Table II. Titration of Anthelmintic Activity of 17

	Dose,[a] mg/kg	Percentage reduction		
		A. suum	*S. obvelata*	*H. nana*[b]
	300	92	100	100
	100	90	100	100
	50	84	100	100
	25	72	99	100
	12.5	26	54	35
Tetramisole	300	Toxic		
	100	99	73	Inactive
	50	100	Inactive	
	25	100		
	12.5	53		
Bunamidine	300	Toxic		
	100	11	Inactive	100
	50	Inactive		59
	25			30
	12.5			13

[a] *A. suum* and *S. obvelata* infected mice were dosed twice a day for 5 days. [b] *H. nana*–taeniacidal activity was detd by use of *H. nana* as described previously by Culbertson[4] using modified techniques of Steward[5] and Standen.[6] In addn, on the 13th day of infection, to the end of testing, the mice were given hydrocortisone (USP–microfine, Merck & Co., Inc., Rahway, N. J.) at the rate of 25 mg/l. in their drinking water to prevent natural worm elimination. Medication was administered twice a day for 3 days (days 18 to 20 inclusive of the infection). Necropsy was performed on infection day 22 and worm counts were made by pressing the small intesting between glass plates and scanning at X7 magnification.

Anthelmintic Testing. The anthelmintic activity of the compounds prepared in this work and of the comparison drugs tetramisole and bunamidine are shown in Table I.[2,3] The most active compounds are those bearing a hydroxyalkylamino substituent in the 4 position. However, no real structure-activity trends are apparent among the hydroxyalkylamino-substituted quinazolines. By normal titration of activity, the most consistently active compound of the series against the two helminthic parasites is **17**. A titration of its anthelmintic activity against *Ascaris suum* and *Syphacia obvelata* and also against the tapeworm *Hymenolepis nana* is shown in Table II. The activities of the reference drugs are also included in the table for comparison purposes.

Experimental Section

Melting points were determined in open capillary tubes using a Mel-Temp melting point apparatus and are uncorrected.

2,3-Dihydro-2-(5-nitro-2-thienyl)quinazolin-4(1*H*)-one (3a). A soln of 5-nitro-2-thiophenecarboxaldehyde (157 g, 1.0 mole) in EtOH (1 l.) was warmed on a steam bath and treated with concd HCl (20 ml). A warm soln of anthranilamide (136 g, 1.0 mole) in EtOH (500 ml) was added with rapid stirring. The stirred reaction mixt was heated under reflux for 1 hr, then chilled in ice, and filtered. After thorough washing with cold aq EtOH and air drying, the product weighed 227 g (83%). An analytical sample was obtd as yellow needles, mp 219–221°, following several recrystns from EtOH (charcoal). *Anal.* ($C_{12}H_9N_3O_3S$) C, H, N.

6-Chloro-2,3-dihydro-2-(5-nitro-2-thienyl)quinazolin-4(1*H*)-one (3b) was prepd as described for **3a**, using 2-amino-5-chlorobenzamide. The crude yield was 67%. Analytically pure product was obtd by recrystn from EtOH, mp 196–198°. *Anal.* ($C_{12}H_8ClN_3O_3S$) C, H, N.

2-(5-Nitro-2-thienyl)quinazolin-4(3*H*)-one (4a). A mixt of **3a** (245 g, 0.89 mole) and *p*-benzoquinone (120 g, 1.1 moles) in EtOH (1.5 l.) and DMF (600 ml) was refluxed with stirring for 6 hr. After chilling, the product was removed by filtration and washed thoroughly with EtOH, then Et_2O. The crude yellow product weighed 160 g (66%). Recrystn from aq DMF provided an analytical sample as yellow needles, mp 350–351°. *Anal.* ($C_{12}H_7N_3O_3S$) C, H, N.

6-Chloro-2-(5-nitro-2-thienyl)quinazolin-4(3*H*)-one (4b) was prepd in 71% yield from **3b** according to the procedure described for **4a**. The crude product was recrystd from DMF to give yellow needles, mp 349–351°. *Anal.* ($C_{12}H_6ClN_3O_3S$) C, H, N.

4-Chloro-2-(5-nitro-2-thienyl)quinazoline (5a). A mixt of **4a** (68 g, 0.25 mole) and PCl_5 (68 g, 0.33 mole) in $POCl_3$ (500 ml) was refluxed with stirring until all the material went into soln. The reaction mixt was heated for an addnl 15 min and then cooled, and the pptd product was removed by filtration. After thoroughly washing with hexane and drying, the product weighed 65 g (89%). Recrystn from $MeNO_2$ gave yellow crystals, mp 187–189°. *Anal.* ($C_{12}H_6ClN_3O_3S$) C, H, N.

4,6-Dichloro-2-(5-nitro-2-thienyl)quinazoline (5b) was prepd in 87% yield from **4b** as described for **5a**. Recrystn from $MeNO_2$ gave pure material, mp 167–169°. *Anal.* ($C_{12}H_5Cl_2N_3O_3S$) C, H, N.

4-(2-Hydroxyethylamino)-2-(5-nitro-2-thienyl)quinazoline (17). A mixt of **5a** (50 g, 0.17 mole) and ethanolamine (24 g, 0.40 mole) in DMF (500 ml) was heated on a steam bath with stirring for 5 hr. After treatment with charcoal, the hot soln was filtered, and the filtrate poured onto ice. The pptd product weighed 45 g (83%) and was recrystd from EtOH to give an analytical sample as yellow crystals.

The remaining compds in Table I were prepd in a similar manner from **5a** or **5b** and the appropriately substituted amine or hydrazine.

Biological Method. *A. suum.* The method was described previously.[1] *S. obvelata.* Natural infections of this parasite were used for drug activity evaluation. The groups of mice used for the *A. suum* tests were concomitantly observed for *S. obvelata.* Worm counts were made by removal of the mouse caecum, splitting it open in a small dish containing 10 ml of physiological saline and incubating at 37° for 1 hr. Each dish was then filled with 10–20 ml of saturated $ZnSO_4$ soln and the worms floating on the surface were counted at X7 magnification by use of a "stereozoom" microscope (Bausch and Lomb).

Compd effectiveness was detd as a percentage reduction in the manner described previously.[1]

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Effects of *S*-(+)- and *R*-(−)-3,4,Dimethoxyphenylisopropylamines in the Rat

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While much information is available about the structure-activity relationships of one-ring psychotomimetics related to mescaline,[1] no data on the relative potency of optical isomers has been reported. Since a cross-tolerance exists between LSD and mescaline-type compounds, it has been suggested that they act *via* the same mechanism. Both compounds are β-arylethylamine derivatives. While most litera-

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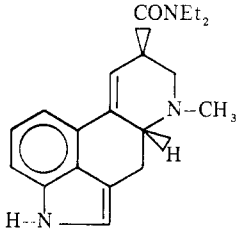
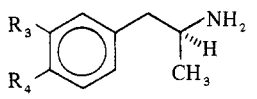
ture views LSD as having the ethylamine side chain arising from the 3 position of the indole nucleus, a closer structural analogy exists when the side chain is joined at the 4 position.[2,3]

If this is a valid analogy in evaluating optically active mescaline-type agents, one might anticipate *a priori* that the isomer whose absolute configuration was the same as the C-5 position of (+)-LSD (natural, 5*R*, 8*R*)[4,5] (**1**) would possess the psychotomimetic activity. The absolute configurations of phenylisopropylamines are *S*-(+) (**2**) and *R*-(−) (**3**), respectively.[6] Schrecker[7] proved by total synthesis that (+)- and (−)-3,4-dimethoxyphenylisopropylamines (3,4-DMA) are *S*-(+) and *R*-(−), respectively. On such a stereochemical basis, the *R*-(−)-3,4-DMA would be expected to have the mescaline-like actions, while its enantiomer, *S*-(+)-3,4-DMA, would be expected to be much less active. In contrast, unsubstituted phenylisopropylamine has its central effects primarily in the *S*-(+) isomer.



1



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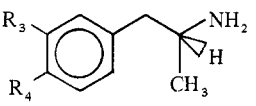

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Pharmacology. The compounds and quasiracemate mixtures were tested for an effect on the conditioned avoidance response in the rat as detailed previously.[8] Tables I and II summarize the results of the testing.

At 12.5 mg/kg racemic 3,4-DMA is reported to be equivalent to 25 mg/kg of mescaline in its effects on the rat.[9] The similarity of effects was confirmed in our laboratories.[8] The characteristic effect of racemic 3,4-DMA and mescaline was not observed with either (+)- or (−)-3,4-DMA at doses from 4 to 16 mg/kg. Each enantiomer caused an effect similar to amphetamine, enhanced performance at low doses and toxicity at higher doses. The *R*-(−) isomer was approximately one-third as active as the *S*-(+) isomer.

Since neither enantiomer was able to produce the characteristic effect in rats, it may be necessary for both enantiomers to be present. This hypothesis was tested by simultaneously administering (−)-3,4-DMA · HCl (6–12 mg/kg) and (+)-amphetamine sulfate (1–4 mg/kg). It was found that such quasiracemates could qualitatively reproduce the effect of racemic 3,4-DMA in the rat. The relationship between these studies and psychotomimetic effects in humans is unclear, since the hallucinogenic activity of 3,4-DMA in humans is questionable.[1,‡] However, the results indicate that further work on the effects of psychotomimetic phenylisopropylamine isomers is warranted.

Experimental Section

The 3,4-DMA di-*O*-(*p*-toluoyl)-*d*- or -*l*-tartrate salt was prepared by the method of Kidd,[10] followed by repeated recrystn from 95% EtOH to const sp rotn. The free base was liberated from the complex and neutralized with HCl, and the salt was recrystallized from *i*-PrOH–Et_2O.

‡A. T. Shulgin, personal communication.

Table I. Effect of Enantiomers in the Rat

Drug	Dose	Effect
(+)-3,4 DMA	0.55	None
	2.1	None
	8.1	Amphetamine-like
	16.2	Onset of amphetamine-like toxicity
(−)-3,4-DMA	6.25	Amphetamine-like (similar to 1 mg/kg of amphetamine sulfate)
	25.0	Amphetamine-like (similar to 4 mg/kg of amphetamine sulfate)
	50.0	Onset of amphetamine-like toxicity

Table II. Effect of Quasiracemate Mixtures in the Rat

Dose, mg/kg		
(−)-3,4 DMA · HCl	(+)-Amphetamine sulfate	Effect
6.25	1.0	Activity similar to 12.5 mg/kg of (±)-3,4-DMA
12.5	1.0	Activity and toxicity similar to ~50 mg/kg of (±)-3,4-DMA
25.0	1.0	Activity and toxicity similar to ~50 mg/kg of (±)-3,4-DMA. Followed by death
8.0	4.0	Activity and toxicity greater than that from 50 mg/kg of (±)-3,4-DMA. Followed by death.

Conditioned Avoidance Studies in Rats. Detailed procedure was published previously.[8]

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4-Amino-2-buten-1-ol Esters†

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In the general structure for the toxic pyrrolizidine alkaloids (**1**) it was noted that the essential feature for toxicity was the presence of an allylic alcohol esterified with a

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