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THE ISOLATION, STRUCTURE DETERMINATION, AND SYNTHESIS OF PLURIDONE, A NOVEL INSECTICIDE FROM ALOE PLURIDENS

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ABSTRACT: The isolation, structural elucidation, and total synthesis of pluridone (**1**), the novel insecticidal principal from *Aloe pluridens*, are described.

As part of our ongoing program dedicated to the isolation of bioactive substances from natural sources, we examined the roots of the South African plant *Aloe pluridens* (Liliaccae). Crude extracts of this material exhibited insecticidal activity against a variety of mosquito species as well as the Southern army worm (inter alia). Therefore, 220 kg of root material were air-dried, pulverized, and soxlet extracted with solvents of increasing polarity. The bioactivity of the various extracts was monitored by observing lethality of samples against freshly hatched *A. egypti* larvae. Most of the insecticidal activity resided in the petroleum ether fraction and consisted of a residue amounting to .01% dry weight. This was further fractionated by preparatory HPLC on a silica column employing a gradient elution of 10 to 100% ethyl acetate in n-hexane.[1] We ultimately obtained a total 0.25mg of pure material, which was named Pluridone. The compound exhibited the following spectroscopic properties:

IR(KBr) 3060,2960,1713,1695,1546,1292,1225,1167 cm^{-1} ; NMR ($CDCl_3$),360 MHz) δ 7.94(m,2H),7.91(d,1H,J=15.0 Hz),7.62(m,1H), 7.50-(m,2H),5.83(d,1H,J=15.0 Hz), 5.41(s,2H),2.38(s,3H); UV(MeOH) λmax 276 (ε=25,800),247(ε=14,700) nm; MASS SPECTRUM 236.0515 (calcd for $C_{12}H_{12}O_3S$, 236.0507).

The presence of two carbonyls was established by the IR spectrum. An examination of the NMR data indicated a monosubstituted phenyl, an isolated methylene, a gem-disubstitued olefin, and an SMe were incorporated in the structure. The connectivity of these various functionalities as well as the disposition of the remaining oxygen

figure 1. However, because of the unusual substitution pattern present on the olefin, the J=15.0 Hz coupling normally associated with an E olefin was deemed to be insufficient to reliably assign the final structure. Therefore, a total stereospecific synthesis of both the E and Z isomers corresponding to the natural product was deemed necessary to unequivocally define the double bond stereochemistry.

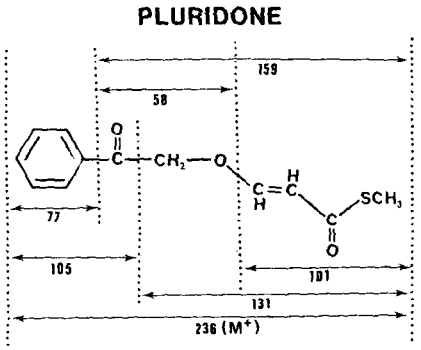
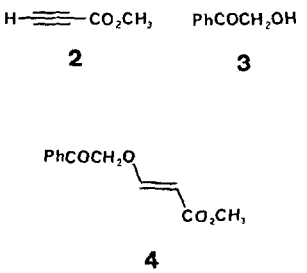
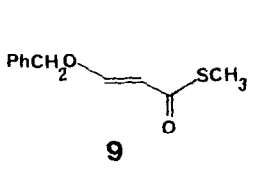
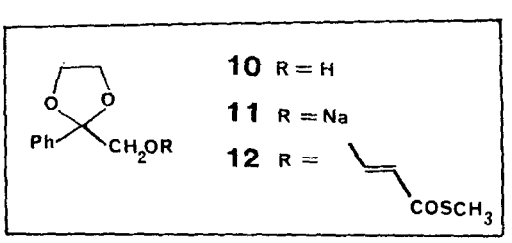


FIGURE 1



In a model study, a Michael reaction was successfully carried out in t-butanol/Et_3N between methyl propiolate (**2**) and hydroxyacetophenone (**3**) to afford the oxa-analog **4** of pluridone, a substance devoid of insecticidal properties. Efforts to prepare the required methyl thiopropiolate from methyl mercaptan and propiolic acid chloride (or various activated esters) were thwarted by a facile double Michael-type addition of methyl mercaptan to the triple bond before the desired acylation took place. This initial complication was turned to our advantage as presented in the scheme. Addition of an excess of the lithium salt of methyl mercaptan to propiolic acid chloride (**5**)[2] afforded the dithioacetal thiolester **6**. Oxidation with two equivalents of m-chloroperoxybenzoic acid yielded the geminal sulfoxide **7** which was converted to the crystalline sulfoxy olefin **8**, mp 70-71° (ether), an "acetylene equivalent" of the originally targeted methylthiopropiolate.[3] The suitability of our sulfoxide intermediate **8** was demonstrated by its smooth addition-elimination reaction with the sodium salt of benzyl alcohol to afford the des-carbonyl analog **9** of pluridone in high yield. The ethylene ketal derivative **10** of hydroxyacetophenone (**3**) was then prepared, and its



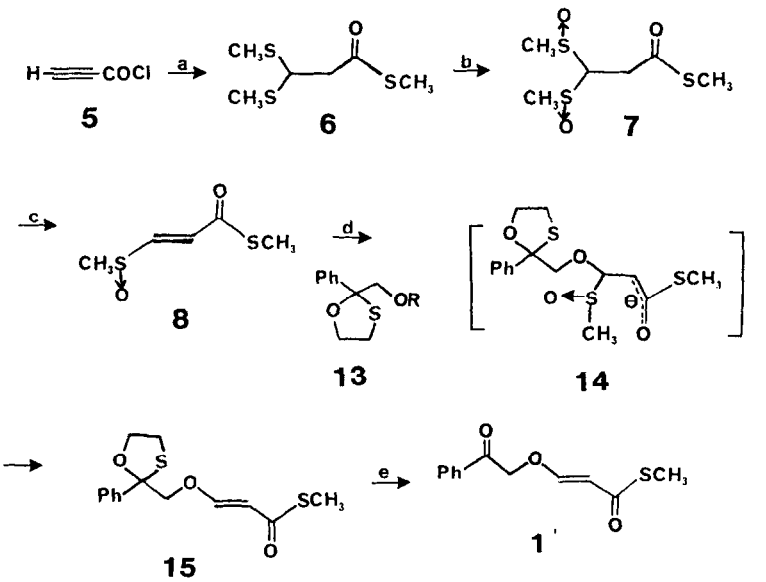


sodium salt **11** was found to couple without complications to the sulfoxide **8**[4]. However, the addition product **12** could not be successfully deprotected owing to the acid-labile enol ether function.

Therefore, the corresponding hemithioketal **13** (R=H) was prepared, and its sodium salt **13** (R=Na) in DMF was treated with the sulfoxide 8 (scheme). The desired product was smoothly produced, presumably via the intemediate anion **14**.[5] The production of only one double bond stereoisomer was observed and was assigned the theoretically preferred E-configuration (J = 15.0 Hz). Deprotection of the ketone function in **15** was now readily accomplished under neutral conditions without disruption of the enol ether to furnish synthetic pluridone, mp 101-102 , (ether/pet. ether), identical in all respects to naturally derived material.

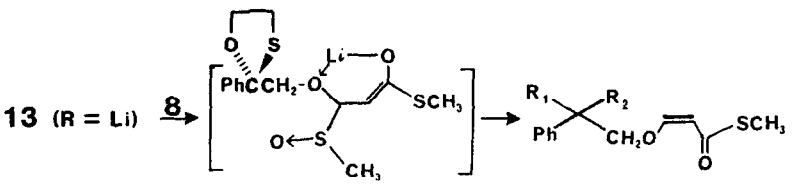
We next turned our attention to the preparation of the Z-isomer of pluridone to provide additional support for our structural assignment of trans olefin stereochemistry. A simple and unexpected solution to this problem was found when the metallic counterion was changed in the Michael addition-elimination step. Reaction of the lithium salt (**13** , R=Li) with the sulfoxide **8** in THF yielded none of

SCHEME



(a) CH_3SLi, THF, -78°C (60%); (b) MCPBA, CH_2Cl_2, 0°C, 1 hr; (c) K_2CO_3, 25°, 4.5 hr (92% from 6); (d) NaH, DMF, 13 (R=H) inverse addition, -45°→25°, 1.5 h, (53%); (e) Chloramine T, CH_3CN/H_2O (1/1), 25°, 1 hr (70%)

the E-isomer **15** but produced exclusively the required Z-isomer **17** in 53% yield. The vicinal olefinic coupling constant in this case was J=12.0 Hz, confirming all our structural assignments. Deprotection of **17** was achieved without a trace of isomerization, affording 81% yield of the Z-isomer **18**, mp 91-92°, (ether, pet. ether), of pluridone. This result was rationalized on the basis of a directing effect of the lithium cation on the configuration of the intermediate enolate as depicted in the chelated species **16**. This serves to stabilize the enolate leading to Z stereochemistry. The absence of such directive effects in the case of the sodium enolate accounts for the sole production of E stereochemistry in that instance.[6]



The obtention of pure samples of both double bond isomers of our target compound completes an unambiguous structure proof of pluridone (**1**), the novel insecticidal principle from *Aloe pluridens*. The implications and generalities of the cation-directing effect observed in the course of these studies is under investigation.

Acknowledgment: We thank the Spectroscopy Division of this Department for their determination of NMR, IR, Mass Spec, and UV data.

REFERENCES AND NOTES

1) The pure insecticide was finally eluted as a single peak on a Zorbax® chromatographic packing CN column (3% EtOH/hexane) and had a retention time of 8.0 min. at a flow rate of 5 ml/min.

2) W.J. Balfour, C.C. Grieg and S. Visaisouk, J. Org. Chem., 1974, 39, 725.

3) For the synthesis of a β-sulfoxy acrylate see: S. Danishefsky, T. Harayama and R.K. Singh, J. Am. Chem. Soc., 1974, 101, 7008.

4) The direct addition of hydroxyacetophenone (**3**) to **8** was not successful using either mild or strong base.

5) The use of THF also led to the trans product but in lower yield.

6) Alternatively, this directing effect may arise from differences in metalation at carbon vs oxygen in the two enolates.

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