STRUCTURE OF MULBERROFURAN K, AN OPTICALLY ACTIVE NATURAL DIELS-ALDER TYPE ADDUCT FROM CHINESE CRUDE DRUG "SANG-BAI-PI" (MORUS ROOT BARK)

Yoshio Hano, a) Toshio Fukai, a) Hideaki Kohno, a)
Kazuhiro Hirakura, a) Taro Nomura, a) and Jun Uzawa b)

a) Faculty of Pharmaceutical Sciences, Toho University, 2-2-1, Miyama, Funabashi-shi, Chiba 274, Japan
b) The Institute of Physical and Chemical Research, Wako-shi, Saitama 351, Japan

Abstract — From the methanol extract of the Chinese crude drug "Sang-Bai-Pi" (Japanese name "Shakuhii"), the root bark of Morus sp. (Moraceae), a 2-arylbenzofuran derivative was isolated and named mulberrofuran K. Its structure was shown to be 1 on the basis of the spectral and chemical evidence. Mulberrofuran K is optically active and regarded biogenetically as a variation of a Diels-Alder type adduct of a chalcone derivative and a dehydroprenyl-2-arylbenzofuran derivative.

In the previous papers, 1 we reported the structure determination of a series of natural Diels-Alder type adducts isolated from the Chinese crude drug "Sang-Bai-Pi" (Japanese name "Shakuhii") imported from the People's Republic of China. In this paper, the structure determination of mulberrofuran K (1) isolated from the crude drug, is described.

The methanol extract of the crude drug was dissolved in ethyl acetate. The ethyl acetate extract was fractionated sequentially by the silica-gel column chromatography and preparative thin layer chromatography, resulting in the isolation of 1 (5 x 10^-4 % yield from the crude drug).

Mulberrofuran K (1), obtained as colorless needles, mp 176 °C (decomp.), [α]_D^21 + 425° (c = 0.024, MeOH), FeCl_3 test (negative), gave the FD-MS which showed the molecular ion peak at m/z 628. Treatment of 1 with dimethyl sulfate and potassium carbonate in acetone effected exhaustive methylation to give the tetramethyl ether (1a) as an amorphous powder. The molecular formula of 1a was determined to be C_{43}H_{40}O_8 by the high-resolution mass...
Fig. 1

1 (=2b=0): R=H
   1a: R=CH₃

1.5% H₂SO₄
EtOH, λυ

1' (=2c)

1.5% H₂SO₄
EtOH, λυ

PdCl₂
MeOH-H₂O

2: R=H
2a: R=CH₃

1 (=2b=0): R=H
   1a: R=CH₃

1.5% H₂SO₄
EtOH, λυ

PdCl₂
MeOH-H₂O

3

1.5% H₂SO₄
EtOH, λυ

Fig. 1
spectr& (M' = 684.2748), and hence 1 could be formulated as C39H32O8. The compound (1) showed the following spectra; \( \text{IR } \nu_{\text{max}} \text{ cm}^{-1} : 3400 \text{ (br)}, 1620, 1600, 1570 \text{ (sh)}, 1430; \text{ uv } \lambda_{\text{max}} \text{ nm (log } \varepsilon \text{ )} : 225 (4.72), 286 (4.29), 306 (4.45), 320 (4.56), 334 (4.47); \text{ uv } \lambda_{\text{max}} \text{ nm (log } \varepsilon \text{ )} : 225 (4.72), 286 (4.29), 306 (4.45), 320 (4.56), 334 (4.47). \) The IR spectrum of 1 showed the absence of carbonyl function. The UV spectrum was similar to those of mulberrofuran F (2), and albahol A, and suggested that 1 is one of the 4'-substituted 6,3',5'-trioxygenated 2-arylbenzofuran derivatives. This suggestion was supported through a comparative examination of the \( ^1\text{H} \) nmr spectrum of 1 (400 MHz, acetone-\( d_6 \)) with those of 2, 3, chalcomoracin (4), and mulberrofuran C (5). The chemical shifts and coupling constants (Hz) of the 2-arylbenzofuran moiety are shown as follows: 6 6.81 (1H, dd, J=2 and 8, C-5-H), 6.94 and 6.95 (each 1H, d, J=2, C-2' and 6'-H), 6.97 (1H, br d, J=2, C-7-H), 7.03 (1H, d, J=1, C-3-H), 7.40 (1H, d, J=8, C-4-H). As the chemical shift values and the coupling constants of the protons of the 2-arylbenzofuran moiety were similar to those of the relevant protons of 2 and 3, it is suggested that 1 has the same substituted pattern on the moiety. The presence of the following moieties was also supported by the comparative examination of the \( ^1\text{H} \) nmr spectrum of 1 with those of 2 and 3. The signals of protons in a 5-oxygenated 2,2-dimethylchromene moiety were observed at 6 1.34, 1.35 (each 3H, s, C-23"-CH\(_3\)), 5.66 (1H, d, J=10, C-22"-H), 6.26 (1H, d, J=9, C-13"-H), 6.68 (1H, d, J=10, C-21"-H), 7.05 (1H, d, J=9, C-14"-H), and those of the aromatic protons in a 2,4-dioxygenated phenyl moiety at 6.37 (1H, d, J=2, C-17"-H), 6.50 (1H, dd, J=2 and 8, C-19"-H), 7.13 (1H, d, J=8, C-20"-H). The presence of trisubstituted methylcyclohexane ring was also supported by the examination of the \( ^1\text{H} \) nmr spectrum of 1a with the aid of sequential decoupling experiments, and the deduced structure is shown in Fig. 2 along with chemical shifts (ppm) and the coupling constants (Hz). The chemical shift values and the coupling constants of the protons on the ring of 1a were similar to those of the relevant protons of 2a. From above results, three possible structures (1, 1', and 1") were suggested. The structure (1") was excluded from the following results. The treatment of mulberrofuran F (2, 39 mg) with palladium chloride (11 mg) in 95 % methanol aqueous solution (5 ml) gave the reaction products, which were purified by preparative TLC (benzene : ethyl acetate = 2 : 1, silica gel) to give the compound (2b, 6 mg) and (2c, 13 mg). The IR spectrum of 2b was in agreement with that of 1. In order to corroborate the structure, 1 was derived from chalcomoracin...
The compound (1) was also derived from L by the following reaction:

\[ \text{H}_2C\text{O} + \text{H}_2\text{O} \rightarrow \text{H}_2\text{C}=\text{O} \text{L} + \text{H}_2\text{O} \]

The product was purified by preparative TLC (silica gel) to give the pure product.

Mechanical attrition solution (5 ml) was kept at room temperature for 2 hr. The products were then filtered off and washed with methanol.

A mixture of 4 (108 mg) and palladium chloride (22 mg) in 95 % ethanol was heated at 100 °C for 2 hr. The solution was filtered and the filtrate was used for the next step.
TLC to give 1 (2 mg), the $^1$H nmr and ir spectra of which were identical with those of mulberrofuran K.

On the other hand, the compound (2c) was derived from 6 as follows: a solution of 6 (17 mg) in ethanol solution containing 1.5 % sulfuric acid was irradiated as described above to give amorphous powder (5 mg), the ir spectrum of which was identical with that of 2c. From above results, we propose the formula (1) for the structure of mulberrofuran K.

ACKNOWLEDGEMENT
We are grateful to Prof. S. Sakai, Faculty of Pharmaceutical Sciences, Chiba University, for mass spectrum measurement, and also grateful to Dr. K. Fukushima, Research Institute for Chemobiodynamics, Chiba University. We also thank to Miss Y. Inomata for technical assistance.

REFERENCES AND FOOTNOTES

Received, 6th September, 1984