Communications to the Editor

[Chem. Pharm. Bull. 30(6)2279—2282(1982)]

INHIBITORS OF PROSTAGLANDIN BIOSYNTHESIS FROM ALPINIA OFFICINARUM

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Three new diarylheptanoids were isolated as inhibitors of prostaglandin biosynthesis from the methanol extract of *Alpinia officinarum* Hance. Their structures were elucidated to be 7-(4"-hydroxy-3"-methoxyphenyl)-1-phenyl-3,5-heptadione (I), 5-methoxy-7-(4"-hydroxy-3"-methoxyphenyl)-1-phenyl-3-heptanone (IV), and 5-hydroxy-7-(4"-hydroxyphenyl)-1-phenyl-3-heptanone (VI) by the interpretation of spectral data.

KEYWORDS —— Zingiberaceae; *Alpinia officinarum; Alpinia oxyphilla;* inhibitor; prostaglandin; biosynthesis; diarylheptanoid

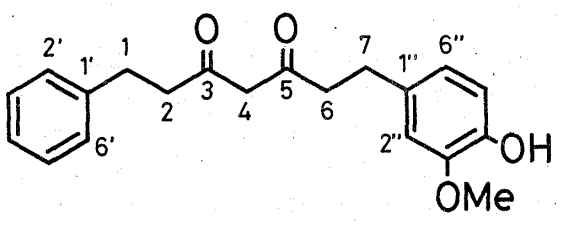
Since Vane first found that aspirin inhibited the biosynthesis of prostaglandin (PG), extensive studies have been carried out to clarify the molecular mechanism of the biological effect of non-steroidal antiinflammatory drugs. It is now well established that non-steroidal antiinflammatory drugs such as aspirin and indomethacin exhibit their biological effects by inhibiting fatty acid cyclooxygenase, the first step of PG biosynthesis.[1] Discovery of non-classical PGs (thromboxane and prostacyclin),[2] the slow-reacting substance of anaphylaxis (SRS-A)[3] and fatty acid peroxides[4] as chemical mediators drew the further attention of many workers to arachidonate metabolism. Compounds possessing modulation effect on arachidonate metabolism are expected to show various biological activities not limited to antiinflammatory effect. In the course of our attempts to find inhibitors of PG biosynthesis from medicinal plants used in traditional medicines, several plants belonging to Zingiberaceae were found to contain ihibitors of PG biosynthesis. In a previous communication we reported the isolation of inhibitors of PG biosynthesis from *Zingiber officinale* (Zingiberaceae).[5] In this communication, we wish to report the isolation and characterization of new diarylheptanoids from the rhizomes of *Alpinia officinarum* Hance (Zingiberaceae), which showed inhibitory effect against PG biosynthesis.

The commercial crude drug purchased in the Japanese market[6] was extracted with methanol, and the extract was fractionated into n-hexane soluble and chloroform soluble fractions by the usual procedure. After chromatographic purification with the guidance of inhibitory effect against PG synthetase,[7] the chloroform soluble fraction gave compounds I, II, III, IV, V and VI. Compounds II, III and V were identified as 7-(4"-hydroxy-3"-methoxyphenyl)-1-phenylhept-4-en-3-one (II),[8] 1,7-diphenyl-5-hydroxy-3-heptanone (III)[9] and 5-hydroxy-7-(4"-hydroxy-3"-methoxyphenyl)-1-phenyl-3-heptanone (V),[10] respectively, by the comparison of their spectral data with those reported.

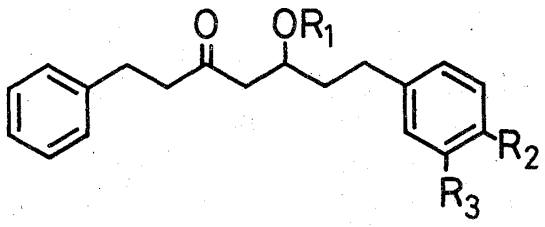
Compound I is a colourless oil, $C_{20}H_{22}O_4$ (M^+: m/z 326.1463, Calcd: 326.1515), MS m/z: 326 (M^+, 32%), 310 (5%), 221 (4%), 193 (4%), 150 (20%), 137 (base peak), 105 (21%), 91 (38%), IR ν_{max}^{Cap} cm^{-1}:

3430 (OH), 1602 (ketone). The ^{1}H-NMR spectrum ($CDCl_3$, δ ppm) of I showed signals of unsubstituted phenyl group (7.18, 5H) and 1,2,4-substituted benzene ring (6.5-6.8, 3H), signals of a hydroxyl proton (5.84, brs, 1H) and an olefinic proton of enol form (5.38, s, 0.8H), a methoxyl signal (3.82, s, 3H), a signal of the methylene protons of diketone form (3.47, s, 0.4H), α-methylene signals of ketones (2.6-3.0, m, 4H) and signals of benzyl protons (2.4-2.6, m, 4H). These spectral data suggested that compound I was 7-(4"-hydroxy-3"-methoxyphenyl)-1-phenyl-3,5-heptadione,[11] a dehydro-derivertive of compound V. This structure was supported by the ^{13}C-NMR spectrum of V (Table I), which also indicated that the ratio of enol and diketone forms of I was approximately 4:1 in chloroform solution.

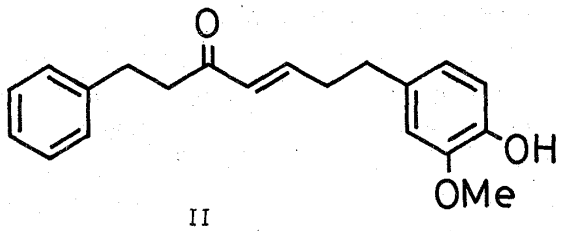
Compound IV is a colourless oil, $C_{21}H_{26}O_4$ (M^+ : m/z 342.1795, Calcd: 342.1828), IR ν_{max}^{Cap} cm^{-1}: 3400 (OH), 1710 (ketone). The ^{1}H-NMR spectrum of IV showed signals of unsubstituted phenyl group and 1,2,4-substituted benzene ring (7.15, 5H and 6.5-6.8, 3H), a hydroxyl proton signal (5.48, s, 1H), aromatic and aliphatic methoxyl proton signals (3.83, s, 3H and 3.28, s, 3H), a methine proton signal (3.66, m, 1H), signals of benzyl protons and α-protons of ketone (2.4-2.9, m, 8H) and a methylene protone signal (1.6-1.8, m, 2H). The mass spectrum of IV showed fragment peaks at m/z 310 (M^+-MeOH, 26%), 205 (6%), 137 (base peak) and 133 (9%), which indicated the position of ketone and aliphatic methoxyl groups. On the basis of these spectral data as well as ^{13}C-NMR spectrum (Table I), compound IV was identified as 5-methoxy-7-(4"-hydroxy-3"-methoxyphenyl)-1-phenyl-3-heptanone. This structure was also confirmed by the fact that base treatment of compound IV gave α,β-unsaturated ketone identical to compound II. Since compound IV is optically inactive, IV seems to be an artefact formed during the extraction of the crude drug by the addition of methanol to the α,β-double bond of II.



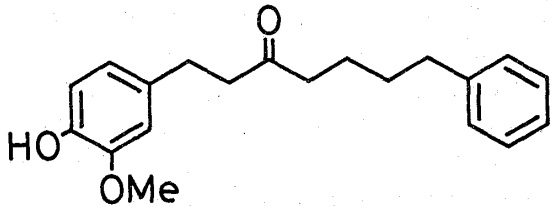
I



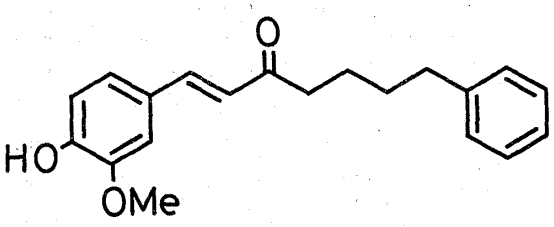
III: R_1=H; R_2=H; R_3=H
IV : R_1=Me; R_2=OH; R_3=OMe
V : R_1=H; R_2=OH; R_3=OMe
VI : R_1=H; R_2=OH; R_3=H



II



VII



VIII

Compound VI is a colourless oil, $[\alpha]_D^{30°}$ -13.3° ($CHCl_3$, c=1.04), $C_{19}H_{22}O_3$ (M^+-H_2O : m/z 280.1481, Calcd: 280.1461), MS m/z: 280 (M^+-H_2O, 2%), 148 (22%), 133 (11%), 107 (base peak) and 105 (39%), IR ν_{max}^{Cap} cm^{-1}: 3360 (OH), 1703 (ketone). The ^{1}H-NMR spectrum of VI showed signals of unsubstituted and *para*-substituted phenyl protons (7.08, 5H and 6.5-6.9, 4H), a signal of hydroxyl proton (6.2, s, 1H), a methine proton signal (4.05, m, 1H), a hydroxyl proton signal (3.35, d, J=3.7Hz, 1H), signals of benzyl protons and α-protons of ketone (2.5-3.0, m, 8H), and a signal of methylene protons (1.4-1.8, m, 2H). On the basis of these spectral data, compound VI was identified as 5-hydroxy-7-(4"-hydroxyphenyl)-1-phenyl-3-heptanone. Degradation of VI with base gave benzylacetone, which was identified by GC-MS, and this finally confirmed the position of ketone and hydroxyl groups.[10] Table I shows ^{13}C-NMR spectral data of compound I-VI. The assignment of signals was established by the comparison of these data with those of model compounds.[12]

IC_{50} (50% inhibitory concentration) values of compounds I-VI against PG biosynthesis were 2.0, 50, 170, 2.3, 4.4 and 19 μM, respectively.[13] Compound V was the main inhibitor contained in the chloroform soluble fraction.

In our previous screening work of medicinal plants, *Alpinia oxyphilla* Miquel (Zingiberaceae) also showed inhibitory effect against the PG synthesizing enzyme system. Recently Itokawa *et al.* isolated a new diarylheptanoid, 1-(4"-hydroxy-3"-methoxyphenyl)-7-phenyl-3-heptanone (VII), from

Table I. ^{13}C-NMR Spectra of Compound I-VI ($CDCl_3$/TMS δ ppm)

No.	I#	II	III	IV	V	VI
1	31.5 t*	30.1 t	29.5 t	29.5 t	29.5 t	29.5 t
2	39.3 t+	41.7 t	45.0 t	45.4 t	45.0 t	45.0 t
3	203.0 s°	199.3 s	210.8 s	208.4 s	211.0 s	211.4 s
4	93.6 d	130.6 d	49.3 t	47.4 t	49.3 t	49.2 t
5	193.1 s°	146.4 d	66.8 d	76.6 d	66.9 d	67.1 d
6	39.0 t+	34.4 t°	38.1 t	36.1 t	38.3 t	38.2 t
7	31.3 t*	34.1 t°	31.7 t	31.1 t	31.4 t	30.8 t
1'	140.6 s	141.2 s	140.6 s	141.0 s	140.6 s	140.6 s
2'	128.2 d	128.3 d	128.2 d	128.2 d	128.2 d	128.2 d
3'	128.5 d	128.4 d	128.5 d	128.4 d	128.5 d	128.5 d
4'	126.2 d	126.0 d	126.2 d	126.0 d	126.2 d	126.2 d
5'	128.5 d	128.4 d	128.5 d	128.4 d	128.5 d	128.5 d
6'	128.2 d	128.3 d	128.2 d	128.2 d	128.2 d	128.2 d
1"	132.5 s	132.5 s	141.8 s	133.6 s	133.6 s	133.4 s
2"	111.0 d	111.0 d	128.4 d	111.0 d	111.1 d	129.4 d
3"	146.4 s	146.5 s	128.4 d	146.4 s	146.5 s	115.3 d
4"	144.0 s	144.1 s	125.8 d	143.8 s	143.7 s	154.0 s
5"	114.4 d	114.4 d	128.4 d	114.3 d	114.3 d	115.3 d
6"	120.8 d	120.9 d	128.4 d	120.9 d	120.9 d	129.4 d
3"-OMe	55.8 q	55.8 q	----	55.8 q	55.8 q	----
5 -OMe	----	----	----	57.0 q	----	----

s: singlet, d: doublet, t: triplet, q: quartet.

*, +, °: changable.

#: Only the data of enol form are shown.

this crude drug.[14] IC_{50} values of VII and its dehydro-derivertive (VIII) were 0.51 and 2.3 μM respectively. Compound VII is one of the most potent inhibitors of PG biosynthesis and may be the main inhibitor of PG biosynthesis contained in *A. oxyphilla*.

ACKNOWLEDGEMENT The authors thank Prof. H. Itokawa of Tokyo College of Pharmacy for his kind gift of samples of diarylheptanoids.

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6) The crude drug was purchased from Uchida Pharmacy (Tokyo).
7) Rabbit renal medulla microsomal fraction was used as the enzyme preparation. Details of assay methods will be reported elsewhere.
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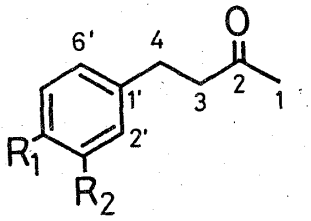
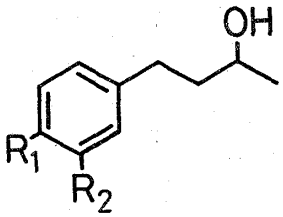
11) The numbering is in accordance with that of compound V for convenience.
12) ^{13}C-NMR spctral data ($CDCl_3$/TMS δ ppm) of these compounds are as follows:

No.	a	b	c	d
1	29.4 q	30.0 q	23.6 q	23.6 q
2	208.3 s	207.5 s	67.5 d	67.4 d
3	45.4 t	45.1 t	41.1 t	40.8 t
4	30.0 t	29.8 t	31.8 t	32.1 t
1'	132.8 s	141.0 s	133.9 s	142.1 s
2'	111.1 d	128.3 d	111.1 d	128.4 d
3'	146.5 s	128.5 d	146.5 s	128.4 d
4'	143.9 s	126.1 d	143.7 s	125.8 d
5'	114.4 d	128.5 d	114.4 d	128.4 d
6'	120.7 d	128.3 d	120.9 d	128.4 d
3'-OMe	55.8 q	----	55.9 q	----

s: singlet, d: doublet, t: triplet, q: quartet.



a: R_1=OH R_2=OMe
b: R_1=H R_2=H



c: R_1=OH R_2=OMe
d: R_1=H R_2=H

13) The IC_{50} value of indomethacin under the same assay condition is 4.9 μM.
14) H. Itokawa, R. Aiyama and A. Ikuta, Phytochemistry, 20, 769 (1981).

(Received May 4, 1982)