Volatile materials were removed *in vacuo* and the residue was dissolved in EtOH containing several ml of 50% aq NaOH and a small vol of H_2O. The mixture was heated under reflux for 2 hr and the solvent was removed *in vacuo*. The residue was triturated with H_2O, collected by filtration, and crystallized from *i*-PrOH-H_2O to give 5.5 g (83%) of pale yellow platelets, mp 148–150°. *Anal.* ($C_{20}H_{31}N_3O$) C,H,N.

***N*-{5,6,7,8-Tetrahydro-4-[(3-piperidinopropyl)amino]-1-naphthyl}propionamide (XXIVb).**—The hydrochloride XXIII[9] (8.4 g, 0.02 mol) and $(EtCO)_2O$ (2.6 g, 0.02 mol) were allowed to react in 70 ml of $EtCO_2H$ and the reaction mixture was processed according to XXIVa. The product (4.5 g, 66%) was obtained as beige crystals from heptane, mp 124–125°. *Anal.* ($C_{21}H_{33}N_3O$) C,H,N.

***N*-{5,6,7,8-Tetrahydro-4-[(3-piperidinopropyl)amino]-1-naphthyl}heptanamide (XXIVc).**—From 8.4 g (0.02 mol) of XXIII[9] and 4.8 g (0.02 mol) of heptanoic anhydride in 75 ml of pyridine utilizing procedure B was obtained 3.0 g (37%) of product as off-white crystals from heptane, mp 91–92°. *Anal.* ($C_{24}H_{41}N_3O$) C,H,N.

***N*-{5,6,7,8-Tetrahydro-4-[(3-piperidinopropyl)amino]-1-naphthyl}hexadecanamide (XXIVd).** From 8.4 g (0.02 mol) of XXIII[9] and 9.9 g (0.02 mol) of palmitic anhydride in 100 ml of pyridine utilizing procedure B was obtained 7.5 g (71%) of product as tan crystals from *i*-PrOH-H_2O, mp 85° dec. *Anal.* ($C_{34}H_{59}N_3O$) C,H,N.

***N*-{5,6,7,8-Tetrahydro-4-[(3-piperidinopropyl)amino]-1-naphthyl}benzamide (XXIVe).** An aq solution of 10.0 g (0.024 mol) of 1-[3-(4-amino-5,6,7,8-tetrahydro-1-naphthylamino)propyl]piperidine·3HCl (XXII)[9] was made basic with NH_4OH and extracted with C_6H_6. The dried C_6H_6 extracts were treated with 5.5 g (0.024 mol) of Bz_2O and the mixture was heated under reflux for 2 hr and cooled. The crude product was collected by filtration, dried, and crystallized twice from *i*-PrOH–EtOH to give 4.1 g (33%) of off-white crystals of the benzoic acid salt, mp 184–186°. *Anal.* ($C_{26}H_{33}N_3O \cdot C_7H_6O_2$) C,H,N.

The alcohol filtrate from the final recrystallization was heated with concentrated NaOH for 1.5 hr. The alcohol layer was decanted, evaporated to dryness, and the residue crystallized from EtOH–H_2O to give 0.62 g of the free base, mp 152–153.5°. *Anal.* ($C_{26}H_{33}N_3O$) C,H,N.

Acknowledgments.—The authors wish to express their appreciation to Dr. Paul E. Thompson, Mr. R. E. Voigtman, and Dr. M. W. Fisher of these laboratories for the antischistosome and antibacterial testing. We also thank Mr. C. E. Childs and associates for the microanalytical data, and Mr. D. F. Worth and Mrs. A. A. Phillips for the preparation of several of the compounds described herein.

Synthesis and Schistosomicidal Activity of 6-Chloro-5-{[2-(diethylamino)ethyl]amino}-8-quinolinemethanol[1]

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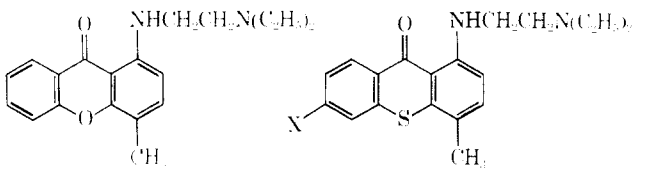
The title compound (XVIII) has been synthesized chemically in a seven-step sequence and also by microbiological oxidation of 6-chloro-5-{[2-(diethylamino)ethyl]amino}-8-methylquinoline,[2] IX, by *Aspergillus sclerotiorum*. The Skraup reaction on 4-chloro-*o*-toluidine produced 6-chloro-8-methylquinoline which was nitrated and then oxidized to 6-chloro-5-nitro-8-quinolinecarboxylic acid. Catalytic reduction of the Me ester followed by NaH-induced alkylation with diethylaminoethyl chloride produced methyl 6-chloro-5-{[2-(diethylamino)ethyl]amino}-8-quinolinecarboxylate. Reduction of the latter compound with LAH at low temperatures gave XVIII. A comparison of the oral and parenteral activities of IX and XVIII against *Schistosoma mansoni* and *S. japonicum* infections has been carried out in mice and hamsters.

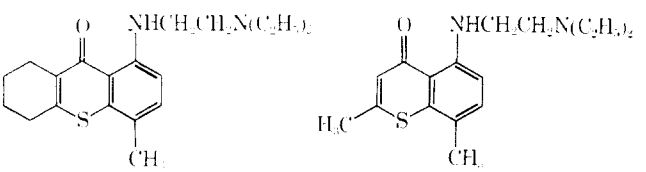
Since the discovery by Kikuth and Gönnert[3] that compounds I–III, synthesized earlier by Mauss,[4] had oral schistosomicidal activity in mice, chemical investigations in various laboratories have produced a number of related compounds (*e.g.*, IV–IX)[2,5] of which IX[2] is most relevant to the present work.

Compelling evidence[3,4,6,7] has been accumulated that the structural feature necessary for biological activity against schistosomes in mice in this broad class of compounds is a dialkylaminoalkylamino group *para* to Me



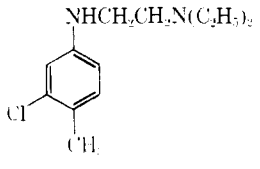
I

II, X = H
III, X = Cl

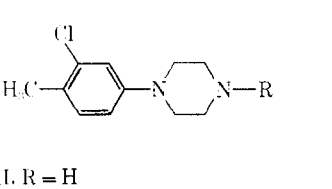


IV

V



VI



VII, R = H
VIII, R = *p*-$(CH_2)_6OC_6H_4C(CH_3)_2C_2H_5$

(1) Presented in part before the Division of Medicinal Chemistry, 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969.

(2) N. W. Bristow, B. Lessel, H. C. Richards, and G. A. H. Williams, *Nature*, **216**, 282 (1967).

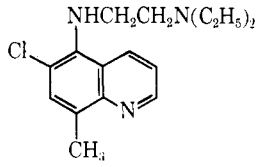
(3) W. Kikuth and R. Gönnert, *Ann. Trop. Med. Parasitol.*, **42**, 256 (1948).

(4) H. Mauss, *Chem. Ber.*, **81**, 19 (1948).

(5) (a) F. Bossert, H. Henecka, and R. Gönnert, German Patent 1,024,980 (1958); (b) F. Bossert and R. Gönnert, German Patent 954,599 (1956); (c) H. Mauss, H. Kolling, and R. Gönnert, *Med. Chem. Abhandl. Med.-Chem. Forschungsstaetten Farbenfabriken Bayer*, **5**, 185 (1956); (d) H. Ruschig, D. M. Schmidt, H. Leditschke, M. Schorr, and G. Lammler, German Patent 1,019,308 (1957); (e) A. O. Geiszler, P. M. Bauman, A. Alter, and G. F. Otto, Reports given at the Annual Meeting of the American Society of Tropical Medicine and Hygiene, New York, N. Y., Nov 7, 1964.

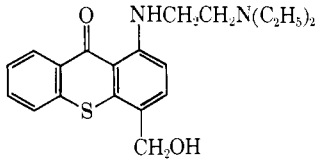
(6) S. Archer and C. M. Suter, *J. Amer. Chem. Soc.*, **74**, 4296 (1952).

(7) D. Rosi, G. Peruzzotti, E. W. Dennis, D. A. Berberian, H. Freele, B. F. Tullar, and S. Archer, *J. Med. Chem.*, **10**, 867 (1967).



IX

on an aromatic ring. Investigations carried out in this laboratory[7,8] have demonstrated that conversion of the aromatic Me into $HOCH_2$ results in a marked increase in activity. The $HOCH_2$ derivatives have been shown for several of the above examples to be the active metabolites responsible for the observed biological activity.[7,8] Hycanthone (X), as an example, is a well-tolerated, highly effective parenteral agent against schistosomiasis in man[9a] while poor human tolerance and lack of parenteral activity of lucanthone (II) make it a less desirable drug for use against *Schistosoma haematobium* and *S. mansoni* infections.[9b]

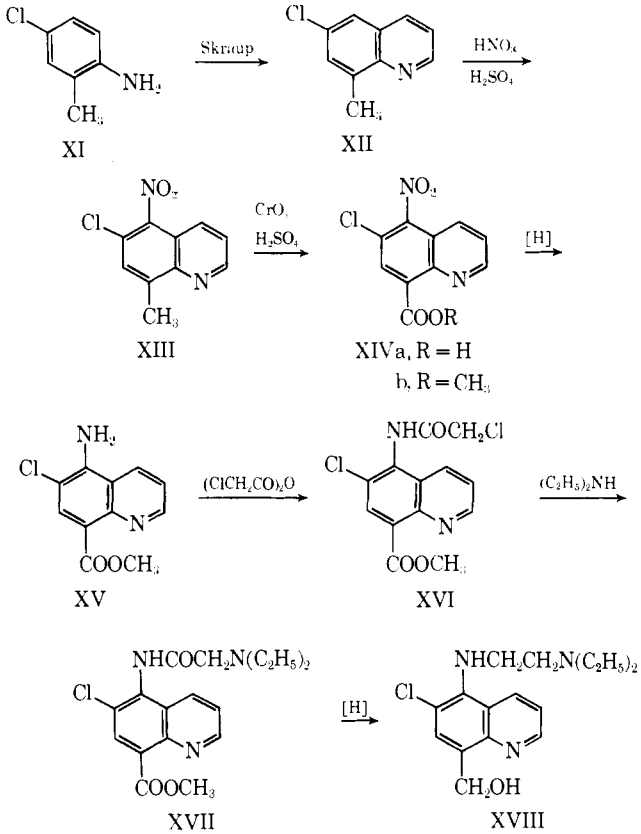


X

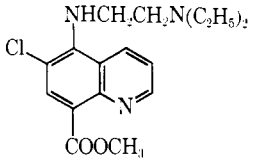
Chemistry.—With this body of evidence in hand, we set out to synthesize XVIII, the hydroxymethyl analog and anticipated active metabolite of compound IX.

The sequence of reactions originally proposed is outlined in Scheme I, the final steps being analogous to those used to produce the $HOCH_2$ analog of VI.[8] The Skraup[10] reaction on 4-chloro-*o*-toluidine using *m*-nitrobenzenesulfonic acid as the oxidant[11] proceeded smoothly, and nitration produced XIII in an average overall yield (from XI) of 50%. 8-Methyl-5-nitroquinoline has been oxidized to 5-nitro-8-quinolinecarboxylic acid[12] and a modification of this procedure gave XIVa. Catalytic reduction of the Me ester (prepared by BF_3-catalyzed esterification) followed by chloroacetylation and subsequent treatment of the chloroacetamide with $NHEt_2$ produced XVII in good overall yield. Attempted reduction of this amido ester with LAH–$AlCl_3$ as previously described[8] resulted in overreduction to IX. Although we were aware of only a single example[13] of the reduction with diborane of a secondary amide of an aromatic amine, we attempted the use of this reagent in the hope of obtaining a selective reduction to give XIX. The results, however, were disappointing, as the ester function was reduced faster than the amide.

SCHEME I



XI XII XIII XIVa, R = H b, R = CH_3 XV XVI XVII XVIII



XIX

An alternative route to XIX was the direct alkylation of XV with diethylaminoethyl chloride. The alkylation of 5-amino-6-methoxyquinoline with diethylaminopropyl chloride using $NaNH_2$ in liquid NH_3 has been described,[14] but application of these conditions to XV gave none of the desired material. However, NaH-induced alkylation in DMF gave an 80% conversion into XIX (glpc analysis). The product was separated from unreacted starting material by extraction from EtOAc with pH 3 buffer and was isolated as a viscous oil in 68% yield. Reduction of XIX in ether with LAH at −22° gave a mixture which contained (glpc) a major fraction comprising 60% of the total, starting material (10%), IX (20%), and two unknown materials (total 10%). The major component was separated by preparative thin-layer chromatography on alumina using 99:1 $CHCl_3$–MeOH as the eluant. The product could not be induced to crystallize. It was characterized by elemental analysis and by solution ir, pmr, glpc, and tlc comparisons with material obtained by fermentation of IX.

Microbiological Transformations.—Incubation of IX[2] with *Aspergillus sclerotiorum* for 5 days resulted in its transformation to at least 5 more polar products. The major component was purified by a combination of solvent extractions and preparative thin-layer chromatography on silica gel plates. Its pmr spectrum showed that the 8-Me signal in the spectrum of IX was replaced by a signal for CH_2 next to oxygen, and the elemental analysis of the free base and dihydro-

(8) D. Rosi, T. R. Lewis, R. Lorenz, H. Freele, D. A. Berberian, and S. Archer, *J. Med. Chem.*, **10**, 877 (1967).

(9) (a) V. De V. Clarke, D. M. Blair, and M. C. Weber, *Centr. Afr. J. Med.*, **15**, 1 (1969); (b) D. M. Blair, *Bull. W. H. O.*, **18**, 989 (1958).

(10) R. H. F. Manske and M. Kulka, *Org. React.*, **7**, 59 (1953).

(11) G. I. Mikhailov, *Novosti Tekhniki.*, No. 3-4, 5) (1940); *Chem. Abstr.*, **34**, 5847 (1940).

(12) J. G. Breckenridge and S. A. G. Singer, *Can. J. Res.* **25B**, 49 (1947).

(13) W. F. Gannon, J. D. Benigni, J. Suzuki, and J. W. Daly, *Tetrahedron Lett.*, 1531 (1967).

(14) L. V. Antik and N. S. Spasokukotskii, *Zh. Obshch. Khim.*, **16**, 2109 (1946); *Chem. Abstr.*, **42**, 909 (1948).

chloride salt confirmed that one O had been introduced into the molecule. The tedious preparative plate chromatography was eventually circumvented when it was discovered that a crystalline methanesulfonate could be obtained directly from partly purified extracts.

When the *in vitro* metabolism of IX was examined, utilizing mouse and hamster liver microsomal preparations, several metabolites were observed in each case. Plate chromatographic examination of the liver systems revealed 3 components which were common to both. One of these corresponded in mobility to unaltered IX. The second was more polar and the third remained at the origin. In addition, the hamster preparation revealed two components which were not observed in the mouse. One component was observed in the mouse preparation which was not observed in the hamster and which was chromatographically indistinguishable from XVIII, having the same R_f in two tlc systems and having identical maxima in the uv.

Based on the similarity of these findings to previous metabolic studies[15] and the fact that IX, like most of the Me compounds described above,[7,8] had diminished or no activity in hamsters,[16] we hoped that XVIII would show enhanced oral activity in mice and hamsters and furthermore would be active in both species when administered parenterally.[17,18]

Biological Results.—The report by Bristow, *et al.*,[2] of the oral activity of IX against *S. mansoni* in mice has been confirmed by Pellegrino, *et al.*[16] We have examined the activity of IX and XVIII after oral and intramuscular administration in both mice and hamsters infected with *S. mansoni* and have confirmed the latter investigators' oral data for IX in these two species. In addition, we have found IX to be ineffective both orally and parenterally in mice infected with more resistant *S. japonicum*. Interestingly, when given as a single intramuscular injection, IX was ineffective in hamsters and active in mice (ED_{50} = 39.5 ± 5.5 mg/kg) infected with *S. mansoni*.

When the hydroxymethyl compound XVIII was administered to hamsters infected with *S. mansoni*, it was found to be *inactive* orally and weakly active parenterally. It did, however, show some increase in milligram potency over IX when given to mice in a single intramuscular injection (Table I).

Conclusions.—Although a number of examples have been cited[7,8] wherein the activity of schistosomicidal agents bearing a dialkylaminoalkylamino moiety *para* to a methyl group on an aromatic ring has been mediated and enhanced by the respective hydroxymethyl analog, it is apparent from the results of the biological screening of XVIII that the generalization cannot be used infallibly to predict the activity of hydroxylated analogs of effective drugs and that caution must be used in projecting existing relationships to new systems.

Table I

Antischistosomal Activity[a]

	IX[b]	XVIII[c]
	Mouse (*S. mansoni*)	
Po[d]	23 ± 8.5	17.0 ± 2.6
Im[e]	39.5 ± 5.5	20.3 ± 2.5
	32.0 ± 4.8	18.0 ± 2.8[f]
	Hamster (*S. mansoni*)	
Po	Inact at 200 mg/kg	Approx 70
Im	Inact at 200 mg/kg	>100
	Mouse (*S. japonicum*)	
Po	Inact at 100 mg/kg	
Im	Inact at 100 mg/kg	

[a] ED_{50} in milligrams per kilogram ± standard error. [b] As monohydrochloride. [c] As dihydrochloride. [d] 5-Day oral medication. [e] Single intramuscular injection. [f] Free base.

Experimental Section[19]

6-Chloro-8-methylquinoline (XII).—4-Chloro-*o*-toluidine was subjected to the Skraup reaction;[20] sodium *m*-nitrobenzenesulfonate[11] was used as the moderator. Unchanged starting material was efficiently separated from the product by distillation through a 1.5 × 23 cm column packed with glass helices. The product [bp 133–138° (10 mm); mp 55–60° (lit.[20] mp 65.5°)] was obtained in 65% yield when prepared on a 1–4 mole scale.

6-Chloro-8-methyl-5-nitroquinoline (XIII).—6-Chloro-8-methylquinoline (100 g, 0.56 mol) was melted and added in a thin stream to 1 l. of 90% HNO_3. The solution was heated 1 hr on a steam bath, during which time copious quantities of brown oxides of N were evolved. Addition of the solution to 2 kg of ice, followed by dilution to 6 l. with H_2O, precipitated the product; dry weight 62.5 (50%), mp 97–99° (lit.[21] mp 99–100°). An additional 25% of less pure product was obtained by neutralization of the acid and extraction with EtOAc.

On a 9-mol scale,[22] air pollution was avoided by performing the nitration in 5 ml of 96% H_2SO_4 and 5 ml of 90% HNO_3/g of starting quinoline. After being heated 1 hr at 55°, the solution was poured onto ice, the resulting mixture was adjusted to pH 8 with 35% NaOH, and the product was isolated by extraction with EtOAc. Recrystallization gave an 82% yield of product, mp 97–98.5° (*i*-PrOH–C_6H_{14}).

6-Chloro-5-nitro-8-quinolinecarboxylic Acid (XIVa).—CrO_3 (4.0 g, 0.04 mol) was added in small portions to a stirred solution of 3.00 g (0.014 mol) of 6-chloro-8-methyl-5-nitroquinoline in 12 ml of coned H_2SO_4 at such a rate that the temperature was maintained at 45–50°. During the following 2 hr occasional cooling was necessary to keep the temperature below 50°. After 4 hr the mixture was poured on ice, and the organic material was taken up in $ClCH_2CH_2Cl$. The desired acid was extracted from the organic solvent with dilute K_2CO_3 (the Na^+ and NH_4^+ salts are comparatively insoluble). Acidification of the K_2CO_3 solution gave 1.43 g (42%) of product, mp 173–176°. Recrystallization from C_6H_6 gave pure material, mp 174.5–176°. *Anal.* ($C_{10}H_5ClN_2O_4$) C, H, Cl, N. Other runs gave polymorphs, mp 154–156° and 184–186°; $CHCl_3$ solutions of the three polymorphs yielded indistinguishable ir spectra. The oxidation has been performed[22] on a 5-mol scale (yield 48%).

Methyl 6-Chloro-5-nitro-8-quinolinecarboxylate (XIVb). Method A.—CH_2N_2[23] (approx 0.03 mol) in damp Et_2O was added dropwise to a solution of 5.0 g (0.02 mol) of 6-chloro-5-

(15) D. Rosi, A. J. Merola, and S. Archer, *Life Sci.*, **6**, 1433 (1967).

(16) J. Pellegrino, N. Katz, and J. F. Scherrer, *J. Parasitol.*, **53**, 1225 (1967).

(17) D. A. Berberian, H. Freele, D. Rosi, E. W. Dennis, and S. Archer, *ibid.*, **53**, 306 (1967).

(18) D. A. Berberian, H. Freele, D. Rosi, E. W. Dennis, and S. Archer, *Amer. J. Trop. Med. Hyg.*, **16**, 487 (1967).

(19) Melting points are uncorrected and were determined on a Mel-Temp apparatus. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Ir and nmr spectra consistent with the structures shown were obtained for all new compounds mentioned in this paper. Glpc analyses were performed on a Hewlett–Packard research chromatograph, model 5751B, equipped with glass columns packed with 3% OV 17 on 100–120 mesh Gas-Chrom Q. Unless stated otherwise, solvents were removed *in vacuo* with the aid of a rotary evaporator.

(20) T. Mazonski, T. Mielecki, and E. Suelarda, *Roczn. Chem.*, **16**, 513 (1936).

(21) T. A. Irving, J. L. Greene, Jr., J. C. Peterson, and J. D. Capps [*J. Amer. Chem. Soc.*, **72**, 4069 (1950)] prepared this compound in 9% yield by subjecting 2-acetamido-5-chloro-4-nitrotoluene to the Skraup reaction.

(22) This experiment was performed by Theodore F. Mayor of the Pilot Laboratory of this Institute.

(23) F. Arndt, "Organic Syntheses," Collected Vol. II, Wiley, New York, N. Y., 1943, p 166, note 3.

nitro-8-quinolinecarboxylic acid in 300 ml of EtOAc; the solution was stirred with a Teflon-coated magnet during the addition and for 1 additional hr. Excess CH_2N_2 was destroyed with HOAc, and the solution was washed with 10% K_2CO_3, H_2O, and saturated aq NaCl. Removal of the solvent from the dry ($MgSO_4$) EtOAc solution gave 5.25 g (98%) of product, mp 116–121°. Recrystallization from MeOH gave analytically pure material, mp 123–125°. *Anal.* ($C_{11}H_7ClN_2O_4$): Cl, N.

Method B.—A solution of 74 g (1.1 mol) of BF_3 in 2.6 l. of MeOH was added to 90.7 g (0.359 mol) of 6-chloro-5-nitro-8-quinolinecarboxylic acid, and the solution was boiled under reflux for 3 hr. Most of the solvent was removed, and the residue was dissolved in EtOAc and excess saturated $NaHCO_3$. The EtOAc solution was washed with saturated NaCl, dried ($MgSO_4$), and evaporated. Recrystallization of the residual solid from MeOH gave 81 g (84%) of ester, mp 123–125°. A second crop, 4.9 g (5%), mp 119–121°, was obtained by concentration of the mother liquor. Both crops yielded ir spectra indistinguishable from that of pure material obtained by method A.

Methyl 5-Amino-6-chloro-8-quinolinecarboxylate (XV). Method A.—A suspension of 20 g (0.075 mol) of methyl 6-chloro-5-nitro-8-quinolinecarboxylate and 5 g of 7% $PdCl_2$–C in 200 ml of 0.375 *N* HCl was hydrogenated using an initial pressure of 3 atm, gauge. After 4 hr reduction was complete, and all of the organic solid had dissolved. The mixture was filtered, the filtrate was made basic with 10% K_2CO_3, and the solid product was isolated by filtration. The product from four such reductions was combined. The crude product suffered some decomposition when dried *in vacuo* at 50°, but was stable when dissolved in boiling C_6H_6 and dried by azeotropic removal of H_2O. Concentration and cooling of the C_6H_6 solution yielded 43 g (60%) of light brown solid; glpc: 99% pure. Recrystallization from *i*-PrOAc gave light yellow solid, mp 129–130°. *Anal.* ($C_{11}H_9ClN_2O_2$): C, H, Cl, N.

Method B.[24]—MeOH (110 ml) was cooled to 0° under N_2. Catalyst (0.56 g of 10% Pd–C) was added, followed by 3.18 g (0.084 mol) of $NaBH_4$ in 110 ml of MeOH containing 5 drops of 10% aq NaOH. Methyl 6-chloro-5-nitro-8-quinolinecarboxylate (11.1 g, 0.042 mol) in 1650 ml of MeOH was cooled to 0° and was added all at once to the stirred reducing mixture. After 30 min the mixture was filtered through diatomaceous earth, and the residue was washed with $CHCl_3$. The filtrate was made slightly acidic with 2 *N* HCl, then adjusted to pH 8 with NH_4OH. The solvent was removed below 50°, and the residue was distributed between $CHCl_3$ and 2 *N* HCl. The product was liberated from the acid solution with 10% aq K_2CO_3, taken up in $CHCl_3$, and washed with saturated aq NaCl. Evaporation of the dried ($MgSO_4$) solution left 5.0 g (51%) of dark brown gum (primarily one compound by tlc). The product was purified by chromatography on 200 g of Florisil. C_6H_6 and Et_2O eluted impurities; EtOAc eluted the desired product. Evaporation of the EtOAc gave a 41% yield of pale green product identical with that obtained by method A.

Methyl 6-Chloro-5-(chloroacetamido)-8-quinolinecarboxylate (XVI).—A solution of 9.0 g (0.038 mol) of methyl 5-amino-6-chloro-8-quinolinecarboxylate, 13 g (0.076 mol) of $(ClCH_2CO)_2O$, 45 g of $ClCH_2CO_2H$, and 5 drops of concentrated H_2SO_4 was heated 24 hr on a steam bath. The melt was poured into H_2O, the mixture was made basic with 10% K_2CO_3, and the product was taken up in EtOAc. The organic solution was washed with 10% K_2CO_3, H_2O, and saturated NaCl. The dried ($MgSO_4$) EtOAc solution was evaporated leaving a light brown solid weighing 10.3 g (87%). Its ir spectrum was the same as pure product, obtained by crystallization from MeOH; mp 200–203° dec. *Anal.* ($C_{13}H_{10}Cl_2N_2O_3$): Cl, N.

Methyl 6-Chloro-5-(diethylaminoacetamido)-8-quinolinecarboxylate (XVII).—A stirred solution of 4.17 g (0.013 mol) of methyl 6-chloro-5-(chloroacetamido)-8-quinolinecarboxylate and 5.5 ml (0.053 mol) of Et_2NH in 60 ml of THF was boiled under reflux for 3 hr. The volatile materials were removed, and the residue was distributed between H_2O and EtOAc. The EtOAc yielded 4.52 g (97%) of brown oil, 96% pure by glpc. Crystallization from Et_2O gave a white solid, mp 85–86°. *Anal.* ($C_{17}H_{20}ClN_3O_3$): Cl, N.

(24) T. Neilson, H. C. S. Wood, and A. G. Wylie, *J. Chem. Soc.*, 371 (1962).

Methyl 6-Chloro-5-{[2-(diethylamino)ethyl]amino}-8-quinolinecarboxylate (XIX).—A solution of 10.4 g (44 mmol) of methyl 5-amino-6-chloro-8-quinolinecarboxylate in 100 ml of DMF was added at room temperature to a stirred suspension of 57 mmol of oil-free NaH (from 2.42 g of 56.7% NaH in mineral oil) in 75 ml of DMF. After gas evolution was complete, 11.9 g (88 mmol) of neat diethylaminoethyl chloride[25] was added dropwise, and stirring was continued for 3 hr. The mixture was poured into 750 ml of H_2O and was extracted with EtOAc, which was then washed thoroughly with H_2O. The product was separated from unchanged starting material by extraction of a solution of the crude product in 1 l. of EtOAc with six 25-ml portions of pH 3 buffer (prepared from 1 *M* NaOAc to which sufficient concentrated HCl had been added to give pH 3). The extracts were made basic with 10% K_2CO_3 and extracted with EtOAc. Analysis by glpc of the residues left on evaporation of the dried ($MgSO_4$) EtOAc solutions showed the best fraction was 98% pure; wt 2.34 g. The combined product weighed 11.4 g (77% yield), 88% pure by glpc. Attempted distillation in an alembic still at 0.0002 Torr resulted in decomposition of the sample.

An EtOAc solution of the crude product from another run was washed with only three 25-ml portions of buffer. When the dried ($MgSO_4$) EtOAc solution was evaporated, the residual oil slowly deposited a small amount of **hydrochloride**, mp 154–156°. *Anal.* ($C_{17}H_{22}ClN_3O_2 \cdot HCl$): Cl, N.

6-Chloro-5-{[2-(diethylamino)ethyl]amino}-8-quinolinemethanol (XVIII). Chemically.—A mixture of 6.7 g (20 mmol) of methyl 6-chloro-5-{(2-(diethylamino)ethyl]amino}-8-quinolinecarboxylate and 2.4 g (63 mmol) of LAH in 120 ml of Et_2O was stirred at −22° for 30 hr. Hydrolysis with 4.6 ml of 10% NaOH and isolation with EtOAc gave 6.0 g of crude carbinol. The product was not completely stable at the high temperatures of glpc, and one of the decomposition products appeared to be the desoxy compound IX. Glpc showed that the crude carbinol contained at least 60% of the desired compound XVIII, not more than 20% of the desoxy compound IX, 10% of unchanged ester XIX, and two unknowns totaling 10%. The conversion of ester XIX into carbinol XVIII is then at least 65%. The desired compound was isolated from the crude product by preparative thin-layer chromatography on alumina; 99:1 $CHCl_3$–MeOH was used as the eluant. The desired carbinol XVIII was obtained as a viscous yellow oil. *Anal.* ($C_{16}H_{22}ClN_3O$): C, H. Its structure was supported by elemental analysis, by its pmr and ir spectra (which are consistent with the proposed structure), and by its identity (as shown by solution ir, pmr, glpc, and tlc) with a sample produced by fermentation of IX (see below).

Microbiologically.—A 10-l. stirred fermentation to which 3 g of 6-chloro-5-{(2-(diethylamino)ethyl]amino}-8-methylquinoline·HCl (IX) had been added was carried out as described earlier[7] for the conversion of lucanthone into hycanthone. The major product was isolated by preparative thin-layer chromatography on silica gel plates; C_6H_{14}–$CHCl_3$–*i*-$PrNH_2$ (8 : 1 : 1) was used as the eluant. The yellow oil obtained was converted into 0.86 g (25% yield) of the **dihydrochloride**, mp 149–152° (EtOH). *Anal.* ($C_{16}H_{22}ClN_3O \cdot 2HCl$): C, H, N; Cl: calcd, 27.93; found, 27.28.

6-Chloro-5-{[2-(diethylamino)ethyl]amino}-8-methylquinoline (IX).—Alkylation of 10 g (0.052 mol) of 5-amino-6-chloro-8-methylquinoline[26] with 21.6 g (0.16 mol) of diethylaminoethyl chloride[25] followed the procedure given above for the preparation of XIX. A temperature of 75° was required for anion formation. After being separated from unchanged starting material with pH 3 buffer, the product in C_6H_6 was treated with one equivalent of HCl in MeOH. The pure **hydrochloride**, mp 164–165° (*i*-PrOAc–*i*-PrOH), was obtained in 35% yield. *Anal.* ($C_{16}H_{22}ClN_3 \cdot HCl$): Cl, N.

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(26) This compound was prepared by reduction of the corresponding nitro compound XIII as in the preparation of XV (method A) or as described by Irving.[21] We obtained 50–65% yields by either method, mp 113–114° (lit.[21] mp 113–114°).