1004. *Halogenation of Flavanones Related to Phloroglucinol.*

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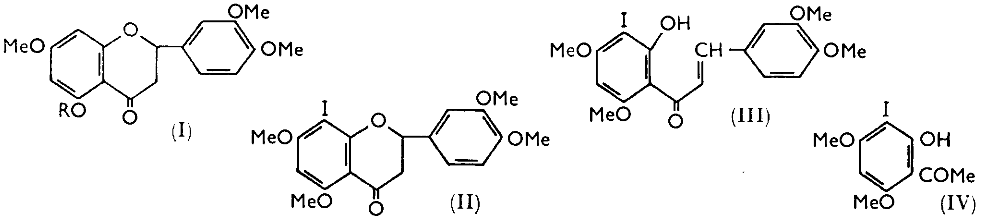
Iodination and bromination of 5,7,3′,4′-tetramethoxyflavanone gives the 8-halogeno-derivative. 5-Hydroxy-7,3′,4′-trimethoxyflavanone similarly gives a 3,6(or 8)-di-iodo-derivative.

EARLIER work in this laboratory on the synthesis of flavans[1] led us to investigate the formation of flavan-3-ols. With this end in view 5,7,3′,4′-tetramethoxyflavanone (I; R = Me) was treated with iodine and silver acetate in ethanol or, preferably, chloroform. The product was the 8-iodoflavanone (II), which was converted by alkali into the chalcone (III). This compound was also synthesised from the corresponding iodoacetophenone (IV) and veratraldehyde. Chen and his collaborators[2] prepared the ketone (IV) by treating the acetophenone with iodine and iodic acid and assumed iodine to have entered the 3-position as shown. That this structure was correct was established by Nakazawa[3] by two unambiguous syntheses of a derived compound. The assignment also follows from the work of Donnelly[4] on the bromination of 2-hydroxy-4,6-dimethoxyacetophenone. Compound (II), when treated with silver acetate in acetic anhydride, formed the corresponding 2′-acetoxychalcone which was readily deacetylated to compound (III).


(I) (II) (III) (IV)

Similar halogenation of the aromatic nucleus was obtained in analogous experiments based on 5,7-dimethoxyflavanone. Further, bromination of compound (I; R = Me) afforded the corresponding 8-bromoflavanone which gave a 3-piperonylidene derivative and was linked through the bromochalcone with the known[4] bromo-analogue of compound (IV).

As shown in a preliminary communication[5] the above iodination results differ from those obtained by Seshadri and his collaborators[6] who failed to halogenate the aromatic nucleus in similar experiments. These workers observed either oxidation to the non-halogenated flavone or aurone, or formation of a 3-iodoflavanone. Since it had been found that the reaction occurred smoothly with 5-hydroxyflavanones, 5-hydroxy-7,3′,4′-trimethoxyflavanone (I; R = H) was then treated with iodine and silver acetate in ethanol and in chloroform. The compound isolated proved to be the corresponding unstable 3,6(or 8)-di-iodoflavanone which lost hydrogen iodide and formed 5-hydroxy-6(or 8)-iodo-7,3′,4′-trimethoxyflavone.

A discrepant result[7] on the iodination of compound (I; R = Me) is given in the Experimental section.

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[1] Keogh, Philbin, Ushioda, and Wheeler, *Chem. and Ind.*, 1961, 2100.

[2] Chen, Chang, and Chen, *J. Org. Chem.*, 1962, **27**, 85.

[3] Nakazawa, *Chem. and Pharm. Bull.* (*Japan*), 1962, **10**, 1032.

[4] Donnelly, *Tetrahedron Letters*, 1959, No. 19, 1.

[5] Keogh, Philbin, Ushioda, and Wheeler, *Chem. and Ind.*, 1963, 412.

[6] Narasimhachari and Seshadri, *Proc. Indian Acad. Sci.*, 1949, **30**, *A*, 151; Narasimhachari and Seshadri, *ibid.*, 1950, **32**, *A*, 17; Goel, Narasimhachari, and Seshadri, *ibid.*, 1954, **39**, *A*, 254; Mahesh and Seshadri, *ibid.*, 1955, **41**, *A*, 210; *J. Sci. Ind. Res., India*, 1955, **14**, *B*, 608.

[7] Chandorkar, Phatak, and Kulkarni, *J. Sci. Ind. Res., India*, 1962, **21**, *B*, 24.

EXPERIMENTAL

8-*Iodo*-5,7,3,',4'-*tetramethoxyflavanone* (II).—A solution of iodine (0·4 g.) in chloroform (10 ml.) was added at the b. p. to a mixture of 5,7,3',4'-tetramethoxyflavanone [8] (I; R = Me) (0·5 g.), silver acetate (1 g.), and chloroform (12 ml.), and refluxing was continued until the iodine colour had disappeared. Addition of light petroleum to the filtered solution precipitated 8-*iodo*-5,7,3',4'-*tetramethoxyflavanone* which, crystallised from chloroform–light petroleum, had m. p. 196—197° (0·4 g.) (Found: C, 48·3; H, 4·0; I, 26·9; OMe, 26·1. $C_{19}H_{19}IO_6$ requires C, 48·5; H, 4·0; I, 27·0; OMe, 26·4%). No useful result was obtained from experiments on the condensation of the iodoflavanone with piperonaldehyde. The flavanone was recovered unaltered after it had been refluxed with pyridine for 1 hr.

The iodoflavanone (0·1 g.) was heated with acetic anhydride (5 ml.) and silver acetate (0·2 g.) for 8 hr. and the filtered solution was poured on ice. The precipitate of 2'-*acetoxy*-3'-*iodo*-3,4,4',6'-*tetramethoxychalcone* crystallised from methanol in needles, m. p. 176—177° (Found: C, 49·6; H, 4·2; I, 24·8; OMe, 24·1. $C_{21}H_{21}IO_7$ requires C, 49·2; H, 4·1; I, 24·8; OMe, 24·2%). Deacetylation to 2'-*hydroxy*-3'-*iodo*-3,4,4',6'-*tetramethoxychalcone* (III) (mixed m. p. and infrared authentication; see below) (Found: C, 48·5; H, 4·1; I, 27·6; OMe, 25·9. $C_{19}H_{19}IO_6$ requires C, 48·5; H, 4·0; I, 27·0; OMe, 26·4%) was effected by aqueous-ethanolic potassium hydroxide. This chalcone, which separated from benzene in orange needles, m. p. 187—189°, and gave a green ethanolic ferric colour, was also obtained from the iodoflavanone (II) by treatment with boiling aqueous-ethanolic sodium hydroxide. An authentic sample was prepared by the condensation (standard procedure) of 2-hydroxy-3-iodo-4,6-dimethoxyacetophenone [3] (IV) with veratraldehyde. Chandorkar, Phatak, and Kulkarni [7] obtained a product, m. p. 212°, by the iodination given above and considered it to be 3-iodo-5,7,3',4'-tetramethoxyflavanone. Treatment of this compound with silver acetate–acetic anhydride, with ethanolic alkali, or with potassium acetate–acetic anhydride afforded, they stated, a substance, m. p. 198—200°, to which the structure 2'-hydroxy-α-iodo-3,4,4',6'-tetramethoxychalcone was assigned.

8-*Iodo*-5,7-*dimethoxyflavanone.*—5,7-Dimethoxyflavanone,[9] when treated with iodine and silver acetate in chloroform, gave 8-iodo-5,7-dimethoxyflavanone, m. p. 198—200° (lit.,[2] 186—188°) (needles from ethanol) (Found: C, 50·3; H, 3·7; I, 31·4; OMe, 15·3. Calc. for $C_{17}H_{15}IO_4$: C, 49·8; H, 3·7; I, 31·0; OMe, 15·2%). This compound was not affected by boiling pyridine. When refluxed for 15 min. with aqueous-ethanolic sodium hydroxide it formed 2'-hydroxy-3'-iodo-4',6'-dimethoxychalcone, m. p. 170° (lit.,[2] 184·5—185°) (orange needles from benzene) (Found: C, 49·8; H, 3·8; I, 31·8; OMe, 14·8. Calc. for $C_{17}H_{15}IO_4$: C, 49·8; H, 3·7; I, 31·0; OMe, 15·2%). An authentic sample of this compound was prepared from 2-hydroxy-3-iodo-4,6-dimethoxyacetophenone [2] (IV) and benzaldehyde and compared (mixed m. p. and infrared) with the iodochalcone of m. p. 170°.

8-*Bromo*-5,7,3',4'-*tetramethoxyflavanone.*—Bromine (0·3 g.) in carbon disulphide (3 ml.) was added dropwise to 5,7,3',4'-tetramethoxyflavanone [8] (I; R = Me) (0·5 g.) in carbon disulphide (5 ml.), and the solvent was removed. The residue, 8-*bromo*-5,7,3',4'-*tetramethoxyflavanone*, separated from methanol in needles (0·6 g.), m. p. 196—197° (Found: C, 53·4; H, 4·5; Br, 18·3. $C_{19}H_{19}BrO_6$ requires C, 53·8; H, 4·5; Br, 18·9%). It was unaffected by boiling pyridine.

A solution of the bromoflavanone (0·5 g.) and piperonaldehyde (0·6 g.) in glacial acetic acid (30 ml.) was saturated with hydrogen chloride and kept at room temperature for 4 hr. Dilution with water afforded 8-*bromo*-5,7,3',4'-*tetramethoxy*-3-*piperonylideneflavanone*, m. p. 212—214° (yellow crystals from methanol) (Found: C, 58·8; H, 4·4; Br, 14·5. $C_{27}H_{23}BrO_8$ requires C, 58·3; H, 4·1; Br, 14·4%). When refluxed with silver acetate and acetic anhydride the bromoflavanone was converted into 2'-*acetoxy*-3'-*bromo*-3,4,4',6'-*tetramethoxychalcone*, m. p. 195° (yellow needles from methanol) (Found: C, 54·0; H, 4·6; Br, 17·6; OMe, 26·5. $C_{21}H_{21}BrO_7$ requires C, 54·2; H, 4·5; Br, 17·2; OMe, 26·7%). Deacetylation by aqueous-ethanolic potassium hydroxide afforded 3'-*bromo*-2'-*hydroxy*-3,4,4',6'-*tetramethoxychalcone*, m. p. 187—188° (orange needles from benzene) (Found: C, 53·9; H, 4·5; Br, 19·2; OMe, 28·8. $C_{19}H_{19}BrO_6$ requires C, 53·9; H, 4·5; Br, 18·9; OMe, 29·3%). This compound was also obtained (mixed m. p. and infrared confirmation) from the bromoflavanone by treatment

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[8] Kostanecki, Lampe, and Tambor, *Ber.*, 1904, **37**, 1402.

[9] Kostanecki, Lampe, and Tambor, *Ber.*, 1904, **37**, 2803.

with aqueous-ethanolic sodium hydroxide and by condensation of 3-bromo-2-hydroxy-4,6-dimethoxyacetophenone [4,10] and veratraldehyde.

5-*Hydroxy*-7,3′,4′-*trimethoxyflavanone* (I; R = H).—A mixture of 5,7,3′,4′-tetramethoxyflavanone (5 g.), anhydrous aluminium chloride (32 g.), and ether (120 ml.) was refluxed for 12 hr. and poured on ice and 10% hydrochloric acid. The precipitate of 5-hydroxy-7,3′,4′-trimethoxyflavanone (1·5 g.) separated from methanol in needles, m. p. 136° (acetate, m. p. 155—156°) (lit.,[11] 136° and 155°).

The flavanone was iodinated by iodine–silver acetate in boiling ethanol or chloroform as described in the preparation of compound (II) above. Crystallisation from methanol of the solid which separated from the filtered solution afforded two compounds (A) and (B). Compound (A), 5-*hydroxy*-3,6(or 8)-*di-iodo*-7,3′,4′-*trimethoxyflavanone*, m. p. 207—210°, $\nu_{max.}$ (in KBr) 1670 cm.$^{-1}$ (C=O), separated on storage (Found: C, 37·8; H, 2·8; I, 43·6; OMe, 16·1. $C_{18}H_{16}I_2O_6$ requires C, 37·1; H, 2·7; I, 43·6; OMe, 16·0%). The compound (B), 5-*hydroxy*-6(or 8)-*iodo*-7,3′,4′-*trimethoxyflavone*, m. p. 156°, $\nu_{max.}$ (in KBr) 1632 cm.$^{-1}$ (C=O), crystallised when the mother-liquor was concentrated or when compound (A) which discoloured on storage was further crystallised (Found: C, 47·7; H, 3·9; I, 28·3; OMe, 20·2. $C_{18}H_{15}IO_6$ requires C, 47·7; H, 3·3; I, 28·1; OMe, 20·5%). This compound was recovered unchanged after it had been refluxed with pyridine for 1 hr.

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[10] Chang, Chen, and Chen, *J. Org. Chem.*, 1961, **26**, 3142.
[11] Shinoda and Sato, *J. Pharm. Soc. Japan*, 1929, **49**, 64.