Table I.

Compd	Formula[a]	Mp, °C	Yield, %	Solvent	Ir, cm^{-1}
1b	$C_{14}H_{22}N_2O$	82–83	52	Petr ether	
1b·HCl	$C_{14}H_{23}ClN_2O$	121–122		EtOH-Et_2O	
1c	$C_{21}H_{26}N_2O_2$	165–166	78	EtOH-petr ether	1630 (C=O)
1d	$C_{30}H_{33}NO_3$	84–85	47	Petr ether	1730 (O–C=O) 1620 (N–C=O)
1e·HCl	$C_{22}H_{30}ClNO$	163–164	94	EtOH-Et_2O	3200 (OH)
2a·HCl	$C_{15}H_{21}ClNO$	158–159	64	EtOH-Et_2O	1120 (O–C–N)
2b[b]	$C_{14}H_{19}NO_2S$	107–108	15	EtOH	1135 (C=S)
3a·picrate	$C_{22}H_{24}N_4O_9$	180–181	40	C_6H_6	1740 (C=O)
3b[c]	$C_{16}H_{19}NO_3$	126–127	73	Me_2CO-cyclohexane	1745 (O–C=O) 1665 (N–C=O)
3c	$C_{15}H_{20}N_2OS$	182–183	36	$CHCl_3$-petr ether	1190 (C=S)
3d·HCl	$C_{16}H_{23}ClN_2OS$	148–149	49	EtOH-Et_2O	1170 (C=S)

[a] All compds were analyzed for C, H, and N and were within ±0.4% of the theoretical values. [b] Shown by tlc and nmr to be a mixt of geometrical isomers (5:1) with the cis isomer predominant.[8] [c] Calcd nmr spectrum in C_6H_6 indicates an envelope conformation.[2]

Table II.

		Phenylquinone-induced writhing[b]		Neuropharmacological Tests[b]					
Compd	LD_{50},[a] mg/kg	% inhibition	ED_{50}, mg/kg	Mydriasis, %	Rotating rod, %	Grip strength, %	Hot plate, %	Tonic extension (pentylenetetrazole), %	Death (pentylenetetrazole), %
1a	30–100		23.5	65	20	20	40	100	100
4	30–100		5	−10	0	20	0	0	0
1d	100–300	26.5		0	20	0	0	0	0
1e	100–300	13.3		0	0	0	0	60	20
2a	30–100	44		−16	0	0	0	80	0
5	30–100		10.5	27	0	0	0	0	20
2c	>300	35.7		−30	20	0	0	40	80
3b	>300	0		−26	0	20	0	10	40

[a] Ip. [b] Sc. [c] Dose levels, 1a, 1d, 1e, 2e, and 3b, 100 mg/kg; 2a, 30 mg/kg; 4 and 5, 10 mg/kg.

This showed considerable anticonvulsant properties against pentylenetetrazole (ED_{50} 3–5 mg/kg sc) but was inactive against electroshock and strychnine-induced convulsions. The *N*-phenethyl analog (4) and the cyclic derivatives showed less activity under the test conditions.

Experimental Section

3-Cyclohexyl-5-phenyloxazolidine (2a). The aminoethanol (1a) (2.19 g) and formalin (1 ml, 40%) in EtOH (20 ml) were refluxed for 12 hr to yield the oxazolidine, bp 126–130 (0.3 mm), isolated as its stable hydrochloride.

3-Cyclohexyl-2-oxo-5-phenyl-1,2,3-oxathiazolidine (2b). $SOCl_2$ (2.3 ml), in CH_2Cl_2 (50 ml) was added slowly (15 min) to the aminoethanol (1a) (6.57 g) and Me_3N (11 ml) in CH_2Cl_2 (150 ml). The mixt was stirred (room temp) for 18 hr to yield 2b.

4-Cyclohexyl-6-phenylmorpholin-2-one (3a). Ethyl bromoacetate (3.34 g) in 1,2-dimethoxyethane (5 ml) was added slowly to the aminoethanol 1a (4.38 g) and $NaHCO_3$ (2 g) in 1,2-dimethoxyethane (20 ml) and the mixt was refluxed for 66 hr. The cooled mixt was dild with Et_2O, washed with H_2O, and distd to yield the morpholinone, bp 150–160° (0.7 mm), characterized as its picrate.

4-Cyclohexyl-6-phenylmorpholine-2,3-dione (3b). The aminoethanol 1a (13.57 g), $(COOEt)_2$ (4.38 g), and PhMe (150 ml) were refluxed for 18 hr during which time PhMe was slowly distd from the mixt. Evapn of residual solvent yielded 3b.

1-Cyclohexyl-1-(2-hydroxyphenethyl)hydrazine (1b). The aminoethanol 1a (21.9 g) in 1 *N* HCl (100 ml) at 50° was treated with $NaNO_2$ (10 g) in H_2O (30 ml) and stirred 2 hr. Et_2O extn yielded the *N*-nitroso compd as a yellow oil (20.2 g, 81%) which was reduced with LAH (8 g) in Et_2O (100 ml) to give the hydrazine.

4-Cyclohexyl-6-phenyl-3,4,5,6-tetrahydro-2*H*-1,3,4-oxadiazine-2-thione (3c). A cold soln of KOH (1.12 g) in H_2O (4 ml) and EtOH (20 ml) was added to the hydrazine 1b (2.34 g) and CS_2 (1.52 g) and the mixt was refluxed for 4 hr. The cooled soln was dild with H_2O (50 ml) and acidified with *N* HCl to ppt 3c. Treatment with Me_2SO_4 yielded the *N*-Me deriv 3d.

1-Cyclohexyl-1-(2-hydroxy-2-phenylethyl)phenethylamine (1e). The aminoethanol 1a (8.7 g), phenylacetyl chloride (13.1 g), and $NaHCO_3$ (10 g) in C_6H_6 (50 ml) refluxed for 4 hr, yielded the *O,N*-diphenylacetyl derivative 1d. Reduction of this amidoester (26.45 g) with LAH (4.6 g) in Et_2O (150 ml) yielded 1e.

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Central Nervous System, Antidiuretic, and Some Other Activities of Pyrazoles

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A number of pyrazoline-4,5-diones and their functional derivatives[1-5] were tested for CNS[6] and antidiuretic[7] activ-

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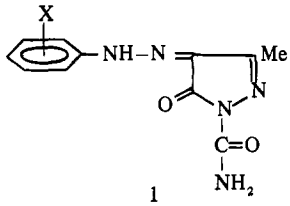
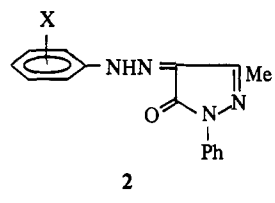
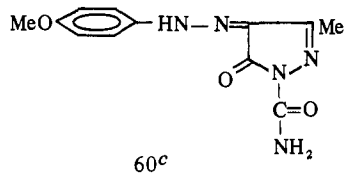
Table I. CNS Activity

No.	X	Mp, °C	Dose, mg/kg	Activity,[g] min Onset	Peak	Duration
	 1			 2		
1a	3-Cl	203[a]	100[b]	65	190	135[c]
b	3-Cl		300[d]			
c	2-Cl	210[a]	300[d]			
d	4-OMe	201[a]	300[d]			
e	2,5-Cl_2	258–259[e]	300[d]			
2a	H	156[f]	300[d]			
b	2,5-Cl_2	224[f]	300[d]			
c	2-Cl	182[f]	300[d]			
d	4-OMe	135[f]	300[d]			

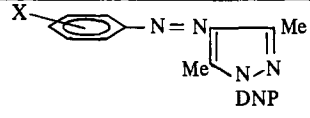
[a]Reference 1. [b]All drugs were administered ip in rats (Pratt). [c]No stimulation; depression was present. [d]Oral administration in rats (Pratt). [e]Reference 2. [f]Reference 3. [g]Reference 6.

Table II. Diuretic Activity[a,b]

Dose, mg/kg po	% excreted	Effect Δ% excreted[d] (test – control)
		
Control	60[c]	
15	64	4
30	70	10

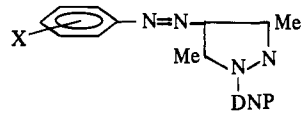
[a]See footnote *a*, Table I. [b]Eight rats per group hydrated with 25 ml/kg of 0.9% NaCl po; length of test, 5 hr. [c]Experience has fixed the control % excretion value at 60 for rats. [d]Reference 7.

Table III. Activity against *Eimeria tenella*

No.	X	Mp, °C	Activity[a,d]
	 DNP		
1	2,5-Cl_2	213–214[c]	*b*
2	2-NO_2	216–218[c]	*b*
3	4-Cl	254–255[c]	*b*

[a]0.05% dose level. [b]Inactive. [c]Reference 5. [d]Reference 8.

Table IV. Antiviral Activity[a,f]

No.	X	Mp, °C	Respiratory syncytial long T[c,e]	A[d,e]	Rhino virus 1059 T[c,e]	A[d,e]	Rhino virus 33342 T[c,e]	A[d,e]
	 DNP							
1	2-NO_2	*b*	0	0	1	0	1	0
2	3-NO_2	*b*	0	0	0	0	1	0

[a]*In vitro*. [b]See footnote *d* of Table II. [c]Cell toxicity. [d]Plaque inhibition. [e]0 = No plaque inhibition; 1 = <10 mm radius zone; 2 = >10 mm radius zone. [f]Reference 9.

ities in rats (Tables I and II, respectively), anthelmintic activity[8] in chickens (Table III), and antiviral activity[9] (Table IV).

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3,3[1]-Ethylenediglutarimide as a Potential Tumor Inhibitor

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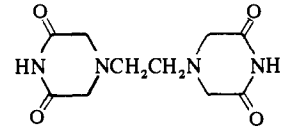
The antitumor activity shown[1] by 4,4[1]-ethylenedipiperazine-2,2[1],6,6[1]-tetrone (1) prompted us to synthesize the corresponding carbon isostere 8.



Dr. S. B. Carter of these Laboratories found that 8 was inactive against the tumor sarcoma 180.

Experimental Section†

2,5-Bis(hydroxymethyl)-1,6-hexanediol (3). A soln of 67.5 g of tetraethyl 1,1,4,4-butanetetracarboxylate (**2**)[2] in 250 ml of Et_2O was added dropwise under N_2 to a stirred soln of 30 g of LAH in 1.5 l. of Et_2O at 0°. The mixt was stirred at room temp for 30 min, refluxed for 2.25 hr, cooled to 0°, and treated, cautiously and in turn, with 30 ml of H_2O, 90 ml of 15% aq NaOH, and finally with 30 ml of H_2O. Solid material was filtered off. Evapn of the filtrate gave a trace of residue. The cake was digested 5 times with 1.5-l. portions of boiling Me_2CO, and the extracts, containing much diacetone alcohol, were evapd *in vacuo*. The residual oil was triturated with Me_2CO and the solid (8.8 g) obtd was combined with 29.3 g of similar material from 3 identical expts, then boiled with 2 l. of Me_2CO.

A colorless by-product, probably polymeric, did not dissolve and crystd from MeOH to give 3.36 g of prisms; mp 222–223°. *Anal.* $(C_5H_{10}O_2)_n$ C, H.

†Melting points are corrected and were determined with a Kofler hot-stage apparatus. Nmr spectra were measured in $CDCl_3$(TMS) with a Varian A60 spectrometer. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.