phenanthryl ketone, obtained as an impure syrup by the general method given (*vide supra*) for 3 mmoles of **I**, was dissolved in 40 ml of absolute EtOH containing 3 mmoles of picric acid, crystallization being complete after 3 days.

Dipropargylaminomethyl 9-Phenanthryl Ketoxime.—A mixture of the amino ketone (**2**) (1.224 g, 4 mmoles) and $HONH_2 \cdot HCl$ (840 mg, 12 mmoles) in 10 ml of absolute EtOH and 5 ml of dry pyridine was refluxed for 2 hr. The mixture was transferred to a small beaker, H_2O was added to incipient turbidity, and the beaker was left in the open for 3 hr. The resulting crystals were filtered off, and four recrystallizations from EtOH–H_2O gave pure oxime; yield 261 mg (20%), mp 159–160°. *Anal.* ($C_{22}H_{18}N_2O$) C, H, N.

9-Phenanthrenemethanols (III) *via* Amino Ketones (II). General Method.—To a solution of 4 mmoles of either **1**, **2**, or **4** in 30 ml of THF and 175 ml of *i*-PrOH was added 152 mg (4 mmoles) of $NaBH_4$, and the mixture was stirred for 18 hr under exclusion of moisture. Me_2CO (30 ml) was added, the solvent was evaporated under diminished pressure, and the residue was coevaporated three times with 30-ml portions of MeOH. For **7** and **10**, the residue was dissolved in 50 ml of $CHCl_3$, and the solution was washed with two 30-ml portions of H_2O and then dried (Na_2SO_4). It was filtered, and the solvent was evaporated under diminished pressure, leaving a syrupy residue that was dissolved in 15 ml of THF. A calculated amount of HCl in Et_2O was added, the mixture was evaporated to dryness, and the products were crystallized as indicated in Table II. Compound **8** was obtained as a crystalline product without prior conversion into its hydrochloride (**9**), which could be prepared from **8** in a manner similar to that for **7** and **10**.

α-(Bromomethyl)-9-phenanthrenemethanol (IV).—To a solution of 12 g (40 mmoles) of **I** in 120 ml of THF and 480 ml of MeOH, precooled to 5°, was added, with stirring, 1.526 g (40 mmoles) of $NaBH_4$, in small portions at intervals of 2 min, the addition being complete in *ca.* 15 min. The mixture was stirred for 1.5 hr at 5–10° and then warmed to room temperature. The mixture was transferred to a 3-l. beaker, H_2O was slowly added, with stirring, to give a total volume of 2.5 l., and the beaker and contents were kept in a well-ventilated hood for 3 hr. The resulting precipitate was collected and recrystallized from THF–EtOH, giving 9.11 g (75%) of IV, mp 153–154.5°, $\nu_{max}^{CHCl_3}$ 3610 cm^{-1} (CHOH), R_f 0.30 on silica gel DF-5 (Camag) with 1:1 $CHCl_3$–benzene. *Anal.* ($C_{16}H_{13}BrO$) C, H, Br.

9-(Epoxyethyl)phenanthrene[7] (V).—To a suspension of 2.11 g (7 mmoles) of IV in 90 ml of absolute MeOH, precooled to 0°, was added 500 mg of Na, in small pieces, with stirring. The mixture became clear in 12 min and was kept at 0° for an additional 15 min. The solvent was removed under diminished pressure at 25°, the residue was suspended in 100 ml of H_2O, and the suspension was extracted with two 150-ml portions of Et_2O. The extract was washed (H_2O), dried (Na_2SO_4), and filtered, and the filtrate was evaporated under diminished pressure at 25° to a colorless syrup, homogeneous on tlc; $\nu_{max}^{CCl_4}$ 1260 (weak), 900, and 850 cm^{-1} (epoxide). An absorption band at 3610 cm^{-1} (CHOH) was absent. The product V was identical (ir and tlc) with a sample prepared from 9-phenanthrenecarboxaldehyde by the method[7] of Duncan and coworkers.

α-[N-(2-Cyanoethyl)cyclohexylaminomethyl]-9-phenanthrenemethanol Picrate (11) and Hydrochloride (12).—A mixture of 4.82 g (16 mmoles) of IV and 14.6 g (96 mmoles) of N-(2-cyanoethyl)cyclohexylamine was heated at 77–81° in a dry atmosphere. After 43 hr, the mixture was cooled and extracted with 100 ml of 1:4 $CHCl_3$–Et_2O, and the extract was filtered. The filtrate was evaporated to a syrup, which was stirred with 100 ml of 1 *M* HCl, and the supernatant liquid was decanted. The residue was dissolved in 250 ml of $CHCl_3$, and the solution was washed [1 *M* HCl (100 ml), H_2O (100 ml), 1% aqueous NaOH (100 ml), H_2O (two 100-ml portions)]. The $CHCl_3$ solution was dried (Na_2SO_4) and filtered, and the filtrate was evaporated under diminished pressure, leaving a syrupy residue that was dried for 24 hr in a vacuum desiccator (P_2O_5). The dried syrup was dissolved in 20 ml of THF, a hot solution of 3.66 g (14.3 mmoles) of picric acid in 100 ml of MeOH was added, and the mixture was heated, with stirring, to remove most of the THF, whereupon the picrate (**11**) began to crystallize.

The picrate (**11**) (2.4 g) was suspended in 250 ml of $CHCl_3$ and the suspension was shaken in a separatory funnel with 120 ml of 1% aqueous NaOH. The $CHCl_3$ layer was extracted with two 75-ml portions of 1% aqueous NaOH and two 75-ml portions of H_2O, dried (Na_2SO_4), filtered, and evaporated under diminished pressure at 30°. The residue was dissolved in 15 ml of THF, and 1.8 ml of 2.26 *M* HCl in Et_2O was added. Et_2O was added to incipient turbidity, inducing crystallization, with additional Et_2O being added, in small volumes at intervals, until crystallization of **12** was complete.

α-[N-(2-Hydroxyethyl)cyclohexylaminomethyl]-9-phenanthrenemethanol Picrate (13) and Hydrochloride (14).—A mixture of 1.5 g (7 mmoles) of V and 6.02 g (42 mmoles) of N-(2-hydroxyethyl)cyclohexylamine was heated at 78–82° for 24 hr, with occasional stirring. The mixture was dissolved in 200 ml of $CHCl_3$, and the solution was washed [8% HCl (three 100-ml portions), 1% NaOH (100 ml), H_2O (two 100-ml portions)]. The $CHCl_3$ layer was dried (Na_2SO_4) and filtered, and the filtrate was evaporated to dryness under diminished pressure at 30°, leaving a yellowish syrup, which was dissolved in 20 ml of THF, followed by the addition of 1.77 g (6.9 mmoles) of picric acid in 75 ml of hot MeOH. The mixture was heated, with stirring, to remove most of the THF, whereupon crystallization of the picrate (**13**) commenced.

The picrate (**13**) (3.42 g, 5.6 mmoles) was suspended in 220 ml of $CHCl_3$ (separatory funnel) and shaken with 100 ml of 1% aqueous NaOH, until dissolution was complete. The $CHCl_3$ layer was washed [1% aqueous NaOH (two 50-ml portions), H_2O (two 50-ml portions)], dried (Na_2SO_4), and filtered. The filtrate was evaporated to dryness under diminished pressure at 30°, the resulting clear syrup was dissolved in 15 ml of dry THF, and 3.1 ml of 2.26 *M* HCl in Et_2O was added. The mixture was evaporated under diminished pressure at 30°, leaving the hydrochloride (**14**) as a white foam, which was dried in a vacuum desiccator (P_2O_5) for 24 hr.

α-[Bis(2-carboxyethyl)aminomethyl]-9-phenanthrenemethanol (15).—A suspension of the methanol hydrochloride (**10**) in 8 ml of 9 *M* HCl and 8 ml of *p*-dioxane was refluxed in an oil bath (105°) for 4 hr. The dark brown mixture was cooled, sufficient 10% aqueous NaOH was added to make it alkaline, and the resulting mixture was heated to 80°. It was then filtered with a little Darco G-60 decolorizing carbon, the pH of the filtrate was adjusted to about 4 with 1 *M* HCl, and the mixture was kept overnight at room temperature. The separated product **15** was recrystallized by acidifying an alkaline solution to pH 3–4.

α-[Bis(3-aminopropyl)aminomethyl]-9-phenanthrenemethanol Trihydrochloride (16).—To a solution of 2.3 g (7 mmoles) of **10** in 10 ml of purified Diglyme was added 50 ml of 1 *M* $NaBH_4$. To this mixture was added (dry box) 6.6 g (15 mmoles) of $AlCl_3$, in small portions with stirring. Stirring was continued for 2 hr, H_2O (25 ml) was carefully added, with stirring, and the mixture was made alkaline with 10% aqueous NaOH. It was then extracted with $CHCl_3$ (three 100-ml portions), and the $CHCl_3$ extracts were combined, washed with H_2O (150 ml), and dried (Na_2SO_4). The solution was filtered, and the filtrate was evaporated to dryness under diminished pressure at 35°, leaving a residue [$\nu_{max}^{CHCl_3}$ 3610 (OH), 3390 (asym NH), and 3315 cm^{-1} (sym NH)], which was dissolved in 20 ml of THF. To this was added 10 ml of 2.24 *M* HCl in Et_2O, followed by the addition of 50 ml of Et_2O. The resulting precipitate was filtered off inside a dry box, in which subsequent recrystallizations were performed.

Esters of Undecanoic Acid with Potential Long-Lasting Insect-Repellent Activity[1]

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We have previously reported on the design and synthesis of novel grisan and coumaranone derivatives anticipated to exert insect repellency following systemic

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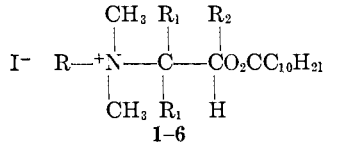
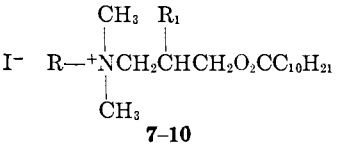
TABLE I
UNDECANOIC ACID ESTERS



1–6



7–10

No.	R	R_1	R_2	Mp, °C[a]	Yield, %	Recrystn solvent[b]	Formula[c]
1	CH_3	H	H	164.5–165.0[d]	74	A	$C_{16}H_{34}INO_2$
2	$C_{12}H_{25}$	H	H	171.8–172.5	40	A	$C_{27}H_{56}INO_2$
3	CH_3	H	CH_3	167.0–168.0	58	A	$C_{17}H_{36}INO_2$
4	$C_{12}H_{25}$	H	CH_3	76.7–79.7[e]	46	E	$C_{28}H_{58}INO_2$
5	CH_3	CH_3	H	218.4[f]	9	A	$C_{18}H_{38}INO_2$
6	$C_{12}H_{25}$	CH_3	H	162.2–162.8	6	A	$C_{29}H_{60}INO_2$
7	CH_3	H		127.0–127.4	45	A	$C_{17}H_{36}INO_2$
8	$C_{12}H_{25}$	H		102.8–103.7	62	A	$C_{28}H_{58}INO_2$
9	CH_3	$O_2CC_{10}H_{21}$		149.3–150.3	83	C	$C_{28}H_{56}INO_4$
10	$C_{12}H_{25}$	$O_2CC_{10}H_{21}$		96.8–98.3	35	A	$C_{39}H_{78}INO_4$

[a] Melting points are corrected; they were determined with a Büchi melting point apparatus. [b] Recrystallization solvents: A = Me_2CO, C = $CHCl_3$, E = Et_2O. [c] Analyses for C, H, I, and N were performed by Drs. G. Weiler and F. B. Strauss of Oxford, England; the analytical values were within ±0.3% of the theoretical values. [d] Lit.[11] mp 164–165°. [e] The compound softened at 60.3°. [f] Melted with decomposition.

administration.[2,3] More recently, we described the preparation of phenolic esters[4] and esters of dihydroxyacetone[5] designed to provide long-lasting insect-repellent efficacy by gradually releasing an active repellent component (*i.e.*, undecanoic acid) subsequent to anchoring to the epidermal surface. As an extension of this work, we prepared a series of undecanoic acid esters (**1–10**, Table I) which contain quaternary ammonium functions. The ability of quaternary ammonium functions to effect dermal substantivity is well known[6,7] and their electronic influence in assisting hydrolysis *in vitro* is also clearly documented.[8,9] In fact, several quaternary ammonium salts have been reported to possess insectifugal properties.[10] Branching in the alkyl chain connecting the ester and quaternary nitrogen functions was anticipated to affect the rate of hydrolysis through the exertion of differing degrees of steric hindrance. Compounds possessing dodecyl substituents on the quaternary nitrogen were expected to have enhanced lipophilic characteristics and, thereby, increase hydrophobic bonding with the skin.

The repellency of a number of the undecanoic acid esters against *Aedes aegypti* mosquitoes is summarized in Table II. The data indicate significant repellencies for several of the compounds. Particularly noteworthy is the effectiveness of the formulations of **1** and **10**; these effected a strikingly significant reduction in biting even after 24 hr on the skin. Although one cannot exclude, entirely, possible contributions of intrinsic factors, in the light of our preceding statements, the repellency data appear to reflect that hydrolysis of the evaluant compounds releases undecanoic acid in quantities capable of decreasing bites, even 24 hr after application, but not in sufficient concentrations to effect *complete* protection. Indications from our current work suggest that our new precursor-type molecules will be capable of releasing the repellent moiety discussed in this paper, and others, at considerably faster rates.

TABLE II
PER CENT OF MOSQUITOES (*Aedes aegypti*) BITING FOREARMS OF HUMAN VOLUNTEERS AT VARIOUS INTERVALS AFTER TOPICAL APPLICATION[a]

		% biting[b] at hours indicated				
Compd	LSD[c]	0	1	4	8	24
4[d]	12.4	20.8	9.2	20.3	18.6	
Control		62.2	62.2	30.8	35.9	
5[d]	12.4	31.3	30.8	41.1	35.9	
Control		55.2	55.2	34.0	55.1	
7[d]	13.5	66.7	40.1	35.1	24.0	
Control		62.2	62.2	41.2	46.3	
8[d]	12.4	65.7	28.6	39.2	38.9	
Control		55.2	55.2	34.0	55.1	
1[e]	13.3			13.3	5.5	14.2
Control				52.9	33.1	40.3
10[e]	16.6			44.3	33.3	28.6
Control				80.2	56.2	66.0

[a] From the laboratory of Dr. C. N. Smith, U. S. Department of Agriculture. [b] Average of three tests on each of three subjects with six mosquitoes/test. [c] Least significant difference at the 0.05 level. [d] Application rate 5 mg/cm²; compound was applied in acetone solution. [e] Application rate 20 mg/cm²; compound was applied as a formulation, 50% w/w, in polyethylene glycol ointment (USP).

Experimental Section

Synthetic Work.—The undecanoic acid esters reported in Table I were prepared by the following method.[11]

3-(N,N-Dimethylamino)-1-propanol Undecanoate Hydrochloride (11).—Freshly distilled 3-(N,N-dimethylamino)-1-propanol (50.4 g, 0.488 mole) was added to a solution of 100 g (0.488 mole) of undecanoyl chloride in 400 ml of anhydrous C_6H_6. The mixture

(2) V. Dev, R. P. Quintana, and A. Lasslo, *J. Med. Chem.*, **9**, 242 (1966).
(3) R. P. Quintana, A. Lasslo, P. P. Boggs, and E. D. Yeaglin, *J. Pharm. Sci.*, **57**, 230 (1968).
(4) R. P. Quintana, L. R. Garson, and A. Lasslo, *Can. J. Chem.*, **46**, 2835 (1968).
(5) R. P. Quintana, L. R. Garson, and A. Lasslo, *ibid.*, **47**, 853 (1969).
(6) R. B. Kundsin and C. W. Walter, *A.M.A. Arch. Surg.*, **75**, 1036 (1957).
(7) P. Dineen and G. Hildick-Smith in "Skin Bacteria and Their Role in Infection," H. I. Maibach and G. Hildick-Smith, Ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1965, p 300.
(8) G. Messwarb, K. Taunus, L. Orthner, R. Reuber, and M. Grossmann, U. S. Patent 3,182,044 (1965).
(9) R. P. Bell and B. A. W. Coller, *Trans. Faraday Soc.*, **60**, 1087 (1964); *cf.* R. P. Bell and F. J. Lindars, *J. Chem. Soc.*, 4601 (1954).
(10) W. V. King (Compiler), "Chemicals Evaluated as Insecticides and Repellents at Orlando, Fla.," Agriculture Handbook No. 69, Entomology Research Branch, Agricultural Research Service, U. S. Department of Agriculture, Washington, D. C., 1954, pp 46–47.
(11) R. Schneider, A. R. Timms, Z. Kyi, and W. Wilson, *Brit. J. Pharmacol.* **12**, 30 (1957).

was stirred at room temperature for 1 hr, heated at reflux for 10 hr, and cooled. The ester hydrochloride (145 g, 96%, mp 145.8–146.7°) obtained by filtration was used without further purification in the preparation of **7**.

3-(Undecanoyloxy)propyltrimethylammonium Iodide (7). Compound **11** (25.0 g, 0.081 mole) was treated with 150 ml of 10% aqueous Na_2CO_3, and the mixture was extracted with C_6H_6 (five 100-ml portions). Removal of the C_6H_6 by distillation under reduced pressure afforded the oily liquid free base of **11**. The latter was dissolved in 200 ml of Me_2CO, 34.6 g (0.244 mole) of MeI was added, and the mixture was heated at reflux for 12 hr. The product, obtained by filtration, was recrystallized four times (Me_2CO); yield 15.1 g (45%), mp 127.0–127.4°.

Evaluation of Insect-Repellent Activity.—Repellency against *Aedes aegypti* mosquitoes was evaluated by Mr. I. H. Gilbert and Mr. H. K. Gouck of the Entomology Research Division, U. S. Department of Agriculture, Gainesville, Fla.[12] Female *Aedes aegypti* mosquitoes, 7–8 days old, were confined in small cylindrical cages (4 × 12 cm). The sides of the cages were clear plastic; one end was covered with gauze and the other end was fitted with a plastic slide closure. Mosquitoes in stock cages were immobilized by a low temperature, and six females were placed in each small cage. The cages were then held in a warm room for at least 1 hr to permit the mosquitoes to recover before tests were begun. Tests were made by placing the end of the cage equipped with the slide in contact with a treated area on a human arm and opening the slide to give the mosquitoes direct access to the treated skin for a period of 1 min. Treated areas of the skin were sprayed with water every hour to simulate the wetting which would occur under sweating conditions; the water was applied with an atomizer to provide wetting but no runoff. In each test period (*cf.* Table II) cages of mosquitoes were exposed to untreated areas of the skin to provide checks on the percentage of mosquitoes biting.

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(12) Communication from the Entomology Research Division, U. S. Department of Agriculture, Beltsville, Md. (Gainesville, Fla.), Sept 1968.

Synthesis and Antitumor Activity of 9-Substituted Nitrogen Mustard Derivatives of Naturally Occurring Purines[1]

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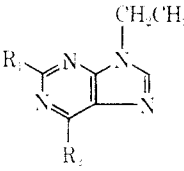
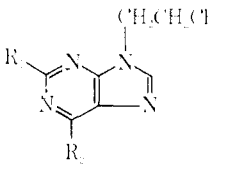
Substitution at position 9 of a number of purines often provided compounds with interesting antitumor activity.[3] That this activity does not result from the *in vivo* dealkylation of the 9-substituted derivatives to the parent purines is illustrated by the confirmed activity of 9-(tetrahydrofur-2-yl)adenine against Ca755.[4] A number of 9-substituted purines were found to inhibit nucleoside cleavage, thus potentiating the antitumor activity of compounds such as thioguanosine.[5] In the area of purine nitrogen mustard derivatives, 9-[bis(β-chloroethyl)aminopropyl]hypoxanthine[6] was found to be active against Ehrlich ascites 6C3HED and several other experimental tumors in mice.[7] Since 9-(β-chloroethyl)adenine was reported to inhibit the growth of the C1300 experimental tumor[8] and since a number of 6-S-substituted 9-(β-hydroxyethyl)- and 9-(β-chloroethyl)purines are active against Ca755, solid Friend virus leukemia, and cell culture testing systems,[9] naturally occurring purines bearing a 9-bis(β-chloroethyl)aminoethyl moiety should be studied. In connection with our previous work in this area,[3,10,11] synthesis of compounds of this type was investigated.

The present investigation includes the preparation of 9-bis(β-chloroethyl)aminoethyl derivatives of adenine (Ia), hypoxanthine (Ib), and guanine (Ic).

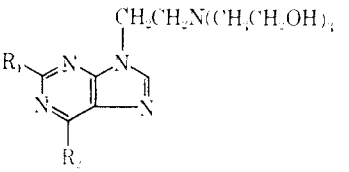


Ia, $R_1 = H$; $R_2 = NH_2$
b, $R_1 = H$; $R_2 = OH$
c, $R_1 = NH_2$; $R_2 = OH$

Treatment of 9-(β-chloroethyl)adenine (IIa) with diethanolamine in refluxing 2-ethoxyethanol, followed by reaction of the resulting solution with anhydrous HCl gave the dihydrochloride salt of 9-[bis(β-hydroxyethyl)aminoethyl]adenine (IIIa). Subsequent treatment of IIIa with $SOCl_2$ under reflux conditions yielded the desired Ia.



IIa, $R_1 = H$; $R_2 = NH_2$
b, $R_1 = NH_2$; $R_2 = SCH_3$



IIIa, $R_1 = H$; $R_2 = NH_2$
b, $R_1 = H$; $R_2 = SCH_3$
c, $R_1 = H$; $R_2 = OH$
d, $R_1 = NH_2$; $R_2 = SCH_3$
e, $R_1 = NH_2$; $R_2 = OH$

Careful treatment of 6-methylthio-9-[bis(β-hydroxyethyl)aminoethyl]purine[3] (IIIb) with dilute aqueous H_2O_2 and HCl yielded the hydrochloride salt of the corresponding hypoxanthine derivative IIIc. Treatment of IIIc with $SOCl_2$ gave Ib, isolated as a dihydrochloride salt.

(1) This investigation was supported in part by the Cancer Chemotherapy National Service Center, National Cancer Institute of the National Institutes of Health, Public Health Service, Contract PH-43-65-94; and in part by research grant CY-4008(C3) from the National Cancer Institute, of the National Institutes of Health, Public Health Service.

(2) Taken in part from the M.S. thesis of James D. Westover, submitted to the Department of Chemistry, Arizona State University, Tempe, Ariz. 1961.

(3) R. K. Robins, *J. Med. Chem.*, **7**, 186, (1964).

(4) W. A. Bowles, F. H. Schneider, L. R. Lewis, and R. K. Robins, *ibid.*, **6**, 471 (1963).

(5) G. A. LePage and I. G. Junga, *Cancer Res.*, **23**, 739 (1963).

(6) H. H. Lin and C. C. Price, *J. Org. Chem.*, **26**, 266 (1961).

(7) R. J. Rutman, F. S. Lewis, S. Buckner, C. C. Price, F. Llewellyn, and E. Owen, *Cancer Res. (Suppl.)*, **22**, 559 (1962).

(8) (a) J. H. Lister and G. M. Timmis, *J. Chem. Soc.*, 327 (1960); (b) S. S. Epstein and G. M. Timmis, *Biochem. Pharmacol.*, **11**, 743 (1962).

(9) D. E. O'Brien, J. D. Westover, R. K. Robins, and C. C. Cheng, *J. Med. Chem.*, **8**, 182 (1965).

(10) H. C. Koppel, R. H. Springer, R. K. Robins, F. H. Schneider, and C. C. Cheng, *J. Org. Chem.*, **27**, 2173 (1962).

(11) H. C. Koppel, R. H. Springer, G. D. Daves, Jr., and C. C. Cheng, *J. Pharm. Sci.*, **52**, 81 (1963).