3-(*p*-Fluorophenyl)-*as*-triazine (4i). A hot aqueous solution of *p*-fluorobenzamidrazone (2 g, 0.013 mol) was added to a hot aqueous solution of glyoxal bisulfite (10 g, 0.043 mol). After 5 min of heating, the reaction mixture was filtered, and the mother liquor was basified and extracted with ether. Removal of the solvent gave a residue which was crystallized from 2-propanol to give 1.1 g (50%) of product: mp 102–106 °C; ^{1}H NMR ($CDCl_3$) δ 9.19 (d, 1, J = 3 Hz), 8.64 (d, 1, J = 3 Hz), 8.54 (m, 2, arom H), 7.20 (m, 2, arom H). Anal. C, H, N, F.

3-(o-Fluorophenyl)-*as*-triazine (4m). A solution of o-fluorobenzamide (10 g, 0.072 mol) and methyl fluorosulfonate (10 mL, excess) in chloroform was refluxed for 3 h. After standing at room temperature for 18 h, the reaction was evaporated in vacuo yielding a white solid which was partitioned between $CHCl_3$ and 5% aqueous $NaHCO_3$. The organic portion was rinsed with water, dried ($MgSO_4$), and evaporated without heat to give a colorless oil. An ethanolic solution (72 mL, 0.001 M) of hydrazine was added and the reaction was allowed to stand at 5 °C for 2.5 days. Evaporation gave a yellow solid which was allowed to react with glyoxal disodium bisulfite (50 g, excess) in hot water. Work-up as described above [cf. 3-(*p*-fluorophenyl)-*as*-triazine (4i)] gave 1.2 g (9%) after crystallization from 2-propanol–hexanes: mp 44–46 °C; ^{1}H NMR ($CDCl_3$) δ 9.21 (d, 1, J = 3 Hz), 8.76 (d, 1, J = 3 Hz), 8.18 (m, 1), 7.46 (m, 3, aromatic). An additional crystallization (2-propanol–hexanes) gave the analytical sample. Anal. C, H, N, F.

Ethyl 5-(*p*-Chlorophenyl)-4*H*-1,2,4-triazole-3-carboxylate (6). An ethanolic solution of diethyl oxalate (1.5 g, 0.01 mol) and *p*-chlorophenylamidrazone (1.7 g, 0.01 mol) was heated on the steam bath for 45 min. After stirring at room temperature for an additional 45 min, the solvent was removed and the resultant product was crystallized from 2-propanol to give 0.7 g of product, mp 220–223 °C. Anal. C, H, N, Cl.

Ethyl 3-(*p*-Chlorophenyl)-5,6-dihydro-5-oxo-*as*-triazine-6-carboxylate (7). This procedure is described by Taylor and Martin.[2a] An ethanolic solution of diethyl 2-ketomalonate (1.75 g, 0.01 mol) and *p*-chlorobenzamidrazone (1.7 g, 0.01 mol) was stirred at room temperature for 18 h. The filtered reaction was evaporated and the residue crystallized from 2-propanol to give 0.9 g (32%): mp 247–250 °C (lit.[2a] mp 244 °C); ^{1}H NMR (Me_2SO-d_6–$CDCl_3$) δ 8.17 (d, 2, J = 10 Hz), 7.52 (d, 2, J = 10 Hz), 4.45 (q, 2, J = 8 Hz), 1.40 (t, 3, J = 8 Hz).

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Synthesis and Antiinflammatory Activity of *cis*-4,5,6,7,8,8a,9-Hexahydro-α-methyl-5*H*-fluorene-2-acetic Acid

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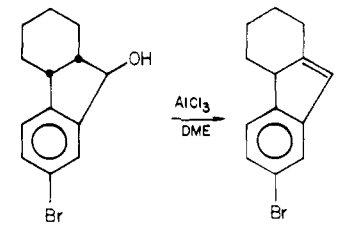
cis-4b,6,7,8,8a,9-Hexahydro-α-methyl-5*H*-fluorene-2-acetic acid was synthesized in an unambiguous way and its antiinflammatory activity compared to α-methylfluorene-2-acetic acid.

The arylacetic acids are currently the most actively investigated class of compounds in the nonsteroidal antiinflammatory area.[1] In our own investigations in this area, we identified **1** as a compound with antiinflammatory activity[2] and initiated a project designed to test the effect on biological activity of partial saturation of the fluorene ring system. To this end we developed the following unambiguous synthesis of **2**, a hexahydro analogue of **1** (see Scheme I).

Chemistry. Standard methods were successful for the synthesis of bromo ketone **5** but the usual procedures for deketonization (Wolff–Kishner, Raney nickel, desulfurization, etc.) failed to give **6** in useful yields. Attempted hydrogenolysis of **5** with a mixed hydride reagent[3] yielded alcohol **5a** but this compound was readily dehydrated to **5b** which was reduced catalytically to **6**.

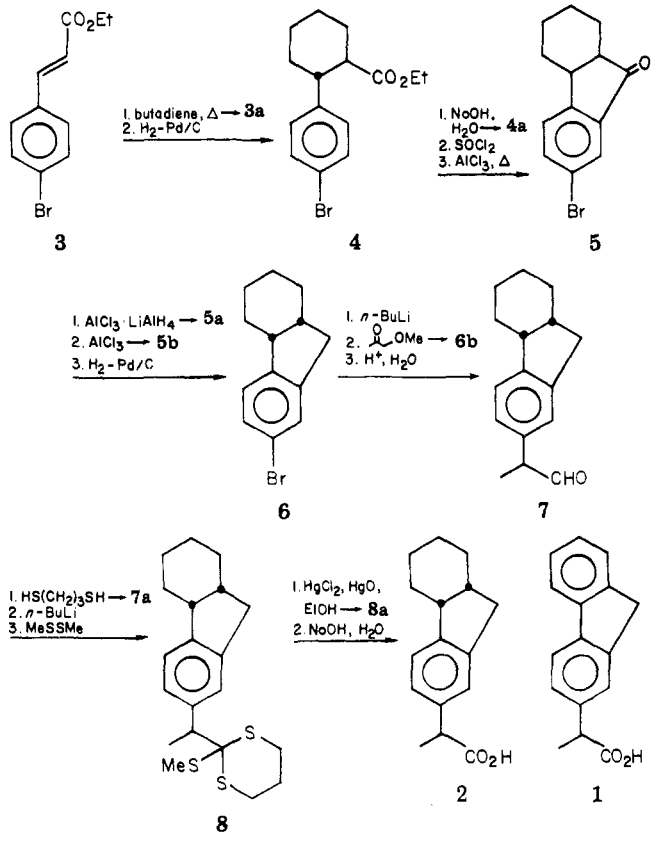
The stereochemistry at the ring junction in **6** was determined to be cis based on the following arguments. In the ^{1}H NMR spectrum of *cis*-1,2,3,4,4a,9a-hexahydro-9-fluorenone[4] (Figure 1, B), the 4a and 9a proton absorptions appear at lower field (multiplets centered at 3.4 and 2.8 ppm) than in the case of the trans isomer (broad multiplet



5a **5b**

at 3.0–2.0 ppm) (Figure 1, C). This sort of deshielding has been noted in other 6,5-fused ring systems[5] and is probably due to the diamagnetic anisotrophy of the neighboring aromatic ring. Inspection of a Dreiding model of the cis compound indicates that in the two conformations in which the saturated ring can exist as a chair form, the 4a and 9a protons, respectively, assume positions equatorial to the five-membered ring in which they are relatively close to the plane of the aromatic ring. Therefore, the chemical shift of these protons should and does appear further downfield for the cis isomer than for the trans isomer in which the 4a and 9a protons are locked in positions axial

Scheme I

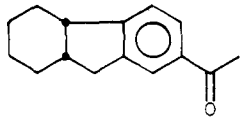


to the five-membered ring and out of the plane of the aromatic ring.

Although somewhat less pronounced, this same chemical shift difference is observed in the ^{1}H NMR spectra of *cis*- and *trans*-1,2,3,4,4a,9a-hexahydrofluorene[6] (Figure 1, D, and 1, E, respectively).

In the ^{1}H NMR spectrum of **6** (Figure 1, A) the 4a and 9a proton chemical shifts are the same as in spectrum 1, D; therefore, the ring junction stereochemistry in **6** is cis.

The aldehyde side chain in **7** was conveniently attached by reaction of the lithio derivative of **6** with methoxyacetone followed by acid-catalyzed rearrangement of the intermediate tertiary alcohol. Aldehyde **7**, however, underwent a cleavage reaction yielding ketone **9** when subjected to normal oxidative methods such as CrO_3–H_2SO_4, CrO_3–pyridine, Ag_2O, or neutral AgO. This



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difficulty was overcome by application of the Ellison procedure[7] (Scheme I) leading to the acid **2** contaminated with ca. 10% of the corresponding α,β-unsaturated acid. Catalytic reduction of this acid mixture gave pure **2** in 30% yield from **7**.

Pharmacology. The propanoic acids **1** and **2** were evaluated in a reversed passive arthus test (RPA)[8] and concurrently in a carrageenin-induced rat paw edema assay (CE).[9] The antiinflammatory activity of **1**, as measured by these tests (Table I), is retained in **2** despite saturation of one of the aromatic rings.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on Perkin-Elmer 621 and 137 spectrophotometers. NMR spectra were recorded using Varian T-60 and Perkin-Elmer R-12B spectrometers using tetramethylsilane as an internal reference. Microanalyses were performed by the analytical department, E. R. Squibb & Sons, Princeton, N.J. Where analyses are indicated by the symbols of the elements, analytical results obtained for these elements were ±0.3% of the theoretical values. All compounds were consistent with their NMR (in $CDCl_3$) and IR (KBr or neat) spectra.

***trans*-6-(*p*-Bromophenyl)-3-cyclohexenecarboxylic Acid Ethyl Ester (3a).** A mixture of *trans*-*p*-bromocinnamic acid ethyl ester (115 g, 0.45 mol), condensed butadiene (175 mL, excess), and hydroquinone (2.55 g, 0.023 mol) in 500 mL of dry benzene was heated at 180 °C in a high-pressure bomb for 120 h. Concentration of the reaction mixture in vacuo gave a brown oil which

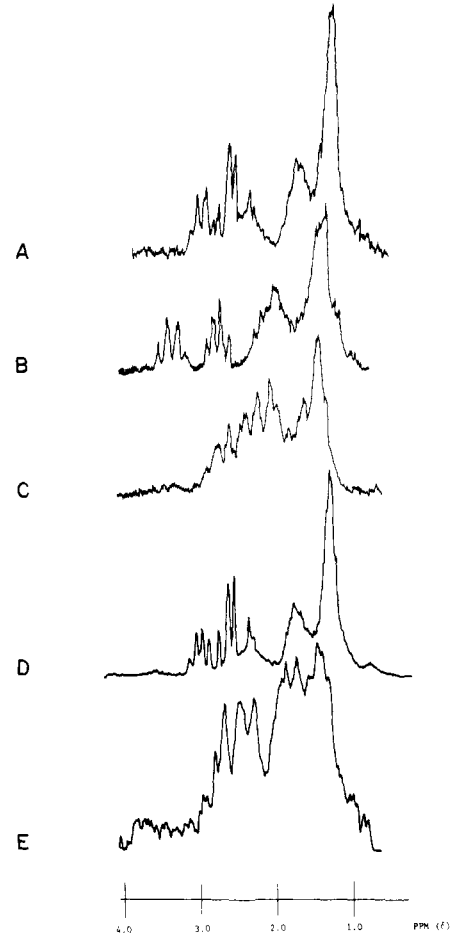

Figure 1. All spectra run in $CDCl_3$ with Me_4Si as internal standard: A, compound **6**; B, *cis*-1,2,3,4,4a,9a-hexahydro-9-fluorenone;[4] C, *trans*-1,2,3,4,4a,9a-hexahydro-9-fluorenone;[4] D, *cis*-1,2,3,4,4a,9a-hexahydrofluorene;[6] E, *trans*-1,2,3,4,4a,9a-hexahydrofluorene.[6]

Table I. Comparison of Compounds 1 and 2 in the Carrageenin Edema (CE) and Reversed Passive Arthus (RPA) Tests

Compd	CE,[a] % inhibn of edema	RPA,[b] % inhibn of edema
1	66 (42-77), n = 12	36 (20-49), n = 13
2	63 (59-66), n = 2	55 (44-60), n = 2
Ibuprofen	56 (46-71), n = 3	54 (39-69), n = 5
Naproxen		55 (43-70), n = 7
Phenylbutazone	59 (56-62), n = 2	44 (22-65), n = 8
Indomethacin		57 (40-77), n = 15

[a] Average values at a dose of 150 mg/kg in rats; range indicated in parentheses; n = number of animals. [b] Average values at a dose of 200 μg per site in rabbits; range indicated in parentheses; n = number of animals.

was chromatographed on alumina. Polymeric by-products were washed off with hexane and cyclohexane was used to elute **3a** (105 g, 76%). Distillation of **3a** causes retro-Diels–Alder decomposition reactions. Anal. ($C_{15}H_{17}BrO_2$) C, H, Br.

***trans*-2-(*p*-Bromophenyl)cyclohexanecarboxylic Acid Ethyl Ester (4).** A mixture of **3a** (75 g, 0.24 mol), 5% Pd/C (950 mg), and glacial acetic acid (200 mL) was hydrogenated on a Parr shaker until hydrogen uptake reached 0.24 mol (4 h). Filtration and concentration in vacuo of the reaction mixture afforded an oil which was chromatographed on alumina (200 mL, activity III) with benzene to yield **4** (70 g, 95%): distilled **4**, bp 121–122 °C (0.2 mm). Anal. ($C_{15}H_{19}BrO_2$) C, H, Br.

***trans*-2-(*p*-Bromophenyl)cyclohexanecarboxylic Acid (4a).** A mixture of **4** (70 g, 0.23 mol), 10% aqueous sodium hydroxide (800 mL), and ethanol (200 mL) was heated at reflux for 4.5 h. The reaction mixture was concentrated in vacuo to one-half its original volume and washed with methylene chloride to remove unreacted ester (7 g). After acidification with concentrated HCl, the aqueous layer was extracted with methylene chloride to yield **4a** [50 g (79%); recrystallized from cyclohexane, mp 141–143 °C]. Anal. ($C_{13}H_{15}BrO_3$) C, H, Br.

7-Bromo-1,2,3,4,4a,9a-hexahydro-9-fluorenone (5). A mixture of **4a** (30 g, 0.11 mol) and thionyl chloride (60 mL, 0.30 mol) was heated at reflux for 40 min. The excess thionyl chloride was removed in vacuo and the residue mixed with powdered aluminum chloride (17 g, 0.13 mol). The mixture was kept at 25 °C for 15 min (cooling with an ice–water bath is required initially) and then diluted with carbon tetrachloride (100 mL) and heated at reflux for 30 min. The reaction mixture was mixed with concentrated HCl and extracted with methylene chloride to yield a crystalline crude product. This material was passed through a short column of alumina (activity III) and then recrystallized from pentane to yield **5** [18.2 g (64%); mp 81–82 °C]. Anal. ($C_{13}H_{13}Br$) C, H, Br.

7-Bromo-2,3,4,4a-tetrahydro-1*H*-fluorene (5b). A solution of **5** (13 g, 0.049 mol) in dimethoxyethane (DME, 250 mL) was added over 20 min to a solution of mixed hydride reagent [prepared by addition of $AlCl_3$ (24.7 g, 0.185 mol) to a solution of $LiAlH_4$ (0.086 mol) in ether (145 mL) at 5 °C] at 25 °C under nitrogen. The mixture was heated at reflux for 1 h, poured into 10% aqueous HCl, and extracted with methylene chloride to yield **5a** (13 g, 99%). A mixture of **5a** (13 g, 0.048 mol), $AlCl_3$ (24.7 g, 0.185 mol), and DME (350 mL) was heated at reflux for 1 h. The mixture was then poured into 10% aqueous HCl and extracted with methylene chloride to yield **5b** [12 g (83%); recrystallized from pentane at −78 °C, mp 64–66 °C]. Anal. ($C_{13}H_{13}Br$) C, H, Br.

***cis*-7-Bromo-1,2,3,4,4a,9a-hexahydrofluorene (6).** A mixture of **5b** (10 g, 0.04 mol), glacial acetic acid (400 mL), 70% aqueous perchloric acid (5 mL), and 5% Pd/C catalyst (750 mg) was hydrogenated at atmospheric pressure until 1 mol of H_2 had been absorbed (6 h, 900 mL). The mixture was filtered and concentrated in vacuo giving an oil which was dissolved in methylene chloride and washed with $NaHCO_3$ solution. Concentration of the organic layer in vacuo afforded crude **6** which was chromatographed on alumina (activity I) with cyclohexane to give **6** [9 g (89%); solidified on standing at 0 °C]. Anal. ($C_{13}H_{15}Br$) C, H, Br.

1-Methoxy-2-(2′-*cis*-4b′,6′,7′,8′,8a′,9′-hexahydrofluorenyl)-2-propanol (6b). A solution of *n*-butyllithium (0.049 mol) in hexane was added dropwise at 0 °C to a solution of **6** (9.1 g, 0.036 mol) in anhydrous ether (200 mL) and the resulting mixture kept at 0 °C under argon for 30 min. Freshly distilled methoxyacetone (6.25 g, 0.071 mol) was added dropwise and the mixture was heated at reflux for 1.5 h. After an additional 1.5 h at 25 °C, the mixture was poured into 10% aqueous HCl and extracted with methylene chloride. Concentration of the extracts in vacuo gave crude **6b** (15 g) which was chromatographed on alumina (activity III) with cyclohexane–benzene (50:50) to yield **6b** (6.8 g, 78%) as an oil.

2-(2′-*cis*-4b′,6′,7′,8′,8a′,9′-Hexahydrofluorenyl)propanol 1,3-Propanedithiol Thioacetal (7a). A mixture of **6b** (6.8 g, 0.026 mol), 48% aqueous HBr (100 mL), and water (500 mL) was heated at reflux under nitrogen with rapid stirring for 20 min. The mixture was extracted with methylene chloride and the extracts were washed with water, aqueous $NaHCO_3$, and water. Concentration of the organic layer in vacuo gave **7** (6.6 g) which was mixed with propane-1,3-dithiol (2.8 mL, 0.024 mol) in chloroform and the mixture was saturated with dry HCl. After 30 min, the mixture was washed with 10% aqueous NaOH and water and then concentrated in vacuo to yield crude **7a** which was chromatographed on alumina (activity III) with pentane giving **7a** (4.87 g, 59%) as an oil. Anal. ($C_{19}H_{26}S_3$) C, H, S.

2-(2′-*cis*-4b′,6′,7′,8′,8a′,9′-Hexahydrofluorenyl)propanoic Acid Methyltrimethylene Trithioorthoester (8). A solution of *n*-butyllithium (0.019 mol) in hexane was added dropwise to a solution of **7a** (4.05 g, 0.017 mol) in dry THF at −78 °C under argon over a 10-min period. The temperature was adjusted to 25 °C and, after 2 h, methyl disulfide (2.6 mL, 0.026 mol) was added dropwise and stirring was continued for 30 min. The mixture was poured into 10% aqueous HCl and extracted with methylene chloride. The extracts were washed with aqueous $NaHCO_3$ and water and concentrated giving crude **8** (5.2 g) which was chromatographed on alumina (activity III) with pentane to yield **8** (4 g, 87%) as an oil. Anal. ($C_{20}H_{28}S_3$) C, H, S.

***cis*-4b,6,7,8,8a,9-Hexahydro-α-methyl-5*H*-fluorene-2-acetic Acid Ethyl Ester (8a).** A mixture of **8** (4 g, 0.014 mol), HgO (4.87 g, 0.022 mol), $HgCl_2$ (15.7 g, 0.058 mol), and 95% ethanol (312 mL) was heated at reflux under nitrogen for 53 h. The mixture was filtered; the filtrate was diluted with water and extracted with methylene chloride. Concentration in vacuo gave crude **8a** which was chromatographed on alumina (activity III) with benzene–cyclohexane (50:50) to yield **8a** (2.4 g, 81%) as an oil contaminated with ca. 10% α,β-unsaturated **8a**.

***cis*-4b,6,7,8,8a,9-Hexahydro-α-methyl-5*H*-fluorene-2-acetic Acid (2).** A mixture of crude **8a** (2.4 g), 10% aqueous NaOH (200 mL), and ethanol (50 mL) was heated at reflux for 75 min. The mixture was poured into water and extracted with methylene chloride. The aqueous layer was acidified with aqueous HCl and extracted again with methylene chloride to yield after concentration in vacuo crude **2** (1.6 g) which was recrystallized from methanol–water (mp 85–99 °C). This material, dissolved in dioxane (100 mL) containing 5% Pd/C (100 mg), was hydrogenated at atmospheric pressure until 19.4 mL of H_2 was absorbed (5 h). Filtration and concentration of the reaction mixture followed by recrystallization from methanol–water gave **2** [1.42 g (66%); mp 103.5–109 °C; sublimed at 98 °C (0.001 mm); mp 104.5–109 °C)]. Anal. ($C_{16}H_{20}O$) C, H.

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