667. *Organic Fluorine Compounds. Part XII.* Preparation and Reactions of Diethyl Fluoromalonate.*

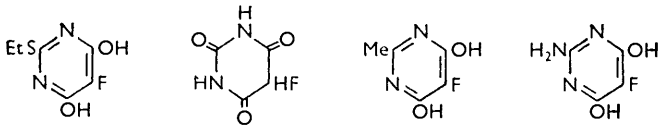
By Ernst D. Bergmann, Sasson Cohen, and Israel Shahak.

The exchange reaction of diethyl bromomalonate with potassium fluoride gives only diethyl difluoromalonate, but diethyl fluoromalonate has been prepared by pyrolysis of diethyl oxalofluoroacetate and by reaction of diethyl sodio-fluoroacetate with ethyl chloroformate. Some reactions of diethyl fluoromalonate have been investigated.

The variety of syntheses possible with diethyl malonate and the biochemical properties of malonic acid made fluoromalonic acid an attractive compound. LaZerte and his co-workers [1] have described an 8-stage synthesis of this acid from trifluorochloroethylene, but a more convenient route appeared to be by reaction of diethyl bromomalonate with potassium fluoride at 180—190°.[2] When this reaction was repeated or carried out in acetamide as solvent,[3] a fairly constant-boiling product was obtained which had the expected carbon and hydrogen content, but contained only half the expected amount of the fluorine; it was a mixture of 3 parts of diethyl malonate and 1 part of diethyl difluoromalonate. The latter was obtained pure by brominating the mixture and separating diethyl difluoromalonate by distillation from the bromination products of the malonate. Also the amides prepared from the mixture could be separated by fractional recrystallisation from water. Difluoromalondiamide had the melting point indicated in the literature [4] for a product obtained by a different route. It seemed possible that the monofluoromalonate first formed might undergo the reaction, $CHF(CO_2Et)_2 + CHBr(CO_2Et)_2 \longrightarrow CH_2(CO_2Et)_2 + CFBr(CO_2Et)_2$, the bromofluoro-ester then undergoing further halogen exchange, but this should lead to a 1 : 1 mixture, so the reaction is clearly more complex.

Diethyl monofluoromalonate was obtained by (*a*) pyrolysis of diethyl oxalofluoroacetate at 210—220° (34% yield), analogously to the formation of diethyl methylmalonate from diethyl oxalopropionate,[5] and (*b*) by reaction of ethyl sodiofluoroacetate, which is fairly stable,[6] with ethyl chloroformate (20—25% yield). A higher-boiling fraction $C_9H_{12}O_5F_2$, obtained in the latter reaction, was diethyl α-fluoro-α-fluoroacetylmalonate, $CH_2F{\cdot}CO{\cdot}CF(CO_2Et)_2$. Hydrolysis and ammonolysis were accompanied by "acid fission" and led to fluoromalonic acid and fluoromalondiamide, respectively. It is assumed that part of the enol of ethyl fluoroacetate is converted into the enol of ethyl αγ-difluoroacetoacetate and only then reacts with ethyl chloroformate (see preceding paper).

In an attempt to prepare 5-fluorobarbituric acid (II), diethyl fluoromalonate was condensed with *S*-ethylisothiouronium bromide in the presence of sodium methoxide.



(I) (II) (III) (IV)

The 2-ethylthio-5-fluoro-4,6-dihydroxypyrimidine (I) obtained gave, with the usual reagents (aqueous hydrochloric, hydrobromic, or chloroacetic acid) only a water-soluble

* Part XI, preceding paper.

[1] LaZerte, Rausch, Koshar, Park, Pearlson, and Lacher, *J. Amer. Chem. Soc.*, 1956, **78**, 5639.
[2] Gryszkiewicz-Trochimowski, Sporzynski, and Wnuk, *Rec. Trav. chim.*, 1947, **66**, 413.
[3] Bergmann and Blank, *J.*, 1953, 3786.
[4] Henne and deWitt, *J. Amer. Chem. Soc.*, 1948, **70**, 1548.
[5] Cox and McElvain, *Org. Synth.*, 1943, Coll. Vol. II, p. 279.
[6] Bergmann and Szinai, *J.*, 1956, 1521; Bergmann, Cohen, and Shahak, preceding paper.

liquid from which no trace of the barbituric acid could be isolated. Similar behaviour of 5-chlorobarbituric acid towards hydrobromic acid has been reported, though 5-bromobarbituric acid is claimed to be stable towards hydrochloric acid.[7] The barbituric acid could also not be obtained from fluoroacetylurea and oxalyl bromide, but it was prepared, in 16% yield, from ethyl fluoromalonate and urea in presence of sodium methoxide. 5-Fluoroalkylbarbituric acids have been described by Bruce and Huber [8] and by O'Neill and Pattison.[9]

Condensation of diethyl fluoromalonate with acetamidine gave 5-fluoro-4,6-dihydroxy-2-methylpyrimidine (III) and with guanidine gave 2-amino-5-fluoro-4,6-dihydroxypyrimidine (IV).

Experimental

Diethyl Difluoromalonate.[10]—Diethyl bromomalonate (300 g.), acetamide (100 g.) and potassium fluoride (113 g.) were heated at 160—170° under reflux with stirring for 1·5 hr., then distilled *in vacuo* to dryness. The distillate was washed repeatedly with water (to remove acetamide), dried (Na_2SO_4), and fractionated. Two fractions were obtained: (*a*) 90 g., b. p. 100—105°/23 mm., (*b*) 20 g., b. p. 110—140°/23 mm., mainly unchanged bromomalonate. Fraction (*a*) contained about 5% of fluorine, equiv. to about 16% of diethyl difluoromalonate. Fraction (*a*) (60 g.) in carbon tetrachloride (60 ml.) was heated with bromine (62 g.) as in the preparation of diethyl bromomalonate.[11] Distillation of the product yielded *diethyl difluoromalonate* (14 g.), b. p. 94—95°/23 mm., $\nu_{max.}$ (liquid film) 3000s, 1750vs, 1450s, 1310vs, 1220—1300vs,br, 1063vs, 1010vs, 840, 862s, 780 cm.$^{-1}$ (Found: F, 19·4. $C_7H_{10}O_4F_2$ requires F, 19·4%).

Difluoromalondiamide.—Diethyl difluoromalonate (5 g.) was treated with excess of concentrated aqueous ammonia, with occasional shaking, and the mixture kept overnight at 0°. The precipitated difluoromalondiamide (2 g., 57%), when washed with water and recrystallized from water, had m. p. 205—206° (lit., 206—207° [4], 200—201° [9]) $\nu_{max.}$ (KBr pellet) 3400, 3200, 1695 (all vs), 1620s, 1390s, 1290, 1130s, 1075s, 695 cm.$^{-1}$ (Found: C, 26·5; H, 3·2; N, 20·7. Calc. for $C_3H_4O_2N_2F_2$: C, 26·1; H, 2·9; N, 20·3%). When 20 g. of fraction (*a*) were treated with an excess of concentrated aqueous ammonia as above, a small amount of difluoromalondiamide, m. p. 205—206°, was obtained. The combined mother-liquors were evaporated to dryness and the residue was recrystallised from ethanol, to yield malonamide (3·5 g.), m. p. and mixed m. p. 169—171°.

Diethyl Fluoromalonate.—(*a*) Diethyl oxalofluoroacetate [12] (31 g.), with a few porcelain chips, was refluxed at 210—220° for 12 hr., then fractionated under reduced pressure. *Diethyl fluoromalonate* (9 g., 34%) had b. p. 121—122°/30 mm., n_D^{27} 1·4040 (Found: C, 47·2; H, 6·1; F, 11·2. $C_7H_{11}O_4F$ requires C, 47·2; H, 6·2; F, 10·7%), $\nu_{max.}$ (liquid) 3000, 1780, 1750 (all vs), 1474, 1455, 1380s, 1340vs, and 1280vs (C–F), 1170vs, 1070vs, 1090, 1040, 860, 790 cm.$^{-1}$.

(*b*) To a suspension of sodium methoxide (8·1 g.) in light petroleum (b. p. 50—70°; 100 ml.), ethyl fluoroacetate (15·9 g.) was added at 15—25° in small portions and with vigorous shaking (not stirring). After further 10 minutes' shaking, the sodio-derivative formed voluminous, yellow crystals. The mass was cooled at −10° and ethyl chloroformate (16·3 g.) in light petroleum (30 ml.) added as quickly as possible, but so that the temperature did not rise above 25°. The mixture was shaken for 1 hr. at room temperature, refluxed for 10 min. and decomposed with water (100 ml.). The organic layer was washed with 1% sodium hydrogen carbonate solution, dried ($MgSO_4$), and distilled through a short column, first at atmospheric pressure, then under 30 mm. The fraction boiling at 100—130°/30 mm. was redistilled under atmospheric pressure (204—205°) and had b. p. 121°/30 mm. (5·5—6·5 g., 20—25%) (Found: C, 47·8; H, 6·1; F, 10·8. Calc. for $C_7H_{11}O_4F$: C, 47·2; H, 6·2; F, 10·7%). A second fraction, b. p. 110—111°/2 mm. (2·4 g., 15%), was *diethyl α-fluoro-α-fluoroacetylmalonate* (Found: C, 46·0; H, 4·2; F, 16·2. $C_9H_{12}O_5F_2$ requires C, 45·4; H, 5·0; F, 16·0%).

(*c*) To the enol, prepared from ethyl fluoroacetate (53 g.) and sodium hydride (12 g.) in

[7] Biltz and Wittek, *Ber.*, 1921, **54**, 1035; Bock, *Ber.*, 1922, **55**, 3400.
[8] Bruce and Huber, *J. Amer. Chem. Soc.*, 1953, **75**, 4668.
[9] O'Neill and Pattison, *ibid.*, 1957, **79**, 1956.
[10] Inman, Oesterling, and Tyczkowski, *J. Amer. Chem. Soc.*, 1958, **80**, 6533.
[11] Palmer and McWherter, *Org. Synth.*, 1942, Coll. Vol. I, p. 245.
[12] Blank, Mager, and Bergmann, *J.*, 1955, 2190.

anhydrous ether (200 ml.), ethyl chloroformate (54·5 g.) in ether (50 ml.) was added at 0° with stirring during 15 min. The mixture was refluxed for 4 hr. and cold water added after 12 hr. The ethereal solution was dried and distilled. The diethyl fluoromalonate (19 g., 21%) was obtained, having b. p. 75—80°/4—5 mm., n_D^{28} 1·4032 (Found: C, 47·5; H, 6·2; F, 10·7%). Another fraction (8 g.) boiled at 110—111°/2 mm. after two distillations, and had n_D^{28} 1·4180. It was mainly ethyl α-fluoro-α-fluoroacetylmalonate, but contained a second substance poorer in fluorine, probably triethyl fluoromethanetricarboxylate; on hydrolysis with a slight excess of alcoholic potassium hydroxide at room temperature it gave crystalline dipotassium fluoromalonate. Treatment of an aqueous solution of this salt with 1 mol. of hydrochloric acid gave hydrated potassium hydrogen fluoromalonate, which, after recrystallisation from water, lost water when heated at 120—130° and decomposed at 180°, and on treatment with an excess of acid, followed by thorough extraction with ether, afforded fluoromalonic acid, m. p. 135—136° (lit.,[1] 135·8—136·5°). With concentrated aqueous ammonia, the higher-boiling fraction gave a product, m. p. 199° (from water), identified as *fluoromalondiamide*, by mixed m. p. (cf. below) and the *X*-ray powder diagram (Found: C, 30·2; H, 3·9; F, 15·9. $C_3H_5O_2N_2F$ requires C, 30·0; H, 4·2; F, 16·0%).

The formation of triethyl fluoromethanetricarboxylate was avoided and pure diethyl α-fluoro-α-fluoroacetylmalonate obtained when ethyl sodiofluoroacetate in ethereal suspension was *added to* the ethyl chloroformate.

Fluoromalondiamide, prepared by treating the pure ester with excess of aqueous concentrated ammonia, as described above, had m. p. 198—199° (from water), $\nu_{max.}$ (potassium bromide pellet) 3400, 3200, 1700 (all vs), 1450s, 1420vs, 1320s, 1115vs, 1075vs, 815, 795, 700s,br cm.$^{-1}$ (Found: C, 30·3; H, 4·2; N, 23·3; F, 15·8. Calc. for $C_3H_5O_2N_2F$: C, 30·0; H, 4·2; N, 23·3; F, 16·0%).

2-*Ethylthio*-5-*fluoro*-4,6-*dihydroxypyrimidine* (I).—A mixture of ethyl fluoromalonate (12 g.), *S*-ethylisothiouronium bromide (12·5 g.) and 2M-sodium methoxide (68 ml.) was kept at 28—30° for 4 days. The methanol was distilled off *in vacuo* and the residue dissolved in a little water and acidified with hydrochloric acid. Recrystallisation from aqueous alcohol gave the *product* (12 g., 95%), m. p. 215—220° (decomp.) (Found: C, 38·1; H, 4·1. $C_6H_7O_2N_2FS$ requires C, 37·9; H, 3·7%).

Fluoroacetylurea.[13]—Fluoroacetyl bromide [2] (40 g.), urea (17 g.), benzene (100 ml.), and concentrated sulphuric acid (1 drop) were refluxed with vigorous stirring for 12 hr. The solid (22 g., 65%) was filtered off, washed with benzene, digested with cold water, and collected. Crystallised from dimethylformamide, it had m. p. 216—218° (Found: C, 30·3; H, 4·3. $C_3H_5O_2N_2F$ requires C, 30·0; H, 4·2%).

With oxalyl bromide a solid product was obtained which, however, did not give 5-fluorobarbituric acid when heated in boiling tetrahydronaphthalene.

5-*Fluorobarbituric Acid* (II).—Urea (3 g.), ethyl fluoromalonate (9 g.), and M-sodium methoxide (50 ml.) were refluxed for 5 hr., then kept for 12 hr. A solid precipitate was filtered off, dissolved in a little water, and acidified with hydrochloric acid. 5-*Fluorobarbituric acid* crystallised and, recrystallised from glacial acetic acid, had m. p. >260° (decomp.) (1 g., 16%) (Found: C, 32·9; H, 2·1; F, 13·0. $C_4H_3O_3N_2F$ requires C, 32·9; H, 2·1; F, 13·0%).

5-*Fluoro*-4,6-*dihydroxy*-2-*methylpyrimidine* (III).—To a solution of acetamidine hydrochloride (2 g.) in 2M-methanolic sodium methoxide (20 ml.), diethyl fluoromalonate (3·5 g.) was added, and the mixture kept overnight. The solvent was removed under reduced pressure and the residue dissolved in a little water. On acidification with hydrochloric acid, the *product* (1·5 g., 53%) crystallised in fine prisms. It was purified by dissolution in dilute sodium hydroxide solution, treatment with charcoal, filtration, and acidification of the filtrate. It decomposed above 300° (Found: C, 41·5; H, 3·5; F, 12·4. $C_5H_5O_2N_2F$ requires C, 41·6; H, 3·5; F, 13·2%), and had $\lambda_{max.}$ (in ethanol) 262 mμ (log ε 3·96), $\nu_{max.}$ (in potassium bromide) 3410, 2800, 2700, 1680vs(CO), 1552, 1450, 1317, 1186, 1050 (C–F), 950, 780, 752 cm.$^{-1}$.

2-*Amino*-5-*fluoro*-4,6-*dihydroxypyrimidine* (IV).—Diethyl fluoromalonate (14 g.) and guanidine hydrochloride (7·5 g.) in 2M-sodium methoxide in methanol (80 c.c.) were kept at room temperature, with occasional shaking, for 48 hr., then evaporated under reduced pressure. The residue was taken up in water and acidified with hydrochloric acid. The precipitate was redissolved in sodium hydroxide solution, treated with charcoal until the filtrate was colourless,

[13] Cf. Stoughton, *J. Org. Chem.*, 1938, **2**, 514.

and precipitated with acid. After filtration and washing with water, alcohol and ether, the yield of *pyrimidine* was 5·5 g. (48%) (Found: C, 32·9; H, 3·0. $C_4H_4O_2N_3F$ requires C, 33·1; H, 2·8%).

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Department of Organic Chemistry, Hebrew University, Jerusalem.
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