[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE AND THE OREGON FOREST PRODUCTS LABORATORY]

The Methylation of Dihydroquercetin[1]

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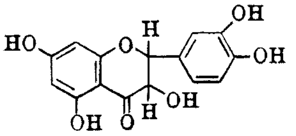
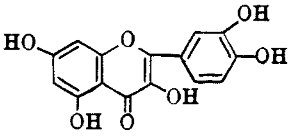
The methylation of dihydroquercetin was studied under a variety of conditions. Mild methylation under neutral or weakly basic conditions resulted in methylation of the phenolic hydroxyl groups. Attempts to methylate the aliphatic 3-hydroxyl group resulted in rearrangement to the corresponding benzylcoumaranone or chalcone.

Methylation is extensively used in constitutional studies of phenolic compounds. Methoxyl derivatives have been prepared from most of the flavanoids and are commonly used for identification purposes. Relatively little attention has been devoted to the conditions of methylation, however. It appeared to be of interest to study the methylation of dihydroquercetin, 3,3′,4′,5,7-pentahydroxyflavanone (I), under a variety of conditions. This compound was selected since it can be obtained in good yields from Douglas-fir bark,[5] a waste material available in large volume in the northwestern United States.


I


II

The 3-hydroxy flavanones differ in several respects from flavanones unsubstituted in this position. This was expected to affect their behavior during methylation. Dihydroquercetin forms insoluble monobasic salts upon treatment with aqueous inorganic basic salts or bases.[6] It is slowly converted to the corresponding flavonol, quercetin (II), upon treatment with aqueous base. The carbonyl group in dihydroquercetin is refractory towards the usual ketonic reagents in contrast to a corresponding flavanone unsubstituted in the 3-position, *i.e.* homoeriodictyol, which reacts readily with 2,4-dinitrophenylhydrazine.[7]

In order to avoid the complications of side reactions in alkaline solution, methylation was initially carried out with dimethyl sulfate and aqueous methanol at a *p*H less than 6.5. This resulted in a mixture of the dimethoxy and trimethoxy derivatives. The latter was separated in pure form and found to be the 3′,4′,7-trimethoxy derivative (III) on the basis of the conversion to the known derivatives, 3′,4′,7-trimethoxyquercetin (IV) or 3′,4′,7-trimethoxyeriodictyol (V). Attempts to further methylate dihydroquercetin at a *p*H less than 6.5 were uniformly unsuccessful even when a large excess of reagents was used.

When dihydroquercetin or the trimethyl derivative (III) was methylated with dimethyl sulfate and an excess of anhydrous potassium carbonate in acetone, a tetramethyl derivative (VI) was obtained in nearly quantitative yield. Extending the duration of treatment or increasing the amounts of reagents did not result in any further methylation. This derivative did not give any color reaction when treated with alcoholic ferric chloride. Complete methylation of the phenolic hydroxyl groups was indicated and the structure is formulated as the 3′,4′,5,7-tetramethyl derivative. This was confirmed by conversion to the known 3′,4′,5,7-tetramethoxyquercetin (IX). Tri- and tetra-methyldihydroquercetin derivatives of undetermined structure have been previously reported by Kondo[8] and Hasegawa and Shirato.[9] Gripenberg[10] has since shown that the source material for these preparations was a mixture of two flavanones.

Treatment of quercetin (II) with dimethyl sulfate and potassium carbonate in acetone resulted in methylation of all the hydroxyl groups. This points out a basic difference in the 3-hydroxyl group in the two compounds. The 3-hydroxyl group in quercetin is acidic[11] and is readily methylated. The corresponding group in dihydroquercetin is an aliphatic hydroxyl group and it resists methylation under all but the most drastic conditions.

In contrast with tetramethyldihydroquercetin

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[5] Hergert and Kurth, *Tappi*, **35**, 59 (1952).

[6] Kurth, Hergert, and Ross, *J. Am. Chem. Soc.*, **77**, 1621 (1955).

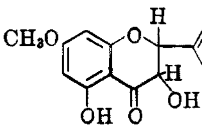
[7] Douglass, Morris, and Wender, *J. Am. Chem. Soc.*, **73**, 4023 (1951).

[8] Kondo, *J. Faculty Agr. Kyushu Univ.*, **10**, 79 (1951) [*Chem. Abstr.*, **47**, 4602 (1953)].

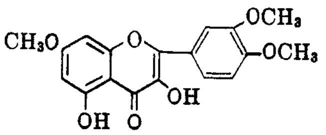
[9] Hasegawa and Shirato, *J. Chem. Soc. Japan*, **72**, 279 (1951).

[10] Gripenberg, *Acta Chem. Scand.*, **6**, 1152 (1952).

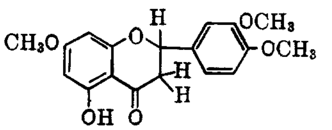
[11] Briggs and Locker, *J. Chem. Soc.*, 3136 (1951).



III



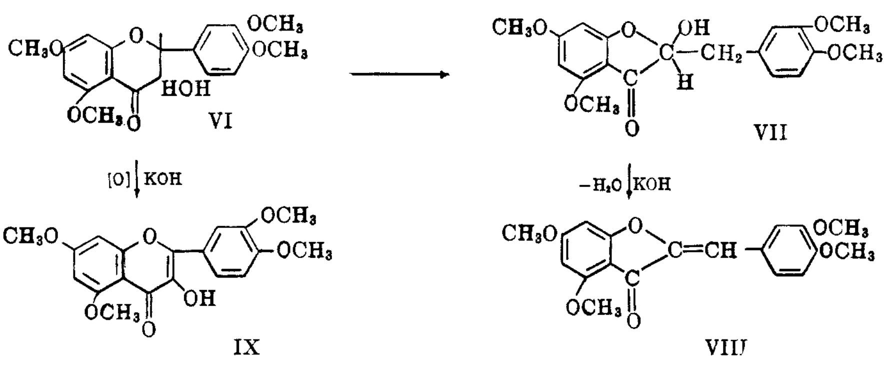
IV



V

(VI), trimethyldihydroquercetin (III) yielded a monomolecular salt upon treatment with alkali. This shows that a 5-hydroxyl group is necessary for salt formation in 3-hydroxy flavanones. Since 5-hydroxy flavanones unsubstituted in the 3-position do not form salts under similar conditions, the 3-hydroxyl group must alter the electron distribution in the vicinity of the 5-hydroxyl and carbonyl groups. Evidence of this has been previously noted in infrared carbonyl frequency shifts of 3-hydroxy flavanones.[12]

A solution of dihydroquercetin in methanol was treated with alternate portions of dimethyl sulfate and aqueous potassium hydroxide so that the *p*H remained above seven for only short periods of time. This resulted primarily in a mixture of tetra (VII) and pentamethyl (X) derivatives. The tetramethyl derivative (VII) could also be obtained by treatment of 3′,4′,5,7-tetramethoxydihydroquercetin (VI) for a few minutes with alcoholic potassium hydroxide. The tetramethyl derivative (VII) had the same elemental analysis as (VI) but had a higher melting point. The ultraviolet spectrum of (VII) was similar to (VI). This indicated that the same or a similar chromophore was present. Of the several possible structures, only two could have similar chromophores: the epimer of (VI) and 2-(3,4-dimethoxybenzyl) - 2 - hydroxy - 4,6 - dimethoxycoumaranone. Examination of the infrared spectrum of VII indicated a shift of the carbonyl frequency from 1660 cm.$^{-1}$ in (VI) to 1675 cm.$^{-1}$ in VII. VII therefore cannot be an epimer, so it is formulated as the benzylcoumaranone.



This is consistent with the infrared spectrum inasmuch as decreasing a 6-membered ring to a five-membered ring ordinarily results in a marked increase of the carbonyl stretching frequency.

Kimura[13] reported the synthesis of a compound presumed to be VI by the acid condensation of 2-hydroxy-4,6,3′,4′,α-pentamethoxychalcone. This compound has the same reported melting point as VII. Recently Gripenberg[14] has shown that this type of cyclization leads to benzylcoumaranones instead of the expected 3-hydroxy flavanones. Further evidence of different ring structure in VII is found in the color reaction with concentrated nitric acid.[15] Both III and VI give a strong blue-green coloration typical of flavanone ethers derived from phloroglucinol. However, a violet coloration is given by VII, indicating that the compound no longer has a flavanone structure. The color reaction with powdered zinc and hydrochloric acid, which is specific for 3-hydroxy flavanones[16] and is given by VI, is no longer given by VII.

The pentamethyl derivative (X) was described in a preliminary report[17] as 3,3′,4′,5,7-pentamethyl dihydroquercetin on the basis of the elemental analysis. The ultraviolet spectrum showed a chromophore which might be expected of the latter. This compound (X) has now been obtained by methylation of the benzylcoumaranone (VII). It also shows a violet nitric acid color reaction and an infrared spectrum very similar to the tetramethylbenzylcoumaranone (VII). The carbonyl band is displaced to a slightly higher wave number (1703 cm.$^{-1}$) which may be attributed to the absence of intermolecular hydrogen bonding. The carbonyl frequency is considerably higher than that which might be expected for pentamethyldihydroquercetin. This indicates that the structure of (X) must therefore be 2-(3,4-dimethoxy benzyl)-2,4,6-

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[12] Hergert and Kurth, *J. Am. Chem. Soc.*, **75**, 1622 (1953).

[13] Kimura, *J. Pharm. Soc. Japan*, **58**, 415 (1938).

[14] Gripenberg, *Acta Chem. Scand.*, **7**, 1323 (1953).

[15] Rao and Seshadri, *Proc. Indian Acad. Sci.*, **30A**, 30 (1949).

[16] Pew, *J. Am. Chem. Soc.*, **70**, 3031 (1948).

[17] Hergert and Kurth, *J. Org. Chem.*, **18**, 521 (1953).

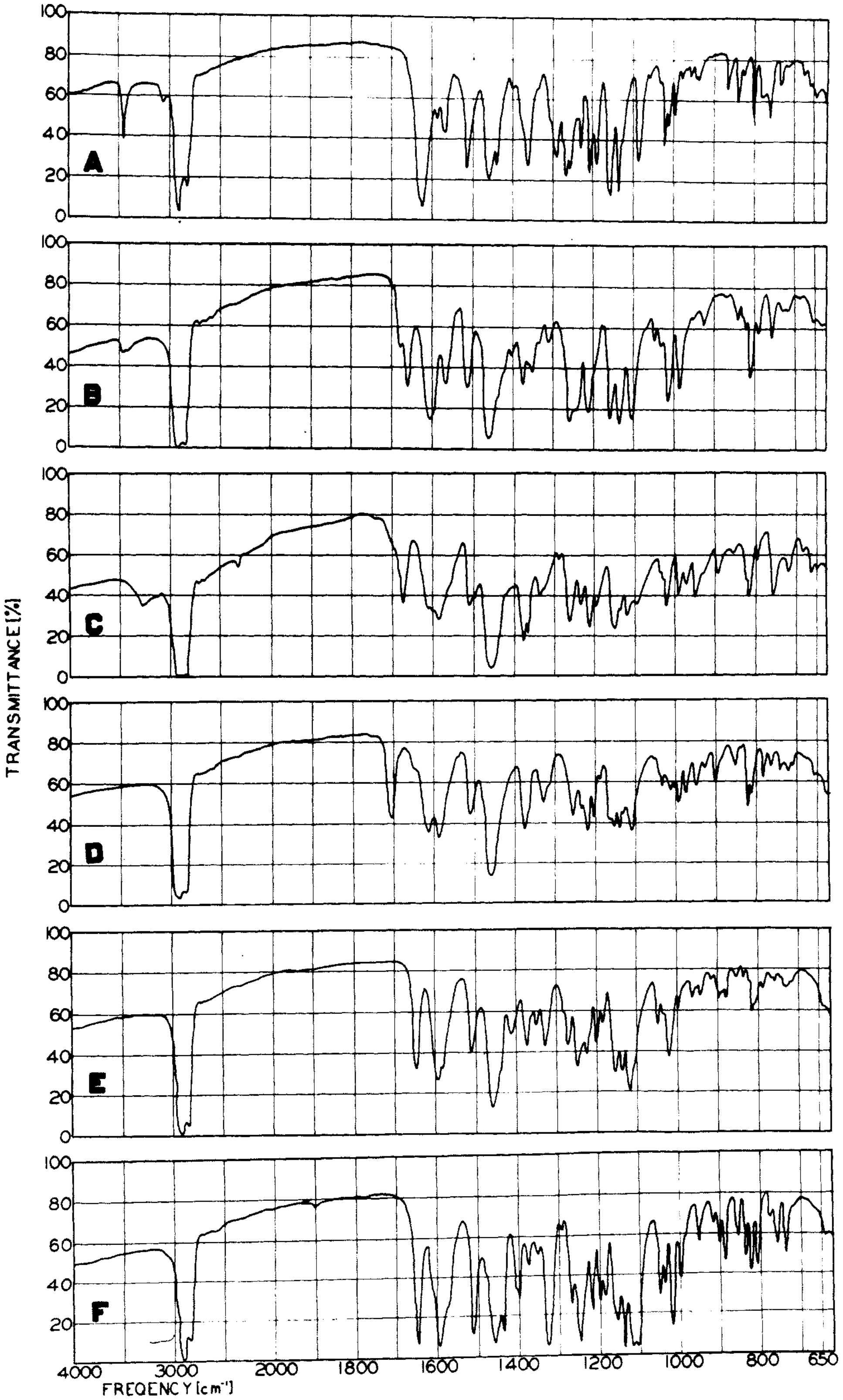
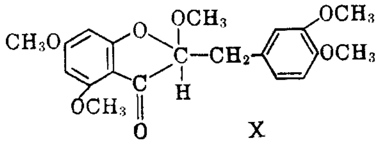


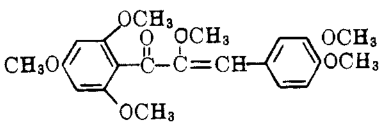
FIG. 1.—INFRARED SPECTRA (paraffin mulls) of A. Trimethoxydihydroquercetin (III), B. Tetramethoxydihydroquercetin (VI), C. Tetramethoxybenzylcoumaranone(VII), D. Pentamethoxybenzylcoumaranone (X), E. Hexamethoxychalcone (XI), F. Epi-hexamethoxychalcone.

trimethoxy coumaranone.[18] In contrast to VII, X was found to be very stable towards alkali.

When tetramethylbenzylcoumaranone (VII) or tetramethyldihydroquercetin is treated with alkali for an hour or more, a yellow compound is obtained upon acidification instead of VII. Elemental analysis indicates the loss of one molecule of water. The ultraviolet spectrum shows a chromophore similar to that of pentamethylquercetin. The same yellow compound was also obtained by treatment of VII with concentrated sulfuric acid. Thus the structure appears to be 2-(3,4-dimethoxy benzal)-4,6-dimethoxycoumaranone (VIII) which would be formed by dehydration.

Low temperature methylation of dihydroquercetin under strongly alkaline conditions resulted in a good yield of 2,3′,4′,4,6,α-hexamethoxychalcone (XI). The ultraviolet spectrum of XI also showed a strong band at 340 mμ very similar to that of 3,3′,4′,5,7-pentamethoxyquercetin. The chromophoric systems of the two compounds both involve carbonyl groups attached to one phenyl ring and conjugated to an additional ring through an ethylenic double bond. When the chalcone (XI) was treated with a mixture of acetone and hydrochloric acid, the melting point was elevated about 25°. The ultraviolet spectrum was unchanged but the infrared spectrum showed important changes in the 1400–600 cm.$^{-1}$ region. Since XI is capable of existing in both *cis* and *trans* forms, the treatment with acid is interpreted as epimerization. It is not possible to assign the specific configuration on the basis of the present experimental data.


X


XI

Dihydroquercetin was methylated with alkali and dimethyl sulfate at elevated temperatures according to the procedure commonly employed for methylation of flavones and flavanones. This resulted in a mixture of the benzylcoumaranones VII and X, the chalcone XI, and trimethylquercetin (III). A completely methylated dihydroquercetin was not obtained. This may be attributed to the observation that strongly alkaline conditions are usually required for methylation of aliphatic hydroxyl groups with dimethyl sulfate, but alkaline conditions cause rearrangement of 3-hydroxy flavanones which do not have a hydroxyl group in the 5 position.

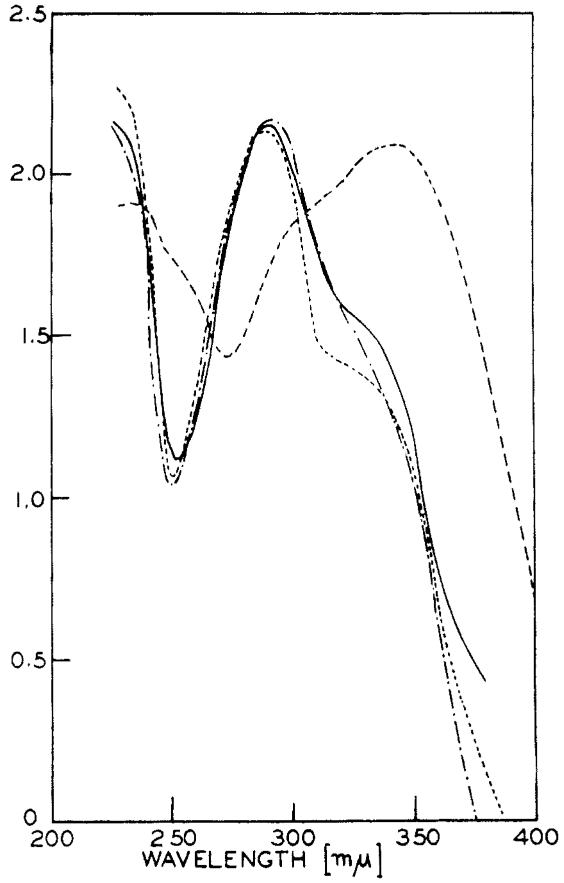


FIG. 2. ULTRAVIOLET SPECTRA OF *dl*-DIHYDROQUERCETIN (I) (————), Trimethoxydihydroquercetin (III) (- - - - -), Pentamethoxybenzylcoumaranone (IX) (–·–·–·–), and Hexamethoxychalcone (X) (– – –).

The course of methylation of dihydroquercetin with dimethyl sulfate may be charted as follows. The 3′- and 4′-, 7-, and 5-hydroxyl groups are methylated in that order. Of these groups, the 5-hydroxyl group is the most difficult to methylate because of chelation with the carbonyl group. This chelation stabilizes the ring towards alkali.[19] Once the 5-hydroxyl group is methylated subsequent treatment with alkali during the methylation either causes rearrangement to a 5-membered ring or the opening of the ring to form a chalcone.

The course of quercetin methylation with alkali and dimethyl sulfate was established through the isolation of 3,3′,4′-trimethyl-, 3,3′,4′,7-tetramethyl- and pentamethyl-quercetin in that order. The 3, 3′, and 4′ hydroxyls are methylated first, then the 7, and, finally, the 5-hydroxyl group.

Methylation of dihydroquercetin with methyl iodide and potassium carbonate in anhydrous

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(18) The original structural assignment should be changed to that given here. The compound obtained by Clemmenson reduction of the carbonyl group of X has since been found not to be identical with an authentic sample of 3,3′,4′,5,7-pentamethylepicatechin.

(19) Narasimhachari and Seshadri, *Proc. Indian Acad. Sci.*, **27A**, 223 (1948).

acetone led to the di-, tri-, and/or tetra-methyl derivatives depending upon the quantities of reagents used and the duration of treatment. Methylation with diazomethane in ether or dioxane led to a mixture of the tri- and tetra-methoxy derivatives. Completely methylated dihydroquercetin was not obtained in either case. Both of these procedures gave rather poor yields and were definitely inferior to the dimethyl sulfate-anhydrous potassium carbonate-acetone procedure for obtaining tetramethyldihydroquercetin (VI).

EXPERIMENTAL

Dihydroquercetin (I). Douglas fir cork was used as the source of *d*-dihydroquercetin.[5] In order to avoid the complications of a mixture of optically active and inactive forms upon methylation, *d*-dihydroquercetin was racemized with concentrated hydrochloric acid.[16] Paper chromatography with a variety of solvent systems[21] showed only one spot. The acetate derivative, m.p. 151–152°, was prepared by treatment with acetic anhydride and pyridine.

Treatment of dihydroquercetin with base. dl-Dihydroquercetin (30 g., 0.10 mole), m.p. 238–240°, and 6.0 g. (0.15 mole) of sodium hydroxide were dissolved in 100 cc. of distilled water and refluxed 1.25 hours. The mixture was acidified with sulfuric acid to *p*H 3.0 and then was cooled. Quercetin (II), m.p. 313–314° (undepressed upon admixture with an authentic sample), was filtered off; yield, 1.2 g. The filtrate was extracted with ether, and the ether extract was evaporated to dryness. The residue was dissolved in 50 cc. of water and allowed to crystallize. The precipitate then was recrystallized from 300 cc. of water. A yield of 25 g. of *dl*-dihydroquercetin, m.p. 238°, was obtained. Spectra and chromatograms were identical with the starting material.

3',4',7-Trimethoxydihydroquercetin (III). Dihydroquercetin (20 g.) was dissolved in 100 cc. of methyl alcohol. To this was added 40 cc. of dimethyl sulfate and a solution of 20 g. of potassium hydroxide in 100 cc. of 50% methanol. The reagents were added alternately in small portions so that the solution did not exceed *p*H 6.5. The mixture was cooled in an ice-bath during the reaction and then was placed in an icebox to stand overnight. The precipitate was filtered off, washed with water, and then was recrystallized several times from ethanol. White granular crystals, m.p. 167–168°, were obtained in a yield of 55%.

Anal. Calc'd for $C_{18}H_{18}O_7$: C, 62.42; H, 5.23; CH_3O, 26.88. Found: C, 62.65; H, 5.27; CH_3O, 26.7.

A red-violet coloration was obtained upon treatment of an ethanol solution of III with 1% aqueous ferric chloride. A strong cerise coloration was obtained with powdered zinc and hydrochloric acid.[16] Treatment of solid III with concentrated nitric acid gave an intense blue coloration.

The mother liquor from the recrystallization of III was evaporated to a small volume. Light yellow needles were deposited upon standing. The crystals were recrystallized several times from a small volume of ethanol. A yield of 0.5 g. of 3,3',4',7-tetramethoxyquercetin, m.p. 158–159° (undepressed upon admixture with authentic specimen), was obtained. The monoacetate prepared with acetic anhydride and fused sodium acetate melted at 168–169° (lit.[22] m.p. 169–170°).

The mother liquor from the recrystallization of III and tetramethoxyquercetin was evaporated to dryness and then was redissolved in a small volume of warm 90% methanol. A white precipitate, m.p. 120–125°, containing adsorbed methanol, was obtained in 25% yield. Recrystallization failed to raise the melting point. Treatment with ferric chloride solution produced a red-black coloration. The compound was dried *in vacuo* over P_2O_5 and paraffin before analysis.

Anal. Calc'd for $C_{17}H_{16}O_7$: CH_3O, 18.68. Found: CH_3O, 20.82.

Dimethoxydihydroquercetin (1.0 g.) was dissolved in 10 cc. of 95% ethanol. Powdered zinc and hydrochloric acid were added in small quantities until the cerise color was dissipated. White crystals were deposited upon standing. After several recrystallizations from ethanol, they melted at 204–205° (lit. m.p. for 3',4'-dimethoxyeriodictyol, 208–210°,[23] 201°.[24]

Treatment of 3',4',7-trimethoxydihydroquercetin with base. The trimethoxy derivative III was dissolved in warm, aqueous 5% sodium carbonate solution. White needles, m.p. 195° (decomp.), were obtained upon cooling.

Anal. Calc'd for $C_{18}H_{17}NaO_7$: Na, 6.1. Found: Na, 6.0.

3',4',7-Trimethoxyquercetin (IV). Trimethoxydihydroquercetin (III), 1.0 g., was dissolved in 50 cc. of hot 1 *N* aqueous sodium hydroxide and was refluxed for one hour. The solution then was acidified, allowed to stand 24 hours, and filtered. The precipitate was dissolved in 95% ethanol and recrystallized several times. Yellow crystals, m.p. 190–191° (lit.[25] m.p. 190°), were obtained in a yield of 0.3 g.

Anal. Calc'd for $C_{18}H_{16}O_7$: C, 62.79; H, 4.68; CH_3O, 27.04. Found: C, 62.92; H, 4.97; CH_3O, 27.1.

Acetylation of the yellow crystals (IV) with pyridine and acetic anhydride gave 3',4',7-trimethoxy-3,5-diacetoxyquercetin, m.p. 185–186° from ethanol (lit.[25] m.p. 187–188°). The mother liquor from the recrystallization of IV consisted of a mixture of IV and unchanged III.

3',4',7-Trimethoxyeriodictyol (V). Powdered zinc (5 g.) and 10 cc. of concentrated hydrochloric acid were added to a solution of 3 g. of trimethoxydihydroquercetin (III) in 25 cc. of ethanol. The mixture was allowed to stand for several hours and then was filtered. The filtrate was diluted with 25 cc. of water. A precipitate was filtered off and recrystallized several times from aqueous ethanol. Yield 0.75 g. of 3',4',7-trimethoxyeriodictyol (V), m.p. 141–142° (lit.[25] 136°). The compound gave a red color with aqueous ferric chloride solution, but did not give any coloration upon subsequent treatment with powdered zinc and hydrochloric acid.

Anal. Calc'd for $C_{18}H_{18}O_6$: CH_3O, 28.2. Found: CH_3O, 28.0.

Methylation of quercetin. Quercetin was methylated under the same conditions as in the preparation of III. The precipitate was recrystallized several times from ethanol. Yellow needles of 3,3',4',7-tetramethoxyquercetin, m.p. 159° (acetate, m.p. 169°) were obtained in 60% yield. Evaporation of the mother liquor to a small volume gave a 10% yield of a second compound, m.p. 240–242°, isomeric with IV.

Anal. Calc'd for $C_{18}H_{16}O_7$: CH_3O, 27.04. Found: CH_3O, 27.0.

Acetylation with pyridine and acetic anhydride gave white needles, m.p. 157°. These properties correspond[26] to 3,3',4'-trimethoxyquercetin, m.p. 244° (acetate[24] m.p. 159–160°).

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(20) Melting points are corrected. Microanalyses by Drs. Weiler and Strauss, Oxford. Ultraviolet spectra were measured in 95% ethanol solution with a Beckman Model DU or a Cary recording spectrophotometer. Infrared spectra measured as paraffin mulls in a Perkin-Elmer model 21 double beam recording spectrophotometer.

(21) Gage, Douglass, and Wender, *Anal. Chem.*, **23**, 1582 (1951).

(22) Gomm and Nierenstein, *J. Am. Chem. Soc.*, **53**, 4408 (1931).

(23) Pew, *J. Am. Chem. Soc.*, **73**, 1678 (1951).

(24) Shinato and Sato, *J. Pharm. Soc. Japan*, **49**, 5 (1929).

(25) Kuhn, *Ber.*, **77**, 202 (1944).

(26) Allan and Robinson, *J. Chem. Soc.*, 2336 (1926).

3',4',5,7-Tetramethoxydihydroquercetin (VI). Dihydroquercetin (3.0 g.) and 25.0 g. of anhydrous potassium carbonate were suspended in 100 cc. acetone and brought to reflux. Dimethyl sulfate (14.0 cc.) was added in one-cc. portions over a period of one hour and the mixture then was refluxed an additional 14 hours. The mixture was filtered and the precipitate was washed with acetone. The filtrates were combined and evaporated to dryness and the residue was recrystallized from 90% ethanol. White needles, m.p. 169–170° (after drying over P_2O_5), were obtained in a yield of 70%.

Anal. Calc'd for $C_{19}H_{20}O_7$: C, 63.33; H, 5.60; CH_3O, 34.4. Found: C, 63.42; H, 5.67; CH_3O, 34.4.

Treatment of VI with concentrated nitric acid gave an intense blue coloration. A cerise coloration was obtained when an alcoholic solution of VI was treated with powdered zinc and concentrated hydrochloric acid. No color was observed with alcoholic ferric chloride solution. Acetylation of VI with pyridine and acetic anhydride gave white needles (from methanol), m.p. 171–172°.

3',4',5,7-Tetramethoxyquercetin (IX). Tetramethoxydihydroquercetin (VI), 3.0 g., and 0.5 g. of potassium hydroxide were dissolved in 50 cc. of hot water. The mixture was boiled for 15 minutes, cooled, and acidified to *p*H 2.5 with hydrochloric acid. The precipitate was filtered off and dissolved in a mixture of hot acetone and ethanol. On cooling, light yellow crystals, m.p. 196° (lit.[27] 194–195°) were obtained in a yield of 0.5 g. Acetylation with acetic anhydride and pyridine gave an acetate derivative, m.p. 162° (lit.[27] m.p. 160–163°).

2-(3,4-Dimethoxybenzyl)-2-hydroxy-4,6-dimethoxycoumaranone (VII). The mother liquor from the recrystallization of IX was evaporated to dryness and taken up in warm methanol. A yield of 1.5 g. of white crystals was obtained upon standing. After several recrystallizations from methanol, m.p. 176° was obtained.

Anal. Calc'd for $C_{19}H_{20}O_7$: C, 63.33; H, 5.60; CH_3O, 34.4. Found: C, 63.20; H, 5.93; CH_3O, 34.5.

No coloration was obtained when an ethanol solution of VII was treated with powdered zinc and hydrochloric acid. Treatment of VII with concentrated nitric acid gave a light violet coloration.

2-(3,4-Dimethoxy benzal)-4,6-dimethoxycoumaranone (VIII). Tetramethyldihydroquercetin (VI) (2.0 g.) and 2.0 g. of potassium hydroxide were dissolved in a mixture of 25 cc. of ethanol and 25 cc. of water. The solution was refluxed for one hour and then was acidified to *p*H 2.0 with hydrochloric acid. Upon cooling and standing, a yellow precipitate settled out which was filtered off. The precipitate was fractionally recrystallized from ethanol. The first and least soluble portion was primarily IX. Subsequent fractions yielded yellow prisms, m.p. 172°. These were combined and recrystallized until they gave a negative test with ferric chloride or magnesium and hydrochloric acid. A yield of 0.5 g. of VIII, m.p. 172–173°, was obtained.

Anal. Calc'd for $C_{19}H_{18}O_6$: CH_3O, 36.3. Found: CH_3O, 36.1.

VIII, m.p. 173°, also was obtained by treating tetramethylbenzylcoumaranone (VII) with base, in the same way. No IX occurred as a byproduct of the reaction. Tetramethylbenzylcoumaranone was dissolved in concentrated sulfuric acid and then the solution was diluted with water. The precipitate was filtered off and recrystallized from ethanol. Yellow prisms, m.p. 171–173°, identical with VIII, were obtained in a yield of about 10%.

2-(3,4-Dimethoxybenzyl)-2,4,6-trimethoxycoumaranone (X). Tetramethyldihydroquercetin (VI, 0.5 g.), was suspended in 5 cc. of methanol and 8 cc. of dimethyl sulfate was added. Then 25% potassium hydroxide solution was slowly added dropwise with cooling until the reaction mixture reached *p*H 10. Water was added to the reaction mixture and the insoluble precipitate was filtered off. Recrystallization of the precipitate from methanol gave 0.3 g. of white crystals, m.p. 118–119°. The product was insoluble in aqueous base and gave a negative test with ferric chloride solution or powdered zinc and hydrochloric acid. Treatment with concentrated nitric acid gave a violet coloration.

Anal. Calc'd for $C_{20}H_{22}O_7$: C, 64.16; H, 5.92; CH_3O, 41.4. Found: C, 64.58; H, 6.05; CH_3O, 41.9.

Tetramethylbenzylcoumaranone (VII), 0.30 g., was dissolved in 10 cc. of acetone. To this was added 8 cc. dimethyl sulfate and 4 g. of sodium hydroxide in 25 cc. of water in small portions over a period of one hour. The mixture then was placed in an icebox for 4 hours. The precipitate was filtered off and recrystallized from ethanol. Yield, 0.28 g. of white crystals, m.p. 118–119°, identical in all respects with X.

Dihydroquercetin (30 g.) was dissolved in 200 cc. of methanol and placed in a round-bottom flask which was surrounded by an ice-salt bath. The flask was equipped with a stirrer, a water-cooled condenser, and two dropping-funnels. Dimethyl sulfate (30 ml.) was added from one funnel and then 72 cc. of 50% potassium hydroxide solution was added in small portions over a period of two hours. The addition was maintained at such a rate as to maintain the solution at a *p*H primarily on the acid side. Subsequently, eight alternate additions of dimethyl sulfate (5 cc. each) and 50% potassium hydroxide (6 cc.) were made so that the solution was raised to *p*H 10 for short periods of time. At the conclusion of the reaction, the slightly basic mixture was poured into 500 cc. of cold water. The mixture was allowed to stand for several hours and then was filtered. The precipitate was recrystallized several times from ethanol. Yield, 20 g. of white crystals, m.p. 118–119°, identical with X (spectra, mixture m.p., color reactions). The basic mother liquors were acidified with hydrochloric acid. A precipitate was filtered off and recrystallized from methanol. Yield, 5 g. of white crystals, m.p. 176°, identical with VII.

2,3',4,4',6,α-Hexamethoxychalcone (XI). Dihydroquercetin (30 g.) was dissolved in 300 cc. of acetone and was methylated with dimethyl sulfate and 50% potassium hydroxide as in the preceding paragraph except that the additions of base were made prior to the addition of dimethyl sulfate. The solution thus was maintained on the basic side. At the conclusion of the reaction, the mixture was diluted with 300 cc. of water and placed in an icebox for 24 hours. The precipitate was filtered off and recrystallized from ethanol. Yield, 22 g. of pale yellow prisms, m.p. 132–133°. The compound gave a negative Wilson boro-citric acid test for flavones, no color with ferric chloride solution, a slight brown coloration with concentrated nitric acid, and a pink coloration with alcoholic hydrochloric acid.

Anal. Calc'd for $C_{21}H_{24}O_7$: C, 64.94; H, 6.23; CH_3O, 47.9. Found: C, 65.45; H, 6.53; CH_3O, 47.5.

Epi-2,3',4',4,6,α-hexamethoxychalcone. Hexamethoxychalcone (XI), 5 g., and 5 cc. of concentrated hydrochloric acid were dissolved in 30 cc. of acetone and refluxed for 30 minutes. The mixture was diluted with 30 cc. of water and the precipitate was filtered off. The precipitate was recrystallized several times from ethanol. Yield, 3 g. of pale yellow prisms, m.p. 156°. The color reactions were similar to those obtained with XI.

Anal. Calc'd for $C_{21}H_{24}O_7$: C, 64.94; H, 6.23. Found: C, 65.40; H, 6.50.

Drastic methylation of dihydroquercetin. Dihydroquercetin (60 g.) was dissolved in 400 ml. methanol and placed in a flask equipped with a magnetic stirrer, two-dropping funnels, and a condenser. To the stirred solution, 50 ml. of dimethyl sulfate was added from one funnel and 30 ml. of 50% potassium hydroxide from the other. An exothermic reaction ensued which caused the solution to reflux. Eight alternate additions of dimethyl sulfate (12.5 ml. each) and 50% potassium hydroxide (16 ml. each) then were made at such a rate as to maintain a state of vigorous reflux (about two hours). The solution was poured into a flask containing

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(27) Herzig and Schonbach, *Monatsh.*, **33**, 678 (1912).

1000 g. of ice and water and then was placed in a refrigerator for 24 hours. The precipitate (35 g.) was filtered off and was fractionally crystallized from ethanol. The less soluble fraction, m.p. 132–133°, was identical with XI, and the other portion, m.p. 116–119°, was identical with X. The alkaline mother liquor was acidified and a gummy precipitate was filtered off. This was also fractionally recrystallized from ethanol giving 0.75 g. of trimethylquercetin (IV) and 10 g. of tetramethylbenzylcoumarone (VII), m.p. 176°.

Methylation with diazomethane. Dihydroquercetin (5 g.) was dissolved in 50 ml. of methanol and treated with 200 ml. of ether containing 5.3 g. of diazomethane generated from nitrosomethylurea. The mixture was placed in an icebox for 24 hours. Three additional 5.3-g. portions of diazomethane were added at 24 hour intervals (the total amount of diazomethane added corresponded to a four fold excess required for the methylation of all the hydroxyl groups). The yellow solution was evaporated to dryness and the residue was taken up in a small volume of methanol. Yield, 1.5 g. of white granular crystals, m.p. 165–167°. The infrared spectrum indicated that the crystals were a mixture of trimethoxy- (III) and tetramethoxy-dihydroquercetin (VI).

Anal. Calc'd for $C_{18}H_{18}O_7$: CH_3O, 26.88. Calc'd for $C_{19}H_{20}O_7$: CH_3O, 34.4. Found: CH_3O: 30.88.

Methylation with smaller quantities of diazomethane gave a mixture of dimethoxy- and trimethoxy-dihydroquercetin.

Methylation with methyl iodide. Methylation of dihydroquercetin with methyl iodide and anhydrous potassium carbonate in acetone according to the procedure of Kondo[8] gave a mixture of trimethoxy- and tetramethoxy-dihydroquercetin, m.p. 160–165°, as characterized by the infrared spectrum.

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