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Attraction of the oriental fruit fly, *Dacus dorsalis*, to methyl eugenol and related olfactory stimulants

(olfaction/receptor/methyl eugenol isosteres)

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ABSTRACT **The attraction of male oriental fruit flies to methyl eugenol and 34 analogues was investigated quantitatively using the characteristic feeding response. Methyl eugenol was the most active compound studied, with a feeding response to 0.01 μg, but saturation of the allyl side chain or replacement of allyl by allyloxy produced compounds almost as effective. Replacement of the methoxy groups by methylenedioxy, methyl, or chloro groups abolished all response. The ring geometry of the methoxy groups was critical, with *ortho*-dimethoxy most active and *meta*-dimethoxy inactive. Replacement of methoxy with hydroxy, methylthio, or amino groups did not abolish the response. The failure of the oriental fruit fly to respond to the methyl and chloro isosteres of methyl eugenol was contrasted with the response of a human odor panel which perceived these compounds as having weak floral odors.**

The olfactory response of the male oriental fruit fly, *Dacus dorsalis*, Hendel to 3,4-dimethoxyallylbenzene (methyl eugenol) is a model example of the specific influence of a chemical on insect behavior. Methyl eugenol is presumably a food lure or aggregation odor (1) for the male fruit fly, since it has been isolated from a number of plants, including the flowers of papaya, mango, a Cycad, *Colocasia antiquorum*, and the blossoms of the golden shower tree *Cassia fistula* L., and leaves of *Pelea anisata* Mann, all of which are strongly attractive to the male fly (1, 2). The presence of 10^{-3}–10^{-2} μg of methyl eugenol on filter paper attracts the fly, and the olfactory threshold approaches that reported for the sex pheromone bombycol of the silkworm, i.e., 10^{-4} μg (3). Steiner (4) reported the attraction of male oriental fruit flies to methyl eugenol from as far as 0.5 miles (0.8 km) and described the characteristic and compulsive feeding behavior of the male fly, which will continue to engorge until it dies from overindulgence. This feeding response, which is not observed in the female fly, is so dominant over other behavioral patterns that the flies feeding on methyl eugenol lose all normal evasive behavior (1) and can be dislodged from treated surfaces only with violence.

The specificity of the male fruit fly response over a concentration gradient of more than 10^8-fold, together with the large number of structural modifications that can be made to various parts of the methyl eugenol molecule, afforded a significant opportunity to study the nature of the interaction between stimulant chemical and antennal receptor. The most plausible sort of interaction seemed to us to be the absorption of the stimulant on a lipoprotein patch of specific dimensions with a resultant depolarization of the sensory cell. This idea is the basis of Amoore's stereochemical theory of odor (5), and may be analogous to the absorption of substrate or inhibitor molecules at the active site of an enzyme. We have attempted a preliminary mapping of the proposed stereospecific receptor patch by studying the response to isosteres of methyl eugenol. This technique has been very useful in our studies of the nature of the active site of acetyl cholinesterase, where stereospecifically equivalent phenyl *N*-methyl-carbamate inhibitors resulted from *ortho*-substitution by CH_3O, CH_3, and Cl with van der Waals radii between 1.8 and 3.4 Å (6).

MATERIALS AND METHODS

The 3,4-dimethoxyallylbenzene, bp 120–2° at 10 mm, $[n]_D^{25}$ 1.5323, was prepared by redistillation of a purified commercial sample. The infrared (IR) and nuclear magnetic resonance (NMR) spectra, doublet τ6.75 (—CH_2—C=C), doublet τ6.3 (ring OCH_3), multiplet τ5.0 (—C—C=CH_2), multiplet τ4.3 (C—CH=C), and a multiplet τ3.4 (aromatic H) were entirely consistent with the proper structure. The 3,4-dimethylallylbenzene, bp 74° at 6.0 mm, $[n]_D^{25}$ 1.5163, was prepared from 3,4-dimethylbromobenzene (7) through the Grignard reagent coupled with allyl bromide. The structure of the product (theory: C = 90.35%, H = 9.65%; found: C = 90.11%, H = 9.77%) was confirmed by IR and NMR spectra, singlet τ7.89 (ring CH_3), doublet τ6.8 (—CH_2—C=C), doublet τ5.0 (—C—C=CH_2), multiplet τ4.3 (—C—CH=C), and multiplet τ3.1 (aromatic H). The 3,4-dichloroallylbenzene, bp 70° at 2.5 mm, $[n]_D^{25}$ 1.5510, was prepared as above from 3,4-dichlorobromobenzene, made from 4-bromocarbanilide (8). The structure of the product (theory: C = 57.44%, H = 4.25%; found: C = 56.57%, H = 4.47%) was confirmed by IR and NMR spectra, doublet τ6.8 (—CH_2—C=C), doublet τ4.9 (—C—C=CH_2), multiplet τ4.25 (—C—CH=C), and multiplet τ2.95 (aromatic H). The 3,4-dimethoxypropylbenzene, bp 119–20° at 10 mm, $[n]_D^{25}$ 1.5148, was prepared by hydrogenation of methyl eugenol. NMR spectrometry showed the proper structure, multiplet τ9.1 (—C—C—CH_3), multiplet τ8.4 (—C—CH_2—C), multiplet τ7.5 (—CH_2—C—C), doublet τ6.2 (ring OCH_3), and multiplet at τ3.2 (aromatic H).

The three isosteric phenyl allyl ethers were prepared unequivocally from the appropriate 3,4-disubstituted phenol by refluxing with allyl bromide in acetone containing sodium carbonate. The 3,4-dimethoxyphenyl allyl ether, bp 95–100° at 1.8 mm, $[n]_D^{25}$ 1.5326, showed the proper IR and NMR

Abbreviations: IR, infrared; NMR, nuclear magnetic resonance.

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spectra, doublet τ6.2 (ring CH_3O), multiplet τ5.5 (—OCH_2—C=C), multiplet τ4.7 (OC—C=CH_2), multiplet τ4.1 (—OC—CH=C), and multiplet τ3.4 (aromatic H). The 3,4-dimethylphenyl allyl ether, bp 58° at 1.1 mm, $[n]_D^{25}$ 1.5192, showed the proper IR and NMR spectra, doublet τ7.8 (ring CH_3), multiplet τ5.5 (—OCH_2—C=C), multiplet τ4.7 (—OC—C=CH_2), multiplet τ4.1 (—OC—CH—C), and multiplet τ3.2 (aromatic H). The 3,4-dichlorophenyl allyl ether, bp 104–10° at 3.2 mm, $[n]_D^{25}$ 1.5520, showed the proper IR and NMR spectra, multiplet τ5.5 (—OCH_2—C=C), multiplet τ4.7 (OC—C=CH_2), multiplet τ4.1 (—OC—CH=C), and multiplet τ3.0 (aromatic H).

A simple and very reproducible assay method for the response of the oriental fruit fly to the "pheromone" was based on the application of known volumes of the liquid attractants to 9-cm discs of Whatman no. 1 filter paper. Dilutions were made v/v in purified acetone, and the requisite quantity was pipetted into the center of the paper. After the acetone had evaporated, the papers were placed in the center of the floor of aluminum cages of 12 cubic inch (30 cubic cm) dimensions containing approximately 200 male *Dacus dorsalis*, 12–20 days old. A positive reaction to the lure was unmistakable, since the male flies immediately oriented toward the treated area of the paper and began the characteristic feeding response to the attractive material. With methyl eugenol, for example, a droplet of approximately 100 μg in a cage of 275 male flies was fed upon by 55% after 5 min, 89% after 10 min, and 97% after 20 min, so that the mass of feeding flies completely obscured the surface of the filter paper. Where a positive reaction was observed to the maximum dosage of 10 μl (about 10 mg), progressive 10-fold dilutions were made until no response was observed after 20 min of exposure. This lowest dilution giving a positive "feeding" response is termed the odor threshold.

RESULTS

Location of Olfactory Receptor. Despite the extensive documentation of the response of the male *Dacus dorsalis* to methyl eugenol, no information was found on the anatomical location of the olfactory organs. Since these seem characteristically to be present on the insect antenna (3), simple amputation experiments were performed under CO_2 anesthesia on 17-day-old male fruit flies subsequently exposed to approximately 100 μg of methyl eugenol. The results are shown in Table 1. Bilateral antennectomy virtually destroys the feeding response to methyl eugenol. The response in a few flies (two after 5 min) is doubtless the result of the relatively crude operation, which removed the arista and large third segment but left a portion of the second segment and the scape of the antenna intact. Although antennectomy may have produced a severe surgical shock, the high level of response after unilateral antennectomy provides a suitable control, and it seems clear that the olfactory receptor for methyl eugenol is located on the male antenna.

Mechanism of Orientation. These experiments provided some insight into the role of olfaction in initiating the seeking and feeding response to methyl eugenol. Flies with the left antenna amputated moved toward the lure in a zig-zag pattern, approaching toward the right side with the intact antenna. The opposite approach was used when the right antenna was amputated. Feeding began immediately after contact with the lure. When both antennae were amputated no orientation resulted, and the flies moved in circles over the surface with pulsating mouthparts as though tasting at random.

Table 1. Effects of amputation of antennae on response of male oriental fruit fly to 0.1 μl of methyl eugenol

Condition	No. of flies	% Showing feeding response		
		5 min	10 min	20 min
Normal	275	55	89	96
Left antenna amputated	50	16	34	70
Right antenna amputated	50	24	52	70
Both antennae amputated	33	6	12	21

Specificity of Olfactory Response. Systematic variations were made in the structure of methyl eugenol: (*a*) in changes in allyl side chain, (*b*) in position isomerism of the methoxy-phenyl substituents, and (*c*) in isosteric replacement of CH_3O by —OCH_2—, CH_3, Cl, OH, CH_3S, and NH_2 groups. The results are indicated by the semiquantitative values for olfactory thresholds shown in Table 2.

Although 3,4-dimethoxyallylbenzene (I) was the most active compound studied, its attraction was decreased less than 10-fold by saturation of the allyl double bond (III) or by introduction of an ether linkage as 3,4-dimethoxyallyloxybenzene (X). However, replacement of the CH_3O groups by methylenedioxy (IV), CH_3 (VIII), or Cl (IX) completely destroyed the olfactory response even at concentrations $>10^6$ the olfactory threshold of methyl eugenol. The inability of the spatially similar CH_3 and Cl substituents to substitute for CH_3O was verified for both the allylbenzenes (VIII, IX) and the allyloxybenzenes (XI, XII). Neither allylbenzene (XIII) nor allyloxybenzene (XIV) was attractive, further indicating the importance of the methoxy groups.

In the isomeric dimethoxybenzenes, *ortho*-dimethoxybenzene (XXVI) showed substantial activity, with a strong feeding response, while the *p*-isomer (XXVIII) was less active and the *m*-isomer (XXVII) inactive. The position of the two methoxy groups relative to a third substituent was investigated with the isomeric dimethoxyphenyl acetates, of which the 3,4-isomer (XIX) was again the most active while the 3,5-isomer (XXIV) showed no activity. The other isomers showed slight activity (XX–XXIII). The strong feeding response to the isomeric dihydroxybenzenes (XXIX–XXXI), $p < o = m$, was surprising. The oxidation product of the *p*-isomer, 1,4-benzoquinone, also showed activity. Replacement of a single CH_3O by CH_3S (XXXII) preserved slight activity, as did replacement by NH_2 (XXXIII).

Outdoor Evaluation. In order that male *D. dorsalis* might be permitted free choice with minimal vapor effects, filter paper discs treated with 10 μl of test substances were fixed vertically at random, 10 cm apart, on a board exposed outdoors in June sunlight (Honolulu) at 4:30 p.m. Twenty-five minutes after approximately 2000 flies were released nearby, the number of flies feeding on each test compound were: methyl eugenol (I), >200; methyl isoeugenol (II), 100; 3,4-dimethoxyallyloxybenzene (X), 28; 3,4-dimethylallylbenzene (VIII), 0; 3,4-dimethylallyloxybenzene (XI), 0; and 3,4-dichloroallyloxybenzene (XII), 0.

Comparison with Human Odor Response. The complete lack of response of male *D. dorsalis* to the CH_3, Cl, and —OCH_2O— isosteres of methyl eugenol was unexpected, as all

Table 2. Response of male oriental fruit fly to methyl eugenol and analogues

Compound	Approximate odor threshold (μg)	Feeding response
I. 3,4-$(CH_3O)_2C_6H_3CH_2CH{=}CH_2$ (methyl eugenol)	10^{-2}	++++
II. 3,4-$(CH_3O)_2C_6H_3CH{=}CHCH_3$ (methyl isoeugenol)	10^{-1}—1.0	++++
III. 3,4-$(CH_3O)_2C_6H_3CH_2CH_2CH_3$	10^{-2}—10^{-1}	++++
IV. 3,4-$(OCH_2O)C_6H_3CH_2CH{=}CH_2$ (safrole)	$>10^4$	0
V. 3,4-$(OCH_2O)C_6H_3CH{=}CHCH_3$ (isosafrole)	$>10^4$	0
VI. 3-CH_3O—4—OH—$C_6H_3CH_2CH{=}CH_2$ (*trans*-eugenol)	10^2	++
VII. 2,5-$(CH_3O)_2C_6H_3CH{=}CHCH_3$	10^4	+
VIII. 3,4-$(CH_3)_2C_6H_3CH_2CH{=}CH_2$	$>10^4$	0
IX. 3,4-$(Cl)_2C_6H_3CH_2CH{=}CH_2$	$>10^4$	0
X. 3,4-$(CH_3O)_2C_6H_3OCH_2CH{=}CH_2$	10^{-1}—1.0	++++
XI. 3,4-$(CH_3)_2C_6H_3OCH_2CH{=}CH_2$	$>10^4$	0
XII. 3,4-$(Cl)_2C_6H_3OCH_2CH{=}CH_2$	$>10^4$	0
XIII. $C_6H_5CH_2CH{=}CH_2$	10^4	+
XIV. $C_6H_5OCH_2CH{=}CH_2$	10^5	?
XV. 3,4-$(CH_3O)_2C_6H_3CH_2OH$	10^1—10^2	+
XVI. 3,4-$(CH_3O)_2C_6H_3CH_2OC(O)C_2H_5$	10^2—10^3	+++
XVII. 3,4-$(CH_3O)_2C_6H_3CH(OH)CH_3$	10^4—10^5	++
XVIII. 4—CH_3O—$C_6H_4CH_2OH$	10^4	+
XIX. 3,4-$(CH_3O)_2C_6H_3OC(O)CH_3$	10^2—10^3	+++
XX. 2,3-$(CH_3O)_2C_6H_3OC(O)CH_3$	10^3—10^4	++
XXI. 2,4-$(CH_3O)_2C_6H_3OC(O)CH_3$	10^3—10^4	++
XXII. 2,5-$(CH_3O)_2C_6H_3OC(O)CH_3$	10^3—10^4	++
XXIII. 2,6-$(CH_3O)_2C_6H_4OC(O)CH_3$	10^4	+
XXIV. 3,5-$(CH_3O)_2C_6H_4OC(O)CH_3$	$>10^4$	0
XXV. 3,4-$(OCH_2O)C_6H_4OC(O)CH_3$	$>10^4$	0
XXVI. 1,2-$(CH_3O)_2C_6H_4$	1—10	+++
XXVII. 1,3-$(CH_3O)_2C_6H_4$	$>10^4$	0
XXVIII. 1,4-$(CH_3O)_2C_6H_4$	10^2	++
XXIX. 1,2-$(OH)_2C_6H_4$	1	++
XXX. 1,3-$(OH)_2C_6H_4$	1	++
XXXI. 1,4-$(OH)_2C_6H_4$	0.1—1	++
XXXII. 1-CH_3O-2-CH_3S-C_6H_4	1—10	+++
XXXIII. 1-OH-4-NH_2-C_6H_4	10—100	+
XXXIV. O=C_6H_4=O (1,4)	10^3—10^4	+

of these compounds are readily detectable by the human nose. For comparison, 10 human subjects were asked to characterize the odor and intensity of the isosteres (Table 3). The odor of the allyloxy series was characterized as less intense than the allyl series, but there were obvious odor similarities. Most of the panel had difficulty in distinguishing the odor of the dimethyl- (VIII) and dichloro- (IX) allylbenzenes, compounds very similar in size and shape. Results in Table 3 clearly support the stereochemical theory of odor (5), predicting that compounds of similar size and shape (Fig. 1) are expected to smell alike. All of the compounds in Table 3 fall into Amoore's category of floral odors.

DISCUSSION

The present studies are reinforced by data from Beroza and Green (9), who used 0.1% aqueous emulsions of over 4000 chemicals to attract male *D. dorsalis* into traps and characterized the response as (*i*) little or none, (*ii*) moderate, and (*iii*) strong. Chen *et al.* (10) evaluated 67 substituted methoxybenzenes as attractants to male *D. dorsalis*, using a rating system similar to that of ref. 9. Where comparisons can be made, the data from both of these studies are in substantial agreement with ours. It seems likely that the chemical transduction process resulting from the impact of lure molecules on the receptor protein involves hydrophobic bonding and van der Waals forces, effecting conformational changes in the receptor protein similar to those occurring in enzyme-substrate interactions (13). These conformational changes are suggested as triggering the nerve depolarization mechanism (11, 12).

Amoore's (5) stereochemical theory of odor has been applied to ant alarm pheromones with a high degree of success (14, 15) and to the sex pheromones of lepidoptera (16, 12). The similarities in odor perception by humans to the isosteric 3,4-disubstituted allyl and allyloxybenzenes (Table 3) provide additional evidence in support of the Amoore theory, since these compounds have very similar overall structural dimensions, as based on silhouettes of molecular models (Fig. 1). The complete failure of the CH_3— and Cl— iso-

Table 3. Characterization of odors of methyl eugenol isosteres by human odor panel

Compound	Odor and intensity
Allylbenzene (XIII)	Sweet (++)
3,4-Dimethoxyallylbenzene (I)	Spicy or clove (+)
3,4-Dimethylallylbenzene (VIII)	Kerosene (+++)
3,4-Dichloroallylbenzene (IX)	Peppermint or sweet (++)
3,4-Methylenedioxyallylbenzene (IV)	Sassafras (+)
Allyloxybenzene (XIV)	Less sweet than allylbenzene (+)
3,4-Dimethoxyallyloxybenzene (X)	Banana (+)
3,4-Dimethylallyloxybenzene (XI)	Licorice (+++)
3,4-Dichloroallyloxybenzene (XII)	Turpentine (+)

steres to elicit the typical feeding response in male *D. dorsalis* suggests interesting comparisons between the generalized human olfactory receptor with its response to a very wide range of organic molecules and the highly specialized receptor of *D. dorsalis*. Either (*a*) the *D. dorsalis* receptor is responsive only to molecules that are iso-electronic with methyl eugenol, in analogy with the ant alarm receptor (15), or (*b*) the receptor is broadly responsive, but a secondary filtering or behavior integrating mechanism exists in the central nervous system of *D. dorsalis* that permits the behavioral orientation toward the methyl eugenol type odor and ignores inconsequential olfactory stimuli, perhaps in analogy with the mammalian response to musks.

Evidence for the highly selective receptor is provided by the data from compounds and responses listed in Table 2. Active compounds all contained the paired-electron rich O atom, and the strength of the response was increased by an adjacent O atom (*ortho*) together with a third lipophilic group, allyl, allyloxy, or propyl, *meta-para* to the O atom. The alkoxy groups evidently need to be free and rotatable, as indicated by the total inactivity of safrole (IV) with its *meta-para* oriented 5-membered methylenedioxy ring. It appears that the presence of at least one electron-rich O atom must be necessary to trigger the conformational change of the receptor that results in depolarization of the sensory cell. This is supported by the observation that the presence of the inactive CH_3 (VIII, XI) and Cl (IX, XII) isosteres at concentrations of up to 10^6 that of methyl eugenol had no observable effect in the olfactory response. The substitution of SCH_3 (XXXII) and NH_2 (XXXIII) for CH_3O still permitted a weak response (10), and these groups also have unshared electron pairs.

The importance of electron density on the O atoms is emphasized by the low activity of *m*-dimethoxybenzene (XXVII) compared to the *o*-isomer (XXVI) and *p*-isomer (XXVIII), together with the relative inactivity of 3,5-dimethoxyphenyl acetate (XXIV) compared to the 3,4-isomer (XIX). This suggests that the CH_3O groups *meta*- to one another substantially decrease the electron density necessary to cause the conformation change of the receptor protein through the $-I$ effect (CH_3O $\sigma_m = 0.115$ compared with $\sigma_p = -0.268$). This may also explain the inactivity of 2,5-dimethoxypropenylbenzene (VII), which has an olfactory

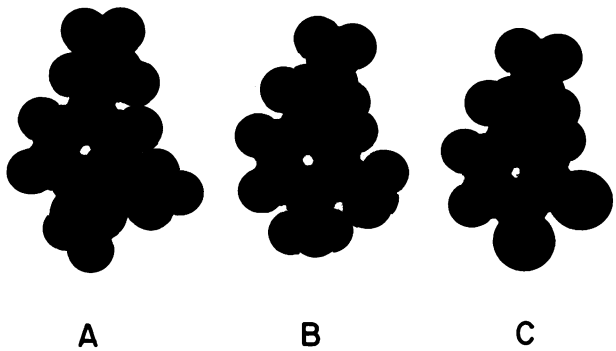

FIG. 1. Comparison of silhouettes of Fisher–Hirschfelder–Taylor molecular models of 3,4-dimethoxyallylbenzene (A), 3,4-dimethylallylbenzene (B), and 3,4-dichloroallylbenzene (C).

threshold 10^5 greater than the 3,4-isomer (II). The order of activity of the isomeric dihydroxybenzenes, $p > o = m$, and the weak activity of quinone are difficult to explain.

The inactivity of the CH_3 and Cl isosteres of methyl eugenol cannot be explained by inadequate adsorption on the olfactory receptor protein. The π values (17) for octanol/water partition of the disubstituted benzenes are: *o*-dimethoxy, 1.47; *o*-dimethyl, 3.49; and *o*-dichloro, 3.31. Furthermore, the human nose perceives the CH_3 and Cl isosteres somewhat better than methyl eugenol (Table 3), perhaps indicating better adsorption on the olfactory protein because of more favorable partition values.

Blum *et al.* (18) have postulated an absolutely complementary antennal receptor in the honeybee *Apis mellifera* for the sex pheromone, 9-keto-*trans* 2-decenoic acid. The methyl eugenol receptor in *Dacus dorsalis* is evidently less absolute in its stereochemical requirements and accepts a wide variety of substituted aromatic compounds (Table 2). The necessity for a planar benzene ring suggests a broad and relatively flattened complementary area, such as proposed by Amoore for floral odorants (5). Accommodation of *o*-alkoxybenzenes up to C_3H_7O (9) suggests a slightly larger area than the broad dimensions of methyl eugenol (about 9–10 Å). The most effective interactions (Table 2) result from a 3- to 4-atom chain in the *m-p*- position to alkoxy groups, and activity is only slightly affected by C=C at C_1 or C_2 or by loss of unsaturation. However, absence of the alkyl or alkoxy chain at C_1 of the benzene ring increases the olfactory threshold about 10^4-fold, and absence of the 3,4-dimethoxy groups about 10^6-fold. Thus, we postulate a receptor site length of about 14 Å.

Perhaps the most remarkable physiological aspect of the study is the effect of the olfactory response in promoting the uninhibited ingestion by the male fly of an array of unpalatable organic chemicals ranging from anisole to hydroquinone. The evolutionary influence in the development of the "methyl eugenol reflex" is demonstrated by failure to find any organic chemical, in over 4000 studied, that has a lower olfactory threshold.

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