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NUCLEOPHILIC SUBSTITUTION IN 5,6,7,8-TETRAFLUORO- and 6,7-DIFLUORO-1,2,3,4-TETRAHYDRO-9-ALKENYL-1,4-METHANONAPHTHALENES AND RELATED COMPOUNDS. A SEARCH FOR HOMOALLYLIC CONJUGATION

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SUMMARY

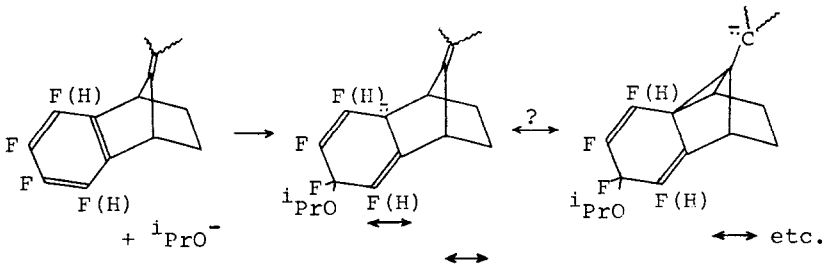
The second-order rate constants for the nucleophilic replacement of fluorine by isopropoxide in 5,6,7,8-tetrafluoro- and 6,7-difluoro-1,2,3,4-tetrahydro-9-alkenyl-1,4-methano-naphthalenes and related 9-alkyl systems have been measured. A factor of 6 - 7 separates the most reactive compounds [the 9-(4'-trifluoromethylbenzylidene) derivatives] from the least reactive compounds [the syn-9-isopropyl derivatives] in both the tetrafluoro- and difluoro-series. It is concluded that homo-allylic conjugation is inoperative in accounting for these small reactivity differences.

INTRODUCTION

The most widely used method for studying homoconjugative interaction of C=C π bonds with a developing carbocationic centre has involved measuring the relative rate constants for the solvolysis reactions of unsaturated and saturated substrates [1]. More recently the nature and structure of the involved carbo-cationic intermediates have been examined in superacid media [2]. While systems involving the stabilisation of carbanionic centres by homoconjugative interaction are relatively rare, a notable example is the stability of the bicyclo[3,2,1]-octa-2,6-dienide anion, a 6π electron bishomocyclopentadienide anion, which has been proposed as the intermediate in some base catalysed deuterium

exchange reactions [3]. The formation of a homoenolate ion in which a carbanionic centre homoconjugates with a carbonyl group has been invoked to account for the epimerisation of exo- and endo-isocamphanone [4].

In this paper we describe experiments designed to assess the importance of a 9-alkenyl substituent on the second order rate constant for nucleophilic replacement of fluoride ion by isopropoxide in 5,6,7,8-tetrafluoro- and 6,7-difluoro-1,2,3,4-tetrahydro-9-alkenyl-1,4-methanonaphthalenes, and compare the results with the saturated 9-alkyl compounds.

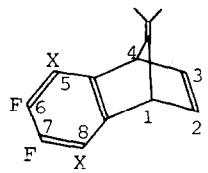


Scheme 1

Scheme 1 shows how homoallylic conjugation could stabilise the p-quinonoid Wheland intermediate of a 9-alkenyl compound. Tanida has shown the effect of 6-substituents in the acetolyses of anti-1,2,3,4-tetrahydro-9-(p-bromobenzenesulphonate)-1,4-methanonaphthalenes (a factor of 386,000 was found between the rates of the methoxy and nitro derivatives) and provides one of the most important pieces of evidence for the reality of homobenzylic participation in these derivatives [5].

SYNTHESES

Two series of compounds were prepared containing (i) 5,6,7,8-tetrafluoro- and (ii) 6,7-difluoro-substituents. The cycloaddition of tetrafluorobenzyne (from pentafluorophenyl lithium) and 4,5-difluorobenzyne (from 2,4,5-trifluorophenylmagnesium bromide) with 6,6-dimethylfulvene gave 5,6,7,8-tetrafluoro-1,4-dihydro-9-isopropylidene-1,4-methanonaphthalene (1) prepared previously [6] and the 6,7-difluoro-analogue (2), respectively. The controlled hydrogenation of both (1) and (2) at 0° - $4^{\circ}C$ in the



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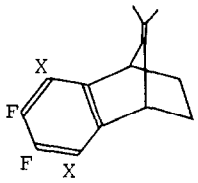

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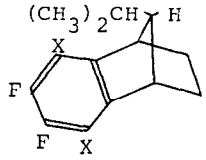

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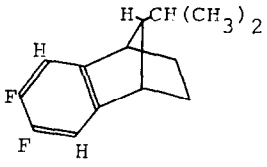
6 X = H



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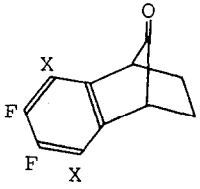
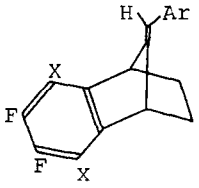


8 X = F

9 X = H



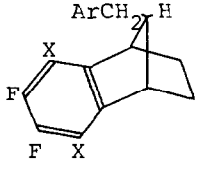
10 X = F; Ar = p-NO_2-C_6H_4-

11 X = F; Ar = p-CF_3-C_6H_4-

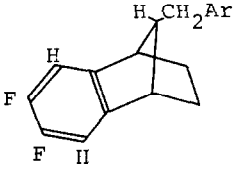
12 X = F; Ar = C_6H_5-

13 X = F; Ar = p-NH_2-C_6H_4-

14 X = H; Ar = p-$CF_3C_6H_4$-



15 X = H; Ar = p-CF_3-C_6H_4-



16 Ar = p-CF_3-C_6H_4-

17 X = F; Ar = p-CF_3-C_6H_4-

18 X = F; Ar = C_6H_5-

presence of palladium-charcoal gave 5,6,7,8-tetrafluoro-1,2,3,4-tetrahydro-9-isopropylidene-1,4-methanonaphthalene (3) prepared previously [6] and the 6,7-difluoro analogue (4), respectively. Further hydrogenation of (3) gave syn-5,6,7,8-tetrafluoro-1,2,3,4-tetrahydro-9-isopropyl-1,4-methanonaphthalene (5) prepared previously [6], the stereochemistry of this compound having been determined by ^{1}H n.m.r. Further hydrogenation of compound (4) gave two products, one of which was readily isolated by fractional crystallisation. The ^{1}H n.m.r. spectrum of this compound had an identical absorption pattern in the region τ 6 - 10 with that of compound (5), albeit that the absorptions were to slightly higher field, and was assigned the structure syn-6,7-difluoro-1,2,3,4-tetrahydro-9-isopropyl-1,4-methanonaphthalene (6). In contrast, the ^{1}H n.m.r. of the second product separated by preparative t.l.c. showed almost identical absorptions to compound (6) at H-1, H-2-exo, and H-2-endo but the absorption attributed to H-9 (anti) in (6) was upfield by 0.10 p.p.m. whereas the absorptions due to the isopropyl group in (6) were downfield by ca. 0.10 p.p.m. These differences in the spectra of the two products are consistent with the second component having the structure anti-5,6,7,8-tetrafluoro-1,2,3,4-tetrahydro-9-isopropyl-1,4-methanonaphthalene (7), in which the ring current in the aryl residue exerts a deshielding of the anti-9-isopropyl protons and a shielding of the syn-9-H proton.

Ozonolysis of compounds (3) and (4) gave 5,6,7,8-tetrafluoro-1,2,3,4-tetrahydro-1,4-methanonaphthalen-9-one (8), prepared previously [6] and the 6,7-difluoro compound (9), respectively. Wittig reactions of the ketone (8) with the appropriate ylid gave 5,6,7,8-tetrafluoro-1,2,3,4-tetrahydro-9-(4'-nitrobenzylidene) 1,4-methanonaphthalene (10)[the selective reduction of the nitro group using hydrogen over platinum black giving the 9-(4'-amino-benzylidene) derivative (13)], the 9-(4'-trifluoromethyl-benzylidene) (11), and the 9-benzylidene derivative (12). Compound (12) was also obtained by reaction of the ketone (8) with benzyl-magnesium chloride followed by dehydration of the resulting tertiary alcohol. The difluoro ketone (9) was converted to 6,7-difluoro-1,2,3,4-tetrahydro-9-(4'-trifluoromethylbenzylidene)-1,4-methanonaphthalene (14) by a Wittig reaction.

The hydrogenation of the 9-alkenyl compound (14) over palladium-charcoal gave two products which were separated by preparative t.l.c. The major differences in the ^{1}H n.m.r. spectra concerned the chemical shifts attributed to benzylic-CH_2- and H-9; in the faster moving component both these absorptions coincided at τ7.64, whereas in the slower moving component H-9 absorbed at τ7.78 while the benzylic-CH_2- absorbed at τ7.38. These results taken in conjunction with the observations made on compounds (6) and (7) indicate that the faster moving compound was syn-6,7-difluoro-1,2,3,4-tetrahydro-9-(4'-trifluoromethylbenzyl)-1,4-methanonaphthalene (15), and the slower moving component was the anti-stereoisomer (16). Catalytic hydrogenation of compounds (11) and (12) and fractional crystallisation of the products gave single isomers in each case, (17) and (18) respectively, though an examination of the mother liquors from the hydrogenation of (11) by t.l.c. showed the presence of what was probably the stereoisomer of (17) with a similar R_f value. The ^{1}H n.m.r. spectra of these products had absorption patterns similar to compound (15), in particular the coincidence of the benzylic-CH_2- and H-9 absorptions. Consequently compound (17) is syn-5,6,7,8-tetrafluoro-1,2,3,4-tetrahydro-9-(4'-trifluoromethylbenzyl)-1,4-methanonaphthalene and (18) is the syn-9-benzyl compound.

KINETICS

In this work, detailed kinetics work was not required. There is abundant evidence for the bimolecular nature of nucleophilic substitution of fluorine in fluoroaromatic systems [7,8] and second order rate constants were calculated on the basis of the known concentrations of the starting materials and after a given time, the extent of the reaction as determined by the integration of appropriate ^{19}F n.m.r. signals.

One problem forseeable in this work was the possible competition between nucleophilic displacement of fluorine and nucleophilic addition to the C=C (or C=O) bond. Potassium isopropoxide in isopropanol gave a complex product with the 9-(4'-nitrobenzylidene) compound (10) and using potassium t-butylthiolate, a small amount of t-butylthiol adduct to the alkene was

isolated, compound (19). Potassium isopropoxide in isopropanol also cleaved the bicyclic ring structure in reaction with (8) with the formation of 5,6,7,8-tetrafluoro-1-isopropoxycarbonyl-1,2,3,4-tetrahydronaphthalene (20). However, in all other cases with 5,6,7,8-tetrafluoro compounds, clean mono substitution of fluorine was obtained; with the less reactive 6,7-difluoro compounds, it was necessary to use potassium isopropoxide in isopropanol dimethyl sulphoxide (1:1 v/v).

The structures of the isopropoxy-trifluoro compounds obtained were based on the differences between the chemical shifts of the fluorine absorptions in the ^{19}F n.m.r. spectra of these compounds and the chemical shifts of the corresponding fluorine atoms in each parent molecule (the isopropoxy substituent effect). Pentafluorophenyl isopropyl ether prepared from hexafluorobenzene and potassium isopropoxide in isopropanol-dimethyl sulphoxide, showed ortho fluorine ca. 6 p.p.m. downfield from hexafluorobenzene as internal standard, whereas meta- and para-fluorine absorptions were shifted upfield by ca. 1 p.p.m. In all the 5,6,7,8-tetrafluoro series of compounds, the ^{19}F-absorptions at the lower field (ca. 147 p.p.m.*) were assigned to the fluorines at positions 5- and 8- (adjacent to the ring junction) while the absorptions at higher field (ca. 159 - 161 p.p.m.) were assigned to the fluorines at positions 6- and 7-. All the isopropoxytrifluoro compounds showed fluorine absorptions at ca. 140 - 141 p.p.m.; 148 - 149 p.p.m.; and 153 - 154 p.p.m., which is consistent only with 6-isopropoxy-5,7,8-trifluoro- and 7-isopropoxy-5,6,8-trifluoro-patterns of substitution.

For the optically inactive 9-isopropylidene and all the 9-alkyl compounds, the asymmetric 6- and 7-isopropoxy substitution compounds will be formed in equal amounts and constitute a racemate in each case. The unsymmetrical 9-alkenyl compounds, however, exist as racemates themselves and the derived isopropoxy substitution compounds will consist of two racemates, but the ^{19}F n.m.r. spectrum did not differentiate between the two orientation patterns which were not important in this work.

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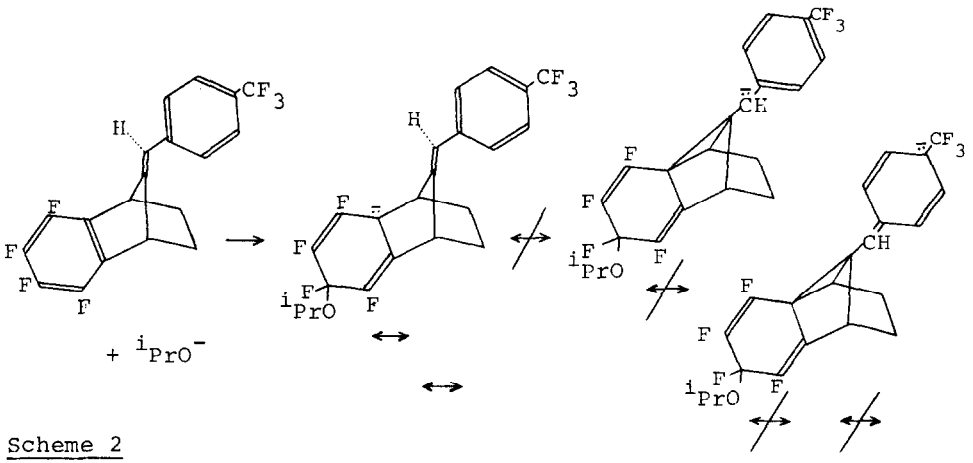
* All ^{19}F chemical shifts refer to solutions in $CDCl_3$ upfield for $CFCl_3$ as internal standard.

RESULTS AND DISCUSSION

The kinetic data are summarised in the Table. In the 5,6,7,8-tetrafluoro series, the reactivity of the 9-isopropylidene (3) and the 9-benzylidene (12) derivatives are identical with their reduction products, the syn-9-isopropyl (5) and the syn-9-benzyl (18) compounds respectively. The 9-(4'-trifluoromethylbenzylidene) compound (11) is more reactive than its reduction product, the syn-9-(4'-trifluoromethylbenzyl) compound (17) by a factor of 3, but this value is small, and since there is only a factor of 6 separating the most reactive compound (11) from the least reactive (3) and (5), there is no justification for interpreting these results in terms of a special homoallylic conjugation - a combination of more subtle effects is responsible for the differences in reactivity, and until more data are available, speculation in attempting to define these effects is fruitless. [See Scheme 2].

TABLE

9-Substituent	Second order rate constants (100.0°C) $dm^3 mol^{-1} min^{-1}$			
	5,6,7,8-Tetrafluoro-compounds in ^{i}PrOH with ^{i}PrOK (0.35M)		6,7-Difluoro-compounds in ^{i}PrOH - DMSO (1:1 v/v) with ^{i}PrOK (0.36M)	
	Compd.		Compd.	
$(CH_3)_2C=$	(3)	0.01	(4)	0.001
syn-$(CH_3)_2CH-$	(5)	0.01	(6)	0.0007
$C_6H_5CH=$	(12)	0.02		
syn-$C_6H_5CH_2-$	(18)	0.02		
4'-NH_2-$C_6H_4CH=$	(13)	0.03		
4'-CF_3-$C_6H_4CH=$	(11)	0.06	(14)	0.005
syn-4'-CF_3-$C_6H_4CH_2-$	(17)	0.02		-



Scheme 2

Factors affecting the reactivity of fluorine substitution in polyfluoroaromatic systems have been examined in some detail [8]. The site of substitution demands the maximum number of fluorine atoms in the positions ortho and meta to the site of attack. Consequently the possibility exists that the rate constants for the 5,6,7,8-tetrafluoro compounds are determined largely by contributions from the remaining three fluorine atoms and that any activation due to homoallylic conjugation is being completely overwhelmed. In order to investigate this possibility further, the 6,7-difluoro-series of compounds were prepared in which only one fluorine could contribute to the reactivity of the other; with a difluoro substrate, product studies could still be followed using ^{19}F n.m.r. spectroscopy. The results show a very small difference in the reactivity between the 9-isopropylidene compound (4) and its reduction product the syn-9-isopropyl compound (6). The most reactive compound was again the 9-(4'-trifluoro-benzylidene) compound (14), and it can be seen that the difference in reactivity between the most reactive and the least reactive compounds in the 6,7-difluoro compounds is essentially the same as in the 5,6,7,8-tetrafluoro series: reduction in the number of fluorine atoms fails to reveal any activation which could be attributed to homoallylic conjugation.

Reaction of both syn- and anti-9-(4'-trifluoromethylbenzyl) compounds, (15) and (16) respectively with potassium isopropoxide gave complete conversion of the CF_3-group to $^{i}PrO(C=O)$ - accompanied by some nucleophilic replacement of aromatic fluorine, giving mixtures of syn-6,7-difluoro- (21) and syn-7-isopropoxy-6-fluoro-1,2,3,4-tetrahydro-9-(4'-isopropoxycarbonylbenzyl)-1,4-methanonaphthalene (22), and the corresponding anti-6,7-difluoro- (23) and anti-7-isopropoxy-6-fluoro- (24) compounds respectively so that kinetic measurements were precluded. These observations can be explained by invoking an increased basicity of the isopropoxide in isopropanol-dimethyl sulphoxide thereby enabling the benzylic hydrogen atoms to be removed and so facilitate loss of fluoride from the 4'-CF_3- group. No such effect was observed with the nucleophile system used with compound (17).

EXPERIMENTAL

^{1}H N.m.r. spectra (90 MHz) were obtained using a Brucker HX-90E spectrometer and ^{19}F n.m.r. spectra (56.4 MHz) using a Varian A56/60 spectrometer ($CFCl_3$ as internal standard, all absorptions being upfield from the reference).

Reaction of 6,6-dimethylfulvene with tetrafluorobenzyne generated from pentafluorophenyl-lithium

The method used was the one published by Heaney [6] and gave 5,6,7,8-tetrafluoro-1,4-dihydro-9-isopropylidene-1,4-methanonaphthalene (1), m.p. 81 - 81.5°C (lit. m.p. 80 - 82°C).

Reaction of 6,6-dimethylfulvene with 4,5-difluorobenzyne generated from 2-bromo-1,4,5-trifluorobenzene

A mixture of 2-bromo-1,4,5-trifluorobenzene (21.0 g) and 6,6-dimethylfulvene (10.8 g) in anhydrous tetrahydrofuran (160 ml) was added to magnesium (3.47 g) [activated with 1,2-dibromoethane (0.5 ml)] in anhydrous tetrahydrofuran (20 ml) at such a rate as to maintain gentle reflux. The addition was complete after 30 min and the mixture was heated for a further 1 hr., then cooled,

diluted with aqueous hydrochloric acid and extracted with ether. The extracts were dried ($MgSO_4$), the solvent evaporated and the residue sublimed at 150° at 0.05 mm to give the crude product (6.1 g). Recrystallisation from methanol gave 6,7-difluoro-1,4-dihydro-9-isopropylidene-1,4-methanonaphthalene (2) m.p. 69.5 - 71.0° (Found: C, 76.72; H, 5.33%; M^+, 218. $C_{14}H_{12}F_2$ requires C, 77.04; H, 5.54%; M, 218).

Hydrogenations

Compound (1) in ethanol was hydrogenated at atmospheric pressure over 10% Pd-C at 4°C to give 5,6,7,8-tetrafluoro-1,2,3,4-tetrahydro-9-isopropylidene-1,4-methanonaphthalene (3), m.p. 98.5 - 99.5°C (from methanol) (lit. [6], m.p. 97 - 99°C). δ_F ($CDCl_3$) 147.7 (F-5, F-8) and 160.8 p.p.m. (F-6, F-7).

Half hydrogenation of compound (2) (1.15 g) in ethyl acetate (30 ml) at atmospheric pressure over 10% Pd-C (0.1 g) at 0° gave 6,7-difluoro-1,2,3,4-tetrahydro-9-isopropylidene-1,4-methanonaphthalene (4) m.p. 82 - 83°C (from methanol). δ_F ($CDCl_3$), 143.5 p.p.m. (Found: C, 76.10; H, 6.50%; M^+, 220. $C_{14}H_{14}F_2$ requires C, 76.34; H, 6.41%; M, 220).

Exhaustive hydrogenation of compound (3) in ethyl acetate at atmospheric pressure over 10% Pd-C at room temperature gave syn-5,6,7,8-tetrafluoro-1,2,3,4-tetrahydro-9-isopropyl-1,4-methanonaphthalene (5) m.p. 49.5 - 51°C (lit. [6] 58 - 59°). τ($CHCl_3$), 6.41 (H-1); 7.99 (H-2, exo); 8.32 (H-9, anti); 8.77 (H-2, endo); 9.14 [$(CH_3)_2CH$-]; 8.96 - 9.33 (region for $(CH_3)_2\underline{CH}$- and $(CH_3)_2$CH-) identical with the published spectrum. δ_F ($CDCl_3$), 147.7 (F-5, F-8) and 160.3 p.p.m. (F-6, F-7).

Exhaustive hydrogenation of compound (4) in ethyl acetate as before gave syn-6,7-difluoro-1,2,3,4-tetrahydro-9-isopropyl-1,4-methanonaphthalene (6) m.p. 62 - 62.5°C (from methanol). $\tau(CHCl_3)_2$ 2.57 (H-5, H-8); 6.82 (H-1); 8.09 (H-2, exo); 8.43 (H-9, anti); 8.89 (H-2, endo); 9.20 [$(CH_3)_2CH$-]; 9.03 - 9.32 (region for $(CH_3)_2\underline{CH}$- and $(CH_3)_2$CH-). δ_F($CDCl_3$) 143.4 p.p.m. (Found: C, 75.56; H, 7.43%; M^+, 222. $C_{14}H_{16}F_2$ requires C, 75.65; H, 7.26%; M, 222).

An examination of the mother liquors from the recrystallisation showed the presence of a second component having an R_f value slightly smaller than that of the major component. Repeated separations of the mixture by preparative t.l.c. on silica (light petroleum as eluant) gave anti-6,7-difluoro-1,2,3,4-tetrahydro-9-isopropyl-1,4-methanonaphthalene (7) m.p. 71 - 72°C (from light petroleum). τ ($CDCl_3$) 3.00 (H-5, H-8); 6.81 (H-1); 8.11 (H-2, exo); 8.53 (H-9, syn); 8.91 (H-2 endo); 9.09 [$(\underline{CH_3})_2CH$-)]; 9.00 - 9.22 (region for $(CH_3)_2\underline{CH}$- and $(CH_3)_2CH$-). δ_F ($CDCl_3$), 143.9 p.p.m. (Found: C, 75.54; H, 6.83%; M, 222).

Ozonolyses

Compound (3) was ozonolised by published method [6] and gave 5,6,7,8-tetrafluoro-1,2,3,4-tetrahydro-1,4-methanonaphthalen-9-one (8), m.p. 87.5 - 88.5°C (from n-hexane) (lit. m.p. 96 - 97°C).

Similarly, ozonolysis of compound (4) gave 6,7-difluoro-1,2,3,4-tetrahydro-1,4-methanonaphthalen-9-one (9) m.p. 64 - 65°C (from petroleum [b.p. 60 - 80°C]) υ_{max} (C=O), 1780 cm^{-1} (Found: C, 68.09; H, 3.95%; M^+, 194. $C_{11}H_8F_2O$ requires C, 68.04; H, 4.15%; M, 194).

Formation of 9-arylidene compounds and their hydrogenation products

(i) 5,6,7,8-Tetrafluoro compounds

The tetrafluoroketone (8) (7.32 g) was suspended in water (200 ml) to which was added the moist stable ylid prepared from p-nitrobenzyl triphenylphosphonium bromide [20 g] and sodium carbonate [10 g] in water (2 l) [9]. The mixture was stirred at room temperature for 75 mins.; 1,4-dioxan (100 ml) was added, and after 18 hr., ether extraction and evaporation of the dried ($MgSO_4$) extracts gave a crystalline residue. Exhaustive sublimation of the residue at 95°C at 0.05 mm Hg removed unchanged ketone (1.97 g) and the residue was separated by chromatography on silica (chloroform as eluant). The first component coming off the column was sublimed at 160° at 0.05 mm Hg to give crude product (2.89 g). Recrystallisation of this material from benzene-light petroleum (b.p. 60 - 80°C) gave racemic 5,6,7,8-tetrafluoro-1,2,3,4-tetra-

hydro-9-(4'-nitrobenzylidene)-1,4-methanonaphthalene (10) m.p. 168.5 - 169.5°C. δ_F ($CDCl_3$) 147.5 (F-6, F-7); 158.8 p.p.m. (F-5, F-6). (Found: C, 61.73; H, 3.43; N, 3.69%; M^+, 349. $C_{18}H_{11}F_4NO_2$ requires: C, 61.89; H, 3.18; N, 4.01%; M, 349).

The hydrogenation of compound (10) in ethyl acetate at atmospheric pressure over platinum black (5% Pt-C) at room temperature was stopped after the absorption of three mole equiv. of hydrogen. The mixture was separated by chromatography on silica (chloroform as eluant) to give two components: the first component was not identified, but the second was crystallised from benzene-light petroleum (b.p. 60 - 80°) to give racemic 5,6,7,8-tetrafluoro-1,2,3,4-tetrahydro-9-(4'-aminobenzylidene)-1,4-methanonaphthalene (13) (0.92 g), m.p. (107.5 - 108.5°). δ_F ($CDCl_3$) 147.0 (F-5, F-8); 159.7 p.p.m. (F-6, F-7). (Found: C, 67.45; H, 3.77; N, 4.00%; M^+, 319. $C_{18}H_{13}F_4N$ requires C, 67.71; H, 4.10; N, 4.39%; M, 319).

Treatment of the ketone (5) (6.05 g) in dry ether (50 ml) with the ylid prepared by reacting p-trifluoromethylbenzyl triphenylphosphonium bromide (15.55 g) in dry ether (250 ml) with n-butyl lithium (10 ml, 2.385M in hexane), heating the mixture under reflux for 30 min. and work up in the usual way gave crude material (15.8 g). Ether-insoluble material was removed by filtration and the residue was distilled in vacuo to give racemic 5,6,7,8-tetrafluoro-1,2,3,4-tetrahydro-9-(4'-trifluoromethylbenzylidene)-1,4-methanonaphthalene (11) (7.23 g) b.p. 123° at 0.01 - 0.05 mm Hg, m.p. 36 - 38.5°C. δ_F ($CDCl_3$) 147.0 (F-5, F-8); 159.3 p.p.m. (F-6, F-7). (Found: C, 61.00; H, 2.76%; M^+, 372. $C_{19}H_{11}F_7$ requires C, 61.30; H, 2.98%; M, 372).

The hydrogenation of compound (11) in ethyl acetate at atmospheric pressure over 10% Pd-C gave syn-5,6,7,8-tetrafluoro-1,2,3,4-tetrahydro-9-(4'-trifluoromethylbenzyl)-1,4-methanonaphthalene (17), m.p. 85 - 86°C (from light petroleum b.p. 60 - 80°C). τ($CDCl_3$) 2.59 ($-C_6\underline{H}_4-$); 6.50 (H-1); 7.99 (H-2, exo); 7.56 (H-9, anti); 7.56 (4'-CF_3-C_6H_4-$C\underline{H}_2$); 8.73 (H-2, endo). δ_F ($CDCl_3$) 146.9 (F-5, F-8); 159.1 p.p.m. (F-6, F-7). (Found: C, 61.10; H, 3.68%; M^+, 374. $C_{19}H_{13}F_7$ requires C, 60.97; H, 3.50%; M, 374).

Treatment of the ketone (8) (2.51 g) in dry ether (50 ml) with the ylid prepared by reacting benzyl triphenylphosphonium bromide (6.5 g) in dry ether (300 ml) with n-butyl-lithium (5 ml, 2.5M in hexane), heating the mixture under reflux for 30 min. and working up the product as in the preparation of (11) gave racemic 5,6,7,8-tetrafluoro-1,2,3,4-tetrahydro-9-benzylidene-1,4-methanonaphthalene (12) (1.96 g), b.p. 119°C at 0.01 - 0.05 mm Hg, m.p. 42.5 - 48°C. $\delta_F(CDCl_3)$ 146.8 (F-5, F-8); 159.6 p.p.m. (F-6, F-7) (Found: C, 71.07; H, 3.65; M^+, 304. $C_{18}H_{12}F_4$ requires C, 71.05; H, 3.98%; M, 304). Reaction of the ketone (13.2 g) in dry ether (50 ml) at 0°C with benzylmagnesium chloride prepared from benzyl chloride (9.5 ml) and magnesium (2.5 g) in dry ether (450 ml), followed by heating under reflux for 2 hrs. and work-up in the usual way gave a crude product (20.8 g) which was purified by chromatography on silica (chloroform as eluant) to yield a 5,6,7,8-tetrafluoro-1,2,3,4-tetrahydro-9-benzyl-1,4-methanonaphthalen-9-ol (24), m.p. 100 - 101° (Found: C, 67.2; H, 4.8%. $C_{18}H_{14}F_4O$ requires: C, 67.08; H, 4.38%). Dehydration of compound (24) (3.0 g) with P_2O_5 (6.0 g) and quinol (0.6 g) in a sealed tube at 150° for 1 hr. yielded compound (12) (0.63 g) which had an i.r. identical with the material prepared by the other method.

The hydrogenation of compound (12) in ethyl acetate at atmospheric pressure over 10% Pd-C gave syn-5,6,7,8-tetrafluoro-1,2,3,4-tetrahydro-9-benzyl-1,4-methanonaphthalene (18), m.p. 58.8 - 60°C (from methanol). $\tau(CDCl_3)$ 2.87 ($C_6\underline{H}_5$); 6.60 (H-1); 8.11 (H-2, exo); 7.68 (H-9, anti); 7.68 ($C_6H_5\underline{CH}_2$-); 8.84 (H-2, endo) $\delta_F(CDCl_3)$ 147.1 (F-5, F-8); 159.4 p.p.m. (F-6, F-7) (Found: C, 70.59; H, 4.94; M^+, 306. $C_{18}H_{14}F_4$ requires C, 70.58; H, 4.61%; M, 306).

(ii) 6,7-Difluoro compounds

The difluoro ketone (9) (1.01 g) in anhydrous ether (30 ml) was treated with the ylid prepared by reacting p-trifluoromethylbenzyl triphenylphosphonium bromide (2.76 g) in anhydrous ether (50 ml) with n-butyl lithium (2.7 ml, 2.0M in hexane), and the mixture was heated under reflux for 4 hr., then cooled, filtered and the filtrate evaporated. The residue (1.84 g) was separated by chromatography on silica (carbon tetrachloride as

eluant) to give crude product (1.27 g) which was crystallised from light petroleum (b.p. 60 - 80°) to give racemic 6,7-difluoro-1,2,3,4-tetrahydro-9-(4'-trifluoromethylbenzylidene)-1,4-methanonaphthalene (14) m.p. 68.5 - 69.5°C. δ_F ($CDCl_3$) 142.0 p.p.m. (F-6,p) (Found: C, 68.03; H, 4.20%; M^+, 336. $C_{19}H_{13}F_5$ requires C, 67.86; H, 3.93%; M, 336).

The hydrogenation of compound (14) in ethanol at atmospheric pressure over 10% Pd-C gave a product which was shown by t.l.c. on silica [light petroleum, b.p. (30 - 40°C)] to contain two components with R_f values 0.38 and 0.47. The faster moving component separated by preparative t.l.c. on silica using light petroleum (b.p. 30 - 40°C) as eluant was syn-6,7,-difluoro-1,2,3,4-tetrahydro-9-(4'-trifluoromethylbenzyl-1,4-methanonaphthalene (15), m.p. 85.5 - 86.5°C. τ ($CDCl_3$) 2.64 ($-C_6H_4-$); 2.92 ($-C_6F_2H_2-$); 6.93 (H-1); 8.07 (H-2, exo), 7.64 (H-9, anti); 7.64 (4'-$CF_3-C_6H_4-\underline{CH}_2-$); 8.86 (H-2, endo). δ_F ($CDCl_3$) 142.5 p.p.m. (Found: C, 67.61; H, 4.14%; M^+, 338). $C_{19}H_{15}F_5$ requires C, 67.45; H, 4.47%; M, 338). The slower moving component obtained by repeated recrystallisation from light petroleum (b.p. 30 - 40°) was anti-6,7-difluoro-1,2,3,4-tetrahydro-9-(4'-trifluoromethylbenzyl)-1,4-methanonaphthalene (16) m.p. 90.5 - 91.3°C. τ ($CDCl_3$) 2.54 ($-C_6H_4-$); 3.07 ($-C_6F_2H_2-$); 6.97 (H-1); 7.93 (H-2, exo); 7.38; (4'-$CF_3C_6H_4-\underline{CH}_2-$); 7.78 (H-9, syn); 8.82 (H-2, endo). (Found: C, 67.82; H, 4.21%; M^+, 338).

Chemical kinetics. Reactions of 5,6,7,8-tetrafluoro compounds with potassium isopropoxide in isopropanol (0.35M) at 100.0°C

(a) Compound (3) (0.1797 g) and the alkoxide solution (10.0 ml) were heated together for 440 min. ^{19}F n.m.r. analysis of the product indicated the formation of 78.5% trifluoro-isopropoxy compound giving the calculated second order rate constant 0.01 $dm^3mol^{-1}min.^{-1}$.

Reaction of compound (3) (0.196 g) with potassium isopropoxide in isopropanol (2 ml, 0.98M) at 100°C for 60 hr. and work up in the usual way followed by distillation in vacuo at ca. 150° at 0.05 mm gave racemic 7-isopropoxy-5,6,8-trifluoro-1,2,3,4-tetrahydro-9-isopropylidene-1,4-methanonaphthalene

(0.18 g) δ_F ($CDCl_3$), 140.6 (F-8); 149.2 (F-5); 154.0 p.p.m. (F-6). (Found: C, 69.16; H, 6.24%; M^+, 296. $C_{17}H_{19}F_3O$ requires C, 68.90; H, 6.46%; M, 296).

(b) A kinetics experiment with compound (5) carried out as in (a) gave the second order rate constant 0.01 $dm^3mol^{-1}min.^{-1}$

Racemic syn-7-isopropoxy-5,6,8-trifluoro-1,2,3,4-tetrahydro-9-isopropyl-1,4-methanonaphthalene was isolated as in (a) by sublimation at 150° at 0.05 mm. Hg. δ_F ($CDCl_3$) 140.7 (F-8); 149.1 (F-5); 153.6 p.p.m. (F-6). (Found: C, 68.68; H, 6.75%; M^+, 298. $C_{17}H_{21}F_3O$ requires C, 68.44; H, 7.10%; M, 298).

(c) A kinetics experiment with compound (12) gave the second order rate constant 0.02 $dm^3mol^{-1}min.^{-1}$

A mixture of two racemates from 6-isopropoxy-5,7,8-trifluoro- and 7-isopropoxy-5,6,8-trifluoro-1,2,3,4-tetrahydro-9-benzylidene-1,4-methanonaphthalene, b.p. 136 - 140° at 0.01 mm Hg was isolated as in (a). δ_F ($CDCl_3$) (for the 7-^{i}PrO-compound), 140.1 (F-8); 148.5 (F-5); 153.1 p.p.m. (F-6). (Found: C, 73.58; H, 5.36%; M^+, 344. $C_{21}H_{19}F_3O$ requires C, 73.24; H, 5.56%; M, 344).

(d) A kinetics experiment with compound (18) gave the second order rate constant 0.02 $dm^3mol^{-1}min.^{-1}$ Racemic syn-7-isopropoxy-5,6,8-trifluoro-1,2,3,4-tetrahydro-9-benzyl-1,4-methanonaphthalene, b.p. 130 - 185°C at 0.01 - 0.05 mm Hg was isolated as in (a). δ_F ($CDCl_3$) 140.2 (F-8); 147.8 (F-5); 153.3 p.p.m. (F-6). (Found: C, 72.88; H, 5.96%; M^+, 346. $C_{21}H_{21}F_3O$ requires C, 72.81; H, 6.11%; M, 346).

(e) A kinetics experiment with compound (13) gave the second order rate constant 0.03 $dm^3mol^{-1}min.^{-1}$

A mixture of two racemates from 6-isopropoxy-5,7,8-trifluoro- and 7-isopropoxy-5,6,8-trifluoro-1,2,3,4-tetrahydro-9-(4'-aminobenzylidine)-1,4-methanonaphthalene, m.p. 181 - 183.5° was isolated as in (a). δ_F ($CDCl_3$) (for the 7-^{i}PrO compound),

140.0 (F-8); 148.3 (F-5); 153.1 p.p.m. (F-6). (Found: C, 70.36; H, 5.33; N, 3.72%; M^+, 359. $C_{21}H_{20}F_3NO$ requires, C, 70.15; H, 5.61; N, 3.90%; M, 359).

(f) A kinetics experiment with compound (11) gave the second order rate constant 0.06 $dm^3mol^{-1}min.^{-1}$

A mixture of two racemates from 6-isopropoxy-5,7,8-trifluoro- and 7-isopropoxy-5,6,8-trifluoro-1,2,3,4-tetrahydro-9-(4'-trifluoromethylbenzylidene)-1,4-methanonaphthalene, b.p. 140 - 190°C at 0.05 mm. Hg was isolated from the kinetics experiment by preparative scale t.l.c. on silica (carbon tetrachloride as eluant δ_F ($CDCl_3$) (for the 7-^{i}PrO compound), 139.9 (F-8); 148.4 (F-5); 152.8 p.p.m. (F-6). (Found: C, 63.74; H, 4.33%; M^+, 412. $C_{22}H_{18}F_6O$ requires C, 64.08; H, 4.40%; M, 412).

(g) A kinetics experiment with compound (17) gave the second order rate constant 0.02 $dm^3mol^{-1}min.^{-1}$ Racemic syn-7-isopropoxy-5,6,8-trifluoro-1,2,3,4-tetrahydro-9-(4'-trifluoromethylbenzyl)-1,4-methanonaphthalene, b.p. 130 - 180°C at 0.01 mm. was isolated as in (f). δ_F ($CDCl_3$) 140.0 (F-8); 148.5 (F-5); 152.9 (F-6). (Found: C, 63.82; H, 4.54%; M^+, 414. $C_{22}H_{20}F_6O$ requires C, 63.76; H, 4.87%; M, 414).

(h) Treatment of the tetrafluoroketone (8) (0.14 g) with potassium isopropoxide in isopropanol (1 ml, 0.98M) at room temperature for 45 min. gave 5,6,7,8-tetrafluoro-1-isopropoxycarbonyl-1,2,3,4-tetrahydronaphthalene (20) (0.05 g) sublimed at 150° at 0.05 mm (Found: C, 58.2; H, 5.3%; H, 5.3%; M^+, 290. $C_{14}H_{14}F_4O_2$ requires C, 57.93; H, 4.86%; M, 290).

Chemical kinetics. Reactions of 6,7-difluoro-compounds with potassium isopropoxide in isopropanol-dimethyl sulphoxide (1:1 v/v) (0.36M)

(a) A kinetics experiment with compound (4) gave the second order rate constant 0.001 $dm^3mol^{-1}min^{-1}$.

Racemic 7-isopropoxy-6-fluoro-1,2,3,4-tetrahydro-9-isopropylidene-1,4-methanonaphthalene, b.p. 110 - 140°C at 0.05 mm Hg was isolated by preparative t.l.c. on silica using light petroleum (b.p. 30 - 40) as eluant. δ_F ($CDCl_3$), 137.3 p.p.m. (F-6). (Found: C, 78.84; H, 7.70%; M^+, 260. $C_{17}H_{21}FO$ requires C, 78.42; H, 8.13%; M, 260).

(b) A kinetics experiment with compound (6) gave the second order rate constant 0.0007 $dm^3mol^{-1}min.^{-1}$ Racemic syn-7-isopropoxy-6-fluoro-1,2,3,4-tetrahydro-9-isopropyl-1,4-methanonaphthalene, m.p. 66.5 - 67°C was obtained as in (a). δ_F ($CDCl_3$) 137.6 p.p.m. (F-6). (Found: C, 77.78; H, 8.86%; M^+, 262. $C_{17}H_{23}FO$ requires C, 77.82; H, 8.84%; M, 262).

(c) A kinetics experiment with compound (14) gave the second order rate constant 0.005 $dm^3mol^{-1}min.^{-1}$ A mixture of two racemates from 6-isopropoxy-7-fluoro- and 7-isopropoxy-6-fluoro-1,2,3,4-tetrahydro-9-(4'-trifluoromethylbenzylidene)-1,4-methanonaphthalene, b.p. 140 - 175°C at 0.01 mm. Hg was obtained by preparative t.l.c. on silica using carbon tetrachloride as eluant. δ_F ($CDCl_3$) (for the 7-^{i}PrO compound), 136.1 p.p.m. (F-6) (Found: C, 70.36; H, 5.12%; M^+, 376. $C_{22}H_{20}F_4O$ requires C, 70.20; H, 5.36%; M, 376).

(d) Treatment of compound (15) (0.2213 g) with potassium isopropoxide in isopropanol-dimethyl sulphoxide (1:1 v/v) (2.3 ml., 1.00M) in a sealed tube at 100° for 20 hr. gave two components which were separated by preparative t.l.c. on silica using chloroform as eluant. The faster moving component was syn-6,7-difluoro-1,2,3,4-tetrahydro-9-(4'-isopropoxycarbonylbenzyl)-1,4-methanonaphthalene (21) (0.0745 g) sublimed at 150° at 0.01 - 0.05 mm Hg. δ_F ($CDCl_3$), 142.8 p.p.m. (Found: C, 74.18; H, 6.40%; M^+, 356. $C_{22}H_{22}F_2O_2$ requires C, 74.14; H, 6.22%; M, 356). The slower moving component was racemic syn-7-isopropoxy-6-fluoro-1,2,3,4-tetrahydro-9-(4'-isopropoxycarbonylbenzyl)-1,4-methanonaphthalene (22) (0.0788 g) sublimed at 160° at 0.01 - 0.05 mm Hg. δ_F ($CDCl_3$) 137.0 p.p.m. (F-6).

(Found: C, 75.80; H, 7.07%; M^+, 396. $C_{25}H_{29}FO_3$ requires C, 75.73; H, 7.37%; M, 396).

(e) Treatment of compound (16) (0.2092) with potassium isopropoxide in isopropanol-dimethyl sulphoxide (1:1 v/v) (2.1 ml, 1.00M) in a sealed tube at 100° for 20 hr. gave two components which were separated as in (d). The faster moving component was anti-6,7-difluoro-1,2,3,4-tetrahydro-9(4'-isopropoxycarbonylbenzyl)-1,4-methanonaphthalene (23) (0.1169 g) m.p. 71.5 - 72°C. δ_F ($CDCl_3$) 143.5 p.p.m. (Found: C, 74.34; H, 6.48%; M^+, 356). The slower moving component was racemic anti-7-isopropoxy-6-fluoro-1,2,3,4-tetrahydro-9-(4'isopropoxy-carbonylbenzyl)-1,4-methanonaphthalene (24) (0.0427 g) sublimed at 160°C at 0.01 mm Hg. δ_F ($CDCl_3$) 137.4 p.p.m. (F-6) (Found: C, 75.88; H, 6.96%; M^+, 396).

Reaction of compound (10) with potassium t-butylthiolate

Compound (10) (0.379 g) in dimethylformamide (25 ml) was treated with potassium t-butylthiolate (0.350 g) in dimethylformamide (10 ml) at -40°C. The mixture was maintained at -20 to -30°C for 1 hr., treated with sulphuric acid (20 ml., 4M) and extracted with ether. The extracts were dried ($MgSO_4$) evaporated and the complex residue was separated by chromatography on silica using chloroform-light petroleum ether (b.p. 60 - 80°) (1:3 v/v) initially, then (4:6 v/v), to give a 5,6,7,8-tetrafluoro-1,2,3,4-tetrahydro-9-t-butylthio-9-(4'-nitrobenzyl)-1,4-methanonaphthalene (19) (0.07 g) m.p. 181 - 183.5°C. (Found: C, 60.56; H, 4.57; M^+ 439. $C_{22}H_{21}F_4NO_2S$ requires: C, 60.12; H, 4.82%; M, 439).

Pentafluorophenylisopropyl ether

Hexafluorobenzene (9.6 g) was treated with potassium isopropoxide in isopropanol (50 ml, 1.0M) at room temperature. The mixture was heated for 1.75 hr. at 100°, cooled, poured into water and extracted with ether. The extracts were washed with water, dried ($MgSO_4$) and the solvent fractionated through an 18" column packed with glass helices. The residue was

distilled in vacuo to give pentafluorophenyl isopropyl ether (8.16 g), b.p. 54.5°C at 12 mm Hg. (Found: C, 48.14; H, 3.06%. $C_9H_7F_5O$ requires: C, 47.79; H, 3.12%). In $CDCl_3$, the ortho fluorine was at 6.3 p.p.m. downfield and the meta- and para-fluorine at ca. 1 p.p.m. upfield from internal C_6F_6.

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