6-ol (25). Similar to the synthesis of the sulfoxide **4a**, from 6.1 g (20 mmol) of the sulfoxide **20** and 4.7 g (80% containing 28 mmol) of MCPBA was obtained 6.0 g (95%) of the sulfone **25** as white crystals. Pure **25** was recrystallized from ethanol: mp 161.5–162.5 °C; IR (Nujol) 3500 cm^{-1} (OH); ^1H NMR ($CDCl_3$) δ 0.70–1.80 (m, 7 H, CH_3 and $2CH_2$), 1.20 (s, 3 H, CH_3), 1.90–3.00 (m, 5 H, $2CH_2$ and OH), 3.35 (m, 1 H, CH), 3.70–4.00 (m, 1 H, CH), 5.40–6.20 (m, 2 H, CH=CH), 7.50–8.20 (m, 5 H, aromatic); mass spectrum, *m/e* 320 (M^+).

Anal. Calcd for $C_{18}H_{24}O_3S$: C, 67.48; H, 7.55. Found: C, 67.19; H, 7.64.

Decomposition Reaction of the Sulfone 25. To a stirred solution of 1.12 g (10 mmol) of potassium *tert*-butoxide in 30 mL of Me_2SO was added a solution of 3.0 g (9.4 mmol) of the sulfone **25** in 20 mL of Me_2SO dropwise at room temperature. The reaction mixture was heated to 100 °C for 8 h and then poured into water and extracted with ether. The extract was washed with water and dried (Na_2SO_4). Removal of the solvent and distillation gave 1.2 g (71%) of ethyl phenyl sulfone (**26**): bp 101–103 °C (1 mm) [mp 41.5–42.5 °C (lit.[20] 42 °C)]; IR (neat) 1300 and 1140 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 1.30 (t, 3 H, J = 7.3 Hz, CH_3), 3.20 (q, 2 H, J = 7.3 Hz, CH_2), 7.60–8.30 (m, 5 H, aromatic); mass spectrum, *m/e* 170 (M^+).

The aqueous layer was acidified with concentrated hydrochloric acid and extracted with $CHCl_3$. The extract was washed with water and dried (Na_2SO_4). Removal of the solvent and bulb-to-bulb distillation at 100–130 °C (3 mm) gave 0.2 g of a yellow liquid. The yellow liquid showed more than three peaks on GLC analysis; mass spectrum showed no peaks at more than *m/e* 150.

Registry No.—1, 66977-59-1; **2a,** 542-92-7; **2b,** 95-13-6; **2c,** 109-92-2; **2d,** 110-87-2; **3a,** 67010-75-7; **3b,** 66977-56-8; **3c,** 66977-57-9; **3d,** 66977-58-0; **4a,** 66977-60-4; **4d,** 69765-58-8; **5a,** 66977-61-5; **5d,** 66977-62-6; **6a,** 538-51-2; **6b,** 6852-58-0; **6c,** 6852-54-6; **7a,** 66977-63-7; **7b,** 66977-64-8; **7c,** 69765-59-9; **8b,** 66977-65-9; **8c,** 69765-60-2; **9a,** 66977-66-0; **10a,** 66977-67-1; **11,** 69765-61-3; **12,** 69765-62-4; **13,** 69765-63-5; **14,** 69765-64-6; **15,** 69765-65-7; **16,** 69765-66-8; **17,** 69765-67-9; **18,** 69765-68-0; **19,** 69765-69-1; **20,** 69765-70-4; **21,** 69765-71-5; **22,** 69765-72-6; **23,** 69765-73-7; **24,** 69765-74-8; **25,** 69765-75-9; **26,** 599-70-2; α-(phenylthio)propanoyl chloride, 29943-30-4; dicyclohexylcarbodiimide, 538-75-0; oxosulfonium methylide, 5367-24-8; methyl iodide, 74-88-4; *n*-butyllithium, 109-72-8.

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(16) The α-methylenecyclobutanone **5a** is very easily polymerized, and further purification was difficult. Thus, for the elemental analysis, the cyclobutanone **5a** was converted into dibromide $C_8H_8OBr_2$ and analyzed.

(17) The elemental analysis showed slight error, but all of the spectral data suggested this structure.

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Synthesis and Properties of (*E*)-2-(Acylmethylene)tetrahydrofurans. 6-Hydroxy-1,3-hexanedione Equivalents

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Substituted 6-hydroxy-1,3-hexanediones **1** were prepared by sodium ethoxide catalyzed condensation of methyl ketones with 4-butyrolactone. Dehydration with triphenylphosphine and carbon tetrachloride or carbon tetrabromide gave the corresponding (*E*)-2-(acylmethylene)tetrahydrofurans **4**, which react with primary amines and hydrazine to give 3-propanol-substituted Schiff bases and 3,4-substituted pyrazoles by Michael additions. The (acylmethylene)tetrahydrofurans **4** are stable at high pH, but hydrolyze readily in the presence of acid to return the hydroxydiones **1**.

The 1,3-diketones as a class of compounds have been extensively investigated and have been frequently used in synthesis. The chemical reactivity of such molecules that makes them synthetically attractive also limits their utility under certain conditions. The condensation of an aldehyde or ketone with a 1,3-diketone (the Knoevanagel reaction) proceeds readily in the presence of base.[1] At high pH 1,3-diketones hydrolyze to ketone and carboxylic acid components.[2] The problems associated with the use of 1,3-diketone units increase with increasing functionality in the molecules.

Our group had need of the chemistry of 6-hydroxy-1,3-hexanediones (**1**) and came across synthetic equivalents of such molecules that were stable at high pH but readily gave the hydroxydiones **1** at low pH.

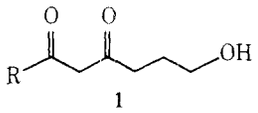
6-Hydroxy-1,3-hexanediones (**1**) have been prepared by the sodium amide catalyzed condensation of methyl ketones with

0022-3263/79/1944-2073$01.00/0

Table I. Physical Data for 6-Hydroxy-1,3-hexanediones (1) and Dehydration Products (4)

product	R	yield, %	mp (solvent) or bp (torr), °C	molecular formula[d]
1a	CH_3	65		$C_7H_{12}O_3$ (144.2)
1b	C_2H_5	61		$C_8H_{14}O_3$ (158.2)
1c	C_6H_5	75	46–47 (hexane)	$C_{12}H_{14}O_3$ (206.2)
1d	p-$CH_3C_6H_4$[a]	79	38–39 (hexane)	$C_{13}H_{16}O_3$ (220.3)
4a	CH_3	89[b]	75–77 (4)	$C_7H_{10}O_2$ (126.2)
4a	CH_3	75[c]		
4b	C_2H_5	91[b]	82–83 (4)	$C_8H_{12}O_2$ (140.2)
4c	C_6H_5	95[b]	46–47 (hexane)	$C_{12}H_{12}O_2$ (188.2)
4c	C_6H_5	89[c]		
4d	p-$CH_3C_6H_4$[a]	91[b]	88–90 (hexane)	$C_{13}H_{14}O_2$ (202.2)

[a] New compound. [b] Ph_3P/CCl_4. [c] Ph_3P/CBr_4–ether. [d] Satisfactory analytical data (±0.3% for C and H) were reported for all new compounds in the table.



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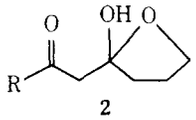

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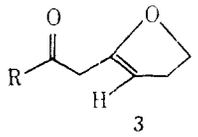

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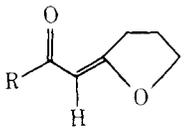


4

a, R = CH_3; b, R = C_2H_5; c, R = C_6H_5; d, R = p-$CH_3C_6H_4$

4-butyrolactone in ether. Isolation of the products was tedious, involving the copper salt method, and resulted in rather low yields. Heating the hydroxydiones **1** led to products of dehydration in 23–59% yield, presumably through the intermediate cyclic hemiketals **2**. The dehydration products were assigned the dihydrofuran structure **3** by earlier workers.[3]

Herein, we report an improved synthesis of 6-hydroxy-1,3-hexanediones (**1**) as well as a new synthesis of (*E*)-2-(acylmethylene)tetrahydrofurans (**4**) from **1**. The reactions of **4** with hydrazine to give pyrazoles and with primary aliphatic amines to give vinylogous amides are described.

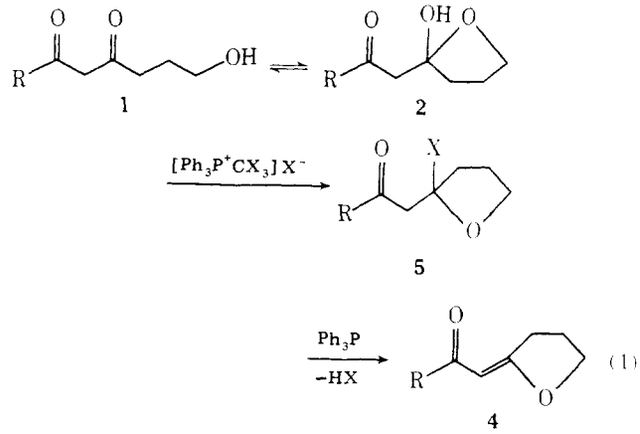
Results and Discussion

We improved the synthesis of the 6-hydroxy-1,3-hexanediones (**1**) by condensing methyl ketones with 4-butyrolactone in ether, using a catalytic amount of ethanol and an excess of sodium hydride,[4] followed by acidification with ammonium sulfate at 0 °C. The aryl-substituted compounds were obtained in satisfactory yield and in good purity by recrystallization of the crude product mixture. The alkyl-substituted products were purified by chromatography on silica gel. Physical data for these compounds are included in Table I.

When the 6-hydroxy-1,3-hexanediones (**1**) were treated with a slight excess of 2 equiv of triphenylphosphine either in carbon tetrachloride[5] or in ether with 2 equiv of carbon tetrabromide,[5] the dehydration products were obtained in nearly quantitative yields. These products were identical in all respects (^1H NMR, IR, UV) with the thermal dehydration products which were obtained by distillation of the hydroxyhexanediones. Appropriate experimental data are in Table I.

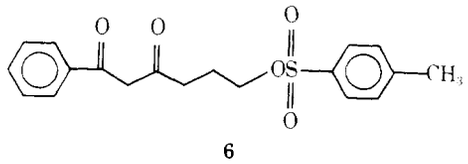
The spectral data and chemical behavior of the dehydration products indicate the (*E*)-2-(acylmethylene)tetrahydrofuran structure (**4**) as opposed to the dihydrofuran structure **3**. The IR spectra of these molecules show strong absorptions centered between 1650 and 1680 cm^{-1} which are consistent with an enone structure. The UV spectra give λ_{max} of 263 nm for the aliphatic and 289 nm for the aromatic (acylmethylene)-tetrahydrofurans (**4**), which indicate a conjugated chromophore. Although the *E* configuration about the carbon–carbon double bond might be assigned on the basis that unfavorable dipole interactions between the oxygens would be minimized,[6] the assignment is further substantiated by the ^1H NMR spectra for these compounds. The single vinyl proton appears as a triplet in each case with a coupling constant of 1.5 Hz. This proton is coupled to the allylic methylene protons which resonate at $\delta \sim 3.1$ as a doublet of triplets. The magnitude of the allylic coupling is best accommodated by the *E* configuration about the double bond, which approximates the *W* form configuration for long-range coupling.[7] The compounds **4** all gave parent ions in the mass spectrum as well as satisfactory analyses.

The formation of the (*E*)-2-(acylmethylene)tetrahydrofurans (**4**) is not simply a dehydration. A 1-equiv amount of triphenylphosphine oxide is formed during the reaction. No dehydration products are observed when the hydroxydiones **1** are treated with triphenylphosphine in ether. The use of 1 equiv of triphenylphosphine in carbon tetrachloride leads to less than 50% reaction. The results are most consistent with the mechanism shown in eq 1. The cyclic hemiketal is attacked



(1)

by the triphenylphosphine–carbon tetrahalide complex to give the halotetrahydrofuran **5** and triphenylphosphine oxide. The second equivalent of triphenylphosphine then acts as a base, initiating dehydrohalogenation to give **4**. The possibility that halogenation might occur initially at the 6 position of the hydroxyhexanedione with subsequent O-alkylation of the 1,3-diketone seems remote since tosylate **6** was recovered



6

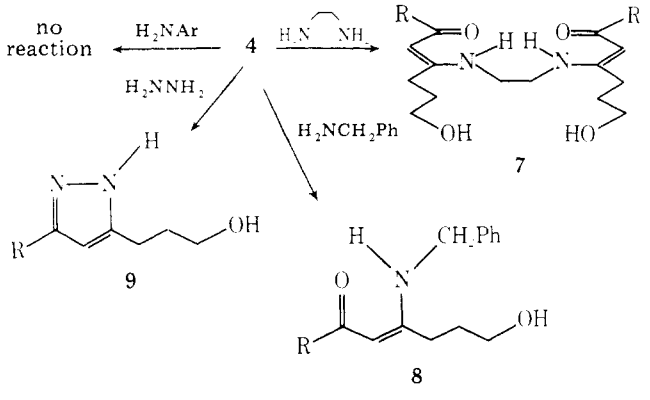
unchanged after refluxing with triphenylphosphine in carbon tetrachloride for extended periods of time.

Although the cyclic hemiketal **2** is implicated in the dehydration, the ^1H NMR spectra of the hydroxydiones **1** in chloroform indicate that these molecules are predominantly

acyclic. None of the cyclic hemiketal was detected, with a limit of detectability of ~5%. The alkyl-substituted hydroxydiones appear to be a mixture of enolic forms, whereas the aryl-substituted ones appear to be predominantly in one enolic form from ^{1}H NMR data.

When the (acylmethylene)tetrahydrofurans **4** were treated with 1 N sodium hydroxide at 40 °C, no hydrolysis could be detected by TLC. However, treatment with warm 10% hydrochloric acid gave slow hydrolysis to the 6-hydroxy-1,3-hexanediones (**1**).

We felt that the reaction of hydroxyhexanediones **1** with primary amines should give excellent yields of secondary vinylogous amides.[8] Reaction of the (acylmethylene)tetrahydrofurans **4** with 0.5 equiv of ethylenediamine in refluxing acetonitrile for 1.0 h gave the corresponding 2:1 addition products **7** in essentially quantitative yield. These compounds



are characterized in their ^{1}H NMR spectra by strongly hydrogen-bonded protons at δ 11.0 and a single vinylic resonance and in their UV spectra by strong absorptions around 322 nm for the aliphatic examples and at 350 nm for the aromatic compounds. The appropriate experimental data for these compounds are in Table II.

Treatment of the (acylmethylene)tetrahydrofurans **4** with benzylamine gave the appropriate addition products **8**. These compounds were isolated as glasses which decomposed upon attempted distillation. The ^{1}H NMR spectra of these compounds indicate strongly hydrogen-bonded protons at δ 11.0 which are coupled to the benzylic methylene protons (J = 6 Hz). The UV spectra indicate vinylogous amide chromophores (315 nm aliphatic, 340 nm aromatic). Table II contains the appropriate experimental data.

Treatment of the (acylmethylene)tetrahydrofurans **4** with hydrazine in hot ethanol gave the 3,4-substituted pyrazoles **9** in virtually quantitative yields. Table II contains the appropriate physical data for these compounds. This method of preparing 1-propanol-substituted pyrazoles appears to be superior to methods involving the 6-hydroxy-1,3-hexanediones (**1**).[9]

Surprisingly, the compounds **4** did not react readily with aromatic amines. Treatment of these molecules with aniline or *p*-anisidine gave no addition products after 12 h in refluxing acetonitrile.

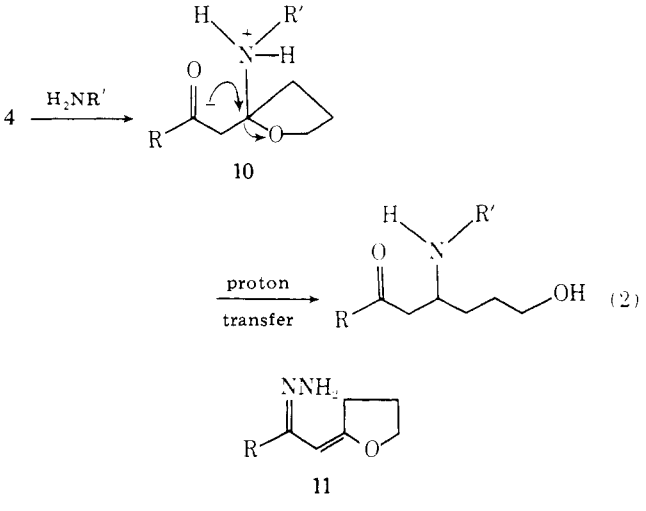
The reactions of (acylmethylene)tetrahydrofurans with primary aliphatic amines are Michael additions most likely occurring as shown in eq 2. The initial addition of the amine to **4** would give intermediate **10**. The zwitterionic intermediate **10** should readily ring open with subsequent proton transfer to give the observed products. For the reaction of **4** with hydrazine, it is not clear whether Michael addition occurs first followed by dehydration to give pyrazoles or whether intermediate **11** is first formed followed by Michael addition.

The (acylmethylene)tetrahydrofurans did not react with aromatic aldehydes under basic conditions, while the hydroxyhexanediones do undergo such coupling reactions. Dye

Table II. Physical Data of Addition Products 7, 8, and 9

product[a]	R	yield, %	mp, °C	molecular formula[b]
7a	CH_3	94	144.5–145.5	$C_{16}H_{28}N_2O_4$ (312.4)
7b	C_2H_5	88	98–98.5	$C_{18}H_{32}N_2O_4$ (340.5)
7c	C_2H_5	89	133–136	$C_{26}H_{32}N_2O_4$ (436.5)
7d	*p*-$CH_3C_6H_4$	91	171–172	$C_{28}H_{36}N_2O_4$ (464.6)
8a	C_2H_5	95		$C_{15}H_{21}NO_2$ (247.3)
8b	C_6H_5	96		$C_{19}H_{21}NO_2$ (295.4)
8c	*p*-$CH_3C_6H_4$	96		$C_{20}H_{23}NO_2$ (309.4)
9a	C_6H_5	90	96–97.5	$C_{12}H_{14}N_2O$ (202.3)
9b	*p*-$CH_3C_6H_4$	91	129–131	$C_{13}H_{16}N_2O$ (216.3)

[a] All products are new compounds. [b] Analytical data (C, H, and N) were reported for compounds **7a–d** and **9a,b**. Mass-spectral parent peaks were reported for **8a–c**.



(2)

formation can be observed when the hydroxyhexanediones and aromatic aldehydes are treated with piperidine in ethanol.[10] The (acylmethylene)tetrahydrofurans thus function both as a synthetic equivalent to as well as a protected form of 6-hydroxy-1,3-hexanediones.

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are corrected. Boiling points are uncorrected. ^{1}H NMR spectra were run on Varian T-60 and EM390 instruments. IR spectra were run on a Perkin-Elmer 137 spectrophotometer. UV spectra were run on a Cary 17 instrument. Mass spectra were recorded on a Du Pont 21-491 instrument. Microanalyses were performed on a Perkin-Elmer 240 C, H, and N analyzer.

General Procedure for 6-Hydroxy-1,3-hexanediones (1). A 50% suspension of sodium hydride in mineral oil (4.8 g, 0.10 mol) was washed with two 100-mL portions of hexane and dried under a stream of nitrogen. The reaction vessel was charged with 300 mL of ether, and 0.25 mL of ethanol was added dropwise. 4-Butyrolactone (4.5 g, 0.052 mol) was added in one portion. The resulting mixture was cooled to 15 °C in a water bath. The methyl ketone (0.050 mol) in 50 mL of ether was added dropwise over 1 h. The resulting mixture was allowed to stir for 24 h at room temperature. The reaction mixture was cooled to 0 °C, and 5 mL of ethanol was added to destroy excess sodium hydride. Cold 10% ammonium sulfate solution (100 mL) was added. The organic layer was separated, dried over sodium sulfate, and concentrated. Recrystallization of the aromatic products from hexane gave pure compounds. Alternatively, chromatography of the reaction

Table III. Spectral Data for 6-Hydroxy-1,3-hexanediones (1) and Dehydration Products (4)

product	MS *m/e* (M^+)	UV (C_2H_5OH) λ_{max} (log ϵ), nm	IR, cm^{-1}	^1H NMR ($CDCl_3$, 60 MHz) δ, ppm
1a	144		3400, 2950, 1710, 1610	5.43 (s, vinyl proton of enol), 3.60 (t, 2 H, J = 6 Hz), 3.55 (s, $-C(=O)CH_2C(=O)$), 2.0 –2.8 (m, 2 H), 2.05 (s, 3 H), 1.88 (m, 2 H)
1b	158		3400, 2950, 1730, 1610	5.53 (s, vinyl proton of enol), 3.63 ($-CH_2OH$ and $-C(=O)-CH_2C(=O)-$), 2.45 (m, CH_3CH_2-), 1.87 (m, 2 H), 1.15 (t, 3 H, J = 6 Hz), 1.10 (m, 2 H)
1c	206		3350, 1605, 1570	7.77 (m, 2 H), 7.42 (m, 3 H), 6.13 (s, 1 H), 3.68 (t, 2 H, J = 6 Hz), 2.55 (t, 2 H, J = 7 Hz), 1.92 (m, 2 H)
1d	220		3400, 2950, 1600	7.63 (d, 2 H, J = 8 Hz), 7.10 (d, 2 H, J = 8 Hz), 6.10 (s, 1 H), 3.65 (t, 2 H, J = 6 Hz), 2.03 (s, 3 H), 2.50 (t, 2 H, J = 7 Hz), 1.80 (m, 2 H)
4a	126	263 (4.23)	3000, 1660, 1570, 1130	5.70 (t, 1 H, J = 1.5 Hz), 4.17 (t, 2 H, J = 7 Hz), 3.07 (d × t, 2 H, J = 1.5, 7 Hz), 2.40–1.80 (m, 2 H), 2.07 (s, 3 H)
4b	140	263 (4.11)	3000, 1680, 1600, 1110	5.72 (t, 1 H, J = 1.5 Hz), 4.17 (t, 2 H, J = 7 Hz), 3.10 (d × t, 2 H, J = 1.5, 7 Hz), 2.60–1.70 (m, 4 H), 1.10 (t, 3 H, J = 7 Hz)
4c	188	289 (4.28) 248 (3.95)	1670, 1600, 1590, 1580, 1250	7.80 (m, 2 H), 7.27 (m, 3 H), 6.43 (t, 1 H, J = 1.5 Hz), 4.17 (t, 2 H, J = 7 Hz), 3.20 (d × t, 2 H, J = 1.5, 7 Hz), 2.00 (quin, 2 H, J = 7 Hz)
4d	202	289 (4.38) 261 sh (4.08)	3000, 1650, 1615, 1575, 1100	7.67 (d, 2 H, J = 8 Hz), 7.05 (d, 2 H, J = 8 Hz), 6.40 (t, 1 H, J = 1.5 Hz), 4.17 (t, 2 H, J = 7 Hz), 3.22 (d × t, 2 H, J = 1.5, 7 Hz), 2.35 (s, 3 H), 2.03 (quin, 2 H, J = 7 Hz)

Table IV. Spectral Data for Addition Products 7, 8, and 9

product	MS *m/e* (M^+)	UV[a] (log ϵ), nm	IR, cm^{-1}	^1H NMR (60 MHz, $CDCl_3$) δ,
7a	312	321 (4.53)	3350,[b] 2900, 1600, 1560, 1300	10.7[d] (br m, 2 H), 4.95 (s, 2 H), 4.42 (br s, 2 H), 3.45 (m, 8 H), 2.20 (m, 4 H), 1.90 (s, 6 H) 1.63 (m, 4 H)
7b	340	323 (4.41)	3400,[b] 2950, 2900, 1600, 1550, 1290	11.0 (br t, 2 H, J = 6 Hz), 5.02 (s, 2 H), 3.57 (m, 8 H), 2.97 (br s, 2 H), 2.27 (m, 8 H), 1.75 (m, 4 H), 1.08 (t, 6 H, J = 6 Hz)
7c	436	348 (4.57) 241 (4.23)	3000,[b] 1575, 1565, 1500	11.7 (br m, 2 H), 7.78 (m, 4 H), 7.38 (m, 6 H), 5.73 (s, 2 H), 3.65 (m, 8 H), 3.10 (br s, 2 H), 2.50 (m, 4 H), 1.80 (m, 4 H)
7d	464	352 (4.58) 252 (4.20)	3400,[b] 2950, 2850, 1580, 1530	11.7 (br m, 2 H), 7.65 (d, 4 H, J = 8 Hz), 7.10 (d, 4 H, J = 8 Hz), 5.67 (s, 2 H), 3.62 (m, 8 H), 3.10 (br s, 2 H), 2.50 (m, 4 H), 2.05 (s, 6 H), 1.78 (m, 4 H)
8a	247	315 (4.31) 242 (4.15)	3400,[c] 2950, 1600, 1550	11.2 (br s, 1 H), 7.28 (s, 5 H), 5.03 (s, 1 H), 4.47 (d, 2 H, J = 6 Hz), 3.62 (t, 2 H, J = 6 Hz), 3.20 (br s, 1 H), 2.28 (q, 2 H, J = 7 Hz), 2.28 (m, 2 H), 1.80 (m, 2 H), 1.10 (t, 3 H, J = 7 Hz)
8b	295	338 (4.48) 241 (4.41)	3400,[c] 2950, 1600, 1550	11.7 (br t, 1 H, J = 6 Hz), 7.77 (m, 2 H), 7.27 (m, 3 H), 7.23 (s, 5 H), 5.70 (s, 1 H), 4.50 (d, 2 H, J = 6 Hz), 3.55 (t, 2 H, J = 6 Hz), 3.23 (br s, 1 H), 2.40 (m, 2 H), 1.80 (m, 2 H)
8c	309	344 (4.64) 249 (4.23)	3400,[c] 2950, 1600, 1550	11.7 (br t, 1 H, J = 6 Hz), 7.72 (d, 2 H, J = 8 Hz), 7.27 (s, 5 H), 7.10 (d, 2 H, J = 8 Hz), 5.75 (s, 1 H), 4.25 (d, 2 H, J = 6 Hz), 3.53 (t, 2 H, J = 6 Hz), 3.27 (br s, 1 H), 2.00 (s, 3 H), 2.07 (t, 2 H, J = 6 Hz), 1.77 (m, 2 H)
9a	202	249 (4.57) 335 (2.11)	3310,[b] 3000, 2900, 1580, 1570, 1450, 1060	7.58[e] (m, 2 H), 7.22 (m, 3 H), 6.32 (s, 1 H), 3.57 (t, 2 H, J = 6 Hz), 2.73 (t, 2 H, J = 7 Hz), 1.85 (m, 2 H)
9b	216	252 (4.60) 320 (1.70)	3320,[b] 2950, 1590, 1450, 1060	7.63[d] (d, 2 H, J = 8 Hz), 7.17 (d, 2 H, J = 8 Hz), 6.38 (s, 1 H), 4.47 (brt, 1 H), 3.52 (t, 2 H, J = 6 Hz), 2.65 (t, 2 H, J = 7 Hz), 1.98 (s, 3 H), 1.77 (m, 2 H)

[a] CH_3OH. [b] KBr. [c] Film. [d] Me_2SO-d_6. [e] CD_3CN.

mixtures on silica gel, eluting with 1:1 (v/v) hexane/ether, readily purifies the reaction mixtures (see Table III for spectral data).

General Procedure for Triphenylphosphine/Carbon Tetrachloride Dehydrations. The hydroxydione 1 (5.0 mmol) was dissolved in 40 mL of carbon tetrachloride. Triphenylphosphine (2.88 g, 0.011 mol) was added. The resulting solution was allowed to stir at room temperature for 24 h. The reaction mixture was concentrated and purified by chromatography on silica gel, eluting with 2:1 (v/v) hexane/ether. The aromatic (acylmethylene)tetrahydrofurans 4 were purified by recrystallization from hexane and the aliphatic compounds by distillation (see Table III).

General Procedure for Triphenylphosphine/Carbon Tetrabromide Dehydrations. The hydroxydione (5.0 mmol) and triphenylphosphine (2.88 g, 0.011 mol) were dissolved in 40 mL of ether. Carbon tetrabromide (3.32 g, 0.100 mol) was added, and the resulting mixture was allowed to stir for 24 h at room temperature. Chromatography of the reaction mixture on silica gel, eluting with 2:1 (v/v) hexane/ether, gave the (acylmethylene)tetrahydrofurans 4 (see Table III).

General Procedure for Ethylenediamine Additions. A solution of (*E*)-2-(acylmethylene)tetrahydrofuran 4 (0.010 mol) and ethylenediamine (0.30 g, 0.005 mol) in 15 mL of acetonitrile was warmed at reflux for 1 h. The solvent was removed in vacuo. The residual crystalline solid was recrystallized from 1:1 (v/v) methylene chloride/hexane to give a white solid, 7 (see Table IV).

General Procedure for Benzylamine Additions. A solution of (*E*)-2-(acylmethylene)tetrahydrofuran 4 (0.010 mol) and benzylamine (1.2 g, 0.011 mol) in 15 mL of acetonitrile was warmed at reflux for 3 h. The solvent was removed in vacuo, and the residual oil was taken up in 25 mL of methylene chloride. The resulting solution was washed with 10% hydrochloric acid and saturated sodium bicarbonate, dried over sodium sulfate, and concentrated in vacuo to give 8 as a glass (see Table IV).

General Procedure for Hydrazine Additions. To a solution of (*E*)-2-(acylmethylene)tetrahydrofuran 4 (1.0 mol) in 3 mL of ethanol was added 0.5 g (10 mmol) of hydrazine hydrate. The temperature of the resulting solution was maintained at 50 °C for 0.5 h. The reaction mixture was poured into 30 mL of cold water, precipitating a

white solid. Recrystallization from ethanol gave the pyrazoles **9** as white solids (see Table IV).

1-Phenyl-6-hydroxy-1,3-hexanedione *p*-Toluenesulfonate (6). *p*-Toluenesulfonyl chloride (2.10 g, 5.50 mmol) was added to hydroxydione **1c** (1.03 g, 5.00 mmol) in 10 mL of cold pyridine. The resulting solution was allowed to stand for 16 h at 0 °C. The reaction mixture was poured into 100 mL of ice water. The product was extracted with methylene chloride (2 × 30 mL). The combined methylene chloride extracts were washed with cold 10% hydrochloric acid (50 mL) and saturated sodium bicarbonate, dried over sodium sulfate, and concentrated. The crude crystalline product was recrystallized twice from 4:1 (v/v) hexane/ether to give 1.13 g (63%) of tosylate **6**: mp 84–86 °C; ^{1}H NMR ($CDCl_3$) δ 7.83 (m, 4 H), 7.37 (m, 5 H), 6.10 (s, 1 H), 4.10 (t, 2 H, J = 6 Hz), 2.52 (t, 2 H, J = 6 Hz), 2.38 (s, 3 H), 2.03 (quin, 2 H, J = 6 Hz); IR (KBr) 3350, 1600, 1570, 1350, 925 cm^{-1}; MS m/e 360.

Anal. Calcd for $C_{19}H_{20}O_5S$: C, 63.3; H, 5.6; S, 8.9. Found: C, 63.2; H, 5.8; S, 9.1.

Registry No.—**1a,** 57245-94-0; **1b,** 69706-62-3; **1c,** 23894-54-4; **1d,** 69745-21-7; **4a,** 69706-63-4; **4b,** 69706-64-5; **4c,** 69706-65-6; **4d,** 69706-66-7; **6,** 69706-67-8; **7a,** 69766-11-6; **7b,** 69706-68-9; **7c,** 69706-69-0; **7d,** 69706-70-3; **8a,** 69706-71-4; **8b,** 69706-72-5; **8c,** 69706-73-6; **9a,** 69706-74-7; **9b,** 69745-22-8; CH_3COCH_3, 67-64-1; $CH_3COCH_2CH_3$, 78-93-3; $CH_3COC_6H_5$, 98-86-2; *p*-$CH_3C_6H_4COCH_3$, 122-00-9; 4-butyrolactone, 96-48-0; ethylenediamine, 107-15-3; benzylamine, 100-46-9; hydrazine, 302-01-2.

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General Synthesis of Hydrocarbon-Soluble Porphyrins

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1,3,5,7-Tetramethyl-2,4,6,8-tetra(*n*-pentyl)porphyrin (**2**) and 2,4,6,8-tetra(*n*-heptyl)-1,3,5,7-tetramethylporphyrin (**3**) were synthesized in good yield by a general route from benzyl 3-formyl-2,4-dimethylpyrrole-5-carboxylate (**4**); the final porphyrin cyclization was brought about by self-condensation of the appropriate pyrromethene salt in hot formic acid. Porphyrins **2** and **3** were shown to be approximately 14 times more soluble in toluene than is etioporphyrin I [2,4,6,8-tetraethyl-1,3,5,7-tetramethylporphyrin (**20**)] and to have considerably lower melting points [**2,** 199 °C; **3,** 124 °C; **20,** >300 °C]. Activation of the porphyrins **2** and **3** for future attachment of thiolate and imidazole-bearing substituents at the meso (methine) positions was carried out by Vilsmeier formylation [of the copper(II) complex], reduction with sodium borohydride, and then treatment of the resulting hydroxymethylporphyrins with acetic anhydride in pyridine to give the electrophilic acetoxymethylporphyrin derivatives.

In connection with synthetic approaches to cytochrome P450[1] and T-form hemoglobin[2] models bearing covalently appended apical ligands, we required porphyrin substrates which, as the hemes, would be soluble in solvents such as benzene or toluene. Moreover, for the cytochrome model, we desired that the complex should have a low oxidation potential and therefore that the target molecule should not only have eight electron-releasing peripheral substituents but also that the attached long-chain apical ligand should be joined to the porphyrin via an electron-releasing meso (methine) functionality. Our requirements seemed satisfied by the generic porphyrin **1** in which R^1 would be a long alkyl side chain and R^2 the thiolate or imidazole-bearing substituent, joined directly to the porphyrin by way of a sp^3-hybridized carbon atom. One other point of strategy was apparent; since, for simplicity, we planned to attach the meso substituent after porphyrin formation, we had to choose the "type I"[3] substituent orientation so that only one meso-substituted product would arise at that time. In this paper, we describe successful and efficient general syntheses of two such porphyrins (**2** and **3**) and report on their comparative solubility characteristics in toluene and on developmental work on elaboration of the meso (R^2 in **1**) substituent.

Results and Discussion

In order to afford maximum variability with respect to the alkyl side chains (R^1 in **1**), we chose to synthesize our lipophilic porphyrin substrates using the 3-formylpyrrole **4** as the key building block. We reasoned that Wittig-type reactions of the formyl group with long-chain alkyl phosphonium salts would provide a versatile entry into the required building blocks after catalytic hydrogenation of the corresponding unsaturated pyrroles **5**. The anticipated products **6** could then be directly inserted into the type I porphyrin synthesis developed earlier.[4]

Reaction between *tert*-butyl acetoacetate and oximinobenzyl acetoacetate under standard Knorr conditions gave the pyrrole mixed ester **7** in 40% yield. In trifluoroacetic acid, the *tert*-butyl ester was deprotected to give a quantitative yield of the pyrrole-3-carboxylic acid **8**, which was decarboxylated in 75% yield using the copper–quinoline procedure,[5] to afford the 3-unsubstituted pyrrole **9**. Gatterman formylation of **9** was unsatisfactory, but a 95% yield of the 3-formylpyrrole **4** was obtained when the Vilsmeier procedure ($POCl_3$/DMF) was used.

At this point, the synthesis diverged such that our final porphyrins might bear five or seven carbons in their alkyl side chains. These particular lengths were chosen arbitrarily but so as to give us a feel for the chain length which would typically give us a hydrocarbon-soluble and also crystalline porphyrin. Clearly, a tetramethyltetraalkylporphyrin with very long alkyl groups (C_{10-20}) would be lipophilic, but we also wished to handle crystalline porphyrins and intermediates for characterization purposes. Our prediction[6] was that C_7 side chains

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