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

A. COWAN*, J. W. LEWIS and I. R. MACFARLANE (introduced by B. A. WHITTLE)
Pharmaceutical Research Laboratories, Reckitt & Colman Pharmaceutical Division, Hull

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

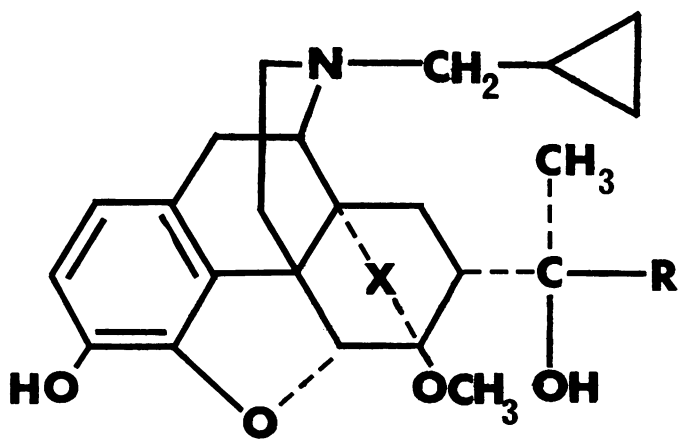

FIG. 1. (i) R & S 289-M: X=—CH=CH—, R=*n*Pr; (ii) R & S 6007-M: X=—$CH_2.CH_2$—, R=*n*Pr; (iii) R & S 6029-M: X=—$CH_2.CH_2$—, R=*t*Bu.

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

hot water test at the usual water temperature of 55°C. At 45°C however, pentazocine is active and produces a bell-shaped log dose response curve with analgesia decreasing at higher, non-toxic doses. The new oripavines show curves of similar shape at 45, 55 and 65°C, respectively, and analgesia can be demonstrated even at the highest temperature. They are considerably more effective than pentazocine in this test but in contrast to etorphine and morphine, their efficacies diminish with increase in stimulus strength. Comparable results have been obtained with these oripavines in the similar rat tail flick test.

Primary dependence studies in mice (method of Saelens, Granat & Sawyer, 1971) suggest that 289-M, 6007-M and 6029-M have physical dependence capacities similar to pentazocine and less than codeine. From 30 day primary dependence studies in monkeys (method of Deneau & Seevers, 1964), the antagonist-precipitated abstinence syndrome (A.S.) can be ranked as follows: pentazocine=6029-M (low A.S.) <6007-M (A.S. absent on day 14 and non morphine-like on day 28) <289-M (moderate A.S.).

REFERENCES

BENTLEY, K. W. & HARDY, D. G. (1967). Novel analgesics and molecular rearrangements in the morphine-thebaine group. III. Alcohols of the 6,14-*endo*-ethenotetrahydrooripavine series and derived analogues of N-allylnormorphine and norcodeine. *J. Am. Chem. Soc.*, **89**, 3281–3292.

BLANE, G. F., BOURA, A. L. A., FITZGERALD, A. E. & LISTER, R. E. (1967). Actions of etorphine hydrochloride (M99): a potent morphine-like agent. *Br. J. Pharmac. Chemother.*, **30**, 11–22.

DENEAU, G. A. & SEEVERS, M. H. (1964). Drug dependence. In: *Evaluation of Drug Activities: Pharmacometrics*, ed. Laurence, D. R. & Bacharach, A. L., vol. **1**, pp. 167–179. London: Academic Press.

DEWEY, W. L., HARRIS, L. S., HOWES, J. F. & NUITE, J. A. (1970). The effect of various neurohumoral modulators on the activity of morphine and the narcotic antagonists in the tail-flick and phenylquinone tests. *J. Pharmac. exp. Ther.*, **175**, 435–442.

JANSSEN, P. A. J., NIEMEGEERS, C. J. E. & DONY, G. H. (1963). The inhibitory effect of Fentanyl and other morphine-like analgesics on the warm water induced tail withdrawal reflex in rats. *Arzneimittel-Forsch.*, **13**, 502–507.

SAELENS, J. K., GRANAT, F. R. & SAWYER, W. K. (1971). The mouse jumping test—a simple screening method to estimate the physical dependence capacity of analgesics. *Archs int. Pharmacodyn. Thér.*, **190**, 213–218.

Some properties of WY 22811, a new analgesic compound

P. G. GOODE* and A. C. WHITE (introduced by D. GREEN)
Wyeth Institute of Medical Research, Taplow, Bucks

Since the discovery that some opiate-antagonist drugs have analgesic properties (Lasagna & Beecher, 1954; Harris & Pierson, 1964) and the subsequent finding that such analgesics have low addiction liability in man (Isbell, 1956; Fraser & Rosenberg, 1964) there has been considerable interest in finding improved compounds of this type.

Wy 22811 (*m*-(3-ethyl-1 methylhexahydro-1*H*-azepin-3-yl) phenol hydrochloride) is a potent analgesic compound which injected by the subcutaneous route is approximately equipotent with pentazocine in the rat tail radiant heat test (Bonnycastle & Leonard, 1950) and the mouse acetylcholine writhing test (Collier, Hammond, Horwood-Barrett & Schneider, 1964). Wy 22811 was well absorbed by the oral route since in the same tests, potencies relative to pentazocine were 3·2 in rats and 15 in mice. Optical resolution of Wy 22811 yielded two enantiomers which showed similar subcutaneous and oral analgesic potencies to the racemate.

Wy 22811 and both enantiomers resemble pentazocine in showing opiate-antagonist activity. Thus, on intravenous infusion, these compounds reversed the symptoms of severe morphinism in rats after a high subcutaneous dose of morphine and also, after