COMPARATIVE NEUROPHYSIOLOGICAL STUDIES OF PSYCHOTOMIMETIC N-DIMETHYLAMINES AND N-DIETHYLAMINES AND THEIR NON-PSYCHOTOMIMETIC CONGENERS DEVOID OF THE N-DIMETHYL OR N-DIETHYL CONFIGURATIONS

HAROLD E. HIMWICH

Thudichum Psychiatric Research Laboratory,
Galesburg State Research Hospital, Galesburg, Illinois 61401

IN THIS paper we shall review some of our results obtained with psychomimetic and non-psychomimetic congeners of three classes of indoleamines: 4-substituted indoleamines, 5-substituted indoleamines, and lysergic acid diethylamide (LSD-25). These observations were made by Brodey *et al.* (1963), Schweigerdt and Himwich (1964) and Schweigerdt *et al.* (1966) respectively. We shall also mention some pilot experiments made by Dr. Yuji Takeo with mescaline and 3,4-dimethyoxyphenylethylamine. The psychomimetic congeners of the indoleamines are in general characterized by possessing a N-dimethylamine or a N-diethylamine structure while the non-psychomimetic congeners are devoid of either of these two chemical configurations. The results of the congeners of the 4-substituted indoleamines, the 5-substituted indoleamines, LSD-25 and the preliminary experiments with the two methoxy catecholamines are presented in that order.

METHOD

Adult albino rabbits weighing from 2·5 to 3·0 kg were used throughout these studies. Animals were tracheotomized under ether and local pontocaine anesthesia, curarized and artificially respired. Brain wave recordings were made on an eight-channel Grass Model III D electroencephalograph (EEG). Monocoaxial electrodes were implanted according to the maps of Sawyer *et al.* (1954) in the anterior cortex (motor) (anterior 3, lateral 4, vertical plus 9); amygdala (anterior 2, lateral 5·5, vertical plus 5); caudate nucleus (anterior

3, lateral 4, vertical plus 4·5); posterior cortex (limbic) (posterior 4, lateral 4, vertical plus 8·5); hippocampus (posterior 4, lateral 4, vertical plus 5·5); thalamus (VPL) (posterior 4, lateral 4, vertical minus 1); and reticular substance (posterior 10, lateral 2, vertical minus 9). For purposes of convenience, these will be referred to as EEG, even though they were direct tissue recordings from cortical and subcortical sites. Histological examinations were undertaken and the placements of electrodes were verified. In addition to the observations on intact animals in the course of these experiments three sections of the brain were performed (Fig. 1) and our observations include one or more sections on each animal. One transection (1) was at the precollicular prepontine level rostral to the midbrain, another (3) was at the post-collicular

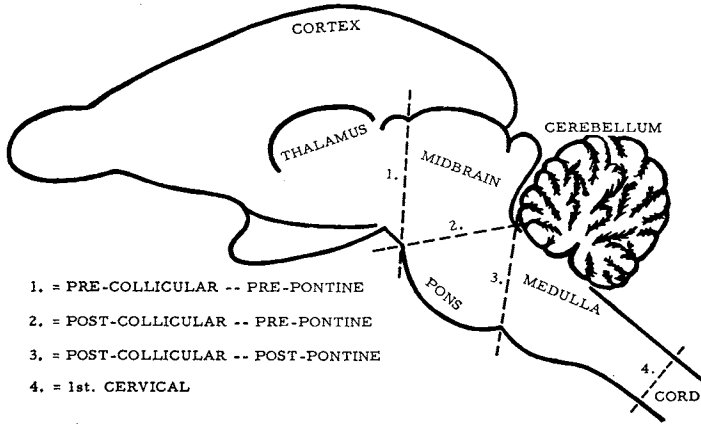


FIG. 1. Schematic representation of the rabbit brain showing planes of transection; in the present experiments transections 1, 3 and 4 were employed.

post-pontine level caudal to the midbrain, and still another (4) was made at C_1. Following each experiment, the animals were sacrificed and the brains removed to ascertain if the transections was complete and in the prescribed plane. All drugs were dissolved in distilled water and injected into the femoral vein via a polyethylene cannula. With 5-hydroxytryptophan (5-HTP), however, in addition to the intravenous route, intracarotid injections were also made. In all experiments blood pressure readings on the animals were monitored by a polyethylene cannula inserted into the femoral artery and connected to a mercury manometer. Animals with tracings that did not show normal maintenance of blood pressure following transection were excluded from the study.

RESULTS

4-substituted indoleamines. Fifty-nine albino rabbits received 4-substituted indoleamine compounds (Fig. 2). The latter were five in number:

(1) *o*-phosphoryl-4-hydroxy-N-dimethyltryptamine (psilocybin), (2) 4-hydroxy-N-dimethyl tryptamine (psilocin), (3) 4-methyl-alpha-methyl tryptamine (MP-809), (4) 4-hydroxy-alpha-methyl tryptamine (MP-14), and (5) 1-methyl psilocybin. Each of these five indoleamines evoked an EEG alert reaction in rabbits with intact brains. Figure 3 illustrates the difference between the EEG pattern before and after the injection of non-psychotomimetic MP-809.

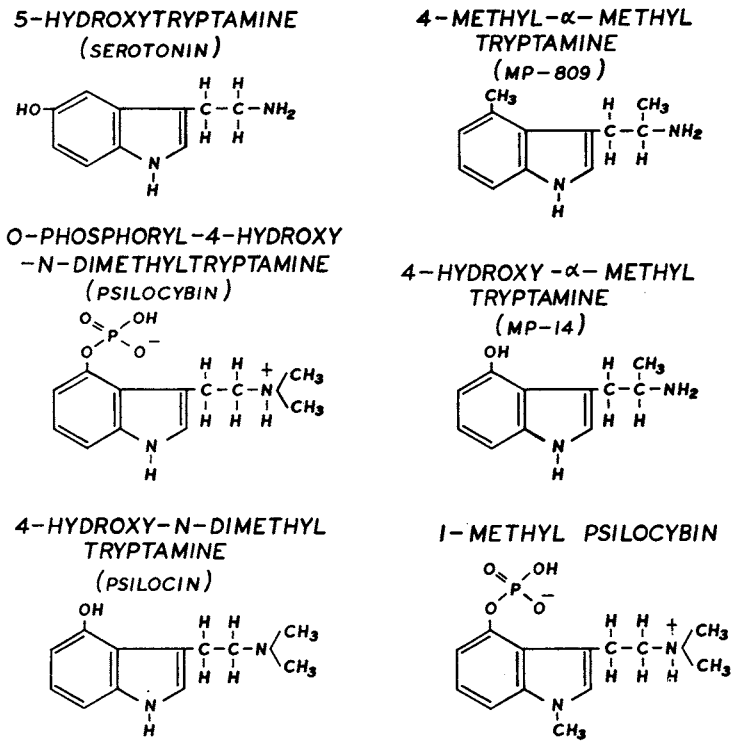


FIG. 2. Chemical structures of serotonin and 4-substituted indoleamines investigated in the present study.

As a next step we transected the rabbit brain at the pre-collicular pre-pontine level (Transection 1, Fig. 1) and EEG alerting could be no longer obtained (Fig. 4). In contrast, a post-collicular post-pontine transection did not prevent the EEG arousal after the injection of MP-809. There was a significant difference between MP-809, however, and its congener, psilocin. Despite psilocin, post-collicular, post-pontine preparation (Transection 3, Fig. 1) did not exhibit alerting (Fig. 5) which, however, was produced after transection at the cervical level. Thus the midbrain preparation was adequate to sustain EEG arousal to the non-psychomimetic congener but with the encephale isolé the psychomimetic one was successful.

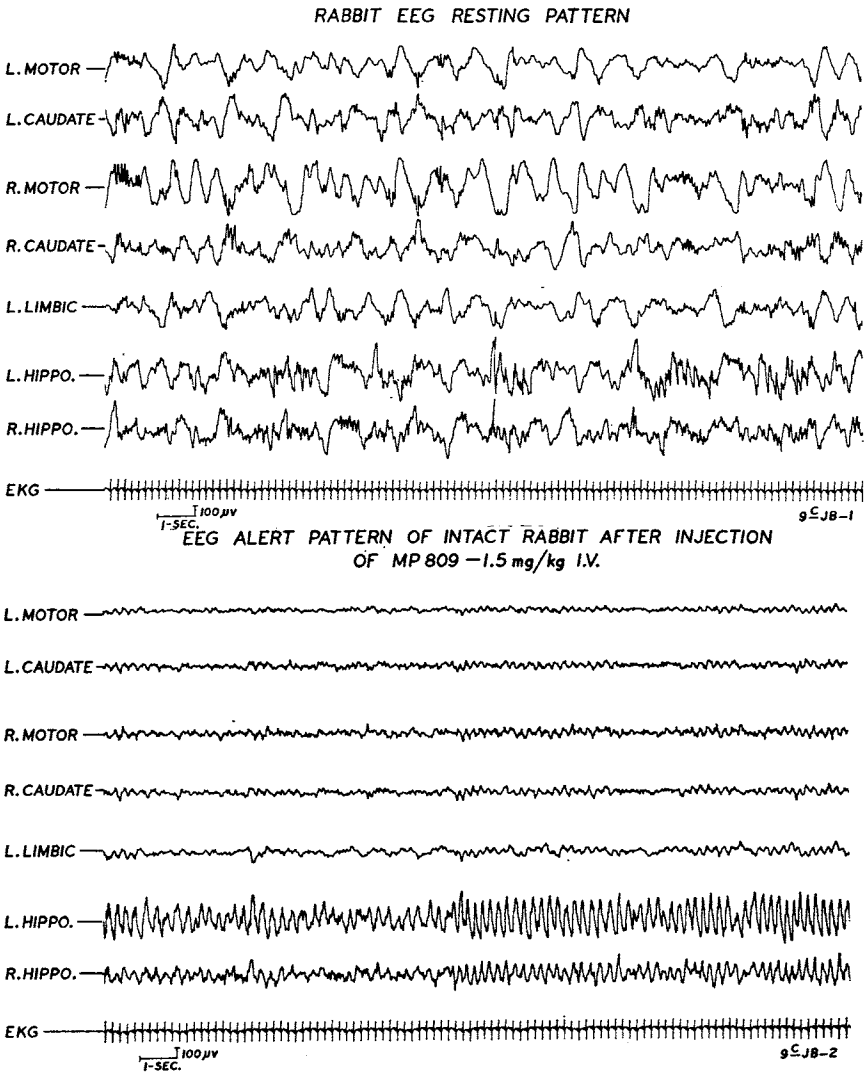


FIG. 3. Top series of tracings: Cerebral electrical activity of a curarized unanesthetized rabbit showing typical synchronized patterns of high-voltage waves and 14/sec spindles. Lower series of tracings: Cerebral electrical activity of rabbit with intact brain after administration of 1·5 mg/kg of MP–809. Notice the desynchronization characterized by low amplitude and absence of sleep spindles and slow waves. As can be seen, the alerting patterns of the hippocampus are different from those of all other brain structures. The leads are (reading downward) (1) left motor cortex, (2) left caudate nucleus, (3) right motor cortex, (4) right caudate nucleus, (5) left limbic cortex, (6) left hippocampus, (7) right hippocampus, (8) EKG.

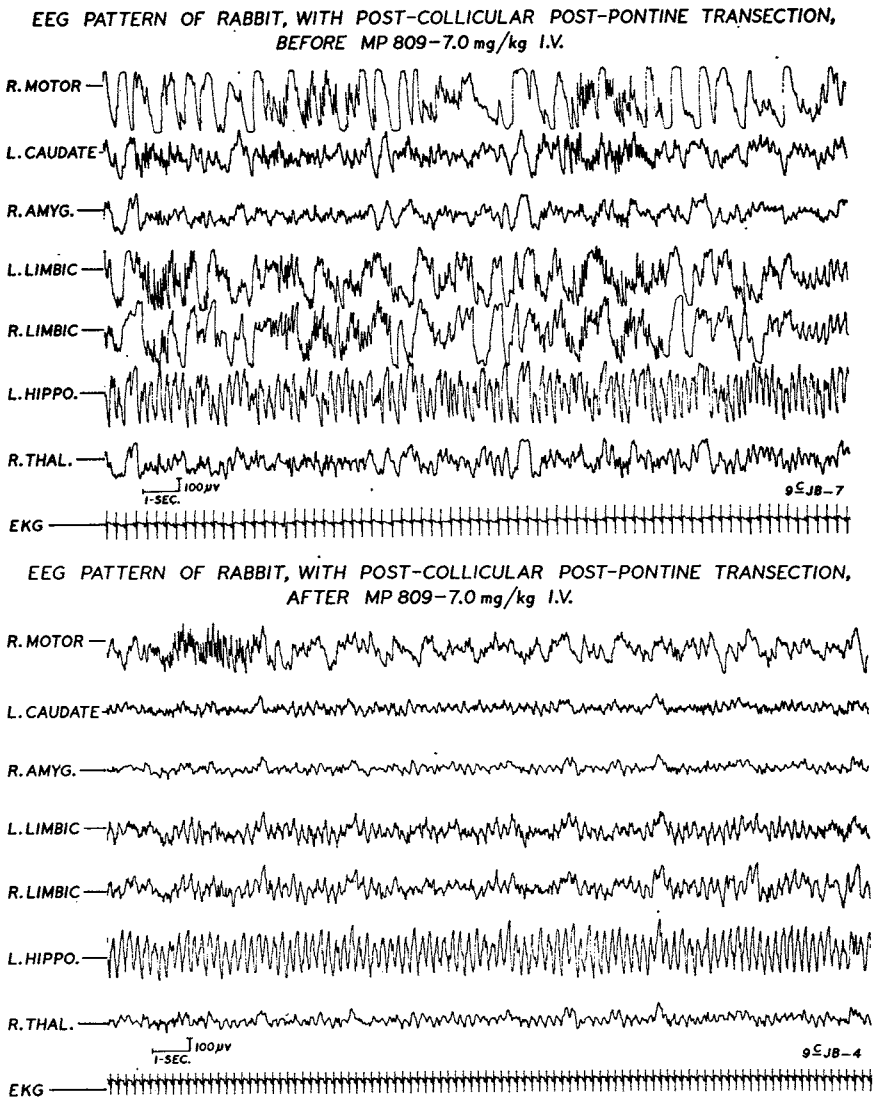


FIG. 4. Cerebral electrical activity of rabbit, transected in a post-collicular post-pontine plane, after MP-809 7·0 mg/kg. The pattern observed in the lower series of tracings resembles EEG arousal presented in the lower series of tracings of Fig. 3 and differ from them only in the somewhat higher amplitudes of the cortical brain waves.

5-substituted indoleamines. We next went on to an examination of bufotenin and serotonin in seventy-three animals, and of these two congeners only bufotenin contains the N-dimethylamine group in its chemical structure

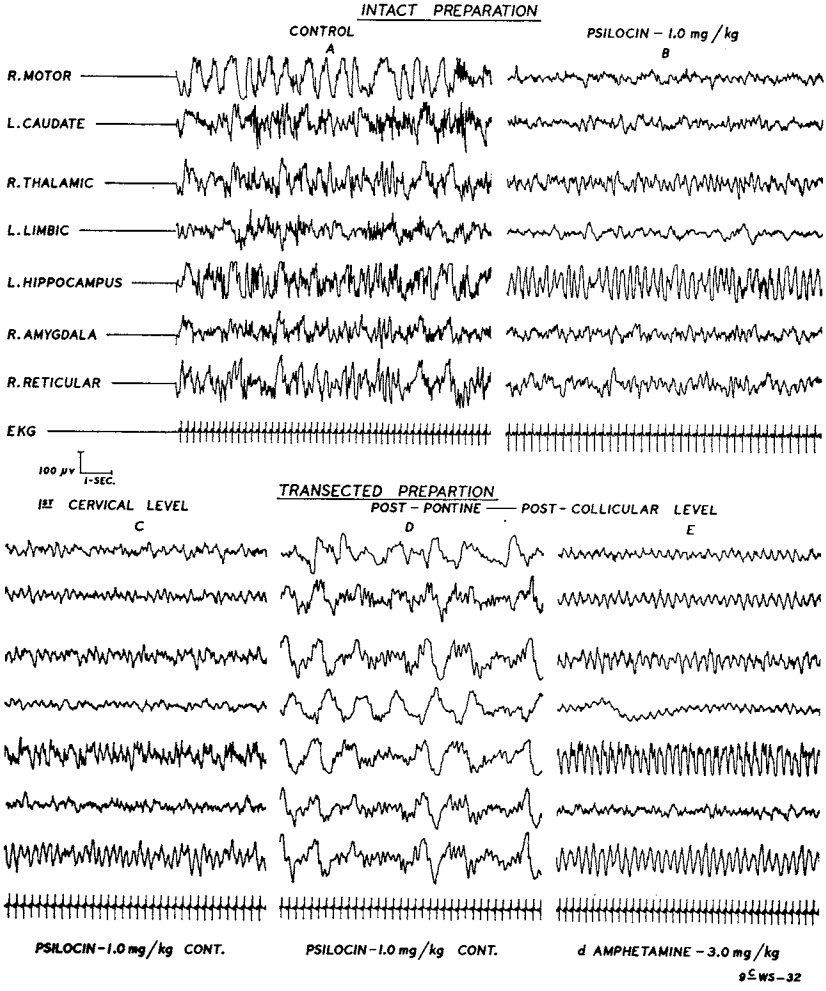


FIG. 5. (A) Predrug resting rhythm, (B) psilocin alerting with intact brain, (C) continued maintenance of psilocin alerting after transection of spinal cord at first cervical vertebra, (D) loss of EEG arousal after second transection caudate to midbrain, and (E) arousal restored by *d*-amphetamine.

(Fig. 6). Because the brain is relatively impermeable to serotonin, we injected 5-HTP instead. Previous work with 5-HTP revealed that four intracarotid injections of 5-HTP, each of 11 mg given about 5 min apart, evoked a persistent alerting pattern which endured at least $\frac{1}{2}$ to 1 hr after the fourth injec-

tion (Costa *et al.*, 1960). These observations also revealed a significant increase in the serotonin content of the brainstem. We therefore again employed the same technique in our present experiments with intravenous bufotenin and intracarotid or intravenous injections of 5-HTP in order to increase brain serotonin. Again we obtained EEG alerting after a total dose of 44 mg intracarotidly or approximately four times as much intravenously, an alert which was also obtained in rabbits transected at the post-collicular post-pontine site (Transection 3, Fig. 1) (Fig. 7). In contrast bufotenin could not induce alerting at the midbrain level but after the first cervical section the EEG arousal reaction was consistently observed (Fig. 8). Thus though bufotenin and serotonin after injection of 5-HTP evoked the alerting reaction in the midbrain preparation, bufotenin was effective at a lower level in the brainstem.

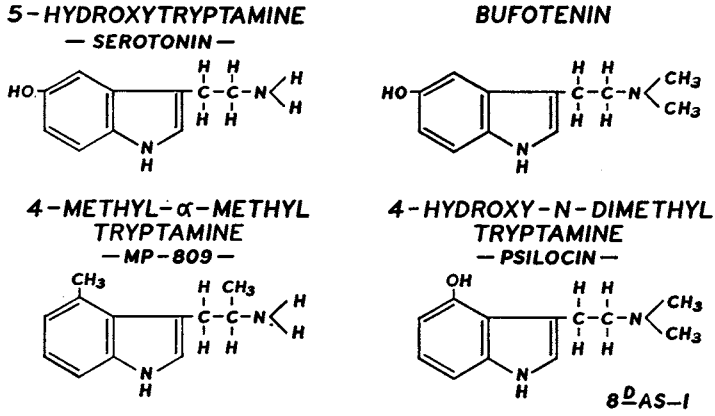


FIG. 6. Chemical structures of serotonin, bufotenin, MP-809 and psilocin.

LSD-25 and 9 congeners. It would seem that we have even a better opportunity to test our concept because of the greater number of possibilities presented by LSD and its congeners (Fig. 9). In these observations we studied a total of ninety-six albino rabbits. For those congeners that gave alerting, minimal dosage was determined and in most instances larger doses were administered to assure alerting. Five of these ten compounds produced alerting: LSD-25, LAE, LSM, MLD and DAM. LSD-25 was able to maintain alerting even after cord transection at the level of C_1 (Fig. 10). In view of the inability of this drug to evoke EEG alerting in animals transected at the post-collicular post-pontine level it would seem that LSD-25 possesses a potent locus of action in the lower brainstem region. Thus this psychomimetic N-diethyl indoleamine appears to have the same ability to evoke alerting at the lower brainstem level as do N-dimethyl indoleamines. In contrast, LSM, MLD and DAM did not exhibit EEG alerting in the encephale isolé preparations. The latter findings are in agreement with those reported

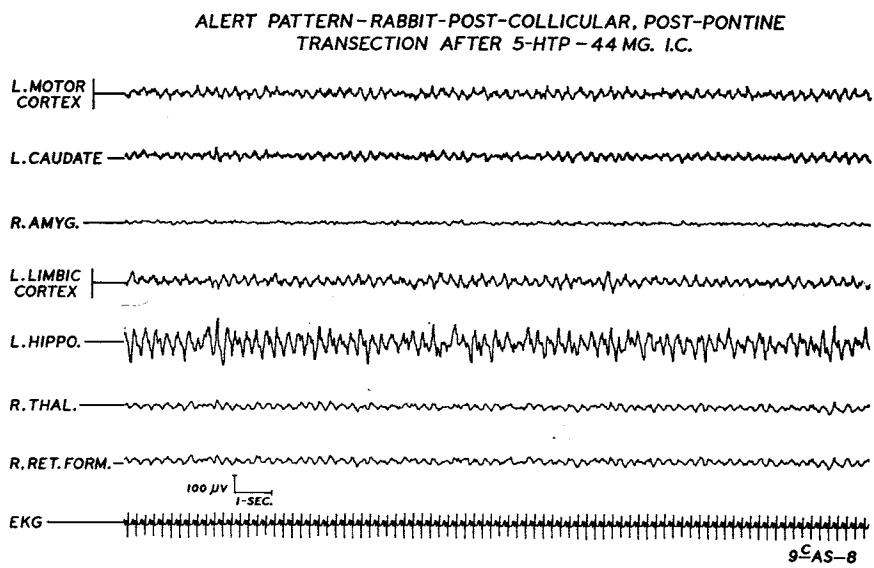


FIG. 7. Continued maintenance of EEG arousal patterns evoked by intracarotid injection of 44 mg 5-HTP in a rabbit after transection in a post-collicular post-pontine plane.

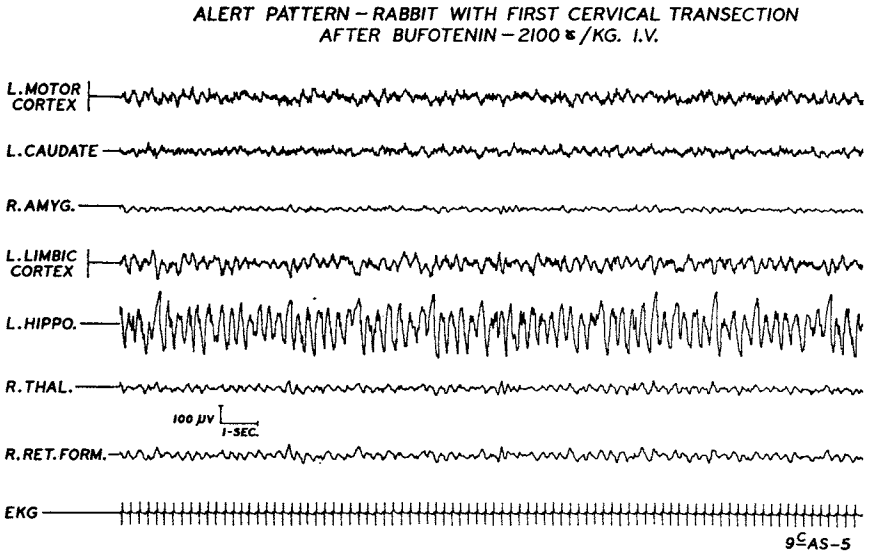


FIG. 8. Continued maintenance of alert pattern after bufotenin (2100 μg/kg i.v.) transection of the spinal cord of a rabbit at the first cervical segment.

CHEMICAL STRUCTURES OF COMPOUNDS

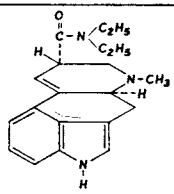
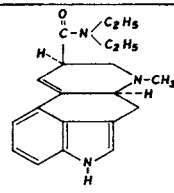
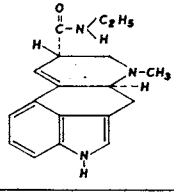
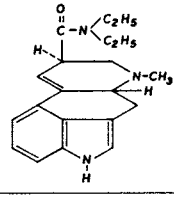
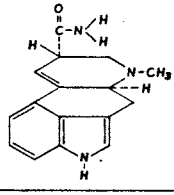
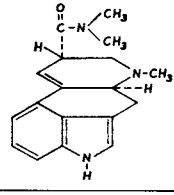
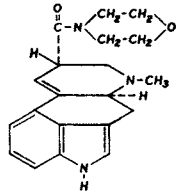
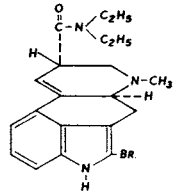
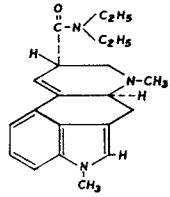
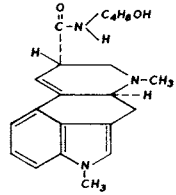
COMPOUNDS ABBR.	STRUCTURAL FORMULA	COMPOUNDS ABBR.	STRUCTURAL FORMULA
D-LYSERGIC ACID DIETHYLAMIDE * LSD		D-ISO-LYSERGIC ACID DIETHYLAMIDE D-ISO-LSD	
D-LYSERGIC ACID MONOETHYLAMIDE * LAE		L-LYSERGIC ACID DIETHYLAMIDE L-LSD	
D-LYSERGIC ACID * LA		D-LYSERGIC ACID DIMETHYLAMIDE * DAM	
D-LYSERGIC ACID MORPHOLIDE * LSM		2-BROM-D-LYSERGIC ACID DIETHYLAMIDE BOL	
D-I-METHYL-LYSERGIC ACID DIETHYLAMIDE * MLD		I-METHYL-D-LYSERGIC ACID BUTANOLAMIDE UML	

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FIG. 9. Chemical structures of LSD-25 and congeners.

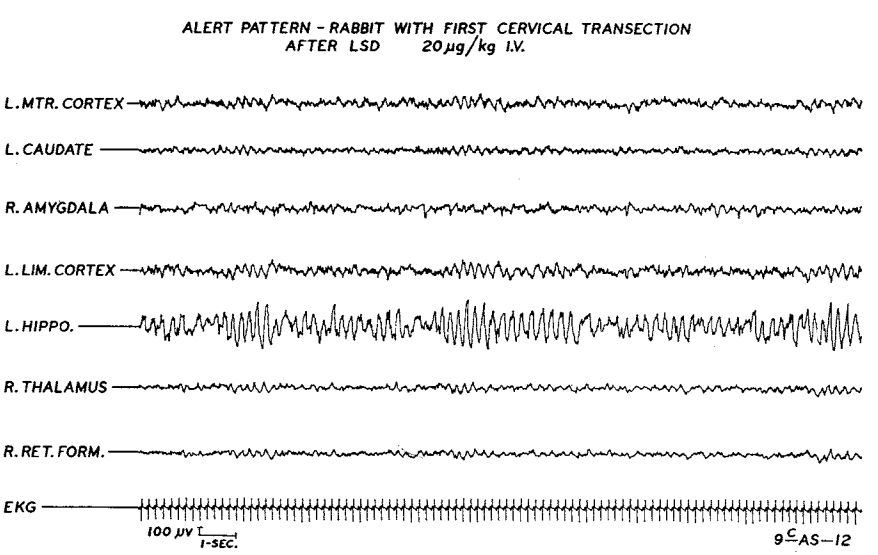

FIG. 10. Continued maintenance of LSD-25 alerting after transection of the spinal cord at the first cervical segment.

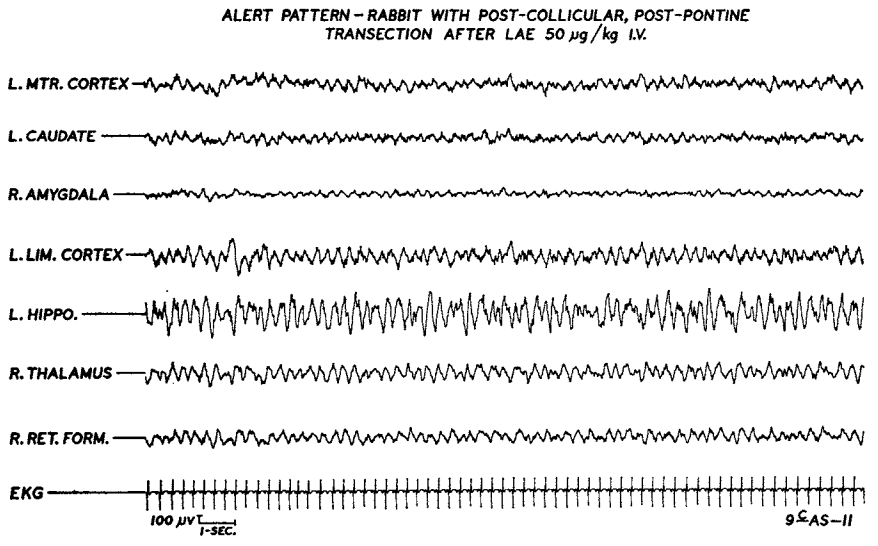

FIG. 11. Continued maintenance of EEG arousal pattern evoked by LAE after transection in a post-collicular post-pontine plane.

by Philip Bradley (1958) that in the cat LSD-25 alerting could be neither initiated nor maintained after cervical transection. Bradley suggests that the action of LSD-25 may be to sensitize receptors at the level of the reticular formation so that they become sensitive to afferent impulses arriving via collaterals and especially those coursing centripetally up the spinal cord. This is similar to our observations with LSM, MLD and DAM which also failed to evoke alerting in the C_1 transected animal. On the other hand, unlike the cat, in the rabbit LSD was still effective in the encephale isolé animal. Thus it seems likely that tonic reticular inputs from super-spinal levels were adequate to elicit EEG arousal with LSD-25 in cervical transected rabbits. That this may be a species difference in rabbits, which could sustain EEG activation after C_1 transection, is indicated by the fact that psilocin and bufotenin may likewise maintain alerting in the cervical transected rabbits. It is noteworthy that the five congeners active in evoking alerting are all regarded as being clinically hallucinogenic (Solms, 1956; Abramson *et al.*, 1955; Isbell *et al.*, 1956). It is interesting that LAE (Fig. 11) with a single ethyl group effected EEG alerting in animals transected caudal to the midbrain level and therefore exhibits a higher site of action at the midbrain level. It seems likely, therefore, that either a diethyl or monoethyl constituent is necessary to evoke alerting though acting at different levels.

One hallucinogen, LA, without an ethyl group in the N position failed to elicit EEG activation. The substitution of a diethyl group in DAM or the closure of the two ethyl groups into a morpholine ring in LSD-25 did not change the ability of these substances to induce EEG alerting. With the addition of a methyl group in the indole ring (MLD) or the substitution of one ethyl radical with a hydrogen (H) as in LAE, a period of latency is seen before the drug-induced arousal. This delay suggests either that these drugs do not pass the blood-brain barrier readily or that some active intermediate is formed in the intervening period. With the exception of BOL the non-hallucinogenic compounds D-iso-LSD, L-LSD and UML failed to elicit alerting. We found it necessary, however, to administer BOL in total dosages which approach toxic levels to obtain even brief periods of activation in some animals. In general, our results show that those psychomimetic congeners of LSD-25 containing the N-diethylamine group act similarly to the indoles containing the N-dimethylamine configurations in exhibiting a locus of action in the lower brainstem level. Furthermore, it is suggested that the indole group and either the N-diethylamine or N-dimethylamine structures are strategically important in producing changes in the site of EEG activation as well as in psychomimetic behavior and both parts of the psychomimetic molecule are necessary to produce alerting.

We have now begun to extend our observations to the catecholamines and have initiated our studies with observations on mescaline and dimethoxyphenylethylamine, of which Dr. Arnold Friedhoff very kindly supplied

samples. Previous work has revealed that mescaline can evoke marked and long-enduring EEG alerting reactions in the intact organism (Himwich, 1959). These observations we have confirmed.

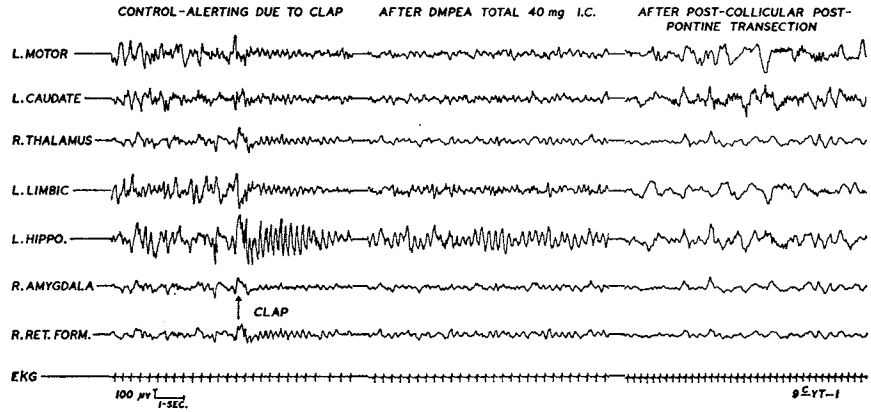

FIG. 12. The alert pattern is shown under three different experimental conditions. In the left-hand series of tracings the alert pattern is evoked as a result of the sound of clapping of the hands. The middle series of tracings reveal the alert pattern evoked by three injections of 10 mg/kg i.v. of mescaline to an animal with intact central nervous system. The series of tracings on the right reveal that this pattern is maintained after transection at C_1.

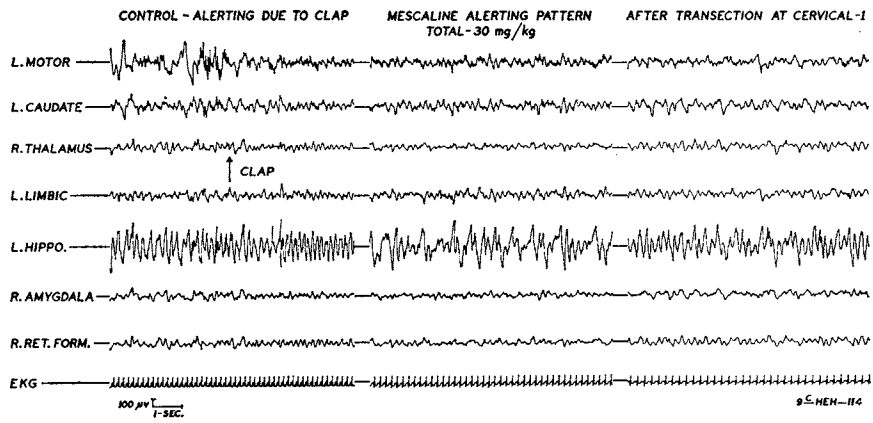

FIG. 13. The left-hand series of tracings reveals the alert pattern evoked by the sound of clapping of the hands. In the middle series of tracings the alerting is produced by four intracarotid injections of 10 mg each of dimethoxyphenylethylamine. The series of tracings on the right reveal that alerting can neither be evoked nor maintained in rabbits transected in the post-collicular post-pontine plane.

In our pilot experiments now going on, mescaline failed to evoke EEG alerting in rabbits sectioned caudal to the midbrain but transections in the C_1 plane left this ability unimpaired. Furthermore, if the animals were transected first, injections of mescaline still excited EEG alerting (Fig. 12). In regard to dimethoxyphenylethylamine, it is of special significance that the pattern for evoking EEG alerting is similar to that of mescaline, ineffective at the midbrain level but successful in the lower brainstem (Fig. 13). We are going to continue observations with these two compounds and in addition study other O-methoxy catecholamines. These preliminary observations, however, reveal that O-methoxy psychotomimetic catecholamines, like N-diethylamine or N-dimethylamine indole compounds, share the characteristic of evoking EEG alerting in the encephale isolé animal but not in those sectioned just caudal to the midbrain.

ACKNOWLEDGMENT

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REFERENCES

ABRAMSON, H. A., JARVIK, M. E., KAUFMAN, M. R., KORNETSKY, C., LEVINE, A. and WAGHER, M. (1955) LSD-25. I. Physiological and perceptual response, *J. Psychol.* **39,** 3–60.

BRADLEY, P. B. (1958) The central action of certain drugs in relation to the reticular formation of the brain, H. H. Jasper, L. D. Proctor, R. S. Knightson, W. C. Noshay and R. T. Costello, eds., *Reticular Formation of the Brain*, pp. 123–49, Little, Brown & Company, Boston.

BRODEY, J. F., STEINER, W. G. and HIMWICH, H. E. (1963) An electrographic study of psilocin and 4-methyl-alpha-methyl tryptamine (MP–809), *J. Pharmacol. Exper. Therap.* **140,** 8–18.

COSTA, E., PSCHEIDT, G. R., VAN METER, W. G. and HIMWICH, H. E. (1960) Brain concentrations of biogenic amines and EEG patterns of rabbits, *J. Pharmacol. Exper. Therap.* **130,** 81–88.

HIMWICH, H. E. (1959) Discussion. P. B. Bradley, P. Deniker and C. Radouco-Thomas, eds. *Neuro-Psychopharmacology*, pp. 129–33, Elsevier, New York–Amsterdam.

ISBELL, H., BELLEVILLE, R. E., FRASER, H. F., WIKLER, A. and LOGEN, C. R. (1956) Studies on lysergic acid diethylamide (LSD–25). I. Effects in former morphine addicts and development of tolerance during chronic intoxication, *AMA Arch. Neurol. Psychiat.* **76,** 468–78.

SAWYER, C. H., EVERETT, J. W. and GREEN, J. D. (1954) The rabbit diencephalon in stereotaxic coordinates, *J. Comp. Neurol.* **101,** 801–24.

SCHWEIGERDT, A. K. and HIMWICH, H. E. (1964) An electrographic study of bufotenin and 5-hydroxytryptophan, *J. Pharmacol. Exper. Therap.* **144,** 253–9.

SCHWEIGERDT, A. K., STEWART, A. and HIMWICH, H. E. (1966) An electrographic study of LSD-25 and nine congeners, *J. Pharmacol. Exper. Therap.* **151,** 353-9.

SOLMS, H. (1956) Relationships between chemical structures and psychoses with the use of psychotoxic substances, *J. Clin. Exp. Psychopathol. & Quart. Rev. Psychiat. Neurol.* **17,** 429–33.