a calcium antagonist with catecholamine-depleting activity. Pd-Ia itself, which has a lower pA_2, may be of little value as a therapeutic drug for angina pectoris after development of several potent calcium antagonists effective in relief of angina such as diltiazem (pA_2 6·90), verapamil (pA_2 7·36) and nifedipine (pA_2 9·43) [pA_2 values according to Imai (1980)]. But its effect is interesting from a comparative view point because Pd-II and Pd-III, which are structurally similar, had no effect in blocking Ca^{2+} influx.

REFERENCES

Chen, Z. X., Huang, B. S., She, Q. L., Zeng, G. F. (1979) Acta Pharmaceutica Sinica 14: 486–496

Deth, R. C. (1978) Am. J. Physiol. 234: C139–145

Fleckenstein, A. (1977) Ann. Rev. Pharmacol. 17: 149–166

Gilman, A. G. (1970) Proc. Natl. Acad. Sci. 67: 305–312

Hata, K., Kozawa, M., Ikeshiro, Y., Yen, K. Y. (1968) Yakugaku Zasshi 88: 513–520 (in Japanese)

Imai, S. (1980) TIPS 1: 87–89

Inatomi, N., Takayanagi, I., Uchida, M., Takagi, K. (1974) Eur. J. Pharmacol. 26: 73–76

Okuyama, T., Shibata, S. (1981) Planta Medica 41: in the press

Tomiyama, A., Takayanagi, I., Takagi, K. (1973) J. Pharm. Pharmacol. 25: 65–68

Uchida, M., Yoshimoto, N. M., Harumi, K., Murao, S. (1978) Jpn. Heart J. 19: 281–296

van Breeman, C., Farinas, B. R., Gerba, P., McNaughton, E. D. (1972) Circ. Res. 30: 44–52

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Structure-activity relationships among hallucinogenic tryptamine derivatives evaluated by schedule-controlled behaviour

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A number of benzo[*b*]thiophenes which are sulphur isosteres of *NN*-dimethyltryptamine (DMT,I) and related hallucinogens have been synthesized (Campaigne et al 1968; Campaigne & Dinner 1970; Campaigne et al 1970; Campaigne & Rogers 1973) and the 1-methylindole and naphthalene isosteres of DMT are also available (Fig. 1). As the effect on animal behaviour of alterations of the indole moiety of such compounds has received little attention, we used the method of Harris (1980) to examine the behavioural effects of DMT, DMT derivatives, and DMT isosteres on schedule-controlled behaviour of the rat. With this system, we have previously found that the potency of hallucinogenic drugs correlates with their potency in producing subjective effects in man (Harris et al 1977, 1978).

Nine rats were used. The apparatus and procedure (lever pressing under a fixed-interval 5-min schedule of food presentation) were essentially as described by Harris (1980), except that animals were divided into two groups. For one group, sessions ended after 11 intervals or 70 min, whichever occurred first. Due to the short duration of action of some of the drugs, data were recorded after the first 30 min of each session. For the other group, sessions ended after 300 min and data were recorded every 30 min throughout the sessions. Sessions were conducted five days each week.

NN-Dimethyltryptamine and 5-methoxy-*NN*-dimethyltryptamine were purchased from Sigma Chemical Co. (St Louis, Mo.); psilocin was kindly provided by the National Institute on Drug Abuse (Rockville, Md.). The remaining compounds (Fig. 1) were synthesized (Campaigne et al 1968; Campaigne & Dinner 1970; Campaigne & Rogers 1973). Drugs were dissolved in 0·9% NaCl and injected intraperitoneally 1 ml kg^{-1} 2 min before the beginning of the behavioural sessions. Dosages were expressed as the free base for DMT, 5-MeO-DMT, psilocin and compound IX, for the remaining compounds as the hydrochloride. Dose-response curves were determined by testing three to four doses of each drug in three to five rats. Each dose was administered twice to each rat. Drug injections were usually on Tuesdays and Fridays, and were separated by at least 72 h. Control data were obtained on Thursdays. The dose of each drug required to reduce responding to 50% of the control rate (ED50) was estimated by plotting percent of control responding versus log dose (Harris et al 1978; Harris 1980). The 95% confidence limits of the ED50 values were determined by the parallel line assay of graded responses (Goldstein 1964).

Control rates of responding were initially low and increased toward the end of each interval, in agreement with Harris et al (1978) and Harris (1980). Average rates of responding were stable under control conditions.

All drugs decreased the average rate of responding during the first 30 min. Their potencies were estimated from dose-response curves (Table 1). The tryptamine derivatives, DMT(I), psilocin (VIII), and 5-MeO-DMT (XII) were the most potent; their sulphur (benzo[*b*]-thiopene) analogues were less so, that of compound (XIII) being about 15 times weaker than 5-MeO-DMT. Addition of a methyl group to the indole nitrogen (1-methylindole) also reduced the potency of DMT

* Correspondence.

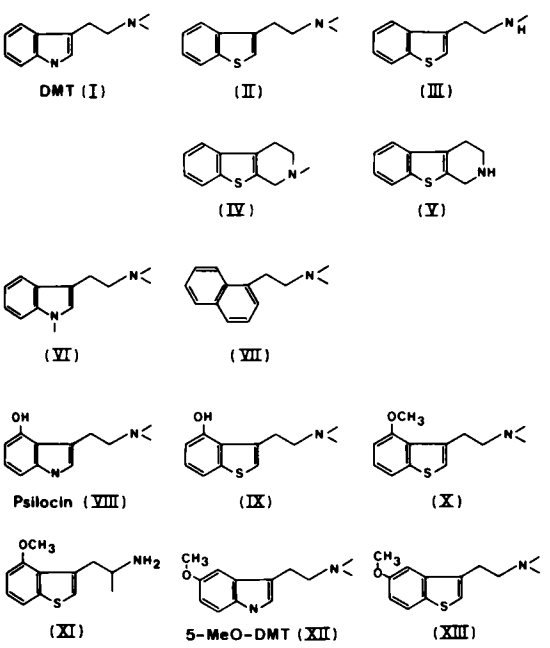

FIG. 1. Structures of the compounds tested.

(Table 1, I vs. VI), as did its conversion to the carbon (naphthalene) isostere (VII). Conversion of II and III to their rigid sulphur analogues (IV,V) did not significantly alter the behavioural potency, nor did conversion of the dimethylaminoethyl side chain of X to a 2-aminopropyl group (XI). Thus, the substituents on the side chain are not critical determinants of the behavioural potencies of the benzo[*b*]thipohene derivatives II, III, X, XI. These observations may also apply to tryptamine derivatives, since an indole analogue of XI,α, *O*-dimethyl 5-HT, is a potent psychotomimetic in man (Shulgin & Nichols 1978).

The duration of action of four drugs was determined by monitoring the rates of responding for 300 min after drug or control injections. Both DMT and its sulphur analogue (II) markedly decreased responding during the first 30 min of the session (Fig. 2), the response returning to control levels by 120 to 150 min and remaining there to the end of the session. Psilocin and 5-MeO-DMT also decreased responding during the first 60 to 90 min, but at 180 to 240 min both compounds increased responding above control levels (Fig. 2), possibly because of active metabolites.

The finding that the sulphur isosteres of DMT, psilocin, and 5-MeO-DMT were less potent than the parent compounds was unexpected, since benzo[*b*]-thiophenes are more lipid soluble than their indole analogues (Chiu et al 1973) and would be expected to cross the blood-brain barrier readily. DMT and its sulphur isostere display similar potencies in contracting the rat fundus (Winter et al 1967) and in producing toxicity in mice (Bosin et al 1976a), but the sulphur

Table 1. Comparison of potencies for reducing responding.

Compound	ED50[a] μmol kg^{-1} (95% C.L.)	mg kg^{-1}
I (DMT)	15 (9–24)	2·9
II (S-DMT)	50 (30–80)	12
III	52 (31–88)	12
IV	83 (49–141)	20
V	17 (17–32)	4
VI	88 (52–150)	21
VII	>340	>80
VIII (Psilocin)	4 (2–7)	0·8
IX (S-Psilocin)	59 (37–94)	13
X	48 (28–82)	13
XI	58 (32–104)	15
XII (5-methoxy DMT)	10 (7–16)	2·1
XIII (S-5-methoxy DMT)	148 (87–252)	40

[a] Dose required to reduce responding to 50% of control value. Values in parentheses represent the 95% confidence limits.

analogue of tryptamine is less potent than the parent compound in producing a pressor response in the rat (Bosin et al 1976b), and that of 5-MeO-DMT (XIII) is less toxic than the parent compound (Bosin et al 1976a). Thus, the relative potencies of the indoles and benzo[*b*]-thiophenes may depend upon both the compound studied and the parameter evaluated. The low potency of the 1-methylindole analogue (VI) of DMT was surprising, since it is lipid soluble (Chiu et al 1973) and has been shown in mice to be more toxic than DMT (Bosin et al 1976a). Many chemical properties of naphthalene are similar to benzo[*b*]thiophene (Campaigne et al 1970), so the effects of VII might be expected to resemble those of II, but it was essentially inactive in the behavioural test. Therefore, different mechanisms may be responsible for the behavioural and toxic effects of these compounds. Taken together, the results demonstrate the importance of the indole nitrogen in the behavioural effectiveness of DMT and its derivatives. In agreement, we have noted that removal of the pyrrole ring from LSD resulted in a compound with a much lower behavioural potency than that of the parent (Harris, Holmfeld & Craig, unpublished). Thus, the pyrrole portion of the indole ring may be an important determinant of the potency of a number of hallucinogens. This would explain the low potency of hallucinogens that lack the pyrrole moiety (e.g., mescaline) (Harris et al 1978).

The potency of indole compounds also differed, indicating a role for the ring substituents in determining the potencies of these compounds. The potency of DMT in this study was similar to that reported by Harris et al (1978), and ring hydroxylation (Psilocin) or methoxylation (5-MeO-DMT) produces compounds more potent than DMT: 5-MeO-DMT is more potent than DMT in affecting avoidance responding (Gessner & Page 1962), and psilocin and 5-MeO-DMT are more potent than DMT in displacing LSD from brain

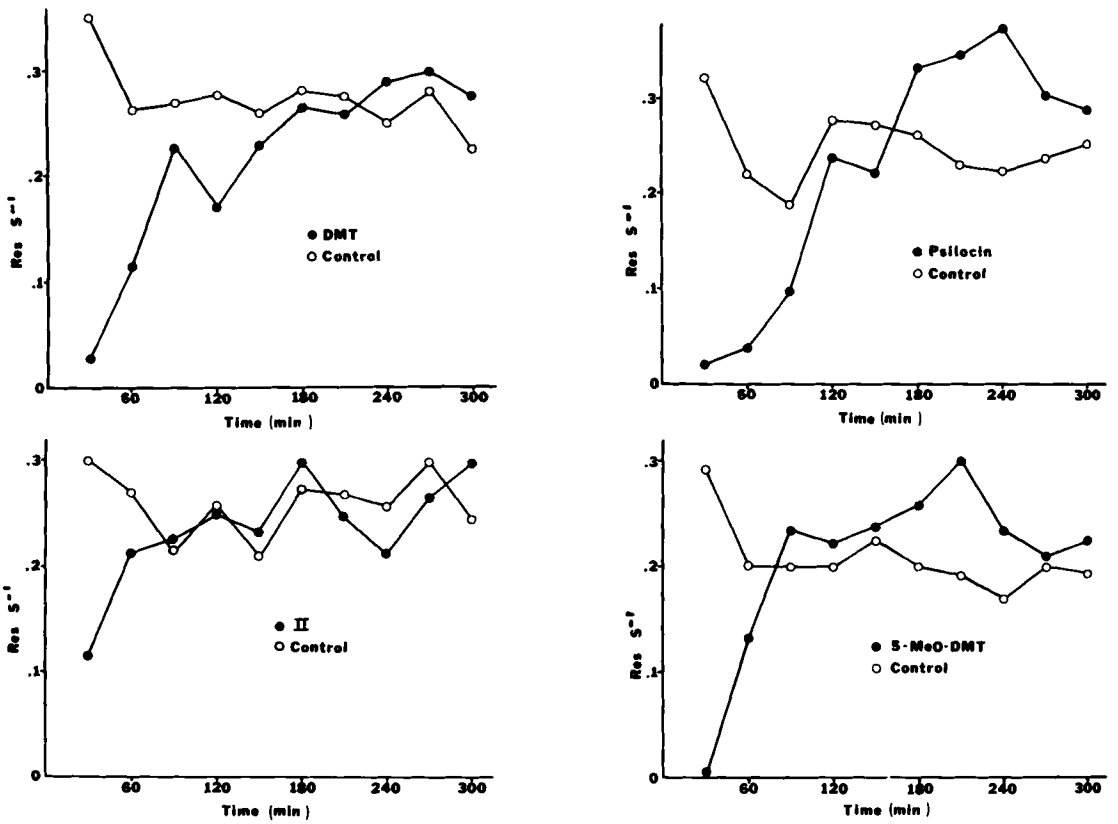

FIG. 2. Time course of the effects of DMT (10 mg kg^{-1}) and psilocin (3 mg kg^{-1}) (upper panels) and compound II (30 mg kg^{-1}) and 5-MeO-DMT (10 mg kg^{-1}) (lower panels). Solid symbols represent response rates following drug injection; open symbols represent saline injections in the same rats. Abscissa: time after injection in min. Ordinate: average rate of responding as responses s^{-1}. For all drugs, the values at 30 min were significantly different from control ($P < 0.01$, Wilcoxon signed rank test). Pooled values from 120 to 300 min were not different from control for DMT and II; for psilocin and 5-MeO-DMT, they are different ($P < 0.05$).

membranes (Bennett & Snyder 1975). The sulphur isosteres were affected differently. Ring hydroxylation or methoxylation of II either did not alter the potency (IX and X) or decreased the potency (XIII).

The results suggest that it may be possible to utilize the sulphur isosteres to reduce the psychotomimetic effects of therapeutically useful tryptamine derivatives.

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REFERENCES

Bennett, J. P., Jr., Snyder, S. H. (1975) Brain Res. 94: 523–544

Bosin, T. R., Campaigne, E., Dinner, A., Rogers, R. B., Maickel, R. P. (1976a) J. Tox. Environ. Health 1: 515–520

Bosin, T. R., Hixson, E. J., Maickel, R. P. (1976b) Br. J. Pharmacol. 56: 25–27

Campaigne, E., Dinner, R. (1970) J. Med. Chem. 13: 1205–1208

Campaigne, E., Rogers, R. B. (1973) J. Heterocyclic Chem. 10: 297–305

Campaigne, E., Neiss, E. S., Pfeiffer, C. C., Beck, R. A. (1968) J. Med. Chem. 11: 1049–1054

Campaigne, E., Knapp, D. R., Neiss, E. S., Bosin, T. R. (1970) in: Harper, N. J., Simmonds, A. B. (eds) Advances in Drug Research Academic Press, New York, pp 1–54

Chiu, P., Harrison, S. D., Jr., Maickel, R. P., Bosin, T. R. (1973) Pharmacologist 15: 184

Gessner, P. K., Page, I. H. (1962) Am. J. Physiol. 203: 167–172

Goldstein, A. (1964) Biostatistics: An Introductory Text. MacMillan, New York, p 61

Harris, R. A. (1980) J. Pharmacol. Exp. Ther. 213: 497–503

Harris, R. A., Snell, D., Loh, H. H. (1977) Pharmacol. Biochem. Behav. 7: 307–310

Harris, R. A., Snell, D., Loh, H. H. (1978) J. Pharmacol. Exp. Ther. 204: 103–117

Shulgin, A. T., Nichols, D. E. (1978) in: Stillman, R. C., Willette, R. E. (eds) The Psychopharmacology of Hallucinogens. Pergamon Press, New York, pp 74–83

Winter, J. C., Gessner, P. K., Godse, D. D. (1967) J. Med. Chem. 10: 856–859