Tetrahedron Letters No. 24, pp. 1623-1629, 1963. Pergamon Press Ltd.
Printed in Great Britain.

# ACETYL-α-GAMBOGIC ACID*

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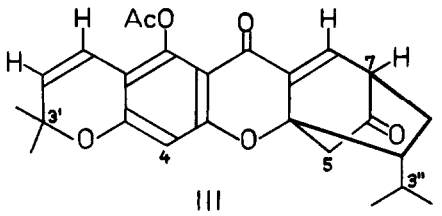
(Received 29 July 1963)

Acetyl-α-gambogic acid (I) is an optically active, yellow, crystalline compound first obtained by Furrer (1) by acetylation of the acidic fraction of gum gamboge, the dried latex of Garcinia morella; the parent acid, α-gambogic acid (II), has not been obtained in crystalline form (1,2,3), although a crystalline pyridine salt has been prepared (3). We propose part-structure III for I (where the angular attachment of the pyran ring is not excluded), and suggest full




III

structure IV on the basis of the assignment of structure V to morellin, a product from the seeds of Garcinia morella (4).

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* Presented in the Merck, Sharp and Dohme Lecture of the Chemical Institute of Canada, June 6, 1963.

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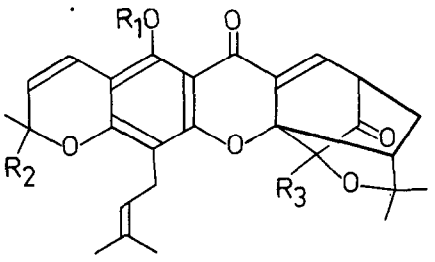


IV $R_1$ = Ac, $R_2$ = $CH_2CH_2CH{=}CMe_2$, $R_3$ = $CH_2CH{=}\overset{\overset{Me}{|}}{C}CO_2H$

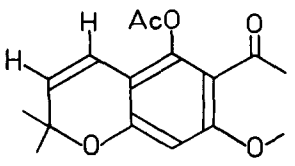
V $R_1$ = H, $R_2$ = Me, $R_3$ = $CH_2CH{=}\overset{\overset{Me}{|}}{C}CHO$

The revised formula $C_{40}H_{46}O_9$ is assigned to I, m.p. 202-203° (Found: C, 71.64, 71.45; H, 6.63, 6.76; Eq.W., 659, 664 (pot. tit.); M.W., 684 (X-ray), 633, 648 (osm.)), confirmed by potentiometric titration of its crystalline octahydro derivative, VI, m.p. 144-145° (Found: C, 70.39, 70.36; H, 8.15, 8.14; Eq.W., 673, 674) and elemental analyses of its reaction product with methanolic sodium methoxide, VII (vide infra), and of the pyridine salt of II (Found: C, 72.87, 72.78; H, 6.96, 7.02; N, 1.66, 2.27, 1.95, 1.85).*

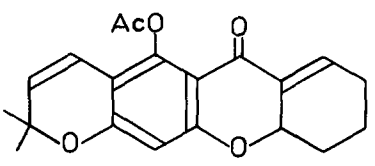
The infrared spectrum of I showed the presence of an o-acetoxyphenyl ketone grouping (5.68, 6.03 μ) and of two additional carbonyl functions (5.76, 5.92 μ), one of which is a conjugated carboxylic acid (5.92 μ), when considered in relation to the infrared spectra of II (5.76, 5.92, 6.12 μ), VI (5.69, 5.77, 5.95 (complex) μ ), and the methyl ester of I (5.68, 5.76, 5.83, 6.00 μ). The presence of this grouping is

* Very recently Dyson and Rigby (5) have also proposed this formula for I on undisclosed grounds.

confirmed by the appearance in the n.m.r. spectra of transformation products of I lacking the acetyl group of a signal at $\tau \sim -2.5$ p.p.m. The isolation of phloroglucinol from the base-fusion of I and of gambogic acid (6), the formation of acetone and acetaldehyde (7) on treatment of I with base, and the presence of an AB pattern of signals in the n.m.r. spectrum of I ($\tau$ = 3.58, 4.40 p.p.m., J = 10 c./s.; absent in the spectrum of VI) (8) indicated the part-structure VIII (or the corresponding structure with angular ring fusion).




VIII




IX

The fact that I is the acetyl derivative of a $C_{38}$ compound suggested strongly that it is a xanthone derivative bearing five isoprenoid side chains or their equivalent (cf. mangostin (9)) and led us to consider the expansion of VIII to the corresponding xanthone. However, the ultra-violet spectra of I and its derivatives are not in accord with this view, although both these and the infrared spectra show that the ketonic group of VIII is further conjugated. Part-structure IX and the corresponding chromone derivative were therefore considered.

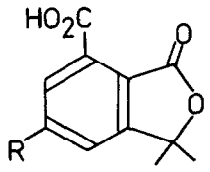
The "methoxide product", VII, $C_{39}H_{48}O_9$, m.p. 201-203° (Found: C, 70.69, 70.75; H, 7.18, 7.19; OMe, 5.16),

forms a monomethyl ester, $C_{40}H_{50}O_9$, m.p. 115-116° (Found: C, 70.99, 71.01; H, 7.30, 7.50; OMe, 9.26), and must be formed by addition of methanol to I accompanied by deacetylation. The reaction may be interpreted as involving the Michael-type addition of methoxide ion to a conjugated enone system in I. In accordance with this view and with part-structure IX, but not the chromone, the n.m.r. spectrum of I shows a one-proton doublet with $\tau$ = 2.56 p.p.m., J = 7 c./s., which is absent in the spectrum of VII (and of VI): this can be assigned to a β vinylic hydrogen atom on the s-cis enone system of IX; the splitting shows that there is at least one hydrogen atom on the $\gamma$ carbon atom. A related reaction of I with basic hydrogen peroxide leads to a compound, $C_{38}H_{44}O_9$, m.p. 183-184° (Found: C, 70.37; H, 6.98), which is considered to be formed by epoxidation of the enone system of IX accompanied by deacetylation.

Base-treatment of gambogic acid (6), I (2) and/or VII gives phloroglucinol, homophthalic acid, isovaleric acid, methylsuccinic acid, 6-methyl-5-hepten-2-ol, and a mixture of amorphous acidic products which on oxidation gives two crystalline acids, $C_{12}H_{10}O_6$ and $C_{11}H_{10}O_4$. The spectral properties of the former and its decarboxylation to 3,3-dimethylphthalide suggested the structure X, which was established by comparison with an authentic sample prepared by oxidation of XI.*

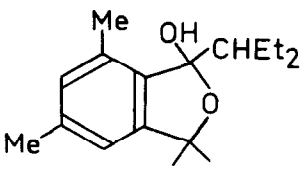
The formation of X demonstrates the presence of

* Compound X has been synthesized by two other routes (5,10); Dyson and Rigby (5) also have shown that it is identical to the degradation product from I, and that the $C_{11}$ acid is XII.



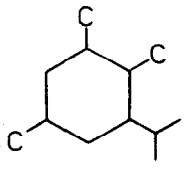

X, R=$CO_2H$

XII, R=H

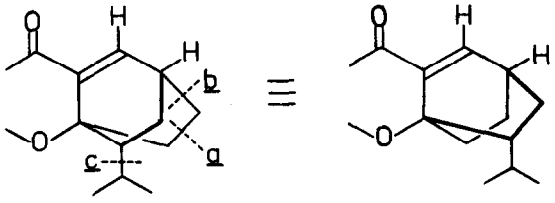



XI

the structural feature XIII, which can be reconciled with the part-structure IX and the view that I is a xanthonoid compound with isoprenoid side chains only in terms of XIV. While formation of X involves cleavage of bond a, cleavage of bonds b and c provides a pathway to another base-fusion product, homophthalic acid. The cleavage of both bonds a




XIII




XIV

and b indicates that the remaining carbonyl group of I (other than the carboxylic acid group) is situated at their juncture. The part-structure III is therefore assigned to I.

Of the five isoprenoid units considered to be attached to the xanthonoid nucleus, two are accounted for in III.

The formation of methylsuccinic acid suggests a modified isoprenoid side chain, $-CH_2CH=\overset{Me}{C}CO_2H$, which can provisionally be located at C.5 in analogy with the related side chain $-CH_2CH=\overset{Me}{C}CHO$ in V (4). The absence of any signal in the n.m.r. spectrum of I assignable to an aromatic hydrogen atom shows that a fourth isoprenoid unit is attached at C.4. The fifth isoprenoid unit must be attached to one of the methyl groups of the isoprenoid units whose positions have already been assigned (other than that at C.5), since oxidation of VI gives 6-methyl-2-heptanone.

The ninth oxygen atom of I must be present as an ether linkage; by analogy with V it is provisionally assigned as bridging the 5 and 3" positions in III. Then, location of the fifth isoprenoid unit on a methyl group attached to either C.3' or C.3" is likely since in either case the formation of 6-methyl-2-heptanone from VI is interpretable in terms of the presence of the grouping $Me_2CHCH_2CH_2CH_2\overset{Me}{C}-O-$ in the reduction product. The former site is favored since it has been found that XII is formed by direct oxidation of I (5). We therefore suggest structure IV for acetyl-α-gambogic acid.

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