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CALOPHYLLUM PRODUCTS. II. BRASILIENSIC AND INOPHYLLOIDIC ACIDS

George H. Stout, Margaret M. Krahn, and George D. Breck
Department of Chemistry, University of Washington, Seattle, Washington 98105

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As part of a continuing study (1) of the products of the Guttiferae, we have isolated a series of acids with unusual structural features from the bark resins of Calophyllum brasiliense Camb. var. Rekoi Standl. and C. inophyllum L. A sample of resin from C. brasiliense var Rekoi from Costa Rica yielded after extraction from hexane with dilute Na_2CO_3 approximately 95% of a greenish acid gum consisting entirely of two isomeric compounds (ratio 7:3), brasiliensic and isobrasiliensic acids. These were separable by careful chromatography on iron-free silica gel. By combustion analysis and high precision mass spectrometry brasiliensic acid (λ_{max}^{EtOH} 245sh (4000), 310 (10,200), 365sh) has the formula $C_{32}H_{46}O_6$ (2).

Samples of C. inophyllum bark from Hawaii, the Philippine Islands, and Australia yielded similar resins containing very largely an additional isomer, inophylloidic acid (λ_{max}^{EtOH} 243sh (5770), 312 (11,040), 363sh (4030)) (3). This has properties very similar to brasiliensic acid but differs in significant, though small,details of the nmr spectrum.

Hydrogenation of brasiliensic acid over Pt in ethanol gave perhydrobrasiliensic acid, $C_{27}H_{42}O_6$, (λ_{max}^{EtOH} 297 (15,200), 350 (2860)) readily closed by acetic anhydride or dicyclohexylcarbodiimide to a perhydrolactone $C_{27}H_{40}O_5$ (λ_{max}^{EtOH} 287 (14,900), 353 (3260)). Similar hydrogenation of inophylloidic acid gave two perhydroacids, $C_{27}H_{42}O_6$ and $C_{22}H_{32}O_6$, which could also be dehydrated to the corresponding lactones. Comparison of the two C_{27} perhydrolactones by nmr, uv, ir, and mass spectrometry indicated the identity of the carbon skeletons (4), although possible stereochemical differences were not excluded.

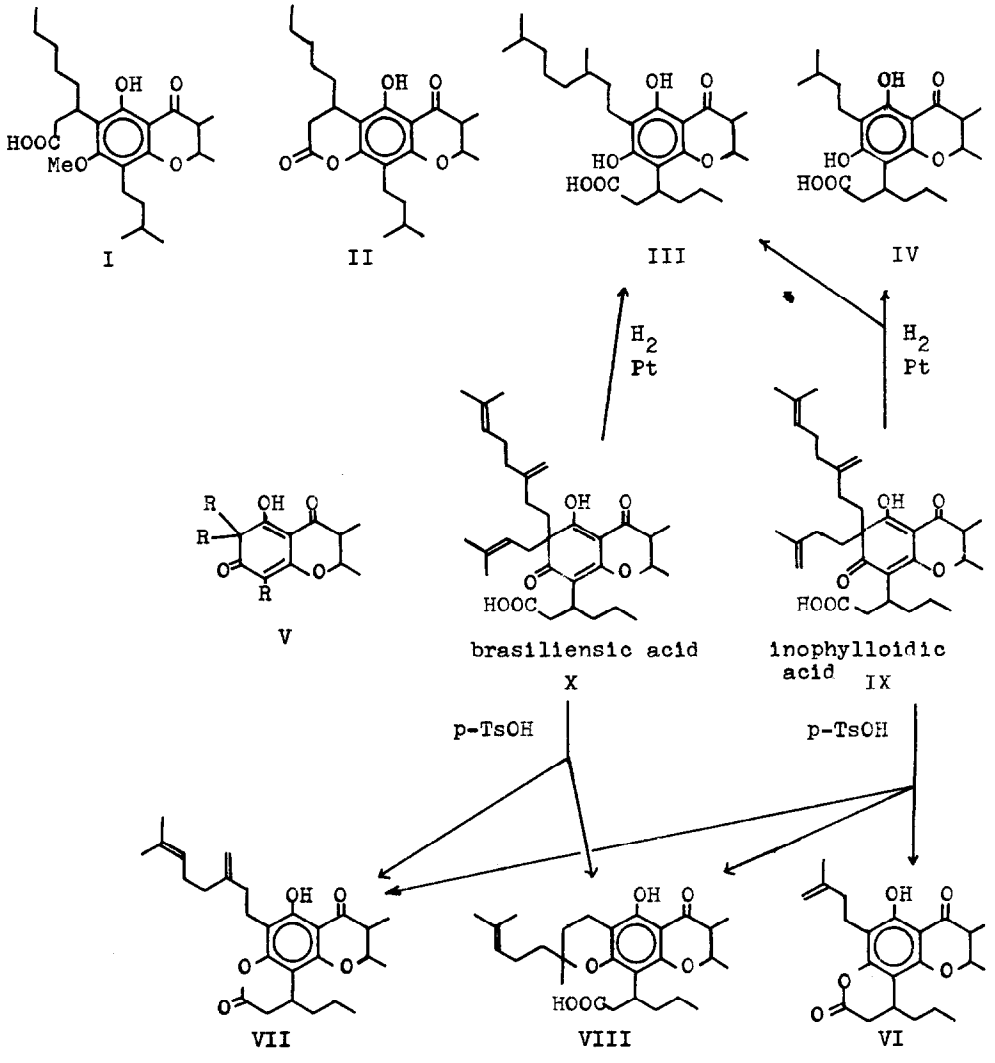
The nmr spectra of these perhydrolactones resemble markedly those of derivatives of dihydropapuanic acid (I) (5), suggesting a close structural relationship. In particular peaks appear at τ5.85 (1H,m), 8.48 (3H,d; J=6 Hz), and 8.79 (3H,d; J=6 Hz), which can be ascribed to the trans-2,3-dimethylchromanone ring (1) frequently found in Calophyllum products (1,5,6,7,8). An additional peak at τ-2.0 (1H,s) shows the presence of a chelated hydroxyl. No aromatic protons are present, but familiar signals at τ6.8 (1H) and 7.4 (2H) suggest a propionic acid side chain bearing a substituent α to the aromatic ring (5). Nitric acid or permanganate oxidation of the parent and perhydro acids identified this substituent by yielding n-propylsuccinic acid from the original carboxylic side chain.

The near-perfect agreement of the uv spectra of the perhydrolactones with that of the papuanic acid derivative II (λ_{max}^{EtOH} 287 (15,200), 351 (3300)) leaves no doubt that the new products contain the same 5,7-dioxychromanone chromophore. Finally, oxidation of the C_{27}perhydroinophylloidic acid also yielded 4,8-dimethylnonanoic acid, thus identifying the last substituent on the aromatic ring as a tetrahydrogeranyl chain.

Both the C_{27} perhydroacids were converted to their 7-methyl ethers. These proved resistant to lactonization under conditions that readily dehydrate I. Consequently the carboxylic side chain must be situated at C-8, and the C_{27} perhydroacids are III.

Comparison of the spectral and chemical properties of the C_{22} perhydroinophylloidic acid and its derivatives showed that these correspond to the C_{27} compounds except for a C_5 group in place of the tetrahydrogeranyl chain. Isolation of isocaproic acid following oxidation of the C_{22}perhydroacid identified this substituent as isopentyl. The structure of the C_{22} acid is thus IV.

The loss of C_5 or C_{10} during the hydrogenation of inophylloidic acid points to a hydrogenolysis, and the accompanying change in the uv spectrum is too great to be caused by the simple cleavage of an allyl ether. Indeed, the structures of the two perhydroacids isolated indicate that C-6 must originally be disubstituted, and lead to the formulation of the parent acid as a cyclohexadienone of the part structure V. Compounds of this type are known from the hop bitter principles, e.g. lupulone (9), and have been shown to undergo similar hydrogenolysis (9,10,11).



The positions of the sidechains in inophylloidic acid are clear from the structures of the derived perhydroacids. The molecular formula of the parent compound, however, requires it to contain three double bonds in these chains. Treatment of inophylloidic acid with p-TsOH in benzene gave, among other products, two unsaturated lactones, $C_{22}H_{28}O_5$ and $C_{27}H_{36}O_5$, which may be hydrogenated to the perhydrolactones obtained earlier. The C_{22} product (VI) shows

nmr absorptions at τ 5.3-5.5 (2H), the position widely observed for protons on terminal double bonds (12), while the C_{27} lactone (VII) has peaks at τ4.9 (1H) and 5.4-5.7 (2H), corresponding to the protons on one terminal and one trisubstituted double bond (12). The assignment of the double bonds as shown in VII was confirmed by the isolation from the same reaction of an acid $C_{27}H_{38}O_6$, stable to reagents normally causing lactonization. Formulated as the cyclic ether VIII, this compound shows a single vinyl proton at 4.8 and two allylic methyls at τ8.3 and 8.4, proving that the terminal double bond is trisubstituted. On the basis of these products, therefore, we propose IX as the structure of inophylloidic acid.

The structural analysis of brasiliensic acid is complicated by the absence of derivatives arising from the loss of a C_{10} fragment. The mass spectra of inophylloidic and brasiliensic acids, however, show great similarity and can be interpreted only in terms of alternative C_5 or C_{10} loss from a single site in both compounds. Thus the skeletons of the two molecules must be the same. The differing behavior on hydrogenation is best explained by the presence in brasiliensic acid of a $\beta\gamma$ rather than a $\gamma\delta$ double bond in the C_5 chain. This chain is then lost preferentially because of the allylic stabilization provided for bond cleavage during hydrogenolysis (11).

Support of this view and evidence of the actual location of the C_{10} double bonds is provided by the isolation, following acid treatment of brasiliensic acid, of an unsaturated C_{27} lactone identical with VII and a cyclized acidic product identical with VIII. Since the nmr spectrum of brasiliensic acid shows the presence of only four vinyl protons, the double bond of the C_5 chain must be trisubstituted. On the basis of these results, brasiliensic acid is assigned the structure X.

The chemical and spectral properties of isobrasiliensic acid are very similar to those of brasiliensic acid. The only significant difference is the shift of a one-proton multiplet from τ 5.8 in brasiliensic acid and its perhydrolactone to τ 5.5 in the isobrasiliensic compounds. This signal has been identified with the C-2 proton of the 2,3-dimethylchromanone ring (1), and the two values correspond to <u>trans</u> and <u>cis</u> methyl arrangements. Thus

isobrasiliensic acid is proposed to be a cis isomer of the same gross structure as the trans brasiliensic acid. By the same argument, inophylloidic acid is also trans. Studies on the stereochemical details are in progress.

The geminal substitution found here is unusual, as are the locations of the double bonds in the side chains. Aside from the much studied hop products (8), the only closely analogous molecule is harunganin (13), also a product of the Guttiferae. Morellin (14) and related materials of the gambogic acid group (15), again from the Guttiferae, show somewhat similar but more complex modifications. These new acids extend the series of Calophyllum products, which, starting from relatively simple coumarins, have now reached an advanced stage of elaboration. These coumarin-related products also provide an interesting contrast to the substituted xanthones isolated from C. brasiliense heartwood (16), a dichotomy which is apparently general in the genus.

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2. All molecular formulas cited herein have been verified by high precision mass spectrometry (A.E.I. MS-9) and most confirmed by combustion analysis.
3. The inophyllic acid isolated in small yield from this source by Mitra (C. Mitra, J. Sci. Ind. Res. 14B, 481 (1955); 16B, 120, 167 (1957)) has properties (uv, $FeCl_3$ color) which suggest that it is related to our inophylloidic acid, but other properties and the degradative results show that the two compounds are not identical.
4. It sould be noted that none of the natural acids or their derivatives has ever been obtained crystalline. Thus all comparisons and tests for homogeneity rest on spectral and chromatographic evidence.

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