CVIII.—*Anthoxanthins. Part XI. A Synthesis of Diosmetin and of Luteolin 3′-Methyl Ether.*

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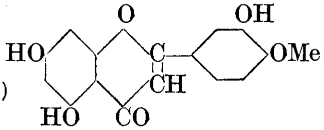
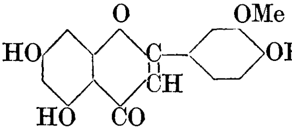
The rhamnoglucoside, diosmin, was isolated in 1925 by Oesterle and Wander (*Helv. Chim. Acta*, **8**, 519) from *Scrophularia nodosa*, *Hyssopus officinalis*, as well as from species of *Conium*, *Barosma*, *Hedeoma*, *Menika*, *Toddalia*, and *Linaria*, and found to yield an aglycone, diosmetin (I), which was shown to be a methyl ether of luteolin. The *iso*vanillin-type of orientation is so infrequently encountered in nature that it was thought desirable to synthesise diosmetin and the isomeride (II) which, according to A. G. Perkin (J., 1900, **77**, 423), stands in a close relationship to scoparin from *Cytisus scoparius* (Link).

(I.)





(II.)

The two flavones have been obtained by debenzylation of the *benzyl* ethers produced by condensation of phloracetophenone with sodium *O*-benzyl*iso*vanillate and *O*-benzylvanillate, respectively. The methods employed are thus quite parallel with that devised for the synthesis of syringetin (Heap and Robinson, Part IX, J., 1929, 67). The synthetic diosmetin and its triacetate were directly compared with specimens of the natural product and of its triacetate kindly sent to us by Professor O. A. Oesterle, to whom we are deeply indebted, and no divergences of behaviour were observed.

EXPERIMENTAL.

iso*Vanillic Acid.*—This substance can be obtained by the hydrolysis of veratric acid by means of acids, the methoxyl group in the *m*-position to the carboxyl being preferentially attacked (compare 4-nitroveratrole; Cardwell and Robinson, J., 1915, **107**, 255). A mixture of veratric acid (20 g.) and hydrobromic acid (200 c.c. of 40%) was boiled under reflux; after 1—1½ hours, a clear yellowish-brown solution was obtained, but in a short time a white substance was deposited; when the voluminous precipitate had become crystalline, it was collected on a sintered-glass filter-plate. The crude material (8—9 g.), m. p. 245—247° after sintering at 235°, was pure enough for many purposes; once crystallised from water, it had m. p. 248—249° (literature, 250°). The hot acid filtrate deposited a white flocculent material on cooling and, by renewed treatment with boiling 40% hydrobromic acid, a further quantity of *iso*vanillic acid (about 1 g.) was obtained (total yield, 50—55%).

O-*Benzyl*iso*vanillic Acid and Derivatives.*—The direct benzylation of *iso*vanillic acid gave indifferent results, owing to separation difficulties, and accordingly we adopted the following processes :

(A) Following Shinoda (*J. Pharm. Soc. Japan*, 1928, **48**, 936), we prepared *iso*vanillin (25 g., m. p. 115°) by the semi-demethylation of veratraldehyde (100 g.) by means of boiling 43% hydrobromic acid (1500 g.) during 3 hours. The dark filtrate from tarry matter was extracted with chloroform, and the residue after removal of the solvent was dissolved in aqueous potassium hydroxide and freed from neutral substances by extraction with ether. The hydroxy-aldehyde was regenerated, isolated by means of chloroform, and crystallised from water (600 c.c.).

*iso*Vanillin (90 g.), dissolved in a solution of potassium hydroxide (34 g.) in water (200 c.c.), was mixed with benzyl chloride (50 g.), and the whole heated (oil-bath at 110—120°) for 7 hours with frequent shaking. The product was isolated by extraction with chloroform and crystallisation from alcohol (yield, 80 g.; recrystallised, 66 g., m. p. 62—63°) in colourless needles, m. p. 63° (Found : C, 74·4; H, 5·8. $C_{15}H_{14}O_3$ requires C, 74·5; H, 5·8%). Mixed with benzylvanillin (m. p. 63°), it melted at about 48°. Oxidation of O-*benzyl*iso*vanillin* was effected by means of potassium permanganate in acetone solution, the best results being obtained in relatively small-scale operations (less than 15 g.). The acid crystallised from alcohol and then from ethyl acetate in white, elongated, hexagonal plates, m. p. 177—178°.

(B) This is the better of the alternatives. *iso*Vanillic acid gave an equal weight of the methyl ester (crystallised from ether–light petroleum; m. p. 65—66°) on treatment in the usual way with methyl alcohol and hydrogen chloride.

Potassium hydroxide (5·5 g.) in methyl alcohol (50 c.c.) was added to a mixture of methyl *iso*vanillate (17 g.), benzyl chloride (12 g.), and methyl alcohol (25 c.c.), and the whole heated on the steam-bath for 5 hours. Potassium chloride and *methyl* O-*benzyl*iso*vanillate* separated from the hot solution and, after cooling, the ester was collected and washed with water (yield, 21·5 g. or 82%; m. p. 121°); recrystallised from methyl alcohol–acetone, it melted at 124° (Found: C, 70·8; H, 6·1. $C_{16}H_{14}O_4$ requires C, 70·6; H, 5·9%). A mixture of methyl *O*-benzyl*iso*vanillate (52 g.), potassium hydroxide (12 g.), and water (120 c.c.) was heated on the steam-bath for 2 hours, and the clear solution then acidified. O-*Benzyl*iso*vanillic acid*, crystallised from acetic acid, had m. p. 177° (Found: C, 69·4; H, 5·6. $C_{15}H_{14}O_4$ requires C, 69·8; H, 5·4%).

O-*Benzyl*iso*vanillic Anhydride*.—A cold ethereal solution of pure thionyl chloride (3·7 g.) was added during 2 hours with stirring to a suspension of powdered benzyl*iso*vanillic acid (12·5 g.) in dry ether (50 c.c.) and pyridine (5·3 g.) cooled in a mixture of ice and salt. The whole was kept at 0° for several hours with occasional shaking, crushed ice was then added, and the solid was collected and triturated successively with ice-cold dilute hydrochloric acid, dilute aqueous sodium carbonate, and water, and dried in a vacuum (yield, 11 g.; a small further quantity was recovered by means of ether). The *anhydride* crystallised from benzene or ethyl acetate in glistening needles, m. p. 156° after softening at 153° (Found: C, 72·3; H, 5·3. $C_{30}H_{26}O_7$ requires C, 72·3; H, 5·2%).

5 : 7 - *Dihydroxy* - 3′ - *benzyloxy* - 4′ - *methoxyflavone* (O - *Benzyldiosmetin*).—An intimate mixture of phloracetophenone (5 g.), *O*-benzyl*iso*vanillic anhydride (60 g.), and sodium *O*-benzyl*iso*vanillate (12 g.) was heated (oil-bath at 190—195°) for 6 hours, and the viscous reddish-brown mass was then poured as completely as possible into alcohol (200 c.c.). The residue in the flask was chipped out when cold and washed out with alcohol and the whole was refluxed for 2 hours. A solution of potassium hydroxide (25 g.) in water (30 g.) was added and the mixture was boiled gently for 30 minutes and then evaporated under diminished pressure. The residue was dissolved in water and saturated with carbon dioxide, giving a yellowish-brown flocculent precipitate, which was redissolved in 2% sodium hydroxide solution and reprecipitated by carbon dioxide (dry wt., 15 g.). Attempts to crystallise this material were unsuccessful, but after treatment with boiling alcoholic potassium

hydroxide about 2 g. of a yellow substance remained undissolved; this was dissolved in 2% sodium hydroxide solution, and the flavone regenerated by means of carbon dioxide. The product now crystallised from acetic acid in pale yellow clusters of needles, m. p. 240° after sintering at 237° (Found : C, 70·6; H, 4·7. $C_{23}H_{18}O_6$ requires C, 70·8; H, 4·6%). The alcoholic potassium hydroxide filtrate was also worked up and, by taking advantage of the insolubility of the impurities in alcohol, a further equal quantity of *benzyldiosmetin*, m. p. 237°, was recovered.

O-*Triacetyldiosmetin.*—A solution of *O*-benzyldiosmetin (0·4 g.) in acetic acid (25 c.c.) was boiled and transferred to the steam-bath; a solution of hydrochloric acid (2 g.) saturated at 0° was then gradually introduced, giving a deep yellow solution. After 10 minutes, a further amount (1 g.) of the acid was added, the heating continued for 30 minutes, and the mixture was finally boiled. Water (30 c.c.) was added to the filtered solution and the pasty precipitate was collected and dried; it could not, however, be crystallised at this stage.

The crude product (0·3 g.) was boiled with acetic anhydride (10 c.c.) and a drop of pyridine for 2 hours and the acetate produced was crystallised from alcohol and then from ethyl acetate, giving colourless needles, m. p. 195—196° (Found : C, 72·3; H, 5·3. Calc. for $C_{22}H_{18}O_9$: C, 72·3; H, 5·2%). This specimen was identical in every way with specimens of triacetyldiosmetin from two sources, kindly supplied by Professor Oesterle. A mixture of the natural and the synthetic specimen gave an undepressed melting point.

Diosmetin (I).—A mixture of the synthetic triacetyldiosmetin (0·3 g.) with alcohol (5 c.c.) and 2% potassium hydroxide solution (10 c.c.) was heated on the steam-bath for 15 minutes, and the flavone isolated from the clear yellow solution by acidification with acetic acid. The substance, crystallised from alcohol and then twice from alcohol–ethyl acetate, formed yellow needles, sintering at 248° and melting at 253—254° (Found in a specimen dried at 150° in a high vacuum : C, 64·3; H, 4·2. Calc. for $C_{16}H_{12}O_6$: C, 64·0; H, 4·0%). A mixture with natural diosmetin (sintering at 245° and melting at 253—255°) sintered at 245° and melted at 253—254°. In all respects, the two specimens had identical properties.

Benzylvanillic Anhydride, $[CH_2Ph{\cdot}O{\cdot}C_6H_3(OMe){\cdot}CO]_2O$. — The benzylation of vanillin (276 g.) was effected in aqueous solution (compare Gomberg and Buchler, *J. Amer. Chem. Soc.*, 1920, **42**, 2059) by means of benzyl chloride (150 g.) and potassium hydroxide, the reaction mixture being heated (oil-bath at 110—120°) for 10½ hours. After crystallisation, 165 g., m. p. 63—64°, were obtained.

On oxidation with potassium permanganate in acetone solution, the aldehyde (70 g.) furnished crystalline *O*-benzylvanillic acid (60 g.), m. p. 168—169°.

O-Benzylvanillic acid (97 g.) was finely ground, suspended in dry ether (375 c.c.) and pyridine (40 g.), to which thionyl chloride (28 g.) in ether (30 c.c.) was added, and the whole kept at 0° for 12 hours. Crushed ice was then introduced and the solid was washed successively with ice-cold 2*N*-hydrochloric acid, water, 2*N*-sodium carbonate, and water and dried (80 g., m. p. 135°; benzylvanillic acid, 9 g., was recovered from the ether and washings). The *anhydride* crystallised from ethyl acetate in slender lustrous needles, m. p. 135—136° (Found: C, 72·2; H, 5·4. $C_{30}H_{26}O_7$ requires C, 72·3; H, 5·2%).

5 : 7-*Dihydroxy*-4′-*benzyloxy*-3′-*methoxyflavone*.—An intimate mixture of phloracetophenone (4·5 g.), sodium *O*-benzylvanillate (12 g.), and *O*-benzylvanillic anhydride (40 g.) was heated (oil-bath at 180—185°) for 3 hours subsequent to fusion to a mobile, dark red liquid. The product was refluxed with alcohol (175 c.c.); a solution of potassium hydroxide (17 g.) in water (20 c.c.) was gradually added, and the boiling continued for 30 minutes. The solution was distilled (170 c.c. collected) and the residue was dissolved in water (200 c.c.), heated to 60°, and saturated with carbon dioxide. The buff precipitate was collected (7 g.), redissolved in aqueous potassium hydroxide, and reprecipitated by carbon dioxide (yield, 5 g.). The crude flavone was then acetylated by gently refluxing it with acetic anhydride (20 c.c.) and a drop of pyridine for 2 hours. The acetyl derivative, which separated on cooling (2 g.), crystallised from ethyl acetate in slender white needles, m. p. 195° (1·6 g.) (Found: C, 68·2; H, 4·8. $C_{27}H_{22}O_8$ requires C, 68·4; H, 4·6%).

This 5 : 7-*diacetoxy*-4′-*benzyloxy*-3′-*methoxyflavone* (1·2 g.) was hydrolysed by means of alcoholic potassium hydroxide on the steam-bath and, when the diluted solution was acidified, a yellow solid was precipitated (1·03 g.). The substance was very sparingly soluble in most organic solvents and could not be crystallised, but after being washed and dried it was almost pure; m. p. 265—267° after softening at 262° (Found: C, 70·0; H, 4·9. $C_{23}H_{18}O_6$ requires C, 70·7; H, 4·6%. $C_{23}H_{18}O_6,\frac{1}{4}H_2O$ requires C, 70·0; H, 4·7%). This 5 : 7-*dihydroxy*-4′-*benzyloxy*-3′-*methoxyflavone* gives a yellow-brown coloration with alcoholic ferric chloride.

5 : 7 : 4′-*Trihydroxy*-3′-*methoxyflavone* (II).—The benzyl derivative last described (0·8 g.) was suspended in acetic acid (45 c.c.), heated on the steam-bath, and treated gradually with concentrated hydrochloric acid (3 c.c.). After 10 minutes, a further quantity (1·5 c.c.) of concentrated hydrochloric acid was added, and the heating

continued for 30 minutes; the mixture was finally boiled. The solution was decanted from a small unattacked residue, and, on addition of water (30 c.c.), gave a flocculent yellow precipitate, which was collected and dried (0·5 g.) (Found : C, 63·9; H, 4·4; MeO, 10·3%). This product was acetylated in the usual manner and gave 0·4 g., m. p. 212°, which, crystallised from ethyl acetate, formed soft white needles, m. p. 220—221° (0·35 g.; recrystallised, 0·29 g., m. p. 220—221°) (Found : C, 61·9; H, 4·4. $C_{22}H_{18}O_9$ requires C, 62·0; H, 4·2%).

On hydrolysis by means of alcoholic potassium hydroxide, 5 : 7 : 4′-*triacetoxy*-3′-*methoxyflavone* gave in the first place bright yellow needles of the potassium salt of the trihydroxymethoxyflavone; these were collected and dissolved in water and afforded on acidification the pure *flavone*, m. p. 328—330°, as a yellow precipitate (Found in material dried in a vacuum : C, 62·8; H, 4·2; MeO, 9·3. $C_{16}H_{12}O_6,\frac{1}{3}H_2O$ requires C, 62·7; H, 4·2; 1MeO, 9·5%). This very sparingly soluble substance crystallised from nitrobenzene in yellow prismatic needles, m. p. 330—331° (Found : C, 63·9; H, 3·9; MeO, 9·8. $C_{16}H_{12}O_6$ requires C, 64·0; H, 4·0; 1MeO, 9·7%). Like diosmetin, the flavone is a very weak mordant dye. It is much more sparingly soluble and intensely coloured than is diosmetin.

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