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# A 2,5-DIMETHOXYTETRAHYDROFURAN FROM *HEMEROCALLIS FULVA* VAR. *KWANSO*

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**Key Word Index**—*Hemerocallis fulva* var. *kwanso*; Liliaceae; 2,5-dimethoxytetrahydrofuran; Ehrlich reaction; NOE.

**Abstract**—A 2,5-dimethoxytetrahydrofuran, fulvanol, has been extracted from *Hemerocallis fulva* var. *kwanso* along with fulvanines‡, 2,5-dihydrofuryl-γ-lactams. The structure of fulvanol has been established as 3-hydroxymethyl-2,5-dimethoxy-3,4-dihydroxytetrahydrofuran by the $^1$H and $^{13}$C NMR spectra. The structure of fulvanol is closely related to the branched-chain tetrofuranose apiose, occurring in the form of UDP-glycoside or as other cell components. [‡Fulvanines were first named for 2,5-dihydrofuryl-γ-lactam derivatives. The authors are concerned about possible confusion with fulvanin, cf. *J. Nat. Prod.* **56**, 527 (1993), which is a name given to a new sesquiterpene.]

## INTRODUCTION

In the course of extensive studies on plant constituents which react with Ehrlich's reagent, the 2,5-dihydrofuryl-γ-lactams, fulvanine A, B, C, D and E, have been extracted from *Hemerocallis fulva* L. var. *kwanso* $R_{EGEL}$ [1, 2]. Furthermore, the methanol extract from the fresh aerial part of the plant was chromatographed to give fulvanol as a minor constituent. We now report on the isolation and characterization of fulvanol.

## RESULTS AND DISCUSSION

Fulvanol (**1**), reddish purple with the Ehrlich test, was obtained as a syrup having $[\alpha]_D$ −3.6° (MeOH). The $^1$H NMR spectrum ($CD_3OD$) showed eleven non-$D_2O$ exchangeable protons, a pattern of chemical shifts identical to that with alkoxy alkyl groups, indicating a vicinal coupling system due to two methine protons at δ 4.90 and 3.88 with a singlet methine proton at δ 4.76, and the six protons appeared as two sets of equivalent methoxy proton signals at δ 3.36 and 3.43, and two proton signals of methylene coupled each other at δ 3.57 and 3.93. Further $^1$H NMR spectrum (DMSO-$d_6$) exhibited three hydroxy proton signals at δ 3.80, 4.27 and 5.05. In the double resonance experiment, irradiation of the signal at δ 4.72 sharpened the methylene signals at δ 3.36 and 3.43, and likewise, irradiation at δ 5.05 transformed the doublet signal at δ 3.88 from a show any changeable proton signal corresponding to the irradiation of hydroxy proton.

In general, furanosyl anomeric protons resonate between 4.9 and 5.0 ppm in glycosides, while in aldoses at 5.2–5.4 ppm. The remaining protons resonate between 3.6 and 4.4 ppm [3]. Therefore, the analogous proton shift values δ 4.76 and 4.90 refer to anomeric protons of a furanosylglycoside ring, and the presence of two methoxy functions; hence the basic structure of this compound is 2,5-dimethoxytetrahydrofuran. These results were indicated by $^{13}$C NMR spectrum in which C-2 and C-5, with attached methoxy group, appeared in the low field range at δ 110.4 and 112.3, and the residual carbon signals at δ 82.4 and 78.2 were assigned to C-3 and C-4, respectively, in regard to the orientation of *exo*-hydroxymethyl or hydroxy function. Accordingly, fulvanol is assumed to be 3-hydroxymethyl-2,5-dimethoxy-3,4-dihydroxytetrahydrofuran (**1**).

It is known that in *erythro*-D form of apiofuranose, the methylene protons of 3-hydroxymethyl group are magnetically equivalent, but in the *threo* form, these protons are non-equivalent [4]. Therefore, the configurations of two hydroxy groups at C-3 and C-4 were presumed to be oriented *trans*, based on the geminal coupled 3-hydroxymethyl protons. Stereochemistry of **1** was determined by the nuclear Overhauser effect (NOE) data: decoupling of the methoxy protons at δ 3.36 and 3.43 gave the significant NOE on the proton at δ 4.76 and 4.90, respectively. In addition, both experi-

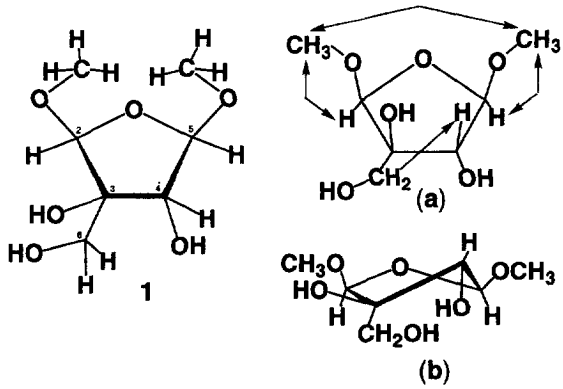


Fig. 1. Structure, NOE (a) and conformation (b) of **1**.

proton at $\delta$ 3.88, and a negative NOE appeared on the proton at $\delta$ 3.57, as a result of geminal coupled relationship with the affected proton.

The tetrahydrofuran ring is flexible, and the interpretation of vicinal spin-coupling in the ring in terms of ring conformation is difficult. However, on the basis of significant information regarding apiofuranose ring conformation, some insight was obtained indicating a more *quasi-axial* orientation of 3-hydroxymethyl group and *cis*-orientation between O-1 and C-5 in L-furanoside $^2T_3$ conformation in these compounds [5]. The structure of **1** was analogous to $\alpha$-L-*threo*-apiofuranose having 3-hydroxymethyl-1,2,3-trihydroxy substituent groups. Since **1** was regarded as 1,4-*cis*-dimethoxy derivative of $\alpha$-L-*threo*-apiose, and the dihedral angle, $\theta$ about 133° was calculated from $J_{H4,H5}$ (4.15 Hz, *trans*) in "Karplus" relationship [6], $^2T_3$ conformation was presumed for **1** with a *quasi-axial* orientation of 3-hydroxymethyl group.

Fulvanol (**1**), is an unusual substance in that the branched-chain methyl-$\alpha$-L-apioside is methoxylated at 4-position of the endomethylene. 2,5-*cis*-Dimethoxytetrahydrofurans have been synthesized from dihydrofuran for the study of stereochemistry of the various aldofuranose [7], but fulvanol is an unprecedented product in nature. It is noteworthy from the biochemical view that the structure of **1** is closely related to the branched aldofuranose, playing an integral role in the

Table 1. $^1$H NMR spectral data for fulvanol (**1**) and apiose ($J_{H-H}$ Hz, in parentheses)

| Position* | **1** (MeOH) | | **1** (DMSO − $d_6$) | | Apiose ($D_2O$)[4] | |
|---|---|---|---|---|---|---|
| | | | | | *α*-L-*threo* | *β*-D-*erythro* |
| 2 (4) | 4.76 *s* | 3.36 *s* ($OCH_3$) | 4.63 *s* | 3.23 *s* ($OCH_3$) | n.d. | 3.85 |
| | | | | | n.d. | 4.13 |
| 3 (3) | | | | 3.80 *br* (OH) | | |
| 4 (2) | 3.88 *d* (4.2) | | 3.69 *br d* (4.0) | 5.05 *br* (OH) | 4.03 | 3.88 |
| 5 (1) | 4.90 *d* (4.2) | 3.43 *s* ($OCH_3$) | 4.77 *d* (4.0) | 3.31 *s* ($OCH_3$) | 5.26 | 5.28 |
| 6 (3') | 3.57 *d* (11.5) | | 3.38 *br d* (11.3) | | 3.70 | 3.65 |
| | 3.73 *d* (11.5) | | 3.49 *br d* (11.3) | | 3.81 | |

*Numbering of apiose is indicated in parentheses.
n.d., not determined.

Table 2. $^{13}$C NMR spectral data for fulvanol (**1**) and apiose[4]

| Position* | Fulvanol (MeOH) | | Apiose ($D_2O$) | |
|---|---|---|---|---|
| | | | *α*-L-*threo* | *β*-D-*erythro* |
| 2 (4) | 110.38 | 55.82 ($OCH_3$) | 75.7 | 74.6 |
| 3 (3) | 82.35 | | 82.7 | 80.5 |
| 4 (2) | 78.20 | | 82.0 | 78.9 |

cell function of plants and 3-hydroxymethyl-2,5-dihydrofuranyl ring of fulvanines and oxypinnatanine in *H. fulva* var. *kwanso* [1].

## EXPERIMENTAL

Optical rotation: 20°, 0.1 dm cell path length; positive FABMS: accelerating voltage 10 KV, emission current 10 mA; $^1$H NMR: 300 MHz, TMS as int. standard; $^1$H–$^1$H NOE: see ref. [8].

*Isolation of fulvanol* (**1**). The water solution of the methanol extract (98 g) from a fresh aerial part of *H. fulva* var. *kwanso* (6.5 kg) was made to flow a Diaion (HP-20) column followed by elution with methanol. The methanol eluate (9.6 g) was chromatographed on Sephadex LH-20 (MeOH) to give four fractions (A, 1.20 g; B, 1.35 g; C, 3.65 g; D, 3.80 g) [1]. Fr. A was subjected in turn to column chromatographies on silica gel ($CHCl_3$–MeOH–$H_2O$, 10:0.2:0.02; $CHCl_3$–MeOH, 50:1) to yield crude fulvanol, monitored by TLC with the Ehrlich reaction. The crude fr. (34 mg) was followed by recycling prep. gel partition chromatography (GS-310, MeOH) to give fulvanol (**1**) (5.0 mg).

*Fulvanol* (**1**). Syruplike, $[\alpha]_D$ −3.64° (0.4, MeOH). Positive FABMS *m/z*: 217 $[M+Na]^+$, 176 $[M-H_2O]$. $^1$H and $^{13}$C NMR: Tables 1 and 2.

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