g (65.4 mmol) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribose] in dry acetonitrile (350 mL). The solution was stirred for 3 days at room temperature. The solvent was evaporated and the residue was dissolved in a minimum amount of $CHCl_3$ and chromatographed on a silica gel column [eluent, acetone–$CHCl_3$ (1:9)]. The fractions containing the glycosylation product were pooled, evaporated to dryness, and treated with MeOH (400 mL), presaturated with NH_3 at 0 °C. The solution was stored in a pressure bottle for 1 week at room temperature. The solvent was evaporated and the residue was triturated with $CHCl_3$. The flocculent precipitate was collected by filtration and reprecipitated from a MeOH solution with Et_2O. The precipitate was crystallized from acetone to give 11.4 g (52%) of **17** as needles: mp 120–122 °C; $[\alpha]^{25}_D$ +24.1° (*c* 1.0, DMF); UV λ_{max}^{pH1} 234 and 315 nm (ϵ 13 500 and 4700), λ_{max}^{pH11} 237 and 315 nm (ϵ 13 200 and 4700). Anal. ($C_{18}H_{20}N_2O_7$) C, H, N.

5-Acetamido-1-(β-D-ribofuranosyl)pyridin-2-one (18). 5-Acetamido-2-methoxypyridine (**7**, 5.0 g, 30 mmol) was added to a solution of **1** [prepared from 15 g (30 mmol) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribose] in dry acetonitrile (65 mL). The solution was stirred for 3 days at room temperature. The insoluble pyridinium salt was removed by filtration. The filtrate was then diluted with $CHCl_3$ (350 mL) and washed with water (3 × 200 mL). The $CHCl_3$ solution was evaporated to dryness and the residue freed from water by coevaporation with absolute EtOH. The syrupy residue was dissolved in a minimum amount of $CHCl_3$ and chromatographed on a silica gel column [eluent, MeOH–$CHCl_3$ (1:19)]. The fractions containing the glycosidation products, **18** tribenzoate, were pooled, evaporated to dryness, and treated with MeOH (300 mL), presaturated with NH_3 at 0 °C. The solution was stored in a pressure bottle for 1 week at room temperature. The solvent was evaporated and the residue was dissolved in water (200 mL), washed with chloroform (3 × 240 mL), and evaporated. The syrupy residue was crystallized and recrystallized from MeOH–$CHCl_3$ to give 5.20 g (61%) of **18** as needles: mp 179–181 °C; the ^1H NMR spectrum of this crystalline sample showed the presence of 0.75 mol of water/mol; $[\alpha]^{25}_D$ −5.6° (*c* 1.0, DMF); UV λ_{max}^{pH1} 248 and 314 nm (ϵ 9100 and 4300), λ_{max}^{pH11} 248 and 314 nm (ϵ 9100 and 4300). Anal. ($C_{12}H_{16}N_2O_6 \cdot 0.75\ H_2O$) C, H, N.

3-Bromo-1-(β-D-ribofuranosyl)pyridin-2-one-5-carboxylic Acid (19). Compound **12** (0.43 g, 1.6 mmol) was treated with 20 mL of bromine water (bromine in water was saturated at room temperature). The reaction mixture was kept 45 min at room temperature. Presence of an excess bromine was indicated by the persistent yellow color of the solution. Bromine and water were evaporated in vacuo. During evaporation of the solvent much of the product began to crystallize out. The product was recrystallized from water. This gave 0.40 g (71%) of **20** as needles: mp 219–220 °C; $[\alpha]^{25}_D$ +42.6° (*c* 1.0, *N,N*-dimethylformamide); λ_{max}^{pH11} 214, 265, and 307 nm (ϵ 18 600, 11 450, and 7300); λ_{max}^{pH7} 212, 257, and 213 nm (ϵ 18 050, 8850, and 7350); λ_{max}^{pH1} 257 and 213 nm (ϵ 8850 and 7350). Anal. ($C_{11}H_{12}NO_7Br$) C, H, N.

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Potential Antitumor Agents. 27. Quantitative Structure–Antileukemic (L1210) Activity Relationships for the ω-[4-(9-Acridinylamino)phenyl]alkanoic Acids

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Simple carboxylic acid derivatives of 9-anilinoacridine (e.g., **1**, R = –COOH) provide high experimental antileukemic (L1210) activity. The homologous 1′-$(CH_2)_n$COOH congeners also prove active, and there is a parabolic interrelationship between maximum increase in life span in L1210 tests and R_m values used as a measure of agent lipophilic–hydrophilic balance. The corresponding carboxamides [1′-$(CH_2)_n$$CONH_2$] provide a similar parabolic relationship, which has an optimum R_m value displaced from that of the acids. Earlier examined 1′-$NHSO_2(CH_2)_nCH_3$ variants, the 3-$NHCOCH_3$ congeners of these, and the carboxamide [1′-$(CH_2)_n$$CONH_2$] and sulfonamide [1′-$(CH_2)_n$$SO_2NH_2$] homologues can be treated as one group and a correlation equation derived that is identical with that for the carboxamide variants alone. The optimum R_m value for this group is displaced from that of the acids by the equivalent of 1.8 log *P* units on the octanol–water scale. In this drug series a carboxylic acid residue acts as an acceptable hydrophilic unit, providing a log *P* contribution intermediate between that of the un-ionized acid and the totally ionized carboxylate anion. Quantitative effects of acridine ring substituents on L1210 activity differ in analogues containing either carboxylic acid or alkanesulfonanilide side chains, supporting the view that different site-binding orientations may be involved with these two drug classes.

Earlier the high experimental antileukemic (L1210) activity of some simple carboxylic acid derivatives of 9-anilinoacridine was described.[1] Carboxylate residues were only acceptable when attached at the 1′ position (e.g.,

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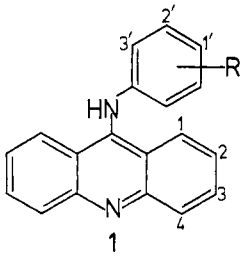
1, R = -COOH), isomerically substituted compounds proving inactive. To find if, as suggested by this screening



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data, there is positional dependence on carboxylate residue attachment, a more detailed examination has been undertaken. Findings in this area, and certain quantitative structure–activity relationships for this class of agent, are presented.

Chemistry. Agent generation involved mild acid-catalyzed coupling of the requisite 9-chloroacridine with an aromatic amine component bearing the required functionality.[1] Aromatic amino acids were prepared by catalytic reduction (Pd/C, H_2) of the corresponding nitro compounds, in turn prepared by direct nitration of the ω-phenylalkanoic acids. Of the latter which were not available commercially, 6-phenylhexanoic acid was prepared by chromic acid oxidation of 1-phenylcyclohexanol[2] and Wolff–Kishner reduction of the resulting 5-benzoylpentanoic acid. Higher alkanoic acids were prepared by the six-carbon homologation method of Fieser.[3] Reaction of benzoyl chloride or ω-phenylalkanoyl chlorides with 1-morpholino-1-cyclohexene provided the corresponding 2-acrylcyclohexanones which were readily alkali cleaved to the ω-phenyl-7-oxoalkanoic acids. Carbonyl group reduction in the latter, by the Wolff–Kishner method, provided necessary ω-phenyalkanoic acids.

Results and Discussion

The bulk of the investigations of substituent effects, on experimental antitumor activity in the 9-anilinoacridine series, has employed drug congeners bearing 1′-$NHSO_2CH_3$ substituents.[4-6] Attempted multiple regression analyses of substituent effects in these analogues have, thus far, been only partially successful but suggest that added ring functions may modulate biologic activity by altering acridine pK_a, ring electron densities, overall $\Sigma\pi$ values, and rates of thiolytic cleavage, as well as site steric and hydrophobic interactions.[4-6] Additionally, marked divergencies in the effects of added acridine ring substituents on biologic activity, in the two subseries bearing either a 1′-$NHSO_2CH_3$ or a 1′-COOH function, have been demonstrated. As a class the 9-anilinoacridines appear to be DNA-intercalating agents,[7] and consideration of drug binding to such a site suggests that relative two-dimensional orientation of the planar intercalating chromophore, within the flanking purine–pyrimidine base pairs, may alter, depending on the site interactions of the substituents employed.[1]

To unequivocally demonstrate the quantitative relationship between overall molecular lipophilic–hydrophilic balance and biologic activity, it earlier proved necessary to prepare and screen the homologous series of 1′-alkanesulfonanilides.[4] As an extension of this strategy the homologous alkanoic acids **2–11** provide a series of agents having a range of lipophilic character without the complications attendant on the use of varying acridine ring substituents. As before[8] R_m values for agent cations, from reversed phase partition chromatography, have been employed as a measure of lipophilic–hydrophilic balance. R_m values and partition coefficients (P) in isobutyl alcohol, for a series of 9-anilinoacridine congeners, provided the following correlation.[8]

$$\log P_{i\text{-BuOH}} = 1.99\ (\pm 0.19)\ R_m + 0.75\ (\pm 0.036)$$
$$n = 32,\ r = 0.964,\ s = 0.095$$

A correlation linking partition coefficients in the isobutyl alcohol–water and 1-octanol–water system has been earlier described.[9] From multiple determinations the standard deviations for R_m values lie within the limits ±0.03.

To ensure that R_m values of agent cations were measured, acidic solvent systems (0.05 M in CH_3SO_3H) have been employed[8] and in such acid media ionization of carboxylic acid residues should be effectively repressed. As carboxylate ions may influence partition-dependent processes, in movement of agents to ultimate site, the optimum R_m value for the anionic variants may be considerably displaced from that observed for purely cationic congeners. Direct comparison of the biologic activities of the methanesulfonanilide and carboxylate variants, in terms of their measured R_m values, would be unwarranted.

From earlier experiences in correlation of antitumor test data,[10] a modified screening evaluation method has been employed. An LD_{10} dose, for the administration schedule employed (ip, qd 1–5), has been derived, employing doses separated by 0.05 log dose units and an acceptably soluble drug formulation.[4] Deaths occurring before day 8, of tumored animals (10^5 L1210 cells ip), have been taken as resulting from drug toxicity. This time period for evaluation of toxicity is shorter than that considered most desirable[11] but permits a very large volume of existent screening data to be utilized and is pertinent to tumor-bearing animals. From the linear regression relating percent probit mortality and the logarithms of the corresponding doses, an LD_{10} value is derived. Dose profiles of antileukemic activity have been obtained employing doses separated by 0.09 log dose units. For significance an L1210 test, at a particular dose level, should provide an increase in life span (ILS = T/C% - 100) greater than 25%. For acceptance of life extensions in the range 20–25%, multiple confirmatory tests at the particular dose level are required. Significant ILS values, obtained at and below the LD_{10} dose, have been linearly correlated with the logarithms of the corresponding doses (Figure 1). In all cases so far examined the correlation coefficients for such linear regressions have been greater than 0.83. The program employed[12] provides a curved 95% confidence band (Figure 1) reflecting the lower weighting afforded the more dispersed data points at both high and low doses. The increase in life span (ILS_{max}) specified by the life extension – log dose regression line at the measured LD_{10} provides a representative measure of antitumor effectiveness at a standard host load in toxicity. This data manipulation method embraces the totality of the screening data and avoids acceptance of an unrealistic maximum increase in life span, which can sometimes be obtained by successfully employing a dose greater than the LD_{10} or other chance event. As necessary, to meet the above criteria, additional animal test data for previously described compounds have been obtained. Evaluation of screening data in this fashion affords both LD_{10} values and ILS_{max} figures which sometimes differ quite appreciably from the optimum doses and "best ever" ILS values obtained directly from screening assays.

Lacking an effective treatment of the confidence limits for ILS_{max} values, we have been guided by the 95% confidence limits about the LD_{10} and ILS – log dose correlations (Figure 1). The extreme values possible on this basis are not equispaced about the ILS_{max}; for the

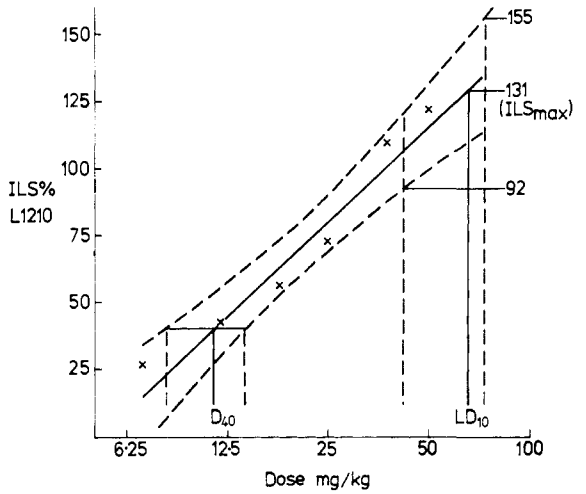

Figure 1. Evaluation of L1210 screening data. Employing groups of six mice per dose level, significant percentage increases in life span (×) (ILS% = T/C% - 100) in L1210 assays, obtained at a series of logarithmically spaced doses below the LD_{10}, were linearly correlated with the logarithms of the corresponding doses. ILS_{max} is provided by the resulting regression line at the LD_{10} dose. Fiducial limits from the correlation equation and for the LD_{10} dose are provided as broken lines. The dose necessary to provide 40% ILS (D_{40}) and associated fiducial limits are readily derived from such diagrams. The screening data employed are that for compound **41**; see Table I.

example of Figure 1 ILS_{max} = 131 (92–155). When converted to logarithms, as in all regression analyses performed, the resulting log ILS_{max} figures are more centrally located between the range figures; from Figure 1, log ILS_{max} = 2.12 (1.96–2.19; ca. ±0.065). Our as yet only moderate experience, with this method of data analysis, suggests that log ILS_{max} values should be reproducible within ±0.1. Extensive replication of such data (Figure 1) is precluded by the large animal numbers required; the strictly limited replicate analyses performed have provided log ILS_{max} values lying comfortably within ±0.1 of the initially observed figures.

The ILS_{max} values for the homologous alkanoic acids **3–11** demonstrate a typical Hanschian type parabolic relationship with R_m values. Data for the first member of the series, the benzoic acid **2**, were not included when deriving this equation. This first variant is considerably more active than expected on the basis of eq 1 (Table I).

$$\log ILS_{max} = -7.50\ (\pm 1.94)\ R_m^2 + 8.86\ (\pm 2.22)\ R_m - 0.28 \quad (1)$$

$$n = 9,\ r = 0.96,\ s = 0.27,\ F_{2,6} = 32.4,\ p < 0.001,\ \text{optimum } R_m \text{ value } 0.59$$

It is questionable if the first aromatic acid **2** should be considered as homologous with the phenylalkanoic acids **3–11**. As evidenced by the linear relationship between acridine pK_a and σ_p values for the 1′-substituent,[1] the electronic contribution by a 1′-COOH (pK_a = 7.17)[1] is appreciably different from those of the remaining 1′-$(CH_2)_nCOOH$ variants (pK_a = 7.92–8.12). Additionally, carboxylic acid pK_a values can be expected to vary, from aromatic to aralkyl members, as will the steric environment about the acid residue.

Consideration of a linear equation in R_m, for the same series of compounds (eq 2), demonstrates the essential need

$$\log ILS_{max} = 0.40\ (\pm 1.09)\ R_m + 1.73 \quad (2)$$

$$n = 9,\ r = 0.27,\ s = 0.33,\ F_{1,7} = 0.54,\ p > 0.2$$

for the R_m^2 term in eq 1.

The additive-constitutive nature of measures of agent lipophilic-hydrophilic balance[13] dictates that there will be some degree of covariance between the number (N) of carbon bonds linking the carboxylate function to the 1′ position and the R_m values. In fact, a less well fit equation results if N is employed in place of R_m (eq 3). However,

$$\log ILS_{max} = -0.034\ (\pm 0.031)\ N^2 + 0.33\ (\pm 0.32)\ N + 1.39 \quad (3)$$

$$n = 9,\ r = 0.66,\ s = 0.27,\ F_{2,6} = 2.3,\ p < 0.2$$

N is a relatively crude locant for the carboxylate function and the lower correlation coefficient seen in eq 2, in relation to that of eq 1, cannot be immediately employed to discard the possibility that carboxylate placement is important for biologic activity.

If it was hypothesized that lipophilic-hydrophilic balance is the biologically important variable, as already demonstrated in the alkanesulfonanilide series,[4] a possible reason for the very low activity of the 1′-CH_2COOH variant **3** would be the more hydrophilic nature of this compound, as shown by R_m values, in relation to those of the neighboring 1′-COOH (**2**) and 1′-$(CH_2)_2COOH$ (**4**) analogues. It has already been pointed out that there is a discontinuity in log P progression, with phenylacetic acid proving more hydrophilic than both benzoic and 3-phenylpropionic acids.[14] Acceptable increase of the lipophilic nature of the 1′-CH_2COOH analogue **3**, on this basis, should then increase activity. From model fitting to a putative DNA-intercalation site,[4,7] 4-substituents of a 9-anilinoacridine should, in most envisaged binding orientations, protrude from the DNA stack on the opposite side to that occupied by the 9-anilino function and should therefore be relatively free from steric influences of the site. By increasing the lipophilic nature of the 1′-CH_2COOH analogue with added 4-CH_3 and 4-C_2H_5 groups, to provide **12** and **13**, more active compounds were obtained, and the antileukemic activities of these were reasonably predicted from their respective R_m values and eq 1 (Table I). That the main role of the 4-alkyl groups employed, in these derivatives, is adjustment of lipophilic character is supported by the reasonably predicted antileukemic activity of the corresponding derivatives (**14** and **15**) of the initially more active propionate analogue **4**. To the same hypothesis the phenoxyacetic acid **17** might also be inactive because of the excessive hydrophilic nature. Increasing lipophilic nature, by extension of the alkoxy chain in such analogues, did provide active agents, and the efficacy of the single compound where the LD_{10} dose could be reached (**19**) was reasonably predicted.

In compounds **12–15** the covariance between N and R_m values has been attenuated, and inclusion of data for these further compounds into eq 1 and 3, furnishing eq 4 and 5, provides a greater separation of the influence of N and

$$\log ILS_{max} = -6.61\ (\pm 1.87)\ R_m^2 + 7.75\ (\pm 2.15)\ R_m + 0.02 \quad (4)$$

$$n = 13,\ r = 0.92,\ s = 0.12,\ F_{2,10} = 28.8,\ p < 0.001,\ \text{optimum } R_m \text{ value } 0.59$$

$$\log ILS_{max} = -0.02\ (\pm 0.03)\ N^2 + 0.21\ (\pm 0.26)\ N + 1.75 \quad (5)$$

$$n = 13,\ r = 0.51,\ s = 0.26,\ F_{2,10} = 1.77,\ p > 0.2$$

R_m values. Relative placement of the carboxylate residue now appears less important. In marked contrast, attempting to modulate lipophilic character of either the 1′-CH_2COOH or 1′-OCH_2COOH variants by substitution with α-alkyl groups (**21–24**) provided agents whose ac-

tivities were low and poorly predicted by eq 4. If, as suggested[4], the 9-anilino ring of these agents resides in the minor groove of DNA, there could be steric intolerance to such chain branching, as already encountered in the sulfonanilide series.[15]

Equation 4 examines the influence of R_m alone and does not consider substituent electronic or steric effects; the electronically perturbed 1′-COOH (**2**) and 1′-O-$(CH_2)_3$COOH (**19**) derivatives, as well as the sterically demanding **21** and **23**, were not included in the data base. Attempts at overall regression analysis of data for all acid variants, for which optimum doses could be reached and therefore ILS_{max} figures derived, provided a significant though clearly less well fit equation (6).

$$\log ILS_{max} = -4.02\ (\pm 2.99)\ R_m^2 + 4.65\ (\pm 3.37)\ R_m + 0.81 \quad (6)$$

$n = 17$ (embracing data values included in eq 4 plus those for agents **2**, **19**, **21**, and **23**), $r = 0.59$, $s = 0.23$, $F_{2,14} = 3.8$, $p < 0.05$, optimum R_m value 0.58

Earlier, certain amide derivatives of the carboxylate variants proved active and extension of the homologous series provided **31–39**. Correlation eq 7 adequately

$$\log ILS_{max} = -1.32\ (\pm 0.56)\ R_m^2 + 0.32\ (\pm 0.30)\ R_m + 2.04 \quad (7)$$

$n = 8$, $r = 0.93$, $s = 0.09$, $F_{2,5} = 16.5$, $p < 0.01$, optimum R_m value 0.12

summarizes the screening data for examples **32–39**. While the first member of this series (**31**) is inactive, eq 7 predicts that it should provide appreciable activity. Again there is a marked discontinuity in the electronic perturbations provided by the substituents in the first [**31**, $\sigma_p(-CONH_2) = 0.36$] and higher [**32**, $\sigma_p(-CH_2CONH_2) = 0.07$] series members. Increasing the steric demand of the side chain, by di-N-methylation as in **40**, again provided an agent of significantly less than predicted activity.

The close correspondence between regression eq 7, developed for the 1′-$(CH_2)_n CONH_2$ variants, and that previously obtained for the homologous 1′-alkanesulfonanilides (**41–54**),[4] prompted an attempt at overall correlation. It was later found that the sulfonamide side-chain variants **56–58** could also be satisfactorily included; again the first more electronically perturbing member of this group [**55**, $\sigma_p(-SO_2NH_2) = 0.57$] was inactive, contrary to the prediction from the resulting equation on the basis of the R_m value alone. The coefficients in the overall correlation eq 8, for agents **32–39**, **41–54**, and **56–58**, are

$$\log ILS_{max} = -1.32\ (\pm 0.26)\ R_m^2 + 0.32\ (\pm 0.15)\ R_m + 2.04 \quad (8)$$

$n = 25$, $r = 0.93$, $s = 0.07$, $F_{2,22} = 72.4$, $p < 0.001$, optimum R_m value 0.12

identical with those seen in eq 7 derived for the 1′-carboxamides alone. There appears no clear difference in the antileukemic efficacy of the side-chain classes grouped to provide eq 8. While there are clearly strictures on the steric bulk of 1′-substituents, and their electronic influence on the 9-anilino ring, a major role of side-chain functionality is to provide adequate hydrophilic character.

The R_m optima for the equations embracing the 1′-carboxylic acids and the neutral side chain species are appreciably different. From the correlation between partition coefficients and R_m values,[8] it can be calculated that this difference in optimum values corresponds to approximately 1.8 log P units on the octanol–water scale. To merge these optima would require the measured R_m values for the carboxylic acids to be decreased by an equivalent factor. The differences between the log P_{oct} values for carboxylic acids and their anions have been found to lie within the range −3.09 to −4.06.[16] If it is accepted that, in the acidic chromatographic system employed (0.05 N in CH_3SO_3H), the R_m values measured are those of the un-ionized acids, then the correction factor necessary does not correspond with the change expected for total ionization of the carboxylate function. In this drug series a carboxylic acid residue appears to make a hydrophilic contribution as a mixture of both acid and anion. Consideration of the acidic pK_a values involved shows that at physiological pH values the acid function should be predominantly present as the anion and would therefore be expected to contribute to overall log P values as such. Hansch[17–19] has already encountered similar cases and suggests that modified π constants (π' values) should be derived, and employed in correlations, when ionization of a substituent may change during transport steps or at the receptor site. Possibly the operational π' value for a benzoic acid derivative (e.g., **2**) is different from those of the ω-phenylalkanoic acids **3–11** and might provide an explanation for the better than predicted activity of **2** when unmodified R_m values are employed in calculations.

Earlier prepared sulfonic acid analogues (cf. **30**) proved L1210 inactive. These powerful acids presumably migrate as the ion in chromatographic systems and would be expected to exist as the anion at physiologically encountered pH values. The operational R_m values of sulfonic acid derivatives would then be as measured. Calculation from eq 8 suggests that to test for biologic acceptability of a sulfonic acid function, a substituent providing a lipophilic contribution equivalent to that of an alkyl chain of three methylene groups would have to be appended before L1210 activity could be expected, and optimum activity could require the addition of the equivalent of six methylene groups.

Earlier qualitative comparisons suggested that acridine ring substituents provide divergent effects on biologic activity in the two subseries bearing either 1′-COOH or 1′-$NHSO_2R$ residues.[1] It was suggested that such effects might result from different site binding orientations of the planar acridine ring system, within a DNA-intercalation site, dictated by the binding interactions of the 1′-substituent.[1] The various regression equations derived now permit quantitative examination of this phenomenon. In the 1′-$NHSO_2R$ series the activity of the 3-$NHCOCH_3$ analogues **47–52** are well predicted from their R_m values; the acetamido substituent appears to make no significant alteration in antileukemic efficacy. While a 3-$NHCOCH_3$ does not appreciably alter acridine pK_a values[1] in this group, it does moderately increase dose potency (cf. **47–52** and **41–46**). In contrast, in the 1′-COOH series a 3-$NHCOCH_3$ group provides a marked drop in dose potency; compare LD_{10} values of **25**, **2**; **26**, **4**; and **27**, **19**. The higher than predicted activity of the benzoate analogue **2** makes effective forecasting of the activity of the corresponding 3-acetamido congener **25** difficult. However, appending a 3-$NHCOCH_3$ function to the well-predicted phenylpropionate **4** provides a compound with substantially less than expected activity (**26**). In this case the acetamido function has provided a clear drop in activity. Similarly, appending a hydrophilic 3-$NHCOCH_3$ to the more lipophilic hexanoic acid **7** should provide an agent of close to optimum lipophilic character and exemplary activity. In

Table I. Structural Details and L1210 Screening Data for the Substituted 9-Anilinoacridines

No.	Substituents in 1	Mp, °C	Formula	Analyses[a]	L1210 R_m[b]	L1210 LD_{10}[c]	L1210 ILS_{max}[d]	L1210 Log ILS_{max}	L1210 Log ILS_{calcd}[e]	L1210 Log ILS[f]
2	1′-COOH	*g*			0.27	72	130	2.11	1.56	+0.55[h]
3	1′-CH_2COOH	*g*			0.23	450	22[i]	1.34	1.36	−0.02
4	1′-$(CH_2)_2COOH$	123–125	$C_{22}H_{18}N_2O_2 \cdot HCl \cdot 1.5H_2O$	C, H, N, Cl	0.44	125	163	2.21	2.16	+0.05
5	1′-$(CH_2)_3COOH$	109–111	$C_{23}H_{20}N_2O_2 \cdot HCl$	C, H, N, Cl	0.59	190	213	2.33	2.34	−0.01
6	1′-$(CH_2)_4COOH$	142–144	$C_{24}H_{22}N_2O_2 \cdot H_2O$	C, H, N	0.64	125	187	2.27	2.32	−0.05
7	1′-$(CH_2)_5COOH$	193–195	$C_{25}H_{24}N_2O_2 \cdot HCl$	C, H, N, Cl	0.75	150	200	2.30	2.15	+0.15
8	1′-$(CH_2)_6COOH$	175–177	$C_{26}H_{26}N_2O_2$	C, H, N	0.79	90	74	1.87	2.04	−0.17
9	1′-$(CH_2)_7COOH$	183–186	$C_{27}H_{28}N_2O_2 \cdot HCl$	C, H, N, Cl	0.82	95	75	1.88	1.94	−0.06
10	1′-$(CH_2)_8COOH$	183–185	$C_{28}H_{30}N_2O_2 \cdot HCl$	C, H, N, Cl	0.85	100	72	1.86	1.83	+0.03
11	1′-$(CH_2)_9COOH$	109–111	$C_{29}H_{32}N_2O_2 \cdot HCl \cdot H_2O$	C, H, N, Cl	0.86	75	75	1.88	1.79	+0.11
12	1′-CH_2COOH, 4-CH_3	205–208	$C_{22}H_{18}N_2O_2 \cdot 0.5H_2O$	C, H, N	0.30	95	80	1.90	1.70	+0.20
13	1′-CH_2COOH, 4-C_2H_5	203–205	$C_{23}H_{20}N_2O_2 \cdot 0.5H_2O$	C, H, N	0.52	200	200	2.30	2.30	0.00
14	1′-$(CH_2)_2COOH$, 4-CH_3	91–92	$C_{23}H_{20}N_2O_2$	C, H, N	0.46	32	124	2.09	2.21	−0.12
15	1′-$(CH_2)_2COOH$, 4-C_2H_5	275–277	$C_{24}H_{22}N_2O_2 \cdot HCl$	C, H, N, Cl	0.66	200	130	2.11	2.29	−0.18
16	1′-CH=CHCOOH	*g*			0.36	450	98	1.99	1.94	+0.05[h]
17	1′-OCH_2COOH	*g*			0.06	>500	*j*		<1.30	
18	1′-$O(CH_2)_2COOH$	249–251	$C_{22}H_{18}N_2O_2 \cdot HCl$	C, H, N	0.31	>500	*j*		1.70	
19	1′-$O(CH_2)_3COOH$	180–182	$C_{23}H_{20}N_2O_3 \cdot HCl$	C, H, N, Cl	0.55	200	160	2.20	2.32	−0.12[h]
20	1′-$O(CH_2)_4COOH$	175–177	$C_{24}H_{22}N_2O_3 \cdot HCl$	C, H, N, Cl	0.65	>500	66[j]	>1.82	2.31	
21	1′-$CH(CH_2CH_3)COOH$	293–295	$C_{23}H_{20}N_2O_2 \cdot HCl$	C, H, N, Cl	0.63	420	79	1.90	2.32	−0.42[h]
22	1′-$OCH(CH_3)COOH$	278–280	$C_{22}H_{18}N_2O_3 \cdot HCl$	C, H, N	0.38	>500	–		2.00	
23	1′-$OCH(CH_2CH_3)COOH$	263–265	$C_{23}H_{20}N_2O_3 \cdot 2H_2O$	C, H, N	0.54	460	42	1.62	2.31	−0.69[h]
24	1′-$OCH(CH_2CH_2CH_3)COOH$	193–196	$C_{24}H_{22}N_2O_3 \cdot HCl$	C, H, N	0.66	>500	33[j]	>1.52	2.30	
25	3-$NHCOCH_3$, 1′-COOH	*g*			0.15	>500	–[j]		1.30	
26	3-$NHCOCH_3$, 1′-$(CH_2)_2COOH$	313–315	$C_{24}H_{21}N_3O_3 \cdot HCl$	C, H, N, Cl	0.27	145		<1.30	1.57	>−0.27[h]
27	3-$NHCOCH_3$, 1′-$(CH_2)_5COOH$	220–221	$C_{27}H_{27}N_3O_3 \cdot HCl$	C, H, N, Cl	0.54	>500	–[j]		2.32	
28	3-$NHCH_3$, 1′-$O(CH_2)_3COOH$	157–159	$C_{24}H_{23}N_3O_3 \cdot HCl$	C, H, N, Cl	0.61	>500	30[j]	>1.48	2.33	
29	3-$NHCH_3$, 1′-$(CH_2)_3COOH$	149–151	$C_{24}H_{23}N_3O_2 \cdot HCl \cdot 0.5H_2O$	C, H, N, Cl	0.67	400	35	1.54	2.29	−0.75[h]
30	1′-SO_3H	*g*			−0.78	420	–	<1.30	<1.30	
31	1′-$CONH_2$	*g*			−0.25	182	–	<1.30	1.88	>−0.53[k]
32	1′-CH_2CONH_2	*g*			−0.33	55	64	1.81	1.79	+0.02
33	1′-$(CH_2)_2CONH_2$	219–222	$C_{22}H_{19}N_3O \cdot H_2O$	C, H, N	−0.17	75	84	1.92	1.95	−0.03
34	1′-$(CH_2)_3CONH_2$	176–179	$C_{23}H_{21}N_3O$	C, H, N	0.09	85	122	2.09	2.06	+0.03
35	1′-$(CH_2)_4CONH_2$	115–117	$C_{24}H_{23}N_3O \cdot MsOH \cdot 0.5H_2O$[m]	C, H, N, S	0.25	110	82	1.91	2.04	−0.13
36	1′-$(CH_2)_5CONH_2$	172–175	$C_{25}H_{25}N_3O \cdot MsOH$	C, H, N, S	0.41	125	97	1.99	1.95	+0.04
37	1′-$(CH_2)_6CONH_2$	176–179	$C_{26}H_{27}N_3O \cdot 0.5H_2O$	C, H, N	0.58	110	71	1.85	1.79	+0.06
38	1′-$(CH_2)_7CONH_2$	185–186	$C_{27}H_{29}N_3O \cdot MsOH$	C, H, N, S	0.68	120	53	1.72	1.66	+0.06
39	1′-$(CH_2)_8CONH_2$	151–153	$C_{28}H_{31}N_3O \cdot MsOH \cdot H_2O$	C, H, N, S	0.77	60	25	1.40	1.51	−0.11
40	1′-$(CH_2)_3CON(CH_3)_2$	152–153	$C_{25}H_{25}N_3O \cdot HCl \cdot H_2O$	C, H, N, Cl	0.68	52	–	<1.30	1.65	>−0.35[k]
41	1′-$NHSO_2CH_3$	*l*			0.00	66	131	2.12	2.04	+0.08
42	1′$NHSO_2CH_2CH_3$	*l*			0.25	330	98	1.99	2.04	−0.05
43	1′-$NHSO_2(CH_2)_2CH_3$	*l*			0.43	350	82	1.91	1.94	−0.03
44	1′-$NHSO_2(CH_2)_3CH_3$	*l*			0.56	350	66	1.82	1.81	+0.01
45	1′-$NHSO_2(CH_2)_4CH_3$	294–295	$C_{24}H_{25}N_3O_2S \cdot HCl$	C, H, N, Cl	0.66	70	55	1.74	1.68	+0.06
46	1′-$NHSO_2(CH_2)_5CH_3$	147–149	$C_{25}H_{27}N_3O_2S \cdot HCl \cdot 2H_2O$	C, H, N, Cl	0.75	120	35	1.54	1.55	−0.01

47	3-NHCOCH$_3$, 1'-NHSO$_2$CH$_3$	*l*	−0.12	19	145	2.16	1.98	+0.18
48	3-NHCOCH$_3$, 1'-NHSO$_2$CH$_2$CH$_3$	*l*	0.10	28	115	2.06	2.06	0.00
49	3-NHCOCH$_3$, 1'-NHSO$_2$(CH$_2$)$_2$CH$_3$	*l*	0.30	33	115	2.06	2.02	+0.04
50	3-NHCOCH$_3$, 1'-NHSO$_2$(CH$_2$)$_3$CH$_3$	*l*	0.46	39	84	1.92	1.91	+0.01
51	3-NHCOCH$_3$, 1'-NHSO$_2$(CH$_2$)$_4$CH$_3$	*l*	0.59	40	61	1.78	1.78	0.00
52	3-NHCOCH$_3$, 1'-NHSO$_2$(CH$_2$)$_5$CH$_3$	*l*	0.70	21	43	1.63	1.62	+0.01
53	3-NHCOCH$_2$CH$_3$, 1'-NHSO$_2$CH$_3$	*l*	0.15	55	119	2.08	2.06	+0.02
54	3-NHCO(CH$_2$)$_2$CH$_3$, 1'-NHSO$_2$CH$_3$	*l*	0.32	92	80	1.90	2.01	−0.11
55	1'-SO$_2$NH$_2$	*g*	−0.57	>500	*j*		1.43	
56	1'-CH$_3$SO$_2$NH$_2$	*g*	−0.36	62	53	1.72	1.75	−0.02
57	1'-(CH$_2$)$_2$SO$_2$NH$_2$	*g*	−0.20	80	68	1.83	1.92	−0.09
58	1'-CH$_2$SO$_2$NH-2-pyridyl	*g*	−0.04	370	99	2.00	2.02	−0.02
59	3-NHCH$_3$, 1'-NHSO$_2$CH$_3$	*n*	−0.01	7	103	2.01	2.04	−0.03
60	3-NHCH$_3$, 3'-OCH$_3$, 1'-NHSO$_2$CH$_3$	*n*	0.17	1.3	94	1.97	2.06	−0.09

[a] Elemental analysis for the elements noted provided results within ±0.4% of the calculated figures for the formulas indicated. [b] Measure of lipophilic–hydrophilic balance from reversed phase chromatography. $R_m = \log(1/R_f - 1)$; see ref 8. [c] Lethal dose for 10% of the animals; determined by the methods detailed in the text. [d] Maximum increase in life span (T/C% − 100) in L1210 assays; taken from ILS − log dose linear regressions at the LD_{10}; see text. [e] Log ILS calculated from regression eq 4 for entries 2–29 and from eq 8 for entries 30–60. [f] Difference between observed and calculated log ILS values. [g] Reference 1. [h] Not included in the derivation of eq 4. [i] Mean of four determinations at the LD_{10} dose. [j] LD_{10} dose not reached; higher doses may provide greater life extensions; − signifies that significant life extension was not observed. [k] Not included in the derivation of eq 8. [l] Reference 4. [m] MsOH = methanesulfonic acid. [n] Reference 20.

fact, the maximum tolerated dose of **27** could not be reached and at employed doses no L1210 activity was observed.

A 3-NHCH$_3$ group, in the 1'-NHSO$_2$R series, has provided the largest observed increases in dose potency (cf. **59**, **60**, and **41**).[20] Antileukemic activities of these analogues (**59** and **60**) are well predicted from their R_m values and eq 8 (Table I). In contrast, appending 3-NHCH$_3$ functions to members of the carboxylic acid series furnished congeners (**28** and **29**) which were less dose potent than their precursors (**19** and **5**). The maximum tolerated dose could be reached for only one analogue (**29**) and the anti-L1210 activity of this agent was markedly depressed below that predicted on R_m grounds. These results, together with the additional examples provided earlier,[1] make it clear that acridine-substituent effects, on both host toxicity and antileukemic activity, are dependent on the 1' function utilized. One explanation for such variation would be that different site-binding orientations are dictated by varying 1'-substituents.

A similar explanation could be tendered for a puzzling feature of the SAR for analogues of miracil D in their effects on growth inhibition of *Bacillus subtilis*, DNA-directed RNA polymerase, and DNA binding.[21-23] These thioxanthenone derivatives are DNA intercalators[24] and bear an Et$_2$NCH$_2$CH$_2$NH– side chain. Alkylation of side chain –NH– group in the series containing an unsubstituted thioanthenone nucleus produces marked decrease in activities, while a nuclear 6-Cl group causes little alteration. However, when there is a 6-Cl substituent present, equivalent side-chain N-alkylation does not produce the marked decreases in activities seen in the parent series. It has already been questioned whether the 6-chloromiracils may form a different type of complex with DNA.[25] Such difference could result from altered positioning of the DNA-intercalated chromophore in relation to the neighboring purine–pyrimidine pairs.

If there is a limited energy barrier to two-dimensional movement of a planar drug nucleus, within the adjacent site base pairs, any added drug substituent which provides maximum effect when it is specifically located, in relation to site functionality, may dictate the adoption of a site orientation which is different from that favored by the unsubstituted parent agent. If site orientations did change, as the nature and the location of drug substitutents altered, then current methods of SAR analysis would not be applicable. It would only be when there were drug features common to a series, which were capable of dictating the adoption of a single site orientation, that the site interactions of further functionality could be effectively analyzed.

Experimental Section

Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Analyses were performed by Dr A. D. Campbell, Microchemical Laboratory, University of Otago, Dunedin, New Zealand. Melting points were determined on an Electrothermal melting point apparatus with the makers' supplied stem corrected thermometer; melting points are as read.

Methods for generation, handling, and purification of the carboxylic acid variants of 9-anilinoacridine have been detailed earlier.[1] Preparation of acridine-substituted variants employed the intermediates and reaction sequences developed earlier.[4-6]

To monitor the progress of reactions, purification of products, etc., TLC on SiO_2 (Merck SiO_2, F_{254}) was used. R_m values for all described agents have been determined employing the reversed phase system employed earlier;[8] figures quoted are the mean of at least three determinations.

6-Phenylhexanoic Acid. To a well-stirred solution of 1-phenylcyclohexanol (40 g, 0.23 mol) in HOAc (500 mL), CrO_3 (115

Table II

ω-Phenyl-7-oxoalkanoic acids	Mp, °C	Formula[a]	Yield, %[b]
7-Phenyl-7-oxoheptanoic	83–84	$C_{13}H_{16}O_3$	59
8-Phenyl-7-oxoheptanoic	47–49	$C_{14}H_{18}O_3$	43
9-Phenyl-7-oxononanoic	78–80	$C_{15}H_{20}O_3$	51
10-Phenyl-7-oxodecanoic	49–51	$C_{16}H_{22}O_3$	54

[a] All compounds analyzed satisfactorily for C and H. [b] From the acid chloride.

g; 1.14 mol) was added at a rate sufficient to maintain the reaction temperature at 30–35 °C. When addition was complete the mixture was stirred for 90 min further and then diluted with H_2O containing EtOH (20 mL). Concentration in vacuo gave a thick gum which was triturated with H_2O and kept several hours at 20 °C until crystallization was complete. The 5-benzoylpentanoic acid was collected, washed with H_2O, and dried in vacuo to give material of mp 74–76 °C (lit.[2] mp 73–75 °C) (31 g, 66%) quite suitable for the following reduction step.

Wolff–Kishner reduction[26] of the above keto acid, followed by the usual workup and purification of the product by fractional distillation in vacuo, provided 6-phenylhexanoic acid: bp 138–142 °C (0.1 mm) [lit.[27] bp 185–187 °C (12 mm)].

ω-Phenylalkanoic Acids. For the purposes of example preparation of 7-phenylheptanoic acid is detailed. A solution of benzoyl chloride (84.5 g, 0.60 mol) in dry, EtOH-free $CHCl_3$ (100 mL) was added in dropwise fashion to a stirred solution of 1-morpholino-1-cyclohexene[27] (100 g, 0.60 mol) and Et_3N (87 mL, 0.625 mol) in dry EtOH-free $CHCl_3$ (600 mL). The temperature was kept below 35 °C during the addition; then the mixture stirred at ambient temperature for 24 h. HCl (6 N, 600 mL) was added, and the two-phase system was heated under reflux conditions for 5 h. After cooling, the organic layer was separated, washed with H_2O, dried, and concentrated to give crude 2-benzoylcyclohexanone (110 g, 95%). Crystallization from *i*-Pr_2O provided pure product as prisms of mp 84–86 °C. Anal. ($C_{13}H_{14}O_2$) C, H.

The above diketone (106 g, 0.55 mol) was suspended in a solution of KOH (90 g, 1.6 mol) in H_2O (450 mL) and heated under reflux conditions until the reaction mixture became homogeneous (ca. 10 min). The solution was then cooled and acidified to pH 4 to precipitate crude 7-phenyl-7-oxoheptanoic acid (Table II). Wolff–Kishner reduction[26] of the keto acid, followed by fractional distillation in vacuo, provided pure 7-phenylheptanoic acid: bp 147–149 °C (1 mm) [lit.[28] bp 135–145 °C (0.5 mm)] (75% yield from 2-benzoylcyclohexanone).

In the preparation of the higher homologues, the noncrystalline diketones resulting in the first step were hydrolyzed with alkali, as above, and the resulting crystalline keto acids (Table II) characterized. All listed keto acids crystallized well from *i*-Pr_2O. Wolff–Kishner reduction[26] of the keto acids, and following purification by fractional vacuum distillation, provided the well-recorded ω-phenylalkanoic acids.

ω-(4′-Nitrophenyl)alkanoic Acids. The following serves as a general example. 5-Phenylpentanoic acid (10 g, 0.06 mol) was added over 2 h to well-stirred HNO_3 (70 mL, *d* 1.42) maintained at 20 °C. The mixture was stirred at 20 °C for 24 h. During the nitration of higher homologues the mixture remained biphasic throughout. Isolation was by dilution with ice plus H_2O; when solid the nitro acid was collected and well washed with H_2O and adhering oily isomers were sucked through the filter. The solid was dried and recrystallized from C_6H_6 (twice). Pure 5-(4′-nitrophenyl)pentanoic acid was obtained as pale prisms of mp 82–84 °C (lit.[29] mp 83–84 °C). Higher homologues crystallized well from *i*-Pr_2O. Formerly unrecorded examples are listed in Table III.

ω-(4′-Nitrophenyl)alkanamides were prepared from the nitro acids in the usual fashion by sequential treatment with thionyl chloride and then cold aqueous ammonia. Crystallization in all cases was from EtOH. Formerly unrecorded examples are listed in Table IV.

Biological Testing. The 10^5 L1210 cells were inoculated intraperitoneally into 18.5–22.5-g C_3H/DBA_2 F_1 hybrid mice. Ip drug treatment started 24 h later and continued for 5 days. An animal dose was contained in a volume of 0.2 mL. Dose levels were arranged as described in the text. There were six animals per dose level and one control group for every six test groups.

Table III

ω-(4′-Nitrophenyl)alkanoic acids	Mp, °C	Formula[a]	Yield, %
7-(4′-Nitrophenyl)heptanoic	73–74	$C_{13}H_{17}NO_4$	32
8-(4′-Nitrophenyl)octanoic	73–75	$C_{14}H_{19}NO_4$	21
9-(4′-Nitrophenyl)nonanoic	67–69	$C_{15}H_{21}NO_4$	17
10-(4′-Nitrophenyl)decanoic	63–64	$C_{16}H_{23}NO_4$	16

[a] All compounds analyzed satisfactorily for C, H, and N.

Table IV

ω-(4′-Nitrophenyl)-alkanamides	Mp, °C	Formula[a]	Yield, %
6-(4′-Nitrophenyl)-hexanamide	122–125	$C_{12}H_{16}N_2O_3$	95
7-(4′-Nitrophenyl)-heptanamide	124–127	$C_{13}H_{18}N_2O_3$	90
8-(4′-Nitrophenyl)-octanamide	111–114	$C_{14}H_{20}N_2O_3$	90
9-(4′-Nitrophenyl)-nonanamide	127–128	$C_{15}H_{22}N_2O_3$	86

[a] All compounds analyzed correctly for C, H, and N.

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(Acylaryloxy)acetic Acid Diuretics. 2. (2-Alkyl-2-aryl-1-oxo-5-indanyloxy)acetic Acids[1a]

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The introduction of an aryl group at the 2 position of the uricosuric diuretics, (1-oxo-2-alkyl-5-indanyloxy)acetic acids, provided compounds with markedly increased potency over their monosubstituted precursors. These compounds were synthesized either by arylation of the corresponding 2-alkyl-5-methoxy-1-indanones with diaryliodonium salts or by alkylation of the 2-aryl-5-methoxy-1-indanones which were cleaved to the corresponding phenols and then converted to the desired oxyacetic acids. Systematic structural variation of the 2-arylindanyloxyacetic acids provided aryl-substituted compounds with varying degrees of uricosuric and diuretic activity.

The discovery that the potent (acryloylaryloxy)acetic acid diuretics could be cyclized intramolecularly to (indanyloxy)acetic acids while still retaining diuretic activity led to a detailed study of these indanyloxy derivatives. The 2-alkyl and 2,2-dialkyl compounds described in paper 1 of this series[1a] exhibited varying degrees of saluretic, diuretic, and uricosuric activity. The series described in this paper retains the 2,2-disubstitution but replaces 2-alkyl by 2-aryl, thus providing new compounds with enhanced diuretic activity as well as significant uricosuric activity as measured in several animal species. The 2-methyl-2-phenyl compound **4a** (MK-196) is currently undergoing clinical evaluation in man.

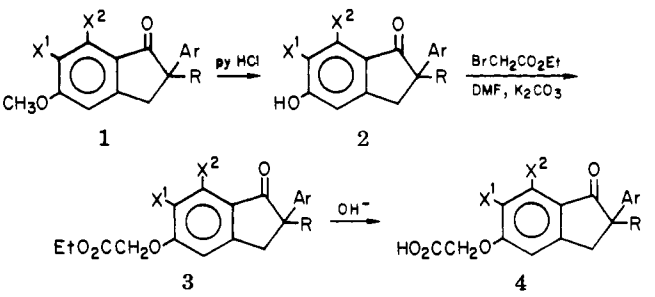
Chemistry. The (2-alkyl-2-arylindanyloxy)acetic acids **4** (Table I) were prepared in several steps (Scheme I) starting with the appropriate anisoles **1** (Tables II and III), following the procedure described in paper 1 of this series.[1a] The 2-alkyl-2-aryl-5-methoxy-1-indanones **1** were synthesized either by arylating 2-alkyl-5-methoxy-1-indanones **5** with a diaryliodonium halide[2] or by alkylating a 2-aryl-5-methoxy-1-indanone **6** (Table II) with an alkyl halide (Scheme II).

A diaryliodonium salt such as diphenyliodonium chloride[3,4] or dithienyliodonium chloride[5] arylated a 2-alkylindanone **5** in *tert*-butyl alcohol–benzene in the presence of potassium *tert*-butoxide to provide the 2-alkyl-2-arylindanone **1**.[6]

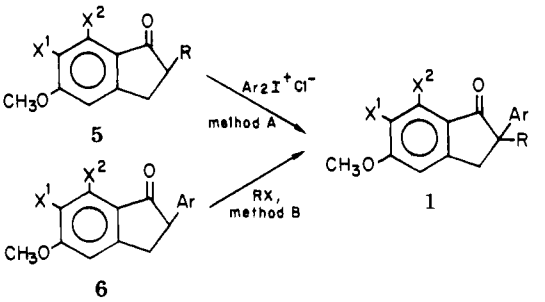
The preparation of the 2-aryl-5-methoxy-1-indanones **6** is illustrated in Scheme III. Preparation of 2-aryl-5-methoxy-1-indanone **6** resulted in complications which were not encountered in the 2-alkyl-5-methoxy-1-indanone synthesis. The Friedel–Crafts acylation of a disubstituted anisole **7** with an arylacetyl chloride in methylene chloride led to poor yields of the aryl benzyl ketone **8**, apparently due to self-acylation by the soluble acid chloride–$AlCl_3$ complex. Use of cyclohexane or carbon disulfide, solvents in which the complex is insoluble, gave excellent yields of clean products, **8** (Table IV).

The standard Mannich reaction with dimethylamine hydrochloride and paraformaldehyde, followed by deamination in DMF to form the α-methylene derivative **9**, was not satisfactory. Treatment of the aryl benzyl ketone **8** with *N,N,N′,N′*-tetramethylmethanediamine and acetic anhydride[7] at temperatures not exceeding 40 °C provided the pure α,β-unsaturated ketones **9** in high yields.

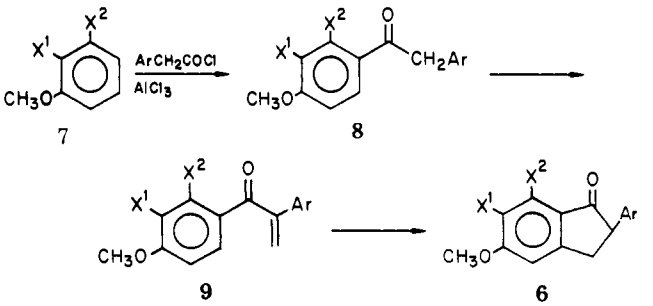
Scheme I



Scheme II



Scheme III



The cyclization of **9** in concentrated sulfuric acid led to poor yields of the indanone **6** and highly fluorescent byproducts. When the acrylophenone in a dilute solution of methylene chloride was added to concentrated sulfuric

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