HETEROCYCLES. Vol. 6, No. 3. 1977

SYNTHESIS OF β-APOPLICATITOXIN TRIMETHYL ETHER[1]

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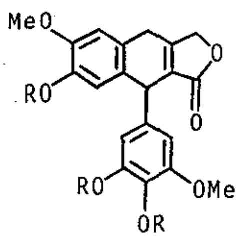
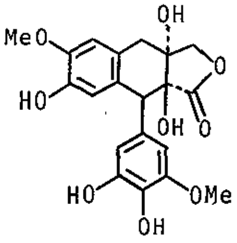
Irradiation of 3-(3,4,5-trimethoxyphenyl)methylene-4-(3,4-dimethoxyphenyl)methylenedihydro-2(3H)-furanone (VIII) afforded β-apoplicatitoxin trimethyl ether (V) and the isomer (IX). The isomer ratio (V/IX) was found solvent-dependent.

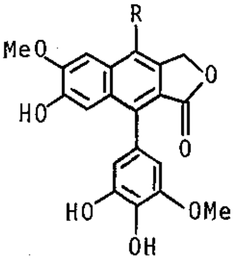
β-Apoplicatitoxin (I)[2] isolated from Thuja plicata Donn is the first natural β-apolignan, and is a possible precursor[3] of the naphthalide lignans found in the same plant, viz., plicatin (II),[4] plicatinaphthol (III),[5] and plicatinaphthalene (IV).[6]



(I) R=H
(V) R=Me



(II)



(III) R=OH
(IV) R=H

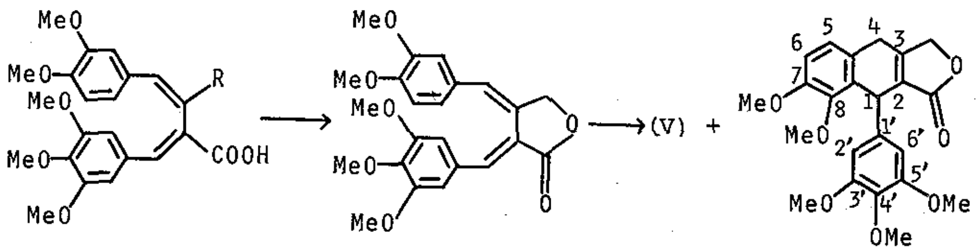
We now report the synthesis of trimethyl ether (V) of I utilizing the photocyclization[7] of a 3,4-bisarylmethylenedihydro-2(3H)-furanone.

The half ester (VI) prepared starting from dimethyl 3,4,5-trimethoxybenzylidene succinate was reduced with lithium aluminum hydride at -15° to give a hydroxy acid (VII) [IR($CHCl_3$)cm^{-1} 1682(C=O); NMR($CDCl_3$)δ 4.27(2H, broad s, $-C\underline{H}_2OH$), 6.6-7.4(6H, m, $-CH=\overset{|}{C}-$ & Ar-H), 7.70(1H, s, $-CH=\overset{|}{C}-$)], treatment of which with p-toluenesulfonic acid in the dark gave a furanone (VIII) [mp 128-135°; IR(KBr)cm^{-1} 1759(C=O), 1627(C=C); NMR($CDCl_3$)δ 4.99(2H, d, J=2Hz, $-CH_2OCO-$), 6.54(1H, d, J=2Hz, $-CH=\overset{|}{C}-$), 7.54(1H, s, $-CH=\overset{|}{C}-$); UV λ_{max}^{EtOH} nm(log ε) 261(4.04), 271(4.04), 357(3.83)].

A solution of VIII (73 mg) in N,N-dimethylformamide (100 ml) was irradiated with a 100 W high-pressure mercury lamp with an ordinary borosilicate glass filter in the presence of 1,4-diazabicyclo[2.2.2]octane (20 mg). Chromatography of the crude product gave V (mp 221-221.5°, 34% yield), identical in IR spectrum and mixture melting point with an authentic sample,[8] and the isomer (IX) (15% yield) [mp 195.5-196°; MS m/e 412(M^+); IR(KBr)cm^{-1} 1748(C=O), 1690(C=C); NMR($CDCl_3$)δ ca. 3.8(2H, m, C_4-H), 4.81(2H, broad s, $-CH_2OCO-$), 5.22(1H, m, C_1-H), 6.43(2H, s, $C_{2'}$- & $C_{6'}$-H), 6.90(1H, d, J=8Hz, C_6-H), 6.99(1H, d, J=8Hz, C_5-H)].

The isomer ratio (V/IX) was found solvent-dependent. For example, the photocyclization in benzene gave V in 5% yield and IX in 16% yield.

Detailed investigations as to the solvent effect in the present system are currently in progress.[9]



(VI) R=COOMe
(VII) R=CH_2OH

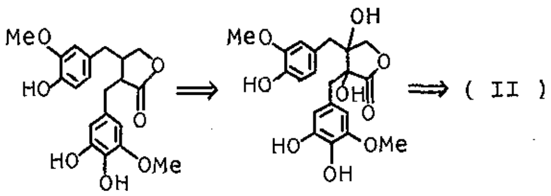
(VIII)

(IX)

ACKNOWLEDGEMENT We are grateful to Dr. E. Schreier for a gift of β-apopicrosikkimotoxin.

NOTES AND REFERENCES

1. A part of this work was presented at the 25th Meeting of Kinki Branch, Pharmaceutical Society of Japan, Kobe, Nov. 1975, Abstracts of Papers, p. 31.
2. B. F. MacDonald and G. M. Barton, Canad. J. Chem., 1973, 51, 482.
3. Swan and his co-workers postulated that the lignans of Thuja plicata Donn are formed in the sequence: thujaplicatin (i) to dihydroxythujaplicatin (ii) to II [E. P. Swan, K. S. Jiang, and J. A. F. Gardner, Phytochemistry, 1969, 8, 345]. The existence of the β-apolignan (I) was discovered later, and there have been found no reports describing a biogenetic situation of I among them.



(i) (ii)

4. J. A. F. Gardner, E. P. Swan, S. A. Sutherland, and H. MacLean, Canad. J. Chem., 1966, **44**, 52.
5. H. MacLean and B. F. MacDonald, ibid., 1969, **47**, 457.
6. H. MacLean and B. F. MacDonald, ibid., 1969, **47**, 4495.
7. A filter of ordinary borosilicate glass was used instead of a Pyrex filter in order to minimize a product from the degenerate photorearrangement of β-apolignan ; see T. Momose, K. Kanai, and T. Nakamura, Heterocycles, 1976, **4**, 1481. Heller and his co-worker reported a selective photocyclization of (E,E)-3,4-bisarylmethylenedihydro-2(3H)-furanones into β-apolignans by irradiation at 366nm [H. G. Heller and P. J. Strydom, J. Chem. Soc., Chem. Commun., 1976, 50].
8. Identified to β-apopicrosikkimotoxin originally synthesized by Schreier [E. Schreier, Helv. Chim. Acta, 1963, **46**, 75]. It was reported to be identical with β-apoplicatitoxin trimethyl ether. A direct comparison with the natural lignan has not been accomplished owing to our failure of receiving a gift of the sample or IR spectrum from the original workers.
9. There are found no previous reports describing the solvent effects on the orientation in ring closure in the photocyclization of 1,4-diphenyl-1,3-butadienes, a partial structure of the present system, and of related compounds.

Received, 21st December, 1976