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

Synthesis of 8- and 3′-Iodoflavones and Related Compounds[1]

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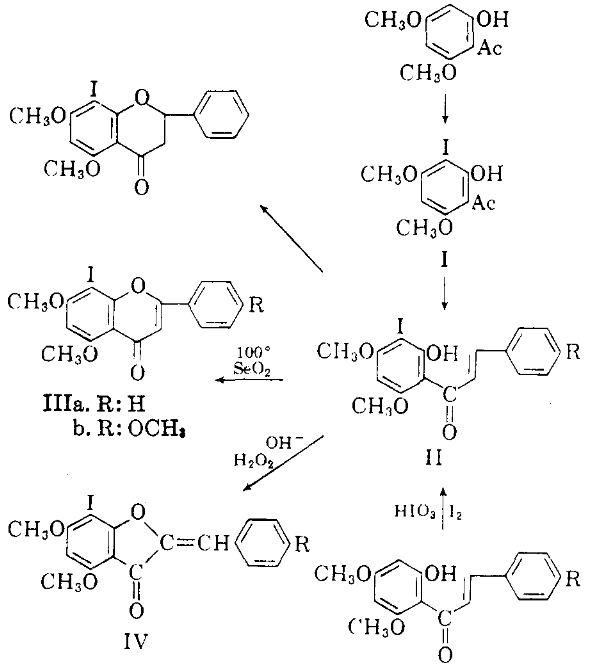
The synthesis of 8-iodo-5,7-dimethoxy-, 8-iodo-, and 3′-iodo-5,7,4′-trimethoxyflavone has been accomplished. Oxidation of the corresponding chalcones with alkaline hydrogen peroxide yielded the aurones. It has been demonstrated that 5-methoxyflavones were converted into the corresponding 8-bromoflavanones by the action of *N*-bromosuccinimide.

In connection with other work in progress in this laboratory, it was necessary to prepare 8- and 3′-iodo-5,7,4′-trimethoxyflavone. No work on the synthesis of those compounds has been reported except a short communication by Nakazawa.[2]

The starting material, 3-iodo-2′-hydroxy-4,4′,6′-trimethoxychalcone (V) was easily prepared by condensation of 3-iodo-4-hydroxybenzaldehyde with phloroacetophenone dimethyl ether, and 2′-hydroxy-3′-iodo-4,4′,6′-trimethoxychalcone (II) was prepared by two methods: (a) by iodination of 2′-hydroxy-4,4′,6′-trimethoxychalcone with iodine and iodic acid, or (b) by condensation of anisaldehyde with 2-hydroxy-3-iodo-4,6-dimethoxyacetophenone (I), which was obtained by the iodination of phloroacetophenone dimethyl ether.



The conversion of the iodochalcone (II and V) into 8- and 3′-iodoflavones (III and VI) can be accomplished readily by treatment with selenium dioxide under the proper conditions in absolute ethanol or dioxane. These flavones reacted readily with concentrated hydrochloric acid to form relatively stable compounds.

By the Algar-Flynn or Oyamada's method, with alkaline hydrogen peroxide, the iodochalcones (IIand V) gave no expected flavanols but produced the corresponding aurones (IV and VII).

On acid isomerization, the iodochalcone (V) yielded 3′-iodoflavanone (VIII) in poor yield. However 8-iodo-5,7-dimethoxyflavanone was smoothly obtained by alkali or acid isomerization of the chalcone (IIa). Although in the acid isomerization of the chalcone (IIb), no 8-iodo-5,7,4′-flavanone could be obtained, a considerable quantity of iodine was produced, and 8-iodoflavone (IIIb) was formed under certain conditions.

Attempts to convert 3′-iodoflavanone (VIII) into flavone (VI) by treatment with *N*-bromosuccinimide led to the formation of a monobromoflavanone.[3] Its structure was confirmed as 8-bromoflavanone (IX), which was treated with cold alcoholic sodium hydroxide and then acidified, gave the corresponding bromochalcone (X). Its structure was proved as 2′-hydroxy-3′-bromo-3-iodo-4,4′,6′-trimethoxychalcone by synthesis from 2 - hydroxy - 3 - bromo - 4,6 - dimethoxyacetophenone (XII). The bromochalcone (X) was subsequently converted by oxidation with selenium dioxide to give the flavone (XI), which was identical with the compound obtained from the chalcone (V) by bromination, followed by heating above the melting point and methylation of the compound (XIV) as shown by the following series of reactions.

A study of the Ullmann reaction to biflavonyls is under way.

EXPERIMENTAL

Ethanol was used for crystallization unless otherwise stated. Microanalyses were performed by Mr. E. Aoyagi, Miike Branch, Mitsui Chemical Laboratory, Ohmuda, Japan. Melting points are uncorrected.

(A) *Synthesis of 8-iodo-5,7-dimethoxy-, 5,7,4′-trimethoxyflavone and related compounds. 2-Hydroxy-3-iodo-4,6-dimethoxyacetophenone* (I). To a solution of iodic acid (0.28 g.) in a small amount of water was added a solution of phloroacetophenone dimethyl ether (1.5 g.) in alcohol (50 ml.) and iodine (0.8 g.). The mixture was stirred for 5 hr. at room temperature. The precipitate was filtered and recrystal-

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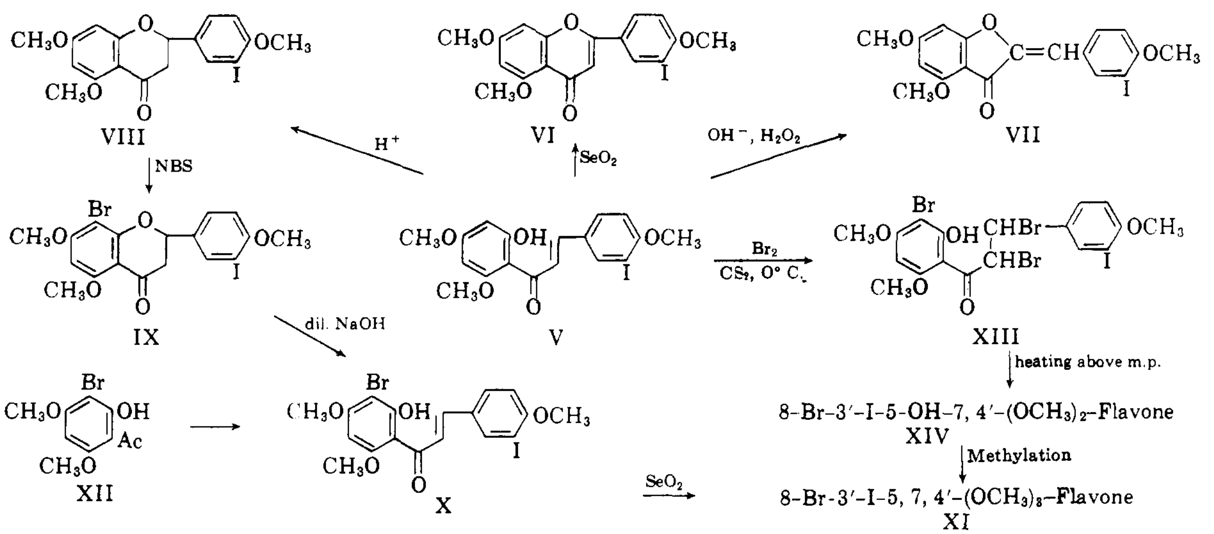
(1) Presented before the 1st IUPAC Symposium on the Chemistry of Natural Products, Australia, August 1960.

(2) K. Nakazawa, *Chem. Pharm. Bull. Japan,* **7**, 748 (1959).

(3) Similar conversion of 5,7,4′-trimethoxy-, 5,7-dimethoxy-, and 5-methoxyflavanone to the corresponding 8-bromoflavanone was also observed (to be published soon).



lized from acetone; it gave fine slightly greenish prisms (2.0 g.), m.p. 199.5–200.5°.

Anal. Calcd. for $C_{10}H_{11}O_4I$: C, 37.29; H, 3.44; I, 39.40. Found: C, 37.42; H, 3.44; I, 40.12.

2'-Hydroxy-3'-iodo-4,4',6'-trimethoxychalcone (IIb). (a) 2'-Hydroxy-4,4',6'-trimethoxychalcone (150 mg.), iodine (55 mg.), and iodic acid (25 mg.) were treated as above. The precipitate was collected and recrystallized from acetone, yielding reddish yellow micro needles (215 mg.), m.p. 178–179° dec.

Anal. Calcd. for $C_{18}H_{17}O_5I$: C, 49.11; H, 3.89; I, 28.83. Found: C, 49.04; H, 3.92; I, 28.53.

(b) To a cooled mixture of 2-hydroxy-3-iodo-4,6-dimethoxyacetophenone (I, 0.7 g.) and anisaldehyde (0.5 g.) in alcohol (30 ml.) was added 60% aqueous potassium hydroxide (10 g.). The mixture was stirred for 20 min. until it became a homogeneous orange-yellow solution, then kept at 20° for 3 days. The mixture was diluted with water and acidified. The precipitated chalcone was collected and crystallized, giving reddish yellow needles (0.85 g.), m.p. 178–179°, identical with the above product.

8-Iodo-5,7,4'-trimethoxyflavone (III). A mixture of 2'-hydroxy-3'-iodo-4,4',6'-trimethoxychalcone (IIb, 1.0 g.), selenium dioxide (0.3 g.), and dioxane (40 ml.) was refluxed for 24 hr. On dilution with water, the solid flavone was collected and crystallized, giving colorless needles (0.55 g.), m.p. 236–237°.

Anal. Calcd. for $C_{18}H_{15}O_5I$: C, 49.33; H, 3.45; I, 28.96. Found: C, 49.02; H, 3.54; I, 28.63.

It reacts readily with concentrated hydrochloric acid in acetone to form deep yellow needles, m.p. 150–151° dec.

Oxidation of 2'-hydroxy-3'-iodo-4,4',6'-trimethoxychalcone. 8-Iodo-5,7,4'-trimethoxyaurone (IV). To a solution of the chalcone (II, 0.15 g.) in methanol (10 ml.) and 16% aqueous sodium hydroxide (1 ml.) was added 15% hydrogen peroxide (1 ml.), with stirring and ice cooling. After 2 days in a refrigerator, it was filtered; the precipitate was collected and crystallized to give yellow needles (0.08 g.), m.p. 229–230°.

Anal. Calcd. for $C_{18}H_{15}O_5I$: C, 49.33; H, 3.45; I, 28.96. Found: C, 48.92; H, 3.34; I, 28.82.

It gave a characteristic deep red color with concd. sulfuric acid, and no color with ferric chloride nor with magnesium–hydrochloric acid in alcoholic solution.

Attempt to prepare 8-iodoflavonone, yielding flavone. A solution of 2'-hydroxy-3'-iodo-4,4',6'-trimethoxychalcone (II, 0.2 g.) and phosphoric acid (d 1.75; 2 ml.) in alcohol (30 ml.) was refluxed for 12 hr. The precipitate was collected and crystallized, giving colorless needles (40 mg.), m.p. 236–237°, which was identical with the above 8-iodoflavone (III) by the mixed melting points.

Similar reaction gave *2'-hydroxy-3'-iodo-4',6'-dimethoxychalcone* (IIa), bright yellow needles (80% yield), m.p. 184.5–185° (*Anal.* Calcd. for $C_{17}H_{15}O_4I$: C, 49.77; H, 3.69; I, 30.94. Found: C, 49.44; H, 3.64; I, 30.73), *8-iodo-5,7-dimethoxyflavone* (IIIa), colorless needles (40% yield), m.p. 239–240° (*Anal.* Calcd. for $C_{17}H_{13}O_4I$: C, 50.02; H, 3.21; I, 31.09. Found: C, 48.83; H, 3.24; I, 31.01), *8-iodo-5,7-dimethoxyaurone* (IVa), yellow needles (65% yield), m.p. 225–226° (*Anal.* Calcd. for $C_{17}H_{13}O_4I$: C, 50.02; H, 3.21; I, 31.09. Found: C, 49.84; H, 3.14; I, 31.31), *8-iodo-5,7-dimethoxyflavone* obtained in 85% yield by alkali isomerization with diluted sodium carbonate in methanol, colorless needles, m.p. 186–188° (*Anal.* Calcd. for $C_{17}H_{15}O_4I$: C, 49.77; H, 3.69; I, 30.94. Found: C, 49.61; H, 3.74; I, 30.80).

(B) *Synthesis of 3'-iodo-5,7,4'-trimethoxyflavone and related compound. 2'-Hydroxy-3-iodo-4,4',6'-trimethoxychalcone* (V). 3-Iodo-4-methoxybenzaldehyde (1.45 g.) and phloroacetophenone dimethyl ether (1.2 g.) were dissolved in alcohol (60 ml.), treated with 60% aqueous potassium hydroxide (20 g.) as above to yield the chalcone (V, 1.9 g.), yellow needles, m.p. 154–155°.

Anal. Calcd. for $C_{18}H_{17}O_5I$: C, 49.11; H, 3.89; I, 28.83. Found: C, 48.91; H, 3.94; I, 28.52.

3'-Iodo-5,7,4'-trimethoxyflavone (VI). The above chalcone (V, 0.1 g.), selenium dioxide (0.07 g.), and dioxane (25 ml.) were refluxed for 24 hr. and treated as above, giving colorless needles (80 mg.), m.p. 206–207° and 221–222°.

Anal. Calcd. for $C_{18}H_{15}O_5I$: C, 49.33; H, 3.45; I, 28.96. Found: C, 48.81; H, 3.43; I, 28.63.

It reacts readily with concd. hydrochloric acid in acetone to give yellow needles, m.p. 171–172°.

Oxidation of 2'-hydroxy-3-iodo-4,4',6'-trimethoxychalcone. 3'-Iodo-5,7,4'-trimethoxyaurone (VII). To a solution of the chalcone (V, 0.2 g.) in methanol (10 ml.) and 16% aqueous sodium hydroxide (1 ml.) was added 15% hydrogen peroxide (1 ml.) and treated as above, yielding greenish yellow needles (0.1 g.), m.p. 218.5–219.5°, which dissolved in concd. sulfuric acid to give an intense red color.

Anal. Calcd. for $C_{18}H_{15}O_5I$: C, 49.33; H, 3.45; I, 28.96. Found: C, 48.94; H, 3.54; I, 28.81.

3'-Iodo-5,7,4'-trimethoxyflavanone (VIII). A solution of the chalcone (V, 0.5 g.) and pyrophosphoric acid (10 g.) in alcohol (150 ml.) was refluxed for 10 days. Concentration of the solution and dilution with water gave colorless needles (0.15 g.), m.p. 176–177°.

Anal. Calcd. for $C_{18}H_{17}O_5I$: C, 49.11; H, 3.89; I, 28.83. Found: C, 49.01; H, 3.84; I, 28.53.

Reaction of 3'-iodo-5,7,4'-trimethoxyflavanone with N-bromosuccinimide. The flavanone (VIII, 0.2 g.) and *N*-bromosuccinimide (0.1 g.) in carbon tetrachloride (10 ml.) were refluxed for 15 min., during which a transient red color appeared. After cooling, the mixture was washed with water, then evaporated yielding colorless needles (150 mg.), m.p. 219–220°.

Anal. Calcd. for $C_{18}H_{16}O_5IBr$: C, 41.64; H, 3.11; Halogen, 39.84. Found: C, 41.74; H, 3.04; Halogen, 39.72.

Its structure was confirmed as *8-bromo-3'-iodo-5,7,4'-trimethoxyflavanone* by conversion to *bromochalcone* (X), which was identical with that obtained from condensation of 2-hydroxy-3-bromo-4,6-dimethoxyacetophenone[4] (XII) with 3-iodo-4-methoxybenzaldehyde, yellow needles, m.p. 224–225°.

Anal. Calcd. for $C_{18}H_{16}O_5IBr$: C, 41.64; H, 3.11; Halogen, 39.84. Found: C, 41.52; H, 3.14; Halogen, 39.70.

By oxidation with selenium dioxide, the bromochalcone (X) was converted into the corresponding *8-bromoflavone* (XI), colorless needles, m.p. 257–258°.

Anal. Calcd. for $C_{18}H_{14}O_5IBr$: C, 41.80; H, 2.73; Halogen, 40.00. Found: C, 41.70; H, 2.94; Halogen, 39.70.

This product was identical with *8-bromo-3'-iodo-5,7,4'-trimethoxyflavone* (XI) obtained from the chalcone (V) by bromination, yielding the *tribromochalcone* (XIII), m.p. 190–191°.

Anal. Calcd. for $C_{18}H_{16}O_5IBr_3$: C, 31.84; H, 2.38; Halogen, 54.00. Found: C, 31.64; H, 2.44; Halogen, 53.50.

After heating above the melting point, it gave yellow needles (XIV). This compound melted at 275.°

Anal. Calcd. for $C_{17}H_{12}O_5IBr$: C, 40.58; H, 2.40; Halogen, 41.11. Found: C, 40.10; H, 2.74; Halogen, 41.00.

Methylation of this compound (XIV) in acetone with dimethyl sulfate and sodium hydroxide in the usual manner yielded the flavone (XI).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, LOS ANGELES]

Diels-Alder Syntheses of 2,6-Dimethylcyclohexanecarboxylic Acids

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Racemic 2,6-dimethylcyclohexanecarboxylic acid is obtained in 50% over-all yield from the Diels-Alder reaction of 1,3-pentadiene and diethyl ethylidenemalonate followed by saponification of the adduct, hydrogenation, and decarboxylation. The reaction of 1,3-pentadiene with crotonic acid or ethyl crotonate yields mixtures of isomers.

2,6-Dimethylcyclohexanecarboxylic acid can exist in two meso-forms (*cis* and *trans*) and in a racemic modification resolvable into enantiomers. The meso forms are readily available,[2] but the racemic modification was obtained in only poor yield by reduction of 2,6-dimethylbenzoic acid with sodium in boiling isoamyl alcohol.[2,3] The racemic form was needed for studies of steric hindrance and an improved synthesis was therefore sought.

The Diels-Alder reaction offers an attractive route for the synthesis of 2,6-dimethylcyclohexanecarboxylic acids. It was reported[4] that 1,3-pentadiene and diethyl ethylidenemalonate gave diethyl 2,6-dimethyl-3-cyclohexene-1,1-dicarboxylate (I) in good yield. I was saponified and decarboxylated to yield a 2,6-dimethyl-3-cyclohexenecarboxylic acid (IV). The structure of IV was shown by selenium dehydrogenation to *m*-xylene which was oxidized to isophthalic acid, but the stereochemistry of IV was not established.

We have repeated this diene synthesis and converted the adduct to 2,6-dimethylcyclohexanecarboxylic acid by two routes: (a) saponification, hydrogenation, decarboxylation (I → II → III → V) and (b) saponification, decarboxylation, hydrogenation (I → II → IV → V). Although mixtures of isomers were present, the main product, racemic 2,6-dimethylcyclohexanecarboxylic acid, was easily isolated. An over-all yield of about 50% was obtained by either route (a) or (b). This synthetic method is the best now available for the racemic isomer. The melting point obtained, 83.0–83.5°, is higher than that of the best sample of racemic acid synthesized by Noyes' method (80.8–81.3°); a mixture of samples prepared by the two methods melted between the temperatures indicated.

Pure racemic acid gives melting point depressions with either of the pure meso isomers. Binary melting point diagrams were obtained for racemic acid with each meso isomer. Neither compound nor solid solution formation was observed. Racemic and meso *cis* isomers form a eutectic mixture at 54% *dl*, m.p. 52–52.4°; racemic and meso *trans* isomers form a eutectic mixture at 40% *dl*, m.p. 77.5–78°.

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[1] Most of the material for this paper is taken from the Ph.D. thesis of Donald M. Fenton, U.C.L.A., 1958. The rest is from the Ph.D. thesis of Russell Reed, U.C.L.A., 1950.

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