XIII.—*Anthoxanthins. Part IX. Syringetin.*

By Tom Heap and Robert Robinson.

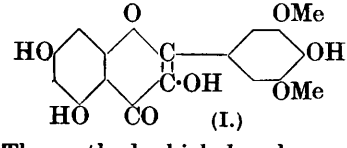
The synthesis of myricetin 3′ : 5′-dimethyl ether (I) was originally undertaken in order to attempt its reduction to the anthocyanidin malvidin (Willstätter and Mieg, *Annalen*, 1915, **408**, 122), but this has not been carried out because the preparation of the flavonol was found to be difficult and the substance was not accessible in adequate amount. Moreover, we have been unable to reduce kaempferol, synthesised by the method of Robinson and Shinoda (J., 1925, **127**,

1980), to pelargonidin salts either directly, following the method of Willstätter and Mallison (*Sitzungsber. K. Akad. Wiss. Berlin*, 1914, 769) for the reduction of quercetin, or indirectly by the acetylating reduction process which succeeded with rhamnetin (Robertson and Robinson, J., 1927, 2196). The products doubtless contained a small proportion of pelargonidin, but it was mixed with so much impurity that we were unable to isolate the pure anthocyanidin.

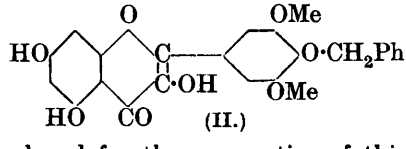
There was no reason to suppose that the myricetin dimethyl ether (dimethoxykaempferol) would behave differently from kaempferol and meanwhile the synthesis of malvidin was effected in another way (Bradley and Robinson, J., 1928, 1541).

In view, however, of the wide distribution of syringidin (malvidin) in nature (Karrer and Widmer, *Helv. Chim. Acta*, 1927, **10**, 5) and of the occurrence of other natural products, such as sinapin, containing the syringic grouping, $C{\cdot}C_6H_2(OH)(OMe)_2$ (4 : 3 : 5), and also in view of the fact that kaempferol, quercetin, *iso*rhamnetin, and myricetin correspond to pelargonidin, cyanidin, peonidin, and delphinidin, respectively, it seemed of interest to place on record the properties of myricetin 3′ : 5′-dimethyl ether, the flavonol corresponding to syringidin.

It seems probable that this substance will ultimately be isolated from natural sources and we propose to term it *syringetin* (I).



(I.)



(II.)

The method which has been developed for the preparation of this flavonol is based on that which we have already used for the synthesis of *iso*rhamnetin (J., 1926, 2336) and consists essentially in the syringoylation of ω-benzoyloxyphloracetophenone,

$$C_6H_2(OH)_3{\cdot}CO{\cdot}CH_2{\cdot}OBz,$$

and hydrolysis of the product.

It was necessary to protect the phenolic hydroxyl group of syringic acid before an anhydride could be formed, and since the use of *O*-benzoylsyringic anhydride did not give satisfactory results we employed *O*-benzylsyringic anhydride in its stead.

When ω-benzoyloxyphloracetophenone was heated with sodium *O*-benzylsyringate and *O*-benzylsyringic anhydride and the product hydrolysed by alkali, *syringetin 4′-benzyl ether* (II) was obtained. Further hydrolysis by means of alcoholic hydrochloric acid yielded syringetin. This was characterised by conversion into a *tetra-acetyl* derivative and on methylation it furnished myricetin hexamethyl ether. At an earlier stage of the work myricetin

3′ : 4′ : 5′-trimethyl ether was prepared, but the requisite conditions for the partial demethylation to syringetin could not be ascertained.

Experimental.

3 : 4 : 5-*Trimethoxybenzoic Anhydride*.—The following method, based on one suggested in D.R.-P. 201325 for the preparation of *o*-acetoxybenzoic anhydride, is more convenient and gives a better yield of a purer product than that described by Kalff and Robinson (J., 1925, **127**, 181). A mixture of finely powdered *O*-trimethylgallic acid (120 g.), dry ether (800 c.c.), and pyridine (75 c.c.) was cooled in melting ice, and thionyl chloride (51 g.; 1·5 mols.) gradually added with shaking. After a few hours (at 0°), crushed ice was added and the mixture was agitated for about 10 minutes and then filtered. The solid was triturated successively with dilute hydrochloric acid, dilute aqueous sodium carbonate, and water, all ice-cold, and then dried in a vacuum (yield, 103 g. or 89·6%; m. p. 159—160°). A similar method applied to anisic acid (100 g.) gave anisic anhydride (92 g.), m. p. 98—99°.

Myricetin 3′ : 4′ : 5′-*Trimethyl Ether*.—An intimate mixture of ω-benzoyloxyphloracetophenone (Heap and Robinson, *loc. cit.*) (9·5 g.; 1 mol.), sodium *O*-trimethylgallate (11·5 g.; 1·5 mols.), and 3 : 4 : 5-trimethoxybenzoic anhydride (94 g.; 7 mols.) was heated (oil-bath at 180—185°) for 9·5 hours and mechanically stirred. The melt, which became deep orange-brown, was dissolved in boiling alcohol (550 c.c.), a solution of potassium hydroxide (33 g.) in water (50 c.c.) was then slowly introduced, and after boiling gently for 30 minutes the alcohol was removed by distillation and the residue dissolved in water. The filtered solution was diluted to 1100 c.c., saturated with carbon dioxide, kept for 12 hours, and again saturated with the gas. The yellow precipitate obtained was dried at 100° (8·8 g.), and 7·9 g. of it, crystallised from acetic acid (charcoal), gave clusters of pale yellow needles (5·7 g.), m. p. 290—293°. The flavonol also crystallised from alcohol in extremely fine, long, pale yellow needles, m. p. 290—293° (Found : C, 59·8; H, 4·7. $C_{18}H_{16}O_8$ requires C, 60·0; H, 4·4%).

Myricetin 3′ : 4′ : 5′-*trimethyl ether* is very sparingly soluble in the simple alcohols, chloroform, acetone, or ethyl acetate and is almost insoluble in benzene, ether, light petroleum, and water; it is not very readily soluble in boiling acetic acid. Addition of mineral acids to a suspension in acetic acid gives deep yellow solutions; in the case of hydrobromic and sulphuric acids the solutions exhibit a green fluorescence, but the deep yellow solution obtained with hydrogen chloride is non-fluorescent. The yellow solution in concentrated sulphuric acid exhibits a weak green fluorescence.

The flavonol gives an intensely yellow solution in aqueous alkali and the addition of ferric chloride to an alcoholic suspension produces a deep brownish-olive-green coloration. The lead salt is a deep yellow precipitate.

The O-*triacetyl* derivative was obtained by the action of boiling acetic anhydride (20 c.c.) and a drop of pyridine on the flavonol (0·5 g.) during 1 hour. It crystallised from alcohol in very fine, nearly white needles, m. p. 195—195·5° (Found: C, 59·0; H, 4·8. $C_{24}H_{22}O_{11}$ requires C, 59·3; H, 4·5%). The substance is sparingly soluble in alcohol, moderately readily soluble in acetic acid and benzene, and very sparingly soluble in ether. The ferric chloride reaction in alcoholic solution was negative.

Action of Fuming Sulphuric Acid on Myricetin Trimethyl Ether.—Syringic acid can be conveniently obtained by the partial demethylation of *O*-trimethylgallic acid by means of 20% fuming sulphuric acid at 40° (Bogert and Isham, *J. Amer. Chem. Soc.*, 1914, **36**, 517; Bogert and Ehrlich, *ibid.*, 1919, **41**, 799) and we therefore attempted the preparation of syringetin analogously.

Finely powdered myricetin trimethyl ether (4·5 g.) was added during 1·5 hours to fuming sulphuric acid (30 c.c. of 20%), mechanically stirred and kept below 40°; the mixture was then maintained at 40—44° for 30 minutes. Next day the deep red liquid was added to water (150 c.c.), but nothing separated. Sulphuric acid (115 c.c.) was then added and a bright yellow solid was precipitated. This was soluble in aqueous sodium bicarbonate and contained sulphur, so that it was clearly a sulphonic acid, and in an attempt to hydrolyse it the mixture was heated in an oil-bath at 150° and a stream of super-heated steam passed for 7 hours. After cooling, the product was added to water and the solid isolated (4·7 g.). The substance crystallised from methyl alcohol in fine yellow needles which darkened at 310° but did not melt at 330° (Found: C, 46·5; H, 3·4; S, 7·8. $C_{16}H_{12}O_{11}S$ requires C, 46·6; H, 2·9; S, 7·8%). It is evidently a *monomethylmyricetinsulphonic acid* and the presence of an *o*-dihydroxybenzene group is suggested by the intense dark olive-green coloration developed in alcoholic solution on the addition of ferric chloride.

The substance is moderately readily soluble to yellow solutions in methyl and ethyl alcohols, ethyl acetate, or acetone, very sparingly soluble in hot acetic acid and chloroform, and almost insoluble in water and benzene. The yellow solution in concentrated sulphuric acid exhibits a green fluorescence and the aqueous alkaline solutions are orange.

O-*Benzoylsyringic Acid and its Chloride.*—Benzoyl chloride (125 g.) was added to a solution of syringic acid (118 g.) in aqueous sodium

hydroxide (95 g. in 1600 c.c.), and the mixture shaken until the smell of the chloride had disappeared. The acids were isolated after acidification and unchanged syringic acid and benzoic acid were removed by extraction of the product with successive volumes of hot water (total, 3200 c.c.). The more sparingly soluble residue, a fine white powder, was dried at 100° (yield, 88 g. or 49%). The *acid* crystallised from acetic acid in almost colourless needles, m. p. 229—232° after softening at 215° (Found: C, 63·3; H, 4·8. $C_{16}H_{14}O_6$ requires C, 63·6; H, 4·6%).

The *chloride*, obtained by the action of phosphorus pentachloride, crystallised from light petroleum in clusters of fine needles (36 g. from 40 g. of the acid), m. p. 116·5—118° (Found: C, 60·1; H, 4·5; Cl, 11·0. $C_{16}H_{13}O_5Cl$ requires C, 59·9; H, 4·1; Cl, 11·1%). On a large scale the use of thionyl chloride was found to be preferable.

The *anhydride* was obtained by following several of the most satisfactory methods, but the products fused variously at temperatures between 200° and 228° and there is some inexplicable difficulty in preparing the pure substance.

Even the crude substance, however, had so high a melting point that a good fluid melt could not be obtained at the stage of the flavonol synthesis and several attempts in this direction failed for this reason. The preparation of galangin was attempted, the temperature of the melt being raised from 165—170° to 200°, but very little of the colouring matter could be isolated as the result of the augmented decomposition which occurred under such conditions. It may be recalled that benzoylvanillic anhydride, successfully applied in the synthesis of *iso*rhamnetin, had m. p. 179—180°.

O-*Benzylsyringic Anhydride*, $[CH_2Ph{\cdot}O{\cdot}C_6H_2(OMe)_2{\cdot}CO]_2O$.—Finely powdered *O*-benzylsyringic acid (144 g.) (Bradley and Robinson, *loc. cit.*) was suspended in an ice-cold mixture of dry ether (500 c.c.) and pyridine (53 g.) and a solution (74 c.c.) of thionyl chloride (37 g.) in ether was added portionwise with vigorous shaking during 1·5 hours. The product (118 g., m. p. 111—113°) was isolated as was trimethoxybenzoic anhydride (above); it crystallised from benzene–light petroleum in long needles, m. p. 112—113° (Found: C, 68·6; H, 5·7. $C_{32}H_{30}O_9$ requires C, 68·8; H, 5·4%).

O-*Benzylsyringic anhydride* is moderately readily soluble in alcohol, acetone, or ethyl acetate, readily soluble in chloroform and benzene, and sparingly soluble in ether and light petroleum.

Syringetin 4′-*Benzyl Ether* (II).—Benzylsyringic anhydride (110 g.; 7 mols.), sodium benzylsyringate (13·1 g.; 1·5 mols.), and ω-benzoyloxyphloracetophenone (8·0 g.; 1 mol.) were ground together and heated for 9 hours in an oil-bath at 180—185°. The mobile, liquid, deep reddish-brown melt was poured as completely

as possible into alcohol (200 c.c.) and the residue in the flask was chipped out when cold and washed out with hot alcohol (200 c.c.). The whole was then refluxed for 2 hours, a solution of potassium hydroxide (29 g.) in water (30 c.c.) gradually added, and the mixture boiled gently for 30 minutes. The liquid was concentrated under diminished pressure to about 100 c.c., the residue dissolved in water and saturated with carbon dioxide, and the precipitate isolated (10·5 g.). This product could not be crystallised and it was judged to be contaminated with benzylsyringoyl derivatives; it was accordingly boiled for 20 minutes with a solution of potassium hydroxide (5 g.) in alcohol (100 c.c.), and the phenol isolated as before (8·0 g.). This material (7·5 g.) gradually dissolved in boiling acetic acid (200 c.c.) and when kept in the ice-chest the solution deposited a mass of small brown needles (4·8 g.), m. p. 240—242°. The *flavonol* was recrystallised from acetic acid, giving fine brownish-orange needles which were dried at 130—140° for several hours and then had m. p. 240—241° (Found: C, 65·7; H, 4·9. $C_{24}H_{20}O_8$ requires C, 66·1; H, 4·6%). This substance is sparingly soluble in most organic solvents and dissolves in aqueous alkalis to deep yellow solutions. The yellow solution in concentrated sulphuric acid exhibits a dull green fluorescence more intense than that due to myricetin trimethyl ether and less intense than that due to syringetin under the same conditions. An alcoholic solution of the flavonol develops an olive-green coloration on the addition of ferric chloride and gives a flocculent yellow precipitate with lead acetate.

Triacetyl Derivative.—Syringetin 4′-benzyl ether (0·4 g.) was acetylated by means of boiling acetic anhydride (15 c.c.) and a drop of pyridine during 1 hour. Slow crystallisation from acetic acid gave rhombic plates and more rapid separation from the same solvent or from alcohol gave small needles, m. p. 191—194° (Found: C, 64·0; H, 4·8. $C_{30}H_{26}O_{11}$ requires C, 64·1; H, 4·6%). The substance is moderately readily soluble in alcohol, acetone, or acetic acid, sparingly soluble in ethyl acetate, chloroform, or ether, and very sparingly soluble in benzene or light petroleum.

Syringetin (5 : 7 : 4′-*Trihydroxy*-3′ : 5′-*dimethoxyflavonol*, I).—Unlike *O*-benzylsyringic acid, *O*-benzylsyringetin was not readily de-benzylated by boiling for a short time with concentrated hydrochloric acid, but on prolonged treatment with a boiling mixture of concentrated hydrochloric acid and alcohol a part of the material was attacked and the unchanged benzyl ether remained undissolved in the acid liquor.

For example, a mixture of *O*-benzylsyringetin (2·3 g.), alcohol (100 c.c.), and concentrated hydrochloric acid (100 c.c.) was boiled for 48 hours. The insoluble residue (0·75 g.) had m. p. 242—243°

and the filtrate, after being concentrated and cooled, deposited brown material (1·3 g.) which crystallised from acetic acid (charcoal) in short, glistening, pale yellow needles. The crystals lost their lustre after being heated for several hours at 130—140° and had m. p. 288—289° after darkening at about 270° (Found in material dried at 160° in a vacuum: C, 58·7; H, 4·1. $C_{17}H_{14}O_8$ requires C, 59·0; H, 4·0%).

Syringetin is moderately readily soluble in methyl and ethyl alcohols, acetone, or acetic acid; it is sparingly soluble in ethyl acetate and chloroform and is insoluble in benzene or light petroleum. The crystals are coloured orange by sulphuric acid and dissolve to a yellow solution exhibiting a green fluorescence; the alkaline solutions are intensely yellow. In dyeing properties and many other respects the substance very closely resembles *iso*rhamnetin, of which it is a methoxy-derivative.

Tetra-acetyl Derivative.—This preparation was carried out like that of the triacetate of *O*-benzylsyringetin and the crude product was crystallised by solution in boiling acetic anhydride and addition of water; when the anhydride was decomposed, the hot liquid was treated with charcoal and filtered. The *derivative* separated in clusters of very slender, white needles, m. p. 224—226° (Found: C, 58·1; H, 4·2. $C_{25}H_{22}O_{12}$ requires C, 58·3; H, 4·3%). The substance is moderately readily soluble in ethyl acetate, chloroform, acetone, or acetic acid, sparingly soluble in the alcohols or benzene, and almost insoluble in ether or light petroleum.

Myricetin Hexamethyl Ether.—Syringetin (0·15 g.) was methylated by the gradual and alternate addition of concentrated aqueous potassium hydroxide and methyl sulphate (5 g.) with shaking; the mixture was finally heated on the steam-bath for 1 hour. The product crystallised from light petroleum in almost colourless needles, m. p. 159—161° (literature, 154—156°). The substance was also prepared for comparison from *O*-tetramethylmyricetin (Kalff and Robinson, *loc. cit.*) and the specimen obtained had m. p. 159—160°. An analysis by the Pregl method gave a low value for carbon and this was overcome by the use of a longer tube, a higher temperature, and a slower combustion (Found: C, 62·5; H, 5·5. Calc. for $C_{12}H_{22}O_8$: C, 62·7; H, 5·5%) (compare Freudenberg, Fikentscher, and Wenner, *Annalen*, 1925, **442**, 314).

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