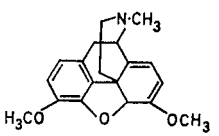
Structure-activity requirements in some novel thebaine-derived analgesics

SIR,—Thebaine (I) an alkaloid present in opium (0·2–0·8%) has no therapeutic activity and little commercial value. Unlike the chemically related central nervous system depressants morphine and codeine, thebaine is devoid of analgesic activity and acts as a central nervous system stimulant. Bentley & Hardy (1963) have recently described the synthesis of a series of dienophil derivatives of thebaine showing high analgesic potencies.

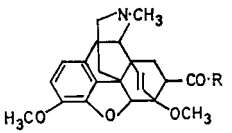
A number of the ketonic adducts, II (Table 1), were found to have analgesic actions similar to that of morphine.

Primary and secondary alcohols, III, produced by the reaction of appropriate Grignard reagents on these and other related ketones were found to possess greater analgesic activity (Table 2).

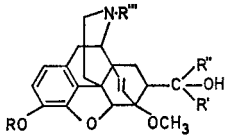
O-Demethylation of the thebaine derivatives to the corresponding oripavines increased the activity in a manner similar to that seen on the conversion of codeine to morphine.



I



II



III

When tested in rats by a modification of the tail-pressure method of Green & Young (1951), as described by Lister (1960) or in mice by the hot-plate method (Eddy & Leimbach, 1953) or by the phenylquinone writhing test in mice (Hendershot & Forsaith, 1959) these compounds showed analgesic potencies ranging from 0·1 to approximately 8,000 times that of morphine. The relative molar analgesic potencies and intravenous toxicity of typical members of these two series are shown in Tables 1 and 2. Although the analgesic activities of members of these series are so high when compared with morphine, their toxicities are not increased to the same degree.

TABLE 1. ANALGESIC ACTIVITIES AND TOXICITIES OF SOME KETONIC DERIVATIVES OF TETRAHYDRO-6,14-*ENDO*ETHENOTHEBAINE

Code No.	Structure II, R =	Molar Potency Ratios: Morphine = 1	
		Analgesia in rats s.c.	Toxicity in mice i.v.
M.61	H	0·6	2·0
M.39	Me	1·2	3·8
M.70	Bu^i	9·0	5·0
M.85	C_6H_5	0·7	2·7
M.88	$[CH_2]_7Me$	0·03	2·3

Further modifications of the molecule have been studied; in some instances acetylation of the phenolic group increased analgesic activity and in others reduced it. *N*-Demethylation to the secondary base reduced activity in all compounds but the analgesic potency retained was still from 0·5 to 6 times that of morphine.

All the compounds described have a pharmacological profile similar to that of morphine. When injected they produce analgesia, depression of the respiratory and the cough centres, inhibition of gastrointestinal motility, lowering of body temperature and other signs characteristic of morphine-like drugs. These pharmacological effects have been observed in the mouse, rat, pig, rabbit, cat, dog, guinea-pig, monkey and man. When the dose of these highly active compounds is increased beyond that necessary to produce analgesia, a tranquillising effect is seen and normally aggressive animals become tractable. Further increase in dosage produces a state of 'total analgesia' or areflexia without apparent loss of consciousness. All these depressant effects are antagonised by nalorphine or levallorphan. Despite the vast increase in potency of many of the compounds in these series, there appears to be only a minor degree of dissociation between their therapeutically desirable and undesirable properties when compared with equianalgesic doses of morphine. The duration of action is found to be less than that of morphine. Unlike morphine and pethidine these potent analgesics do not liberate histamine even in doses many times higher than that required to produce analgesia.

TABLE 2. ANALGESIC ACTIVITIES AND TOXICITIES OF SOME ALCOHOLIC DERIVATIVES OF TETRAHYDRO-6,14-*ENDO*ETHENOTHEBAINE

Code No.	Structure III				Molar Potency Ratios Morphine = 1	
	R =	R′=	R″=	R‴=	Analgesia in rats s.c.	Toxicity in mice i.v.
M.50	Me	Me	Me	Me	2·5	3·1
M.53	Me	Me	Pr^n	Me	89	4·2
M.53A	Me	Pr^n	Me	Me	0·7	3·2
M.99	H	Me	Pr^n	Me	2,060	10·8
M.183	COMe	Me	Pr^n	Me	5,330	16·7
M.74	H	Me	Me	Me	49	2·5
M.150	H	H	Me	Me	35	1·5
M.217	H	H	H	Me	13	1·2
M.89	Me	Pr^n	Pr^n	Me	3·8	6·3
M.79	Me	Me	Pr^n	Me	1·2	2·6
M.140	H	Me	$CH_2CH_2\overset{Me}{\overset{\vert}{C}}H-Me$	Me	7,800	27·5
M.191	H	Me	Pr^n	H	40	6·1

The introduction of the bridged system and the creation of a further centre at position 7 capable of chemical modification has made possible the synthesis of a large number of variants of the basic molecule.

Examination of the structure-activity relationships in the two series discussed, reveals a need to revive even further the classical ideas of these relationships in the morphine series first proposed by Braenden, Eddy & Halbach (1955).

In the ketonic series, Table 1, maximum activity was found in compound II with the substituent R = isobutyl (M. 70).

Examination of the analgesic activities of the alcoholic derivatives shown in Table 2 shows that optimal activity tends to occur under the following conditions.

1. The oripavine derivatives, R = H, or their acetylated derivatives, R = COMe, are more active analgesics than the corresponding thebaine derivatives R = Me, e.g. M.99 and M.183 > M.53.
2. The nature of the alcohol grouping attached to C7 is important; tertiary alcohols show a higher potency than secondary alcohols, e.g. M.74, > M.150, > M.217.
3. One of the substituents R′ or R″ on the carbon atom attached to C7 should be small, preferably methyl, e.g. M.53 > M.89.
4. Peak analgesic activity is found when the second of these substituents is an alkyl group with an overall chain length of 3–6 carbon atoms, e.g. M.99 and M.140.
5. The unsymmetrical tertiary alcohols exhibit optical isomerism with the two diastereoisomers showing marked differences in analgesic potencies, e.g. M.53 and M.53A. Difficulty has been encountered in assigning the configurations of the isomers but in all instances the isomer with the higher melting-point is found to be more active.
6. The piperidino-nitrogen atom is tertiary. The corresponding secondary amines are found to be less active, M.191 > M.99.

The preliminary results indicate that the simplified concept of the nature of the morphine receptor site proposed by Beckett (1959) must be revised to account for these new facts. These compounds have a more rigid molecular structure than morphine which may fit the receptor surface more closely and this may be a factor in explaining the greatly increased activity found in this series. A second binding site for the group at position 7 must be postulated and this appears to highly selective, judging by the differences in analgesic activity found in diastereoisomers.

Despite the vast increase in analgesic potency found in members of these series, no marked differentiation between analgesic activity and the other centrally mediated properties has been demonstrated. This suggests that these drugs may be acting on areas in the central nervous system through which pass afferent impulses to the specific controlling centres; these areas are likely to be in the mid-brain and reticular system.

Further work is in progress to evaluate the structure activity relationships in these series and to determine their site and mode of action.

J. F. Macfarlan & Co. Ltd.,
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