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Relation between Thrombosis on Metal Electrodes and the Position of Metal in the Electromotive Series

INTEREST in the electrochemical nature of thrombosis[1,2] has prompted us to study thrombus deposition on metal electrodes inserted through side branches into the carotid and femoral arteries of mongrel dogs. Magnesium, aluminium, cadmium, nickel, copper, gold and platinum, which cover a wide range in the electromotive series, were chosen for the present investigation.

The electrodes were carefully cleaned to ensure the absence of any oxides or other impurities on their surfaces, and their spontaneous potentials were measured in normal (0·9 per cent) saline solution. In the first series of experiments four electrodes of the same metal were inserted through side branches into the carotid and both the femoral arteries in healthy anaesthetized (1/2 ml./kg of 'Diabutal' intramuscular injection) mongrel dogs; care was taken to prevent injury to the intimal surface. The spontaneous potential set up by each of these electrodes, after their insertion, was measured with respect to a standard calomel electrode (contained in a beaker with saturated potassium chloride solution). An electrolyte bridge was made between the experimental animal and the beaker containing the calomel electrode by inserting a fine polyethylene tubing into a second branch of one of the femoral arteries. The back flow of blood into this tubing was allowed to clot. The electrodes were kept in position within the lumen of the arteries for a period of 30–40 min.

The dog was killed and the four vessels containing the electrodes were gently clamped both proximally and distally, so as to include the electrode, but without disturbing the position. Formalin was then slowly injected into the portions of the blood vessels between clamps so as to fix any deposits of thrombi on the electrodes. Finally, the vessels were gently slit open and the electrodes within these were examined for any thrombus deposition.

The results were striking. Electrodes of metals establishing a negative interfacial potential (NHE), magnesium, aluminium and cadmium, showed no thrombus deposition (on their electrodes), whereas metals with a positively charged surface—copper, nickel, gold and platinum—showed a measurable deposition of thrombus along the length of the electrode. The interfacial potentials set up by metals in contact with blood *in vivo*, their corresponding standard electrode potentials and the occurrence or otherwise of thrombus deposition on their surfaces, are summarized in Table 1. As expected, there is a direct correlation between the spontaneous potentials set up by these metals in blood *in vivo* and their respective standard electrode potentials.

Table 1. DEPENDENCE OF THROMBUS DEPOSITION AT METAL ELECTRODES ON POSITION OF METAL IN ELECTROMOTIVE SERIES

Metal	M/M^{n+} standard electrode potential (V, NHE)	Resting potential at metal–blood interface (V, NHE)	Occurrence (✓) or non-occurrence (×) of thrombus deposition
Mg	−2·375	−1·360	×
Al	−1·670	−0·750	×
Cd	−0·402	−0·050	×
Cu	+0·346	+0·025	✓
Ni	−0·230	+0·029	✓
Au	+1·420	+0·120	✓
Pt	+1·200	+0·125	✓

In an attempt to confirm these results further, experiments were carried out using electrodes of two different types of metals, one on the electropositive, and the other on the electronegative side. These were inserted into ipsilateral, carotid and femoral arteries in the same animal in the conditions of the previous experiments. The results confirmed the earlier set.

The present series of experiments conclusively proves that thrombus deposition on metals *in vivo* depends, at least partly, on the interfacial potential. The more positively charged interfaces are thrombogenic; those negatively charged are non-thrombogenic. These findings are of considerable fundamental importance in the search for suitable non-thrombogenic surfaces for incorporation into various artificial internal organs.

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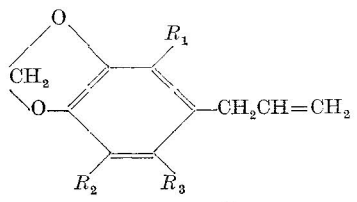
Psychotropic Phenylisopropylamines derived from Apiole and Dillapiole

IT is an interesting fact that most of the known psychotropic phenylisopropylamines (amphetamines) possess ring-substitution patterns identical to those of natural essential oils. (The single exception is the active 2-methoxy - 4,5 - methylenedioxyamphetamine (MMDA-2, II*d*[1]); neither the allyl nor the propenyl counterpart has been observed in plant extracts.) Thus 3,4-methylenedioxyamphetamine (MDA, II*a*) is related to safrole (I*a*)[2] (Table 1), 3,4,5-trimethoxyamphetamine (TMA) to elemicin[3], 3 - methoxy - 4,5 - methylenedioxyamphetamine (MMDA, II*c*) to myristicin (I*c*)[4] (Table 1), 2,4,5-trimethoxyamphetamine to asarone, and 2-methoxy-3,4-methylenedioxyamphetamine (MMDA-3a, II*b*) to croweacin (I*b*) (Table 1). C. F. Barfknecht, of Idaho University, tells us that there is preliminary evidence that these olefines may be aminated in the living organism, and this reaction can be readily performed *in vitro*. There are two additional essential oils known that contain the methylenedioxy ring. These are apiole (I*e*) and dillapiole (I*f*) (Table 1).

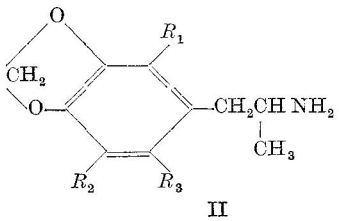
These two naturally occurring aromatic ethers are the two possible ring-methoxylated analogues of myristicin.

We have synthesized the two amphetamines which correspond in structure to these essential oils, that is, 2,5 - dimethoxy - 3,4 - methylenedioxyamphetamine (DMMDA, II*e*) and 2,3-dimethoxy-4,5-methylenedioxyamphetamine (DMMDA-2, II*f*).

Table 1. A COMPARISON OF THE STRUCTURES OF THE NATURAL ESSENTIAL OILS (I) AND THE AMPHETAMINES (II)



I



II

	R_1	R_2	R_3	I	II	Potency (mescaline units)
a	H	H	H	Safrole	MDA	3
b	OCH_3	H	H	Croweacin	MMDA-3a	18
c	H	OCH_3	H	Myristicin	MMDA	2
d	H	H	OCH_3	(Unknown)	MMDA-2	21
e	OCH_3	OCH_3	H	Apiole	DMMDA	12
f	H	OCH_3	OCH_3	Dillapiole	DMMDA-2	5

DMMDA was synthesized directly from apiole (obtained from oil of parsley) using the same sequence of steps (isomerization, β-nitration, and hydrogenation) that was successful in the conversion of myristicin to MMDA[4]. It was not possible to isolate useful quantities of dillapiole, so it was obtained synthetically[5] and converted through the above steps to DMMDA-2.

A threshold intoxication with DMMDA in human volunteers was consistently recognized at about 200 μg/kg (calculated as the free base and administered orally as the hydrochloride). With most subjects* concentrations within the range 250–300 μg/kg produced a psychotropic episode with the following chronology. The initial 1–1·5 h, preceding the first indications of mental change, were quite free of the signs of the autonomic distress that have frequently been observed with both mescaline and TMA, but only occasionally within the MMDA series. Mild incoordination marked the start of the intoxication period which lasted 2–4 h. During this interval there were only mild perceptual distortions and, in common with MDA, there were increased generalizations of the thought processes, increased emotional affect and empathy, as well as euphoria and a lack of anxiety. The colour exaggerations of mescaline and the eyes-closed images characteristic of MMDA were absent. The gradual disappearance of this syndrome was complete in 8–12 h and the subjects' recall of these events and interpretations was unimpaired, as has been consistently true with the related amphetamines. The syndrome of DMMDA-2 intoxication was qualitatively similar in nature; the threshold was first observed at 400 μg/kg and an effective dose range was established as lying between 600–1,000 μg/kg. DMMDA-2 has therefore an activity intermediate between DMMDA and MMDA, the latter being active in the vicinity of 2–2·5 mg/kg.

Two arguments must be considered in any explanation of the activity of compounds such as these. First, it has been suggested that β-phenethylamines may participate in central nervous system metabolism through ring closure with the formation of an indole intermediate. This cyclization has been argued as involving an electrophilic attack by the protonated amine on the aromatic ring. In this manner both epinephrine[6] and the demethylation products of mescaline[7] have been oxidatively cyclized *in vitro*, although no evidence has appeared to support such reactions *in vivo*. At first appearance this argument is supported by the observation that the addition of a methoxyl group to either of the ortho-positions of MMDA (to produce DMMDA or DMMDA-2) increases the potency of the product *in vivo*. Such substitutions would certainly enhance electrophilic ring closure. Specifically, the dose levels of DMMDA and DMMDA-2 reported here allow assignments of potencies of 12 and 5 mescaline units (MU)[1], respectively, whereas the trisubstituted counterpart MMDA has a rating of about 3 MU.

An alternate indole synthesis route must also be considered. It will be noted that if the *meta*-methoxyl group were removed from either of these tetrasubstituted amphetamines (so actually reducing its theoretical ease of cyclization) MMDA-3*a* (II*b*) would be obtained from DMMDA, and MMDA-2 (II*d*) from DMMDA-2, yet both of these simpler bases are of still higher potencies (MU of 18 and 21, respectively). Thus it may not be the presence, but rather the position, of the additional group that leads to an enhanced activity. This latter route would then suggest an interaction of the amino-groups with a quinonic intermediate in which the oxygen atom of the ortho-methoxyl group participates.

A second argument is that several phenolic amines are known to act as neurotransmitters. Methylated and methoxylated analogues might function directly (without chemical modification) either as inhibitors or as false transmitters in the specific neural networks served. On the basis of this hypothesis a psychotomimetic molecule should be resistant to chemical attack, rather than sensitive to it, as would be required for conversion to an indole.

Any attempts to understand the mechanisms of action of these materials must still consider the qualitative distinctions that have been noted, however. The two new psychotropic agents reported here, as is true with the two-oxygen methylenedioxy analogue MDA, exhibit changes in affect and empathy and in general are intoxicants, but they should not be classified as psychotomimetics. It seems that this property occurs, at least among the phenylisopropylamines only in those which are trisubstituted.

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* All subjects were familiar with the other materials mentioned in these comparisons, MDA, MMDA, MMDA-3a.

PATHOLOGY

Effect of Previous Injection of Homologous Embryonic Tissue on the Growth of Certain Transplantable Mouse Tumours

IN a previous communication Buttle, Eperon and Menzies[1] reported that injections of suspensions of human embryonic tissues into weanling rats prevented the growth of the transplantable human tumour *HS*.1 when the