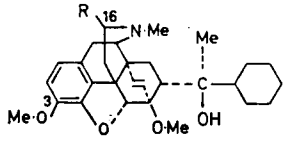
Structural requirements for antitussive activity in some novel 16-substituted derivatives of 6,14-*endo*ethenotetrahydrothebaine

SIR,—Powerful morphine-like analgesics and narcotic antagonists have been found in derivatives of 6,14-*endo*ethenotetrahydrothebaine (Bentley, Boura & others, 1965; Bentley and Hardy, 1967; Blane, Boura & others, 1967). Many of these compounds resemble other narcotics by causing depression of medullary centres mediating the cough reflex, and a search was therefore made within this series for an antitussive agent in which some dissociation of other morphine-like properties was apparent. The work led to the finding that substitution in the 16-position with an alkyl group resulted in the production of compounds possessing powerful antitussive properties, but having less prominent analgesic and other morphine-like actions than the unsubstituted compound (I; R=H) which is a highly potent analgesic.



I

Compounds having structure I (R = alkyl or aryl) were prepared from the parent carbinol via the 15-dehydro derivatives and reaction with Grignard reagents.

The antitussive activities of these compounds, as assessed by the method of Winter & Flataker (1954) after oral administration to guinea-pigs, were compared with those of methadone, morphine and codeine. The evidence (Table 1) indicates that the 16-methyl compound (R & S 6420-M) is the most active, being slightly more potent than methadone and 12 times more potent than codeine. Gradually increasing the length of the alkyl chain on R led progressively to decreased potency. The 16-phenyl derivative was inactive at the highest dose level used.

The 16-substituted compounds showed dissociation of antitussive and analgesic properties. Thus, whereas after oral administration the methyl and ethyl compounds respectively were approximately 12 and 4 times more potent than codeine as antitussive agents, they appeared 2–5 times less active as analgesics as indicated by the rat tail pressure method of Green & Young (1951). Demethylation of the phenolic ether group gave the corresponding oripavine which showed relatively more prominent analgesic properties (Table 1).

As R & S 6420-M was the most potent drug suppressing cough in the guinea-pig it was decided to compare its actions with those of several other antitussive agents on the cough reflex of cats, under pentobarbitone sodium anaesthesia, using the technique of Domenjoz (1952). The mean dose of each drug, when given intravenously, which was necessary to inhibit by 50% expiratory gasps elicited either by stimulation of the superior laryngeal nerve or by irritation of the trachea, is shown in Table 2. In this test situation R & S 6420-M, although less active than methadone, was about 8 times more potent than codeine. Comparison of the times during which cough was suppressed after injection of single equi-antitussive doses (2 × ED50) indicated that the duration of action of R & S 6420-M was intermediate between that of methadone and that of codeine (Table 2).

TABLE 1. RELATION BETWEEN THE DOSE LEVELS OF 16-SUBSTITUTED DERIVATIVES OF 6,14-*endo*-ETHENOTETRAHYDROTHEBAINE, CODEINE, MORPHINE AND METHADONE REQUIRED TO CAUSE AN ANTITUSSIVE ACTION IN THE GUINEA-PIG, AND AN ANALGESIC EFFECT IN THE RAT. ED50's are expressed in terms of the base and 95% confidence limits are shown in parentheses

Compound	3 subs.	16 subs.	N subs.	Antitussive ED50 (mg/kg P.O.)	Potency ratio (codeine = 1·0)	Analgesic ED50 (mg/kg)		
						I.p.	Oral	Oral potency ratio (codeine = 1·0)
R & S 6420-M	MeO	Me	Me	1·97 (0·71–5·51)	11·6	11·2 (7·2–17·4)	54 (33·8–86·4)	0·4
R & S 6439-M	MeO	Et	Me	5·92 (1·94–18·1)	3·9	>100	>100	<0·2
R & S 6446-M	MeO	nPr	Me	>30	<0·8	27·0 (15·0–48·6)	44·0 (32·0–54·4)	0·5
R & S 6441-M	MeO	nBu	Me	52·8 (17·9–156·0)	0·4	>100	>100	<0·2
R & S 7721-M	MeO	Ph	Me	>100	<0·2	>100	>100	<0·2
R & S 8002-M	MeO	Me	H	56·0 (10·3–303·0)	0·4	11·2 (7·4–16·8)	>100	<0·2
R & S 7719-M	OH	Me	Me	2·97 (1·14–7·71)	7·7	0·11 (0·05–0·24)	2·7 (1·35–5·4)	8·2
Methadone ..	H	—	Me	3·04 (1·34–6·96)	7·5	0·57 (0·43–0·75)	1·9 (0·89–4·1)	11·7
Morphine ..	OH	H	Me	5·39 (2·74–10·6)	4·2	1·3 (0·92–1·79)	21·1 (10·0–44·4)	1·0
Codeine ..	MeO	H	Me	22·9 (11·7–44·8)	1·0	13·3 (10·3–17·1)	22·2 (11·6–43·0)	1·0

TABLE 2. RELATIVE POTENCIES OF R & S 6420-M, METHADONE, CODEINE, PHOLCODINE AND DEXTROMETHORPHAN AS COUGH AND RESPIRATORY DEPRESSANTS AFTER INTRAVENOUS ADMINISTRATION TO ANAESTHETIZED CATS.

(Doses are expressed in terms of the base)

Drug	No. of cats	Mean dose required to reduce amplitude of cough by 50% (mg/kg)	Mean dose required to block respiratory movements (mg/kg)	Ratio	Duration of antitussive action	
					No. of cats	Time (min)
R & S 6420-M ..	5	0·43	7·9	18·4	3	116
Methadone	4	0·14	1·7	12·1	2	163
Codeine	6	3·4	21·2	6·2	3	20
Pholcodine	4	3·6	22·8	6·3	—	—
Dextromethorphan ..	3	2·3	3·0	1·3	—	—

The effects of R & S 6420-M on respiration of the anaesthetized cat resembled those of methadone rather than those of the other antitussive agents examined. After being given intravenously, at dose levels close to those depressing cough, both R & S 6420-M and methadone caused some decrease in the depth and frequency of respiratory movements whereas codeine, pholcodine and dextromethorphan usually reduced the depth but increased the rate of breathing. Nevertheless, after high doses had been administered, respiratory depression was the main toxic action of each drug and a measure of the relative prominence of this effect was obtained by comparing the mean dose required to cause cessation of respiratory movements to the dose required for production of an antitussive effect (Table 2). The ratio was found to be high for R & S 6420-M and methadone, significantly lower for codeine and pholcodine and very low for dextromethorphan.

It is of immediate interest that modification of the piperidine ring in the region of the basic nitrogen atom leads to the production of drugs in which antitussive actions are dissociated from some other morphine-like properties.

Departments of Pharmacology and
Organic Chemistry,
Reckitt and Sons,
Hull, England.

A. L. A. BOURA
D. I. HADDLESEY
E. J. R. HARRY
J. W. LEWIS
P. A. MAYOR

September 27, 1968

References

Bentley, K. W. & Hardy, D. G. (1967). *J. Am. chem. Soc.*, **89**, 3281–3292.
Bentley, K. W., Boura, A. L. A., Fitzgerald, A. E., Hardy, D. G., McCoubrey, A., Aikman, M. L. & Lister, R. E. (1965). *Nature, Lond.*, **206**, 102–103.
Blane, G. F., Boura, A. L. A., Fitzgerald, A. E. & Lister, R. E. (1967). *Br. J. Pharmac. Chemother.*, **30**, 11–22.
Domenjoz, R. (1952). *Arch. exp. Path. Pharmak.*, **215**, 19–24.
Green, A. F. & Young, P. A. (1951). *Br. J. Pharmac. Chemother.*, **6**, 572–585.
Winter, C. A. & Flataker, L. (1954). *J. Pharmac. exp. Ther.*, **112**, 99–108.

Uptake of [^{3}H]noradrenaline in the rat heart during increased sympathetic nervous activity associated with cold

SIR,—It is known that tissue with adrenergic innervation including the heart can take up noradrenaline from the blood or from the surrounding fluid. After administration, [^{3}H]noradrenaline crosses the neuronal membrane of the sympathetic nerve endings into the cytoplasm. It is then taken up and retained within dense core vesicles where it gradually equilibrates with endogenous noradrenaline stores. [^{3}H]Noradrenaline is released in response to sympathetic nerve stimulation, Hertting & Axelrod (1962), and is inactivated enzymatically or by re-uptake and binding in the sympathetic neuron. The physiological importance of noradrenaline re-uptake may consist not only in termination of its influence on the receptor sites of the effector organ, but also in the conservation of the sympathetic transmitter. Gillis, Schneider & others (1965) have shown that increased sympathetic nervous activity results in an increased retention of [^{3}H]noradrenaline. They found, after labelling the endogenous stores of catecholamines 3 hr before the experiment, that continuous stimulation of the sympathetic nerves of the isolated atria for 50 min (at a rate of 10 shocks/sec) caused an increase in the specific activity of noradrenaline recovered from the atria. Similarly Chang & Chiueh (1968) observed that the intermittent stimulation of the cervical sympathetic trunk caused an increase of radioactivity in submaxillary glands. Less information is available about this mechanism *in vivo*. The present study was undertaken to determine whether or not there is an increased retention of [^{3}H]noradrenaline in the rat heart during increased sympathetic nervous activity associated with cold. To gain insight into the mechanism involved, the effect of various drugs on the retention of [^{3}H]noradrenaline during increased sympathetic nervous activity was examined.

Male albino rats of the Holtzman strain, 200–225 g, were used. To elicit sympathetic stimulation, rats placed in individual cages, were exposed to cold for 6 hr at 4°. Exposure to cold is known to result in increased sympathetic nervous activity and release of catecholamines (Euler, 1956).

(±)-Noradrenaline-[7-^{3}H]hydrochloride (specific activity 0·040–0·05 mc/mg) obtained from New England Nuclear Corporation was diluted to 6·5 μc/ml with isotonic saline before each experiment. To stimulate sympathetic nervous activity, rats were exposed to cold for 5 hr. Thereafter they were injected with 6·5 μc/100 g with [^{3}H]noradrenaline. The animals remained a further 1 hr in