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Synthetic Studies of the Flavone Derivatives. IX.[*1]
The Syntheses of Axillarin and Its Related Compounds[*2]

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By using the method of Allan-Robinson's flavone synthesis, the condensation of 3,ω-dimethoxy-2,4,6-trihydroxyacetophenone with 3,4-dibenzyloxybenzoic anhydride gave a mixture of 3,6- and 3,8-dimethoxy-3′,4′-dibenzyloxy-5,7-dihydroxyflavone (X and XI). The catalytic debenzylation of the above flavones then gave axillarin (I) and 3,8-dimethoxy-5,7,3′,4′-tetrahydroxyflavone (IV) respectively. Axillarin 7-*O*-methyl ether(III) was prepared by the partial methylation of X, followed by catalytic debenzylation.

Axillarin (quercetagetin 3,6-dimethyl ether) was first isolated from the leaves of cocklebur (*Xanthium pensylvanicum*)1) and later from the flowers and leaves of *Iva axillaris* Pursh. ssp. *robustor*.2) Its structure was identified as 3,6-dimethoxy-5,7,3′,4′-tetrahydroxyflavone (I) (quercetagetin type) on the basis of spectral data1) and by a comparison of the tetraethyl ether (II) of I with a synthetic sample.2) 5,3′,4′-Trihydroxy-3,6,7-trimethoxyflavone (III) (7-*O*-methyl ether of I) was also isolated from the leaves of *Cyanostegia microphylla*.3) On the other hand, 3,8-dimethoxy-5,7,3′,4′-tetrahydroxyflavone (IV) (gossypetin type), an isomer of I, was isolated from *Ricinocarpus muricatus* Muell. Arg.4) Recently, a synthesis of IV starting from 4-benzyloxy-2-hydroxy-3,6,ω-trimethoxyacetophenone (V) has been reported.5)

In previous papers,6,7) the authors reported the

[*1] Part VIII of this series: K. Fukui, T. Matsumoto, M. Nakayama and T. Horie, This Bulletin, **41**, 2805 (1968).

[*2] This has previously been reported in a preliminary form: K. Fukui, M. Nakayama and T. Horie, *Experientia*, **24**, 769 (1968).

1) A. O. Taylor and E. Wong, *Tetrahedron Letters*, **1965**, 3675.

2) W. Herz, L. Farkas, V. Sudarsanam, H. Wagner, L. Hörhammer and R. Rüger, *Chem. Ber.*, **99**, 3539 (1966).

3) E. L. Ghisalberti, P. R. Jefferies and C. I. Stacey, *Australian J. Chem.*, **20**, 1049 (1967).

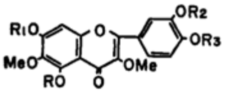
4) C. A. Henrick and P. R. Jefferies, *Tetrahedron*, **21**, 3219 (1965).

5) L. Farkas and M. Nogradi, *Tetrahedron Letters*, **1966**, 3759.

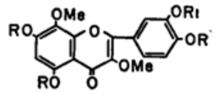
6) K. Fukui, T. Matsumoto, S. Nakamura, M. Nakayama and T. Horie, *Experientia*, **24**, 108 (1968); This Bulletin, **41**, 1413 (1968).

7) K. Fukui, M. Nakayama and T. Horie, *Experientia*, **24**, 417 (1968); K. Fukui, T. Matsumoto, M. Nakayama and T. Horie, This Bulletin, **41**, 2805 (1968).

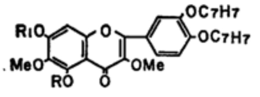
syntheses of jaceidin (VI) and 5,7,4′-trihydroxy-3,8,3′-trimethoxyflavone (VII) from 3,ω-dimethoxy-2,4,6-trihydroxyacetophenone (VIII). The present paper will describe the total syntheses of I and III, and a new synthesis of IV from the ketone VIII in a manner similar to that previously described.[6,7)]



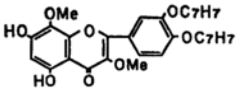
I $R=R_1=R_2=R_3=H$
II $R=R_1=R_2=R_3=Et$
III $R=R_2=R_3=H$, $R_1=Me$
VI $R=R_1=R_3=H$, $R_2=Me$
XII $R=R_1=R_2=R_3=Ac$
XV $R=R_2=R_3=Ac$, $R_1=Me$



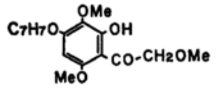
IV $R=R_1=H$
VII $R=H$, $R_1=Me$
XVI $R=R_1=Ac$
XVII $R=R_1=Et$
XVIII $R=Ac$, $R_1=Me$
XIX $R=Et$, $R_1=Me$



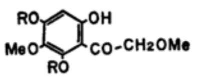
IX $R=R_1=Ac$
X $R=R_1=H$
XIV $R=H$, $R_1=Me$



XI



V



VIII $R=H$
XIII $R=Et$

By using the method of Allan-Robinson's flavone synthesis, the reaction of the ketone VIII with 3,4-dibenzyloxybenzoic anhydride and potassium 3,4-dibenzyloxybenzoate, followed by treatment with alcoholic potassium hydroxide, yielded a mixture of flavones. The mixture was then acetylated without further purification. After repeated recrystallizations of the acetylated product from methanol, 5,7-diacetoxy-3′,4′-dibenzyloxy-3,6-dimethoxyflavone (IX), $C_{35}H_{30}O_{10}$, mp 135—136.5°C, was obtained as colorless needles. The NMR spectrum[*3] of IX showed a singlet at δ 7.19 (1H) which could be attributed to the C-8 proton (not the C-6 proton) on the basis of a comparison with the spectra data of some of the flavones reported on in the literature (Table 1).[4,8)] The treatment of IX with dilute alkali gave 3′,4′-dibenzyloxy-5,7-dihydroxy-3,6-dimethoxyflavone (X), mp 147.5—148.5°C. From the mother-liquor of the recrystallization of IX, 3′,4′-dibenzyloxy-5,7-dihydroxy-3,8-dimethoxyflavone (XI), mp 180—181.5°C (from ethyl acetate), was obtained after treatment with aqueous potassium hydroxide.

The catalytic debenzylation of X gave the desired flavone I, which was shown to be identical with natural axillarin[*4] by a mixed-melting-point determination and by a comparison of their ultraviolet spectra. Moreover, the IR-spectra of natural quercetagetin 3,6-dimethyl ether,[*5] natural axillarin,[*4] and the synthetic axillarin were superimposable upon one another. I was also obtained from IX by debenzylation and subsequent hydrolysis.

The synthetic axillarin (I) was converted to tetraacetate XII and tetraethyl ether II by the usual methods. The tetraethyl ether II was also synthesized by the Allan-Robinson reaction of

TABLE 1. THE NMR SPECTRAL DATA OF FLAVONES[*3]

Proton	Compound					
	IX	XII	II	XV	XVI	XVII
Arom. *H*						
C-8	7.19_{s}	7.33_{s}	6.78_{s}	6.90_{s}		
C-6					6.81_{s}	6.47_{s}
C-2′	$7.77_{d'}$	7.99_{bs}	7.71_{bs}	8.08_{bs}	$8.06_{d'}$	$7.89_{d'}$
C-5′	7.08_{d}	7.41_{d}	7.02_{d}	7.39_{d}	7.38_{d}	7.03_{d}
C-6′	7.64_{q}	8.07_{q}	7.74_{q}	8.01_{q}	8.09_{q}	7.88_{q}

s, singlet; bs, broader singlet; d, doublet ($J_{ortho}=9.0$ Hz); d′, doublet ($J_{meta}=2.5$ Hz); q, quartet ($J_{ortho}=9.0$ Hz; $J_{meta}=2.5$ Hz).

[*3] The NMR spectra were measured with a Hitachi R-20 spectrometer, using tetramethylsilane as the internal standard (δ-value in $CDCl_3$).

8) a) C. A. Henrick and P. R. Jefferies, *Australian J. Chem.*, **17**, 934 (1962); b) J. Massicot and J-P. Marthe, *Bull. Soc. Chim. France*, **1962**, 1962; c) J. Massicot, J-P. Marthe and S. Heitz, *ibid.*, **1963**, 2712.

[*4] The natural axillarin and its tetraethyl ether were kindly supplied by Professor W. Herz, Florida State University.

[*5] The IR-spectrum of natural quercetagetin 3,6-dimethyl ether was kindly supplied by Dr. E. Wong, Plant Chemistry Division, Department of Science and Industrial Research, New Zealand.

4,6-diethoxy-5,ω-dimethoxy-2-hydroxyacetophenone (XIII)[6] with 3,4-diethoxybenzoic anhydride.

The partial methylation of X gave 3′,4′-dibenzyloxy-5-hydroxy-3,6,7-trimethoxyflavone (XIV). The debenzylation of XIV yielded axillarin 7-*O*-methyl ether (III). Its triacetate (XV) was prepared by acetylation. The properties of these compounds were identical with those described by Ghisalberti *et al.*[3]

On the other hand, the debenzylation of XI afforded a tetrahydroxyflavone (IV) whose identity with the natural substance[*6] was confirmed by a mixed-melting-point determination and by a comparison of their ultraviolet spectra. Its tetraacetate (XVI) and tetraethyl ether (XVII) were prepared by the usual methods. The NMR spectra of these compounds (XVI and XVII) show one proton signal corresponding to the C-6 proton at δ 6.81 and 6.47 respectively; these values are in accordance with those observed for the triacetate (XVIII) and triethyl ether (XIX) of VII.[3,7]

Experimental[*7]

3,6-Dimethoxy- (X) and 3,8-dimethoxy-3′,4′-dibenzyloxy-5,7-dihydroxyflavone (XI). A mixture of the ketone (VIII)[6] (3.1 g), 3,4-dibenzyloxybenzoic anhydride (29 g), and potassium 3,4-dibenzyloxybenzoate (13 g) was heated at 170°C for 5 hr and then at 180°C for 8 hr under reduced pressure. The reaction mixture was then cooled and refluxed for 20 min with a solution of potassium hydroxide (15 g) in aqueous ethanol (80%; 350 m*l*). After the evaporation of the solvent under a vacuum, the residue was dissolved in water and saturated with carbon dioxide. The resulting precipitate was extracted with ethyl acetate. The extract was washed with water, dried, and evaporated to 25 m*l*. The separating crystals (3,4-dibenzyloxybenzoic acid) were then filtered off and washed with ethyl acetate. The combined filtrate was evaporated, and the residue was recrystallized from methanol to give a crude flavone mixture (about 4.7 g).

A mixture of the crude flavones, acetic anhydride (12 g), and pyridine (1.0 m*l*) was heated at 120°C for 2 hr and then poured into water. The resulting mixture was extracted with ether, and the extract was washed with dilute hydrochloric acid and a dilute sodium carbonate solution and then allowed to stand in a refrigerator for one day. The separating crystals were collected and recrystallized from methanol and then ethanol to give 5,7-diacetoxy-3′,4′-dibenzyloxy-3,6-dimethoxyflavone (IX) in the form of colorless needles, mp 135—136.5°C; yield, 2.13 g (26% from VIII). IR: 1764, 1641, 1609, 1601 cm^{-1}. UV: $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε); 252 (4.32), 350 (4.21).

Found: C, 69.08; H, 4.80%. Calcd for $C_{35}H_{30}O_{10}$: C, 68.84; H, 4.95%.

A solution of IX (1.47 g) in ethanol (200 m*l*) was gently refluxed with aqueous potassium hydroxide (10%; 10 m*l*) for 3 min. The resulting solution was acidified with dilute hydrochloric acid, and the solvent was evaporated under a vacuum. The resulting precipitate was collected and recrystallized from methanol to give X in the form of pale yellow needles, mp 147.5—148.5°C; yield, 1.2 g (95%). It gave a green color with an alcoholic ferric chloride solution. IR: 3430, 1653, 1613, 1593 cm^{-1}. UV: $\lambda_{\max}$ mμ (log ε); (EtOH) 255 (4.27), 273 (4.23), 347 (4.35); (EtOH-AcONa) 276 (4.36), 322 (4.38), 364 (4.23); (EtOH-EtONa) 277 (4.47), 298 (4.18), 312 (4.18), 384 (4.27); (EtOH-$AlCl_3$) 262, 285, 368.

Found: C, 70.66; H, 4.76%. Calcd for $C_{31}H_{26}O_8$: C, 70.71; H, 4.98%.

The concentration of the methanolic filtrate which was obtained in the case of recrystallization of IX, followed by hydrolysis with aqueous potassium hydroxide (a 2% potassium hydroxide solution (25 m*l*) and methanol (75 m*l*)), yielded yellow crystals. On repeated crystallizations from ethyl acetate, XI was obtained in the form of yellow needles, mp 180—181.5°C; yield, 1.32 g (18% from VIII). It gave a green color with an alcoholic ferric chloride solution. IR: 3155 (broad), 1653, 1604, 1592, 1577 cm^{-1}. UV: $\lambda_{\max}$ mμ (log ε); (EtOH) 258 (4.28), 277 (4.32), 339 (4.21), 355 (4.20); (EtOH-AcONa) 257.5 (4.04), 284 (4.38), 320 (4.18), 366 (4.08); (EtOH-NaOEt) 233 (4.21), 286.5 (4.40), 316 (4.11), 390 (3.98); (EtOH-$AlCl_3$) 263, 287, 306_i,[*8] 360, 420.

Found: C, 70.99; H, 4.97%. Calcd for $C_{31}H_{26}O_8$: C, 70.71; H, 4.98%.

Axillarin (3,6-Dimethoxy-5,7,3′,4′-tetrahydroxyflavone) (I). *a) From the dihydroxyflavone X.* A mixture of X (560 mg) and Pd-C (5%; 1.0 g) in methanol-ethyl acetate (2:1; 150 m*l*) was shaken in an atmosphere of hydrogen until 2.1 mol of hydrogen had been absorbed. After the catalyst had been filtered, the filtrate was evaporated under a vacuum; the residue was recrystallized from acetonitrile to give I in the form of yellow needles, mp 207—208°C (192—193°C sinter); yield 292 mg (80%). It gave a green color with an alcoholic ferric chloride solution.

Found: C, 56.11; H, 4.26%. Calcd for $C_{17}H_{14}O_8\cdot H_2O$: C, 56.04; H, 4.43%.

After drying at 120—130°C/0.2 mmHg for 3 hr, this substance had a mp of 207—208°C or 217—218°C (207—209°C sinter). It was identified with natural axillarin by a mixed-melting-point determination and by a comparison of their infrared and ultraviolet sepctra. IR: 3380, 3130, 1652, 1602 cm^{-1}. UV: $\lambda_{\max}$ mμ (log ε); (EtOH) 259 (4.25), 295 (3.91), 358 (4.32); (EtOH-AcONa) 272 (4.27), 300 (3.95), 367 (4.24); (EtOH-EtONa) 273 (4.32), 410 (4.35); (EtOH-$AlCl_3$) 278, 410. Natural axillarin:[*4] mp 207.5—209°C. IR: 3390, 3130, 1653, 1604 cm^{-1}. UV: $\lambda_{\max}$ mμ (log ε); (EtOH) 259 (4.26), 296 (3.92), 355 (4.33); (EtOH-AcONa) 273 (4.27), 299 (3.94), 369 (4.25). (lit mp 207—209°C,[1]) mp 211—213°C,[2]) mp 199—200°C.[9]) UV:[2]) $\lambda_{\max}^{\mathrm{EtOH}}$ mμ (log ε); 260 (4.37), 270_i

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[*6] The natural pigment and its tetraacetate were kindly supplied by Professor P. R. Jefferies, University of Western Australia.

[*7] All the melting points are uncorrected; the infrared spectra were measured in Nujol.

[*8] i=Inflection.

9) D. K. Bhadwaj, S. Neelakantan and T. R. Seshadri, *Indian J. Chem.*, **4**, 417 (1966).

(4.33), 295_{i} (4.04), 358 (4.42)).

Found: C, 58.86; H, 3.96%. Calcd for $C_{17}H_{14}O_8$: C, 58.96; H, 4.08%.

Axillarin Tetraacetate (XII): hot acetic anhydride - pyridine method; mp 161—161.5°C (colorless needles from methanol). IR: 1769, 1758, 1639, 1616 cm^{-1}. UV: $\lambda_{\max}^{\text{EtOH}}$ mμ (log ε); 256 (4.16), 320 (4.06), 340_{sh} (4.03).[*9]

Found: C, 58.29; H, 4.34%. Calcd for $C_{25}H_{22}O_{12}$: C, 58.37; H, 4.31%.

b) From the diacetoxyflavone IX. A mixture of IX (450 mg), Pd-C (5%: 1.0 g), and methanol - ethyl acetate (2 : 1 : 150 m*l*) was treated by a method similar to that used for a). Then, the crude product was hydrolyzed with 20% sulfuric acid (5 m*l*) in methanol (25 m*l*) for 2 hr. After the addition of water (10 m*l*), the solvent was evaporated under a vacuum. The resulting precipitate was recrystallized from acetonitrile, mp 207—208°C (192—193°C sinter); yield, 180 mg (71%). It was identical with the sample described in a).

Axillarin Tetraethyl Ether (3,6-Dimethoxy-5,7,3′,4′-tetraethoxyflavone) (II). *a) From Axillarin (I).* A mixture of synthetic axillarin (I) (80 mg), anhydrous potassium carbonate (2.0 g), and diethyl sulfate (1.0 m*l*) in dry acetone (20 m*l*) was refluxed for 24 hr, and then the reaction mixture was treated in the usual manner. Recrystallization from *n*-hexane give II in the form of colorless needles, mp 99.5—100.5°C; yield, 100 mg (89%). After drying at 80°C/0.1 mmHg for 1 hr, it had a mp of 110—111.5°C. It was identified with natural axillarin tetraethyl ether by a mixed-melting-point determination and by a comparison of their ultraviolet spectra. IR: 1641, 1623, 1607 cm^{-1}. UV: $\lambda_{\max}^{\text{EtOH}}$ mμ (log ε); 240 (4.31), 335 (4.36). Natural one:[*4] mp 109.5—111°C. UV: $\lambda_{\max}^{\text{EtOH}}$ mμ (log ε); 240 (4.29), 335 (4.33). (lit mp 109°C,[2] mp 108—110 °C[2]).

Found: C, 65.25; H, 6.56%. Calcd for $C_{25}H_{30}O_8$: C, 65.49; H, 6.60%.

b) From the ketone XIII. A mixture of XIII[6] (1.0 g), 3,4-diethoxybenzoic anhydride (3.0 g), and potassium 3,4-diethoxybenzoate (1.0 g) was treated by a method similar to that used for X and XI. The crude product was recrystallized from *n*-hexane to give II, mp 99.5—100.5°C (after drying; mp 110—111.5°C; yield, 200 mg (13%). It was identical with the sample described in a).

Found: C, 65.30; H, 6.61%. Calcd for $C_{25}H_{30}O_8$: C, 65.49; H, 6.60%.

3′,4′-Dibenzyloxy-5-hydroxy-3,6,7-trimethoxyflavone (XIV). To a solution of X (400 mg) in ethyl acetate (30 m*l*), an ethereal diazomethane solution was added; then the solution was allowed to stand in a refrigerator for 24 hr. After the evaporation of the solvent, the residue was recrystallized from ethanol to give XIV in the form of pale yellow needles, mp 151.5—153°C; yield, 380 mg (93%). It gave a green color with an alcoholic ferric chloride solution. IR: 1652, 1640, 1615, 1599 cm^{-1}. UV: $\lambda_{\max}$ mμ (log ε); (EtOH) 239 (4.28), 256 (4.31), 274 (4.26), 345 (4.39); (EtOH-$AlCl_3$) 265, 286, 366.

Found: C, 70.78; H, 5.25%. Calcd for $C_{32}H_{28}O_8$: C, 71.10; H, 5.22%.

Axillarin 7-*O*-Methyl Ether (3′,4′,5-Trihydroxy-3,6,7-trimethoxyflavone) (III). A mixture of XIV (300 mg), Pd-C (5%; 450 mg), and methanol - ethyl acetate (1:1; 150 m*l*) was treated by a method similar to that used for I. The crude product was recrystallized from methanol to give III in the form of pale yellow prisms, mp 237—238°C; yield, 160 mg (80%). It gave a green color with an alcoholic ferric chloride solution. IR: 3380, 1651, 1603, 1593 cm^{-1}. UV: $\lambda_{\max}$ mμ (log ε); (EtOH) 260 (4.32), 356 (4.37); (EtOH-$AlCl_3$) 279, 415. (lit[3] mp 235—236°C. UV: $\lambda_{\max}^{\text{EtOH}}$ mμ (log ε); 271 (4.29), 360 (4.31)).

Found: C, 60.21; H, 4.47%. Calcd for $C_{18}H_{16}O_8$: C, 60.00; H, 4.48%.

The Triacetate (XV); hot acetic anhydride - pyridine method; mp 158—159°C (colorless needles from methanol). IR: 1764, 1636_{sh}, 1622 cm^{-1}. UV: $\lambda_{\max}^{\text{EtOH}}$ mμ (log ε); 262_{sh} (4.19), 326 (4.25). (lit[3] mp 159—160°C. UV: $\lambda_{\max}^{\text{EtOH}}$ mμ (log ε); 262 (4.25), 317 (4.37)).

3,8-Dimethoxy-5,7,3′,4′-tetrahydroxyflavone (IV). A mixture of XI (590 mg), Pd-C (5%; 1.0 g) and methanol - ethyl acetate (1:1; 200 m*l*) was treated by a method similar to that used for I. The crude product was recrystallized from methanol - water to give IV in the form of yellow needles, mp 297—299°C; yield, 300 mg (77%). It gave a green color with an alcoholic ferric chloride solution. It was identified with the natural pigment by a mixed-melting-point determination and by a comparison of their ultraviolet spectra. IR: 3440, 3360, 3290, 1657, 1616 cm^{-1}. UV: $\lambda_{\max}$ mμ (log ε); (EtOH) 262 (4.34), 275 (4.31), 298 (3.98), 368 (4.27); (EtOH-AcONa) 266_{i} (4.27), 277 (4.34), 374 (4.17); (EtOH-$AlCl_3$) 283, 380_{i}, 440. Natural pigment:[*6] mp 296—298°C. UV: $\lambda_{\max}$ mμ (log ε); (EtOH) 261 (4.33), 274 (4.32), 298 (3.99), 366 (4.27); (EtOH-AcONa) 266_{i} (4.29), 276.5 (4.33), 370 (4.19); (EtOH-$AlCl_3$) 283, 380_{i}, 435. (lit mp 301—303°C,[4] mp 300—301°C.[5] UV:[4] $\lambda_{\max}^{\text{EtOH}}$ mμ (log ε); 267_{sh} (4.35), 276 (4.40), 338_{sh} (4.15), 373 (4.21)).

Found: C, 58.87; H, 3.83%. Calcd for $C_{17}H_{14}O_8$: C, 58.96; H, 4.08%.

The Tetraacetate (XVI): hot acetic anhydride - pyridine method; mp 157—158°C (colorless needles from methanol). IR: 1765 (broad), 1641, 1611 cm^{-1}. UV: $\lambda_{\max}^{\text{EtOH}}$ mμ (log ε); 249_{i} (4.23), 255 (4.24), 311 (3.93), 354 (4.05). (lit mp 149—150°C,[4] mp 158—160°C,[5] mp 150—151°C[5]). This was identified with the natural derivative by a mixed-melting-point determination.

Found: C, 58.67; H, 4.18%. Calcd for $C_{25}H_{22}O_{12}$: C, 58.37; H, 4.31%.

The Tetraethyl Ether (XVII): mp 124.5—125.5°C (colorless needles from aqueous methanol) (lit.[4] mp 125—126°C).

Found: C, 65.62; H, 6.44%. Calcd for $C_{25}H_{30}O_8$: C, 65.49; H, 6.60%.

The authors are grateful to Professor W. Herz, the Florida State University, for samples of axillarin and its tetraethyl ether, to Professor P. R. Jefferies, the University of Western Australia, for samples of natural pigment and its acetate, and to Dr. E. Wong, Department of Science and Industrial Research, New Zealand, for supplying IR spectrum of quercetagetin 3,6-dimethyl ether. This work was supported in part by a grant-in-aid from the Ministry of Education.

[*9] sh=shoulder.