Antimalarial Amino Alcohols II: Anthraceneaminoethanols and Anthraceneaminopropanols (1- and 9-Substituted)

J. T. TRAXLER ˣ, M. J. MOATS, E. P. LIRA, and C. W. HUFFMAN

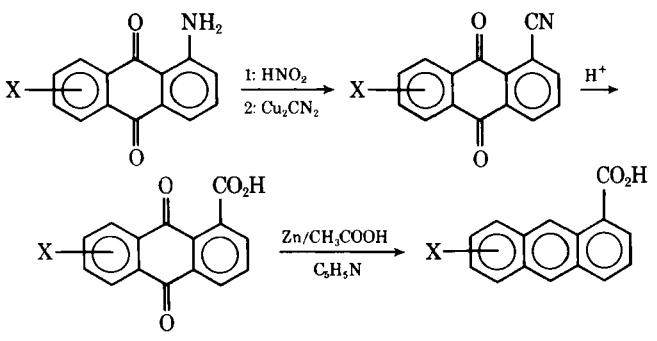
Abstract □ The syntheses of seven anthracene amino alcohols with one, two, or three additional substituents are described. These compounds include three 1-aminoethanols, two 9-aminoethanols, and two 9-aminopropanols, prepared from substituted anthraquinones or from 10-chloro-9-anthraldehydes. The antimalarial activity of these compounds, as well as tentative structure–activity relationships, is discussed in the light of previously published work.

Keyphrases □ Amino alcohols—synthesis of substituted 1- and 9-anthraceneaminoethanols and aminopropanols □ Anthraceneaminoethanols and aminopropanols—synthesis from anthraquinones or anthraldehydes

A previous report (1) summarized earlier investigations into the antimalarial activity of anthracene amino alcohols. Considerably enhanced activity is induced in anthracene-9-aminoethanols if a halogen (preferably chlorine) is substituted for the 10-hydrogen on the anthracene nucleus. Thus, 9-(di-*n*-heptylamino-1-hydroxyethyl)anthracene hydrochloride (2) was curative at 320 mg/kg (two cures out of five[1]) against *Plasmodium berghei* in mice, while the 1-chloro analog (1) was curative (two cures out of five) at 80 mg/kg in the same screen.

Further synthetic work by Stogryn (3), who prepared a series of halogen-substituted anthracene-1-, 2-, and 9-aminoethanols, indicated higher activity (four cures out of five at 80 mg/kg) for 9-(2-di-*n*-heptylamino-1-hydroxyethyl)-4,5-dichloroanthracene. Significant activity (two cures at 320 mg/kg) also was shown (3) by the 1-aminoethanol analog, *i.e.*, 1-(2-di-*n*-heptylamino-1-hydroxyethyl)anthracene, and this activity was increased to three cures out of five at 160 mg/kg by the substitution of chlorine at the 4- and 8-positions. Stogryn's work also showed that anthracenes with the aminoethanol moiety at the 2-position were active but not curative at the highest treatment level used (640 mg/kg).

In an effort to extend these studies and to derive increased antimalarial activity and/or useful structure–activity relationships, the synthesis of additional halogen-substituted anthracene 1- and 9-amino alcohols was undertaken.



Scheme I

RESULTS AND DISCUSSION

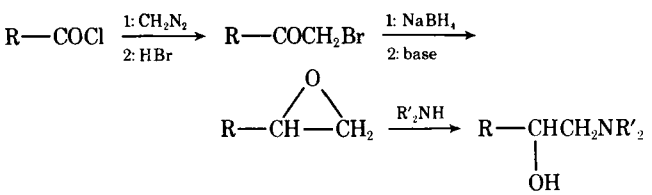
The anthracene-1-aminoethanols were prepared from commercially available 1-aminoanthraquinones by a diazonium salt–Sandmeyer combination to give the 1-cyanoanthraquinone derivatives. This preparation was followed by hydrolysis and reduction to the corresponding anthroic acids (Scheme I), which permitted entry into the now classical sequence (4, 5) for the conversion of carboxylic acids to aminoethanols (Scheme II).

Considerable isolation difficulties and poor yields were encountered in the preparation of 6,7-dichloro-1-cyanoanthraquinone until it was realized, on the basis of IR and TLC evidence, that the crude product contained at least one cyanohydrin, formed presumably by reaction of hydrocyanic acid with the anthraquinone carbonyl(s). Oxidation of the crude product with chromium trioxide in acetic acid resulted in a fairly facile isolation procedure for the desired product.

The reduction of 6,7-dichloroanthraquinone-1-carboxylic acid to the corresponding anthroic acid with zinc in ammonium hydroxide resulted in low yields (20–40%) of difficult-to-purify products. It was then found that reduction of the anthraquinone proceeded efficiently if carried out with zinc and acetic acid in pyridine (6).

Because of the finding (3) that several anthracene 1- and 2-amino alcohols could be efficiently prepared by the displacement of the bromine in anthracene 1- and 2-bromomethyl ketones, but not 9-bromomethyl ketones (7), this alternative route to target aminoethanols also was investigated. Reaction of pure (by IR and TLC) 1-bromoacetyl-6,7-dichloroanthracene with di-*n*-butylamine in tetrahydrofuran or dimethylformamide gave the desired amino ketone, but the yield was poor because of the formation of large amounts of di-*n*-butylammonium-6,7-dichloro-1-anthroate[2]. Scarcity of starting material induced the adoption of the sequence given in Scheme II for the preparation of further target anthracene-1-aminoethanols.

This sequence of reactions (Schemes I and II) also was carried out with 1-amino-5-chloroanthraquinone. In this case, however, preparation of the 5-chloro-1-anthroic acid by reduction of the an-

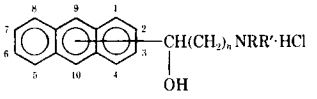


Scheme II

[1] R. E. Strube, Amino Alcohol Antimalarial Conference, Walter Reed Army Institute of Research, Washington, D.C., May 1969.

[2] Presumably arising through a Favorski- or haloform-type reaction on the bromomethyl ketone. Water was not rigorously excluded from the reaction solution.

Table I—Antimalarial Activity of Anthracene Amino Alcohols



Compound	Position: Side Chain	Position: Substituent	R[a]	R'[a]	n	Antimalarial Activity[b,c]: 20	40	80	160	320	640
Ia	1	5-Cl	C_4	C_4	1	0.1	0.5	1.1	3.5	5.1	6.1*
Ib	1	5-Cl	C_7	C_7	1	0.1	1.7	2.7	4.9	5.9	9.9*
Ic	1	6,7-Cl_2	C_4	C_4	1	0.1	3.9	5.1	7.7*	9.9*	11.9*
IIa	9	2,3-Cl_2	C_4	C_4	1	1.1	2.7	4.1	5.9	8.5*	3C[d]
IIb[e]	9	10-Br, 2,3-Cl_2	C_4	C_4	1	—	—	—	—	—	—
IIIa	9	10-Cl	C_4	H	2	0.3	0.3	0.7	4.9	10.5*	12.7*
IIIb	9	10-Cl, 3-CF_3	C_4	H	2	1.9[f]	3.7	7.3*	10.1*	—	—

[a] All *n*-alkyl groups. [b] For details of test procedure, see Ref. 19. Test data were supplied by the Walter Reed Army Institute of Research. [c] Increase in mean survival time (IMST) for mice infected with *Plasmodium berghei* after treatment at indicated dosage (in milligrams per kilogram). IMST >6.0 days = active (*); IMST >60 = cure (C). [d] Out of five. [e] Insufficient sample (14.3 mg); not tested. [f] Dosage = 10 mg/kg.

thraquinone with zinc and acetic acid in pyridine gave 5-chloro-1-anthroic acid and 5-chloro-9,10-dihydro-1-anthroic acid in a ratio of about 2:1. Conversion of the anthroic acid to the aminoethanols proceeded *via* Scheme II as expected.

An attempt to prepare other substituted anthracene-1-aminoethanols from benzanthrones (*i.e.*, 7-oxo-7*H*-benz[*d,e*]anthracenes) also was undertaken. The route envisioned involved the preparation of a suitably substituted benzanthrone, followed by oxidation to the anthraquinone-1-carboxylic acid, thus permitting entry into Scheme II after reduction to the corresponding 1-anthroic acid.

The reduction of 6-iodoanthraquinone-1-carboxylic acid [prepared by iodination of benzanthrone (8), followed by oxidation with chromium trioxide in acetic acid] with the classical zinc–ammonium hydroxide procedure resulted, not unexpectedly, in displacement of iodine to give 1-anthroic acid. Use of the much milder basic borane solution (prepared *in situ* from sodium borohydride and boron trifluoride) of Sanchorawala *et al.* (9) gave only a trace of the expected 6-iodo-1-anthroic acid after several experimental modifications. The original plan was to prepare 6-trifluoromethyl-1-anthroic acid by treatment of 6-iodo-1-anthroic acid with trifluoromethyl copper according to McLaughlin and Thrower (10, 11); but in view of the discussed difficulties and of the instability of the trifluoromethyl group to anthraquinone reduction conditions[3], this route was not pursued further.

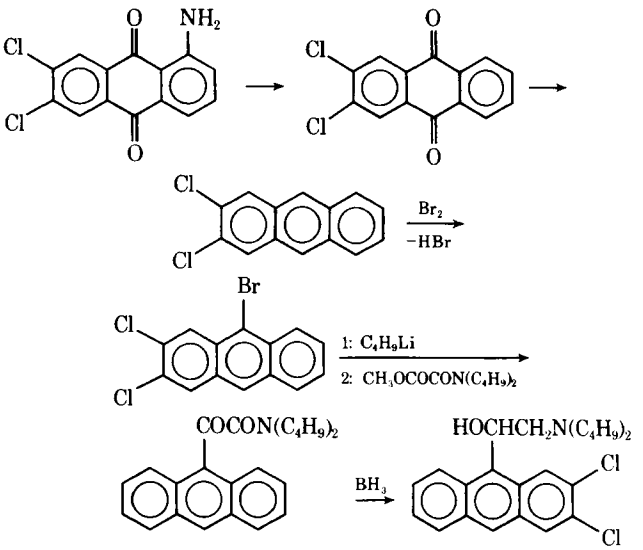
The preparation of anthracene-9-aminoethanols was achieved from 1-amino-6,7-dichloroanthraquinone by diazo deamination, reduction to the anthracene, and bromination–dehydrobromination to give 9-bromo-2,3-dichloroanthracene (Scheme III). The conversion of this material to 9-(2-di-*n*-butylamino-1-hydroxyethyl)-2,3-dichloroanthracene was carried out by the convenient procedure of Temple *et al.* (12). Good recoveries of starting materials resulted from treatment of *N,N*-dibutyl-2,3-dichloro-9-anthrylglyoxylamide and 6,7-dichloro-1-anthroic acid (13, 14) with bromine in acetic acid, as well as from treatment of the glyoxylamide and of 6,7-dichloro-1-anthroyl chloride with bromine in carbon tetrachloride. Reaction of the glyoxylamide with two equivalents of *N*-bromosuccinimide, however, gave a product from which, after reduction with borane, a small amount of 9-(2-di-*n*-butylamino-1-hydroxyethyl)-10-bromo-2,3-dichloroanthracene could be isolated.

The preparation of anthracene-9-aminopropanols was undertaken because of the possibility of increased antimalarial activity, since, with the same substitution pattern and *N*-alkyl groups in the phenanthrenes, the aminopropanols are more active than the aminoethanols[4] (15). The present efforts involved 10-chloro-9-anthraldehydes as starting materials because of their availability (1). Attempts to prepare *N,N*-dibutyl-1-(10-chloro-9-anthryl)-2-hydroxypropionamide *via* a modified Reformatsky procedure (15), as well as the preparation of lithio-*N,N*-dibutylacetamide (for subsequent reaction with 10-chloro-9-anthraldehyde), were unsuccessful.

In view of the higher antimalarial activity of phenanthrene monoalkyl aminoethanols compared to phenanthrene dialkyl aminoethanols (16) and the reactivity of monoalkyl acetamide dianions with phenanthraldehydes (17), attention was turned toward the conversion of the available 10-chloro-9-anthraldehydes to monoalkyl aminopropanols by reaction with dilithio-*N*-butylacetamide, followed by reduction of the amide with borane in tetrahydrofuran. These reactions proceeded generally as expected in the two cases indicated but with poor yields of very crude products. In other instances (*i.e.*, 10-methyl-, 3,10-dichloro-, and 3,6-dibromo-10-chloro-9-anthraldehydes), the presence of the expected crude products was indicated by IR and TLC, but none of the anticipated anthraceneaminopropanols could be isolated after reduction with borane. The complications in the latter three cases may have been caused by the presence of reactive fragments arising from the recently elucidated (18) degradation of tetrahydrofuran by butyl lithium, since excess butyl lithium was used.

The antimalarial activity of these compounds (19) is shown in Table I. The data bear out and extend tentative structure–activity relationships obtained earlier (1, 3) for anthracene amino alcohols. Thus, the *n*-heptyl alkyl groups lend slightly more activity than *n*-butyl (Ia *versus* Ib) (1, 3). With the side chain attached to C_1, monohalogen substitution removed from steric interference with the side chain [*e.g.*, C_5—Cl; Ia and Ib or C_3—Cl (3)] is more active than proximal halogen [*e.g.*, C_8—Cl (3)], and, furthermore, symmetrical [*e.g.*, C_4— and C_8—Cl (3) *versus* Ic] double chlorine substitution is more active than either. Chlorine at C_3, however, is the most active to date in the C_1-side-chain series (3).

The presence of the dialkyl amino alcohol side chain at C_9 on the unsubstituted anthracene nucleus already has been shown[1] to



Scheme III

[3] J. T. Traxler, unpublished observations.

[4] R. E. Strube, Walter Reed Army Institute of Research, personal communication.

be slightly more active than at C_1 (2, 3) and much more active than at C_2 (3). The presence of chlorine and, to a lesser extent, bromine, at C_{10} markedly increases activity (1). Unsymmetrical double halogen substitution (II*a*) is moderately active (curative), but symmetrical double halogen substitution [*e.g.*, 4,5-dichloro (3)] presently is the most active substitution pattern in the anthracene amino alcohols.

The anthracene-9-monoalkyl aminopropanols are much less active than the dialkyl aminoethanols [III*a versus* 9-(2-di-*n*-butylamino-1-hydroxyethyl)-10-chloroanthracene (1)], contrary to the indications cited for the phenanthrenes. As expected, the presence of C_3—CF_3 (III*b*) increases the activity of the 9-monoalkyl aminopropanols but not the level available in the halogen-substituted 9-dialkyl aminoethanols.

EXPERIMENTAL[5]

6,7-Dichloro-1-cyanoanthraquinone—To a stirred solution of 29.2 g (0.10 mole) of 1-amino-6,7-dichloroanthraquinone in 200 ml of sulfuric acid at 5° was added 7.6 g (0.11 mole) of solid sodium nitrite in small portions. The resulting yellow-orange solution was added to about 1.2 liters of ice, stirred well, and filtered. The damp salmon-colored solid was suspended in 200 ml of water and added to a solution of sodium cuprous cyanide [prepared by adding a solution of 38 g (0.77 mole) of sodium cyanide in 100 ml of water to a solution of 46 g (0.184 mole) of cupric sulfate pentahydrate in 200 ml of water and adjustment of the solution pH to 6–7 with sulfuric acid] in a 4-liter beaker at 25° over 2–3 min.

The foamy suspension was warmed to 70° (steam bath) for 2 hr and allowed to stand at 25° overnight. The resulting brown solid was filtered, washed with water, and partially air dried. This material was slurried in 500 ml of acetic acid, and 6.0 g of chromium trioxide in 10 ml of water was slowly added at 25° to oxidize the cyanohydrin. After 0.5 hr under reflux, the acetic acid solution was cooled to 25°, filtered, washed, and air dried to give 24.5 g (81.2%) of red-brown solid, mp 314–318°. A sample of this material was purified by recrystallization from chlorobenzene (two times) followed by sublimation at 200°/0.05 mm to give an analytical sample, mp 326–328°; IR: ν_{max} 2220 (CN) and 1670 (CO) cm^{-1}; TLC (benzene): R_f 0.82.

Anal.—Calc. for $C_{15}H_5Cl_2NO_2$: C, 59.52; H, 1.68; N, 4.64. Found: C, 59.15; H, 1.59; N, 4.35.

6,7-Dichloroanthraquinone-1-carboxylic Acid—To a suspension of 6.0 g (0.02 mole) of 6,7-dichloro-1-cyanoanthraquinone in 20 ml of water was added 75 ml of sulfuric acid in a thin stream with good stirring. Reflux for 0.5 hr gave a dark-brown solution. The reaction mixture was added at about 40° to 600 ml of ice, and the resulting suspension was stirred for 0.5 hr and filtered. Then the precipitate was washed with 50 ml of water and air dried to give 4.5 g of gray solid.

This solid was recrystallized from 50 ml of acetic acid (treated with charcoal[6]) to give 2.65 g of red-brown crystals, mp 275–279° [lit. (20) mp 275–276°]. An additional 0.56 g of product was obtained by concentration of the acetic acid filtrate, giving a total of 3.21 g (50%); IR: ν_{max} 2640 (OH), 1705 (CO), 1675 ($C_{9,10}O$), and 938 (OH) cm^{-1}; TLC (benzene): R_f 0.06.

6,7-Dichloro-1-anthroic Acid—To a solution of 4.1 g (12 mmoles) of 6,7-dichloroanthraquinone-1-carboxylic acid and 15.3 g of zinc dust (0.24 mole) in 150 ml of pyridine, at reflux, was added 65 ml of 80% aqueous acetic acid over 5 hr. The resulting yellow solution was stirred under reflux for an additional 0.5 hr, kept at 25° overnight, and added to a cold (10°) solution of 200 ml of concentrated hydrochloric acid in 1300 ml of water. The mixture was stirred for 15 min and filtered, and the yellow solid was washed with water and dried in a vacuum oven at 80° to give 3.4 g (97.2% crude) of product, mp 302–309°.

Recrystallization from 750 ml of acetic acid gave 1.73 g of product, mp 316–321°. An earlier analytical sample had a melting point of 320–321°. An additional crop of product was obtained by concentration of the acetic acid filtrate, giving a total yield of 2.13 g (61%); IR: ν_{max} 2640 (OH), 1670 (CO), 936 (OH), and 904 ($C_{9,10}H$) cm^{-1}; TLC [benzene–ether (1:2)]: R_f 0.85.

Anal.—Calc. for $C_{15}H_8Cl_2O_2$: C, 61.88; H, 2.78. Found: C, 62.28; H, 2.74.

6,7-Dichloro-1-bromoacetylanthracene—A suspension of 6,7-dichloro-1-anthroyl chloride (1.5 g, 4.8 mmoles, prepared in 65% yield by treatment of 10 mmoles of the acid in benzene with 30 mmoles of oxalyl chloride and recrystallization from methylcyclohexane, mp 193–195°) in 60 ml of tetrahydrofuran was cooled to 0°, and into this magnetically stirred mixture was distilled about 3.0 g of diazomethane (generated from 21.4 g, 0.01 mole, of *p*-tolylsulfonylmethylnitrosamide[7]) in ether over 45 min. Solution was complete after the addition of about one-third of the diazomethane. The reaction solution was allowed to warm to 25° and then was concentrated to 100 ml with a stream of nitrogen at 25°; to the resulting yellow solution at 10° was added 2.0 ml of 48% HBr dropwise.

The stirred solution was allowed to reach 25° and kept at that temperature overnight. The yellow-brown reaction mixture was added to 350 ml of ice water, filtered, washed with water, and air dried to give 1.71 g (96% crude) of yellow solid, mp 150–155°. A sample of this material was recrystallized four times from benzene to give an analytical sample, mp 162–163°; IR: ν_{max} 1675 (CO) and 904 ($C_{9,10}H$) cm^{-1}; TLC (benzene–petroleum ether): R_f 0.91.

Anal.—Calc. for $C_{16}H_9BrCl_2O$: C, 52.21; H, 2.45. Found: C, 52.33; H, 2.81.

5-Chloroanthraquinone-1-carboxylic Acid and Methyl Ester—A solution of 1-amino-5-chloroanthraquinone (39 g, 0.15 mole) in 200 ml of concentrated sulfuric acid was treated portionwise with good magnetic stirring at 5–10° with 12.5 g (0.15 mole) of solid sodium nitrite. The brown solution was stirred at about 5° for 0.25 hr, added to 500 ml of ice, filtered, and dried to a wet cake. The salmon-colored solid was added in portions at 25° to a solution of sodium cuprous cyanide, prepared according to Vogel (21) from 42.0 g of cupric sulfate pentahydrate. The resulting brown foamy mixture was heated for 1 hr on the steam bath and kept at about 60° overnight.

This mixture was filtered, the brown solid was washed with 200 ml of water, and the partially air-dried product was slurried with 600 ml of hot 3% NaOH. The insoluble solid was filtered and washed with 200 ml of hot 3% NaOH, followed by excess water. The partially air-dried 5-chloro-1-cyanoanthraquinone was then added to 800 ml of 65% H_2SO_4 at 25°, and the mixture was heated slowly to reflux, ~125°. After heating for 2 hr at 115–125°, the mixture was cooled to 25° and filtered through a fritted filter. The solid was washed with water and dried to a wet cake on the funnel. Then the filter cake was added to 1200 ml of 20% NH_4OH, and the mixture was heated and stirred at 60° for about 20 min and then filtered to remove 14.55 g of insoluble black solid.

The red filtrate was cooled in an ice bath and acidified with concentrated hydrochloric acid. The resulting yellow-brown solid was filtered, washed, and dried *in vacuo* at 80° to give 9.90 g of a brownish-black solid, mp 304–314° [lit. mp 306° (22) and mp 312° (23)]. An additional 0.60 g of product was obtained by reextracting the brownish-black solid with 750 ml of 20% NH_4OH, giving a total crude yield of 10.5 g (24.7%); IR: ν_{max} 2660 (OH), 1680 (CO), 1670 ($C_{9,10}O$), and 940 (OH) cm^{-1}; TLC (5% ether in benzene): R_f 0.56.

This combined material was very difficult to purify by recrystallization because of its low solubility, so the methyl ester was prepared in 63% yield from methyl iodide by the method of Shaw *et al.* (24) to give a melting point of 177–180° after recrystallization from methanol [lit. (22) mp 181°]; IR: ν_{max} 1725 (CO) and 1275 (OCH_3) cm^{-1}; TLC [benzene–ether (3:1)]: R_f 0.97.

5-Chloro-1-anthroic Acid and 5-Chloro-9,10-dihydro-1-anthroic Acid—Excess zinc dust (12.1 g) was added to a solution of 2.6 g (92 mmoles) of 5-chloroanthraquinone-1-carboxylic acid in 125 ml of pyridine, and the mixture was heated to reflux with mag-

[5] The chemicals 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 are not corrected. Most reactions and purification procedures were followed by TLC on Gelman SG (silica gel) sheets. Visualization was accomplished with short- or longwave UV, 0.2% $KMnO_4$ in 1.0% Na_2CO_3, 0.4% bromphenol blue in methanol (for bases; adjust to pH ~8 for acids), iodine vapor, or 0.04% 2,4-dinitrophenylhydrazine in 2 *N* HCl. IR spectra were determined in mineral oil mulls (unless otherwise indicated) with a Beckman IR-5A prism instrument. NMR data were determined at 60 MHz in dimethyl sulfoxide-d_6 with a Varian A-60D instrument by Sadtler Research Laboratories, Philadelphia, Pa. Elemental analyses were carried out with a Hewlett-Packard model 185 carbon, hydrogen, and nitrogen analyzer by the IMC Organic Analysis Group under the direction of Mr. L. Ferrara.

[6] Darco G-60, Atlas Chemical Division of ICI America.

[7] Diazald, Aldrich Chemical Co.

netic stirring. To this refluxing solution was added dropwise, over 5.5 hr, 50 ml of 80% acetic acid. The red solution changed to yellow after about 0.5 hr; after the addition was complete, the clear yellow solution was stirred under reflux for an additional 0.5 hr and kept at 25° overnight. The excess zinc (2.3 g) was removed by filtration, and the filtrate was added to a solution of 150 ml of concentrated hydrochloric acid.

The mixture was stirred and filtered, and the solid was washed and air dried to give 1.4 g of yellow-brown solid, mp 255–285°. The product was recrystallized from 80 ml of acetic acid to give, after treatment with charcoal[6] and standing overnight at 25°, 0.50 g of yellow crystals, mp 285–289°. The filtrate was concentrated on a rotary evaporator to ~70 ml and kept at 10° overnight to give 0.20 g of brown crystals, mp 243–249°. An additional 0.10 g of material was obtained by concentration of this filtrate to 10 ml after standing overnight at 10°.

The higher melting-point product was recrystallized three times more from acetic acid to give an analytical sample, mp 293–294°, of 5-chloro-1-anthroic acid; IR: ν_{max} 2640 (OH), 1660 (CO), 938 (OH), and 901 ($C_{9,10}H$) cm^{-1}; TLC (10% ether in benzene): R_f 0.73; NMR: δ 7.26–7.86 (m, 3H, aromatic), 8.03–8.51 (m, 3H, aromatic), 8.94 (s, 1H, $C_{10}H$), 9.74 (s, 1H, C_9H), and ~13.0 (COOH).

Anal.—Calc. for $C_{15}H_9ClO_2$: C, 70.19; H, 3.53. Found: C, 70.02; H, 3.56.

The lower melting-point solid was recrystallized six times from acetic acid to give an analytical sample of 5-chloro-9,10-dihydro-1-anthroic acid, mp 250–252°; IR: ν_{max} 2640 (OH), 1675 (CO), and 918 (OH) cm^{-1}; TLC (10% ether in benzene): R_f 0.86; NMR: δ 4.08 (broad s, 2H, $C_{10}H_2$), 4.38 (broad s, 2H, C_9H_2), 7.15–7.85 (m, 6H, aromatic), and ~12.7 (b, 1H, COOH).

Anal.—Calc. for $C_{15}H_{11}ClO_2$: C, 69.65; H, 4.28. Found: C, 69.68; H, 4.35.

6-Iodoanthraquinone-1-carboxylic Acid—3,9-Diiodobenzanthrone [1.0 g, 2 mmoles, prepared in 55% yield from benzanthrone by the method of Gotoh and Li (8)] was dissolved in 20 ml of refluxing acetic acid with magnetic stirring. A solution of 2.0 g of chromium trioxide in 25 ml of 25% aqueous acetic acid was added dropwise at reflux over 35 min. The dark-green mixture was stirred under reflux for 2 hr (iodine fumes), 40 ml of warm water was added in a thin stream, and the mixture was allowed to stir while cooling at 25°.

The resulting solid (0.34 g, mp 307–310°) was removed by filtration, and the filtrate was chilled to give a second crop (0.01 g). The chromium salts were neutralized by the addition of 3.7 ml (6.8 g) of concentrated sulfuric acid; and by reducing the volume of the resulting liquid, an additional 0.19 g of product was obtained, giving a total yield of 0.54 g (71%). The combined product was recrystallized from acetic acid to give 0.40 g of light-yellow crystals, mp 309–311°.

A small sample was dissolved in hot ammonium hydroxide and filtered, and the solution was acidified. The resulting solid was recrystallized from acetic acid (three times) to give an analytical sample, mp 314–315°; IR: ν_{max} 2660 (OH), 1700 (shoulder, CO), 1680 ($C_{9,10}O$), and 910 (OH) cm^{-1}; TLC [benzene–ether (1:1)]: R_f 0.44.

Anal.—Calc. for $C_{15}H_7IO_4$: C, 47.64; H, 1.86. Found: C, 47.24; H, 1.96.

9-Bromo-2,3-dichloroanthracene—A suspension of 2.4 g (0.01 mole) of 2,3-dichloroanthracene (prepared in 41% overall yield by diazo deamination of 1-amino-6,7-dichloroanthraquinone followed by zinc–ammonia reduction) in 75 ml of acetic acid at 25° was treated dropwise with 1.6 g (0.01 mole) of bromine in 2 ml of acetic acid. The mixture was stirred at about 30° for 18 hr (hydrogen bromide), heated to boiling, and cooled to 10°. Filtration gave 2.67 g (83.5%) of yellow solid, mp 162–172°, which was recrystallized from toluene (after treatment with charcoal[6]) to give 1.80 g (56.4%) of product, mp 175–182°. An analytical sample was prepared by successive recrystallization of this material from toluene, acetone, and cyclohexane, mp 192–194°; TLC (petroleum ether): R_f 0.96.

Anal.—Calc. for $C_{14}H_7BrCl_2$: C, 51.58; H, 2.17. Found: C, 51.51; H, 2.03.

1-(2-Di-*n*-butylamino-1-hydroxyethyl)-5-chloroanthracene Hydrochloride (Ia)—5-Chloro-1-anthroic acid (3.39 g, 13.4 mmoles) was suspended in 300 ml of benzene, and 3.5 ml (5.06 g, 40 mmoles) of oxalyl chloride was added dropwise with good magnetic stirring. The mixture was stirred at reflux for 2.5 hr (solution after 2 hr) and kept at 25° overnight. A small amount of insoluble brown material was removed by filtration, and the yellow solution was concentrated on a rotary evaporator to give 3.6 g (100%) of yellow crude 5-chloro-1-anthroyl chloride, mp 147–155°; IR: ν_{max} 1750 (CO) and 901 ($C_{9,10}H$) cm^{-1}.

To a solution of 3.6 g (13.4 mmoles) of 5-chloro-1-anthroyl chloride in 100 ml of tetrahydrofuran at 0° was added about 3.0 g (70 mmoles) of diazomethane, generated from 21.4 g of *p*-tolylsulfonylmethylnitrosamide[7]. After stirring at 0° (yellow solid formed) for 0.75 hr, the reaction mixture was concentrated at 25° with a stream of nitrogen to about 100 ml, and 3 ml of 48% HBr was added dropwise with good stirring at 25°. The yellow reaction solution was stirred for 1 hr, added to 600 ml of ice water, and filtered. The yellow solid was washed and air dried to give a golden-yellow solid, 4.07 g, mp 126–132°, 92.7% yield of crude 1-bromoacetyl-5-chloroanthracene; IR: ν_{max} 1665 (CO) and 906 ($C_{9,10}H$) cm^{-1}; TLC (petroleum ether): R_f 0.16.

A solution of crude 1-bromoacetyl-5-chloroanthracene (4.0 g, 12.4 mmoles) in 50 ml of tetrahydrofuran and 30 ml of anhydrous ethanol was treated dropwise at 25° with excess (1.0 g) sodium borohydride in 30 ml of anhydrous ethanol. The solution was stirred at 25° for 0.5 hr and a solution of 3.0 g of sodium hydroxide in 10 ml of water was added dropwise at about 10° with good magnetic stirring, resulting in the separation of a white viscous liquid phase. After the mixture was stirred for 2.5 hr at about 20° (light-yellow solid after 15 min), the reaction mixture was filtered to give, after washing and air drying, 0.36 g of light-yellow product, mp 141–144°; TLC (2% methanol–benzene): R_f 0.94, one major spot; IR: ν_{max} 974 and 842 (epoxide) and 900 ($C_{9,10}H$) cm^{-1}.

The filtrate was added to 1 liter of ice water and stirred well for 0.5 hr; then the solid was washed and air dried to give 2.51 g of light-yellow solid, mp 106–124°. This material was recrystallized from 155 ml of methanol to give an additional 1.34 g of yellow-brown crystalline epoxide, mp 130–134°, shown by TLC and mixed melting point to be slightly less pure than the previous material. The total yield of 5-chloro-1-anthrylethylene oxide was 1.70 g (54.6%).

A mixture of 1.0 g (4.0 mmoles) of 5-chloro-1-anthrylethylene oxide and 7.0 ml of di-*n*-butylamine was stirred at 100° under nitrogen for 18 hr (light-brown solution in about 15 min). The solution was concentrated (rotary evaporator) to give 1.60 g of viscous brown oil, which was dissolved in 300 ml of anhydrous ether and chilled in an ice bath. A saturated solution of hydrogen chloride in ether was added dropwise with good magnetic stirring until a strongly acidic reaction was obtained with moist pH paper. The mixture was kept at 10° for 2 hr, and the light-brown solid was filtered to give 1.10 g, mp 117–130°.

An additional 0.37 g of crude sticky product was obtained by concentration of the ethereal filtrate. The combined product was recrystallized twice from isopropanol to give 1.01 g (58.8%), mp 194–197°. A sample of this material was further recrystallized for analysis from isopropanol (Table II); IR (KBr): ν_{max} 3210 (OH), 2900 and 2855 (CH_2), 2550 (R_3N^+), and 904 ($C_{9,10}H$) cm^{-1}; TLC (free base, 2% methanol–benzene): R_f 0.56.

1-(2-Di-*n*-heptylamino-1-hydroxyethyl)-5-chloroanthracene Hydrochloride (Ib)—A mixture of crude 5-chloro-1-anthrylethylene oxide (0.70 g, 2.67 mmoles, mp 135–145°) and 5.0 ml of di-*n*-butylamine was stirred under nitrogen at 100° for 18 hr (cloudy solution after about 4 hr). The reaction solution was transferred to a 65-mm Hickman still with tetrahydrofuran, and excess amine was removed at 100°/0.02 mm. A small amount of unidentified (nonproduct) yellow sublimate was deposited on the walls of the still. The viscous oily residue in the still was transferred with benzene and concentrated on the rotary evaporator to give 1.0 g of oily product which was dissolved in 250 ml of anhydrous ether. Then a few milliliters of ether was removed by distillation (to dry), the solution was chilled in ice water, and excess hydrogen chloride in ether was added with good magnetic stirring.

The solution (no precipitate formed) was concentrated on a rotary evaporator, and the oily residue was recrystallized from 50 ml of hot methylcyclohexane to give, after standing at 25° and then at 0° overnight, 0.92 g (66.6%) of pink crystals, mp 62–67°. A sample of this material was recrystallized from methylcyclohexane containing a few drops of ethereal hydrogen chloride to give an analytical sample (Table II); IR (KBr): ν_{max} 3210 (OH), 2900 and 2855 (CH_2), 2535 (R_3N^+), and 916 ($C_{9,10}H$) cm^{-1}; TLC (free base) (2% methanol–benzene): R_f 0.84.

1-(Di-*n*-butylamino-1-hydroxyethyl)-6,7-dichloroanthra-

Table II—Anthracene Amino Alcohols

Compound	Yield, %	Melting Point	Formula	Analysis, % Calc.	Found
Ia	59[a]	197–200°	$C_{24}H_{31}Cl_2NO$	C 68.57	68.72
				H 7.43	7.44
				N 3.33	3.25
Ib	67[a]	66–68°	$C_{30}H_{43}Cl_2NO$	C 71.41	71.09
				H 8.59	8.75
				N 2.77	2.71
Ic	24[b]	232–235°	$C_{24}H_{30}Cl_2NO$	C 63.35	63.44
				H 6.65	6.78
				N 3.08	2.99
IIa	13[c]	220–223°	$C_{24}H_{30}Cl_3NO$	C 63.35	63.57
				H 6.65	6.93
				N 3.08	2.89
IIb	8[c]	241–242°	$C_{24}H_{29}BrCl_2NO$	C 53.99	53.95
				H 5.47	5.80
				N 2.62	2.53
IIIa	6[d]	238–239°	$C_{21}H_{25}Cl_2NO$	C 66.68	66.49
				H 6.65	6.80
				N 3.70	3.70
IIIb	5[d]	185–190°	$C_{22}H_{24}Cl_2F_3NO$	C 59.19	58.99
				H 5.42	5.39
				N 3.13	3.02

[a] From epoxide and R_2NH. [b] From bromomethyl ketone and R_2NH. [c] From 10-bromo-2,3-dichloroanthracene. [d] From the aldehyde.

cene Hydrochloride (Ic)—To a solution of 6,7-dichloro-1-bromoacetylanthracene (2.15 g, 5.85 mmoles) in 35 ml of tetrahydrofuran was added 1.6 g (11.7 mmoles) of di-*n*-butylamine in 5 ml of tetrahydrofuran, dropwise, with good stirring. The resulting solution was stirred at 25° for 1.5 hr and concentrated on a rotary evaporator, and the resulting brown semisolid was extracted with about 50 ml of petroleum ether (bp 60–110°). After filtration, the solid was washed with about 100 ml of petroleum ether. The air-dried solid, 1.60 g, represented 130% recovery of the calculated amount of di-*n*-butylammonium bromide (see *Results and Discussion*).

The combined petroleum ether solutions were concentrated (rotary evaporator) to give 2.2 g of a yellow-brown viscous oil, which was dissolved in 40 ml of tetrahydrofuran and 20 ml of anhydrous ethanol. To this solution was added a solution of 0.44 g (11.6 mmoles) of sodium borohydride in 10 ml of anhydrous ethanol. The cloudy mixture was stirred at 25° overnight and concentrated on a rotary evaporator. The viscous semisolid residue was dissolved in 110 ml of ether and washed three times with water (100, 50, and 50 ml), and the ether layer was concentrated and dried azeotropically with acetone to give 1.7 g of clear brown viscous oil. This material was dissolved in 250 ml of ether and cooled to 0°, and excess hydrogen chloride in ether was added dropwise with good magnetic stirring.

After stirring at 0° for 0.5 hr, the mixture was filtered to give 0.82 g of light-tan solid, mp 195–205°. Concentration of the ether solution gave 1.0 g of a viscous oil, the IR of which showed carbonyl absorption and no hydroxy or tertiary amine functions. This oil could not be identified by treatment with sodium borohydride, aqueous methanolic sodium hydroxide, or di-*n*-butylamine.

The light-tan solid was recrystallized several times from isopropanol to give a melting point of 232–235°. An analytical sample was recrystallized again from isopropanol (Table II); IR (KBr): ν_{max} 3230 (OH), 2920 and 2852 (CH_2), 2600 (R_3N^+), and 912 ($C_{9,10}H$) cm^{-1}; TLC (free base, 2% methanol–benzene): R_f 0.90.

9-(2-Di-*n*-butylamino-1-hydroxyethyl)-2,3-dichloroanthracene Hydrochloride (IIa)—To a solution of 7.0 g (21.5 mmoles) of crude 9-bromo-2,3-dichloroanthracene in 500 ml of anhydrous ether (nitrogen atmosphere) at 0° was added 10.0 ml of 15% butyl lithium in hexane dropwise over 10 min. The yellow cloudy solution was stirred at 0° for 15 min and cooled to −60° with an isopropanol bath. A solution of 5.1 g (24 mmoles) of methyl-*N,N*-dibutyl oxamate (12) in 75 ml of anhydrous ether was added dropwise at −60°. The resulting reddish solution was stirred for 0.5 hr at −60°, allowed to warm to 25°, and then stirred for 17 hr. The reaction was then quenched by the addition of 250 ml of water in a thin stream with good magnetic stirring.

The layers were separated after filtration of 1.35 g of insoluble material (starting material and 2,3-dichloroanthracene by IR), and the aqueous layer was extracted twice more with 50 ml of ether. The combined ether layers were washed with water (2 × 50 ml), dried with phase separation paper, and concentrated on a rotary evaporator at 65° and then on a vacuum pump at 50°/0.10 mm to give 7.35 g (85.4% crude) of red-brown semisolid, 9-(2,3-dichloroanthryl)-*N,N*-di-*n*-butylglyoxylamide. The crude material could be purified with difficulty by recrystallization from 95% ethanol to give a yellow solid, mp 110–114°; IR: ν_{max} 1670 and 1630 (CO) cm^{-1}; TLC (5% ether–petroleum ether): R_f 0.58.

The crude anthrylglyoxylamide was dissolved in 75 ml of dry (refluxed over and distilled from sodium hydride) tetrahydrofuran and added dropwise to 100 ml of 1 *M* BH_3–tetrahydrofuran, diluted with 75 ml of dry tetrahydrofuran, at 0–5° over 20 min. The yellow solution was stirred for 0.5 hr at 0°, allowed to warm to 25°, stirred under reflux for 1 hr, and allowed to stand at 25° overnight. TLC indicated the absence of starting material, so the solution was cooled to 10° and treated cautiously with 120 ml of 6 *N* HCl.

After no more hydrogen evolution, the tetrahydrofuran was evaporated (steam bath, 1 atm) and the mixture was stirred under reflux for 0.5 hr to hydrolyze the boron complex. To the cooled mixture was added 150 ml of chloroform, the pH was adjusted to 6.5–7.0 with solid sodium bicarbonate, the layers were separated, and the aqueous layer was extracted with chloroform. The combined organic layers were washed (three times) with 75 ml of water and dried with phase separation paper, and the red-brown solution was concentrated on a rotary evaporator to give 6.2 g of red-brown semisolid, to which was added 175 ml of ether. The resulting yellow insoluble solid (0.81 g) was removed by filtration, and the filtrate was diluted with 125 ml of ether and cooled to 10°. An excess of hydrogen chloride in ether was added dropwise with good stirring. After standing (10°) overnight, the yellow sticky solid was filtered and dissolved in 25 ml of isopropanol.

The product was obtained in two crops, mp 213–219° and 212–215°, with a total yield of 1.48 g (15.2%). Recrystallization from isopropanol gave 1.10 g, mp 222–225°. A sample of the product from an earlier exploratory preparation was recrystallized from isopropanol (Table II); IR (KBr): ν_{max} 3190 (OH), 2920 and 2850 (CH_2), ~2540 (R_3N^+), and 900 ($C_{10}H$) cm^{-1}; TLC (free base, 5% ether–petroleum ether): R_f 0.23.

9-(2-Di-*n*-butylamino-1-hydroxyethyl)-10-bromo-2,3-dichloroanthracene Hydrochloride (IIb)—A solution of recrystallized 9-(2,3-dichloroanthryl)-*N,N*-di-*n*-butylglyoxylamide (1.9 g, 4.4 mmoles) in 40 ml of carbon tetrachloride and 0.80 g (4.4 mmoles) of *N*-bromosuccinimide was stirred under reflux for 20 hr, at which time all insoluble material was on top of the solution, but TLC indicated the presence of considerable starting material. An additional 0.80 g (4.4 mmoles) of *N*-bromosuccinimide was added, and the solution was stirred under reflux for an additional 24 hr. Filtration of the cooled solution gave 0.84 g (97.8%) of suc-

cinimide. Concentration of the filtrate on a rotary evaporator gave 2.01 g of crude product, which was recrystallized from anhydrous ethanol to give, after filtration, a yellow-brown insoluble material, mp 140–150°. This material showed one major spot on TLC (5% ether–petroleum ether) at R_f 0.74; IR (film): ν_{max} 2950 and 2850 (CH_2) and 1655 and 1630 (CO) cm^{-1}.

The crude bromodichloroglyoxylamide (2.0 g, about 3.9 mmoles) in 20 ml of dry (refluxed over and distilled from sodium hydride) tetrahydrofuran was added to a solution of 30 ml of 1 *M* BH_3 in tetrahydrofuran in 20 ml of pure tetrahydrofuran at 0–3° over 20 min under nitrogen. The reaction mixture was stirred for 0.5 hr at 0°, allowed to reach 25°, and refluxed for 2.5 hr (monitored for disappearance of starting material by TLC). Then the reaction mixture was cooled to 5°, and 40 ml of 5 *N* HCl was added dropwise with good stirring.

After decomposition of excess borane, the tetrahydrofuran was evaporated on the steam bath and the mixture was stirred under reflux for 0.5 hr. Chloroform (60 ml) was added to the cooled hydrolysis mixture, which was then neutralized with solid sodium bicarbonate to about pH 7 (pH paper). The layers were separated, and the aqueous layer was extracted once with chloroform. The combined organic layers were washed with water, dried with phase separation paper, concentrated on the rotary evaporator, and dried at 60°/0.01 mm to give 1.6 g of brown viscous liquid.

To this material was added 300 ml of ether, 0.25 g of insoluble material (nonproduct) was removed by filtration, and the chilled (0°) solution was treated with excess hydrogen chloride in ether. The resulting mixture was kept at 0° for 2 hr and filtered to give 0.23 g of air-dried brown solid, mp 205–215°. Further concentration of the filtrate gave 0.12 g of a mixture of 2,3-dichloro- and 9-bromo-2,3-dichloroanthracene as well as 0.94 g of an unidentifiable brown viscous oil.

Recrystallization of the product (0.23 g) twice from isopropanol gave light-yellow crystals, mp 241–242°. A sample of this material was recrystallized from isopropanol for analysis (Table II); IR (KBr): ν_{max} 3200 (OH), 2940 and 2860 (CH_2), and ~2550 (R_3N^+) cm^{-1}; TLC (free base) (2% methanol–benzene): R_f 0.84.

9-(3-*N*-*n*-Butylamino-1-hydroxypropyl)-10-chloroanthracene Hydrochloride (IIIa)—A solution of *N*-*n*-butylacetamide (2.76 g, 24 mmoles) in 100 ml of dry tetrahydrofuran was cooled to about −5° under nitrogen. To this vigorously stirred solution was added dropwise a solution of 1.6 *M* butyl lithium in hexane (30 ml, 48 mmoles). The resulting cloudy solution was stirred at from −5 to −10° for 2 hr and then treated dropwise with a solution of 10-chloro-9-anthraldehyde (3.61 g, 15 mmoles) in 150 ml of dry tetrahydrofuran; it was then stirred at −5° for 2 hr.

The reaction mixture was stirred at room temperature overnight and then at reflux for 1.5 hr. The yellowish-red solution was cooled to 2–5° and then treated with acetic acid (3.5 ml) in tetrahydrofuran (20 ml). The solution was stirred for 15 min, water was added, and the solution was stirred for an additional 30 min. Then the mixture was stripped to near dryness and partially taken up with chloroform (500 ml) and water (200 ml). The solid at the interface was isolated by filtration to yield the crude product, 1.8 g (21.5%), mp 208–210° dec. This sample was recrystallized from acetone to yield 1.15 g, mp 208–210° dec., one spot on TLC (50% ether–benzene); IR: ν_{max} 3310 (OH) and 1600 (CO) cm^{-1}.

The chloroform solution was washed with aqueous sodium carbonate and then water, dried, reduced in volume by one-half, and cooled to yield the pure product, 1.4 g (26%), mp 208–210° dec. The combined product was used in the following borane reduction.

To a −5° solution of 1 *M* BH_3 (12 ml, 12 mmoles) in tetrahydrofuran (15 ml) under a nitrogen atmosphere was added dropwise a solution of *N*-*n*-butyl-3-(10-chloro-9-anthryl)-3-hydroxypropionamide (2.3 g, 6.08 mmoles) in 90 ml of tetrahydrofuran. The reaction solution was maintained at −5° for 2 hr, at room temperature overnight, and then at 60° for 23 hr. More borane (10 ml, 10 mmoles) was then added, and the solution was heated for 2.5 hr at 60°.

The solution was cooled and treated cautiously with water and then evaporated to dryness *in vacuo* to give an off-white solid. This solid was taken up in methanol (60 ml) and 10% H_2SO_4 (9 ml) and then heated at reflux for 3 hr. The solution was cooled in ice, and the pH was adjusted to 10.5 with 1 *N* NaOH. The precipitated solid was partitioned between ether and water.

The resulting three-phase system was then filtered to give 0.66 g, mp 151–153° (starting material and unidentified by-products by IR), the layers were separated, and the ether layer was concentrated on a rotary evaporator to give, after azeotropic drying with benzene, 1.5 g of a yellow semisolid. The semisolid was dissolved in about 400 ml of ether, the solution was cooled in an ice bath, and excess hydrogen chloride in ether was added dropwise. The mixture was stirred at 0° for 1 hr, kept at 10° overnight, and filtered to give a light-pink solid, mp 190–213° dec.

Recrystallization of this solid from isopropanol (color change to yellow upon heating) gave 0.82 g of a yellow solid, mp 240–242° dec. Several smaller crops were obtained by concentration and by addition of ether to the filtrates, giving a total yield of 0.98 g. The combined product was suspended in ether–tetrahydrofuran (2:1) and treated with 25 ml of 2 *N* NaOH. The layers were separated and the organic layer was washed with water to pH 7, concentrated on a rotary evaporator, and dried with benzene to give 0.86 g of light-yellow solid. This solid was dissolved in 400 ml of ether and treated with excess hydrogen chloride–ether dropwise in an ice bath. The resulting pink precipitate (0.62 g, mp 211–214°) was recrystallized from 20 ml of isopropanol to give 0.55 g of a yellow solid, mp 234–236° dec. An analytical sample was prepared by recrystallizing this material from isopropanol and then from chloroform–ethanol–cyclohexane (Table II); IR (KBr): ν_{max} 3300 (OH), 2900 and 2840 (CH_2), and 2750 (R_2NH^+) cm^{-1}; TLC (free base) [methanol–benzene (1:1)]: R_f 0.80.

9-(3-*n*-Butylamino-1-hydroxypropyl)-10-chloro-3-trifluoromethylanthracene Hydrochloride (IIIb)—To a solution of *N*-*n*-butylacetamide (1.19 g, 10.3 mmoles) in 43 ml of dry tetrahydrofuran under a nitrogen atmosphere, cooled to about −5°, was added dropwise a solution of 1.6 *M* *n*-butyl lithium in hexane (12.9 ml, 20.7 mmoles). After the resulting cloudy solution was stirred for 3 hr at from −5 to −10°, a solution of 10-chloro-3-trifluoromethyl-9-anthraldehyde (2.00 g, 6.47 mmoles) in 60 ml of dry tetrahydrofuran was added dropwise at −5°. The cooling bath was slowly allowed to rise to 25° while the reaction mixture was stirred overnight.

The reaction mixture was refluxed on a steam bath for 1.5 hr and subsequently found to contain no unreacted starting material *via* TLC, using 10% ether in hexane on silica gel sheets. The dark-brown solution was cooled in ice and hydrolyzed by the dropwise addition of 10% ammonium acetate (130 ml). The pH was adjusted to 7 with acetic acid, and the layers were separated. The aqueous phase was extracted with 4 × 25 ml chloroform, and the combined organic layers were dried over anhydrous sodium sulfate.

Evaporation of the solvent gave a brown oil, which yielded 2.0 g of yellow-brown solid, mp 120–135°, on trituration with hexane. TLC (10% ether–benzene) showed the amide to have R_f 0.33 and to be contaminated with slight impurities at the origin and at R_f 0.8; IR: ν_{max} 3280 (OH), 1600 (CO), and 1168 and 1120 (CF_3) cm^{-1}. The crude *N*-*n*-butyl-3-(10-chloro-3-trifluoromethyl-9-anthryl)-3-hydroxypropionamide was used in the subsequent reduction.

To a stirred solution of 10 ml of 1 *M* BH_3–tetrahydrofuran in 21 ml of dry tetrahydrofuran, cooled to −5° under nitrogen, was added dropwise a solution of *N*-*n*-butyl-3-(10-chloro-3-trifluoromethyl-9-anthryl)-3-hydroxypropionamide (2.0 g, 4.72 mmoles) in 85 ml of dry tetrahydrofuran. The mixture was allowed to stir overnight, then 20 ml of 1 *M* BH_3–tetrahydrofuran was added, and the mixture was refluxed for 24 hr. At the end of the reflux period, no carbonyl absorption could be detected in the IR.

The yellow reaction mixture was cooled in ice and hydrolyzed by the dropwise addition of 5 ml of water–tetrahydrofuran (1:1). The solution was stripped to dryness under vacuum, and the yellow semisolid was refluxed with a solution of 7 ml of 10% H_2SO_4 in 30 ml of methanol for 4 hr. The solution was then cooled in ice, and the pH was adjusted to 10–11 with 1 *N* NaOH. The solution and precipitate were extracted with 3 × 50 ml of ether, and the ether extracts were washed with water and dried over anhydrous sodium sulfate. The ethereal solution was evaporated to a small volume and then diluted to 500 ml with ether. This process was repeated an additional time, and the resulting solution of amine in 500 ml of ether was used to prepare the hydrochloride.

The ethereal solution of amine was cooled in an ice bath, and 50 ml of hydrogen chloride in ether was added dropwise with stirring. The precipitated hydrochloride salt was filtered and washed with ether. The salt was dissolved in 4 ml of isopropanol and chilled to give the yellow hydrochloride, mp 185–190° dec. Concentration of the ethereal filtrate gave an oil, which yielded additional hydrochloride on crystallization from isopropanol–hexane.

A total of 150 mg (7.1%) of the hydrochloride was isolated. Recrystallization from isopropanol gave an analytical sample (Table II); TLC (free base) (5% methanol–benzene): R_f 0.44; IR (KBr): ν_{max} 3300 (OH), 2930 and 2850 (CH_2), 2750 (R_2NH^+), and 1165 and 1120 (CF_3) cm^{-1}. On standing, the melting point of the salt dropped to 120–130°, although TLC showed a single spot with the same R_f. TLC in two additional systems also showed a single component. The decrease in melting point may have been due to crystalline polymorphism.

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Synthesis and Biological Evaluation of Potential Hypoglycemic Agents I: Carnitine Analogs

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Abstract □ A series of 4-dialkylamino-3-hydroxybutyric acid hydrochlorides and methochlorides, analogs of carnitine, was synthesized by treatment of *tert*-butyl 3,4-epoxybutyrate with the appropriate amine or amine hydrochloride in methanol followed by mild acid hydrolysis. The compounds had no effect on blood glucose or serum fatty acid levels in rats.

Keyphrases □ Carnitine analogs—potential hypoglycemic agents, synthesis, biological evaluation, IR and NMR spectra □ Hypoglycemic agents, potential—carnitine analogs, synthesis, biological evaluation, IR and NMR spectra

For years, diabetes mellitus has been described as a disorder of carbohydrate metabolism and the changes observed in lipid metabolism were thought to be secondary. Recently, however, Randle (1) suggested that the primary event in the development of diabetes mellitus might be an abnormality of glyceride metabolism.

Randle suggested a possible mechanism involving an increased release of free fatty acids. This release, in turn, produces a resistance to the hypoglycemic action of insulin, thereby causing a rise in fasting glucose levels and eventual exhaustion of the pancreatic β-cells. As a result of the increased serum free fatty acid levels, a corresponding increase in the rate of fatty acid oxidation is noted. This increase causes the tissue concentration of acetyl coenzyme A to rise, which results in a disruption of carbohydrate metabolism (2) through inhibition of several enzymes (pyruvate dehydrogenase, phosphofructokinase, and hexokinase).

If this hypothesis is correct, a possible approach to the treatment of diabetes mellitus would involve the design of agents that would decrease the high rate of fatty acid oxidation and increase glucose oxidation. Evidence in support of this approach is provided by the hypoglycemic activity of α-bromopalmitic acid (3), a known inhibitor of fatty acid oxidation (4).

Using the Randle hypothesis as a basis, Stewart