Partially Fluorinated Heterocyclic Compounds. Part 22.[1] The Preparation of Allyl 2,5,6-Trifluoropyrimidin-4-yl Ether and Related Compounds and a Study of their Claisen Rearrangement Reactions. A New Route to 5-Fluorouracil and Barbituric Acid Derivatives

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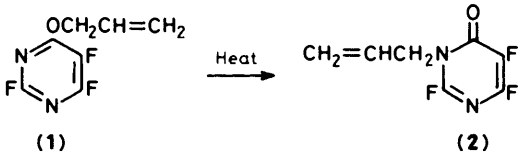
Vapour phase thermolyses of allyl 2,5,6-trifluoropyrimidin-4-yl, (**1**), 2,5-difluoro-6-methoxypyrimidin-4-yl, (**5**), 2,5-difluoropyrimidin-4-yl, (**6**), and 5,6-difluoro-2-methoxypyrimidin-4-yl, (**7**), ethers gave the Claisen rearrangement products (**2**), (**17**), (**18**), and (**20**) respectively, in which N-3 is the migration terminus, but the 2-allyl derivative (**10**) was inert. In other thermolyses with allyl 5-fluoropyrimidin-4-yl ethers where a preliminary reaction results in the localisation of the C-4 to C-5 double bond, C-5 is the migration terminus: barbituric acid derivatives (**28**) and (**26**) are formed from (**5**) and allyl 2,5-difluoro-6-hydroxypyrimidin-4-yl ether (**13**) respectively after hydrolysis of each rearrangement product and (**14**) also gave (**26**); 2,4-diallyl-5-fluoro-6-methoxypyrimidine (**11**) gave (**29**) (with the loss of CH_3) and 2,4,6-triallyloxy-5-fluoropyrimidine (**12**) was isomerised to (**30**). Allyl 2,6-dimethoxy-5-fluoropyrimidin-4-yl ether (**8**) gave both N-3 and C-5 migration termini products (**21**) and (**33**) respectively. Hydrolysis of (**2**), (**17**), and (**18**) gave the 5-fluorouracil derivatives (**22**), (**23**), and (**24**) respectively.

In a previous paper,[2] the thermolyses of allyl 2,3,5,6-tetrafluoro-4-pyridyl and 2,4,5,6-tetrafluoro-3-pyridyl ethers were shown to give intramolecular Diels–Alder adducts from presumed Claisen rearrangement intermediates. We now report an investigation using some fluorine-containing pyrimidyl allyl ethers.

Tetrafluoropyrimidine[3] reacted with allyl alcohol at room temperature in the presence of potassium carbonate to give allyl 2,5,6-trifluoropyrimidin-4-yl ether (**1**) (61%). When compound (**1**) was heated at 190 °C for 46 h in the vapour phase (static vapour-phase pyrolysis, abbreviated s.v.p.) no reaction occurred, in contrast with the related tetrafluoropyridyl compounds.[2] However when (**1**) was distilled under reduced pressure through a quartz tube packed with silica wool at 440 °C (flash vapour phase pyrolysis, abbreviated f.v.p.), the Claisen rearrangement product 3-allyl-2,5,6-trifluoropyrimidin-4(3*H*)-one (**2**) (53%) was formed by a 3,3-sigmatropic shift in which N-3 was the migration terminus rather than to the alternative site, C-5 (Scheme 1). The structure of (**2**) was

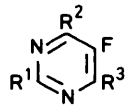


(**1**) (**2**)

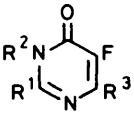
Scheme 1.

deduced by using the deuterium-labelled allyl ether (**3**) under the same conditions; the ^1H n.m.r. spectrum of the product (**16**) (45%) showed that only one inversion of the allyl group had taken place. The ether (**3**) was prepared by a sequence of reactions involving the reaction of tetrafluoropyrimidine with prop-2-ynyl alcohol–K_2CO_3 to give the ether (**4**) (60%) which was then reduced with 1 mol equiv. of deuterium (^2H/Pd–$BaSO_4$).

We have also prepared and thermolysed two other allyl pyrimidinyl ethers (**5**) and (**6**). Reaction of (**1**) with 1 mol equiv. of sodium methoxide in methanol at reflux temperature



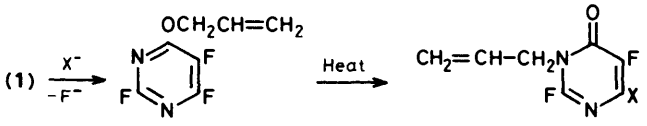
(**1**) R^1,R^3 = F, R^2 = $OCH_2CH=CH_2$
(**3**) R^1,R^3 = F, R^2 = $OCH_2CD=CHD$
(**4**) R^1,R^3 = F, R^2 = $OCH_2C\equiv CH$
(**5**) R^1 = F, R^2 = $OCH_2CH=CH_2$, R^3 = OMe
(**6**) R^1 = F, R^2 = $OCH_2CH=CH_2$, R^3 = H
(**7**) R^1 = OMe, R^2 = $OCH_2CH=CH_2$, R^3 = F
(**8**) R^1,R^3 = OMe, R^2 = $OCH_2CH=CH_2$
(**9**) R^1 = H, R^2 = $OCH_2CH=CH_2$, R^3 = F
(**10**) R^1 = $OCH_2CH=CH_2$, R^2,R^3 = OMe
(**11**) R^1,R^2 = $OCH_2CH=CH_2$, R^3 = OMe
(**12**) R^1,R^2,R^3 = $OCH_2CH=CH_2$
(**13**) R^1 = F, R^2 = $OCH_2CH=CH_2$, R^3 = OH
(**14**) R^1 = OH, R^2 = $OCH_2CH=CH_2$, R^3 = F
(**15**) R^1 = OH, R^2,R^3 = OMe



(**2**) R^1,R^3 = F, R^2 = $CH_2CH=CH_2$
(**16**) R^1,R^3 = F, R^2 = $CHDCD=CH_2$
(**17**) R^1 = F, R^2 = $CH_2CH=CH_2$, R^3 = OMe
(**18**) R^1 = F, R^2 = $CH_2CH=CH_2$, R^3 = H
(**19**) R^1 = F, R^2 = Me, R^3 = $OCH_2CH=CH_2$
(**20**) R^1 = OMe, R^2 = $CH_2CH=CH_2$, R^3 = F
(**21**) R^1,R^3 = OMe, R^2 = $CH_2CH=CH_2$

gave three products: (**5**) (66%), (**7**) (10%), and (**8**) (14%), while (**1**) and 1 mol equiv. of lithium aluminium hydride in ether gave a mixture of (**6**) and (**9**) in the ratio of 75:25 respectively (96%) which could not be separated.

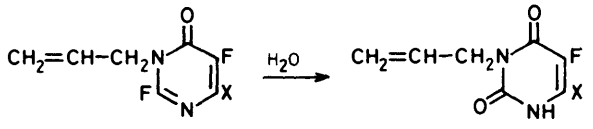
The f.v.p. of (**5**) at 475 °C gave (**17**) (65%) along with unchanged (**5**) (14%) while the f.v.p. of an enriched mixture of (**6**) and (**9**) (91:9 respectively) at 470 °C gave (**18**) (67%) (Scheme 2). The structures of (**17**) and (**18**) were inferred by their u.v. spectra which were very similar to that of (**2**).



(**5**) X = OMe
(**6**) X = H
(**17**) X = OMe
(**18**) X = H

Scheme 2.

We have found that the fluorine at C-2 in each of the compounds (**2**), (**17**), and (**18**) is susceptible to hydrolysis with the formation of derivatives of 5-fluorouracil: (**22**) (76%), (**23**) (89%), and (**24**) (41%) respectively (Scheme 3).

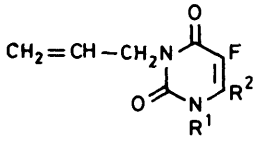


(**2**) X = F
(**17**) X = OMe
(**18**) X = H
(**22**) X = F
(**23**) X = OMe
(**24**) X = H

Scheme 3.

The formation of 3-allyl-5-fluoropyrimidine-2,4-(1*H*,3*H*)-dione (**24**) is of particular significance since alkylation of 5-fluorouracil with allyl bromide gives only the 1-allyl derivative.[4]

An alternative synthesis of (**1**) from 4-hydroxy-2,5,6-trifluoropyrimidine,[3] allyl bromide and potassium carbonate in acetone did give this compound (48%) but it was also accompanied by (**2**) (1%), compound (**22**) (7%), and the further allylated derivative of (**22**), compound (**25**) (4%). Clearly *N*-alkylation competes with *O*-alkylation initially, followed by hydrolysis to give (**22**). Under anhydrous conditions in tetrahydrofuran, the preformed sodium salt of the 4-hydroxypyrimidine and allyl bromide gave the *O*- and *N*-alkylated materials (**1**) (4%) and (**2**) (12%) respectively.

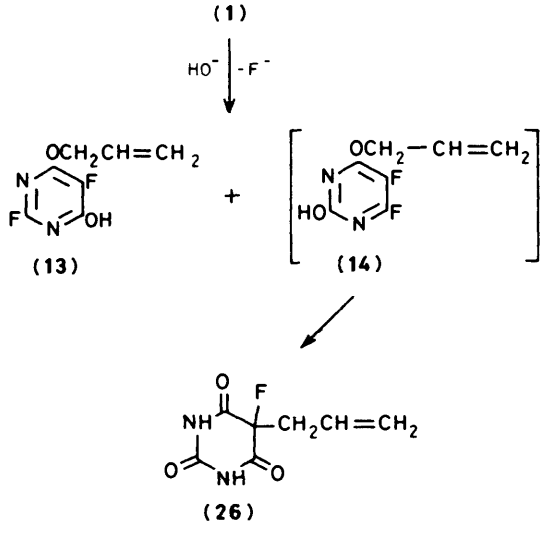


(**22**) R^1 = H, R^2 = F
(**23**) R^1 = H, R^2 = OMe
(**24**) R^1 = H, R^2 = H
(**25**) R^1 = $CH_2CH{=}CH_2$, R^2 = F

Earlier investigations of the Claisen rearrangement in some 2-substituted allyl pyrimidin-4-yl ethers had shown that C-5 is preferred over N-3 as the migration terminus[5] (by a factor of 1.6 for the 2-methyl compound and 2.6 for the benzylthio compound). Consequently we have sought other fluorine-containing allyl pyrimidinyl ethers which might have carbon as the migration terminus in a 3,3-sigmatropic shift reaction.

Reaction of allyl 2,5,6-trifluoropyrimidin-4-yl ether (**1**) with 2 mol equiv. of sodium methoxide gave the 2,6-dimethoxy compound (**8**) in 96% yield. 2,5-Difluoro-4,6-dimethoxypyrimidine reacted with 1 mol equiv. of the sodium salt of allyl alcohol in THF to give (**10**) (99%), but with 1.3 mol equiv. in allyl alcohol the 2,4-diallyloxy- and 2,4,6-triallyloxy-pyrimidine compounds (**11**) (9%) and (**12**) (29%) respectively were formed *via* transetherification reactions. The tris ether (**12**) was also prepared in 63% yield from tetrafluoropyrimidine and an excess of the sodium salt of allyl alcohol.

The introduction of a hydroxy group into fluorine-containing allyl pyrimidinyl ethers proved less straightforward than for methoxy. The reaction of (**1**) with aqueous sodium hydroxide in dioxane gave a mixture of three components, shown by ^{19}F n.m.r. spectroscopy to be present in the ratio 64:27:9. The major component was allyl 2,5-difluoro-6-hydroxypyrimidin-4-yl ether (**13**) (32%) but during the isolation procedure, the second major component, the 2-hydroxy compound (**14**) underwent further reaction (Claisen rearrangement: hydrolysis) to give the known barbituric acid derivative (**26**)[6] (11%). The minor component was not identified. (Scheme 4). The presence

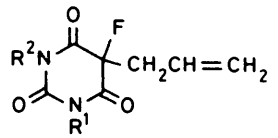


(**13**)
(**14**)
(**26**)

Scheme 4.

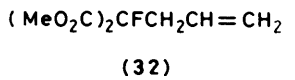
of the 2-hydroxy compound (**14**) in the original reaction product was confirmed in a separate experiment by treatment of the crude reaction product with an excess of diazomethane from which the 2-methoxy compound (**7**) (6%) was isolated; in addition there was isolated the 6-methoxy compound (**5**) (6%) and the *N*-methylated product (**19**) (3%) [both formed from (**13**)], and the *N*,*N*'-dimethyl barbiturate derivative (**27**) (1%), formed from (**26**). In a separate experiment, diazomethane reacted with (**13**) to give (**5**) (67%) and (**19**) (19%).

The attempted replacement of two fluorines in the ether (**1**) using aqueous potassium hydroxide in dioxane gave a ring-opened product; a carboxylic acid, conveniently handled as the methyl ester (**31**) (14%) by reaction with diazomethane. Under

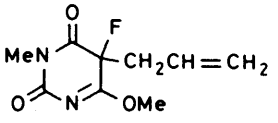


(26) R^1,R^2 = H
(27) R^1,R^2 = Me
(28) R^1 = Me, R^2 = H
(29) R^1 = H, R^2 = $CH_2CH=CH_2$
(30) R^1,R^2 = $CH_2CH=CH_2$

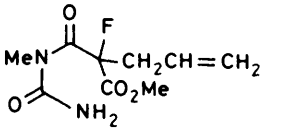
(31)



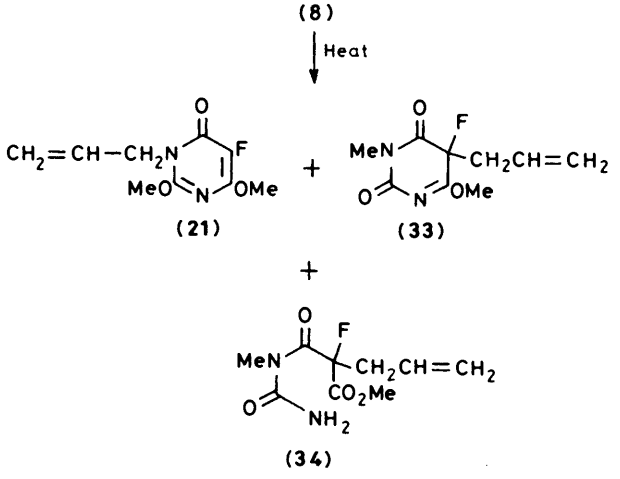
(32)



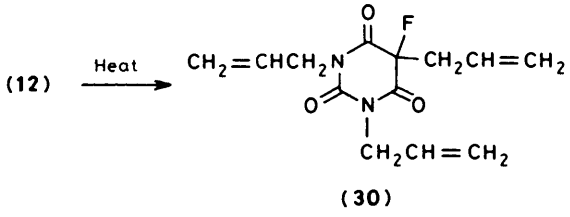
(33)



(34)



Scheme 5.



Scheme 6.

different conditions with sodium hydroxide, the same procedure gave a mixture of two esters (**32**) (26%) and (**31**) in the ratio 85:15 respectively, their structures showing that a Claisen rearrangement to C-5 had preceded the ring cleavage.

The 6-hydroxy compound (**13**) gave polymeric materials under s.v.p. conditions at 162 °C/22 h, but when subjected to f.v.p. at 450 °C, the barbiturate (**26**) (11%) was isolated, fluorine being lost by hydrolysis during work-up.

In contrast to the formation of (**17**) by f.v.p., the 6-methoxy compound (**5**) under s.v.p. at 210 °C gave the N-1 methyl barbituric acid derivative (**28**) (6%) fluorine being lost by hydrolysis. The f.v.p. of the 2-methoxy compound (**7**) at 470 °C gave the isomer (**20**) (65%).

The only pyrimidine derivative which we have prepared having just one allyloxy substituent which is between the two nitrogen atoms, compound (**10**), proved to be completely resistant towards the Claisen rearrangement reaction. It was recovered unchanged under f.v.p. conditions at 450 °C, while at 505 °C, the allyl group was lost to give the 2-hydroxy compound (**15**) (26%) which was also prepared from 2,5-difluoro-4,6-dimethoxypyrimidine and potassium hydroxide in t-butyl alcohol.

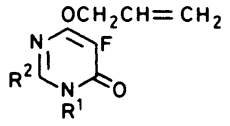
A complex mixture of products resulted from the f.v.p. of allyl 2,6-dimethoxy-5-fluoropyrimidin-4-yl ether (**8**) at 470—480 °C, the proportions of the individual components not being reproducible under supposedly identical conditions. Three products were identified: the isomeric N-migration terminus product (**21**) (9%); an isomeric C-5 migration terminus product (**33**) (4%); and the ring-opened hydrolysis product from (**33**), compound (**34**) (22%), a reaction which was demonstrated in a separate experiment. The ratio of migration of the allyl group to the nitrogen and to carbon varied from 1:2 respectively to 1:10.7 (by ^{19}F n.m.r.; see Scheme 5).

The s.v.p. of the 2,4-diallyloxy-6-methoxy compound (**11**) at 196 °C gave the barbituric acid derivative (**29**) (51%) during which the methyl group was lost.

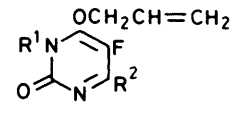
The triallyloxypyrimidine compound (**12**) was converted into the isomeric barbituric acid derivative (**30**) (88%) by s.v.p. at 194 °C (Scheme 6).

In this paper, the Claisen rearrangement reaction of derivatives of allyl 5-fluoropyrimidin-4-yl ether have been shown to give isomers in which the terminus for the migration of the allyl group is N-3, *provided* that there is no preceding reaction which localises a double bond between C-4 and C-5— in which case C-5 is the migration terminus. Thus, compounds (**1**), (**5**), (**6**), (**7**), and (**8**) give the corresponding 3-allylpyrimidin-4(3*H*)-one derivatives (**2**), (**17**), (**18**), (**20**), and (**21**) respectively.

Under s.v.p. conditions, (**5**) is converted into the 1-methylbarbituric acid derivative (**28**). A well known but unusual reaction of pyrimidine compounds containing the structural feature –N=C–OMe is its thermal conversion into N(Me)C=O.[7] Consequently (**5**) is presumably first isomerised to (**19**), the 3,3-sigmatropic rearrangement then terminates at C-5, and the remaining –N=CF– group is hydrolysed on work-up to –NH–C=O. Intermediates of similar structure to (**19**) can be invoked in the conversion of (**13**) into (**26**) [tautomer (**35**)]; (**11**) to (**29**) [(**36**)]; and (**12**) to (**30**) [(**37**)]. With the 2,6-dimethoxy compound (**8**), an initial methyl shift to give (**38**) followed by the Claisen rearrangement accounts for the formation of (**33**). The conversion of the 2-hydroxy compound (**14**) into (**26**) can also be rationalised on the intermediacy of the tautomer (**39**) followed by hydrolysis.



(35) R^1 = H, R^2 = F
(36) R^1 = H, R^2 = $OCH_2CH=CH_2$
(37) R^1 = $CH_2CH=CH_2$, R^2 = $OCH_2CH=CH_2$



(38) R^1 = Me, R^2 = OMe
(39) R^1 = H, R^2 = F

Experimental

^1H (60 MHz) and ^{19}F N.m.r. (56.4 MHz) spectra were obtained with a Varian EM360L spectrometer, or ^1H (300 MHz) spectra with a Brüker WM 300WB spectrometer situated in the

Chemistry Department in Newcastle University. Chemical shifts are downfield from internal TMS (δ_H), or upfield from internal $CFCl_3$ (δ_F).

A *Reactions of Tetrafluoropyrimidine*.[3]—(a) *With allyl alcohol.* Tetrafluoropyrimidine (26.87 g), allyl alcohol (65 ml), and sodium carbonate (4 g) were stirred together at room temperature for 7 days. The mixture was diluted with water, acidified with sulphuric acid (2M), and extracted with ether. The extracts were dried ($MgSO_4$), the solvent distilled through a fractionating column (48 × 1.5 cm), and the residue distilled *in vacuo* to give *allyl* 2,5,6-*trifluoropyrimidin*-4-*yl ether* (**1**) (20.4 g, 61%), b.p. 74—76 °C/17 mmHg (Found: C, 43.95; H, 2.65; N, 14.7%; M^+, 190. $C_7H_5F_3N_2O$ requires C, 44.22; H, 2.65; N, 14.74%; *M*, 190); $\delta_F(CDCl_3)$, 47.8 (d, 2-F), 82.1 (d, 6-F), and 176.7 p.p.m. (dd, 5-F), $J_{2\text{-}F,5\text{-}F}$ 25 Hz, $J_{5\text{-}F,6\text{-}F}$ 17 Hz; $\delta_H(CDCl_3)$ ($OCH_2CH_X{=}CH_BH_A$, Z-H_X,H_B), 5.03 (CH_2), 5.40 (H_B), 5.51 (H_A), and 6.10 (H_X); J_{AX} 18 Hz; J_{BX} 10.5 Hz; $J_{CH_2,X}$ 6 Hz; J_{AB} 1.5 Hz.

(b) *With sodium allyl oxide.* Tetrafluoropyrimidine (5.15 g) and sodium allyl oxide in allyl alcohol (1.25M; 100 ml) were heated under reflux for 42 h and worked up as before to give 2,4,6-*triallyloxy*-5-*fluoropyrimidine* (**12**) (5.65 g 63%), b.p. 96—98 °C/0.01 mmHg (Found: C, 58.9; H, 5.65; N, 10.55%; M^+, 266. $C_{13}H_{15}FN_2O_3$ requires C, 58.64; H, 5.68; N, 10.52%; *M*, 266); $\delta_F(CDCl_3)$ 183.8 p.p.m. (s, 5-F).

(c) *With prop*-2-*ynyl alcohol.* Tetrafluoropyrimidine (20.5 g), prop-2-ynyl alcohol (10 ml), and anhydrous potassium carbonate (10 g) reacted exothermically when mixed. After 3 h at room temperature, the mixture was worked up as in (a) to give *prop*-2-*ynyl* 2,5,6-*trifluoropyrimidin*-4-*yl ether* (**4**) (17.56 g, 69%), m.p. 39.5—40 °C [from light petroleum (b.p. 30—40 °C)] (Found: C, 44.95; H, 1.45; N, 14.8%; M^+, 188. $C_7H_3F_3N_2O$ requires C, 44.69; H, 1.61; N, 14.89%; *M*, 188); $\delta_F(CDCl_3)$ 46.8 (d, 2-F), 80.1 (d, 6-F) and 175.9 p.p.m. (dd, 5-F, $J_{2\text{-}F,\ 5\text{-}F}$ 24 Hz, $J_{5\text{-}F,\ 6\text{-}F}$ 15 Hz). The ether (**4**) in ethyl acetate reacted with deuterium/Pd–$BaSO_4$ at room temperature to give [2,3-$^2H_2$]allyl 2,5,6-trifluoropyrimidin-4-yl ether (**3**), b.p. 74—78 °C/17 mmHg (Found: M^+, 192. $C_7H_3D_2F_3N_2O$ requires *M*, 192); $\delta_H(CDCl_3)$ [$OCH_2CD_X{=}CD_BH_A$ (Z-D_X,D_B) and $OCH_2CD_X{=}CH_BD_A$ (Z-D_X,H_B) in the ratio 4.5:1 respectively], 5.00 (CH_2), 5.39 (H_B), and 5.48 (H_A).

B *Reactions of Allyl* 2,5,6-*Trifluoropyrimidin*-4-*yl Ether* (**1**).—(a) *With sodium methoxide.* The ether (**1**) (3.7 g) and sodium methoxide in methanol (1.3M; 15.5 ml) were heated under reflux for 5.75 h. The three-component product was separated by chromatography on silica (20 × 5 cm) using CH_2Cl_2 as eluant to give *allyl* 2,5-*difluoro*-6-*methoxypyrimidin*-4-*yl ether* (**5**) (2.6 g, 66%), m.p. 25 °C [from light petroleum b.p. (40—60 °C)] (Found: C, 47.45; H, 4.3; N, 13.75%; M^+, 202. $C_8H_8FN_2O_2$ requires C, 47.53; H, 3.99; N, 13.86%; *M*, 202); $\delta_F(CDCl_3)$ 48.8 (d, 2-F) and 178.4 p.p.m. (d, 5-F), $J_{2\text{-}F,5\text{-}F}$ 26 Hz. The second component eluted from the column was *allyl* 5,6-*difluoro*-2-*methoxypyrimidin*-4-*yl ether* (**7**) (0.4 g, 10%) a liquid obtained by molecular distillation (Found: C, 47.4; H, 4.05; N, 14.25%; M^+, 202. $C_8H_8FN_2O_2$ requires C, 47.53; H, 3.99; N, 13.86%; M, 202); $\delta_F(CDCl_3)$ 83.8 (d, 6-F) and 183.1 p.p.m. (d, 5-F), $J_{5\text{-}F,6\text{-}F}$ 19 Hz. The component eluted last was *allyl* 5-*fluoro*-2,6-*dimethoxypyrimidin*-4-*yl ether* (**8**) (0.57 g, 14%), m.p. 42—43.5 °C [from light petroleum b.p. (30—40 °C)] (Found: C, 50.7; H, 5.4; N, 13.1%; M^+, 214. $C_9H_{11}FN_2O_3$ requires C, 50.46; H, 5.18; N, 13.08%; *M*, 214); $\delta_F(CDCl_3)$ 186.2 p.p.m. (s, 5-F). Reaction of (**1**) with 2 mol equiv. of sodium methoxide in methanol gave (**8**) (96%).

(b) *With lithium aluminium hydride.* The ether (**1**) (6.695 g, 35 mmol) in dry ether (60 ml) and lithium aluminium hydride in ether (0.233M, 160 ml, 37 mmol) were stirred at room temperature for 135 min and worked up as in A(a) to give a mixture of two products (**6**) and (**9**) (5.82 g, 96%) in the ratio 75:25 respectively (by ^{19}F n.m.r.). Chromatography on silica (18 × 5 cm) using $CHCl_3$ as eluant gave a mixture of *allyl* 2,5-*difluoropyrimidin*-4-*yl ether* (**6**) and *allyl* 5,6-*difluoropyrimidin*-4-*yl ether* (**9**) (1.52 g) b.p. 74—78 °C/11 mmHg in the ratio 91:9 respectively (Found: C, 49.05; H, 3.5; N, 16.6%; M^+, 172. $C_7H_2F_2N_2O$ requires C, 48.84; H, 3.51; N, 16.28%; *M*, 172); compound (**6**), $\delta_F(CDCl_3)$ 49.4 (d, 2-F) and 159.8 p.p.m. (d, 5-F), $J_{2\text{-}F,5\text{-}F}$ 27 Hz; compound (**9**), $\delta_F(CDCl_3)$ 86.0 (d, 6-F) and 171.8 p.p.m. (d, 5-F), $J_{5\text{-}F,6\text{-}F}$ 19 Hz.

(c) *With sodium hydroxide.* The addition of aqueous sodium hydroxide (2M; 39 ml) to a solution of the ether (**1**) (5.03 g) in dioxane (80 ml) resulted in a temperature rise of 20 °C above room temperature. The mixture was allowed to cool to room temperature over 105 min and worked up as in A(a), ^{19}F n.m.r. spectroscopy revealing the presence of two compounds (**13**) and (**14**) in the ratio 70:30 respectively. The attempted fractional crystallisation of the crude product with undried light petroleum (b.p. 100—120 °C) resulted in the further reaction of the minor component (**14**) to give a new compound (**26**). The mixture was sublimed at 50 °C/0.05 mmHg to give *allyl* 2,5-*difluoro*-6-*hydroxypyrimidin*-4-*yl ether* (**13**) (1.57 g, 32%), m.p. 123—124 °C [from light petroleum (b.p. 100—120 °C)] (Found: C, 44.9; H, 3.2; N, 15.3%; M^+, 188. $C_7H_6F_2N_2O_2$ requires C, 44.69; H, 3.21; N, 14.89%; *M*, 188); $\delta_F(CDCl_3)$ 51.7 (d, 2-F) and 178.2 p.p.m. (d, 5-F), $J_{2\text{-}F,5\text{-}F}$ 25 Hz. Continued sublimation at 75—120 °C/0.05 mmHg and successive crystallisation of the sublimate from water followed by toluene gave 5-*allyl*-5-*fluoropyrimidine*-2,4,6-*trione* (**26**) (0.56 g, 11%), m.p. 170—171 °C (lit.,[6] 163—164 °C) (Found: C, 45.0; H, 3.5; N, 14.65%; M^+, 186. $C_7H_7FN_2O_3$ requires C, 45.16; H, 3.79; N, 15.05%; *M*, 186); $\delta_F(CDCl_3)$ 171.9 p.p.m. (t) J_{CH_2CF} 15 Hz. The precursor to (**26**), allyl 5,6-difluoro-2-hydroxypyrimidin-4-yl ether (**14**), $\delta_F(CDCl_3)$ 85.3 (d, 6-F) and 185.3 p.p.m. (d, 5-F), $J_{5\text{-}F,6\text{-}F}$ 18 Hz could not be isolated.

(d) *With sodium hydroxide followed by diazomethane.* The ether (**1**) (2.63 g), aqueous sodium hydroxide (2M; 20 ml), and dioxane (40 ml) were allowed to react as in (c); the crude product was then treated with an excess of diazomethane in ether and the methylated material separated on silica (20 × 5 cm) using CH_2Cl_2 as eluant to give the 6-methoxy compound (**5**) (0.18 g, 6%) followed by the 2-methoxy compound (**7**) (0.17 g, 6%). Further development of the column using ether and sublimation at 40 °C/0.05 mmHg gave 6-*allyloxy*-2,5-*difluoro*-3-*methylpyrimidin*-4(3H)-*one* (**19**) (0.08 g, 3%), m.p. 42—44 °C (Found: C, 47.2; H, 4.0; N, 13.7%; M^+, 202. $C_8H_8F_2N_2O_2$ requires C, 47.53; H, 3.99; N, 13.86%; *M*, 202); $\delta_F(CDCl_3)$ 56.7 (d, 2-F) and 176.5 p.p.m. (d, 5-F), $J_{2\text{-}F,5\text{-}F}$ 24 Hz; $\delta_H(CDCl_3)$ 3.51 (N–CH_3); $\lambda_{max.}$(cyclohexane) 233 (ε 3 100) and 272 nm (3 300). The component eluted last was 5-*allyl*-1,3-*dimethyl*-5-*fluoropyrimidine*-2,4,6-*trione* (**27**) (0.03 g, 1%), m.p. 75—76 °C [from light petroleum (b.p. 60—80 °C)] (Found: C, 50.5; H, 4.8; N, 12.8%; M^+, 214. $C_9H_{11}FN_2O_3$ requires C, 50.46; H, 5.18; N, 13.08%; *M*, 214); $\delta_F(CDCl_3)$ 164.4 p.p.m. (t), J_{CH_2CF} 14 Hz; $\delta_H(CDCl_3)$ 3.32 (2 × N–CH_3).

The 6-hydroxy compound (**13**) (0.815 g) with an excess of diazomethane in ether gave only the 6-methoxy compound (**5**) (0.585 g, 67%) and (**19**) (0.166 g, 19%).

(e) *With hot aqueous alkali followed by diazomethane.* The ether (**1**) (2.45 g), potassium hydroxide (1.5 g), water (25 ml), and dioxane (25 ml) were heated under reflux for 64 h and the product was worked up as in (d) to give *methyl* 2-*fluoropent*-4-*enoate* (**31**) (0.236 g, 14%), b.p. 54—56 °C/13 mmHg (Found: C, 54.45; H, 6.75%; $M^+ - HF$, 112. $C_6H_9FO_2$ requires C, 54.54; H, 6.87%; *M*, 132); $\delta_F(CDCl_3)$ 192.4 p.p.m. (dt), J_{CHF} 48 Hz, J_{CH_2CF} 24 Hz. The ether (**1**) (5.546 g), aqueous sodium hydroxide (2M; 58.5 ml), and dioxane (30 ml) were heated under

reflux for 22 h and the product worked up as in (d) to give the two products (**31**) and (**32**) in the ratio 15:85 respectively. Compound (**31**) was evaporated at 25 °C/12 mmHg and the residue was distilled to give *dimethyl 2-allyl-2-fluoropropanedioate* (**32**) (1.43 g, 26%), b.p. 105—110 °C/12 mmHg (Found: C, 50.75; H, 6.15%; M^+, 190. $C_8H_{11}FO_4$ requires C, 50.52; H, 5.83%; *M*, 190); $\delta_F(CDCl_3)$ 166.2 p.p.m. (t), J_{CH_2CF} 23 Hz.

C *Reactions of* 2,5-*Difluoro*-4,6-*dimethoxypyrimidine*.—(a) *With sodium allyl oxide in THF*. Sodium hydride was added to allyl alcohol (0.378 g) in THF until the evolution of hydrogen ceased after which the pyrimidine compound (1.09 g) was added, and the mixture heated under reflux for 1 h. The work-up procedure as in A(a) gave *allyl 5-fluoro*-4,6-*dimethoxypyrimidin*-2-*yl ether* (**10**) (1.32 g, 99%), m.p. 41.5—42.5 °C [from light petroleum (b.p. 30—40 °C)] (Found: C, 50.4; H, 5.5; N, 12.9%; M^+, 214. $C_9H_{11}FN_2O_3$ requires C, 50.46; H, 5.18; N, 13.08%; *M*, 214); $\delta_F(CDCl_3)$ 185.9 p.p.m. (s).

(b) *With sodium allyl oxide in allyl alcohol*. A mixture of the dimethoxy compound (2.027 g) and sodium allyl oxide in allyl alcohol (1.25M; 12 ml) was heated under reflux for 17 h and worked up as in A(a). Chromatography on silica (15 × 5 cm) using CH_2Cl_2 gave the triether (**12**) (0.892 g, 29%) followed by 2,4-*diallyloxy*-5-*fluoro*-6-*methoxypyrimidine* (**11**) (0.24 g, 9%), m.p. 23—25.5 °C [from light petroleum (b.p. 30—40 °C)] (Found: C, 54.95; H, 5.3; N, 11.35%; M^+, 240. $C_{11}H_{13}FN_2O_3$ requires C, 54.99; H, 5.45; N, 11.66%; *M*, 240); $\delta_F(CDCl_3)$ 185.1 p.p.m. (s).

(c) *With potassium hydroxide*. A mixture of the dimethoxy compound (0.066 g), potassium hydroxide (0.101 g), and t-butyl alcohol (5 ml) was heated under reflux for 18 h and worked up as in A(a) to give 5-*fluoro*-2-*hydroxy*-4,6-*dimethoxypyrimidine* (**15**) (0.052 g, 80%), m.p. 183—185 °C (from diethyl ether) (Found: C, 41.75; H, 3.7; N, 16.2%; M^+, 174. $C_6H_7N_2FO_2$ requires C, 41.38; H, 4.05; N, 16.09%; *M*, 174); $\delta_F([^2H_6]acetone)$, 187.0 p.p.m. (s).

Reaction of the Sodium Salt of 2,5,6-*trifluoro*-4-*hydroxypyrimidine with Allyl Bromide*.—The 4-hydroxy compound (2.39 g) was treated with an excess of sodium hydride in THF (10 ml) and the supernatant liquid and further THF washings (20 ml) were allowed to react with allyl bromide (1.65 ml) under reflux for 3 d. The product was separated by chromatography on silica (20 × 5 cm) using CH_2Cl_2 to give compound (**1**) (0.128 g, 4%) followed by 3-*allyl*-2,5,6-*trifluoropyrimidin*-4(3H)-*one* (**2**) (0.365 g, 12%), m.p. 33—34 °C [from light petroleum (b.p. 30—40 °C)] (Found: C, 44.15; H, 2.5; N, 14.5%; M^+, 190. $C_7H_5F_2N_2O_2$ requires C, 44.22; H, 2.65; N, 14.74%; *M*, 190); $\delta_F(CDCl_3)$ 57.1 (dd, 2-F), 90.4 (dd, 6-F), and 172.4 p.p.m. (dd, 5-F), $J_{2\text{-}F,5\text{-}F}$ 23 Hz, $J_{2\text{-}F,6\text{-}F}$ 8.5 Hz, $J_{4\text{-}F,6\text{-}F}$ 13 Hz; $\delta_H(CDCl_3)$ ($CH_2CH_X{=}CH_BH_A$, $Z\text{-}H_XH_B$) 4.64 (CH_2), 5.35 (H_A), 5.37 (H_B), 5.89 (H_X), J_{AX} 17 Hz, J_{BX} 10 Hz, J_{CH_2X} 6 Hz; $\lambda_{max.}$(cyclohexane) 221 (ε 4 400) and 265 nm (3 900).

Reaction of 2,5,6-*Trifluoro*-4-*hydroxypyrimidine with Allyl Bromide*.—The 4-hydroxy compound (2.23 g), allyl bromide (1.90 g), anhydrous potassium carbonate (1.5 g), and acetone (20 ml) were heated under reflux for 23 h and gave two fractions on sublimation: fraction (i) at room temperature/0.05 mmHg, consisting of (**1**) (1.35 g, 48%) and (**2**) (1%); and fraction (ii) at 70 °C/0.05 mmHg which was separated by chromatography on silica using CH_2Cl_2 to give 1,3-*diallyl*-5,6-*difluoropyrimidine*-2,4(1H,3H)-*dione* (**25**) (0.128 g, 4%), a liquid obtained by molecular distillation (Found: C, 52.75; H, 4.3; N, 12.5%; M^+, 228. $C_{10}H_{10}F_2N_2O_2$ requires C, 52.63; H, 4.42; N, 12.28%; *M*, 228); $\delta_F(CDCl_3)$ 116.8 (d, 6-F) and 187.8 p.p.m. (d, 5-F), $J_{5\text{-}F,6\text{-}F}$ 8.5 Hz. The non-sublimable residue was acidified, extracted with ether and fractionally sublimed (25 °C and 70 °C/0.05 mmHg) to give unchanged pyrimidin-4-ol (0.31 g, 14%) and 3-*allyl*-5,6-*difluoropyrimidine*-2,4(1H,3H)-*dione* (**22**) (0.186 g, 7%), m.p. 95—96 °C [from light petroleum (b.p. 100—120 °C)] (Found: C, 44.55; H, 3.35; N, 14.6%; M^+, 188. $C_7H_6F_2N_2O_2$ requires C, 44.68; H, 3.22; N, 14.89%; *M*, 188); $\delta_F(CDCl_3)$ 115.8 (d, 6-F) and 186.4 (d, 5-F), $J_{5\text{-}F,6\text{-}F}$ 8 Hz.

Flash Vapour-Phase Pyrolysis (*F.V.P.*) *Reactions*.—(a) The allyl ether (**1**) (2.30 g) was distilled through a quartz tube [60 cm × 1.5 cm packed with silica fibre (20 × 1.5 cm)] heated at 440 °C, into a trap cooled with liquid air connected to a high vacuum system (0.005 mmHg). The crude product was separated by distillation and sublimation to give unchanged (**1**) (12%) and the *N*-allyl isomer (**2**) (1.23 g, 53%).

(b) The deuterium-containing ether (**3**) (1.361 g) was allowed to react as in (a) and the crude product was separated by chromatography on silica (10 × 3.5 cm), using CH_2Cl_2 to give 3-[1,2-$^2H_2$]*allyl*-2,5,6-*trifluoropyrimidin*-4(3H)-*one* (**16**) (0.61 g, 45%), m.p. 32—34 °C [from light petroleum (b.p. 30—40 °C)] (Found: M^+, 192. $C_7H_3D_2F_2N_2O_2$ requires *M*, 192); $\delta_F(CDCl_3)$ 57.1 (dd, 2-F), 90.4 (dd, 6-F), and 172.4 p.p.m. (dd, 5-F), $J_{2\text{-}F,5\text{-}F}$ 23 Hz, $J_{2\text{-}F,6\text{-}F}$ 8.5 Hz, and $J_{5\text{-}F,6\text{-}F}$ 13 Hz; $\delta_H(CDCl_3)$ ($CHDCD_X{=}CH_BH_A$, $Z\text{-}D_X,H_B$), 4.63 (CHD), 5.36 (H_A), 5.38 (H_B) in the ratio 1:1.05:1.05 respectively; $\lambda_{max.}$(cyclohexane) 226 (ε 2 800) and 263 nm (3 800).

(c) A mixture of the ethers (**6**) and (**9**) (91:9 respectively) (0.642 g) was allowed to react at 470 °C as in (a). ^{19}F N.m.r. spectroscopy showed that the product contained two products in the ratio 94:6, which was separated as in (b) to give the major component 3-*allyl*-2,5-*difluoropyrimidin*-4(3H)-*one* (**18**) (0.432 g, 67%), m.p. 37—39 °C [from diethyl ether–light petroleum (b.p. 40—60 °C)] (Found: C, 49.1; H, 3.45; N, 16.25%; M^+, 172. $C_7H_2F_2N_2O$ requires C, 48.84; H, 3.5; N, 16.28%; *M*, 172); $\delta_F(CDCl_3)$ 58.7 (d, 2-F) and 152.7 p.p.m. (d, 5-F), $J_{2\text{-}F,5\text{-}F}$ 24.5 Hz; $\lambda_{max.}$(cyclohexane) 218 (ε 2 800) and 266 nm (3 900).

(d) The ether (**5**) (0.542 g) was allowed to react at 475 °C as in (a) and the product was separated as in (b) to give unchanged (**5**) (0.077 g, 14%) and 3-*allyl*-2,5-*difluoro*-6-*methoxypyrimidin*-4(3H)-*one* (**17**) (0.353 g, 65%), m.p. 72—72.5 °C [from light petroleum (b.p. 30—40 °C)] (Found: C, 47.75; H, 4.25; N, 13.6%; M^+, 202. $C_8H_8F_2N_2O_2$ requires C, 47.53; H, 3.99; N, 13.86%; *M*, 202); $\delta_F(CDCl_3)$ 58.2 (d, 2-F) and 176.8 p.p.m. (d, 5-F), $J_{2\text{-}F,5\text{-}F}$ 24 Hz; $\lambda_{max.}$(cyclohexane) 233 (ε 3 500) and 272 nm (3 900).

(e) The ether (**7**) (0.673 g) was allowed to react at 470 °C as in (a) and the product was separated as in (b) to give unchanged (**7**) (0.108 g, 16%) and 3-*allyl*-5,6-*difluoro*-2-*methoxypyrimidin*-4(3H)-*one* (**20**) (0.44 g, 65%), a liquid obtained by molecular distillation (Found: C, 47.65; H, 3.78; N, 13.55%; M^+, 202. $C_8H_8F_2N_2O_2$ requires C, 47.53; H, 3.99; N, 13.86%; *M*, 202); $\delta_F(CDCl_3)$ 90.3 (d, 6-F) and 180.4 p.p.m. (d, 5-F), $J_{5\text{-}F,6\text{-}F}$ 14 Hz; $\lambda_{max.}$(cyclohexane) 219 (ε 4 500) and 266 nm (6 200).

(f) The ether (**8**) (2.149 g) was allowed to react at 480 °C as in (a) and separated as in (b) using CH_2Cl_2–ethyl acetate (80:20, v/v) as eluant to give (i) unchanged (**8**) (0.248 g, 11%); (ii) 3-*allyl*-5-*fluoro*-2,6-*dimethoxypyrimidin*-4(3H)-*one* (**21**) (0.196 g, 9%), m.p. 71—72 °C (from diethyl ether) (Found: C, 50.75; H, 5.4; N, 13.1%; M^+, 214. $C_9H_{11}FN_2O_3$ requires C, 50.46; H, 5.18; N, 13.08%; *M*, 214); $\delta_F(CDCl_3)$ 183.3 p.p.m. (5-F); $\lambda_{max.}$(cyclohexane) 230 (ε 3 600) and 271 nm (6 400); (iii) N-*methyl*-N-(2-*fluoro*-2-*methoxycarbonylpent*-4-*enoyl*)*urea* (**34**) (0.511 g, 22%) a liquid obtained by molecular distillation (Found: C, 46.75; H, 5.3; N, 11.75%; M^+, 232. $C_9H_{13}FN_2O_4$ requires C, 46.55; H, 5.64; N, 12.07%; *M*, 232); $\delta_F(CDCl_3)$ 165.6 p.p.m. (t), J_{CFCH_2} 21 Hz; the mass spectrum showed a significant peak with *m/z* 101 due to $C_3H_5N_2O_2^+$; and (iv) 5-*allyl*-5-*fluoro*-6-*methoxy*-3-*methylpyrimidine*-2,4-(3H,5H)-*dione* (**33**) (0.092 g, 4%), m.p. 125—126 °C (from benzene) (Found: C, 50.7; H, 4.95; N, 12.8%;

M^+, 214. $C_9H_{11}FN_2O_3$ requires C, 50.46; H, 5.18; N, 13.08%; *M*, 214); $\delta_F(CDCl_3)$ 171.8 p.p.m. (t), J_{CFCH_2} 18 Hz.

Prior to chromatographic separation, the ratio (**8**):(**21**):(**34**):(**33**):unknown was 11:27:51:5:6 respectively (by ^{19}F n.m.r.) giving the overall N:C migration terminus ratio as 1:2 [27:(51 + 5)] respectively. In another reaction this ratio was 1:10.7 [7:(23 + 52)].

Compound (**33**) (0.197 g) was converted into compound (**34**) (0.205 g, 96%) in acetone (10 ml) and water (0.103 g) at reflux temperature for 14 h.

(g) The ether (**13**) (0.585 g) was allowed to react at 450 °C as in (a) and separated as in (b) using ethyl acetate to give the barbiturate derivative (**26**) (0.062 g, 11%).

(h) The ether (**10**) (0.342 g) was allowed to react at 505 °C as in (a) and separated as in (b) to give unchanged (**10**) (0.056 g, 16%) and after elution with diethyl ether, compound (**15**) (0.073 g, 26%).

Static Vapour-Phase Pyrolysis (S.V.P.) Reactions.—(a) The ether (**5**) (0.56 g) was sealed *in vacuo* in a 2 l flask and heated at 210 °C for 69 h to give 5-*allyl*-5-*fluoro*-1-*methylpyrimidine*-2,4,6-(1H,3H,5H)-*trione* (**28**) (0.036 g, 6%) [from light petroleum (b.p. 80—100 °C)] (Found: C, 48.25; H, 4.35; N, 13.75%; M^+, 200. $C_8H_9FN_2O_3$ requires C, 48.00; H, 4.53; N, 14.00%; *M*, 200); $\delta_F(CDCl_3)$ 160.1 p.p.m. (t, 5-F), J_{CFCH_2} 14.5 Hz.

(b) The diether (**11**) (0.087 g) was allowed to react as in (a) at 196 °C for 7 h and the product was separated by thick layer chromatography on silica (20 × 20 cm) using CH_2Cl_2 to give unchanged (**11**) (0.028 g, 32%) and 3,5-*diallyl*-5-*fluoropyrimidine*-2,4,6(1H,3H,5H)-*trione* (**29**) (0.042 g, 51%), m.p. 87.5—89 °C (from benzene) (Found: C, 53.0; H, 5.05; N, 12.2%; M^+, 226. $C_{10}H_{11}FN_2O_3$ requires C, 53.09; H, 4.90; N, 12.39%; *M*, 226); $\delta_F(CDCl_3)$ 166.6 (t), J_{CFCH_2} 15 Hz.

(c) The triether (**12**) (2.07 g) was allowed to react in a 10 l flask as in (a) at 194 °C for 16.5 h to give 1,3,5-*triallyl*-5-*fluoropyrimidine*-2,4,6-(1H,3H,5H)-*trione* (**30**) (1.82 g, 88%), m.p. 52—54 °C [from light petroleum (b.p. 30—40 °C)] (Found: C, 58.55; H, 5.4; N, 10.2%; M^+, 266. $C_{13}H_{15}FN_2O_2$ requires C, 58.64; H, 5.68; N, 10.52%; *M*, 266); $\delta_F(CDCl_3)$ 165.5 p.p.m. (t), J_{CFCH_2} 15 Hz.

Hydrolysis of 3-*Allyl*-2,5-*difluoropyrimidin*-4(3H)-*ones.*—(a) Compound (**2**) (0.049 g), potassium carbonate (0.033 g), and undried acetone (5 ml) were heated under reflux for 24 h to give compound (**22**) (0.037 g, 76%).

(b) Compound (**17**) (0.059 g), acetone (5 ml), and aqueous sodium hydroxide (2M; 0.3 ml) were stirred at room temperature for 17 h to give 3-*allyl*-5-*fluoro*-6-*methoxypyrimidine*-2,4-(1H,3H)-*dione* (**23**) (0.52 g, 89%), m.p. 149—151 °C (from benzene) (Found: C, 48.2; H, 4.25; N, 14.35%; M^+, 200. $C_8H_9FN_2O_3$ requires C, 48.00; H, 4.53; N, 14.00%; *M*, 200) $\delta_F(CDCl_3)$ 191.0 p.p.m. (5-F).

(c) Compound (**18**) (0.229 g), acetone (12 ml), and aqueous sodium hydroxide (2M; 1.4 ml) were stirred at room temperature for 10 min to give a mixture of three components (by ^{19}F n.m.r.), present in the ratio 70:15:15. The major component, separated by sublimation 40 °C/0.05 mmHg and chromatography on silica–ethyl acetate gave the major component, 3-*allyl*-5-*fluoropyrimidine*-2,4-(1H,3H)-*dione* (**24**) (0.092 g, 41%), m.p. 78.5—80 °C (Found: C, 49.2; H, 4.2; N, 16.8%; M^+, 170. $C_7H_7FN_2O_2$ requires C, 49.41; H, 4.15; N, 16.47%; *M*, 170); $\delta_F([^2H_6]acetone)$ 169.0 p.p.m. (d) $J_{5\text{-}F,6\text{-}H}$ 5 Hz.

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