FLUORINATED HETEROCUMULENES

13*. REACTION OF N-PHENYLBIS(TRIFLUOROMETHYL)KETENIMINE WITH VINYL ETHERS AND KETENE ACETALS

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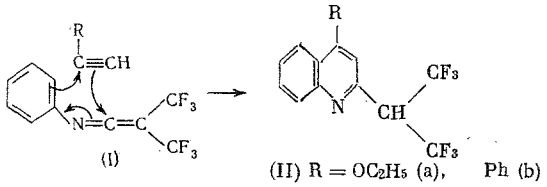
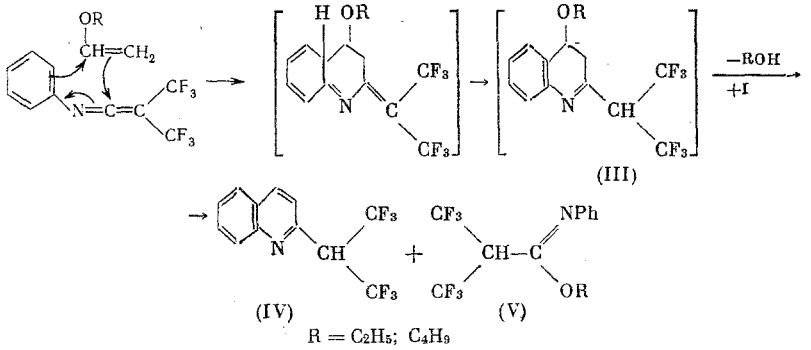
It has been shown previously [2] that N-phenylbis(trifluoromethyl)ketenimines (I) react with phenyl- and ethoxyacetylenes as heterodienes with participation of the aromatic ring of the ketenimine, with the formation of substituted quinolines (II). The yield of the ethoxyquinoline (IIa) was only 3%, since ethoxyacetylene causes dimerization of the ketenimine. When this reaction was carried out in hexane solution, the dimerizing effect of the ethoxyacetylene was reduced, and the yield of the ethoxyquinoline (IIa) rose to 43%.



(I) (II) R = OC_2H_5 (a), Ph (b)

The reactions of ketenimines with vinyl ethers and keten acetals have not previously been recorded. It appears that the ketenimine (I) reacts slowly with ethyl and butyl vinyl ethers at ~ 20° to give ultimately 2-hexafluoroisopropylquinoline (IV), i. e. also via 1,4-cycloaddition.



(III)

(IV) (V)

R = C_2H_5; C_4H_9

An intermediate product in the reaction of the ketenimine (I) with vinyl ethers is apparently the 4-alkoxydihydroquinoline (III). This is indicated by the IR spectrum (ν 1640 cm^{-1}) and ^{19}F PMR spectrum (doublet with chemical shift −14.4 ppm, J_{H-F} = 8.85 Hz) of the reaction product. It was not possible to isolate this product; vacuum distillation of the reaction product resulted in elimination of a molecule of alcohol to give the quinoline (IV). If the alcohol had been eliminated in the course of the reaction, half of the ketenimine (I) would have been consumed in forming the iminoether (V). In fact, the quinoline (IV) was formed in over 50% yield, and the iminoether in traces.

In contrast to the vinyl ethers, ketene acetal reacts with the ketenimine to give the quite stable azetidine (VI) by addition to the C = N bond of the ketenimine. On long keeping at room temperature, and

* For No. 12, see [1].

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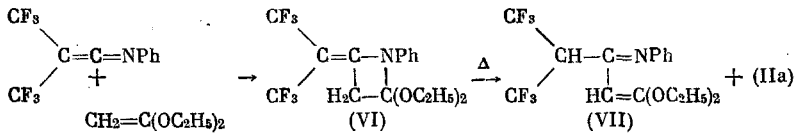
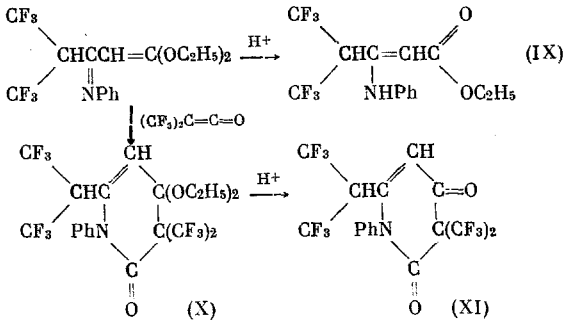
partially on vacuum distillation or heating to 100°, the azetidine (VI) is converted into the open-chain compound β,β-diacetoxyvinyl hexafluoroisopropyl ketone anil (VII)* in addition to the ethoxyquinoline (IIa).

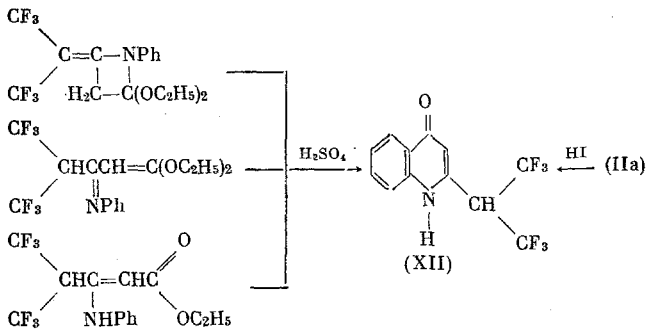


This isomerization is accompanied by characteristic changes in the spectra — disappearance of the quartets of the two nonequivalent CF_3 groups bonded to the sp^2-hybridized C atom in the azetidine (VI), and the appearance of a doublet due to the $(CF_3)_2CH$ group in the anil (VII) in the ^{19}F NMR spectrum. In the PMR spectrum, the four signals with intensities 6:5:4:2 are replaced by five signals with intensities 6:5:4:1:1, the ethoxy groups becoming nonequivalent. This nonequivalence persists up to 100°.

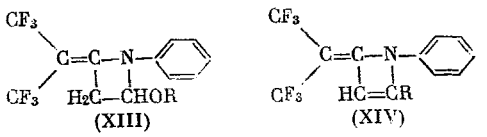
The structure of the anil (VII) was confirmed by acid hydrolysis to the ethyl ester of β,N-phenylamino-γ,γ-bis(trifluoromethyl)crotonic acid (IX), and by its reaction with bis(trifluoromethyl)keten by 1,4-cycloaddition to give the substituted dihydro-2-pyridone (X). The dihydro-2-pyridone (X) on treatment with conc. H_2SO_4 or HCl was converted into the dioxotetrahydropyridine (XI).



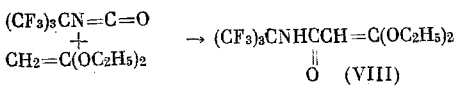
On treatment with conc. H_2SO_4 at room temperature, both the azetidine (VI) and its open-chain isomer (VII), and the crotonic acid derivative (IX) were converted into the 4-quinolone (XII), the structure of which was confirmed by synthesis from the ethoxyquinoline (IIa) by a known method (cf. [4]).



The isolation of the azetidine (VI) from the reaction of ketenimine (I) with keten acetal, and its conversion into the quinoline derivative (II) suggests that in the reactions of this ketenimine with vinyl ethers and acetylenes, there may be formed intermediate azetidines (XIII) and azetines (XIV).



*Perfluoro-tert-butyl isocyanate reacts with ketene acetal at temperatures as low as 20° to form the linear amide (VIII) (cf. [3]).



The failure of attempts to isolate these latter compounds may be due to their rapid cyclization into the quinoline derivatives (II) and (III). The literature records a number of instances of the conversion of four-membered rings with aryl substituents into six-membered rings by reaction of the aromatic ring [5-7].

Thus, the range of reactions of N-arylbis(trifluoromethyl)ketenimines which occur with involvement of the aromatic ring and which leads to a convenient synthesis of fluorinated quinolines has been extended.

EXPERIMENTAL METHOD

The IR spectra were recorded on a UR-20 instrument, and the UV spectra on a "Hitachi EPS-3T." PMR spectra were taken on a Perkin—Elmer R-12 (60 MHz) instrument with HMDS as internal standard. ^{19}F NMR spectra were recorded on a "Hitachi H-60" (57 and 46 MHz), with CF_3COOH as internal standard. Chemical shifts are given on the δ-scale in ppm from HMDS or CF_3COOH, respectively.

2-Hexafluoroisopropyl-4-ethoxyquinoline (IIa). To a solution of 0.5 g of ethoxyacetylene in 5 ml of hexane was added with cooling 1.8 g of the ketenimine (I) in 5 ml of hexane. The mixture was kept at ~20° for 40 days, and the precipitate was filtered off to give 1 g (43%) of the ethoxyquinoline (IIa), mp 146-149° (from hexane) [2].

2-Hexafluoroisopropylquinoline (IV). A mixture of 1.5 g of the ketenimine (I) and 0.8 g of ethyl vinyl ether was kept at ~20° (the progress of the reaction was followed by GLC and ^{19}F NMR). After 30 days, distillation of the reaction mixture under reduced pressure gave 1 g (61%) of the quinoline (IV), bp 51-54° ($8 \cdot 10^{-3}$ mm), mp 57-58° (from hexane). Found: C 51.59; H 2.82; F 40.85; N 4.87%. $C_{12}H_7F_6N$. Calculated: C 51.61; H 2.51; F 40.86; N 5.01%. UV spectrum (in hexane, λ_{max}, nm) (log ε): 224 (4.72); 227 (4.75); 231 (4.71); 275 (3.69); 302 (3.60); 315 (3.64) PMR spectrum (in CCl_4): 4.58 g [$(CF_3)_2CH$, J_{H-F} = 8.12 Hz]; 7.3-8.15 m (aromatic). ^{19}F NMR spectrum (in CCl_4): 14.4 d [$(CF_3)_2CH$, J_{H-F} = 8.86 Hz]. Molecular weight 279 (by mass spectrometry).

Under similar conditions, from 1 g of the ketenimine (I) and 1 g of butyl vinyl ether there was obtained 0.7 g (63%) of the quinoline (IV), mp 57-59° (from hexane).

1-Phenyl-2,2-diethoxy-4-hexafluoroisopropylideneazetidine (VI). To 2.53 g of the ketenimine (I) was added 1.16 g of ketene acetal. When the exothermic reaction was complete, the reaction mixture was kept for 2 h at ~20°, and distilled to give 3.3 g (89%) of the azetidine (VI), bp 89-91° ($1 \cdot 10^{-2}$ mm); N_D^{23} 1.4644. Found: C 51.51; H 4.08; F 31.22; N 3.57%. $C_{16}H_{17}F_6NO_2$. Calculated: C 52.03; H 4.60; F 30.89; N 3.79%. IR spectrum (ν, cm^{-1}): 1670 (C = C). PMR spectrum (in CCl_4): 1.07 t (CH_3); 3.5 c (OCH_2), $J_{CH_2CH_3}$ = 7.35 Hz; 3.25 broad s (CH_2); 7.15 s (aromat.), ^{19}F NMR spectrum in CCl_4: −22.8 q (CF_3C=); −24.6 q (CF_3C=), J_{F-F} = 8.05 Hz. Mol. wt. 369 (by mass spectrometry).

β,β-Diethoxyvinylhexafluoroisopropylketone Anil (VII). The azetidine (VI) (1.2 g) was heated at 100° for 7 h, and distilled to give 0.9 g (75%) of the anil (VII), bp 95-98° ($1 \cdot 10^{-2}$ mm), containing a small quantity of crystals. Found: C 52.18; H 4.62; F 31.59%. $C_{16}H_{17}F_6NO_2$. Calculated: C 52.03; H 4.60; F 30.89%. IR spectrum (ν, cm^{-1}): 1595 (C = C), 1620 (C = N). PMR spectrum (in CCl_4): 1.1 t (CH_3); 1.25 t (CH_3); 3.54 q (OCH_2); 4.07 q (OCH_2), $J_{CH_2CH_3}$ = 7.35 Hz; 5.2 sept. [$(CF_3)_2CH$, J_{H-F} = 8.12 Hz]; 6.45-7.35 (aromat.). ^{19}F NMR spectrum (in CCl_4): −14.8 d [$(CF_3)_2CH$, J_{H-F} = 8.2 Hz]. Molecular weight 369 (by mass spectrometry).

The crystals, after decantation of the anil (VII) and washing with hexane, were identified as the ethoxyquinoline (IIa).

β,β-Diethoxyacrylic N-Perfluoro-tert-butylamide (VIII). To a solution of 2.6 g of perfluoro-tert-butyl isocyanate in 2 ml of absolute ether was added a solution of 1.1 g of keten acetal in 3 ml of absolute ether, and the mixture was kept at ~20° for 16 h. Removal of the ether afforded 2.3 g (61%) of the amide (VIII) as hygroscopic crystals, mp 74-76° (from hexane). Found: C 34.73; H 3.12; F 44.77; N 4.13%. $C_{11}H_{12}F_9NO_3$. Calculated: C 35.01; H 3.18; F 45.35; N 3.71%. IR spectrum (ν, cm^{-1}): 1615 (C = C), 1695 (C = O), 3385 (NH). PMR spectrum (in CCl_4): 1.28 t (CH_3); 3.95 q (OCH_2); 4.1 q (OCH_2), $J_{CH_2CH_3}$ = 7.47 Hz; 4.34 s (CH=); 7.65 s (NH). ^{19}F NMR spectrum (in CCl_4): −10.9 s [$(CF_3)_3C$].

Ethyl β,N-Phenylamino-γ,γ-bis(trifluoromethyl)crotonate (IX). a) To 1 g of the anil (VII) was added 3 ml of conc. HCl, and the mixture was kept for 3 h at ~ 20°. The precipitate which separated was filtered off and washed with water to give 0.5 g (54%) of the ester (IX), mp 51-52° (from 70% alcohol). Found: C 49.41; H 3.89; N 4.02%. $C_{14}H_{13}F_6NO_2$. Calculated: C 49.29; H 3.82; N 4.1%. IR spectrum (ν, cm^{-1}): 1625 (C = C), 1675 (C = O), 3210, 3260 (NH). PMR spectrum (in CCl_4): 1.22 t (CH_3); 4.12 q (OCH_2), $J_{CH_2CH_3}$ =

7.35 Hz; 4.08 Sept [$(CF_3)_2CH$, J_{H-F} = 8 Hz]; 7.45-7.98 m (aromatic). ^{19}F NMR spectrum (in CCl_4): −14.3 d [$(CF_3)_2CH$, J_{H-F} = 8.05 Hz].

b) To a solution of 1 g of the anil (VII) in 5 ml of absolute ethanol was added 3 drops of conc. H_2SO_4, and the mixture was boiled for 5 h. Removal of the solvent gave 0.6 g (65%) of the ester (IX), mp 50-52° (from 70% alcohol).

1-Phenyl-3,3-bis(trifluoromethyl)-4,4-diethoxy-6-hexafluoroisopropyl-3,4-dihydro-2-pyridone (X). Bis(trifluoromethyl)keten (1 ml) was passed into a solution of the anil (VII) in 3 ml of absolute ether with ice cooling, and the mixture was kept at ~20° for 16 h. Removal of the solvent gave 1.1 g (73%) of the dihydropyridone (X), mp 106-108° (from hexane). Found: C 43.62; H 3.16; F 41.69%. $C_{20}H_{17}F_{12}NO_3$. Calculated: C 43.87; H 3.1; F 41.68%. IR spectrum (ν, cm^{-1}): 1680 (C=C), 1720 (C=O). PMR spectrum (in CCl_4): 1.22 t (CH_3); 3.81 q (OCH_2), $J_{CH_2CH_3}$ = 7.35 Hz; 3.63 sept [$(CF_3)_2CH$, J_{H-F} 8 Hz]; 5.9 s (CH=); 6.9-7.6 (aromatic). ^{19}F NMR (in CCl_4): −14.8 d [$(CF_3)_2CH$, J_{H-F} = 8.05 Hz]; −18.8 s (CF_3).

1-Phenyl-3,3-bis(trifluoromethyl)-6-hexafluoroisopropyl-2,4-dioxo-1,2,3,4-tetrahydropyridine (XI). a) A solution of 0.7 g of the dihydropyridone (X) in 2 ml of conc. H_2SO_4 was kept at 20° for 16 h, and the precipitate which separated was filtered off to give 0.6 g (98%) of the dioxotetrahydropyridine (XI), mp 85-87° (from hexane). Found: C 40.10; H 1.52; F 48.54%. $C_{16}H_7F_{12}NO_2$. Calculated: C 40.59; H 1.47; F 48.20%. IR spectrum (ν, cm^{-1}): 6130 (C=C), 1690 (C=O). PMR spectrum (in CCl_4): 3.77 sept. [$(CF_3)_2CH$, $J_{H-F} \simeq 8$ Hz]; 6.1 s (CH=); 7-7.8 (aromat.). ^{19}F NMR spectrum (in CCl_4): −14.2 d [$(CF_3)_2CH$, J_{H-F} = 8.05 Hz]; −15.1 s (CF_3).

b) A suspension of 0.5 g of the dihydropyridone (X) in 5 ml of conc. HCl was kept at ~20° for 48 h, and the resulting precipitate was filtered off to give 0.4 g (93%) of (XI), mp 85-87° (from hexane), identical with that obtained in a) above.

2-Hexafluoroisopropyl-4-quinolone (XII). a) A solution of 0.9 g of the azetidine (VI) in 2 ml of conc. H_2SO_4 was kept at ~20° for 48 h, then poured onto ice and the precipitate filtered off to give 0.5 g (69%) of the quinolone (XII), mp 174-176° (decomp., from 50% alcohol). Found: C 48.87; H 2.35; F 38.94; N 4.70%. $C_{12}H_7F_6NO$. Calculated: C 48.81; H 2.37; F 38.64; N 4.74%. UV spectrum (in CH_3OH, λ_{max}, nm) (log ε): 212(4); 228 (3.84); 318 (3.54); 33) (3.57). IR spectrum (ν, cm^{-1}): 1530, 1580, 1610, 1645, 2690-3320. ^{19}F NMR spectrum (in acetone): −12.8 d [$(CF_3)_2CH$, J_{H-F} = 8.85 Hz].

b) A solution of 0.4 g of the anil (VII) in 1 ml of conc. H_2SO_4 was kept at ~20° for 48 h, and poured onto ice to give 0.25 g (78%) of (XII), mp 167-169° (decomp., from 50% alcohol), giving no depression of melting point with a sample obtained as in a) above.

Under similar conditions, 0.5 g of the ester (IX) and 2 ml of conc. H_2SO_4 gave 0.35 g (81%) of the quinolone (XII), mp 168-170° (decomp., from 50% alcohol).

c) A mixture of 0.3 g of the ethoxyquinoline (IIa) in 3 ml of HI was boiled for 12 h, and poured onto ice. The precipitate was filtered off to give 0.2 g (73%) of (XII), mp 174-176° (decomp.).

CONCLUSIONS

An investigation has been carried out into the cycloaddition of alkoxy-substituted alkenes to N-phenylbis(trifluoromethyl)ketenimine, leading to the synthesis of fluorinated quinolines and azetidine.

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