Synthesis of Kavain, Dihydrokavain, and Analogues†[1]

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The synthesis of kavain, dihydrokavain, and a number of new analogues of kava pyrones is described. Kavain and dihydrokavain were synthesized by a modification of the Reformatsky reaction in yields severalfold higher than described before. A novel analogue of kavain was obtained by this procedure. Several new analogues of the naturally occurring kava pyrones were synthesized in 10–60% yields by condensing the appropriate aldehyde with 4-methoxy-6-methyl-2-pyrone. The pyrones dehydrokavain and yangonin were obtained in much improved yields. Catalytic hydrogenation of pyrones gave new analogues of dihydrokavain.

The root, rhizome, and the base of the stem of *Piper methysticum* Forster (Kava)[2] have been used for centuries to prepare an intoxicating beverage.[3] Kava was used in Europe before World War I for the treatment of gonorrhea, cystitis, and gout.[4] The active principle of Kava resin consists of a number of α-pyrones and reduced pyrones (nine lactones and two chalcones)[5-10] which have a variety of pharmacological properties (soporific and sedative, potentiation of barbiturate narcosis, protection against chemo- and electroshock, local anesthetic, spasmolytic and smooth muscle relaxant, analgetic, antimycotic, and antiedemic).[5,8,11-26]

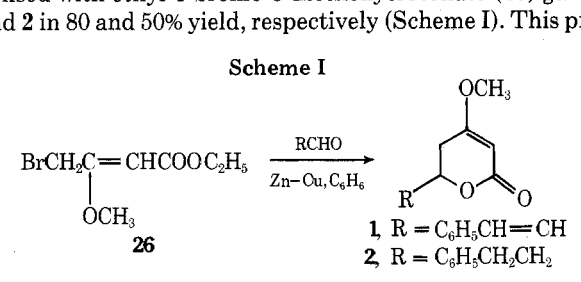
To obtain analogues of the naturally occurring kava lactones we investigated several possible general synthetic methods for the preparation of α-pyrones and reduced pyrones. A number of new analogues of kava lactones were synthesized, and the yield of several known compounds was improved severalfold.

The structures of the kava lactones described here are given in Table I. Only kavain (**1**)[27-31] 7,8-dihydrokavain (**2**),[31] yangonin (**3**),[10,32-35] 5,6-dehydrokavain (**4**),[35] and 7,8-dihydro-5,6-dehydrokavain (**5**)[34] had previously been synthesized (in low yields).

We synthesized kavain, dihydrokavain, and analogues by two methods: (a) modifications of the Reformatsky reaction, and (b) catalytic reduction of the corresponding dehydrokavains.

(a) By using Neuwland and Daly's modification of the Reformatsky reaction,[36] the appropriate aldehydes when condensed with ethyl 4-bromo-3-methoxycrotonate (**26**) gave **1** and **2** in 80 and 50% yield, respectively (Scheme I). This procedure was not successful in the synthesis of the *p*-*N*,*N*-dimethylamino analogue of kavain (**6**). However, when the aldehyde group was activated toward nucleophilic attack (by conversion of the *p*-*N*,*N*-dimethylamino group to a quaternary nitrogen with chloromethyl methyl ether), the activated aldehyde underwent modified Reformatsky reaction to give **6** in 26.5% yield.

Scheme I



Kavain (**1**) was also obtained (25% yield) by the condensation of the *N*-butylamine Schiff base of cinnamaldehyde under Reformatsky conditions. This approach was also unsuccessful in the synthesis of **6**.

(b) Hydrogenation of dehydrokavains in THF (over Pd/C) resulted in the stepwise reduction of $\Delta^{7,8}$ and $\Delta^{5,6}$ bonds ($\Delta^{7,8}$ reduced faster than $\Delta^{5,6}$) to give the corresponding kavains and dihydrokavains (Table II) in good yields. In EtOH, the reduction products were mainly tetrahydrokavaic acid (**23**) and analogues (obtained by opening of lactone ring and subsequent hydrogenation); however, the model compound 4-methoxy-6-methyl-2-pyrone (**27**) was reduced to the intact lactone 3-methoxy-5-hydroxy-2-hexenoic acid lactone (**28**) in 85% yield.

Reduction of dehydrokavains with $NaBH_4$ (which occurred only when α-pyrones were refluxed in alcoholic KOH for 4–6 h with a 30-fold excess of $NaBH_4$) yielded kavaic acid (**20**) and analogues instead of the expected dihydropyrones.

For the synthesis of dehydrokavains, the procedure of Bu'lock and Smith[33] was modified. Compounds **3** and **4** were obtained in much higher yield than reported previously. A number of new analogues (**10–12, 15–19**) were obtained in yields of 10–60%.

Experimental Section

Melting points were determined on a calibrated Thomas-Hoover melting point apparatus and are corrected. The uv spectra were recorded on a Cary recording spectrophotometer Model 14. The ir spectra were taken on a Beckman IR-8 and IR-10 infrared spectrophotometer. NMR spectra (reported in δ) were recorded on a Varian A-60 and A-60A spectrometer using tetramethylsilane and 3-(trimethylsilyl)propanesulfonic acid sodium salt as internal standards. Elemental analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind., and on a F and M Carbon, Hydrogen and Nitrogen Analyzer Model 185, University of Kansas.[37] Mass spectra were obtained by The Analytical Instrument Division of Varian on a M-66 mass spectrometer. Solvents were removed by evaporation in vacuo by using a Calab Model C rotary evaporator normally at room temperature.

3-Methoxy-5-hydroxy-7-phenyl-2,6-heptadienoic acid Lactone (Kavain, 1). Kavain was synthesized by a modification of the Reformatsky reaction[36] (using Zn–Cu couple instead of Zn). Thus, 13.2 g (0.1 mol) of cinnamaldehyde and 44.4 g (0.2 mol) of ethyl 4-bromo-3-methoxycrotonate (**26**) were condensed in the presence of 19.6 g (~0.3 mol) of Zn–Cu couple (95% Zn) to give 18.5 g (80% yield) of colorless needles (THF), mp 146–147.5 °C (lit.[31] mp 145–146 °C).

3-Methoxy-5-hydroxy-7-phenyl-2-heptenoic acid Lactone (Dihydrokavain, 2). Synthesis was carried out as for **1** using 13 g (0.1 mol) of hydrocinnamaldehyde. The product was isolated by column chromatography (silica gel 0.05–0.2 mm, Et_2O–petroleum ether, bp 55–65 °C) to give 11.6 g (50% yield) of **2**, recrystallized from CCl_4 as colorless needles: mp 69–71 °C (lit.[31] 65–69 °C); NMR (CCl_4) δ 7.15 (s, 5, aromatic), 5.05 (s, 1, –CH=), 4.5–4.0 (complex, 1, methine H), 3.66 (s, 3, $-OCH_3$), and 2.9–1.65 (complex, 6, methylene H).

***p*-(*N*,*N*-Dimethyl-*N*-methoxymethylammonium)cinnamaldehyde Chloride.** *p*-*N*,*N*-Dimethylaminocinnamaldehyde (17.5 g, 0.1 mol) and chloromethyl methyl ether (37.5 ml, 40.5 g, 0.5 mol) were mixed under an atmosphere of N_2 and allowed to stand at room temperature for 48 h. The precipitated solid was collected by filtration, washed several times with C_6H_6, and dried at 80 °C to give 24.7

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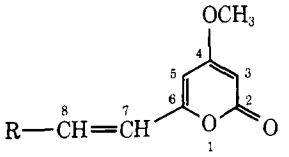
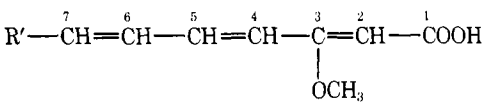
Table I. Structure of Kava Type Lactones and Acids



	R	$\Delta^{5,6}$	$\Delta^{7,8}$	Name
1	Phenyl	Reduced		Kavain[a]
2	Phenyl	Reduced	Reduced	7,8-Dihydrokavain[a]
3	4-Methoxyphenyl			Yangonin[a]
4	Phenyl			5,6-Dehydrokavain[a]
5	Phenyl		Reduced	7,8-Dihydro-5,6-dehydrokavain[a]
6	4-*N*,*N*-Dimethylaminophenyl	Reduced		
7	4-*N*,*N*-Dimethylaminophenyl		Reduced	
8	3,4,5-Trimethoxyphenyl		Reduced	
9	2-Thienyl		Reduced	
10	4-*N*,*N*-Dimethylaminophenyl			
11	3,4,5-Trimethoxyphenyl			
12	2-Thienyl			
13	4-*N*,*N*-Dimethylaminophenyl	Reduced	Reduced	
14	3,4,5-Trimethoxyphenyl	Reduced	Reduced	
15	2-Pyridyl			
16	3-Pyridyl			
17	4-Pyridyl			
18	Styryl			
19	Phenylethyl			



	R′	$\Delta^{4,5}$	$\Delta^{7,8}$	Name
20	Phenyl			Kavaic acid[a]
21	4-Methoxyphenyl			
22	3,4,5-Trimethoxyphenyl			
23	Phenyl	Reduced	Reduced	Tetrahydrokavaic acid
24	4-*N*,*N*-Dimethylaminophenyl	Reduced	Reduced	
25	3,4,5-Trimethoxyphenyl	Reduced	Reduced	

[a] Known compounds.

g (97% yield) of a brownish powder which was used without further purification. The product absorbs moisture very quickly upon exposure.

3-Methoxy-5-hydroxy-7-(4-*N*,*N*-dimethylaminophenyl)-2,6-heptadienoic Acid Lactone (6). Compound 6 was synthesized by a further modification of the Reformatsky reaction: Zn–Cu couple (4.0 g, 0.06 mol) was suspended in thiophene-free C_6H_6 (150 ml) and about 30 ml of C_6H_6 was distilled through the Dean-Stark trap. A crystal of iodine was added followed by 6 ml of a mied solution of the above described quaternary compound (4.6 g, 0.018 mol) in Me_2SO (20 ml) and **28** (13.2 g, 0.06 mol) in C_6H_6 (20 ml). The greenish brown reaction mixture was heated under reflux with stirring for 10 min after which the remainder of the aldehyde–ester mixture was added dropwise in 1 h maintaining a gentle reflux. After the addition was over the reaction mixture was stirred under reflux for 4 h and then for another 2.5 h at room temperature. A saturated solution of NH_4Cl (75 ml) was added and the stirring continued for 20 min. The organic layer was separated and combined with four 100-ml C_6H_6 extracts[38] of the H_2O layer and the combined C_6H_6 solution was washed with H_2O four times and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was taken in 50 ml of C_6H_6 and diluted with Et_2O (150 ml). The yellow precipitate which formed (300 mg) was removed by filtration and the filtrate was concentrated under reduced pressure. On cooling in an ice bath the residue deposited light colored crystals. The product was recrystallized from C_6H_6 as pale yellow needles: 1.2 g (26.5% yield) as hydrobromide, mp 172–172.5 °C; ν_{CO} (KBr) 1705 cm^{-1}; NMR ($DCCl_3$) δ 7.78–6.65 (complex, 6, aromatic and –CH=CH–), 5.26 (s, 1, –CH=), 5.2–4.9 (complex, 1, methine H), 3.78 (s, 3, $-OCH_3$), 3.0 (s, 6, NCH_3), and 2.95–2.5 (complex, 2, $-CH_2-$): mass spectrum *m/e* (rel intensity) parent peak 273 (7), base peak 133 (100). Anal. ($C_{16}H_{19}NO_3$·HBr) C, H, N. H: calcd, 5.65; found, 5.10.

***n*-Butylamine-*N*-cinnamalydine.** The Schiff base was prepared by a procedure similar to that of Robertson.[39] A mixture of *n*-butylamine (8.05 g, 0.11 mol) and cinnamaldehyde (13.2 g, 0.1 mol) in thiophene-free C_6H_6 (50 ml) was heated under reflux (1 h). The H_2O (2 ml) which formed during the reaction was removed by using a Dean-Stark trap. The solvent and the excess amine were removed under vacuum. The residue, 20.6 g (89% yield), was used without further purification.

Modified Reformatsky Condensation of *n*-Butylamine-*N*-cinnamalydine with 26. The procedure for the synthesis of kavain described earlier was followed. The above described Schiff base (11.2 g, 0.05 mol) and **26** (22.2 g, 0.1 mol) were condensed in the presence of Zn–Cu couple (10 g, 0.15 mol) to give light colored crystals, 2.2 g (22% yield), of **1**, mp 145–147 °C (THF).

3-Methoxy-7-phenyl-2,4,6-heptatrienoic Acid (Kavaic Acid, 20). Dehydrokavain (**4**, 340 mg) was dissolved in warm MeOH (50 ml) containing 1 g of KOH. $NaBH_4$ (340 mg) was added and the mixture was heated under reflux for 4 h. After cooling, the mixture was acidified (20% HOAc) and the precipitate was collected by filtration. The precipitate was washed with H_2O and Et_2O and recrystallized from hot acetone to give colorless neeles of **20** (40% yield): mp 180–182 °C (lit. 184,[27] 178–178.5 °C[40]); ν_{CO} (KBr) 1675 cm^{-1}; NMR (CD_3COCD_3) δ 7.15–6.25 (complex, 9, aromatic and –CH=CH–), 4.62 (s, 1, –CH=), and 3.18 (s, 3, $-OCH_3$).

3-Methoxy-7-(4-methoxyphenyl)-2,4,6-heptatrienoic Acid (21). Yangonin (**3**) was converted to the acid **21** by the method used for **20**: light yellow crystals ($CHCl_3$, 60% yield); mp 164–165 °C; ν_{CO} (KBr) 1659 cm^{-1}; NMR (CD_3COCD_3) δ 7.3–6.4 (complex, 8, aromatic and –CH=CHCH=CH–), 4.8 (s, 1, –CH=), 3.4 and 3.35 (s, 6, $-OCH_3$). Anal. ($C_{15}H_{16}O_4$), C, H. C: calcd, 69.22; found, 68.72.

3-Methoxy-7-(3,4,5-trimethoxyphenyl)-2,4,6-heptatrienoic Acid (22). The acid was obtained from pyrone **11** by the procedure described for **20**: yellow needles from $CHCl_3$ (64% yield); mp 174.5–175.5 °C; ν_{CO} (KBr) 1670 cm^{-1}; NMR ($DCCl_3$) δ 7.9–6.8 (complex, 4, –CH=CHCH=CH–), 6.75 (s, 2, aromatic), 5.22 (s, 1, –CH=), 3.97 (s, 9, aromatic $-OCH_3$), and 3.8 (s, $-OCH_3$); mass spectrum *m/e* (rel intensity) parent peak 320 (0.5), base peak 181 (100). Anal. ($C_{17}H_{20}O_6$), C, H.

General Procedure for the Catalytic Hydrogenation of Pyrones. The compound was dissolved in the appropriate solvent and exposed to H_2 in a microhydrogenator at room temperature in the presence of palladium on charcoal (Table II). After a certain time period the catalyst was removed by filtration and the filtrate was

Table II. Catalytic Hydrogenation of Pyrones[a]

Starting material	Registry no.	Product[b]	Registry no.	Yield, %	Mp, °C (solvent)	Analyzed for	Reaction conditions[c]
1		2		92	69.5–71.5 (Et_2O–petroleum ether) (lit.[31] 65–69)	d	THF/0.1/15/1.3
4		5		60	94.5–95.5 (Et_2O) (lit.[34] 96–97[31])	d	THF/0.1/50/6.5
10	60427-78-3	7	60427-82-9	97	92.5–94.5 (Et_2O–CCl_4)	$C_{16}H_{19}NO_3$ C, H, N	THF/0.1/50/48
11	60427-79-4	8	60427-83-0	30	128–130 (Et_2O–petroleum ether)	$C_{17}H_{20}O_6$ C, H	THF/0.12/15/0.2
12	60427-80-7	9	60427-84-1	52	69.5–71.5 (CCl_4)	$C_{12}H_{12}O_3S$ C, H	THF/0.3/15/40
10		13	60427-85-2	90	76.5–78.5 (petroleum ether)	$C_{16}H_{21}NO_3$ C, H, N	THF/0.2/50/72
11		14	60427-86-3	90	75.3–76.2 (Et_2O–CCl_4)	$C_{17}H_{22}O_6$ C, H	THF/0.2/50/16
27	672-89-9	28	3791-79-5	85	62–64 (Et_2O–petroleum ether) (lit.[41] 68)	$C_7H_{10}O_3$ C, H	EtOH/0.12/15/6.5
1	1635-33-2	23	60427-87-4	13	108–109 (CCl_4)	$C_{14}H_{18}O_3$ C, H	EtOH/0.1/15/24
10		24	60427-88-5	4	102.5–105.5 (Et_2O–petroleum ether)	e	EtOH/0.2/15/19
22	60427-81-8	25	60427-89-6	83	120.5–121 (CCl_4)	$C_{17}H_{24}O_6$ C, H	THF/0.1/15/1

[a] The catalyst was 10% Pd/C except in the case of products 24 and 28, where 30% Pd/C was used. [b] All products were obtained as colorless crystals except 9 which was yellow. Compound 14 was obtained as rhombic crystals. [c] The reaction conditions employed are indicated as solvent/catalyst:substrate (w/w) ratio/H_2 pressure (psi)/time (h). [d] Known compounds. [e] Identification based on spectral data only.

concentrated in vacuo. The residue was recrystallized. The reaction conditions, yields, and physical properties of the products are given in Table II. The spectroscopic properties are listed below.

3-Methoxy-5-hydroxy-7-phenyl-2,4-heptadienoic Acid Lactone (5): ν_{CO} (KBr) 1730 cm^{-1}; NMR (CCl_4) δ 7.17 (s, 5, aromatic) 5.58 (d, 1, J = 2 Hz, -CH=), 5.28 (d, 1, J = 2 Hz, -CH=), 3.75 (s, 3, $-OCH_3$), and 2.83 (sym m, 4, $-CH_2CH_2-$).

3-Methoxy-5-hydroxy-7-(4-*N,N*-dimethylaminophenyl)-2,4-heptadienoic Acid Lactone (7): ν_{CO} (KBr) 1730 cm^{-1}; NMR (CCl_4) δ 6.78 (doublet of d, 4, J = 8.5 Hz, aromatic), 5.57 (d, 1, J = 2 Hz, -CH=), 5.27 (d, 1, J = 2 Hz, -CH=), 3.73 (s, 3, $-OCH_3$), 2.89 (s, 6, $-NCH_3$), and 2.72 (sym m, 4, $-CH_2CH_2-$).

3-Methoxy-5-hydroxy-7-(3,4,5-trimethoxyphenyl)-2,4-heptadienoic Acid Lactone (8): ν_{CO} (KBr) 1705 cm^{-1}; NMR ($DCCl_3$) δ 6.78 (s, 2, aromatic), 6.08 (d, 1, J = 2 Hz, -CH=), 5.75 (d, 1, J = 2 Hz, -CH=), 4.06 and 4.00 (s, 12, $-OCH_3$), and 3.00 (sym m, 4, $-CH_2CH_2-$).

3-Methoxy-5-hydroxy-7-(2-thienyl)-2,4-heptadienoic Acid Lactone (9): ν_{CO} (KBr) 1720 cm^{-1}; NMR (CCl_4) δ 7.45–6.67 (complex, 3, aromatic), 5.68 (d, 1, J = 2 Hz, -CH=), 5.34 (d, 1, J = 2 Hz, -CH=), 3.76 (s, 3, $-OCH_3$), and 3.0 (sym m, 4, $-CH_2CH_2-$).

3-Methoxy-5-hydroxy-(4-*N,N*-dimethylaminophenyl)-2-heptenoic Acid Lactone (13): ν_{CO} (KBr) 1710 cm^{-1}; uv λ_{max} (CH_3OH) 246 nm (log ϵ 5.26), 301 (4.26); NMR (CCl_4) δ 6.79 (doublet of d, 4, J = 9 Hz, aromatic), 4.25 (broad, 1, methine H), 3.69 (s, 3, $-OCH_3$), 2.86 (s, 6, $-NCH_3$), and 2.95–1.75 (complex, 4, $-CH_2-CH_2-$).

3-Methoxy-5-hydroxy-7-(3,4,5-trimethoxyphenyl)-2-heptenoic Acid Lactone (14): ν_{CO} (KBr) 1695 cm^{-1}; NMR (CCl_4) δ 6.35 (s, 2, aromatic), 5.02 (s, 1, -CH=), 4.25 (broad, 1, methine H), 3.77 and 3.69 (s, 12, $-OCH_3$), and 2.9–1.65 (complex, 6, $-CH_2-$).

3-Methoxy-5-hydroxy-2-hexenoic Acid Lactone (28): ν_{CO} (KBr) 1700 cm^{-1}; NMR (CCl_4) δ 5.05 (s, 1, -CH=), 4.47 (sym m, 1, -CH<), 3.74 (s, 3, $-OCH_3$), 2.48–2.22 (m, 2, $-CH_2-$), and 1.4 (d, 3, J = 6 Hz, $-CH_3$).

3-Methoxy-7-phenyl-2-heptenoic Acid (23): ν_{CO} (KBr) 1690 and 1655 cm^{-1}; NMR (CCl_4) δ 11.93 (broad s, 1, -COOH), 7.1 (s, 5, aromatic), 4.95 (s, 1, -CH=), 3.65 (s, 3, $-OCH_3$), 3.00–2.33 and 1.95–1.35 (broad complex, 8 and 2, $-CH_2-$).

3-Methoxy-7-(4-*N,N*-dimethylaminophenyl)-2-heptenoic Acid (24): ν_{CO} (KBr) 1665 cm^{-1}; NMR (CCl_4) δ 10.86 (broad s, 1, -COOH), 6.74 (doublet of d, 4, J = 7 Hz, aromatic), 4.93 (s, 1, -CH=), 3.63 (s, 3, $-OCH_3$), 2.85 (s, 6, $-NCH_3$), 3.0–2.28 and 1.75–1.25 (broad complex, 8, $-CH_2-$).

3-Methoxy-7-(3,4,5-trimethoxyphenyl)-2-heptenoic Acid (25): ν_{CO} (KBr) 1690 cm^{-1}; NMR (CCl_4) δ 11.66 (broad s, 1, -COOH), 6.28 (s, 2, aromatic), 4.99 (s, 1, -CH=), 3.78 (s, 9, aromatic $-OCH_3$), 3.68 (s, 3, $-OCH_3$), 3.00–2.32 (complex, 4, $-CH_2CH_2-$), and 1.7–1.4 (complex, 4, $-CH_2CH_2-$).

3-Methoxy-5-hydroxy-7-(3,4,5-trimethoxyphenyl)-2,4,6-heptatrienoic Acid Lactone (11). A solution of 3,4,5-trimethoxybenzaldehyde (19.6 g, 0.1 mol) and 4-methoxy-6-methyl-2-pyrone (**27**, 16.8 g, 0.12 mol) in absolute MeOH (40 ml) was added dropwise with stirring to a suspension of magnesium methoxide (prepared from 7.5 g of Mg turnings) in MeOH (100 ml) in 45 min, maintaining a gentle reflux and an atmosphere of N_2. After the addition was complete, the reaction mixture was stirred under gentle reflux for 6 h. The solvent was removed under reduced pressure at 40 °C and the residue was treated with dilute HOAc (45 g of glacial HOAc diluted to 225 ml) and extracted with CH_2Cl_2 (500 ml). The CH_2Cl_2 extract was washed with H_2O (80 ml), dried (Na_2SO_4), and filtered. The filtrate was evaporated under reduced pressure and the residue was triturated with Et_2O (150 ml) and filtered. The yellow, crystalline solid was washed with Et_2O followed by a small amount of MeOH, and then dried in vacuo at 80 °C: 19.1 g (60% yield), recrystallized from MeOH, shiny yellow plates; mp 196.5–197.5 °C; uv λ_{max} 345 nm (log ϵ 4.38), 362 (4.36), 224 (4.29); ν_{CO} (KBr) 1710 cm^{-1}; NMR ($DCCl_3$) δ 7.02 (doublet of d, 2, J = 15.5 Hz, -CH=CH-), 6.8 (s, 2, aromatic), 6.02 (d, 1, J = 2 Hz, -CH=), 5.50 (d, 1, J = 2 Hz, -CH=), 3.93 (s, 9, aromatic $-OCH_3$), and 3.85 (s, 3, $-OCH_3$); mass spectrum m/e 318, parent peak. Anal. ($C_{17}H_{18}O_6$), C, H.

3-Methoxy-5-hydroxy-7-(4-methoxyphenyl)-2,4,6-heptatrienoic Acid Lactone (Yangonin) (3). This compound was synthesized by the procedure described for **11**. Anisaldehyde (6.8 g, 0.05 mol), **27** (8.5 g, 0.06 mol), and magnesium methoxide (from 1.2 g of Mg) gave 5.3 g (41.5%) of the product, recrystallized from MeOH as yellow needle clusters, mp 156–157 °C (lit.[35] 155–157 °C).

3-Methoxy-5-hydroxy-7-phenyl-2,4,6-heptatrienoic Acid Lactone (5,6-Dehydrokavain) (4). The procedure for the synthesis of pyrone 11 was followed using benzaldehyde (6.2 g, 0.06 mol), **27**

(10.2 g, 0.07 mol), and magnesium methoxide (from 2.5 g of Mg). The product, 6.1 g (44% yield), was recrystallized from MeOH as colorless, fine needles, mp 134–136 °C (lit.[35] yellow needles, mp 139–141 °C). Anal. ($C_{14}H_{12}O_3$), C, H.

3-Methoxy-5-hydroxy-7-(4-*N,N*-dimethylaminophenyl)-2,4,6-heptatrienoic Acid Lactone (10). This compound was synthesized by a modified procedure of that described for the synthesis of the pyrone **11**. A solution of *p*-*N,N*-dimethylaminobenzaldehyde (36 g, 0.24 mol) and **27** (40.8 g, 0.29 mol) in absolute MeOH (200 ml) was added dropwise with stirring to a suspension of magnesium methoxide (prepared from 10 g of Mg) in MeOH (200 ml) in 2 h, while maintaining a gentle reflux under an atmosphere of N_2. The reddish brown reaction mixture was stirred under reflux for an additional 15 h, after which period it was cooled and treated with 15% HOAc (60 g of glacial HOAc diluted to 400 ml) and extracted exhaustively with C_6H_6 (ten portions of 150 ml each). The C_6H_6 extract was washed with H_2O, dried (Na_2SO_4), and filtered. The solvent was removed under reduced pressure at 40 °C and the residue triturated with Et_2O. The solid was filtered, washed with MeOH and Et_2O, and then dried in vacuo, 26.5 g (40% yield). The product was recrystallized (MeOH) to give silky yellow, shiny plates: mp 201–202 °C; uv (CH_3OH) λ_{max} 408 nm (log ϵ 5.58), 245 (5.21), 232 (5.2); ν_{CO} (KBr) 1705 cm^{-1}; NMR ($DCCl_3$) δ 7.62–6.25 (groups of multiplets, 6, aromatic and –CH=CH–), 5.86 (d, 1, J = 2 Hz, –CH=), 5.45 (d, 1, J = 2 Hz, –CH=), 3.82 (s, 3, $-OCH_3$), and 3.01 (s, 6, $-NCH_3$). Anal. ($C_{16}H_{17}NO_3$), C, H, N. C: calcd, 70.85; found, 70.38.

3-Methoxy-5-hydroxy-7-(2-pyridyl)-2,4,6-heptatrienoic Acid Lactone (15). The procedure for the synthesis of the pyrone **11** was followed using 2-pyridinecarboxaldehyde (5.4 g, 0.05 mol), **27** (8.5 g, 0.06 mol), and magnesium methoxide (from 2.8 g of Mg). The crude product, 1.5 g (13.1% yield), was obtained as a brown powder, ν_{CO} (KBr) 1705 cm^{-1}. The modified procedure as described for the synthesis of the pyrone **10** did not give the product.

3-Methoxy-5-hydroxy-7-(3-pyridyl)-2,4,6-heptatrienoic Acid Lactone (16). The procedure for the synthesis of the pyrone **11** was followed using 3-pyridinecarboxaldehyde (6.5 g, 0.06 mol), **27** (10.1 g, 0.07 mol), and magnesium methoxide (from 2.5 g of Mg). The product, 1.4 g (10% yield), was recrystallized (MeOH) to give pale yellow needles: mp 180.5–182 °C; ν_{CO} (KBr) 1735 cm^{-1}; NMR ($DCCl_3$) δ 8.8–6.58 (complex, 6, aromatic and –CH=CH), 6.09 (d, 1, J = 2 Hz, –CH=), 5.59 (d, 1, J = 2 Hz, –CH=), and 3.89 (s, 3, $-OCH_3$). Anal. ($C_{13}H_{11}NO_3$), C, H, N.

3-Methoxy-5-hydroxy-7-(4-pyridyl)-2,4,6-heptatrienoic Acid Lactone (17). The procedure for the synthesis of the pyrone **11** was followed, using 4-pyridinecarboxaldehyde (5.4 g, 0.05 mol), **27** (8.5 g, 0.06 mol), and magnesium methoxide (from 2.8 g of Mg). The crude product, 2.0 g (17.5% yield), was obtained as a pinkish brown powder.

The modified procedure as described for the synthesis of the pyrone **10** gave the product in 5% yield, recrystallized from MeOH–Et_2O: light brown needles; mp 146–150 °C dec; ν_{CO} (KBr) 1735 cm^{-1}; NMR ($DCCl_3$) δ 8.88 and 7.58 (pair of d, 4, J = 6 Hz, aromatic), 7.3 (doublet of d, 2, J = 16.5 Hz, –CH=CH–), 6.22 (d, 1, J = 2 Hz, –CH=), 5.59 (d, 1, J = 2 Hz, –CH=), and 3.87 (s, 3, $-OCH_3$). Anal. ($C_{13}H_{11}NO_3$) C, H, N.

3-Methoxy-5-hydroxy-7-(2-thienyl)-4,6-heptatrienoic Acid Lactone (12). The procedure for the synthesis of the pyrone **10** was followed, using 2-thiophenecarboxaldehyde (6.7 g, 0.06 mol), **27** (10.1 g, 0.07 mol), and magnesium methoxide (from 2.5 g of Mg). The product, 6.0 g (42.8% yield), was recrystallized (MeOH) to give yellow crystals mp 176.5–177.5 °C; ν_{CO} (KBr) 1735 cm^{-1}; NMR ($DCCl_3$) δ 7.8–6.28 (complex, 5, aromatic and –CH=CH–), 5.94 (d, 1, J = 2 Hz, –CH=), 5.52 (d, 1, J = 2 Hz, –CH=), and 3.83 (s, 3, $-OCH_3$). Anal. ($C_{12}H_{10}O_3S$) C, H.

3-Methoxy-5-hydroxy-9-phenyl-2,4,6,8-nanotetraenoic Acid Lactone (18). The procedure for the synthesis of the pyrone **11** was followed, using 6.6 g (0.05 mol) of cinnamaldehyde, 8.4 g (0.06 mol) of **27**, and magnesium methoxide (from 2.5 g of Mg). The product, 2.0 g (15.7% yield), was recrystallized (MeOH) to give bright yellow plates: mp 188.5–190 °C; ν_{CO} (KBr) 1730 cm^{-1}; NMR ($DCCl_3$) δ 7.02–6.02 (complex, 9, aromatic and –CH=CHCH=CH–), 5.86 (d, 1, J = 2 Hz, –CH=), 5.46 (d, 1, J = 2 Hz, –CH=), and 3.8 (s, 3, $-OCH_3$). Anal. ($C_{16}H_{14}O_3$) C, H. C: calcd, 75.59; found, 75.14.

3-Methoxy-5-hydroxy-9-phenyl-2,4,6-nanotrienoic Acid Lactone (19). The procedure for the synthssis of the pyrone **11** was followed using hydrocinnamaldehyde (6.7 g, 0.05 mol), **27** (8.4 g, 0.06 mol), and magnesium methoxide (from 2.5 g of Mg). The crude product obtained was a syrupy liquid. The modified procedure as that employed for the synthesis of the pyrone **10** also gave the same product, ν_{CO} (neat) 1730 cm^{-1}.

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Appendix

The following new compounds were synthesized as intermediates, by-products, or model compounds (for details see ref 1). 3,4,5-Trimethoxycinnamaldehyde, mp 106–108.5 °C (Et_2O–petroleum ether). Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.99; H, 6.38. Methyl 5-keto-7-phenylheptanoate, bp 144–146 °C (0.95 mm). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.54; H, 7.68. 2,6-Diketo-4-(2-phenylethyl)heptane-1,3,5,7-tetracarboxylic acid tetramethyl ester, mp 184–185 °C (EtOAc). Anal. Calcd for $C_{23}H_{28}O_{10}$: C, 59.48; H, 6.08. Found: C, 59.12; H, 6.10. 2,6-Diketo-4-styrylheptane-1,3,5,7-tetracarboxylic acid tetramethyl ester, mp 180.5–181.5 °C (EtOAc). Anal. Calcd for $C_{23}H_{26}O_{10}$: C, 59.74; H, 5.67. Found: C, 59.86; H, 5.72.

Registry No.—**2,** 587-63-3; **3,** 500-62-9; **4,** 1952-41-6; **5,** 3155-51-9; **6,** 60427-90-9; **15,** 60427-94-3; **16,** 15317-59-6; **17,** 15317-60-9; **18,** 60427-92-1; **19,** 60427-95-4; **20,** 501-73-5; **21,** 60427-93-2; **26,** 1116-51-4; $C_{16}H_{19}NO_3 \cdot CH_2Cl_2$; 60427-91-0; cinnamaldehyde, 104-55-2; hydrocinnamaldehyde, 104-53-0; *p*-(*N,N*-dimethyl-*N*-methoxymethylammonium)cinnamaldehyde chloride, 60427-96-5; butylamine-*N*-cinnamalydine, 15286-55-2; 3,4,5-trimethoxybenzaldehyde, 86-81-7; anisaldehyde, 123-11-5; benzaldehyde, 100-52-7; *p*-*N,N*-dimethylaminobenzaldehyde, 100-10-7; 2-pyridinecarboxaldehyde, 1121-60-4; 3-pyridinecarboxaldehyde, 500-22-1; 4-pyridinecarboxaldehyde, 872-85-5; 2-thiophenecarboxaldehyde, 98-03-3; 3,4,5-trimethoxycinnamaldehyde, 34346-90-2; methyl 5-keto-7-phenylheptanoate, 60427-97-6; 2,6-diketo-4-(2-phenylethyl)heptane-1,3,5,7-tetracarboxylic acid tetramethyl ester, 60427-98-7; 2,6-diketo-4-styrylheptane-1,3,5,7-tetracarboxylic acid tetramethyl ester, 60427-99-8.

References and Notes

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Synthesis of *C*-Glycosyl Thiazoles

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Condensation of 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosylthiocarboxamide (**1**) with α-chloroketo compounds yielded the corresponding 2-*C*-glycosyl thiazole nucleosides (**4a** and **7**) as the major products along with the 2-(thiazol-2-yl)-5-benzoyloxymethylfuran derivatives (**5a** and **8**). Reaction of **1** with ethyl bromopyruvate gave as the only resulting compound the 2-*C*-glycosyl thiazole nucleoside **12**. A similar series of reactions was carried out with 5-benzoyloxymethylfuran-2-thiocarboxamide (**2**) and α-halo ketones. Finally, treatment of methyl 6-deoxy-6-diazo-2,3-*O*-isopropylidene-β-D-*ribo*-hexofuranosid-5-ulose (**24**) with thiourea afforded the 4-*C*-glycosyl thiazole **26**.

Of the several synthetic procedures described in the literature for obtaining thiazole derivatives, the reaction of thioamides and related compounds with α-halocarbonyl derivatives has been the most extensively used.[1] By application of this method, some acyclic sugar 2- and 4-thiazolyl nucleoside analogues have been prepared starting from suitable aldonic acid thioamides[2] or α-haloketoses,[3] respectively. More recently Tronchet et al.[4] have described the synthesis of 4-*C*-glycosyl thiazoles by reacting thiourea or thioacetamide with an α-halocarbonyl sugar derivative, namely 6-*S*-benzyl-6-chloro-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-*xylo*-6-thiohexofuranos-5-ulose.

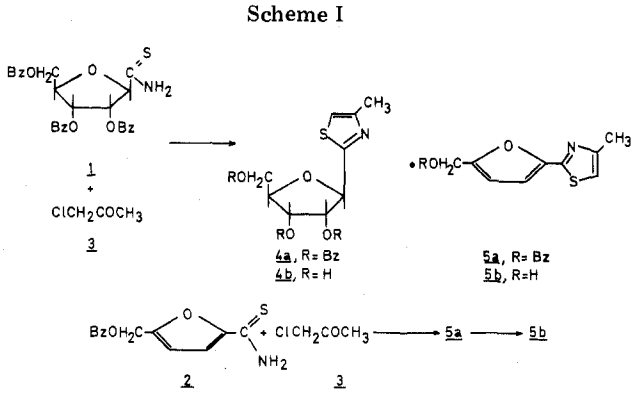
In a recent preliminary communication[5] we have reported on the synthesis of a 2-*C*-glycosyl thiazole nucleoside and also the synthesis of several acyclic sugar 4-thiazolyl nucleoside analogues. Now we wish to give a full account of this and related work.

The starting material in our synthesis of 2-glycosyl thiazole nucleosides, the hitherto unknown 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosylthiocarboxamide[5,6] (**1**), was obtained in 20% yield as an amorphous solid by reaction of 2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl cyanide[7] with hydrogen sulfide. It should be noted that the furan derivative **2** resulting from the elimination of two benzoyloxy groups was also separated from the reaction. Similar base-catalyzed eliminations of these protecting groups have been already reported.[8]

The assignment of the anomeric configuration of **1** was made on the basis of the known configuration of the nitrile used as starting material, since the doublet corresponding to the anomeric proton of **1** (τ 4.92) showed a coupling constant larger than 1 Hz ($J_{1,2}$ = 5 Hz). This assignment was further supported by the consistent application of Imbach's criterion[9] on the 2′,3′-*O*-isopropylidene-β-D-ribofuranosyl nucleoside **14**, obtained from **1** as described below.

Reaction of the thiocarboxamide **1** with chloroacetone in ethanol afforded a mixture of 2-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-4-methylthiazole (**4a**) in 32% yield and the furan derivative **5a** in 15% yield. Debenzoylation of these products with methanolic ammonia gave the deblocked compounds **4b** and **5b**, respectively (Scheme I). Similarly, reaction of the furan thiocarboxamide **2** with chloroacetone gave a 35% yield of **5a** identical with the compound obtained in the foregoing reaction.

Scheme I



The thiocarboxamide **1** reacted smoothly with ethyl oxalochloroacetate to give a mixture of the blocked C-nucleoside **7** and the elimination product **8** which were isolated by preparative layer chromatography in yields of 31 and 27%, respectively. Compound **8** was also obtained from the reaction of furan thiocarboxamide **2** with ethyl oxalochloroacetate (Scheme II).

Treatment of compounds **7** and **8** with methanol saturated with ammonia gave the corresponding deblocked dicarboxamides in low yields. In the case of compound **7**, TLC of the crude reaction showed a complex mixture of products. Separation by preparative thick layer chromatography gave the expected deblocked β anomer **9** in 25% yield. ^1H NMR spectra of other minor bands showed the presence of the α anomer along with traces of compound **10**. It should be noted that no anomerization was detected in the debenzoylation reactions of the other 2-*C*-glycosyl thiazole nucleosides described in this paper.

In a similar fashion the thiocarboxamide **1**, when treated with ethyl bromopyruvate at reflux in ethanol solution, gave the protected *C*-glycosyl nucleoside **12** in 55% yield as a syrup. Although a furan derivative was expected, no compound of this type was found. Treatment of **12** with methanolic am-

† The present paper is dedicated to the memory of Professor García-Muñoz.