ANTICONVULSANT ACTIVITY

Derivatives of Succinimide, Glutarimide, Thiazolidinedione and Methanol, and some Miscellaneous Compounds

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Anticonvulsant activity has been associated with several types of compound, particularly the barbiturates, ureides, and hydantoins, and various members of these groups have proved of clinical value. The use of oxazolidinediones and in particular 3-allyl-5-methyl-oxazolidinedione, aloxidone[1], in the treatment of petit mal is also already well known, the latter being a particularly useful drug on account of the absence of the "glare phenomenon" usually associated with the clinical use of some other members of this group, e.g., troxidone. The anticonvulsant action of 5:5-diethyl- and 5:5-dimethyl-thiazolidinedione has also been reported[2]. More recently Chen, Portman, Ensor and Bratton[3] have described a number of α-phenylsuccinimides, several of which were found to be particularly effective anticonvulsants.

The purpose of the present paper is to describe screening tests for anticonvulsant activity which have been carried out on other derivatives of succinimide and some derivatives of the homologous glutarimide, one of which (Compound 415[4], α-methyl-α-phenylglutarimide) appears to be particularly active. In addition some derivatives of thiazolidinedione and of methanol, and some miscellaneous compounds have been investigated, and the results are reported here.

The method of test adopted was essentially the same as the maximal leptazol seizure pattern test used by Goodman, Swinyard, Brown, Schiffman, Grewal and Bliss[5]. Thus, an estimate of the relative activity of any given compound, compared with aloxidone, was obtained by determining the doses which would afford a certain degree of protection against leptazol-induced convulsions in mice. Groups of animals were premedicated with varying doses and, after a standard interval of two hours, which was chosen as a result of previous experience with troxidone and aloxidone, all the animals were injected intravenously with a "certainly convulsant dose" of leptazol. An estimate was thereby obtained of the dose required to abolish the hindleg extensor component of the maximal seizure in 50 per cent. of the animals (median protective dose, PD50).

Experimental

Female albino mice of Schofield strain, weighing approximately 20 g. and starved from the previous day, were divided by random selection into groups of 6. The compounds for test were dissolved or suspended in a 5 per cent. solution of gum acacia, and serial dilutions were prepared.

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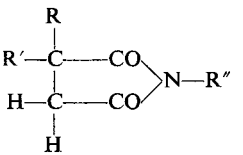
Volumes of 0·5 ml. per 20 g. of body weight were then administered orally, so that the animals received 506, 337, 225, and 150 mg. of the compound per kg. of body weight. Where the PD50 was found to be less than 150 mg./kg. the test was repeated with an appropriate reduction in the initial amount of the compound, the above geometrical progression of doses being continued.

After 2 hours, all the animals were given an intravenous injection of a previously determined "certainly convulsant dose" of leptazol (60 mg./kg.

TABLE I

SUCCINIMIDE DERIVATIVES

General formula:



Compound	Substituent Groups		PD50 mg/kg.	PD50 of aloxidone mg/kg.	Activity Ratio
	on C-atom	on N-atom			
Succinimide	—	—	>510	210	<0·4
348	—	allyl	280	160	0·6
356	phenyl	allyl	>510	220	<0·4
379	benzylidine	—	>510	130	<0·3
384	benzylidine	methyl	>510	170	<0·3
386	benzylidine	allyl	>510	170	<0·3
385	benzylidine	phenyl	>510	170	<0·3
388	benzylidine	benzyl	>510	140	<0·3
387	benzylidine	*cyclo*hexyl	>510	140	<0·3
366	*spiro-cyclo*hexyl	—	*		
362	*spiro-cyclo*hexyl	methyl	*		
376	*spiro-cyclo*hexyl	allyl	>510	150	<0·3
369	*spiro-cyclo*hexyl	hydroxyethyl	>510	150	<0·3
363	*spiro-cyclo*hexyl	phenyl	>510	150	<0·3
365	*spiro-cyclo*hexyl	benzyl	340	150	0·4
364	*spiro-cyclo*hexyl	*cyclo*hexyl	>510	150	<0·3
370	dimethyl	—	280	150	0·5
374	dimethyl	methyl	130	150	1·1
375	dimethyl	allyl	220	150	0·7
367	dimethyl	phenyl	150	140	0·9
371	dimethyl	benzyl	>510	150	<0·3
368	dimethyl	*cyclo*hexyl	>510	170	<0·3
357	methyl, phenyl	methyl	<150	220	>1·5
408	methyl, benzyl	—	165	145	0·9
410	methyl, benzyl	methyl	220	145	0·7
409	methyl, benzyl	allyl	>510	145	<0·3
411	methyl, benzyl	phenyl	>510	180	<0·4

*Compound itself induced convulsions, even at dose level of 150 mg/kg.

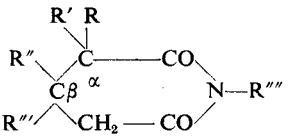
of body weight). This dose had been found to induce clonic-tonic convulsions in all but very insensitive mice, and this was confirmed in every test by the responses observed in a control group of animals receiving no premedication. Only those mice showing the tonic extensor component of the leptazol-induced seizure were regarded as showing a positive response, and the percentage of animals protected in each group was calculated from the number failing to give this response.

In view of the small numbers of animals used, these values were then

TABLE II

GLUTARIMIDE DERIVATIVES

General formula:

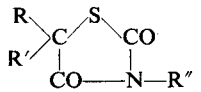


Compound	Substituent Groups			PD50 mg/kg.	PD50 of aloxidone mg/kg.	Activity Ratio
	on α-C-atom	on β-C-atom	on N-atom			
415	methyl, phenyl	—	—	> 70	130	>1·9
413	methyl, phenyl	—	methyl	110	130	1·2
394	—	phenyl	—	340	110	0·3
377	—	phenyl	methyl	380	150	0·4
383	—	phenyl	benzyl	>510	120	<0·2
381	—	dimethyl	methyl	510	130	0·3
391	—	dimethyl	allyl	240	130	0·5
395	—	dimethyl	benzyl	>510	150	<0·3

TABLE III

THIAZOLIDINE 2 : 4-DIONE DERIVATIVES

General formula:

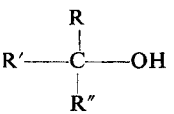


Compound	Substituted Groups		PD50 mg/kg.	PD50 of aloxidone mg/kg.	Activity Ratio
	on C-atom	on N-atom			
354	—	—	>510	160	<0·3
353	—	allyl	290	150	0·5
351	methyl	—	>510	150	<0·3
350	methyl	allyl	300	210	0·7
349	methyl	benzyl	>510	210	<0·4
359	dimethyl	—	280	210	0·8
360	dimethyl	methyl	340	200	0·6
361	dimethyl	allyl	>510	200	<0·4

TABLE IV

CARBINOLS

General formula:

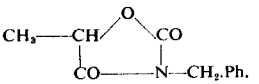
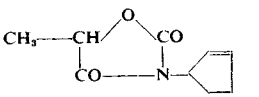
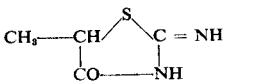
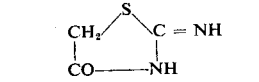
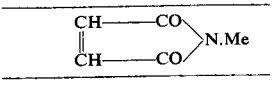
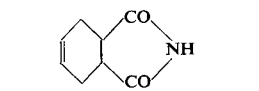
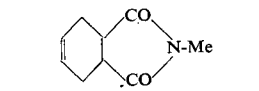
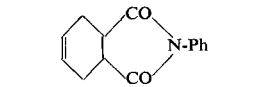
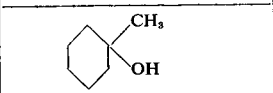
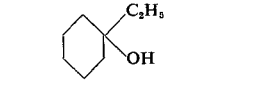


Compound	Substituent Groups			PD50 mg/kg.	PD50 aloxidone mg/kg.	Activity Ratio
	R	R′	R″			
396	methyl	methyl	*n*-propyl	150	180	1·2
404	methyl	methyl	*iso*butyl	150	280	1·9
389	methyl	ethyl	ethyl	150	140	0·9
397	methyl	ethyl	*n*-propyl	200	180	0·9
406	methyl	*n*-propyl	*n*-propyl	210	280	1·3
399	ethyl	ethyl	ethyl	<150	120	>0·8
methylpentynol	methyl	ethyl	ethinyl	60	140	2·3
333	methyl	*n*-propyl	ethinyl	55 and 67	120 and 110	2·2 and 1·6
339	methyl	*iso*butyl	ethinyl	190	160	0·8
343	methyl	*n*-amyl	ethinyl	>510	180	<0·4

treated where possible by the method of Thomson (described by Gaddum[6]) for obtaining estimates of median effective doses from the results of screening tests. The dose-response curve was smoothed by taking each

TABLE V

MISCELLANEOUS COMPOUNDS

Compound	Formula	PD50 mg/kg.	PD50 of aloxidone mg/kg.	Activity Ratio
378	$Ph.CH_2.CO.NH_2$	340	130	0·4
382	$Ph.CH_2.CO.NH.CH_3$	430	120	0·3
390	$Ph.CH_2.CO.NH.CO.CH_3$	>510	140	<0·3
398	$Ph.CH_2.CO.NMe.CO.CH_3$	>510	150	<0·3
347		210	160	0·8
403		>510	150	<0·3
352		>510	160	<0·3
355		>510	210	<0·4
393		>510	150	<0·3
400		>510	120	<0·2
402		340	150	0·4
401		510	150	0·3
407		190	160	0·8
392		170	130	0·8

set of 3 successive doses in turn, calculating the average effect in each set, and plotting these values against the middle doses of the sets. The median effective dose was then determined by inter-or extra-polation.

Where the screening tests indicated appreciable anticonvulsant activity, repeat tests were performed, using 2 to 4 dose levels and 10 to 30 animals

per dose. The values for the percentage protection were plotted against the respective doses of anticonvulsant on log-probability paper, and the PD50 and its confidence limits (P = 0·95) determined by the method of Litchfield and Wilcoxon[7].

In some instances preliminary toxicity tests were carried out in the usual manner, by oral administration of the compound as a solution or suspension in 5 per cent. acacia solution, and the number of deaths was recorded after 5 days.

RESULTS

In Tables I to V the results of the anticonvulsant screening tests are given, the values recorded being the estimated PD50 of the compound, the estimated PD50 of aloxidone in a parallel test, and the activity of the compound relative to that of aloxidone taken as unity.

TABLE VI

DETAILED COMPARISON OF ANTICONVULSANT ACTIVITY OF SELECTED COMPOUNDS WITH THAT OF ALOXIDONE

Compound	Median Protective Dose (confidence limits, P = 0·95, in brackets)	Activity Ratio
	mg/kg.	
aloxidone	165 (135–201)	
357 (α-methyl-α-phenyl *N*-methyl succinimide) ..	69 (55-87)	2·4
aloxidone	130 (100–170)	
374 (αα′-dimethyl *N*-methyl succinimide) ..	124 (92–167)	1·0
aloxidone	162 (109–239)	
333 (Methyl *n*-propyl ethinyl carbinol)	89 (79–101)	1·8
aloxidone	158 (133–188)	
399 (Tri-ethyl carbinol) ..	130 (97–174)	1·2
aloxidone	149 (122–182)	
methylpentynol	70 (57–86)	2·1
aloxidone	168 (139–203)	
troxidone	270 (206–354)	0·6

TABLE VII

COMPARISON OF ACUTE TOXICITY WITH THAT OF ALOXIDONE

Compound	Number of deaths at 0·7 g./kg.	1·0 g./kg.	1·5 g./kg.	2·3 g./kg.	3·4 g./kg.	5·1 g./kg.	LD50 g./kg.	Toxicity Ratio
aloxidone ..		0/5	5/5	5/5	5/5	5/5	1·3	
348 ..		2/5	3/5	5/5	5/5	5/5	1·2	1·1
aloxidone ..		0/5	2/5	5/5			1·5	
350 ..		2/5	4/5	5/5			1·0	1·5
aloxidone ..	1/10	3/10	6/10	9/10			1·4	
357 ..	3/10	7/10	10/10	10/10			0·9	1·6
aloxidone ..		1/5	3/5	5/5			1·5	
353 ..		3/5	5/5	5/5			1·0	1·5

Table VI contains the results of the larger tests carried out on 5 selected compounds. Results obtained with troxidone have been included for comparison. The final column contains the Activity Ratio of the compound (aloxidone = 1·0), derived from the PD50 of the compound and the PD50 of aloxidone obtained in a parallel test.

Discussion

Of the 66 compounds tested, only a few were found to be equal or superior to aloxidone in anticonvulsant potency, the majority being relatively inactive. Thus, none of the α-benzylidine derivatives of succinimide afforded any protection against leptazol at the dose levels usually employed. The same may be said, too, of all except one of the α-*spiro-cyclo*hexyl derivatives, and two of them were found actually to induce leptazol-like convulsions themselves. It might prove of value to investigate the possible use of these two (compounds 362 and 366) as analeptics. Varying degrees of activity were found among the αα-dimethyl succinimides, the most active being the *N*-methyl (confirmed by a large-scale test) and *N*-phenyl derivatives, which were similar in potency to aloxidone. Unsubstituted α-methyl- α-benzyl succinimide also appeared to be about as potent as aloxidone, but the introduction of *N*-substituents resulted in loss of activity. The most active succinimide tested was α-methyl-α-phenyl *N*-methyl succinimide which, in a large scale test, appeared to be 2·4 times as potent as aloxidone. It is also, however, 1·6 times as toxic. Chen *et al*[3] were the first to describe this compound as having a high degree of anticonvulsant activity.

In the glutarimide series, Compound 415 (α-methyl-α-phenylglutarimide) was found to be particularly active, and it has been the subject of considerable study, the results of which will be reported separately. Compound 413 (α-methyl-α-phenyl *N*-methylglutarimide) also appears to be more potent than aloxidone, but the β-phenyl-, and ββ-dimethyl-glutarimides were relatively inactive.

Thiazolidine 2:4-dione and its derivatives are all less active than aloxidone, the most potent (the 5:5-dimethyl derivative) having only about 80 per cent. of the activity of aloxidone (compare Hazard *et al.*[2]).

All the carbinols tested show a fairly high order of activity, methylpentynol (methyl-ethyl-ethinyl carbinol), in particular, being about twice as active as aloxidone. The anticonvulsant activity of methylpentynol has also been reported by P'an, Gardocki, Harfenist and Bauley[8] and P'an Markarian, McLamore and Bauley[9] and Reinhard, Kimura and Scudi[10]. Of the others, compound 333 (methyl *n*-propyl ethinyl carbinol) also appears to be about twice as active as aloxidone. It may also be noted here that other alcohols have been found to possess anticonvulsant properties e.g., *iso*propanol[11] and 2:2-diethyl-1:3-propanediol[12]. However, it must be borne in mind that many of the carbinols are potent narcotics, and, in addition, inspection of the results (unpublished) of toxicity studies with methylpentynol as reference compound indicates that many are more toxic than aloxidone. Compound 333, for example, appears to be at least twice as toxic.

None of the miscellaneous compounds listed in Table V was as active as aloxidone, and most showed little or no activity.

It is of some interest to endeavour to relate the chemical constitution of the various groups of compounds to the existence of anticonvulsant activity. The following compounds all exhibit considerable activity:—phenobarbitone, phenurone, diphenylhydantoin, aloxidone, a group of succinimide derivatives, and a glutarimide derivative (Compound 415 above) All of these contain the grouping

where R is alkyl or H and R′ and R″ are alkyl, phenyl, or hydrogen, and in the most active at least one substituent (R′ or R″) is phenyl. Phenobarbital is by far the most active, but it suffers from certain disadvantages that are well known, and further research in this field may yet bring to light a substance with more desirable overall therapeutic properties.

Summary

1. The anticonvulsant activity of some derivatives of succinimide, glutarimide, thiazolidinedione, and methanol, and of some miscellaneous compounds has been investigated.

2. Earlier work on the activity of some derivatives of succinimide has been confirmed.

3. The most promising compounds appear to be methylpentynol (methyl-ethyl-ethinyl carbinol), methyl-*n*-propyl ethinyl carbinol, and α-methyl-α-phenyl-glutarimide. The last-named is to be the subject of more detailed investigation.

The authors acknowledge with pleasure the detailed chemical work involved in the preparation of the compounds, by Mr. P. A. McCrea, Dr. J. A. Baker, and Miss M. V. A. Chapman. They also thank Miss Needham for technical assistance.

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