Derivatives of 6,8-Dihydroxyflavone

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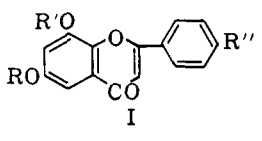
Conditions are described for the preparation of 2-hydroxy-3,5-dimethoxyacetophenone and from this, 6,8-dimethoxyflavone and -flavonol, their 4'-methyl ethers, and the corresponding hydroxy compounds. Under mild demethylating conditions, 6,8-dimethoxyflavone and its derivatives suffer selective cleavage of the 6-methoxyl group giving compounds whose structures have been established by synthesis.

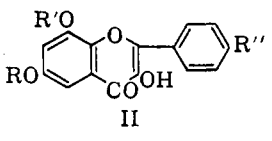
6,8-Dihydroxyflavone and its derivatives have proved unexpectedly difficult to synthesize because the preferred intermediate, 2-hydroxy-3,5-dimethoxyacetophenone, has been difficultly accessible. An account[1] of the preparation, in 4% yield, of 6,8-dimethoxyflavone by Mentzner's method[2] and a note[3] on the synthesis of that compound and its 4'-methyl ether by the present method have been published.

Since early attempts[4] to synthesize 2,5-dihydroxy-3-methoxyacetophenone resulted in poor yields, an alternative route to this compound was examined. 2-Hydroxy-3-methoxyacetophenone was coupled with diazotized sulfanilic acid and the resulting azo dye reduced to 5-amino-2-hydroxy-3-methoxyacetophenone. Attempts to complete the final stage of the synthesis, namely replacement of the amino group by hydroxyl, were not successful immediately. This route, therefore, was abandoned when it was found that the Elbs[5,6] persulfate oxidation of 2-hydroxy-3-methoxyacetophenone, under modified conditions, furnished the desired quinol in good yields. Partial methylation of the quinol with molar quantities of methyl sulfate then gave 2-hydroxy-3,5-dimethoxyacetophenone.

The last compound was condensed with benzaldehyde and with anisaldehyde to give the corresponding chalcones. Oxidative cyclization with selenium dioxide[7] then provided the flavones (I, R″ = H and OCH_3, R = R′ = CH_3) and treatment with alkaline hydrogen peroxide[8] afforded the flavonols (II, R = R′ = CH_3, R″ = H, and R = R′ = CH_3, R″ = OCH_3). On demethylation by hydrobromic acid these furnished the corresponding hydroxyflavones (I, R = R′ = R″ = H and R = R′ = H, R″ = OH) and hydroxyflavonols (II, R = R′ = R″ = H and R = R′ = H, R″ = OH). 3-Hydroxy-4,6,8-trimethoxyflavone proved unexpectedly difficult to demethylate in this way, but was smoothly converted to the tetrahydroxy compound by treatment with magnesium iodide.[9]



I



II

On heating with hydrobromic acid for much shorter periods than were necessary to achieve complete demethylation, 6,8-dimethoxyflavone and 3-hydroxy-6,8-dimethoxyflavone were found to yield monomethyl ethers and 4′,6,8-trimethoxyflavone a dimethyl ether. It seemed likely that these were 6-hydroxy compounds since the positive charge on the pyrone oxygen atom, arising either from direct protonation or from its conjugation with the protonated ring carbonyl group, would be expected to hinder the approach of hydroxonium ions to the 8-methoxyl group. The 6-methoxyl group, being unconjugated with the pyrone carbonyl, would, in contrast, be expected to cleave readily.[10] Similarly, the dihydroxy compound obtained from 4′,6,8-trimethoxyflavone under slightly more vigorous conditions was expected to be 4′,6-dihydroxy-8-methoxyflavone. These predictions were confirmed by synthesis of authentic 6-hydroxy-8-methoxyflavones from appropriate isopropylated intermediates.[11] 2,5-Dihydroxy-3-methoxyacetophenone was treated with isopropyl sulfate giving 2-hydroxy-3-methoxy-5-isopropoxyacetophenone, which on condensation with benzaldehyde, anisaldehyde, and with *p*-isopropoxybenzaldehyde yielded the corresponding chalcones. Dehydrogenation with selenium dioxide and oxidation with alkaline hydrogen peroxide furnished the isopropoxymethoxyflavones and -flavonols, which were then deisopropylated under mild conditions.

4′-Hydroxy-6,8-dimethoxyflavone, and -flavonol, required to complete the series, were prepared in the same way from 4-benzyloxy-2′-hydroxy-3′,5′-dimethoxychalcone with subsequent removal under acid conditions of the benzyl group.

Experimental

All melting points were determined on a Kofler block and are corrected.

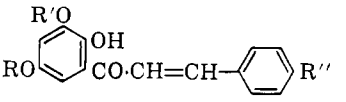
2,5-Dihydroxy-3-methoxyacetophenone. (a).—The diazonium salt prepared from sulfanilic acid (0.28 g.) was added with shaking to an ice-cold suspension of 2-hydroxy-3-methoxyacetophenone[12] (0.2 g.) in 4% aqueous sodium hydroxide (5 ml.). After 1 hr., the azo dye was collected, dissolved in 4% aqueous sodium hydroxide, reduced by the addition of excess sodium hydrosulfite, and the solution neutralized with hydrochloric acid. After being saturated with ammonium sulfate, the pale yellow solution was exhaustively extracted with ether and the extract evaporated *in vacuo* to give a residue which on crystallization from benzene–petroleum ether (b.p. 80–100°) furnished 5-amino-2-hydroxy-3-methoxyacetophenone as yellow prisms (0.09 g.), m.p. 145.5–147°.

Anal. Calcd. for $C_9H_{11}O_3N$; C, 59.7; H, 6.1; N, 7.7. Found: C, 59.8; H, 6.1; N, 7.6.

(1) J. E. Gowan, S. P. M. Riogh, G. T. MacMahon, S. O'Cleirigh, E. M. Philbin, and T. S. Wheeler, *Chem. Ind.* (London), 1672 (1955); *Tetrahedron*, **2**, 116 (1958).
(2) C. Mentzner, D. Molho, and P. Vercier, *Compt. rend.*, **232**, 1488 (1951).
(3) T. H. Simpson, *Chem. Ind.* (London), 1672 (1955).
(4) W. Baker, N. C. Brown, and J. A. Scott, *J. Chem. Soc.*, 1922 (1939).
(5) K. Elbs, *J. prakt. Chem.*, **48**, 179 (1893).
(6) W. Baker and N. C. Brown, *J. Chem. Soc.*, 2303 (1948).
(7) H. S. Mahal and K. Venkataraman, *ibid.*, 569 (1936).
(8) J. Algar and J. P. Flynn, *Proc. Roy. Irish Acad.*, **42B**, 1 (1934).
(9) A. Schonberg and R. Moubasher, *J. Chem. Soc.*, 462 (1944).
(10) T. H. Simpson and J. L. Beton, *ibid.*, 4065 (1954).
(11) T. H. Simpson, *Sci. Proc. Roy. Dublin Soc.*, **27**, 111 (1956).
(12) W. Baker and A. R. Smith, *J. Chem. Soc.*, 347 (1936).

TABLE I

CHALCONES

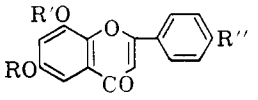


R	R′	R″	Crystalline form	M.p., °C.	Yield,[a] %	Molecular formula	Calcd. C	Calcd. H	Found C	Found H
CH_3	CH_3	H	Garnet prisms	81–83	80	$C_{17}H_{16}O_4$	71.8	5.7	71.8	5.7
CH_3	CH_3	CH_3O	Garnet prisms	121.5–122.5	85	$C_{18}H_{18}O_5$	68.8	5.8	69.0	5.8
$(CH_3)_2CH$	CH_3	H	Red prisms	73–74	70	$C_{19}H_{20}O_4$	73.1	6.5	72.9	6.4
$(CH_3)_2CH$	CH_3	CH_3O	Red needles	112–113	70	$C_{20}H_{22}O_5$	70.2	6.5	70.3	6.5
$(CH_3)_2CH$	CH_3	$(CH_3)_2CHO$	Red needles	92–94	70	$C_{22}H_{26}O_5$	71.3	7.1	71.3	7.1
CH_3	CH_3	$C_6H_5CH_2O$	Red prisms	172–174	60	$C_{24}H_{22}O_5$	73.8	5.7	73.6	5.9

[a] Based on quantity of ketone.

TABLE II

FLAVONE DERIVATIVES



R	R′	R″	Crystalline form	M.p., °C.	Yield, %	Molecular formula	Calcd. C	Calcd. H	Calcd. OCH_3	Found C	Found H	Found OCH_3
CH_3	CH_3	H	Cream colored needles	148–149 and[a] 152–153 (dimorphic)	75	$C_{15}H_8O_2(OCH_3)_2$	72.3	5.0	21.9	72.3	5.1	22.0
CH_3	CH_3	CH_3O	Cream colored needles	187–187.5	80	$C_{16}H_7O_2(OCH_3)_3$	69.2	5.2	29.7	69.3	5.2	29.7
$(CH_3)_2CH$	CH_3	H	Colorless needles	150–151	70	$C_{19}H_{18}O_4$	73.5	5.9	...	73.6	5.8	...
$(CH_3)_2CH$	CH_3	CH_3O	Cream colored prisms	182–183	70	$C_{20}H_{20}O_5$	70.6	5.9	...	70.6	5.8	...
$(CH_3)_2CH$	CH_3	$(CH_3)_2CHO$	Colorless prisms	94–96	65	$C_{22}H_{24}O_5$	71.7	6.6	...	71.7	6.5	...
CH_3	CH_3	$C_6H_5CH_2O$	Yellow needles	183–185	70	$C_{24}H_{20}O_5$	74.2	5.2	...	74.3	5.3	...
H	H	H	Yellow needles	278 dec.[a]	80	$C_{15}H_{10}O_4$	70.9	4.0	...	71.0	4.2	...
CH_3CO	CH_3CO	H	Colorless needles	198–200[a]	..	$C_{19}H_{14}O_6$	67.5	4.2	...	67.4	4.2	...
H	H	HO	Yellow needles	>300 dec.	80	$C_{15}H_{10}O_5$	66.7	3.7	...	66.5	3.7	...
CH_3CO	CH_3CO	CH_3COO	Colorless needles	240–242	..	$C_{21}H_{16}O_8$	63.6	4.1	...	63.8	4.2	...
C_2H_5	C_2H_5	C_2H_5O	Colorless prisms	161–162	..	$C_{15}H_7O_2(OC_2H_5)_3$	71.2	6.3	38.1	71.1	6.3	38.8
H	CH_3	H	Pale yellow needles	244–245	65	$C_{15}H_9O_5OCH_3$	71.6	4.5	11.6	71.4	4.6	11.5
CH_3CO	CH_3	H	Colorless needles	190–192	..	$C_{18}H_{14}O_6$	69.7	4.6	...	69.8	4.7	...
H	CH_3	CH_3O	Yellow needles	257–259 dec.	60	$C_{16}H_8O_3(OCH_3)_2$	68.5	4.7	20.8	68.4	4.8	20.5
CH_3CO	CH_3	CH_3O	Colorless needles	206–209	..	$C_{19}H_{16}O_6$	67.1	4.8	...	67.0	4.9	...
H	CH_3	HO	Yellow needles	>288 dec.	60	$C_{15}H_9O_4OCH_3$	67.6	4.3	10.9	67.8	4.2	10.6
CH_3CO	CH_3	CH_3COO	Colorless needles	215–217	..	$C_{20}H_{16}O_7$	65.2	4.4	...	65.1	4.3	...
CH_3	CH_3	HO	Pale yellow prisms	199–200	85	$C_{15}H_8O_3(OCH_3)_2$	68.5	4.7	20.8	68.3	4.7	20.5
CH_3	CH_3	CH_3COO	Colorless needles	172–175	..	$C_{19}H_{16}O_6$	67.0	4.8	...	67.1	4.8	...

[a] See ref. 1.

Attempts to convert this compound to the corresponding quinol by diazotization and hydrolysis or to the intermediate quinone by oxidation were unsuccessful.

(b).—A saturated solution of potassium persulfate (18 g., 0.066 mole) at 0° was added during 2 hr. to an ice-cold suspension of 2-hydroxy-3-methoxyacetophenone (10 g., 0.06 mole) in 10% aqueous sodium hydroxide (60 ml., 0.15 mole) containing sodium sulfite (7.6 g.); stirring was continued and the temperature maintained at 0° for a further 18 hr. The solution was then neutralized by hydrochloric acid, precipitated starting ketone (1.2 g.) recovered, and filtrate extracted with ether (three 50-ml. portions). Benzene (300 ml.) and sodium sulfite (7 g.) were added to the aqueous liquor, the mixture made strongly acid by the addition of concentrated hydrochloric acid (100 ml.), and then heated under reflux for 20 min. After cooling, the benzene layer was separated and the aqueous layer extracted with ether (four 100-ml. portions). Evaporation of the combined benzene and ether extracts to low bulk and cooling furnished 2,5-dihydroxy-3-methoxyacetophenone in yellow prisms (2.8 g.), m.p. 173–176°, which after crystallization from benzene and from water had m.p. 172–174° (lit.[4] m.p. 172°). Its diacetate formed colorless plates, m.p. 127–128° (lit.[4] m.p. 127°), from methanol.

2-Hydroxy-3,5-dimethoxyacetophenone and 2-Hydroxy-3-methoxy-5-isopropoxyacetophenone.—A solution of the foregoing quinol (5 g.) and methyl sulfate (4.2 g.) in acetone (50 ml.) was refluxed with excess anhydrous potassium carbonate in an atmosphere of carbon dioxide. After 3 hr. the mixture was filtered, the combined filtrate and washings evaporated *in vacuo*, and the residue dissolved in ether (100 ml.). After washing with 2% aqueous sodium carbonate (three 20-ml. portions), the ether layer was extracted with aqueous sodium hydroxide (4%, six 150-ml. portions) and the extract acidified. 2-Hydroxy-3,5-dimethoxyacetophenone was obtained in yellow needles (2.9 g.), m.p. 84–86°, from ethanol.

Anal. Calcd. for $C_8H_6O_2(OCH_3)_2$: C, 61.2; H, 6.2; OCH_3, 31.6. Found: C, 61.4; H, 6.2; OCH_3, 31.3.

It gave an intense red ferric coloration in ethanol. Its **2,4-dinitrophenylhydrazone** formed red needles, m.p. 246–248°, from *n*-butyl alcohol.

Anal. Calcd. for $C_{16}H_{16}O_7N_4$: C, 51.1; H, 4.3; N, 14.9. Found: C, 51.1; H, 4.2; N, 14.8.

Partial isopropylation of the same quinol (5 g.) with isopropyl sulfate (6 g.) was carried out in the same way and furnished 2-hydroxy-3-methoxy-5-isopropoxyacetophenone in yellow prisms (2.5 g.), m.p. 70–72°, from aqueous ethanol; it gave a red ethanolic ferric coloration.

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.3; H, 7.2. Found: C, 64.2; H, 7.2.

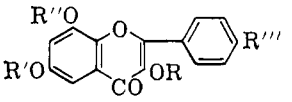
Its 2,4-dinitrophenylhydrazone formed red needles, m.p. 242–245°.

Anal. Calcd. for $C_{18}H_{20}O_7N_4$: C, 53.5; H, 5.0; N, 13.9. Found: C, 53.5; H, 4.8; N, 13.9.

Preparation of Chalcones.—Aqueous sodium hydroxide (3 g.) was added with shaking to a solution of one of the *o*-hydroxy ketones described before (1 g.) and an excess of the appropriate aldehyde, *viz.*, benzaldehyde (1.5 g.), anisaldehyde (1.5), *p*-isopropoxybenzaldehyde (2–3 g.), or *p*-benzyloxybenzaldehyde (3 g.) in ethanol (10 ml.). After 1 hr., the reaction product was diluted with water, acidified, and extracted with ether. The extract was then washed in succession with 2% aqueous sodium hydrogen carbonate, 25% aqueous sodium hydrogen sulfite, and then water. Evaporation of the ether furnished the chalcone which

TABLE III

FLAVONOL DERIVATIVES



R	R′	R″	R‴	Crystalline form	M.p., °C.	Yield %	Molecular formula	Calcd. C	Calcd. H	Calcd. OCH₃	Found C	Found H	Found OCH₃
H	CH_3	CH_3	H	Cream colored prisms	198–200	66	$C_{15}H_8O_3(OCH_3)_2$	68.5	4.7	20.8	68.4	4.7	21.1
CH_3CO	CH_3	CH_3	H	Colorless needles	194–196	..	$C_{19}H_{16}O_6$	67.1	4.8	...	67.0	4.8	...
CH_3	CH_3	CH_3	H	Colorless plates	165–166	..	$C_{15}H_7O_2(OCH_3)_3$	69.2	5.2	29.8	69.4	5.4	29.9
H	CH_3	CH_3	CH_3O	Cream colored prisms	218–220	75	$C_{15}H_7O_3(OCH_3)_3$	65.9	4.9	27.8	65.8	4.7	28.0
CH_3CO	CH_3	CH_3	CH_3O	Colorless needles	119–122	..	$C_{20}H_{18}O_7$	64.9	4.9	...	64.8	4.8	...
CH_3	CH_3	CH_3	CH_3O	Colorless prisms	164–165 and 167–168 (dimorphic)	..	$C_{15}H_6O_2(OCH_3)_4$	66.7	5.3	36.3	66.7	5.2	36.4
H	$(CH_3)_2CH$	CH_3	H	Cream colored needles	183–184	60	$C_{19}H_{18}O_5$	69.9	5.6	...	69.7	5.5	...
CH_3CO	$(CH_3)_2CH$	CH_3	H	Colorless prisms	205–206	..	$C_{21}H_{20}O_6$	68.5	5.5	...	68.5	5.5	...
H	$(CH_3)_2CH$	CH_3	CH_3O	Cream colored prisms	163–164	65	$C_{20}H_{20}O_6$	67.4	5.7	...	67.4	5.7	...
CH_3CO	$(CH_3)_2CH$	CH_3	CH_3O	Colorless prisms	178–180	..	$C_{22}H_{22}O_7$	66.3	5.6	...	66.6	5.6	...
H	$(CH_3)_2CH$	CH_3	$(CH_3)_2CHO$	Pale yellow needles	152–155 and 160–161 (dimorphic)	60	$C_{22}H_{24}O_6$	68.7	6.3	...	68.7	6.2	...
CH_3CO	$(CH_3)_2CH$	CH_3	$(CH_3)_2CHO$	Colorless needles	155–156	..	$C_{24}H_{26}O_7$	67.6	6.2	...	67.7	6.2	...
H	CH_3	CH_3	$C_6H_5CH_2O$	Yellow needles	198–200	65	$C_{24}H_{20}O_6$	71.3	5.0	...	71.5	4.8	...
CH_3CO	CH_3	CH_3	$C_6H_5CH_2O$	Colorless prisms	191–193	..	$C_{26}H_{22}O_7$	69.9	5.0	...	70.1	5.2	...
H	H	H	H	Yellow needles	257–260	85	$C_{15}H_{10}O_5$	66.7	3.7	...	66.7	3.9	...
CH_3CO	CH_3CO	CH_3CO	H	Colorless needles	181–183	..	$C_{21}H_{16}O_8$	63.6	4.1	...	63.7	4.2	...
H	H	H	HO	Pale yellow needles	>300 dec.	55	$C_{15}H_{10}O_6$	62.9	3.5	...	62.9	3.7	...
CH_3CO	CH_3CO	CH_3CO	CH_3COO	Colorless needles	211–213	..	$C_{23}H_{18}O_{10}$	60.8	4.0	...	60.9	4.1	...
H	H	CH_3	H	Colorless needles	258–262 dec.	65	$C_{15}H_9O_4.O.CH_3$	67.6	4.3	10.9	67.7	4.2	10.7
CH_3CO	CH_3CO	CH_3	H	Colorless needles	211–212	..	$C_{20}H_{16}O_7$	65.2	4.4	...	65.1	4.4	...
H	H	CH_3	CH_3	Pale yellow needles	258–264 dec.	65	$C_{15}H_8O_4(OCH_3)_2$	65.0	4.5	19.7	64.9	4.3	20.1
CH_3CO	CH_3CO	CH_3	CH_3	Colorless prisms	176 and 194.5 (dimorphic)	..	$C_{21}H_{18}O_8$	63.3	4.6	...	63.3	4.6	...
H	H	CH_3	HO	Pale yellow needles	>300° dec.	65	$C_{15}H_9O_5OCH_3$	64.0	4.0	10.3	64.0	4.1	10.4
CH_3CO	CH_3CO	CH_3	CH_3COO	Colorless needles	219–222	..	$C_{22}H_{18}O_9$	62.0	4.3	...	62.0	4.4	...
H	CH_3	CH_3	HO	Pale yellow needles	260 dec.	80	$C_{15}H_8O_4(OCH_3)_2$	65.0	4.5	19.7	65.0	4.4	19.3
CH_3CO	CH_3	CH_3	CH_3COO	Colorless needles	188–191	..	$C_{21}H_{18}O_8$	63.3	4.6	...	63.5	4.8	...

was purified by crystallization from ethanol, in the case of methyl ethers, or in the case of isopropyl compounds, petroleum ether (80–100°). Melting points and crystalline forms of the chalcones together with the results of microanalyses are reported in Table I.

Oxidation of Chalcones with Selenium Dioxide.—A solution of the appropriate chalcone (1 g.) and excess selenium dioxide (resublimed, 3 g.) in *n*-pentyl alcohol (25 ml.) was heated under reflux for 18 hr., filtered, the residue washed repeatedly with boiling ethanol, and the combined filtrate and washings distilled in steam to remove the pentanol. The remaining solid was dissolved in chloroform, dried, and chromatographed on a column of alumina (Spence, grade "O") using chloroform as the eluent). Final purification of the flavone was achieved by crystallization from ethanol and from petroleum ether (b.p. 80–100°).

Analytical data, melting points, etc., of flavones prepared by this method are listed in the first section of Table II.

Oxidation of Chalcones with Alkaline Hydrogen Peroxide.—The following general method was used for the preparation of flavonols from chalcones. Aqueous sodium hydroxide (4%, 30 ml.) and hydrogen peroxide (100 vol., 10 ml.) were added in succession to a solution of the appropriate chalcone (200 mg.) in hot ethanol (15 ml.). After 15 min., the pale yellow solution was acidified and the precipitated flavonol then purified by crystallization from ethanol. Melting points, analytical data, etc., are listed in the first section of Table III. Acetates were prepared by the acetic anhydride–pyridine method and were crystallized from ethanol; methyl ethers were prepared by reaction with methyl sulfate in aqueous ethanolic sodium carbonate. All the flavonols gave intense red-brown colorations with ferric chloride in ethanol.

Complete Demethylation of Flavones and Flavonols.—A solution of the methoxy compound (200 mg.) in aqueous hydrobromic acid (48% w./w., 80 ml.) was heated under reflux for 5 hr., diluted with water, and partially neutralized with sodium hydroxide. The precipitated hydroxy compound was filtered, washed with water until neutral, and purified by crystallization from aqueous acetic acid and from aqueous ethanol.

3-Hydroxy-4′,6,8-trimethoxyflavone furnished only a poor yield of the desired tetrahydroxy compound, contaminated with much intractable resin when it was demethylated by the previous method; therefore, the following procedure was used. A solution of magnesium iodide, prepared from iodine (500 mg.) and excess magnesium in anhydrous ether (50 ml.), was added to 3-hydroxy-4′,6,8-trimethoxyflavone (50 mg.) in anhydrous benzene (20 ml.), the solvents were evaporated *in vacuo*, and the residue heated to 180° for 2 hr. The complex was then decomposed with dilute sulfuric acid and the precipitate collected and dissolved in boiling water. After being thrice extracted with boiling benzene, the aqueous solution was cooled, depositing 3,4′,6,8-tetrahydroxyflavone.

All the hydroxyflavonols prepared by these methods gave dark brown colorations with ferric chloride in ethanol; hydroxyflavones gave negative ferric reactions. Melting points, analytical results, etc., of these compounds and of their acetates, prepared by the pyridine–acetic anhydride method and crystallized from ethanol, are listed in the second section of Tables II and III.

Partial Demethylation of Flavones and Flavonols. (a) **6-Hydroxy-8-methoxyflavone.**—A solution of 6,8-dimethoxyflavone (170 mg.) in acetic acid (3.5 ml.) and hydrobromic acid (48% w./w., 25 ml.) was refluxed for 12 min., diluted with water, treated with sodium hydroxide, and extracted with ether to remove unchanged starting material. Acidification furnished a precipitate from which a small quantity of dihydroxyflavone was obtained by crystallization from aqueous ethanol. Chromatographic examination of the residue (85 mg.) on "Separa" paper using the upper phase of benzene–pyridine–water (100:0.6:100) as irrigant, showed it to contain two hydroxymethoxyflavones, one in relatively small concentration. Two crystallizations from benzene furnished pure 6-hydroxy-8-methoxyflavone (45 mg.).

(b) **6-Hydroxy-4,8-dimethoxyflavone.**—A solution of 4′,6,8-trimethoxyflavone (150 mg.) in acetic acid (4 ml.) and hydrobromic acid (48% w./w., 50 ml.) was refluxed for 20 min., diluted with water, and brought to pH 5.0 with sodium hydroxide. The resulting precipitate was dissolved in boiling aqueous acetic acid (50%, 50 ml.), the solution thrice extracted with boiling petroleum ether (b.p. 100–120°, 20 ml.), and the raffinate cooled, depositing needles (90 mg.). Crystallization from benzene–petroleum ether and from aqueous ethanol furnished 6-hydroxy-4′,8-dimethoxyflavone (65 mg.).

(c) **4′,6-Dihydroxy-8-methoxyflavone.**—A solution of the

trimethoxyflavone in the same quantities of acetic and hydrobromic acid as in the last experiment was refluxed for 40 min., diluted with water, neutralized, and the resulting precipitate dissolved in aqueous acetic acid (50%, 50 ml.) and extracted with boiling benzene (three 20-ml. portions). The cooled aqueous liquors deposited a solid which, after trituration with boiling benzene and crystallization from aqueous acetic acid, afforded 4',6-dihydroxy-8-methoxyflavone.

(d) **3,6-Dihydroxy-8-methoxyflavone.**—3-Hydroxy-6,8-methoxyflavone (100 mg.) was partially demethylated in boiling acetic (5 ml.) and hydrobromic acids (48% w./w., 40 ml.) during 15 min., the product isolated as before, and dissolved in boiling aqueous acetic acid (50%, 75 ml.). After extraction with boiling petroleum ether (100–120°, three 20-ml. portions), the aqueous liquors were heated with charcoal. The yellow needles obtained on cooling were crystallized from benzene–petroleum ether and then from aqueous ethanol yielding 3,6-dihydroxy-8-methoxyflavone (24 mg.).

The melting points of these compounds were undepressed on admixture with the appropriate authentic specimen obtained from the corresponding isopropoxymethoxyflavone. All four compounds were readily soluble in aqueous sodium hydroxide but only the flavonol gave a ferric coloration (dark brown in ethanol). Analytical data, etc., of these compounds and their acetates, crystallized from ethanol or aqueous ethanol, are summarized in the third sections of Tables II and III.

Deisopropylation of Methoxyisopropoxyflavones.—The following general method of effecting selective cleavage of the isopropyl groups of isopropoxymethoxy compounds was employed. To a solution of the isopropoxymethoxyflavone or -flavonol (150 mg.) in boiling acetic acid (2 ml.), boiling hydrobromic acid (48% w./w., 10 ml.) was added; the mixture was heated for a further 3 min. and poured into water (100 ml.). The resulting solid was collected, washed with water, and freed from starting material either (if a flavone) by dissolving in aqueous sodium hydroxide and extracting uncleaved ethers with benzene or (if a flavonol) by dissolving in boiling aqueous acetic acid (1:1, 180 ml.) and extracting these with boiling petroleum ether (b.p. 100–120°, three 2-ml. portions). Purification from demethylated compounds was then effected by crystallization from aqueous acetic acid or aqueous methanol. The characteristics of hydroxymethoxyflavones and -flavonols prepared in this way, and of their acetates are listed in the third sections of Tables II and III.

4'-Hydroxy-6,8-dimethoxy- and 3,4'-Dihydroxy-6,8-dimethoxyflavones.—The corresponding 4-benzyl ethers (150 mg.) were dissolved in acetic acid (10 ml.) and concentrated hydrochloric acid (10 ml.), heated in the steam bath for 1 hr., and evaporated *in vacuo*. Crystallization of the residue from aqueous ethanol furnished the 4'-hydroxyflavones; melting points, analytical data, etc., of these compounds and of their acetates are recorded in the third sections of Tables II and III.

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The Δ^4-Ethylene Ketals of Testosterone and Testosterone Acetate[1]

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Ketalization of testosterone acetate with ethylene glycol by conventional methods with a low concentration of *p*-toluenesulfonic acid catalyst produced a mixture of 3,3-ethylenedioxyandrost-4-en-17β-ol acetate and the well known Δ^5-ketal. Under similar conditions, analogous results were obtained with testosterone. The structures of these new isomeric ketals have been demonstrated by both chemical and physical methods. The Δ^4-ketal of testosterone acetate has been converted by acid catalysis to its Δ^5-isomer.

During the preparation of the ethylene glycol ketal of testosterone acetate (3,3-ethylenedioxyandrost-5-en-17β-ol acetate) as an intermediate for other work, a compound having markedly different physical properties was isolated in fair yield (34%), in addition to the desired product. The analytical data of the new compound were correct for the desired Δ^5-ketal, but the compounds differed in melting point (159–161° *vs.* 202–204° for the known[2] ketal) and in optical rotation (+80.0° *vs.* −52.1° for the known ketal). Neither compound absorbed in the ultraviolet region of the spectrum. A comparison of the infrared spectra showed only minor differences, the most notable of which was the appearance of a weak absorption band at 6.04–6.05 μ in the spectrum[3] of the isomeric compound; a less well defined weak band appeared in the spectrum of the known ketal just below 6.00 μ. These observations led to the tentative conclusion that the isomeric ketal (II, see Fig. 1) possessed a double bond in position 4,5 of the steroid nucleus, in contrast to the 5,6-double bond of the known compound.

Saponification of the acetoxy ketal II led to a hydroxy ketal III which was isomeric with the known Δ^5-ketal[2] of testosterone. Differing physical properties were evident here as with the 17β-acetoxy compounds; there was a different melting point (225–232° *vs.* 185–187° for the known Δ^5-ketal) and a difference in optical rotation (+95.1° *vs.* −45.5° for the Δ^5-isomer). In addition, the infrared spectrum of the new hydroxy ketal displayed a weak absorption band at 6.04 μ in contrast to the 5.98-μ band[3] of the known Δ^5-compound[2] V.

By azeotropic ketalization of testosterone (IV) under similar conditions the Δ^4-ketal of testosterone III was prepared in 30% yield, along with the known Δ^5-ketal V (26% yield). Compound III was identical with that obtained by saponification of the Δ^4-ketal of testosterone acetate and could be converted to the latter by acetylation (see Fig. 1).

Of particular interest were the molar rotational differences between the members of each pair of isomeric compounds.

M_D of Δ^4-17β-Acetoxy ketal II (+300) *minus*	ΔM_D
M_D of Δ^5-17β-Acetoxy ketal VI (−195)	= 495
M_D of Δ^4-17β-Hydroxy ketal III (+320) *minus*	
M_D of Δ^5-17β-Hydroxy ketal V (−151)	= 471

(1) Abstracted in part from the Ph.D. dissertation of J. W. D., Rensselaer Polytechnic Institute, January, 1962.

(2) R. Antonucci, S. Bernstein, R. Lenhard, K. J. Sax, and J. H. Williams, *J. Org. Chem.*, **17**, 1341 (1952).

(3) G. Roberts, B. S. Gallagher, and R. N. Jones, "Infrared Absorption Spectra of Steroids," Vol. II, Interscience Publishers, Inc., New York, N. Y., 1958, p. 11. Δ^5-Steroids are reported to absorb in the 5.97–6.00-μ region, and Δ^4-compounds at *ca.* 6.04 μ.