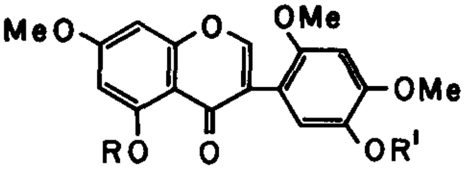
THE SYNTHESIS OF 5,5'-DIHYDROXY-7,2',4'-TRIMETHOXYISOFLAVONE AND ITS ISOMER: A REVISED STRUCTURE OF DERRUGENIN

Masao Tsukayama,* Tokunaru Horie, Yoshiro Yamashita,
Mitsuo Masumura, and Mitsuru Nakayama**
Department of Applied Chemistry, Faculty of Engineering,
Tokushima University, Minami-Josanjima, Tokushima 770, Japan
**Department of Chemistry, Faculty of Science, Hiroshima
University, Higashisenda-machi, Naka-ku, Hiroshima 730, Japan

Abstract --- 5,5'-Dihydroxy-7,2',4'-trimethoxyisoflavone (1) and 5,4'-dihydroxy-7,2',5'-trimethoxyisoflavone (2) were unambiguously synthesized from the corresponding chalcones using the oxidative rearrangement with TTN. It was found that the structure of derrugenin was not the proposed structure (1), but its isomer (2).

Derrugenin has recently been isolated from the seed shells of *Derris robusta.*[1)] Its structure has been shown to be 5,5'-dihydroxy-7,2',4'-trimethoxyisoflavone (1) on the basis of spectral data along with the degradative studies of its diethyl ether derivatives.1) In this paper, we wish to report the unambiguous synthesis of the isoflavone (1) and its isomer, 5,4'-dihydroxy-7,2',5'-trimethoxyisoflavone (2), to confirm the proposed structure of natural derrugenin.

The Baeyer-Villiger oxidation of vanillin benzyl ether,2) followed by the methylation with dimethyl sulfate afforded 1-benzyloxy-2,4-dimethoxybenzene. The formylation of the benzene derivative by the Vilsmeier reaction gave 5-benzyloxy-2,4-dimethoxybenzaldehyde (3) (mp 98-100°C).3) The condensation of the benzaldehyde (3) with phloroacetophenone dimethyl ether in the presence of piperidine in ethanol gave the corresponding chalcone (4) (mp 136-138°C), which was readily acetylated to give the acetate (5) (mp 148-149°C). The oxidative rearrangement of the acetate (5) with thallium nitrate (TTN) in methanol4) and the subsequent hydrolysis of the resulting compound with dilute hydrochloric acid gave 5'-benzyloxy-5,7,2',4'-tetramethoxy-

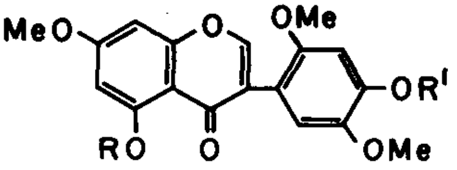


(1) $R=R^1=H$

(6) $R=Me$, $R^1=CH_2Ph$

(7) $R=Me$, $R^1=H$

(8) $R=R^1=Ac$

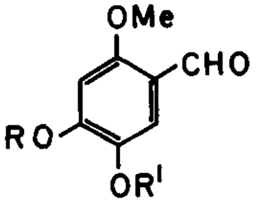


(2) $R=R^1=H$

(14) $R=Me$, $R^1=CH_2Ph$

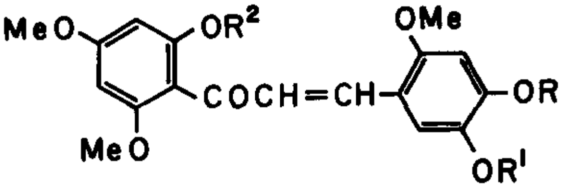
(15) $R=Me$, $R^1=H$

(16) $R=R^1=Ac$



(3) $R=Me$, $R^1=CH_2Ph$

(11) $R=CH_2Ph$, $R^1=Me$



(4) $R=Me$, $R^1=CH_2Ph$, $R^2=H$

(5) $R=Me$, $R^1=CH_2Ph$, $R^2=Ac$

(12) $R=CH_2Ph$, $R^1=Me$, $R^2=H$

(13) $R=CH_2Ph$, $R^1=Me$, $R^2=Ac$

Table 1 MP and UV spectral data of isoflavones

Compds	MP, °C		λ_{max}^{EtOH} nm (logε)		
Derrugenin[1]	218-219		260	315sh	
		($AlCl_3$)	270	312	365
Derrugenin diacetate[1]	230-231				
(1)	174-175		259 (4.40)	295 (4.15)	
		($AlCl_3$)	271 (4.42)	299 (4.21)	376 (3.60)
(8)	176-178				
(2)	212-213		259 (4.41)	294 (4.15)	
		($AlCl_3$)	270 (4.40)	296 (4.20)	376 (3.58)
(16)	227-229				

Table 2 ^{1}H-NMR data of isoflavones

Compds	solvent	Arom H			OMe	OAc	OH
		C_2-H	A ring	B ring			
Derrugenin diacetate[1]	$CDCl_3$	7.80s	6.59d 6.77d	6.69s 6.95s	3.69s 3.77s 3.88s	2.30s 2.37s	
(1)	DMSO	8.21s	6.37d 6.62d	6.72s(2H)	3.68s 3.82s 3.85s		8.55bs 12.91s
(8)	$CDCl_3$	7.76s	6.56d 6.72d	6.55s 6.95s	3.75s 3.82s 3.85s	2.25s 2.35s	
(2)	DMSO	8.17s	6.36d 6.58d	6.56s 6.83s	3.62s 3.71s 3.84s		9.14s 12.87s
(16)	$CDCl_3$	7.81s	6.59d 6.78d	6.71s 6.96s	3.70s 3.79s 3.89s	2.31s 2.38s	

s; singlet, d; doublet (J=2.5 Hz), bs; broad doublet

isoflavone (6) (mp 148-149°C) in high yield. The NMR spectrum of (6) ($CDCl_3$) exhibits a singlet peak at δ7.69 ppm due to the C_2-proton of the isoflavone skeleton. The isoflavone (6) was then debenzylated by the catalytic hydrogenolysis with palladium charcoal (10 %) to give a 5'-hydroxyisoflavone derivative (7) [mp 190-192°C, 79% yield, NMR (DMSO) δ3.63 (3H, OMe), 3.80 (6H, OMe), 3.86 (3H, OMe), 6.47 and 6.62 (each 1H, d, J=2 Hz, Arom H), 6.62 and 6.69 (each 1H, s, Arom H), 7.93 (s, 1H), 8.43 (s, 1H, OH)]. The isoflavone(7) was transformed to the desired isoflavone (1) by the partial demethylation with anhydrous aluminium chloride in dry acetonitrile. However, the physical data of this synthetic isoflavone (1) and its acetate (8) were inconsistent with those of natural derrugenin and its acetate as shown in Table 1 and 2, showing that the structure of derrugenin is not the proposed structure (1). The NMR spectrum of the acetate (8) is similar to that of the derrugenin diacetate except the chemical shifts of the protons of the B ring. The higher-field singlet peak at δ3.69 ppm in the NMR spectrum of the derrugenin diacetate may be attributed to the methoxyl group at the $C_{2'}$-position of the B ring.[5,6] These facts suggest that the structure of derrugenin is 5,4'-dihydroxy-7,2',5'-trimethoxyisoflavone (2), an isomer of the isoflavone (1).

The isoflavone (2) was unambiguously synthesized by the following method. The

Baeyer-Villiger oxidation of 2,5-dimethoxyacetophenone,[7] followed by the hydrolysis and benzylation gave 1-benzyloxy-2,5-dimethoxybenzene, which was further converted into benzaldehyde (11)[3] (mp 134-137°C) by the Vilsmeier reaction. The benzaldehyde (11) was transformed to the desired isoflavone (2) by the similar method as used in the synthesis of the isoflavone (1) via the corresponding chalcones [12 (mp 160-162°C) and 13 (mp 126-128°C)], benzyloxyisoflavone (14) (mp 172-174°C), and hydroxyisoflavone (15) [mp 191-193°C, NMR (DMSO) δ3.59, 3.69, 3.80, and 3.86 (each 3H, OMe), 6.47 and 6.60 (each 1H, d, J=2 Hz, Arom H), 6.52 and 6.76 (each 1H, s, Arom H), 7.94 (s, 1H), 9.10 (brs, 1H, OH)]. The physical properties of the synthetic isoflavone (2) and its acetate (16) were fully consistent with those of natural derrugenin and its acetate, respectively, as shown in Table 1 and 2. Consequently, the structure of derrugenin was revealed to be 5,4'-dihydroxy-7,2',5'-trimethoxyisoflavone (2).

REFERENCES AND NOTES

1. S. S. Chibber and R. P. Sharma, Phytochemistry, 1979, 18, 1583.
2. A. Lovecy, R. Robinson, and S. Sugasawa, J. Chem. Soc., 1930, 817.
3. The NMR spectra of the benzaldehyde (3) and (11) suggest their structures. (3); δppm ($CDCl_3$) 3.86 and 3.91 (each 3H, s, OMe), 5.06 (2H, s), 6.48 and 7.34 (each 1H, s, Arom H), 7.40 (brs, 5H, Arom H), 10.26 (1H, s), (11); δppm ($CDCl_3$) 3.76 and 3.83 (each 3H, s, OMe), 5.17 (2H, s), 6.45 and 7.26 (each 1H, s, Arom H) 7.31 (brs, 5H, Arom H), 10.56 (1H, s).
4. L. Farkas, A. Gottsegen, M. Nogradi, and S. Antus, J. Chem. Soc. Perkin 1, 1974, 305.
5. S. H. Harper and W. G. E. Underwood, J. Chem. Soc., 1965, 4203.
6. R. V. M. Campbell, S. H. Harper, and A. D. Kemp, J. Chem. Soc., (C), 1969, 1787.
7. W. M. Lauer and E. E. Renfrew, J. Amer. Chem. Soc., 1945, 67, 808.

Received, 4th June, 1980