516. *The Acetylation of Some Dihalogenobenzenes in which the Halogen Atoms are Different.*

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o- and *m*-Chlorofluorobenzene, in carbon disulphide, undergo Friedel–Crafts acetylation in the position *para* to the fluorine atom; *p*-chlorofluorobenzene reacts only under drastic conditions. *o*-Bromochlorobenzene in carbon disulphide was acetylated in the position *para* to the chlorine atom, but *m*-bromochlorobenzene could not be acetylated under the same conditions. Some theoretical implications of these experiments are discussed.

In Friedel–Crafts acetylation of nuclear-halogenated toluenes, orientation of the acetyl group is governed by the halogen, whether it be fluorine,[1] chlorine,[2] or bromine.[3] Hence it was of interest to investigate the behaviour of dihalogenobenzenes bearing two different halogens, and to determine whether the orienting influence of the halogens would follow the order of their Pauling electronegativity values (F > Cl > Br > I). Chlorofluoro- and bromochloro-benzenes were found suitable, but fluoroiodo- and chloroiodo-benzenes either were unreactive or decomposed.

o-Chlorofluorobenzene was readily acetylated in carbon disulphide in the presence of aluminium chloride to give 3-chloro-4-fluoroacetophenone, whose structure was determined by Beckmann rearrangement of its oxime to 3-chloro-4-fluoroacetanilide; the isomeric

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[1] Buu-Hoï and Jacquignon, *J.*, 1952, 4173; Buu-Hoï and Xuong, *J.*, 1953, 386.
[2] Claus, *J. prakt. Chem.*, 1891, **43**, 361.
[3] Claus, *J. prakt. Chem.*, 1892, **46**, 21; Mayer and Freund, *Ber.*, 1922, **55**, 2052.

4-chloro-3-fluoroacetophenone was formed at most in traces, whereas it is known that in the nitration of *o*-chlorofluorobenzene [4] the directing influence of the chlorine atom leads to 21%. Similarly, *m*-chlorofluorobenzene was acetylated to a liquid ketone, which vapour-phase chromatography showed to be a single product; this was 2-chloro-4-fluoroacetophenone, as proved by its oxidation to 2-chloro-4-fluorobenzoic acid, and Beckmann rearrangement of its oxime to 2-chloro-4-fluoroacetanilide. Here again, Friedel–Crafts acetylation contrasted with nitration, the latter being orientated by the chlorine atom to an appreciable degree. *p*-Chlorofluorobenzene was considerably less reactive than its two isomers, since it resisted acetylation in carbon disulphide, although we were able to confirm Bergmann and Berkovic's observation [5] that it underwent the reaction without solvent, to give 2-chloro-5-fluoroacetophenone; Beckmann rearrangement of the oxime of this ketone afforded 2-chloro-5-fluoroacetanilide.

o-Bromochlorobenzene easily underwent acetylation in carbon disulphide to a homogeneous ketone, which was 3-bromo-4-chlorobenzoic acid, as its oxime underwent Beckmann rearrangement to 3-bromo-4-chloroacetanilide; the same experimental conditions, however, were insufficient to bring about appreciable acetylation of *m*-bromochlorobenzene. Here again, the Friedel–Crafts reaction stands in contrast with nitration, where the orienting influence of the bromine atom is notable.

Thus, in the Friedel–Crafts acetylation reaction, there is a sharp contrast between the *p*-dihalogenobenzenes and their *ortho*- and *meta*-isomers; the preferential acetylation of *p*-chlorofluorobenzene in the position *ortho* to chlorine could be ascribed to the polar deactivation by the strongly electronegative fluorine atom,[5,6] but this does not explain the facts observed with the *ortho*- and *meta*-isomers; here, the relative magnitude of the directing influence of the halogens is consistent with the results of halogenotoluene acetylations, and both are consistent with the scale of electronegativities, $F > Cl > Br > Me$; it is interesting also that 4-fluorobiphenyl is acetylated to 4-acetyl-4′-fluorobiphenyl.

Since completion of this study, the work of Baltzly, Sheehan, and Stone [7] has come to our notice, in which they report successful acetylation of *o*-chlorofluorobenzene, in low yield, to a ketone formulated as 3-chloro-4-fluoroacetophenone, on the indirect basis of the analysis of the phenylhydrazone and semicarbazone of its reaction product with sodium thiophenoxide.

Synthesis of some derived heterocyclic compounds for biological testing is briefly recorded.

EXPERIMENTAL

Acetylation of o-*Chlorofluorobenzene*.—A stirred mixture of *o*-chlorofluorobenzene (45 g.), acetyl chloride (40 g.), aluminium chloride (70 g.), and carbon disulphide (200 c.c.) was refluxed for 50 hr.; after cooling, and decomposition with dilute hydrochloric acid, the organic layer was washed with aqueous sodium hydroxide, then with water, dried (Na_2SO_4), and evaporated, and the residue was fractionated *in vacuo*. This gave 3-chloro-4-fluoroacetophenone (47 g., ~80%), b. p. 226°, prisms, m. p. 43° (lit.,[7] m. p. 41—42°) (from hexane) (Found: C, 55·5; H, 3·6. Calc. for C_8H_6ClFO: C, 55·7; H, 3·5%). Yields after various periods of heating were: 47%, 16 hr.; 67%, 26 hr.; 76%, 36 hr. Replacement of carbon disulphide by methylene chloride (at 40°) led to zero yields after 25 hr. and 43% after 50 hr. Tetrachloroethane was more satisfactory (47% after 26 hr., and 80% after 50 hr.) but necessitated a boiling reaction mixture. An attempt to isolate a second ketone from the mother-liquors of crystallisation was unsuccessful; the infrared absorption spectrum of 3-chloro-4-fluoroacetophenone showed the presence of two vicinal hydrogen atoms (band at *ca.* 825 cm.$^{-1}$) and of a single nuclear hydrogen atom (band at *ca.* 885 cm.$^{-1}$). The ketone gave a 2,4-*dinitrophenylhydrazone*, red prisms, m. p. 238° (from

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[4] Ingold and Vass, *J.*, 1928, 417, 2262.

[5] Bergmann and Berkovic, *J. Org. Chem.*, 1961, **26**, 918.

[6] Ingold, "Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, Ithaca, 1963, p. 260.

[7] Baltzly, Sheehan, and Stone, *J. Org. Chem.*, 1961, **26**, 2353.

acetic acid) (Found: C, 48·0; H, 3·2. $C_{14}H_{10}ClFN_4O_4$ requires C, 47·7; H, 2·9%), *thiosemicarbazone*, colourless needles, m. p. 206° (from ethanol) (Found: C, 44·6; H, 3·8. $C_9H_9ClFN_3S$ requires C, 44·0; H, 3·7%), and oxime, prisms, m. p. 97° (from ethanol).

2-*Chloro*-4-*ethyl*-1-*fluorobenzene*.—A mixture of the foregoing ketone (18 g.), 98% hydrazine hydrate (60 g.), and diethylene glycol (120 g.) was refluxed for a few minutes, and potassium hydroxide (20 g.) was added after cooling. After a further 3 hours' refluxing and acidification with dilute hydrochloric acid, the product was taken up in chloroform, the chloroform solution washed with water and dried (Na_2SO_4), the solvent removed, and the residue fractionated, giving a colourless *product* (11 g.), b. p. 159°, n_D^{20} 1·5022 (Found: C, 60·7; H, 5·2. C_8H_8ClF requires C, 60·6; H, 5·1%).

Constitution of 3-*Chloro*-4-*fluoroacetophenone*.—(*a*) A solution of the oxime (18·7 g.) in anhydrous ether (100 c.c.) was shaken for a few minutes with powdered phosphorus pentachloride (31·2 g.), and the solvent distilled off; the residue was treated with ice, and the precipitate formed was washed with water and recrystallised from ethanol, giving 3-*chloro*-4-*fluoroacetanilide* (15 g.), leaflets, m. p. 115° (Found: C, 51·1; H, 3·5. C_8H_7ClFNO requires C, 51·2; H, 3·8%). Hydrolysis by hydrochloric acid in ethanol yielded, after basification, 3-chloro-4-fluoroaniline, b. p. 227—228°, m. p. 44° (from hexane) (lit.,[4] b. p. 226°, m. p. 44°). This amine afforded *tetrachloro*-N-3-*chloro*-4-*fluorophenylphthalimide*, colourless needles, m. p. 190° (from acetic acid) (Found: C, 40·3; H, 0·6. $C_{14}H_3Cl_5FNO_2$ requires C, 40·7; H, 0·7%), 2-*chloro*-3-(3-*chloro*-4-*fluoroanilino*)-1,4-*naphthaquinone*, m. p. 158° (from ethanol) (Found: C, 53·7; H, 2·3. $C_{14}H_{18}Cl_2FNO$ requires C, 54·0; H, 2·6%), and 2,5-*dichloro*-3,6-*di*-(3-*chloro*-4-*fluoroanilino*)-1,4-*benzoquinone*, m. p. 252° (from ethanol) (Found: C, 43·2; H, 1·9. $C_{16}H_8Cl_4F_2N_2O_2$ requires C, 43·7; H, 1·8%).

(*b*) An ice-cold aqueous solution of sodium hypobromite [from bromine (41 g.) and sodium hydroxide (81 g.) in water (450 c.c.)] was shaken for 1 hr. with 3-chloro-4-fluoroacetophenone (40 g.), and the reaction completed by a brief heating at 60°; the aqueous layer was treated with sodium hydrogen sulphite and acidified with hydrochloric acid, and the precipitate recrystallised from benzene, giving 3-*chloro*-4-*fluorobenzoic acid*, needles (30 g.), m. p. 136° (Found: C, 48·3; H, 2·5. $C_7H_4ClFO_2$ requires C, 48·2; H, 2·3%). This acid was characterised by its *amide*, prisms, m. p. 132° (from ethanol) (Found: C, 48·2; H, 3·1. C_7H_5ClFNO requires C, 48·5; H, 2·9%), and *diethylamide*, pale yellow, viscous oil, b. p. 169°/13 mm., n_D^{23} 1·5278 (Found: C, 57·2; H, 5·7. $C_{11}H_{13}ClFNO$ requires C, 57·6; H, 5·7%); it gave the *acyl derivatives* of 2-aminopyridine, leaflets, m. p. 143° (Found: C, 57·2; H, 3·4. $C_{12}H_8ClFN_2O$ requires C, 57·5; H, 3·2%), *p*-anisidine, leaflets, m. p. 159° (Found: C, 63·4; H, 4·1. $C_{14}H_{11}ClFN_2O$ requires C, 63·8; H, 4·2%), 1-naphthylamine, leaflets, m. p. 198° (Found: C, 67·9; H, 3·9. $C_{17}H_{11}ClFNO$ requires C, 68·2; H, 3·7%), and 3-morpholinopropylamine, prisms, b. p. 267°/22 mm., m. p. 21° (Found: C, 56·0; H, 6·2. $C_{14}H_{18}ClFN_2O$ requires C, 56·0; H, 6·0%).

2-*Chloro*-4-*fluoroacetophenone*.—Prepared from *m*-chlorofluorobenzene (b. p. 196—197°, n_D^{22} 1·4978) in carbon disulphide, as for the *ortho*-isomer but in slightly lower yield (77%), this *ketone* was a pale yellow oil, b. p. 110°/19 mm., n_D^{24} 1·5310 (Found: C, 56·0; H, 3·4. C_8H_6ClFO requires C, 55·7; H, 3·5%). Vapour-phase chromatography (100—250°, 11° per min.) showed a single peak. The product also gave a single semicarbazone, prisms, m. p. 193° (from ethanol), a 2,4-*dinitrophenylhydrazone*, red needles, m. p. 167° (from acetic acid) (Found: C, 47·7; H, 3·1; N, 15·7. $C_{14}H_{10}ClFN_4O_4$ requires C, 47·7; H, 2·9; N, 15·9%), and an *oxime*, needles, m. p. 131° (Found: C, 51·6; H, 3·9. C_8H_7ClFNO requires C, 51·2; H, 3·8%). Rearrangement of this oxime with phosphorus pentachloride, performed as above, yielded 2-chloro-4-fluoroacetanilide, crystallising from ethanol as needles, m. p. 117° (lit.,[8] m. p. 117°).

2-*Chloro*-4-*fluorobenzoic Acid*.—Obtained from the foregoing ketone and sodium hypobromite, this *acid* formed colourless needles, m. p. 176°, from benzene (Found: C, 48·4; H, 2·6. $C_7H_4ClFO_2$ requires C, 48·2; H, 2·3%).

Acetylation of p-*Chlorofluorobenzene*.—This compound, treated with acetyl chloride and aluminium chloride in carbon disulphide as were its isomers, resisted acetylation; Bergmann and Berkovic's procedure,[5] however, gave an excellent yield of 2-chloro-5-fluoroacetophenone, which gave an *oxime*, prisms, m. p. 88° (from ethanol) (Found: C, 51·0; H, 4·0%). The yield of ketone obtained (67%) was significantly higher than that recorded in the literature (54%). Beckmann rearrangement, performed as above, gave 2-chloro-5-fluoroacetanilide, b. p. 153—

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[8] Finger, Gortatowski, Shiley, and White, *J. Amer. Chem. Soc.*, 1959, **81**, 94.

154°/13 mm., m. p. 99° (from ethanol); Ingold and Vass [4] gave m. p. 91° for a compound which probably contained some 5-chloro-2-fluoroacetanilide.

Acetylation of o-*Bromochlorobenzene*.—To a solution of *o*-bromochlorobenzene (150 g.) and acetyl chloride (110 g.) in carbon disulphide (400 g.), aluminium chloride (180 g.) was added in small portions, and the mixture refluxed with stirring for 50 hr. After cooling, the product was worked up in the usual way, to give a 67% yield of 3-*bromo*-4-*chloroacetophenone*, prisms, m. p. 75° (from hexane) (Found: C, 41·4; H, 2·9. C_8H_6BrClO requires C, 41·1; H, 2·6%) [*thiosemicarbazone*, prisms, m. p. 180° (from ethanol) (Found: C, 34·9; H, 3·0. $C_9H_9BrClN_3S$ requires C, 35·3; H, 3·0%); 2,4-*dinitrophenylhydrazone*, red prisms, m. p. 186° (from ethanol) (Found: C, 40·8; H, 2·4. $C_{14}H_{10}BrClN_4O_4$ requires C, 40·7; H, 2·5%); *oxime*, prisms, m. p. 93° (from ethanol) (Found: C, 38·4; H, 3·1. $C_8H_7BrClNO$ requires C, 38·7; H, 2·8%)]. Beckmann rearrangement of the oxime (25 g.) with phosphorus pentachloride (31 g.) in ether (100 c.c.) afforded an 85% yield of 3-bromo-4-chloroacetanilide, m. p. 130° (lit.,[9] m. p. 127—128°,[10] 130°). Degradation of the ketone with sodium hypobromite gave 3-bromo-4-chlorobenzoic acid, m. p. 215° (lit.,[11] m. p. 215—216°).

An attempt to acetylate *m*-bromochlorobenzene under the same conditions failed, and most of the starting product was recovered.

			Required (%)		Found (%)	
Cinchoninic acids	M. p.	Formula	C	H	C	H
2-(3-Chloro-4-fluorophenyl)-	220°	$C_{16}H_9ClFNO_2$	63·8	3·0	64·0	3·3
6-Bromo-2-(3-chloro-4-fluorophenyl)-	194	$C_{16}H_8BrClFNO_2$	50·6	2·1	50·3	2·3
6-Bromo-(2-chloro-4-fluorophenyl)-	197	$C_{16}H_8BrClFNO_2$	50·6	2·1	50·3	2·3
2-(3-Bromo-4-chlorophenyl)-	245	$C_{16}H_9BrClNO_2$	53·0	2·5	53·2	2·6
6-Bromo-2-(3-bromo-4-chlorophenyl)-	254	$C_{16}H_8Br_2ClNO_2$	43·5	1·8	43·8	2·0
Quinolines						
2-(3-Chloro-4-fluorophenyl)-	108	$C_{15}H_9ClFN$	70·0	3·5	69·8	3·2
6-Bromo-2-(3-chloro-4-fluorophenyl)-	154	$C_{15}H_8BrClFN$	53·5	2·1	53·2	2·4
2-(2-Chloro-4-fluorophenyl)-	99	$C_{15}H_9ClFN$	70·0	3·5	70·3	3·8

4-*Acetyl*-4′-*fluorobiphenyl*.—To a solution of 4-fluorobiphenyl (35 g.) and acetyl chloride (40 g.) in carbon disulphide (150 c.c.), aluminium chloride (70 g.) was added in small portions, and the mixture was refluxed with stirring for 50 hr. The *ketone* obtained (27 g.) crystallised from hexane as prisms, m. p. 90°, b. p. 198°/15 mm. (Found: C, 78·4; H, 5·0. $C_{14}H_{11}FO$ requires C, 78·6; H, 5·2%). The *oxime*, prisms, m. p. 148° (from ethanol) (Found: C, 80·0; H, 5·5. $C_{14}H_{12}FNO$ requires C, 80·1; H, 5·8%), on Beckmann rearrangement gave a 90% yield of 4-acetamido-4′-fluorobiphenyl, leaflets, m. p. 205° (in accordance with the literature[12]).

Polyhalogenated Heterocyclic Compounds.—These were synthesised for investigation of their toxic properties. 1-(3-*Chloro*-4-*fluorophenyl*)-2,5-*dimethylpyrrole*, prepared by refluxing for 45 min. a mixture of 3-chloro-4-fluoroaniline (2 g.) and hexane-2,5-dione (6 g.), was a pale yellow oil (2 g.), b. p. 137°/18 mm., n_D^{17} 1·4847 (Found: C, 64·2; H, 4·7. $C_{12}H_{11}ClFN$ requires C, 64·5; H, 5·0%); 1-(3-*chloro*-4-*fluorophenyl*)-2-*methyl*-5-*phenylpyrrole*, similarly prepared with phenacylacetone, had b. p. 184°/15 mm., n_D^{18} 1·5625 (Found: C, 71·8; H, 4·4. $C_{17}H_{13}ClFN$ requires C, 71·5; H, 4·6%). 2-(3-*Chloro*-4-*fluorophenyl*)*indole*, prepared by cyclisation of the phenylhydrazone of 3-chloro-4-fluoroacetophenone, formed colourless prisms, m. p. 178° (from ethanol), b. p. 198°/17 mm. (Found: C, 68·6; H, 3·7. $C_{14}H_9ClFN$ requires C, 68·5; H, 3·7%). *Cinchoninic acids* were prepared from the appropriate acetophenones by Pfitzinger reactions, and are listed in the Table, together with the corresponding *quinolines*, obtained by thermal decarboxylation; the cinchoninic acids and the quinolines were recrystallised from ethanol.

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[9] Crowther, Curd, Davey, Hendry, Hepworth, and Rose, *J.*, 1951, 1777.

[10] Chattaway and Orton, *J.*, 1901, **79**, 466.

[11] Hodgson and Beard, *J.*, 1927, 26.

[12] Van Hove, *Bull. Soc. chim. belges*, 1923, **32**, 52.