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Pharmacological activity of some bis-benzylisoquinoline alkaloids

Marsh & Herring (1949, 1950) and Marsh, Sleeth & Tucker (1948) tested a number of bis-benzylisoquinoline alkaloids for neuromuscular blocking activity. None of the compounds was as potent as (+)-tubocurarine, and none of them showed properties which would indicate any clinical superiority to (+)-tubocurarine, with the exception of "*OO*-dimethyltubocurarine:" commercial samples of this substance have been shown by Bick & McLeod (1974) to consist in fact of *OO'*, *N*-trimethyltubocurarine. Marshall, Murray & others (1967) have made and tested a number of derivatives of curine and chondrocurine and the activity of some other bis-benzylisoquinoline alkaloids has been reported from time to time (Review by Craig, 1955).

Most of the active compounds appear to be of the head-to-tail, head-to-tail type. However, few of the head-to-head, tail-to-tail type molecules appear to have been tested and it was decided to test those which are available. The structures of the alkaloids are shown in Fig. 1. They have been screened for neuromuscular and

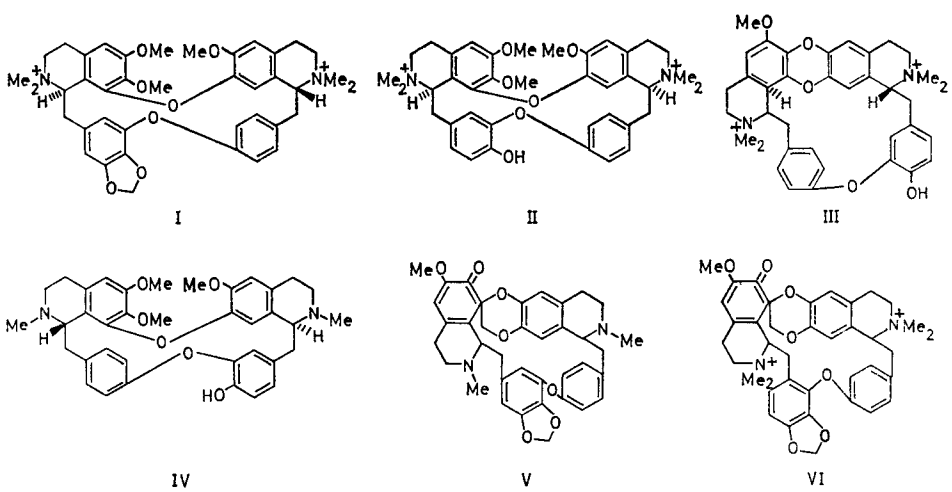

FIG. 1. I; *NN'*-dimethyltenuipine (Bick & others, 1963). II; *NN'*-dimethylberbamine (Bick & others, 1956). III; *NN'N'*-trimethylmicranthine (Bick & others, 1972). IV; repandine (Bick & Todd, 1948). V; repanduline (Bick & others, 1967; Harley-Mason & others, 1967). VI; *NN'*-dimethylrepanduline.

Table 1. *Molar potencies relative to* (+)-*tubocurarine* (= 1).

Compound	Blocking activity on cat tibialis	Blocking activity on cat superior cervical ganglion	Rotating drum
(+)-Tubocurarine	1	1	1
Repandine	0·008	<0·002	<0·02
Repanduline	<0·002	<0·002	<0·02
*NN'*Dimethylrepanduline	<0·002	<0·002	<0·05
NN'-Dimethyltenuipine	<0·002	<0·002	0·001
NN'-Dimethylberbamine	0·7	0·4	0·6
NN'N'-Trimethylmicranthine	<0·002	<0·002	<0·8

ganglion blocking activity. An indication of any central nervous system effect on co-ordination has also been obtained.

The methods used to determine neuromuscular and ganglion blocking activities are those of Bick & McLeod (1974). The rotating mesh cylinder method of Collier, Hall & Fieller (1949) was used for estimating neuromuscular blocking activities and also because it may have indicated any significant central nervous system effect on co-ordination if compared with the peripheral effects on muscle and ganglia. The drum of 6·25 inch diameter was rotated at 2·1 rev min^{-1}. Groups of twenty mice were used for each dose of drug and the activities of the compounds relative to (+)-tubocurarine were determined by a 2+ 1 assay procedure using graphs of log-dose against probit percentage paralysed. The results recorded in Table 1 represent in each case an average of at least three experiments. None of the compounds tested showed activity which could reasonably be compared with (+)-tubocurarine. With the exception of *NN'*-dimethylberbamine the activity of the compound could not be estimated precisely because it was not possible to make strong enough solutions of the relatively insoluble compounds. *NN'*-dimethylberbamine was soluble at 10^{-3}M and was slightly active on the preparations used. The other compounds, however, were not active at concentrations less than 10^{-3}M and stronger solutions could not be prepared.

The head-to-tail arrangement of the bis-benzylisoquinolines seems to confer greater activity than the head-to-head arrangement. A study of Dreiding models shows that the head-to-head, tail-to-tail types of alkaloid are rather less flexible than the head-to-tail types to which (+)-tubocurarine belongs, and morever the molecules are much less planar, which would presumably result in much less effective contact with the receptor. The number of oxy substitutents in the two different structural types is the same. If the oxy substituents are important for binding to the receptor, as suggested by Marshall & others (1967), then the more folded nature of the head-to-head, tail-to-tail types would be expected to reduce their effectiveness in providing centres for hydrogen bonding with the receptor. The molecules of repanduline and micranthine are particularly rigid and folded on account of their fused dioxan rings; on the other hand, the molecule of berbamine is able to adopt a rather more planar conformation than the others, which may account for its distinctly higher activity.

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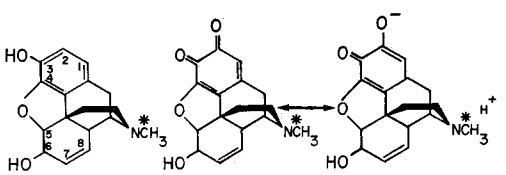
Some physicochemical and pharmacological properties of morphine-2,3-quinone, the morphine metabolite in the rat brain

Evidence for the formation *in vitro* and *in vivo* of a 2,3-catechol type of metabolite by aromatic hydroxylation of morphine in rat brain has been presented earlier (Misra, Mitchell & Woods, 1971; Misra, Vadlamani & others, 1973). The chromatographic properties of this metabolite were similar to the zwitterionic morphine-2,3-quinone. This communication describes some physicochemical, pharmacological properties and binding characteristics *in vitro* of [^{14}C]morphine-2,3-quinone with some biological macromolecules.

[^{14}C]Morphine-2,3-quinone was prepared from morphine-*N*-Me[^{14}C] as previously described (Misra & others, 1973). The partition coefficients of water-soluble [^{14}C]-morphine-2,3-quinone and [^{14}C]morphine in 1-octanol–phosphate buffer pH 7·4 at



[^{14}C]Morphine [^{14}C]Morphine-2,3-quinone

*Position of label