

of 1.34 g (25.0 mmol) of  $\text{NH}_4\text{Cl}$  in  $\text{H}_2\text{O}$  was added to the reaction mixture. The mixture was stirred for 1 h and filtered and the solids were washed with THF. The combined filtrate and washes were washed with  $\text{H}_2\text{O}$  and brine, dried ( $\text{Na}_2\text{SO}_4$ ), and spin evaporated in vacuo to afford a white powder which was recrystallized from  $\text{CHCl}_3$ -hexanes: yield, 3.10 g (87%); mp 156–157 °C. An additional recrystallization afforded the analytical sample: mp 160–161 °C.

**1-(4-Imidazolyl)ethanol Hydrochloride (6b). Method B.** A solution of 19.5 g (55.0 mmol) of **5b** in 200 mL of 2 N HCl was heated on a steam bath for 40 min during which time a voluminous precipitation of  $\text{Ph}_3\text{COH}$  occurred. The reaction mixture was cooled and filtered, and the solids were washed with  $\text{H}_2\text{O}$ . The combined filtrate and washes were evaporated to two-thirds the original volume when additional precipitation occurred. This mixture was again cooled and filtered, and the filtrates were spin evaporated in vacuo. EtOH was added to the residual syrup and evaporated to remove the last traces of  $\text{H}_2\text{O}$ . This syrup was digested with  $\text{Et}_2\text{O}$  to give a solid which was recrystallized from EtOH-Et<sub>2</sub>O: yield, 6.71 g (82%); mp 121–124 °C. The analytical sample had mp 123–124 °C.

**Ethyl  $\alpha$ -Acetamido- $\alpha$ -carbethoxy- $\beta$ -(4-imidazolyl)butyrate Hydrate (9b). Method C.** To 6.65 g (44.7 mmol) of **6b** hydrochloride in a 100-mL round-bottomed flask topped with a condenser and cooled on an ice bath was added 20 mL of thionyl chloride. Vigorous effervescence ensued and after a few seconds subsided. The resultant solution was heated at reflux for 20 min, cooled, diluted with benzene, and spin evaporated in vacuo. The residue was covered with benzene and reevaporated several times to remove the last traces of  $\text{SOCl}_2$ , then dissolved in ethanol-benzene (1:1), and spin evaporated in vacuo to give 1-(4-imidazolyl)ethyl chloride hydrochloride (**7b**) as a hygroscopic solid: yield, 7.20 g (96%); mp 92–96 °C which was used without further purification.

To a solution of 2.68 g (49.6 mmol) of NaOMe and 50 mL of anhydrous EtOH in a 200-mL round-bottom flask equipped with a magnetic stirrer,  $\text{CaCl}_2$  drying tube, and  $\text{N}_2$  inlet tube was added 5.36 g (24.6 mmol) of diethyl acetamidomalonate. After 0.5 h the solution was cooled on an ice bath and 3.74 g (22.4 mmol) of crude **7b** hydrochloride in 20 mL of EtOH was added. After 18 h at ambient temperature the reaction mixture was filtered, and the solids were washed with EtOH. The combined filtrate and wash was spin evaporated in vacuo and the residue was dissolved in 100 mL of  $\text{CHCl}_3$  which was washed with four 10-mL portions of  $\text{H}_2\text{O}$  and 10 mL of brine, dried ( $\text{MgSO}_4$ ), and spin evaporated in vacuo. The residual syrup was crystallized by trituration with wet ether: yield, 4.40 g (59%); mp 63–66 °C. Recrystallization of a portion from water gave the analytical sample: mp 66–71 °C.

**$\alpha$ -Amino- $\beta$ -(4-imidazolyl)butyric Acid (10b). Method D.** A solution of 3.36 g (10.2 mmol) of **9b** hydrate and 50 mL of 12 N HCl was heated on a steam bath for 19 h. The reaction mixture was cooled, filtered to remove some tar, and spin evaporated in vacuo to afford the amino acid hydrochloride as a syrup. An aqueous solution of this material was applied to a column of 70 g of ion-exchange resin [Rexyn 101(H)] and washed with  $\text{H}_2\text{O}$ , and the free amino acid was eluted with dilute  $\text{NH}_4\text{OH}$ . The eluate was spin evaporated in vacuo to afford a hard foam: yield, 1.67 g (91%); mp 218–224 °C dec. Recrystallization of 0.540 g from EtOH- $\text{H}_2\text{O}$  afforded the analytical sample: yield, 0.344 g (59%); mp 231–233 °C dec.

**Methyl  $\alpha$ -Amino- $\beta$ -(4-imidazolyl)butyrate Dihydrochloride (11b). Method E.** To a stirred, ice-bath-cooled mixture of 0.50 g (2.95 mmol) of **10b** and 5 mL of MeOH was cautiously added 2 mL of  $\text{SOCl}_2$ . The resultant solution was stirred at ambient temperature with protection from moisture for 24 h and then heated at reflux for 6 h. The solution was spin evaporated in vacuo to give a foam which was crystallized from Et<sub>2</sub>O-MeOH: yield, 0.180 g (24%); mp 188–189 °C eff.

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## References and Notes

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## 3-Aryl-*as*-triazines as Potential Antiinflammatory Agents

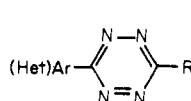
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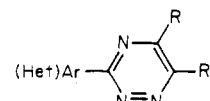
A number of 3-aryl-*as*-triazines were synthesized as analogues of 3-aryl-*s*-triazines which have extensive anti-inflammatory activity. The 3-aryl-*as*-triazines displayed activity when tested against carrageenan-induced edema in the rat but were inactive in further evaluation.

Aryl-*s*-triazines (**1**)<sup>1</sup> displayed antiinflammatory activity when tested against carrageenan-induced edema in the rat, UV-induced erythema in the guinea pig, and adjuvant-induced arthritis in rats. These agents were also active analgesics but caused a lowering of the red blood cell count in normal healthy rats. As an extension of these studies, a number of structurally related aryl-*as*-triazines (**2**) were prepared and their antiinflammatory effects were examined.

**Chemistry.** *as*-Triazines were prepared by the condensation of  $\alpha,\beta$ -dicarbonyl compounds and amidrazones<sup>2</sup>



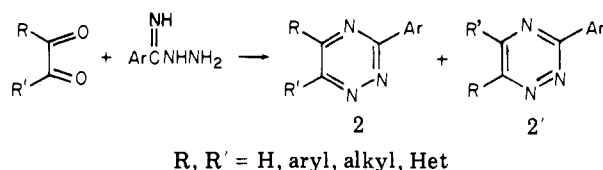
1, R = H,  $\text{CH}_3$ ,  $\text{C}_2\text{H}_5$



2

as described in Scheme I. The reaction of aryl amidrazones, generated in situ,<sup>3</sup> and  $\alpha,\beta$ -dicarbonyl compounds gave varying results with substantial amounts of polymeric materials and/or self-condensation products also being produced. Reaction of free amidrazones with bisulfite

Scheme I

Table I. Amidrazones Prepared<sup>a</sup>

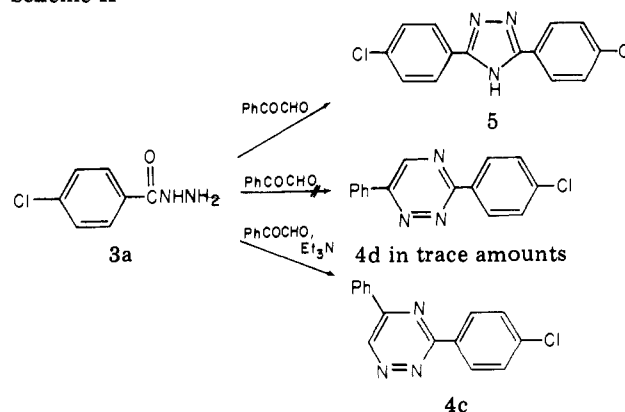
	Ar	Mp, °C	% crude yield
3a	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	88-92 <sup>b</sup>	58
3b	<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	108-112	56
3c	<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	75-215	50
3d	<i>p</i> -FC <sub>6</sub> H <sub>4</sub>	49-123	72
3e	<i>m</i> -ClC <sub>6</sub> H <sub>4</sub>	Semisolid	71 <sup>c</sup>
3f	C <sub>6</sub> H <sub>5</sub>	Semisolid	52 <sup>c,d</sup>
3g	2-Pyridyl	98-99	61 <sup>e</sup>
3h	<i>o</i> -FC <sub>6</sub> H <sub>4</sub>	<i>f</i>	<i>f</i>

<sup>a</sup> Isolated crude only and used as is. <sup>b</sup> Lit.<sup>2</sup> mp 87-89 °C. <sup>c</sup> Not characterized, semisolids. <sup>d</sup> Lit.<sup>2a</sup> compound. <sup>e</sup> Lit.<sup>2b</sup> mp 95-96 °C. <sup>f</sup> Not isolated.

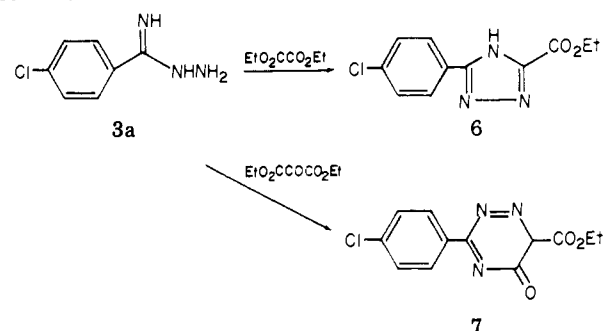
addition products of diketones or dialdehydes gave the desired *as*-triazines in satisfactory yields with some carboxamides as side products. Where R = R', only one product was obtained. Where R ≠ R', a mixture generally resulted but the proportions of 2 or 2' could be altered by catalysis. Attempted production of 4d as described in the literature<sup>3</sup> gave only traces of 4d. The self-condensation product 5, 3,5-di-*p*-chlorophenyl-1,2,4-triazole, was isolated in 55% yield. Using Et<sub>3</sub>N as a catalyst, a 32% yield of isomeric 4c was obtained (Scheme II). (See Tables I and II.) Since side reactions appeared of major importance, the free amidrazones were prepared<sup>2</sup> and allowed to react then in hot aqueous medium with the sodium bisulfite addition products of a variety of α,β-diketo materials.<sup>4</sup> In this procedure, hydrolysis of amidrazones was not of prohibitive proportions, although carboxamides were present as side products.

*o*-Fluorophenylamidrazone (3h) was prepared by a two-step sequence from *o*-fluorobenzamide via initial activation with methyl fluorosulfonate and subsequent

Scheme II



Scheme III



reaction with hydrazine. The crude product was converted without purification into the expected triazine 4m in 9% yield.

The reaction of *p*-chlorobenzamidine (3a) with diethyl oxalate and 2-ketomalonnate gave 5-carbethoxy-2-(*p*-chlorophenyl)triazole (6) and 6-carbethoxy-3-(*p*-chlorophenyl)-5(4*H*)-*as*-triazole (7), respectively (Scheme III).

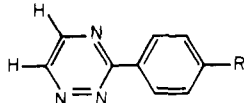
**Pharmacology.** The aryl-*as*-triazines were tested against carrageenan-induced edema in the rat, as described in the literature.<sup>1</sup> These compounds (4e and 4i) which were active were tested against adjuvant-induced edema in rats.<sup>1</sup> The results from the carrageenan-induced edema in rats are expressed as a ratio of C/T. The differences in edema were considered to be due to drug efficacy and

Table II. *as*-Triazines Prepared

	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	Yield, %	Formula <sup>a</sup>	Mp, °C
4a	2-Pyridyl	H	C <sub>6</sub> H <sub>5</sub>	64	C <sub>14</sub> H <sub>10</sub> N <sub>4</sub> <sup>e</sup>	142.5-145 <sup>b</sup>
4b	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	C <sub>6</sub> H <sub>5</sub>	76	C <sub>21</sub> H <sub>14</sub> ClN <sub>3</sub> <sup>e,f</sup>	155-156 <sup>c</sup>
4c	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	H	C <sub>6</sub> H <sub>5</sub>	32	C <sub>15</sub> H <sub>10</sub> ClN <sub>3</sub> <sup>e</sup>	131-132
4d	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	C <sub>6</sub> H <sub>5</sub>	H	Trace	C <sub>15</sub> H <sub>10</sub> ClN <sub>3</sub> <sup>e</sup>	187-188
4e	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	H	H	14	C <sub>9</sub> H <sub>6</sub> ClN <sub>3</sub> <sup>e</sup>	113-114
4f	C <sub>6</sub> H <sub>5</sub>	H	H	55	C <sub>9</sub> H <sub>7</sub> N <sub>3</sub> <sup>g</sup>	52-55 <sup>d</sup>
4g	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	CH <sub>3</sub>	18	C <sub>11</sub> H <sub>10</sub> ClN <sub>3</sub> <sup>g</sup>	140-142.5
4h	<i>m</i> -ClC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	CH <sub>3</sub>	34	C <sub>11</sub> H <sub>10</sub> ClN <sub>3</sub> <sup>f,g</sup>	134-135.5
4i	<i>p</i> -FC <sub>6</sub> H <sub>4</sub>	H	H	50	C <sub>11</sub> H <sub>10</sub> FN <sub>3</sub> <sup>e</sup>	102-106
4j	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	H	15	C <sub>10</sub> H <sub>8</sub> ClN <sub>3</sub> <sup>f,g</sup>	127-130
4k	<i>p</i> -FC <sub>6</sub> H <sub>4</sub>	CH <sub>3</sub>	CH <sub>3</sub>	25	C <sub>11</sub> H <sub>10</sub> FN <sub>3</sub> <sup>g,h</sup>	126-128
4l	<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	H	H	60	C <sub>10</sub> H <sub>9</sub> N <sub>3</sub> O <sup>h,i</sup>	99-103
4m	<i>o</i> -FC <sub>6</sub> H <sub>4</sub>	H	H	9	C <sub>9</sub> H <sub>6</sub> FN <sub>3</sub> <sup>h,i</sup>	44-46
4n	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	-(CH <sub>2</sub> ) <sub>4</sub> -		45	C <sub>13</sub> H <sub>12</sub> ClN <sub>3</sub> <sup>e,f,j</sup>	148-150

<sup>a</sup> All new compounds have correct elemental analyses and supportive spectral data. <sup>b</sup> Lit.<sup>7</sup> mp 140-141 °C. <sup>c</sup> Lit.<sup>9</sup> mp 152-153 °C. <sup>d</sup> Lit.<sup>8</sup> mp 53-54 °C. <sup>e</sup> Recrystallized from 2-propanol. <sup>f</sup> Prepared as described for 4g. <sup>g</sup> Recrystallized from hexane. <sup>h</sup> Recrystallized from 2-propanol-hexane. <sup>i</sup> Anal. F: calcd, 10.85; found, 10.50. <sup>j</sup> Anal. Cl: calcd, 14.43; found, 13.93. <sup>k</sup> Prepared as described for 4e.

Table III. Antiinflammatory Testing

	Carrageenan-induced edema results, <sup>a</sup> C/T	Adjuvant-induced arthritis results, <sup>b</sup> RSA
4e, R = Cl	2.25 <sup>c</sup>	1 <sup>c,d</sup>
4i, R = F	2.67 <sup>c</sup>	1 <sup>c,d</sup>
<i>p</i> -Chlorophenyl- <i>s</i> -tetrazine <sup>e</sup>	3.07 <sup>c</sup>	0.54 <sup>f</sup>
<i>p</i> -Fluorophenyl- <i>s</i> -tetrazine <sup>e</sup>	2.80 <sup>c</sup>	0.46 <sup>f</sup>
Aspirin	2.80 <sup>g</sup>	0.55 <sup>h</sup>
Controls	1.00	1.00

<sup>a</sup> Numbers are an average of four tests; compounds with C/T greater than 1.43 are considered active. <sup>b</sup> RSA = mean relative surface area which is an average of three tests; compounds with mean RSA less than 0.74 are accepted as active. <sup>c</sup> Dosage 250 mg/kg by gavage. <sup>d</sup> I = inactive. <sup>e</sup> References 1 and 6. <sup>f</sup> Dosage 50 mg/kg/day by gavage. <sup>g</sup> Dosage 50 mg/kg by gavage. <sup>h</sup> Dosage 400 mg/kg/day by gavage.

are expressed as a control (C) to treated (untreated/treated) efficacy ratio (the ratio of the mean edema of eight control animals which received carrageenan injection and no drugs over the mean edema of two drug and carrageenan-treated rats). The results from the adjuvant-induced arthritis test in rats are expressed as RSA (relative surface area). This is a ratio expressed as mean surface area of paws of three treated rats (rats which received drug and adjuvant) over the mean surface area of 60 control rats (rats which received adjuvant and no drug). (See Table III.)

## Discussion

3-Aryl-*s*-tetrazines displayed broad aspirin-like activity in arthritic models<sup>1</sup> but had toxic properties<sup>1</sup> which would hinder any medicinal use. The 3-aryl-*as*-triazine system has one less nitrogen atom but is geometrically related. It was postulated that this system may have similar activity but reduced or absent toxicity.

Of the 3-aryl-*as*-triazines prepared, only 4e and 4i were active when tested against carrageenan-induced edema in rats. Both compounds compared favorably with 3-aryl-*s*-tetrazines and aspirin in the amount of reduction of edema. The carrageenan-induced edema screen is a general test for the discovery of antiarthritic agents<sup>10</sup> but is nonspecific and a large number of miscellaneous drugs with varying pharmacological activity, without established antiarthritic value, give positive results.<sup>11</sup>

The adjuvant-induced arthritis assay is a more specific model of chronic arthritis and 4e and 4i when evaluated at 250 mg/kg in this assay displayed no activity. In contrast, the 3-aryl-*s*-tetrazines<sup>1</sup> displayed aspirin-like activity when evaluated in the adjuvant-induced arthritis assay. The lack of activity in a more specific arthritic model of the 3-aryl-*as*-triazine compounds precluded further investigation.

## Experimental Section

The melting points were taken in capillary tubes in a Mel Temp apparatus and are uncorrected.

The arylamidrazones used in these studies were prepared, generally, via the imidate hydrochloride. These preparations under Pinner conditions<sup>5</sup> have been previously described. Generation of the free imidate in alcohol, followed immediately by treatment with hydrazine hydrate, gave amidrazones of

sufficient purity for further reactions. In most cases the "crude" amidrazones were contaminated with minor amounts of amide. The specific materials prepared by the general procedure outlined below are listed in Table II. 2-Pyridylamidrazones were synthesized directly from 2-cyanopyridine according to the method of Case<sup>4</sup> and is listed also in Table II.

The aryl imidate (0.05 mol) was partitioned between ether (100 mL) and aqueous NaOH (5%, 100 mL). The organic layer was rinsed with water, dried (sieves), and evaporated to a residual oil. To this was added NH<sub>2</sub>NH<sub>2</sub>·H<sub>2</sub>O (1.25 mL) in ether (5 mL) and ethanol (25 mL). The amidrazones were isolated by evaporation or filtration after 2 days standing at 5 °C.

**5-Phenyl-3-(2-pyridyl)-*as*-triazine (4a).** An ethanol solution of 2-pyridylamidrazones (1.36 g, 0.01 mol) and phenylglyoxal (1.52 g, 0.01 mol) was refluxed for 2 h. The cooled solution was diluted with water and the resultant precipitate filtered: 1.5 g (64%); mp 142.5–145 °C (lit.<sup>7</sup> 140–141 °C); <sup>1</sup>H NMR δ 9.92 (s, 1), 8.83 (d, 1, *J* = 5 Hz), 8.52 (m, 3), 7.96 (m, 1), 7.53 (aromatic H's). Anal. C, H, N.

**3,5-Bis(*p*-chlorophenyl)-4*H*-1,2,4-triazole (5).** *p*-Chlorobenzamidrazones hydrochloride (2.2 g, 0.011 mol) was mixed with freshly distilled phenylglyoxal (0.74 g, 0.0055 mol) in methanol. A solution of methanol saturated with HCl gas was added and the reaction stirred at room temperature overnight. After cooling, the mixture was filtered and the resultant solid (1.8 g) was refluxed in methanol-water (1:1, 100 mL) for 3 h. The resultant precipitate was filtered to give 1.1 g (52%), mp 290–291 °C. A small sample was crystallized (2-propanol) to give the analytical sample: mp 286–289 °C; <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>-CDCl<sub>3</sub>) δ 8.12 (m, 4), 7.57 (m, 4). Anal. C, H, N, Cl.

**3-(*p*-Chlorophenyl)-5-phenyl-*as*-triazine (4c).** A methanolic solution of phenylglyoxal (1.52 g, 0.01 mol) was refluxed for 4 h and then cooled in acetone-dry ice. To this was added Et<sub>3</sub>N (1 mL) and *p*-chlorophenylamidrazones hydrochloride (0.01 mol) and the reaction mixture was stirred overnight. After evaporation, the residue was crystallized from 2-propanol to give 0.85 g (32%) of product: mp 131–132 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 9.58 (1, s), 8.58 (d, 2, *J* = 9 Hz), 8.26 (m, arom, 2), 7.55 (m, arom, 5). Anal. C, H, N, Cl.

**3-(*p*-Chlorophenyl)-6-phenyl-*as*-triazine (4d).** A methanolic solution of phenylglyoxal (1.52 g, 0.01 mol) was depolymerized by refluxing for 4 h and then cooled in acetone-dry ice. To this was added *p*-chlorophenylamidrazones hydrochloride (0.01 mol) and the reaction mixture was stirred overnight. After evaporation the residue was partitioned between dilute HCl and CHCl<sub>3</sub>. Basification of the aqueous portion gave intractable tar. The chloroform extract yielded a residue which was crystallized from 2-propanol to give traces of material: mp 187–188 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 9.02 (1, s), 8.52 (d, 2, *J* = 9 Hz), 8.13 (m, 2, arom), 7.55 (m, 5, arom). Anal. C, H, N, Cl.

**3-(*p*-Chlorophenyl)-*as*-triazine (4e).** An aqueous solution of glyoxal bisulfite (2.7 g, 0.01 mol, in 16 mL) was heated to 80 °C and added to *p*-chlorobenzamidrazones (1.7 g, 0.011 mol) suspended in water (16 mL). The mixture was heated for 15 min at 70 °C, cooled, and subsequently filtered. The basified filtrate was extracted with ether, and after evaporation of solvent the residue was crystallized from 2-propanol to give 0.28 g (14%), of product: mp 113–114 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 9.15 (d, 1, *J* = 2.4 Hz), 8.64 (d, 1, *J* = 2.4 Hz), 8.48 (d, 2, *J* = 9 Hz), 7.50 (d, 2, *J* = 9 Hz). Anal. C, H, N, Cl.

**3-Phenyl-*as*-triazine (4f).** This procedure is identical with that described for 3-(*p*-fluorophenyl)-*as*-triazine (4i): yield, 55% (hexanes); mp 52–55 °C (lit.<sup>8</sup> 53–54 °C); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 9.13 (d, 1, *J*<sub>bc</sub> = 3 Hz, H<sub>b</sub>), 8.64 (d, 1, *J*<sub>bc</sub> = 3 Hz, H<sub>c</sub>), 8.52 (m, 2, arom H<sub>a</sub>), 7.54 (m, 3). Anal. C, H, N.

**3-(*p*-Chlorophenyl)-5,6-dimethyl-*as*-triazine (4g).** An aqueous solution of dimethylglyoxal (0.86 g, 0.01 mol) and sodium bisulfite (2.08 g, 0.02 mol) was heated on the steam bath for a few minutes until the yellow color of the free diketone disappeared. *p*-Chlorophenylamidrazones (1.7 g, 0.01 mol) was added and the mixture stirred on the steam bath for 5 min. After filtration the aqueous mother liquor was filtered, basified, extracted with ether, dried (MgSO<sub>4</sub>), and, after solvent removal, crystallized from hexanes to give 0.4 g (18%) of product: mp 140–142.5 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.43 (d, 2, *J* = 9 Hz), 7.44 (d, 2, *J* = 9 Hz), 2.78 [s, 3, CH<sub>3</sub>(6)], 2.58 [s, 3, CH<sub>3</sub>(5)]. Anal. C, H, N, Cl.

**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; <sup>1</sup>H NMR (CDCl<sub>3</sub>) 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<sub>3</sub> and 5% aqueous NaHCO<sub>3</sub>. The organic portion was rinsed with water, dried (MgSO<sub>4</sub>), 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; <sup>1</sup>H NMR (CDCl<sub>3</sub>) 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.<sup>2a</sup> 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.<sup>2a</sup> mp 244 °C); <sup>1</sup>H NMR (Me<sub>2</sub>SO-*d*<sub>6</sub>-CDCl<sub>3</sub>) 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- $\alpha$ -methyl-5*H*-fluorene-2-acetic Acid

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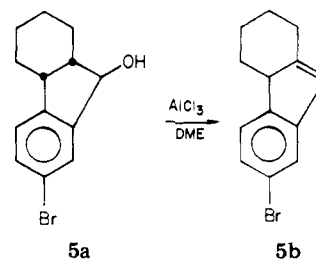
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*cis*-4b,6,7,8,8a,9-Hexahydro- $\alpha$ -methyl-5*H*-fluorene-2-acetic acid was synthesized in an unambiguous way and its antiinflammatory activity compared to  $\alpha$ -methylfluorene-2-acetic acid.

The arylacetic acids are currently the most actively investigated class of compounds in the nonsteroidal antiinflammatory area.<sup>1</sup> In our own investigations in this area, we identified 1 as a compound with antiinflammatory activity<sup>2</sup> 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<sup>3</sup> 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 <sup>1</sup>H NMR spectrum of *cis*-1,2,3,4,4a,9a-hexahydro-9-fluorenone<sup>4</sup> (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



at 3.0–2.0 ppm) (Figure 1, C). This sort of deshielding has been noted in other 6,5-fused ring systems<sup>5</sup> and is probably due to the diamagnetic anisotropy 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