# *Calophyllum* Products. III. The Structure of Blancoic Acids[1a-c]

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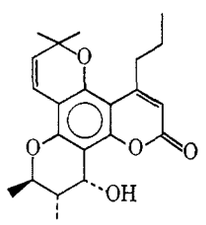
Blancoic acid, the major constituent of the bark resin of *Calophyllum blancoi* Pl. and Tr., is shown to have the structure **24**. The synthesis of the derivative methyl O-methyldihydroblancoate (**13**) is described, and the stereochemistry of blancoic acid is discussed in part. This compound represents a new extension of the complex coumarin derivatives found generally in *Calophyllum* resins.

As part of our study of the products of the botanical family Guttiferae, we have recently examined the bark resins of a number of species from the genus *Calophyllum*, a widely distributed group of tropical trees. One of these is *Calophyllum blancoi* Pl. and Tr., a member of the genus native to the Philippine Islands, where it is used as a source of dye and in the treatment of wounds. Extraction of the powdered bark yields *ca.* 5% of a yellow resin. Thin layer chromatography (tlc) of this resin showed it to consist largely (>75%) of one compound. We have isolated this material in chromatographically and spectrally homogeneous, though noncrystalline, form and have named it blancoic acid.[2]

**Structure.**—Blancoic acid, on the basis of combustion, titrimetric, and mass spectral analyses, is a monocarboxylic acid with the molecular formula $C_{24}H_{32}O_6$. The uv spectrum is complex, but is not suggestive of a coumarin, despite the frequent occurrence of this system in *Calophyllum*[3-5] and related genera.[6-8]

Upon catalytic hydrogenation over Adams catalyst in ethanol, blancoic acid absorbs 1 mol of hydrogen, leading to dihydroblancoic acid $C_{24}H_{34}O_6$. This reduction is attended by a marked simplification of the uv spectrum, which now resembles that of an oxygenated acetophenone.

The nmr spectrum of blancoic acid (Figure 1) is highly informative, especially when compared with those of costatolide (**1**), from *Calophyllum costatum* F. M. Bailey, and its derivative oxodihydrocostatolide (**2**).[4] Among the peaks found are those at $\tau$ 3.45 (d, $J$ = 10 Hz), 4.65 (d, $J$ = 10 Hz), and 8.56 (s), characteristic of the 2,2-dimethylchromene ring (**3**), a common element in *Calophyllum* products.[3-5] Chemical confirmation of the presence of this system was obtained from its characteristic degradation in hot aqueous base to yield acetone and acetaldehyde.[3,4] As would be expected, the low-field doublets vanish from the spectrum of dihydroblancoic acid to be replaced by triplets at $\tau$ 8.27 and *ca.* 7.4, indicating that it is the double bond of this ring that is reduced.



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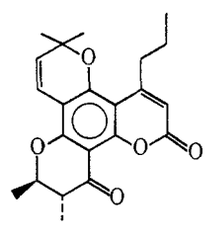

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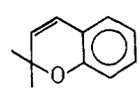
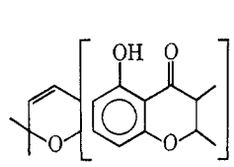


3

Also visible in the spectrum of blancoic acid are a six-line multiplet (~~1 H~~) at $\tau$ 5.96 and two doublets (each 3 H) at 8.52 and 8.82. The first doublet is partially obscured by the signal at $\tau$ 8.56 from the methyl groups of the 2,2-dimethylchromene ring but is revealed when this shifts to 8.67 in dihydroblancoic acid. These peaks correspond in detail with those recorded for the 2,3-dimethylchromanone ring of **2**[4] and suggest the presence of the same system in blancoic acid. In agreement and extension, both the ir (6.14 $\mu$) and nmr ($\tau$ −2.28) spectra indicate a conjugated carbonyl group with an adjacent chelated hydroxyl function. Thus the partial structure may be elaborated as **4**.



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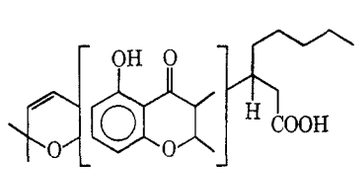


5

The nmr spectrum of blancoic acid shows no signals resulting from aromatic protons; so a group $C_8H_{15}O_2$ containing the carboxyl function must be attached at the sixth position on the benzene ring. Signals which can be attributed to this fragment are found at $\tau$ 6.43 (1 H), 7.36 (2 H), and 9.15 (3 H). The last is a highly skewed triplet, of the sort arising from the terminal methyl group of a long *n*-alkyl chain.[9] The common occurrence of 4-alkylcoumarins in the subfamily Calophylloideae[4-7] suggests that we may be dealing with an acid related to a hydrolyzed dihydrocoumarin and leads to the extended structure **5**. In this case the benzylic methine would give rise to the signal at $\tau$ 6.43 and the methylene adjacent to the carboxyl to that at

(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. Thesis of K. D. Sears, University of Washington, 1968. (b) For previous papers in this series, see part II, G. H. Stout, M. M. Krahn, and G. D. Breck, *Tetrahedron Lett.*, 3285 (1968); part I, G. H. Stout and K. L. Stevens, *J. Org. Chem.*, **29**, 3604 (1964). (c) Supported in part by Public Health Service Grant GM-12095 from the National Institute of General Medical Sciences. (d) Institute of Forest Products Research Fellow, University of Washington, 1964–1966.

(2) It should be noted that, with the exception of dihydroblancolide (**10**), all derivatives of blancoic acid are similarly noncrystalline. Thus all comparisons between compounds and all tests for homogeneity rest on chromatographic and spectral properties.

(3) J. Polonsky, *Bull. Soc. Chim. Fr.*, 1079 (1957); J. Polonsky and Z. Baskevitch, *ibid.*, 929 (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) C. Djerassi, E. J. Eisenbraun, R. A. Finnegan, and B. Gilbert, *J. Org. Chem.*, **25**, 2164 (1960); R. A. Finnegan, M. P. Morris, and C. Djerassi, *ibid.*, **26**, 1180 (1961); R. A. Finnegan and W. H. Mueller, *ibid.*, **30**, 2342 (1965).

(7) L. Crombie, D. E. Gaines, and A. McCormick, *Tetrahedron Lett.*, 145, 151 (1966).

(8) T. R. Govindachari, B. R. Pai, P. S. Subramaniam, U. R. Rao, and N. Muthukumaraswamy, *Tetrahedron*, **23**, 4161 (1967).

(9) *Cf.* spectra 216 and 282: W. S. Bhacca, D. P. Hodis, L. F. Johnson, E. A. Pier, and J. N. Shoolery, "NMR Spectra Catalog," Vol. I, Varian Associates, Palo Alto, Calif., 1962.

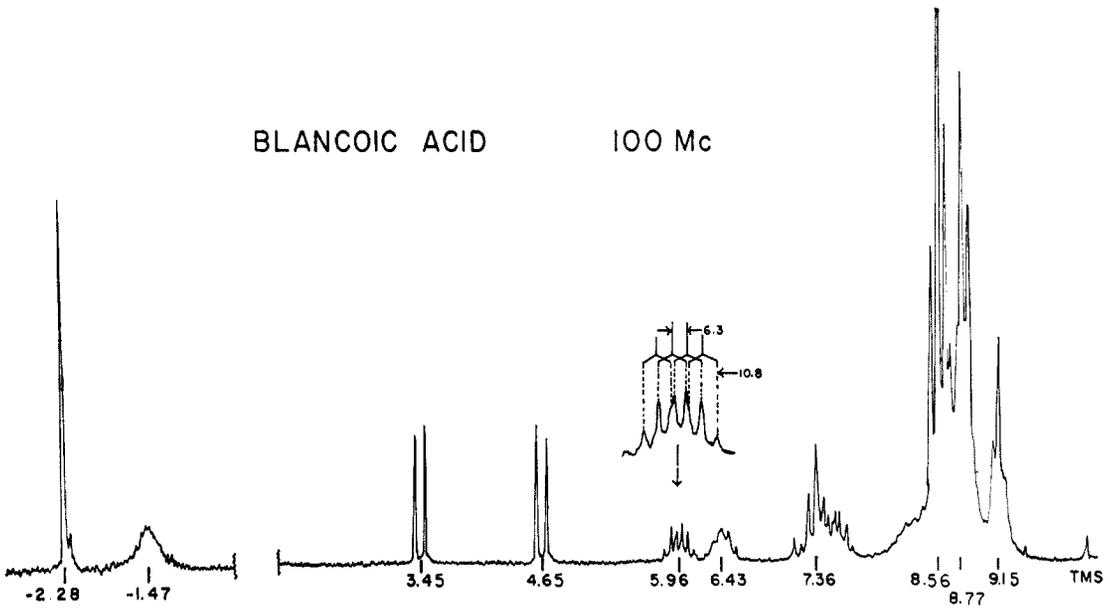



Figure 1.—The 100-MHz nmr spectrum of blancoic acid in $CCl_4$. The region below the break has twice the amplitude of the rest of the spectrum.

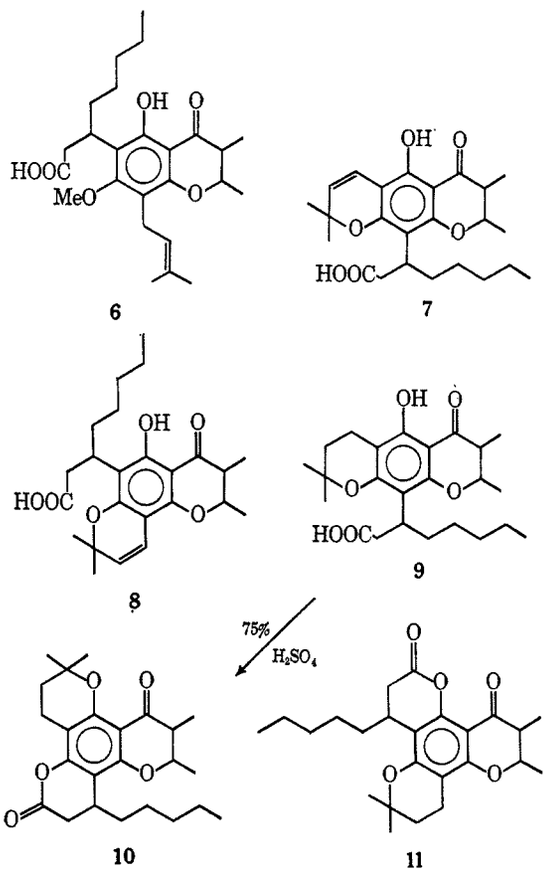
7.36. Oxidation of blancoic acid with dilute nitric acid confirmed the proposed structure by yielding *n*-pentylsuccinic acid, identified by comparison with an authentic sample.

Once the various aromatic substituents have been identified, the remaining problem is to orient them properly about the central ring. The coumarins and related products from the Guttiferae have uniformly been based on a phloroglucinol oxygenation.[3-8] Biosynthetic analogy suggests strongly that the pattern will hold as well for blancoic acid. Furthermore the excellent agreement between the uv spectra of dihydroblancoic acid and similar derivatives of papuanic acid (**6**),[1a,10] for which independent evidence exists showing the disposition of the oxygens, requires that they possess the same substitution. If the remaining oxygen is placed to conform to these arguments, two structures, **7** and **8**, are possible for blancoic acid.

Of these possibilities, **8** has been rejected because of the failure of blancoic acid and its derivatives to lactonize under the influence of either acetic anhydride or dicyclohexylcarbodiimide, reagents which readily induce lactonization in **6**.[10] Thus we propose **7** as the structure of blancoic acid.

Early in the study of these compounds, however, a lactonic product was obtained by the prolonged stirring of dihydroblancoic acid (**9**) in 75% sulfuric acid. Clearly this material, dihydroblancolide, cannot be a simple lactone derived from **7**. Instead, we propose that it has the structure **10**, arising by acid-catalyzed rearrangement of the dimethylchroman ring followed by lactonization onto the now available hydroxyl. Such rearrangements have been observed previously in similar systems.[11]

Evidence for the proposed structure derives from several sources. First, the material having the structure **11**, *i.e.*, the dihydrolactone related to **8**, has been prepared from papuanic acid and is clearly different




from dihydroblancolide.[10] Second, comparison of the uv spectra of dihydroblancolide and **11**, which may be viewed as dioxyacetophenones since one oxygen atom has been effectively "removed" by esterification, shows that the former exhibits the marked bathochromic shift of its long-wavelength band characteristic of 2,6-dihydroxyacetophenone, while the latter resembles 2,4-dihydroxyacetophenone instead (Table I). Finally, the possibility of an alternative rearrangement of the chromanone ring, rather than the chroman, can be

(10) G. H. Stout, G. L. Hickernell, and K. D. Sears, *J. Org. Chem.*, **33**, 1491 (1968).

(11) G. A. Howard, J. R. A. Pollock, and A. R. Tatchell, *J. Chem. Soc.*, 174 (1955).

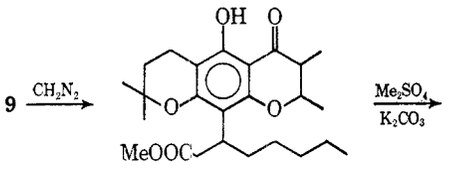
TABLE I

UV SPECTRA OF DIHYDROBLANCOLIDE AND RELATED COMPOUNDS

| | $\lambda_{max}$, mμ | ε | $\lambda_{max}$, mμ | ε |
|---|---|---|---|---|
| Dihydroblancolide (10) | 281 | 17,000 | 336 | 5200 |
| 2,6-Dihydroxyacetophenone | 269 | 12,900 | 341 | 3500 |
| 2,4-Dihydroxyacetophenone | 278 | 15,100 | 315 | 7100 |
| Cyclodemethylpapuanolide (11) | 284 | 13,700 | 314 | 3600 |

ruled out since this would again lead to a product having the gross structure and uv spectrum of **11**.

**Synthesis.**—To confirm the arguments leading to the proposed structure, we undertook to synthesize a derivative of dihydroblancoic acid. Methyl O-methyldihydroblancoate (**13**), prepared by methylation of dihydroblancoic acid first with diazomethane and then with dimethyl sulfate and potassium carbonate, was elected as a suitable meeting point of the natural and synthetic routes.

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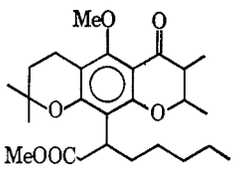



13

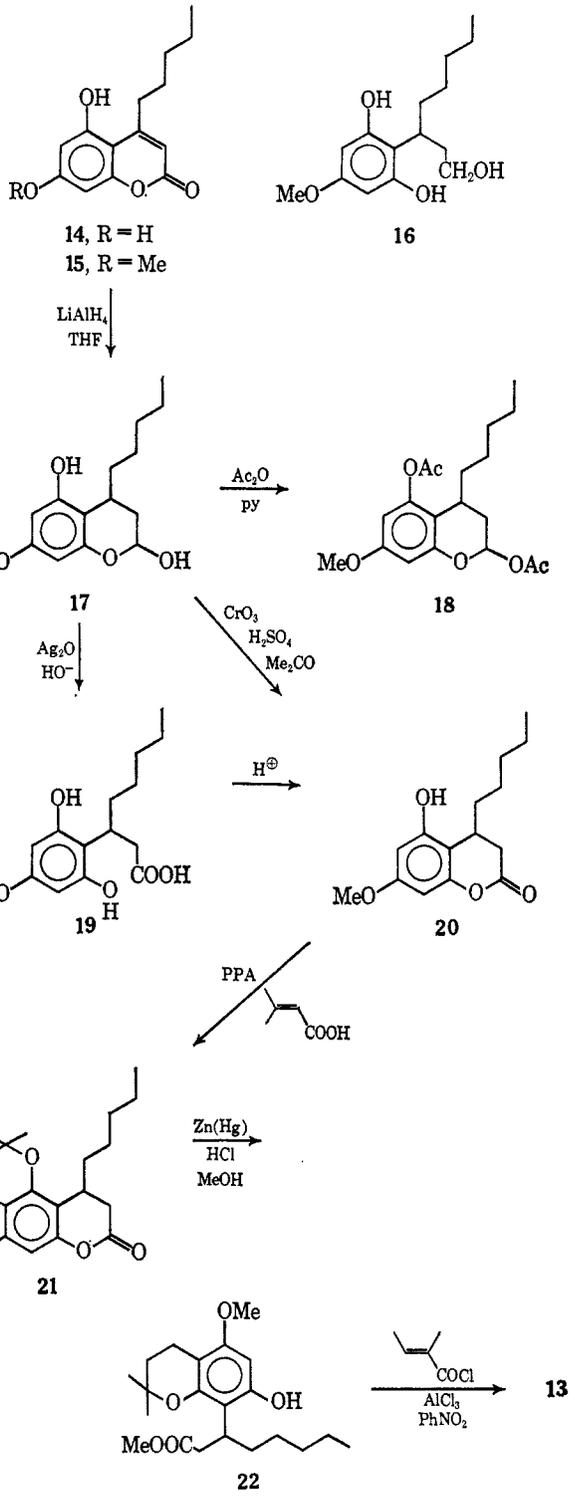
The two major problems encountered in the synthesis were the preparation of the dihydrocoumarin system and the necessity for devising routes that led unambiguously to the orientation of the various rings. The first was ultimately solved by the method described below and the second by the combination of a blocking group and a symmetrical intermediate.

The synthetic sequence began with treatment of phloroglucinol with ethyl 3-ketooctanoate under the classical von Pechmann conditions.[12] A good yield of 4-*n*-pentyl-5,7-dihydroxycoumarin (**14**) was obtained. Partial methylation with dimethyl sulfate and aqueous sodium carbonate gave a mixture of monomethylated products, from which the desired 7-methyl ether (**15**) could be isolated by taking advantage of its failure to extract into dilute carbonate solutions.

Reduction of coumarin with lithium aluminum hydride has been shown to give reasonable yields of 3-(2-hydroxyphenyl)propanol.[13] Treatment of **15** with this reagent in refluxing tetrahydrofuran, however, led to a product whose nmr spectrum was entirely inconsistent with its formulation as the phenylpropanol **16**. Analytical results, although allowing the expected $C_{15}H_{24}O_4$, favored $C_{15}H_{22}O_4$. The uv and ir spectra indicated that both the ester and the double bond had been reduced, but a diffuse triplet at $\tau$ 4.62 (1 H) had appeared instead of the signal expected for a methylene bearing a hydroxyl. Treatment with acetic anhydride and pyridine, even under forcing conditions, led to only a diacetate in which the diffuse triplet had

(12) See S. Wawzonek in "Heterocyclic Compounds," Vol. II, R. C. Elderfield, Ed., John Wiley & Sons, Inc., New York, N. Y., 1951, pp 181–187.

(13) F. A. Hochstein, *J. Amer. Chem. Soc.*, **71**, 305 (1945).




shifted to $\tau$ 3.7. In view of these data, a positive Tollens test, and the ready oxidation to an acid or lactone (see below), the reduction product is formulated as the cyclic hemiacetal **17**.

Although lithium aluminum hydride has occasionally been used to form hemiacetals from lactones, these reactions have usually involved carefully controlled conditions.[14] Thus the isolation of such a product from a reaction conducted at elevated temperatures with a large excess of reductant is unexpected.[15]

(14) G. E. Arth, *ibid.*, **75**, 2413 (1953); M. Hinder and M. Stoll, *Helv. Chim. Acta*, **37**, 1866 (1954).

(15) See also K. Heusler and A. Wettstein, *ibid.*, **45**, 347 (1962), and references cited there.

Oxidation of **17** with alkaline silver oxide led to the acid **19**, which closed readily in the presence of mineral acids to the lactone **20**. Better yields of **20** were later obtained by direct oxidation of **17** with Jones reagent.[16]

Acylation of **20** with senecioic acid in polyphosphoric acid (PPA) gave the desired chromanone **21**. Because of the symmetry of the molecule resulting from the opening of the lactone ring in **20**, possible intramolecular ester interchange represented no threat at this time.

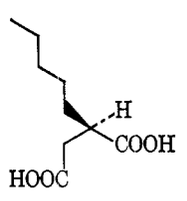
Clemmensen reduction of **21**, carried out with methanol as a cosolvent, produced simultaneous reduction of the chromanone carbonyl and the conversion of the lactone to the corresponding methyl ester (**22**).

Various methods, including the use of PPA, were studied for the introduction of tiglic acid to form the 2,3-dimethylchromanone ring, but the most successful was the use of tigloyl chloride, aluminum chloride, and nitrobenzene to effect a one-step acylation and ring closure onto **22**. Under these conditions **13** was obtained in fair yield as a mixture of stereoisomers, which could be separated by preparative tlc into two fractions. One of these, although presumably still a mixture of diastereomers (see below), was identical chromatographically and in its uv, ir, and nmr spectra with methyl O-methyldihydroblancoate prepared from dihydroblancoic acid.

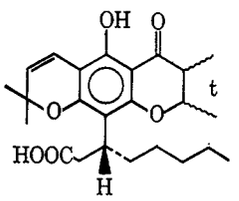
The spectral identity of the natural and synthetic materials thus justifies the arguments made during the analysis of blancoic acid and confirms particularly the presence of the phloroglucinol oxygenation pattern and the location of the acid side chain as in **7**.

**Stereochemistry.**—Blancoic acid is optically active and contains three asymmetric centers, two in the chromanone ring and one in the acidic chain. The nmr signal at $\tau$ 5.96 results from the proton at C-2 in the chromanone ring and has a coupling constant of 11 Hz with the adjacent C-3 proton. As discussed previously in the case of costatolide,[4] this value is consistent only with *trans* diaxial protons or (2e,3e) methyl substitution.

The stereochemistry of the acid chain is given absolutely by the isolation of optically active (*R*)(+)-pentylsuccinic acid (**23**)[17] from the oxidative degradation of blancoic acid. Thus a partial representation of the stereochemistry of the system is **24**. The relationship between the two asymmetric regions is under study in connection with the stereochemistry of papuanic acid and the other members of this group of compounds, but a detailed discussion is reserved for a later paper.[18]




**23**




**24**

The synthetic **13** was resolved by tlc into two fractions, although four *dl* pairs are expected. The more mobile fraction, which corresponded to the natural material, has the nmr spectrum of a *trans*-dimethylchromanone and presumably includes both epimers at the position bearing the *n*-pentyl chain. The other fraction, which has the same uv spectrum but is formed in smaller amounts, is assumed to be the corresponding mixture of *cis* products, since we have found that these are uniformly more polar than their *trans* isomers. Studies on derivatives of papuanic acid have indicated that isomers differing only in the configuration of the asymmetric center in the acid chain can be separated chromatographically only when the free rotation of this chain is prevented by lactonization.

## Discussion

Blancoic acid was the first dihydrocoumarinic acid isolated from the resins of a *Calophyllum* species. Since it was first discovered, others have been found. Papuanic and isopapuanic acids have been obtained from *C. papuanum*,[1a,10] and apetalic acid, from *C. apetalum*.[19] All four compounds are very similar, apetalic acid differing from blancoic acid only in having a *cis*-dimethylchromanone ring and the more common *n*-propyl chain in place of *n*-pentyl.

These compounds, like their coumarin analogs,[4,5] show the tendency of this genus to elaborate derivatives containing an even number of carbon atoms linearly disposed in an acidic side chain. Such a chain may be reasonably supposed to be derived from acetate, the connection to the aromatic ring then arising in formal analogy to the von Pechmann reaction. Support of this view is provided by the recent evidence of Kunesch and Polonsky that the acid chain in the related 4-phenylcoumarins of *C. inophyllum* is derived from phenylalanine without any rearrangement.[20]

Since the completion of our studies on blancoic acid, we have encountered it again as the principal component of the resin extracted from *Calophyllum saigonensis* Pierre. This species, obtained from Thailand, gave extracts whose appearance on tlc plates resembled greatly that of similar extracts from *C. blancoi*. Although the major constituents were the same, the minor components were not however; so the two samples were not identical.

## Experimental Section

All melting points were taken on a Kofler hot stage and are corrected. The infrared spectra were taken on a Perkin-Elmer Model 21 spectrophotometer. The letter in parentheses signifies a strong, medium, or weak absorption. Most of the nmr spectra were obtained on a Varian A-60 spectrometer; a few were taken by Mr. B. J. Nist on a Varian HR-60. The letter in parentheses refers to the multiplicity and the number following the letter, when given, is the estimated intensity. All column chromatography used 922 silica gel, <200 mesh, supplied by Grace–Davidson Chemical Co., with mixtures of hexane and ethyl acetate as elutants. Tlc plates were prepared with silica gel G from Brinkman Instruments. Solutions were dried with anhydrous magnesium sulfate unless otherwise stated. Combustion analyses were performed by Dr. A. Bernhardt of Mülheim (Ruhr), West Germany. Uv spectra were taken in 95% EtOH.

(16) A. Bowers, T. G. Halsall, and E. R. H. Jones, *J. Chem. Soc.*, 2548 (1953).

(17) 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).

(18) G. H. Stout and G. L. Hickernell, to be published.

(19) T. R. Govindachari, D. Prakash, and N. Visiwanathan, *Tetrahedron Lett.*, 4177 (1967).

(20) G. Kunesch and J. Polonsky, *Chem. Commun.*, 317 (1967).

**Isolation of Blancoic Acid (7).**—The ground bark (35 g) of *Calophyllum blancoi* Pl. and Tr. (Guttiferae) was extracted in a Soxhlet extractor with pentane for 5 hr. The yellow solution was extracted twice with 5% $Na_2CO_3$, and the pentane layer was discarded. The aqueous extract was acidified with HCl and extracted with ether, which was dried and evaporated to give 1.62 g of a viscous yellow liquid (4.6%). Tlc of this material showed that it was predominantly blancoic acid. Column chromatography (1:20 EtOAc–hexane) gave 0.78 g (2.2%) of purified blancoic acid. Analytically pure material was obtained by sublimation (120°, $10^{-5}$ Torr) of a sample pure by tlc. A yellow glass was obtained (blancoic acid is soluble in all common organic solvents and all attempts at crystallization failed): ir ($CCl_4$) 5.85 (s), 6.08 (s), 6.15 (s), 6.37 $\mu$ (m); uv max (95% EtOH), 255 sh, 267 m$\mu$ ($\epsilon$ 39,900), 275 (42,200), 300 (11,300), 312 (11,800), 365 (2160); nmr ($CCl_4$) $\tau$ 9.15 (t), 8.82 (d), 8.62, 8.56 (s), 8.47, 7.16–7.83 (m, 3), 5.73–6.60 (m, 2), 4.65 (d, 1), 3.45 (d, 1), −1.60 (broad, 1), −2.28 (s, 1) [the nmr spectrum at 100 MHz resolved the multiplet between $\tau$ 5.73 and 6.60 into discrete multiplets: 5.96 (m, $J$ = 6.3, 10.8 $H_2$, 1) and 6.43 (m, 1) (Figure 1)]; $[\alpha]^{25}D$ −66.7° ($c$ 0.0712, $CHCl_3$).

*Anal.* Calcd for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74; mol wt, 416. Found: C, 69.10; H, 7.66; mol wt (titration), 409.

**Dihydroblancoic Acid (9).**—Blancoic acid (100 mg, 0.24 mmol) was added to 15 mg of prereduced platinum oxide in ethanol. Hydrogen uptake was rapid and was complete after 1 hr (0.22 mmol). The platinum was filtered off, and the ethanol was evaporated to yield a viscous light yellow liquid. Tlc showed that no blancoic acid remained and that the product was essentially pure 9. An analytical sample was prepared by column chromatography and sublimation (120°, $10^{-5}$ Torr) to give a light yellow glass: ir ($CCl_4$) 5.83 (s), 6.12 (s), 6.26 $\mu$ (m); uv max (95% EtOH) 298 m$\mu$ ($\epsilon$ 15,300), 342 (2200); nmr ($CCl_4$) $\tau$ 9.15 (t), 8.82 (d), 8.67 (s), 8.52 (d), 8.27 (t, 2), 7.16–7.83 (m, 5), 5.73–6.60 (m, 2), −1.18 (broad, 1), −2.28 (s, 1).

*Anal.* Calcd for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 68.86; H, 8.21.

**Dihydroblancolide (10).**—Dihydroblancoic acid (0.94 g, 2.2 mmol) was added to 15 ml of 75% aqueous sulfuric acid, and the solution was stirred for 3 days at room temperature. When it was poured into ice–water, a gummy mass formed. Tlc showed the presence of a trace of starting material in addition to two major fluorescent spots behind the starting material, the one with higher $R_f$ being much larger. This material was separated by preparative tlc to give 210 mg (24%) primarily of the compound constituting the front fluorescent spot and 70 mg (8%) of material from the back spot. The major product, dihydroblancolide, was rechromatographed by preparative tlc and crystallized several times to yield **10** as a white solid from hexane: mp 153.5–154.5°; ir ($CCl_4$) 5.62 (s), 5.92 (s), 6.28 $\mu$ (s); uv max 281 m$\mu$ ($\epsilon$ 17,000), 336 (5180); nmr ($CCl_4$) $\tau$ 9.15 (t), 8.92 (d), 8.65 (s), 8.28 (t, 2), 7.15–8.00 (m, 5), 6.82 (m, 1), 5.96 (m, 1).

*Anal.* Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 71.93; H, 8.14.

The material constituting the back spot gave uv max 281 and 336 m$\mu$; ir ($CCl_4$) 5.62 (s), 5.92 (s), 6.28 $\mu$ (s).

**Methyl Dihydroblancoate (12).**—Dihydroblancoic acid (131 mg, 0.31 mmol) in methanol was treated at 4° with excess freshly distilled ethereal diazomethane. After 10 min the solvent and excess diazomethane were evaporated to give a yellow oil. An analytical sample was obtained by preparative tlc and sublimation (100°, $10^{-5}$ Torr): uv max 298 m$\mu$ ($\epsilon$ 15,300), 340 (2280); nmr ($CCl_4$) $\tau$ 9.14 (t), 8.82 (d), 8.65 (s), 8.50 (d), 8.26 (t, 2), 6.50 (s, 3), −2.28 (s, 1).

*Anal.* Calcd for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.61; H, 8.56.

**Methyl O-Methyldihydroblancoate (13).**—Methyl dihydroblancoate (100 mg, 0.23 mmol) dissolved in acetone was refluxed 2 days with dimethyl sulfate (0.1 ml) and excess anhydrous $K_2CO_3$. The solution was filtered, poured into a 5% $Na_2CO_3$ solution, and extracted twice with ether; the ethereal extract was dried and evaporated to give a yellow oil. This was purified by preparative tlc to obtain 54 mg (53%) of a slightly viscous light yellow oil that was purified again by preparative tlc and sublimed (100°, $10^{-5}$ Torr) before analysis: ir ($CCl_4$) 5.74 (s), 5.89 (s), 6.28 (s), 6.85 $\mu$ (s); uv max 290 m$\mu$ ($\epsilon$ 15,700), 335 sh; nmr ($CCl_4$) $\tau$ 9.15 (t), 8.88 (d), 8.67 (s), 8.53 (d), 8.28 (t, 2), 7.40 (d), 6.54 (s, 3), 6.28 (s, 3).

*Anal.* Calcd for $C_{26}H_{38}O_6$: C, 69.93; H, 8.58. Found: C, 70.08; H, 8.79.

**Base Degradation of Blancoic Acid.**—A small pear-shaped flask fitted with a condenser and a nitrogen tube was charged with blancoic acid (200 mg) and 10 ml of 5% NaOH. A tube led from the top of the condenser into a solution of 2,4-dinitrophenylhydrazine reagent. After the reaction mixture had refluxed for 3 hr, an orange precipitate had formed in the 2,4-dinitrophenylhydrazine solution. The precipitate was chromatographed on Whatman No. 1 paper using the organic phase of cyclohexane (60), methanol (12), acetic acid (1), and water (2) as the solvent.[4] The sample separated into two spots that had the same $R_f$'s as samples of acetone and acetaldehyde DNP's run simultaneously.

**(*R*)-(+)-*n*-Pentylsuccinic Acid from Dihydroblancoic Acid.**—Dihydroblancoic acid (207 mg) was treated with 25 ml of 50% nitric acid in a 50-ml boiling flask fitted with a reflux condenser. The mixture was kept at room temperature for 1 day and then heated gently on a steam bath for 2 days. It was allowed to cool, and the excess nitric acid was reduced with sodium bisulfite before the aqueous solution was extracted exhaustively with ether. The ethereal extracts were dried, filtered, and evaporated to give a light yellow oil (12.8 mg). The oil was dissolved in 2 ml of 5:1 hexane–benzene and refrigerated for several weeks. The white crystals of pentylsuccinic acid were filtered, washed with hexane, and air dried (3.2 mg, 3.4%): mp 79–82°; mmp 79–83°; ir ($CHCl_3$) 3.43 (m), 3.50 (w), 5.84 (s), 6.26 (w), 7.75 $\mu$ (w); ORD (95% EtOH) ($c$ 0.054), $[\phi]_{500}$ +32°, $[\phi]_{450}$ +63°, $[\phi]_{400}$ +115°, $[\phi]_{350}$ +197°, $[\phi]_{300}$ +350°, $[\phi]_{250}$ +770°, $[\phi]_{225}$ +2070° (peak), $[\phi]_{206}$ 0°.

**Ethyl 3-Ketocaprylate.**—A suspension of sodium hydride in mineral oil containing *ca.* 48 g (2 mol) of NaH was filtered with a coarse sintered-glass filter and the residue was washed three times with petroleum ether (bp 30–60°). The hydride was transferred to a nitrogen-swept three-necked 2-l. flask fitted with a condenser, stirrer, and a 500-ml dropping funnel. The hydride was covered with 250 ml of anhydrous ether, and ethyl carbonate (236 g, 2 mol) was added. 2-Heptanone (114 g, 1 mol), dissolved in 250 ml of anhydrous ether, was added dropwise over 5 hr with stirring and refluxing. After 12 hr the solution was cooled to room temperature, and the stirring was stopped. The following day the sodium salt was decomposed by the gradual addition of 125 ml of glacial acetic acid. Upon the addition of water the precipitated sodium acetate dissolved, and two phases separated. The aqueous phase was extracted twice with ether. The ethereal extracts were combined, washed twice with 5% $NaHCO_3$, and dried. The solvent was removed on the steam bath and the residue distilled. The fraction with bp 102–108° (10 mm) [lit.[21] bp 108–110° (11 mm)] was collected to give 114 g (61%) of ethyl 3-ketocaprylate.

**4-*n*-Pentyl-5,7-dihydroxycoumarin (14).**—To an ice-cold mixture of phloroglucinol (50 g, 0.397 mol) and ethyl 3-ketocaprylate (77.5 g, 0.417 mol) was added 450 ml of 75% $H_2SO_4$ over 2 hr. After the addition the reaction was stirred at room temperature for 4 hr. The yellow precipitate that formed was poured into 2000 ml of ice–water, filtered, and washed with water. The material was recrystallized twice from 50% EtOH–$H_2O$ and dried to yield 59 g (60%) of light cream-colored crystals, mp 230–250°. Tlc showed the product to give predominantly one fluorescent spot. An analytical sample was prepared by column chromatography. White crystals, mp 235–237°, were obtained after recrystallization from ethyl acetate–hexane: uv max 252 m$\mu$ ($\epsilon$ 1180), 260 (6830), 328 (13,500).

*Anal.* Calcd for $C_{14}H_{16}O_4$: C, 67.43; H, 6.50. Found: C, 67.62; H, 6.58.

**4-*n*-Pentyl-5-hydroxy-7-methoxycoumarin (15).**—To a 1-l. round-bottomed flask containing 600 ml of methanol and 50 ml of water were added **14** (20 g, 0.081 mol) and dimethyl sulfate (16 ml, 21.3 g, 0.17 mol). The mixture was stirred while a solution of $Na_2CO_3$ (25 g, 0.236 mol) in 125 ml of water was added dropwise over 7 hr. After 15 hr the solution, in which some precipitate had formed, was poured into 800 ml of water, acidified with HCl, and extracted with three portions of ether. The combined extracts (1200 ml) were extracted with three 300-ml portions of 10% $Na_2CO_3$, followed by two 200-ml portions of 5% NaOH. The ether layer was washed with water, dried, and evaporated to give 1.74 g of the dimethylated coumarin. The carbonate extracts were acidified with HCl and extracted twice with ether. The extract was dried and evaporated to yield 11.73

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g of starting material, which also contained some of the undesired monomethylated product. This material may be recycled to prepare more of the desired product. The hydroxide extracts were acidified with HCl and extracted with ether. As the dried ethereal solution was concentrated on the steam bath, the product began to crystallize from the solution. When approximately 75 ml remained, evaporation was stopped and after 2 hr 4.56 g (*ca.* 52%, based on unrecovered starting material) of white crystals, mp 156–160°, were filtered off. Tlc showed one major fluorescent spot of **15** ahead of a trace of starting material. An analytical sample was obtained by column chromatography followed by crystallization from ethyl acetate–hexane: mp 160–162°; uv max 250 mμ (ε 6090), 258 (7200), 321 (14,700); nmr ($CF_3COOH$) τ 9.05 (t, 3), 8.50 (m, 6), 6.92 (m, 2) 6.12 (s, 3), 3.78 (s, 1), 3.52 (s, 2).

*Anal.* Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.65; H, 6.77.

**2,5-Dihydroxy-4-*n*-pentyl-7-methoxychroman (17).**—Dry tetrahydrofuran (100 ml) and $LiAlH_4$ (3 g) were placed in a 1-l. three-necked flask equipped with a condenser, $N_2$ inlet tube, and dropping funnel. After the solution was brought to reflux, **15** (8 g, 0.031 mol) in 300 ml of dry THF was added dropwise over 7 hr. After 13 hr the reaction vessel was cooled and ice–water was added slowly. When the excess $LiAlH_4$ had reacted the solution was swamped with water, acidified with HCl, and extracted three times with ether. Drying of the ethereal extract and evaporation gave 8.5 g of a red viscous liquid. Tlc showed several products; the major one had the spot with the highest $R_f$. Column chromatography gave 3.45 g (43%) of white crystals: mp 102–103° after recrystallization from $CH_2Cl_2$–hexane; ir ($CH_2Cl_2$) 2.80 (m), 3.05 (w), 6.15 (s), 6.27 μ (s); uv max 270 mμ (ε 700), 278 sh; nmr ($CDCl_3$) τ 9.10 (t, 3), 7.02 (m, 1), 6.32 (s, 3), 4.62 (t, 1), 4.02 (q, 2).

*Anal.* Calcd for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33. Found: C, 67.58; H, 8.59.

**2,5-Diacetoxy-4-*n*-pentyl-7-methoxychroman (18).**—The chroman **17** (52 mg) was treated with pyridine (2 ml) and acetic anhydride (1 ml). After 24 hr the solution was poured into ice–water and extracted twice with ether; the ether was washed with 2 *N* HCl and water, dried, and evaporated to yield 47 mg of an oil. Preparative tlc gave 38 mg (55%) of liquid product with an $R_f$ greater than that of the starting material. The same product was obtained when the reaction was carried out on the steam bath for 2 hr: ir ($CCl_4$) 5.75 (s), 6.13 (s), 6.30 μ (m); nmr ($CDCl_3$) τ 9.10 (t, 3), 7.90 (s, 3), 7.67 (s, 3), 7.12 (m, 1), 6.30 (s, 3), 3.71 (m, 3).

*Anal.* Calcd for $C_{19}H_{26}O_6$: C, 65.12; H, 7.48. Found: C, 64.88; H, 7.83.

**4-*n*-Pentyl-5-hydroxy-7-methoxydihydrocoumarin (20).**—A solution of **17** (3.70 g) in 15 ml of reagent grade acetone was cooled to 4°. Chromic acid reagent[16] was slowly added until the solution had a faint red-orange tinge. A green precipitate formed during the reaction. After 10 min the solution was poured into a large excess of water and extracted three times with ether. The ethereal extract was washed twice with water, dried, and evaporated to give 3.32 g of a viscous orange liquid. Column chromatography gave 1.61 g (44%) of white crystals: mp 99–100° after recrystallization from hexane–$CH_2Cl_2$; ir ($CH_2Cl_2$) 2.74 (m), 2.90 (w), 5.65 (s), 6.12 (s), 6.24 (s), 6.60 μ (s); uv max 297 mμ sh, 293 (ε 1870); nmr ($CDCl_3$) τ 9.13 (t, 3), 8.21 (m, 2), 6.65 (m, 1), 6.28 (s, 3), 3.75 (q, 2).

*Anal.* Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.33; H, 7.76.

**3,4,9,10-Tetrahydro-2,2-dimethyl-5-methoxy-10-*n*-pentyl-4,8-dioxo-2H,8H-[1,2-*b*:3,4-*b'*]benzodipyran (21).**—Senecioic acid (3-methylcrotonic acid, 200 mg, 2.00 mmol) was mixed thoroughly with **20** (400 mg, 1.51 mmol) to form a finely powdered mixture. This was placed in a small weighing bottle (12 ml), and approximately 11 g of polyphosphoric acid was added. The mixture was stirred on a Thermix hot plate maintained at 120°. After 0.5 hr the hot dark red solution was dumped into ice–water. After dissolution of the red gummy mass which formed, the solution was extracted three times with ether. The combined ether layers were washed twice with 5% $NaHCO_3$, dried, and evaporated to give 448 mg of a dark cream-colored solid. Recrystallization from hexane–$CH_2Cl_2$ gave 350 mg (67%) of white product, mp 150–152°. A sample suitable for analysis was prepared by preparative tlc: mp 151.5–152.5°; ir ($CH_2Cl_2$) 5.63 (s), 5.90 (s), 6.26 μ (s); uv max 276 mμ (ε 15,700), 322 (4080); nmr ($CDCl_3$) τ 9.10 (t, 3), 8.53 (s, 6), 7.26 (m, 4), 6.71 (m, 1), 6.12 (s, 3), 3.78 (s, 1).

*Anal.* Calcd for $C_{20}H_{26}O_5$: C, 69.34; H, 7.57. Found: C, 69.53; H, 7.63.

**Methyl 3-[8-(2,2-Dimethyl-5-methoxy-7-hydroxy)chromanyl]-octanoate (22).**—Into a 50-ml pear-shaped flask containing a magnetic stirring bar were placed 20 ml of methanol, 4 ml of water, 8 ml of glacial acetic acid, 16 g of freshly prepared zinc amalgam, and the chromanone **21** (284 mg). Concentrated HCl (6 ml) was added and stirring was begun. After 3 hr the solution was decanted into a large excess of water, the zinc amalgam was rinsed several times with ether–water; and the washings were added to the water. This was extracted three times with ether, and the ether was washed with 5% $NaHCO_3$, dried, and evaporated to give 264 mg of crude product. Tlc showed two major spots, both having $R_f$'s higher than starting material, and the ir spectra indicated the presence of some of the chroman lactone. The crude product was dissolved in 17 ml of methanol; 3 drops of concentrated $H_2SO_4$ were added; and the solution was refluxed for 0.25 hr. The reaction was poured into a large excess of water and extracted three times with ether. The extracts were washed with water, dried, and evaporated to give 245 mg of product. Column chromatography gave 155 mg (52%) of desired methyl ester **22** as white crystals: mp 93–95° after recrystallization from hexane; ir ($CCl_4$) 2.98 (w), 5.84 (s), 6.19 (s), 6.27 μ (s); uv max 272 mμ (ε 770), 280 sh; nmr ($CCl_4$) τ 9.25 (t), 8.70 (s), 8.28 (t, 3), 6.39 (s, 3), 6.28 (s, 3), 4.08 (s, 1).

*Anal.* Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85. Found: C, 69.08; H, 8.95.

A 44-mg (16%) sample of the chroman lactone was also obtained, mp 89–91° after recrystallization from methanol.

**Synthetic Methyl O-Methyldihydroblancoate (13).**—The chroman ester **22** (106 mg) in 6 ml of nitrobenzene was placed in a small pear-shaped flask. Tigloyl chloride[4] (144 mg) and a large excess of anhydrous $AlCl_3$ were added. The flask was stoppered and stirred magnetically for 2 days. The reaction mixture was poured into ice–water and dilute HCl. The solution was heated on the steam bath for 0.25 hr, cooled, and extracted twice with ether. The ethereal extract was washed once with 5% $NaHCO_3$ and twice with water and then steam distilled to remove the ether and nitrobenzene. The cooled residual solution was extracted twice with $CH_2Cl_2$, and the extracts were dried and evaporated to give a yellow oil. Tlc showed two spots which were identically fluorescent; the upper spot had the same $R_f$ and fluorescence as natural methyl O-methyldihydroblancoate. Preparative tlc gave 20 mg of a slightly viscous light yellow oil corresponding to the upper spot. The sample was purified for analysis by tlc and sublimation (100°, $10^{-5}$ Torr): ir ($CCl_4$) 5.74 (s), 5.89 (s), 6.28 (s), 6.85 μ (s); uv max 290 mμ (ε 14,700), 335 sh; nmr ($CCl_4$) τ 9.15 (t), 8.88 (d), 8.67 (s), 8.53 (d), 8.28 (t, 2), 7.40 (d), 6.54 (s, 3), 6.28 (s, 3).

*Anal.* Calcd for $C_{26}H_{38}O_6$: C, 69.93; H, 8.58. Found: C, 70.13; H, 8.74.

The lower spot gave 9 mg (7%) of a light yellow oil with uv max 290 and 335 sh mμ.

**Registry No.**—**9,** 17244-43-8; **10,** 17244-44-9; **11,** 17244-45-0; **12,** 17243-88-8; **13,** 17243-89-9; **14,** 17243-90-2; **15,** 17243-91-3; **17,** 17243-92-4; **18,** 17243-93-5; **20,** 17243-94-6; **21,** 17243-95-7; **22,** 17243-96-8; **23,** 3975-91-5; **24,** 17243-98-0; 2,6-dihydroxyacetophenone, 699-83-2; 2,4-dihydroxyacetophenone, 89-84-9.

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