

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

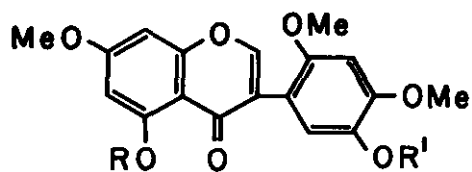
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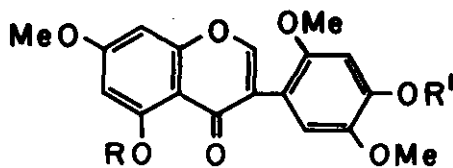
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Abstract --- 5,5'-Dihydroxy-7,2',4'-trimethoxyisoflavone (1) and
5,4'-dihydroxy-7,2',5'-trimethoxyisoflavone (2) were unambiguously
synthesized from the corresponding chalcones using the oxidative
rearrangement with TTN. It was found that the structure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

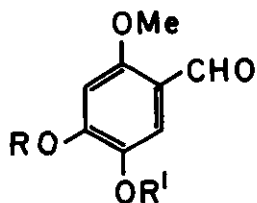
Derrugenin has recently been isolated from the seed shells of *Derris robusta*.¹⁾
Its structure has been shown to be 5,5'-dihydroxy-7,2',4'-trimethoxyisoflavone (1)
on the basis of spectral data along with the degradative studies of its diethyl
ether derivatives.¹⁾ In this paper, we wish to report the 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-dimethoxy-
benzaldehyde (3) (mp 98-100°C).³⁾ The condensation of the benzaldehyde (3) with
phloracetophenone 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-



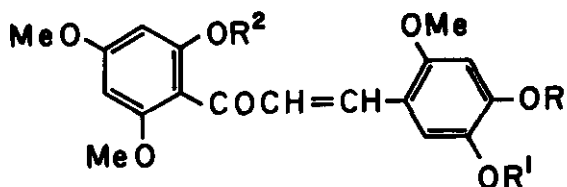
- (1) $R=R^1=H$
 (6) $R=Me, R^1=CH_2Ph$
 (7) $R=Me, R^1=H$
 (8) $R=R^1=Ac$



- (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 (log ϵ)		
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 ¹H-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	
(<u>1</u>)	DMSO	8.21s	6.37d 6.62d	6.72s(2H)	3.68s 3.82s 3.85s		8.55bs 12.91s
(<u>8</u>)	CDCl ₃	7.76s	6.56d 6.72d	6.55s 6.95s	3.75s 3.82s 3.85s	2.25s 2.35s	
(<u>2</u>)	DMSO	8.17s	6.36d 6.58d	6.56s 6.83s	3.62s 3.71s 3.84s		9.14s 12.87s
(<u>16</u>)	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) (CDCl₃) exhibits a singlet peak at δ7.69 ppm due to the C₂-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 C₂-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) δ 3.59, 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

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3. The NMR spectra of the benzaldehyde (3) and (11) suggest their structures. (3); δ ppm (CDCl₃) 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); δ ppm (CDCl₃) 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).
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