# 305. *Organic Fluorine Compounds. Part VII.* The Perkin and Similar Reactions with Fluoroacetic Acid.*

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Fluoroacetic acid and its derivatives can be condensed with aromatic aldehydes in reactions of the Perkin type. α-Fluorocinnamic acid and its *p*-nitro-derivative, 1-fluoro-4-phenylbutadiene-1-carboxylic acid, and β-*o*-chlorophenyl-α-fluoro-β-hydroxypropionic acid have thus been synthesised; the yields are low. *m*-Nitrobenzaldehyde gives complicated products.

The ability of fluoroacetates to form relatively stable enolates (see preceding paper) should express itself also in a tendency of the acid and its derivatives to condense with aromatic aldehydes to form compounds of the α-fluorocinnamic acid type. It is assumed today[1] that, *e.g.*, the Perkin reaction proceeds *via* the enolate of the acid anhydride used in the condensation. Indeed, Swarts[2] has reported that, from benzaldehyde, methyl fluoroacetate, and sodium, α-fluorocinnamic acid can be obtained (in unspecified yield), and

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* Part VI, preceding paper.

[1] Gilman, " Organic Chemistry," Vol. III, p. 112, Wiley and Sons, New York, 1953.

[2] Swarts, *Bull. Soc. chim. France*, 1919, **25**, 325.

Bergmann, Kalmus, and Vromen[3] have described the alkaline condensation of benzaldehyde and ω-fluoroacetophenone in 40% yield. Ethyl bromofluoroacetate can also take part[4] in Reformatsky reactions. A systematic study of the condensation of aromatic aldehydes with fluoroacetic acid and its derivatives appeared, therefore, desirable.

In the condensation of benzaldehyde with sodium fluoroacetate and fluoroacetic anhydride, vigorous evolution of hydrogen fluoride took place, but α-fluorocinnamic acid could be isolated in a yield of only 2%. When benzaldehyde was condensed with ethyl fluoroacetate in ether in the presence of sodium hydride, a complex mixture was obtained: benzaldehyde, benzoic acid, ethyl benzoate, ethyl αγ-difluoroacetoacetate, cinnamic acid, and, in 15% yield, α-fluorocinnamic acid were isolated. (The mixture was treated with alcohol and hydrochloric acid to destroy the excess of sodium hydride; this may explain the formation of ethyl benzoate.) It is surprising that the product contains free acids, but even more so that, from the unidentified liquid fractions, we obtained a 2 : 4-dinitrophenylhydrazone which, according to the analysis and the ultraviolet spectrum (see below), was that of α-fluorocinnamaldehyde. Reduction has not been reported before in sodium hydride condensations.

The sodium hydride-catalysed condensation between cinnamaldehyde and ethyl fluoroacetate gave a mixture of 1-fluoro-4-phenylbuta-1 : 3-diene-1-carboxylic acid (14%) and its ethyl ester (20%). From *p*-nitrobenzaldehyde, a 13% yield of α-fluoro-*p*-nitrocinnamic acid was obtained by Perkin's method.

When *o*-chlorobenzaldehyde was condensed with ethyl fluoroacetate in the presence of sodium hydride, the reaction proceeded only to the stage of β-*o*-chlorophenyl-α-fluoro-β-hydroxypropionic acid, probably owing to the stabilising effect of a hydrogen bond between the hydroxyl group and the *o*-chlorine atom. Indeed, in the infrared spectrum of the acid, one finds in addition to the usual (3325 cm.$^{-1}$) band of the alcoholic hydroxyl, an intense absorption at 2560 cm.$^{-1}$, indicating a very strongly hydrogen-bonded aliphatic hydroxyl group; the carbonyl absorption lies at 1725 cm.$^{-1}$, *i.e.*, in the region characteristic of a saturated carboxylic acid.

The condensation of *m*-nitrobenzaldehyde with fluoroacetic acid under various conditions gave a number of abnormal products which will be reported later. In a Perkin-type condensation, for example, a compound $C_{16}H_{13}O_8N_2F$ was obtained, whose infrared spectrum suggests an *iso*butyric acid, $NO_2\cdot C_6H_4\cdot CH(OH)\cdot CF(CO_2H)\cdot CH(OH)\cdot C_6H_4\cdot NO_2$.

*Spectra.*—Comparison of the spectra of α-fluorocinnamic acid and 1-fluoro-4-phenylbutadiene-1-carboxylic acid with those of the corresponding non-fluorinated compounds shows that the fluorine atom exerts a hypsochromic influence (—160 and —120 Å, respectively):

| | Max. (Å) | Min. (Å) |
|---|---|---|
| α-Fluorocinnamic acid | 2620 (log ε 4·36) | 2260 (log ε 3·70) |
| Cinnamic acid [a] | 2780 | 2350 |
| 1-Fluoro-4-phenylbutadiene-1-carboxylic acid | 3020 (log ε 4·63) | 2470 (log ε 3·64) |
| 4-Phenylbutadiene-1-carboxylic acid [b] | 3140 | 2500 |

[a] Landolt–Börnstein, "Physikalisch-chemische Tabellen," Vol. I, Part 3, p. 134. [b] Smakula, *Angew. Chem.*, 1934, **47**, 657; 1935, **48**, 152.

Equally, the 2 : 4-dinitrophenylhydrazone of our supposed α-fluorocinnamaldehyde shows maxima at 3710 (4·21) and 2500 Å (3·92) and minima at 3010 (3·37) and 2440 Å (3·89), whilst for cinnamaldehyde dinitrophenylhydrazone maxima at 3890 (4·68), 3040 (4·18), and 2365 Å (4·32) and minima at 3265 (3·95) and 2830 Å (4·04) are observed. Johnson[5] reports the longest maximum of cinnamaldehyde 2 : 4-dinitrophenylhydrazone at 3910 Å (4·59). The hypsochromic effect of the fluorine atom in this case is —180 Å (for the longest absorption band).

For α-fluoro-*p*-nitrocinnamic acid, the maxima lie at 2500 (4·03) and 3120 Å (4·17) and a minimum at 2630 Å (3·64). As Purvis[6] reported for *p*-nitrocinnamic acid an absorption maximum at 2940 Å, the fluorine atom would exert in this case a slightly bathochromic

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[3] Bergmann, Kalmus, and Vromen, *J. Amer. Chem. Soc.*, 1955, **77**, 2494.

[4] McBee, Pierce, and Christman, *ibid.*, p. 1581.

[5] Johnson, *ibid.*, 1953, **75**, 2720.

[6] Purvis, *J.*, 1915, **107**, 966.

effect, as compared with the cinnamic acid, provided that the steric arrangement is the same as in α-fluorocinnamic acid. In this respect, it is recalled that α-fluorobenzylideneacetophenone has practically the same spectrum as the non-fluorinated compound.[3]

In the infrared spectrum,[7] the C:CF grouping absorbs at 1100—1200 cm.$^{-1}$, *i.e.*, in a region in which also many oxygenated compounds absorb and which, therefore, is not very convenient for the structural analysis of the compounds described here. In ethyl 1-fluoro-4-phenylbutadiene-1-carboxylate, the bands characteristic of the conjugated double bond and the conjugated ester grouping lie at 1643 and 1720 cm.$^{-1}$, respectively. The corresponding bands in the corresponding free acid and in α-fluoro-*p*-nitrocinnamic acid have been observed at 1639 and 1690 cm.$^{-1}$ and at 1606 and 1704 cm.$^{-1}$, respectively.[8,9] In the last compound, the C=CF band at 1124 cm.$^{-1}$ is very conspicuous.

## EXPERIMENTAL

For the preparation of fluoroacetic acid and its anhydride the following modifications of known [10] methods have proved advantageous: Dry sodium fluoroacetate (50 g.) was added to concentrated sulphuric acid (100 ml.) in a Claisen flask. By gentle heating and stirring, a homogeneous solution was obtained. This was distilled *in vacuo*; the acid (37·1 g., 95%) on redistillation had b. p. 167—169°/760 mm.

Fluoroacetyl chloride [10] (38·7 g.) and sodium fluoroacetate (42·0 g.) were added to mineral oil (150 ml.) which had been freed from volatile constituents at 200°/30 mm. The mixture was heated under reflux at 110—120° for 90 min. and then distilled under 30—45 mm. pressure. The distillate was collected up to 116° and redistilled; the anhydride (44·4 g., 88%) had b. p. 90—93°/20 mm.

*Condensation of Benzaldehyde and Fluoroacetic Acid*.—(*a*) The mixture of freshly distilled benzaldehyde (16 g.), dry sodium fluoroacetate (15 g.), and fluoroacetic anhydride (20·7 g.) was heated under reflux for 8 hr. The product was steam-distilled; from the remaining aqueous liquor, α-fluorocinnamic acid (1·0 g., 2%) slowly crystallised. After being sublimed *in vacuo*, it melted at 157° (lit., 157·6°) (Found: C, 64·6; H, 4·3. Calc. for $C_9H_7O_2F$: C, 65·0; H, 4·2%).

(*b*) To sodium hydride (7·2 g., 0·3 mole) and anhydrous ether (65 ml.), contained under nitrogen, a solution of benzaldehyde (31·0 g., 0·3 mole) and ethyl fluoroacetate [11] (31·8 g., 0·3 mole) in anhydrous ether (100 ml.) was added slowly with stirring; stirring was continued for 8 hr. Anhydrous alcohol (14 ml., 0·3 mole) was added cautiously, followed by 20% hydrochloric acid. The aqueous layer was extracted with ether, and the combined ethereal solutions were extracted with 10% sodium hydrogen carbonate solution, dried, and concentrated. Distillation of the residue gave some benzaldehyde, ethyl benzoate (6·5 g.), ethyl αγ-difluoroacetoacetate (8·2 g., b. p. 99—101°/20 mm.), and a higher-boiling mixture from which by the usual procedure *α-fluorocinnamaldehyde* 2 : 4-*dinitrophenylhydrazone* (0·6 g.) was obtained. This melted, after recrystallisation from ethyl acetate–ethanol, at 200—203° (Found: C, 54·6; H, 3·8. $C_{15}H_{11}O_4N_4F$ requires C, 54·5; H, 3·4%). The sodium carbonate extract, upon acidification, gave α-fluorocinnamic acid (7·5 g., 15%), m. p. 157°, after a little benzoic and cinnamic acid had been removed by sublimation *in vacuo*.

*Cinnamaldehyde and Ethyl Fluoroacetate*.—By the method described above, freshly distilled cinnamaldehyde (19·8 g.) was condensed with ethyl fluoroacetate (15·9 g.) in the presence of sodium hydride (3·6 g.). The mixture was refluxed with stirring for 10 hr. and decomposed with the equivalent amount (0·15 mole) of aqueous hydrochloric acid. The acidic product, 1-*fluoro*-4-*phenylbutadiene*-1-*carboxylic acid*, was twice sublimed at 2 mm. at 140° and formed crystals (4 g., 14%), m. p. 192·5—193° (Found: C, 69·1; H, 4·8; F, 9·8. $C_{11}H_9O_2F$ requires C, 68·7; H, 4·7; F, 9·9%). The neutral fraction was redistilled at 119°/0·75 mm.; it crystallised and melted at 40—42°. *Ethyl* 1-*fluoro*-4-*phenylbutadiene*-1-*carboxylate* decomposes gradually (Found: C, 71·2; H, 6·0%; *M*, 190. $C_{13}H_{13}O_2F$ requires C, 70·9; H, 5·9%; *M*, 220). Hydrolysis gave the free acid.

*α-Fluoro*-p-*nitrocinnamic Acid*.—The mixture of *p*-nitrobenzaldehyde (5·0 g.), sodium fluoroacetate (4·5 g.), and fluoroacetic anhydride (9·4 g.) was heated at 145° for 13 hr. The desired *acid* was isolated by extraction with aqueous ammonia and acidification of the extract.

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[7] Colthup, *J. Opt. Soc. Amer.*, 1950, **40**, 397.
[8] Dauben and Hance, *J. Amer. Chem. Soc.*, 1953, **75**, 3352.
[9] Grove and Willis, *J.*, 1951, 877.
[10] Saunders and Stacey, *J.*, 1948, 1773.
[11] Bergmann and Blank, *J.*, 1953, 3786.

The yellowish product was purified by sublimation (170°/0·9 mm.) and then had m. p. 200—202° (yield 0·9 g., 13%). The carbon analysis was somewhat low (Found: C, 50·5; H, 3·0; N, 6·7; F, 9·5. $C_9H_6O_4NF$ requires C, 51·2; H, 2·8; N, 6·6; F, 9·0%).

β-o-*Chlorophenyl-α-fluoro-β-hydroxypropionic Acid.*—In the manner described above, *o*-chlorobenzaldehyde (21·0 g.) and ethyl fluoroacetate (15·9 g.) were condensed in the presence of sodium hydride (3·6 g.). The resulting *acid* was successively recrystallised from water and benzene and formed platelets (yield 4·8 g., 15%), m. p. 136° (Found: Cl, 16·2; F, 8·7. $C_9H_8O_3ClF$ requires Cl, 16·1; F, 8·7%).

2-*Fluoro*-1 : 3-*dihydroxy*-1 : 3-*di*-m-*nitrophenylpropane*-2-*carboxylic Acid.*—The Perkin condensation of fluoroacetic acid and *m*-nitrobenzaldehyde was carried out as described for the *p*-isomer. The *acid* (yield 2·1 g., 33%) was purified by sublimation (155°/0·9 mm.) and melted at 174—176° (Found: C, 49·2; H, 3·2; N, 7·3; F, 5·0. $C_{16}H_{13}O_8N_2F$ requires C, 50·5; H, 3·4; N, 7·4; F, 4·8%).

*Infrared Spectra.*—These were determined on suspensions in Nujol, except for ethyl 1-fluoro-4-phenylbutadiene-1-carboxylate whose spectrum was measured in chloroform (0·0414 g. in 1 ml.).

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