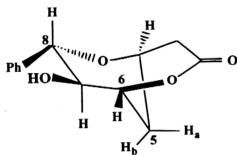


## ABSTRACT

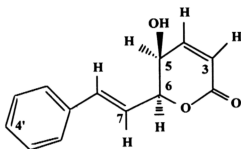
Chemical and cytotoxicity studies were made on twelve plant species of the genus *Goniothalamus* and one plant species each of the genera *Disepalum* and *Mezzetia* (Annonaceae). These plants were mostly used as insect repellents by the Iban community in Sarawak, East Malaysia.

The chemical investigations on the plant species covered larvicidal principles such as annonaceous acetogenins, styrylpyrones, flavonoids, alkaloids and essential oils (mainly sesquiterpenes). Detail studies were carried out on four *Goniothalamus* species (*G. andersonii*, *G. dolichocarpus*, *G. malayanus* and *G. velutinus*), *Disepalum anomalum* and *Mezzetia umbellata*. Natural products were isolated using chromatographic techniques and identified using spectroscopic methods (including 2-D NMR). Eight other *Goniothalamus* species (*G. ridleyi*, *G. macrophyllus*, *G. uvarioides*, *G. macranii*, *G. sinclairinius*, *G. gigantifolius*, *G. umbrosus* and *G. montanus*) were screened for selected larvicidal principles using thin layer chromatography, gas chromatography and gas chromatography-mass spectrometry.

The four *Goniothalamus* species which were studied in detail provided styrylpyrone derivatives (+)-goniothalamine, (+)-goniothalamine epoxide, (+)-goniodiol, (+)-goniothalenol, two new natural products (-)-iso-5-deoxygonioppyrone and (+)-5 $\beta$ -hydroxygoniothalamine and essential oils which mainly contained a mixture of sesquiterpenes. The two new natural products were characterised spectroscopically.



**(-)-Iso-5-deoxygoniopyrpyrone**



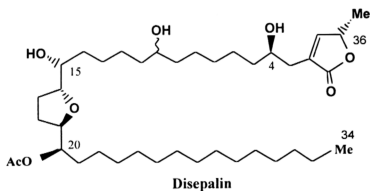
**(+)-5β-Hydroxygoniothalamine**

The structure assigned for (-)-iso-5-deoxygoniopyrpyrone is consistent with a stereoisomer of the known (+)-5-deoxygoniopyrpyrone previously isolated from *G. giganteus*. NOE difference spectra of the acetylated compound show NOE enhancement between the phenyl protons and H-7 and H-8, these effects suggesting that H-7 and the phenyl group are in close proximity. For an assumed preferential average conformation of the phenyl group in a quasi-equatorial position H-7 and H-8 will assume a transoid geometry. A coupling constant value of 10.4 Hz between H-7 and H-8 is in agreement of an almost antiparallel geometry of the two hydrogens. In contrast, a singlet is reported for H-8 in the compound (+)-5-deoxygoniopyrpyrone due to an almost orthogonal H-7 - H-8 orientation. This new compound was synthesised from the *erythro*-(6*R*, 7*S*, 8*S*)-goniodiol using a catalytic amount of DBU in THF.

The structure of (+)-5β-hydroxygoniothalamine was assigned using  $^1\text{H}$ - $^1\text{H}$  COSY,  $^1\text{H}$ - $^{13}\text{C}$  HETCOR and NOE difference spectra. A coupling constant value of 2.9 Hz between H-5 and H-6 indicates a dihedral angle of approximately  $50^\circ$ . Moreover, the acetate derivative also shows a similar  $J_{5,6}$  coupling of 2.9 Hz. There is no NOE enhancement between H-7 and H-5. This new compound and its diastereomer (+)-5α-hydroxygoniothalamine were synthesised by reacting

goniothalamine with selenium dioxide and refluxing in dioxane for three and a half hours.

*Goniothalamus dolichocarpus* furnished two very cytotoxic flavonoids naringenin and pinocembrin. The four *Goniothalamus* species also provided very cytotoxic annonaceous acetogenins, annonacin and goniothalamycin along with the phenanthrene lactam, aristolactam BII and the dioxoaporphine ouregidione. Annonacin and aristolactam BII were also present in *Mezzetia umbellata*. *Disepalum anomalum* gave a common oxoaporphine liriodenine and a new annonaceous C-39 acetogenin was found for the first time in this genus. The new natural product disepalin has a mono-THF ring with an adjacent acetate group at the C-20 position. The structural assignments of this compound were determined using 2D-NMR (HMBC, COSY, H-C HETCOR, NOESY), NOE difference spectra and mass spectrometric techniques. Stereochemical assignments were by correlations with reported NMR data in addition to the new NMR data obtained.



The eight other *Goniothalamus* species were also found to have (+)-goniothalamine, (+)-goniothalamine epoxide, (+)-goniothalenol, (+)-goniodiol, (+)-

goniodiol diacetate and the complex mixture of essential oils containing sesquiterpenes. Other natural products such as (-)-iso-5-deoxygonioppyrone, naringenin and pinocembrin, aristolactam BII and ouregidione were also found to be present in some of these plants. Annonacin was detected only in *Goniiothalamus macranii*. The various styrylpyrones, alkaloids, flavonoids and acetogenins isolated were tested on the larvae of *Aedes aegypti* using the WHO (1981a) standard procedures with slight modifications. The pure compounds tested showed moderate to good larvicidal activity, the most cytotoxic compounds being naringenin and annonacin (LC<sub>50</sub> values 3.7 and 9.5 µg/ml respectively).

Crude stem bark extracts of all twelve *Goniiothalamus* species, *Disepalum anomalum* and *Mezzetia umbellata* were screened for their larvicidal activity against the larvae of *Aedes aegypti*. Most crude hexane extracts were moderately cytotoxic except for that from *G. gigantifolius*, while that of *Disepalum anomalum* and *Mezzetia umbellata* mildly cytotoxic. The crude ethanol extracts of *G. sinclairinus* and *G. montanus* were not cytotoxic to the larvae of *Aedes aegypti*, while the rest of the extracts showed larvicidal activity. The mosquito larvae of *Aedes aegypti* were susceptible to the methanol-soluble fractions partitioned from the ethanol extracts and good activity was found. Preliminary *in vitro* cytotoxicity screening against P388 cell lines was also carried out on the crude extracts and some bioactivity was detected which corroborates the presence of bioactive acetogenins and some of the styrylpyrone derivatives.