compounds also contain some of the structural features common to the active compounds.[33]

Determination of Dipole Orientation and Development of a Quantitative Structure-Activity Relationship. The energy-optimized final atomic coordinates from the molecular mechanics calculations were translated to the new center of mass and transferred into SYBYL. The calculated dipole moment vector from MM2(85) was added to the SYBYL graphics display for each molecule. This vector was extended to the plane of the proposed pharmacophore defined by the Cl, O, N, and 1-phenyl or 1-benzyl centroids. A normal was constructed to that plane through the center of mass. The angle, θ, between the dipole vector and the normal to the plane of the proposed pharmacophore (Figure 7) was measured for each molecule and its cosine was evaluated. The value of cos θ for (*R*)-1 was given a negative sign to account for the opposite stereochemistry from the *S* isomers of the tetrahydroisoquinoline test compounds. The cos θ values were evaluated in a second-order polynomial regression analysis with the D_1 binding potency of the test compounds. Biological activity was expressed as the $-\log K_i$ (with the K_i values of **4**-**6** halved as previously described) for purposes of the regression analysis.

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Supplementary Material Available: Tables of X-ray parameters for (+)-**2** (13 pages); observed and calculated structure amplitudes (10 pages). Ordering information is given on any current masthead page.

Synthesis and Anthelmintic Activity of a Series of Pyrazino[2,1-*a*][2]benzazepine Derivatives

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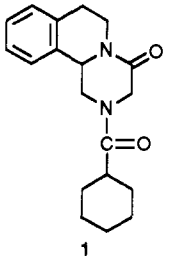
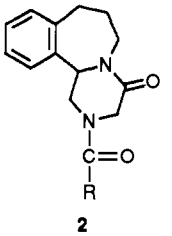
A series of 1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-*a*][2]benzazepine derivatives was prepared and the cestocidal activity of the compounds evaluated in an in vitro *Taenia crassiceps* screen. Many of these derivatives proved to be highly active, and 2-(cyclohexylcarbonyl)-4-oxo-1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-*a*][2]benzazepine, epsiprantel (BAN) (**22**), was selected for further development. The structure-activity relationships are discussed.

The discovery of the anthelmintic activity of various pyrazinoisoquinoline derivatives culminated in the development[1] of 2-(cyclohexylcarbonyl)-1,2,3,6,7,11b-hexahydro-4*H*-pyrazino[2,1-*a*]isoquinoline (praziquantel, **1**) as a potent cestocide. Many related heterocyclic systems were subsequently examined, but all were devoid of substantial anthelmintic activity.[2]

During our investigation of related heterocyclic systems we discovered the high cestocidal potency of derivatives of the pyrazino[2,1-*a*][2]benzazepine system (**2**). Here, we report on the synthesis and structure-activity relationships of these derivatives.



1

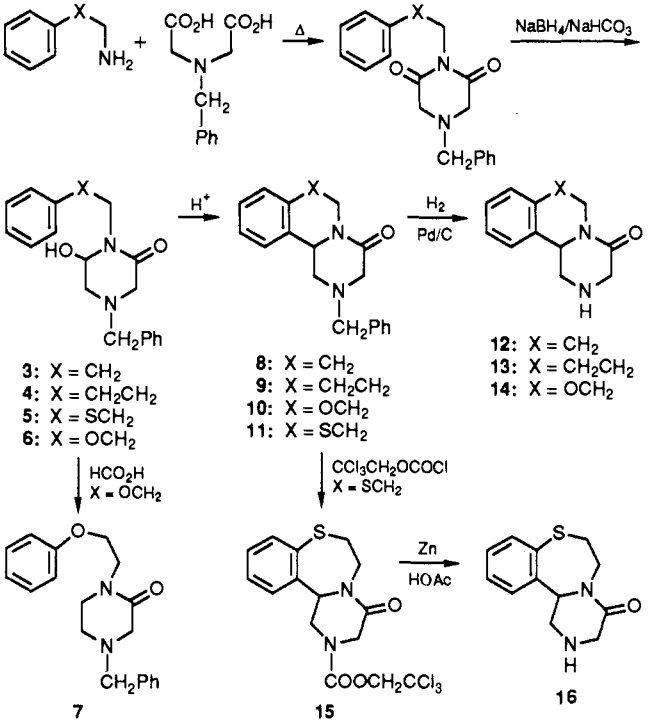


2

Chemistry

During our investigation of the pyrazino[2,1-*a*]isoquinoline ring system we developed a synthesis (Scheme I) of the nucleus based on the methodology of Speckamp[3] which utilizes the cyclization of an α-hydroxy lactam (**3**). Several other groups[4-6] have subsequently published related syntheses.

Scheme I



This synthesis was readily extended to give the ring-expanded analogues **2**, utilizing either polyphosphoric acid

[†] Beecham Pharmaceuticals Research Division, Walton Oaks.
[‡] Beecham Pharmaceuticals Research Division, Great Burgh.
[§] Beecham Pharmaceuticals Research Division, Brockham Park.

(1) Seubert, J.; Pohlke, R.; Loebich, F. *Experientia* **1977**, *33*, 1036.
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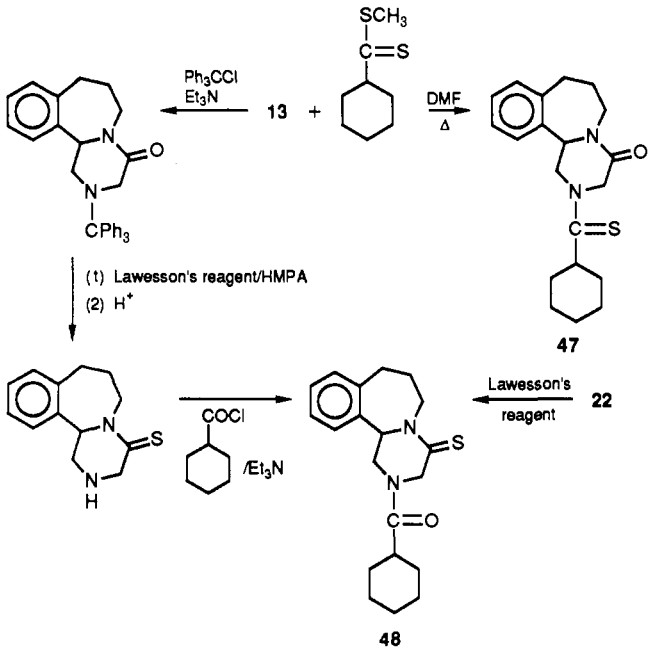
Scheme II



or concentrated sulfuric acid to effect cyclization of the α-hydroxy lactams **4–6**. Interestingly, attempts to effect the cyclization of the oxygen analogue **6** with formic acid, under reflux conditions, gave the amide **7**.

Hydrogenolysis of the benzyl derivatives **8–10** gave the amines **12–14**. In the case of the sulfur analogue **11**, hydrogenolysis of the benzyl group was unsuccessful and debenzylation was achieved by converting the benzylamine **11** to the 2′,2′,2′-trichloroethyl carbamate **15** and subsequently cleaving the carbamate with zinc dust in acetic acid.[7]

The amines **12–14** and **16** were acylated under standard conditions to give the amides **17–44**. The aminobenzoyl derivatives **33** and **35** were prepared by reduction of the corresponding nitro derivatives **32** and **34** with sodium borohydride/nickel chloride.

The amine **13** was resolved into its (−)- and (+)-isomers by crystallization of the (−)- and (+)-tartrate salts, respectively. Acylation of these isomers with cyclohexanoyl chloride gave the amides **45** and **46**, respectively.

The thioamide **47** was prepared by condensation of amine **13** with methyl cyclohexanecarbodithioate in DMF at reflux.

The thioamide **48** was prepared initially by protection of amine **13** followed by thionation with Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide] and deprotection followed by acylation as shown in Scheme II. Subsequently, it was found that treatment of the diamide **22** with Lawesson's reagent gave preferential thionation of the endocyclic carbonyl group to yield **48** directly.

The aryl-substituted derivatives **50** and **51** were prepared by using suitably substituted phenylpropylamines and the synthesis outlined in Scheme I.

Reduction of the amide **9** with borane followed by hydrogenolysis of the benzyl group and acylation of the resulting amine gave the amide **49**.

Biological Results and Discussion

The synthetic derivatives were evaluated in an in vitro tapeworm assay[8] using *Taenia crassiceps* as the test organism. By use of this model, the activity of the test compounds covered several orders of magnitude. The activities of the 2-acylbenzazepine derivatives are given in Table I.

The cyclopentyl (**21**) and cyclohexyl (**22**) derivatives both showed a considerable improvement in activity over the simple alkyl derivatives **17–19**. The effect of changes in ring size was also marked, with the activity increasing on going from cyclobutyl (**20**) to cyclopentyl (**21**) to cyclohexyl (**22**) and then decreasing dramatically with the cycloheptyl derivative **23**. The cyclohexenyl derivatives **24** and **25** both possessed moderate activity, although both were less active than the fully saturated derivative **22**.

The tetrahydrothiopyran **27** was more active than the tetrahydropyran **26**, but both were less active than the cyclohexyl derivative **22**. The benzoyl (**28**) and pyridyl (**42**) derivatives were also less active than the fully saturated system (**22**), and no improvement in activity was achieved with the substituted benzoyl derivatives **29–41**. The effect of heteroatoms being introduced into the propyl bridge was also investigated (Table II), but neither the introduction of oxygen (**43**) nor the introduction of sulfur (**44**) improved the activity over the methylene derivative **22**. The cyclohexyl derivative **22** was also prepared in its two optically active forms **45** and **46**. The (−)-isomer **45** was considerably more active than the (+)-isomer **46**, although the latter compound also possessed some activity.

The presence of the C-4 carbonyl group was essential for good biological activity (Table III) since neither the thioamide **48** nor the reduced derivative **49** possessed good anthelmintic activity. In contrast, the 2-thioacyl derivative **47** possessed good anthelmintic activity although the activity was slightly lower than that of the corresponding acyl derivative **22**. The introduction of electron-releasing substituents into the 10- and 11-positions (**50** and **51**) was also detrimental to anthelmintic activity.

Those analogues that demonstrated good activity in vitro were further evaluated in vivo. The cyclohexanoyl derivative **22** was found to possess high cestocidal activity in dogs (Table IV) and has been selected for further development.

Experimental Section

Melting points were determined on a Büchi capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on either a Jeol GX 270-MHz instrument or a Perkin-Elmer Hitachi Model R24A 60-MHz instrument with tetramethylsilane as internal standard. Elemental analyses are within ±0.4% of the calculated values except where noted. All HRMS determinations were within 4 millimass units of the theoretical values.

1-(3-Phenylpropyl)-4-benzyl-2,6-piperazinedione. 3-Phenyl-1-propylamine (3.63 g, 0.027 mol) and *N*-benzyliminodiacetic acid (6.0 g, 0.027 mol) were mixed and heated to 200 °C under a nitrogen atmosphere. The mixture was stirred at this temperature for 1 h, cooled, and purified by column chromatography (SiO_2, 40–60 °C petroleum ether/chloroform) to give the title material as a pale orange liquid (5.53 g, 64%).

1-(3-Phenylpropyl)-4-benzyl-2-hydroxy-6-oxopiperazine (4). Saturated aqueous sodium bicarbonate solution (20 mL) was added to a solution of 1-(3-phenylpropyl)-4-benzyl-2,6-piperazinedione (5.35 g, 0.017 mol) in ethanol (170 mL) at 5 °C and sodium borohydride (1.23 g, 0.03 mol) added portionwise to

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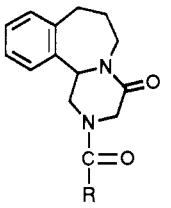
Table I. Biological Activity of 2-Acylbenzazepine Derivatives



compd	R	mp, °C	molecular formula	anal.	MIC, *T. crassiceps*[a]
praziquantel (1)					++++
nitroscanate (4,4′-$O_2NC_6H_4OC_6H_4NCS$)					++
17	CH_3	137–9	$C_{15}H_{18}N_2O_2$	C, H, N	+
18	$CH(CH_3)_2$	162–3	$C_{17}H_{22}N_2O_2$	C, H, N	+
19	$(CH_2)_4CH_3$	91–2	$C_{19}H_{26}N_2O_2$	C, H, N	+
20		157–9	$C_{18}H_{22}N_2O_2$	C, H, N	+
21		154–5	$C_{19}H_{24}N_2O_2$	C, H, N	+++
22		189–90	$C_{20}H_{26}N_2O_2$	C, H, N	++++
23		160–5	$C_{21}H_{28}N_2O_2$	C, H, N	+
24		149–50	$C_{20}H_{24}N_2O_2$	C, H, N	++
25		183–5	$C_{20}H_{24}N_2O_2$	C, H, N	++
26		212–4	$C_{19}H_{24}N_2O_3 \cdot 0.33H_2O$	C, H, N	+
27		164–5	$C_{19}H_{24}N_2O_2S$	C, H, N, S	+++
28	C_6H_5	166–7	$C_{20}H_{20}N_2O_2 \cdot 0.33H_2O$	C, H, N	++
29	4-$CH_3OC_6H_4$	167–71	$C_{21}H_{22}N_2O_3$	C, H, N	+
30	4-ClC_6H_4	184–6	$C_{20}H_{19}N_2O_2Cl$	C, H, N	+
31	4-$CH_3C_6H_4$	179–81	$C_{21}H_{22}N_2O_2$	C, H, N	++
32	4-$NO_2C_6H_4$	217–8	$C_{20}H_{19}N_3O_4$	C, H, N	+
33	4-$NH_2C_6H_4$	217–8	$C_{20}H_{21}N_3O_2 \cdot H_2O$	C, H, N[b]	++
34	3-$NO_2C_6H_4$	170–1	$C_{20}H_{19}N_3O_4$	C, H, N	+
35	3-$NH_2C_6H_4$	98–101	$C_{20}H_{21}N_3O_2 \cdot H_2O$	C, H, N	+
36	4-HOC_6H_4	190–5	$C_{20}H_{20}N_2O_3 \cdot 0.5H_2O$	C, H, N	+
37	4-FC_6H_4	168–9	$C_{20}H_{19}N_2O_2F$	C,[c] H, N	+
38	3-$CH_3C_6H_4$	152–3	$C_{21}H_{22}N_2O_2$	C, H, N	+
39	3-ClC_6H_4	148–51	$C_{20}H_{19}N_2O_2Cl$	C, H, N	+
40	2-$CH_3C_6H_4$	127–8	$C_{21}H_{22}N_2O_2$	C, H, N	+
41	4-$(CH_3)_2NC_6H_4$	197–8	$C_{22}H_{25}N_3O_2$	C, H, N	+
42	3-pyridyl	170–71	$C_{19}H_{19}N_3O_2$	C, H, N	+

[a] Concentration required to prevent all movement of cysts and evaginated scoleces: ++++ = MIC ≤ 0.1 μg/mL; +++ = 0.1 μg/mL < MIC ≤ 1.0 μg/mL; ++ = 1.0 μg/mL < MIC ≤ 10 μg/mL; + = MIC > 10 μg/mL. [b] N: calcd, 11.89; found, 11.43. [c] C: calcd, 70.99; found, 70.33.

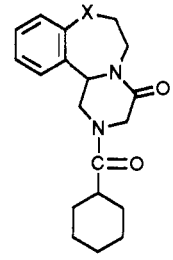
the resulting mixture at 5 °C over a period of 2 h. The mixture was stirred for a further 1 h at 5 °C and the solvent removed in vacuo. Water (50 mL) was added and the mixture extracted with dichloromethane (3 × 50 mL). The extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent gave the title compound as a white solid (4.36 g, 81%).

2-Benzyl-4-oxo-1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-*a*][2]benzazepine (9). 1-(3-Phenylpropyl)-4-benzyl-2-hydroxy-6-oxopiperazine (2.6 g, 8.0 mmol) and polyphosphoric acid (53 g) were mixed, heated at 180 °C, and maintained at this temperature for $^3/_4$ h. The mixture was cooled to 60 °C and water (200 mL) added. The mixture was cooled, basified with sodium hydroxide solution, and extracted with chloroform (3 × 50 mL). The solvent was evaporated and the product crystallized from diethyl ether to give the title compound (0.78 g, 32%); mp 125–8 °C.

2*H*-4-Oxo-1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-*a*][2]benzazepine (13). Hydrogenolysis of 2-benzyl-4-oxo-1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-*a*][2]benzazepine (1.39 g, 4.54 mmol) in solution in ethanol (40 mL) with hydrogen at 45 °C and atmospheric pressure in the presence of a palladium on charcoal catalyst (0.3 g) gave the title compound (0.6 g, 61%): ^1H NMR ($CDCl_3$) δ 7.10–7.25 (m, H-9, H-10, H-11, H-12), 4.82 (dd, 10.3 Hz, 4.4 Hz, H-12b), 4.29 (dd, 13.4 Hz, 7.5 Hz, H-6a), 3.66 (s, H-3a + H-3b), 3.23 (dd, 13.3 Hz, 4.4 Hz, H-1a), 3.03 (dd, 13.3 Hz, 10.4 Hz, H-1b), 3.00 (m, H-8a), 2.82 (ddd, 13.4 Hz, 11.5 Hz, 6.5 Hz, H-6b), 2.54 (ddd, 13.8 Hz, 5.2 Hz, 2.1 Hz, H-8b), 2.32 (m, H-7a), 1.80 (s, NH), 1.59 (m, H-7b).

2-(Cyclohexylcarbonyl)-4-oxo-1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-*a*][2]benzazepine (22). Cyclohexanoyl chloride (0.34 g, 2.32 mmol) was added to a solution of 2*H*-4-oxo-1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-*a*][2]benzazepine (0.5 g, 2.32 mmol) in chloroform (20 mL, ethanol free) maintained at 0 °C and triethylamine (0.26 g) added. The mixture was maintained at 0 °C for 30 min and then at room temperature for 5 h. The solution was washed with dilute hydrochloric acid followed by sodium bicarbonate solution. The chloroform solution was dried ($MgSO_4$) and evaporated. The residue was recrystallized

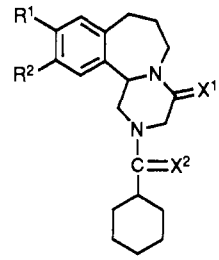
Table II. Effects on Biological Activity of the Presence of Heteroatoms in Propyl Bridge and Resolution of Optical Isomers



compd	X	mp, °C	molecular formula	anal.	MIC, *T. crassiceps*[a]
22	CH_2	189–90	$C_{20}H_{26}N_2O_2$	C, H, N	++++
43	O	92–3	$C_{19}H_{24}N_2O_3$	C, H, N	++
44	S	oil	$C_{19}H_{24}N_2SO_2$	HRMS [M^+]	+
45[b]	CH_2 (−)-isomer	oil	$C_{20}H_{26}N_2O_2$	HRMS[M^+]	++++
46[c]	CH_2 (+)-isomer	oil	$C_{20}H_{26}N_2O_2$	HRMS [M^+]	++

[a] See footnote *a*, Table I. [b] $[\alpha]^{22}_D$ −42° (CH_3OH). [c] $[\alpha]^{22}_D$ +41° (CH_3OH).

Table III. Effect on Biological Activity of Changes to the Carbonyl Group and Substitution in the Aromatic Ring



compd	R^1	R^2	X^1	X^2	mp, °C	molecular formula	anal.	MIC, *T. crassiceps*[a]
47	H	H	O	S	oil	$C_{20}H_{26}N_2OS$	HRMS[M^+]	+++
48	H	H	S	O	150–1	$C_{20}H_{26}N_2OS$	C, H, N	+
49	H	H	H_2	O	208–10	$C_{20}H_{28}N_2O$·HCl	C, H, N, Cl	+
50	OCH_3	OCH_3	O	O	oil	$C_{22}H_{30}N_2O_4$	HRMS [M^+]	+
51	H	CH_3	O	O	oil	$C_{21}H_{28}N_2O_2$	HRMS [M^+]	++

[a] See footnote *a*, Table I.

Table IV. Controlled Test with **22** against Experimental Infections of *Taenia pisiformis* in Dogs

group[a]	treatment	dose,[b] mg/kg	tapeworms found at autospy	% act.
1	**22**	1	0	100
2	**22**	2.5	0	100
3	**22**	5	0	100
4	praziquantel (control)	5[c]	0	100
5	placebo (lactose)	100	3, 5, 7	

[a] Three dogs per group. [b] Oral dose in gelatin capsule. [c] Recommended dose.

from chloroform/40–60 °C petroleum ether to give white crystals of the title compound (0.48 g, 64%); mp 189–90 °C; MS, *m/z* 326 [M^+]. Anal. ($C_{20}H_{26}N_2O_2$) C, H, N.

Major Rotamer: ^{1}H NMR ($CDCl_3$) δ 7.27–7.13 (m, 9-H, 10-H, 11-H, 12-H), 4.80 (dd, 8.1 Hz, 4.1 Hz, 12b-H) 4.43 (dd, 13.5 Hz, 5.2 Hz, 6-H), 4.38 (d, 17.5 Hz, 3-H), 4.31 (dd, 13.8 Hz, 3.7 Hz, 1-H), 4.10 (d, 17.3 Hz, 3-H), 3.65 (m, 1-H), 3.01–2.90 (m, 6-H, 8-H), 2.73 (dt, 14.2 Hz, 4.8 Hz, 8-H), 2.45 [tt, 11.5 Hz, 3.2 Hz, C(=O)C*H*], 2.13 (m, 7-H), 1.70 (m, 7-H), 1.87–1.20 (m, cyclohexyl).

Minor Rotamer: ^{1}H NMR ($CDCl_3$) δ 7.27–7.13 (m, 9-H, 10-H, 11-H, 12-H), 4.89 (dd, 9.5 Hz, 3.3 Hz, 12b-H), 4.75 (d, 18.7 Hz, 3-H), 4.35 (m, 6-H), 3.97 (dd, 13.1 Hz, 3.0 Hz, 1-H), 3.84 (d, 18.8 Hz, 3-H), 3.60 (m, 1-H), 3.01–2.90 (m, 8-H), 2.85 (m, 6-H), 2.67 (m, 8-H), 2.45 [m, C(=O)C*H*], 2.25 (m, 7-H), 1.60 (m, 7-H), 1.87–1.20 (m, cyclohexyl).

Resolution of 2*H*-4-Oxo-1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-*a*][2]benzazepine (13). (±)-2*H*-4-oxo-1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-*a*][2]benzazepine (3.2 g, 0.0148 mol) was dissolved in methanol (35 mL) and a solution of (−)-tartaric acid (2.45 g, 0.0163 mol) in methanol (140 mL) added. The mixture was heated on a steam bath, filtered while hot, and allowed to cool. White crystals were deposited, and these were filtered and recrystallized from methanol (250 mL) to give the (−)-tartrate salt of (−)-2*H*-4-oxo-1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-*a*][2]benzazepine (2 g, 78%); $[\alpha]^{22}$ −149° (H_2O). The optical rotation was not improved by further recrystallizations. A solution of this salt in water gave, upon basification with ammonium hydroxide and extraction with chloroform, the free base (−)-2*H*-4-oxo-1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-*a*][2]benzazepine as a white solid; $[\alpha]^{22}$ −221° (CH_3OH). Similarly, with (+)-tartaric acid in place of (−)-tartaric acid the following were obtained: (+)-2*H*-4-oxo-1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-*a*][2]benzazepine (+)-tartrate [$[\alpha]^{22}$ +153° (H_2O)] and (+)-2*H*-4-oxo-1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-*a*][2]benzazepine free base [$[\alpha]^{22}$ +212° (CH_3OH)].

2-(Triphenylmethyl)-4-oxo-1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-*a*][2]benzazepine. Triphenylmethyl chloride (0.47 g, 1.68 mmol) was added to a mixture of 2*H*-4-oxo-1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-*a*][2]benzazepine (0.31 g, 1.44 mmol) and triethylamine (0.25 ml) in chloroform (25 mL, ethanol free) at 0 °C. The mixture was maintained at 0 °C for 30 min and then at room temperature for 90 min. The solution was washed with saturated sodium bicarbonate solution, dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography (SiO_2, Et_2O) to give the title compound (0.66 g, 100%) as a white powder.

2*H*-4-Thioxo-1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-*a*][2]benzazepine. A mixture of 2-(triphenylmethyl)-4-oxo-1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-*a*][2]benzazepine (0.66 g, 1.44 mmol) and Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide] (0.29 g, 0.72 mmol) in HMPA (10 mL) was heated to 80 °C under a nitrogen

atmosphere. The mixture was stirred at this temperature for 3 h, cooled, and partitioned between water and diethyl ether. The organic layer was washed with water and evaporated to a yellow foam. This residue was dissolved in acetone (20 mL) and cooled to 0 °C, and concentrated hydrochloric acid (0.5 mL) was added. After stirring at room temperature for 30 min, the mixture was evaporated and the residue partitioned between dilute hydrochloric acid and chloroform. The aqueous fraction was basified with sodium carbonate and extracted with chloroform. This chloroform fraction was washed with brine, dried (K_2CO_3), and evaporated to give the crude title compound as a white solid which was used directly in the following step.

2-(Cyclohexylcarbonyl)-4-thioxo-1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-*a*][2]benzazepine (48). Cyclohexanoyl chloride (0.16 g, 1.09 mmol) was added to a mixture of 2*H*-4-thioxo-1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-*a*][2]benzazepine (0.24 g, 1.09 mmol) and triethylamine (0.25 mL) in chloroform (20 mL, ethanol free) at 0 °C. The mixture was maintained at 0 °C for 30 min and then at room temperature for 5 h. The solution was washed with dilute hydrochloric acid, followed by sodium bicarbonate solution. The chloroform solution was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (SiO_2, Et_2O) and recrystallized from dichloromethane/40–60 °C petroleum ether to give white crystals of the title compound (55 mg, 16%); mp 150–1 °C. Anal. ($C_{20}H_{26}N_2OS$) C, H, N.

2-(Cyclohexylcarbonyl)-4-thioxo-1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-*a*][2]benzazepine (48). A mixture of 2-(cyclohexylcarbonyl)-4-oxo-1,2,3,4,6,7,8,12b-octahydropyrazino-[2,1-*a*][2]benzazepine (0.30 g, 0.92 mmol) and Lawesson's reagent (0.19 g, 0.47 mmol) in HMPA (4 mL) was heated to 80 °C under a nitrogen atmosphere. The mixture was stirred at this temperature for 3 h, cooled, and poured into water. The water was extracted with diethyl ether. The organic layer was washed with water, dried ($MgSO_4$), and evaporated. The residue was purified by column chromatography (SiO_2, Et_2O) and crystallized (CH_2Cl_2/40–60 °C petroleum ether) to give white crystals of the title compounds (0.13 g, 41%); mp 150–1 °C.

2-(Cyclohexylthiocarbonyl)-4-oxo-1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-*a*][2]benzazepine (47). Methyl cyclohexanecarbodithioate (0.24 g, 1.4 mmol) was added to a solution of 2*H*-4-oxo-1,2,3,4,6,7,8,12b-octahydropyrazino[2,1-*a*][2]benzazepine (0.3 g, 1.39 mmol) in dimethylformamide (5 mL). The mixture was refluxed for 4 h, cooled, and poured into water. The solution was extracted with diethyl ether, and the ether solution was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (SiO_2, diethyl ether) to give the title compound as an oil (35 mg, 7%). MS: calcd for $C_{20}H_{26}N_2OS$, m/z 342.1766; found, m/z 342.1770 [M^+].

Biological Methods. In Vitro *T. crassiceps* Test Method. The drug suspension (60 μL, 1000 μg/mL in phosphate-buffered methylcellulose) was added to the well of a Linbro plate. The culture medium (5 mL) was added to the well and the plate maintained at 37 °C.

Culture medium[9] consisted of the following: CMRL medium 1066 (+glutamine), 10.4 g; fetal calf serum, 400 mL; D-glucose, 6.96 g; sodium taurocholate, 16 mg; yeast extract, 7.2 g; sodium bicarbonate, 7.72 g; HEPES, 7.70 g; benzylpenicillin, 160 mg; amphotericin B (250 μg/mL), 24 mL; streptomycin sulphate (200 mg/mL), 4 mL; and water 1187 mL. Medium was sterilized by membrane filtration (0.45 μm).

T. crassiceps cysts were removed from mice and incubated for 5 min in 0.05% pepsin (in HCl, pH 2.0) at 37 °C with occasional gentle mixing. The cysts were drained and washed three times with one volume of Hank's balanced salt solution. One milliliter of cysts was added to each well of the Linbro plate, thereby giving a drug concentration of 10 μg/mL, which was then maintained at 37 °C for the duration of the test. The activity of the invaginated and evaginated cysts was monitored after 24 and 48 h. Drug activity manifested itself either by destruction of the cysts or by totally immobilizing them within the 48-h incubation period. Active compounds were then titrated to give the minimum inhibitory concentration of the agent in this screen.

Dog Test. Fifteen adult dogs were each infected with 15–20 metacestodes of *Taenia pisiformis*. When mature *T. pisiformis* infections had been confirmed in the dogs, by the presence of tapeworm proglottides in the feces, they were allocated to five groups of three animals. The dogs were treated with the test compounds, and 4 days after treatment all animals were necropsied. The intestinal contents and mucosal surface were examined for entire worms and scoleces. Activity was calculated by comparison of the average worm numbers with those in the untreated control group.

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Registry No. 1, 55268-74-1; (±)-**3**, 121654-39-5; (±)-**4**, 121654-40-8; (±)-**5**, 121654-41-9; (±)-**6**, 121654-42-0; (±)-**7**, 121654-43-1; (±)-**8**, 121654-44-2; (±)-**9**, 121654-45-3; (±)-**10**, 121654-46-4; (±)-11, 121654-47-5; (±)-**12**, 55375-90-1; (±)-**13**, 98123-61-6; (−)-**13**, 98123-62-7; (+)-**13**, 98123-64-9; (−)-**13**·(−)-tartrate, 98123-63-8; (+)-**13**·(+)-tartrate, 98123-65-0; (±)-**14**, 121654-48-6; (±)-**15**, 121654-49-7; (±)-**16**, 121654-50-0; (±)-**17**, 121654-51-1; (±)-**18**, 121654-52-2; (±)-**19**, 121654-53-3; (±)-**20**, 121654-54-4; (±)-**21**, 121654-55-5; (±)-**22**, 121654-56-6; (±)-**23**, 121654-57-7; (±)-**24**, 121654-58-8; **25**, 98123-53-6; (±)-**26**, 121654-59-9; (±)-**27**, 121654-60-2; (±)-**28**, 121654-61-3; (±)-**29**, 121654-62-4; (±)-**30**, 121654-63-5; (±)-**31**, 121654-64-6; (±)-**32**, 121654-65-7; (±)-**33**, 121654-66-8; (±)-**34**, 121654-67-9; (±)-**35**, 121654-68-0; (±)-**36**, 121654-69-1; (±)-**37**, 121654-70-4; (±)-**38**, 121654-71-5; (±)-**39**, 121654-72-6; (±)-**40**, 121654-73-7; (±)-**41**, 121654-74-8; (±)-**42**, 121654-75-9; (±)-**43**, 121654-76-0; (±)-**44**, 121654-77-1; (−)-**45**, 98123-67-2; **46**, 98123-66-1; (±)-**47**, 121654-78-2; (±)-**48**, 121654-79-3; (±)-**49**, 121654-80-6; (±)-**50**, 121654-81-7; (±)-**51**, 121654-82-8; $Ph(CH_2)_2NH_2$, 64-04-0; $Ph(CH_2)_3NH_2$, 2038-57-5; $PhS(CH_2)_2NH_2$, 2014-75-7; $PhO(CH_2)_2NH_2$, 1758-46-9; Cl_3CCH_2OCOCl, 17341-93-4; $(CH_3)_2CHCOCl$, 79-30-1; $CH_3(CH_2)_4COCl$, 638-29-9; $4\text{-}CH_3OC_6H_4COCl$, 100-07-2; $4\text{-}ClC_6H_4COCl$, 122-01-0; $4\text{-}CH_3C_6H_4COCl$, 874-60-2; $4\text{-}NO_2C_6H_4COCl$, 122-04-3; $3\text{-}NO_2C_6H_4COCl$, 121-90-4; $4\text{-}HOC_6H_4COCl$, 28141-24-4; $4\text{-}FC_6H_4COCl$, 403-43-0; $3\text{-}CH_3C_6H_4COCl$, 1711-06-4; $3\text{-}ClC_6H_4COCl$, 618-46-2; $2\text{-}CH_3C_6H_4COCl$, 933-88-0; $4\text{-}(CH_3)_2NC_6H_4COCl$, 4755-50-4; $MeC_6H_4\text{-}p\text{-}(CH_2)_3NH_2$, 54930-39-1; 1-(2-phenylethyl)-4-benzyl-2,6-piperazinedione, 106148-27-0; *N*-benzyliminodiacetic acid, 3987-53-9; 1-(3-phenylpropyl)-4-benzyl-2,6-piperazinedione, 98123-84-3; 1-(2-thiophenylethyl)-4-benzyl-2,6-piperazinedione, 121654-83-9; 1-(2-oxyphenylethyl)-4-benzyl-2,6-piperazinedione, 98123-71-8; cyclobutanecarbonyl chloride, 5006-22-4; cyclopentanecarbonyl chloride, 4524-93-0; cycloheptanecarbonyl chloride, 6557-86-4; 1-cyclohexenecarbonyl chloride, 36278-22-5; (±)-3-cyclohexenecarbonyl chloride, 84094-95-1; tetrahydro-2*H*-pyran-4-carbonyl chloride, 40191-32-0; tetrahydro-2*H*-thiopyran-4-carbonyl chloride, 121654-84-0; 3-pyridinecarbonyl chloride, 10400-19-8; methyl cyclohexanecarbodithioate, 5874-05-5; Ph_3CCl, 76-83-5; 2-(triphenylmethyl)-4-oxo-1,2,3,4,5,6,7,8,12b-octahydropyrazino[2,1-*a*][2]-benzazepine, 121654-85-1; 2*H*-4-thioxo-1,2,3,4,5,6,7,8,12b-octahydropyrazino[2,1-*a*][2]benzazepine, 121654-86-2; 3-(3,4-dimethoxybenzyl)propylamine, 14773-42-3; cyclohexanecarbonyl chloride, 2719-27-9.

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