Table III. *N*-Trityldialkanolamine Dialkanesulfonates 7

| x | y | z | Mp, °C | Formula | Recrystn solvent | Analyses |
|---|---|---|---|---|---|---|
| 2 | 2 | 0 | 143-144[a] | $C_{25}H_{29}NO_6S_2$ | $C_6H_6$ | C, H, N, S |
| 2 | 2 | 1 | 103-104 | $C_{27}H_{33}NO_6S_2$ | *i*-$Pr_2O$ | C, H, N, S |
| 2 | 2 | 2 | 121-122 | $C_{29}H_{37}NO_6S_2$ | $C_6H_6$-petr ether | C, H, N, S |
| 3 | 3 | 0 | 51-51.5 | $C_{27}H_{33}NO_6S_2$ | $C_6H_6$-petr ether | C, H, N, S |
| 2 | 6 | 0 | 41-41.5 | $C_{29}H_{37}NO_6S_2$ | $C_6H_6$-petr ether | C, H, N, S |

[a] Lit.[5] mp 144 °C.

from the medium; with more lipophilic members it was necessary to add small volumes of $C_6H_6$ to initiate crystallization. The crystalline products were collected and washed free of trityl chloride with $C_6H_6$, $Et_2O$, or *i*-$Pr_2O$, taking care to minimize exposure of the crystals to the air. Products were dried in an evacuated desiccator over $P_2O_5$. In cases where the precursor *N*-trityl derivative had been obtained crystalline, the melting point of product obtained directly from the reaction mixture could not be improved by recrystallization. When the precursor had not been obtained crystalline, one recrystallization was necessary to obtain product hydrochloride of maximum melting point. Agents were stored at all times in an evacuated desiccator over $P_2O_5$.

The 3,3′-iminodi-1-propanol dimethanesulfonate 8 ($x = y = 3$; $z = 0$) prepared by the above route had the same melting point as an authentic sample which had been prepared by the interaction of methanesulfonic anhydride with 3,3′-imino-di-1-propanol in acetonitrile solution.[25] There was no melting point depression on admixture of the samples and these could not be distinguished or separated using the described reversed-phase TLC system.

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# Potential Antitumor Agents. 22. Latentiated Congeners of the 4′-(9-Acridinylamino)methanesulfonanilides

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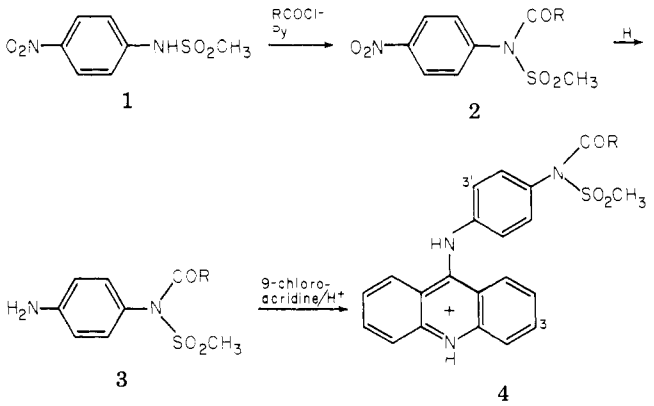
$N^1$-Acyl derivatives of the tumor inhibitory 4′-(9-acridinylamino)methanesulfonanilide agents act as prodrugs undergoing deacylation to liberate the core agents on incubation with pH 7.5 buffer or mouse blood. Against L1210 tumor implanted remotely from the drug administration site, lower acyl derivatives often provide enhanced effects over that obtained with nonacylated precursor alone. In certain homologous series of acyl derivatives, toxicity first increased with increasing lipophilic character, until greater than that of the core agent alone, and then at higher lipophilic levels decreased. Tumor inhibitory properties of the acyl derivatives in such series appeared inversely related to their toxicity. Several 3-(3,3-dialkyl-1-triazeno)acridine-substituted congeners provided excellent L1210 activity. Contrasting with most other tumor-active triazenes, one alkyl group need not be a methyl group for antileukemic activity to be observed. 3-Methyl-3-propyl-1-triazene and 3,3-diethyl-1-triazene analogues had comparable lipophilic–hydrophilic balance, toxicity, and antileukemic effectiveness; usual metabolic activation of the triazene *N*-methyl group may make little contribution to antitumor properties in the examples presented. Prepared as a nonalkylated triazene analogue, a 3-azidoacridine congener had high L1210 activity.

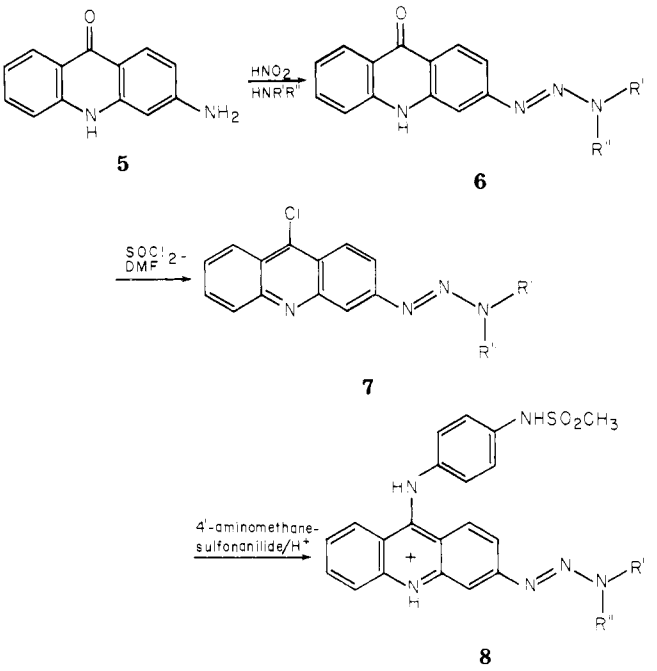
Earlier, active members of the 4′-(9-acridinylamino)-alkanesulfonanilide antitumor agents were screened using early, limited period, intraperitoneal (ip) dosing of animals implanted with L1210 leukemia at different anatomic sites.[1] It was found that the drug congeners most active against the leukemia implanted at sites remote from the point of drug administration were more lipophilic than considered optimal for ip implanted L1210.

If drug selectivity between leukemic cells and those of host tissues providing dose limitation could be effectively assayed in vitro, an optimum agent lipophilic–hydrophilic balance (log $P_0$) for selectivity would likely be found.

Scheme I



Scheme II



When drugs are screened against remotely implanted leukemia in animals, the necessary first step of drug translocation imposes additional pharmacokinetic requirements and, depending on relative rates of drug equilibration through tissues, excretion and/or deactivation may lead to a displacement of the in vitro observed log $P_0$. Providing applied drug is the ultimately active species, such drug pharmacokinetic properties must be of lesser importance when drug is applied directly (ip) to ip implanted tumor. The optimum drug log $P$ observed using ip dosed ip implanted tumor should then approach more closely to the log $P_0$ seen in in vitro conditions.

Although more lipophilic agents, that is, those with log $P$ greater than log $P_0$, can apparently distribute more effectively from the peritoneal cavity to an anatomically distant site,[1] these agents must necessarily have less than optimal activity against a tumor population. If suitable pharmacokinetic properties could be impressed upon an agent having a log $P$ value close to log $P_0$, so that it was then effectively ferried to distant sites, greater tumor cell kill at those sites should then result.

This publication described attempts to impress more desirable pharmacokinetic properties on certain members of this drug series by application of various prodrug strategies.

**Chemistry.** Vigorous acylation of 4'-nitromethanesulfonanilide (1, Scheme I) provides the *N*-acyl derivatives **2**. Nitro group reduction then generates an aromatic amine **3** which, on coupling with a 9-chloroacridine by the standard procedure[2] (method A), provides the latentiated agents **4**. Alternatively, if compatible with acridine ring substituents present, the sulfonamide function of a preformed 4'-(9-acridinylamino)methanesulfonanilide could be converted to the Na or K salt and this reacted with acyl halides in anhydrous media; more conveniently $Et_3N$ can be used in such acylations as base (RCOCl, $Me_2CO$, $Et_3N$) and homogeneous reaction mixtures then result (method B). 3-Aminoacridine variants (Table I, **59–66**) were prepared by reduction ($Fe/H^+$) of the corresponding nitro compounds **46–53** (method C).[3]

The dialkyltriazene function present in **69–73** was appended at the 9(10*H*)-acridone stage by diazotization of 3-aminoacridone and reaction of the resulting diazonium salt with the requisite amine (Scheme II). The remarkably stable 3-(3,3-dialkyl-1-triazeno)acridones (**6**) could be readily converted to the corresponding 9-chloroacridines ($SOCl_2$–DMF)[2] and then coupled with aromatic amines by a modification of the standard synthesis (method D). Triazenes so prepared from 2-aminoacridone were appreciably less stable and homogeneous products (cf. **8**) were not obtained by this route (Scheme II). The azide function necessary for **67** and **68** was similarly introduced at the acridone stage and the resulting 3-azidoacridone further elaborated, essentially as in Scheme II. The amine group of 4'-(3-amino-9-acridinylamino)methanesulfonanilide could not be satisfactorily diazotized, eliminating the prospect of a single-step synthesis of the triazenes **69–73** and the azides **67** and **68**.

## Results and Discussion

The prodrug strategy employs temporary drug masking functions to modulate pharmacologic properties of a core agent and thereby endows more desirable clinical attributes.[4,5] With time the use of the term latentiated drug derivative has become accepted as virtually synonymous with that of a prodrug.[6] Liberation of core agents from prodrugs already utilizes a wide range of release mechanisms.[4-9] Logical categorization of these mechanisms will inevitably prove desirable and it is suggested that a first step in this direction would be to retain the original meaning of the term latentiation.[9] Latentiated drugs would then be prodrugs from which there is enzyme-mediated liberation of the core active agent. The generic term prodrug can be applied to all precursors which ultimately deliver core agent to site and can be applied regardless of the drug release mechanisms employed.

Triggered removal of masking groups from latentiated derivatives of the acridines discussed could be mediated by intratumor or organ specific enzyme(s). The high local levels of agent could then increase effectiveness against tumor cells in those release areas. Such increased effectiveness against select tumors has as its cost less uniform drug distribution and a limiting of tumor action spectrum; high drug concentrations will be released in those organs and/or tumors with appreciable levels of triggering enzyme(s). Preferring to attempt to retain the wide spectrum of our acridine agents,[9,10] but impose more acceptable drug distribution patterns, we have sought release mechanisms which do not require organ or tissue specific enzymatic action.[11]

Functional groups used in prodrugs must necessarily be sufficiently stable to withstand manipulation of the laboratory. The major release mechanisms presently under consideration embrace (a) latentiated derivatives containing ester functions which, on reaching circulating blood,

Table I. Agent Properties and L1210 Screening Data for the 4'-(9-Acridinylamino)alkanesulfonanilide Congeners

| No. | Substituents in 4 R | Mp, °C | Formula | Analyses[a] | Method | $R_m$[b] | O.D.[c] | ILS[d] L1210 ip | ILS[d] L1210 sc |
|---|---|---|---|---|---|---|---|---|---|
| 9 | *e* | | | | | 0.00 | 45 | 107 | 28 |
| 10 | $CH_3$ | 236 dec | $C_{22}H_{19}N_3O_3S \cdot HCl$ | C, H, N, Cl | A, B | −0.14 | 160 | 109 | 68 |
| 11 | $CH_3CH_2$ | 255 dec | $C_{23}H_{21}N_3O_3S \cdot HCl$ | C, H, N, Cl | A | 0.07 | 300 | 88 (2) | 56 |
| 12 | $(CH_2)_2CH_3$ | 254 dec | $C_{24}H_{23}N_3O_3S \cdot HCl \cdot H_2O$ | C, H, N, Cl | A | 0.28 | 400 | 31 | |
| 13 | $(CH_2)_3CH_3$ | 247 dec | $C_{25}H_{25}N_3O_3S \cdot HCl$ | C, H, N, Cl | A | 0.34 | 400 | 68 | 28 |
| 14 | $(CH_2)_4CH_3$ | 236 dec | $C_{26}H_{27}N_3O_3S \cdot HCl \cdot H_2O$ | C, H, N, Cl | A | 0.45 | 150 | 41 | |
| 15 | $(CH_2)_5CH_3$ | 224 dec | $C_{27}H_{29}N_3O_3S \cdot HBr$ | C, H, N, Br | A | 0.54 | 150 | 61 | 27 |
| 16 | $(CH_2)_6CH_3$ | 182–185 | $C_{28}H_{31}N_3O_3S \cdot HCl$ | C, H, N, Cl | A | 0.68 | 400 | 41 | |
| 17 | $(CH_2)_7CH_3$ | 182–184 | $C_{29}H_{33}N_3O_3S \cdot HCl \cdot H_2O$ | C, H, N, Cl | A | 0.74 | 400 | 31 | |
| 18 | 3'-$OCH_3$ | | | | | 0.18 | 6.7 | 114 (2) | 27 |
| 19 | 3'-$OCH_3$ | $CH_3$ | 192–194 | $C_{23}H_{21}N_3O_4S \cdot HCl$ | C, H, N, Cl | A, B | 0.05 | 6 | 70 | 33 |
| 20 | 3'-$OCH_3$,4-$CH_3$ | | | | | 0.24 | 6 | 111 | 47 |
| 21 | 3'-$OCH_3$,4-$CH_3$ | $CH_3$ | 222–223 | $C_{24}H_{23}N_3O_4S$ | C, H, N, S | A | 0.11 | 7.5 | 38 | |
| 22 | 3'-$OCH_3$,4-$CH_3$ | $CH_2CH_3$ | 196–198 | $C_{25}H_{25}N_3O_4S$ | C, H, N, S | A | 0.37 | 25 | 31 | |
| 23 | 3'-$OCH_3$,4-$CH_3$ | $(CH_2)_2CH_3$ | 206–207 | $C_{26}H_{27}N_3O_4S$ | C, H, N, S | A | 0.53 | 75 | 52 | |
| 24 | 3'-$OCH_3$,4-$CH_3$ | $(CH_2)_3CH_3$ | 194–195 | $C_{27}H_{29}N_3O_4S$ | C, H, S; N[f] | B | 0.66 | 250 | 50 | |
| 25 | 3'-$OCH_3$,4-$CH_3$ | $(CH_2)_4CH_3$ | 185–186 | $C_{28}H_{31}N_3O_4S$ | C, H, N, S | B | 0.79 | 66 | 39 | |
| 26 | 3'-$OCH_3$,4-$CH_3$ | $(CH_2)_2COOC_2H_5$ | 125–128 | $C_{28}H_{29}N_3O_6S$ | C, H, N, S | B | 0.62 | 18 | 43 | |
| | | | 250–252 | $C_{28}H_{29}N_3O_6S \cdot MsOH \cdot 1.5H_2O$[g] | C, H, N, S | | | 13.3 | 40 | |
| 27 | 3'-$OCH_3$,4-$CH_3$ | $(CH_2)_2COO(CH_2)_2CH_3$ | 142–143 | $C_{29}H_{31}N_3O_6S$ | C, H, N, S | B | 0.75 | 75 | | |
| 28 | 3-$NHCOCH_3$ | | | | | | −0.12 | 13 | 114 (2) | 33 |
| 29 | 3-$NHCOCH_3$ | $CH_3$ | 268–269 | $C_{24}H_{22}N_4O_4S \cdot HCl$ | C, H, N, Cl | A | −0.19 | 28 | 118 (2) | 43 |
| 30 | 3-$NHCOCH_3$ | $CH_2CH_3$ | 255–256 | $C_{25}H_{24}N_4O_4S \cdot HCl$ | C, H, N, Cl | A | 0.00 | 40 | 135 (3) | 88 |
| 31 | 3-$NHCOCH_3$ | $(CH_2)_2CH_3$ | 265 dec | $C_{26}H_{26}N_4O_4S \cdot HCl$ | C, H, N, Cl | A | 0.22 | 50 | 98 | 62 |
| 32 | 3-$NHCOCH_3$ | $(CH_2)_3CH_3$ | 267–268 | $C_{27}H_{28}N_4O_4S \cdot HCl$ | H, N, Cl; C[h] | A | 0.36 | 80 | 89 | 63 |
| 33 | 3-$NHCOCH_3$ | $(CH_2)_4CH_3$ | 254–255 | $C_{28}H_{30}N_4O_4S \cdot HCl$ | C, H, N, Cl | A | 0.51 | 42 | 81 | 43 |
| 34 | 3-$NHCOCH_3$ | $(CH_2)_5CH_3$ | 253–254 | $C_{29}H_{32}N_4O_4S \cdot HBr \cdot H_2O$ | C, H, N, Br | A | 0.63 | 14 | 71 | 47 |
| 35 | 3-$NHCOCH_3$ | $(CH_2)_6CH_3$ | 233–234 | $C_{30}H_{34}N_4O_4S \cdot HBr$ | C, H, N, Br | A | 0.69 | 22 | 83 (2) | 45 |
| 36 | 3-$NHCOCH_3$ | $(CH_2)_7CH_3$ | 232 dec | $C_{31}H_{36}N_4O_4S \cdot HBr$ | C, H, N, Br | A | 0.72 | 45 | 143 (2) | 83 |
| 37 | 3-$NHCOCH_3$ | $(CH_2)_8CH_3$ | 232 dec | $C_{32}H_{38}N_4O_4S \cdot HBr \cdot H_2O$ | C, H, N, Br | A | 0.76 | 50 | 98 | 65 |
| 38 | 3-$NHCOCH_3$ | $(CH_2)_9CH_3$ | 237 dec | $C_{33}H_{40}N_4O_4S \cdot HBr$ | C, H, N, Br | A | 0.79 | 30 | 64 | 39 |
| 39 | 3-$NHCOCH_3$ | $(CH_2)_{10}CH_3$ | 241 dec | $C_{34}H_{42}N_4O_4S \cdot HBr$ | C, H, N, Br | A | 0.81 | 30 | 72 | 41 |
| 40 | 3-$NHCOCH_3$ | $(CH_2)_{16}CH_3$ | 207–208 | $C_{40}H_{54}N_4O_4S$ | C, H, N, S | A | 0.87 | 450 | 68 | 39 |
| 41 | 3-$NHCOCH_3$ | $CH(CH_3)_2$ | 271 dec | $C_{26}H_{26}N_4O_4S \cdot HCl$ | C, H, N, Cl | A | 0.29 | 50 | 93 | 57 |
| 42 | 3-$NHCOCH_3$ | $CH(CH_3)CH_2CH_3$ | 266 dec | $C_{27}H_{28}N_4O_4S \cdot HCl \cdot 0.5H_2O$ | C, H, N, Cl | A | 0.38 | 50 | 68 | 31 |
| 43 | $C(CH_3)_3$ | 216 dec | $C_{25}H_{26}N_3O_3S \cdot HCl \cdot H_2O$ | C, H, N, Cl | A | 0.31 | 250 | 47 | | |
| 44 | $OCH_3$ | 233–234 | $C_{22}H_{19}N_3O_4S \cdot HCl$ | C, H, N, Cl | A | 0.07 | 250 | 67 | 36 | |
| 45 | 3-$NO_2$ | | | | | −0.07 | 25 | 123 (2) | 43 | |
| 46 | 3-$NO_2$ | $CH_3$ | 266–267 | $C_{22}H_{18}N_4O_5S$ | C, H, N, S | A | −0.08 | 50 | 138 (2) | 61 |
| 47 | 3-$NO_2$ | $CH_2CH_3$ | 241–242 | $C_{23}H_{20}N_4O_5S \cdot H_2O$ | C, H, N, S | A | 0.13 | 50 | 162 (2) | 57 |
| 48 | 3-$NO_2$ | $(CH_2)_2CH_3$ | 231–232 | $C_{24}H_{22}N_4O_5S$ | C, H, N, S | A | 0.27 | 50 | 52 | |
| 49 | 3-$NO_2$ | $(CH_2)_3CH_3$ | 211–213 | $C_{25}H_{24}N_4O_5S$ | C, H, N, S | A | 0.32 | 26 | 91 | 57 |
| 50 | 3-$NO_2$ | $(CH_2)_4CH_3$ | 171–172 | $C_{26}H_{26}N_4O_5S$ | C, H, N, S | A | 0.41 | 5 | 57 | 39 |
| 51 | 3-$NO_2$ | $(CH_2)_5CH_3$ | 206–208 | $C_{27}H_{28}N_4O_5S$ | C, H, N, S | A | 0.50 | 9 | 48 | 41 |
| 52 | 3-$NO_2$ | $(CH_2)_6CH_3$ | 223–224 | $C_{28}H_{30}N_4O_5S$ | C, H, N, S | B | 0.61 | 10 | 62 | 47 |
| 53 | 3-$NO_2$ | $(CH_2)_7CH_3$ | 208–209 | $C_{29}H_{32}N_4O_5S$ | C, H, N, S | B | 0.71 | 75 | 144 (2) | 61 |
| 54 | 3-$NO_2$,5-$CH_3$ | | | | | −0.01 | 100 | 113 (2) | 98 (2) | |
| 55 | 3-$NO_2$,5-$CH_3$ | $CH_3$ | 266–267 | $C_{23}H_{20}N_4O_5S$ | C, H, N, S | A | −0.03 | 200 | 217 (1) | 188 (1) |
| 56 | 3-$NO_2$,5-$CH_3$ | $CH_2CH_3$ | 243–244 | $C_{24}H_{22}N_4O_5S$ | C, H, N, S | A | 0.20 | 50 | 81 | 27 |
| 57 | 3-$NO_2$,5-$CH_3$ | $(CH_2)_2CH_3$ | 227–229 | $C_{25}H_{24}N_4O_5S$ | C, H, N, S | A | 0.31 | 50 | 71 | 31 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 58 | 3-$NH_2$ | $CH_3$ | 255–256 | $C_{22}H_{20}N_4O_3S$·HCl | C, H, N, Cl | C | −0.17 | 2.5 | 81 (1) | | |
| 59 | 3-$NH_2$ | $CH_2CH_3$ | 214–216 | $C_{23}H_{22}N_4O_3S$·HBr·1.5$H_2O$ | C, H, N, Br | C | −0.22 | 2 | 74 | | |
| 60 | 3-$NH_2$ | $(CH_2)_2CH_3$ | 244 dec | $C_{24}H_{24}N_4O_3S$·HCl | C, H, N, Cl | C | −0.04 | 2 | 49 | | |
| 61 | 3-$NH_2$ | $(CH_2)_3CH_3$ | 219–220 | $C_{25}H_{26}N_4O_3S$·HCl | C, H, N, Cl | C | 0.13 | 1 | 53 | | |
| 62 | 3-$NH_2$ | $(CH_2)_4CH_3$ | 184–186 | $C_{26}H_{28}N_4O_3S$·HCl | C, H, N, Cl | C | 0.31 | 1 | 61 | | |
| 63 | 3-$NH_2$ | $(CH_2)_5CH_3$ | 176–178 | $C_{27}H_{30}N_4O_3S$·HCl·1.5$H_2O$ | C, H, N, Cl | C | 0.43 | 2 | 46 | | |
| 64 | 3-$NH_2$ | $(CH_2)_6CH_3$ | 178–181 | $C_{28}H_{33}N_4O_3S$·HCl·$H_2O$ | C, H, N, Cl | C | 0.51 | 2 | 31 | | |
| 65 | 3-$NH_2$ | $(CH_2)_7CH_3$ | 171–173 | $C_{29}H_{34}N_4O_3S$·HCl·0.5$H_2O$ | C, H, N, Cl | C | 0.57 | 2.5 | 119 | | |
| 66 | 3-$N_3$ | | 282 dec | $C_{20}H_{18}N_6O_2$·HCl | C, H, N, Cl | D | 0.59 | 2.5 | 64 | | |
| 67 | 3-$N_3$,3'-$OCH_3$ | | 282–283 | $C_{21}H_{18}N_6O_3S$·HCl·0.5$H_2O$ | C, H, N, Cl | D | −0.02 | 16 | 216 (2) | 64 | |
| 68 | | | | | | | 0.14 | 8 | 118 (3) | 47 | |
| | Substituents in **8** | | | | | | | | | | |
| | R' | R'' | | | | | | | | | |
| 69 | $CH_3$ | $CH_3$ | 253–254 | $C_{22}H_{21}N_6O_2S$·HCl | C, H, N, Cl | D | 0.22 | 8 | 110 (3) | 38 | |
| 70 | $C_2H_5$ | $C_2H_5$ | 222–225 | $C_{24}H_{26}N_6O_2S$ | C, H, N, S | D | 0.49 | | | | |
| | | | 226–228 | $C_{24}H_{26}N_6O_2S$·MsOH | C, H, N, S | | | 25 | 96 | 28 | |
| 71 | $CH_3$ | $(CH_2)_2CH_3$ | 149–151 | $C_{24}H_{26}N_6O_2S$·MsOH | C, H, N, S | D | 0.47 | 15 | 98 (1) | 27 | |
| 72 | 3'-$OCH_3$ | $CH_3$ | 195–198 | $C_{23}H_{24}N_6O_3S$·HCl | C, H, N, Cl | D | 0.38 | 10 | 141 (1) | 34 | |
| 73 | 3'-$OCH_3$ | $(CH_2)_2CH_3$ | 159–161 | $C_{25}H_{28}N_6O_3S$·MsOH | C, H, N, S | D | 0.65 | 15 | 100 | 29 | |

[a] Analyses for the elements indicated were within ±0.4% of the theoretical figures for the formulas quoted. [b] Measure of lipophilic–hydrophilic balance from partition chromatography, see ref 7 and 8. [c] Optimum dose, that providing maximum increase in life span, quoted in mg/kg/day for a dq 1–5 ip dosing schedule. [d] ILS = increase in life span in L1210 assays (=T/C% − 100) when tumor ($10^5$ cells) implanted intraperitoneally (ip) or subcutaneously (sc) above the right axialla. The number of 50-day survivors, from a group of six mice, is given in parentheses. [e] Nonacylated derivative for comparison purposes. [f] N: calcd, 8.55; found, 8.0. [g] MsOH = methanesulfonic acid. [h] C: calcd, 59.9; found, 60.4.

will be hydrolyzed by ubiquitous serum esterases, thereby initiating the drug release sequence, and (b) prodrugs which are of sufficient stability to be laboratory handled at low temperature, at nonphysiologic pH, or in anhydrous media, these latter to be unstable at the temperature, physiologic pH, or aqueous milieu encountered on administration to animals, thereby priming drug release. Preliminary chemical data necessary for one approach to type (a) release have been described.[12] Two attempts to utilize in vivo instability are detailed below.

*N*-Acyl derivatives of sulfonamides have varying ease of hydrolysis depending on the degree of N-substitution. Acylsulfonamides such as $N^1$-acetylsulfanilamide (sulfacetamide) are strong acids and at physiologic pH bear an anionic charge which slows further hydroxide ion attack, presumably by Coulombic effect; such compounds are relatively alkali stable. In contrast, *N*-acyl derivatives of *N*-aryl- (or alkyl-) sulfonamides cannot adopt a negative charge and are quite susceptible to hydrolysis at alkaline pH. Prodrugs such as $N^1$-acetylsulfisoxazole[13] are stable in acid media but at pH 8 slowly release sulfisoxazole. Administration to patients of $N^1$-acetylsulfisoxazole provides more prolonged therapeutic levels of the core sulfisoxazole.[13] Similarly, acylsulfonamides **2**–**4** are extremely susceptible to alkaline cleavage and, as monitored by thin-layer chromatography, undergo slow deacylation in pH 7.5 buffer at 37 °C. More pertinently **4** (R = $CH_3$) incubated with mouse blood at 37 °C slowly released the core 4'-(9-acridinylamino)methanesulfonanilide. *N*-Acyl-*N*-arylsulfonamides (e.g., **4**) then provide an example of type (b) drug release.

$R_m$ values from reversed-phase chromatography have again been utilized as a measure of agent lipophilic–hydrophilic balance.[14,15] Sulfonamide N-acetylation has in all cases provided derivatives more hydrophilic than the parent agent (**9**, **10**; **18**, **19**; **28**, **29**; **45**, **46**; **54**, **55**; **58**, **59**). As before,[1] early, limited period, intraperitoneal (ip) dosing of animals with depots of L1210 implanted at different anatomic sites has been used to assess capacity of an agent to distribute to a remote site. Homologues more lipophilic than that found optimal for ip dosed, ip implanted tumor earlier provided greater life extensions when assayed against subcutaneously (sc) implanted tumor.[1] In contrast, with the present prodrugs the more hydrophilic *N*-acetyl derivative (**10**) of the series parent **9** provided greater inhibition of the sc tumor. More lipophilic acyl congeners **11**–**17** were less effective than the acetyl derivative **10** against sc tumor implants although the propionyl congener **11** still appeared more active than the precursor **9**. There appeared to be a downward trend in activity against both ip and sc L1210 as lipophilic character increased (**10**–**17**), with an additionally impressed alternation in activity with changing alkyl chain length. A possible explanation for the apparent discrepancy in the role of lipophilic character for inhibition of sc tumor with members of the parent series and the *N*-acyl derivatives could reside in the relative ease of thiolytic cleavage of these compounds. We have noted that thiols readily replace the methanesulfonanilide ring of these agents with formation of L1210 inactive acridine 9-thioethers.[16,17] Comparison of half-lives ($t_{1/2}$) of the parent **9** and the *N*-acetyl derivative **10** in thiolytic assays as before[16,17] (0.1 M 2-mercaptoethanol, pH 7.4, $^1/_{15}$ M $PO_4^-$; MeOH; 1:1, 37 °C) provided figures of 55 and 396 min, respectively; i.e., *N*-acylation stabilizes these agents to thiolytic cleavage. The apparent need for a greater lipophilic character to reach sc tumor in the parent series may reflect a need for more rapid movement to the sc site in the face of continual drug decay by thiolytic cleavage

additional to normal metabolic deactivation and excretion.

Lipophilic character compatible with L1210 activity (cf. **16** and **17**) is higher in the acyl derivatives than permissible in the 4′-(9-acridinylamino)alkanesulfonanilides where the butanesulfonanilide ($R_m$ = 0.56) is inactive.[2] Such data lend some support to the view that acyl derivatives such as **16** and **17** are active because of in vivo hydrolysis to the sulfonanilide **9** although increased stability to thiolysis may also play a role.

An added 3′-$OCH_3$ group increases dose potency with full activity retention (**18**)[18] and produces a twofold lengthening of $t_{1/2}$ in thiolytic assays.[16,17] The $N^1$-acetyl derivative **19** of this compound was not as L1210 active as its demethoxy counterpart **10**. A 4-$CH_3$ group appears to assist drug translocation[1] (cf. **20** and **18**) while having only marginal effects on $t_{1/2}$ in thiolytic assays.[16,17] $N^1$-Acyl derivatives of a 4-$CH_3$ bearing example, **20**, provided a series of poorly active agents (**21–25**). With the thought that these lower activities might have resulted from excessive overall lipophilic character (cf. **10** and **21**), the ester homologues **26** and **27** were prepared, theorizing that serum esterase activity would liberate the considerably more hydrophilic acid hemisuccinate derivatives. The ethyl ester **26** provided a poor level of activity while the propyl homologue **27** was inactive.

With the hydrophilic 3-acetamido congener (**28**) as core agent, the short-chain acyl congeners (**30–32**) provided better levels of activity against sc tumor but with maximum activity now being seen with the propionyl derivative **30**. To attempt to find if there was a cut-off in biologic activity at high lipophilic character, an extended series of 3-acetamido congeners was prepared but activity persisted up to the palmitoyl derivative **40**. This series provides several further interesting points; there is not a constant increase in $R_m$ values with increasing chain length, and similar discontinuities in log $P$ additivity have been noted when there are long alkyl chains which can form intramolecular hydrophobic contacts.[19] Further, employing the optimum dose (O.D., Table I) as a measure of toxicity, it can be seen that this first drops with increasing $R_m$ values (**30–32**), then increases (**32–34**) to a level exceeding that of the core agent (**28**) on a molar basis, and then decreases again (**34–40**). Antitumor activity alters in inverse fashion to the changes in toxicity. Similar results were observed when the hydrophilic 3-nitro variant **45** was utilized as core agent (**46–53**); toxicity increased to a level greater than that of the parent agent (cf. **45** and **50**), L1210 effectiveness dropping at the same time. With further increases in lipophilic nature (**51–53**) toxicity dropped and antitumor activity climbed to close to that of the parent **45**. The 3-nitro-5-methyl congener **54** shows excellent activity against sc tumor[1] and the $N$-acetyl derivative **55** shows exemplary activity but there is a very rapid decrease in activity on further homologation (**56, 57**). Agents with an unshielded 3-amino group formerly provided no activity against sc implanted L1210[1] and it was of interest to determine if on sulfonamide N-acylation significant sc activity resulted. As seen by entries **59–66** no sc activity was encountered. Once more, as lipophilic character first increased, toxicity increased (**61, 62**), and then at yet higher levels decreased (**65**) when L1210 activity comparable to that of core agent (**58**) was again encountered. Similar changes in toxicity and L1210 activity have been seen in the three series bearing nitrogen-containing acridine 3-substituents (**29–40, 46–53, 59–66**) but not the two (**10–17, 21–25**) without such groups. In those three series showing increasing toxicity the $N^1$-acyl derivatives of median lipophilic nature might more successfully permeate a host sensitive tissue which then provides dose limitation with a consequent reduction in antileukemic efficacy. Access to that site must then be proscribed as acyl chain length is further increased and, with the higher doses then possible, greater antileukemic activity is observed. The most active of the hydrophilic $N$-acyl congeners, against sc and ip L1210, have $R_m$ values close to nought, that is, in the area considered necessary for optimum activity against ip L1210 in the parent series.[2] In some series high activity has again been observed at higher lipophilic levels when the acyl function had a C-6 or C-7 alkyl chain (**36, 53, 65**). It is clear that activity against remotely implanted tumor can be favorably influenced by sulfonamide N-acylation; $N$-acyl groups, containing polar functionality but providing prodrugs with necessary $R_m$ values, might then have desirable pharmacokinetic properties and also be more amenable to pharmaceutical formulation.

Ease of hydrolysis of the $N^1$-acyl function would be expected sensitive to steric bulk of groups close to the carbonyl group and changes in toxicity and antitumor activity might then result. However, examples with $\alpha$-branched acyl groups (**41, 42**) were comparable in toxicity and activity to congeners of like lipophilic character (**31, 32**). Dibranching, as in the pivaloyl derivative **43**, also provided an unremarkable agent (cf. **12, 13**). A $N^1$-urethane could also be expected to have greater stability but it provided a further unremarkable molecule (**44**). These various analogues all liberate core agent when incubated with pH 7.5 buffer at 37 °C. We earlier reported the L1210 inactivity of the corresponding $N^1$-(methanesulfonyl)methanesulfonamide[18] analogue which is extremely stable, requiring treatment with NaOMe–MeOH for effective cleavage, and it is not hydrolyzed at discernable rate in buffer of physiologic pH.

With the tumor inhibitory[20] 5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide as an example, a dimethyltriazene can, with cultured bacterial and mammalian cells in the light, act as a precursor of 5-diazoimidazole-4-carboxamide.[21,22] In the absence of light in such cultures, or in vivo, the triazene acts as a methylcarbonium ion source and it liberates 5-aminoimidazole-4-carboxamide.[20–26] The in vivo antitumor properties of this triazene likely result from liberated methylcarbonium ion,[20] although the 5-diazo compound also has carcinostatic properties.[27,28] With our acridine agents an added dimethyltriazeno function could then act as a latentiating group delivering an aminoacridine derivative in vivo. Additionally, the triazeno group, by acting as a source of either carbonium ion or a diazonium compound, might confer added tumor inhibitory properties. The triazenes prepared **69–73** show excellent activity for their $R_m$ values which are higher than deemed optimal in the parent series.[2] Either these agents are precursors to more hydrophilic ultimate agents or more hydrophilic agents might provide even greater activity. At least one triazene methyl group has been shown essential for L1210 activity in the triazenoimidazoles.[29] This is not so in the present series where the corresponding 3,3-diethyl- and 3-methyl-3-propyltriazenes **70** and **71** have comparable $R_m$ values, toxicity, and levels of antileukemic activity. There appears to be no marked advantage associated with those agents having triazene methyl groups (**69, 71–73**), making it unlikely that usual routes of triazene metabolic activation[20–26] are here of critical importance. The relative lack of responsiveness to triazene alkyl groups and the high lipophilic character of the examples prepared (**69–73**) prompted examination of a compound without such alkyl groups but retaining an unsaturated chain of three nitrogen

Table II. *N*-Acyl-*N*-(R-phenyl)methanesulfonamides

| Acyl function | R | Mp, °C | Formula | Analyses |
|---|---|---|---|---|
| $CH_3CO$ | 4-$NO_2$ | 192-193 | $C_9H_{10}N_2O_5S$ | C, H, N |
| $CH_3CH_2CO$ | 4-$NO_2$ | 188-189 | $C_{10}H_{12}N_2O_5S$ | C, H, N, S |
| $CH_3(CH_2)_2CO$ | 4-$NO_2$ | 158-159 | $C_{11}H_{14}N_2O_5S$ | C, H, N |
| $CH_3(CH_2)_3CO$ | 4-$NO_2$ | 125-126 | $C_{12}H_{16}N_2O_5S$ | C, H, N, S |
| $CH_3(CH_2)_4CO$ | 4-$NO_2$ | 129-130 | $C_{13}H_{18}N_2O_5S$ | C, H, N, S |
| $CH_3(CH_2)_5CO$ | 4-$NO_2$ | 111-112 | $C_{14}H_{20}N_2O_5S$ | C, H, N, S |
| $CH_3(CH_2)_6CO$ | 4-$NO_2$ | 102-103 | $C_{15}H_{22}N_2O_5S$ | C, H, N, S |
| $CH_3(CH_2)_7CO$ | 4-$NO_2$ | 97-98 | $C_{16}H_{24}N_2O_5S$ | C, H, N, S |
| $CH_3(CH_2)_8CO$ | 4-$NO_2$ | 94-95 | $C_{17}H_{26}N_2O_5S$ | C, H, N, S |
| $CH_3(CH_2)_9CO$ | 4-$NO_2$ | 89-90 | $C_{18}H_{28}N_2O_5S$ | C, H, N, S |
| $CH_3(CH_2)_{10}CO$ | 4-$NO_2$ | 90-91 | $C_{19}H_{30}N_2O_5S$ | C, H, N, S |
| $CH_3(CH_2)_{16}CO$ | 4-$NO_2$ | 99-100 | $C_{25}H_{42}N_2O_5S$ | C, H, N, S |
| $(CH_3)_2CHCO$ | 4-$NO_2$ | 139-140 | $C_{11}H_{14}N_2O_5S$ | C, H, N |
| $CH_3CH_2(CH_3)CHCO$ | 4-$NO_2$ | 130-131 | $C_{12}H_{16}N_2O_5S$ | C, H, N |
| $CH_3OCO$ | 4-$NO_2$ | 145-146 | $C_9H_{10}N_2O_6S$ | C, H, N |
| $(CH_3)_3CCO$ | 4-$NO_2$ | 126-127 | $C_{12}H_{16}N_2O_5S$ | C, H, N, S |
| $CH_3CO$ | 3-$OCH_3$,4-$NO_2$ | 162-163 | $C_{10}H_{12}N_2O_6S$ | C, H, N, S |
| $CH_3CO$ | 4-$NH_2$ | 160-161 | $C_9H_{12}N_2O_3S$ | C, H, N |
| $CH_3CH_2CO$ | 4-$NH_2$ | 148-149 | $C_{10}H_{14}N_2O_3S$ | C, H, N |
| $CH_3(CH_2)_2CO$ | 4-$NH_2$ | 156-157 | $C_{11}H_{16}N_2O_3S$ | C, H, N, S |
| $CH_3(CH_2)_3CO$ | 4-$NH_2$ | 143-144 | $C_{12}H_{18}N_2O_3S$ | C, H, N, S |
| $CH_3(CH_2)_4CO$ | 4-$NH_2$ | 137-138 | $C_{13}H_{20}N_2O_3S$ | C, H, N, S |
| $CH_3(CH_2)_5CO$ | 4-$NH_2$ | 125-126 | $C_{14}H_{22}N_2O_3S$ | C, H, N, S |
| $CH_3(CH_2)_6CO$ | 4-$NH_2$ | 136-137 | $C_{15}H_{24}N_2O_3S$ | C, H, N, S |
| $CH_3(CH_2)_7CO$ | 4-$NH_2$ | 129-130 | $C_{16}H_{26}N_2O_3S$ | C, H, N, S |
| $CH_3(CH_2)_8CO$ | 4-$NH_2$ | 134-135 | $C_{17}H_{28}N_2O_3S$ | C, H, N, S |
| $CH_3(CH_2)_9CO$ | 4-$NH_2$ | 132-133 | $C_{18}H_{30}N_2O_3S$ | C, H, N, S |
| $CH_3(CH_2)_{10}CO$ | 4-$NH_2$ | 134-135 | $C_{19}H_{32}N_2O_3S$ | C, H, N, S |
| $CH_3(CH_2)_{16}CO$ | 4-$NH_2$ | 132-133 | $C_{25}H_{44}N_2O_3S$ | C, H, N, S |
| $(CH_3)_2CHCO$ | 4-$NH_2$ | 184-185 | $C_{11}H_{16}N_2O_3S$ | C, H, N |
| $CH_3CH_2(CH_3)CHCO$ | 4-$NH_2$ | 109-110 | $C_{12}H_{18}N_2O_3S$ | C, H, N, S |
| $CH_3OCO$ | 4-$NH_2$ | 175-176 | $C_9H_{12}N_2O_4S$ | C, H, N |
| $CH_3CO$ | 3-$OCH_3$,4-$NH_2$ | 167-168 | $C_{10}H_{14}N_2O_4S$ | C, H, N, S |

atoms, that is, an azide. The azides prepared (67, 68) have very high levels of L1210 activity. While there is no good reason to assume that the azide group is acting as other than merely an acceptable acridine substituent, such functionality should be examined in situations where a dialkyltriazene group has of itself conferred antitumor activity.

## Experimental Section

Where analyses are indicated only by symbols of the elements, analytical results obtained for these 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 maker's supplied stem corrected thermometer; melting points are as read.

To monitor the progress of reactions, purification of products, etc., TLC on $SiO_2$ (Merck $SiO_2$, $F_{254}$) was used. Most valuable solvents were $CHCl_3$ or $CH_2Cl_2$ containing 0–12% of MeOH, EtOAc–petroleum ether mixtures, and the top phase of a mixture of *n*-BuOH–HOAc–$H_2O$ (5:1:4, v/v).

***N*-Acyl-*N*-(4-nitrophenyl)methanesulfonamides** were readily prepared by heating a pyridine solution of 4'-nitromethanesulfonanilide containing 2 mol equiv of acyl chloride under reflux conditions until TLC monitoring demonstrated reaction was complete. After removal of excess pyridine in vacuo on the steam bath, crude product could be precipitated by addition of sufficient ice-cold 2 N HCl to neutralize remaining pyridine. When lower molecular weight acyl chlorides were used, further purification merely required crystallization of dry crude product from anhydrous solvents. When higher molecular weight acyl chlorides were employed, lavage of an EtOAc solution of crude product with 10% $KHCO_3$ facilitated removal of adhering acid by-product. Concentration of the dried ($Na_2SO_4$) EtOAc solution, addition of petroleum ether to turbidity, and then cooling normally provided crystalline products. These acyl derivatives are readily cleaved by alkaline media; attempted washing of crude solid with even mild bases such as $KHCO_3$ invariably led to some deacylation.

Alternatively, the 4'-nitromethanesulfonanilide could be converted to the Na salt by employing the theoretical quantity of NaOMe in MeOH, the solvent then removed, and the residual salt dried in vacuo. Stirred suspensions of this salt in dry $Me_2CO$ or THF on treatment with 1.05 mol equiv of acid chloride rapidly provided the required *N*-acyl derivatives. Work-up by removal of NaCl and evaporation of solvent invariably provided crystalline product which was crystallized from anhydrous nonprotic solvents.

***N*-Acyl-*N*-(4-aminophenyl)methanesulfonamides** could be readily prepared by either $Fe/H^+$ [2] or catalytic (Pd/C; EtOAc, 45 psi of $H_2$) reduction of the above nitro compounds. Although products are somewhat more stable to alkalies than the precursor nitro compounds, contact with bases, particularly $NH_3$, must be avoided (see Table II).

Methods of preparation of 9-chloroacridines, coupling of these with amine components (method A), etc., have been well described.[2,3] Final products (4) are best purified as either the salts from acid aqueous media (pH <5) or as the free base from anhydrous nonprotic solvents. Solution in neutral aqueous media will, particularly in the hot, provide some deacylation.

**Method B.** 4'-(9-Acridinylamino)methanesulfonanilide hydrochloride salts were converted to the free base by treatment of EtOH–$H_2O$ solutions with the theoretical quantity of $KHCO_3$ as before.[2] The base could be converted to Na or K salts of the sulfonamide function by treatment with the theoretical quantity of NaOH or KOH–MeOH, removal of solvent, and drying. Treatment of the dry salt in $Me_2CO$ or THF suspension with acyl chlorides, essentially as earlier described for the *N*-acyl-*N*-(4-nitrophenyl)methanesulfonamides, then provided crude products. More conveniently, the dried (100 °C, vacuum) base (0.05 mol) was dissolved in dry $Me_2CO$ (75 ml) by stirring and addition of $Et_3N$ (0.052 mol). To the ice-cooled well-stirred solution the requisite acyl chloride (0.055 mol) was added at a rate providing an internal temperature not greater than 5 °C. When addition was complete the reaction mixture was stirred for 1 h and then $Me_2CO$ removed in vacuo at room temperature. Ice-cold EtOAc (100 ml) and 10% $KHCO_3$ (20 ml) were added and the organic layer was washed well with $H_2O$, dried ($Na_2SO_4$), and evaporated. Products were recrystallized as before as the base or converted to hydrochloride or methanesulfonate salt by addition of a dry

Table III. 9(10*H*)-Acridones

| Substituent | Mp, °C | Formula | Analyses |
|---|---|---|---|
| 3-$N_3$ | >360 | $C_{13}H_8N_4O$ | C, H, N |
| 3-N=NN($CH_3$)$_2$ | 285-287 | $C_{15}H_{14}N_4O$ | C, H, N |
| 3-N=NN($C_2H_5$)$_2$ | 297-298 | $C_{17}H_{18}N_4O$ | C, H, N |
| 3-N=NN($CH_3$)($CH_2$)$_2$$CH_3$ | 275-278 | $C_{17}H_{18}N_4O$ | C, H, N |

solution of the required acid in EtOAc and following crystallization of the precipitated salt as detailed above.

**Method C.** Nitro congeners were reduced by the method detailed in full earlier using $FeCl_3$ as starter.[3] It is important in work-up of the reduction mixture that, to remove Fe salts, excess Cl ion added as starter be just neutralized by addition of the theoretical quantity of $CaCO_3$, with stirring for 30 min. Employment of soluble alkalies to remove Fe salts will inevitably provide some deacylation of product and this will be readily apparent on TLC of the crude product. The 3-amino variants were purified as detailed above.

**3-(3,3-Dialkyl-1-triazeno)-9(10*H*)-acridones.** 3-Aminoacridone (5 g, 0.024 mol) was dissolved in boiling 5 N HCl (50 ml) and the solution was cooled rapidly with stirring to provide a fine suspension of the hydrochloride salt. To the well-stirred suspension, a solution of $NaNO_2$ (1.73 g, 0.024 mol) in $H_2O$ (10 ml) was added at 0–5 °C. A deep red solution of the diazonium compound resulted. The diazo solution was added in dropwise fashion to a well-stirred, ice-cooled solution of $Na_2CO_3$ (28 g, 0.265 mol) and the appropriate secondary amine (0.03 mol) in $H_2O$ (100 ml). The precipitated red-brown crystalline solid was collected, washed well with $H_2O$, dried at 20 °C, and then crystallized from EtOH (see Table III).

**9-Chloro-3-(3,3-dialkyl-1-triazeno)acridines.** The triazenoacridone (5.6 mmol) was treated at 20 °C with $SOCl_2$ (5 ml) containing DMF (0.02 ml). There was rapid dissolution of the solid and after the solution had stood for 10 min at 20 °C, the volatiles were removed in vacuo at 20 °C. The residue was immediately dissolved in ice-cold, dry, EtOH-free $CHCl_3$, and the solution was added to a well-stirred mixture of excess $NH_3$ and ice. The organic layer was separated and dried ($CaCl_2$) and the solvent was removed in vacuo (bath temperature 40 °C). The residue was extracted twice with hot ligroine (50 ml), and the combined clarified extracts were evaporated in vacuo. The 9-chloroacridines were obtained as labile, crystalline yellow solids which were immediately coupled with the requisite amines by the following modified procedure.

**Method D.** The appropriate 9-chloro-3-triazenoacridine (2.8 mmol) was dissolved in EtOH (15 ml) at 20 °C by stirring and a solution of the requisite 4-aminomethylsulfonanilide component (3 mmol) in EtOH, also at 20 °C, was added. Acid catalyst (4 N HCl, 0.02 ml) was added and the solution was stored at 10 °C for 2 h and the separated crystalline product hydrochloride was then collected. The crystals were dissolved in the minimal amount of $H_2O$ at 60 °C (ca. 100 ml); the solution was clarified and rewarmed to 60 °C, and concentrated aqueous $NH_4Cl$ was added until the crystallization point; slow cooling then provided homogeneous crystalline products **69–73**. For those triazenes required as the methanesulfonate salts, the crude hydrochloride (5 mmol) was dissolved in EtOH–$H_2O$ (8:1, 200 ml) at 20 °C and the free base was precipitated by the addition of aqueous $KHCO_3$ (5.5 mmol). The precipitated base was well washed with $H_2O$ and then suspended in $H_2O$ (200 ml), and $CH_3SO_3H$ was added (5.2 mmol, 10% in $H_2O$). Warming (60 °C) and stirring provided a clear solution to which concentrated aqueous ammonium methanesulfonate was added until crystallization commenced; slow cooling then provided the methanesulfonate salts as yellow crystalline solids (Table I).

**3-Azido-9(10*H*)-acridone.** 3-Aminoacridone (3 g, 0.0143 mol) was diazotized by the procedure detailed above. A solution of $NaN_3$ (1.05 g, 0.016 mol) was then added in dropwise fashion to the stirred solution of the diazonium compound at 0–5 °C. The precipitated product was well washed with $H_2O$, dried at 20 °C, and recrystallized from EtOH (400 ml) providing the required azide as colorless, light-sensitive needles.

The azide was converted to the 9-chloro compound by the method described above for the triazene examples and coupled to the aminomethanesulfonanilide component by method D. Products crystallized readily from $H_2O$–$NH_4Cl$.

**Biologic Testing.** The $10^5$ L1210 cells were inoculated, either intraperitoneally or subcutaneously above the right axilla, into 18.5–22.5-g $C_3H$/$DBA_2$ $F_1$ hybrid mice. Daily ip drug treatment started 24 h later and continued for 5 days. When possible agents were screened as water-soluble formulations; the methanesulfonate salts often provided sufficient water solubility when the hydrochlorides were not acceptably soluble. Insufficiently water-soluble agents were administered as homogenized suspensions in aqueous methylcellulose. Detailed description of the screening procedure, dose intervals employed, etc., for sc L1210 tests have been provided earlier.[1]

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