

Anticonvulsant Activity of Some 4-Aminobenzamides

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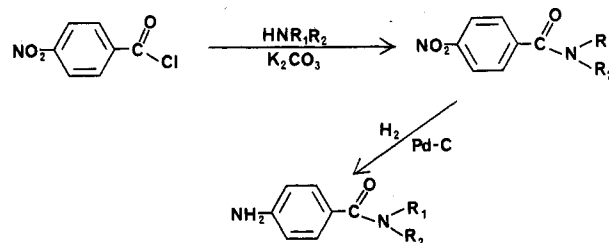
A series of 4-aminobenzamides of some simple primary and secondary amines were prepared and evaluated for anticonvulsant effects. The compounds were tested in mice against seizures induced by electroshock and pentylenetetrazole (metrazole) and in the rotorod assay for neurologic deficit. For those *N*-alkyl amides tested, 4-amino-*N*-amylbenzamide (6) was the most potent against maximal electroshock seizures (MES): ED₅₀ = 42.98 mg/kg; however, the *N*-cyclohexylbenzamide (8) showed the greatest protective index (PI = TD₅₀/ED₅₀), 2.8. The introduction of a second aromatic ring produced more potent compounds, with *d,l*-4-amino-*N*-(α -methylbenzyl)-benzamide (12) showing the highest level of activity. This compound has an anti-MES ED₅₀ of 18.02 mg/kg in mice when administered intraperitoneally (ip) and a TD₅₀ of 170.78 mg/kg (PI = 9.5) in the same species. These data compare quite favorably with those for phenobarbital and phenytoin in the same assays.

Epilepsy has been defined as a symptom of excessive temporary neuronal discharge, characterized by discrete recurrent episodes, in which there is a disturbance of movement, sensation, behavior, perception, and/or consciousness.¹ Epileptic seizures vary widely intraindividually and interindividually with respect to magnitude, duration, and frequency of occurrence.² It has been estimated that from 0.5 to 1% of the population is affected by some form of epilepsy.³ More than half of the persons suffering from epilepsy have more than one type of seizure.²

In a recent review, Bruni⁴ pointed out that with the drugs available today, significant seizure control can be achieved in 70–80% of persons with epilepsy, and complete control can be obtained in 60%. Infantile spasms and complex partial seizures pose the most difficult therapeutic problems.⁴ The management of epilepsy is a dynamic process, and the control of seizures may vary from time to time. Gradual and orderly changes in antiepileptic drug therapy are often required, and there is still a need for new anticonvulsants with more selective action and fewer toxic effects.

Numerous compounds are reported each year as having anticonvulsant properties.⁵ Many such compounds are benzodiazepine derivatives; however, others represent a diverse group of chemical types. Structurally, some of the simplest compounds possessing anticonvulsant properties are the carboxylic acids and their amides.⁶ Valproic acid is perhaps the best known example of this class of compounds. The anticonvulsant properties of valproic acid (di-*n*-propylacetic acid) and its value in the treatment of epilepsy are well documented.⁷ The amide of dipropylacetic acid has been shown⁸ to be as effective as the acid at half the dose. The local anesthetic amide lidocaine has been shown to suppress the electroencephalogenic manifestations of epileptic seizures in cats.⁹ Some amides of

Scheme I



substituted benzoic acids are reported⁶ to be effective in preventing both electroshock and metrazole-induced seizures in mice and rats. Balsamo et al.¹⁰ have described the anticonvulsant effects of some substituted cinnamamides.

Recent reports^{11–13} have indicated a renewed interest in the pharmacological activity of substituted benzamides. Benzamide drugs, such as metoclopramide,¹¹ and clebopride,¹² produce neuroleptic activity through an antidopaminergic mechanism. Metoclopramide and related benzamides differ in some clinical and pharmacological respects from other antipsychotic drugs, and it has been suggested that these compounds act on a specific subpopulation of cerebral dopamine receptors.¹¹ Iwanami¹³ and co-workers have reported the neuroleptic activity of a group of benzamides, some of which exhibited greater potency than haloperidol. The studies reported herein focus on the synthesis of some simple 4-aminobenzamides substituted at the amide nitrogen with alkyl- and arylalkyl groups and an evaluation of the anticonvulsant activities of these compounds.

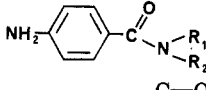
Results and Discussion

Chemistry. A series of 4-amino-*N*-substituted-benzamides were prepared and their anticonvulsant properties evaluated. The compounds were synthesized according to the methods outlined in Scheme I. The 4-nitrobenzamides were prepared from 4-nitrobenzoyl chloride and the appropriate amine or amine salt under Schotten-Baumann-type¹⁴ conditions. The aromatic nitro group was reduced by low-pressure catalytic hydrogenation.¹⁵ The yields from the formation of the 4-nitrobenzamides and the hydro-

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Table I. Physical Properties of 4-Amino-*N*-substituted-benzamides^a

no.	R ₁	R ₂			mp, °C	formula	anal.
			wavenumbers, cm ⁻¹				
1	H	H	1640, 1615		175–179	C ₇ H ₉ N ₂ O	C, H, N
2	CH ₃	H	1635, 1605		178–180	C ₈ H ₁₀ N ₂ O	C, H, N
3	CH ₂ CH ₃	H	1635, 1620		oil	C ₉ H ₁₂ N ₂ O	C, H, N
4	CH ₂ CH ₂ CH ₃	H	1640, 1620		72–74	C ₁₀ H ₁₄ N ₂ O	C, H, N
5	CH ₂ CH ₂ CH ₂ CH ₃	H	1635, 1620		97–98	C ₁₁ H ₁₆ N ₂ O	C, H, N
6	CH ₂ CH ₂ CH ₂ CH ₂ CH ₃	H	1635, 1620		97–99	C ₁₂ H ₁₈ N ₂ O	C, H, N
7	CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CH ₃	H	1635, 1620		111–112	C ₁₃ H ₂₀ N ₂ O	C, H, N
8	cyclohexyl	H	1635, 1620		180–183	C ₁₃ H ₁₈ N ₂ O	C, H, N
9	CH ₂ CH ₂ CH ₃	CH ₂ CH ₂ CH ₃	1615		80–83	C ₁₃ H ₂₀ N ₂ O	C, H, N
10	C ₆ H ₅	H	1660, 1620		138–140	C ₁₃ H ₁₂ N ₂ O	C, H, N
11	CH(CH ₃)-C ₆ H ₅	H	1640, 1620		110–113	C ₁₄ H ₁₄ N ₂ O	C, H, N
12	CH(CH ₃)-C ₆ H ₅	H	1650, 1625		155–157	C ₁₅ H ₁₆ N ₂ O	C, H, N
13	CH ₂ CH ₂ -C ₆ H ₅	H	1640, 1620		145–147	C ₁₅ H ₁₆ N ₂ O	C, H, N
14	CH(CH ₃)CH ₂ -C ₆ H ₅	H	1640, 1620		165–167	C ₁₆ H ₁₈ N ₂ O	C, H, N
15	CH ₂ CH(CH ₃)-C ₆ H ₅	H	1640, 1620		135–137	C ₁₆ H ₁₈ N ₂ O	C, H, N
16	CH ₂ -C ₆ H ₅	CH ₃	1620		113–115	C ₁₅ H ₁₆ N ₂ O	C, H, N
17	CH(C ₆ H ₅) ₂	H	1645, 1620		195–198	C ₂₀ H ₁₈ N ₂ O	C, H, N

^aThe infrared and nuclear magnetic resonance (¹H) spectra were consistent with structural assignments.**Table II.** Anticonvulsant Activity of 4-Amino-*N*-substituted-benzamides

no.	MES ^a		scMet ^a		toxicity ^{a,b}	
	30 min	4 h	30 min	4 h	30 min	4 h
1	—	—	++	—	—	—
2	+	—	—	—	—	—
3	+++	++	+	+	+	+
4	+++	++	++	++	+++ ^c	+
5	+++	<i>d</i>	<i>d</i>	<i>d</i>	+++ ^e	++
6	+++	<i>f</i>	+++	<i>f</i>	+++	<i>f</i>
7	+++	<i>f</i>	<i>f</i>	<i>f</i>	+++ ^g	<i>f</i>
8	+++	+++	+++	—	++	+
9	+++	++	++	++	+++ ^e	++
10	++++	++	+++	—	+++ ^c	++
11	++++	+++	—	++	+++ ^h	++
12	++++	+++	+++	++	++	++
13	++	++	++	+	+	+
14	+	+	+	—	—	—
15	+	++	++	++	++	++
16	+++	+++	++++	++	+++ ^c	++
17	—	—	—	—	—	—

^a +, ++, +++ and ++++ signify activity at 30, 100, 300 and 600 mg/kg, respectively; — denotes no activity observed at 600 mg/kg. ^b Determined by the rotorod test. ^c Loss of righting reflex at less than 600 mg/kg. ^d No activity at 300 mg/kg. ^e Loss of righting reflex at less than 300 mg/kg, LD₅₀ less than 600 mg/kg. ^f No activity at 100 mg/kg. ^g LD₅₀ less than 300 mg/kg. ^h Loss of righting reflex at less than 300 mg/kg.

genation reaction were 70 and 80%, respectively. The physical properties of the 4-aminobenzamides are reported in Table I.

Pharmacology. Initial anticonvulsant activity and toxicity data for the 4-aminobenzamides are reported in Table II. The intermediate 4-nitrobenzamides exhibited only minimal anticonvulsant activity in all tests. The unsubstituted 4-aminobenzamide (1) showed some slight activity against subcutaneous metrazole (scMet) induced seizures and no activity against maximal electroshock (MES) induced seizures at 600 mg/kg. The *N*-methyl amide 2 exhibited anti-MES activity at 600 mg/kg, while compounds 3–8 were effective against MES at 100 mg/kg. These compounds were effective against scMet at less than toxic doses. The toxic effects of the *N*,*n*-alkylbenzamides 2–7 appear to increase with the chain length. For example, the *n*-propyl amide 4 exhibited rotorod toxicity at 300 mg/kg in all animals tested, and loss of righting reflex occurred at less than 600 mg/kg. This trend continues through the highest homologue tested, with the *n*-hexyl amide showing rotorod toxicity at 100 mg/kg in all animals tested and lethality in all animals at 300 mg/kg. The *N*-cyclohexylbenzamide 8 was more potent against MES and scMet than the *n*-hexyl amide 7 or the other *n*-alkyl amides. Compound 8 also exhibited much less rotorod toxicity than even the *n*-propyl amide 4. The activity profile of the *N*,*N*-di-*n*-propyl amide 9 is similar to that for 8.

From the initial screening results on the *N*-alkylbenzamides, compounds 5, 6, 8, and 9 were selected for quantitation of anticonvulsant activities and toxic effects. The results of these evaluations are given in Table III. The ED₅₀ values were determined against MES and scMet-induced convulsions, and TD₅₀ values were measured by

Table III. Quantitative Anticonvulsant Activity of Selected 4-Amino-*N*-substituted-benzamides

no.	TD ₅₀ ^{a,b}	MES		scMet	
		ED ₅₀ ^b	PI ^c	ED ₅₀ ^b	PI ^c
5	104.74 (93.12–122.86) ^d	47.71 (44.79–52.24) ^d	2.2	83.04 (61.19–134.75) ^d	1.3
6	68.55 (65.60–70.90)	42.98 (34.16–50.11)	1.6	57.27 (46.56–67.86)	1.2
8	188.56 (154.16–232.82)	67.18 (58.42–76.79)	2.8	123.34 (49.27–228.07)	1.5
9	115.54 (104.55–134.32)	61.66 (52.49–70.87)	1.9	no act.	
10	111.30 (98.01–127.65)	50.54 (40.81–59.43)	2.2	59.11 (32.85–102.81)	1.9
11	83.44 (76.58–89.70)	23.30 (20.68–26.09)	3.6	no act.	
12	170.78 (153.02–189.96)	18.02 (13.41–21.43)	9.5	41.72 (38.83–46.00)	4.1
16	98.10 (81.05–112.82)	52.60 (40.13–60.85)	1.9	81.70 (54.06–111.62)	1.2

^a Rotorod procedure. ^b Doses reported are in milligrams per kilogram. ^c PI = protective index = TD₅₀/ED₅₀. ^d 95% confidence limits.

the rotorod procedure for evaluating neurologic deficit. Quantitative data were obtained for all compounds against MES-induced convulsions, with 6 being the most potent on a weight basis. However, the *N*-cyclohexylbenzamide 8 has the highest protective index (PI), 2.8. The PI is defined as TD50/ED50. All the *N*-alkyl amides showed lower activity against scMet-induced convulsions, with a PI of <2.0 for all compounds. The time of peak anticonvulsant effect was in the 1-h range.

The initial anticonvulsant evaluation of the compounds containing an aromatic ring (10–16) in the amine component of the amides are reported in Table I. These results indicate that one additional aromatic ring produces optimal activity. The *N*-benzyl amide 11 shows anti-MES activity of 30 mg/kg, indicating greater potency than any of the *N*-alkyl amides. However, the addition of a second phenyl group as in 17 drastically decreases the anticonvulsant effects. Compounds 10–12 display maximum anti-MES activity, with compound 12 appearing to be the most potent. This indication is confirmed in Table III, which shows 12 to have an ED50 of 18.02 mg/kg against MES and an scMet ED50 of 41.72 mg/kg. The TD50 for this compound was determined to be 170.78 mg/kg, yielding a PI of 9.5 for MES and 4.1 for scMet. Thus, the *N*- α -methylbenzyl group produced maximal anticonvulsant activity of those *N*-substituents examined in this study. A substantial drop in activity was observed when the *N*- α -methylbenzyl group of 12 was replaced by the isomeric β -phenylethyl group (13) or the *N*-benzyl-*N*-methyl derivative (16). The time of peak anticonvulsant effect for these compounds occurred at approximately 1 h after administration.

Horrom and Lynes¹⁶ have described the anticonvulsant properties of a series of aminohalobenzamides. Maximum activity was observed for 4-amino-*N*-cyclopropyl-3,5-dichlorobenzamide; this compound showed an ED50 of 59 mg/kg for electroshock-induced convulsions, an ED50 of 17 mg/kg against metrazole, and an ED50 of 34 mg/kg against strychnine. The 4-amino-*N*-cyclopropyl-3,5-dibromobenzamide displayed a similar spectrum of anticonvulsant activity. Alteration of the position of the amino group resulted in decreased activity. The most potent nonhalogenated 4-aminobenzamide examined was 4-amino-*N*-cyclopropylbenzamide, with an ED50 of 139 mg/kg against electroshock and ED50 of >300 for both metrazole and strychnine. The corresponding nitro amides as in this study were inactive in all assays.

The data for compound 12 in Table III can be compared to that for the anticonvulsant drugs phenobarbital and phenytoin. The tests for these drugs were conducted in the same assay procedure. Phenobarbital administered ip produced a TD50 of 69.01 mg/kg, a MES ED50 of 21.78 mg/kg (PI = 3.17), and a scMet ED50 of 13.17 mg/kg (PI = 5.24). Phenytoin yielded a TD50 of 65.46 mg/kg and a MES ED50 of 9.50 mg/kg (PI = 6.80). Phenytoin (ip) gave no protection against scMet-induced convulsions at up to 300 mg/kg. In most cases the slope of the regression lines for toxicity and activity are not parallel, and the PI value is valid only at the dose-50 response. Thus, it is important to note the effect of the slope by comparing the safety ratio (SR = TD3/ED97) for these compounds. In the MES test, compound 12 showed an SR of 3.5, and in the metrazole assay, it showed an SR of 2.2. Phenobarbital gave SR values of 2.3 and 2.5 against MES and metrazole, respectively. Phenytoin produced a MES SR of 3.6. These results show 12 to have significant anticonvulsant activity

in screening procedures used to evaluate drugs which affect seizure spread and seizure threshold.

The general toxicity profile for 12 was measured in mice by administering the TD50, 2 \times TD50, and 4 \times TD50 doses intraperitoneally. The activity of the compound is characterized by decreased motor activity, ataxia, muscular relaxation, and rotorod toxicity. Decreased respiration, cyanosis, and spasticity were also observed in some animals, particularly those given the higher doses. The animals were free of overt toxic effects 24 h after administration. The hypnotic dose (HD50) and lethal dose (LD50) for compound 12 were determined to be 461.76 and 718.18 mg/kg, respectively. These values are higher than those for phenobarbital (135.45 and 264.70 mg/kg), phenytoin (178.34 and 229.61 mg/kg), mephentyoin (405.97 and 567.97 mg/kg), or carbamazepine (172.24 and 628.70 mg/kg). Rats pretreated orally twice daily for 7 days with 28 mg/kg of 12 showed no change in hexobarbital sleep time as compared to control animals. The hexobarbital was administered approximately 24 h after the last dose of 12.

The anticonvulsant activity profile for 12 was further examined by using a series of chemically induced seizures in mice. Against bicuculline-induced threshold seizures, 12 showed an ED50 of 39.07 mg/kg while providing a maximum of only 37.5% protection against strychnine-induced convulsions at 170 mg/kg. The ED50 against picrotoxin was determined to be 191.23 mg/kg, slightly higher than the TD50 value. Bicuculline blocks γ -aminobutyric acid (GABA) receptors, thus interfering with the function of this inhibitory neurotransmitter,¹⁷ and picrotoxin is a noncompetitive GABA antagonist at presynaptic sites.¹⁷ Strychnine blocks postsynaptic inhibition mediated by glycine.¹⁸ The activity of 12 against bicuculline suggests that at least a portion of its anticonvulsant activity is mediated by a GABA-agonist effect.

Although the 4-aminobenzoyl-moiety does at least superficially resemble GABA, it would not be expected to have zwitterionic characteristics. The aromatic amino group should exist almost totally in the unprotonated form at physiological pH, and the amide NH would certainly be nonionic. Thus, these compounds do not appear to possess binding sites similar to the classic GABA agonists.¹⁷ Additional pharmacological and toxicological studies on 12, as well as further studies on the relationship between benzamide structure and anticonvulsant activity, are currently being conducted.

Experimental Section

Melting points were determined in open glass capillaries with a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were recorded in chloroform solutions in matched sodium chloride cells or as fluorocarbon mulls with a Beckman 4230 spectrophotometer. NMR spectra were measured in CDCl₃ on a Varian T-60A spectrometer with an internal standard of tetramethylsilane. Elemental analyses (C, H, and N) were performed by Atlantic Microlab Inc., Atlanta, GA.

4-Nitrobenzamides. A solution of amine or amine salt (0.03–0.07 mol) in 35 mL of tetrahydrofuran and 200 mL of a 20% (w/v) solution of potassium carbonate were added to a 1-L three-necked flask equipped with a magnetic stirrer, reflux condenser, addition funnel, and a heating mantle. A solution of *p*-nitrobenzoyl chloride (2-fold molar excess) in 35 mL of tetrahydrofuran was added dropwise, and the resulting mixture was refluxed for 12 h. The mixture was maintained at or above pH 8 during the reaction period. The solution was then cooled to room temperature and extracted with chloroform (3 \times 100 mL).

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The extracts were combined, dried over magnesium sulfate, and evaporated. The resulting residues were purified by recrystallization from a petroleum ether-benzene mixture or by column chromatography on silica gel (40 mesh) with a stepwise solvent gradient of petroleum ether and diethyl ether.

4-Aminobenzamides. A solution of 5.0 g of the appropriate *p*-nitrobenzamide in absolute ethanol (150 mL) was added to a Paar hydrogenation bottle along with 250 mg of 5% palladium on carbon and subjected to low-pressure hydrogenation (45 psi) for 3 h. The bottle was then removed, and the contents were filtered through Celite. The filtrate was evaporated, and the resulting residue was purified by recrystallization from benzene-petroleum ether mixtures or by column chromatography on silica gel (40 mesh) with a stepwise solvent gradient of petroleum ether (boiling range 30–60 °C) and diethyl ether.

Pharmacology.¹⁹ Initial anticonvulsant evaluation of these compounds was conducted with at least three dose levels (30, 100, and 300 mg/kg) and in some cases a fourth dose of 600 mg/kg. All tests were performed with male Carworth Farms number-one mice. Test solutions of all compounds were prepared in 30% polyethylene glycol 400, and animals were dosed intraperitoneally at 30 min prior to testing.

Maximal electroshock seizures (MES) were elicited with a 60 cycle alternating current of 50-mA intensity delivered for 0.2 s via corneal electrodes. A drop of 0.9% saline was instilled in the eye prior to application of electrodes. Abolition of the hindlimb tonic extension component of the seizure was defined as protection in the MES test.

The subcutaneous pentylenetetrazole (metrazol) seizure threshold test (scMet) was conducted by administering 85 mg/kg

of pentylenetetrazole as a 0.5% solution in the posterior midline. Protection in this test was defined as a failure to observe a single episode of clonic spasms of at least 5-s duration during a 30-min period following administration of the test compound.

Neurological deficit was measured in mice by the rotorod test. The dosed animal was placed on a 1-in. diameter knurled plastic rod rotating at 6 rpm. Neurologic toxicity was defined as the failure of the animal to remain on the rod for 1 min. The median anticonvulsant potency (ED₅₀) and toxicity (TD₅₀) were determined by the graphical method.

Acknowledgment. The authors deeply appreciate the assistance of the Anticonvulsant Drug Development Program, Epilepsy Branch, NINCDS, in the pharmacological testing of these compounds. The help of Gill D. Gladding of the ADD Program is gratefully acknowledged.

Registry No. 1, 2835-68-9; 2, 6274-22-2; 3, 89399-17-7; 4, 38681-78-6; 5, 51207-84-2; 6, 85592-76-3; 7, 85592-77-4; 8, 17675-42-2; 9, 79868-19-2; 10, 782-45-6; 11, 54977-92-3; 12, 85592-75-2; 13, 61251-99-8; 14, 13004-65-4; 15, 89399-18-8; 16, 85592-78-5; 17, 89399-19-9; *p*-nitrobenzamide, 619-80-7; *p*-nitrobenzoyl chloride, 122-04-3; *N*-methyl-4-nitrobenzamide, 2585-23-1; *N*-ethyl-4-nitrobenzamide, 50445-50-6; 4-nitro-*N*-propylbenzamide, 2585-24-2; *N*-butyl-4-nitrobenzamide, 51207-98-8; 4-nitro-*N*-pentylbenzamide, 89399-20-2; *N*-hexyl-4-nitrobenzamide, 89399-21-3; *N*-cyclohexyl-4-nitrobenzamide, 7506-46-9; *N,N*-di-propyl-4-nitrobenzamide, 79868-22-7; 4-nitro-*N*-phenylbenzamide, 3460-11-5; *N*-benzyl-4-nitrobenzamide, 2585-26-4; *d,l*-4-nitro-*N*-(α -methylbenzyl)benzamide, 85592-74-1; 4-nitro-*N*-phenethylbenzamide, 62497-65-8; 4-nitro-*N*-(β -methylphenethyl)benzamide, 15269-43-9; 4-nitro-*N*-(α -methylphenethyl)benzamide, 89399-22-4; *N*-benzyl-*N*-methyl-4-nitrobenzamide, 89399-23-5; 4-nitro-*N*-(α -phenylbenzyl)benzamide, 88229-34-9.

(19) The pharmacological evaluation of these compounds was conducted in the laboratories of the Anticonvulsant Drug Development Program, Epilepsy Branch, NINCDS, Bethesda, MD.

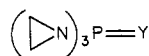
In the Search for New Anticancer Drugs. 9. Synthesis and Anticancer Activity of Spin-Labeled Analogues of *N,N,N',N',N'',N'''*-Tri-1,2-ethanediylphosphoric Triamide and *N,N,N',N',N'',N'''*-Tri-1,2-ethanediylphosphorothioic Triamide

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A number of *N,N,N',N',N'',N'''*-tri-1,2-ethanediylphosphoric triamide (TEPA) and *N,N,N',N',N'',N'''*-tri-1,2-ethanediylphosphorothioic triamide (thio-TEPA) derivatives containing either two aziridine moieties (1a) or two (2-chloroethyl)amino functions (1b) and either a 2,2,6,6-tetramethylpiperidine, 1-oxy-2,2,6,6-tetramethylpiperidine or 1-hydroxy-2,2,6,6-tetramethylpiperidine component were synthesized and tested against lymphocytic leukemia P388 in mice. In a structure-activity comparison it was found that at optimum dose all compounds containing the nitroxyl radical were more active than the corresponding hydroxylamine derivatives. The open-chain compounds (1b) were less active than the corresponding aziridine ring compounds (1a). The replacement of the X = bridge in 1a with the X = N(CH₃) group resulted in lowering of the anticancer activity.

Thio-TEPA [*N,N,N',N',N'',N'''*-tri-1,2-ethanediylphosphorothioic triamide (1, Y = S)] is a clinically used



1, Y = S, O

anticancer agent that is effective against the Hodgkin's disease and carcinoma of the breast, bladder, and ovary.^{1,2} TEPA [*N,N,N',N',N'',N'''*-tri-1,2-ethanediylphosphoric triamide (1, Y = O)] is not used clinically. The synthesis of 1 and of a number of thio-TEPA derivatives containing either two or three substituted or unsubstituted di-1,2-ethanediylimine (aziridine, ethylenimine) groups at the

pentavalent phosphorus has been reported.³⁻¹² Although only 1, Y = S, is clinically used, several other com-

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