[CONTRIBUTION FROM THE RESEARCH INSTITUTE OF CHEMISTRY, NATIONAL TAIWAN UNIVERSITY]

Synthesis of 8-Bromoflavone and Related Compounds[1]

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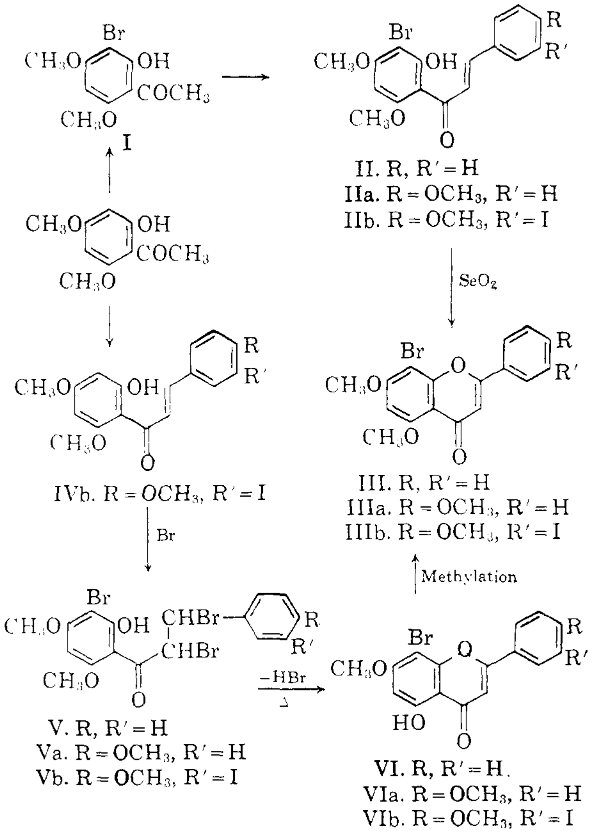
Received January 27, 1961

Synthesis of 8-bromo-5,7-dimethoxyflavone (III), 8-bromo-5,7,4′-trimethoxyflavone (IIIa), 8-bromo-5,7,4′-trimethoxy-3′-iodoflavone (IIIb), the corresponding chalcones (II, IIa, and IIb), their tribromides (V, Va, and Vb), and the acetophenone (I) is described. The products, m.p. 242° and 250°, formed from the dehydrobromination of the tribromochalcones, by heating above the melting point under pressure, reported earlier[3] as 6-bromo-5,7-dimethoxyflavone and 6-bromo-5,7,4′-trimethoxyflavone, are proved to be 8-bromo-5-hydroxy-7-methoxyflavone (VI) and 8-bromo-5-hydroxy-7,4′-dimethoxyflavone (VIa), respectively, showing that the 5-methoxy group is easily demethylated during the elimination of hydrogen bromide of the corresponding tribromochalcones (V and Va).

In a previous paper[4] from this laboratory, the synthesis of 8-iodo-5,7,4′-trimethoxyflavone and related compounds was described. Iodination of phloracetophenone dimethyl ether and 2′-hydroxy-4,4′,6′-trimethoxychalcone *ortho* to the hydroxyl group was accomplished with iodic acid and iodine.

The preparation of 8-bromo compounds by similar nuclear halogenation has been accomplished and is reported in this paper. The melting points of these compounds (III, 253° and IIIa 236°) are markedly different from those reported by previous investigators[3] (242° and 250°) formed by the dehydrobromination of the so-called 5′-(actually 3′)-bromochalcones (V and Va).[5]



In the present synthetic study, it has now been found that the yellowish products, obtained by the elimination of hydrogen bromide of 3-bromo-2-hydroxy-4,6-dimethoxyphenyl α,β-dibromo-β-phenyl ethyl ketone (V) and the analogues (Va and Vb), give an intense color with ferric chloride, and are insoluble in cold dilute alkaline solution, showing the presence of a free hydroxy group at position 5. By acetylation of the above yellowish products (VI, VIa, and VIb), colorless monoacetates are formed and the methylated colorless compounds are identical with the compounds III, IIIa, and IIIb, respectively. It is clear that the demethylation at position 5 occurs easily during the dehydrobromination of the corresponding tribromochalcones (V, Va, and Vb).

EXPERIMENTAL[6]

3-Bromo-2-hydroxy-4,6-dimethoxyacetophenone (I). To a stirred solution of phloroacetophenone dimethyl ether (1.6 g., m.p. 82–83°) in glacial acetic acid (30 ml.) was added dropwise a solution of bromine (1.36 g.) in glacial acetic acid (20 ml.) at room temperature. A yellow precipitate separated rapidly. On dilution with water, further precipitate was isolated. The product was recrystallized from alcohol; yield 0.96 g. of yellow needles, m.p. 186–187°.

Anal. Calcd. for $C_{10}H_{11}O_4Br$: C, 43.66; H, 4.03; Br, 29.04. Found: C, 43.54; H, 4.33; Br, 29.22.

3′-Bromo-2′-hydroxy-4′,6′-dimethoxychalcone (II). To a cooled mixture of 3-bromo-2-hydroxy-4,6-dimethoxyacetophenone (I., 0.8 g.) and benzaldehyde (0.6 g.) in alcohol (10 ml.) was added 60% potassium hydroxide (10 g.) dropwise with stirring. The reaction mixture was kept at 0° for 2 days

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(1) Presented in part before the IUPAC Symposium on the Chemistry of Natural Products, Melbourne, Australia, August, 1960: a preliminary report appeared in the "Abstracts of Papers" of the Annual Meeting of the Chinese Chemical Society, Taipei, December, 1960.

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(3) W. A. Hutchins and T. S. Wheeler, *J. Chem. Soc.*, 91 (1939), cf. Nadkarni and Wheeler, *J. Univ. Bombay*, **6**, ii, 107 (1937).

(4) A Preliminary Report: C. T. Chang, T. S. Chen, T. Ueng, S. T. Choong and F. C. Chen, *J. Formosan Sci.*, **14**, No. 1, 14 (1960).

(5) That the bromine is in the 3′ position has been proven by Donnelly. J. A. Donnelly, *Tetrahedron Letters*, No. **19**, 1 (1959).

(6) Capillary melting points were determined for all compounds and were uncorrected. We are indebted to Mr. T. Ueng for technical assistance in many of the preparations described.

with occasional shaking. The mixture was then diluted with water and acidified with acetic acid. The precipitated chalcone was collected and recrystallized from alcohol; it gave orange yellow needles (10 g.), m.p. 185–186° (lit.[6,7] m.p. 185–187°).

Anal. Calcd. for $C_{17}H_{15}O_4Br$: C, 56.21; H, 4.16; Br, 22.00. Found: C, 56.12; H, 4.06; Br, 22.10.

3′-Bromo-2′-hydroxy-4,4′,6′-trimethoxychalcone (IIa). 3-Bromo-2-hydroxy-4,6-dimethoxyacetophenone (I., 0.8 g.) and anisaldehyde (0.7 g.) dissolved in alcohol (10 ml.) were treated with 60% potassium hydroxide (10 g.) as above, to give orange yellow needles (1.1 g.), m.p. 184–185°.

Anal. Calcd. for $C_{18}H_{17}O_5Br$: C, 54.98; H, 4.36; Br, 20.32. Found: C, 54.88; H, 4.39; Br, 20.34.

3′-Bromo-3-iodo-2′-hydroxy-4,4′,6′-trimethoxychalcone (IIb). 3-Bromo-2-hydroxy-4,6-dimethoxyacetophenone (I., 0.2 g.) and 3-iodo-4-methoxybenzaldehyde[8,9] (0.2 g.) dissolved in alcohol (10 ml.) were treated with 60% potassium hydroxide (5 g.) at room temperature as above. The crude chalcone recrystallized from acetone gave orange yellow crystals (0.3 g.), m.p. 224–225°.

Anal. Calcd. for $C_{18}H_{16}O_5BrI$: C, 41.64; H, 3.11; Halogen, 39.84. Found: C, 41.55; H, 2.72; Halogen, 39.67.

8-Bromo-5,7-dimethoxyflavone (III). A mixture of 3′-bromo-2′-hydroxy-4′,6′-dimethoxychalcone (II., 0.5 g.), selenium dioxide (0.3 g.), and dioxane (20 ml.) was refluxed for 16 hr. The reaction mixture was diluted with water, the precipitate was collected and recrystallized as needles (0.3 g.), m.p. 253° from dioxane or acetone.

Anal. Calcd. for $C_{17}H_{13}O_4Br$: C, 56.53; H, 3.63; Br, 22.13. Found: C, 56.22; H, 3.92; Br, 22.54.

8-Bromo-5,7,4′-trimethoxyflavone (IIIa). 3′-Bromo-2′-hydroxy-4,4′,6′-trimethoxychalcone (IIa., 0.5 g.), selenium dioxide (0.3 g.), 1 and dioxane (20 ml.) were treated as above, and gave colorless needles (0.32 g.), m.p. 236°.

Anal. Calcd. for $C_{18}H_{15}O_5Br$: C, 55.26; H, 3.87; Br, 20.43. Found: C, 54.81; H, 3.87; Br, 20.33.

8-Bromo-3′-iodo-5,7,4′-trimethoxyflavone (IIIb). 3′-Bromo-3-iodo-2′-hydroxy-4,4′,6′-trimethoxychalcone (IIb., 0.2 g.), selenium dioxide (0.1 g.) and dioxane (10 ml.) were treated as above, and gave colorless crystals (0.12 g.), m.p. 257–258°.

Anal. Calcd. for $C_{18}H_{14}O_5BrI$: C, 41.81; H, 2.73; Halogen, 39.99. Found: C, 41.70; H, 3.08; Halogen, 39.68.

8-Bromo-5-hydroxy-7-methoxyflavone (VI). 3-Bromo-2-hydroxy-4,6-dimethoxyphenyl α,β-dibromo-β-phenylethyl ketone[3,10] (V., 0.6 g., m.p. 186° dec.) was gradually heated to 195° under reduced pressure (3 mm.) until it decomposed to release hydrogen bromide. After cooling, it was extracted with dioxane or acetone. The extract was concentrated and the crystals obtained were recrystallized from alcohol or acetone to yield 0.3 g. of yellowish needles, m.p. 242°, which gave an intense dark brown color with ferric chloride, but were insoluble in cold dilute potassium hydroxide solution.

Anal. Calcd. for $C_{16}H_{11}O_4Br$: C, 55.35; H, 3.19; Br, 23.02. Found: C, 55.11; H, 3.45; Br, 23.22.

Acetylation of VI using acetic anhydride and pyridine at room temperature gave colorless needles, m.p. 215°, which did not give a color with alcoholic ferric chloride.

Methylation of VI *to* III. 8-Bromo-5-hydroxy-7-methoxyflavone (VI., 0.2 g.), anhydrous potassium carbonate powder (2 g.), dimethyl sulfate (1 ml.), and acetone (10 ml.) were refluxed for 4 hr. on a water bath. Then the acetone was distilled and water was added to dissolve the inorganic substances. The precipitate, recrystallized from acetone, gave colorless needles, m.p. 253°, and showed no depression on a mixed melting point determination with the product (III) obtained by the oxidation of 3′-bromo-2′-hydroxy-4′,6′-dimethoxychalcone (II) by means of selenium dioxide. It did not give a color with alcoholic ferric chloride.

8-Bromo-5-hydroxy-7,4′-dimethoxyflavone (VIa). 3-Bromo-2-hydroxy-4,6-dimethoxyphenyl α,β-dibromo-β-p-anisylethyl ketone[3,10] (Va., 0.7 g., d.p. 165°), when treated at 170° as above, gave yellowish needles (0.3 g.), m.p. 250° which gave a strong brown ferric chloride reaction but did not dissolve in dilute alkali.

Anal. Calcd. for $C_{17}H_{13}O_5Br$: C, 54.13; H, 3.47; Br, 21.19. Found: C, 53.81; H, 3.62; Br, 20.96.

The acetate, recrystallized from alcohol, was obtained in colorless needles, m.p. 216–218°, which gave no ferric chloride reaction.

Methylation of VIa *to* IIIa. 8-Bromo-5-hydroxy-7,4′-dimethoxyflavone (VIa., 0.2 g.) when methylated as above, gave colorless needles, m.p. 236°, and a negative test with ferric chloride. The identity of this substance with the product (IIIa) obtained from the selenium dioxide oxidation of 3′-bromo-2′-hydroxy-4,4′,6′-trimethoxychalcone (IIa) was established by a mixed melting point test.

3-Bromo-2-hydroxy-4,6-dimethoxyphenyl α,β-dibromo-β-3-iodo-4-methoxyphenylethyl ketone (Vb). To a stirred solution of 2′-hydroxy-3-iodo-4,4′,6′-trimethoxychalcone[4] (IVb., 0.25 g., m.p. 154–155°) in carbon disulfide (60 ml.) was dropped a solution of bromine (0.17 g.) in carbon disulfide (20 ml.). An hour later, the solvent was removed under reduced pressure, and the residue was recrystallized from chloroform or carbon tetrachloride to give yellow needles (0.28 g.), m.p. 190–191°, decomp.

Anal. Calcd. for $C_{18}H_{16}O_5Br_3I$: C, 31.84; H, 2.38; Halogen, 54.00. Found: C, 31.55; H, 2.56; Halogen, 54.47.

8-Bromo-5-hydroxy-3′-iodo-7,4′-dimethoxyflavone (VIb). 3-Bromo-2-hydroxy-4,6-dimethoxyphenyl α,β-dibromo-β-3-iodo-4-methoxyphenylethyl ketone (Vb., 0.2 g.) was treated at 200° as above. The product formed was extracted with ether and recrystallized from acetone, and then from 70% dioxane to give yellow needles (70 mg.), m.p. 275°.

Anal. Calcd. for $C_{17}H_{12}O_5BrI$: C, 40.58; H, 2.40; Halogen, 41.11. Found: C, 40.11; H, 2.65; Halogen, 41.00.

Methylation of VIb *to* IIIb. 8-Bromo-5-hydroxy-3′-iodo-7,4′-dimethoxyflavone (VIb., 50 mg.) when methylated as above, gave colorless needles (30 mg.), m.p. 257–258°, which showed no depression on a mixed melting point with the product (IIIb), obtained by the oxidation of 3′-bromo-3-iodo-2′-hydroxy-4,4′,6′-trimethoxychalcone by means of selenium dioxide.

Acknowledgment. The authors are pleased to acknowledge the kindness of Professor Simon H. Wender of the University of Oklahoma for reading the manuscript, and of Professor E. Sebe of Japan for microanalyses data. Financial support from the Asia Foundation and the National Council on Science Development, as well as encouragement from President S. L. Chien, were also greatly appreciated.

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