Calophyllum Products. IV. Papuanic and Isopapuanic Acids[1a-c]

GEORGE H. STOUT, GARY K. HICKERNELL,[1d] AND KARL D. SEARS[1e]

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

Received April 8, 1968

Papuanic acid from the bark resin of *Calophyllum papuanum* Lauterb. is shown to have the structure and absolute stereochemistry **29a** by a combination of degradative, synthetic, and X-ray crystallographic methods. Isopapuanic acid, also present in the resin, is the C-2 epimer **30a**. The stereochemistry and conformations of these compounds and their epimerization and bromination products are discussed. The synthesis of a derivative of papuanic acid is described.

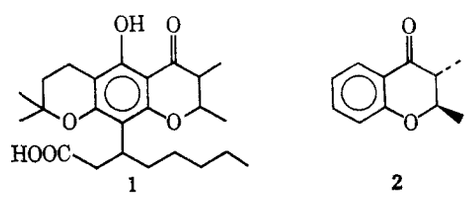
Pentane extraction of the ground bark of *Calophyllum papuanum* Lauterb., a New Guinea species of the family Guttiferae, yields a surprising 13% of yellow-green resin. Thin layer chromatography (tlc) showed this to consist of *ca.* 95% of two similar compounds, with only a small amount of impurities. The major components can be extracted from the pentane solution with aqueous carbonate, and careful chromatography on silica gel then yields pure papuanic and isopapuanic acids.[2] Both compounds are monocarboxylic acids of the formula $C_{25}H_{36}O_6$, as shown by combustion analyses, titration, and high resolution mass spectrometry. Although papuanic acid, the major product, may be obtained as a solid following prolonged cooling of the pure material, neither compound can be crystallized from solvents. Consequently they and most of their derivatives have been handled only as glasses.

Structure.—Catalytic hydrogenation of papuanic acid led to the rapid uptake of 1 mol of hydrogen and the formation of dihydropapuanic acid, $C_{25}H_{38}O_6$. The uv spectra of the starting material and product are nearly identical. These spectra are very similar to that of dihydroblancoic acid (**1**)[1b] and clearly represent the same oxygenated acylphenone system.

The nmr spectrum of papuanic acid (Figure 1) is very clear and allows the identification of nearly every proton in the molecule. It shows no aromatic protons, requiring that the benzene ring indicated by the uv spectrum be fully substituted as in **1** and other *Calophyllum* products.[3-6] Among the substituents are clearly a methoxyl group (τ 6.28, 3 H) and a chelated hydroxyl (−2.34, 1 H).

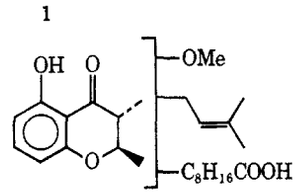
A group of signals at τ 5.88 (m, 1 H), 8.51 (d, 3 H), and 8.84 (d, 3 H) represents the now familiar *trans*-2,3-dimethylchromanone **2**, which has appeared so repeatedly in *Calophyllum*.[1b,3,5,7] The carbonyl group gives rise as expected to a band at 6.11 μ in the ir spectrum and must be adjacent to the hydroxyl mentioned above.

Another group of signals at τ 4.90 (t, 1 H), 6.81 (d, 2 H), 8.28 (s, 3 H), and 8.34 (s, 3 H) is readily assigned to an isopentenyl chain, a common substituent throughout the Guttiferae.[8] In dihydropapuanic acid the vinyl signal at 4.90 vanishes, and the benzylic–allylic doublet at 6.81 becomes a broad triplet at 7.45. These changes confirm that it is the double bond of this chain that is reduced.



1

2



3

These fragments and the remainder of the molecule can be combined as in **3**. The side chain bearing the carboxyl group produces clear signals in the nmr spectrum of papuanic acid only at τ 7.18 (d, 2 H), the methylene adjacent to the carboxyl, and 9.16 (t, 3 H), the terminal methyl of a *n*-alkyl chain. The shift of the isopentenyl benzylic methylene in dihydropapuanic acid reveals an additional multiplet at 6.55 (1 H), which represents a benzylic methine. Comparison of these signals with those of blancoic acid[1b] suggests that papuanic acid contains the same 3-aryloctanoic acid system (**4**). The isolation of *n*-pentylsuccinic acid after vigorous oxidation of papuanic acid substantiates this proposal.

Treatment of papuanic acid under mild conditions with either acetic anhydride–pyridine or dicyclohexylcarbodiimide (DCC) led to the formation of papuanolide, $C_{25}H_{34}O_5$. This product is characterized by the absence from its nmr spectrum of the signals corresponding to both the chelated hydroxyl and the carboxylic proton (τ −1.76). In addition the ir band of the acid function shifts from 5.84 to 5.60 μ expected for a phenolic ester, while the chromanone carbonyl absorption moves from 6.11 to 5.89. These results show that lactonization must have occurred onto the

(1) (a) Presented in part at the 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, No. S078. Taken in part from the Ph.D. Theses of G. L. Hickernell and K. D. Sears, University of Washington, 1968. (b) For the previous paper in this series, see G. H. Stout and K. D. Sears, *J. Org. Chem.*, **33**, 4185 (1968). (c) Supported in part by Public Health Service Grant GM-12095 from the National Institute of General Medical Sciences. (d) National Science Foundation Cooperative Fellow, 1964–1966. National Science Foundation Fellow, 1966–1968. (e) University of Washington Institute of Forest Products Research Fellow 1964–1966.

(2) Although papuanic acid may be isolated chromatographically without prior carbonate extraction, the isopapuanic acid so obtained is contaminated with a neutral oil.

(3) J. Polonsky, *Bull. Soc. Chim. Fr.*, 1079 (1957).

(4) G. H. Stout and K. L. Stevens, *J. Org. Chem.*, **29**, 3604 (1964).

(5) S. K. Nigam, C. R. Mitra, G. Kuensch, B. C. Das, and J. Polonsky, *Tetrahedron Lett.*, 2633 (1967).

(6) T. R. Govindachari, D. Prakash, and N. Viswanathan, *ibid.*, 4177 (1967).

(7) G. H. Stout, M. M. Krahn, and G. D. Breck, *ibid.*, 3285 (1968).

(8) *Inter alia:* B. F. Burrows, W. D. Ollis, and L. M. Jackman, *Proc. Chem. Soc.*, 177 (1960); G. H. Stout, V. F. Stout, and M. J. Welsh, *Tetrahedron*, **19**, 667 (1963); B. Jackson, H. D. Locksley, and F. Scheinmann, *J. Chem. Soc., C*, 178 (1966).

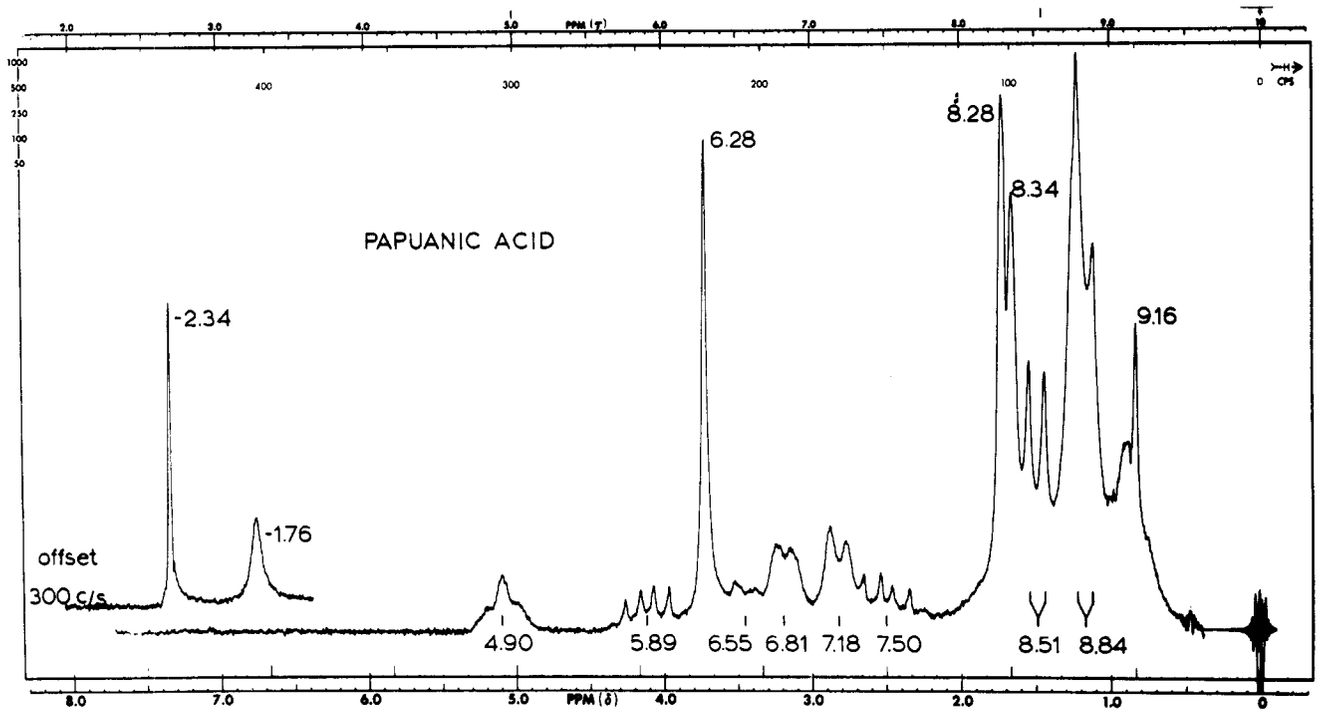
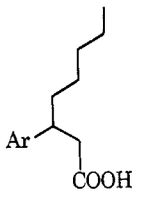
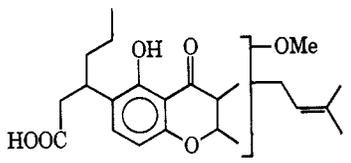


Figure 1.—The 60-MHz nmr spectrum of papuanic acid in CCl_4.

chelated hydroxyl, and thus that the carboxylic chain must occupy the adjacent position (**5**).

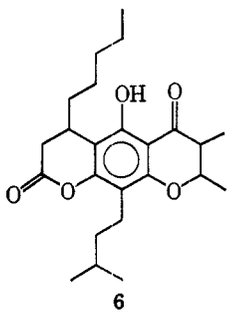


4

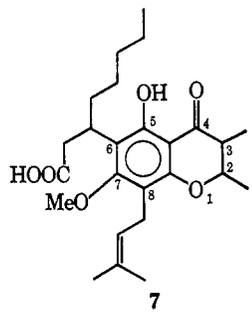


5

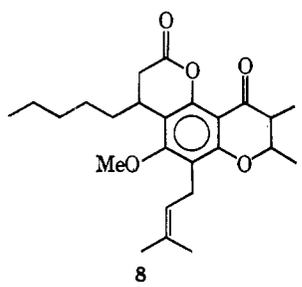
Although it may be assumed by analogy with blancoic acid and other products of *Calophyllum* species that oxygenation of papuanic acid is based on a phloroglucinol pattern, independent evidence is available to prove the point. Demethylation of dihydropapuanic acid by brief treatment with hydriodic acid in acetic anhydride gave demethyldihydropseudopapuanolide, $C_{24}H_{34}O_5$, a lactone similar in its properties to papuanolide. The new product, however, shows a nmr signal at τ −2.10 (1 H) and an ir band at 6.12 μ, indicating that the chelated hydroxyl is still present. Lactone formation must therefore involve a newly formed hydroxyl at the remaining position *ortho* to the carboxylic chain, and consequently demethyldihydropseudopapuanolide has the structure **6**. The corresponding structure for papuanic acid is thus **7**, and papuanolide is **8**.



6

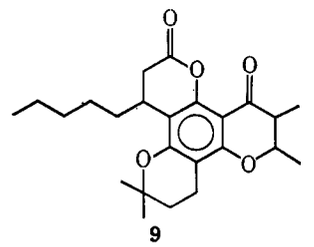


7

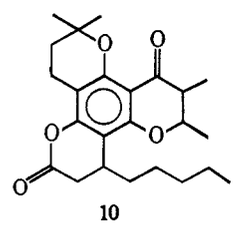


8

Demethylation of papuanic acid under the same conditions, followed by treatment with DCC, led to yet another lactone, cyclodemethylpapuanolide (**9**). The absence of the nmr and ir signals associated with the chelated hydroxyl shows the direction of lactonization, while the nmr spectrum now shows the peaks [τ 7.40 (t, 2 H), 8.32 (t, 2 H), 8.67 (s, 2 H)] expected for a 2,2-dimethylchroman ring rather than those of an isopentenyl chain. The product **9** was particularly important because it differs from dihydroblancolide (**10**) only in an interchange of the lactone and chroman rings, and a comparison of the two compounds illuminated the rearrangement leading to **10**.[1b]



9



10

Isopapuanic acid shows the same chemical and physical behavior as papuanic acid, and the close similarity is maintained throughout the parallel series of derivatives. In particular, isopapuanic acid also yields pentylsuccinic acid on oxidation and also lactonizes onto the chelated hydroxyl group. A significant

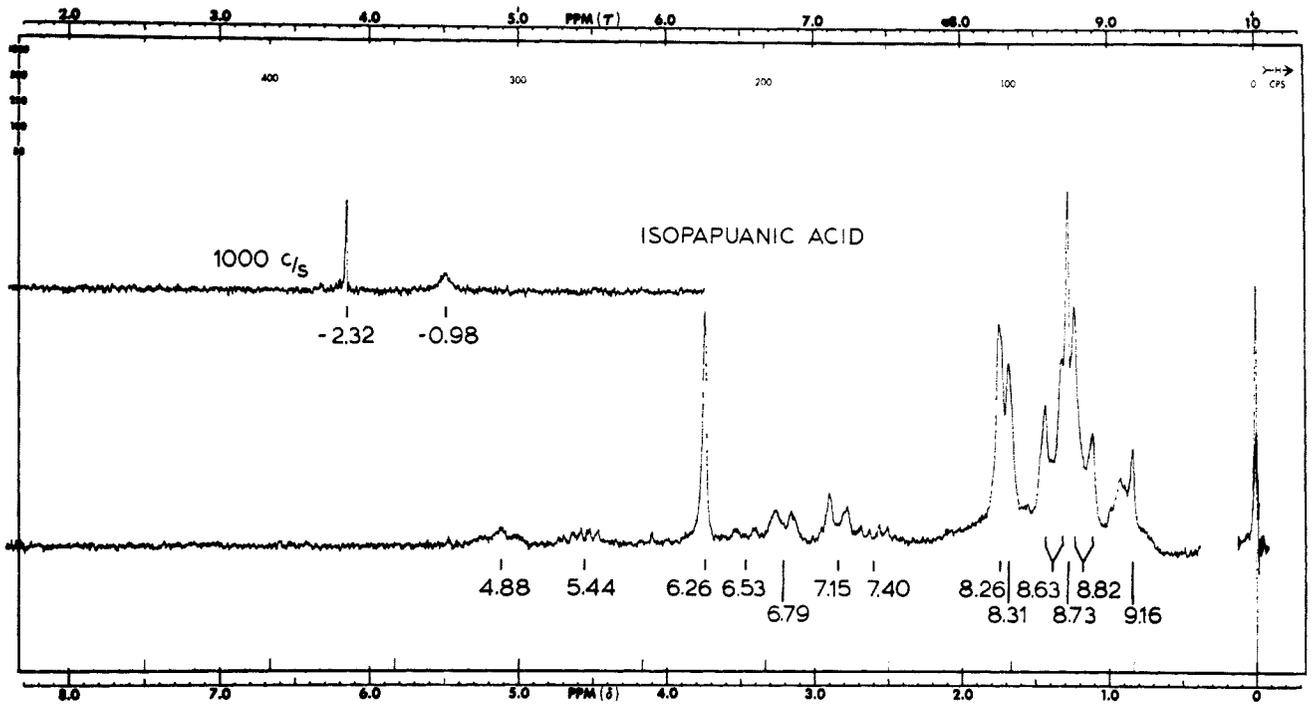
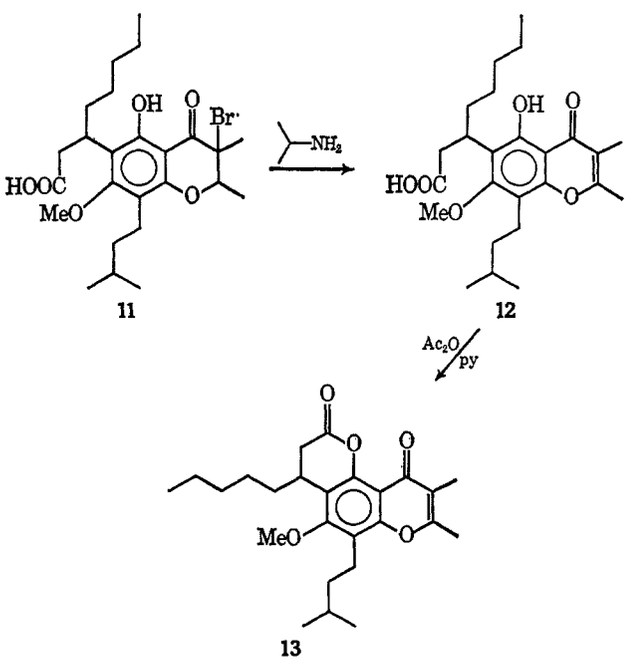


Figure 2.—The 60-MHz nmr spectrum of isopapuanic acid in CCl_4.

difference between the two molecules does appear, however, in the nmr spectra (Figure 2). Isopapuanic acid shows the signals resulting from the 2,3-dimethylchromanone ring at τ 5.44 (m, 1 H), 8.63 (d, 3 H), and 8.82 (d, 3 H). Besides the shift in position, the low-field multiplet also shows J = 3, 6 Hz instead of J = 10, 6 Hz as found in papuanic acid. As has been discussed in analogous cases,[4,6,7] these changes are indicative of *cis*-2,3-dimethyl substitution in isopapuanic acid, in contrast to the *trans* arrangement in papuanic.

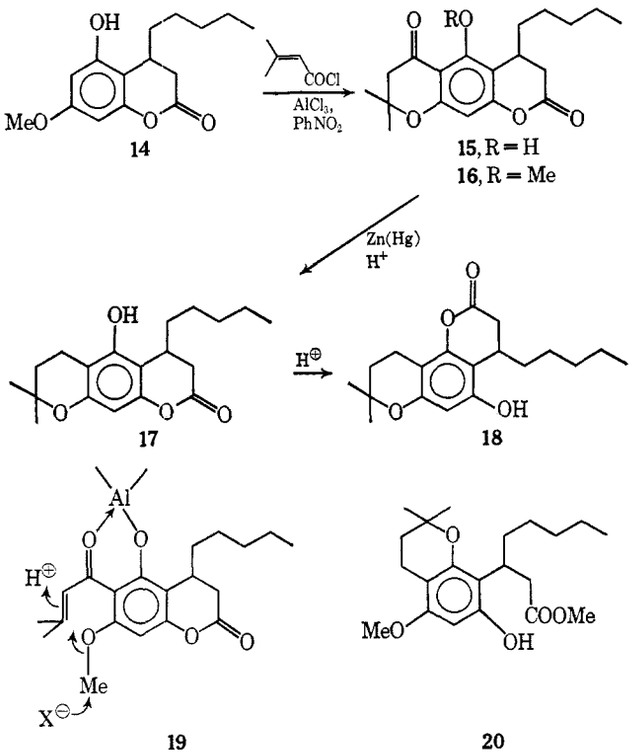
To confirm that both papuanic and isopapuanic acids have the structure **7**, differing only in stereochemistry, both compounds were converted into the same chromone (**13**). Bromination of either dihydropapuanic or dihydroisopapuanic acid with bromine in glacial acetic acid led to mixtures of *cis*- and *trans*-3-bromo derivatives (**11**). Dehydrohalogenation of the *trans* isomers gave the acid **12**, neopapuanic acid, which was lactonized in the usual way to **13**, neopapuanolide. Products obtained from both starting materials were identical chromatographically and in all spectral details.



Synthesis.—The structure deduced for papuanic acid was confirmed by the synthesis of a derivative, methyl cyclodemethylpapuanate (**26**). The key intermediate in this synthesis proved to be the hydroxychromanone lactone **22**, whose methyl ether **21** had previously been prepared in the synthesis of methyl O-methyldihydroblancoate.[1b]

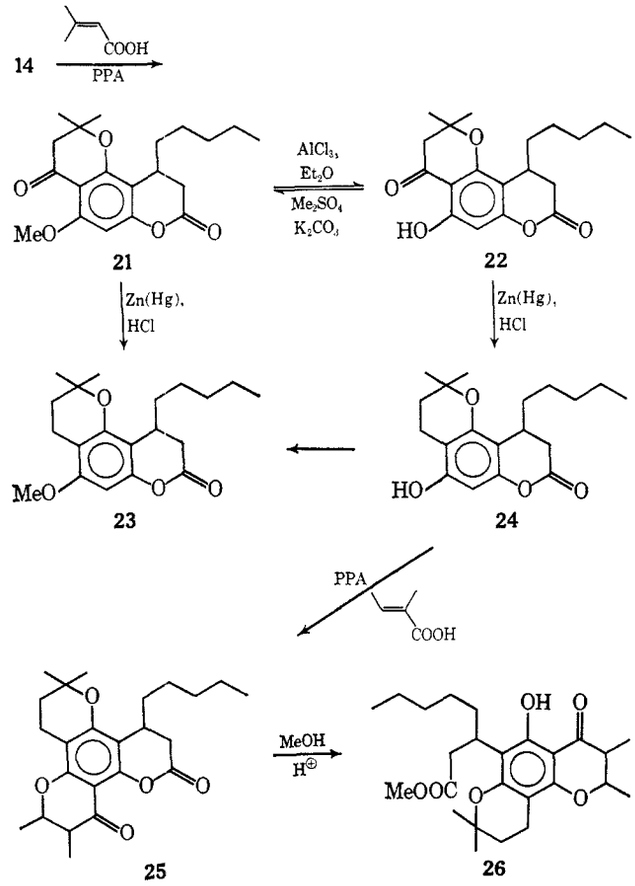
During early attempts to synthesize **21**, it was observed that treatment of the dihydrocoumarin **14** with senecioyl chloride and aluminum chloride in nitrobenzene led to a lactonic product containing a chelated hydroxyl but no methoxyl group. This was assumed to be **22**, arising by simple demethylation, although such a reaction is surprising since the conditions used generally do not cause ether cleavage. Clemmensen reduction of this material, however, led to *two* chroman products, one of which was formed at the expense of the other upon prolonged reaction. Since the conditions were too mild to produce rearrangement of the chroman ring, a lactone interchange, although incompatible with structure **22**, appeared to be involved. Evidence that the starting chromanone was in fact **15**, the only alternative structure consistent with the spectra, was obtained by its methylation to a methyl ether (**16**) different from **21**. On this basis the two reduction products are assigned the structures **17** and **18**.

To account for this unexpected result, we suggest that the demethylation observed is a consequence of the particular unsaturated acid used in the acylation. If the aromatic substitution occurs in a complex in which coordination of the carbonyl and hydroxyl groups with aluminum holds the side chain in a favorable orientation, electrophilic attack on the double bond can transmit electron demand to the ether oxygen as shown in



19 and increase the ease of demethylation. It is possible that this reaction depends on the ability of senecioic acid to generate a tertiary carbonium ion upon protonation of its double bond, since the reaction of **20** with tigloyl chloride under very similar conditions did not lead to demethylation.[1b]

The desired product, **22**, was ultimately obtained by the demethylation of **21** using aluminum chloride in ether.[9] Methylation returned **21**, showing the absence of rearrangement. Clemmensen reduction of **22** gave a single product, **24**, whose structure was confirmed by methylation to **23**, previously prepared by reduction of **21**.[1b]



The insertion of the 2,3-dimethylchromanone system into **24** was accomplished with tiglic acid and polyphosphoric acid, tigloyl chloride and aluminum chloride, the reagents of choice in the blancoic acid series, proving inferior here. The product **25**, a mixture of stereoisomers (see below), proved difficult to extract from silica gel plates and was converted with acidic methanol into the corresponding methyl esters (**26**). These could be separated into two fractions, of which the more mobile showed the nmr characteristics of a *trans* chromanone and the less mobile those of the *cis* compounds. These products were identical in their chromatographic behavior and their uv, ir, nmr, and mass spectra with corresponding fractions obtained by esterification of the cyclodemethyl acids prepared by hydriodic acid demethylation of the natural mixture of papuanic and isopapuanic acids.

Stereochemistry.—Papuanic acid possesses three asymmetric centers, two in the chromanone ring and one in the octanoic acid chain. As has already been discussed, it differs from isopapuanic acid in having *trans* rather than *cis* substitution in the chromanone, *i.e.*, in *one* of these centers. The stereochemical identity of the acidic chains of the two molecules was shown by the correspondence of the ORD curves of samples of neopapuanolide (**13**) prepared from each acid. Further confirmation and evidence of the absolute configuration at this center was obtained by the isolation of (+)-(*R*)-*n*-pentylsuccinic acid (**27**)[10] from the oxidative degradations of both papuanic and isopapuanic acids.

Treatment of papuanic acid with dilute base gave a mixture of starting material and an isomeric product, epipapuanic acid. The nmr spectrum of epipapuanic acid is clearly that of a *cis*-2,3-dimethylchromanone and is essentially indistinguishable from that of isopapuanic acid. The two compounds are clearly different, however, since they show opposite signs of rotation. Since the third asymmetric center must be the same in both, epipapuanic and isopapuanic acids are not enantiomers, but they must have opposite configurations at both C-2 and C-3. Since epimerization of papuanic acid at C-3 leads to epipapuanic acid, a single inversion at C-2 must therefore be required to produce isopapuanic acid, and the two molecules differ only with respect to the stereochemistry at that center.

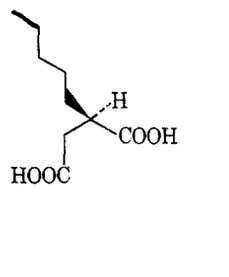
In confirmation, base-catalyzed epimerization of isopapuanic acid gave epiisopapuanic acid, similar in nmr absorption to papuanic acid but again differing in sign of rotation. Similarly, reactions involving strong acid treatment (*e.g.*, HI demethylation) lead to pairs of products epimeric at C-3 and different in the papuanic and isopapuanic acid series.

Corresponding to the epimerization experiments, bromination of dihydropapuanic and dihydroisopapuanic acids also produces mixtures of different *cis*- and *trans*-3-bromo derivatives.

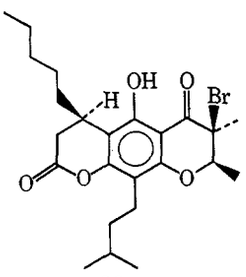
(9) W. Baker, *J. Chem. Soc.*, 662 (1941).

(10) A. Fredga, *Tetrahedron*, **8**, 126 (1960); A. Fredga, J. P. Jennings, W. Klyne, P. M. Scopes, B. Sjöberg, and S. Sjöberg, *J. Chem. Soc.*, 3928 (1965).

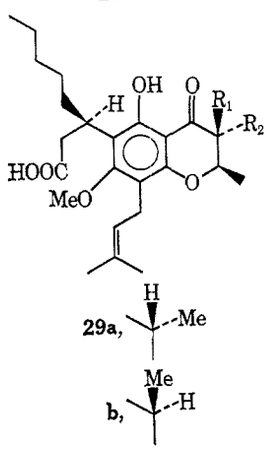
Extensive degradative attempts to obtain one or the other of the asymmetric centers of the chromanone ring in a form proving the absolute configuration were unsuccessful. Ultimately a crystalline bromo compound (**28**) was obtained from dihydrodemethylpseudopapuanolide (**6**) and was shown by X-ray crystallographic techniques to have the structure and absolute configuration indicated.[11] Since the preparation of this compound leaves the configuration at C-2 unchanged, papuanic acid is therefore **29a**, and isopapuanic is acid **30a**. Epipapuanic and epiisopapuanic acids are **29b** and **30b**, respectively.

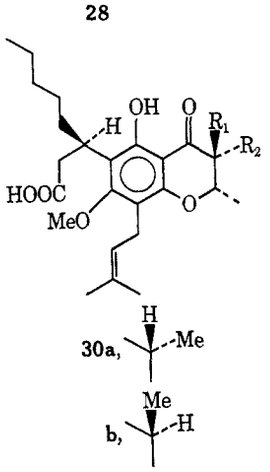


27



28





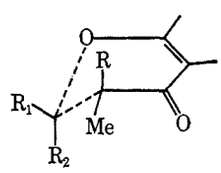
The availability of a complete set of stereoisomers in this series of compounds permits us to consider the conformational differences which exist among them. As has previously been discussed,[4] the change in $J_{2,3}$ between the *trans* and *cis* compounds reflects a change from a (2e,3e) methyl arrangement to (2e,3a) or (2a,3e). A decision in favor of the latter orientation can be made on the basis of the chemical shifts of the various signals associated with the chromanone ring (Table I).

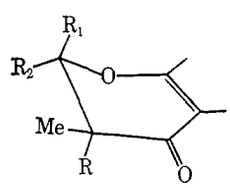
TABLE I
CHROMANONE NMR SIGNALS OF VARIOUS PAPUANIC ACID STEREOISOMERS

	C-2H, τ	C-2Me, τ	C-3H, τ	C-3Me, τ
Papuanic acid (**29a**)	5.89	8.51	7.50	8.84
Isopapuanic acid (**30a**)	5.44	8.63	7.40	8.82
Epipapuanic acid (**29b**)	5.50	8.62	7.55	8.77
Epiisopapuanic acid (**30b**)	5.88	8.50	7.50	8.81

It is clear from Table I that the C-2 proton signal shifts downfield and the methyl signal upfield on passing from the *trans* to the *cis* compounds. The C-3 signals, however, are only slightly affected. Since axial substituents are more shielded than their equatorial counterparts,[12] these changes indicate that it is the C-2 methyl group that becomes axial in the *cis* isomers.[13] This occurs regardless of whether actual inversion occurs at C-2, as in isopapuanic acid, or at C-3, as in epipapuanic acid. To achieve this result, however, the basic epimerization of papuanic acid must be accompanied as shown by a conformational flip of the chromanone ring.[14]

The structural assignment and conformational analysis of the 3-bromo derivatives is complicated by the absence of $J_{2,3}$. Nevertheless the desired results can be obtained by a more roundabout argument. Comparison of the ir and uv spectra of dihydropapuanic and isopapuanic acids with those of their *cis*- and *trans*-3-bromo derivatives (Table II) shows that in all cases bromination is accompanied by marked shifts of the uv maxima to longer wavelengths and by no significant changes in the ir carbonyl absorption.





29a, R = H; R_1 = Me; R_2 = H
30a, R = H; R_1 = H; R_2 = Me
31a, R = Br; R_1 = Me; R_2 = H
32a, R = Br; R_1 = H; R_2 = Me

29b, R = H; R_1 = Me; R_2 = H
30b, R = H; R_1 = H; R_2 = Me
31b, R = Br; R_1 = Me; R_2 = H
32b, R = Br; R_1 = H; R_2 = Me

TABLE II
SPECTRAL PROPERTIES OF BROMINATED DIHYDROPAPUANIC ACIDS

	Ir, μ	Uv, mμ
Dihydropapuanic acid	6.11	285, 356
trans-3-Bromo (**31a**)	6.12	292, 367
cis-3-Bromo (**31b**)	6.11	296, 373
Dihydroisopapuanic acid	6.12	287, 358
cis-3-Bromo (**32a**)	6.13	294, 369
trans-3-Bromo (**32b**)	6.15	296, 369

These results are consistent only with an axial orientation of the bromine atom, since an equatorial bromine causes a hypsochromic shift in the carbonyl-stretching band[15] and has relatively little effect on the uv spectrum.[16] Such a result is expected in view of the unfavorable dipole–dipole interactions in equatorial α-bromo ketones and the small difference in energy between the *cis*- and *trans*-methyl arrangements in this series.

Given the axial orientation of the bromine atoms, the conformation at C-2 follows from the observation

(11) I. Singh and G. H. Stout, in preparation.

(12) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Amer. Chem. Soc.*, **80**, 6098 (1958); L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, pp 115–119.

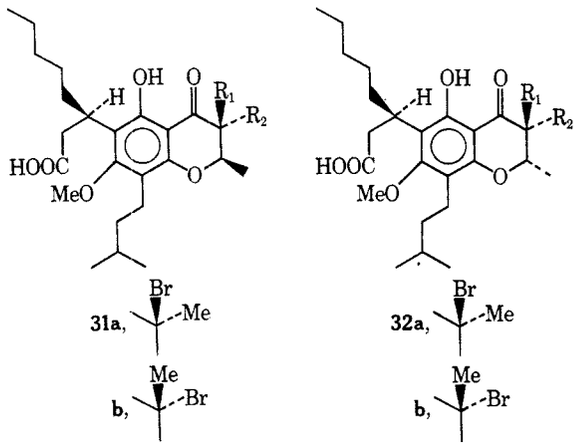
(13) This is presumably a consequence of the "3-alkyl ketone effect." See N. L. Allinger and L. A. Freiberg, *J. Amer. Chem. Soc.*, **84**, 2201 (1962).

(14) The structures are represented in the "sofa" form [E. M. Philipin and T. S. Wheeler, *Proc. Chem. Soc.*, 167 (1958)] rather than the more familiar half-chair conformation because the former is in much better accord with the X-ray results on **28**.

(15) R. N. Jones, D. A. Ramsey, F. Herling, and K. Dobriner, *J. Amer. Chem. Soc.*, **74**, 2828 (1952); E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience Publishers, New York, N. Y., 1965, pp 460–469.

(16) R. C. Cookson, *J. Chem. Soc.*, 282 (1954).

that the nmr signal from the C-2 proton appears in one isomer of each pair at τ 5.3 and in the other at *ca.* 6.2.[17] The former is clearly the product with the equatorial proton and *cis* methyls, *i.e.*, **31b** and **32a**, while the latter is the *trans* compound with the axial proton, **31a** and **32b**.



In confirmation of these arguments, only those isomers assigned the *trans* configuration, 3-bromodihydropapuanic acid (**31a**) and 3-bromodihydroepiisopapuanic acid (**32b**), are dehydrobrominated when treated with isopropylamine. The *cis* isomers are unaffected. This result is entirely in agreement with the proposed configurations, since only the *trans* isomers have the large dihedral angle between the proton and bromine needed for easy elimination.

Final support of these views was obtained from the crystallographic structure analysis of **28**, which was selected as a *trans* isomer on the basis of its nmr spectrum and so proved to be. In addition the axial orientation of the bromine was also confirmed, at least in the solid state.[11]

The epimerization experiments on both papuanic and isopapuanic acids led to equilibrium mixtures in which the ratio of *trans/cis* isomers was *ca.* 2:1. These findings indicate a relatively small energy difference between the two configurations, as might be expected from the reduced number of axial–axial interactions possible in this system. Bromination of the two dihydro acids, on the other hand, leads to 2:1 *cis/trans* product ratios. This result is reasonable, however, if the reaction is assumed to proceed through the chromanone enol, in which favored bromine approach is from the side away from the C-2 methyl group.

Discussion

Papuanic and isopapuanic acids represent the first pair of stereoisomeric products isolated from a species of *Calophyllum*. The results outlined above, together with those obtained for other related dihydrocoumarinic acids from this genus,[1b,7] suggest a common stereochemistry (*R*) for the asymmetric center of the acid side chain but greater variation in the chromanone ring. Since the difference between papuanic and isopapuanic acids occurs at the very stable C-2 and not, as might have been expected, at the readily epimerizable C-3, it must reflect a true lack of specificity in the biosynthesis.

The determination of the absolute stereochemistry of papuanic acid and its isomers now provides a basis for the extension of studies into the stereochemistry of the related members of this series by ORD and CD methods. These compounds also provide relatively rigid models for investigations more generally into the interaction of molecular asymmetry and the acylphenone chromophore. Studies in both of these areas are currently in progress and will be described in subsequent papers.[18]

Since lactonization is possible in papuanic acid, it may be regarded formally as a hydrolyzed dihydrocoumarin, unlike the previously reported blancoic[1b] and apetalic[6] acids, which are incapable of lactone formation without rearrangement. As a result it can no longer be suggested that the formation of these acids occurs only in those cases in which the normal biosynthetic paths leading to coumarins are blocked. It would clearly be of interest, therefore, to know at what stage in the biosynthesis the reduction occurs which produces papuanic acid rather than its coumarin analog. Comparison with the other *Calophyllum* products suggests that some precursor other than the coumarin itself is involved, but a clear decision will have to await further studies.

Experimental Section

All melting points were taken on a Kofler hot stage and are corrected. Combustion analyses were performed by Dr. A. Bernhardt of Mülheim (Ruhr), West Germany. Silica gel 922 (200–325 mesh) from Grace–Davisson Chemical Co. was used in all column chromatography with various concentrations of hexane and ethyl acetate as elutants. For tlc Merck silica gel G was used, again with mixtures of hexane and ethyl acetate. Unless otherwise stated, anhydrous $MgSO_4$ was used to dry solutions. Uv spectra were taken on a Cary Model 14 spectrophotometer in 95% EtOH. Ir spectra were taken on a Perkin-Elmer Model 21 with a NaCl prism. The letter in parentheses signifies a strong (s), medium (m), or weak (w) absorption band. Most nmr spectra were obtained on a Varian A-60 spectrometer, but some were taken by Mr. B. J. Nist on a Varian HR-60. The letter in parentheses refers to the multiplicity of the peak. The number following the letter, when given, is the estimated integrated intensity of the peak. In some instances the area could be measured and this is indicated. Mass spectra were determined on an AEI Model MS 9 with the aid of Mrs. M. M. Krahn.

Isolation of Papuanic and Isopapuanic Acids.—The ground bark (418 g) from *Calophyllum papuanum* Lauterb. (Guttiferae), collected near Lae, New Guinea, was extracted with pentane in a Soxhlet extractor for 2 hr. Most of the yellow material was extracted at the end of 1/2 hr. Upon evaporation of the pentane 52 g (12%) of a viscous yellow-green resin was obtained.

The crude resin (1.99 g) in 50 ml of hexane was extracted with Na_2CO_3 (0.57 g) in 50 ml of water. The hexane layer was extracted a second time with Na_2CO_3 (0.10 g) in 25 ml of water. Each of the two base fractions was acidified carefully with 5% HCl to pH 7 and extracted once with 25 ml of ether. The bright yellow ether solutions were dried and filtered. After evaporation of the ether extract i contained a bright yellow oil (1.55 g) and extract ii a yellow-brown oil (0.28 g). The carbonate-insoluble substances remaining in the hexane were isolated as a yellow-green oil (0.09 g).

Column chromatography of 9.50 g of the yellow–green crude resin on 450 g of silica gel gave eight major fractions, of which three were homogeneous by tlc. The elutant (7:1 hexane–ethyl acetate) was not changed during the course of the separation. Data from the chromatogram are shown in Table III.

(17) This region is obscured by other signals, and it is not possible to locate the peak exactly.

(18) G. H. Stout and G. L. Hickernell, unpublished results.

TABLE III
CHROMATOGRAPHY OF *C. papuanum* RESIN

Fraction	Composition[a]	Vol., ml	Wt, g	Resin, %
1	X	75	0.175	2
2	X	375	0.145	2
3	P	225	3.266	34
4	P > I	60	0.587	6
5	P = I	75	0.591	6
6	I > P	360	1.657	17
7	I	630	1.286	14
8	I, X	300	0.222	2

[a] P = papuanic acid, I = isopapuanic acid, X = impurity.

Papuanic Acid.—A bright yellow oil (3.27 g) was obtained after evaporation of solvent from fraction 3. The oil was soluble in all common organic solvents, and attempts to crystallize it were unsuccessful. A yellow solid was obtained, however, upon refrigeration of pure papuanic acid: mp 73–77°; nmr (CCl_4) (integrated intensities measured) τ −2.34 (s, 1), −1.76 (s, 1), 4.90 (t, 1), 5.89 (m, 1), 6.28 (s, 3), 6.3–6.6 (m, 1), 6.81 (d, 2), 7.18 (d, 2), 7.50 (m, 1), 8.28 (s, 3), 8.34 (s, 3), 8.51 (d, 3), 8.73, 8.84 (d), 9.16 (t, 3) (Figure 1) (HR-60); uv max 286 mμ (ε 13,300), 357 (3300); ir (CCl_4) 3.35 (m), 5.84 (s), 6.11 (s), 6.31 (w), 6.95 (m), 7.21 (w), 7.43 (w), 7.70 (w), 7.86 (w), 8.63 (m), 8.75 (m), 9.11 μ (m); $[\phi]_{589}$ +350° (*c* 1.91 × 10^{-1}, EtOH).

Anal. Calcd for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39; mol wt, 432.251. Found: C, 69.37; H, 8.28; mol wt, 432.255.

Isopapuanic Acid.—Fraction 7 contained a greenish yellow oil (1.29 g) after evaporation of the solvents. A portion of this material (0.51 g) in 25 ml of hexane was extracted with Na_2CO_3 (0.14 g) in 25 ml of water. The aqueous phase was acidified with 5% HCl to pH 7 and extracted once with 25 ml of ether. The ethereal solution was dried, filtered, and evaporated to give a bright yellow oil (0.24 g). Isopapuanic acid is soluble in all common organic solvents and could not be crystallized [nmr (CCl_4) (integrated intensities measured) τ −2.32 (s, 1), −0.98 (s, 1), 4.88 (t, 1), 5.44 (m, 1), 6.26 (s, 3), 6.35–6.65 (m, 1), 6.79 (d, 2), 7.15 (d, 2), 7.40 (m, 1), 8.26 (s, 3), 8.31 (s, 3), 8.63 (d), 8.73, 8.82 (d), 9.16 (t, 3) (Figure 2) (HR-60); uv max 280 mμ (ε 12,700), 360 (3000); ir (CCl_4), 3.35 (m), 5.84 (s), 6.11 (s), 6.30 (w), 6.95 (m), 7.21 (w), 7.42 (w), 7.66 (w), 7.75 (m), 8.61 (m), 8.78 (m), 9.15 μ (w); $[\phi]_{589}$ −100° (*c* 8.90 × 10^{-2}, EtOH)].

Anal. Calcd for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39; mol wt, 432.251. Found: C, 69.64; H, 8.52; mol wt, 432.255.

Dihydropapuanic Acid.—Papuanic acid (97 mg, 2.24 × 10^{-4} mol) was treated with hydrogen in ethanol using prereduced platinum oxide catalyst. Reaction was complete in 1/2 hr, at which time 5.9 ml (5.1 ml at STP, 2.28 × 10^{-4} mol) of hydrogen had been consumed. The molecular weight of papuanic acid calculated from this value is 434 ± 10. The solution was filtered, and the solvent was evaporated to give a yellow oil: nmr (CCl_4) (integrated area measured) τ −2.40 (s, 1), −1.38 (s, 1), 5.81 (m, 1), 6.25 (s, 3), 6.3–6.7 (m, 1), 7.16 (d, 2), 7.45 (t, 2), 7.3–7.7 (m, 1), 8.50 (d, 3), 8.81 (d), 9.06 (d), 9.16; uv max 285 mμ (ε 13,500), 356 (3260); ir (CCl_4) 3.43 (m), 3.51 (m), 5.84 (s), 6.11 (s), 6.32 (w), 7.00 (m), 7.21 (w), 7.42 (w), 7.66 (m), 8.40 (w), 8.60 (w), 8.78 (m), 8.91 (m), 9.30 μ (w).

Anal. Calcd for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 69.33; H, 8.91.

Dihydroisopapuanic Acid.—Isopapuanic acid was similarly reduced using prereduced platinum oxide and hydrogen at 1 atm. Hydrogen uptake was complete after 20 min of brisk stirring. The solution was filtered and evaporated to give a yellow oil: nmr (CCl_4) τ −2.32 (s, 1), −0.2 (broad, 1), 5.48 (m, 1), 6.24 (s, 3), 6.3–6.7 (m, 1), 7.18 (d, 2), 7.48 (t, 2), 7.4–7.7 (m, 1), 8.61 (d), 8.74, 8.82 (d), 9.05 (d), 9.17; uv max 287 mμ (ε 12,700), 358 (3250); ir (CCl_4) 3.44 (m), 3.51 (w), 5.85 (s), 6.12 (s), 6.32 (w), 6.97 (m), 7.21 (w), 7.45 (w), 7.70 (w), 7.85 (2), 8.42 (w), 8.60 (m), 8.75 (m), 8.94 (m), 9.25 μ (w).

Anal. Calcd for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 69.35; H, 8.65.

Papuanolide (8).—Papuanic acid (72 mg) was dissolved in 5 ml of 2:1 acetic anhydride–pyridine and allowed to stand at room temperature for 1/2 hr. The excess reagents were removed *in vacuo* to give a light yellow oil (72 mg): nmr (CCl_4) (integrated areas measured) τ 4.93 (t, 1), 5.87 (m, 1), 6.25 (s, 3), 6.80 (d and m), 7.30 (d, 2), 7.85 (m, 1), 8.27 (s, 3), 8.33 (s, 3), 8.53 (d), 8.70, 8.93 (d), 9.13; uv max 231 mμ (ε 22,000), 269 (12,100), 328 (4000); ir (CCl_4) 3.45 (s), 3.52 (m), 5.60 (s), 5.89 (s), 6.25 (s), 6.95 (s), 7.23 (m), 7.45 (m), 8.02 (w), 8.42 (w), 8.80 (s), 9.12 (s), 9.37 μ (w).

Anal. Calcd for $C_{25}H_{34}O_5$: C, 72.43; H, 8.27. Found: C, 72.44; H, 8.08.

Isopapuanolide (8).—Isopapuanic acid (59 mg) was treated with 2 ml of 2:1 acetic anhydride–pyridine at room temperature for 1/2 hr. The reagents were removed *in vacuo* to give a nearly colorless oil (57 mg): nmr (CCl_4) τ 4.93 (t, 1), 5.44 (m, 1), 6.24 (s, 3), 6.78 (d, 2), 6.5–7.0 (m, 1), 7.40 (d, 2), 7.8–8.2 (m, 1), 8.27 (s, 3), 8.33 (s, 3), 8.64 (d), 8.91 (d), 9.12 (t, 3); uv max 231 mμ (ε 21,400), 270 (10,100), 329 (3600); ir (CCl_4) 3.33 (m), 5.57 (s), 5.86 (s), 6.22 (s), 6.93 (s), 7.22 (w), 8.01 (w), 8.40 (w), 8.85 (s), 9.10 μ (m).

Anal. Calcd for $C_{25}H_{34}O_5$: C, 72.43; H, 8.27. Found: C, 72.48; H, 8.10.

Cyclodemethylation of Papuanic and Isopapuanic Acids.—A mixture of papuanic and isopapuanic acids (520 mg) was dissolved in 10 ml of acetic anhydride in a 50-ml boiling flask. Hydriodic acid (50%, 7 ml) was added very carefully, and the mixture was heated under reflux at 135° for 3 hr. The cooled reaction mixture was poured into 20 ml of water containing 4 g of $NaHSO_3$. The organic substances were extracted with benzene, washed with 10% aqueous bisulfite, and dried (Na_2SO_4). A light orange oil (460 mg) was obtained after evaporation of the benzene. Chromatography of a portion of this oil (50 mg) gave two fractions, one containing the *trans* isomers (28 mg) and one the *cis* (21 mg).

Sublimation of the *trans* isomers gave a mixture of cyclodemethylpapuanic acid and cyclodemethylepiisopapuanic acid as a light yellow solid: mp 53–57°; nmr (CCl_4) τ 5.90 (m, 1), 6.37 (m, 1), 7.24, 7.36, 7.46, 7.57, 8.18, 8.29, 8.50 (d, 3), 8.62, 8.67, 8.70, 8.74, 8.88, 9.14 (t, 3) (HR-60 with CAT); uv max 218 mμ (ε 21,300), 299 (19,400), 344 (3400); ir (CCl_4) 3.43 (m), 3.50 (w), 5.84 (s), 6.10 (s), 6.27 (w), 6.91 (m), 7.21 (w), 7.40 (m), 8.61 (m), 8.92 μ (m).

Anal. Calcd for $C_{24}H_{34}O_6$: C, 68.88; H, 8.19. Found: C, 69.06; H, 8.21.

Sublimation of the *cis* isomers gave a similar mixture of cyclodemethylisopapuanic acid and cyclodemethylepipapuanic acid as a yellow glassy solid: mp 44–50°; nmr (CCl_4) τ −2.12 (s, 1), −0.62 (broad, 1), 5.48 (m, 1), 6.2–6.5 (m, 1), 7.24, 7.37, 7.45, 7.55, 8.16, 8.28, 8.40, 8.61 (d), 8.67, 8.76, 8.84 (d), 9.15 (t, 3); uv max 217 mμ (ε 21,000), 300 (19,500), 345 (2760).

Anal. Calcd for $C_{24}H_{34}O_6$: C, 68.88; H, 8.19. Found: C, 69.04; H, 8.36.

Methyl Cyclodemethylpapuanate and Its Stereoisomers (26).—The mixture of cyclodemethyl acids prepared above (80 mg) was treated with methanol and a few drops of concentrated H_2SO_4. The solution was refluxed for 2 hr, poured into an excess of 5% $NaHCO_3$, and extracted twice with ether. The ethereal extract was washed with water, dried, and evaporated to give 61 mg of a yellow oil. Tlc showed two spots with identical rust-colored fluorescences. Separation by preparative tlc gave 37 mg (43%) of a yellow oil corresponding to the upper spot and 18 mg (21%) corresponding to the lower spot. The material from the upper spots (*trans*) had nmr (CCl_4) τ −2.22 (s, 1), 5.90 (m 1), 6.50 (s, 3), 7.48 (t), 8.29 (t), 8.53 (d), 8.65 (s), 8.84 (d), 9.17 (t); ir (CCl_4) 5.75 (s), 6.13 (s), 6.27 (m), 6.91 μ (s); uv max 298 mμ (ε 18,900), 342 (2450).

Anal. Calcd for $C_{25}H_{36}O_6$: 69.42; H, 8.39; mol wt, 432.251. Found: C, 69.34; H, 8.55; mol wt, 432.253.

The material from the lower spot (*cis*) had nmr (CCl_4) τ −2.15 (s, 1), 5.45 (m, 1), 6.48 (s, 3), 7.48 (t), 8.27 (t), 8.61 (d), 8.63 (s), 8.82 (d), 9.15 (t); uv max 298 mμ (ε 19,800), 342 (2780); ir (CCl_4) 5.75 (s), 6.14 (s), 6.29 (m), 6.94 μ (m).

Anal. Calcd for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39; mol wt, 432.251. Found: C, 69.59; H, 8.54; mol wt, 432.250.

Cyclodemethylpapuanolide (9).—Cyclodemethylpapuanic acid (50 mg) prepared as described above from pure papuanic acid was treated with dicyclohexylcarbodiimide (40 mg) in 5 ml of dichloromethane. After 15 min, 5 ml of 80% acetone was added. The solvents were evaporated, and the material was taken up in 5 ml of CH_2Cl_2. Precipitated dicyclohexylurea was removed by filtration, and the solution was chromatographed on a preparative tlc plate. A light yellow glass was obtained (35 mg): nmr

(CCl_4) τ 5.86 (m, 1), 6.85 (m, 1), 6.85 (m, 1), 7.40, 7.6–7.9 (m, 1), 8.11, 8.23, 8.32, 8.54 (d), 8.67, 8.75, 8.87 (d), 9.12; uv max 240 (ϵ 19,600), 285 (13,700), 320 sh (3360); ir (CCl_4) 3.44 (m), 3.53 (m), 5.60 (s), 5.90 (s), 6.22 (s), 6.90 (s), 7.23 (w), 7.54 (m), 8.11 (m), 8.61 (s), 8.83 (s), 8.94 μ (s).

Anal. Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 72.17; H, 8.28.

Cyclodemethylisopapuanolide (9).—Cyclodemethylisopapuanic acid prepared from pure isopapuanic acid was dehydrated with dicyclohexylcarbodiimide as described above. A light yellow oil was obtained: ir (CCl_4) 3.43 (m), 3.51 (w), 5.60 (s), 5.90 (m), 6.21 (s), 6.90 (m), 7.22 (w), 7.53 (w), 8.09 (m), 8.62 (s), 8.84 (s), 8.92 μ (s).

Demethyldihydropseudopapuanolide and Demethyldihydropseudoepipapuanolide (6).—Dihydropapuanic acid (198 mg) dissolved in 2 ml of acetic anhydride was mixed carefully with 1 ml of 50% HI. The solution was heated on a steam bath for 10 min, poured into 15 ml of 10% $NaHSO_3$, stirred, and extracted twice with ether. The combined ethereal extracts were washed twice with water and dried. Preparative tlc yielded demethyldihydropseudopapuanolide (78 mg) and demethyldihydropseudoepipapuanolide (34 mg).

Demethyldihydropseudopapuanolide was sublimed to give a light yellow solid, mp 94–98°. A sample was dissolved in hot acetone–water and cooled to −15° to give light yellow crystals: mp 91–95°; nmr (CCl_4) τ −2.14 (s, 1), 5.87 (m, 1), 6.75 (m, 1), 7.36, 7.45, 7.57, 8.48 (s), 8.65, 8.80 (d), 9.07 (d); uv max 216 mμ (ϵ 26,000), 287 (15,200), 351 (3300); ir (CCl_4) 3.39 (m), 5.60 (s), 6.12 (s), 6.90 (s), 7.24 (m), 7.43 (w), 7.66 (w), 7.85 (w), 8.05 (w), 8.32 (w), 8.60 (m), 8.80 (s), 9.50 μ (w).

Anal. Calcd for $C_{24}H_{34}O_5$: C, 71.67; H, 8.51; mol wt, 402.240. Found: C, 71.84; H, 8.59; mol wt, 402.242.

Sublimation of demethyldihydropseudoepipapuanolide yielded a light yellow solid: mp 94–97°; nmr (CCl_4) τ −1.94 (s, 1), 5.5 (m, 1), 6.8 (m, 1), 7.35, 7.45, 7.57, 8.59 (d), 8.81 (d), 9.06 (d); uv max 215 mμ (ϵ 27,400), 286 (16,200), 352 (3500); ir (CCl_4) 3.39 (s), 5.60 (s), 6.11 (s), 6.90 (s), 7.22 (m), 7.43 (w), 7.66 (w), 7.85 (w), 8.05 (w), 8.60 (m), 8.80 μ (s).

Nitric Acid Oxidation of Papuanic Acid.—Papuanic acid (400 mg) in a 50-ml boiling flask fitted with a reflux condenser was treated with 20 ml of 50% HNO_3. This mixture was heated gently on a steam bath for 3 days. After the solution had cooled, solid Na_2CO_3 was added until it was basic to litmus. The solution was evaporated to dryness and concentrated HCl (2 ml) and CH_2Cl_2 (25 ml) were added. The layers were separated, and the CH_2Cl_2 solution was dried, filtered, and evaporated to give a light yellow oil (82 mg). An ethanolic solution of this oil was treated with Norit and filtered to obtain a colorless solution. The ethanol was evaporated, and the oil was dissolved in 1 ml of benzene, to which was rapidly added 5 ml of hexane. A white solid began to form, and the solution was refrigerated. The resulting crystals were filtered, washed with hexane, and air dried to give 10.4 mg (6%) of *n*-pentylsuccinic acid: mp 79–83° after sublimation; mmp 79–82° with an authentic sample of racemic *n*-pentylsuccinic acid; ir ($CHCl_3$) 3.45 (m), 5.84 (s), 7.05 (w), 7.80 (w), 8.05 μ (w); ORD (*c* 0.104, EtOH) $[\phi]_{589}$ +43°, $[\phi]_{500}$ +60°, $[\phi]_{350}$ +160°, $[\phi]_{250}$ +630°, $[\phi]_{225}$ +1560°, $[\phi]_{207}$ 0°.

Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.23; H, 8.62.

Synthetic *n*-Pentylsuccinic Acid.—Succinic anhydride (30.0 g) was placed in a 250-ml boiling flask fitted with a Dean–Stark water trap, together with *p*-toluenesulfonic acid monohydrate (1.25 g), 50 ml of absolute ethanol, 100 ml of benzene, and 0.5 ml of water. In the course of 54 hr of refluxing, 14 ml of ethanol–water was drawn off. After an initial distillation of the benzene and ethanol, diethyl succinate (51 g, 98%) was distilled at 101° (15–20 mm).

A three-neck 200-ml flask was fitted with a reflux condenser and a mechanical stirrer. Diethyl succinate (10.4 g, 0.06 mol) and freshly distilled *n*-valeraldehyde (4.3 g, 0.05 mol) were added to KO-*t*-Bu (6.15 g, 0.055 mol) in 60 ml of refluxing *t*-butyl alcohol (distilled from Na) over a 10-min period. The solution was stirred and refluxed for 2.5 hr. After distillation of most of the solvent under reduced pressure, the residue was acidified with 50 ml of 10% HCl. The remainder of the butanol was removed, and the resulting mixture was extracted with three 50-ml portions of ether. The yellow extracts were washed with 50 ml of water and four 25-ml portions of 10% Na_2CO_3. The carbonate extracts were combined and washed with 50 ml of ether which was added to the previous ethereal solution. This was dried, filtered, and evaporated to give a 67% recovery of diethyl succinate (6.95 g).

Excess concentrated HCl (50 ml) was added to the carbonate extracts, which were then extracted with three 50-ml portions of ether. The ethereal extracts were dried and evaporated to yield a light yellow oil (2.0 g). This was dissolved in CCl_4 and filtered to remove succinic acid (0.14 g).

The CCl_4 was evaporated, and the residue (1.86 g) was refluxed with 15 ml of 10% NaOH for 22 hr. Additional NaOH (1 g) was added and heating continued for several hours. The solution was cooled and extracted with two 10-ml portions of CH_2Cl_2. The aqueous solution was treated with Norit, heated, and filtered, before being acidified with 10 ml of concentrated HCl. Extraction of the acidic solution with four 20-ml portions of ether, followed by evaporation of the ether, gave a soft yellow solid (1.14 g), mp 147–154°.

The entire crude product was dissolved in glacial acetic acid and reduced at 1 atm of hydrogen over Adams catalyst. After hydrogen uptake had ceased, the solution was filtered, and the solvent was evaporated. The product was dissolved in 20 ml of benzene, and 10 ml of hexane was added. Crystals of succinic acid (0.151 g) formed and were filtered off. The filtrate was evaporated, and the remaining oil was dissolved in 15 ml of 2:1 hexane–CCl_4. Upon refrigeration white crystals of *n*-pentylsuccinic acid (0.386 g, 4%) formed and were filtered, washed with hexane, and air dried: mp 73–77° [sublimation and repeated crystallization from benzene–hexane raised the melting point to 80–82° (lit.[19] mp 80°)]; nmr (CH_2Cl_2) τ −1.34 (s, 2), 7.10, 7.30, 7.33, 7.42, 7.48, 7.65, 8.57, 8.66, 8.72, 9.12 (t, 3); ir ($CHCl_3$) 3.30 (w), 3.45 (m), 3.80 (w), 5.85 (s), 7.02 (w), 8.03 (w), 10.65 μ (w).

Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.57; H, 8.65.

Nitric Acid Oxidation of Isopapuanic Acid.—Isopapuanic acid (460 mg) was placed in a 50-ml boiling flask fitted with a reflux condenser. A 25-ml portion of 50% HNO_3 was added, and a spontaneous reaction began. After the reaction had subsided the mixture was heated gently on a steam bath for 2 days. The cooled solution was treated with solid $NaHSO_3$ until no more brown gases were given off and was then evaporated to a thick oil. The oil was dissolved in CH_2Cl_2, dried, and evaporated to give a yellow oil (129 mg). This was dissolved in 1 ml of benzene; 5 ml of hexane was added rapidly; and the solution was refrigerated. *n*-Pentylsuccinic acid (13 mg, 6%) was obtained by filtration: mp 80–85°; mmp 78–84° with authentic racemic *n*-pentylsuccinic acid; ir ($CHCl_3$) 3.45 (m), 3.52 (w), 5.84 (s), 6.25 (w), 7.00 (w), 7.75 μ (w); ORD (*c* 0.129, EtOH), $[\phi]_{589}$ +45°, $[\phi]_{500}$ +66°, $[\phi]_{350}$ +184°, $[\phi]_{250}$ +758°, $[\phi]_{225}$ +1835° (peak).

Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.53; H, 8.45.

3-Bromodihydropapuanic Acid (31a).—Dihydropapuanic acid (165 mg) was dissolved at room temperature in 1 ml of glacial acetic acid which was 1 *M* in Br_2. After 30 hr the acetic acid and bromine were evaporated to give a bright yellow oil (241 mg). This was chromatographed on three preparative plates, and three fractions were taken. Fraction i (least mobile) contained 3-bromodihydroepipapuanic acid (**31b**) (65 mg); ii contained both isomers (50 mg); and iii (most mobile) contained **31a** (48 mg): nmr (CCl_4) τ −1.45 (s, 1), −1.24 (s, 1), 6.0–6.7 (m, 2), 6.24 (s, 3), 7.18 (d, 2), 7.50 (t, 2), 8.20 (s, 3), 8.42 (d), 8.56, 8.75, 8.80, 8.86, 9.08 (d), 9.17; uv max 292 mμ (ϵ 12,700), 367 (2830); ir (CCl_4) 3.40 (m), 3.50 (m), 5.86 (s), 6.12 (s), 6.17 (m), 6.32 (w), 6.95 (m), 7.20 (m), 7.45 (w), 7.68 (w), 8.30 (w), 8.74 (m), 8.90 μ (s).

Anal. Calcd for $C_{25}H_{37}O_6Br$: C, 58.47; H, 7.26. Found: C, 58.66; H, 7.32.

3-Bromodihydroepipapuanic Acid (31b).—This material was isolated as described above: nmr (CCl_4) τ −1.50 (s, 1), −1.20 (s, 1), 5.34 (q, 1), 6.26 (s, 3), 6.3–6.8 (m, 1), 7.18 (d, 2), 7.51 (t, 2), 8.20 (s, 3), 8.50 (d), 8.76, 8.79, 9.08 (d), 9.16; uv max 296 mμ (ϵ 12,800), 373 (2800); ir (CCl_4) 3.39 (m), 3.49 (w), 5.85 (s), 6.11 (s), 6.18 (m), 6.35 (w), 7.00 (m), 7.22 (w), 7.52 (w), 7.71 (m), 8.38 (w), 8.85 μ (m).

3-Bromodihydroisopapuanic Acid (32a).—Dihydroisopapuanic acid (185 mg) was dissolved in 1 ml of glacial acetic acid, 1 *M* in Br_2, and left for 18 hr at room temperature. After evaporation of the acetic acid and bromine, a bright yellow oil was obtained

(19) F. Wrede and A. Rothhaas, *Z. Physiol. Chem.*, **226**, 95 (1934).

(255 mg). A portion of this (235 mg) was separated into two fractions by preparative tlc. Fraction i (less mobile) contained a mixture of the two isomers (86 mg), and fraction ii (more mobile) contained **32a** (10 mg): nmr (CCl_4) τ −1.48 (s, 1), −1.10 (s, 1), 5.32 (q, 1), 6.25 (s, 3), 6.3–6.8 (m, 1), 7.17 (d, 2), 7.52 (t, 2), 8.19 (s, 3), 8.50 (d), 8.76, 8.80, 9.08 (d), 9.18; uv max 294 mμ (ε 11,600), 369 (2460); ir (CCl_4) 3.42 (m), 5.84 (s), 6.13 (s), 6.35 (w), 7.00 (w), 7.27 (w), 7.55 (w), 7.75 (w), 8.41 (w,) 8.91 (m), 9.15 (w), 9.35 μ (w).

Anal. Calcd for $C_{25}H_{37}O_6Br$: C, 58.47; H, 7.26. Found: C, 58.73; H, 7.11.

3-Bromodihydroepiisopapuanic Acid (32b).—Fraction i from above was chromatographed on a preparative tlc plate to give **32a** (12 mg) and **32b** (61 mg): nmr (CCl_4) τ −1.43 (s, 1), −0.90 (broad, 1), 6.27 (s, 3), 6.1–6.9 (m, 2), 7.20 (d, 2), 7.50 (t, 2), 8.21 (s, 3), 8.45 (d), 8.58, 8.66, 8.77, 8.80, 9.10 (d), 9.19; uv max 296 mμ (ε 12,800), 369 (2600); ir (CCl_4) 3.42 (m), 5.89 (s), 6.15 (s), 6.20 (sh), 6.35 (w), 7.00 (w), 7.27 (w), 7.53 (w), 7.75 (w), 8.37 (w), 8.80 (m), 8.94 μ (s).

Neopapuanic Acid (12) from Papuanic Acid.—3-Bromodihydropapuanic acid (41 mg) was refluxed in 15 ml of isopropylamine for 4 hr. After solvent evaporation, the product was chromatographed on a preparative plate to give neopapuanic acid (21 mg): nmr (CCl_4) τ −2.70 (s, 1), 6.24 (s, 3), 6.58 (m), 7.05, 7.17, 7.31, 7.45, 7.71 (s, 3), 8.13 (s, 3), 8.48, 8.61, 8.82, 9.07 (d), 9.19; uv max 249 mμ (ε 22,500), 340 (4240); ir (CCl_4) 3.40 (s), 3.49 (m), 5.85 (s), 6.06 (s), 6.27 (m), 6.97 (m), 7.28 (w), 7.51 (m), 7.75 (w), 8.37 (m), 8.82 μ (m).

Anal. Calcd for $C_{25}H_{36}O_6$: Mol wt, 432.251. Found: Mol wt, 432.255.

Neopapuanic Acid (12) from Isopapuanic Acid.—3-Bromodihydroepiisopapuanic acid (38 mg) was refluxed in 15 ml of isopropylamine for 5 hr. The solvent was evaporated, and the product was chromatographed on a preparative plate to give neopapuanic acid (21 mg): nmr (CCl_4) τ −2.74, (s, 1), 6.23 (s, 3), 6.57 (m, 1), 7.03, 7.16, 7.33, 7.47, 7.68 (s, 3), 8.10 (s, 3), 8.45, 8.58, 8.75, 8.78, 9.05 (d), 9.18; uv max 248 mμ (ε 21,900), 341 (4160); ir (CCl_4) 3.40 (s), 3.50 (m), 5.85 (s), 6.06 (s), 6.27 (m), 6.95 (m), 7.27 (w), 7.50 (m), 7.75 (w), 8.36 (m), 8.80 μ (m).

Anal. Calcd for $C_{25}H_{36}O_6$: Mol wt, 432.251. Found: Mol wt, 432.255.

Neopapuanolide (13). A.—Neopapuanic acid from papuanic acid (2.6 mg) was dissolved in 1 ml of 2:1 acetic anhydride–pyridine and left at room temperature for 1/2 hr. The reagents were evaporated to give a colorless oil: nmr (CCl_4) τ 6.17 (s, 3), 6.6–7.1 (m, 1), 7.25, 7.30, 7.70 (s, 3), 8.16 (s, 3), 8.66, 8.75, 9.02 (d), 9.11; uv max 240 mμ (ε 30,000), 270 sh (7100), 313 (7000); ir (CCl_4) 3.41 (s), 3.51 (m), 5.61 (s), 6.07 (s), 6.23 (m), 6.85 (w), 6.95 (m), 7.20 (w), 7.35 (w), 7.52 (m), 7.80 (w), 8.13 (w), 8.42 (w), 8.81 μ (s); ORD (*c* 4.6 × 10^{-2}, EtOH) $[\phi]_{589}$ +325°, $[\phi]_{500}$ +600°, $[\phi]_{400}$ +1750°; ORD (*c* 2.3 × 10^{-3}) $[\phi]_{375}$ +3100°, $[\phi]_{346}$ +6000° (peak), $[\phi]_{333}$ 0°, $[\phi]_{320}$ −13,100° (trough), $[\phi]_{306}$ 0°, $[\phi]_{290}$ +14,400°, $[\phi]_{282}$ +16,300° (peak), $[\phi]_{267}$ +10,600° (trough), $[\phi]_{263}$ +11,200° (peak), $[\phi]_{250}$ 0°.

Anal. Calcd for $C_{25}H_{34}O_5$: Mol wt, 414.241. Found: Mol wt, 414.242.

B.—Neopapuanic acid (4.2 mg) was treated with 1 ml of 2:1 acetic anhydride–pyridine at room temperature for 1/2 hr. The reagents were evaporated, and a colorless oil was obtained [uv max 240 (ε 29,200), 270 sh (6850), 313 (6800); ir (CCl_4) 3.42 (s), 3.50 (m), 5.60 (s), 6.06 (s), 6.24 (m), 6.83 (w), 6.95 (m), 7.05 (w), 7.15 (w), 7.31 (w), 7.47 (m), 7.75 (w), 8.06 (w), 8.40 (w), 8.81 μ (s); ORD (*c* 8.0 × 10^{-2}, EtOH) $[\phi]_{589}$ +175°, $[\phi]_{500}$ +430°, $[\phi]_{400}$ +1400°; ORD (*c* 8.0 × 10^{-3}) $[\phi]_{375}$ +1160°, $[\phi]_{344}$ +4900° (peak), $[\phi]_{334}$ 0°, $[\phi]_{320}$ −13,400° (trough), $[\phi]_{305}$ 0°, $[\phi]_{283}$ +13,600° (peak), $[\phi]_{268}$ +8200° (trough), $[\phi]_{263}$ +9000° (peak), $[\phi]_{252}$ 0°].

3,4,6,7-Tetrahydro-2,6-dioxo-8,8-dimethyl-4-*n*-pentyl-5-hydroxy-2H,8H-benzo[1,2-*b*:5,4-*b*']dipyran (15).—Excess aluminum chloride, senecioyl chloride (185 mg, 1.38 mmol), and 5-hydroxy-4-*n*-pentyl-7-methoxydihydrocoumarin (**14**, 187 mg, 0.71 mmol) were mixed in 8 ml of $C_6H_5NO_2$. The reaction mixture was allowed to stand at room temperature for 2 days, after which it was poured into ice and dilute HCl. The solution was heated on a steam bath for 1/4 hr, cooled, and extracted twice with ether. The ethereal extract was washed twice with water before the ether was evaporated, and the $C_6H_5NO_2$ was removed by steam distillation. The pot residue was extracted with CH_2Cl_2, which was dried and evaporated to give 200 mg of a yellow oil. Column chromatography gave 143 mg (59%) of product **15** as white crystals: mp 99–100° after crystallization from hexane–CH_2Cl_2; nmr ($CDCl_3$) τ −1.28 (s, 1), 3.98 (s, 1), 6.70 (m, 1), 7.26 (m, 4), 8.53 (s, 6), 9.25 (t, 3); uv max 283 mμ (ε 15,000), 342 (3130); ir (CH_2Cl_2) 5.61 (s), 6.09 (s), 6.27 μ (m).

Anal. Calcd for $C_{19}H_{24}O_5$: C, 68.65; H, 7.28. Found: C, 68.73; H, 7.26.

Methylation of **15** with excess dimethyl sulfate and solid K_2CO_3 in acetone yielded a methyl ether (**16**) much more mobile than **21** on tlc comparison.

Clemmensen Reduction of 3,4,6,7-Tetrahydro-2,6-dioxo-8,8-dimethyl-4-*n*-pentyl-5-hydroxy-2H,8H-benzo[1,2-*b*:5,4-*b*']dipyran.—The chromone lactone **15** (380 mg) was treated 1.75 hr at room temperature with 16 g of freshly amalgamated zinc, 23 ml of glacial acetic acid, and 6 ml of concentrated HCl. The solution was decanted into water, neutralized with $NaHCO_3$, and extracted with ether. The extracts were washed with water and 5% $NaHCO_3$, dried, and evaporated to yield 380 mg of oil, shown by tlc to be largely a mixture of two products, **18** (more mobile) and **17**, with **17** predominating. Samples of the individual compounds were obtained by chromatography of this mixture, but methylation with dimethyl sulfate and K_2CO_3 in acetone led in both cases to products chromatographically distinct from **23**.

A similar reduction carried out for 16 hr led to the same two products, but with **18** predominating.

3,4,9,10-Tetrahydro-2,2-dimethyl-5-hydroxy-10-*n*-pentyl-4,8-dioxo-2H,8H-benzo[1,2-*b*:3,4-*b*']dipyran (22).—Into a 100-ml pear-shaped flask containing 75 ml of anhydrous ether was placed 3,4,9,10-tetrahydro-2,2-dimethyl-5-methoxy-10-*n*-pentyl-4,8-dioxo-2H,8H-benzo(1,2-*b*:3,4-*b*')dipyran[1b] (**21**, 860 mg). Excess aluminum chloride was added. The flask was fitted with a condenser equipped with a drying tube, and the solution was refluxed for 31 hr, after which it was poured into a mixture of dilute HCl and ice. The solution was heated on the steam bath for 1/2 hr, cooled, and extracted three times with ether. The ethereal extract was washed twice with water, dried, and evaporated to give 810 mg of crude product. Preparative tlc gave 500 mg (62%) of white crystalline product: mp 86–87° after recrystallization from hexane–CH_2Cl_2; nmr (CCl_4) τ −1.40 (s, 1), 3.95 (s, 1), 6.75 (m, 1), 7.28 (m, 4), 8.49 (s, 6), 9.11 (t, 3); uv max 283 mμ (ε 15,500), 342 (3250); ir (CCl_4) 5.60 μ (s), 6.07 (s), 6.14 (s), 6.25 (m).

Anal. Calcd for $C_{19}H_{24}O_5$: C, 68.65; H, 7.28. Found: C, 68.88; H, 7.33.

A small sample of the hydroxy compound was remethylated with dimethyl sulfate and K_2CO_3 in acetone. Tlc comparison showed the product to be identical with **21**.

3,4,9,10-Tetrahydro-2,2-dimethyl-5-hydroxy-10-*n*-pentyl-8-oxo-2H,8H-benzo[1,2-*b*:3,4-*b*']dipyran (24).—The chromanone **22** (250 mg) and 4 ml of concentrated HCl were added to 14 ml of glacial acetic acid, 3 ml of CH_2Cl_2, and 5 g of freshly amalgamated zinc. The mixture was stirred for 4 hr, poured into water, and neutralized with solid $NaHCO_3$. The solution was extracted three times with ether, which was washed twice with water, dried, and evaporated to give 240 mg of solid crude product. Preparative tlc gave 108 mg (45%) of white crystalline **24**: mp 163.5–165.5° after recrystallization from hexane; nmr ($CDCl_3$) τ 3.78 (s, 1), 6.76 (m, 1), 7.33 (m, 4), 8.22 (t), 8.67 (s), 9.03 (t); ir (CCl_4) 2.80 μ (w), 3.00 (w), 5.66 (s), 6.17 (s).

Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.59; H, 8.35.

Methylation of a small sample of **24** with dimethyl sulfate, K_2CO_3, and acetone yielded a product (**23**) identical with that obtained[1b] by Clemmensen reduction of **21**.

Synthetic Methyl Cyclodemethylpapuanate (26) and Its Stereoisomers.—Tiglic acid (38 mg, 0.38 mmol) was mixed thoroughly with finely powdered chroman **24** (76 mg, 0.24 mmol). The mixture was placed in a small weighing bottle (12 ml), and approximately 9 g of polyphosphoric acid was added. A magnetic stirring bar was placed in the bottle, which was stoppered and put on a Thermix hot plate maintained at 130°. After being stirred 1/2 hr the hot, dark red solution was dumped into ice–water. After dissolution of the polyphosphoric acid, the solution was extracted three times with ether. The combined ether layers were washed twice with 5% $NaHCO_3$, dried, and evaporated to give 65 mg of yellow oil. Tlc showed three similar fluorescent spots, which were identical chromatographically in all respects with the three spots representing a mixture of stereo-

isomeric cyclodemethylpapuanolides prepared from mixed papuanic and isopapuanic acids.

A portion of this material (57 mg) was refluxed with methanol and a trace of H_2SO_4 for 2 hr. The solution was poured into an excess of 5% $NaHCO_3$ and extracted twice with ether. The ethereal extract was washed with water, dried, and evaporated to give 55 mg of crude product as a yellow oil. This showed two identically fluorescent spots on tlc, and separation by preparative plates gave 34 mg (16%) of products in fractions i (more mobile), 14 mg, and ii, 18 mg. Both fractions were identical in all respects on tlc with the spots constituting natural **26** prepared from mixed papuanic and isopapuanic acids. For analysis the oils were sublimed (100°, 10^{-5} torr).

Fraction i: nmr (CCl_4) τ −2.22 (s, 1), 5.90 (m, 1), 6.50 (s, 3), 7.48 (t), 8.29 (t), 8.53 (d), 8.65 (s), 8.84 (d), 9.17 (t) (HR-60); uv max 298 mμ (ϵ 19,200), 342 (2720); ir (CCl_4) 5.75 (s), 6.13 (s), 6.27 (m), 6.91 μ (s).

Anal. Calcd for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39; mol wt, 432.251. Found: C, 69.61; H, 8.55; mol wt, 432.250.

Fraction ii: nmr (CCl_4) τ −2.15 (s, 1), 5.45 (m, 1), 6.48 (t, 3), 7.48 (t), 8.27 (t), 8.61 (d), 8.63 (s), 8.82 (d), 9.15 (t) (HR-60); uv max 298 mμ (ϵ 19,600), 342 (2730); ir (CCl_4) 5.75 (s), 6.14 (s), 6.29 (m), 6.94 μ (s).

Anal. Calcd for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39; mol wt, 432.251. Found: C, 69.57; H, 8.60; mol wt, 432.253.

Epipapuanic Acid (29b).—Papuanic acid (130 mg) was dissolved in 5 ml of 95% ethanol, 0.1 *N* in KOH. The bright yellow solution was left at room temperature for 6 hr. The ethanol was evaporated, and the remaining solution was acidified with 10% HCl. The water-insoluble material was dissolved in CH_2Cl_2, which was dried (Na_2SO_4) and evaporared to give a yellow oil (125 mg). The mixture was separated by preparative tlc to give papuanic acid (48 mg) and epipapuanic acid (19 mg): nmr (CCl_4) τ −2.20 (s, 1), 4.93 (t, 1), 5.50 (m, 1), 6.30 (s 3), 6.3–6.7 (m, 1), 6.83 (d, 2), 7.19 (d, 2), 7.4–7.7 (m, 1), 8.30, 8.34, 8.62 (d), 8.77 (d), 9.16 (t, 3); uv max 285 mμ (ϵ 13,000), 358 (3200); ir (CCl_4) 3.35 (m), 5.85 (s), 6.11 (s), 6.31 (w), 6.95 (m), 7.21 (w), 7.43 (w), 7.66 (w), 7.75 (w), 8.62 (m), 8.77 (m), 9.15 μ (m); ORD $[\phi]_{589}$ +265° (*c* 1.50 × 10^{-1}, EtOH).

Anal. Calcd for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.21; H, 8.53.

Epiisopapuanic Acid (30b).—Isopapuanic acid (87 mg) was dissolved in 5 ml of 0.1 *N* KOH in 95% ethanol. After 6 hr at room temperature the ethanol was evaporated, and the residue was acidified with 10 ml of 10% HCl. The organic materials were extracted with ether and dried (Na_2SO_4). The isomers were separated by preparative tlc to give isopapuanic acid (23 mg) and epiisopapuanic acid (49 mg, more mobile): nmr (CCl_4) τ −2.28 (s, 1), 4.95 (t, 1), 5.88 (m, 1), 6.30 (s, 3), 6.35–6.70 (m, 1), 6.83 (d, 2), 7.18 (d, 2), 7.3–7.7 (m, 1), 8.27 (s, 3), 8.32 (s, 3), 8.50 (d, 3), 8.81 (d), 9.17 (t, 3); uv max 284 mμ (ϵ 13,100), 357 (3200); ir (CCl_4) 3.43 (m), 3.50 (w), 5.83 (s), 6.10 (s), 6.30 (w), 6.91 (m), 6.99 (m), 7.20 (w), 7.42 (m), 7.70 (m), 7.85 (m), 8.40 (w), 8.60 (m), 8.75 (m), 9.10 (m), 9.22 μ (w); ORD $[\phi]_{589}$ −140° (*c* 1.93 × 10^{-1}, EtOH).

Anal. Calcd for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.57; H, 8.51.

Bromination of Dihydrodemethylpseudopapuanolide.—Dihydropapuanic acid (101 mg) was dissolved in 2 ml of acetic anhydride, and 1 ml of 50% HI was added carefully. The solution was heated to 100° for 20 min, cooled, and poured into 20 ml of 10% $NaHSO_3$. After extraction with two 20-ml portions of ether, the combined extracts were washed with water, dried, and evaporated to give a yellow oil (87 mg). This was dissolved in 1 ml of glacial acetic acid, 1 *M* in Br_2, and left at room temperature for 12 hr. The solvent and bromine were evaporated, and the resulting bright yellow oil was chromatographed on a preparative plate. Three fractions were obtained [(i) (most mobile) 3-bromodihydrodemethylpseudoepipapuanolide (34 mg), (ii) 3-bromodihydrodemethylpseudopapuanolide (18 mg), and (iii) 3-bromodihydropapuanic acid (both epimers, 18 mg)].

3-Bromodihydrodemethylpseudopapuanolide (28).—The melting point of this compound after crystallization from ethanol was 89–93°: nmr (CCl_4) τ −2.14 (s), 5.9–6.7 (m), 7.22, 7.29, 7.40, 7.46, 8.13 (s, 3), 8.36 (d), 8.61, 8.72, 9.03 (d); uv max 295 mμ (ϵ 14,700), 363 (2950); ir (CCl_4) 3.40 (m), 3.48 (w), 5.60 (s), 6.13 (s), 6.90 (m), 7.25 (w), 7.52 (w), 7.70 (w), 8.05 (w), 8.35 (w), 8.85 μ (s).

3-Bromodihydrodemethylpseudoepipapuanolide.—Fraction ii exhibited the following data: nmr (CCl_4) τ −1.30 (s, 1), 5.32 (q, 1), 6.72 (m), 7.33, 7.45, 7.56, 8.17 (s, 3), 8.50 (d), 8.65, 8.74, 8.86, 9.06 (d); uv max 292 mμ (ϵ 13,800), 359 (2960); ir (CCl_4) 3.39 (m), 3.50 (w), 5.59 (s), 6.13 (s), 6.25 (w), 6.90 (m), 7.22 (w), 7.37 (w), 7.73 (w), 8.01 (m), 8.40 (w), 8.84 μ (s).

Registry No.—Demethyldihydropseudoepipapuanolide, 17278-15-8; papuanolide, 17230-49-8; isopapuanolide, 17230-50-1; cyclodemethylpapuanolide, 17230-51-2; cyclodemethylisopapuanolide, 17278-16-9; dihydropapuanic acid, 17230-77-2; dehydroisopapuanic acid, 17230-78-3; cyclodemethylpapuanic acid, 17230-79-4; cyclodemethylepiisopapuanic acid, 17230-80-7; cyclodemethylisopapuanic acid, 17278-24-9; cyclodemethylepipapuanic acid, 17230-81-8; demethyldihydropseudopapaunolide, 17230-82-9; 3-bromodihydrodemethylpseudoepipapuanolide, 17230-83-0; **12,** 17230-52-3; **13,** 17230-53-4; **15,** 17230-54-5; **22,** 17230-55-6; **24,** 17230-56-7; **26** (*trans*), 17230-57-8; **26** (*cis*), 17278-25-0; **28,** 17230-58-9; **29a,** 17230-75-0; **29b,** 17230-59-0; **30a,** 17230-76-1; **30b,** 17230-60-3; **31a,** 17278-17-0; **31b,** 17230-61-4; **32a,** 17230-73-8; **32b,** 17230-74-9.

Acknowledgments.—We wish to express our thanks to Dr. P. van Royen for a generous supply of *C. papuanum* bark.