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PARTIALLY FLUORINATED HETEROCYCLES. PART 25[1]. THE FORMATION OF FUSED-RING 3H-AZEPINE DERIVATIVES: 6,7,8,9-TETRAFLUORO-2,4-DIPHENYL-3H-1-BENZAZEPINE AND 6,7,8,9,10,11-HEXAFLUORO-2,4-DIPHENYL-3H-NAPHTH[2,1-b]AZEPINE *

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SUMMARY

Pentafluoroaniline(1) and 1,3,4,5,6,7,8-heptafluoro-2-naphthylamine(2) react with acetophenone in tetralin at reflux temperature in the presence of anhydrous zinc chloride to give the 3H-azepine derivatives 6,7,8,9-tetrafluoro-2,4-diphenyl-3H-1-benzazepine (5) and 6,7,8,9,10,11-hexafluoro-2,4-diphenyl-3H-naphth[2,1-b]azepine (6) respectively, in addition to the Schiff bases (3) and (4), found previously. The self-condensation product of acetophenone, β-benzoyl-α-methylstyrene ("dypnone"), is an intermediate in the ring-forming reactions. The heterocycles (5) and (6) exhibit fluxional behaviour which at 297K is fast for (5) but slow for (6) on the NMR time-scale.

* Dedicated to Emeritus Professor W.K.R. Musgrave on the occasion of his 70th birthday.

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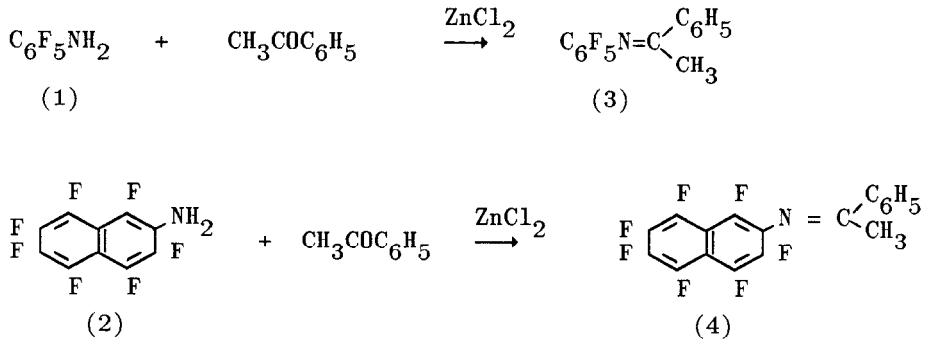
INTRODUCTION

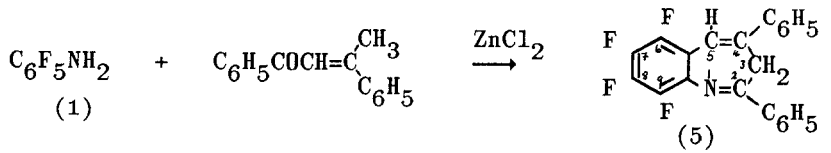
Pentafluoroaniline(1) and 1,3,4,5,6,7,8-heptafluoro-2-naphthylamine(2) have been shown to react with acetophenone in tetralin at reflux temperature in the presence of anhydrous zinc chloride to give the Schiff bases (3) and (4) respectively[2], Scheme 1. Both of these reactions have been re-examined and in this paper we report the isolation and characterisation of a further product, a heterocyclic compound from each experiment.



Scheme 1

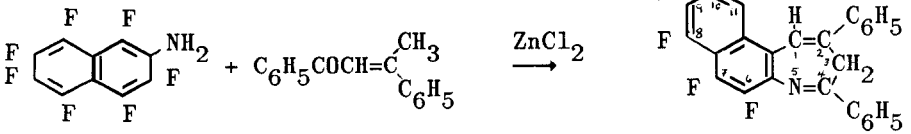
RESULTS AND DISCUSSION

Chromatographic separation of the product from the reaction of pentafluoroaniline(1) and acetophenone gave (3)(30%) and a second compound now identified as the 3H-azepine derivative(5)(9%). β-Benzoyl-α-methylstyrene('dypnone'), the self-condensation product of acetophenone[3], also reacted with pentafluoroaniline in tetralin at reflux temperature in the presence of anhydrous zinc chloride to give (5)(20%), Scheme 2. Likewise, the products from the reaction of the



Scheme 2

2-naphthylamine(2) with acetophenone have been separated to give the Schiff base (4)(5%) and a second compound, the 3H-azepine derivative (6)(9%). Compound (6)(17%) was also formed from (2), β-benzoyl-α-methylstyrene and anhydrous zinc chloride in tetralin at reflux temperature, Scheme 3.



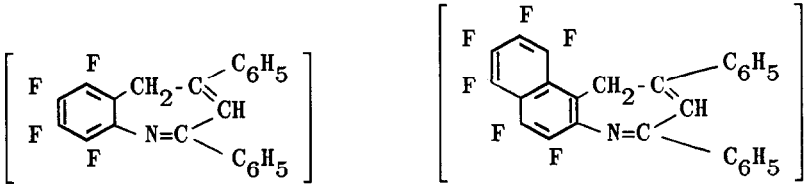
(2) (6)

Scheme 3

Significantly, neither of the Schiff bases (3) or (4) reacted with acetophenone to give (5) or (6) respectively under the conditions originally used to prepare the heterocyclic compounds.

The constitution of compounds (5) and (6) was plainly evident from their elemental analyses and the molecular ions in their mass spectra. The ^{19}F NMR spectrum of (5) showed four magnetically different fluorines while that of (6) showed six fluorines with only one pair showing a large peri coupling (J_{F-F} 67Hz), indicative of ring-cyclisation to the 1-position rather than the 3-position in the original naphthalene ring.

The absence of an N-H absorption in the infra-red spectra of the aniline- and 2-naphthylamine-derived heterocycles showed that they could only be the 3H azepine derivatives (5) and (6) or their isomers (7) and (8), respectively.



(7) (8)

Surprisingly, the ^{1}H NMR signals of the aliphatic protons in the two heterocycles were quite different at room temperature (297K): the aniline-derived heterocycle had a relatively broad signal at δ3.0(in C_6D_6) integrating for two protons, whereas the 2-naphthylamine-derived heterocycle in the same solvent showed one proton at δ1.72(broad) and one at δ4.43(broad). Not surprisingly, because of the nitrogen in the molecules, deuterotrifluoroacetic acid proved to be an excellent solvent for both heterocycles, enabling variable-temperature studies to be carried out. At room temperature (297K), the aniline-derived heterocycle still showed a broad signal due to two protons, but more deshielded at δ4.16; at 273K, this signal was very broad and at 253K it split into two separate signals at δ3.16 and δ5.30. The 2-naphthylamine-derived heterocycle in CF_3COOD still showed two separate aliphatic protons at 297K, again, more deshielded than in C_6D_6: at δ2.93 and at δ5.30 - almost identical to the position of the signals found in the aniline-derived heterocycle at 253K. When the temperature was raised to 310K these two aliphatic absorptions although not shifted became very broad. The chemical shifts of the other protons in both heterocycles remained essentially unchanged during the variable-temperature measurements.

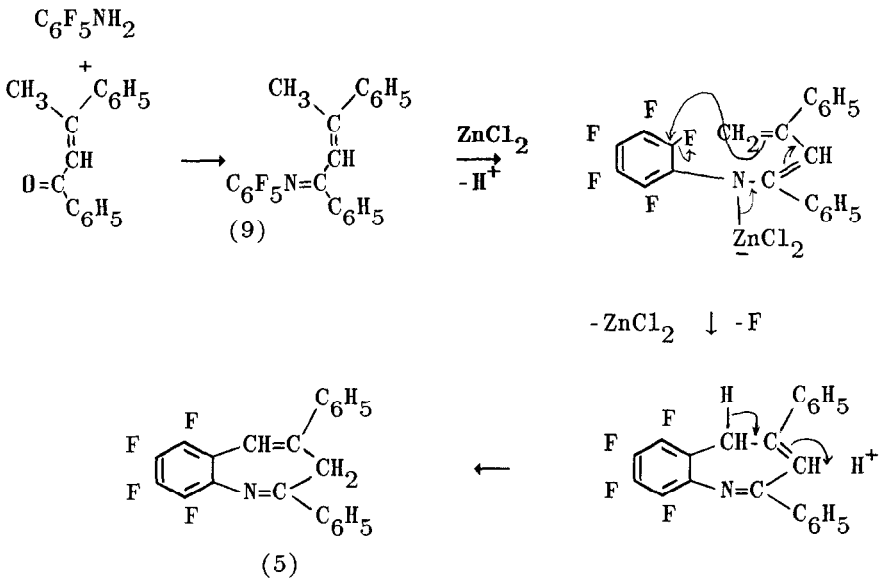
In C_6D_6, no single proton could be resolved in the spectrum of the aniline-derived heterocycle which might be due to an olefinic proton but the spectrum of the 2-naphthylamine-derived heterocycle was shown by proton decoupling to contain a unique proton, a doublet (J,7Hz) at δ7.67, not coupling to any other proton. Consequently it was inferred that this olefinic proton must be coupling with a fluorine and this was demonstrated by heteronuclear decoupling which showed that the proton was coupling to the least shielded fluorine in the ^{19}F NMR spectrum at δ-138.36ppm. The ^{19}F NMR spectrum of the aniline-derived heterocycle showed two triplet-like absorptions in C_6D_6 at δ-158.94 and δ-162.57 [assigned to 7-F/8-F]; the other two absorptions occurred at δ-145.17ppm(a doublet of doublets,J,21 and 11Hz; there are additional couplings <2Hz) and at δ-148.23 (a sharp doublet of

doublets in this case,J,21 and 11Hz). Heteronuclear decoupling of the four protons centred at δ6.99 increased the resolution of the fluorine at δ-145.17 and showed the approximate shift of the olefinic proton (see below).

The only structure consistent with these data are the 3H-azepine derivatives (5) and (6) in which the olefinic proton is adjacent to the fused benzene and naphthalene rings, respectively, rather than being remote as in the alternative structures (7) and (8). The olefinic proton 5-H in (5)(at ca.δ6.99) couples to only a slight extent with the fluorine at δ-145.17 now assigned to 6-F, whereas in (6) the olefinic 1-H couples strongly (7Hz) with the fluorine at δ-138.36 now assigned to the peri-fluorine 11-F due to its close proximity.

^{1}H NMR spectroscopy has played a vital role in the study of the conformationally mobile tub-shaped ring-systems found in azepines and their benzologues[4] and the variable temperature effects in the ^{1}H shifts of the aliphatic protons in (5) and (6) are noteworthy. In CF_3COOD at room-temperature the absorptions due to the two protons in the CH_2 group of (5)(δ4.16) is the average of the values found at 253K (δ3.16 and δ5.30) where fluxional changes in the tub-shaped portion of the molecule have been slowed down on the NMR time-scale. This interchange of conformers is slow at room-temperature (297K) in compound (6), a fact which is now interpreted in terms steric hindrance between the olefinic proton 1-H and the fluorine 11-F.

The mechanism of formation of the heterocyclic rings in the two systems studied is of interest and is considered here for the reaction involving $C_6F_5NH_2$. The experiments reported in this paper clearly implicate 'dypnone', the self-condensation product of acetophenone in the reaction. Since nucleophilic substitution in pentafluoroaniline is known to bring about mainly the replacement of the fluorine meta to the NH_2 group[5], it is proposed that the first intermediate in the reaction is the zinc chloride catalysed carbonyl condensation product (9). The Lewis-acid catalyst could also serve to bring about the formation of a dienamine-type intermediate as a precursor to the formation of the final C-C bond in the ring cyclisation reaction, and an acid catalysed isomerisation completes the reaction, shown in Scheme 4.



Scheme 4

EXPERIMENTAL

^{1}H (250MHz) and ^{19}F (235MHz) NMR spectra were measured with a Bruker AC250 spectrometer. Chemical shifts are positive upfrequency from TMS and $CFCl_3$, hence all ^{19}F shifts are negative. Mass spectrometry data was obtained with a VG 7070E instrument.

Reaction of pentafluoroaniline with acetophenone.

A mixture of pentafluoroaniline (1)(2.22g), acetophenone(1.48g) and anhydrous zinc chloride(0.5g) in dry tetralin (20ml) was heated under reflux for 24hr and worked up by the addition of water and extraction with ether. The extracts were dried ($MgSO_4$), the solvent evaporated and the

tetralin distilled under reduced pressure(0.05mm Hg) using an external water-bath at 55°C. The crude black product was sublimed at 110°C/0.05mm Hg to give pentafluoro-N-(α-methylbenzylidene)aniline(3) (1.05g,30%). Continued sublimation gave a mixture(0.5g) consisting of compound (3), compound (5)[see below] and other unidentified materials. The unsublimed tarry residue(1.27g) was separated by chromatography on silica (2'6"×1") using a mixture of $CHCl_3$-CCl_4(50:50 v/v) as eluant to give 6,7,8,9-tetrafluoro-2,4-diphenyl-3H-1-benzazepine(5)(0.38g,9%)nc m.p.161-162°C [from light petroleum, b.p.100-120°C] (Found: C, 71.62; H, 3.33; N, 3.54; M^+, 367. $C_{22}H_{13}F_4N$ requires C, 71.93; H, 3.57; N, 3.81%; M, 367); $\delta_F(C_6D_6)$ -145.17(dd, 6-F), -148.23(dd, 9-F), and -158.94/-162.57 (t,t respectively, 7-F/8-F), $J_{6\text{-}F,7\text{-}F}$ 21Hz; $J_{6\text{-}F,9\text{-}F}$ 11Hz; $J_{7\text{-}F,8\text{-}F}$ 21Hz; $J_{8\text{-}F,9\text{-}F}$ 21Hz; $\delta_H(C_6D_6)$ 3.01(b,CH_2), 6.99(m, 4 overlapping protons), 7.09(m, 3 overlapping protons), 7.17(m, 2 protons), and 7.96(m, 2 protons); $\delta_H(CF_3COOD)$ at 297K 4.16(b, 2 protons), 7.43(m, 3 protons), 7.58(m, 3 protons), 7.65(t, 2 protons), 7.89(t, 1 proton), and 8.06(d, 2 protons); $\delta_H(CF_3COOD)$ at 273K, shifts identical with those at 297K, only the absorption at 4.16 was very broad; $\delta_H(CF_3COOD)$ at 253K, 3.16(b, 1 proton), and 5.30(b, 1 proton).

Reaction of pentafluoroaniline with β-benzoyl-α-methylstyrene.

A mixture of pentafluoroaniline(1)(0.54g), β-benzoyl-α-methylstyrene(0.66g), anhydrous zinc chloride(0.42g) and dry tetralin(10ml) was heated under reflux for 24hr and worked up as before. The crude product was separated by chromatography on silica using a mixture of $CHCl_3$-CCl_4 (50:50 v/v) as eluant to give the 3H-benzazepine derivative(5)(0.21g, 20%).

Reaction of 1,3,4,5,6,7,8-heptafluoro-2-naphthylamine with acetophenone.

A mixture of the 2-naphthylamine derivative(2)(3.77g), acetophenone(2.05g), anhydrous zinc chloride(1.39g) in dry tetralin(20ml) was heated under reflux for 23.5hr and worked up as before. The crude product was separated by chromatography on silica (48"×1.5") using a mixture of $CHCl_3$-CCl_4 (50:50 v/v) as eluant to give 1,3,4,5,6,7,8-heptafluoro-N-(α-methylbenzylidene)-2-naphthylamine(4)(0.24g, 5%) and a mixture from which unreacted 2-naphthylamine (1)(1.44g) was removed by sublimation at 60°C in vacuo at 0.05mm Hg. The unsublimed residue(0.57g, 9%) was recrystallised from toluene-light petroleum[bp 100-120°C] to give 6,7,8,9,10,11-hexafluoro-2,4-diphenyl-3H-naphth[2,1-b]azepine (6) nc mp 230.5-232°C (Found: C, 68.75; H, 3.00; N, 2.96; M^+, 453. $C_{26}H_{13}F_6N$ requires C, 68.87; H, 2.89; N, 3.09%; M, 453); $\delta_H(C_6D_6)$ 1.72(vb, 1 proton), 4.43(vb, 1 proton), 7.03(m, 3 protons), 7.12(m, 3 protons), 7.33(d, 2 protons), 7.67((d, 1-H), 8.04(m, 2 protons) $J_{1\text{-}H,11\text{-}F}$ 7Hz; $\delta_F(C_6D_6)$ -138.36(m, 11-F), -143.6(m, 6-F), -145.98,-146.22(peri AB 7-F/8-F), -157.39/-157.55(m,m respectively, 9-F/10-F); $J_{7\text{-}F,8\text{-}F}$ 67Hz; $\delta_H(CF_3COOD)$ at 297K 2.93(bd, 1 proton), 5.30(bd, 1 proton), 7.41(m, 3 protons), 7.57(m, 2 protons), 7.68(t, 2 protons), 7.90(t, 1 proton), 8.08(d, 2 protons), 8.21(d, 1-H); $\delta_H(CF_3COOD)$ at 310K: shifts identical with those at 297K only the absorptions at 2.93 and 5.30 were very broad.

Reaction of 1,3,4,5,6,7,8-heptafluoro-2-naphthylamine with β-benzoyl-α-methylstyrene

A mixture of the 2-naphthylamine derivative(2)(0.59g), β-benzoyl-α-methylstyrene(0.50g), anhydrous zinc chloride(0.31g) and dry tetralin(10ml) was heated under reflux for 24hr and worked up as before. The crude product was separated by chromatography on silica(30"x1") using a mixture of $CHCl_3$-CCl_4

(50:50 v/v) as eluant to give a mixture from which the unreacted 2-naphthylamine derivative(2)(0.38g) was removed by sublimation at 95°C in vacuo at 0.05mm Hg; the unsublimed residue was the 3H-naphth[2,1-b]azepine derivative(6)(0.17g, 17%).

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