REACTIONS OF POLYFLUOROCARBONYL COMPOUNDS WITH 1,2,3,4-TETRAHYDROQUINOLINE

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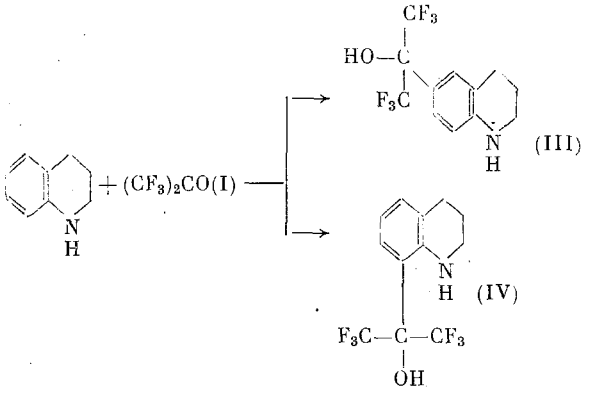
As reported in the patent literature [1], indoline and 1,2,3,4-tetrahydroquinoline (THQ) react with hexafluoroacetone (I) under severe conditions in the presence of catalysts go give C^5- and C^6-alkylation products, respectively. We have also shown that the reaction of equimolar amounts of indoline with (I) takes place even at temperatures of −60°C to +20°C to give C^7-alkylation products, or when an excess of (I) is used, $C^{5,7}$-dialkylation products [2]. In this context, we here examine the reaction of THQ with (I), and with methyl trifluoropyruvate (II), which we used previously for the C-alkylation of arylamines [3, 4].

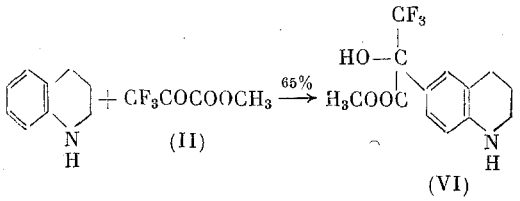
THQ was found to react in chloroform with an equimolar amount of (I) to give a mixture of 6- and 8-(α-hydroxyhexafluoroisopropyl)-1,2,3,4-tetrahydroquinolines (III) and (IV), in proportions which varied with the reaction temperature



Mixing the reactants at −60°C, followed by thermostating at −20°C gave (III) and (IV), the proportion of (III) being 65% according to high-resolution liquid chromatography (Table 1). When the mixture was heated rapidly to 20°C and maintained at this temperature, the amount of (III) increased to 79%. When (I) was bubbled through a solution of THQ in boiling chloroform, the proportion of isomer (III) reached 91%. The pure isomers (III) and (IV) could be isolated from the reaction mixture (20°C, 2 h) by crystallization, and these failed to isomerize even on prolonged boiling in chloroform.

As expected, the reaction of two equivalents of (I) with THQ at 20°C gave 6,8-di-(α-hydroxy-hexafluoroisopropyl)-1,2,3,4-tetrahydroquinoline (V), in 88% yield.

When THQ reacted with the methyl ester (II), the sole product was 6-(α-hydroxy-α-methoxycarbonyltrifluoroethyl) 1,2,3,4-tetrahydroquinoline (VI).



Compounds (III), (V), and (VI) were converted into the corresponding substituted quinolines (VII)-(IX) by treatment with activated MnO_2 [5] in benzene, with azeotropic removal of water.

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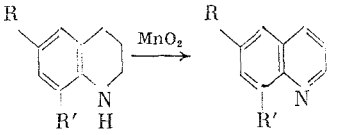
TABLE 1. Properties of (III)-(XI)

Compound	Yield, %	Mp, °C	R_f	Found/Calculated, %				Empirical formula $[M-CF_3]^+$
				C	H	N	F	
(III) *	61	116–118	0,50	48,44 / 48,16	3,89 / 3,68	4,41 / 4,68	37,91 / 38,13	$C_{12}H_{11}NOF_6$
(IV) †	12	89–91	0,75	47,90 / 48,16	3,92 / 3,68	4,38 / 4,68	37,85 / 38,13	$C_{12}H_{11}NOF_6$
(V)	88	118–120	0,44	38,29 / 38,71	2,61 / 2,37	2,88 / 3,01	48,69 / 49,03	$C_{15}H_{11}NO_2F_{12}$
(VI)	65	92–94	0,47	54,21 / 53,98	5,06 / 4,84	4,48 / 4,84	19,37 / 19,72	$C_{13}H_{14}NO_3F_3$
(VII)	81	270–272	0,21	48,48 / 48,81	2,14 / 2,37	4,51 / 4,75	38,19 / 38,64	$C_{12}H_7NOF_6$
(VIII)	79	198–200	0,44	39,00 / 39,04	1,73 / 1,52	2,81 / 3,04	49,12 / 49,46	$C_{15}H_7NO_2F_{12}$
(IX)	76	165 (decomp.)	0,24	55,01 / 54,73	3,86 / 3,51	4,60 / 4,91	19,59 / 20,00	$C_{13}H_{10}NO_3F_3$
(X)	88	158–160	0,46	34,26 / 34,45	1,10 / 1,12	2,34 / 2,23	54,18 / 54,55	$C_{18}H_7NO_3F_{18}$ (558)
(XI)	82	218–220	0,27	42,69 / 42,55	2,08 / 2,26	3,26 / 3,31	40,13 / 40,43	$C_{15}H_{10}NO_3F_9$

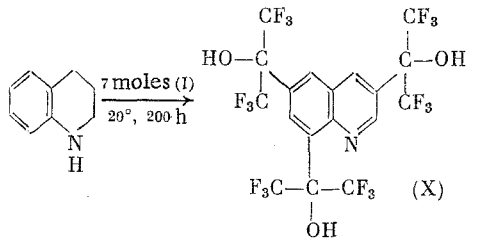
*R_t = 5.2 min, for liquid chromatography (see Experimental).
†R_t = 8.0 min.



(III), (V), (VI) (VII)—(IX)

R = $C(CF_3)_2OH$, R′ = H (III), (VII); R = R′ = $C(CF_3)_2OH$ (V), (VIII);
R = $C(CF_3)(COOCH_3)OH$, R′ = H (VI), (IX).

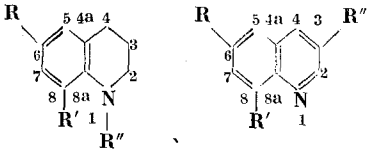
An unusual result was obtained when THQ was reacted with (I) in a ratio of 1:7 at 20°C for 200 h in chloroform. It was found that 3,6,8-tri(α-hydroxyhexafluoroisopropyl)-quinoline (X) was formed in 88% yield, i.e., aromatization of the nitrogenous ring had taken place, with simultaneous substitution thereof by a hexafluoroacetone residue



Proof of the fact that substitution in the pyridine ring takes place before full aromatization of the system is provided by the observation that neither quinoline itself nor its 6,8-disubstituted derivative (VIII) reacts with the ketone (I) under these conditions.

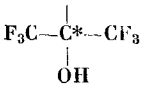
In order to examine more closely the aromatization of the tetrahydroquinoline system by polyfluorocarbonyl compounds, we studied the reaction of the disubstituted tetrahydroquinoline (V) with the ketoester (II). It was found that when these compounds were reacted in chloroform at 20°C in a ratio of 1:5, no changes took place in the system over periods as long as one month. When the mixture was heated in a sealed ampul (120°C, 8 h), two pure compounds were isolated, namely 3,5H-1-hydroxy-7-(α-hydroxyhexafluoroisopropyl)-1-trifluoromethyl-2a-aza-2-oxoacenaphthene (XI), yield 40%, and the disubstituted quinoline (VIII), yield 52%. No C-alkylation of the pyridine ring took place.

TABLE 2. ^{13}C NMR Spectra of (III)-(XI)

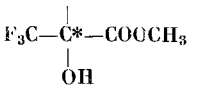


(III)—(VI), (XI)

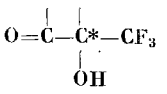
(VII)—(X)



(A)



(B)

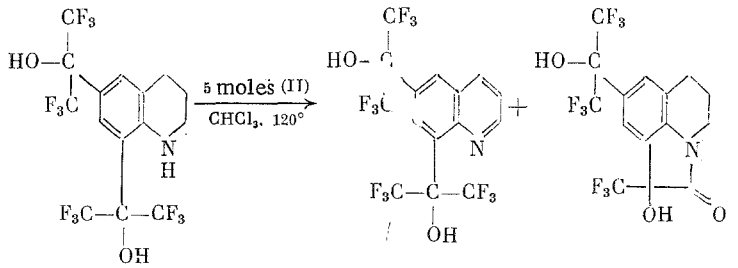


(C)

Compound	R	Chemical shifts, δ, ppm (acetone)													$^1J_{C-F}$	$^2J_{C-F}$
		2	3	4	4a	5	6	7	8	8a	CF_3	C *	C=O	OCH_3	Hz	
(III)	R=A; R′=R″=H	41,9	22,3	27,8	121,4	125,9	118,1	128,5	114,0	147,1	124,3	77,9	–	–	286,3	30,5
(IV)	R=R″=H; R′=A	42,6	22,5	28,0	129,7	126,7	120,3	131,8	117,3	145,4	124,5	81,3	–	–	282,2	30,5
(V)	R=R′=A; R″=H	42,3	21,6	29,3	124,8	126,3	117,6	130,0	111,6	148,1	124,3 124,5	77,7 81,6	–	–	287,3 288,8	30,4 30,6
(VI)	R=Б; R′=R″=H	42,0	22,4	27,9	121,1	125,7	120,8	128,0	113,9	147,1	124,6	79,5	169,8	53,5	284,3	30,5
(VII)	R=A; R′=R″=H	152,3	122,3	137,0	129,0	127,9	127,3	129,5	126,9	147,9	123,5	77,2	–	–	286,8	29,3
(VIII)	R=R′=A; R″=H	150,7	123,7	141,1	130,6	129,6	125,0	131,8	129,8	148,7	124,2 124,6	78,5 82,7	–	–	288,8 287,3	29,5 30,5
(IX)	R=Б; R′=R″=H	152,5	122,8	137,4	128,5	128,0	127,9	130,3	127,7	149,2	124,6	79,5	169,0	54,1	284,6	29,2
(X)	R=R′=R″=A	148,6	125,0	140,8	128,8	132,8	125,1	131,1	131,5	131,0	123,9 124,0 124,3	77,8 78,4 82,4			287,3 288,8 290,3	29,5 30,1 30,5
(XI)	R=A; R′, R″=B	39,5	21,3	24,9	125,3	122,9	123,5	129,9	122,2	143,1	124,0 124,4	77,2 78,1	169,9		287,3 283,2	31,2 27,1

TABLE 3. ^1H and ^{19}F NMR Spectra of (III), (V), (VI), and (X)

Compound	Chemical shifts, δ, ppm (acetone, d_6)							
	^1H (J, Hz)							^{19}F
	2	3	4	5	7	8	OCH_3	
(III)	3,25 m	1,85 m	2,74 t	7,14 br.s	7,10 br.d (9,0)	6,44 d	–	–1,7 s
(V)	3,30 m	1,84 m	2,77 t	7,23 br.s	7,50 br.d	–	–	–1,7 s –3,0 s (1 : 1)
(VI)	3,25 m	1,85 m	2,74 d	7,14 br.s	7,11 br. d. (9,0)	6,44 d	3,82 s	0,05 s
(X)	9,31 m	– (1,8)	9,12 d	8,77 d	8,59 br.d (1,6)	–	–	–2,4 s –2,2 s 1,2 br.s (1 : 1 : 1)



(V) (VIII) (XI)

It followed that the ketoester (II), like the ketone (I), was capable of oxidizing the tetrahydropyridine ring in THQ, but not of alkylating it. On the other hand, the ketoester (II) on heating displaces the hexafluoroacetone residue to form the tricyclic product (XI). No ring aromatization occurs here, apparently as a result of the difficulty of oxidation of the acyl derivative (XI).

The tricyclic product (XI) has also been obtained by direct synthesis, by reacting (III) with the ketoester (II) in chloroform at 20°C.

Compounds (III)-(XI) are stable, crystalline solids (Table 1). Their structures were established from the ^{13}C NMR spectra (Table 2), elemental analyses, ^{1}H and ^{19}F NMR spectra (III), (V), (VI), (X) (Table 3), and mass spectrum (X).

The shapes of the signals and the coupling constants in the PMR spectra of (III), (V), (VI), and (X) enabled the positions of the substituents in the aromatic rings to be established unambiguously. Assignment of the ^{13}C NMR spectral signals was made on the basis of the PMR spectra of (III), (V), (VI), and (X), and by comparing them with the ^{13}C NMR spectra of unsubstituted quinoline [6] and derivatives (VII)-(X).

EXPERIMENTAL

^{1}H, ^{19}F, and ^{13}C NMR spectra were obtained on a Bruker WP-200SY spectrometer, operating frequencies 200.13, 188.31, and 50.31 MHz, respectively. Chemical shifts were measured relative to TMS (^{1}H, ^{13}C) and CF_3COOH (external standard) (^{19}F). The mass spectrum of (X) was obtained on an AEI MS-30. High resolution liquid chromatography was carried out on an Altex 322-HP with a reversed-phase column of dimensions 4.6 × 250 mm, sorbent Likhosorb RP-2.5 μ; mobile phase 70% methanol in water, elution rate 1.0 ml/min; UV detector (260 nm). Rf values were obtained on Silufol UV-254 plates in the system CCl_4–acetone, 3:1, the compounds being visualized by UV.

6-(α-Hydroxyhexafluoroisopropyl)-1,2,3,4-tetrahydroquinoline (III) and 8-(α-Hydroxyhexafluoroisopropyl)-1,2,3,4-tetrahydroquinoline (IV). Into a solution of 8.4 g of THQ in 20 ml of chloroform at −60°C was condensed 10.5 g of (I), and the ampul was sealed and kept at 20°C for 2 h.* It was then cooled to −60°C, opened, the solvent removed in vacuo, and the residue crystallized from hexane and Freon-113 to give 11.52 g of (III) and 2.27 g of (IV).

6,8-Di-(α-hydroxyhexafluoroisopropyl)-1,2,3,4-tetrahydroquinoline (V). Obtained from 3.2 g of THQ and 8 g of (I) as for the synthesis of (III) and (IV). Recrystallization from CCl_4 gave 9.85 g of (V).

6-(α-Hydroxy-α-methoxycarbonyltrifluoroethyl)-1,2,3,4-tetrahydroquinoline (VI). To a solution of 4 g of THQ in 15 ml of CCl_4 at −10°C was added 4.7 g of (II), and the mixture kept at 20°C for 24 h with exclusion of moisture. The solvent was then removed under reduced pressure, and the residue recrystallized from a mixture of benzene and hexane to give 5.65 g of (VI).

6-(α-Hydroxyhexafluoroisopropyl)quinoline (VII). To a solution of 3 g of (III) in 100 ml of dry benzene was added 12 g of activated MnO_2, and the mixture boiled with azeotropic removal of water for 4 h. The MnO_2 was filtered off and washed with hot acetone, the solution concentrated to 50 ml, and the solid which separated was filtered off and washed with CCl_4 to give 2.4 g of (VII).

*The isomer ratios were measured in all instances following removal of the solvent in vacuo.

6,8-Di-(α-hydroxyhexafluoroisopropyl)quinoline (VIII). a) Obtained from 3 g of (V) and 9 g of MnO_2, as described for (VII). Removal of the solvent in vacuo followed by recrystallization from benzene gave 2.37 g of (VIII).

b) In a glass ampul were placed a solution of 5 g of (V) in 25 ml of dry chloroform and 8.4 g of (II). The mixture was then heated at 120°C for 8 h, cooled to 20°C, and the solid filtered off. The mother liquors were evaporated, and the residue crystallized from CCl_4 to give 2.58 g of (VIII).

6-(α-Hydroxy-α-methoxycarbonyltrifluoroethyl)quinoline (IX). Obtained as for (VII), from 3 g of (VI) and 12 g of MnO_2. Removal of the solvent under reduced pressure and recrystallization from CCl_4 gave 2.25 g of (IX).

3,6,8-Tri-(α-hydroxyhexafluoroisopropyl)quinoline (X). In a glass ampul was placed a solution of 2.8 g of THQ in 15 ml of dry chloroform, 24.5 g of (I) condensed in at −60°C, sealed, and kept for 200 h at 20°C. It was then cooled to −60°C, opened, excess (I) recondensed, the solvent removed under reduced pressure, and the residue recrystallized from chloroform to give 11.58 g of (X).

3,5H-1-Hydroxy-7-(α-hydroxyhexafluoroisopropyl)-1-trifluoromethyl-2a-aza-2-oxoacenaphthene (XI). a) To a solution of 4 g of (III) in 20 ml of dry chloroform was added 4.17 g of (II), and the mixture kept at 20°C for 24 h with exclusion of moisture. The solid which separated was filtered off and washed with CCl_4 to give 4.64 g of (XI).

b) The solid obtained in the synthesis of (VIII) (b) was washed with CCl_4 to give 1.82 g of (XI).

CONCLUSIONS

1. Tetrahydroquinoline reacts with hexafluoroacetone to give, depending on the proportions of the reactants, mono- or di-$C^{6,8}$-alkylation products of tetrahydroquinoline, together with the tri-$C^{3,6,8}$-alkylated quinoline.

2. Methyl trifluoropyruvate, in addition to C-alkylation and aromatization of the tetrahydropyridine ring, affords a tricyclic product as a result of simultaneous C^8-alkylation and N-acylation.

3. Dehydrogenation of the C-alkylation products of tetrahydroquinoline by polyfluorocarbonyl compounds has given several substituted quinolines.

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