# The Structure of Eurycomalactone

By LE-VAN-THOI and NGUYEN-NGOC-SUONG,
(*Faculty of Sciences, University of Saigon, Viet-Nam*)
and PIERRE CRABBÉ*
(*Research Laboratories, Syntex, S.A., Mexico City, Mexico*)

*Eurycoma longifolia* Jack, a bush common in Viet-Nam, belongs to the family Simaroubaceae.[1] The extracts of the bark of this tree, called "cây bá binh" ("tree which cures hundreds of diseases") are used in the Vietnamese pharmacopoeia for their antiamoebic and antidysenteric properties.

Investigation of the chemical constituents of *Eurycoma longifolia* led to the isolation of a bitter principle named eurycomalactone, besides $\beta$-sitosterol, campesterol, and 2,6-dimethoxybenzoquinone. Eurycomalactone (**1**), m.p. 268—270°; $[\alpha]_D$ + 100°†, which corresponds to $C_{19}H_{24}O_6$ ($M^+$ 348), forms a mono- and a bis-2,4-dinitrophenylhydrazone and possesses two readily acetylated hydroxy-groups, a conjugated ketone (1679, 1621 cm.$^{-1}$; $\lambda_{max.}$ 241 nm., log $\epsilon$ 3·85), which is homoconjugated with a saturated carbonyl (1709 cm.$^{-1}$; $\lambda_{max.}$ 290 nm., log $\epsilon$ 2·24), and a $\gamma$-lactone grouping (1770 cm.$^{-1}$). Four methyl groups are identified by n.m.r., namely one secondary (1·16 p.p.m., d., $J$ 7 Hz.), one vinylic (1·94 p.p.m.) and two tertiary (1·25 and 1·55 p.p.m.).

Catalytic hydrogenation (Pd–C) of (**1**) gives dihydroeurycomalactone (**2**), m.p. 247—248°; $[\alpha]_D$ + 23° (dioxan), whose new secondary methyl signal appears as a doublet at 0·95 p.p.m. ($J$ 7 Hz.).

The saturated keto-group of (**1**) is located at C-6, since it is easily converted by acetic anhydride–pyridine treatment at 90° into the enol acetate (**3**), m.p. 248°; $[\alpha]_D$ −95°; 1792, 1742 cm.$^{-1}$; $\lambda_{max.}$ 285 nm., log $\epsilon$ 4·37.

Chromic acid oxidation[2] of dihydroeurycomalactone (**2**) provides the tetra-ketone (**4**a), m.p. 275°; $[\alpha]_D$ −57°, thus showing the secondary nature of both hydroxy-groups. Clemmensen reduction of (**2**) gives the monohydroxy-derivative (**5**a), m.p. 220°; $[\alpha]_D$ + 40°, which indicates the

† All new compounds had the correct composition as evidenced by microanalysis. The spectral data supported the structures assigned. Unless otherwise stated, all rotations were measured for chloroform solutions, i.r. spectra were determined in KBr discs, and n.m.r. spectra with an A-60 spectrometer in $CDCl_3$ containing $Me_4Si$ as an internal reference.

hydroxy-group at C-12 to be sterically hindered (see below).

Acetylation and oxidation of the hydroxy-group of (**5a**) gives the acetate (**5b**), m.p. 135°; $[\alpha]_D$ + 30°; $M^+$ 306, and the ketone (**5c**), m.p. 198—200°; $[\alpha]_D$ − 75°, respectively.

The α-ketol grouping in ring A of (**1**), a feature common to many bitter principles of this series,[1,3] is easily detected by i.r. spectroscopy[4] and confirmed by bismuth oxide oxidation[5] of dihydroeurycomalactone (**2**), which affords the triketone (**4b**) (amorph., 3520, 1773, 1724, and 1706 cm.$^{-1}$). Moreover, zinc–acetic acid treatment[6] of (**2**) provides the monohydroxy-diketo-lactone (**4c**), m.p. 262°; $[\alpha]_D$ + 11°.

The location of an angular methyl at C-10 is shown by sodium borohydride reduction of (**1**) giving a tetraol, which, by methyl migration and aromatization under acid treatment, affords eurycomol (**6a**), m.p. 265°; $[\alpha]_D$ + 14°; $\lambda_{max.}$ 224, 270, 279, and 308 nm.; log ε 4·08, 2·68, 2·57, and 1·55. The monoacetate of eurycomol (**6b**), m.p. 257—260°; $[\alpha]_D$ + 40°, is typified by an n.m.r. signal corresponding to two aromatic protons (*ca.* 6·98 p.p.m.) and two aromatic methyls (2·31 and 2·67 p.p.m.). Such a dehydration accompanied by methyl migration and aromatization has ample precedent in this series of natural products.[7]

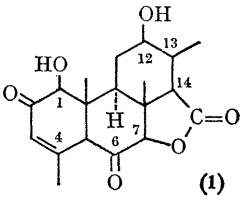
The position of the γ-lactone in eurycomalactone (**1**) and its derivatives was assigned on the basis of the following experiments. On the one hand, when eurycomol (**6a**) is treated in hydrogen atmosphere with platinum in acetic acid, deoxyeurycomol (**6c**), m.p. 215°; $[\alpha]_D$ + 25°, is formed. On the other hand, (**6a**) when reduced with lithium aluminium hydride gives the tetraol (**7**), (amorph., 3560 and 1650 cm.$^{-1}$), which is readily oxidized with periodic acid, thus showing the presence of an α-glycol group in (**7**).

By analogy with other bitter principles of the family Simaroubaceae,[1,3,8] the second tertiary methyl is situated at C-8, whereas the secondary methyl group of (**1**) is located at C-13.

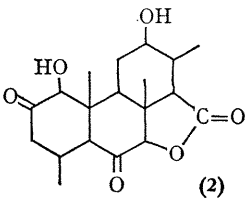
The c.d. curve of eurycomalactone (**1**) is reminiscent of that of chaparrinone[9,10] between 700 and 350 nm.; moreover, a marked negative Cotton effect which appears around 300 nm. is indicative[10] of the homoconjugation between the unsaturated ketone of ring A and the 6-keto-chromophore.

Dihydroeurycomalactone (**2**) exhibits a double-humped c.d. curve with a negative maximum at 304 nm. ($[\theta]$ = −2780) and a positive maximum at 275 nm. ($[\theta]$ = + 2450), probably indicative of the 5α-H configuration. A strong negative Cotton effect would be expected[10] for the 5β-stereochemistry.

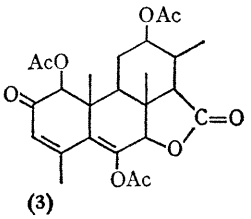
Oxidation of the acetoxy-alcohol (**6b**), formed by mild acetylation of (**6a**), gives the ketone (**6d**), m.p. 225°; $[\theta]_{295}$ = − 3930], which is recovered unchanged when treated with boiling pyridine.[9] Since 9α-H-11-keto-derivatives of this type are known[9] to isomerize readily to the 9β-compounds (to suppress the 1-methyl–11-keto-interactions), this seems to exclude the location of the carbonyl at C-11, thus supporting structure (**1**) suggested for eurycomalactone on the basis of data presently available. Further work is contemplated when conditions allow the collection of more starting material.



(1)



(2)



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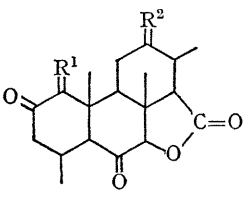
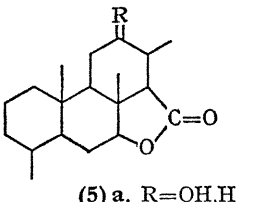
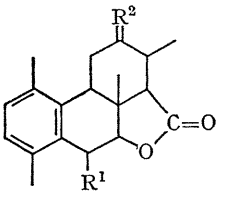


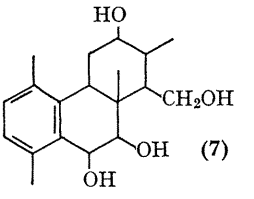

(4) **a**, $R^1$=$R^2$=O
**b**, $R^1$=O, $R^2$=OH,H
**c**, $R^1$=$H_2$, $R^2$=OH,H




(5) **a**, R=OH,H
**b**, R=OAc,H
**c**, R=O




(6) **a**, $R^1$=OH, $R^2$=OH,H
**b**, $R^1$=OAc, $R^2$=OH,H
**c**, $R^1$=H, $R^2$=OH,H
**d**, $R^1$=OAc, $R^2$=O



(7)

Eurycomalactone constitutes the first instance in the Simaroubaceae family where a carbonyl has been observed at C-6 and a γ-lactone between positions 14 and 7.

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