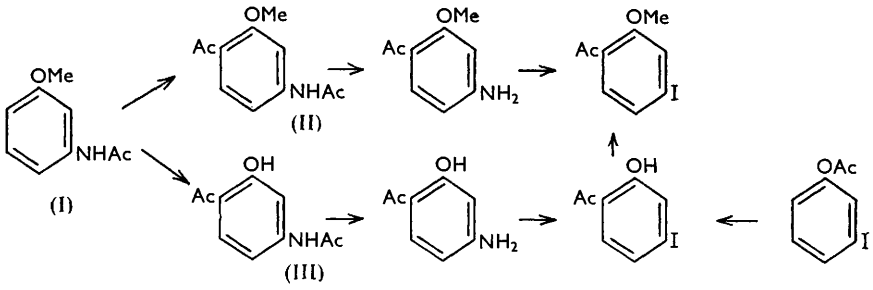
30. *Synthesis of 7-Halogenoflavone and Related Compounds.*

By F. C. Chen and C. T. Chang.

From 4-halogeno-2-hydroxyacetophenone as starting material, 7-iodo-, 7-bromo-, and 7-chloro-flavanone, -flavone, and -flavonol and the corresponding chalcones have been prepared for the first time except 7-chloroflavone. The Friedel–Crafts reaction with aceto-*m*-anisidide and the Fries rearrangement of ethyl *m*-halogenophenylacetate have been more thoroughly investigated. A convenient technique for the preparation of 4-halogeno-2-hydroxyacetophenone from *m*-halogenophenyl acetate is devised.

Our interest in the synthesis of bisflavonoids, to which class belongs the structure postulated for ginkgetin by Nakazawa[1] and assigned recently to sciadopitysin,[2] kayaflavone, sotetsuflavone, and hinokiflavone by Kariyone and his collaborators,[3] led us to investigate the halogenoflavones. Since 4-halogeno-2-hydroxyacetophenone was required for the synthesis of 7-halogenoflavones in previous papers, we described its preparation by (i) Fries rearrangement of *m*-halogenophenyl acetates[4] and (ii) diazotisation of 4-amino-2-hydroxyacetophenone, followed by the replacement of the diazonium group with a halogen atom.[5] Owing to the difference of the melting points of the 2-hydroxy-4-iodoacetophenone (53—54°) obtained by the method (i) from that of the Friedel–Crafts product (69—70°) the product (m. p. 91°), obtained by the Friedel–Crafts reaction from aceto-*m*-anisidide and its de-acetylated derivative (m. p. 122—123°) (described as 4-acetamido- and 4-amino-2-hydroxyacetophenone respectively by Gibson and Levin[6]) have been revised to the 2-methoxy-structure (cf. Julia and Baillarge[7]).



In this communication a further investigation on the Friedel–Crafts reaction on aceto-*m*-anisidide, Fries rearrangement of *m*-halogenophenyl acetate and the synthesis of 7-halogeno-flavanone, -flavone, -flavonol and corresponding chalcone have been made.

It is now found that a Friedel–Crafts reaction of aceto-*m*-anisidide (I) with acetyl chloride in carbon disulphide at *ca.* 50° afforded 4-acetamido-2-methoxy- (II) (60%) and 4-acetamido-2-hydroxy-acetophenone (III) (10%), but at *ca.* 90° gave 55% of the phenol (III) with a minute yield of the ether (II). The other reactions illustrated prove the structures.

The products (II) and (III), on being dried *in vacuo* at 60°, have m. p. 135—136° and 146—147° respectively, but the melting points are variable unless precautions are taken to remove the solvent by heat. The melting points of (II) observed by Gibson and Levin (91°) and by Julia and Baillarge (87°) may be due to the retention of solvents.

[1] Nakazawa, *J. Pharm. Soc. Japan*, 1941, **61**, 174, 228.
[2] Kariyone and Kawano, *ibid.*, 1956, **76**, 448, 451, 453, 457.
[3] Kariyone and Sawada, "Complete Publication in Memory of Prof. T. Kariyone," 1956, p. 16.
[4] Chen and Chang, *J. Taiwan Pharm. Assoc.*, 1952, **4**, 38.
[5] *Idem*, *J. Chinese Chem. Soc.*, 1954, Series II, *I*, 159.
[6] Gibson and Levin, *J.*, 1931, 2402.
[7] Julia and Baillarge, *Bull. Soc. chim. France*, 1952, 639.

Fries rearrangement of *m*-chloro-, *m*-bromo-, and *m*-iodo-phenyl acetate gave the 4-halogeno-2-hydroxyacetophenones, usually in good yield. The products and their methyl ethers were identical with the compounds prepared by Friedel–Crafts reactions.

By condensation with benzaldehyde 4-halogeno-2-hydroxyacetophenones gave the halogenochalcones, which underwent ring closure to 7-halogenoflavanones. These were dehydrogenated by *N*-bromosuccinimide,[8] yielding 7-halogenoflavones [4] which were also obtained by the action of selenium dioxide in pentyl alcohol on the corresponding chalcones, according to Venkataraman's method.[9] Algar–Flynn oxidation [10] of the chalcone, or Oyamada's method [11] with hydrogen peroxide in methanolic sodium hydroxide, gave the 7-halogenoflavonols in good yield.[12] The only known compound of this class appears to be 7-chloroflavone.[13] The chloro-, bromo-, and iodo-substituted members of these various series, as well as the 4'-methoxy-compounds, have been prepared, and preparation of the fluoro-compounds is being studied.

Experimental

Ethanol was used for crystallisation unless otherwise stated.

Friedel–Crafts Reaction of Aceto-m-*anisidide.*—(a) *Acetylation at* 50—60°. To an ice-cooled solution of aceto-*m*-anisidide (3 g.) and acetyl chloride (3·5 g.) in dry carbon disulphide (10 c.c.) was added anhydrous aluminium chloride (9 g.) in portions, with stirring, during about 10 min. The mixture was stirred at room temperature for 30 min., then heated at 50—60° for 1·5 hr. After decomposition with ice-water the yellow product was collected and extracted with 10% aqueous potassium hydroxide. The alkali-insoluble product was washed with cold benzene (to remove oil) and crystallised from 30% aqueous alcohol (charcoal) as colourless needles (2·1 g.) of 4-acetamido-2-methoxyacetophenone dihydrate, shrinking at *ca.* 80° and melting at 132°. When dried previously at 50—60°/1 mm. it melted consistently at 135—136° (lit., 91°,[6] 87° [7]) (Found: C, 63·5; H, 6·5; N, 6·8. Calc. for $C_{11}H_{13}O_3N$: C, 63·7; H, 6·3; N, 6·8. Found: loss at 60° *in vacuo*, 14·8. Calc. for $C_{11}H_{13}O_3N,2H_2O$: loss, 14·9%).

The alkali-soluble portion obtained in the above separation, on acidification with acetic acid, gave 4-acetamido-2-hydroxyacetophenone monohydrate, which formed colourless needles from 30% aqueous alcohol. It melted partially at *ca.* 105°, but did not clear till 110°, resolidified at 117°, and remelted at 141—142°. When dried previously or rapidly crystallised from anhydrous benzene it gave colourless crystals (0·4 g.), m. p. 146—147° (lit., 142°,[14] 142—144° [15]) (Found: C, 62·0; H, 5·9; N, 7·3. Calc. for $C_{10}H_{11}O_3N$: C, 62·2; H, 5·7; N, 7·2. Found: loss at 60°/1 mm.: 8·8. Calc. for $C_{10}H_{11}O_3N,H_2O$: loss, 8·9%).

(b) *Acetylation at* 80—90°. To a solution of aceto-*m*-anisidide (8 g.) and acetyl chloride (10 c.c.) in dry carbon disulphide (25 c.c.), aluminium chloride (24 g.) was added in small portions with stirring, and the mixture kept at 80—90° for 1·5 hr. The product was worked up as described above. It consisted mainly of alkali-soluble 4-acetamido-2-hydroxyacetophenone (5·1 g.), with only a minute yield of 4-acetamido-2-methoxyacetophenone.

4-Acetamido-2-methoxyacetophenone (2 g.) was boiled with 15% hydrochloric acid (4 c.c.) for 20 min. Neutralisation with aqueous ammonia afforded 4-amino-2-methoxyacetophenone (1·2 g.), needles, m. p. 121—122° (lit.,[7] 122—123°) (Found: C, 65·4; H, 6·8; N, 8·6; OMe, 19·0. Calc. for $C_9H_{11}O_2N$: C, 65·5; H, 6·6; N, 8·5; 1OMe, 18·9%).

4-*Amino*-2-*hydroxyacetophenone.*—4-Acetamido-2-hydroxyacetophenone (4 g.) was boiled with 15% hydrochloric acid (7 c.c.) for 15 min., as described above, giving 4-amino-2-hydroxyacetophenone (2·7 g.), lemon-yellow needles, m. p. 129—130° (lit.,[7] 130°) (Found: C, 63·8; H, 6·1; N, 9·5. Calc. for $C_8H_9O_2N$: C, 63·6; H, 5·9; N, 9·3%).

4-*Iodo*-2-*methoxyacetophenone.*—4-Amino-2-methoxyacetophenone (0·5 g.) in water (10 c.c.) and concentrated sulphuric acid (1 c.c.; *d* 1·82) was diazotised at 0° with sodium nitrite (0·3 g.)

[8] Chen, *J. Taiwan Pharm. Assoc.*, 1951, **3**, 9.
[9] Mahal, Rai, and Venkataraman, *J.*, 1935, 866; 1936, 569.
[10] Algar and Flynn, *Proc. Roy. Irish Acad.*, 1934, *B*, **42**, 1.
[11] Oyamada, *J. Chem. Soc. Japan*, 1934, **55**, 1256.
[12] Chen and Shu, *J. Taiwan Pharm. Assoc.*, 1953, **5**, 49.
[13] Cramer and Elschnig, *Chem. Ber.*, 1956, **89**, 1.
[14] Bapat and Venkataraman, *Proc. Indian Acad. Sci.*, 1955, **49**, *A*, 336.
[15] Feldman and Simeonov, *Zhur. obshchei Khim.*, 1953, **23**, 2043.

in water (1 c.c.) during 5 min. After a further 10 minutes' stirring, potassium iodide (0·7 g.) in water (2 c.c.) and copper bronze (0·05 g.) were added. Then the temperature was slowly raised and kept at 75—80° until no more nitrogen was evolved. The resulting mixture was cooled and extracted with chloroform. The chloroform layer was washed with water and steam-distilled. After the chloroform a slightly reddish product was obtained from the distillate, this was decolorised by sodium thiosulphate solution, giving colourless needles (0·45 g.) of the *iodo-compound*, m. p. 69—70° (Found: C, 39·3; H, 3·5; I, 47·8; OMe, 11·0. $C_9H_9O_2I$ requires C, 39·1; H, 3·3; I 46·0; 1OMe, 11·2%).

2-Hydroxy-4-iodoacetophenone.—4-Amino-2-hydroxyacetophenone (0·5 g.), treated as above, yielded *2-hydroxy-4-iodoacetophenone* (0·4 g.), needles, m. p. 53—54° (Found: C, 36·5; H, 2·9; I 50·2. $C_8H_7O_2I$ requires C, 36·5; H, 2·7; I, 48·4%).

Fries Rearrangement of m-*Halogenophenyl Acetates.*—(1) *2-Hydroxy-4-iodoacetophenone*: (*a*) In chlorobenzene. To *m*-iodophenyl acetate (10·5 g.) in redistilled chlorobenzene (52 c.c.) anhydrous aluminium chloride (7 g.) was added quickly. The mixture was stirred and kept at 125—135° for 4·5 hr. The mixture was cooled and the complex decomposed by ice-water and then made alkaline with 10% aqueous sodium hydroxide. The solution was steam-distilled, then made slightly acidic with hydrochloric acid, and steam-distilled again. The product from the distillate crystallised in colourless prisms (6·8 g., 64%), m. p. 53—54°, identical with the product from the Friedel–Crafts reaction.

(*b*) In nitrobenzene. *m*-Iodophenyl acetate (13 g.) and anhydrous aluminium chloride (6 g.) in nitrobenzene (100 c.c.) were treated at 140° for 4 hr., then decomposed with ice-water and dilute hydrochloric acid. The mixture was washed with water and extracted with 10% aqueous potassium hydroxide. The extract was slightly acidified and steam-distilled. The colourless product from the distillate crystallised in prisms (5·5 g., 42%), m. p. 53—54°.

This phenol (0·1 g.), anhydrous potassium carbonate (0·1 g.), and excess of methyl iodide (0·8 g.) in acetone (2 c.c.) were refluxed for 8 hr. The excess of methyl iodide and acetone was distilled off and the residue washed with 5% aqueous potassium hydroxide and with water. Crystallisation gave needles (0·08 g.), m. p. 69—70°, alone or mixed with a specimen obtained from the Friedel–Crafts reaction.

(2) *4-Bromo-2-hydroxyacetophenone.* *m*-Bromophenyl acetate (29 g.) and aluminium chloride (60 g.), heated at 170° for 3 hr., then decomposed with dilute hydrochloric acid and steam-distilled, gave the *ketone* (25·5 g.), m. p. 42—43° (Found: C, 44·6; H, 3·4; Br, 37·0. $C_8H_7O_2Br$ requires C, 44·8; H, 3·2; Br, 37·2%).

(3) *4-Chloro-2-hydroxyacetophenone.* *m*-Chlorophenyl acetate (6·8 g.) and aluminium chloride (12·7 g.) were heated at 175—180° for 1·5 hr. The mixture was treated with hydrochloric acid and steam-distilled. The distillate was extracted with chloroform, and the combined extracts were re-extracted with 10% aqueous potassium hydroxide. Then the combined aqueous alkaline solution was washed with chloroform, acidified, and extracted with chloroform again. Removing solvent gave a pale orange liquid which was dried in a desiccator and purified by vacuum-distillation, giving a colourless oil (5·8 g., 85%), b. p. 121—124/15 mm. (lit.,[13] 126°/16 mm.).

Synthesis of 4'-Halogeno-2'-hydroxychalcones.—*2'-Hydroxy-4'-iodochalcone.* To a cooled mixture of 2-hydroxy-4-iodoacetophenone (1 g.) and benzaldehyde (0·8 g.) in alcohol (12 c.c.) was added cold 60% aqueous potassium hydroxide (11 c.c.). The mixture was securely stoppered and kept at 0° for 2 days with occasional shaking. The mixture was diluted with water and acidified with dilute hydrochloric acid. The precipitated *chalcone* was collected and crystallised, giving yellow needles (1·1 g.), m. p. 112—113° (Found: C, 51·2; H, 3·3; I, 37·5. $C_{15}H_{11}O_2I$ requires C, 51·4; H, 3·1; I, 36·2%).

Similarly were prepared *4'-bromo-2'-hydroxychalcone*, needles (87%), m. p. 115—116° (Found: C, 59·8; H, 3·8; Br, 26·1. $C_{15}H_{11}O_2Br$ requires C, 59·4; H, 3·6; Br, 26·3%), *4'-chloro-2'-hydroxychalcone*, needles (77%), m. p. 124—125° (Found: C, 69·4; H, 4·4; Cl, 13·9. $C_{15}H_{11}O_2Cl$ requires C, 69·6; H, 4·2; Cl, 13·7%), *2'-hydroxy-4'-iodo-4-methoxychalcone*, needles (73%), m. p. 161—162° (Found: C, 50·3; H, 3·6; I, 34·7; OMe, 7·9. $C_{16}H_{13}O_3I$ requires C, 50·5; H, 3·4; I, 33·4; OMe, 8·1%), *4'-bromo-2'-hydroxy-4-methoxychalcone*, needles (84%), m. p. 136—137° (Found: C, 57·3; H, 4·2; Br, 24·4; OMe, 9·0. $C_{16}H_{13}O_3Br$ requires C, 57·6; H, 3·9; Br, 24·0; OMe, 9·3%), and *4'-chloro-2'-hydroxy-4-methoxychalcone*, orange needles (80%), m. p. 136—137° (Found: C, 66·2; H, 4·8; Cl, 12·5; OMe, 10·4. $C_{16}H_{13}O_3Cl$ requires C, 66·5; H, 4·5; Cl, 12·3; OMe, 10·7%).

Syntheses of 7-Halogenoflavanones.—(1) *7-Iodoflavanone.* A solution of 2′-hydroxy-4′-iodochalcone (1 g.) and phosphoric acid (*d* 1·75; 4·5 c.c.) in alcohol (150 c.c.) was refluxed for 48 hr. Concentration the solution (to 50 c.c.) gave colourless needles (0·5 g.), m. p. 114—115° (Found: C, 51·1; H, 3·4; I, 37·6. $C_{15}H_{11}O_2I$ requires C, 51·4; H, 3·1; I, 36·2%).

(2) *7-Bromoflavanone.* A solution of 4′-bromo-2′-hydroxychalcone (2·5 g.) and phosphoric acid (*d* 1·75; 10 c.c.) in alcohol (375 c.c.) was refluxed for 72 hr. The solution was concentrated to about 70 c.c. and cooled. Unchanged chalcone was then precipitated and decanted. The *flavanone* crystallised as colourless needles (1 g.), m. p. 79—80° (Found: C, 59·1; H, 3·9; Br, 26·7. $C_{15}H_{11}O_2Br$ requires C, 59·4; H, 3·6; Br, 26·3%).

(3) *7-Chloroflavanone.* To 4′-chloro-2′-hydroxychalcone (1·5 g.) in alcohol (150 c.c.) phosphoric acid (*d* 1·75; 6·5 c.c.) was added. The mixture was refluxed for 72 hr., then after concentration gave the *flavanone* as needles, m. p. 54—55·5° (Found: C, 69·3; H, 4·6; Cl, 13·9. $C_{15}H_{11}O_2Cl$ requires C, 69·6; H, 4·3; Cl, 13·7%).

(4) *7-Iodo-4′-methoxyflavanone.* 2′-Hydroxy-4′-iodo-4-methoxychalcone (1 g.) and phosphoric acid (*d* 1·75; 4·5 c.c.) in alcohol (150 c.c.), as above, gave the *flavanone* as needles (from dioxan), m. p. 166·5—167·5° (Found: C, 50·2; H, 3·6; I, 34·4; OMe, 8·0. $C_{16}H_{13}O_3I$ requires C, 50·5; H, 3·4; I, 33·4; OMe, 8·1%).

(5) *7-Bromo-4′-methoxyflavone,* prepared from 4′-bromo-2′-hydroxy-4-methoxychalcone as above, formed needles, m. p. 130—130·5° (Found: C, 57·4; H, 4·1; Br, 22·5; OMe, 9·1. $C_{16}H_{13}O_3Br$ requires C, 57·7; H, 3·9; Br, 23·9; OMe, 9·3%.

Synthesis of 7-Halogenoflavones.—(1) *7-Iodoflavone.* (*a*) With selenium dioxide. A mixture of 2′-hydroxy-4′-iodochalcone (1 g.), selenium dioxide (1 g.), and pentyl alcohol (14 c.c.) was refluxed for 10 hr. The precipitated selenium was then filtered off and washed with hot ethanol, and the filtrate was subjected to steam-distillation. After the removal of pentyl alcohol, the solid *flavone* was collected and crystallised from 75% aqueous dioxan, giving colourless needles (0·6 g.), m. p. 167—168° (Found: C, 51·5; H, 2·8; I, 37·5. $C_{15}H_9O_2I$ requires C, 51·7; H, 2·6; I, 36·4%).

(*b*) With *N*-bromosuccinimide. 7-Iodoflavanone (0·1 g.) and *N*-bromosuccinimide (0·07 g.) in carbon tetrachloride (10 c.c.) were refluxed for 1 hr., during which a transient red colour appeared, then faded. After cooling, the mixture was filtered, the filtrate evaporated, and the residual product crystallised, to give 7-iodoflavone (70 mg.), m. p. 168—169°, identical with the preceding product.

(2) *7-Bromoflavone.* Reactions as in (*a*) or (*b*) above gave this *flavone* which crystallised from alcohol and finally from dioxan, as needles, m. p. 167—168° (Found: C, 59·5; H, 3·3; Br, 26·9. $C_{15}H_9O_2Br$ requires C, 59·8; H, 3·0; Br, 26·5%) [(*a*) 1·94 g. from 3·0 g., (*b*) 55 mg. from 0·12 g.

(3) *7-Chloroflavone.* 4′-Chloro-2′-hydroxychalcone (1·6 g.), selenium dioxide (1·5 g.), and pentyl alcohol (23 c.c.) were treated, as above, giving colourless needles (0·73 g.), m. p. 156—157° (lit.,[13] 158°) (Found: C, 69·7; H, 3·7; Cl, 13·5. Calc. for $C_{15}H_9O_2Cl$: C, 70·1; H, 3·5; Cl, 13·8%).

(4) *7-Bromo-4′-methoxyflavone* was prepared from 4′-bromo-2′-hydroxy-4-methoxychalcone (2 g.), selenium dioxide (2 g.), and pentyl alcohol (35 c.c.), as needles (0·9 g.), m. p. 184—185° (Found: C, 58·4; H, 3·7; Br, 23·8; OMe, 9·8. $C_{16}H_{11}O_3Br$ requires C, 58·0; H, 3·3; Br, 24·1; OMe, 9·5%).

(5) *7-Chloro-4′-methoxyflavone,* prepared from 4′-chloro-2′-hydroxy-4-methoxychalcone (1 g.), selenium dioxide (1 g.), and pentyl alcohol (14 c.c.), formed needles (0·5 g.), m. p. 190·5—191·5° (Found: C, 66·6; H, 4·3; Cl, 12·5; OMe, 11·3. $C_{16}H_{11}O_3Cl$ requires C, 67·0; H, 3·9; Cl, 12·3; OMe, 10·8%).

(6) *7-Iodo-4′-methoxyflavone,* from 2′-hydroxy-4′-iodo-4-methoxychalcone (1 g.), selenium dioxide (1 g.), and pentyl alcohol (14 c.c.), formed needles (0·2 g.), m. p. 205—206° (Found: C, 50·5; H, 3·2; I, 32·2; OMe, 8·5. $C_{16}H_{11}O_3I$ requires C, 50·8; H, 2·9; I, 33·6; OMe, 8·2%).

Synthesis of 7-Halogenoflavonols.—*7-Iodoflavonol.* 2′-Hydroxy-4′-iodochalcone (0·5 g.) was added to a mixture of methanol (15 c.c.) and 16% aqueous sodium hydroxide (2 c.c.). To the resulting solution was added dropwise 15% hydrogen peroxide (2 c.c.) with stirring and ice-cooling. After 24 hr. in a refrigerator, it was filtered and acidified with dilute hydrochloric acid, to give pale yellow prisms (0·35 g.), m. p. 188·5—189·5° (Found: C, 49·1; H, 2·9; I, 36·0. $C_{15}H_9O_3I$ requires C, 49·5; H, 2·5; I, 34·9%).

Similar reactions gave *7-bromoflavonol,* needles, m. p. 178—179° (Found: C, 56·4; H, 3·3;

Br, 25·5. $C_{15}H_9O_3Br$ requires C, 56·8; H, 2·9; Br, 25·2%), *7-chloroflavonol*, yellow prisms (84%), m. p. 180·5—181·5° (Found: C, 65·4; H, 3·6; Cl, 13·5. $C_{15}H_9O_3Cl$ requires C, 66·1; H, 3·3; Cl, 13·0%), *7-chloro-4'-methoxyflavonol*, pale yellow needles (82%), m. p. 192—193° (Found: C, 63·1; H, 3·6; I, 12·9; OMe, 10·6. $C_{16}H_{11}O_4Cl$ requires C, 63·5; H, 3·4; I, 11·7; OMe, 10·2%), *7-bromo-4'-methoxyflavonal*, as pale yellow needles, m.p. 193—194° (Found: C, 55·1; H, 3·5; Br, 22·8; OMe, 8·7. $C_{16}H_{11}O_4Br$ requires C, 55·3; H, 3·2; Br, 23·0; OMe, 8·9%), and *7-iodo-4'-methoxyflavonol*, as yellow needles, m. p. 206—207° (Found: C, 48·4; H, 3·0; I, 33·3; OMe, 8·2. $C_{16}H_{11}O_4I$ requires C, 48·8; H, 2·8; I, 32·2; OMe, 7·9%).

The authors thank Professor T. S. Wheeler for reading the manuscript, Professors S. Hattori and E. Sebe for microanalytical data, which were carried out at the laboratory of Microanalysis, University of Tokyo and University of Kumamoto, President S. L. Chein and Professor E. Sebe for helpful advice and encouragement, and Miss M. Hung, Miss L. S. Wang, and Mr. Y. C. Lin for their co-operation in carrying out the experiments.

National Taiwan University, Taipei, Formosa. [*Received, August 9th*, 1957.]