

TRITERPENOID COMPOUNDS. VI.* THE CONSTITUTION OF
MELALEUCIC ACID - II.**

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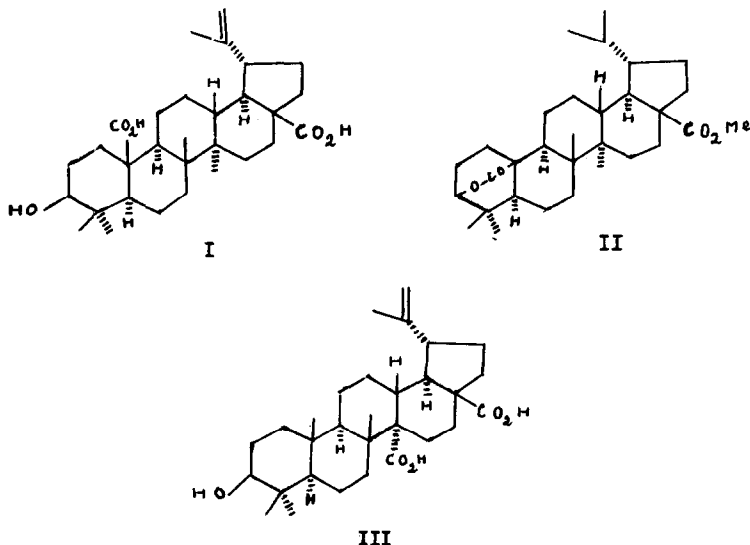
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In a previous communication (1), it was suggested that melaleucic acid was β -hydroxylup-20(29)-en-25,28-dioic acid (I). One carboxyl group was shown to be similar to that in betulinic acid, while the second, more hindered, carboxyl was placed at C₂₅ because it formed with the β -hydroxyl group a lactone, absorbing at 1762 cm^{-1} and hence considered to be the δ -lactone (II).

It has now been shown that saponification of this lactone, with potassium hydroxide at 220° , affords an unsaturated acid containing a tri-substituted double bond (absorption at 3025 and 814 cm^{-1} in CS_2 ; single vinylic hydrogen at $\delta = 4.62$ p.p.m. in N.M.R.). This was readily converted back to the original lactone on treatment with acid, and hence it was concluded that rearrangement had taken place during the initial lactonization.

* Part V. J.O. Knight and D.E. White, Tetrahedron Letters, No. 3, 100 (1961).

** Part I. Ref.(1).



This is already known in the quinovic-novic acid transformation (2), and a similar rearrangement has been suggested in this case (3). This would require melaleucic acid to be (III).

Examination of the N.M.R. spectra of a number of derivatives of melaleucic acid also suggests that the C-25 methyl group is still present. Lehn and Ourisson (4) have shown that the C-23, C-24 and C-25 methyl groups are together responsible for the bands at $\delta = 0.85$ (2 x Me) and 0.81 p.p.m. (1 x Me) in lupane. These appear at 0.93, 0.85 and 0.75 p.p.m. in methyl melaleucate and its dihydro-derivative, and at 0.90, 0.86 and 0.80 p.p.m. in the corresponding 3 α -epimers. Since the epimerization is more likely to affect the C-23 and C-24 methyls than the C-25 methyl, it is considered that the band at $\delta = 0.85$ -0.86 p.p.m. is due to the latter group (cf. Shoolery and Rogers; 5).

Now Lehn and Ourisson (4) have shown for the lupane series that,

upon replacement of a C-28 methyl (or hydroxymethyl) by a methoxycarbonyl group, the signal for the C-26 methyl group is shifted by about 0.12 p.p.m. to higher field. At the same time, because of the diamagnetic anisotropy of the methoxycarbonyl group, the chemical shift of the C-27 methyl is hardly affected. One would thus expect the signal from the C-25 methyl to be similarly displaced by the second methoxycarbonyl group were it located at C-26. No such displacement is observed in the spectra of any of the melaleucic acid derivatives examined, which suggests that the second carboxyl group of melaleucic acid is at C-27.

The C-26 methyl group in methyl melaleucate and the derivatives mentioned above gives rise to a signal at $\delta = 1.00$ p.p.m. The corresponding values reported (4) for methyl lupan-28-oate and methyl betulinate are 0.92 and 0.91 p.p.m. respectively, indicating that replacement of the C-27 methyl by a methoxycarbonyl group deshields the adjacent trans-methyl by about 0.08 p.p.m. This signal is moved to lower field by about 0.05 - 0.07 p.p.m. on replacing the C-28 methoxycarbonyl by a hydroxymethyl group, confirming that it arises from the C-26 and not the C-27 methyl.

Hence the structure of melaleucic acid is considered to be 3 β -hydroxylup-20(29)-en-27,28-dioic acid (III).

This has now been confirmed unambiguously by an X-ray crystallographic investigation of methyl melaleucate iodoacetate.

Crystals suitable for X-ray photography were obtained by slow crystallization from methanol. They were colourless orthorhombic needles, stable at room temperature. The cell dimensions were calculated from measurements on precession photographs to be $a = 15.719 \pm 5$, $b = 24.533 \pm 7$ and $c = 8.618 \pm 5$. The density measured by flotation was 1.37 ± 1 , which agrees favourably with 1.366 ± 1 calculated from the cell dimensions,

assuming four molecules per unit cell. The systematic absences in the reflections established the space group to be $P2_1 2_1 2_1$, which has four equivalent positions per unit cell and therefore one molecule per asymmetric unit.

Three-dimensional intensity data were estimated visually from Weissenburg photographs about the a and c axes using $Cu K_\alpha$ radiation. As iodine is an anomalous scatterer for this radiation (6) and the space group is non-centrosymmetric, the intensities of reflection from the h k l and $\bar{h} \bar{k} \bar{l}$ planes are nonequivalent (7,8), and were measured separately. Lorentz, polarization, absorption and correlation factors determined from the relative intensities of common reflections were applied to the data, which was then placed on an absolute scale by means of a Wilson plot (9). The Bijvoet inequality (10) was calculated for all reflections. The position of the iodine atom was determined from two projection Patterson syntheses, and an approximate set of reflection phases was calculated directly from the anomalous dispersion measurements (11,12,13,14). A three dimensional Fourier synthesis evaluated using these phases gave the positions of all the non-hydrogen atoms except the doubly-bonded oxygen in the acetyl group. Structure factors were calculated and the position of this oxygen atom was obtained from a difference synthesis. The structure has been refined by Fourier and least squares methods to a reliability factor of 0.14. A summary of a three dimensional Fourier at this stage with the molecule in its correct configuration is shown in Fig. 1. Thus structure (III) for melaleucic acid is confirmed.

Refinement is being continued, and further chemical investigations are proceeding.

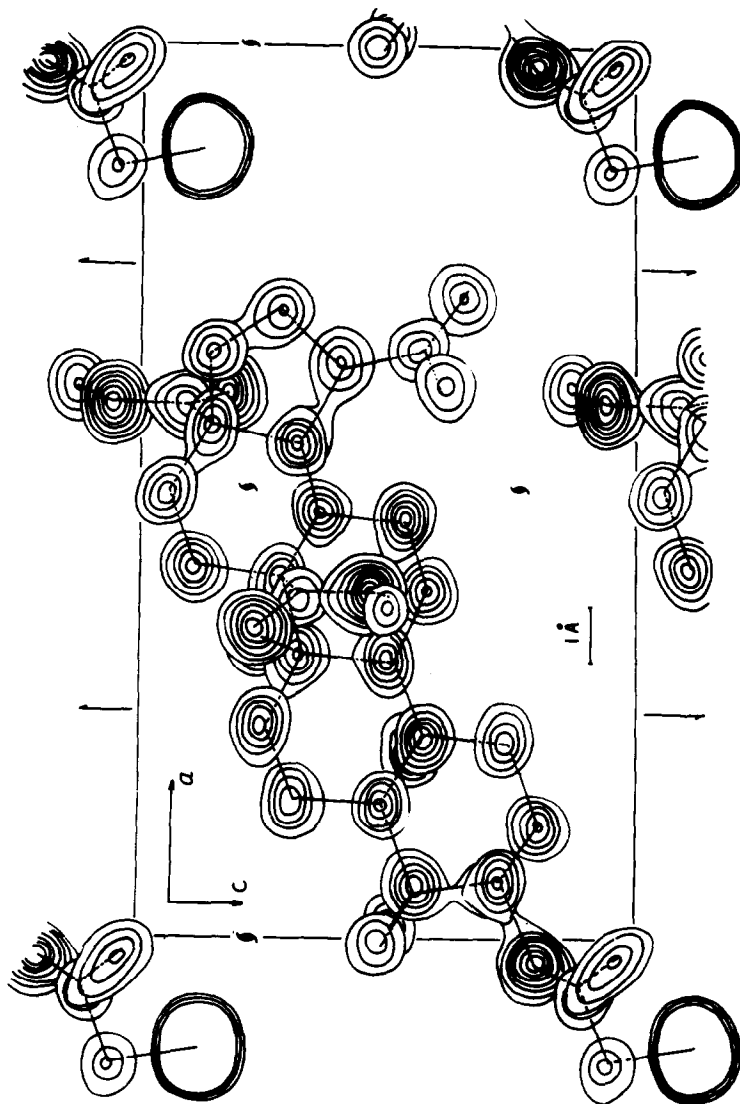


FIG. 1. Composite electron density of methyl melaleucate iodoacetate viewed along b ; contours are at $1\sigma^2$, first contour at $2\sigma^2$.

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