THE RELATIONSHIP BETWEEN CHEMICAL CONSTITUTION AND TASTE

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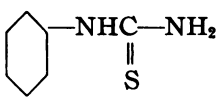
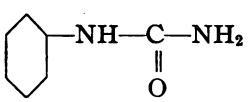
Some time ago the author had occasion to prepare a quantity of phenyl thio carbamide, and while placing it in a bottle the dust flew around in the air. Another occupant of the laboratory, Dr. C. R. Noller, complained of the bitter taste of the dust, but the author, who was much closer, observed no taste and so stated. He even tasted some of the crystals and assured Dr. Noller they were tasteless but Dr. Noller was equally certain it was the dust he tasted. He tried some of the crystals and found them extremely bitter. With these two diverse observations as a starting point, a large number of people were investigated and it was established that this peculiarity was not connected with age, race or sex. Men, women, elderly persons, children, negroes, Chinese, Germans and Italians were all shown to have in their ranks both tasters and non-tasters.

At first it was thought that this phenomenon was connected with the acidity or alkalinity of the mouth, but experiment soon showed there was no connection whatever.

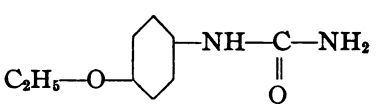
This peculiar phenomenon offered an interesting opportunity for a chemical study of related compounds. Phenyl thio carbamide has the structure



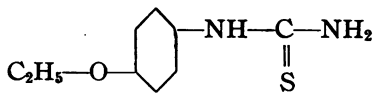
which is closely related to phenyl carbamide, with the structure



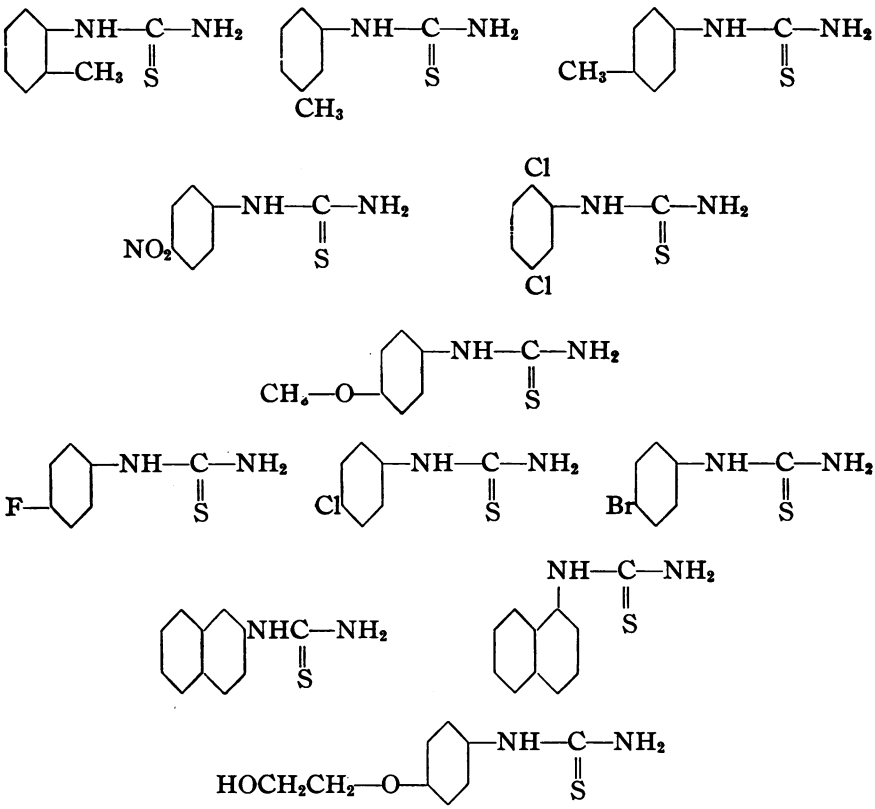
If an ethoxy group is introduced para to the nitrogen a product is obtained which is three hundred times sweeter than sugar, and which is used as a commercial sweetening agent under the trade name Dulcin. It has the structure



It was therefore of interest to investigate the taste properties of the sulphur analog of Dulcin, that is, para ethoxy phenyl thio carbamide.

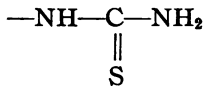


This compound was doubly interesting to investigate because some forty-six years ago Berlinerblau (*J. Prakt. Chem.* **2**, 30, 108) described this compound as being very bitter, and more recently Lange and Reed (*J. A. C. S.* **48**, 1070) stated that the replacement of oxygen by sulphur in many compounds caused bitterness, the most striking compound cited by them being Dulcin. Therefore this compound was prepared and it was found to exhibit this same peculiar property. A wide variety of other aryl thio carbamides were then prepared, of which the following are some of the more interesting.

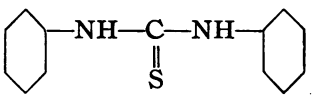


These were all shown to possess the same property.

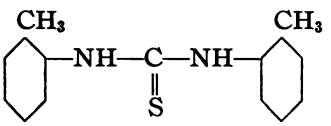
It was apparent, therefore, that the portion of the molecule rendering taste was the aliphatic portion, viz.,

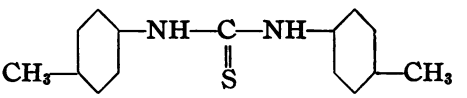


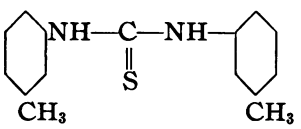
The question then presented itself as to what effect on the taste properties a change in the structure of this portion of the molecule would produce. The simplest method of changing this structure would be the replacement of one of the hydrogen atoms of the $—NH_2$ group with an aryl group. This would produce symmetrical diaryl thio carbamide, the simplest of which is symmetrical diphenyl thio carbamide (thio carbanilide). This compound was prepared by Hofmann (*Ann* **70**, 147 (1849)) some seventy-two years ago and described by him as having an intensely bitter taste. Lange and Reed (loc. cit.) also refer to this compound as being extremely bitter. This compound

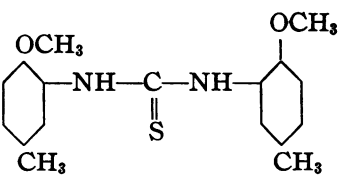


was prepared and the very surprising result noted that it, too, had this same peculiar taste difference according to the individual. It was found to be absolutely tasteless to certain people, while to others it had the intensely bitter taste described by Hofmann. Several other symmetrical diaryl thio carbamides of the following structures were examined,



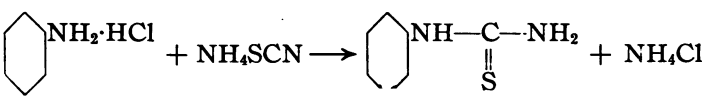




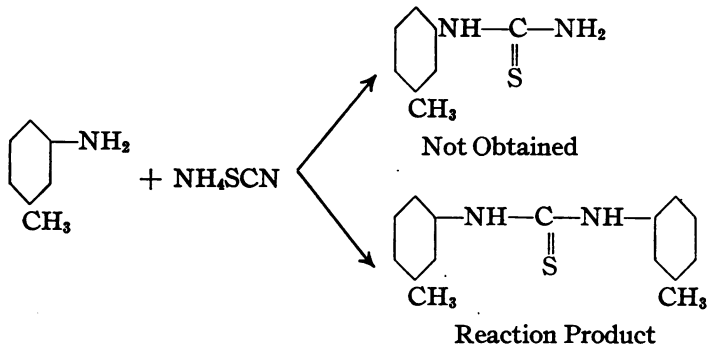


and all these were shown to possess this property.

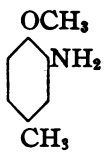
At this point a slight degression should be made to point out a very peculiar chemical reaction that occurred in the preparation of these compounds. The aryl thio carbamides were made from ammonium thio cyanate and a primary amine hydrochloride



It was shown, however, in two cases that under exactly similar conditions not a mono aryl thio carbamide but a diaryl thio carbamide was obtained. Thus when m-toluidine was heated with ammonium thio cyanate under usual conditions sym-di m-tolyl thio carbamide was obtained and not the expected m-tolyl thio carbamide.

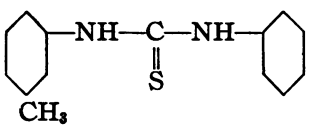


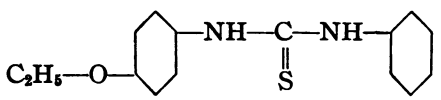
The other amine which gave this peculiar behavior was cresidine,



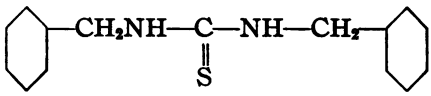
and this product also has a methyl group meta to the amine. It is probable that this meta substituent is responsible for this peculiar behavior and the author proposes to investigate this interesting point.

As symmetrical di-aryl thio carbamides were shown to possess this taste differentiation it became of interest to see whether unsymmetrical diaryl thio carbamides would also show this. In view of the wide structural changes made in previous compounds it was to be anticipated this taste peculiarity would persist and it was shown to do so. The following were made and examined, among others



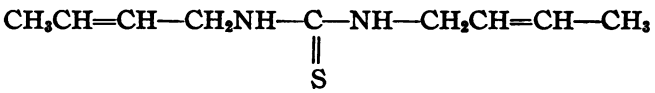


All the compounds so far reported on were aryl or diaryl thio carbamides. It became of interest therefore to examine some aralkyl and alkyl thio carbamides. The first investigated was di benzyl thio carbamide



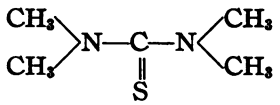
which was shown to have a similar property.

Di-crotyl thio carbamide

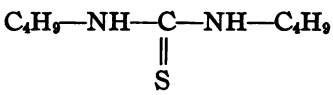


was shown to have a slightly bitter taste to non-tasters, but an extremely bitter taste to tasters.

Tetra methyl thio carbamide

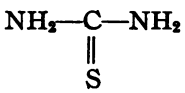


was shown to have a sour but not lasting taste to both tasters and non-tasters, and di-butyl thio carbamide



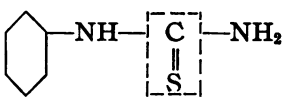
was somewhat bitter to both classes.

Thio carbamide itself



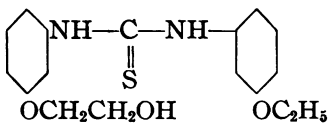
has a nauseating taste, not bitter but sour, to both tasters and non-tasters alike.

From the foregoing discussion it has become apparent that the taste of these compounds is closely connected with the C=S linkage, viz.,



because although the aryl group may be changed to many others this peculiar property remains. Also if a hydrogen of the NH_2 group is replaced with aryl the property remains. The fact that Dulcin, a sweet compound, is formed when the sulfur in *p*-ethoxy phenyl thio carbamide is replaced by oxygen indicates the taste-giving portion of the molecule is in the C=S linkage.

It is believed that this peculiar phenomenon is due to the difference in solubility of the products in the saliva of various individuals. For example, one product was examined



which was found to be tasteless to both tasters and non-tasters. This compound, however, is extremely insoluble, notwithstanding the hydroxy ethoxy group present. Another example was noted containing a solublizing group and this was found to be bitter to both tasters and non-tasters. Some experiments by A. F. Blakeslee have also indicated it is due to a difference in solubility. If this is the case, however, it remains just as inexplicable why these products should be insoluble in the saliva of some individuals and soluble in others. One possible explanation, offered with no experimental proof, is that the extremely small quantity necessary to produce taste is soluble in the saliva of all individuals, while the non-tasters have in their saliva a product, possibly a protein or colloid, which precipitates this as a very insoluble product and thus causes no taste to be sensed. One argument against this hypothesis is that non-tasters can place large quantities of these products on their tongues and not experience any taste. It would seem that the excess of reagent would precipitate all available protein and would then give a sense of taste, a sort of delayed taste. This, in fact, is experienced by some people, but whether this is due to the explanation offered is not known.

Inasmuch as this phenomenon is somewhat similar in its manifestations to color blindness it has been designated taste blindness. It is admitted that there is not an exact scientific analogy but the term taste blindness so effectively describes this phenomenon its use is believed permitted.

GENETICS OF SENSORY THRESHOLDS: TASTE FOR PHENYL THIO CARBAMIDE

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Dr. A. L. Fox[1] first showed that many people cannot detect the bitter taste in crystals of phenyl thio carbamide. In an earlier publication, Salmon and the writer[2] showed that inability to taste the crystals appears to be inherited as a Mendelian recessive. (The same conclusion has been reached independently by L. H. Snyder.[3]) In addition to "non-tasters" of the crystals, we were able to classify the "tasters" of the crystals roughly