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PARTIALLY FLUORINATED HETEROCYCLIC COMPOUNDS—X[1]

SYNTHESIS OF N-PHENYL-4,5,6,7-TETRAFLUORO-2-PHENYLINDOLE BY A NEW CYCLIZATION REACTION AND ATTEMPTED SYNTHESES OF RELATED COMPOUNDS BY CONVENTIONAL METHODS

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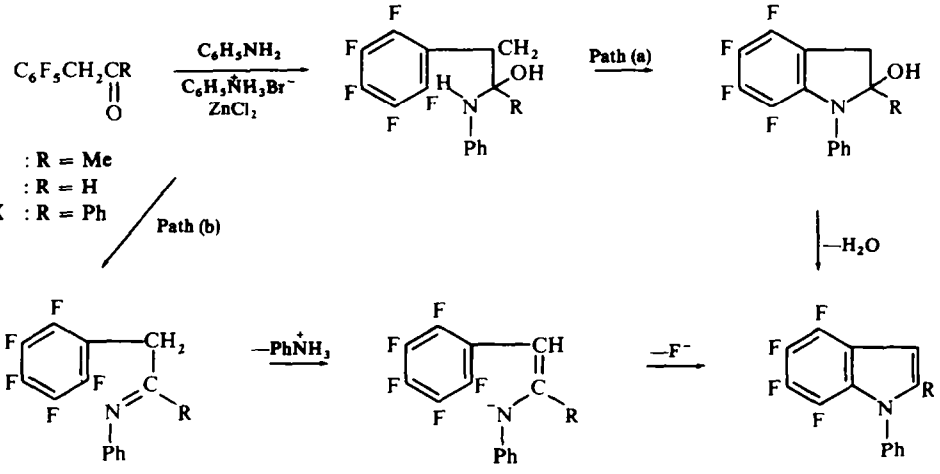
Abstract—N-Phenyl-4,5,6,7-tetrafluoro-2-phenylindole has been prepared by the reaction of phenyl 2,3,4,5,6-pentafluorobenzyl ketone with aniline. The attempted cyclization of 2,3,4,5-tetrafluorophenylglycine failed, but octafluoroindigo has been synthesized from 6-carboxy-N-(2,3,4,5-tetrafluorophenyl)-glycine.

THE PREPARATION of N-phenyl-4,5,6,7-tetrafluoro-2-methylindole (IV) by the reaction of methyl 2,3,4,5,6-pentafluorobenzyl ketone (I) with aniline has been described in an ealier paper in this series.[2]



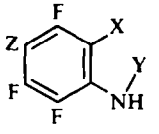
We have now investigated this method further using different carbonyl compounds. Treatment of 2,3,4,5,6-pentafluorophenylacetaldehyde[1] (V) with excess aniline,

aniline hydrobromide and anhyd. $ZnCl_2$ under conditions similar to those under which IV was formed in 47% yield, gave a complex mixture containing at least five components, none of which has been identified as N-phenyl-4,5,6,7-tetrafluoroindole (VIII). However, using phenyl 2,3,4,5,6-pentafluorobenzyl ketone[1] (IX), N-phenyl-4,5,6,7-tetrafluoro-2-phenylindole (XII) was formed in 76% yield.

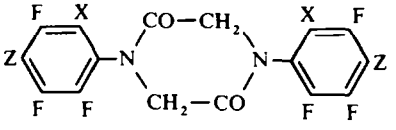
Two possible mechanisms for the cyclization reaction need to be considered: Path (a), in which the five membered heterocyclic ring is formed before the Lewis acid-catalysed elimination of water; and Path (b), in which the Schiffs' bases II, VI and X are formed initially, followed by proton abstraction by excess aniline to III, VII, and XI (in which the C_6F_5-group and the nitrogen are *cis*-orientated with respect to the double bond), and finally, nucleophilic replacement of fluorine.

We have attempted to isolate the Schiffs' base (X) using a shorter reaction time, but only unchanged starting material (I) and cyclized material (XII) were isolated, with an essentially quantitative mass balance. Nevertheless, of the two possible reaction pathways, Path (b) is expected to be the one more susceptible to steric effects, in that the stability of the geometrical isomers III, VII and XI will be determined by the size of the group R. The variation in the yields of the cyclized products, 76% (XII), 47% (IV), 0% (VIII) could be explained, in part, by the decreasingly favourable disposition of the bulky C_6F_5- and R-groups to adopt the stable *trans*-configuration with respect to each other in the intermediates XI, III and VII respectively. For R = H, the *trans*-configuration of the C_6F_5-group and the Ph-N^--group will be more stable than the configuration represented by VII. The same effects have been invoked, in part, to account for the similar trend in the relative ease of formation of benzo[b]furan compounds from the NaH initiated cyclization of the carbonyl compounds IX, I and V.[1]

The formation of fluorinated indole derivatives using two conventional types of cyclization reaction have been investigated: (i) the electrophilic replacement of nuclear hydrogen starting from N-(2,3,4,5-tetrafluoro-phenyl)glycine (XIII); and (ii) the nucleophilic replacement at a carbonyl group starting from 6-carboxy-N-(2,3,4,5-tetrafluorophenyl)glycine (XIV). In order to determine the best conditions for the



XIII : X = H; Y = CH_2CO_2H; Z = F
XIV : X = CO_2H; Y = CH_2CO_2H; Z = F
XVII : X = Z = F; Y = CH_2CO_2H
XVIII : X = F; Y = CH_2CO_2H; Z = H
XX : X = CO_2Et, Y = CH_2CO_2Et, Z = F



XV : X = Z = F
XVI : X = F, Z = H
XIX : X = H, Z = F

preparation of the phenylglycine (XIII) for use by Route (i), model experiments were carried out using the more readily available pentafluoroaniline[3] and 2,3,5,6-tetrafluoroaniline.[4] Treatment of these amines with NaH in THF followed by reaction with ethyl chloroacetate gave the 2,5-diketopiperazines XV and XVI respectively, which were hydrolysed to the corresponding phenylglycines (XVII and XVIII). In the same

way. 2,3,4,5-tetrafluoroaniline[4] was converted first into N,N'-*bis*-(2,3,4,5-tetrafluorophenyl)-2,5-diketopiperazine (XIX) and this in turn was hydrolyzed to N-(2,3,4,5-tetrafluorophenyl)glycine (XIII). Alternatively, XIII could be prepared without prior isolation of XIX.

The attempted cyclization of XIII to 4,5,6,7-tetrafluoroindoxyl using polyphosphoric acid failed, which was surprising in view of previous successful electrophilic cyclization reactions on closely related compounds, *viz.* Skraup reactions using 2,3,4,5-tetrafluoroaniline[5] and the Fischer–Indole synthesis with the hydrazone formed from 2,3,4,5-tetrafluorophenyl-hydrazine and acetophenone.[6]

The second conventional route, (ii), to fluorinated indoles required as starting material, 6-carboxy-N-(2,3,4,5-tetrafluorophenyl)glycine (XIV), and we report two syntheses of this compound. Treatment of N-(2,3,4,5-tetrafluorophenyl)glycine (XIII) with 3·5 molar equivalents of n-BuLi followed by reaction with CO_2 gave XIV in 52% overall conversion accompanied by N-(2,3,4,5-tetrafluorophenyl)aminomethyl n-butylketone. Alternatively, the reaction of 3,4,5,6-tetrafluoroanthranilic acid[7] with bromoacetic acid in Na_2CO_3 aq also gave XIV in 23% overall conversion. We synthesized the previously known anthranilic acid by treating 2,3,4,5-tetrafluoroaniline with excess n-BuLi followed by reaction with CO_2 in extension of our previous work for the preparation of substituted carboxylic acids.[8] Tamborski has reported the metallation and carbonation of 2,3,5,6-tetrafluoroaniline to give 4-amino-2,3,5,6-tetrafluorobenzoic acid.[9]

The hydrocarbon analogue of XIV, on treatment with NaOAc in Ac_2O gave the N-acetyl-3-acetoxy indole.[10] Treatment of the tetrafluoro-compound (XIV) under similar conditions gave an impure sample of N-acetyl-3-acetoxy-4,5,6,7-tetrafluoroindole which was identified by its mass spectrum. Hydrolysis of the crude N-acetyl-3-acetoxy compound with dilute NaOH to 4,5,6,7-tetrafluoroindoxyl and rapid aerial oxidation gave the deep blue octafluoroindigo, which was identified by its mass spectrum (parent peak) and by its IR spectrum. We also attempted the synthesis of ethyl 6-ethoxy-N-(2,3,4,5-tetrafluorophenyl)-glycine (XX) for base-catalysed cyclization to an indole derivative, in view of the ready cyclization of the analogous oxygen and sulphur compounds to benzo[b]furan[11] and benzo[b]thiophen[12] derivatives. 3,4,5,6-Tetrafluoroanthranilic acid was converted into the ethyl ester which in turn was reacted with ethyl bromoacetate in benzene, under conditions which were used to prepare the corresponding hydrocarbon compound.[13] However no reaction occurred, even over a period of several days.

EXPERIMENTAL

N-Phenyl-4,5,6,7-tetrafluoro-2-phenylindole (XII). Phenyl 2,3,4,5,6-pentafluorobenzyl ketone (IX)[1] (1·04 g), aniline hydrobromide (1·19 g), anhyd. $ZnCl_2$ (1·39 g) and aniline (75 ml) were heated under reflux for 1 hr after which the mixture was distilled and the distillate (55 ml) discarded. The residue was heated under reflux for 15 hr, cooled, diluted with ether and the mixture washed with HCl (5N). The ether extracts were dried ($MgSO_4$), the solvent evaporated and the crude product chromatographed on silica using initially petroleum ether (b.p. 60–80°]) followed by increasing amounts of C_6H_6 in this solvent, until it was 50% v/v to give *N-phenyl-4,5,6,7-tetrafluoro-2-phenylindole* (XII). (0·940 g), m.p. 125·5–126·5° (from benzene-petroleum ether (b.p. 60–80°]) (Found: C, 70·2; H, 3·0; N, 4·4. $C_{20}H_{11}F_4N$ requires C, 70·4; H, 3·2; N, 4·1%). The ^{19}F NMR spectrum of XII in $CDCl_3$ showed four multiplets of equal intensity centred at 11·0 and 3·3 p.p.m. downfield and 3·2 and 6·8 p.p.m. upfield, respectively, from C_6F_6 as internal reference. The ^1H NMR spectrum in $CDCl_3$ showed bands centred at 2·75τ (due to two Ph groups) and at 3·2τ (a doublet due to the proton at position 3).

In an attempt to form the Schiffs base (X), the ketone (IX) (1·10 g), aniline hydrobromide (0·90 g), anhyd. $ZnCl_2$ (1·04 g) and aniline (4·26 g) were heated together under reflux for 45 min. C_6H_6 (20 ml) was added, the mixture distilled and the distillate (15 ml) discarded. The residue was filtered, the solid washed with hot C_6H_6 and the combined filtrates evaporated and chromatographed on silica using C_6H_6–petroleum ether (b.p. 60–80°) [50% v/v] as eluent. The indole (XII (0·335 g) and unreacted starting material (IX) (0·717 g) were readily separated and identified by IR spectroscopy, and amounted to over 90% mass balance recovery. There were at least four minor components in the later fractions which were not identified.

N,N'-*bis*(*Pentafluorophenyl*)-2,5-*diketopiperazine* (XV). Pentafluoroaniline (5·0 g) in THF (50 ml) was treated with a suspension of NaH (0·63 g) in THF (25 ml) over 3 hr at −30 to −20°. Ethyl chloroacetate (3·37 g) in THF (25 ml) was added at room temp and the mixture heated under reflux for 1 hr. After being cooled, the mixture was poured into water (1:1) which was extracted with ether (2 × 75 ml). The extracts were dried ($MgSO_4$) and evaporated and the residue distilled *in vacuo* (140–160°/0·01 mm) to give N,N'-*bis*(*pentafluorophenyl*)-2,5-*diketopiperazine* (XV), 3·3 g), m.p. 171–173·5° (from C_6H_6–petroleum ether [b.p. 60–80°]) (Found: C, 43·3; H, 1·0; F, 43·3. $C_{16}H_4F_{10}N_2O_2$ requires C, 43·1; H, 0·9; F, 42·6%).

N,N'-*bis*(2.3.5.6-*Tetrafluorophenyl*)-2.5-*diketopiperazine* (XVI). 2.3.5.6-Tetrafluoroaniline (5·0 g) in THF (50 ml) was treated first with NaH (0·72 g) in THF (25 ml), followed by reaction with ethyl chloroacetate (3·71 g) in THF (25 ml) under conditions identical with those in the previous experiment. The product was isolated as before by distillation (160–180°/0·01 mm) and recrystallization (C_6H_6) to give N,N'-*bis*(2.3.5.6-*tetrafluorophenyl*-2.5-*diketopiperazine* (XVI), (3·0 g), m.p. 219–225°. (Found: C, 46·9; H, 1·5; F, 36·8. $C_{16}H_6F_8N_2O_2$ requires C, 46·8; H, 1·5; F, 37·1%).

N,N'-*bis*(2.3.4.5-*Tetrafluorophenyl*)-2.5-*diketopiperazine* (XIX). 2.3.4.5-Tetrafluoroaniline (5·0 g), NaH (0·65 g) and ethyl chloroacetate (3·71 g) were reacted together in THF as in the previous experiment, and the product was isolated by distillation (200–210°/0·01 mm) and recrystallization (THF–petroleum ether [b.p. 60–80°]) to give N,N'-*bis*(2.3.4.5-*tetrafluorophenyl*)-2.5-*diketopiperazine* (XIX) (1·8 g) m.p. 259–263°. (Found: C, 47·1; H, 1·7; F, 36·8%).

N-(*Pentafluorophenyl*)*glycine* (XVII). The 2.5-diketopiperazine (XV) (0·25 g) was heated under reflux with NaOH aq (50 ml, 1N) for 30 min. The mixture was cooled, neutralized with HCl (1N), and the solution extracted with ether. The ether extracts were dried ($MgSO_4$), the solvent evaporated and the crude product sublimed at 70–80°/0·01 mm. The sublimate (0·2 g) was recrystallized from water to give N-(*pentafluorophenyl*)*glycine* (XVII), m.p. 120–122·5°. (Found: C, 39·6; H, 1·8; F, 39·2. $C_8H_4F_5NO_2$ requires C, 39·2; H, 1·7; F, 39·4%).

N-(2,3,5,6-*Tetrafluorophenyl*)*glycine* (XVIII). The 2,5-diketopiperazine (XVI) (0·3 g) was heated under reflux with NaOH (25 ml, 30% w/v) for 3 hr. The product, isolated as in the previous experiment, was sublimed at 60–70°/0·01 mm and the sublimate (0·22 g) recrystallized from water (≤80° to avoid decomposition) to give N-(2.3.5.6-*tetrafluorophenyl*)*glycine* (XVIII), m.p. 105–107·5°. (Found: C, 43·5; H, 2·3; F, 33·6. $C_8H_5F_4NO$ requires C, 43·1; H, 2·2; F, 34·1%).

N-(2,3,4.5-*Tetrafluorophenyl*)*glycine* (XIII). The 2.5-diketopiperazine (XIX) (0·82 g) was heated under reflux with NaOH (50 ml, 2N) for 15 min. The product, isolated as in the previous experiment, was sublimed at 120°/0·01 mm and the sublimate (0·8 g) recrystallized from water to give N-(2.3.4.5-*tetrafluorophenyl*)-*glycine* (XIII) m.p. 175–178·5°. (Found: C, 43·0; H, 2·3; F, 33·8%).

The glycine (XIII) was also prepared without the prior isolation of the 2.5-diketopiperazine (XIX). 2.3.4.5-Tetrafluoroaniline (10·0 g) in ether (10 ml) was treated with a suspension of NaH (1·25 g) in ether (50 ml) at reflux temp over 15 min. The mixture was heated under reflux for a further 7·5 hr, cooled to −70° and ethyl bromoacetate (10·5 g) in ether (15 ml) was added over 5 min. The temp of the reactants was allowed to rise to room temp over 15 hr, the solvent was evaporated and the residue heated under reflux with NaOH (100 ml, 2N) for 30 min. The solution was cooled, acidified with H_2SO_4 (4N) and the precipitate filtered and dried. This material was sublimed as before to give N-(2.3.4.5-tetrafluorophenyl)glycine (7·6 g) (XIII), identical with material prepared previously.

3.4.5.6-*Tetrafluoroanthranilic acid*. 2.3.4.5-Tetrafluoroaniline (22·1 g) in THF (150 ml) was treated with n-BuLi in hexane (200 ml, 2·35N) over 1·5 hr at −70 to −65°. CO_2 was passed into the solution for 1·25 hr, the temp being maintained below −50° throughout. The solution was allowed to warm to room temp over 4 hr, water was added (50 ml) and the mixture acidified with H_2SO_4 (4N). The organic phase was separated, the aqueous phase extracted with ether and the combined organic phase and extracts were pumped at room temperature/0·1 mm to remove solvent and other volatile materials. The solid residue was recrystallized from petroleum ether (b.p. 100–120°) and the crude product (5·0 g) was sublimed *in vacuo* at 100°/0·01 mm. Further recrystallization from petroleum ether (b.p. 100–120°) gave pure 3,4,5,6-

tetrafluoroanthranilic acid, m.p. 141·5–142·5° (lit.[7] m.p. 141–142°). (Found: C, 40·1; H, 1·3; F, 36·3. $C_7H_3F_4NO_2$ requires C, 40·2; H, 1·4; F, 36·4%).

Ethyl 3,4,5,6-tetrafluoroanthranilate. 3,4,5,6-Tetrafluoroanthranilic acid (3·6 g), EtOH (20 ml) and H_2SO_4 (20 ml, d. 1·84) were heated under reflux for 16 hr. The mixture was diluted with water, extracted with ether and the dried ($MgSO_4$) extracts evaporated. The residue was sublimed *in vacuo* at 50°/0·1 mm and the sublimate (2·8 g) recrystallized from petroleum ether (b.p. 40–60°) to give *ethyl 3,4,5,6-tetrafluoroanthranilate*, m.p. 65–66°. (Found: C, 45·4; H, 2·7; F, 31·9. $C_9H_7F_4NO_2$ requires C, 45·6; H, 2·9; F, 32·1%).

6-Carboxy-N(2.3.4.5-tetrafluorophenyl)glycine (XIV). (a) From N-(2.3.4.5-tetrafluorophenyl)glycine (XIII). The glycine (XIII) (2·05 g) in THF (90 ml) was treated with n-BuLi (18 ml, 2·35N) over 30 min, at −73 to −68°. After 1 hr at −70°, CO_2 was bubbled through the solution for 5 hr during which time the temp was allowed to rise to room temp. The mixture was made alkaline with NaOH and extracted with ether. The ether extracts were dried ($MgSO_4$) and evaporated to give crude N-(2.3.4.5-tetrafluorophenyl)-amino methyl butyl ketone (0·38 g), the structure of which was based on its correct molecular weight (263 by MS), and from its IR spectrum: strong absorptions at 3410 cm^{-1} (due to >N—H stretch) and at 1730 cm^{-1} (due to ketonic >C=O).

The aqueous solution was acidified with H_2SO_4 (4N), extracted with ether and the dried ($MgSO_4$) extracts evaporated. Sublimation of the residue *in vacuo* at 0·05 mm gave two fractions: (i) (0·78 g) subliming at 130°, which was identified as unchanged starting material (XIII), by IR spectroscopy; and (ii) (0·79 g) subliming at 170°. Recrystallization from EtOAc–petroleum ether (b.p. 60–80°) gave pure *6-carboxy-N-(2.3.4.5-tetrafluorophenyl)glycine* (XIV) m.p. 178–179°. (Found: C, 40·2; H, 1·9; F, 28·7. $C_9H_5F_4NO_4$ requires C, 40·4; H, 1·9; F, 28·5%).

(b) From 3.4.5.6-tetrafluoroanthranilic acid. The acid (1·3 g), bromoacetic acid (1·5 g), Na_2CO_3 (1·5 g) and water (20 ml) were heated under reflux for 17 hr. The mixture was cooled, acidified with H_2SO_4 (4N) and extracted with ether. The dried ($MgSO_4$) extracts were evaporated and sublimed at 0·05 mm to give two fractions: (i) (0·3 g) subliming at 100°, identified as unchanged 3,4,5,6-tetrafluoroanthranilic acid by IR spectroscopy; and (ii) (0·3 g) subliming at 160°, identified as the dicarboxylic acid (XIV) by IR spectroscopy.

Octafluoroindigo. 6-Carboxy-N-(2,3,4,5-tetrafluorophenyl)glycine (XIV) (0·13 g), anhyd. NaOAc (0·5 g) and AcOH (15 ml) were heated under reflux for 15 min. The mixture was diluted with water (30 ml) and heated under reflux for 15 min. The solution was cooled, made alkaline with Na_2CO_3 and extracted with ether. Evaporation of the dried ($MgSO_4$) extracts and sublimation of the residue at 80°/0·05 mm gave a sublimate (0·05 g) which was recrystallized from petroleum ether (b.p. 40–60°). Further sublimation at 70°/0·05 mm gave an impure product (20 mg) m.p. 105–115°, identified as N-acetyl-3-acetoxy-4.5.6.7-tetrafluoroindole by the correct parent peak at mass 289 in its mass spectrum. Treatment of this indole derivative with NaOH (10 ml, 4N) at 60° for 15 min, and acidification with H_2SO_4 (4N) gave a deep blue precipitate, identified as octafluoroindigo by the parent peak at 406 in the mass spectrum. The IR spectrum showed strong vibrations at 3335 cm^{-1} (due to N—H stretch) and at 1680 and 1665 cm^{-1} (due to >C=O).

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