Studies on Gastrointestinal Action.—Strips of isolated guinea pig ileum were suspended in Tyrode's soln according to the method of Magnus.[18] The soln at 37° was gassed with 95% O_2–5% CO_2. Contractions were recorded with a Brush isotonic muscle transducer on a Heath Model EU-20B servorecorder. 5-Methylfurtrethonium was used as a muscarinic std.[19]

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Antimalarials. 8[1]. 2,3-Trimethylene-4-quinoline Amino Alcohols. 5,7-Dichloro-2,3-dihydro-1*H*-cyclopenta[*b*]quinoline-9-(α-di-*n*-butylaminomethyl)methanol

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The title compound (**1**) was synthesized to provide, for antimalarial testing, an example of a 4-quinoline amino alcohol in which position 2 was blocked by the CH_2 group of the rigid 2,3-trimethylene ring.[3] It was hoped that this arrangement would prevent rapid biodegradation,[4] and, through lack of conjugation of the type involved in the 2-aryl series, would minimize phototoxicity.[5]

The synthesis started from 5,7-dichloroisatin (**2**) and proceeded by the classical route,[6] namely, Pfitzinger condensation with cyclopentanone to 6,8-dichloro-2,3-trimethylenecinchoninic acid (**3**),[7] followed by diazomethylation of the acid chloride **4** to **5**, hydrobromination to bromo ketone **6**, reduction by $NaBH_4$–NaOH to the epoxide **7**, and aminolysis with Bu_2NH.

Biological Activity.[1d,8]—Target compound **1** proved to be only moderately active against *Plasmodium berghei* in mice, doubling survival time at a dosage of 320 mg/kg, and trebling it at 640 mg/kg.

Experimental Section[9]

6,8-Dichloro-2,3-trimethylenecinchoninic Acid (5,7-Dichloro-2,3-dihydro-1*H*-cyclopenta[*b*]quinoline-9-carboxylic Acid) (3) (*Cf.* **the Unchlorinated Acid**[7]).—The purple slurry from addition of 21.6 g (0.1 mole) of **2** to 16.8 g (0.3 mole) of KOH in 125 ml of H_2O was added under stirring to 20 g (0.238 mole) of cyclopentanone in 150 ml of abs EtOH. After refluxing (25 hr) and evapn *in vacuo*, the residue was dissolved in 700 ml of H_2O. Acidification with AcOH gave **3**; this was dissolved in KOH–H_2O, repptd by AcOH, and washed successively with dil AcOH, H_2O, and cold EtOH: 23 g (81.6%); mp 272–274° dec. *Anal.* ($C_{13}H_9Cl_2NO_2$) C, H, N.[9b]

3·Potassium Salt (8).—A hot soln of 5 g of KOH in 20 ml of abs EtOH was added with stirring to a suspension of 21.9 g of **3** in 150 ml of warm EtOH. Chilling, filtering, and washing with cold EtOH and with 250 ml of Et_2O gave 21.47 g: unchanged at 325°; ir (cm^{-1}) 2975, 2930, 1580 (C=O). *Anal.* ($C_{13}H_8Cl_2KNO_2$) C, H, N.

3·Methyl ester (9) was prepd by CH_2N_2–Et_2O on **3**; crystd from EtOH–hexane: mp 177–178°; ir (cm^{-1}) 1720 (C=O); nmr ($CDCl_3$), δ 8.30 (1 H, doublet), 7.30 (1 H, d), 4.13 (3 H, s), 3.31 (4 H, triplet), 2.25 (2 H, quintuplet). *Anal.* ($C_{14}H_{11}Cl_2NO_2$) C, H, N.

3·Amide (10) was prepd from **4** by aq NH_3; crystd from Et_2O–hexane: mp 285–287° dec; ir (cm^{-1}) 3350, 3160, 1680. *Anal.* ($C_{13}H_{10}Cl_2N_2O$) C, H, N.

6,8-Dichloro-4-bromoacetyl-2,3-trimethylenequinoline (6).—A C_6H_6 soln of **3·acid chloride, 4**,[10] was prepared from 13.8 g of 3·HCl by reaction with PCl_5 (100°, 30 min) and extg with dry C_6H_6[11] (quenching of an aliquot in ice–NH_3 gave **10**). This was added (below 10°, over 0.5 hr) to 5.61 g of dry CH_2N_2 in 700 ml of Et_2O (KBr pellets; H_2O present at this point readily converts **4** through **3** and CH_2N_2 to **9**). After warming to room temp (2 hr) 48% HBr–H_2O was added (stirring, 40 min). The Et_2O layer was washed successively with 48% HBr, H_2O, and NaCl–H_2O, dried ($MgSO_4$), and evapd *in vacuo*. The residual oil in 700 ml of petr ether (bp 65–110°) was decolorized (charcoal, reflux) and successively concd and cooled giving **6**: recrystd (hexane), mp 125–127° (still impure); ir (cm^{-1}) 3090, 3000, 2970, 2940, 1720; nmr ($CDCl_3$), 7.80 (1 H, d), 7.60 (1 H, d), 4.38 (2 H, s), 3.21 (4 H, overlapping triplets), 2.37 (2 H, quintuplet).

(1) (a) This work was supported by the U. S. Army Medical Research and Development Command, Office of the Surgeon General; Contract No. DA-49-193-MD-2955, R. E. Lutz, Responsible Investigator. (b) Contribution No. 934 of the Army Research Program on Malaria. (c) Presented in part at the Southeast Regional Meeting of the American Chemical Society, Richmond, Va., Nov 1969, Abstract 255. (d) Antimalarial test results were supplied by the Walter Reed Army Institute of Research.
(2) Postdoctoral Research Associates.
(3) (a) Cf. reported antimalarial properties of derivatives of β-quininidene: (b) M. S. Chadha, K. K. Chakravarti, and S. Siddiqui, *J. Sci. Indian Res.*, **10B**, 1 (1951); *Chem. Abstr.*, **46**, 4545 (1952).
(4) R. T. Williams, "Detoxication Mechanisms," Wiley, New York, N. Y., 1959, p 655.
(5) W. E. Rothe and D. P. Jacobus, *J. Med. Chem.*, **11**, 366 (1968).
(6) R. E. Lutz, *et al.*, *J. Amer. Chem. Soc.*, **68**, 1813 (1946).
(7) *cf.* V. Q. Yen, N. P. Buu-Hoi, and N. D. Xuong, *J. Org. Chem.*, **23**, 1858 (1958).
(8) The method of T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).
(9) Instruments: (a) Thomas-Hoover apparatus for mp; (b) ir, Perkin-Elmer 337; (c) nmr, Hitachi-Perkin Elmer R-20; (d) anal. (Gailbraith Lab, Inc.) were correct within ±0.4%.
(10) First attempted prepns of **4** using PCl_5 were frustrated by facility of hydrolysis. Use of $SOCl_2$ (with or without DMF), and oxalyl chloride [J. Szmuszkovic, *J. Org. Chem.*, **29**, 843 (1964)], gave amorphous orange products, except in one of the latter experiments using **3·K salt (8)** (not successfully repeated) where MeOH quench gave **3·Me ester (9**, 87%).
(11) *Cf.* the tetrahydroacridine analogs; G. K. Patnaik, M. M. Vohra, J. S. Bindra, C. P. Garg, and N. Arnand, *J. Med. Chem.*, **9**, 483 (1966).

6,8-Dichloro-4-epoxyethyl-2,3-trimethylenequinoline (7).—A soln of 1 g (0.026 mole) of $NaBH_4$ in 10 ml of H_2O and 7 ml of 2 *N* NaOH, was added dropwise over 10 min to a stirred suspension of 4.65 g (0.013 mole) of nearly pure **6** (above) in 50 ml of MeOH. Stirring for an addl 1.5 hr, cooling for 15 min, filtering, and washing with MeOH gave 3.42 g (94.5%) of **7** (mp 134–139°); recrystd from Et_2O–hexane, mp 144–145°; ir (cm^{-1}) 2960, 2980, 3100, none for C=O; nmr ($CDCl_3$), 8.02 (1 H, d), 7.71 (1 H, d), 4.26 (1 H, m), 3.10 (5 H, m), 2.17 (2 H, quintuplet). *Anal.* ($C_{14}H_{11}Cl_2NO$) C, H, N.

5,7-Dichloro-2,3-dihydro-1*H*-cyclopenta[*b*]quinoline-9-(α-di-*n*-butylaminomethyl)methanol·HCl (1).—A suspension of 3.6 g of **7** in 12 ml of Bu_2NH was stirred for 4.5 hr at 105–110°, monitoring disappearance of **7** (4 hr) by tlc (silica gel G, 1:1 Et_2O–hexane). After evapn *in vacuo* of Bu_2NH (60°) the oil (5.1 g), dissolved in 150 ml of Et_2O, was treated with increments of Et_2O·HCl, each sufficient to give 0.2–0.4 g of **1** (each fraction being washed with Et_2O). Fractions 1–4 contd decreasing amts of Bu_2NH·HCl; and 5–8 were largely **1** (2.65 g). Repeated recrystn from EtOH–Et_2O gave 0.5 g, light tan, mp 160–162° dec; ir (cm^{-1}) 3440, 3220 (OH), 2960, 2940, 2880 (CH), 2670, 2620, 2530 ($\overset{+}{N}H$). *Anal.* ($C_{22}H_{30}Cl_2N_2O$·HCl) C, H, N, Cl.

Incidental and Preliminary Experiments. Attempts to add 2-PyLi and MeLi to the 2,3-trimethylenecinchoninic acids were unsuccessful, presumably because of steric interference of the 3-CH_2 group and/or the activity of the 2-CH_2 hydrogens (*cf.* ref 12).

2,3-Trimethylenecinchoninic acid·HCl (11), pptd from Et_2O, mp 252–255° dec, was treated with PCl_5 (steam bath for 30 min, addn of C_6H_6, and reflux for 2 hr), giving a ppt presumed to be the **acid chloride·HCl (12)** (sublimed, 8%, mp 245° dec).

2,3-Trimethylenecinchoninamide (13) was prepd from **12** by treatment with H_2O–NH_3; crystd from EtOH, mp 276–277°; ir (cm^{-1}) 3330 (s), 3140 (s) (NH_2), 1688 (C=O). *Anal.* ($C_{13}H_{14}N_2O$) C, H.

4-Bromoacetyl-2,3-trimethylenequinoline·HBr (14).—CH_2N_2–Et_2O with 3 g of **12** (overnight) gave orange cubes of diazo ketone. Treatment with 10 ml of 48% HBr–H_2O gave **14**; crystd from EtOH; 2.1 g (70%); mp 208° dec; ir (cm^{-1}) 1730 (C=O), 2500 ($\overset{+}{N}H$). *Anal.* ($C_{14}H_{13}Br_2NO$) N.

Derivatives of 2,3-trimethylene-4-quinolones were made by the action of the appropriate aniline on ethyl cyclopentanone-2-carboxylate, cyclizing at 250°, and crystn from EtOH:[3b,13] **15,** (a) 6,8-Cl_2, 26%, mp 305–307° (b) cyclization by refluxing Ph_2O, recrystd, mp 314–315° (lit.[3b] 313°) [*Anal.* ($C_{12}H_9Cl_2NO$) C, H, N]; **16**, 6,8-Me_2, 60%, mp 326–327° [*Anal.* ($C_{14}H_{15}NO$) N]; **17**, 6-Me, 39%, mp 319–322° [*Anal.* ($C_{13}H_{13}NO$) C, H]; **18**, 8-OMe, 26%, mp 212–213° [*Anal.* ($C_{13}H_{13}NO_2$) C, H, N]; **19**, 8-Cl, 21%, mp 269–270° [*Anal.* ($C_{12}H_{10}ClNO$) C, H, N]; **20**, 8-F, 15%, mp 292–293° [*Anal.* ($C_{12}H_{10}FNO$) C, H, N].

4-Bromo-2,3-trimethylenequinolines were prepd by treating the quinolone[13] with $POBr_3$ at 120°; crystd from EtOH: **21** (parent compd), 50%, mp 72–73° [*Anal.* ($C_{12}H_{10}BrN$), C, H, N]; **22**, 6,8-Me_2, from **16**, 69%, mp 124–125° [*Anal.* ($C_{14}H_{14}BrN$) C, H].

4,6,8-Trichloro-2,3-trimethylenequinoline (23) was prepd by refluxing $POCl_3$ on **15**, crystd from EtOH, 80%, mp 160–162°. *Anal.* ($C_{12}H_8Cl_3N$) C, H, N.

Attempted preparation of 4-lithio-2,3-trimethylenequinolines from **21** and **22** by BuLi and addns to 2-pyridaldehyde were unsuccessful, presumably because of the activities of the 2-CH_2 groups.[12]

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*N,N*¹-α,ω-Alkylenebis(nitroacetamides)

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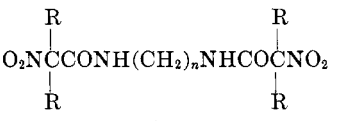
Some bis(nitroacetamides) with the general structure **1** were required for screening as antispermatogenic agents. The amides were readily prepared by heating the appropriate amine with the desired nitro ester without solvent and recrystallizing the resulting solid from a suitable solvent.

The compds prepared are listed in Table I. While

TABLE I



1

	R	*n*	Yield, %	Mp, °C	Rxt solv	Formula[a]
1	H	6	34.1	143–144	CH_3CN	$C_{10}H_{18}N_4O_6$
2	H	8	50.3	147–148	95% EtOH	$C_{12}H_{22}N_4O_6$
3	CH_3	2	12.8	183–185	CH_3CN	$C_{10}H_{18}N_4O_6$
4	CH_3	3	21.7	105–108	C_6H_6–*n*-C_6H_{14}	$C_{11}H_{20}N_4O_6$
5	CH_3	4	14.7	207–208	CH_3CN	$C_{12}H_{22}N_4O_6$
6	CH_3	6	30.6	168–170	CH_3CN	$C_{14}H_{26}N_4O_6$
7	CH_3	8	23.0	138–141	CH_3CN	$C_{16}H_{30}N_4O_6$

[a] All compds were anal. for C, H, N.

no antispermatogenic activity was found in this series anthelmintic activity was discovered. For example, **1** (R = H; *n* = 6) when administered orally to Swiss mice naturally infected with *Aspicularis tetraptera* (pinworm) cleared 100% of the mice (5/5 per dose level) at 100 mg/kg per day for 4 days and **1** (R = H; *n* = 8) cleared 100% of the mice (5/5 per dose level) at 200 mg/kg per day for 4 days; also, **1** (R = CH_3; *n* = 8) cleared 80% of the mice (4/5 per dose level) infected with the tapeworm *Hymenolepis nana* at 400 mg/kg per day for 4 days.

Experimental Section[1]

***N,N*¹-Hexamethylenebis(nitroacetamide).**—Ethyl nitroacetate (11.2 g, 0.0855 mole) was added to hexamethylenediamine (9.94 g, 0.855 mole). The mixt became hot and liquefied, after which a white solid pptd. The mixt was heated for 3 hr on a steam bath. It slowly turned to a thick orange liquid. The mixt was acidified with alcoholic HCl and poured into H_2O. The white solid was collected and recrystd from MeCN, mp 147–148° dec.

The other compds were prepd similarly except that in the case of the compds with no free H α to NO_2, 1 equiv of diamine was treated with 2 equiv of nitro ester and the alcoholic HCl treatment was unnecessary.

(1) Melting points were measured in open capillary tubes in a bath and are corrected.

Tricyclic Heterocycles Derived From 4-Oxo-4,5,6,7-tetrahydrothianaphthenes[1]

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Recently we described the synthesis of a variety of tricyclic heterocycles from 4-oxo-4,5,6,7-tetrahydroin-

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