Summary

1. Phenyl mustard oil and *o*-tolyl mustard oil are satisfactory reagents for many primary aromatic amines, forming well-crystallizing and sharply melting thiocarbanilides in good yields.
2. The reagents do not react with water or alcohol, and a determination may be made in their presence.
3. There are no by-products of the reaction.

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SOME UREAS AND THIOUREAS DERIVED FROM VANILLYLAMINE. RELATIONS BETWEEN CONSTITUTION AND TASTE OF PUNGENT PRINCIPLES

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Capsaicin, the pungent principle of cayenne pepper, and piperin or chavicin, the pungent principle of black pepper, are both acid amides; capsaicin (I) is the vanillyl amide of Δ^6-8-methylnonenic acid; piperin, δ-piperonylvinylacrylopiperidide, is the piperidine amide of piperic acid; spilanthol, the reduction product of the pungent principle of para-cress is *n*-deco*iso*butyl amide.[1]

Since these natural pungent principles are acid amides, it is naturally conceivable that a relation might exist between pungency and the amide structure. The synthesis of a number of more or less closely related amides has indeed shown this relation to exist and has also led to conclusions as to the effect on pungency which accompanies changes in the molecular structure. Thus in compounds similar to capsaicin it has been found that a free phenolic group (preferably in the para position to the side chain) in the amine portion is necessary to produce pungency, that the methoxy group in the meta position exerts a favorable influence toward pungency (aromatic bases resembling aniline when replacing the hydroxy benzylamine bases diminish pungency), that the pungency is a maximum when the acid portion consists of nine to ten carbon atoms and that the pungency is not influenced by the position of the double bond in the acid portion. As to the effect of the presence or absence of un-

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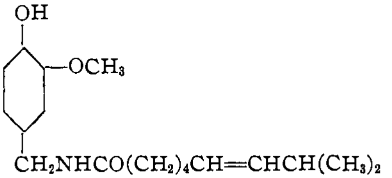
[1] Nelson, THIS JOURNAL, **41**, 1115 (1919); *ibid.*, **41**, 2121 (1919); Nelson and Dawson, *ibid.*, **45**, 2179 (1923); Ott and Eichler, *Ber.*, **55**, 2653 (1922); Ott and Lüdemann, *ibid.*, **57**, 214 (1924); Ott and Zimmermann, *Ann.*, **425**, 314 (1921); Jones and Pyman, *J. Chem. Soc.*, **127**, 2588 (1925); Kobayashi, *Rikagaku Kenkyujo Iho*, **4**, 527 (1925); Kobayashi, *Inst. Phys. Chem. Research* (*Tokyo*), **6**, 166 (1927); Staudinger and Schneider, *Ber.*, **56**, 699 (1923); Staudinger and Müller, *ibid.*, **56**, 711 (1923); Lapworth and Royle, *J. Chem. Soc.*, **115**, 1109 (1919); Asahina and Asano, *J. Pharm. Soc. Japan*, **1922**, 85.

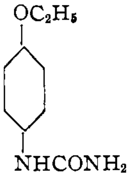
saturation in the acid portion there is still a difference of opinion, some investigators believing that pungency is diminished by the absence of a double bond while others find the saturated derivatives to be equal in pungency to the unsaturated acid derivatives. Capsaicin and closely related substances, aside from the pungent taste, are practically devoid of odor and flavor; dulcin (II) which is the carbamic amide of phenetidine is many times as sweet as cane sugar; studies which have been made on compounds closely related to dulcin have shown that nearly every change in structure causes a lowering or complete loss of sweetness.[2] Recently attention has been called to the same effect when one or more of the hydrogen atoms of the nitrogens of the urea are replaced by groups.[3]

Since both capsaicin and dulcin are acid amides derived from an amine having a *p*-hydroxybenzene structure, it seemed of interest to prepare a series of compounds which would have a rather close similarity to both. As typical of such a condition series of carbamicamides of vanillylamine (III) were prepared and tested particularly for their taste.



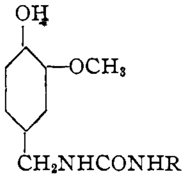
I

Capsaicin, pungent



II

Dulcin, sweet



III

Vanillylamine prepared by the reduction of vanillyl oxime[1] formed the starting product for these syntheses, being converted into the thiourea or urea by treatment with a thiocyanate or cyanate. In this way the following compounds were prepared: vanillylurea, vanillylthiourea, phenylvanillylurea, phenylvanillylthiourea, *p*-tolylvanillylthiourea and *o*-tolylvanillylthiourea. None of these compounds are sweet but the last three possess pungent properties.

Experimental Part

Preparation of Vanillylurea (*p*-**Hydroxy**-*m*-**methoxybenzylurea**), $(HO)(OCH_3)$-$C_6H_3CH_2NHCONH_2$.—This compound was obtained by mixing 1 mol of vanillylamine hydrochloride with 1.2 mol of potassium cyanate in water solution. Upon standing overnight, light brown crystals of the urea separated and were purified by recrystallizing first from hot water and then from hot alcohol; yield, 90%. It is fairly soluble in ethyl alcohol, methyl alcohol or water; very slightly soluble in ether, acetone, carbon tetrachloride or chloroform and insoluble in benzene or petroleum ether; m. p. 178.5° (corr.); it is tasteless in the dry state and in aqueous or alcoholic solutions. The values obtained

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[2] Boedecker and Rosenbusch, *Ber. pharm. Ges.*, **30**, 251 (1920); Speckan, *ibid.*, **32**, 83 (1922); Thoms, *Z. angew. Chem.*, **37**, 809 (1924); Lange and Reed, THIS JOURNAL, **48**, 1069 (1926).

[3] Lorang, *Rec. trav. chim.*, **47**, 179 (1928).

on analysis do not agree as closely as they should with the calculated composition; however, repeated attempts at further purification changed neither the analytical values nor the melting point; from the method of preparation we assume that the product was vanillylurea.

Anal. Calcd. for $C_9H_{12}O_3N_2$: C, 55.07; H, 6.17; N, 14.3. Found: C, 55.96, 55.74, 55.96; H, 6.79, 6.74, 6.77; N, 14.0.

Preparation of Vanillylthiourea (*p*-Hydroxy-*m*-methoxybenzylthiourea), $(HO)(OCH_3)C_6H_3CH_2NHCSNH_2$.—To 9.5 g. of vanillylamine hydrochloride dissolved in a small volume of water, 5.9 g. of potassium thiocyanate was added. After a few minutes a light brown product began to separate. This solution with its precipitate was evaporated to dryness on a steam-bath and the residue was extracted with boiling water. The vanillylthiourea crystallized from the hot extract. On recrystallizing from water, the solution supercools and no crystals separate until after several hours; a 60% yield was obtained; m. p. 167.5° (corr.). The dry compound as well as the aqueous and alcoholic solutions were tasteless. It is soluble in ethyl alcohol, or methyl alcohol, fairly soluble in water, very slightly soluble in acetone or chloroform and insoluble in ether, carbon tetrachloride, benzene or petroleum ether.

Anal. Calcd. for $C_9H_{12}O_2N_2S$: C, 50.90; H, 5.70. Found: C, 50.28; H, 5.63.

Preparation of Phenylvanillylurea (α-Phenyl-β-*p*-hydroxy-*m*-methoxybenzylurea), $C_6H_5NHCONHCH_2C_6H_3(OCH_3)(OH)$.—Vanillylamine base was prepared from the aqueous hydrochloride solution by adding the calculated amount of sodium hydroxide to neutralize the combined hydrochloric acid, shaking and allowing the mixture to stand for several hours, then filtering, washing with cold water and drying in a desiccator; it is easily decomposed by alkalies, boiling water or continued exposure to light. Equimolecular amounts of the base and phenylisocyanate were mixed in a beaker. Heat was evolved and the mixture soon solidified, giving a 63% yield of the urea. Colorless crystals of phenylvanillylurea are obtained by recrystallizing from ethyl alcohol. The compound is fairly soluble in ethyl alcohol, methyl alcohol or acetone, very slightly soluble in ether, chloroform, carbon tetrachloride or benzene and insoluble in water or petroleum ether; m. p. 190.5° (corr.). Solutions of this compound in alcohol are tasteless.

Anal. Calcd. for $C_{15}H_{16}O_3N_2$: C, 66.14; H, 5.93. Found: C, 66.26; H, 5.92.

Preparation of Phenylvanillylthiourea (α-Phenyl-β-*p*-hydroxy-*m*-methoxybenzylthiourea), $C_6H_5NHCSNHCH_2C_6H_3(OCH_3)(OH)$.—Five g. of vanillylamine and 4.4 g. of phenylisothiocyanate are mixed; after an initial warming to start the reaction, it proceeds rapidly with an evolution of heat and the formation of a solid mass. The compound was obtained in 92% yield; on treatment with charcoal and recrystallization from alcohol it gave colorless crystals, m. p. 138–138.5° (corr.); it is soluble in acetone, fairly soluble in ethyl alcohol, methyl alcohol or benzene, slightly soluble in chloroform or carbon tetrachloride, very slightly soluble in ether and insoluble in water or petroleum ether. Solutions of the compound in alcohol have a decidedly pungent taste accompanied by a slightly bitter taste

Anal. Calcd. for $C_{15}H_{16}O_2N_2S$: C, 62.45; H, 5.60; S, 11.1. Found: C, 62.67; H, 5.57; S, 10.8.

Preparation of *p*-Tolylvanillylthiourea (α-*p*-Tolyl-β-*p*-hydroxy-*m*-methoxybenzylthiourea), $CH_3C_6H_4NHCSNHCH_2C_6H_3(OCH_3)(OH)$.—A mixture of 4.6 g. of *p*-tolylisothiocyanate and 4.8 g. of vanillylamine was warmed on a steam-bath for three hours and then recrystallized from alcohol; a 75% yield of *p*-tolylvanillylthiourea was obtained; the compound is fairly soluble in ethyl alcohol, methyl alcohol, chloroform, acetone or benzene, very slightly soluble in carbon tetrachloride or ether and insoluble in water or petroleum ether; m. p. 138.5–139° (corr.). Solutions of the compound in alcohol have a decidedly pungent taste accompanied by a slightly bitter taste.

Anal. Calcd. for $C_{16}H_{18}O_2N_2S$: C, 63.53; H, 6.00; S, 10.6. Found: C, 64.04; H, 6.06; S, 10.4.

Preparation of *o*-Tolylvanillylthiourea (α-*o*-Tolyl-β-*p*-hydroxy-*m*-methoxybenzylthiourea), $CH_3C_6H_4NHCSNHCH_2C_6H_3(OCH_3)(OH)$.—Equimolecular quantities of *o*-tolylisothiocyanate and vanillylamine are mixed and then warmed. The compound, obtained in 80% yield, on treatment with charcoal and recrystallization from alcohol gave colorless crystals; m. p. 138–138.5° (corr.); it is soluble in acetone, fairly soluble in ethyl alcohol, methyl alcohol, chloroform or benzene, very slightly soluble in ether or carbon tetrachloride and insoluble in water or petroleum ether. Solutions of the compound in alcohol have a decidedly pungent taste accompanied by a slightly bitter taste.

Anal. Calcd. for $C_{16}H_{18}O_2N_2S$: C, 63.53; H, 6.00; S, 10.6. Found: C, 63.51; H, 5.95; S, 10.7.

Summary

Six different substituted ureas and thioureas have been described; these ureas, being the carbamic or thiocarbamic amides of vanillylamine, are the analogs of the pungent principle of cayenne pepper—a carboxylic amide of the same amine. Three of the thiocarbamides were found to have the property of pungency but to a lesser degree than capsaicin. None of the compounds has a sweet taste, the effect of the phenyl and tolyl groups, which are known to repress the sweetness of compounds, predominating over the favorable effect of the methoxy group; the slightly bitter taste which is characteristic of many thioureas was also observed in several of these compounds.

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[CONTRIBUTION FROM THE DEPARTMENT OF RESEARCH IN PURE CHEMISTRY, MELLON INSTITUTE OF INDUSTRIAL RESEARCH, UNIVERSITY OF PITTSBURGH]

THE ALGINIC ACID FROM MACROCYSTIS PYRIFERA[1,2]

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The earlier researches on the chemistry of the carbohydrates in algae were mostly concerned with the isolation and identification of the sugars formed on the hydrolysis of the plant as a whole. The first attempt at separation of a particular carbohydrate component was made by Stanford[3] and was based on the fact that most marine algae contain a highly polymerized acid fraction which may be extracted by means of dilute alkali

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[1] Presented before the Organic Chemistry Division of the American Chemical Society at the Swampscott Meeting, September, 1928.

[2] *Cf.* Cretcher and Nelson, *Science*, **67**, 537 (1928), for a preliminary discussion of this subject.

[3] Stanford, *Chem. News*, **47**, 254, 267 (1883).