Inhibitors of Platelet Aggregation. 3. {[(Dialkylamino)alkyl]thio}heterocyclic Compounds[1]

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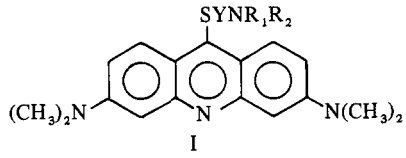
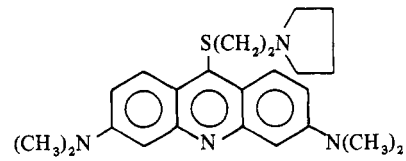
Received July 16, 1971

In a search for novel antithrombotic agents, various {[(dialkylamino)alkyl]thio}heterocyclic derivatives containing acridine, 1,2,3,4-tetrahydroacridine, benz[*c*]acridine, benzo[*b*][1,5]naphthyridine, benzo[*b*][1,10]phenanthroline, benzo[*f*]quinoline, [1]benzothieno[3,2-*b*]quinoline, phthalazine, quinazoline, and thioxanthenone nuclei were prepared. The compds were obtained in 12–95% yield by the condensation of the requisite chloroheterocycle with the appropriate [(dialkylamino)alkyl]thiol. Five compds produced ≥50% inhibition of platelet aggregation *in vitro* at a concn of 10^{-5} *M*. 7-{[3-(Dimethylamino)propyl]thio}benz[*c*]acridine dihydrochloride also caused 30–100% inhibition of platelet aggregation in plasma from rabbits given single iv 6–12 mg/kg doses.

The importance of adenosine diphosphate (ADP) in platelet aggregation and thrombosis[2-7] has stimulated a search for inhibitors of ADP-induced platelet aggregation in anticipation that such substances may be useful for the prevention and treatment of thrombosis and embolism. In a recent communication from these laboratories,[1] it was reported that certain 3,6-bis(dimethylamino)-9-{[(dialkylamino)alkyl]thio}acridines (I) and related substances were potent inhibitors of ADP-induced platelet aggregation *in vitro* and in plasma from rabbits that had been treated with these substances. Moreover, 3,6-bis(dimethylamino)-9-{[2-(1-pyrrolidinyl)ethyl]thio}acridine (**1**) also caused a significant increase in both primary and secondary bleeding time from a micropuncture wound in the mouse mesentery 4 and 24 hr after a single iv 10 mg/kg dose.[1]



I



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To enable an assessment of the importance of the [(dialkylamino)alkyl]thio side chain and the (dialkylamino)acridine moieties relative to the antithrombotic effects of the 9-{[(dialkylamino)alkyl]thio}-2- and 3-(dialkylamino)acridines,[1] a variety of {[(dialkylamino)alkyl]thio}heterocyclic compds were synthesized and evaluated as inhibitors of platelet aggregation. The results of these studies are summarized in the present communication.

Chemistry. The condensation of 3-(dimethylamino)-1-propanethiol hydrochloride with 6,9-dichloro-2-methoxyacridine,† 6,9-dichloro-2-methoxyacridine 10-oxide,[8] and 9-chloro-2-methoxy-6-nitroacridine[9] in PhOH afforded 6-chloro-9-{[3-(dimethylamino)propyl]thio}-2-methoxyacridine dihydrochloride (**10**) (77%), 6-chloro-9-{[3-(dimethylamino)propyl]thio}-2-methoxyacridine 10-oxide (**11**) (27%), and 9-{[3-(dimethylamino)propyl]thio}-2-methoxy-6-nitroacridine hydrochloride (**12**) (43%), respectively (procedures I, II, Table I). Clinton and Suter[10] previously reported the synthesis of several thioacridine analogs from 6,9-dichloro-2-methoxyacridine utilizing the corresponding [(dialkylamino)alkyl]thiol and Na in EtOH. The PhOH procedures were also employed successfully in the prepn of the following {[(dialkylamino)alkyl]thio}heterocyclic compds (Table I) *via* the requisite chloroheterocycles:[11-18] 2-{[2-(dimethylamino)ethyl]thio}-3-(2-pyridyl)quinoxaline (**6**) (52%); 7-chloro-10-{[3-(dimethylamino)propyl]thio}-2-methoxybenzo[*b*][1,5]naphthyridine dihydrochloride (**7**) (93%); 3-{[3-(dimethylamino)propyl]thio}benzo[*f*]-quinoline (**8**) (12%); 1-{[3-(dimethylamino)propyl]-thio}-4-phenylphthalazine (**13**) (40%); 4-{[3-(dimethylamino)propyl]thio}-2-phenylquinazoline (**14**) (53%); 7-{[3-(dimethylamino)propyl]thio}benzo[*b*][1,10]phenanthroline dihydrochloride (**16**) (69%); 2-butoxy-7-chloro-10-{[3-(dimethylamino)propyl]thio}benzo[*b*][1,5]naphthyridine (**17**) (44%); and 7-{[3(dimethylamino)propyl]thio}benz[*c*]-acridine dihydrochloride (**18**) (95). The condensation of 9-chloro-1,2,3,4-tetrahydroacridine‡ and 1,6-dichloro-4-methylthioxanthen-9-one[19] with the anion of 3-(dimethylamino)-1-propanethiol and 2-(diethylamino)ethanethiol in EtOH afforded 9-{[3-(dimethylamino)propyl]thio}-1,2,3,4-tetrahydroacridine dihydrochloride (**9**) (38%) and 6-chloro-1-{[2-(diethylamino)ethyl]thio}-4-methylthioxanthen-9-one (**15**) (36%), respectively (procedure III, Table I).

6-{[3-(Dimethylamino)propyl]thio}[1]benzothieno[3,2-*b*]-quinoline dihydrochloride (**5**) (Table I) was obtained as outlined in Scheme I. Treatment of potassium anthranilate with 3-bromobenzo[*b*]thiophene[20] (**2**) in DMF in the presence of 4-ethylmorpholine and $CuBr_2$ afforded *N*-(benzo[*b*]thien-3-yl)anthranilic acid[21] (**3**) in 32% yield. Cyclization of **3** with $POCl_3$ gave 6-chloro[1]benzothieno[3,2-*b*]quinoline (**4**) (65%), which was condensed with 3-(dimethylamino)-1-propanethiol hydrochloride in PhOH to give **5** (75%).

Biology. The {[(dialkylamino)alkyl]thio}heterocyclic compds **5** and **7–18** (Table I) were tested as inhibitors of

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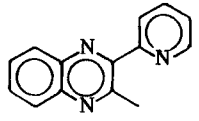
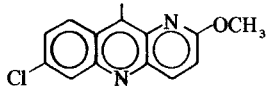
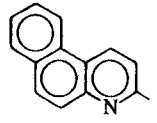
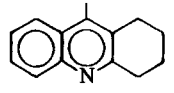
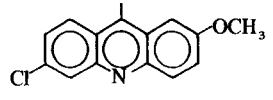
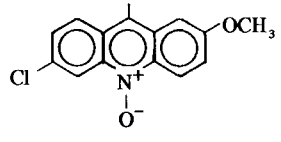
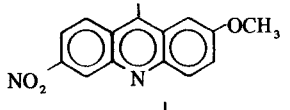
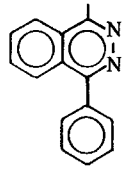
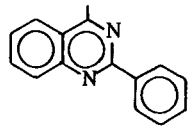
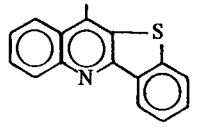
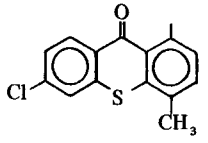
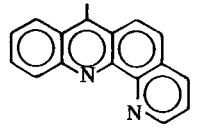
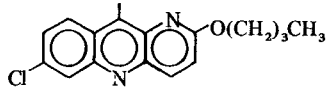
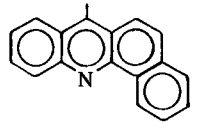
‡Aldrich Chemical Co., Inc., Milwaukee, Wis. 53233.

Table I. {[(Dialkylamino)alkyl]thio}heterocyclic Compounds

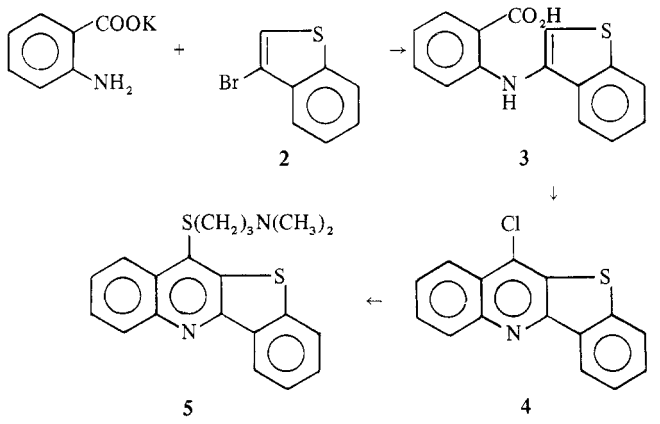
No.	Het	x	NR_1R_2	Mp, °C	Yield purified, %	Purifcn solvent	Procedure	Chloro-hetero-cycle reference	Formula	Analyses	Inhibition of platelet aggregation *in vitro* Concn, $M \times 10^{-5}$	% inhibition
						Het–S–$(CH_2)_xNR_1R_2$						
6		2	$N(CH_3)_2$	70–72	52	*n*-Heptane	I	11	$C_{17}H_{18}N_4S$	C, H, N		
7		3	$N(CH_3)_2$	196–197	93	Me_2CO	II	12	$C_{18}H_{20}ClN_3OS \cdot 2HCl \cdot 2.5H_2O$	C, H, N, Cl^-, S; H_2O[a]	1 0.1	32 0
8		3	$N(CH_3)_2$	73–75	12	MeCN	I	13	$C_{18}H_{20}N_2S$	C, H, S; N[b]	1	44
9		3	$N(CH_3)_2$	210–211	38	*i*-PrOH	III	*c*	$C_{18}H_{24}N_2S \cdot 2HCl \cdot H_2O$	C, H, N, S, H_2O	1	50
10		3	$N(CH_3)_2$	205–208	77	Me_2CO	II	*d*	$C_{19}H_{21}ClN_2OS \cdot 2HCl \cdot H_2O$	C, H, N, S, H_2O	1	0
11		3	$N(CH_3)_2$	112–113	27	*n*-Heptane	I	8	$C_{19}H_{21}ClN_2O_2S$	C, H, N	1	30
12		3	$N(CH_3)_2$	262–264	43	MeCN	II	9	$C_{19}H_{21}N_3O_3S \cdot HCl$	C, H, N, Cl^-, S	1	0
13		3	$N(CH_3)_2$	74–75	40	*i*-Pr_2O	I	14	$C_{19}H_{21}N_3S$	C, H, N	1	45

14		3	$N(CH_3)_2$	65–66	53	MeCN	I	15	$C_{19}H_{21}N_3S$	C, H, N, S	1	61
5		3	$N(CH_3)_2$	224–226	75	MeCN	II	4	$C_{20}H_{20}N_2S_2 \cdot 2HCl$	C, H, N; Cl^- [e]	1 0.1	62 31
15		2	$N(C_2H_5)_2$	229 dec	36	EtOH–Me_2CO	III	19	$C_{20}H_{22}ClNOS_2 \cdot HCl$	C, H, N, Cl^-	1	53
16		3	$N(CH_3)_2$	197–199	69	*i*-PrOH	II	16	$C_{21}H_{21}N_3S \cdot 2HCl \cdot 1.33H_2O$	C, H, N, Cl^-, S, H_2O	1	41
17		3	$N(CH_3)_2$	74–74.5	44	MeCN	I	17	$C_{21}H_{26}ClN_3OS$	C, H, N, S	1 0.1	28 3
18		3	$N(CH_3)_2$	206–208	95	Me_2CO	II	18	$C_{22}H_{22}N_2S \cdot 2HCl \cdot H_2O$	C, H, N, Cl^-, S, H_2O	1 0.1	50 30

3,6-Bis(dimethylamino)-9-{[2-(1-pyrrolidinyl)ethyl]thio}acridine **(1)**[f]	1	67
	0.1	35
5,10-Dihydro-3-(*o*-methoxyphenyl)thiazolo[3,2-*b*][2,4]benzodiazepine hydrobromide[g]	5	100,80,73
	1	44,43,39
Methapyrilene hydrochloride	100	42
	50	25
	10	17
Adenosine	10	61
	1	25
N^2-(*p*-Tolylsulfonyl)-L-arginine ethyl ester hydrochloride; TAME · HCl	500	80
	50	53

[a] H_2O: calcd, 9.38; found, 8.90. [b] N: calcd, 9.45; found, 9.04. [c] Aldrich Chemical Co., Inc., Milwaukee, Wis. 53233. [d] Winthrop Laboratories, New York, N. Y. 10016. [e] Cl^-: calcd, 16.67; found, 16.22. [f] See reference 1. [g] See reference 2.

Scheme I



ADP-induced platelet aggregation *in vitro* utilizing a modification[2] of the method of Born and Cross.[5] Briefly, when ADP is added to rabbit platelet-rich plasma (prp) and the prp is gently agitated, the individual platelets aggregate, or stick together, to form clumps. Each clump contains a large number of platelets. The consequent decrease in the number of particles in suspension causes a decrease in the optical density of the prp. Compds that inhibit platelet aggregation minimize or prevent this decrease in the optical density. Colorimetric measurements afford a quantitative measure of the amount of the platelets.[2,5]

Five substances (**5**, **9**, **14**, **15**, **18**) produced ≧ 50% inhibition of platelet aggregation *in vitro* at a concn of $10^{-5}M$ (Table I), and were thus comparable with or superior to the reference drugs 3,6-bis(dimethylamino)-9-{[2-(1-pyrrolidinyl)ethyl]thio}acridine (**1**),[1] 5,10-dihydro-3-(*o*-methoxyphenyl)thiazolo[3,2-*b*][2,4]benzodiazepine hydrochloride,[2] methapyrilene hydrochloride,[2,22,23] adenosine,[2] and TAME · HCl.[2] It is especially noteworthy that the 9-{[(dialkylamino)alkyl]thio}acridines (**10–12**) and benzo[*b*][1,5]naphthyridines (**7**, **17**), which lack a nuclear dialkylamino substituent, were inactive or only weakly active.

Several of the {[(dialkylamino)alkyl]thio}heterocyclic compds (**5**, **8**, **9**, **13–16**, **18**) were also evaluated for their effects on platelet aggregation in prp taken from rabbits that had received a single iv dose of the drug prior to blood sampling. As in previous work,[2] female rabbits (New Zealand strain) were anesthetized and a jugular vein and a carotid artery were cannulated for drug administration and blood sampling, respectively. The drug was added to saline and injected during a 5-min period. Blood samples were drawn prior to and at 30- and 60-min intervals posttreatment. Each animal was dosed only once and was sacrificed at the termination of the test. Platelet-rich plasma (prp) was prepared[2] and an aliquot was added to a tube containing $(HOCH_2)_3CNH_2$ and NaCl, pH 7.0. The mixt was stirred in a Bryston platelet aggregometer with continuous recording of the optical density. An aliquot of a soln of 2.5 or 5.0 μg/ml of ADP in saline was added and the decrease in optical density measured. The effect of the thio compd on platelet aggregation by ADP was determined by comparing the values obtained with the pre- and posttreatment samples of prp.

In the above *in vitro–in vivo* test, **5**, **8**, **9**, and **13–16** failed to produce a significant inhibition of platelet aggregation 30 or 60 min after single iv doses ranging from 6.25 to 25 mg base/kg. 7-{[3-(Dimethylamino)propyl]thio}benz[*c*]acridine dihydrochloride (**18**) produced strong inhibition of platelet aggregation in the prp from a single rabbit at 12 mg/kg (Table II), but was only weakly active or inactive at lower doses. Thus **18** was much less promising than 3,6-bis(dimethylamino)-9-{[2-(1-pyrrolidinyl)ethyl]thio}acridine (**1**)[1] and related 9-{[(dialkylamino)alkyl]thio}-3-(dimethylamino)acridines (I) reported previously.[1]

Table II. Inhibition of Platelet Aggregation in Plasma from Rabbits Treated with 7-{[3-(Dimethylamino)propyl]thio}benz[*c*]acridine Dihydrochloride (**18**)

Single iv dose, mg of base/kg	No. of rabbits tested	% inhibition[a] of ADP-induced platelet aggregation at post-treatment periods: 30 min	60 min	Final ADP concn, μg/ml
12.0	1	100	100	0.5
6.0	3	31 (19–55)	30 (20–41)	0.5
6.0	1	16	21	0.25
1.5	3	3 (0–8)	12 (0–23)	0.5

[a] Average and (range) of values.

The overall results of the present study and previous work[1] suggest that a dialkylamino substituent on the heterocyclic moiety plays a key role in conferring optimal antithrombotic properties among various {[(dialkylamino)alkyl]thio}-heterocyclic compds.

Experimental Section§,#

{[(Dialkylamino)alkyl]thio}heterocyclic Compounds (5–18, Table I). Procedure I. A mixt of 10.0 g (0.041 mole) of 4-chloro-2-phenylquinazoline,[15] 6.8 g (0.041 mole) of 85% 3-(dimethylamino)-1-propanethiol hydrochloride (Evans), and 30 g of PhOH was stirred and heated on a steam bath for 3 hr. The mixt was cooled and poured into 1 l. of Me_2CO with vigorous stirring. The Me_2CO suspension was boiled on a steam bath for 5 min and chilled. The crude HCl salt was collected by filtration, dried *in vacuo* at 60° for 18 hr, and dissolved in 100 ml of H_2O. The soln was made alk with 50% aq NaOH and the base was extd with $CHCl_3$. The combined $CHCl_3$ exts were dried (K_2CO_3) and the $CHCl_3$ was removed *in vacuo*. The residue was crystd from MeCN to give 7.0 g (53%) of 4-{[3-(dimethylamino)propyl]thio}2-phenylquinazoline (**14**) as colorless crystals, mp 65–66°.

Procedure II. A mixt of 6.0 g (0.022 mole) of 6-chloro[1]benzothieno[3,2-*b*]quinoline (**4**), 4.0 g (0.022 mole) of 85% 3-(dimethylamino)-1-propanethiol hydrochloride, and 20 g of PhOH was stirred and heated on a steam bath for 3 hr. The reaction mixt was processed according to procedure I, but the free base did not crystallize. The crude base was dissolved in Et_2O and the Et_2O soln was treated with excess HCl. The HCl salt that pptd was collected and crystd from MeCN. The desired 6-{[3-(dimethylamino)propyl]thio}-[1]benzothieno[3,2-*b*]quinoline dihydrochloride (**5**) (7.0 g, 75%) was obtained as yellow crystals, mp 224–226°.

Procedure III. To a warm soln of 4.6 g of Na in 100 ml of EtOH was added in one portion 15.6 g (0.1 mole) of 3-(dimethylamino)-1-propanethiol hydrochloride and the mixt was heated to reflux. To it was added dropwise over 0.5 hr a soln of 21.8 g (0.1 mole) of 9-chloro-1,2,3,4-tetrahydroacridine‡ in 100 ml of EtOH, and the mixt was boiled under reflux for 4 hr and chilled. It was filtered, and the residue was triturated with MeCN and extd with Et_2O. The combined Et_2O exts were treated with HCl and the crude HCl salt was crystd from MeOH–Et_2O (24.0 g, mp 199–201°). The HCl salt was dissolved in 200 ml of H_2O and the soln was made basic with 50% aq NaOH and extd with Et_2O. The combined Et_2O exts were dried (K_2CO_3) and treated with HCl. Crystn of the HCl salt from *i*-PrOH gave 15.0 g (38%) of 9-{[3-(dimethylamino)propyl]-thio}-1,2,3,4-tetrahydroacridine dihydrochloride monohydrate (**9**) as pale yellow crystals, mp 210–211°.

***N*-(Benzo[*b*]thien-3-yl)anthranilic Acid (3).** A mixt of 28.0 g (0.13 mole) of 3-bromobenzo[*b*]thiophene,[20] 35.0 g (0.20 mole) of

§ Melting points (corrected) were taken on a Thomas-Hoover capillary melting point apparatus.

Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values.

potassium anthranilate, 16.4 ml of 4-ethylmorpholine, 2.5 g of $CuBr_2$, and 50 ml of DMF was stirred under reflux for 2 hr and made alk with aq NaOH. The mixt was filtered warm to remove insoluble impurities, and the filtrate was acidified to ppt the crude product as an oil which soon solidified. Recrystn first from EtOH–H_2O (decolorizing charcoal), then from C_6H_6, afforded 11.2 g (32%) of yellow needles, mp 202–204°. *Anal.* ($C_{15}H_{11}NO_2S$) C, H, N, S.

6-Chloro[1]benzothieno[3,2-*b*]quinoline (4). *N*-(Benzo[*b*]-thien-3-yl)anthranilic acid (**3**) (10.0 g, 0.037 mole) was added to 100 g of $POCl_3$, and the mixt was cautiously warmed on a steam bath with stirring. An exothermic reaction ensued. The mixt was heated under reflux for 1.5 hr, cooled, and poured slowly with vigorous stirring into 1 kg of ice. After hydrolysis of the $POCl_3$, the mixt was made alk with an excess of 50% aq NaOH in ice and the product was extd with $CHCl_3$. The combined $CHCl_3$ exts were washed with H_2O, and the $CHCl_3$ was removed *in vacuo*. The residue was crystd from MeCN to give 6.5 g (65%) of pale yellow needles, mp 157–158°. *Anal.* ($C_{15}H_8ClNS$) C, H, Cl, N.

Acknowledgments. The authors are indebted to Dr. E. D. Nicolaides for assistance and advice as chemical coordinator of the program and to Mr. George D. Dodd, Jr., for technical assistance in the platelet aggregation studies. We also thank Dr. J. M. Vandenbelt and coworkers for the spectral determinations, and Mr. Charles E. Childs and associates for the microanalyses.

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Tumor Inhibitors. 70. Structure–Cytotoxicity Relationships among *N*-Acyltriamines Related to Solapalmitine[1]†

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The results of a study directed toward determination of the structural requirements for growth-inhibitory activity among *N*-acyltriamines and other relatives of solapalmitine (**1**) are reported. Most of the synthetic derivatives were prepared *via* hydrogenation of tertiary aminonitriles (**4**) to the appropriate secondary amines (**5**) and acylation to the *N*-acyltriamines (**6**). It was found that, for maximal cytoxicity, *N*-acyltriamines require an acyl residue at least 12 C in length. The number of CH_2's between the tertiary amine functions and the amide N is not crucial, and variation from 2 to 7 CH_2 groups causes no major change in activity. Reduction of the amides to the corresponding N^2-alkyltriamines afforded products with potent cytotoxicity in the series wherein the N^2-alkyl group is at least 12 C in length. Ten of the most cytotoxic compounds were found to show significant *in vivo* inhibitory activity against the Walker 256 carcinosarcoma in the rat. The palmitamide and solamine moieties appear to represent the optimal structural characteristics for *in vivo* inhibitory activity. Four of the most cytotoxic compounds inhibited the growth of *Escherichia coli* at very low concns. The mode of action of these *N*-acyltriamines appears to be disruption of surface properties of the cell walls.

In the course of a continuing search for tumor inhibitors of plant origin, 2 new liquid alkaloids, solapalmitine (**1**) and solapalmitenine (**2**), were isolated from an alcoholic extract of *Solanum tripartitum* Dunal (Solanaceae).[2] Both alkaloids showed significant inhibitory activity *in vivo* against the Walker 256 im carcinosarcoma in rats (WM) and *in vitro* against cells derived from the human carcinoma of the nasopharynx (KB). We report herewith the results of a study directed toward the determination of the structural requirements for biological activity among *N*-acyltriamines and other compounds related to solapalmitine.

†This work was supported by grants from the National Cancer Institute (CA 11718) and the American Cancer Society (T-275).

$(CH_3)_2N(CH_2)_4NR(CH_2)_4N(CH_3)_2$
1, R = $CO(CH_2)_{14}CH_3$
2, R = $COCH{=}CH(CH_2)_{12}CH_3$ (*trans*)
3, R = H

Biological evaluation of solamine (**3**) revealed that this triamine was devoid of *in vivo* or *in vitro* growth inhibitory activity. Consequently, the first synthetic efforts were directed toward *N*-acyltriamines bearing the general structure **6** (Table I). The acylsolamines **15–23** were prepared by acylation of solamine in Et_2O with the appropriate acyl chloride in the presence of a 10-fold excess of Et_3N. The next series was addressed to the effect of varying the distance between the terminal tertiary amino functions and