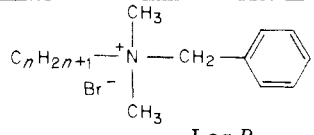
Table II. Equations Correlating the Micelle Formation Tendency, Partition Coefficient, and Protein Binding Constant with the Chain Length and the Surface Area

Eq		n^a	r^b	s^c	F	Sign. level, %
	Micelle Formation					
1	Log 1/CMC = 0.369 (±0.009)[d] n − 2.251 (±0.134)[d]	11	0.999	0.045	$F_{1,9}$ = 7968	99.99
2	Log 1/CMC = 18.425 (±1.386) log SA − 24.372 (±2.052)	11	0.995	0.134	$F_{1,9}$ = 904	99.99
3	Log P_{oct} = 0.450 (±0.093) n − 4.094 (±0.832)	6	0.989	0.374	$F_{1,9}$ = 179	99.95
	Protein Binding					
4	Log K = 0.133 (±0.067) n − 5.857 (±0.963)	11	0.830	0.328	$F_{1,9}$ = 19.9	99.5
5	Log K = −0.019 (±0.017) $(n)^2$ + 0.640 (±0.466) n − 9.117 (±3.077)	11	0.910	0.259	$F_{1,8}$ = 6.37	95.0
6	Log K = 6.902 (±3.107) log SA − 14.214 (±4.601)	11	0.859	0.301	$F_{1,9}$ = 25.3	99.9
7	Log K = −33.963 (±84.724) $(\log SA)^2$ + 107.049 (±248.43) log SA − 87.549 (±181.811)	11	0.611	0.494		N.S.

[a] The number of data points used in the correlation. [b] The correlation coefficient. [c] The standard deviation of the correlation. [d] 95% confidence limit.

Table III. Octanol-Water Partition Coefficients and the Chain Length of Quaternary Ammonium Compounds



Chain length n	Log P Obsd[a]	Log P Calcd[b]
2	−3.38	−3.19
4	−1.85	−2.29
6	−1.53	−1.39
8	−0.29	−0.49
10	−0.08	0.41
16	3.28	3.11

[a] From ref 4. [b] Calculated from eq 3.

not unlimited. Since there is a collinearity between log P and n (see eq 3), a similar parabolic equation should be obtained if one uses log P instead of n. Due to the lack of reliable experimental log P values for the quaternary ammonium compounds examined, we elect to use n for the correlation. When less discriminatory techniques like dialysis are used, additional secondary sites may also be taken into account and the cut-off point may then be moved upward. This may consequently give rise to the linear equation frequently observed for drug–albumin interactions. It has been shown that differences in solution conditions and in albumin purity may affect the binding data significantly.[14,15]

Fatty acids[16,17] and long-chain alkyl sulfates and sulfonates[18,19] also show a maximum in their binding energies following interaction with bovine serum albumin.

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A Potential Amphetamine Antagonist, Adamantanamine Derivative of Fluphenazine[1]

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Fluphenazine adamantylcarbamate was prepared and tested for antagonism of amphetamine-induced increase in spontaneous motor activity and shock avoidance response in rats. This compound exerts weaker antiamphetamine action than fluphenazine.

Neuroleptic drugs can effectively inhibit the agitation and stereotyped gnawing behavior induced in rats by amphetamine.[2] The antagonism of amphetamine hyperthermia by several neuroleptic drugs in rats[3a] and more specifically by pimozide in rabbits[3b] has been reported. An undesirable side effect of neuroleptic drugs is the production of extrapyramidal, Parkinson-like symptoms which probably arise from drug action on the corpus striatum.[4]

Table I. Effects of Pretreatment with Fluphenazine Adamantanylcarbamate Dihydrochloride (1) and Fluphenazine Dihydrochloride on *d*-Amphetamine-Induced Increased Spontaneous Locomotor Activity

	Percent of control	
Day	1	Fluphenazine
1	55.7 ± 6.1	5.0 ± 2.4[b]
2	51.9 ± 36.7[a]	8.4 ± 2.3[b]
4	71.2 ± 8.9	41.4 ± 9.0[c]
7	101.2 ± 11.2	43.1 ± 8.9[c]

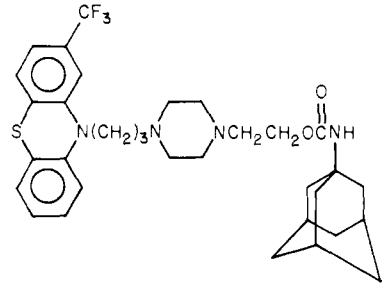
[a] Significantly different from the amphetamine control group, $p < 0.05$. [b] $p < 0.001$. [c] $p < 0.01$. Each value represents the mean (±SEM) of six rats.

Table II. Effects of Fluphenazine Adamantanylcarbamate Dihydrochloride (1) on the Spontaneous Locomotor Activity

Day	% of saline control
1	52.8 ± 6.2
2	47.8 ± 8.0[a]
4	29.6 ± 9.4[a]
7	26.6 ± 4.1[a]

[a] $p < 0.01$. Each value represents the mean (±SEM) of six rats.

Adamantanamine (Amantadine, Symmetrel) has been shown clinically to improve akinesia, rigidity, and tremor in patients with Parkinson's disease.[5] Moreover, the compound appears to antagonize certain drug-induced extrapyramidal symptoms in man.[6] The structure of the compound under study, fluphenazine adamantanylcarbamate (1), contains both fluphenazine and adamantanamine moieties, and it would be anticipated that hydrolysis of the carbamate linkage to release the parent neuroleptic drug and adamantanamine might provide dual action such as the blockade of the receptors for amphetamine activity and the alleviation of extrapyramidal symptoms usually caused by known neuroleptic drugs. This study intends to compare the amphetamine antagonist properties of 1 and fluphenazine as evaluated by antagonism to the effects of amphetamine.



1

The adamantanylcarbamate 1 was prepared by refluxing fluphenazine with adamantanyl 1-isocyanate in xylene. In a previous experiment, 1 was obtained in considerably lower yield by first treating fluphenazine with phosgene in benzene to form the corresponding chloroformate, followed by reacting with adamantanamine in ethyl acetate to give 1. Tables I and II show the antiamphetamine activities of 1 as determined by its effects of the *d*-amphetamine-induced increases in both spontaneous locomotor activity and shock avoidance responses. These two aspects of amphetamine action were chosen for testing inasmuch as the effects of amphetamine on locomotor activity and avoidance behavior are well known. The avoidance testing was conducted 30 min postinjection in order to minimize responses attributable to the increase in motor activity. A significant blockade ($p < 0.05$) of amphetamine-induced stimulation was observed 2 days after injection of 1 (Table I), while the antagonism of amphetamine's shock avoidance responses lasted for at least 4 days (Table III). However, 1 exhibited weaker activities than the parent compound, fluphenazine, in the two tests performed. Four days after receiving fluphenazine, animals still appeared to be sedated; no catalepsy was observed. Animals injected with 1 showed slight sedation for 2 days following drug treatment. Compound 1 alone exhibits depressant properties (Table II); however, it also increases the shock avoidance response similar to amphetamine (Table IV). This is in contrast to fluphenazine, which lowers both spontaneous locomotor activity and the avoidance response as compared to saline.[7] Adamantanamine has previously been reported to also be active in this respect.[8] Whether the adamantanamine moiety of 1 or the compound 1 as a whole entity is causing this effect has not been determined.

Table III. Effects of Pretreatment with Fluphenazine Adamantanylcarbamate Dihydrochloride (1) and Fluphenazine Dihydrochloride on *d*-Amphetamine-Induced Increase in Avoidance Response

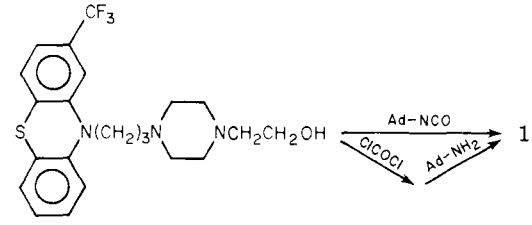
	1		Fluphenazine	
Day	Av no. of avoidance responses	% of control	Av no. of avoidance responses	% of control
1	6.2 ± 2.9[b]	16.7 ± 7.8	0[b]	0
2	17.5 ± 1.7[c]	47.0 ± 4.6	1.0 ± 0.32[b]	2.9 ± 0.9
4	23.0 ± 4.2[a]	61.8 ± 11.3	1.0 ± 1.0[b]	2.9 ± 2.9
7	34.4 ± 4.6	92.5 ± 12.4	1.6 ± 0.81[b]	4.7 ± 2.4

[a] Significantly different from the amphetamine control group, $p < 0.05$. [b] $p < 0.001$. [c] $p < 0.01$. Each value represents the mean (±SEM) of five rats.

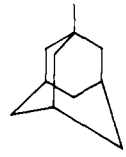
Table IV. Comparison of the Effects on Avoidance Response of Fluphenazine Adamantanylcarbamate Dihydrochloride (1) and *d*-Amphetamine

	Av no. of avoidance responses		% of *d*-amphetamine responses[a]
Day	1	*d*-Amphetamine	
1	26.6 ± 5.2	37.2 ± 2.9	71.5 ± 14.0
2	30.6 ± 6.7		82.2 ± 18.0
4	33.8 ± 3.8		90.9 ± 10.2
7	26.8 ± 6.2		72.0 ± 16.7

[a] None of the values were significantly different from *d*-amphetamine. Each value represents the mean (±SEM) of six rats. A group of animals injected only with saline showed an average number of avoidance responses of 16.6 ± 4.9 (44.6 ± 13.1% of *d*-amphetamine avoidance response, $p < 0.01$).



fluphenazine

Ad =  (adamantanyl)

Experimental Section

The melting point was determined in a "Mel-Temp" apparatus and is uncorrected. Elemental analyses, indicated by symbols of the elements, were within ±0.2% of the theoretical values. The ir spectrum was consistent with the proposed structure.

4-[3-(2-Trifluoromethyl)phenothiazin-10-yl]propyl-1-piperazineethyl *N*-(1-Adamantyl)carbamate Dihydrochloride (Fluphenazine Adamantylcarbamate, 1). A mixture of fluphenazine[9] [4-[3-(2-trifluoromethyl)phenothiazin-10-yl]-propyl-1-piperazineethanol, 3.06 g, 7 mmol], 1-adamantanyl isocyanate[10] (1.25 g, 7 mmol), and 150 ml of xylene was stirred and heated at reflux for 36 h. The reaction mixture was allowed to cool to room temperature and filtered to remove suspended solids, and the xylene was removed in vacuo. The residue, dissolved in the minimum of benzene, was placed on a silica gel column (2.5 × 35.5 cm). The carbamate was then eluted with $CHCl_3$. The elution was followed by silica gel TLC ($CHCl_3$–EtOH, 18:1). The fractions containing the carbamate were combined and the $CHCl_3$ was removed in vacuo leaving 2.13 ml of yellow oil. A solution of the oil in absolute EtOH was added to ether saturated with HCl. The resulting precipitate was filtered and dried to give 1.64 g of 1 as a white powdered dihydrochloride salt: mp 220–223° dec; yield, 42% based on recovered fluphenazine dihydrochloride (0.7 g). Anal. ($C_{33}H_{43}Cl_2F_3N_4O_2S$) C, H, N.

Spontaneous Locomotor Activity. Eighteen male Sprague–Dawley rats housed individually were divided into three groups. Two groups of animals were injected subcutaneously with either 0.1 mmol of 1·2HCl (70 mg/kg) or fluphenazine dihydrochloride (50 mg/kg) in sesame oil; the third group received the vehicle only (sesame oil). After the initial injections, 2 mg/kg of *d*-amphetamine in saline was administered on the first, second, fourth, and seventh day to all three groups of animals, and the motor activity of the rats was measured immediately after each injection for 30 min with an electronic motility meter (Motron-Produkter, Stockholm, Sweden, Model 40Fc). Results are expressed as the percentage counts of the experimental group in relationship to the vehicle control group. Each animal's motility was measured at the same time of day to minimize the diurnal effect.

Shock Avoidance Responses. A shuttle box was used for behavioral testing. Each trial began with the onset of light and tone (conditioned stimulus) followed in 5 s by an electronic shock (unconditioned stimulus). The electric shock of 0.8 mA (ac, 60 cycle) was delivered through a scrambler to the grid floor, while the light and tone continued without interruption. A crossing by the animal from one end to the other tilted the box and terminated the shock; crossing before the onset of shock constituted the avoidance response. The onset of light and tone was on a variable interval 60-s schedule. Termination of the trial also resulted if the animal did not respond to the shock within 30 s of its onset.

Fifty rats in groups of five were used for the study. Each group of animals were pretreated subcutaneously with 0.1 mmol of 1·2HCl or fluphenazine dihydrochloride 1, 2, 4, or 7 days prior to the administration of 2 mg/kg of *d*-amphetamine sulfate. A control group of animals received only amphetamine with no pretreatment with the test drugs. The animal was placed on one end of the shuttle box 30 min after the injection of amphetamine. None of the animals were used for more than one session. All sessions were conducted at the same time of day and counter-balanced according to pretreatment time. The number of avoidance responses in a total of 50 trials was recorded, and the percentage of avoidance responses for the experimental group in relationship to the amphetamine control group was calculated.

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2-Azabicyclo[2.2.2]octane Analogues of the Prodine Analgetics

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The synthesis and analgetic activity of analogues of prodine-type analgetics in which the conformation of the piperidine ring is restricted in the boat form using the 2-azabicyclo[2.2.2]octane nucleus are reported. One of these analogues, 2-methyl-6-*trans*-phenyl-6-*cis*-propionoxy-2-azabicyclo[2.2.2]octane (**3**), showed significant analgetic activity (ED_{50} = 3.1 mg/kg).

Conformational requirements at the analgetic receptor have been studied extensively and theories regarding the nature of the receptor have been postulated. By using the morphine structure as a mirror, Beckett and Casy[1] published a detailed description of the analgetic receptor. An analysis of the meperidine molecule in relation to this receptor led to the conclusion that an axial-phenyl arrangement was necessary for this drug to interact with the receptor. These postulations have stimulated a great deal of research and newer theories regarding the nature of the analgetic receptor have been developed.[2] The use of rigid drug models to examine the stereochemical requirements in 4-phenylpiperidine analgetics has led to conflicting results concerning the conformational requirements for the phenyl group.[3,4] Casy[5] has used the results of the studies on the preferred conformation of various piperidine analgetics in water solution to predict the conformational requirements for analgetic activity. It was concluded that the preferred conformation of the piperidine ring in analgetics of this class is the skew-boat form. Further examination of the prodine-type derivatives of 1,2,5-trimethylpiperidine indicated that the isomers best able to