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Synthetic Studies of the Flavone Derivatives. VII.*1 The Synthesis of Jaceidin

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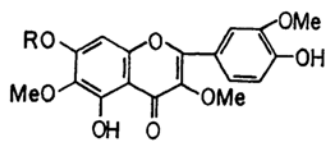
The Hoesch reaction of iretol with methoxyacetonitrile yielded 2,4,6-trihydroxy-3,ω-dimethoxyacetophenone. According to the Allan-Robinson flavone synthesis with *O*-benzylvanillic anhydride, the acetophenone afforded 4'-benzyloxy-5,7-dihydroxy-3,3',6-trimethoxyflavone. The catalytic debenzylation of the flavone gave jaceidin, 4',5,7-trihydroxy-3,3',6-trimethoxyflavone, which had previously been isolated from Centaurea species. Its triethyl ether was prepared from 3,5-diethoxy-4-methoxyphenol *via* the corresponding acetophenone, followed by the above-mentioned flavone synthesis with *O*-ethylvanillic anhydride. The ultraviolet spectra of these flavones will also be reported.

Jaceidin (I) was isolated from the leaves and stems of *Centaurea jacea* L. by Farkas *et al.*[1] Their hydrolysis of I with hydrochloric acid afforded an aglycone, jaceidin. They established the structure of jaceidin to be 4',5,7-trihydroxy-3,3',6-trimethoxyflavone (II) on the basis of analytical data, the results of the degradation reaction, and a comparison of the triethyl ether (III) with a synthetic sample.

Recently, I and II have also been isolated from the Centaurea species by Bowie *et al.*[2] and by Bohlmann *et al.*[3]



I R=Glycosyl
II R=H

The present paper deals with the total synthesis of jaceidin (II) and confirms the proposed structure. The Hoesch reaction of iretol (IV) with methoxyacetonitrile yielded 2,4,6-trihydroxy-3,ω-dimethoxyacetophenone (V). According to Allan-Robinson's flavone synthesis, the condensation of V with *O*-benzylvanillic anhydride (VI) in the presence of triethylamine, followed by treatment with alcoholic potassium hydroxide, affords a hydroxyflavone, which then gives a diacetate. Two structures (VII and VIII) may be expected for this hydroxyflavone. In order to elucidate the structure of the flavone, a diethyl derivative, which was easily obtained with diethyl sulfate and anhydrous potassium carbonate in dry acetone, was synthesized by the following unambiguous method.

3,5-Diethoxy-4-methoxyphenol (IX) was converted to 4,6-diethoxy-2-hydroxy-5,ω-dimethoxyacetophenone (X) by a Hoesch condensation with methoxyacetonitrile or by a Friedel-Crafts reaction with methoxyacetyl chloride. The ketone (X),

*1 This has been reported in a preliminary form: K. Fukui, T. Matsumoto, S. Nakamura, M. Nakayama and T. Horie, *Experientia*, **24**, 108 (1968).

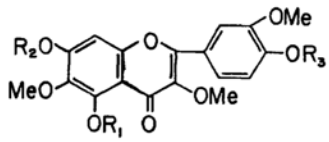
Part VI of this series: T. Horie, M. Masumura, K. Fukui and M. Nakayama, This Bulletin, **41**, 1460 (1968).

1) L. Farkas, L. Hörhammer, H. Wagner, H. Rösler and R. Gurniak, *Chem. Ber.*, **97**, 610 (1964).

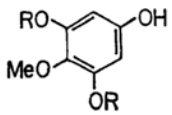
2) J. H. Bowie and D. W. Cameron, *J. Chem. Soc.*, **1965**, 5651.

3) F. Bohlmann and C. Zdero, *Tetrahedron Letters*, **No. 33**, 3239 (1967).

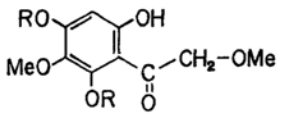
when subjected to the Allan-Robinson flavone synthesis using VI, gave 4'-benzyloxy-5,7-diethoxy-3,3',6-trimethoxyflavone (XI), which was identified by a direct comparison with the diethyl derivative obtained by the ethylation of the hydroxyflavone. Furthermore, the partial methylation of the hydroxyflavone with diazomethane gave the monomethyl ether (XII), which was then debenzylated to give 4',5-dihydroxy-3,3',6,7-tetramethoxyflavone (XIII). This was also identified by direct comparison with an authentic sample, prepared by the method of



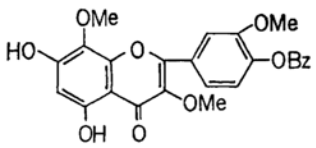
III $R_1=R_2=R_3=Et$
VII $R_1=R_2=H$, $R_3=Bz$
XI $R_1=R_2=Et$, $R_3=Bz$
XII $R_1=H$, $R_2=Me$, $R_3=Bz$
XIII $R_1=R_3=H$, $R_2=Me$
XIV $R_1=R_2=R_3=Ac$
XV $R_1=R_2=R_3=Me$
XVI $R_1=H$, $R_2=R_3=Me$



IV R=H
IX R=Et



V R=H
X R=Et



VIII

Bz=Benzyl

Hörhammer *et al.*[4] From these facts, the structure of the hydroxyflavone was established as 4'-benzyloxy-5,7-dihydroxy-3,3',6-trimethoxyflavone (VII).

The catalytic debenzylation of VII gave the desired flavone (II), which was shown to be identical with natural jaceidin by a mixed-melting-point determination, and by NMR, infrared, and ultraviolet spectral comparisons.

The infrared and ultraviolet spectra of synthetic and natural jaceidin are superimposable, as is shown in Figs. 1 and 2 and in Table 1. By the addition of fused sodium acetate,[5] the short-wavelength bands of jaceidin (II) and 4'-benzyl ether (VII) in ethanol undergo bathochromic shifts (18 mμ and 20.5 mμ), which show the presence of a free 7-hydroxyl group. The 5-hydroxyl group in II and VII is indicated by the bathochromic shifts (20 mμ and 19 mμ) of the

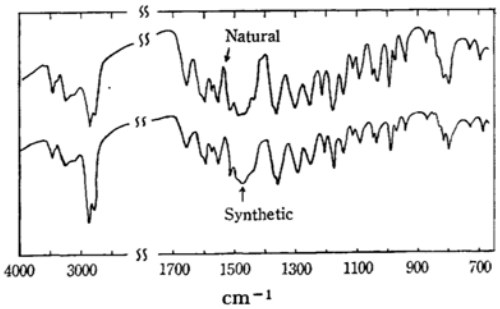


Fig. 1. Infrared spectra of natural and synthetic jaceidin in Nujol.

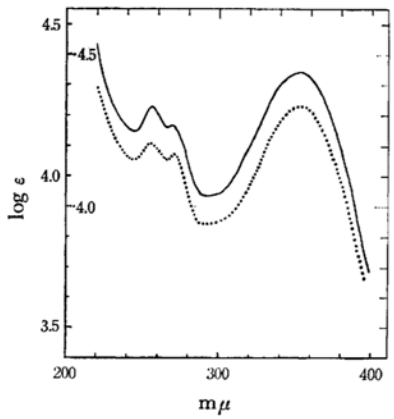


Fig. 2. Ultraviolet spectra of natural (·····) and synthetic jaceidin (——) in ethanol.

long-wavelength band in the presence of aluminum chloride.[6] The large bathochromic shift (64.5 mμ) of the long-wavelength band, without a decrease in its relative intensity, observed on making the ethanol solution of II alkaline indicates a 4'-hydroxyl group.[6] Both II and VII are stable in an alkaline solution, for when the alkaline solution is acidified, the spectra change to the parent respective spectrum in ethanol.

The synthetic jaceidin was converted to triacetate (XIV), trimethyl ether (XV), triethyl ether (III), and artemetin (XVI) by the usual method. The triethyl ether (III) was also synthesized by the

4) L. Hörhammer, H. Wagner, E. Graf and L. Farkas, *Chem. Ber.*, **98**, 548 (1965).

5) L. Jurd and R. M. Horowitz, *J. Org. Chem.*, **22**, 1618 (1957).

6) L. Jurd, "The Chemistry of Flavonoid Compounds," ed. by T. A. Geissman, Pergamon Press, Oxford (1962), Chap. 5.

Table 1. Ultraviolet spectra of natural and synthetic jaceidin (II) and its 4'-benzyl ether (VII)

	λ_{max}, mμ (log ε)				
	EtOH	NaOAc*3	$AlCl_3$*4	NaOH*4	NaOH-HCl*5
Synthetic jaceidin (II)	257 (4.23) 272.5(4.17) 353 (4.34)	275 (4.32) 323 (4.09) 373 (4.24)	265.5(4.21) 281.5(4.19) 373 (4.32)	273.5(4.33) 339 (4.15) 417.5(4.48)	257.5(4.21) 270*2 (4.14) 353 (4.30)
Natural jaceidin	257 (4.21) 272.5(4.16) 354 (4.33)	275 (4.31) 323 (4.08) 373 (4.23)	265.5(4.20) 281.5(4.18) 373 (4.31)		
VII	256 (4.21) 274 (4.20) 347 (4.31)	276.5(4.39) 315 (4.10) 381 (4.19)	262.5(4.21) 284.5(4.19) 366 (4.31)	277 (4.46) 314 (4.18) 382 (4.24)	256.5(4.22) 272.5(4.18) 346 (4.31)

Allan-Robinson reaction of the ketone (X) with *O*-ethylvanillic anhydride.

Experimental*6

2, 4, 6-Trihydroxy-3, ω-dimethoxyacetophenone (V). A mixture of iretol (IV)[7] (5.0 g), methoxyacetonitrile (3.0 g), and anhydrous zinc chloride (8.2 g) in anhydrous ether (500 m*l*) was saturated with dried hydrogen chloride in an ice bath and then allowed to stand overnight. After the ether layer had been decanted, the ketimine hydrochloride was washed with anhydrous ether and then hydrolyzed with water (200 m*l*) on a steam-bath for 30 min. The mixture was evaporated under a vacuum, and the residue (*ca.* 50 m*l*) was extracted with ethyl acetate. The extract was washed with water, dried, and evaporated. The residue was recrystallized from water to give colorless needles, mp 79—80°C.

Found: C, 45.49; H, 5.96%. Calcd for $C_{10}H_{12}O_6 \cdot 2H_2O$: C, 45.45; H, 6.10%.

These needles were recrystallized from dry toluene to give colorless needles, mp 157—158°C; yield 4.3 g. They gave a dark green ferric chloride reaction in ethanol.

Found: C, 52.94; H, 5.31%. Calcd for $C_{10}H_{12}O_6$: C, 52.63; H, 5.30%.

4'-Benzyloxy-5, 7-dihydroxy-3, 3', 6-trimethoxyflavone (VII). A mixture of the ketone (V) (1.0 g), *O*-benzylvanillic anhydride (8.7 g), and triethylamine (2.2 g) was heated at 170°C for 5 hr under a stream of nitrogen. The reaction mixture was then cooled, powdered, and refluxed with a solution of potassium hydroxide (9.5 g) in aqueous ethanol (70%; 100 m*l*) for 20 min. After the evaporation of the solvent under a vacuum, the residue was dissolved in water (150 m*l*) and saturated with carbon dioxide. The precipitate was collected, washed with water, and recrystallized from aqueous acetone to give yellow needles, mp 181.5—183°C, which gave a dark green ferric chloride reaction in ethanol; yield 670 mg.

Found: C, 66.86; H, 5.06%. Calcd for $C_{25}H_{22}O_8$: C, 66.66; H, 4.92%.

Diacetate of VII: hot acetic anhydride-pyridine method; mp 161.5—162.5°C (colorless needles from ethanol). It gave a negative ferric chloride reaction.

Found: C, 65.30; H, 4.84%. Calcd for $C_{29}H_{26}O_{10}$: C, 65.16; H, 4.90%.

4,6-Diethoxy-2-hydroxy-5,ω-dimethoxyacetophenone (X). *a) Friedel-Crafts Reaction.* With stirring and cooling at 10°C, methoxyacetyl chloride (8 g) was added, drop by drop, to a solution of anhydrous aluminum chloride (12.5 g), 3,5-diethoxy-4-methoxyphenol (IX)[8] (10 g) and anhydrous ether (50 m*l*). After stirring below 20°C for 3 hr, the mixture was poured into a mixture of ice and dilute hydrochloric acid, and extracted with ether. The ether extract was washed successively with water, aqueous sodium carbonate, and water. After drying over sodium sulfate, the solvent was evaporated; the residue was distilled under a vacuum to give the ketone (X) as a pale yellow oil, bp 145—146°C/0.2 mmHg; yield 9.7 g.

Found: C, 59.24; H, 7.37%. Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09%.

b) Hoesch Condensation. A mixture of IX (10 g), methoxyacetonitrile (7.1 g), anhydrous ether (300 m*l*), and anhydrous zinc chloride (10 g) was treated by a method similar to that used for V. The crude product was distilled under a vacuum to give X, bp 145—146°C/0.2 mmHg, which was proved identical with the sample of a) by infrared spectral comparison; yield 1.0 g.

4'-Benzyloxy-5, 7-diethoxy-3, 3', 6-trimethoxyflavone (XI). *a) From VII.* A mixture of VII (130 mg), diethyl sulfate (1.0 g), anhydrous potassium carbonate (2.5 g), and dry acetone (25 m*l*) was refluxed for 24 hr, then the acetone was, after addition of water, evaporated. The precipitate was collected, washed with water, and recrystallized from aqueous ethanol to give the diethyl ether (XI) as colorless needles, mp 116—117°C, which gave a negative ferric chloride reaction; yield 115 mg. UV: λ_{max}^{EtOH} mμ (log ε); 336 (4.27).

Found: C, 69.03; H, 6.04%. Calcd for $C_{29}H_{30}O_8$: C, 68.76; H, 5.97%.

b) From X. A mixture of the ketone (X) (1.0 g), *O*-benzylvanillic anhydride (3.5 g), and triethylamine (1.7 g) was treated by a method similar to that used for

*2 Inflection.
*3 Saturated with anhydrous sodium acetate.
*4 0.002 mol/*l*.
*5 The alkaline solution was acidified with dilute hydrochloric acid.
*6 All melting points and boiling points are uncorrected.

7) R. E. Damschroder and R. L. Shringer, *J. Am. Chem. Soc.*, **59**, 931 (1937).

8) M. Krishnamuri and T. R. Seshadri, *Proc. Indian Acad. Sci.*, **39A**, 144 (1954).

VII. The crude product was recrystallized from ethanol to give XI; mp 117—118°C, which was undepressed on admixture with the sample of a); yield 400 mg.

Found: C, 68.50; H, 5.77%. Calcd for $C_{29}H_{30}O_8$: C, 68.76; H, 5.97%.

4'-Benzyloxy-5-hydroxy-3,3',6,7-tetramethoxyflavone (XII). To a solution of VII (1.2 g) in acetone (150 m*l*), an ethereal diazomethane solution was added, then the solution was allowed to stand at room temperature for 2 hr. After the evaporation of the solvent, the residue was recrystallized from ethyl acetate to give yellow needles, mp 167.5—168.5°C, which gave a dark green ferric chloride reaction in ethanol; yield 1.0 g.

Found: C, 67.23; H, 5.16%. Calcd for $C_{26}H_{24}O_8$: C, 67.23; H, 5.21%.

Monoacetate of XII: hot acetic anhydride - pyridine method; mp 222.5—223.5°C (almost colorless needles from ethyl acetate). It gave a negative ferric chloride reaction.

Found: C, 66.17; H, 5.11%. Calcd for $C_{28}H_{26}O_9$: C, 66.39; H, 5.17%.

4',5-Dihydroxy-3,3',6,7-tetramethoxyflavone (XIII). A solution of XII (750 mg) in ethyl acetate (250 m*l*) was submitted to catalytic reduction at room temperature in the presence of Pd-C (10%: 1.0 g). After the catalyst had been filtered, the filtrate was evaporated under a vacuum and the residue was recrystallized from methanol to give yellow needles, mp 181.5—182.5°C (reported[4] mp 181—182°C), which gave a dark green ferric chloride reaction in ethanol; yield 450 mg. The melting point was undepressed on admixture with a sample prepared by the method of Hörhammer *et al.*[4] UV: λ_{max}^{EtOH} mμ (log ε); 258.5 (4.33), 270*2 (4.28), 352 (4.42).

Found: C, 60.79; H, 4.80%. Calcd for $C_{19}H_{18}O_8$: C, 60.96; H, 4.85%.

Diacetate of XIII: hot acetic anhydride - pyridine method; mp 191—192°C (colorless needles from methanol), (reported[4] mp 191—192°C), undepressed on admixture with a sample prepared by the method of Hörhammer *et al.*[4] It gave a negative ferric chloride reaction.

Found: C, 60.11; H, 4.81%. Calcd for $C_{23}H_{22}O_{10}$: C, 60.26; H, 4.84%.

Jaceidin (4',5,7-Trihydroxy-3,3',6-trimethoxyflavone) (II). A mixture of VII (2.40 g,) Pd-C (10%: 2.0 g), and ethyl acetate (460 m*l*) was treated by the method described for XIII. The product was then recrystallized from aqueous methanol to give pale yellow needles, mp 130—135°C (reported[1,2] mp 127—133°C, 99—100°C, 111—112°C and 165—166°C),*7 which gave a green ferric chloride reaction in ethanol; yield 1.76 g. This was identified with natural jaceidin by a mixed-melting-point determination and by infrared and ultraviolet spectral comparisons. NMR*8 in $CDCl_3$: 3.88(s), 3.99(s), 4.06(s) (OMe), 6.03(s), 6.56(s) (C_7-OH, $C_{4'}$-OH), 6.61(s) (C_8-H), 7.09 (d: J_{ortho}=9.0 cps) ($C_{5'}$-H), 7.76 (dd: J_{ortho}=9.0 cps, J_{meta}=2.5 cps) ($C_{6'}$-H), 7.78 (d: J_{meta}=2.5 cps) ($C_{2'}$-H), 12.96(s) (C_5-OH). (Reported[2] NMR in $CDCl_3$: 3.86, 3.97, 4.04 (OMe), 6.59 (C_8-H), 7.05 ($C_{5'}$-H), 7.68 ($C_{6'}$-H), 7.70 ($C_{2'}$-H), 12.86 (C_5-OH); J_{ortho}=9.0 cps, J_{meta}=2.0 cps).

Found: C, 58.57; H, 4.82%. Calcd for $C_{18}H_{16}O_8 \cdot \frac{1}{2}H_2O$: C, 58.54; H, 4.61%.

After drying at 50—60°C/0.1 mmHg for 2 hr, it had a mp of 166—166.5°C (sintering at 127°C).

Found: C, 59.86; H, 4.48%. Calcd for $C_{18}H_{16}O_8$: C, 60.00; H, 4.48%.

Jaceidin Triacetate (XIV): hot acetic anhydride - pyridine method; mp 163—164°C (colorless needles from ethyl acetate) (reported[2] mp 159—160°C). It gave a negative ferric reaction. UV: λ_{max}^{EtOH} mμ (log ε); 248.5 (4.34), 326 (4.26) (reported[2] UV: λ_{max}^{EtOH} mμ (log ε); 248 (4.29), 325 (4.17)). NMR*8 in $CDCl_3$: 2.36(s), 2.38(s), 2.52(s) (OAc), 3.82(s), 3.89(s), 3.92(s) (OMe), 7.22 (d: J_{ortho}=9.0 cps) ($C_{5'}$-H), 7.30(s) (C_8-H), 7.72 (dd: J_{ortho}=9.0 cps, J_{meta}=2.5 cps) ($C_{6'}$-H), 7.78 (d: J_{meta}=2.5 cps) ($C_{2'}$-H). Reported[2] NMR in $CDCl_3$: 2.37, 2.39, 2.44 (OAc), 3.83, 3.89, 3.92 (OMe), 7.20 ($C_{5'}$-H), 7.29 (C_8-H), *ca.* 7.70 ($C_{2'}$-H, $C_{6'}$-H).

Found: C, 58.94; H, 4.42%. Calcd for $C_{24}H_{22}O_{11}$: C, 59.26; H, 4.56%.

Hydrolysis of Jaceidin Triacetate (XIV). A solution of XIV (400 mg) in ethanol (8 m*l*) was gently refluxed with aqueous potassium hydroxide (30%: 3 g) for 10 min. After the evaporation of the solvent under a vacuum, the residue was dissolved in water (20 m*l*) and filtered, and the filtrate was acidified. The precipitate was collected, washed with water, and recrystallized from ethanol to give yellow needles, mp 130—135°C, which gave a green ferric chloride reaction in ethanol; yield 250 mg. This yield was identical with that of natural jaceidin.

Jaceidin Triethyl Ether (4',5,7-Triethoxy-3,3',6-trimethoxyflavone) (III). *a) From Jaceidin (II).* A mixture of synthetic jaceidin (II) (150 mg), anhydrous potassium carbonate (4.0 g), diethyl sulfate (1.5 g), and dry acetone (15 m*l*) was treated by a usual method. The crude product was recrystallized from aqueous ethanol to give colorless needles, mp 118—119°C (reported[1] mp 118°C); yield 155 mg. UV: λ_{max}^{EtOH} mμ (log ε); 334 (4.31).

Found: C, 64.60; H, 6.32%. Calcd for $C_{24}H_{28}O_8$: C, 64.85; H, 6.35%.

b) From the Ketone (X). A mixture of X (1.0 g), *O*-ethylvanillic anhydride (2.7 g), and triethylamine (1.7 g) was treated by a method similar to that used for VII. The crude product was recrystallized from aqueous ethanol to give colorless needles, mp 118—119°C which was undepressed on admixture with the sample of a); yield 120 mg.

Found: C, 64.82; H, 6.27%. Calcd for $C_{24}H_{28}O_8$: C, 64.85; H, 6.35%.

Jaceidin Trimethyl Ether (3,3',4',5,6,7-Hexamethoxyflavone) (XV). A mixture of synthetic jaceidin (II) (500 mg), dimethyl sulfate (0.4 m*l*), anhydrous potassium carbonate (5.0 g) and dry acetone (50 m*l*) was treated by a method similar to that of Farkas *et al.*[1] The crude product was then recrystallized from aqueous ethanol to give colorless needles, mp 142—143°C (reported mp 142°C[1] and 142—

*7 Depend on the crystallization conditions. The same results were also obtained with a synthetic sample.

*8 The NMR spectra were taken on a Hitachi Model R-20 NMR spectrometer (60 Mc/sec), using tetramethylsilane as an internal standard; their chemical shifts are presented in terms of δ values; s: singlet, d: doublet, dd: double doublet.

143°C[2]), which gave a negative ferric chloride reaction; yield 490 mg. UV: λ_{max}^{EtOH} mμ (log ε); 335 (4.29).

Found: C, 62.52; H, 5.45%. Calcd for $C_{21}H_{22}O_8$: C, 62.68; H, 5.51%.

Jaceidin Dimethyl Ether (5-Hydroxy-3,3',4',6,7-pentamethoxyflavone) (XVI). Synthetic jaceidin (II) (380 mg) in acetone (70 ml) was partially methylated with diazomethane, and the product was recrystallized from methanol to give yellow needles, mp 161—162°C (reported mp 161—162°C[4] and 158—159°C[2,9]), which gave a dark green ferric chloride reaction in ethanol; yield 380 mg. UV: λ_{max}^{EtOH} mμ (log ε); 257 (4.38), 274 (4.34), 348 (4.45).

Found: C, 61.58; H, 5.05%. Calcd for $C_{20}H_{20}O_8$: C, 61.85; H, 5.19%.

Monoacetate of XVI: hot acetic anhydride - pyridine method; mp 163—163.5°C (colorless needles from ethanol) (reported[9] mp 160.5—161.5°C). It gave a negative ferric chloride reaction.

Found: C, 59.84; H, 5.22%. Calcd for $C_{22}H_{22}O_9 \cdot \frac{1}{2}H_2O$: C, 60.13; H, 5.24%.

9) W. Herz, *J. Org. Chem.*, **26**, 3014 (1961).

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