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THE SEDATIVE AND ANTICONVULSANT ACTIVITY OF SOME SUBSTITUTED PYRROLIDONES AND PIPERIDONES

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A series of substituted pyrrolidones and piperidones has been synthesized (Taub, unpublished) in an attempt to produce new compounds with hypnotic or anticonvulsant activity. Whilst it is relatively easy to evaluate anticonvulsant activity in small laboratory animals such as the mouse and rat, difficulties are encountered in assessing true hypnotic activity in such species.

Kleitman (1939) suggested that sleep is accompanied by unconsciousness and loss of righting mechanisms. If the subject cannot be easily aroused from such a condition, then central depression has passed from the stage of sedation to that of hypnosis. The additional loss of reflex responses to sensory and motor stimuli indicates the final stage of general anaesthesia.

We have investigated the properties of some substituted pyrrolidones and piperidones and have selected 5-ethyl-5-phenylpyrrolid-2-one for a detailed examination of its pharmacological activity.

METHODS

Male, Schofield albino mice weighing about 20 g, Sprague-Dawley albino rats, male Tuck albino guinea-pigs, New Zealand White rabbits, cats, dogs (whippets), squirrel-monkeys (*Saimi sciurea*) and small Essex-Large White Cross pigs of either sex were used. The sex and weight range of the Sprague-Dawley rats will be referred to in the appropriate sections.

Drugs

In addition to those listed in Table 1 the following drugs were used: (±)-amphetamine sulphate, chlorpromazine hydrochloride, phenytoin sodium, glutethimide, leptazol, meprobamate, phenobarbitone and strychnine hydrochloride.

General procedures

In all experiments, except when otherwise stated, the compounds (dissolved or suspended in 5% acacia) were administered intraperitoneally at various dose levels to groups of five animals. Dose volumes were adjusted to 2.5 ml./100 g body weight and 1.0 ml./100 g body weight for the mouse and rat respectively. The following parameters were estimated: ED50, median effective dose; HD50, median hypnotic dose

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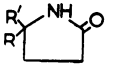
TABLE 1

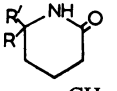
THE CENTRAL NERVOUS DEPRESSANT PROPERTIES OF SOME SUBSTITUTED PYRROLIDONES AND PIPERIDONES AFTER INTRAPERITONEAL ADMINISTRATION TO MICE

A. Substituted pyrrolidones



No.	R	R^1	Dose range study (mg/kg) LD50	MD50	HD50	ED50 (mg/kg) Potentiation of hexobarbitone narcosis	Prevention of fighting episodes	Anticonvulsant activity against Electroshock	Leptazol	Strychnine
1	C_6H_5	CH_3	750	375	375	>200	62	20	27	>200
2	C_6H_5	C_2H_5	750	375	375	145	107	27	25	80
3	C_6H_5	n–C_3H_5	500	190	500	133	81	35	35	>150
4	C_6H_5	C_3H_7	750	190	750	170	>200	41	62	107
5	C_6H_5	C_3H_7i	750	375	375	>200	62	22	9	123
6	C_6H_5	C_4H_9	500	190	ca 250	>125	>200	123	ca 200	>200
7	*p*-Cl.C_6H_4	C_2H_5	500	250	375	>200	53	14	13	50
8	*p*-Cl.C_6H_4	n–C_3H_5	500	250	500	>200	>200	54	107	>200
9	*p*-$CH_3O.C_6H_4$	C_2H_5	750	375	500	>200	185	61	>200	>150
10	*p*-$C_2H_5O.C_6H_4$	C_2H_5	2,000	750	750	>200	>200	142	81	>200
11	C_6H_{11}	CH_3	375	375	375	>150	ca 150	92	ca 150	>150
12	C_6H_{11}	C_2H_5	375	>375	250	>150	>150	122	>150	>150
13	C_6H_{11}	C_3H_7	190	>190	>190	>75	>50	>50	>75	>50
	Diphenylhydantoin		375					2·6	3·1	

B. Substituted piperidones



14	C_6H_5	CH_3	375	190	375	>150	61	31	40	ca 150
15	C_6H_5	C_2H_5	375	190	190	>150	81	23	62	107
16	C_6H_5	C_4H_9	375	250	190	>150	93	35	53	93
17	C_6H_{11}	C_4H_9	500	373	500				>100	>100
18	C_6H_{11}	C_6H_{11}	1,500	1,500	>2,000				>400	>400
	Diphenylhydantoin		375					2·6	3·1	

indicated by loss of righting reflex; MD50, median dose producing inhibition of motor co-ordination; and LD50, median lethal dose.

All ED50, HD50, MD50 and LD50 values in Table 1 were estimated by Kärber's (1931) formula. Further ED50 values, except when otherwise stated, were estimated by the method of Litchfield & Wilcoxon (1949).

Dose-range studies

In all species the changes in behaviour and general condition of the animals were recorded on the day of the experiment and, when necessary, on subsequent days.

Mice. The HD50, MD50 and LD50 (after 7 days) values were determined.

Rats. The compounds were administered orally to male rats weighing 170 to 200 g. The HD50 values were estimated on the day of the experiment and the LD50 values after 7 days.

Other species. The compounds were administered orally to guinea-pigs (500 to 700 g), rabbits (2.6 to 4.1 kg), cats (2 to 3 kg), dogs (6 to 10 kg), squirrel-monkeys (500 to 550 g) and small pigs (10.5 to 13 kg). For each species one animal per dose level was used.

Acute toxicity

The compounds were administered orally to groups of twenty mice. The mortalities were recorded after 7 days and the LD50 values were calculated.

Potentiation of hexobarbitone narcosis

At 1 hr after the administration of each compound to mice a solution of hexobarbitone sodium (2 mg/ml. in 0.9% saline) was infused intravenously into a tail vein at a rate of 0.05 ml./10 sec (McCance, 1964). The end point was reached when loss of righting reflex occurred for more than 10 sec. The ED50 values were determined graphically, by plotting the percentage reduction in the volume required to cause loss of righting reflex when compared with controls against the log dose of the compound.

Potentiation of a subhypnotic dose of alcohol

At 30 min after the administration of each compound to mice a subliminal dose of ethyl alcohol (1.9 to 2.0 g/kg) in distilled water was injected by the intraperitoneal route. The ED50 values were estimated from the number of animals exhibiting loss of righting reflex.

Anticonvulsant activity in mice

The prevention of maximal electroshock seizure was determined by a modification of the method of Swinyard, Brown & Goodman (1952). A separate group of animals was used at each time interval to prevent the development of tolerance to the electroshock. At 1, 2 and 3 hr after dosing an electroshock (25 mA of 50 cycles/sec for 0.2 sec) was delivered to each mouse through corneal electrodes. The electroshock source was a Hans Technical Electroshock Seizure Apparatus (Model 2c).

Antagonism of maximal leptazol-induced seizures (Goodman, Grewal, Brown & Swinyard, 1952) and of strychnine-induced seizures was determined after the intravenous injection of 1.0 ml./100 g body weight of a 0.6% w/v aqueous solution of leptazol and a 0.006% w/v aqueous solution of strychnine hydrochloride. The leptazol was injected 2 hr and the strychnine 30 min after the administration of the compounds under test.

The ED50 values were estimated in all procedures from the number of animals in which tonic extension of the hind-limbs failed to occur.

Prevention of fighting episodes in mice

The taming or sedative effects of the compounds were determined 1 hr after dosing by a modification of the procedure described by Tedeschi, Tedeschi, Mucha, Cook, Mattis & Fellows (1959). The ED50 values were estimated from the number of pairs of mice in which the frequency of fighting episodes was reduced to four bouts or less within a 3-min period.

Inhibition of motor co-ordination

At 1 hr after their administration the effect of the compounds on motor co-ordination was determined in mice, using a Rotarod (Dunham & Miya, 1957). Trained mice were placed on a rod rotating at 15 revs/min. The MD50 values were determined from the number of animals which remained on the rod at the end of the 2-min test period.

Antagonism of amphetamine-induced behavioural changes

The compounds were administered orally to groups of ten female rats weighing 110 to 140 g. After 1 hr each rat was injected intravenously with 0.5 ml./100 g body weight of an 0.04% w/v aqueous solution of amphetamine sulphate. The ED50 values were determined graphically from the number of rats in which the typical amphetamine reaction, characterized by excessive vertical and lateral movements of the head, was absent when the animals were observed 15 min after the injection of the amphetamine.

Prevention of minimal leptazol-induced seizures in rats

The " sedative," " hypnotic " and " anaesthetic " effects of a barbiturate-like agent can be quantitatively titrated by suppression of leptazol-induced clonic seizures in rats or mice (Chen & Portman, 1952). The end-point in the present investigation was dependant on the presence or absence of facial and fore-limb clonus. The various stages, ranging from " sedation " to " hypnosis," have not been individually titrated.

The compounds were administered to groups of ten male rats weighing 160 to 220 g. After 2 hr each animal was injected intravenously with 0.5 ml./100 g body weight of a 0.32% w/v solution of leptazol in 0.9% saline. The animals were then observed for a period of 1 min and the ED50 values were estimated from the number of animals in which facial and fore-limb clonus were absent.

Effect on the performance of squirrel-monkeys responding in a multiple fixed-interval fixed-ratio schedule

This type of schedule is maintained by a positive reinforcement (food reward) in contrast to the negative reinforcement (electric shock) employed in shock avoidance studies. Positively motivated behavioural studies can be selective for drugs that are ineffective in blocking specifically the classical conditioned avoidance response. The multiple fixed-interval fixed-ratio test was first described by Ferster & Skinner (1957).

Initially a 10-min fixed-interval occurs in which the first response occurring after 10 min is reinforced by food. This is followed by a 30-response fixed-ratio in which every thirtieth response is reinforced with food. The stimuli cease for a 2.5-min time-out after each food reinforcement. Responses occurring during time-out periods are not reinforced.

Effect on leptazol-induced petit mal*-like cerebral dysrhythmias in rabbits*

Goodman, Toman & Swinyard (1946) reported the appearance of brief episodes of slow wave (3 to 4 cycles/sec) activity in the optic-associative cortex of rabbits after the subcutaneous injection of a sub-convulsant dose of leptazol. These discharges are similar to the dysrhythmic episodes found in patients with *petit mal* epilepsy. The effect of the compound on such abnormal cortical activity in rabbits was examined.

RESULTS

Dose-range studies

Mice. All compounds listed in Table 1 were examined before further testing. General effects observed were loss of righting reflex, clonic-tonic convulsions, hypotonia and hypertonia (see Table 5). Compounds 2, 5 and 7 produced loss of righting reflex which lasted for between 6 and 18 hr. This was taken as initial evidence that the compounds may be producing hypnosis. 5-Ethyl-5-phenylpyrrolid-2-one (Compound 2, Table 1) was selected and examined in further species as follows.

TABLE 2

HYPNOTIC EFFECT OF 5-ETHYL-5-PHENYLPYRROLID-2-ONE, GLUTETHIMIDE, PHENOBARBITONE AND CHLORPROMAZINE AFTER INTRAPERITONEAL ADMINISTRATION TO MICE

Drug	Acute toxicity, LD50 (mg/kg)	Hypnotic activity, HD50 (mg/kg)	Ratio LD50 : HD50
5-Ethyl-5-phenylpyrrolid-2-one (Compound 2)	750	375	2·0
Glutethimide	500	190	2·6
Phenobarbitone	375	125	3·0
Chlorpromazine	375	375	1·0

Rats, guinea-pigs and rabbits. 5-Ethyl-5-phenylpyrrolid-2-one produced effects qualitatively similar to those observed in mice with the exception that hypertonia (limb rigidity or spasticity) was absent.

Cats, dogs, monkeys and pigs. The effects observed were again qualitatively similar to those exhibited in mice. As with rats, guinea-pigs and rabbits, glutethimide was included as a reference drug and produced true hypnosis. 5-Ethyl-5-phenylpyrrolid-2-one failed to induce sleep, even at near toxic doses, and, unlike glutethimide, induced severe intermittent spastic rigidity of fore- and hind-limbs.

The hypnotic activity of 5-ethyl-5-phenylpyrrolid-2-one in mice is summarized in Table 2 and, from the LD50 : HD50 ratio, lies midway between those of phenobarbitone and chlorpromazine.

The acute toxicity, potentiation of hexobarbitone and alcohol narcosis, prevention of fighting episodes and anticonvulsant activity in mice are shown in Table 3. This is additional evidence regarding the sedative properties of 5-ethyl-5-phenylpyrrolid-2-one. The anticonvulsant activity of this compound is much weaker than that of phenobarbitone.

Table 4 summarizes the hypnotic, anti-minimal leptazol and anti-amphetamine effects of 5-ethyl-5-phenylpyrrolid-2-one, glutethimide, phenobarbitone, meprobamate and chlorpromazine in rats. Again, as in mice, the hypnotic activity lies between those of phenobarbitone and chlorpromazine. However, from the ratio obtained by relating the LD50 to ED50 values for anti-minimal leptazol and anti-amphetamine tests it can be seen that, whilst phenobarbitone possesses a high value in the former and a low value in the latter test, chlorpromazine exhibits entirely opposite properties. 5-Ethyl-5-phenylpyrrolid-2-one parallels the sedative (meprobamate) and sedative-hypnotic (glutethimide and phenobarbitone) drugs.

The results in Table 5 again demonstrate (see Laycock & Shulman, 1963) that it is possible to pass from pure convulsant activity (agonist) to pure anticonvulsant activity (antagonist) within a series of compounds. We have regarded compounds as agonists if they produced hypertonia or convulsions in the dose-range study and possessed only weak anticonvulsant activity, as partial agonists if they possessed mixed properties and as antagonists if they produced hypotonia in the dose-range study and in addition possessed anticonvulsant or hypnotic properties.

(±)-5-Ethyl-5-phenylpyrrolid-2-one was resolved and the laevo-isomer showed weaker activity than the racemic form. No attempt was made to obtain the dextro-isomer (Table 6).

TABLE 3

COMPARATIVE CENTRAL NERVOUS DEPRESSANT EFFECTS OF 5-ETHYL-5-PHENYLPYRROLID-2-ONE, GLUTETHIMIDE, PHENOBARBITONE, MEPROBAMATE AND CHLORPROMAZINE AFTER ORAL ADMINISTRATION TO MICE

Confidence limits (P=0·95) are shown in parentheses. There were twenty mice per dose group

Drug	Acute toxicity, LD50 (mg/kg)	Inhibition of motor co-ordination, MD50 (mg/kg)	ED50 (mg/kg)					
			Potentiation of hexobarbitone narcosis	Potentiation of alcohol narcosis	Prevention of fighting episodes	Anticonvulsant activity against		
						Electroshock	Leptazol	Strychnine
5-Ethyl-5-phenyl-pyrrolid-2-one (Compound 2)	1,360 (1,148–1,659)	285 (232–351)	157	43 (26–69)	77 (58–102)	30 (21–43)	32 (26–40)	100 (76–132)
Glutethimide	750 (641–878)	175 (156–196)	115	24 (18–31)	56 (37–85)	20 (15–27)	18 (12–28)	83 (59–116)
Phenobarbitone	263 (245–283)	83 (74–93)	85	18 (12–27)	52 (40–67)	7·0 (5·0–9·6)	4·8 (3·4–6·8)	93 (25–60)
Meprobamate	1,530 (1,297–1,805)	270 (208–351)	224	72 (51–102)	116 (89–151)	80 (64–100)	62 (48–81)	150 (106–213)
Chlorpromazine	150 (75–300)	8·8 (6·9–11·2)	2·4	1·0 (0·7–1·5)	11 (7·7–16)	70 (45–109)	7·0 (4·8–6·9)	50 (33–75)

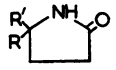
TABLE 4

HYPNOTIC, ANTI-MINIMAL LEPTAZOL AND ANTI-AMPHETAMINE EFFECTS OF 5-ETHYL-5-PHENYLPYRROLID-2-ONE, GLUTETHIMIDE, PHENOBARBITONE, MEPROBAMATE AND CHLORPROMAZINE AFTER ORAL ADMINISTRATION TO RATS

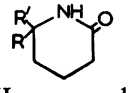
Drug	Acute toxicity, LD50 (mg/kg)	Hypnotic activity, HD50 (mg/kg)	Ratio LD50 : HD50	Anti-minimal leptazol, ED50ML (mg/kg)	Ratio LD50 : ED50ML	Anti-amphetamine, ED50A (mg/kg)	Ratio LD50 : ED50A
5-Ethyl-5-phenylpyrrolid-2-one (Compound 2)	600	300	2·0	38	16	250	2·4
Glutethimide	300	190	1·6	32	9·4	280	1·0
Phenobarbitone	430	93	4·6	8·7	49	160	2·7
Meprobamate	1,072	750	1·4	58	18	1,070	1·0
Chlorpromazine	930	>1,000	<1·0	>200	<4·7	2·0	465

TABLE 5

THE CONVULSANT AND ANTICONVULSANT PROPERTIES OF SOME SUBSTITUTED PYRROLIDONES AND PIPERIDONES IN MICE

A. Substituted pyrrolidones 

Agonist Hypertonia or convulsions			Partial agonist Hypertonia, convulsions, anticonvulsant or hypnotic			Antagonist Hypotonia, anticonvulsant or hypnotic		
No.	R	R^1	No.	R	R^1	No.	R	R^1
8	*p*-Cl.C_6H_4	n-C_3H_5	2	C_6H_5	C_2H_5	1	C_6H_5	CH_3
11	C_6H_{11}	CH_3	3	C_6H_5	n-C_3H_5	4	C_6H_5	C_3H_7
13	C_6H_{11}	C_3H_7	6	C_6H_5	C_4H_9	5	C_6H_5	C_3H_7i
						7	*p*-Cl.C_6H_4	C_2H_5
						9	*p*-$CH_3O.C_6H_4$	C_2H_5
						10	*p*-$C_2H_5O.C_6H_4$	C_2H_5

B. Substituted piperidones 

14	C_6H_5	CH_3	15	C_6H_5	C_2H_5
17	C_6H_{11}	C_4H_9	16	C_6H_5	C_4H_9

TABLE 6

THE CENTRAL NERVOUS DEPRESSANT PROPERTIES OF (−)-5-ETHYL-5-PHENYLPYRROLID-2-ONE COMPARED WITH THE PARENT STRUCTURE AFTER ORAL ADMINISTRATION TO MICE

		ED50 (mg/kg)				
				Anticonvulsant activity against		
Drug	Acute toxicity, LD50 (mg/kg)	Potentiation of hexobarbitone narcosis	Prevention of fighting episodes	Electro-shock	Leptazol	Strychnine
(±)-5-Ethyl-5-phenylpyrrolid-2-one (Compound 2)	812	155	93	27	27	47
(−)-5-Ethyl-5-phenylpyrrolid-2-one	536	>200	107	23	41	81

Effect on the performance of squirrel-monkeys responding in a multiple fixed-interval fixed-ratio schedule

5-Ethyl-5-phenylpyrrolid-2-one, 100 mg/kg orally, invariably decreased the rate of responding in the fixed-interval component.

Effect on leptazol-induced petit mal*-like cerebral dysrhythmias in rabbits*

5-Ethyl-5-phenylpyrrolid-2-one, 500 mg/kg orally, abolished the dysrhythmia induced by a subcutaneous injection of leptazol.

DISCUSSION

5-Ethyl-5-phenylpyrrolid-2-one was selected from a group of pyrrolidones and piperidones and subjected to a detailed examination in numerous species in the hope that it might lead to a new compound with hypnotic properties. Further investigations showed that the compound was not a hypnotic, even at near toxic doses, but appeared to be a general sedative and in addition possessed anticonvulsant activity.

In order to differentiate between the tranquillizers and the sedative-hypnotic drugs, Chen (1962) developed two test procedures in rats and mice. Using mice, he evaluated compounds for anti-excitant activity against methylamphetamine-induced excitement and for their sedative-hypnotic activity against leptazol-induced clonic seizures. He showed that chlorpromazine was effective at low dose levels in antagonizing methylamphetamine-induced excitation but was ineffective at similar doses in suppressing the clonic seizures induced by leptazol. This compares with the lack of hypnotic activity of chlorpromazine. In contrast, the sedative-hypnotic drugs did not suppress methylamphetamine-induced excitation at non-neurotoxic dose levels. They were, however, very effective suppressants of minimal clonic seizures induced by leptazol.

We have attempted to differentiate between these types of drugs in rats, using the prevention of amphetamine-induced behavioural changes as a criterion of anti-excitant activity and the antagonism of minimal leptazol seizures to determine sedative-hypnotic activity. The results presented in Table 4 confirm the work of Chen (1962) regarding the sedative-hypnotic activity of phenobarbitone and the anti-excitatory activity of chlorpromazine. Phenobarbitone was extremely active in preventing the occurrence of minimal leptazol seizures but exhibited activity against amphetamine only at neurotoxic doses. Conversely, chlorpromazine was extremely active against amphetamine and only weakly active against leptazol. 5-Ethyl-5-phenylpyrrolid-2-one paralleled phenobarbitone in this respect, although it was much less active than phenobarbitone in suppressing minimal leptazol seizures.

In rodents the sedative activity appears to be similar to that of meprobamate and phenobarbitone, although 5-ethyl-5-phenylpyrrolid-2-one is slightly more active as an anticonvulsant than meprobamate but much less active than phenobarbitone as a sedative. However, in studies on positively motivated behaviour in squirrel-monkeys, this compound, like chlorpromazine and phenobarbitone, decreased the rate of responding in the fixed-interval component, whereas meprobamate increased the rate of responding. Thus 5-ethyl-5-phenylpyrrolid-2-one, whilst lacking hypnotic activity, possesses properties common to phenobarbitone.

Towards the completion of our studies a report was presented (Carvajal, Russek, Tapia & Massieu, 1964) regarding the anticonvulsant activity of both the 5-methyl- and 5-ethyl-derivatives of 5-phenylpyrrolid-2-one. It was suggested that these drugs might be effective in *petit mal* as well as *grand mal* epilepsy since they were active in controlling both drug- and electrically-induced seizures. These workers believed that clinical trials would show the new drugs to be at least as effective as diphenylhydantoin (Russek, 1964). Our studies show similar activity for the 5-methyl- and 5-ethyl-derivatives (Compounds 1 and 2, Table 1), although the activity, relative to diphenylhydantoin in mice, is very weak. We find these compounds to have approximately one-tenth of the activity of diphenylhydantoin (Table 1). We have shown that 5-ethyl-5-phenylpyrrolid-2-one is capable of preventing leptazol-induced minimal (clonic) seizures and also in brief studies that it will antagonize leptazol-induced *petit mal*-like cerebral dysrhythmias in rabbits. In contrast, diphenylhydantoin is incapable of suppressing leptazol-induced minimal seizures (Chen, 1962) and is also completely inactive at 300 mg/kg against leptazol-induced cerebral dysrhythmias. This correlates with the lack of activity of diphenylhydantoin against *petit mal* in man. Since 5-ethyl-5-phenylpyrrolid-2-one does not parallel diphenylhydantoin in this respect, it

seems unlikely that the drug will be active against *grand mal*. However, phenobarbitone, whilst antagonizing minimal clonic seizures induced by leptazol, is widely used in the treatment of *grand mal* but is of no value against *petit mal* epilepsy.

In our studies evidence has been accumulated for the production, in several species, of severe limb rigidity of both fore- and hind-limbs after the administration of 5-ethyl-5-phenylpyrrolid-2-one. While the 5-methyl-derivative might lack this undesirable property (it was, however, only examined in mice and not in higher species), clinical evaluation of these compounds was considered to be unwarranted.

Laycock & Shulman (1963) have reported the existence of partial agonists among a series of β-substituted glutarimides and related drugs, with actions in mice ranging from convulsant and analeptic (agonist) to anticonvulsant and hypnotic (antagonist). These workers have concluded that the existence of drugs structurally related to agonists and antagonists and which show agonist and antagonist activity supports the postulate that convulsions and hypnosis are initiated by these drugs at common receptor sites. The pyrrolidones and piperidones we have examined show similar properties ranging from agonist to antagonist but an insufficient number of compounds have been evaluated for any definite conclusions regarding structure-function relationships.

The decreased activity of the laevo-form of 5-ethyl-5-phenylpyrrolid-2-one in relation to the racemate agrees with the findings of Branchini, Casini, Ferappi & Gulinelli (1960) for the laevo-form of α-ethyl-α-phenylglutarimide.

SUMMARY

1. A series of substituted pyrrolidones and piperidones has been evaluated for sedative and anticonvulsant activity.

2. 5-Ethyl-5-phenylpyrrolid-2-one was selected and its sedative and anticonvulsant properties were examined in detail relative to glutethimide, phenobarbitone, meprobamate and chlorpromazine.

3. The effects of 5-ethyl-5-phenylpyrrolid-2-one on normal behaviour were investigated in several species.

4. 5-Ethyl-5-phenylpyrrolid-2-one resembles phenobarbitone with regard to its sedative and anticonvulsant properties, although it lacks hypnotic activity.

5. The anticonvulsant activity of 5-ethyl-5-phenylpyrrolid-2-one is relatively weak when compared with diphenylhydantoin or phenobarbitone.

6. Severe limb rigidity was produced by 5-ethyl-5-phenylpyrrolid-2-one in several species, namely mouse, cat, dog, monkey and pig.

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