R01-Da-01023-01, National Institute on Drug Abuse.

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(2-Carboxy-1,4-dihydro-4-oxoquinolyl)oxamic Acids and (2-Carboxy-1,4-dihydro-4-oxobenzo[*h*]quinolyl)oxamic Acids as Antiallergy Agents

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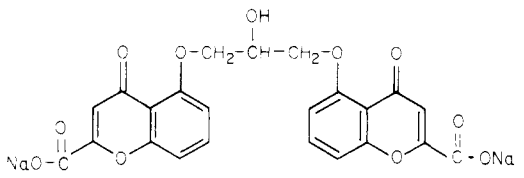
A group of (2-carboxy-1,4-dihydro-4-oxoquinolyl)oxamic acids (**5**) containing the oxamic acid group in the 5, 6, or 7 positions were synthesized and investigated for antiasthma activity as indicated by the passive cutaneous anaphylaxis (PCA) reaction in rats. Also synthesized and investigated were two (2-carboxy-1,4-dihydro-4-oxobenzo[*h*]-quinolyl)oxamic acids (**9** and **10**). Several of the compounds synthesized (viz. **5e**, **5f**, and **10**) showed activity in the PCA test approximately 25 times that shown by disodium cromoglycate (**1**), as measured by the ID_{50} doses.

Disodium cromoglycate (**1**) is an antiasthma agent that



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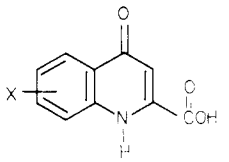
is thought to act by inhibition of the liberation of the mediators of allergic reactions initiated by antigen–antibody interactions.[1] This activity has been measured conveniently in rats by means of the passive cutaneous anaphylaxis (PCA) reaction.[2]

Previously we[3] have reported on 2-carboxy-1,4-dihydro-4-oxoquinolines (**2**) which, like disodium cromoglycate, show antiallergy activity, as measured by the rat



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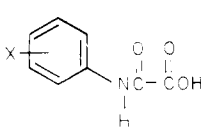
PCA test. In previous publications, various investigators[4-6] have reported on the activity of oxanilic acids (**3**) and of dioxanilic acids (**4**).



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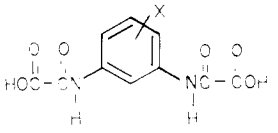

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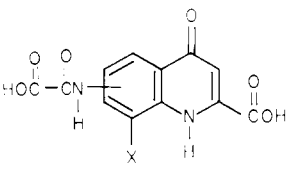
It appeared of interest, therefore, to investigate the effect of the introduction of the oxamic acid moiety, present in **3** and **4**, into the quinoline structure **2** to prepare compounds of the type **5**.



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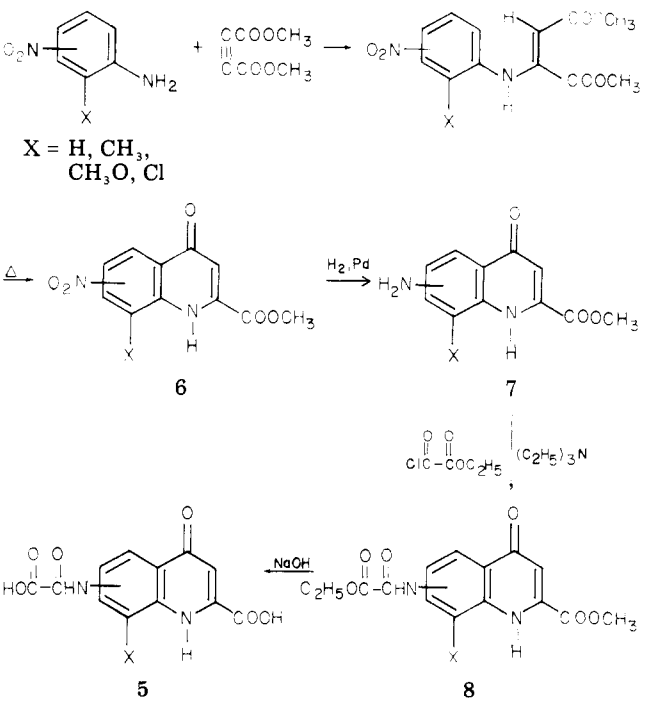
Scheme I

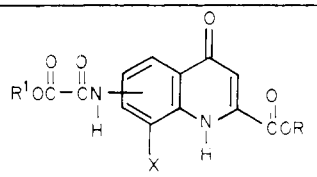


Chemistry. The compounds were synthesized according to Scheme I. Most of the nitro-substituted quinolones (**6**) and amino-substituted quinolones (**7**) were reported previously.[3] Treatment of the aminoquinolones (**7**) with ethyloxalyl chloride in the presence of triethylamine gave the ethyl oxanilates (**8**) in good yields. Hydrolysis of the ester with sodium hydroxide solution followed by acidification gave the desired (2-carboxy-1,4-dihydro-4-oxoquinolyl)oxamic acids (**5**) (see Table I).

In an analogous way (2-carboxy-1,4-dihydro-4-oxobenzo[*h*]quinol-6-yl)oxamic acid (**9**) and (2-carboxy-1,4-dihydro-4-oxobenzo[*h*]quinol-7-yl)oxamic acid (**10**) were prepared from the corresponding suitably substituted aminonitronaphthalenes (Scheme II). All of the steps in the reaction sequence proceeded readily and in good yield.

In the two synthetic schemes mentioned above, the compounds synthesized are written in the 4-oxo form. It is understood, however, that the compounds may exist

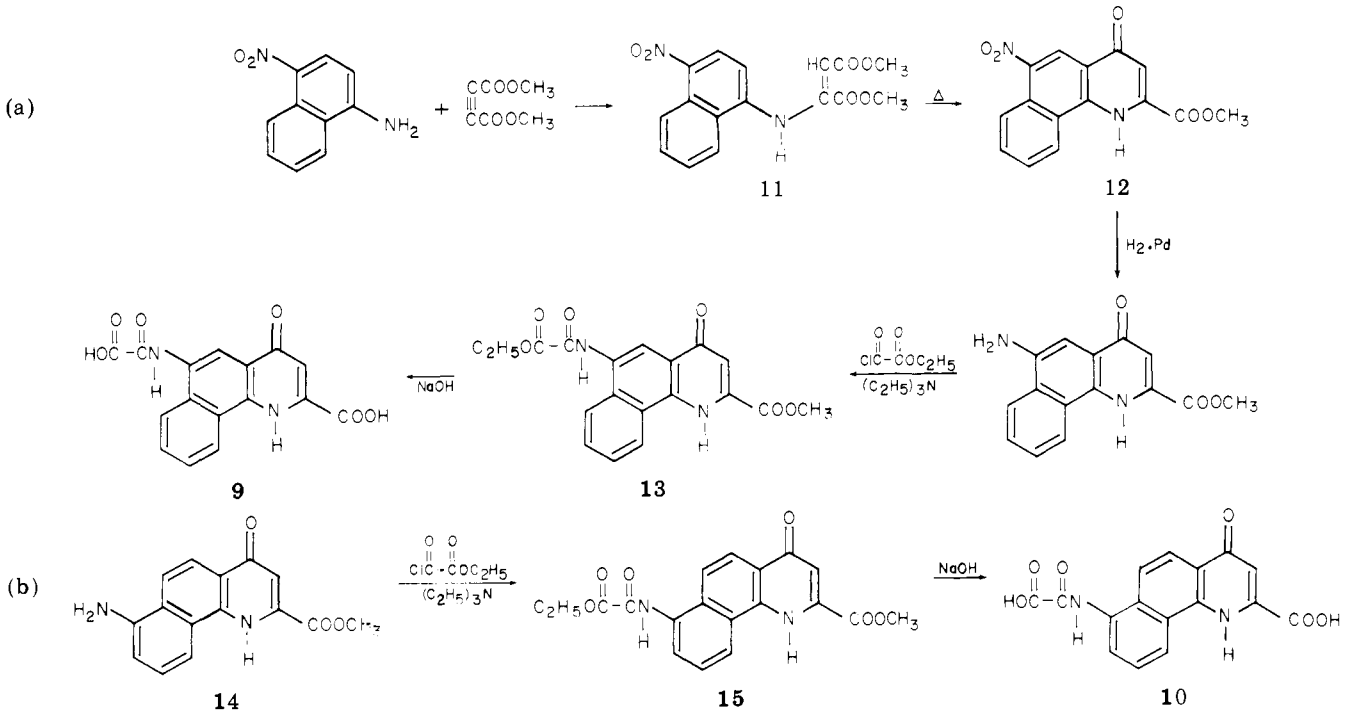
Table I. (2-Carboxy-1,4-dihydro-4-oxoquinolyl)oxamates



Compd	X	Position of oxamate group	R	R¹	Formula	Mp, °C	Yield, %	Analyses
8a	CH_3	5	CH_3	C_2H_5	$C_{16}H_{16}N_2O_6$	250-252	80[a]	C, H, N
5a	CH_3	5	H	H	$C_{13}H_{10}N_2O_6$	275 dec	97	H, N; C[b]
5b	Cl	5	H[c]	H[c]	$C_{12}H_7ClN_2O_6$	279 dec		C, H, Cl N
8c	CH_3O	5	CH_3	C_2H_5	$C_{16}H_{16}N_2O_7$	241-242	100[a]	C, H, N
5c	CH_3O	5	H	H	$C_{13}H_{10}N_2O_7$	281 dec	88	H, N; C[d]
8d	H	6	CH_3	C_2H_5	$C_{15}H_{15}N_2O_6$	295 dec	74	H, N; C[e]
5d	H	6	H	H	$C_{12}H_8N_2O_6 \cdot H_2O$	305 dec	57	H, N; C[f]
5e	CH_3	6	H[c]	H[c]	$C_{13}H_{10}N_2O_6$	240-241		H, N; C[g]
5f	CH_3	7	H[c]	H[c]	$C_{13}H_{10}N_2O_6$	275 dec		C, H, N

[a] Recrystallized from DMF. [b] C: calcd, 53.80; found, 53.09. [c] The intermediate diester was not analyzed. [d] C: calcd, 50.98; found, 50.25. [e] C: calcd, 56.60; found, 56.13. [f] C: calcd, 48.98; found 48.51. [g] C: calcd, 53.80; found, 52.67.

Scheme II



partially or completely in the tautomeric 4-hydroxy form.

Biological Methods and Results. The oxamic acids synthesized (**5a–f**, **9**, and **10**) were tested in tris(hydroxymethyl)aminomethane (THAM) solution for their ability to inhibit the passive cutaneous anaphylaxis (PCA) reaction in rats passively sensitized to egg albumin as follows.[7]

Rat homocytotropic antibody was elicited to egg albumin (EA) by the injection (ip) of 0.5 mg of EA + 0.5 cm^3 of *H. pertussis* vaccine (Michigan Department of Public Health, 4.5×10^{10} heat killed organisms) per rat. After 18–20 days the serum was collected and frozen until use. The antibody was shown to be of the 72-h latency type and to be destroyed by heating 1.0 h at 56 °C. Five 0.1-ml volumes of an appropriate dilution of this serum were inoculated into the shaved dorsal surface of a 200-g Sprague–Dawley rat. Saline controls were run and showed less than 4-mm spots. After 72 h the rat was challenged iv with 4 mg per animal of EA + 0.5% Evans blue dye. In the case of drug-treated animals, the materials were given iv at the time of antigen challenge. Results were reported as the inhibition of the number of spots per animal (regardless of size) that were seen at five dilutions of serum. The number of spots from a number of sensitization sites in drug-treated animals was compared with the spot score (number of total spots divided by the number of animals) obtained from the same number of sites in untreated animals. Eight animals for control and six for treated were used to calculate the ID_{50}. A dose–response curve was established by running three to four doses, six animals each. The percent inhibition of the PCA reaction was then calculated.

It has been found that in repeat runs for disodium cromoglycate the inhibitions can be reproduced with an approximate 8% standard error for duplicate assays. The results obtained are listed in Table II. The results are expressed as the doses which inhibit 50% of the PCA reaction in the rats (ID_{50}).

While no clear structure–activity relationship is evident from Table II, it is clear that several of the compounds (e.g., **5e**, **5f**, and **10**) were potent inhibitors of the PCA

Table II. (2-Carboxy-1,4-dihydro-4-oxoquinolyl)oxamic Acids and (2-Carboxy-1,4-dihydro-4-oxobenzo[*h*]quinolyl)oxamic Acids

Inhibition of the rat PCA reaction			
Compd	ID_{50}, mg/kg	Compd	ID_{50}, mg/kg
1	2.5[a]	5e	0.1[b]
5a	0.4[b]	5f	0.1[b]
5b	0.3[b]	9	0.5[b]
5c	0.7[b]	10	0.1[b]
5d	7.0[b]		

[a] Based on 30 repeat determinations, six animals each. [b] Based on two repeat determinations, six animals each.

reaction in rats (ID_{50} = 0.1 mg/kg). They were, therefore, approximately 25 times as active in this test as disodium cromoglycate (1, ID_{50} = 2.5 mg/kg).

Experimental Section

The melting points (capillary) are uncorrected. The ir spectra were measured on a Perkin-Elmer Infracord spectrometer. For these compounds with sufficient solubility in D_2O, Me_2SO-d_6, or $DCCl_3$, the NMR spectra were measured on a Varian A-60 or a Varian T-60 spectrometer. The ir and NMR spectra were run on all of the compounds. The spectra were consistent with the assigned structure in all cases. The results of elemental analysis were within ±0.4% of the theoretical values except where noted.

Dimethyl 2-Methoxy-5-nitroanilinobutenedioate. To a stirred solution of 50.46 g (0.3 mol) of 2-methoxy-5-nitroaniline in 750 ml of methanol was added 42.6 g (0.3 mol) of dimethyl acetylenedicarboxylate. The mixture was stirred for 2 h and the mixture was filtered. There was obtained 84.1 g (90%) of yellow needles melting at 154–156 °C. Recrystallization from methanol gave material melting at 155–156 °C. Anal. ($C_{13}H_{14}N_2O_7$) C, H, N.

Methyl 1,4-Dihydro-8-methoxy-5-nitro-4-oxoquinaldate. To 500 ml of refluxing Dowtherm A was added 54.5 g (0.174 mol) of dimethyl 2-methoxy-5-nitroanilinobutenedioate. The mixture was heated under reflux for 1 h, allowed to cool to room temperature, and was filtered. There was obtained 38.7 g (80%) of yellow needles melting at 238–240 °C. Recrystallization from a dimethylformamide–methanol mixture gave material melting at 239–240 °C. Anal. ($C_{12}H_{10}N_2O_6$) C, H, N.

Methyl 5-Amino-1,4-dihydro-8-methoxy-4-oxoquinaldate. A suspension of 13.9 g (0.05 mol) of methyl 1,4-dihydro-8-methoxy-5-nitro-4-oxoquinaldate in 100 ml of dimethylformamide was hydrogenated at 3 atm of hydrogen using 1 g of 10% palladium on charcoal as catalyst. The catalyst was removed by filtration and the filtrate was poured into 1.8 l. of water. The resulting red precipitate was removed by filtration. There was obtained 8.21 g (66%) of material melting at 188–190 °C. Recrystallization from methanol gave material melting at 189–190 °C. Anal. ($C_{12}H_{12}N_2O_4$) C, H, N.

Ethyl (2-Carbomethoxy-1,4-dihydro-4-oxoquinolyl)oxamates (8). Typical reaction conditions for the preparation of ethyl (2-carbomethoxy-1,4-dihydro-4-oxoquinolyl)oxamates (8) are given below. To a stirred solution of the appropriate methyl amino-1,4-dihydro-4-oxoquinaldate[3] (7) (0.10 mol) in DMF (500 ml) cooled to 0–5 °C in an ice bath was added triethylamine (0.12 mol) followed, dropwise, by ethyloxalyl chloride (0.12 mol). The reaction mixture was stirred in the ice bath for 2 h and then allowed to stand overnight at room temperature. The precipitate was removed by filtration, washed with water, and recrystallized from a suitable solvent.

(2-Carboxy-1,4-dihydro-4-oxoquinolyl)oxamic Acids (5). Typical reaction conditions for the preparation of (2-carboxy-1,4-dihydro-4-oxoquinolyl)oxamic acids (5) are given below. A solution of 0.1 mol of the ethyl (2-carbomethoxy-1,4-dihydro-4-oxoquinolyl)oxamate (8) in 750 ml of methylene chloride was shaken in a separatory funnel for 15 min with 500 ml of 1 N sodium hydroxide solution. The aqueous layer was separated and acidified with 1 N hydrochloric acid. The precipitate was removed by filtration and washed with water. The product was purified by dissolving it in a dilute sodium bicarbonate solution, filtering, and reacidifying with 1 N hydrochloric acid. The precipitate was removed by filtration and washed with ethanol.

Dimethyl [(4-Nitro-1-naphthyl)amino]butenedioate (11). A solution of 37.64 g (0.20 mol) of 1-amino-4-nitronaphthalene and 28.4 g (0.20 mol) of dimethyl acetylenedicarboxylate in 2.5 l. of methanol was heated under reflux for 1 h and allowed to stand overnight at room temperature. The precipitate was removed by filtration. Additional material was obtained by concentration of the filtrate. There was obtained 40.3 g (61%) of yellow needles melting at 139–142 °C. Recrystallization from methanol gave material melting at 140–141 °C. Anal. ($C_{16}H_{14}N_2O_6$) C, H, N.

Methyl 1,4-Dihydro-6-nitro-4-oxobenzo[*h*]quinoline-2-carboxylate (12). To 370 ml of refluxing Dowtherm A was added 37.0 g (0.112 mol) of dimethyl [(4-nitro-1-naphthyl)amino]butenedioate. The mixture was refluxed for 10 min and then allowed to cool to room temperature. The precipitate was removed by filtration and washed with petroleum ether. There was obtained 29.3 g (88%) of material melting at 290 °C dec. Recrystallization from DMF–methanol gave material possessing the same melting point. Anal. ($C_{15}H_{10}N_2O_5$) C, H, N.

Ethyl (2-Carbomethoxy-1,4-dihydro-4-oxobenzo[*h*]-quinol-6-yl)oxamate (13). A solution of 10.15 g (0.0324 mol) of methyl 1,4-dihydro-6-nitro-4-oxobenzo[*h*]quinoline-2-carboxylate in 1 l. of methyl cellosolve was hydrogenated at 3 atm of hydrogen using 1 g of 10% palladium on charcoal as catalyst. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure.

To a stirred solution of the amine obtained above and 3.16 g of triethylamine in 30 ml of dry DMF at 0 °C was added, dropwise, 4.35 g of ethyloxalyl chloride. The mixture was allowed to stand at room temperature for 48 h. The precipitate was removed by filtration and the filtrate was poured into 400 ml of water. The resulting yellow precipitate was removed by filtration and recrystallized from ethanol. There was obtained 5.15 g (43%) of material melting at 120 °C dec. Anal. ($C_{19}H_{16}N_2O_6$) C, H, N.

(2-Carboxy-1,4-dihydro-4-oxobenzo[*h*]quinol-6-yl)oxamic Acid (9). A mixture of 4.15 g (0.0112 mol) of ethyl (2-carbomethoxy-1,4-dihydro-4-oxobenzo[*h*]quinol-6-yl)oxamate and 160 ml of a 5% sodium hydroxide solution was stirred for 20 min. The mixture was transferred to a separatory funnel and extracted with methylene chloride. The aqueous layer was separated and acidified with 1 N hydrochloric acid and the precipitate was removed by filtration and washed with hot water and then with ethanol. There was obtained 3.03 g (83%) of material melting at 245 °C dec. A sample was purified for analysis by dissolving the sample in a solution of tris(hydroxymethyl)aminomethane, filtering the solution, and reacidifying with dilute hydrochloric acid. Anal. ($C_{16}H_{10}N_2O_6$) H, N; C: calcd, 58.90; found, 58.44.

Ethyl (2-Carbomethoxy-1,4-dihydro-4-oxobenzo[*h*]-quinol-7-yl)oxamate (15). To a stirred solution of 11.75 g (0.044 mol) of methyl 1,4-dihydro-7-amino-4-oxobenzo[*h*]quinoline-2-carboxylate[3] (14) and 5.05 g (0.05 mol) of triethylamine in 100 ml of DMF cooled to 0 °C was added, dropwise, 6.83 g (0.0484 mol) of ethyloxalyl chloride. The mixture was then allowed to stand overnight at room temperature.

The precipitate was removed by filtration and the filtrate was poured into 1 l. of water. The resulting yellow precipitate was removed by filtration. There was obtained 15.5 g (93%) of material melting at 235 °C dec. Recrystallization from ethanol gave yellow needles melting at 239 °C dec. Anal. ($C_{19}H_{16}N_2O_6$) C, H, N.

(2-Carboxy-1,4-dihydro-4-oxobenzo[*h*]quinol-7-yl)oxamic Acid Hydrate (10). A mixture of 4.15 g (0.0112 mol) of ethyl (2-carbomethoxy-1,4-dihydro-4-oxobenzo[*h*]quinol-7-yl)oxamate and 160 ml of a 5% sodium hydroxide solution was stirred at room temperature for 20 min. The mixture was transferred to a separatory funnel and extracted with methylene chloride. The aqueous layer was separated and acidified by the addition of 1 N hydrochloric acid. The cream-colored precipate was removed by filtration. There was obtained 3.80 g (98%) of material melting at 315 °C dec. Anal. ($C_{16}H_{10}N_2O_6 \cdot H_2O$) C, N; H: calcd, 3.51; found, 2.96.

Acknowledgment. We are grateful to the Physical and Analytical Department of The Upjohn Co. for determining the elemental analyses and for measuring the ir spectra. We express our gratitude also to Miss Christine VanHout

and Mr. Nelson Major for providing expert technical assistance.

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Synthesis and Antiinflammatory Activity of Some 2-Substituted 4- and 7-Benzoxazoleacetic and α-Methylacetic Acids

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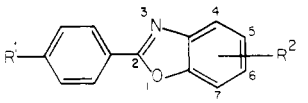
Received February 2, 1976

4- and 7-benzoxazoleacetic and α-methylacetic acids substituted in the 2 position with phenyl and substituted phenyl groups have been synthesized and tested on the carrageenan-induced rat paw edema assay. The only compound found to have significant activity, albeit of a low order, was 2-phenyl-α-methyl-7-benzoxazoleacetic acid.

2-(4-Chlorophenyl)-α-methyl-5-benzoxazoleacetic acid, benoxaprofen [1, R^1 = Cl; R^2 = 5-$CH(CH_3)CO_2H$], was found to be a potent inhibitor of carrageenan-induced edema[1] and adjuvant arthritis in rats and is undergoing clinical trials as a new nonsteroidal antiinflammatory agent. It was therefore of interest to determine the effect



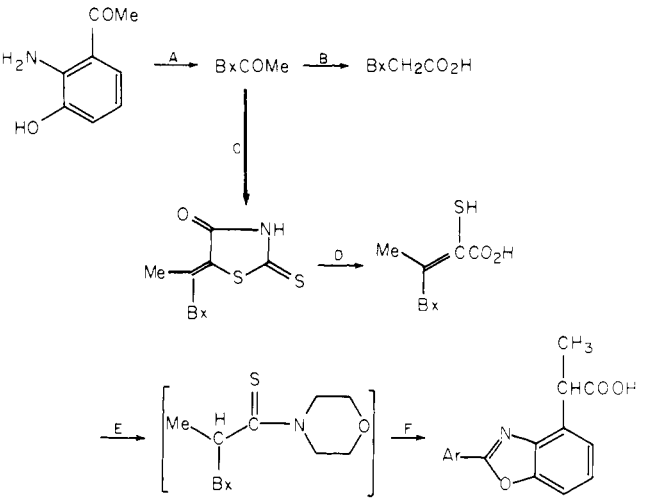
on pharmacological activity of moving the side chain R^2 onto other positions of the benzoxazole system and this paper reports the synthesis and results from pharmacological assay of compounds in which the benzoxazole system was substituted in the 4 and 7 positions with acetic acid and α-methylacetic acid side chains.

Chemistry. Compounds in the series having substituents in the 4 and 7 positions were prepared according to the routes indicated in Schemes I and II. Further details are given in Table I and the Experimental Section. The sequence C to F is an adaptation of the method of Moreau and Durand-Henchoz.[2] Examination of the product from method D by NMR spectroscopy showed that it had an α-mercaptocinnamic acid structure in solution, rather than the thiopyruvic acid tautomer. The latter was expected from the paper by Moreau and Durand-Henchoz. However, the α-mercaptocinnamic acid structure does agree with the findings of Campaigne and Cline who examined the uv spectra of some α-mercaptocinnamic acids[3] and of Nishio and Ho, who used NMR spectroscopy and reached the same conclusion for α-mercaptocinnamic acid.[4] Our product from method D had a strong ir band at 1690 cm^{-1} (in KBr), so in the solid state the compound probably also exists as an α-mercaptocinnamic acid.

Antiinflammatory Activity. The results of antiinflammatory testing against carrageenan-induced foot edema of Winter et al.[5] in rats, modified as indicated in ref 1, are reported in Table I. Only one compound, **5**, showed significant reduction of swelling at 2 × 100 mg/kg po compared with controls, but the magnitude of the result compared with those obtained using the control compounds, hydrocortisone and phenylbutazone, did not encourage further development of the compound.

Two correlations emerge from Table I. (i) In the 7-substituted series, compound **6**, having *p*-chloro substitution in the 2-phenyl ring, was inactive, while its unsubstituted analogue (**5**) was active. This is the opposite of the situation in the benoxaprofen series,[1] where para substitution with chlorine increased the activity of the unsubstituted analogue. (ii) Compound **3**, in the series having the side chain in the 4 position of the benzoxazole nucleus, was inactive although its equivalent **5** in the 7-substituted series was active. Such a difference between the activities is surprising as the only difference between the compounds lies in the positions of the isosteric oxygen and nitrogen atoms. Differences in metabolism, shape, and/or physicochemical parameters could be responsible for this difference[6] but an examination of the pK_a and partition coefficients (cf. Table I) shows that the pK_a is not involved since all of the measured values were very close to each other. It is possible, however, that the amount of difference in the *p* values of **3** and **5** could contribute to their difference in activity.

Scheme I. Preparation of 2-Arylbenzoxazole-4-alkanoic Acids[a]



[a] Reagents for method A, ArCOCl-pyridine, heat; B, (1) S + H-c-$N(CH_2CH_2)_2O$, (2) concentrated HCl; C, 2-thioxo-4-thiazolidinone, NaOAc; D, 0.33 N NaOH; E, as B (1); F, concentrated HCl and AcOH; Bx = 4-substituted 2-arylbenzoxazole.

Experimental Section

Melting points are uncorrected. Microanalyses were carried out by Mr. G. Maciak and associates, Eli Lilly & Co., Indianapolis,