Organic Fluorine Compounds. Part XL.[1] Further Reactions of Diethyl Fluoro-oxaloacetate with Aldehydes

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The scope of the synthesis of α-fluoro-unsaturated acids from aliphatic and aromatic aldehydes and diethyl fluoro-oxaloacetate has been studied. α-Formyl derivatives of ketones and esters react in their aldehydic forms. 2-Fluoro-3-(2-thienyl)acrylic acid could be nitrated, probably in the 5-position of the thiophen ring. 2-Fluoro-3-(1-naphthyl)acrylic acid cyclized to 2-fluoro-4,5-benzinden-1-one (VIII).

In two previous papers [2,3] the formation of ethyl α-fluoroacrylates by condensation of aldehydes with diethyl fluoro-oxaloacetate (I) has been described. The reaction proceeds according to the following scheme:

$$RCHO + EtO_2C{\cdot}CO{\cdot}CHF{\cdot}CO_2Et\ (I) \longrightarrow RCH{=}CF{\cdot}CO_2Et.$$

The reaction has now been applied successfully to the following aldehydes: chloral, dichloroacetaldehyde, glycidaldehyde, α-phenylpropionaldehyde, methacraldehyde, 3- and 4-acetoxybenzaldehyde, 4-nitrobenzaldehyde, 1-naphthaldehyde, 2-furaldehyde, thiophen-2-aldehyde, 1-acetylindole-3-aldehyde, and terephthalaldehyde. The following aldehydes give no defined condensation products: indole-3-aldehyde, 2-nitrobenzaldehyde, anthracene-9-aldehyde, acridine-9-aldehyde, and *N*-phthaloylanthranilaldehyde. Phenylacetaldehyde polymerized under the reaction conditions employed. A few of the observations made in this work are noteworthy: in contrast to di- and tri-chloroacetaldehyde, the monochloro-compound gave no defined product, the chlorine atom being eliminated to a large extent. Diethyl oxaloacetate, too, has been successfully condensed with chloral, but not with chloroacetaldehyde.[4]

The product obtained from 2-phenylpropionaldehyde was ethyl 2-fluoro-4-phenylpent-2-enoate (II); the position of the double bond is substantiated by the carbonyl peak at 1720 cm.$^{-1}$.

The product obtained from methacraldehyde, ethyl 2-fluoro-4-methylpenta-2,4-dienoate, polymerized easily and could thus be obtained only with some difficulty. When methacraldehyde was condensed with (I) with piperidine acetate as catalyst,[2] a different product, $C_{12}H_{17}FO_6$, was obtained. This formula is the sum of those of the two reactants. As the compound still contained the terminal methylene group (peak at 880 cm.$^{-1}$) and a hydroxy-group (3480 cm.$^{-1}$), it appears to be an aldol-type condensation product of formula (III)

The α-formyl derivatives of ketones and esters reacted with (I) in their aldehydic form. Thus, diethyl 2-formylsuccinate gave triethyl 4-fluorobut-3-ene-1,2,4-tricarboxylate (IV), 2-formylcyclohexanone gave ethyl 2-fluoro-3-(2-oxocyclohexyl)acrylate (V), both unstable,

[1] Part XXXIX, E. D. Bergmann, I. Shahak, and I. Gruenwald, *J. Chem. Soc.* (*C*), 1967, 2206.

[2] E. D. Bergmann and I. Shahak, *J. Chem. Soc.*, 1960, 5261; cf. H. Gault, D. Rouge, and E. Gordon, *Compt. rend.*, 1960, **250**, 1073.

[3] E. D. Bergmann and I. Shahak, *J. Chem. Soc.*, 1961, 4033.

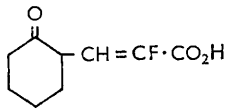
[4] L. Erichomovitch, *Ann. Chim.* [12], 1951, **6**, 276.

and α-formylbutyrophenone gave, after hydrolysis of the primary product, the crystalline 4-benzoyl-2-fluorohex-2-enoic acid (VI).

$$PhCHMe\cdot CH=CF\cdot CO_2Et \quad (II)$$

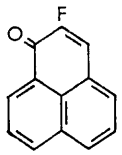
$$EtO_2C\cdot CO\cdot CF(CO_2Et)\cdot CHOH\cdot CMe=CH_2 \quad (III)$$

$$EtO_2C\cdot CH(CH_2\cdot CO_2Et)\cdot CH=CF\cdot CO_2Et \quad (IV)$$

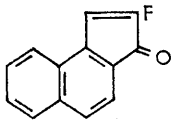


(V)

$$BzCHEt\cdot CH=CF\cdot CO_2H \quad (VI)$$



(VII)



(VIII)

2-Fluoro-3-(2-thienyl)acrylic acid could be nitrated to give a mononitro-derivative; by analogy with previous experience it is assumed that nitration attacked the 5-position of the thiophen ring. The product is a powerful vesicant.

With 2-fluoro-3-(1-naphthyl)acrylic acid, cyclisation was attempted. Polyphosphoric acid at 140° yielded a product which could be either 2-fluorophenalen-1-one (VII) or 2-fluoro-4,5-benzinden-1-one (VIII). The spectral properties of the compound indicate that formula (VIII) is correct. The carbonyl absorption at 1700 cm.$^{-1}$ is characteristic for the indenone system; phenalenones show the carbonyl band at 1630 cm.$^{-1}$.[5] The electronic spectrum of our compound is practically identical with that of 4,5-benzinden-1-one, whilst phenalen-1-one has an entirely different spectrum:[6] 4,5-benzinden-1-one, 230, 252, and 348·5 mμ; phenalen-1-one, 345, 260, 340, 355, and 380 mμ; our compound, 228, 252, and 350 mμ.

It has, in fact, been observed in many cases that α-fluorination of αβ-unsaturated carbonyl compounds does not affect the electronic spectrum significantly.

Fluorofumaric acid has previously been obtained[3] from butyl glyoxalate and (I), but not in pure form. The pure acid, now prepared, had the m.p. (232°) indicated in the literature,[7] where also the configuration of the product has been established.

EXPERIMENTAL

Fluorofumaric Acid.—This was prepared by the literature method.[3] The butyl ethyl ester (50 g.) was hydrolysed with concentrated hydrochloric acid (50 g.) and glacial acetic acid (50 g.) by refluxing the mixture for 6 hr. and distilling in a column to dryness. The residue was dissolved in the minimum of hot acetone, benzene was added to turbidity, and the solution was left to cool slowly. The hydrolysis proceeded with 36% yield; m.p. 232° (Found: C, 35·4; H, 2·3; F, 14·0. Calc. for $C_4H_3FO_4$: C, 35·8; H, 2·2; F, 14·2%). Ascending paper chromatography by an adaptation of the method used for the separation of dicarboxylic acids in t.l.c.[8] showed that the product was free from the isomer and impurities.

Dimethyl Fluorofumarate.—This *ester* was obtained in quantitative yield by treatment with diazomethane in anhydrous methanol, b.p. 105°/15 mm., m.p. 32° (from methanol) (Found: C, 44·7; H, 4·5; F, 12·0. $C_6H_7FO_4$ requires C, 44·4; H, 4·3; F, 11·7%).

Ethyl 4,4,4-Trichloro-2-fluorocrotonate.—By the method previously described,[3] chloral (29·5 g., 0·2 mole) was condensed with diethyl fluoro-oxaloacetate in xylene (anhydrous chloral was prepared by distillation of chloral hydrate with concentrated sulphuric acid). The *ester* (29·5 g., 51%), b.p. 54°/0·1 mm., decomposed on standing, liberating hydrogen fluoride, and therefore no satisfactory analysis could be obtained (Found: C, 31·1; H, 2·9; Cl, 45·0; F, 7·7. $C_6H_6Cl_3FO_2$ requires C, 30·6; H, 2·6; Cl, 45·2; F, 8·1%); $\nu_{max.}$ (film) 3070, 1760, 1690, 1460, 1030, and 930 cm.$^{-1}$.

4,4-Dichloro-2-fluorocrotonic Acid.—The *ester* obtained from dichloroacetaldehyde (22·6 g., 0·2 mole) in xylene was contaminated with small amounts of diethyl fluoro-oxaloacetate. The crude ester (15 g.) was therefore mixed with concentrated hydrochloric acid (25 ml.), and the mixture was made homogeneous by addition of glacial acetic acid and refluxed for 7 hr. The solution was brought to dryness *in vacuo*, and the residue was taken up in water and again brought to dryness. The resulting oil was dissolved in benzene (which leaves oxalic acid undissolved), and the solution was dried and distilled *in vacuo*. The acid (9·6 g., 75%, based on the ester) was an oil, b.p. 96°/0·4 mm. (Found: C, 27·8; H, 1·8; Cl, 40·4; F, 10·7. $C_4H_3Cl_2FO_2$ requires C, 27·8; H, 1·7; Cl, 41·0; F, 11·0%).

Ethyl 4,5-Epoxy-2-fluoropent-2-enoate.—The reaction with glycidaldehyde in xylene gave the *ester* (44%), b.p. 84·5—85°/3 mm.; $\nu_{max.}$ (film) 1730 and 1690 cm.$^{-1}$ (Found: C, 52·7; H, 5·6; F, 11·8. $C_7H_9FO_3$ requires C, 52·5; H, 5·6; F, 11·9%).

Ethyl 2-Fluoro-4-phenylpent-2-enoate (II).—This was prepared from 2-phenylpropionaldehyde[9] with dibutyl ether as solvent. The *product* (50%) had b.p. 127—130°/0·05 mm. (Found: C, 70·7; H, 6·8; F, 8·6. $C_{13}H_{15}FO_2$ requires C, 70·3; H, 6·8; F, 8·6%); $\nu_{max.}$ (film) 1720 (conjugated C=O), 1660, 1080, and 1020 (C–F) cm.$^{-1}$.

Ethyl 2-Fluoro-4-methylpenta-2,4-dienoate.—Reaction with methacraldehyde in dibutyl ether gave the easily polymerizable *ester* (20%), b.p. 72·5°/2 mm.; $\nu_{max.}$ (film) 1720 and 1670 cm.$^{-1}$ (Found: C, 60·5; H, 6·9; F, 11·7. $C_8H_{11}FO_2$ requires C, 60·8; H, 7·0; F, 12·0%).

Ethyl 3-Ethoxycarbonyl-3-fluoro-4-hydroxy-5-methyl-2-oxohex-5-enoate (III).—Diethyl fluoro-oxaloacetate (62 g.), methacraldehyde (20·5 g.), and piperidine (5 drops) in glacial acetic acid (3 ml.) were kept at room temperature for 10 days. The mixture was diluted with benzene (100 ml.) and the solution was washed with 10% hydrochloric acid,

[5] E. Campaigne, D. R. Maulding, and W. L. Roelofs, *J. Org. Chem.*, 1964, **29**, 1543.
[6] R. D. Campbell and N. H. Cromwell, *J. Amer. Chem. Soc.*, 1957, **79**, 3456.
[7] U. S. Raasch, R. E. Miegel, and J. E. Castle, *J. Amer. Chem. Soc.*, 1959, **81**, 2678.
[8] D. Braun and H. Geenen, *J. Chromatog.*, 1962, **7**, 56.
[9] C. F. H. Allen and J. Van Allan, *Org. Synth.*, Coll. Vol. III, 1955, p. 733.

dried, and concentrated at 25 mm. The *product* was purified by repeated distillation at 0·5 mm. pressure; $\nu_{max.}$ (film) 3430 (broad; bonded OH), 2970, 1720 (C=O), 1670 (C=O), and 880 (terminal CH_2) cm.$^{-1}$ (Found: C, 51·9; H, 6·0; F, 6·8. $C_{12}H_{17}FO_6$ requires C, 52·2; H, 5·9; F, 6·9%).

α-Fluorocinnamylideneacetic Acid.—The ethyl ester, obtained in the condensation of (I) with cinnamaldehyde, was a highly viscous oil, b.p. 120—140°/1 mm., and was converted into the free acid by adding 25% aqueous potassium hydroxide to a solution of the ester in methanol at a temperature not exceeding 30° and at such a rate that the alkali was used up quickly. The *potassium salt* of the desired acid was insoluble in water (Found: F, 8·2. $C_{11}H_8FKO_2$ requires F, 8·3%); it was converted into the *free acid* by keeping for 12 hr. with 18% hydrochloric acid, m.p. 201° (from aqueous ethanol or by sublimation) (lit.,[10] 201°) (Found: C, 68·7; H, 4·9; F, 9·9. Calc. for $C_{11}H_9FO_2$: C, 68·6; H, 4·7; F, 9·9%); $\nu_{max.}$ (KBr) 1700, 1650, and 1100 cm.$^{-1}$.

Triethyl 4-Fluorobut-3-ene-1,2,4-tricarboxylate (IV).—When diethyl fluoro-oxaloacetate was condensed with diethyl 2-formylsuccinate[11] in dibutyl ether, an oil was obtained, b.p. 141°/0·5 mm., which was very unstable but gave the correct analysis for fluorine (Found: F, 6·4. $C_{13}H_{19}FO_6$ requires F, 6·5%); $\nu_{max.}$ (film) 1750, 1100, and 1030 cm.$^{-1}$. Hydrolysis with alkali or acid caused an almost complete loss of the fluorine.

Ethyl 2-Fluoro-3-(2-oxocyclohexyl)acrylate (V).—A condensation of diethyl sodiofluoro-oxaloacetate with 2-formylcyclohexanone[12] in dibutyl ether gave an oil (20%), b.p. 120—125°/30 mm., which darkened very quickly after isolation (Found: F, 8·7. $C_{11}H_{15}FO_3$ requires F, 8·9%); $\nu_{max.}$ (film) 1750, 1100, and 1020 cm.$^{-1}$.

4-Benzoyl-2-fluorohex-2-enoic Acid (VI).—The product of the analogous condensation with α-formylbutyrophenone[13] in dibutyl ether was an oil (40%), b.p. 140—150°/1 mm., which was hydrolysed with alkali as described. The oily acid was reprecipitated from its solution in sodium hydrogen carbonate and solidified on standing; m.p. 71°, $\nu_{max.}$ (KBr) 1720, 1680, 1600, 1095, and 1000 cm.$^{-1}$ (Found: C, 66·3; H, 5·4; F, 8·4. $C_{13}H_{13}FO_3$ requires C, 66·1; H, 5·5; F, 8·1%).

Ethyl 3-Acetoxy-α-fluorocinnamate.—This was obtained (28·6 g., 62%) from (I) and 3-acetoxybenzaldehyde[14] (33 g.; b.p. 263°), b.p. 172—176°/3 mm., m.p. 45° (from ethanol); $\nu_{max.}$ (KBr) 1730 (superposition of the two carbonyl frequencies), 1600, and 1100 (C–F) cm.$^{-1}$ (Found: C, 62·0; H, 5·5; F, 7·5. $C_{13}H_{13}FO_4$ requires C, 61·9; H, 5·2; F, 7·5%).

3-Hydroxy-α-fluorocinnamic Acid.—Methanolic potassium hydroxide (5 mol.) was added to the foregoing ester (12·5 g.) in methanol so that the temperature did not rise above 30°. After a further 2 hr. at room temperature, the solvent was removed *in vacuo* and the residue was dissolved in water and acidified with concentrated hydrochloric acid. The *acid* (30%) had m.p. 169—170° (from water); $\nu_{max.}$ (KBr) 3300—2800, 1720—1680, 1100, and 840 cm.$^{-1}$ (Found: C, 59·3; H, 4·0; F, 10·3. $C_9H_7FO_3$ requires C, 59·3; H, 3·8; F, 10·4%).

Ethyl 4-Acetoxy-α-fluorocinnamate.—This was obtained analogously (70%) from 4-acetoxybenzaldehyde[15] (33 g.). It had b.p. 114—120°/0·1 mm., m.p. 69° (from ethanol); $\nu_{max.}$ (KBr) 1730, 1650, 1280, and 1100 cm.$^{-1}$ (Found: C, 62·2; H, 5·1; F, 7·5. $C_{13}H_{13}FO_4$ requires C, 61·9; H, 5·2; F, 7·5%).

4-Hydroxy-α-fluorocinnamic Acid.—The foregoing ester was hydrolysed as indicated for the *meta*-isomer. The *acid* (80%) had m.p. 248° (from water); $\nu_{max.}$ (KBr) 3300—2500, 1700, 1630, 1110, and 840 cm.$^{-1}$ (Found: C, 59·8; H, 4·0; F, 10·4. $C_9H_7FO_3$ requires C, 59·3; H, 3·8; F, 10·4%).

Ethyl 3-(1-Acetylindol-3-yl)-2-fluoroacrylate.—The condensation of 1-acetylindole-3-aldehyde (13·2 g.)[16] was carried out in the usual manner in dibutyl ether. The *product* (10 g., 60%) solidified, m.p. 107—108° (from dibutyl ether or xylene) (Found: C, 65·7; H, 5·0; F, 6·8. $C_{15}H_{14}FNO_3$ requires C, 65·5; H, 5·1; F, 6·9%); $\nu_{max.}$ (KBr) 1720, 1650, 1100, and 1020 cm.$^{-1}$.

Ethyl 4-Nitro-α-fluorocinnamate.—The usual procedure gave the *ester* (52%), which crystallized spontaneously from the solution, m.p. 138—139° (from ethanol) (Found: C, 55·0; H, 4·3; F, 8·3. $C_{11}H_{10}FNO_4$ requires C, 55·2; H, 4·2; F, 8·0%); $\nu_{max.}$ (KBr) 1720, 1600, 1100, and 1020 cm.$^{-1}$.

2-Fluoro-3-(2-furyl)acrylic Acid.—The method, applied to 2-furaldehyde, gave ethyl 2-fluoro-3-(2-furyl)acrylate (38%), b.p. 126—128°/30 mm., as a very unstable oil, liberating gradually hydrogen fluoride, so that the analysis gave somewhat low fluorine values. The *free acid* was stable. To the ester (9·2 g.) in methanol (50 ml.) 25% aqueous potassium hydroxide solution was added at a temperature not exceeding 30° and at such a rate that the alkali was used up quickly. When the solution remained basic for 30 min. the solution was brought to pH 8 and the methanol distilled off *in vacuo*. Water (25 ml.) was added and the solution acidified with concentrated hydrochloric acid to give the *acid* (7·05 g., 90%), m.p. 148° (from aqueous ethanol) (Found: C, 53·9; H, 3·4; F, 12·3. $C_7H_5FO_3$ requires C, 53·8; H, 3·2; F, 12·2%).

Diethyl α,α'-Difluoro-p-phenylenediacrylate.—When terephthalaldehyde (0·1 mole) was treated with the enolate (0·2 mole) obtained from ethyl fluoroacetate and oxalate in dibutyl ether, the product crystallized spontaneously, but not completely. The remainder had to be isolated by concentrating the dibutyl ether solution. After recrystallization from dibutyl ether, the *ester* had m.p. 99—100° (Found: C, 62·2; H, 5·1; F, 12·1. $C_{16}H_{16}F_2O_4$ requires C, 62·0; H, 5·2; F, 12·3%); $\nu_{max.}$ (KBr) 1720, 1620, 1095, and 1025 cm.$^{-1}$.

2-Fluoro-3-(2-thienyl)acrylic Acid.—The condensation of thiophen-2-aldehyde (b.p. 97—100°/27 mm.) with (I), carried out in dibutyl ether, gave ethyl 2-fluoro-3-(2-thienyl)acrylate (60%), b.p. 125—130°/30 mm., which was directly hydrolysed with alkali. The *free acid* (90%) was recrystallized from aqueous alcohol (70%); m.p. 165° (Found: C, 48·1; H, 3·2; F, 11·2; S, 18·1. $C_7H_5FO_2S$ requires C, 48·8; H, 2·9; F, 11·1; S, 18·6%); $\nu_{max.}$ (KBr) 1700, 1100, and 1050 cm.$^{-1}$.

2-Fluoro-3-(5-nitro-2-thienyl)acrylic Acid.—At a temperature not exceeding −5°, the foregoing acid (8·5 g.) was added slowly to a mixture of fuming nitric acid (10 g.; *d* 1·52) and concentrated sulphuric acid (28 g.). The

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[11] W. Wislicenus and F. Bokler, *Annalen*, 1908, **363**, 340.
[12] V. A. Petrow, *J. Chem. Soc.*, 1942, 694.
[13] S. Takagi and H. Yasuda, *Chem. Abs.*, 1959, **53**, 18,003.
[14] F. Tiemann and R. Ludwig, *Ber.*, 1882, **15**, 2043.
[15] P. E. Papadakis, *J. Amer. Chem. Soc.*, 1945, **67**, 1799.
[16] R. Majima and M. Kotake, *Ber.*, 1925, **58**, 2037.

solution, from which part of the product crystallized spontaneously, was poured into an excess of ice–water; the *acid* (5·4 g., 50%) was recrystallized from 50% aqueous ethanol, m.p. 225° (decomp.) (Found: C, 38·5; H, 1·9; F, 9·0; S, 14·9. $C_7H_4NFO_4S$ requires C, 38·7; H, 1·9; F, 8·80; S, 14·8%); $\nu_{max.}$ (KBr) 1700, 1095, and 1020 cm.$^{-1}$.

2-*Fluoro*-3-(1-*naphthyl*)*acrylic Acid*.—The *ethyl ester* obtained in dibutyl ether from (I) and 1-naphthaldehyde in 48% yield had b.p. 145—148°/0·5 mm., $\nu_{max.}$ (KBr) 1730 and 1630 cm.$^{-1}$ (Found: C, 73·5; H, 5·4; F, 7·7. $C_{15}H_{13}FO_2$ requires C, 73·8; H, 5·3; F, 7·8%). Alkaline hydrolysis as described gave the *free acid* (90%), m.p. 160° (Found: C, 72·3; H, 4·4; F, 8·7. $C_{13}H_9FO_2$ requires C, 72·2; H, 4·2; F, 8·8%); $\nu_{max.}$ (KBr) 1700, 1630, and 1100 cm.$^{-1}$.

2-*Fluoro*-4,5-*benzinden*-1-*one* (VIII).—A mixture of the preceding acid (3 g.) and polyphosphoric acid (60 g.) was heated at 140° for 3 hr.; part of the product sublimed on to the colder parts of the reaction vessel. The solution was diluted with water and the *product* (1 g., 30%) filtered and sublimed at 150—160°/30 mm., m.p. 147°. The solution in ethanol showed a violet and that in concentrated sulphuric acid a yellow-green fluorescence (Found: F, 9·8. $C_{13}H_7FO$ requires F, 10·0%).

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