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TOXIC FLUORINE COMPOUNDS CONTAINING THE C—F LINK—XII*

SOME REACTIONS OF ω-FLUOROACETOPHENONE[1]

D. L. E. BRONNERT[2] and B. C. SAUNDERS
University Chemical Laboratory, Lensfield Rd, Cambridge

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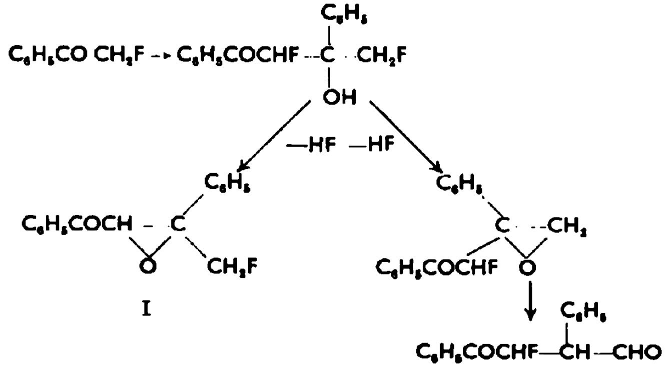
Abstract—The reaction between ω-fluoroacetophenone and sodium methoxide in methanolic solution has been investigated. The condensation at room temperature results in the formation of 2,3-epoxy-4-fluoro-1,3-diphenylbutan-1-one (I) and 2-fluoro-1,3-diphenyl-butan-1-one-4-al (II). From the latter 3-fluoro-2,4-diphenylfuran (V) has been prepared. A general method for preparing substituted fluorofurans thus becomes possible.

IN THE course of our investigations into the stability of the carbon–fluorine bond in 2-fluoroethanol,[3] the stability of ω-fluoroacetophenone came into consideration. We found that a methanolic solution of ω-fluoroacetophenone gave a white organic solid when treated with 10% sodium hydroxide solution at room temperature. It was thought that this might prove worth investigation, and so the experiment was repeated under more specific conditions using a methanolic solution of sodium methoxide. When a methanolic solution of ω-fluoroacetophenone was treated in this way a yellow colour rapidly appeared and gradually deepened to orange and a white precipitate came down. The latter was an organic solid (contaminated with sodium carbonate and sodium fluoride). It crystallized from methanol in long white acicular needles and was proved by analysis, degradation and IR, UV, and NMR spectra to be 2,3-epoxy-4-fluoro-1,3-diphenylbutan-1-one (I). The filtrate from the reaction yielded a dark red, low melting solid, which on the basis of spectra and of its reaction with conc. hydrochloric acid to produce 3-fluoro-2,4-diphenylfuran (V) is thought to be 2-fluoro-1,3-diphenylbutan-1-one-4-al (II). A fluoride determination showed that 65% of the fluorine in the original ω-fluoroacetophenone had been eliminated as F⁻.

The reactions postulated to account for the formation of I and II are set out below.



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* Part XI *Tetrahedron* 10, 160 (1960).

[1] This paper is based in part on a lecture given by one of us (B. C. S.) to the *American Chemical Society*, New York, September (1960).

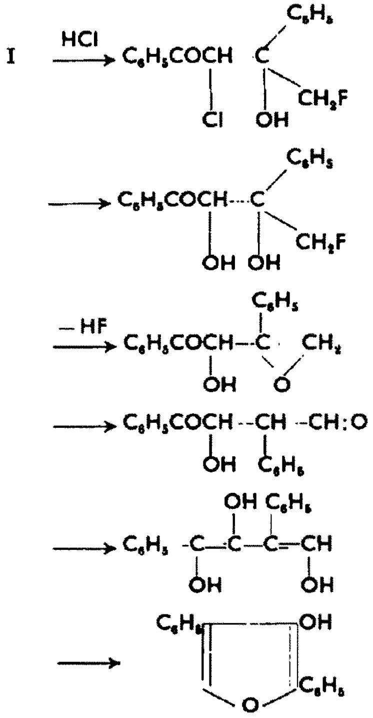
[2] We acknowledge with thanks a Department of Scientific and Industrial Research maintenance grant to one of us (D. L. E. B.).

[3] D. L. E. Bronnert and B. C. Saunders, *Tetrahedron* 10, 160 (1960).

The first step is an "aldol" condensation giving a compound containing two fluorine atoms, each of which is α to the hydroxyl group. We suggested in our work on 2-fluoroethanol[3] that compounds of this type readily lose hydrogen fluoride to form an epoxide. In addition, ω-fluoroacetophenone is known to react with aluminium isopropoxide to give 2-phenylethanol,[4,5] and whichever of the mechanisms postulated by these two sets of workers is the correct one, it is clear that the intermediate which eliminates hydrogen fluoride has, in effect, fluorine and hydroxyl groups on adjacent carbon atoms. In the reaction between sodium methoxide and ω-fluoroacetophenone, the primary product can eliminate hydrogen fluoride in two ways to give two different compounds. The present work shows that both are formed, and that the proportions are comparable.

The formation of the epoxyfluoro-compound (I) finds a parallel in organic fluorine chemistry in the formation of ethylene oxide from 2-fluoroethanol;[3] the reaction is similar to the Darzens glycidic ester condensation[6] and not unrelated to the reaction between benzaldehyde and chloroacetophenone[7] which results in the formation of an epoxy-compound. It should be noted that fluoroacetophenone on condensation with benzaldehyde has been reported to eliminate water and not hydrogen fluoride in the presence of sodium hydroxide.[7]

By heating I with methanolic hydrogen chloride we have been able to open the



III

IV

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[4] W. E. Truce and R. H. Sack, *J. Amer. Chem. Soc.* 70, 3959 (1948).

[5] F. Bergmann and A. Kalmus, *J. Amer. Chem. Soc.* 76, 4137 (1954).

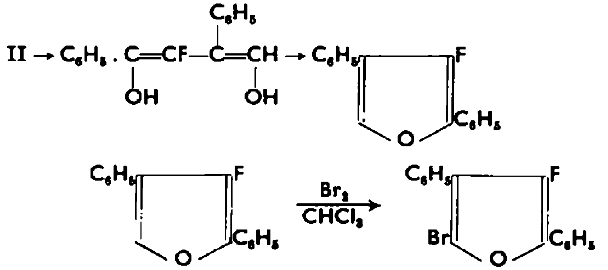
[6] M. S. Newman and B. J. Magerlein, *Organic Reactions* V, 413.

[7] M. Ballester and P. D. Bartlett, *J. Amer. Chem. Soc.* 75, 2042 (1953).

[8] S. Winstein and R. B. Henderson, in *Heterocyclic Compounds* (Elderfield) Wiley, I, 32.

epoxide ring and have thus obtained 2-chloro-4-fluoro-3-hydroxy-1,3-diphenylbutan-1-one (III) and 2,3-dihydro-3-oxo-2,4-diphenylfuran (IV). The structure of III is based on analogous reactions.[8] The structure assigned to IV is based on spectra and a probable sequence of reactions is shown on page 2.

On treating II with conc. hydrochloric acid, 3-fluoro-2,4-diphenylfuran (V) was readily obtained. Compound V was readily brominated by bromine in chloroform to give 5-bromo-3-fluoro-2,4-diphenyl furan (VI).



V

VI

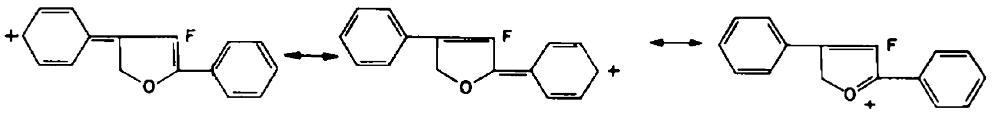
Since II is effectively a 1,4-diketone, it should be possible to obtain other heterocycles containing fluorine in the 3-position, and if this reaction is general with ketones containing the FCH_2CO group a wide range of heterocycles can be envisaged.

Many of the above mentioned compounds give colourations with conc. sulphuric acid. It should be noted that the parent ω-fluoroacetophenone gives no colouration, nor does III. Compound II changes into V on being dissolved in conc. sulphuric acid. The changes observed are set out in the Table 1.

TABLE 1

Compound	Colour in daylight	Colour in UV light
I	Dark red	—
IV	Dark green	—
V	Pale yellow with intense light blue fluorescence	Intensified blue fluorescence
VI	Yellow, changing to green on standing	Light green fluorescence on standing
VII	Intense violet	—

It is highly probable that the colours are caused by the protonation of these compounds, and the consequent.shift of the absorption bands in the UV towards the visible region. The UV absorption maxima and extinction coefficients are set out in the Experimental. Almost all the compounds are highly conjugated and therefore have fairly intense absorption spectra (in ethanol) in the UV region. The effect of protonation by sulphuric acid is to increase the number of contributing resonance end-forms. For instance, among the possible end forms of V, contributing to the resonance hybrid in conc. sulphuric acid, are:



Charged end-forms of this type have a marked effect on the UV spectra, shifting the absorption bands to longer wavelengths.

EXPERIMENTAL

Fluoroacetophenone. Fluoroacetyl chloride was prepared by the method of Saunders and Stacey[5] from methyl fluoroacetate (100 g), using the intermediates barium fluoroacetate and fluoroacetic acid. The fluoroacetyl chloride was allowed to react with benzene in CH_2Cl_2 in the presence of $AlCl_3$ according to the method of Bergmann and Kalmus.[6] Yield of fluoroacetophenone, 80 g from methyl fluoroacetate (100 g) 56%, b.p. 65–70°/0·1 mm.

Reaction between sodium methoxide and fluoroacetophenone. Fluoroacetophenone (5 g, 0·036 mole) was dissolved in MeOH (80 ml), and Na (1 g, 0·043 mole) dissolved in MeOH (20 ml) was added with stirring. A yellow colouration developed rapidly and then deepened to orange. After 30 min a precipitate appeared: stirring was continued for 5 hr and the mixture allowed to stand overnight. The precipitate was filtered off and washed with MeOH. On evaporating the combined filtrate and washings a red solid was obtained and this was boiled with MeOH (15 ml) and filtered. The residue after washing with more hot MeOH (15 ml) was then colourless (1.45 g): it was a mixture of NaF and Na_2CO_3.

On cooling the methanolic extract, colourless needles of I came down. Evaporation of the filtrate gave a dark red solid (II).

Examination of compound (I), 2,3-*epoxy-4-fluoro*-1,3-*diphenylbutan*-1-*one*. Compound I was recrystallized from MeOH as long colourless needles (0·6 g), m.p. 187–188°. (Found: C, 75·35; H, 5·35; F, 7·1, mol. wt., 245, 255. $C_{16}H_{13}FO_2$ requires: C, 75·0; H, 5·15; F, 7·4% mol. wt., 256.)

The IR spectrum showed strong bands at 1,687 cm^{-1} ($>C{=}O$ conjugated to a benzene ring) and 1,251 cm^{-1} (epoxy group).

The UV spectrum had λ_{max} 246 mμ (ε 12,880). This is comparable with acetophenone λ_{max} 244 mμ (ε 16,000) and indicates $>C{=}O$ conjugated to a benzene ring.

NMR spectra were obtained at 40 Mc/s using a Varian Associates V4300B Spectrometer and 12″ electromagnet with flux stabilization and sample spinning.

The NMR spectrum had bands with chemical shifts relative to chloroform of −2·12, −0·1, +0·67, +1·10 ppm. The band with a chemical shift of 0·67 corresponds to a solitary H atom with no H atoms on adjacent C atoms. The bands with chemical shifts −0·1, +1·10 correspond to a CH_2F group with no H atoms on adjacent C atoms.

Compound I (2–3 mg) dissolved in conc. H_2SO_4 (3 ml) giving a deep red solution which did not fluoresce in UV light. UV spectrum of the solution had λ_{max} 298 mμ (ε 6,550), 261 mμ (ε 20,750) and λ_{min} 286 mμ (ε 6,290), 230 mμ (ε 9,300).

Compound I was heated with 4-methylquinoline (1 ml) in ethylene glycol (2 ml) at 170°. A magenta colour developed indicating an epoxide.

2,3-*Epoxy-4-fluoro*-1,3-*diphenylbutan*-1-*one*, 2,4-*dinitrophenylhydrazone*. Compound I (0·1 g) was heated in MeOH (3 ml) and boiling Brady's reagent (5 ml) was added. The mixture was boiled for 10 min and allowed to cool. The orange 2,4-*dinitrophenylhydrazone* crystallized and was filtered off and recrystallized from glacial acetic acid, m.p. 213–215°. (Found: N, 12·8. $C_{22}H_{17}FN_4O_5$ requires: N, 12·8%.)

The IR spectrum did not show any bands that could be attributed to a $>C{=}O$ group and thus confirmed that compound I has only one carbonyl group.

2-*Chloro-4-fluoro*-3-*hydroxy*-1,3-*diphenylbutan*-1-*one* (III). Compound I (0·5 g, 0·002 mole) was heated under reflux with sat methanolic HCl (100 ml). A deep orange colour developed and heating was continued for 1 hr. After removing the MeOH and HCl under red. press. a yellow solid (III, 0·1 g) and an orange coloured fluorine-free compound (IV, 0·3 g) were obtained. Compound III [2-chloro-4-fluoro-3-hydroxy-1,3-*diphenylbutan*-1-*one*] was recrystallized from MeOH as almost white crystals: m.p. 116–117°. (Found: C, 65·8; H, 5·5. $C_{16}H_{14}ClFO_2$ requires: C, 65·6; H, 4·8%.)

IR spectrum showed strong bands at 1,676 cm^{-1} (carbonyl conjugated to benzene ring) and 3,410 cm^{-1} (hydroxyl group). There was no band at 1,251 cm^{-1} thus confirming opening of epoxide ring of I.

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[5] B. C. Saunders and G. J. Stacey, *J. Chem. Soc.* 1773 (1948).

2,3-*Dihydro*-3-*oxo*-2,4-*diphenylfuran* (IV). Compound IV obtained in the previous reaction was recrystallized from MeOH and gave orange coloured crystals of 2,3-*dihydro*-3-*oxo*-2,4-*diphenylfuran* m.p. 126–127°. (Found: C, 81·2; H, 5·0. $C_{16}H_{12}O_2$ requires: C, 81·3; H, 5·1%.)

IR spectrum showed a strong band at 1,698 cm^{-1} ($>$C=O) and a medium band at 1,626 cm^{-1} ($>$C=C$<$).

UV spectrum in EtOH had λ_{max} 410 mμ (ε, 1,276), λ_{min} 354 mμ (ε, 1,070) and inflexion λ 277 mμ (ε, 4,390), 235 mμ (ε, 8,940).

Solution of compound IV *in conc. sulphuric acid.* The compound (3 mg) dissolved in conc. H_2SO_4 (3 ml) gave a dark green solution which did not fluoresce in UV light. The UV spectrum had λ_{max} 447 mμ (ε, 4,810), λ_{min} 397 mμ (ε, 3,570), and inflexion λ 297 mμ (ε, 7,110).

2-*Fluoro*-1,3-*diphenylbutan*-1-*one*-4-*al* (II). The dark red solid II, obtained together with I by the action of MeONa on fluoroacetophenone, was not obtained pure, but was identified by its IR spectrum and its ready conversion to 3-fluoro-2,4-diphenylfuran (see below).

IR spectrum showed strong bands at (a) 1,710 cm^{-1} and (b) 1,650 cm^{-1}. Band (a) is consistent with an aldehyde group whose absorption frequency has been lowered by enolization. Band (b) indicates carbonyl conjugated to a benzene ring. There is also a band at 3,420 cm^{-1} characteristic of a hydroxyl group due possibly to enolization of the aldehyde group.

3-*Fluoro*-2,4-*diphenylfuran* (V). To I (1 g) was added conc. HCl (20 ml). A yellow solid was formed immediately and was filtered off, washed with water and the *furan* crystallized from MeOH as irridescent lemon coloured plates (0·57 g), m.p. 84–85°. (Found: C, 81·1; H, 4·45; F, 7·7, mol. wt., 238. $C_{16}H_{11}FO$ requires: C, 80·7; H, 4·25; F, 8·0%, mol. wt., 238.)

IR spectrum had a medium band at 1,637 cm^{-1} characteristic of $>$C=C$<$. There were no bands attributable to $>$C=O or OH.

An ethanolic solution of the furan showed an intense blue fluorescence in UV light. The UV spectrum had λ_{max} 274 mμ (ε, 21,800), 243 mμ (ε, 19,400), 223 mμ (ε, 15,120), 217 mμ (ε, 16,100) and λ_{min}257 mμ (ε, 16,700), 229 mμ (ε, 12,320), 221 mμ (ε, 14,980), 215 mμ (ε, 15,900). This is characteristic of a highly conjugated system; λ_{max} 274 mμ (ε, 21,800) should be compared with λ_{max} 276 mμ (ε, 21,800) for 2,4-diphenylfuran.[10]

NMR spectrum has bands with chemical shifts relative to chloroform of −2·65, −2·55, −2·25, −2·05 and −1·95 ppm. These bands correspond to H atoms in an aromatic ring.

3-Fluoro-2,4-diphenylfuran (3 mg) was dissolved in conc. H_2SO_4 and gave a yellow solution with pale blue fluorescence. In UV light the fluorescence was intensified (cf. 2,4-diphenylfuran which gives a similar fluorescence). The UV spectrum had λ_{max} 420 mμ (ε, 61,000), 315 mμ (ε, 8,330), 310 mμ (ε, 8,330), 241 mμ (ε, 2,590), and λ_{min} 335 mμ (ε, 4,150), 303 mμ (ε, 8,300), 267 mμ (ε, 339), 235 mμ (ε, 2,500).

5-*Bromo*-3-*fluoro*-2,4-*diphenylfuran* (VI). 3-Fluoro-2,4-diphenylfuran (0·2 g) was dissolved in $CHCl_3$ (3 ml) and ice-cooled. Bromine (0·15 g) in $CHCl_3$ (1·5 ml) was added drop by drop. The Br_2 was immediately decolourized and HBr was evolved. When a faint permanent colour of Br_2 persisted, diethylamine (1 g) was added to remove HBr. After distilling off the $CHCl_3$, the resultant 5-*bromo*-3-*fluoro*-2,4-*diphenylfuran* was washed with water and recrystallized from MeOH, yield 0·2 g, m.p. 64°. (Found: C, 60·9; H, 3·9. $C_{16}H_{10}BrFO$ requires: C, 60·6; H, 3·2%.)

The IR spectrum showed a band of medium intensity at 1,645 cm^{-1} characteristic of a C=C bond.

An ethanolic solution gave an intense fluorescence in UV light. The UV spectrum had λ_{max} 292 mμ (ε, 25,000), 240 mμ (ε, 20,700), 218 mμ (ε, 19,000), and λ_{min} 256 mμ (ε, 15,600), 230 mμ (ε, 15,950), 213 mμ (ε, 18,000). The spectrum is similar to that for V, but is shifted to longer wavelengths.

The bromofluorofuran (3 mg) dissolved in conc. H_2SO_4 (3 ml) gave a yellow solution which did not fluoresce in daylight nor in UV light. On standing, the solution became green with a pale green fluorescence in UV light. The UV spectrum in conc. H_2SO_4 had λ_{max} 565 mμ (ε, 1,043), 423 mμ (ε, 30,500), 340 mμ (ε, 9,360), and λ_{min} 525 mμ (ε, 895), 368 mμ (ε, 6,970), 280 mμ (ε, 1,350).

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[10] H. H. Szmont and C. M. Alfonso, *J. Amer. Chem. Soc.* **78**, 1064 (1956).