CCXIII.—*The Reimer–Tiemann Reaction with* m-*Fluorophenol and the Nitration of 4-Fluoro-2-hydroxy- and 2-Fluoro-4-hydroxy-benzaldehydes.*

By Herbert Henry Hodgson and Joseph Nixon.

The influence of fluorine in the meta-position on the Reimer–Tiemann reaction is similar to that of the other halogens (compare Hodgson and Jenkinson, this vol., p. 469). The ratio, 0·87, of *o*- to *p*-hydroxy-aldehyde obtained shows that the deactivation (I) of the hydrogen atom in the para-position (*o*/*p* ratio for phenol, 0·6) is much greater than that produced by *m*-substituted chlorine (*o*/*p* ratio, 0·71). [Correction is necessary of (5) (*loc. cit.*, p. 470), where the results are not in accordance with the usually accepted deactivation order Cl>Br>I: for the present, no conclusions are drawn from the divergence.] That fluorine deactivates to a greater extent than chlorine is also shown by the fact that, for nitration, 4-fluoro-3-bromo- and 4-fluoro-5-bromo-2-hydroxybenzaldehydes require more drastic treatment than the chloro-analogues.

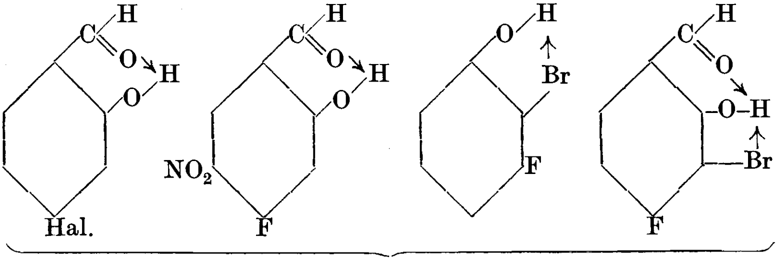
The sodium derivatives of the 4-halogeno-2-hydroxybenzaldehydes, like the sodium derivative of salicylaldehyde, are bright yellow and are sparingly soluble in water, in marked contrast to the readily soluble, colourless sodium derivatives of the 2-halogeno-4-hydroxybenzaldehydes, and the copper and chromium derivatives are more deeply coloured than the corresponding derivatives of the latter aldehydes. These facts are to be expected from the well-established co-ordination of salicylaldehyde itself. Co-ordination may also account for the unexpected volatility in steam of 4-fluoro-5-nitro-2-hydroxybenzaldehyde and for the liquid nature of 3-fluoro-2-bromophenol and of 4-fluoro-3-bromo-2-hydroxybenzaldehyde (II).

The mononitration of 4-*fluoro*-2-*hydroxy*- and of 2-*fluoro*-4-*hydroxy-benzaldehydes* resembles that of the other halogeno-analogues (Hodgson and Jenkinson, J., 1928, 2272) in that only the 5-*nitro*-derivative is obtained in each case. In dinitration, which is readily accomplished, the first nitro-group apparently enters position 5, since nitration of 4-fluoro-3-bromo-2-hydroxybenzaldehyde gives the same product as bromination of the mononitrated 4-fluoro-2-hydroxybenzaldehyde. For comparison, the isomeric 4-*fluoro*-5-*bromo*-3-*nitro*-2-*hydroxybenzaldehyde* has been prepared, and the above product has thus been identified as 4-fluoro-3-bromo-5-nitro-2-hydroxybenzaldehyde. The sodium derivative of the former is bright red and that of the latter is yellow, indicating their respective *o*- and *p*-nitrophenolic structure. Similarly, nitration of 2-fluoro-3-bromo-4-hydroxybenzaldehyde gives the same product as bromination of the mononitrated 2-fluoro-4-hydroxybenzaldehyde, which must therefore be 2-fluoro-3-bromo-5-nitro-4-hydroxybenzaldehyde.

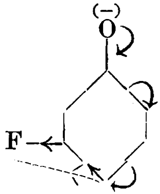
It is noteworthy that, whereas 4-fluoro-5-nitro-2-hydroxybenzaldehyde is yellow, the isomeric 2-*fluoro*-5-*nitro*-4-*hydroxybenzaldehyde*, which has an o-*nitrophenolic structure*, is colourless but acquires a yellow colour on bromination to 2-fluoro-3-bromo-5-nitro-4-hydroxybenzaldehyde; also that the p-*nitrophenylhydrazones* of 4-fluoro-2-methoxy- and 2-fluoro-4-methoxy-benzaldehydes give no colour with aqueous sodium hydroxide, showing repression of ionisation of the imino-hydrogen by substitution of methoxyl for hydroxyl.

The brown colours produced by the action of alkali on the phenylhydrazones of certain substituted *m*-nitrobenzaldehydes are in accordance with the observations of Chattaway and Clemo (J., 1923, **123**, 3043).

Although *4-fluoro-2-methoxybenzoic acid* (IV) readily loses its methyl group on treatment with concentrated hydriodic acid, the isomeric *2-fluoro-4-methoxybenzoic acid* (III) cannot be demethylated. This difficulty was also encountered with the other 2-halogeno-4-methoxybenzoic acids and might be accounted for on the assumption that the activities of the lone pairs of electrons on the methoxyl oxygen are suppressed by the combined general effect (Allan, Oxford, Robinson, and Smith, J., 1926, 401) of the fluoro- and carboxyl groups (III), thereby preventing formation of the unstable oxonium salt with hydriodic acid prior to separation of methyl iodide. That greater activity is shown in the 4-halogeno-2-methoxybenzoic acids may be due to a possible co-ordination between the methoxyl oxygen and the loosely bound carboxylic hydrogen which enables the remaining lone pair to function (IV).



(II.)



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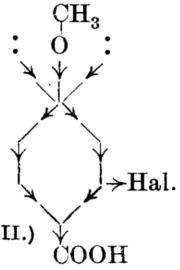

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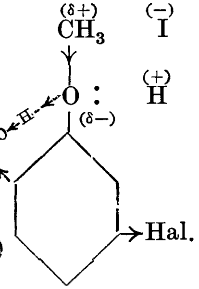

(IV.)

EXPERIMENTAL.

Unless otherwise stated, the methods of preparation of the compounds described below are identical with those for the other halogeno-analogues (Hodgson and Jenkinson, J., 1927, 1740, 3041; 1928, 2272). The colours produced by alcoholic alkalis with alcoholic solutions of the hydrazones and *p*-nitrophenylhydrazones are given immediately after the m. p.'s.

Reimer–Tiemann Reaction.—Quantities: *m*-Fluorophenol (15 g.), sodium hydroxide (36 g.), chloroform (36 g.), water (120 c.c.).

4-*Fluoro*-2-*hydroxybenzaldehyde* (yield, 3·5 g.) is very volatile in steam, very soluble in water and the usual organic solvents, and crystallises from alcohol or dilute acetic acid in colourless needles, m. p. 69° (Found: C, 59·7; H, 3·4. $C_7H_5O_2F$ requires C, 60·0; H, 3·6%). It has an odour of walnuts which is even more pronounced than that of its halogeno-analogues, gives a brown precipitate with ferric chloride, and does not reduce ammoniacal silver nitrate or Fehling's solution. The bright yellow sodium derivative is sparingly soluble in water; the copper and chromium derivatives are light and dark green respectively. The *oxime* is very soluble in the usual organic solvents and crystallises from alcohol in colourless needles, m. p. 125° (Found: N, 9·2. $C_7H_6O_2NF$ requires N, 9·0%). The p-*nitrophenylhydrazone* crystallises from glacial acetic acid in orange needles, m. p. 248°; cherry-red (Found: N, 15·6. $C_{13}H_{10}O_3N_3F$ requires N, 15·3%). The *semicarbazone* crystallises from glacial acetic acid in yellow micro-needles, m. p. 236° (Found: N, 21·5. $C_8H_8O_2N_3F$ requires N, 21·3%).

2-*Fluoro*-4-*hydroxybenzaldehyde* (yield, 3·8 g.) crystallises from acetic acid in colourless needles, m. p. 171° (Found: C, 59·7; H, 3·8%). Ferric chloride does not give a precipitate but imparts a deep port-wine colour, and ammoniacal silver nitrate and Fehling's solution are unaffected. The copper and chromium derivatives are of a lighter green colour than those of the 4-fluoro-2-hydroxy-isomerides, and the sodium derivative is much more soluble in water, from which it crystallises in long colourless needles. The p-*nitrophenylhydrazone* crystallises from glacial acetic acid in deep red needles, m. p. 261° (Found: N, 15·5%), and gives a bluer red colour with caustic alkalis than does the 4-fluoro-isomeride. The *oxime* separates from alcohol in colourless micro-plates, m. p. 151° (Found: N, 9·2%). The *semicarbazone* crystallises from alcohol or dilute acetic acid in pale yellow micro-plates, m. p. 238° (Found: N, 21·4%), and the *benzoate* in pale yellow needles, m. p. 63° (Found: C, 68·5; H, 3·9. $C_{14}H_9O_3F$ requires C, 68·8; H, 3·7%).

Nitration of 4-*Fluoro*-2-*hydroxybenzaldehyde.*—(a) Mononitration. 4-*Fluoro*-5-*nitro*-2-*hydroxybenzaldehyde* is slowly volatile in steam and crystallises from alcohol in yellow needles, m. p. 120° (Found: N, 7·8. $C_7H_4O_4NF$ requires N, 7·6%). The *phenylhydrazone* crystallises from glacial acetic acid in pale yellow needles, m. p.

173° (decomp.); brownish-yellow (Found: N, 15·5. $C_{13}H_{10}O_3N_3F$ requires N, 15·3%). The p-*nitrophenylhydrazone* crystallises from alcohol or glacial acetic acid in small, golden-yellow needles, m. p. 340° (decomp.); bluish-red (Found: N, 17·7. $C_{13}H_9O_5N_4F$ requires N, 17·5%).

(b) Dinitration. 4-*Fluoro*-3 : 5-*dinitro*-2-*hydroxybenzaldehyde* crystallises from benzene in long, pale yellow needles, m. p. 165° (Found: N, 12·3. $C_7H_3O_6N_2F$ requires N, 12·2%). It neither reduces Fehling's solution nor gives a precipitate with bromine water. The *phenylhydrazone* crystallises from dilute hydrochloric acid in deep orange micro-needles, m. p. 221° (Found: N, 17·6. $C_{13}H_9O_5N_4F$ requires N, 17·5%), and the p-*nitrophenylhydrazone* in brownish-yellow micro-needles, m. p. 254° (decomp.); bluish-red (Found: N, 19·4. $C_{13}H_8O_7N_5F$ requires N, 19·2%).

Nitration of 2-*Fluoro*-4-*hydroxybenzaldehyde*.—(a) Mononitration. 2-*Fluoro*-5-*nitro*-4-*hydroxybenzaldehyde* is readily volatile in steam and crystallises from alcohol in long, colourless needles, m. p. 126° (Found: N, 7·6%), which give deep yellow solutions in caustic alkalis. The *phenylhydrazone* crystallises from acetic acid in bronze needles, m. p. 153°; red (Found: N, 15·5%), and the p-*nitrophenylhydrazone* in salmon micro-needles, m. p. 270° (decomp.) (Found: N, 17·6%), which give a red colour with aqueous and violet-red with alcoholic potassium hydroxide. The *semicarbazone* crystallises from aqueous alcohol in pale yellow needles, m. p. 258° (decomp.) (Found: N, 23·3. $C_8H_7O_4N_4F$ requires N, 23·1%), and the *oxime* in pale yellow needles, m. p. 132° (Found: N, 14·2. $C_7H_5O_4N_2F$ requires N, 14·0%).

(b) Dinitration. The non-volatile 2-*fluoro*-3 : 5-*dinitro*-4-*hydroxybenzaldehyde*, when recrystallised from glacial acetic acid and then from benzene, formed pale yellow needles, m. p. 138° (Found: N, 12·4%), which were sparingly soluble in cold but readily soluble in hot water. The *phenylhydrazone* crystallises from alcohol or glacial acetic acid in silky brown-orange needles, m. p. 212°; magenta in strong alkalis, turning bluer on dilution (Found: N, 17·7%), and the p-*nitrophenylhydrazone* in brownish-yellow micro-needles, m. p. 260° (violent decomp.); cherry-red (Found: N, 19·7%).

Preparation of 3-*Fluoro*-2-*bromophenol*.—*m*-Fluorophenol (20 g.) was added gradually to cooled oleum (120 g.; 27% SO_3). The mixture was kept over-night and was then heated (2 hours) on the water-bath to complete the disulphonation, cooled, added cautiously to cold water (100 c.c.), and monobrominated by the gradual addition of bromine (24 g.) with vigorous shaking. On hydrolysis in a current of steam, 3-*fluoro*-2-*bromophenol* passed over. It was extracted from the distillate in ether and fractionally distilled; the main bulk boiled at 123°/80 mm., but did not solidify at —20° (Found : Br, 41·6. C_6H_4OFBr requires Br, 41·8%). It gave only a moderate yield of aldehydes in the Reimer–Tiemann reaction under Hodgson and Jenkinson's conditions (*loc. cit.*).

4-*Fluoro*-3-*bromo*-2-*hydroxybenzaldehyde* is a colourless liquid which does not solidify at —20° (Found : Br, 36·4. $C_7H_4O_2FBr$ requires Br, 36·5%). *Phenylhydrazone*, yellow-brown needles, m. p. 138° (Found : Br, 25·8. $C_{13}H_{10}ON_2FBr$ requires Br, 25·9%). p-*Nitrophenylhydrazone*, orange micro-needles, m. p. 215° ; ruby-red (Found : Br, 22·6. $C_{13}H_9O_3N_3FBr$ requires Br, 22·6%).

2-*Fluoro*-3-*bromo*-4-*hydroxybenzaldehyde* is very slowly volatile in steam and crystallises in colourless needles, m. p. 106° (Found : Br, 36·3%). *Phenylhydrazone*, light brown micro-needles, m. p. 85° ; golden-yellow (Found : Br, 25·8%). p-*Nitrophenylhydrazone*, deep red micro-needles, m. p. 258° (decomp.); violet (Found : Br, 22·5%). *Oxime*, colourless needles, m. p. 148° (Found : Br, 34·0. $C_7H_5O_2NBrF$ requires Br, 34·2%). *Semicarbazone*, light yellow micro-needles, m. p. 210° (Found : Br, 28·9. $C_8H_7O_2N_3BrF$ requires Br, 29·0%).

Correction : In J., 1928, p. 2275, 3-chloro-2-bromo-4-hydroxybenzaldehyde should read 2-chloro-3-bromo-4-hydroxybenzaldehyde.

Nitration of 4-*Fluoro*-3-*bromo*-2-*hydroxybenzaldehyde*.—The nitration of the aldehyde (1·5 g.), dissolved in glacial acetic acid, with nitric acid (1 g. ; *d* 1·5) was best carried out at 100° for 30 minutes, the lower temperature employed for the chloro-analogue (*loc. cit.*) proving insufficient. 4-*Fluoro*-3-*bromo*-5-*nitro*-2-*hydroxybenzaldehyde* crystallised from glacial acetic acid in pale yellow needles, m. p. 151° (Found : N, 5·5; Br, 30·1. $C_7H_3O_4NFBr$ requires N, 5·3; Br, 30·3%). *Phenylhydrazone*, pale yellow micro-needles, m. p. 193° ; brown (Found : Br, 22·4. $C_{13}H_9O_3N_3FBr$ requires Br, 22·6%). p-*Nitrophenylhydrazone*, lemon-yellow micro-needles, m. p. 270° (decomp.) ; ruby-red (Found : Br, 20·2. $C_{13}H_8O_5N_4FBr$ requires Br, 20·05%).

Bromination of 4-*Fluoro*-5-*nitro*-2-*hydroxybenzaldehyde*.—4-Fluoro-3-bromo-5-nitro-2-hydroxybenzaldehyde was obtained in pale yellow needles, m. p. 151° (Found : N, 5·4; Br, 30·2%). The m. p. was unaltered when this product was mixed with the foregoing one, and the respective phenylhydrazones and *p*-nitrophenylhydrazones gave mixed m. p.'s which indicated identity.

Preparation of 4-*Fluoro*-5-*bromo*-2-*hydroxybenzaldehyde*.—This was carried out by Hodgson and Jenkinson's method (*loc. cit.*, p. 2276). The product, which was volatile in steam, crystallised from light petroleum in colourless needles, m. p. 81° (Found : Br, 36·3%).

Phenylhydrazone, orange-brown micro-needles, m. p. 166° (Found : Br, 25·9%). p-*Nitrophenylhydrazone*, brick-red needles, m. p. 242°; bluish-red (Found : Br, 22·4%).

Nitration of 4-*Fluoro*-5-*bromo*-2-*hydroxybenzaldehyde*.—The process for the chloro-analogue (*loc. cit.*, p. 2276) was adopted, except that the nitration was conducted at 100° for 30 minutes. 4-*Fluoro*-5-*bromo*-3-*nitro*-2-*hydroxybenzaldehyde* crystallised from dilute alcohol in pale yellow plates, m. p. 115° (Found : Br, 30·4%), giving a bright red sodium derivative. The *phenylhydrazone* crystallised from glacial acetic acid in orange-brown needles, m. p. 215°; golden-brown (Found : Br, 22·5%), and the p-*nitrophenylhydrazone* in brown needles, m. p. 258°; deep red-violet (Found : Br, 20·1%). The m. p.'s of mixtures with the isomerides above were depressed.

Nitration of 2-*Fluoro*-3-*bromo*-4-*hydroxybenzaldehyde*.—This process was carried out as for 4-fluoro-3-bromo-2-hydroxybenzaldehyde, but at 30—40° for 1 hour. 2-*Fluoro*-3-*bromo*-5-*nitro*-4-*hydroxybenzaldehyde* crystallises from glacial acetic acid in long, pale yellow needles, m. p. 111° (Found : Br, 30·2%). Bromination as described above of the mononitration product of 2-fluoro-4-hydroxybenzaldehyde gave an identical product, m. p. and mixed m. p. 111°. The identical phenylhydrazones crystallised from glacial acetic acid in deep purple needles, m. p. 166°; brown-red, turning yellow on standing (Found : Br, 22·4, 22·3. Calc. : Br, 22·6%), the *p*-nitrophenylhydrazones in orange-pink micro-needles, m. p. 256° (decomp.); purple-red (Found : Br, 20·1, 20·2. Calc. : Br, 20·0%), and the semicarbazones from alcohol in pale yellow needles, m. p. 230° (Found : Br, 24·8, 25·0. Calc. : Br, 24·9%).

4-*Fluoro*-2-*methoxybenzaldehyde* is prepared by intimately mixing 4-fluoro-2-hydroxybenzaldehyde (8 g.) with potassium carbonate (10 g.) and then with xylene (40 c.c.) and, after the addition of methyl sulphate (10 c.c.), boiling the mixture under reflux for 2 hours. The product is steam-distilled until a sample of the substance in the distillate solidifies when treated with caustic alkali. The distillate is then collected separately, sodium hydroxide added, and the separated 4-fluoro-2-methoxybenzaldehyde recrystallised from light petroleum; it forms colourless needles, m. p. 53° (Found : C, 62·1; H, 4·3. $C_8H_7O_2F$ requires C, 62·4; H, 4·5%). p-*Nitrophenylhydrazone*, bright red-orange needles, m. p. 213° (Found : N, 14·6. $C_{14}H_{12}O_3N_3F$ requires N, 14·5%); it gives no colour with aqueous sodium hydroxide but a magenta with alcoholic potassium hydroxide which does not change on dilution. The *oxime* crystallises from aqueous alcohol in long colourless needles, m. p. 128° (Found : N, 8·5. $C_8H_8O_2NF$ requires N, 8·3%). The *semicarbazone* separates from alcohol in clusters of light yellow needles,

m. p. 162° (Found : N, 20·1. $C_9H_{10}O_2N_3F$ requires N, 19·9%). 4-*Fluoro-2-methoxybenzoic acid*, prepared by oxidising the aldehyde with aqueous alkaline permanganate, crystallises from water in colourless needles, m. p. 136° (Found : C, 56·2; H, 4·2. $C_8H_7O_3F$ requires C, 56·5; H, 4·1%).

2-*Fluoro-4-methoxybenzaldehyde*, prepared in the same way as its isomeride (during steam distillation it solidifies without alkali treatment), crystallises from glacial acetic acid in small colourless needles, m. p. 47° (Found : C, 62·2; H, 4·2. $C_8H_7O_2F$ requires C, 62·4; H, 4·5%). The *phenylhydrazone* crystallises from glacial acetic acid in small, light brown plates, m. p. 101° (Found : N, 11·7. $C_{14}H_{13}ON_2F$ requires N, 11·5%); no colour is given with aqueous or alcoholic caustic alkalis. p-*Nitrophenylhydrazone*, silky orange needles, m. p. 217° (Found : N, 14·7%); no colour is given with aqueous sodium hydroxide but with alcoholic potassium hydroxide a deep ruby-red is obtained which does not change on dilution. *Oxime*, colourless needles, m. p. 95° (Found : N, 8·4%). *Semicarbazone*, colourless needles, m. p. 228° (Found : N, 20·0%). 2-*Fluoro-4-methoxybenzoic acid* crystallises from water in colourless needles, m. p. 192° (Found : C, 56·3; H, 4·3%).

Demethylation of 4-*Fluoro-2-methoxybenzoic Acid.*—This is readily brought about by boiling concentrated hydriodic acid (*d* 1·7); the 4-*fluoro-2-hydroxybenzoic acid* obtained crystallises from water in colourless needles, m. p. 186° (Found : C, 53·6; H, 3·0. $C_7H_5O_3F$ requires C, 53·8; H, 3·2%).

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