ANTI-CONVULSANT EFFECT OF PHTHALAZINO-2,3b-PHTHALAZINE-5(14H),12(7H)-DIONE (L-5418).

I. BEHAVIORAL EFFECT

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Abstract—Since it had been demonstrated that L-5418 has an anti-convulsant effect with no relation to its anti-inflammatory properties, comparative studies were carried out with the use of currently available anti-convulsant agents as controls. L-5418 inhibited tonic convulsions induced by maximal electroshock and strychnine in mice and prevented animals from the death sequence. L-5418 had an inhibitory effect on tonic convulsions induced by pentetrazol and N-sulfamoyl-hexahydroazepinc (SaH 41-178), but not on clonic convulsions by those compounds at even a high dosage or on clonic convulsions induced by picrotoxin and bemegride. Trimethadione produced an inhibitory effect on both tonic and clonic convulsions. The hypnotic agents, phenobarbital and glutethimide inhibited both convulsions, but a higher dose was required in the case of clonic convulsions. Anti-convulsant agents are classified into three different groups according to their mode of action. L-5418 had the same mode of action as seen with diphenylhydantoin and carbamazepine. As L-5418 did not inhibit tremor induced by tremorine, an anti-Parkinson effect was ruled out. When L-5418 was administered alone, the animals did not lose the righting reflex nor show muscle relaxation observed in inclined screen and rotarod tests. Moreover, the compound had no influence on the aggressive behavior induced by electrical stimulation or olfactory bulb ablation. L-5418 possesses a selective anti-convulsant effect, yet has no sedative, tranquilizing or disturbing effects on movement such as equilbrium disturbance or muscle relaxation. L-5418 may prove useful for grand mal epilepsy as it is less toxic than diphenylhydantoin and carbamazepine.

We reported that L-5418 is an unique drug which differs from the currently available anti-inflammatory agents, as the inhibitory effect is more potent on subacute or chronic inflammatory reaction than on acute reaction. L-5418 is a basic compound in chemical structure and gastric mucosal disturbances are nil. On the other hand, it was observed that L-5418 possesses a characteristic anti-convulsant effect (1). It is most interesting that L-5418 has an anti-convulsant effect without regard to anti-inflammatory effect. Pharmacological studies on behavioral effect were carried out and comparisons were made with central nervous depressants such as currently available anti-convulsant agents.

MATERIALS AND METHODS

The chemical structure and physical properties of the test drug, L-5418 have already been reported (1). The test drug was provided by Dow Lepetit (Japan) Limited. As control drugs, the following were used; diphenylhydantoin (Aleviatin, Dainippon Seiyaku, DPH), trimethadione (Minoaleviatin, Dainippon Seiyaku, TMD), carbamazepine (Tegretol,
Fujisawa Yakuhin Kogyo, CMA), phenobarbital (Fujinaga Seiyaku, PB), glutethimide (Doriden, Takeda Yakuhin Kogyo, GM), chlordiazepoxide (Contol, Takeda Yakuhin Kogyo, CDO), diazepam (Cercin, Takeda Yakuhin Kogyo, DA). Those drugs were used in form of suspension in 0.5% tragant gum solution.

**Influence on convulsions and tremor**

**Maximal electroshock convulsions:** According to preliminary tests, electroshock of 140 V, 100 Hz, 0.4 sec was applied by electronic stimulator (Nihonkoden, MSE-3) as a condition that produces 100% tonic extensor convulsions and death. Male dd mice weighing 18 to 20 g were used. The test drug was administered p.o. and electroshock was applied through corneal electrodes in 1, 3 and 6 hr later. The inhibitory effect of the drug was studied on tonic extensor convulsions.

**Chemically induced convulsions:** One hr after the drug administration to a group of mice, the convulsion-inducing agents were injected i.p. and the inhibitory effect of test drugs on clonic and tonic convulsions was observed. Convulsion-inducing agents were as follows; pentetrazol 150 mg/kg (2), SaH 41-178 50 mg/kg, picrotoxin 12 mg/kg, bemegride 30 mg/kg, strychnine 2 mg/kg. The test with pentetrazol was also examined in male Wistar rats weighing 120 to 140 g as well as mice. SaH 41-178, N-sulfamoyl-hexahydroazepine, has been reported by Iorio et al (3, 4) to be a drug with anti-dotal activity against barbiturate-induced depression in mice and as a convulsant agent in characterizing the anti-convulsant profiles of drugs: anti-convulsants with trimethadione-like and diphenylhydantoin-like properties can be readily differentiated. SaH 41-178 produced within 2 min after administration a short episode of clonic convulsions followed immediately by a tonic flexion-extension sequence and death.

**Tremorine induced tremor:** According to the method of Everett et al (5), groups of 10 male mice weighing 18 to 20 g were administered p.o. test drugs and 1 hr later, 20 mg/kg of tremorine was injected i.p. The inhibitory effect on the tremor and salivation was observed for 15 min.

**Influence on Straub-tail reaction induced by morphine**

The same mice as above mentioned were used. At 1 hr after the test drug administration by p.o. route, 20 mg/kg of morphine was injected s.c. The inhibitory rates of the drugs were measured in 10, 30 and 60 min after the injection of morphine. A less inclination than 45° of Straub-tail was regarded as the inhibitory effect.

**Influence on barbital induced sleep**

According to the method of Fujimori (6), groups of 10 male mice were administered the test drug and 15 min later, 130 mg/kg of barbital-Na was injected i.p. The mice were observed for 2 hr and the number of animals with a loss of righting reflex for 5 min or more was counted.

**Influence on experimentally induced aggressive behavior**

**Mild footshock in mice:** The experiment was carried out according to the method of Tedeshi et al (7) with slight modifications. Groups of 12 male dd mice weighing 18 to 20 g
were used. The employed apparatus was a transparent acryl box (12 × 12 cm in width, 16 cm high) which consisted of a metallic grid floor (0.3 cm in diameter). A pair of mice was placed in this box and an electric current (90 V, 1 mA, 3 Hz) was sent through the floor for one min, in order to induce a fighting reaction. The mice were given the footshock at 1, 2 and 4 hr after the p.o. administration of the drug and the absence of response was regarded as the inhibitory effect. ED50 was determined by the inhibitory rates at each measuring time and comparisons were made.

Olfactory bulb ablation in rats (O.B. rats): According to the method of Ueki et al (8, 9), male, Wistar rats weighing 300 to 400 g were anesthetized with sodium pentobarbital (30 mg/kg, i.p.), the olfactory bulbs were bilaterally removed by suctioning and the animal was kept in an individual cage. The rats with ablation of the olfactory bulbs were used for experiments from 10 days after the surgery. The influence on emotional behavior was observed at 0.5, 1, 2, 4 and 24 hr after the drug administration.

Disturbing effect on movement

Inclined screen test: The test drugs were given to male dd mice weighing 18 to 20 g (a group of 10 mice) and the mice were slowly placed on rough surface glass plates with a 30° inclination at 0.5, 1 and 2 hr later. When mice fell from the inclined screen within 10 sec, such was regarded as a disturbance of movement and the ED50 at each measuring time was calculated.

Rotarod test: Mice able to stay for 1 min or more on a wooden rod of 4 cm in diameter rotating at a speed of 12 times per min, were selected and divided into groups of 10. The test drugs were given p.o. and then 1 hr later mice were placed on the rotating rod again. Animals which fell from the rod within 1 min were categorized as a disturbance of movement and the ED50 of each drug was calculated.

Acute toxicity test

Acute toxicity studies were carried out in mice given oral administrations. LD50 of each drug was calculated from the rate of death at 72 hr after the administration. All the ED50 and LD50's were calculated using Litchfield and Wilcoxon’s method (10).

RESULTS

Influence on convulsions and tremor

Maximal electroshock convulsions: The inhibitory effects of the test drug on tonic convulsions induced by electrical stimulation in mice are shown in Table 1. L-5418 inhibited the convulsions and death. The ED50 at 1 hr after the administration was 43 mg/kg. The efficacy was weaker than that of DPH, CMA and PB, but stronger than TMD. The anti-convulsant effect of L-5418 decreased with the lapse of time. However, even 6 hr later, the anti-convulsant effect was observed and the ED50 was 180 mg/kg. In the case of CMA and GM, the maximal anti-convulsant effect was obtained 1 hr later after which the effect decreased. In the case of DPH and PB, even 6 hr later, the anti-convulsant activity was found to be similar to that at 1 hr.
Chemically induced convulsions: When 150 mg/kg of pentetrazol was given i.p. to mice, a fine twitch appeared in all four legs first after 1 min, clonic convulsions came next, and tonic and extensor convulsions occurred before death. The influence of the test drugs on the process of convulsions, from clonic to tonic convulsions was studied and the results are shown in Table 2. L-5418 did not inhibit twitch, clonic convulsions and death, but did inhibit tonic convulsions. The ED50 was 29 mg/kg. The same effect was observed in the case of DPH and CMA, and their activity was more potent than that of L-5418. PB and GM inhibited twitch, both forms of convulsion and death, but the inhibitory effect was the most active on tonic convulsions. TMD inhibited twitch, both forms of convulsion and death at an equal dosage, though a larger dose was required than the other drugs. The anti-convulsant activity of drugs was found to be the same in rats as in mice, but L-5418 showed a marked anti-convulsant effect in rats rather than in mice. The inhibitory effect of L-5418 on tonic convulsions was as potent as that of CMA, and more active than that of DPH.

With the i.p. injection of 50 mg/kg of SaH 41-178, convulsions similar to those seen with pentetrazol were induced. As shown in Table 3, L-5418 did not inhibit twitch, clonic convulsions and death, but did inhibit tonic convulsions. The ED50 was 45 mg/kg. DPH

### Table 1. Effect of L-5418 and reference compounds on maximal electroshock convulsion in mice

| Compounds       | ED50 (95% C.L.) mg/kg, p.o. in anti-convulsant effect |
|-----------------|------------------------------------------------------|
|                 | 1 hr     | 3 hr     | 6 hr*    |
| L-5418          | 43 (38~48) | 142 (91~220) | 180 (113~288) |
| Diphenylhydantoin | 12 (8.0~18) | 6.6 (5.6~7.7) | 6.0 (5.3~6.8) |
| Trimethadione    | 433 (344~546) | 480 (440~523) | >500 |
| Carbamazepine    | 12 (10~14) | 21 (15~30) | >100 |
| Phenobarbital    | 11 (10~13) | 11 (7.9~14) | 13 (9.6~19) |
| Glutethimide     | 21 (19~25) | 38 (34~42) | >50 |

* Time after administration of test compounds. Maximal electroshock = 100 Hz, 140 V, 400 msec.

### Table 2. Effect of L-5418 and reference compounds on pentetrazol convulsion in mice and rats

| Compounds       | Tonic conv. Mice | Clonic conv. | Tonic conv. Rats | Clonic conv. |
|-----------------|------------------|--------------|------------------|--------------|
| L-5418          | 29 (23~36)       | No           | 22 (17~28)       | No           |
| Diphenylhydantoin | 8.0 (6.4~10)   | No           | 40 (22~72)       | No           |
| Trimethadione    | 354 (334~375)    | 354 (334~375)| 390 (315~484)    | 390 (315~484)|
| Carbamazepine    | 9.5 (8.1~11)     | No           | 18 (13~24)       | No           |
| Phenobarbital    | 12 (9.0~16)      | 30 (21~43)   | 22 (14~34)       | 40 (24~68)   |
| Glutethimide     | 25 (20~31)       | 52 (42~65)   | 63 (49~81)       | 82 (86~98)   |

No = No effect. Pentetrazol = 150 mg/kg, i.p.
and CMA inhibited only tonic convulsions to a greater extent than did L-5418. PB and GM had an inhibitory effect on all symptoms, with a higher dose required for twitch, clonic convulsions and death. TMD was effective for twitch, both forms of convulsion and death at equally large dosages.

L-5418 did not inhibit the clonic convulsions and death induced by picrotoxin, as shown in Table 4. It had no influence whatever even at the highest dose of 1000 mg/kg. The other drugs except PB also were without effect even at a relatively large dose.

Clonic convulsions and death were induced by bemegride. As shown in Table 4, L-5418, DPH and CMA had no anti-convulsant effect even with a considerably large dose. PB and GM had definite anti-convulsant effects and TMD, to some extent, inhibited convulsions and death.

All the drugs used except for TMD had an inhibitory effect on strychnine induced tonic convulsions and death. The activity of L-5418 was lower than that of PB, but the same as that of DPH and more potent than that of GM and CMA. The convulsions were followed by death. All the test drugs prevented death by electrical stimulation and strychnine in proportion to the respective inhibitory effect on tonic convulsions. But, the drugs that did not inhibit clonic convulsions failed to prevent death following clonic convulsions induced by pentetrazol, SaH 41-178, picrotoxin and bemegride.

Tremorine induced tremor: L-5418 had no inhibitory effects on tremor even at a high

| Compounds         | ED50 (95% C.L.) mg/kg, p.o. in anti-convulsant effect |
|-------------------|-------------------------------------------------------|
|                   | Tonic conv.  | Clonic conv.  |
| L-5418            | 45 (38~54)  | No            |
| Diphenylhydantoin | 14 (11~18)  | No            |
| Trimethadione     | 560 (459~683) | 560 (459~683) |
| Carbamazepine     | 12 (9.7~15) | No            |
| Phenobarbital     | 22 (19~26)  | 27 (23~32)   |
| Glutethimide      | 35 (29~42)  | 50 (40~62)   |

No = No effect. SaH 41-178 = 50 mg/kg, i.p.

| Compounds         | ED50 (95% C.L.) mg/kg, p.o. in anti-convulsant effect |
|-------------------|-------------------------------------------------------|
|                   | Picrotoxin  | Bemegride  | Strychnine |
| L-5418            | No         | No         | 108 (85~137) |
| Diphenylhydantoin | No         | No         | 105 (58~189) |
| Trimethadione     | No         | 530 (460~610) | No         |
| Carbamazepine     | No         | No         | 150 (114~198) |
| Phenobarbital     | 22 (17~29) | 40 (33~48) | 25 (20~32) |
| Glutethimide      | No         | 74 (59~93) | 124 (95~161) |

No = No effect. Picrotoxin = 12 mg/kg, i.p., Bemegride = 30 mg/kg, i.p., Strychnine = 2 mg/kg, i.p.
dose of 800 mg/kg of p.o. administration. DPH, CMA, PB and GM inhibited the tremor at the dose sufficient for the onset of ataxia and sleeping, but not at a lower dose. The salivation after tremorine dosing was not inhibited by these anti-convulsants even at the dosage sufficient to produce an anti-tremor effect. On the other hand, atropine 5 mg/kg inhibited the tremor at the rate of 100% and also had a 100% inhibitory effect on salivation.

Influence on Straub-tail reaction induced by morphine

As shown in Table 5, L-5418 inhibited the Straub-tail reaction at 10 min after injection of morphine and the effect decreased with the lapse of time. DPH had a weak effect 10 min after injection of morphine, but 60 min later, a 50% inhibitory effect with 200 mg/kg was observed. TMD had no effect, and CMA had only 20 to 30% an inhibitory rate at 200 mg/kg. PB and GM had an inhibitory effect of 100% at 100 mg/kg and 100%, at 200 mg/kg respectively. CDO also had an inhibitory effect of 60% with 10 mg/kg, and 80% with 20 mg/kg.

Influence on barbital induced sleep

As shown in Table 6, L-5418 did not induce loss of the righting reflex in mice even at the high dose of 2000 mg/kg. DPH and TMD produced no sleeping effects. CMA did

| Compounds            | Dose  | Inhibitory % |
|----------------------|-------|--------------|
|                      | mg/kg | 10m  | 30m  | 60m  |
| L-5418               | 50    | 0    | 10   | 20   |
|                      | 100   | 40   | 30   | 20   |
|                      | 200   | 60   | 50   | 30   |
| Diphenylhydantoin    | 50    | 10   | 20   | 20   |
|                      | 100   | 20   | 40   | 40   |
|                      | 200   | 30   | 30   | 50   |
| Trimethadione        | 50    | 0    | 0    | 0    |
|                      | 100   | 0    | 0    | 0    |
|                      | 200   | 10   | 10   | 30   |
| Carbamazepine        | 50    | 10   | 20   | 20   |
|                      | 100   | 30   | 30   | 20   |
|                      | 200   | 20   | 20   | 30   |
| Phenobarbital        | 50    | 10   | 10   | 70   |
|                      | 100   | 100  | 80   | 90   |
|                      | 200   | 100  | 100  | 100  |
| Glutethimide         | 50    | 20   | 10   | 10   |
|                      | 100   | 50   | 50   | 50   |
|                      | 200   | 100  | 100  | 100  |
| Chlordiazepoxide     | 10    | 60   | 60   | 60   |
|                      | 20    | 70   | 90   | 80   |
show a sleeping effect in mice and the ED50 was 280 mg/kg at 1 hr after the administration, and 440 mg/kg 3 hr. On the other hand, the hypnotic agents, PB and GM had potent effects of all the same grade 2 hr after the administration. Next, a test of the righting reflex with a combination of barbital-Na was made. Since barbital-Na alone could not induce a loss of the righting reflex, the dosage (ED50) of combined drugs which produces a 50% loss of righting reflex was determined. As shown in Table 7, L-5418 revealed an ED50 at 34 mg/kg and a strong synergistic action on barbital-Na was observed as in the case of CMA. The synergisms observed in DPH and TMD were rather weak. GM also showed a weaker synergism than L-5418.

### Table 6. Effect of L-5418 and reference compounds on righting reflex in mice

| Compounds      | 1hr | 2hr | 3hr* |
|----------------|-----|-----|------|
| L-5418         | No  | No  | No   |
| Diphenylhydantoin | No  | No  | No   |
| Trimethadione  | No  | 2000:20% | 2000:20% |
| Carbamazepine  | 280 (243~322) | 350 (310~396) | 440 (386~506) |
| Phenobarbital  | 140 (111~176) | 130 (104~163) | 117 (98~139) |
| Glutethimide   | 242 (210~278) | 238 (218~259) | 258 (211~315) |

No = No effect in 2000 mg/kg, p.o.  *Time after administration of test compounds.

### Table 7. Effect of L-5418 and reference compounds on barbital-Na hypnosis in mice

| Compounds         | ED50 (95% C.L.) mg/kg, p.o. in loss of righting reflex |
|-------------------|------------------------------------------------------|
| L-5418            | 34 (29~40)                                           |
| Diphenylhydantoin | 160 (137~187)                                        |
| Trimethadione     | 500 (390~640)                                        |
| Carbamazepine     | 40 (29~54)                                           |
| Glutethimide      | 86 (68~108)                                          |

Barbital-Na 130 mg/kg, i.p. alone did not lose righting reflex.

Influence on experimentally induced aggressive behavior

*Mild footshock in mice:* As shown in Table 8, L-5418 of 800 mg/kg p.o. did not inhibit

### Table 8. Taming effect of L-5418 and reference compounds on fighting mice induced by electrical stimulation to the feet

| Compounds         | ED50 (95% C.L.) mg/kg, p.o. |
|-------------------|-----------------------------|
|                   | 1hr | 2hr | 4hr* |
| L-5418            | No  | No  | No   |
| Diphenylhydantoin | No  | No  | No   |
| Chloralosemepoxide | 31.0 (25.2~38.1) | 28.5 (20.8~39.0) | 30.0 (23.8~37.8) |
| Diazepam          | 12.0 (7.6~18.8) | 11.6 (8.0~16.8) | 10.6 (7.1~15.9) |

* Time after administration of test compounds. No = No effect.
fighting in mice induced by electrical stimulation, nor did DPH. CDO and DA proved to have potent inhibitory effects with ED50 of 30 mg/kg and 10 mg/kg respectively. The same grade of activity was maintained for 4 hr after the administration.

Olfactory bulb ablation in rats: Effects of drugs on hyper-emotionality in O.B. rats are shown in Fig. 1 as the total score for each checking point. A significant decreasing effect was not observed at 400 and 800 mg/kg of L-5418. Therefore, no inhibition whatever occurred with L-5418 at 2 hr after the administration, and the drug had no influence on muricide. CDO, however, decreased the total score and produced an inhibitory effect of dose dependence. CDO proved to have an inhibitory effect on all factors including muricide which was inhibited about 70% at 50 mg/kg.

Disturbing effect on movement

Inclined screen test: The dosages required for half the number of all mice to fall from inclined screen at 30 min, 1 and 2 hr after the test drug administration are shown in Table 9. At a dose of 900 mg/kg of L-5418, the mice did not fall from the inclined screen. TMD was also without effect. With DPH, the mice fell at 1 hr after administration and CMA produced the effect at 30 min later. Both DPH and CMA showed an ED50 with about 100 mg/kg. PB and GM produced potent effects at 30 min and such was maintained for 2 hr.

Rotarod test: ED50's of the test drugs required for the mouse to fall from a wooden
rod are shown in Table 9. L-5418 showed an ED50 at 530 mg/kg and such was almost at an equal level with that of TMD. DPH and CMA showed a potent effect and the ED50 was 160 and 64 mg/kg respectively. With PB and GM, the mice fell from the wooden rod after ingesting the same dosage as in the case of DPH and CMA.

**Acute toxicity test**

Acute toxicity of L-5418 was exceedingly low and only a slight decrease of spontaneous motor activity was evident. In the case of DPH and TMD, a sedative effect only was noted. LD50's of the drugs are shown in Table 10. The LD50 of TMD was noted at 2,450 mg/kg and DPH at 365 mg/kg. With CMA, PB and GM, the animals died in a sleeping state and a loss of righting reflex. CMA had almost the same LD50 as that of TMD. PB and GM had a potent toxicity similar to that of DPH. Therefore, judging from the LD50 of 17,600 mg/kg, the acute toxicity of L-5418 was apparently extremely low.

**DISCUSSION**

L-5418, a new type of anti-inflammatory agent of phthalazine derivatives, possesses an anti-convulsant effect, regardless of its anti-inflammatory effect (1). Pharmacological studies on the behavioral effect of L-5418 have been carried out in comparison with commonly available anti-convulsant agents. Experimentally, various types of convulsions were induced...
in animals, and such were similar to actual convulsive states in humans. A different anti-convulsant agent often shows a respective mode of action in the inhibitory effect on various types of convulsions. Since the effect varies with the type of convulsion, the anti-convulsant agents should be carefully investigated employing many different types of induced convulsions. With the use of the maximal electroshock and various kinds of chemically induced convulsions, the anti-convulsant effect of L-5418 was studied. L-5418 showed an inhibitory effect on the convulsions induced by the maximal electroshock, that is to say, tonic and extensor convulsions. CMA, or PB and GM among the hypnotic agents showed an inhibitory effect similar to that of L-5418. Therefore, no significant differences in a mode of action were noted among those drugs. The activity and duration of the anti-convulsant effect of L-5418 were lower and shorter than those of reference drugs.

Against the convulsions induced by pentetrazol and SaH 41-178, L-5418 inhibited tonic convulsions, but occasionally aggravated clonic convulsions. Such a mode of action is similar to that seen with DPH and CMA, because clonic convulsions are not inhibited by these compounds. The hypnotic agents, PB and GM, inhibited both forms of convulsions, but a higher dose was required in the case of clonic convulsions. TMD inhibited both convulsions at the same dosage. Therefore, three different modes of action were observed. The site of action of pentetrazol is in the brain stem. With a high dose of pentetrazol, asynchronized clonic convulsions occurred and were followed by tonic ones. These clonic convulsions are considered to be extremely close to petit mal epilepsy or myoclonus in humans. From the fact that L-5418 inhibited tonic convulsions, but not clonic ones, L-5418 is considered to involve a different mechanism, that is no effect on petit mal seizures and to be a drug similar to DPH. Toman et al (11) reported that DPH converts tonic to clonic convulsions, and tonic convulsions could totally disappear but clonic ones could be promoted after conversion. It is also conceivable that L-5418 is a drug with a similar mode of action to that of DPH, because clonic convulsions are aggravated by L-5418, DPH and CMA. Iorio et al (4) reported that anti-convulsant agents can be classified into three groups according to their mode of action, as determined with SaH 41-178, a compound which induces convulsions: a group that is effective on tonic convulsions but not on clonic ones, a group that is effective on clonic convulsions with a larger dose than the effective dose for tonic convulsions, and a group that is effective for both convulsions, with administration of the same dose of the drug. L-5418 demonstrated an inhibitory effect on tonic convulsions but not on clonic ones with the same mechanism as seen with DPH and CMA. Therefore, L-5418 is expected to be a drug effective for grand mal seizures, yet differs from PB and GM, hypnotic agents.

The convulsions seen with picrotoxin and bemegride are caused by stimulation of the brain stem and are mainly clonic. L-5418 did not produce an inhibitory effect on those convulsions as do DPH and CMA. L-5418 had an inhibitory effect on the same tonic convulsions by strychnine as by the maximal electroshock, and the activity was as potent as that seen with DPH. All the convulsions mentioned above have different mechanisms, different forms of onset, and produce different characteristics. Judging from the results
of tests with various drugs, the mode of action of L-5418 was most similar to that of DPH. As a anti-convulsant agent, L-5418 may be effective for grand mal but not for petit mal seizures. L-5418, as in the case of DPH, showed no inhibitory effect on tremorine induced tremor. Other test drugs also did not reveal an anti-tremor effect, but rather inhibited a tremor with a large dosage which would be sufficient to produce a loss in righting reflex. Therefore L-5418 may not possess an anti-Parkinson effect. To the Straub-tail reaction, one of the central nervous stimulative actions induced by morphine, L-5418 showed an inhibitory effect of approx. 50% at a dose of 100 to 200 mg/kg. This activity was equal to that of DPH, with some differences regarding onset and duration of action. However, PB and GM inhibited almost 100% the tail reaction at a dose that was sufficient to induce loss of righting reflex. The inhibitory effect on tremor and Straub-tail reaction is considered to be one of the central depressive actions. If total anesthesia, sleep or muscle relaxation were also induced at an anti-convulsant dose, the anti-convulsant effect might not be conceivably a true effect.

L-5418 administered alone did not induce a loss of the righting reflex. On the other hand, CMA, PB and GM induced a loss of righting reflex and a sedative effect at a dose larger than the effective one for anti-convulsions. Though L-5418 and DPH possess no sedative effect, a synergistic action with the central nervous depressive agents, such as with barbital-Na was noted. From the inclined screen and rotarod test, L-5418 seems to have almost no disturbing effects on movements such as total anesthesia, equilibrium disturbances or muscle relaxation. Though DPH has relatively similar characteristics to that of L-5418 in anti-convulsant action, it seemed to be more potent in a disturbing effect on movements. CMA, PB and GM have a hypnotic effect and mice fell from the inclined screen after a lower dosage than the effective one for sleeping action. Taming effect on hyper-emotionality is considered to be one of the pharmacological properties of tranquilizers that showed clinically an anti-anxiety effect. Muricide in olfactory bulb ablation rats is inhibited selectively by psycholeptics. In studies on aggressive behavior induced in animals experimentally, L-5418 had no influence. Therefore, L-5418 proved to be a drug different from tranquilizers such as CDO and DA. From the present data, L-5418 has no sedative and tranquilizing effects, however, it does inhibit extensor tonic convulsions and has properties of an anti-convulsant agent.

With respect to the molecular structure, L-5418 and DPH are not analogous, but both have two benzenes, two N- and two CO-radicals. Interesting enough, the molecular weight in both compounds is different only by the weight which is equivalent to one carbon. L-5418 has an anti-convulsant activity of 1/2 to 1/3 on that of DPH, and the duration of action is slightly shorter than that of DPH. However, in the comparative studies of acute toxicity, it has been found that the LD50 of L-5418 is about 50 times greater than that of DPH, and the toxicity is remarkably low.

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