

THE CONSTITUENTS OF HARUNGANA MADAGASCARIENSIS POIR.

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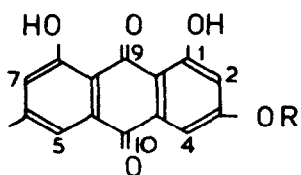
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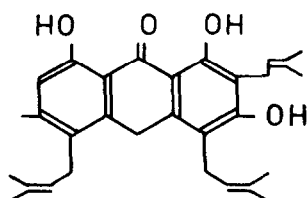
Harungana madagascariensis Poir. (syn. Haronga madagascariensis Chois.), (family Guttiferae), a small tree native to Africa and Madagascar is said (1) to be used for a variety of medicinal purposes by the indigenous peoples. From the bark which produces a brilliant orange sap, Stout *et al.* (2) reported in 1962, the isolation of a pigment, harunganin, to which structure (VI) was assigned as a result of X-ray crystallographic studies. The pigment was not characterised in any other way.

At this time we also had isolated harunganin as the major pigment of bark obtained from Babinda, Nth. Queensland, where the tree occurs as an introduced species. In addition we have separated so far, eight other constituents: the triterpenoids, betulic acid and friedelin, identified by direct comparison with authentic specimens, the known pigments euxanthone, chrysophanic acid and physcion (I), also identified by direct comparison with authentic specimens, and the new pigments madagascin (II), madagascin anthrone (III), and harongin anthrone (IV). Chemical and physical evidence for the structures of these pigments and of harunganin is now presented.

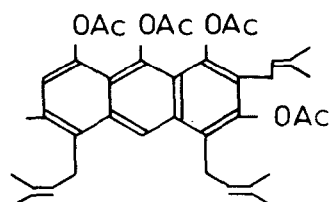
The light absorption properties and the nuclear magnetic resonance spectrum (Table I) of physcion (I) provided useful reference information. A long-range coupling ( $J \sim 1$  c/s) of the methyl protons with the adjacent aromatic protons is observable in this and related anthraquinones, which allows the signals due to H(5) and H(7) to be distinguished from those of H(2) and H(4):



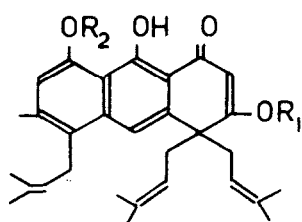
- I R = CH<sub>3</sub>  
 II R = CH<sub>2</sub>CH=C(CH<sub>3</sub>)<sub>2</sub>  
 III R = CH<sub>2</sub>CH=C(CH<sub>3</sub>)<sub>2</sub>,  
 (10) CH<sub>2</sub> for (10) C=O



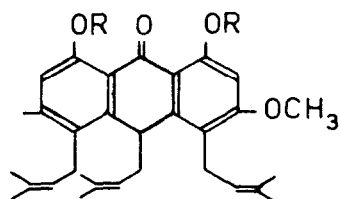
IV



V



- VI R<sub>1</sub> = R<sub>2</sub> = H  
 VII R<sub>1</sub> = CH<sub>3</sub>, R<sub>2</sub> = H  
 VIII R<sub>1</sub> = R<sub>2</sub> = CH<sub>3</sub>



- X R = H  
 XI R = COCH<sub>3</sub>

the assignment of all the signals may then be made straightforwardly as set out.

Madagascin,  $C_{20}H_{18}O_5$ , m.p. 156-157°, possesses a u.v. spectrum identical with that of physcion and shows in its n.m.r. spectrum (Table I) similar signals except for the absence of a methoxyl signal and the addition of signals from a  $\gamma\gamma$ -dimethylallyl group attached to oxygen, namely, a triplet ( $J = 7$  c/s) at  $\delta$  5.5 (C=C-H), a doublet ( $J = 7$  c/s) at  $\delta$  4.67 (O-CH<sub>2</sub>-C=C) and a broad singlet at  $\delta$  1.83 (2 C = C-CH<sub>3</sub>). This identification of madagascin as emodin 3- $\gamma\gamma$ -dimethylallyl ether (II), was confirmed by the formation of emodin on dealkylation with hydrobromic acid and by its synthesis by O-alkylation of emodin with  $\gamma\gamma$ -dimethylallyl bromide in dimethylformamide in the presence of potassium carbonate.

A buff-colored pigment,  $C_{20}H_{20}O_4$ , m.p. 168°, is considered to be madagascin anthrone (III) since its u.v. spectrum ( $\lambda_{max}$ . 220, 254, 272, 306, 357 m $\mu$ ) is typical of a 1,8-dihydroxy-10-anthrone (3) and its n.m.r. spectrum (Table I) is similar to that of madagascin, except for the presence of an extra two proton singlet at  $\delta$  4.10 assignable to H(10). The changes in the chemical shifts of the aromatic protons are consistent with the decreased quinonoid character of the anthrone structure.

Harungin anthrone,  $C_{30}H_{36}O_4$ , m.p. 208°, also shows typical light absorption properties of a 1,8-dihydroxy-10-anthrone. Its n.m.r. spectrum shows in addition to the signals noted in Table I, signals due to three  $\gamma\gamma$ -dimethylallyl groups attached to an aromatic nucleus. Of the possible structures (IV) is considered the most likely in view of the chemical shifts of H(7) and on biogenetic grounds (see below). Acetylation of the pigment with acetic anhydride in pyridine at room temperature yields an intensely fluorescing tetra-acetate,  $C_{38}H_{44}O_8$ , m.p. 130°, which is clearly an anthracene derivative from its light absorption properties. Its formulation as (V) is also in accord with its n.m.r. spectrum (Table I).

TABLE I  
N.M.R. Spectral Assignments<sup>a</sup>

|      | H(2)              | H(4)              | H(5)              | H(7)              | H(10) | (O)H <sup>f</sup> | (OO)H <sub>3</sub> | (C)H <sub>3</sub> |
|------|-------------------|-------------------|-------------------|-------------------|-------|-------------------|--------------------|-------------------|
| I    | 7.71 <sup>b</sup> | 7.4 <sup>b</sup>  | 7.69 <sup>c</sup> | 7.11 <sup>c</sup> | -     | 12.3,12.53        | 4.03               | 2.5 <sup>d</sup>  |
| II   | 6.63 <sup>b</sup> | 7.27 <sup>b</sup> | 7.53 <sup>c</sup> | 7.02 <sup>c</sup> | -     | 12.03,12.2        | -                  | 2.45 <sup>d</sup> |
| III  | 6.63 <sup>e</sup> | 6.6 <sup>e</sup>  | 6.6 <sup>e</sup>  | 6.33 <sup>e</sup> | 4.1   | 12.1,12.8         | -                  | 2.3               |
| IV   | -                 | -                 | -                 | 6.33              | 4.0   | 12.5,12.8,<br>8.0 | -                  | 2.1               |
| V    | -                 | -                 | -                 | 6.93              | 8.63  | -                 | -                  | 2.43              |
| VI   | 5.85              | -                 | -                 | 6.80              | 7.39  | 9.67,16.0<br>4.82 | -                  | 2.4               |
| VII  | 5.75              | -                 | -                 | 6.68              | 7.36  | 10.0,16.67        | 3.8                | 2.4               |
| VIII | 5.75              | -                 | -                 | 6.65              | 7.38  | 15.58             | 3.78,<br>4.02      | 2.46              |
| IX   | 5.86              | -                 | -                 | 6.64              | 7.33  | 15.58             | 4.01               | 2.46              |
| X    | 6.4               | -                 | -                 | 6.73              | 4.79  | 12.3,12.65        | 3.88               | 2.3               |
| XI   | 6.57              | -                 | -                 | 6.85              | 4.82  | -                 | 3.88               | 2.34              |

a Other important assignments are discussed in the text. Resonances are quoted in p.p.m. from tetramethylsilane and were determined in CDCl<sub>3</sub>, except for harongin anthrone when diglyme and acetone were used. Signals are sharp singlets unless otherwise indicated.

b Doublet, J=3 c/s.

c Unresolved signal, half width 4 c/s.

d Broad singlet, half width 2 c/s.

e Superimposed singlets.

f Signals removed on addition of deuterium oxide.

Harunganin (VI), m.p. 190° (Kofler block) had the formula,  $C_{30}H_{36}O_4$ , confirmed by a mass-spectrometric determination of molecular weight (460). The u.v. spectrum ( $\lambda_{max}$ . 242, 260, 280, 316, 334, 411 m $\mu$ ) did not immediately suggest the chromophore, but in the i.r. spectrum there was inter- and intramolecularly hydrogen-bonded hydroxyl and hydrogen-bonded carbonyl absorption. The pigment was sensitive towards most reagents, but crystalline monomethyl - (m.p. 101°) and dimethyl-derivatives (m.p. 150°), (VII) and (VIII), could be prepared. Their light absorption properties were similar to those of harunganin as were also those of dimethylhexahydroharunganin (IX) m.p. 140°; in particular, all had a strongly hydrogen-bonded carbonyl system.

Specific information on the functional groups was obtained from the n.m.r. spectra of (VI), (VII), (VIII) and (IX). Typically, the spectrum of the dimethyl ether shows the presence of one  $\gamma$ -dimethylallyl group attached to a benzene ring and two such groups attached to a saturated carbon. This follows from the 2 proton doublet at  $\delta$  3.61 (allylic-benzylic  $CH_2$ ) and the 4 proton multiplet at  $\delta$  2.7, due to two sets of allylic methylene groups in a slightly deshielded location adjacent to an aromatic nucleus. The methyl groups of these two units give a signal at  $\delta$  1.42, which suggests that the groups lie over the plane of an aromatic ring and are being shielded by the ring current. The signals of the other groups (Table I) are consistent with the structure type (VI). These conclusions are confirmed by the spectra of the monomethyl ether and the changes in the spectra which result when the dimethyl-ether is hydrogenated to its hexahydro-derivative.

When harunganin was distilled with zinc dust a small yield of a partly crystalline product was obtained which had the u.v. spectrum of an alkyl-anthracene. More information on the basic ring system was forthcoming from a study of the pyrolysis of the mono-methyl derivative. Brief heating at 180°/0.2 m.m. yielded a colourless gum possessing u.v. absorption ( $\lambda_{max}$ . 230, 258, 278, 310, 370 m $\mu$ ) similar to that of a 1,8-dihydroxy-10-anthrone (3).

The gum was characterized by its crystalline diacetate  $C_{35}H_{42}O_6$ , m.p. 128-130° ( $\lambda_{max}$ . 231, 248, 270, 304  $\mu$ ). The structures (X) and (XI) respectively are proposed for these compounds, since the n.m.r. spectra now show signals for two  $\gamma\gamma$ -dimethylallyl groups attached to a benzene ring and only one such groups attached to a saturated carbon atom. All other features of the spectra accord with these proposals. Dreiding models suggest that steric repulsions between the groups at C(4), C(10), and C(5) force the dimethylallyl group at C(10) out of the general plane of the molecule, so that the terminal methyl groups of this chain can then be over one of the two benzene rings in the zone of shielding by the aromatic ring current. This arrangement would account for the appearance of allylic methyl signals at  $\delta$  0.92 and 1.48; also the presence of the repulsions explains why the anthrone does not enolize and allow the formation of a triacetyl derivative (cf. barbaloin (3) (4)). This rearrangement reaction, possibly involving a series of 1,2-shifts is considered to be strong evidence for the structure of harunganin.

Madagascin (II), harongin anthrone (IV) and harunganin (VI) represent the three possible modes of alkylation of a phenolic ring system and it is of some interest that they have all been detected in the one plant.

#### REFERENCES

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