Tetrahedron Letters No.23, pp. 1999-2002, 1970. Pergamon Press. Printed in Great Britain.

CALOPHYLLUM PRODUCTS: VI. THE SIDECHAINS OF THE C. INOPHYLLUM ACIDS. (1)

George H. Stout and George D. Breck

Department of Chemistry, University of Washington, Seattle, Washington, 98105

(Received in USA 14 April 1970; received in UK for publication 20 April 1970)

An earlier communication in this series (2) described the isolation of a material, inophylloidic acid, $C_{32}H_{46}O_6$, from the bark resins of Calophyllum inophyllum L. (Guttiferae). This and the closely related brasiliensic acids from C. brasiliense were shown to have the same basic structure, 1. It was suggested that the sidechains were double bond isomers of the common prenyl and geranyl systems, being αa in inophylloidic acid and βa in brasiliensic acid. Further studies on inophylloidic acid have now shown that it is in fact a complex mixture of isomers, differing in the nature of the C_{10} sidechain and in the direction of cyclization of the heterocyclic ring.

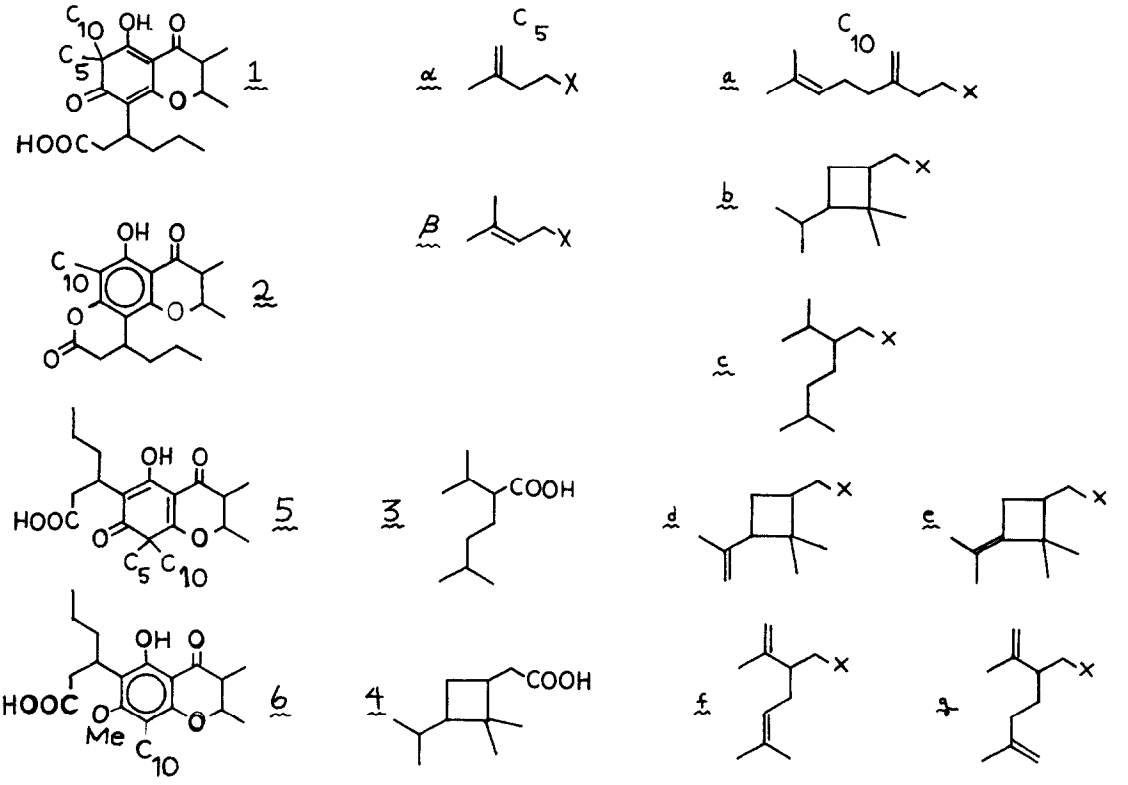
Careful preparative TLC of C. inophyllum resin on Brinkman silica gel HR yielded two fractions, both $C_{32}H_{46}O_6$, which differ in their ultraviolet spectra and fluorescent properties. The major and more mobile (A) corresponded chromatographically and spectrally to the earlier samples of "inophylloidic acid" and to brasiliensic acid. Further chromatography of fraction A on silica gel HR containing 3% $AgNO_3$ yielded two bands, of which the slower moving was pure (compound A3) while the faster yielded a pure material (A1) from its leading edge and a mixture of A1 and A2 from its tail. All these products were isomeric and showed the spectral properties described previously. Like the earlier mixtures, all the acids were non-crystalline, but their homogeneity (except in a stereochemical sense) was indicated by TLC, by improved NMR spectral detail and integrations, and particularly by the formation of single, unique degradation products.

Hydrogenation over Pt was accompanied by hydrogenolysis of a C_5 chain (isolated as isopentane) and led to perhydrolactones (2), $C_{27}H_{40}O_5$ (2c) from A2 and A3, and $C_{27}H_{38}O_5$ (2b) from A1. Oxidation of the A2/A3 products with aqueous HNO_3 and GLC analysis of the steam-volatile acids on Reoplex 400 + 1% H_3PO_4 (3) showed $C_{11}H_{22}O_2$ and $C_{10}H_{20}O_2$ as the major degradation products. These differed, however, from 4,8-dimethylnonanoic acid and tetrahydrogeranic acid, both in retention times and in mass spectra.* The absence of a C_9 acid, a major product from the similar oxidation of authentic tetrahydrogeranyl sidechains, suggested a branch point β to the aromatic system, and direct comparison (GLC, mass spec) of the C_{10} acid with synthetic 2-isopropyl-5-methyl hexanoic acid (3) confirmed their identity.

Similar oxidation of the A1 perhydrolactone yielded $C_{11}H_{20}O_2$ and $C_{10}H_{18}O_2$, but again no C_9 product. Other considerations suggested a cyclobutane ring, and direct comparison showed the C_{11}

* Previous comparisons (2) were based on TLC analysis of the acid phenylhydrazides, a method incapable of distinguishing the various C_{10} and C_{11} isomers.

acid to be identical with trans-2,2-dimethyl-3-isopropylcyclobutyl acetic acid (4) prepared from α-pinene.



Treatment of the A isomers with TsOH in C_6H_6 at room temperature also removes the C_5 chain and yields unsaturated lactones, $C_{27}H_{36}O_5$ (2), which give the above perhydro compounds on hydrogenation. The lactone from A1 shows (aside from the signals associated with the 2,3-dimethylchromanone ring) two singlet methyls (τ 8.78, 9.06) on saturated C, one allylic methyl (τ 8.34), and a terminal $=C<^{H}_{H}$ (τ 5.23, 5.43) and so must have the 2d structure. Extended acid treatment yields a new product (2e) containing 2 allylic methyls and no vinyl protons, which yields on hydrogenation (slow) and oxidation largely (cis-2,2-dimethyl-3-isopropylcyclobutyl) acetic acid.

A3 lactone shows three vinyl protons, one as the triplet (τ 5.01) characteristic of $C-\overset{C}{\underset{|}{C}}=CH-CH_2-$ systems and two as $\overset{C}{\underset{C}{>}}C=CH_2$ (τ 5.50, 5.60). The absence of the doublet ca. τ 6.8 expected for a methylene simultaneously benzylic and allylic then requires the structure to be 2f.

A2 lactone shows two sets of vinyl methylene signals (τ 5.43 (3H), 5.55 (1H)) and must be 2g.

In all cases, the nmr spectra of the purified natural acids show corresponding methyl and vinyl signals, with the addition of one vinyl proton and two allylic methyls from a 3-methyl-2-butenyl (β) chain. Since the mass spectra show the major fragmentation to be $-C_{10}$ $-C_4$ and

$-C_5$ $-C_9$, with no evidence for aromatization via loss of the acid chain, the C_5 and C_{10} chains must, as previously proposed, be attached at the same point. In confirmation, the tertiary proton of the acid sidechain absorbs ∿ τ 6.6 and must be allylic. Thus the structures A1 — A3 are 1 βd, 1 βg, and 1 βf.

Similar $AgNO_3$ chromatography of the less mobile fraction (B) from the original resin yielded principally an elongated spot from which again a pure fraction (B1) and a mixture (B1 and B2) could be separated. These materials differed from the A compounds in their UV spectra (λ_{max}^{EtOH} 246 (9900), 296 (10,900), 355 (1730)) and in showing a NMR chelated OH signal at ca τ - 1.87. Hydrogenation or acid treatment again led to loss of a C_5 unit and formation of materials with the same aromatic chrom phore as the A products. Oxidation of the perhydrolactones yielded 4 from B1 and 3 from B2, while TsOH products showed NMR spectra nearly identical with those of A1 and A2, confirming the identity of the sidechains.

The mass spectra of the A and B products are in close agreement and require that both have the C_5 and C_{10} chains attached to a single quaternary carbon. The differing UV spectra require significant changes in the chromophore, however, and are accommodated by regarding the two series as representing alternative modes of closure of the heterocyclic ring. Thus B1 and B2 are 5βd and 5βg. In confirmation, the 7-methyl ethers(6) of the B perhydroacids lactonize under mild conditions onto the 5-OH to give products with no chelated OH ($FeCl_3$) and with a UV spectrum (232 (30,300), 272 (14,600), 329 (5400)) very close to that of the homolog papuanolide (4). In contrast, the 7-methyl ether of the A series are inert to lactonizing reagents (2).

Reexamination of our small remaining sample of C.brasiliense resin showed that it consisted largely of A2 (brasiliensic acid) with smaller amount of A3 ("isobrasiliensic acid"). Thus the name inophylloidic acid may be reserved for A1.

Aromatization of the A natural acids, either by hydrogenation or TsOH, leads to mixtures of distinguishable trans/cis 2,3-dimethylchromanone products, even under conditions which do not cause equilibration of these products. Thus it appears that these compounds occur as mixtures of stereoisomers, and indeed separation of the natural materials has been obtained by TLC in a sandwich system.

In the previous communication, it was suggested that hydrogenation of "inophylloidic acid" yielded C_{22} as well as C_{27} compounds. Reexamination of the data indicates that this represented misinterpretations of mass spectra of mixtures of the reduced sidechains in which varying amounts of cleavage were regarded as indicating the presence of mixtures of C_{22} and C_{27} molecules.

The sidechains found in these molecules are unique in the Guttiferae(5) and to our knowledge in phenolics in general. They relate to the uncommon 1,2 isoprene linkage of lavandulol (6), both in the carbon skeleton and in the tendency, presumably associated with the biosynthetic coupling of the isoprenoid units, to show isopropenyl rather than isopropylidene termini. The even more uncommon cyclobutyl unit represents an obvious closure from the open chain system.

Acknowledgment.--This work was supported in part by a grant from the U.S. Public Health Service, GM-12095.

References

1) For the previous paper in this series see C. D. Breck and G. H. Stout, J. Org. Chem. in press.

2) G. H. Stout, M. M. Krahn, and C. D. Breck, Tetrahedron Letters 3285 (1968).

3) J. Krivnak and V. Palo, J. Cas Chromatog. 5, 325 (1966).

r) G. H. Stout, G. K. Hickernell, K. D. Sears, J. Org. Chem. 33, 4191 (1968).

5) Note Added in Proof: Since the submission of this letter, the lavandulyl sidechain has been reported in a xanthone isolated from Hypericum maculatum. P. Arends, Tetrahedron Letters 4893 (1969).

6) H. Schinz and C. F. Seidel, Helv. 25, 1572 (1942); H. Schinz and J. P. Bourquin, ibid 25, 1591 (1942); M. Soucek and L. Dolejs, Coll. Czech. Chem. Commun. 24, 3802 (1959).