Table II. Quaternary Salts

No.	Formula	Mp, °C	Analyses
9	$C_{31}H_{36}Br_2N_6O_2 \cdot H_2O$	174-176	C, H, N, Br
10	$C_{33}H_{40}Cl_2N_6O_{10}$	194-195	C, H, N, Cl
11	$C_{32}H_{38}Br_2N_6O_2 \cdot 2H_2O$	280-281	C, H, N, Br
12	$C_{34}H_{42}Br_2N_6O_2$	214-216	C, H, N, Br
13	$C_{50}H_{52}N_6O_{10}S_2$	323 dec	C, H, N, S
14	$C_{52}H_{56}N_6O_{10}S_2 \cdot H_2O$	329-330	C, H, N, S
15	$C_{54}H_{60}N_6O_{10}S_2$	279-280	C, H, N, S

crystallization from N-methyl-2-pyrrolidone–H_2O provided TLC homogeneous product as colorless prisms of mp >360 °C (3.90 g, 91%). Anal. ($C_{34}H_{32}N_6O_4$) C, H, N.

Quaternization, essentially as described above, and crystallization of the quaternary salts from 5% NaOTs–H_2O provided colorless crystals of agents **13–15** (Table II).

Biologic Testing. 10^5 L1210 cells were implanted intraperitoneally into 18.5–22.5-g C3H/DBA2 F_1 hybrid mice on day 0; ip drug treatment was initiated 24 h later and continued daily for 5 days. Drugs were tested from dose levels which were clearly toxic, providing toxic deaths before those of control animals. Twofold dilutions were then screened until a nontoxic or nonactive dose level was reached. All dosage has been intraperitoneal in 0.2-ml volume, H_2O being used as medium. Groups of six animals per dose level have been used with one control group for every six test groups. Compounds that have been tested under these conditions and have given no significant (>25%) increase in life span have been classed as negative.

Acknowledgment. We are indebted to Dr. J. C. Kauer, E. I. du Pont de Nemours and Co., for a generous sample of dimethyl bicyclo[2.2.2]oct-2-ene-1,4-dicarboxylate. The Misses Noeline Price and Carolin West ably assisted with the biologic testing. This work was supported by the Auckland Division of the New Zealand Cancer Society and in part by the Medical Research Council of New Zealand.

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Para-Substituted N-Acetyl-L(S)- and -D(R)-α-amino-N-phenylglutarimides. A Structure–Activity Study of Substituent Effects on Stereoselective Anticonvulsant Activity[1]

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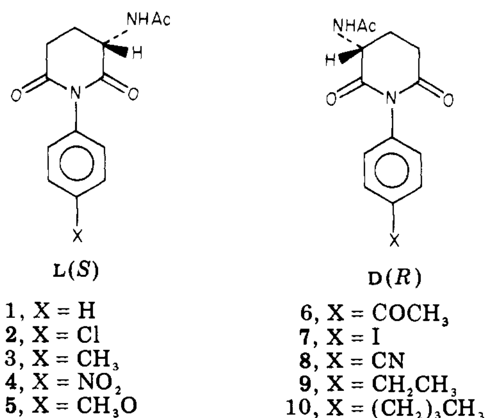
Received March 22, 1976

For purposes of carrying out structure–activity studies on a series of pure R and S enantiomorphs of various para-substituted N-acetyl-α-amino-N-phenylglutarimides, we synthesized the p-acetyl, iodo, cyano, ethyl, and n-butyl analogues. These compounds complimented previous R and S isomers (unsubstituted and the p-chloro, methyl, nitro, and methoxyl analogues) synthesized in our laboratories from amino acids of known absolute configuration. The neurotoxic doses (TD_{50}'s), anticonvulsant potencies [maximal electroshock seizures (MES) and subcutaneous metrazole (sc Met) ED_{50}'s], protective indices (PI = TD_{50}/ED_{50}), and effects on minimal seizure threshold (iv Met) were compared with similar values concomitantly determined for clinically employed anticonvulsants. A parallel relationship was shown between neurotoxicity (TD_{50}) and potency (ED_{50}) for the R and S analogues. In most cases R isomers had a more rapid onset of action and possessed greater neurotoxicity and greater anticonvulsant potency.

We previously reported a qualitative stereostructure–activity analysis of certain enantiomorphic succinimide and glutarimide (**1–5**) anticonvulsants of known absolute configuration.[2] Since several analogues compared favorably with well-known clinically employed anticonvulsants, and readily could be synthesized from amino acids of known absolute configuration, we extended the glutarimide series to those having para substituents **6–10** for purposes of analyzing the results by computerized multiparameter regression analysis.[3] However, no acceptable QSAR analysis could be obtained within this extended series wherein substituents show no covariance between parameter values.[4] For these reasons, the results are only discussed from a qualitative point of view.



Pharmacological Results and Qualitative Discussion. The pharmacological data for R and S isomers **1–5** have been compared with several standard anticonvulsive drugs and reported previously;[2] biological data obtained for R and S analogues **6–10** are found in Table I. The anticonvulsive activities obtained for standard drugs (diphenylhydantoin, trimethadione, and ethosuximide) in this study were found to be similar to those which we previously reported.[2] Since the pharmacological procedures employed in the evaluation of all drugs were virtually identical, analysis of the data for **1–10** appeared justified.

We previously showed[2] that for glutarimides **1–5** the order of decreasing toxicity of these compounds as judged

Table I. Anticonvulsant Activity of Standard and Experimental Drugs[a,b]

Compd	Time peak effect, min	TD_{50}, mmol/kg	Max electroshock seizures (MES)		Subcutaneous Met seizures (sc Met)		Seizure threshold (iv Met)	
			ED_{50}, mmol/kg	PI = TD_{50}/ED_{50}	ED_{50}, mmol/kg	PI = TD_{50}/ED_{50}	Dose, TD_{50}	Threshold ratio
Diphenylhydantoin sodium salt	45	0.22 (0.18-0.26)	0.022 (0.017-0.028)	10.00 (7.46-13.40)	ED_0; ineffective to 0.22	*c*	0.5	0.99 (0.86-1.15)
Trimethadione	5	3.98 (3.16-5.01)	3.72 (3.29-4.20)	1.07 (0.78-1.43)	2.23 (1.83-2.73)	1.78 (1.31-2.40)	0.5	1.94 (1.64-2.30)
Ethosuximide	5	2.32 (1.99-2.72)	ED_0; ineffective to 2.32	*c*	0.86 (0.68-1.09)	2.69 (2.03-3.55)	0.5	1.76 (1.53-2.04)
6, X = $COCH_3$								
R	60	6.41 (5.58-7.38)	1.73 (0.99-3.01)	3.70 (2.09-6.54)	1.77 (1.37-2.29)	3.62 (2.49-5.24)	0.5	3.07 (2.68-3.50)
S	45	5.72 (4.37-7.48)	2.08 (1.55-2.78)	2.75 (1.99-3.79)	2.60 (1.95-3.45)	2.20 (1.60-3.01)	0.5	1.46 (1.22-1.72)
7, X = I								
R	60	4.43 (3.31-5.94)	3.60 (2.50-5.18)	1.23 (0.76-1.96)	3.08 (1.65-5.75)	1.43 (0.72-2.81)	0.5	1.28 (1.11-1.46)
S	90	4.94 (4.08-5.99)	4.76 (3.72-6.1)	1.03 (0.42-2.47)	ED_{30} = 4.94	*c*	0.5	1.08 (0.98-1.18)
8, X = CN								
R	30	1.29 (0.70-1.81)	0.36 (0.25-0.50)	3.58 (2.02-6.33)	0.92 (0.65-1.29)	1.40 (0.79-2.47)	0.5	1.50 (1.24-1.78)
S	60	1.49 (1.16-1.92)	0.63 (0.45-0.88)	2.36 (1.55-3.58)	Ineffective to 1.49	*c*	0.5	1.08 (0.96-1.21)
9, X = Et								
R	15	3.79 (3.13-4.59)	0.74 (0.48-1.13)	5.12 (3.24-8.08)	1.27 (1.04-1.55)	2.98 (2.25-3.93)	0.5	1.51 (1.36-1.68)
S	45	5.03 (4.68-5.42)	1.67 (1.33-2.11)	3.10 (2.42-3.96)	2.91 (1.83-4.64)	1.72 (1.07-2.75)	0.5	1.00 (0.91-1.21)
10, X = *n*-Bu								
R	15	0.52 (0.20-1.32)	0.11 (0.08-0.15)	4.72 (1.78-12.8)	0.23 (0.17-0.30)	2.26 (0.86-5.89)	0.5	1.28 (1.20-1.36)
S	30	1.03 (0.71-1.50)	0.31 (0.27-0.36)	3.32 (2.24-4.91)	ED_{30} = 1.03	*c*	0.5	1.25 (1.17-1.33)

[a] All compounds were administered ip to CD-1 male mice (Charles River) in groups of 6-12 mice. [b] Numbers in parentheses refer to 95% confidence limits, as calculated by the method of Litchfield and Wilcoxon.[8] [c] PI (protective index) could not be calculated because drug was insufficiently active to provide 50% protection (ED_{50}).

Table II. Yields and Properties of *N*-Acetyl-(*S*)- and -(*R*)-α-amino-para-substituted Phenylglutarimides

Compd		Yield, %	Mp, °C	$[\alpha]^{22}_{578}$, deg
6, X = COMe	*R*[a]	81	201-202	-17.9
	S	94	201-202	+23.6
7, X = I	*R*[a,b]	72	224-225	-16.9
	S	75	224-225	+18.9
8, X = CN	*R*	94	190-191	+0.20
	S[a]	89	190-191	-0.20
9, X = Et	*R*	88	176.5-177	-17
	S[a]	95	176.5-177	+17
10, X = *n*-Bu	*R*	74	134-135	-14.1
	S[a]	47	134-135	+16.3

[a] Analyses were performed on the indicated optical isomer. Anal. C, H, N. [b] Anal. C, H, N, I.

from the TD_{50} is similar; i.e., for the *R* series Cl > H ~ CH_3 > NO_2 > CH_3O in order of decreasing toxicity; for the *S* series Cl ~ H > CH_3 > NO_2 > CH_3O. Against MES and sc Met the order of decreasing potency followed the order of decreasing neurotoxicity. For the *R* antipodes (MES ED_{50}) Cl > H > CH_3 ~ NO_2 > CH_3O; for the *S* isomers Cl ~ H > CH_3 > NO_2 > CH_3O. Similarly, against sc Met (ED_{50}) the order of decreasing potency for the *R* isomers was Cl ~ H > CH_3 > NO_2 > CH_3O; for the *S* antipodes Cl ~ H > CH_3 > NO_2 > CH_3O.

Interestingly, glutarimides **6–10** exhibited a similar relationship. The order of decreasing neurotoxicity of these compounds, as judged from the TD_{50} for the *R* enantiomorphs, is $CH_3(CH_2)_3$ ~ CN > Et ~ I ≥ $COCH_3$; for the *S* series $CH_3(CH_2)_3$ ~ CN > I ~ Et ≥ $COCH_3$. Only relatively minor differences in ordering are observed when comparing TD_{50} and MES ED_{50} values for *R* and *S* antipodes; for the *R* series the order of decreasing potency in these tests is $CH_2(CH_2)_3$ > CN ~ CH_2CH_3 ≥ $COCH_3$ ~ I; for the *S* isomers $CH_3(CH_2)_3$ > CN > CH_2CH_3 ~ $COCH_3$ > I. A similar relationship [$CH_3(CH_2)_3$ > CN ~ CH_2CH_3 ≥ $COCH_3$ ~ I] was observed for the *R* enantiomorphs in the sc Met test. We could not rank order the *S* isomers according to ED_{50} values in the sc Met because some compounds [(*S*)-**7**, **8**, and **10**] failed to provide 50% protection; testing for anticonvulsant activity at doses >TD_{50} did not seem warranted. At the TD_{50} dose, (*S*)-**8** (CN) was inactive and (*S*)-**7** (I) and (*S*)-**10** [$CH_3(CH_2)_3$] elicited only 30% protection (ED_{30}). However, at the ED_{30} (*S*)-**10** is approximately five times as potent and neurotoxic as (*S*)-**7**. Further, (*S*)-**6** ($COCH_3$) and (*S*)-**9** (CH_2CH_3) exhibited approximately equivalent ED_{50} and TD_{50} values.

In general, the *R* enantiomorphs had a more rapid onset of action (i.e., a shorter time of peak effect, TPE), were more potent than their *S* isomers in eliciting minimal neurotoxicity, and were more active in their ability to protect mice against electrically and chemically induced seizures; (*S*)-**1**, **5**, and **6** were equipotent or slightly more active than their respective *R* enantiomorphs. These results suggest that the *R* enantiomorphs may preferentially cross the blood–brain barrier and thereby achieve greater concentrations at the biophase in the central nervous system and/or these compounds may possess greater intrinsic activity in selectively depressing the central neurons activated by the chemical or electrical stimuli.

Swinyard[5] has suggested that compounds possessing activity in the maximal electroshock seizures (MES) test may be of potential clinical value for the treatment of grand mal and psychomotor seizures, while the subcutaneous metrazole (sc Met) test may be predictive of compounds useful in the management of petit mal seizures. On the basis of the protective indices (PI = TD_{50}/ED_{50}) obtained in this and the previous studies evaluating glutarimide anticonvulsants, (*R*)-**2**, **4**, **5**, and **9** and (*S*)-**5** compared favorably with diphenylhydantoin, having PI's at least 50% of that of this reference compound. Of the 20 (*R* and *S*) glutarimides studied in the sc Met test, five had more favorable PI's than ethosuximide [(*R*)-**4**, **5**, **6**, and **9** and (*S*)-**5**].

Experimental Section

Synthesis. The desire imides were prepared from the crude anilides which were synthesized from the appropriate para-substituted aniline and D(*R*)- or L(*S*)-*N*-acetylglutamic acid according to methods previously described.[2] Approximately 6 g of the crude anilides was treated with 100 ml of Ac_2O in a 250-ml round-bottom flask, equipped with a dry N_2 inlet and a drying tube (Drierite), and stirred in an oil bath with a magnetic stirring hot plate. The reaction slurry was heated to 60 °C. After 1 h, the solid dissolved and heating was continued for 8 h. The solvent was removed under reduced pressure and the crude imide was chromatographed on silica gel 60 using AcOEt as the eluting solvent. The first fractions contained imide and, if necessary, were decolorized with Norit A, filtered, and concentrated under reduced pressure. The residue was recrystallized from MeOH–H_2O (1:1) affording crystalline imides (Table II). Specific rotations were determined on 1–3% solutions of the imides in acetone using the mercury 578-nm wavelength.

Pharmacology. The animals used in the pharmacological evaluation of the glutarimides (**6–10**) were male albino CD-1 mice (18–25 g). All compounds were administered to mice in an aqueous vehicle in a constant volume of 1.0 ml/100 g of body weight.

The time of maximal central activity and the median neurotoxic dose (TD_{50}) were determined employing the rotarod. The end point for minimal neurotoxicity was muscle incoordination and was based upon the inability of the mouse to remain on a horizontal rod rotating at 6 rpm for 1 min. All seizure studies were carried out at the time of peak activity.

Anticonvulsant potencies (the ED_{50} values) were determined by an electrical and a chemical test. Drugs were evaluated for their ability to (1) prevent the hind limb extensor component of maximal electroshock seizures (MES) evoked by a supramaximal current (50 mA ac, 0.2-s stimulus duration, employing corneal electrodes), and (2) afford complete protection against convulsions induced by a subcutaneous injection of metrazole (sc Met, 80 mg/kg).[7]

For the determination of the ED_{50} and TD_{50}, groups of 6–12 mice were given a range of doses of the test compound until at least three points were established in the range of 10–90% seizure protection or minimal neurotoxicity. The results were plotted points by eye. From this plot of the data, the respective ED_{50}, TD_{50}, 95% confidence intervals, and protective indices (PI = TD_{50}/ED_{50}) were calculated by the method of Litchfield and Wilcoxon.[8] The PI was not calculated for compounds providing less than 50% protection.

The ability of saline or the 0.5 TD_{50} dose of test compounds to modify minimal seizure threshold was determined using a timed intravenous infusion of metrazole (0.5%, 0.51 ml/min; iv Met). The threshold ratio was calculated as the mean mg/kg of pentylenetetrazole required to produce clonic seizures in drug-treated mice divided by the mg/kg of this convulsant required in saline-treated animals. Threshold ratios with corresponding 95% confidence intervals greater than 1.00 denote a significant increase in seizure threshold or a protective (anticonvulsive) effect.[9]

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Carcinogenicity of Derivatives of Polynuclear Compounds

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In contrast to the enhanced carcinogenic activity of alkylating derivatives of polynuclear hydrocarbons and aminoacridines, a number of other derivatives, including conjugates with amino acids and peptides, showed little significant activity at comparable doses.

There is substantial evidence, reviewed by Miller and Miller,[1] that ultimate carcinogens are electrophiles. Accordingly, a "carcinogen" such as a polynuclear aromatic hydrocarbon which has no such chemical property must undergo metabolism to a reactive form. Candidate reactive forms include (1) K region epoxides[2] and (2) the carbonium ion derived from mesomethyl hydrocarbons.[3] Flesher and Sydnor's evidence is consistent with the latter possibility,[4] as is our recent finding that halomethyl derivatives of aromatic hydrocarbons are more carcinogenic than the parent hydrocarbons.[5] Alkylating derivatives of acridines, benzacridines, and their analogues are also potent carcinogens.[5]

The nucleophilic target of these alkylating carcinogens is of primary interest. The broad correlation of their carcinogenic potency with mutagenic potency, as shown by a number of investigators, most recently by McCann, Choi, Yamasaki, and Ames,[6] implicates DNA as the ultimate locus. In order to investigate whether or not the reaction could be through an intermediate conjugate with normal nucleophilic body constituents, we prepared a number of products that might be produced endogenously, as well as other conjugates designed to enhance hydrophilic character, and tested their carcinogenic activity by the same convenient mouse pulmonary adenoma assay used previously for the corresponding alkylating agents.[5]

Biological Assay. Carcinogens of essentially every known type are capable of eliciting pulmonary tumors in Strain A mice, in a convenient and relatively rapid assay.[7] Using a single low (15 μmol/kg or less) iv dose we found high activity in a number of alkylating agents that are also active both as antitumor agents[8,9] and as mutagens,[6] including agents that had been previously classified as noncarcinogenic on the basis of ip administration in the same system.[10] Small numbers of mice proved ample for detection of carcinogenicity with these potent compounds.[5]

Table I shows ten compounds bearing polynuclear groups which, when associated with an electrophilic function, are highly carcinogenic.[5] The induction period was extended somewhat over the usual 20 weeks to detect any minimal activity.

Results and Discussion

Only compound **2**, the *S*-arylmethylhomocysteine derivative, showed any significant carcinogenic activity. This structure, it should be noted, is an analogue of methionine, a biological methylating agent. In separate tests, compounds **1-3**, **8**, and **10** gave negative results in Ames' mutagenesis test.[11]

Negative data do *not* establish absence of carcinogenic potential, only that this potential is not comparable with that of the highly electrophilic parent compounds. Therefore, the actual formation of a covalent bond by the reaction of these compounds or their related carbonium ion seems necessary to explain the high level of activity of these compounds as carcinogens,[5] mutagens,[6] and antitumor compounds.[8,9] That is, two moieties are necessary for these three related activities—a highly structure-specific polynuclear group and an electrophilic function.

Experimental Section

Melting points were taken in open capillary tubes in a Hershberg apparatus using total immersion thermometers and are reported as uncorrected values. Elemental analyses were carried out by Atlantic Microlab, Inc., of Atlanta, Ga., and unless otherwise noted were within ±0.4% of theory.

***S*-(12-Methyl-7-benz[*a*]anthrylmethyl)cysteine (1).** To a stirred solution of 2.5 g of L-cysteine hydrochloride in 90 ml of EtOH were added (1) 150 ml of C_6H_6; (2) 4.8 g of 7-iodomethyl-12-methylbenz[*a*]anthracene;[12] and about 0.5 min later, 28 ml of 1 N NaOH–MeOH. After 25 min of stirring, the bright orange color had changed to light yellow, and the voluminous precipitate was filtered, washed with EtOH and hexane, and dried. The crude product (5 g) was dissolved in 250 ml of EtOH and 16 ml of 1 N NaOH, filtered from undissolved residue, and precipitated with 16 ml of 1 N HCl. The precipitation from alcoholic alkali was repeated to give 3.25 g (69%) of product, mp 219–221 °C dec. Anal. ($C_{23}H_{21}NO_2S$) C, H, N, S.

***S*-(12-Methyl-7-benz[*a*]anthrylmethyl)homocysteine (2).** To a solution, stirred in an ice bath, of 3.0 g of DL-homocysteine thiolactone hydrochloride, 65 ml of 1 N NaOH–MeOH, and 100 ml each of EtOH and C_6H_6 was added portionwise 4.9 g of 7-iodomethyl-12-methylbenz[*a*]anthracene.[12] After stirring 20 min, 40 ml of 1 N AcOH was added, and the nearly clear solution diluted to 400 ml. The aqueous–alcoholic layer was removed, and the C_6H_6 layer was extracted three times with NaOH in 70% EtOH. The extracts were acidified with AcOH to give 3.7 g (74%) of product, mp 219–222 °C dec. Three precipitations from aqueous alcoholic alkali failed to change the analysis. Anal. ($C_{24}H_{23}NO_2S$) C, H, N, S; C: calcd, 74.0; found, 72.65.

***S*-(12-Methyl-7-benz[*a*]anthrylmethyl)glutathione (3).** To a stirred, cooled solution of 1.3 g of glutathione in 20 ml of MeOH, 12 ml of 1 N NaOH–MeOH, and 8 ml of C_6H_6 was added 0.75 g of 7-iodomethyl-12-methylbenz[*a*]anthracene.[12] After 1 h of stirring, the mixture was filtered and the crude product (salt) precipitated with hexane (1.1 g). This was redissolved in 30 ml of 1:1 H_2O–MeOH, filtered, and acidified with AcOH to give a gelatinous precipitate, which was digested by overnight stirring at 30–40 °C, when filtration was possible; the yield was 0.4 g (36%). Needles were obtained by recrystallization from 1.5 ml of 50% EtOH (40% recovery): mp 207–210 °C dec. Anal. ($C_{30}H_{31}N_3SO_6$) C, H, N, S.

***S*-(12-Methyl-7-benz[*a*]anthrylmethyl)thioglycerol (4).** A solution of 2.4 g of thioglycerol (Evans) in 20 ml of 1 N NaOH–MeOH and 10 ml of C_6H_6 was stirred and cooled while 2.1 g of 7-iodomethyl-12-methylbenz[*a*]anthracene[12] was added. After 3 h of stirring at 0 °C, the clear mixture was diluted with