparative t.l.c. on silica gel with chloroform–ethyl acetate–formic acid (50 : 10 : 2.5 v/v/v) as eluant and recrystallised from ethyl acetate–chloroform, m.p. 130—132 °C, c.d. $\lambda_{max.}$ 214 nm, Δε +0.81.

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