Ring-Closure Reactions. 16.[1] An Improved Procedure for the Synthesis of (2,5)Thiophenophan-1-ones and Its Application to a Convenient Preparation of *dl*-Muscone

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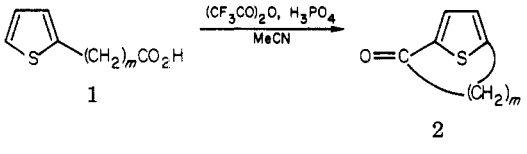
Some (2,5)thiophenophan-1-ones in the ring size range of 12–21 have been prepared by means of a very convenient, straightforward procedure involving the macrocyclization of the proper ω-(2-thienyl)alkanoic acids promoted by $(CF_3CO)_2O$–H_3PO_4 in MeCN solution. The present work provides a further example of the advantage of knowing the kinetic parameters of cyclization reactions for a reliable prediction of the proper conditions under which macrocyclic compounds can be synthesized. The present cyclization procedure has been conveniently applied to the preparation of the key intermediate of a five-step synthesis of *dl*-muscone.

One of us has recently reported[2] that acylation of activated aromatic and heteroaromatic compounds can be carried out with alkanoic acids in MeCN solution in the presence of excess $(CF_3CO)_2O$ and catalytic amounts of H_3PO_4. The intermediacy of a highly reactive mixed anhydride, which is formed in situ and need not be isolated, makes this acylation method effective and convenient. Moreover, the reactions are run in homogeneous medium under mild conditions, which proved to be suitable for kinetic measurements, as shown in a preceding paper[3] on the kinetics of formation of the 12-, 13-, 15-, 17-, and 21-membered (2,5)thiophenophan-1-ones **2** via intramolecular acylation of the ω-(2-thienyl)alkanoic acid precursors **1** (eq 1).



(1)

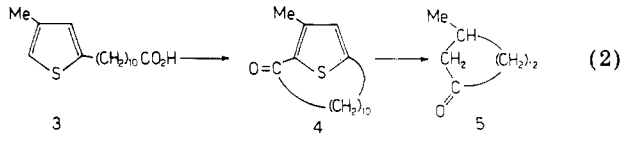
1 **2**

The improvement of synthetic procedures leading to many-membered-ring compounds is one of the goals of our investigation of the quantitative aspects of intramolecular reactions of bifunctional chain molecules. In a few instances we have shown[4,5] that knowledge of the kinetic features of cyclization reactions, as well as that for a suitably chosen intermolecular model reaction, is a valuable guide for adjusting appropriate synthetic conditions.

In the present case, kinetic measurements have provided the basic information for an attempt at a nonempirical approach to the synthesis of ring compounds **2** (m = 8, 9, 11, 13, and 17), avoiding unduly long addition times and large volumes of solvent.

Ring compounds **2** not only are interesting per se but also are interesting because they can easily undergo reductive desulfurization in high yields to afford macrocyclic cycloalkanones.[6]

We now report the results of such an investigation, which also includes the convenient preparation of the macrocyclic ketone **4**, as the key intermediate for the synthesis of *dl*-muscone (**5**) (eq 2).

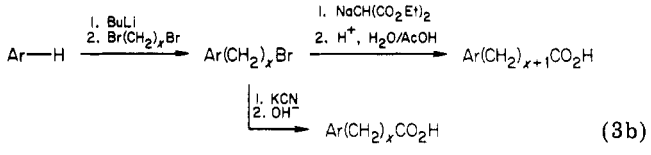


(2)

3 **4** **5**

Results and Discussion

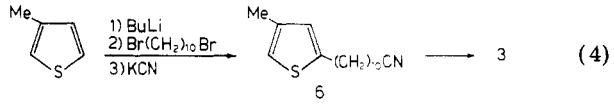
Synthesis of ω-(2-Thienyl)alkanoic Acids. Generally, to build up the required carbon skeleton, we attached the polymethylene chain to the thiophene nucleus by alkylation of the 2-lithium derivative with the proper α,ω-dibromoalkane (eq 3, Ar = 2-thienyl). The resulting



(3b)

ω-(2-thienyl)-1-bromoalkanes were not obtained in a pure form, since we found it difficult to separate the mono- from the dithienyl derivatives. Therefore, the crude reaction mixtures were subjected as such to the action of either diethyl sodiomalonate or sodium cyanide. The resulting monomalonyl or monocyano derivatives could be easily obtained in pure form by column chromatography and subsequently were converted into the desired acids **1**.

The route of eq 3b was followed for the preparation of 11-(4-methyl-2-thienyl)undecanoic acid (**3**) as the open-chain precursor of **4** (eq 4). Lithiation of 3-methyl-



(4)

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thiophene with BuLi had been reported previously[7] to give exclusively the 5-lithium derivative. However, other authors[8] have shown later on that metalation does not take place exclusively at the 5-position and that significant amounts of the 2-lithium derivative were also formed. Our work confirms the latter finding. Judging from the ^1H NMR spectrum (see Experimental Section), **3** was contaminated with about 10% of the isomeric 11-(3-methyl-2-thienyl)undecanoic acid, clearly resulting from alkylation at the α position adjacent to the methyl group.

Cyclization Reactions. α,ω-Disubstituted chain molecules can undergo cyclization or polymerization, de-

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Table I. Yields and Physical Constants of (2,5)Thiophenophan-1-ones[a]

compd	$10^6 v_f$, mol $L^{-1} s^{-1}$	yield[b]	lit. yield, % (ref)	n_D or mp, °C	ϵ_{max}, $cm^{-1} M^{-1}$ (λ_{max}, nm, in MeCN)
2, m = 8[c]	1.8	9[d]	8 (6)	n^{23}_D 1.5376	10 300 (290)
2, m = 9	4.1	31	54 (6)	n^{20}_D 1.5675[e]	11 100 (295)
2, m = 11	4.7	59[f]	62 (6)	mp 27-29[g]	11 050 (295)
2, m = 13	4.2	64		n^{19}_D 1.5430	10 850 (295)
2, m = 17	4.5	66		mp 20-21[h]	10 900 (294)
4	4.4	59	33 (11)	mp 71.5-73	11 350 (293)

[a] All compounds showed the expected molecular ion in the mass spectra. Satisfactory analytical data were obtained for compounds 2 (m = 9, 11, 13, and 17) (maximum deviation: ±0.31 for C; ±0.11 for H). [b] Isolated yield from column chromatography. [c] Semicarbazone, mp 189-191 °C (lit.[6] mp 191.5-193.5 °C). [d] The dimeric cyclic compound 7 (m = 8) was also isolated in 58% yield: mp 80-82 °C; mass spectrum, m/e 444 (M^+). [e] Gol'dfarb[6] describes this compound as a solid, mp 40-41 °C. We could not obtain our sample in a solid form, in spite of the fact that it did not show any detectable impurity. [f] The dimeric cyclic compound 7 (m = 11) was also isolated in 8% yield: mp 102-107 °C; mass spectrum, m/e 528 (M^+). [g] lit.[6] mp 31-32 °C. [h] n^{19}_D 1.5248 (supercooled liquid).

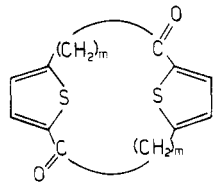
pending on the reaction conditions. In reactions carried out under Ziegler's high-dilution conditions,[9] the decisive factor for the intramolecular course of the reaction is the adjustment of the rate of feed of the bifunctional precursor into the reaction medium, in order to attain a sufficiently low stationary concentration of the bifunctional precursor itself. As shown in a previous paper,[4] the yield of cyclic product, in the absence of competing reactions other than polymerization, depends on the feed rate v_f (in mol $L^{-1} s^{-1}$) and the rate constants for the intra- and intermolecular reactions as shown by the approximate expression given in eq 5. For example, when v_f equals the ratio k_{intra}^2/k_{inter},

$$\frac{\%\ \text{yield}}{100} = \frac{2}{1 + \left(1 + \frac{8v_f}{k_{intra}^2/k_{inter}}\right)^{1/2}} \quad (5)$$

eq 5 predicts a theoretical yield of 50%. Thus, very favorable conditions for cyclization are met when the feed rate is smaller than k_{intra}^2/k_{inter}. In practice it will suffice that v_f is adjusted to be one order of magnitude lower. Any further reduction of v_f will result in impractically long addition times with little yield improvement.

Considering now the kinetic results[3] for the cyclization reaction at hand, one finds that, for instance, the k_{intra}^2/k_{inter} ratio for the cyclization of 12-(2-thienyl)dodecanoic acid (1, m = 11) [in MeCN at 50 °C in the presence of 0.1 M $(CF_3CO)_2O$ and 1×10^{-4} M H_3PO_4] is 5×10^{-6} mol L^{-1} s^{-1}. Hence, an experimentally convenient feed rate of the above order of magnitude should be suitable for the preparation in satisfactory yield of the 15-membered macrocycle 2 (m = 11). Accordingly, we have cyclized on a small scale compound 1 (m = 11) under the stated conditions, using a rate of feed of 2.4×10^{-6} mol L^{-1} s^{-1}. The yield of cyclic product, as determined by VPC analysis, was 51%, which compares fairly well with a theoretical yield of 60%, as predicted by eq 5. In order to further increase the yield of cyclic product, one could in principle adopt longer addition times. Instead, we have increased the temperature from 50 °C to the boiling point of the solvent (81 °C) and the concentration[3] of H_3PO_4 from 1×10^{-4} to 1×10^{-2} M in order to speed the reaction up and to attain a more favorable k_{intra}^2/k_{inter} ratio. Under these conditions and with a rate of feed of 3.7×10^{-6} mol L^{-1} s^{-1}, the yield of the same cyclic product was 73%.

Although a full optimization has not been carried out, the latter procedure was considered to be satisfactory and was employed for the cyclization of the other ω-(2-thienyl)alkanoic acids. The results are reported in Table I. Isolated yields from column chromatography are fairly good for the higher members of the series and decrease rapidly with decreasing ring size, in qualitative agreement with rate studies.[3] In some cases, occasional further elution afforded varying amounts of the dimeric compounds 7.



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The preparation of ring compounds 2 with ring sizes in the range of 12–16 had been reported previously by Gol'dfarb and his co-workers[6,10] by acylation of the chlorides of the proper ω-(2-thienyl)alkanoic acids 1 with $AlCl_3$–Et_2O in $CHCl_3$. The practicability of the above procedure was severely hampered not only by the difficult purification by distillation of the high-boiling acyl chloride intermediates but also mainly by the tedious cyclization step, run under conditions of extremely high dilution, namely, a few grams of reactant added to several liters of solvent over periods of several days. Typical feed rates adopted by Gol'dfarb[10] were on the order of 10^{-9} mol L^{-1} s^{-1}, i.e., well over three orders of magnitude lower than those used in this work. Our cyclization method is far more convenient than that of Gol'dfarb, since it affords comparable yields of cyclic product (Table I) with amounts of solvent one order of magnitude lower and addition times two orders of magnitude shorter.

The usefulness of the present procedure is well illustrated by the achievement of the relatively simple and convenient five-step synthesis of *dl*-muscone (5) in 14% overall yield from the readily available 3-methylthiophene and 1,10-dibromodecane. The key intermediates 3 and 4 are common to an earlier seven-step synthesis in 8% overall yield reported by Gol'dfarb,[11] but again, the major accomplishment of our method is to make the former long and inconvenient cyclization step a half-day procedure.

Experimental Section

IR spectra were obtained on a Perkin-Elmer Model 257 spectrophotometer, from 2% solutions in CCl_4. ^1H NMR spectra were recorded in CCl_4 solutions on a JEOL JNM-C60HL spectrometer, with Me_4Si as the internal reference. UV spectra were recorded on a Beckman DB-GT instrument. Mass spectra were

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Table II. Analytical Data

compd	mol wt[a] calcd	mol wt[a] found	anal. calcd C	anal. calcd H	anal. found C	anal. found H
2, m = 8	222	222				
2, m = 9	236	236	71.14	8.53	71.45	8.64
2, m = 11	264	264	72.68	9.15	72.88	9.20
2, m = 13	292	292	73.92	9.65	73.84	9.62
2, m = 17	348	348	75.80	10.41	75.66	10.35
4	264	264				

[a] By mass spectrometry.

obtained on a AEI MS-12 spectrometer. VPC analyses were carried out on an Erba Fractovap Model G instrument. A Sage Instruments syringe pump, Model 355, was employed. Elemental analyses were performed by the Alfred Bernhardt Mikroanalitisches Laboratorium. The analytical data are given in Table II.

Materials. Thiophene (Merck), 3-methylthiophene (Aldrich), 1,8-dibromooctane (Fluka), 1,10-dibromodecane (Aldrich), diethyl malonate (Erba RP), and trifluoroacetic anhydride (Merck) were used as received. BuLi (2 M in hexane) was from Aldrich. Reagent-grade MeCN was refluxed over P_2O_5 and distilled therefrom. Methyl hydrogen octadecanedioate was available from a previous investigation.[12] Raney nickel W-2 was prepared according to a literature method.[13]

Lithiation of thiophene and 3-methylthiophene and their subsequent alkylations with α,ω-dibromoalkanes were carried out as previously reported for the analogous reaction of benzothiophene.[3]

The purity of all intermediates and final products was thoroughly tested by TLC using several eluents, and their structure was routinely checked by IR and/or ^{1}H NMR spectroscopy.

9-(2-Thienyl)nonanoic Acid (1, m = 8). The crude product derived from the alkylation of thiophene with 1,8-dibromooctane was refluxed for 18 h with KCN in EtOH/CH_3CN (1:1). 8-(2-Thienyl)octanonitrile was obtained in 45% overall yield upon chromatography with benzene on silica gel; n^{20}_D 1.5112. Hydrolysis of the nitrile with excess KOH in boiling glycerol for 7 h gave the desired compound in 60% yield (mp 32–33 °C) after sublimation in vacuo (lit.[6] mp 35–36 °C).

10-(2-Thienyl)decanoic Acid (1, m = 9). The crude product derived from the alkylation of thiophene with 1,8-dibromooctane treated with diethyl sodiomalonate gave, after chromatography on silica gel, 8-(2-thienyl)octyl malonate in 31% yield; n^{20}_D 1.4878. Hydrolysis and decarboxylation of the latter afforded the title compound in 80% yield: bp 183–184 °C (0.6 mmHg); n^{22}_D 1.5048 (of the supercooled liquid); mp 27–28 °C (lit.[6] mp 33–34 °C).

12-(2-Thienyl)dodecanoic acid (1, m = 11) was synthesized in 50% overall yield according to Gol'dfarb et al.;[14] mp 41.0–42.5 °C, after sublimation in vacuo (lit.[6] mp 39.0–40.5 °C).

14-(2-Thienyl)tetradecanoic Acid (1, m = 13). This compound was prepared according to the same procedure as that adopted for 1 (m = 9), with the sole difference that 1,8-dibromooctane was replaced by 1,12-dibromododecane. 12-(2-Thienyl)dodecyl malonate was obtained in 12% overall yield; n^{21}_D 1.4812. This compound was converted into 1 (m = 13) in 85% yield (mp 51.5–53.0 °C, after sublimation in vacuo).

Anal. Calcd for $C_{18}H_{30}O_2S$: C, 69.63; H, 9.74. Found: C, 69.51; H, 9.62.

18-(2-Thienyl)octadecanoic Acid (1, m = 17). Acylation[2] of thiophene with methyl hydrogen octadecanedioate gave crude 2-[17-(carbomethoxy)heptadecanoyl]thiophene, ArCO-$(CH_2)_{16}CO_2Me$, in 80% yield; mp 70–75 °C. Simultaneous hydrolysis of the ester function and reduction of the ketonic carbonyl was achieved by treatment with NH_2NH_2/OH^-. Compound 1 (m = 17) was obtained in 82% yield; mp 67.0–68.5 °C, after crystallization from MeOH followed by sublimation in vacuo.

Anal. Calcd for $C_{22}H_{38}O_2S$: C, 72.08; H, 10.45. Found: C, 71.71; H, 10.40.

11-(4-Methyl-2-thienyl)undecanoic Acid (3). This compound was prepared from 3-methylthiophene and 1,10-dibromodecane, according to the same procedure reported for the synthesis of 1 (m = 8). This nitrile 6 was obtained in 39% yield; n^{21}_D 1.5001. After alkaline hydrolysis, compound 3 was obtained in 70% yield; mp 48–51 °C (from MeOH).

Contamination by ca. 10% of the isomer with the methyl group in the 3-position was detected in the ^{1}H NMR spectrum as a very distorted AX system[8b,15] centered at δ 6.8 (J = 4.5 Hz). Compound 3 exhibited an AB pattern,[2,8b] centered at δ 6.5 ($J \approx 2$ Hz).

Cyclization Experiments. The procedure given below for the cyclization of 1 (m = 11) is typical. A dried two-necked flask fitted with reflux condenser and protected with a $CaCl_2$ guard tube was charged with 85% phosphoric acid (0.23 g, 2.0 mmol) and $(CF_3CO)_2O$ (1.8 mL, 12.6 mmol) dissolved in dry MeCN (120 mL). To this solution, vigorously stirred and kept simmering, was added a solution of 1 (m = 11) (1.3 g, 4.6 mmol) in dry MeCN (40 mL) over 2 h by means of a motor-driven syringe through a capillary tube dipping into the solution. During the addition the clear solution became cloudy and eventually pink. After the addition was over, heating was continued for 10 min. After cooling, the mixture was worked up with ether and salt (NaCl) water. Removal of the solvent left 1.1 g of an orange liquid, which upon chromatography on silica gel (benzene) afforded 0.72 g (59% yield) of 2 (m = 11): IR $\nu_{C=O}$ 1665 cm^{-1}; ^{1}H NMR δ 7.45 (d, 1 H, J = 4.5 Hz), 6.75 (d, 1 H, J = 4.5 Hz), 2.85 (t, 2 H, $ArCH_2$), 2.65 (t, 2 H, CH_2COAr), 1.8–1.0 (br m, 18 H, "central" methylene protons).

Yields and physical constants of all the synthesized ring compounds are listed in Table I. In agreement with the expected structures, all compounds gave IR and ^{1}H NMR spectra similar to those reported above for compound 2 (m = 11). In the ^{1}H NMR spectrum of 4 the aromatic proton appeared as a singlet at δ 6.6, accompanied by a small signal at δ 7.5, probably due to contamination by a small amount (ca. 5%) of the isomeric cycle with the aromatic proton adjacent to the carbonyl group.

***dl*-Muscone (5).** Reductive desulfurization of 4 to 5 was carried out in boiling EtOH with Raney nickel W-2 under vigorous stirring.[13] The crude material was extracted in a Soxhlet apparatus[16] and, after removal of the solvent, 5 was obtained in a pure form (TLC) in 89% yield: n^{21}_D 1.4781 (lit.[17] n^{17}_D 1.4802); IR $\nu_{C=O}$ 1705 cm^{-1}; semicarbazone, mp 131–132.5 °C (lit.[17] mp 134 °C).

Registry No. 1 (m = 8), 21010-08-2; 1 (m = 9), 21010-09-3; 1 (m = 11), 21010-10-6; 1 (m = 13), 71948-92-0; 1 (m = 17), 26359-19-3; 2 (m = 8), 71948-93-1; 2 (m = 8) semicarbazone, 73177-17-0; 2 (m = 9), 886-42-0; 2 (m = 11), 6907-25-1; 2 (m = 13), 6907-40-0; 2 (m = 17), 6907-44-4; 3, 36152-06-4; 3 (3-methyl isomer), 36152-04-2; 4, 36152-11-1; 5, 956-82-1; 5 semicarbazone, 14224-83-0; 6, 73177-18-1; 7 (m = 8), 73177-19-2; 7 (m = 11), 73177-20-5; thiophene, 110-02-1; 1,8-dibromooctane, 4549-32-0; 8-(2-thienyl)octanonitrile, 26511-71-7; diethyl sodiomalonate, 73177-21-6; 8-(2-thienyl)octyl malonate, 73177-22-7; 1,12-dibromododecane, 3344-70-5; 12-(2-thienyl)dodecyl malonate, 73177-23-8; methyl hydrogen octadecanedioate, 72849-35-5; 2-[17-(carbomethoxy)heptadecanoyl]thiophene, 73177-24-9; 3-methylthiophene, 616-44-4; 1,10-dibromodecane, 4101-68-2.

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