dry ether (10 ml.) in the cold, the hydrochloride of the base (0.15 g.) separated immediately. The latter was crystallized from a mixture of absolute alcohol and dry ether in colorless rods, m.p. 195–196°. Synthetic calycotomine hydrochloride caused no depression in melting point on admixture with an authentic sample of (±)-calycotomine hydrochloride, and their infrared spectra (Nujol) were found to be identical and superimposable.

Anal. Calcd. for $C_{12}H_{18}NO_3Cl$: C, 55.49; H, 6.93; N, 5.40; —OCH_3, 23.89. Found: C, 55.72; H, 7.12; N, 5.51; —OCH_3, 24.01.

3,4-Dihydroxy-β-phenylethylamine hydrochloride. Homoveratrylamine (5.0 g.) was heated with concentrated hydrochloric acid (8 ml.) in a sealed tube at 160–170° for 8 hr. when complete demethylation occurred. After cooling in an ice bath, the whole solution solidified. The base hydrochloride (4.0 g.) thus obtained was crystallized from acetone containing a little water in fine silky needles, m.p. 241° (yield, 80%).

Anal. Calcd. for $C_8H_{12}O_2NCl$: N, 7.38. Found: N, 7.45.

Synthesis of 6,7-demethylcalycotomine. 3,4-Dihydroxy-β-phenylethylamine hydrochloride (1.0 g.) and glycolic aldehyde (0.6 g.) dissolved in water (10 ml.) were adjusted to *p*H 3–4 and kept for 3 days at 25–26°. The mixture was concentrated *in vacuo* and the crystals (0.85 g.) which separated were crystallized from a mixture of alcohol and acetone (1:1) in shining colorless needles, m.p. 208–209° dec. (yield, 70–75%). It showed λ_{max}^{alc} in the ultraviolet region at 288 mμ (log ε, 3.57).

Anal. Calcd. for $C_{10}H_{13}NO_3$, HCl: C, 51.83; H, 6.05; N, 6.05. Found: C, 51.77; H, 6.01; N, 6.03.

Synthesis of 3-carboxy-6,7-demethylcalycotomine. DOPA hydrochloride was prepared by adding dry ethereal hydrogen chloride (10 ml.) to DOPA (0.2 g.) dissolved in ether. It crystallized from dry methanol in plates, m.p. 246° dec. (yield, 0.18 g.). An aqueous solution (5 ml.) of DOPA hydrochloride (0.15 g.) was condensed with glycolic aldehyde (0.08 g.) at *p*H 4–5 and allowed to stand at 25–26° for 3 days. On concentrating the solution, 3-carboxydemethylcalycotomine crystallized in fine needles (yield, 0.1 g.) which were insoluble in alcohol, acetone, chloroform, ethyl acetate, and benzene. The compound crystallized from water, m.p. 281–282° dec. 3-Carboxydemethylcalycotomine showed λ_{max}^{alc} in the ulraviolet region at 280 mμ (log ε, 3.54).

Anal. Calcd. for $C_{11}H_{13}NO_5$: C, 55.23; H, 5.44; N, 5.85. Found: C, 55.01; H, 5.43; N, 5.82.

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Synthesis of 8-Halogenoflavones[1]

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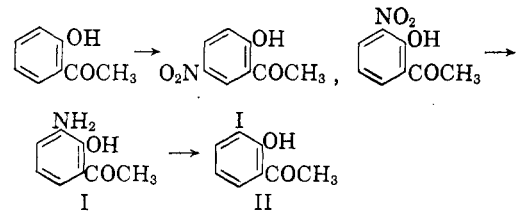
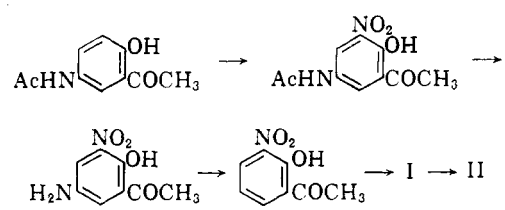
No work on 8-halogenoflavones and related compounds except on 8-chloroflavone,[4] 8-bromo-5,7-dimethoxy-, and 5,7,4′-trimethoxyflavone,[5] has previously been reported. In continuing the studies of 6-[6] and 7-halogenoflavones,[7] 8-bromoflavone was prepared in good yield applying the procedure of Ruhemann. 8-Fluoro- and 8-iodoflavone, -flavanone, -flavonol, and the 4′-methoxy compounds, including the corresponding chalcones, were prepared by the usual way,[6,7] starting from 3-fluoro- and 3-iodo-2-hydroxyacetophenone, respectively.

3-Fluoro-2-hydroxyacetophenone was prepared by the Fries rearrangement of *o*-fluorophenyl acetate. Attempts to synthesize 2-hydroxy-3-iodo-, bromo-, and chloroacetophenone by this method were unsuccessful,[8] producing 2,4-diiodophenol[9] or 3-halogeno-4-hydroxyacetophenone[8] and nearly none of the expected product. The synthesis of 2-hydroxy-3-iodoacetophenone was accomplished by two routes: (a) nitration of *o*-hydroxyacetophenone as described in previous papers on the synthesis of 6-halogenoflavones,[6,10]



and (b) nitration of 5-acetamino-2-hydroxyacetophenone,[11] followed by diazotization and reduction[12] as shown in the accompanying equation.



3-Fluoro- and 3-iodo-2-hydroxyacetophenone were condensed smoothly with benzaldehyde or anis-

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TABLE I

8-FLUOROFLAVONES AND RELATED COMPOUNDS

Compound	Color and Cryst. Shape	M.P.	Yield, %	Formula	Calcd., % C	Calcd., % H	Found, % C	Found, % H
2′-Hydroxy-3′-fluorochalcone	Deep yellow needles	110–111	72	$C_{15}H_{11}O_2F$	74.37	4.58	74.2	4.7
2′-Hydroxy-3′-fluoro-4-methoxychalcone	Orange-yellow needles	123–124	80	$C_{16}H_{13}O_3F$	70.58	4.81	70.3	4.9
8-Fluoroflavanone	Colorless plates	81–82	30	$C_{15}H_{11}O_2F$	74.37	4.58	74.0	4.7
8-Fluoro-4′-methoxyflavanone	Colorless needles	90–90.5	5	$C_{16}H_{13}O_3F$	70.58	4.81	70.2	4.9
8-Fluoroflavone	Cream-yellow needles	125–126	65	$C_{15}H_9O_2F$	74.99	3.77	74.6	3.9
8-Fluoro-4′-methoxyflavone	Greenish white needles	144–145	60	$C_{16}H_{11}O_3F$	71.11	4.10	70.8	4.4
8-Fluoroflavonol	Light yellow needles	179–180.5	75	$C_{15}H_9O_3F$	70.31	3.54	70.1	3.7
8-Fluoro-4′-methoxyflavonol	Light yellow needles	205–206	82	$C_{16}H_{11}O_4F$	67.13	3.87	66.9	4.0

TABLE II

8-IODOFLAVONES AND RELATED COMPOUNDS

Compounds	Color and Cryst. Shape	M.P.	Yield, %	Formula	Calcd., % C	Calcd., % H	Calcd., % I	Found, % C	Found, % H	Found, % I
2′-Hydroxy-3′-iodochalcone	Yellow needles	138–138.5	78	$C_{15}H_{11}O_2I$	51.45	3.17	36.25	51.6	3.4	36.1
2′-Hydroxy-3′-iodo-4-methoxychalcone[a]	Yellow and red prisms	152–152.5 158–158.5	76	$C_{16}H_{13}O_3I$	50.55	3.45	33.38	50.3	3.6	33.2
8-Iodoflavanone	Colorless needles	79–81	12	$C_{15}H_{11}O_2I$	51.45	3.17	36.25	51.5	3.3	36.1
8-Iodo-4′-methoxyflavanone	Colorless needles	108–109	10	$C_{16}H_{13}O_3I$	50.55	3.45	33.38	50.3	3.6	33.1
8-Iodoflavone	Colorless needles	187–188	55	$C_{15}H_9O_2I$	51.75	2.61	36.45	51.5	2.8	36.3
8-Iodo-4′-methoxyflavone	Yellowish needles	197–197.5	68	$C_{16}H_{11}O_3I$	50.82	2.93	33.56	50.6	3.1	33.4
8-Iodoflavonol	Light yellow needles	195–196	71	$C_{15}H_9O_3I$	49.48	2.49	34.85	49.1	2.6	34.7
8-Iodo-4′-methoxyflavonol	Yellow needles	240–240.5	83	$C_{16}H_{11}O_4I$	48.75	2.81	32.20	48.1	3.3	32.0

[a] Two crystalline forms of 2′-hydroxy-3′-iodo-4-methoxychalcone were observed. When the raw product was crystallized from acetone or alcohol, bright yellow prisms, m.p. 152–152.5°, more soluble in these solvents, and brick red prisms, m.p. 158–158.5° were obtained. The brick red form was converted into the yellow form by prolonged boiling in methyl alcohol. The reverse change was effected by heating the yellow form slightly above the melting point, then resolidifying it at 145–150°, and then melting it again at 158°.

aldehyde in presence of alcoholic alkali to the chalcones, which were oxidized by means of selenium dioxide in amyl alcohol to 8-fluoro- and -iodoflavone, respectively. On acid isomerization, the halogenochalcones yielded 8-halogenoflavanones, and by the Algar-Flynn[13] or Oyamada's method,[14] afforded 8-halogenoflavonols.

It was noted that two forms of 2′-hydroxy-3′-iodo-4-methoxychalcone exist, each with characteristic color and melting point and that interconversion of the forms may be accomplished under certain conditions, as described in Table II.

EXPERIMENTAL[15]

(A) *Synthesis of 8-fluoroflavone, -flavanone, and -flavonol. 2-Hydroxy-3-fluoroacetophenone. o*-Fluorophenyl acetate (0.29 g., b.p. 76.5–77° at 11 mm., lit.[16] b.p. 192–194° at 737 mm.) and anhydrous aluminum chloride (0.4 g.) were kept at 190° for 1.5 hr. The mixture was cooled, and the complex was decomposed by ice water and was steam distilled, yielding steam volatile 2-hydroxy-3-fluoro-acetophenone as colorless needles (47 mg., 16% yield), m.p. 72–73°.

Anal. Calcd. for $C_8H_7O_2F$: C, 62.34; H, 4.58. Found: C, 62.1; H, 4.8.

By condensation with benzaldehyde or anisaldehyde, these compounds gave the halogenochalcones, from which 8-fluoroflavone, -flavanone, -flavonol, and 4′-methoxy compounds were prepared by the procedure previously described.[7] General procedures for distinguishing between isomeric chalcone, flavanone, and possibly 2-benzylcoumaranone derivatives were inferred from the facts: (1) flavanones were colorless and give no color with ferric chloride; (2) chalcones were yellow and gave positive ferric chloride test; and (3) 2-benzylcoumaranone derivatives were golden yellow and usually gave red color with concd. sulfuric acid and gave no color with ferric chloride.

(B) *Synthesis of 8-iodoflavone, -flavanone, and-flavonol. 2-Hydroxy-3-iodoacetophenone.* 2-Hydroxy-3-aminoacetophenone [0.75 g., m.p. 93–94°, prepared by nitration of (a) *o*-hydroxyacetophenone[6] or (b) 2-hydroxy-5-acetaminoacetophenone[11, 12]] was dissolved in a mixture of ice (3 g.) and concd. sulfuric acid (sp. gr. 1.84, 9. ml.). This solution was cooled at 0° and sodium nitrite (0.48 g.) in water (6 ml.) was added dropwise until a positive test for nitrous acid was obtained. After stirring at 0° for 20 min., more sulfuric acid (3 ml.) was added and then potassium iodide (0.8 g.) in water (10 ml.) and copper bronze (0.05 g.) were

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(14) T. Oyamada, *J. Chem. Soc. Japan*, **55**, 1256 (1934).

(15) All melting points are uncorrected. The analyses were carried out by Mr. E. Aoyagi of Mitsui Chemical Laboratory, Ohmuda, Japan.

(16) J. T. Minor and C. A. Vanderwerf, *J. Org. Chem.*, **17**, 1425 (1952).

added. The temperature was slowly raised and kept at 65° until no more nitrogen was evolved. Then the reaction mixture was steam distilled. The solid distillate collected was recrystallized from 70% alcohol giving colorless needles, m.p. 58–59°.

Anal. Calcd. for $C_8H_7O_2I$: C, 36.67; H, 2.69; I, 48.4. Found: C, 36.22; H, 2.91; I, 48.2.

2′-Hydroxy-3′-iodochalcone, 8-iodoflavone, -flavanone, -flavonol and the 4′-methoxy compounds were prepared as described earlier,[7] and the melting points and analytical data are shown in Table II.

(C) *Synthesis of 8-bromoflavone by Ruhemann method. Ethyl β-(o-bromophenoxy)cinnamate.* To a solution of metallic sodium (1.2 g.) in absolute ethanol (30 ml.), *o*-bromophenol (8.8 g.) was added. The solution was evaporated, then heated at 140°. To this dry solid, *o*-bromophenol (11 g.) and ethyl phenyl propiolate (8.7 g.) were promptly added, and the mixture was kept at 165–175° for 3 hr. The reaction mixture was cooled and decomposed with 2*N* sulfuric acid. The mixture was extracted with ether, and the ether solution washed successively with 2*N* aqueous potassium hydroxide and water. The ether solution was dried over calcium chloride, evaporated, and the remaining yellow oil was distilled to yield a light yellowish liquid, b.p. 226–228° at 17 mm., which solidified soon, and recrystallized from alcohol yielding colorless leaflets (7.2 g.), m.p. 76–77°.

Anal. Calcd. for $C_{17}H_{15}O_3Br$: C, 58.80 H, 4.36; Br, 23.02. Found: C, 58.6; H, 4.5; Br, 23.0.

β-(o-Bromophenoxy)cinnamic acid. The above ester (7.2 g.) was refluxed with 2% alcoholic potassium hydroxide (55 ml.) for 1 hr. The solution was evaporated, then water was added and the solution neutralized with 2*N* hydrochloric acid. The precipitate was collected and recrystallized from 50% alcohol, yielding colorless prisms (6 g.), m.p. 148° (shrinking at 132°).

Anal. Calcd. for $C_{15}H_{11}O_3Br$: C, 56.45; H, 3.47; Br, 25.04. Found: C, 56.2; H, 3.6; Br, 25.1.

8-Bromoflavone. To a suspension of the above acid (5 g.) in absolute benzene (50 ml.), phosphorus pentachloride (3.5 g.) was added. After standing at room temperature for awhile, the mixture became clear, then anhydrous aluminum chloride (10 g.) was added. The mixture was poured over ice and extracted with ether. The ether-benzene layer was separated and washed with dilute potassium hydroxide. The ether-benzene was removed, and the remaining yellowish material was recrystallized from ethanol to produce colorless needles (4 g.), m.p. 178.5–179°.

Anal. Calcd. for $C_{15}H_9O_2Br$: C, 59.84; H, 2.99; Br, 26.53. Found: C, 59.9; H, 3.1; Br, 26.3.

(D) *Synthesis of 8-chloroflavone.* Reaction similar to the one above gave *ethyl β-(o-chlorophenoxy)cinnamate*, b.p. 218–220° at 17 mm.; *β-(o-chloro-phenoxy)cinnamic acid*, colorless cubes from 50% alcohol and *8-chloroflavone*, colorless needles from ethanol, m.p. 167–168° (recorded,[4] 169–170°).

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Reduction of Substituted Nitrobenzenes. I. Reduction of Monohalogenated Nitrobenzenes with Reducing Sugars in Alkaline Medium

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A survey of the chemical literature shows that nitrobenzenes have been reduced to a variety of products by means of different reducing agents. One of the reducing agents used on nitrobenzene itself was glucose in alkaline medium.[2a] In later work, Opolonick[2b] studied the reduction of nitrobenzene with the same reducing agent and found that the main product was azoxybenzene with some azobenzene and aniline being formed as well. When a great excess of glucose was used the principal product was azobenzene. Bigelow and Palmer[3] have also reduced nitrobenzene with glucose in

TABLE I

Reductions of Nitrobenzene

Sugar	Time, Min.	Temp.	Products, % Recovered Nitro.	Azoxy.	Amine
[a] Galactose	60	88	8.2	66.1	Nil
	120	98			
[a] Fructose	60	60–90	12.2	67.3	Nil
	120	95			
[b] Lactose	45	83	10.0	19.5	Nil
[b] Maltose	45	85–90	5.0	19.5	Nil

[a] Nitrobenzene, 0.166 mole; sugar, 0.117 mole; sodium hydroxide, 0.738 mole; and water, 100 ml. [b] Half quantities of the materials shown in footnote *a* were used, except for water, 100 ml.

TABLE II

Reductions of Chloronitrobenzenes[a]

Compound	Sugar	Products, % Recovered Nitro.	Azoxy.	Amine
3-Chloronitro-benzene	Glucose	0.04	87.0	Nil
	Galactose	0.10	91.6	Nil
	Fructose	0.74	86.3	Nil
	Lactose	Nil	81.4	Nil
	Maltose	Nil	69.9	Nil
4-Chloronitro-benzene	Glucose	15.4	67.3	0.5
	Galactose	13.1	70.8	0.5
	Fructose	14.2	73.5	0.5
	Lactose	0.01	55.3	13.9
	Maltose	1.80	65.5	10.2

[a] Substituted nitrobenzene, 0.17 mole; sugar, 0.13 mole; sodium hydroxide, 0.75 mole; water, 285 ml.; reaction time, 40–45 min.; and reaction temperatures, 70–85°C.

(1) Graduate research assistant.

(2)(a) E. Noetling, *Ber.*, **37**, 1019 (1904). (b) N. Opolonick, *Ind. Eng. Chem.*, **27**, 1045 (1935).

(3) H. E. Bigelow and A. Palmer, *Org. Syntheses*, Coll. Vol. II, 59 (1943).