with excess MeI at 5° overnight. The reaction mixt was evapd to dryness and the residue was crystd from Me_2CO-Et_2O to furnish colorless needles of VIb in almost quantitative yield: mp 195°; the quaternary *N*-Me group signaled at 3.30 (9 H, s) in the nmr (D_2O) spectrum.

2,3-Dihydrohelenalin (II). 2,3-Dihydrohelenalin could be readily synthesized in quantitative yield from any one of the following 3 methods.

(a) A soln of VIb (30 mg) in H_2O (1 ml) was heated on a steam bath for 30 min. The reaction mixt was acidified with 5% HCl and extd with $CHCl_3$, washed with H_2O, dried (Na_2SO_4), and evapd. The residue was purified in $CHCl_3$ by passing through a column of silica gel (0.6 × 3.5 cm) to provide II as fine colorless silky needles after one recrystn from CH_2Cl_2-hexane: mp 154–155°; nmr 4.88 (1 H, t, J = 7.5 cps, H-8), 4.30 (1 H, d, J = 3 cps, H-6), 1.08 (3 H, d, J = 6 cps, C_{10}-CH_3) and 0.78 (3 H, s, C_5-CH_3).

(b) A soln of VIb (67 mg) in MeOH (20 ml) was treated with excess of freshly prepared Ag_2O and stirred for 30 min at room temp. The reaction mixt was filtered and evapd *in vacuo* to yield II as an oil. This was chromatogd in $CHCl_3$ on silica gel (0.3 × 3 cm) to give colorless needles (35 mg) after one recrystn from PhH–EtOH: mp 154–155°.

(c) A soln of VIb (18 mg) in 5% aq $NaHCO_3$ soln (5 ml) was stirred at room temp for 1 hr. The reaction mixt was acidified with dil HCl and extd with $CHCl_3$. The $CHCl_3$ ext was washed with H_2O, dried (Na_2SO_4), and evapd to yield 10 mg of II as colorless needles after 1 recrystn from benzene–EtOH: mp 154–155°.

Helenalin from Method b. Treatment of Vb (20 mg) in a similar manner as described for II (method b) afforded I as colorless needles. The identity of this compd with helenalin was established by tlc, ir comparison, and mmp determination.

11,13-Dihydrohelenalin (III) was prepd according to the method of Adams and Herz.[4]

2,3,11,13-Tetrahydrohelenalin (IV) was prepd by the method of Clark[5] and melted at 171–173°.

Helenalin Piperidine Adduct (Vg). A soln of helenalin (I) (100 mg) in freshly distd piperidine (1 ml) was allowed to stand at room temp overnight. The reaction mixt was dild with H_2O and extd with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried (Na_2SO_4), and evapd under reduced pressure to yield a residue (30 mg) which crystd upon addn of Et_2O. Recrystn from CH_2Cl_2-Et_2O gave colorless needles (Vg): mp 203–205°; nmr 7.70 (1 H, dd, J = 6 cps, 1.5, H-2), 6.10 (1 H, dd, J = 6.3 cps, H-3), 4.95 (1 H, m, H-8), 4.55 (1, H, br, s, H-6), 1.30 (3 H, d, J = 6 cps, C_{10}-CH_3) and 1.18 (3 H, s, C_5-CH_3).

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Potential Antitumor Agents. 12. 9-Anilinoacridines

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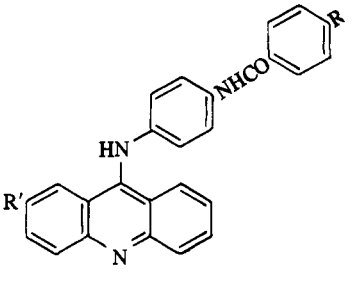
Development of a series of L1210 active 9-(R-substituted-anilino)acridines is described. R should be an electron-donating substituent and should be placed at either or both of the 3′ and 4′ positions. It is suggested that the 9-(R-anilino)acridines described can be considered as nonquaternary analogs of the 5-alkyl-6-phenylphenanthridinium salts.

A consideration of the mode of binding and factors governing the distribution of antileukemic bisquaternary salts[1] described earlier led us to prepare the L1210 active nonquaternary base **1a**. It has been postulated[2] that the corresponding base **1b** was inactive in the L1210 system because at physiological pH values the amount of un-ionized species present is too small to allow penetration of cellular barriers at sufficiently high rates by passive diffusion to elicit the required biological response. The higher percentage of neutral form present in the more weakly basic pyrimidine **1a** allows readier distribution and thus the intrinsic activity of the molecular type can be demonstrated. To investigate the contribution made to biologic activity by the weakly basic pyrimidine function in **1a** the simpler **1c** was prepared; suitable intermediates for this being already at hand.[1] Compd **1c** was only slightly less active in the early ip L1210 test than **1a**. The progressively simpler molecules **1d** then **1e** were prepared and found to have low but significant levels of antileukemic activity. Further simplification to the anilinoacridine **2** provided a molecule with a



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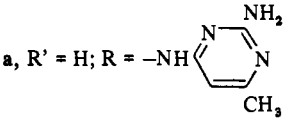


a, R′ = H; R = –NH

b, R′ = H; R = –NH

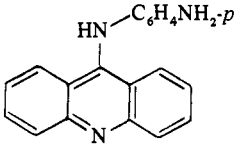
c, R′ = NH_2; R = NH_2
d, R′ = NH_2; R = H
e, R′ = R = H

Table I

Drug	Substituent R in 4	Mp, °C	Formula	Analyses[c]	L1210[d]
2	4'-NH_2	315-317	$C_{19}H_{15}N_3 \cdot HCl \cdot 0.5H_2O$	C, H, N, Cl	+
5	2'-NH_2	320-322	$C_{19}H_{15}N_3 \cdot HCl$	C, H, N, Cl	–
6	3'-NH_2	299-301	$C_{19}H_{15}N_3 \cdot HCl$	C, H, N, Cl	±
7	2'-OH	342 dec	$C_{19}H_{14}N_2O \cdot HCl \cdot 0.5H_2O$	C, H, N, Cl	–
8	3'-OH	329-331	$C_{19}H_{14}N_2O \cdot HCl$	C, H, N, Cl	–
9	4'-OH	350-352	$C_{19}H_{14}N_2O \cdot HCl$	C, H, N, Cl	+
10	3'-$NHCH_3$	174-176	$C_{20}H_{17}N_3 \cdot HBr$	C, H, N	–
11	4'-$NHCH_3$	291-292	$C_{20}H_{17}N_3 \cdot HBr$	C, H, N, Br	+
12	3'-$N(CH_3)_2$	204-205	$C_{21}H_{19}N_3$	C, H, N	–
13	4'-$N(CH_3)_2$[a]	296-297	$C_{21}H_{19}N_3 \cdot HCl$	C, H, N, Cl	±
14	4'-NHC_2H_5	264-265	$C_{21}H_{19}N_3 \cdot HBr$	C, H, N, Br	±
15	4'-$N(C_2H_5)_2$	268-269	$C_{23}H_{23}N_3 \cdot HBr$	C, H, N, Br	–
16	3'-$NHCOCH_3$	215-217	$C_{21}H_{17}N_3O \cdot HCl$	C, H, N, Cl	±
17	4'-$NHCOCH_3$	318-319	$C_{21}H_{17}N_3O \cdot HCl$	C, H, N, Cl	+
18	3'-$N(CH_3)COCH_3$	248-249	$C_{22}H_{19}N_3O \cdot HBr \cdot H_2O$	C, H, N, Br	–
19	4'-$N(CH_3)COCH_3$	284-285	$C_{22}H_{19}N_3O \cdot HBr$	C, H, N, Br	±
20	3'-$NHCOOCH_3$	283-284	$C_{21}H_{17}N_3O_2 \cdot HCl$	C, H, N, Cl	–
21	4'-$NHCOOCH_3$	286-287	$C_{21}H_{17}N_3O_2 \cdot HBr$	C, H, N, Br	+
22	4'-$NHCOOC_2H_5$	272-273	$C_{22}H_{19}N_3O_2 \cdot HCl \cdot 0.5H_2O$	C, H, N, Cl	+
23	4'-OCH_3	295-296	$C_{20}H_{16}N_2O \cdot HBr \cdot H_2O$	C, H, N, Br	–
24	4'-SO_2NH_2[b]	317-318	$C_{19}H_{15}N_3O_2S \cdot HCl$	C, H, N, S	–
25	4'-$CONH_2$	303-304	$C_{20}H_{15}N_3O \cdot HCl$	C, H, N, Cl	–
26	4'-$NHCOCH_2CH_3$	357-358	$C_{22}H_{19}N_3O \cdot HBr$	C, H, N, Br	±
27	4'-$NHCO(CH_2)_2CH_3$	284-285	$C_{23}H_{21}N_3O \cdot HCl$	C, H, N, Cl	+
28	4'-$NHCO(CH_2)_3CH_3$	304-306	$C_{24}H_{23}N_3O \cdot HCl$	C, H, N, Cl	±
29	4'-$NHCO(CH_2)_4CH_3$	287-289	$C_{25}H_{25}N_3O \cdot HCl$	C, H, N, Cl	±
30	4'-$NHCOCH(CH_3)_2$	327-328	$C_{23}H_{21}N_3O \cdot HCl$	C, H, N, Cl	+
31	4'-$NHCOCH_2CH(CH_3)_2$	321-323	$C_{24}H_{23}N_3O \cdot HCl$	C, H, N, Cl	±
32	4'-$NHCO(CH_2)_2CH(CH_3)_2$	319-320	$C_{25}H_{25}N_3O \cdot HCl$	C, H, N, Cl	±
33	4'-$NHCOCH(C_2H_5)_2$	214-216	$C_{25}H_{25}N_3O \cdot HCl$	C, H, N, Cl	±
34	4'-$NHCOC_6H_{11}$	319-320	$C_{26}H_{25}N_3O \cdot HCl$	C, H, N, Cl	–
35	4'-$NHCOCH_2C_6H_5$	309-310	$C_{27}H_{21}N_3O \cdot HCl$	C, H, N, Cl	–
36	3'-NH_2, 4'-NO_2	254-255	$C_{19}H_{14}N_4O_2$	C, H, N	–
37	3'-NO_2, 4'-NH_2	318-319	$C_{19}H_{14}N_4O_2 \cdot HCl \cdot 0.5H_2O$	C, H, N, Cl	–
38	3',4'-$(NH_2)_2$	281-282	$C_{19}H_{16}N_4 \cdot HBr \cdot 0.5H_2O$	C, H, N, Br	++
39	4'-$NHSO_2CH_3$	309-310	$C_{20}H_{17}N_3O_2S \cdot HCl$	C, H, N, Cl	++
40	3'-$NHSO_2CH_3$	319-320	$C_{20}H_{17}N_3O_2S \cdot HCl$	C, H, N, S	±
41	3',4'-$(NHSO_2CH_3)_2$	284-285	$C_{21}H_{20}N_4O_4S_2 \cdot HCl$	C, H, N, Cl	±
42	3'-NO_2, 4'-$NHSO_2CH_3$	308-310	$C_{20}H_{16}N_4O_4S \cdot HCl$	C, H, N, Cl	–
43	3'-NH_2, 4'-$NHSO_2CH_3$	235 dec	$C_{20}H_{18}N_4O_2S \cdot HCl \cdot 1.5H_2O$	C, H, N, Cl	++
44	4'-$NHSO_2C_6H_5$	322-323	$C_{25}H_{19}N_3O_2S \cdot HCl$	C, H, N, Cl	++

[a] See ref 4 and 5. [b] Granapathi[9] quotes the free base of this compound. [c] Where analyses are indicated only by symbols of the elements analytical results for these elements were within ±0.4% of the theoretical values. [d] L1210 results according to our experimental procedure. Increase in life-span 25-50%, ±; 50-100%, +; >100%, ++.

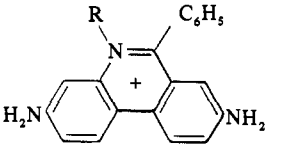
substantial proportion of the activity observed with the parent 1a. Removal of the primary amino group from 2 yielded the previously prepared 9-anilinoacridine[3] which proved inactive in the L1210 system.



2

From the site approaches suggested earlier and the reasoning which led to the ideas expressed in 1a we tend to consider 2 as a nonquaternary analog of the 6-phenylphenanthridinium salts, for example, dimidium (3, R = CH_3), which is also active against the L1210 leukaemia.[1]†

A literature search in the immediate area of 2 showed that the corresponding dimethylamino compound (4,



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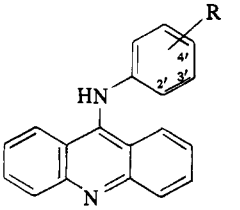

4

R = 4'-NMe_2) had been previously prepared and its antitumor properties described.[4,5] This agent is quoted as inhibiting the L1210 system and the Walker 256 tumor. Despite the interesting experimental activity of this compound we can find no record of synthetic endeavors in this area; except for those noted, the compounds listed in Table I have not previously been recorded.

It is clear from the presented data (Table I) that a strongly

†The obvious prediction is that quaternary salts derived from 2 should show similar structure-activity requirements to the phenanthridinium salts, *e. g.*, 3. This is in fact the case and the correlations between quaternary salts will be dealt with in a future publication.

electron-donating substituent on the anilino ring is required for activity and this is best placed at the 4′ position; more weakly active agents result from placement in the 3′ position; 2′-substitution is ineffective.

The importance of lipophilic-hydrophilic balance with these agents is not clear from the evidence at hand. Alkyl substitution on a 4′-amino group persistently produces a small drop in activity but it is certainly not clear on the available evidence that this is due to increase in lipophilic character. The series of amides and urethanes listed in Table I was prepared in an attempt to clarify the importance of hydrophilic-lipophilic balance and to investigate facets of distribution phenomena.[1] There is not a rapid change in activity as higher homologs are examined (**17**, **26-29**) but we have no evidence to eliminate the possibility that these agents undergo *in vivo* cleavage to the active parent amine, **2**.

If it were assumed that the requirement for a strong electron-donating substituent on the anilino function was due to this ring acting as a π donor in a charge-transfer complex with a site component, then it might prove possible to replace the π by an n-donor system.[6] To this end we have screened against L1210 a series of 9-substituted acridines: 2′-hydroxyethylamino, 2′-methylthioethylamino, and 2′-(morpholin-1-yl)ethylamino,‡ but no activity was encountered among these.

A series of 9-dialkylaminoalkylaminoacridines has been reported as active against various experimental tumors,[8] principally sarcoma 180. The preparation of these agents was repeated and they were screened against L1210; none was found that would affect this particular tumor in this laboratory.

The independent activity of both the 3′- (**6**) and 4′-amino (**2**) compounds prompted an examination of the 3′,4′-diamino species (**38**) which was found to be considerably more active than either monoamino compound. However, such 1,2,4-triaminobenzene systems are subject to ready aerial oxidation giving rise to highly colored toxic materials.

If it were taken that either or both of the 3′- or 4′-amino groups in **38** were acting as a point electron donor to an acceptor at the site, then molecular models suggested that a 3′- or 4′-sulfonamide function would retain the positioning of one N and could place an electron-rich O of the sulfonamide close to where the second N of the diamine **38** would normally reside.§ Also, a sulfonamide, supplying a small proportion of species having negatively charged N, should act as efficient electron-donor substituent. The isomeric 3′- and 4′-methanesulfonamides (**40** and **39**) were prepared. The 4′ isomer had comparable activity to the 3′,4′-diamino compound (**38**). Addition of an ortho amino group (**43**) did not appear to further increase activity. The 4′-benzenesulfonamide (**44**) appeared of comparable activity to the methanesulfonamide (**39**).

Experimental Section

When 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, a 2°/min heating rate from 20° below the melting point was used.

9-Anilinoacridines. All the variants in Table I were prepd by the same method, *viz.*, condn of the substituted aniline with 9-chloracridine in acid soln. The requisite aniline and 9-chloracridine in equal molar proportions were dissolved in the minimum possible vol of boiling EtOH-H_2O (2:1). Concd HCl was added to the soln in a quantity sufficient to convert the aniline to its hydrochloride plus a further 0.1 of this quantity of concd HCl. After checking that the reaction mixt had a pH below 6, it was heated on the water bath for 40 min. Often product sepd during the heating. The crude product, obtd by filtration or, if necessary, by evapn, was dissolved in EtOH-H_2O, filtered from a trace of acridone, and crystd by addn of a salt of the requisite anion as noted in the tables, and/or by removal of some EtOH.

Acetylamino functions were cleaved (*e. g.*, 17 → 2) by heating under reflux condns with 2 *N* HCl-EtOH for 45 min. Often a dihydrochloride sepd as the reaction proceeded. The dihydrochloride, recovered by filtration or evaporation, was dissolved in H_2O by the addn of the min vol of boiling EtOH, and solid NaAc was added to a pH of 7. Addition of excess NaCl or NaBr pptd the monosalt in crude form. Recrystn was from EtOH-H_2O plus NaCl or NaBr. The salts listed in Table I have a marked tendency to sep from soln in a gelatinous form, this is best combated by crystg from solns contg greater than 10% of NaCl or NaBr and keeping the EtOH concn high and the total vol of soln low.

Variants. Compd 5 was prepd best by interaction of 9-chloracridine and a 10-fold excess of *o*-phenylenediamine in acid soln. The fraction of the reaction mixt soluble in boiling 0.2 *N* HCl was pptd with NaOH and dissolved in a little EtOH-H_2O-HCl, the pH adjusted with solid NaAc, and product pptd with excess satd aqueous NaCl. It proved very difficult to condense *o*-nitroaniline with 9-chloracridine by the standard method. A quantitative yield of acridone resulted.

The disinclination for *o*-nitroanilines to condense with 9-chloracridine allowed a very simple direct prepn of 36 and 37 from the corresponding nitrophenylene diamines. Both 36 and 37 on Fe reduction[10] gave the diamine 38.

The methanesulfonanilides 39–44 could be purified readily by dissolving in 5% KOH-H_2O by warming, clarifying, and pptg with HCl plus NaCl.

Methanesulfonanilides. The requisite aniline was dissolved in dry pyridine, sufficient vol being used so that on cooling to −5° no solid sepd. The vigorously stirred soln was maintained at −5° while the theoretical quantity of MsCl was added dropwise. After 1 hr at temp below 0° the mixt was allowed to warm to room temp, then excess Py removed *in vacuo* on a water bath. H_2O and ice were added to the gummy residue followed by sufficient HCl to neutralize the remaining Py. Once the deriv could be induced to cryst it was removed by filtration and washed well. There was usually a small amt of di-*N*-mesyl compd present, the proportion being higher if the temp was not maintained below 0° during the reaction. Purification was best affected by soln in excess cold 1 *N* NaOH with

Table II

Compd	Mp, °C	Formula	*Anal.*
Methanesulfonanilides			
2-Methanesulfonamido-4-nitro-[a]	283–285	$C_8H_{11}N_3O_6S_2$	C, H, N, S
4-Acetamido-2-nitro-[b]	183–185	$C_9H_{11}N_3O_5S$	C, H, N, S
4-Amino-2-nitro-	135–136	$C_7H_9N_3O_4S$	C, H, N, S
3-Amino-	120–121	$C_7H_{10}N_2O_2S$	C, H, N, S
Acridines			
2-Nitro-9-(*p*-[*p*-nitrobenzamido]anilino)-	323–324	$C_{26}H_{17}N_5O_5 \cdot HCl$	C, H, N, Cl
2-Amino-9-(*p*-[*p*-aminobenzamido]anilino)-	228–230	$C_{26}H_{21}N_5O \cdot HBr$	C, H, N, Br
9-(*p*-Benzamido)anilino-	351–352	$C_{26}H_{19}N_3O \cdot HCl$	C, H, N, Cl

[a] Fe reduction gave an easily autoxidized product which was accordingly immediately reacted with 9-chloracridine in acid solution to produce **41**. [b] NaOH-insoluble dimesyl by-product, mp 229–230°, *Anal.* ($C_{10}H_{15}N_3S_2O_7$) C, H, N, S.

‡ The 2′-(1-morpholinyl)ethylamino system was used since the predicted second p*k* value[7] should be below 5 ensuring that the morpholine nitrogen atom would remain uncharged and therefore act as an n-donor system.† A more strongly basic side chain existing as a cation at physiological pH values would be expected to act in the reverse way, *i. e.*, as an acceptor component.

§ This is the line of reasoning which led us to prepare these sulfonamides, it is not wished to imply from the high activity of 39 that there is in fact any basis to such arguments.

Table III[a]

Drug	Dose, mg/kg per day	Survivors	Weight change, g	Average days of survival		*T/C*, %	50-day survivors
				Treated	Control		
1c·monohydrobromide	150	6	−2.6	15.9	9.8	162	
	100	6	−1.2	19.4	10.1	192	
	67	6	0.2	16.3	10.3	158	
1d·monohydrobromide	135	6	−1.5	14.3	9.7	147	
	89	6	+1.3	14.6	10.2	143	
1e·monohydrobromide	150	5	−2.8	12.6	10.1	125	
	100	6	−1.2	14.3	10.3	139	
	67	6	+0.7	14.3	9.9	141	
2	50	6	−3.4	15.0	10.2	147	
	33	6	−1.8	17.7	10.3	172	
	22	6	−0.3	15.9	10.3	154	
6	60	5	−4.2	13.1	9.9	132	
	40	6	−2.2	15.0	10.3	146	
	27	6	+1.2	12.8	10.3	129	
9	150	6	−2.7	13.9	10.4	134	
	100	6	−0.7	16.1	10.2	158	
	67	6	+1.2	14.4	10.2	141	
11	60	5	−3.8	13.9	9.7	143	
	40	6	−1.1	15.0	9.9	151	
	27	6	+1.2	12.5	9.9	126	
13	60	6	−1.3	13.9	9.7	143	
	40	6	−0.2	12.5	9.9	126	
14	100	6	−1.4	14.1	9.9	142	
16	30	6	−0.4	14.0	10.5	133	
17	45	4	−4.3	14.4	10.4	138	
17	30	6	−1.2	15.0	10.3	146	
	20	6	−0.2	15.8	10.3	153	
	13	6	+0.3	14.7	9.7	142	
19	50	6	−1.4	14.5	10.2	142	
21	75	4	−4.3	14.0	9.9	138	
	50	6	−1.2	16.7	10.3	162	
	33	6	0.0	14.4	10.3	139	
22	50	6	−1.8	15.4	9.7	158	
	33	6	+0.3	15.0	10.1	149	
	22	6	+3.5	12.7	10.1	126	
26	50	6	−2.3	14.3	9.4	152	
	33	6	−1.0	14.2	9.6	136	
27	100	6	−3.2	13.1	10.1	133	
	67	6	−0.8	15.9	10.3	164	
	44	6	+0.7	14.9	10.3	153	
	30	6	+2.4	13.0	9.7	126	
28	60	5	−2.8	13.8	9.6	133	
	40	6	−0.6	16.0	9.9	158	
	27	6	+1.2	12.6	9.9	127	
29	80	6	−2.1	12.8	9.7	132	
30	180	5	−3.4	16.5	10.4	158	
	120	6	−1.3	17.1	9.7	166	
	80	6	+0.8	15.2	9.7	157	
	53	6	+3.5	13.2	10.1	131	
31	80	6	−1.2	16.4	9.7	169	
	53	6	−0.3	15.8	10.4	152	
	35	6	+4.1	12.2	9.6	127	
32	50	6	−1.3	16.8	9.7	173	
	33	6	−0.1	16.0	10.1	159	
	22	6	+1.5	13.1	10.3	127	
33	50	5	−3.5	17.0	9.7	175	
	33	6	−0.8	14.8	10.1	147	
38	40	6	−2.9	18.5	10.1	183	
	27	6	−0.3	20.7	9.7	213	
	18	6	+1.4	15.8	9.7	163	
39	75	6	−5.0	15.2	9.3	163	1
	50	6	−1.5	20.5	9.4	218	4
	33	6	−0.4	19.5	9.4	207	1
	22	6	+1.9	14.9	9.1	163	
	15	6	+2.1	12.7	9.7	131	
40	500	5	−4.3	16.8	9.3	181	
	330	6	−1.2	18.2	9.4	193	
	220	6	−0.9	17.0	9.4	181	
	150	6	−0.4	15.7	9.7	161	
	100	6	+0.9	14.9	9.7	153	
	67	6	+1.4	12.3	9.6	128	
41	250	5	−3.9	14.9	9.7	153	
	168	6	−1.4	14.8	10.4	142	
	110	6	+0.8	13.5	10.4	130	

Table III[a] (Continued)

Drug	Dose, mg/kg per day	Survivors	Weight change, g	Average days of survival: Treated	Average days of survival: Control	T/C, %	50-day survivors
43	75	6	−4.8	15.4	9.8	157	1
	50	6	−2.5	21.3	10.3	207	2
	33	6	−2.1	19.1	10.3	197	
	22	6	+1.0	16.3	10.2	159	
	15	6	+1.7	12.1	9.6	126	
44	53	6	−1.5	17.2	9.6	179	1
	37	6	−2.1	19.1	10.3	197	2
	24	6	−0.9	18.9	10.3	195	
	16	6	−0.4	17.0	9.8	173	
	11	6	+1.8	15.1	9.8	154	
	7	6	+1.3	13.6	10.2	133	

[a] Only those results providing significant T/C values have been given. Doses *ca.* 0.2 log higher than the greatest dose quoted were toxic; those 0.2 log lower than lowest quoted gave T/C's $\leq$ 125%.

vigorous stirring, clarifying, and repptg with acid. Most of the examples examined crystd well from EtOH-H_2O.

The amide intermediates necessary for 26-35 were prepd by phosphorazo coupling[10] of acid and amine component. Nitro functions were reduced to the amines with Fe as previously described.[10]

Compounds previously not reported are shown in Table II.

9-(2-Methylthio)ethylaminoacridine. Equimolar proportions of 1-methylthioethylamine and 9-chloracridine were heated together in 2 vol of anhyd PhOH at 120° for 40 min. After addn of excess cold 4 *N* NaOH, product was removed in PhH. The solvent layer, after thorough washing with 4 *N* NaOH and H_2O, was shaken with successive small vol of 4 *N* HCl, the cryst hydrochloride resulting being removed progressively. Crystn from MeOH-H_2O-NaCl afforded yellow needles (68%), mp 268-269°. *Anal.* ($C_{16}H_{16}N_2S \cdot HCl$) C, H, N, S

9-[2-(Morpholin-1-yl)ethylamino]acridine. Essentially the same experimental conditions as above produced the desired product as the dihydrochloride, yellow needles from small vol of 3 *N* HCl (54% yield), mp 282-283°. *Anal.* ($C_{19}H_{21}N_3O \cdot 2HCl$) C, H, N, Cl.

Biological Testing. The routine test consists of ip inoculation of 10^5 L1210 cells into 18.5-22.5 g C_3H/DBA_2F_1 hybrids on day 1; drug treatment was initiated 24 hr later and contd for 5 days. Dosage was in 0.2 ml vol, H_2O being used as the suspending medium. Groups of 6 animals per dose level were used with one control group for every 5 tests. The wt change column in Table III records the difference between initial wt and that at day 8 for survivors. The number of animals surviving as long or longer than controls is listed under survivors. Doses have been rounded off to 2 significant figures. Details of testing of inactive comps have not been given.

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Potential Antitumor Agents. 8. Derivatives of 3- and 5-Benzyloxy-2-formylpyridine Thiosemicarbazone

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A series of derivatives of 3- and 5-benzyloxy-2-formylpyridine thiosemicarbazone was synthesized and their antineoplastic activity was measured against sarcoma 180 ascites tumor cells. 3-(*m*-Aminobenzyloxy)-2-formylpyridine thiosemicarbazone was a potent antitumor agent, increasing the life-span of tumor-bearing mice over untreated animals by a factor of 2.4 at the optimal daily dose level of 80 mg/kg with no demonstrable signs of toxicity to the host. 5-(*m*-Hydroxybenzyloxy)-2-formylpyridine thiosemicarbazone and 5-(*m*-acetaminobenzyloxy)-2-formylpyridine thiosemicarbazone were marginally active.

The antineoplastic effect of a variety of thiosemicarbazones of α-(N-heterocyclic) carboxaldehydes has been actively investigated during the past few years.[1-11] The pyridine and isoquinoline rings have been found to be the most biologically active systems investigated.[2] Intensive studies on structure-activity relationships based on the modification of these two ring systems have indicated that no simple parametric rationale explains the effect of various substituents on activity against neoplastic cells. These findings may in part be due to the poor water solubility of this type of compound which limits their cellular uptake *in vivo*. The relative insolubility also imposes a limitation on the practi-