ing of the C_4 methyl and both carbonyls will cause a shielding of the C_{10} group. Change of solvent leads to strong shielding of both methyl groups. With the bromo compound (**3b**), the change of solvent leads to a slight shielding of both methyl groups. This may be due to the fact that in this compound the 7-ketone group is turned upward more than in any other compound in the series so that the C_{10} methyl group is close to its reference plane. However, the proximity of a highly polar substituent can alter the effect of the ketone group.[23] The shifts of the C_5 and C_6 protons on changing from deuteriochloroform to benzene may be similarly analyzed.

The behavior of the bromo ketone (**3b**) with base[8] deserves some comment. Contrary to the normal situation, increasing the hindrance in the base (from hydroxide to pyridine to collidine) increases the amount of substitution to give **1** and decreases the amount of elimination to **5**. The reason for this anomaly is not clear. However, with the stereochemistry (**3b**) the mechanism of the elimination poses no problem;[8] the dihedral angle between the bromine and hydrogen is about 140°. The formation of the lactone (**1**) must involve displacement of the bromine by the collidine followed by attack of the ester group on the 6 position. Using our ideas on the conformation of the ester group, we suggest that the carbonyl oxygen attacks the 6 position.[8] The methyl group of the ester must be removed as methyl collidinium bromide.

Experimental Section[26]

Methyl O-Methyl-6β-bromo-7-oxopodocarpate (3b).—The bromo ketone (**3b**) was prepared from podocarpic acid by a three-step synthesis.[2] The bromination of **3a** was done with N-bromosuccinimide in carbon tetrachloride[2,8,10] or with pyridinium bromide perbromide in tetrahydrofuran. The former conditions gave better yields though the product was sometimes contaminated with a by-product (see below). The bromo ketone after crystallization from aqueous methanol had mp 135–137° (single spot on thin layer chromatography) (lit.[2] 142–144.5° and 121–125.5° in one preparation; 141–142°[10] and 123–126°[8]); ν_{max} 2950, 1729, 1684, 1604, 1575, 1487, 1466, 1383, 1324, 1274, 1254, 1215, 1154, 1129, 1077, 1062, 1036, 1007, 981, 952, 924, and 877 cm^{-1}. The bromo ketone (**3b**) had $\nu_{max}^{CCl_4}$ (in carbonyl region) 1732, 1691, and 1603 cm^{-1}; the keto ester (**3a**) had $\nu_{max}^{CCl_4}$ (in carbonyl region) 1733, 1685, and 1603 cm^{-1}. Other physical data for **3b** are given in Tables I and II.

Sometimes we isolated from the bromination (with N-bromosuccinimide) material with mp 128–130°, or slightly lower. This material had the same infrared spectrum as **3b** but, in addition, had a shoulder at 1660 cm^{-1}. Thin layer chromatography on silicic acid (solvent system ethyl acetate 10%–benzene 90%) showed this material to be a mixture which on preparative thin layer chromatography was separated into **3b** and **5**.

Lactone of O-Methyl-6β-hydroxy-7-oxopodocarpic Acid (1).—This was prepared by boiling **3b** with collidine.[8] The product after crystallization from aqueous methanol had mp 195–197° (ν_{max} 3050, 2975, 2945, 1781, 1694, 1603, 1568, 1482, 1456, 1386, 1336, 1311, 1264, 1218, 1170, 1106, 1060, 1026, 1009, 944, 877, 852, and 815 cm^{-1}) identified as **1** by comparison (melting point, mixture melting point, and infrared spectrum) with a sample supplied by Dr. Bible. Other physical data are in Tables I and II.

Attempts to improve the yield of **1** by heating **3b** with aqueous sodium hydroxide or pyridine led to increased amounts of unsaturated ketone **5**.

Attempts to convert **1** into the lactone of O-methyl-6β-hydroxypodocarpic acid by the Clemmensen or Wolff-Kishner reduction failed.

(26) See part II[27] for general details. Unless otherwise specified, infrared spectra were taken in CH_2Cl_2 solutions. Melting points are uncorrected.

(27) S. K. Roy and D. M. S. Wheeler, *J. Chem. Soc.*, 2155 (1963).

Thioketal of the Keto Lactone (1).—Dry hydrogen chloride was passed slowly through a cooled solution of the keto lactone (**1**, 494 mg) in ethanedithiol (10 ml) for 2 hr.[28] Solid potassium carbonate was added (a little more was added after foaming had stopped). Ether (70 ml) was added and the ethereal solution was washed with water, then repeatedly with dilute, aqueous potassium hydroxide until the dithiol odor had gone, and finally with water, and was dried (Na_2SO_4). Removal of solvent gave a residue which on crystallization from aqueous methanol had mp 135–140° (202 mg), raised to mp 150–152.5° when crystallized from ether–petroleum ether (bp 30–60°). For analysis the compound had mp 158–159°; ν_{max} 3050, 1774, 1608, 1569, 1481, 1381, 1291, 1240, 1217, 1183, 1112, 1065, 1046, 1020, 1008, 966, 940, 925, 882, 863, 845, 811, and 779 cm^{-1}. For nmr data see Table I.

Anal. Calcd for $C_{20}H_{24}O_3S_2$: C, 63.82; H, 6.43; O, 12.75; S, 17.00. Found: C, 63.69; H, 6.54; O, 12.91; S, 17.23.

O-Methylpodocarpic Acid (2a).[29]—A solution of the keto lactone (**1**, 500 mg) in ethyl acetate (50 ml) and concentrated sulfuric acid (1 ml) was hydrogenated in the presence of palladized charcoal (200 mg). Three moles of hydrogen was absorbed. The catalyst was filtered off and the filtrate was washed with dilute, aqueous sodium hydrogen carbonate and was dried (Na_2SO_4). Removal of the solvent gave O-methylpodocarpic acid (**2a**), mp 154–156° (390 mg), identified by comparison (melting point, mixture melting point, and infrared spectrum) with authentic **2a**, prepared by lithium in ammonia cleavage of methyl O-methylpodocarpate.[4]

A similar result (but in poorer yield) was obtained when **1** was reduced with lithium in liquid ammonia.

Registry No.—**1**, 10037-24-8; **2b**, 10037-26-0; **3a**, 901-36-0; **3b**, 10060-22-7; **4**, 10037-25-9.

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(28) V. Schwarz, V. Černý, and F. Šorm, *Collection Czech. Chem. Commun.*, **24**, 1851 (1959).

(29) This experiment was tried after we had been informed by Bible[2] that "hydrogenation of **1** over Pd–C in ethanol gave an 80% yield of O-methylpodocarpic acid."

Intramolecular Transesterifications. Syntheses of α-Hydroxybenzylidene-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolides and 3-Phenacylcoumarins

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Recently 3-phenacylcoumarin was prepared in a moderate yield by the reaction of β-benzoylpropionic acid and 2-hydroxybenzaldehyde in the presence of a sulfur trioxide–dimethylformamide complex.[1] It is conceivable that this reaction involves a cyclodehydration of β-benzoylpropionic acid to γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide, which in turn would be alkylated at the α-methylene carbon of the lactone skeleton. Subsequent elimination of water would give rise to the

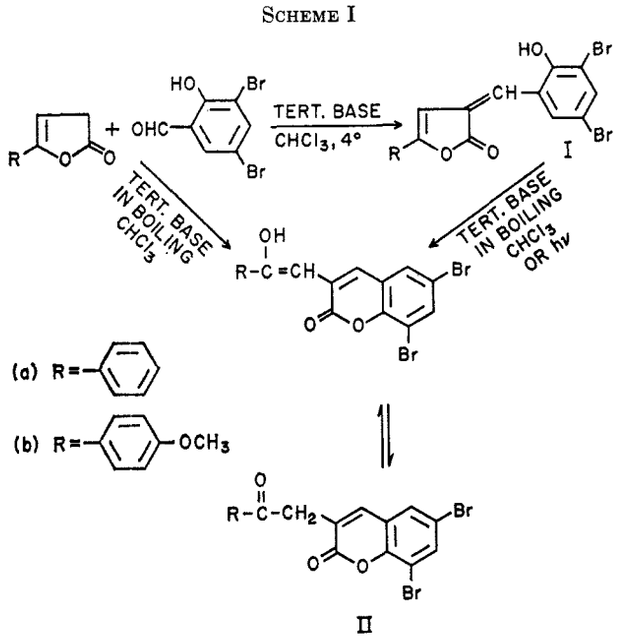
(1) E. Baltazzi and E. A. Davis, *Chem. Ind.* (London), 1653 (1962).

intermediary α-(2-hydroxybenzylidene)-$\Delta^{\beta,\gamma}$-butenolide; under more rigorous reaction conditions, intramolecular transesterification might yield 3-phenacylcoumarin.

The purpose of this study was twofold: (a) to investigate whether the condensation between γ-phenyl-$\Delta^{\beta,\gamma}$-butenolides and 2-hydroxybenzaldehydes at approximately 60° yields 3-phenacylcoumarins, and (b) to determine whether experimental conditions for the condensation reaction could be established which would be gentle enough to enable the isolation of the postulated α-(2-hydroxybenzylidene)-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide. That such an endeavor might be fruitful was suggested by the successful syntheses of structurally related unsaturated α-(2-hydroxybenzylidene)lactones, *viz.* α-(2-hydroxybenzylidene)-2(3H)-coumaranones[2] and α-(2-hydroxybenzylidene)-$\Delta^{\beta,\gamma}$-angelicalactone[3] under mild and carefully controlled reaction conditions.

It was found that the condensation between γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide,[4,5] obtained by cyclodehydration of β-benzoylpropionic acid with acetic anhydride, and 2-hydroxy-3,5-dibromobenzaldehyde indeed does proceed smoothly upon heating in chloroform in the presence of a tertiary base. The major product of the reaction was apparently the 3-phenacyl-6,8-dibromocoumarin (IIa), while no trace of α-(2-hydroxy-3,5-dibromobenzylidene)-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide (Ia) was detected (Scheme I). Similarly, only 3-(4-

SCHEME I



methoxyphenacyl)-6,8-dibromocoumarin (IIb) was isolated when γ-(4-methoxyphenyl)-$\Delta^{\beta,\gamma}$-butenolide[5-7] was employed as the nucleophile. To illustrate the superiority of condensing an unsaturated lactone rather than its corresponding β-acyl acid with phenolic aldehydes, γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide was allowed to react with 2-hydroxybenzaldehyde. The 3-phenacylcoumarin was isolated in an approximately threefold increased yield compared with that obtained when the sulfur trioxide–dimethylformamide complex was used as a dehydrating agent.[1]

When the γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide was allowed to react with 2-hydroxy-3,5-dibromobenzaldehyde in chloroform at 4°, the two crystalline isomers (Ia and IIa) resulted. Material Ia was extracted from the mixture with chloroform at room temperature and isolated in long, yellow needles upon cooling of the chloroform solution. Analogously, when γ-(4-methoxyphenyl)-$\Delta^{\beta,\gamma}$-butenolide was utilized as nucleophile, it was possible to separate the α-(2-hydroxy-3,5-dibromobenzylidene)-γ-(4-methoxyphenyl)-$\Delta^{\beta,\gamma}$-butenolide (Ib) from the corresponding coumarin isomer (IIb). The identification of these type-I compounds presents no difficulties. They are intensely chromatic whereas the corresponding coumarins are achromatic. In the infrared region they exhibit the carbonyl stretching absorption at higher frequencies than coumarins. Moreover, they react characteristically with bases at an elevated temperature (see below), while coumarins are recovered unchanged under identical conditions.

The butenolide Ia was converted to the corresponding coumarin IIa in excellent yields upon exposure to base at an elevated temperature. The coumarin IIa was likewise formed upon irradiation of an ethanolic solution of the butenolide Ia with a low-intensity light source. This light-catalyzed cyclization of Ia was accompanied by a hypsochromic shift of the absorption maxima and by three isosbestic points [wavelength and molar absorptivity of the isosbestic points: 251 mμ (ε 18,000), 266 (12,800), and 304 (4000)] in the ultraviolet region. The final spectrum recorded during this reaction was superimposable on that of IIa prepared by other methods. Qualitatively similar results were obtained when Ib was treated with base or irradiated [isosbestic points: 241 mμ (ε 13,000), 261 (15,800), and 331 (5200)]. This intramolecular transesterification to coumarins appears to be a feature characteristic of α-(2-hydroxybenzylidene)lactones and has to date been successfully demonstrated for butyrolactones,[8] 5(4H)-oxazolones,[9,10] 2(3H)-coumaranones,[2] and $\Delta^{\beta,\gamma}$-angelicalactones.[3]

The isolation of the butenolides Ia and Ib with an unaffected phenolic hydroxyl function in the 2 position of the benzylidene group provides the first experimental evidence for the hypothesis that α-(2-hydroxybenzylidene)-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolides play a role as intermediates during the formation of 3-phenacylcoumarins. Mild reaction and isolation techniques provided the clue to their preparation. Characteristically, they are labile compounds readily converted to 3-phenacylcoumarins. The elucidation of the sequence and intricacies of events leading from I to II remains as a challenge for future investigation.

Experimental Section[11]

γ-Phenyl-$\Delta^{\beta,\gamma}$-butenolide.—The β-benzoylpropionic acid (20 g) suspended in 40 ml of acetic anhydride was heated under an-

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(7) L. S. El-Assal and A. H. Shehab, *ibid.*, 1658 (1961).
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(9) H. Beringer and K. Falkenberg, *Chem. Ber.*, **96**, 1428 (1963).
(10) R. Walter, T. C. Purcell, and H. Zimmer, *J. Heterocyclic Chem.*, **3**, 235 (1966).
(11) Infrared spectra were recorded by a double-beam grating Perkin-Elmer Model 337 spectrophotometer. The samples were measured at a concentration of 0.3% in KBr disks. Ultraviolet spectra were determined on a Cary Model 14 recording spectrophotometer in 95% ethanol. Elementary analyses were carried out by Galbraith Laboratores, Knoxville, Tenn.

hydrous conditions with a gradual increase of temperature to 80° during the next 2 hr. The reaction mixture was kept at 80° for 3 hr. The product which precipitated upon cooling was isolated by filtration and recrystallized from petroleum ether (bp 90–120°) to give the lactone in colorless flakes (yield 8 g), mp 93–94°.[4,5] The molecular weight was determined in chloroform and found to be 158. The infrared spectrum exhibited the lactone carbonyl absorption at 1802 and 1790 cm^{-1}.[7,12]

Anal. Calcd for $C_{10}H_8O_2$: C, 75.0; H, 5.03. Found: C, 74.9; H, 4.95.

α-(2-Hydroxy-3,5-dibromobenzylidene)-γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide (Ia).—Following cooling of the 10-ml chloroform solution of γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide (1.6 g) and 2-hydroxy-3,5-dibromobenzaldehyde (2.8 g), 6 drops of dried and freshly redistilled triethylamine was added over the next 30 min while the reaction vessel was continuously swirled in ice water. After 5 hr of storage at 4° the crystalline material consisting of Ia and IIa was collected by filtration. The precipitate (1.22 g), washed with 5 ml of cold ethanol, was subsequently extracted for 5 min at room temperature with 5 ml of chloroform. After removal of the insoluble coumarin IIa the filtrate was stored at 4° with exclusion of light. The resulting yellow needles were collected the following day, washed with 1 ml of ethanol, and dried *in vacuo* at room temperature again with exclusion of light, yielding 0.4 g, mp 200–205°. The infrared spectrum showed the phenol absorption at 3370 and the lactone carbonyl absorption at 1780 and 1768 cm^{-1} (poorly resolved doublet). The spectrum between 200 and 600 mμ exhibited four maxima: 231 mμ (ε 15,300), 250 (16,300), 404 (21,400), and 505 (3200).

Anal. Calcd for $C_{17}H_{10}Br_2O_3$: C, 48.4; H, 2.39; Br, 37.9. Found: C, 48.6; H, 2.47; Br, 37.9.

α-(2-Hydroxy-3,5-dibromobenzylidene)-γ-(4-methoxyphenyl)-$\Delta^{\beta,\gamma}$-butenolide (Ib).—As in the condensation reaction above γ-(4-methoxyphenyl)-$\Delta^{\beta,\gamma}$-butenolide[5-7] (1.9 g) was allowed to react with 2-hydroxy-3,5-dibromobenzaldehyde in the presence of 6 drops of triethylamine at 0°. The resulting crystalline mixture was extracted at room temperature with 25 ml of chloroform for 15 min and undissolved coumarin IIb was removed by filtration. The filtrate, stored overnight at 4°, yielded orange needles which were once more recrystallized from chloroform in the manner just described yielding 1.2 g, mp 205–207°. The infrared spectrum exhibited the phenol absorption at 3380 and the carbonyl absorption at 1780 with a shoulder at 1770 cm^{-1}. In the ultraviolet and visible region the following maxima were observed: 225 mμ (ε 12,100), 270 (13,700), 416 (23,800), and 500 (2900).

Anal. Calcd for $C_{18}H_{12}Br_2O_4$: C, 47.8; H, 2.68; Br, 35.4. Found: C, 47.9; H, 2.80; Br, 35.4.

3-Phenacyl-6,8-dibromocoumarin (IIa). Method A.—The γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide (0.8 g) and 2-hydroxy-3,5-dibromobenzaldehyde (1.4 g) were dissolved in 10 ml of chloroform and refluxed for 1 hr with 0.5 ml of pyridine (or triethylamine). An infrared spectrum of the crude reaction product revealed the absence of Ia. Upon removal of the solvent a residue resulted which was recrystallized from a large excess of ethanol, yielding 1.6 g, mp 235–237°.

The infrared spectrum showed the δ-lactone carbonyl absorption at 1730 and the ketone carbonyl absorption at 1665 cm^{-1}. A weak but broad absorption in the hydroxyl region centered around 3440 cm^{-1} suggested that the phenacyl group in position 3 of the coumarin is partially enolized. In the ultraviolet spectrum three maxima were recorded: 228 mμ (ε 29,100), 280 (17,200), and 325 (4900).

Anal. Calcd for $C_{17}H_{10}Br_2O_3$: C, 48.4; H, 2.39; Br, 37.9. Found: C, 48.5; H, 2.54; Br, 37.9.

Method B.—Two-tenths of a gram of Ia was dissolved in 2 ml of pyridine and heated for 1 hr to 80°. The solvent was removed and the remaining residue was recrystallized from ethanol, yielding 180 mg, mp 237°. Mixture melting points with samples prepared according to method A were not depressed.

3-(4-Methoxyphenacyl)-6,8-dibromocoumarin (IIb). Method A.—A solution of γ-(4-methoxyphenyl)-$\Delta^{\beta,\gamma}$-butenolide (1.3 g) and 2-hydroxy-3,5-dibromobenzaldehyde (1.8 g) in 10 ml of chloroform was refluxed with 0.5 ml of pyridine (or triethylamine). The solvent was removed after 1 hr *in vacuo* and the resulting solid material was crystallized from chloroform in white needles, yielding 2.2 g, mp 225–226°.

The lactone and the ketone carbonyl absorptions were located at 1730 and 1665 cm^{-1}, respectively. A broad absorption of considerable intensity centered around 3440 cm^{-1} suggests an increased enolization of IIb as compared with IIa. The ultraviolet spectrum showed three maxima at 220 mμ (ε 35,700), 284 (32,900), and 325 (5800).

Anal. Calcd for $C_{18}H_{12}Br_2O_4$: C, 47.8; H, 2.68; Br, 35.4. Found: C, 47.5; H, 2.63; Br, 35.7.

Method B.—Two-tenths of a gram of butenolide Ib was converted to coumarin IIb as described for IIa (method B). The product was recrystallized from boiling chloroform yielding white needles, (190 mg), mp 225–226°. Mixture melting points with samples from preparation A remained unchanged.

3-Phenacylcoumarin.—A solution of γ-phenyl-$\Delta^{\beta,\gamma}$-butenolide (0.8 g) and 2-hydroxybenzaldehyde (0.6 g) was refluxed for 1 hr in 10 ml of chloroform in the presence of 0.5 ml of triethylamine. After this period the volatile substances were removed under reduced pressure. From the resulting solid material a red by-product was extracted with 10 ml of warm methanol. The product was subsequently recrystallized from chloroform–benzene (1:1) and finally, to remove the last traces of color, from 500 ml of ether, yield 0.9 g, mp 165–166°.[1] Characteristic absorption bands in the infrared spectrum were located at 3450 (broad), 1720, and 1685 cm^{-1}. In the ultraviolet region three maxima were detected: 242 mμ (ε 14,400), 276 (15,000), and 310 (8200).

Anal. Calcd for $C_{17}H_{12}O_3$: C, 77.3; H, 4.57. Found: C, 77.5; H, 4.26.

Registry No.—α-Phenyl-$\Delta^{\beta,\gamma}$-butenolide, 1955-39-1; Ia, 10075-43-7; Ib, 10075-44-2; IIa, 10075-45-3; IIb, 10075-46-4; 3-phenacylcoumarin, 10075-47-5.

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Oxidation of Steroid Digitonides[1]

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Of the many ways known for the protection of hydroxyl groups,[2] one of the most unique is the use of digitonin for the protection of a steroidal 3β-hydroxyl group.[3,4] A remarkable feature of this method is that the digitonin is not attached to the steroid molecule by a covalent bond; rather, digitonides are molecular complexes, easily disrupted by dissolving in pyridine.[5] Steroidal hydroxyl groups at C-17[3] and at C-20[4] have been oxidized with simultaneous digitonide protection of the 3β-hydroxyl group, but oxidations by this method at positions closer to C-3 have not been reported. We have explored the possibility of carrying out selective oxidations at C-16, C-12, C-11, C-6, and C-2 on steroid digitonides.

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