A Sterically Efficient Synthesis of (Z)-5-Fluoro-2-methyl-1-(p-methylthiobenzylidene)-3-indenylacetic Acid and Its S-Oxide,[1,2] Sulindac[1]

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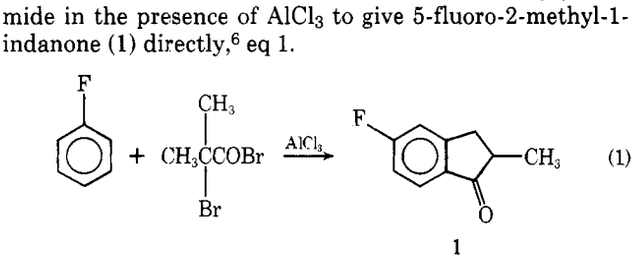
Synthesis of (Z)-5-fluoro-2-methyl-1-(p-methylthiobenzylidene)-3-indenylacetic acid (**12**) via its Z diene tautomer (**10**) was carried out virtually free of interference from the corresponding E isomers (**11** and **13**). The sequence may have general application to synthesis of a wide variety of 1,2,3-trisubstituted indenes. The synthesis proceeds from fluorobenzene to 5-fluoro-2-methyl-1-indanone (**1**) by a Friedel–Crafts acylation–cyclization. Preparation in good yield of p-methylthiobenzylmagnesium chloride (**3**) for reaction with **1** was dependent on solvent polarity and on excess of magnesium, and dehydration of the resulting carbinol (**5**) afforded product with an endocyclic double bond, indene **6**. Elaboration of the acetic acid side chain was effected with glyoxylic acid and tetraalkylammonium hydroxides which are uniquely suited as catalysts compared to alkali hydroxides. This condensation was studied and a rationale for the role of R_4NOH based on solubility and steric bulk is presented. Successful condensation afforded (Z)-6-fluoro-2-methyl-3-(p-methylthiobenzyl)-1-indenylideneacetic acid (**10**) which was efficiently isomerized with concentrated HCl/CH_3CO_2H to **12** (>90% yield). From **10** and **12** the corresponding sulfoxides **14** and **15** were prepared, and tautomerization of **14** was studied briefly.

Results and Discussion

Since disclosure of the synthesis of indene isosteres of indomethacin,[3] the assignment for the most stable double bond configuration at C-1 for one of these isosteres, (Z)-1-(p-chlorobenzylidene)-5-methoxy-2-methyl-3-indenylacetic acid,[4] was confirmed by x-ray and NMR data.[5] We now wish to report a sterically efficient synthesis of one (**12**) of this family of 1-benzylidene 3-indenylacetic acids and its S-oxide (**15**) by preparation and isomerization of a diene tautomer (**10**). The sequence discussed contains several points of interest and should be of use as a facile, general synthesis of 1,2,3-trisubstituted indenes constructed from a variety of benzene derivatives or indanones.

Entry to **10** is conveniently provided by preparation and reaction of the appropriate indanone with a benzyl Grignard reagent, dehydration of the carbinol, and condensation of glyoxlic acid with the resulting indene.

Thus, fluorobenzene reacted with α-bromoisobutyryl bromide in the presence of $AlCl_3$ to give 5-fluoro-2-methyl-1-indanone (**1**) directly,[6] eq 1.



(1)

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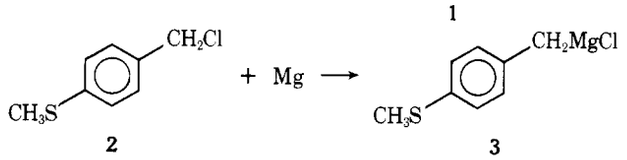
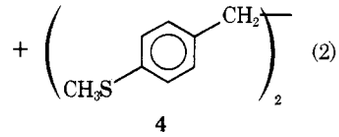


2 **3**



(2)

4

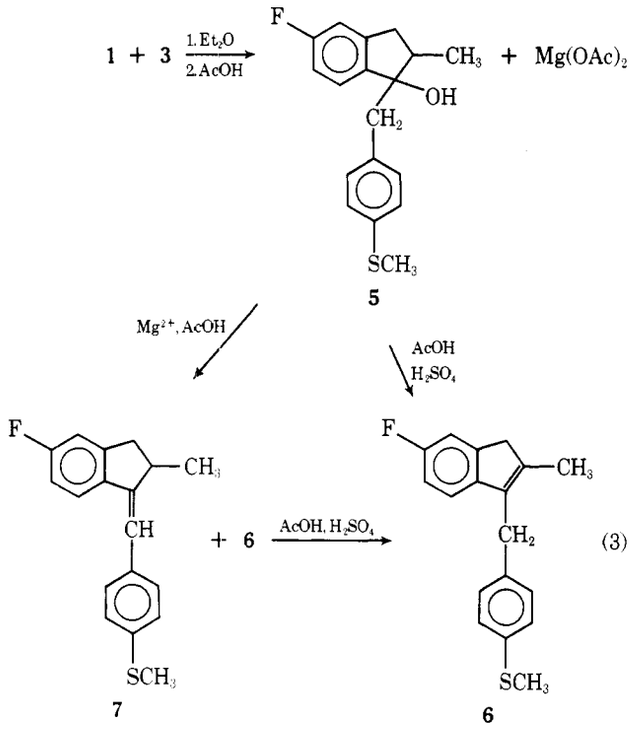
Preparation of p-methylthiobenzylmagnesium chloride (**3**) for reaction with **1** required an excess of magnesium to suppress competitive coupling which leads instead to 1,2-bis(p-methylthiophenyl)ethane (**4**), eq 2. Ether was also shown to be crucial to successful formation of **3**. Formation of **3** in diminishing volumes of ether produced a discernible drop in the yield of **3** as summarized in Figure 1.

Substitution of THF for ether led to a large quantity (42%) of **4** and lower yield (26.6%) of **3** as did increasing substitution of benzene or toluene, also in place of ether. On one hand the higher polarity of THF probably promotes coupling by direct displacement of chloride, and on the other hand dilution of ether with benzene (or toluene) undoubtedly interferes with solvation of the organomagnesium halide with a corresponding increase in its nucleophilicity toward p-methylthiobenzyl chloride. A similar rate-accelerating effect of THF on coupling reactions of aryllithiums with alkyl halides has also been noted.[7]

Addition of **1** to an ethereal solution of **3** is characterized by a transient (1–2 s), highly localized, blood-red color where the reagents contact each other. The decreasing intensity of this color and its eventual absence was used to determine complete conversion of the Grignard reagent and generally agreed quite well with the titration method given in the Experimental Section. Addition of **1** past this point (ca. 0.85 mol of **1**) gave no increase in yield of products **5** or **6**.

Although carbinol **5** could be isolated, it was more convenient to quench directly and to dehydrate the Grignard mixture with a solution of acetic and sulfuric acids to obtain product with an endocyclic double bond, 6-fluoro-2-methyl-3-(p-methylthiobenzyl)indene (**6**), eq 3. If quenched into acetic acid only, the mixture contained an additional product with an R_f by TLC slightly faster than **6**. This was isolated by preparative GLC and by independent synthesis as the exocyclic isomer, **7**, an indan arising from dehydration catalyzed by Mg^{2+}. By TLC, solutions containing **7** were converted wholly to **6** with H_2SO_4 in acetic acid, but no dehydration or prototropic shift occurred in acetic acid alone.

Two-carbon homologation by condensation of glyoxylic acid or its esters with a variety of acidic methylene compounds is recorded. Representative of these are α-tetralones,[8] ethyl acetoacetate,[9] and acetophenones.[10,11] Also, formation of indenyl anion is reported to occur readily and the anion to undergo oxidation,[12] alkylation,[13] prototropism,[13b,14] condensation,[12a,13b,15] and carboxylation.[16] In no instance, however, were we similarly able to obtain measurable reaction of **6** with glyoxylic acid to afford **8** either with alkali hydroxides or alkoxides, ordinary tertiary organic amines, or heat.



Indeed, all attempts to obtain useful solubility of sodium or potassium glyoxylate in nonaqueous systems failed, and in water the Cannizzaro reaction of glyoxylic acid with NaOH or KOH was shown to proceed quite rapidly at 37 °C in a ^{1}H NMR probe. Both difficulties, solubility and the Cannizzaro reaction, were circumvented by use of tetraalkylammonium hydroxides (Triton B or Me_4NOH) in stoichiometric quantities. This afforded not only solubility for glyoxylate ion but permitted only very slow conversion via the Cannizzaro reaction. Figure 2 compares the relative effect of three caustic bases (NaOH, KOH, Triton B) on conversion of glyoxylate to glycolate and oxalate ions. The striking difference of 100:10:1 in relative rates as shown in Figure 2 is attributed to increasing size of the cation. The generally accepted mechanism[17,18] for the Cannizzaro reaction requires formation of a termolecular complex comprised of 2 mol of an aldehyde and 1 mol of the base, each properly aligned for concerted reaction; but a tetralkylammonium cation quite likely is too bulky to be comfortably accommodated in such a complex. The effect of cationic size and charge number on the rate of the Cannizzaro reaction of formaldehyde is known but no difference between sodium and potassium was reported.[17] In similar fashion the steric bulk of triethylbenzylammonium ion was recently invoked to account for the slower Cannizzaro reaction of benzaldehyde in favor of its condensation with dimethyl sulfone.[19]

Thus, use of Triton B to effect condensation and dehydration between **6** and glyoxylic acid led to isolation of (*Z*)-6-fluoro-2-methyl-3-(*p*-methylthiobenzyl)-1-indenylideneacetic acid (**10**) in 75% yield. Indene also reacted under identical conditions to give (*Z*)-1-indenylideneacetic acid. Evidence for the *Z* configuration about the exocyclic double bond as shown for **10** (eq 4) was obtained when irradiation of the C_2 CH_3 group during ^{1}H NMR produced a nuclear Overhauser enhancement measured as 49% for the vinylic side-chain proton α to $-CO_2H$. Examination by ^{1}H NMR of crystallization liquors from **10** provided evidence of only a few percent of the *E* isomer (**11**), the preponderant material being **10**. Isomer **11** was crystallized from mother liquors and characterized. 1-Indenylideneacetic acid was assigned the *Z* configuration because the upfield position (δ 6.75) of the side-chain proton was similar to that (δ 6.5) for **10**.

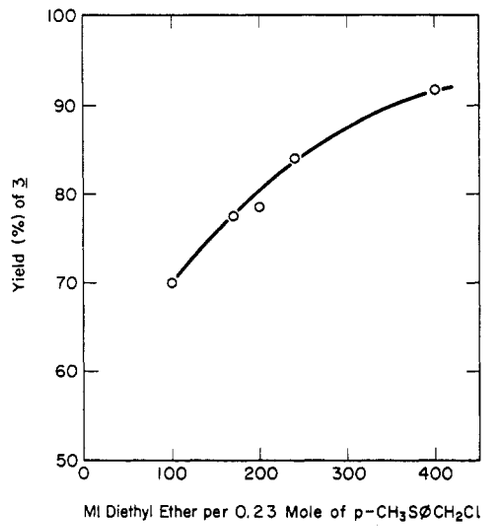
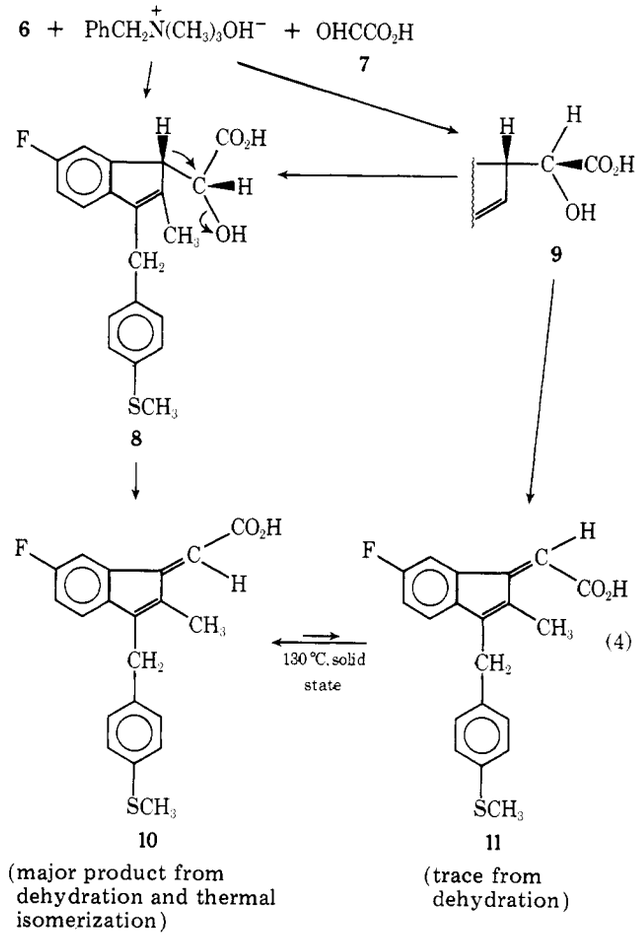


Figure 1. Yield of *p*-methylthiobenzylmagnesium chloride (**3**) vs. mL of ether. Assayed by direct titration with 2-butanol and 2,2′-biquinoline. See Experimental Section.



(major product from dehydration and thermal isomerization)

(trace from dehydration)

The high preference for **10** suggests that base-catalyzed dehydration occurs rapidly on only one of the two possible enantiomeric pairs of carbinols. Two of the diastereomers are shown in eq 4 as **8** and **9**. If dehydration occurs by E2 elimination of hydroxide then **10** would be expected from **8** rather than from **9**. At the same time there is evidence that **9** is converted to **8** either by epimerization at the α carbon or by a retrograde reaction to starting materials followed by recondensation. Indeed, two carbinols are observed by TLC and one disappears much more rapidly, but not completely until the overall reaction is done. The phenomenon was also observed

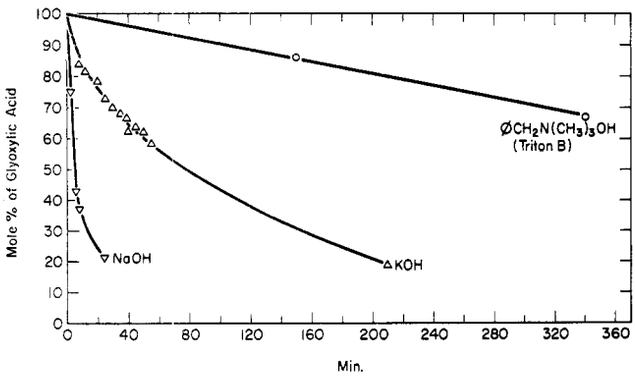


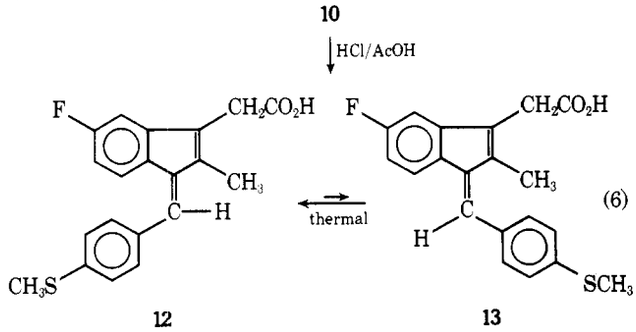
Figure 2. Effect of 4 equiv each of three caustic bases on conversion of glyoxylic acid in D_2O (35 °C) to oxalic and glycolic acids as measured by ^1H NMR. Relative rates at 67 mol % remaining (33% conversion), NaOH:KOH:Triton B = 100:10:1.

by crystallization of a carbinol believed to be **9**, followed by its dehydration to **10** with Triton B. During dehydration of pure **9** a second material (8?) slightly less polar by TLC again rapidly formed and persisted after disappearance of **9**. That **11** arises from **9** was demonstrated by treating pure **10** with methanolic Triton B and observing no trace of isomerization at 50 °C, the usual reaction temperature. Carbinol **9** was formed from **6** and glyoxylic acid with no dehydration under catalysis by 1,1,3,3-tetramethylguanidine in DMF, whereas triethylamine and pyridine failed (eq 5). Only with OH^-

$$6 + OHCCO_2H + (CH_3)_2NC(=NH)N(CH_3)_2 \longrightarrow 9 \not\rightarrow 10 \quad (5)$$

(Triton B or Me_4NOH) was **10** formed. Mineral acids were without dehydrative effect on **8** and **9**.

Tautomerism of **10** with HCl proved facile and highly productive of the single isomeric product **12**. Heating an orange-colored slurry of **10** in a solution of hydrochloric acid in acetic acid (95 °C, 10 h) afforded a yellow slurry of **12** in 85% yield. Inspection by ^1H NMR of the filtrate solids revealed only about 2% each of **10** and of **13**, the *E* isomer of **12**. We know of no similarly specific diene tautomerism used for preparative purposes. An authentic sample of **13** was obtained by fractional crystallization from mother liquors of **12**.



(6)

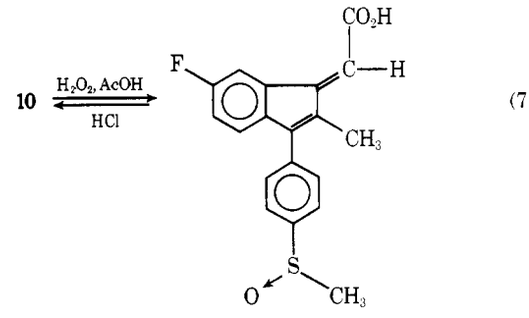
12 (major product from **10** and thermal isomerization) **13**

An attempt to discern the site(s) of protonation and/or of addition of HCl to **10** was wholly unsuccessful in a sealed NMR tube with CD_2ClCD_2Cl saturated with HCl. Heating the sealed probe at 100 °C gave slow tautomerization, but no new proton resonances or intermediates were observed.

The superiority of hydrogen chloride over a caustic base for diene isomerization is amply demonstrated by the equilibrium mixture of products observed by ^1H NMR. One mole of **10** and 2 mol of Triton B in pyridine gives 72% of **12**, 9% of **13**, and 19% of starting material **10**.

Thermal $Z \rightleftarrows E$ isomerization was studied briefly, both in solution and in the crystalline state. Either **12** or **13** could be converted to an equilibrium mixture of 82:18 (**12**/**13**) as measured by ^1H NMR. At 110 °C the half-lives are 45 min in pyridine-d_5 and 20 min in Me_2SO-d_6. At 135 °C crystalline **13** was converted largely to **12**, whereas **12** was virtually unchanged when heated in the solid state. Similarly, **11** at 130 °C afforded mostly **10** by TLC. In no instance was thermally induced diene tautomerism observed between **10** and **12**.

Oxidation of **10** and **12** to the corresponding sulfoxides **14** and **15** was facile and straightforward with hydrogen peroxide in the presence of acetic acid. Attempted tautomerization of **14** to **15** by HCl was accompanied by extensive deoxygenation to **10** and general decomposition. Isomerization of **14** with Triton B in pyridine afforded an equilibrium mixture of sulfoxides similar in composition to the analogous sulfides **10**, **11**, and **12** obtained from **10** and Triton B. From such a mixture **16**, the *E* isomer of **15**, was isolated.



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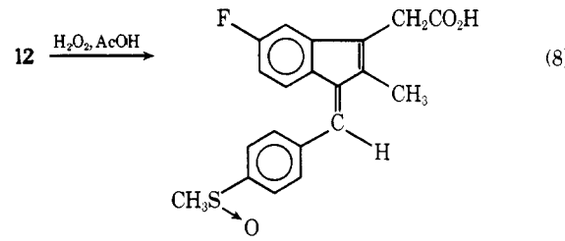

(8)

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Experimental Section

General Procedures. Melting points are uncorrected and were taken on a Thomas-Hoover apparatus. Proton magnetic resonance spectra using tetramethylsilane as an internal standard were taken on Hitachi Perkin-Elmer R-24A, Varian A-60A, and JEOL C-60HL spectrometers, many by Dr. A. Douglas and Messrs. R. Zerfing and R. Reamer. Mass spectra were obtained at 70 eV on an LKB 9000 spectrometer by Mr. J. Smith. Elemental analyses were performed by Mr. J. Gilbert and his staff. Much of the gas–liquid chromatography was carried out by Mr. R. J. Phillips on a Hewlett-Packard 7620A gas chromatograph with a flame ionization detector including a 3370B integrator and 7660A multilevel temperature programmer. Tetracosane was used as an internal standard through a 6 ft × 0.125 in. stainless steel column packed with 10% SP-2401 on 100/120 mesh Supelcoport. The rest was performed on a Varian 2700 gas chromatograph with a thermal conductivity detector mated to a Hewlett-Packard integrator and using a 6 ft × 0.25 in. stainless steel column packed with 10% OV-101 on 80/100 mesh Supelcoport. Thin layer chromatography (TLC) was done on Quantum Q1-F silica gel plates and viewed under UV light. Compounds **5** (R_f 0.4–0.5) and **6** (R_f 0.9–0.95) were eluted in benzene. In 3:1 hexane–benzene **6** (R_f 0.65) is separated from its isomer **7** (R_f 0.7). Compounds **8** (R_f 0.15–0.25), **9** (R_f 0.1–0.2), **10** (R_f 0.5), and **12** (R_f 0.6) are separated with 9:1 PhH–CH_3OH. If the plate is dried and eluted a second time, then **11** (slightly slower than **10**) and **13** (slightly slower than **12**) separate. Sulfoxides **14** (R_f 0.3), **15** (R_f 0.5), and **16** (R_f 0.4) separate also in 9:1 benzene–CH_3OH. For separation of **8** (R_f 0.40) and **9** (R_f 0.25 a mixture of 25 $CHCl_3$:1 dioxane:1 CH_3CO_2H is much preferred. Spotting 5 μL of dilute solutions (≤1%) gave the best separation of components.

Direct, Colorimetric Titration of *p*-Methylthiobenzylmagnesium Chloride (3). This procedure is adapted from the elegant method of Watson and Eastham.[20]

A 125-mL filter flask was fitted with a rubber stopper carrying a nitrogen inlet and a 25-mL buret. In the flask under nitrogen were placed 20 mL of anhydrous ether, 1–2 mg of 2,2′-biquinoline as an indicator, and a magnetic stirring bar. **3** (25 mL) in ether, THF, or toluene was transferred to the indicator solution. This stirred, red-purple, thin slurry was titrated with anhydrous 1 N 2-butanol in xylene accompanied by gradual decolorization to a neutral gray and a green end point. The amount of 2-butanol required to reach the end point is equivalent to the amount of **3** in the sample.

6-Fluoro-2-methyl-3-(p-methylthiobenzyl)indene (6). Twenty-five grams (1.04 mol) of magnesium turnings, a crystal of iodine, and 2 mL of *p*-methylthiobenzyl chloride[21] (**2**) were stirred in 400 mL of anhydrous ether under nitrogen at reflux until Grignard formation commenced. Gentle heating (5–10 min) was usually required. A total of 39.7 g (0.23 mol, including the initial 2 mL) of **2** was added dropwise so as to maintain a gentle reflux. Refluxing was continued for 15 min. The thin precipitate present was shown in a separate experiment to be the coupled product **4**. A 25–30% solution of 5-fluoro-2-methyl-1-indanone (**1**) in toluene was added dropwise over 45–50 min at 25–35 °C to the Grignard solution with careful visual observation. At the point of contact of the indanone and Grignard solutions a transient reddish coloration appeared. This indicator effect was used to determine complete conversion of **3**. There was usually required 0.199 mol (32.6 g) of **1** and further addition gave no increase in yield. The reaction solution and suspended solids were sucked away from unreacted magnesium through a 1-mm opening in a glass pipet or dropper and the magnesium was rinsed with toluene. Over 15 min the combined reaction mixture and toluene rinse was quenched with 120 mL of 3 N sulfuric acid at 30–35 °C. The aqueous layer was discarded and the organic layer containing **5** was stirred vigorously for 1 h with 80 mL of 1:10 concentrated H_2SO_4–acetic acid. This was washed with 2 × 100 mL of water, 200 mL of 2 N NaOH, and again with water. The organic layer was concentrated under vacuum to an oil which assayed by GLC as 47.5 g (84.3% based on **1**) of **6** suitable for condensation with glyoxylic acid. By GLC **4** was measured in 10% yield.

Purification of 6. For characterization **6** was purified by dissolving 40 g of crude oil in 75 mL of 6:1 hexane–benzene. This was chromatographed through 600 g of 60–200 mesh silica gel (J. T. Baker) using the same solvent system. After 1.4–1.5 L of forerun was discarded, a rich cut of 2.4 L was concentrated to 44 g of oil which slowly crystallized from 160 mL of hexane. After filtration at 0–5 °C, washing with cold hexane, and vacuum drying at 25 °C, there was obtained 27.7 g of **6**, mp 57–59 °C. This was recrystallized from 160 mL of hexane to give 21.9 g: mp 58–60 °C; UV max 257.5 nm (ε 25 000); ^{1}H NMR ($CDCl_3$) δ 2.1 (s, 3, C_2CH_3), 2.3 (s, 3, SCH_3), 3.2 (s, 2, C_1H), 3.7 (s, 2, aromatic CH_2), 6.7–7.2 (m, 7, aromatic H).

Anal. Calcd for $C_{18}H_{17}FS$: C, 76.02; H, 6.03; F, 6.68. Found: C, 76.32; H, 5.89; F, 6.68.

1,2-Bis(*p*-methylthiophenyl)ethane (**4**) was obtained from early column chromatography fractions (see above) which were concentrated to dryness and the residue (10 g) recrystallized from toluene (2 mL/g residue) to give 2.7 g (8.6%) of **4**: mp 140–143 °C; UV max 260 nm (0.1 N HCl in CH_3OH, ε 5200); ^{1}H NMR ($CDCl_3$) δ 2.4 (s, 6, SCH_3), 2.8 (s, 4, CH_2), 7.1 (d, 8, aromatic H).

Anal. Calcd for $C_{16}H_{18}S_2$: C, 70.02; H, 6.61. Found: C, 70.33; H, 6.63.

When run in a similar volume of 3:1 toluene–Et_2O the yield of indene **6** was 26.6% (GLC) based on **2**, and the only other detectable product was a large quantity of **4**, 70% by GLC.

In a similar volume of 4:1 THF–toluene the yield of **6** was 23% (GLC) and **4** was estimated at 42% by GLC.

5-Fluoro-1-hydroxy-1-(p-methylthiobenzyl)-2-methylindan (5). Carbinol **5** was prepared by treating **3** with **1** as in the preparation of **6**, except that the reaction mixture was stirred for 2 h, during which time a heavy precipitate formed. The slurry of white solids was siphoned away from unreacted magnesium, and the slurry was filtered and thoroughly washed with ether and toluene. The cake was stirred in ether (250 mL) with 3 N H_2SO_4 (65 mL). The ether layer was washed with water, dried (Na_2SO_4), and evaporated to an oil 34.5 g. After 7 days the oil partially crystallized. The crystals were broken up and the entire mass slurried in hexane for several hours, filtered, and air dried: yield 27.3 g (39%); mp 56–61 °C; ^{1}H NMR ($CDCl_3$) δ 0.9 and 1.1 (two doublets, 3, isomeric C_2CH_3), 2.5–2.8 (m, 3, C_2 H and C_3 H), 3.0 (s, 2, benzyl CH_2), 6.7–7.2 (m, 7, aromatic H); mass spectrum *m/e* 284 ($M^+ - H_2O$, 302 − 18).

Anal. Calcd for $C_{18}H_{19}FOS$: C, 71.45; H, 6.33; F, 6.28; S. 10.60. Found: C, 71.35; H, 6.54; F, 6.01; S, 10.86.

This material was recrystallized from warm hexane, recovery 72%, mp 55–60 °C.

5-Fluoro-2-methyl-1-(p-methylthiobenzylidene)indan (7). Method A. Mother liquor solids from isolation of **6** were dissolved in an equal volume of acetone, and 5 mg of the second largest peak was isolated by preparative GLC over 10% OV-101 (230–235 °C): ^{1}H NMR ($CDCl_3$) δ 1.2 (d, 3, C_2CH_3), 2.5 (s, 3, SCH_3), 2.7–3.8 (m, 3, C_2 and C_3 H), 6.7–7.6 (m, 8, aromatic and vinyl H); mass spectrum *m/e* 284 (M^+).

Method B. To 168 mg (1.5 mmol) of *t*-BuOK in 2 mL of Me_2SO was added 651 mg (1.5 mmol) of *p*-methylthiobenzyltriphenylphosphonium chloride in 1 mL of Me_2SO followed by 270 mg (1.65 mmol) of indanone **1** in 2 mL of Me_2SO. The dark solution was heated at 75 °C for 17.5 h. By TLC some of **1** was unreacted. The reaction mixture was diluted with 10 mL of benzene and 5 mL of water, and the benzene layer was washed twice with water. The organic layer was filtered slowly through 8 g of silica gel which was also washed with benzene. The filtrate was concentrated to an oil, 372 mg. The major TLC spot was isolated by elution through 15 g of silica gel with hexene to give 96 mg of **7**, mp 67–70 °C, spectrally identical with that from Method A.

(Z)-6-Fluoro-2-methyl-3-(p-methylthiobenzyl)-1-indenylideneacetic Acid (10). Crude oil assaying as 11.1 g (0.039 mol) of **6** was placed under nitrogen, warmed to 42 °C, and to it was added 42.6 mL of 37.8% benzyltrimethylammonium hydroxide (Triton B; 14.73 g on a dry basis, 0.088 mol) in methanol. To this stirred, two-phase mixture at 37 °C was added 6.56 mL (4.34 g on a dry basis, 0.0586 mol, *d* = 1.313 g/mL) of 50% glyoxylic acid in water. For 45 min the reaction mixture was stirred at 50 °C. It was transferred hot to a stirred, jacketed, three-necked separatory flask and diluted with water (67 mL) and toluene (100 mL). The pH was adjusted to 2.0–2.2 with ca. 3–8 mL of H_2SO_4. With steam on the jacket the mixture was stirred at 70–75 °C until complete solution was obtained. The water layer was discarded and the washing repeated with hot water. One percent NH_4Cl (67 mL) was added and the pH adjusted to 8.5 with NH_4OH (15 mL). The toluene layer was extracted again at pH 8.5 with hot 1% NH_4Cl. To the combined aqueous extracts was added 1,2-dichloroethane (105 mL) and the temperature adjusted to 65–68 °C. The pH was adjusted to 2 with concentrated HCl and the mixture stirred at 70 °C for 1 h. The organic layer was separated, cooled, filtered, and washed to give 10 g (75%) of orange product, mp 182–184 °C. Recrystallization from hot toluene (18 mL/g) gave product in 95% recovery: mp 184–185 °C; UV max 261 nm (0.1 N HCl in CH_3OH, ε 40 500); ^{1}H NMR (Me_2SO-d_6) δ 2.1 (s, 3, C_2CH_3), 2.4 (s, 3 SCH_3), 3.9 (s, 2 benzyl CH_2), 6.5 (s, 1, vinyl H), 7.0–7.4 (m, 6, aromatic H), 8.2 and 8.4 (d, 1, aromatic C_7 H).

Anal. Calcd for $C_{20}H_{17}FO_2S$: C, 70.57; H, 5.03; F, 5.58. Found: C, 70.62; H, 4.82; F, 5.48.

Irradiation of the C_2CH_3 in a degassed Me_2SO-d_6 solution gave a 49% nuclear Overhauser enhancement of the vinylic proton. This is evidence for the assigned *Z* configuration of **10**.

(E)-6-Fluoro-2-methyl-3-(p-methylthiobenzyl)-1-indenylideneacetic Acid (11). Mother liquors from several isolations of **10** were taken to dryness under vacuum. The residue (5.4 g) was digested in 100 ml of refluxing CCl_4 for several hours and subsequently cooled to give **11**, 1.25 g, as nearly pure material. Recrystallization two times from ethanol produced pure **11** as orange-red needles: mp 166–168 °C; UV max 260 nm (0.1 N HCl in CH_3OH, ε 41 600; ^{1}H NMR (Me_2SO-d_6) δ 2.18 (s, 3, C_2CH_3), 2.3 (s, 3, SCH_3), 3.8 (s, 2, CH_2), 6.85–7.3 (m, 3, vinyl and indene aromatic), 7.1 (s, 4, aromatic), 7.6 (m, 1, C_7 H).

Anal. Calcd for $C_{20}H_{17}FO_2S$: C, 70.57; H, 5.03. Found: C, 70.31; H, 5.25.

6-Fluoro-2-methyl-3-(p-methylthiobenzyl)indene-1-glycolic Acid (9). To indene **6** (20 g, 0.0704 mol) and 1,1,3,3,-tetramethylguanidine (18.2 g, 0.1585 mol) in DMF (50 mL) was added 50% glyoxylic acid (7.82 g dry basis, 0.1055 mol). The solution was heated at 52–55 °C for 1 h, quenched with 2 mL of H_2SO_4, and transferred with 75 mL of toluene to a jacketed, 500-ml, three-necked separatory funnel. Water (150 mL) was added and the pH adjusted to 2 with H_2SO_4 at 50 °C. The water layer was discarded and the hot organic layer was washed with 1% NaCl. A second portion of 1% NaCl (100 mL) was added and the pH raised to 8.5–9.0 with NaOH at >78 °C. The hot water layer was combined with 100 mL of toluene, the pH lowered to 2 with concentrated HCl, and the separated toluene layer dried by azeotropic removal of water. Product crystallized over 3 days as a fine, white solid: yield 8.26 g (32.7%); mp 179.5–181 °C; UV max 259 nm (0.1 N HCl in CH_3OH, ε 19 150); IR (CH_2Cl_2) 3550 (OH), 2900 (carboxyl OH), 1700–1725 cm^{-1} (C=O); ^{1}H NMR (Me_2SO-d_6) δ 2.1 (s, 3, C_2CH_3), 2.4 (s, 3, SCH_3), 3.8 (s, 3, benzyl CH_2 and C_1H), 4.7 (d, 1, HCO), 6.9–7.2 (m, 7, aromatic H); D_2O exchange, δ 4.7 (s, 2, HOD).

Anal. Calcd for $C_{20}H_{19}FO_3S$: C, 67.02; H, 5.34; F, 5.30. Found: C, 66.90; H, 5.41; F, 5.20.

Compound **9** could also be isolated when the Triton B catalyzed reaction of **6** with glyoxylic acid was worked up after a few minutes of reaction.

Dehydration of 9 to 10. Attempts to dehydrate **9** under acidic conditions failed. The reagents used were I_2, HCl, or $Mg(OH)_2$ in acetic acid, and H_2SO_4 in acetic anhydride.

Dehydration of **9** to **10** was rapid with 1.5–2.0 equiv of Triton B in methanol, pyridine, or DMF at 50 °C and was followed by TLC.

(*Z*)-1-Indenylideneacetic Acid. To indene (13.5 g, 0.116 mol) under nitrogen was added tetramethylammonium hydroxide (93 mL of 2.81 M in methanol, 0.261 mol) and glyoxylic acid (19.65 mL of 50% solution in water, 0.174 mol). The reaction mixture was stirred at 55 °C for 70 min. Water (150 mL) and toluene (150 mL) were added, the pH adjusted to 2 with H_2SO_4, and the layers separated. The water layer was extracted with 2 × 50 mL of 1,2-dichloroethane, and the toluene and 1,2-dichloroethane extracts were combined. After washing with water (50 mL) the organic extracts were stripped to dryness under vacuum. The solid residue (10.4 g, 52%) crystallized from ethyl acetate (110 mL) and was dried at 50 °C under vacuum: yield 4.8 g (24%); mp 198–201 °C dec; UV max 259 nm (0.1 M HCl in CH_3OH, ϵ 27 850); TLC, single component on silica gel (9 C_6H_6–1 CH_3OH), R_f 0.35; ^1H NMR (Me_2SO-d_6) δ 6.75 (s, 1, vinyl H), 7.0–7.5 (m, 5, aromatic H and indenyl H), 7.7–7.9 (m, 1, aromatic H).

Anal. Calcd for $C_{11}H_8O_2$: C, 76.73; H, 4.68. Found: C, 76.81; H, 4.87.

(*Z*)-5-Fluoro-2-methyl-1-(*p*-methylthiobenzylidene)-3-indenylacetic Acid (12). A solution of glacial acetic acid (200 mL), concentrated HCl (60 mL), and water (20 mL) was prepared. There was added 19 g (0.056 mol) of **10** and the slurry was heated at 90–95 °C for 10 h, during which the suspended solids changed from orange to yellow. The cooled mixture was filtered, washed with water, and vacuum dried at 80–90 °C to give 17.7 g (93%) of **12**, mp 180–184 °C, with <2% of either **10** or **13** by NMR. Purification was achieved by digesting 7.5 g in 38 mL of refluxing 1,2-dichloroethane for 3 h. The mixture was cooled, filtered, and washed with fresh solvent: recovery 6.5 g (87%) of single-spot material; mp 189.5–192.5 °C; UV max 350 nm (ϵ 17 500) and 258 (19 400) in 0.1 N HCl in CH_3OH; ^1H NMR (Me_2SO-d_6) δ 2.2 (s, 3, C_2 CH_3), 2.6 (s, 3, SCH_3), 3.6 (s, 2, C_3 $CH_2CO_2^-$), 6.6–7.7 (m, 8, aromatic vinyl H).

Anal. Calcd for $C_{20}H_{17}FO_2S$: C, 70.57; H, 5.03; F, 5.58. Found: C, 70.70; H, 5.02; F, 5.36.

(*E*)-5-Fluoro-2-methyl-1-(*p*-methylthiobenzylidene)-3-indenylacetic Acid (13). The 1,2-dichloroethane mother liquors from several preparations of **12** were combined and partially concentrated under vacuum to collect a small second crop of **12.** The filtrate was taken to dryness in vacuo and the residue (25 g) dissolved in a small amount of benzene. Four grams of yellow solids crystallized over 2 weeks. By ^1H NMR this was comprised of a 70:30 mixture of **13:12** which was recrystallized three times from ethanol to give 1 g of **13:** mp 187.5–191 °C; UV max 267 and 349 nm (0.1 N HCl in CH_3OH, ϵ 20 700 and 22 200); ^1H NMR ($CDCl_3$ + CD_3OD) δ 1.88 (s, 3, C_2 CH_3), 2.5 (s, 3, CH_3S), 3.53 (s, 2, CH_2), 7.5 (s, 1, vinyl), 6.5–7.6 (m, 3, indene aromatic), 7.25 (s, 4, aromatic).

Anal. Calcd for $C_{20}H_{17}FO_2S$: C, 70.57; H, 5.03. Found: C, 70.50; H, 5.10.

^1H NMR Isomerization Study of 10 to 12. A solution of **10** (21 mg) in CD_2ClCD_2Cl (0.6 mL) was saturated with HCl and sealed in an NMR tube. The tube was heated at 100 °C and spectra obtained periodically over 48 h. Only peaks attributed to known compounds were observed; no evidence for a substantial population of a protonated intermediate or adduct of HCl was detected. At 70% conversion of **10** impurity peaks appeared. Compounds **10** and **12** are differentiated by their CH_2 singlets at δ 3.9 and 3.6 (Me_2SO-d_6), respectively.

Triton B Isomerization of 10 to 12 and 13. There was pipetted 0.34 mL (0.704 mmol) of 38% Triton B in methanol into 4 mL of anhydrous pyridine. This solution was stripped under vacuum to 2–3 mL, and 100 mg (0.294 mmol) of **10** was added and stirred under nitrogen at 25 °C. After 1 h TLC showed conversion largely to **12.** Two milliliters of acetic acid and some water were added. This was extracted with 1:1 benzene–ether. The organic layer was washed with 4 × 25 mL of HCl and 2 × 25 mL of 5% NaCl, then dried (Na_2SO_4) and stripped to dryness. After flushing with 2 mL of $CDCl_3$, ^1H NMR ($CDCl_3$) showed the composition to be 19% **10,** 72% **12** and 9% **13.** Similar results were obtained when isomerization was conducted in warm, methanolic Triton B.

Thermal Isomerism of 10 and 11. A crystalline sample of **11** was almost completely isomerized to **10** (TLC) when left in a melting point capillary at 130 °C for several hours. No trace of **12** or **13** was observed by TLC.

Thermal Isomerism of 12 and 13. Each isomer, **12** or **13,** was converted in NMR solvents at 110 °C to an equilibrium mixture of 82:18 of **12:13.** The half-lives were 45 min in pyridine-d_5 and 30 min in Me_2SO-d_6 based on the shift in the C_2 CH_3 peaks.

In the crystalline state over 18 h at 135 °C **13** was changed largely to **12,** whereas **12** remained virtually unchanged by TLC. No tautomerism to **10** or **11** was detected.

(*Z*)-6-Fluoro-2-methyl-3-(*p*-methylsulfinylbenzyl-1-indenylideneacetic Acid (14). To 1.0 g (2.94 mmol) of **10** slurried in 10 mL of $CHCl_3$ and 10 mL of acetic acid was added 0.6 mL (5.3 mmol) of 30% H_2O_2. This was stirred for 30 min and complete solution occurred. Water (40 mL) was added and the product extracted into 20 mL of 1:1 PhH/ether. The organic layer was washed four times with water, dried (Na_2SO_4), and stripped to dryness under vacuum. The crude solid (1.12 g) was crystallized from 35 mL of 50% methanol to give yellow-orange crystals: 0.905 g (86%); mp 160–163 °C; UV max 263 nm (0.1 N HCl in CH_3OH, ϵ 32 800); ^1H NMR (Me_2SO-d_6) δ 2.1 (s, 3, C_2 CH_3), 2.7 (s, 3, SCH_3), 4.0 (s, 2, CH_2), 6.5 (s, 1, vinyl), 7.0 and 7.2 (d, 2, C_4 H and C_5 H), 7.4–7.7 (m, 4 aromatic), 8.2 and 8.4 (m, 1, aromatic C_7 H).

Anal. Calcd for $C_{20}H_{17}FO_3S$: C, 67.40; H, 4.81; F, 5.33. Found: C, 67.71; H, 5.00; F, 5.14.

(*Z*)-5-Fluoro-2-methyl-1-(*p*-methylsulfinylbenzylidene)-3-indenylacetic Acid (15). To 34 g (0.1 mol) of **12** in 240 mL of 65:35 chloroform–acetic acid was added 0.103 mol of 30% hydrogen peroxide. The resulting solution was stirred at 35 °C for 4 h, at which time TLC showed reaction to be complete. After washing with water, the chloroform layer was concentrated under vacuum and the residue crystallized from ethanol to afford 32–33 g (90–92%) of product, mp 180.5–183.5 °C. Repeated recrystallization raised the melting point to 187–188 °C; UV max 256 nm (0.1 N HCl in CH_3OH, ϵ 11 400); ^1H NMR ($CDCl_3$ + CD_3OD) δ 2.2 (s, 3, C_2 CH_3), 2.8 (s, 3, SCH_3), 3.5 (s, 2, CH_2), 6.3–7.45 (m, 4, indene aromatic and vinylic), 7.7 (s, 4, benzyl aromatic); mass spectrum *m/e* (rel intensity) 357 (25), 356 (M^+, 85), 342 (24), 341 (100), 340 (17), 281 (28), 248 (39), 247 (28), 246 (39), 234 (25), 233 (89), 220 (12).

Anal. Calcd for $C_{20}H_{17}FO_3S$: C, 67.40; H, 4.81. Found: C, 67.63; H, 4.72.

Triton B Isomerization of 14. To 1.5 mL of pyridine were added 159 mg (0.446 mmol) of **14** and 0.43 mL (0.9 mmol) of Triton B (38% in CH_3OH). This was stirred for 1 h at 25 °C under N_2 and worked up by addition of 50 mL of 1:1 benzene–ether which was washed with several portions of 1 N HCl and water. The organic layer was dried (Na_2SO_4) and evaporated under vacuum. By ^1H NMR ($CDCl_3$) it was composed of 19% **14,** 72% **15,** and 9% **16,** the *E* isomer of **15.**

(*E*)-5-Fluoro-2-methyl-1-(*p*-methylsulfinylbenzylidene)-3-indenylacetic Acid (16). Ca. 690 mg of residue enriched in **16** was chromatographed through 250 g of silica gel H with 9:1 CCl_4–CH_3CO_2H. The column was sucked dry of solvent before elution of the product, and the adsorbent was extruded in small segments. Each segment was eluted with methanol and checked by TLC. From the combined eluents of segments highly enriched in **16** a yellow solid was obtained, and it was recrystallized from 1:1 methanol–water: 47 mg; mp 178–181 °C; UV max 331 nm (ϵ 15 700), 282 (24 000), and 240 (11 500) in 0.1 N HCl in CH_3OH; ^1H NMR ($CDCl_3$) δ 1.8 (s, 3, C_2 CH_3), 2.8 (s, 3, SCH_3), 3.5 (s, 2, CH_2), 6.55–7.8 (m, 8, aromatic and vinyl); mass spectrum *m/e* (rel intensity) 357 (11), 356 (M^+, 49), 342 (15), 341 (71), 297 (20), 281 (22), 248 (30), 247 (35), 246 (33), 234 (33), 233 (100), 220 (17).

Isomerization of 14 with Concentrated HCl–Acetic Acid. Isomerization of **14** under conditions for the isomerization of **10** to **12** results in formation (TLC) of **12** accompanied by considerable decomposition as evidenced by blackening and formation of dark, insoluble materials.

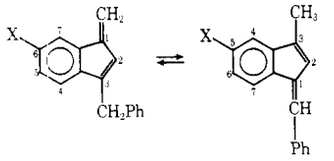
Registry No.—**1,** 41201-58-5; **2,** 874-87-3; **3,** 61812-40-6; **4,** 61812-41-7; **5,** 41201-59-6; **6,** 41201-60-9; **7,** 55507-46-5; **9,** 61812-42-8; **10,** 61812-43-9; **11,** 61812-44-0; **12,** 49627-27-2; **13,** 61812-45-1; **14,** 61849-35-2; **15,** 38194-50-2; **16,** 61812-46-2; *p*-methylthiobenzyltriphenylphosphonium chloride, 58477-22-8; glyoxylic acid, 298-12-4; (*Z*)-1-indenylideneacetic acid, 61812-47-3.

References and Notes

(1) (a) The *S*-oxide **15** is a potent antiinflammatory agent with the generic name sulindac. (b) T. Y. Shen, B. E. Witzel, H. Jones, B. O. Linn, J. McPherson, R. Greenwald, M. Fordice, and A. Jacob, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **31,** 577 (1972) (c) T. Y. Shen in "Clinoril in the Treatment of Rheumatic Disorders", E. C. Huskisson and P. Franchimont, Ed., Raven Press, New York, N.Y., 1976, p 1.

(2) Because this paper deals in part with tautomerism of a conjugated diene system comprised of an indene and an exocyclic double bond, this note

is added to clarify nomenclature. Indene is numbered beginning with the saturated carbon, C-1, of the five-membered ring. A prototropic shift must result in a new saturated carbon and, therefore, in reversal of the direction of numbering of the entire carbon skeleton. For example, a 6-subsituted



3-benzyl-1-methylideneindene upon isomerization of both double bonds becomes a 5-substituted 1-benzylidene-3-methylindene.

(3) Generic name for 1-(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid; a potent, widely used antiinflammatory agent.
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The Regioselective Behavior of Unsaturated Keto Esters toward Vinylogous Amides

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The regioselective reactivity of unsaturated keto ester **8** toward vinylogous amides **7** and **11** is presented, along with further evidence as to the effect of solvent on the course of the reaction.

The regioselective synthesis of indoles or quinolines from the coupling of diacyl ethylenes (**2**) and primary enamino ketones (**1**) has been reported.[1] Under acidic or neutral reaction conditions the indole derivatives (**4**) are formed whereas basic and/or dehydrogenation conditions provide the corresponding quinolines (**6**) (Scheme I). Use of an unsymmetrical

Scheme I