peak at 1720 cm^{-1} (COOH) as compared with the two peaks (1780 and 1725) for the starting lactone acid.

Relactonization was effected by boiling the heterogenous mixture of diacid **8** (10 mg) with 30 ml of benzene for 2 hr. The single spot (R_f 0.19) obtained when the relactonized material was developed on a plate showed that only 2-carboxydeoxypicropodophyllin had been formed. The infrared absorption spectrum (mineral oil mull) was identical with that of 2-carboxydeoxypicropodophyllin. Exposing the relactonized material dissolved in tetrahydrofuran to ethereal diazomethane produced 2-carbomethoxydeoxypicropodophyllin (see below), which ran side by side on a silica gel plate with authentic ester (R_f 0.42 using carbon tetrachloride–ether, 4:1). Removing all solvent left a solid residue, which when mixed with authentic ester (mp 190–191°) showed mp 187–190°. The infrared absorption curves of the two esters were identical.

Methyl Ester of 2-Carboxydeoxypicropodophyllin. a. From the Acid.—A solution of 2-carboxydeoxypicropodophyllin (0.20 g) in 15 ml of pure tetrahydrofuran was treated with excess ethereal diazomethane. After 15 min, volatiles were removed, and the residue (0.21 g; homogeneous according to thin layer chromatography) was crystallized from methylene chloride–hexane. The resulting 2-carbomethoxydeoxypicropodophyllin (**7**), mp 189.5–191°, weighed 0.17 g (84%): $[\alpha]_D$ 110° (*c* 0.4, pyridine) or $[\alpha]_D$ 83° (*c* 0.4, $CHCl_3$); ir (CCl_4) 1787 for lactone carbonyl and 1731 cm^{-1} for ester carbonyl; nmr ($CDCl_3$) resembles the curve for deoxypicropodophyllin with δ 6.80, 6.58, and 6.38 (aromatic H's), 5.88 (s, methylenedioxy H's), multiplets with close-lying chemical shifts (12, 4, CH_3O), multiplets for all other protons.

Anal. Calcd for $C_{24}H_{24}O_9$: C, 63.15; H, 5.30; $4CH_3O$, 26.76. Found: C, 62.72, H, 5.29; CH_3O, 26.69.

b. From Enolate 5 with Methyl Chloroformate.—A 1 *M* butyllithium solution in hexane (0.84 ml, *ca.* 0.8 mmol) was added dropwise from a small graduated syringe sticking through a serum cap septum to a vigorously stirred solution of dry deoxypodophyllotoxin (**3**) (0.43 g, 1.1 mmol) and 0.26 g of triphenylmethane (1.1 mmol) in 20 ml of tetrahydrofuran that had just been distilled from calcium hydride. The resulting orange mixture was stirred further for 0.5 hr before dropwise injection of a solution of pure methyl chloroformate (0.13 g, 1.1 mmol) in 2 ml of dry tetrahydrofuran. After 1 hr, water was added, and the mixture was brought to pH 5.5 with a few drops of hydrochloric acid. The lower aqueous layer was extracted with ether, and the combined ether and hexane solutions were washed with water, dried, and stripped of volatiles. The residue was chromatographed through a 1-ft column of 60–100 mesh silica gel, with 50 ml of benzene serving to remove triphenylmethane and 100 ml of benzene–acetone (4:1) serving to remove product. The crude product was crystallized twice from methanol to give 0.28 g (56%) of 2-carbomethoxydeoxypicropodophyllin (**7**), mp 187–190°. This material showed a single spot on a Gelman silica gel strip (chloroform–ether, 4:1) with the same R_f as that from the methyl ester derived from acid **6** and spotted on the same plate; ir ($CHCl_3$) was identical with curve from the methylation product; the melting point was not depressed when the two esters were mixed.

Activity.—2-Carboxydeoxypicropodophyllin (**6**) was submitted to Cancer Chemotherapy National Service Center for screening. When tested against cell cultures of human epidermoid carcinoma of the nasopharynx,[13] a solution of the compound (NSC No. 92321) in dimethylformamide showed a confirmed ED_{50} toxicity (dose causing 50% growth inhibition) at less than 1.9 μg/ml, possible in the 0.2–0.5-μg/ml range.

Registry No.—**3**, 19186-35-7; **6**, 33369-69-6; **7**, 33369-70-9; **8**, 33369-71-0.

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Enol Acetylation of Methyl 12-Oxopodocarp-13-en-19-oate and Methyl 12-Oxopodocarp-8(14)-en-19-oate

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The enol acetylation of alicyclic unsaturated ketones has been largely restricted to the steroid series[2] where interest has been focused on reagents which result in either thermodynamically or kinetically controlled[3,4] reaction products. In connection with a diterpenoid synthesis problem we wished to prepare a specific ring C acetoxy diene from methyl 12-oxopodocarp-13-en-19-oate[5,6] (**1**), and we report here the acetoxy dienes obtainable under both thermodynamically and kinetically controlled conditions.

Enol acetylation of **1** with isopropenyl acetate and toluenesulfonic acid[7] (kinetic control) gave only the 11,13-diene **2** and starting ketone. Acetic anhydride and *p*-toluenesulfonic acid enol acetylation gave 30% diene **2**, 50% 8(14),12-diene **3**, 5% nonconjugated diene **9**, and 5% methyl podocarpate **10**. To ensure that a true thermodynamic equilibrium was present, the 11,13-diene **2** was subjected to acetic anhydride–toluenesulfonic acid equilibration, and the same ratio of 3:5 for **2** to **3** was obtained. The product composition in all experiments was determined by integration of the vinylic signals at 5.40 and 5.87 ppm together with the C-20 methyl absorptions in the pmr spectra of the direct reaction mixtures (see Experimental Section).[8]

The thermodynamic ratio of 3:5 noted for **2** to **3** is unexpected on the basis of double bond stabilities[9] which should lead to an equilibrium ratio of 1:9. The discrepancy must arise from other factors, and previous authors[10] have pointed out the dominance of steric interactions in determining the enol acetate ratios observed for simple cyclic ketones. To probe

(1) Graduate Fellow of National Research Council of Canada.

(2) H. H. Inhoffen, *Chem. Ber.*, **69**, 2141 (1936); I. M. Heilbron, T. Kennedy, F. S. Spring, and G. Swain, *J. Chem. Soc.*, 869 (1938); L. F. Fieser and W.-Y. Huang, *J. Amer. Chem. Soc.*, **75**, 5356 (1953); L. Ruzicka and W. H. Fischer, *Helv. Chem. Acta*, **19**, 806 (1936); O. R. Rodig and G. Zanati, *J. Org. Chem.*, **32**, 1423 (1967); A. J. Liston and P. Toft, *ibid.*, **33**, 3109 (1968); P. Toft and A. J. Liston, *Tetrahedron*, **27**, 969 (1971).

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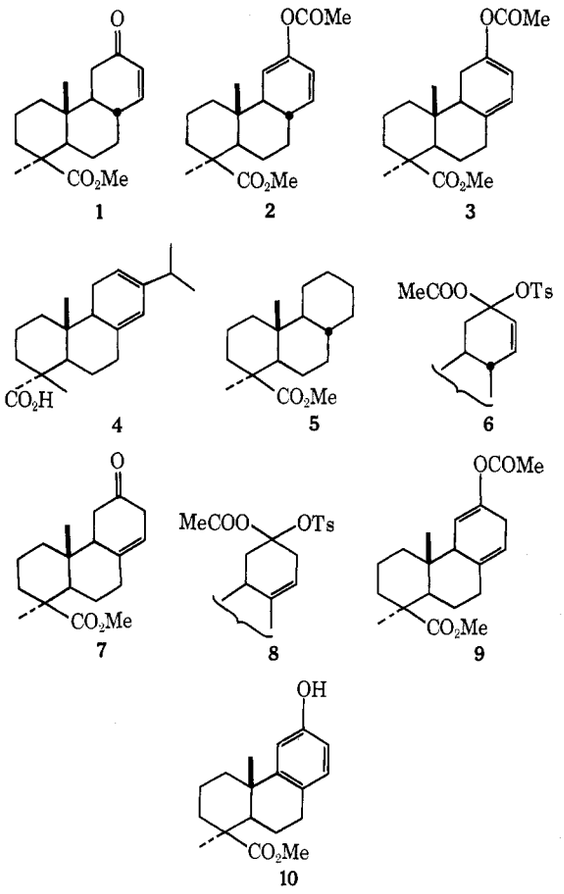

this point further we examined the optical rotatory dispersion (ORD) curves[11] exhibited by **2** and **3** and found that **2** showed a plain, positive curve while **3** displayed an intense, negative Cotton effect (molecular amplitude 443). This latter Cotton effect is similar to that shown by levopimaric acid **4** (molecular amplitude 344)[12] and suggests that **3** possesses the same B/C folded conformation[13] which levopimaric acid is forced to adopt because of the interaction between the C-11 β-H and the C-20 CH_3 group.[14] The plain ORD curve of **2** is a result of the severe steric interaction between the C-1 β-H and the C-11 β-H which distorts ring C and allows the 11,13-diene to adopt a planar conformation. Application of the allylic axial bond chirality treatment[18] for this planar conformation then suggests a minimal Cotton effect. We can conclude then that the factors causing the thermodynamic ratio between the two dienes **2** and **3** are the result of a delicate balance between double bond stabilities and steric interactions.

The sole formation of **2** in the kinetically controlled experiments can be rationalized by the Mazur[19] intermediate acetoxy tosylate **6**. Here the rate of E2 elimination of the tosylate group toward C-11 will be greatly enhanced by the loss in steric compression energy between the C-11 and C-1 hydrogens, while loss of the C-8 proton occassions no such steric acceleration and is therefore negligibly slow. The results obtained for the kinetically controlled enol acetylation of the β,γ-unsaturated ketone **7**[5b] show a similar trend. Loss of the tosylate of intermediate **8** with elimination toward C-11 is again sterically accelerated and the nonconjugated diene **9** comprised 60% of the product. However, the increased acidity of the C-13 protons of **8** allows elimination toward C-13 to become competitive, and diene **3** was formed in 25% yield. The presence of 5% **9** in the thermodynamic enol acetylation mixture indicates that it is of comparable stability to the conjugated dienes **2** and **3**. Presumably the increased relative stability of **9** is a result of the relief of subtle steric interactions which are not directly apparent from molecular models.

Experimental Section[20]

Methyl 12-Acetoxypodocarp-8(14),12-dien-19-oate (3).—*p*-Toluenesulfonic acid monohydrate, 80 mg, in 15 ml of acetic anhydride was heated to boiling in a flask fitted with a Dean–Stark trap until 5 ml of distillate was obtained. A solution of 240 mg (0.83 mmol) of methyl 12-oxopodocarp-13-en-19-oate (**1**) (mp 126–130°) in 10 ml of acetic anhydride was then added and distillation continued for 3.5 hr in such a manner that 10 ml of distillate was collected. The reflux ratio was controlled by a positive pressure of nitrogen. After cooling the reaction was worked up *via* hexane and, upon solvent evaporation, gave 280 mg (98%) of the mixture of acetoxy dienes as a light brown oil. Analysis of the pmr spectrum by integration of the vinyl and C-20 methyl absorptions showed the crude reaction mixture consisted of 10% unsaturated ketone **1**, 50% diene **3**, 30% diene **2**, 5% nonconjugated diene **9**, and 5% aromatized material, methyl podocarpate **10**. Chromatography on silica gel led to removal of aromatic material and starting ketone, and elution with 1% ethyl acetate–benzene gave the mixed acetoxy dienes **2** and **3** in the ratio 2:3. Solution in methanol and cooling to −20° yielded 80 mg (28%) of acetoxy diene **3** as colorless crystals. A second crystallization from methanol gave the analytical sample as clusters of needles: mp 96–97°; ir 1755 (acetate C=O), 1730 (ester C=O), 1680, 1630 cm^{-1} (diene); uv λ_{max} 257 mμ (sh) (ϵ 5200), 263.5 (7700), 282.5 (7800), 295 (sh) (5000); ORD (concn 0.10 mg/ml, CH_3OH) 22°, $[\Phi]_{650}$ 0°, $[\Phi]_{589}$ −1550°, $[\Phi]_{290}$ −21,300°, $[\Phi]_{232}$ +23,000°, $[\Phi]_{210}$ +15,600°, mol amplitude a = 443; pmr δ 0.78 (s, 3, C-20 CH_3), 1.19 (s, 3, C-18 CH_3),

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(14) An interesting feature of the folded conformation is the absence of any significant shielding effect of the 8(14),12-diene on the pmr absorption signal of the C-20 methyl. The observed signal at 0.78 ppm is similar to that recorded for methyl podocarpan-19-oate **5** (0.73 ppm).[15] Even one double bond in the 8(14) position has a strong shielding influence on the C-20 methyl, moving the signal into the 0.50–0.55-ppm region[6b,16] (*cf.* the nonconjugated diene **9** at 0.60 ppm). Either we must assume that the 12(13) double bond is deshielding the C-20 methyl by an amount sufficient to offset the shielding effect of the 8(14) double bond or we must conclude that the simple arithmetic addition of screening constants[17] of olefins is not a valid procedure for conjugated systems but rather the diene must be considered as a whole. No *ab initio* calculations are currently available to check this point.

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2.08 (s, 3, $OCOCH_3$), 3.58 (s, 3, $COOCH_3$), 5.40 ppm (q, 2, J_{AB} = 6.3 Hz, $\delta\nu_{AB}$ = 3.9 Hz).

Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.23; H, 8.44.

Methyl 12-Acetoxypodocarp-11,13-dien-19-oate (2).—The procedure of Dauben, *et al.*, was used.[9] To a solution of 1.00 g (3.58 mmol) of unsaturated keton 1 (mp 126–130°) in 30 ml of isopropenyl acetate was added 0.300 g of *p*-toluenesulfonic acid monohydrate, and the mixture was heated at reflux under nitrogen, using the same apparatus and technique as above, for 4.5 hr. At the end of this period, 20 ml of distillate was obtained and, after cooling, the organic product was isolated *via* hexane extraction. Evaporation of the solvents gave 1.13 g (95%) of a light yellow oil, the pmr spectrum of which showed it to consist of 90% of acetoxy diene **2** and 10% of ketone **1**. There were no discernible absorptions of the acetoxy diene **3** present. Crystallization from dry hexane at 0° gave 0.80 g (70%) of **2** as colorless needles: mp 78–80°; ir 1760 (acetate C=O), 1730 (ester C=O), 1650, 1600 cm^{-1} (diene); uv λ_{max} 262 mμ (ϵ 3400); ORD (concn 0.1 mg/ml CH_3OH), 22°, $[\Phi]_{650}$ +1000°, $[\Phi]_{589}$ +1500°, $[\Phi]_{400}$ +1500°, $[\Phi]_{250}$ +7000°, $[\Phi]_{220}$ +12,600°; pmr δ 0.69 (s, 3, C-20 CH_3), 1.22 (s, 3, C-18 CH_3), 2.18 (s, 3, $OCOCH_3$), 3.77 (s, 3, $COOCH_3$), 5.70 (s, 2, $W_{1/2}$ = 4 Hz, C-13 and C-14 vinylic H), 5.87 ppm (d, 1, J = 1.0 Hz, C-11 H).

Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.40; H, 8.38.

When the pure acetoxy diene **2** was heated at reflux under nitrogen in acetic anhydride for 2 hr in the presenec of a crystal of *p*-toluenesulfonic acid and worked up *via* hexane, the thermodynamic mixture of 59% **3**, 36% **2**, and 5% **9** was obtained.

Methyl 12-Acetoxypodocarp-8(14),11-dien-19-oate (9).—To a solution of 100 mg (3.6 mmol) of methyl 12-oxopodocarp-8(14)-en-19-oate (**7**) in 5.0 ml of isopropenyl acetate was added 25 mg of *p*-toluenesulfonic acid monohydrate, and the mixture was heated at reflux under nitrogen in the same apparatus as above for 3 hr. At the end of this period 3.0 ml of distillate was obtained and, after cooling, the organic product was isolated *via* hexane. Evaporation of the solvents afforded 108 mg (94%) of oily crystals. The pmr spectrum of this showed the product to consist of 60% **9**, 25% **3**, and 15% methyl podocarpate **10**. Chromatographhy on Florisil removed the methyl podocarpate but did not achieve separation of **9** and **3**. Tlc on silica gel in a number of solvents was similarly unsuccessful. An enriched sample of **9** (containing 17% of **3** by integration of the C-20 CH_3 absorptions) was obtained by repeated crystallization from hexane and it showed ir 1760 (acetate C=O), 1730 (ester C=O), 1670 cm^{-1} (olefinic); uv (featureless except for absorption due to 17% of **3**); pmr δ 0.60 (s, 3, C-20 CH_3), 1.15 (s, 3, C-18 CH_3), 2.05 (s, 3, $OCOCH_3$), 2.5–2.85 (m, 2, C-14 allylic H), 3.58 (s, 3, $COOCH_3$), 5.35 ppm (m, 2, $W_{1/2}$ = 10 Hz, C-11 and C-14 H).

Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.12; H, 8.67.

Registry No.—**1**, 24402-16-2; **2**, 33608-33-2; **3**, 33495-78-2; **7**, 24412-03-1; **9**, 33537-22-3.

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19-Hydroxy Steroids. III. Reactions with Lead Tetraacetate[1]

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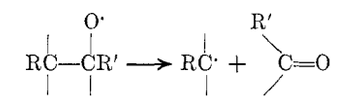
Since it was first reported[2] that treatment of secondary alcohols with lead tetraacetate could lead to cyclic ethers, this reaction has been used extensively to functionalize or to remove the methyl group at C-10 of certain steroids[3] in attempts to enhance the biological activity of such compounds and as a means of preparing estrogens[4] from androgens.

In addition to these important applications, the reaction *per se* has been extensively investigated and a number of generalizations[5] have been found to apply. One of these correlations relates to the limits of favorable internuclear distance (2.5–2.7 Å) between the oxyradical and the carbon atom from which hydrogen atoms can be abstracted intramolecularly. If more than one alkyl group is appropriately situated for hydrogen atom abstraction, it has been found that the reactivity of hydrogen atoms decreases in the order tertiary > secondary > primary. Hydrogen atoms attached to an oxygen-bearing carbon atom are more reactive than those attached to a carbon atom having another carbon atom as neighbor. More recently,[6] the effects of a methoxy group adjacent to the reacting hydroxy group have been evaluated.

Once an oxygen radical has been produced by oxidation with lead tetraacetate, fragmentation can also take place, as shown below. The amount of cleavage which occurs increases with the stability of the alkyl radical formed[5] but a number of other factors can also influence the course of this reaction.



While investigating approaches to the synthesis of cardiac-active steroids some model compounds containing a hydroxy group at C-19 were prepared. Following is a report of the course of the lead tetraacetate oxidation of one of these compounds in which it is shown that the reaction proceeds by intramolecular hydrogen abstraction.

Steroids with a double bond at C-5,C-6 are normally unaffected[7] in reactions with lead tetraacetate. However, Moriarty and Kapadia[8] have reported that the lead tetraacetate oxidation of 3β-acetoxycholest-5-en-19-ol (**1**) results in oxidative fragmentation, with loss of the hydroxymethyl group at C-10, yielding a product tentatively identified as 3β,6β-diacetoxy-19-norcholest-5(10)-ene (**2b**). The authors postulated a mechanism involving the concerted intramolecular transfer of an acetoxy group from the C-19 lead ester to C-6 which implies stereospecificity in the resulting C-6 acetoxy group. An analogous fragmentation reaction has also been observed[9] in the lead tetraacetate oxidation of the diethylene ketal of 19-hydroxyandrost-5-ene-3,17-dione.

The preparation of the 5α,6α- and 5β,6β-oxides (**3** and **4**) (Scheme I) from 3β-acetoxycholest-5-en-19-ol

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