Tetrahedron Letters No.46, pp. 4803-4806, 1968. Pergamon Press. Printed in Great Britain.

THE STRUCTURE OF NEOANDROGRAPHOLIDE - A DITERPENE GLUCOSIDE FROM ANDROGRAPHIS PANICULATA NEES

W. R. Chan, D.R. Taylor and C.R. Willis
Chemistry Department, University of the West Indies, Kingston 7, Jamaica
H.-W. Fehlhaber
Organisch-Chemisches Institut, Universität Bonn.

(Received in USA 3 July 1968; received in UK for publication 16 August 1968)

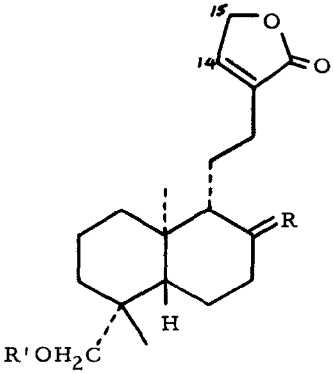
The isolation of neoandrographolide from Andrographis paniculata Nees was reported in 1952 by Kleipool.[1] He advanced the molecular formula $C_{23}H_{38}O_8$, deduced the presence of an α,β-unsaturated γ-lactone from solubility experiments and a positive Legal test and prepared an acetate, m.p. 157°, which he considered to be an anhydro-tetraacetate. We have reexamined this problem and now propose the structure (I) for neoandrographolide.

Neoandrographolide (I), $C_{26}H_{40}O_8$, has m.p. 167-168°, $[\alpha]_D$ -48° (pyridine), $\lambda_{max.}$ 205nm. (ε 10,400), $\nu_{max.}$ 3290, 1748, 1639, 900 cm.$^{-1}$ Acetylation with acetic anhydride and pyridine afforded the normal acetate (II), $C_{34}H_{48}O_{12}$, m.p. 155-157°, $\nu_{max.}$ 1742, 1639, 909 cm.$^{-1}$ which is reconverted to the parent alcohol by potassium bicarbonate in aqueous methanol. The n.m.r. spectrum (δ values) of the acetate (II) showed, inter alia, signals for two tertiary C-methyls (0.67, 0.92) and four acetates [2.00(3H), 2.02(6H), 2.07(3H)]. A narrow multiplet at 7.10 ($W_{\frac{1}{2}}$=4 c./sec.) can be assigned to the β-proton of the α,β-unsaturated lactone system. The small coupling constant indicates that the double bond is endocyclic.

Reaction of the acetate (II) with osmium tetroxide gave the diol (III), $C_{34}H_{50}O_{14}$, m.p. 143-145°, $\lambda_{max.}$ 207 nm. (ε 8000), $\nu_{max.}$ 3333, 1745 cm.$^{-1}$ which on periodate oxidation afforded formaldehyde and the norketone (IV), $C_{33}H_{46}O_{13}$, *M* (mass spectrum) 650, m.p. 145-147° (dec.), $\lambda_{max.}$ 207 nm. (ε 8950), $\nu_{max.}$ 1754-1739, 1701 cm.$^{-1}$, n.m.r.: two tertiary methyls (0.70, 1.02), four acetates [2.00, 2.02(6H), 2.07] and the β-proton of the α,β-unsaturated lactone (7.16, $W_{\frac{1}{2}}$=4 c./sec.). The C.D. curve[2] of (IV) [$\Delta\varepsilon_{max.}$ +2.74 at 293 nm., inflexions at 300 nm. ($\Delta\varepsilon$ +2.64) and 310 nm. ($\Delta\varepsilon$ +1.56)] which was virtually superimposable on that of the andrographolide derivative (V)[3] [$\Delta\varepsilon_{max.}$ +2.67 at 289 nm., inflexions at 297 nm. ($\Delta\varepsilon$ +2.41) and 305 nm. ($\Delta\varepsilon$ +1.39)] locates the ketone and indicates an identity in the relative and absolute configurations of the decalin systems.

Treatment of neoandrographolide (I) with hydrochloric acid in ethanol furnished glucose together with the *iso* aglucone (VI), $C_{20}H_{30}O_3$, *M* (mass spectrum) 318, m.p. 121-123°. Acetylation of (VI) gave the monoacetate (VII), *M* (mass spectrum) 360, m.p. 111-113°, $[\alpha]_D$ -61°, also obtained from (I) by treatment with acetic acid and concentrated sulphuric acid. The n.m.r. spectrum of (VII) showed two tertiary methyls (0.97, 6H), a methyl attached to a double bond (1.62), an acetate (2.05), an acetoxymethyl as an AB quartet (4.10, 2H, J_{AB}=11.5 c./sec , δ_{AB}=19.6 c./sec.), a doublet (4.78, 2H, J=1.3 c./sec., H-15) and a narrow multiplet (7.17, $W_{\frac{1}{2}}$=4 c./sec., H-14). The shift of the acetoxymethyl group is in good agreement with that found in *o*-methyl podocarpyl acetate[4] and in andrographolide derivatives[3] where this group is axial.

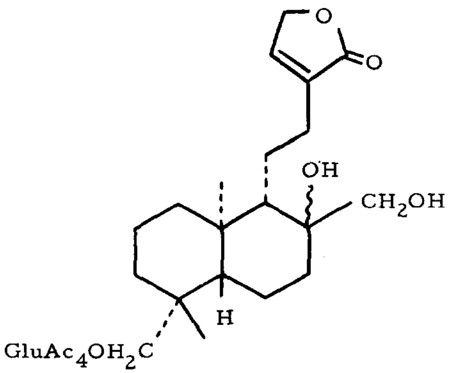
The mass spectrum of the norketone (IV) shows a surprisingly strong molecular ion peak in addition to fragments at m/e 331, 271, 169, 145, 115 and 109 characteristic of tetraacetylhexoses.[5] Other fragmentations of (IV) and (VII) are in accord with the assigned structures and will be detailed in the full paper.



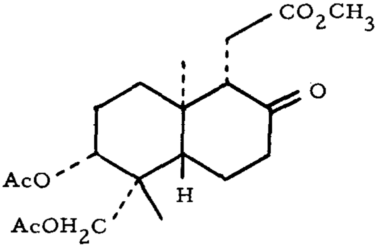
(I) R = CH_2, R' = Glu

(II) R = CH_2, R' = GluAc$_4$

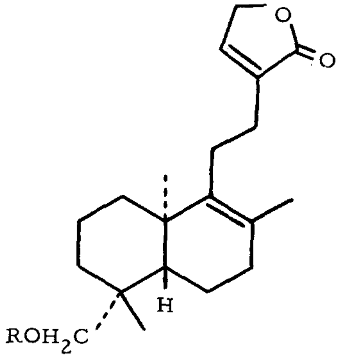
(IV) R = O , R' = GluAc$_4$



(III)

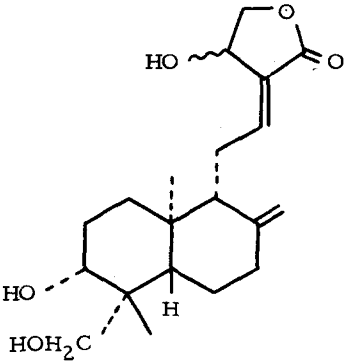


(V)



(VI) R = H

(VII) R = Ac



(VIII)

The evidence presented indicates a skeletal structure similar to andrographolide (VIII)[3] found in the same plant and taking this into account it leads to the structure (I) for neoandrographolide.

References

1. R.J.C. Kleipool, Nature, 69, 33 (1952).
2. Measured by Dr. G. Snatzke, Universität Bonn, whom we thank.
3. M.P. Cava, W.R. Chan, R.P. Stein and C.R. Willis, Tetrahedron, 21, 2617 (1965).
4. E. Wenkert and P. Beak, Tetrahedron Letters, 358 (1961)
5. K. Heyns, H.F. Grützmacher, H. Scharmann and D. Müller, Fortschr. chem. Forsch., 5, 448 (1966); H. Budzikiewicz, C. Djerassi and D.H. Williams, Structure Elucidation of Natural Products by Mass Spectrometry, Vol. II, Holden-Day, Inc., San Francisco (1964), p. 203; I.A. Pearl and S.F. Darling, Phytochem., 7, 831, (1968).