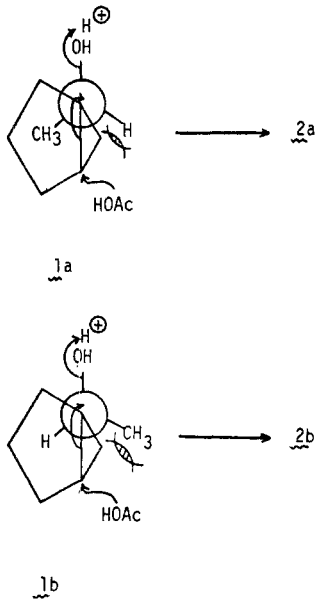

Figure 2. Newman projections of a concerted reaction.

could be separated from an almost equal quantity of an inseparable mixture of **2b** and acetates **1g** and **1h**. The 300-MHz ^1H NMR analyses clearly showed that >50% of the mixed fraction obtained from **1a** and ≤50% of the mixed fraction from **1b** were cyclopropyl acetates **1g** and **1h**.

Time and Temperature Studies of the Acetolysis Reaction. Solutions of 3 μL of compound in 10 μL of glacial acetic acid were submitted to various temperature and time intervals. They were then quenched in aqueous sodium bicarbonate solution, extracted, and analyzed by thin-layer chromatography or analytical high-pressure LC using a suitable hexane–ether elution system. In this way it was found that at 25 °C **1a** and **1b** were stable to glacial acetic acid for up to 8 h.

The product ratio of acetates obtained by heating either **1a** or **1b** in glacial acetic acid at 110–11 °C over intervals between 10 min and 16 h were not significantly different.

The products **2a** and **2b** were not interchanged significantly over a period of 24 h at 110 °C in glacial acetic acid.

(*E*)-3-Ethylidenecyclohexanol 3,5-Dinitrobenzoate. A solution of 290 mg of **2a** and 180 mg of potassium hydroxide in 4 mL of methanol was refluxed under nitrogen for 1.5 h. The reaction mixture was concentrated to dryness and treated with water. The product was extracted into ether, washed with water (4×), dried ($MgSO_4$), and isolated as a liquid. This material was eluted through 18 g of silica gel to give 88 mg of 3-ethylidenecyclohexanol: ^1H NMR ($CDCl_3$, 60 MHz) 5.24 (1 H, q, J = 7 Hz, HC=C), 3.69 (1 H, heptet, CHO), 2.55 (1 or 2 H, narrow m, allylic CH), 1.60 ppm (3 H, d, J = 7 Hz, CH_3CH).

A solution of this material in 3.0 mL of pyridine was treated with 175 mg of 3,5-dinitrobenzoyl chloride at −5 °C for 20 min and then stirred at 25 °C for 24 h. Water was added and the mixture extracted with ether. The organic layer was washed successively with aqueous $NaHCO_3$ solution (3×), water, 1% hydrochloric acid, water, and saturated NaCl. After being dried ($MgSO_4$) and concentrated, the resulting heavy oil was eluted through silica gel with 1:1 hexane–ether. The product crystallized from ethyl acetate to give 39 mg: mp 56–57 °C; mass spectrum, *m/e* 195, 149, 108 (base), 93, 79.

Registry No. (±)-**1a**, 71129-81-2; (±)-**1b**, 71183-85-2; (±)-**1c**, 71129-82-3; (±)-**1d**, 71183-86-3; (±)-**1e**, 71129-83-4; (±)-**1f**, 71183-87-4; (±)-**1g**, 71129-84-5; (±)-**1h**, 71183-88-5; (±)-**2a**, 71129-85-6; (±)-**2b**, 71129-86-7; (±)-1-acetylbicyclo[3.1.0]hexane, 71129-87-8; 1-acetylcyclopentene, 16112-10-0; (±)-(*E*)-3-ethylidenecyclohexanol 3,5-dinitrobenzoate, 71129-88-9; (±)-(*E*)-3-ethylidenecyclohexanol, 71129-89-0; α-naphthyl isocyanate, 86-84-0.

Supplementary Material Available: A table of fractional coordinates and thermal factors (1 page). Ordering information is given on any current masthead page.

Synthesis of Naturally Occurring Furan Fatty Acids

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Several years ago a novel group of fatty acids with a furan ring in their structure was reported from lipids of fish[1] and, very recently, also from latex of *Hevea brasiliensis*.[2] In contrast to an earlier reported furan fatty acid from *Exocarpus* seed oil,[3] these acids are tri- and tetrasubstituted furan compounds. In fish lipids, 11-(5-pentyl-3,4-dimethyl-2-furyl)undecanoic acid (**8**) and 11-(5-pentyl-3-methyl-2-furyl)undecanoic acid (**14**) are prominent examples. The furan fatty acids of fish may also vary in chain lengths of alkyl and alkylcarboxyl substituents. With furan being the common structural feature, the abbreviations F_1, F_2, . . . were used for them, with F_6 and F_5, respectively, being those named above.[1b]

The widespread occurrence and often high levels of F acids in liver and testes lipids of fish, their preferential esterification to cholesterol, and the apparent correlation of amounts to reproduction[1a,c] make desirable further biochemical and biological investigations. For such a purpose, syntheses of F_6 and of F_5 were undertaken. The syntheses verify the structures of the biological materials which had been deduced by degradation and spectrometric methods.[1b] They open the way to a variety of these tri- and tetrasubstituted furan compounds, including minor components in the group of F acids which so far have been identified only by GLC–MS.[4]

Syntheses of furan-type acids with an alkylcarboxyl and an alkyl group in ring positions 2 and 5, respectively, have been reported. However, the synthetic acids were either lacking the methyl group(s) at the furan ring[5] or were isomers with regard to the natural furan acids.[5d]

For the synthesis of F_6 **8** (Scheme I), 3,4-bis(acetoxymethyl)furan (**1**) was chosen as the starting material. Condensation with valeric acid anhydride[6] yielded the butyl ketone **2**, and its reduction with hydrazine gave the pentylfuran diol **3**. Conversion of the hydroxymethyl to

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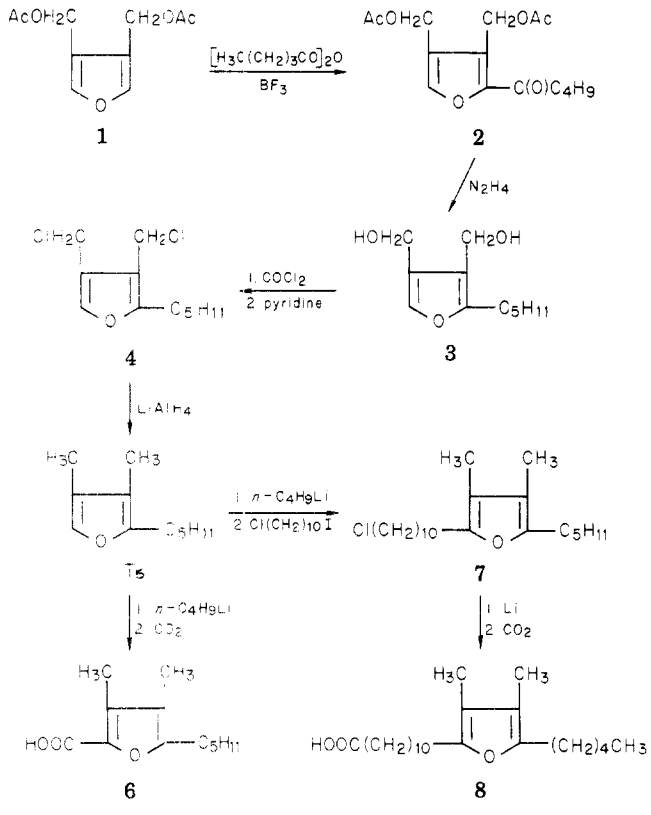
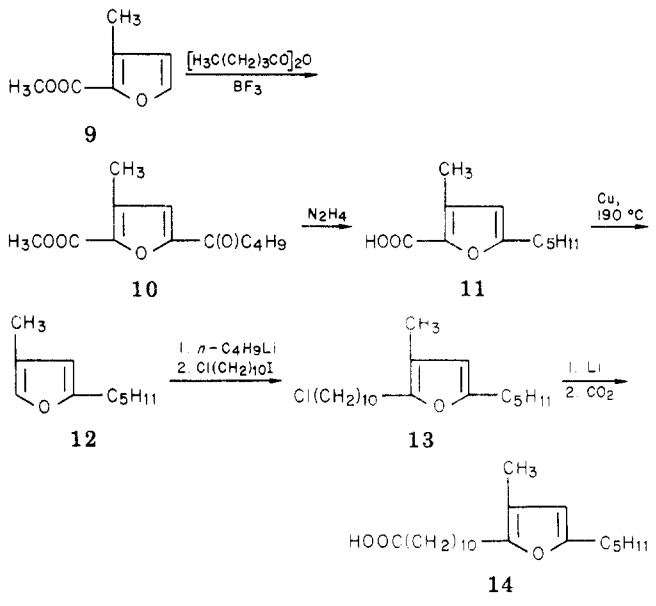
(6) (a) J. V. Heid and R. Levine, *J. Org. Chem.*, **13**, 409 (1948); (b) R. Levine, J. V. Heid, and M. W. Farrar, *J. Am. Chem. Soc.*, **71**, 1207 (1949).

0022-3263/79/1944-3420$01.00/0

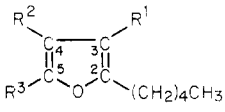
Scheme I



Scheme II



Scheme III



3, $R^1 = CH_2OH$; $R^2 = CH_2OH$; $R^3 = H$
5, $R^1 = CH_3$; $R^2 = CH_3$; $R^3 = H$
8, $R^1 = CH_3$; $R^2 = CH_3$; $R^3 = (CH_2)_{10}COOCH_3$
12, $R^1 = H$; $R^2 = CH_3$; $R^3 = H$
14, $R^1 = H$; $R^2 = CH_3$; $R^3 = (CH_2)_{10}COOCH_3$

methyl groups was planned via the dichloro compound **4** which due to conjugation to the heteroaromatic ring should be reduced by $LiAlH_4$ without destruction of the ring.

Attempts to obtain **4** from **3** by the usual methods with thionyl or oxalyl chloride gave unsatisfactory results. However, quality and yield of **4** were satisfactory when phosgene was used to replace the hydroxyl groups by chlorine. The use of phosgene for such reactions is unusual.[7] Most likely, an intermediate bis(chloroformate) is decomposed similar to the pyridine-initiated decomposition of chloroglyoxalates, obtained from oxalyl chloride, to alkyl chlorides[8] or of fluoroformate esters to alkyl fluorides.[9] As anticipated, **4** was easily reduced to the furan **5**. It underwent metal interchange with *n*-butyllithium[5e,10] monitored by carbonation of an aliquot and quantitation of acid **6**.[11] The Li derivative of **5** reacted with 1-chloro-10-iododecane[12] to give ω-chloroalkylfuran **7**. This was converted to the desired acid **8** by reaction with Li metal and subsequent carbonation. In a variation of the latter reactions, 1-chloro-6-iodohexane was used to obtain 7-(5-pentyl-3,4-dimethyl-2-furyl)heptanoic acid. This acid is a likely metabolite of F_6 and F_4 and can serve as precursor for synthesis of these acids labeled with ^{14}C (D. M. Sand and H. Schlenk, unpublished).

For the synthesis of F_5 **14** (Scheme II), 3-methyl-2-furoate[13] **9** was used, condensing it with valeric acid anhydride to obtain unambiguous placement of the methyl group in reference to the alkyl chain. Ketoester **10** could be obtained pure, but the yield was less than that of the corresponding ketone **2** in the synthesis of F_6 or that reported in the literature for a similar reaction.[14] The ketoester **10** was reduced and concurrently saponified to the acid **11** which by decarboxylation yielded the dialkylfuran **12**. Quinoline and copper are recommended for decarboxylation of **9**,[15] but with **11** the presence of quinoline did not facilitate the decarboxylation and made the purification of **12** more difficult. The furoic acid **13** and the desired furan acid **14** were prepared from **12** as outlined for **6** and **8** from **5**.

The identities of **8** and **14** with F_6 and F_5 methyl esters, respectively, were established by comparison of mass and other spectral data and of GLC and TLC properties.

Alternate methods for substitution of the furan ring by the alkylcarboxyl chain were investigated. Reaction of vinyl ω-alkylcarboxymethyl ketones with furan or α-alkylfurans[5h,i] was tested using vinyl 7-heptylcarboxylmethyl ketone[5i] and **5** for preparation of **8**, but the yield of pure product was disappointingly low. The same was experienced in a different approach[5l,m] where dicarboxylic acid anhydrides[16] were subjected to condensation with **12** for preparation of F_5-type acids. The method involving lithium compounds appears preferable for introducing the alkylcarboxyl chain into **5** or **12**.

It is well known that reactivity of the furan ring depends greatly on the type and number of substituents.[17] This

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Table I. Chemical Shifts in ^{13}C NMR Spectra of 2-Pentylfuran and Substituted 2-Pentylfurans[a]

	compd					
carbon	3[b]	5	8	12	14	2-pentylfuran[c]
2	154.3	151.5	148.4	156.7	153.5	156.6
3	118.3	114.4	114.4	107.5	107.7	104.5
4	124.9	121.0	114.4	120.4	113.9	110.0
5	138.1	136.3	148.4	137.2	149.5	140.6
1'[d]	31.4	31.5	31.5	31.5	31.5	31.4
2'[d]	28.3	28.3	*e*	28.1	*e*	28.0
3'[d]	26.2	26.3	26.1	27.8	26.0	27.8
R[1][f]	55.5	8.4	8.3			
R[2][g]	55.1	7.9	8.3	9.8	9.9	
R[3][h]			31.5		31.5	

[a] Proton-decoupled spectra of 1-[3,4-bis(hydroxymethyl)-2-furyl]pentane (3), 1-(3,4-dimethyl-2-furyl)pentane (5), 11-(5-pentyl-3,4-dimethyl-2-furyl)undecanoic acid (8), 4-methyl-2-pentylfuran (12), and 11-(5-pentyl-3-methyl-2-furyl)undecanoic acid (14). [b] Assignments verified by off-resonance decoupling. [c] Assignments based on values for 2-methylfuran (T. F. Page Jr., T. Alger, and D. M. Grant, *J. Am. Chem. Soc.*, 87, 5333 (1965)). [d] All compounds, carbons of C-2 pentyl moiety: 1', CH_2 adjacent (α) to C-2; 2', β-CH_2; 3', γ-CH_2. Additional signals: 4' CH_2, δ 22.4-22.5 and 5' CH_3, δ 13.9-14.0. Assignment of signals based on the additivity rule for alkanes. [e] Unresolved signal not observable due to the overlapping methylene envelope $(CH_2)_n$ signal. [f] Compound 3, R[1] = CH_2OH; compounds 5 and 8, R[1] = CH_3. [g] Compound 3, R[2] = CH_2OH; compounds 5, 8, 12, and 14, R[2] = CH_3. [h] Compounds 8 and 14, R[3] = 1'' CH_2 adjacent to C-5*. Additional signals: 2'', 4''-8'' CH_2 (methylene envelope), δ 28.4-29.5; 3'' CH_2, δ 26.0-26.3; 9'' CH_2, δ 25.0; 10'' CH_2, δ 34.2; 11'' CO δ 174.2; ester CH_3, δ 51.3.

was found also for the different type F acids in hydrogenation, hydrogenolysis, and hydrolysis[1b] and was encountered in reactions described here. In addition, it may be mentioned that F esters of the dimethyl-substituted type are markedly more subject to autoxidation and polymerization than those of the monomethyl type.

The compounds listed in Scheme III were characterized by ^{13}C NMR, and these data are compiled in Table I together with data for 2-pentylfuran[18] for discussion of substituent effects in the furan ring. A methyl group at ring C-4 as in 12 produces an expected α-deshielding effect, 10.4 ppm. The β effects at C-3 and C-5 are similar in value, 3.0 and 3.4 ppm, but are of opposite sign. Such effects are also caused by the additional methyl group C-3 of 5. In this compound, the α-deshielding effect at C-3 is 6.9 ppm, and the β effects on C-2 and on C-4 are again of opposite sign. The C-2 is shielded by 5.2 ppm to δ 151.5, whereas C-4 is deshielded by 0.6 ppm. The deshielding β effects at positions C-3 and C-4 of the furan ring suggest that the methyl groups cause deformation of the ring. This is in agreement with differences of the UV spectra of 3,4-dimethyl-2,5-disubstituted and 2,5-disubstituted furans. The molar absorptivity of 8, 7400 at 227 nm,[1b] is reduced and shifted when compared to that of the disubstituted reference compound, 8990 at 220 nm,[1b] without 3,4-dimethyl substitution.

In addition, ^{13}C NMR reveals a steric effect when a methyl group and an alkyl chain are substituents on adjacent furan ring carbons. In 2-pentylfuran and in 4-methyl-2-pentylfuran 12, the signals for 2' and 3' CH_2 of the pentyl group are δ 28.1 and 27.8, respectively. The remaining compounds of Table I have the substituents on adjacent carbons, and there the 3' CH_2 signals are shielded to δ 26.1-26.3. Mutual shielding is also observed for hydroxymethyl and for the methyl groups in C-3 and C-4 positions.

The apparent steric compression effects suggest additional strain in the furan ring system which may contribute to the differences in reactivity of the furan compounds having various methyl substitution in C-3 and C-4.

Experimental Section

General. Preparations were handled under nitrogen, except for reactions with lithium organic compounds which were carried out under argon. Diethyl ether and benzene were dried over sodium ribbon, and THF was distilled over $LiAlH_4$[19] immediately before use. Organic solvents wet from aqueous extractions were dried over Na_2SO_4 and evaporated under reduced pressure at <40 °C.

TLC and GLC were extensively used for evaluating the course of reactions and the purity of products. TLC was done on 0.5-mm silica gel H plates with developing solvents hexane–diethyl ether–chloroform–methanol–acetic acid (80:20:10:5:1, by volume) or hexane–diethyl ether–acetic acid (85:15:1). Spots were detected by charring with CrO_3–H_2SO_4. Preparative TLC (PLC) was carried out on layers, 5 mm thick, of the same adsorbent with hexane–ether (85:15) as solvent. GLC was done in a Beckman GC-2 instrument with an H_2 flame detector in an aluminum column $^1/_8$ in. × 4 ft, packed with 3% OV-1 on Gas Chromosorb Q, 100–120 mesh at 190 °C; or in a Packard 427 instrument with H_2 flame detector and dual columns packed with 10% CS-5 on Chromosorb W-AW, 100–120 mesh, under temperature programming from 100–240 °C at 5 °C/min gradient. When necessary, methyl palmitate or stearate was used as internal standard for quantitation.

IR spectra were recorded with a Perkin-Elmer 21 spectrophotometer from liquid films between NaCl plates. NMR spectra were recorded with a Varian CFT-20 instrument at 79.54 MHz for ^1H and at 20 MHz for ^{13}C, using $CDCl_3$ as solvent. Chemical shifts are expressed in parts per million (δ) downfield from Me_4Si, with designations as described in Scheme III and Table I. Low-resolution MS was carried out in an LKB 9000 gas chromatography–mass spectrometer with GLC conditions similar to those above, at 290 °C ion source temperature and at 20 eV ionization potential.

Elemental analyses were carried out by M-H-W Laboratories, Phoenix, Ariz.

1-[3,4-Bis(acetoxymethyl)-2-furyl]pentanone (2). Valeric acid anhydride (21.0 g, 0.11 mol) and 3,4-bis(acetoxymethyl)furan (1) (20.0 g, 0.09 mol) were dissolved in 20 mL of benzene. BF_3–etherate (3 mL) was added dropwise under stirring at room temperature, and stirring was continued for 5 h. The reaction was stopped by addition of 25 mL of H_2O. Concentration of the organic phase gave a brown oil to which 20 mL of methanol was added. At 0 °C, 15% aqueous NH_3 was added in small portions, with stirring, until the solution remained alkaline for more than 0.5 h, indicating complete hydrolysis of unreacted valeric acid anhydride. After the addition of 50 mL of H_2O, the mixture was extracted with ether (3 × 150 mL). The combined ether extract was thoroughly washed with aqueous NH_3 and then with H_2O. Evaporation of the solvent left a residue of 25 g of crude ketone 2: MS *m/e* (rel intensity) 296 (M^+, 0.9), 254 (49), 194 (100), 193 (41), 134 (33).

1-[3,4-Bis(hydroxymethyl)-2-furyl]pentane (3). Crude ketone 2 (25 g) was dissolved in 250 mL of diethylene glycol. Hydrazine hydrate (21.0 g) and KOH pellets (16.5 g) were added. The mixture was heated in a silicone oil bath to 145 °C and maintained at that temperature for 1 h under an air condenser. This was then replaced by a distillation adapter, and the temperature was raised further to 190 °C for 3 h to remove H_2O and excess hydrazine. After cooling, the solution was poured on ice and extracted with ether (3 × 200 mL), and the combined extract was washed with 10% aqueous NaCl. The solvent was evaporated, and the brown residue was distilled to give 11.2 g of 3, a colorless

(18) Prepared from furan and valeric acid anhydride as described for 2 and 3.

(19) See "Organic Synthesis", Collect. Vol. IV, Wiley, New York, 1963, supplement to p 474.

viscous liquid: bp 131–133 °C (0.5 mm), 99% pure according to GLC (60% from 1); IR 3280, 1630, 1570, 765 cm^{-1}; ^{13}C NMR, see Table I; MS *m/e* (rel intensity) 198 (M^+, 100), 180 (30), 167 (34), 141 (94), 123 (86), 95 (60).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15; O, 24.21. Found: C, 66.73; H, 9.25; O, 24.36.

1-[3,4-Bis(chloromethyl)-2-furyl]pentane (4). A solution of **3** (5.9 g, 0.3 mol) in 5 mL of toluene was added dropwise with stirring to 60 mL of toluene containing 20% phosgene (0.13 mol) at 0 °C. The mixture was allowed to come to room temperature, and stirring was continued for 4 h. Toluene and excess phosgene were removed at 12 mm pressure and <50 °C. The reddish liquid residue was cooled to 0 °C, and 1 mL of pyridine was added dropwise to avoid excessive gas evolution. When gas evolution had ceased, H_2O was added, and the mixture was extracted with ether (2 × 50 mL). The combined extracts were washed with H_2O before drying. The solution was then concentrated in vacuo to 40 mL volume.

1-(3,4-Dimethyl-2-furyl)pentane (5). $LiAlH_4$ (4.7 g, 0.13 mol) was dissolved in 300 mL of diethyl ether by refluxing for 1.5 h under vigorous stirring. The solution of dichloride **4** was added dropwise over a period of 0.5 h, and the mixture was then refluxed for 4 h. After the solution was cooled, excess $LiAlH_4$ was decomposed by first adding wet ether then a small amount of H_2O. The precipitate was filtered off under suction and washed with ether. The solvent was removed to yield 5.2 g of crude **5**. The material was chromatographed in two equal portions on 15 g of activated Unisil (100–200 mesh), 3.2 cm high. The eluting solvent was hexane–diethyl ether (98:2), and the first 200 mL contained 1.6 g of **5** in 93% purity (76% from **3**): IR 1630, 1510, 1365, 750 cm^{-1}; ^1H NMR δ 7.01 (s, 1 H, R^3), 2.51 (t, 2 H, 1′ CH_2), 1.90 (d, 3 H, R^2), 1.85 (s, 3 H, R^1), 0.88 (t, 3 H, 5′ CH_3); ^{13}C NMR, see Table I; MS *m/e* (rel intensity) 166 (M^+, 29), 109 (100).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91; O, 9.62. Found: C, 79.40; H, 11.06; O, 9.78.

5-Pentyl-3,4-dimethyl-2-furoic Acid (6) and 10-(5-Pentyl-3,4-dimethyl-2-furyl)-1-chlorodecane (7). *N*-Butyllithium in hexane (7 mL, 1.4 N organic Li,[20] 9.8 mmol) was mixed with 25 mL of THF, and a solution of **5** (1.6 g, 9.6 mmol in 4 mL of THF) was added at 0 °C. The mixture was allowed to come to room temperature and stirred for 5 h. For monitoring the reaction, **6** was prepared by transferring 3.5 mL of the red solution into diethyl ether containing a large excess of dry ice. The resulting acid was recovered and esterified by CH_2N_2 for quantitation by GLC: IR 1700, 1620, 1560 cm^{-1}; ^1H NMR δ 3.85 (s, 3 H, R^3 = $COOCH_3$), 2.59 (t, 2 H, 1′ CH_2), 2.24 (s, 3 H, R_2), 1.88 (s, 3 H, R^1), 0.88 (t, 3 H, 5′ CH_3); MS *m/e* (rel intensity) 224 (M^+, 36), 193 (4), 167 (100), 109 (4).

Anal. Calcd for $C_{13}H_{20}O$: C, 69.61; H, 8.98; O, 21.40. Found: C, 69.40; H, 8.92; O, 21.27.

For preparation of **7**, the solution of lithium compounds was cooled to −20 °C, and 1-chloro-10-iododecane (3.0 g, 9.8 mmol, prepared as described for 1-chloro-9-iodononane,[12] purity 96%) in 4 mL of THF was added. The mixture was kept for 1 h at that temperature and then poured onto crushed ice. Extraction with ether (2 × 50 mL) gave, after evaporation of the solvent, 1.9 g of **7** in 70% purity (58% from **5**) according to GLC. It contained 1-chloro-10-iododecane with a small amount of **5**.

11-(5-Pentyl-3,4-dimethyl-2-furyl)undecanoic Acid (8). Crude **7** (1.9 g) was dissolved in 20 mL of ether. Approximately 3 mL of this solution was added to a stirred suspension of 0.1 g of Li, cut from freshly hammered sheet, in 20 mL of ether. After 15–20 min, the solution turned cloudy, indicating the start of the reaction. At this point, the solution was cooled from room temperature to 0 °C, and the remainder of **7** was slowly added within 10 min. After an additional hour with stirring at 0 °C, the solution was transferred by syringe to react with CO_2 as described for **6**. A small amount of methanol was added, and the solution was then acidified with 2 N HCl. The phases were separated, and the aqueous phase was extracted with ether (2 × 50 mL). The combined extracts were washed with H_2O, and the contents were esterified using CH_2N_2. Evaporation of solvent and purification of the residue by PLC gave 0.6 g of the methyl ester of **8** in a purity of 95% according to GLC (32% from **7**), containing 5% methyl undecanoate. The latter was removed by repeated PLC for analyses of **8**: IR 1730, 1645, 1595 cm^{-1}; ^1H NMR δ 3.65 (s, 3 H, $COOCH_3$), 2.48 (t, 4 H, 1′ and 1″ CH_2), 2.29 (t, 2 H, 10″ CH_2COO), 1.82 (s, 6 H, R^1 and R^2), 0.88 (t, 3 H, 5′ CH_3) [F_6, lit.[1b] 3.7, 2.6, 2.3, 1.8]; ^{13}C NMR, see Table I; MS *m/e* (rel intensity) 364 (M^+, 78), 307 (M − C_4H_9, 61), 179 (M − $C_9H_{18}CO_2Me$, 100), 123 (M − C_4H_9 − $C_9H_{18}CO_2Me$, 5.5) [F_6, lit.[1b] 364 (M^+, 32), 307 (39), 179 (100), 123 (18), at 70 eV].

Anal. Calcd for $C_{23}H_{40}O_3$: C, 75.77; H, 11.06; O, 13.16. Found: C, 75.62; H, 10.92; O, 13.36.

Methyl 3-Methyl-5-pentanoyl-2-furoate (10). Methyl 3-methyl-2-furoate[13] (**9**) (26 g, 0.18 mol) and valeric acid anhydride (43 g, 0.21 mol) were dissolved in 20 mL of benzene. The solution was cooled in an ice bath and BF_3–etherate (5 mL) was added over a period of 5 min. The dark-brown solution was stirred at room temperature for 24 h and then at 60–65 °C for an additional 48 h. The crude keto ester **10** was recovered in the same manner as that described for **2**. From two preparations a total of 67 g of crude material was obtained. It was distilled at 0.5 mm, and the fraction collected between 118 and 130 °C was 16.1 g of **10** (20%) of 99% purity: MS *m/e* (rel intensity) 224 (M^+, 1.4), 193 (2.4), 182 (100), 167 (19).

3-Methyl-5-pentyl-2-furoic Acid (11). The keto ester **10** (16.1 g, 0.07 mol) was dissolved in 200 mL of diethylene glycol. Hydrazine hydrate (18 g, 0.36 mol) and KOH pellets (10 g, 0.18 mol) were added. The stirred solution was heated under reflux to 145 °C and maintained at this temperature for 1 h. The temperature was then raised to 190 °C for 3 h. After the solution was cooled, it was poured on crushed ice, acidified with 6 N HCl, and extracted with ether (3 × 150 mL). After washing the residue with 10% aqueous NaCl and with H_2O, 12.8 g (85%) of **11** was obtained as residue from the extraction. An aliquot was esterified by CH_2N_2 for analysis by GLC which showed a purity of 93%: MS *m/e* (rel intensity) 210 (M^+, 62), 179 (11), 153 (100), 151 (12), 95 (17), 82 (12).

4-Methyl-2-pentylfuran (12). Copper powder (2.5 g) and **11** (12.8 g, 0.06 mol) were placed in a distilling flask with a low sidearm and a receiver cooled with dry ice. The mixture was heated in a silicone bath and, at approximately 160 °C, the first drops of pale yellow liquid distilled. The bath temperature was raised within 0.5 h to 190 °C and maintained there until no further distillate was observed (0.5 h). A total of 4.7 g (51%) of **12** was collected. The purity according to GLC was >99%: IR 1610, 1550, 1380, 1115 cm^{-1}; ^1H NMR δ 7.04 (s, 1 H, R^3), 5.82 (s, 1 H, R^1), 2.55 (t, 2 H, 1′ CH_2), 1.97 (s, 3 H, R^2), 0.89 (t, 3 H, 5′ CH_3); ^{13}C NMR, see Table I; MS *m/e* (rel intensity) 152 (M^+, 43), 123 (3.2), 109 (10), 95 (100), 82 (12).

Anal. Calcd for $C_{10}H_{16}O$: C, 79.89; H, 10.59. Found: C, 79.16; H, 10.36.

10-(5-Pentyl-3-methyl-2-furyl)-1-chlorodecane (13). The furan **12** (1 g, 6.5 mmol) was dissolved in 5 mL of THF and added to *n*-butyllithium (5.0 mL of hexane solution, 7.0 mmol) in 20 mL of THF, at −15 °C. The temperature of the stirred solution was allowed to rise to 0 °C and held there for 2 h. **11** was prepared by carbonation and quantitated in the same way as that described for **6**, using 2 mL of the reaction mixture. **13** was prepared and purified identically to **7**, using 1-chloro-10-iododecane (2.4 g, 8.0 mmol). Recovery gave 2.8 g of material which, according to GLC, contained 1.1 g of **13**: MS *m/e* (rel intensity) 326 (M^+, 11), 290 (1.7), 269 (15), 165 (100).

11-(5-Pentyl-3-methyl-2-furyl)undecanoic Acid (14). This compound was prepared in the same way as that described for **8**, using **13** (2.8 g) and Li cuttings (0.3 g) to obtain 1.7 g of crude **14**. After esterification, PLC gave 0.7 g of methyl ester of **14** (56% from **13**), with 10% methyl undecanoate as contaminant. For analyses, an aliquot was further purified by PLC: IR 1730, 1685, 1565, 1380, 1110 cm^{-1}; ^1H NMR δ 5.71 (s, 1 H, R′), 3.65 (s, 3 H, $COOCH_3$), 2.50 (t, 4 H, 1′ and 1″ CH_2), 2.29 (t, 2 H, 10″ CH_2COO), 1.88 (s, 3 H, R^2), 0.88 (t, 3 H, 5′ CH_3) [F_5 lit.[1b] 5.7, 3.7, 2.5, 2.3, 1.8]; ^{13}C NMR, see Table I; MS *m/e* (rel intensity) 350 (M^+, 50), 293 (M − C_4H_9, 12), 165 (M − $C_9H_{18}CO_2Me$, 100), 109 (M − C_4H_9 − $C_9H_{18}CO_2Me$, 4) [F_5 lit.[1b] 350 (M^+, 22), 293 (8), 165 (100), 109 (14), at 70 eV].

Anal. Calcd for $C_{22}H_{38}O_3$: C, 75.45; H, 11.04; O, 14.18. Found: C, 75.38; H. 10.93; O, 13.70.

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Registry No. 1, 30614-73-4; 2, 71041-45-7; 3, 71060-27-0; 4, 71041-46-8; 5, 71041-47-9; 6 methyl ester, 71041-48-0; 7, 71060-26-9; 8 methyl ester, 71041-49-1; 9, 6141-57-7; 10, 71041-50-4; 11 methyl ester, 71041-51-5; 12, 51080-20-7; 13, 71041-52-6; 14 methyl ester, 71041-53-7; valeric acid anhydride, 2082-59-9; 1-chloro-9-iodononane, 57152-87-1.

An Entirely Beaded Poly(dimethylacrylamide) Support for Peptide Synthesis

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During the last decade extensive experience with polystyrene-based resins used in the Merrifield method of peptide synthesis[1] has shown that the insoluble support has a dynamic influence on the synthesis of the peptide attached to it. Unfortunately, the physiochemical incompatibility of polystyrene with the attached peptide negatively influences mass transport of reagents, solvation of polymer matrix and attached peptide, and reaction rates (acylation as well as deprotection).[2] In extreme cases this incompatibility has even led to disintegration of the polymer beads at some stage of the synthesis.[2,3] Consequently, there is a need to improve the technique of peptide synthesis through the development of insoluble polymeric supports which are physicochemically compatible with the backbone structure of a peptide.

In order to offer a serious alternative to the overwhelmingly popular polystyrene supports, any new polymeric support must have distinctly improved properties and be easy to obtain and to use. As a general type, polyacrylamide resins have properties that should make them highly suited for use as supports for peptide synthesis.[4,5] We have been working on procedures to make acrylamide polymers readily available in a beaded form suitable for use in equipment presently employed for solid-phase peptide synthesis, and we recently reported the preparation by a reverse-phase suspension technique of an entirely beaded poly(acrylylpyrrolidine) resin.[6,7] Another acrylamide polymer that has been prepared and used in peptide synthesis is one based on dimethylacrylamide.[8-10] This resin was synthesized in a partially beaded form, and attempts to scale up the procedure from 5 to 50 g resulted in totally amorphous material.[9] While the physical form of a polymer does not change the chemical properties, in our experience the handling of amorphous polymer poses technical problems and requires special procedures. *For routine use a beaded resin is essential. Of equal importance is the ability to precisely control the degree of functionalization.* In the reported preparation of the poly(dimethylacrylamide) resin only 66% of the functionalizing agent *N*-(*tert*-butyloxycarbonyl)-β-alanyl-*N'*-acrylyl-1,6-diaminohexane was incorporated into the polymer.[8] We have reported a high-yield synthesis of *N*-acrylyl-1,6-diaminohexane·HCl, a monomer which we have found useful for the introduction into the polymer of a derivatizable primary amine.[11] Because of its high polarity and resulting water solubility, this monomer does not partition into the organic phase and the quantity of functional group is controlled simply by the amount of *N*-acrylyl-1,6-diaminohexane·HCl in the monomer solution.

This report describes the application of our reverse-phase suspension procedure[6,7] to the synthesis of completely beaded poly(*N,N*-dimethylacrylamide) cross-linked with *N,N'*-bisacrylyl-1,2-diaminoethane to the extent of 10 mol %, which was the composition reported by Atherton et al.[8] By using *N*-acrylyl-1,6-diaminohexane·HCl rather than *N*-(*tert*-butyloxycarbonyl)-β-alanyl-*N'*-acrylyl-1,6-diaminohexane,[8] we were able to incorporate into the polymer the theoretical quantity of amino function. Entirely beaded resin was prepared on both a small (7 g) and large (50 g) scale by reverse-phase suspension copolymerization of the constituent monomers with oxidation–reduction initiation. An aqueous solution of the monomers and the first half of the redox initiator ammonium peroxydisulfate was suspended in a heptane–CCl_4 mixture and the composition was adjusted so that the density of the two phases was approximately equal.

Importantly, the use of this organic phase prevents partitioning of the monomers from the aqueous phase and therefore allows for the precise control of polymer composition. The bead size was adjusted by the stirring rate and the addition of sorbitan sesquioleate; the reaction was initiated by addition of the second half of the redox system *N,N,N',N'*-tetramethyl-1,2-diaminoethane. After approximately 30 min the beaded product was filtered and washed with 2-propanol, $CHCl_3$, EtOH, H_2O, EtOH, and ethyl acetate. Beads are obtained of such uniform size that they are used without additional sizing other than flotation in $CHCl_3$ to remove the fines.

Verification of the amount of functionalizing group present in the resin was accomplished by completely acylating it with Boc-norvaline and then analyzing, after hydrolysis, for norvaline; found 0.47 mmol of norvaline per

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