

The Chemistry and Psychopharmacology of Nutmeg and of Several Related Phenylisopropylamines

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Our report today has been divided into two separate portions. The discussion of nutmeg and its composition, and of the possible involvement of its chemical components. The psychotropic intoxication has a natural division into two areas of presentation. The first is a brief description of the plant; a presentation of the methods and procedures for the isolation and the identification of the many components in the oil from the plant, and a careful definition of those components that are most probably involved in the intoxicative syndrome.

The extension of these components in to the corresponding amphetamines, their effectiveness in humans, and the likelihood of their being an acceptable explanation of the effects of the total nutmeg, will constitute the latter part of this report. In the previous paper there was presented some of the history of nutmeg, and a description of the style and extent of its usage in various cultures. In the reports that will follow, specific descriptions of the human syndrome of intoxication, and some of the pharmacological ramifications of its study, will be presented.

At this point we would like to present a factual description of the various chemical materials that have been found to make up the volatile (and presumed active) fraction of nutmeg. On the hypothesis that one or more components may be appropriately assigned the responsible role for the nutmeg intoxication, there is a need for an exact chemical definition of nutmeg. But even before this, we must define in botanical terms just what is meant by the name nutmeg.

Properly the nutmeg tree is any plant found in the Genus *Myristica*. Two species are known to be native to India. *M. malabarica* produces a seed some four centimeters long and elliptically shaped, and *M. canarica* produces a small spherical seed about two centimeters across. Both contain primarily fats and myristic acid, and being virtually without odor or volatile oil have achieved no position of importance. In the East Indies the seeds of *M. succedanea*, known as "Pala Maba" in the Indonesian areas, are also small and quite elongate in shape, but they have proven valuable as rich sources of the nutmeg essential oils. Another species, *M. argentea*, has actually been used

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in the spice trade under the name of "New Guinea Nutmegs" or "Long Nutmegs". However the quantity and quality of the volatiles from its seeds are quite low. The plant that has achieved the widest study and commercial exploitation, and which is the subject of this portion of this symposium, is *M. fragrans*. This species originated in the Mollucas and has been propagated throughout the adjoining Indonesian islands, giving rise to the so-called East Indian nutmeg of commerce.

A little over a hundred years ago, the tree was introduced into the Caribbean area and since the end of World War II has led to the establishment of a major industry. Grenada, of the windward islands, now supplies a major portion of the world's needs. The West Indian nutmeg is generally conceded as being of a somewhat lower quality than its East Indian forebears; the best grade of mace still comes from Asia.

The tree has also been translocated into Ceylon, and much of the early analytical work on the composition of the natural extracts was conducted on nutmegs from this source. It is no longer possible to obtain commercial samples with this designation however, and it must be assumed that any product from this area has been absorbed into the East Indian category.

The three areas of the plant *M. fragrans* that have received any analytical attention are the leaf, the arillode (which lies within the husk but outside of the shell of the seed, and which is known as mace), and the kernel of the seed itself, the nutmeg. The leaves have received only a cursory examination, which has indicated that although there is only a small amount of steam-distillable material present (about 1.5% of the dry weight) its composition is substantially the same as that of the plant parts associated with the seed (1). The studies that concern the volatile oils of mace are best presented later in direct comparison with the analysis of nutmeg itself. As it is only the nutmegs that are invested with the reputation of psychotropic efficacy, they have served as the primary focal point of our analysis.

The actual nutmeg, when removed from its hard brown shell or testa is a spherical kernel that weighs about five grams. The thorough work of Power and Salway (2) must serve as a definitive study of the composition of the entire nutmeg. There are two classical ways of extracting the potentially interesting materials from the whole fruit.

Figure 1 shows the approximate distribution to be expected with the employment of these methods. The process of expression, or the extraction with an organic solvent, provides about a third of the total original weight. This fraction is known as the fixed oils, and has also been called Nutmeg Butter or "Oleum Myristicae expressum". This fraction is substantially free of volatiles, and is composed primarily of triglycerides. Myristic acid is the principle compound here, although both oleic acid and linoleic acid are also found. This fraction has been used as a source of trimyristin (3). The small non-fat remainder is composed of unsaponifiable compounds, primarily oxygenated polyterpenes and phytosterols.

The subjection of the total crushed seed to distillation with live steam removes some 10 to 15% of the weight, known as the volatile oil fraction. The small overlap that is shown with the expression fraction is due to the

CHEMICAL GROUP DISTRIBUTION IN NUTMEG

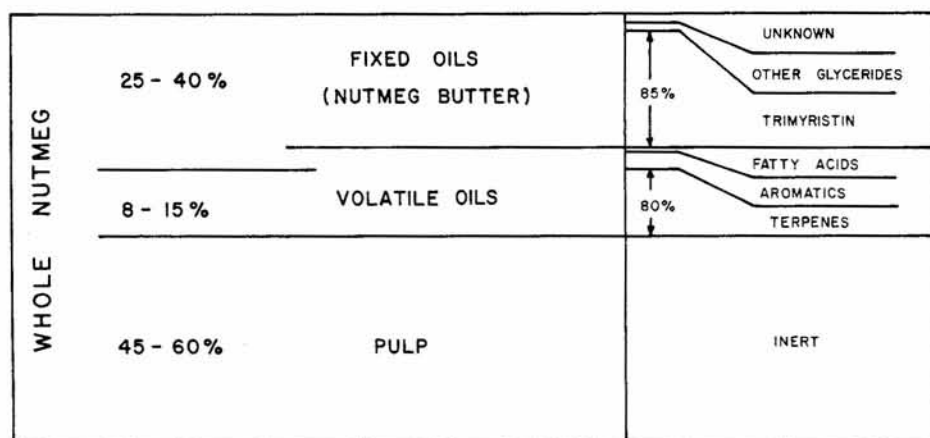


FIG. 1

fact that some of the volatile components are removed in the solvent extraction and are held tightly by the fixed components present. This volatile fraction is composed primarily of terpenes, which make up some 80% of its total weight. The remainder is the aromatic fraction, composed of ethers and phenolic bodies.

The residue that remains after the expression of the solubles and the distillation of the volatiles constitutes some 50% of the original mass of the nutmeg. It is presumably a cellulose-like pulp, and it remains totally unexplored as far as any chemical analysis is concerned.

It must be stated here, in anticipation of later discussions on the pharmacology of nutmeg, that no definitive evaluation of these fractions (fats and pulp) have been made. It has, however, been generally accepted that it is the volatile oil fraction to which one must look for the effective agents of nutmeg, and it is this "Oil of Nutmeg" that has been admitted to the U.S. Pharmacopeia as a medicinal. This oil comprises between an eighth and a twelfth of the entire fruit, and it serves as the object of the present study.

An exacting analysis of this volatile fraction has been performed. To this end a five pound sample of West Indian Oil of Nutmeg (from the George Lueders Company, New York) was subjected to fractional distillation employing a 70 tray Oldershaw column. Fractions were collected in a continuous sequence and each of these was in turn analysed and further fractionated employing a preparative gas liquid chromatographic procedure. Identity of each component was established by direct isolation, (employing a Varian A-700 Autoprep) and spectral comparison to reference samples (through infra-red and high resolution mass spectroscopy). Quantitative measurements were achieved employing a Varian Aerograph 1200 with a flame detector, and peak areas were established with an Aerograph 475 Integration System.

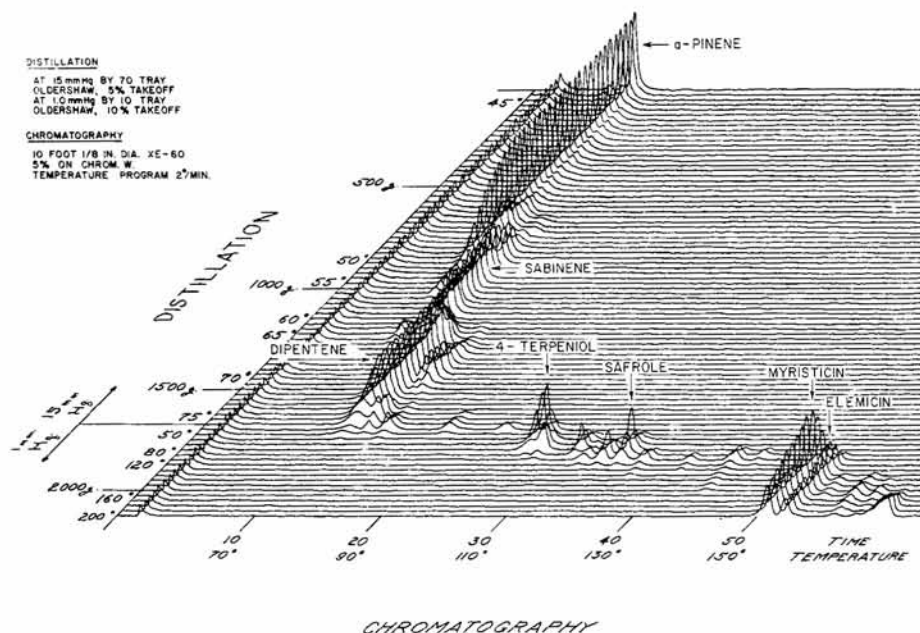


FIG. 2

Figure 2 shows what might well be called a fingerprint of the oil of nutmeg. On the z-axis is shown the results of the distillation. This was continued on the 70 tray column at 15 mm/Hg until the aromatic fraction was reached. Then the distillation was completed at 1 mm/Hg through a shorter column. Although the actual fractions collected were not exactly of 25 grams as is presented in the figure, the weights have been normalized to this amount, and each horizontal line thus represents an equal weight of distillate.

The x-axis represents the progress of gas liquid chromatographic separation. The time required for desorption of each of the peaks is shown, and as the system has been programmed for a rise of 2°/min., this also represents the temperature of desorption.

The y-axis is peak height and, as it is characteristic of temperature programmed GLC spectra to display a constant peak half-width, this height is proportional to peak area.

Several peaks (components) are obvious that would be superimposed by one of the techniques alone (GLC or distillation), but are readily separated by applying the other.

The long ridge down the left hand side of the presentation, parallel to the z-axis, represents the similar terpenes α -pinene, sabinene, and dipentene, and this is separated in a natural division from the second and smaller group, the aromatics.

The preponderance of α -pinene has been mentioned, but both sabinene and γ -terpinene (1, 4-menthadiene) warrant special note as neither has been observed in nutmeg before. The terpenyl alcohols have been included in this

group as are the two aromatic hydrocarbons cymene and the previously undetected toluene. On the other hand both cineole and camphor have been recently reported to be present to the extent of a percent or two, and citronellol and citronellal have been reported in trace amounts (4); none of these were present in the sample we investigated. d-Borneol, which had originally been assigned to nutmeg on indirect evidence (5) was not present in our sample.

The second and smaller group, the aromatic ether fraction, is the more interesting and as will be shown later is the more likely to be implicated in the psychopharmacology of nutmeg. In Table I are shown the nine aromatics that have definitely been established as being present in nutmeg, and it also shows the extent of their contribution to the sample analysed.

The three major components, myristicin, elemicin, and safrole constitute nearly 9/10 of the group. In the previously reported studies of nutmeg, myristicin has always been recognized as a major component, and has thus often been thought to be responsible for the psychopharmacological activity of the total extract. In the thorough study conducted on the Ceylonese Oil of Nutmeg (5) safrole was found only in very small quantities, but recently its identity as a significant component of East Indian oils has been reported, (6) although it appeared to be absent in the West Indian varieties.

COMPOSITION OF OIL OF NUTMEG LUEDELS WEST INDIAN

<u>TERPENIC FRACTION</u>	<u>%</u>	<u>AROMATIC FRACTION</u>	<u>%</u>
α -PINENE	36.16	SAFROLE	1.29
β -PINENE	6.16	METHYLEUGENOL	0.62
CAMPHERE	2.97	EUGENOL	0.17
SABINENE	12.75	METHYLISOEUGENOL	0.36
1,4-p-MENTHADIENE	3.47	ISOEUGENOL	0.19
1,4(8)-p-MENTHADIENE	1.12	MYRISTICIN	7.04
1,8-p-MENTHADIENE	12.78	ELEMICIN	2.36
TOLUENE	0.10	ISOELEMICIN	0.11
p-CYME	1.82	METHOXYEUGENOL	0.25
1-MENTHENE-4-OL	2.93	<u>OTHERS</u>	
1-MENTHENE-8-OL	0.41		
LINALOOL	0.15	MYRISTIC ACID	2.87
GERANYL ACETATE	0.20	UNIDENTIFIED	3.72

TABLE I.

DISTRIBUTION OF THE PRINCIPLE AROMATICS IN
VARIOUS MYRISTICA OILS

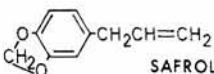
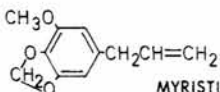
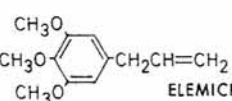
	L. WI. NUTMEG	F. WI. NUTMEG	L. EI. NUTMEG	F. EI. NUTMEG	D. ? NUTMEG	L. ? MACE	F. EI. MACE	D. ? MACE
 SAFROLE	1.29	1.43	1.09	2.69	1.38	0.53	3.42	1.41
 MYRISTICIN	7.04	5.58	8.08	8.48	5.62	3.86	12.78	5.53
 ELEMICIN	2.36	0.02	0.48	0.02	0.99	2.07	0.05	0.69
% OF TOTAL OIL THAT IS AROMATIC	12.7	7.5	10.7	12.5	8.2	7.2	18.2	8.1
% OF TOTAL AROMATIC THAT IS ACCOUNTED FOR ABOVE	84	94	90	90	94	90	89	95

TABLE II.

We have made a comparative study of the aromatic fraction of several samples of Oil of Nutmeg from different geographical origins, and of Oil of Mace as well. These results are shown in Table II. Here the surprisingly wide variation that can occur between these principle components is apparent. The single consistent item is the presence of myristicin as a major component. In the figure the F found at the heads of the columns represents the source, Fritzsche Bros., New York. Similarly, L stands for Lueders Co. and D for Dreyers Co. The WI represents West Indian sources, and EI East Indian. The question marks refer to samples whose origin was undesigned. Safrole has been found in both East and West Indian oils and appears, in this analysis, to be present in an amount from 15-30% of the myristicin present. The amount of elemicin present is most erratic. It has been found to vary from over 2% in the Lueders West Indian Oil of Nutmeg, to only trace amounts in the Fritzsche samples. The various oils of mace show neither consistency nor correlation with the nutmeg samples, except that again, myristicin appears as the principle component.

The assignment of the chemical structures of these compounds is a direct and simple matter when compared to the task of assigning responsibility for the intoxicating and psychotropic properties of nutmeg. The kernel itself is the only component of the tree that is invested with the reputation for biological activity. Further, it may be asserted that the psychoactive compound or compounds probably reside in the volatile oil fraction of the nutmeg, for this fraction has been shown in animal toxicology studies to carry the effectiveness of the entire seed. Human experiments with ground nutmeg depleted of its volatiles have failed to show psychopharmacological responses (?).

With the satisfactory assignment of the identities of the various conspicuous components to be found in nutmeg, one must examine how each of these individually, or more likely in concert, may achieve a role in a reasonable explanation of the activity of the entire seed. Here there are two groups of compounds to consider, the terpenes and the aromatic ethers. It is tempting to dismiss the terpenes out of hand. Although they constitute by far the larger portion of the volatile fraction, the terpene hydrocarbons are generally held to be of biological effectiveness mainly as irritants. Turpentine has a composition quite similar in make-up to this terpene fraction; it has been widely used in many home remedies, but it has certainly not commanded reputation as an intoxicant. It may, however, have some function in assisting in the absorption of the various aromatic compounds through the gut.

The aromatic fraction, then, would seem to be the most likely source of the psychotropic activity of nutmeg. Table III shows the structure of each of the compounds we have found in the aromatic fraction. Also shown is the amount in milligrams of each of these components that would be present in 20 g. of the whole nutmeg, 20 g. being assumed to be that required to produce

AROMATIC FRACTION OF OIL OF NUTMEG

STRUCTURE	NAME	AMOUNT TO BE FOUND IN 20 GRAMS TOTAL NUTMEG (IN MILLIGRAMS)
	SAFROLE	39
	METHYLEUGENOL	18
	EUGENOL	5
	METHYLISOEUGENOL	11
	ISOEUGENOL	6
	MYRISTICIN	210
	ELEMICIN	70
	ISOELEMICIN	3
	METHOXYEUGENOL	8

TABLE III.

psychotropic effects. As stated earlier, safrole, myristicin, and elemicin account for some 84% of the aromatic fraction, and thus are the primary materials that we will consider. The possibility must always be kept in mind that one of the minor components could have an unusually high potency and thus contribute to the activity.

Of the primary constituents, myristicin is by far the most abundant, and for this reason was tested specifically for psychotropic activity by Truitt, *et al* (7). Doses of 400 mg. myristicin, almost twice the amount present in 20 g. of typical nutmeg, were given to human volunteers and the observed symptoms were at least suggestive of psychotropic effects in 6 out of 10 subjects. It will be seen later that those effects which might be expected from myristicin may be rather subtle, and so may require some synergistic activity of some of the other aromatic compounds to produce the full nutmeg syndrome.

Safrole is also a component of other natural oils and spices, the most notable being the Oil of Sassafras which contains some 80%. Both the oil and the derived sassafras tea have enjoyed wide use, modestly as a flavoring, and in larger amounts as an internal medicament; yet neither has a reputation for psychotropic activity as does nutmeg.

Elemicin is unusual in that among the flavoring oils and spices, it occurs in appreciable amounts only in nutmeg. Further, as mentioned earlier, even in nutmeg the amount of elemicin is highly variable and depends upon the source of the extract. It also occurs in several obscure essential oils, none of which have been reported to have been used pharmacologically. It is, further, not separable from myristicin by fractional distillation. The myristicin employed in all earlier pharmacology (including the human studies mentioned) was obtained by distillation from oil of nutmeg, and was taken to be the single substance myristicin. It thus may or may not have contained elemicin as well, depending on the origin of the oil. The variability of elemicin may account for the apparently highly variable degree of reported psychoactive effects of nutmeg, which in turn implies that elemicin may indeed be an active component. Of the aromatic components present in lesser amounts, only eugenol and isoeugenol have found use either as flavoring agents or as medicinals. They comprise about 80% of the Oil of Cloves for example, but again search of the literature on such natural products for some reputation for abuse as an intoxicant has been futile.

There are thus several possibilities by which one or more of the aromatic components might be implicated as psychotropic agents;

1. One of the compounds that is present only in very small amounts may have unusually high potency,
 2. Elemicin may be a major contributor of activity, or
 3. A combination of two or more of the aromatics present may be involved.
- The three most abundant ones, myristicin, elemicin and safrole may be sufficient to account for the total activity.

It is worth noting that nutmeg is the only plant source within which these three compounds have been reported as occurring together in any appreciable

quantity, and as will be seen later, each may contribute slightly different aspects to the total psychotropic effect.

With the exception of myristicin none of the individual components of the aromatic fraction have been evaluated specifically as to their psychological effects. The ring substitution patterns of these compounds are notable in that several of them, specifically myristicin, elemicin and safrole, are identical to the ring structures of materials of established psychogenic activity. The allylic side chain is amenable to chemical modification, as shown is Fig. 3, which could convert the naturally occurring compounds into ones of known psychotropic activity. It has been suggested (8) that the *in vivo* addition of ammonia to the olefinic site in either the allyl or the propenyl isomer would yield amphetamines directly. To speak of amphetamines as a chemical class is not strictly correct, but we use it to refer to variously methoxylated phenylisopropylamines. The "RO" in the figure indicates the presence of any variety of ether groups on the ring, and thus would include all of the aromatic ethers in the oil of nutmeg and in many other natural oils as well. The possible mechanisms of such an *in vivo* transformation have been elaborated upon, and are plausible to the extent that each of the reactions has been achieved *in vitro*. Support for this transformation occurring *in vivo* has been obtained by Barfknecht (9), who found evidence for the production of amphetamine in rats after feeding them allylbenzene. This corresponds to ammonia addition in Fig. 3 without the "RO" ether groups.

CONVERSION OF AROMATIC ESSENTIAL ETHERS TO ALKOXYAMPHETAMINES

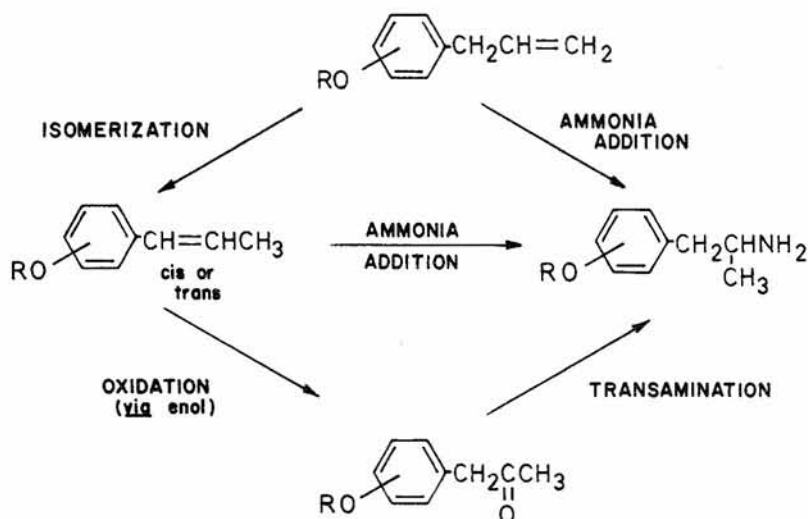


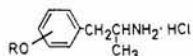
FIG. 3.

Throughout the general area of spices and of essential oils from plant sources there is about a score of substituted phenylpropenes, all of which are characterized by ring substitution of either methoxy groups or a methylenedioxy group (or both) and by the allyl or the propenyl side chain mentioned above. Of these a total of eleven different ring substitution patterns have been reported as occurring; the balance of the twenty known aromatics consists of isomeric variations of the side chain. The addition of an amine to this olefinic system might be extremely sensitive to substitutions near it, that is, whether the side chain be allyl, *cis*-propenyl or *trans*-propenyl. It may thus be in turn a determining factor in the psychotropic activity of any such substance under consideration.

In the preparation for the study of this possible *in vivo* amination of these ring-substituted natural oils, a series of amphetamines that would be the result of such an addition has been completed. These are tabulated in Table IV, showing the principle natural source of each of the natural oils, the common name as they occur in the allyl (A) or propenyl (P) form, the orientation of the ring substituents, the code letter abbreviation of the resulting base, the cogent physical and chemical data, and the potency of the compound in mescaline units. The latter measure is defined as the quotient of the effective dose of mescaline (assumed to be 3.75 mg/Kg as the base) divided by the effective dose of the substance in question, as determined by human titration. This ratio permits a direct comparison of relative potencies, based on mescaline equaling one. Mescaline has a ring substitution pattern identical with number 6, TMA, except that the side chain has only two carbons instead of three.

It will be noted that several of the possible amphetamine derivatives of the components of the aromatic fraction of nutmeg do not appear here;

AMPHETAMINES RELATED TO THE NATURAL ESSENTIAL OILS



COMMON NAME	PRINCIPLE SOURCE	RING ORIENTATION	CODE	SYNTHETIC ROUTE	M.P./°C	YIELD	POTENCY MESCALINE=1
1. ESTRAGOLE (A)	O. OF ANISE	4-OCH ₃	MA	A	211	60	?
2. NOTHOSMYRROL (P)	O. OF <u>N. JAPANEICUM</u>	2,4-(OCH ₃)	2,4 DMA	A	147	90	?
3. METHYLEUGENOL (A)	O. OF CITRONELLA	3,4-(OCH ₃)	DMA	A	147	76	?
4. SAFFROLE (A)	O. OF SASSAFRAS	3,4-(OCH ₂ O)	MDA	A	186	29	2
5. ASARONE (P)	O. OF CALAMUS	2,4,5-(OCH ₃)	TMA-2	B	181	60	18
6. ELEMICIN (A)	O. OF ELEMI	3,4,5-(OCH ₃)	TMA	A	209	63	2
7. CROWEACIN (A)	O. OF <u>E. CROWEI</u>	2-OCH ₃ -3,4-(OCH ₂ O)	MMDA-3a	A	154	59	18
8. MYRISTICIN (A)	O. OF NUTMEG	3-OCH ₃ -4,5-(OCH ₂ O)	MMDA	B	191	60	3
9. — (A)	O. OF PARSLEY SEED	2,3,4,5-(OCH ₃) ₄	Tetra MA	C	136	13	?
10. DILLAPIOLE (A)	O. OF DILL	2,3-(OCH ₃) ₂ -4,5-(OCH ₂ O)	DMMDA-2	C	130	94	?
11. APIOLE (A)	O. OF PARSLEY SEED	2,5-(OCH ₃) ₂ -3,4-(OCH ₂ O)	DMMDA	B	175	64	?

A: VIA BENZALDEHYDE, NITROETHANE, LiAlH₄.

B: VIA CLAISEN REARRANGEMENT, METHYLATION, ISOMERIZATION, CINO₂, LiAlH₄.

C: VIA NATURAL ALLYL COMPOUND, ISOMERIZATION, CINO₂, LiAlH₄.

TABLE IV.

namely those which contain an OH substituent in addition to the methoxyl groups. These comprise some 5% of the aromatic fraction, and still remain to be explored in the human subject, either as purified components themselves, or as their amphetamine extensions. Should the free hydroxyl group of any of these several materials confer an unusually high psychotropic potency on any of these compounds or on the corresponding amphetamines, this would contribute to the nutmeg intoxication beyond the explanations considered here. Eugenol itself has had some known medical uses however, and it would seem reasonable to expect that its psychotropic activity would have been noted had it existed.

Published detail has appeared on the psychotropic effects in normal human subjects for the four compounds that are trisubstituted, numbers 5, 6, 7 and 8 (10). In every case the compounds had a greater potency than that of the reference substance mescaline.

The base that corresponds to safrole, number 4, is 3,4-methylenedioxyamphetamine, or MDA. This was first described pharmacologically by Gordon Alles (11) who reported visual effects at some 120 mg. Subsequent experience (12) on a more extensive number of subjects has shown modest, if any, distortion or change of either visual or auditory perception, but rather a pronounced increase in emotional effect, which has proved to be of considerable value in psychotherapy.

The base that would be the result of the addition of ammonia to myristicin, number 8, is 3-methoxy-4,5-methylenedioxyamphetamine, or MMDA. A complete description of the animal and human pharmacology and psychopharmacology of this compound is forthcoming (13). With regard to the work mentioned earlier in which 400 mg. of myristicin was tested in human subjects, the experience with MMDA indicates that the effects although identifiable in a psychotherapeutic setting, or in subjects trained to identify psychotropic effects, are rather subtle and may not have been detected by the psychological tests used in the study. The psychotropic effects of MMDA are rather similar to those of MDA, but in addition some 30% of the subjects reported rather vivid and well structured visual images appearing when the eyes are closed, although there are virtually no changes in eyes-open perception. The possibility that myristicin in the amounts present in nutmeg may contribute to the total effects of nutmeg, cannot at this point be discarded.

The base that corresponds to number 6 is 3,4,5-trimethoxyamphetamine, TMA. This has been known as a psychotropic agent for some time (14, 10a). It has variously been described as having potent hallucinatory effects and as leading to apparently hostile reactions. More extensive appraisal of this compound in psychotherapeutic settings has confirmed the eyes-opened distortions and occasional hallucinatory phenomena, and strongly suggests that its characteristic property is one of causing projection, in the psychological sense, by the subject. This can produce visual distortions, delusions (alterations in social perceptions), and sometimes apparently hostile projections which, however, have never led to any overt actions.

The analogous bases that correspond to the eugenols have not yet been evaluated, and as mentioned earlier represent another group of compounds that could contribute to the activity of nutmeg.

There are two ways in which further investigations might be pursued; namely human evaluation of the individual compounds of the aromatic fraction of the oil of nutmeg, preferably synthetically derived to avoid contamination, and secondly, the further evaluation of the effects of the amine derivatives. It is entirely possible that the combination of the amines derivable from the essential oil aromatics could produce the psychological effects of nutmeg, while the clearly toxic effects could be due to the terpene fraction. Human evaluation of a mixture of these amines, in the proportions found in nutmeg, would explore the possibility of any synergistic amplification of the activity of these compounds. A corollary study would involve the chemical investigation of the metabolic fate of both the essential oils and the derived amines, on administration to human subjects, and may clarify whether or not these oils are in fact converted to amines *in vivo*. From the results of these studies, it is hoped that the interrelationship between the complex composition, and the yet more complex psychopharmacological structure of nutmeg, can be resolved.

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