# Partially Fluorinated Heterocyclic Compounds. Part 12.† Novel Internal Diels–Alder Adducts *via* Claisen Rearrangement Intermediates from Tetrafluoro-4- and -3-pyridyl Prop-2-enyl Ethers. Syntheses of Tetrafluoro-3-aza- and -4-aza-tricyclo[3.3.1.$0^{2,7}$]non-3-en-6-one

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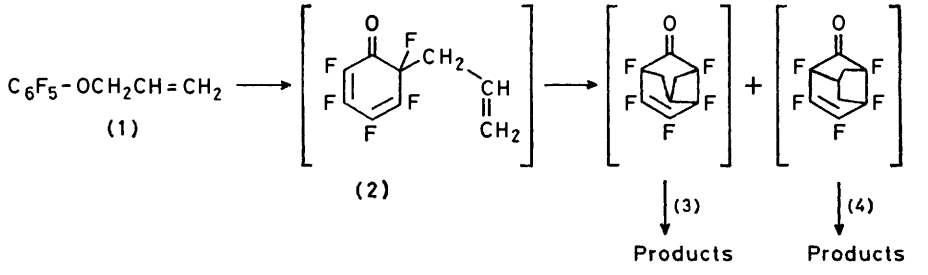
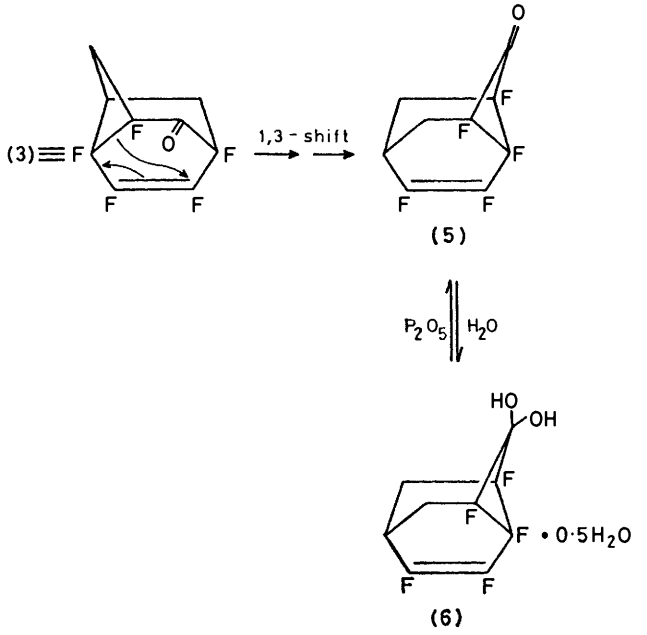
Vapour-phase thermolyses of 2,3,5,6-tetrafluoro-4-pyridyl prop-2-enyl ether and 2,4,5,6-tetrafluoro-3-pyridyl prop-2-enyl ether gave 2,4,5,7-tetrafluoro-3-azatricyclo[3.3.1.$0^{2,7}$]non-3-en-6-one (14) and 2,3,5,7-tetrafluoro-4-azatricyclo[3.3.1.$0^{2,7}$]non-3-en-6-one (21) respectively by internal Diels–Alder reactions of Claisen rearrangement intermediates. 4-Bromo-2,3,5-trifluoro-6-pyridyl prop-2-enyl ether gave 4-bromo-3,5-difluoro-3-prop-2-enyl-pyridine-2,6(1*H*, 3*H*)-dione (19) the product of hydrolysis of a Claisen intermediate. Compounds (14) and (21) underwent ready hydrolysis to the corresponding cyclic lactams, in which the ketonic carbonyl group at C-6 in both cases had also been converted into a *gem*-diol [compounds (15) and (22), respectively]. Hydrolytic cleavage of (22) followed by oxidative cleavage with periodic acid and reaction with diazomethane gave a trimethoxycarbonyl compound (25) containing a difluorocyclobutane ring.

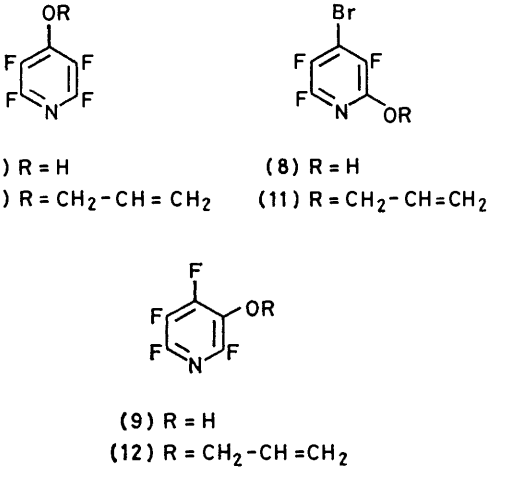
In previous papers,[1] we reported that the vapour-phase pyrolysis of pentafluorophenylprop-2-enyl ether (1) at 440—480 °C gives a variety of products whose formation was rationalised in terms of reactions of both possible intermediate Diels–Alder adducts, (3) and (4), of the intermediate 2,3,4,5,6-pentafluoro-6-prop-2-enylcyclohexa-2,4-dienone (2) (Scheme 1). Under milder conditions (137—141 °C for 13 d) we isolated the hydrated compound (6), the formation of which was rationalised by invoking a step-wise [1,3]-sigmatropic rearrangement of (3) (Scheme 2).[2] We have now begun a systematic study of this thermolysis reaction with polyfluoroheteroaromatic compounds and in this Paper we report the results of our work with some polyfluoro-2-, -3-, and -4-pyridyl prop-2-enyl ethers.




Scheme 1




Scheme 2



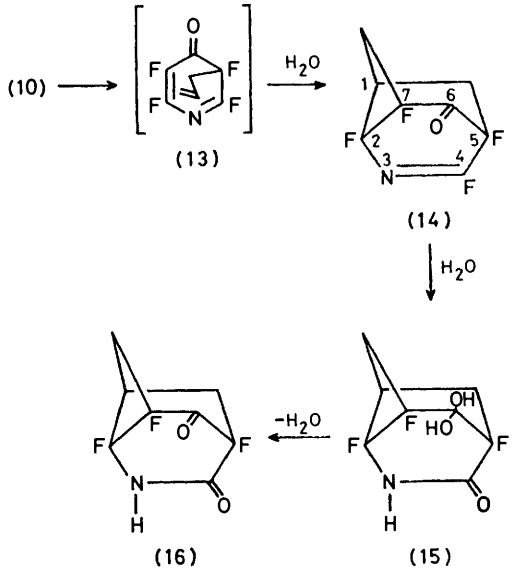

Before this work began tetrafluoro-4-hydroxypyridine [3] (7) and 4-bromo-2,3,5-trifluoro-6-hydroxypyridine [4] (8) (but not the 2,3,4,5-tetrafluoro-6-hydroxy-

† Part 11, G. M. Brooke and Md. Abul Quasem, *J.C.S. Perkin I*, 1973, 429.

pyridine) were readily accessible materials, while tetrafluoro-3-hydroxypyridine (9) was unknown. We have now prepared the last compound from 2,3,4,6-tetrafluoropyridine by metallation in ether with n-butyllithium in hexane at $<-70$ °C,[5] followed by reaction with trimethyl borate and oxidation of the product with hydrogen peroxide, a method used previously to prepare polyfluorophenols.[6] The hydroxy-compounds (7), (8), and (9) were readily converted into the corresponding prop-2-enyl ethers (10), (11), and (12) respectively, using prop-2-enyl bromide and anhydrous potassium carbonate in acetone (*cf.* ref. 1).

## RESULTS AND DISCUSSION

2,3,5,6-Tetrafluoro-4-pyridyl prop-2-enyl ether (10) was heated in the vapour phase at 138 °C for 10 d. The product consisted of unchanged ether (10) (15%), 3-aza-2,4,5,7-tetrafluorotricyclo[3.3.1.$0^{2,7}$]non-3-en-6-one (14) (16%), its hydrated hydrolysis product (15) (9%), and polymeric material (54%) (Scheme 3).




SCHEME 3

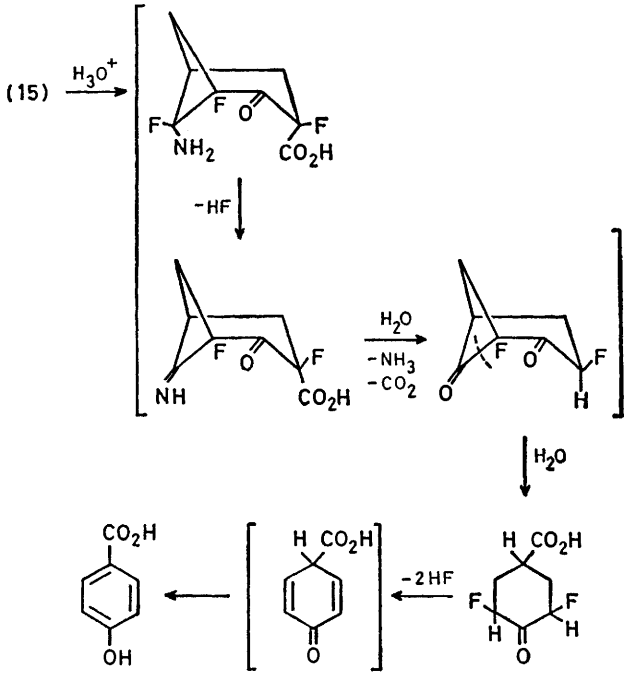
The N=CF bond in the intramolecular Diels–Alder adduct (14) was highly susceptible to reaction with water but compound (15) was quite stable, even with the *gem*-diol function, though sublimation *in vacuo* did give the 6-keto-compound (16). The overall structure of the tricyclic ring system was established by the quantitative conversion of (15) into 4-hydroxybenzoic acid, rationalised by the sequence shown in Scheme 4.

The thermolysis of 4-bromo-2,3,5-trifluoro-6-pyridyl prop-2-enyl ether (11) at 160 °C for 139 h was an inefficient process. The product consisted of unchanged ether (11) (62%) and the imide (19) (7%), resulting from the hydrolysis of the intermediate dienone (17) and/or (18) (Scheme 5).

The structure of (19) was deduced on the basis of spectroscopic data and elemental analysis. In particular the mass spectrum showed parent peaks at *m/e* 265 and 267 of almost equal intensity characteristic of the mono-bromo-compound and an intense peak at 41 due to $[CH_2{=}CH{-}CH_2]^+$. The $^{19}$F n.m.r. spectrum showed only two absorptions, of equal intensity, at $\delta$ 116.4 and 142.6, the latter being a triplet ($J_{H-F} = 9.6$ Hz) resulting from $CF{-}CH_2$ coupling. The i.r. spectrum showed strong absorptions at 2 860, 3 080, and 3 195 cm$^{-1}$, due to the presence of –CO–NH–CO–, and there were similar absorptions in this region in succinimide, examined as a convenient model compound.

The thermolysis of 2,4,5,6-tetrafluoro-3-pyridyl prop-2-enyl ether (12) at 185 °C for 112.8 h was the most efficient reaction we have studied so far: the product consisted of 14% unchanged ether (12), and 2,3,5,7-tetrafluoro-4-azatricyclo[3.3.1.$0^{2,7}$]non-3-en-6-one (21) (81%). Compound (21) was noticeably less susceptible to hydrolysis than was the isomer (14), but nevertheless was easily converted into the hydrated hydrolysed product (22) (Scheme 6).

The skeletal structure of (22) was determined by cleaving two of the ring systems while preserving the cyclobutane ring, and was effected by the following sequence of reactions. Acid hydrolysis of (22) and

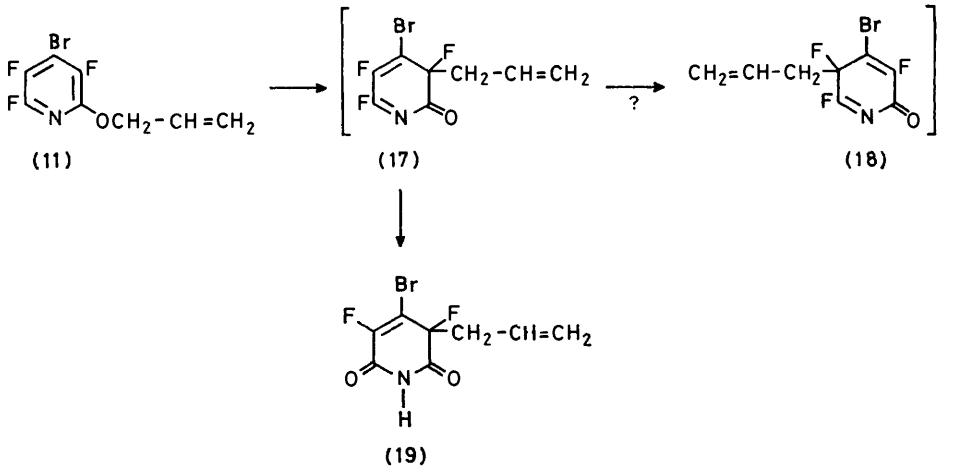



SCHEME 4

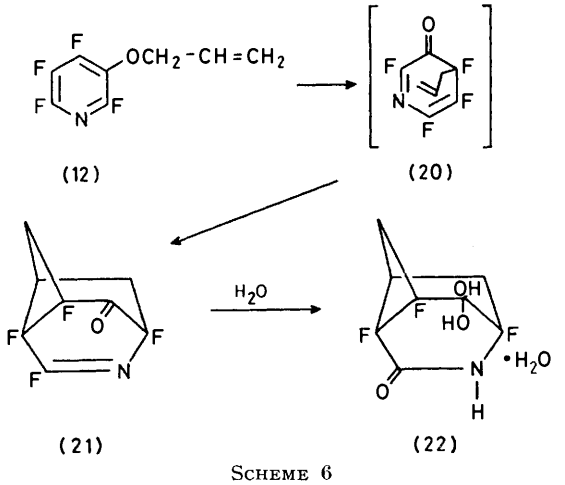
periodic acid oxidation of the crude diketone (23) gave the tricarboxylic acid (24) which was not characterised but was converted conveniently into the trimethyl ester (25) (81% yield) (Scheme 7) readily identifiable by spectroscopic methods.

Although compound (25) failed to show a parent ion in the mass spectrum at 280, the highest peak at *m/e* 249 ($M^+$ — MeO) could readily be accounted for on the basis of an intramolecularly stabilised acylium cation. The $^1$H n.m.r. spectrum showed three distinct absorptions due to methyl ester groups, but the $^{19}$F n.m.r. spectrum

was particularly informative and entirely consistent with the structure assigned to (25). There were two absorptions of equal intensity at δ 159.4 (doublet, $J_{HF}$ 21 Hz) and 173.2 (triplet, $J_{HF}$ = 26 Hz) which collapsed to singlets on broad-band decoupling of the protons [which showed that $J_{FF}$ *ca.* 0 Hz]. These data exclude the internal Diels–Alder adduct being formulated as (26), the aza-analogue of (4), since the above sequence of reactions would have given (27) a symmetrical cyclopentane derivative which would have shown only *one* fluorine absorption (Scheme 8).




SCHEME 5

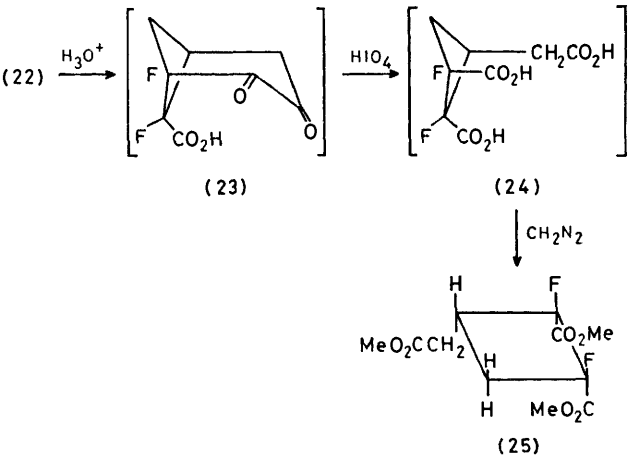



SCHEME 6

Somewhat surprisingly, thermolysis of both (10) and (12) *failed* to give the aza-analogues of (5), which would result from overall 1,3-shifts in the Diels–Alder adducts (14) and (21).

Claisen rearrangement reactions with prop-2-enyl and related ethers in the pyridine series are limited.[7] Attempted rearrangement with 4-pyridyl prop-2-enyl ether led largely to polymeric products and no characterisable rearrangement product could be isolated,[8] also no viable synthesis of 3-pyridyl prop-2-enyl ether has been published. However, 2-pyridyl prop-2-enyl ether gave approximately equal amounts of rearrangement to nitrogen and to the carbon at position 3, and 2-pyridyl 1-methylprop-2-enyl ether gave similar proportions of the expected 'inverted' products, 1-but-2-enyl- and 3-but-2-enyl-2-pyridones.[9] Of particular interest here, however, was the observation that 2-pyridyl but-2-enyl ether (28) gave initially the expected inverted product at C-3, namely 3-(1-methylprop-2-enyl)-2-pyridone (29), but with increasing reaction time, up to 60% of the product consisted of 1-but-2-enyl-2-pyridone (31), in which *no* 'inversion' had occurred in the side-chain. This is an example of an *ortho–ortho* rearrangement reaction which can be rationalised [10] in terms of the stepwise decomposition of the internal Diels–Alder adduct (30) (Scheme 9).

The work described in this paper exploits fluorine as a substituent in two ways: (*i*) as a blocking group (not H) to prevent rearomatisation of intermediate 2,4-dienones; and (*ii*) as a substituent which renders a 1,3-diene

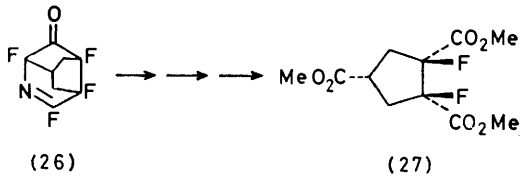



SCHEME 7

system electron-poor and which consequently is expected to have an 'inverse' electron demand,[11] in a (4 + 2) reaction, its LUMO interacting more readily with the HOMO of an electron rich dienophile.[12] The participation of fluorinated 2-aza-1,3-dienes in thermally promoted Diels–Alder reactions has only one precedent: *i.e.* the

addition of ethene to the product of photochemical addition of ethene across the 3,4-positions in pentafluoropyridine.[13]

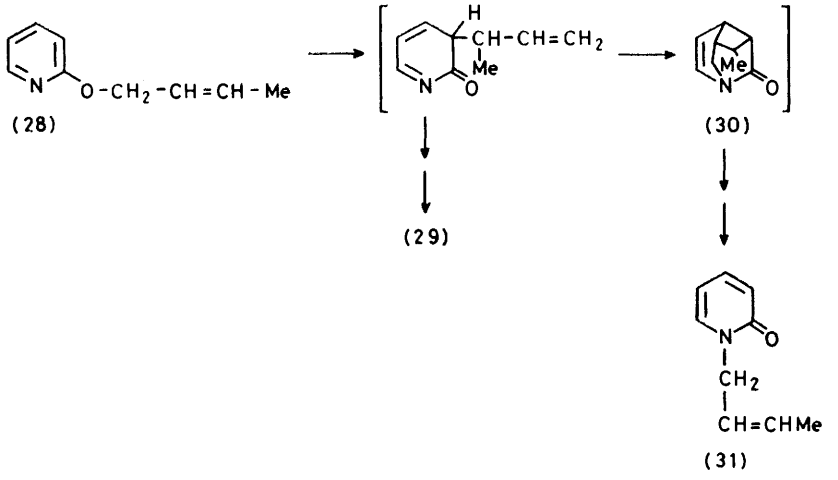
Two observations need to be made concerning our experiments. (*i*) The prop-2-enyl group in the 2-pyridyl ether (11) migrates *exclusively* away from



(26) (27)

SCHEME 8

nitrogen (unlike the hydrocarbon analogue), as it also does in the 3-pyridyl ether (12). (*ii*) Intramolecular Diels–Alder adducts are formed only from 2-aza-1,3-diene moieties, as in the intermediates (13) and (20); no adducts are formed from (17) which has a 1-aza-1,3-diene unit (though the large bromine atom in the terminal



SCHEME 2

position of the 1-aza-1,3-diene system may be partially responsible for the lack of reactivity), and it can be seen that with the 3-pyridyl ether (12), *if* rearrangement towards nitrogen had taken place, the resulting intermediate would also have had a 1-aza-1,3-diene unit. We are currently engaged in a theoretical investigation aimed at gaining an understanding of the specificities of the reactions outlined in (*i*) and (*ii*).

## EXPERIMENTAL

$^1$H N.m.r. (90 MHz) and $^{19}$F n.m.r. (84.67 MHz) spectra were obtained with a Brücker HX-90E spectrometer.

2,4,5,6-*Tetrafluoro*-3-*hydroxypyridine* (9).—2,3,4,6-Tetrafluoropyridine (54.4 g) in dry diethyl ether (100 ml) at −65 °C was treated under nitrogen with n-butyl-lithium in hexane (256 ml, 1.5M) and the mixture maintained at this temperature for 4 h. Trimethyl borate (48.1 g) was added, followed by hydrogen peroxide (90 ml, '400 vol') and the mixture was allowed to warm to room temperature over 16 h. The solution was acidified with sulphuric acid (1M), extracted with ether, and the dried ($MgSO_4$) extracts evaporated. Attempted distillation of the residue *in vacuo* (0.05 mmHg) resulted in sublimation of the crude product (44.8 g). Recrystallisation from a large volume (*ca.* 1 700 ml) of light petroleum [b.p. 60—80 °C] gave pure *hydroxy-compound* (9), m.p. 62.5—63.5 °C (Found: C, 36.2; H, 0.3; N, 8.2. $C_5HF_4NO$ requires C, 35.9; H, 0.6; N, 8.4%).

2,3,5,6-*Tetrafluoro*-4-*pyridyl Prop*-2-*enyl Ether* (10).—Treatment of the hydroxy-pyridine (7) with prop-2-enyl bromide and anhydrous potassium carbonate in anhydrous acetone by the method used previously [6] gave the *ether* (10), b.p. 80 °C at 16 mmHg (Found: C, 46.5; H, 2.8; N, 7.1; $C_8H_5F_4NO$ requires C, 46.4; H, 2.4; N, 6.8%).

2,4,5,6-*Tetrafluoro*-3-*pyridyl Prop*-2-*enyl Ether* (12).—Treatment of the hydroxy-pyridine (9) as above gave the ether (12), b.p. 52.5 °C at 7 mmHg (Found: C, 46.4; H, 2.4; N, 6.9%).

4-*Bromo*-2,3,5-*trifluoro*-6-*pyridyl Prop*-2-*enyl Ether* (11).—Treatment of the hydroxy-pyridine (8) as above gave the ether (11), b.p. 58 °C at 0.05 mmHg (Found: C, 35.6; H, 1.8; N, 4.9. $C_8H_5BrF_3NO$ requires C, 35.8; H, 1.9; N, 5.2%).

*Thermolysis Reactions.*—(a) *Using* 2,3,5,6-*tetrafluoro*-4-*pyridyl prop*-2-*enyl ether* (10). The ether (10) (2.83 g) was sealed in a 10-l flask *in vacuo* and heated at 138 °C for 10 d. The products were condensed into a side-arm cooled in liquid air, and volatile material was removed *in vacuo* and identified as unchanged ether (10) (0.44 g) by i.r. The solid remaining in the side arm was dissolved in dried acetone, the solvent evaporated, and the residue sublimed at room temperature *in vacuo* (0.005 mmHg) to give crude tricyclic material (14) (0.45 g) leaving behind the crude hydrolysed hydrated product (15) (0.28 g) and polymeric material (1.52 g) on the walls of the reaction vessel. Recrystallisation of crude (14) from benzene–light petroleum (b.p. 60—80 °C), followed by sublimation as before gave 2,4,5,7-*tetrafluoro*-3-*azatricyclo*[3.3.1.$0^{2,7}$]*non*-3-*en*-6-*one* (14), m.p. 81.5—83 °C (Found: C, 46.7; H, 2.4; N, 7.1%; $M^+$, 207. $C_8H_5F_4NO$ requires C, 46.4; H, 2.4; N, 6.8%; *M*, 207); $\delta_F$[$(CD_3)_2CO$] 61.5 (F-4), 163.5 (F-2), 176.2 (F-7), and 192.2 (F-5) upfield from internal $CFCl_3$; $\nu_{max.}$ 1 702 (N=CF) and 1 778 cm$^{-1}$ (C=O).

Compound (14) (0.45 g) was dissolved in wet acetone and the solvent was allowed to evaporate slowly at room temper-

ature. The crude product (0.48 g) was recrystallised from butan-2-one–light petroleum (b.p. 60—80 °C) to give 2,5,7-*trifluoro*-6,6-*dihydroxy*-3-*azatricyclo*[3.3.1.$0^{2,7}$]*nonan*-4-*one* (15), m.p. 167—168 °C (Found: C, 43.2; H, 4.0; N, 6.4. $C_8H_8F_3NO_3$ requires C, 43.1; H, 3.6; N, 6.3%); $\delta_F$[$(CD_3)_2$CO], 13.6 (F-2), 14.0 (F-7) and 28.6 (F-5) upfield from internal $C_6F_6$; $\nu_{max.}$ 1 725 (NH–*C*=*O*), 3 170, 3 280, and 3 420 $cm^{-1}$ (O–H, N–H region).

Sublimation of (15) at 100 °C and 0.005 mmHg effected dehydration to give 2,5,7-*trifluoro*-3-*aza*-*tricyclo*[3.3.1.$0^{2,7}$]-*nonane*-4,6-*dione* (16), m.p. 172—174 °C (Found: C, 47.1; H, 2.7; N, 7.2. $C_8H_6F_3NO_2$ requires C, 46.8; H, 2.9; N, 6.8%); $\delta_F$[$(CD_3)_2$CO] 13.4 (F-7), 16.9 (F-2), and 23.6 (F-5) upfield from internal $C_6F_6$; $\nu_{max.}$ 1 735 (NH–C=O), 1 780 (C=O), 3 100 and 3 200 $cm^{-1}$ (N–H region).

(b) *Using* 2,4,5,6-*tetrafluoro*-3-*pyridyl prop*-2-*enyl ether* (12). The ether (12) (5.05 g) was heated as in (a) at 185 °C for 112.8 h and worked-up as before to give unchanged starting material (0.72 g), and the crude tricyclic material (21) (4.11 g), which was separated from unidentified involatile material (0.07 g) by sublimation. Recrystallisation of crude product from benzene–light petroleum [b.p. 60—80 °C] and sublimation at 90 °C and 0.05 mmHg gave 2,3,5,7-*tetrafluoro*-4-*azatricyclo*[3.3.1.$0^{2,7}$]*non*-3-*en*-6-*one* (21), m.p. 104—105.5 °C (Found: C, 46.6; H, 2.5; N, 7.2. $C_8H_5F_4NO$ requires C, 46.4; H, 2.4; N, 6.8%); $\delta_F$[$(CD_3)_2$CO], 57.4 (F-3), 147.7 (F-5), 175.9 (F-7), and 203.8 (F-2) upfield from internal $CFCl_3$; $\nu_{max.}$ 1 687 (CF=N) and 1 778 $cm^{-1}$ (C=O).

Compound (21) (1.82 g) was boiled with a mixture of acetone (15 ml) and water (0.5 ml) for 1 min and the solvent allowed to evaporate slowly at room temperature. Recrystallisation of the residue from water gave 2,5,7-*trifluoro*-6,6-*dihydroxy*-4-*azatricyclo*[3.3.1.$0^{2,7}$]*nonan*-3-*one monohydrate* (22), m.p. 202—203 °C (loss of $H_2O$ at *ca.* 160 °C) (Found: C, 39.6; H, 4.5; N, 5.9. $C_8H_{10}F_3NO_4$ requires C, 39.8; H, 4.2; N, 5.8%); $\delta_F$[$(CD_3)_2$CO] (F-5), 173.6 (F-7), and 204.6 (F-2), upfield from internal $CFCl_3$; $\nu_{max.}$ 1 685 (NH–*C*=*O*), 3 220 and 3 480 $cm^{-1}$ (O–H and N–H region).

(c) *Using* 4-*bromo*-2,3,5-*trifluoro*-6-*pyridyl prop*-2-*enyl ether* (11). The ether (11) (5.44 g) was heated at 160 °C for 139 h and worked-up as before to give unchanged starting material (3.37 g), and the residue was dissolved in ether and solvent evaporated to give a solid–liquid mixture (0.74 g). Sublimation of this material at 70 °C and 0.05 mmHg, and further purification of the sublimate (0.39 g) by preparative-scale t.l.c. on silica using chloroform as eluant, followed by recrystallisation from toluene–light petroleum (b.p. 60—80 °C), gave 4-*bromo*-3,5-*difluoro*-3-*prop*-2-*enylpyridine*-2,6(1H,3H)-*dione* (19), m.p. 136.5—137.5 °C (Found: C, 36.2; H, 2.4; N, 5.2%. $M^+$, 265, 267. $C_8H_6BrF_2NO_2$ requires C, 36.1; H, 2.3; N, 5.3%; *M*, 266); $\delta_F$[$(CD_3)_2$CO], 116.4 (F-5) and 142.6 (F-3, t, $J_{HF}$ 9.6 Hz), upfield from internal $CFCl_3$; $\nu_{max.}$ 2 860, 3 080, and 3 195 $cm^{-1}$ (CO–*NH*-CO region).

*Hydrolytic Cleavage of* (15).—The tricyclic compound (15) (95 mg) was boiled with sulphuric acid (10 ml, 50% v/v) for 5 min. The solution was diluted with water, extracted with ether, and the dried ($MgSO_4$) extracts evaporated to give a solid (59 mg), the i.r. of which was identical with an authentic sample of 4-hydroxybenzoic acid.

*Hydrolytic Cleavage of* (22) *and Periodic Acid Oxidation of the Product.*—Compound (22) (2.85 g) was heated under reflux with sulphuric acid (50 ml; 1M) for 6 h, and the mixture continuously ether-extracted for 2 d. The extracts were dried ($MgSO_4$) and solvent evaporated to give a viscous liquid (2.85 g). A sample of this liquid (2.58 g) was dissolved in water (50 ml) to which was added, in turn, $Na_3H_2IO_6$ (5.03 g), sulphuric acid (50 ml; 1M), and water (100 ml), and after allowing the mixture to stand at room temperature for 15 h, it was continuously extracted with ether for 2 d. Evaporation of the dried ($MgSO_4$) extracts, and treatment of the residue with an excess of diazomethane in ether gave the *trimethyl ester* (25) (2.69 g), b.p. 106 °C at 0.01—0.05 mmHg (Found: C, 47.0; H, 5.2%; $M^+ - 31$, 249. $C_{11}H_{14}F_2O_6$ requires C, 47.1; H, 5.0%; *M* – MeO, 249); $\delta_F$[$(CD_3)_2$CO], 159.4 (d of t, $J_{FH}$ 21, 5.5, and 5.5 Hz) and 173.2 (t of d, $J_{FH}$ 26, 26, and 4 Hz); $J_{FF}$ *ca.* 0; τ 6.17, 6.21, and 6.32 (three Me groups in $CO_2Me$).

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