(19.0), 296 (sh) (15.8); MS (EI), m/z 499 (M^+); ^1H NMR (Me_2SO-d_6) δ 1.79 (s, 5-CH_3), 2.25 (m, 2 $H_{2'}$), 3.0-4.0 (br, H_2O), 4.25 (d, $H_{3'}$, $H_{4'}$, ICH_2), 6.38 (t, $H_{1'}$), 7.9 (m, phenyl protons), 8.06 (s, H_6), 10.6 (s, NHCO), 11.4 (s, 3 NH of pyrimidine). Anal. ($C_{18}H_{18}IN_3O_6 \cdot H_2O$) C, H, N.

5'-[[4-(Bromoacetyl)benzoyl]amino]-5'-deoxythymidine (16). A suspension of 4-(bromoacetyl)benzoic acid[15] (300 mg, 1.23 mmol) in benzene (5 mL) and $SOBr_2$ (2 mL) was refluxed under N_2 for 1.75 h to give a clear solution, which was evaporated to dryness in vacuo and evaporated with toluene (2 × 4 mL) to remove traces of $SOBr_2$. A solution of the acyl bromide in DMAC (5 mL) was added dropwise over 20 min to an ice-cooled, stirred mixture of 5'-amino-5'-deoxythymidine[10] (15; 282 mg, 1.17 mmol); anhydrous, finely powdered NaBr (2.00 g, 19.4 mmol); and *N,N*-diisopropylethylamine (220 μL, 1.23 mmol) in DMAC (15 mL). The suspension was stirred for 30 min at 25 °C, filtered, and evaporated to dryness under high vacuum. The gummy residue was triturated with Et_2O (3 × 10 mL), followed by H_2O (2 × 10 mL). A solution of the dried solid in a minimum of hot MeOH was applied to four Brinkmann silica gel plates (20 cm × 20 cm × 2 mm) and developed with $CHCl_3$–MeOH (9:1). The product band was extracted with EtOH (300 mL), and the extract was evaporated to dryness. The residue was washed with Et_2O and then H_2O and dried in vacuo (P_2O_5): yield 142 mg (26%); mp 210 °C dec (Kofler-Heizbank); TLC $CHCl_3$–MeOH (9:1); UV λ_{max} ($\epsilon \times 10^{-3}$) at pH 1, 259 nm (23.6); at pH 7, 259 (24.0). Anal. ($C_{19}H_{20}BrN_3O_6$) C, H, N.

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Registry No. 1, 5983-15-3; 2, 89299-46-7; 3, 89299-47-8; 4, 89254-77-3; 5, 80647-12-7; 6, 80647-13-8; 7, 80647-14-9; 8, 89196-50-9; 9, 89196-51-0; 10, 3544-99-8; 11, 80647-05-8; 12, 80647-04-7; 13, 89196-52-1; 14, 89196-53-2; 15, 25152-20-9; 16, 89196-54-3; 3'-*O*-acetylthymidine, 21090-30-2; triphenylacetonylphosphorane, 89196-55-4; triphenylchloroacetonylphosphorane, 89196-56-5; 2-(*p*-aminophenyl)-2-(chloromethyl)-1,3-dioxolane, 2705-89-7; 4-(bromoacetyl)benzoic acid, 20099-90-5; 4-(bromoacetyl)benzoyl bromide, 89196-57-6.

Amnesia-Reversal Activity of a Series of *N*-[(Disubstituted-amino)alkyl]-2-oxo-1-pyrrolidineacetamides, Including Pramiracetam†

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A series of *N*-[(dialkylamino)alkyl]-2-oxo-1-pyrrolidineacetamides was synthesized. The title compounds reversed electroconvulsive shock (ECS) induced amnesia in mice when administered subsequent to the ECS treatment and were inactive in a general observational test for central nervous system (CNS) activity. Active compounds exhibited an inverted U-shaped dose–response curve. Among the compounds with the broadest dose–response curve, as well as the most potent, were those with the *N*-[2-[bis(1-methylethyl)amino]ethyl] or 2,6-dimethylpiperidinoethyl residues as amide substituent. The *N*-(dialkylamino) substituent markedly enhances amnesia-reversal activity, with ethylene providing the optimal chain length. *N*-[2-[Bis(1-methylethyl)amino]ethyl]-2-oxo-1-pyrrolidineacetamide *N*-(dialkylamino) substituent was selected for preclinical toxicological evaluation, assigned the investigational number CI-879 and the U.S. adopted name (USAN) pramiracetam. Pramiracetam demonstrated a wide margin of safety in animals and was well tolerated in normal human volunteers. It has shown encouraging activity in an open label trial in patients with primary degenerative dementia (PDD or senile dementia of the Alzheimer's type).

Congnitive dysfunctions occur in persons of all ages. They may result from disease, accidents, injury, developmental defects, or aging. Recent increases in average longevity and the accompanying rise in the number of elderly persons, however, have made the development of new treatments for age-related cognitive impairments a particularly urgent goal of medical science. An agent that reverses or ameliorates cognitive impairments, especially in aged patients, would be of enormous medical, social, economic, and scientific importance.[1,2]

Cognitive impairments in the elderly were long attributed to atherosclerotic disruption of cerebral blood flow. Recent evidence indicates, however, that as few as 10% of senile patients have such circulatory disorders.[3,4] The majority suffer from senile dementia of the Alzheimer's type (SDAT). The primary symptoms of SDAT are as follows: (1) forgetfulness, poor memory, and memory loss; (2) confusion and disorientation in space and/or time; (3) poor attention or distractability; (4) affective disturbances (agitation, depression, apathy, and lethargy).[5]

Drugs reported to treat the cognitive impairments of the elderly have shown only limited benefits and therefore are not widely accepted.[6,7] Many useful reviews covering drug effects upon cognition and neurotransmitters involved in cognition have been written.[8-12]

† This paper has been presented in part, see: "Abstracts of Papers", 186th National Meeting of the American Chemical Society, Washington, DC, Aug 28–Sept 2, 1983; American Chemical Society: Washington, DC, 1983, Abstr MEDI 70.

‡ Chemistry Department.

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0022-2623/84/1827-0684$01.50/0

Table I. Amnesia Reversal Produced by Various CNS-Active Drugs

drug[b]	amnesia reversal, %, at the following mg/kg doses									
	0.31	0.63	1.25	2.5	5.0	10	20	40	80	160
d-amphetamine	10	15	40	*c*	*c*					
caffeine	10	5	0	10	0					
chlorpromazine	15	20	10	0	0					
cocaine	15	10	10	15	10					
imipramine					10	10	5	15		
lithium chloride		15	10	15	15	30	25	30	20	
metrazol				15	20	10	15	15		
nicotine	20	5	0	5	0					
metrazol + nicotinic acid					0		0		9	
pemoline				20	20	56	44	56		
PRL-8-53					5	10	10	5	10	
picrotoxin	5	5	5	5	5					
piracetam[d]					10		20		15	
ritalin			15	10	15	10	15			
tranylcypromine			10	5	15	10				
zarontin						15	12	10	10	10

[a] Results in this table were calculated by subtracting the percent correct scores of control group from those of the drug group. [b] Drugs administered ip 1 h prior to retention testing. [c] Not testable, mice too excited. [d] Amnesia-reversal activity was seen with this drug using very short (0.2 s) ECS duration.

The methodological and conceptual problems encountered in searching for a compound to reverse or ameliorate the early symptoms of senility are formidable. A common complaint in this area is the lack of reliable test methods.[13] The success of a drug-discovery program in this area is as dependent upon the animal test models selected as it is upon the types of compounds synthesized for testing.

We earlier reported on an agent, CI-844, that improved memory for a single-trial passive avoidance task in mice.[14] Subsequent studies found positive effects with this agent in other animal models of cognition.[15-17] Using modifications to our earlier test methods which uncovered CI-844, we have continued our search for new compounds to improve impaired cognition.

This report describes results from our search for a drug for the treatment of the early symptoms of senility. Described below are the rationale, test methods, and structure–activity relationships of a series of compounds that led to the identification of a new potential therapeutic entity for the treatment of cognitive disorders in the early senile patient, pramiracetam (CI-879).

Pharmacology. Since no drugs have currently been shown to significantly improve impaired cognition in elderly patients, it was not possible to develop an animal model or biological test system on the basis of the activity of a prototype drug. The methods we employed in our search for new cognition activators were, therefore, primarily behavioral. They were selected because they have a degree of face validity.[8]

The testing of new chemical entities for potential cognition-activation properties was conducted in two phases. First, all compounds were evaluated in a general observational test for gross central nervous system (CNS) effects using highly trained observers.[18,19] Those that passed this first test were evaluated for effects upon cognition in mice.

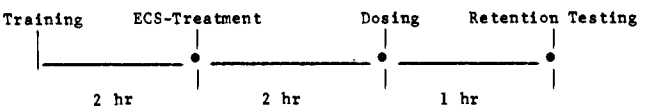

Figure 1. Test sequence for amnesia-reversal procedure.

This initial screening served two purposes. First, it excluded compounds with pronounced toxicity. Second, it identified those compounds with obvious CNS depressant activity that might produce false positives in the subsequent behavioral test procedures. Such compounds were not tested further.

Since our objective was to find treatments for impaired, geriatric patients, many of whom have concurrent illnesses or are in failing health, we searched for compounds with extremely wide therapeutic ratios. Only those compounds that did not produce any appreciable effects, measured using the observational technique, at doses up to 250 mg/kg intraperitoneally (ip) were submitted to the second phase of testing.

Those compounds that were inactive in the general CNS inventory test were studied further for activity in reversing the amnesia produced by electroconvulsive shock (ECS) in mice. Our test program was based on the assumption that an agent that reverses the amnesia for inhibitory avoidance learning produced by ECS in otherwise normal animals might also improve the cognitive functioning of patients experiencing memory loss, confusion, and other symptoms of dementia.

Amnesia and confusion have long been known to occur as side effects of electroconvulsive therapy in humans[20,21] and also after ECS in rodents.[22-24] ECS-induced amnesia has been used extensively to explore the functioning of memory mechanisms and to study the biological basis of memory.[25-27] Numerous studies have reported various

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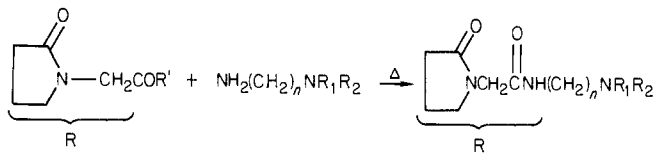
Scheme I



pharmacological agents that alter the effects of ECS upon memory.[28-30]

The behavioral task we employed, single trial inhibitory avoidance learning, was similar to that developed by Essman and Alpern,[31] modified as described by Butler et al.[14] Others have used similar behavioral procedures and ECS-induced impairments to study drug effects upon memory in rodents.[30,32-35]

Briefly, mice were individually trained during a single training trial to avoid entering a darkened chamber. Two hours after training on the task the animals were convulsed by using electroshock in order to produce a retrograde amnesia for the inhibitory avoidance task.

Since we did not want to interfere with initial learning of the task or memory consolidation and were not looking for potential anticonvulsant activity, the experimental compounds were administered 2 h *after* ECS. Therefore, training on the task was followed by a memory consolidation period. Then ECS was administered, followed by a 2-h recovery period, drug administration, a period for absorption of the drug and for the compound to exert its biological activity, and, finally, retention testing (Figure 1).

Many reference agents, a number of which have been claimed to have positive effects upon cognition or have been employed clinically to treat disorders of cognition, were initially tested by these inhibitory avoidance procedures in mice. The results of these studies were generally negative (Table I). Few of the compounds showed any positive effects in reversing ECS-induced amnesia by these procedures. Thus, this test system was found to be generally insensitive to the activity of psychomotor stimulants, antidepressants, anxiolytics, or neuroleptics. Only pemoline showed any significant reversal of ECS-induced amnesia in thse initial studies.

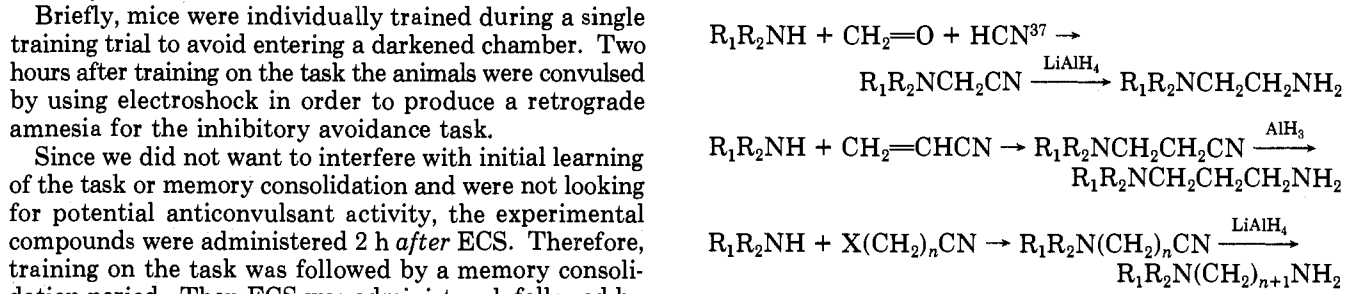
Chemistry. Once a reliable and somewhat specific test system was operational, our goal was to discover a compound that would reverse ECS-induced amnesia over a broad dose range, without central nervous system side effects and with an extremely high therapeutic ratio. A group of compounds was selected from a file containing approximately 86 000 compounds. These were submitted to the general CNS evaluation, and those that met our previously stated requirements were submitted to the inhibitory avoidance test.

One of the compounds selected for study contained a portion of the piracetam molecule as part of its structure. This was *N*-[2-(2,6-dimethyl-1-piperidinyl)ethyl]-2-oxo-1-pyrrolidineacetamide (1, Table II).[36] In contrast to piracetam, which was inactive at 0.5-s ECS (Table I), this compound was found to have good amnesia-reversal activity (A ratings) over a tenfold dose range. This level of activity led us to synthesize a diverse series of related compounds in an attempt to maximize the amnesia-reversing activity and the breadth of the inverted U-shaped efficacy curve.

The compounds were readily synthesized from the appropriately substituted 2-oxo-1-pyrrolidineacetate and the corresponding (dialkylamino)alkylamine as outlined in Scheme I.

A number of the requisite diamines were commercially available or could be readily synthesized as outlined in Scheme II.

Scheme II



Structure–Activity Relationships. Table II is organized so that the compounds are grouped by the length of the carbon spacer. Within these groupings, the smallest substituent on carbon (R) in the 2-oxo-1-pyrrolidineacetamide portion of the molecule is placed first when the amine substituent is the same. In addition, the amino substituents (R_1, R_2) are ordered with the highest molecular weight compounds (also usually the most hindered) first. A few of the compounds were tested at unusual doses, and these results are given in footnotes.

For comparison, Table III contains compounds unsubstituted on the nitrogen atom of the acetamide and compounds on the periphery of the biologically active structure (**42** and **43** to delinate some outer limits of activity).

Several structure–activity relationship (SAR) generalizations can be made from the data in Tables II and Table III: (1) The (dialkylamino)alkyl side chain markedly enhances amnesia-reversal activity. (Compare the majority of the compounds in Table II with the N-unsubstituted compounds **38–40** in Table III.) (2) The optimal separation between the two nitrogen atoms appears to be ethylene, since this separation will tolerate the largest variation in each half of the molecule (Table II). (3) Hindrance around the amine moiety enhances activity, with the diisopropylamino or 2,6-dimethylpiperidino substituent giving the most active compounds. The hindrance can also be on the alkyl side of the nitrogen atom, as evidenced by **14**. (4) Wide variations in substitution at any position of the pyrrolidin-2-one can be tolerated, and activity can be retained. (5) The cyclic lactam must be the pyrrolidin-2-one, as the corresponding piperidin-2-one with a usually effective side chain (**41**) is markedly less active. (6) The acetamide spacing is critical, since the corresponding propionamide (**42**), with a good side chain, is almost inactive. (7) The presence of the inverted U-shaped dose–effect curve can be seen repeatedly in the results in Table II. (8) The best compounds are considered to be those with

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(38) Compound **2** with the 2-(*trans*-2,6-dimethylpiperidinyl)ethylamine side chain is an exception.

the greatest amount of amnesia reversal and the broadest active dose range. These include the following compounds: **1**, **2**, **4**, **8**, **22**, **26**, and **33**.

Preclinical and Clinical Findings. A number of these compounds were submitted for extensive secondary evaluation.[39] These tests, in addition to the marked amnesia-reversal activity, led to the recommendation of *N*-[2-[bis(1-methylethyl)amino]ethyl]-2-oxo-1-pyrrolidineacetamide (**8**) as its 1:1 sulfate salt (CI-879) for preclinical toxicological studies. CI-879 was designated pramiracetam by the USAN council. Compound **8** demonstrated a wide margin of safety in animal species and in normal healthy volunteers.

Poschel et al.[40] have reported that **8** reverses the arousal deficit seen in the quantitative EEG of aged rats. Single neuron studies indicate that these arousal effects arise from increased firing rates from cholinergic neurons having their cell bodies in the medial septal nucleus and the ventral global pallidus. Pugsley et al.[41] have reported that **8** does not bind to muscarinic receptors but at certain doses in vivo causes a significant increase in sodium-dependent high-affinity choline uptake into rat hippocampal synaptosomes. Piracetam was ineffective in the same model. This finding suggests that **8** increases activity of rat cholinergic neurons and may represent the mechanism by which **8** exerts its positive effects upon impaired cognition.

Freedman et al.[42] established that the quantitative EEG effects of **8** in normal volunteers were similar to those of known vigilance-enhancing compounds. Most significantly, Branconnier et al.[43] have found useful activity in an open-label trial of **8** in patients diagnosed as having primary degenerative dementia (PDD), also known as senile dementia of the Alzheimer's type (SDAT). The "significant other" ratings on the IPSC-E scale revealed statistically significant improvement over pretreatment values in the depression, anxiety tension, hostility, and memory factors, as well as the total test score (p values <0.05) in patients receiving 50 and 100 mg/kg, t.i.d., of **8**. Qualitative analysis of the "significant other" evaluations suggest that PDD patients treated with **8** showed an increase in "goal directed" behavior.[43]

Patients receiving higher doses (250 mg/kg, t.i.d.) of **8** in these early, open-label studies did not show the improvement in symptoms noted at lower doses (there were no side effects observed). This effect might have been predicted on the basis of the inverted U-shaped curve seen in animals.

The significance of the inverted U-shaped dose–response curve cannot be overemphasized, since it is central to the concept of a "therapeutic window". Given a compound with minimal toxicity, the tendency in clinical practice is to overdose a patient by using higher than necessary doses to achieve a therapeutic effect. While no overt signs of toxicity may be observed with such a compound, the positive cognitive effects will be lost if the "window" is exceeded.

In conclusion, we have demonstrated the following: (1) A carefully designed behavioral test,[44] ECS-induced amnesia reversal, can be used for the discovery and subsequent refinement of a series of active compounds leading to a new potential therapeutic agent to treat cognitive disorders. (2) A general CNS prescreen will remove compounds with objectionable toxicity and side effects that might otherwise impede behavioral testing and confound results. (3) Compounds exist that will reverse ECS-induced amnesia in rodents over a broad inverted U-shaped dose–response curve. These series show SAR's around the length of the side chain and substitutions on the ring and side chain. (4) Compound **8** reverses ECS-induced amnesia in mice at doses producing no other obvious CNS signs or symptoms. (5) The reversal of ECS-induced amnesia is predictive of activity in other animal models and, perhaps, of therapeutic effects in impaired patients based upon preliminary results with pramiracetam.[40-43]

Experimental Section

Observational Test for CNS Signs. The initial observational test was similar to that described by others[18,19] and was conducted as follows. A group of five male albino mice (Swiss Webster, 20 and 25 g) were injected ip with 250 mg/kg of the test compound and immediately placed into a cylindrical (20-cm deep, 24-cm diameter) wire-mesh cage. For the next hour each animal was rated by a highly practiced observer for the presence or absence of the signs and symptoms of known psychoactive drugs, such as changes in motor activity, grasping, righting reflexes, corneal and pineal reflexes, body posture, lacrimation, straub tail, piloerection, sedation, hypersensitivity, mydriasis, etc. Subsequent groups of mice were administered smaller doses, 125, 63, 31, ..., mg/kg, until no drug effect was observed. Surviving animals were held for 24 h to establish a provisional acute toxicity level.

Amnesia-Reversal Testing. Male mice (Carworth, CF-1 strain, 20–25 g) were divided into five groups of 20 mice each. Each mouse was placed, one at a time, on a small shelf attached to the outside wall of a square chamber (24 × 24 × 18 cm). In this position the mouse was supended in space, and it almost immediately (<5 s) escaped from the shelf through a small hole (3-cm diameter) into the darkened interior of the box.

As soon as the mouse had all four feet within the chamber, the grid floor was electrified, 1.5 mA for 3 s. Once the foot shock was delivered, the mouse was removed from the test chamber and placed into a group holding cage.

Two hours after training, the mice were administered a single electroconvulsive shock, 20 mA for 0.5 s, delivered through spring clips attached to the ears. Immediately after the tonic/clonic convulsion produced by the ECS, the mice were again returned to the group holding cage to recover.

Two hours after ECS, the groups of mice were injected intraperitoneally with one of the doses of the chemical being tested or placebo (vehicle alone). Typically, three doses of the test compound were tested along with base-line and ceiling control groups.

One hour after treatment with the test compound, the mice were individually returned to the small shelf attached to the test chamber in order to measure retention of the inhibitory avoidance response. Any mouse remaining on the shelf for 60 s without entering the box was scored as having remembered the earlier

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(42) Freedman, A. M.; Itil, T. M.; Mukherjee, S.; Dayican, G.; Shapiro, D. M.; Borgen, L. A. Annual Meeting of the American College of Neuropsychopharmacology Dec 15–17, 1982, American College of Neuropsychopharmacology; Nashville; Abstracts.

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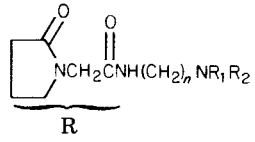
(44) This type of test uses large numbers of animals and is labor intensive; it has appreciable levels of random variation that result in odd (nonlinear) results; the criteria for a successful test are not met more than 50% of the time during certain seasons, resulting in few tests and large amounts of test chemicals consumed.

Table II



no.	n	R	R_1	R_2	emp formula	mp or bp (mmHg), °C	recrystn solvent	yield, %	amnesia reversal, %, at the following mg/kg doses							
									0.63	1.25	2.5	5.0	20.0	80.0	160	320
1	2	H	$CH(CH_3)(CH_2)_3$	$CH(CH_3)$[a]	$C_{15}H_{27}N_3O_2$	93–94.5	EtOAc–pentane	80	10	20	50	70	70	10		
2	2	H	$CH(CH_3)(CH_2)_3$	$CH(CH_3)$[b]	$C_{15}H_{27}N_3O_2$	177–178 (0.07)		71		45	82	48	25	17		
3	2	α-CH_3	$CH(CH_3)(CH_2)_3$	$CH(CH_3)$	$C_{16}H_{29}N_3O_2$	168–170 (0.1)		57				17	42	61		
4	2	5-CH_3	$CH(CH_3)(CH_2)_3$	$CH(CH_3)$	$C_{16}H_{29}N_3O_2$	117–118	cyclohexane	65	33	58	67	55	36	0		
5	2	5,5-$(CH_3)_2$	$CH(CH_3)(CH_2)_3$	$CH(CH_3)$	$C_{17}H_{31}N_3O_2 \cdot {}^1/_2H_2O$	94–94.5	hexane	29					22	44	80	
6	2	5-C_2H_5	$CH(CH_3)(CH_2)_3$	$CH(CH_3)$	$C_{17}H_{31}N_3O_2$	125–126	cyclohexane	63				27	40	27		
7	2	4-Ph	$CH(CH_3)(CH_2)_3$	$CH(CH_3)$	$C_{21}H_{31}N_3O_2$	115–116	cyclohexane	56	0	10	40	67	44	33		
8	2	H	$CH(CH_3)_2$	$CH(CH_3)_2$	$C_{14}H_{27}N_3O_2$	162–164 (0.15)		69	0	30	60	96	82	18		
9	2	5-CH_3	$CH(CH_3)_2$	$CH(CH_3)_2$	$C_{15}H_{29}N_3O_2$	73–74	hexane	33				0	0	56		
10	2	5-C_2H_5	$CH(CH_3)_2$	$CH(CH_3)_2$	$C_{16}H_{31}N_3O_2$	125–125.5	cyclohexane	37	20	20	58	58[c]	17			
11	2	H	$-(CH_2)_5-$		$C_{13}H_{23}N_3O_2$	185–187 (0.5)		79	18	64	45	45	0	0		
12	$CH_2CH(CH_3)$	H	$-(CH_2)_5-$		$C_{14}H_{25}N_3O_2$	77–78	cyclohexane	52				0	0	0		
13	$CH_2CH(CH_3)$	5-CH_3	$-(CH_2)_5-$		$C_{15}H_{27}N_3O_2$	112–113	heptane	71				18	36	45		
14	$CH_2C(CH_3)_2$	H	$-(CH_2)_5-$		$C_{15}H_{27}N_3O_2$	68–69	heptane	44				18	27[d]	55	45	27
15	2	H	$CH_2CH(CH_3)_2$	$CH_2CH(CH_3)_2$	$C_{16}H_{31}N_3O_2$	65–66	*n*-heptane	54		25	33	54[e]	25	15		
16	2	H	C_2H_5	C_2H_5	$C_{12}H_{23}N_3O_2$	156–157 (0.2)		69				15	46	31		
17	2	4-Ph	C_2H_5	C_2H_5	$C_{18}H_{27}N_3O_2$	oil[f]		28	0	0	27	42	0	8		
18	2	H	CH_3	$CH(CH_3)_2$	$C_{12}H_{23}N_3O_2 \cdot {}^1/_2H_2O$	151–152 (0.07)		58				21	0	0		
19	2	H	CH_3	CH_3[g]	$C_{10}H_{19}N_3O_2 \cdot HCl$	135–136	*i*-PrOH–Et_2O	60				50				
20	3	H	$CH(C_2H_5)(CH_2)_3CH(C_2H_5)$[h]		$C_{18}H_{33}N_3O_2$	183–185 (0.2)		53		0	0	42	42	17		
21	3	H	$C(CH_3)_2CH_2CH(CH_3)CH_2CH(CH_3)$		$C_{18}H_{33}N_3O_2$	86–87	diethyl ether	37				9	18	45		
22	3	H	$CH(CH_3)(CH_2)_3CH(CH_3)$		$C_{16}H_{29}N_3O_2$	69–70	*n*-heptane	34		25	33	50	55	100	60	L[i]
23	3	α-CH_3	$CH(CH_3)(CH_2)_3CH(CH_3)$		$C_{17}H_{31}N_3O_2$	167–170 (0.1)		46				8	50	23	30	
24	3	5-CH_3	$CH(CH_3)(CH_2)_3CH(CH_3)$		$C_{17}H_{31}N_3O_2$	165–168 (0.1)		51				0	30	10		
25	3	5,5-$(CH_3)_2$	$CH(CH_3)(CH_2)_3CH(CH_3)$		$C_{18}H_{33}N_3O_2$	85–86	isooctane	29				25	58	50	33	
26	3	5-C_2H_5	$CH(CH_3)(CH_2)_3CH(CH_3)$		$C_{18}H_{33}N_3O_2$	92–92.5	cyclohexane	15		20	50	50	42[i]	42		
27	3	4-Ph	$CH(CH_3)(CH_2)_3CH(CH_3)$		$C_{22}H_{33}N_3O_2$	90–91	hexane	40				0	0	50		

28	3	3-Ph	$CH(CH_3)(CH_2)_3CH(CH_3)$	$C_{22}H_{33}N_3O_2$	198–200 (0.1)	44				50	67	0					
29	3	H	$CH(CH_3)(CH_2)_4$	$C_{15}H_{27}N_3O_2$	180–182 (0.2)	66	0	0	10	33	33	17					
30	3	H	$CH_2CH(CH_3)_2CH_2CH(CH_3)_2$	$C_{17}H_{33}N_3O_2$	179–180 (0.15)	54			0	8	0						
31	3	H	$CH(CH_3)_2$	$CH(CH_3)_2$	$C_{15}H_{29}N_3O_2$	155–156 (0.1)	43	0	9	0	30	20	30				
32	3	5-CH_3	$CH(CH_3)_2$	$CH(CH_3)_2$	$C_{16}H_{31}N_3O_2$	165–168 (0.1)	47				40	0	30	20			
33	3	4-Ph	$CH(CH_3)_2$	$CH(CH_3)_2$	$C_{21}H_{33}N_3O_2$	oil[f]	96	9	0	45	82	55	27				
34	3	H	$(CH_2)_2O(CH_2)_2$		$C_{13}H_{25}N_3O_3$	101–102	60				0	17	58	54	15		
35	3	H	CH_3	CH_3	$C_{11}H_{21}N_3O_2$	157–159 (0.15)	70				31	46	46				
36	4	H	$CH(CH_3)(CH_2)_3$	$CH(CH_3)$	$C_{17}H_{31}N_3O_2$	194–195 (0.8)	76				50	60	100	60	L[i]		
37	4	H	$CH(CH_3)_2$	$CH(CH_3)_2$	$C_{16}H_{31}N_3O_2$	180–182 (0.2)	64	0	8	8	31	31	15				

[a] *cis*-2,6-Dimethylpiperidine, unless otherwise noted. [b] *trans*-2,6-Dimethylpiperidine. [c] Amnesia reversal = 60 at 10 mg/kg. [d] Amnesia reversal = 73 at 40 mg/kg. [e] Amnesia reversal = 25 at 10 mg/kg. [f] This was purified by heating at 100 °C and 0.1 mm for 16 h to give analytical quality material. [g] This compound was only tested at 5.0 mg/kg against 0.5 s ECS. [h] Mixture of (*cis*- and *trans*-2,6-diethylpiperidinyl)ethylamine, predominately *cis*. [i] 18 of 20 mice died at this dose before completion of the test. [j] Amnesia reversal = 40 at 10 mg/kg.

training. Animals entering the box within the 60-s test period were counted as having amnesia or having forgotten the training.

Two groups of control animals were used on each experimental day: (1) a ceiling control group (no ECS plus placebo injection), to ensure that the training was successful and that untreated animals remembered the task; and (2) a base-line control group (ECS plus placebo), to ensure that ECS produced amnesia for the task in untreated animals.

Typically, 70–100% of the control animals receiving no ECS following training would remember the response and remain on the shelf for 60 s. Conversely, control animals receiving ECS generally remembered to remain on the shelf less than 30% of the time.

Since there was significant variability in the scores of the control groups, the results for each agent tested were expressed as a percent amnesia reversal, in order to make comparisons between days and across experimental compounds. The equation employed was as follows:

$$\%\ \text{amnesia reversal} = \frac{\text{drug group} - \text{base-line control group}}{\text{ceiling control group} - \text{base-line control group}} \times 100$$

If the base-line control group had more than 25% of the animals remembering the task, the data for the entire day was discarded. If there was not a separation between base-line and ceiling control groups of at least 40% correct retention, the data for the entire day was similarly disregarded.

These criteria were established to ensure adequate retention and amnesia in control animals and to make data collected across days more comparable. We have found, for example, that certain seasons of the year produce more erratic results in control animals. Only data from days showing good retention and good amnesia in control groups were used in our analysis.

Chemistry. The melting points were determined in open capillary tubes in a Thomas-Hoover apparatus and are uncorrected. The boiling points are uncorrected and are very sensitive to the distillation rate.

IR spectra were determined with a Beckman IR-9 spectrophotometer. NMR spectra were recorded with a Varian A-60 instrument with Me_4Si as the internal standard. Concentration was carried out under reduced pressure. IR and NMR spectra were obtained for all compounds and were consistent with the assigned structures.

C, H, and N analyses were performed on all compounds prepared and, unless otherwise noted, checked within ±0.4%. In general, the compounds were highly water soluble, and the yields have not been optimized.

Starting Materials. The following compounds were purchased (source indicated), resynthesized as described in the cited reference, or synthesized by a different chemical route but had physical characteristics comparable to that in the cited reference: 2-(*cis*-2,6-dimethylpiperidinyl)ethylamine;[45] *N,N*-diisopropylethanediamine, *N,N*-dimethylethanediamine, 2-(piperidinyl)-ethylamine, and *N,N*-diethylethanediamine (Ames Laboratories); *N,N*-diisobutylethanediamine;[46] 3-(2,2,4,6-tetramethylpiperidinyl)propylamine;[47] 3-(2-methylpiperidinyl)propylamine (Aldrich Chemical Co.); *N,N*-diisopropylpropanediamine;[48] 3-(4-morpholinyl)propylamine and *N,N*-dimethylpropanediamine (Ames Laboratories); 1-(*cis*-2,6-dimethylpiperidinyl)butylamine and *N,N*-diisopropylbutanediamine;[47] 2-(1-piperidinyl)propylamine;[49] 2-methyl-2-(1-piperidinyl)propylamine;[50] ethyl 2-(2-oxo-1-pyrrolidinyl)propanoate, ethyl 2-(2-methyl-5-oxo-1-pyrrolidinyl)acetate, and ethyl 2-(2-ethyl-5-oxo-1-pyrrolidinyl)-propanoate;[51] ethyl 2-(2-oxo-4-phenyl-1-pyrrolidinyl)acetate;[52]

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(46) Eli Lilly British Patent 614 164; *Chem. Abstr.* **1950** *43*, 4703*g*.
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(48) Burckhalter, J. H.; Jones, E. M.; Holcomb, W. F.; Sweet, L. A. *J. Am. Chem. Soc.* **1943**, *65*, 2012–2105.
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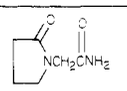
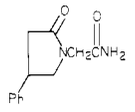
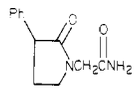
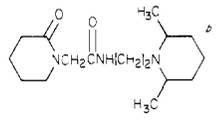
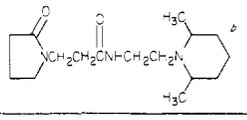
Table III. Miscellaneous Compounds for Comparison

no.	structure	emp formula	mp, °C	recrystn solvent	yield, %	amnesia reversal, %, at the following mg/kg dose 0.63	1.25	2.5	5.0	20.0	80.0	160	320
38		$C_6H_{10}N_2O_2$	151-153[a]	methanol					15	20	10		
39		$C_{12}H_{14}N_2O_2$	128-129	ethyl acetate	75	0	0	0	15	0	0		
40		$C_{12}H_{14}N_2O_2$	141-143	ethanol	77				8	17	33		
41		$C_{16}H_{29}N_3O_2$	138-139	acetone	46				20	10	60		
42		$C_{16}H_{29}N_3O_2$	74-75	cyclo-hexane	61				33	42	17		

[a] Piracetam reported in ref 22. [b] *cis*-2,6-Dimethylpiperidine.

ethyl 2-(2-oxo-1-piperidinyl)acetate;[53] ethyl 3-(2-oxo-1-pyrrolidinyl)propanoate;[54] 3-phenylpyrrolidin-2-one;[55] *cis*- and *trans*-2,6-diethylpiperidine;[56] *trans*-2,6-dimethylpiperidine.[57]

The synthetic procedures used are exemplified by the following typical examples.

Ethyl 2-Oxo-1-pyrrolidineacetate (43). A suspension of sodium hydride (57% in mineral oil, 45 g, 1.07 mol) in tetrahydrofuran (1.5 L) was stirred, and a solution of 2-pyrrolidinone (Aldrich Chemical Co.; 85 g, 1.0 mol) in tetrahydrofuran (200 mL) was added in a slow stream. After the hydrogen gas evolution had subsided, the mixture was heated to reflux, and ethyl 2-bromoacetate (Eastman Kodak; 184 g, 1.1 mol) was added dropwise. The mixture was refluxed for 16 h, cooled, and diluted with diethyl ether, 2 L. The resulting slurry was filtered to remove solids and concentrated on a rotary evaporator. The resulting two-phase oil was washed twice with petroleum ether (500 mL) and carefully distilled[58] to yield 130 g (76%) of **43**, bp 140–145 °C (20 mm). Anal. ($C_8H_{13}NO_3$) C, H, N.

***N*-[2-[Bis(1-methylethyl)amino]ethyl]-2-oxo-1-pyrrolidineacetamide (8).** A solution of ethyl 2-oxo-1-pyrrolidineacetate (**43**; 17.1 g, 0.1 mol) in *N,N*-bis(1-methylethyl)-1,2-ethanediamine (Ames Laboratories; 28.8 g, 0.2 mol) was heated at 100 °C with stirring for 16 h, removing ethanol as it was produced. The mixture was concentrated to an oil on the rotary evaporator and was rapidly distilled through a short Vigreaux column to yield 18.6 g (69%) of **8**, bp 162–164 °C (0.15 mm). Anal. ($C_{14}H_{27}N_3O_2$) C, H, N.

***cis*- and *trans*-2,6-Diethyl-1-piperidinepropanenitrile (44).** A mixture of *cis*- and *trans*-2,6-diethylpiperidine[56] (62.4 g, 0.44 mol), acrylonitrile (112 g, 2.0 mol), water (1 mL), and formamide (15 mL) was refluxed for 48 h. The mixture was cooled, diluted with diethyl ether (500 mL), and filtered through a layer of filter aid. The solution was dried over anhydrous $MgSO_4$ overnight and filtered, and the filtrate was concentrated at reduced pressure and distilled to yield 67 g (78.4%) of **44**, bp 123–125 °C (10 mm). Anal. ($C_{12}H_{22}N_2$) C, H, N.

***cis*- and *trans*-2,6-Diethyl-1-piperidinepropanamine (45).** Aluminum hydride was prepared at 0 °C from lithium aluminum hydride (23 g, 0.6 mol) in anhydrous diethyl ether (1.5 L) and a solution of anhydrous aluminum chloride (27 g, 0.2 mol) in toluene–anhydrous diethyl ether. A solution of **44** (62 g, 0.32 mol) in toluene (100 mL) was added dropwise, and the mixture was stirred and refluxed for 6 h. After the mixture was cooled, water (24 mL) was added dropwise, followed by 25% sodium hydroxide solution (108 g). The mixture was filtered and distilled to yield 47 g (74%) of **45**, bp 125–127 °C (10 mm). A sample of **45** converted to the dihydrochloride had a melting point of 195–198 °C. Anal. ($C_{12}H_{26}N_2 \cdot 2HCl \cdot {}^1/_2H_2O$) C, H, N.

Synthesis and Physical Characteristics of Other New Intermediates. *trans*-2,6-Dimethyl-1-piperidinepropanamine (**47**) was prepared in 80% yield by aluminum hydride reduction of crude *trans*-2,6-dimethyl-1-piperidinepropanenitrile (**46**), synthesized in the same manner as **44**. Compound **47** had a bp of 118–119 °C (18 mm). Anal. ($C_9H_{22}N_2$) H, N; C: calcd, 74.17; found, 74.77.

***N*-Methyl-*N*-(1-methylethyl)-1,2-ethanediamine (49)** was synthesized in 53% yield by lithium aluminum hydride reduction of crude *N*-methyl-*N*-[(1-methylethyl)amino]acetonitrile (**48**), obtained by the method of Luten.[37] Compound **49** had a bp of 145–147 °C (760 mm). Anal. ($C_6H_{16}N_2$) C, H, N.

Ethyl 2-oxo-3-phenyl-1-pyrrolidineacetate (50) was synthesized in 45% yield by alkylation of 3-phenyl-2-pyrrolidinone[42] with ethyl 2-bromoacetate and with sodium hydride as the base. Purification involved chromatography over SiO_2 with dichloromethane as eluant, concentration of the solution and distillation. Compound **50** had a bp of 115–117 °C (0.1 mm). Anal. ($C_{14}H_{17}NO_3$) C, H, N.

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Registry No. *cis*-**1**, 68497-56-3; *trans*-**2**, 88981-71-9; **3**, 88981-72-0; **4**, 88995-78-2; *cis*-**5**, 68497-78-9; **6**, 88981-73-1; **7**, 88981-74-2; **8**, 68497-62-1; **9**, 68497-77-8; **10**, 88995-79-3; **11**, 68497-61-0; **12**, 88995-80-6; **13**, 68497-76-7; **14**, 68497-69-8; **15**,

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(56) Hill, R. K.; Morgan, J. W. *J. Org. Chem.* **1966**, *31*, 3451–3452.
(57) Marcuse, A.; Wolffenstein, R. *Chem. Ber.* **1899**, *32*, 2525.
(58) If alkylation is incomplete, unreacted pyrrolidin-2-one is most readily removed by chromatography on SiO_2 with dichloromethane as eluant.

68497-65-4; **16**, 70717-47-4; **17**, 68644-48-4; **18**, 70717-53-2; **19**, 70717-51-0; **19**·HCl, 70717-52-1; *cis*-**20**, 88981-75-3; *trans*-**20**, 88981-76-4; **21**, 68497-80-3; *cis*-**22**, 68497-67-6; **23**, 88981-77-5; **24**, 88981-78-6; *cis*-**25**, 68497-71-2; **26**, 88981-79-7; **27**, 88981-80-0; **28**, 88981-81-1; **29**, 88981-82-2; **30**, 88981-83-3; **31**, 88981-84-4; **32**, 88981-85-5; **33**, 68497-64-3; **34**, 68497-79-0; **35**, 70717-46-3; *cis*-**36**, 88981-86-6; **37**, 88981-87-7; **38**, 7491-74-9; **39**, 77472-70-9; **40**, 88981-88-8; *trans*-41, 88981-89-9; *trans*-**42**, 88981-90-2; **43**, 61516-73-2; *cis*-44, 88981-91-3; *trans*-44, 88982-01-8; *cis*-**45**, 88981-92-4; *trans*-**45**, 88982-02-9; *cis*-**45**·2HCl, 88981-93-5; *trans*-**45**·2HCl, 88982-03-0; **46**, 88981-94-6; **47**, 88981-95-7; **48**, 62842-31-3; **49**, 14157-00-7; **50**, 88981-96-8; $H_2N(CH_2)_2N[CH(CH_3)_2]_2$, 121-05-1; $H_2N(CH_2)_2N(CH_3)_2$, 108-00-9; $H_2N(CH_2)_2N[CH_2CH(CH_3)_2]_2$, 14156-98-0; $H_2N(CH_2)_2N(C_2H_5)_2$, 100-36-7; $H_2NC(CH_2)_3N[CH(CH_3)_2]_2$, 53485-05-5; $H_2N(CH_2)_3N(CH_3)_2$, 109-55-7; $H_2N(CH_2)_4N[CH(CH_3)_2]_2$, 13901-39-8; $BrCH_2COOC_2H_5$, 105-36-2; 2-(*cis*-2,6-dimethylpiperidinyl)ethylamine, 1788-35-8; 2-(piperidinyl)ethylamine, 27578-60-5; 3-(2,2,4,6-tetramethylpiperidinyl)propylamine, 13901-37-6; 3-(2-methylpiperidinyl)propylamine, 25560-00-3; 3-(4-morpholinyl)propylamine, 123-00-2; 4-(*cis*-2,6-dimethylpiperidinyl)butylamine, 88981-97-9; 2-(1-piperidinyl)propylamine, 54151-70-1; 2-methyl-2-(1-piperidinyl)propylamine, 54151-73-4; ethyl 2-(2-oxo-1-pyrrolidinyl)propanoate, 70717-55-4; ethyl 2-(2-methyl-5-oxo-1-pyrrolidinyl)acetate, 33927-64-9; ethyl 2-(2-ethyl-5-oxo-1-pyrrolidinyl)propanoate, 88981-99-1; ethyl 2-(2-oxo-4-phenyl-1-pyrrolidinyl)acetate, 70291-40-6; ethyl 2-(2-oxo-1-piperidinyl)-acetate, 22875-63-4; ethyl 3-(2-oxo-1-pyrrolidinyl)propanoate, 61930-87-8; *trans*-2,6-dimethylpiperidine, 10066-29-2; 2-pyrrolidinone, 616-45-5; *cis*-2,6-diethylpiperidine, 88981-98-0; *trans*-2,6-diethylpiperidine, 88982-00-7; acrylonitrile, 107-13-1; 3-phenyl-2-pyrrolidinone, 6836-97-1.

Synthesis of Some Phosphonates with Antiherpetic Activity

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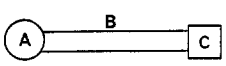
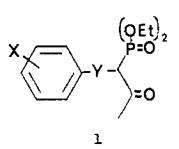
Several keto phosphonates, phosphonoacetates, and dialkyl phosphonates containing (aryloxy)aryl groups were synthesized and evaluated for antiherpteic activity. Two of the most active compounds, **12** and **16**, were evaluated topically in the mouse vaginal model against herpes simplex virus (HSV) type 2. Compound **16** exhibited an increased survival rate, as well as increased survival time. Evaluation of **16** in the guinea pig skin test against HSV-2 produced a reduction in virus titer, as well as in mean vesicle score.

During the past several years, we have been engaged in the synthesis of a class of compounds with antiviral activity, whose structure may be graphically represented by 1. We have shown the necessity of having an aromatic ring in position A, and thus far, a β-diketone[1-4] or pyrazole ring[5] in position C, the aforementioned being separated by a bridge of five to eight carbon atoms or the equivalent.

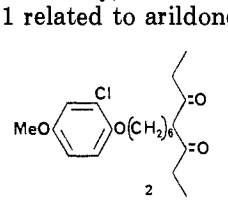


In pursuing this approach, we have synthesized some compounds where C contains a phosphonate group. The presence of the phosphonate group in an antiherpetic agent is not novel, since phosphonoacetic[6] and phosphonoformic acid[7,8] have been investigated as topical agents. Phosphonoacetic acid causes irritation when applied topically[8,9] and has been found to accumulate in bone;[10] however, phosphonoformic acid has been reported to be less irritating.[11]

The introduction of the phosphonate group into our work was based on the isosteric similarity between the phosphonate and ketone groups. Initially, our intent was to prepare keto phosphonates 1 related to arildone (2),



1

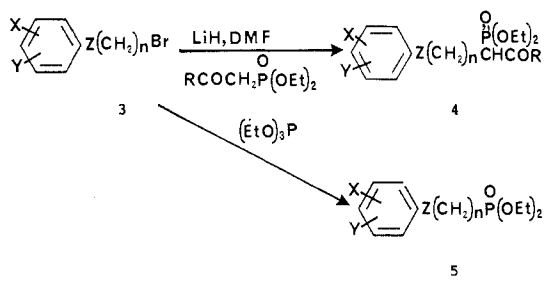


2

which is currently undergoing clinical trials against herpetic infections. However, more simplified structures have been prepared and tested.

Chemistry. Most of the compounds were prepared according to the sequence outlined in Scheme I.

Scheme I



3 4 5

The appropriate bromide **3** was reacted with the lithium salt of a β-keto phosphonate or phosphonoacetic acid ester

† Deceased.

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