Deuterium Oxide Quenching Experiments. The previously described procedures were used, except that after 10 min at −78 °C from run 4, Table I, or warming to room temperature overnight for runs 6 and 7, Table I, the reactions were quenched with 0.5 mL of D_2O. After extractive workup, the reaction mixtures were analyzed by ^1H NMR. The spectrum of run 4 showed no singlet at δ 5.18, indicating almost complete deuterium incorporation into the 2-position of phenyldithiane. The ^1H NMR of runs 6 and 7 showed a singlet at δ 5.18, but the multiplet at δ 2.50 was missing, indicating almost complete deuteration of the α-position of **8**.

Equilibration Experiments of 9a and 9b. Two alcohols (**9a** and **9b**) were separately treated with 1.1 equiv of *n*-BuLi in 2 mL of THF at −78 °C and allowed to warm to room temperature overnight. The ^1H NMR of the reaction mixture involving **9a** showed no change, whereas the ^1H NMR spectrum of the reaction mixture involving **9b** showed the presence of 2-phenyl-1,3-dithiane and phenyl cyclopropyl ketone, but none of **9b**.

Reaction of 4 with *cis*-2,2,6,6-Tetramethyl-4-hepten-3-one (10a) (Representative Procedure). To a solution of **4a** prepared from 1,3-dithiane (49.8 mg, 0.414 mmol) and *n*-BuLi (0.456 mmol) in 2 mL of THF at −22 °C was added 2.0 equiv of **10a** (140 mg, 0.829 mmol) in 2 mL of THF. (In reactions involving HMPA or *p*-dinitrobenzene, the additive was added immediately before the addition of **10a**.) After extractive workup, the product yield was estimated by ^1H NMR and the composition of the enone isomers was determined by GC analysis. The pure product **11** was obtained by preparative TLC (10% diethyl ether in hexane on SiO_2): oil; IR ($CHCl_3$) 3510, 3350, 2950, 2900, 1640, 1460, 1420, 1350, 1195, 1095, 1005 cm^{-1}; ^1H NMR δ 1.12 (s, 9 H), 1.22 (s, 9 H), 2.00 (m, 2 H), 2.87 (m, 5 H), 4.29 (s, 1 H), 5.45 (q, 2 H, J = 13.5 Hz); ^{13}C NMR δ 142.7, 127.5, 81.8, 59.5, 39.8, 32.6, 31.7, 29.7,26.7, 25.6; MS, m/z (relative intensity) 288 (M^+, not present), 231 (1.4), 202 (0.2), 182 (43.3), 169 (12.8), 151 (2.0), 120 (19.1), 119 (43.3), 105 (5.3), 95 (13.6), 83 (34.2), 57 (100). Anal. Calcd for $C_{15}H_{28}OS_2$: C, 62.50; H, 9.72. Found: C, 61.99; H, 10.00.

The reaction of **4b** with **10a** similarly produced **12**: mp 40–41 °C; IR ($CHCl_3$) 3050, 2960, 2900, 1700, 1590, 1480, 1420, 1360, 1275, 1215, 1060 cm^{-1}; ^1H NMR δ 0.62 (s, 9 H), 1.25 (s, 9 H), 1.83 (m, 2 H), 2.35–3.0 (m, 6 H), 3.85 (m, 1 H), 7.30 (m, 3 H), 8.10 (m, 2 H); ^{13}C NMR δ 214.0, 142.7, 131.0, 127.9, 126.8, 67.6, 53.1, 44.1, 39.3, 36.9, 30.1, 27.7, 27.4, 27.1, 25.1; MS, m/z (relative intensity) 364 (M^+, 1.2), 258 (47.2), 201 (49.0), 195 (43.0), 145 (32.3), 121 (27.3), 115 (28.9), 91 (6.1) 77 (9.3), 57 (100). Anal. Calcd for $C_{21}H_{32}OS_2$: C, 69.23; H, 8.79. Found: C, 68.73; H, 8.51.

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Registry No. 1, 88180-26-1; **4a**, 36049-90-8; **4b**, 53178-41-9; **5**, 2695-47-8; **6a**, 88563-40-0; **6b**, 88563-41-1; **8**, 3481-02-5; **9a**, 88563-42-2; **9b**, 88563-43-3; **10a**, 29569-89-9; **11**, 88563-44-4; **12**, 88563-45-5.

Intramolecular Hydrogen Bonding and Acidity of Some γ-Hydroxy- and γ-Methoxy-α,β-unsaturated Carboxylic Acids

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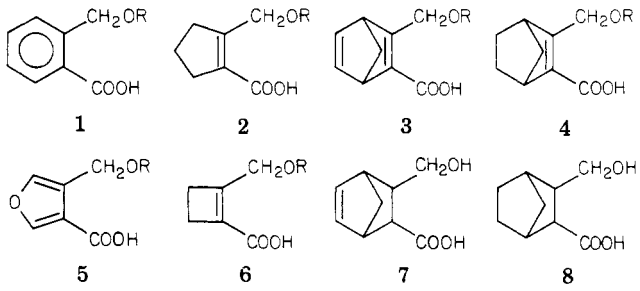
In earlier work, the effect of intramolecular hydrogen bonding on acidity as a function of the distance between the carboxyl groups in dicarboxylic acids was examined.[1] An obvious extension of that work is the determination in a similar manner the effect of intramolecular hydrogen bonding on the acidity of γ-hydroxy and γ-methoxy carboxylic acids—in effect analogues of the dicarboxylic acids and their half methyl esters in which a carbonyl has been replaced by methylene. For comparison with the previous study,[1] the requisite compounds are various cyclic and bicyclic γ-hydroxy- and γ-methoxy-α,β-unsaturated acids. The present paper describes the preparation and acidities of a set of such compounds (**1–6**).



1 **2** **3** **4**

5 **6** **7** **8**

a, R = H; b = CH_3

Of these, **1a**,[2] **1b**,[2] **2a**,[3] and **2b**[4] have been reported, but in each case the synthesis was not of a general character. Since the corresponding dicarboxylic acids are known and readily available, it seemed possible that a general approach could be used. Thus, either the diacid (c) or the diester (d) could be converted to the half-ester, half-acid (e), reduced to the hydroxymethyl ester (f), saponified to the hydroxy acid (a), and subsequently converted to the methoxy acid (b). This sequence worked satisfactorily for **2**, **5**, and **6**.

Although **1e** was examined briefly in this sequence, the much simpler hydrolysis of readily available phthalide was used to prepare **1a**[5] and subsequently **1b**.

The bicyclic systems **3** and **4** presented many problems. Compounds of the **3** series (dienes) were prepared, and in appropriate cases these were partially reduced to the **4** series (monoenes). Several procedures for half-saponification of **3d** were tried, but all gave less than 10% yield of **3e**. However, **3e** (R = ethyl) was prepared in 58% yield by Diels–Alder reaction between cyclopentadiene and the ethyl half-ester of acetylenedicarboxylic acid. After the attempted conversion of **3e** to **3f**, the crude product "**3f**" was saponified directly. Instead of **3a**, only a compound believed to be **7** was isolated. Similarly, **4e** gave a product presumed to be **8**.

In an attempt to circumvent this difficulty, the acetate of **3a** was prepared by Diels–Alder reaction between cyclopentadiene and 4-acetoxytetrolic acid;[6] the acetate of **4a** was prepared by partial reduction of **3a** acetate. Hydrolysis of these acetates produced materials that appeared by NMR and IR spectra to contain the desired compounds **3a** and **4a**. Unfortunately, the crude products on standing for a few hours were transformed into insoluble, possibly polymeric substances; earlier attempted purification by chromatography resulted in gross structural changes and a complex mixture, e.g., IR spectra and qualitative tests indicated the presence of aldehyde.

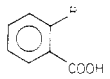
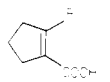
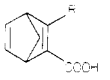
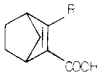
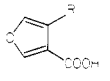
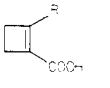
Compound **3b** was obtained by reaction of cyclopentadiene and 4-methoxytetrolic acid.[7] This acid also appeared to be somewhat unstable, but clearly more stable than **3a**. Partial reduction of **3b** did not lead to any material identifiable as **4b**.

(1) McCoy, L. L. *J. Am. Chem. Soc.* **1967**, *89*, 1673.

(2) Gilman, H.; Brown, G. E.; Webb, F. J.; Spatz, S. M. *J. Am. Chem. Soc.* **1940**, *62*, 977.
(3) Perrotti, E.; Palladino, N.; Greco, M. *Ann. Chim.* **1966**, *56*, 1358.
(4) Brook, P. R.; Duke, A. J. *J. Chem. Soc. C* **1971**, 1764.
(5) Hessert, J. *Chem. Ges. Ber.* **1877**, *10*, 1445.
(6) Dupont, G.; Dulou, R.; Lefebvre, G. *Bull. Soc. Chim. Fr.* **1954**, 816.
(7) Heaton, C. D.; Noller, C. R. *J. Am. Chem. Soc.* **1949**, *71*, 2948.

0022-3263/84/1949-0939$01.50/0

Table I. pKa's of Some β-Substituted-α,β-unsaturated Acids

acid	R					
	CH_2OH[a]	CH_2OCH_3[a]	CH_2OAc[a]	C(O)OH[b]	$C(O)OCH_3$[b]	$C(O)O^-$[b]
	3.84	3.85		2.95	3.29	5.41
	4.54	4.50		1.64	2.94	7.27
		4.59	4.56	1.32	3.02	7.77
		(4.74)[c]	4.68	1.32	3.19	8.00
	4.07	4.35		1.44	3.75	7.84
	4.16	4.31		1.12	3.32	7.63

[a] Present work. [b] Reference 1. [c] Calculated by assuming the ΔpKa for the bicyclic diene and monoene is similar to ΔpKa for the corresponding acetoxy and methyl half-ester compounds (these ΔpK values were averaged).

The pKa's of the hydroxy and methoxy acids and the two acetoxy bicyclic acids were determined as described previously.[1,12] The results as well as those of some related acids are shown in Table I.

Discussion

The original intent had been to compare the acidities of the hydroxy and methoxy acids in the same way that pK_1 of the corresponding diacids was compared to pK_E of the half-esters.[1] Unfortunately, the bicyclic hydroxy compounds were not obtained, so the comparison is incomplete. In spite of this, it is obvious where these comparisons can be made that the hydroxy–methoxy pairs show very small or no differences as compared to the diacid–half-ester pairs.

Analysis of the effect of intramolecular H bonding on the acidities of the diacids and hydroxy acids is complicated by the fact that such bonding may occur in both the acids and the related anions, and not necessarily to the same degree in both types of species. Westheimer and Benfey[8] have treated the diacid case, and they were able to place upper and lower limits on the degree of intramolecular hydrogen bonding in the monoanion. On the basis of this work, the degree of intramolecular H bonding in some diacids has been related to the distance (geometry) between the two carboxyl groups; near the optimum geometry, intramolecular H bonding is a major contributor to increased acid strength of the diacid.[1] If the same type of analysis presented by Westheimer and Benfey is applied to the hydroxy and methoxy acids and it is assumed similarly that hydroxy and methoxy are electrically equivalent[9] and that only one dissociable hydrogen is present in the hydroxy acid, then

$$K_H' = \frac{K_{hydroxy}}{K_{methoxy}} - 1$$

where K_H' is the ratio of H-bonded to non-H-bonded forms of the hydroxy acid anion and the other K's are acid dissociation constants. The data of Table I show that for the benzene and cyclopentene systems within experimental error there is no intramolecular H bonding in the anion, and even in the furan and cyclobutene cases, $K_H' < 1$, the amount of H-bonded species is appreciably less than 50%. This is in marked contrast to the dicarboxylic acid systems where with the exception of the benzene case ($K_H' = 1.19$), K_H' ranges between 19 and 203, the intramolecularly H-bonded anion effectively is the only monoanion species present, and intramolecular H bonding is a major contributor to increased acidity.[10]

In the hydroxy acid systems, the present results are inadequate to define with precision the optimum geometry for intramolecular H bonding as was done in the diacid case.[1] However, the small effects observed in the furan and cyclobutene cases suggest that the optimum O···H···O distance is about the same as in the diacid case.

For the methoxy acids it is conceivable that intramolecular H bonding might stabilize the acid and that this affect would increase as the optimum geometry for such bonding was approached. This would result in decreased acidity with increased H bonding.[11] In the present work, the results obtained for the methoxy acids (Table I) do seem to support this proposal. However, the acidities of β-alkyl-α,β-unsaturated acids examined earlier show very similar trends,[12] and clearly for these compounds no in-

(8) Westheimer, F. H.; Benfey, O. T. *J. Am. Chem. Soc.* **1956**, *78*, 5309.
(9) Westheimer and Benfey assumed electrical equivalence of carboxyl and carbalkoxyl groups (see ref 8).

(10) For the diacids,

$$K_H' = \frac{\text{“}K_{hydroxy}\text{”}}{\text{“}K_{methoxy}\text{”}} - 1 = \frac{K_a'}{K_E} - 1$$

where K_a' is the first dissociation constant of the diacid and K_E is the dissociation constant of the half-ester. The complete analysis by Westheimer and Benfey[8] places an additional factor (arising from statistical considerations) in $K_{H'}$. Thus

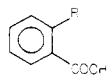
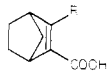
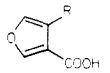
$$K_H' = \left[\frac{K_a'}{K_E}\right] f - 1$$

where f depends on the amount of intramolecular H bonding in the ester and is restricted to the range from $^1/_2$ to 1. Omission of this factor should have no effect on the conclusions cited.

(11) Suggestions that intramolecular H bonding in appropriately substituted carboxylic acids may lead to decreased acidity are not new; e.g.: R. N. McDonald, R. N.; Reitz, R. R. *J. Am. Chem. Soc.* **1976**, *98*, 8144.

(12) McCoy, L. L.; Riecke, E. E. *J. Am. Chem. Soc.* **1973**, *95*, 7407.

Table II. ΔpKa ($pK_R - pK_H$) of Some β-Substituted-α,β-unsaturated Acids

	R						
	H	CH_2OCH_3[a]	ΔpK	CH_2CH_3[b]	ΔpK	$CH(CH_3)_2$[b]	ΔpK
	4.20[c,d] 5.38[b,e]	3.85[c]	−0.35	5.30[e]	−0.08	5.15[e]	−0.23
	4.66[c,f] 5.84[b]	4.74[c]	0.08	6.70	0.86	6.76[e]	0.92
	4.03[c,g]	4.35[c]	0.32				

[a] Present work. [b] Reference 12. [c] H_2O, 25 °C. [d] Reference 21. [e] CH_3OH-H_2O, 25 °C. [f] Estimated by assuming the same ΔpKa as observed for the H_2O and H_2O-CH_3OH solvent systems in the case of benzoic acid. [g] Ferraz, J. P.; do Amaral, L. *J. Org. Chem.* **1976**, *41*, 2350.

tramolecular H bonding is present. Unfortunately, direct comparison is very limited as the skeletal systems in the two studies are not indentical. For benzene and one bicyclic system (both in 50% aqueous methanol rather than water), a comparison can be made and this is shown in Table II. Although the solvent systems are different, the relative change from one ring system to the other should not be affected. The structural types shown in Table II are arranged in order of increasing distance between the substituents. For both ethyl and isopropyl derivatives it can be seen that $pK_R - pK_H$ increases as the distance between substituents increases; this is also true for the methyl and *tert*-butyl substituents and for several skeletal systems giving intermediate distances. This decrease in acidity as the distance increases is in the absence of intramolecular H bonding and probably arises as a combination of effects—steric inhibition of resonance, steric inhibition of solvation, etc.—as discussed previously.[12] In the same way and to about the same extent, $pK_{CH_2OCH_3} - pK_H$ also increases as the distance increases. Because of the parallel changes for both the methoxymethyl and the alkyl groups, it is suggested that the methoxy acid acidities can be rationalized in terms of the bulk effect of the methoxymethyl group and that intramolecular H bonding plays at most a very minor role. It is reasonable that the methoxy oxygen cannot compete effectively with an abundance of solvent molecules—water, methanol—as an H-bond acceptor.

The present work shows that optimum geometry and some restriction of conformation are not sufficient alone to produce large affects on acidity from intramolecular H bonding in aqueous systems. The large effects noted in the dicarboxylic acids[1] as compared to the small effects in hydroxy acids reported here quite possibly correspond to the strong H-bond donor properties of the carboxyl group as compared to the much weaker donor ability of the alcohol hydroxyl group; of the common H-bonding functions these two groups may lie near the extremes of donor ability. On this basis, it would be expected that groups with intermediate H-bond donor capacity, e.g., phenols, would show an effect intermediate between the diacids and the hydroxy acids. An appropriate set of phenolic carboxylic acids with various distances between the groups would test this;[13] work in this direction has been initiated.

In a similar way, the methoxy group may be considered as a relatively weak H-bond acceptor. Better acceptors (more basic?) might result in clear-cut examples of reduced acidity due to intramolecular H bonding.[14]

Experimental Section

Melting points were obtained on a Thomas-Hoover melting apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 710B spectrophotometer while proton NMR spectra were recorded on a 60-MHz Hitachi-Perkin-Elmer Model R-24B instrument. Microanalyses were performed at Galbraith Laboratories, Inc., or Spang Microanalytical Laboratories. Hydrogenations were carried out in a Brown[2] hydrogenator. All organic starting materials were obtained from Aldrich Chemical Co., unless otherwise noted. Infrared and NMR spectra of all compounds are consistent with their structures.

Compounds of the cyclopentene, cyclobutene, and furan series were prepared by the standard sequence. The half-esters were prepared as follows: the furan diethyl ester (Aldrich) and the cyclopentene dimethyl ester[15] were half-saponified by 1 equiv of sodium hydroxide in methanol to the known methyl half-esters: cyclobutene-1,2-dicarboxylic acid obtained by hydrolysis[16] of 1,2-dicyanocyclobutene[17] was converted to the known methyl half-ester by a general method of esterification reported by Rao.[18] The half-esters were reduced to the hydroxymethyl esters by a general procedure,[19] and these partially purified compounds were saponified to the hydroxy acids **2a** (mp 96–98 °C (lit.[3] mp 98–99 °C)), **5a** (mp 130–132 °C (ethyl acetate)), and **6a** (mp 152–153 °C (ethyl acetate)).

Anal. (**5a**) Calcd for $C_6H_6O_4$: C, 50.71; H, 4.26. Found: C, 50.62; H, 4.33.

Anal. (**6a**) Calcd for $C_8H_8O_3$: C, 56.24; H, 6.29. Found: C, 56.20; H, 6.27 2-(Hyroxymethyl)benzoic acid, prepared by hydrolysis of phthalide:[5] mp 120–122 °C (lit.[2] mp 120.5–121.5 °C).

The hydroxy acids were converted to the methoxy acids by a general procedure illustrated by the preparation of the furan compound.

4-(Methoxymethyl)furan-3-carboxylic Acid. In a 100-mL three-necked flask equipped with a magnetic bar, nitrogen inlet, and an injection port were placed 0.3 g (0.006 mol) of sodium hydride (50% in mineral oil) and 15 mL of dry toluene. After

(13) In spite of the classically cited example of salicylic acid and some substituted salicylic acids, no study of the effect of geometry on acidities in phenolic carboxylic acids has been made. At least one study (Dunn, G. E.; Penner, T. L. *Can. J. Chem.* **1967**, *45*, 1699) has brought forth the suggestion that intramolecular H bonding in salicylic acid is *not* important in water. Salicylic acid does not appear to be able to attain the optimum geometry for intramolecular H bonding.

(14) Amino acids might fall into this class, or analogously, the cationic forms (diacids) might correspond to dicarboxylic acids. There do not appear to be any available systematic studies of the effect of geometry on the acidity of amino acids. If such amino acids, restricted and near optimal geometry for intramolecular H bonding, should show similarities to the dicarboxylic acids and monoanions, such results might be of use in analyzing some biochemical pathways involving flexible amino acids such as glutamic acid and γ-aminobutyric acid when they are conformationally restricted by complexation with proteins (enzymes).

(15) McDonald, R. N.; Reitz, R. R. *J. Org. Chem.* **1972**, *37*, 2418.

(16) Cobb, R. L.; Mahan, J. E. *J. Org. Chem.* **1977**, *42*, 1948.

(17) Bellus, D.; von Bredow, K.; Sauter, H.; Weis, C. D. *Helv. Chim. Acta* **1973**, *56*, 3004.

(18) Rao, C. G. *Org. Prep. Proc. Int.* **1980**, *12*, 225.

(19) Ishizumi, K.; Koga, K.; Yamada, S. *Chem. Pharm. Bull* **1968**, *16*, 492.

being stirred briefly, the mixture was allowed to stand until the sodium hydride had settled. The toluene layer was removed then with a syringe. Methyl iodide (5 g, 0.035 mol) followed by a solution of 0.43 g (0.003 mol) of 4-(hydroxymethyl)furan-3-carboxylic acid in 10 mL of THF was introduced into the flask, and the resulting mixture was stirred vigorously. After 42 h, the sodium salts were filtered, washed with 10 mL of ether, and then dissolved in 4 mL of water. The pH of this solution was brought to 3 by acidification with concentrated hydrochloric acid. The solid that separated from the aqueous phase was filtered, washed with 2 mL of water, dried, and recrystallized from ethyl acetate to yield 0.25 g (53%) of the methoxy acid **5b**; mp 132.5–133 °C.

Anal. Calcd for $C_7H_8O_4$: C, 53.85; H, 5.17. Found: C, 53.74; H, 5.12.

Similarly, **1b** had mp 95–96 °C (lit.[2] mp 94–95 °C), **2b** had mp 68–71 °C (lit.[4] mp 65–68 °C), and **6b** had mp 67–69 °C (petroleum ether).

Anal. (**6b**) Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 59.23; H, 7.13.

3-(Methoxymethyl)bicyclo[2.2.1]hepta-2,5-diene-2-carboxylic Acid (3b). A mixture of 5.94 g (0.09 mol) of freshly prepared cyclopentadiene and 5.7 g (0.05 mol) of 4-methoxytetrolic acid[7] in 3 mL of THF was stirred at room temperature for 3 days. After removal of the solvent, the residue was dissolved in 50 mL of ether and extracted with saturated aqueous sodium bicarbonate solution (4 × 20 mL). The combined bicarbonate layers were acidified at 0–5 °C with concentrated hydrochloric acid to pH 3.5 and then extracted with ether (4 × 50 mL). The ether solution was dried ($MgSO_4$) and then concentrated to a brown liquid (4.5 g). This residue was a mixture of methoxytetrolic acid (largely) and the bicyclic acid.

Separation was accomplished by fractional extraction of an ether solution of the mixture with aqueous sodium bicarbonate solution;[20] the bicyclic acid was observed in later fractions. Combination of the appropriate fractions and several recrystallizations of the bicyclic acid from petroleum ether gave **3b**; 0.17 g, mp 35–37 °C. On prolonged standing, this acid changes to a gummy material: IR (KBr pellet) cm^{-1} 3300–2300, 1670, 1620, 1430, 1500, 1270, 1200, 1110, 940, 730; NMR ($CDCl_3$) δ 10.94 (s, 1 H), 6.6–7.0 (m, 2 H), 4.61 ($^1/_2$ of AB quartet, 1 H, J = 14.0 Hz), 4.30 ($^1/_2$ of AB quartet, 1 H, J = 14.0 Hz), 3.7–4.05 (m, 2 H), 3.32 (S, 2 H), 1.9–2.25 (m, 2 H).

Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.53; H, 6.64.

3-(Acetoxymethyl)bicyclo[2.2.1]hepta-2,5-diene-2-carboxylic Acid. A solution of 3.0 g (0.021 mol) of 4-acetoxytetrolic acid[6] in 2 mL of ether was mixed with 3.0 g (0.045 mol) of freshly prepared cyclopentadiene and stirred at ambient temperature. After 68 h, the mixture was diluted with 20 mL of a 1:1 mixture of benzene and ether to decrease the viscosity. The solution was extracted with saturated aqueous sodium bicarbonate (3 × 10 mL). The combined aqueous solution on acidification at 0 °C with concentrated hydrochloric acid afforded a solid. Recrystallization from benzene gave 1.3 g (30%) of the bicyclic acetoxy acid, mp 91–93 °C. Further recrystallization gave an analytical sample: mp 93–94 °C; IR (KBr pellet) cm^{-1} 3500–2300, 1730, 1650, 1610, 1435, 1375, 1340, 1300, 1260, 1235, 1200, 1050, 940, 860, 715; NMR ($CDCl_3$) δ 8.6–9.5 (br, 1 H), 6.55–7.0 (m, 2 H), 5.31 ($^1/_2$ of AB quartet, 1 H, J = 14.5 Hz), 4.97 ($^1/_2$ of AB quartet, 1 H, J = 14.5 Hz), 3.8–4.0 (m, 1 H), 3.6–3.8 (m, 1 H), 2.0–2.3 (m, 5 H).

Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.84; H, 5.79.

3-(Acetoxymethyl)bicyclo[2.2.1]hept-2-ene-2-carboxylic Acid. A solution of 2.08 g (0.010 mol) of the diene acetate in 25 mL of ethyl acetate containing 0.2 g of 5% Pd/C was reduced in a Brown[2] hydrogenator. After consumption of 1 molar equiv of hydrogen, the reduction was stopped. Removal of the catalyst and evaporation of the solvent left a white solid. Two recrystalizations from benzene–petroleum ether gave the desired monoene acetate: mp 59–61 °C; IR (KBr pellet) cm^{-1} 3500–2200, 1725, 1660, 1610, 1415, 1295, 1235, 1045; NMR ($CDCl_3$) δ 11.2 (s, 1 H), 5.25 ($^1/_2$ of AB quartet, 1 H, J = 14.0 Hz), 4.92 ($^1/_2$ of AB quartet, 1 H, J = 14.0 Hz), 3.0–3.4 (m, 2 H), 2.10 (s, 3 H), 1.0–2.0 (m, 6 H).

Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 62.82; H, 6.70.

Titrations were carried out at 25.0 ± 0.1 °C by using the apparatus[12] and the procedure (pK_2)[1] described previously. All of the acid samples were of analytical purity. The scatter of pKa values during single titrations and between different titrations was ±0.01–0.02 for all acids except the methoxy cyclobutene compound where ±0.03 was observed. Zone-refined benzoic acid was used as a reference standard; frequent determinations of pKa gave 4.20 ± 0.01, in excellent agreement with the best available values for this acid.[21] Calculation of the pKa values was carried out as described by Albert and Serjeant with corrections for volume changes and activity coefficients.[22]

Registry No. **1a**, 612-20-4; **1b**, 88550-19-0; **2a**, 14668-74-7; **2b**, 32401-29-9; **3a** (acetate), 88550-20-3; **3b**, 88550-21-4; **4a** (acetate), 88550-22-5; **4b**, 88550-23-6; **5a**, 88550-24-7; **5b**, 88550-25-8; **6a**, 88550-26-9; **6b**, 88550-27-0; cyclopentadiene, 542-92-7; 4-methoxytetrolic acid, 24303-64-8; 4-acetoxytetralic acid, 88550-28-1.

(20) Carpino, L. A. *J. Am. Chem. Soc.* **1958**, *80*, 601.

(21) Kortüm, G.; Vogel, W.; Anrussow, K. "Dissociation Constants of Organic Acids in Aqueous Solution"; Butterworths: 1961.

(22) Albert, A.; Serjeant, E. P. "Ionization Constants of Acids and Bases"; Methuen: London, 1962; pp 62–63. Essentially, eq 3.15 modified for monobasic acids rather than bases was used. "These calculations take a great deal of time." (p 63); this was no problem with a simple program used in a Hewlett-Packard Model 25 calculator.

Revised Structure of Podolactone C, the Antileukemic Component of *Podocarpus milanjianus* Rendle

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The genus *Podocarpus* (Podocarpaceae) is distributed in tropical and subtropical areas of eastern Asia and the southern hemisphere.[1] Phytochemical studies of a number of species in this genus have led to elucidation of various terpenoids,[2] including the important nor- and dinorditerpenoid dilactone groups.[2,3] These compounds are of interest on the basis of their novel structures and biological activities including antitumor activity,[3-5] plant growth regulatory activity,[6,7] termiticidal activity,[8] and cytotoxicity toward insect larvae.[9,10] In a continuation of our studies involving the isolation of antineoplastic agents from higher plants, we have carried out an activity-directed fractionation of the stem bark of *Podocarpus milanjianus* Rendle, a conifer occurring in West Africa. We reported earlier that the stem bark, collected in Kenya, contained four norditerpenoid dilactones, nagilactones F and G and mi-

(1) Dallimore, W.; Jackson, A. B. "A Handbook of Coniferae and Ginkogoaceae"; Revised by Harrison, S. G; Edward Arnold: London, 1966.

(2) Ito, S.; Kodama, M. *Heterocycles* **1976**; *4*, 596.

(3) Hayashi, Y.; Matsumoto, T.; Tashiro, T. *Gann* **1979**, *70*, 369.

(4) Hayashi, Y. Sakan, T.; Sakurai, Y.; Tashiro, T. *Gann* **1975**, *66*, 587.

(5) Kupchan, S. M.; Baxter, R. L.; Ziegler, M. R., Smith, P. M.; Bryan, R. F. *Experientia* **1975**, *31*, 137.

(6) Galbraith, M. N.; Horn, D. H. S.; Ito, S.; Kodama, M.; Sasse, J. M. *Agric. Biol. Chem.* **1972**, *36*, 2393.

(7) Hayashi, Y., Sakan, T. "Plant Growth Substances 1973" (Proceedings of the 8th International Conference on Plant Growth Substances), Hirokawa, Tokyo, 1974, p 525.

(8) Saeki, I., Sumimoto, M.; Kondo, T. *Holzforschung* **1970**, *24*, 83.

(9) Russell, G. B.; Genemore, P. G.; Singh, P. *J. Chem. Soc., Chem. Commun.* **1973**, 166.

(10) Singh, P.; Russell, G. B.; Hayashi, Y.; Gallagher, R. T.; Fredericksen, S. *Entomol. Exp. Appl.* **1979**, *25*, 121.

0022-3263/84/1949-0942$01.50/0