Anthoxanthins. Part II. Derivatives of Katuranin and Kaempferol.*

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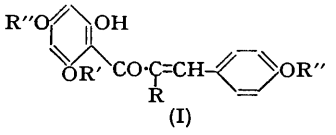
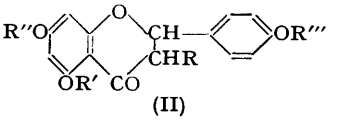
The synthesis of the 7-methyl, 5 : 7- and 7 : 4′-dimethyl, and 5 : 7 : 4′-trimethyl ethers of katuranin (II; R = OH, R′ = R″ = R‴ = H) is described. Bismuth acetate smoothly oxidised these compounds to the corresponding derivatives of kaempferol (III; R = R′ = R″ = R‴ = H) which were also prepared by standard methods.

In Part I * it was shown that flavone hydroxyl groups in flavones are not all equally reactive and that by suitable choice of conditions some selectivity in methylation can be achieved. Since the differences between the methylation rates of 7- and 4′-hydroxyl groups and between those of 3- and 4′-hydroxyl groups are small, satisfactory monomethylation of 7 : 4′- and 3 : 4′-dihydroxyflavones proved difficult. It was considered that these partial methylations might more readily be accomplished if the pyrone ring were reduced (Seshadri, *Ann. Reviews Biochem.*, 1951, **20**, 487). The present investigation of 3-hydroxyflavanones as intermediates in the synthesis of partially methylated flavonols was undertaken as a preliminary to syntheses of naturally occurring flavone glycosides.



(I)



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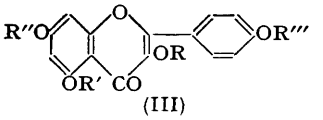
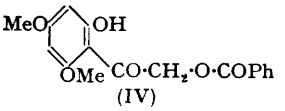


(III)



(IV)

Oxidation of 4 : 2′-dihydroxy-4′ : 6′-dimethoxychalkone (I; R = R‴ = H, R′ = R″ = Me) with alkaline hydrogen peroxide (Reichel and Steudel, *Annalen*, 1942, **553**, 83) gave 3 : 4′-dihydroxy-5 : 7-dimethoxyflavanone (II; R = OH, R′ = R″ = Me, R‴ = H) which had no ferric reaction in ethanol and with zinc and hydrochloric acid gave the intense cherry red colour characteristic of 3-hydroxyflavanones (Pew, *J. Amer. Chem. Soc.*, 1948, **70**, 3031). With methyl sulphate and aqueous alkali, the 3-hydroxyflavanone yielded its 4′-methyl ether, previously obtained by Goel, Narasimhachari, and Seshadri (*Proc. Indian Acad. Sci.*, 1954, **39**, *A*, 254) by methylation of katuranin (II; R = OH, R′ = R″ = R‴ = H). This structure has also been ascribed by Kimuru (*J. Pharm. Soc. Japan*, 1938, **58**, 415; *Chem. Abs.*, 1938, **32**, 6649) to the product of acid-catalysed cyclisation of 2′-hydroxy-α : 4 : 4′ : 6′-tetramethoxychalkone (I; R = OMe, R′ = R″ = R‴ = Me); this product, m. p. 158—159°, is probably a different racemate from that described by Seshadri *et al.* (*loc. cit.*) and the present authors.

3-Hydroxyflavanones have been converted into the corresponding flavonols (III) by alkaline hydrogen peroxide (Reichel and Steudel, *loc. cit.*), by aerial oxidation in acid (Pew, *loc. cit.*) or alkaline (Reichel and Steudel, *loc. cit.*) solution and by catalysed hydrogen transfer (Kotake and Kubota, *Annalen*, 1940, **544**, 253). In our hands, however, the yields obtained by these procedures were variable and low. This transformation may be envisaged as a two-stage process involving (*a*) oxidation of the acyloin structure and (*b*) enolisation of the resulting α-diketone. Since bismuth acetate is known (Rigby, *J.*, 1951, 793; Holden and Rigby, *ibid.*, p. 1924) to be a specific reagent for step (*a*), its reaction with 3-hydroxyflavanones was investigated. 3 : 4′-Dihydroxy-5 : 7-dimethoxyflavanone

* Part I, *J.*, 1954, 4065.

was oxidised almost quantitatively to 3 : 4′-dihydroxy-5 : 7-dimethoxyflavone (III; R = R‴ = H, R′ = R″ = Me); and 3-hydroxy-5 : 7 : 4′-trimethoxyflavanone gave the flavonol (III; R = H, R′ = R″ = R‴ = Me), identical with the product from the Allan–Robinson condensation of ω-benzoyloxy-2-hydroxy-4 : 6-dimethoxyacetophenone (IV) with *p*-anisic anhydride and potassium *p*-anisate. Selective demethylation of these compounds was achieved by fusion with aniline hydrochloride (Schonberg and Aziz, *J. Amer. Chem. Soc.*, 1953, **75**, 3265), 3 : 4′-dihydroxy-5 : 7-dimethoxyflavone yielding rhamnocitrin (III; R = R′ = R‴ = H, R″ = Me), and 3-hydroxy-5 : 7 : 4′-trimethoxyflavone giving 3 : 5-dihydroxy-7 : 4′-dimethoxyflavone (III; R = R′ = H, R″ = R‴ = Me). The last-named compound was also obtained, though in unexpectedly poor yield (cf. Part I), by partial methylation of kaempferide (III; R = R′ = R″ = H, R‴ = Me) with methyl sulphate and sodium hydrogen carbonate in acetone. On remethylation with methyl sulphate and aqueous-alcoholic sodium carbonate, 3 : 4′-dihydroxy-5 : 7-dimethoxy- and 3 : 5-dihydroxy-7 : 4′-dimethoxy-flavones yielded their 3-methyl ethers (III; R = R′ = R″ = Me, R‴ = H; and R = R″ = R‴ = Me, R′ = H).

The oxidation of flavanones to 3-hydroxyflavanones and thence to flavonols was next investigated. Naringenin (II; R = R′ = R″ = R‴ = H) was converted by methyl sulphate and sodium hydrogen carbonate in acetone (Part I) into its 7-methyl ether, sakuranetin, in 70% yield (cf. Narasimhachari and Seshadri, *Proc. Indian Acad. Sci.*, 1948, **27**, *A*, 227; Shinoda and Sato, *J. Pharm. Soc. Japan*, 1928, **48**, 933; *Chem. Abs.*, 1929, **23**, 2956). Oxidation with alkaline hydrogen peroxide then gave 3 : 5 : 4′-trihydroxy-7-methoxyflavanone (II; R = OH, R′ = R‴ = H, R″ = Me), the melting point of which is slightly higher than that reported by Uoda, Fukushima, and Kondô (*J. Agr. Chem. Soc. Japan*, 1943, **19**, 467; *Chem. Abs.*, 1951, **45**, 9136). Further methylation by methyl sulphate with aqueous alkali or potassium carbonate–acetone furnished the 7 : 4′-dimethyl ether, *OO*-dimethylkaturanin (Uoda *et al.*, and Goel *et al.*, *locc. cit.*); attempts to prepare this by peroxide oxidation of 5-hydroxy-7 : 4′-dimethoxyflavanone (II; R = R′ = H, R″ = R‴ = Me) proved unsuccessful, the product being apparently a difficultly separable mixture of benzylidenecoumaranone and hydroxyflavanone (cf. Geissman and Fukushima, *J. Amer. Chem. Soc.*, 1948, **70**, 1686).

Goel *et al.* (*loc. cit.*) failed to achieve the aerial oxidation of 3 : 5-dihydroxy-7 : 4′-dimethoxyflavanone in acid solution, dehydration yielding apigenin dimethyl ether. Oxidation with bismuth acetate has now given, normally, 3 : 5-dihydroxy-7 : 4′-dimethoxyflavone, identical with the previous specimen. In the same way, 3 : 5 : 4′-trihydroxy-7-methoxyflavanone was smoothly converted into rhamnocitrin.

Experimental

M. p.s were measured on a Kofler block and are corrected.

4 : 2′-*Dihydroxy*-4′ : 6′-*dimethoxychalkone* (I; R = R‴ = H, R′ = R″ = Me).—A solution of sodium hydroxide (12 g. in the minimum of boiled water), 2-hydroxy-4 : 6-dimethoxyacetophenone (5 g.), and *p*-hydroxybenzaldehyde (6 g.) in oxygen-free alcohol was refluxed under nitrogen for 30 min. The crude product, isolated by acidification of the cooled, diluted solution was recrystallised from ethanol, furnishing the *chalkone* in orange needles (4·8 g.), m. p. 194—196°, giving a dark brown ethanolic ferric colour [Found: C, 67·8; H, 5·2; OMe, 20·8. $C_{15}H_{10}O_3(OMe)_2$ requires C, 68·0; H, 5·4; OMe, 20·7%].

3 : 4′-*Dihydroxy*-5 : 7-*dimethoxy*- (II; R = OH, R′ = R″ = Me, R‴ = H) *and* 3-*Hydroxy*-5 : 7 : 4′-*trimethoxy*- (II; R = OH, R′ = R″ = R‴ = Me) *flavanone*.—The foregoing chalkone (500 mg.) was oxidised with hydrogen peroxide (100-vol; 1·3 ml.) in aqueous sodium hydroxide (5%; 25 ml.) at 0° overnight. The 3 : 4′-*dihydroxy*-5 : 7-*dimethoxyflavanone* precipitated on acidification recrystallised from ethanol as colourless rectangular tablets (350 mg.), m. p. 226—230°, which gave an intense cherry-red colour with zinc and concentrated hydrochloric acid but no ethanolic ferric reaction [Found: C, 64·7; H, 5·0; OMe, 19·7. $C_{15}H_{10}O_4(OMe)_2$ requires C, 64·6; H, 5·1; OMe, 19·6%].

Methyl sulphate (0·8 ml.) was added to a solution of the foregoing hydroxyflavanone (300 mg.) in alcohol (3 ml.), aqueous N-sodium carbonate (6 ml.), and N-sodium hydroxide (1 ml.).

The mixture was kept at 30° for 15 min. (crystals started to separate after 5 min.), diluted with water, and acidified. Recrystallisation from methanol gave *3-hydroxy-5 : 7 : 4′-trimethoxyflavanone* as colourless tablets (200 mg.), m. p. 141—143°, insoluble in aqueous sodium hydroxide, giving an intense red colour with zinc and concentrated hydrochloric acid and no ferric reaction in ethanol (Found : C, 65·5; H, 5·4. $C_{18}H_{18}O_6$ requires C, 65·4; H, 5·5%).

3 : 4′-Dihydroxy-5 : 7-dimethoxyflavone (III; R = R‴ = H, R′ = R″ = Me).—(*a*) A solution of 3 : 4′-dihydroxy-5 : 7-dimethoxyflavanone (1 g.) in aqueous sodium hydroxide (15%; 30 ml.) and "AnalaR" hydrogen peroxide (100-vol.; 2 ml.) was kept at 0° for 24 hr. and acidified. When twice recrystallised from acetic acid, the precipitate furnished the *flavonol* (III; R = R‴ = H, R′ = R″ = Me) in cream-coloured needles (300 mg.), m. p. 278—280°, giving a green-brown ferric colour in ethanol [Found : C, 65·1; H, 4·6; OMe, 19·5. $C_{15}H_8O_4(OMe)_2$ requires C, 65·0; H, 4·5; OMe, 19·7%]. Its *diacetate* formed colourless needles, m. p. 207—209°, from ethanol (Found : C, 63·4; H, 4·4. $C_{21}H_{18}O_8$ requires C, 63·3; H, 4·6%).

(*b*) A mixture of the 3-hydroxyflavanone (300 mg.), basic bismuth carbonate (600 mg.), 2-ethoxyethanol (12 ml.), and acetic acid (8 ml.) was gently refluxed for 1½ hr., then filtered and the combined filtrate and washings were evaporated *in vacuo*. The resulting complex was dissolved in 10% aqueous sodium hydroxide and acidified with dilute hydrochloric acid. On recrystallisation from acetic acid, the pale yellow precipitate yielded 3 : 4′-dihydroxy-5 : 7-dimethoxyflavone in cream-coloured needles (230 mg.), m. p. and mixed m. p. 278—280°.

3-Hydroxy-5 : 7 : 4′-trimethoxyflavone (III; R = H, R′ = R″ = R‴ = Me).—(*a*) Hydrogen peroxide (100-vol.; 1·5 ml.) was added to the slurry from 3-hydroxy-5 : 7 : 4′-trimethoxyflavanone (500 mg.), ethanol (5 ml.), and aqueous sodium hydroxide (40%; 1 m.). After the vigorous reaction had ceased (10 min.) the mixture was diluted with water and acidified. Recrystallisation from methanol gave 3-hydroxy-5 : 7 : 4′-trimethoxyflavone as yellow needles (90 mg.), m. p. 149—150°, giving a green brown ethanol ferric colour [Found : C, 65·8; H, 4·9; OMe, 27·6. Calc. for $C_{15}H_7O_3(OMe)_3$: C, 65·9; H, 4·9; OMe, 27·8%]. Its acetate formed colourless needles, m. p. 193—194° (lit., 190—191°), from aqueous alcohol (Found : C, 65·1; H, 5·1. Calc. for $C_{20}H_{18}O_7$: C, 64·9; H, 4·9%).

(*b*) The 3-hydroxyflavanone (200 mg.) was refluxed with basic bismuth carbonate (400 mg.), 2-ethoxyethanol (6 ml.), and acetic acid (5 ml.), and the complex isolated, as in the previous experiment. Dissolution in warm methanol by the addition of 10% aqueous sodium hydroxide, acidification, and recrystallisation from methanol gave 3-hydroxy-5 : 7 : 4′-trimethoxyflavone in yellow needles (150 mg.), m. p. and mixed m. p. 149—150°.

(*c*) ω-Benzoyloxyphloroacetophenone (2·8 g.) (Heap and Robinson, *J.*, 1926, 2340) was refluxed with methyl sulphate (2·6 g.), potassium carbonate, and acetone for 5 hr. The *dimethyl ether* separated from light petroleum (b. p. 80—100°) in colourless needles (2·4 g.), giving a dark red ethanol ferric reaction (Found : C, 64·7; H, 5·2. $C_{17}H_{16}O_6$ requires C, 64·6; H, 5·1%). An intimate mixture of this ketone (1·5 g.), potassium *p*-anisate (1·5 g.), and *p*-anisic anhydride (9 g.) was heated to 170° for 2¾ hr. The melt was then hydrolysed with alcoholic potassium hydroxide, and the product isolated by the standard method. After repeated recrystallisation from methanol, 3-hydroxy-5 : 7 : 4′-trimethoxyflavone formed yellow needles (300 mg.), m. p. and m. p. on admixture with the product from (*a*) and from (*b*), 149—150°.

Rhamnocitrin (III; R = R′ = R‴ = H, R″ = Me) *and 3 : 5-Dihydroxy-7 : 4′-dimethoxyflavone* (III; R = R′ = H, R″ = R‴ = Me).—(*a*) An intimate mixture of 3 : 4′-dihydroxy-5 : 7-dimethoxyflavone (300 mg.) and aniline hydrochloride (500 mg.) was fused over a naked flame, heated in an oil-bath at 180° for 1 hr., cooled, and triturated with water. A portion of the insoluble material was chromatographed on Whatman No. 1 paper with benzene–pyridine–water (Simpson and Garden, *J.*, 1952, 4639) and found to contain rhamnocitrin and a small amount of kaempferol. Recrystallisation of the remainder from ethanol furnished rhamnocitrin in pale yellow needles or leaflets (120 mg.), giving an olive-green ethanolic ferric colour; the m. p. alone or on admixture with rhamnocitrin kindly supplied by Professor Seshadri was 221—223° (Found : C, 63·8; H, 4·1. Calc. for $C_{16}H_{12}O_6$: C, 64·0; H, 4·0%). Its triacetate separated from ethanol in colourless needles, m. p. 202° (Found : C, 62·0; H, 4·3. Calc. for $C_{22}H_{18}O_9$: C, 62·0; H, 4·3%).

(*b*) 3-Hydroxy-5 : 7 : 4′-trimethoxyflavone (200 mg.) was fused with aniline hydrochloride (700 mg.), and the product worked up as before. When thrice recrystallised from ethanol, *3 : 5-dihydroxy-7 : 4′-dimethoxyflavone* was obtained in yellow needles (85 mg.), m. p. 180—182°, giving an olive-green ethanolic ferric colour [Found : C, 65·1; H, 4·5; OMe, 19·9. $C_{15}H_8O_4(OMe)_2$ requires C, 65·0; H, 4·5; OMe, 19·7%]. Its *diacetate* formed colourless needles, m. p. 196—198°, from ethanol (Found : C, 63·4; H, 4·7. $C_{21}H_{18}O_6$ requires C, 63·3; H, 4·6%).

With an excess of methyl sulphate and potassium carbonate in boiling acetone during 24 hr., it yielded tetra-*O*-methylkaempferol in colourless plates, m. p. and mixed m. p. 164—165°.

(*c*) A mixture of kaempferide (500 mg.), sodium hydrogen carbonate (10 g.), methyl sulphate (210 mg.), and acetone (100 ml.) was refluxed with stirring for 48 hr. under carbon dioxide, and the product isolated by the standard method. Fractional crystallisation (from ethanol) of the alkali-insoluble portion furnished 3 : 5-dihydroxy-7 : 4′-dimethoxyflavone (30 mg.), m. p. 180—182°, and 5-hydroxy-3 : 7 : 4′-trimethoxyflavone (70 mg.), m. p. 152—153°.

5-Hydroxy-3 : 7 : 4′-trimethoxy- (III; R = R″ = R‴ = Me, R′ = H) *and 4′-Hydroxy-3 : 5 : 7-trimethoxy-flavone* (III; R = R′ = R″ = Me, R‴ = H).—Methyl sulphate (0·5 ml.) was added to a solution of 3 : 5-dihydroxy-7 : 4′-dimethoxyflavone (100 mg.) in alcohol (5 ml.) and aqueous N-sodium carbonate (8 ml.). After 15 min., the mixture was diluted with water and acidified and the solid recrystallised from ethanol. 5-Hydroxy-3 : 7 : 4′-trimethoxyflavone was obtained in pale yellow needles (70 mg.), m. p. and mixed m. p. 152—153° [Found : C, 65·7; H, 4·9; OMe, 28·2. Calc. for $C_{15}H_7O_3(OMe)_3$: C, 65·9; H, 4·9; OMe, 27·8%].

The alkali-soluble portion of the product from the similar methylation of 3 : 4′-dihydroxy-5 : 7-dimethoxyflavone (500 mg.) was repeatedly recrystallised from acetic acid, yielding 4′-hydroxy-3 : 5 : 7-trimethoxyflavone in pale yellow plates (30 mg.), m. p. 278—280°, giving no colour with ferric chloride and ethanol.

3 : 5 : 4′-Trihydroxy-7-methoxy- (II; R = OH, R′ = R‴ = H, R″ = Me) *and 3 : 5-Dihydroxy-7-4′-dimethoxy-flavanone* (II; R = OH, R′ = H, R″ = R‴ = Me).—Naringenin (3 g.), methyl sulphate (1·55 g., 1·1 mols.), anhydrous sodium hydrogen carbonate (20 g.), and acetone (100 ml.) were refluxed, with stirring, in carbon dioxide for 4 days. Isolation by the standard method and recrystallisation from aqueous ethanol and then from benzene yielded sakuranetin (II; R = H, R′ = R‴ = H, R″ = Me) in cream-coloured prisms (2·1 g.), m. p. 149·5—150·5°. A solution of this (500 mg.) in 2N-sodium hydroxide (20 ml.) and hydrogen peroxide (100-vol.; 1 ml.) was kept at 0°. Next day, more hydrogen peroxide (1 ml.) was added, and the mixture kept at 0° for a further 24 hr., then acidified with acetic acid. Recrystallisation from aqueous methanol gave 3 : 5 : 4′-trihydroxy-7-methoxyflavanone, pale yellow needles (320 mg.), m. p. 187—190°, giving a red-brown ferric colour in ethanol and an intense cherry-red colour with zinc and concentrated hydrochloric acid (Found : C, 63·4; H, 4·6. Calc. for $C_{16}H_{14}O_6$: C, 63·6; H, 4·7%).

The last-named compound (300 mg.) in alcohol (2 ml.), aqueous N-sodium carbonate (6 ml.), and N-sodium hydroxide (1 ml.) with methyl sulphate (0·8 ml.) (15 min.) gave 3 : 5-dihydroxy-7 : 4′-dimethoxyflavanone in colourless needles (150 mg.), m. p. 185—189° (from alcohol). Sparingly soluble in aqueous sodium hydroxide, it gave a red-brown ethanolic ferric colour, a cherry-red colour with zinc and concentrated hydrochloric acid, and a red colour with magnesium and concentrated hydrochloric acid (Found : C, 64·7; H, 4·9. Calc. for $C_{17}H_{16}O_6$: C, 64·6; H, 5·1%).

The same compound (80 mg.) was obtained from the hydroxyflavanone (150 mg.) by methyl sulphate (63 mg.) and potassium carbonate in acetone during 5 hr.

Rhamnocitrin and 3 : 5-Dihydroxy-7 : 4′-dimethoxyflavone.—3 : 5 : 4′-Trihydroxy-7-methoxyflavanone (100 mg.), basic bismuth carbonate (200 mg.), 2-ethoxyethanol (4 ml.), and acetic acid (3 ml.) were refluxed for 1½ hr. and the complex was isolated and decomposed as before. Rhamnocitrin separated from ethanol in yellow needles (65 mg.), m. p. and mixed m. p. 221—223°.

3 : 5-Dihydroxy-7 : 4′-dimethoxyflavanone (50 mg.) similarly gave 3 : 5-dihydroxy-7 : 4′-dimethoxyflavone, yellow needles (30 mg.), m. p. and mixed m. p. 180—182°, from ethanol.

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