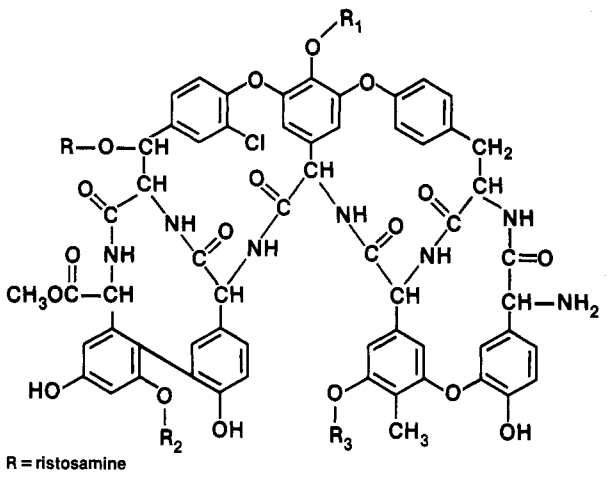
Chart I



2

actaplanins	R_1	R_2	R_3
A	mannosylglucose	mannose	mannose
B_1	rhamnosylglucose	mannose	mannose
B_2	glucose	mannose	mannose
B_3	mannosylglucose	mannose	H
C_1	rhamnosylglucose	mannose	H
G	glucose	mannose	H
C_2 (≡ X)	H	mannose	mannose
D_1 (≡ Y)	H	mannose	H
ψ (≡ Z)	H	H	H
C_3	glucose	H	mannose

of mannose from D-5 is the only possibility for the formation of new hydrolysis products. Structures M and N (see Table V) were assigned to these components. The HPLC retention characteristics of compounds K, L, M, N, and O are consistent with their assigned structures and in agreement with the HPLC retention of other actaplanins.

The structural relationships among the various actaplanins are indicated by structure 2; 2 is consistent with all the lines of evidence discussed in this paper (Chart I).

In the major hydrolysis pathways the actaplanins all lose the sugar R_1 as the first degradation step, converting A, B_1, and B_2 into C_2 and converting B_3, C_1, and G into D_1. Actaplanin C_2 is converted to D_1 by loss of R_3, and removal of R_2 from D_1 produces the ψ-aglycon 1. Actaplanins G and C_3 are isomeric; it seems reasonable that isomers of B_3 and C_1 also exist and will be degraded (along with C_3) by a third hydrolysis pathway. Compounds K and L are the proposed isomers, but their hydrolysis characteristics have not been studied.

Conclusions

The complexity of the actaplanin family of glycopeptides arises from the large number of family members. The structural relationships are not complex, however, but are readily described by structure 2. All actaplanins contain ristosamine in the ψ-aglycon 1, and they all contain either one or two mannose moieties, attached as monosaccharides at phenolic sites. An additional phenolic site in each actaplanin is occupied by either glucose, mannosylglucose, or rhamnosylglucose.

Registry No. Actaplanin A, 88357-81-7; actaplanin B_1, 88357-82-8; actaplanin B_2, 88357-83-9; actaplanin B_3, 88357-84-0; actaplanin C_1, 88357-85-1; actaplanin G, 83381-73-1; actaplanin C_2, 88357-86-2; actaplanin D_1, 88357-87-3; actaplanin ψ, 88288-92-0; actaplanin C_3, 88357-88-4; actaplanin D_2, 88357-89-5; actaplanin K, 88357-90-8; actaplanin L, 88357-91-9; actaplanin M, 88357-92-0; actaplanin N, 88357-93-1; actaplanin O, 88357-94-2.

5,8-Quinoflavone. Synthesis and Addition Reactions

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A synthesis of 5,8-quinoflavone (3) from primetin (2) is described. An improved Elbs persulfate oxidation procedure for 2 is presented. Addition of halogens and of hydrogen chloride to 3 is described, together with chemical and spectral data establishing the structure of the hydrogen chloride adduct (4) as 6-chloro-5,8-dihydroxyflavone. Chemical data include an independent synthesis of 4 via 6-chloro-5-hydroxyflavone (9). Methylation studies support the structural assignment given 2-methoxy-3-chloro-6-hydroxyacetophenone (5), from which 9 was synthesized in a four-step synthesis. Carbon-13 NMR spectral data for 4 are presented.

Quinones from flavonoid precursors have been reported by several workers.[12] In the present paper, we describe synthetic studies leading to primetin and 5,8-quinoflavone. Addition of halogens and hydrogen chloride to the quinone is described, together with data establishing the structure of the hydrogen chloride adduct.

Primetin (2) was obtained in 50% yield by a modification of the Elbs persulfate oxidation procedure,[3] in which tetraethylammonium hydroxide was the base. Removing oxygen from the reaction medium by nitrogen purging increased yields as much as 15%. Use of tetramethylammonium hydroxide in the oxidation gave yields of 2 under 10%, and tetra-n-propylammonium hydroxide and benzyltrimethylammonium hydroxide gave traces of 2.

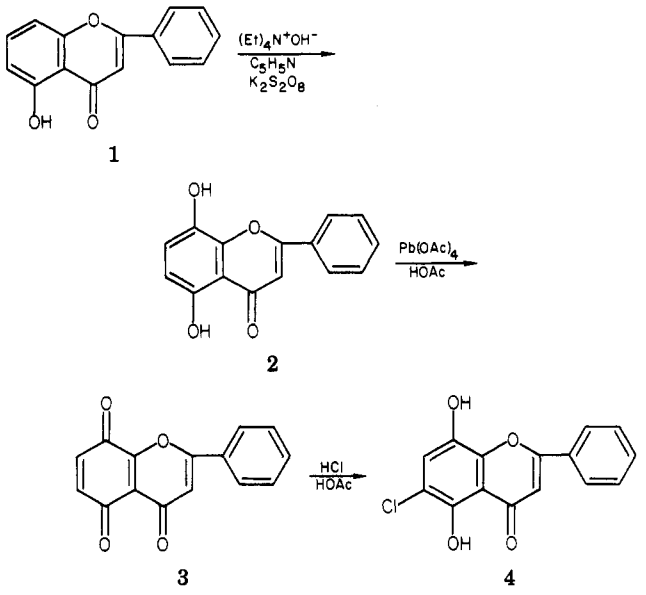
Primetin was oxidized to 5,8-quinoflavone (3) with lead tetraacetate in either benzene or acetic acid. The yield of 3 in the latter solvent was 68%, and in benzene 37%. For

(1) Stenhouse, J.; Groves, C. E. *J. Chem. Soc.* **1877**, *31*, 551.
(2) Rao, K. V.; Seshadri, T. R. *Proc. Indian Acad. Sci. Sect. A* **1947**, *25A*, 397. Rao, G. S. K.; Rao, K. V.; Seshadri, T. R. *Ibid.* **1948**, *27A*, 245 *Ibid.* **1948**, *27A*, 103.

(3) Elbs, K. *J. Prakt. Chem.* **1893**, *48*, 179. Sethna, S. M. *Chem. Rev.* **1951**, *49*, 91. Seshadri, T. R. *Proc. Indian Acad. Sci. Sect. A* **1947**, *25A*, 417.

0022-3263/84/1949-0645$01.50/0

Chart I



1 2 3 4

completely satisfactory results, 2 must be very pure.

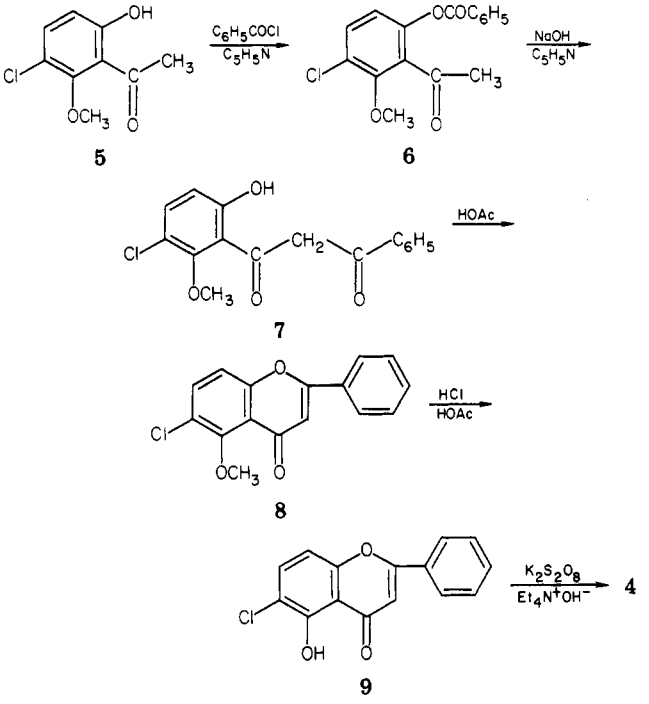
In order to ascertain whether 3 has typical quinone reactivity,[4] addition of bromine, chlorine, and hydrogen chloride has been investigated. Addition of bromine to 3 in chloroform gave a bromodihydroxyflavone, the infrared spectrum of which resembled that of 2. Possibly bromoflavone derivative was formed by dehydrobromination after initial addition of bromine and subsequent reduction of the dehydrobromination product. Addition of chlorine also occurs. Product analytical numbers, especially a high chlorine value, and a negative ferric chloride test indicated dichloroquinone derivatives probably were present.

Addition of dry hydrogen chloride to 3 in both acetic acid and chloroform occurs (Chart I). Reaction of hydrogen chloride with 3 in boiling acetic acid leads to a single chlorodihydroxyflavone (4). However, in chloroform at 40 °C there resulted a mixture which could not be resolved by column chromatography. Analysis indicated the presence of chlorodihydroxyflavones.

The hydrogen chloride adduct 4 could have the chlorine atom at either the 6 or the 7 position, assuming 5,8-hydroxyl substitution. An independent synthesis (Chart II) and ^{13}C NMR data (sequel) indicate a halogen atom at C_6. The chloroacetophenone 5, from sulfuryl chloride halogenation of 2-hydroxy-6-methoxyacetophenone (10)[5] (Chart III), was aroylated to give 6. Baker–Venkataraman rearrangement[6] gave the diaroylmethane 7. Ring closure to the flavone 8 occurred readily in acetic acid. Demethylation of 8 gave 6-chloro-5-hydroxyflavone (9), oxidized by potassium peroxydisulfate to 4. Both 4 and its dibenzoate were identical with the corresponding substances from 5,8-quinoflavone (Chart I).

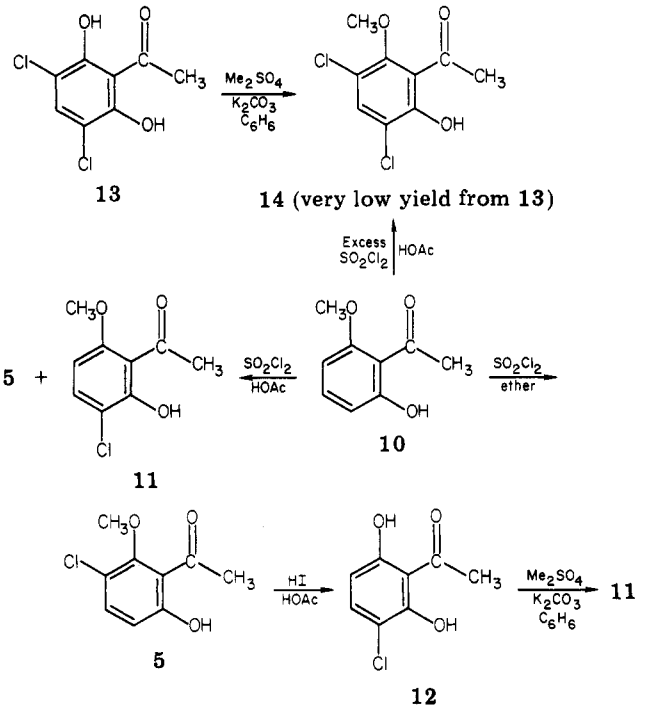
Chemical reactions in support of the structure assigned 5 are in Chart III. Chlorination of 10 in ether gave 5 in 90% yield. Demethylation of 5 afforded 12,[7] methylated to 11, the isomer of 5. That 11 is the methylation product of 12 is expected, because the 2-hydroxyl group in 12 is both hydrogen bonded and diortho substituted, whereas the 6-hydroxyl is only hydrogen bonded. Confirmation of

Chart II



5 6 7 8 9

Chart III



13 14 (very low yield from 13) 5 + 11 10 5 12

difficulty in methylation of such a 2-hydroxyl group is found in the very low yield methylation of 13, 92% of which was recovered unreacted.

To confirm the structure of the hydrogen chloride adduct of 3, the ^{13}C NMR spectrum of 4 has been determined (Table I). Assignments are in reasonable agreement with shifts calculated from flavone values[8] and standard aromatic correction factors. Only the A ring resonances of flavone require adjustment. The B and C ring calculated values are those observed for flavone itself[8] (zero correction). If a chlorine atom were at C_7, then the $^{13}C_6$ resonance is calculated as 113.6 ppm. No peak near this value

(4) Finley, K. T. In "The Chemistry of the Quinonoid Compounds"; Patai, S., Ed.; Interscience: London, 1974; pp 929–933.
(5) Baker, W. *J. Chem. Soc.* **1939**, 956.
(6) Baker, W. *J. Chem. Soc.* **1933**, 1381. Mahal, H. S.; Venkataraman, K. *Ibid.* **1934**, 1767.
(7) Setalvad, J. I.; Shah, N. M. *J. Indian Chem. Soc.* **1953**, *30*, 377.
(8) Kingsbury, C. A.; Looker, J. H. *J. Org. Chem.* **1975**, *40*, 1120.

Table I. ^{13}C NMR Spectral Data for 6-Chloro-5,8-dihydroxyflavone

C	obsd[a]	calcd[b]
2	164.95[c]	163.0
3	106.3	107.3
4	183.5	178.0
4a		113.7
5	147.4[d]	145.4
6	122.4[e]	119.8
7	122.4	121.2
8	139.2	137.5
8a	139.2[f]	142.8
1′	131.2[d]	131.5
2′, 6′	127.5	126.0
3′, 5′	129.8	128.8
4′	133.2	131.3

[a] For Me_2SO-d_6 solution in ppm downfield from Me_4Si. [b] From flavone values (cf. ref 8) adjusted by use of aromatic correction factors (Levy, G. C.; Lichter, R. L.; Nelson, G. L. "Carbon-13 Nuclear Magnetic Resonance Spectroscopy"; Wiley-Interscience: New York, 1980; pp 111-112). [c] One of three weak peaks near 165; others at 166.0 and 166.7. [d] Weak peak. [e] Only peak near 120 is that at 122.4; assignment tentative. [f] Only peak near 140 is that at 139.2; assignment tentative.

is present. In compound 4, with a hydrogen at C_7, the observed and calculated resonance values for C_7 are in satisfactory agreement. The peak at 122.4 ppm is of moderate intensity, exceeded only by peaks for the carbonyl carbon and for $C_{2'}$,$C_{6'}$,$C_{3'}$, and $C_{5'}$.

Experimental Section[9]

A. Synthesis of 5,8-Quinoflavone. 5,8-Dihydroxyflavone (Primetin). 5-Hydroxyflavone (1) (8 g) was dissolved with stirring in 280 mL of tetraethylamminium hydroxide (10% aqueous solution) and 8 mL of pyridine in a 1-L three-necked flask equipped with dropping funnel, stirrer, and fritted-glass gas dispersion rod. The solution was purged with nitrogen for 1.5 h to remove dissolved oxygen. Under a nitrogen atmosphere, 13.7 g of potassium peroxydisulfate in 300 mL of oxygen-free water was added dropwise over a period of 4 h with stirring. After standing overnight at room temperature, the solution was acidified to Congo red paper with concentrated HCl (ca. 75 mL) and the mixture was filtered through porous filter paper to remove gum-like material. The filtrate was extracted twice with 150-mL portions of ether which were discarded. The filtrate then was acidified with an additional 50 mL of concentrated HCl and placed on a steam bath for 1.5 h. The 5,8-dihydroxyflavone which formed was collected by filtration, washed well with water, and air-dried; the yield of crude product was 4.4 g (51.5%), mp 215–218 °C. Two crystallizations from 1:1 (vol) dioxane–water (charcoal) gave pure primetin, mp 231–232 °C (lit.[10] mp 230–232 °C).

5,8-Quinoflavone. To 500 mg of 5,8-dihydroxyflavone (mp 228 °C) in 20 mL of glacial acetic acid at room temperature was added, in four equal portions over a 20-min period, 1.5 g of lead tetraacetate (moist with acetic acid) with vigorous stirring. The clear red solution resulting was permitted to stand at room temperature for 2 h and then was added to 120 mL of water in a separatory funnel. After shaking vigorously, the aqueous mixture was extracted with two 20-mL portions of chloroform, which were combined, washed with water, dried over anhydrous $MgSO_4$, and filtered. Dilution of the resulting chloroform solution with petroleum ether (bp 30–60 °C) precipitated the 5,8-quinoflavone as a dull tan crystalline product; the yield was 340 mg (68%), mp 195–197 °C. Two crystallizations from chloroform–petroleum ether gave the substance as an orange solid, mp 209.5–210 °C. The infrared spectrum showed no peak for hydroxyl groups, and a $FeCl_3$ test was negative.

Anal. Calcd for $C_{15}H_8O_4$: C, 71.40; H, 3.17. Found: C, 71.09; H, 3.51.

The infrared spectrum ($CHCl_3$, 5 mg/mL, 1 mm cell, 21) contained three peaks at 1691 (sh), 1689 (s), and 1665 (w sh) attributed to quinone carbonyls and a peak at 1642 (s) (flavone CO).

B. Reactions of 5,8-Quinoflavone. Addition of Hydrogen Chloride. Dry hydrogen chloride was passed through a solution of 250 mg of 5,8-quinoflavone in 12 mL of boiling glacial acetic acid for 3.5 min. Dilution of the hot acetic acid solution with water followed by filtration gave an orange-yellow product which was washed well with water and air-dried; yield, 270 mg (94%), mp 243–248 °C. After three crystallizations from ethanol (first with C), the hydrogen chloride adduct was obtained as yellow needles, mp 249–250 °C.

Anal. Calcd for $C_{15}H_9ClO_4$: C, 62.39; H, 3.12; Cl, 12.31. Found: C, 62.51; H, 3.14; Cl, 12.13.

The infrared spectrum (KBr, 237) contained absorption bands at 1653 (s) (flavone CO) and 1605 (s) (aromatic in-plane-skeletal mode).

The dibenzoate, mp 223.5–225 °C, of the hydrogen chloride adduct was obtained from benzoyl chloride and pyridine in the usual manner with recrystallization three times from ethanol.

Anal. Calcd for $C_{29}H_{17}ClO_6$: C, 70.09; H, 3.42; Cl, 7.15. Found: C, 70.04; H, 3.63; Cl, 7.11.

Attempted application of the above general hydrogen chloride addition method to the quinoflavone in chloroform solution at 40 °C gave a substance, mp 230–231 °C, for which the following analytical numbers were obtained: C, 63.06; H, 3.55; Cl, 13.00. Slight changes in reaction conditions gave products of widely varying melting points, and all attempts at separation into pure components, including column chromatography, were unsuccessful.

Addition of Bromine (x-Bromo-5,8-dihydroxyflavone). Bromine was added dropwise with stirring at room temperature to 100 mg of 5,8-quinoflavone in 10 mL of chloroform. Addition of bromine was continued until a permanent red color of the reaction medium was obtained. The reaction mixture was cooled and diluted with petroleum ether to precipitate the product, mp 236–238 °C, unchanged after two additional crystallizations from chloroform–petroleum ether. The substance gave a greenish-black color with $FeCl_3$, was soluble in base, and contained an OH peak in the IR spectrum.

Anal. Calcd for $C_{15}H_9BrO_4$: C, 54.18; H, 2.71; Br, 24.10. Found: C, 54.20; H, 2.99; Br, 25.28.

The infrared spectrum (KBr, 21) contained absorption bands at 1653 (m) (flavone CO) and 1608 cm^{-1} (m) (aromatic in-plane-skeletal mode).

Application of the above general procedure to 200 mg of 5,8-quinoflavone in 20 mL of glacial acetic acid gave, after addition of water to the reaction mixture, a gold-colored product, mp 207–210 °C. The substance gave a negative $FeCl_3$ test and was recrystallized from chloroform–alcohol–petroleum ether to yield a bright yellow substance, mp 255–257 °C. The latter material was obtained in insufficient yield to permit complete purification, but analysis (34.81% Br) indicated that probably a dibromide was the major reaction product.

C. Synthesis of 5,8-Dihydroxy-6-chloroflavone. 3-Chloro-6-hydroxy-2-methoxyacetophenone. 2-Hydroxy-6-methoxyacetophenone[5] (34.5 g) was dissolved in 300 mL of absolute ether in a 500-mL three-necked flask equipped with condenser, drying tube, stirrer, and dropping funnel. The reaction mixture was cooled to 0 °C in a salt–ice bath, and 18.2 mL of sulfuryl chloride was added dropwise over a 5-h period. The temperature slowly rose to room temperature during the addition, and then the mixture was refluxed for an additional 4 h. The ether solution was washed with four 200-mL portions of water (discarded) and then with three 50-mL portions of 10% aqueous sodium hydroxide. The latter extracts were retained. Ice was added as necessary during extractions to cool the ether solution. The combined sodium hydroxide extracts, cooled in ice, were acidified to Congo red with concentrated HCl. An oil formed which solidified upon standing overnight in a refrigerator. The solid was collected by filtration and transferred immediately to

(9) The melting points of compounds 4 and its dibenzoate were determined on a Kofler hot stage. Other melting points were taken by capillary tube method. IR spectra were recorded on a Perkin-Elmer Model 21 or PE Model 237 spectrophotometer and are indicated in the Experimental Section by 21 or 237.

(10) Rajagopalan, S.; Rao, K. V.; Seshadri, T. R. *Proc. Indian Acad. Sci. Sect. A* **1947**, *25A*, 432.

warm petroleum ether. Any water which was present was removed with the aid of a separatory funnel. The petroleum ether solution then was shaken for 15 min with anhydrous $MgSO_4$ and charcoal, filtered, and the filtrate cooled in a dry ice chest. A yellow product precipitated (28.5 g) and was collected by filtration; the filtrate yielded an additional 10 g; total yield, 38.5 g (92.7%). An analytically pure substance was obtained by vacuum distillation, bp 40 °C (10^{-3} mm). The substance melted unsharply near 31 °C.

Anal. Calcd for $C_9H_9ClO_3$: C, 53.86; H, 4.49; Cl, 17.71. Found: C, 53.70; H, 4.52; Cl, 17.74.

3-Chloro-2-methoxy-6-(benzoyloxy)acetophenone. To 33 g of 3-chloro-6-hydroxy-2-methoxyacetophenone in 50 mL of dry pyridine was added 24.8 g of benzoyl chloride. The resulting mixture was heated for 30 min on a steam bath and poured with vigorous stirring onto 150 mL of a concentrated HCl–ice mixture. A gummy product resulted and was collected by filtration after standing overnight. The crude product was recrystallized from methanol (charcoal) to yield 43.5 g (87.4%) of fine colorless needles, mp 60–62 °C. Two additional crystallizations from methanol gave an analytically pure substance, mp 63–64 °C.

Anal. Calcd for $C_{16}H_{13}ClO_4$: C, 63.05; H, 4.27; Cl, 11.66. Found: C, 63.09; H, 4.15; Cl, 11.41.

(3-Chloro-6-hydroxy-2-methoxybenzoyl)benzoylmethane. 3-Chloro-2-methoxy-6-(benzoyloxy)acetophenone (24.5 g, mp 62–63 °C) and 24 g of powdered sodium hydroxide were shaken for 4 h in 110 mL of pyridine in a stoppered 250-mL flask at room temperature. The reaction mixture was poured into an excess of concentrated HCl and ice to yield a bright orange precipitate. Crystallization from methanol (charcoal) yielded 17.5 g (71.5%) of yellow needles, mp 98–99 °C. Recrystallization from ethanol gave the analytically pure substance, mp 103–104 °C.

Anal. Calcd for $C_{16}H_{13}ClO_4$: C, 63.05; H, 4.27; Cl, 11.66. Found: C, 63.16; H, 4.21; Cl, 11.41.

6-Chloro-5-methoxyflavone. (3-Chloro-6-hydroxy-2-methoxydibenzoyl)methane (17.5 g) was heated under reflux for 4 h in 625 mL of glacial acetic acid. The reaction mixture then was poured onto 1.5 L of ice water to precipitate the flavone. The product was collected by filtration and partially dried in air. A small quantity was recrystallized twice from ethanol to give analytically pure, colorless 6-chloro-5-methoxyflavone, mp 178.5–180 °C.

Anal. Calcd for $C_{16}H_{11}ClO_3$: C, 67.01; H, 3.84; Cl, 12.39. Found: C, 67.32; H, 3.89; Cl, 12.28.

6-Chloro-5-hydroxyflavone. 6-Chloro-5-methoxyflavone (prepared as in the preceding section and still moist, the total product except for analytical sample) was dissolved in 400 mL of hot glacial acetic acid and 200 mL of concentrated HCl. There resulted a clear yellow solution, which was heated under reflux for 4 h; the yellow hydroxyflavone precipitated from solution. After cooling, the product was collected by filtration, washed with cold ethanol, and dried overnight at 120 °C in vacuo; yield, 13 g, mp 182–183 °C. An additional gram of pure product was obtained from the mother liquors; total yield, 14 g (89.3%, based on the dibenzoylmethane). One additional crystallization from ethanol gave analytically pure 6-chloro-5-hydroxyflavone, mp 183–184.5 °C.

Anal. Calcd for $C_{15}H_9ClO_3$: C, 66.05; H, 3.30; Cl, 13.03. Found: C, 66.25; H, 3.24; Cl, 12.94.

The infrared spectrum ($CHCl_3$, 5 mg/mL; 1-mm cell; 21) contained absorption bands at 1651 (s) (flavone CO) and 1616 (aromatic in-plane skeletal mode) cm^{-1}. A broad weak peak(s) was (were) present in the region 3200–3300 (phenolic OH).

6-Chloro-5,8-dihydroxyflavone. 6-Chloro-5-hydroxyflavone (4 g) was dissolved in 280 mL of a 10% aqueous solution of tetraethylammonium hydroxide and 9 mL of pyridine in a 1-L three-necked flask equipped with dropping funnel, stirrer, and fritted-glass gas dispersion rod. The resulting solution was purged with nitrogen for 1.5 h at 30–35 °C. There followed the dropwise addition to the stirred solution of 6.85 g of potassium peroxydisulfate in 150 mL of oxygen-free water over a 4-h period. An additional 9 mL of pyridine was added after 2 h to maintain a homogeneous mixture. The reaction mixture was stirred an additional 20 h at 30–35 °C and filtered to give 1.25 g of the potassium salt of 6-chloro-5-hydroxyflavone, and the filtrate was acidified with concentrated HCl to Congo red. The filtrate was neutralized with very dilute sodium hydroxide (ca. 1%), and the resulting tan-colored precipitate (3.4 g) was collected by filtration. (Filtrate (F) retained). The tan precipitate was dissolved in 40 mL of cold 5% sodium hydroxide and filtered, and ca. 200 mg of dark colored solid was collected and discarded. The filtrate was acidified to Congo red with concentrated HCl, and the resulting tan precipitate was collected and dried. The tan material then was placed in 80 mL of hot water, and the pH was adjusted to 7.5–8.0 with 1% sodium hydroxide solution. The resulting mixture was stirred for 15 min and filtered, and the dark brown precipitate was discarded. To the filtrate was added 25 mL of concentrated HCl, and the acidified filtrate was heated 2 h on a steam bath. 6-Chloro-5,8-dihydroxyflavone was obtained as a yellow powder and collected by filtration; yield, 1.02 g (34% based on 2.84 g of starting material), mp 244–247 °C. One crystallization from ethanol gave the pure substance, mp 248–249 °C, mmp with the hydrogen chloride adduct from 5,8-quinoflavone, 247–248 °C. The mixed melting point of the dibenzoate with that of the HCl adduct dibenzoate, mp 223.5–225 °C, was 223–224 °C.

The filtrate (F) from the original crude product isolation was acidified with 25 mL of concentrated HCl and heated on a steam bath and 360 mg of the crude substance was collected. Chromatography of the latter on a column of Florex/Celite (5:1 wt), with ethyl acetate as solvent, gave an additional 30 mg of 6-chloro-5,8-dihydroxyflavone, thus making the total yield 1.05 g.

D. Additional Reactions Utilized in the Chemical Proof of the Structure of 4. Chlorination of 2-Hydroxy-6-methoxyacetophenone in Acetic Acid. Preparation of 3-Chloro-2-hydroxy-6-methoxyacetophenone and 3,5-Dichloro-2-hydroxy-6-methoxyacetophenone. Into a 1-L three-necked flask equipped with condenser, dropping funnel, and stirrer were placed 40 g of 2-hydroxy-6-methoxyacetophenone[5] and 435 mL of glacial acetic acid. The resulting solution was cooled to 10 °C, and 20.3 mL of sulfuryl chloride was added dropwise to the stirred solution. The reaction mixture was heated at approximately 115 °C (not refluxed) for 1.5 h and then refluxed for 30 min. The mixture was poured onto excess ice to precipitate the product. The resulting mixture was permitted to stand in a refrigerator until the product solidified completely and then was filtered, and the precipitate dried briefly over P_2O_5 in a desiccator. Further drying in vacuo in a desiccator overnight gave a predominantly liquid product containing a small quantity of yellow solid. The solid (1 g) was collected by filtration (Filtrate (F) retained) and crystallized twice from petroleum ether (first with charcoal) to give yellow needles of 3-chloro-2-hydroxy-6-methoxyacetophenone, mp 88.5–89 °C.

Anal. Calcd for $C_9H_9ClO_3$: C, 53.87; H, 4.49; Cl, 17.71. Found: C, 53.95; H, 4.29; Cl, 17.59.

The benzoate of 3-chloro-2-hydroxy-6-methoxyacetophenone was prepared by the pyridine–benzoyl chloride method and crystallized twice from ethanol, mp 86–88.5 °C.

Anal. Calcd for $C_{16}H_{13}ClO_4$: C, 63.05; H, 4.27; Cl, 11.66. Found: C, 63.17; H, 4.31; Cl, 11.70.

The oily Filtrate F was recrystallized from petroleum ether to give 32 g of the low-melting 3-chloro-6-hydroxy-2-methoxyacetophenone. A more satisfactory synthesis of the latter is presented in Section C of the Experimental Section. If a slight excess of sulfuryl chloride was employed in refluxing acetic acid, a third yellow product was isolated and crystallized from petroleum ether to yield 3,5-dichloro-2-hydroxy-6-methoxyacetophenone, mp 98.5–100 °C.

Anal. Calcd for $C_9H_8Cl_2O_3$: C, 45.96; H, 3.40; Cl, 30.21. Found: C, 45.83; H, 3.37; Cl, 30.41.

3-Chloro-2,6-dihydroxyacetophenone. 2,6-Dihydroxyacetophenone (20 g) was dissolved in 280 mL of glacial acetic acid in a 500-mL three-necked flask equipped with condenser, stirrer, and dropping funnel and cooled to 10 °C. After adding 11.3 mL of sulfuryl chloride slowly to the stirred solution, the reaction mixture was heated under gentle reflux for 2 h. Then it was poured into water to precipitate the 3-chloro-2,6-dihydroxyacetophenone, which was collected, washed well with water, and dried; yield, 21.2 g (90.5%) mp 128–129 °C. Two recrystallizations from benzene gave the pure substance, mp 135 °C (lit.[7] mp 134–135 °C).

Monomethylation of 3-Chloro-2,6-dihydroxyacetophenone. 3-Chloro-2,6-dihydroxyacetophenone (2 g), anhydrous potassium carbonate (4 g), and 1.05 mL of dimethyl sulfate were heated under

reflux for 24 h in 20 mL of benzene in a flask equipped with a condenser and protected by a drying tube. Sufficient water to dissolve the carbonate was added, the layers were separated, and the aqueous layer was neutralized to yield 1.1 g of starting material. The benzene phase then was extracted with 10 mL of 10% aqueous NaOH and neutralized with HCl to give 0.82 g of crude product. After two crystallizations from petroleum ether, the substance was obtained with mp 88–89 °C and mp, with chlorination product (11) of 2-hydroxy-6-methoxyacetophenone, 88–89 °C.

Monomethylation of 3,5-Dichloro-2,6-dihydroxyacetophenone. 3,5-Dichloro-2,6-dihydroxyacetophenone[11] (1 g), anhydrous potassium carbonate (2 g), and dimethyl sulfate (0.57 g) were heated under reflux for 24 h in 25 mL of benzene, with protection from atmospheric moisture. Sufficient water then was added to dissolve the potassium carbonate and the resulting two phases were separated. Neutralization of the aqueous layer gave 920 mg of starting material. The benzene phase was extracted with 5 mL of 10% NaOH, and the sodium hydroxide solution was neutralized to yield 30 mg of 3,5-dichloro-2-hydroxy-6-methoxyacetophenone; mp, after one crystallization from petroleum ether (charcoal), 97–98 °C, mmp, with 2-hydroxy-6-methoxyacetophenone chlorination product (mp 98.5–100 °C), 97–99 °C.

E. ^{13}C NMR Spectral Data. Spectra were determined at 25.2 MHz on a Varian XL-100 instrument at normal probe temperature. The concentration of 4 was ca. 50 mg/3 mL of Me_2SO-d_6. The error in signal position, as indicated by the computer was ±2.5 Hz; 30 000 total transients were collected under block acquisition conditions. The approximate tipping angle was 50°. A 5-K spectral width was used, with a 0.4 s acquisition time and a 0.2 s pulse delay. Five watts of decoupling power were used with a band width of 1.5 K. The Me_2SO-d_6 peak at 40.4 ppm from Me_4Si was taken as standard.

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Registry No. 1, 491-78-1; 2, 548-58-3; 2 (bromo deriv), 87953-96-6; 3, 87953-83-1; 4, 87953-84-2; 4 (dibenzoate), 87953-85-3; 5, 87953-86-4; 6, 87953-87-5; 7, 87953-88-6; 8, 87953-89-7; 9, 87953-90-0; 10, 703-23-1; 11, 87953-91-1; 11 (benzoate), 87953-92-2; 12, 87953-93-3; 13, 87953-95-5; 14, 87953-94-4; 2,6-dihydroxyacetophenone, 699-83-2.

(11) Looker, J. H.; Edman, J. R.; Dappen, J. I. *J. Heterocycl. Chem.* **1964**, *1*, 141.

Synthesis and Characterization of *trans*-, 13-*cis*-, and 11-*cis*,13-*cis*-12-(Hydroxymethyl)retinols

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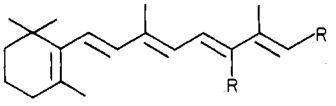
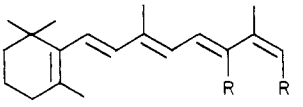
Whereas reduction of *trans*- and 11-*cis*,13-*cis*-12-carboxyretinoic acid dimethyl esters gives the trans and 11-cis,13-cis corresponding diols, reduction of 13-*cis*-12-carboxyretinoic acid dimethyl ester gives essentially no 13-cis diol with trans and 11-cis,13-cis diols being the major products. 12-(Hydroxymethyl)retinol with 13-cis stereochemistry is obtained by reduction of the configurationally locked retinoids 13-*cis*-12-carboxyretinol δ-lactone and 13-*cis*-12-(hydroxymethyl)retinoic acid δ-lactone.

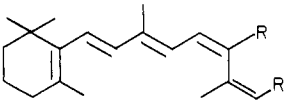
The demonstrated effectiveness of retinoids in preventing or delaying the progression of preneoplastic lesions to malignant, invasive carcinomas in epithelial tissues[1-3] and in bringing about regressions with skin papillomas,[2-4] carcinomas, and some types of murine melanomas[2,3,5] has generated substantial interest in the synthesis of novel retinoids. We have recently reported the synthesis, stereochemistry, and conformations of 12-carboxyretinoic acids[6,7] and of related anhydrides[7] and lactones.[8] We now report the methods for preparing *trans*-, 13-*cis*-, and 11-*cis*,13-*cis*-12-(hydroxymethyl)retinol (1–3), present chemical and spectral data establishing their structure and stereochemistry, and discuss their relative stability.



1, R = CH_2OH
4, R = CO_2CH_3



2, R = CH_2OH
5, R = CO_2CH_3



3, R = CH_2OH
6, R = CO_2CH_3

Results and Discussion

Lithium aluminum hydride reduction of retinoid esters has been shown to proceed with retention of the stereochemistry of the retinoid backbone.[9] It was, therefore, expected that reduction of the dimethyl esters of *trans*-, 13-*cis*-, and 11-*cis*,13-*cis*-12-carboxyretinoic acids (4–6,

(1) Sporn, M. B.; Newton, D. L.; Smith, J. M.; Acton, M.; Jacobson, A. E.; Brossi, A. In "Carcinogens: Identification and Mechanism of Action"; Griffin, A. C., Shaw, C. R., Eds.; Raven Press: New York, 1979; p 441.
(2) Lotan, R. *Biochim. Biophys. Acta* **1980**, *605*, 33.
(3) Hill, D. L.; Grubbs, C. J. *Anticancer Res.* **1982**, *2*, 111.
(4) Sporn, M. B.; Newton, D. L. In "Inhibition of Tumor Induction and Development", Zedeck, M. S.; Lipkin, M., Eds.; Plenum Press: New York 1981.
(5) Bollag, W. *Cancer Chemother. Pharmacol.* **1979**, *3*, 207.
(6) Lewin, A. H.; Carroll, F. I.: Moreland, C. G. *J. Am. Chem. Soc.* **1981**, *103*, 6527.
(7) Lewin, A. H.; Whaley, M. G.; Parker, S. R.; Carroll, F. I.; Moreland, C. G. *J. Org. Chem.* **1982**, *47*, 1799.
(8) Lewin, A. H.; Rector, D. H.; Parker, S. R.; Wani, M. C.; Carroll, F. I. *J. Org. Chem.* **1983**, *48*, 222.
(9) Robeson, C. D.; Cawley, J. D.; Weister, L.; Stern, M. H.; Eddinger, C. C.; Chechak, A. J. *J. Am. Chem. Soc.* **1955**, *77*, 4111.

0022-3263/84/1949-0649$01.50/0