56.31; H, 4.60; N, 21.70.

Registry No.—**1**, 55043-79-3; **2**, 55043-81-7; **4**, 62493-12-3; **5**, 62493-13-4; **6**, 62493-14-5; **7**, 62493-15-6; **8**, 62493-16-7; **9**, 62493-17-8; **10**, 62493-18-9; **11**, 62493-19-0; **12**, 62493-20-3; **13**, 62493-21-4; **14**, 62493-22-5; **15**, 607-19-2; **16**, 62493-23-6; **17**, 62493-24-7; **25**, 59169-47-0; **27**, 3530-13-0; **30**, 62493-25-8; **32**, 1793-07-3; **33**, 62493-26-9; **34**, 62493-27-0; ethyl iodide, 75-03-6; benzyl bromide, 100-39-0; 2-dimethylaminoethyl chloride HCl, 4584-46-7; pyrrolidine, 123-75-1; ethyl bromoacetate, 105-36-2.

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Cycliacylation Studies on 3,5-Disubstituted Phenylalkanoic Acids[1]

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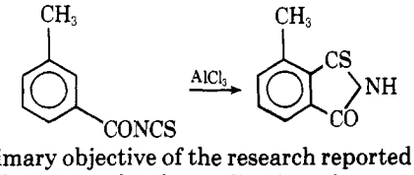
The syntheses of 4-(3-chloro-5-methylphenyl)butanoic acid (**1**), 4-(3-methoxy-5-methylphenyl)butanoic acid (**4**), 3-(3-chloro-5-methylphenyl)propanoic acid (**7**), and 3-(3-methoxy-5-methylphenyl)propanoic acid (**10**) are described. The ring closure of these acids to mixtures of 6,8-disubstituted tetralones and 5,7-disubstituted indanones by five reagents (anhydrous HF, polyphosphoric acid, $AlCl_3$ on RCOCl in benzene and in nitroethane, and $SnCl_4$ on RCOCl in benzene) were studied. For acids **1** and **7**, ring closure took place predominantly (2:1) at the position para to the chlorine. For acids **4** and **10**, ring closure took place predominantly (66–91%) para to the methoxy group.

Relatively little systematic study has been made on preferential intramolecular Friedel–Crafts-type acylation reactions. The cases studied include mainly the cyclization of dibasic acids which gave six-membered ring compounds in preference to five- and seven-membered rings,[3] and monobasic acids which can react with either of two different rings or with one ring in two different locations.[3] One interesting such reaction involves the cyclization of *m*-tolyl isothiocyanate exclusively to 2a-thio-3-methylphthalimide[4] although the para position is available.



The primary objective of the research reported herein was to study the intramolecular cyclization of unsymmetrical 4-(3,5-disubstituted phenyl)butanoic acids to isomeric 6,8-disubstituted tetralones. We hoped to learn something about the relative directive influence of substituents on the aromatic ring in cyclization experiments and about the effect of cyclizing reagent on the proportions of isomers found. The products obtained might provide new intermediates for the synthesis of trisubstituted naphthalenes desired as starting materials in certain projected syntheses. As the work progressed, we included studies on the cyclization of unsymmetrical 3-(3,5-disubstituted phenyl)propanoic acids to yield isomeric 5,7-disubstituted indanones because, by so doing, the effects in ring closures to five-membered rings might be compared to the effects in six-membered rings. The substituents chosen for study involved methyl vs. chlorine and methyl vs. methoxy.

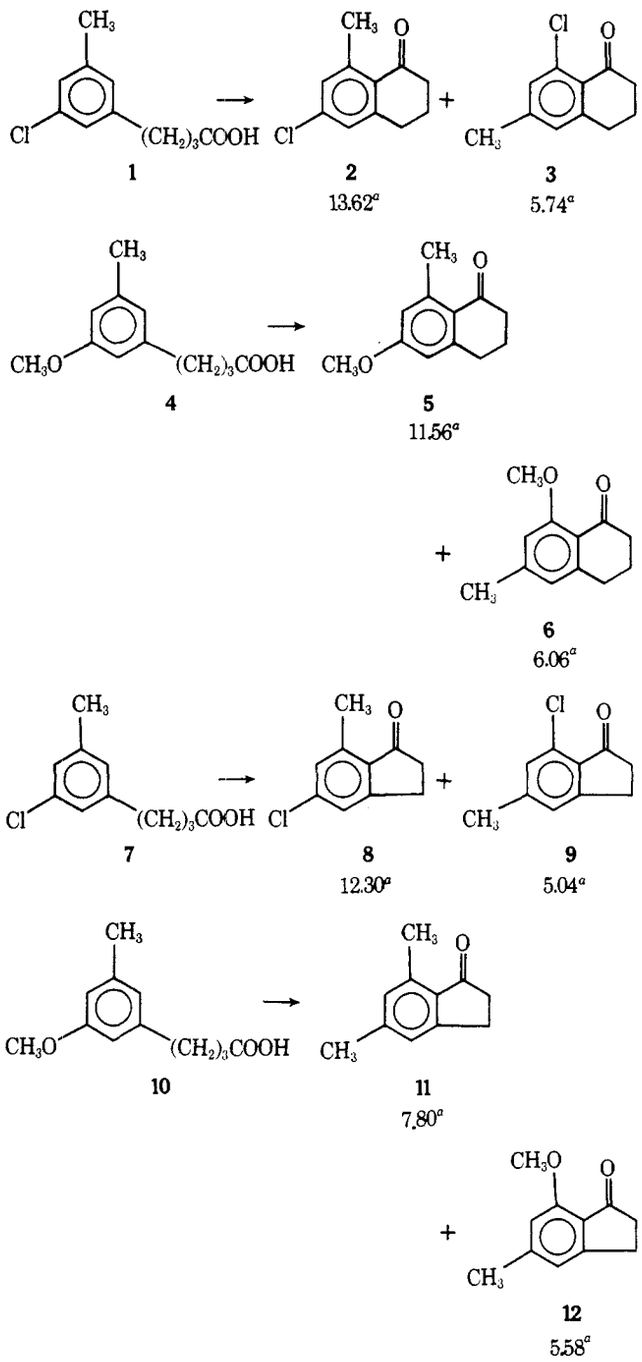
To fulfill the above objectives, we synthesized 4-(3-chloro-5-methylphenyl)butanoic acid (**1**), 4-(3-methoxy-5-methylphenyl)butanoic acid (**4**), 3-(3-chloro-5-methylphenyl)propanoic acid (**7**), and 3-(3-methoxy-5-methylphenyl)propanoic acid (**10**). All were cyclized to the tetralones and indanones shown in Scheme I.

The cyclizations of the acids were accomplished by means of the following reagents: (A) hydrogen fluoride, (B) polyphosphoric acid (PPA), (C) aluminum chloride in benzene using acid chloride, (D) aluminum chloride in nitroethane using acid chloride, and (E) stannic chloride in benzene using acid chloride. The results are summarized in Table I.

The results listed in Table I show that the proportions of isomers formed are essentially the same in comparable cases when a five- or six-membered ring ketone was formed. Furthermore, there is very little effect on the proportions of isomers formed when the cyclization conditions were changed. In the cases of both the chloro- and methoxy-substituted compounds, the reagent which gave the least selectivity was the action of aluminum chloride on the acid chloride in benzene. This lack of selectivity was more pronounced in the methoxy compounds than in the chloro compounds. The best selectivity was obtained with the methoxy compounds using aluminum chloride in nitroethane to give products in which the ketone function was produced by cyclization para to the methoxy group.

The proportions of isomeric ketones formed in each case represents the resultant of a number of parameters which must relate to the tendencies to react para to one function and ortho to the other. Since no quantitative data relating to ortho substitution in Friedel–Crafts acylations are at hand, no attempt to calculate the expected ratios was made.

Scheme I



[a] Extrapolated molar-shift values obtained with Eu(DPM)$_3$ (see Experimental Section).

The acids **1**, **4**, **7**, and **10**, were synthesized as shown in Scheme II.

Several unsuccessful attempts were made to isomerize 2,5-dimethylchlorobenzene to 3,5-dimethylchlorobenzene by acidic catalysts since acid-catalyzed rearrangements of trimethylbenzenes to mesitylene are known.[5] The desired 3,5-dimethylchlorobenzene was readily obtained from 3,5-dimethylaniline.[6]

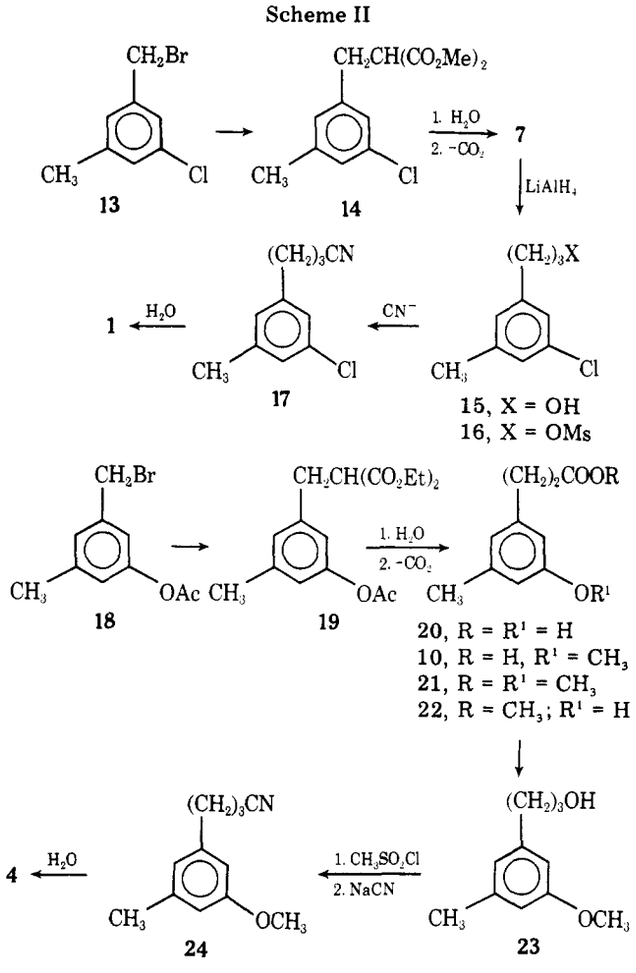
In general, all of the steps outlined in Scheme II proceeded in high yields and are described in the Experimental Section. The introduction of a bromine atom into a methyl group of 3,5-dimethylphenol by means of *N*-bromsuccinimide (NBS) could be accomplished only with 3,5-dimethylphenyl acetate. If the free phenol or the methyl ether were used, only nuclear bromination, mainly in the 4 position, occurred. The conversion of 3-hydroxy-5-methylphenylpropanoic acid (**20**) into methyl 3-(3-methoxy-5-methylphenyl)propanoate (**21**) was best accomplished (overall yield 84.6%) by esterification to methyl 3-(3-hydroxy-5-methylphenyl)propanoate (**22**), followed by treatment with sodium hydride and methyl iodide in DMF. The preparation of 3-(3-methoxy-5-methylphenyl)-propanoic acid (**10**) from **20** was carried out in 85% yield by treatment of the disodium salt of **20** in DMF with 1 equiv of methyl iodide. This reaction represents the advantage of using a bis-anion for selective alkylation.

Table I. Effect of Cyclizing Agent on Relative Yields of Major Product Isomer of Selected 3,5-Disubstituted Phenylalkanoic Acids

Reagent	2[a]	8[a]	5[a]	11[a]
1. HF[b]	66	64	84	82
2. PPA[b]	67	65	84	83
3. 3. $AlCl_3/C_6H_6$[b]	61	62	66	69
4. $AlCl_3/C_2H_5NO_2$[b]	66	65	91	91
5. $SnCl_4/C_6H_6$[b]	68	70	87	86

[a] Major isomer, the remainder consisted of the compounds **3**, **9**, **6**, and **12**, respectively. [b] See Experimental Section for description of experimental details.

Scheme II



Experimental Section[7]

Attempts to Isomerize 2,5-Dimethylchlorobenzene. (1) A mixture of 10 mL of 2,5-dimethylchlorobenzene, 50 mL of HF, and 7 g of BF_3 (loss of weighed cylinder) was held at room temperature in a stainless-steel bomb for 3 h. Only starting chloro compound was present, as shown by gas-chromatographic analysis. (2) A mixture of 27 mL of chloro compound and 7 g of $SnCl_4$ showed only starting compound up to 5 days at room temperature. (3) In an experiment similar to (2), except that 3.5 g of $AlCl_3$ and 1 mL of concentrated HCl

Table II. Proton Shift Data

Compd[a]	Parent Peak		Shift	
	CH_3	OCH_3	CH_3	OCH_3
2	2.50		0.137	
3	2.36		0.057	
5	2.48	3.66	0.117	0.026
6	2.35	3.74	0.060	0.073
8	2.46		0.123	
9	2.38		0.050	
11	2.47	3.75	0.078	0.016
12	2.32	3.79	0.056	0.067

[a] All spectra were taken in CCl_4, $(CH_3)_4Si$ standard, δ, and in tared NMR tubes for quantitative solution preparation. Each shift was determined with five different compound/LSR ratios. The average of five closely agreeing shift ratios is reported in the shift column.

was used instead of $SnCl_4$, analysis showed many products, including *p*-xylene and higher molecular weight substances.

3,5-Dimethylchlorobenzene. Using essentially the procedure described,[8] 3,5-dimethylaniline was converted into 3,5-dimethylchlorobenzene, bp 73 °C at 15 mm, in 72% yield.

Dimethyl 3-Chloro-5-methylbenzylmalonate* (14). A mixture of 140.5 g (1.0 mol) of 3,5-dimethylchlorobenzene, 141 g (0.8 mol) of *N*-bromosuccinimide, 5 g of benzoyl peroxide, and 1 L of CCl_4 was refluxed for 6 h and cooled. After filtration of the succinimide, the product in the filtrate was fractionated to yield 45 g (0.32 mol) of 3,5-dimethylchlorobenzene, bp 73 °C at 15 mm, and 132 g (0.60 mol, 72% yield based on unrecovered chloro compound) of 3-chloro-5-methylbenzyl bromide (**13**), bp 145 °C at 15 mm, 78 °C at 0.2 mm, mp 57–58 °C. Because of instability in air, **13** was used as soon as distilled. No sample was sent for elemental analyses. To the sodium methoxide solution prepared from 30 g (1.3 mol) of sodium and 1 L of absolute methanol was added 300 g (2.5 mol) of dimethyl malonate under N_2 followed by 214 g (1.2 mol) of **13** during 30 min. After 16 h at reflux, most of the methanol was distilled, the residue was diluted with dilute acid, and the product was isolated as usual to yield 157 g of dimethyl malonate and 294 g (91%) of **14**, bp 154 °C at 1 mm.

3-(3-Chloro-5-methylphenyl)propanoic Acid* (7). A mixture of 122 g of **14**, 100 g of NaOH, and 1.2 L of water was refluxed for 8 h. The homogeneous solution was cooled and acidified with 400 mL of concentrated HCl. After 2 h of reflux, decarboxylation was complete. A conventional work-up afforded 79 g (88%) of **7**, bp 110 °C at 0.2 mm.

3-(3-Chloro-5-methylphenyl)-1-propanol* (15). To a mixture of 38 g of $LiAlH_4$ and 700 mL of anhydrous ether which had been refluxed for 1 h was added dropwise a solution of 65 g of **14** in 50 mL of ether. After 18 h at reflux, the cooled mixture was treated as described.[9] Distillation of the product afforded 58.0 g (95%) of **15**, bp 110 °C at 1 mm.

3-(3-Chloro-5-methylphenyl)-1-propyl Methanesulfonate* (16). To an ice-cooled solution of 41.0 g of **15** and 25 g of triethylamine in 400 mL of benzene was added dropwise a solution of 27 g of mesyl chloride in 150 mL of benzene. The mixture was allowed to stand at 20–25 °C for 3 h and the $(Et)_3NHCl$ was filtered. From the filtrate after work-up in the usual manner (dilute HCl extraction) was obtained 57 g (98%) of **16** which was analytically pure without recrystallization, and used in the next step.

3-(3-Chloro-5-methylphenyl)-1-propyl Cyanide* (17). A phase-transfer[10] mixture containing 40.0 g of **16**, 23 g of KCN, 1 g of Aliquat-336,[11] 20 mL of water, and 200 mL of benzene was stirred and heated to reflux for 5 h. After the usual work-up, distillation afforded 25.0 g (85%) of **17**, bp 126 °C at 0.75 mm.

4-(3-Chloro-5-methylphenyl)butanoic Acid* (1). A mixture of 22.0 g of **17**, 40 g of NaOH, 10 mL of methanol, and 400 mL of water was refluxed for 2 days. After acidifying with 200 mL of concentrated HCl, the mixture was refluxed for 8 h. The organic acid fraction of the product was distilled to yield 22.5 g (94%) of **1**, bp 155 °C at 0.2 mm, mp 45.0–46.5 °C when crystallized from hexane.

3,5-Dimethylphenyl Acetate. To a solution of 244 g of 3,5-dimethylphenol (Aldrich) in 170 g of pyridine and 2 L of ether was added dropwise 156 g of acetyl chloride. After 16 h at reflux, the mixture was filtered and the filtrate was washed with 5% HCl and worked up as usual to yield 320 g (97%) of 3,5-dimethylphenyl acetate, bp 125 °C at 15 mm (lit.[12] bp 115–117 °C at 14 mm).

3-(Bromomethyl)-5-methylphenyl Acetate* (18). A mixture of 164 g (1.0 mol) of 3,5-dimethylphenyl acetate, 141 g (0.80 mol) of NBS, 5 g of benzoyl peroxide, and 1 L of CCl_4 was stirred and heated at reflux for 6 h, cooled, and filtered. After working up as usual, fractionation through a Widmer column (18 in.) yielded 53 g (32%) of recovered 3,5-dimethylphenyl acetate, bp 50 °C at 0.2 mm, and 158 g (96% allowing for recovered starting acetate) of **18**, bp 95 °C at 0.2 mm. The yield was much better than when equivalent amounts of NBS were used. The compound is an extremely irritating lachrymator.

Dimethyl (3-Acetoxy-5-methylbenzyl)malonate (19). Dimethyl malonate was alkylated with **18** essentially as described for the preparation of **14**. The product, **19**, bp 168–170 °C at 0.2 mm, was obtained in 52% yield: NMR (CCl_4) δ 2.09 (s, 3, ArO_2CCH_3), 2.23 (s, 3, $ArCH_3$), 3.06 (d, 2, CH_2CH), 3.53 (t, 1, CH_2CH), 3.55 (s, 6, $COOCH_3$), 6.68 (m, 3, ArH); ms *m/e* 294. Because of a slight impurity which was not removed on distillation, the C,H analyses were off. This material was used for the next step.

3-(3-Hydroxy-5-methylphenyl)propanoic Acid* (20). A mixture of 120 g of **19**, 120 g of NaOH, and 1.2 L of water was boiled for 6 h. After careful acidification with 500 mL of concentrated HCl, boiling was continued for 18 h (no further evolution of CO_2). After the usual work-up, distillation yielded 66 g (89%) of **20**, bp 190–200 °C at 1 mm, mp 83–84 °C after crystallization from pentane and heptane.

3-(3-Methoxy-5-methylphenyl)propanoic Acid* (10). To a stirred solution of 36.0 g (0.2 mol) of **20** in 350 mL of pure dimethylformamide (DMF) was added 10 g (0.42 mol) of NaH. After gas evolution had subsided, 29.0 g (0.2 mol) of CH_3I was added dropwise. The reaction mixture was warmed and then heated nearly to reflux of DMF during 1 h. After the usual work-up, the product was distilled to yield 33.0 g (85%) of **10**, bp 138 °C at 0.8 mm. The same compound was obtained in 73% yield when the methylation was performed in absolute methanol using 2 equiv of $NaOCH_3$ and 1 equiv of CH_3I.

Methyl 3-(3-Hydroxy-5-methylphenyl)propanoate* (22). Esterification of 90 g of **20** with methanolic H_2SO_4 afforded 89 g (92%) of **22**, bp 170–172 °C at 0.8 mm.

Methyl 3-(3-Methoxy-5-methylphenyl)propanoate* (21). Esterification of 97.5 g of **10** with methanolic H_2SO_4 afforded 97.0 g (93%) of **21**, bp 143–149 °C at 0.8 mm. By treatment of 39.0 g of **20** with a solution of 10 g of NaOH in 175 mL of water followed by addition of 25 g of $(CH_3)_2SO_4$ there was obtained 32 g (72%) of **21**.

Alternately, a mixture of 19.4 g (0.1 mol) of **22** in 175 mL of DMF was treated with 2.4 g (0.1 mol) of NaH in portions. When hydrogen was no longer evolved, 15 g (0.11 mol) of CH_3I was added dropwise. After 1 h of reflux, the mixture was added to 1 L of water and worked up as usual to yield 19.3 g (92%) of **21**.

3-(3-Methoxy-5-methylphenyl)-1-propanol* (23). A solution of 104 g of **21** in 400 mL of ether was added during 1 h to a mixture of 40 g of $LiAlH_4$ in 600 mL of ether. After being held at reflux for 16 h, the mixture was worked up as described[9] to yield 87 g (96%) of **23**, bp 166–167 °C at 0.8 mm.

4-(3-Methoxy-5-methylphenyl)-1-propyl Cyanide* (24). By treatment similar to that described above for conversion of **15** to **16**, 45 g of **23** was converted into the mesylate of **23**, mp 47–48 °C, in 91% yield (characterized by *m/e* 242 and NMR[2]). This mesylate was treated as described for **17** to yield **24**, bp 140–141 °C at 0.1 mm, in 95% yield.

4-(3-Methoxy-5-methylphenyl)butanoic Acid* (4). Hydrolysis of **24** was carried out essentially as described above for **1** to yield 91% of **4**, mp 50.5–51.5 °C.

5-Chloro-7-methyl-1-indanone* (8) and 7-Chloro-5-methyl-1-indanone* (9). To 35 mL of HF in a polyethylene bottle was added 5.0 g of **7**. After standing for 6 h, the residue was treated with ice and the products were extracted by ether. After the usual work-up, distillation afforded 4.0 g (88%) of a mixture of **8**, mp 67–68 °C, and **9**, mp 37–38 °C, separated by preparative GLC[7] (see Table I). The assignments of structure to **8** and **9** were made with the aid of tris(2,2,6,6-tetramethylheptane-3,5-dionato)europium[13], $Eu(DPM)_3$ (see Table II for NMR assignments).

6-Chloro-8-methyl-3,4-dihydro-1(2*H*)-naphthalenone* (2) and 8-Chloro-6-methyl-3,4-dihydro-1(2*H*)-naphthalenone* (3). The cyclization of **1** into a mixture of **2**, mp 65.5–66.5 °C, and **3**, mp 122–123 °C, was accomplished in 92% yield as described for the preparation of **8** and **9**. The separation was performed by preparative GLC.[7] See Tables I and II for the proportions of **2** and **3** and their structure proofs.

5-Methoxy-7-methyl-1-indanone* (11) and 7-Methoxy-5-methyl-1-indanone* (12). The cyclization of **10** was performed as in the case of **7** to yield 74% of a mixture of **11**, mp 83–85 °C, and **12**, mp 35–41 °C,[14] which were separated by preparative GLC.[7] See Ta-

bles I and II for relative amounts formed and assignment of structure.

6-Methoxy-8-methyl-3,4-dihydro-1(2*H*)-naphthalenone* (5) and 8-Methoxy-6-methyl-3,4-dihydro-1(2*H*)-naphthalenone (6). The cyclization of **4** as described for **7** afforded 93% of a mixture of **5**, mp 69–70 °C (lit.[3b] mp 70.5 °C), and **6**, separated by GLC.[7] The amounts formed and assignments of structure are listed in Tables I and II.

Standard Cyclization Procedures. Method A (HF). To 30 mL of HF in a 50-mL polyethylene bottle was added about 2 g of the acid to be cyclized. After 3–6 h at room temperature, the contents was treated with ice and the organic product was taken into ether. After removal of uncyclized acid by alkaline extraction, the ketone mixture was isolated as usual. The yields were generally high. In the case of cyclization of **10**, the HF solution was worked up after 3 h because on longer standing the formation of high-molecular-weight products occurred.

Method B (PPA). The acids were dissolved in PPA at 80 °C and the reaction was interrupted after 10–30 min. In general, about 80% yields of ketones were obtained.

Method C (RCOCl, $AlCl_3$, Benzene). The requisite acid chlorides were prepared by treatment of the acids in CH_2Cl_2 with 1 equiv of PCl_5 at reflux. The solvent and $POCl_3$ were removed in vacuo and solutions of the acid chlorides in benzene were added to stirred suspensions of $AlCl_3$ in benzene.[15] The cyclizations were run from 30 to 60 min at room temperature, after which the mixtures were poured on ice and the ketonic fraction of the products was isolated in high yield as usual.

Method D (RCOCl, $AlCl_3$, $C_2H_5NO_2$). These reactions were run in purified nitroethane and the ketone fractions were isolated as described above in method C.

Method E (RCOCl, $SnCl_4$, Benzene). In these reactions the acid chloride was purposely contaminated with small amounts of $POCl_3$[16] and dissolved in benzene. Stannic chloride was added to the mixture at 10–20 °C and the reactions were interrupted after 10–30 min. The ketone fraction was isolated in high yield in the usual way.

Analyses of Ketone Mixtures. The isomeric ketone mixtures obtained by the above cyclization procedures were analyzed by quantitative GLC techniques[7] and the individual isomers in each mixture were separated by preparative GLC.[7] The assignments of structure to the cyclized ketones were made on the basis of the shifts in the NMR spectra caused by tris(2,2,6,6-tetramethylheptane-3,5-dionato)europium ($Eu(DPM)_3$). Since all lanthanide shift-reagent (LSR) studies were done at essentially the same concentration and temperature, it was possible to extrapolate what the induced shifts would be under these conditions and equimolar amounts of LSR and substrate. Linear-regression analysis of the shift data using the regression function of the SPSS[17] showed a high correlation between shift and LSR concentration for each isomer. Extrapolation for 100% $Eu(DPM)_3$ using linear-equation solutions provide the molar-shift values listed by the ketones in Scheme I. The order of decreasing molar shift lists ketones before others.[13]

In order to determine if the ketone mixtures formed were the result of kinetic rather than thermodynamic factors, portions of ketones rich in the minor isomer were subjected to the same experimental conditions which controlled their formation. In no case was a difference noted in the ratio of isomeric ketones after treatment. Thus, the results reflect kinetic control.

Registry No.—**1**, 62358-67-2; **2**, 62358-75-2; **3**, 62358-76-3; **4**, 18458-09-8; **5**, 62358-79-6; **6**, 62358-80-9; **7**, 62358-63-8; **8**, 62358-73-0; **9**, 62358-74-1; **10**, 22524-05-6; **11**, 62358-77-4; **12**, 62358-78-5; **13**, 62358-81-0; **14**, 62358-62-7; **15**, 62358-64-9; **16**, 62358-65-0; **17**, 62358-66-1; **18**, 62358-68-3; **19**, 62358-82-1; **20**, 60549-28-2; **21**, 62358-71-8; **22**, 62358-70-7; **23**, 22524-06-7; **24**, 62358-72-9; 3,5-dimethylchlorobenzene, 556-97-8; dimethyl malonate, 108-59-8; 3,5-dimethylphenyl acetate, 877-82-7; 3,5-dimethylphenol, 108-68-9.

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(6) This route is simple but expensive because of the high cost of 3,5-dimethylaniline (Aldrich Chemical Co.). See ref 2 for alternate syntheses.
(7) All melting points and boiling points are uncorrected. Single boiling points refer to the boiling point of a small sample taken from the center of a fraction. This sample was used for analyses, NMR, and mass spectra. All compounds marked with an asterisk gave C, H analyses (done by Robertson Labs, Florham Park, N.J.) within ±0.3% of theory; NMR and mass spectra were consistent with expected values (see ref 2 for details). Quantitative GLC analyses were done on a F&M Model 609 instrument (flame-ionization detector) using a 10 ft × 0.25 in. column packed with 20% Carbowax 20M on 60–80 mesh Chromosorb W. Preparative GLC was done on a F&M Model 500 instrument (thermal-conductivity detector) using a 20 ft × 0.25 in. column packed with 20% Se-30 on 60–80 mesh Chromosone W. Flow rates were usually 15 mL/min and temperatures of 180 and 200 °C were used. Mass spectra were done by M. R. Weisenberger using a CEC-MS9 instrument (70 eV). The term "worked up in the usual way" means that an ether or ether–benzene solution of the products was washed with dilute Na_2CO_3 and/or HCl, and saturated NaCl solution, and was then dried by passing through a cone of $MgSO_4$. Solvent was then removed on a rotary evaporator.
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