[CONTRIBUTION FROM AVERY LABORATORY, THE UNIVERSITY OF NEBRASKA]

THE O-METHANESULFONATION OF QUERCETIN AND OTHER FLAVONOLS

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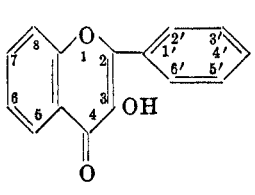
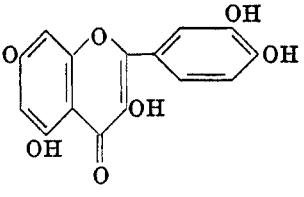
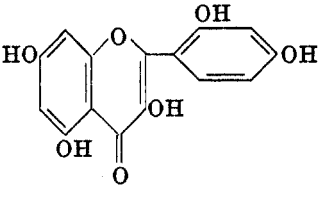
Sulfonic esters of flavonoid substances have been prepared infrequently. A tribenzenesulfonate of luteolin (1) and a tetrabenzenesulfonate of datiscetin (2) have been reported. *p*-Toluenesulfonic esters of the complex isoflavones osajin, pomiferin, isoösajin, and isopomiferin were described in the course of characterizing these substances (3). To our knowledge, however, no methanesulfonic esters of flavonoid materials have been prepared, and no systematic investigation of the esterification of flavone-like materials by any sulfonyl halide has been described. The present paper describes the esterification of flavonol (I), quercetin (II), rhamnetin (III), and morin (IV) by methanesulfonyl chloride in pyridine. Methanesulfonyl chloride in aqueous alkali reacts with quercetin to give a product different from the ester obtained from pyridine. O-methanesulfonation of the flavonols I, II, III, and IV in pyridine solution has been compared with acetylation in the same solvent.



I



II, R = H
III, R = CH_3



IV

Flavonol (I) is smoothly esterified by excess methanesulfonyl chloride in pyridine to give the colorless ester. Flavonol methanesulfonate, in the solid state, shows a remarkable photochromism, changing color from colorless to red in bright sunlight. In a dark place, the red form becomes colorless and in acetone gives a colorless solution.

Quercetin pentamethanesulfonate was obtained by reacting a 1% solution of quercetin (II) in pyridine with a 300% excess of methanesulfonyl chloride. The crude sulfonic ester is considerably more difficult to purify than quercetin pentaacetate, but when pure, yields large, colorless, well-defined crystals from glacial acetic acid. The anomalous melting point of quercetin pentamethanesulfonate imposes a limitation on its utility as a derivative, however. Quercetin pentamethanesulfonate gives negative tests with ferric chloride and magnesium-hydrochloric acid (4). The stability of the methanesulfonoxy group toward acid hydrolysis (5–8) may cause the negative test with the latter reagent, for both quercetin pentaacetate and quercetin pentamethyl ether give positive results. Quercetin pentamethanesulfonate is not hydrolyzed by boiling 6 *N* alcoholic

hydrochloric acid, nor is it attacked appreciably by boiling acetic acid-sulfuric acid. In a mixture of acetone and 40% sodium hydroxide, the sulfonic ester of quercetin yields at room temperature a yellow hydrolysis product, acetylation of which affords quercetin pentaacetate.

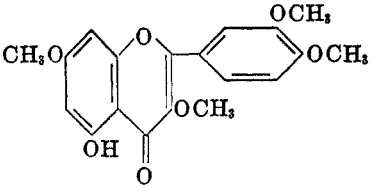
The conditions used for preparing quercetin pentamethanesulfonate have been extended to the naturally occurring flavonols III and IV to give rhamnetin tetramethanesulfonate and morin pentamethanesulfonate respectively, which are also colorless, well-defined crystalline solids. Morin pentamethanesulfonate is probably the most readily prepared derivative of morin, especially since morin pentaacetate does not appear to have been prepared in pure form.[1] Myricetin (3,3′,4′,5,5′,7-hexahydroxyflavone) (V) reacts with methanesulfonyl chloride in pyridine to yield a colorless product resembling the other sulfonic esters in appearance. However, upon attempted purification from boiling acetone, a brilliant yellow solution was obtained, indicating probable alteration or decomposition of the primary reaction product.

In order to compare methanesulfonation with acetylation, the procedure employed by Freudenberg (9) for the preparation of quercetin pentaacetate from quercetin and acetic anhydride in pyridine has been extended to the other flavonols available for investigation. Flavonol (I) and myricetin (V) react smoothly, to give in high yield flavonol acetate and myricetin hexaacetate, the melting points of which are identical with those of the known acetates prepared by alternative procedures. Rhamnetin (III) and morin (IV), however, give impure acetylation products, which resisted attempted purification by simple crystallization techniques. The preparation of pure methanesulfonic esters by the reaction of methanesulfonyl chloride with III and IV in pyridine solution thus acquires added significance. In contrast to acetylation, esterification with methanesulfonyl chloride was effected in a very dilute pyridine solution of the flavonol.

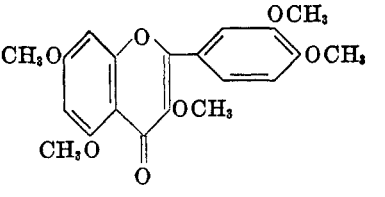
The reaction of quercetin with a large excess of methanesulfonyl chloride in aqueous sodium hydroxide affords in low yield a pale yellow, crystalline tetramethanesulfonic ester of quercetin. The latter ester (VI) gives a wine-red color with alcoholic ferric chloride, reacts with methanesulfonyl chloride in pyridine to give a product identical in properties with quercetin pentamethanesulfonate, and in dioxane solution reacts with ethereal diazomethane to give the monomethyl ether (VII). The non-identity of VII with rhamnetin tetramethanesulfonate demonstrates that the free hydroxyl of VI is not at the 7-position of the chromone core. Observations that only 3- and 5-hydroxyl groups of flavonol derivatives give ferric chloride tests (10, 11), combined with the resistant character of the 5-hydroxyl of quercetin 3,3′,4′,7-tetramethyl ether toward diazomethane methylation (12) and toward esterification by methanesulfonyl chloride in pyridine (this study), indicate that the free hydroxyl of VI is probably at the

[1] An impure, crystalline product was obtained by the acetylation of morin with either acetic anhydride-sodium acetate or acetyl chloride by Bablich and A. G. Perkin [*J. Chem. Soc.*, **69**, 795 (1896)].

3-position. Analytical data and melting points of the methanesulfonic esters prepared are listed in Table I.

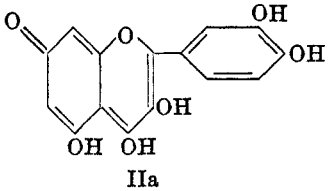


VIII

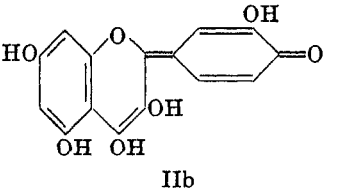


IX

The 5-hydroxyl of quercetin 3,3′,4′,7-tetramethyl ether (VIII) is not esterified by methanesulfonyl chloride in pyridine, as previously noted herein. Yet all of the hydroxyl groups, including the 5-hydroxyl, of quercetin itself are esterified under these conditions, a fact which suggests that the reactivity of the 5-hydroxyl of quercetin is markedly different from that in VIII. A similar marked difference of reactivity in the 5-hydroxyl in II and VIII has been observed by Herzig (12), who reported the complete methylation of quercetin by ethereal diazomethane to give quercetin pentamethyl ether (IX), whereas VIII does not react with ethereal diazomethane to give IX. Gomm and Nierenstein, upon adding an ethereal solution of diazomethane to a dioxane solution of quercetin, obtained VIII from quercetin instead of IX, and obtained IX from VIII by the agency of dimethyl sulfate and solid potassium hydroxide (13). In the methanesulfonation reaction, the enhanced reactivity of the 5-hydroxyl of quercetin may prove attributable to the formation in pyridine solution of quinoid tautomers of the type shown in IIa and IIb. The tendency of the 5-hydroxyl of flavonoid substances to react slowly, or only under conditions which may be described as vigorous, or to react not at all in some cases, has been generally attributed to hydrogen bonding, resident in the hydroxy-carbonyl system at the 4- and 5-positions. It is apparent that the existence of structures IIa and IIb, in equilibrium with II, affords a device whereby the 4-carbonyl is effectively removed to a more distant site, relative to the 5-position.[2]



IIa



IIb

[2] The existence of quinoid tautomeric forms of flavonoid substances has been postulated by A. G. Perkin [*J. Chem. Soc.*, **75**, 451 (1899)], Watson and Meek [*J. Chem. Soc.*, **107**, 1567 (1915)], and by Attree and A. G. Perkin [*J. Chem. Soc.*, 235 (1927)]. Recently, Weygand and Csendes reported that kaempferol (3, 4′, 5, 7-tetrahydroxyflavone) reacts with titanous chloride in methanolic pyridine (in a reaction shown to be characteristic of enediols) to give a solid complex, and raised the question of the existence of a quinoid tautomer to explain complex formation [*Chem. Ber.*, **85**, 45 (1952)].

Throughout this and other investigations, we have observed the formation in methanesulfonation reaction mixtures of a water-soluble, pyridine-insoluble compound, m.p. 185° (uncorr.). On the basis of manner of preparation (Experimental), analysis, and failure of its aqueous solution to precipitate silver chloride from silver nitrate solutions, this compound appears to be the salt, pyridinium methanesulfonate (X). The latter could be formed in several ways, one of which involves the reaction of water with methanesulfonyl chloride to give hydrochloric and methanesulfonic acid, which then reacts with pyridine to give X. We have observed that freshly distilled methanesulfonyl chloride does not react with pyridine immediately to give X, whereas the sulfonyl halide, after standing for prolonged periods, even in glass-stoppered bottles, reacts with pyridine with rapid formation of X. This observation affords a method for giving quickly an indication of the degree of purity of methanesulfonyl chloride.

EXPERIMENTAL

Melting points are uncorrected, with the exception of those reported in Table I. Analyses are by the Clark Microanalytical Laboratory, except where otherwise noted. *Flavonol* and *methanesulfonyl chloride* were obtained from Eastman Kodak Co., *xanthorhamnin* and *rutin* from S. B. Penick and Co., and *myricitrin* and *morin* from L. Light and Co. Ltd. The procedures used for isolation of the aglycons are slight modifications of known methods.

Quercetin. Hydrolysis of 40 g. of rutin trihydrate in 600 ml. of 5% hydrochloric acid at the boiling point for 10 minutes gave the bright yellow aglycon, which, after recrystallization from glacial acetic acid, gave m.p. 305–310° (dec.) [lit. m.p. (14), 313–314°]. This material was sufficiently pure for this study.

Rhamnetin. Xanthorhamnin (10 g.) and 10 ml. of conc'd hydrochloric acid in 300 ml. of water were heated under reflux for one hour to give 3.3 g. of rhamnetin, m.p. approx. 280° (dec.). [lit. m.p. (15a), above 300°]. Acetylation of 0.2 g. of rhamnetin by heating with 4 ml. of acetic anhydride and 1.0 g. of fused sodium acetate for 45 minutes, with isolation of the crude acetate in the usual manner, gave 0.29 g., m.p. 130–160°. Recrystallization from abs. ethanol (charcoal), followed by reacetylation and crystallization from 95% ethanol, gave

TABLE I

METHANESULFONIC ESTERS OF FLAVONOLS

Sulfonic Ester	M.P., °C.[a]	Empirical Formula	Analysis					
			Calc'd			Found		
			C	H	S	C	H	S
Flavonol methanesulfonate	122	$C_{16}H_{12}O_5S$	60.75	3.82	10.13	60.82	3.83	10.15
Quercetin pentamethanesulfonate	205	$C_{20}H_{20}O_{17}S_5$	34.68	2.91	23.14	34.95	3.05	23.43
Morin pentamethanesulfonate	205	$C_{20}H_{20}O_{17}S_5$	34.68	2.91	23.14	35.02	2.99	23.45
Rhamnetin tetramethanesulfonate	220	$C_{20}H_{20}O_{15}S_4$	38.21	3.21	—	38.11[b]	3.44[b]	—

[a] Melting points are corrected, and are those obtained for the repeatedly crystallized esters, dried 4–5 hours at 100° *in vacuo* (with the exception of quercetin pentamethanesulfonate, which was dried *in vacuo* at room temperature for one week).

[b] Analysis by ALK.

0.10 g. of rhamnetin tetraacetate, m.p. of air-dried material, 179–181° [lit. m.p.'s, 190–192° (15a), 183–185° (15b), 181–183° (15c)].

Myricetin. A 10-g. quantity of myricitrin was heated in 500 ml. of 2% hydrochloric acid at the boiling point for one hour, and permitted to stand at room temperature for two weeks. Then, after addition of 24 ml. of conc'd hydrochloric acid, the hydrolysis mixture was heated under reflux for 2 hrs. to give 6.9 g. of the bright yellow aglycon. The myricetin employed in methanesulfonation studies was a fraction obtained as a residue after extraction with ethyl acetate, which fraction melted above 300°, and 1 g. of which gave upon acetylation (sequel) 1.52 g. (85%) of crude hexaacetate, m.p. 207–211° [lit. m.p. (16), 211–212°].

Flavonol methanesulfonate (3-methanesulfonoxyflavone). Flavonol (1.19 g.), dissolved in 20 ml. of pyridine, was subjected to the action of 1.15 g. of methanesulfonyl chloride (dissolved in *ca.* 2 ml. of pyridine). After standing 47 hrs. in an ice-chest, the reaction mixture was poured into 200 ml. of water to give 1.41 g. (89%) of crude ester, m.p. 115–120°. Four crystallizations from methanol, with protection from light, gave analytically pure material, m.p. 120–122°.

Quercetin pentamethanesulfonate (3, 3', 4', 5, 7-pentamethanesulfonoxyflavone). To a solution prepared by dissolving 1 g. of quercetin in 100 ml. of dry pyridine was added at 0–5° slowly, 6 g. of methanesulfonyl chloride in a few ml. of pyridine. After standing 48 hrs. at 5–10°, the reaction mixture was poured into 500 ml. of ice-water. After standing several hours, the crude solid was collected by filtration, washed well with water, and air-dried; yield of crude ester, 2.2 g. (96%), m.p. *ca.* 150–190°. The crude ester can be purified initially from glacial acetic acid (charcoal), with very slow cooling of the hot solution. Rapid cooling caused oil deposition. Alternatively, the crude product was purified by dissolving in acetone, adding charcoal, filtering, cooling the filtrate, then adding absolute ethanol to incipient crystallization. Upon standing, a cream-colored solid, m.p. 193–195°, was obtained. Further crystallization from acetone, under conditions permitting slow evaporation of the solvent, gave the colorless, analytically pure ester, m.p. 197.5–199°, unchanged after boiling in 6 *N* alcoholic hydrochloric acid (prepared by adding 7.5 ml. of conc'd acid to 7.5 ml. of 95% ethanol) for three hours. Recrystallization from glacial acetic acid, followed by thorough air-drying, gave the ester with m.p. 188–191°, which was changed to 199–201° after the ester was dried in a vacuum desiccator over phosphorus pentoxide and potassium hydroxide at room temperature.

In one instance, a sample of ester, elaborately purified from acetone and dried at the boiling point of water 5 hrs. *in vacuo* without grinding, gave a m.p. of approx. 180°. Thorough grinding in an agate mortar raised the m.p. to 190–193°. Recrystallization from glacial acetic acid gave material with m.p. 188–191°, which, after drying the sample *in vacuo*, was raised to 199–201°. This body of melting point data is interpreted as indicating that quercetin pentamethanesulfonate probably is capable of existing in dimorphous forms, one melting *ca.* 180°, and the other melting at 199–201°. The high-melting form seems capable of forming a solvate with acetic acid. Conversion of a low-melting form to a high-melting form by grinding in an agate mortar has been previously reported for rotenone (17) and for 2-methyltetrahydroösajin dimethyl ether (18).

Rhamnetin tetramethanesulfonate (7-methoxy-3,3',4',5-tetramethanesulfonoxyflavone). Methanesulfonyl chloride (10 g.; previously cooled in ice) was added at 0–5° to a solution of 1 g. of rhamnetin in 100 ml. of dry pyridine. After standing in an ice-chest for 48 hrs., the crude ester was isolated by pouring the reaction mixture into a large volume of ice-water; yield, 1.5 g. (76%), melting at 205–210°. Purification in a manner similar to that described for quercetin pentamethanesulfonate, with crystallization from acetone, gave rhamnetin tetramethanesulfonate, m.p. 212–215°, with sintering at 205°. Recrystallization from glacial acetic acid gave the analytically pure ester, m.p. 213–215°, with sintering at 210°.

Morin pentamethanesulfonate (2',3,4',5,7-pentamethanesulfonoxyflavone). Methanesulfonyl chloride (6 g.) was added to a solution of 1 g. of morin in 100 ml. of dry pyridine, previously cooled to 0°. The reaction mixture was permitted to stand for 48 hrs. at 0–5°, and was then poured into a large volume of ice-water. The precipitated crude ester [yield 2.0 g.

TABLE II

ACETIC ANHYDRIDE-PYRIDINE ACETYLATION OF FLAVONOLS

Flavonol	Yield, Crude Acetate, g.(%)[a]	M.P., °C., Crude	M.P., °C., Recrystd. Ester	Lit. M.P., °C.
Flavonol	1.07 (91)	100–107	108–110	110–111[b]
Myricetin	1.52 (85)	207–211	210–212	211–212[c]
Rhamnetin	0.64 (83)	75–135	—	190–192,[d] 183–185[e]
Morin	1.43 (84)[f]	80–135	—	—

[a] Based on the completely acetylated flavonol. [b] Kostanecki and Szabranski, *Ber.*, **37**, 2820 (1904). [c] Ref. (16) in text. [d] Ref. (15a) in text. [e] Ref. (15b) in text. [f] Yield after reacetylation in pyridine.

(87%), m.p. 171–178°] was recrystallized three times from glacial acetic acid to give fluffy, colorless needles, m.p. 185–187°, raised to 190–192° after drying *in vacuo* over potassium hydroxide and phosphorus pentoxide for one week. Further crystalization from acetone, followed by drying at 100° *in vacuo*, gave analytically pure material, m.p. 199–201°; mixture m.p. with quercetin pentamethanesulfonate (m.p. 199–201°), 170–178°, with marked softening at 165°.

Acetic anhydride-pyridine acetylation of flavonols. To 1-g. quantities of flavonol, morin and myricetin, suspended in 0.6 ml., 2.6 ml., and 3.1 ml. respectively of acetic anhydride, were added 3-ml. quantities of dry pyridine. A 0.5-g. quantity of rhamnetin, suspended in 1.3 ml. of acetic anhydride, was treated with 1.5 ml. of dry pyridine. After standing 3–4 hrs., the crude acetylation products were isolated by pouring reaction mixtures into *ca.* 30 ml. of water. The body of data collected is summarized in Table II.

Methanesulfonation of quercetin with methanesulfonyl chloride in aqueous sodium hydroxide. Approximately 1 g. of quercetin, dissolved in 5% sodium hydroxide, was added to approximately 500 ml. of very dilute sodium hydroxide, to which several ml. of methanesulfonyl chloride (large excess) and a few ml. of pyridine had been previously added. The reaction mixture was stirred vigorously. There occurred a precipitation of solid material, which was dissolved by addition of pyridine to the aqueous mixture. A gummy material settled out of solution gradually. After two hours, the aqueous solution was decanted from the gum, which was covered with water and permitted to stand for 72 hrs. There occurred by this process a conversion of gum to solid material, which was collected, washed with ethanol-ethyl acetate (1:2 by vol.), and air-dried. Crystallization from acetone-water, followed by two crystallizations from butanone gave pale yellow, crystalline material (VI), m.p. 201–203°, unchanged by further crystallization from butanone. In acetone solution, the substance gave a wine-red color with alcoholic ferric chloride. This substance also showed anomalous melting behavior. By drying an elaborately purified sample at 100° *in vacuo*, a m.p. of approx. 175–180° was obtained. Sufficient material was not available to clarify completely the nature of the phenomenon.

Anal. Calc'd for $C_{19}H_{18}O_{16}S_4$: C, 37.14; H, 2.95; S, 20.86.
Found: C, 37.56; H, 2.95; S, 20.85.

An attempt to repeat the preparation of this quercetin derivative, using more precisely defined and controlled conditions, was not successful. A mixture was obtained, which appeared to contain at least three different substances.

Methanesulfonation of quercetin tetramethanesulfonate (VI) *in pyridine solution.* To 0.10 g. of VI, m.p. 198–203°, in 10 ml. of pyridine was added 1.0 g. of methanesulfonyl chloride. After standing 5 minutes, the pyridine solution was poured into *ca.* 100 ml. of water, and the precipitated, pale yellow solid collected by filtration; yield 0.11 g., m.p. 180–190°. Difficulty was encountered in removing the last traces of color from this product. Two recrystallizations from acetic acid, followed by crystallization from acetone-ethanol, with a

final crystallization from glacial acetic acid gave, in low yield, a colorless material, m.p. 183–186°, presumed to be quercetin pentamethanesulfonate (as solvate or addition compound with acetic acid).

Diazomethane methylation of quercetin tetramethanesulfonate (VI). An ethereal diazomethane solution was prepared from nitrosomethyl urea, utilizing the procedure of Arndt (19).

To a solution of 100 mg. of quercetin tetramethanesulfonate (VI) in 15 ml. of dioxane, previously cooled to 5°, was added 2 ml. of ethereal diazomethane (containing approx. 56 mg. of diazomethane). The mixture was cooled strongly, and an additional 1.5 ml. of ethereal diazomethane was added. After standing in an ice-chest for 20 hrs., the solvent was evaporated at room temperature and the residual oil dissolved in acetone. The crude ether was precipitated by addition of water, collected by filtration, and air-dried; yield, 95 mg., m.p. 151–161°. Repeated crystallization from acetic acid gave colorless, crystalline material; m.p. of analytical sample 177–179°, lowered to 155–170° upon admixture with rhamnetin tetramethanesulfonate.

Anal. Calc'd for $C_{19}H_{17}O_{14}S_4(OCH_3)$: OCH_3, 4.94. Found: OCH_3, 3.92.

Alkaline hydrolysis of quercetin pentamethanesulfonate. A 0.5-g. quantity of quercetin pentamethanesulfonate, m.p. 193–195°, was suspended in 50 ml. of 40% aqueous sodium hydroxide; solution was very incomplete. The aqueous mixture was covered with 50 ml. of acetone, and the resulting heterogenous system was shaken vigorously. The acetone layer became orange-colored; upon continued very vigorous shaking of the mixture, the orange color virtually disappeared from the acetone layer, with concomitant formation of a yellow salt in the aqueous phase. Upon standing overnight, the yellow salt dissolved partially to give an orange-colored aqueous phase. After evaporation of the acetone *in vacuo* at room temperature, the aqueous mixture was acidified with hydrochloric acid to give a yellow solid, which was collected by filtration, washed well with water, and air-dried; yield, 0.14 g., m.p. 265–275° with sintering at 250°. The substance gave a greenish color, with a reddish cast, with alcoholic ferric chloride, and a reddish-pink color in ethanol with magnesium-hydrochloric acid (4). Upon sodium fusion, followed by addition of lead acetate, a slight precipitate of lead sulfide was obtained, indicating that hydrolysis was incomplete.

Acetylation of 0.1 g. of the crude hydrolysis product by solution in 0.3 ml. of dry pyridine, addition of 0.3 ml. of acetic anhydride, and permitting acetylation mixture to stand 7 hrs., gave 0.11 g. of acetylation product, m.p. approx. 100–170°. Fractionation with 95% ethanol gave three fractions, the most, and least soluble of which were rejected. The fraction of intermediate solubility gave m.p. 185–190°, raised to 194–196°, after two additional crystallizations from 95% ethanol [lit. m.p. (9), 193–194°]. Admixture of this acetylation product with quercetin pentaacetate, prepared by Freudenberg's procedure, gave m.p. 191–194°. This slight depression is considered probably insignificant.

Attempted methanesulfonation of quercetin 3,3′,4′,7-tetramethyl ether (VIII). Quercetin was methylated by the method of Waliaschko (20), with retention of the product, m.p. 155–157°, considered by Waliaschko to be a trimethyl ether, but subsequently shown (13) to be VIII, thus confirming Herzig's contention (12).

A 1-g. quantity of quercetin 3,3′,4′,7-tetramethyl ether (VIII), was dissolved in 1 l. of dry pyridine and methanesulfonation was attempted by addition of 6 g. of methanesulfonyl chloride in a few ml. of pyridine. After standing for 48 hrs., starting material was recovered in 75–85% yield, upon pouring the reaction mixture into water. The crude recovered product was sulfur-free, and, after recrystallization from 95% ethanol-ethyl acetate, gave m.p. and mixture m.p. 156–157°; the material gave a deep-green color with alcoholic ferric chloride. A run in which the reaction mixture was heated two hours under reflux gave only starting material. Addition of hydrochloric acid, sulfuric acid, and pyridinium chloride to the methanesulfonation mixture did not effect methanesulfonation. Addition of acetic acid led to the formation of 5-acetoxy-3,3′,4′,7-tetramethoxyflavone (21), instead of the methanesulfonate.

Pyridinium methanesulfonate. Methanesulfonic acid (2 g.) was added dropwise, with

strong cooling, carefully, to 30 ml. of reagent pyridine. A quantitative yield of pyridinium methanesulfonate was obtained. Two recrystallizations from ethanol, followed by drying at 78° for 12 hrs. *in vacuo*, gave the pure salt, m.p. 185°.

Anal. Calc'd for $C_6H_9NO_3S$: C, 41.15; H, 5.18; S, 18.30.
Found: C, 41.26; H, 5.29; S, 18.72.

SUMMARY

Flavonol methanesulfonate, quercetin pentamethanesulfonate, morin pentamethanesulfonate, and rhamnetin tetramethanesulfonate have been prepared by reaction of methanesulfonyl chloride with the flavonol in pyridine solution.

Acetylation of flavonol and myricetin in pyridine solution, according to the procedure of Freudenberg (9), has given the completely acetylated flavonol. Morin and rhamnetin give products (presumably mixtures) having large melting ranges upon acetylation by the same procedure (9).

A crystalline tetramethanesulfonate, characterized as its monomethyl ether, has been isolated from the action of methanesulfonyl chloride on quercetin in aqueous sodium hydroxide containing pyridine, and evidence presented for tentatively formulating it as 3-hydroxy-3′,4′,5,7-tetramethanesulfonoxyflavone.

Quercetin 3,3′,4′,7-tetramethyl ether (VIII) has proven resistant towards attempted methanesulfonation in pyridine. The reactivity of the 5-hydroxyl group in quercetin and in VIII is discussed.

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