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.

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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.

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$(CH_3)_2N(CH_2)_4NR(CH_2)_4N(CH_3)_2$
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

the amide N, and compounds of type **6** with n = 2–7 were prepared. The requisite triamines were made by hydrogenation of tertiary aminonitriles (**4**) with Rh-Al_2O_3 catalyst,[3] which gave a mixture of primary, secondary, and tertiary amines. The secondary amines (**5**) were isolated by chromatography on Al_2O_3 and acylated to the respective N-acyltriamines (**6**). Some of the aminonitriles were commercially available; the others were prepared from the corresponding chloronitriles and secondary amines. The hydrogenations were carried out in MeOH with a 4–5% ratio of catalyst (5% Rh-Al_2O_3), and under 0.7–1.26 kg/cm^2. Dimethylaminoacetonitrile required 70.3 kg/cm^2, and even under the higher pressure gave a very low yield of the desired secondary amine, presumably because of the competing elimination reaction.[4] The secondary amine was prepared in better yield by treatment of bis(2-chloroethyl)amine with Me_2NH.

The effect of varying the size of the substituents on the terminal amine moieties of the triamines of type **5** was also investigated. Treatment of 4-chlorobutyronitrile with Et_2NH or i-Pr_2NH yielded the corresponding precursorial aminonitriles (**4**), and hydrogenation was effected under 2.81–3.02 kg/cm^2 for 3–6 days. The N-acyltriamine **36** (Table II), bearing terminal primary amino groups, was prepared by treatment of bis(3-cyanopropyl)amine with palmitoyl chloride, followed by selective hydrogenation of the two nitrile functions with 30% Pd/C in AcOH. Additional variants included the bis-quaternary derivatives **37** and **38**, the N-acyldiamine **39**, and the N-acylmonoamine **40**.

Finally, to evaluate the potential importance of the amide function for cytotoxic activity, a series of N^2-alkyltriamines of type **41** were prepared, by LAH reduction of the corresponding amides (Table III).

$$\underset{4}{2R_2N(CH_2)_{n-1}CN} \xrightarrow{H_2\text{-}Rh\text{-}Al_2O_3} \underset{5}{[R_2N(CH_2)_n]_2NH} \rightarrow [R_2N(CH_2)_n]_2NCO(CH_2)_mCH_3 \quad (6)$$

Table I

Compd	R	n	m	% yield	Bp (mm), °C	Formula	ED_{50}
				$[R_2N(CH_2)_n]_2NCO(CH_2)_mCH_3$ (6)			
7	Me	2	2	75	57 (0.01)	$C_{12}H_{27}N_3O$	90
8	Me	2	6	93	85 (0.01)	$C_{16}H_{35}N_3O$	22
9	Me	2	10	84	110 (0.01)	$C_{20}H_{43}N_3O$	0.46
10	Me	2	14	57	127 (0.01)	$C_{24}H_{51}N_3O$	0.33
11	Me	3	2	31	72 (0.01)	$C_{14}H_{31}N_3O$	32
12	Me	3	6	31	90 (0.01)	$C_{18}H_{39}N_3O$	2.6
13	Me	3	10	43	105 (0.01)	$C_{22}H_{47}N_3O$	0.041
14	Me	3	14	30	130 (0.01)	$C_{26}H_{55}N_3O$	0.024
15	Me	4	2	81	80 (0.01)	$C_{16}H_{35}N_3O$	>100
16	Me	4	4	79	80 (0.01)	$C_{18}H_{39}N_3O$	59
17	Me	4	6	86	115 (0.01)	$C_{20}H_{43}N_3O$	24
18	Me	4	8	62	120 (0.02)	$C_{22}H_{47}N_3O$	2.5
19	Me	4	10	74	125 (0.03)	$C_{24}H_{51}N_3O$	0.28
20	Me	4	12	63	145 (0.05)	$C_{26}H_{55}N_3O$	0.36
1	Me	4	14	81	*a*	$C_{28}H_{59}N_3O$	0.36
21	Me	4	16	66	*a*	$C_{30}H_{63}N_3O$	0.28
22	Me	4	18	86	175 (0.01)	$C_{32}H_{67}N_3O$	1.6
23	Me	4	20	68	185 (0.01)	$C_{34}H_{71}N_3O$	2.0
24	Me	5	2	93	93 (0.01)	$C_{18}H_{39}N_3O$	>100
25	Me	5	6	83	125 (0.02)	$C_{22}H_{47}N_3O$	9.0
26	Me	5	10	99	143 (0.02)	$C_{26}H_{55}N_3O$	0.72
27	Me	5	14	87	165 (0.01)	$C_{30}H_{63}N_3O$	0.92
28	Me	6	10	99	208 (0.4)	$C_{28}H_{59}N_3O$	0.28
29	Me	6	14	90	220 (0.3)	$C_{32}H_{67}N_3O$	0.31
30	Me	7	10	99	217 (0.5)	$C_{30}H_{63}N_3O$	0.021
31	Me	7	14	92	245 (0.8)	$C_{34}H_{71}N_3O$	0.21
32	Et	4	10	90	184 (0.3)	$C_{28}H_{59}N_3O$	0.60
33	Et	4	14	79	207 (0.1)	$C_{32}H_{67}N_3O$	0.79
34	i-Pr	4	10	99	206 (0.1)	$C_{32}H_{67}N_3O$	0.22
35	i-Pr	4	14	39	240 (1.5)	$C_{36}H_{75}N_3O$	2.0

[a] Compound purified by chromatography.

Table II

Compd	R	R′	m	ED_{50}
	$R(CH_2)_4$ \ N–$CO(CH_2)_mCH_3$ / $R'(CH_2)_4$			
36	H_2N	H_2N	14	23
37	$(CH_3)_3N^+$	$(CH_3)_3N^+$	10	30
38	$(CH_3)_3N^+$	$(CH_3)_3N^+$	14	6.8
39	$(CH_3)_2N$	H	14	2.2
40	H	H	14	>100

Table III

Compd	n	m	% yield	Bp (mm), °C	Formula	ED_{50}
			$[(CH_3)_2N(CH_2)_n]_2N(CH_2)_mCH_3$ (41)			
42	4	3	95	75 (0.01)	$C_{16}H_{37}N_3$	3.8
43	4	7	70	110 (0.01)	$C_{20}H_{45}N_3$	1.9
44	4	11	91	144 (0.7)	$C_{24}H_{53}N_3$	0.20
45	4	15	86	150 (0.01)	$C_{28}H_{61}N_3$	0.068
46	4	19	68	190 (2.0)	$C_{32}H_{69}N_3$	0.26
47	5	3	99	121 (1.8)	$C_{18}H_{41}N_3$	>100
48	5	7	99	130 (1.5)	$C_{22}H_{49}N_3$	5.6
49	5	11	98	139 (0.01)	$C_{26}H_{57}N_3$	0.20
50	5	15	94	157 (0.02)	$C_{30}H_{65}N_3$	0.064

Biological Activity. All of the compounds in Tables I–III were evaluated for growth inhibitory activity *in vitro* against cell culture of human carcinoma of the nasopharynx (KB) and *in vivo* against the Walker im carcinosarcoma 256 in rats.‡ The results of the KB testing indicate that, among the N-acyltriamines, an acyl residue at least 12 C in length is required for maximal cytotoxicity. The number of CH_2 groups between the terminal tertiary amino functions and the amide N does not appear to be crucial, for variation of these chains from 2 to 7 CH_2's caused no major change in activity. Similarly, changes in the size of the substituents on the terminal tertiary amino functions did not appear to affect the cytotoxicity (Table I). In contrast, replacement of the terminal tertiary amine functions by quaternary ammonium groups, primary amine functions, or H atoms led to a profound diminution in cytotoxic activity (Table II). Reduction of the amides to the corresponding N^2-alkyltriamines afforded products with potent cytotoxicity in the series wherein the N^2-alkyl group was at least 12 C in length (Table III).

Ten compounds showed significant *in vivo* activity against the Walker carcinosarcoma 256; **1**, **10**, **14**, **18**, **19**, **20**, **29**, **31**, **44**, and **49**. Most of the *in vivo* actives figured among

‡Assays were performed under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, by the procedures described in reference 5. The evaluation of the KB assay results is such that a compd is considered to show significant cytotoxicity if the ED_{50} (*i.e.*, the dose in micrograms per milliliter that inhibits the growth of cell cultures to 50% of control growth) $\leq$ 1 μg/ml. A compd is considered to show significant *in vivo* activity against the Walker carcinosarcoma 256 if it causes reduction of tumor wt in treated (T) animals to 42% or less of the tumor wt in control (C) animals (*i.e.*, $T/C \leq 42\%$).

the compounds with the highest KB cytotoxicity. Among the *N*-acyltriamines, significant *in vivo* activity was noted among 5 of the 6 palmitamides tested (*viz.*, **1**, **10**, **14**, **29**, and **31**). Indeed, the only other palmitamide, **27**, showed a $T/C = 45\%$ at 5.00 mg/kg, and this compound would very probably meet the criteria for significant inhibitory activity at a slightly higher dose. Four of the 8 active *N*-acyltriamines contained the solamine moiety; the C_4-chain length between the tertiary nitrogens and the amide N thus appears to be advantageous for *in vivo* inhibitory activity. Among the N^2-alkyltriamines, the C-12 alkyl group appears to be most advantageous for *in vivo* activity.

In an attempt to elucidate a possible mechanism of action of the acyltriamines, **4** of the most cytotoxic compounds (*viz.*, **1**, **10**, **21**, and **29**) were evaluated for their effects upon cell permeability and active transport in *Escherichia coli*.[6] All **4** compounds were found to be growth inhibitory for *E. coli* at very low concns. The mode of action appears to be disruption of surface properties (the cells did not lyse), since at inhibitory concns the cells became leaky and lost radioactive K^+ and thiomethyl galactoside. The specific energy dependent accumulation of K^+ and thiomethyl galactoside was also inhibited. When $10^{-4}M$ solapalmitine (**1**) was added to KB cells that had been accumulating ^{28}Mg for over 2 hr, a rapid loss of more than 95% of the accumulated ^{28}Mg was noted.[7] The loss of ^{28}Mg was so rapid that the cells were examined under the phase-contrast microscope. Some of the effects of the compound on membrane permeability were deemed not to be due to cell lysis. The cells looked normal under phase microscopy for the duration of the experiments in $10^{-5}M$ solapalmitine. However, in the presence of high ($10^{-4}M$) concns of solapalmitine, the KB cells rapidly developed blebs and disintegrated. Monolayers of KB cells after exposure to $10^{-5}M$ solapalmitine for 1 hr at 37°, followed by rinsing with fresh medium, remained attached to the plastic surface and apparently viable 24 hr later. However, with exposure to $10^{-5}M$ solapalmitine overnight, the cells detached and became permeable to trypan blue.

Experimental Section§

Aminonitriles (4). The following aminonitriles were commercially available: dimethylaminoacetonitrile (4, R = Me, n = 2), K&K 7050, 3-dimethylaminopropionitrile (4, R = Me, n = 3), K&K 22996, and 4-dimethylaminobutyronitrile (4, R = Me, n = 4), K&K 15060.

5-Dimethylaminovaleronitrile (4, R = Me, n = 5) was obtd from 5-chlorovaleronitrile (Aldrich C 7300) and Me_2NH according to Price, *et al.*:[8] bp 56–59° (1.0 mm) (vapor temp) [lit.[8] 106–108° (30 mm)].

6-Dimethylaminocapronitrile (4, R = Me, n = 6). A mixt of 13.1 g (0.10 mole) of 6-chlorocapronitrile (Pfalz & Bauer), 75 g (0.42 mole) of 25% Me_2NH in H_2O, and 1.0 g of KI was stirred at 40° for 1.5 days to give 8.50 g (61%) of the aminonitrile: bp 75° (1.0 mm) [lit.[9] 94–96° (7 mm)].

7-Dimethylaminocaprylonitrile (4, R = Me, n = 7). A mixt of 14.6 g (0.10 mole) of 7-chlorocaprylonitrile (K&K 3221), 100 g (0.55 mole) of 25% Me_2NH in H_2O, and 1.0 g of KI was stirred for 2.5 days at room temp. Excess Me_2NH was evapd *in vacuo*, and the remaining yellow soln was acidified with concd HCl dropwise. After extn with 3 × 100 ml of Et_2O to remove unreacted starting material, the soln was made alk by dropwise addn of 10 *M* NaOH, satd with anhyd K_2CO_3, and extd with 3 × 100 ml of Et_2O. The exts were dried ($MgSO_4$) and evapd to give 13.02 g (84%) of 4 (R = Me, n = 7): bp 60–64° (0.3 mm) (vapor temp). *Anal.* ($C_9H_{18}N_2$).

4-Diethylaminobutyronitrile (4, R = Et, n = 4) was prepd from 4-chlorobutyronitrile (Aldrich C 3000-0) and Et_2NH at room temp: yield, 44%; bp 55° (1.2 mm) [lit.[10] 91–100° (14 mm)].

4-Diisopropylaminobutyronitrile (4, R = *i*-Pr, n = 4) was obtd from 4-chlorobutyronitrile, *i*-Pr_2NH, and KI according to Shonle and Corse:[11] bp 80° (1.1 mm) [lit.[11] 124–127° (33 mm)].

Bis(5-dimethylaminopentyl)amine (5, R = Me, n = 5). A mixt of 6.3 g (0.05 mole) of 5-dimethylaminovaleronitrile and 0.25 g of 5% Rh–Al_2O_3 in 250 ml of MeOH was hydrogenated at 0.703 kg/cm² for 3 hr. The catalyst was removed by filtration, and the soln was evapd to give 6.25 g of an oily residue. Tlc on silica gel showed the presence of primary, secondary, and tertiary amines. After sepn on a column of 240 g of neutral Al_2O_3 (Woelm), activity grade III, with 500 ml of C_6H_6 and 1500 ml of Et_2O as eluants, 2.9 g (47%) of the bis(5-dimethylaminopentyl)amine was obtd as a yellow oil: bp 61° (0.01 mm) [lit.[3] 132–135° (2.0 mm)]. *Anal.* ($C_{14}H_{33}N_3$).

Bis(2-dimethylaminoethyl)amine (5, R = Me, n = 2). A. Dimethylaminoacetonitrile (10 g, 0.12 mole) was hydrogenated with 10% ratio of catalyst and at 70 kg/cm² for 2 days. Since the amine was very volatile and tended to distil together with the MeOH, HCl was bubbled through the mixt, and the MeOH was then evapd *in vacuo* to give a partly solid residue. After making alk with 10 *M* NaOH, the mixt was extd with 2 × 150 ml of Et_2O. The exts were dried ($MgSO_4$) and evapd to give a colorless oil, which after sepn on neutral Al_2O_3, activity grade I, gave 0.46 g (5%) of bis(dimethylaminoethyl)amine.[12]

B. A mixt of 6.8 g (0.048 mole) of bis(2-chloroethyl)amine and 100 ml (0.49 mole) of 22% Me_2NH in H_2O was stirred for 24 hr at room temp. It was made alk with 5 *M* NaOH, satd with anhyd K_2CO_3, and extd with 3 × 150 ml of Et_2O. The exts were dried ($MgSO_4$) and evapd to give 4.36 g of a colorless oil. After sepn on a column of 180 g of neutral Al_2O_3, activity grade I, with 500 ml of C_6H_6, 500 ml of Et_2O, and 500 ml of 2% MeOH–Et_2O eluants, 1.58 g (21%) of the amine was obtd: bp 85° (15 mm) [lit.[12] 198° (760 mm)].

Bis(3-dimethylaminopropyl)amine (5, R = Me, n = 3) was prepd from 9.8 g (0.10 mole) of 3-dimethylaminopropionitrile, 4% ratio of catalyst, and at 0.99 kg/cm² of H_2 for 3 days. After work-up as for **5** (R = Me, n = 2) above, 0.77 g (8%) of a colorless oil was obtd: bp 55° (0.5 mm), 113–114° (15 mm) (vapor temp) [lit.[13] 145–150° (20 mm)]. *Anal.* ($C_{10}H_{25}N_3$).

Bis(6-dimethylaminohexyl)amine (5, R = Me, n = 6) was prepd from 7.0 g (0.05 mole) of 6-dimethylaminocapronitrile, 4% ratio of catalyst, and at 0.7 kg/cm² of H_2 for 24 hr and 2.8 kg/cm² for an addl 20 hr: yield, 30% (based on unrecovered nitrile; 34% of nitrile was recovered); bp 135° (0.1 mm). *Anal.* ($C_{16}H_{37}N_3$).

Bis(7-dimethylaminoheptyl)amine (5, R = Me, n = 7). Hydrogenation of 7.7 g (0.05 mole) of 7-dimethylaminocaprylonitrile, 5% ratio of catalyst, and at 1.005 kg/cm² of H_2 for 16 hr gave a 59% yield of the secondary amine: bp 143–148° (0.6 mm) (vapor temp). *Anal.* ($C_{18}H_{41}N_3$).

Bis(4-diethylaminobutyl)amine (5, R = Et, n = 4) was obtd from 4-diethylaminobutyronitrile, 6% catalyst ratio, 0.7 kg/cm² of H_2 for 2 days, 1.4 kg/cm² for 1 day, and at 2.8 kg/cm² for an addl 2.5 days. The yield was 25.5%: bp 102° (0.1 mm) [lit.[14] 125–126° (2 mm)]. *Anal.* ($C_{16}H_{37}N_3$).

Bis(4-diisopropylaminobutyl)amine (5, R = *i*-Pr, n = 4) was prepd from 7.0 g (0.042 mole) of 4-diisopropylaminobutyronitrile, 4% ratio of catalyst, and at 3.02 kg/cm² of H_2 for 6 days: yield, 21.6% of the secondary amine (based on unrecovered nitrile; 67% of the nitrile was recovered); bp 127° (0.3 mm). *Anal.* ($C_{20}H_{45}N_3$).

Amides. General Procedure. *N,N*-Bis(4-dimethylaminobutyl)dodecanamide (19). A soln of 2.40 g (0.011 mole) of dodecanoyl chloride in 50 ml of anhyd Et_2O was added dropwise to a mixt of 2.16 g (0.010 mole) of bis(4-dimethylaminobutyl)amine, and 10.1 g (0.10 mole) of Et_2NH in 400 ml of Et_2O, cooled in an ice bath. After stirring for 1 hr at 0° and 3 hr at room temp, $Et_2NH \cdot HCl$ was filtered, and the soln was evapd to give 4.10 g of a colorless oil. Purification on a column of 160 g of basic Al_2O_3 (Woelm, activity grade III) and elution with 400 ml of C_6H_6, 400 ml of C_6H_6–Et_2O (1:1), and 1 l. of Et_2O gave 3.75 g (94%) of colorless **19**.

LAH Reduction of the Amides. General Procedure. *N,N*-Bis(4-dimethylaminobutyl)dodecanamide (44). A soln of 1.98 g (0.005 mole) of *N,N*-bis(4-dimethylaminobutyl)dodecanamide in 50 ml of

§ Melting points were detd on a Thomas-Hoover (Uni-Melt) apparatus and are uncor. Distn temps are block temp, unless otherwise stated. Ir absorption spectra were recorded on a Beckmann Model 5A ir recording spectrophotometer. Mass spectra were detd on a Hitachi RMU-6A mass spectrograph. Tlc was conducted on silica gel F-254 (Merck) using the solvent system: MeOH–Me_2CO–Et_2NH (5:4:1 or 20:16:1), unless otherwise stated. Iodoplatinate and/or Dragendorff reagent were used as visualizing sprays, the plates being dried at 110° prior to spraying. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich., and satisfactory results for C, H, N were obtained.

anhyd Et_2O was added dropwise to a mixt of 0.3 g (0.008 mole) of LAH and 150 ml of anhyd Et_2O. The mixt was refluxed for 3 hr. After cooling, 2 ml of H_2O, 4 ml of 5 *M* NaOH, and 6 ml of H_2O were added, and the mixt was stirred vigorously for 20 min. The Et_2O was decanted from the solid $Al(OH)_3$, which was washed with 2 × 100 ml of Et_2O. The Et_2O solns were dried ($MgSO_4$) and evapd to give 1.90 g of a colorless oil. Purification on a column of 80 g of neutral Al_2O_3 (Woelm), activity grade III, and elution with 500 ml of C_6H_6, 500 ml of C_6H_6–Et_2O (1:1), and 250 ml of Et_2O afforded 1.75 g (91%) of a colorless oil: bp 144° (0.7 mm).

Bis(3-cyanopropyl)amine was prepd by a modification of the procedure of Iorio, *et al.*[15] 4-Chlorobutyronitrile and liq NH_3 were kept in an autoclave for 3.5 days. After work-up including fractional distn and sepn on a neutral Al_2O_3 column, 2.74 g of a colorless oil was obtd (bp 120–128° (0.3 mm) (vapor temp)]. Tlc showed 1 major and 2 minor spots. Prepn of the hydrochloride in Et_2O and recrystn from abs EtOH gave 2.78 g of white needles: mp 172–173°. *Anal.* ($C_8H_{14}ClN_3$).

The base was liberated by addn of 10 *M* NaOH, the mixt was satd with anhyd K_2CO_3, extd with 3 × 50 ml of $CHCl_3$, dried ($MgSO_4$), and evapd to give 2.19 g (15%) of a colorless oil: homogeneous on tlc; bp 121–124° (0.2 mm) (vapor temp) [lit.[15] 119–122° (0.12 mm)].

***N,N*-Bis(3-cyanopropyl)hexadecanamide** was prepd from bis(3-cyanopropyl)amine and palmitoyl chloride (99% yield) following the general procedure. The colorless crystals were recrystd from EtOH–H_2O: mp 66–68°; bp 250° (0.1 mm). *Anal.* ($C_{24}H_{43}N_3O$).

***N,N*-Bis(4-aminobutyl)hexadecanamide (36).** A soln of 0.60 g (0.0015 mole) of *N,N*-bis(3-cyanopropyl)hexadecanamide in 300 ml of AcOH was hydrogenated with 0.225 g of 30% Pd/C as catalyst. The H_2 pressure was kept at 4.2 kg/cm² for 2.5 days. Evapn of the solvent gave an oil, which was dissolved in 10 ml of H_2O and extd with 15 ml of $CHCl_3$ to remove unreacted starting material. The aq soln was made alk by dropwise addn of 10 *M* NaOH, satd with anhyd K_2CO_3, and extd with 3 × 40 ml of $CHCl_3$. After drying ($MgSO_4$) and evapn, 0.72 g of amorphous solid was obtd. The solid was dissolved in Et_2O and treated with an Et_2O soln of oxalic acid, whereupon the dioxalate salt sepd. Recrystn from abs EtOH–Et_2O yielded (16%) colorless crystals, mp 188–190° dec. *Anal.* ($C_{28}H_{55}N_3O_9$).

Bismethiodide Salt of *N,N*-Bis(4-dimethylaminobutyl)dodecanamide (37). To 0.50 g (0.0013 mole) of *N,N*-bis(4-dimethylaminobutyl)dodecanamide in 50 ml of abs EtOH was added 3.55 g (0.025 mole) of MeI. The mixt was stirred for 24 hr at room temp. Anhyd Et_2O was added and a yellow-white ppt was formed. The ppt was washed thoroughly with anhyd Et_2O. After drying in a desiccator 0.65 g (76.5%) of yellow crystals was obtd: mp 126–128°. Tlc on a silica plate in MeOH–Me_2CO–2 *N* HCl–AcOH (14:3:6:3) showed 1 spot. *Anal.* ($C_{26}H_{57}I_2N_3O$).

Bismethiodide Salt of Solapalmitine (38). Solapalmitine was quaternized as above and gave light yellow crystals in 67.4% yield: mp 234–235°. Tlc as above showed one spot. *Anal.* ($C_{30}H_{65}I_2N_3O$).

***N*-(4-Dimethylaminobutyl)butyramide** was prepd from 1.16 g (0.01 mole) of 4-dimethylaminobutylamine (K&K 3044) and 1.17 g (0.011 mole) of PrCOCl in 100 ml of Et_2O in the presence of 10.1 g (0.10 mole) of Et_3N according to the general procedure described above. After purification on an Al_2O_3 column, 1.30 g (70%) of a colorless oil was obtd: bp 115° (0.5 mm). The monooxalate salt was prepd in Et_2O: mp 125–126°. *Anal.* ($C_{12}H_{24}N_2O_5$).

***N*-Butyl-*N*-4-dimethylaminobutylamine** was obtd by LAH reduction of *N*-(4-dimethylaminobutyl)butyramide according to the general procedure. After purification on neutral Al_2O_3, a colorless oil (49%) was obtd: bp 75° (1.0 mm). The dioxalate salt was prepd in Et_2O: mp 152–154° dec. *Anal.* ($C_{14}H_{28}N_2O_8$).

***N*-Butyl-*N*-(4-dimethylaminobutyl)hexadecanamide (39)** was synthesized from *N*-butyl-*N*-4-dimethylaminobutylamine and palmitoyl chloride in 72% yield according to the general procedure. The colorless oil had bp 171° (0.4 mm). *Anal.* ($C_{26}H_{54}N_2O$).

***N,N*-Di-*n*-butylpalmitamide (40).** Acylation of *n*-Bu_2NH (1.42 g) with palmitoyl chloride (1.38 g) in anhyd Et_2O (200 ml) by the usual procedure, and chromatography on Al_2O_3 (100 g, Woelm, grade III) gave a homogeneous colorless oil (1.86 g). The oil had bp 235° (1.5 mm). *Anal.* ($C_{24}H_{49}NO$).

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Mixed Bifunctionality. 4. Antitumor Activity of Alkylating Derivatives of Polycyclic Aromatic Hydrocarbons as a Function of Structure and of Vehicle†

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The activity of this class of hydrophobic antitumor agent is dependent on its *in situ* availability as well as on the geometry of the aromatic moiety and to a lesser extent on the reactivity of the alkylating function. 9,10-Bis(chloromethyl)anthracene is curative for the Ehrlich ascites mouse tumor at a total dosage of less than two-thirds of a microgram when given in the colloidal state.

Simple chloromethyl derivatives of polynuclear aromatic hydrocarbons are extremely potent antitumor agents. We have previously shown marked increases in potency following administration of these solutions in sesame oil over those given as fine saline dispersions.[1] Other vehicles were considered, partly with a view to finding a procedure adaptable to intravenous injection.

An emulsion in saline was found to be stabilized for hours (or longer, as a function of concentration) by a minimal amount of sesame oil. As a measure of agent availability *in situ* in such dispersions, testing of a representative group of previously tested chloromethyl hydrocarbons and of some

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