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PHOMENOLACTONE, AN ANTIFUNGAL SUBSTANCE FROM *PHOMA LINGAM*

MICHEL DEVYS, RAVINDRA SATISH TOPGI, JEAN-PIERRE FÉRÉZOU, LILIANE QUAINO, JEAN-FRANÇOIS BOUSQUET*, ALBERT KOLLMANN* and MICHEL BARBIER

Institut de Chimie des Substances Naturelles, CNRS, 91190 Gif-sur-Yvette, France; *Station de Pathologie Végétale, CNRA, 78000 Versailles, France

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Key Word Index—*Phoma lingam*; fungus; antifungal substance; phomenolactone; structure; synthesis.

Abstract—The structure of phomenolactone, an antifungal substance isolated from the fungus *Phoma lingam* was established by reaction of phomenoic acid with dipyrridyl 2,2′-disulphide in the presence of triphenylphosphine (yield 90%). Anhydrophomenolactone is obtained as a secondary product during this synthesis in a yield of 10%.

INTRODUCTION

The fungus *Phoma lingam* is a common pest of many Cruciferae species and investigations in this laboratory have previously lead to the isolation of bio-active molecules such as the sirodesmins PL [1], phomamide [2] and phomenoic acid [3]. This last substance is accompanied by a related metabolite first described as PLM II [4] from which it has been separated by chromatography. The second substance is a lactone for which we now propose the name phomenolactone. This substance has shown antifungal properties *in vitro*. In spite of having been isolated some years ago, the structure of phomenolactone was never completely demonstrated, due to the minute amounts available from the mycelium and to consequent spectrometric difficulties. As six hydroxyl groups occur in phomenoic acid (**1**), one of which is a primary one at C-31, there are several possibilities for such a lactone. In the present publication, we establish the structure **2** for phomenolactone, which has been synthesized from **1** using a double activation method.

RESULTS AND DISCUSSION

Phomenolactone (**2**), mp 112–114°, $[\alpha]_D^{20^\circ} = +92$ (MeOH); UV λ_{max}^{MeOH} nm (ε): 233 (1.1×10^4); elemental analysis and FAB-MS m/z 577 $[M+1)^+$ in agreement with $C_{34}H_{56}O_7$; IR 1710 cm^{-1}, δ-lactone confirmed by ^{13}C NMR, (DMSO-d_6) 169.9 ppm, by comparing with signals reported [5] for mevinoline and compactine which have a similar 3-hydroxy lactone group. ^1H NMR were carried out on **2** and **3** and compared with **1** and the results are reported on the formulae.

When treated with diazomethane in methanol–ether, phomenolactone (**2**) gives the methyl ester of **1** through transesterification [6, 7] (mp 126–130° mass spectrum, ^1H, ^{13}C NMR, direct comparison). The stereochemistry of phomenolactone could not be determined, as for phomenoic acid, which has nine asymmetric centres.

The synthesis of **2** was carried out by the method of double activation [8] using dipyridyl 2,2′-disulphide and triphenylphosphine, starting from **1**, yield 90%. This product was shown to be identical to natural substance **2**.

Silica gel chromatography of the reaction mixture afforded 10% of anhydrophomenolactone (**3**), mp 114–116°; $[\alpha]_D^{20^\circ} = +38$ (MeOH); UV λ_{max}^{MeOH} nm (ε): 207 (1.27×10^4), 233 (1.14×10^4), elemental analysis and FAB-MS, m/z 559 $[M+1]^+$ in agreement with $C_{34}H_{54}O_6$ derived from **2** by dehydration. We did not succeed in producing **3** from **2** by using $KHSO_4$ as previously reported for compactine [9], the reaction resulting in a breaking of the molecule into many fragments. It appears that the anhydro compound **3** is obtained from **2** by *Z*-elimination of the corresponding triphenylphosphonium derivative under the action of the reagent.

EXPERIMENTAL

Phomenolactone was obtained from the ground mycelium of *P. lingam* Tode through extraction with EtOH and partition between H_2O and EtOAc of the concd extract. The EtOAc supernatant, dried over Na_2SO_4, was evapd *in vacuo* and the mixture of phomenoic acid and phomenolactone ppted by Et_2O (yields: **1** 50 mg; **2**: 5 mg/l. of culture medium). The final separation of the compounds was carried out by HPLC on reversed phase Lichrosorb RP 18 by elution with MeOH–H_2O (3:1) in 0.5% HOAc.

The conditions used for the synthesis using dipyridyl 2,2′-disulphide and triphenylphosphine were those reported [8] using DMSO at 25° and the yield was 90%.

The ^1H and ^{13}C NMR spectra were recorded on a 400 MHz instrument with TMS as int. standard, δ (ppm) coupling constants in Hz, solvents indicated on formulae.

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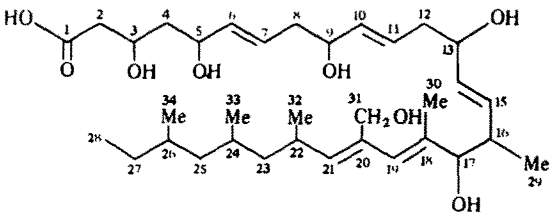
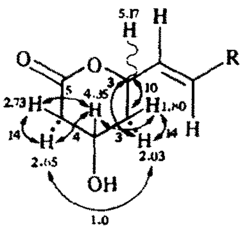
REFERENCES

1. Férézou, J. P., Riche, C., Quesneau-Thierry, A., Pascard-Billy, C., Barbier, M., Bousquet, J. F. and Boudart, G. (1977) *Nouv. J. Chim.* **1**, 327.
2. Férézou, J. P., Quesneau-Thierry, A., Barbier, M., Kollmann,



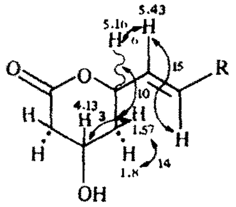
1

Phomenoic acid



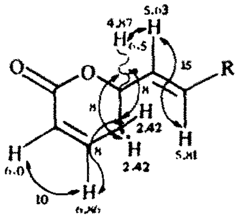
2

^{1}H NMR phomenolactone on the best resolved C-31 TBDPS derivative ($CDCl_3$)



2'

^{1}H NMR phomenolactone (pyridine-d_5)



3

^{1}H NMR anhydrophomenolactone ($CDCl_3$)

A. and Bousquet, J. F. (1980) *J. Chem. Soc. Perkin Trans.* 1, 113.
3. Devys, M., Férézou, J. P., Topgi, R. S. and Barbier M. (1984) *J. Chem. Soc. Perkin Trans.* 1, 2133.
4. Kollmann, A., Bousquet, J. F., Devys, M. and Férézou, J. P. (1981) FP 2 498 204; *Chem. Abstr.* (1982) **97**, 214, 254 n.
5. Chan, J. K., Moore, R. N., Nakashima, T. T. and Vederas, J. C. (1983) *J. Am. Chem. Soc.* **105**, 334.
6. Bredereck, H., Sieber, R. and Kamphenkel, L. (1956) *Chem. Ber.* 1169.
7. Cristopher-Young, J. (1975) *Can. J. Chem.* **53**, 2530.
8. Corey, E. J., Nicholaou, K. C. and Tory, T. (1975) *J. Am. Chem. Soc.* **97**, 2287.
9. Brown, A. G., Smale, T. C., King, T. J., Hasenkamp, R. and Thomson, R. H. (1976) *J. Chem. Soc. Perkin Trans.* 1, 1165.