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The Syntheses of Centaureidin and 5,7,3'-Trihydroxy-3,8,4'-trimethoxyflavone^{*1}

Tokunaru HORIE

Department of Applied Chemistry, Faculty of Engineering, University of Tokushima, Tokushima

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Centaurein (I) was first isolated from the roots of *Centaurea jacea* L. by Bridel and Charaux.¹⁾ The hydrolysis of I with sulfuric acid afforded an aglycone, centaureidin (5,7,3'-trihydroxy-3,6,4'-trimethoxyflavone (II)).²⁾ Recently, II has also been

isolated from the *Centaurea* species by Bohlmann and Zdero.³⁾ A structural isomer of II, jaceidin (III), has been isolated from the same plant.^{3,4)} The present author and his collaborators achieved the syntheses of III,⁵⁾ axillarin (IV),⁶⁾ and two

^{*1} Synthetic Studies of the Flavone Derivatives. XIII. Part XII of this series: K. Fukui, M. Nakayama and T. Horie, *This Bulletin*, **42**, 2327 (1969). This has already been partly reported in a preliminary from: T. Horie, *Experientia*, **24**, 880 (1968).

1) M. Bridel and G. Charaux, *Compt. rend.*, **175**, 833, 1168 (1922).

2) L. Farkas, L. Hörhammer, H. Wagner, H. Rösler and R. Gurniak, *Chem. Ber.*, **97**, 1666 (1964).

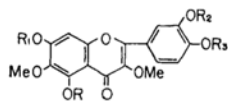
3) F. Bohlmann and C. Zdero, *Tetrahedron Letters*, **1967**, 3239.

4) L. Farkas, L. Hörhammer, H. Wagner, H. Rösler and R. Gurniak, *Chem. Ber.*, **97**, 610 (1964); J. H. Bowie and D. W. Cameron, *J. Chem. Soc.*, **1965**, 5651.

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

6) K. Fukui, M. Nakayama and T. Horie, *Experientia*, **24**, 769 (1968); *This Bulletin*, **42**, 1649 (1969).

isomers, V⁷⁾ and VI,⁶⁾ from 3,ω-dimethoxy-2,4,6-trihydroxyacetophenone (VII).⁵⁾ The present paper is concerned with the total syntheses of II and 5,7,3'-trihydroxy-3,8,4'-trimethoxyflavone (VIII) from VII.



I R = R₂ = H, R₁ = Glu, R₃ = Me

II R = R₁ = R₃ = H, R₂ = Me

III R = R₁ = R₃ = H, R₂ = Me

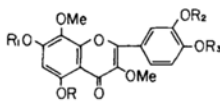
IV R = R₁ = R₂ = R₃ = H

V R = R₁ = H, R₂ = C₆H₅CH₂, R₃ = Me

VI R = H, R₂ = Ac, R₃ = C₆H₅CH₂, R₄ = Me

VII R = R₁ = R₂ = Ac, R₃ = Me

VIII R = R₁ = R₂ = Et, R₃ = Me



IX R = R₁ = R₃ = H, R₂ = Me

X R = R₁ = R₂ = R₃ = H

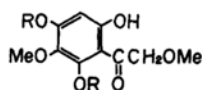
XI R = R₁ = R₂ = H, R₃ = Me

XII R = R₁ = H, R₂ = C₆H₅CH₂, R₃ = Me

XIII R = R₁ = Ac, R₂ = C₆H₅CH₂, R₃ = Me

XIV R = R₁ = R₂ = Ac, R₃ = Me

XV R = R₁ = R₂ = Et, R₃ = Me



VI R = H

IV R = Et

According to the method of Allan-Robinson's flavone synthesis, the condensation of the ketone VII with *O*-benzylisovanillic anhydride and potassium *O*-benzylisovanillate, followed by treatment with alcoholic potassium hydroxide, was found to afford two isomeric cyclization products, the 3'-benzyl ether (IX) of II and 3'-benzyloxy-5,7-dihydroxy-3,8,4'-trimethoxyflavone (X). After the usual acetylation of the above mixtures, the reaction products could be separated into two crystals, A and B, by fractional crystallization from ether. The crystal A (mp 159–160°C, C₂₉H₂₆O₁₀) gave

TABLE I. NMR DATA OF FLAVONES*2,5

	XI	XIII	XVI
Arom. H C-6	6.80 _s		6.82 _s
C-8		7.25 _s	
C-2'	7.82 _d	7.77 _d	7.96 _d
C-5'	7.06 _{d'}	7.03 _{d'}	7.16 _{d'}
C-6'	7.81 _d	7.98 _q	8.15 _q
C ₆ H ₅ CH ₂	7.45 _{bs} (5H)		
C ₆ H ₅ CH ₂	5.28 _s (2H)		
CH ₃ O	4.00 _s (3H)	3.89 _s (3H)	4.02 _s (3H)
	3.95 _s (3H)	3.84 _s (3H)	3.96 _s (3H)
	3.65 _s (3H)	3.78 _s (3H)	3.86 _s (3H)
CH ₃ CO	2.45 _s (3H)	2.50 _s (3H)	2.47 _s (6H)
	2.39 _s (3H)	2.36 _s (3H)	2.38 _s (3H)
		2.33 _s (3H)	

*5 s, singlet; bs, broad singlet; d, doublet (*J*_{meta} = 2.5 Hz); d', doublet (*J*_{ortho} = 9.0 Hz); q, quartet (*J*_{ortho} = 9.0 Hz, *J*_{meta} = 2.5 Hz).

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

a negative ferric chloride reaction, and there was no band attributable to a hydroxyl group in its infrared spectrum. Further, from a comparison of the NMR spectrum (Table I)*2 of this compound with those of 5,7,8-oxygenated flavones,^{7,8)} the signal at δ 6.80 (1H) (singlet) can be assigned to the C₆-H at the A ring of the flavone nucleus. Thus, the crystal A is formulated as 3'-benzyloxy-5,7-diacetoxy-3,8,4'-trimethoxyflavone (XI).

The mild hydrolysis of the crystal B gave pale yellow needles (mp 131.5–132.5°C), 7-acetoxy-3'-benzyloxy-5-hydroxy-3,6,4'-trimethoxyflavone (XII), *via* a partial acetylation. The NMR spectrum exhibits two singlets, at δ 6.78 and 12.87, due to the C₆-H of the A ring and to the hydroxyl protons respectively. The treatment of XII with dilute alkali afforded the 3'-benzyloxy-5,7-dihydroxy-compound IX. The catalytic hydrogenolysis of IX over palladium charcoal gave the desired flavone, II, which was easily converted to the triacetate, XIII. The synthetic flavone, II, and its triacetate, XIII, were found to be identical with natural centaureidin*3 and its triacetate*4 in mixed-melting-point determinations and in infrared- and ultraviolet-spectral comparisons. The triethyl ether (XIV) of II was easily obtained with diethyl sulfate in anhydrous acetone. The ether, XIV, was also prepared from 4,6-diethoxy-5,ω-dimethoxy-2-hydroxyacetophenone (XV)⁵⁾ and

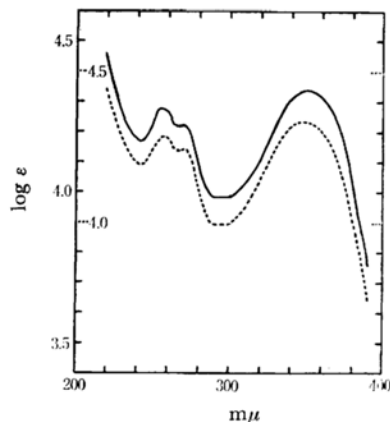


Fig. 1. Ultraviolet spectra of natural (-----) and synthetic (—) centaureidin in ethanol.

*2 The NMR spectra were measured with a Hitachi R-20 spectrometer, using tetramethylsilane as the internal standard (δ-value in CDCl₃).

8) a) J. Massicot and J.-P. Marthe, *Bull. Soc. Chim. France*, **1962**, 1962; b) C. A. Henrick and P. R. Jefferies, *Australian J. Chem.*, **17**, 934 (1964); *Tetrahedron*, **21**, 3219 (1965); c) K. Fukui, T. Matsumoto, M. Nakayama and T. Horie, *Experientia*, **25**, 349 (1969).

*3 Natural centaureidin was kindly supplied by Professor F. Bohlmann, Berlin University.

*4 This compound was prepared from natural centaureidin*3 in this laboratory.

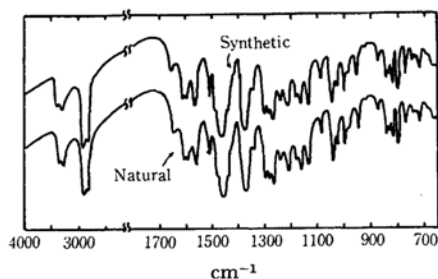


Fig. 2. Infrared spectra of natural and synthetic centaureidin in Nujol.

TABLE 2. ULTRAVIOLET SPECTRA OF NATURAL AND SYNTHETIC CENTAUREIDIN (II) AND ITS 4'-BENZYL ETHER (IX)

	EtOH	λ_{\max} m μ (log ϵ) NaOAc	AlCl ₃
Synthetic	257 (4.29)	274(4.31)	266 (4.25)
centaureidin	271 (4.22)	364(4.23)	279 (4.22)
(II)	351 (4.35)		369 (4.29)
Natural	256.5(4.29)	274(4.38)	266.5(4.26)
centaureidin	271 (4.24)	367(4.24)	280 (4.22)
	350 (4.34)		369 (4.30)
IX	255 (4.28)	275(4.34)	261 (4.24)
	272 (4.21)	298(4.05)	366 (4.31)
	348 (4.34)	364(4.22)	

3-ethoxy-4-methoxybenzoic anhydride. The properties of the product were found to be identical with those of the above compound (XIV) by a direct comparison. The infrared and ultraviolet spectra of synthetic centaureidin superimpose on those of the natural compound (Figs. 1 and 2 and Table 2). A partial synthesis of the glucoside I¹ had been carried out earlier,² so the total synthesis of I is now accomplished.

On the other hand, the diacetoxyl substance, XI, on treatment with dilute alkali, was easily converted to the 5,7-dihydroxyflavone, X. The catalytic debenzoylation of X over palladium charcoal afforded the flavone, VIII. Its triacetate, XVI, and triethyl ether, XVII, were prepared by usual methods. The NMR spectrum of the triacetate, XVI, shows one proton signal corresponding to the C₆-H (δ 6.82) at a field higher than that of the C₈-H (δ 7.25) in the triacetate, XIII (Table I). They are in accordance with those shown in earlier reports.⁸

Experimental*⁵

3'-Benzyloxy-5,7-diacetoxy-3,8,4'-trimethoxyflavone (XI) and 7-Acetoxy-3'-benzyloxy-5-hydroxy-3,6,4'-trimethoxyflavone (XII). A mixture of the ketone (VII)⁷ (2.0 g), *O*-benzylisovanillic anhydride (16 g),

and potassium *O*-benzylisovanillate (7.5 g) was heated at 180°C under a vacuum for 10 hr. The reaction mixture was then cooled and refluxed with a solution of potassium hydroxide (10 g) in aqueous ethanol (75%; 350 ml) for 15 min. After the solvent had been evaporated in a vacuum, the residue was dissolved in water and saturated with carbon dioxide. The separated precipitate was collected, washed with water, and dried to give a crude flavone mixture.

A mixture of the crude flavones, acetic anhydride (10 ml), and anhydrous pyridine (1.0 ml) was heated at 110°C for 2 hr and then poured into water and extracted with ether. The ether layer (about 200 ml) was washed with a sodium carbonate solution and water, and allowed to stand in a refrigerator for one week. The separating crystals were collected to give the diacetate crystal B (about 0.9 g). The mother liquor was concentrated to 15–20 ml and then cooled at 0°C for one week. The separating crystals were corrected to give the diacetate crystal A (about 1.5 g).

The diacetate crystal A was recrystallized from methanol to give colorless needles of XI; mp 159–160°C, yield 330 mg (7%). It gave a negative ferric chloride reaction. IR: 1762, 1755, 1646 cm⁻¹. UV: λ_{\max} m μ (log ϵ): (EtOH) 250 (4.04), 369 (4.22).

Found: C, 65.28; H, 4.82%. Calcd for C₂₉H₂₈O₁₀: C, 65.16; H, 4.90%.

A solution of the diacetate crystal B in methanol (100 ml) was gently refluxed with aqueous potassium hydroxide (5%; 20 ml) for 3 min. After the solvent had then been evaporated under a vacuum, the resulting residue was dissolved in water and saturated with carbon dioxide. The precipitate thus separated was collected, heated with acetic anhydride-pyridine (10 : 1; 1.5 ml) for 2 min on a steam bath, cooled, and added to ether (10 ml). The crystals which separated were collected, washed with ether, and recrystallized from methanol to give pale yellow needles of XII; mp 131.5–132.5°C; yield, 210 mg (5%). It gave a dark green color with an alcoholic ferric chloride solution. IR: 1760, 1652 cm⁻¹. UV: λ_{\max} m μ (log ϵ), (EtOH) 257 (4.64), 274_{sh} (4.50),^{*} 352 (4.60); (EtOH-AlCl₃) 259 (4.56), 360 (4.57). NMR:^{*2,5} 12.87_{bs}(OH); 7.80_q(C-6'); 7.79_d(C-2'); 7.49_{bs}(5H, C₆H₅); 7.02_{d'}(C-5'), 6.78_s(C-8); 5.28_s(2H, C₆H₅CH₂); 4.01_s, 3.96_s, 3.72_s (each 3H, CH₃O); 2.40_s(CH₃CO).

Found: C, 65.69; H, 4.66%. Calcd for C₂₇H₂₄O₉: C, 65.85; H, 4.91%.

3'-Benzyloxy-5,7-dihydroxy-3,6,4'-trimethoxyflavone (IX). A solution of XII (190 mg) in methanol (50 ml) was gently refluxed with aqueous potassium hydroxide (3%; 10 ml) for 2 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 IX as pale yellow needles; mp 163–164°C; yield, 150 mg (86%). It gave a green color with an alcoholic ferric chloride solution. IR: 3350, 1658 cm⁻¹. Found: C, 66.41; H, 4.90%. Calcd for C₂₅H₂₂O₈: C, 66.66; H, 4.92%.

Centaureidin (5,7,3'-Trihydroxy-3,6,4'-trime-thoxyflavone) (II). A mixture of IX (130 mg) and Pd-C (5%: 150 mg) in methanol (70 ml) was shaken in an atmosphere of hydrogen until 1.1 mol of hydrogen

*⁵ All the melting points are uncorrected; the infrared spectra were measured in Nujol.

*⁶ sh=shoulder.

had been absorbed. After the catalyst had been filtered, the filtrate was evaporated. The residue was recrystallized from aqueous methanol to give II as yellow needles; mp 196—197°C (reported¹¹ mp 196°C) (natural centaureidin,^{14,8} mp 196—197°C); yield, 85 mg (82%). It gave a dark green color with an alcoholic ferric chloride solution. IR: 3460, 3380, 1651 cm^{-1} . This was identified with natural centaureidin by a mixed-melting-point determination and by infrared- and ultraviolet-spectral comparisons.

Found: C, 59.79; H, 4.35%. Calcd for $\text{C}_{18}\text{H}_{16}\text{O}_8$: C, 60.00; H, 4.48%.

Centaureidin Triacetate (XIII): hot acetic anhydride-pyridine method; mp 174—175.5°C (colorless prisms from methanol) (Natural Centaureidin Triacetate,¹⁴ mp 174—175.5°C). IR: 1768, 1641 cm^{-1} . UV: λ_{max} $m\mu$ (log ϵ); (EtOH) 328 (4.00), 344 (4.06).

Found: C, 59.01; H, 4.62%. Calcd for $\text{C}_{24}\text{H}_{22}\text{O}_{11}$: C, 59.26; H, 4.56%.

Centaureidin Triethyl Ether (5,7,3'-Triethoxy-3,6,3'-trimethoxyflavone) (XIV). a) **From Centaureidin (II).** A mixture of synthetic centaureidin (II) (21 mg), anhydrous potassium carbonate (1.0 g), and diethyl sulfate (0.3 ml) in anhydrous acetone (20 ml) was refluxed for 20 hr, and then the reaction mixture was treated in the usual manner. Recrystallization from methanol give XIV as colorless prisms; mp 77—78°C; yield, 22 mg (85%).

After XIV had been dried at 70—80°C/0.1 mmHg for 1 hr, it had a mp of 104.5—105.5°C. IR: 1635 cm^{-1} . UV: λ_{max} $m\mu$ (log ϵ); 258_i (4.18),¹⁰ 358 (4.10). NMR:^{12,5} 7.75_d (C-2'); 7.73_q (C-6'); 6.98_{d'} (C-5'); 6.72_s (C-8); 4.19_q (6H, $J=7.0$ Hz, $\text{CH}_3\text{CH}_2\text{O}$); 3.95_s, 3.91_s, 3.84_s (each 3H, CH_3O); 3.51_t (9H, $J=7.0$ Hz, $\text{CH}_3\text{CH}_2\text{O}$).

Found: C, 64.77; H, 6.24%. Calcd for $\text{C}_{24}\text{H}_{28}\text{O}_8$: C, 64.85; H, 6.35%.

b) **From the Ketone XV.** A mixture of XV⁹ (1.0 g), 3-ethoxy-4-methoxybenzoic anhydride (3.0 g), and triethylamine (2 ml) was heated at 170°C for 8 hr. The reaction mixture was then cooled and refluxed with a solution of potassium hydroxide (1.5 g) in aqueous ethanol (80%; 100 ml) for 15 min. After the evaporation of the solvent under a vacuum, the residue was dissolved in water (60 ml). The resulting precipitate was collected and recrystallized from methanol to give colorless prisms of XIV; mp 77.5—78.5°C (after drying; mp 104.5—105.5°C); yield, 250 mg (16%). It was

identical with the sample described in a).

3'-Benzoyloxy-5,7-dihydroxy-3,8,4'-trimethoxyflavone (X). A mixture of XI (320 mg), methanol (10 ml), and aqueous potassium hydroxide (10%; 5 ml) was treated by a method similar to that used for IX. The crude product was recrystallized from methanol to give yellow needles of X; mp 148—149°C; yield, 230 mg (85%). It gave a green color with an alcoholic ferric chloride solution. IR: 3340, 1655 cm^{-1} . UV: λ_{max} $m\mu$ (log ϵ); (EtOH) 257.5 (4.30), 276 (4.27), 340 (4.20), 362_{sh} (4.20).

Found: C, 66.61; H, 4.91%. Calcd for $\text{C}_{25}\text{H}_{22}\text{O}_8$: C, 66.66; H, 4.92%.

5,7,3'-Trihydroxy-3,8,4'-trimethoxyflavone (VIII).

A mixture of X (205 mg) and Pd-C (5%; 200 mg) in methanol (100 ml) was treated by a method similar to that used for III. The resulting precipitate was recrystallized from methanol to give yellow needles of VIII; mp 213.5—214.5°C; yield, 138 mg (84%). It gave a dark green color with an alcoholic ferric chloride solution. IR: 3400, 3300, 1648 cm^{-1} . UV: λ_{max} $m\mu$ (log ϵ); (EtOH) 260 (4.44), 275.5 (4.47), 360 (4.33).

Found: C, 59.91; H, 4.37%. Calcd for $\text{C}_{18}\text{H}_{16}\text{O}_8$: C, 60.00; H, 4.48%.

Triacetate (XVI): hot acetic anhydride-pyridine method; mp 144—145°C (colorless needles from methanol). IR: 1767, 1751, 1636 cm^{-1} . UV: λ_{max} $m\mu$ (log ϵ); (EtOH) 247_i (4.24), 351 (4.03), 360_{sh} (4.02).

Found: C, 59.16; H, 4.65%. Calcd for $\text{C}_{24}\text{H}_{22}\text{O}_{11}$: C, 59.26; H, 4.56%.

5,7,3'-Triethoxy-3,8,4'-trimethoxyflavone (XVII).

A mixture of VIII (35 mg), anhydrous potassium carbonate (1.5 g), and diethyl sulfate (0.5 ml) in anhydrous acetone (15 ml) was treated in the usual manner. Recrystallization from methanol give XVII as colorless needles; mp 152.5—153°C; yield, 37 mg (76%). IR: 1633 cm^{-1} . UV: λ_{max} $m\mu$ (log ϵ); (EtOH) 253 (4.35), 272 (4.33), 353 (4.31). NMR:^{12,5} 7.87_q (C-6'); 7.84_d (C-2'); 7.00_{d'} (C-5'); 6.43_s (C-6); 4.17_q (2H), 4.23_q (4H) (each $J=7.0$ Hz, $\text{CH}_3\text{CH}_2\text{O}$); 1.56_t (6H), 1.51_t (3H) (each $J=7.0$ Hz, $\text{CH}_3\text{CH}_2\text{O}$).

Found: C, 65.12; H, 6.49%. Calcd for $\text{C}_{24}\text{H}_{28}\text{O}_8$: C, 64.85; H, 6.35%.

The author wishes to express his deep gratitude to Professor Kenji Fukui, Hiroshima University, for his guidance and encouragements throughout the course of this work, and also to Professor F. Bohlmann, University of Berlin, for supplying the natural centaureidin.

¹⁰ Natural centaureidin was measured in this laboratory.

¹¹ i=inflexion point.