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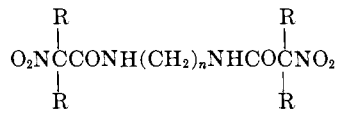
Some bis(nitroacetamides) with the general structure **1** were required for screening as antispermatogenic agents. The amides were readily prepared by heating the appropriate amine with the desired nitro ester without solvent and recrystallizing the resulting solid from a suitable solvent.

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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(1) Presented in part before the Medicinal Chemistry Division at the 161st National Meeting of the American Chemical Society, Los Angeles, Calif., March 1971, MEDI-23.

TABLE I
COMPOUNDS ACTIVE IN THE CARRAGEENIN ANTIINFLAMMATORY ASSAY IN RATS

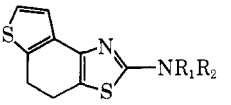
Compd	*C/T* efficacy ratios,[a] at 250 mg/kg oral dose			
4b	4.0	2.6	4.8	1.2
4c	1.8	2.2	1.8	3.2
Aspirin[b]	1.6			
Indomethacin[b]	2.1			

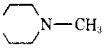
[a] The *C/T* ratio represents the mean edema vol of 8 control rats divided by the mean edema vol of 2 treated rats. For each treated rat measurements of the vol of the carrageenin-inflamed right paw (challenged by injection into the plantar tissue) and left paw (unchallenged) were determined 4 hr after the challenge. The method of determining paw vol (Hg immersion) was that described by C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962). Other details of the assay procedure also are given in this reference. [b] The *C/T* ratios for aspirin and indomethacin represent mean values for data from 50 rats.

The tricyclic compounds described herein represent new ring systems, with the exception of the system of **4**.[9] The tetracyclic system of **12** is also known.[10]

Biological Activities.—Compounds **7**, **8**, and all of the series **4a–4g** were active in the *p*-quinone writhing assay at 200 mg/kg oral dose in rats, as conducted according to a standard procedure for evaluating potential analgetics.[11] Of these compounds, the 2-methylamino and 2-allylamino derivatives **4b** and **4c** showed good activities in the carrageenin antiinflammatory assay in rats. These activities are compared with those of standard antiinflammatory drugs in Table I. The activities of isosteric pyrrolo[2,3-*e*]benzothiazoles in this assay[3] were approximately equal to those of the thieno[2,3-*e*]benzothiazoles in Table I.

TABLE II
2-SUBSTITUTED-4,5-DIHYDROTHIENO[3,2-*e*]BENZOTHIAZOLES

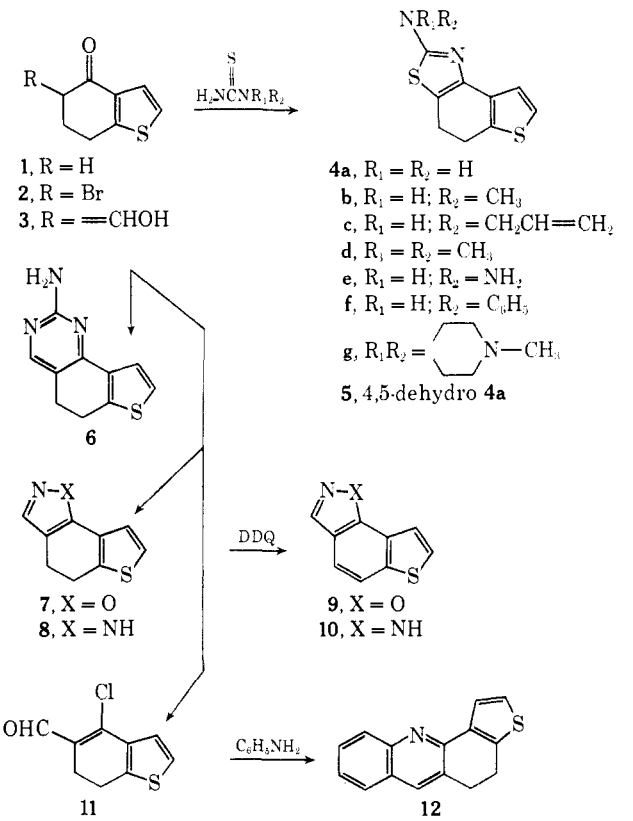


Compd	R_1R_2	Yield, %	Mp, °C	Formula	Analysis
4a·HBr	H, H	52	235–236	$C_9H_8N_2S_2 \cdot HBr$	C, H, N, S, Br
4b	H, CH_3	95	165–167	$C_{10}H_{10}N_2S_2$	C, H, N, S
4c	H, $CH_2CH{=}CH_2$	68	128–130	$C_{12}H_{12}N_2S_2$	C, H, N, S
4d·HCl	CH_3, CH_3	49	245–250	$C_{11}H_{12}N_2S_2 \cdot HCl$	C, H, N, S, Cl
4e·HBr	H, NH_2	58	182–183.5	$C_9H_9N_3S_2 \cdot HBr$	C, H, N, S, Br
4f	H, C_6H_5	66	163–166	$C_{15}H_{12}N_2S_2$	C, H, N, S
4g·HBr		89	262–264	$C_{14}H_{17}N_3S_2 \cdot HBr$	C, H, N, S, Br

doles.[2,3] Certain of these compounds showed interesting biological activity, especially in standard antiinflammatory assays.[3,4] In the hope that related tricyclic heterocycles might also show biological activity, we undertook the preparation of certain compounds from the readily available[5] 4-oxo-4,5,6,7-tetrahydrothianaphthene (**1**), an isostere of 4-oxo-4,5,6,7-tetrahydroindole.

The 5-hydroxymethylene derivative **3**[6] was prepared from **1** and condensed with a variety of bifunctional nucleophiles as described in the Experimental Section. Thus guanidine, hydroxylamine, and hydrazine gave the corresponding aminopyrimidine, isoxazole, and pyrazole analogs **6**, **7**, and **8**, resp. Dehydrogenation of **7** and **8** gave the corresponding fully aromatic compounds **9** and **10**.

Condensation of the 5-bromo derivative **2**[7] of **1** with certain substituted thioureas (Experimental Section) afforded the substituted 2-amino-4,5-dihydrothieno-[3,2-*e*]benzothiazoles (**4a–4g**). Vilsmeier–Haack formylation of **1** gave 4-chloro-6,7-dihydro-5-carboxaldehyde derivative **11**, which was converted into dihydrothieno[2,3-*c*]acridine **12** when it was heated with aniline.[8]



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(4) F. J. McEvoy, J. M. Smith, Jr., and D. S. Allen, Jr., U. S. Patent 3,404,157 (1966) see *Chem. Abstr.*, **65**, 20134c (1966).
(5) Aldrich Chemical Company, Milwaukee, Wis.
(6) M. Maillet and M. Michael Sy, *C. R. Acad. Sci., Ser. C*, **266**, 1545 (1968).
(7) J. Sam and G. Advani, *J. Pharm. Sci.*, **54**, 753 (1965).
(8) Based upon the quinoline synthesis of J. M. F. Gagan and D. Lloyd, *Chem. Commun.*, 1043 (1967).
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(10) N. P. Buu-Hoi and N. H. Khoi, *Recl. Trav. Chim. Pays-Bas*, **69**, 1053 (1950).
(11) See E. N. Greenblatt and A. C. Osterberg, *Toxicol. Appl. Pharmacol.*, **7**, 566 (1965), for details of the assay as performed in these laboratories.

Motor depression in mice was shown by **9** and **4a** at doses of 17 and 20 mg/kg ip, resp.[12]

The fully aromatic analogs **5**, **9**, and **10** were less interesting in the antiinflammatory assays than the corresponding dihydro derivatives.

Experimental Section

General.—Melting points were detd on a Mel-Temp melting point apparatus and are corrected. Uv spectra were detd in MeOH on a Cary recording spectrophotometer, and ir spectra in KBr with a Model 21 Perkin-Elmer spectrophotometer. Nmr spectra were detd in the indicated solvents on a Varian A-60 spectrometer (Me_4Si). Solns were dried ($MgSO_4$) and concd under reduced pressure on a rotary evaporator. Where analyses are indicated only by symbols of the elements, anal. results obtained for those elements were within ±0.4% of the theor values.

2-Substituted-4,5-dihydrothieno[3,2-*e*]benzothiazoles (4a–4g). (A) Isolated as Hydrobromides.—Equimolar quants of **2**[7] and appropriate thiourea derivs (thiourea, 1,1-dimethylthiourea, 4-methyl-1-piperazinethiocarboxamide,[3] and thiosemicarbazide) in 3.3 ml of EtOH per mmole of **2** were heated at reflux temp for 16 hr, partially concd, and cooled, whereupon the prods crystd. They were recrystd two times from EtOH prior to anal. Their uv spectra had typical max at 225 (ε 23,000), 240 (13,000), 275 (8300) mμ. Other data are in Table II.

(B) Isolated as Free Bases.—Equimolar quants of **2**, Et_3N, and apprropriate thiourea derivs (1-methylthiourea, 1-allylthiourea, 1-phenylthiourea) in 10 ml of EtOH per mmole of **2** were heated at reflux temp for 5 hr, concd, and treated with H_2O, whereupon the prods pptd. They were recrystd from MeOH or Et_2O–hexane. Their uv spectra had typical max at 228 (ε 42,000), 242 (19,000), 268 (12,000), and 3212 (2900) mμ. Other data are in Table II.

2-Aminothieno[3,2-*e*]benzothiazole (5).—A soln of 2.09 g of **4a** in 10 ml of dioxane was stirred and treated dropwise with 2.27 g of 2,3-dichloro-5,6-dicyanobenzoquinone in 3 ml of dioxane. After 30 min the mixt was filtered and the filtrate was concd. Recrystn of the residual solid (1.45 g) from EtOH (charcoal) gave white crystals: mp 238–241°; uv max 230 (ε 28,000), 290 (11,000), 313 (7400), 323 (7600) mμ. *Anal.* ($C_9H_6N_2S_2$) C, H, N; S: calcd, 31.09; found, 31.57.

2-Amino-5,6-dihydrothieno[2,3-*h*]quinazoline (6).—A mixt of 5.41 g of **3**,[6] 3.34 g of guanidine·HCl, and 200 ml of AcOH was heated on a steam bath for 6 hr, cooled, and the cryst product **6**·HCl (2.46 g) was collected. It was converted by NaOH into the free base: mp 211–214° after recrystn from dioxane; uv max 230 (ε 12,800), 245 (12,800), 265 (6300), 322 (8700), 383 (1500) mμ. *Anal.* ($C_{10}H_9N_3S$) C, H, N, S.

4,5-Dihydrothieno[2,3-*g*]-1,2-benzisoxazole (7).—A mixt of 5.09 g of **3**, 2.9 g of hydroxylamine·HCl, and 200 ml of AcOH was heated on a steam bath for 6 hr, treated with charcoal, filtd, and poured onto 350 g of ice. The resulting mixt gave crystals (2.15 g, 43%), mp 40–41.5°, upon storage at 5°. Low-temp recrystn from hexane gave mp 41–42°; uv max 237 (ε 13,000), 244 (12,500), 289 (9100) mμ. *Anal.* (C_9H_7NOS) C, H, N, S.

4,5-Dihydro-2*H*-thieno[2,3-*g*]indazole (8).—A mixt of 3.60 g of **3**, 2.0 ml of hydrazine hydrate, and 80 ml of EtOH was heated at reflux temp for 3 hr, cooled, and treated gradually with H_2O, whereupon crystals formed (2.87 g, 81%). Recrystn from EtOH gave white plates: mp 166–168°; uv max 222 (ε 13,800), 233 (9300), 240 (6700), 263 (6300) mμ. *Anal.* ($C_9H_8N_2S$) C, H, N, S.

Thieno[2,3-*g*]-1,2-benzisoxazole (9) was prepd by the procedure described for **5**. From 1.5 g of **7** was obtd 1.05 g of crude **9**. Recrystn from 50% aq EtOH, followed by low-temp recrystn from hexane gave a white solid: mp 62–63°; uv max 229 (ε 42,000), 256 (6200), 290 (4000), 302 (7000), 313 (7500) mμ. *Anal.* (C_9H_5NOS) C, H, N, S.

2*H*-Thieno[2,3-*g*]indazole (10) was prepd by the procedure described for **5**. From 180 mg of **8** was obtained 170 mg of crude **10**. Recryst from 50% aq EtOH (charcoal) gave mp 221.5–224.5°; uv max 220 (ε 34,000), 268 (5800), 278 (6600), 288 (5800), 299 (10,300), 312 (13,800) mμ. *Anal.* ($C_9H_6N_2S$) C, H, N, S.

(12) See W. B. Wright, Jr., H. J. Brabander, R. A. Hardy, and A. C. Osterberg, *J. Med. Chem.*, **9**, 852 (1966), for details of this assay.

4-Chloro-6,7-dihydrothianaphthene-5-carboxaldehyde (11).—To an ice-cooled soln of Vilsmeier–Haack reagent, prepd from 6.13 g of $POCl_3$ and 30 ml of DMF, was added a soln of 6.08 g of **1** in 30 ml of DMF. The mixt was heated on a steam bath for 1 hr, cooled, and poured onto 200 g of ice. The resulting mixt was made alk with NaOH and extd with CH_2Cl_2. This ext was washed with satd NaCl, dried, and concd to a syrup which crystd upon trituration with Et_2O. Recrystn from hexane gave 1.3 g (17%) of white prisms, mp 60–61°. That substitution had not occurred in the thiophene ring of **11** was shown by the retention of the 2 and 3 protons in the nmr ($CDCl_3$) at δ 7.3 (d, J = 5.5 Hz) and 7.15 (d, J = 5.5 Hz) ppm. *Anal.* (C_9H_7ClOS) C, H, Cl, S.

4,5-Dihydrothieno[2,3-*c*]acridine·HCl (12).—A mixt of 746 mg of **11**, 744 mg of aniline, and 5 ml of AcOH was heated at reflux temp for 3 hr and then concd.[8] Trituration of the residue with Et_2O gave 734 mg (67%) of yellow solid. Recrystn from $CHCl_3$–hexane gave yellow solid, mp 256–259° dec; uv max 222 (ε 31,000), 252 (16,500), 272 (16,300), 333 (8300), 349 (12,000), 377 12,100) mμ. *Anal.* ($C_{15}H_{11}NS$·HCl) C, H, N, S.

The free base had mp 121–124° after recrystn from CH_2Cl_2–hexane.

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Synthesis and Alkylation of Tetrahydropyrrolo[3,4-*c*]pyrazoles

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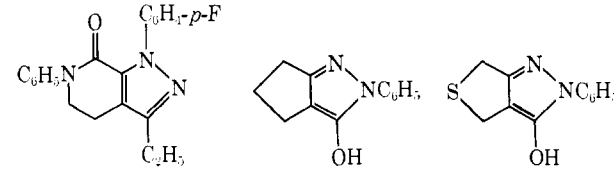
The pyrazole nucleus is found in a number of antiinflammatory–analgetic drugs such as phenylbutazone,[1] benzydamine,[1] and tetrydamine.[2] Recently, the antiinflammatory activity of the pyrazolopyridone **1** was reported.[3] As an extension of our work on cyclopentapyrazole (**2**)[4] and thienopyrazole (**3**)[5] analogs of the



1 2 3

pyrazole class of antiinflammatory agents, we now describe a brief study of some pyrrolo[3,4-*c*]pyrazoles.

Condensation of ethyl 4-oxo-1-phenyl-3-pyrrolidinecarboxylate (**4**)[6] with appropriate phenylhydrazines gave the hydrazino esters **5a–5e** (solid state ir, 6.0 μ, indicates the enamino ester tautomeric form). Treat-

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