g of 80%, 12 mmol). The resulting solution was stirred at room temperature until TLC showed disappearance of 10. The solution was evaporated, and the residue was partitioned between CH_2Cl_2 and 1 M HCl (50 mL each). The organic layer was washed with additional 1 M HCl (3 × 50 mL) and saturated brine (2 × 50 mL), dried over Na_2SO_4, filtered, and evaporated to give a solid, which was filtered through silica gel with CH_2Cl_2 as eluant and recrystallized from hexane–dichloromethane to yield 1.19 g (2.18 mmol, 87%): mp 272 °C (lit.[2d] mp 277–279 °C from benzene–methanol); NMR 7.85 (s, 2 H), 7.42 (s, 2 H), 4.05 (sept, 2 H, J = 7 Hz), 3.97 (s, 6 H), 3.92 (s, 6 H), 3.57 (s, 6 H), 2.20 (s, 6 H), 1.55 (d, 12 H, J = 7 Hz); IR 2950, 1595, 1475, 1450, 1410, 1350, 1275, 1235, 1210, 1135, 1025, 1010, 825; ^{13}C NMR 20.00, 22.27, 27.05, 55.50, 60.57, 100.71, 120.51, 124.84, 126.56, 128.87, 132.90, 135.21, 152.05, 152.92. Anal. Calcd for $C_{34}H_{42}O_6$: C, 74.70; H, 7.74. Found: C, 74.56; H, 7.88.

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Registry No. 2, 77256-01-0; 3, 77256-02-1; 4, 77256-03-2; 6, 77256-04-3; 7, 77256-05-4; 8, 77256-06-5; 9, 77256-07-6; 10, 77256-08-7; 11, 7144-61-8; 3-methoxysalicylic acid, 877-22-5; *tert*-butyl crotonate, 3246-27-3.

Ring-Closure Reactions. 18.[1] Application of the Malonic Ester Synthesis to the Preparation of Many-Membered Carbocyclic Rings

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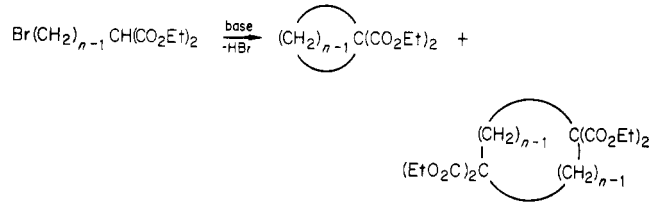
Alkylation of malonic ester derivatives with alkyl halides is a very well-known method for C–C bond formation. The intramolecular version of this reaction has been used for the synthesis of small and common carbocyclic rings.[2] Herein we describe a modification of the intramolecular malonic ester synthesis which permits the cyclization of long-chain diethyl ω-bromoalkylmalonates to many-membered 1,1-bis(ethoxycarbonyl)cycloalkanes under high dilution conditions.



The critical parameter to be adjusted in a high-dilution cyclization is the rate of feed of the bifunctional reactant into the reaction medium.[3] This is because of the necessity of achieving a stationary concentration of the reactant low enough as to favor the intramolecular reaction. The usefulness of many macrocyclization procedures is often hampered by the exceedingly low rates of feed required to fulfill the above condition, which result in very long addition times and large amounts of solvent to cyclize a synthetically significant amount of material. Since, other things being equal, the rate of feed has to be lower, the lower the rate of the reaction at hand,[3] it is of considerable advantage to carry out a cyclization reaction under conditions (solvent, temperature, catalyst, etc.) corresponding to the highest reactivity of the functional groups. Accordingly, cyclization was carried out in Me_2SO, which, as shown by literature data,[4] is the best of several tested solvents for the alkylation of the alkali derivatives of alkylmalonic esters with alkyl bromides. The base used was EtOK·18-crown-6 (1:1 mole ratio). Replacement of Na^+ for K^+, as well as omission of 18-crown-6, resulted in poorer yields. For instance, the yield of the 12-membered ring dropped from 21% to 13% with EtONa·18-crown-6 and to 3% with EtOK alone. This clearly indicates that dissociate enolate ions improve the yield. By virtue of the above solvent–base combination, the high-dilution condition could be attained with a relatively high rate of feed of the reactants into the reaction medium, namely, 6×10^{-7} mol L^{-1} s^{-1}. This permitted the total addition time to be kept conveniently within 3 to 4 h.

Table I. Cyclization of $Br(CH_2)_{n-1}CH(CO_2Et)_2$ with EtOK·18-Crown-6 in Me_2SO at 80 °C under High-Dilution Conditions

monomeric rings, n	6	7	8	9	10	11	12	13	17	21
isolated yield, %[a]		68	22				32[b]	52	62	55
GLC yield, %	72	70	22	3[c]	0.1[c]	1[c]	34	52		
dimeric rings, $2n$	12	14	16	18	20	22	24	26	34	42
isolated yield, %[d]			30	22	10	50	19	9		

[a] From column chromatography. All new compounds gave satisfactory analytical data (maximum deviation ±0.24 for C; ±0.20 for H). [b] mp 115–117 °C after sublimation in vacuo. All the other isolated monomeric rings behave as liquids at room temperature. It is known (Dale, J. *J. Chem. Soc.* **1963**, 93) that a series of ring compounds may show very irregular melting point patterns often characterized by large differences between even- and odd-membered rings, with higher melting points for the even-membered ones. Thus, the 12-membered ring being the only one to behave as a solid is not surprising, since the larger-than-12-membered rings are all odd membered. [c] Characterized by GLC–MS analysis. [d] From column chromatography. The dimeric rings (ring size in parentheses) had the following melting points (°C): (16) 128–130 from MeOH; (18) 128–130 from MeOH; (20) 100–102 from MeOH; (22) 111–112 from low-boiling petroleum ether; (24) 106–107 from low-boiling petroleum ether; (26) 110–113 from ligroin.

One further advantage of Me_2SO is that in this solvent the acid–base reaction between the malonic ester derivatives and EtO^- is virtually quantitative even in very dilute solutions,[5] so that if exactly equivalent amounts of base and bifunctional substrate are allowed to flow into the reaction medium, cyclization can take place in the virtual absence of the undesirable side reaction between EtO^- and the CH_2Br end. This aim was achieved by the use of a pair of motor-driven syringes which, also, allowed use of exactly the same rate of feed for all substrates.

The cyclization was successful in producing fairly good yields of common and large-sized carbocyclic rings (Table I). The medium rings were obtained in distinctly lower yields and were accompanied by significant amounts of the dimeric ring products. Contrary to expectation, worse results were obtained on prolonging the addition time to

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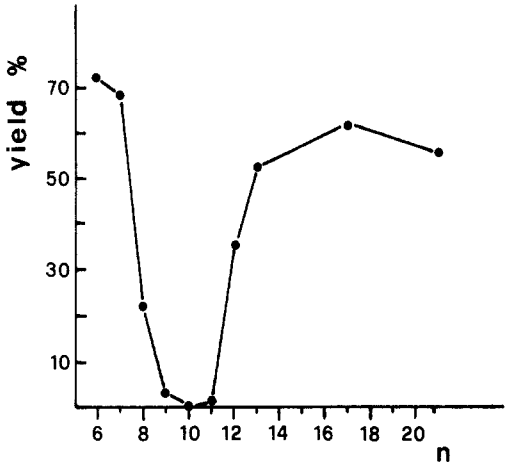

Figure 1. Plot of yields vs. ring size n for the cyclization of diethyl ω-bromoalkylmalonates in Me_2SO at 80 °C.

24 h. This finding and the failure to obtain quantitative yield of cyclic product even in the common ring region suggests the reaction might involve side reactions other than polymerization.[5] Keeping in mind the difficulties one has to overcome to generate a carbanion and to have it survive long enough to give the desired reaction, we suspect that better results than those reported here can probably not be obtained in the formation of wholly saturated carbocycles via intramolecular nucleophilic substitution.

Yield data from the present work may be compared with those reported for other cyclization reactions via C–C bond formation.[6] A plot of yields vs. ring size for the cyclization of ω-bromoalkylmalonates (Figure 1) has the familiar shape of the yield profiles for classical cyclization reactions, such as the Ruzicka, Thorpe–Ziegler, and Dieckmann reactions.[6] It is worth noting that the minimum is located at ring sizes 9 to 11, which exactly corresponds to the maximum strain energy of cycloalkanes.[6] Since the same rate of feed was used throughout the series, the yield data very likely reflect the relative ring-closure tendencies, thus providing additional evidence as to the importance of strain on the ease of cyclization of bifunctional chain molecules.

Experimental Section

The diethyl ω-bromoalkylmalonates were prepared and purified as previously reported.[2b,7] The preparation of $Br(CH_2)_5CH(CO_2Et)_2$ also gave 1,1-bis(ethoxycarbonyl)cyclohexane as a by-product, bp 100–104 °C (3 mmHg) [lit.[8] bp 105–106 °C (5mmHg)]. A.R. grade Me_2SO (ERBA RPE) was purged with argon before use. 18-Crown-6 was from Aldrich.

A Sage Instrument syringe pump Model 355 was used. ^1H NMR spectra were taken from CCl_4 solutions on a JEOL JNM-C60 HL spectrometer. Mass spectra were obtained on a AEI MS 12 spectrometer. For GLC–MS analyses the latter instrument was matched to a Varian Aerograph Series 1400 gas chromatograph. GLC analyses were performed by the internal standard method on a Hewlett-Packard Model 5830 A instrument, fitted with a 1.8-m OV-17 column operated in the range of 100 to 220 °C, depending on molecular weight.

Cyclization Procedure. All operations were carried out under pure nitrogen. The reaction was run in a 250-mL three-necked flask containing a well-stirred solution of 18-crown-6 (2.2 mmol) in Me_2SO (200 mL) heated at 80 °C. The reagents were added separately and simultaneously over a 3.5-h period by means to two identical motor-driven syringes. One syringe contained 2 mmol of the proper ω-bromoalkylmalonic ester in 30 mL of Me_2SO and the other 2 mmol of KOH in 30 mL of Me_2SO–EtOH (93:7, v/v). After being stirred at 80 °C for an additional 15 min, the mixture was cooled to room temperature, poured into ice–water containing $Ba(NO_3)_2$, and worked up with ether. A small portion of the ether solution was used for GLC analysis. The remaining part was evaporated and the residue was eluted with benzene/CCl_4 (1:1) on aluminum oxide 90 (Merck). The dimeric cycles were obtained upon further elution with benzene.

All the isolated monomeric rings were further purified by sublimation or microdistillation in vacuo and found to be at least 99.5% pure (GLC). They were characterized by elemental analysis data, and ^1H NMR and mass spectra. Along with the expected molecular ion, all the compounds showed a strong peak at m/e 173, possibly due to the fragment $[CH_2CH(CO_2Et)_2]^+$. The 9-, 10-, and 11-membered rings were detected and characterized by GLC–MS analysis. The dimeric rings showed ^1H NMR spectra very similar to those of the monomeric isomers and mass spectra consistent with the assigned structures.

Registry No. 1,1-Bis(ethoxycarbonyl)cyclohexane, 1139-13-5; 1,1-bis(ethoxycarbonyl)cycloheptane, 6557-83-1; 1,1-bis(ethoxycarbonyl)cyclooctane, 76999-11-6; 1,1-bis(ethoxycarbonyl)cyclononane, 76999-12-7; 1,1-bis(ethoxycarbonyl)cyclodecane, 76999-13-8; 1,1-bis(ethoxycarbonyl)cycloundecane, 76999-14-9; 1,1-bis(ethoxycarbonyl)cyclododecane, 76999-15-0; 1,1-bis(ethoxycarbonyl)cyclotridecane, 37689-04-6; 1,1-bis(ethoxycarbonyl)cycloheptadecane, 76999-16-1; 1,1-bis(ethoxycarbonyl)cycloheneicosane, 76999-17-2; 1,1,9,9-tetrakis(ethoxycarbonyl)cyclohexadecane, 76999-18-3; 1,1,10,10-tetrakis(ethoxycarbonyl)cyclooctadecane, 76999-19-4; 1,1,11,11-tetrakis(ethoxycarbonyl)cycloeicosane, 76999-20-7; 1,1,12,12-tetrakis(ethoxycarbonyl)cyclodocosane, 37689-02-4; 1,1,13,13-tetrakis(ethoxycarbonyl)cyclotetracosane, 76999-21-8; 1,1,14,14-tetrakis(ethoxycarbonyl)cyclohexacosane, 37689-00-2; $Br(CH_2)_5CH(CO_2Et)_2$, 1906-95-2; $Br(CH_2)_6CH(CO_2Et)_2$, 6557-85-3; $Br(CH_2)_7CH(CO_2Et)_2$, 76999-22-9; $Br(CH_2)_8CH(CO_2Et)_2$, 77011-21-3; $Br(CH_2)_9CH(CO_2Et)_2$, 76999-23-0; $Br(CH_2)_{10}CH(CO_2Et)_2$, 76999-24-1; $Br(CH_2)_{11}CH(CO_2Et)_2$, 76999-25-2; $Br(CH_2)_{12}CH(CO_2Et)_2$, 35295-45-5; $Br(CH_2)_{16}CH(CO_2Et)_2$, 76999-26-3; $Br(CH_2)_{20}CH(CO_2Et)_2$, 63099-18-3.

(5) Diethyl butylmalonate can be spectrophotometrically titrated with EtOK in Me_2SO owing to the strong absorption of its conjugate base (λ_{max} 274 nm; ϵ_{max} 2.4×10^4 M^{-1} (cm^{-1}). The absorption is not stable, but disappears with a half-life time of ~16 min at room temperature. The fate of the carbanion is unknown.

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Practical Approach to High-Yield Enzymatic Stereospecific Organic Synthesis in Multiphase Systems

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The stereoselective synthesis of epoxides is of current interest because of the large number of stereospecific reactions undergone by epoxides.[1] There have been many attempts to prepare optically active epoxides via asymmetric oxidation using chiral peracids,[2-4] chiral phase-transfer catalysts,[5,6] and organometallic complexes with chiral ligands.[7-9] Some of these procedures have been quite successful. Using chiral titanium complexes, Sharpless has epoxidized allyl alcohols in optical yields above 90%.[9] Epoxidation of α,β-unsaturated ketones with chiral catalysts has, however, not exceeded 55% enantiomeric excess (ee).[6] The preparation of nonfunctionalized chiral epoxides of high enantiomeric purity remains a

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