THE ACTION OF MESCALINE AND SOME RELATED COMPOUNDS

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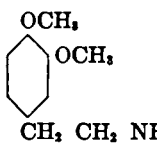
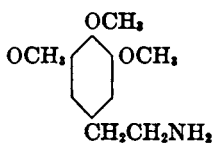
Epstein, Gunn and Virden (1) investigated a series of derivatives of phenylethylamine, especially with regard to their actions on the sympathetic nervous system. They found that p-methoxy-phenylethylamine, m-methoxy-phenylethylamine, and methylene-dioxy-phenylethylamine stimulated the sympathetic terminations in the cat but not in the rabbit. They stimulated also the central nervous system. Dimethoxy-phenylethylamine, on the other hand, was found to have no sympathomimetic action in either of these animals, a rather surprising result in view of the fact that in the last compound the methoxy groups are in the same relative portion as the hydroxy groups in the adrenaline molecule. This compound depressed the central nervous system. Though these compounds were investigated primarily from the point of view of the relation between chemical constitution and sympathomimetic action, dimethoxy-phenylethylamine possessed an additional interest on account of its close relationship to the alkaloid mescaline, the latter being trimethoxy-phenylethylamine. The relationship between the two is seen from the following structural formulae:

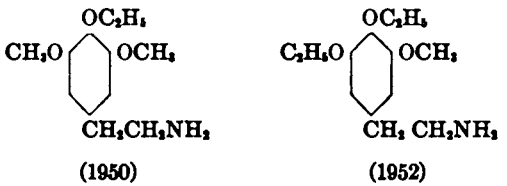


Dimethoxy-phenylethylamine



Trimethoxy-phenylethylamine (mescaline)

Dr. Guggenheim kindly sent to Professor Gunn several compounds related to mescaline, which had been synthesised in the Hoffmann L. Roche Laboratories at Basle, and the latter suggested that I might investigate the following two compounds:



(1950) (1952)

in the former of which (1950) one methoxy group is replaced by an ethoxy group, in the latter (1952) two methoxy groups are similarly replaced. In order to compare their actions with those of mescaline itself, parallel experiments were done with the latter.

Mescaline is an alkaloid which occurs in the cactus, Anhalorium Lewinii, and it is unnecessary here to traverse the literature concerned with the subjective effects of mescaline or of the "mescal buttons." The experiments on laboratory mammals recorded in this paper throw no direct light on the well known "colour visions" or other subjective effects produced by mescaline in man. Some reference is necessary, however, to the literature on mescaline, so far as it is relevant to this paper.

Anhalorium Lewinii contains several alkaloids and much of the confusing earlier work was done with impure alkaloids and, therefore, only those investigations in which pure mescaline was used need be mentioned.

Heffter (2) found that mescaline produced paralysis of the central nervous system in frogs. He did a few indecisive experiments on laboratory mammals. In man he described the following symptoms: slowing of the pulse, dilatation of the pupils, nausea and vomiting, occipital headache and colour visions.

Dixon (3) who probably did not have the alkaloid pure, found in frogs a mixture of paralysis with increased spinal reflexes and muscular twitching, and in cats ataxia, exaggerated reflexes, with later a stage of paralysis. He found that mescaline produced slowing of the frog's heart, not prevented by atropine. In

cats small doses produced an initial fall of blood pressure followed by a considerable and persistent rise, large doses a deeper fall of pressure with slowing of the heart, unaffected by atropine. Mogilewa (4) found slowing of the intact or perfused frog's heart uninfluenced by atropine, which he assigned to paralysis of the motor ganglia.

Raymond-Hamet (5) has recently reinvestigated the actions of mescaline in greater detail. He found that in dogs, under chloralose anaesthesia and artificial respiration and with both vagi cut, mescaline produced in small doses (2 to 8 mgm. per kilogram) either a slight fall or a slight rise of blood pressure. Larger doses (20 mgm. per kilogram or more) produced always a fall with slowing of the heart. Large doses abolished the effects of vagus stimulation on the heart, but left the action of nicotine unaffected. The movements of the intestine *in situ* were with small doses inhibited, with larger doses first stimulated and then inhibited. He concluded that mescaline has no sympathomimetic action.

The object of the present paper was to compare the effects of the two ethoxy-substitution compounds, already mentioned, with those of mescaline. Some new data have been obtained with regard to mescaline itself.

A. LETHALITY

Owing to the relatively small supplies of the alkaloids available, it was not possible to do lethality experiments on large animals, but the minimum lethal dose was determined for each compound on frogs (R. temporaria) and mice, and, in the case of mescaline, also for guinea pigs. For these determinations, injections were made into the dorsal lymph sac in frogs; into the peritoneal cavity in mice, and hypodermically in guinea pigs. Table 1 gives the

TABLE 1

M.L.D. in grams per kilogram

	FROGS (HYPODERMIC)	MICE (INTRAPERITONEAL)	GUINEA PIGS (HYPODERMIC)
Mescaline	0.75	0.5–0.6	0.5
1950	0.3	0.3	
1952	0.3	0.3	

approximate M.L.D. Preparations 1950 and 1952 were therefore about equal in activity and were roughly twice as toxic as mescaline itself.

B. SYMPTOMS

The symptoms produced by the three compounds were, so far as could be made out, identical. In frogs the chief symptoms were progressive motor paralysis, arrest of respiration and abolition of reflexes. In guinea pigs there was a similar motor paralysis with failure of respiration and asphyxial convulsions. Death was due to respiratory failure.

So far as the frog is concerned, these experiments agreed with those of Heffter. No evidence was obtained of a strychnine-like action such as was described by Dixon. In both frogs and mammals the main effect of these alkaloids is undoubtedly a depression of the central nervous system.

C. ACTION ON VOLUNTARY MUSCLE

All three compounds are found to exert an effect on the isolated voluntary muscle of the frog.

Figure 1 shows the effect of 1:4000 solution of preparation 1952 on the isolated gastrocnemius muscle. The record was taken on a slowly revolving drum and the muscle was stimulated directly every three minutes, the position of the secondary coil remaining unchanged throughout the experiment.

After replacement of the Ringer's solution by the drug solution, the muscle was gradually paralysed until, after about twenty minutes, it ceased to respond to stimuli at all. The same result was also obtainable in the same concentration of preparation 1950, but mescaline, in any weaker strength than 1:500 had no action at all on the gastrocnemius muscle.

If much stronger concentrations are used (e.g., 1:500) all three compounds will not only paralyse but will also shorten the muscle, while the individual contractions are diminished as the result of restricted relaxation.

Mescaline (1:500) requires about fifty minutes to paralyse completely the gastrocnemius muscle, while the same concentra-

tion of the other two substances paralysed in about eight minutes. A control muscle was kept in each experiment.

Dixon found no effect produced by painting an isolated frog's sartorius "with the standard solution," which was presumably 1 per cent. From the differences between his results and mine, it is evident, as Mogelewa suggests, that Dixon could not have been dealing with pure mescaline.

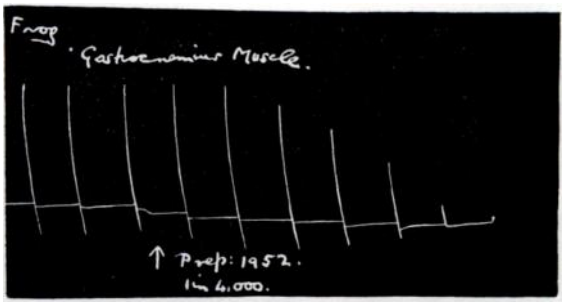


FIG. 1. ISOLATED GASTROCNEMIUS MUSCLE OF FROG SHOWING EFFECT OF PREPARATION 1952, 1:4000

D. ACTION ON THE CIRCULATION AND RESPIRATION

1. Blood pressure and respiration

Blood pressure experiments were performed on cats and rabbits anaesthetised in some cases by a mixture of ether and chloroform, and in others by urethane (2 grams per kilogram injected subcutaneously). The blood pressure was recorded by a mercury manometer connected to a cannula inserted in the left carotid artery, and respiration was recorded by a frontal writing lever attached to the wall of the thorax by a thread, as described by Gunn. Injections were made into the right external jugular vein.

All three compounds produce depression of the respiration accompanied by a fall in blood pressure. Figure 2 shows the effect of 0.01 gram per kilogram of mescaline injected into a cat anaesthetised by ether and chloroform. In this experiment the blood-pressure fell from about 110 to 50 mm. of mercury. During this time the respiration had almost ceased but as soon as it improved

the blood pressure immediately returned to normal. There is no appreciable slowing of the heart rate accompanying this fall of blood pressure though the strength of the beat is definitely weakened.

Figure 3 shows the effect of the same dose of mescaline on the blood pressure (*B.P.*), intestine (*I.*) and non-pregnant uterus (*U.*) of a cat anaesthetised with urethane.

Preparations 1950 and 1952 produced the same effect as mescaline, but both were more toxic. One-hundredth gramme of

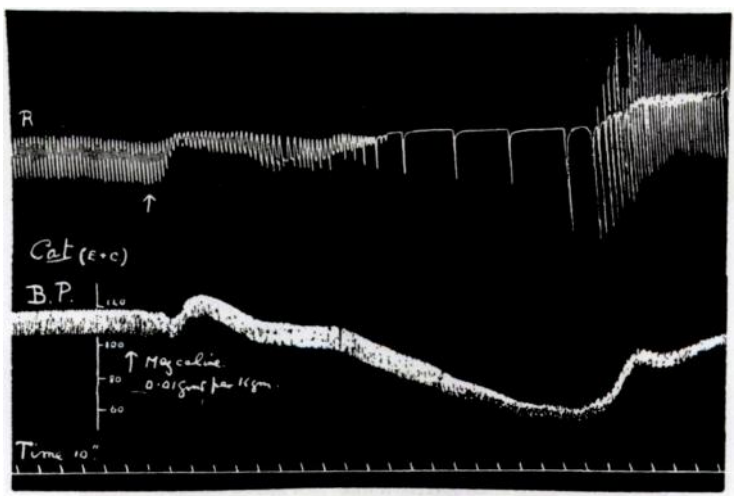


FIG. 2. ANAESTHETISED CAT SHOWING EFFECT OF MESCALINE ON BLOOD PRESSURE (*B.P.*) AND RESPIRATION (*R.*)

preparation 1950 injected into a cat stopped the respiration altogether and, after about two and one-half minutes the blood pressure fell almost to zero, but on applying artificial respiration it returned to normal. After about another minute the cat began spontaneous respiration and thereafter was quite normal.

In each case the effect appears to be central for if any of the compounds are injected into cats whose vagi have been cut, or whose parasympathetic nervous system has been paralysed by a previous dose of atropine (as shown by stimulation of the vagus), the typical effect of the alkaloid is completely abolished. In

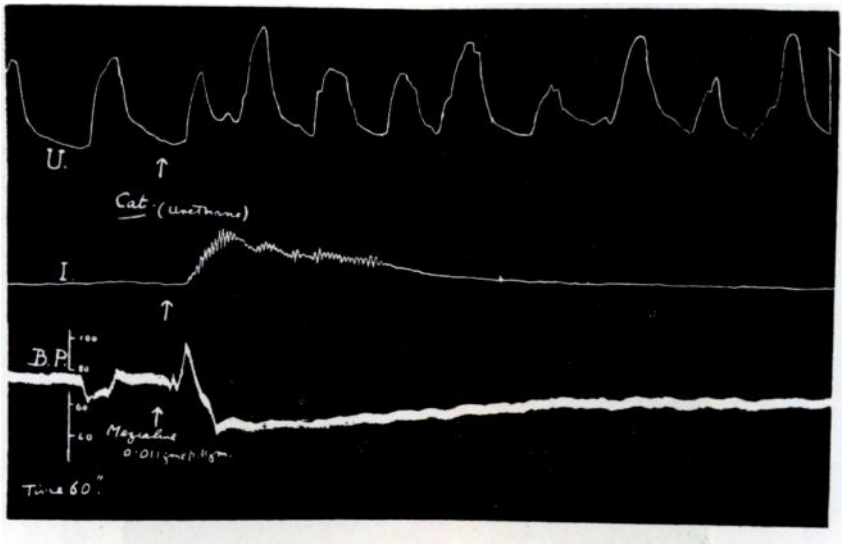


FIG. 3. ANAESTHETISED CAT SHOWING EFFECT OF MESCALINE ON BLOOD PRESSURE (*B.P.*), INTESTINE (*I.*) AND UTERUS (*U.*)

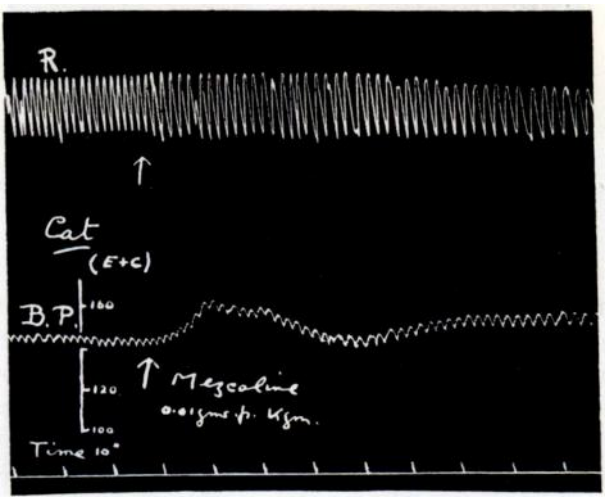


FIG. 4. ANAESTHETISED CAT SHOWING EFFECT OF MESCALINE ON BLOOD PRESSURE (*B.P.*) AND RESPIRATION (*R.*) AFTER ATROPINE

each case the respiration is unimpaired and, with mescaline and with preparation 1950 a slight rise in blood pressure occurs. Figure 4 shows the effect of an injection of mescaline after the vagus had been paralysed by atropine.

In the decerebrate cat the typical effect is again obtained with all three compounds but is abolished by section of the vagi or by atropine. The technique used for decerebration was that described by Sherrington.

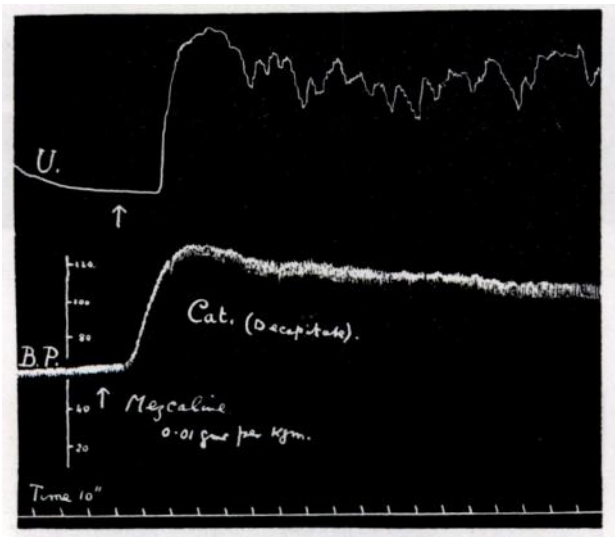


FIG. 5. DECAPITATE CAT SHOWING EFFECT OF MESCALINE ON BLOOD PRESSURE (*B.P.*) AND UTERUS (*U.*)

In the cats decapitated by Sherrington's or Burn's methods, the compounds do not act alike. Mescaline produces a marked rise of blood pressure with strong contraction of the intestine and uterus, whether the latter is in the pregnant condition or not. Figure 5 shows this effect on a decapitate cat, in this case blood pressure rose from 60 to 120 mm. of mercury. Under the same conditions preparation 1950 produced only a rise in blood pressure of 20 mm.—from 80 to 100 mm. of mercury; while preparation 1952 gave a fall of 20 mm.—from 80 to 60 mm. (fig. 6). It appears as if the further the compound is from mescaline the less the

pressor action is obtained in the decapitate preparation. If the nerve ganglia are previously paralysed with nicotine, the mescaline effect is still obtained.

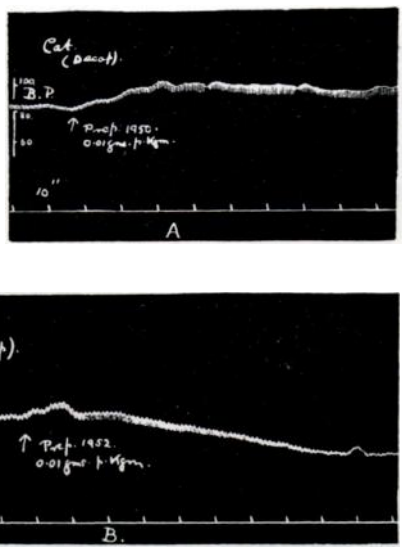


FIG. 6. DECAPITATE CAT SHOWING EFFECT ON BLOOD PRESSURE OF PREPARATION 1950 (*A*) AND PREPARATION 1952 (*B*)

2. Isolated heart

a. Frog. The exsected heart was perfused by means of a cannula inserted into the sinus venosus and connected to two flasks, one containing Ringer's solution and the other the solution of the drug. A hook in the tip of the ventricle was connected to a lever which recorded systole upwards.

With all three drugs, in weak concentrations (e.g., 1:50,000), the only effect obtained is a slight diminution of the size of the beat without any alteration in the rate, the heart rapidly recovering when the drug is replaced by Ringer's solution.

In more concentrated solutions the drugs first of all decrease the amplitude of the beat, then the heart is slowed, heart block occurs, and finally the heart is stopped in almost complete diastole. The slowing is caused by an increase in the time of the

diastolic pause and is almost certainly due to a direct action on the cardiac muscle, for it is not removed by atropine. The concentrations necessary to stop the isolated frog's heart with each of the three compounds was 1:1000. If, at any time before the heart stops, the drug solution is replaced by Ringer's solution the heart rapidly recovers.

b. Rabbit. The apparatus used for the perfusion of the mammalian heart was that described by Gunn.

As in the case of the perfusion of the frog heart, the sequence of events is decrease in amplitude of the beat, slowing of the rate, heart block and finally arrest of the heart in diastole.

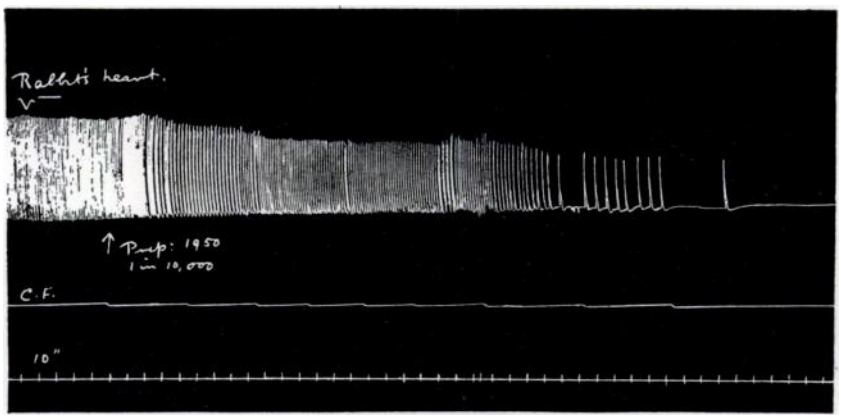


FIG. 7. ISOLATED RABBIT'S HEART SHOWING EFFECT OF PREPARATION 1950 1:10,000

A strength of 1:50,000 mescaline will cut down the amplitude without any alteration in the rate; 1:10,000 will slow the heart very considerably in addition, in one instance from 17 to 10 beats in ten seconds after three minutes perfusion with the drug. Thereafter it continued perfectly regular at this rate. A strength of 1:1000 mescaline is necessary completely to stop the heart in diastole.

Preparation 1950 seems to be much more toxic to the isolated rabbit's heart than the other two compounds. A concentration of 1:25,000 will rapidly bring about a 2:1 heart block although the heart is not arrested, but with a strength of 1:10,000 the heart is quickly stopped in diastole as is shown in figure 7. Prep-

aration 1952 appears to be intermediate in strength between the other two compounds for the heart is stopped by a concentration of 1:5000.

A record of the coronary flow was taken in each experiment by means of a syphon recorder but the drugs appeared to have no action on the coronary vessels. The record was simply a passive curve following the rate of the heart beats.

E. ACTION ON INVOLUNTARY MUSCLE

As convenient examples of smooth muscle the intestine and uterus were used. In each case experiments were carried out on the isolated tissue and also in the intact animal. The following results were obtained.

1. Intestine

The animals used were rabbits and cats, in each case the duodenum being used.

On the isolated intestine none of the drugs have any effect. Using each drug, concentrations of from 1:100,000 to 1:2500 were tried without any effect being obtained. The same negative effects were obtained if defibrinated blood was used instead of Locke's solution.

In the intact animal intestinal records were taken by the following technique. The animal was anaesthetised, the abdomen opened, a thread attached to the duodenum and taken to a writing lever, the lower part of the body being immersed in a warm saline bath.

Under these conditions each drug, by an intravenous injection, produced a powerful contraction. Figure 3 (*I.*) shows the result of injecting 0.011 gram per kilogram of mescaline injected into a cat. This contraction of the intestine *in situ* can be completely abolished by a previous injection of atropine.

Figure 8 is a comparison of the effects of mescaline on the isolated intestine of a rabbit (*A*) and on the intestine in the intact animal (*B*).

2. Uterus

The effects of the alkaloids were tried on the isolated uterus of the cat, rabbit, guinea pig and rat. The results obtained were

identical with those on the isolated intestine, no effect being observed with any concentration used (1:5000 to 1:100,000).

Experiments on the uterus in situ were performed on cats and rabbits using the same technique as that described for the intestine. An injection of any of the three drugs produced an immediate tonic contraction without abolition of the normal rhythmic movements as shown in figure 3 (*U.*). In this case the uterus was in the non-pregnant condition. The same result was

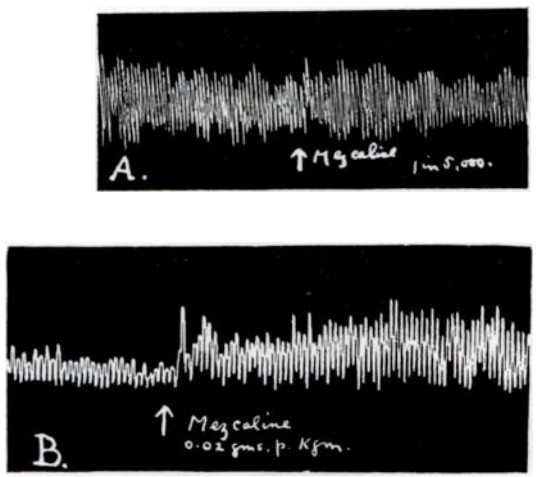


FIG. 8. RABBIT'S INTESTINE SHOWING EFFECT OF MESCALINE, (*A*) ON ISOLATED TISSUE, (*B*) IN SITU

obtained on the decapitate cat and is shown in figure 5 (*U.*). This contraction is not abolished by previously paralysing the nerve ganglia with nicotine.

3. Action on the mammalian pupil

For this experiment again two methods were used: (*a*) A cat was anaesthetised lightly with ether and a tracheal cannula inserted connected to a Woulff's bottle containing ether to control the depth of anaesthesia. A cannula was inserted into an external jugular vein and 10 mgm. of mescaline per kilogram of body-weight injected. The size of the pupil was not affected in any way. A control of adrenaline was then injected in the same way and the pupil was immediately dilated. (*b*) Several

drops of a 2 per cent solution of the alkaloids were dropped into the right eye of a rabbit, the left eye being used as a control. Here again no result was obtained.

DISCUSSION

The derivatives of mescaline here investigated qualitatively resemble mescaline itself in most of their actions. My experiments confirm Heffter's experiments with mescaline in finding that this alkaloid has a depressant and not a stimulant action on the central nervous system. They also confirm Raymond-Hamet's conclusion in regard to mescaline that it has no true sympathomimetic action.

There are, as Raymond-Hamet has also found, some puzzling features of the action of this group on the autonomic nervous system. Raymond-Hamet's experiments were done chiefly on dogs, under chloralose anaesthesia and artificial respiration and with both vagi cut. My experiments were done on cats and rodents. Our experiments agree on many points and, where they differ, the differences may be due to the species of animal used or the altered physiological conditions.

In regard to blood pressure, the action seems to be complicated. Raymond-Hamet obtained sometimes a rise and sometimes a fall with medium doses (2 to 8 mgm. per kilogram) of mescaline, and always a fall with large doses (20 mgm.). In the anaesthetised cat, with vagi intact, I obtained always a fall with doses of 10 mgm. per kilogram, but in the decapitate animal this dose of mescaline produces a considerable rise of pressure. Pilocarpine was found by Heaton and Mackeith (6) to produce similar effects and they ascribed this pressor effect to an "action on the preganglionic sympathetic fibres, disclosed only when their central connections are divided." In regard to the mescaline group it is difficult to suggest any conventional explanation which can account for all the effects so far described.

With regard to involuntary muscle, Raymond-Hamet found that medium doses of mescaline produced a marked stimulation of intestinal movements *in situ*, followed by lowered tonus, an effect similar to that produced by nicotine. Unlike nicotine, however, mescaline still produced this stimulant action after a

large dose of sparteine, wherefore he concluded that this effect is muscular in nature. Using comparable doses I have also obtained a stimulant effect both on the intestine and uterus *in situ*, both in the anaesthetised and decapitate cat. The difficulty of ascribing this effect in my experiments to a direct action on muscle arises from the facts that the intestinal stimulation is prevented by atropine and that no such stimulant effect is obtained on the isolated uterus or intestine even with high concentrations. It is possible that the relative intensity of muscular and ganglionic stimulations may vary in different species of animal.

SUMMARY

The actions of 3.5-dimethoxy-4 ethoxy-phenylethylamine (preparation 1950) and of 3.4-diethoxy-5 methoxy-phenylethylamine (preparation 1952) have been compared with those of 3.4.5. trimethoxy-phenylethylamine (mescaline).

The former two compounds are about twice as toxic as mescaline. All produce motor paralysis due to depression of the central nervous system and death from respiratory failure.

They produce a fall of blood pressure which is prevented by vagotomy or atropine. Mescaline and preparation 1950 produce a rise of blood pressure in the decapitate cat, possibly due to stimulation of sympathetic ganglia. Strong solutions arrest the perfused heart in diastole, due to a direct action on cardiac muscle.

They stimulate the contractions of the intestine and uterus *in situ* but not when exsected.

Preparations 1950 and 1952 paralyse voluntary muscle of the frog in concentrations of about 1:4000. Stronger solutions (1:500) of all three compounds cause contracture with loss of excitability.

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