118-93-4; **17**, 490-78-8; **18**, 31165-67-0; **19**, 21766-81-4; **20**, 1450-74-4; **21**, 42972-62-3; **22**, 533-31-3; **23**, 114250-16-7; **24**, 66003-50-7; **25**, 93097-10-0; **26**, 35292-10-5; **27**, 19545-61-0; **28**, 114250-17-8; **29**, 114250-18-9; **30**, 56926-48-8; **31**, 114250-19-0; **32**, 114273-19-7; **33**, 114250-20-3; **34**, 114250-21-4; **35**, 114250-22-5; **36**, 114250-23-6; **37**, 114250-24-7; **38**, 114250-25-8; **39**, 114250-26-9; **41**, 114250-27-0; **42**, 114250-28-1; **43**, 114250-29-2; **44**, 114250-30-5; **45**, 114250-31-6; **46**, 114250-32-7; **47**, 114250-33-8; **48**, 114250-34-9; **50**, 5284-32-2; **51**, 75307-57-2; **52**, 114250-35-0; **53**, 114250-36-1; **54**, 114250-37-2; **55**, 114250-38-3; **56**, 114250-39-4; **57**, 114250-40-7; H_3CCOCl, 75-36-5; ethyl phenylmethoxyacetate, 33224-90-7; 5-(phenylmethoxy)-1,3-benzodioxole, 66177-24-0; *tert*-butylhydroquinone, 1948-33-0; 2-bromo-4-phenylphenol, 92-03-5; *cis*-2-(acetyloxy)-1-cyclohexanecarboxylic acid, 114250-43-0; *trans*-2-acetoxy-1-cyclohexanecarboxylic acid, 114250-44-1; ascorbic acid, 50-81-7.

Supplementary Material Available: Discussion of the determination of redox potentials for ascorbic acid and experimental *aci*-reductones and antilipidemic methods and results and tables listing the influence of **1**, **2**, **5a,b–7**, and **9** on the serum cholesterol concentrations in rats fed a high-cholesterol diet (13 pages). Ordering information is given on any current masthead page.

Predictive Structure–Activity Relationships in a Series of Pyranoquinoline Derivatives. A New Primate Model for the Identification of Antiallergic Activity

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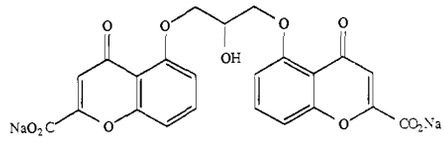
A new primate model has been developed for the evaluation of antiallergic agents. Compounds are tested for their ability to inhibit anti-IgE induced histamine release from the bronchoalveolar mast cells lavaged from the lungs of *Macaca arctoides* infected with the parasite *Ascaris suum*. A number of 6-substituted pyranoquinoline derivatives have been evaluated and the activities were subjected to Hansch analysis. A highly significant correlation with lipophilicity (π) and Hammett σ_p values was obtained. The relationship was used to predict further compounds for synthesis giving rise to new, potent analogues. Some apparently anomalous results could be explained by differences in the ionization of, or tautomerism in, the quinoline ring.

The difficulties associated with identifying prophylactic antiallergic drugs related to sodium cromoglycate (cromolyn sodium) (1) have been discussed in previous publications.[1,2] In our search for potent new analogues with topical activity (as opposed to orally effective agents) some of the problems have been obviated, but that of the poorly predictive nature of the pharmacological screens still remains. We have therefore developed an in vitro primate model using bronchoalveolar mast cells from *Macaca arctoides* monkeys infected with the nematode *Ascaris suum*.[1,3] This lumenal mast cell is particularly relevant to reversible obstructive airways disease as it is among the first to encounter both inhaled antigen and drug. The use of primate cells also minimized concern about interspecies variability. This paper describes the synthesis of a series of 6-substituted pyranoquinolines and their evaluation in the monkey lung lavage model. The biological results have been subjected to a Hansch analysis which has been used to predict new compounds for synthesis.



1

Chemistry

Thirty-one pyranoquinoline derivatives (**30–60**, Table I) were tested in the monkey bronchoalveolar lavage mast cell screen. The syntheses of some compounds have previously been described;[1] routes to all other analogues are summarized in Schemes I–V. Compounds for biological testing (except **48**) were prepared as their disodium salts (or trisodium salt in the case of **35**). With only two exceptions (**38** and **41**, see below) these were obtained from the corresponding diesters by hydrolysis with the theoretical quantity of sodium hydroxide in refluxing methanol.

Scheme I. Ethyl methyl 4,6-dioxo-10-propyl-*4H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylate (**2**)[1] was brominated with phosphoryl bromide in methylene chloride to give the 6-bromo compound **3**. This was converted into the perfluoroalkyl diesters **4–6** by a modification of the procedure of Kobayashi et al.,[4] using the appropriate perfluoroalkyl iodide in HMPA with an activated copper catalyst.

The pyranoquinolinone **2** was also converted to diethyl 6-amino-4-oxo-10-propyl-*4H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylate (**7**) with chlorosulfonyl isocyanate, by the procedure described by Wright.[5] This amine was converted to the 1-pyrrolyl **8** and phenylureido **9** diesters by standard methods.

Scheme II. The 6-methylpyranoquinoline derivative **10**[1] was condensed with benzaldehyde in acetic acid with tosic acid as catalyst to produce the styryl derivative **18**. Compound **10** was also used to prepare the key 6-formylpyranoquinoline derivative **11** by oxidation with selenium dioxide. The aldehyde **11** was converted to the difluoromethyl diester **12** with (diethylamido)sulfur trifluoride[6] in methylene chloride and was also used in the synthesis of the diesters of the benzoylhydrazone **13**,

(1) Cairns, H.; Cox, D.; Gould, K. J.; Ingall, A. H.; Suschitzky, J. L. *J. Med. Chem.* **1985**, *28*, 1832.
(2) Suschitzky, J. L.; Sheard, P. *Prog. Med. Chem.* **1984**, *21*, 1.
(3) (a) Wells, E.; Harper, S. T.; Jackson, C. G.; Mann, J.; Eady, R. P. *J. Immunol.* **1986**, *137(12)*, 3933. (b) Wells, E.; Harper, S. T.; Jackson, C. G.; Mann, J.; Eady, R. P. *J. Immunol.* **1986**, *137(12)*, 3941.
(4) (a) Kobayashi, Y.; Kumadaki, I.; Sato, S.; Hara, N.; Chikami, E. *Chem. Pharm. Bull.* **1970**, *18*, 2334. (b) Kobayashi, Y.; Kumadaki, I.; Yamamoto, K. *Chem. Commun.* **1977**, 536.
(5) Wright, R. G. McR. *Synthesis* **1970**, 1058.
(6) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574.

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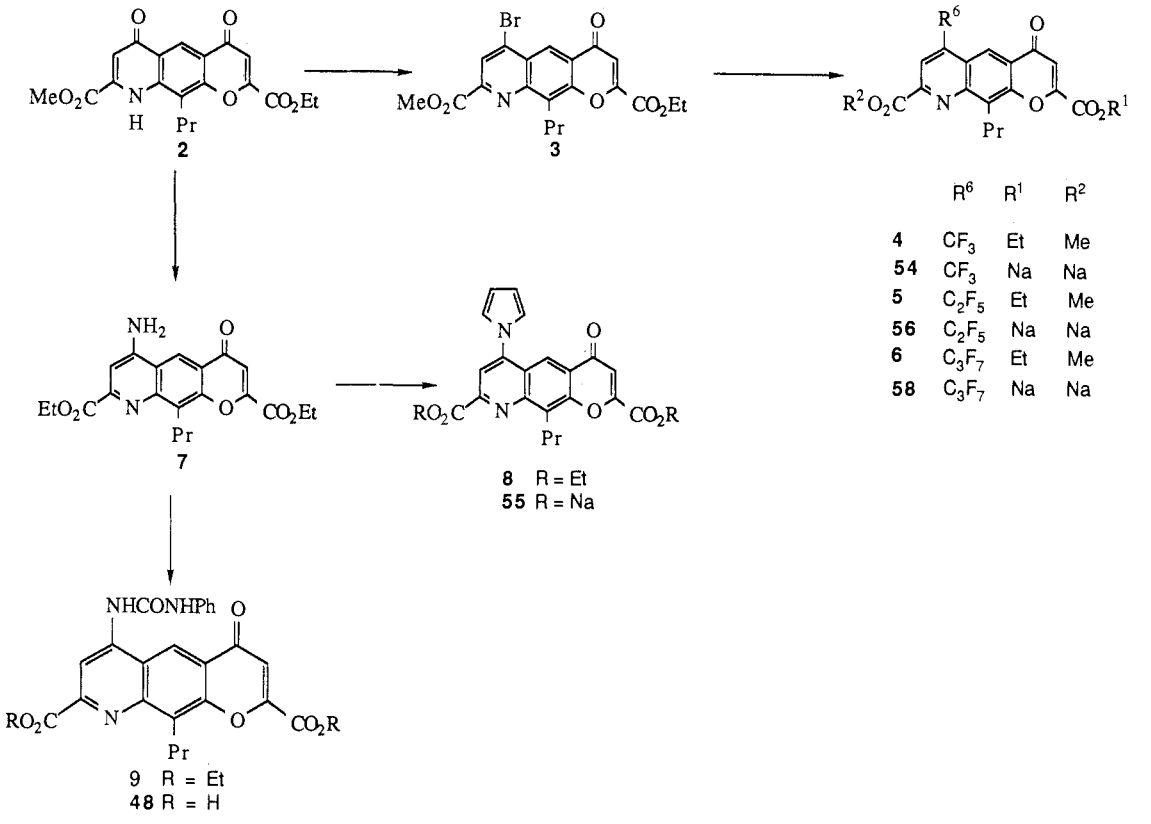
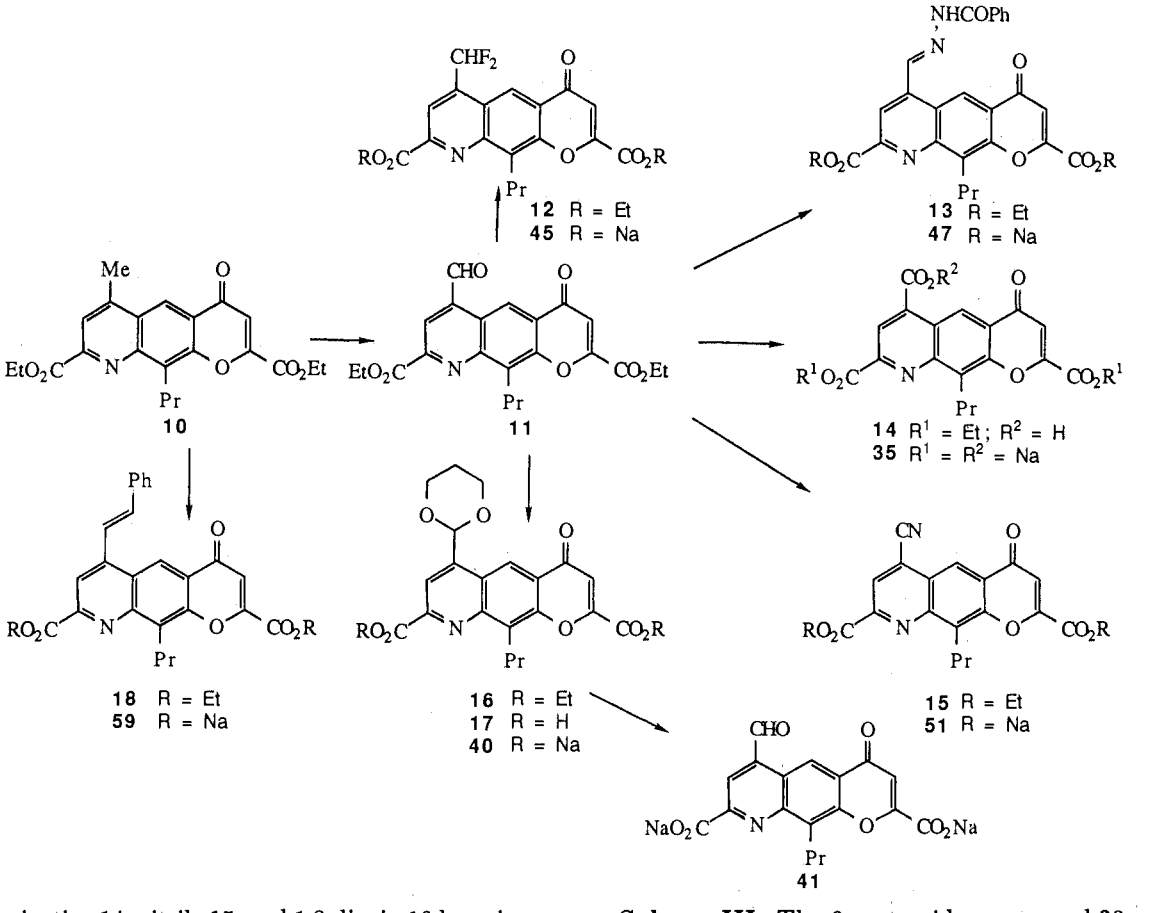
Scheme I



Scheme II

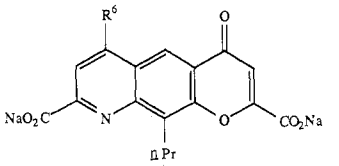


carboxy derivative **14**, nitrile **15**, and 1,3-dioxin **16** by using standard synthetic methodology. The 6-formyl disodium salt **41** was obtained by acid hydrolysis of the dioxin diacid **17**.

Scheme III. The 6-acetamido compound **38** was synthesized from the known tosylamine diester **19**[5] in two steps.

Scheme IV. Methyl 6-acetyl-4-chloro-7-hydroxy-8-

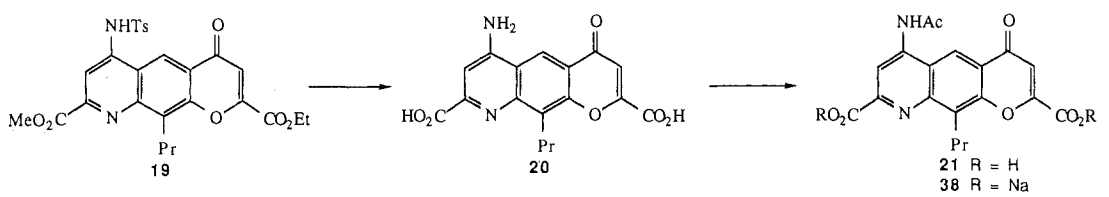
Table I. Observed and Calculated Monkey Lung Lavage Potency Ratios for 31 Pyranoquinoline Derivatives



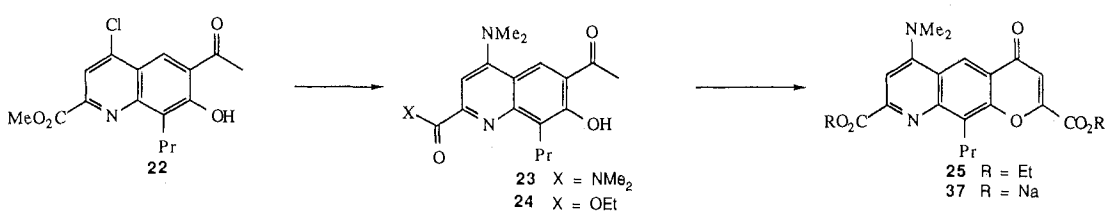
entry	compd	R^6	PR	log PR (obsd)	log PR (calcd)[a]	π	σ_p
1	**30**[g]	NHEt	0.007	−2.15	−0.85	0.08	−0.61
2	**34**	NHC_5H_{11}	0.053	−1.27	0.17	1.70[b]	−0.61[b]
3	**38**	NHCOMe	0.065	−1.19	−1.14	−0.97	0.00
4	**39**[g]	H	0.100	−1.00	−0.53	0.00	0.00
5	**40**	1,3-dioxinyl	0.179	−0.75	−1.08	−0.83[b]	−0.05[b]
6	**41**	CHO	0.237	−0.63	−0.68	−0.65	0.42
7	**42**[g]	Me	0.379	−0.42	−0.28	0.56	−0.17
8	**43**[g]	OEt	0.400	−0.40	−0.44	0.38	−0.24
9	**46**[g]	NHPh	0.706	−0.15	0.09	1.37	−0.40
10	**48**[h]	NHCONHPh	0.895	−0.05	−0.05	0.96[b]	−0.20[b]
11	**49**[g]	Br	1.040	0.02	0.15	0.86	0.23
12	**50**[g]	Cl	1.096	0.04	0.06	0.71	0.23
13	**52**[g]	SEt	2.249	0.35	0.16	1.07	0.03
14	**54**	CF_3	2.530	0.40	0.35	0.88	0.54
15	**31**[g]	N(Me)COMe	0.009	−2.05	−0.96	−0.93[b]	0.26
16	**35**	COONa	0.053	−1.27	−0.46	−0.32	0.45
17	**32**[g]	NHMe	0.012	−0.66[c]	−1.19	−0.47	−0.59
18	**37**	NMe_2	0.063	−0.29[f]	−0.86	0.18	−0.72
19	**44**[g]	SOOPh	0.536	−0.27	0.05	0.27	0.68
20	**45**	CHF_2	0.586	−0.23	−0.06	0.44[b]	0.32
21	**47**	CH=NNHCOPh	0.748	−0.13	0.05	0.43	0.51
22	**51**	CN	1.161	0.07	−0.49	−0.57	0.66
23	**36**[g]	NH_2	0.057	0.12[e]	−1.71	−1.23	−0.66
24	**33**[g]	*N*-pyrrolidinyl	0.017	0.14[d]	−0.31	1.22[b]	−0.90
25	**53**[g]	OH	2.366	0.37	−1.18	−0.67	−0.37
26	**55**	*N*-pyrrolyl	2.686	0.43	0.29	0.95	0.37
27	**56**	CF_2CF_3	2.832	0.45	0.70	1.45[b]	0.52
28	**57**[g]	OPh	3.244	0.51	0.76	2.08	−0.03
29	**58**	$CF_2CF_2CF_3$	3.725	0.57	0.98	1.93[b]	0.48
30	**59**	CH=CHPh	6.326	0.80	1.12	2.68	−0.07
31	**60**[g]	SPh	7.536	0.88	0.94	2.32	0.02

[a] Calculated from eq 2. [b] Calculated values. Values in the table are corrected for ionization. [c] log PR (obsd) = −1.91; pK_3 = 8.63. [d] log PR (obsd) = −1.77; pK_3 = 9.31. [e] log PR (obsd) = −1.25; pK_3 = 8.75. [f] log PR (obsd) = −1.20; pK_3 = 8.26. [g] Synthesis described in ref 1. [h] Tested as the diacid.

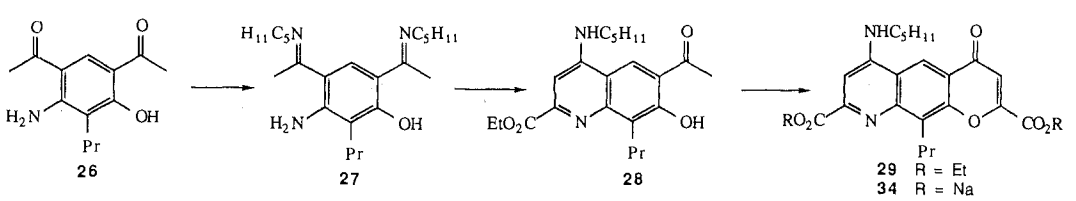
Scheme III



Scheme IV



Scheme V

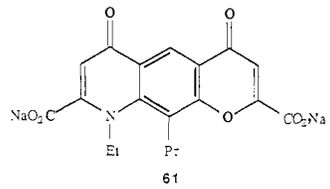


propylquinoline-2-carboxylate (**22**) was heated in a sealed tube in ethanolic dimethylamine to give the corresponding 4-(dimethylamino)quinoline-2-carboxamide **23**. Treatment with ethanolic HCl gave the ester **24**, from which the 6-(dimethylamino)pyranoquinoline diester **25** was obtained via a Claisen ester condensation with diethyl oxalate.

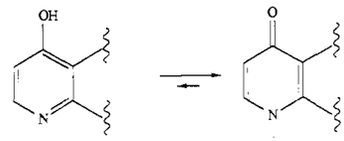
Scheme V. The known acetylacetophenone **26**[7] was converted into the bis(pentylimine) **27** with pentylamine in toluene with tosic acid as catalyst. Two consecutive Claisen ester condensations with diethyl oxalate (using lithium diisopropylamide to form the pyridine ring and sodium ethoxide to form the pyrone ring) gave the 6-(pentylamino)pyranoquinoline diester **29**.

Results and Discussion

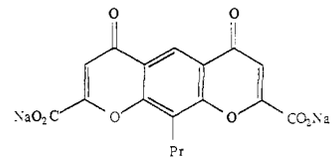
Biology. Nedocromil sodium **61** but not cromolyn sodium **1** has been shown to inhibit the bronchoconstriction produced when ascaris-sensitive macaques were challenged with antigen in vivo.[8] Mast cells lavaged from the lungs of these animals release histamine, LTC_4, and PGD_2 on immunological challenge,[3a] and mediator release from these cells, which is blocked by nedocromil sodium but not cromolyn, appears to be responsible for the initiation of the bronchoconstriction observed in vivo.[3b] There is an increasing interest in human bronchoalveolar mast cells as these are among the first cells to encounter inhaled antigen (and drug) and may play a pivotal role in initiating antigen-induced bronchoconstriction. We have therefore developed the macaque mast cell screen as a readily available, highly antigen sensitive model. As cromolyn sodium is virtually inactive in this model,[3b] we believe that it may contain features of the disease in patients who receive little benefit from cromolyn therapy. This might be supported by reports that nedocromil sodium is clinically effective in older steroid-dependent patients.[9,10]



61



62a 62b



63

Structure–Activity Relationships. Initially a series of 14 6-substituted pyranoquinolines was synthesized and their activities in the monkey lung lavage test were determined (Table I, entries 1–14). The results are expressed as potency ratio values relative to a standard benzodipyran derivative (see the Experimental Section). The ratios were correlated with the overall physicochemical properties of the compounds and particularly with those of the substituent at the pyranoquinoline 6-position (subsequently referred to as R^6). All of the compounds are pyranoquinoline-2,8-dicarboxylic acids. Earlier antiasthmatic agents such as cromolyn sodium **1**[11] ($pK_{a_1} = 1.0 \pm 0.8$, $pK_{a_2} = 1.93 \pm 0.03$[12,13]) are derived from strong dicarboxylic acids. Similarly, all members of the present series of compounds are strongly acidic and thus highly ionized (>99.999%) and hence hydrophilic at the pH (7.4) of biological test. For example, minocromil sodium **32**[1] gives $pK_{a_1} = 0.5 \pm 0.2$ and $pK_{a_2} = 1.62 \pm 0.06$ (partition method[14]). For the purposes of structure–activity analysis, the degree of carboxy group ionization is taken as constant throughout the series. Biological activity is expressed as the potency ratio (PR) of the compound relative to a standard compound **63**, as follows:

$$PR = IC_{30}(\text{compound } \mathbf{63})/IC_{30}(\text{compound})$$

Regression analysis of the biological potency ratios for the 14 compounds (Table I) was carried out with steric (MR, *B*, *L*), lipophilic (π), and electronic (σ, *F*, *R*) substituent constants. Examination of potency vs parameter plots showed a relationship between potency and lipophilicity but revealed the compounds having R^6 = NHEt, NHC_5H_{11} to be obvious outliers, with low potency. This is perhaps not surprising since these amino substituents will render the quinoline nitrogen more strongly basic, therefore remaining partially protonated at physiological pH. For other compounds in the group, the quinoline nitrogen is not protonated at pH 7.4.

The dissociation constants of the three compounds in the group, where R^6 = NHEt, NHC_5H_{11}, and NHC_6H_5, were obtained by the spectrophotometric method[14] (Table II). These values, together with the corresponding fraction un-ionized (*f*) at pH 7.4, were used to calculate a corrected potency ratio relevant to the un-ionized concentration of the compound present under the test conditions:

$$\log PR\ (\text{corrected}) = \log PR\ (\text{obsd}) + \log (1/f) \quad (1)$$

Corrected log PR values for these three compounds were then used for the regression analysis.

A multiple regression equation in the two parameters π and σ_p was obtained, these parameters not being significantly intercorrelated for the present series of 14 compounds:

$$\log PR = 0.63\pi + 0.61\sigma_p - 0.53 \quad (2)$$
$$(\pm 0.08)\ \ (\pm 0.18)$$

$$n = 14,\ r^2 = 0.86,\ F = 33.9,\ p = 0.001,\ SD = 0.22$$

The substituent constants, observed potency ratios, and the corresponding log PR values recalculated from the regression are given in Table I and represented graphically in Figure 1. The relationship in eq 2 indicates an increased potency to be associated with increased lipophilicity (positive π) and with electron withdrawal (positive σ_p) by the substituent R^6. On this basis a second set of

Table II. Correction for Ionization of Three 6-Aminopyranoquinolines

R^6	quinoline pK_a	% U at pH 7.4	fraction un-ionized (*f*)	log PR (obsd)	log PR[a]
NHC_2H_5	8.64	5.5	0.055	−2.15	−0.89
NHC_5H_{11}	8.70	4.8	0.048	−1.27	0.05
NHC_6H_5	7.78	29	0.290	−0.15	0.39

[a] Calculated from eq 1.

(7) Coltman, C. W.; Eyley, S. C.; Raphael, R. A. *Synthesis* **1984**, 150.
(8) Eady, R. P.; Greenwood, B.; Jackson, D. M.; Orr, T. S. C.; Wells, E. *Br. J. Pharmacol.* **1985**, *85*, 823.
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(14) Albert, A.; Serjeant, E. P. *The Determination of Ionisation Constants*, 3rd ed.; Chapman and Hall: London, 1984.

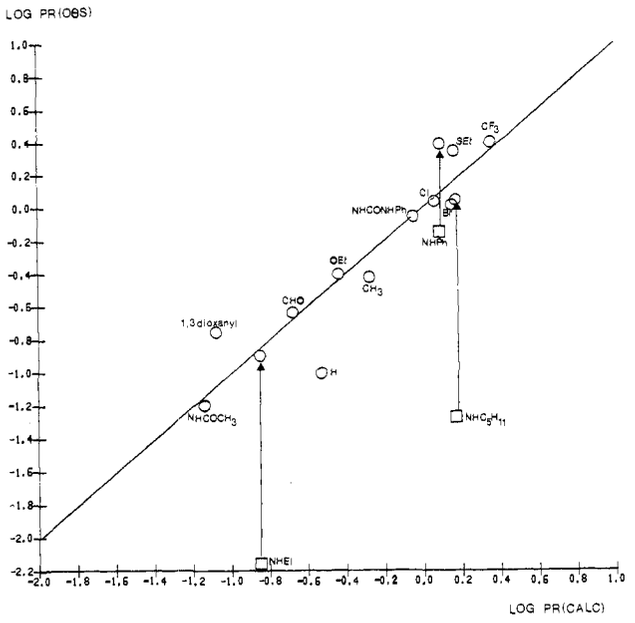

Figure 1. Observed and calculated potency ratios of 14 pyranoquinoline derivatives. (□) Observed potency of amines prior to ionization corrections.

17 compounds was selected for synthesis and testing (Table I, entries 15–31). These included some substituents not commonly employed, but predicted to have increased potency ratios, since they embodied the electronic and lipophilic characteristics identified in eq 2. Other substituents were included in order to verify the structure–activity relationship.

The potency ratio of each 6-amino-substituted compound was corrected for the fraction ionized (protonated quinoline nitrogen), as described earlier. Table I includes the corrected observed potency ratios, together with the experimental values for the aminoquinoline dissociation constant (pK_3). The difference between calculated and observed potency ratios was greatest for the hydroxy (+1.55) and amino (+1.83) substituents, which led to a consideration of their physicochemical properties in an attempt to understand the divergence from the regression relationship.

Both the hydroxy and amino substituents are small in size (compound **53** and **36**, respectively) and are potentially able to participate in intermolecular hydrogen bonding. This suggests the group to have an additional beneficial receptor interaction not available to the other substituents in the series. Such an interaction would be apparently at odds with the main regression, however, where increased potency was positively correlated with lipophilicity. The hydroxy and amino substituents are both able to receive an external H bond, and also to act as an H-bond donor. In solution hydroxypyridines **62a** have been found by spectroscopic techniques to exist almost exclusively in the keto tautomeric form **62b**.[15]

In contrast, measurements and calculations in the gas phase showed the hydroxy tautomer **62a** to be favored energetically.[16] In Table I it can be seen that the other potentially H-bonding amino derivatives **32**, **37**, and **33** were consistently more active than would be predicted, as was the 6-cyano compound **51**.

The generally hydrophilic ionized properties of the present series of compounds suggest an aqueous biological receptor environment, favoring the keto (hydrogen-bond acceptor) form (of the hydroxy compound). These findings were used to predict a further new family of antiasthmatic compounds which were more potent than any previously synthesized, and which have now been published.[1]

The 6-carboxy compound **35** was less active than would be calculated with the substituent constants (π and σ_p) for its undissociated state (Table I). The pK_a of the 6-carboxy group was estimated to be approximately 2.2 (by reference to the value for pyridine-2,4-dicarboxylic acid[17]), indicating almost complete (>99.99%) ionization at the pH of the biological test. However, calculated potency ratios for this compound based on substituent constants for the carboxylate anion still gave a gross overestimate of activity. It was inferred that the presence of this additional anionic function gave rise to an unfavorable interaction which was unaccounted for in the regression relationship.

The 6-(acetylmethylamino) compound **31** is much less active than calculated with the normal aromatic substituent constants (π, σ_p). In this particular compound, however, peri interactions between the substituent and the quinoline 5-hydrogen are severe. Inhibition of coplanarity of the substituent and the pyranoquinoline ring would be expected to give properties more like an aliphatic amide to the function. The much reduced lipophilicity which would follow from this limitation would be consistent with the low observed potency ratio.

Finally, a further correlation was carried out to include both the original group of 14 compounds, together with the later predicted group. The amino compound potency ratios were again corrected to include only the un-ionized form. The acetylmethylamino **31**, carboxy **35**, amino **36**, and hydroxy **53** derivatives were omitted for reasons discussed earlier. The relationship obtained is shown in eq 3 and Figure 2. This figure also shows points (solid circles) for compounds **31**, **35**, and **53** calculated from the relationship in eq 3. In summary, potency in the monkey lung

$$\log (PR) = 0.50\pi + 0.33\sigma_p - 0.43 \quad (3)$$
$$(\pm 0.05) \quad (\pm 0.11)$$

$$n = 27,\ r^2 = 0.82,\ p = 0.0001,\ F = 53.2,\ SD = 0.25$$

lavage screen was positively correlated with 6-substituents in the pyranoquinoline system which were lipophilic and electron withdrawing. Ionization of functional groups within the system in addition to the two carboxy groups was detrimental to activity.

Experimental Section

Monkey Lung Lavage Test. Inhibition of histamine release from mast cells recovered by bronchoalveolar lavage of ascaris-infected *Macaca arctoides* was as previously described.[3a] Mast cells were challenged by addition of 0.05 mL of cells, at a density of 10^5 mast cells/mL in HEPES-buffered Tyrode (pH 7.4) containing 1 mg/mL gelatin, to 0.05 mL of buffer containing both anti-human IgE and inhibitor. After the mixture was incubated for 20 min at 37 °C, 0.25 mL of ice-cold 2 mM EDTA in Ca^{2+}, Mg^{2+}-free buffer was added. After centrifugation, 0.2 mL of supernatant was removed for histamine analysis by the double isotope method,[18] modified as previously described.[19] The challenge level was selected to give approximately 20–25% release of total histamine. Drugs were tested at four concentrations in

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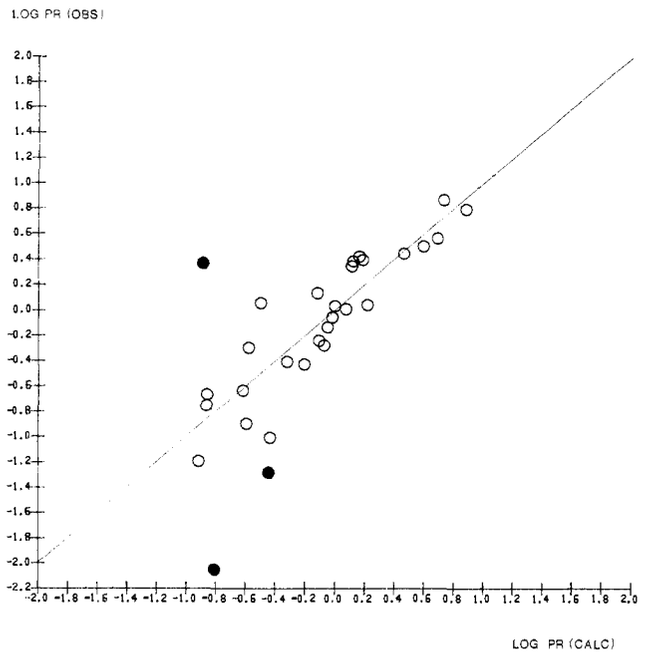

Figure 2. Observed and calculated potency ratios of 30 pyranoquinoline derivatives.

triplicate, and an IC_{30} value was calculated. The maximum level of inhibition attainable was to some extent dependent on the severity of challenge. A standard compound, the benzodipyran derivative **63**,[20] was therefore included in each experiment and the result expressed as a potency ratio (PR), defined earlier. The PR value used in the regression analysis was the geometric mean of two independent experiments with the exception of compounds **32**, **38**, and **54** (three experiments) and compound **31** (one experiment). The reproducibility of the assay is demonstrated by the finding that compound **63** had a mean IC_{30} of 1.04×10^{-7} M with 95% confidence limits $(0.74\text{–}1.47) \times 10^{-7}$ M in the 31 experiments reported here. Furthermore, the variation of PR determinations is less than that of IC_{30} data because of interexperimental standardization.

Physical Chemistry. 1. Quantitative Structure–Activity Relationship Methods. In order to establish any quantitative relationships between biological activity and physicochemical properties for the series of pyranoquinolines, QSAR analyses were carried out by single and multiple stepwise regression, using the RS1 statistics package of Bolt, Beranek and Newman Research Systems, Cambridge, MA. The physicochemical properties of the substituent at the 6-position, which were used in the regression analysis, were expressed by the following parameters.

(i) **Lipophilic effects**: Hansch aromtic π values were used, taken from the literature where available[21] or calculated.[22]

(ii) **Steric effects**: (a) The molar refractivity, MR, of the substituent.[21] (b) Verloop Sterimol parameters B_1, B_4, and L,[23] i.e. the minimum width, maximum width, and length, respectively (in angstroms).

(iii) **Electronic effects**:[21] Hammett σ values, field F, and resonance R. Values not available in the literature were obtained by comparison with those of closely related substituents.

2. **Activity Data.** The activity of each compound, obtained by the monkey lung lavage screen, is expressed as the logarithm of the potency ratio (log PR). In the majority of cases two or more activity values were available, and in these cases the geometric mean of all results was taken. The reference compound **63** has a potency ratio of 1.0 (see previous section).

3. **pK_a Measurements.** (a) All ionization constants of the quinoline nitrogens were measured by the spectroscopic method, as described by Albert and Serjeant.[14] Measurements were carried out at 25 °C at an ionic strength of 0.01. Potassium chloride was used as the electrolyte. At least 10 data points were obtained for each determination, and the pK_{a_3} quoted is the value calculated from the experimental results by using the RS1 Fit Function technique. (b) Ionization constants for carboxylic acid functions were obtained by using the partition method.[14] In some cases a simple two-phase separator, the filter–probe,[12] was employed, the acid being titrated in the presence of octanol–water, with spectroscopic measurement of the two phases. The titration apparatus used was essentially the same as that of Cantwell and Mohammed.[13]

Computer programs have been developed which allow K_1, K_2, and P (the partition coefficient of the compound) to be obtained from the distribution–pH data by a least-squares optimization technique.

Synthetic Chemistry. Melting points were determined with a Büchi melting point apparatus. The structures of all compounds were consistent with their ^{1}H NMR spectra, which were determined on a Bruker WP 80-MHz spectrometer. Where represented by elemental symbols, the analyses of these elements are within ±0.4% of the theoretical values. Petrol refers to petroleum ether (bp 40–60 °C).

General Procedure for Hydrolyses. Analytically pure diester (1 equiv) was suspended in AR methanol (50 mL/mmol) maintained under reflux, and 0.1 M NaOH solution (2 equiv) was added dropwise over ca. 1 h. After the addition was completed, heating was continued for 15 min. To isolate the acid, the reaction solution was cooled, poured into water, and made slightly acid with dilute HCl. The precipitate was collected either by filtration or, if not practicable, by ethyl acetate extraction, drying, and evaporation. Alternatively, the disodium salt was isolated directly from the hydrolysis reaction by evaporation to a small volume and dilution with AR acetone. The resulting precipitate was collected, redissolved in deionized water, filtered through a Millipore filter, and freeze-dried.

The free acids were normally converted into the corresponding disodium salts by treatment with the theoretical amount of AR sodium bicarbonate in deionized water, Millipore filtration, and freeze-drying.

Ethyl Methyl 6-Bromo-4-oxo-10-propyl-4*H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylate (3). A solution of ethyl methyl 4,6-dioxo-10-propyl-4*H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylate (2)[1] (40 g, 108 mmol) and phosphorus oxybromide (62 g, 216 mmol) in CH_2Cl_2 (2.5 L) was heated under reflux stirring for 3 h. The mixture was cooled and filtered, and methanol (1 L) was added. The solution was evaporated to dryness and the residue triturated with petrol to afford **3**: 21.8 g (45%); mp 177–178 °C; NMR ($CDCl_3$) δ 1.02 (3 H, t), 1.50 (3 H, t), 1.83 (2 H, m), 3.64 (2 H, t), 4.07 (3 H, s), 4.50 (2 H, q), 7.15 (1 H, s), 8.43 (1 H, s), 9.00 (1 H, s). The compound was unstable and discolored rapidly.

Ethyl Methyl 4-Oxo-10-propyl-6-(trifluoromethyl)-4*H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylate (4). A suspension of **3** (12.5 g, 28 mmol), trifluoromethyl iodide (50 g, 25 mmol), and activated copper powder (50 g, prepared by precipitation from cupric sulfate and zinc) in HMPA (200 mL) was heated in a

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(21) Hansch database published by Pomona College, Claremont, CA.

(22) These π values were obtained from a listing of substituent parameters produced by the Pomona College Medicinal Chemistry Project (June 1983), supplemented by constants calculated from an early version (3.33) of the MedChem Computer Program. A referee has suggested that it is now preferable to make use of the current, more highly developed, version (3.52)* of the software to systematically estimate the hydrophobicity (f) of all 31 substituents. This approach yielded the following relationship:

$$f = 0.87\pi + 0.66 \quad (\pm 0.08)$$

$$n = 31,\ r^2 = 0.79,\ F = 108.5,\ p = 0.0001,\ \mathrm{SD} = 0.47$$

Use of the recalculated f values in eq 2 and 3 of the present work produced changes in the coefficients, but did not alter the underlying relationships. (*Details available from Dr. A. Leo, Pomona College Medicinal Chemistry Project, Seaver Chemistry Laboratory, Claremont, CA 91711.)

(23) Verloop, A.; Hoogenstraaten, W.; Tipker, J. *Drug Design*; Ariens, E. J., Ed.; Academic: New York, 1976; Vol. VII, pp 165–207.

pressure vessel with stirring under nitrogen for 3 h. The mixture was allowed to cool and diluted with water (1 L), and the solid was collected. This was taken into CH_2Cl_2, filtered to remove undissolved copper, dried, and evaporated to give a brown solid. Chromatography on silica gel, eluting with ether/petrol (3:1) afforded **4**: 2.5 g (20%); mp 172–173 °C; NMR ($CDCl_3$) δ 1.07 (3 H, t), 1.49 (3 H, t), 1.87 (2 H, m), 3.70 (2 H, t), 4.15 (3 H, s), 4.54 (2 H, q), 7.17 (1 H, s), 8.41 (1 H, s), 9.03 (1 H, s).

Disodium 4-Oxo-10-propyl-6-(trifluoromethyl)-4*H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylate (54). Diester **4** was hydrolyzed by the standard method to afford **54**: (97%); NMR (DMSO-d_6) δ 0.97 (3 H, t), 1.83 (2 H, m), 3.61 (2 H, m), 6.77 (1 H, s), 8.36 (1 H, m), 8.62 (1 H, m). Anal. ($C_{18}H_{10}F_3NNa_2O_6 \cdot 14\%$ H_2O) C, H, N.

Ethyl Methyl 4-Oxo-6-(pentafluoroethyl)-10-propyl-4*H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylate (5). Compound **3** was treated with pentafluorethyl iodide, by using the experimental procedure employed in the preparation of **6**, to give the diester **5**: 1.22 g (37%); mp 136–139 °C; NMR ($CDCl_3$) δ 1.07 (3 H, t), 1.49 (3 H, t), 1.86 (2 H, m), 3.70 (2 H, t), 4.13 (3 H, s), 4.51 (2 H, q), 7.17 (1 H, s), 9.01 (1 H, s). Anal. ($C_{22}H_{18}F_5NO_6$) C, H, N.

Disodium 4-Oxo-6-(pentafluoroethyl)-10-propyl-4*H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylate (56). Diester **5** was hydrolyzed by the standard method to give **56**: 1.13 g (75%); NMR (DMSO-d_6) δ 0.97 (3 H, t), 1.80 (2 H, m), 3.63 (2 H, m), 6.75 (1 H, s), 8.30 (1 H, s), 8.74 (1 H, br s). Anal. ($C_{19}H_{10}F_5NNa_2O_6 \cdot 11\%$ H_2O) C, H, N.

Ethyl Methyl 6-(Heptafluoropropyl)-4-oxo-10-propyl-4*H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylate (6). Activated copper powder (10 g) was washed several times with 0.02 M aqueous EDTA and water, filtered, washed with water, and dried. A suspension of the dry powder, bromoquinoline **3** (10 g, 22.4 mmol), and perfluoropropyl iodide (25 g, 173 mmol) in HMPA (100 mL) was heated in a 100-mL sealed tube at 110 °C for 24 h. The cooled reaction mixture was poured into water (500 mL) and filtered. The residue was taken into CH_2Cl_2, filtered, dried, and evaporated to afford a brown solid. Chromatography on silica gel, eluting with CH_2Cl_2/toluene (9:1), and recrystallization from ethanol afforded **6**: 1.8 g (15%); mp 144–144.5 °C; NMR ($CDCl_3$) δ 1.07 (3 H, t), 1.49 (3 H, t), 1.87 (2 H, m), 3.70 (2 H, t), 4.13 (3 H, s), 4.52 (2 H, q), 7.17 (1 H, s), 8.43 (1 H, s), 8.99 (1 H, s). Anal. ($C_{23}H_{18}F_7NO_6$) C, H, N.

Disodium 6-(Heptafluoropropyl)-4-oxo-10-propyl-4*H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylate (58). Diester **6** was hydrolyzed to **58** by the standard method: (67%); NMR (DMSO-d_6) δ 0.96 (3 H, t), 1.80 (2 H, m), 3.60 (2 H, m), 6.74 (1 H, s), 8.27 (1 H, s), 8.81 (1 H, m). Anal. ($C_{20}H_{10}F_7NNa_2O_6 \cdot 11\%$ H_2O) C, H, N.

Diethyl 6-Amino-4-oxo-10-propyl-4*H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylate (7). A solution of ethyl methyl 4,6-dioxo-10-propyl-4*H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylate (**2**) (11.55 g, 30 mmol) in dried CH_2Cl_2 (100 mL) was cooled to −78 °C and stirred during the dropwise addition of chlorosulfuryl isocyanate (6.0 g, 42.4 mmol). The reaction mixture was allowed to attain room temperature and stirred for 2.5 h, poured into ethanol, and left to evaporate in the fume cupboard overnight. The yellow solid was dissolved in ethanol saturated with HCl (250 mL) and heated under reflux for 2 h. The mixture was cooled, poured onto ice, basified with solid $NaHCO_3$, and extracted with $CHCl_3$ (three times). The combined organics were washed with water (three times), dried (Na_2SO_4), and evaporated to give **7** as an orange solid: 3.6 g (30%); mp 243–246 °C dec; NMR ($CDCl_3$) δ 1.13 (3 H, t), 2.52 (6 H, t), 1.80 (2 H, m), 3.71 (2 H, t), 4.46 (4 H, q), 5.24 (3 H, br s), 7.02 (1 H, s), 7.28 (1 H, s), 8.55 (1 H, s). Anal. ($C_{21}H_{22}N_2O_6$) C, H, N.

Diethyl 4-Oxo-10-propyl-6-pyrrol-1-yl-4*H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylate (8). A mixture of **7** (2 g, 5 mmol) and 2,5-dimethoxytetrahydrofuran (0.8 g, 6 mmol) in AcOH (40 mL) was heated under reflux for 45 min, cooled, and poured into water. The precipitated product was collected and recrystallized from ethanol to give **8**: 1.92 g (86%); NMR ($CDCl_3$) δ 1.06 (3 H, t), 1.46 (6 H, 2 t), 1.75 (2 H, m), 3.74 (2 H, m), 3.48 (4 H, 2 q), 6.63 (2 H, t), 7.13 (2 H, t), 7.23 (1 H, s), 8.06 (1 H, s), 8.85 (1 H, s). Anal. ($C_{25}H_{24}N_2O_6$) C, H, N.

Disodium 4-Oxo-6-pyrrol-1-yl-10-propyl-4*H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylate (55). The ester **8** was hydrolyzed by the standard manner to give **55**: 1.52 g (92%); NMR (DMSO-d_6) δ 0.96 (3 H, t), 1.78 (2 H, q), 3.57 (2 H, t), 6.44 (2 H, d), 6.63 (1 H, s), 7.28 (2 H, d), 7.75 (1 H, s), 8.47 (1 H, s). Anal. ($C_{21}H_{14}N_2Na_2O_6 \cdot 14.0\%$ H_2O) C, H, N.

Diethyl 4-Oxo-6-[[(phenylamino)carbonyl]amino]-10-propyl-4*H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylate (9). Phenyl chloroformate (2.9 mL, 22.8 mmol) was added over 5 min to a suspension of amine **7** (4.5 g, 11.3 mmol) in dry pyridine (50 mL). After the mixture was stirred overnight at room temperature, water (200 mL) was added to the solid collected. This was taken into CH_2Cl_2 (35 mL) when aniline (1.88 mL, 20.6 mmol) and triethylamine (2.9 mL, 20.8 mmol) were added. After the mixture was stirred overnight at room temperature, the precipitated solids were collected, washed, and recrystallized from MeOH/THF to give **9**: 2.0 g (34%); mp 234 °C; NMR (DMSO-d_6) δ 1.04 (3 H, t), 1.41 (6 H, 2 t), 1.83 (2 H, m), 4.07 (4 H, 2 q), 7.03 (1 H, s), 7.40 (5 H, m), 8.97 (2 H, 2 s), 9.60 (1 H, s), 9.73 (1 H, br s). Anal. ($C_{28}H_{27}N_3O_7$) C, H, N.

4-Oxo-6-[[(phenylamino)carbonyl]amino]-10-propyl-4*H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylic Acid (48). The diester **9** was converted to the diacid **48** by the standard method: 0.47 g (44%); mp 260 °C dec; NMR (DMSO-d_6) δ 0.98 (3 H, t), 1.80 (2 H, m), 3.55 (2 H, m), 6.98 (1 H, s), 7.37 (2 H, t), 7.60 (2 H, d), 7.70 (1 H, t), 8.97 (2 H, s), 9.00 (1 H, s), 9.60 (1 H, s), 9.73 (1 H, s). Anal. ($C_{24}H_{19}N_3O_7 \cdot 6\%H_2O$) C, H, N.

Diethyl 6-Formyl-4-oxo-10-propyl-4*H*-pyrano[3,2-*g*]-quinoline-2,8-dicarboxylate (11). A mixture of **10**[1] (19 g, 46.2 mmol), selenium dioxide (21 g, 191 mmol), and glacial AcOH (950 mL) was heated on a steam bath for 2 h. The resulting suspension was cooled, filtered, and poured into brine (8 L). The resulting precipitate was collected by filtration, taken into CH_2Cl_2, filtered, dried, and evaporated to dryness. Chromatography on silica gel, eluting with CH_2Cl_2/EtOAc (25:1), afforded **11**: 13.6 g (72%); mp 183–187 °C; NMR ($CDCl_3$) δ 1.00 (3 H, t), 1.50 (6 H, 2 t), 1.80 (2 H, m), 3.70 (2 H, t), 4.50 (4 H, 2 q), 7.15 (1 H, s), 8.55 (1 H, s), 9.75 (1 H, s), 10.60 (1 H, s). Anal. ($C_{22}H_{21}NO_7$) C, H, N.

Diethyl 6-(Difluoromethyl)-4-oxo-10-propyl-4*H*-pyrano-[3,2-*g*]quinoline-2,8-dicarboxylate (12). The aldehyde **11** (2 g, 4.9 mmol) in CH_2Cl_2 (20 mL) was added to a solution of (diethylamido)sulfur trifluoride (0.6 mL, 4.9 mmol) in CH_2Cl_2 at 25 °C. After 3 h further (diethylamido)sulfur trifluoride (0.06 mL, 0.5 mmol) was added and stirring continued for 2 h. The resulting mixture was poured cautiously into water and extracted with EtOAc, and the extract was dried and evaporated. Chromatography on silica gel, eluting with EtOAc/petrol (1:2), followed by dry column chromatography, eluting with toluene/EtOAc (1:9), gave **12**: 1.37 g (65%); NMR ($CDCl_3$) δ 1.07 (3 H, t), 1.49 (3 H, t), 1.52 (3 H, t), 2.87 (2 H, m), 3.69 (2 H, t), 4.22 (4 H, 2 q), 7.15 (1 H, s), 7.30 (1 H, t), 8.35 (1 H, s), 8.90 (1 H, s).

Disodium 6-(Difluoromethyl)-4-oxo-10-propyl-4*H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylate (45). Diester **12** was hydrolyzed by the standard method to give **45**: 1.14 g (80%); NMR (DMSO-d_6) δ 0.97 (3 H, t), 1.80 (2 H, m), 3.64 (2 H, m), 6.78 (1 H, s), 8.20 (1 H, t), 8.71 (1 H, s). Anal. ($C_{18}H_{11}F_2NNa_2O_6 \cdot 11.5\%$ H_2O) C, H, N.

Diethyl 4-Oxo-6-[[(phenylcarbonyl)hydrazono]-methyl]-10-propyl-4*H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylate (13). To a stirred solution of aldehyde **11** (1.5 g. 3.64 mmol) and tosic acid (1 mg) in benzene (50 mL) heated under reflux was added a hot solution of benzoylhydrazine (0.55 g, 4 mmol) in benzene (50 mL). The resulting suspension was allowed to cool and diester **13** collected and dried: 1.85 g (96%); mp >270 °C; NMR (DMSO-d_6) δ 0.90 (3 H, t), 1.40 (3 H, m), 1.70 (2 H, m), 3.45 (5 H, m), 4.40 (4 H, m), 6.85 (1 H, br s), 7.60 (3 H, m), 8.00 (2 H, m), 8.30 (1 H, br s), 8.60 (1 H, br s), 9.10 (1 H, br s). Anal. ($C_{29}H_{27}N_3O_7$) C, H, N.

Disodium 4-Oxo-6-[[(phenylcarbonyl)hydrazono]-methyl]-10-propyl-4*H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylate (47). Diester **13** was hydrolyzed by the standard method to give **47**: 1.3 g (78%); NMR (DMSO-d_6·D_2O) δ 0.96 (3 H, t), 1.80 (2 H, m), 3.70 (2 H, m), 6.80 (1 H, s), 7.60 (3 H, m), 8.05 (2 H, m), 8.35 (1 H, s), 9.20 (1 H, s), 9.33 (1 H, s). Anal. ($C_{25}H_{17}N_3Na_2O_7 \cdot 13\%$ H_2O) C, H, N.

2,8-Bis(ethoxycarbonyl)-4-oxo-10-propyl-4*H*-pyrano[3,2-*g*]quinoline-6-carboxylic Acid (14). Jones reagent (chromium trioxide (26.7 g) in concentrated H_2SO_4 diluted to 100 mL with

water) was added dropwise to a stirred suspension of crude aldehyde **11** (6 g, ~10 mmol) in AR acetone (350 mL). After 10 mL had been added, the mixture was poured into water (1.5 L) and the precipitated solid taken into $CHCl_3$, washed, dried, and evaporated. Recrystallization from 2-propanol gave **14**: 2 g (47%); mp 249–252 °C dec; NMR (DMSO-d_6) δ 1.00 (3 H, t), 1.40 (6 H, 2 t), 1.80 (2 H, m), 3.50 (2 H, t), 4.40 (4 H, 2 q), 6.95 (1 H, s), 8.40 (1 H, s), 9.30 (1 H, s). Anal. ($C_{22}H_{21}NO_8$) C, H, N.

Trisodium 4-Oxo-10-propyl-4*H*-pyrano[3,2-*g*]quinoline-2,6,8-tricarboxylate (35). Diester **14** was hydrolyzed by the standard manner (3 equiv of NaOH) to give **35**: (33%); NMR (DMSO-d_6) δ 1.00 (3 H, t), 2.80 (2 H, m), 3.60 (2 H, m), 6.60 (1 H, s), 7.80 (1 H, s), 9.20 (1 H, s). Anal. ($C_{18}H_{10}NNa_3O_8 \cdot 24.0\%$ H_2O) C, H, N.

Diethyl 6-Cyano-4-oxo-10-propyl-4*H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylate (15). Crude aldehyde **11** (6.3 g, ~10 mmol) was dissolved in formic acid (40 mL, 99%), treated with sodium formate (1.12 g, 16.5 mmol) and hydroxylamine hydrochloride (11 g, 158 mmol), and heated on a steam bath with stirring for 6 h. Further hydroxylamine hydrochloride (0.38 g, 5.5 mmol) and sodium formate (0.56 g, 8.2 mmol) were added, and heating was continued for 3 h. The reaction mixture was cooled and poured into water, and the precipitated product was recrystallized from ethanol to give **15**: 1.15 g (28%); mp 207–209 °C; NMR ($CDCl_3$) δ 1.00 (3 H, t), 1.50 (6 H, 2 t), 1.90 (2 H, m), 3.70 (2 H, t), 4.50 (4 H, 2 q), 7.10 (1 H, s), 8.40 (1 H, s), 9.00 (1 H, s).

Disodium 6-Cyano-4-oxo-10-propyl-4*H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylate (51). Diester **15** was hydrolyzed by the standard method to give **51**: 0.4 g (38%); NMR (D_2O) δ 0.90 (3 H, t), 1.80 (2 H, m), 3.50 (2 H, t), 6.90 (1 H, s), 8.40 (2 H, s). Anal. ($C_{18}H_{10}N_2Na_2O_6 \cdot 17.0\%$ H_2O) C, H, N.

Diethyl 6-(1,3-Dioxan-2-yl)-4-oxo-10-propyl-4*H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylate (16). A mixture of aldehyde **11** (3 g, 7.3 mmol), 1,3-propanediol (0.58 mL, 80 mmol), and tosic acid (10 mg) in benzene (50 mL) was heated under reflux for 8 h. The solvent was evaporated and the residue was recrystallized from ethanol to give **16**: 2.59 g (76%); mp 170–172 °C; NMR ($CDCl_3$) δ 1.03 (3 H, t), 1.57 (3 H, t), 1.58 (3 H, t), 1.80 (3 H, m), 2.40 (1 H, m), 3.68 (2 H, t), 4.30 (4 H, m), 4.50 (4 H, 2 q), 6.21 (1 H, s), 7.14 (1 H, s), 8.40 (1 H, s), 9.00 (1 H, s). Anal. ($C_{25}H_{27}NO_8$) C, H, N.

Disodium 6-(1,3-Dioxan-2-yl)-4-oxo-10-propyl-4*H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylate (40). Diester **16** was hydrolyzed by the usual method to afford **40**: 1.90 g (66%); NMR (DMSO-d_6) δ 0.90 (3 H, t), 1.90 (4 H, m), 3.60 (2 H, t), 4.20 (4 H, m), 6.21 (1 H, s), 6.71 (1 H, s), 8.05 (1 H, s), 8.82 (1 H, s). Anal. ($C_{21}H_{17}NNa_2O_8 \cdot 16\%$ H_2O) C, H, N.

Disodium 6-Formyl-4-oxo-10-propyl-4*H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylate (41). Diester **16** was hydrolyzed by the standard method to give the corresponding diacid **17**. Cleavage of the dioxane ring with concentrated HCl/AcOH at room temperature overnight, followed by reaction with $NaHCO_3$, gave **14**: 0.29 g (13%); NMR (DMSO-d_6) δ 0.97 (3 H, t), 1.80 (2 H, m), 3.65 (2 H, m), 6.76 (1 H, s), 8.50 (1 H, s), 9.60 (1 H, s), 10.50 (1 H, s). Anal. ($C_{18}H_{11}NNa_2O_7 \cdot 24\%$ H_2O) C, H, N.

Diethyl 4-Oxo-6-(*trans*-2-phenylethenyl)-10-propyl-4*H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylate (18). A mixture of diester **10**[1] (1 g, 2.58 mmol), benzaldehyde (0.32 mL, 3.1 mmol), and tosic acid (5 mg) in AcOH was heated under reflux for 24 h. Further benzaldehyde (0.3 mL, 2.9 mmol) was added and heating continued for 3 h. The solution was allowed to evaporate to about half-volume when further AcOH (25 mL) was added and heating continued for 24 h. After removal of volatiles, the residue was taken into EtOAc, washed with water and brine, dried, and evaporated. Chromatography on silica gel, eluting with CH_2Cl_2/EtOAc mixtures, gave **18**: 0.28 g (22%); mp 153–156 °C; NMR ($CDCl_3$) δ 1.05 (3 H, t), 1.47 (3 H, t), 1.51 (3 H, t), 1.85 (2 H, m), 3.68 (2 H, t), 4.50 (4 H, 2 q), 7.15 (1 H, s), 7.80 (6 H, m), 7.98 (1 H, d), 8.38 (1 H, s), 9.05 (1 H, s).

Disodium 4-Oxo-6-(*trans*-2-phenylethenyl)-10-propyl-4*H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylate (59). Diester **18** was hydrolyzed in the standard manner to give **59**: 0.22 g (70%); NMR (DMSO-d_6) δ 0.95 (3 H, t), 1.80 (2 H, m), 3.60 (2 H, t), 7.80 (7 H, m), 8.16 (1 H, s), 8.88 (1 H, s). Anal. ($C_{25}H_{17}NNa_2O_6 \cdot 15\%$ H_2O) C, H, N.

6-Amino-4-oxo-10-propyl-4*H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylic Acid (20). Sulfonamide **19** (5 g, 9.2 mmol) in concentrated H_2SO_4 (7.5 mL) was heated at 85 °C for 2 h with stirring. The cooled reaction mixture was poured into water (100 mL) and the suspension heated under reflux for 2 h. The reaction mixture was cooled by the addition of ice, and 0.880 ammonia (16 mL) was added to give a clear solution. After filtration, concentrated HCl (20 mL) was added and the precipitate collected, washed with water, and dried to give **20** as crude product: (100%); NMR (DMSO-d_6) δ 1.00 (3 H, t), 1.75 (2 H, m), 3.45 (2 H, t), 6.90 (1 H, s), 7.30 (1 H, s), 9.10 (1 H, s).

6-(Acetylamino)-4-oxo-10-propyl-4*H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylic Acid (21). The diacid **20** (2.8 g, 8.1 mmol) in acetic anhydride (28 mL) was heated with stirring at 120 °C for 1.5 h. The cooled suspension was poured into water (300 mL) and stirred for 1 h, when the precipitate was collected, washed, and dried. The product was purified by reverse-phase HPLC (Waters Prep) to give **21**: 1.5 g (48%); mp 264–265 °C dec; NMR (DMSO-d_6) δ 1.05 (3 H, t), 1.80 (2 H, m), 2.35 (3 H, s), 3.60 (2 H, t), 7.00 (1 H, s), 8.85 (1 H, s), 9.20 (1 H, s), 10.80 (1 H, s). Anal. ($C_{19}H_{16}N_2O_7 \cdot 1\%$ H_2O) C, H, N.

Disodium 6-(Acetylamino)-4-oxo-10-propyl-4*H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylate (38). Diacid **21** was converted to **38** by the standard method: 1.33 g (79%); NMR (DMSO-d_6) δ 1.00 (3 H, t), 1.75 (2 H, m), 2.30 (1 H, s), 3.45 (2 H, t), 6.70 (1 H, s), 8.40 (1 H, s), 8.95 (1 H, s), 11.65 (1 H, s). Anal. ($C_{19}H_{14}N_2Na_2O_7 \cdot 15\%$ H_2O) C, H, N.

***N*,*N*-Dimethyl-6-acetyl-4-(dimethylamino)-7-hydroxy-8-propylquinoline-2-carboxamide (23).** Chloroquinoline **22**[1] (10 g, 31.1 mmol) was heated with a 30% ethanolic solution of dimethylamine (60 mL) in a sealed tube at 100 °C for 30 h. After removal of volatiles, the product was crystallized from 2-propanol to give **23**: 5.54 g (52%); mp 182–186 °C; NMR ($CDCl_3$) δ 0.97 (3 H, t), 1.75 (2 H, m), 2.03 (6 H, s), 2.74 (3 H, s), 3.22 (6 H, s), 3.64 (2 H, m), 6.98 (1 H, s), 8.48 (1 H, s), 11.90 (1 H, s).

Ethyl 6-Acetyl-4-(dimethylamino)-7-hydroxy-8-propylquinoline-2-carboxylate (24). Amide **23** (5 g, 14.6 mmol) was heated under reflux in ethanol (100 mL) and concentrated HCl (30 mL) for 24 h. Ethanolic HCl was added while the solvent was distilled for 1 h, when volatiles were removed in vacuo. The residue was cooled to 0 °C and treated with 0.880 ammonia to pH 6. Water was added and the mixture extracted with $CHCl_3$, washed, dried, and evaporated. Chromatography on silica gel, eluting with $CHCl_3$, gave **24**: 1.14 g (23%); NMR ($CDCl_3$) δ 0.96 (3 H, t), 1.44 (3 H, t), 1.73 (2 H, m), 2.71 (3 H, s), 3.23 (6 H, s), 3.47 (2 H, m), 4.44 (2 H, q), 7.01 (1 H, s), 8.85 (1 H, s).

Diethyl 6-(Dimethylamino)-4-oxo-10-propyl-4*H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylate (25). A solution of ester **24** (1.1 g, 3.19 mmol) in dry ethanol (20 mL) was added to sodium ethoxide, from Na (0.37 g, 16 mmol) in ethanol (50 mL). Diethyl oxalate (2.2 mL, 16 mmol) was added and the mixture heated under reflux for 2 h. After concentration in vacuo, water was added and the mixture neutralized with dilute HCl, extracted with ether, washed, dried, and evaporated. The residue was taken into ethanolic HCl and heated under reflux for 1 h. The solvent was removed and the residue slurried with aqueous ammonia. The product was collected and recrystallized from ethanol to give **25**: 0.85 g (62%); NMR ($CDCl_3$) δ 0.97 (3 H, t), 1.46 (6 H, 2 t), 1.75 (2 H, m), 3.22 (6 H, s), 3.52 (2 H, m), 4.47 (4 H, 2 q), 7.05 (1 H, s), 7.44 (1 H, s), 8.85 (1 H, s).

Disodium 6-(Dimethylamino)-4-oxo-10-propyl-4*H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylate (37). Diester **25** was hydrolyzed by the standard method to give **37**: 0.64 g (78%); NMR (DMSO-d_6) δ 0.94 (3 H, t), 1.75 (2 H, m), 3.03 (6 H, s), 3.65 (2 H, m), 6.69 (1 H, s), 7.32 (1 H, s), 8.65 (1 H, s). Anal. ($C_{19}H_{16}N_2Na_2O_6 \cdot 12\%$ H_2O) C, H, N.

3-Amino-4,6-bis[1-(pentylimino)ethyl]-2-propylphenol (27). A mixture of diacetyl compound **26**[7] (10 g, 42.5 mmol), pentylamine (20 mL, 172 mmol), and tosic acid (100 mg) in toluene was heated under reflux for 72 h. After cooling, the reaction mixture was washed quickly with dilute $NaHCO_3$ solution, separated, dried, and evaporated. The residue was recrystallized from EtOAc to give **27**: 7.78 g (49%). The compound was unstable.

Ethyl 6-Acetyl-7-hydroxy-4-(pentylamino)-8-propylquinoline-2-carboxylate (28). A solution of lithium diisopropylamide (2 mmol) in dry THF (10 mL) was added with

stirring to a solution of the bisketimine **27** (0.38 g, 1 mmol) in dry THF (10 mL) at −78 °C under nitrogen. Diethyl oxalate (0.15 mL, 1.1 mmol) was added and the mixture allowed to warm to room temperature. The reaction mixture was added to ethanol (50 mL) and concentrated HCl (5 mL), the mixture was stirred for a further 4 h, and volatiles were removed in vacuo. The product was extracted into $CHCl_3$, washed with water, dried, and evaporated. The residue was chromatographed on silica gel, eluting with petrol/EtOAc (1:1) and recrystallized to give **28**: 0.3 g (78%); mp 159–163 °C; NMR ($CDCl_3$) δ 0.97 (6 H, 2 t), 1.44 (3 H, t), 1.73 (8 H, m), 2.74 (3 H, s), 3.33 (4 H, m), 4.47 (2 H, q), 5.35 (1 H, br s), 7.03 (1 H, s), 8.17 (1 H, s).

Diethyl 4-Oxo-6-(pentylamino)-10-propyl-4*H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylate (29). A solution of sodium ethoxide, from sodium (0.1 g, 4.3 mmol) in ethanol (10 mL), was added to a mixture of ester **28** (0.95 g, 2.46 mmol) and diethyl oxalate (0.6 mL, 4.4 mmol) in dry ethanol (10 mL). The reaction mixture was heated under reflux for 10 min, cooled, and acidified with ethanolic HCl. After further heating for 2 h and evaporation of volatiles, the product was taken into CH_2Cl_2, washed with dilute aqueous ammonia, dried, and evaporated. Recrystallization from ethanol gave **29**: 0.67 g (58%); NMR ($CDCl_3$) δ 1.03 (6 H, 2 t), 1.50 (6 H, 2 t), 1.75 (8 H, m), 3.50 (4 H, m), 4.47 (4 H, 2 q), 7.03 (1 H, s), 7.13 (1 H, s), 8.68 (1 H, s).

Disodium 4-Oxo-6-(pentylamino)-10-propyl-4*H*-pyrano[3,2-*g*]quinoline-2,8-dicarboxylate (34). Diester **29** was hydrolyzed in the standard manner to give **34**: NMR (DMSO-d_6) δ 0.89 (6 H, t), 1.40 (4 H, m), 1.75 (4 H, m), 3.45 (4 H, m), 6.60 (1 H, s), 6.86 (1 H, s), 8.85 (1 H, s). Anal. ($C_{22}H_{22}N_2Na_2O_6 \cdot 13\%$ H_2O) C, H, N.

Acknowledgment. We thank P. A. Cage, D. Cox, I. D. Dicker, H. A. Dowlatshahi, S. King, I. Sharma, J. Shipman, and R. G. McR Wright for assistance with chemical synthesis and S. T. Harper for biochemical support.

Registry No. **2**, 69049-59-8; **3**, 99370-25-9; **4**, 99370-26-0; **5**, 114184-12-2; **6**, 99370-27-1; **7**, 75453-75-7; **8**, 114184-13-3; **9**, 114184-14-4; **10**, 75452-74-3; **11**, 114184-15-5; **12**, 99370-84-0; **13**, 114184-16-6; **14**, 114184-17-7; **15**, 99370-45-3; **16**, 114184-18-8; **17**, 114184-19-9; **18**, 114184-20-2; **19**, 86694-89-5; **20**, 114184-21-3; **21**, 114184-22-4; **22**, 75452-57-2; **23**, 114184-23-5; **24**, 75453-51-9; **25**, 75453-52-0; **26**, 79324-47-3; **27**, 114184-24-6; **28**, 114184-25-7; **29**, 114184-26-8; **30**, 75453-49-5; **31**, 98331-60-3; **32**, 75452-62-9; **33**, 75453-37-1; **34**, 114184-27-9; **35**, 114184-28-0; **36**, 98331-59-0; **37**, 75453-53-1; **38**, 114184-29-1; **39**, 75453-25-7; **40**, 114184-30-4; **41**, 114184-31-5; **42**, 75452-76-5; **43**, 75453-70-2; **44**, 98331-58-9; **45**, 99369-73-0; **46**, 75453-59-7; **47**, 114184-32-6; **48**, 114184-33-7; **49**, 75452-70-9; **50**, 75452-50-5; **51**, 99369-81-0; **52**, 75452-65-2; **53**, 114184-34-8; **54**, 114184-35-9; **55**, 114184-36-0; **56**, 99369-72-9; **57**, 75453-28-0; **58**, 99369-71-8; **59**, 114184-37-1; **60**, 75453-62-2; 2,5-dimethoxytetrahydrofuran, 696-59-3.

4-Hydroxy-3-quinolinecarboxamides with Antiarthritic and Analgesic Activities

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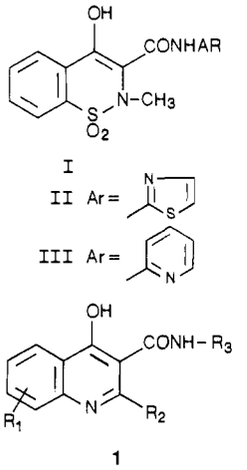
A series of 4-hydroxy-3-quinolinecarboxamides has been synthesized and evaluated by the oral route as antiinflammatory agents in carrageenin-induced foot edema and adjuvant-induced arthritis and as analgesic agents in the acetic acid induced writhing test. Among the most active molecules, some have shown both analgesic and acute antiinflammatory activities. Others, such as compounds **24**, **37**, and **52**, were only powerful peripherally acting analgesics. Compound **52**, being active at 1 mg/kg (ED_{50}), is the most potent compound in the series. Some analogues, substituted in the 2-position by an alcohol, ester, or amine function, displayed potent antiarthritic activity in the same range as that of piroxicam and were also active in acute tests of inflammation and nociception. They inhibited the activity of both cyclooxygenase and 5-lipoxygenase at micromolar concentrations. Compound **102** (RU 43526) showed potent antiarthritic activity (adjuvant-induced arthritis, ED_{50} = 0.7 mg/kg, po) and gastrointestinal tolerance (ED_{100} > 250 mg/kg, po) and thus it is presently undergoing an extensive pharmacological evaluation.

Since the discovery of indomethacin and ibuprofen in the 1960s, extensive research has been undertaken in many laboratories in order to find new highly potent nonsteroidal antiinflammatory agents with weak side effects. Although most of these compounds give only palliative treatment of arthritis, numerous papers still deal with the synthesis and evaluation of the antiinflammatory and analgesic activities of new leads (for reviews, see ref 1–3). At the beginning of the last decade a wide-ranging program was initiated in our company, the objective of which was to develop new nonsteroidal antiinflammatory compounds that are well tolerated at the gastrointestinal level. First of all, we carried out work in the field of arylacetic acids[4] but soon turned our attention to the work of Lombardino et al.,[5] which led to the discovery of the new class of oxicams (I) of which sudoxicam (II) and piroxicam (III) are the prototypes.[6]

For a long time our research group had been interested in quinoline chemistry[7] and this situation prompted us to study 4-hydroxy-3-quinolinecarboxamides 1, which could



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actually be regarded as possible bioisosteres of oxicams I. Furthermore, the antiarthritic potency of the antimalarial

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(1) For a review and references, see: Lombardino, J. G. *Annual Reports in Medicinal Chemistry*; Hess, H. J., Ed.; Academic: New York, 1981; p 189.

0022-2623/88/1831-1453$01.50/0