Both the unchanged drug and its demethylated metabolite were detected in the 24 h urine of rats by thin layer, paper and gas–liquid chromatography after the oral administration of either labelled or unlabelled methsuximide (100 mg/kg). These excretory products have also been detected in the urine of human volunteers receiving methsuximide (300 mg, orally).

Rats receiving unlabelled methsuximide (100 mg/kg, orally) exhibited measurable anticonvulsant (anti-leptazol) activity for up to 6 hours. At this time little methsuximide is present in the brain as judged from the pattern of radioactive distribution so that anticonvulsant activity cannot be due to the unchanged drug. As 2-methyl-2-phenyl succinimide possesses anticonvulsant activity it is possible that this demethylated metabolite contributes to the overall effectiveness of methsuximide. A similar phenomenon occurs with certain other N-alkylated anti-epileptic drugs (Butler & Waddell, 1958).

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REFERENCES

BUTLER, T. & WADDELL, W. (1958). N-methylated derivatives of barbituric acid, hydantoin and oxazolidinedione used in the treatment of epilepsy. *Neurology*, **8**, 106–112.

CHEN, G., WESTON, J. & BRATTON JR. A. (1963). Anticonvulsant activity and toxicity of phensuximide, methsuximide and ethosuximide. *Epilepsia*, **4**, 66–76.

## Anti-thrombotic activity of a benzo[c][1,6]naphthyridine

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A new group of synthetic compounds inhibits platelet aggregation *in vitro*. The activity of one of these substances, cis-1,2,3,4,4a,10b-hexahydro-8,9-dimethoxy-2-methyl-6-phenylbenzo[c][1,6]naphthyridine, is described. Citrated human and rabbit platelet rich plasma (PRP) was prepared by the method of Born & Cross (1963). The PRP was diluted with saline to give a platelet count of $3 \times 10^8$/ml. Aggregation of platelets was measured by the tubidimetric method of Born & Cross (1963). The compound was added to 1 ml of PRP, 1 min before the addition of a concentration of adenosine diphosphate (ADP) producing a submaximal aggregation of platelets. Concentrations of 10–50 $\mu$M produced a dose dependent inhibition of aggregation. Similar concentrations also inhibited aggregation of human platelets induced by adrenaline and collagen. Adrenaline abolishes the effects of several substances which inhibit ADP-induced aggregation (Ardlie, Glew & Schwartz, 1966). The inhibition of ADP-induced aggregation of rabbit platelets by the compound was not reversed by adrenaline, but was significantly potentiated ($P<0{\cdot}005$).

Antithrombotic activity has also been found in *in vivo* models. Administration of 10 mg/kg intravenously of the compound to rabbits anaesthetized with pentobarbitone reduced the adhesion of platelets to glass beads (Philp & Lemieux, 1968). In this test, samples of blood (2·5 ml) are citrated and pumped through a column of glass beads. The difference in the platelet count before and after the column enables adhesiveness to be measured. Using the rat carotid artery thrombosis test (Chan, 1967), in which a small piece of polythene tubing is inserted into the carotid artery, the compound reduced thrombus formation proximal and distal to the polythene tubing. Thrombi

from treated rats were compared histologically with those from control animals. The fibrin network was much looser and fewer platelets were observed in the thrombi from treated animals than in thrombi from control animals.

REFERENCES

ARDLIE, N. G., GLEW, G. & SCHWARTZ, C. J. (1966). Influence of catecholamines on nucleotide-induced platelet aggregation. *Nature, Lond.*, **212**, 415–417.

BORN, G. V. R. & CROSS, M. J. (1963). The aggregation of blood platelets. *J. Physiol., Lond.*, **168**, 178–195.

CHAN, K. E. (1967). Experimental production of acute arterial thrombosis in the carotid artery of the rat. *Thromb. Diath. haemorrh.*, **18**, 565–569.

PHILP, R. B. & LEMIEUX, V. (1968). Comparison of some effects of dipyridamole and adenosine on thrombus formation, platelet adhesiveness and blood pressure in rabbits and rats. *Nature, Lond.*, **218**, 1072–1074.

## Analgesic and dependence studies with oripavine partial agonists

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The structures of three N-cyclopropylmethyl-oripavines closely related to etorphine (Bentley & Hardy, 1967; Blane, Boura, Fitzgerald & Lister, 1967) are shown below.

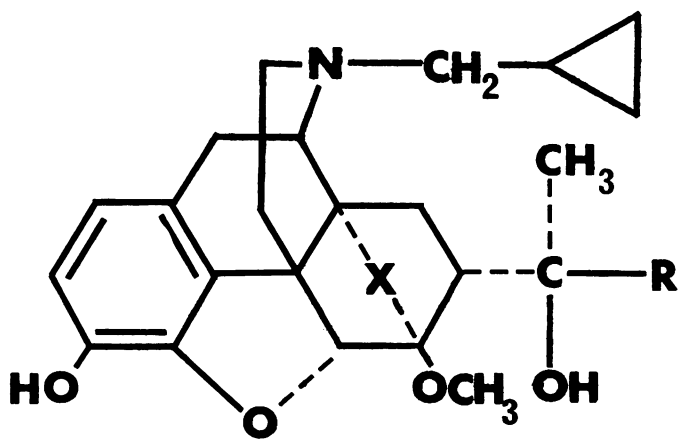


FIG. 1. (i) R & S 289-M: X=—CH=CH—, R=*n*Pr; (ii) R & S 6007-M: X=—$CH_2.CH_2$—, R=*n*Pr; (iii) R & S 6029-M: X=—$CH_2.CH_2$—, R=*t*Bu.

289-M, 6007-M and 6029-M are potent analgesics intraperitoneally in the mouse phenylquinone test (320, 640 and 90 times as active as morphine, respectively) and rat tail pressure test (350, 220 and 70).

As morphine antagonists in the mouse tail flick test, using hot water as the nociceptive stimulus (Janssen, Niemegeers & Dony, 1963), 6029-M has a potency 5 times greater, and 6007-M 5 times less, than nalorphine while 289-M and nalorphine are equipotent.

In the mouse tail flick test the analgesic effects of these compounds have received detailed study in comparison with etorphine, morphine and pentazocine. Narcotic antagonist analgesics are inactive in the conventional tail flick (radiant heat) procedure (Dewey, Harris, Howes & Nuite, 1970). This has been confirmed for pentazocine in the