Phytochemistry, 1978, Vol 17, pp. 1609–1612. © Pergamon Press Ltd Printed in England 0031-9422/78/0901-1609 $02.00/0

MUELLITOL, A NOVEL TRIALKENYL INOSITOL FROM *EVODIELLA MUELLERI*

Hussan Fazldeen*, Mervyn P. Hegarty† and Francis N. Lahey
Chemistry Department, University of Queensland, Brisbane, Australia

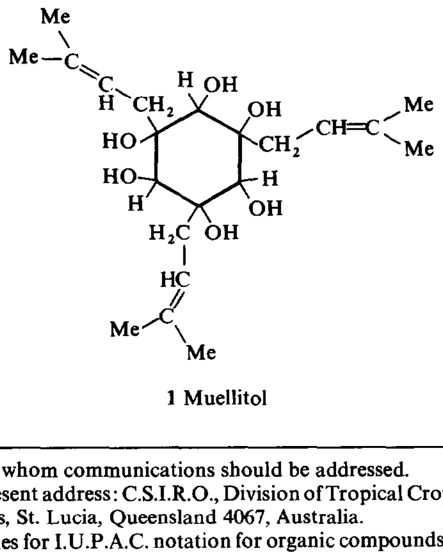
(*Received* 27 *February* 1978)

Key Word Index—*Evodiella muelleri*; Rutaceae; muellitol; new *C*-alkenylinositol; structural determination.

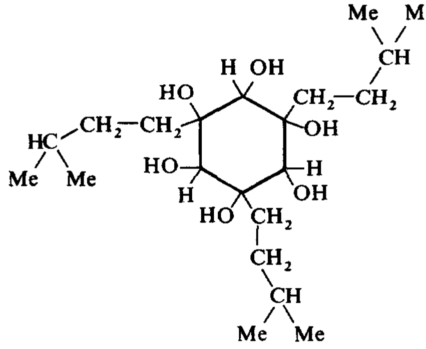
Abstract—Muellitol has been isolated from the leaves of *Evodiella muelleri* and the structure established as 1,3,5-tri-(3-methyl-2-butenyl)cyclohexane-*r*-1-*t*-2-*c*-3-*t*-4-*c*-5-*t*-6-hexol. Chemical and spectroscopic examination of the compound and its derivatives showed it to be conformationally similar to scyllitol. This is the first report of the natural occurrence of a triprenylinositol.

INTRODUCTION

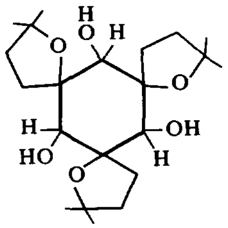
The only naturally occurring *C*-alkyl inositols so far reported are the *C*-methyl inositols which are found in lower invertebrates and sea weed [1–6]. This paper details the characterization of a unique triprenyl inositol from the leaves of *Evodiella muelleri* (Engle) van der Linden (syn. *Acronychia muelleri* W. D. Francis). The plant is a Queensland rain-forest subumberal shrub growing to a height of *ca* 5 m. The compound we wish to describe is 1,3,5-tri-(3-methyl-2-butenyl)-cyclohexane-*r*-1-*t*-2-*c*-3-*t*-4-*c*-5-*t*-6-hexol‡ but since it is a derivative of scyllitol it has been named 'Muellitol' (**1**). The high state of symmetry of the molecule renders it optically inactive. The two main derivatives in the proof of its structure are hexahydromuellitol [1,3,5-tri(3-methylbutyl)cyclohexane-*r*-1-*t*-2-*c*-3-*t*-4-*c*-5-*t*-6-hexol] (**2**) and isomuellitol [1,3,5-trispiro-(5,5-dimethyltetrahydrofuranyl)cyclohexane-*r*-2-*c*-4-*c*-6-triol] (**3**).



1 Muellitol



2 Hexahydromuellitol



3 Isomuellitol

RESULTS AND DISCUSSION

The compound **1** was isolated as a precipitate from a benzene extract of the air dried leaves of *Evodiella muelleri*. On purification by reprecipitation from methanolic NaOH with CO_2, a mp of 127–128° was obtained. The MS indicated a M^+ at *m/e* 384 ($C_{21}H_{36}O_6$). The main features of the IR spectrum were a strong broad band for ν_{O-H} 3345 cm^{-1}, $\nu_{C=C}$ 1670 cm^{-1} and for the geminal dimethyl groups a strong doublet at ν_{CH_3} 1390 cm^{-1} and 1375 cm^{-1}. The PMR spectrum included two separate peaks at δ 1.71 (9H) and δ 1.81 (9H) for the three sets of geminal dimethyl groups, a doublet ($J = 8$ Hz) at δ 2.69

---

* To whom communications should be addressed.

† Present address: C.S.I.R.O., Division of Tropical Crops and Pastures, St. Lucia, Queensland 4067, Australia.

‡ Rules for I.U.P.A.C. notation for organic compounds: Rule 10.4 p.75 (1961) Longman.

(6H) a pair of coupled doublets ($J = 7$ Hz) at δ 2.95 (3H) and δ 3.69 (3H), a singlet at δ 3.55 (3H) and a triplet ($J = 8$ Hz) at δ 5.46 (3H). The triplet was broad and shouldered indicating the weak coupling between the vinyl protons and the geminal dimethyls. The UV spectrum indicated λ_{max} 190 nm (ε 21 150) which is in agreement with the presence of more than one tri-substituted double bond. Since the Zerewitinoff determination of active hydrogen revealed six such atoms per molecule and the IR spectrum showed neither a carbonyl nor a carboxyl group, these were assigned to alcoholic hydroxyl groups. The unsaturation was quantitatively determined by the Kuhn–Roth method of ozonolysis and the acetone yield indicated 2.9 isopropylidene units per molecule, hence three double bonds.

By catalytic hydrogenation **2** mp 139–140° was obtained. This compound showed no unsaturation. A M^+ at m/e 390 is in agreement with the uptake of three moles of hydrogen for a molecular formula of $C_{21}H_{42}O_6$. The IR spectrum revealed a broad strong band at 3380 cm^{-1} for the inter-molecular hydrogen-bonded hydroxyl groups. The band at $\nu_{C=C}$ 1670 cm^{-1} in the original spectrum had disappeared. The PMR spectrum indicated that the equivalent 18 protons of the three sets of geminal dimethyl groups were a doublet ($J = 6$ Hz) δ 0.92 while the methylene protons were represented as a broad multiplet centred at δ 1.45 (12H). The newly introduced methine protons were similarly shown as a broad multiplet centred at δ 1.78 (3H). Two sets of doublets were assigned to the secondary hydroxyl protons δ 2.94 (3H) ($J = 7$ Hz) and the carbinol protons δ 3.6 (3H) ($J = 7$ Hz). The tertiary hydroxyl protons were identified as a singlet at δ 4.13 (3H). In an exchange experiment using DCl in D_2O the hydroxyl peaks were smeared out and the carbinol doublet collapsed to a single peak at δ 3.6.

On treating **1** with conc HCl for a short time then isolating the product by diluting and neutralizing the solution with Na_2CO_3 a fawn coloured powder was collected. The material after crystallization was a white finely crystalline substance with mp 201–202°, compound **3**. In the IR spectrum ν_{O-H} 3598 cm^{-1} appeared as a sharp strong absorption. This is either due to free hydroxyls or intramolecular H-bonding. There was an absence of $\nu_{C=C}$ 1670 cm^{-1} and an appearance of a ν_{C-O-C} 1150 cm^{-1} and 1135 cm^{-1} indicating the formation of an ether.

The PMR spectrum of **3** showed the geminal dimethyl protons as a singlet δ 1.32 (18H) and the methylenes also appeared as a singlet δ 1.98 (12H). The secondary hydroxyl protons were seen as a doublet δ 2.12 (3H) ($J = 3.6$ Hz) and the coupled carbinol protons doublet was at δ 3.55 (3H) ($J = 3.6$ Hz). There was no resonance corresponding to the tertiary hydroxyl protons observed in **1** and **2**. When deuterium exchange experiments were carried out the doublet at δ 2.12 was smeared out and the doublet at δ 3.55 collapsed to a singlet at δ 3.54. The MS gave M^+ m/e 384 so isomerization took place causing the side-chains to cyclize onto the tertiary hydroxyls forming spiro-tetrahydrofuran rings (Fig. 1).

The dramatic change in the hydroxyl bands from the IR spectra of **1** and **2** to that of **3** indicated a conformational change or a change in the bond angles of the ring carbons preventing the close packing of several molecules by strong intermolecular H-bonding.

Compound **2** was acetylated under relatively mild

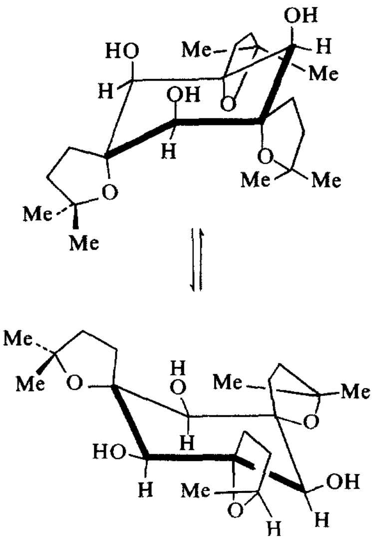
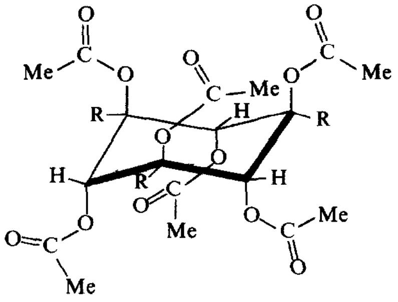
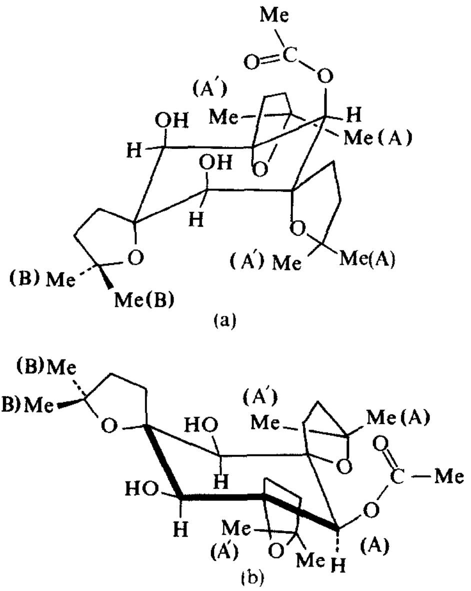


Fig. 1.



R = $CH_2CH_2CHMe_2$

Fig. 2.



(a)

(b)

Fig. 3.

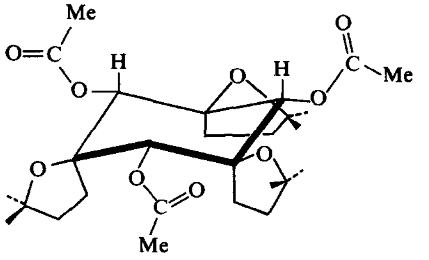


Fig. 4.

conditions (Py catalyst) in an attempt to distinguish between different orientations of the hydroxyl groups [7]. No acetylated product was obtained so a more drastic procedure was adopted ($ZnCl_2$ catalyst) and this produced a hexaacetate (Fig. 2).

Compound 3 was subjected to both methods of acetylation. In the first a monoacetate was obtained and with the second a triacetate was produced. The six hydroxyl groups in **2** were obviously all axial and required vigorous conditions to achieve acetylation. The monoacetylation of **3** could have been achieved in two ways. With the formation of the spiro-tetrahydrofuran rings the three remaining secondary hydroxyl groups were drawn further apart as indicated by the change in the IR spectrum. This meant that the strong intermolecular H-bonding no longer existed and free access for acetylation was made. Once one group was acetylated then steric hindrance would prevent ready acetylation of the other two groups (Fig. 3). In the second case all three secondary groups were acetylated and the resulting conformation would allow the acetate units to be equatorial (Fig. 4).

The PMR spectrum of the monoacetate of **3** revealed some complex changes from the original simple spectrum. The geminal dimethyl groups were no longer isochronous. They appeared as two separate peaks, one at δ 1.15 and the other, a bifurcated peak, at δ 1.29. The splitting of the peak at δ 1.29 was caused by the effect of the acetoxy groups on the adjacent pairs of geminal dimethyls. The proximal methyls (A) experienced a slightly different environment from the distal methyls (A′) while the most distant geminal dimethyl group (B) was represented by the δ 1.15 resonance. The PMR spectrum of the triacetate of **3** (Fig. 4) showed a reversion to a simple single geminal dimethyl peak δ 1.13.

Although the chemical shifts of the acetate protons [8] in the mono- and triacetates of **3** do not clearly indicate if they are axial or equatorial these groups must be considered to have the same orientation as the chemical shifts appear at δ 2.15 and δ 2.13 respectively. The acetate protons of the hexaacetate of **2** resonate as two environmentally different groups at δ 2.03 and δ 2.08.

These chemical shifts are sufficiently close to show that all three compounds have the same conformation and, as **2** and its hexaacetate must have axial hydroxyl and acetoxy groups respectively, then the two derivatives of **3** would be expected to have axial acetates. However if the chemical shifts of the ring hydrogens are considered then the difference is clear. The hexaacetate of **2** shows a PMR chemical shift for such protons at δ 6.4 while the PMR of the monoacetate and triacetate of **3** show chemical shifts at δ 5.09 and δ 5.3 respectively. This clearly shows that the protons under consideration are equatorial in the first example and axial in the other two cases. The conformation of the monoacetate and the triacetate of **3** are as shown in Figs. 3(b) and 4.

The conformation of **1** is therefore the same as **2** which contains six axial hydroxyl groups. This unique conformation of the all *trans* hydroxyl groups is similar to that present in scyllitol, but favouring the axial orientation due to the large hydrocarbon side-chains. This conformation ideally lends itself to orthophosphate and tridentate borate ester formations. The preparation and properties of these compounds will be reported in a subsequent paper.

EXPERIMENTAL

The IR spectra were taken as KBr discs and in CCl_4. The PMR spectra were taken in $CDCl_3$ with TMS as internal standard and CCl_4. All mps were determined on a Mettler F.P.I. and Hitachi recorder attachment. Microanalyses were carried out by the University of Queensland, Chemistry Department Microanalytical service.

Isolation of compound (**1**). Most of the muellitol used in this investigation was isolated from a large sample of leaves of *Evodiella muelleri* (Engle) van der Linden collected and identified by Mr. V. K. Moriarty, then field botanist, C.S.I.R.O., Division of Applied Chemistry. A voucher specimen (SN 8694, May 1969) is lodged in the Herbarium Australiensis, Canberra. Air dried leaves of *E. muelleri* (4 kg) were extracted with petrol, dried and extracted with C_6H_6 (8 l.) in a large Soxhlet. The petrol solution was concentrated and stored in the refrigerator but no crystalline material was obtained from it. The C_6H_6 extract was passed through an alumina column (10 × 40 cm) and the alumina was washed with warm C_6H_6.

The total vol. of C_6H_6 soln including the washings, which was free from the majority of fats and waxes, was then concentrated to *ca* 1.5 l. below 40° and stored in the refrigerator for several days. The concentrate was then filtered and the solid was washed with chilled C_6H_6. This gave a pale green crystalline solid (70 g) which was impure **1**. The concentrated mother liquor contains the lignan (+)-asarinin which was isolated and structurally identified by Sutherland and Davenport [9].

The substance was taken up in 420 ml MeOH. H_2O was added dropwise to the boiling soln which was set up with a reflux condenser. 50 g NaOH was then added and allowed to dissolve. Additional H_2O (1000 ml) was allowed to run in slowly. **1** began to precipitate and on the addition of CO_2 more compound pptd. The filtered product was first vacuum dried at room temp. and then crystallized from hot C_6H_6 as plates, mp 127–128° (64 g, 1.6%).

To ascertain that **1** was a true extractant and not an artifact of the NaOH treatment, a sample of the pale green crude product was treated with decolourizing charcoal in C_6H_6 and crystallized × 3. The final product was needles mp 127°. The analytical figures were identical with those obtained for the material isolated by the previously described method. (Found: C, 65.74; H, 9.43; $C_{21}H_{36}O_6$ requires: C, 65.59; H, 9.44%).

Preparation of (**2**). **1** was hydrogenated in EtOH in the presence of Pd/C and the product crystallized from C_6H_6 and CCl_4 with mp 140°. (Found: C, 64.70; H, 10.88; $C_{21}H_{42}O_6$ requires: C, 64.58; H, 10.84%). Acetylation of **2** by heating at 100° for 1 hr with $Ac_2O/ZnCl_2$ gave the hexaacetate, mp 230–231.5°. (Found: C, 61.43; H, 8.46; $C_{33}H_{54}O_{12}$ requires: C, 61.66, H, 8.47%). Acetyl estimation (methanolic NaOH) = 40.7% which, when using MW 642.76, gives acetyl units per molecule = 6.2.

Preparation of (**3**). 1 g **1** was treated with 25 ml conc HCl, 150 ml water added and heated for 15 min at 100°. After neutralizing with solid Na_2CO_3, the product was crystallized from petrol (bp 40–60°)–EtOAc with mp 201.4°. (Found: C, 65.59; H, 9.43; $H_{21}H_{36}O_6$ requires: C, 65.59; H, 9.44%). **3** was acetylated with Ac_2O/Py at 100° for 1 hr to yield the monoacetate mp 210° from EtOH. (Found: C, 64.67; H, 9.02; $C_{23}H_{38}O_7$

requires: C, 64.76; H, 8.98%). Acetyl estimation (methanolic NaOH) = 8.6% using MW 426.53, the acetyl units per molecule = 0.85. Significant absorptions in the IR spectrum taken as a KBr disc, were ν_{O-H} 3625 cm^{-1} which was strong and considered to be free while ν_{O-H} 3565 cm^{-1} of medium intensity was bonded. The carbonyl frequency was a strong absorption at 1730 cm^{-1}. The δ_s —CH_3 for the gem-dimethyl groups showed a doublet at 1390 cm^{-1} and 1370 cm^{-1}. The C-H vibration at 1240 cm^{-1} appeared much stronger than the 1465 cm^{-1} band and this may be interpreted as containing the extra methyl of the acetate group. The PMR spectral data showed the geminal dimethyl groups as a single peak at δ 1.15 (6H) and a bifurcated peak at 1.28–1.31 ppm (12H). The methylene protons appeared as a broad multiplet between δ 1.90 and δ 2.13 (12H). The secondary hydroxyl protons were a doublet at δ 2.02 and δ 2.09 (2H) (J = 4 Hz) but hidden under the methylene band. The methyl protons of the acetate unit showed as a singlet at δ 2.15 (3H). The carbinol protons were a doublet at δ 3.65 and δ 3.72 (J = 4 Hz) (2H) while the single proton attached to the carbon carrying the acetate group was a singlet at δ 5.09. The spectrum was run again in CCl_4 with TMS an internal reference. All the peak positions were slightly altered but the change was sufficient to show clearly the secondary hydroxyl protons as a doublet at δ 2.20–2.27 (J = 4 Hz) and the carbinol protons at δ 3.52–3.58 (J = 4 Hz). All systems appeared to move upfield a small amount while the hydroxyl groups moved downfield

3 was acetylated with $Ac_2O/ZnCl_2$ for 1 hr at 100° to yield the triacetate ex. EtOH., mp 344° (in sealed tube). (Found: C, 63.54; H, 8.30; $C_{27}H_{42}O_9$ requires: C, 63.51; H, 8.29%). Acetyl estimation (methanolic NaOH) = 21.8% thus using MW 510.6 gives 2.6 acetyl units per molecule. The IR spectral data revealed an absence of any hydroxyl frequency but the carbonyl band was present at 1746 cm^{-1}. The strong broad band at 1230 cm^{-1} indicated the presence of an ester. The PMR spectrum showed the acetate protons at δ 2.15 as a singlet but superimposed on the multiplet of the methylene protons The three carbocyclic protons were a singlet at δ 5.3.

Acknowledgements—The authors wish to thank Dr. L. J. Webb and Mr. J. G. Tracey, C.S.I.R.O., Division of Plant Industry and Mr. V. K. Moriarty, C.S.I.R.O., for collecting and identifying samples of *Evodiella muelleri*.

REFERENCES

1. Jansen, B. C. P. (1913) *Z. Physiol. Chem.* **85**, 231.
2. Ackerman, D. and Janka, R. (1954) *Z. Physiol. Chem.* **296**, 283.
3. Ackerman, D. and Janka, R. (1954) *Z. Physiol. Chem.* **298**, 65.
4. Lindberg, B. (1955) *Acta Chem. Scand.* **9** 1325.
5. Wickberg, B. (1957) *Acta Chem. Scand.* **11**, 506.
6. (a) Woeber, G. and Hoffmann-Ostenhof, O. (1960) *Monatsh. Chem.* 100. (b) Woeber, G. and Hoffmann-Ostenhof, O. (1960) *Monatsh. Chem.* 369.
7. Barton, D. H. R. (1950) *Experientia* **6**, 316.
8. Pople, J. A., Schneider, W. G. and Bernstein, H. J. (1959) in *High-resolution Nuclear Magnetic Resonance* p. 394. McGraw-Hill, New York.
9. Davenport, J. B. and Sutherland, M D. (1954) *Aust. J. Chem.* **7**, 385.