Anal. Calcd for $C_{18}H_4N_8S_8$: C, 36.73; H, 0.68; N, 19.05; S, 43.54. Found: C, 35.02; H, 0.64; N, 19.22; S, 43.66.

Reaction of 3a with TTF. A solution of **3a** (0.15 g, 5.8×10^{-4} mol) and TTF (0.239 g, 1.17×10^{-3} mol) was prepared by dissolving the respective compounds in 25 mL of CH_3CN. When the reactants were mixed, shiny black platelets were deposited. After being allowed to stand at ambient temperature for 8 h, the mixture was filtered and continuously washed with CH_3CN until the filtrate was colorless. The nonstoichiometric complex (see below) exhibited a compressed-pellet resistivity of 1000 Ω cm.

On the basis of the results of the analytical data, a molecular formula of $C_{27}H_{15}N_{10}O_5S_{12}$ was calculated. Varying the molar ratio of TTF had no effect on this formulation.

Anal. Calcd for $C_{27}H_{15}N_{10}O_5S_{12}$: C, 34.34; H, 1.60; N, 14.83; O, 8.47; S, 40.68. Found: C, 34.49; H, 1.59; N, 14.59; O, 8.52; S, 41.26.

Acknowledgment. Special thanks go to D. J. Freed and A. Mujsce for mass spectroscopy and S. Vincent for qualitative X-ray fluorescence analysis.

Registry No. 1, 17989-89-8; 2, 74007-35-5; **3a**, 74007-36-6; **3b**, 74007-37-7; **5a**, 74007-38-8; **6a**, 74007-39-9; **6b**, 74007-40-2; **7a**, 74019-23-1; tetracyanoethylene, 670-54-2; carbon disulfide, 75-15-0.

Unidirectional Dieckmann Cyclizations on a Solid Phase and in Solution

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Dieckmann cyclization of 2% divinylbenzene–copolystyrene resin alkyl pimelates and analogous benzyl alkyl pimelates is reported. The use of uniquely single-labeled dioate esters has allowed analysis of the direction of closure via decarboxylation of the keto ester products. The influence of steric factors on the competition between enolate condensation and transesterification and upon the direction of closure of the cyclization has been evaluated, and the conditions for achieving >99% regioselective closure are described. Modifications in the conditions of solid-phase peptide synthesis required for successful high-temperature enolate cyclization have been developed and the results are compared to solution reactions of benzyl alkyl esters under similar conditions. The resin attachment afforded a clear benefit over the benzyl models and greatly simplified isolation and purification of the resulting β-keto esters.

Introduction

Success in the synthesis of carbocyclic compounds from open-chain precursors is dependent upon the competitive interplay of a number of factors, among the most important of which is ring size.[2] Entropy effects dictate a decreased rate of closure with increasing probability of separation of the terminal C-α and C-β carbons. On the other hand, the summed effects of interactions occurring as the atoms in the chain assume the cyclic transition state is an enthalpy effect and is a complex function of ring size. The resultant of these two effects affords maximum rates of formation for five- and six-membered carbocycles and minimum rates for nine- and ten-membered rings.

An α,ω-bifunctional molecule can lead to cyclization and/or polymerization, depending upon the relative rates of intra- and intermolecular condensations. Recognition that the cyclization rate has a first-order, while polymerization has a second-order, dependence upon concentration led to introduction of the high-dilution principle.[3] Useful yields of ring compounds containing 12 or more carbons have been obtained; however, for nine- or ten-membered rings, this relative advantage has been insufficient to provide practical synthetic processes.[4] A further technique, restriction of the mobility of the reacting termini by adsorption on a surface which effects cyclization,[5] was applied successfully to the preparation of nine- and ten-membered carbocycles in the acyloin reaction.[6,7]

An ideal cyclization will possess the following characteristics: (1) cyclization should be the fastest reaction taking place; (2) competitive polymerization should be prevented, e.g., by high dilution,[2,3] immobilization,[6,7] or some equivalent technique; (3) closure should lead to a single or predominate carbocycle, easily separable from other products. Solid-phase synthesis[8,9] appeared to offer a superior technique for the development of a cyclization method which meets a number of these criteria. Preliminary reports[10] have appeared of the solid-phase cyclization of pimelates and of the less successful cyclization of sebacate analogues. Also, solid-phase organic synthesis, including cyclization, has been the subject of several comprehensive reviews, and experimental ambiguities in this field have been critically examined.[11]

We now describe the detailed experimental conditions required to achieve Dieckmann closures of resin-bound pimelate esters and benzylic model compounds and the synthetic utility of mixed-ester substrates. Dieckmann

(1) IBM Research Laboratory, San Jose, CA.
(2) Sicher, J. In "Progress in Stereochemistry"; de la Mare, P. B. D., Klyne, W., Eds.; Butterworth: Washington, 1962; Vol. 3, p 222.
(3) (a) Ruggli, P. *Justus Liebigs Ann. Chem.* **1912**, *392*, 92. (b) Ziegler, K.; Eberle, H.; Ohlinger, H. *Ibid.* **1933**, *504*, 94.
(4) Leonard, N. J.; Schimelpfenig, C. W., Jr. *J. Org. Chem.* **1958**, *23*, 1708.
(5) Hansley, V. L. U.S. Patent 2 226 268, 1941.
(6) Stoll, M.; Rouve, A. *Helv. Chim. Acta* **1934**, *17*, 1283.
(7) (a) Prelog, V.; Frenkiel, L.; Kobelt, M.; Barman, P. *Helv. Chim. Acta* **1947**, *30*, 1741. (b) Bloomfield, J. J.; Owsley, D. C.; Nelke, J. M. *Org. React.* **1976**, *23*, 259.
(8) (a) Merrifield, R. B. *Adv. Enzymol.* **1969**, *32*, 221. (b) Erickson, B. W.; Merrifield, R. B. "The Proteins", 3rd ed.; Neurath, H., Hill, R. L., Eds.; Academic Press: New York, 1976; Vol. 2. (c) Wieland, T.; Birr, C.; Frodl, R.; Lochinger, W.; Stahnke, G. *Justus Liebigs Ann. Chem.* **1972**, *757*, 136.
(9) Stewart, J. M.; Young, J. D. "Solid Phase Synthesis"; W. H. Freeman: San Francisco, 1969.
(10) (a) Crowley, J. I.; Rapoport, H. *J. Am. Chem. Soc.* **1970**, *92*, 6363. (b) Crowley, J. I.; Harvey, T., III; Rapoport, H. *J. Macromol. Sci., Chem.* **1973**, *A7*, 1118.
(11) (a) Leznoff, C. C. *Chem. Soc. Rev.* **1974**, *3*, 65. (b) Pitman, C. U., Jr.; Evans, G. O. *CHEMTECH* **1973**, 560. (c) Overberger, C. G.; Sannes, K. N. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 159. (d) Crowley, J. I.; Rapoport, H. *Acc. Chem. Res.* **1976**, *9*, 135. (e) Neckers, D. C. *CHEMTECH* **1978**, 108. (f) Leznoff, C. C. *Acc. Chem. Res.* **1978**, *11*, 327. (g) Maxur, S.; Jayalekshmy, P. *J. Am. Chem. Soc.* **1979**, *101*, 677.

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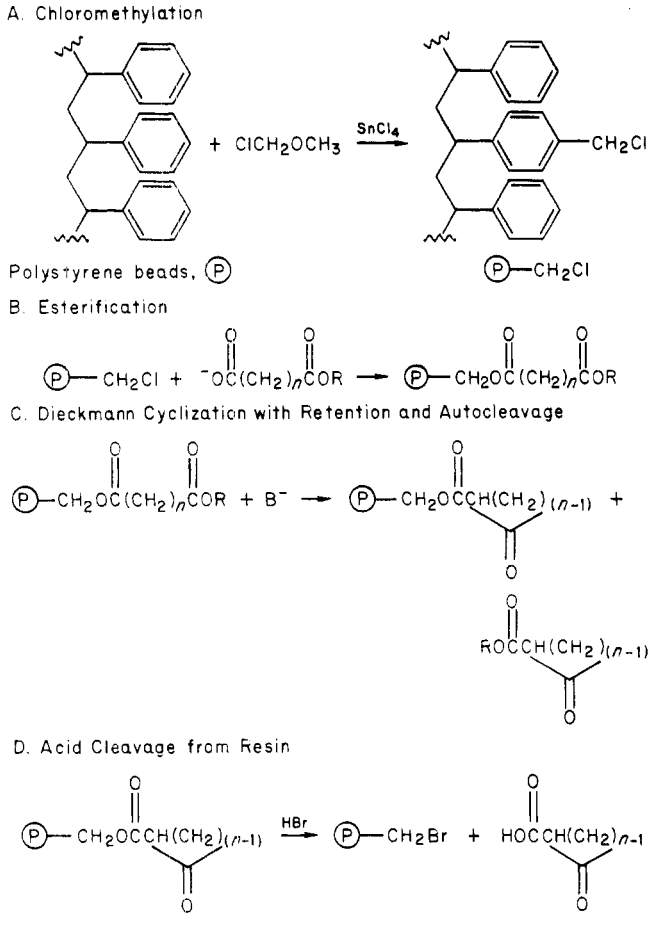
Scheme I. Dieckmann Cyclization on a Solid Phase



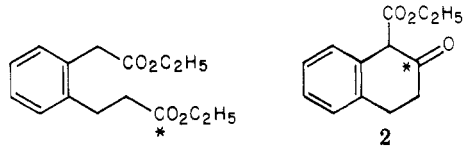
cyclization of dicarboxylic esters was selected as a test of the usefulness of solid-phase cyclization because of the following. (1) The Dieckmann reaction has been the subject of numerous investigations since it was originally reported in 1894,[12] and many details of its mechanism have been elucidated. (2) Successful cyclization could extend the range of solid-phase reaction conditions to include enolate condensations at elevated temperatures. (3) Dieckmann cyclization is one of the most general methods for preparing five- and six-membered rings.[13] Variously substituted starting materials are available, stable to the reaction conditions, and cyclized products are versatile intermediates for the synthesis of more complex structures. (4) The yield as a function of ring size[4] is well-established with a definite maximum at five and six carbons and a minimum at nine and ten. (5) The diester starting materials are compatible with convenient methods for attachment of the substrate to the solid phase.

The Dieckmann reaction has been reviewed[13,14] and a brief consideration of the effect of substituents on the direction of closure has been reported.[15] It can, in principle, lead to at least two products. Mixed diesters have been utilized to a very limited extent. These fall almost completely into one of two classes, the restricted case of substituted benzoic esters[16] or analogues and diesters of which one carbonyl is lactonized.[17] In another example,[18]

Table I. Analytically Significant Infrared Spectral Peaks of 7-(*p*-Cymyl) Chloride and Derivatives and Resin Analogues

compd	infrared absorption maxima, cm^{-1}	resin analogue
7-(*p*-cymyl) chloride	1267 (sharp, intense)	1250
7-(*p*-cymyl) bromide	1205, 1225 (doublet)	1200, 1170
7-(*p*-cymyl) methyl ether	1100 (intense)	
7-(*p*-cymyl) acetate	1730 (sharp, intense), 1230 (intense)	1725
7-(*p*-cymyl) methyl sebacate	1720 (sharp, intense), 1160 (medium, br)	1725 1170
7-(*p*-cymyl) alcohol	3230 (medium, br)	
all compounds	800-860 (doublet)	830

employing a methyl ethyl diester, the acidity of the benzylic proton, as well as thermodynamic preference, led to a single product (e.g., 1 → 2); a mixed ethyl *tert*-butyl diester cyclization yielded both keto esters in another case.[19]



The original plan of our synthesis for Dieckmann cyclization on a solid phase (Scheme I) was developed without regard to the intervention of side reactions. In its application, we found it necessary to elaborate analytical procedures to characterize each functionalized resin intermediate. To achieve higher yields and regioselective control of the closure it was necessary to employ esters of increasingly more hindered alcohols. Our results provide evidence for the striking effects of steric hindrance in the tetrahedral Dieckmann transition state and in some cases afforded pure products of closure in a single direction, contrary to results customarily reported.

Results

Infrared Analytical Procedures. Each step in the synthetic sequence results in a polymer product, the analysis of which presents difficulties because neither NMR nor mass spectral methods can be used. Elemental analysis in the most favorable case, the chloromethylated resin, required multiple samples to achieve modest levels of precision, due to the small percentage of chlorine in the resin samples. The low percentage of reactive substrate in the subsequent resin products made carbon–hydrogen analysis useless as an analytical method.

Infrared difference spectra of functionalized resin relative to untreated polystyrene provided the best analytical information. Infrared spectra of functionalized polystyrene in potassium bromide displayed the complex features of the polystyrene spectrum together with absorptions due to additional functionality as weak shoulders on the intense bands of the polystyrene skeleton. However, when the reference beam was attenuated by a control sample containing an appropriate quantity of untreated resin, the difference spectrum of each of the functionalized resins was substantially simplified. These difference spectra were essentially identical with the spectra of appropriate model compounds in which the polystyryl residue had been replaced with benzyl or 7-(*p*-cymyl) moieties. Examination

(12) Dieckmann, W. *Chem. Ber.* **1894**, *27*, 102.
(13) Schaefer, J. P.; Bloomfield, J. *Org. React.* **1967**, *15*, 1.
(14) Vul'fson, N. S.; Zaretsky, V. I. *Reakts. Metody Issled. Org. Soedin.* **1963**, *12*, 7.
(15) Chakravarti, R. N. *J. Proc. Inst. Chem. (India)* **1961**, *33*, 261.
(16) Bardhan, J. C.; Adhya, R. N.; Bhattacharyya, K. C. *J. Chem. Soc.* **1956**, 1346.
(17) Narang, S. A.; Dutta, P. C. *J. Chem. Soc.* **1964**, 1119.
(18) Schwarz, R.; Capek, K. *Monatsh. Chem.* **1953**, *84*, 595.
(19) Clark, E. R.; Howes, J. G. B. *J. Chem. Soc.* **1956**, 1152.

of the infrared spectra of model compounds and substituted resins revealed the analytically significant absorptions listed in Table I.

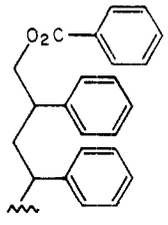
Chloromethylated beads in the range of 0.6 to 5.4% chlorine (1.8 to 16% of phenyls substituted) have been examined. All these spectra display a sharp intense singlet at about 1250 cm^{-1}, not possessed by the original polystyrene beads nor by the esterified product, which is probably due to H–C–Cl bending motions. A good Beer's Law plot of log absorbance vs. percent chlorine was obtained and this band was used as the basis for a quantitative analysis of the extent of chloromethylation of the polystyrene beads.

The difference spectra of the chloromethylated beads in the 900- to 665-cm^{-1} region is also similar to that of the 7-(*p*-cymyl) chloride when the extent of chloromethylation is 3% (1% chlorine). Below this level it is difficult to compensate for the two very intense broad bands of polystyrene at 760 and 700 cm^{-1} with sufficient precision to resolve the spectral details of the modified aromatic centers. However, the absorption at 830 cm^{-1} due to para disubstitution is easily seen and appears as a poorly resolved doublet, relatively symmetrical, similar to the doublet in the cymyl chloride.

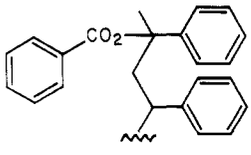
The spectral features listed in Table I were used to monitor the progress of esterification via the loss of benzylic chloride and the displacement of carboxylate by bromide during subsequent HBr cleavage of the resin ester. More accessible benzyl models were examined, and a number of the spectral features were found to be similar to those of the functionalized resins. However, the benzylic compounds lack the para-disubstituted aromatic absorptions, while other features, such as the H–C–Br bending motion, are much more intense in the benzyl compound. On the other hand, the 7-(*p*-cymyl) model was the source of one difficulty when carried through the Dieckmann sequence. Under these conditions *p*-isopropylbenzoic acid was isolated in nearly quantitative yields from cymyl methyl sebacate. We believe this resulted from reduction of the keto ester by alkoxide resulting from the Claisen condensation.

These results demonstrate the special utility of infrared difference spectra in monitoring the solid-phase synthetic sequence. Alternative procedures were considered but were unacceptable because they required each intermediate product to be cleaved from the resin for characterization.

Debenzoylation of Resin Beads. Among the products isolated from the crude Dieckmann and acid cleavage reactions during some of our early experiments was benzoic acid, which was identified by its mass and infrared spectra. Its most likely source was the benzoyl peroxide originally employed as a catalyst in the preparation of the resin beads and retained as polymeric chain termini as in 3 or 4.



3



4

Refluxing polystyrene beads with potassium *tert*-butoxide in toluene removed the benzoyl residues which, after acetic acid quenching, were recovered as benzoic acid from the filtrate and hexane washings of the beads. Infrared difference spectra comparing polystyrene with debenzoylated polystyrene showed the absence of a weak ester carbonyl band at 1715 cm^{-1} in the debenzoylated beads. Accordingly debenzoylation usually followed by etherification of the unmasked hydroxyl groups was routinely incorporated into our synthetic plan prior to chloromethylation. After this modification, no benzoic acid nor benzoyl groups were observed in products from resin reactions.

Chloromethylation. We originally employed both commercial chloromethylated polystyrene (Bio-Beads) and those we prepared by standard procedures.[8,9] Both displayed intense peaks at 1100 cm^{-1} accompanied by a doublet at 985 and 975 cm^{-1}, characteristic of dioxane. In the case of products from two separate chloromethylations, both absorptions decreased upon heating at 100 °C in vacuo. Clearly, all of the dioxane introduced into the polystyrene matrix during the chloromethylation procedure was removed by the recommended washing and drying procedure. For facilitation of removal of all solvent peaks, after two to four washes with the reaction solvent to which the resin product had been most recently exposed, the following schedule was rigorously applied: washing with methanol, water, methanol, dioxane, water, methanol, methylene chloride, methanol, methylene chloride, methanol, ethyl ether, followed by drying at 55 °C (5 mm). The resin is extensively swollen in dioxane and methylene chloride, while in water and methanol it is relatively compressed. The alternation between swelling solvents and compressing solvents exerts a sponge-like action which was beneficial in removing species such as hydrogen chloride, potassium acetate, dioxane, and chloroform.

A complication of the infrared spectral analysis of the extent of chloromethylation on the basis of the band at 1250 cm^{-1} occurs in beads which are not free of dioxane. Dioxane has an absorption of medium intensity which nearly coincides with the H–C–Cl band, and in such beads, the peak height or area of the unresolved double peak does not reflect the true extent of chloromethylation. This situation results in a resolved double peak in the case of the commercial chloromethylated beads, in which both bands are fairly strong.

Failure of early Dieckmann cyclizations and cleavage reactions to provide complete recovery of diester originally bound to the resin led us to examine the completeness of acid cleavage of resin ester which had not been subjected to cyclization conditions. These experiments suggested the complete displacement or complete cleavage of resin ester did not occur unless chloromethylated resin containing 1.4% chlorine or less was employed. A series of chloromethylation experiments established the effect of variations in time, temperature, amount of catalyst, and purity of the chloromethyl ether on the extent of chloromethylation. The results led to reproducible procedures for the preparation of chloromethylated resin of 0.5 to 5% Cl content.

Resin Ester Preparation. Resin ester preparation was carried out at first in accordance with the original conditions for peptide synthesis,[8a,9] triethyl ammonium carboxylate and chloromethylated resin in ethanol, but these reactions were unsatisfactorily incomplete. It was necessary to conduct three serial esterifications of 10 h each with interspersed thorough washing and drying in order to achieve 95% displacement of chloride. In addition to the difficulty of effecting complete esterification, this method presented a further problem, the competitive formation of quaternary ammonium sites at the chloromethylated loci.[8] We have observed both carboxylate and chloride counterions in our resin esters. The carboxylate was seen as an absorbance at 1565–1610 cm^{-1} in the resin ester IR

difference spectra whether the acyloxy function was acetate, monomethyl or mono-*tert*-butyl adipate or sebacate. This band had an appreciable intensity in the case of the mono-*tert*-butyl adipate resin ester, presumably because we had used a small excess of triethylamine to prevent acid cracking of the *tert*-butyl group. The carboxylate counterion could be removed by washing with a 1/1 mixture of methylene chloride and trifluoroacetic acid, although not with aqueous or alcoholic solutions of acid. The chloride was observed in elemental analyses of samples which possessed no residual covalent chlorine by IR. An alternative method of resin ester formation was required because essentially no Dieckmann reaction took place with either adipoyl or sebacyl resin esters containing these quaternary sites.

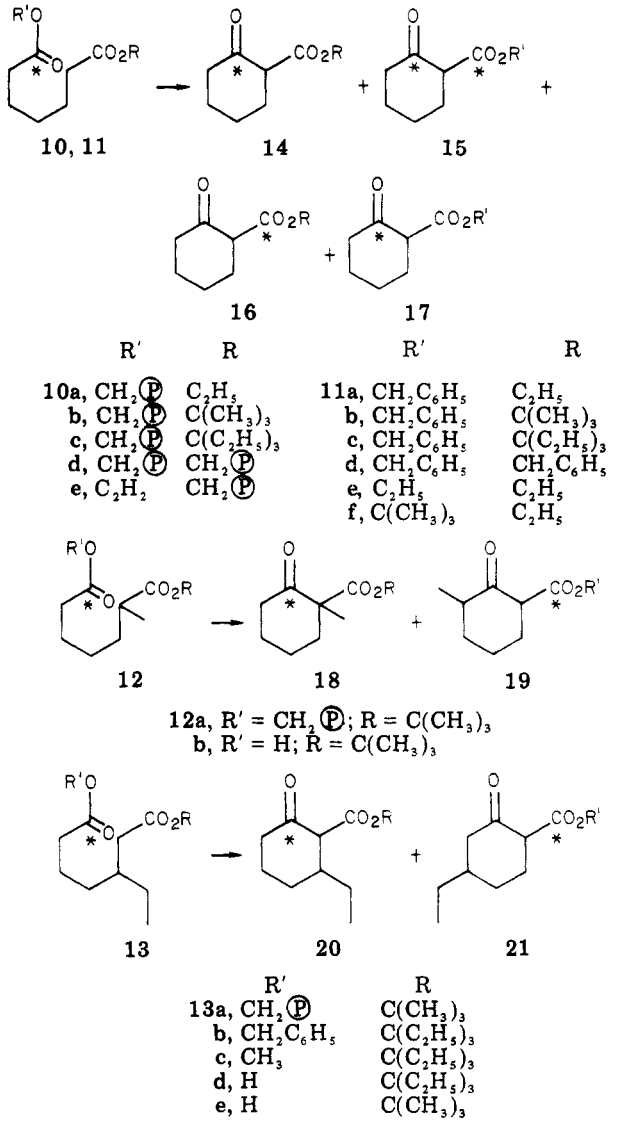
The formation of resin acetate has been reported[20a] by heating chloromethylated resin with potassium acetate in benzyl alcohol at 80 °C as well as its conversion to hydroxylmethyl resin by refluxing for 4 h in ethanolic sodium hydroxide, and these changes were followed by examination of the infrared spectrum of the product beads. In our hands, heating the potassium acetate–chloromethylated resin–benzyl alcohol mixture led gradually to a mixture of hydroxymethyl resin and resin acetate; the reaction mixture was converted completely to hydroxymethyl resin on continued heating for 24 h. Refluxing the mixed hydroxymethyl–acetoxymethyl resin with ethanolic sodium hydroxide for 7 h failed to yield completely hydrolyzed resin. These results were unchanged by using potassium acetate melted in situ prior to addition of solvent and benzyl alcohol distilled from calcium hydride. The intervention of crosslinking via bis resin benzylic ether linkages has been identified as responsible for this incomplete reaction.[20b]

Mono-*tert*-butyl sebacyl resin ester and mono-*tert*-butyl adipoyl resin ester were both best prepared by reaction of the potassium salt of the half ester with chloromethylated resin in DMF for 6 to 16 h at 125 °C.[21] Also, substitution of diisopropylethylamine for triethylamine in the original procedure resulted in esterification without quaternization. Thus a satisfactory method for the preparation of resin ester was developed, which did not introduce additional functionality into the resin beads. Since reactive substrate represented a relatively small percentage of the total resin ester used in a Dieckmann reaction, extreme precautions were required to ensure that the resin ester was dry. These precautions involved extended vacuum-oven drying of the resin ester, which was handled thereafter in a nitrogen atmosphere. In this way a chemical system was developed for preparation of polystyrene-bound diesters suitable for Dieckmann cyclization, a system differing in a number of ways from that employed in the solid-phase synthesis of peptides.

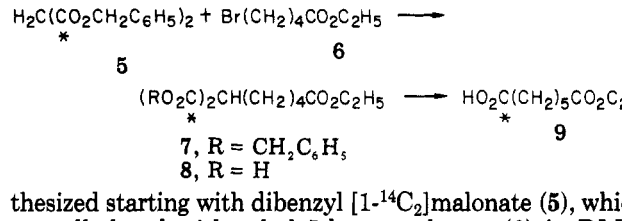
Dieckmann Cyclization of Pimelates. Preliminary cyclization experiments aimed at establishing conditions for solid-phase Dieckmann reactions provided the observation that monomethyl and mono-*tert*-butyl adipoyl resin ester, cyclized with potassium *tert*-butoxide, yielded as exclusive autocleavage products methyl and *tert*-butyl 2-oxocarboxylates, respectively. The facility with which these products were isolated in high purity recommended the process as a potential source of unambiguously unidirectionally cyclized Dieckmann keto esters.

In order to ascertain whether this was indeed the nature of the reaction and to explore its generality, we carried out

Scheme II. Dieckmann Closure of Diesters



the synthesis and cyclization of a series of unambiguously ^{14}C-labeled 7-alkyl 1-resinbenzyl [1-^{14}C]pimelates (**10**)[22] and their nonresin models, the alkyl benzyl mixed esters (**11**)[22] (Scheme II). Monoethyl [1-^{14}C]pimelic acid (**9**) was synthesized starting with dibenzyl [1-$^{14}C_2$]malonate (**5**), which was alkylated with ethyl 5-bromovalerate (**6**) in DMF. Crude triester **7** was converted to diacid monoester **8** by hydrogenolysis, and **8** was decarboxylatively distilled followed by fractional distillation to give pure ethyl hydrogen pimelate (**9**). A Hunsdiecker type decarboxylation[23] was employed to establish the integrity of the label in the ethyl hydrogen pimelate **9** and gave an excellent yield of ethyl 6-bromohexanoate with <5% scrambling.



When 1-benzyl 7-ethyl [1-^{14}C]pimelate (**11**) was treated with potassium *tert*-butoxide, the product obtained in 66% yield contained no *tert*-butyl groups by NMR analysis.

(20) (a) Bodanzky, M.; Sheehan, J. T. *Chem. Ind. (London)* **1966**, 1597. (b) Frechet, J.; de Smet, M.; Fanal, J. *Polymer* **1979**, *20*, 675.
(21) Gisin, B. F. *Helv. Chim. Acta* **1973**, *56*, 1476.
(22) To avoid confusion in the nomenclature of these ^{14}C-labeled mono- and diesters, the ^{14}C carboxyl has always been numbered 1.
(23) Wiberg, K.; Lampman, G. M. *J. Am. Chem. Soc.* **1966**, *88*, 4429.

Column chromatography provided a product which was a 70/30 mixture of cyclic ethyl (**14**) and benzyl (**15**) keto esters. The mixture was decarboxylated under acidic conditions since alkaline hydrolysis might cause Claisen reversal and label scrambling. The decarboxylation proceeded smoothly in aqueous ethanolic 3 N HCl, and the cyclohexanone was recovered with benzene rather than hexane, with which the ketone forms a minimum-boiling azeotrope. The pertinent radioactivity results for this nonresin reaction are recorded in Table II.

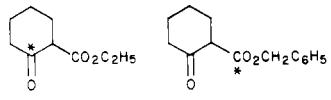
We have established that the two components of the keto ester mixture are being decarboxylated at approximately the same rate by comparing the specific activities of the first and second samples of $BaCO_3$ trapped, 7700 dpm/mmol and 6231 dpm/mmol, respectively. To determine whether equilibration of label took place during the Dieckmann cyclization, it was first necessary to prove that no unanticipated scrambling occurred during formation of the potassium salt of the half-ester or of the benzylic ester. One portion of this proof was obtained by HgO/Br_2 decarboxylation of labeled ethyl hydrogen pimelate (**9**) recovered from the synthesis of resin ester. Decarboxylation and chromatographic purification resulted in a bromo ester with 0.2% retention of label. Thus no equilibration took place during formation of the half-ester, and the neutral diester seems even less likely to undergo scrambling. These data confirm our earlier conclusion that no interchange took place during the fractional distillation of the monoester.

The additional resin and benzyl esters included in this study were 7-*tert*-butyl (**10b**, **11b**), 7-triethylcarbinyl (**10c**, **11c**), 7-*tert*-butyl 6-methyl (**12**), 7-triethylcarbinyl 5-ethyl (**13a,b**) pimelates, and 1-methyl 7-triethylcarbinyl [1-^{14}C]5-ethylpimelate (**13c**). The *tert*-alkyl hydrogen pimelates were prepared from 7-ethyl hydrogen [1-^{14}C]-pimelate (**9**) by transesterification and subsequently converted to diesters as described. Potassium ethoxide, *tert*-butoxide, and triethylcarbinolate were employed in the cyclizations.

tert-Butyl hydrogen 6-methyl[1-^{14}C]pimelate (**12b**) was prepared and converted to benzyl and resin ester, using methyl 2-methyl-5-bromovalerate obtained from diethyl methylmalonate and 1,3-dibromopropane in a manner analogous to the unsubstituted pimelates. 7-Triethylcarbinyl hydrogen 5-ethyl[1-^{14}C]pimelate (**13d**) was similarly prepared,[24] except that the triethylcarbinyl half-ester could not be obtained by transesterification. The *tert*-butyl half-ester **13e** was prepared by transesterification, converted to the 7-methyl 1-*tert*-butyl diester **13f** with methyl iodide, cleaved with anhydrous TFA to 7-methyl half-ester **13g**, and converted through the ester acid chloride to 1-triethylcarbinyl 7-methyl diester **13c** with lithium triethylcarbinylate.[25] The diester was hydrolyzed with 1 equiv of potassium hydroxide in diglyme/water/THF and then lyophilized, and the lyophilizate in DMF was attached to the resin.

Our first attempt to prepare the benzyl triethylcarbinyl diester **13b** by hydrolysis followed by benzylation with benzyl bromide resulted in a mixture of methyl and benzyl triethylcarbinyl diesters. This mixture, however, was converted in better than 90% yield to benzyl triethylcarbinyl diester **13b** by transesterification in benzyl alcohol with a trace of potassium benzylate in 8 h at room temperature, removing the methanol at reduced pressure as it was produced.

Table II. Solution Dieckmann Cyclization of 1-Benzyl 7-Ethyl[1-^{14}C]pimelate (11) with *tert*-Butoxide

compd	specific activity: dpm/mg	dpm × 10^{-3}/mmol	total,[a] dpm × 10^{-3}
$C_2H_5O_2C(CH_2)_5CO_2H$ **9** *	1123	211	1.175
$C_2H_5O_2C(CH_2)_5CO_2CH_2C_6H_5$ **11a** *	739	205	952
 **14a** **15a**	983	192	109[a]
$BaCO_3$	39.0	7.7[b]	56[c]
	82.4	8.07[d]	51[e]
 [f]	68.8	6.74[g]	

[a] The total count represents only a portion of the mixed keto ester produced in this reaction. The hot material was mixed with cold 30:70 benzyl ethyl keto ester mix to provide mixed ester with a calculated specific activity of 14 650 dpm/mmol. [b] This specific activity is for the first portion of CO_2 trapped during decarboxylation and contains CO_2 equivalent to more than 85% of the CO_2 of the keto ester sample. The second sample trapped contains CO_2 equivalent to 3–5% of the CO_2 of the keto ester and has a specific activity of 6231 dpm/mmol. [c] Total count included the activity of all three samples trapped during the decarboxylation. [d] Result was obtained by counting a benzene distillate from the crude benzene extract of the decarboxylation mix. The amount of cyclohexane was determined by VPC to be 8.48 mg. [e] Result was obtained by counting a sample of the total crude benzene extract of the decarboxylation mixture and a VPC analysis suggesting that all the components boiling higher than the ketone, excluding benzyl alcohol, amount to less than 5% of the ketone. [f] This line represents material from the latter portion of the decarboxylation. [g] Result was obtained by counting a sample of the residue after most of the benzene was removed by fractional distillation from the crude benzene extract. The amount of cyclohexanone was determined to be 17% of the residue by GC, and sample weight equivalent to 12.36 mg of ketone was weighed on an analytical balance.

Decarboxylation was again employed to determine label distribution within the 5-ethylpimelate, since a number of steps had been required in its preparation. The suitable substrate was the methyl ester **13g** rather than the triethylcarbinyl ester **13d**, since the latter might be expected to cleave under the conditions of the HgO/Br_2 reaction due to the presence of traces of HBr. The methyl ester **13c** was obtained by methyl iodide treatment of the residual DMF solution of 7-triethylcarbinyl hydrogen 5-ethylpimelate after preparation of the resin ester. The methyl triethylcarbinyl diester **13c** was cleaved with anhydrous TFA to the methyl monoester which was treated with HgO/Br_2, yielding $BaCO_3$ with <1% of the original activity. The very low activity of the $BaCO_3$ confirms that the location of the label was not scrambled during the synthesis of the substituted pimelic half-ester.

In order to separate the effect upon label scrambling due to Claisen reversal subsequent to cyclization and that due to transesterification prior to cyclization, a portion of the first unsymmetrically labeled ethyl keto ester **14a** was

(24) We are grateful to Dr. James Cason for a generous gift of 3-ethylglutaric acid, which was used in the preparation of methyl 3-ethyl-5-bromovalerate.

(25) (a) Hauser, C. R.; Chambers, W. J. *J. Am. Chem. Soc.* **1956**, *78*, 3837. (b) Indeed, in work reported earlier (ref 10b) we have shown that this is a predominant pathway for a slower reaction.

Table III. Distribution of ^{14}C between Keto and Carboxyl Carbonyl in a Series of Dieckmann Products from Unambiguously Labeled Pimelate and Substituted Pimelate Esters and Resin Esters

compd	base[a]	reaction time, min	specific activity, (dpm/mM) × 10^{-4}				% scrambling[b]
			ester	keto ester	$BaCO_3$	ketone	
10a, resin ethyl	$^tBuO^-$	25	63.4	7.50	2.66	4.44	71
10a, resin ethyl[c]	$^tBuO^-$	120	21.1	3.90	1.36	2.62	70
10a, resin ethyl[d]	$^tBuO^-$	5	14.4	4.25	1.26	3.05	59
Claisen reversal[e]	$EtO^-/^tBuO^-$	15	-	4.25	1.39	2.74	65
10b, resin *tert*-butyl[f]	$^tBuO^-$	2	34.0	32.4	2.58	29.9	15
10b, resin *tert*-butyl[f]	$TECO^-$	2	34.0	36.4	0.43	33.3	2.6
10c, resin TEC[g]	$TECO^-$	2	7.88	8.05	0.025	8.50	0.6
12, resin *tert*-butyl 6-methyl[h]	$TECO^-$	1.5	63.2	55.5	25.8	25.3	81
13a, resin TEC 5-ethyl[i]	$TECO^-$	2	53.0	46.5	1.52	-	5.5
11a, ethyl benzyl[j]	EtO^-	1.5	9.80	-	4.05	4.56	83
11a, ethyl benzyl[j]	$^tBuO^-$	1.5	9.80	0.875	0.26	0.39	58.5
11b, *tert*-butyl benzyl[g]	$^tBuO^-$	2	7.88	6.80	1.48	4.70	38
11b, *tert*-butyl benzyl[g]	$TECO^-$	2	7.88	8.60	0.16	8.20	4
11c, TEC benzyl[g]	$TECO^-$	2	7.88	-	0.13	-	3.4
13b, TEC benzyl 5-ethyl[i]	$TECO^-$	2	53.0	-	1.69	-	6.4
13c, TEC methyl 5-ethyl[i]	$TECO^-$	2	53.0	53.0	1.88	-	7.3

[a] 450 mol % indicated base, as the potassium salt, was used per mol of diester. Resin ester or diester was added in a single batch to refluxing toluene containing the base, except as indicated. TEC represents triethylcarbinyl. [b] Percent scrambling is shown as twice the percent label found in the $BaCO_3$, since this reaction must take place through a symmetrical intermediate, producing equal quantities of labeled and unlabeled ester carbonyl. Percent scrambling is calculated from $BaCO_3$ activity and keto ester activity; ketone specific activity is employed only as a check. [c] Reaction carried out at room temperature in drybox. [d] Hot keto ester mixed with cold keto ester, column chromatographed, and counted to obtain specific activity of keto ester. [e] Keto ester from 5-min reaction used with 60 mol % EtO^- and 450 mol % $^tBuO^-$. [f] Ester specific activity calculated from counting column-chromatographed and solvent-free *tert*-butyl pimelate half-ester. [g] Ester specific activity calculated from that of hot and cold ethyl half-ester, which was calculated from specific activity of hot ethyl ester and the weight of hot and cold ester in the mixture. [h] Ester specific activity calculated from that of undiluted hot ethyl half-ester. [i] Ester specific activity calculated from that of the mixture of hot and cold diethyl malonate, which was counted and checked by calculation. [j] Ester specific activity calculated from specific activity of hot ethyl half-ester mixed with cold in known amount.

treated under Dieckmann conditions for 15 min, reisolated and decarboxylated, and the products were counted. The data for location of label before and after Claisen reversal establish that the extent of scrambling increased no more than 9% in 15 min (Table III). A further Deickmann cyclization was performed on **11**, the closure being carried out at room temperature for 2 h. Under these conditions, we found 70% rather than 59% scrambling.

Column chromatography on silica was used to purify all half-esters, diesters, and keto esters. Mixtures of alkyl and benzyl keto esters could not be separated, however. For the Dieckmann product from the methyl triethylcarbinyl diester, the methyl keto ester was most concentrated in the earlier fractions and eluted with considerably less polar solvent than that required to remove ethyl cyclohexanone-2-carboxylate. The chromatographed mixture of keto esters was free of other contaminants, and alkyl benzyl mixtures were then hydrogenolyzed, converting the benzyl keto esters to keto acids. The keto acid/keto ester mixture was washed with sodium bicarbonate, leaving alkyl keto esters, which were decarboxylated. Attempted selective hydrolysis of the methyl and triethylcarbinyl keto ester mixture with 1 equiv of base at room temperature led only to recovery of mixed keto esters. Treatment of the mixed keto esters with anhydrous TFA resulted in keto acid which could be purified and counted as labeled keto acid rather than keto ester.

Dieckmann reaction of alkyl benzyl pimelates yielded mixtures of alkyl and benzyl keto ester. We established that, for mixtures of ethyl (**14a**) and benzyl cyclohexanone-2-carboxylates (**14d**), integration values for benzyl and ethyl methylenes, δ 4.5 (s) and 4.10 (q), respectively, provided an accurate analysis of composition. This was done by using sample mixtures whose composition was independently determined by using the hydrogenolysis procedure described above. For *tert*-butyl and benzyl mixtures, the *tert*-butyl resonance (δ 1.40 (s)) was compared with that for phenyl (δ 7.10 (s)), and for triethylcarbinyl and benzyl mixtures the comparison was made between the triethylcarbinyl methyl (δ 0.77 (t)) and the phenyl singlet. These latter analyses are not as good as the benzyl/ethyl analyses; however, they are useful for estimation of the composition of keto ester mixtures arising from benzyl alkyl Dieckmann reactions and for ensuring completeness of hydrogenolysis and bicarbonate extraction of the mixtures when purifying alkyl keto esters for decarboxylation.

The distribution of label in the keto esters resulting from Dieckmann reactions on pimelate esters are shown in Table III and yield data are shown in Table IV. The primary counting data obtained from the resin ester syntheses and Dieckmann and decarboxylation reactions are shown in Table V and those for the alkyl benzyl esters in Table VI.

Discussion

Our results present a clearly authenticated case in which steric control of the direction of closure in the Dieckmann reaction is attained by the use of mixed esters. Reactions of this sort have not been previously studied, except for casual observations noted in the introduction. Utilization of unambiguously single-labeled 7-ethyl 1-resin (**10a**) [1-^{14}C]pimelate [or benzyl (**11a**)] and potassium *tert*-butoxide in toluene has disclosed that four cyclic products are formed. Products **14a** and **15a** arise by direct cyclization of starting material. The precursors for **16a** and **17a** must be diethyl pimelate (**11e**) and the bis resin ester (**10d**), respectively, or transformed starting material with the label in the ethoxycarbonyl carbonyl. The conversion of **10a** to cyclic product can thus be described by the series of reactions in Chart I.

Of these, reactions 1 and 2 lead in a single step to products in which the label is not scrambled. Reactions 3 and 4 are unobservable under the conditions of our ex-

Table IV. Yields in Formation of Unsymmetrical Pimelate Diesters and in Their Dieckmann Cyclizations and Composition of Resulting Keto Esters

ester	base	yields: diester	yields: β-keto ester	mol % benzyl or resin β-keto ester
10a, resin ethyl	^{t}BuO$^-$	48	35	35
10b, resin *tert*-butyl	^{t}BuO$^-$	68	39	20
10b, resin *tert*-butyl	TECO$^-$	68	41	16
10c, resin TEC	TECO$^-$	84	46	22
12, resin *tert*-butyl 6-methyl	TECO$^-$	52	12	39
13a, resin TEC 5-ethyl	TECO$^-$	47	15	27
11a, ethyl benzyl	EtO$^-$	79	28	3.2
11a, ethyl benzyl	^{t}BuO$^-$	79	31	37
11b, *tert*-butyl benzyl	^{t}BuO$^-$	66	35	17
11b, *tert*-butyl benzyl	TECO$^-$	66	20	23
11c, TEC benzyl	TECO$^-$	70	34	10
13b, TEC benzyl 5-ethyl	TECO$^-$	90	36	21
13c, TEC methyl 5-ethyl	TECO$^-$	100	63	26[a]

[a] Mol % methyl keto ester in β-keto ester mixture.

periments. Reactions 5 and 6 require, in addition to the initial cyclization, Claisen reversal and recyclization and lead to scrambled label. Transesterification reactions 7 and 8 require only two steps and lead to scrambled label, while 9 and 10 require two steps, but lead to unscrambled esters **14a** and **15a**, as well as the *tert*-butyl keto esters **14b** and **16b**. Reaction 11 requires two transesterification steps followed by cyclization and leads to scrambled product. Kinetic competition among these reactions must account for the label distribution observed. Data collected in several of our experiments permit an evaluation of the relative importance of these processes.

Chart I. Various Paths for the Conversion of 7-Ethyl 1-Resin [1-^{14}C]Pimelate (10a) to Cyclic Products

$$10a + {}^-OC(CH_3)_3 \rightleftharpoons \textcircled{P}CH_2O^- + 14a \quad (1, 3)$$
$$\rightleftharpoons C_2H_5O^- + 15a \quad (2, 4)$$
$$14a + C_2H_5O^- \rightarrow 11e \xrightarrow{{}^-OC(CH_3)_3} 14a + 16a \quad (5)$$
$$15a + \textcircled{P}CH_2O^- \rightarrow 10d \xrightarrow{{}^-OC(CH_3)_3} 17a + 15a \quad (6)$$
$$10a + C_2H_5O^- \rightarrow 11e \rightarrow 14a + 15a \quad (7)$$
$$10a + \textcircled{P}CH_2O^- \rightarrow 10d \rightarrow 14d + 15a \quad (8)$$
$$10a \xrightarrow{{}^-OC(CH_3)_3} 11f \rightarrow 17f + 16f \quad (9)$$
$$10a \xrightarrow{{}^-OC(CH_3)_3} 10b \rightarrow 14b + 15b \quad (10)$$
$$10d + C_2H_5O^- \rightarrow 10e \rightarrow 17a + 16a \quad (11)$$

In particular, we have established that Claisen reversal took place to the extent of only 9% when a 70:30 mixture of **14a** and **16a** was subjected to Dieckmann conditions for 15 min. The keto ester obtained from this treatment was a 2:1 mixture of **14a** and **16a**. Since only 9% Claisen reversal scrambling occurred in an interval three times as long as that required to produce 60% scrambling in the Dieckmann product, we conclude that Claisen reversal can only intervene to the extent of 3/60, or 5%, in the scrambling observed in the ethyl keto ester produced by autocleavage. These results do not rigorously exclude a different kinetic relationship among the reactions leading to **15a** and **17a**, although we would expect reaction 6 to be slower than reaction 5 on the basis of steric considerations.

The cyclization of *tert*-butyl resin pimelate established that reaction 10 yields predominantly **14b** while reaction 9, by analogy with the cyclization of 1-methyl 7-benzyl 3-ethyl[1-^{14}C]pimelate (**13b**), the only unsymmetrical dialkyl ester studied, should yield mainly **16b**. Since purified keto ester mixtures from **10a** and **11a** contain no *tert*-butyl species, reactions 9 and 10 can be ignored as kinetically

Table V. Primary Yield and Radioanalytical Results for Resin Ester Cyclizations and Decarboxylations

ester	base	reaction time, min	wt, g	total counts, dpm × 10^{-5}: ester	keto ester	decarboxylation[a] sample	$BaCO_3$	ketone
10a, ethyl	^{t}BuO$^-$	25	3.0	2.61	0.62	0.35	0.13	0.22
10a, ethyl	^{t}BuO$^-$	5	4.0	2.61	0.42	0.13	0.043	0.080
10b, Bu^t	^{t}BuO$^-$	2	3.0	4.10	1.59	1.56	0.14	1.30
10b, Bu^t	TECO$^-$	2	2.9	3.94	1.62	1.30	0.016	1.13
10c, TEC	TECO$^-$	2	7.0	1.62	1.37	0.32	0.0084	0.25
12, 6-methyl Bu^t	TECO$^-$	2	5.5	6.60	0.76	0.70	0.22	0.16
13a, 5-ethyl TEC	TECO$^-$	2	6.0	5.00	0.74	0.68	0.021	0.61

[a] A specific portion of the purified keto ester product was weighed into the decarboxylation apparatus for each Dieckmann reaction. $BaCO_3$ plus ketone total counts should be the same as decarboxylation sample total counts.

Table VI. Primary Yield and Radioanalytical Results for Alkyl Benzyl Ester Cyclizations and Decarboxylations

ester	base	total counts, dpm × 10^{-5}: ester	keto ester	decarboxylation sample[a]	$BaCO_3$	ketone
11a, ethyl	EtO$^-$	5.04	3.11	-	0.41	-
11a, ethyl	^{t}BuO	3.40	1.93	0.43	0.22	0.23
11a, ethyl	^{t}BuO$^-$			0.16[b]	0.053	0.059
11b, Bu^t	^{t}BuO$^-$	0.71	0.46	0.23[b]	0.051	-
11b, Bu^t	TECO$^-$	1.27	0.75	0.71	0.15	0.54
11b, Bu^t	TECO$^-$	0.80	-	0.16[b]	0.016	0.14
11c, TEC	TECO$^-$	0.91	0.42	0.30	0.016	0.22
11c, TEC	TECO$^-$	0.43	0.14	0.11[b]	0.0027	0.089
13b, 5-ethyl TEC	TECO$^-$	1.92	0.69	0.48[b]	0.0091	0.48
13c, 5-ethyl TEC methyl	TECO$^-$	5.43	2.98	0.58[b]	0.024	0.52

[a] A specific portion of the purified keto ester product was weighed into the decarboxylation apparatus for each Dieckmann reaction. $BaCO_3$ plus ketone total counts should be the same as decarboxylation sample total counts. [b] These samples were hydrogenolyzed, extracted to remove acid, and chromatographically purified to remove ketone, in order to provide specific activity of pure keto ester.

Table VII. Summary of Results: Resin and Benzyl Alkyl Pimelate Dieckmann Cyclizations and Decarboxylations

		yield of cyclic keto ester, %			mol % benzyl keto ester		% scrambling		
ester	base	resin autocleaved	resin retained	solution alkyl-benzyl	resin	solution	resin autocleaved alkyl	solution alkyl	solution[a] mixture
10a, 11a, Et	EtO^-	-	-	28	-	3.2	-	83	100
10a, 11a, Et	$^tBuO^-$	35	35	31	35	37	59	58	100
10b, 11b, Bu^t	$^tBuO^-$	39	20	35	20	17	15	38	
10b, 11b, Bu^t	$TECO^-$	41	16	20	16	23	2.6	4.0	42
10c, 11c, TEC	$TECO^-$	46	22	34	22	10	0.6	3.4	18
12, 6-Me Bu^t	$TECO^-$	12	39	-	39	-	41[b]	-	-
13a,b, 5-Et TEC	$TECO^-$	15	27	36	27	21	5.5	6.4	48
13c, 5-Et TEC Me	$TECO^-$	-		63		26	-	7.3	-

[a] In some cases samples of the alkyl/benzyl keto ester mixture from solution (rather than resin) Dieckmann reactions were submitted to decarboxylation in order to determine scrambling on the mixture. This affords a calculated percent scrambling for the benzyl keto ester. [b] Percent scrambling is the percent activity in the $BaCO_3$ rather than twice the percent activity since the diester is unsymmetrical.

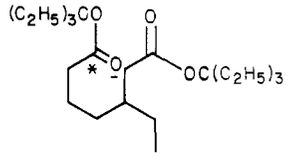
inconsequential. The same reasoning requires that other three-step transesterification processes involving *tert*-butoxide be excluded. Thus transesterification by ethoxide followed by cyclization must be responsible for the scrambling observed in keto ester autocleavage products. Reaction 11 implies that a significant amount of scrambled alkyl keto ester occurs by way of the double transesterification and cannot be excluded on the basis of our results.[25b] Pertinent results are summarized in Table VII to facilitate comparison of resin ester and alkyl benzyl ester data. The alkyl benzyl ester results do not differ qualitatively from those for resin esters; quantitatively, the resin reactions produced higher yields of purer keto ester in almost every case.

Results for the four unsubstituted pimelates show that the scrambling reaction is very sensitive to the steric demand of the departing alkoxide. The cyclization–transesterification ratio increases 100-fold upon changing from ethyl ester/*tert*-butoxide to triethylcarbinyl ester/triethylcarbinyloxide. The decrease in scrambling when ethyl ester is replaced by *tert*-butyl ester without a change in base must be due to the elimination of all ethoxide from the reaction mixture.

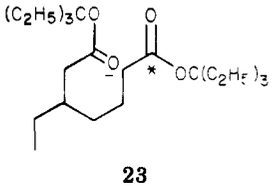
Transesterification by ethoxide must be at least 100 times more rapid than by *tert*-butoxide. This conclusion is based on the fact that 1% *tert*-butyl keto ester would be detectable by NMR in the presence of ethyl keto ester, and none was detected. Reduced scrambling observed in the *tert*-butoxide *tert*-butyl resin ester cyclization confirms that the *tert*-butoxide transesterification of *tert*-butyl resin ester is slower. The absence of triethylcarbinyl keto ester in the product from *tert*-butyl ester triethylcarbinyloxide reaction and a further reduction in scrambling suggest the same rate relationship between *tert*-butoxide and triethylcarbinyloxide catalysis. However, the expected 50–100-fold reduction in scrambling when ethyl ester was replaced with *tert*-butyl ester did not occur; reduction was on the order of 4-fold. This fact is best acommodated by assuming that the rate of Dieckmann cyclization is also reduced as the bulk of alkoxide and of ester group adjacent to the nucleophilic carbanion is increased. Thus, 100-fold reduction in the rate of transesterification occurring concurrently with 25-fold reduction in the rate of cyclization would result in an observed 4-fold rate decrease in transesterification relative to cyclization.

The cyclization results for the substituted resin pimelates are consistent with the conclusion that the direction of closure is determined by steric control. For the *tert*-butyl 1-resin ester of 6-methylpimelic acid, formation of keto ester from closure in both directions was accompanied by formation of di-*tert*-butyl 6-methyl pimelate which did not cyclize. The rate of cyclization of this resin ester is substantially slower than that of triethylcarbinyl pimeloyl resin ester. The triethylcarbinyl 5-ethylpimeloyl resin ester (**13a**) yielded keto ester which was a 97:3 mixture of 6-ethyl and 4-ethyl cyclohexanone-2-carboxylate, containing nine times as much labeled ester carbonyl as was observed in the unsubstituted case. Again, this supports the conclusion that steric hindrance has reduced the rate of cyclization at the more hindered carbanion relative to transesterification at the other end of the molecule and cyclization via a less hindered carbanion.

The percent scrambling figure reported for the unsubstituted resin ester pimelates is properly reported as scrambling. Scrambling must occur via a symmetrical dialkyl pimelate cleaved from the resin by transesterification or by a double transesterification process yielding scrambled resin ester. However, for the substituted pimelates, this is not the situation. The product of transesterification is an unsymmetrical diester, which can cyclize to a different extent in each direction. The two substituted pimelates are themselves different cases. For the 5-ethylpimelate diester **13c**, the anionic species prior to cyclization, assuming transesterification, would be **22** and **23**. Arguments could be advanced that **23** is the more



22



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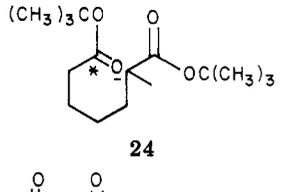

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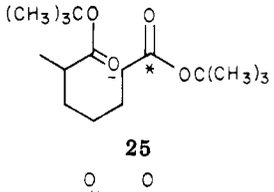

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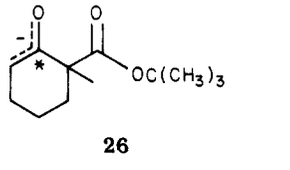

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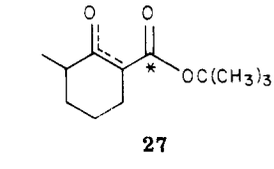


27

stable species on the grounds of basicity and that the tetrahedral intermediate resulting from **22** is less crowded. Thus it could be expected that all or most of the product observed from transesterified 5-ethylpimelate would be keto ester yielding labeled $BaCO_3$; indeed, this is the conclusion drawn in the literature.[13,15] It is quite likely the intervention of transesterification is only five times as

great as in the unsubstituted case.

It is more difficult to assess the extent of steric strain in the analogous species from the 6-methylpimelates **24** and **25**, although the same relative relationship probably exists, with **25** being less strained than **24**. Furthermore, our data on Claisen reversal were obtained for the unsubstituted case. We do not know whether substituted cyclohexanonecarboxylates undergo Claisen reversal at rates similar to the unsubstituted compounds. Particularly in the case of the 6-methyl compound, whose anionic keto ester enol pairs **26** and **27** are of very different stability, it seems probable that Claisen reversal of **26**, followed by formation of **27**, might be a very rapid reaction, kinetically competitive with transesterification and with the original cyclization to form **26**. It is synthetically and theoretically significant that 60% of the keto ester formed has the thermodynamically disfavored 2-methyl-2-alkoxycarbonyl structure.

Since reversal of cyclization does not occur at a rate sufficient to intrude into the results in the methyl triethylcarbinyl case, the effect of the basicity of the leaving alkoxide may be ignored. The kinetic competition being measured for cyclization of **13c** then can be seen as one between paths a and b, Scheme III, without transesterification. From this point of view, the dominant effect must be the relative steric hindrance to the formation of the tetrahedral intermediate with triethylcarbinyloxide bonded to a ring carbon, and with methoxide (or benzyloxide in the benzyl case) similarly bonded. Interestingly, in these reactions the resin benzyl group behaves as a moiety with small steric demand.

The chief contribution of the resin attachment is the assistance which it provides to purification. Benzyl/alkyl or mixed alkyl keto esters are very difficult to separate by chromatography, probably because mixtures of keto esters are present in the nonpolar eluting solvents mainly as dimers. In a mixture containing a small quantity of methyl along with triethylcarbinyl 6-ethylcyclohexanone-2-carboxylate, the methyl keto ester was present in substantial admixture with the tertiary alkyl keto ester in the earliest fractions. This result can be rationalized if the methyl keto ester is tied up preferentially in a mixed hydrogen-bonded dimer whose existence is sterically favored over the bis tertiary alkyl keto ester dimer. Thus it is more reasonable to find poor resolution of these dimers than of the monomeric keto esters. Our evidence suggests that the use of resin esters permits the best separation of unscrambled autocleavage products from the resin-bound isomers. In the case of the benzyl models, alternative chemical methods can be employed to effect this separation, but only after alteration of the products. The utility of the resin method is easily perceived in cases where the nature of the Dieckmann product precludes the use of chemical methods; e.g., olefinic keto esters would rule out the application of hydrogenolysis.

With regard to our transesterification findings, numerous observations have been reported of *tert*-butyl ester products from reactions, Dieckmann and otherwise, employing *tert*-butoxide and primary alkyl esters.[26,27] However, except for some rarely cited reports[28] and more recently molecular sieve assisted transesterifications,[29] these results have been treated as isolated or unique occurrences of little general utility. It is likely that this reaction occurred many times but has not been observed because the actual product is a mixture of esters, some resulting from the alkoxy group in the starting material and some from transesterification. The substantially less polar behavior of the *tert*-butyl esters, their consequent greater mobility during column chromatography, and their lability to mineral acid, may lead to the loss of the *tert*-butyl esters before they can be observed.[30]

The tetrahedral intermediate[13,31] deduced from hydrolysis experiments can be invoked since the same transesterification has been observed for a benzoate,[26] the reaction taking place in refluxing *tert*-butyl alcohol in 45 min, a rate relatively similar to those we have observed. While we had considered the possibility that a different mechanism was operating, in which α-proton removal by base preceded transesterification through some transition state different from the usual tetrahedral intermediate,[32] the fact that a similar reaction takes place with an ester having no α protons argues against this change in mechanism.

An interesting aspect of these results is that in extending the synthetic application of transesterification to these severely strained conversions, we appear to have defined cases sufficiently strained as to be not synthetically useful. While 7-*tert*-butyl hydrogen 5-ethylpimelate can be prepared in moderate yield by transesterification, the yield of ester from the 6-methyl analogue was quite low. Several attempts at the preparation of 7-triethylcarbinyl hydrogen 5-ethylpimelate by transesterification failed. Under the most favorable conditions, the yield of triethylcarbinyl ester was only 25% of the yield of diacid. This appears to be the result of rapid alkaline cracking of the triethylcarbinyl half-ester to olefin and carboxylate salt. Presumably the yield picture would be even worse in the case of the triethylcarbinyl 6-methyl half-ester.

The best conditions for transesterification developed from the observation that lower temperatures kinetically favor transesterification, while higher temperatures favor Claisen condensation. This observation in the case of the Dieckmann reaction proved equally true in the bimolecular case. Thus, when trial transesterifications of half-esters were conducted at the temperature of refluxing benzene/*tert*-butyl alcohol or benzene/triethylcarbinol, Claisen dimer formed at the unchanged ester carbonyls was the major product. On the other hand, when these transesterifications were conducted at lower temperatures, employing a moderate vacuum to azeotropically remove ethanol or methanol, virtually no Claisen dimer was observed, and the major product was transesterified ester. The contaminant present in largest quantity was unchanged methyl or ethyl half-ester.

Our results establish that the rate of cyclization of pimelic diesters is very sensitive to the relative bulk of the esterifying alcohols. With large enough differences be-

(26) Johnson, W. S.; McCloskey, A. L.; Dunnigan, D. A. *J. Am. Chem. Soc.* **1950**, *72*, 514.
(27) Beyerman, H. C.; Hindriks, H.; de Leer, E. W. B. *Chem. Commun.* **1968**, 1668.
(28) (a) Baltes, J.; Weghorst, F.; Wechmann, O. *Fette, Seifen, Anstrichm.* **1961**, *63*, 413. (b) Baltes, J.; Wechann, O. *Ibid.* **1961**, *63*, 413.
(29) Roelofsen, D. P.; DeGraaf, J. W. M.; Hagendoorn, J. A.; Verschoor, H. M.; van Bekkum, H. *Recl. Trav. Chim. Pays-Bas* **1970**, *89*, 193.
(30) A significant consequence of the prevalence of transesterification during the Dieckmann is the need to reinterpret widely utilized data on yields of closure to rings of various sizes (see ref 4). When difficult, slow closures are attempted, for example, to cyclooctanones or cyclotetradecanones with potassium *tert*-butoxide, transesterification proceeds more rapidly than cyclization. Thus yields of ketone reported from this procedure result from decarboxylation of the *tert*-butyl keto ester or from mixtures of the ethyl and *tert*-butyl keto esters. The relative rates of closure which are frequently estimated from these yields are actually for closure of the *tert*-butyl esters. Competition between monomeric and dimeric cyclization are valid for the *tert*-butyl esters but may not be valid for the diethyl esters, as is currently assumed.
(31) Bender, M. L. *J. Am. Chem. Soc.* **1953**, *75*, 5986.
(32) (a) Bender, M. L. *J. Am. Chem. Soc.* **1951**, *73*, 1626. (b) Pratt, R. F.; Bruice, T. C. *J. Am. Chem. Soc.* **1970**, *92*, 5956.

tween these alkyl groups, closure of substituted diesters can be effected in the direction opposite to that predicted by the literature discussed above. Since these reactions do not involve significant equilibration (less than 5%), this effect is almost certainly steric rather than electronic.

We have observed the intervention of transesterification reactions which compete kinetically with Dieckmann closure and have established that these reactions are even more sensitive to steric hindrance than the Dieckmann reaction, although much more hindered transesterification reactions take place than is generally recognized. Cyclization reactions as well as noncyclic Claisen reactions in toluene show dramatically larger increases in rate with increases in temperature than do the transesterifications.

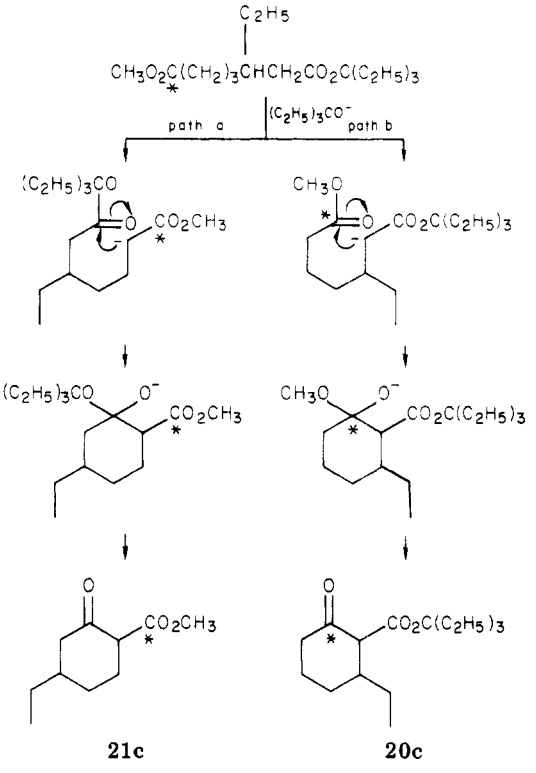
A particularly significant result of this work is the unidirectional closure of 7-triethylcarbinyl 1-aralkyl pimelates described here which provides a superior route to unambiguously labeled or substituted cyclohexanone-2-carboxylates. Our method requires few steps and is capable of extension to the synthesis of other than six-carbon rings. The use of esters in which one carboxyl provides attachment to a resin support affords a clear benefit over the benzyl case in specificity and greatly simplifies isolation and purification of the mixed diester and β-keto ester. These results are summarized in Table VII. We are presently investigating the generalization of this method, although the utilization of hyperentropic effects from solid-phase mixed esters will require more rigid resins than the 2% cross-linked polystyrene we have used.

Experimental Section[33]

Infrared Spectra of Resin Samples. Infrared difference spectra were obtained by inserting pellets of the sample resin in the sample beam and pellets of unmodified debenzoylated polystyrene beads in the reference beam. Two mixes of KBr and resin beads were used as follows: 10 mg of beads and 190 mg of KBr, and 36 mg of beads and 750 mg of KBr, and the resin beads were weighed into the Wig-L-Bug capsule and to this was added the KBr. After two 1-min periods of mixing, the sample was transferred to a pellet die warmed to 50 °C. The pressing was preceded by a manual compression of the mix with the ram of the die, the quality of pellets being very dependent on this prepressing of the KBr–polystyrene mixture. Pressing was carried out for 1 min, followed by 30 s of heating of the assembled die and pellet at 50 °C, followed by repressing for 1 min, both pressings at 20 000 lbs/sq in. The quantities of modified resin in the sample pellets were adjusted so as to result in pellets containing approximately the same amount of unmodified phenyl residues as are contained in 10 mg of unreacted polystyrene beads.

(33) Infrared spectra were obtained on a Perkin-Elmer Infracord 137 or 237; UV spectra were taken on a Cary Model 14 spectrophotometer; and NMR spectra were obtained on Varian Associates A-60 or T-60 instrument and are reported as δ values relative to internal tetramethylsilane. Low-resolution mass spectra were obtained on a CEC 21-110B spectrometer. Radioactive counting was performed on a Nuclear Chicago Corporation Mark I liquid scintillation counter (Model 6880). All counts are in disintegrations per minute (dpm) relative to external or internal standards. All liquid scintillation counting was carried out with 15-mL aliquots of either a solution of 18 g of 2,5-diphenyloxazole (PPO), 0.4 g of 1,4-bis[2-(5-phenyloxazoyl)]benzene (POPOP), and 4 L of toluene for samples containing no water and soluble therein, or a solution of 18.0 g of PPO, 0.4 g of POPOP, 200 g of naphthalene, 1 L of ethanol, 1.4 L of toluene, and 1.6 L of dioxane for aqueous samples and for resin beads. In the case of resin beads, 0.4 g of Cab-O-Sil was added directly to the scintillation vial, and the solution was deaerated in an ultrasonic bath before counting. Chromatography was carried out on silica gel for chromatography, extra pure, E. Merck, and elutions were with hexane–diethyl ether mixtures, varying from 2:1 for the most polar to 50:1 for the least polar compounds. All solvents and reagents were purified and fractionally distilled where feasible; otherwise reagent-grade materials were used. All solutions of reaction products were dried over Na_2SO_4 and concentrated in vacuo by using a Berkeley rotary evaporator. Elemental analyses were performed by the Analytical Laboratory, Department of Chemistry, University of California, Berkeley.

Scheme III. Alternative Paths for Cyclization of Methyl Triethylcarbinyl 5-Ethylpimelate



The same standard pellet of 10 mg of polystyrene beads and 190 mg of KBr was used as a reference pellet for most spectra.

Debenzoylation of Polystyrene Beads. Bio-Beads SX-2 (20 g, from Bio-Rad, Richmond, CA) and potassium *tert*-butoxide (2 g) were refluxed in toluene for 30 min. The reaction was cooled, 4.5 g of acetic acid in 15 mL of toluene was added with stirring and the suspension filtered. The toluene/acetic acid filtrate was combined with two hexane washes, extracted with aqueous bicarbonate, and concentrated. Benzoic acid (0.059 g, 0.3%) was recovered from the bicarbonate solution. From the organic phase, 0.226 g of residue was recovered which appeared to be mainly styrene and low molecular weight polystyrenes. We saw no NMR evidence of *tert*-butyl benzoate or benzaldehyde. The resin was washed, as were all succeeding resin reaction products, by passing solvents through the filter funnel on which it was retained. Each wash consisted of sufficient solvent to produce a slurry in the filter funnel, and this slurry was thoroughly stirred after the addition of each new solvent. The washing schedule consisted of methanol (3×), water (6×), methanol (3×), CH_2Cl_2 (2×), methanol (3×), CH_2Cl_2 (2×), methanol (3×), and ether (2×). This wash was followed by 16 h of drying at 55 °C (5 mm). The debenzoylated resin resulting from this treatment showed a weak hydroxylic absorption and weak negative peaks in the ester carbonyl (1740 cm^{-1}) and C–O stretching (1280–1270 cm^{-1}) regions. Unmasked hydroxyl groups were methylated by suspending 20 g of debenzoylated resin in 200 mL of toluene, distilling the toluene, and adding 200 mL of dry tetrahydrofuran. To the vigorously stirred suspension in an argon atmosphere was added 10 mL of 15% butyllithium in hexane and after 30 min, 30 g of methyl iodide was added and the mixture heated at reflux for 18 h. The resin was then reisolated and dried in the usual way, yielding 18.7 g of material free of OH absorption.

Chloromethylation of Polystyrene. Chloromethylation of Bio-Beads was carried out generally in a manner similar to that reported.[8a,9] Bio-Beads SX-2 (100 g) were stirred in chloromethyl methyl ether (400 mL) for 1 h at 25 °C and then cooled to −3 °C. A solution of $SnCl_4$ in chloromethyl methyl ether, cooled in the same bath, was quickly added with stirring and the stirring was continued for 12 min. At this point, stirring was discontinued and the reaction mixture was filtered as rapidly as possible through a coarse 600-mL sintered-glass funnel modified to maintain a dry nitrogen atmosphere; filtration was carried out by a combination of nitrogen pressure and aspirator vacuum. When the main flow

of chloromethyl methyl ether had ceased, the resin was washed in portions in the same apparatus with 2 L of dioxane/water (3:1), followed by 2 L of dioxane/3 N HCl (3:1), and further washed with distilled water until the washing was completely free of chloride, as monitored with $AgNO_3$ solution. The resin was then washed and dried as described above.

The amount of $SnCl_4$ was generally 1.50 mL, but because of considerable variation in extent of chloromethylation from batch to batch, a 10-g pilot batch of chloromethylated resin was prepared each time a new sample of Bio-Beads or freshly distilled ether was employed. The actual amount of catalyst and time of reaction were adjusted on the basis of the results of the pilot reaction. This procedure yielded resin of 0.7–1.5% Cl, according to quantitative IR analysis.

Monoethyl Pimeloyl Resin Ether. Ethyl hydrogen pimelate (564 mg) and K_2CO_3 (220 mg) in 150 mL of DMF were heated at 150 °C in a nitrogen atmosphere with stirring for 30 min. Chloromethylated resin (10 g, 0.7% Cl), equivalent to 67 mol % of the monoethyl pimelate, was added, and heating and stirring were continued at 150 °C for 10 h. The reaction mixture was cooled to 25 °C, filtered, washed, and dried to yield 9.95 g (% Cl <0.1%).

Dieckmann Reaction of Resin Esters. The Dieckmann reaction was carried out in dry nitrogen atmosphere with vigorous stirring. In general the procedures were patterned after those of Leonard and Schimmelpfenig.[4] All reactions on resin esters as well as benzyl or methyl *tert*-alkyl pimelates were accomplished by addition of ester to a refluxing toluene solution of alkoxide, 450 mol % base in 15 mL of toluene per gram of resin ester. Reactions were conducted for various lengths of time and these data appear in the tables. Potassium *tert*-butoxide was weighed into the apparatus in a drybox and the apparatus was immediately blanketed with dry nitrogen before being brought to reflux temperature. Potassium triethylcarbinolate was prepared from a weighed quantity of potassium in an excess of triethylcarbinol, which was then codistilled from the flask with a fivefold excess of toluene, with which it appears to form a mixture boiling at about 125 °C. The residual carbinolate was transferred in the closed distillation apparatus to the drybox, removed, and allowed to cool.

At the end of the reaction, the mixture was cooled to room temperature, a small excess of acetic acid was added, the mixture was filtered, and the resin was washed twice with two 100-mL portions of hexane. The toluene filtrate and hexane washes were combined and extracted with saturated aqueous sodium bicarbonate, the organic phase was concentrated, and the residue was purified by chromatography. On several occasions the bicarbonate solution was acidified with acetic acid and extracted with ethyl ether, and the ether solution was washed five times with water and concentrated. Infrared and NMR analyses always suggested that this material was mainly diacid. The resin was washed with three 100-mL portions of methanol which were combined and concentrated, the residue was dissolved in ether, washed three times with water, and reconcentrated. The resin was washed and dried according to the usual schedule. Product resin spectra are consistent with cleavage of a portion of the original ester and retention of a portion as keto ester.

7-(*p*-Cymyl) Chloride. Cumene (150 mL, 129 g) and $ClCH_2OCH_3$ (300 mL) were mixed and 10 mL of $SnCl_4$ was added. This reaction mixture was stirred at 0 °C for 2 h, washed with water, cold concentrated HCl, and water, dried over $CaCl_2$, filtered, and distilled in the spinning-band column. Cumene (50 g, 40.2%) contaminated with formaldehyde polymers was collected at 48–53 °C (35 mm). 7-(*p*-Cymyl) chloride[34] (51.3 g, 28.4% yield, bp 126–130 °C (35 mm), 116 °C (18 mm), 91–95 °C (6 mm)) was collected as the major fraction: IR 1254 (d, CH_2Cl), 825 and 840 cm^{-1} (d, *p*-disubstituted Ar).

7-(*p*-Cymyl) Methyl Ether. 7-(*p*-Cymyl) chloride (2 mL) was added to 25 mL of 1 N sodium methoxide in methanol and stirred at room temperature for 16 h. The product was washed with water and extracted with ethyl ether, and the ether solution was dried, filtered, and evaporated. The residue was fractionated and 7-(*p*-cymyl) methyl ether[35] collected at 110 °C (25 mm): IR 1110 (CH_3O), 820 and 845 cm^{-1} (d, *p*-disubstituted Ar).

7-(*p*-Cymyl) Acetate. 7-(*p*-Cymyl) chloride (62.75 g), glacial acetic acid (23.4 g), triethylamine (28.2 g), and 315 mL of ethyl acetate were refluxed overnight. The reaction mixture was cooled in an ice–water bath, the triethylammonium chloride was removed by filtration, and the ethyl acetate solution was washed with water, aqueous sodium bicarbonate, and twice with water, dried, filtered, and evaporated. The residue was fractionated to yield cymyl chloride (19 g, 30.2%, bp 126–130 °C (35 mm)) and cymyl acetate[36] (40 g, 55.7%, bp 150–157 °C (35 mm)): IR 1735 cm^{-1} (C=O).

7-(*p*-Cymyl) Alcohol. 7-(*p*-Cymyl) acetate (55 g) was refluxed for 3 h in 300 mL of 90% aqueous methanol containing 20 g of sodium hydroxide. The reaction mixture was evaporated and extracted with ethyl ether, the ether solution was washed twice with water, once with sodium bicarbonate, and once with water, dried, and filtered, and the ether was evaporated. The residue was fractionated, yielding cymyl alcohol (31 g, 72%, 157 °C (35 mm)) and residue, mainly dicymyl ether (10 g, 24%). Cymyl alcohol[37] was identified by its IR spectrum, and the ether was identified by its IR spectrum and the fact that treatment with HBr in methylene chloride produced only cymyl bromide: IR 3310 cm^{-1} (OH), no carbonyl.

Cymyl Bromide. Hydrogen bromide was passed through a solution of 25 g of cymyl alcohol in 25 mL of glacial acetic acid, maintained at 45 °C, for 1 h. The resulting mixture was cooled to 5 °C, dissolved in 50 mL of hexane, washed with ice water and an ice-cold solution of saturated sodium bicarbonate, dried, and filtered. The resulting hexane solution was fractionated to give cymyl bromide:[34] bp 125–127 °C (21 mm); NMR (CCl_4) δ 1.10, 1.23 (d, CH_3, 6 H), 2.80 (heptet, $CHMe_2$, 1 H), 4.28 (s, $C_6H_5CH_2$, 2 H), 7.12, 7.15 (d, Ar, 4 H); IR 1225 and 1200 (d), 820 and 830 cm^{-1} (*p*-disubstituted Ar).

7-(*p*-Cymyl) Methyl Sebacate. 7-(*p*-Cymyl) chloride (2.08 g), methyl hydrogen sebacate (2.70 g), and triethylamine (1.14 g) dissolved in 35 mL of ethyl acetate were refluxed for 16 h. Isolation was carried out in the same manner as for the acetate. The crude material crystallized at 0 °C and was identified as 7-(*p*-cymyl) methyl sebacate: IR 1715 cm^{-1} (C=O).

Dibenzyl malonate was prepared from diethyl malonate as directed.[38] Radioactive material was prepared by adding 250 μCi of diethyl [1-^{14}C]malonate to 71.0 g of diethyl malonate. This material had a specific activity of 8260 dpm/mg and 1.320×10^6 dpm/mmol.

Ethyl 5-Bromovalerate. 5-Bromovaleronitrile (100 g) was hydrolyzed[39] to the acid by refluxing for 17 h in 48% HBr, cooling the mixture to room temperature, dissolving the organic phase in ether, and extracting the aqueous layer twice with ether. The combined ether portions were washed with water, filtered, dried, and evaporated. The product was digested in 1400 mL of hexane/ether (25:1), decanting hot from any remaining insoluble material, and recrystallized at −5 °C to yield 45 g (38%) of 5-bromovaleric acid, mp 40 °C (lit.[40] mp 40 °C).

The bromo acid was refluxed with 40 mL of absolute ethanol, 20 mL of toluene, and 6 drops of H_2SO_4 for 1.5 h, during which time 35 mL of solvent was collected in a Dean–Stark trap. The reaction mixture was cooled to room temperature, dissolved in ether/hexane (1:1), washed with water and saturated $NaHCO_3$, dried, filtered, and evaporated. The yield was 46 g (88.5%) of ester which possessed satisfactory NMR and IR spectra.

1-Benzyl 7-Ethyl 2-((Benzyloxy)carbonyl)pimelate (7). Dibenzyl sodiomalonate was prepared in benzene and the benzene was partly evaporated, leaving a viscous mass which solidified on cooling. Ethyl 5-bromovalerate (21 g) in 100 mL of DMF was added, the dropping funnel was washed with an additional 50 mL of DMF, the bath temperature was raised to 132 °C, distilling any remaining benzene from the solution, and refluxing was continued for 1.5 h. The reaction mixture was allowed to cool to room temperature and 0.25 mL of glacial acetic acid was added.

(34) Baker, J. W.; Nathan, W. S. *J. Chem. Soc.* **1935**, 1844.
(35) Sharp, D. B.; Patrick, T. M., Jr. *J. Org. Chem.* **1961**, *26*, 1389.
(36) Tommila, E. *Ann. Acad. Sci. Fenn. Ser. A* **1942**, No. 4, 3.
(37) Cooke, R. G.; Gillespie, D. T.; Macbeth, A. K. *J. Chem. Soc.* **1938**, 1825.
(38) Bowman, R. E. *J. Chem. Soc.* **1950**, 325.
(39) Kendall, E. C.; McKenzie, B. "Organic Syntheses"; Wiley: New York, 1941; Collect. Vol. 1, p 131.
(40) Boorman, E. J.; Linstead, R. P.; Rydon, H. N. *J. Chem. Soc.* **1933**, 568.

Water was added and the organic materials were extracted with three portions of ether/hexane (5:1) which were combined, washed with water and saturated $NaHCO_3$, dried, filtered, and evaporated, yielding 43 g (83%) of crude triester.

5-(Ethoxycarbonyl)-1,1-pentanedicarboxylic Acid (8). Crude triester (34.0 g) was dissolved in 30 mL of ether, 3.5 g of 10% Pd/C was added, and the mixture was shaken at 40 lbs of hydrogen pressure for 90 min at which time hydrogen uptake ended. The solution was filtered, the catalyst cake was washed with ether, and the ether solutions were combined and evaporated, yielding 22.3 g of crude triacid monoester: specific activity 4834 dpm/mg, 1.121×10^6 dpm/mmol, corresponding to 1.078×10^8 dpm total count, radiochemical yield of 77%.

Ethyl Hydrogen Pimelate (9). Crude triacid monoester was distilled at 190 °C (5 mm), yielding 10.72 g of ethyl hydrogen pimelate, specific activity 3360 dpm/mg, 6.317×10^5 dpm/mmol, 3.595×10^7 dpm total, overall radiochemical yield of 55% based on diethyl malonate. Inactive triacid monoester (4.79 g), previously prepared in the same manner and purified by recrystallization, was added and decarboxylative distillation was continued, yielding a further 4.08 g of ethyl hydrogen pimelate: specific activity 1009 dpm/mg, 4.12×10^5 dpm/mmol, an additional 6.2% radiochemical yield. To this 4.08 g of monoester was added 1.90 g of inactive monoethyl pimelate and this material was fractionally distilled, yielding 4.6 g of pure ethyl hydrogen pimelate, specific activity 503 dpm/mg, bp 170–176 °C (11 mm). The 10.72 g of hemiester was similarly fractionated, yielding 7.33 g of pure material, specific activity 3293 dpm/mg. To the residue from this distillation was added 2.39 g of inactive half-ester. Continued fractionation yielded 2.43 g of less radioactive ester. This material was combined with 2.72 g of the other low-activity fraction, yielding 5.15 g of pure ethyl hydrogen pimelate, specific activity 1123 dpm/mg.

Analytical Decarboxylation of Ethyl Hydrogen Pimelate. Monoethyl pimelate was decarboxylated with HgO/Br_2[23] in a radiochemical yield of 95%. Isolation was accomplished by filtering the reaction mixture and evaporating to remove CCl_4. The residue was counted prior to any other treatment and was then purified by column chromatography, eluting with hexane/ether (9:1).

1-Benzyl 7-Ethyl [1-^{14}C]Pimelate (11a). Monoethyl pimelate (carboxyl labeled, 2.07 g) was added to 75 mL of DMF, followed by 0.79 g of powdered K_2CO_3. The mixture was heated under nitrogen to 130–160 °C for 30 min and then benzyl chloride (1.39 g) in 5 mL of DMF was added. Stirring at 160 °C under nitrogen was continued for 3 h, followed by cooling, adding 150 mL of water, and extracting the organic material with ether. The ether solution was washed with saturated $NaHCO_3$ and water, hexane (20% by volume) was added, and the ether/hexane solution was dried, filtered, and evaporated, yielding 2.64 g of 1-benzyl 7-ethyl [1-^{14}C]pimelate: specific activity 739 dpm/mg, 1.759×10^5 dpm/mmol, total activity 1.951×10^6, radiochemical yield of 84%.

7-*tert*-Butyl Hydrogen 6-Methyl[1-^{14}C]pimelate (12b). Diethyl sodiomethylmalonate was prepared from sodium ethoxide and diethyl methylmalonate (38.8 g) in 40 mL of dry benzene. This mixture was added over 1 h to a stirred solution of 1,3-dibromopropane (170 g) in 120 mL of dry benzene at 80 °C. The reaction mixture was cooled and poured over ice, hexane was added, and the organic phase was washed with water. The hexane solution was dried, filtered, and distilled, yielding a forerun of 1,3-dibromopropane (125 g), a fraction containing starting malonate and diethyl (3-ethoxypropyl)methylmalonate (14.2 g), bromo diester (27.5 g), and a pot residue (4.3 g) of tetraester. The bromo diester was hydrolyzed by refluxing in ethanol/4 N HBr (1:3) for 48 h, distilling at reduced pressure, and esterifying in absolute ethanol containing a trace of 48% HBr. The product was extracted into hexane, washed with bicarbonate, dried, filtered, and distilled to yield 7.2 g (14.3%) of 1-ethyl hydrogen 2-methylpimelate, bp 103–111 °C (13 mm).

7-Ethyl hydrogen 6-methyl[1-^{14}C]pimelate was prepared as above and as previously described for labeled monoethyl pimelic acid, except that it was purified by column chromatography rather than distillation; yield 21%. 7-*tert*-Butyl hydrogen 6-methyl[1-^{14}C]pimelate was prepared from the ethyl half ester by transesterification.

7-Triethylcarbinyl Hydrogen 5-Ethyl[1-^{14}C]pimelate (13d). 3-Ethylglutaric acid was converted to the anhydride[41] as directed except that a small quantity of acetyl chloride was added to the reaction mixture as an acetic acid scavenger: yield, 96%; bp 160–163 °C (13 mm). The 3-ethylglutaric anhydride (75.7 g) in dry ether was added under nitrogen to a 35% excess of $LiAlH_4$ in ether at room temperature with stirring. After 3 h of reflux, the reaction mixture was decomposed with ammonium chloride solution and extracted twice with water, the aqueous layers were combined and extracted twice with ethyl acetate, and the organic phase was dried, filtered, and concentrated to yield 63 g of a mixture of β-ethyl-δ-valerolactone and δ-hydroxy acid. A 40-g portion of this mixture was refluxed for 3 h with 160 g of 48% HBr, extracted with CH_2Cl_2, and esterified with 60 mL of methanol and 0.5 mL of 48% HBr at reflux for 3 h. This reaction mixture was extracted with hexane, washed with saturated aqueous $NaHCO_3$, dried, filtered, and distilled to yield methyl δ-bromovalerate[42] (36.2 g, 39% overall from 3-ethylglutaric anhydride).

7-Methyl hydrogen 5-ethyl[1-^{14}C]pimelate was prepared as previously described for monoethyl pimelate and the 2-methyl half-ester. Starting material of 143×10^6 dpm yielded 19 g of pure half-ester, 48×10^6 dpm; radiochemical yield, 68%.

7-*tert*-Butyl Hydrogen 5-Ethyl[1-^{14}C]pimelate (13e). In 100 mL of *tert*-butyl alcohol in a 500-mL flask affixed to the bottom of a spinning-band column and with a gentle dry nitrogen purge, potassium (5.3 g) was dissolved with stirring and refluxing. The solution was cooled to room temperature and 7-methyl hydrogen 5-ethyl[1-^{14}C]pimelate (13.7 g, 32.4×10^6 dpm) was added with stirring. Benzene (60 mL) was added and the pressure was reduced to 100 mm so that gentle reflux took place with the still-head temperature at 50 °C. This was continued for 48 h with a reflux ratio of 25:1 to 50:1. The reaction mixture was cooled to room temperature, 8.2 g of acetic acid in benzene was added, the reaction mixture was washed with water, the water was reextracted with benzene, and the benzene layers were combined, washed again with water containing 0.5 g of $NaHCO_3$, dried, filtered, concentrated, and chromatographed to yield 7.15 g, 14×10^6 dpm, of *tert*-butyl ester and 3.4 g of recovered methyl ester; radiochemical yield, 57.5%.

7-*tert*-Butyl 1-Methyl 5-Ethyl[1-^{14}C]pimelate (13a). The *tert*-butyl half-ester (6.02 g) was converted to the potassium salt in DMF with a 15% excess of K_2CO_3 and heated at 100 °C with 4.50 g of methyl iodide, using a dry ice/acetone cooled cold-finger reflux condenser. This reaction was continued for 6 h, cooled, taken up in hexane, washed three times with water and once with saturated aqueous $NaHCO_3$, filtered, and concentrated to yield 5.74 g, 11.5×10^6 dpm; radiochemical yield, 95.5%.

7-Triethylcarbinyl 1-Methyl 5-Ethyl[1-^{14}C]pimelate (13b). The *tert*-butyl methyl diester (4.64 g) was dissolved in 15 g of trifluoroacetic acid and evaporated to constant weight, and the residue was dissolved in ether. To this solution was added 600 mol % thionyl chloride and the reaction mixture was stirred under nitrogen for 8 h. Concentration left 3.59 g of acid chloride which was used without further purification. Lithium triethylcarbinolate, 105 mol %, was prepared by adding the equivalent quantity of *n*-butyllithium in hexane to a solution of triethylcarbinol in ether,[25] cooled with liquid nitrogen. This suspension of alkoxide was added to the acid chloride in ether, allowed to stand for 4 h, and then refluxed for 2 h. The product was extracted with hexane, the hexane was washed with cold $NaHCO_3$, dried, filtered, and concentrated, and the residue was purified by column chromatography.

Potassium 7-Triethylcarbinyl 5-Ethyl[1-^{14}C]pimelate. The potassium salt of the triethylcarbinyl half-ester was obtained by treatment of the triethylcarbinyl methyl diester in 20 mL of diglyme with 105 mol % KOH. This solution was maintained at 35 °C for 1 h, the entire hydrolysis mixture was lyophilized, and the residue was employed in the usual manner in the synthesis of triethylcarbinyl 3-methyl pimeloyl resin ester.

Decarboxylation and Counting of Keto Ester Products. The decarboxylation of the keto ester products and collection of the carbon dioxide were carried out in an apparatus which consisted of a 100-mL flask sealed to the bottom of a 1-ft water-cooled

(41) Cason, J.; Gastaldo, C.; Glusker, D.; Allinger, J.; Ash, L. *J. Org. Chem.* **1953**, *18*, 1129.
(42) Fieser, L. F. et al. *J. Am. Chem. Soc.* **1948**, *70*, 3206.

reflux condenser and connected in series to a CO_2 collection apparatus; CO_2-free nitrogen was introduced through a soda–lime and $CaCl_2$ tube as a slow purging stream at the head of the reflux condenser. The CO_2 was caught in carbonate-free NaOH of sufficient concentration to exceed (in each trapping vial) the stoichiometric requirements anticipated from the sample. This carbonate solution was converted to barium carbonate by addition of $BaCl_2$, protected from the air with a serum cap, and alternatively washed and centrifuged until neutral; it was then washed twice with acetone, filtered, dried, weighed, and counted by the technique described.[43]

Estimation and Counting of Cyclic Ketones from Decarboxylation. The aqueous ethanolic HCl solution containing cyclic ketone after decarboxylation was extracted six times with benzene and the benzene solutions were combined, washed with saturated aqueous $NaHCO_3$, and distilled through a small vacuum-jacketed column. The last 0.5 mL of distillate was collected separately and further distilled in a small apparatus. The pot residue (0.1–0.2 g) was analyzed by GC (SE-30, 10 ft × $^1/_6$ in.) for cyclic ketone, in comparison with benzene solutions of authentic ketone. Extrapolations were made over no more than 10% of the concentration of ketone. Occasionally, analyses were interpolated between two standards differing by no more than 25% from the sample. Samples of 5 μL were injected.

If the concentration of ketone was too low in the concentrated distillate, the pot residue was distilled in a bulb-to-bulb unit, and distillate was analyzed. A portion of the distillate, after analysis, was weighed into a scintillation vial and counted, and the specific activity of the cyclic ketone was computed.

(43) Woeller, F. H. *Anal. Biochem.* **1961**, *2*, 508.

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Registry No. 7, 73789-73-8; **8**, 73789-74-9; **9**, 73789-75-0; **11a**, 73789-76-1; **11b**, 73789-77-2; **11c**, 30857-75-1; **12b**, 73789-78-3; **13b**, 73789-79-4; **13c**, 73789-80-7; **13d**, 73789-81-8; **13e**, 73789-82-9; **14a**, 73789-83-0; **15a**, 73789-84-1; polystyrene, 9003-53-6; ethyl hydrogen pimelate, 33018-91-6; 7-(*p*-cymyl) chloride, 2051-18-5; 7-(*p*-cymyl) methyl ether, 73789-85-2; 7-(*p*-cymyl) acetate, 59230-57-8; 7-(*p*-cymyl) alcohol, 536-60-7; cymyl bromide, 73789-86-3; 7-(*p*-cymyl) methyl sebacate, 73789-87-4; methyl hydrogen sebacate, 818-88-2; dibenzyl malonate, 15014-25-2; ethyl 5-bromovalerate, 14660-52-7; 5-bromovaleric acid, 2067-33-6; dibenzyl sodiomalonate, 65460-99-3; diethyl sodiomethylmalonate, 18424-77-6; 1-ethyl hydrogen 2-methylpimelate, 73789-88-5; 3-ethylglutaric acid, 620-36-0; methyl δ-bromovalerate, 14273-90-6; 7-methyl hydrogen 5-ethyl[1-^{14}C]-pimelate, 73789-89-6; cumene, 98-82-8; [1-^{14}C]cyclohexanone, 13952-89-1.

Potassium on Alumina as a Reagent for Reductive Decyanation of Alkylnitriles

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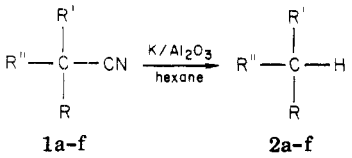
Highly dispersed potassium over neutral alumina (K/Al_2O_3), easily prepared by melting potassium over alumina in an inert atmosphere, is capable of effecting reductive cleavage of the cyano group in alkylnitriles in hexane at room temperature in 70–91% yield. This decyanation method is applied in the key step of a novel synthesis of (*Z*)-9-dodecen-1-yl acetate, the sex pheromone of *Paralobesia viteana*.

A very active area of research in organic chemistry involves the use of reagents supported on porous solids to effect synthetic transformations. Such reactions often occur under mild conditions with easy chemical operations. Recently alumina has been used as a support for different reagents to achieve highly selective organic reactions.[1] For example, alumina-supported metals have been used as hydrogenation catalysts.[2] More recently, a synthesis of nitriles[3] with cyanide ion impregnated over neutral alumina and a malonic ester synthesis[4] on basic alumina have been described.

We report that high-surface-area potassium on neutral alumina (K/Al_2O_3) in hexane is capable of effecting reductive cleavage of the cyano group in alkylnitriles (**1a–f**) to afford the corresponding alkanes (**2a–f**).[5]



1a–f **2a–f**

(1) (a) G. H. Posner, *Angew. Chem., Int. Ed. Engl.*, **17**, 487 (1978); (b) S. Quici and S. L. Regen, *J. Org. Chem.*, **44**, 3437 (1979).

(2) R. L. Augustine, "Catalytic Hydrogenation", Marcel Dekker, New York, 1965.

(3) S. L. Regen, S. Quici, and S. J. Liaw, *J. Org. Chem.*, **44**, 2029 (1979).

(4) G. Bram and T. Fillenbeen-Khan, *J. Chem. Soc., Chem. Commun.*, 522 (1979).

(5) The hydrogen incorporated into the decyanated product may derive either from the hydroxyl groups of alumina or from the solvent.

It is known that the same reduction[6] occurs when nitriles are treated with dissolved alkali metals in hexamethylphosphoric triamide in the presence of *tert*-butyl alcohol as a protic cosolvent[7] or with sodium in ammonia.[8] However, these methods suffer from the expensive or troublesome use of poisonous hexamethylphosphoric triamide or liquid ammonia.

The reagent K/Al_2O_3 is prepared by melting potassium over neutral alumina at 150 °C with vigorous stirring in an inert atmosphere. The alkylnitrile **1** in hexane is then added to this reagent at room temperature to obtain the corresponding decyanated product **2** in 70–91% yield.[9] As shown in Table I, the procedure is very efficient for the

(6) An analogous reductive decyanation of alkylnitriles promoted by the $Fe(acac)_3$–sodium sand system has been described by E. E. van Tamelen, H. Rudler, and C. Bjorklund, *J. Am. Chem. Soc.*, **93**, 7113 (1971).

(7) (a) T. Cuvigny, M. Larcheveque, and H. Normant, *Bull. Soc. Chim. Fr.*, 1174 (1973); (b) M. Larcheveque and T. Cuvigny, *Tetrahedron Lett.*, 3851 (1975); (c) A. Debal, T. Cuvigny, and M. Larcheveque, *Synthesis*, 391 (1976).

(8) (a) C. Favre, M. H. A. Salem, and Z. Welvart, *Bull. Soc. Chim. Fr.*, 178 (1975); (b) J. A. Marshall, C. P. Hagan, and G. A. Flynn, *J. Org. Chem.*, **40**, 1162 (1975); (c) S. Yamada, K. Tomioka, and K. Koga, *Tetrahedron Lett.*, **61**, (1976); (d) J. A. Marshall and R. Bierenbaum, *J. Org. Chem.*, **42**, 3309 (1977).

(9) Al_2O_3 is not strictly necessary; however, by dispersing potassium over this support a higher surface area, and consequently an enhanced reactivity, is obtained. In two parallel experiments conducted with K/Al_2O_3 and K alone, first melted and then cooled with stirring, the conversion of **1a** to **2a** after 1 h under the same conditions is 95% and 60%, respectively. Moreover, quenching of the excess potassium in the second case is more hazardous.

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