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115. Keijiro Takagi, Yutaka Kasuya, and Minoru Watanabe: Experimental Study on the Pharmacology of N-(α-Methyl-3,4-methylenedioxyphenethyl)propionamide.

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We have synthesized some acid amides and amino acid amides of α-methyl-3,4-methylenedioxyphenethylamine and have found that N-propionyl derivative (SA-8) has analgesic action comparable to that of aminopyrine.[1] Since we have observed that this compound markedly depresses locomotor activity of mice without loss of righting reflex even at large doses, and that it markedly prolongs the hexobarbital-induced sleep in mice, we have experimentally studied the CNS action, mainly the tranquillizing action, of the compound. Some general pharmacological properties of other derivatives have also been studied.

Methods

1. Reduction of Spontaneous Activity——Reduction of spontaneous activity was studied essentially according to the climbing test as described by Sandberg.[2] A group of 10 mice was given with a drug intraperitoneally, and was put in a box with a ladder for 10 min. once before and five times (15, 30, 60, 120 and 240 min.) after the injection. The number of animals which climbed the ladder once or more within the 10 min. period was recorded. Three minimal numbers out of the five trials after the injection were averaged, and this mean was expressed as per cent and was transformed into probit. Thus dose-response line was obtained for each drug tested. Activity of SA-8 was compared with those of chlorpromazine hydrochloride and meprobamate. SA-8 and meprobamate were suspended in CMC solution containing 0.9% NaCl. Chlorpromazine hydrochloride was dissolved in physiological saline.

2. Antagonism to Methamphetamine-induced Hyperactivity——Szymanski type-like activity cage as described by Takagi and Shibata[3] was used. A triangular plastic cage is hung with a thread at the center and with three springs at the three corners, and a mercury contact is set at each of the three corners. These contacts are connected to three electromagnetic signals. When a mouse in the cage comes to a corner of it, the mercury contact is closed and this is recorded kymographically with one of the signals. When the animal goes to the next corner, another signal is driven electrically. Thus a three channel recording is obtained, and from the recording, movements of the animal in the cage are analyzed. When a mouse moves from one corner to another, activity is regarded as one, and activities are counted from the recording.

One hour after oral administration of the compounds, *d*-methamphetamine hydrochloride, 4 mg./kg., was injected subcutaneously and the activities of the animals for five min. were counted from 20, 40, 60, 120 and 240 min. after the injection. Also activities immediately before the oral administration of the test compounds and the injection of methamphetamine were counted. When animals were out of the apparatus, they were caged in a group of three with foods and water. Fasting markedly influenced the activity of animals.

3. Anticonvulsant Test——Anticonvulsant activity was studied according to the method as described by Bastian, *et al.*[4]: an injection needle was inserted into the tail vein of a mouse, and through a 50 cm. length of 1 mm. diameter polyethylene tubing which connected the needle and the syringe, 300 mg./kg. of pentylenetetrazol in 0.6 ml. of saline was infused at constant rate in 3 min. A mouse could freely move about in a cage during the infusion period. Drugs were given orally, at a given interval before the infusion. Times from the beginning of the infusion to onset of the flexor tonus and to the death, and the number of animals with extensor tonus were recorded. Time of death was observed and recorded up to 10 min. from the start of infusion. According to Bastian, above three endpoints are differently affected by various CNS drugs, forming the basis for the classification of drug specificity.

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1) K. Takagi, Y. Kasuya, K. Fujie, M. Watanabe, S. Kayaoka: This Bulletin, **11**, 654 (1963).
2) F. Sandberg: Arzneim.-Forsch., **9**, 203 (1959).
3) K. Takagi, M. Shibata: Folia Pharmacol. Japon., **56**, 26§ (1960).
4) J. W. Bastian, *et al.*: J. Pharmacol. Exptl. Therap., **127**, 75 (1956).

4. Antipyretic Activity in Rabbits——Rectal temperature of male rabbits weighing 2.0～2.5 kg. was recorded by animal thermometer once before and 1, 2, and 4 hr. after the simultaneous injection of typhoid paratyphoid vaccine, J.P. (0.2 ml./kg., i.v.) and test compounds (i.p.). The experiment was carried out at constant room temperature (22°).

5. Hypothermic Activity in Rats——Rectal temperature of male albino rats weighing 130～170 g. was recorded by animal thermometer twice before and 0.5, 1, 2 and 4 hr. after the intraperitoneal administration of SA-8 (140 mg./kg.), chlorpromazine hydrochloride (5 mg./kg.) or saline, in a room maintain ed at 22°. Ten animals were used for each dose.

6. Influence of SA-8 on Conditioned Response in Rats——Influence of SA-8 on conditioned avoidance and escape reactions in male albino rats was studied essentially according to the methods as described by Warner[5] and Verhave.[6] Two wooden boxes with a frontglass were used. Each box was divided into two compartments, each 20×15 cm. inside, by a fence of 5 cm. in height, and the bottom of the cage consisted of two separately wired grid floors. The top of this fence was wired into the shock circuit with two solid copper wires, to prevent animals from sitting on the fence. Five successive buzzer signals were presented as conditioned stimuli within five seconds, until the animal ran into another compartment, that is, until an avoidance response occurred. If the animal failed to respond to these five signals, unconditioned stimuli (five instantaneous electroshocks of AC 40V.), in a rate of one shock per second, were presented after 2 seconds with a pushbutton-switch. There were 10 trials per session, with 50～70 seconds between trials. Albino rats weighing 300～400 g. were used. No animal was used for the test until its performance became better than 95% successful avoidance responses out of more than 100 seccessive trials. Before any drug was given, less than 40 performances were run, and animals that made more than 19 avoidance responses out of successive 20 trials, received drugs tested. Generally, 3% suspension of SA-8 in physiological saline containing 0.5% Tween 80 and 0.8% CMC or containing 3% acacia instead of CMC, and 0.084% chlorpromazine hydrochloride solution in the latter vehicle, were injected intraperitoneally.

7. Effect of SA-8 on Cerebral Electrical Activity of the Cat——Effect of SA-8 on cerebral electrical activity of the cat was studied. Curarized cats, weighing 2～3 kg., were fixed to stereotaxic apparatus, and the electrical activities of the following areas of brain were recorded with a 12 channel ink-writing oscilograph (Nihonkoden, Model ME-1260); anterior sigmoid gyrus, caudate nucleus, lateral or basal nucleous of amygdala, centromedian nucleus of thalamus, midbrain reticular formation, fornix, posterior hypothalamus, posterior hippocampus of left hemisphere. The cortical record was taken directly from the pial surface with a silver bipolar electrode, and the other subcortical records were taken with coaxial bipolar stainless-steel electrodes. These electrodes were also used for stimulation of the brain stem. Rectangular pulses from a Nihonkoden electronic stimulator were employed routinely. Femoral blood pressure was recorded with Nihonkoden transducer. SA-8 was suspended in 3% acacia containing 0.9% NaCl and was injected into the cephalic vein.

8. Spasmolytic Activity——Relative spasmolytic activities (atropine-like and papaverine-like action) were determined with the Magnus apparatus as modified by Takagi, *et al.*[7] Two strips of mouse ileum were suspended in a single 30 ml. bath maintained at 26°. The concentration of the spasmogens (acetylcholine) was 10^{-7} for assay of atropine-like, and 10^{-4} g./ml. for assay of papaverine-like action.[8]

9. Effects on Blood Pressure and Respiration in Cats——Three urethane-narcotized cats were used. The mean arterial pressure was recorded by means of a mercury manometer from the femoral artery, and respiration was recorded simultaneously by means of a Marey tambour. SA-8 was injected into the cephalic vein, dissolved in large volume of warm saline (about 4 mg./ml.), or suspended in acacia solution, since SA-8 is poorly soluble in water. Control experiments were carried out with the requisite volume of vehicle.

10. Acute Toxicity——Acute toxicities (24-hr.) of SA-8 and N-dimethylaminoacetyl and N-piperidinoacetyl derivatives were determined in mice after subcutaneous administration by up-and-down method. SA-8 in suspension was administered orally to ten mice for each of five doses. LD_{50} (72-hr.) was calculated according to the method of Litchfield and Wilcoxon.[9]

Results

1. Reduction of Spontaneous Activity——The results are given in Fig. 1. Dose-response lines for the three drugs tested were all nearly linear. Using the method of

5) L.H. Warner: J. genel. Psychol., **41**, 57 (1932).
6) T. Verhave, Jr., J.E. Owen, O.H. Slater: "Progress in Neurobiology," III, 267 (1958). Ed. S.R. Korey, J.I. Nurnberger, Paul B. Hoeber Inc., N.Y.
7) K. Takagi, M. Kimura: This Bulletin, **4**, 440 (1956).
8) K. Takagi, I. Takayanagi: *Ibid.*, **5**, 580 (1957).
9) J.T. Litchfield, Jr., F. Wilcoxon: J. Pharmacol. Exptl. Therap., **96**, 99 (1949).

Litchfield and Wilcoxon,[9] the median climbing dose (CD_{50}), the dose at which 50% (calculated as described above) of the animals failed to climb the ladder, and fiducial limits were calculated for each drug (Table I).

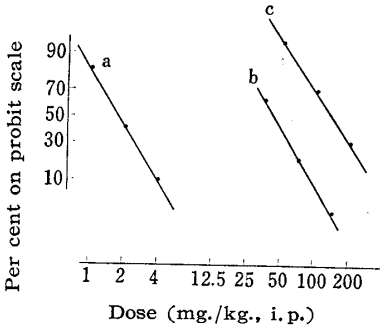


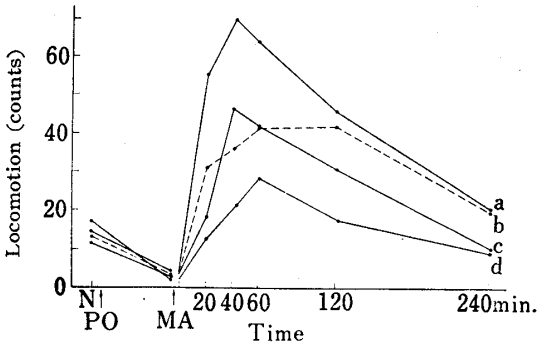
Fig. 1. Depression of Spontaneous Motor Activity in Mice by SA-8, Chlorpromazine Hydrochloride and Meprobamate, by means of Climbing Test of Sandberg

a : Chlorpromazine hydrochloride
b : SA-8
c : Meprobamate

TABLE I. CD_{50} and 95% Fiducial Limits of SA-8, Chlorpromazine Hydrochloride and Meprobamate

Compound	CD_{50} (mg./kg.)	Fiducial limits (95%)
SA-8	42	27 ~ 60
Chlorpromazine hydrochloride	1.7	0.67~ 2.6
Meprobamate	140	91 ~126

2. Antagonism to Methamphetamine-Induced Hyperactivity——Methamphetamine-induced hyperactivity was rather reduced by a dose of SA-8 of 140 mg./kg., and the characteristic behavioral patterns by methamphetamine were normalized. Salivations were seen more often than after methamphetamine only. A dose of meprobamate of 200 mg./kg. showed approximately equal inhibition ratio, but had longer duration of effect than SA-8. A dose of chlorpromazine hydrochloride of 2.5 mg./kg. showed apparent antagonistic effect. Activities measured immediately before the injection of *d*-methamphetamine were inhibited by both the effect of drugs and the shock given by the oral administration itself (Fig. 2).



N : normal activity immediately before the oral pretreatment
MA : injection of *d*-methamphetamine hydrochloride (4 mg./kg., s.c.) one hour after the pretreatment
a : saline (p.o.)
b : SA-8 (140 mg./kg., p.o.)
c : meprobamate (200 mg./kg., p.o.)
d : chlorpromazine hydrochloride (2.5 mg./kg., p.o.)
Ordinate : locomotor activity expressed as counts
Abscissa : minutes after the injection of *d*-methamphetamine hydrochloride

Fig. 2. Inhibition of Methamphetamine-induced Hyperactivity by SA-8, Chlorpromazine Hydrochloride and Meprobamate

3. Anticonvulsant Test——As shown in Table II, SA-8 little affected the effects of pentylenetetrazol or rather shortened the time to flexor tonus. SA-8 rather resembled the specificity of chlorpromazine or reserpine, though larger dosage was required, according to the classification by Bastian, *et al.*[4]

4. Antipyretic Activity in Rabbits——The results are given in Fig. 3. Only aminopyrine in a dose of 100 mg./kg. significantly suppressed the rise of body temperature ($p<0.01$). SA-8 in a dose of 140 mg./kg. suppressed it a little, but this modification was not significant ($p>0.1$).

Table II. Effects of SA-8 and Some Other Drugs on Flexor Tonus, Extensor Tonus and Death induced by Pentylenetetrazol

Compound	Dose (mg./kg.)	Time[a] (min.)	Tonic[b] Flexor (sec.)	No. ET[c] / No. Used	Time to death (sec.)
Control	—	—	65± 5	30/32	95±17
Chlorpromazine HCl	10	60	72±11	10/10	91± 9
Meprobamate	100	30	127±13	9/10	260±56
N-Acetyl deriv.	200	45	73± 9	6/10	113±18
SA-8	200	45	50± 9	8/10	88±21
SA-8	400	45	47± 8	8/10	70± 5

a) Time from drug administration to start of pentylenetetrazol infusion
b) Mean time in seconds from beginning of infusion to onset of tonic flexor
c) $\frac{\text{No. ET}}{\text{No. Used}}$ = number of mice with extensor tonus to total number of mice tested

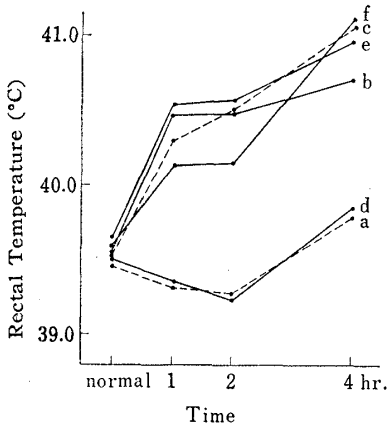


Fig. 3. Antipyretic Activities of Aminopyrine and SA-8 in Rabbits

Abscissa : hours after injection of vaccine and test compounds
Ordinate : rectal temperature in °C
a : requisite volume of vehicle without vaccine (8)
b : vehicle (13)
c : aminopyrine 25 mg./kg. (4)
d : aminopyrine 70 mg./kg. (4)
e : SA-8 100 mg./kg. (4)
f : SA-8 140 mg./kg. (3)

Numbers in parentheses are number of animals used.

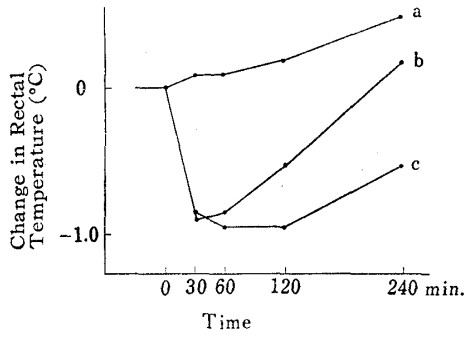


Fig. 4. Time Course of Hypothermic Action of SA-8 in Rats

Abscissa : minutes after the injection of compounds
Ordinate : change in rectal temperature in °C
a : requisite volume of saline
b : SA-8 140 mg./kg.
c : chlorpromazine hydrochloride 5 mg./kg.

Ten animals were used for each dose.

5. Hypothermic Activity in Rats——As seen in Fig. 4, SA-8 (140 mg./kg.) and chlorpromazine hydrochloride (5 mg./kg.) significantly lowered the body temperature of rats ($p<0.01$), but chlorpromazine showed longer duration of action.

6. Influence of SA-8 on Conditioned Response in Rats——Results were shown in Fig. 5a~g. The effect of SA-8 appeared 2~3 minutes after application and disappeared relatively rapidly. Ataxia was observed in animals which received doses of 100 or 140 mg./kg. of SA-8, and in a dose of 140 mg./kg., some of them lost righting reflex for a short period (1~2 minutes). Tremor occurred immediately after intravenous administration of SA-8 suspended in acacia solution in doses of 60~70 mg./kg., and a loss of righting reflex was seen for 2~3 minutes period. After the regaining of the reflex, animals were not ataxic. These symptoms nearly agreed with those in case of intraperitoneal injection. With oral administration, even at 400 mg./kg., SA-8 was not sedative and had not influence on conditioned responses at all. When SA-8 and chlorpromazine hydrochloride were given simultaneously, these drugs potentiated the effect of

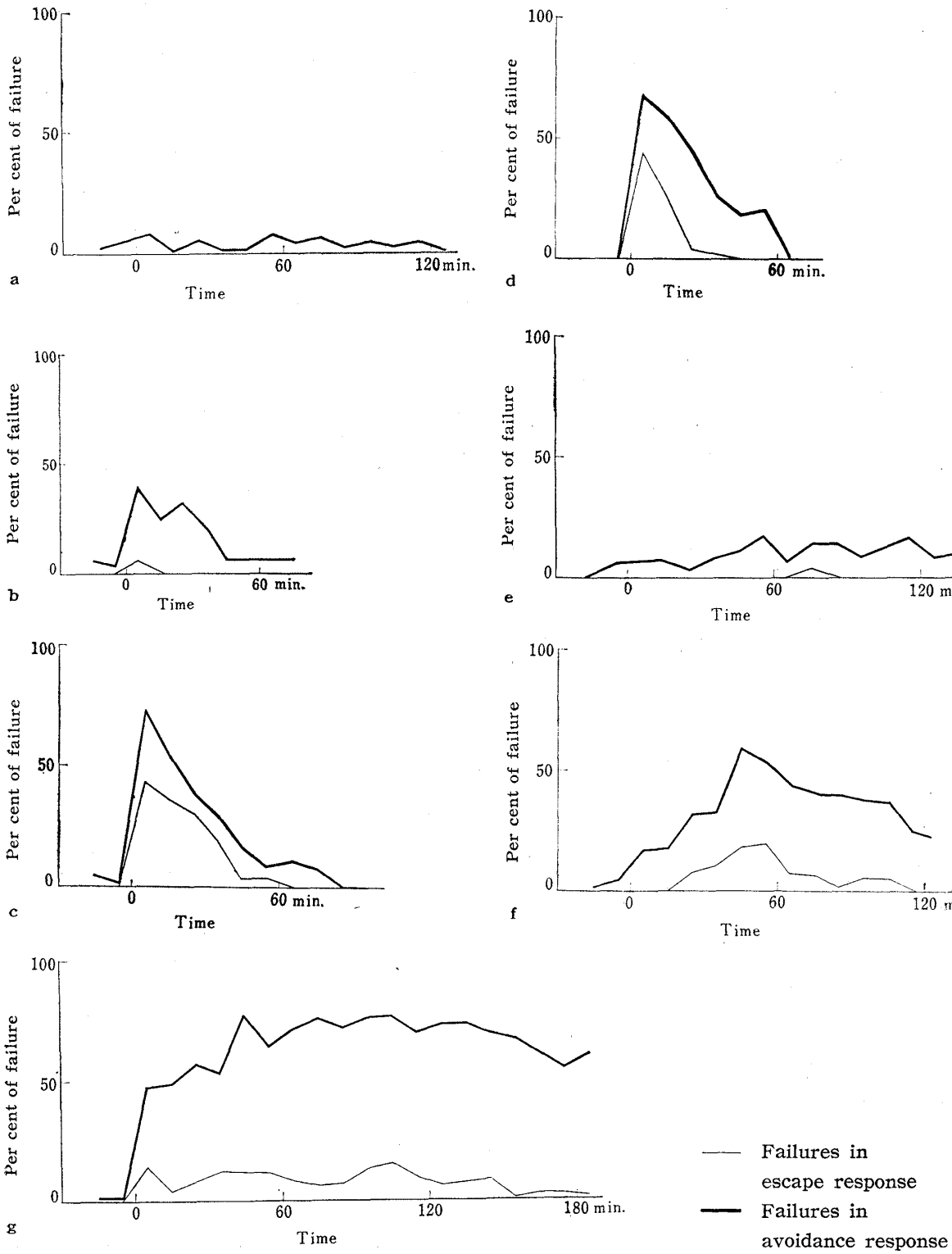


Fig. 5. Influence of SA-8 and Chlorpromazine on the Conditioned Avoidance and Escape Responses of Rats

a : requisite volume of vehicles (CMC or acacia in saline) (7)
b : SA-8 70 mg./kg. i. p. (5) c : SA-8 100 mg./kg. i. p. (7) d : SA-8 140 mg./kg. i. p. (5)
e : chlorpromazine hydrochloride 2.0 mg./kg. i. p. (2)
f : chlorpromazine hydrochloride 2.8 mg./kg. i. p. (6)
g : chlorpromazine hydrochloride 2.0 mg./kg. and SA-8 70 mg./kg. i. p. (11)
Numbers in parentheses are number of animals used.

each other on avoidance response and markedly prolonged the duration of action, as shown in Fig. 5g. Regarding the duration of action of the drugs, it is adequitely said that SA-8 potentiated the effect of chlorpromazine rather than chlorpromazine potentiated that of SA-8. The combined dose less affected the escape response than 2.8 mg./kg. of chlorpromazine, whose maximal effect on avoidance response was approximately equal to that of the combined dose. When animals were given with chlorpromazine alone, they were often excited with buzzer signals and failed to avoid, but this was not the case when the animals were given with the combination.

7. Effect of SA-8 on Cerebral Electrical Activity of the Cat——a) Influence on spontaneous electrical activity of brain: Fig. 6 shows a lowered activity or a drowsy pattern of motor cortex and hippocampus following a dose of 20 mg./kg. In doses of from 10 up to 30 mg./kg., SA-8 generally lowered the activity of hippocampus, and sometimes lowered that of cortex. Further doses of SA-8, 20 mg./kg., were given every 7 minutes, and Fig. 7 shows the activity when the total dose reached 100 mg./kg. Immediately after injection, so-called "hippocampal arousal pattern" appeared temporarily, in contrast to Fig. 6, as if depressive effect on hippocampus was lost, and the lowering of cortical activity was not observed. But this difference in effect may be caused by the difference in the effects on blood pressure. As shown in Fig. 8, following single dose of 60 mg./kg., remarkable high voltage fast waves appeared in the motor cortex bilaterally and in midbrain reticular formation. Hippocampal activity was little affected. At larger doses, such as 120 mg./kg., these activated patterns in reticular formation(so to speak, "RF arousal") and cortical leads became more striking, and synchronized spike activities, typical of "grand-mal" type seizure discharges, suddenly appeard throughout the whole records (Fig. 9). Sensory stimuli proned to evoke the seizure discharge. Even at a dose of 90 mg./kg., spikes, and later, "RF arousal" pattern, appeared in reticular formation records by claps or knockings at the ear bar, and further claps or knockings induced seizure discharges in the whole records. These

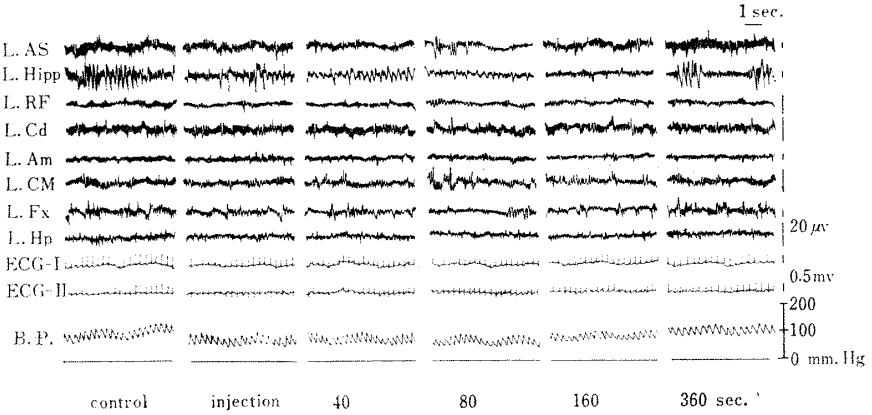


Fig. 6. Influence of SA-8 (20 mg./kg. i.v.) on the Spontaneous Electrical Activities of the Brain of the Cat

L. AS : left anterior sigmoid gyrus
L. Hipp : left posterior hippocampus
L. RF : left mesencephalic reticular formation
L. Cd : left caudate nucleus
L. Am : left lateral or basal nucleous of amygdala
L. CM : left centromedian nucleus of thalamus
L. Fx : left fornix
L. Hp : left posterior portion of hypothalamus
ECG-I and II : electrocardiogram, lead I and II
BP : blood pressure

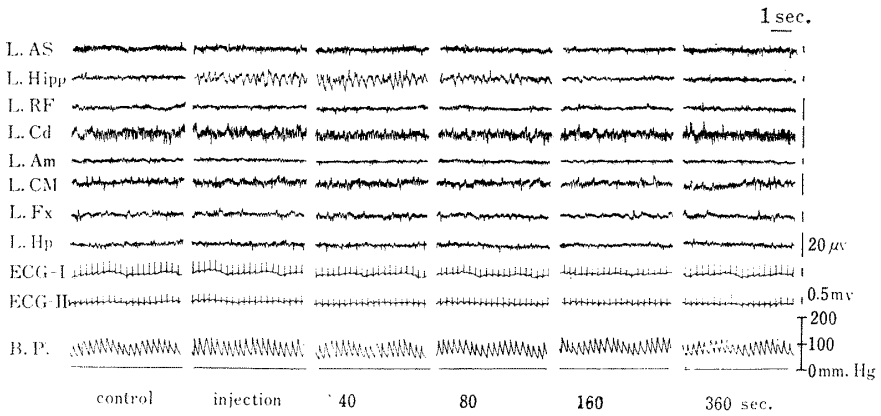


Fig. 7. Influence of SA-8 (100 mg./kg., i.v.) on the Spontaneous Electrical Activities of the Brain of the Cat

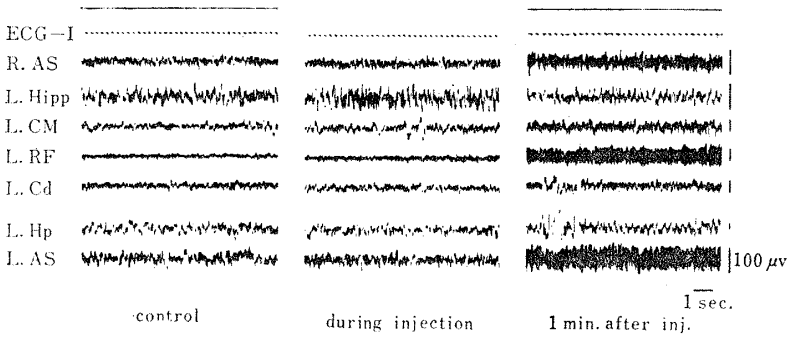


Fig. 8. Marked Arousal Pattern in Reticular Formation ("RF arousal") as well as in Bilateral Motor Cortices, after 60 mg./kg. of Intravenous SA-8

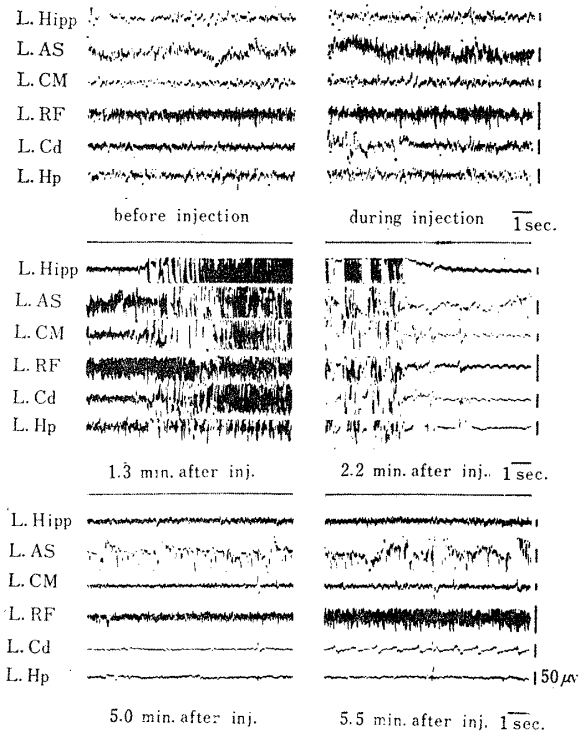


Fig. 9. Process of Development of Seizure Discharges by SA-8 (120 mg./kg., i.v.) and the Quick Recovery of Reticular Formation from After-depression

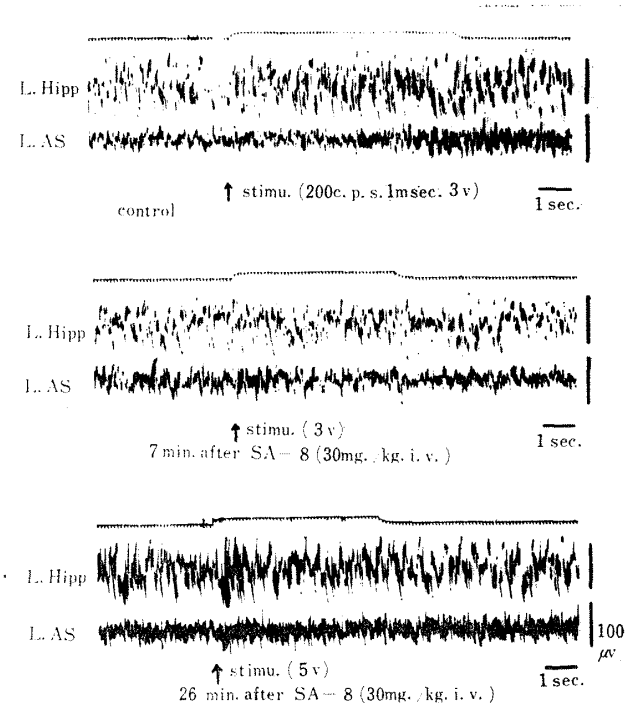


Fig. 10. Influence of SA-8 on Hippocampal Arousal evoked by Posterior Hypothalamic Stimulation

seizure discharges generally lasted for 0.5～2 minutes and when ceased, after-depressions came. The activity of RF recovered preceding those of other areas, and resulted in burst of fast waves. After complete recovery of whole records, seizure discharge was rarely evoked again by sensory stimuli, but further doses of SA-8 mostly evoked them. Intravenous thiopenthal, 3 mg./kg., simultaneous with the onset of seizure discharge, shortened the duration of seizure discharge.

b) Influence on the response to electrical stimulation: Cortical arousal elicited by electrical stimulation (200 c.p.s., 1 msec. rectangular pulses) of midbrain reticular formation was not influenced by lower doses of SA-8. At higher doses of it, spontaneous cortical and "RF arousal" were too predominant for us to detect the response to the stimulation. Threshold voltage and pattern of recruiting response to the stimulation (8 c.p.s., 1 msec.) of thalamic diffuse system were rarely affected by even higher doses. Threshold voltage of induced spindle by caudate single shock stimulation was also hardly affected. As showh in Fig. 10, hippocampal arousal evoked by stimulation of posterior hypothalamus (200 c.p.s., 1 msec.) was somewhat depressed. This suggests that the hypothalamic activating system advocated by Tokizane, *et al.*[10] is rather depressed by SA-8.

c) Antagonistic effect of SA-8 to barbiturates: Since SA-8 prolongs the duration of sleep induced by hexobarbital in mice,[1] interaction between SA-8 and barbiturates was studied by means of electroencephalography. Cortical drowsy pattern was clearly induced with intravenous thiopental, 2 mg./kg., but when the animal had been injected with a dose of SA-8, 20 mg./kg., the same dose of thiopental failed to induce the drowsy pattern as before, as shown in Fig. 11. Similar result was obtained when hexobarbital (3 mg./kg.) was used, as shown in Fig. 12. In this case, induced spindles by caudate single shock were also suppressed by SA-8 pretreatment.

8. Spasmolytic Activity——As seen in Table III, spasmolytic activities of compounds were very weak, as compared with atropine and papaverine.

10) H. Kawamura, Y. Nakamura, T. Tokizane: Japan. J. Physiol., 11, 564 (1961).

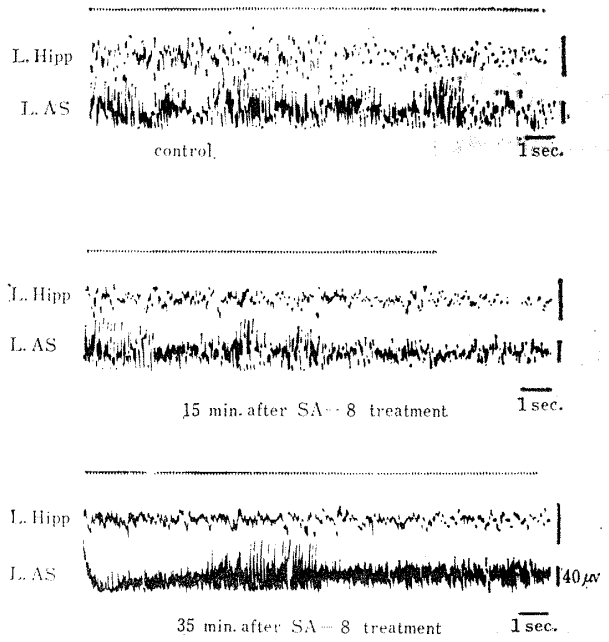


Fig. 11. Influence of SA-8 Pretreatment (20 mg./kg., i.v.) on the Drowsy Pattern induced by Thiopental

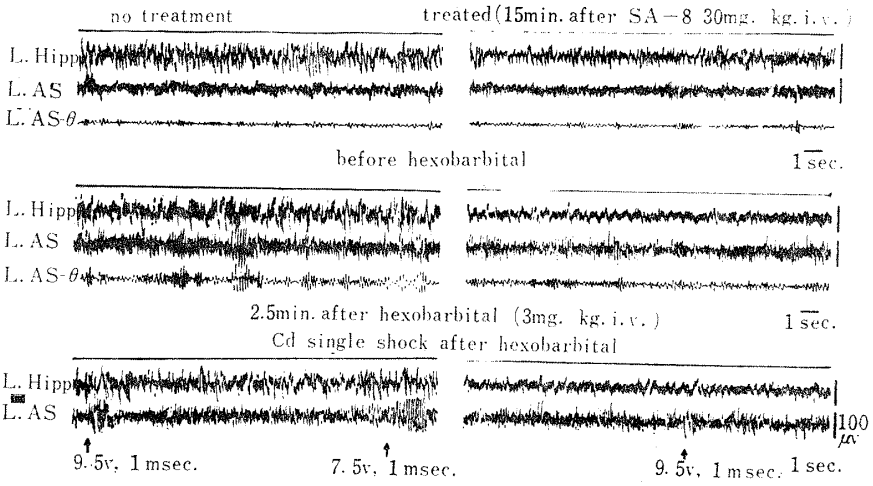


Fig. 12. Protection of Slow Waves Induced by Hexobarbital (3 mg./kg., i.v.) and the Suppression of Induced Spindles by Caudate Single Shock by SA-8 (30 mg./kg., i.v.) Pretreatment

Table III. Spasmolytic Activity of α-Methyl-3,4-methylenedioxyphenethylamine Derivatives

Compounds	Atropine-like action (atropine=1) (wt. basis)	Papaverine-like action (papaverine=1) (wt. basis)
N-Dimethylaminoacetyl-	1.1×10^{-5}	1.9×10^{-2}
N-Diethylaminoacetyl-	3.8×10^{-5}	1.6×10^{-2}
N-Piperidinoacetyl-	1.2×10^{-4}	5.6×10^{-2}
N-Acetyl-	3.2×10^{-5}	6.8×10^{-3}
N-2-Dimethylaminopropionyl-	3.9×10^{-6}	1.6×10^{-2}
N-2-Diethylaminopropionyl-	2.0×10^{-4}	3.0×10^{-2}
N-2-Piperidinopropionyl-	1.3×10^{-4}	7.1×10^{-2}
N-Propionyl- (SA-8)	3.5×10^{-6}	1.5×10^{-2}

9. Effects on Blood Pressure and Respiration in Cats——As shown in Fig. 13b, intravenous SA-8 in doses of 30mg./kg. lowered mean arterial pressure about 20 mm. Hg, and this returned to normal after 5 minutes, while requisite volume of saline (7 ml./kg.) raised it a little (Fig. 13a). N-2-Piperidinopropionyl derivative of the amine in a dose

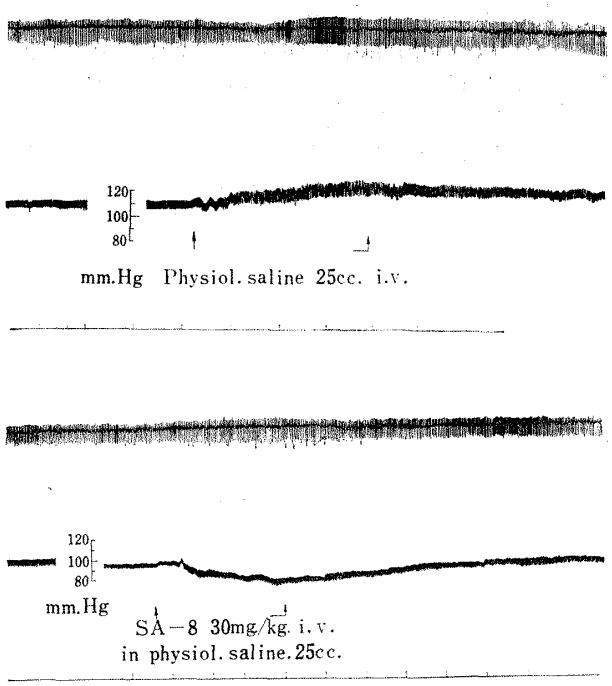


Fig. 13. Influence of SA-8 on the Respiration and Blood Pressure of the Cat anesthetized by Urethan

of 20 mg./kg. lowered it about 40 mm. Hg, and this returned to normal 10 minutes after the injection. Respiration was little affected by either drug.

10. Acute Toxicities——In N-dimethylaminoacetyl- and N-piperidinoacetyl-derivatives sedative action was not seen even with subtoxic doses. With highly toxic doses, clonic and tonic convulsions or violent clonic movements and ataxia were seen.

With doses of SA-8, death occured mostly within 24 hour period. Animals which survived were almost normal in the second and third day. With the lethal doses of SA-8, salivation, ataxia, loss of righting reflex, occasional tremor and temporary tonic convulsions were seen. LD_{50} values were shown in Table IV. Even with highly ataxic doses, muscular relaxation and loss of righting reflex were not seen.

Table IV. Acute Toxicities of Some α-Methyl-3,4-methylenedioxyphenethylamine Derivatives

Compounds	Route	No. of animals used	LD_{50} (mg./kg.)	Method
N-Dimethylaminoacetyl-	s.c.	21	523	up-and-down method
N-Piperidinoacetyl-	〃	21	340	
SA-8	〃	20	388	
SA-8	p.o.	50	450 (357～567)	Litchfield-Wilcoxon's method

Figures in parentheses are the 95 % fiducial limits.

Discussion

These experimental results except electrophysiological one, suggest that SA-8 rather resembles chlorpromazine or azacyclonol in its pharmacological spectrum. That is to say, chlorpromazine and SA-8 have no anticonvulsive effect, lower body temperature, reduce locomotor activity, and prolong hexobarbital induced sleep, although dose levels of them are very different. But the effect on conditioned response of them are rather

different, and furthermore combined treatment of them caused potentiation instead of addition. Regarding their effects on electrical activities of brain in cats, they depress the hippocampal arousal induced by posterior hypothalamic stimulation, and they affect little the arousal reaction evoked by reticular stimulation. It is known that chlorpromazine induces synchronization in cortical and reticular activities, and depresses the arousal reaction to sensory stimuli. Again, SA-8 and chlorpromazine induce seizure discharges that propagate to the whole brain at larger doses, but the seizure discharges following chlorpromazine initiate from amygdala, in contrast to those following SA-8 that initiate from reticular formation. Furthermore, following SA-8, seizure discharges propagate to amygdala somewhat later, than to other areas. SA-8 depresses little, and rather activates in larger doses, the electric activity of cortex or hippocampus of cat on the one hand, and it depresses the behavior of mice or rats on the other hand. This fact suggests that SA-8 may excites cats just like morphine does. Thus SA-8 in a dose of 60 mg./kg. was administered intravenously in intact cats to find temporary decrease in spontaneous motor activity and no sign of motor excitation. Corresponding to EEG patterns, in experiments with curarized cats, at 90 mg./kg. or more, SA-8 produced tonic extensor (opistotonus). The effects of morphine on the electrical activities of brain of cats with chronically implanted electrodes were studied by Yamamoto,[11,12] who found that the recruiting response to thalamic stimulation, cortical arousal response to sensory stimulation and hippocampal arousal response to hypothalamic stimulation were all depressed. We also observed that the activity of reticular formation was not affected by morphine, even immediately before the seizure discharge following large doses in curarized cats. From these findings it may be concluded that SA-8 and morphine are different in modes of exciting action in cats. α-Methyl-3,4-methylenedioxyphenethylamine is a highly active central stimulant comparable to amphetamine or methamphetamine.

Though SA-8 is very stable *in vitro*, it might be decomposed *in vivo*, and the amine might be liberated, particularly in cats. But the electroencephalographic influence of amphetamine known is different from that of SA-8. It could be possible that electroencepha lographic arousal pattern of cortex and RF was induced in mice or rats without reference to behavioral depression by SA-8, as seen after atropine or physostigmine. This possibility is suggested by the fact that the temporay tonic convulsions was elicited under depressed condition in mice at lethal doses of SA-8. Poorly developped neocortical system and prevailing limbic system might possibly have resulted in depressive effects of SA-8 in mice or rats, and on the contrary it may possible that SA-8 could be a central stimulant in man. After all, the exact character of SA-8 as a tranquillizer might be able to be obtained through only the clinical experiments.

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Summary

General pharmacology of N-(α-methyl-3,4-methylenedioxyphenethyl)propionamide (SA-8), previously synthesized by us, was described with emphasis at the effects on central nervous system.

SA-8 reduced the spontaneous and methamphetamine-induced locomotor activity of mice rather stronger than meprobamate did.

11, 12) K. Yamamoto : Folia Pharmacol. Jap., **56**, 205 § (1960).

SA-8 did not protect mice from tonic convulsion and death by infused pentylenetet razol. It had hypothermic effect in rast but no antipyretic effect in rabbits at higher doses.

SA-8 itself had weak specificity for the conditioned avoidance response in rats, but it markedly potentiated the effect of chlorpromazine on the response.

The influence of SA-8 on the EEG in curarized cats was investigated. SA-8, administered intravenously, at small doses (20～40 mg./kg.) depressed spontaneous activities of cortex and hippocampus, but at larger doses (60～90 mg./kg.), it activates cortex and reticular formation, and if further doses were injected, seizure discharges throughout the whole brain occurred. Studies by means of electrical stimulation revealed that SA-8 in small doses depressed the hypothalamic activating system, but that it little affected the reticular activating system in cats. SA-8 antagonized to the depressive effect of hexobarbital on the electrical activity of brain in cats, contrary to the results reported in previous paper that SA-8 prolonged the hexobarbital induced sleep in mice.

SA-8 had little spasmolytic activity *in vitro* in mice.

It lowered blood pressure in cats.

LD_{50} value of orally administered SA-8 was 450 mg./kg. (357～567, $p=0.05$).

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116. Fumio Yoneda und Yoshihiro Nitta: Pyridazin-derivate. I. Synthese der Derivate des Oxypyridazins.

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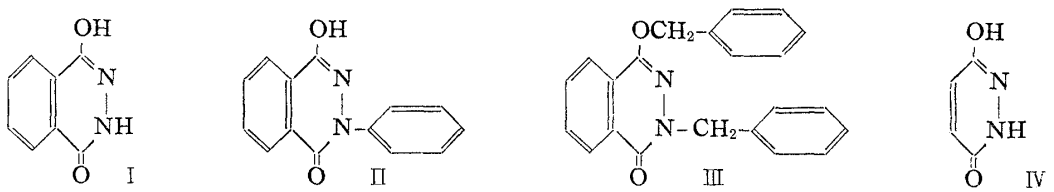
Seitdem Jouin und Buu-Hoï[1] berichtet haben, daß Phthalsäurehydrazid (I) eine tuberklostatische Wirkung besitzt, wurden unter diesen Abkömmlingen einige *in vivo* tuberklostatisch hochwirksame Verbindungen aufgefunden: z. B. 2-Phenyl-4-hydroxy-1(2*H*)-phthalazinon (II), 2-Benzyl-4-benzyloxy-1(2*H*)-phthalazinon (III) u.s.w. zeigten eine ausgezeichnete Aktivität bei der chronischen Form der Maustuberkulose.[2,3]



Schema 1.

Diesmal synthetisierten wir die Benzylderivate des Maleinsäurehydrazides, das strukturell dem Phthalsäurehydrazid nahesteht, um ihre antibakteriellen und anderen pharmakologischen Wirkungen zu prüfen, worüber hier berichtet werden soll.

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2) A.R. Ratsimamanga, *et al.*: Arch. intern. Pharmacodynamic, **91**, 52 (1952).
3) E.M. Bavin, *et al.*: J. Pharm. Pharmacol., **4**, 844 (1952).