78. *Carcinogenic Nitrogen Compounds. Part XIV.* Friedel–Crafts Reactions with* m- *and* p-*Fluorotoluene.*

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The behaviour of *m*- and *p*-fluorotoluene in Friedel–Crafts acylations has been studied. With the former, the reaction is rigidly proved to involve the position *para* to the fluorine atom, and with the latter, the ketone groups are assumed by analogy to occupy the position *ortho* to fluorine. Numerous other aromatic and heterocyclic fluorine-containing compounds have been prepared.

m-Chloro- and *m*-bromo-toluene undergo acetylation (Claus, *J. pr. Chem.*, 1891, **43**, 361) and chloroacetylation (Kunckell, *Ber.*, 1908, **41**, 2648) at the position *para* to the halogen atom. We have now found *m*-fluorotoluene to be readily acetylated in a Friedel–Crafts reaction; the constitution of the product as 4-fluoro-2-methylacetophenone was proved by conversion into its oxime, Beckmann rearrangement, and hydrolysis to 4-fluoro-2-methylaniline, prepared from 4-fluoro-2-methyl-1-nitrobenzene (Schiemann, *Ber.*, 1929, **62**, 1797). The constitution of 4-fluoro-2-methyl-propiophenone, -*n*-butyrophenone, and -phenylacetophenone was proved similarly. Sodium hypobromite oxidation of 4-fluoro-2-methylacetophenone gave the hitherto unknown 4-fluoro-2-methylbenzoic acid.

Since the fluorine atom predominates over the methyl group in orienting acylation of *m*-fluorotoluene, just as in acetylation of *o*-fluorotoluene (Buu-Hoï and Jacquignon, *J.*, 1952, 4173), and since acetylation of *p*-chloro- and *p*-bromo-toluene occurred mainly at the position *ortho* to the halogen atom (Claus, *J. pr. Chem.*, 1892, **46**, 21, 26; Mayer and Freund, *Ber.*, 1922, **55**, 2052), the acetylation, propionylation, and phenylacetylation of *p*-fluorotoluene probably also occur at this position. Beckmann rearrangement of 2-fluoro-5-methylpropiophenone oxime yielded a base which is probably 2-fluoro-5-methylaniline.

As we are interested in substituted 2-phenylcinchoninic acids, and particularly in the

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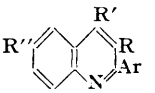
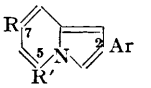
effect of fluorine therein, we prepared a series of fluorine-containing 2-arylcinchoninic acids (I; R′ = CO_2H), 2-arylquinolines (I; R′ = H) and 2-arylpyrrocolines (II) from the

(I) 

 (II)

ketones mentioned above. The cinchoninic acids, prepared by Pfitzinger's reaction, are listed in Table 1, and the quinolines obtained by thermal decarboxylation in Table 2. 2-(4-Fluoro-3-methylphenyl)pyrrocoline and its 5- and 7-methyl homologues were prepared from ω-bromo-4-fluoro-2-methylacetophenone and α-picoline or 2 : 4- and 2 : 6-lutidine by Tschitschibabin's reaction (*Ber.*, 1927, **60**, 1607; Borrows, Holland, and Kenyon, *J.*, 1946, 1069, 1075, 1083; Buu-Hoï and Hoán, *Rec. Trav. chim.*, 1949, **68**, 441).

TABLE 1. *Fluorinated cinchoninic acids* (I; R′ = CO_2H).

Subst.				Found, % :		Reqd., % :	
R	R″	M. p.	Formula	C	H	C	H
H	H	220°	$C_{17}H_{12}O_2NF$	72·4	4·1	72·6	4·3
H	Br	240	$C_{17}H_{11}O_2NBrF$	56·4	3·2	56·7	3·1
H	Me	230	$C_{18}H_{14}O_2NF$	73·0	4·8	73·2	4·7
Me	Me	329	$C_{19}H_{16}O_2NF$	73·5	5·4	73·8	5·2
Me	H	306	$C_{18}H_{14}O_2NF$	73·1	5·0	73·2	4·7
Me	Br	309—310	$C_{18}H_{13}O_2NBrF$	57·6	4·0	57·8	3·5
Et	H	304	$C_{19}H_{16}O_2NF$	73·5	5·1	73·8	5·2
Ph	H	314	$C_{23}H_{16}O_2NF$	77·1	4·3	77·3	4·5
Ph	Br	318	$C_{23}H_{15}O_2NBrF$	63·0	3·2	63·3	3·4
Ph	Me	>330	$C_{24}H_{18}O_2NF$	77·3	4·8	77·6	4·9
H	H	235°	$C_{17}H_{12}O_2NF$	72·4	4·2	72·6	4·3
H	Me	234	$C_{18}H_{14}O_2NF$	73·0	4·7	73·2	4·7
H	Cl	238	$C_{17}H_{11}O_2NClF$	64·4	3·6	64·7	3·5
H	Br	246	$C_{17}H_{11}O_2NBrF$	56·5	3·2	56·7	3·1
Me	H	291	$C_{18}H_{14}O_2NF$	73·0	4·8	73·2	4·7
Me	Cl	300	$C_{18}H_{13}O_2NClF$	65·5	3·9	65·6	4·1
Me	Br	279	$C_{18}H_{13}O_2NBrF$	57·4	3·6	57·8	3·7
Ph	H	>320	$C_{23}H_{16}O_2NF$	77·0	4·3	77·3	4·5
Ph	Cl	312	$C_{23}H_{15}O_2NClF$	70·6	3·9	70·8	3·8
Ph	Br	>320	$C_{23}H_{15}O_2NBrF$	63·0	3·2	63·3	3·4

TABLE 2. (a) *Fluorinated 2-arylquinolines* (I; R′ = H).

Subst.				Found, % :		Reqd., % :	
R	R″	M. p.	Formula	C	H	C	H
Ar = 4-Fluoro-2-methylphenyl.							
H	Br	118°	$C_{16}H_{11}NBrF$	60·6	3·6	60·8	3·5
Me	Br	130	$C_{17}H_{13}NBrF$	61·6	4·2	61·8	3·9
Ph	Br	136	$C_{22}H_{15}NBrF$	67·1	4·0	67·3	3·8
Ar = 2-Fluoro-5-methylphenyl.							
H	Cl	73	$C_{16}H_{11}NClF$	70·4	4·2	70·7	4·0
Ar = 2-Fluoro-5-methylphenyl.							
H	Br	72°	$C_{16}H_{11}NBrF$	60·5	3·5	60·8	3·5
Me	H	80	$C_{17}H_{14}NF$	81·1	5·4	81·3	5·6
Me	Cl	128	$C_{17}H_{13}NClF$	71·2	4·4	71·4	4·5
Me	Br	132	$C_{17}H_{13}NBrF$	61·5	3·6	61·8	3·9
Ph	H	130	$C_{22}H_{16}NF$	84·0	5·2	84·3	5·1
Ph	Br	154	$C_{22}H_{15}NBrF$	67·0	3·5	67·3	3·8

(b) *Picrates of fluorinated 2-arylquinolines* (I; R′ = H).

Subst.				Found, %:	Reqd., %:
R	R″	M. p.	Formula	N	N
Ar = 4-Fluoro-2-methylphenyl.					
H	H	190°	$C_{22}H_{15}O_7N_4F$	12·0	11·7
Ph	Br	182	$C_{28}H_{18}O_7N_4BrF$	9·0	9·2
Ar = 2-Fluoro-5-methylphenyl.					
H	Me	210	$C_{23}H_{17}O_7N_4F$	11·7	11·4
Me	Me	171	$C_{24}H_{19}O_7N_4F$	11·3	11·5
H	H	198	$C_{22}H_{15}O_7N_4F$	12·0	12·3
Ar = 2-Fluoro-5-methylphenyl.					
H	Cl	195°	$C_{22}H_{14}O_7N_4ClF$	11·2	11·0
H	Br	207	$C_{22}H_{14}O_7N_4BrF$	10·3	10·0
Me	H	192	$C_{23}H_{17}O_7N_4F$	11·7	11·3
Me	Cl	194	$C_{23}H_{16}O_7N_4ClF$	10·9	10·6
Me	Br	185	$C_{23}H_{16}O_7N_4BrF$	10·0	10·2
Ph	H	216	$C_{28}H_{19}O_7N_4F$	10·3	10·0

EXPERIMENTAL

4-Fluoro-2-methylacetophenone.—A mixture of *m*-fluorotoluene (30 g.) and acetyl chloride (24 g.), in dry carbon disulphide (100 c.c.), and powdered aluminium chloride (48 g.), was kept at room temperature for 24 hours and subsequently refluxed for 2 hours. After the usual treatment, the ketone was obtained as a mobile liquid (40 g.), b. p. 206°, n_D^{20} 1·5120 (Found: C, 71·0; H, 5·8. C_9H_9OF requires C, 71·1; H, 5·9%); *oxime*, prisms (from ether), m. p. 88° (Found: N, 8·1. $C_9H_{10}ONF$ requires N, 8·4%); p-*dimethylaminobenzylidene* derivative, long, orange-yellow needles (from methanol), m. p. 109° (Found: N, 4·9. $C_{18}H_{18}ONF$ requires N, 4·9%).

4-Fluoro-2-methylbenzoic Acid.—4-Fluoro-2-methylacetophenone (19 g.) was shaken with aqueous sodium hypobromite (from bromine, 21·4 c.c.; sodium hydroxide, 42 g.); the resulting bromoform was decanted, and the excess of hypobromite destroyed by sodium hydrogen sulphite. Acidification with hydrochloric acid precipitated the *acid*, which formed silky sublimable needles (from benzene), m. p. 168° (Found: C, 62·0; H, 4·6. $C_8H_7O_2F$ requires C, 62·3; H, 4·5%).

4-Fluoro-2-methylaniline.—To an ice-cooled solution of 4-fluoro-2-methylacetophenone oxime (9 g.) in anhydrous ether (100 c.c.), finely powdered phosphorus pentachloride (12 g.) was added with shaking (15 min.). The mixture was poured on ice, the ethereal layer washed with water, the solvent removed, and the residue refluxed for 1 hour with concentrated hydrochloric acid. The amine obtained on basification was taken up in benzene and purified by vacuum-distillation; it formed a pale yellow oil (4 g.), b. p. 90—92°/16 mm., n_D^{23} 1·5335, which gave a picrate, m. p. 199°, and an *N*-benzoyl derivative, m. p. 165—166° (Schiemann, *loc. cit.*, gave m. p. 199° and 166°, respectively).

4-Fluoro-2-methylpropiophenone.—This *ketone*, obtained in 80% yield as for the lower homologue, had b. p. 220° (119°/13 mm.), n_D^{20} 1·5081 (Found: C, 71·1; H, 6·6. $C_{10}H_{11}OF$ requires C, 72·3; H, 6·6%). *4-Fluoro-2-methyl-n-butyrophenone* (85% yield) formed a pale yellow liquid, b. p. 233° (135°/13 mm.), n_D^{20} 1·5005 (Found: C, 73·3; H, 7·5. $C_{11}H_{13}OF$ requires C, 73·3; H, 7·2%); its *oxime* was a pale yellow oil, b. p. 155°/18 mm., n_D^{25} 1·5172 (Found: N, 7·0. $C_{11}H_{14}ONF$ requires N, 7·2%), which underwent a Beckmann rearrangement to give the same amine as above. *4-Fluoro-2-methyl-α-phenylacetophenone* had b. p. 308° (196°/14 mm.), n_D^{20} 1·5630 (Found: C, 78·8; H, 5·8. $C_{15}H_{13}OF$ requires C, 78·9; H, 5·7%), giving a *thiosemicarbazone*, m. p. 138° (Found: N, 13·7. $C_{16}H_{16}N_3SF$ requires N, 14·0%).

2-(4-Fluoro-2-methylphenyl)pyrrocoline (II; R = R′ = H).—ω-Bromo-4-fluoro-2-methylacetophenone, prepared from 4-fluoro-2-methylacetophenone (10·5 g.) and bromine (11 g.), had b. p. 140°/15 mm., n_D^{18} 1·5603. A solution of this compound (1·5 g.) and α-picoline (0·6 g.) in ethanol (10 c.c.) was refluxed for 30 min.; on addition of ether, a precipitate of the acylpyridinium salt was obtained, and this was collected and treated with a boiling aqueous solution of sodium hydrogen carbonate for 10 min.; the *pyrrocoline* obtained formed from ethanol fine, shiny prisms (1 g.), m. p. 86° (Found: C, 79·8; H, 5·5. $C_{15}H_{12}NF$ requires C, 80·0; H, 5·3%). *2-(4-Fluoro-2-methylphenyl)-7-methylpyrrocoline* (II; R = Me, R′ = H), similarly prepared from 2 : 4-lutidine (0·8 g.), formed from ethanol shiny leaflets, m. p. 74° (Found: C, 80·1; H, 6·1. $C_{16}H_{14}NF$ requires C, 80·3; H, 5·9%). The analogous *5-methylpyrrocoline* (II; R = H, R′ = Me), prepared from 2 : 6-lutidine, was an oil (Found: N, 6·1. $C_{16}H_{14}NF$ requires N, 5·9%), and gave a *picrate* as brownish prisms (from ethanol), m. p. 155—156° (Found: N, 12·2. $C_{22}H_{17}O_7N_4F$ requires N, 12·0%).

2-Fluoro-5-methylacetophenone.—Obtained from *p*-fluorotoluene (35 g.) as a liquid (20 g.), b. p. 208—209°, n_D^{21} 1·5090 (Found: C, 71·1; H, 6·0. C_9H_9OF requires C, 71·1; H, 5·9%), this *ketone* formed a p-*dimethylaminobenzylidene* derivative, shiny yellow leaflets, m. p. 99° (Found: N, 4·6. $C_{18}H_{18}ONF$ requires N, 4·9%), from methanol.

2-Fluoro-5-methylpropiophenone.—The *ketone*, obtained in 78% yield, had b. p. 22°, n_D^{21} 1·4999 (Found: C, 72·2; H, 7·4. $C_{10}H_{11}OF$ requires C, 72·3; H, 7·2%); its *oxime*, a viscous oil, b. p. 150°/18 mm., $n_D^{25\cdot5}$ 1·5268 (Found: N, 7·5. $C_{10}H_{12}ONF$ requires N, 7·7%), gave on Beckmann rearrangement *2-fluoro-5-methylaniline*, a pale yellow oil, b. p. 88—90°/17 mm., n_D^{23} 1·5312 (Found: C, 67·1; H, 6·2. C_7H_8NF requires C, 67·2; H, 6·4%); its *N-acetyl* derivative crystallised from ligroin–benzene as silky leaflets, m. p. 70° (Found: C, 64·6; H, 6·2. $C_9H_{10}ONF$ requires C, 64·7; H, 6·07.). *2-Fluoro-5-methyl-α-phenylacetophenone*, obtained in 75% yield, was a pale yellow oil, b. p. 316° (204—206°/17 mm.), n_D^{21} 1·5600 (Found: C, 78·6; H, 5·7. $C_{15}H_{13}OF$ requires C, 78·9; H, 5·7%).

Pfitzinger Reactions.—These were performed as described by Buu-Hoï (*J.*, 1946, 795). The cinchoninic *acids* (Table I) obtained were recrystallised from ethanol or acetic acid; the corresponding *quinolines* (Table 2*a*) were prepared by heating the well-dried acids above their m. p. in a vacuum, distilling the residue, and crystallising the distillate from ethanol.

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