304. *Organic Fluorine Compounds. Part VI.* The Enolates of Alkyl Fluoroacetates.*

By Ernst D. Bergmann and S. Szinai.

Treatment of ethyl fluoroacetate with sodium alkoxide or hydride gave an enolate which could be alkylated with benzyl bromide, *p*-bromobenzyl bromide, ethyl bromoacetate, and allyl bromide. Fluorosuccinic acid is too alkali-sensitive to be accessible by alkaline hydrolysis of its alkyl esters. The reaction with allyl bromide gave a saturated product, believed to be ethyl 1-fluoro*cyclo*butane-1-carboxylate.

Enolates of the esters of aliphatic acids are generally not stable; they are quickly transformed into the corresponding acetoacetates and are, therefore, not alkylated by alkyl halides or similar reagents. Analogously, when in certain Michael reactions products of the type $(RO_2C)_2CH{\cdot}CH_2{\cdot}CH{:}C(ONa){\cdot}OR'$ are formed, the course of their methylation is explained by the assumption that they rearrange to $RO{\cdot}C(ONa){:}C(CO_2R){\cdot}CH_2{\cdot}CH_2{\cdot}CO_2R$.[1,2] Even if, perhaps for steric reasons, stable enolates are formed, as, *e.g.*, from diethyl 3-methylbutane-2 : 3-dicarboxylate and triphenylmethylsodium, they do not appear to be very reactive.[3] Phenylacetates, on the other hand, give enolates which are both relatively stable and sufficiently responsive to alkylating agents.[4-10] The enolate of diphenylacetic acid has been isolated in crystalline form by Schlenk, Hillemann, and Rodloff,[11] and its alkylation reactions have been studied.[12,13] It appeared possible that negative substituents other than phenyl would have an analogous effect. Indeed, it has been found that ethyl fluoroacetate, when treated with sodium alkoxide or sodium hydride, gives an enolate which forms ethyl $\alpha\gamma$-difluoroacetoacetate sufficiently slowly to permit alkylation with reactive alkyl halides, such as benzyl or allyl bromide and ethyl bromoacetate. Normal alkyl halides fail to give significant amounts of alkylated fluoroacetates.

Benzyl bromide gave ethyl α-fluoro-β-phenylpropionic acid in 27 and 20% yield, respectively, when alcoholic sodium ethoxide or sodium hydride in ether was employed for the preparation of the enolate. Analysis and molecular refraction supported the formula of the ester, which could be converted into the corresponding acid and its amide without loss of the fluorine atom. Analogously, *p*-bromobenzyl bromide and sodium ethoxide led to a 20% yield of ethyl β-*p*-bromophenyl-2-fluoropropionate, from which the free acid and the amide have been prepared.

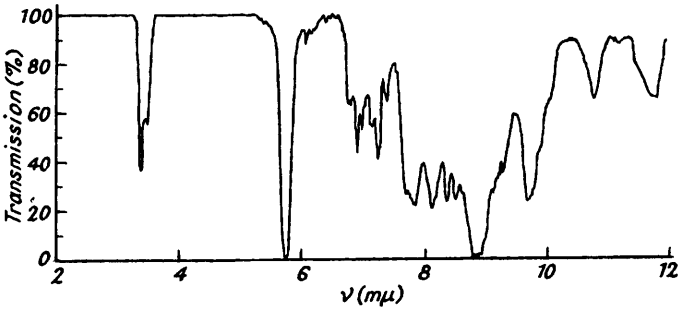
With ethyl bromoacetate, a 25·5% yield of diethyl fluorosuccinate was obtained which, however, lost fluorine even under mild conditions of alkaline hydrolysis. Also with aqueous ammonia only fumaramide was obtained. In an attempt to circumvent the alkaline hydrolysis of the fluorosuccinate, dibenzyl fluorosuccinate was prepared from the

* Part V, preceding paper.

[1] Thorpe, *J.*, 1900, **77**, 923.
[2] Ingold and Powell, *J.*, 1921, **119**, 1976.
[3] Talakdar and Bagchi, *J. Org. Chem.*, 1955, **20**, 13.
[4] Ramart and Haller, *Compt. rend.*, 1924, **178**, 1583.
[5] Scheibler, Marhenkel, and Bassanoff, *Ber.*, 1925, **58**, 1198.
[6] Snell and McElvain, *J. Amer. Chem. Soc.*, 1931, **53**, 750.
[7] Mueller, Gawlick, and Kreutzmann, *Annalen*, 1935, **515**, 97.
[8] Roberts and McElvain, *J. Amer. Chem. Soc.*, 1937, **59**, 2007.
[9] Hauser, *ibid.*, 1938, **60**, 1957.
[10] Hauser and Hudson, *ibid.*, 1940, **62**, 62.
[11] Schlenk, Hillemann, and Rodloff, *Annalen*, 1931, **487**, 135.
[12] Staudinger and Meyer, *Helv. Chim. Acta*, 1922, **5**, 656.
[13] Ramart, *Compt. rend.*, 1924, **178**, 93, 396; *Bull. Soc. chim., France*, 1924, **35**, 196

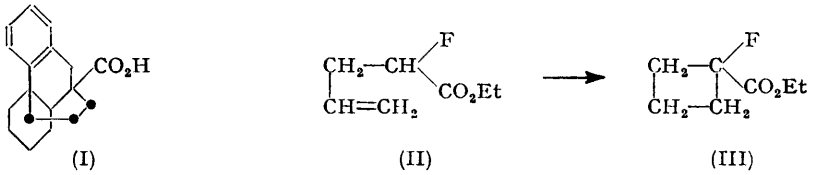
enolate of benzyl fluoroacetate and benzyl bromoacetate. The ester decomposed partly even upon distillation under 1·25 mm. pressure; upon hydrogenolysis, only fumaric acid could be isolated. A similar instability has been noted for αβ-difluorosuccinic acid which in contact with water gives acetylenedicarboxylic acid.[14]

The product isolated in 45% yield from allyl bromide, and the amide prepared from it, gave the correct analytical results for the expected ethyl 2-fluoropent-4-enoate and the derived amide; however, the ester was saturated towards bromine and catalytically activated hydrogen, and did not show the characteristic [15] infrared band for mono-substituted ethylenes at 1643 cm.$^{-1}$ (see Fig.). Also the C–H stretching frequencies in the 3010—3040 and 3075—3095 cm.$^{-1}$ regions and the C–H out-of-plane deformation frequency at 985—995 cm.$^{-1}$ were absent. As Grewe [16] has observed that 4*a*-allyl-



Infrared spectrum of ethyl 1*-fluoro-*cyclo*butane-*1*-carboxylate (in carbon tetrachloride solution).*

1 : 2 : 3 : 4 : 9 : 10 : 4*a* : 10*a*-octahydrophenanthrene-10-carboxylic acid isomerizes spontaneously to the compound (I), it is assumed that ethyl 2-fluoropent-4-enoate (II) isomerizes [17] spontaneously to ethyl 1-fluoro*cyclo*butane-1-carboxylate (III). The infrared



(I) (II) (III)

spectrum shows, indeed, a band at 927 cm.$^{-1}$, where a band typical of the *cyclo*butane ring is said to occur.[18] The C–F band at 1030 cm.$^{-1}$ has also been found; the ester-carbonyl frequency is situated at 1740 cm.$^{-1}$, whilst for ethyl fluoroacetate McBee and Christman [19] report a frequency of 1778 cm.$^{-1}$.

Analogous attempts to prepare and utilize the enolate of *tert.*-butyl instead of ethyl fluoroacetate failed. This enolate is formed only at high temperatures, at which the conversion into *tert.*-butyl αγ-difluoroacetoacetate is too rapid.

A convenient synthesis of *tert.*-butyl fluoroacetate from *iso*butene and fluoroacetic acid in the presence of concentrated sulphuric acid or boron trifluoride–ether complex is described.

Experimental

Ethyl α-Fluoro-β-phenylpropionate.—(*a*) A solution of ethyl fluoroacetate (53 g., 0·5 mole) in anhydrous alcohol (100 ml.) was added dropwise (30 min.) to a solution of sodium ethoxide [from sodium (11·5 g.) and anhydrous alcohol (200 ml.)]. After 1 hr. at room temperature, freshly distilled benzyl bromide (94 g., 0·55 mole) was added slowly (1 hr.) at 20° with vigorous agitation. The mixture was kept for 12 hr., filtered, and distilled through a short Vigreux

[14] Kharasch, U.S.P. 2,426,224; *Chem. Abs.*, 1948, **42**, 213.
[15] Sheppard and Simpson, *Quart. Reviews*, 1952, **6**, 1.
[16] Grewe, *Ber.*, 1943, **76**, 1076.
[17] Vejdelek and Kakac, *Chem. Abs.*, 1955, **49**, 9565.
[18] Bellamy, "The Infra-red Spectra of Complex Molecules," pp. 28—29, Wiley, London and New York, 1954.
[19] McBee and Christman, *J. Amer. Chem. Soc.*, 1955, **77**, 755.

column, the fraction of b. p. 95—145°/20 mm. being collected. Fractionation of this distillate gave benzyl ethyl ether, b. p. 129—130°/20 mm. (50 g.), and *ethyl α-fluoro-β-phenylpropionate* (26 g., 27%), b. p. 136—137·5°/20 mm., $d_0^{14\cdot5}$ 1·1211, $n_D^{14\cdot5}$ 1·4890, $[R]_M$ 50·51 (Calc.: 50·75) (Found: C, 67·2; H, 6·8; F, 9·4. $C_{11}H_{13}O_2F$ requires C, 67·4; H, 6·7; F, 9·7%).

(*b*) Sodium hydride (12 g., 0·5 mole) was suspended under nitrogen in anhydrous ether (200 ml.), and at 0°, a solution of ethyl fluoroacetate (53 g., 0·5 mole) in ether (200 ml.) was added during 4 hr. (If evolution of hydrogen does not set in within 10 min., reaction is initiated by addition of two drops of anhydrous alcohol.) Stirring was continued for 4 hr. more, and anhydrous alcohol (50 ml.) and a solution of benzyl bromide (94 g.) in anhydrous ether (200 ml.) were added successively. After 21 hr. the mixture was poured into the theoretical quantity of 20% sulphuric acid, the organic layer separated, and the aqueous phase extracted twice with ether. The combined ethereal solutions were washed with 10% sodium hydrogen carbonate solution, dried, and distilled; the product (20 g., 20%) had b. p. 136—137·5°/20 mm.

α-Fluoro-β-phenylpropionic Acid.—The preceding ester (6·8 g.) was added to a solution of potassium hydroxide (2·8 g.) in anhydrous alcohol (20 ml.), and after 30 min., the precipitate was filtered off, washed with alcohol and ether (weight, 6·5 g.), and dissolved in water, and the solution acidified with hydrochloric acid and extracted with ether. Distillation (b. p. 103°/0·3 mm.; 155°/10 mm.) or recrystallisation from low-boiling light petroleum gave the pure *acid* (5·2 g., 90%), m. p. 73·2° (Found: C, 64·5; H, 5·7; F, 11·1. $C_9H_9O_2F$ requires C, 64·3; H, 5·4; F, 11·4%).

α-Fluoro-β-phenylpropionamide.—A mixture of the ethyl ester (2·0 g.) and concentrated aqueous ammonia (20 ml.) was stirred at 50—60° until homogeneous. On cooling, the *amide* crystallized. It was recrystallized twice from water and melted at 134° (yield, 1·0 g., 60%) (Found: C, 64·9; H, 6·3; F, 11·2. $C_9H_{10}ONF$ requires C, 64·7; H, 6·0; F, 11·4%).

Analogously, the following compounds were prepared from *p*-bromobenzyl bromide.[20] *Ethyl* β-p-*bromophenyl-α-fluoropropionate*, b. p. 102°/0·3 mm. (yield, 20%) d_4^{15} 1·4280, n_D^{15} 1·5230, $[R]_M$ 58·83 (Calc.: 58·71) (Found: C, 47·8; H, 4·8; Br, 28·8; F, 6·8. $C_{11}H_{12}O_2BrF$ requires C, 48·0; H, 4·4; Br, 29·1; F, 6·9%). β-p-*Bromophenyl-α-fluoropropionic acid*, from benzene, m. p. 159°, yield 83% (Found: C, 43·5; H, 3·2; Br, 32·6; F, 7·8. $C_9H_8O_2BrF$ requires C, 43·8; H, 3·3; Br, 32·4; F, 7·7%). β-p-*Bromophenyl-α-fluoropropionamide* (from water), m. p. 167°; yield, 52% (Found: C, 43·6; H, 3·4; N, 6·1; F, 7·8. C_9H_9ONBrF requires C, 43·9; H, 3·7; N, 5·7; F, 7·7%).

Diethyl Fluorosuccinate.—The enolate of ethyl fluoroacetate was prepared from sodium ethoxide as described above, and ethyl bromoacetate (91·8 g.; 0·5 mole) was added. Diethyl fluorosuccinate forms a liquid, b. p. 70—71°/0·8 mm., which could not be obtained pure; yield 24·5 g. (25·5%); n_D^{23} 1·4240, d_4^{23} 1·1090, $[R]_M$ 44·23 (Calc.: 42·34) (Found: C, 48·5; H, 6·5. Calc. for $C_8H_{13}O_4F$: C, 50·0; H, 6·7%). With sodium hydride as enolizing agent, a yield of 8 g. (8%), b. p. 68—72°/0·5 mm., was obtained.

Fumardiamide.—When diethyl fluorosuccinate was heated with aqueous ammonia at 50° for 0·5 hr., a crystalline product of m. p. 265—268° (decomp.) was obtained. By analysis and comparison with an authentic specimen [21] it was shown to be fumardiamide (Found: C, 42·2; H, 5·7; N, 25·6. Calc. for $C_4H_6O_2N_2$: C, 42·1; H, 5·3; N, 24·5%).

Benzyl Fluoroacetate.—A mixture of ethyl fluoroacetate (106 g.), benzyl alcohol (108 g.), and toluene-*p*-sulphonic acid (2 g.) was heated under a Fenske column, so that the ethanol formed distilled off continuously. After the desired amount of alcohol had been removed and the mixture cooled to room temperature, it was washed with 10% sodium carbonate solution and water and dried; the product (129 g.; 78%) had b. p. 137—141°/22 mm.

Benzyl Bromoacetate.—The same method was employed, but toluene (140 g. per mole) was added, in order to facilitate removal of the alcohol as azeotrope (90 ml.); the product (yield, 85%) had b. p. 166—170°/22 mm.

Dibenzyl Fluorosuccinate.—An ethereal solution of benzyl fluoroacetate (16·8 g.) was added dropwise to sodium hydride (2·4 g.) in refluxing ether. The mixture was stirred for 1 hr. at reflux temperature, and benzyl bromoacetate (22·9 g.) added dropwise. After 12 hr., the mixture was poured into ice-water, containing sulphuric acid (50 g.). After being repeatedly washed with 10% sodium carbonate solution and water and dried, the product was distilled at 1·25 mm. The distillation was accompanied by decomposition, and the last two fractions were strongly coloured. The last fraction, b. p. 160—190°/1·25 mm. (8 g.) after having been

[20] Weizmann and Patai, *ibid.*, 1946, **68**, 150.
[21] Hell and Poliakoff, *Ber.*, 1892, **25**, 640.

decolorised with Norite and redistilled (b. p. 165—170°/1 mm.), gave analytical results indicating that it consisted of impure dibenzyl fluorosuccinate.

Ethyl 1-*Fluoro*cyclo*butane*-1-*carboxylate*.—From ethyl fluoroacetate (55 g.) and sodium ethoxide (11·5 g. of sodium) the enolate was prepared as above; it was treated with freshly distilled allyl bromide (66·5 g., 0·55 mole). Working-up gave the desired *ester* (III) (33 g., 45%), b. p. 75—76°/35 mm., $d_4^{14\cdot5}$ 1·0062, $n_D^{14\cdot5}$ 1·4090 (Found : C, 57·5; H, 7·8; F, 13·0. $C_7H_{11}O_2F$ requires C, 57·5; H, 7·6; F, 13·0%). When an attempt was made to hydrogenate this ester (544 mg.) in 96% alcohol (13 ml.) at 29°, using platinum oxide as catalyst, only 0·8 ml. of hydrogen was absorbed.

1-*Fluoro*cyclo*butane*-1-*carboxyamide*.—A mixture of the foregoing ester (1·5 g.) and concentrated aqueous ammonia (10 ml.) was stirred at 80—90° until dissolution was complete. After 12 hr. at room temperature, the solution was repeatedly extracted with ether, and the ether residue recrystallized from low-boiling light petroleum; the product (0·85 g., 73%) had m. p. 70—71° (Found : C, 51·3; H, 7·2; N, 11·9; F, 16·0. C_5H_8ONF requires C, 51·3; H, 6·9; N, 12·0; F, 16·2%). In contradistinction with the ethyl ester, the *amide* slowly absorbed hydrogen, activated by platinum oxide. However, no stoicheiometric quantities of hydrogen were consumed even after 2·5 hr. (total absorption : 0·283 mole).

tert.-*Butyl Fluoroacetate*.—A mixture of fluoroacetic acid (78 g., 1 mole), *iso*butene (112 g., 2 mole), and concentrated sulphuric acid (3 ml.) or boron trifluoride–ether complex (3 ml.) was shaken for 2 hr. at room temperature. The slightly exothermic reaction was kept under control by immersing the bottle in ice-water from time to time. After 12 hr. at room temperature, the product was cooled to −15° and poured into a mixture of sodium hydroxide (70 g.), water (250 ml.), and ice (250 g.). The aqueous layer was extracted with ether, and the organic layer, combined with the extract, washed with 2N-sodium hydroxide solution and water, dried, and distilled twice; the ester (75%) had b. p. 42°/20 mm.

Analogously, *tert.*-butyl chloro- and bromo-acetate and ethyl *tert.*-butyl malonate can be prepared in good yield. As far as the use of concentrated sulphuric acid is concerned, the method is an adaptation of that of Fonken and Johnson [22] and of Johnson, McCloskay, and Dunnigan.[23]

The carbon and hydrogen determinations were carried out according to Bodenheimer and Goldstein,[24] the fluorine determinations according to Eger and Yarden.[25]

SCIENTIFIC DEPARTMENT, MINISTRY OF DEFENCE,
TEL-AVIV, ISRAEL. [*Received, October 24th*, 1955.]

[22] Fonken and Johnson, *J. Amer. Chem. Soc.*, 1952, **74**, 831.
[23] Johnson, McCloskay, and Dunnigan, *ibid.*, 1950, **72**, 514.
[24] Bodenheimer and Goldstein, *Bull. Res. Council Israel*, 1953, **3**, 53.
[25] Eger and Yarden, *ibid.*, 1954, **4**, 305; *Analyt. Chem.*, 1956, **28**, in the press.