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PHARMACOLOGICAL ACTIVITY OF 5-PHENYL-1 : 3 : 4-THIADIAZOLE (L 1538), 2-AMINO-5-PHENYL-1 : 3 : 4-THIADIAZOLE (L 1460) AND 2-AMINO-5-(2'-THIENYL)-1 : 3 : 4-THIADIAZOLE (L 1458)

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The pharmacological actions of 5-phenyl-1 : 3 : 4-thiadiazole (L 1538), 2-amino-5-phenyl-1 : 3 : 4-thiadiazole (L 1460) and 2-amino-5-(2'-thienyl)-1 : 3 : 4-thiadiazole (L 1458) have been studied and compared with those of other muscular relaxant drugs. The three compounds have paralysing effects in mice, rats, cats, and dogs. They block the tonic component of maximal electroshock seizures and protect against strychnine, though not against leptazol-induced convulsions in mice. Like other centrally acting paralysing drugs, they depress spinal polysynaptic transmission in doses which leave monosynaptic transmission relatively unaffected. The rigidity of the decerebrate cat is reduced but not always abolished. The compounds do not induce synchronization in epidural electroencephalogram recordings. In doses not greatly affecting muscular tone and spontaneous activity, they prolong the hypnotic effects of pentobarbitone and other barbiturates in mice. Autonomic functions are only slightly affected. The similar actions of substituted thiadiazoles and 2-amino-benzothiazoles confirm a previous hypothesis that pharmacological equivalence may result either from condensing heterocyclic nuclei with aromatic nuclei or from introducing aryl substituents into them.

In a previous paper (Maffii, Testa, and Ettorre, 1958) the synthesis and depressant activity on the central nervous system of a series of substituted 1 : 3 : 4-thiadiazoles were described. A possible analogy, from the pharmacological point of view, with substituted benzothiazoles studied by Domino, Unna, and Kerwin (1952) was suggested.

We now report further studies of three of the most interesting compounds in the series of 1 : 3 : 4-thiadiazoles: 5-phenyl-1 : 3 : 4-thiadiazole (L 1538), 2-amino-5-phenyl-1 : 3 : 4-thiadiazole (L 1460), and 2-amino-5-(2'-thienyl)-1 : 3 : 4-thiadiazole (L 1458).

MATERIALS AND METHODS

CF-1 mice, both male and female, weighing 20 to 25 g., and CF-Wistar rats weighing 120 to 180 g. were used. Experiments were also carried out on 14 cats and 12 mongrel dogs.

Because of the low solubility of the three compounds, 20% propyleneglycol was used as a solvent for intravenous administration; for other routes suspensions in 5% aqueous gum acacia were used. These were administered orally by stomach tube, except to dogs, which received gelatin capsules.

The anticonvulsant action of L 1538, L 1460, and L 1458 was tested in mice and rats, by intraperitoneal injection, against maximal electroshock seizures and leptazol and strychnine-induced convulsions, as previously described (Maffii *et al.*, 1958).

The effects of L 1538, L 1460, and L 1458 on spinal reflexes were tested using the techniques of Berger (1949). The knee jerk was elicited in cats anaesthetized with pentobarbitone, or in spinal cats, by mechanical tapping of the patellar tendon at a rate of 1/sec. The flexor reflex was elicited by electrical stimulation of the central stump of the posterior tibial nerve. Rectangular pulses of 15 V. and of 0.5 msec. duration delivered at a rate of 400/sec. for a period of 0.1 sec. were used as stimuli. Contractions of the tibialis anterior muscle were recorded.

The effect on decerebrate rigidity was studied in cats in which the brain stem had been sectioned at the level of the superior colliculi and the brain destroyed.

Electromyograms from decerebrate cats were recorded with an electroencephalograph. The electrodes were implanted in the skin over the hyperactive muscles.

Electroencephalograms were recorded from cats. The animals were anaesthetized with ether while the operative procedure was being carried out. The

trachea was cannulated for artificial respiration. The calvarium was exposed and gramophone needles were placed in the bone with their tips in contact with the dura. Placements were made in the frontal, parietal, and occipital regions on the right side and in the parietal or frontal region on the left side. An indifferent electrode was placed in the soft palate. Animals were then curarized. In some experiments the blood pressure by carotid cannulation was also recorded. All experiments were started more than 1½ hr. after the ether had been withdrawn.

Other actions of L 1460 and L 1458 were studied in cats and dogs. Respiratory movements were recorded by tambour connected to the tracheal cannula, and the blood pressure by a mercury manometer from the carotid artery. The peripheral stump of the vagus nerve was stimulated by rectangular pulses (0.5 msec., 10 V., 300/sec., for 0.5 sec.). Carotid occlusion was performed manually using a haemostat. The electrocardiogram was recorded by needle electrodes placed in each foreleg.

Potentiating action on barbiturate-induced hypnosis was tested by injecting the compounds intraperitoneally 20 min. before the selected barbiturate was administered intramuscularly. The duration of loss of righting reflex was measured. The median sleeping time was determined by the graphical method of Litchfield (1949).

Antipyretic action was tested in albino rabbits of both sexes weighing between 2 and 3.5 kg. Rectal thermocouples were used and galvanometer readings were taken half-hourly over a period of 2 hr. before and 5 hr. after intravenous injection of 1 ml./kg. of saline containing pyrogen from *Pseudomonas aeruginosa*. The thiadiazoles were given intraperitoneally 2 hr. after the pyrogen.

To obtain LD50 values and other quantal estimates, the method of Litchfield and Wilcoxon (1949) was followed.

Results

Physical and Chemical Properties

L 1538 crystallized in light-brown, brilliant, odourless platelets with slightly bitter taste. It melted at 36 to 38°. It was almost insoluble in water, but soluble in most organic solvents. L 1460 was an odourless, pink-white, crystalline powder. It melted at 226 to 227° and was very sparingly soluble in water (0.13 g./l. at 38°). L 1458 was first synthesized in our chemical department in 1955 (Maffii *et al.*, 1958). It was a white-yellow crystalline powder. It melted at 243 to 244° and was very sparingly soluble in water (0.23 g./l. at 38°).

Effects in Mice and Rats

A dose of 10 mg./kg. of L 1538, intraperitoneally, in mice had, after a latency of 5 to 10 min., a slight sedative effect: spontaneous activity was slightly decreased as well as reactivity to changes in the environment (cage). After 30 mg./kg., the sedative effect was more pronounced and slight ataxia and impairment of the righting reflex appeared. After 100 mg./kg. spontaneous activity was greatly reduced as well as reactivity to touch and to transfer from cage. The righting reflex was markedly impaired and muscular tone greatly reduced. A slight decrease in corneal reflex was also observed. After 300 mg./kg. the mice were in complete flaccid paralysis which began in the hind limbs. The righting reflex and muscular tone were completely absent. Corneal and pinna reflexes were decreased but not absent.

Other signs were first observed after 30 mg./kg. of L 1538: the respiration rate fell and slight cyanosis, lachrymation and hypothermia were observed. Depression of respiration increased progressively with dose and death was due to respiratory paralysis.

L 1460 produced substantially the same changes. Complete paralysis, however, was observed at a lower dose, namely, 200 mg./kg. Muscular tone was not completely lost and some rigidity, particularly of the forelimbs, was observed in some animals. In the first stage of paralysis some tremors also occurred. Side effects, such as depression of respiration, cyanosis, and mydriasis, appeared to be more marked than with L 1538.

L 1458 had about the same activity as L 1460, but no rigidity occurred and side effects were less marked.

No hyperexcitability before the loss of righting reflex and paralysis was ever seen in mice injected with any of the three compounds.

After oral administration the effects of L 1538, L 1460, or L 1458 were the same as after intraperitoneal administration, if the dose was increased by 75 to 100%.

The activity of the three substituted thiadiazoles was also compared with that of other paralysing drugs and benzimidazole. After intraperitoneal administration, 250 mg./kg. of mephenesin produced a complete relaxation of body muscles within 3 to 5 min. without tremor. The pinna reflex was lost, but autonomic effects were almost absent. Respiration was depressed during paralysis.

Meprobamate (300 mg./kg. intraperitoneally) caused paralysis after an induction period of 20 to 25 min. The duration of paralysis was about 2 hr. In most animals muscular tone did not completely disappear in the forelimbs and twitches were occasionally observed. The pinna reflex was retained.

Mice injected with 100 mg./kg. of benzimidazole intraperitoneally showed only slight muscular hypotonia and a slightly decreased corneal reflex. After 300 mg./kg. ataxia and an impairment of the righting reflex with a more consistent muscular hypotonia were observed.

Zoxazolamine (2-amino-5-chlorobenzoxazole) caused at a dose of 30 mg./kg. a very slight impairment of the righting reflex and at 100 mg./kg. a marked muscular hypotonia without signs of ataxia; in this respect it resembled mephenesin. The corneal and pinna reflexes were unaffected at this dose though higher doses abolished them.

The paralysing actions of L 1538, L 1460, and L 1458 in rats were qualitatively similar to those in mice, but were observed at lower doses. The mean paralysing dose and duration of action of L 1538, L 1460, L 1458, mephenesin, and meprobamate in mice and rats are given in Table I.

TABLE I

THE MEAN PARALYSING DOSES (PD50) AND DURATION OF ACTION OF L 1538, L 1460, L 1458, MEPHENESIN AND MEPROBAMATE ADMINISTERED INTRAPERITONEALLY TO MICE AND RATS

Comp.	Animals	PD50 (mg./kg.)	Approximate Duration (min.)
L 1538..	Mice	180	150
	Rats	150	120
L 1460..	Mice	140	>240
	Rats	70	120
L 1458..	Mice	130	90
	Rats	90	120
Mephenesin	Mice	180	12
	Rats	80	15
Meprobamate	Mice	200	90
	Rats	200	90

Effects on Cats and Dogs

When administered intraperitoneally to cats at 50 mg./kg., L 1538 caused slight ataxia and mydriasis lasting for about 90 min. After 100 mg./kg., a slight impairment of the righting reflex was observed as well as weakness of the hind limbs, salivation, emesis, and marked ataxia. L 1460 by the same route in the cat at 50 mg./kg. produced salivation, slight ataxia and mydriasis. After 100 mg./kg., the cat could not walk, ataxia was severe, and mydriasis occurred. The muscular tone was retained. After 150 mg./kg., the righting reflex was lost, voluntary movements disappeared and muscular tone decreased. Mydriasis was extreme and the pupillary reflex to light impaired. After 3 hr., isolated muscular twitches and tremors were observed. Respiration was depressed and death occurred within 8 to 10 hr. L 1458 induced less marked side effects. Salivation, mydriasis, and emesis were observed after 80 mg./kg. With 100 mg./kg., muscle relaxation was still moderate, but the righting reflex was markedly impaired and moderate ataxia was present. 150 mg./kg. caused weakness of fore and especially hind limbs, muscle relaxation preceded by rigidity, mydriasis, and salivation. Twenty hr. after the injection the animal appeared normal, and only spontaneous activity was still reduced. After oral administration the same effects were observed at about the same doses.

In the dog 25 mg./kg. of L 1460 intraperitoneally did not produce any change in behaviour. After 75 mg./kg., ataxia, vomiting and salivation were observed. After 100 mg./kg., the righting reflex was impaired and paralysis appeared within 90 min. Muscular tone was decreased although it was still present. After 150 mg./kg., respiration was affected and death occurred in extreme prostration within 10 hr.

L 1458, in doses of 75 mg./kg., caused ataxia, vomiting, salivation, and slight impairment of the righting reflex; after 125 mg./kg., motor incoordination was extreme, with weakness of limbs and moderate muscle relaxation. After 150 mg./kg., respiration was depressed but the animal survived. Twenty hr. after the administration, the movements of the dog were normal although signs of general depression were present.

Before the onset of neurotoxic signs no sedative effect was ever observed. Dogs injected with L 1460 and L 1458 tried to rise and walk although their movements were greatly impaired. Dogs treated with doses of meprobamate producing a similar degree of paralysis did not show any tendency to walk; and their curiosity and general reactivity to environmental changes was decreased. However, ataxia was present and sometimes emesis occurred.

Anticonvulsant Activities

Table II gives the mean doses of L 1538, L 1460, and L 1458 which prevented the appearance of the

TABLE II

ANTICONVULSANT ACTIVITY OF L 1538, L 1460, L 1458, MEPROBAMATE AND MEPHENESIN INJECTED INTRAPERITONEALLY INTO MICE. ALL DOSES ARE EXPRESSED IN MG./KG.

Comp.	Animals	ED50 (Electroshock)	ED50 Leptazol		ED50 Strychnine	
			Death	Convulsions	Death	Convulsions
L 1538 ..	Mice	70	>200	>200	<100	>200
	Rats	<12·5	>200	>200	~150	>200
L 1460 ..	Mice	20	>200	>200	85	130
	Rats	12	>100	>100	<100	>100
L 1458 ..	Mice	70	>200	>200	80	100
	Rats	18	>100	>100	<100	>100
Meprobamate	Mice	75	30	80	150	>500
	Rats	60	<100	>100	>100	>100
Mephenesin ..	Mice	85	>400	>400	350	400
	Rats	70				

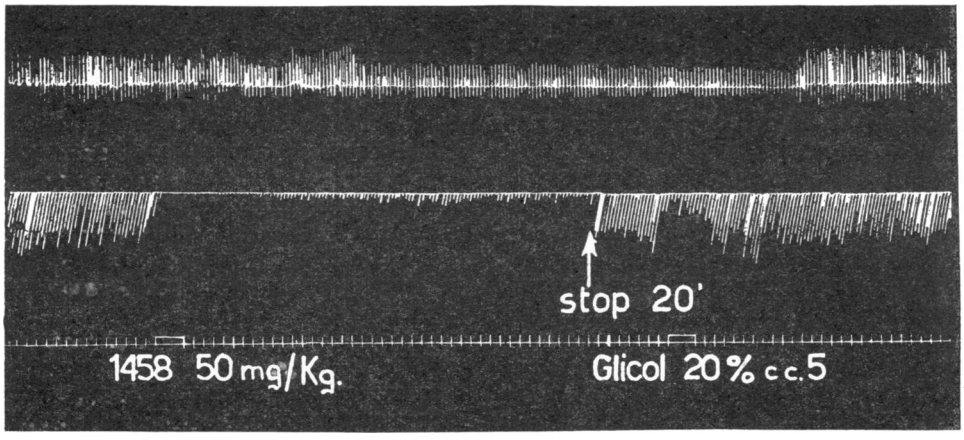

FIG. 1.—Cat, pentobarbitone anaesthesia. The effect of L 1458 (50 mg./kg. i.v.) on the knee jerk and flexor reflex. Upper trace, knee jerk; middle trace, flexor reflex; lower trace, time, 2 sec. and injection signal. Glicol 20% c.c.5 = control injection of 5 ml. of 20% propylene glycol. Stop 20' = drum stopped for 20 min.

tonic extensor component of maximal electrical seizures in mice and rats and the mean doses protecting both species from the convulsant and lethal effects of leptazol and strychnine.

The effectiveness of L 1458 in preventing the onset of the extensor phase of electroshock seizure was also confirmed in rabbits at a dose of 30 mg./kg. intraperitoneally.

Effect on Reflexes in Cats and Rabbits

The intravenous administration of L 1460 (20 mg./kg.) and L 1458 (20 mg./kg.) dissolved in 20% aqueous propylene glycol abolished the flexor reflex after a few minutes. The knee jerk was retained but usually reduced in amplitude (Fig. 1). The duration of action was about 35 min. These effects of L 1460 and L 1458 could also be observed after intraperitoneal injection of comparable doses.

Effect on Decerebrate Rigidity

The effects of L 1460 and L 1458 on decerebrate rigidity were tested at doses of 50 mg./kg. given intravenously in cats. Rigidity was usually reduced but occasionally it was abolished (Fig. 2). The duration of this action of L 1458 was substantially shorter than that of paralysis induced by the same dose in the intact cat. Rigidity was less affected by L 1460. Complete relaxation was observed after 50 mg./kg. of mephenesin or 100 mg./kg. of meprobamate.

Effect on Electroencephalogram

In preliminary experiments doses of 50 mg./kg. of L 1458 were injected intravenously or intraperitoneally in four cats. No consistent effects on electroencephalographic tracings were observed. Mephenesin (50 mg./kg.) induced slowing and increases in amplitude.

Potentiating Effect on Barbiturate-induced Hypnosis

Prolongation by L 1458 and L 1460 of hypnosis induced by pentobarbitone, thiopentone, quinalbarbitone, and hexobarbitone was studied in mice.

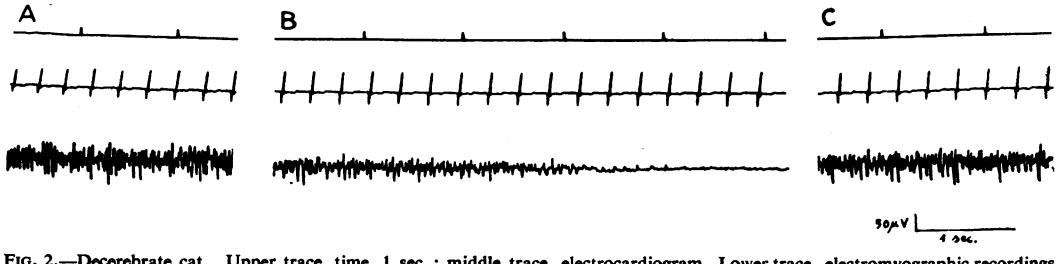

FIG. 2.—Decerebrate cat. Upper trace, time, 1 sec.; middle trace, electrocardiogram. Lower trace, electromyographic recordings from extensor muscles of the hind right leg. A, normal; B, at the end of an intravenous injection of L 1458 (15 mg./kg.); C, recording made 18 min. after the injection.

Table III gives the median sleeping time (ST50) as determined with various doses of thiadiazoles and meprobamate administered to groups of animals. L 1458 and L 1460 in doses of 15 mg./kg. significantly increased the sleeping time of mice treated with pentobarbitone and quinalbarbitone. In the same dose only L 1460 prolonged thiopentone and hexobarbitone hypnosis.

TABLE III

EFFECTS OF L 1458, L 1460 AND MEPROBAMATE ON THE SLEEPING TIME OF MICE INJECTED INTRAPERITONEALLY WITH SOME BARBITURATES

ST50=Median sleeping time (min.). C.L.=Confidence limits for 95% probability. R=Sleeping time ratio=$ST50_1/ST50_2$. fR=Ratio factor. The value of R will exceed the value of fR if the two median times being compared are significantly different for 95% probability (Litchfield, 1949).

Treatment	mg./kg.	No. of Animals	ST50 (C.L.)	R	fR
Pentobarbitone	40	40	34 (23–49)		
+L 1460 ..	15	40	215 (172–268)	6·32	1·53
+L 1458 ..	15	40	60 (49–73)	1·765	1·52
+Meprobamate	15	10	80 (70–91)	2·35	1·48
Hexobarbitone ..	80	10	35 (25–47)		
+L 1460 ..	15	10	125 (91–172)	3·57	1·56
+L 1458 ..	15	10	47 (26–84)	1·34	1·94
+Meprobamate	15	10	54 (51–57)	1·54	1·36
Quinalbarbitone	40	10	107 (74–155)		
+L 1460 ..	15	10	>310	—	—
+L 1458 ..	15	10	220 (157–308)	2·05	1·65
+Meprobamate	15	10	160 (140–183)	1·49	1·47
Thiopentone ..	45	40	18 (11–28)		
+L 1460 ..	15	10	100 (75–134)	5·52	1·71
+L 1458 ..	15	10	20 (11–36)	1·11	2·08
+Meprobamate	15	20	44 (23–82)	2·44	2·15

Under the same conditions meprobamate was less active than L 1460 and only slightly more active than L 1458. Neither the thiadiazoles nor meprobamate produced any impairment of motor activity in mice at the dose of 15 mg./kg. used in these experiments.

Antipyretic Activity

The antipyretic activity of L 1460 and L 1458 (20 and 40 mg./kg. intraperitoneally) was studied in 20 rabbits. Only L 1460 at 40 mg./kg. had an antipyretic action. The effect of the two doses of L 1458 and of the smaller dose of L 1460 was not significant. Under the same experimental conditions meprobamate, 20 and 40 mg./kg., also had a very poor effect.

Other Actions

In cats anaesthetized with pentobarbitone, L 1538 in a dose of 50 mg./kg. intraperitoneally produced within 15 min. a fall of blood pressure of about 10 mm. Hg, which lasted more than 30 min. The heart rate also fell. The response to carotid occlusion or to adrenaline or acetylcholine, intravenously, was not affected. The effect of 150 mg./kg. on blood pressure was greater and more prolonged. The response to vagal stimulation or carotid occlusion was slightly depressed. After 250 mg./kg. blood pressure, heart rate, and respiration were greatly depressed and death occurred within 60 to 90 min.

L 1458 had similar but larger effects on blood pressure and respiration. After 100 mg./kg., in two animals respiration was blocked and death would have occurred if artificial respiration had not been started. L 1460 was similar to L 1458.

The three compounds did not modify the response of the nictitating membrane to preganglionic cervical sympathetic stimulation.

On the smooth muscle of isolated rat ileum, L 1538, L 1460, and L 1458 showed a slight antagonism to acetylcholine at a bath concentration of 10^{-5} (w/v).

Toxicity

The acute toxicity of L 1538, L 1460, and L 1458 in mice was compared with that of mephenesin and meprobamate, after their administration intraperitoneally as suspensions in 5% gum acacia. Animals were observed for one week. The LD50 was calculated by the method of Litchfield and Wilcoxon (1949) and the values found are given in Table IV.

TABLE IV

ACUTE TOXICITY IN MICE BY INTRAPERITONEAL ADMINISTRATION

Confidence limits are given in parentheses (95% probability). All doses are expressed in mg./kg.

Comp.	LD50
L 1538	442 (507–387)
L 1460	264 (322–216)
L 1458	374 (408–343)
Meprobamate	719 (745–694)
Mephenesin	518 (559–480)

In a subacute toxicity test, two groups of three dogs each were given daily oral doses of 200 mg./kg. of L 1458 and 150 mg./kg. of L 1460 respectively for two weeks. Salivation, emesis, anorexia, ataxia, and variable degrees of paresis were seen after the first or the second administration and during all the period of treatment. At the end of the two weeks all the animals had lost weight and were in bad condition. There was prostration and paralysis. Urine analysis showed biliary pigments after the third day, and albumin near the end of the experiment. Complete blood counts during and at the conclusion of the experiments showed a progressive increase of neutrophils. The blood-clotting time was slightly increased after 8 days of treatment.

Gross and histological examination of the autopsied animals 15 days from the beginning of

treatment showed congestion of viscera and albuminous and fatty degenerative lesions of liver and kidneys.

A chronic toxicity test was carried out with three oral doses (30, 60, and 180 mg./kg.) of L 1458, administered daily to groups of ten rats each. 10% gum acacia was used to suspend the product; a volume of 2.0 ml./kg. was given. The duration of treatment was 17 weeks. During this period two animals receiving the dose of 180 mg./kg. died; no death was observed with the doses of 60 and 30 mg./kg. Only the rats given 180 mg./kg. of L 1458 grew significantly less well than controls: the mean body weight after 18 weeks of treatment was 280 g. and that of controls 330 g.

Blood counts during and at the end of the experiment did not differ significantly from observations before dosing.

Gross and microscopic examination of the autopsied animals at the end of treatment showed degenerative lesions in liver and kidney of some rats given 180 mg./kg.

Discussion

Studies of the action of the three thiadiazoles on the central nervous system have shown that these compounds, like other centrally-acting paralysing drugs, depress the activity of polysynaptic arcs of the spinal cord. Monosynaptic transmission is less affected. The action of L 1458 and L 1460 on spinal reflexes is similar to that of meprobamate, mephenesin, 2-aminobenzothiazoles, and other spinal depressant and centrally-acting paralysing drugs. However, hypnotics, anticonvulsants, analgesics, local anaesthetics, and drugs used in the treatment of paralysis agitans have been shown to depress polysynaptic reflexes without affecting the patellar reflex (Domino, 1956). In view of this, and of the presumed polysynaptic nature of most neuronal arcs concerned in central nervous activity, it may be concluded that selective action on spinal polysynaptic reflexes is almost aspecific. Such an action does not demonstrate an analogy between thiadiazoles and mephenesin-like compounds.

From gross observation in mice it also appears clearly that substantial differences do exist in the action of various central paralysing compounds. These differences concern principally their effects on motor functions and reflexes.

According to Goodsell, Toman, Everett, and Richards (1954) centrally acting relaxants of the mephenesin type abolish the pinna reflex earlier than the corneal reflex and show a smooth onset and a great deal of relaxation. Ataxia does not precede muscle weakness and paralysis. Our results with mephenesin are in full accord with these. Among the drugs studied by us only zoxazolamine resembled mephenesin. Meprobamate produced a good relaxation; however, in some animals it was less effective than mephenesin in this respect. Moreover meprobamate affected only slightly the pinna reflex. Berger (1954) reported a similar observation. Mice injected with benzimidazole show some ataxia before relaxation, and both the pinna and corneal reflexes are simultaneously and only moderately depressed.

L 1538, L 1460, and L 1458 produced slight relaxation, preceded by ataxia and impairment of the righting reflex. The corneal and pinna reflexes were simultaneously affected.

Other differences noted concerned the duration of paralysis which was about 10 min. with mephenesin, 2 hr. with meprobamate, 3 hr. with benzimidazole, about the same with L 1458 and L 1538, and more than 4 hr. with L 1460.

The different properties of centrally-acting muscle relaxants strongly suggest that such known and new compounds may act on different parts of the central nervous system and that they probably belong to different classes of drugs.

Other pharmacological studies on the three thiadiazoles L 1538, L 1460, and L 1458 confirm this point of view. The three products show anticonvulsant properties in mice and rats. They prevent electrical and strychnine-induced convulsions, but fail to protect animals against leptazol-induced seizures. In this respect thiadiazoles differ substantially from meprobamate which is especially effective in preventing leptazol-induced convulsions. On the contrary, they resemble mephenesin and benzimidazole which show a very poor anti-leptazol effect (Maffii *et al.*, 1958), and perhaps also the 2-aminobenzothiazoles, the anticonvulsant action of which against only electrically and strychnine-induced seizures has been reported (Domino, 1956).

L 1458 and L 1460 have shown some effect in reducing decerebrate rigidity in cats, but their effectiveness is poor compared with that of mephenesin. Moreover, L 1458 and L 1460 do not synchronize cortical electrical activity. From this point of view also their action differs from that of meprobamate (Hendley, Lynes, and Berger, 1954) and mephenesin (Toman and Davis, 1949) which slow and increase the amplitude of the cortical electroencephalogram. The 2-aminobenzothiazoles are also said to lack synchronizing action on the electroencephalogram (Funderburk,

King, Domino, and Unna, 1953; Funderburk, King, and Unna, 1953).

Thus, though the action of thiadiazoles on the spinal cord appears quite evident, the failure to antagonize the action of leptazol, the slight inhibition of decerebrate rigidity, the lack of electroencephalographic changes and the effects on behaviour demonstrate that any action of these drugs on higher levels of the central nervous system is doubtful.

On the other hand, highly effective centrally-acting muscle relaxants such as mephenesin, meprobamate, zoxazolamine and benzimidazole also displayed significant differences in activity on higher centres. The meaning of this fact is debatable and will remain so until knowledge of neuropharmacology is more adequate.

The similarity in activities of substituted thiadiazoles and benzothiazoles has been confirmed by our results. Common findings with the two series of products as described by Funderburk *et al.* (1953) or investigated by us are: spinal depressant activity, protection against electrical and strychnine-induced seizures and lack of synchronizing effect on the electroencephalogram. These findings give further support to the hypothesis (Maffii *et al.*, 1958) of pharmacological equivalence between the structures of aromatic nuclei condensed with heterocyclic rings, such as benzothiazoles, and the structures of heterocyclic nuclei containing aromatic substituents, such as the thiadiazole derivatives.

It is also interesting to observe that, in the thiadiazole series, substitution in position 5 either with phenyl or 2-thienyl leads to compounds that do not qualitatively differ in their pharmacological action.

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