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Short Communication

2, 3, 5, 6-Tetrafluorophenacetin and some related acyl derivatives of 4-ethoxy-2, 3, 5, 6-tetrafluoroaniline

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The analgesic and antipyretic properties of phenacetin (*p*-ethoxyacetanilide) are well known, though the drug has undesirable side-effects[1,2]. However, it was of interest to prepare *N*-acyl derivatives of 4-ethoxy-2,3,5,6-tetrafluoroaniline.

Early attempts[3] to react pentafluoroacetanilide with sodium ethoxide in ethanol were unsuccessful. Also the reaction between ethoxypentafluorobenzene and ammonia gave mixtures of products arising from de-*O*-alkylation as well as nucleophilic displacement of fluoride ion.

The synthetic sequence chosen therefore was *via* 4-ethoxy-2,3,5,6-tetrafluoronitrobenzene. Pentafluoronitrobenzene (prepared in excellent yield from pentafluorobenzene[4]) with an ethanolic solution of sodium ethoxide at room temperature gave 4-ethoxy-2,3,5,6-tetrafluoronitrobenzene and a small amount (~6%) of the *ortho* isomer, 2-ethoxy-3,4,5,6-tetrafluoronitrobenzene, which was separated with difficulty by gas–liquid chromatography. Mixtures of isomers can be obtained[5] when pentafluorophenyl derivatives (C_6F_5X) with electron-withdrawing groups are treated with alkoxides, the *o*/*p* ratio depending on the solvent.

Fortunately, however, the displacement of fluoride from pentafluorobenzene by ethoxide gave exclusively 1-ethoxy-2,3,5,6-tetrafluorobenzene which was readily nitrated to give 4-ethoxy-2,3,5,6-tetrafluoronitrobenzene, thus avoiding the difficult isomer separation.

4-Ethoxy-2,3,5,6-tetrafluoronitrobenzene was catalytically hydrogenated to give an excellent yield of 4-ethoxy-2,3,5,6-tetrafluoroaniline. This aniline was acylated in the usual way using the anhydrides of acetic, propionic, n-butyric, chloroacetic and trifluoroacetic acid to give the corresponding *N*-acyl derivatives (Table 1) which crystallised readily from aqueous ethanol.

TABLE 1

p-$EtOC_6F_4NHCOR$	Yield (%)	M.p. (°C)	Found		Requires	
			C (%)	H (%)	C (%)	H (%)
R, CH_3 (nc)	82	149	48.1	3.4	48.0	3.2
C_2H_5 (nc)	65	122	50.0	3.9	49.8	4.2
n-C_3H_7 (nc)	69	131	51.8	4.6	51.6	4.7
CH_2Cl (nc)	78	118	42.0	3.0	42.0	2.8
CF_3 (nc)	84	110	39.4	1.8	39.3	2.0

Preliminary tests suggest that these compounds possess no useful biological activity.

Experimental

1-Ethoxy-2,3,5,6-tetrafluorobenzene

Sodium (7.5 g) was dissolved in dry ethanol (300 ml) and pentafluorobenzene (50.15 g) was added dropwise over 30 min. The mixture was boiled under reflux for 12 h and poured into water. Extraction with ether and distillation from phosphorus pentoxide *in vacuo* gave 1-ethoxy-2,3,5,6-tetrafluorobenzene, (nc), (47.05 g, 81% yield), b.p. 157°. (Found: C, 49.4; H, 3.1%. $C_8H_6F_4O$ requires C, 49.5; H, 3.1%.) The ^{19}F NMR spectrum showed two multiplets at 140.5 and 157.35 φ* of equal intensity and the ^1H NMR spectrum showed signals at 3.29 (multiplet, aryl H), 5.72 (quartet, $-OCH_2-$) and 8.58 τ (triplet, $-CH_3$) of relative intensity 1:2:3.

4-Ethoxy-2,3,5,6-tetrafluoronitrobenzene

(a) A solution of sodium ethoxide (1.02 *N*, 135.2 ml) was added dropwise over 2 h to a stirred solution of pentafluoronitrobenzene (26.63 g) in dry ethanol (300 ml) at 25°. After a further 2 h, most of the ethanol was removed by distillation and the residue poured into water. The mixture was extracted continuously with ether for 24 h and the ether removed from the dried extract ($MgSO_4$) by distillation to leave a yellow oil from which pure 4-ethoxy-2,3,5,6-tetrafluoronitrobenzene was isolated with difficulty by gas–liquid chromatography.

(b) 1-Ethoxy-2,3,5,6-tetrafluorobenzene (45.31 g) was added dropwise to a vigorously stirred saturated solution of boron trifluoride in fuming nitric acid (14.3 ml) and sulpholane (50 ml). The mixture was heated to 60–70° for 3 h, poured into ice water and distilled in steam. Extraction with ether followed by distillation *in vacuo* from phosphorus pentoxide gave 4-ethoxy-2,3,5,6-tetrafluoronitrobenzene[5] (34.6 g, 62%) b.p. 226.5° (decomp.). (Found: C, 40.4; H, 2.4%. $C_8H_5F_4NO_3$ requires C, 40.2; H, 2.1%.)

4-Ethoxy-2,3,5,6-tetrafluoroaniline

4-Ethoxy-2,3,5,6-tetrafluoronitrobenzene (25.99 g) in ether (100 ml) was hydrogenated at atmospheric pressure in the presence of a palladium/charcoal catalyst. The solution was filtered and evaporated to leave a residue (22.18 g) which on recrystallisation (pet. ether b.p. 80–100°) afforded 4-ethoxy-2,3,5,6-tetrafluoroaniline, (nc), (18.51 g, 82%) m.p. 48.5°. (Found: C, 45.5; H, 3.5%. $C_8H_7F_4NO$ requires C, 45.9; H, 3.4%.)

The N*-acylation of 4-ethoxy-2,3,5,6-tetrafluoroaniline*

4-Ethoxy-2,3,5,6-tetrafluoroaniline (0.72 g) and acetic anhydride (0.5 ml) were heated at 100° for 10–15 min. The mixture was poured into water, boiled for

10 min, cooled and the precipitate collected. Recrystallisation from aqueous ethanol gave 4-ethoxy-2,3,5,6-tetrafluoroacetanilide (tetrafluorophenacetin), (nc). The other new acyl derivatives (Table 1) were prepared similarly.

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