666. *Organic Fluorine Compounds. Part XI.* Ethyl Fluoroacetoacetates and Fluoropyrimidines.*

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Ethyl bromo(or chloro)acetate condenses with ethyl fluoroacetate, and ethyl chlorofluoroacetate with ethyl acetate, in Reformatzky-type reactions to give ethyl γ- and α-fluoroacetoacetate, respectively. The enol from ethyl fluoroacetate condensed with acetyl chloride, benzoyl chloride, ethyl trifluoroacetate, and ethyl pentafluoropropionate to give the β-keto-esters. Fluoroacetone and acetic anhydride under catalysis by boron trifluoride give a β-diketone, probably 3-fluoropentane-2,4-dione.

By condensation of the available β-diketo-compounds with *S*-ethylisothiouronium bromide or urea, acetamidine, and guanidine several fluorine-containing pyrimidines have been prepared. Their ultraviolet and infrared spectra are discussed.

The purpose of the present study was to prepare fluoropyrimidines, which we expected to be antagonists of the corresponding hydrogen compounds. This expectation, which was based on the powerful antimetabolite properties of, *e.g.*, fluorophenylalanines and 5-fluorotryptophan, has meanwhile been borne out [1] to some extent for 5-fluorouracil, 5-fluoro-orotic acid, and 5-fluoroadenine.

First, fluorinated β-dicarbonyl compounds had to be made available. Several [2] are known, but their preparation is not always easy. Ethyl γ-fluoroacetoacetate, for example, has been prepared by Szinai [2] from fluoroacetyl chloride and ethyl dihydropyranyl malonate, and from ethyl t-butyl malonate (Fraser *et al.*[2]), but both methods are cumbersome, and the product requires lengthy purification.[3] It has now been found that ethyl γ-fluoroacetoacetate is easily accessible by reaction between ethyl bromoacetate (or better chloroacetate), ethyl fluoroacetate, and activated magnesium, though in $>40\%$ yield. The reaction has been extended to the preparation of ethyl α-methyl- and (not quite pure) α-ethyl-γ-fluoroacetoacetate from ethyl α-bromo-propionate and -butyrate, respectively. The analogous reaction between ethyl bromofluoroacetate (which has already been used for Reformatzky reactions with aldehydes and ketones [4]), zinc, and ethyl acetate to give ethyl α-fluoroacetoacetate was made impracticable by the difficulty of preparing the brominated ester and its instability.[5] However, the analogous ethyl chlorofluoroacetate, which is accessible both by chlorination of ethyl fluoroacetate [6] and by hydrolysis of the ethanol adduct of chlorotrifluoroethylene,[7] gives the same Reformatzky-type reaction as the bromo-analogue.[8] Thus, ethyl α-fluoroacetoacetate was obtained from ethyl chlorofluoroacetate, an excess of ethyl acetate, and activated magnesium in 20% yield. As a by-product, ethyl γ-chloro-αγ-difluoroacetoacetate was formed. The latter was the principal product, when ethereal ethyl chlorofluoroacetate was refluxed with activated magnesium. Acceptable yields of ethyl α-fluoroacetoacetate can also be obtained by the reaction between the enol of ethyl fluoroacetate (prepared with sodium

* Part X, 1959, 1418.

[1] Duschinsky, Pleven, and Heidelberger, *J. Amer. Chem. Soc.*, 1957, **79**, 4559; Heidelberger and Duschinsky, U.S.P. 2,802,005; Heidelberger, Chaudhuri, Danneberg, Mooren, Griesbach, Duschinsky, Schnitzer, Pleven, and Scheiner, *Nature*, 1957, **179**, 6653; Montgomery and Hewson, *J. Amer. Chem. Soc.*, 1957, **79**, 4559.

[2] McBee, Pierce, Kilbourne, and Wilson, *J. Amer. Chem. Soc.*, 1953, **75**, 3152; Szinai, Thesis, Jerusalem, 1955; Fraser and Pattison, *Nature*, 1955, **176**, 696; Desirant, *Bull. Sci. Acad. roy. belges*, 1928, **15**, 966; Henne, Newman, Quill, and Staniforth, *J. Amer. Chem. Soc.*, 1947, **69**, 1819.

[3] Fraser, Millington, and Pattison, *J. Amer. Chem. Soc.*, 1957, **79**, 1959.

[4] McBee, Pierce, and Christman, *ibid.*, 1955, **77**, 1581.

[5] Haszeldine, *J.*, 1952, 4259; Swarts, *Rec. Trav. chim.*, 1898, **17**, 238; cf. Szinai.[6]

[6] Bergmann, Moses, Neeman, Cohen, Kaluszyner, and Reuter, *J. Amer. Chem. Soc.*, 1957, **79**, 4174.

[7] Young and Tarrant, *ibid.*, 1948, **71**, 2432; Englund, *Org. Synth.*, 1954, **34**, 49.

[8] Cf. Shriner, *Organic Reactions*, 1942, Vol. 1, p. 1.

hydride [9]) and acetyl chloride or acetic anhydride. Analogously, benzoyl chloride afforded ethyl α-benzoyl-α-fluoroacetate which is usually accompanied by some ethyl αα-dibenzoyl α-fluoroacetate. Reactions of the sodio-enolate of sodium acetate have been described recently.[10] Incidentally, it was found that the enol of ethyl fluoroacetate can be prepared even more easily from the ester with sodium ethoxide in low-boiling light petroleum.

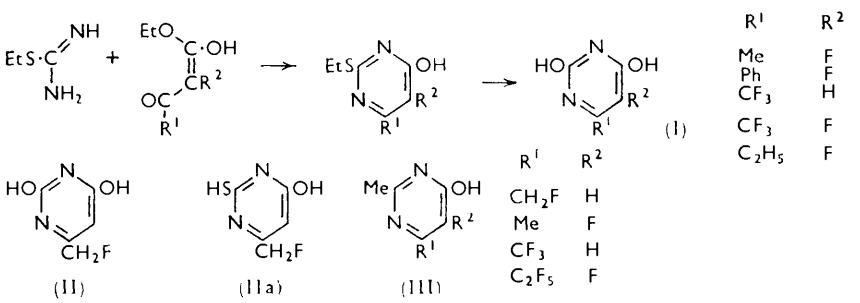
More highly fluorinated derivatives of ethyl acetoacetate can be obtained easily by reaction, catalyzed by sodium hydride, between ethyl fluoroacetate and ethyl trifluoroacetate or ethyl pentafluoropropionate.

Condensation of fluoroacetone and acetic anhydride in the presence of boron trifluoride gave an impure β-diketone, characterized as its copper chelate derivative. This is probably 3-fluoropentane-2 : 4-dione, the methylene group being favoured in such acylations,[11] but the position of the fluorine atom has not been rigidly established. An attempt to fluorinate 3-chloropentane-2 : 4-dione with potassium fluoride in ethylene glycol [12] gave only fluoroacetone, and this in low yield.

Pyrimidine Derivatives.—For the preparation of the pyrimidine derivatives, the condensation of the β-diketo-compounds with *S*-ethylisothiouronium bromide, in the presence of a basic catalyst, and subsequent hydrolysis with hydrochloric (in some cases, hydrobromic) acid [13] proved the best method. Thus were prepared the five compounds (I).

Ethyl γ-fluoroacetoacetate reacted with urea in the presence of hydrochloric acid [14] and gave 6-fluoromethyluracil (II), and with thiourea and sodium methoxide gave the mercaptopyrimidine (IIa), both in good yield.

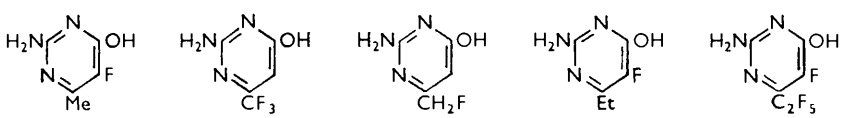
Acetamidine was condensed easily by Snyder and Foster's method [15] with ethyl γ- and α-fluoro- and γγγ-trifluoro-acetoacetate and αγγδδδ-hexafluoro-β-oxovalerate to give the pyrimidines (III).



	R¹	R²
(I)	Me	F
	Ph	F
	CF_3	H
	CF_3	F
	C_2H_5	F

	R¹	R²
(III)	CH_2F	H
	Me	F
	CF_3	H
	C_2F_5	F

Finally, guanidine carbonate in boiling water [16] with ethyl α-fluoro- and γγγ-trifluoroacetoacetate gave compounds (IV) and (V), respectively. Also, guanidine condensed with



ethyl γ-fluoroacetoacetate, α-fluoro-α-propionylacetate, and αγγδδδ-hexafluoro-β-oxovalerate in methanol, affording compounds (VI—VIII).

[9] Bergmann and Szinai, *J.*, 1956, 1521.
[10] DePree and Closson, *J. Amer. Chem. Soc.*, 1958, **80**, 2311.
[11] Hauser, Swamer, and Adams, *Organic Reactions*, 1954, Vol. 8, p. 98.
[12] Cf. Hoffmann, *J. Amer. Chem. Soc.*, 1948, **70**, 2596.
[13] Wheeler and Merriam, *Amer. Chem. J.*, 1903, **29**, 472; Johnson and Heyl, *ibid.*, 1907, **37**, 628.
[14] Cf. Donleavy and Kise, *Org. Synth.*, 1943, Coll. Vol. II, p. 422.
[15] Snyder and Foster, *J. Amer. Chem. Soc.*, 1954, **76**, 118.
[16] Wheeler and Johnson, *Amer. Chem. J.*, 1903, **29**, 496; Johnson and Clapp, *ibid.*, 1904, **32**, 130.

We have also condensed[17] urea and ethyl orthoformate with ethyl γ-fluoro- and γγγ-trifluoro-acetoacetate, obtaining the two α-ureidomethylene-compounds, but could not cyclize these products without some loss of fluorine.

Ultraviolet and infrared spectra of substituted 4-*hydroxypyrimidines* (*in alcoholic solution and* KBr *pellets, respectively*).

Substituents 2	5	6	$\lambda_{max.}$ (mμ) (log ε)	$\nu_{max.}$ (cm.$^{-1}$) *
OH	H	CH_2F	212 (3·90); 260 (3·92)	3200s, 3000s, 2890s, 1670s (CO), 1500m, 1430s, 1320m, 1245s, 1100, 1040 (C–F), 990, 900m, 795m, 765
OH	F	Me	268 (3·90)	3190s, 3050s, 2830s, 1667 (CO), 1500m, 1430s, 1320s, 1170, 1075s (C–F), 1020s (C–F), 885, 843s, 769m, 699m
OH	H	CF_3	262 (3·80)	3400, 3100s, 3000s, 2840s, 1730s and 1680s (CO), 1525m, 1440m, 1375s, 1280s (CF_3), 1215s (CF_3), 1170s (CF_3), 1110m, 995m, 900, 847m
OH	F	CF_3	223 (3·28); 272 (3·40); 310 (3·36)	3430, 3190s, 3050s, 2840s, 1680s (carbonyl), 1440, 1360s, 1290s (CF_3), 1182s (CF_3), 1045 (C–F), 925, 808m
OH	F	C_2F_5	212 (3·74); 272 (sh) (3·56)	3500, 3200m, 2850, 1680s (CO), 1430m, 1340m, 1285m, 1230m, 1170m, 1070m, 1030m, 990, 875, 800, 750
Me	H	CH_2F	224 (3·60); 273 (3·43)	3420, 3080s, 2860s, 2780s, 1680s (CO), 1620s, 1570m, 1448m, 1390m, 1350m, 1310, 1240, 1205m, 1080s (C–F), 995m, 955m, 920m, 886m, 860m, 765
Me	F	Me	226 (3·72); 270 (3·60)	3400, 3030, 2941, 2857m, 2778m, 1667s (CO), 1620s, 1450, 1389m, 1316m, 1205s, 1107, 1040 (C–F), 990, 952, 917m, 769m
Me	H	CF_3	219 (3·80); 280 (3·45)	2900s, 2800m, 1680s (CO), 1625m, 1600m, 1425m, 1320, 1290m, 1200s, 1120s, 1055, 1000, 963, 930, 895m, 772
Me	F	C_2F_5	221 (3·70); 280 (3·56)	3400, 3060m, 2950m, 2885m, 2880m, 1690s (CO), 1650m, 1388m, 1340m, 1316m, 1221s, 1175s, 1070m (C–F), 1030s (C–F), 935, 850, 781m, 735m, 690
Me	Me	CH_2F	220 (3·82); 272 (3·54)	
EtS	F	Me	237 (3·82); 290 (3·74)	3450, 2880m, 2810m, 2730m, 1660s (CO), 1610s, 1550s, 1460, 1410, 1380, 1360, 1270s, 1225s, 1170, 1130, 1090, 1065, 970m, 940m, 902m, 763m, 736m
EtS	F	CF_3	216 (3·90); 296 (3·61)	3400, 3080m, 3000m, 2900m, 2750m, 2650m, 1680s (CO), 1630m, 1560m, 1410s, 1270s, 1210s, 1190s, 1155s, 1063, 1010s, 970, 910, 875, 700m
EtS	F	C_2F_5	215 (4·01); 300 (3·54)	3500, 3000m, 2900m, 1680 (CO), 1610, 1550s, 1460, 1400m, 1340m, 1280s, 1220s, 1185s, 1160s, 1065s, 990s, 920, 838, 755, 725m, 690
EtS	F	Ph	208 (4·43); 250 (4·31); 306 (3·84)	3470, 3100m, 3000m, 2900m, 2800m, 2700m, 1670s (CO), 1600s, 1570s, 1500, 1450, 1420, 1385, 1320, 1270s, 1220, 1165, 1065, 1040, 1000m, 920m, 860, 760m, 740m, 690m, 680
NH_2	H	CF_3	223 (3·78); 295 (3·95)	3333s, 3200s, 2950, 1667s (CO), 1587s, 1495m, 1460s, 1360s, 1290s, 1205s, 1160s, 1040, 990s, 909, 833m, 800, 732m, 705m
NH_2	F	Me	220 (3·82); 292 (3·71)	3380s, 3140s, 3000s, 1667s (CO), 1630s, 1500s, 1450m, 1395m, 1370, 1260, 1240m, 1170, 1120, 1050, 1020m, 808m, 778m, 730, 665, 650m

* Bands not marked are of low strength.

Apart from certain fluorouracils (Duschinsky *et al.*[1]) and trifluoromethyl-,[18] fluorophenyl-, and fluorobenzyl-pyrimidines,[19] the compounds described here are the only known fluoro-derivatives of the pyrimidine series. [After completion of this study, two of the compounds prepared by us (I; $R^1 = CF_3$, $R^2 = H$) and (V) were described.[20]] Their toxicological and biochemical properties are being studied.

Spectra.—The ultraviolet spectra of pyrimidines have been studied by various authors;

[17] Whitehead, *J. Amer. Chem. Soc.*, 1952, **74**, 4267; 1953, **75**, 671.

[18] Miller, Dessert, and Anderson, *ibid.*, 1948, **70**, 500; Rutter and Gustafson, *J. Franklin Inst.*, 1954, **258**, 413.

[19] Curd and Rose, B.P. 581,347; Hitchings, Russell, and Falco, U.S.P. 2,594,309; Saijo, *J. Pharm. Soc. Japan*, 1952, **72**, 1444.

[20] Giner-Sorolla and Bendich, *J. Amer. Chem. Soc.*, 1958, **80**, 5744; see also Barone, Peters, and Tieckelmann, *J. Org. Chem.*, 1959, **24**, 198.

however, direct comparison with published data is difficult, because they have been determined in aqueous solutions of a given pH, whilst the present study is concerned with the neutral molecules (in alcohol). From the results summarized in the Table, we conclude that, whilst a 6-trifluoromethyl group has no appreciable effect on the spectrum of uracil, in which the chromophoric group is believed to be C:C·C:O, the addition of a 5-fluorine atom causes a significant bathochromic shift. The same is true for 4-hydroxy-2-methyl- and 2-ethylthio-4-hydroxy-pyrimidines.

Some infrared spectra of pyrimidine derivatives have also been reported.[21] Our observations (for the solid state) are summarized in the Table. In all compounds examined the carbonyl stretching frequency is very conspicuous, though Short and Thompson [21] did not find such a peak in the spectrum of 4-hydroxy-6-methyl-2-methylthiopyrimidine. The C–F band is well pronounced in the pyrimidines that contain trifluoromethyl and pentafluoroethyl groups; if the fluorine is attached to the 5-position, the band is either weak or appears to be shifted.

Experimental

Ethyl γ-Fluoroacetoacetate.—(*a*) To a stirred mixture of ethyl fluoroacetate (21 g.), magnesium turnings (7·2 g.), mercuric chloride (0·5 g.), and anhydrous ether (70 ml.), 10—20 ml. of a solution of ethyl bromoacetate (33 g.) in ether (50 ml.) were added and the mixture was heated until an exothermic reaction set in. The remainder of the bromoacetate solution was then added during 30—45 min., with cooling if necessary. The mixture was refluxed for 30 more min., cooled, and decomposed with ice and sulphuric acid. The ethereal layer was separated, and the aqueous layer extracted once with ether; the combined ethereal extracts were dried (Na_2SO_4) and distilled, giving ethyl γ-fluoroacetate (6 g., 20%), b. p. 87—88°/24 mm. (Found: C, 48·1; H, 5·8. Calc. for $C_6H_9O_3F$: C, 48·6; H, 6·1%).

(*b*) A mixture of magnesium (18 g.), mercury (about 10 g.), and anhydrous ether (30 ml.) was refluxed gently, with stirring, until a homogeneous grey suspension had been formed. A mixture (10—20 ml.) of ethyl fluoroacetate (80 g.), ethyl chloroacetate (62 g.), and ether (300 ml.) was added. Usually, an exothermic reaction set in at once; if not, heating was continued until reaction started. The balance of the solution was then added at such a rate that the mixture continued to boil, without external heating. The product was finally refluxed for 30 min., cooled, and decomposed with ice and sulphuric acid. After a head fraction of ethyl fluoroacetate (16—20 g.), the product (50 g.) boiled at 96—99°/30 mm.

Analogously, *ethyl γ-fluoro-α-methylacetoacetate* was obtained (4 g., 19%) from ethyl fluoroacetate (15 g.), magnesium (5 g.), mercuric chloride, and ethyl α-bromopropionate (25 g.). It had b. p. 90—93°/25 mm., $\nu_{max.}$ (liquid) 3500, 3000, 1730, and 1705s (doublet, C=O), 1460, 1370, 1100(br), 1050(br), 865, 810 $cm.^{-1}$ (Found: C, 51·8; H, 6·7. $C_7H_{11}O_3F$ requires C, 51·8; H, 6·8%).

Impure ethyl α-ethyl-γ-fluoroacetoacetate, obtained in 19% yield from ethyl fluoroacetate (21 g.), magnesium (7·2 g.), mercuric chloride, and ethyl α-bromobutyrate (37 g.), had b. p. 89—91°/22 mm. (Found: C, 52·3; H, 7·1. Calc. for $C_8H_{13}O_3F$: C, 54·5; H, 7·4%).

Ethyl α-Fluoroacetoacetate.—(*a*) To a stirred mixture of ethyl acetate (dried over P_2O_5) (54 g.), magnesium turnings (4·8 g.), mercuric chloride, and absolute ether (100 ml.), 10—15 ml. of a solution of ethyl chlorofluoroacetate (28 g.) in ether (50 ml.) were added, and heat was applied until reaction set in. The remainder of the chlorofluoroacetate solution was added dropwise in 30—45 min., then the mixture was refluxed for about 30 min., cooled, and worked up as described above. Distillation gave ethyl α-fluoroacetoacetate, b. p. 83—85°/19 mm. (6 g., 20%), and ethyl γ-chloro-αγ-difluoroacetoacetate, b. p. 103—104°/19 mm. (1·5 g., 8%).

(*b*) Ethyl fluoroacetate (36 g.) was added dropwise to a suspension of sodium hydride (8 g.) in anhydrous ether, under nitrogen, after the reaction had been initiated by addition of 0·5 ml. of anhydrous ethanol.[9] The suspension was stirred at room temperature for about 3 hr., during which most of the hydride reacted; anhydrous ether was added from time to time in order to keep the mixture fluid. Then acetyl chloride (26 g.) in ether (50 ml.) was added, with cooling, during 20 min. The mixture was stirred for 1 hr. at room temperature, then poured on ice and sulphuric acid, and the organic material was isolated as usual, giving ethyl α-fluoroacetoacetate

[21] Brownlie, *J.*, 1950, 3062; Short and Thompson, *J.*, 1952, 168; Brown and Short, *J.*, 1953, 331; Brown, Hoerger, and Mason, *J.*, 1955, 211.

(16·5 g., 34%), b. p. 83—85°/19 mm., n_D^{27} 1·4046 (decomposes on prolonged storage and gives off acid fumes), $\nu_{max.}$ (liquid) 3500, 3000s, 2950, 1750, and 1725vs (doublet, carbonyl), 1475, 1450, 1425, 1365vs, 1290—1260vs, 1120vs, 1020vs, 970, 940, 863, 765 cm.$^{-1}$.

A fraction (6 g.) of n_D^{24} 1·4210 and b. p. 93—94°/1 mm. was also isolated. It was thought to be ethyl αα-diacetyl-α-fluoroacetate in analogy with benzoylation of the enol of ethyl fluoroacetate; however, analysis showed that the product contained a substance richer in fluorine (Found: F, 14·6. Calc. for $C_8H_{11}O_4F$: F, 10·0%). It is assumed that some ethyl αγ-difluoroacetoacetate is formed which is further acetylated in the α-position to yield $CH_2F{\cdot}CO{\cdot}CFAc{\cdot}CO_2Et$ (calc.: F, 18·5%).

(*c*) To a suspension of sodium methoxide (1·8 g.) in light petroleum (b. p. 40—60°; 100 ml.), ethyl fluoroacetate (15·9 g.) was added slowly at 15—25° with shaking. Thus a homogeneous, microcrystalline suspension of the yellowish voluminous enolate was obtained. After 10 minutes' additional shaking, freshly distilled acetyl chloride (11·5 g.) was added, and the mixture shaken at room temperature for 1 hr., refluxed for 10 min., and treated with water. The organic layer was separated, washed with 1% sodium hydrogen carbonate solution, dried, and concentrated in a short column. The residue boiled at 87—90°/23 mm. (5 g., 15%). When instead of the acetyl chloride, acetic anhydride (15·7 g.) was used, a yield of 10% (3·5 g.) of ethyl α-fluoroacetoacetate was obtained (Found: C, 48·4; H, 5·9; F, 13·0. Calc. for $C_6H_9O_3F$: C, 48·6; H, 6·1; F, 12·8%).

Ethyl α-Fluoro-β-oxovalerate.—To the enolate, prepared from ethyl fluoroacetate (53 g.) and sodium hydride (12 g.), propionyl chloride (47 g.) was added dropwise. The solution was stirred and refluxed for 4 hr. Water was added with stirring and the ethereal layer separated, dried (Na_2SO_4) and distilled. Thus were obtained: (a) *ethyl α-fluoro-β-oxovalerate* (17 g., 21%), b. p. 105—107°/32 mm., n_D^{30} 1·4090, $\nu_{max.}$ (liquid film) 3000s, 1735vs, 1450, 1220—1280vs,br, 1136vs, 1105vs, 1020, 940, 855 cm.$^{-1}$ (Found: C, 50·5; H, 6·9. $C_7H_{11}O_3F$ requires C, 51·8; H, 6·8%); and (b) a fraction, b. p. 105—106°/3 mm. (10 g.), probably a mixture of ethyl αα-dibenzoyl-α-fluoroacetate and α-fluoro-α-fluoroacetyl-β-oxovalerate.

Ethyl γ-Chloro-αγ-difluoroacetoacetate.—A stirred mixture of ethyl chlorofluoroacetate (29 g.), magnesium turnings (2·4 g.), mercuric chloride (0·5 g.), and anhydrous ether (100 ml.) was refluxed gently until all the magnesium had disappeared. After one more hour at the b. p., the mixture was poured on ice and sulphuric acid, and the *ester* (10·5 g., 52%) isolated as usual; it had b. p. 101—104°/19 mm., $\nu_{max.}$ (liquid) 3400s, 2950, 1730s(CO), 1400, 1380, 1310, 1230, 1090—1100, 1050—1060, 880, 860, 790 cm.$^{-1}$ (Found: C, 35·8; H, 4·1. $C_6H_7O_3ClF_2$ requires C, 36·0; H, 3·5%).

Ethyl α-Benzoyl-α-fluoroacetate.—(*a*) To a suspension of the enol of ethyl fluoroacetate (53 g.), prepared with sodium hydride (12 g.) in anhydrous ether (200 ml.) as described above, benzoyl chloride (71 g.) was added with stirring and cooling in 30 min. Stirring at room temperature was continued for 2 hr., then the mixture was poured into ice-cold sulphuric acid, and the ethereal layer was separated, washed with water and dilute sodium carbonate solution, and dried (Na_2SO_4). The *ester* (32 g., 30%), on redistillation, had b. p. 125—128°/4 mm. (Found: C, 62·1; H, 5·0; F, 9·7. $C_{11}H_{11}O_3F$ requires C, 62·9; H, 5·2; F, 9·1%).

(*b*) To the enol of ethyl fluoroacetate, prepared as above from the ester (15·9 g.) and sodium methoxide (1·8 g.) in light petroleum (100 ml.), benzoyl chloride (21 g.) was added. The product was worked up as described for the analogous preparation of ethyl α-fluoroacetoacetate and isolated by distillation *in vacuo*, b. p. 125—130°/1 mm. (6 g., 20%) (Found: C, 63·2; H, 5·1%).

The 2 : 4-*dinitrophenylhydrazone*, which recrystallized from nitromethane, melted at 190° (Found: C, 52·3; H, 3·7; N, 14·2. $C_{17}H_{15}O_6N_4F$ requires C, 52·3; H, 3·8; N, 14·4%).

A second fraction (10 g., 22%) boiled at 165—170°/1 mm., and was identified by the analysis as *ethyl αα-dibenzoyl-α-fluoroacetate* (Found: C, 69·1; H, 4·7; F, 5·9. $C_{18}H_{15}O_4F$ requires C, 68·8; H, 4·8; F, 6·0%).

Ethyl γγγ-Trifluoro- and αγγγ-Tetrafluoro-acetoacetate.—These were prepared as described by McBee *et al.*[2] The infrared spectrum of the second ester was measured (liquid film): 3500, 3050, 1770, 1695, 1460, 1390, 1130 (all vs), 925, 862, 790, 680 cm.$^{-1}$.

Ethyl αγγδδδ-Hexafluoro-β-oxovalerate.—Ethyl fluoroacetate (21 g.) was added with stirring to a boiling mixture of ethyl pentafluoropropionate (38 g.), sodium hydride (5 g.), and anhydrous ether (100 ml.) in 3 hr. Stirring and heating were continued for a further 4 hr., then the mixture was decomposed with sulphuric acid and ice and extracted with ether, and the extract distilled

under reduced pressure. The *ester* (35 g., 70%), on redistillation from phosphorus pentoxide, had b. p. 63—64°/27 mm., n_D^{27} 1·3394, $\nu_{max.}$ (liquid) 3450, 3000, 1750sh, 1720, 1170vbr, 860 cm.$^{-1}$ (Found: C, 33·4; H, 2·8. $C_7H_6O_3F_6$ requires C, 33·3; H, 2·4%).

6-Fluoromethyluracil (II).—A mixture of finely powdered urea (8·5 g.), ethyl γ-fluoroacetoacetate (19·5 g.), anhydrous ethanol (5 c.c.), and concentrated hydrochloric acid (2—3 drops) in a loosely covered porcelain dish was placed in an evacuated desiccator for 5—6 days; from time to time the mass was broken up. The resulting solid, finely powdered, was added to a solution of sodium hydroxide (8 g.) in water (120 ml.) at 90—95°. When all the solid had dissolved, the solution was cooled rapidly and excess of hydrochloric acid added, whereupon *6-fluoromethyluracil* crystallized (12 g., 73%); it had m. p. 270—272° (from acetic acid) (Found: C, 41·8; H, 4·0; F, 13·6. $C_5H_5O_2N_2F$ requires C, 41·7; H, 3·5; F, 13·2%).

6-Fluoromethyl-4-hydroxy-2-mercaptopyrimidine (IIa).—Ethyl γ-fluoroacetoacetate (9 g.), thiourea (4·6 g.) and 2M-methanolic sodium methoxide (30 ml.) were kept together for 48 hr. at room temperature. The solvent was removed under reduced pressure, the residue dissolved in water, and the solution acidified with acetic acid and left overnight. The *pyrimidine* (6·5 g., 67%) that had crystallized was filtered off and washed with water. After recrystallization from acetic acid, it melted at 232—236° (decomp.) (Found: F, 12·0. $C_5H_5ON_2FS$ requires F, 11·9%).

Reactions with S-Ethylisothiouroninm Bromide.—*2-Ethylthio-5-fluoro-4-hydroxy-6-methylpyrimidine.* A mixture of ethyl α-fluoroacetoacetate (19 g.), *S*-ethylisothiouronium bromide (24 g.), and 2M-methanolic sodium methoxide (64 ml.) was refluxed for 12 hr. The solvent was removed under reduced pressure and the residue taken up in water and acidified with hydrochloric acid. A little ether was added and the mixture stirred vigorously to induce crystallization. The *product* (11 g., 46%) had m. p. 190—192° (from ethyl acetate) (Found: C, 44·4; H, 4·8. $C_7H_9ON_2FS$ requires C, 44·7; H, 4·8%).

2-Ethylthio-5-fluoro-4-hydroxy-6-phenylpyrimidine. A mixture of ethyl α-benzoyl-α-fluoroacetate (19 g.), *S*-ethylisothiouronium bromide (19 g.), and 2M-sodium methoxide (50 ml.) was refluxed for 6 hr. The *pyrimidine* (4·5 g., 20%) had m. p. 235—240° (from ethyl acetate) (Found: C, 57·3; H, 4·7. $C_{12}H_{11}ON_2FS$ requires C, 57·6; H, 4·4%).

2-Ethylthio-4-hydroxy-6-trifluoromethylpyrimidine. The crude *product* from ethyl γγγ-trifluoroacetoacetate (32 g.), *S*-ethylisothiouronium bromide (32 g.) and 2M-sodium methoxide (70 ml.) was dissolved in a little ethyl acetate and precipitated by excess of ether. It (17 g., 45%) had m. p. 176—178° (Found: C, 37·6; H, 3·4. $C_7H_7ON_2F_3S$ requires C, 37·5; H, 3·1%).

2-Ethylthio-5-fluoro-4-hydroxy-6-trifluoromethylpyrimidine. The crude *product* (11 g., 25%) formed from ethyl αγγγ-tetrafluoroacetoacetate (37 g.), *S*-ethylisothiouronium bromide (34 g.) and 2M-sodium methoxide (92 ml.) and recrystallized from aqueous acetic acid and then from light petroleum (b. p. 60—70°) had m. p. 136—138° (Found: C, 35·3; H, 2·6. $C_7H_6ON_2F_4S$ requires C, 34·2; H, 2·5%).

2-Ethylthio-5-fluoro-4-hydroxy-6-pentafluoroethylpyrimidine. Ethyl αγγδδδ-hexafluoro-β-oxovalerate (25 g.), *S*-ethylisothiouronium bromide (18·5 g.) and a solution of sodium (4 g.) in methanol (50 ml.) gave a *product* which after recrystallization from aqueous acetic acid melted at 159—160° (10 g., 35%) (Found: F, 38·4; N, 9·0. $C_8H_6ON_2F_6S$ requires F, 39·0; N, 9·6%).

5-Fluoro-2,4-dihydroxy-6-methylpyrimidine (I; R^1 = Me, R^2 = F).—2-Ethylthio-5-fluoro-4-hydroxy-6-methylpyrimidine (3 g.) was refluxed for 3 hr. with acetic acid (15 ml.) and concentrated hydrochloric acid (4 ml.). Upon cooling, 1 g. (44%) of the *dihydroxypyrimidine* was obtained; it recrystallized from acetic acid and decomposed above 300° (Found: C, 41·9; H, 3·6; F, 13·0. $C_5H_5O_2N_2F$ requires C, 41·7; H, 3·5; F, 13·2%).

5-Fluoro-2,4-dihydroxy-6-phenylpyrimidine (I; R^1 = Ph, R^2 = F) was obtained from 2-ethylthio-5-fluoro-4-hydroxy-6-phenylpyrimidine (3 g.) with refluxing acetic acid (15 ml.) and 40% hydrobromic acid (15 ml.) for 3 hr. On cooling, 1 g. (41%) of material was obtained, having m. p. 290—295° (from acetic acid) (Found: C, 58·1; H, 3·5; F, 10·1. $C_{10}H_7O_2N_2F$ requires C, 58·3; H, 3·4; F, 9·2%).

2,4-Dihydroxy-6-trifluoromethylpyrimidine (I; R^1 = CF_3, R^2 = H) was obtained by refluxing 2-ethylthio-4-hydroxy-6-trifluoromethylpyrimidine (17 g.) with acetic acid (60 ml.) and concentrated hydrochloric acid (40 ml.) for 8 hr. On cooling, 10 g. (73%) of the pyrimidine, m. p. 225—227° (from ethyl acetate), was obtained (Found: C, 33·4; H, 2·0; F, 30·5. $C_5H_3O_2N_2F_3$ requires C, 33·3; H, 1·7; F, 31·3%).

5-Fluoro-2,4-dihydroxy-6-trifluoromethylpyrimidine (I; R^1 = CF_3, R^2 = F) was prepared

by refluxing for 24 hr. 2-ethylthio-5-fluoro-4-hydroxy-6-trifluoromethylpyrimidine (10 g.) with acetic acid (25 ml.) and 40% hydrobromic acid (50 ml.). The solution was brought to dryness under reduced pressure, and the residue refluxed with carbon tetrachloride (100 ml.) for 5—6 hr. which removed impurities without dissolving the product. The latter was filtered off and recrystallized from ethyl acetate [4 g., 47%; m. p. 224—227° (from ethyl acetate)] (Found: C, 30·5; H, 0·7; F, 38·3. $C_5H_2O_2N_2F_4$ requires C, 30·3; H, 1·0; F, 38·4%).

5-Fluoro-2,4-dihydroxy-6-pentafluoroethylpyrimidine (I; $R^1 = C_2F_5$, $R^2 = F$).—When 2-ethylthio-5-fluoro-4-hydroxy-6-pentafluoroethylpyrimidine (8 g.) was refluxed for 30 hr. with acetic acid (20 ml.) and 40% hydrobromic acid (40 ml.), the product crystallized on cooling. Recrystallized from aqueous acetic acid, it (5 g., 68%), had m. p. 221—222°. In spite of the sharp m. p., no satisfactory analysis could be obtained (Found: C, 30·3; H, 1·3. Calc. for $C_6H_2O_2N_2F_6$: C, 29·0; H, 0·8%).

4-Fluoromethyl-6-hydroxy-2-methylpyrimidine (III; $R^1 = CH_2F$, $R^2 = H$).—A mixture of acetamidine hydrochloride [22] (6·5 g.), ethyl γ-fluoroacetoacetate (10 g.), and 2M-sodium methoxide (34 ml.) was kept over sulphuric acid under reduced pressure, until a dry residue was left. This was extracted with hot ethanol, and the *product* (2 g., 21%) precipitated by ether. After recrystallization from ethanol, it melted at 204—207° (Found: C, 50·9; H, 4·8. $C_6H_7ON_2F$ requires C, 50·7; H, 4·9%).

5-Fluoro-4-hydroxy-2,6-dimethylpyrimidine (III; $R^1 = Me$, $R^2 = F$).—Ethyl α-fluoroacetoacetate (15 g.) was added to a solution of acetamidine hydrochloride (9·5 g.) in 2M-methanolic sodium methoxide (100 ml.), whereupon an exothermic reaction took place. The mixture was left overnight, the solvent was removed under reduced pressure, and the residue taken up with a little water, acidified with acetic acid, and brought to dryness under reduced pressure. From boiling ethanol, 8 g. (56%) of the *product*, m. p. 177—178°, were obtained (Found: C, 50·9; H, 5·3%).

4-Hydroxy-2-methyl-6-trifluoromethylpyridimine (III; $R^1 = CF_3$, $R^2 = H$).—To a mixture of acetamidine hydrochloride (9·5 g.) and ethyl γγγ-trifluoroacetoacetate (18·4 g.), powdered sodium hydroxide (4 g.) was added in small portions, with stirring; an exothermic reaction took place. The mixture was kept under reduced pressure over sulphuric acid till dry, powdered, mixed with sodium hydrogen carbonate, and extracted with ethyl acetate (Soxhlet). On evaporation of the solvent under reduced pressure, a *product* (14 g., 73%) was obtained, which was washed with water and recrystallized from toluene, then having m. p. 134—136° (Found: C, 40·9 H, 3·0. $C_6H_5ON_2F_3$ requires C, 40·5; H, 2·8%).

5-Fluoro-4-hydroxy-2-methyl-6-pentafluoroethylpyrimidine (III; $R^1 = C_2F_5$, $R^2 = F$).—Ethyl αγγδδδ-hexafluoro-β-oxovalerate (4·5 g.) was added to a solution of acetamidine hydrochloride (1·9 g.) in 2M-methanolic sodium methoxide (20 ml.). The mixture was kept overnight, the solvent removed under reduced pressure, the residue dissolved in a little water, and the solution acidified with hydrochloric acid. The *product* (2 g., 43%), recrystallized from aqueous ethanol, melted at 105—106° (Found: C, 34·3; H, 1·6. $C_7H_4ON_2F_6$ requires C, 34·1; H, 1·6%).

2-Amino-5-fluoro-4-hydroxy-6-methylpyrimidine (IV).—Ethyl α-fluoroacetoacetate (15 g.) was added to a solution of guanidine carbonate (18 g.) and potassium hydroxide (6 g.) in water (50 ml.) and refluxed for 3 hr., cooled, and acidified carefully with acetic acid. The resulting precipitate was digested with boiling acetic acid, filtered, and recrystallized from dimethylformamide. The *pyrimidine* was a buff-coloured powder (8 g., 46%), decomp. >300° (Found: C, 42·5; H, 4·8; F, 13·7. $C_5H_6ON_3F$ requires C, 42·0; H, 4·2; F, 13·3%).

2-Amino-4-hydroxy-6-trifluoromethylpyrimidine (V).—Ethyl γγγ-trifluoroacetoacetate (4 g.), guanidine carbonate (4 g.), and a solution of sodium hydroxide (2 g.) in water (10 ml.) were refluxed for 2 hr. On cooling and neutralization with acetic acid, the *product* (13 g., 26%) was precipitated. It recrystallized from acetic acid and liquefied in the neighbourhood of 170° (but sublimation is too rapid to permit accurate determination of the m. p.) (Found: C, 33·8; H, 2·1. $C_5H_4ON_3F_3$ requires C, 33·5; H, 2·2%).

2-Amino-4-fluoromethyl-6-hydroxypyrimidine (VI).—Ethyl γ-fluoroacetoacetate (14·8 g.) and guanidine hydrochloride (9·6 g.) in 2M-sodium methoxide (100 ml.) were kept at room temperature for 48 hr. with occasional shaking. The solvent was removed under reduced pressure, and the solid residue dissolved in water, filtered, and acidified with acetic acid, whereupon the *pyrimidine* crystallized in quantitative yield (14 g.). Recrystallized from hot glacial acetic acid, it had m. p. 250—260° (decomp.) (Found: F, 12·9. $C_5H_6ON_3F$ requires F, 13·2%).

[22] Dox, *Org. Synth.*, 1942, Coll. Vol. I, p. 5.

2-Amino-4-ethyl-5-fluoro-6-hydroxypyrimidine (VII).—This compound was prepared by the same procedure from ethyl α-fluoro-α-propionylacetate (6·5 g.), guanidine hydrochloride (4 g.), and methanolic 2M-sodium methoxide (40 ml.). The *pyrimidine* (3 g., 48%) crystallized from the acidified aqueous solution in 48 hr. The analytical sample was prepared by sublimation at 220°/1 mm. (Found: C, 45·3; H, 5·4; F, 12·2. $C_6H_8ON_3F$ requires C, 45·9; H, 5·1; F, 12·1%).

2-Amino-5-fluoro-4-hydroxy-6-pentafluoroethylpyrimidine (VIII) —Ethyl α-fluoro-α-pentafluoropropionylacetate (17 g.) and guanidine hydrochloride (6·7 g.) in 2M-methanolic sodium methoxide (67 ml.) were kept at room temperature for 48 hr. with occasional shaking. After removal of the solvent under reduced pressure, the residue was taken up in water and acidified with excess of acetic acid; the solution was brought to dryness and the residue shaken with ether to induce crystallization. The *product* was filtered off (8 g., 49%) and purified by sublimation *in vacuo*. It then melted at 265—268° (Found: C, 29·6; H, 1·0; F, 45·9. $C_6H_3ON_3F_6$ requires C, 29·2; H, 1·2; F, 46·1%).

Ethyl γ-Fluoro-α-ureidomethyleneacetoacetate.—A mixture of urea (3 g.), ethyl orthoformate (8 g.), and ethyl γ-fluoroacetoacetate (7·5 g.) was refluxed for 6 hr., cooled and diluted with excess of ether. The crude *product* (4·8 g., 36%) which was precipitated was purified by washing with water and recrystallization from hot ethanol; it decomposed above 200° (Found: C, 44·6; H, 5·3; F, 9·0. $C_8H_{11}O_4N_2F$ requires C, 44·0; H, 5·1; F, 8·7%).

Cyclization with refluxing sodium methoxide solution [17] gave only a brown ill-defined product.

Ethyl γγγ-Trifluoro-α-ureidomethyleneacetoacetate.—A mixture of urea (4·5 g.), ethyl orthoformate (12 g.), and ethyl γγγ-trifluoroacetoacetate (14 g.) was refluxed for 6 hr., cooled, and diluted with much ether. The *product* (10 g., 52%), recrystallized from ethanol, melted at 170—172° (Found: C, 37·8; H, 3·6. $C_8H_9O_4N_2F_3$ requires C, 37·8; H, 3·6%). After the product (5 g.) had been refluxed for 30 min. with sodium hydroxide (1 g.) in water (10 c.c.), acidification with hydrochloric acid gave a compound (2 g.), m. p. 261—265° (from acetic acid), which contained 6% less fluorine than the expected 2-hydroxy-6-trifluoromethylpyrimidine-4-carboxylic acid.

Acylation of Fluoroacetone with Acetic Anhydride.—A mixture of fluoroacetone [23] (38 g.) and acetic anhydride (130 g.) was saturated with boron trifluoride at $\not>10°$. Then, water (750 ml.) and anhydrous sodium acetate (150 g.) were added and the mixture was distilled. Most of the diketone was found in the first 500 ml. of distillate. To this portion, a filtered solution of copper acetate (60 g.) in hot water (200 ml.) was added, and the light blue chelate salt filtered off after 12 hr. and washed with water. It was taken up with a solution of sulphuric acid (40 ml.) in water (200 ml.) and extracted repeatedly with ether. The ethereal extract was dried (Na_2SO_4) and distilled, to yield 26 g. (49%) of fluoroacetylacetone, b. p. 49—51°/30 mm. As the compound decomposed on storage, no satisfactory analysis could be obtained. Attempts to condense it with urea by using sulphuric acid,[24] or with guanidine carbonate by using fuming sulphuric acid, failed.

3-Chloropentane-2,4-dione and Potassium Fluoride.—When the dione [26] (180 g.) was added dropwise to a stirred mixture of potassium fluoride (116 g.) and ethylene glycol (200 g.) at 180° and the fluorinated material allowed to distil off continuously, only impure fluoroacetone (25 g.) was obtained.

This work was sponsored by the United States National Institute of Health.

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[*Received, January 23rd,* 1959.]

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[24] Hale, *J. Amer. Chem. Soc.*, 1914, **36**, 104.
[25] Roblin, Winnek, and English, *ibid.*, 1942, **64**, 567.
[26] von Auwers and Auffenberg, *Ber.*, 1917, **50**, 929.