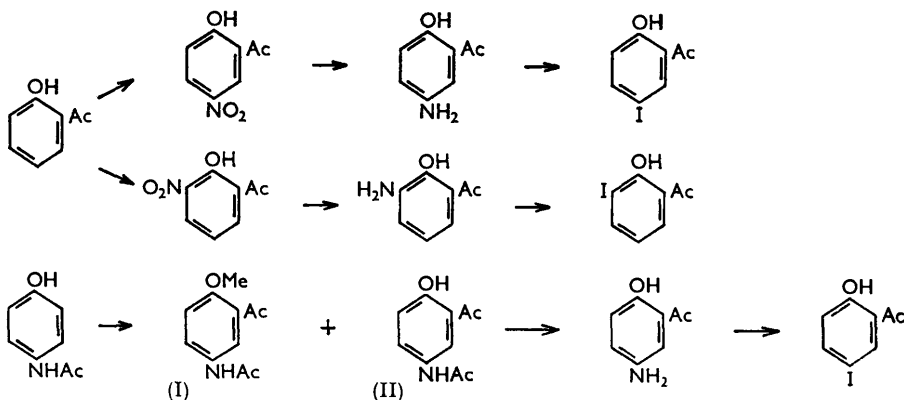


664. Synthesis of 6-Halogenoflavones and Related Compounds.

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Preparation of several new 6-halogeno-flavones, -flavanones, and -flavonols, and corresponding chalcones is described. The nitration of *o*-hydroxyacetophenone and the Friedel-Crafts reaction of *N*-acetyl-*p*-anisidine, expected to yield the acetophenone required as the starting material for the synthesis of 6-iodo-compounds, have been investigated.

IN continuation of previous studies on the halogenoflavones,¹ further compounds were synthesized several years ago.²⁻⁵ 6-Fluoro,⁶ 6-chloro,⁷ and 6-bromo-flavone⁸ were prepared in good yield in the usual way from 2-hydroxy-5-halogenoacetophenones which were obtained by Fries rearrangement of *p*-halogenophenyl acetates. However, later, in this Laboratory,⁴ attempts to prepare 2-hydroxy-5-iodoacetophenone by this method gave mainly 2,4-di-iodophenol.⁹ The iodoacetophenones have now been obtained by the two routes shown in the charts.



¹ Chen and Chang, *J.*, 1958, 146.

² F. Chen, D.Sc. Dissertation, 1949, Tôhoku Univ., Sendai, Japan; Chen and Yang, *J. Taiwan Pharm. Assoc.*, 1951, **3**, 39.

³ Chen and Chang, *J. Formosan Sci.*, 1954, **8**, 74; Chen and Shu, *J. Taiwan Pharm. Assoc.*, 1953, **5**, 49.

⁴ T. S. Chen, B.Sc. Thesis, 1956, Nat. Taiwan Univ., Formosa.

⁵ Chen, Chang, and Chen, *J. Formosan Sci.*, 1958, **12**, 151; 1959, **13**, 94.

⁶ Chen, Chang, Hsu, and Lin, *J. Formosan Sci.*, 1954, **8**, 23.

⁷ Chen and Hsu, *J. Formosan Sci.*, 1953, **7**, 51.

⁸ Chen, Lai, and Hsieh, *J. Formosan Sci.*, 1953, **7**, 57.

⁹ Chang and Chen, *J. Chinese Chem. Soc.*, Series II, 1960, **7**, 69.

The Friedel-Crafts reaction of *N*-acetyl-*p*-anisidine with acetyl chloride in carbon disulphide at 25° afforded 83% of 2-methoxy-5- (I) and only 4% of 2-hydroxy-5-acetamidoacetophenone (II), but at 90° these proportions were reversed.

The 2-hydroxy-5-halogenoacetophenones condensed smoothly with benzaldehyde or *p*-anisaldehyde in presence of alcoholic alkali, giving chalcones, which were cyclized in phosphoric acid to 6-halogenoflavanones. These were easily dehydrogenated by *N*-bromosuccinimide to 6-halogenoflavones, which were also obtained by direct oxidation of the chalcones by selenium dioxide in pentyl alcohol.¹⁰ The 6-halogenoflavonols^{3b} were prepared in good yield by cold alkaline hydrogen peroxide.^{11,12} When this present work was complete,^{5,13} we noted the synthesis of 6-iodoflavone and related compounds in other laboratories.¹⁴

EXPERIMENTAL

M. p.s were determined in capillary tubes and are uncorrected. Ethanol was used for crystallisation otherwise stated. Microanalyses were made by Mr. E. Aoyagi, Miike Branch, Mitsui Chemical Laboratory, Ohmuda, Japan.

2-Hydroxy-5-fluoro-, -chloro-, and -bromo-acetophenone.—*p*-Fluoro-, *p*-chloro-, and *p*-bromophenyl acetates were treated with anhydrous aluminium chloride, yielding colourless acetophenones as shown in Table 1.

2-Hydroxy-5-iodoacetophenone.—*Method I.* Nitration of *o*-hydroxyacetophenone by the procedure of Allan and Loudon¹⁵ gave steam-volatile 2-hydroxy-5-nitroacetophenone, m. p.

TABLE 1. *Fries rearrangement of p-halogenophenyl acetates to 2-hydroxy-5-halogenoacetophenones.*

| <i>p</i> -Halogeno-phenyl acetate | AlCl ₃ (g.) | Temp. | Time (hr.) | Product | |
|-----------------------------------|------------------------|-------|------------|-----------|---|
| | | | | Yield (%) | M. p. (lit.) |
| F 30 g. | 45 | 150° | 1 | 88 | 57—58 (62%, 56—56.5° ^a) |
| Cl 30 g. | 45 | 120 | 1 | 70 | 53—54 (52—54%, ^b 54, ^c 55, ^d 57 ^e) |
| Br 30 g. | 45 | 110 | 1 | 50 | 59—60 (57%, ^f 61—62 ^g) |

^a Suter, Lawson, and Smith, *J. Amer. Chem. Soc.*, 1939, **61**, 161. ^b Karrer, Yen, and Reichstein, *Helv. Chim. Acta*, 1930, **13**, 1315. ^c Claus, D.R.-P. 96,659. ^d Auwers and Wittig, *Ber.*, 1924, **57**, 1275. ^e Nencki and Stoeber, *ibid.*, 1897, **30**, 1768. ^f Klarmann, Gates, Shternov, and Cox, *J. Amer. Chem. Soc.*, 1933, **55**, 4657. ^g Feuerstein and Kostanecki, *Ber.*, 1898, **31**, 716, 2953.

TABLE 2. *2'-Hydroxy-5'-halogenochalcones and the 4-methoxy-compounds.*

| 2'-Hydroxy-chalcone * | M. p. | Yield (%) | Found (%) | | | Formula | Required (%) | | |
|-----------------------|------------------------|-----------|-----------|------|------|--|--------------|-----|------|
| | | | C | H | Hal | | C | H | Hal |
| 5'-F | 103—104° | 83 | 74.15 | 4.89 | — | C ₁₅ H ₁₁ FO ₂ | 74.4 | 4.6 | 7.9 |
| 5'-Cl | 111—112 ^h | 90 | — | — | 13.8 | C ₁₅ H ₁₁ ClO ₂ | 69.6 | 4.3 | 13.7 |
| 5'-Br | 109.5—110 ⁱ | 92 | 59.4 | 3.8 | 26.4 | C ₁₅ H ₁₁ BrO ₂ | 59.4 | 3.7 | 26.4 |
| 5'-I | 107—108 ^j | 86 | 51.2 | 3.3 | 35.5 | C ₁₅ H ₁₁ IO ₂ | 51.5 | 3.2 | 36.2 |
| 5-F-4-MeO | 125—126 | 74 | 77.15 | 4.9 | — | C ₁₆ H ₁₃ FO ₃ | 70.6 | 4.8 | 7.0 |
| 5'-Cl-4-MeO | 111—112 | 71 | 66.2 | 4.9 | 12.1 | C ₁₆ H ₁₃ ClO ₃ | 66.6 | 4.5 | 12.3 |
| 5'-Br-4-MeO | 115—116 | 90 | 57.55 | 4.1 | 23.8 | C ₁₆ H ₁₃ BrO ₃ | 57.7 | 3.9 | 24.0 |
| 5'-I-4-MeO | 130 | 70 | 50.45 | 3.75 | 33.6 | C ₁₆ H ₁₃ IO ₃ | 50.6 | 3.5 | 33.4 |

* All yellow needles. ^h Ref. *b* of Table I gives m. p. 108°; Kinckell (*Ber.*, 1911, **44**, 3654) gives m. p. 109—110°. ⁱ Kostanecki and Ludwig (*Ber.*, 1898, **31**, 2951) give m. p. 107—108°. ^j Lit.,¹⁴ m. p. 138°.

101—102° (29%) (lit.,¹⁵ 98—99°, 19%), and involatile 2-hydroxy-3-nitroacetophenone, m. p. 84—84.5° (1.9%) (lit.,¹⁵ 82—83°, 1.9%), which were reduced with stannous chloride and hydrochloric acid, yielding 5-amino-2-, m. p. 112—113° (Found: C, 63.0; H, 6.4; N, 9.1. C₈H₉O₂N requires C, 63.6; H, 6.0; N, 9.3%), and 3-amino-2-hydroxyacetophenone, m. p. 93—94° (Found: C,

¹⁰ Mahal, Rai, and Venkataraman, *J.*, 1935, 866; 1936, 569.

¹¹ Algar and Flynn, *Proc. Roy. Irish Acad.*, 1934, **42**, B, 1.

¹² Oyamada, *J. Chem. Soc. Japan*, 1934, **55**, 1256.

¹³ Chen, Chang, Hung, Lin, and Choong, *Proc. Chem. Soc.*, 1959, 232.

¹⁴ Mulchandani and Shah, *Chem. Ber.*, 1960, **93**, 1913.

¹⁵ Allan and Loudon, *J.*, 1949, 821.

63.2; H, 6.3; N, 9.2%), all yellow needles. Diazotisation, etc., then yielded 2-hydroxy-5-(75%), m. p. 90—91° (lit.,¹⁴ 90°) (Found: C, 37.1; H, 2.9; I, 50.1. Calc. for C₈H₇IO₂: C, 36.5; H, 2.7; I, 48.4%), and 2-hydroxy-3-iodoacetophenone (50%), m. p. 58—59° (Found: C, 36.22; H, 2.91; I, 48.2%), both as colourless needles.

Method II. (a) *Acetylation at 80—90°.* To a solution of *N*-acetyl-*p*-anisidine (20 g.) and acetyl chloride (25 c.c.) in dry carbon disulphide (50 c.c.) was added anhydrous aluminium chloride (55 g.) in portions, with stirring, and the mixture was kept at 80—90° for 1.5 hr., while

TABLE 3. *6-Halogenoflavanoncs and the 4'-methoxy-compounds.*

| Flavanone * | M. p. | Yield (%) | Found (%) | | | Formula | Required (%) | | |
|-------------------|------------------|-----------|-----------|-----|-------|--|--------------|-----|------|
| | | | C | H | Hal | | C | H | Hal |
| 6-FI | 77—78° | 70 | 74.1 | 4.9 | — | C ₁₅ H ₁₁ FO ₂ | 74.4 | 4.6 | 7.9 |
| 6-Cl-† | 96—97 | 50 | — | — | 13.9 | C ₁₅ H ₁₁ ClO ₂ | 69.6 | 4.3 | 13.7 |
| 6-Br | 118—119 | 60 | — | — | 26.4 | C ₁₅ H ₁₁ BrO ₂ | 59.4 | 3.7 | 26.4 |
| 6-I | 137 ^k | 91 | 51.5 | 3.4 | 34.9 | C ₁₅ H ₁₁ IO ₂ | 51.5 | 3.2 | 36.2 |
| 6-F-4'-MeO | 88—89 | 50 | 70.2 | 5.0 | — | C ₁₆ H ₁₃ FO ₂ | 70.6 | 4.8 | 7.0 |
| 6-Cl-4'-MeO | 106—106.5 | 45 | 66.4 | 4.7 | 12.15 | C ₁₆ H ₁₃ ClO ₂ | 66.6 | 4.5 | 12.3 |
| 6-Br-4'-MeO | 111.5—112.5 | 40 | 57.3 | 4.2 | 23.8 | C ₁₆ H ₁₃ BrO ₂ | 57.7 | 3.9 | 24.0 |
| 6-I-4'-MeO | 112 ^l | 58 | 50.4 | 3.9 | 33.2 | C ₁₆ H ₁₃ IO ₂ | 50.6 | 3.5 | 33.4 |

† Prisms; previously reported by Karrer, Yen, and Reichstein (*Helv. Chim. Acta*, 1930, **13**, 1315) who give no m. p. ^k Lit.,¹⁴ m. p. 136°. ^l Lit.,¹⁴ m. p. 101°.

TABLE 4. *6-Halogenoflavones and the 4'-methoxy-compounds.*

| Flavone * | M. p. | Yield † (%) | Found (%) | | | Formula | Required (%) | | |
|-------------------|----------------------|-----------------|-----------|-----|------|--|--------------|-----|------|
| | | | C | H | Hal | | C | H | Hal |
| 6-F | 128—129° | 53 | 74.8 | 4.0 | — | C ₁₅ H ₉ FO ₂ | 75.0 | 3.8 | 7.9 |
| 6-Cl | 182—183 ^m | 61 | — | — | 13.9 | C ₁₅ H ₉ ClO ₂ | 70.2 | 3.5 | 13.8 |
| 6-Br | 189—190 ⁿ | 42 | — | — | 26.5 | C ₁₅ H ₉ BrO ₂ | 59.8 | 3.0 | 26.5 |
| 6-I | 190—191 ^o | 74 ^p | 51.7 | 2.9 | 36.4 | C ₁₅ H ₉ IO ₂ | 51.8 | 2.6 | 36.5 |
| 6-F-4'-MeO | 159—160 | 50 | 70.6 | 4.8 | — | C ₁₆ H ₁₁ FO ₂ | 71.1 | 4.1 | 7.0 |
| 6-Cl-4'-MeO | 180—181 | 77 | 66.9 | 4.1 | 12.3 | C ₁₆ H ₁₁ ClO ₂ | 67.0 | 3.9 | 12.4 |
| 6-Br-4'-MeO | 192—193 | 76 | 57.9 | 3.7 | 23.9 | C ₁₆ H ₁₁ BrO ₂ | 58.0 | 3.4 | 24.1 |
| 6-I-4'-MeO | 183 | 71 | 50.7 | 3.2 | 33.3 | C ₁₆ H ₁₁ IO ₂ | 50.8 | 2.9 | 33.6 |

* Colourless needles. ^m Wittig, Bangert, and Richter (*Annalen*, 1925, **446**, 155) give m. p. 181°; Ruheman (*Ber.*, 1921, **54**, 912) gives m. p. 183—184°. ⁿ Ref. *i* of Table 2 gives m. p. 189—190°; Bhagwat and Wheeler (*J.*, 1939, 96) give m. p. 192—193°. ^o Lit.,¹⁴ m. p. 184°. ^p Lit.,¹⁴ m. p. 167°. [†] All obtained by the selenium dioxide method; the last compound was also prepared in 55% yield by the *N*-bromosuccinimide method.

carbon disulphide was distilled off. After decomposition with ice-water, the product was collected and extracted with 5% aqueous sodium hydroxide. After acidification of the alkaline solution with hydrochloric acid, the precipitated 5-acetamido-2-hydroxyacetophenone (II) was collected and crystallised as pale yellowish crystals (19.2 g., 82%), m. p. 167—168° (lit.,¹⁶ 165°).

The alkali-insoluble product was recrystallised, giving 5-acetamido-2-methoxyacetophenone (0.7 g., 3%), m. p. 189—190° (lit.,¹⁶ 186—188°).

(b) *Acetylation at 25°.* *N*-Acetyl-*p*-anisidine (20 g.) was treated as above but at 20—25° for 12 hr., then worked up as above, yielding 5-acetamido-2-hydroxyacetophenone (I) (1 g., 4%) and 5-acetamido-2-methoxyacetophenone (II) (20.5 g., 83%).

5-Acetamido-2-methoxyacetophenone (II, 5 g.), anhydrous aluminium chloride (5 g.), and chlorobenzene (25 c.c.) were boiled for 1 hr., then decomposed with ice-water. The chlorobenzene was steam-distilled off, and the precipitate was collected and extracted with 10% aqueous sodium hydroxide. The precipitate formed from the alkaline solution on acidification was collected and crystallised, giving 5-acetamido-2-hydroxyacetophenone (II) (4.3 g., 90%).

5-Amino-2-hydroxyacetophenone.—5-Acetamido-2-hydroxyacetophenone (II) (20 g.) was boiled with 15% hydrochloric acid (25 c.c.) for 40 min., then neutralized with aqueous ammonia and crystallized from 10% ethanol, affording *5-amino-2-hydroxyacetophenone* (13.2 g., 84%), yellow needles, m. p. 112—113° (Found: C, 63.0; H, 6.4; N, 9.1. C₈H₉O₂N requires C, 63.6; H, 6.0; N, 9.3%); its hydrochloride formed colourless plates, m. p. 230—240° (decomp.) (lit.,¹⁴ 118°).

¹⁶ Mathieson and Newberry, *J.*, 1949, 1135.

2-Hydroxy-5-iodoacetophenone.—5-Amino-2-hydroxyacetophenone (5 g.) and ice (20 g.) in 18N-sulphuric acid (18 c.c.) were treated with sodium nitrite (2.4 g.) in water (4 c.c.). When diazotization was complete, more concentrated sulphuric acid (3 c.c.), copper powder (0.1 g.), and potassium iodide (6.3 g.) in water (10 c.c.) were added. Then the temperature was slowly

TABLE 5. 6-Halogenoflavonols and the 4'-methoxy-compounds.*

| Flavonol † | M. p. | Found (%) | | | Formula | Required (%) | | | Acetate, m. p. |
|-------------------|----------------------|-----------|------|------|--|--------------|-----|------|-------------------|
| | | C | H | Hal | | C | H | Hal | |
| 6-F | 163—165° | 70.1 | 3.75 | — | C ₁₅ H ₉ FO ₃ | 70.3 | 3.5 | 7.4 | |
| 6-Cl | 162—163 ^r | 66.0 | 3.55 | 12.8 | C ₁₅ H ₉ ClO ₃ | 66.1 | 3.3 | 13.0 | |
| 6-Br | 183—184 | 56.7 | 3.1 | 25.0 | C ₁₅ H ₉ BrO ₃ | 56.8 | 2.9 | 25.2 | 143—144° |
| 6-I | 191—192 ^s | 49.3 | 2.9 | 34.5 | C ₁₅ H ₉ IO ₃ | 49.5 | 2.5 | 34.9 | 175—176 |
| 6-F-4'-MeO | 207—208 | 66.9 | 4.25 | — | C ₁₆ H ₁₁ FO ₄ | 67.1 | 3.9 | 6.6 | |
| 6-Cl-4'-MeO | 205—206 | 63.3 | 3.9 | 11.4 | C ₁₆ H ₁₁ ClO ₄ | 63.5 | 3.7 | 11.7 | 160—161 |
| 6-Br-4'-MeO | 193—194 | 55.2 | 3.5 | 22.7 | C ₁₆ H ₁₁ BrO ₄ | 55.4 | 3.2 | 23.0 | |
| 6-I-4'-MeO | 179—180 ^t | 48.7 | 3.0 | 32.0 | C ₁₆ H ₁₁ IO ₄ | 48.8 | 2.8 | 32.2 | 187—188 |

* Preliminary reports; Chen and Shu, *J. Taiwan Pharm. Assoc.*, 1953, **5**, 49. † Yellow needles.
^r Minton and Stephen (*J.*, 1922, **121**, 1598) give m. p. 163°. ^s Lit.,¹⁴ m. p. 194°. ^t Lit.,¹⁴ m. p. 186°.

raised and kept at 65° until no more nitrogen was evolved. Steam-distillation and recrystallization yielded 2-hydroxy-5-iodoacetophenone (7 g., 80%) as colourless needles, m. p. 91—92°, identical with the product obtained by method I.

The 6-halogeno-flavones, -flavanones, -flavonols, and corresponding chalcones were prepared as described in a previous paper,¹ and are listed in Tables 2—5.

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