Communications to the Editor

Chem. Pharm. Bull.
31(9)3330—3333(1983)

TODDALENONE: A NEW COUMARIN FROM *TODDALIA ASIATICA* (*T. ACULEATA*)[1] STRUCTURAL ESTABLISHMENT BASED ON THE CHEMICAL CONVERSION OF LIMETTIN INTO TODDALENONE

Hisashi Ishii,* Jun-Ichi Kobayashi, and Tsutomu Ishikawa

Faculty of Pharmaceutical Sciences, Chiba University, 1-33, Yayoi-cho, Chiba 260, Japan

Toddalenone, a new coumarin, was isolated from *Toddalia asiatica* (L.) Lam. (*T. aculeata* Pers.). Its structure was established as the formula (1) by correlation with limettin (2). Vilsmeier-Haack formylation of limettin (2) gave 8-formyllimettin (10) in good yield. Aldol condensation of this material (10) with acetone afforded toddalenone (1).

KEYWORDS— *Toddalia asiatica*; *Toddalia aculeata*; structural establishment; toddalenone; 5-methoxysuberenon; Vilsmeier-Haack formylation of limettin; natural occurrence of 6-formyllimettin

Toddalia asiatica (L.) Lam. (*T. aculeata* Pers.) is widely used as a folk-medicine[2] in India. In our country, this plant is also used for the same purpose in the Okinawa area. Thus, a number of research groups[2,3] has studied the chemical constituents of the plant in the world. In the course of the studies on the chemical constituents of Rutaceous plants,[1] we occasionally had a chance to investigate the chemical constituents of this plant collected at Ishigaki Island, Okinawa, and isolated a new coumarin (1) designated as toddalenone along with ten known alkaloids (chelerythrine, avicine, norchelerythrine, chelerythrine ψ-cyanide, arnottianamide, skimmianine, 4-methoxy-1-methyl-2-quinolone, integriquinolone, oxychelerythrine, and N-methylflindersine), ten known coumarins [toddalolactone, isopimpinellin, coumurrayin, toddanone, toddaculin, toddanol, 5,7,8-trimethoxycoumarin, toddasin, 6-(3-chloro-2-hydroxy-3-methylbutyl)-5,7-dimethoxycoumarin, and 6,7-dimethoxy-8-isopentenylcoumarin], and β-amyrin from the same plant. In this report, we describe the structure of toddalenone (1) based on its transformation from commercially available limettin (2).

Toddalenone (1) was obtained as colorless prisms, mp 244-246°C (MeOH) [$C_{15}H_{14}O_5$, IR (KBr) cm^{-1}: 1715 (C=O), UV λ_{max}^{MeOH} nm (log ε): 214 (4.34), 248 (3.96), 320 (4.45), PMR ($CDCl_3$) δ: 2.39 (3H, s, COMe), 3.98 (6H, s, OMe × 2), 6.15 (1H, d, J=10.0 Hz, C_3-H), 6.31 (1H, s, C_6-H), 7.18 (1H, d, J=16.5 Hz, COCH=CHAr), 7.88 (1H, d, J=16.5 Hz, COCH=CHAr), 7.95 (1H, d, J=10.0 Hz, C_4-H)], from the root bark in 0.0028% yield. The spectral data suggest that toddalenone (1) is a coumarin having two methoxy groups and a *trans* MeCOCH=CH- group as a side chain. In the PMR spectrum of toddalenone (1), the signal of the C_4-H appears at δ 7.95, indicating that toddalenone (1) has a methoxy group at the C_5-position, because simple couma-

rins bearing no C_5-alkoxy group show the C_4-H signal between δ 7.57 and 7.70,[4] while simple 5-alkoxycoumarins show the corresponding signal between δ 7.81 and 7.95,[4] due to an anisotropic effect of the 5-alkoxy group. Since all of the naturally occurring coumarins isolated from Rutaceous plants have an oxygen atom at the C_7-position, as far as we know, the location of the other methoxy group was expected to be at the C_7-position in toddalenone (1). This assumption left only two formulae (1 and 3) as the possible structures of toddalenone.

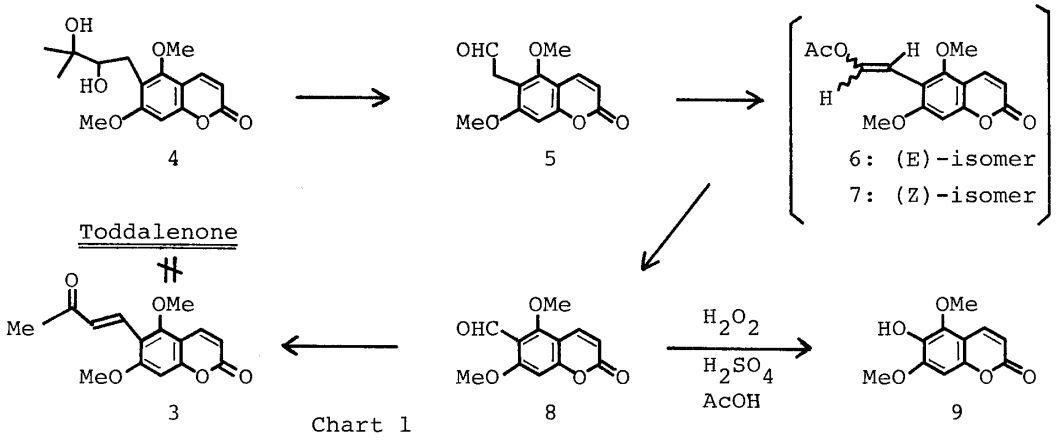

Chart 1

Since various kinds of 5,7-dimethoxycoumarin derivatives[2b,3a,b] having a C_5-unit side chain at the C_6-position and related compounds[3c] occur naturally in *T. asiatica*, we speculated that toddalenone might have the structure (3), 5-methoxysuberenon, in a biogenetical sense. Thus, we, initially, aimed at converting toddalolactone (4), mp 134-140°C (lit.[3a] mp 132.5°C), a major component of *T. asiatica*, into 5-methoxysuberenon (3), to directly compare it with toddalenone (1). Treatment of toddalolactone (4) with $NaIO_4$ in aqueous MeOH gave the coumarylacetaldehyde[5] (5), mp 140-143°C (lit.[5] mp 142-142.5°C), in 87.9% yield. This material (5) was convertible into a mixture of (*E*)- and (*Z*)-enolacetate (6 and 7) in 66.9% yield by treatment with isopropenylacetate and TsOH. Column chromatography of the mixture (6 and 7) on SiO_2 with benzene-AcOEt gave each component, (*E*)-enolacetate (6) [colorless needles, mp 185-187°C ($CHCl_3$-MeOH), $C_{15}H_{14}O_6$, IR (Nujol) cm^{-1}: 1750 and 1720 (C=O), PMR ($CDCl_3$) δ: 2.20 (3H, s, COMe), 3.80 and 3.92 (each 3H, s, OMe), 6.22 (1H, d, J=10.0 Hz, C_3-H), 6.51 (1H, d, J=13.0 Hz, CH=C<u>H</u>Ar), 6.62 (1H, s, C_8-H), 7.86 (1H, d, J=10.0 Hz, C_4-H), 8.19 (1H, d, J=13.0 Hz, CH=C<u>H</u>OAc)] and (*Z*)-enolacetate (7) [colorless needles, mp 119-122°C ($CHCl_3$-Et_2O), $C_{15}H_{14}O_6$, IR (Nujol) cm^{-1}: 1750 (C=O), PMR ($CDCl_3$) δ: 2.09 (3H, s, COMe), 3.75 and 3.88 (each 3H, s, OMe), 5.80 (1H, d, J=7.0 Hz, CH=C<u>H</u>Ar), 6.20 (1H, d, J=10.0 Hz, C_3-H), 6.60 (1H, s, C_8-H), 7.25 (1H, d, J=7.0 Hz, CH=C<u>H</u>OAc), 7.90 (1H, d, J=10.0 Hz, C_4-H)], in 42.7% and 10.9% yield, respectively. Lemieux oxidation[6] of the mixture with OsO_4-$NaIO_4$ in aqueous dioxane afforded 6-formyllimettin[7] (8) [colorless needles, mp 194-195°C (MeOH) (lit.[7] mp 192°C), $C_{12}H_{10}O_5$, IR (KBr) cm^{-1}: 1750 and 1695 (C=O), PMR ($CDCl_3$) δ: 3.97 (6H, s, OMe × 2), 6.27 (1H, d, J=10.0 Hz, C_3-H), 6.64 (1H, s, C_8-H), 7.93 (1H, d, J=10.0 Hz, C_4-H), 10.37 (1H, s, CHO)]. It should be added here that, although the aldehyde (8) had already been derived from bergapten, in the present work we have newly isolated it from *T. asiatica* as a naturally occurring product. Baeyer-Villiger oxidation of the alde-

hyde (8) gave fraxinol[8] (9), showing that the aldehyde group was located at the C_6-position of the product (8). Aldol condensation of the aldehyde (8) with acetone gave the desired 5-methoxysuberenon (3) [colorless needles, mp 199-200°C ($CHCl_3$-MeOH), $C_{15}H_{14}O_5$, IR (Nujol) cm^{-1}: 1735 (C=O), PMR ($CDCl_3$) δ: 2.40 (3H, s, COMe), 3.87 and 3.98 (each 3H, s, OMe), 6.27 (1H, d, J=10.0 Hz, C_3-H), 6.68 (1H, s, C_8-H), 7.12 (1H, d, J=16.0 Hz, OCC<u>H</u>=CHAr), 7.78 (1H, d, J=16.0 Hz, OCCH=C<u>H</u>Ar), 7.90 (1H, d, J=10.0 Hz, C_4-H)], which was not identical with toddalenone.

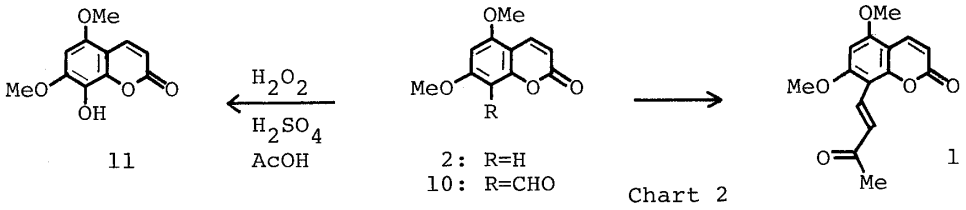

Chart 2

It is well known in coumarin chemistry that the formation of a coumarin skeleton is an obstacle to synthesis. Although there has been no report on the Vilsmeier-Haack reaction of coumarin derivatives until now, as far as we know, we expected that limettin (2), which is commercially available, would undergo formylation either at the C_6- or at the C_8-position by Vilsmeier-Haack formylation. Especially, the C_8-position could be more susceptible to the formylation, because its C_6-position was hindered by two methoxy groups situated at the ortho position of both sides. Actually, treatment of limettin (2) with $POCl_3$ in DMF at 80°C for 8 h gave the desired 8-formyllimettin (10) [colorless prisms, mp 274-275°C ($CHCl_3$-MeOH), $C_{12}H_{10}O_5$, IR (Nujol) cm^{-1}: 1730 and 1685 (C=O), PMR ($CDCl_3$ + CD_3OD) δ: 4.05 and 4.07 (each 3H, s, OMe), 6.24 (1H, d, J=10.0 Hz, C_3-H), 6.45 (1H, s, C_6-H), 8.05 (1H, d, J=10.0 Hz, C_4-H), 10.41 (1H, s, CHO)] in 75.7% yield. Baeyer-Villiger oxidation of the formylcoumarin (10) gave 8-hydroxy-5,7-dimethoxycoumarin[9] (leptodactylone[9b]) (11), mp 166-167°C (AcOEt) (lit. mp 160-161°C[9a]; mp 152-155°C[9b]) [yellow needles, $C_{11}H_{10}O_5$, IR (Nujol) cm^{-1}: 3400 (OH) and 1720 (C=O), PMR ($CDCl_3$) δ: 3.89 and 3.99 (each 3H, s, OMe), 5.00 (1H, br s, OH), 6.12 (1H, d, J=9.5 Hz, C_3-H), 6.35 (1H, s, C_6-H), 7.95 (1H, d, J=9.5 Hz, C_4-H)], demonstrating the location of the aldehyde group at the C_8-position. Aldol condensation of 8-formyllimettin (10) with acetone gave toddalenone (1), mp 244-246°C, in 42.2% yield. This evidence unequivocally establishes the structure of toddalenone as the formula (1).

In conclusion, introduction[10] of a 3,3-dimethylallyl side chain into the C_8-position of umbelliferone *via* 3,3-sigmatropic rearrangement of 7-(1,1-dimethylallyloxy)coumarin is well known as a method for insertion of a carbon chain into a coumarin skeleton. Now we emphasize that formylation of coumarins by the Vilsmeier-Haack reaction is another useful tool for insertion of a carbon side chain into a coumarin skeleton. Studies of the Vilsmeier-Haack reaction of umbelliferone derivatives are going on in our laboratoy. The results will be reported in the near future as a full paper.

REFERENCES AND NOTES

1) This communication forms part LIII of the series "Ishii, Studies on the Chemical Constituents of Rutaceous Plants." Part LII, H. Ishii, I.-S. Chen, and

T. Ishikawa, Chem. Pharm. Bull. in press (1983).

2) a) B.B. Dey, P.P. Pillay, J.C. David, and N. Rajamanikam, Indian J. Med. Res., 22, 765 (1935); P.N. Sharma, A. Shoeb, R.S. Kapil, and S.P. Popli, Phytochemistry, 19, 1258 (1980); b) idem, ibid., 20, 335 (1981).

3) a) E. Späth, B.B. Dey, and E. Tyray, Ber., 72B, 53 (1939); b) P. Dutta, J. Indian Chem. Soc., 19, 425 (1942); G. Combes, R. Pernet, and R. Pierre, Bull. Soc. Chim. Fr., 1961, 1609; c) P.D. Desai, T.R. Govindachari, K. Nagarajan, and N. Viswanathan, Indian J. Chem., 5, 41 (1967); d) T.R. Govindachari and B.S. Thyagarajan, J. Chem. Soc., 1956, 769; T.R. Govindachari and N. Viswanathan, Indian J. Chem., 5, 280 (1967); M.N. Deshmukh, V.H. Desphande, and A.V.R. Rao, Phytochemistry, 15, 1419 (1976); P.N. Sharma, A. Shoeb, R.S. Kapil, and S.P. Popli, Indian J. Chem., 17B, 299 (1979); idem, Phytochemistry, 21, 252 (1982).

4) These ranges were applicable to only coumarins having a simple skeleton. For the coumarins bearing a fused ring, other ranges should be used. In furanocoumarins, for example, the corresponding signals appeared between δ 7.72 and 7.78 in the C_5-H coumarins, and between δ 8.08 and 8.14 in the C_5-methoxycoumarins.

5) E. Späth, B.B. Dey, and E. Tyray, Ber., 71B, 1825 (1938).

6) When MeOH was used as a solvent, the (Z)-isomer (7) was recovered along with the desired 6-formyllimettin (8).

7) A. Schönberg, N. Badran, and N.A. Starkowsky, J. Am. Chem. Soc., 77, 5390 (1955).

8) H. Ishii, I.-S. Chen, M. Akaike, T. Ishikawa, and S.-T. Lu, Yakugaku Zasshi, 102, 182 (1982).

9) a) V.K. Ahluwalia and C. Prakash, Indian J. Chem., 15, 808 (1977); b) F.M. Dean, A.M.B.S.R.C.S. Costa, J.B. Harborne, and D.M. Smith, Phytochemistry, 17, 505 (1978).

10) J. Hlubucek, E. Ritchie, and W.C. Taylor, Chem. Ind. (London), 1969, 1780; R.D.H. Murray, M.M. Ballantyne, and K.P. Mathai, Tetrahedron Lett., 1970, 243; idem, Tetrahedron, 27, 1247 (1971).

ADDED IN PROOF (August 8, 1983) Just after this paper was submitted, we found that Reisch *et al.* reported isolation work in the same plants. [J. Reisch and H. Strobel, Pharmazie, 37, 862 (1982); Chem. Abstr., 98, 122831r(1983)]. They isolated a new coumarin having two methoxy groups and a $CH_3COCH=CH-$ group as a side chain. From spectral and biogenetical considerations, they claimed that the coumarin was 5-methoxysuberenon. However, since there are some discrepancies between the data for their new coumarin and our synthetic 5-methoxysuberenon on melting point (their data: mp 176-180°C) and the chemical shift of the signal due to a $CH_3COCH=CH$ [their data: δ 6.60 (1H, d, J=17.0 Hz)], even though the PMR spectra of both products were measured in the same solvent ($CDCl_3$), we are asking Prof. Reisch, Westfälischen Wilhelms-Universität, to send his sample to us for direct comparison.

We thank Dr. R.D.H. Murray, University of Glasgow, for his valuable information on 5-methoxysuberenon.

(Received July 2, 1983)