Rearrangement Reactions of Bicyclic Systems. Part IV.[1] Acid-catalysed Rearrangements of 5,6,7,8-Tetrafluoro-1,4-dihydro-1-methoxy-3,9-dimethyl-1,4-ethenonaphthalene (1-Methoxy-3,5-dimethyltetrafluorobenzobarrelene)

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The rearrangement of the title compound in trifluoroacetic acid was shown to be directed by the methyl groups, giving 5,6,7,8-tetrafluoro-3,4-dihydro-4,10-dimethyl-1,4-ethenonaphthalen-2(1*H*)-one (5). On the other hand the title compound gave the lactone 7,8,9,10-tetrafluoro-1,2,5,6-tetrahydro-2,6-dimethyl-2,6-methano-3-benzoxocin-4-one (4) in 98% sulphuric acid, and in 70% sulphuric acid 5,6,7,8-tetrafluoro-3-methyl-1-naphthylacetone (6) was an important product. The mechanisms operating have been studied by using deuteriated acids; the results establish that none of the protonation steps occurs stereospecifically.

In the preceding paper [1] we discussed the acid-catalysed rearrangements of 1-methoxytetrafluorobenzobarrelene (1) (5,6,7,8-tetrafluoro-1,4-dihydro-1-methoxy-1,4-ethenonaphthalene). The three major ketonic products were shown to be produced in a non-equilibrating system. On the other hand other workers have shown [2] that the hexamethylbenzobarrelenone (2) rearranges in acidic media to afford an equilibrium mixture of four ketones. We now report a study of the acid-catalysed rearrangement reactions of 5,6,7,8-tetrafluoro-1,4-dihydro-1-methoxy-3,9-dimethyl-1,4-ethenonaphthalene (3), prepared [3] by the reaction of tetrafluorobenzyne with 3,5-dimethylanisole.[4]

[1] Part III, N. J. Hales, H. Heaney, and S. V. Ley, preceding paper.

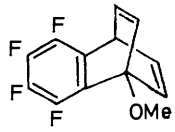
[2] H. Hart and G. M. Love, *Tetrahedron Letters*, 1971, 2267.

[3] P. C. Buxton, N. J. Hales, B. Hankinson, H. Heaney, S. V. Ley, and R. P. Sharma, *J.C.S. Perkin I*, 1974, 2681.

[4] Preliminary communication, H. Heaney and S. V. Ley, *Chem. Comm.*, 1971, 1342.

We hoped that when we subjected compound (3) to acid-catalysed rearrangements, the initial protonation would be directed by the presence of the methyl groups to give initially a cation at C-3. When compound (3) was dissolved in sulphuric acid (98%) and then immediately added to an excess of ice, a quantitative yield of a single product, $C_{14}H_{12}F_4O_2$, was obtained. The i.r. carbonyl stretching band was observed at 1730 cm^{-1} and the absorptions due to methylene groups were not resolved in the 60 MHz ^1H n.m.r. spectrum. This product was eventually identified, by chemical and spectroscopic methods (see later), as the lactone (4).

In an attempt to isolate intermediates we carried out reactions of compound (3) under less vigorous conditions. Heating under reflux in trifluoroacetic acid gave the lactone (4) (9·5%) and the ethenonaphthalenone (5)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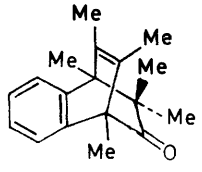
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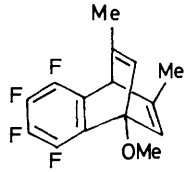
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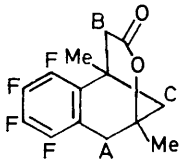
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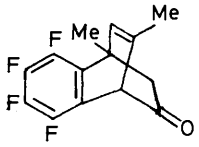
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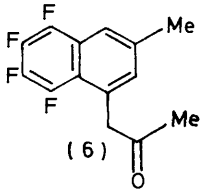
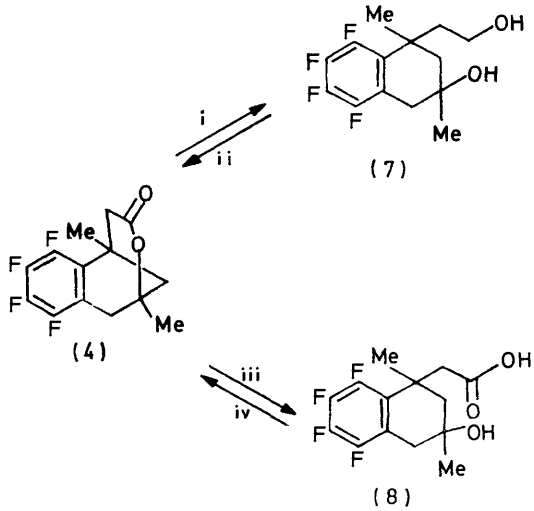

(6)

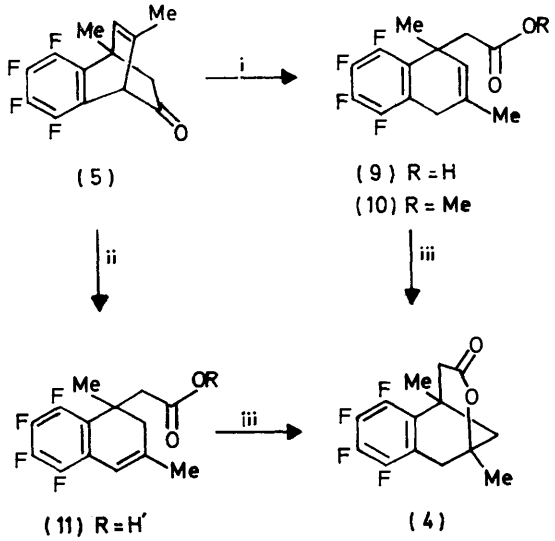
(82%). The lactone (4) was obtained in 94% yield when the ketone (5) was dissolved in 98% sulphuric acid and immediately quenched with ice. The rearrangement of compound (3) was also studied at 0° in 70% sulphuric acid in the hope that the cations produced might be trapped. Three products were isolated from this reaction: the ketone (5) (14%), the lactone (4) (39%), and the naphthylacetone (6) (40%). Neither of compounds (4) and (5) was converted into the ketone (6) under the reaction conditions. Compound (5) was already known [3] as the minor product from the reaction of tetrafluorobenzyne with 3,5-dimethylanisole. The structure of the ketone (6) was evident from its spectral data (see Experimental section).

Having established that the ketone (5) could be converted into the compound (4), we carried out various chemical transformations on the latter. Reduction with lithium aluminium hydride gave a diol (7) which was converted back into the lactone (4) on oxidation with Jones reagent. The lactone (4) was hydrolysed by base to the hydroxy-acid (8), which gave back the lactone on warming in solution in chloroform (Scheme 1).


(7) (4) (8)

SCHEME 1 Reagents: i, $LiAlH_4$; ii, CrO_3–H_2SO_4; iii, NaOH; iv, warm in $CHCl_3$

Ring opening reactions of tetrafluorobenzobarrelenone by means of base have been studied previously.[5] We carried out reactions of the ketone (5) with aqueous sodium hydroxide in tetrahydrofuran. At room temperature we obtained the acid (9), characterised as its methyl ester (10). On the other hand the acid (11), characterised as its methyl ester (12), was obtained from a similar reaction carried out under reflux. Both the acids (9) and (11) were readily cyclised to the lactone (4)

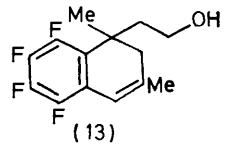

(5) (9) R = H (10) R = Me (11) R = H (12) R = Me (4)

SCHEME 2 Reagents: i, aq. NaOH–THF at room temp.; ii, aq. NaOH–THF at reflux; iii, (9) or (11) in 98% sulphuric acid

in the presence of sulphuric acid (98%). These reactions are summarised in Scheme 2.

[5] I. F. Mikailova and V. A. Barkhash, *J. Org. Chem.* (*U.S.S.R.*), 1970, **6**, 2335.

Although the signals due to the methylene groups in the lactone (4) were not resolved in the 60 MHz ^{1}H n.m.r. spectrum, they did appear as three well resolved AB quartets in the 220 MHz spectrum. The resonances due to the protons A were observed at τ 6·72 and 7·19 ($|J|$ *ca.* 18 Hz), those due to the protons B at 7·07 and 7·52 ($|J|$ *ca.* 18 Hz), and those due to the protons C at 7·85 and 8·07 ($|J|$ *ca.* 16 Hz, further split by long-range ^{1}H,^{19}F coupling).



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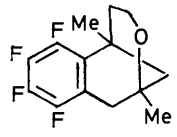

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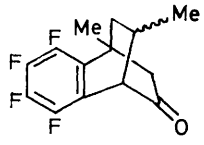


(15)

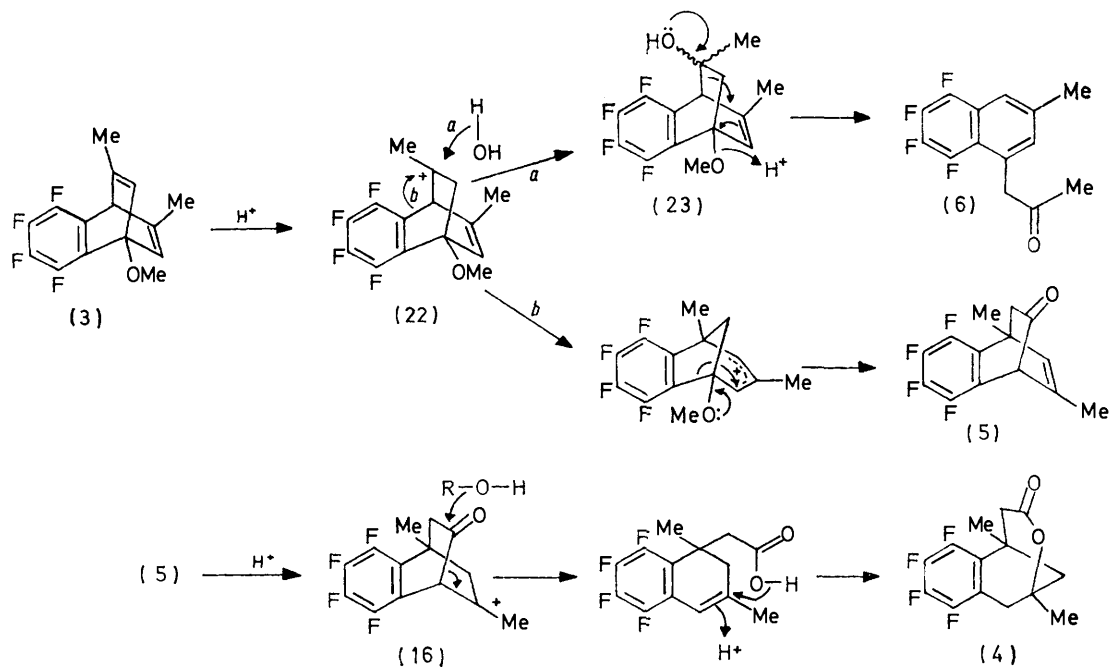
The ease with which the hydroxy-acid (8) and the olefinic acids (9) and (11) cyclise to the lactone (4) was found to be paralleled by reactions of the diol (7) and of the hydroxy-olefin (13) obtained by reduction of the acid (11) with lithium aluminium hydride. Thus compounds (7) and (13) gave the cyclic ether (14) in phosphoric acid.

In order to establish that the second double bond in the ketone (5) was necessary for fragmentation and re-cyclisation to occur, we reduced the benzobarrelenone (5) to the ketones (15) and treated the products with 98% sulphuric acid; they were recovered unchanged.

The foregoing data suggest that the lactone (4) and the ketone (6) are formed by the mechanism shown in Scheme 3. The protonation steps have been followed by the use of deuteriated acids. A number of the steps in Scheme 3 are shown as being concerted, but they may, in fact, not be so. Thus for example the fragmentation of the ion (16) may not occur as a result of attack at the carbonyl carbon atom by a nucleophile. In the strongly acidic medium, fragmentation to an acylium ion is perhaps more likely.

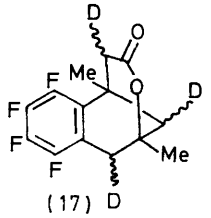
Rearrangement of compound (3) in deuteriosulphuric acid followed by quenching with deuterium oxide gave the lactone (4) which was predominantly trideuteriated (17). Rearrangement of the compound (3) in trifluoroacetic [^{2}H]acid gave the [^{2}H]benzobarrelenone (18), which on further reaction in sulphuric acid gave the [^{2}H]lactone (19). Rearrangement of compound (5) in deuteriosulphuric acid gave the [$^2H_2$]lactone (20).

The deuteriation levels in the products were determined by mass spectrometry. However, the values obtained were not of high accuracy because of the low abundance of the molecular ions. The analysis was also complicated by the incorporation of deuterium into the 2-methyl group in the lactone (4), presumably *via* the ion (16). The 220 MHz ^{1}H n.m.r. spectra of the lactones (17), (19), and (20) revealed that the incorporation of deuterium was



SCHEME 3

not stereospecific at any of the three positions. Thus, for example, broadened singlets were observed for each of the six possible methylene protons in the lactone (17). The rearrangement of compound (3) in deuteriosulphuric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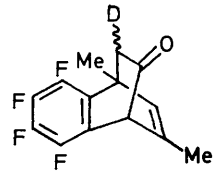
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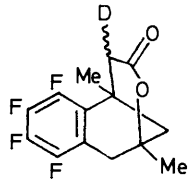
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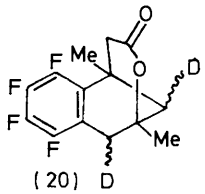
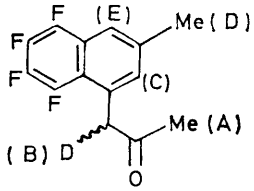

(20) D


(21)

acid–deuterium oxide (7 : 3) gave the ketone (21). The incorporation of deuterium into the methylene group was also complicated by incorporation at other positions (Table), which could have occurred in the ion (22) or the alcohol (23).

^{1}H N.m.r. integration values for compound (21)

Protons:		A	B	C	D	E
Relative integral	obs.	2·5	0·65	0·71	2·9	1·0
	calc.	3·0	1·0	1·0	3·0	1·0

EXPERIMENTAL

General methods used are given in ref. 6.

Rearrangements of 5,6,7,8-Tetrafluoro-1,4-dihydro-1-methoxy-3,9-dimethyl-1,4-ethenonaphthalene (3).—(i) *In 98% sulphuric acid.* Compound (3) [3] (2·0 g) was dissolved in 98% sulphuric acid (25 ml) at room temperature and was immediately added to crushed ice (150 g). The precipitate was washed with water until the washings were no longer acidic and then dried to leave 7,8,9,10-*tetrafluoro*-1,2,5,6-*tetrahydro*-2,6-*dimethyl*-2,6-*methano*-3-*benzoxocin*-4-*one* (4) (2·02 g, 100%), m.p. 170—171° (from ethanol) (Found: C, 58·2; H, 4·2; F, 26·4%; M^+, 288. $C_{14}H_{12}F_4O_2$ requires C, 58·35; H, 4·2; F, 26·35%; M, 288), τ ($CDCl_3$; 60 MHz) 6·6—8·4 (6H, m), 8·38 (3H, s), and 8·4 (3H, d, $|J|_{H,F}$ 1·5 Hz), $\nu_{max.}$ 1730 cm^{-1}; $\lambda_{max.}$ (EtOH) 262 nm (ε 660).

(ii) *In aqueous sulphuric acid.* Compound (3) (200 mg) was added to 70% sulphuric acid (10 ml) at 0° and stirred at that temperature for 3 h before pouring onto crushed ice (20 g). The mixture was extracted with ether (3 × 10 ml) and the combined extracts were washed with water, dried, and evaporated to leave an oil which was separated by preparative layer chromatography to give, in order of decreasing R_F value, (i) starting material (3) (19 mg, 1%); (ii) 5,6,7,8-tetrafluoro-3,4-dihydro-4,10-dimethyl-1,4-ethenonaphthalene-2(1*H*)-one (5) (24 mg, 14%), identical (t.l.c., g.l.c., and ^{1}H n.m.r. spectroscopy) with an authentic sample; (iii) 5,6,7,8-*tetrafluoro*-3-*methyl*-1-*naphthylacetone* (6) (69 mg, 40%), m.p. 104·5° (from hexane) (Found: C, 61·6; H, 3·7%; M^+, 270·0667. $C_{14}H_{10}F_4O$ requires C, 62·25; H, 3·7%; M, 270·0668), τ ($CDCl_3$) 2·15—2·35 (1H, m), 2·8—2·9 (1H, m), 5·8 (2H, d, $|J|_{H,F}$ 7 Hz), 7·5br (3H, s), and 7·7 (3H, s); $\nu_{max.}$ ($CHCl_3$) 1725 cm^{-1} (CO), $\lambda_{max.}$ (EtOH) 275 (ε 5470), 281 (6020), and 290 nm (5350) (naphthalene chromophore); and (iv) compound (4) (71 mg, 39%), identical (m.p. and mixed m.p., t.l.c., and ^{1}H n.m.r. spectroscopy) with authentic material (above).

The ketone (6) and the lactone (4) were not converted into one another in separate experiments carried out under the above conditions.

(iii) *In trifluoroacetic acid.* Compound (3) (300 mg) in trifluoroacetic acid (10 ml) was heated under reflux for 6 h. Removal of the solvent left an oil which was separated by preparative layer chromatography into the ketone (5) (234 mg, 82%) and the lactone (4) (28 mg, 9·5%).

In a similar experiment a solution of compound (3) in chloroform was added to a 1 : 1 mixture of 98% sulphuric acid and trifluoroacetic acid at 0°; the usual work-up gave compounds (5) and (4) in 87 and 12% yields, respectively.

Rearrangement of the Ethenonaphthalenone (5) *in 98% Sulphuric Acid.*—The ketone (5) was dissolved in 98% sulphuric acid at room temperature. The usual work-up gave the lactone (4) (94%), identical (t.l.c., and i.r. and ^{1}H n.m.r. spectroscopy) with an authentic sample.

Reduction of the Lactone (4) *with Lithium Aluminium Hydride.*—The lactone (4) (500 mg) was reduced, in ethereal solution, with an excess of lithium aluminium hydride. The usual work-up gave 2-(5,6,7,8-*tetrafluoro*-1,2,3,4-*tetrahydro*-3-*hydroxy*-1,3-*dimethyl*-1-*naphthyl*)*ethanol* (7) (490 mg, 97%), m.p. 105—106° (from ethanol) (Found: C, 57·5; H, 5·55%; M^+, 292. $C_{14}H_{16}F_4O_2$ requires C, 57·55; H, 5·5%; M, 292), τ ($CDCl_3$) 5·7—6·1 (2H, m, exchangeable), 6·1—6·5 (2H, m), 6·8—8·9 (6H, m), 8·6 (3H, d, $|J|_{H,F}$ 2·5 Hz), and 8·65 (3H, s), $\nu_{max.}$ ($CHCl_3$) 3350 cm^{-1}.

Oxidation of the Diol (7) *with Jones Reagent.*—A solution of chromium trioxide in sulphuric acid (Jones reagent) was added dropwise to a solution of the diol (7) (100 mg) in acetone (10 ml) until the yellow colour persisted for 5 min. Water (20 ml) was then added and conventional work-up gave the lactone (4) (100 mg, 100%), identical (m.p. and mixed m.p., t.l.c., and i.r. and ^{1}H n.m.r. spectroscopy) with an authentic sample (above).

Hydrogenation of the Ketone (5) *and Attempted Rearrangement of the Ketones* (15).—A solution of the ketone (5) in ethanol was hydrogenated over palladium–carbon to give the 5,6,7,8-tetrafluoro-3,4-dihydro-4,10-dimethyl-1,4-ethanonaphthalen-2(1*H*)-ones (15) (99%), τ ($CDCl_3$) 6·1—6·3 (1H, m), 7·6—8·9 (5H, m), 8·35 (3H, d, $|J|_{H,F}$ 6 Hz), 8·85 (1H, m, $|J|$ 7 Hz), and 9·18 (2H, d, $|J|$ 7 Hz).

The ketones (15) (100 mg) were dissolved in 98% sulphuric acid (2 ml) at room temperature; work-up in the usual way after 1 h gave starting material (99%), as shown by t.l.c. and ^{1}H n.m.r. spectroscopy.

Hydrolysis of the Lactone (4).—The lactone (4) (586 mg) in ethanol (10 ml) and aqueous sodium hydroxide (15 ml) was

[6] J. P. N. Brewer, H. Heaney, S. V. Ley, and T. J. Ward, *J.C.S. Perkin I*, 1974, 2688.

heated under reflux for 10 min. The cold mixture was added to water and hydrochloric acid was added (to pH 2). Extraction with ether gave 5,6,7,8-tetrafluoro-1,2,3,4-tetrahydro-3-hydroxy-1,3-dimethyl-1-naphthylacetic acid (8) (310 mg, 50%), m.p. 126—127° (from chloroform), $\nu_{max.}$ 3350br and 1722 cm^{-1}; $M^{\ddagger}$ 306. The acid (8) was readily converted into the lactone (4) by heating a solution in chloroform for ½ h. In the solid state the acid (8) was slowly (1 week) converted into the lactone (4). Elemental analysis was thus uninformative.

Preparation of Methyl 5,6,7,8-*Tetrafluoro*-1,4-*dihydro*-1,3-*dimethyl*-1-*naphthylacetate* (10).—The ketone (5) (100 mg) was dissolved in tetrahydrofuran (0·4 ml) and aqueous sodium hydroxide (1·75 ml; 2N) and stirred at room temperature for 39 h. Water (3 ml) was then added and the mixture was extracted with ether. The aqueous phase was neutralised with hydrochloric acid (pH 2) and extracted with ether (3 × 3 ml). The combined extracts were washed with water, dried, and evaporated to leave 5,6,7,8-tetrafluoro-1,4-dihydro-1,3-dimethyl-1-naphthylacetic acid (9) (107 mg, 100%), an oil, τ ($CDCl_3$) 0·7—1·2br (1H, s), 4·6—4·8 (1H, m), 6·7—6·9 (2H, m), 6·95 (1H, d, $|J|$ 14·5 Hz), 7·45 (1H, d, $|J|$ 14·5 Hz), 8·2 (3H, s), and 8·56 (3H, d, $|J|_{H,F}$ 1·5 Hz), $\nu_{max.}$ 3400—2600br and 1720 cm^{-1}.

Treatment of the acid (9) in ethereal solution, with an excess of ethereal diazomethane gave the *methyl ester* (10) (100%) (Found: $M^{\ddagger}$, 302·0900. $C_{15}H_{14}F_4O_2$ requires M, 302·0930), τ ($CDCl_3$) 4·6—4·8 (1H, m), 6·5 (3H, s), 6·7—6·9 (2H, m), 6·92 (1H, d, $|J|$ 15 Hz), 7·45 (1H, d, $|J|$ 15 Hz), 8·15 (3H, s), and 8·56 (3H, d, $|J|_{H,F}$ 1·5 Hz); $\nu_{max.}$ 1745 cm^{-1}.

Preparation of Methyl 5,6,7,8-*Tetrafluoro*-1,2-*dihydro*-1,3-*dimethyl*-1-*naphthylacetate*.—The ketone (5) (500 mg) was heated under reflux in tetrahydrofuran (5 ml) and aqueous sodium hydroxide (15 ml; 2N) during 18 h. Work-up as in the previous experiment gave 5,6,7,8-tetrafluoro-1,2-dihydro-1,3-dimethyl-1-naphthylacetic acid (11) (450 mg, 84%), τ ($CDCl_3$) −0·4 to −0·15br (1H, s), 3·5—3·7 (1H, m), 6·8—7·8 (4H, m), 8·05 (3H, s), and 8·52 (3H, d, $|J|_{H,F}$ 3 Hz), $\nu_{max.}$ 3500—2500br and 1720 cm^{-1}.

The acid (11) was methylated with an excess of diazomethane as above to give the *methyl ester* (12) (Found: $M^{\ddagger}$, 302·0939. $C_{15}H_{14}F_4O_2$ requires M, 302·0930), τ ($CDCl_3$) 3·5—3·7 (1H, m), 6·4 (3H, s), 7·0—7·85 (4H, m), 8·08br (3H, s), and 8·59 (3H, d, $|J|_{H,F}$ 3 Hz), $\nu_{max.}$ 1745 cm^{-1}.

Cyclisation of the Acid (9).—The acid (9) (100 mg) was dissolved in 98% sulphuric acid (5 ml), and after 5 min the solution was poured onto ice (10 g). The usual work-up gave the lactone (4) (96 mg, 100%), identical (t.l.c. and i.r. and ^1H n.m.r. spectroscopy) with an authentic sample.

Cyclisation of the Acid (11).—The acid (11) (130 mg) was dissolved in 98% sulphuric acid (2 ml), and after 5 min the solution was poured onto ice (15 g). The usual work-up gave the lactone (4) (125 mg, 96%), identical (t.l.c. and i.r. and ^1H n.m.r. spectroscopy) with an authentic sample.

Reduction of the Acid (13) *with Lithium Aluminium Hydride and Cyclisation to the Ether* (14).—The acid (13) (1 g) was reduced with an excess of lithium aluminium hydride in ether and gave, after the usual work-up, 2-(5,6,7,8-tetrafluoro-1,2-dihydro-1,3-dimethyl-1-naphthyl)ethanol (13) (804 mg, 85%), τ ($CDCl_3$) 3·5—3·75 (1H, m), 6·4 (2H, t, $|J|$ 7 Hz), 6·6—6·9br (1H, s, exchangeable), 7·7—8·3 (4H, m), 8·15br (3H, s), and 8·68 (3H, d, $|J|_{H.F}$ 4 Hz).

The alcohol (13) (300 mg) was shaken at room temperature for 4 days in orthophosphoric acid (6 ml; 88%) and then poured into water (50 ml). Extraction with ether (5 × 10 ml) and the usual work-up gave 7,8,9,10-*tetrafluoro*-1,2,5,6-*tetrahydro*-2,6-*dimethyl*-2,6-*methano*-4H-3-*benzoxocin* (14) (270 mg, 90%) (Found: C, 61·45; H, 5·1%; $M^{\ddagger}$, 274. $C_{14}H_{14}F_4O$ requires C, 61·3; H, 5·15%; M, 274), τ ($CDCl_3$) 6·05—7·0 (3H, m), 7·1—7·3 (2H, m), 8·1—8·8 (4H, m), 8·5 (3H, d, $|J|_{H,F}$ 5·5 Hz), and 8·77 (3H, s).

Cyclisation of the Diol (7).—The diol (7) (100 mg) was dissolved in orthophosphoric acid (2 g; 88%) and heated at 100° for 1 h. The cold mixture was added to ice and, after the usual work-up and preparative layer chromatography, gave the ether (14) (38 mg, 40%), identical (t.l.c. and i.r. and ^1H n.m.r. spectroscopy) with the compound prepared as above.

Deuteriation Experiments.—Trifluoroacetic [^2H]*acid.* Addition of deuterium oxide to trifluoroacetic anhydride (over 2 days) followed by distillation gave trifluoroacetic [^2H] acid.

Rearrangement reactions with deuteriated acids. The deuteriation experiments were carried out as in the experiment with non-deuteriated acids and gave compound (18), τ (CCl_4) 3·75—3·95 (1H, m), 5·4—5·6 (1H, m), and 7·85—8·2 (7H, m), *m/e* 271 ($M^{\ddagger}$, ^2H >99%) and 228 (M − 43); compound (17), τ ($CDCl_3$; 220 MHz) 6·78br (s), 7·14br (s), 7·22br (s), 7·55br (s), 7·89br (s) and 8·12 br (s); compound (19), τ ($CDCl_3$; 220 MHz) 6·72 (1H, d, $|J|$ *ca.* 18 Hz), 7·14br (s), 7·19 (1H, d, $|J|$ *ca.* 18 Hz), 7·55br (s), 7·85 (1H, d, $|J|$ *ca.* 16 Hz), and 8·07 (1H, d, $|J|$ *ca.* 16 Hz); and compound (20), τ ($CDCl_3$; 220 MHz) 6·78br (s), 7·07 (1H, d, $|J|$ *ca.* 18 Hz), 7·22br (s), 7·52 (1H, d, $|J|$ *ca.* 18 Hz), 7·89br (s), and 8·12br (s).

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