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PARTIALLY FLUORINATED HETEROCYCLIC COMPOUNDS. PART 24.[1] A PLAUSIBLE MECHANISM FOR THE FORMATION OF THE FISCHER INDOLE PRODUCT FROM ACETOPHENONE 1,3,4,5,6,7,8-HEPTAFLUORO-2-NAPHTHYLHYDRAZONE IN WHICH o-FLUORINE IS LOST

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SUMMARY

Acetophenone 1,3,4,5,6,7,8-heptafluoro-2-naphthylhydrazone (1) reacts in tetralin at reflux to give 4,5,6,7,8,9-hexafluoro-2-phenylbenz[e]indole (2) as the major product, accompanied by other materials including acetophenone 3,4,5,6,7,8-hexafluoro-2-naphthylhydrazone (4) which is proposed as the true precursor to the Fischer indole product (2) since it gives (2) under the same conditions. The presence of α-tetralone in the reaction mixture provides the clue to a reductive elimination of F^- from (1).

INTRODUCTION

In previous papers in this series [2,3] it has been demonstrated that the pentafluorophenyl- and 1,3,4,5,6,7,8-heptafluoro-2-naphthylhydrazones of a variety of ketones and even of acetaldehyde when heated in tetralin at reflux temperature give complex mixtures of products, the major ones surprisingly being indole derivatives with yields ranging from a mere 1.5% from acetaldehyde pentafluorophenylhydrazone to 42% from 1,2-diphenylethanone-1,3,4,5,6,7,8-heptafluoro-2-naphthylhydrazone. In all these cyclisation reactions, an o-fluorine is displaced [e.g. the conversion of (1) into (2)

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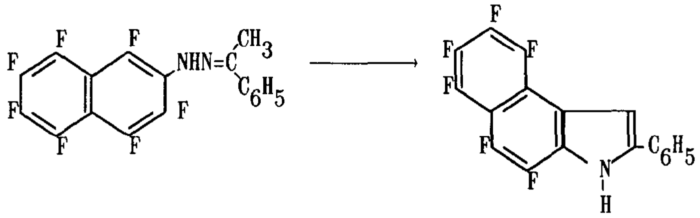
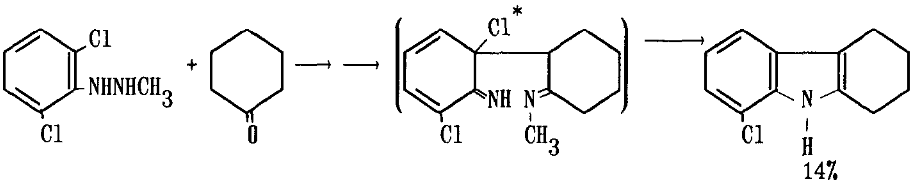
Scheme 1] whereas the displacement of o-hydrogen (as H^+) takes place in the conventional Fischer indole reaction.



(1) (2)(37%)

Scheme 1

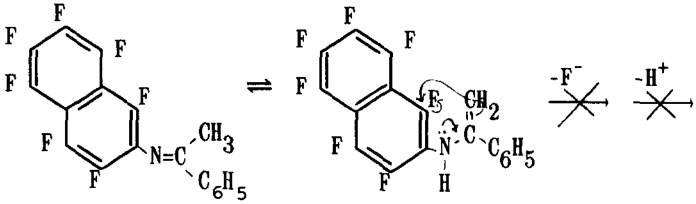
Two other related cyclisation reactions have been described in the literature both involving the loss of an o-chlorine. In the first reaction shown in Scheme 2, it was proposed that the chlorine (Cl^*) is lost in a reduction process by some (unidentified) readily oxidizable species in the reaction mixture [4]. The second reaction was the high yield conversion of



Scheme 2

acetophenone pentachlorophenylhydrazone into 4,5,6,7-tetrachloro-2-phenylindole (81%) using polyphosphoric acid; no 3-chloro derivative was obtained [5].

A plausible route to (2) emerged when it was discovered that the Schiff base, $C_6F_5N{=}C(C_6H_5)CH_3$ (2%) was produced in the thermal decomposition of acetophenone pentafluorophenylhydrazone [2]. However, although the corresponding Schiff base (3) was not isolated in the reaction involving (1) it was synthesised independently, but it failed to undergo the cyclisation reaction shown in Scheme 3. This paper reports the isolation of further



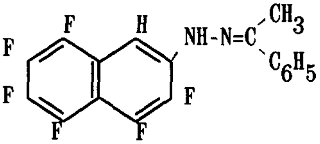
(3) (1)

Scheme 3

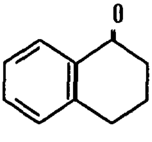
minor components from the thermolysis reaction of one hydrazone which sheds light on the formation of Fischer indole products when fluorine occupies all sites ortho to the hydrazone functional group.

RESULTS AND DISCUSSION

In 1983 we reported that the thermolysis of the 2-naphthylhydrazone (1) gave in addition to the indole derivative (2), 1,3,4,5,6,7,8-heptafluoro-2-naphthylamine (21%) and 1,1',2,2',3,3',4,4'-octahydro-1,1'-bisnaphthyl (6%) derived by the initial homolysis of the N-N bond and subsequent hydrogen atom abstraction reactions on the solvent tetralin [2]. A fourth component has now been identified in this experiment: acetophenone 3,4,5,6,7,8-hexafluoro-2-naphthylhydrazone (4)(0.5%), but in a separate experiment specifically conducted to isolate this material, it was obtained in an improved yield (3%). In one other thermolysis reaction of (1) in which the indole (2) (33%) and 1,3,4,5,6,7,8-heptafluoro-2-naphthylamine (20%) were obtained, α-tetralone (5) (8%) was also isolated.



(4)

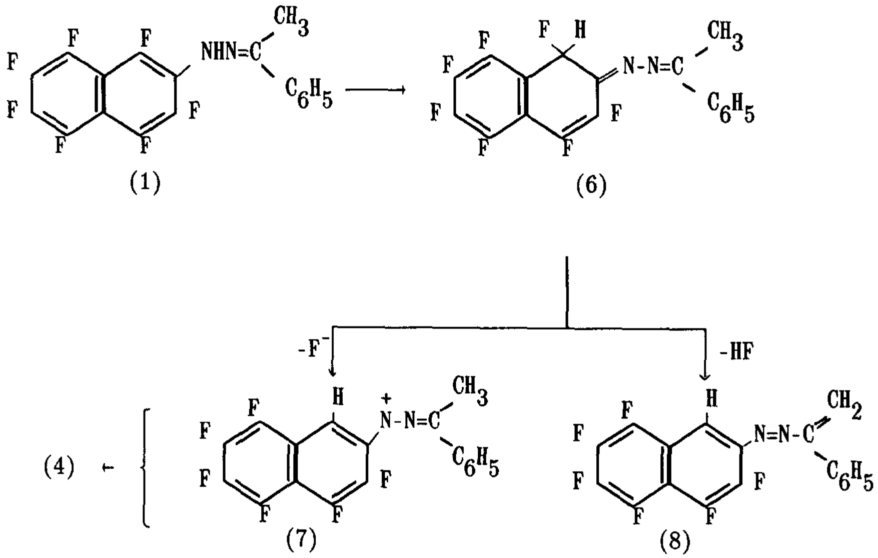


(5)

The composition of (4) was evident from its elemental analysis and the molecular ion in its mass spectrum which showed that one fluorine in the starting material (1) had been replaced by hydrogen. The extra hydrogen in (4) was shown by a proton decoupling experiment to be aromatic, absorbing at δ 7.80, coincident with the N-H on the side chain at the 2-position on the naphthalene ring. The ^{19}F nmr showed only one large peri $J_{F,F}$ coupling constant (47 Hz) which indicated that the extra hydrogen was situated at a peri site, and the 1-H position was identified by a chemical reaction since in refluxing tetralin, (4) was converted into (2) (28%) via a classical Fischer indole reaction.

The isolation of the 2-naphthylhydrazone (4) with an o-hydrogen clearly implicates this and presumably other o-hydrogen-containing polyfluoroaromatic hydrazones as the true precursors for the cyclisation reaction via the classical Fischer indole reaction, and the only problem remaining is the mechanism of formation of the o-hydrogen-containing compounds from the o-fluorine-containing starting materials.

Earlier work by Haszeldine [6] and Tamborski [7] showed that pentafluorophenylhydrazine and related compounds on treatment with alkali resulted in the loss of o- and p-fluorine (as HF) followed by the loss of nitrogen. It is now proposed that the first stage of this mechanism operates with hydrazones. The initial isomerisation, a self-catalysed (base) reaction giving (6) is followed by re-aromatisation either by loss of F^- [giving (7)] and/or HF[giving (8)] but thereafter the formation of the 2-naphthylhydrazone (4) becomes less clear (Scheme 4). However, the isolation of α-tetralone (5) from the product clearly implicates the solvent and water (from HF + glass vessel) in the overall reaction and one rationisation could be as follows: hydride abstraction by (7) from the α-CH_2 of tetralin would give the 2-naphthylhydrazone (4) for the classical Fischer indole reaction and a benzylic cation which would form α-tetralol with water. This benzylic alcohol would be even more prone than tetralin to hydride abstraction from the α-CH(OH) group followed by loss of a proton giving α-tetralone.



Scheme 4

In the light of the findings reported in this paper, it seems probable that 2,6-dichloro-N(1)-methylphenylhydrazone in Scheme 2, or the immediate product formed by its reaction with cyclohexanone, is first converted to the o-hydrogen-containing hydrazine or -hydrazone prior to the usual Fischer indole reaction taking place. However, a related process is not obvious with acetophenone pentachlorophenylhydrazone [5].

EXPERIMENTAL

The ^1H (360 MHz) spectrum of (4) was obtained on the Bruker WH360 spectrometer located in the Chemistry Department of the University of Edinburgh and the ^{19}F (235 MHz) was obtained with a Bruker AC 250 spectrometer. Chemical shifts are upfield from internal $CFCl_3$ (δ_F), or downfield from TMS using the $CHDCl_2$ at 5.33 ppm in the CD_2Cl_2 solvent as the internal reference. Mass spectroscopy data was obtained with a VG 7070E instrument.

Reaction of Acetophenone 1,3,4,5,6,7,8-Heptafluoro-2-naphthylhydrazone (1) in Tetralin

(a) The experiment using the 2-naphthylhydrazone (1)(2.137 g) has been described previously [2]. The crude product was separated by chromatography on silica using $CHCl_3$-CCl_4 (50:50 v/v) as eluant and the fastest moving components collected as one fraction, were further separated by thick layer chromatography on silica with the same solvent to give 1,1',2,2',3,3',4,4'-octahydro-1,1'-bisnaphthyl (0.089 g, 6%) followed by *acetophenone 3,4,5,6,7,8-hexafluoro-2-naphthylhydrazone (4)* (0.018 g, 0.5%) nc mp 201-202.5^{o}C [from toluene/light petroleum (bp 100-120^{o}C)] (Found: C, 58.38; H, 2.64; N, 7.62; M^+, 368. $C_{18}H_{10}F_6N_2$ requires C, 58.70; H, 2.74; N, 7.61%; M, 368); δ_F(acetone) 146.55 (dd, 4-F), 149.15 (dt, 5-F), 150.71 (t, 8-F), 155.12 (nm, 3-F), 159.57/163.75 (t,t respectively 6-F/7-F) in the ratio 1:1:1:1:1:1; $J_{4\text{-}F,5\text{-}F}$ 47 Hz; $\delta_H(CD_2Cl_2)$ 2.37 (s, CH_3), 7.43 (complex m, 3 x H), 7.80 [bd, CH *and* NH (shown by a decoupling experiment)] and 7.85 (complex d, 2 x H); ν_{max} 3380 cm^{-1} (N-H) [c.f. ν_{max} 3370 cm^{-1} in (1)].

Compound (4) (0.032 g) and dry tetralin (5 ml) were heated under reflux for 20 h and worked up as previously [2]. Thick layer chromatography of the crude product on silica gave the indole derivative (2) (0.0086 g, 28%) identified by i.r.

(b) In a separate experiment, the 2-naphthylhydrazone (1) (4.06 g) and dry tetralin (40 ml) were heated under reflux for 18.5 h and gave acetophenone 3,4,5,6,7,8-hexafluoro-2-naphthylhydrazone (4) (0.111 g, 3%).

(c) The 2-naphthylhydrazone (1) (2.011 g) and dry tetralin (20 ml) were heated under reflux for 47 h and separated by chromatography as in (a) to give 1,3,4,5,6,7,8-heptafluoro-2-naphthylamine (0.278 g, 20%) [8] and the indole derivative (2) (0.602 g, 33%). The slower moving components were eluted from the column using $CHCl_3$-CCl_4 (67:33 v/v), combined and rechromatographed on silica using $CHCl_3$. One fraction was sublimed in vacuo at room temperature/0.05 mm Hg to give an oil (0.199 g) which was further separated by thick layer chromatography using $CHCl_3$ as eluant to give α-tetralone (5) (0.065 g, 8%) identical with an authentic sample.

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