CuCN to 130–200° and following the course of the reaction spectroscopically from samples taken from the reaction mixture. After completion of the reaction, the mixture was cooled and the slurry was taken up in $CHCl_3$ or C_6H_6, filtered, and distilled *in vacuo*, unless stated otherwise: *o*-chlorophenylglyoxylonitrile,[9] mp 35–37°, lit.[9] bp 101–105° (1.5–1.6 mm); *m*-chlorophenylglyoxylonitrile,[9] mp 36–40°, lit.[9] mp 35–37°; *p*-chlorophenylglyoxylonitrile,[10,11] mp 35–37°, lit.[10] mp 41–42.5°, lit.[11] mp 37–39°; 2,4-dichlorophenylglyoxylonitrile, mp 58–70°; *o*-fluorophenylglyoxylonitrile, bp 68–70° (0.1 mm); *p*-fluorophenylglyoxylonitrile,[11] bp 99–104° (aspirator vacuum), lit.[11] mp 20–22°; (α,α,α-trifluoro-*o*-tolyl)glyoxylonitrile, bp 53–56° (0.75 mm); (α,α,α-trifluoro-*m*-tolyl)glyoxylonitrile), bp 53–56° (0.75 mm); (α,α,α-trifluoro-*p*-tolyl)glyoxylonitrile, bp 39–40° (0.25 mm); (α,α,α,α′,α′,α′-hexafluoro-3,5-xylyl)-glyoxylonitrile, bp 44–46.5° (0.25 mm); *p*-methoxyphenylglyoxylonitrile,[11,12] mp 52–55°, lit.[11] mp 56–57°, lit.[12] mp 57–58°; 3,4,5-trimethoxyphenylglyoxylonitrile, mp 134–135° (recrystd from petroleum ether), lit.[13] mp 133–134°; 3,3-dimethyl-3-phenylpyruvonitrile, bp 75–77° (0.5 mm); 3-(3,4-dichlorophenyl)-3,3-dimethylpyruvonitrile, bp 91–93° (0.15 mm); *p*-trifluoromethoxyphenylglyoxylonitrile, bp 172–173° (760 mm). Under the described conditions we were unable to prepare 2,6-dichlorophenylglyoxylonitrile.

The following compounds were prepared according to a procedure of Mauthner[14] (Et_2O, pyridine, HCN): phenylpyruvonitrile, mp 54–64°; 3,4,5-trimethoxyphenylpyruvonitrile, mp 125–135°.

3,5-Diamino-6-(α,α,α-trifluoro-*p*-tolyl)-*as*-triazine (9). (α,α,α-Trifluoro-*p*-tolyl)glyoxylonitrile (226.0 g, 1.21 moles) in 250 ml of DMSO was added dropwise to a stirred solution of aminoguanidine HCO_3 (169.8 g, 1.26 moles) in 1880 ml of 8 *N* HNO_3 at 0–5°. The suspension [which at the start of the reaction consisted mostly of (α,α,α-trifluoro-*p*-tolyl)glyoxylonitrile] was stirred overnight at room temperature, and the ppt was filtered the next morning. The amidinohydrazone HNO_3 (358.7 g) was used in the next step without further purification.

The amidinohydrazone HNO_3 (233.75 g) was added to 2.5 l. of 10% KOH in EtOH and refluxed under N_2 for 1 hr. Then H_2O (1.054 l.) was added, and the whole was vacuum evaporated until a cryst ppt separated. A total of 67.9 g of cryst compound was obtained.

3-Amino-6-(α,α,α-trifluoro-*p*-tolyl)-*as*-triazin-5-ol (17). The aqueous mother liquor from the preceding reaction was acidified with concd HCl to pH 1, when a solid began to separate; 105.5 g of **17** was obtained by filtration.

The high-resolution mass spectrum showed the molecular ion at 256.0582 (calcd 256.0570) and a fragment peak at 186.0314 for the elemental composition $C_9H_5OF_3$ (calcd 186.0292), indicating the hydroxyl function to be attached at position 5 of the *as*-triazine nucleus rather than at position 3.

3,5-Diamino-6-(α,α,α-trifluoro-*p*-tolyl)-*as*-triazine Pamoate. 3,5-Diamino-6-(α,α,α-trifluoro-*p*-tolyl)-*as*-triazine hydrochloride (2.8 g) was dissolved in boiling MeOH (200 ml), 4.51 g of the disodium salt of pamoic acid dissolved in MeOH (25 ml) was added, and the whole was left at room temperature. After 24 hr, H_2O was added and the solution was concd *in vacuo*. The resulting crystals were filtered, yielding 3.1 g of the pamoate salt, mp 193–198°. *Anal.* ($C_{43}H_{32}O_6N_{10}F_6$) C, H, N.

Acknowledgments. Tests with *P. berghei* and *P. gallinaceum* were conducted by Dr. Leo Rane, those with drug-resistant *P. berghei* by Dr. Paul Thompson, those with *P. cynomolgi* by Dr. E. Ross Hart, and those with *P. falciparum* in *Aotus trivirgatus* by Dr. Leon H. Schmidt. To these gentlemen the authors extend their thanks.

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Synthesis of Halogenated Anthraldehydes and Their Conversion to Antimalarial Amino Alcohols†

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As part of the current U. S. Army Research Program on malaria, we undertook the syntheses of substituted anthracene amino alcohols. The goal was increased activity against the drug-resistant strain of *Plasmodium falciparum*. The intensive antimalaria testing program during World War II did not include anthracene compounds,[1] but shortly thereafter, several anthracenes with C_9-$CH_2NHCH_2CH(OH)R$ groups[2] were found to be inactive against *P. gallinaceum* in chickens, while tetrahydroanthracene aminomethanols with unspecified side-chain position and 9,10-dihydroanthracene 9-aminomethanols were slightly active and inactive, respectively.[3]

An earlier unsuccessful attempt to prepare anthracene 9-aminomethanols was noted in 1948.[4] However, in 1968, the synthesis of 9-(2-di-*n*-heptylamino-1-hydroxyethyl)-anthracene was reported by Duncan, *et al.*,[5] and this compound was curative[6] against *P. berghei* in mice (Table II) at 320 mg/kg. Our work reports the preparation of 10-haloanthracene 9-amino alcohols, some of which are shown to be curative at considerably lower dose levels (*e.g.*, 80 mg/kg) in the same test.

We prepared the intermediate substituted 9-anthraldehydes in Table I by Vilsmeier[7] or reductive[8] formylation of the corresponding anthrone or 2-chloroanthraquinone, respectively. Anthrone intermediates to aldehydes D and E were prepared by the method of Bergmann and Loewenthal[9] from the corresponding 3-arylphthalides.

Aldehydes A and B gave corresponding 9-anthrylethylene oxides in 67 and 96% yields, respectively, by methylene transfer with dimethylsulfonium methylide.[5,18] A marked substituent effect was noted with aldehydes C, D, and E: none of the corresponding epoxides could be obtained from these compounds using several modifications of the dimethylsulfonium methylide procedure. That ylid attack on the aldehyde carbonyl of E had occurred was indicated by the disappearance of the aldehyde proton peak at 10.88 ppm in the nmr spectrum of the crude reaction mixture.

Readily available 10-chloro-9-anthraldehyde (B of Table I) was used as a model compound in a search for alternate routes to amino alcohols. Attempts at entry into the more

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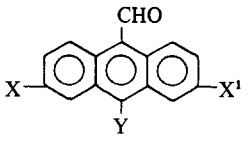
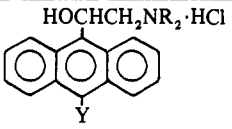
Table I. Substituted 9-Anthraldehydes



Compd	Y	X	X'	% yield[a]	Recrystn solvent	Mp, °C	Formula[h]
A	Br	H	H	25	Me_2CO–THF	220–221[b]	
B[c]	Cl	H	H	97	MeOH	216.5–217[d]	
C	Cl	Cl	H	66	95% EtOH	170–171[e]	($C_{15}H_8Cl_2O$)
D[f]	Cl	Br	Br	50	THF	236–237.5	($C_{15}H_7Br_2ClO$)
E[g]	Cl	CF_3	H	60	MeOH	122.5–123.5	($C_{16}H_8ClF_3O$)

[a]From the corresponding anthrone or anthraquinone. [b]Kuhn and Fischer[10] give mp 218°. [c]Aldehyde B originally was prepared as indicated. It became commercially available during the course of this investigation. [d]Lit.[11] mp 216°. [e]Lit.[11] mp 174°. [f]Prepared by the sequence: 6-nitrophthalide,[12] 6-bromophthalide,[13] 5-bromophthalaldehydic acid[14] (78% from NBS, followed by hydrolysis), 6-bromo-3-(4-bromophenyl)phthalide [60% crude (by Grignard reaction), mp 157–158.5° (aq Me_2CO), *Anal.* ($C_{14}H_8Br_2O_2$) C, H], 5-bromo-2-(4-bromobenzyl)benzoic acid [82%, mp 166–168° (C_6H_6), *Anal.* ($C_{14}H_{10}Br_2O_2$) C, H], 2,7-dibromo-9-anthrone [100%, mp 212–215°, *Anal.* ($C_{14}H_8Br_2O$) C, H; converted by heat or air to mp >300°, which can be reconverted to the anthrone with Sn–HCl–$PtCl_4$[15]]. [g]3-(4-Trifluoromethylphenyl)phthalide [mp 101.5–102° (petr ether), *Anal.* ($C_{15}H_9F_3O_2$) C, H] was prepared in 86% yield by $NaBH_4$ redn of sodium 2-(4-trifluoromethylbenzoyl)benzoate.[16,‡] Subsequent steps gave 3-(4-trifluoromethylbenzyl)benzoic acid [84%, mp 129–131° (petr ether), *Anal.* ($C_{15}H_{11}F_3O_2$) C, H] and 2-trifluoromethyl-9-anthrone [85%, mp 149.5–151.5° (anhyd EtOH), *Anal.* ($C_{15}H_9F_3O$) C, H]. [h]Where formula is given compounds were analyzed for C, H.

Table II. 9-Anthryl Amino Alcohols



Y	R[a]	Mp, °C	Yield, %	Formula[b]	Antimalarial activity[c,d] 20	40	80	160	320	640
Cl	C_4H_9	227–228 dec	59[e]	$C_{24}H_{31}Cl_2NO$	6.0[f]	11.2	12.2	4C	5C	5C
Cl	C_7H_{25}	130–132.5	37[e]	$C_{30}H_{43}Cl_2NO$	5.1	9.4	2C	4C	5C	5C
Br	C_4H_9	237–238 dec	18[g]	$C_{24}H_{31}BrClNO$	1.6	5.9	14.5	15.9	*i*	*i*
H	C_7H_{15}[h]				1.6	6.6	6.8	8.6	2C	4C

[a]*n*-Alkyl groups. [b]Correct analyses for C, H, and N were obtained for all compounds. [c]For details of test procedure, *cf.* ref 28. Test data supplied by Walter Reed Army Institute of Research. [d]Increase in mean survival time (IMST) of mice infected with *P. berghei* after treatment at indicated dosage (in mg/kg); IMST > 6.0 days = active. C = cures (IMST > 60). Data for substituted amino alcohols are two-test averages. [e]From 10-chloro-9-anthrylethylene oxide, prepared in 96% yield, mp 130.5–132.5° (anhyd EtOH). *Anal.* ($C_{16}H_{11}ClO$) C, H. [f]IMST = 0.7 at 10 mg/kg. [g]From 10-bromo-9-anthrylethylene oxide, prepared in 67% yield (crude) and used without further purification. [h]Ref 5 and 6. [i]Not tested.

classical sequence§ by treatment of aldehyde B with Ag_2O,[19] *tert*-BuOCl,[20] or SO_2Cl_2[21]–AIBN gave good recoveries of B, rather than the anticipated carboxylic acid or acid chloride. Treatment with CrO_3–HOAc or $KMnO_4$–Na_2CO_3 at several temperatures gave anthraquinone (*ca.* 86% yield).

Formation of the corresponding nitrile from B was accomplished in high yield. Extensive decomposition occurred during unsuccessful attempts to hydrolyze the 10-chloro-9-anthronitrile to the carboxylic acid with anhyd H_3PO_4[22] or 50% H_2SO_4–HOAc, or to the amide with $H_2SO_4 \cdot H_2O$.

Treatment of either aldehydes B or C with excess MeMgX (X = Cl, Br) gave good recoveries of starting material. The Wittig reaction proceeded successfully with B to give 10-chloro-9-vinylanthracene, which could not be epoxidized with *m*-chloroperbenzoic acid or peroxybenzimidic[23] acid.

‡Violent explosions have been noted in the large scale (5–10 moles) preparations of *m*-trifluoromethylphenylmagnesium bromide[17] and *o*-trifluoromethylphenylmagnesium bromide as well as the corresponding lithium compound (Marshallton Research Laboratories, Inc., Catalog 6/15/71). We have not encountered these difficulties with *p*-bromobenzotrifluoride in small scale (≤0.4 mole), although a very vigorous exotherm occurred after a 15-min induction period during a 0.1-mole scale preparation. Due caution therefore should be exercised in these reactions, particularly in larger-scale preparation.

§*Cf.*, for example, ref 27.

Treatment of 10-chloro-9-vinylanthracene in H_2SO_4–HOAc with H_2O_2[24] gave ir and tlc evidence for the presence of glycol monoacetate but epoxide could not be obtained by modification of the experimental conditions. An attempt to produce the corresponding chlorohydrin from 10-chloro-9-vinylanthracene by treatment with *tert*-BuOCl[25] gave an apparently dimeric product which was not characterized. The ir showed no OH, $CH{=}CH_2$, or C=O: new peak at 1028 cm^{-1} (activated dialkyl ether?), with small shifts in fingerprint region. C, H analysis approximate for $(C_{16}H_{11}Cl_2)_2O$.

The antimalarial activity of the 10-halo-9-anthryl amino alcohols (Table II) was considerably higher than that of the 1- and 4-phenanthrene amino alcohols we described earlier[26,27] and of the unsubstituted anthracene amino alcohols noted above.[5,6] Further, the intermediate 2-trifluoromethyl-9-anthrone showed antimalarial activity against *P. berghei* in mice at 640 mg/kg, while 2-(4-trifluoromethylbenzoyl)benzoic acid gave 5 (out of 5) toxic deaths at 320 and 640 mg/kg in the same test. None of the intermediates submitted were active against *P. gallinaceum* in chickens, but 5-bromo-2-(4-bromobenzoyl)benzoic acid and 10-bromo-9-anthraldehyde each gave one (out of 5) toxic death at 120 mg/kg in this test. The target compound 9-(2-di-*n*-butylamino-1-hydroxyethyl)-10-bromo-

anthracene hydrochloride was active at 160 mg/kg (the only level tested) against *P. gallinaceum* in chickens.

The increased antimalarial activity of these 10-halo-9-anthryl amino alcohols, along with the generally higher activity of the unsubstituted 9-anthryl amino alcohols over the unsubstituted 9-phenanthryl amino alcohols[6] indicates that substituents in other positions on the anthracene nucleus should lead to enhanced antimalarial activity. Further credence for such a conclusion lies again in the 9-phenanthryl amino alcohols, where the symmetrical (*i.e.*, 3,6-) dihalo or bis(trifluoromethyl) substituents markedly increase the antimalarial activity.[6] We plan the preparation of additional substituted anthracene amino alcohols.

Experimental Section#

Preparative methods and physical properties for the substituted 9-anthraldehydes prepared are given in Table I.

The target compounds listed in Table II were prepared by the method of Duncan, *et al.*,[5] using a 2-fold excess of ylid.

10-Chloro-9-anthronitrile. 10-Chloro-9-anthraldehyde was refluxed with $NH_2OH \cdot HCl$ and HCO_2Na in HCO_2H[29] for 3 hr. The resulting soln was cooled and filtered to give, in 96% yield, crude 10-chloro-9-anthronitrile, mp 238–241°. Six recrystns from HOAc gave mp 256–257°, lit.[30] 255°. *Anal.* ($C_{15}H_8ClN$) C, H, N.

10-Chloro-9-vinylanthracene. To a yellow suspension of 5.5 mmoles of triphenylphosphonium methylide (prepared[31] under N_2 from *tert*-BuOK–*tert*-BuOH in THF and methyl triphenylphosphonium iodide in Et_2O) was added 1.20 g (5 mmoles) of 10-chloro-9-anthraldehyde in 50 ml of THF (refluxed over and distd from NaH) dropwise over *ca.* 10 min. The resulting yellow mixture was stirred at 25° for 1 hr and concd on a rotary evaporator at 65° to give a yellow-green semisolid, which was extd 3 times with 50, 25, and 25 ml of hot petr ether. After cooling the combined extracts, the resulting yellow-orange crystals were filtered and discarded, as was the next crop, obtained after concg to 15 ml. The following two crops (0.76 g, 68% yield) of crude 10-chloro-9-vinylanthracene had mp 107–113°. Recrystn from EtOH and petr ether gave mp 113–114°. *Anal.* ($C_{16}H_{11}Cl$) C, H.

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#The chemicals employed in this investigation were used as obtained from chemical supply houses without purification unless otherwise noted. Melting points were determined with a Thomas-Hoover capillary melting point apparatus and have not been corrected. Most reactions and purification procedures were followed by tlc on Gelman SG sheets; a convenient general purpose solvent system for these compounds on this medium is 5–15% Et_2O in petroleum ether (60–110°). Target hydrochlorides were separated on Mallinckrodt Chromar 1000 in a similar solvent system after over spotting with dilute Et_3N in THF. Visualization was accomplished with shortwave uv, 0.2% $KMnO_4$ in 1.0% aqueous Na_2CO_3, 0.4% Bromophenol Blue in MeOH (for bases; adjust to pH ≈ 8 for acids), or 0.04% 2,4-dinitrophenylhydrazine in 2 *N* HCl. Ir spectra were detd on a Beckman IR 5A prism instrument and nmr spectra were detd at 60 MHz by W. Simon Associates, Elgin, Ill. Elemental analyses were carried out with a Hewlitt Packard Model 185 CHN analyzer by the IMC Organic Analysis Group under the supervision of Mr. L. Ferrara. When analyses are indicated only by the symbols of the elements, the results were within ±0.4% of the theoretical values.

3-Chromanamine Hydrochlorides with Central Stimulant Activity

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The synthesis of a number of 3-chromanamine hydrochlorides that reduce the hyperirritability of rats that have been lesioned in the septal area of the brain and/or which suppress the killer instinct in rats has been carried out in these laboratories.[1] Many of these compounds caused some central excitation in rats as determined by the increase in locomotor activity determined with jiggle cages† using the procedure of Schulte, *et al.*[2] However, when some 3-chromanamine hydrochlorides with two alkyl groups in the aromatic ring were studied, it was found that many of them were potent stimulants when examined by this technique. This paper describes the preparation of such compounds and the examination of their stimulant activity.

Chemistry. The 3-chromanamine hydrochlorides have been prepared from 3-amino-4-chromanone hydrochlorides by conventional synthetic methods. Their physicochemical

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†D. A. McCarthy, unpublished observations.