[CONTRIBUTION FROM THE SMITH, KLINE AND FRENCH LABORATORIES, PHILADELPHIA, AND THE ORGANIC CHEMISTRY LABORATORY OF THE UNIVERSITY OF LIVERPOOL]

Some Isoflavones Derived from Genistein[1,2]

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The unequivocal synthesis of 4′,5,7-trihydroxy-8-methylisoflavone (VI) by several mutually confirmatory methods has conclusively demonstrated that the substances previously described as (VI), 7-hydroxy-4′,5-dimethoxy-8-methylisoflavone (X) and 2,4-dihydroxy-6-methoxy-3-methylphenyl 4-methoxybenzyl ketone (IX) are incorrectly designated and furthermore that the so-called "methylgenistein" isolated from Soya beans has not the structure (VI), previously allocated to it. Similarly, the synthesis of 2′,5,7-trimethoxy-8-methylisoflavone (XIX) indicates that a second compound isolated from the same source and termed "methylisogenistein" (XVIII) is also incorrectly formulated. The preparation of several isoflavones closely allied to genistein is described together with the synthesis of genistein 4′,5-dimethyl ether (XXVIII), and an unequivocal proof for the formulation of the C-methylation product of genistein as 5-hydroxy-4′,7-dimethoxy-6-methylisoflavone (XXX) is detailed.

The isolation from Soya beans of three substances to which the structures 4′,5,7-trihydroxy-8-methylisoflavone (VI, methylgenistein), 2′,5,7-trihydroxy-8-methylisoflavone (XVIII, methylisogenistein) and 2′,5,7-trihydroxyisoflavone (XXV, isogenistein) were allocated on the basis of degradative experiments, is described by Okano and Beppu.[3]

With the object of preparing methylgenistein (VI), Shriner and Hull[4] condensed 2,6-dihydroxy-4-methoxytoluene (VIII) with *p*-methoxyphenylacetonitrile and obtained, they believed, 2,4-dihydroxy-6-methoxy-3-methylphenyl 4-methoxybenzyl ketone (IX). Cyclization of this ketone (IX) with sodium and ethyl formate gave rise to a product which was apparently 7-hydroxy-4′,5-dimethoxy-8-methylisoflavone (X). Demethylation of (X) with hydriodic acid furnished a substance to which they assigned the structure of 4′,5,7-trihydroxy-8-methylisoflavone (VI), the properties of which were in accordance with those described[3] for "methylgenistein," although direct comparison of the natural and synthetic products was not made. The possibility, which is a very real one with oxygen heterocyclics, of isomerization having occurred during the demethylation[5] of (V), to give not (VI), but the isomeric 4′,5,7-trihydroxy-6-methylflavone (XXXI), does not seem to have been considered by Shriner and Hull.[4]

In view of this possibility which these authors did not exclude, together with the recently described[6] facile method for the preparation in quantity of C-methylphloroglucinol, it seemed desirable to repeat the synthesis of Shriner and Hull[4] with the object of clarifying this obvious ambiguity and also to attempt the syntheses of methylisogenistein (XVIII) and of isogenistein (XXV).

The condensation of 2-hydroxy-4,6-dimethoxytoluene (III) with *p*-methoxyphenylacetonitrile readily furnished the ketone (IV) whilst methylphloroglucinol (I) and the same nitrile produced the ketone (II) which on methylation gave (IV) in accordance with the well established behavior of phloroglucinol and its derivatives.[7] Cyclization of 2-hydroxy-4,6-dimethoxy-3-methylphenyl 4-methoxybenzyl ketone (IV) with sodium and methyl formate gave 4′,5,7-trimethoxy-8-methylisoflavone (V), (O-trimethylmethylgenistein) of m.p. 180° as opposed to the melting point 154–155° recorded by Okano and Beppu.[3] The demethylation of the isoflavone (V) proceeded smoothly to yield 4′,5,7-trihydroxy-8-methylisoflavone (VI), the structure of which was clearly authenticated by the regeneration of 4′,5,7-trimethoxy-8-methylisoflavone (V) upon remethylation. The properties of this synthetic isoflavone (VI) are not in accordance with those described by Okano and Beppu[3] or by Shriner and Hull[4] for their respective compounds.

Seeking cause for the latter discrepancy, 2,6-dihydroxy-4-methoxytoluene (VIII) was condensed with *p*-methoxyphenylacetonitrile exactly as described by Shriner and Hull[4] with the production of 2,4-dihydroxy-6-methoxy-3-methylphenyl 4-methoxybenzyl ketone (IX), m.p. 162°. The American authors record a melting point of 125–127°. The authenticity of the present specimen of the phenylbenzyl ketone IX was proven by methylation to give 2-hydroxy-4,6-dimethoxy-3-methylphenyl 4-methoxybenzyl ketone (IV) identical with the products prepared by the alternate methods described in this memoir. Furthermore, cyclization of (IX) with sodium and methyl formate gave 7-hydroxy-4′,5-dimethoxy-8-methylisoflavone (X) of m.p. 298° (dec.) as opposed to the m.p. 272° described[4]; in addition, the structure of (X) was placed beyond all doubt by demethylation to a product identical with the previously prepared 4′,5,7-trihydroxy-8-methylisoflavone (VI) and by methylation to 4′,5,7-trimethoxy-8-methylisoflavone (V) which was identical with the previously prepared specimens. Specimens of 2,6-dihydroxy-4-methoxytoluene prepared by two alternative methods (see Experimental) gave the same ketone (IX) and isoflavone (X).

Further evidence for the authenticity of our products was provided by the condensation of 2,6-di-

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(2) Presented before the Division of Organic Chemistry of the American Chemical Society, Atlantic City, N. J., September 14 to 19, 1952.

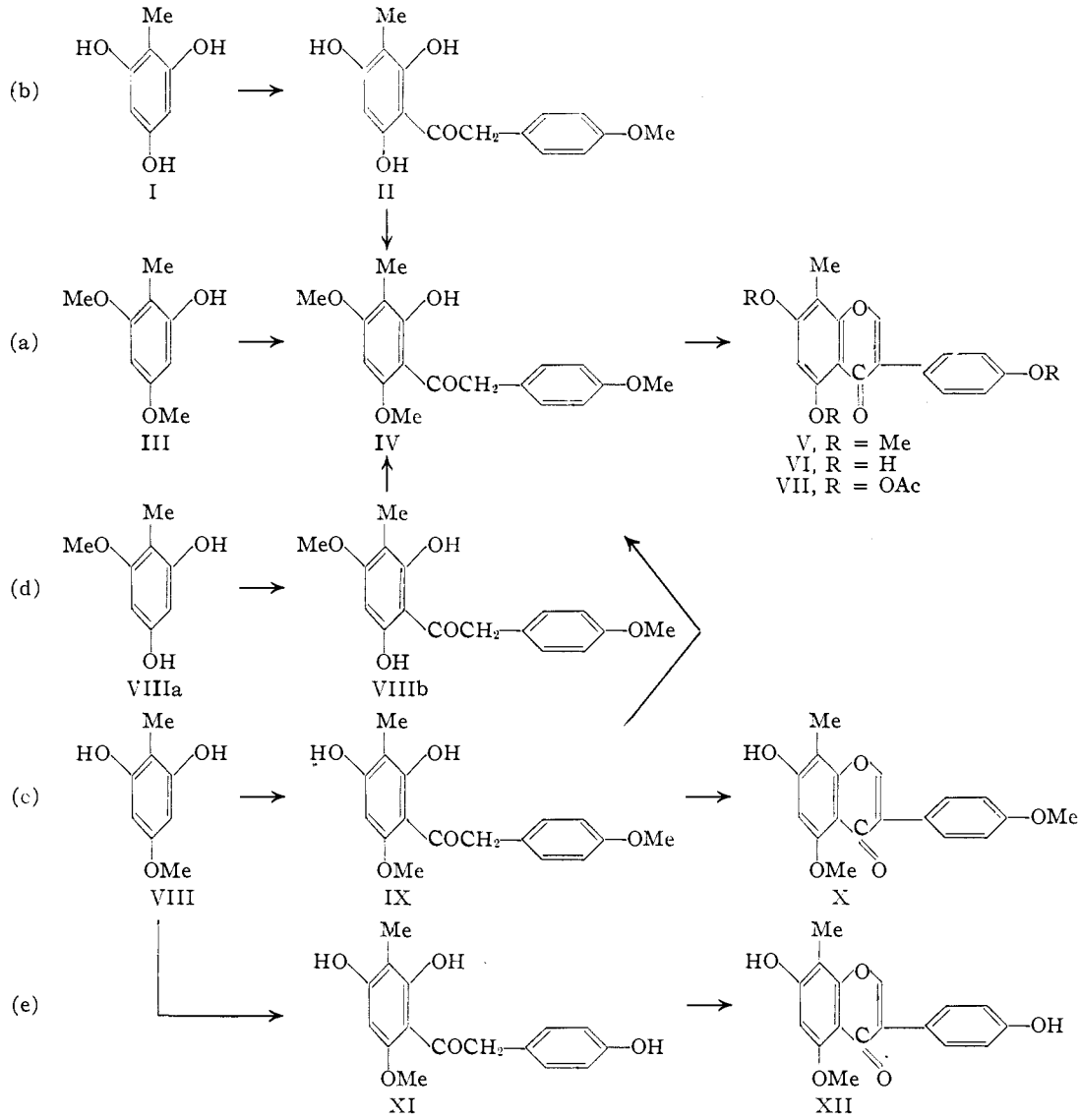
(3) K. Okano and I. Beppu, *J. Agr. Chem. Soc. Japan*, **15**, 645 (1939) [*C. A.*, **34**, 429 (1940)].

(4) R. L. Shriner and C. J. Hull, *J. Org. Chem.*, **10**, 228 (1945).

(5) See for example the production of (a) 5′,6-dihydroxyflavone from 5,8-dimethoxyflavone, W. Baker, N. C. Brown and J. A. Scott, *J. Chem. Soc.*, 1922 (1939); (b) 5,7-dihydroxy-2,8-dimethylchromone from 5-hydroxy-7-methoxy-2,6-dimethylchromone, H. Schmid and A. Bolleter, *Helv. Chim. Acta*, **33**, 917 (1950); (c) isovisnagin from visnagin methyl ether, J. R. Clarke, G. Glaser and A. Robertson, *J. Chem. Soc.*, 2260 (1948).

(6) A. Robertson and W. B. Whalley, *ibid.*, 3355 (1951).

(7) F. Curd and A. Robertson, *ibid.*, 437 (1933).



hydroxy-4-methoxytoluene (VIII) with *p*-hydroxyphenylacetonitrile to produce 2,4-dihydroxy-6-methoxy-3-methylphenyl 4-hydroxybenzyl ketone (XI), which gave rise to (IV) upon methylation and to 4′,7-dihydroxy-5-methoxy-8-methylisoflavone (XII) upon cyclization with sodium and methyl formate. Methylation of this isoflavone (XII) furnished 4′,5,7-trimethoxy-8-methylisoflavone (V) whilst demethylation formed the corresponding trihydroxymethylisoflavone (VI).

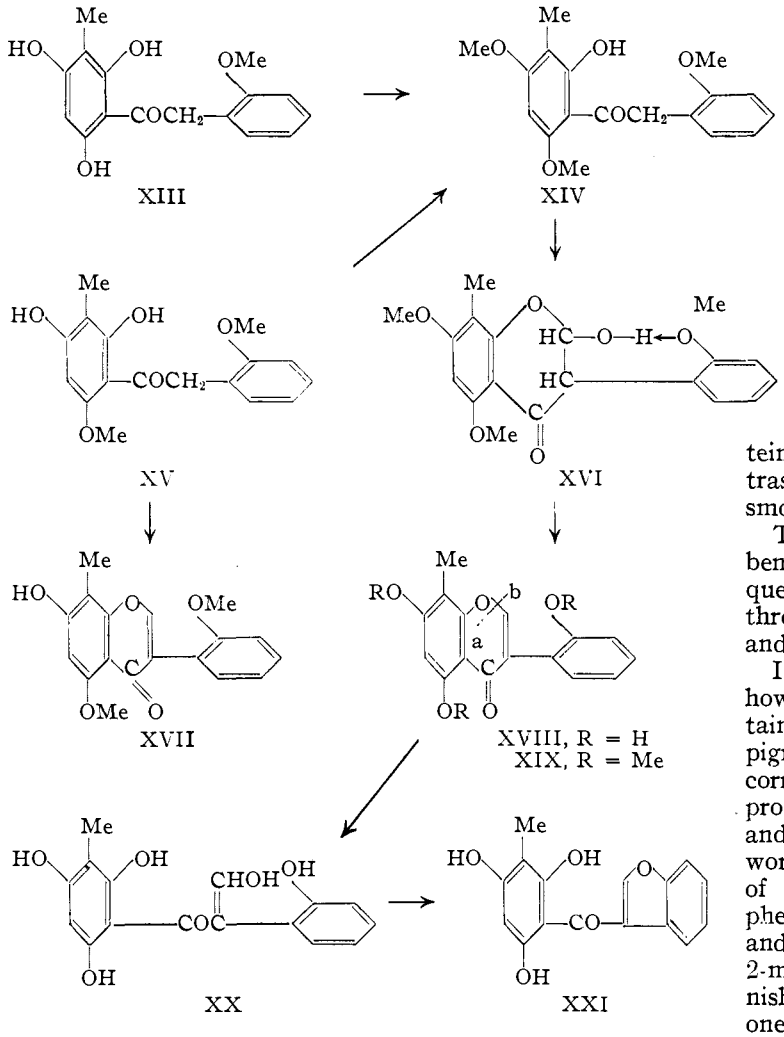
Finally, the condensation of 2,4-dihydroxy-6-methoxytoluene (VIIIa) with *p*-methoxyphenylacetonitrile furnished 2,6-dihydroxy-4-methoxy-3-methylphenyl 4-methoxybenzyl ketone (VIIIb) which was readily converted by methylation into 2-hydroxy-4,6-dimethoxy-3-methylphenyl 4-methoxybenzyl ketone (IV), identical with the previously prepared specimens.

The authenticity of the *p*-methoxyphenylacetonitrile was proven by hydrolysis in almost quantitative yield to *p*-methoxyphenylacetic acid, identical with an authentic specimen, and by the condensation of this nitrile with phloroglucinol to form 2,4,6-trihydroxyphenyl 4-methoxybenzyl ketone, identical with an independently prepared specimen.[8]

Consequently the conclusion appears inevitable that the "methylgenistein" of Okano and Beppu[3] is not identical with 4′,5,7-trihydroxy-8-methylisoflavone (VI) and furthermore that the substances designated as 2,4-dihydroxy-6-methoxy-3-methylphenyl 4-methoxybenzyl ketone (IX), 4′,5,7-trihydroxy-8-methylisoflavone (VI) and 7-hydroxy-4′,5-dimethoxy-8-methylisoflavone (X) by Shriner and Hull[4] are otherwise.

The synthesis of methylisogenistein (XVIII) was now investigated. Interaction of methylphloroglucinol and *o*-methoxyphenylacetonitrile furnished 2,4,6-trihydroxy-3-methylphenyl 2-methoxybenzyl ketone (XIII), which was converted by methylation to 2-hydroxy-4,6-dimethoxy-3-methylphenyl 2-methoxybenzyl ketone (XIV), identical with the product obtained by the Hoesch condensation of 2-hydroxy-4,6-dimethoxytoluene (III) and *o*-methoxyphenylacetonitrile. Cyclization of this ketone (XIV) in the usual way yielded 2′,5,7-trimethoxy-

(8) G. G. Badcock, G. W. K. Cavill, A. Robertson and W. B. Whalley, *J. Chem. Soc.*, 2961 (1950).



8-methylisoflavone (XIX), the m.p. 185° of which also differed very considerably from that of 154° recorded for the trimethyl ether of the methylisogenistein of Okano and Beppu.[3] Furthermore, the condensation of 2,6-dihydroxy-4-methoxytoluene (VIII) with *o*-methoxyphenylacetonitrile gave rise to the ketone (XV) which readily furnished (XIV) on methylation and 7-hydroxy-2',5-dimethoxy-8-methylisoflavone (XVII) upon cyclization. Thus it would appear from the available evidence that the so-called methylisogenistein does not possess the structure (XVIII). Repeated attempts to demethylate (XIX) under a wide variety of conditions were unsuccessful: extensive and rapid decomposition occurred even under the most mild circumstances. As far as we are aware no 2'-hydroxyisoflavones have ever been synthesized and the failure to produce one here may well be due to the opening of the chromone ring under the influence of acid reagents across the dotted line (a, b in XIX), with the production of an intermediate of type (XX) which would be readily converted into an α-unsubstituted benzofuran of type (XXI) possessing a very high sensitivity to acid.

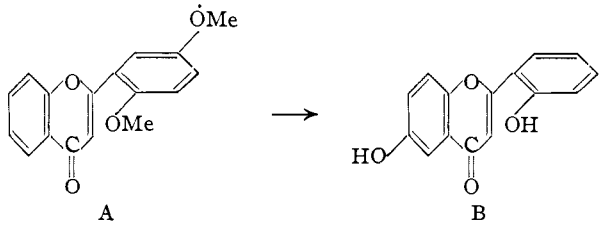
The production of a derivative of type (XXI) could of course occur only with 2'-methoxyisoflavones and in agreement with this hypothesis the demethylation of 3'- and 4'-methoxylated isoflavones proceeds normally.[9]

Similarly 2',5,7-trimethoxyisoflavone (XXVI) prepared by standard methods by way of the phenyl benzyl ketones (XXII and XXIII) could not be successfully demethylated. Cyclization with sodium and methyl formate of the ketone (XXVII) prepared from phloroglucinol monomethyl ether and *p*-methoxyphenylacetonitrile readily gave rise to 7-hydroxy-4',5-dimethoxyisoflavone (XXVIII), thus providing the first synthesis of genistein 4',5-dimethyl ether which in contrast to the 2'-methoxyisoflavones was smoothly demethylated to yield genistein.

The cyclization of *o*-hydroxyphenyl benzyl ketones to isoflavones has frequently been postulated as proceeding through intermediates of type (XXIV)[10] and (XXIVa).

In only a very small number of instances however, namely, the conversion of certain derivatives of the complex orange pigments Osajin and Pomiferin[10b] into the corresponding isoflavones have crystalline products of type (XXIV) been isolated and characterized. During the present work it has been observed that cyclization of 2-hydroxy-4,6-dimethoxy-3-methylphenyl 2-methoxybenzyl ketone (XIV) and of 2-hydroxy-4,6-dimethoxyphenyl 2-methoxybenzyl ketone (XXIII) furnished stable compounds which contained one molecule of water in excess of that required by the respective isoflavones. These intermediates were readily converted to the corresponding isoflavones when boiled in acetic acid solution: they sublimed with decomposition. The absence of aldehydic reducing properties, the insolubility in cold 2 *N* sodium hydroxide solution, together with the decomposition on sublimation to produce phenolic ketones and the exhibition of negative Wilson boric acid tests[9] indicates that these compounds are almost certainly the 2-hydroxy-2,3-dihydroisoflav-

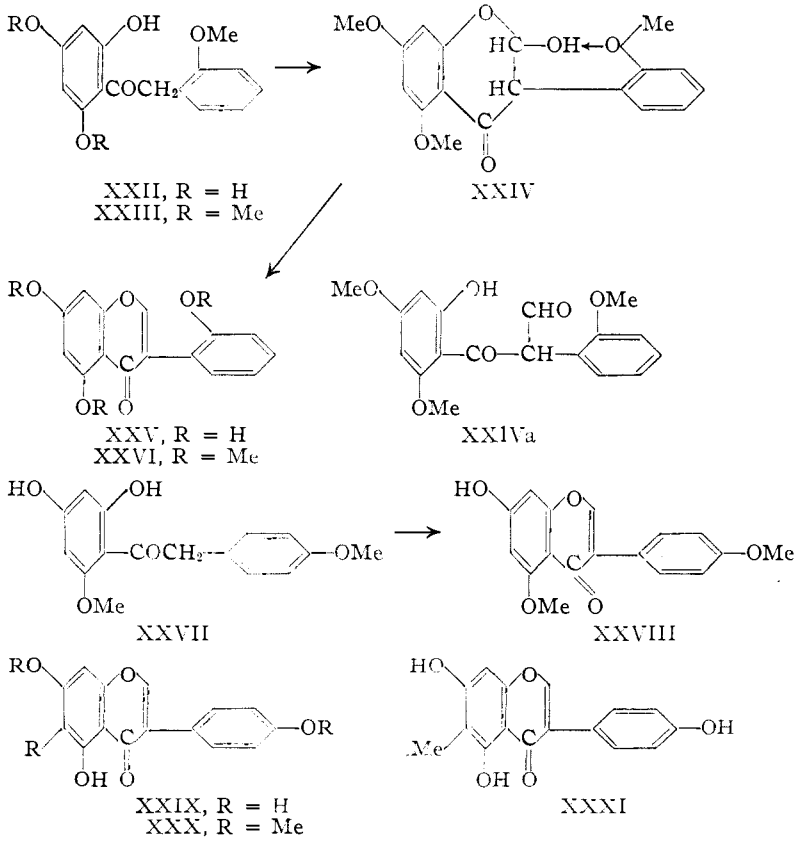
(9) (a) See *inter alia*, A. Robertson, C. W. Suckling and W. B. Whalley, *J. Chem. Soc.*, 1671 (1949); (b) the observation of E. M. Philbin and T. S. Wheeler, *Chemistry and Industry*, 449 (1952), published after the completion of this manuscript, and recording the formation of 2',6-dihydroxyflavone (B) by the demethylation of 2',5'-dimethoxyflavone (A) is probably significant in connection with the hypothesis advanced here to explain the abnormal demethylation of 2'-methoxyisoflavones.



(10) (a) E. Späth and E. Lederer, *Ber.*, **63**, 743 (1930); (b) M. L. Wolfrom, J. E. Mahan, P. W. Morgan and G. F. Johnson, THIS JOURNAL, **63**, 1248 (1941).

ones (XVI) and (XXIV) rather than the open chain type of intermediate (XXIVa) or mere hydrates of the corresponding isoflavones. This view is also supported by a comparison of the ultraviolet absorption spectra of (XVI) and (XIX), Fig. 1, and of (XXIV) and (XXVI), Fig. 2. As far as we are aware this is the first recorded example of the isolation of such products from the isoflavone cyclization of simple *o*-hydroxyphenyl benzyl ketones and the stability of the products may be attributed in part at least to the possibility of hydrogen bonding of the type shown in (XVI) and (XXIV).

When genistein (XXIX) is methylated with methyl iodide in sodium methoxide solution a C-methyl-O-dimethyl ether[11] which has been formulated as (XXX) is formed. A specimen of this methyldimethylgenistein prepared as described was demethylated smoothly with hydriodic acid to yield 4′,5,7-trihydroxy-6-methylisoflavone (XXXI) the structure of which was clearly authenticated by the non-identity with the isomeric 4′,5,7-trihydroxy-8-methylisoflavone (VI) and by remethylation to regenerate (XXX). The correctitude of the structure (XXX) allocated to this methylation product of genistein was thus established. The position of entry of the C-methyl residue is in accordance with the established behavior of the phloroglucinol system and parallels the production, under similar conditions, of eugenitin from 5,7-dihydroxy-2-methylchromone.[12]



(11) W. Baker and R. Robinson, *J. Chem. Soc.*, 2713 (1926).
(12) W. B. Whalley, THIS JOURNAL, **74**, 5795 (1952).

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Experimental

Starting Materials.—Since the results reported in this communication differ considerably from those of previous investigators the sources and physical constants of the important starting materials may be usefully summarized as

Starting material	Method of preparation	M.p., °C.
2-Hydroxy-4,6-dimethoxytoluene	Ref. 6	67
2,4,6-Trihydroxytoluene	Ref. 6	215
2,6-Dihydroxy-4-methoxytoluene	Ref. 6,7	124
2,4-Dihydroxy-6-methoxytoluene	Ref. 6	119 (anhydrous
o-Methoxyphenylacetonitrile	By the azlactone method from *o*-methoxybenzaldehyde	68
p-Methoxyphenylacetonitrile	Ref. 4	B.p. 130–132 (10 mm.)

4′,5,7-Trimethoxy-8-methylisoflavone (V). Method (a). 2-Hydroxy-4,6-dimethoxy-3-methylphenyl 4-Methoxybenzyl Ketone (IV).—A solution of 2-hydroxy-4,6-dimethoxytoluene (2.5 g.) and *p*-methoxyphenylacetonitrile (3 g.) in ether (75 ml.) containing anhydrous zinc chloride (1.5 g.) was saturated at 0° with hydrogen chloride. Three days later the viscous oily red layer was separated, washed with ether and hydrolyzed with water (50 ml.) on the steam-bath during 20 minutes. The crystalline solid that separated on cooling was purified from methanol and then ethanol to form the ketone (1.8 g.) in almost colorless, slender needles, m.p. 116°, having an intense red-brown ferric reaction in alcohol.

Anal. Calcd. for $C_{18}H_{20}O_5$: C, 68.34; H, 6.32. Found: C, 68.48; H, 6.48.

Concentration of the alcoholic mother liquors gave rise to a compound which appeared to be the isomeric **4-hydroxy-2,6-dimethoxy-3-methylphenyl 4-methoxybenzyl ketone** in amounts too small for purification.

4′,5,7-Trimethoxy-8-methylisoflavone.—A solution of the previous ketone (1.5 g.) in methyl formate (40 ml.) was added to powdered sodium (1.5 g.) at −10°. After 24 hours at −5° and 2 days at room temperature, the reaction mixture was decomposed by the addition of ice-water. Extraction with ether gave rise to the parent ketone (100 mg.). Ether extraction of the acidified aqueous solution furnished an almost colorless oil which exhibited an intense red-brown ferric reaction in alcohol and could not be crystallized. When a solution of this oil in acetic acid (5 ml.) was refluxed for 25 minutes and the reaction mixture diluted with water (100 ml.) a colorless crystalline solid (1.19 g.) separated. Purification from ethyl acetate gave rise to 4′,5,7-trimethoxy-8-methylisoflavone in squat, stout, colorless tablets, m.p. 180°, having a negative ferric reaction in alcohol and insoluble in 2 *N* sodium hydroxide solution. Sublimation at 190° (0.01 mm.) did not change the m.p.

Anal. Calcd. for $C_{19}H_{18}O_5$: C, 69.93; H, 5.56. Found: C, 69.92; H, 5.61.

Method (B). 2,4,6-Trihydroxy-3-methylphenyl 4 Methoxybenzyl Ketone (II).—A solution of C-methylphloroglu-

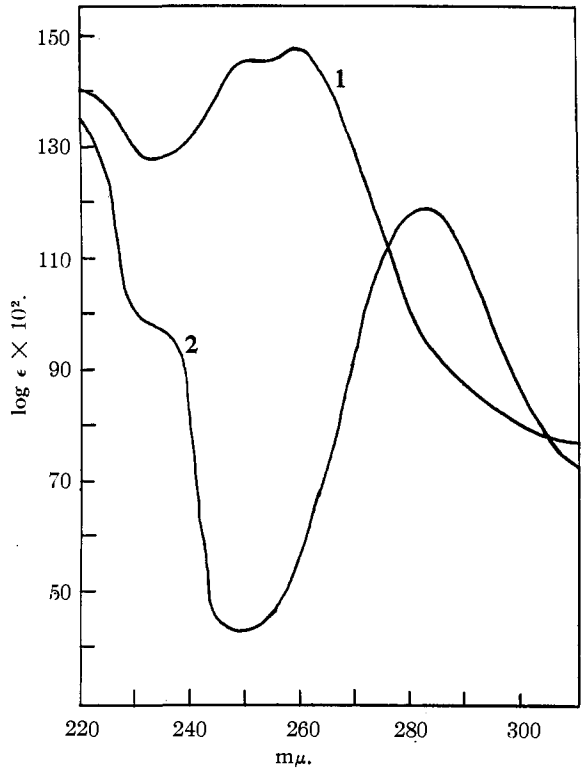

Fig. 1.—Curve 1, 2′,5,7-trimethoxy-8-methylisoflavone; curve 2, 2,3-dihydro-2-hydroxy-2′,5,7-trimethoxy-8-methylisoflavone.

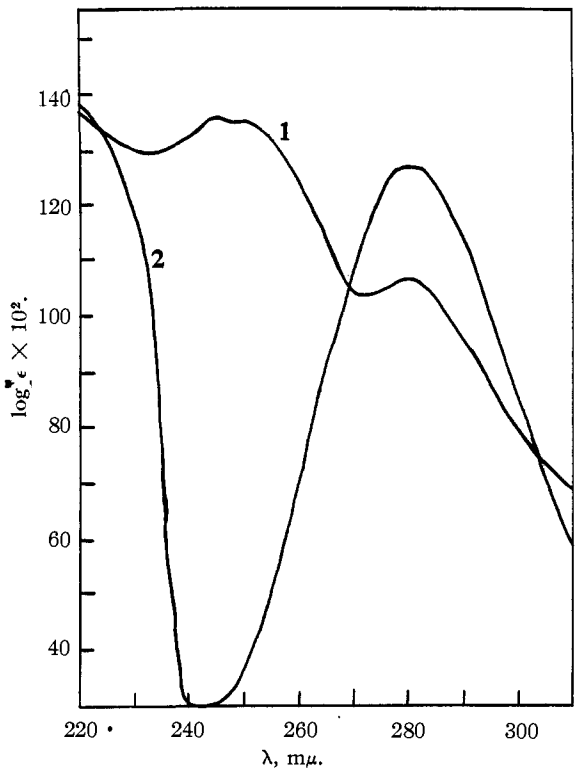

Fig. 2.—Curve 1, 2′,5,7-trimethoxyisoflavone; curve 2, 2,3-dihydro-2-hydroxy-2′,5,7-trimethoxyisoflavone.

cinol (6 g.) and *p*-methoxyphenylacetonitrile (5 g.) in absolute ether (100 ml.) containing zinc chloride (3 g.) was saturated with hydrogen chloride at 0° and two days later the product after isolation in the usual way was purified from aqueous methanol to furnish the ketone (2.5 g.) in almost colorless, slender needles, m.p. 228°.

Anal. Calcd. for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.59; H, 5.64.

This compound exhibits an intense green-brown ferric reaction in alcohol and sublimed at 160° (0.01 mm.) to give very pale yellow needles, m.p. 228°.

Methylation of the foregoing ketone (2 g.) in boiling acetone (75 ml.) containing potassium carbonate (7 g.) and dimethyl sulfate (2 g.) during 3 hours and isolation of the product in the usual way gave rise to 2-hydroxy-4,6-dimethoxyphenyl 4-methoxybenzyl ketone (1.5 g.) which separated from methanol in almost colorless slender needles, m.p. 116°, and identical with the product prepared by method (a). Cyclization to the isoflavone as in (a) gave rise to a product identical in every way with the isoflavone prepared by route (a).

Method (c). 2,4-Dihydroxy-6-methoxy-3-methylphenyl 4-Methoxybenzyl Ketone (IX).—A solution of 2,6-dihydroxy-4-methoxytoluene[13] (3 g.) and *p*-methoxyphenylacetonitrile (2.5 g.) in ether (75 ml.) containing zinc chloride (2 g.) was saturated at 0° with hydrogen chloride. Isolation of the product in the usual way gave rise to the ketone (1.7 g.) which separated from aqueous methanol in slender, colorless needles, m.p. 162°, and having an intense violet-brown ferric reaction in alcohol.

Anal. Calcd. for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C, 67.49; H, 6.38.

Shriner and Hull[4] record the m.p. 125–127°.

Methylation of this ketone by the methyl iodide–potassium carbonate method gave rise to 2-hydroxy-4,6-dimethoxy-3-methylphenyl 4-methoxybenzyl ketone (IV) identical with the products prepared by methods (a) and (b).

(13) This phenol was prepared by two methods: (a) F. Curd and A. Robertson, *J. Chem. Soc.*, 437 (1933); (b) W. B. Whalley, *ibid.*, 3229 (1951). Each preparation gave the same ketone (IX) with *p*-methoxyphenylacetonitrile.

7-Hydroxy-4′,5-dimethoxy-8-methylisoflavone (X).—A solution of 2,4-dihydroxy-6-methoxy-3-methylphenyl 4-methoxybenzyl ketone (1.6 g.) in methyl formate (30 ml.) was added slowly to powdered sodium (0.8 g.) at 0°. After 24 hours at 0° and 2 days at room temperature the product was isolated according to the method of Shriner and Hull[4] to give 7-hydroxy-4′,5-dimethoxy-8-methylisoflavone (0.5 g.) which separated from a large volume of alcohol in colorless, glistening, stout prisms, m.p. 298° (dec.). Shriner and Hull[4] record the m.p. 272°.

Anal. Calcd. for $C_{18}H_{16}O_5$: C, 69.23; H, 5.12. Found: C, 69.29; H, 5.67.

This compound is sparingly soluble in methanol and ethanol, very sparingly soluble in ethyl acetate, readily soluble in 2 *N* sodium hydroxide solution and has a negative ferric reaction in alcohol.

Methylation of this isoflavone (100 mg.) in boiling acetone (50 ml.) containing potassium carbonate (1 g.) and dimethyl sulfate (1 g.) during 8 hours, and isolation of the product in the usual way furnished 4′,5,7-trimethoxy-8-methylisoflavone (100 mg.), m.p. 180°, identical with the products prepared by method (a) and (b).

Method (d). 2,6-Dihydroxy-4-methoxy-3-methylphenyl 4-Methoxybenzyl Ketone.—Prepared from 2,4-dihydroxy-6-methoxytoluene[6] (0.75 g.), *p*-methoxyphenylacetonitrile (1 g.) and zinc chloride (1 g.) in ether (50 ml.) the ketone (0.6 g.) separated from aqueous methanol in shimmering, pale-yellow plates, m.p. 192°, exhibiting an intense olive-green ferric reaction in alcohol.

Anal. Calcd. for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C, 67.01; H, 6.46.

Methylation of this ketone by the dimethyl sulfate–acetone–potassium carbonate method furnished a quantitative yield of 2-hydroxy-4,6-dimethoxy-3-methylphenyl 4-methoxybenzyl ketone (IV), m.p. 116°, identical in every way with the products prepared by methods (a), (b) and (c).

Method (e). 2,4-Dihydroxy-6-methoxy-3-methylphenyl 4-Hydroxybenzyl Ketone (XI).—A solution of 2,6-dihydroxy-4-methoxytoluene[13] (1.5 g.) and *p*-hydroxyphenylacetonitrile (1.5 g.) in ether (75 ml.) containing zinc chloride (1 g.) was saturated at 0° with hydrogen chloride. Isolation of the product 8 hours later gave rise to the ketone (1.4 g.) which

separated from aqueous methanol in slender, pale-yellow needles, m.p. 207°, having an intense violet-brown ferric reaction in alcohol.

Anal. Calcd. for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59; OMe (1), 10.76. Found: C, 66.24; H, 5.86; OMe, 11.32.

Methylation of this ketone by the dimethyl sulfate–acetone–potassium carbonate method furnished 2-hydroxy-4,6-dimethoxy-3-methylphenyl 4-methoxybenzyl ketone (IV), m.p. 116°, identical with the product prepared by methods (a), (b), (c) and (d).

7,4′-Dihydroxy-5-methoxy-8-methylisoflavone (XII).—A solution of 2,4-dihydroxy-6-methoxy-3-methylphenyl 4-hydroxybenzyl ketone (XI) (1 g.) in methyl formate (40 ml.) was added to powdered sodium (1.3 g.) at −5°. After 24 hours at 0° and a further 8 hours at room temperature, the product, isolated in the usual manner, crystallized from aqueous acetic acid to give 7,4′-dihydroxy-5-methoxy-8-methylisoflavone (0.3 g.) in very pale yellow prisms, m.p. 304° (dec.), readily soluble in 2 *N* sodium hydroxide solution and having a negative ferric reaction in alcohol.

Anal. Calcd. for $C_{17}H_{14}O_5$: C, 68.45; H, 4.73. Found: C, 68.63; H, 4.95.

Methylation of this isoflavone with dimethyl sulfate in acetone gave rise to 4′,5,7-trimethoxy-8-methylisoflavone in quantitative yield identical with the product prepared by methods (a) and (b).

4′,5,7-Trihydroxy-8-methylisoflavone (VI).—Demethylation of any of the previously prepared specimens of 4′,5,7-trimethoxy-8-methylisoflavone (1 g.) by refluxing with hydriodic acid (sp. gr. 1.7) (10 ml.) during 5 hours, and dilution with water gave rise to a semi-crystalline precipitate which upon purification from aqueous methanol furnished an almost quantitative yield of 4′,5,7-trihydroxy-8-methylisoflavone in pale yellow prisms, m.p. 252° (dec.), having an intense green ferric reaction in alcohol.

Anal. Calcd. for $C_{16}H_{12}O_5$: C, 67.60; H, 4.26. Found: C, 67.63; H, 4.44.

Remethylation of this isoflavone by the dimethyl sulfate–acetone method furnished a quantitative yield of 4′,5,7-trimethoxy-8-methylisoflavone, identical in every way with the parent compound.

The demethylation of 4′,7-dihydroxy-5-methoxy-8-methylisoflavone likewise gave rise to 4′,5,7-trihydroxy-8-methylisoflavone.

4′,5,7-Triacetoxy-8-methylisoflavone (VII).—Acetylation of 4′,5,7-trihydroxy-8-methylisoflavone (0.5 g.) in boiling acetic anhydride (5 ml.) containing fused acetate (1 g.) during 2.5 hours gave rise to 4′,5,7-triacetoxy-8-methylisoflavone (0.5 g.) in colorless slender needles, m.p. 218°, insoluble in 2 *N* sodium hydroxide solution and exhibiting a negative ferric reaction in alcohol. The acetate was sparingly soluble in methanol and ethanol.

Anal. Calcd. for $C_{22}H_{18}O_8$: C, 64.39; H, 4.42. Found: C, 64.29; H, 4.71.

2′,5,7-Trimethoxy-8-methylisoflavone. Method (a). 2-Hydroxy-4,6-dimethoxy-3-methylphenyl 2-Methoxybenzyl Ketone (XIV).—A solution of 2-hydroxy-4,6-dimethoxytoluene (3.5 g.) and *o*-methoxyphenylacetonitrile in ether (100 ml.) containing zinc chloride (2 g.) was saturated at 0° with hydrogen chloride. Two days later the product was isolated in the usual manner and purified from methanol to give 2′,4,6-trimethoxy-2-hydroxy-3-methyldeoxybenzoin (2.5 g.) in colorless, shimmering flat prisms, m.p. 148°, having an intense red-brown ferric reaction in alcohol.

Anal. Calcd. for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37; OMe (3), 29.43. Found: C, 68.44; H, 6.72; OMe, 29.77.

2′,5,7-Trimethoxy-8-methylisoflavone (XIX).—A solution of the previous ketone (1.5 g.) in methyl formate (40 ml.) was added at −10° to powdered sodium (1.5 g.). After 24 hours at 0° and a further 48 hours at room temperature the reaction mixture was decomposed by the addition of ice-water and acidified with dilute hydrochloric acid. After evaporation of the excess methyl formate the product separated from ethyl acetate in colorless needles, m.p. 186° (dec.), of 2,3-dihydro-2-hydroxy-4′,5,7-trimethoxy-8-methylisoflavone (1.5 g.).

Anal. Calcd. for $C_{19}H_{20}O_6$: C, 65.87; H, 5.82. Found: C, 65.74; H, 6.00.

This compound was insoluble in 2 *N* sodium hydroxide solution, readily soluble in ethyl acetate, gave no ferric reaction in alcohol and decomposed upon attempted sublimation at 0.001 mm. to a phenolic substance exhibiting a strong ferric reaction. When a solution of this 2,3-dihydroisoflavone (0.5 g.) in acetic acid (5 ml.) was refluxed for 30 minutes, cooled and diluted with water, 2′,5,7-trimethoxy-8-methylisoflavone (0.45 g.) separated and was purified from a large volume of ethyl acetate in stout, flat, colorless prisms, m.p. 185°. The mixed m.p. with the parent 2,3-dihydroisoflavone was *ca.* 165°.

Anal. Calcd. for $C_{19}H_{18}O_5$: C, 69.93; H, 5.56. Found: C, 70.05; H, 5.86.

This compound had a negative ferric reaction in alcohol, was insoluble in 2 *N* sodium hydroxide solution and sublimed unchanged at 200° (0.01 mm.).

Method (b). 2,4,6-Trihydroxy-3-methylphenyl 2-Methoxybenzyl Ketone (XIII).—Prepared from C-methylphloroglucinol (6 g.), *o*-methoxyphenylacetonitrile (4 g.) and zinc chloride (3 g.) in ether (100 ml.) followed by isolation in the usual manner, the ketone (3.5 g.) separated from aqueous methanol in almost colorless, stout, prisms, m.p. 206°, unchanged by sublimation at 160° (0.01 mm.), and having an intense violet-brown ferric reaction in alcohol.

Anal. Calcd. for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.59; H, 5.76.

Methylation of this ketone (2.5 g.) in boiling acetone (75 ml.) containing potassium carbonate (8 g.) and dimethyl sulfate (2.5 g.) during 3 hours gave rise to 2-hydroxy-4,6-dimethoxyphenyl 2-methoxybenzyl ketone (1.8 g.) identical with the product prepared by method (a) and converted to the same isoflavone (XIX) on cyclization.

Method (c). 2,4-Dihydroxy-6-methoxy-3-methylphenyl 2-Methoxybenzyl Ketone (XV).—When a solution of 2,6-dihydroxy-4-methoxytoluene (3.2 g.) and *o*-methoxyphenylacetonitrile (2.8 g.) in ether (75 ml.) containing zinc chloride (1.5 g.) was saturated with hydrogen chloride at 0° and 24 hours later the semi-crystalline precipitate was hydrolyzed on the steam-bath with water (100 ml.) during 2 hours, a crystalline product separated. Purification from methanol gave rise to the ketone (1.8 g.) in pale yellow, silky needles, m.p. 195°, having an intense violet-brown ferric reaction in alcohol.

Anal. Calcd. for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C, 67.44; H, 6.04.

Methylation of this ketone in the usual manner furnished a quantitative yield of 2-hydroxy-4,6-dimethoxy-3-methylphenyl 2-methoxybenzyl ketone, identical with the product prepared by methods (a) and (b).

7-Hydroxy-2′,5-dimethoxy-8-methylisoflavone (XVII).—A suspension of 2,4-dihydroxy-6-methoxy-3-methylphenyl 2-methoxybenzyl ketone (1.7 g.) in methyl formate (50 ml.) was added to sodium dust (0.9 g.) at 0°. After 24 hours at 0° and 48 hours at room temperature followed by isolation in the usual manner the isoflavone (0.4 g.) separated from aqueous acetic acid in colorless, silky needles, m.p. 314° (dec.), almost insoluble in methanol and ethanol, sparingly soluble in ethyl acetate and acetone, readily soluble in cold 2 *N* sodium hydroxide solution and having a negative ferric reaction in alcohol.

Anal. Calcd. for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16. Found: C, 69.31; H, 5.62.

2,4,6-Trihydroxyphenyl 2-Methoxybenzyl Ketone (XXII).—Prepared in the usual manner from a solution of phloroglucinol (5 g.) and *o*-methoxyphenylacetonitrile (6 g.) in ether (125 ml.) containing zinc chloride (4 g.), the ketone (4 g.) separated from aqueous methanol in pale fawn-colored needles, m.p. 169°, having an intense red-brown ferric reaction in alcohol and readily soluble in alcohol and acetone.

Anal. Calcd. for $C_{15}H_{14}O_5 \cdot H_2O$: C, 61.64; H, 5.52. Found: C, 61.70; H, 5.72. Calcd. for $C_{15}H_{14}O_5$: C, 65.69; H, 5.15. Found (on specimen sublimed at 120° (0.04 mm.)): C, 65.54; H, 5.42.

2-Hydroxy-4,6-dimethoxyphenyl 2-Methoxybenzyl Ketone (XXIII).—Methylation of the foregoing ketone (2.5 g.) in boiling acetone (100 ml.) containing potassium carbonate (7 g.) and dimethyl sulfate (2.5 g.) during 3.5 hours gave 2-hydroxy-4,6-dimethoxyphenyl 2-methoxybenzyl ketone (1.6 g.) which separated from aqueous methanol in rosettes of stout, colorless prisms, m.p. 122°, having an intense red-brown ferric reaction in alcohol.

Anal. Calcd. for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00; OMe (5), 30.80. Found: C, 67.43; H, 6.13; OMe, 30.84.

2′,5,7-Trimethoxyisoflavone (XXVI).—Cyclization of this ketone (1.5 g.) in methyl formate (50 ml.) with sodium dust (1 g.) in the usual way followed by acidification of the reaction mixture with excess 2 *N* hydrochloric acid gave rise to a crystalline precipitate of 2,3-dihydro-2-hydroxy-2′,5,7-trimethoxyisoflavone (XXIV) (1.3 g.) which separated from a large volume of ethyl acetate in rosettes of colorless needles, m.p. 196° (dec.). This compound was insoluble in cold 2 *N* sodium hydroxide, exhibited a negative ferric reaction in alcohol and decomposed on attempted vacuum sublimation.

Anal. Calcd. for $C_{18}H_{18}O_6$: C, 65.44; H, 5.49. Found: C, 65.48; H, 5.63.

When a solution of this 2,3-dihydroisoflavone (1 g.) in acetic acid (7 ml.) was refluxed for 30 minutes and the product isolated by dilution with water followed by purification from ethyl acetate, 2′,5,7-trimethoxyisoflavone (0.9 g.) separated in colorless, massive rectangular prisms, m.p. 140°, insoluble in cold 2 *N* sodium hydroxide solution, having a negative ferric reaction in alcohol and subliming unchanged at 200° (0.01 mm.).

Anal. Calcd. for $C_{18}H_{16}O_6$: C, 69.22; H, 5.16; OMe (3), 29.80. Found: C, 69.43; H, 5.25; OMe, 30.73.

2,4-Dihydroxy-6-methoxyphenyl 4-Methoxybenzyl Ketone (XXVII).—Prepared from phloroglucinol monomethyl ether (2.5 g.) and *p*-methoxyphenylacetonitrile (2.5 g.) in the usual manner, the ketone (1.5 g.) separated from aqueous methanol or aqueous acetic acid in slender, colorless needles, m.p. 129–130°, having an intense red-brown ferric reaction in alcohol.

Anal. Calcd. for $C_{16}H_{16}O_5$: C, 66.65; H, 5.59. Found: C, 66.58; H, 5.82.

7-Hydroxy-4′,5-dimethoxyisoflavone (XXVIII). (Genistein 4′,5-Dimethyl Ether).—The previous ketone (1.4 g.) was cyclized with methyl formate (25 ml.) and sodium dust (0.5 g.) and the product, which could not be induced to crystallize, was isolated with chloroform and refluxed with acetic acid (10 ml.) during 10 minutes. Isolation of the product by dilution with water followed by purification from a large volume of methanol gave rise to 7-hydroxy-4′,5-dimethoxyisoflavone (0.5 g.) in pale fawn-colored prisms m.p. 294–5° (dec.), readily soluble in cold 2 *N* sodium hydroxide solution, having a negative ferric reaction in alcohol and demethylated almost quantitatively during 3 hours refluxing with hydriodic acid (sp. gr. 1.7) to genistein, m.p. 296–298°.

Anal. Calcd. for $C_{17}H_{14}O_5$: C, 68.45; H, 4.73. Found: C, 68.01; H, 5.13.

Waltz[14] records the m.p. 290–293° for a specimen of genistein 4′,5-dimethyl ether prepared by the partial demethylation of genistein trimethyl ether.

4′,5,7-Trihydroxy-6-methylisoflavone (XXXI).—Genistein was methylated by the method of Baker and Robinson[11] to yield 5-hydroxy-4′,7-dimethoxy-6-methylisoflavone (XXX). When a solution of this isoflavone (1 g.) in hydriodic acid (25 ml., sp. gr. 1.7) was refluxed during 3 hours and the product isolated in the usual way, 4′,5,7-trihydroxy-6-methylisoflavone (0.7 g.) separated from aqueous methanol in very pale yellow needles, m.p. 274°, unchanged by sublimation at 150° (0.01 mm.), and having an intense green ferric reaction in alcohol.

Anal. Calcd. for $C_{16}H_{12}O_6$: C, 67.60; H, 4.26. Found: C, 67.24; H, 4.51.

Remethylation of this isoflavone with dimethyl sulfate in boiling acetone gave an almost quantitative yield of 5-hydroxy-4′,7-dimethoxy-6-methylisoflavone.

(14) E. Waltz, *Ann.*, **489**, 118 (1931).

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Reactions of Methylcyclopropylcarbinyl Derivatives[1]

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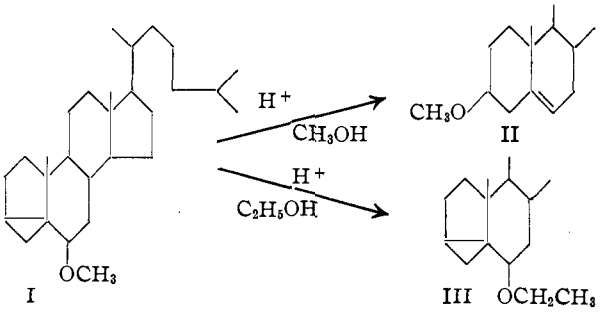
The methylcyclopropylcarbinyl system is treated as an analog of the *i*-cholesteryl system. Methylcyclopropylcarbinol in acidic methanol readily forms methylcyclopropylcarbinyl methyl ether. In acidic ethanol, exchange occurs to the corresponding ethyl ether. Rearrangement to 3-penten-1-yl methyl ether is accomplished only with considerable difficulty.

The unusual reactivity of *i*-cholesterol and *i*-cholesteryl methyl ether (I)[2] prompted us to investigate some of the reactions of methylcyclopropylcarbinyl derivatives. *i*-Cholesteryl methyl ether rearranges rapidly in acidic methanol solution to form the normal cholesteryl methyl ether (II). It has also been shown that in dilute acidic ethanol I exchanges at the 6-position and *i*-cholesteryl ethyl ether (III) may be isolated[2c] before appreciable rearrangement to the normal ether.

The methylcyclopropylcarbinyl structure would seem to be analogous to the *i*-cholesteryl one, in that it also has a secondary carbon atom adjacent to a cyclopropane ring, and thus might react similarly. We have found that methylcyclopropylcarbinol (IV) reacts with dilute acidic methanol to give methylcyclopropylcarbinyl methyl ether (V). In acidic ethanol, V reacts further with the solvent to give methylcyclopropylcarbinyl ethyl ether (VI). After prolonged reflux with acidic methanol, V will rearrange to give some 3-penten-1-yl methyl ether (VII), analogous to the transformation of I to II.



The extreme tendency of cyclopropylcarbinyl derivatives to rearrange in reactions where intermediate carbonium ions may be postulated to

(1) Taken in part from a thesis presented by Stanley H. Langer in partial fulfillment of the requirements for the degree of Doctor of Philosophy in August, 1951.

(2) (a) *Cf.* L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd Ed., Reinhold Publishing Corp., New York, N. Y., 1949, p. 256; (b) L. C. King, R. M. Dodson and L. A. Subluskey, THIS JOURNAL, **70**, 1176 (1948); (c) S. Winstein and A. Schlesinger, *ibid.*, **70**, 3528 (1948).