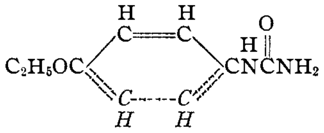
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ARKANSAS]

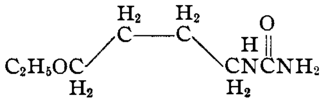
Benzylbenzaldoxime[1]

BY E. WERTHEIM

Experimental work with dulcin has now fairly well established the fact that the sweet taste of the compound depends upon the presence of the ethoxy and carbamido groups in para placement[2] and unaltered by substituents.[3] It has yet to be determined what particular effect is contributed by the benzene ring; this may function merely as a rigid framework to hold the two main taste groups in a preferred position, or the "tension" between these groups as fixed by the electrical structure of the ring may be a more important factor.

If the space orientation of the taste groups is a predominating factor, *d*-ethoxybutyl urea should be sweet, since at any time some of the molecules of this compound will have the spacing exhibited by dulcin.[4]





The writer is accordingly preparing *d*-ethoxybutyl urea which will be described in a later paper. This work was just begun when Gilman announced the preparation of 5-benzyl-2-*syn*-furaldoxime, a compound 690 times as sweet as sucrose.[5] It thus became of interest to prepare *p*-benzylbenzaldoxime (which, though built upon a different nucleus, has very nearly the same space orientation of its taste groups as has Gilman's compound) because of its bearing upon the problem stated above.

Certain taste analogies are already known between benzene para compounds and 2,5-furan derivatives, as illustrated by the following table which also shows the similarity of melting points between several of these compounds.

The number of such analogies is at present too small to permit generalizations to be made, but one may infer from an inspection of the table that space orientation has an influence in determining the taste of these compounds.[6]

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[1] Paper No. 312, Journal Series, University of Arkansas.

[2] *o*-Phenetyl urea is tasteless: *cf.* Wertheim, THIS JOURNAL, **52**, 4167 (1930). *m*-Phenetyl urea was recently prepared in this Laboratory and found to be tasteless.

[3] Hydrogen on the nitrogen next the ring may be substituted by *small* groups without lessening the sweetness. For references to the literature see the first paper of this series, Wertheim, THIS JOURNAL, **53**, 200 (1931).

[4] The unsaturation of the ring in dulcin may be taken as a negligible factor, perhaps detracting slightly from the sweetness. The writer has prepared cyclohexyl urea, which has a faintly sweet taste; phenyl urea is pronounced faintly bitter by most observers in this Laboratory, though some report a sweet after-taste.

[5] Gilman, THIS JOURNAL, **52**, 2010 (1930).

[6] In this connection it would be interesting to know the taste of 5-ethoxy-2-furyl urea, the furan isolog of dulcin.

TABLE I

TASTE CORRELATIONS

Furan compound	Taste	Benzene compound	Taste
Furonitrile[1]	Sweet, 100 × sugar	Benzonitrile[2a]	Brennend
Furylalanine[2b]	Intensive süss, darauf bitter	*d*-Phenylalanine[2c]	Ausgesprochen süss
5-Nitro-2-furaldoxime,[3] m. p. 121°	Slightly sweet	*p*-Nitrobenzaldoxime (*anti*),[2d] m. p. 128.5–129°; 133°	Schwach süss
5-Bromo-2-furaldoxime,[4] m. p. 150–152°	Pleasant sweet	*p*-Bromobenzaldoxime (*anti*)[6]	Pleasant sweet, burning
		(*syn*),[6] m. p. 157°	Pleasant sweet
5-Chloro-2-furaldoxime,[5] m. p. 84°	Less sweet than Br compound	*p*-Chlorobenzaldoxime (*anti*),[6] m. p. 106–108°	Burning, slightly sweet
		(*syn*)[6]	Faintly sweet, then bitter and burning

[1] *Iowa State Coll. J. Sci.*, [IV] **1**, 27 (1929).

[2] Cohn, "Die organischen Geschmacksstoffe," Siemenroth, Berlin, 1914. (a) p. 727; (b) p. 604; (c) p. 602; (d) p. 293.

[3] THIS JOURNAL, **52**, 2553 (1930).

[4] *Ibid.*, **52**, 1171 (1930).

[5] *Rec. trav. chim.*, **50**, 833 (1931).

[6] Prepared and tasted in this Laboratory.

Of the benzylbenzaldoximes only the *syn* form could be prepared. While this compound has a lasting sweet taste, the pungent effect characteristic of some aromatic aldoximes predominates. On the other hand, benzylbenzaldehyde is quite sweet and only very slightly pungent while furaldehyde is said to have a spicy taste.

Work on this topic will be continued in this Laboratory.

Experimental Part

***p*-Benzoylbenzoic Acid,** $C_6H_5COC_6H_4COOH$.—Published directions for the preparation of this compound were found unsatisfactory. Twenty-five grams of phenyl *p*-tolyl ketone was dissolved in 130 cc. of warm acetic acid in a 1000-cc. flask under reflux condenser. A solution of 35 g. of chromic oxide in 80 cc. of water, 130 cc. of acetic acid, and 25 cc. of concd. sulfuric acid, was added slowly through the condenser while the reaction mixture was kept just below the boiling point. When all the oxidizing mixture had been added the preparation was quietly boiled for forty-five minutes and the liquid portion then decanted into sufficient cold water to give 2 liters of solution. The solid which precipitated was collected on a large Buchner funnel and washed with cold water until perfectly white. It was dissolved in hot water by the addition of potassium hydroxide solution, and after filtration the acid was precipitated by the addition of an excess of concd. hydrochloric acid solution. After filtration and washing with cold water, the compound was recrystallized from ethanol; yield, 18–20 g.; m. p. about 197–200°, when the bath is rapidly heated.[7]

***p*-Benzylbenzoic Acid,** $C_6H_5CH_2C_6H_4COOH$.—Twenty grams of benzoylbenzoic acid was well mixed with 3.3 g. of red phosphorus and sealed in a bomb tube with 45 g. of hydriodic acid (b. p. 127°). After being heated for eight hours at 160–170°, the tube was opened and the contents ground in a mortar with an excess of potassium hydroxide solution. After solution of the compound was complete the mixture was filtered and the acid precipitated by the addition of an excess of concd. hydrochloric acid solution. The

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(7) Zincke, *Ann.*, **161**, 100 (1872), gives a melting point of 194°.

precipitate was washed with cold water until free of hydriodic acid, then recrystallized from ethanol: yield, about 14 g.; m. p. 159–160°[8] in a rapidly heated bath. This product was compared and found to be identical with acid made by the hydrolysis of *p*-cyanodiphenylmethane (from *p*-cyanobenzyl chloride, benzene and aluminum chloride).[9,10]

***p*-Cyanodiphenylmethane,** $C_6H_5CH_2C_6H_4CN$.—*p*-Benzylbenzoyl chloride was made from a mixture of 20 g. each of the corresponding acid and phosphorus pentachloride. After distillation (b. p. 193° at 8 mm.) it was transformed to the amide, which was recrystallized from dilute ethanol: yield, about 15 g.; m. p. 172–173°. Ten grams each of the amide and phosphorus pentoxide gave *p*-cyanodiphenylmethane (b. p. 195–197° at 13 mm.); recrystallized from dilute ethanol: yield, 7 g.; m. p. 50–52°;[11] tasteless.

***p*-Benzylbenzaldehyde,** $C_6H_5CH_2C_6H_4CHO$.—A modified Stephen method was used.[12] Twenty grams of finely powdered anhydrous stannous chloride was covered with 200 cc. of acetic acid and the mixture saturated with dry hydrogen chloride. A large part of the salt dissolved. Ten grams of *p*-cyanodiphenylmethane was added. The tightly corked flask was shaken frequently; during the next two hours the remainder of the salt dissolved, giving a milky solution. In from three to six hours white crystals of the aldehyde imide salt appeared. In twenty-four hours this compound was removed by filtration and washed with ether. It was decomposed by the addition of hot water and a few drops of concd. hydrochloric acid, and the aldehyde was then extracted with ether, etc.; yield, about 3.5 g.; b. p. 189–190° at 14 mm. The aldehyde is practically colorless, odor floral; faint, pleasant sweet taste, followed by a cinnamon-like taste. The sweet taste is persistent. The customary tests are shown with Schiff solution and ammoniacal silver nitrate solution.[13]

***p*-Benzylbenzaldoxime** (*syn*), $C_6H_5CH_2C_6H_4CHNOH$.—In one experiment 3 g. of the aldehyde in 65 cc. of ethanol was brought into reaction with 1.1 g. of hydroxylamine hydrochloride in 8 cc. of water and 2.5 g. of sodium carbonate in 15 cc. of water. This experiment and others which were modified in various ways yielded an oxime with m. p. 89–91°. It apparently had the *syn* configuration. Attempts to force a shift to the *anti* structure were unsuccessful; faint, pleasant sweet taste, followed by burning sensation. The sweet taste is persistent and outlasts the pungency.

The above oxime was boiled with 10 molar proportions of acetic anhydride for two minutes; the addition of water caused the separation of a solid which was recrystallized from dilute acetic acid; m. p. 64–66°. A portion of this acetyl compound when heated at 23 mm. pressure lost acetic acid and gave a solid which after purification melted at 48–49° and proved to be *p*-cyanodiphenylmethane.

TABLE II

ANALYTICAL DATA

Compound	Formula	Carbon, % Calcd.	Carbon, % Found		Hydrogen, % Calcd.	Hydrogen, % Found		Nitrogen, % Calcd.	Nitrogen, % Found	
Benzylbenzamide	$C_{14}H_{13}NO$	79.61	79.98	79.66	6.16	6.10	5.85	6.63	6.59	6.63
Benzylbenzaldehyde	$C_{14}H_{12}O$	85.70	85.71	85.62	6.12	6.00	6.18			
Benzylbenzaldoxime	$C_{14}H_{13}NO$	79.61	79.60	79.54	6.16	6.45	6.08	6.63	6.25	6.53
Benzylbenzaldoxime acetate	$C_{16}H_{15}NO_2$	75.90	76.11	75.95	5.93	5.62	5.51	5.53	5.94	5.65

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(8) The melting points 154–155° and 157–158° are given in the literature.

(9) *Cf.* Moses, *Ber.*, **33**, 2627 (1900).

(10) The Clemmensen method was used several times to make this acid, giving a smaller yield and an impure product. However, this method appears to hold out some promise and will therefore be tested thoroughly in this Laboratory at an early date.

(11) Moses, Ref. 9, quotes a melting point of 50–51°.

(12) Stephen, *J. Chem. Soc.*, **127**, 1874 (1925).

(13) The dehydration of stannous chloride as recommended by Stephen was found to be difficult and impractical. In this work $SnCl_2 \cdot 2H_2O$ was heated to (just) 180°, then finely powdered and preserved over sulfuric acid.

Summary

p-Benzylbenzaldehyde and its oxime have been prepared. Both have a sweet taste, followed by a pungent or burning sensation. The influence of space orientation of groups upon taste in benzene and furan compounds is discussed in connection with the sweet taste of dulcin. Taste analogies are pointed out between benzene para compounds and 2,5-furan compounds.

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Synthesis and Physiological Action of Alpha Substituted N-Methylpyrrolidines

BY LYMAN C. CRAIG[1]

Introduction

Nicotine has long been recognized as a compound possessing unusual toxicity both to warm and to cold blooded animals. It is a compound of rather simple structure when compared to the other outstanding organic insecticides, the pyrethrins and rotenone. Accordingly it seems strange that with the exception of the recently synthesized Neonicotine[2] or Anabasine no other closely related compounds having high toxicity have been prepared or discovered.

Attempts to locate a specific atomic linkage or "Toxifore" grouping responsible for its unusual activity have been without result and have led previous investigators[3] to believe that such a grouping does not exist but that the make-up of the molecule as a whole is responsible for the physiological action. This is undoubtedly true in one sense as each atomic linkage must contribute something to the chemical behavior of the compound as a whole. However, the separate linkages must vary in the degree of their contribution to the chemical behavior and thus to the physiological action.

As part of a systematic study of structure and physiological action in the nitrogen heterocyclics it seemed desirable to prepare and study a series of α-substituted N-methylpyrrolidines. Such a study should establish whether or not the "Toxifore" grouping is contained in the pyrrolidine nucleus provided a series having the proper distribution of radicals could be obtained. From a structural standpoint nicotine may be considered as a member of the series. This paper reports the study mentioned.

(1) National Research Fellow.

(2) Smith, THIS JOURNAL, **54**, 39 (1932).

(3) LaForge, *ibid.*, **50**, 2471 (1928); Harlan, Ph.D. Dissertation, Iowa State College, 1928; Tattersfield, *J. Agr. Sci.*, **17**, 181–208; Tattersfield and Gimmingham, *Ann. Appl. Biol.*, **14**, 217 (1927); Richardson and Shepard, *J. Agr. Res.*, **40**, 1007 (1930).